Contributions to the development of new agents for tumor therapy: Synthesis of 7,19-epoxysteroids as well as precursors of the natural product camporidine A

Inaugural-Dissertation

zur

Erlangung des Doktorgrades

der Mathemathisch-Naturwissenschaftlichen Fakultät

der Universität zu Köln

vorgelegt von

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Köln, Juni 2023

Die vorliegende Arbeit wurde im Zeitraum November 2019 bis Juni 2023 am Institut für Organische Chemie der Universität zu Köln unter der Anleitung von Prof. Dr. Hans-Günther Schmalz angefertigt.

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Tag der Disputation:	01.09.2023

Abstract

This work concerns the early evaluation of synthetic strategies towards the recently discovered natural product camporidine A, which displays a pronounced anti-metastatic activity. Three conceptually different strategies were evaluated including an imino Diels-Alder reaction, an *aza*-Michael/aldol sequence and an intramolecular [2+3] cycloaddition. With the final cycloaddition approach it was possible to synthesize the central bicyclic tetrahydropyridine containing core-structure of camporidine A.
In the second part of this work the multi-gram scale synthesis and derivatization of 7,19-epoxysteroids, which display characteristic anti-metastatic properties, were performed. The 7,19-epoxysteroids were evaluated in the context of their potential for apoptosis induction on a series of cancer cell lines as well as their synergistic and resistance breaking effects on leukemia cells and some promising candidates were identified.

Zusammenfassung

Diese Arbeit befasst sich mit der Synthese des kürzlich entdeckten Naturstoffs Camporidin A, welcher eine ausgeprägte anti-metastatische Aktivität aufweist. Drei konzeptionell unterschiedliche Synthesestrategien wurden untersucht, darunter eine Imino Diels-Alder Reaktion, eine *Aza*-Michael/Aldol Sequenz und eine intramolekulare [2+3]-Cycloaddition. Durch den finalen Cycloadditionsansatz war es möglich, die zentrale bicyclische Kernstruktur von Camporidin A zu synthetisieren.
Im zweiten Teil dieser Arbeit wurde die Synthese im multi-Gramm-Maßstab und die Derivatisierung von 7,19-Epoxysteroiden, die charakteristische anti-metastatische Eigenschaften aufweisen, verfolgt. Die 7,19-Epoxysteroide wurden im Hinblick auf ihr Potenzial zur Apoptoseinduktion bei einer Reihe von Krebszelllinien sowie auf ihre synergistischen und resistenzbrechenden Wirkungen auf Leukämiezellen untersucht und einige vielversprechende Derivate wurden identifiziert.

Acknowledgement

I would first like to thank my advisor Prof. Dr. Hans-Günther Schmalz for giving me the opportunity to work in his working group under excellent working conditions and constant support and guidance over the last years. Although the Covid-pandemic began shortly after the beginning of my PhD-studies, I could always rely on him and the working group, that we find the best way through such a crisis. I want to thank him for always being positive and motivating, while trusting me to develop the projects I was working on freely. He did especially trust me in the context of the 7,19-epoxysteroid project, while always strengthening my back.

I would as well like to thank Prof. Dr. Stephanie Kath-Schorr for accepting to review this thesis and for being a valuable discussion partner on several occasions. My thank does also go to Prof. Dr. Ines Neundorf for being the chairman and Dr. Jörg-Martin Neudörfl for being part of my committee.

I want to thank my friend and former colleague Dr. Ömer Taspinar, who introduced me into the fascinating world of steroids, helped me in numerous experiments and has made a major contribution to the success of the steroid project. It was a honor for me to work with you during my time in this working group! I really appreciate your exceptionally kind and always helpful attitude.

I want to thank Dr. Daniel Friedrich, Dr. Nils Schlörer and whole NMR team for the nuclear magnetic resonance analysis. I want to thank Prof. Dr. Mathias Schäfer and his team for performing mass analysis of my samples. For X-Ray analysis, I would like to thank Dr. Jörg Neudörfl.

A special thank goes to the current as well as former members of the Schmalz group for helping, whenever help was needed, for the nice working atmosphere and for all the interesting discussions. I am extremely thankful for those who directly worked with me and supported me during my whole studies over the last years. The group has always been a source of good friendship and collaboration.

I want to thank all my supporters and practical students for their contributions to my projects: Nora Korber, Jan Phillip Niessen, Sebastian Barutzki, Andre Wesseling, Marvin Schmitz, Sophie Lüggert, Niklas Zips, Lukas Lehmann, Katharina Klupsch and David Kaplik.

I want to express my gratitude to all members of the Institute of Organic Chemistry, especially Dietmar Rutsch, Andreas Wallraf, Herbert Hartmann and his workshop

team, Sylvia Rakovac and her team including Nihad El Ghachtoun and Ingo Müller. Further I appreciate Susanne Geuer in every administrational and Andreas Adler in every technical support. Very special thanks go to Anja Bitners for administrative support and nice conversations over the last years. I want to acknowledge the GoBio initial program for financial support which enabled me to pursue the steroid project and to participate in conference “Medicinal Chemistry Frontiers” in Boston 2023.
I thank Alicia Köcher and Ömer Taspinar for careful and fast proofreading of this thesis and I appreciate all the helpful suggestions.
Finally, I would like to express my special gratitude to the closest people in my life for all their unconditional love, support, patience and understanding in every possible way. Without you, none of these accomplishments would have come true.

1. Introduction

Natural products play an important role in the history of mankind and in the evolution of a modern, scientific based medicine. Already in ancient times hunters knew how to use the toxins of deadly nightshade (*atropa belladonna*) as effective tools. In 1806 Sertürner was able to isolate morphine from opium in a pure fashion, followed by the isolation of strychnine and quinine by Pelletiere in 1820. These are only a few milestones in the isolation of natural products, but each compound has affected humankind in a remarkable and very diverse fashion.[1,2]

Later, organic synthetic chemists became highly interested in natural products giving rise to an essential field of research. Increasing numbers of natural products were only isolated in decreasing quantities, when at the same time the demand for such compounds rose dramatically. Therefore, organic chemists like Woodward and many others tried to establish synthetic approaches to supply those compounds in greater amounts. They were inspired by the structural complexity and variety of natural products and used this as a driving force for the development of new methods in organic synthesis, which resulted in the establishment of powerful new methodologies.[1]

Nowadays, synergistic effects between the scientific disciplines surrounding the natural products play an increasing role. New natural products with interesting biological properties are identified, organic chemists develop synthetic tools and efficient routes towards increasingly complex natural products, and finally medicinal chemistry develops the most fitting match for biological targets that should be addressed.

All of this shows that organic synthesis is crucial in this cluster of the surrounding scientific fields and towards the development of an even more efficient medicine, which can treat an increasing number of diseases with less side effects, all leading to a better quality of life.

2. Part 1: Synthesis of Precursors of the Natural Product Camporidine A

2.1. State of the Art

2.1.1. Natural Products

The broad field of natural products includes all molecules synthesized by nature. To this class of compounds belong an overwhelming number of molecules. Therefore, it is necessary to introduce subclasses of the natural products. Amino acids, peptides and proteins are a few well-known examples for such subclasses. For instance, many functional compounds in nature, including enzymes, which serve as highly selective catalysts, or membrane proteins, acting as pumps for either special molecules or ions, belong to the subclass of proteins. Besides these few examples, there are a lot more subclasses of natural products such as carbohydrates, lipids, isoprenoids or alkaloids and either one could be differentiated in more detail.[1,2] Especially the alkaloids depict an interesting compound class, which should be looked at more closely.

2.1.1.1. Alkaloids

The first isolated alkaloid was morphine in 1806 by Sertürner[1] and only 20 years later the first industrial isolation of morphine was accomplished by Merck. Historically, alkaloids have been described as natural products bearing a basic nitrogen moiety. Especially in the early days of natural product isolation the alkaloids were differentiated from other natural products due to their reactivity towards acidic workup methods. Upon identification of more compounds, the alkaloids were divided into subclasses, which are either defined by their botanic heritage (solanum alkaloids, papaver alkaloid, etc.) or by their chemical heritage (pyridine-, quinoline-, steroid-alkaloids).[2]

An example for a simple alkaloid known in a broader, public context is coniine (**1**), which is a highly potent toxin and can be isolated from the poison hemlock (*Conium maculatum*), and γ-coniceine (**2**), which can be isolated from the same plant, but is 20 times more toxic than coniine (**1**) itself. Ephedrine (**3**) as well as nicotine (**4**), which is a pyridine-based alkaloid mainly found in tobacco, act as central nervous system stimulants (Figure 1).[2]

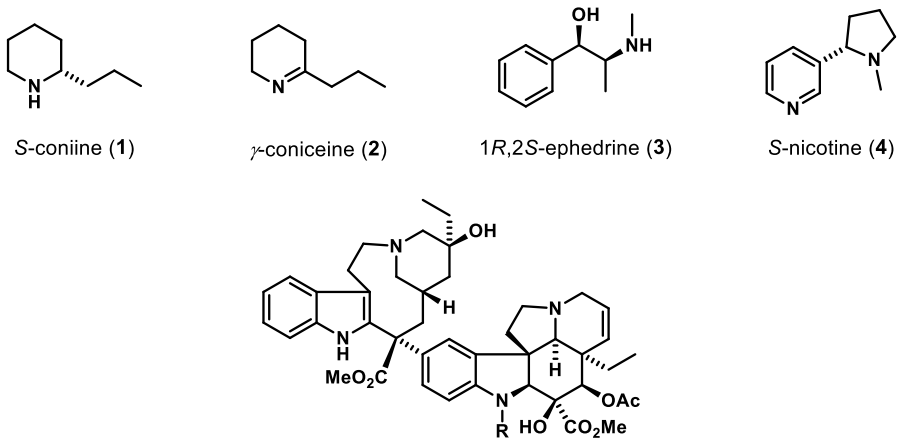


Figure 1: Chemical structure of the natural alkaloids *S*-coniine (**1**), γ-coniceine (**2**), 1*R*-2*S*-ephedrine (**3**), *S*-nicotine (**4**), vinblastine (**5**) and vincristine (**6**).

Two more complex alkaloids isolated from *vinca rosea* are vinblastine (**5**) and vincristine (**6**), which belong to the indol-indoline alkaloids. Both natural products are of high importance due their antitumoral activity. As important tools in modern tumor therapy, they are used as cytostatics in oncology.[2,3]

Many more alkaloids like penicillin (antibiotic), ivermectin (antiparasitic), cyclosporin (immunosuppressant), mevinolin (cholesterol reducer) or phosphinothricine (herbicide) could be mentioned in this context, but this would go beyond the scope of this chapter.[1]

2.1.2. [4.3.0] Piperidine Alkaloids

2.1.2.1. Camporidine A

Camporidine A (**7**) was first isolated from the gut bacteria (*Streptomyces* sp. STA1) of the carpenter ant *camponotus kiusiuensis* and characterized by Hong and coworkers.[4] Camporidine A (**7**) belongs to the class of alkaloids and bears several interesting structural motifs condensed on a relatively small molecule (Figure 2). It is worth to highlight the 2-*aza* [4.3.0] bicyclo nonane core structure with an additional epoxide on the central piperidine ring forming in total a 6/5/3 tricyclic core motif. This tricyclic core structure in combination with the conjugated side chain represents an interesting and challenging structural motif for synthetic chemists. Especially the central piperidine-derived core structure sets a promising starting point for synthetic efforts.[4]

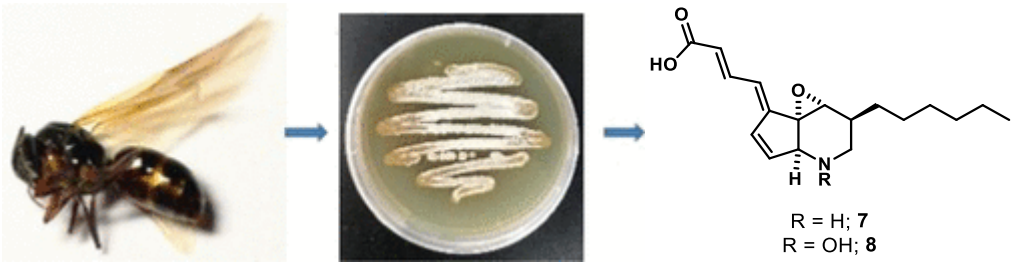


Figure 2: Left: *Camponotus Kiusiuensis*; Middle: Cultivated gut bacteria of the genus *Streptomyces*; Right: Camporidine A (**7**). [Reprinted and adapted with permission from (*Journal of Natural Products* **2019,** *82* (4), 903-910). Copyright (2020) American Chemical Society.)][4]

Camporidine A (**7**) possesses an antimetastatic activity by the suppression of cell migration of metastatic breast cancer cells in a concentration dependent manner (50% at 20 μM, 73% at 40 μM) and by the suppression of cell invasion (20% at 20 μM, 36% at 40 μM). Furthermore, it exhibits an anti-inflammatory effect by suppression of the nitric oxide production induced by lipopolysaccharide after treatment of mouse macrophages (IC_{50} = 16.9μM).[4]

Interestingly, camporidine B (**8**), which only bears an additional hydroxy moiety at the secondary amine, exhibits no measurable antimetastatic nor anti-inflammatory activity. The free amine functionality in combination with the conjugated side chain and the terminal carboxylic acid moiety, reminds of a vinylic amino acid and seems to be of central importance to the activity of camporidine A (**7**). Due to the introduction of a hydroxylamine moiety the biological activity of camporidine B is drastically decreased.[4]

2.1.2.2. Related 2-*aza* [4.3.0] Bicyclo Nonane Alkaloids

Besides camporidine A (**7**) and B (**8**), a series of other alkaloids displaying an 2-aza [4.3.0] bicyclo nonane alkaloid skeleton have been described in the literature.[5] This chapter aims to deliver a concise overview of the structurally closely related natural products and of their currently known synthesis routes. All these compounds bear the same characteristic *aza* [4.3.0] bicyclo nonane ring system and in many cases also an epoxide moiety. Nevertheless, the concrete functionalization at the bicyclic core motif varies. Dihydroabikoviromycin (**9**)[6-11], *N*-hydroxydihydroabikoviromycin (**10**) and epostatin (**11**)[12,13] are the closest relatives to camporidine A (**7**) and contain the same tricyclic core structure (Figure 3). Abikoviromycin (**12**)[6-8,10,11,14,15] and kobutimycin A (**16**) and B (**17**)[16] have an oxidized conjugated imine in the core motif. Streptazone A

(**13**), B_1 (**14**) and B_2 (**15**)[17] share a characteristic enaminone moiety. Finally, streptazolin (**18**)[17], which features a cyclic carbamate, is be the natural product from this compound class with the most synthetic approaches established.

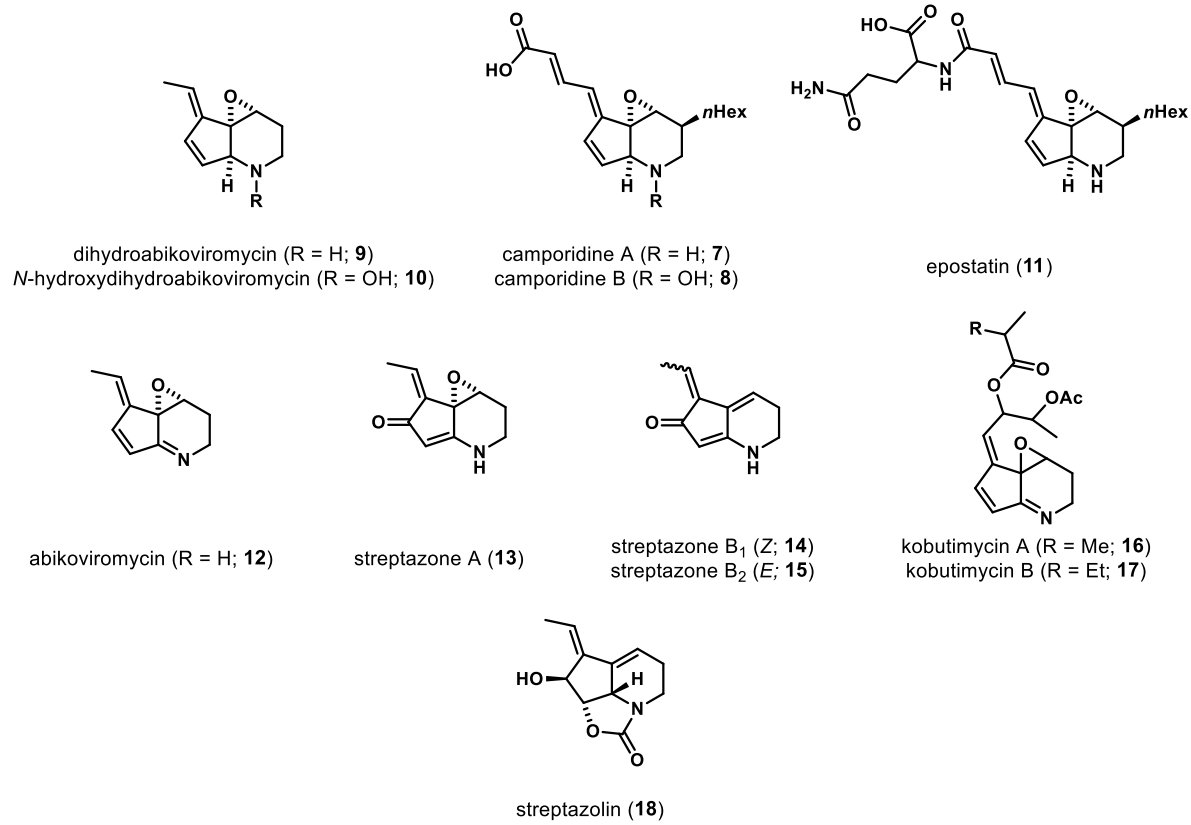


Figure 3: Chemical structures of 2-aza [4.3.0] bicyclo nonane alkaloids.

Epostatin (**11**) is structurally the closest relative of camporidine A (**7**) and B (**8**) featuring the complete camporidine A structure and is additionally condensed with one molecule of glutamine to the free carboxylic acid moiety. It has been reported to act as an efficient inhibitor of the dipeptidyl peptidase II (DPP-II), which is involved in the breakdown of peptides into their fragments and related to rheumatoid arthritis.[12,13] To our knowledge no synthetic route towards epostatin (**11**) has been described in the literature yet. The material tested for their biological activity has been isolated from the fermentation broth of the strain *Streptomyces sp.* MJ995-OF5.[12]

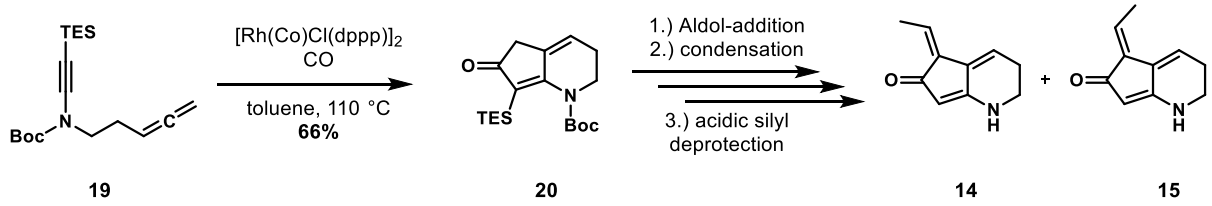
Dihydroabikoviromycin (**9**) and *N*-hydroxydihydroabikoviromycin (**10**) share the structural core motif of camporidine A (**7**) and B (**8**). However, the structures are lacking the *n*hexyl side chain with the corresponding stereocenter and display a shortened conjugated side chain, missing the third alkene unit and the carboxylic acid moiety.[11] Dihydroabikoviromycin (**9**) has been briefly described as the reduction

product of abikoviromycin (**12**) upon treatment with $NaBH_4$.[10,11] Later the absolute configuration was reported by Maruyama.[8] A series of different biological properties has been described for dihydroabikoviromycin (**9**) including a decent genotoxicity, which was shown in repair deficient *E. coli*, and a cytotoxicity in a low μM range.[6,7]

Structurally closely related to dihydroabikoviromycin (**9**) is the compound abikoviromycin (**12**), in the early literature also called latumcidin[18], and kobutimycin A (**16**) and B (**17**). Abikoviromycin (**9**) was first isolated from *Streptomyces abikoensum* and *Streptomyces rubescens* in 1951 by Fukuyama[14] and later in 1968 the structural elucidation was carried out by Gurevich *et al*.[10,11] The absolute configuration was revised 1971 by Saito based on X-ray crystallography.[19]

Abikoviromycin (**12**) has been reported to be very unstable even at low temperatures such as -50 °C, which leads to a relatively fast polymerization. Only handling under highly dilute conditions enables working with this compound.[11] Later, it was discovered, that the picrate and hydrogen sulfate salts of abikoviromycin can be stored for several months at 0 °C.[10] In contrast to dihydroabikoviromycin (**9**) and *N*-hydroxydihydroabikoviromycin (**10**), abikoviromycin (**12**) exhibits antiviral and antibiotic properties, it inhibits eastern and western encephalitis and has a series of additional biological activities.[8,10,11,14,19,20]

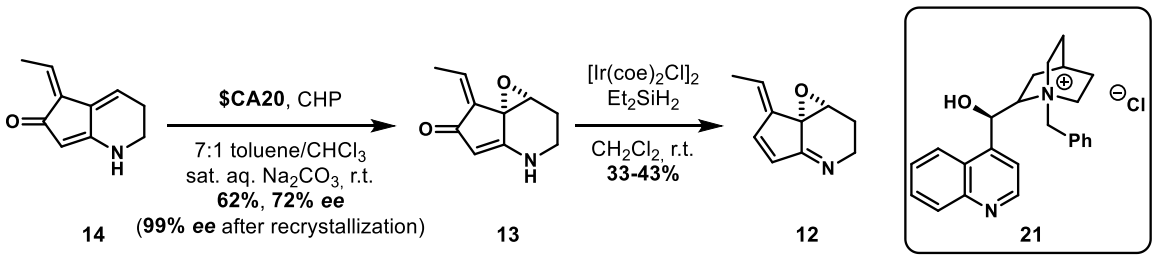
Up to date only one synthesis of streptazone B_1 (**14**) and streptazone B_2 (**15**) with a total of 7 steps has been reported by the working group of Poulsen *et al*. (Scheme 1).[5,15] Their key transformation to construct the central 2-aza [4.3.0] bicyclo nonane core structure is an intramolecular rhodium-catalyzed Pauson-Khand reaction. The ethylene side chain is introduced by an aldol-addition followed by elimination of the β-hydroxy moiety establishing the corresponding enone in an 45/55 (*E*/*Z*) ratio. The two formed isomers correspond to the desired natural products streptazone B_1 (*Z*; **14**) and streptazone B_2 (*E*; **15**), which were isolated after an acid-mediated silyl- and Boc-deprotection.[15]



19 **20** **14** **15**

Scheme 1: Synthetic access to streptazone B_1 (**14**) and streptazone B_2 (**15**) reported by Poulsen *et al*.[15]

With streptazone B_1 (**14**) in hand, Poulsen and coworkers were able to perform an enantio- and regioselective epoxidation of the 3,4-double bond by employing cumene hydroperoxide in combination with the chiral cinchona alkaloid-based phase transfer catalyst **21** (Scheme 2). Finally, it was possible to perform a selective reduction of the enaminone to the corresponding conjugated imine employing an iridium-diethyl silane system furnishing abikoviromycin (**12**).[15]



Scheme 2: Synthesis of streptazone A (**13**) and abikoviromycin (**12**) from streptazone B_1 (**14**) reported by Poulsen *et al*.[15]

2.1.3. Total Syntheses of Streptazolin

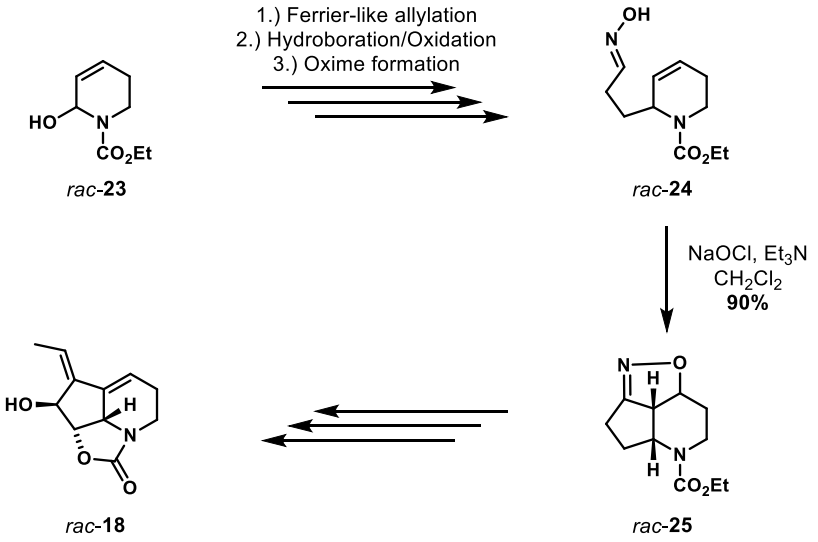
Streptazolin (**18**) is the most prominent example of the 2-*aza* [4.3.0] bicyclo nonane alkaloids. It was first isolated and characterized in 1981 by Drautz and Zahner from *Streptomyces viridochromogenes*.[21] Its structural elucidation was performed with its dihydroacetate derivative **22**, because streptazolin (**18**) itself tends to polymerize at higher concentration.[22] The naphthoquinone Diels-Alder adduct of streptazolin has been reported to possess fundamental fungicidal and bactericidal activities. Additionally, antitumor activity on leukemia L1210 cells has been reported.[23]

streptazolin (**18**) dihydrostreptazolin acetate (**22**)

Figure 4: Chemical structures of streptazolin (**18**) and its more stable derivative dihydrostreptazolin acetate (**22**) described by Drautz *et al*.[21]

The first total synthesis of streptazolin (*rac*-**18**) was established by Park *et al*. in 1985 (Scheme 3). The synthesis route starts with the *aza*-analogue of a Ferrier-like reaction to introduce the sidechain followed by a hydroboration of the terminal alkene with 9-BBN and subsequent oxidation to the aldehyde. Upon treatment with

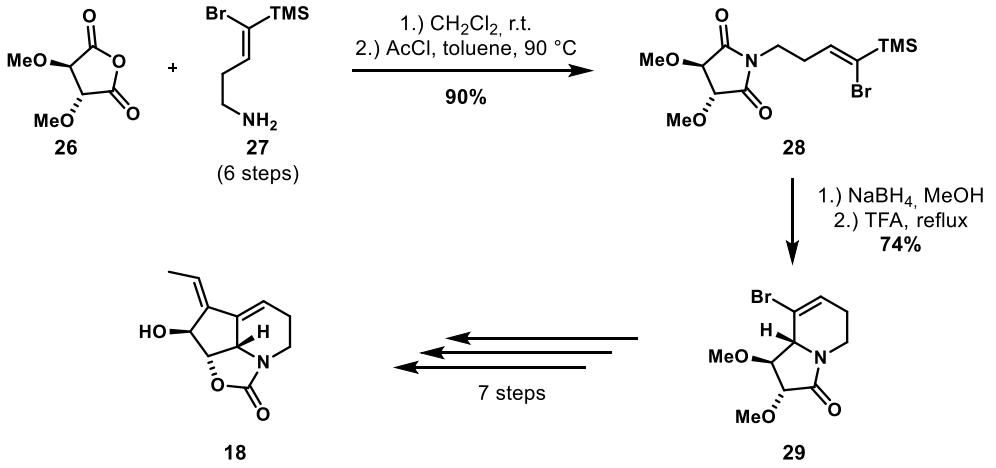
hydroxylamine the oxime *rac*-**24** was furnished. The key step to establish the 2-aza [4.3.0] bicyclo nonane core motif was a 1,3-dipolar cycloaddition by oxidation of the oxime *rac*-**24** to the corresponding nitrile oxide and subsequent led to the formation of the desired tricyclic product *rac*-**25**. 12 further steps were necessary to finish the total synthesis of racemic streptazolin (*rac*-**18**). Due to these synthetic efforts Park *et al*. were able to show by NOE experiments, that the ethylidene substituent in streptazoline (**18**) is *Z*-configured.[24]



Scheme 3: First total synthesis of racemic streptazolin (*rac*-**18**) reported by Park *et al*.[24]

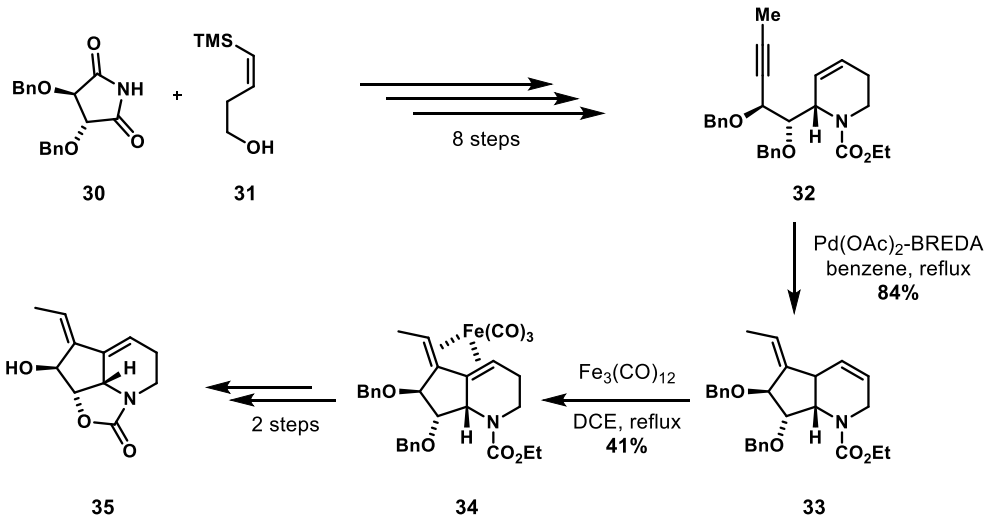
In 1987, Overman *et al*. reported the first enantioselective total synthesis of streptazolin (**18**).[25] By making use of the chiral pool the chiral pool, tartaric anhydride dimethylether (**26**) was applied to obtain streptazolin (**18**) in a substrate controlled, diastereoselective fashion over 15 steps from but-3-yn-1-ol (Scheme 4). The reaction sequence to construct the central tetrahydropyridine moiety in an enantioselective fashion consists of an imide formation between L-tartaric anhydride dimethyl ether (**26**) and amine (**27**), which undergoes subsequent reduction with $NaBH_4$ to the desired hemiaminal. The cyclization was performed under acidic conditions to form the corresponding iminium electrophile, which is attacked by the alkene in an intramolecular fashion followed by the elimination of the TMS group to give the cyclized product **29**. Further 7 steps, including the amide bond cleavage, halogen lithium exchange of the vinylbromide and intramolecular cyclization with the terminal ester, were necessary to furnish enantiopure streptazolin (**18**). This route

unfortunately lacks selectivity for the introduction of the ethylidene substituent *via* a Wittig reaction forming predominantly the undesired *E*-alkene in a 2:1 ratio.[25]



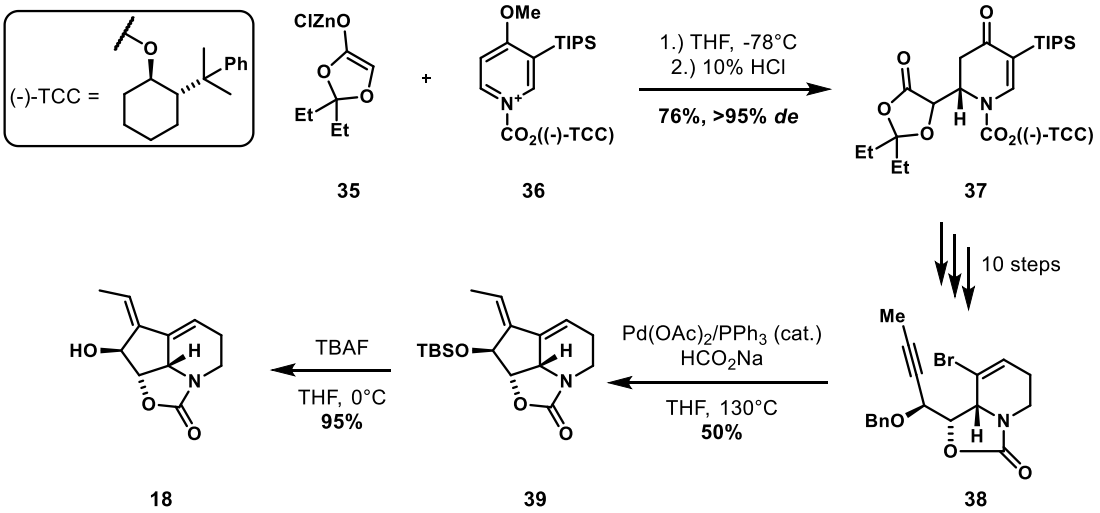
Scheme 4: First enantioselective total synthesis of streptazoline (**18**) reported by Overman *et al*.[25]

This lack of selectivity has been addressed by Kibayashi *et al*. in 1996. The synthesis of the tetrahydropyridine derivative **32** was closely related to the work performed by Overman *et al.*[25], but they used a palladium-catalyzed enyne cyclization followed by an iron-mediated alkene isomerization to obtain the central 2-*aza* [4.3.0] bicyclo nonane core structure **34** (Scheme 5). This protocol led to the formation of the *Z*-ethylidene unit in a stereoselective fashion solving the selectivity issues encountered by Overman *et al.* by avoiding the introduction of the ethylidene substituent by a Wittig olefination. The reaction sequence was finished upon deprotection of the benzyl ethers and iron complex with BBr_3, followed by an intramolecular carbamate formation under basic conditions. In total, this route ended up with 18 steps starting from diethyl tartrate.[26]



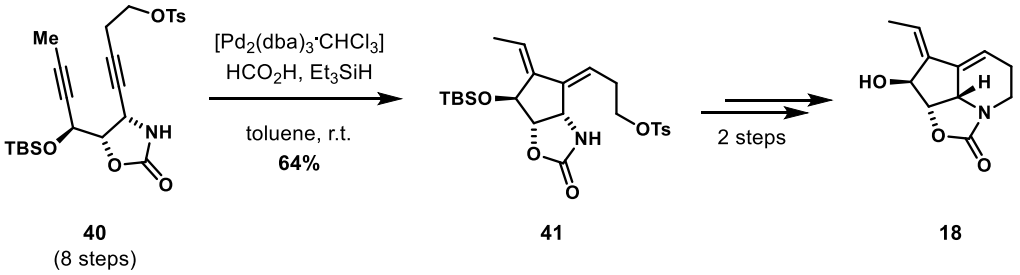
Scheme 5: Total synthesis of streptazolin (**18**) reported by Kibayashi *et al*.[26]

Comins *et al*. reported another enantioselective total synthesis of streptazolin (**18**) in 2000 (Scheme 6).[27] They were able to construct the tetrahydropyridine core structure **37** by a chiral auxiliary mediated diastereoselective metallo-enolate addition of **35** to a chiral *N*-acyl pyridinium salt **36** to obtain the corresponding *N*-acyl dihydropyridinone **37**. This methodology has previously been established in the working group of Comins in a number of examples.[28-36] The 3-TIPS substituent acts as an effective directing group for the selective addition of nucleophiles to the 6-position of 3-TIPS-*N*-acylpyridinium derivatives. The readily available chiral auxiliary (+/-)-TCC renders the reaction diastereoselective.[27,28,31-34,36] Further transformations, such as Weinreb-amide formation followed by a nucleophilic addition of prop-1-ynyllithium, α-bromination, enaminone reduction and vinylbromide formation by elimination of the corresponding triflate furnishes the precursor **38** for the subsequent ring-closing reaction of the central five-membered ring. This palladium catalyzed ring-closure starts from the corresponding vinylbromide **38** and therefore directly leads to the desired dienylic streptazoline precursor **39** without the need of a subsequent double bond isomerization. A TBS-deprotection under standard conditions finalizes the streptazolin (**18**) synthesis in a total of 14 steps.[27]



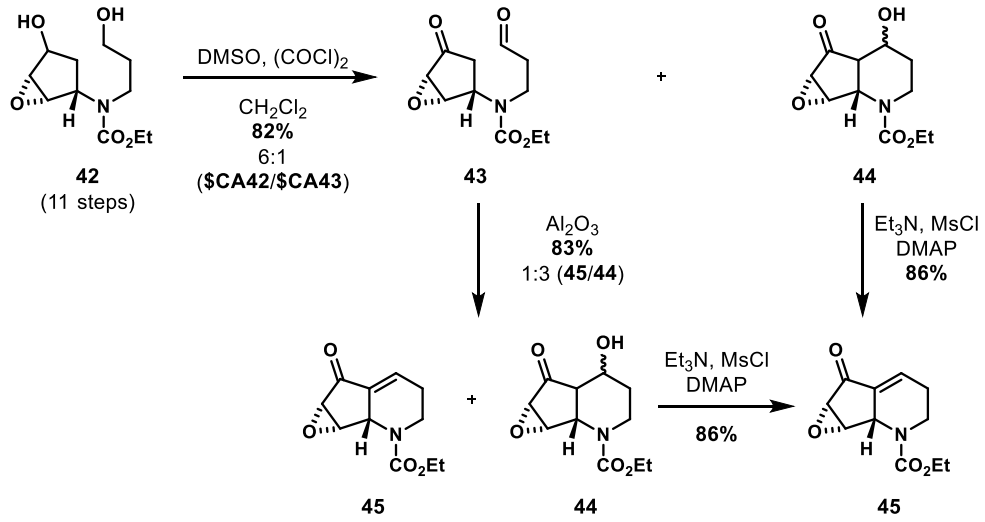
Scheme 6: Total synthesis of streptazolin (**18**) reported by Comins *et al*.[27]

In 2004 two more total synthetic approaches towards streptazolin (**18**) were reported by Trost *et al*.[37] and by Miller *et al.*[38,39]. The route reported by Trost *et al*. relies on a central palladium-catalyzed reductive diyne cyclization followed by a S_N2-type intramolecular attack of the carbamate **41** to the terminal tosylate resulting in the ring closure of the tetrahydropyridine substructure (Scheme 7).[37]



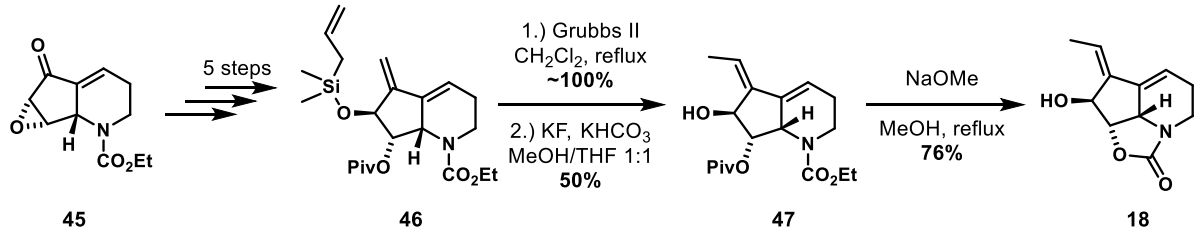
Scheme 7: Total synthesis of streptazolin (**18**) reported by Trost et al.[37]

Miller *et al.* followed a completely different approach by establishing the tetrahydropyridine core structure *via* an Aldol condensation (Scheme 8). Already upon the initial oxidation to the keto-aldehyde **43** some of the desired aldol addition-product **44** was isolated. Nevertheless, to drive the aldol condensation to completion it was necessary to treat **43** with basic Al_2O_3 followed by the elimination of the β-hydroxy moiety using MsCl and Et_3N.[39]



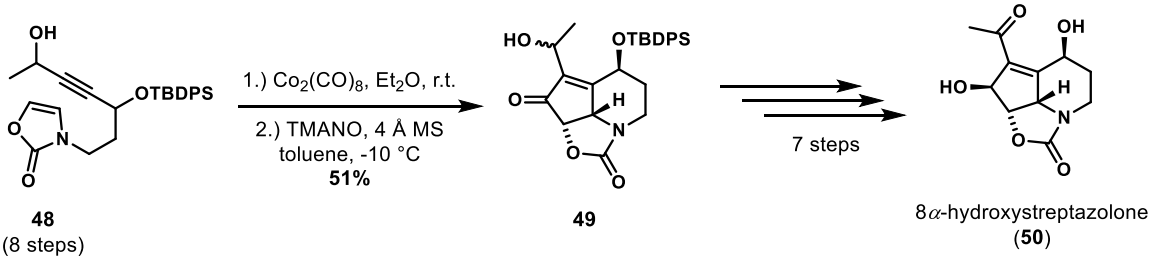
Scheme 8: Central intramolecular aldol condensation in the course of the total synthesis of streptazolin (**18**) reported by Miller *et al*.[38]

The final *Z*-selectivity of the ethylidene bridge was forced by an intramolecular silane-tethered olefin metathesis resulting in the formation of a six-membered ring (Scheme 9). Finally, the Si-C-bond was cleaved with fluoride and the final carbamate was formed under basic conditions to yield streptazolin (**18**) over 16 steps.[39]



Scheme 9: Final steps of the total synthesis of streptazolin (**18**) *via* an intramolecular olefin metathesis reported by Miller *et al*.[38]

Another related total synthesis of 8α-hydroxystreptazolone (**50**) was reported in 2002 by Mukai *et al.* employing an intramolecular Pauson-Khand reaction to construct the full 2-aza [4.3.0] bicyclo nonane core motif in just one transformation (Scheme 10). This was the first non-sequential route to such a core structure reported.[40]

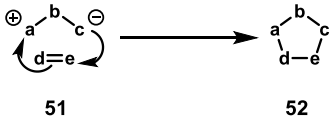


Scheme 10: Total synthesis of 8α-hydroxystreptazolone (**50**) reported by Mukai *et al*.[40]

2.1.4. Cycloadditions

2.1.4.1. [2+3] Dipolar Cycloaddition

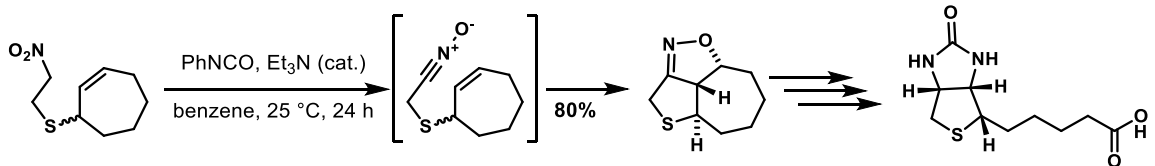
As already shown for the streptazolin synthesis by Park *et al.*[24] 1,3-dipolar cycloadditions are an efficient tool to build isoxazolidines. 1,3-dipolar cycloadditions describe the reaction of a 1,3-dipol and a dipolarophile (Scheme 11). Common dipolarophiles can be simple unactivated alkenes as well as electron deficient alkenes or alkynes. In contrast to Diels-Alder reactions, even unactivated alkenes are good dipolarophiles, which can be explained by the ability of 1,3-dipoles to react either *via* their HOMO or LUMO. Common 1,3-dipoles encountered in literature are for example nitrones and nitrile oxides. One of the most prominent 1,3-dipolar cycloaddition reaction is the Click reaction introduced by Sharpless in 2001 and honoured with the Nobel prize in 2022.[41,42] The copper-catalyzed Click reaction can be performed selectively and in a bio-orthogonal fashion under physiological conditions, which was one important reason to choose this reaction as a worthy "Nobel prize reaction".[43,44]



51 **52**

Scheme 11: Schematic representation of a 1,3-dipolar cycloaddition according to Huisgen.[45]

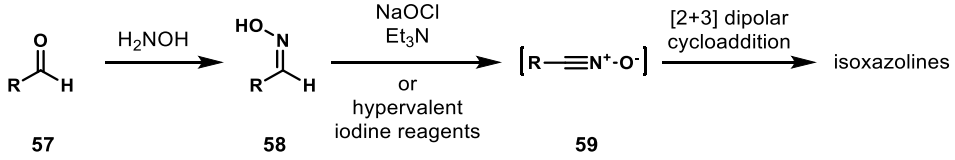
Another prominent example of a [2+3] dipolar cycloaddition is the synthesis of racemic biotin (*rac*-**56**) by Confalone *et al.* (Scheme 12).[46] The 1,3-dipolar cycloaddition plays a crucial role in the formation of one of the two central five-membered rings. The nitro compound (*rac*-**53**) was chosen as a suitable precursor to form the nitrile oxide (*rac*-**54**) by dehydration with phenyl isocyanate. *rac*-**54** directly undergoes an intramolecular [2+3] dipolar cycloaddition with the alkene and forms the desired tricyclic product *rac*-**55**. After further reactions including a central Beckmann rearrangement racemic biotin (*rac*-**56**) can be obtained.[46]



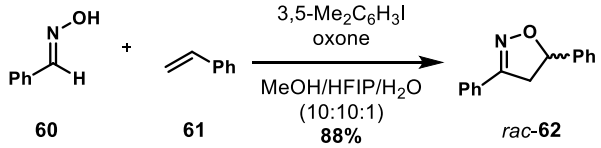
rac-**53** *rac*-**54** *rac*-**55** (+/-)-biotin (*rac*-**56**)

Scheme 12: Racemic stereoselective total synthesis of (+/-)-biotin (*rac*-**56**) by Confalone *et al*. including an intramolecular 1,3-dipolar cycloaddition of a nitrile oxide to an alkene.[46]

Nitrile oxides are encountered regularly in the context of 1,3-dipolar cycloaddition reactions as they can be prepared easily *via* the dehydration of nitro groups with phenyl isocyanate (as can be seen in the stereoselective total synthesis of biotin (*rac*-**56**) by Confalone *et al*.[46]) or with Boc_2O/DMAP[47]. A third possibility to generate nitrile oxides is the condensation of hydroxylamines with an aldehyde of type **57** to the corresponding aldoxime of type **58** followed by the oxidation to the desired nitrile oxide **59** (Scheme 13). Some of the more commonly used protocols are the oxidation with sodium hypochlorite and triethylamine[48] or with catalytic amounts of hypervalent iodine reagents in combination with stoichiometric oxidants, such as oxone (Scheme 14).[49] Besides the introduced examples, many more methods have been described in the literature.[50-52]



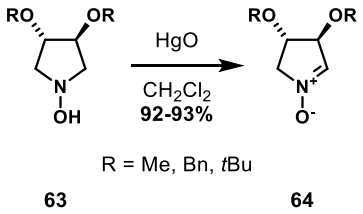
Scheme 13: *In situ* generation of nitrile oxides *via* oxime formation and subsequent oxidation by NaOCl or hypervalent iodine reagents.



Scheme 14: 1,3-dipolar cycloaddition of an *in situ* generated nitrile oxide from **60** with styrene (**61**) reported by Yoshimura *et al*.[49]

Besides nitrile oxides, nitrones can be directly employed in [2+3] dipolar cycloaddition reactions. In the literature several ways to generate *N*-alkyl nitrones are described, for instance by condensation of *N*-alkylhydroxylamines with aldehydes or ketones or by oxidation of *N,N*-dialkylhydroxylamines with oxygen, IBX or heavy metal containing oxidation agents, like mercuric oxide or lead oxide.[53] In the majority of examples the desired nitrones are *N*-alkylated nitrones such as the nitrones of type

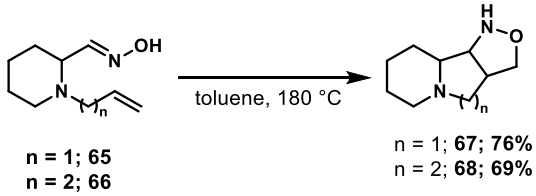
64, can be prepared reliably by the oxidation of the corresponding hydroxylamines of type **63** (Scheme 15).[54]



Scheme 15: Oxidative preparation of a cyclic *N*-alkyl nitrone with stoichiometric HgO reported by Cicchi *et al*..[54]

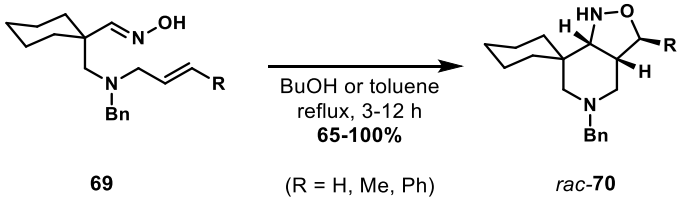
Simple unsubstituted nitrones are tautomeric structures of oximes and are mainly generated as reactive intermediates by heating of the parent oximes. For this reaction a thermal 1,2-hydrogen shift was proposed by Grigg *et al*.[55-57] In general, the generation of nitrones is not as reliable as the generation of nitrile oxides, hence the employment of such high temperatures may lead to the degradation of other functional groups present in the starting material. Nevertheless, a variety of mostly intramolecular transformations has been described in the literature.[58]

Hassner *et al*. reported an intramolecular 1,3-dipolar cycloaddition of an aldoxime and a terminal alkene by simply heating the compound in an apolar solvent at 180 °C (Scheme 16). This furnished the desired tricyclic isoxazolidine.[59]



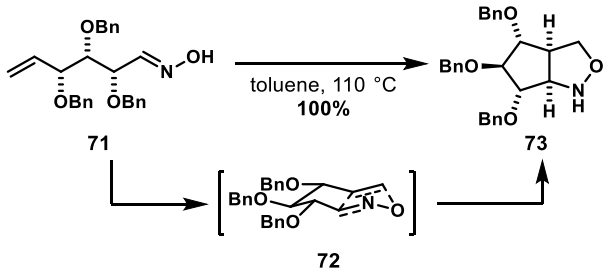
Scheme 16: Intramolecular 1,3 dipolar nitrone cycloaddition by Hassner *et al*..[59]

In other cases it was reported that the reaction does as well work in protic polar solvents such as BuOH with excellent yields (Scheme 17).[60]



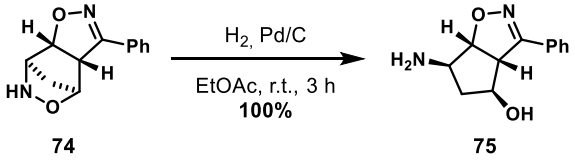
Scheme 17: Intramolecular 1,3-dipolar cycloaddition of **69** to *rac*-**70** by Noguchi *et al*..[60]

A diastereoselective version of this reaction under relatively mild conditions has been described by Shipman *et al*. (Scheme 18).[61] The oxime **71**, which was derived from α-D-glucopyranoside, underwent a smooth intramolecular 1,3-dipolar cycloaddition in a diastereoselective fashion. The three benzyloxy-substituents occupy the equatorial positions in the transition state and therefore render the reaction diastereoselective.[61]



Scheme 18: Diastereoselective 1,3-dipolar cycloaddition by Shipman *et al*..[61]

Common subsequent reactions of those isoxazolidines can be the oxidation to the corresponding isoxazoline followed by the N-O-bond cleavage or the direct reductive N-O-bond cleavage to the 1,3-amino alcohol. Memeo *et al*. were able to show that a selective hydrogenation of the isoxazolidine **74** is possible even in the presence of a second isooxazoline moiety (Scheme 19).[62]



Scheme 19: Reductive N-O-bond cleavage in the presence of an isoxazoline reported by Memeo *et al*..[62]

2.1.4.2. [4+2] Imino Diels-Alder Reaction

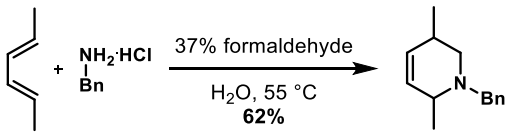
The Diels-Alder (DA) reaction is a useful reaction to build six-membered ring systems. The reaction was explored by Otto Diels and Kurt Alder who were awarded with the Noble Prize in 1950 for their development.[63-66] In many cases it is possible to achieve a good regiocontrol and up to four new stereocenters can be formed in a stereoselective fashion.

The imino DA reaction is a special case of the DA reaction using an imine or iminium dienophile to construct a tetrahydropyridine moiety, which has been proven to be a powerful tool in the synthesis of several natural compounds. In many cases simple unactivated imines do not react in imino DA reactions. Therefore, as in common all-

carbon DA reactions the use of electron deficient imine dienophiles is advantageous. This can be achieved by the introduction of electron withdrawing functionalities such as *N*- or *C*-acyl groups conjugated to the imine. Furthermore, Lewis or Brønsted acid catalysis is a common activation strategy.[67-69] Some Lewis acids, which have been used are for example $BF_3{\cdot}OEt_2$, $ZnCl_2$, $SnCl_2$, Et_2AlCl or lanthanide triflates.[70]

Imino DA reactions employing electron rich dienes, such as Danishefsky´s diene are well described in the literature and usually lead to a successful transformation. Nevertheless, it is far more challenging, in regards to regioselectivity as well as general reactivity, to perform this reaction with unactivated dienes.[70]

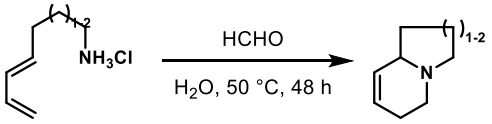
Brønsted acids have found wide application in the activation of imino dienophiles. Grieco and coworkers developed a general procedure to react simple unactivated dienes with *in situ* generated iminium dienophiles under aqueous conditions (Scheme 20). As amine sources several primary amine hydrochlorides have been applied and it was even possible to perform iminium DA reactions with ammonium hydrochloride in combination with formaldehyde and cyclopentadiene.[71-73]



76 **77** *rac*-**78**

Scheme 20: Brønsted acid catalysed iminium DA reaction according to Grieco *et al.*[71]

Besides these intermolecular iminium Diels-Alder reactions, Grieco *et al*. were able to develop as well intramolecular approaches. The treatment of substrates including a primary amine hydrochloride and a diene moiety with aqueous formaldehyde at elevated temperatures furnished the desired tetrahydropyridines in moderate to excellent yields. This way it was possible to react the imino Diels-Alder precursor of type **79** to the desired bicyclic tetrahydropyridines *rac*-**80** and *rac*-**81** (Scheme 21).[71]

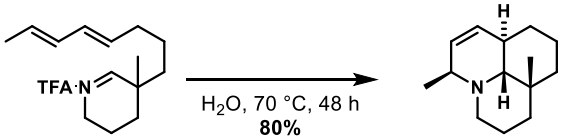


79

n = 1; *rac*-**80**; **95%**
n = 2; *rac*-**81**; **65%**

Scheme 21: Iminium dienophile generation followed by subsequent intramolecular iminium Diels-Alder reaction to form dehydro σ-coniciene *rac*-**80** and *rac*-**81** reported by Grieco *et al*.[71]

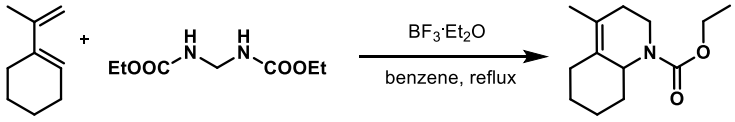
In another example it was necessary to activate the imine by the addition of TFA to generate the iminium dienophile (Scheme 22). This resulted in the smooth formation of the desired tricyclic amine *rac*-**83**.[74] One major disadvantage of the procedure developed by Grieco is the dependance on aqueous reaction conditions, which in parts cannot be used in combination with apolar substrates.



rac-**82** *rac*-**83**

Scheme 22: Intramolecular imino Diels-Alder reaction of the TFA iminium adduct *rac*-**82** to the corresponding tetrahydropyridine *rac*-**83** reported by Grieco et al.[74]

One of the early Lewis acid catalyzed imino DA reactions was performed by Merten *et al*.[75] They reacted the simple unactivated diene **84** with an *in situ* generated *N*-acyl imino dienophile (Scheme 23). The dienophile was generated by the treatment of diethyl methylene-bisethylcarbamate (**85**) with the strong Lewis acid $BF_3{\cdot}Et_2O$. This resulted in the desired *N*-substituted tetrahydropyridine *rac*-**86**.[75]

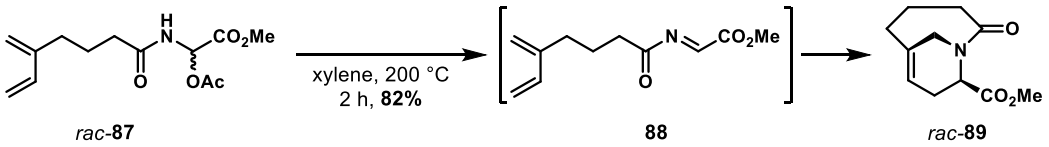


84 **85** *rac*-**86**

Scheme 23: Lewis acid catalyzed imino DA reaction using the unactivated diene **84** according to Merten *et al.*[75]

Besides these intermolecular *N*-acyl imino Diels-Alder reactions some intramolecular versions have been described in the literature as well. The intramolecular reaction shows a high diastereoselectivity in most cases, which are usually driven by a strong substrate control. *N*-acylimines are generally electron deficient, however, it is not possible to isolate them due to their high instability towards nucleophilic attacks. Therefore, they are generated *in situ*, where they can directly undergo an intramolecular imino Diels-Alder reaction. One interesting example was reported by Shea *et al*., where the stable *N*-acyl-acetoxy-hemiaminal *rac*-**87**, derived from the corresponding free amide and methyl glyoxylate, was synthesized. It was subsequently heated in xylenes at 200 °C to force the elimination of acetic acid and the formation of the corresponding *N*,*C*-diacylimine **88** (Scheme 24). The imine **88**

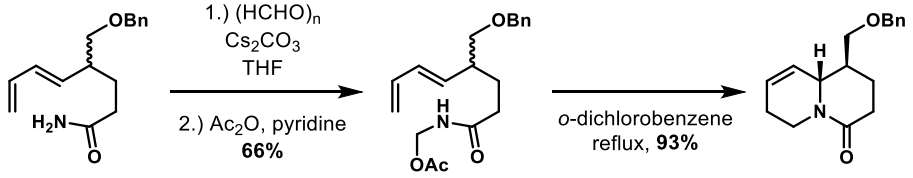
directly reacted in an intramolecular imino Diels-Alder reaction forming the desired tetrahydropyridine *rac*-**89**.[76]



rac-**87** **88** *rac*-**89**

Scheme 24: Intramolecular imino Diels-Alder reaction of the *N*-acylimine precursor *rac*-**87** to yield the strained bicyclic bridgehead amide *rac*-**89** reported by Shea *et al.*.[76]

Bremmer *et al.* were able to show that this type of intramolecular imino Diels-Alder reaction can be performed under milder conditions as well (Scheme 25). Therefore, the desired *N*-acyl methylol acetate *rac*-**91** was synthesized from the corresponding free amide *rac*-**90** by the addition to formaldehyde and subsequent acetate protection of the hemiaminal alcohol. The *N*-acyl methylol acetate *rac*-**91** was heated in *ortho*-dichlorobenzene to reflux to prepare the desired *N*-aclyimine *in situ*, which directly underwent an imino Diels-Alder reaction to form the *epi*-lupinine precursor *rac*-**92** in a yield of 93%.[77] The natural products σ-coniceine, tylophorine, elaeokanine A and elaeokanine B were synthesized employing this procedure.[78]



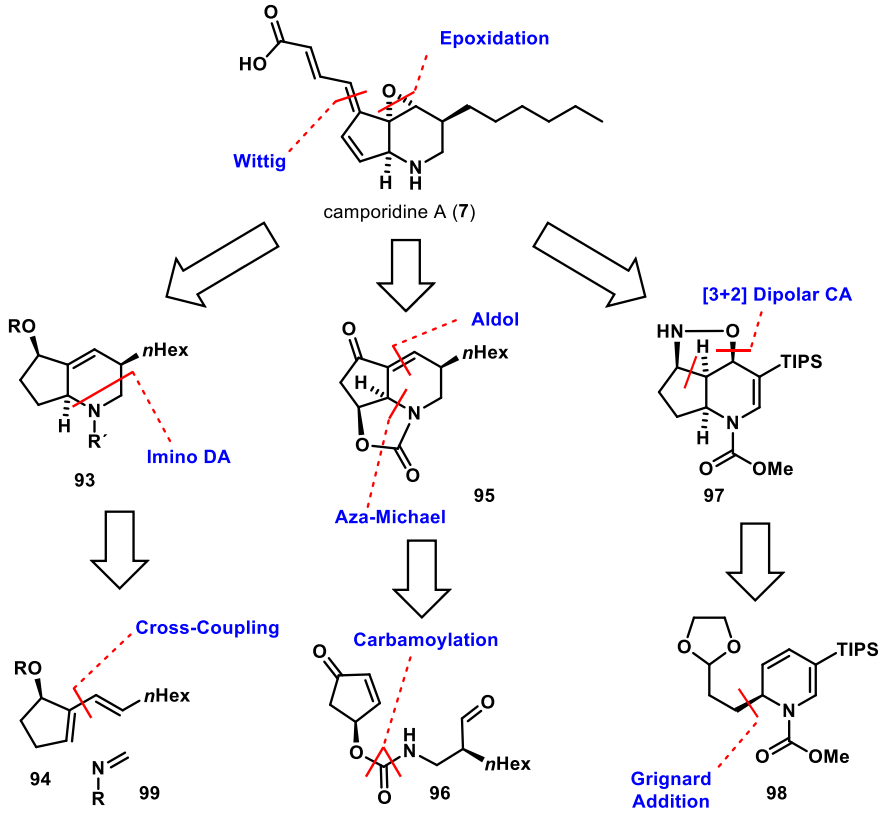
rac-**90** *rac*-**91** *rac*-**92**

Scheme 25: Intramolecular imino Diels-Alder reaction of an *N*-acyl formimine with an unactivated diene as part of the total synthesis of *epi*-lupinine reported by Bremmer *et al.*[77]

Finally, it must be noted that the iminium DA reaction is a powerful tool to construct tetrahydropyridine substructures, especially when it comes to intramolecular reactions.

2.2. Motivation

Camporidine A (**7**) is a structurally interesting natural product with antimetastatic and anti-inflammatory activities. Therefore, camporidine A (**7**) is an attractive synthetic target on our way to make a contribution to the field of new cancer treatments. Especially, finding a synthetic access to such compounds may help to identify important biological activities. One main research topic of the working group around Prof. Schmalz lies in the use of polycyclic amino acid derivatives to treat a variety of different diseases. Camporidine A (**7**) with the carboxylic acid in combination with the allylic secondary amine resembles an elongated amino acid analogue. It thus represents together with the other functional groups condensed on a small space an interesting synthetic challenge.



Scheme 26: Strategic key disconnections to construct camporidine A (**7**).

In our retrosynthetic considerations three distinct approaches towards the construction of the key 2-*aza* bicyclo [4.3.0] nonane core structure should be examined (Scheme 26). In a first approach, the tetrahydropyridine substructure should be synthesized by an imino DA reaction, inducing the stereoselectivity of the two newly formed stereocenters through the dienylic substituent, rendering the

reaction diastereoselective in a substrate-controlled fashion. Ideally, the imino DA reaction would be performed in an intramolecular fashion to ensure the desired regio- and diastereoselectivity. At the same time potential undesired side reactions of the imino/iminium dienophile should be circumvented.

A second approach envisions the construction of the central tetrahydropyridine substructure **95** by an *aza*-Michael/Aldol sequence. This reaction sequence is as well expected to deliver the correct diastereomer in a substrate-controlled fashion and the aldol reaction of a similar substrate has already been used in the synthesis of streptazolin reported by Miller *et al* (Scheme 8).[38] The carbamate precursor **96** can be synthesized elegantly in a modular fashion from accessible precursors.

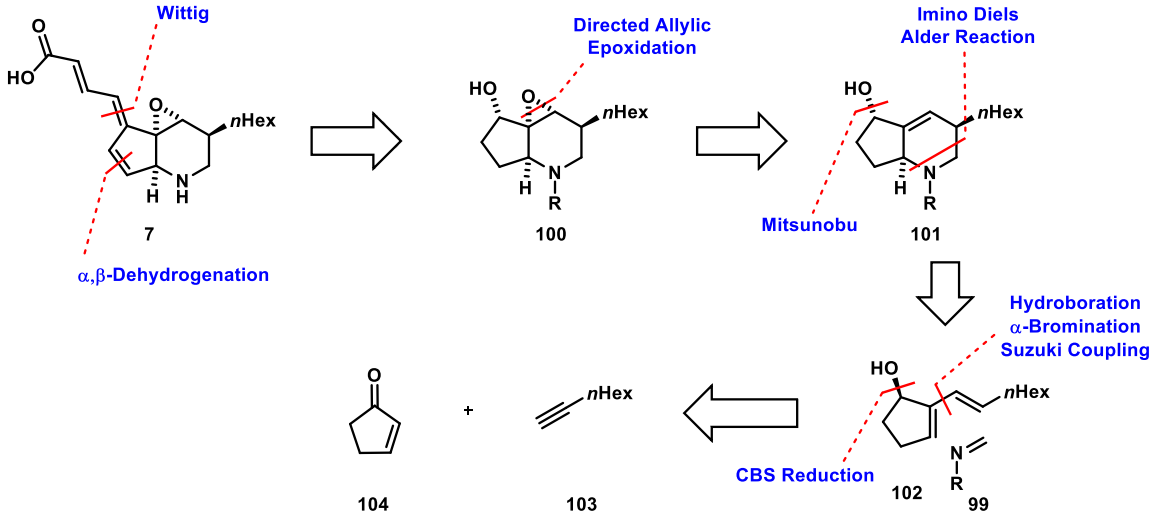
In contrast to the first two approaches the third idea suggests the formation of the 2-aza [4.3.0] bicyclo nonane core structure by the construction of the five-membered ring *via* an intramolecular 1,3-dipolar cycloaddition. The central six-membered ring should be introduced by the starting material 3-bromopyridine. The key intramolecular 1,3-dipolar CA would be related to the one applied in the total synthesis of streptazolin (**18**) reported by Park *et al.* (Scheme 3).[24] This strategy would open an extremely fast access to the central bicyclic core structure. Each of the three retrosynthetic approaches will be discussed in the following sections in detail.

2.3. Results and Discussion

The presentation of the results regarding the total synthesis of camporidine A (**7**) is divided into five main parts, starting with the inter- and intramolecular imino Diels-Alder approaches. This is followed by the aza-Michael/aldol approach and lastly by the 1,3 dipolar cycloaddition approach.

2.3.1. Intermolecular Imino Diels-Alder Approach

2.3.1.1. Conception



Scheme 27: Retrosynthetic analysis of camporidine A (**7**) employing a central intermolecular imino Diels-Alder reaction, a late-stage introduction of the conjugated side chain by a HWE- or Wittig-type olefination and the construction of the dienol (**102**) from cyclopentenone (**104**) and octyne (**103**) *via* a central Suzuki cross coupling.

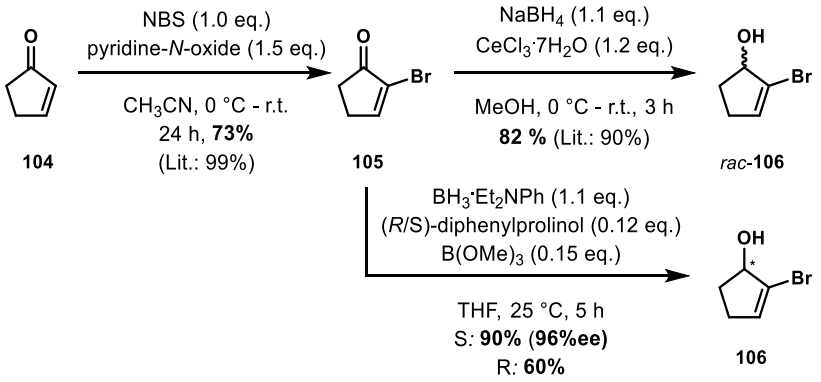
All approaches towards the synthesis of camporidine A (**7**) include a projected late-stage introduction of the conjugated side chain *via* a Wittig- or HWE-type olefination of the corresponding enone (Scheme 27). The epoxide should be introduced diastereoselectively from the corresponding allylic alcohol **101** exploiting the Henbest effect, followed by oxidation of the alcohol to the corresponding ketone. The introduction of the enone double bond should be achieved by an α-bromination/elimination sequence or a hypervalent iodine-mediated dehydrogenation. As the key step to establish the tetrahydropyridine core structure, including the two stereocenters, an intermolecular imino Diels-Alder reaction has been envisioned. This reaction should be guided from the upper face of the molecule by the dienol **102** through attractive interactions with the iminium dienophile. Ideally,

the usage of a Lewis acid would accelerate the reaction by coordination of the dienol-OH group and activation of the imino dienophile. The synthesis of the dienol **102** itself should be performed by α-bromination of cyclopentenone (**104**), hydrometallation of octyne (**103**) to selectively obtain the *E*-1-octenyl metal intermediate, which coupled with a suitable cyclopentene derivative by a cross coupling approach like a Suzuki reaction.

2.3.1.2. Diene Synthesis (Intermolecular Approach)

First the α-bromination of cyclopentenone (**104**) was tackled by employing a procedure reported by Nishida *et al*.[79] Therefore, a combination of pyridine-*N*-oxide as the nucleophilic catalyst and NBS was employed to obtain the desired α-bromocyclopentenone **105** in a yield of 73% (Scheme 28). This reaction is mechanistically closely related to the Baylis-Hillman reaction, hence the pyridine-*N*-oxide attacks the enone in the β-position at first, followed by the nucleophilic attack of the enolate at the electrophilic NBS-bromide. Subsequent elimination of the pyridine-*N*-oxide leads to the formation of the desired α-vinylbromide **105**.[80] In contrast to the commonly employed reaction conditions, such as the bromination of enone double bonds with bromine followed by elimination of the β-bromine[81], the reaction conditions reported by Nishida *et al*. avoid the use of harmful bromine by implementing NBS.[79]

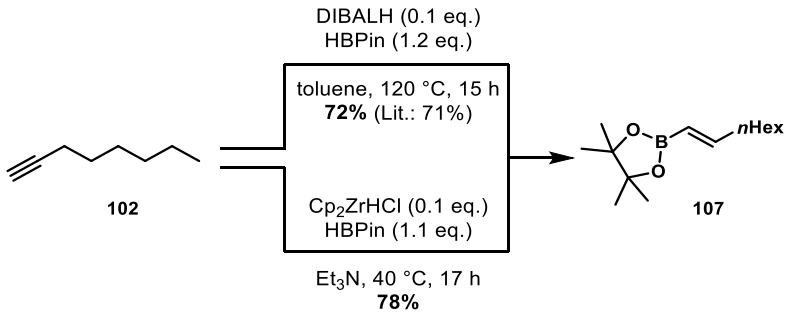
Next, the reduction of the α-bromoenone **105** was tackled by performing a Luche reduction, which smoothly gave rise to the slightly volatile racemic allylic alcohol **106** in 82% yield.[82] To render this reduction enantioselective a CBS reduction was envisioned and a procedure reported by Ikoma *et al*. was transferred to our system.[83] These reaction conditions furnished the desired *R*-enantiomer **106** in 60% yield, but it was not possible to determine the enantiomeric excess reliably, because of the overlap of the enantiomer signals on the chiral GC-MS. Therefore, the undesired *S*-enantiomer *ent*-**106** was synthesized as well by the same method using the corresponding *R*-diphenyl prolinol catalyst. By carefully controlling the reaction conditions the yield was improved to 90% and the desired product *S*-**106** was obtained in 96%*ee*.



Scheme 28: α-Bromination of cyclopentenone (**104**), subsequent Luche reduction and CBS reduction.

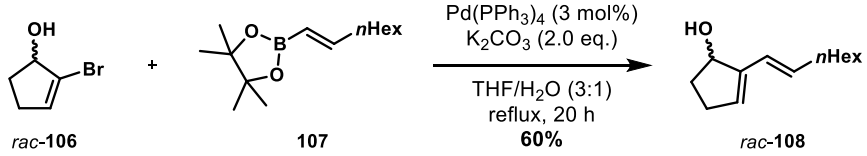
For the synthesis of the second building block **107**, two distinct approaches were evaluated (Scheme 29). The method of choice to install the *E*-alkene moiety as a terminal vinylboronate is a hydroboration reaction. Hence the direct hydroboration of octyne (**103**) with pinacol borane suffers a low reactivity and very long reaction times, a procedure reported by Bismuto *et al.* was employed, using DIBALH as a hydrometallation catalyst.[84] DIBALH readily underwent regioselective hydroalumination with octyne, followed by subsequent transmetallation with pinacolborane furnishing the desired *E*-vinylboronate **107** in a yield of 72% and restoring DIBALH as the active catalyst. We explored an alternative approach towards the synthesis of the desired vinyl pinacolboronate **107** as well, because the DIBALH catalyzed reaction suffered drawbacks. The starting materials for example were hard to monitor by TLC or GC-MS, making it hard to follow the reaction progress and to decide whether full conversion was reached or if the catalyst was still active. Therefore, DIBALH was exchanged by Schwartz´s reagent which slightly increased the yield to 78%. Under these reaction conditions the temperature was lowered to 40 °C instead of 120 °C. Nevertheless, this small increase in yield was not satisfying enough to justify the use of the more expensive Schwartz´s reagent instead of DIBALH. In the end, the reaction control by GC-MS was optimized by starting the

detection shortly after the fading of the toluene solvent signal to judge whether octyne (**102**) is still present.



Scheme 29: Hydroboration of octyne (**102**) employing DIBALH or Schwartz´s reagent as catalysts.[84]

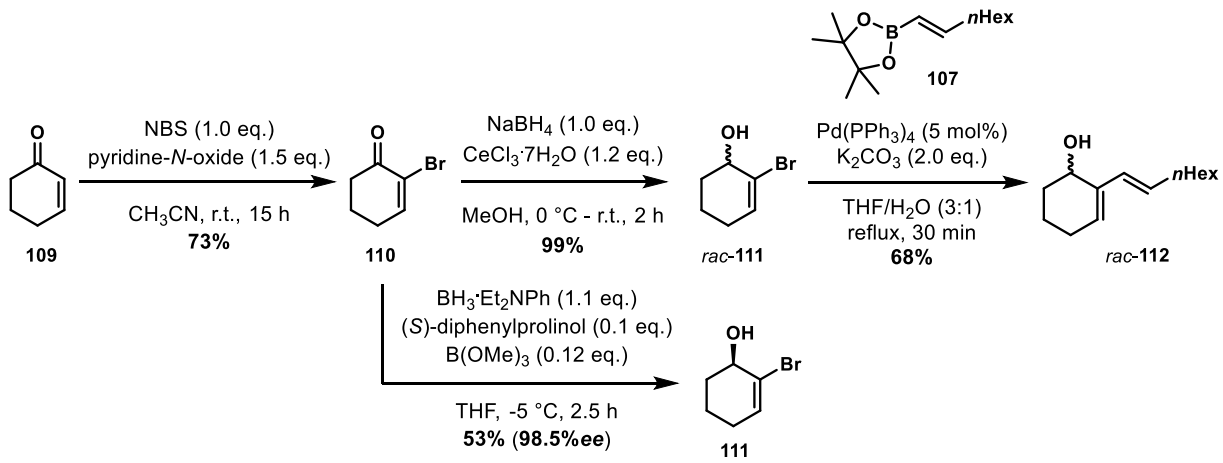
With vinyl bromide *rac*-**106** and pinacolboronate **107** in hand, the following cross coupling was targeted. Under standard Suzuki conditions with $Pd(PPh_3)_4$ as Pd^0-source and K_2CO_3 as base, the formation of the desired diene **108** was achieved in a yield of 60% (Scheme 30). A few other Pd-sources, bases and solvents were tested, but did not lead to a superior reaction outcome.



Scheme 30: Suzuki cross coupling of vinylbromide *rac*-**106** with vinylboronate **70**.

For the further development of the imino Diels-Alder reaction a test system derived from cyclohexenone **109** was chosen. Cyclopentenone (**104**) is about seven times more expensive than to cyclohexenone (**109**), based on prices from Sigma Aldrich. It was possible to transfer the reaction conditions developed for the cyclopentenone-derived system to the cyclohexenone-derived test system (Scheme 30).

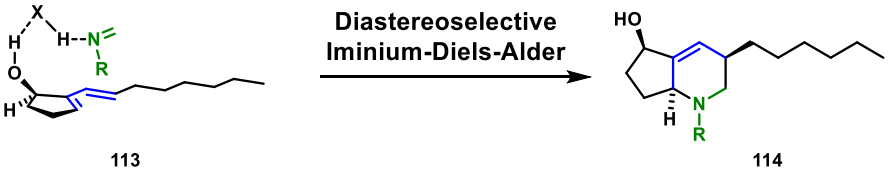
First, the α-bromination was performed in a similar yield of 73% employing the procedure described by Nishida *et al*.[79] The Luche reduction furnished the desired allylic alcohol *rac*-**111** in almost quantitative yield and after CBS reduction the allylic alcohol **111** was isolated in a yield of 53% with an 98.5%*ee*, which is even higher than for the cyclopentenone-derived system (Scheme 28). Finally, the Suzuki cross coupling was performed under the same conditions furnishing the desired dienol **112** in 68% yield.



Scheme 31: α-Bromination, CBS reduction, Luche reduction and Suzuki cross coupling according to the procedures established for the cyclopentenone-derived system.

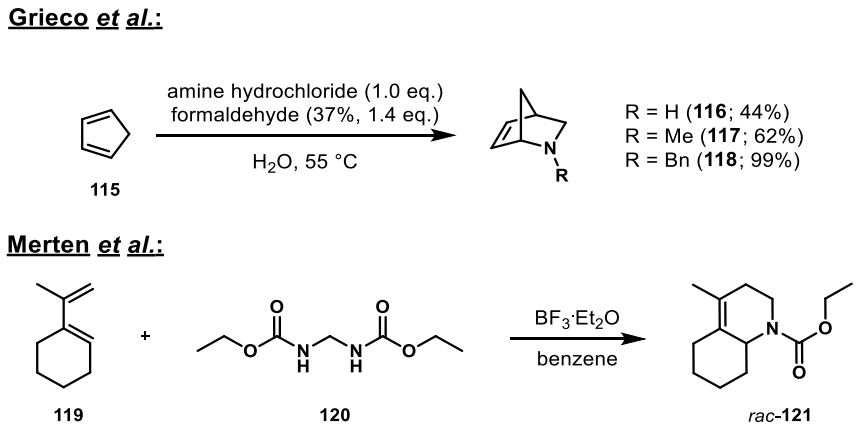
2.3.1.3. Attempted Intermolecular Imino Diels-Alder Reaction

With the diene building block in hand the investigation of the intermolecular imino Diels-Alder reaction was started. As some examples for similar intermolecular imino DA reactions employing unactivated dienes in combination with iminium dienophiles have already been reported by Grieco *et al.*, Merten *et al.*, Bailey *et al.* and others, we decided to transfer these procedures to our diene system **113**.[71-75,85-88] Attractive interactions like hydrogen bonding should guide the imino dienophile to the desired face of the diene and control the regiochemistry, which is not clearly determined by the electronic properties of the substrate (Scheme 32).



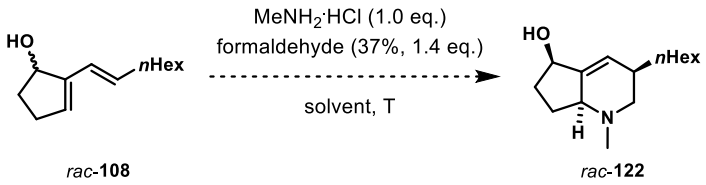
Scheme 32: Conception of an ideal substrate controlled imino Diels-Alder reaction.

In the literature two main methods to prepare the iminium dienophile are described (Scheme 33). One is the formation of a formiminium dienophile from an amine hydrochloride and formaldehyde. The other relies on the formation of the imino dienophile from methylene bisurethane (**85**) upon activation with $BF_3{\cdot}OEt_2$.[71,75] Both procedures were successfully used in the synthesis of bridged bicyclic tetrahydropyridine derivatives.



Scheme 33: Iminium Diels-Alder procedures by Grieco *et al*.[71] and by Merten *et al*.[75]

First the reaction conditions described by Grieco *et al.* were tested with the dienol *rac*-**108**. In water at r.t. no conversion was observed and upon heating to 70 °C only decomposition was detected (Table 1, entry 1). One major problem in performing the reaction was the bad solubility of the diene *rac*-**108** in THF/DMF-water mixtures, especially on a small scale. Employing a 1:1 THF/H_2O mixture led to no conversion of the dienol *rac*-**108** at r.t., but to decomposition at 80 °C (Table 1, entry 2). By slowly increasing the temperature from r.t. it was possible to identify 50 °C as the temperature, when the reaction slowly starts. Although the reaction was well controlled at 50 °C, again only the formation of a complex product mixture was observed. The same counts for a 1:1 DMF/H_2O solvent mixture at r.t. where as well only decomposition of the dienol *rac*-**108** was observed (Table 1, entry 4).

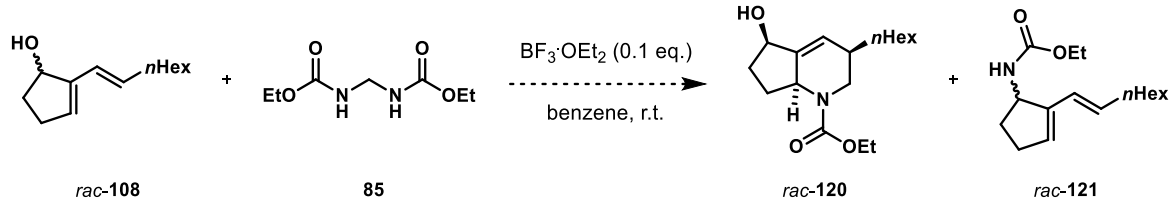


Scheme 34: General reaction conditions for the intermolecular iminium Diels-Alder reaction according to a procedure by Grieco *et al*.[71]

Table 1: Results from the first iminium Diels-Alder test reactions of dienol *rac*-**108** with *in-situ* generated methyl formimine. [a]Determination by TLC and GC-MS.

entry	solvent	T [°C]	T [h]	result[a]
1	H_2O	r.t.	1.25	no conv.
		70 °C	25	decomp.
2	THF/H_2O (1:1)	r.t.	20	no conv.
		80 °C	9	decomp.
3	THF/H_2O (1:1)	50 °C	20	decomp.
4	DMF/H_2O (1:1)	r.t.	20	decomp.

Since no sign of formation of the desired iminium Diels-Alder product *rac*-**119** was observed, an alternative procedure reported by Merten *et al*. was followed.[75] Herein, a *N*-acylamino dienophile should be generated *via* the addition of $BF_3{\cdot}OEt_2$ to the reaction mixture containing methylene bisurethane (**85**). In the first attempt the standard reaction conditions described by Merten *et al*. were used, but only the decomposition of the dienol *rac*-**108** was observed (Table 2, entry 1). Next, the concentration was lowered to 0.2 M. In this case it was possible to isolate the mayor product, which turned out to be *rac*-**121,** in a yield of 20%, while at the same time no formation of the desired iminium Diels-Alder product was observed (Table 2, entry 2). The formation of *rac*-**121** indicates a mayor instability of the dienol *rac*-**108**, forming an allylic cation due to the elimination of the hydroxy moiety upon contact with the strong Lewis acid $BF_3{\cdot}OEt_2$. This stabilized cation may then be attacked by nucleophiles to form substitution products, including *rac*-**121**. To confirm the instability of *rac*-**108** in the presence of $BF_3{\cdot}OEt_2$ another test reaction without the addition of methylene bisurethane **85** was performed, and indeed, a complete decomposition of the dienol *rac*-**108** was observed (Table 2, entry 3). Due to the instability of the dienol *rac*-**108** towards the tested reaction conditions, the dienol *rac*-**108** should be protected prior to following imino Diels-Alder test reactions.



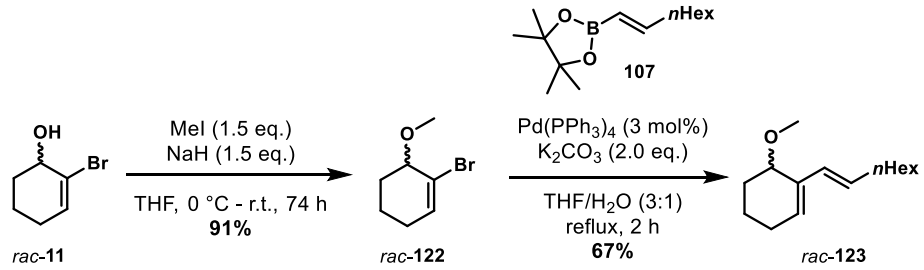
Scheme 35: General reaction conditions for the intermolecular iminium Diels-Alder reaction according to a procedure by Merten *et al*.[75]

Table 2: Results from the iminium Diels-Alder test reactions.

entry	eq. aminal	conc. [M]	t [h]	result
1	1.05	1.0	48	decomp.
2	1.05	0.2	68	20% *rac*-**121**
3	0	0.2	68	decomp.

2.3.1.4. Derivatization of the Dienol Systems

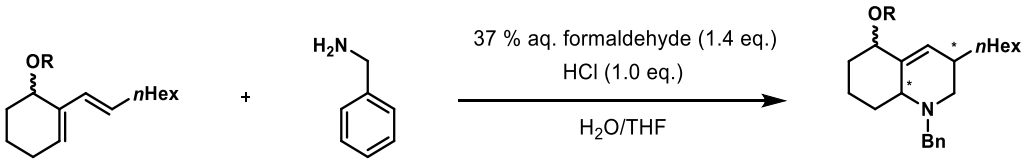
As already mentioned earlier, the cyclohexanol derivative is the cheaper starting material and was therefore chosen for further derivatization and imino Diels-Alder test reactions. The allylic alcohol *rac*-**111** was methylated using NaH and MeI in a yield of 91% (Scheme 36). The following Suzuki cross coupling reaction furnished the corresponding diene *rac*-**123** in virtually the same yield of 67%, which was previously achieved for the free alcohol *rac*-**112**.



Scheme 36: Methylation of the allylic alcohol *rac*-**111** and subsequent Suzuki cross coupling with vinyl pinacolboronate **107** to diene *rac*-**123**.

Due to the better handling of the reaction and the higher yields achieved in the literature, the following iminium Diels-Alder reactions were performed with benzylamine (**124**) instead of methylamine. First, a short screening using the free alcohol *rac*-**112** was performed by treatment with benzylamine hydrochloride and formaldehyde in a water-THF mixture of varying compositions (Table 3, entries 1-4). Using only water as solvent led to solubility issues and it was not possible to observe any conversion of the diene *rac*-**112** (Table 3, entry 1). To increase the solubility of

rac-**112** a 1:1 THF/H_2O solvent mixture was selected (Table 3, entry 2). In this case no conversion was observed at r.t. after 22 h. Upon heating of the reaction mixture to 50 °C a slow conversion was detected, leading to a complex product mixture. Heating the reaction mixture to 70 °C just increases the decomposition rate. Further modification of the solvent mixture to a 1:4 H_2O/THF ratio (Table 3, entry 3) slowed down the reaction rate drastically. After 6 days at 70 °C no conversion of the diene was observed. Further heating of the reaction mixture under refluxing conditions only led to the unselective decomposition of the diene *rac*-**112**. When using only THF as solvent, again only an unselective decomposition of the diene *rac*-**112** was observed (Table 3, entry 4). At this point the instability of such dienol systems, as already observed earlier, could be confirmed. Therefore, the methylated dienol *rac*-**123** was evaluated next. Due to the even worse solubility of *rac*-**123** in water, a 1:1 H_2O/THF mixture was directly employed (Table 3, entry 5). But neither at r.t., 50 °C nor 70 °C any conversion of the diene *rac*-**123** was observed. Similar conditions for the free alcohol *rac*-**112** led to decomposition. Reacting the methylether *rac*-**123** solely in THF at 60 °C again did not lead to any conversion (Table 3, entry 6).



R = H: *rac*-**112**
R = Me: *rac*-**123**

124

R = H: *rac*-**125**
R = Me: *rac*-**126**

Scheme 37: General scheme for the attempted iminium Diels-Alder test reactions inspired by the reaction conditions reported by Grieco *et al*.[71]

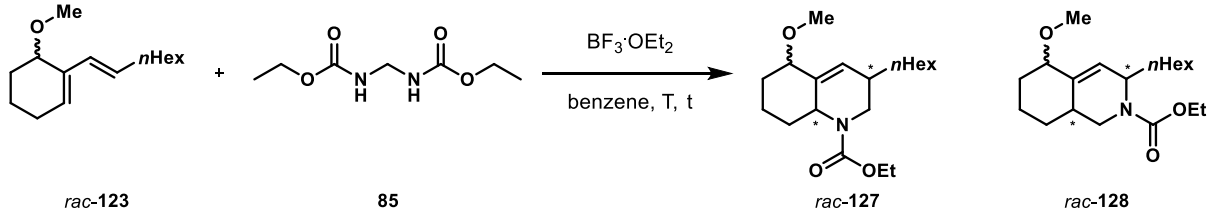
Table 3: Attempted iminium Diels-Alder test reactions according to the general procedure reported by Grieco *et al*.[71]

entry	R	H_2O/THF	T [°C]	t [h]	results[b]
1	H	1:0	r.t.	8 d	no conv.
2	H	1:1	r.t.	22	no conv.
			50	7	slow conv.
			70	17	decomp.
3	H	1:4	70	6 d	no conv.
			reflux	6 d	decomp.
4	H	0:1	60	6 d	decomp.

5	Me	1:1	r.t. 50 70	22 7 17	no conv.
6	Me	0:1	60	6 d	no conv.

Due to the low reactivity of the methylether *rac*-**123** in the previous screening the reaction conditions described by Merten *et al*. employing the strong Lewis acid $BF_3{\cdot}OEt_2$ accelerating the generation of the desired electron poor *N*-acyl imine were evaluated next. Upon addition of methylene bisurethane (**85**) and catalytic amounts of $BF_3{\cdot}OEt_2$, a mixture of inseparable regio- and diastereomers of type *rac*-**127** were isolated in a combined yield of 21% (Table 4, entry 1). Unfortunately, only a poor selectivity was observed. Performing the reaction at reflux did improve the yield slightly, but the selectivity could not be improved (Table 4, entry 2).

In conclusion, it was possible to improve the stability of the diene towards strong Lewis acids such as $BF_3{\cdot}OEt_2$ and to induce an imino DA reaction by methylation of dienol *rac*-**112**. Unfortunately, no significant substrate control was observed, when it comes to the regio- and diastereoselectivity of the imino DA reaction.



rac-**123** **85** *rac*-**127** *rac*-**128**

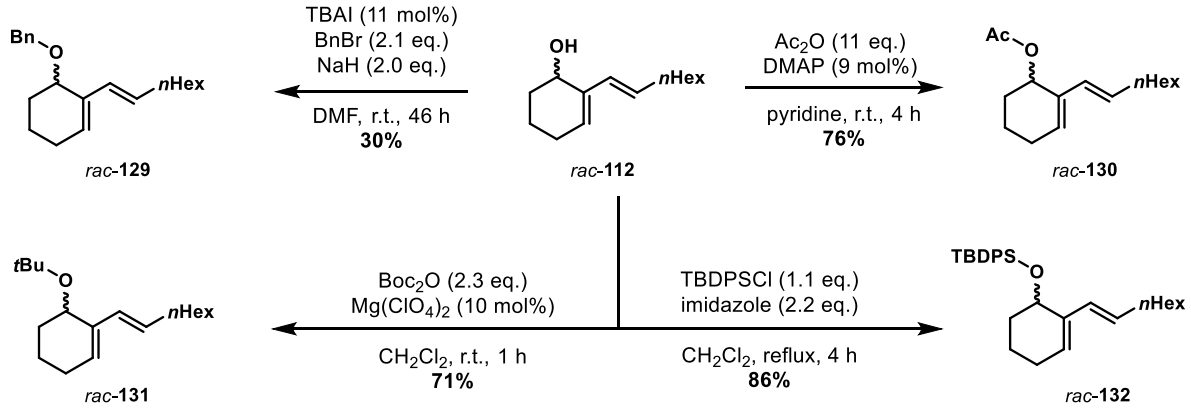
Scheme 38: Intermolecular imino Diels-Alder reaction screening for diene *rac*-**123**.

Table 4: Results of the intermolecular imino Diels-Alder reaction for the methylated test system *rac*-**123**.

entry	**eq. $BF_3{\cdot}OEt_2$**	**T [°C]**	**t [h]**	**result**
1	0.10	r.t. 70	22 24	Slow conversion **21%** of *rac*-**127**
2	0.15	reflux	3	**28%** of *rac*-**127**

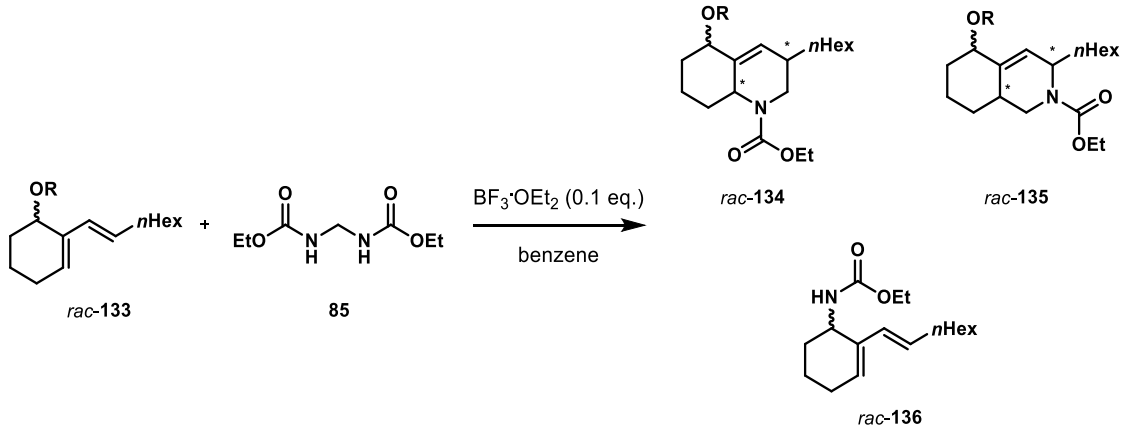
Therefore, different protecting groups were introduced, such as a *tert*-butyl ether, benzyl ether and TBDPS ether. With the greater steric demand of these protecting groups, shielding of one face of the diene system was expected to lead to a higher degree of diastereoselectivity. Additionally, an acetate was introduced, hoping the

Lewis basicity of the carbonyl group could exhibit an attractive directing effect by either an interaction with a Lewis acid or through the development of hydrogen bonds towards iminium dienophiles. The desired modifications were introduced by the protection of the free alcohol moiety. All protecting steps were performed under standard reaction conditions and furnished the desired protected dienylic alcohols in moderate to good yields.[89]



Scheme 39: Derivatization of *rac*-**112** protection of the free alcohol moiety.

First, the benzyl, TBDPS and acetate protected dienols of type *rac*-**133** were reacted under the *aza*-DA conditions, which have already led to promising results for the methylated diene system *rac*-**123** (Table 5, entries 1-3). Unfortunately, in all three cases mainly decomposition towards carbamate *rac*-136 was observed. Employing $BF_3{\cdot}OEt_2$ as a strong Lewis acid seems to lead to an elimination of the protected alcohol moieties by forming a stabilized allylic cation. This could have been attacked by the free ethyl carbamate, which should be formed in stoichiometric amounts from methylene bisurethane **85** during the imine formation. Due to this observed decomposition the reaction was repeated with all four protected dienol substrates of type *rac*-**133** at a lowered temperature of 30 °C (Table 5, entries 4-7). This time the acetate and *t*Bu protected derivatives did again decompose to the allylic carbamate *rac*-136 whereas the benzyl and TBDPS protected derivatives stayed intact, but no conversion was observed. By gently warming the benzyl and TBDPS protected derivatives to 50 °C again only decomposition to the allylic ethylcarbamate *rac*-136 was observed.



Scheme 40: Imino Diels-Alder reaction screening of protected dienols of type *rac*-**133** employing the reaction conditions described by Merten *et al*.[75]

Table 5: Reaction conditions and results for the imino Diels-Alder reaction screening described in Scheme 40.

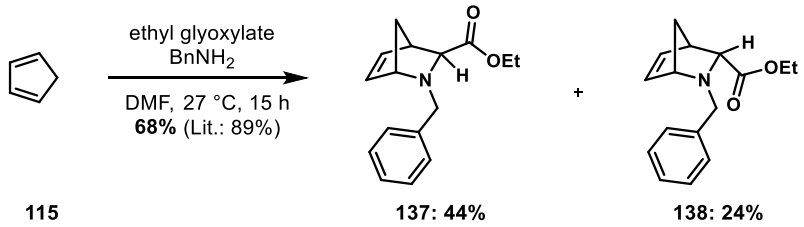
entry	R	T [°C]	t [h]	results[a,b]
1	Bn	60	30	major formation of *rac*-**136**
2	TBDPS	60	30	major formation of *rac*-**136**
3	Ac	60	30	major formation of *rac*-**136**
4	Ac	30	2.5	major formation of *rac*-**136**
5	^{t}Bu	30	6.5	major formation of *rac*-**136**
6	Bn	30	23	no conv.
		50	28	major formation of *rac*-**136**
7	TBDPS	30	23	no conv.
		50	28	major formation of *rac*-**136**

[a]All reactions were performed on a 0.09 mmol scale. [b] Combined results from TLC and GC-MS reaction controls on small scale reactions.

Due to the negative results obtained in the attempted imino DA reaction according to the procedures described by Grieco *et al*. and Merten *et al*., we decided to vary the dienophile further. The imino dienophile generated from benzylamine and formaldehyde is a relatively unreactive dienophile because it lacks electron withdrawing substituents. By the addition of hydrochloric acid as a Brønsted acid the corresponding iminium dienophile should be formed. But again, either no conversion or decomposition was observed in such reactions. The same problem arose for the methylene bisurethane-derived *N*-acylimine activated by $BF_3{\cdot}OEt_2$. Although the free allylic alcohol moiety was protected, mainly the substitution of these allylic moieties

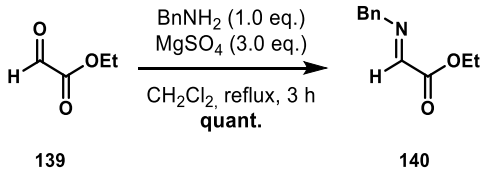
was observed. Especially *C*-unsubstituted formimin derivatives, which were employed until now, are relatively susceptible towards side reactions such as nucleophilic attacks on the carbon center.

One attractive alternative would be the generation of the corresponding imine from ethyl glyoxylate and a suitable primary amine. Bailey *et al*. could show, that these imino dienophiles, formed under very mild conditions, readily react in imino DA reactions (Scheme 41).[87] Ethyl glyoxylate has a strong tendency to form imines, aminals, geminal diols etc. Therefore, ethyl glyoxylate must be freshly distilled in the presence of dehydrating agents such as phosphorous pentoxide.[90]



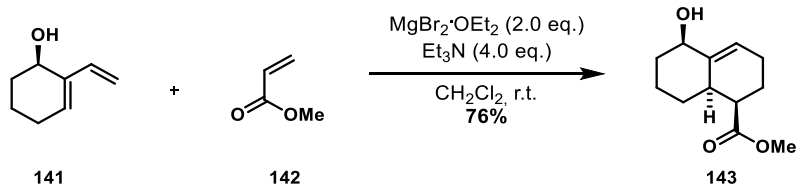
Scheme 41: Iminium Diels-Alder test reaction with cyclopentadiene as diene source according to Bailey *et al*.[87]

The desired ethyl glyoxylate-derived *C*-acylimines were successfully prepared under dehydrative conditions (Scheme 42). The addition of $MgSO_4$ or working under Dean-Stark conditions were equally suitable.



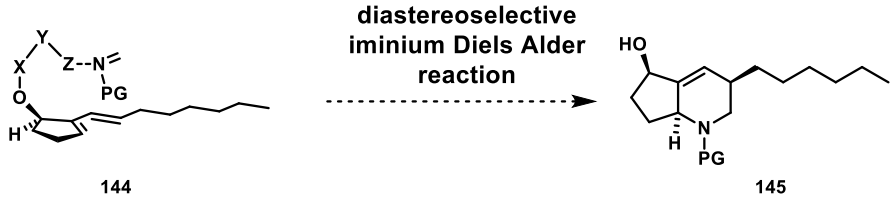
Scheme 42: Preparation of *N*-benzyl glyoxylimin **140**.

Another interesting example from literature emphasizing the possibility to exploit allylic alcohol moieties as directing groups was reported by Barriault *et al*. (Scheme 43).[91] They were able to perform an intermolecular all carbon Diels-Alder reaction on the very similar diene system **141** in combination with methyl acrylate **142**. Interestingly, by using stoichiometric amounts of $MgBr_2{\cdot}OEt_2$, they were able to activate the dienophile and render the reaction diastereoselective.[91]



Scheme 43: Highly diastereoselective substrate controlled all carbon Diels-Alder reaction guided by a Mg based coordination reported by Barriault *et al*.[91]

Inspired by this dienylic alcohol guided all carbon Diels-Alder reaction, we derived a general scheme for the size of a suitable linker guiding the intermolecular imino Diels-Alder reaction (Scheme 44). In our case the direct coordination to an *N*-acyl group was not desired. Instead, the coordination should directly be employed to the imino nitrogen itself. In such a scenario a linker containing three atoms would be needed and different possibilities were evaluated.

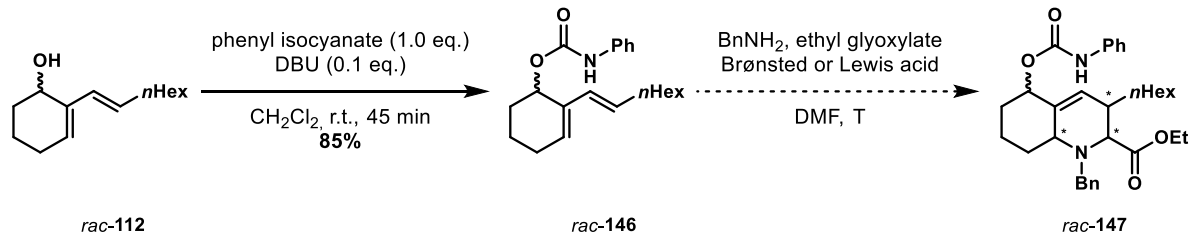


Scheme 44: Conceptional approach of a guided imino Diels-Alder reaction inspired by Barriault *et al*.[91]

Phenyl carbamate *rac*-**146** was identified as promising precursor with a linker fitting in the general scheme **144**. It is easily prepared from phenyl isocyanate in 85% yield and bears Lewis basic sites on the carbamate nitrogen and on the carbonyl hydrogen bond acceptors and donors as well. This way the phenyl carbamate was envisioned to coordinate with iminium dienophiles by the formation of a hydrogen bond or in combination with a Lewis acid.

First, the diene *rac*-**146** was reacted under Brønsted acidic conditions with the imino dienophile derived from ethyl glyoxylate and benzylamine. Upon addition of TFA at 80 °C no conversion was observed (Table 6, entry 1). The activation of the imino dienophile with hydrochloric acid was performed at r.t. and at 80 °C (Table 6, entries 2 and 3). At r.t. no conversion was observed, but upon warming to 80 °C an unselective decomposition occurred. As an alternative, the imine activation with Lewis acids was evaluated next. The use of $ZnCl_2$ as a mild Lewis acid did not lead to any conversion (Table 6, entry 4). Using $BF_3{\cdot}OEt_2$ at r.t. again resulted in no conversion, and interestingly, increasing the temperature to 80 °C after a reaction

time of 24 h at r.t. did not lead to a detectable conversion. When the reaction was performed directly at 80 °C decomposition of the carbamate to the allylic alcohol *rac*-**112** was observed. These results indicate on the one hand, that the imino dienophile decomposes over time in the presence of $BF_3{\cdot}OEt_2$. On the other hand, it implies that the carbamate is not stable under strongly Lewis acidic conditions at higher temperatures, which is in accordance with the results from previous screening approaches (see chapter 2.3.1).



rac-**112** *rac*-**146** *rac*-**147**

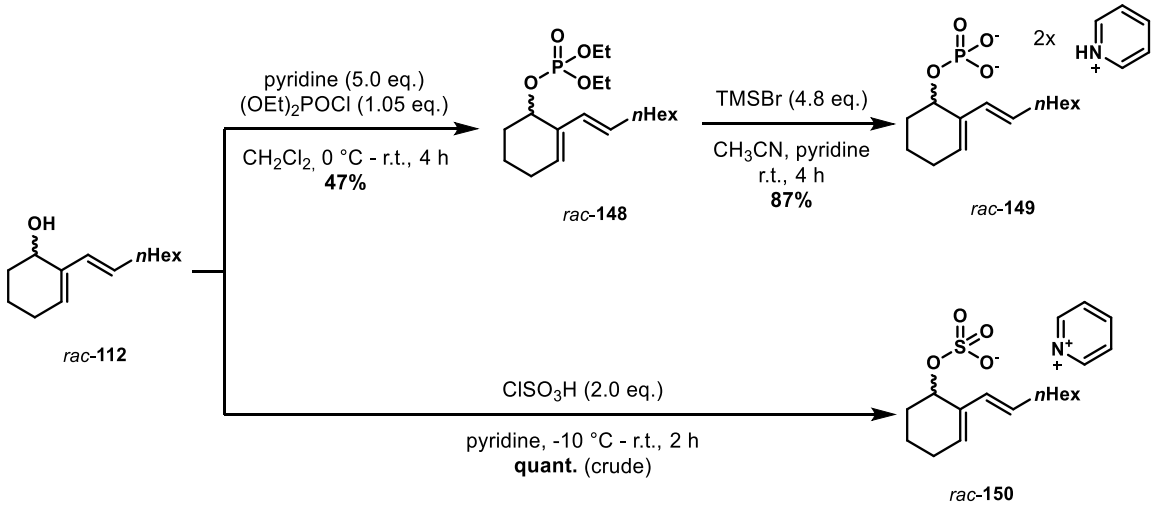
Scheme 45: Phenylcarbamate formation followed by an attempted iminium Diels-Alder reaction.

Table 6: Reaction conditions and results for the attempted, phenylcarbamate directed imino Diels-Alder reaction screening described in Scheme 45.

entry	Lewis acid	Brønsted acid	T [°C]	t [h]	results
1	/	TFA	80	72	no conv.
2	/	HCl ($BnNH_3Cl$)	r.t.	24	no conv.
3	/	HCl ($BnNH_3Cl$)	80	72	decomp.
4	$ZnCl_2$	/	80	72	no conv.
5	$BF_3{\cdot}OEt_2$	/	r.t. 80	24 72	no conv.
6	$BF_3{\cdot}OEt_2$	/	80	72	mainly formation of *rac*-**112**

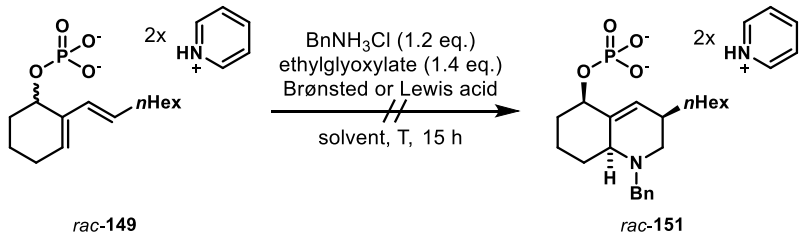
With these results in hand, we decided to evaluate, whether a Brønsted acidic directing group, such as a phosphate or a sulfate, is suitable to enhance the intramolecular iminium Diels-Alder reaction. The phosphate *rac*-**149** was prepared *via* the corresponding diethyl phosphate *rac*-**148** by treatment of the allylic alcohol *rac*-**112** with diethyl chlorophosphate and subsequent deprotection using TMSBr (Scheme 46). The sulfate *rac*-**150** was obtained by the reacting the allylic alcohol *rac*-**112** with chlorosulfuric acid under basic conditions. Both the phosphate *rac*-**149** as well as the sulfate *rac*-**150** could only be isolated as the crude pyridinium salts. It was not possible to perform column chromatography nor recrystallization. The sulfate was very instable upon contact with water and permitted further aqueous workup. The fact that phosphates and sulfates are good leaving groups, especially when

leaving behind an allylic cation, explains the instability of the substrates *rac*-**149** and *rac*-**150**. In both cases the formation of the corresponding allylic alcohol was observed, although the pyridinium phosphate did only decompose slowly under aqueous conditions.



Scheme 46: Phosphorylation and sulfatation of *rac*-**112**.

A first reaction screening was performed with pyridinium phosphate *rac*-**149** in combination with benzylamine hydrochloride and ethyl glyoxylate to generate the desired iminium dienophile. As benzylamine hydrochloride was employed, the reaction was performed without addition of an external Brønsted acid at 25 °C (Table 7, entry 1). Under these conditions no conversion, and, as a positive result, only minor decomposition was observed. Next, hydrochloric acid in dioxane was added under the same reaction conditions to ensure the formation of the corresponding iminium dienophile. Again, no conversion was observed even upon heating the reaction mixture (Table 7, entry 2) or upon addition of TFA as another strong Brønsted acid (Table 7, entry 3 & 4). Employing $ZnCl_2$ as a mild Lewis acid also did not result in the desired conversion of phosphate *rac*-**149** (Table 7, entry 5), while the addition of the strong Lewis acid $BF_3{\cdot}OEt_2$ led to the decomposition (Table 7, entry 6).



rac-**149** *rac*-**151**

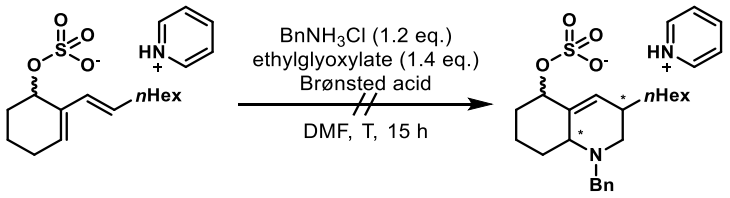
Scheme 47: Attempted intermolecular imino Diels-Alder test reactions employing phosphate *rac*-**149** as the diene.

Table 7: Reaction conditions for the intermolecular imino Diels-Alder test reactions employing *rac*-**149** as the diene and benzylamine hydrochloride with ethyl glyoxylate as the iminium dienophile. The reactions were performed on a 100 mg scale with a concentration of 0.25 M.

entry	solvent	Lewis acid	Brønsted acid	T [°C]	results
1	DMF	/	/	25	no conv.
2	DMF	/	HCl	25	no conv.
				50	no conv.
3	DMF	/	TFA	25	no conv.
4[a]	DMF	/	TFA	50	no conv.
5[a]	CH_2Cl_2	$ZnCl_2$	/	-78	no conv.
				25	no conv.
6[a]	THF	$BF_3{\cdot}OEt_2$	/	-78	decomp.

[a]c =0.5 M

Although the sulfate *rac*-**150** seemed to be less stable under the workup conditions, a short screening was performed. However, upon addition of $BnNH_3Cl$ and ethyl glyoxylate in DMF at different temperatures, no conversion was observed (Table 8, entry 1). Therefore, additional hydrochloric acid was added to force the formation of the iminium dienophile. Unfortunately, this only resulted in the decomposition of the starting material (Table 8, entry 2).



rac-**150** *rac*-**152**

Scheme 48: Attempted intermolecular imino Diels-Alder test reactions employing sulfate *rac*-**150** as the diene.

Table 8: Reaction conditions for the intermolecular imino Diels-Alder test reactions employing *rac*-**150** as the diene and benzylamine hydrochloride with ethyl glyoxylate as the iminium dienophile. The reactions were performed on a 100 mg scale with a concentration of 0.25 M.

entry	Brønsted acid	T [°C]	results
1	/	25	no conv.
		50	no conv.
		70	no conv.
2	HCl	25	no conv.
		50	decomp.

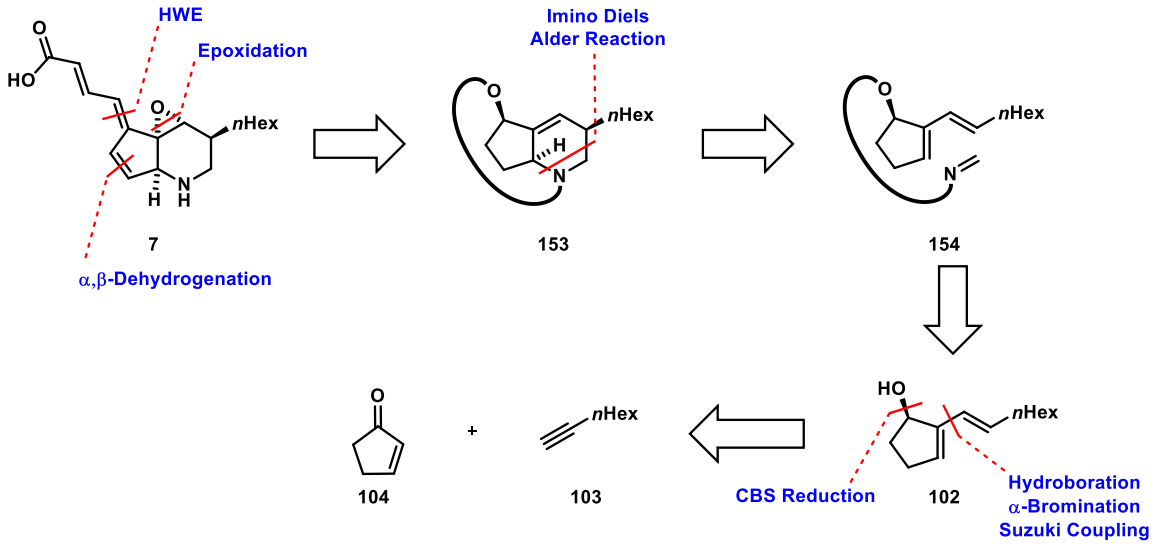
In conclusion, all attempts to achieve a directed intermolecular imino Diels-Alder reaction were unsuccessful so far, either because of the instability of the allylic directing groups under Lewis or Brønsted acidic conditions, or because of a lack of diastereo- and regioselectivity in case of the relatively stable dienylic methyl ether *rac*-**127**. In view of these results, it was decided to test different tethered substrates in intramolecular imino Diels-Alder reactions.

2.3.2. Intramolecular Imino Diels-Alder Approach (Northern Route)

2.3.2.1. Conception

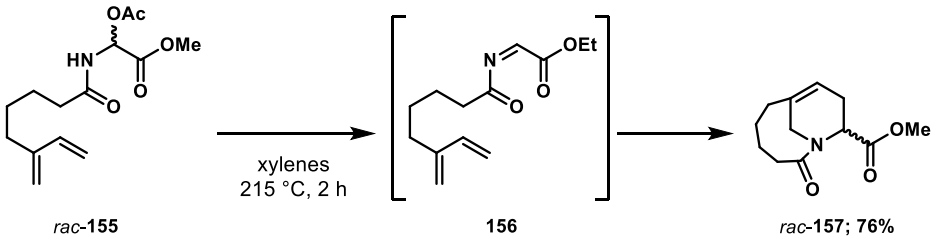
Building on the experience gained during the previous experiments (intermolecular imino Diels-Alder approach), it was decided to test an intramolecular imino Diels-Alder reaction. Retrosynthetically, a similar route to the intermolecular version should be followed, including a late-stage HWE/Wittig-reaction to introduce the conjugated sidechain (Scheme 49). One interesting feature of this approach is the introduction of the epoxide while the linker is still attached. By blocking the upper face of the diene, the epoxidation should occur from the opposite face of the molecule ensuring the desired diastereoselectivity. The epoxidation itself would even help to relief strain

from intermediate **153** by changing the hybridization of the bridgehead sp^2 alkene-carbon to a sp^3 centre. The intramolecular imino Diels-Alder reaction itself should be directed by a linker attached to the allylic alcohol moiety of **102**, which is already known from the previous approach.



Scheme 49: Retrosynthetic concept using an intramolecular imino Diels-Alder reaction to construct camporidine A (**7**).

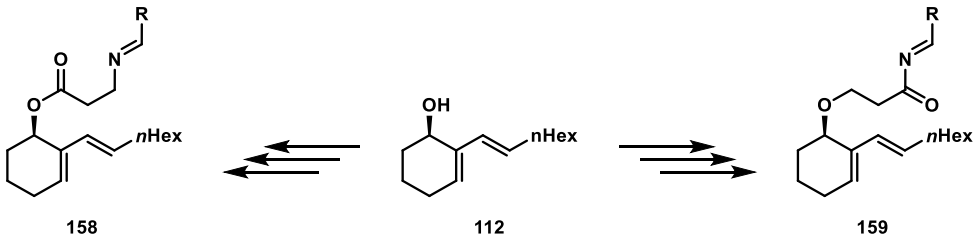
The idea to use an intramolecular reaction was inspired by Lease *et al*, who reported the formation of *rac*-**157** by thermolysis of *rac*-**155** and subsequent imino Diels-Alder reaction (Scheme 50). In this example neither a Lewis nor Brønsted acid needed to be employed to activate the iminium dienophile towards the unactivated diene.[92]



Scheme 50: Intramolecular imino Diels-Alder reaction reported by Lease *et al*.[92]

Based on this report two different types of linkers were envisioned and should be synthesized starting from the already established cyclohexenone-derived allylic alcohol **112**. First, the cyclohexenone-derived test system **112** was used instead of the cyclopentenone-derived real system to save costs, while the chemistry performed, should be transferable to the real system. The first tethered amine **158** should be derived from β-alanine and be prepared by esterification of the allylic

alcohol **112**, followed by amine deprotection and formation of the imine by condensation with formaldehyde or ethyl glyoxylate **139**. The second linker of type **159** should be obtained by an *oxa*-Michael addition of alcohol **112** to acrylonitrile, followed by selective hydrolysis of the resulting nitrile to the corresponding amide and subsequent condensation with a suitable aldehyde such as ethyl glyoxylate **139**.

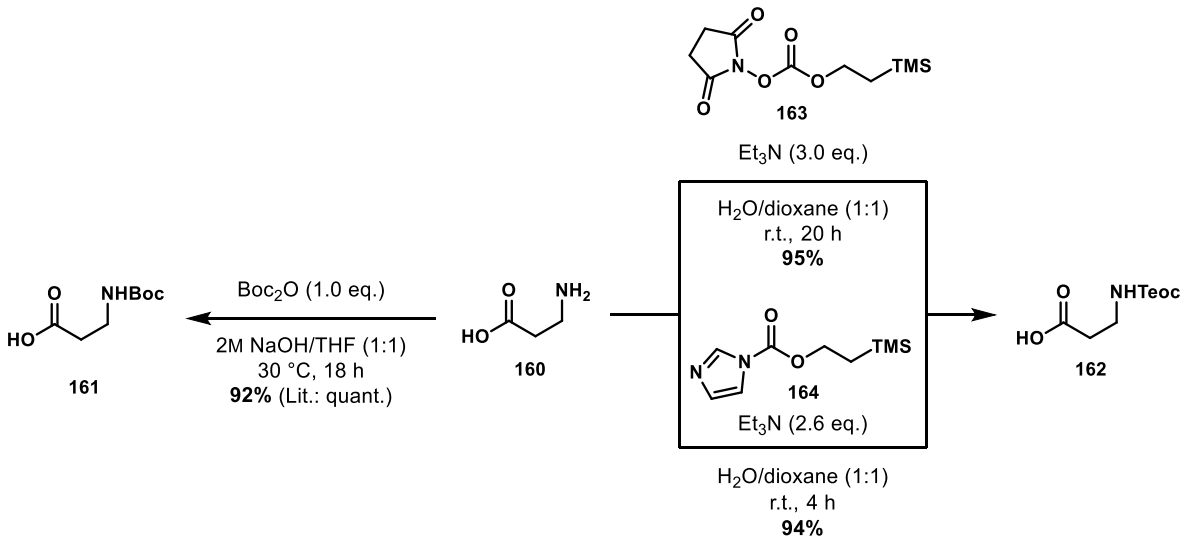


Scheme 51: Overview of the envisioned functionalization of allylic alcohol **112** by introduction of β-alanine and acrylonitrile-derived linkers.

Both types of linkers have their advantages and disadvantages. On the one hand, the β-alanine-derived imine **158** can be synthesized relatively easy from readily available and non-toxic β-alanine, but the ester moiety in the dienylic position might be sensitive towards elimination reactions. On the other hand, the acrylonitrile-derived imine **159** needs harsher reaction conditions to form the imine due to the additional *N*-acyl substituent, however, the allylic ether linker may be advantageous against allylic elimination.

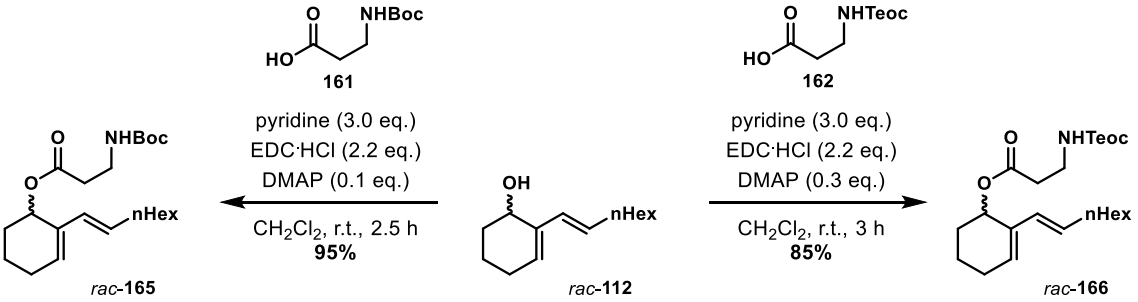
2.3.2.2. Attempted Intramolecular Imino Diels-Alder Reaction Using Ester-Linked Substrates

First, the synthesis of the β-alanine-derived diene **158** was investigated. Therefore, β-alanine (**160**) was Boc-protected according to a procedure reported by Laughlin *et al*.[93] and a Teoc-protecting group was introduced *via* two different routes (Scheme 52). First, the commercially available, but relatively expensive, protection agent Teoc-OSu **163** was used to obtain the desired *N*-Teoc protected β-alanine **162** in 95% yield. A second and less expensive protection strategy was tested according to a modified procedure by Shute *et al.* by freshly preparing the Teoc-protection agent **164** from CDI and 2-trimethylsilyl-ethan-1-ol. **164** was reacted with β-alanine **161**, which furnished the desired *N*-Teoc-β-alanine **162** again in an excellent yield of 94%.[94]



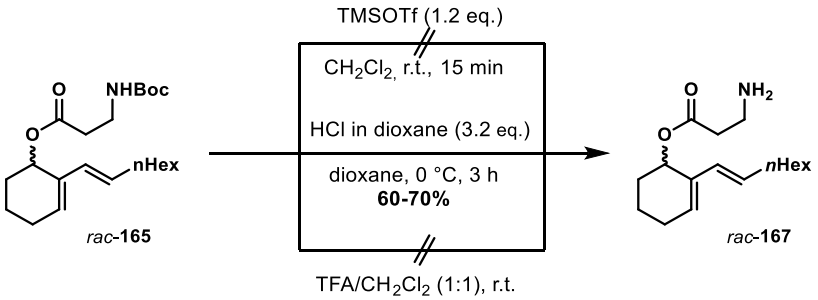
Scheme 52: Boc- and Teoc-protection of β-alanine (**160**) according to a procedure reported by Laughlin *et al*.[93]

The Steglich esterification of allylic alcohol *rac*-**112** with *N*-Boc β-alanine **161** and *N*-Teoc β-alanine **162** afforded the esters *rac*-**165** and *rac*-**166** in 95% and 85% yield (Scheme 53).



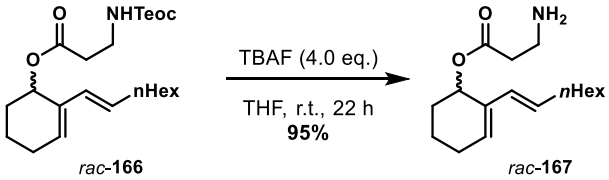
Scheme 53: Steglich esterification of allylic alcohol *rac*-**112** with *N*-Boc β-alanine **161** and *N*-Teoc β-alanine **162**.

The following Boc-deprotection of *rac*-**165** proved to be more challenging than expected. Deprotection under standard conditions using TMSOTf or TFA did not lead to the formation of the desired free amine *rac*-**167** (Scheme 54). Instead, a fast decomposition to a black reaction mixture was observed. Luckily, careful treatment of *rac*-**165** with HCl in dioxane at 0 °C using a syringe pump and subsequent basic workup furnished the desired free amine *rac*-**167** in 60-70% yield. It is important to control the reaction conditions carefully, otherwise diminished yields are obtained. Especially a slow addition of the hydrochloric acid is necessary to get good results.



Scheme 54: Boc deprotection of *rac*-**165**.

In contrast, the Teoc-deprotection of *rac*-**166** using TBAF furnished the desired free amine *rac*-**167** in almost quantitative yield. To summarize, both routes resulted in a successful formation of the desired β-alanine ester *rac*-**167**. Utilizing the Teoc-protecting group promises high yields and reliable reaction outcomes, but more expensive reagents are required. In contrast employing the Boc-protecting group is cheaper, but especially the Boc-deprotection must be controlled carefully.



Scheme 55: Teoc-deprotection using TBAF.

With the free amine *rac*-**167** in hand the imine formation and intramolecular imino Diels-Alder reactions were investigated. First, amine *rac*-**167** was treated with formaldehyde under Dean-Stark conditions to form the corresponding formimin *rac*-**169** (Table 9, entry 1). It was possible to observe full conversion to the dioxazine condensation product *rac*-**168** (Figure 5).

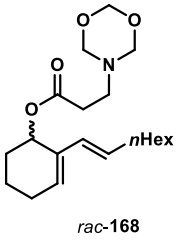
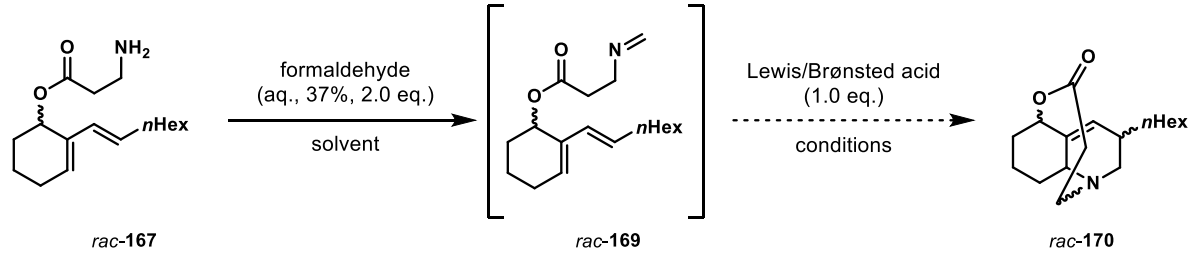


Figure 5: Dioxazine product formed upon treatment of amine *rac*-**167** with formaldehyde under Dean Stark conditions.

Formaldehyde is known to form such dioxazines in combination with primary amines. Besides the formation of dioxazine *rac*-**168** no formation of the desired imino DA

product *rac*-**170** was observed. Upon addition of the mild Lewis acid $ZnCl_2$ only decomposition of the starting material was observed (Table 9, entry 2). In contrast, the addition of HCl as a Brønsted acid catalyst led only to the formation of different condensation products, but again no sign of the desired imino DA product was visible (Table 9, entry 3-5). In this context, a series of solvents miscible with water were tested.



rac-**167** *rac*-**169** *rac*-**170**

Scheme 56: Attempted intramolecular imino Diels-Alder test reactions using amine *rac*-**167** and formaldehyde in combination with a Lewis or Brønsted acid.

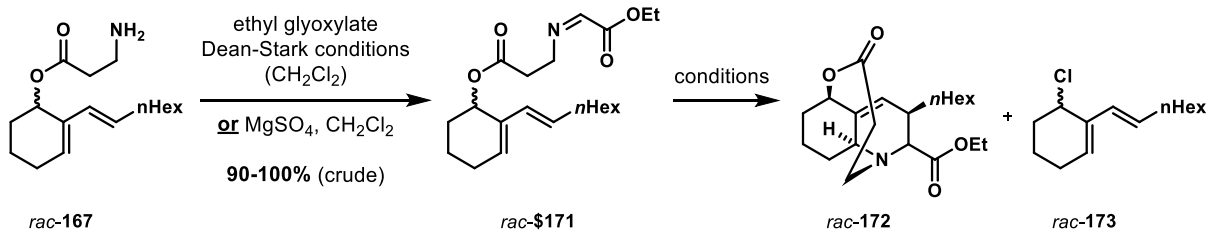
Table 9: Selected results of the intramolecular imino Diels-Alder screening.

entry	solvent	additive	T [°C]	t [h]	conv.[a]	results
1	$CHCl_3$	/	reflux Dean-Stark	3.5	100%	formation of dioxazine *rac*-**168**
2	$CHCl_3$	$ZnCl_2$	reflux Dean-Stark	3	100%	decomp.
3	dioxane	HCl	50	1.5	100%	decomp.
4	THF	HCl	50	18	100%	decomp.
5	THF/H_2O (1:1)	HCl	50	21	100%	decomp.

[a] Determined by TLC.

In search for a more suitable aldehyde to form an electron deficient imino dienophile, formaldehyde was exchanged by ethyl glyoxylate, which has been shown to form imines with primary amines reliably in previous cases. And indeed, upon reaction of the primary amine *rac*-**167** with ethyl glyoxylate the corresponding imine formed under various mild dehydrating reaction conditions. Either Dean-Stark conditions employing low boiling CH_2Cl_2 or the addition of $MgSO_4$ at ambient temperature led to the formation of the desired imine *rac*-**171**, which was clearly identified by crude NMR. However, heating of imine *rac*-**171** in DMF, xylenes or toluene did not lead to any conversion to the desired imino DA product *rac*-**172** (Table 10, entry 1). Instead, imine

rac-**171** stayed intact in all three cases. When imine *rac*-**171** was heated in DMF under microwave irradiation complete decomposition was observed (Table 10, entry 2). Addition of hydrochloric acid to imine *rac*-**171** in toluene led to a slow decomposition by forming the corresponding primary amine *rac*-**167** (Table 10, entry 3). The addition of $BF_3{\cdot}OEt_2$ also induced only a fast decomposition to amine *rac*-**167** (Table 10, entry 4) and $ZnCl_2$ led to the formation of *rac*-**173** in an excellent yield of 94% (Table 10, entry 5). This indicates a facile elimination of the linker in dienylic position as the reason for the observed decomposition. To conclude this set of experiments, none of the tested reaction conditions resulted in the formation of the desired intramolecular imino DA products. The ethyl glyoxylate-derived imine *rac*-**171**, which was characterized, was obviously not reactive enough. Therefore, a second type of even more electron deficient imine precursors was synthesized.



Scheme 57: Selected results from the attempted intramolecular imino Diels-Alder screening using amine *rac*-**167** and ethyl glyoxylate in combination with a Lewis or Brønsted acid.

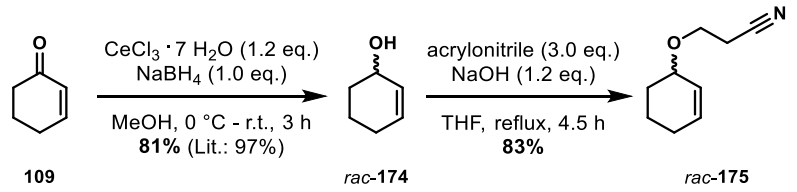
Table 10: Selected results for the intramolecular imino Diels-Alder screening employing imine *rac*-**171**.

entry	Lewis acid	Brønsted acid	solvent	T [°C]	conv.[a]	results
1	/	/	DMF/xylenes/ toluene	reflux	0%	*rac*-**171** stays stable
2[b]	/	/	DMF	90-100	100%	decomposition
3	/	HCl (0.1 eq.)	toluene	110	90-100%	Slow decomposition to *rac*-**167**
4	$BF_3{\cdot}OEt_2$ (0.1 eq.)	/	toluene	r.t.	90-100%	Fast decomposition to amine *rac*-**167**
5	$ZnCl_2$ (1.0 eq.)	/	toluene	r.t.	100%	Formation of *rac*-**173** (94 %)

[a] Determined by TLC. [b] The reaction was performed under microwave irradiation.

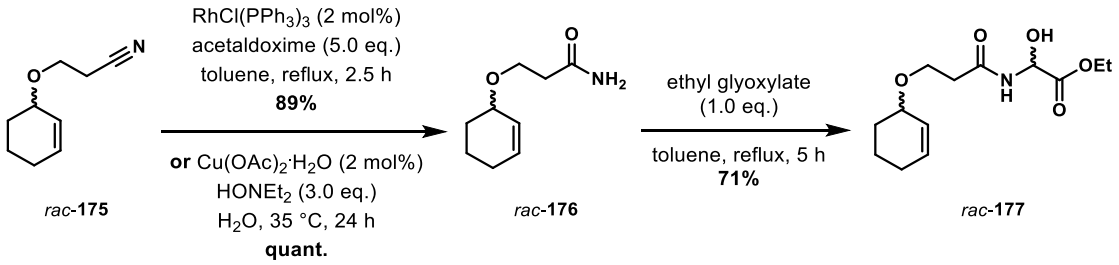
2.3.2.3. Attempted Intramolecular Imino Diels-Alder Reaction Using Ether-Linked Substrates

Besides the β-alanine-derived intramolecular imino Diels-Alder precursors a second kind of imino Diels-Alder precursors was synthesized, featuring a stable ether bond to connect the diene and imino moieties. Therefore, a Luche reduction of cyclohexenone (**109**) was performed to yield the desired cyclohex-2-en-1-ol (*rac*-**174**) in a yield of 81% as a test system to explore suitable reaction conditions (Scheme 58).[95] The minor product losses can be explained by the volatility of the obtained product, which should not be a problem anymore as soon as the reaction conditions are transferred to the less volatile real system with a *n*hexyl side chain attached. Afterwards, an *oxa*-Michael addition of the allylic alcohol *rac*-**174** to acrylonitrile was performed under basic reaction conditions and yielded the desired nitrile *rac*-**175** in a yield of 83%.



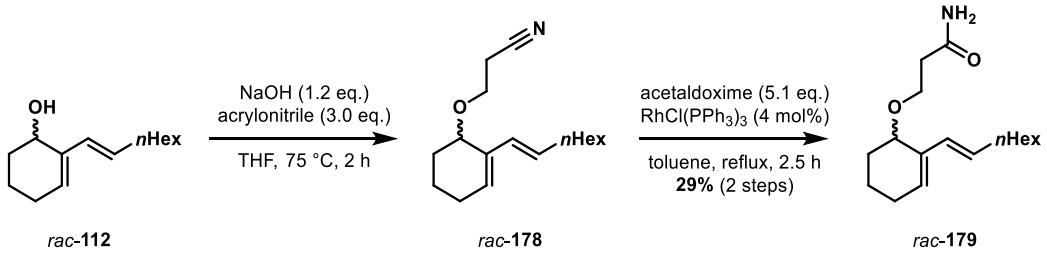
Scheme 58: Luche reduction of cyclohexenone (**109**) to cyclohex-2-en-1-ol (*rac*-**174**) and subsequent *oxa*-Michael addition to acrylonitrile.[95]

For the selective hydrolysis of nitrile *rac*-**175** to the corresponding amide *rac*-**176** a wide variety of different metal-mediated methods has been described in the literature[96] of which two distinct procedures were tested (Scheme 59). The first procedure reported by Lee *et al.* employed the Wilkinson´s catalyst under anhydrous reaction conditions using acetaldoxime as an organic formal water source.[97] It was possible to successfully transfer these reaction conditions to our system and to yield the desired amide *rac*-**176** in 89% yield. Nevertheless, the second set of reaction conditions reported by Marcé *et al.* employing $Cu(OAc)_2$ as metal catalyst, but working under aqueous conditions, was even more successful in catalyzing the hydrolysis to amide *rac*-**176** in a quantitative yield.[98] The amide *rac*-**176** readily undergoes addition to ethyl glyoxylate to form hemiaminal *rac*-**177** in 76% yield.



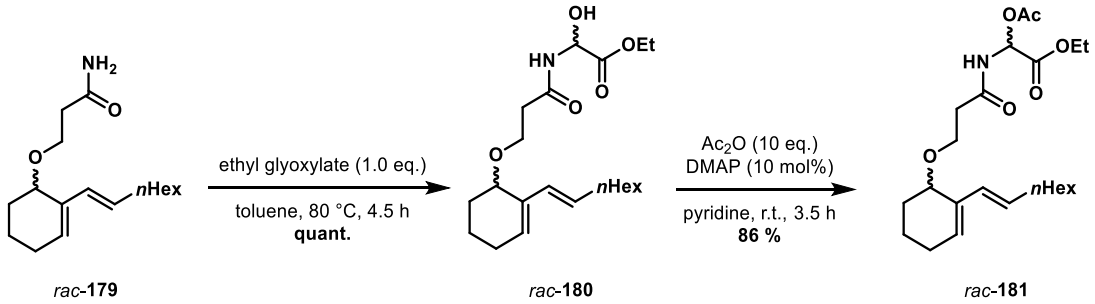
Scheme 59: Hydrolysis of nitrile *rac*-**175** to amide *rac*-**176** followed by addition to ethyl glyoxylate forming the corresponding hemiaminal *rac*-**177**.

Next, the reaction conditions established for the test system were transferred to the dienylic system *rac*-**112** by performing an *oxa*-Michael addition of *rac*-**112** to acrylonitrile. The formed nitrile *rac*-**178** was subsequently hydrolyzed upon treatment with the Wilkinson´s catalyst and acetaldoxime as reported by Lee *et al.* (Scheme 60).[97] Although nitrile *rac*-**178** is a stable compound its separation from residual *rac*-**112** was not successful due to an identical R_f-value of both compounds. In this two-step procedure a yield of only 29% was achieved. This is mainly due to the sensitivity of the dienylic alcohol *rac*-**112** under the *oxa*-Michael reaction conditions causing decomposition and loss of yield.



Scheme 60: *Oxa*-Michael addition of dienylic alcohol *rac*-**112** to acrylonitrile and subsequent hydrolysis of the nitrile *rac*-**178** to the corresponding amide *rac*-**179**.

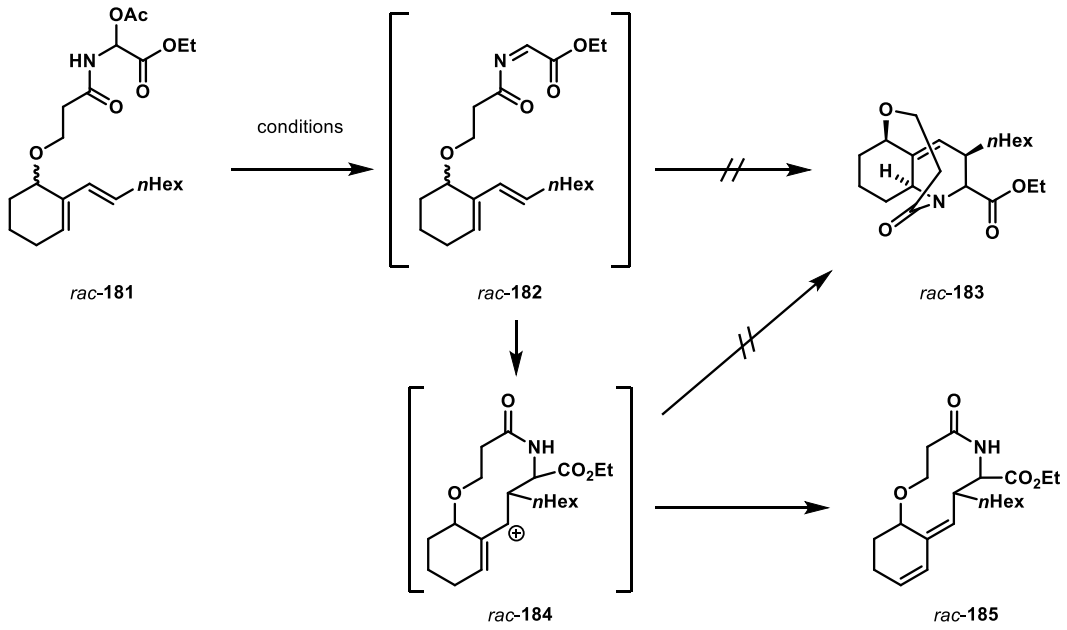
Nevertheless, enough material was obtained to perform the hemiaminal formation by treatment of the amide *rac*-**179** with ethyl glyoxylate, which furnished *rac*-**180** in quantitative yield (Scheme 61). The acetate protection of hemiaminal *rac*-**180** afforded *rac*-**181** in 86% yield, which was used in the following experiments as a *N*,*C*-diacylimine precursor.



rac-**179** *rac*-**180** *rac*-**181**

Scheme 61: Hemiaminal formation by treatment of *rac*-**179** with ethyl glyoxylate and subsequent acetate protection.

With rac-**181** in hand, a series of reaction conditions was screened. Upon simple heating of *rac*-**181** in mesitylene to induce the pyrolysis of the *O*-acetoxy hemiaminal moiety forming imine *rac*-**182**, only decomposition of the starting material to a complex product mixture was observed (Table 11, entry 1). Possibly, the *in situ* generated acetic acid had caused the decomposition. Therefore, one equivalent of triethylamine was added to avoid acid-mediated side reactions, such as elimination of the dienylic ether moiety, and the temperature was lowered to 100 °C (Table 11, entry 2). Nevertheless, still a major, although slower, decomposition was observed. In the next attempt the imine moiety should be further activated by the addition of *p*TsOH at r.t. (Table 11, entry 3). Again, only the formation of a complex product mixture was observed under these acidic reaction conditions. In a last try, the strong Lewis acid $BF_3{\cdot}OEt_2$ was used to activate the imine (Table 11, entry 4). This did mainly lead to the decomposition of *rac*-**181**, but a minor amount of the side product *rac*-**185** was isolated (1-2 mg) and characterized by NMR. The formation of *rac*-**185** indicates the formation of imine *rac*-**182** followed by a subsequent electrophilic attack of the imine moiety at the diene to form the allylic carbocation *rac*-**184**, as it could as well happen in a stepwise iminium Diels-Alder reaction. At this point the elimination of an adjacent proton could have led to the formation of diene *rac*-**185** instead of the intramolecular cyclization necessary to form the imino Diels-Alder product *rac*-**183**. One obvious reason for the failure of the cyclization step could be the ring strain of the resulting product *rac*-**183** preventing the nucleophilic nitrogen atom in *rac*-**184** to come into contact with the allylic cation.



Scheme 62: Selected results from the attempted intramolecular imino Diels-Alder screening employing *rac*-**181** for the *in situ* formation of the *N*,*C*-diacylimine *rac*-**182**.

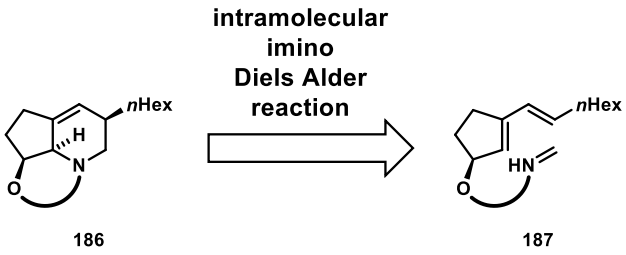
Table 11: Selected results from the attempted intramolecular imino Diels-Alder screening described in Scheme 62.

entry	solvent	additive	T [°C]	t [h]	results
1	mesitylene	/	reflux	3	decomp.
2	toluene	Et_3N (1.0 eq.)	100	3	slow decomp.
3	toluene	*p*TsOH (0.2 eq.)	r.t.	4	decomp.
4	CH_2Cl_2	$BF_3{\cdot}OEt_2$ (1.0 eq.)	-78	1.5	decomp. +traces of *rac*-**185**

Therefore, we decided to focus on another approach connecting the tether to the terminal, southern dienylic position to avoid the relatively high ring strain of the bridged bicyclic ring system.

2.3.3. Intramolecular Imino Diels-Alder Approach (Southern Route)

2.3.3.1. Conception

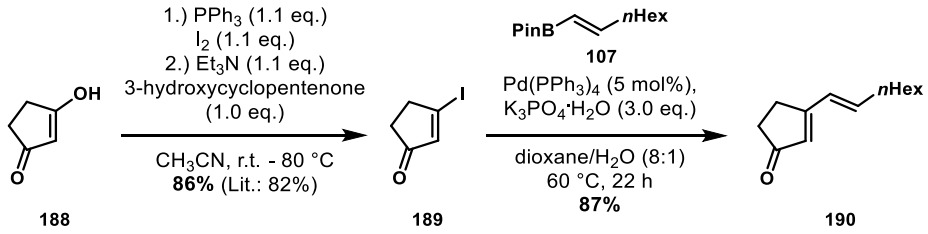


Scheme 63: Envisioned intramolecular imino Diels-Alder reaction with a tether attached to the southern part of the diene.

As already mentioned, the attachment of the imine linker to the southern dienylic position was believed to be advantageous with regard to the minimized ring strain, since no bridged bicyclic Diels-Alder product would be formed in this case. The nature and length of the envisioned linker should be varied and explored in this section. Possible linkers could be based on amino acids such as glycine and β-alanine or be in accordance with the previously established routes by the introduction of acrylonitrile-derived carbamates.

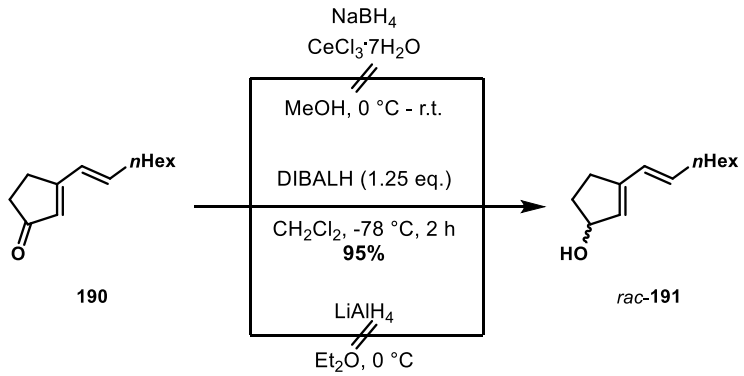
2.3.3.2. Ester-Linked Imino Diels-Alder Precursor Synthesis

The synthesis of all "southern" imino Diels-Alder precursors was based on the dienylic alcohol *rac*-**191**. The synthesis followed an initial Appel type iodination by treating cyclopenta-1,3-dione (**188**) with PPh_3 and I_2, which led to the formation of the desired β-iodocyclopentenone (**189**) (Scheme 64). The vinylic iodide **189** was reacted in a Suzuki coupling with the previously synthesized vinylboronate **107** and gave rise to the dienone **190** in a yield of 87%.



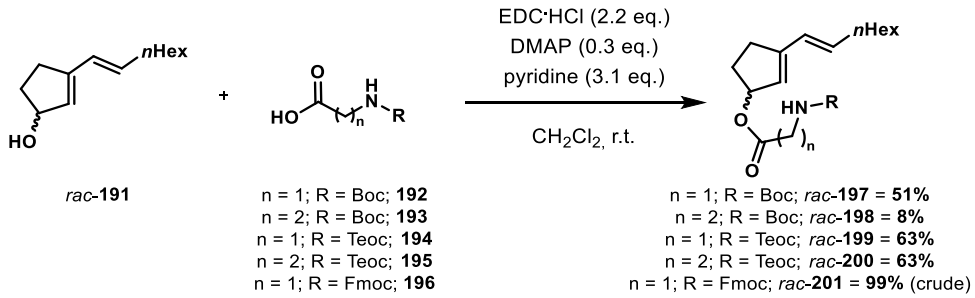
Scheme 64: Iodination of 1,3-cyclopentadione (**188**) according to Lemiére *et al.*[99] followed by a subsequent Suzuki coupling.

The following reduction of dienone **190** to the corresponding dienol *rac*-**191** proved to be more challenging than expected in the beginning. A Luche reduction led to the complete decomposition of the starting material in a few minutes (Scheme 65). Also, the reduction using $LiAlH_4$ at 0 °C led the decomposition of the starting material. A major threat regarding the reduction of this dienone **190** might be the instability of the resulting alcohol *rac*-**191**, which is susceptible towards elimination. The intermediate dienylic carbocation would be well delocalized and therefore very stable. Nevertheless, upon further lowering the temperature to -78 °C and treating the dienone **190** with DIBALH yielded the desired dienol *rac*-**191** in 95% yield. We decided to evaluate the potential of this approach first on this racemic test system and upon success of the intramolecular imino Diels-Alder reaction an enantioselective reduction like a CBS reduction should be tackled.



Scheme 65: Reduction of dienone **190** to the corresponding dienol *rac*-**191**.

In the next step the dienol *rac*-**191** was esterified under Steglich conditions with Boc-, Teoc- and Fmoc-protected glycine (**192**, **194**, **196**) and β-alanine derivatives (**193**, **195**) (Scheme 66). These esters **197**-**201** were obtained in isolated yields from 8% to 63%. The strong deviations could be traced back to the instability of the corresponding dienylic esters during the purification conditions. All esters were very sensitive towards Brønsted acids including the silica used for column chromatography (although Et_3N was used as additive for the solvent mixture). The Fmoc-ester *rac*-**201** was only obtained as a crude product, because the necessary addition of Et_3N during column chromatography could cause direct deprotection on the column.



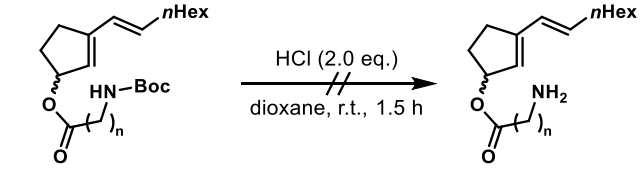
rac-**191**

n = 1; R = Boc; **192**
n = 2; R = Boc; **193**
n = 1; R = Teoc; **194**
n = 2; R = Teoc; **195**
n = 1; R = Fmoc; **196**

n = 1; R = Boc; *rac*-**197** = **51%**
n = 2; R = Boc; *rac*-**198** = **8%**
n = 1; R = Teoc; *rac*-**199** = **63%**
n = 2; R = Teoc; *rac*-**200** = **63%**
n = 1; R = Fmoc; *rac*-**201** = **99%** (crude)

Scheme 66: Esterification of dienol *rac*-**191** with a series of amino acid-derived carboxylic acids under standard Steglich conditions.

As already expected due to the lability towards silica, the Boc-deprotection of the glycine ester *rac*-**197** and the β-alanine ester *rac*-**198** could not be accomplished under standard acidic conditions (Scheme 67). Instead, a complete decomposition of the esters was observed. To avoid acidic deprotection conditions, Fmoc- and Teoc-protecting groups were introduced which can be cleaved under basic conditions.

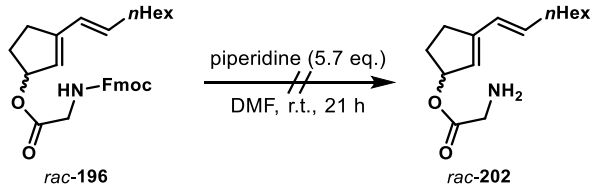


n = 1; R = Boc; *rac*-**197**
n = 2; R = Boc; *rac*-**198**

n = 1; *rac*-**202**
n = 2; *rac*-**203**

Scheme 67: Attempted Boc-deprotection using acidic conditions.

Unfortunately, the Fmoc-deprotection of *rac*-**201** using piperidine as a relatively mild base was not successful and only resulted in the decomposition of the starting material (Scheme 68).

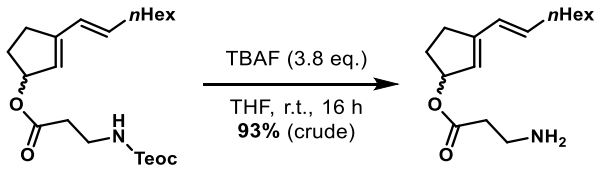


rac-**196**

rac-**202**

Scheme 68: Attempted basic Fmoc-deprotection.

Finally, it was possible to perform the deprotection of the Teoc-protected β-alanine ester *rac*-**200** upon treatment with TBAF. Like for the previously described protected esters, the purification of the primary amine *rac*-**203** by column chromatography was hardly possible. Due to the relatively clean conversion, the crude product was used in the following reactions without further purification.



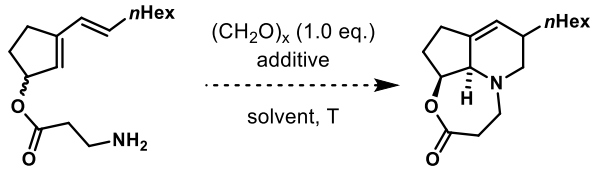
rac-**200** *rac*-**203**

Scheme 69: Standard Teoc-deprotection of *rac*-**200** towards the free amine *rac*-**203**.

2.3.3.3. Attempted Imino Diels-Alder Reactions

With amine *rac*-**203** in hand, the investigation of the projected imino Diels-Alder reaction was performed. Beforehand, the activation energy for this reaction was estimated by density functional theory calculations (DFT-calculations) with the functionals B3LYP, or BP86[100-102] and by using the def2-TZVP-base[103]. The activation energy for the imino Diels-Alder reaction of imine *rac*-**203** was determined as ΔE = 125 ±25 kJ/mol.[104]

Therefore, the first reaction was performed by simply adding paraformaldehyde without any additives under Dean-Stark conditions to generate the formimine intermediate. However, after 3.5 h only decomposition of the starting material was detected (Table 12, entry 1). The next reaction was performed at r.t. in CH_2Cl_2 to avoid side reactions. In this case, a slower decomposition was observed, without a sign of the desired imino Diels-Alder product *rac*-**204** (Table 12, entry 2). To ensure the imine formation even at r.t., $MgSO_4$ was added as a dehydrating agent, however, still only decomposition was observed (Table 12, entry 3). In a last attempt 1.0 eq. TFA was added to the reaction mixture to enhance the reactivity of the formed imine by the formation of the corresponding iminium ion (Table 12, entry 4). This did again only result in an even faster decomposition of the starting material.



rac-**203** *rac*-**204**

Scheme 70: General scheme for the attempted imino Diels-Alder screening employing *rac*-**203** for the *in-situ* formation of the corresponding imine *rac*-**204**.

Table 12: Selected results from the attempted intramolecular imino Diels-Alder screening described in Scheme 70.

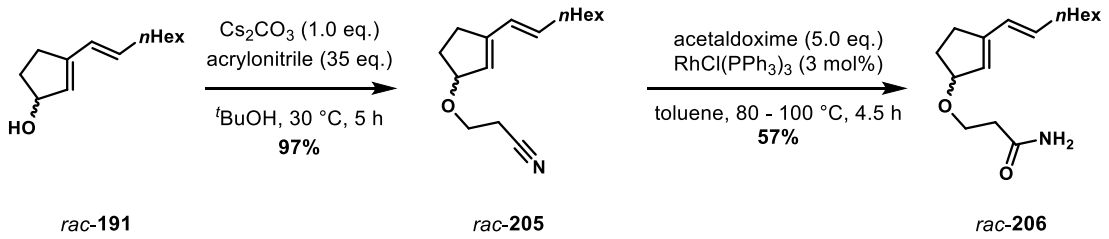
entry	solvent	additive	T [°C]	t [h]	results
1[a]	toluene	/	110	3.5	decomp.
2	CH_2Cl_2	/	r.t.	22	decomp.
3	CH_2Cl_2	$MgSO_4$ (4.0 eq.)	r.t.	22	decomp.
4	CH_2Cl_2	TFA (1.0 eq.)	r.t.	4	decomp.

[a] The reaction was performed under Dean-Stark conditions.

To summarize, the attempted imino Diels-Alder reaction could not be realized, as only decomposition products of the starting material occurred, even under mild reaction conditions (Table 12, entry 2). The inherent instability of the starting material in mind, no further experiments were performed with *rac*-**101**. Instead, a more stable derivative should be synthesized.

2.3.3.4. Ether-Linked Imino Diels-Alder Precursor Synthesis

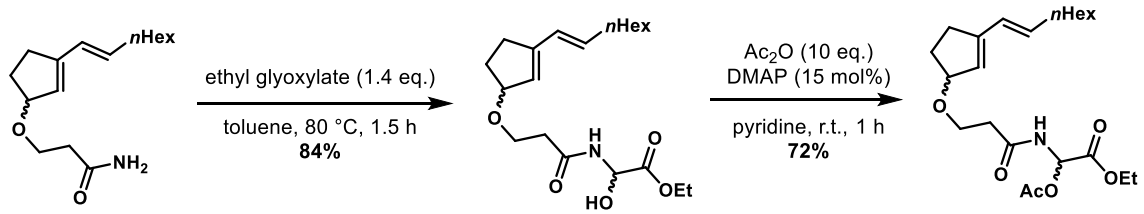
The introduction of an ether linker instead of the previously employed ester linker was considered as a suitable solution to circumvent the instability towards elimination or substitution, as it has been already proven in the case of the attempted “northern” imino Diels-Alder reaction. The corresponding leaving group in the dienylic ethers (alkoxide) is less stable and far more basic than the carboxylate. The ether was introduced by an *oxa*-Michael addition of the alcohol *rac*-**191** to acrylonitrile. Using Cs_2CO_3 as base and ^{t}BuOH as solvent the nitrile *rac*-**205** was obtained in 97% yield. Performing the reaction in THF with NaOH as base resulted in poor yields and in the formation of a range of side products. The hydrolysis of nitrile *rac*-**205** to amide *rac*-**206** was performed according to the procedure described by Lee *et al.* to afford the desired amide *rac*-**206** in 57% yield.



rac-**191** *rac*-**205** *rac*-**206**

Scheme 71: *Oxa*-Michael addition of alcohol *rac*-**191** to acrylonitrile and subsequent nitrile hydrolysis to form amide *rac*-**206**.

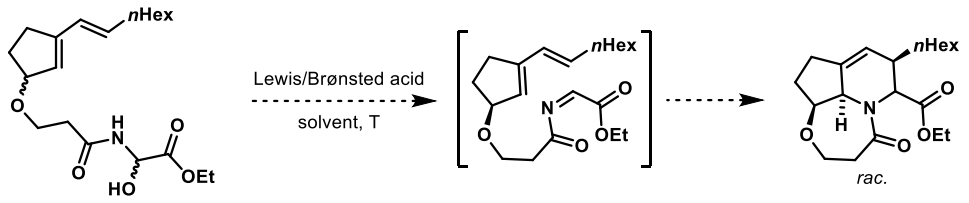
N,*C*-Diacylimines are not stable and must therefore be prepared *in situ*. In this case the method of choice was the formation of an *O*-acetoxy hemiaminal from amide *rac*-**206** and ethyl glyoxylate (Scheme 72). Ethyl glyoxylate bears a high tendency to undergo addition reactions with a variety of nucleophiles including amides and could previously already successfully be employed in imine formations. Therefore, amide *rac*-**206** was treated with ethyl glyoxylate at elevated temperatures to obtain *N*-acyl hemiaminal *rac*-**207** in 84% yield. To facilitate the imine formation, the hemiaminal was *O*-acetylated using standard conditions to obtain *O*-acetoxy-*N*-acyl hemiaminal *rac*-**208** in 72% yield. Both, the hemiaminal *rac*-**207** as well as the *O*-acetoxy hemiaminal *rac*-**208**, were then tested in the planned intramolecular imino Diels-Alder reaction.



rac-**206** *rac*-**207** *rac*-**208**

Scheme 72: Synthesis of the *O*-acetoxy-*N*-acyl hemiaminal *rac*-**208**.

Warming of hemiaminal *rac*-**207** in toluene to 80 °C resulted in the slow cleavage of the hemiaminal and formation of amide *rac*-**206** (Table 13, entry 1). To facilitate the elimination of water, acetic acid was added as a mild Brønsted acid (Table 13, entry 2). Herein, no conversion at r.t. and at 100 °C cleavage of the hemiaminal *rac*-**207** to the corresponding amide *rac*-**206** was observed. Upon addition of TFA as a strong Brønsted acid only an unselective decomposition was observed (Table 13, entry 3). In a last attempt $BF_3{\cdot}OEt_2$ was added as a strong Lewis acid, but even at -78 °C only decomposition of the starting material was observed (Table 13, entry 4).



rac-**207** *rac*-**209** *rac*-**210**

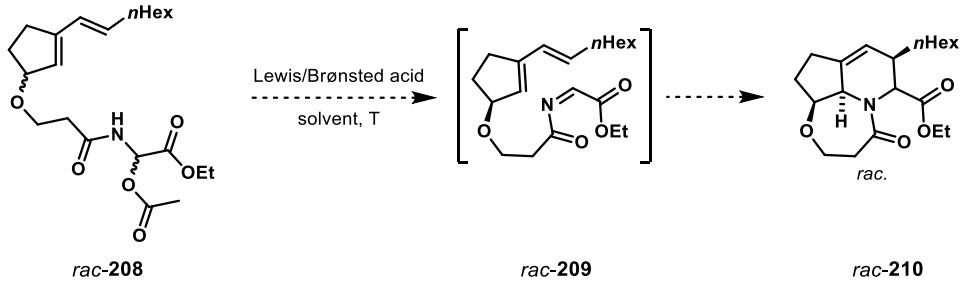
Scheme 73: Attempted intramolecular imino Diels-Alder screening starting from hemiaminal *rac*-**207**.

Table 13: Selected results from the attempted intramolecular imino Diels-Alder screening described in Scheme 73.

entry	Lewis acid	Brønsted acid/base	solvent [0.02 M]	T [°C]	t [h]	results
1	/	/	toluene	80	1.5	slow conv. to *rac*-**206**
2	/	AcOH (1.4 eq.)	toluene	r.t. 100	0.5 1.0	no conv. conv. to *rac*-**206**
3	/	TFA (1.0 eq.)	toluene	100	4.5	decomp.
4	$BF_3{\cdot}OEt_2$ (1.0 eq.)	/	CH_2Cl_2	-78	1.0	decomp.

The *O*-acetoxy hemiaminal *rac*-**208** was employed in a second reaction screening. First, the stability of the *N*,*O*-diacylimine precursor *rac*-**208** was investigated by heating to reflux in toluene (Table 14, entry 1). The compound did not decompose and seemed more stable in comparison to hemiaminal *rac*-**207**. Even upon warming to 170 °C in a microwave no conversion of the starting material was observed. Only upon heating the reaction mixture to 200 °C in the microwave a decomposition was observed. Unfortunately, a complex product mixture formed and none of the products could be assigned to the desired imino Diels-Alder product *rac*-**210** (Table 14, entry 1). Next, the mild Lewis acid $ZnBr_2$ was added resulting in decomposition of the starting material already at r.t. (Table 14, entry 2). The treatment of the starting material with $BF_3{\cdot}OEt_2$ at different temperatures led to decomposition as well (Table 14, entry 3). Next, a series of different Brønsted acidic or basic additives were tested. Addition of the two strong Brønsted acids *p*TsOH·H_2O and TFA resulted in the decomposition of the starting material (Table 14, entry 4 & 5). Especially unipolar elimination products seem to emerge from strong Brønsted acidic reaction conditions.

Addition of acetic acid as a relatively weak Brønsted acid led to a slow decomposition (Table 14, entry 6) and Et_3N as Brønsted base resulted in the stabilization of the starting material *rac*-**705** at reflux (Table 14, entry 7).



rac-**208** *rac*-**209** *rac*-**210**

Scheme 74: Attempted intramolecular imino Diels-Alder reaction starting from *O*-acetoxy-hemiaminal *rac*-**208**.

Table 14: Selected results from the attempted intramolecular imino Diels-Alder screening described in Scheme 74.

entry	Lewis acid	Brønsted acid/base	solvent [0.01 M]	T [°C]	results
1	/	/	toluene	reflux 170 (MW, 10 min) 200 (MW, 10 min)	0% conv. 0% conv. decomp.
2	$ZnBr_2$ (1.0 eq.)	/	toluene	r.t.	slow decomp.
3	$BF_3{\cdot}OEt_2$ (0.5 eq.)	/	CH_2Cl_2	-84 -40 r.t.	slow decomp. fast decomp. decomp.
4	/	*p*TsOH·H_2O (1.0 eq.)	toluene	r.t.	decomp.
5	/	TFA (0.5 eq.)	CH_2Cl_2	-40 r.t.	slow decomp. decomp.
6	/	AcOH (1.0 eq.)	toluene	reflux	slow decomp.
7	/	Et_3N (2.0 eq.)	toluene	reflux	0% conv.

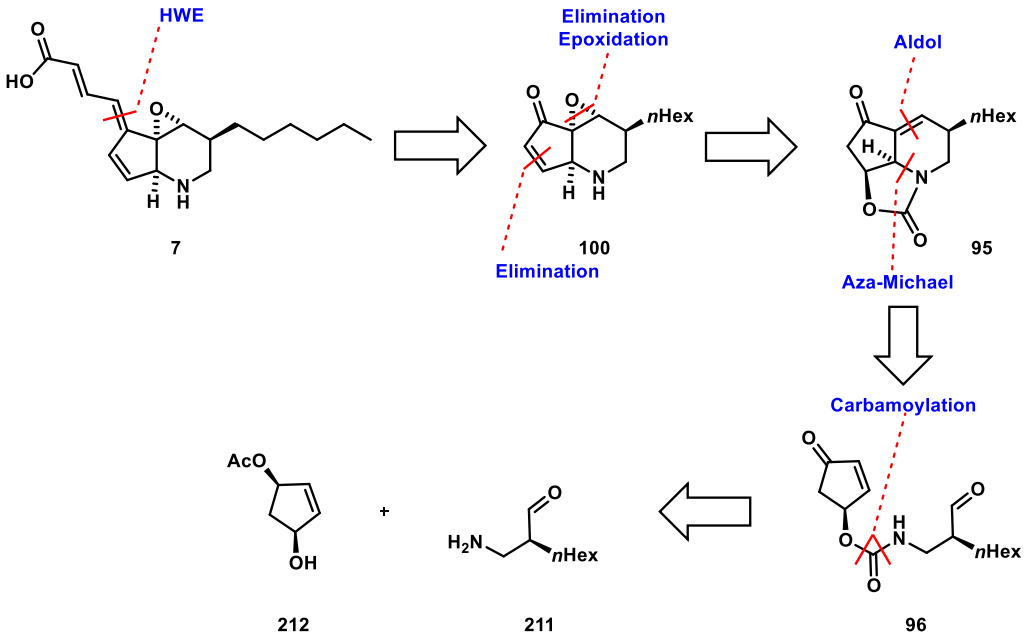
All the reaction conditions tested resulted either in no conversion or decomposition of the starting material, without forming the desired imino Diels-Alder product, hence other strategies had to be followed. The instability of the diverse imino Diels-Alder

precursors towards Lewis and Brønsted acids represents a serious, especially, due to the high tendency of the dienylic substrates to undergo elimination or substitution under various reaction conditions.

2.3.4. *Aza*-Michael/Aldol Approach

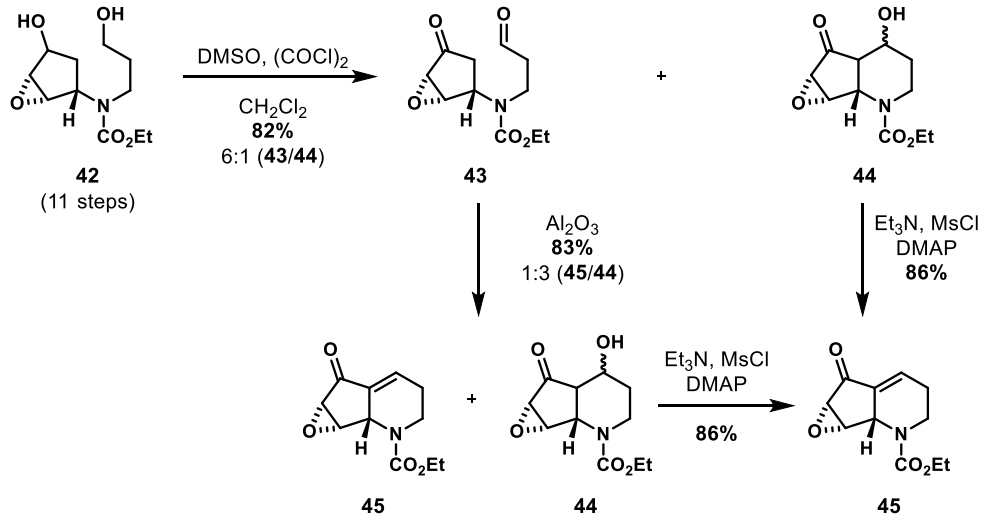
2.3.4.1. Conception

In the conceived synthetic approach towards camporidine A (**7**) the conjugated sidechain should be introduced on a late stage by a HWE-type reaction and the enone system should be obtained by elimination of CO_2 from the former carbamate (Scheme 75). A new way to construct the bicyclic tetrahydropyridine core structure **95** would be an intramolecular *aza*-Michael addition followed by an aldol reaction. This *aza*-Michael addition should occur in a substrate controlled, diastereoselective fashion while the *aza*-Michael precursor **96** should be assembled from the corresponding 4-hydroxy cyclopentenone **212**. Enantiopure 1-acetoxy-4-hydroxycylopentene (**212**) can be obtained through dihydroxylation of cyclopentadiene by singlet oxygen followed by acetylation and enantioselective enzymatic mono deacetylation.



Scheme 75: Retrosynthetic conception of route towards the construction of camporidine A (**7**) featuring a central *aza*-Michael/aldol sequence.

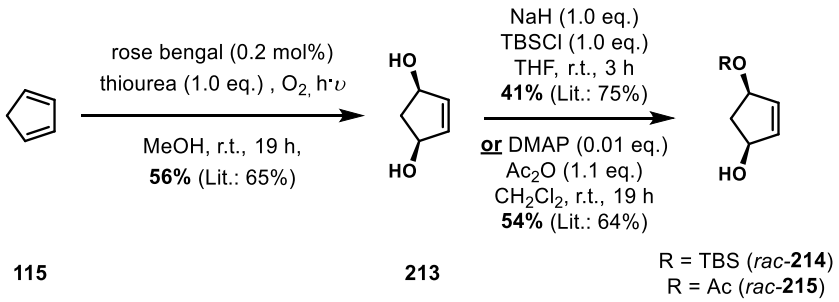
This approach was inspired by the total synthesis of streptazoline (**18**) by Miller *et al.*, who used an intramolecular aldol addition/condensation to assemble the bicyclic core motif in an elegant fashion (Scheme 76).[38]



Scheme 76: Key aldol condensation employed in the total synthesis of streptazoline reported by Miller *et al*.[38]

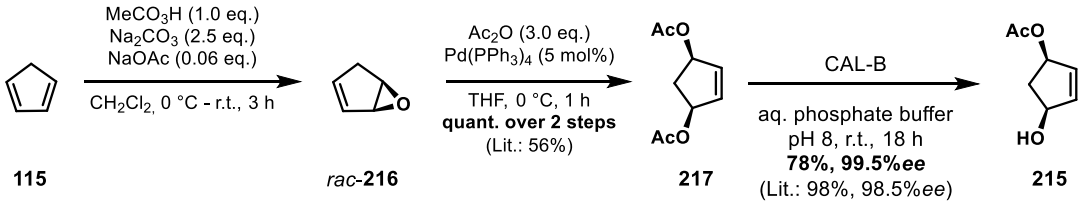
2.3.4.2. Synthesis of the Carbamate

This route was started by a *cis*-selective dihydroxylation of cyclopentadiene (**115**) *via* a Diels-Alder reaction with singlet oxygen according to a procedure by Tietze *et al.* (Scheme 77).[105] The singlet oxygen was generated by excitation of oxygen in the presence of bengal rose as a sensitizer using a mercury vapor lamp. This procedure furnished the desired *cis*-diol **213** in 56% yield after reduction of the primarily formed peroxide with thiourea. Although this reaction is relatively clean and atom economic, it has two major drawbacks. It is necessary to work at relatively low concentrations, which leads to small batch sizes, and due to long reaction times side products were formed, *e.g.* dicyclopentadiene. Next, the diol **213** was monoprotected with a TBS and an acetate protecting group according to literature known procedures in a racemic fashion to yield the desired allylic alcohols *rac*-**214** and *rac*-**215** in moderate yields.[106,107] The double protection of the second identical alcohol moiety was the main problem in both cases. This led to a diminished yield of the otherwise clean reactions.



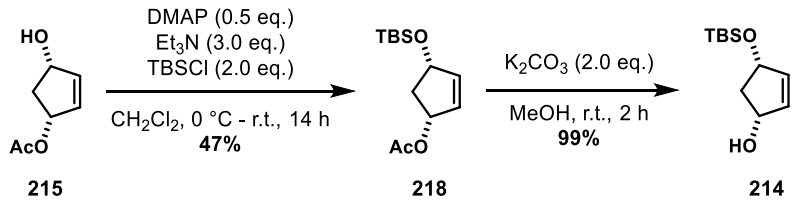
Scheme 77: *cis*-Selective dihydroxylation of cyclopentadiene (**115**) *via* a Diels-Alder reaction with singlet oxygen followed by racemic mono acetate and TBS protection.[105-107]

Due to the drawbacks of the singlet oxygen Diels-Alder reaction a second literature known approach was tested, which involved the epoxidation of cyclopentadiene (**115**) with peracetic acid followed by a palladium-catalyzed epoxide opening and subsequent acetate protection (Scheme 78).[105] This reaction sequence resulted in a quantitative conversion of cyclopentadiene (**115**) to the corresponding *cis*-diacetate **217**. It must be mentioned that the reaction employing peracetic acid was performed very carefully under cooling and the solvent was never removed completely to avoid high concentrations of peracetic acid, which could lead to the formation of an explosive mixture. The diacetate **217** was mono-deprotected in an enantioselective fashion using *Candida Albicans Lipase B* (CAL-B) as a selective enzyme catalyst.[108] The desired alcohol **215** was obtained in a good yield and high enantioselectivity of up to 99.5%*ee*. This enantioselective route towards the asymmetric mono-acetate **215** proved to be even more efficient as the racemic route, hence the *cis*-diacetylation was performed easily on a larger scale with a superior yield. A second improvement was the very selective and high yielding mono-acetate deprotection using CAL-B.



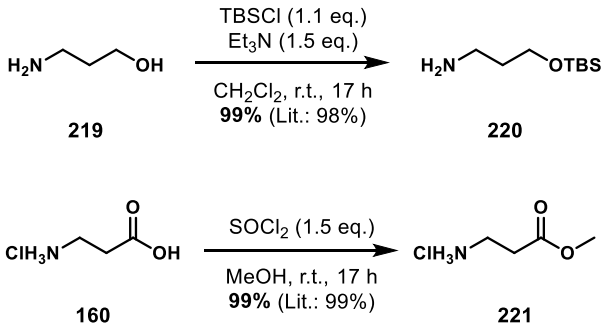
Scheme 78: Epoxidation of cyclopentadiene (**115**), Pd-catalyzed epoxide-opening and acetate protection, followed by an enzymatic mono acetate cleavage.[105,108]

Starting from allylic alcohol **215** TBS-protection followed by acetate deprotection was performed to obtain the non-racemic TBS-protected allylic alcohol **214** (Scheme 79).



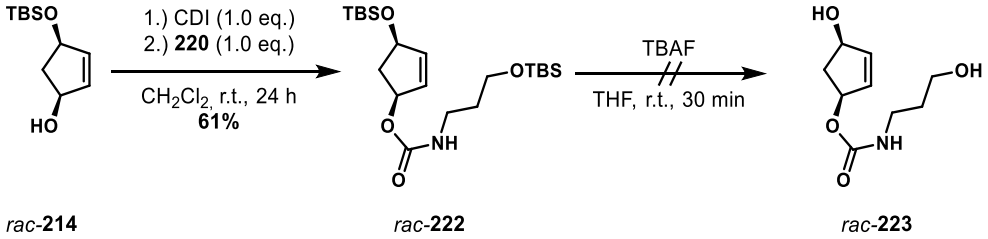
Scheme 79: TBS-protection of the allylic alcohol **715** followed by an acetate deprotection under standard conditions to form allylic alcohol **214**.

With the mono-acetyl-protected diol **215** and the mono-TBS protected alcohol *rac*-**R114** in hand the carbamate formation was investigated. For this purpose, β-alanine methylester (**221**) and 3-(*tert*-butyldimethylsilanyloxy)propylamine (**220**) were synthesized starting from β-alanine (**160**) and 3-aminopropanol (**219**) according to literature known procedures (Scheme 80).[109,110]



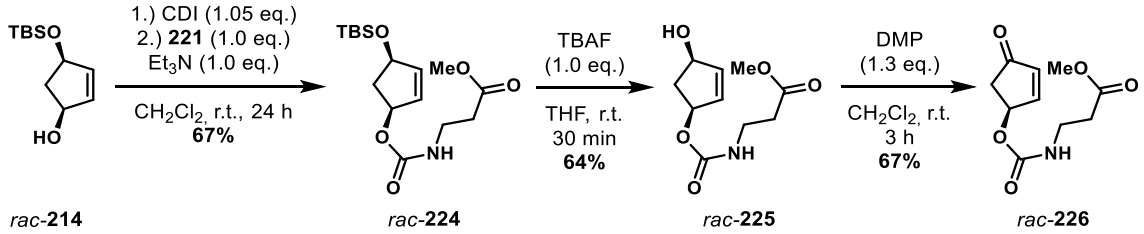
Scheme 80: TBS-protection of 3-aminopropanol (**219**) according to van de Winckel *et al*.[109] and methylester formation from β-alanine hydrochloride (**160**) according to Dekker *et al*.[110]

Next, the racemic mono TBS-protected diol *rac*-**214** was coupled with amine **220** using carbonyldiimidazole (CDI) as a phosgene analogue, which is a less toxic, and non-volatile lab equivalent (Scheme 81). When reacting CDI with the secondary allylic alcohol *rac*-**214**, it reacts only once at the carbonyl center, hence the reaction speed of a second attack is far slower due to the steric demand of the secondary alcohol.[111] Subsequently, the primary amine **220** was added to the reaction mixture to furnish the carbamate *rac*-**222** in a yield of 61%. Unfortunately, the following TBS-deprotection did result in complete decomposition of the starting material *rac*-**222**.



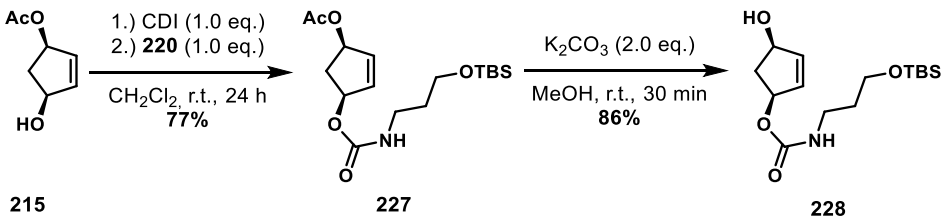
Scheme 81: Carbamate formation of alcohol *rac*-**214** and amine **220** using carbonyldiimidazole (CDI) followed by an unsuccessful attempt to perform the TBS-deprotection.

To simplify the system a carbamate with orthogonal protecting groups was envisioned. Therefore, the secondary alcohol *rac*-**214** was coupled with CDI and β-alanine methylester (**221**) to give *rac*-**224** in 67% yield (Scheme 82). This time the TBS-deprotection proceeded smoothly in a yield of 64% and subsequent DMP oxidation of the allylic alcohol *rac*-**225** gave the enone *rac*-**226** in 67% yield.



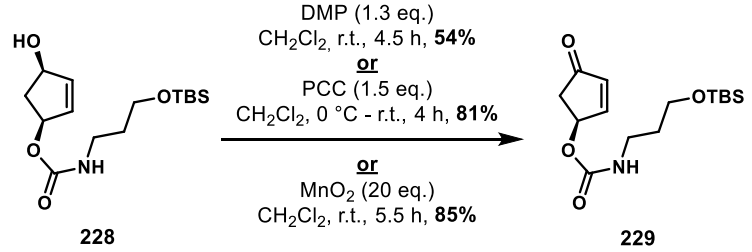
Scheme 82: Carbamate formation between alcohol *rac*-**214** and amine **221** using carbonyldiimidazole (CDI) followed by a TBS-deprotection and subsequent oxidation of the allylic alcohol *rac*-**225** to the corresponding enone *rac*-**226**.

With this procedure in mind, an alternative substrate with orthogonal protecting groups was also prepared (Scheme 83). Thus, the secondary alcohol **215** was converted to the carbamate **227** in 77% yield using CDI and the amine **220**. The acetate protecting group was then cleaved under standard conditions to form allylic alcohol **228**.



Scheme 83: Carbamate formation between alcohol **215** and amine **220** using carbonyl-diimidazole (CDI) followed by an acetate deprotection forming the secondary allylic alcohol **228**.

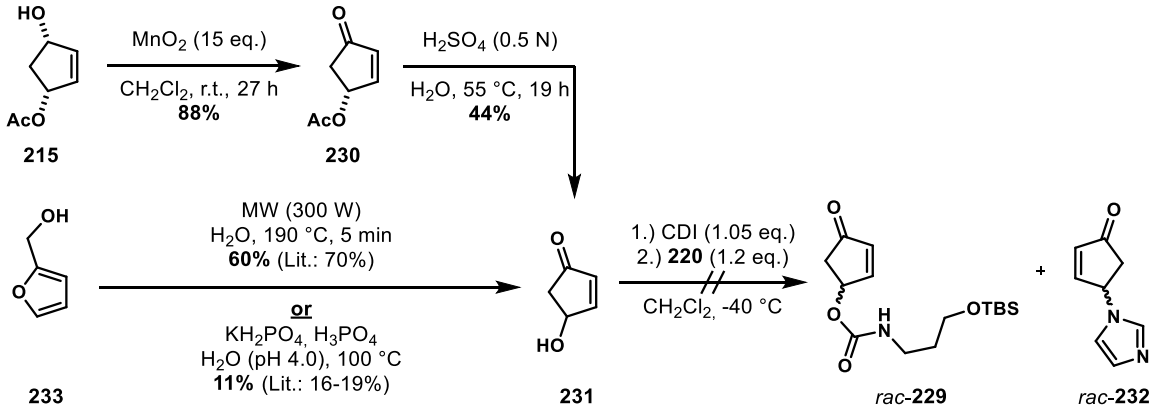
Subsequently, oxidation of the alcohol **228** to the corresponding enone **229** was tested employing three different oxidation agents (DMP, PCC and MnO_2) (Scheme 84). Especially the PCC and MnO_2 oxidations gave good yields and the operational simplicity of the MnO_2 oxidation method, which was marked by the easy workup procedure (simple filtration) and the formation of only few side products, were good reasons to employ it as the method of choice.



Scheme 84: Oxidation of the allylic alcohol **228** to the corresponding enone **229** using DMP, PCC and MnO_2 as oxidation agents.

For further investigation of the *aza*-Michael/Aldol sequence a shorter and more convergent synthesis of the enone building block **229** was desired. According to a procedure reported by Ulbrich *et al.* it was possible to synthesize *rac*-**231** from cheap and "green" furfurylalcohol in only one step in 60% yield (Scheme 85).[112] The reaction was carried out in a closed microwave reactor in only a few minutes. One drawback of this reaction is the necessity to work under a high dilution to obtain good yields, which makes it hard to perform this reaction on a larger scale. Nevertheless, according to a procedure reported by Watson *et al.* it was possible to perform the reaction at ambient pressure in higher concentration to prepare *rac*-4-hydroxyclyclopentenone (*rac*-**231**) on a larger scale, although suffering a decreased yield of 11%.[113] In the non-racemic series the allylic alcohol **215** was oxidized to the corresponding enone **230** in 88% yield. The acetate deprotection proved to be difficult due to side reactions, when employing basic reaction conditions like K_2CO_3 in MeOH, which only resulted in the substitution of the acetate group by a methoxy group. Employing acidic reaction conditions led to the formation of 4-hydroxycyclopentenone (**231**) in a moderate yield. The subsequent carbamate synthesis did not afford the desired carbamate, instead 4-imidazoyl-cyclopentenone (*rac*-**232**) was formed. It can be assumed, that an initial substitution of one imidazole in CDI by the secondary allylic alcohol *rac*-**231** forms the corresponding mono-imidazole carbamate. A subsequent attack of the released imidazole at the enone

moiety followed by elimination of the carbamate attached in β-position of the ketone would lead to the release of CO_2. This could be a serious driving force. Due to the observed instability of 4-substituted cyclopentenones (visible during the acetate deprotection of **230** and the carbamate formation of *rac*-**229**), this approach was not followed any further.



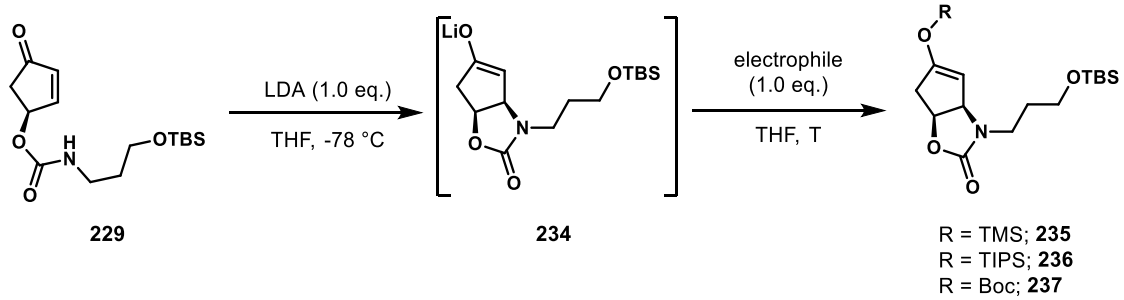
Scheme 85: Racemic one step synthesis of 4-hydroxycyclopentenone (*rac*-**231**) starting from furfurylalcohol or starting from **215** by allylic oxidation and acidic acetate deprotection in the enantioenriched series. Followed by attempts towards the CDI mediated formation of carbamate *rac*-**229**.

2.3.4.3. *Aza*-Michael/Aldol Reactions

With enone **229** in hand, the intramolecular *aza*-Michael reaction was tackled. Only the addition of one equivalent of LDA resulted in the formation of the desired enolate **234** (Scheme 86). Using weak bases, such as Et_3N, or Lewis acids, like $BF_3{\cdot}OEt_2$ or TMSOTf, led to decomposition of **229**. Nevertheless, it was not possible to isolate **234** in any case, because it decomposed rapidly during workup. It can be assumed, that the ketone, which forms after protonation and tautomerization, can undergo elimination of the carbamate in β-position. This way CO_2 would be generated driving the decomposition reaction. Nevertheless, the formation of enolate **234** was detected by TLC.

Instead of further isolation attempts, the direct protection of the enolate **234** was attempted. First, TMSOTf and TIPSOTf were tested as electrophiles (Table 15, entry 1 & 2). Both experiments exclusively led to decomposition of the product during workup, which may be caused by the Lewis acidity of both reagents. Therefore, Boc_2O was tested as a suitable electrophile and, indeed, it was possible to isolate the corresponding Boc-enol-carbonate **237** (Table 15, entry 3-5). When using DMAP as

catalyst, the reaction was finished relatively fast after only 45 min. In comparison the reaction without DMAP as nucleophilic catalyst takes 19 h until completion, but the yields are similar in both cases. To prevent decomposition of the enolate intermediate **234** an *in-situ* quench approach was tested by addition of Boc_2O to a cooled solution of **229** followed by the addition of LDA to start the *aza*-Michael reaction. This did result in a lower yield of **237** and further attempts into this direction were discarded.



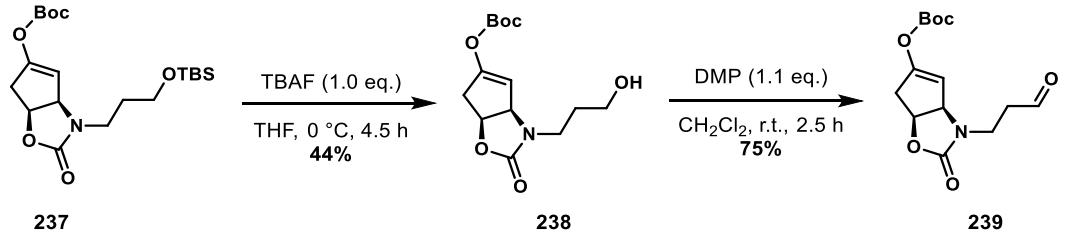
Scheme 86: Intramolecular *aza*-Michael reaction followed by trapping of the resulting enolate.

Table 15: Selected results for reaction conditions regarding the enolate trapping shown in Scheme 86.

entry	electrophile	T [°C]	t [h]	results
1	TMSOTf	-78	30 min	no conv.
		0	30 min	decomp. during workup
2	TIPSOTf	-78	45 min	decomp. during workup
3[a]	Boc_2O	-78 – r.t.	40 min	38%
4	Boc_2O	-78 – r.t.	19	41%
5[c]	Boc_2O	-78	2	12%

[a] DMAP was added to the reaction mixture. [b] Boc_2O was added to **728** before addition of LDA.

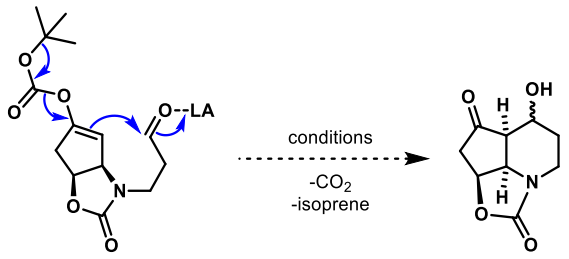
With the Boc-protected enol-carbonate **237** in hand the TBS-group was removed upon addition of TBAF resulting in the formation of the primary alcohol **238** in a moderate yield. A subsequent DMP oxidation of the primary alcohol afforded the desired aldehyde **239** in 75% yield.



Scheme 87: TBS-deprotection of **237** followed by the oxidation of the primary alcohol **238** to the corresponding aldehyde **239** using DMP.

To achieve the intramolecular cyclization of the aldehyde with the Boc-enolcarbonate moiety in an aldol-type reaction was envisioned, by activation of the aldehyde with a Lewis acid. This should induce the intramolecular attack of the trapped enol-carbonate on the aldehyde under cleavage of the Boc-protecting group and release of isobutene and CO_2, which could be a driving force both in terms of entropy and in shifting the Aldol equilibrium to the product side.

First, $ZnCl_2$ was evaluated as a relatively mild Lewis acid (Table 16, entry 1). This did only result in the slow decomposition of **239**. Employing stronger Lewis acids such as TIPSOTf and $TiCl_4$ (Table 16, entry 2+3) resulted in an even faster decomposition of **239**. Using Lewis acids in this context may be a problem, because with the carbonate and carbamate moieties two relatively strong Lewis basic moieties are present in the molecule. This could lead to a desactivation and trapping of the Lewis acids as well as to the desactivation of the enol-carbonate by lowering its electron density. A last attempt was started by the addition of HCl as a Brønsted acid (Table 16, entry 4). In this reaction one mayor product besides a few side products was observed by TLC. Nevertheless, upon workup the formed product decomposed and could not be identified. In conclusion, neither Lewis nor Brønsted acids led to the formation of the desired aldol product. The main reason for this may be the relatively strong Lewis basicity of the carbamate and carbonate moieties present in the molecule.



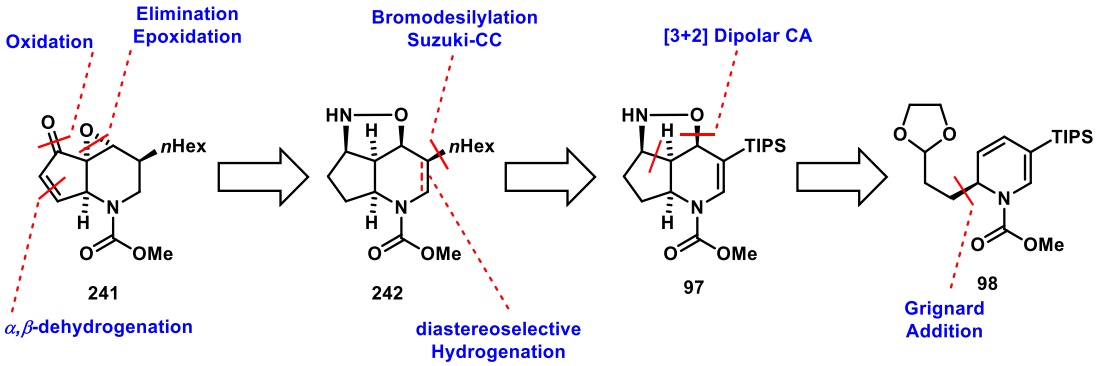
Scheme 88: Attempted intramolecular Aldol-type reaction approach.

Table 16: Reaction conditions and selected results from the attempted intramolecular aldol type reaction described in Scheme 88.

entry	additive	solvent	T [°C]	t [h]	results
1	$ZnCl_2$	THF	0 – reflux	25	slow decomp.
2	TIPSOTf	THF	0 – r.t.	1	decomp.
3	$TiCl_4$	CH_2Cl_2	-78 – 0	4	decomp.
4	HCl	THF	0 – reflux	6	decomp. during workup

2.3.5. 1,3-Dipolar Cycloaddition Approach

2.3.5.1. Conception



Scheme 89: Retrosynthetic analysis of the construction of the central tricyclic core motif of camporidine A (**7**).

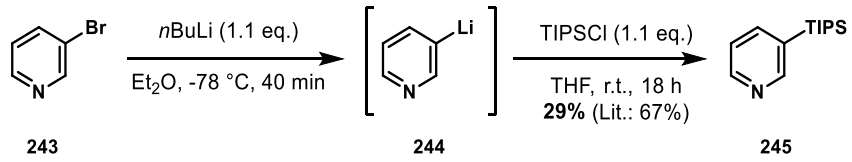
Inspired by the total synthesis of Park *et al*. the last synthetic approach towards camporidine A (**7**), discussed in this work, should be based on the construction of the core structure by a [3+2] dipolar cycloaddition (Scheme 89). The acetal **98** should be transformed into a suitable oxime or nitrile oxide to prepare for the 1,3-dipolar cycloaddition. In subsequent reactions the TIPS group should be exchanged by a halide and a cross-coupling reaction should be used to introduce the hexyl sidechain followed by a diastereoselective hydrogenation of the enamine double bond to introduce the missing stereocenter. Further functional group interconversions should then lead to camporidine A (**7**).

2.3.5.2. Forward Synthesis

The alkylation of substituted and unsubstituted pyridine derivatives has been extensively described by Comins *et al.* in a series of publications.[28,30,31] The preferred regioselectivity of alkyl Grignard reagents on substituted and unsubstituted *N*-acyl pyridinium species are as followed: a) Unsubstituted pyridinium species are preferentially attacked in 4-position.[28] b) Pyridinium species bearing a bromine or methyl group in 3-position result in the formation of product mixtures of 2-, 3- and 6-substituted dihydropyridines. The selectivity is dependent on the sterical demand of the nucleophile.[30] c) The use of a catalytic amount of a Cu(I) source shifts the selectivity towards the formation of the 4-substituted dihydropyridine derivative. d)

Introducing bulky substituents such as TIPS or $SnBu_3$ in the 3-position leads to the formation of 6-addition products.[30,31]

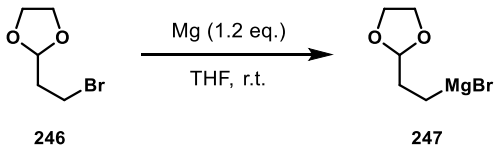
Therefore, the 3-TIPS pyridine **245** was prepared according to a procedure described by Wanner *et al*., by the treatment of 3-bromopyridine (**243**) with *n*BuLi to induce a bromine-lithium exchange followed by the nucleophilic attack of the lithiated species **244** on TIPS-Cl (Scheme 90). The 3-TIPS pyridine (**245**) was isolated in a yield of 29%.[114] To optimize the reaction and to avoid undesired side reactions, an *in-situ* quench approach was tested, in which first the 3-bromo pyridine (**243**) and TIPS-Cl were combined followed by the addition of *n*BuLi. It is known that halogen-lithium exchanges take place rapidly in comparison to the nucleophilic attack of Grignard reagents. Therefore, the bromine-lithium exchange was expected to be faster than the competing direct attack of *n*BuLi on TIPS-Cl. Unfortunately, a similar yield of 26% was obtained, which shows neither an improvement nor a deterioration to the standard conditions employed in the beginning.



243 244 245

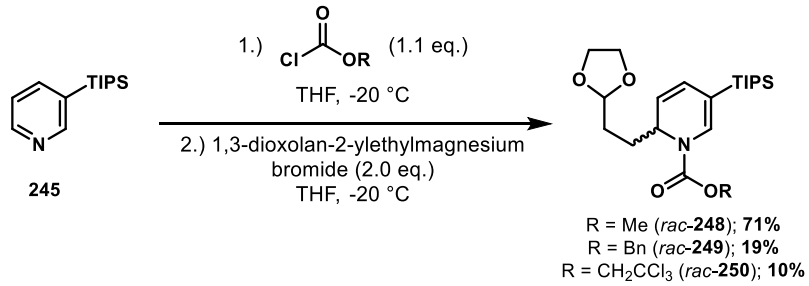
Scheme 90: Silylation of 3-bromopyridine (**243**) by bromine-lithium exchange followed by trapping with TIPSCl.according to Wanner *et al.*[114]

The second building block for the functionalization of 3-TIPS pyridine (**245**) is the Grignard reagent **247** (Scheme 91). This reagent must be prepared freshly right before use, as the concentration of the reagent decreases drastically over time. Although this reagent has been described well in the literature[115,116], we experienced mayor side reactions, such as the substitution reaction of the Grignard with the corresponding alkylbromide **246**. From a screening of reaction conditions some conclusions could be drawn: a) THF is the superior solvent in comparison to Et_2O. b) Temperatures below r.t. lead to a very slow and incomplete Grignard formation. c) Warming the reaction to reflux leads to full conversions, but as well to low concentrations of the Grignard reagent. d) At r.t. concentrations of up to 0.25 M could be reached although 0.50 M would have been the maximal concentration.[117]



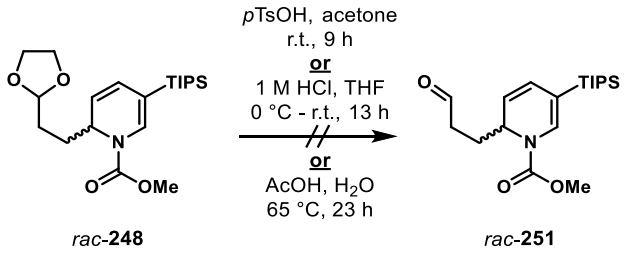
Scheme 91: Formation of the Grignard reagent **247**.

The Grignard addition of **247** to form the corresponding 6-substituted 3-TIPS-*N*-acyl pyridines *rac*-**248**-**250** was performed with three different substituents at the carbamate (Scheme 92). Each carbamate can be cleaved easily in the upcoming reaction sequence, but only the introduction of a methyl carbamate resulted in a satisfying yield of 71%.



Scheme 92: Pyridinium salt formation followed by the attack of Grignard reagent **247** in 6-position.

To synthesize the desired oxime, the acetal deprotection of *rac*-**248** was investigated. Three standard conditions were examined including the use of *p*TsOH in acetone, 1 M HCl in THF and the very mild reaction conditions of acetic acid in water (Scheme 93). All these reaction conditions led to the full conversion of the acetal *rac*-**248**, but in neither of the cases any of the desired product *rac*-**251** was isolated nor detected.

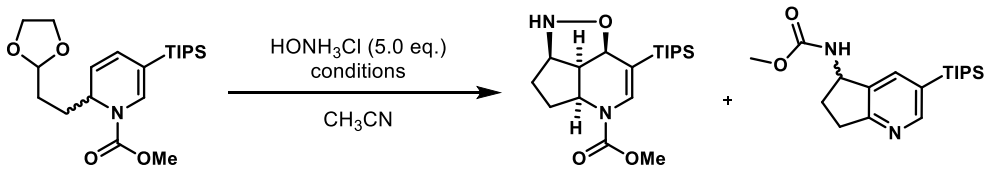


Scheme 93: Attempted acetal deprotection under acidic standard conditions.

Although the deprotection of the acetal did not work under acidic conditions we aimed for an *in-situ* acetal deprotection followed by the trapping of the aldehyde by hydroxylamine in form of an oxime. Upon a first try with H_2SO_4 as additive, we were

surprised to directly observe the formation of the 1,3-dipolar cycloaddition product *rac*-**252** resulting from the oxime we intended to synthesize. Besides this cycloaddition product, the aromatic side product *rac*-**253** was formed as well, but both yields were relatively low (Table 17, entry 1). Although the similarities of *rac*-**252** and *rac*-**253** are minor, *rac*-**253** seems to be a decomposition product of *rac*-**252**. To verify this, some of *rac*-**252** was heated under the reaction conditions previously already employed and the formation of the side product *rac*-**253** was indeed observed. The aromatization of the tetrahydropyridine core structure towards the pyridine seems to be the main driving force behind this reaction.

To get a better understanding of the reaction, a short screening of the reaction conditions was performed. As expected, increasing the amount of H_2SO_4 did exclusively lead to a faster decomposition of the acetal *rac*-**248** and was not evaluated any further. Addition of sodium acetate as a mild base to neutralize the acidity of hydroxylamine hydrochloride, inhibited the cleavage of the acetal (Table 17, entry 2), which seems to be the consequence from the necessity to have mildly acidic reaction conditions to perform the acetal cleavage. Under microwave irradiation very short reaction times, such as 5 min, still with full conversion and increased yields could be realized without the addition of acids or bases (Table 17, entry 3). Nevertheless, the ratio of *rac*-**252** to *rac*-**253** was still unsatisfactory. Lowering the reaction time even further did only slightly increase the ratio towards *rac*-**252** (Table 17, entry 4), while decreasing the concentration resulted in a ratio of *rac*-**252** to *rac*-**253** of 3:1 (Table 17, entry 5). Due to the low concentration an upscaling of the reaction was not possible in the microwave, so the optimized reaction conditions were transferred to the reaction in a flask and it was possible to obtain the desired product *rac*-**252** in 41% yield (Table 17, entry 6).



rac-**248** *rac*-**252** *rac*-**253**

Scheme 94: One-pot acetal deprotection, oxime formation and intramolecular 1,3-dipolar cycloaddition to form *rac*-**252**.

Table 17: Selected results from the screening of the reaction conditions of the 1,3-dipolar cycloaddition described in Scheme 94.

entry	additive	conc.	T [°C]	t [h]	result[c]
1	H_2SO_4 (0.5 eq.)	0.083 M	70	1.75	**15%** *rac*-**252** **19%** *rac*-**253**
2	NaOAc (2.5 eq.)	0.083 M	70	67	no conv.
3	/	0.083 M	100[a]	5 min	**25%** *rac*-**252** **28%** *rac*-**253**
4	/	0.083 M	100[a]	1 min	**1.2:1**[b] (*rac*-**252**: *rac*-**253**)
5	/	0.010 M	100[a]	5 min	**3:1**[b] (*rac*-**252**: *rac*-**253**)
6	/	0.010 M	reflux	1.5	**41%** *rac*-**252**

[a] The reaction was performed under microwave irradiation with 300 W. [b] The ratio was determined by crude NMR. [c] Yields are given as isolated yields.

It was possible to obtain a crystal structure of both the desired product *rac*-**252** and the undesired sideproduct *rac*-**253**. The crystal structure of *rac*-**252** confirmed that the intramolecular 1,3-dipolar cycloaddition reaction indeed happens in a diastereoselective fashion resulting in a total of 4 bridgehead stereocenters. The hydrogen atoms of all these bridgeheads point into the same direction forming a basket-like tricyclic structure.

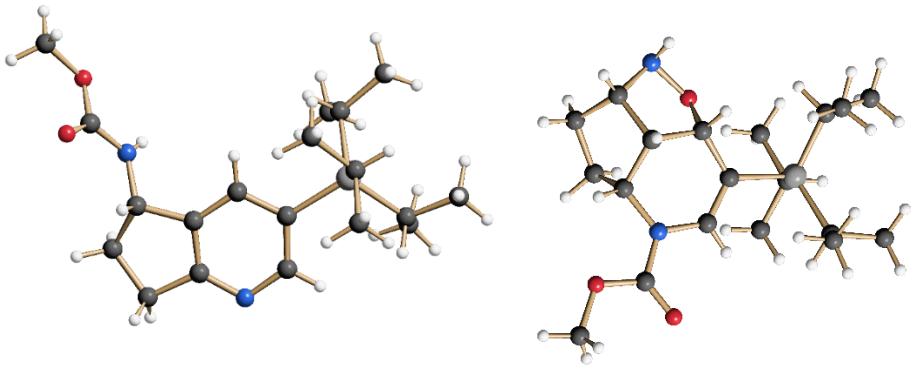
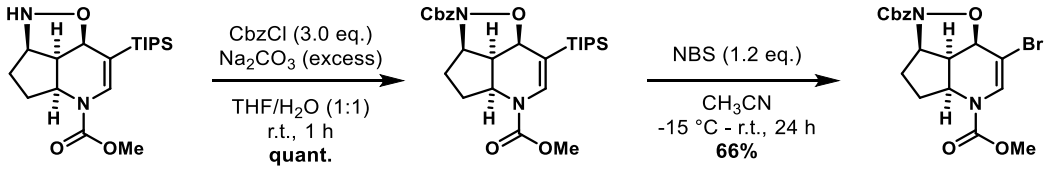


Figure 6: Left: Crystal structure of *rac*-**253**. Right: Crystal structure of *rac*-**252**.

Next, the bromodesilylation of the TIPS-enamine *rac*-**252** was tackled. Direct bromination of *rac*-**252** was not successful, due to decomposition of the starting material. The main problem during this reaction was identified to be the unprotected

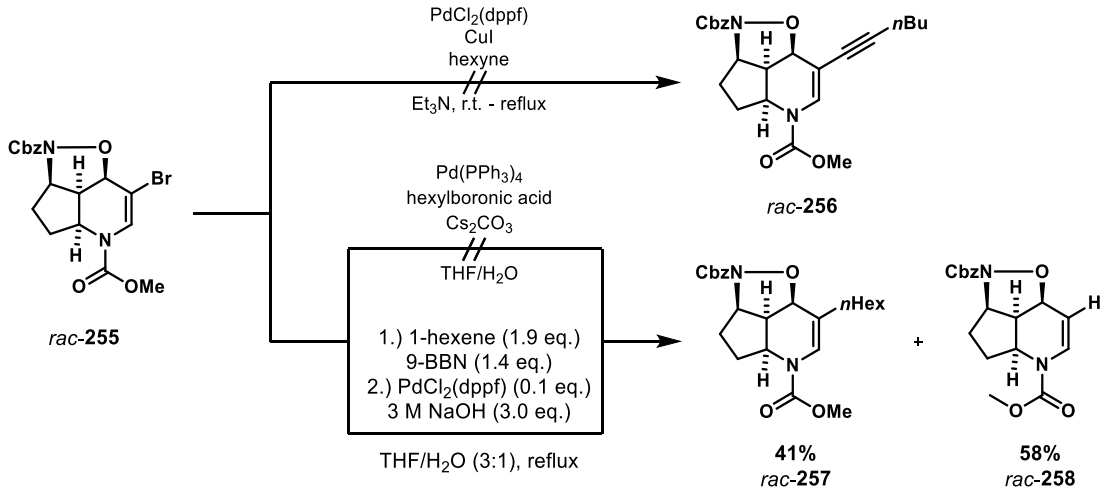
amine, which undergoes undesired side reactions with NBS. Therefore, first a Cbz-protection under standard conditions was performed in a quantitative yield (Scheme 95). This product was reacted with NBS to obtain the vinyl bromide *rac*-**255** in 66% yield. During the reaction it was important to first react *rac*-**254** with NBS at -15 °C until full conversion of the starting material was observed by TLC. Only then slow warming to r.t. led to the formation of the desired vinyl bromide *rac*-**255**. The intermediate formed in the first place may be the iminium species resulting from the nucleophilic attack of *rac*-**254** on NBS, which was followed by the elimination of the TIPS-cation to generate *rac*-**255**.



rac-**252** *rac*-**254** *rac*-**255**

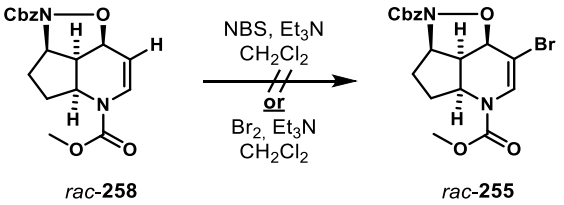
Scheme 95: Cbz-protection of the secondary amine *rac*-**252** followed by bromodesilylation.

To introduce the *n*hexyl sidechain, vinylbromide *rac*-**255** was investigated in the context of cross coupling reactions. First a Sonogashira reaction of the vinylbromide *rac*-**255** with hexyne was tested, which only led to the decomposition of the starting material the formation of the homocoupling product of hexyne (Scheme 96). Next, two different Suzuki reactions were investigated. Using hexylboronic acid as the coupling partner with simple $Pd(PPh_3)_4$ as catalyst did only form the debrominated product *rac*-**258**. This reaction product may result from a β-hydrogen elimination of the hexylsidechain attached to the palladium catalyst after transmetallation prior to the reductive elimination. The hydrogen bound to the palladium species could in this case undergo reductive elimination to form *rac*-**258**. A short screening of Suzuki reaction conditions was performed in which *in-situ* prepared *n*hexyl-9BBN has proven to be the best hexylboron species in combination with $PdCl_2$(dppf). This way it was possible to reach quantitative conversion, although *rac*-**257** could only be isolated in 41% yield and further optimization should be performed at this stage. Especially vinylboronates or other Sonogashira cross coupling conditions should be tested.



Scheme 96: Attempts towards cross coupling reactions using the vinyl bromide *rac*-**255**.

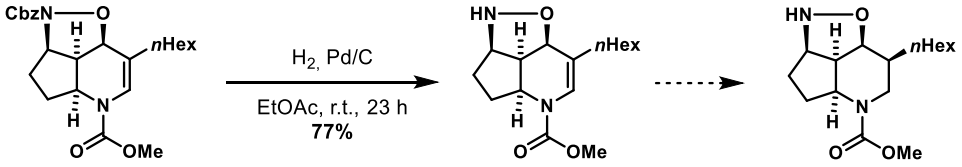
To save some of the material, lost as the undesired sideproduct *rac*-**258**, the bromination of *rac*-**258** was investigated (Scheme 97). Like during the bromodesilylation approach, first NBS in combination with Et_3N was evaluated. This did unfortunately only result in decomposition of the starting material. Directly using bromine as the electrophile in combination with Et_3N as a mild base did not result in the regeneration of the desired vinylbromide *rac*-**255**.



Scheme 97: Bromination attempts of *rac*-**258** to regenerate *rac*-**255**.

With *rac*-**257** in hand the diastereoselective hydrogenation of the enamine double bond was tackled (Scheme 98). The diastereoselectivity of this reaction should be ensured by the basket-like conformation of the tricyclic core-structure. This way the hydrogenation was expected to exclusively occur from the lower face of the molecule. Under standard hydrogenation conditions employing Pd/C as the catalyst with hydrogen at ambient pressure a clean conversion of *rac*-**257** to the corresponding Cbz-deprotected derivative *rac*-**259** was observed. Unfortunately, no sign of enamine hydrogenation was visible and neither increasing the hydrogen pressure to 10 bar nor using PtO_2 as the catalyst resulted in the hydrogenation of the enamine double bond.

Due to time constraints no further experiments were performed, but the hydrogenation of the enamine double bond would be the next hurdle pending.

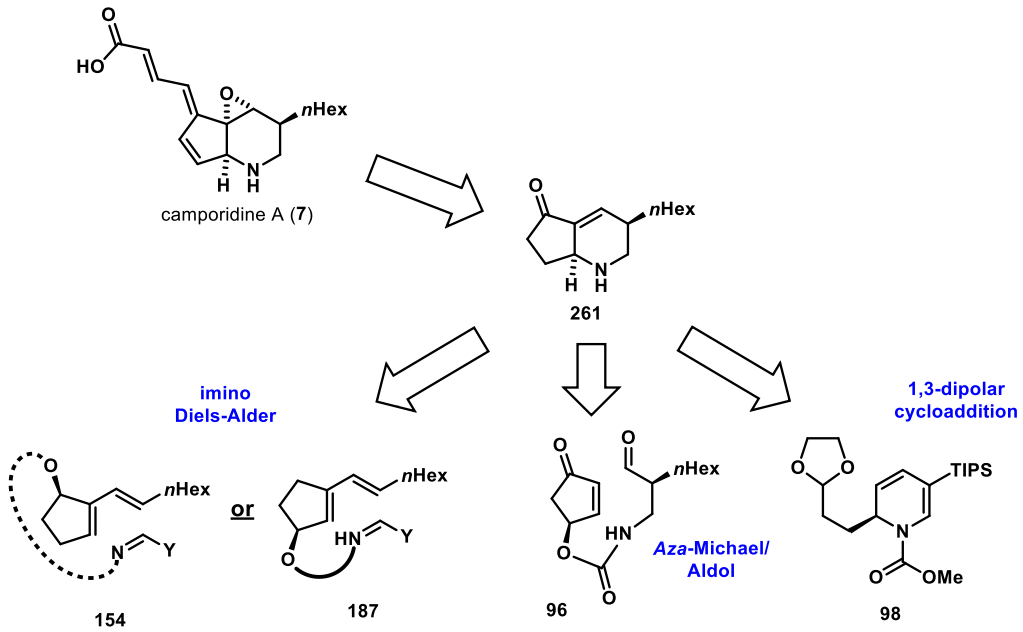


rac-**257** *rac*-**259** *rac*-**260**

Scheme 98: Cbz-deprotection of *rac*-**257** without the hydrogenation of the enamine double bond.

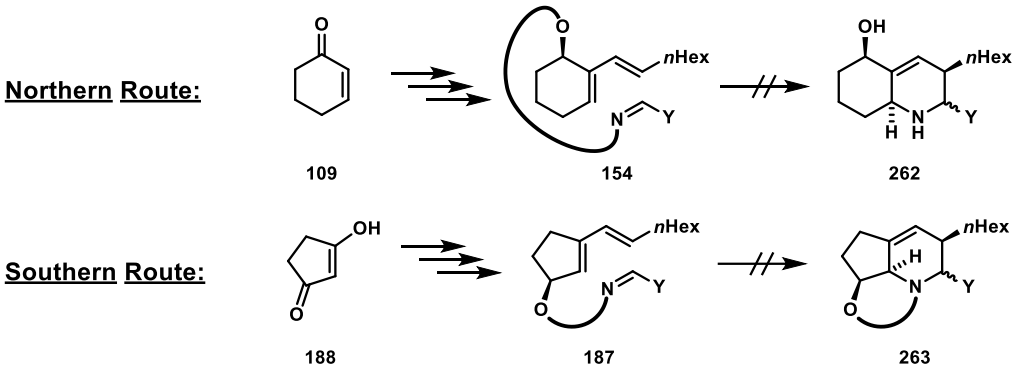
2.4. Summary

This part of the thesis concerns the early evaluation of synthetic strategies towards the recently discovered natural product camporidine A (**7**), which is of interest due to its pronounced anti-metastatic activity.[4] Three conceptionally different strategies were considered and sketched in Scheme 99, including: 1.) an imino Diels-Alder reaction, 2.) an *aza*-Michael/aldol sequence and 3.) an intramolecular [2+3] cycloaddition.



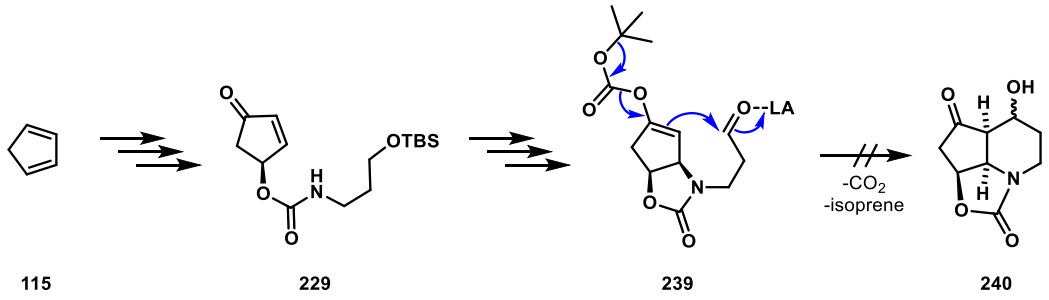
Scheme 99: Overview about the three conceptionally different strategies towards the construction of camporidine A (**7**).

At first, a series of different dienes of type **154** and **187** were synthesized, using a Suzuki cross coupling as key step. However, the planned imino Diels-Alder cycloaddition could not be realized, neither inter- nor intramolecularly (Scheme 100). A variety of conditions, including the variation of the linker, of the imino dienophile and the use of Lewis and Brønsted acids as activators, were investigated.



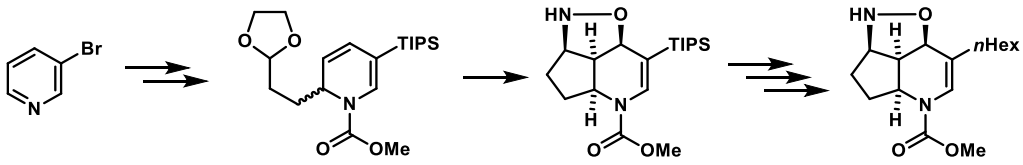
Scheme 100: Northern and southern intramolecular imino Diels-Alder approach.

To investigate the second strategy, namely the *aza*-Michael/aldol approach, a series of different 4-carbamate substituted cyclopentenones were synthesized in an enantioselective fashion (Scheme 101). The carbamate **229** was successfully converted to the enol-carbonate **239** in an intramolecular *aza*-Michael addition. However, the Boc-enol-carbonate **237** did not undergo the projected Aldol-cyclization under a variety of conditions.



Scheme 101: *Aza*-Michael/aldol approach towards the synthesis of the camporidine A core structure.

In the third approach, finally a short access to the camporidine A core structure was established using an intramolecular 1,3-dipolar cycloaddition (Scheme 102). The required precursor *rac*-**98** was prepared by means of a Grignard addition to an *N*-acyl pyridinium species, easily derived from 3-bromo pyridine **243**. Notably, the preparation of *rac*-**97**, already displaying the structural core of camporidine A (**7**), was achieved in only three steps. The hexyl-sidechain was successfully introduced by a bromodesilylation/Suzuki cross coupling sequence. Only the hydrogenation of the enamine double bond is pending to reach a core structure, at which this route can be merged with a different approach independently established by Alicia Köcher.

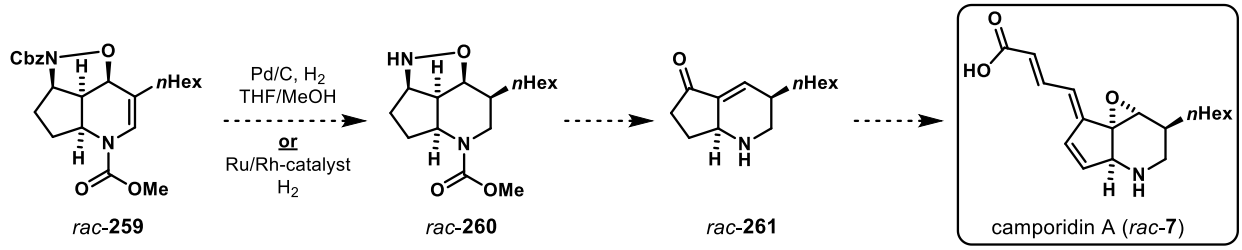


243 *rac*-**98** *rac*-**97** *rac*-**259**

Scheme 102: Intramolecular 1,3-dipolar cycloaddition approach towards the synthesis of the camporidine A core structure.

2.5. Outlook

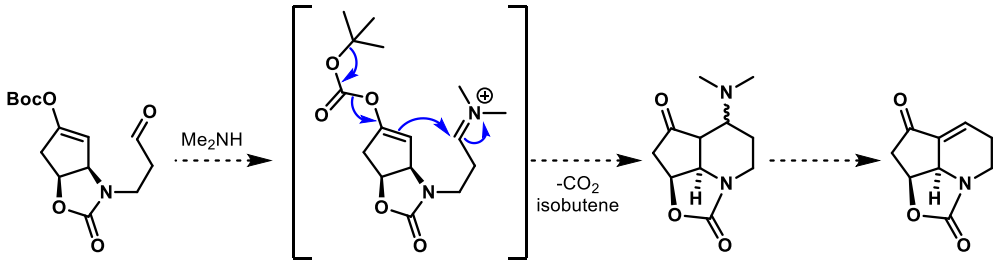
The successful realization of the 1,3-dipolar cycloaddition approach to prepare compound *rac*-**259** represents a major breakthrough for this project. Next, the hydrogenation of enamine **259** should be tackled in orientation to the procedures described in literature (Scheme 103). Especially, the solvent seems to have a huge impact on the success of the reaction.[118-120] Besides the variation of the solvent, other hydrogenation catalysts based on ruthenium or rhodium, such as the Noyori-catalyst, could be employed.[121]



rac-**259** *rac*-**260** *rac*-**261**

Scheme 103: Possible approaches towards the hydrogenation of enamine *rac*-**259** to carbamate *rac*-**260** and final route towards the synthesis of the natural product camporidine A (**7**).

Even though the first two strategies were identified as difficult to realize, there are still ideas for the *aza*-Michael/Aldol route, that could not be explored within the scope of this work. In addition to screening further catalysts for the Aldol condensation, there would also be the possibility of exploiting a Mannich-like reaction to realize the ring closure (Scheme 104).



239 **264** **265** **266**

Scheme 104: Formation of the corresponding dimethyl iminium ion from **239** to induce an intramolecular aldol addition under the release of CO_2 and isoprene to form **265** followed by the elimination of the dimethylamine to generate enone **266**.

3. Part 2: Synthesis of 7,19-Epoxysteroids

3.1. State of the Art

3.1.1. Steroid Nomenclature

Steroids resemble a physiologically important and immensely variable class of natural products, counting to the class of terpene-derived lipids. All steroids have the tetracyclic sterane core motif **267** in common (Figure 7). The sterane core can sequentially be expanded by the addition of further alkyl groups, leading to a more precise definition of steroid subclasses like the estranes (**267**), androstanes (**269**), pregnanes (**270**), cholanes (**271**), cholestanes (**272**), ergostanes (**273**) and stigmastanes (**274**). Steroid derivatives do as well have the same nomenclature in common. As shown for the sterane core motif **267,** the first six membered ring on the left is defined as the A-ring, the next one as the B-ring etc. Substituents pointing to the lower face of the plane of the steroid, which is defined as the side opposite to the 18- and 19-methyl groups, are called α-standing substituents, whereas substituents on the same face as the methyl groups are in the so-called β-position.[122]

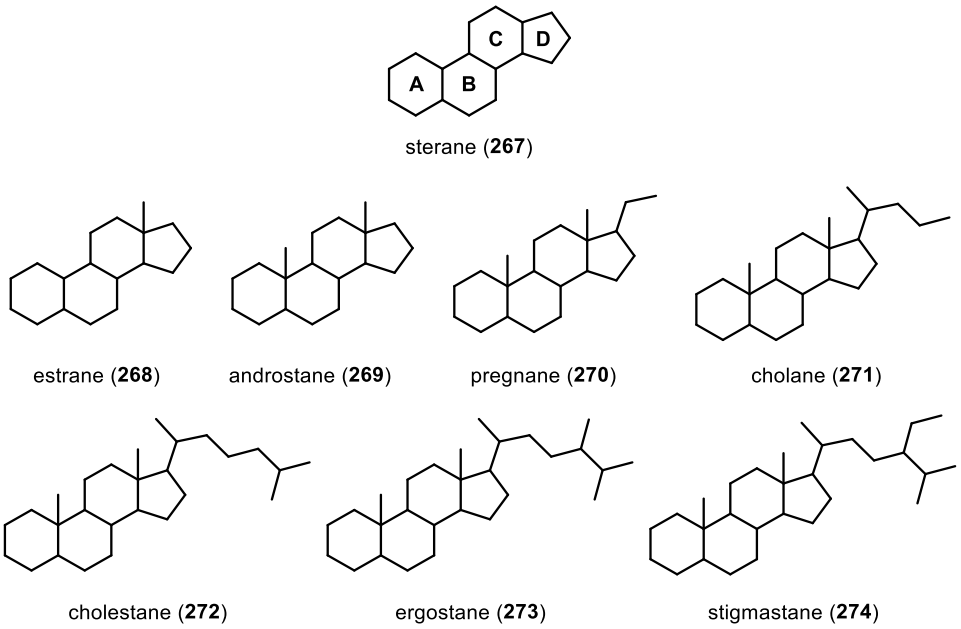
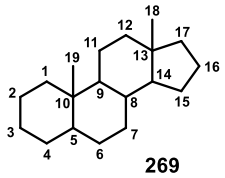


Figure 7: Core skeletons of common steroid classes.

The atoms are numbered, as shown for **269**, starting at the upper corner of the A-ring, following the A-ring, over the B- and C-ring to the D-ring (Figure 8). Finally, the

two methyl groups are defined as C18 and C19.[122] This nomenclature is valid for all the steroid subclasses.



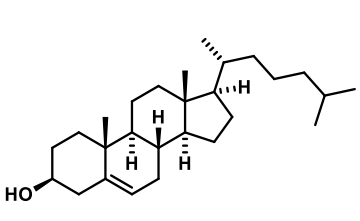
269

Figure 8: Androstane core motif with numbered carbon atoms.

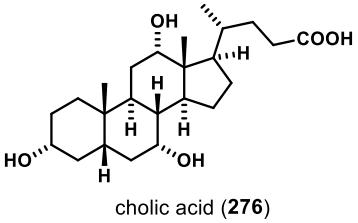
3.1.2. Important Steroids in Nature

Steroids resemble an essential class of natural products occurring in diverse biological contexts. One remarkable feature is their wide field of biological function, which ranges from the stabilization of cell walls (cholesterol (**275**), etc.) over the activity as sexual hormones (testosterone (**282**), estradiol (**280**), etc.) to highly effective toxins (digitoxigenin (**286**)). Although all these compounds exhibit completely different biological activities, they share the same core motif with only minor structural deviations from each other.

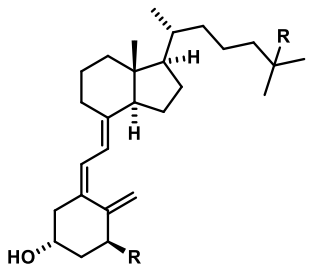
The steroid cholesterol (**275**) is one great example for the importance and versatility of steroids. It is an essential part of every cell wall and as one of the most abundant steroids it plays a crucial role in the biosynthesis of almost all other steroids like bile acids, steroid hormones or vitamin D_3.[122] Chemists discovered cholesterol (**275**) already in the late 17th and early 18th centuries from gallstones in a crystalline form.[123] The so-called bile acids are formed in the bile of mammals and help to digest especially lipophilic parts of the food. They normally act as surfactants and therefore ease the absorption of lipophilic nutrients. Cholic acid (**276**) is one of the prominent representatives of the bile acids. In many cases the characteristic 24-carboxylic acid moiety forms the corresponding amides with glycine or taurine. [122]



cholesterol (**275**)



cholic acid (**276**)



R = H; cholecalciferol (vitamine D_3, **277**)
R = OH; calcitriol (**278**)

Figure 9: Chemical structure of the important steroids cholesterol (**275**), cholic acid (**276**), cholecalciferol (**277**) and calcitriol (**278**).

Besides these abundant steroids, another class of steroids are the hormonally active steroids. Compounds like vitamin D_3 (**277**), estradiol (**280**), estrone (**279**), testosterone (**282**), androsterone (**281**) and progesterone (**283**) belong to this class of steroids. Vitamin D_3 (**277**) plays a crucial role in calcium metabolism as a prohormone for calcitriol (**278**). It can be synthesized in the skin under UV-B irradiation.

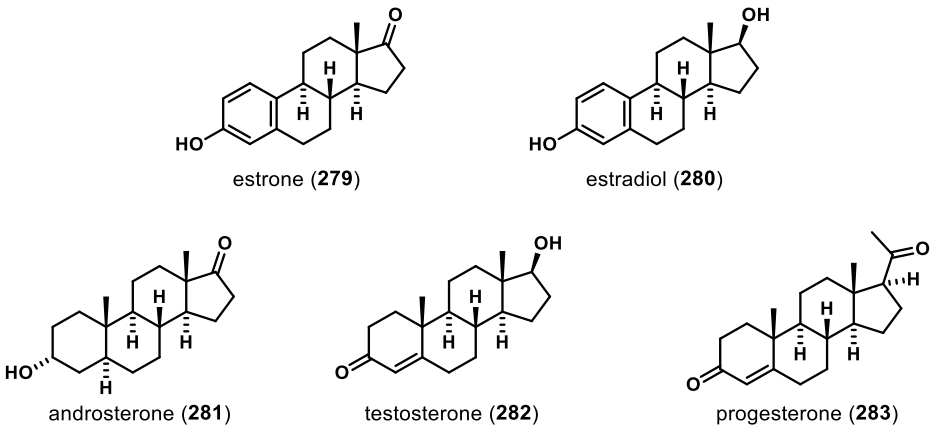


Figure 10: Chemical structure of important sexual steroid hormones.

The other steroid hormones can be further categorized as gestagens, glucocorticoids, mineralocorticoids, androgens and oestrogens. The gestagens, like progesterone (**283**), prepare the female uterus for the implantation of the fertilized ovum and continues to play an important role during the pregnancy. Androgens, like testosterone (**282**) and androsterone (**281**), are the male sexual hormones and are responsible for the expression of secondary male sexual characteristics. In contrast, the female sexual hormones, like estrone (**279**) and estradiol (**280**), belong to the class of estrogens and are responsible for the expression of female secondary sexual characteristics. Both, the androgens and estrogens, occur in varying amounts in the male as well as female bodies and take over important tasks as signalling molecules.[122]

The last two classes of cholesterol-derived steroid hormones are the glucocorticoids, like cortisol (**285**), and the mineralocorticoids, like aldosterone (**284**). Both compounds are structurally similar but exhibit completely different biological effects. The glucocorticoids are known to support gluconeogenesis and fat degradation,

whereas the mineral corticoids are responsible for inducing the resorption of sodium and the excretion of potassium from the kidney.[122]

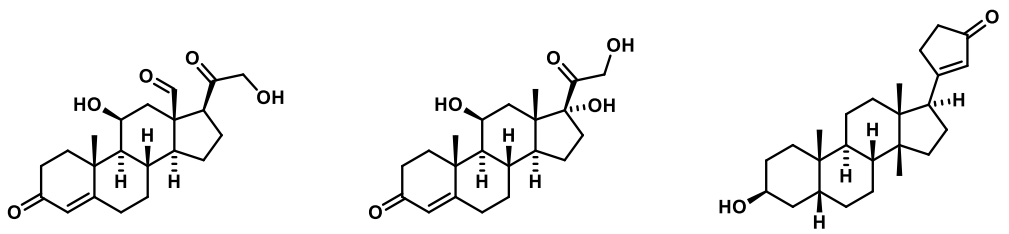


Figure 11: Chemical structure of aldosterone (**284**) and cortisol (**285**) as important representatives of the glucocorticoids and mineralocorticoids as well as digitoxigenin (**286**) as a famous steroid based toxin.

Besides these hormone-active classes of steroids other highly effective steroids are known. Steroids like digitoxigenin (**286**) are found in the foxglove (*digitalis purpurea*) and are very potent heart-active steroids, acting by inhibition of the Na^+-K^+ pump. Depending on the dosage, it can be a very toxic compound leading to a fast death or, if applied carefully on a low dosage, it can be used to treat congestive heart failure. It was already used in this context at the end of the 18th century by William Withering.[122]

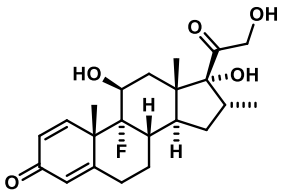


Figure 12: Chemical structure of dexamethasone (**287**), a synthetic cytostatic agent.

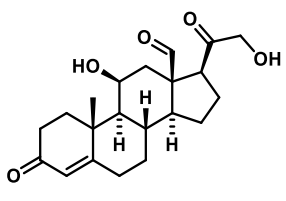
For the treatment of various diseases, a broad variety of synthetic steroids were synthesized. These synthetic steroids often overcome natural steroids both in effectiveness and selectivity. Dexamethasone (**287**) is a good example of a synthetic steroid, which has a strong glucocorticoid effect, about 25 times stronger than the effect of natural cortisol (**285**), without the mineral corticoid effects of most natural glucocorticoids.[124] Other important synthetic steroids are the synthetic contraceptives mainly developed by C. Djerassi and G. Pincus. These steroid-based oral contraceptives are among the most prescribed drugs in many western countries and have changed the lifestyle of many women around the world.[125] This short overview

about a small number of important steroids emphasizes the huge impact steroid derivatives have in a biological context.

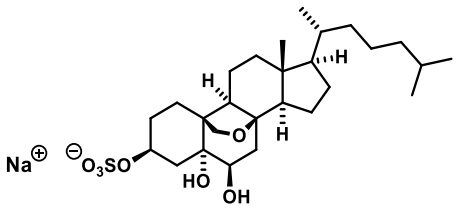
3.1.3. Synthesis of C18/19 Functionalized Steroids

In nature, specialized enzymes like cytochrome P450 are capable of performing highly selective oxidation reactions at unfunctionalized positions in steroids and do therefore play an important role in steroid biosynthesis and metabolism.[126]

Common naturally occurring steroids with a C-18 or C-19 functionalized core structure are for example aldosterone (**284**), with an 18-aldehyde functionality, and eurysterol A with an 8β,19-epoxy moiety.[127] Although the introduction of such functionalities is common in a biological, enzyme-mediated context, addressing non-activated positions in the steroid skeleton represents a challenging task for chemists. The first, who solved this problem was Barton and his working group.



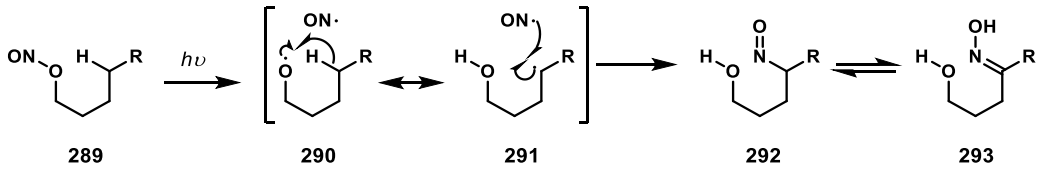
aldosterone (**284**)



eurysterol A (**288**)

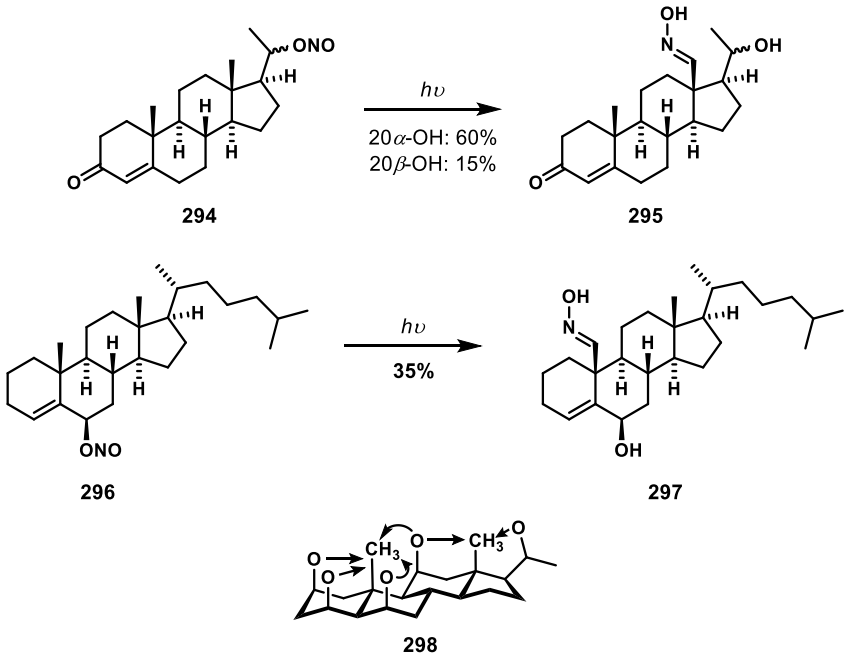
Figure 13: Chemical structure of aldosterone (**284**) and eurysterol A (**288**) as examples for C18 and C19 functionalized natural steroids.

Barton *et al*. were able to introduce 11β- and 20-nitrite esters, which were able, upon a photochemical degradation reaction, to attack the 18-methyl group in a radical fashion and to introduce an oxime at the C18-methyl group, which can be further derivatized. The initial photolytic cleavage of the nitrite ester (**289**) forms the corresponding *oxy*-radical (**290**) (Scheme 105). The *oxy*-radical abstracts a hydrogen from a hydrocarbon in close proximity and a subsequent radical recombination with the nitrosyl radical leads to the formation of the corresponding nitroso compound, which undergoes a subsequent tautomerization to the oxime (**293**). Barton was awarded the Nobel Prize in 1969 for this reaction in combination with his work on understanding conformations of organic molecules with steroids as prominent examples.[128,129]



Scheme 105: Mechanism of the remote functionalization by Barton *et al.*[128,129]

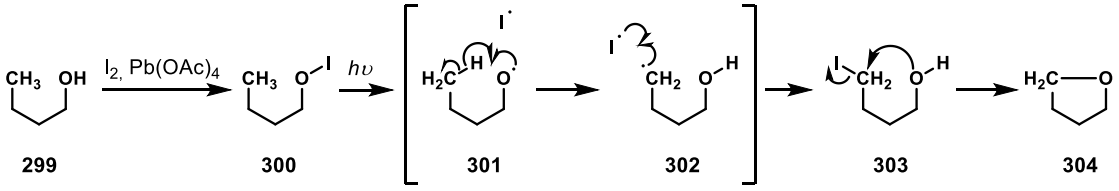
In general, a close proximity between the *in situ* generated alkoxy radical and the position that should be addressed, is necessary. This means that for steroidal systems in the first place, only 1,3-diaxial alkoxyradicals with regards to the axial methyl group can be utilized for such kinds of remote functionalizations (Scheme 106).[130]



Scheme 106: Remote-functionalization of the C-18 and C-19 methyl group according to Barton *et al.*[128,131] and potential axial *oxy*-radical positions, which are able to induce a remote functionalization of the C-18 and C-19 methyl groups.

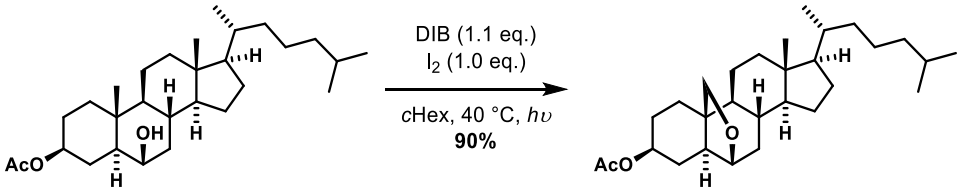
An alternative to performing a remote functionalization of this kind, is the hypoiodide reaction, which was introduced by Jeger shortly after the first reports of Barton. This procedure was directly used in the partial synthesis of aldosterone by Wettstein *et al.*[132,133] But the development of the reaction was mainly driven forward by Heusler and Kalvoda by the irradiation of different angular hydroxy groups of type **299** in the presence of $Pb(OAc)_4$ and iodine. In such cases, a hypoiodite intermediate of type **300** is formed, which is subsequently cleaved in a homolytic fashion to the

corresponding alkoxy and iodine radical of type **301**. The alkoxy radical undergoes an analogous intramolecular radical reaction like that already shown by Barton, forming a methyl radical of type **302** followed by a subsequent recombination with the iodine radical. The formed methyl iodide of type **303** can now undergo further reactions like S_N2-type substitution with the axial alcohol by forming the corresponding ether **304**.[134]



Scheme 107: Mechanism of the hypoiodite mediated remote functionalization by according to Pellissier *et al*.[135]

One major improvement of the hypoiodide reaction introduced by Suarez *et al.* was the introduction of DIB instead of the former used lead tetraacetate (Scheme 108). This reaction generally works smoothly and the yields obtained are higher. Another important factor is the avoidance of toxic heavy metal salts.[135-137] The Barton reaction as well as the hypoiodite reaction have wide applications in the functionalization of steroids and offer an important tool for every steroid chemist.[130,135,138,139]

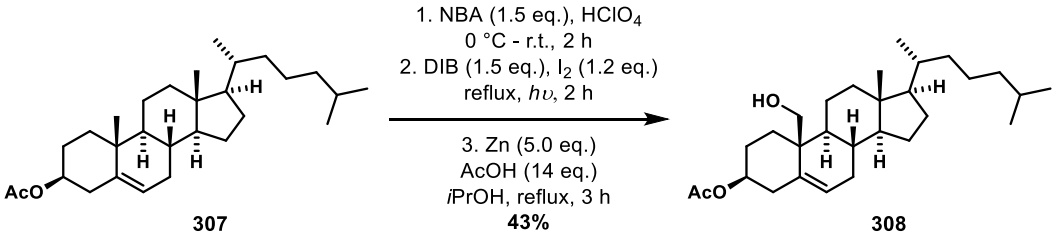


Scheme 108: Remote functionalization of the C-19 methyl group using DIB and I_2 reported by Suarez *et al*.[136]

3.1.4. Synthesis of 7β,19-Epoxysteroids

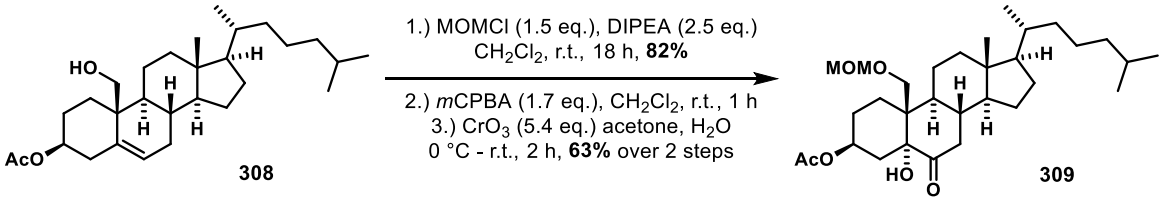
Up to date only two structures containing a 7β,19-epoxysteroidal core structure have been reported in the literature, both by our working group.[140] The synthesis of such 7β,19-epoxysteroids starts with cheap and easily available cholesteryl acetate (**307**) (Scheme 109). First a bromohydrin is formed upon addition of NBA, which is followed by a hypoiodite reaction by exploiting the directing effect of the 6β-hydroxy moiety to address the C-19 methyl group and to form the corresponding 5α-bromo-6β,19-epoxy core structure. Upon treatment with zinc and acetic acid, the corresponding

organozinc bromide can be formed, which subsequently leads to the elimination of the 6β,19-epoxy moiety and finally forms the desired 19-hydroxy-cholesteryl acetate **308** in an overall yield of 43% over 3 steps. The main problem in this reaction sequence is the formation of different isomers of the bromohydrin, which is responsible for the relatively low yield in the first place.[140]



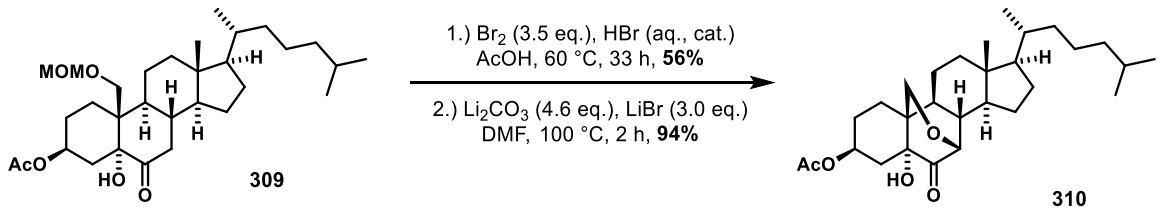
Scheme 109: Remote functionalization of cholesteryl acetate (**307**) by Taspinar *et al*.[140]

The remote functionalization is followed by the MOM protection of the 19-hydroxy moiety and by an epoxidation/oxidation sequence of the Δ^5-double bond leading to the corresponding 5α-hydroxy-6-keto derivative **309** (Scheme 110).[140]



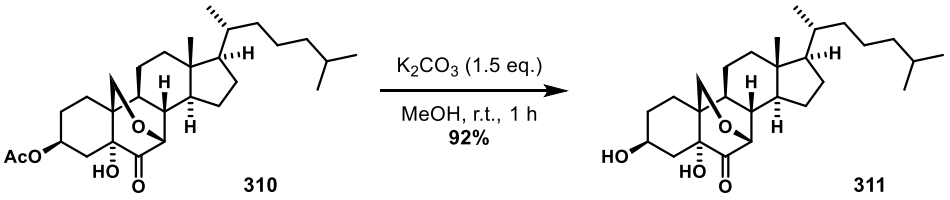
Scheme 110: MOM-protection and subsequent oxidation of the Δ^5-double bond to the corresponding ketol **309**.[140]

Upon treatment with bromine and catalytic amounts of hydrobromic acid, the α-bromination at C-7 with a simultaneous MOM-deprotection and formation of the corresponding hemiaminal of the 19-hydroxy and 6-keto moiety can be achieved (Scheme 111). Subsequent treatment with Li_2CO_3 and LiBr leads to the formation of the desired 7β,19-epoxy moiety and restoration of the 6-keto moiety in compound **310**.[140]



Scheme 111: α-Bromination and intramolecular nucleophilic substitution leading to the formation of the 7β,19-epoxy bridge.[140]

A final acetate deprotection leads to the 3β,5α-dihydroxy-7β,19-epoxycholestan-6-on (**311**). **310** and **311** are the first representatives of a new compound class containing such a 7β,19-epoxy core structure (Scheme 112).[140]



Scheme 112: Final acetate deprotection under standard conditions to yield the desired free alcohol **311**.[140]

3.2. Motivation

In the course of my master´s thesis[141], we discovered a new 7β,19-epoxy-bridged class of steroids. The core structure of these steroids is conformationally very unusual, due to the 7,19-epoxy-bridge, which forces the normally chair-like B-ring into a boat-like conformation. The first two synthesized compounds **310** and **311** were tested for their biological properties in the context of acute lymphoblastic leukemia by our cooperation partner Prof. Dr. Aram Prokop.

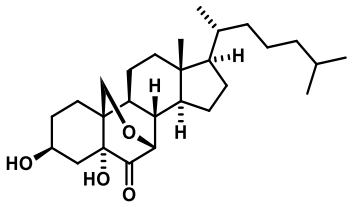


Figure 14: Chemical structure of the 7β,19-epoxysteroid **311** (**WIL-071**).[140]

And indeed, the compounds showed an array of different interesting biological activities, such as selective cytotoxicity against lymphoma, multiresistant leukemia cells and other solid tumors. With this promising data in hand, we decided to open the field for a more intense research. The main goal was to perform a series of chemical modifications to identify first structure activity relationships and to synthesize sufficient material for ongoing biological evaluations as well as chemical derivatizations. These derivatizations can be divided into four categories:

1) Modification at C-3 by esterification or other modifications;
2) Oxidation/Reduction at various positions of the A-ring;

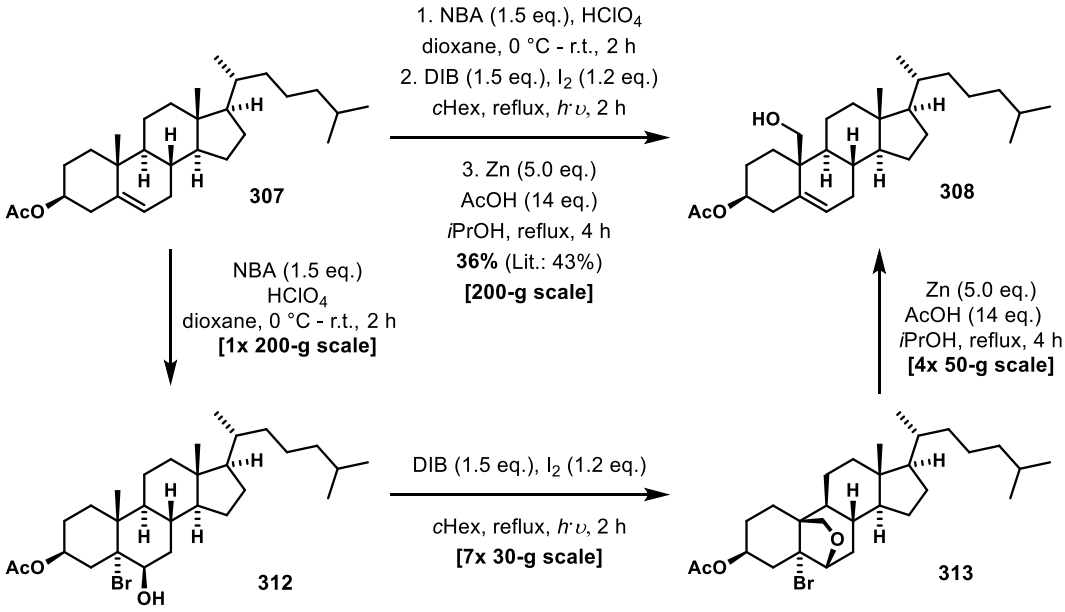
3) Derivatization of the side chain by the synthesis of a stigmastane analogue;
4) Further derivatizations.

The potential of the derivatives to induce selective apoptosis in cancer cell lines should be evaluated by our cooperation partner Prof. Dr. Aram Prokop and help to identify the most potent candidate for the development of a potential drug candidate.

3.3. Results and Discussion

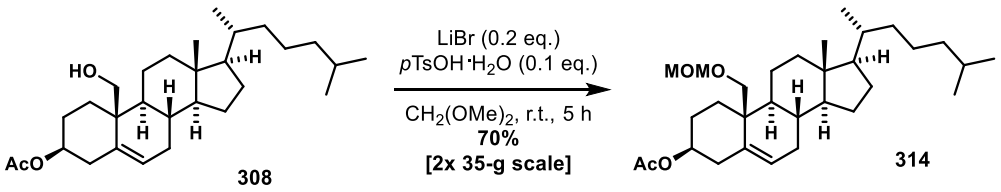
3.3.1. Large Scale Synthesis of 311 (WIL-071)

In the first place, we planned to synthesize a large amount of **311** (**WIL-071**) for derivatizations and for the ongoing biological evaluation by our cooperation partner Prof. Dr. Aram Prokop. The synthesis starts with the remote functionalization of cholesteryl acetate (**307**) (Scheme 113). The initial literature-known remote functionalization was scaled to a 200-g batch size with only minor losses in yield.[140] Commercially available cholesteryl acetate (**307**) was treated with *N*-bromoacetamide (NBS) and perchloric acid to form the desired bromohydrine **312**. Upon reacting the crude bromohydrine **312** with (diacetoxyiodo)benzene (DIB) and iodine under the irradiation of a mercury vapor lamp and refluxing conditions, we were able to access the desired 6,19-epoxy-5β-bromo-cholestane **313**, which was directly used as a crude product. In the next step, the 6,19-epoxy bridge should be opened in a reductive fashion by treating the bromide **313** with zinc and acetic acid. The so-formed organozinc bromide induces the elimination of the neighboring 6,19-epoxy-bridge forming the desired 19-hydroxy cholesteryl acetate (**308**) in a yield of 36% over three steps on a 200-g scale. The main drawback of this reaction sequence is the relatively poor selectivity of the initial bromohydrine formation towards the desired 3β-acetoxy-5α-bromo-6β-hydroxy-cholestane **312**, as other possible regioisomers are also formed in substantial amounts (~74 g).



Scheme 113: C-19 remote functionalization of cholesteryl acetate on a 200-g scale in accordance with our published procedure.[140]

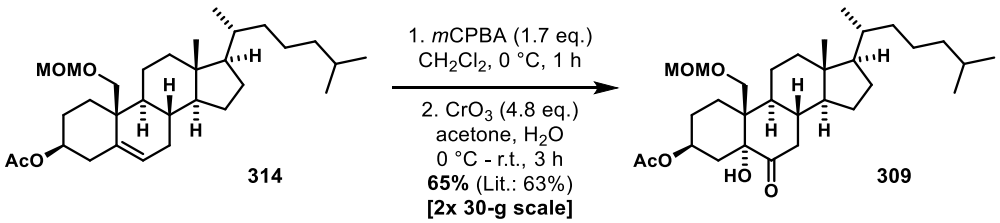
In search of an alternative protocol for the MOM-protection of the C-19 alcohol, to avoid the use of commercial MOMCl, which is expensive to use on a large scale and toxic due to a contamination with bis(chloromethyl) ether, we decided to employ a procedure reported by Zimmerman *et al*. using dimethoxymethane as the solvent and MOM-source in the presence of catalytic amounts of LiBr and *p*TsOH·H_2O (Scheme 114).[140,142] The use of this protocol afforded the desired 19-methoxymethyl cholesteryl acetate **314** in a yield of 70%. This way, we were able to render the reaction compatible with a safe large-scale synthesis. Dimethoxymethane, which substitutes the previously used MOMCl, is very cheap, due to its commercial use as solvent. The new catalysts LiBr and *p*TsOH·H_2O are also cheap and well accessible.



Scheme 114: Large scale MOM-protection of 19-hydroxy cholesteryl acetate (**308**) according to a procedure described by Zimmerman *et al*.[142]

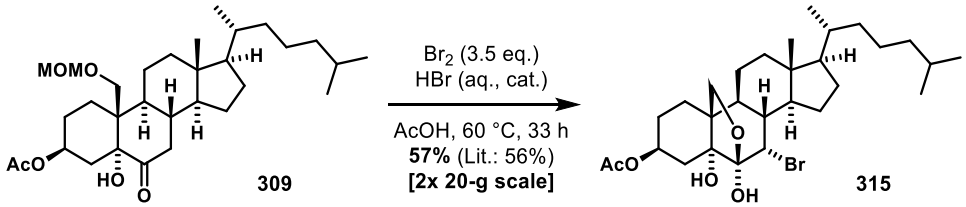
The oxidation of the Δ^5-double bond was then performed in accordance with the previously reported protocol, by an initial epoxidation of the alkene, followed by oxidation with CrO_3 (Scheme 115).[140] With regard to a possible development towards

a pharmaceutically used substance, this step should be further improved to avoid the use of chromium, hence Cr^6 is considered genotoxic in small amounts already.[143-146] Possible alternatives could be 1.) the use of $KMnO_4/Fe(ClO_4)_3$ as a less genotoxic reagent[147], 2.) the use of catalytic amounts of $RuCl_3$ in combination with oxone as the oxidation agent[148] or 3.) the dihydroxylation of the alkene followed by oxidation of the secondary alcohol with IBX derivatives. In the latter case, catalytic amounts of 2-iodoxybenzensulfonic acid in the presence of stoichiometric amounts of oxone could be tested in the future.[149]



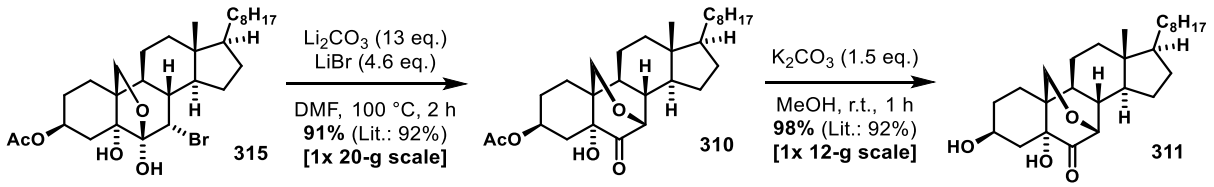
Scheme 115: Oxidation of the Δ^5-double bond of 19-MOM cholesteryl acetate (**314**) to the corresponding ketol **309** according to Taspinar *et al.*[140,141]

With the α-hydroxyketone **309** in hand, the α-bromination at C-6 and the simultaneous MOM-deprotection were performed using a solution of bromine in acetic acid under HBr-catalysis ()Scheme 116). Interestingly, the 19-hydroxy functionality formed directly the corresponding hemiacetal **315** with the 6-keto group.[140]



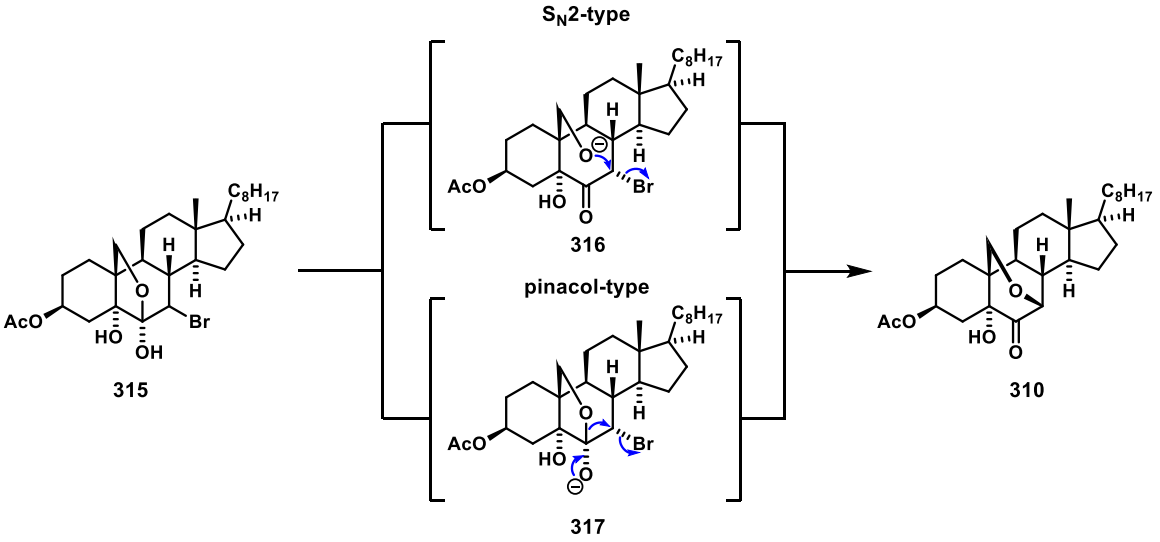
Scheme 116: α-Bromination and simultaneous MOM-deprotection of **309** to give hemiacetal **315** according to our published procedure.[140,141]

The hemiaminal **315** was converted to the 7,19-epoxy-bridged steroid **310** under basic conditions using Li_2CO_3 and LiBr at elevated temperatures (Scheme 117). The resulting acetate was subsequently deprotected under standard conditions.[140]



Scheme 117: Intramolecular formation of the 7β,19-epoxy steroid **310** followed by the acetate deprotection forming **311**.[140,141]

The formation of the 7β,19-epoxy moiety could follow two different reaction mechanisms (Scheme 118). The first one would be the cleavage of the hemiacetal **315** under basic conditions to form the alcoholate intermediate **316**, followed by a subsequent S_N2-type replacement of the 7α-bromide. The second possible mechanism would include a pinacol-type mechanism to replace the 7α-bromide without opening the hemiacetal in the first place.



Scheme 118: Possible intramolecular 7β,19-epoxy bridge formation following a S_N2-type or pinacol-type reaction mechanism.

Both the acetate **310** and the free alcohol **311** were recrystallized to yield pure samples for further *in vitro* and *in vivo* characterization of their biological potential. Starting from 200 g of cholesteryl acetate (**307**) we were able to synthesize a total of 5 g of the acetate **310** and 10 g of the alcohol **311** in a highly pure form. This is sufficient material for the ongoing biological evaluations. All biological experiments were performed by our cooperation partner, Prof. Dr. Aram Prokop, and will be discussed in a separate section of this thesis.

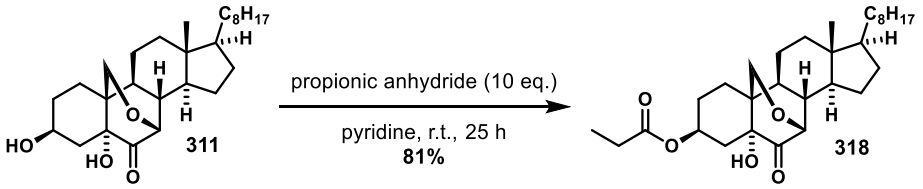
3.3.2. Derivatization of WIL-071 (311)

With a larger amount of the 3β,5α-dihydroxy-7β,19-epoxycholestan-6-one (**311**) in stock, we decided to perform a series of derivatizations. Subsequently, the biological potential of the derivatives should be evaluated. Prior to performing the derivatization, we defined two main goals. First, we wanted to optimize the effectivity of our steroid derivatives in the context of selective apoptosis induction against tumor cells and in the context of their resistance-breaking activity against multiresistant tumor cells. Additionally, possible structure-activity relationships should be identified by systematical derivatization of key functionalities. The main obstacle in this context was the fact that we did not know the biological targets and modes of action of the substrates. The derivatization of our new 7,19-epoxy steroids can be rationalized in four different categories:

1) Modification at C-3 by esterification or other modifications;
2) Oxidation/Reduction at various positions of the A-ring;
3) Derivatization of the side chain by the synthesis of a stigmastane analogue;
4) Further derivatizations.

3.3.3. Modification at C-3

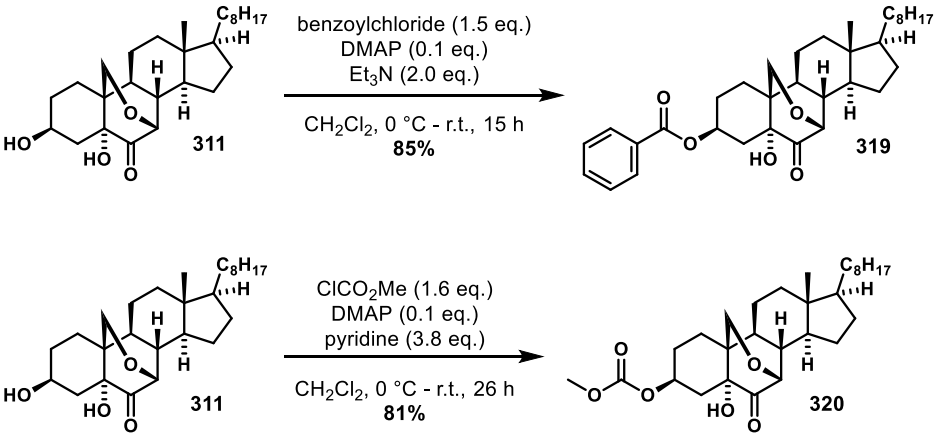
In the beginning, we started with the simplest kind of modification, which is the modification at C-3. Due to the good steric availability of the 3-hydroxy moiety in contrast to the tertiary 5-hydroxy moiety and the few possible side reactions under various reaction conditions, this starting point seemed to be a good one. The most straightforward approach was to introduce a series of different esters to the 3β-hydroxy function of **311** (**WIL-071**). First, the 3β-hydroxy functionality was esterified with propionic anhydride under standard conditions in a yield of 81% (Scheme 119).



Scheme 119: Synthesis of the propionic ester **318** under standard conditions.

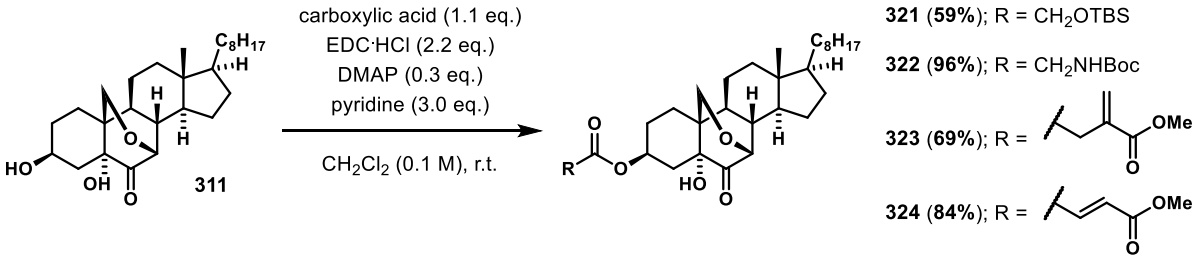
The benzylic acid ester derivative **319** was obtained using benzoylchloride in combination with DMAP as a nucleophilic catalyst (Scheme 120). This furnished the

benzylic acid ester derivative **319** in 85% yield, while the methyl carbonate **320** was synthesized using methylchloroformiate with catalytic amounts of DMAP in 81% yield.



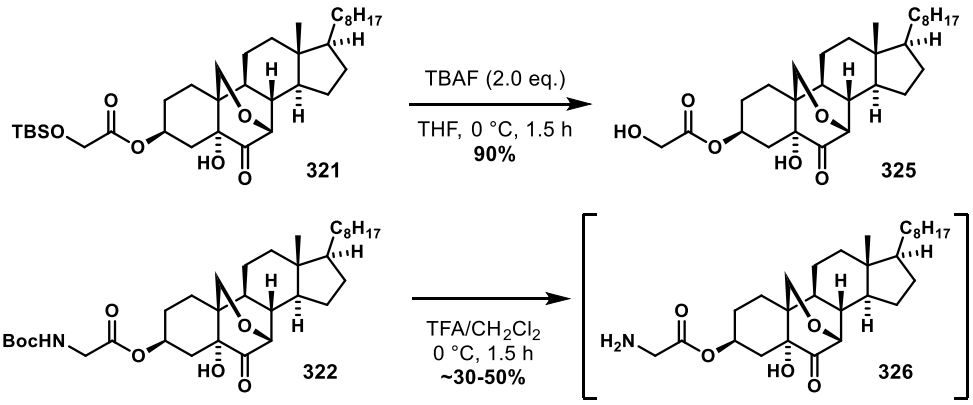
Scheme 120: Formation of the benzylester **319** and methylcarbonate **320**.

Four more esters were prepared by a standard Steglich esterification procedure employing EDC·HCl, DMAP, pyridine and the respective carboxylic acid (Scheme 121).[150] This way, the TBS-protected glycolic acid ester **321**, the respective *N*-Boc alanine ester **322**, the methyl itaconic ester **323** and the methylfumarate ester **324** were obtained in moderate to high yields.



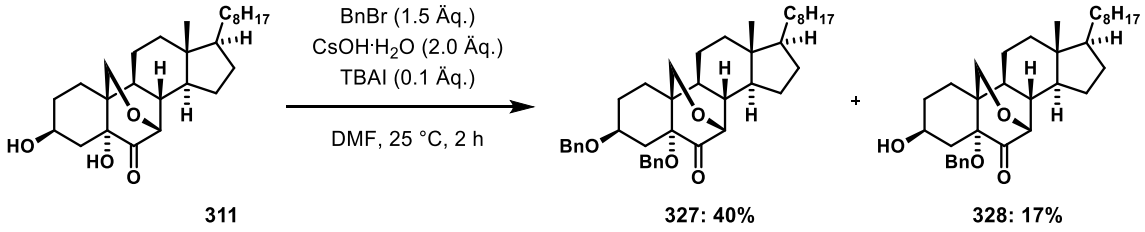
Scheme 121: Steglich esterification of **311** to form a series of new esters.

The TBS-protected glycolic acid ester **321** was deprotected under standard TBAF conditions to give the glycolic acid ester **325** in 90% yield (Scheme 122). In contrast, the *N*-Boc-alanine ester **322** was deprotected employing TFA as an acidic reagent. However, the resulting free amine **326** proved to be instable under standard conditions. Contact with silica during column chromatography as well as staying in solution at r.t. in deuterated chloroform led to a rather fast decomposition of amine **326**. Due to this instability, we decided not to characterize it further. This severe instability, especially under already slightly acidic conditions, indicates a presumably short lifespan under physiological conditions.



Scheme 122: TBS- and Boc-deprotection of the respective steroids **321** and **322**.

One last modification, that should be mentioned here, is the formation of the benzyl ether at C-3 (Scheme 123). The etherification was performed using a combination of benzyl bromide, cesium hydroxide monohydrate and catalytic amounts of TBAI (tetrabutylammonium iodide). Surprisingly, under these conditions a completely adverse reactivity of the two hydroxy groups at C-3 and C-5 was observed. Normally, the tertiary 5-hydroxy group shows a lower reactivity; in most cases, it is almost inert in contrast to the 3-hydroxy group. This low reactivity can be rationalized by the steric surrounding at the axial 5α-position, which is shielding this position well. Nevertheless, under the employed reaction conditions, it was possible to isolate the dibenzylether **327** as the mayor product in a yield of 40% besides the 5-monobenzylether **328** as the second product fraction in a yield of 17%. Other product fractions could not be isolated. This inverse reactivity may be interesting for further derivatizations targeting the 5-hydroxy function.

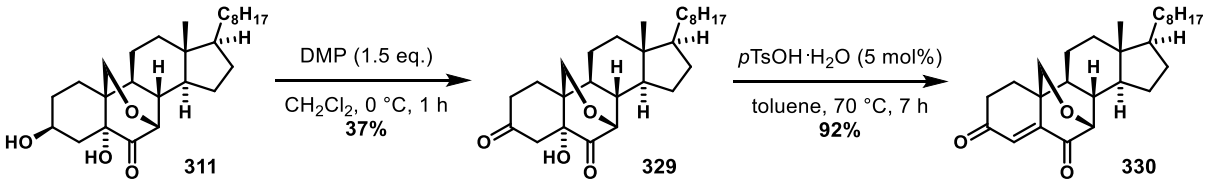


Scheme 123: Benzylation of the 3-hydroxy and 5-hydroxy moieties to form **327** and **328**.

3.4. Oxidation/Reduction at Various Positions of the A-Ring

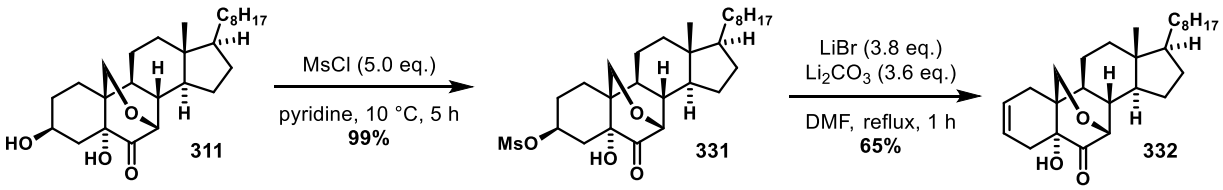
In the next series of modifications, we focused on the oxidative and reductive variation of various positions on the A-ring. The first straightforward oxidation was at the 3β-hydroxy, which led to the formation of the corresponding ketone **329** (Scheme

124). Employing Dess-Martin periodinane furnished the desired ketone in a yield of 37%, which was followed by the elimination of the 5α-hydroxy group under acidic conditions using *p*TsOH·H_2O in catalytic amounts. The corresponding endione **330** was isolated in 92% yield.



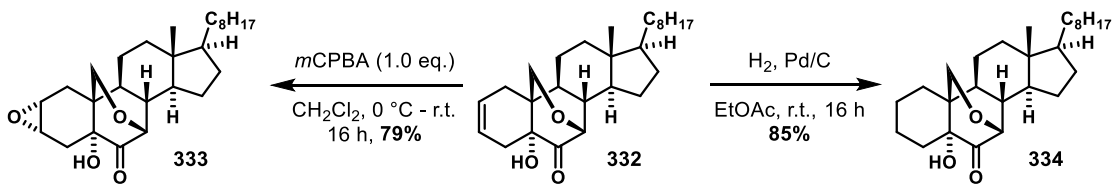
Scheme 124: Oxidation of **311** to the corresponding diketone **329** and elimination of the 5-hydroxy moiety to the endione **330**.

Next, the elimination of the 3α-hydroxy moiety was attempted (Scheme 125). For this purpose, the 3α-hydroxy moiety of **311** was first mesylated under standard conditions, yielding the corresponding mesylate **331** in an almost quantitative yield. The subsequent elimination under basic conditions then furnished the Δ^2-derivative **332** in a good yield. Under the employed conditions, the Δ^3-elimination product was formed in detectable amounts.



Scheme 125: Mesylation of the 3-hydroxy moiety followed by the elimination to furnish the Δ^2-derivative **332**.

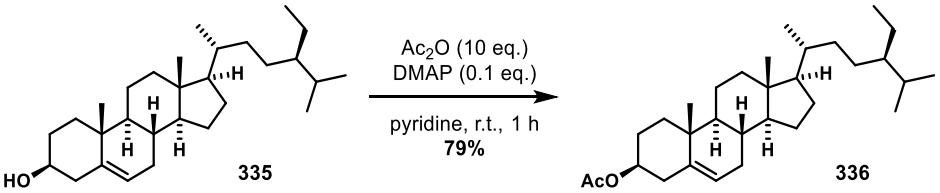
The Δ^2-derivative **332** was further converted to the corresponding 2α,3α-epoxide **333** by treatment with *m*CPBA (Scheme 126). Interestingly, solely the formation of the 2α,3α-epoxide **333** was observed, without evidence of the 2β,3β-derivative. The transformation of **332** to the corresponding hydrogenated product **334** employing standard hydrogenation conditions under Pd/C catalysis worked smoothly in a good yield.



Scheme 126: Epoxidation and hydrogenation of the Δ^2-double bond.

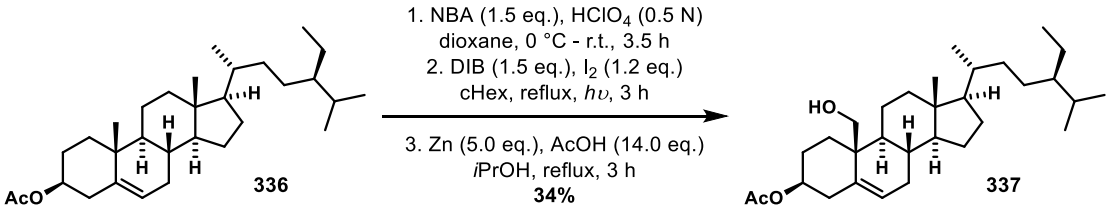
3.4.1. Derivatization at the Cholestane Sidechain

Next, we were interested in determining if modifications at the cholestane side chain have any influence on the biological properties of this compound class. Hence, a late-stage derivatization of our previously synthesized 7,19-epoxysteroids would be very hard to accomplish, due to the lack of functional groups in the cholestane side chain, we decided to introduce a 24-ethyl substituent, which corresponds to the stigmastane core structure. Thus, our previously established route to introduce the 7,19-epoxy-bridge was applied to the sitosterol-derived substrates. The synthesis was initiated by the acetate protection of sitosterol (**335**) according to a slightly modified literature procedure (Scheme 127).[151] Due to a minor impurity of campesterol, which is the 24-methyl derivative of sitosterol (**335**), the desired acetate **336** could not be isolated in a completely pure form. This impurity was present in all following products of this series. In the case of an improved biological activity of the sitosterol-derived target steroids, further quantitative HPLC purification could possibly be performed at latest at the stage of the final product. The campesterol impurity did not interfere with the further synthesis, so it was ignored at this stage.



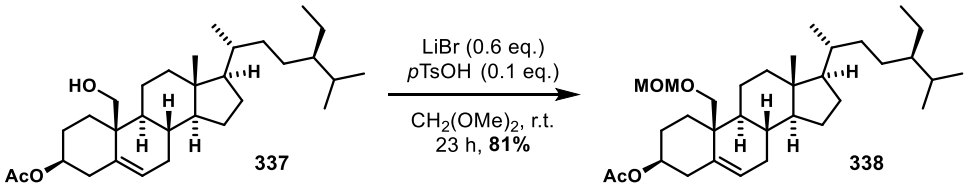
Scheme 127: Acetate protection of sitosterol (**335**).[151]

From now on, the established procedure for the cholesterol-derived compound was followed only with minor modifications.[140] The remote functionalization to introduce the 19-hydroxy moiety yielded the desired product **337** in a yield of 34% over three steps (Scheme 128).



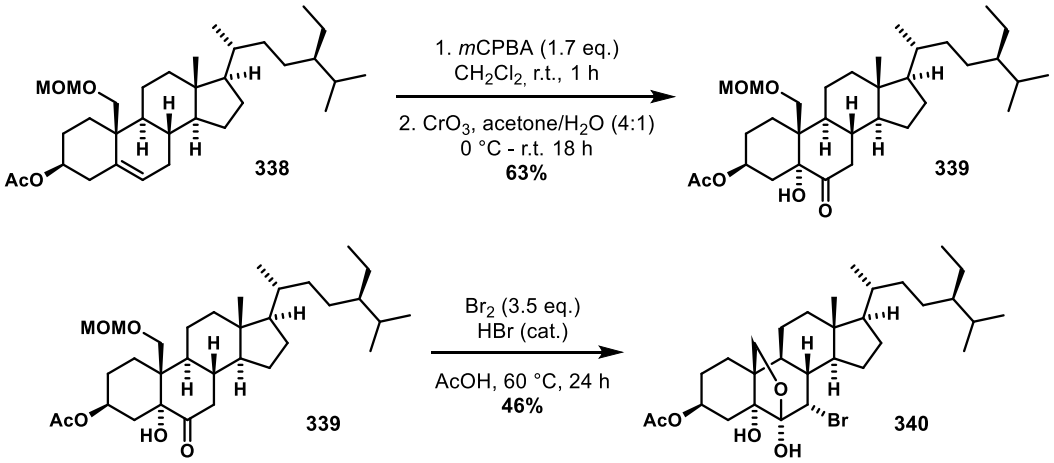
Scheme 128: Remote functionalization of sitosterylacetate (**336**).

By increasing the amount of LiBr from 0.2 eq. to 0.6 eq., it was possible to perform the MOM protection of **337** in a yield of 81% (Scheme 129).[140]



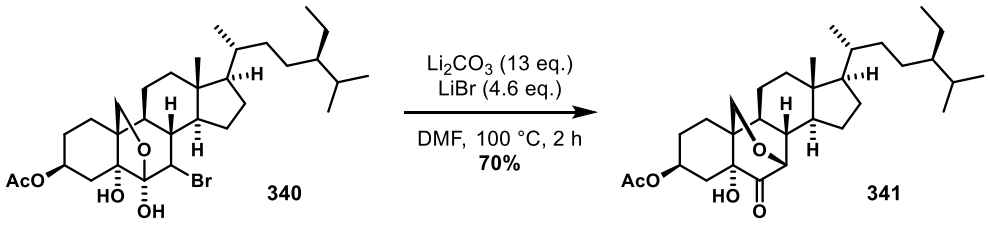
Scheme 129: MOM-protection of the 19-hydroxy moiety in **337**.

The oxidation of the Δ^5-double bond in **338** to the corresponding α-hydroxyketone **339** proceeded smoothly in a yield of 63%, followed by the combined α-bromination and MOM-deprotection to afford the hemiacetal **340** in a yield of 46% (Scheme 130).



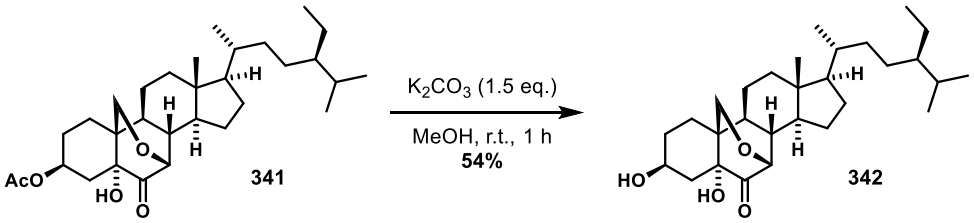
Scheme 130: Oxidation of the Δ^5-double bond followed by the α-bromination and MOM deprotection forming hemiacetal **340**.

The first 7,19-epoxy derivative **341** with a stigmastane core structure by a subsequent intramolecular S_N2-or pinacol-type substitution of the 6α-bromide by the 19-hydroxy oxygen (Scheme 131).



Scheme 131: Intramolecular nucleophilic bromine substitution followed to construct the 7,19-epoxy bridge of compound **341**.

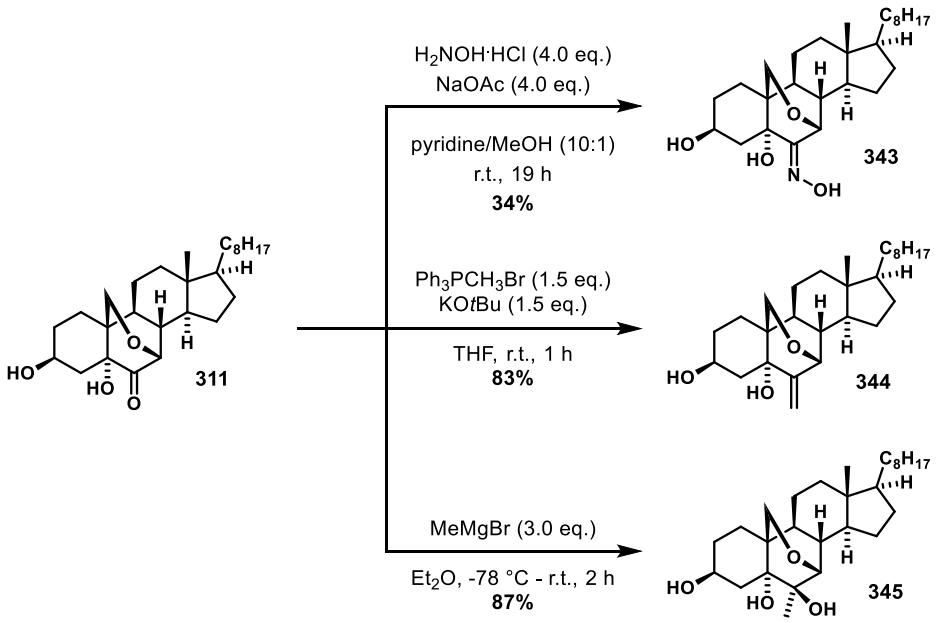
Finally, the 3β-acetate was deprotected with K_2CO_3 in methanol under standard conditions in 54% yield (Scheme 132). Compounds **341** and **342** were submitted to Prof. Dr. Aram Prokop to evaluate their biological potential.



Scheme 132: Acetate deprotection of **341** to yield **342**.

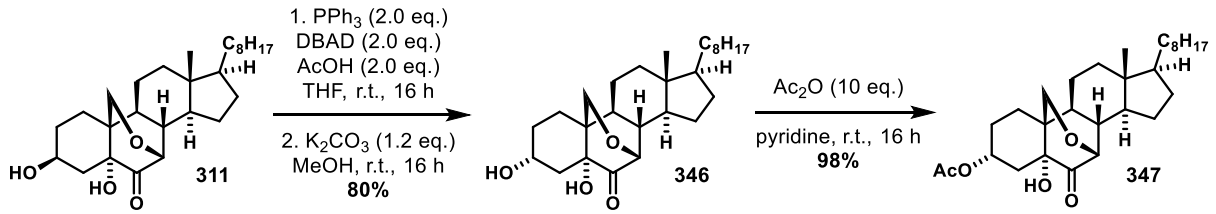
3.4.2. Further Modifications

To finish the synthetic part of this thesis, a few further modifications of the 7β,19-epoxysteroids were envisioned, mainly targeting the 6-keto moiety and the inversion of the configuration at C-3. Starting with the focus on the ketone, the conversion of **311** to the corresponding oxime **343** was achieved with hydroxylamine hydrochloride under basic conditions (Scheme 133). Although full conversion and only a few side products were observed by TLC, the isolated yield was only 34%. This might be due to the very low solubility of oxime **343** in most organic solvents and the resulting difficulties during purification. Only recrystallization led to a satisfying result. Even the solubility of **343** in DMSO (for NMR) was relatively low. Next, a standard Wittig olefination was performed to introduce a methylene group at C-6. The reaction furnished the desired product **344** smoothly in a yield of 83%. Finally, a nucleophilic attack of methyl magnesium bromide to ketone **311** was performed yielding solely the 6β-hydroxy diastereomer **345** as the reaction product. This indicates a generally well-shielded β-face of our steroid derivatives. Although the introduction of the 7β,19-epoxy bridge is expected to force the B-ring into a boat-like conformation and therefore relieve the steric hindrance for nucleophiles attacking from the β-face, the steric hindrance still seems to be greater from the β-face.



Scheme 133: Formation of the oxime **343**, Wittig olefination to obtain alkene **344** and methyl Grignard addition to the 6-keto moiety to yield the corresponding tertiary alcohol **345**:

The inversion of the stereocenter of the 3-hydroxy moiety was performed by a Mitsunobu reaction (Scheme 134). Unfortunately, the acetate, which was formed under the initially employed Mitsunobu conditions, could not be isolated in a pure fashion. Therefore, the acetate function in the crude Mitsunobu product was deprotected, which led to a significant improvement in the purity of alcohol **346** after column chromatography. As we were also interested in the corresponding acetate **347**, the 3α-hydroxy steroid **346** was subsequently reacetylated to give acetate **347** in a nearly quantitative yield.



Scheme 134: Inversion of the stereocenter of the 3-hydroxy moiety under Mitsunobu reaction conditions followed by the acetate protection of the 3α-hydroxy moiety.

All the derivatives of **311**, which were synthesized up to this point, were sent to our cooperation partner Prof. Dr. Aram Prokop for their biological evaluation in the context of a potential apoptosis induction against cancer cells, such as the multiresistant acute lymphoblastic leukemia and tumors in the central nervous system.

3.4.3. Biological Results

The steroid **311** (**WIL-071**) was the first compound of this series and initially tested in an assay investigating its potential as an apoptosis inducing agent. And indeed, significant apoptosis induction was observed on Nalm6-cells – which is a human cell line representing B-cell precursors for leukemia - at a concentration of 20 μM. The same result was obtained upon treatment of BJAB cells - representing a human Burkitt lymphoma cell line. At the same time, healthy leukocytes were not affected and remained healthy (Figure 15).

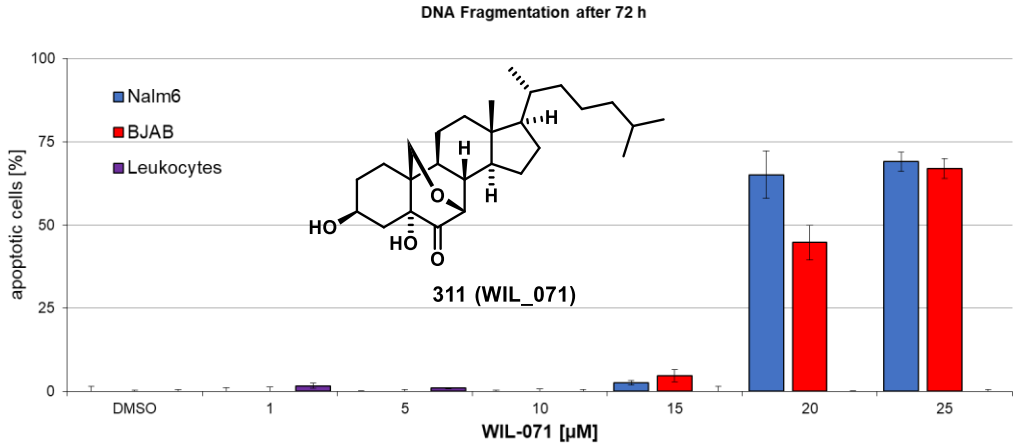


Figure 15: DNA-fragmentation of Nalm6, BJAB cells and healthy leukocytes after treatment with **311** (**WIL-071**) in a concentration-dependent manner.

Based on these initial, promising results, a series of experiments regarding potential resistance breaking mechanisms of our new substance class was performed. The development of resistances against cytostatic agents, used for the treatment of cancer patients, resembles a huge risk for a successful treatment. For example, ALL patients suffering from prednisolone resistance are commonly called “poor responders”, due to their drastically decreased survival rates and their poor response to therapeutic schemes.[152]

In this context, a series of modified cell lines, obtained from Nalm6 and BJAB cells, was treated with **311** (**WIL-071**). These cells were resistant against commonly employed cytostatic agents, such as prednisolone, daunorubicine, vincristine, methotrexate and 4-OH-cyclophosphamide. These resistances are caused by distinct resistance mechanisms for each cytostatic agent (Table 18). The cells were treated with **311** (**WIL-071**) and a 50% maximal apoptosis induction concentration (AC_{50}) was observed in the range of 10-25 µM for all resistant cell lines. Hence the AC_{50}-values

for the non-resistant parent cell lines Nalm6 and BJAB were in the same range, it was shown that the new class of 7,19-epoxysteroids is able to circumvent the resistance mechanisms against many common cytostatic agents.

Table 18: Resistance-breaking properties of **311** (**WIL-071**) against a series of resistant Nalm6 and BJAB cells.

cell line	AC_{50}	resistance mechanism	cytostatic resistance
Nalm6/Naku (leukemia)	17.5 µM	FLT-3	prednisolone
Nalm6/ Ndau (leukemia)	15 µM	p-glycoprotein	daunorubicin
Nalm6/ NVCR (leukemia)	15 µM	p-glycoprotein	vincristine
Nalm6/JeBa (leukemia)	10 µM	P53/MCL-1, FLT1	methotrexate (MTX)
Nalm6/Ncyclo (leukemia)	15 µM	ERB B4	4-OH-cyclophosphamide
BJAB/7CCA (lymphoma)	10 µM	caspase 3	doxorubicin
BJAB/Bibo (lymphoma)	25 µM	Bcl-2	vincristine

Up to date, the action mechanism of **311** (**WIL-071**) is not known, although a mechanism different from common steroids, such as prednisolone, can be assumed, because the resistant cell lines do not show a decreased susceptibility towards **311** (**WIL-071**) in comparison to the Nalm6 and BJAB cells. To gain a deeper understanding of the biological action mechanism of **311** (**WIL-071**) further experiments should be performed in the future. Especially, computational approaches in combination with proteomics and genetic screens seem to be promising approaches.

In another set of experiments, it was investigated, whether **311** (**WIL-071**) exhibits a synergistic effect in combination with other cytostatic agents, like vincristine. A synergistic effect can be seen, when the apoptosis-induction rate of the combined addition of **311** (**WIL-071**) and vincristine exceeds the sum of the individual effects. Interestingly, it was possible to observe such a synergistic effect of **311** (**WIL-071**) and vincristine (Figure 16). This effect was especially dominant at 12.5 μM of **311** (**WIL-071**) and 0.8 nM vincristine showing a synergy of 126%. The fact that such an effect was measured, indicates that a potential combined use of a later, optimized

7,19-epoxysteroid with other cytostatic agents, could be a valid and beneficial treatment option, that could potentially improve current state-of-the-art treatments.

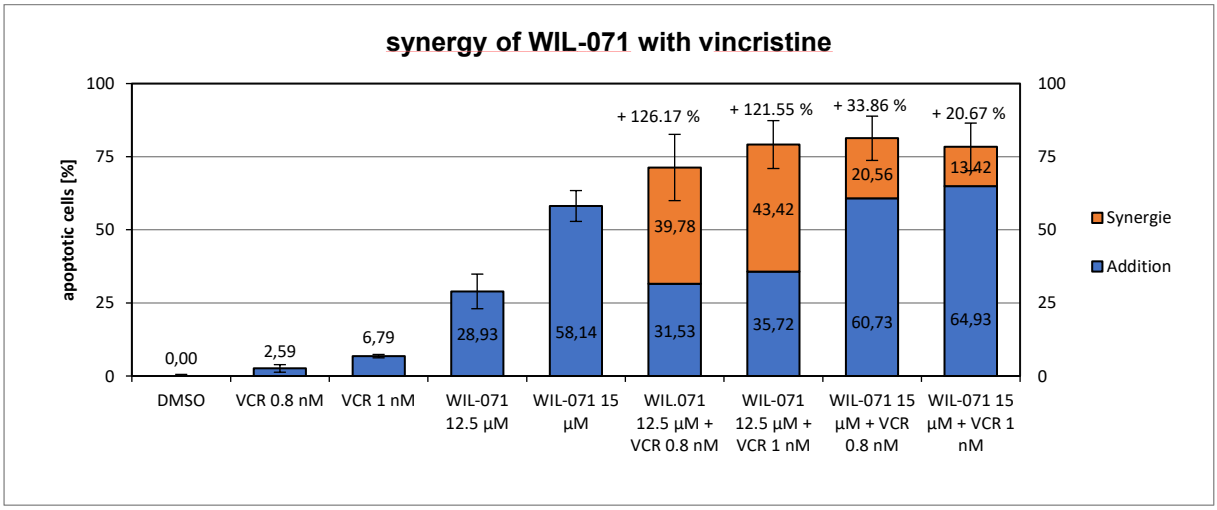


Figure 16: Evaluation of synergistic effects of **311** (**WIL-071**) with vincristine on Nalm6 cells.

The resistance mechanisms of vincristine-resistant NVCR cells, which was overcome by **311** (**WIL-071**), relies on the overexpression of p-glycoprotein and leads to the resistance against vincristine and daunorubicine. p-Glycoprotein is especially interesting due to its importance in the context of the blood-brain barrier, where it is the basis for one of the major efflux mechanisms, leading to the excretion of harmful substances from the central nervous system. Actually, one of the main problems in treating cancer in the central nervous system is the unavailability of many cytostatic agents, due to their inability to pass the blood-brain-barrier. Due to the circumvention of this efflux mechanism by **311** (**WIL-071**), we hoped to be able to address tumors in the central nervous system. Therefore, **311** (**WIL-071**) was tested on a series of solid tumors, which includes some tumors originating from the central nervous system. And indeed, it was possible to induce apoptosis in many of the tested cells, including cell lines derived from neuroblastoma, glioblastoma, CML and Ewing sarkoma (Table 19). This indicates a possible general applicability of **311** (**WIL-071**) as a new apoptosis inducing agent. The fact that **311** (**WIL-071**) can overcome the p-glycoprotein induced resistance mechanism and is effective against glioblastoma cells, is a positive sign, that such tumors can be addressed as well in *in vivo* systems. Importantly, other steroid cytostatic agents, such as prednisolone and dexamethasone, are not able to induce apoptosis in solid tumors and do even protect

the tumor-cells from apoptosis in certain cases.[153,154] Therefore, a completely new set of important target tumors can possibly be addressed by the 7,19-epoxysteroids.

Table 19: Resistance-breaking properties of **311** (**WIL-071**) against a series of resistant cancer cells.

cell line	AC_{50}	resistance mechanism	cytostatic resistance
SKNAS/Lion (Neuroblstoma)	20 µM	caspase 8	cisplatin
H3WT/K27M (Glioblastoma)	40 µM	H3-K27 mutation	/
K562/K562AraC (CML)	20 µM	GALNT-5,APP	cytarabine
K562/K562Dau (CML)	20 µM	harakiri	daunorubicine
VH64/VH64 Doxo (Ewingsarkoma)	20 µM	p-glycoprotein	doxorubicine
VH64/ VH64 Etop (Ewingsarkoma)	20 µM	p-glycoprotein	etoposide

311 (**WIL-071**) did even induce apoptosis in the glioblastoma cell line K27M carrying a central mutation, which is located at the histone 3 (H3) isoform and leads to certain death after a few months (Figure 17).[155,156] The median survival time of this special type of glioblastoma is between 9 to 15 months.[157] The development of treatment options for such highly lethal, malignant tumor entities would be a huge step for patients suffering from these tumors.

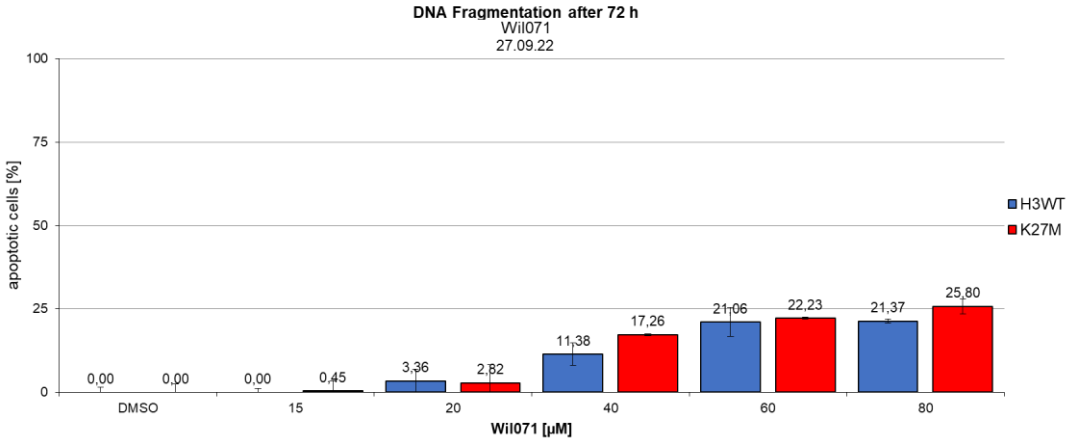


Figure 17: DNA-fragmentation of H3WT and K27M cells after treatment with **311** (**WIL-071**) in a concentration dependent manner.

On our way to use **311** (**WIL-071**) against tumors in the central nervous system, a study, to estimate the compatibility of **311** (**WIL-071**) under *in vivo* conditions prior to a xenograft mouse model, was commissioned. **311** (**WIL-071**) showed a good compatibility in living mice up to a concentration of 150 mg/kg. Additionally, the concentration of **311** (**WIL-071**) in the brain after 1, 2, 8 and 24 h was determined (Figure 18). In accordance with our prior assumptions, we were able to identify significant amounts of **311** (**WIL-071**) in the brain tissue of the mice. These results are a very important step towards the application of 7,19-epoxysteroids in the context of tumors in the central nervous system.

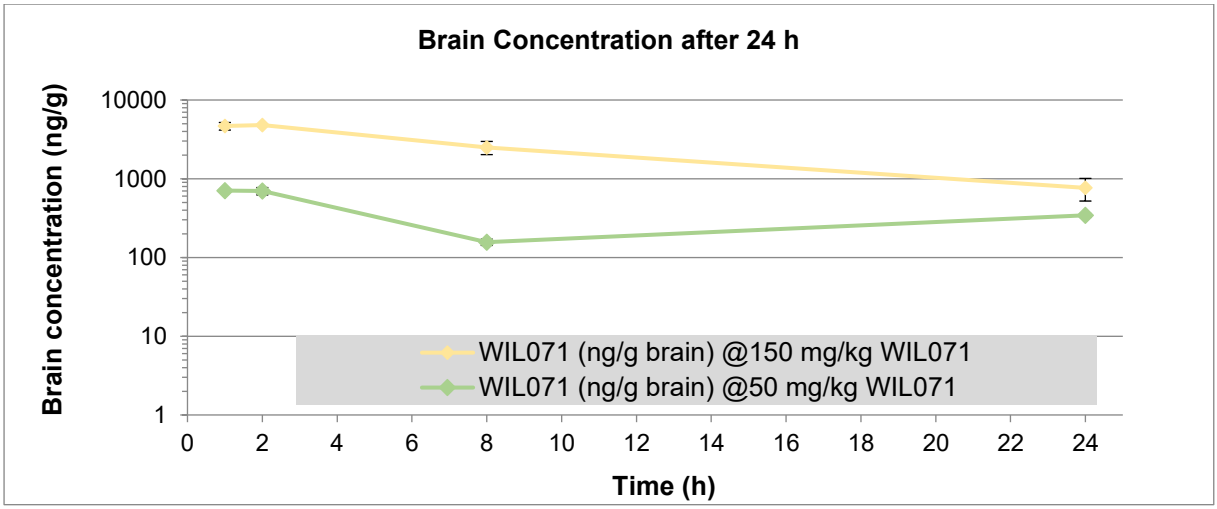


Figure 18: Concentration of **311** (**WIL-071**) in the brain of mice after one intravenous dose of **311** (**WIL-071**) at four different times.

As described in an earlier part of this thesis, derivatizations of **311** (**WIL-071**) were performed and the corresponding derivatives were tested regarding their apoptosis inducing effect on Nalm6 cells and on prednisolone resistant NaKu cells (Table 20). It can be summarized, that almost half of the tested derivatives were still active in a similar concentration range like **311** (**WIL-071**) and all derivatives were equally active in Nalm6 and prednisolone resistant NaKu cells. Some derivatives, such as the methyl itaconate **323**, the methyl fumarate **324** and the 6β-methyl-6α-hydroxy derivative **345** were even more active than the parent compound **311** (**WIL-071**). The oxidation of the 3-hydroxy (**329**) and elimination of the 5-hydroxy moiety (**330**) did not result in a major loss of activity. However, the introduction of a relatively stable protecting group at the 3α-hydroxy moiety resulted in a decreased activity (**319**, **320**, **327** and **328**). A special case is oxime **343**, which showed only a very low solubility

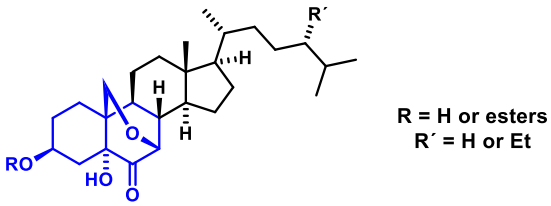
in most organic solvents and in water. The solubility may have been the reason for the low activity of **343**. The introduction of an additional ethyl group in the cholestane side chain (**342**) resulted in no major change in the activity. Removing or inverting of the 3α-hydroxy moiety (**332**, **333**, **334**, **346**, **347**) resulted in a loss of activity. Therefore, we concluded that this moiety may take part in the main binding event, leading to the desired apoptosis induction. Also, the exchange of the 6-keto moiety (**344**) by a methylene unit through Wittig reaction led to a loss of activity.

Table 20: AC_{50}-values of different steroid derivatives towards Nalm6 and NaKu cells. The AC_{50}-values were determined by DNA fragmentation after 72 h of incubation with the corresponding substance.

Substance	AC_{50} (Nalm6)	AC_{50} (Naku)
WIL071 (311)	~17.2 µM	~16 µM
WIL232 (310)	~25 µM	~17.5 µM
WIL367 (323)	~8 µM	~12.5 µM
WIL369 (324)	~3 µM	5 µM
TAS-S406 (345)	13 µM	~ 17 µM
WIL241 (329)	~32 µM	~22.5 µM
WIL270 (330)	20 µM	18 µM
WIL362 (319)	> 100 µM	> 100 µM
WIL357 (320)	> 50 µM	>50 µM
WIL242 a (327)	>50 µM	>50 µM
WIL242 b (328)	~37 µM	~40 µM
WIL313 (318)	~47 µM	~40 µM
WIL360 (322)	> 20 µM	20 µM
WIL364 (325)	~18 µM	~17.5 µM
TAS-S389 (331)	~20 µM	~30 µM
WIL368 (343)	> 100 µM	> 100 µM
WIL-DK-08 (341)	50 µM	~40 µM
WIL-DK-09 (342	~15 µM	~38 µM
TAS-S392 (332)	~46 µM	~ 39 µM
TAS-407 (333)	> 100 µM	> 100 µM
TAS-S398 (334)	~80 µM	~ 67 µM
TAS-S403 (346)	100 µM	20 µM
TAS-S405 (347)	90 µM	~ 20 µM
TAS-S399 (344)	50 µM	~ 75 µM

The first major conclusion from these biological evaluations is, that the availability of some sort of 3α-hydroxy or -keto moiety is necessary for the biological activity, although some esters are tolerated at this position (Figure 19). It is not clear, if these

esters are cleaved under physiological conditions by an esterase. In general, it seems necessary to have a hydrogen acceptor in the 6-position. It was shown, that either a 6-keto or 6-hydroxy moiety is able to achieve good results, but further modifications should be evaluated. At the same time the introduction of an additional ethyl substituent in the side chain, did not affect the activity of the compounds.

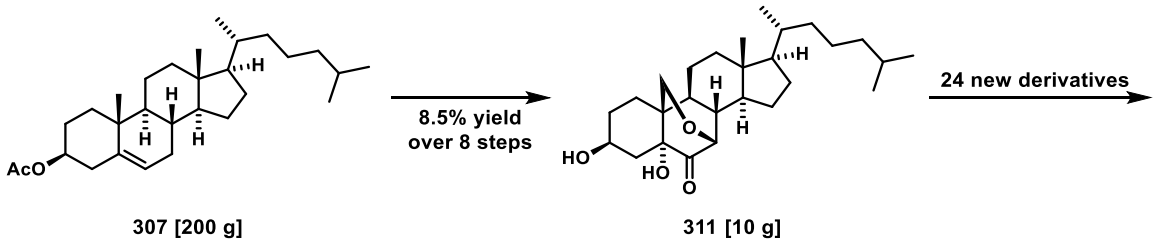


348

Figure 19: Representation of the core pharmacophore **348** of the 7β,19-epoxy steroids tested so far.

Notably, compound **311** (**WIL-071**) was also tested against various other cancer cells from different origins, not all of which are mentioned in this thesis. The fact, that the compounds are active against more than 10 cancer cell lines, including glioblastoma, acute lymphoblastic leukemia, lymphoma, chronic myeloid leukemia, medulloblastoma, pancreatic carcinoma, neuroblastoma, Ewing sarcoma, rhabdomyosarcoma and osteosarcoma, demonstrates a stunning versatility and justifies further development of this project.

3.5. Summary



Scheme 135: Successful big-scale synthesis of **311** followed by derivatization at various positions.

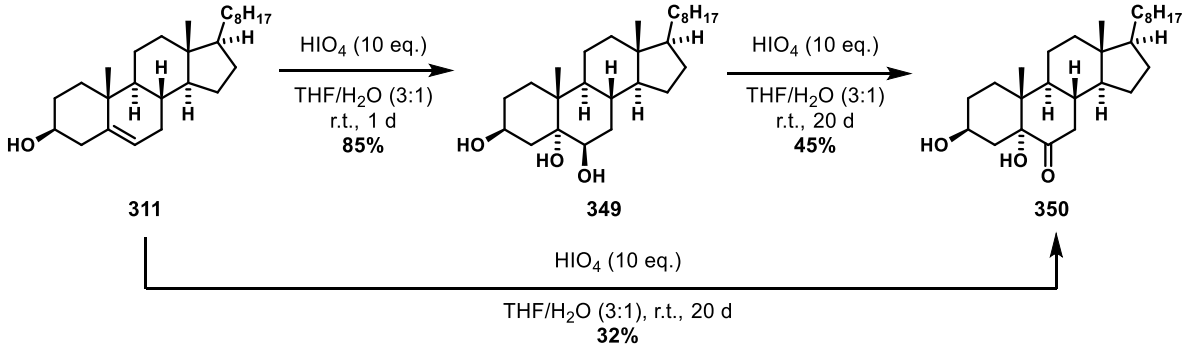
In summary, more than 10 g of **311** (**WIL-071**) was synthesized in an optimized yield of 8.5% over 8 steps. This way more than sufficient material is available for future *in vitro* experiments and a systematic ADME-Tox evaluation. Additionally, a total of 24 new derivatives, containing the 7β,19-epoxy steroid moiety, were synthesized and evaluated in regards of apoptosis induction.

The *in vitro* results of most derivatives showed outstanding and even selective cytotoxic activity of **311** (**WIL-071**) against several resistant ALL cells, while healthy leukocytes were not affected. Besides the strong resistance-breaking activity against common resistance mechanisms (e.g. p-glycoprotein overexpression), a strong synergistic effect in combination with other cytostatic agents, such as vincristine, was observed. Furthermore, **311** (**WIL-071**) was tested on solid tumors, which are characterized by low survival rates withstanding most treatment options. This includes tumors occurring in the central nervous system, like glioblastoma, etc. Patients suffering from one of these cancer types have in most cases a very bad prognosis and the 7β,19-epoxy steroids could be an important contribution to find an effective treatment. Especially remarkable is the ability of these steroids to pass the blood-brain barrier, which was shown in a mouse model. This renders the tumors from the central nervous system targetable and may therefore overcome a key problem in modern treatment of such diseases.

3.6. Outlook

One very important task for the future is the evaluation of the crucial basic ADME-Tox parameters of the discovered steroid derivatives. This is already in progress in the context of a GoBio *initial* funded project. Before performing a broader derivatization, it would be crucial to identify the action mechanism regarding apoptosis-induction and resistance-breaking activities. This would go hand in hand with the identification of the biological target addressed by **311** (**WIL-071**). A wide array of methods can be applied here, including computational/machine learning methods, chemical proteomics and the use of genetically modified cell lines.[158] Once the target is identified and the structural details of the binding interaction have been elucidated (X-Ray or NMR), a straightforward optimization of the structure-activity relationship should be performed by computational methods, like docking studies, and subsequent synthesis of tailored structures.

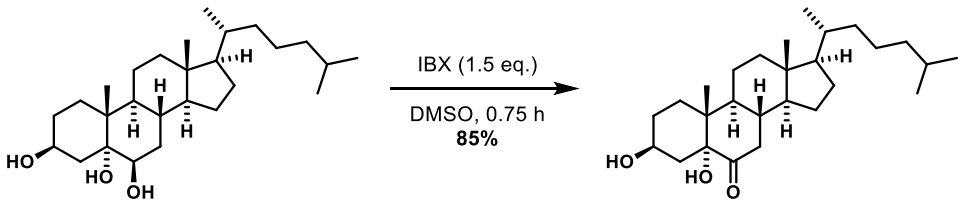
A optimization regarding the big-scale synthesis of **311** (**WIL-071**) should target the development of a shortened synthesis, while avoiding the use of heavy metals, especially CrO_3. Interestingly, Poirot *et al*. described the oxidation of cholesterol **275** to cholestane-3β,5α,6β-triol (**349**) and 6-oxo-cholestane-3β,5α-diol (**350**) by using periodic acid, depending on the reaction time (Scheme 136).[159] This reaction should be transferrable to our 19-hydroxy-cholesterol (**308**) even without the need to introduce a 19-hydroxyl protecting group.



Scheme 136: Direct oxidation of cholesterol (**275**) to cholestantriol (**349**) or 6-oxo-cholestandiol (**350**) reported by Poirot *et al*.[159]

Due to potentially low yields for the direct oxidation to the 6-oxo derivative (**350**) using periodic acid, an alternative oxidation of the 5α,6β-diol to the corresponding

5α-hydroxy-6-oxo steroid could be achieved by selective IBX or NBS oxidation, as shown by Kuhakarn *et al*. and Frigerio *et al.* (Scheme 137).[160,161]



349 **350**

Scheme 137: Oxidation of cholestantriol **349** to the corresponding 6-oxo-cholestandiol **350** reported by Frigerio *et al*.[161]

Especially in the context of the GoBio *initial* funded project, a proof that the 7,19-epoxysteroids can exhibit cytostatic properties in a xenograft mouse model would be a serious step towards the further development of this compound class in the direction of a potential drug candidate.

4. Experimental Part

4.1. General Experimental Conditions and Analytic Methods

Reagents and solvents

For the reactions in general, reagents and solvents were used from commercial suppliers, such as *Acros, Carbolution*, *Merck* and *Sigma-Aldrich*, in purities of ≥ 95%. CH_2Cl_2 was distilled over CaH_2. Et_2O, THF and toluene were distilled over Na/benzophenone. The other dry solvents were purchased from commercial suppliers in septum bottles and used directly, or they were purchased in a technical quality and freshly distilled before use.

Working under inert conditions

Oxygen or water sensitive reactions were performed under inert conditions under the use of Schlenk techniques. Therefore, reaction vessels were flame dried under an oil pump vacuum at a *Schlenk* apparatus prior to the use in a reaction. Argon (99.996%) from *Linde* was used as inert gas source. The addition of liquids was performed with plastic syringes and metal cannulas. Sensitive chemicals were stored in a glovebox (Unilab by M. Braun Inertgas-Systeme GmbH), keeping the O_2 and H_2O concentrations below 1 ppm.

Evaporation of solvent

Solvents were removed at a rotary evaporator at reduced pressure and in a heated water bath (40 °C). All non-volatile compounds were dried under an oil pump vacuum.

Column and thin-layer chromatography (TLC)

Column chromatography was performed using silica gel 60 (0.035-0.070 mm) from *Acros Organics*. For thin layer chromatography silica gel plates 60 F_{254} from *Merck* (0.20 mm silica gel, fluorescence indicator) were used. Visualization of the substance spots was accomplished using either UV-detection (254 nm), an aq. cerium ammonium molybdate solution, an aq. $KMnO_4$ solution or an ethanolic vanillin solution.

Gas chromatography with a mass selective detector (GC-MS)

GC-MS analysis was performed on an *Agilent* HP6890N with the mass detector 5937N. As carrier gas hydrogen (1.2 bar) was used and the column was an Optima 1 MS (30 m x 0.25 mm) column from *Macherey-Nagel*. The measurement option 50-300M was used.

High resolution mass spectrometry (HR-MS)

HR-MS measurements were performed on a Thermo Scientific LTQ Orbitrap XL mass spectrometer by electron sprac ionization and with a FTMS Analyzer.

Nuclear magnetic resonance spectroscopy (NMR)

NMR spectra were obtained from a *Bruker Avance II 300* or *Bruker Avance III 500* spectrometer operating at 500 MHz for proton nuclei. High-field measurements were performed on a *Bruker Avance III 500* (500 MHz) or on a *Bruker Avance II+ 600* (600 MHz). $CDCl_3$ and DMSO-d_6 with TMS as internal standard were used as solvents for the NMR analytics. The chemical shifts are given in ppm and TMS was set as reference at 0.00 ppm in ^1H NMR. In ^{13}C NMR $CDCl_3$ was set as reference at 77.16 ppm. In a ^1H NMR singlets are labeled with „s“, doublets with „d“, triplets with „t“ and quartets with „q“. In case of an unclear splitting the signal was declared as multiplet labeled with „m“. If a signal is assigned to different numbered atoms, the indices are separated with a comma (1,2…). If the assignment is uncertain the indices are separated with a slash (1/2…). The assignments were carried out using 2D NMR spectra, such as COSY, HSQC and HMBC.

Fourier Transform Infrared Spectroscopy (FT-IR)

The IR-spectra were measured with a *Perkin-Elmer* UATR Two FT-IR-Spectrometer. All spectra were measured at r.t. The wavenumbers are given in cm^{-1} and the intensity of the bands was marked as the following: „s“ (strong), „m“ (medium), „w“ (weak), „b“ (broad).

Specific Optical Rotation ($[\alpha]_\lambda^{20}$)

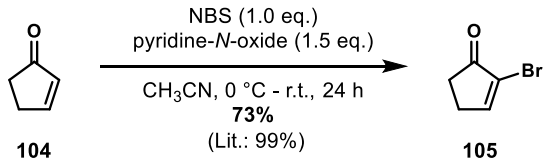
The specific optical rotation values were obtained with an *Anton Paar* MCP 200 Polarimeter. All measurements were performed at 20 °C in chloroform.

X-Ray Crystallography (X-Ray)

X-Ray crystallographic measurements on single crystals were performed on a "SC-XRD *Bruker* D8 Venture". More detailed data are given in the corresponding data sets of the depending compounds. All structures inclusively the data sets are stored by *Dr. Jörg-Martin Neudörfl* (Department of Organic Chemistry, University of Cologne, Greinstraße 4, 50939 Cologne).

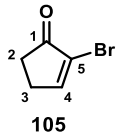
4.2. Synthesis of Compounds Regarding the Intermolecular Imino Diels Alder Approach

4.2.1. 2-Bromo-cyclopent-2-ene-1-one



104 **105**

According to a procedure by Nishida *et al.*[79], to a solution of cyclopentenone **104** (2.0 ml, 24 mmol, 1.0 eq.) in CH_3CN (120 ml) was added pyridine-*N*-oxide (3.50 g, 36.8 mmol, 1.5 eq.). The solution was subsequently cooled to 0 °C and NBS (4.37 g, 24.6 mmol, 1.0 eq.) was added. The solution was stirred for 20 min at 0 °C and stirred for further 24 h at r.t. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc and water. The aq. phase was extracted thrice with EtOAc, the combined org. phases were washed with a sat. aq. NaCl solution and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 7:1) and the desired product **105** was obtained as a colorless solid (2.83 g, 17.6 mmol, 73%, Lit.[79]: 99%).



105

Formula: C_5H_5BrO

M: 161.00 g/mol

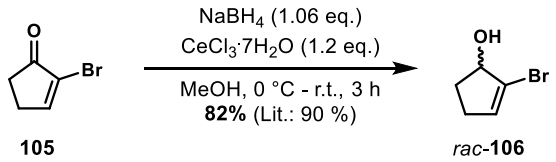
R_f: 0.23 (SiO_2, 7:1, *c*Hex/EtOAc).

^{1}H NMR: (300 MHz, $CDCl_3$): δ [ppm] = 7.77 (t, *J* = 2.9 Hz, 1H, H-4), 2.69 (ddd, *J* = 4.4, 3.6, 2.2 Hz, 2H, H-2), 2.58 – 2.46 (m, 2H, H-3).

^{13}C NMR: (75 MHz, $CDCl_3$): δ [ppm] = 201.8 (C-1), 161.9 (C-4), 126.4 (C-5), 32.5 (C-2), 28.1 (C-3).

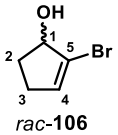
The analytical data are in accordance with the literature.[79]

4.2.2. *rac*-2-Bromo-cyclopent-2-ene-1-ol



105 *rac*-**106**

According to a procedure by Ramadhar *et al.*[82], a solution of bromoenone **105** (2.00 g, 12.4 mmol, 1.0 eq.) and $CeCl_3$ heptahydrate (5.58 g, 14.9 mmol, 1.2 eq.) in MeOH (34 ml) was cooled to 0 °C and subsequently $NaBH_4$ (497 mg, 13.1 mmol, 1.06 eq.) was added in one portion. The reaction mixture was stirred at 0 °C for 1 h and then stirred for 2 h at r.t. After full conversion of the starting material (TLC), the reaction was terminated upon careful addition of an aq. 1M HCl solution and the mixture was stirred for 15 min. The aq. phase was extracted thrice with CH_2Cl_2, the combined org. phases were washed with a sat. aq. NaCl solution and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 5:1). The desired allylic alcohol *rac*-**106** was obtained as a colorless oil (1.85 g, 10.1 mmol, 82%, Lit.[82]: 90%).



rac-**106**

Formula: C_5H_7BrO

M: 163.01 g/mol

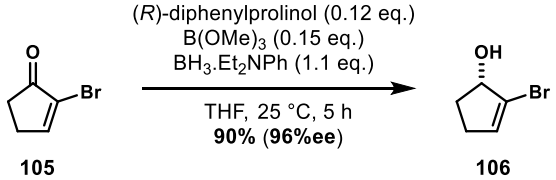
R_f: 0.19 (SiO_2, 4:1, *c*Hex/EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 6.06 (td, *J* = 2.6, 0.9 Hz, 1H, H-4), 4.76 – 4.66 (m, 1H, H-1), 2.51 – 2.35 (m, 2H, H-2, H-3), 2.31 – 2.24 (m, 1H, H-3), 2.02 (d, *J* = 5.2 Hz, 1H, OH), 1.87 (ddt, *J* = 13.6, 9.0, 4.5 Hz, 1H, H-2).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 134.2 (C-4), 125.0 (C-5), 79.4 (C-1), 30.2 (C-3), 31.9 (C-2).

The analytical data are in accordance with the literature.[82]

4.2.3. (*S*)-2-Bromo-cyclopent-2-ene-1-ol

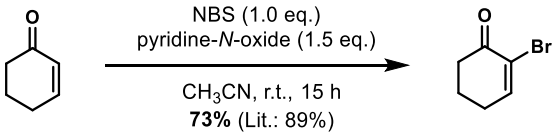


105 106

According to a modified procedure by Kobayashi *et al.*[83], to a solution of (*R*)-diphenylprolinol (17 mg, 0.067 mmol, 0.12 eq.) in THF (1.2 ml) was added $B(OMe)_3$ (0.010 ml, 0.089 mmol, 0.15 eq.). After stirring for 30 min at r.t., $BH_3{\cdot}Et_2NPh$ (0.12 ml, 0.64 mmol, 1.1 eq.) was added and the reaction mixture was stirred for further 15 min at r.t. Then, it was cooled to 0 °C, followed by the slow addition of the bromoenone **105** (94 mg, 0.58 mmol, 1.0 eq.) in THF (6.0 ml). The reaction mixture was slowly warmed to r.t. and stirred for 5 h. The reaction was terminated by addition of an aq. 1M HCl solution and MeOH. The aq. phase extracted thrice with EtOAc, the combined org. phases were washed with a sat. aq. $NaHCO_3$ solution and with a sat. aq. NaCl solution. The org. phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 4:1) and the desired allylic alcohol **106** was obtained as a colorless oil (84 mg, 0.52 mmol, 90%, 96%ee).

The analytical data are in accordance with the literature and the previously synthesized *rac*-2-bromo-cyclopent-2-ene-1-ol (*rac*-**106**).[82]

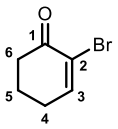
4.2.4. 2-Bromo-cyclohex-2-ene-1-one



109 110

According to a procedure by Bovonsombat *et al.*[162], to a solution of 2-cyclohexene-1-one (**109**) (8.0 ml, 83 mmol, 1.0 eq.) in 410 ml CH_3CN was added pyridine-*N*-oxide (11.8 g, 125 mmol, 1.5 eq.) and NBS (14.9 g, 83.7 mmol, 1.0 eq.) of. The reaction mixture was stirred for 15 h at r.t. After full conversion of the cyclohexanone, water was added and the aq. phase was extracted thrice with MTBE. The combined org. phases were washed with sat. aq. NaCl solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column

chromatography (SiO_2, 7:1, *c*Hex/EtOAc) and the desired bromoenone **110** was obtained as a yellow solid (10.5 g, 60.1 mmol, 73%, Lit.[162]: 89%)



110

Formula: C_6H_7BrO

M: 175.03 g/mol

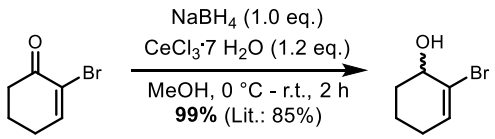
R_f: 0.32 (SiO_2, 7:1, *c*Hex/EtOAc).

^{1}H NMR: (300 MHz, $CDCl_3$): δ [ppm] = 7.44 (t, *J* = 8.9 Hz, 1H, H-3), 2.65 (t, *J* = 13.5 Hz, 2H, H-6), 2.50 - 2.44 (m, 2H, H-5), 2.13 – 2.05 (m, 2H, H-4).

^{13}C NMR: (75 MHz, $CDCl_3$): δ [ppm] = 151.1 (C-1), 123.9 (C-3), 38.3 (C-2), 28.3 (C-6), 26.9 (C-5), 22.6 (C-4).

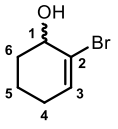
The analytical data are in accordance with the literature.[163]

4.2.5. *rac*-2-Bromocyclohex-2-ene-1-ol



110 *rac*-**111**

According to a procedure by Suffert *et al.*[164], a solution of 2-bromocyclohex-2-en-1-on (**110**) (4.64 g, 26.8 mmol, 1.0 eq.) and $CeCl_3 \cdot 7H_2O$ (12.0 g, 32.2 mmol, 1.2 eq.) in 70 ml MeOH was cooled to 0 °C. $NaBH_4$ (1.02 g, 26.8 mmol, 1.0 eq.) was added in portions and the reaction mixture was stirred for 30 min at 0 °C. It was subsequently warmed to r.t. and stirred for further 30 min. Then, the reaction was stopped by careful addition of an aq. 1M HCl solution. The aq. phase was extracted thrice with CH_2Cl_2, the combined org. phases were washed with a sat. aq. NaCl solution and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (SiO_2, 6:1, cHex/EtOAc). The desired alcohol *rac*-**111** was obtained as a colorless oil (4.70 g, 26.5 mmol, 99%, Lit.[164]: 85%).



rac-**111**

Formula: C_6H_9BrO

M: 177.04 g/mol

R_f: 0.26 (SiO_2, 4:1, cHex/EtOAc).

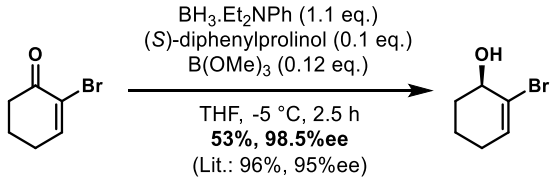
^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 6.22 – 6.20 (t, *J* = 4.1 Hz, 1H, H-3), 4.21 (q, *J* = 4.7 Hz, 1H, H-1), 2.22 (d, *J* = 4.3 Hz, 1H, OH), 2.18 – 2.10 (m, 1H,

H-4), 2.05 (m, 1H, H-4), 1.99 – 1.86 (m, 2H, H-6), 1.74 (m, 1H, H-5), 1.68 – 1.60 (m, 1H, H-5).

^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 132.6 (C-3), 125.8 (C-2), 69.8 (C-1), 32.0 (C-6), 27.8 (C-4), 17.6 (C-5).

The analytical data are in accordance with the literature.[164]

4.2.6. (*R*)-2-Bromocyclohex-2-ene-1-ol

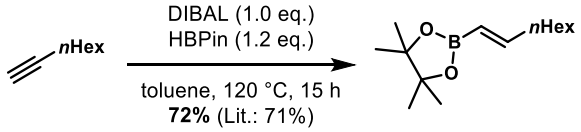


110 **111**

According to a procedure by Kobayashi *et al.*[83], a solution of (*S*)-diphenylprolinol (0.58 g, 2.3 mmol, 0.1 eq.) and $B(OMe)_3$ (0.31 ml, 2.7 mmol, 0.12 eq.) in 48 ml THF was stirred for 1 h at r.t. under an argon atmosphere. Then, $BH_3{\cdot}Et_2NPh$ (4.5 ml, 25 mmol, 1.1 eq.) was added at -12 °C. After stirring for 10 min, a 0.01M solution of bromonenone **110** (4.00 g, 22.9 mmol, 1.0 eq.) in 230 ml THF was added dropwise over 1 h at -5 °C to -2 °C. The mixture was stirred for 4.5 h and the reaction was terminated by addition of MeOH (30 ml) and 1M HCl (30 ml). The aq. phase was extracted thrice with EtOAc, the combined org. phases were washed with a sat. aq. $NaHCO_3$ solution and with a sat. aq. NaCl solution. They were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 9:1). The alcohol **111** was obtained as a colorless oil (2.04 g, 1.15 mmol, 53%, 98.5%ee, Lit.[83]: 96%, 95%ee).

The analytical data are in accordance with the previously synthesized *rac*-2-bromocyclohex-2-ene-1-ol (*rac*-**111**).[83]

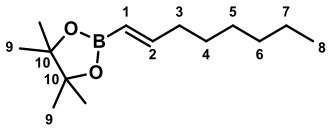
4.2.7. (*E*)-4,4,5,5-Tetramethyl-2-(oct-1-enyl)-1,3,2-dioxaborolane



103 **107**

According to a procedure by Cowley *et al.*[84], to a solution of octyne (**103**) (8.0 ml, 55.9 mmol, 1.0 eq.) and DIBALH (1M in THF, 5.5 ml, 5.5 mmol, 1.0 eq.) in 215 ml toluene was added pinacolborane (10.0 ml, 68.1 mmol, 1.2 eq.). The reaction mixture

was stirred at reflux for 15 h until full conversion of the starting material was observed (GC-MS). The reaction mixture was filtered through a pad of SiO_2 and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 49:1) and the desired pinacolboronate **107** was obtained as a colorless oil (9.58 g, 40.3 mmol, 72%, Lit.[84]: 71%).



107

Formula: $C_{14}H_{27}BO_2$

M: 238.18 g/mol

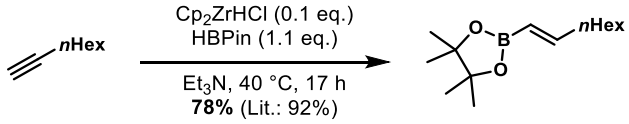
R_f: 0.45 (SiO_2, 24:1, *c*Hex/EtOAc).

^{1}H NMR: (300 MHz, $CDCl_3$): δ [ppm] = 6.63 (dt, *J* = 18.0, 6.4 Hz, 1H, H-2), 5.42 (dt, *J* = 17.9, 1.6 Hz, 1H, H-1), 2.18-2.12 (m, 2H, H-3), 1.42-1.37 (m, 2H, H-4), 1.31-1.25 (m, 18H, H-5, H-6, H-7, H-9), 0.86 (t, *J* = 7.0 Hz, 3H, H-8).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 154.9 (C-2), 83.0 (C-1), 35.9 (C-10), 31.7 (C-3), 28.9 (C-4), 28.2 (C-5), 26.9 (C-6), 24.8 (C-9), 22.6 (C-7), 14.1 (C-8).

The analytical data are in accordance with the literature.[84]

4.2.8. (*E*)-4,4,5,5-Tetramethyl-2-(oct-1-enyl)-1,3,2-dioxaborolane

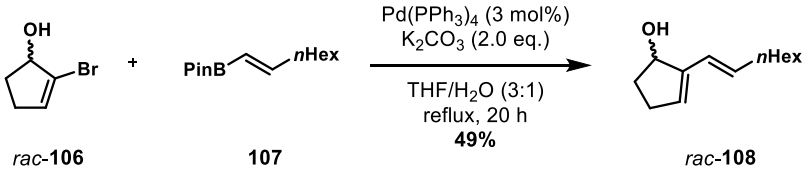


103 **107**

According to a procedure by Wai Lam *et al.*[165], to a mixture of 1-octyne (**103**) (5.4 ml, 36 mmol, 1.0 eq.), pinacolborane (5.6 ml, 39 mmol, 1.1 eq.) and Et_3N (0.51 ml, 3.6 mmol, 0.10 eq.) was added Cp_2ZrHCl (0.940 g, 3.63 mmol, 0.10 eq.) at r.t. The reaction mixture was warmed to 40 °C, stirred for 17 h and the reaction was terminated upon addition of 50 ml water. The aq. phase was extracted thrice with MTBE, the combined org. phases were washed with a sat. aq. NaCl solution and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 99:1 → 98:2 → 96:4). The pinacolboronate **107** was obtained as a pale-yellow oil (6.76 g, 28.4 mmol, 78%, Lit.[165]: 92%).

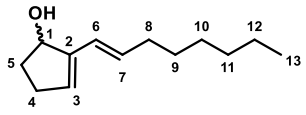
The analytical data are in accordance with the literature and with the previously synthesized pinacolboronate **107**.

4.2.9. *rac*-1-Hydroxy-2-(1-octen-1-yl)-cyclopent-2-ene



rac-**106** **107** *rac*-**108**

To a solution of *rac*-2-bromocyclopent-2-ene-1-ol (**106**) (980 mg, 6.01 mmol, 1.0 eq.), K_2CO_3 (1.76 g, 12.7 mmol, 2.0 eq.), $Pd(PPh_3)_4$ (215 mg, 0.185 mmol, 0.03 eq.) in a water/THF mixture (6.5 ml/18.5 ml) was added pinacolboronate **107** (1.55 g, 6.45 mmol, 1.05 eq.). The reaction mixture was heated to reflux and stirred for 20 h. After confirmation of full conversion of the starting material (TLC), it was cooled to r.t. and the reaction was stopped by addition of 1M aq. HCl. The aq. phase was extracted thrice with MTBE, the combined org. phases were washed with a sat. aq. NaCl solution and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 19:1). The desired alcohol *rac*-**108** was obtained as a colorless oil (587 mg, 3.02 mmol, 49%).



rac-**108**

Formula: $C_{13}H_{22}O$

M: 194.32 g/mol

R_f: 0.20 (SiO_2, 6:1, cHex/EtOAc).

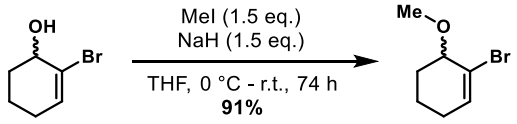
^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 6.14 (d, *J* = 15.9 Hz, 1H, H-6), 5.96 – 5.87 (dt, *J* = 15.9, 6.94 Hz, 1H, H-7), 5.74 (t, *J* = 2.4 Hz, 1H, H-3), 4.96 (dd, *J* = 4.7, 2.7 Hz, 1H, H-1), 2.60 – 2.49 (m, 1H, H-5), 2.34 – 2.20 (m, 2H, H-5, H-4), 2.11 (dq, *J* = 13.8, 6.9 Hz, 2H, H-8), 1.88 – 1.80 (m, 1H, H-4), 1.52 (s, 1H, OH), 1.45 – 1.37 (m, 2H, H-9), 1.34 – 1.24 (m, 6H, H-10, H-11, H-12), 0.93 – 0.84 (m, 3H, H-13).

^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 144.2 (C-2), 132.5 (C-7), 131.2 (C-3), 124.6 (C-6), 76.4 (C-1), 34.1 (C-4), 33.2 (C-8), 31.9 (C-11), 30.3 (C-5), 29.4 (C-9), 29.1 (C-10), 22.8 (C-12), 14.2 (C-13).

HR-MS: (GC-EI-MS, 70 eV) *m/z* (%): 176.1559 (55, [M-H_2O]), 119.0856 (20, [M-$C_4H_{11}O$]), 105.0699 (100, [M-$C_5H_{13}O$]), 91.0543 (95, [M-$C_6H_{15}O$]), 79.0543 (45).

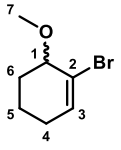
FT-IR (ATR): $\tilde{\upsilon}$ [cm^{-1}]: 3331 (bw), 3034 (w), 2956 (m), 2924 (s), 2852 (m), 1456 (m), 1435 (w), 1378 (w), 1312 (w), 1222 (w), 1150 (w), 1043 (s), 964 (s), 937 (m), 838 (m), 813 (w), 723 (w), 614 (w).

4.2.10. *rac*-2-Bromo-1-methoxycyclohex-2-ene



rac-**111** *rac*-**122**

A suspension of NaH (339 mg, 14.1 mmol, 1.5 eq.) in 20 ml THF was cooled to 0 °C. Then, a solution of alcohol *rac*-**111** (1.61 g, 9.09 mmol, 1.0 eq.) and MeI (0.87 ml, 14 mmol, 1.5 eq.) in 4.3 ml THF was added slowly to the previously described suspension over 1 h. After 1.5 h, the reaction mixture was warmed to r.t. and stirred for further 20 h. Hence still starting material could be detected (TLC), further NaH (340 mg, 14.1 mmol, 1.5 eq.) and MeI (0.58 ml, 9.3 mmol, 1.0 eq.) were added to the reaction mixture. After 72 h full conversion of the starting material was detected (TLC) and the reaction was stopped by addition of sat. aq. NH_4Cl. The aq. phase was extracted thrice with MTBE, the combined org. phases were washed once with sat. aq. NaCl solution and dried over $MgSO_4$. The crude product was purified by column chromatography (SiO_2, 24:1, *c*Hex/EtOAc) and the methylether *rac*-**122** was obtained as a colorless oil (1.58 g, 8.27 mmol, 91%).



rac-**122**

Formula: $C_7H_{11}BrO$

M: 191.07 g/mol

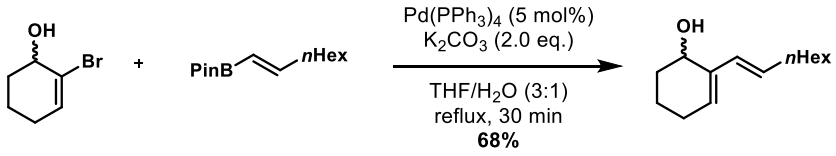
R_f: 0.17 (SiO_2, 24:1, *c*Hex/EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 6.24 (dd, *J* = 4.9, 3.3 Hz, 1H, H-3), 3.75 (dd, *J* = 4.1, 2.9 Hz, 1H, H-1), 3.45 (s, 3H, H-7), 2.18 – 2.08 (m, 1H, H-4), 2.08 – 1.97 (m, 2H, H-4, H-6), 1.78 – 1.64 (m, 2H, H-5, H-6), 1.65 – 1.54 (m, 1H, H-5).

^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 133.5 (C-3), 122.7 (C-2), 78.6 (C-1), 57.4 (C-7), 28.4 (C-6), 27.8 (C-4), 17.0 (C-5).

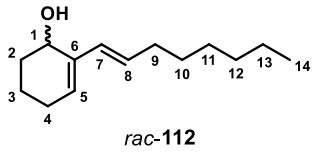
The analytical data are in accordance with the literature.[166]

4.2.11. *rac*-1-Hydroxy-2-(1-octen-1-yl)-cyclohex-2-ene



rac-**111** **107** *rac*-**112**

To a solution of *rac*-2-bromocyclohex-2-en-1-ol (*rac*-**111**) (2.00 g, 11.3 mmol, 1.0 eq.), K_2CO_3 (3.12 g, 22.6 mmol, 2.0 eq.) and $Pd(PPh_3)_4$ (652 mg, 0.565 mmol, 0.05 eq.) in a water (11.5 ml)/THF (34 ml) mixture was added pinacolboronate **107** (2.83 g, 11.9 mmol, 1.05 eq.). The reaction mixture was heated to reflux and stirred for 30 min. After confirmation of full conversion by (TLC), the reaction mixture was cooled to r.t. and the reaction was stopped by addition of 1M aq. HCl. The aq. phase was extracted thrice with MTBE, the combined org. phases were washed with sat. aq. NaCl solution and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, 19:1, *c*Hex/EtOAc). The alcohol *rac*-**112** was obtained as a colorless oil (1.59 g, 7.63 mmol, 68%).



rac-**112**

Formula: $C_{14}H_{24}O$

M: 208.35 g/mol

R_f: 0.21 (SiO_2, 14:1, *c*Hex/EtOAc).

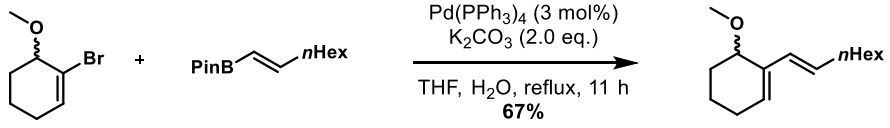
^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 5.95 (d, *J* = 16.0 Hz, 1H, H-7), 5.85 (dt, *J* = 15.9, 6.6 Hz, 1H, H-8), 5.74 (dd, *J* = 4.87, 3.28 Hz, 1H, H-5), 4.44 (s, 1H, H-1), 2.17 (m, 1H, H-4), 2.13 – 2.01 (m, 3H, H-4, H-9), 1.95 – 1.88 (m, 1H, H-2), 1.78 – 1.57 (m, 4H, H-2, H-3, OH), 1.39 (q, *J* = 7.3 Hz, 2H, H-10), 1.35 – 1.22 (m, 6H, H-11, H-12, H-13), 0.88 (t, *J* = 6.9 Hz, 3H, H-14).

^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 137.3 (C-6), 131.0 (C-7), 129.8 (C-5), 128.8 (C-8), 63.7 (C-1), 33.1 (C-9), 31.9 (C-12), 31.2 (C-2), 29.6 (C-10), 29.1 (C-11), 26.0 (C-4), 22.8 (C-13), 17.2 (C-3), 14.3 (C-14).

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}]: 3338 (bw), 2924 (s), 2855 (m), 1456 (m), 1437 (m), 1378 (w), 1357 (w), 1334 (w), 1252 (w), 1158 (m), 1080 (m), 1053 (m), 986 (s), 964 (s), 920 (m), 873 (w), 836 (w), 797 (m), 724 (w), 564 (w).

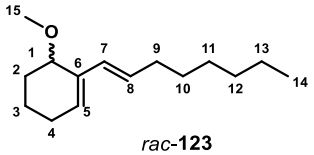
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{14}H_{24}ONa$ $[M+Na]^+$ 231.1719 u, found: 231.1721 u.

4.2.12. *rac*-1-Methoxy-2-(1-octen-1-yl)-cyclohex-2-ene



rac-**122** **107** *rac*-**123**

To a solution of bromide *rac*-**122** (1.40 g, 7.33 mmol, 1.0 eq.), K_2CO_3 (2.07 g, 14.9 mmol, 2.0 eq.) and $Pd(PPh_3)_4$ (254 mg, 0.220 mmol, 0.03 eq.) in a THF/water (22 ml/7.5 ml) mixture was added pinacolboronate **107** (1.83 g, 7.69 mmol, 1.05 eq.). The reaction mixture was heated at reflux for 11 h. After cooling to r.t., the reaction was stopped by addition of 10% aq. HCl. The aq. phase was extracted thrice with MTBE, the combined org. phases were washed with sat. aq. NaCl solution and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 49:1). The desired diene **123** was obtained as a colorless oil (1.05 g, 4.90 mmol, 67%.)



rac-**123**

Formula: $C_{15}H_{26}O$

M: 222.37 g/mol

R_f: 0.35 (SiO_2, 24:1, *c*Hex/EtOAc).

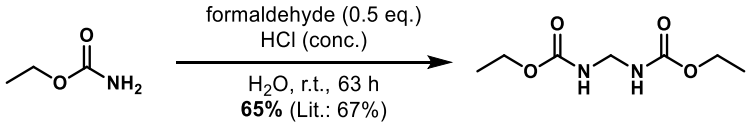
^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 5.95 (d, *J* = 15.8 Hz, 1H, H-7), 5.80 – 5.76 (m, 1H, H-5), 5.68 (dd, *J* = 15.8, 6.9 Hz, 1H, H-8), 3.89 (s, 1H, H-1), 3.38 (s, 3H, H-15), 2.21 – 2.00 (m, 5H, H-2, H-4, H-9), 1.77 – 1.67 (m, 1H, H-3), 1.57 – 1.50 (m, 1H, H-3), 1.47 – 1.36 (m, 3H, H-2, H-10), 1.34 – 1.24 (m, 6H, H-11, H-12, H-13), 0.88 (t, *J* = 7.0 Hz, 3H, H-14).

^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 135.9 (C-6), 131.3 (C-7), 130.3 (C-5), 128.2 (C-8), 72.7 (C-1), 56.2 (C-15), 33.1 (C-9), 31.9 (C-12), 29.7 (C-10), 29.1 (C-11), 26.0 (C-4), 25.9 (C-2), 22.8 (C-13), 17.3 (C-3), 14.3 (C-14).

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}]: 2925 (s), 1855 (m), 1638 (w), 1455 (m), 1435 (w), 1358 (m), 1333 (w), 1253 (w), 1187 (w), 1146 (w), 1091 (s), 1071 (s), 960 (s), 942 (w), 915 (m), 849 (w), 809 (w), 724 (w), 673 (w).

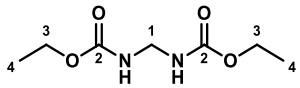
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{15}H_{27}O$ $[M+H]^+$ 223.2056 u, found: 223.2058 u; $C_{15}H_{26}ONa$ $[M+Na]^+$ 245.1876 u, found: 245.1876 u.

4.2.13. Diethyl methylenedicarbamate



352 **85**

According to a procedure by Frauenfelder[167], to a solution of urethane **352** (11.2 g, 125 mmol, 1.0 eq.) and aq. formaldehyde (37 w%, 5.0 ml, 62 mmol, 0.5 eq.) in 50 ml water was added 0.75 ml conc. aq. HCl. The reaction mixture was stirred at r.t. for 63 h and was subsequently cooled to 0 °C. The precipitate was filtered and washed with cold water. The colorless solid was dried under reduced pressure and recrystallized from EtOH/H_2O. The desired diethyl methylenedicarbamate (**85**) was obtained as a colorless solid (7.57 g, 39.8 mmol, 65%, Lit.[167]: 67%).



85

Formula: $C_7H_{14}N_2O_4$

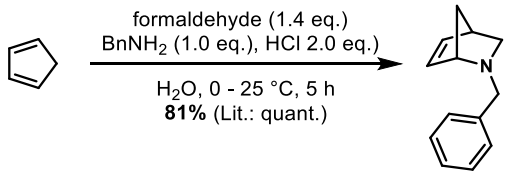
M: 190.20 g/mol

^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 5.88 – 5.39 (m, 2H, NH), 4.49 (t, *J* = 6.6 Hz, 2H, H-1), 4.11 (q, *J* = 7.1 Hz, 4H, H-3), 1.23 (t, *J* = 7.1 Hz, 6H, H-4).

^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 157.0 (C-2), 61.3 (C-1), 48.1 (C-3), 14.7 (C-4).

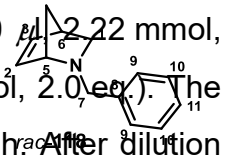
The analytical data are in accordance with the literature.[167]

4.2.14. *rac*-*N*-Benzyl-2-azanorbornene



115 ***rac*-118**

According to a procedure by Larsen *et al.*[71], to a cooled suspension (0 °C) of benzylamine (0.17 ml, 1.6 mmol, 1.0 eq.) and conc. aq. HCl (12M, 260 µl, 3.12 mmol, 2.0 eq.) in 620 µl water was added aq. formaldehyde (37 w%, 180 µl, 2.22 mmol, 1.4 eq.) and freshly distilled cyclopentadiene **115** (260 µl, 3.15 mmol, 2.0 eq.). The reaction mixture was subsequently warmed to r.t. and stirred for 5 h. After dilution with water, the aq. phase was washed twice with MTBE, basified by addition of KOH and extracted thrice with MTBE. The combined org. phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The desired product *rac*-**118** was obtained as a colorless oil (233 mg, 1.26 mmol, 81%, Lit.[71]: quant.)



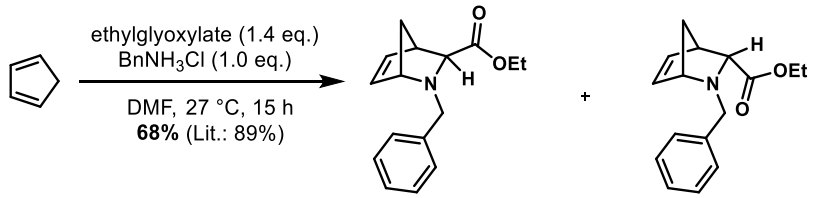
Formula: $C_{15}H_{13}N$

M: 185.27 g/mol

^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 7.36 – 7.20 (m, 5H, H-9, H-10, H-11), 6.37 (dd, *J* = 5.0, 3.4 Hz, 1H, H-3), 6.08 (dd, *J* = 5.6, 1.8 Hz, 1H, H-2), 3.82 – 3.80 (m, 1H, H-5), 3.57 (d, *J* = 13.1 Hz, 1H, H-7), 3.33 (d, *J* = 13.1 Hz, 1H, H-7´), 3.17 (dd, *J* = 8.7, 3.1 Hz, 1H, H-1), 2.92 (s, 1H, H-6), 1.63 (d, *J* = 8.1 Hz, 1H, H-4), 1.52 (dd, *J* = 8.6, 1.4 Hz, 1H, H-1), 1.43 – 1.38 (m, 1H, H-4).

The analytical data are in accordance with the literature.[168]

4.2.15. *rac-N*-Benzyl-2-azanorbornene-1-carboxylic acid ethyl ester

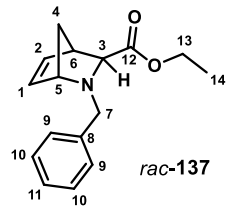


115 **1.83** (*rac*-**137**) : **1** (*rac*-**138**)

According to a procedure by Bailey *et al.*[87], a solution of freshly distilled cyclopentadiene **115** (331 mg, 5.01 mmol, 2.0 eq.), freshly distilled ethyl glyoxylate in toluene (50 w%, 714 mg, 3.50 mmol, 1.4 eq.) and $BnNH_2$·HCl (360 mg, 2.51 mmol, 1.0 eq.) in 10 ml DMF was was stirred overnight at r.t. Then, the mixture was diluted with a sat. aq. $NaHCO_3$ solution and the aq. phase was extracted thrice with MTBE. The combined org. phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 9:1). The received *endo* (*rac*-**138**) and *exo* (*rac*-**137**) products were

obtained as yellow orange oils with a combined yield of 434 mg (1.68 mmol, 68%, Lit.[87]: 89%). The isolated yields for the *exo* product (*rac*-**137**) was 284 mg (1.10 mmol, 44%), while the isolated yield of the *endo* (*rac*-**138**) product was 156 mg (0.606 mmol, 24%).

Analytical data for the *exo*-product (*rac*-**137**):



rac-**137**

Formula: $C_{16}H_{19}NO_2$

M: 257.33 g/mol

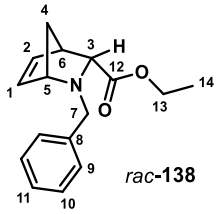
R_f: 0.30 (SiO_2, 9:1, *c*Hex/EtOAc).

^{1}H NMR: (300 MHz, $CDCl_3$): δ [ppm] = 7.44 – 7.11 (m, 5H, H-9, H-10, H-11), 6.48 (m, 1H, H-2), 6.25 (dd, *J* = 5.6, 2.0 Hz, 1H, H-1), 4.05 (q, *J* = 7.1 Hz, 2H, H-13), 3.89 (s, 1H, H-3), 3.61 (d, *J* = 12.6 Hz, 1H, H-7), 3.42 (d, *J* = 12.6 Hz, 1H, H-7´), 3.08 (m, 1H, H-6), 2.29 (s, 1H, H-5), 1.98 (dt, *J* = 8.3, 1.7 Hz, 1H, H-4), 1.39 (d, *J* = 9.5, 1.4 Hz, 1H, H-4´), 1.14 (t, *J* = 7.1 Hz, 3H, H-14).

^{13}C NMR: (75 MHz, $CDCl_3$): δ [ppm] = 174.0 (C-12), 139.3 (C-8), 136.6 (C-9), 133.6 (C-10), 129.1 (C-11), 128.2 (C-2), 127.0 (C-1), 64.9 (C-13), 64.3 (C-3), 60.5 (C-7), 59.0 (C-6), 48.5 (C-5), 46.6 (C-4), 14.2 (C-14).

The analytical data are in accordance with the literature.[87]

Analytical data for the *endo*-product (*rac*-**138**):



rac-**138**

Formula: $C_{16}H_{19}NO_2$

M: 257.33 g/mol

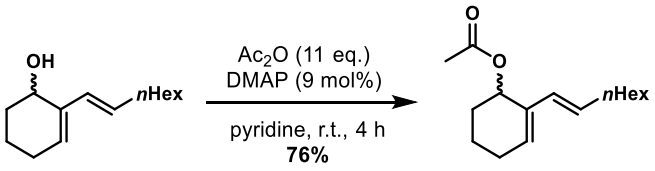
R_f: 0.10 (SiO_2, 9:1, *c*Hex/EtOAc).

^{1}H NMR: (300 MHz, $CDCl_3$): δ [ppm] = 7.47 – 7.13 (m, 5H, H-9, H-10, H-11), 6.48 (dd, *J* = 5.7, 3.0 Hz, 1H, H-2), 6.22 – 6.08 (m, 1H, H-1), 4.11 – 3.93 (m, 2H, H-13), 3.86 (d, *J* = 2.5 Hz, 2H, H-5, H-6), 3.71 (s, 1H, H-3), 3.42 - 3.33 (m, 2H, H-7), 1.87 – 1.80 (m, 1H, H-4), 1.57 (dt, *J* = 8.6, 1.3 Hz, 1H, H-4´), 1.14 (t, *J* = 7.1 Hz, 3H, H-14).

^{13}C NMR: (75 MHz, $CDCl_3$): δ [ppm] = 173.0 (C-12), 139.3 (C-8), 138.7 (C-9), 135.1 (C-10), 129.2 (C-11), 128.2 (C-2), 127.0 (C-1), 66.1 (C-13), 65.0 (C-3), 61.0 (C-7), 60.3 (C-6), 47.9 (C-5), 45.3 (C-4), 14.2 (C-14).

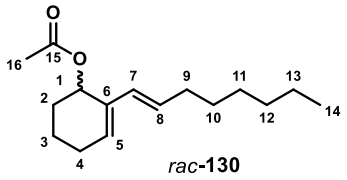
The analytical data are in accordance with the literature.[87]

4.2.16. *rac*-1-Acetoxy-2-(1-octen-1-yl)-cyclohex-2-ene



rac-**112** *rac*-**130**

To a solution of dienol *rac*-**112** (302 mg, 1.45 mmol, 1.0 eq.) in 1.8 ml pyridine was added DMAP (16 mg, 0.13 mmol, 0.09 eq.) and Ac_2O (1.5 ml, 16 mmol, 11 eq.) at r.t. After 4 h, the solution was diluted with MTBE and water. The aq. phase was extracted thrice with MTBE, the combined org. phases were washed with water and sat. aq. NaCl solution and finally dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 19:1). The desired product *rac*-**130** was obtained as a colorless oil (290 mg, 1.10 mmol, 76%).



rac-**130**

Formula: $C_{16}H_{26}O_2$

M: 250.38 g/mol

R_f: 0.15 (SiO_2, 19:1, *c*Hex/EtOAc).

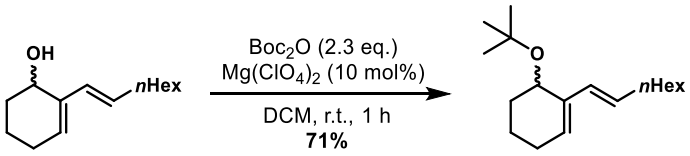
^{1}H NMR: (400 MHz, $CDCl_3$) δ [ppm]: 5.96 – 5.89 (m, 2H, H-5, H-7), 5.62 (t, *J* = 2.9 Hz, 1H, H-1), 5.54 (dt, *J* = 15.8, 6.9 Hz, 1H, H-8), 2.28 – 2.19 (m, 1H, H-4), 2.01 – 2.15 (m, 6H, H-4, H-9, H-16), 1.97 – 1.90 (m, 1H, H-2), 1.71 – 1.60 (m, 3H, H-2, H-3), 1.39 – 1.22 (m, 8H, H-10, H-11, H-12, H-13), 0.87 (t, *J* = 6.8 Hz, 3H, H-14).

^{13}C NMR: (101 MHz, $CDCl_3$) δ [ppm]: 170.9 (C-15), 133.8 (C-6), 132.0 (C-5), 130.3 (C-7), 128.8 (C-8), 66.1 (C-1), 33.1 (C-9), 31.9 (C-12), 29.6 (C-10), 29.0 (C-11), 28.8 (C-2), 25.7 (C-4), 22.8 (C-13), 21.5 (C-16), 17.5 (C-3), 14.2 (C-14).

FT-IR (ATR): $\tilde{\upsilon}$ [cm^{-1}]: 2926 (m), 2855 (w), 1731 (s), 1455 (w), 1439 (w), 1370 (m), 1360 (w), 1338 (w), 1234 (s), 1158 (w), 1053 (m), 1013 (m), 989 (m), 965 (m), 932 (w), 915 (m), 799 (w), 724 (w), 610 (w).

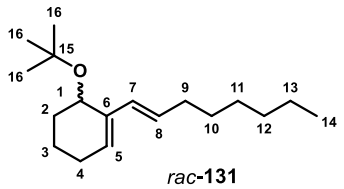
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{16}H_{26}O_2Na$ $[M+Na]^+$ 273.1825 u, found: 273.1827 u.

4.2.17. *rac*-1-(1,1-Dimethylethoxy)-2-(1-octen-1-yl)-cyclohex-2-ene



rac-**112** *rac*-**131**

$Mg(ClO_4)_2$ (32 mg, 0.14 mmol, 0.1 eq.) was heated to 130 °C under vacuum for 4 h. Then, the flask was filled with argon and cooled to r.t., followed by the suspension of the $Mg(ClO_4)_2$ in 2.2 ml CH_2Cl_2. Dienol *rac*-**112** (297 mg, 1.43 mmol, 1.0 eq.) and Boc_2O (0.71 ml, 3.3 mmol, 2.3 eq.) were added to the suspension and the reaction mixture was stirred for 1 h at r.t. After full conversion of the starting material (TLC), water was added and the aq. phase was extracted thrice with CH_2Cl_2. The combined org. phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 199:1) and the desired product *rac*-**131** was obtained as a colorless oil (266 mg, 1.01 mmol, 71%).



rac-**131**

Formula: $C_{18}H_{32}O$

M: 264.45 g/mol

R_f: 0.14 (SiO_2, 19:1, *c*Hex/EtOAc).

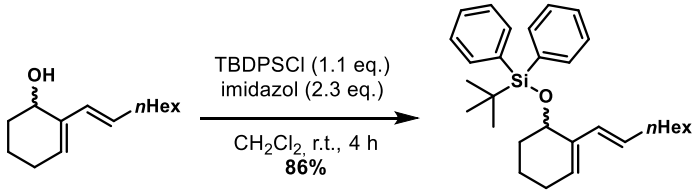
^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 5.91 (d, *J* = 15.7 Hz, 1H, H-7), 5.81 (t, *J* = 3.9 Hz, 1H, H-5), 5.76 (dd, *J* = 15.6, 6.8 Hz, 1H, H-8), 4.18 (s, 1H, H-1), 2.15 (dq, *J* = 18.4, 4.8 Hz, 1H, H-4), 2.09 – 1.96 (m, 3H, H-4, H-9), 1.92 – 1.76 (m, 2H, H-2, H-3), 1.58 – 1.48 (m, 2H, H-2, H-3), 1.42 – 1.34 (m, 2H, H-10), 1.34 – 1.23 (m, 15H, H-11, H-12, H-13, H-16), 0.88 (t, *J* = 7.0 Hz, 3H, H-14).

^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 137.2 (C-6), 131.2 (C-7), 128.7 (C-8), 128.1 (C-5), 73.8 (C-15), 65.7 (C-1), 33.1 (C-9), 31.9 (C-12), 31.2 (C-2), 29.7 (C-10), 29.6 (C-16), 29.1 (C-11), 26.0 (C-4), 22.8 (C-13), 17.4 (C-3), 14.3 (C-14).

FT-IR (ATR): $\tilde{\upsilon}$ [cm^{-1}]: 2958 (m), 2925 (s), 2855 (m), 1456 (w), 1387 (m), 1362 (m), 1332 (w), 1250 (w), 1229 (w), 1192 (s), 1157 (m), 1062 (s), 1005 (s), 961 (s), 907 (w), 928 (m), 798 (w), 724 (w), 570 (w), 462 (w).

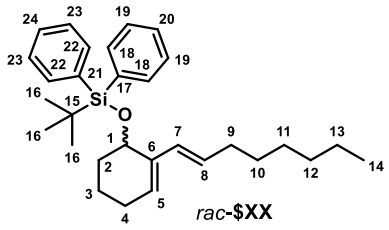
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{18}H_{32}ONa$ $[M+Na]^+$ 287.2345 u, found: 287.2347 u.

4.2.18. *rac*-1-(*tert*-Butyldiphenylsilyloxy)-2-(1-octen-1-yl)-cyclohex-2-ene



rac-**112** *rac*-**132**

To a solution of imidazole (225 mg, 3.31 mmol, 2.3 eq.) in 2.9 ml DMF was added dienol **112** (303 mg, 1.45 mmol, 1.0 eq.) and TBDPSCl (0.41 ml, 1.6 mmol, 1.1 eq.). The solution was stirred at r.t. for 4 h and after confirmation of full conversion of the starting material (TLC), it was diluted with MTBE and water. The aq. phase was extracted thrice with MTBE, the combined org. phases were washed with an aq. 1M HCl and with a sat. aq. NaCl solution. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 49:1). The desired product *rac*-**132** was obtained as a colorless oil (530 mg, 1.23 mmol, 86%).



rac-**$XX**

Formula: $C_{30}H_{42}OSi$

M: 446.75 g/mol

R_f: 0.61 (SiO_2, 19:1, *c*Hex/EtOAc).

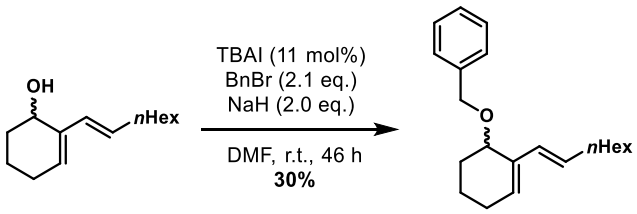
^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 7.69 (dd, *J* = 8.0, 1.4 Hz, 4H, H-18, H-22), 7.44 – 7.33 (m, 6H, H-19, H-20, H-23, H-24), 5.79 (d, *J* = 15.8 Hz, 1H, H-7), 5.71 (dd, *J* = 4.3, 2.6 Hz, 1H, H-5), 5.32 (dt, *J* = 15.6, 6.8 Hz, 1H, H-8), 4.30 (t, *J* = 3.2 Hz, 1H, H-1), 2.24 – 2.16 (m, 1H, H-4), 2.06 – 1.92 (m, 2H, H-3, H-4), 1.90 – 1.80 (m, 3H, H-2, H-9), 1.56 – 1.48 (m, 1H, H-3), 1.44 – 1.35 (m, 1H, H-2), 1.30 – 1.22 (m, 2H, H-13), 1.22 – 1.10 (m, 6H, H-10, H-11, H-12), 1.04 (s, 9H, H-16), 0.87 (t, *J* = 7.2 Hz, 3H, H-14).

^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 137.8 (C-6), 136.4 (C-18/C-22), 136.2 (C-18/C-22), 134.9 (C-17/C-21), 134.2 (C-17/C-21), 130.9 (C-7), 129.6 (C-20/C-24), 129.5 (C-20/C-24), 128.8 (C-8), 128.3 (C-5), 127.5 (C19/C-23), 127.4 (C-19/C-23), 65.7 (C-1), 32.9 (C-9), 31.9 (C-12), 31.9 (C-2), 29.3 (C-10), 29.1 (C-11), 27.2 (C-16), 26.1 (C-4), 22.8 (C-13), 19.5 (C-15), 17.3 (C-3), 14.3 (C-14).

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}]: 3071 (w), 2928 (m), 2856 (m), 1472 (w), 1427 (m), 1389 (w), 1360 (w), 1334 (w), 1253 (w), 1190 (w), 1159 (w), 1109 (m), 1082 (m), 1062 (m), 1015 (m), 998 (m), 964 (m), 931 (w), 897 (w), 821 (m), 804 (w), 738 (m), 700 (s), 614 (m), 589 (w), 505 (s), 485 (s).

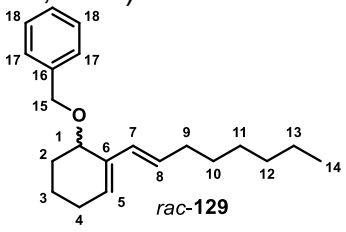
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{30}H_{42}OSiNa$ $[M+Na]^+$ 469.2897 u, found: 469.2900 u.

4.2.19. *rac*-1-(Benzyloxy)-2-(1-octen-1-yl)-cyclohex-2-ene



rac-**112** *rac*-**129**

To a suspension of NaH (60 w%, 117 mg, 2.93 mmol, 2.0 eq.) in 14 ml DMF was added TBAI (58 mg, 0.16 mmol, 0.11 eq.), dienol *rac*-**112** (300 mg, 1.44 mmol, 1.0 eq.) and benzylbromide (0.36 ml, 3.0 mmol, 2.1 eq.). The reaction mixture was stirred for 46 h at r.t. Then, the reaction mixture was neutralized upon addition of a sat. aq. NH_4Cl solution, the aq. phase was extracted thrice with MTBE and the combined org. phases were washed with a sat. aq. NaCl solution. They were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 39:1) and the desired product *rac*-**129** was obtained as a colorless oil (130 mg, 0.436 mmol, 30%).



rac-**129**

Formula: $C_{21}H_{30}O$

M: 298.47 g/mol

R_f: 0.55 (SiO_2, 9:1, *c*Hex/EtOAc).

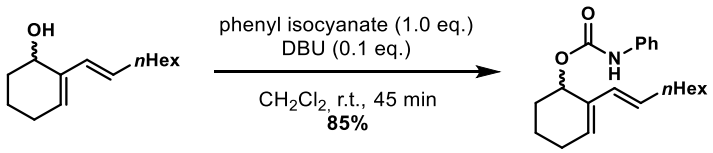
^{1}H NMR: (400 MHz, $CDCl_3$) δ [ppm]: 7.38 – 7.23 (m, 5H, H-17, H-18, H-19), 5.94 (d, *J* = 15.8 Hz, 1H, H-7), 5.80 (t, *J* = 4.5, 3.4 Hz, 1H, H-5), 5.59 (dt, *J* = 15.7, 6.9 Hz, 1H, H-8), 4.66 (d, *J* = 11.5 Hz, 1H, H-15), 4.48 (d, *J* = 11.5 Hz, 1H, H-15), 4.16 (t, *J* = 3.3 Hz, 1H, H-1), 2.23 – 2.01 (m, 5H, H-2, H-4, H-9), 1.82 (tddd, *J* = 13.2, 10.5, 5.8, 2.8 Hz, 1H, H-3), 1.62 – 1.54 (m, 1H, H-3), 1.49 (tt, *J* = 13.5, 3.3 Hz, 1H, H-2), 1.38 – 1.22 (m, 8H, H-10, H-11, H-12, H-13), 0.88 (t, *J* = 6.7 Hz, 3H, H-14).

^{13}C NMR: (101 MHz, $CDCl_3$) δ [ppm]: 139.0 (C-16), 135.8 (C-6), 131.3 (C-7), 130.5 (C-5), 128.4 (C-8), 128.3 (C-19), 128.2 (C-17), 127.6 (C-18), 71.0 (C-1), 70.7 (C-15), 33.2 (C-9), 32.0 (C-12), 29.7 (C-10), 29.1 (C-11), 26.6 (C-2), 26.1 (C-4), 22.8 (C-13), 17.4 (C-3), 14.3 (C-14).

FT-IR (ATR): $\tilde{\upsilon}$ [cm^{-1}]: 3028 (w), 2925 (s), 2854 (m), 1721 (w), 1496 (w), 1453 (m), 1438 (w), 1378 (w), 1354 (w), 1333 (w), 1247 (w), 1206 (w), 1158 (w), 1089 (m), 1067 (s), 1027 (m), 962 (s), 919 (w), 797 (w), 731 (s), 695 (s), 606 (w), 465 (w).

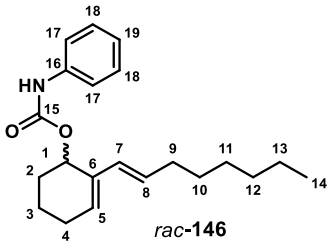
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{21}H_{30}ONa$ $[M+Na]^+$ 321.2189 u, found: 321.2186 u.

4.2.20. *rac*-2-((*E*)-1-Octen-1-yl)-cyclohex-2-en-1-yl phenylcarbamate



rac-**112** *rac*-**146**

To a solution of the dienylic alcohol *rac*-**112** (500 mg, 2.40 mmol, 1.0 eq.) in 2.4 ml CH_2Cl_2 was added phenylisocyanate (0.27 ml, 2.5 mmol, 1.0 eq.) and DBU (0.04 ml, 0.3 mmol, 0.1 eq.). The reaction mixture was stirred at r.t. for 45 min until full conversion of the starting material was observed (TLC). The reaction mixture was diluted with CH_2Cl_2 (15 ml), followed by washing of the org. phase with an aq. 1M HCl solution (3 x 10 ml), with water (2 x 10 ml) and with a sat. aq. NaCl solution (10 ml). The org. phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 9:1) and the desired carbamate *rac*-**146** was obtained as a colorless oil (665 mg, 2.03 mmol, 85%).



rac-**146**

Formula: $C_{21}H_{29}NO_2$

M: 327.47 g/mol

R_f: 0.55 (SiO_2, 2:1, *c*Hex/EtOAc).

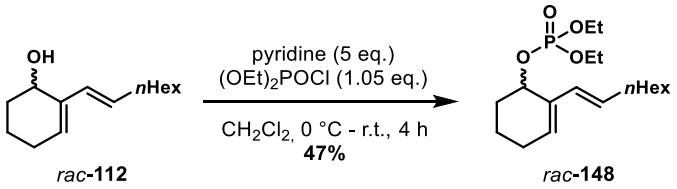
^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 7.39 (d, *J* = 7.9 Hz, 2H, H-17), 7.30 (t, *J* = 8.0 Hz, 2H, H-18), 7.05 (tt, *J* = 7.5, 1.0 Hz, 1H, H-19), 6.63 (s, 1H, NH), 5.99 – 5.92 (m, 2H, H-5, H-7), 5.71 (dt, *J* = 15.5, 6.9 Hz, 1H, H-8), 5.61 (s, 1H, H-1), 2.24 (dt, *J* = 18.6, 3.7 Hz, 1H, H-4), 2.16 – 2.02 (m, 4H, H-2, H-4´, H-9), 1.74 – 1.64 (m, 3H, H-2´, H-3), 1.39 – 1.30 (m, 2H, H-10), 1.28 – 1.19 (m, 6H, H-11, H-12, H-13), 0.83 (t, *J* = 6.9 Hz, 3H, H-14).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 153.3 (C-15), 138.2 (C-16), 133.8 (C-6), 132.1 (C-5), 130.2 (C-7), 129.2 (C-8), 129.2 (C-18), 123.4 (C-19), 118.6 (C-17), 67.0 (C-1), 33.1 (C-9), 31.9 (C-12), 29.5 (C-10), 29.0 (C-11), 28.9 (C-2), 25.8 (C-4), 22.7 (C-13), 17.4 (C-3), 14.2 (C-14).

FT-IR (ATR): ν [cm^{-1}] = 3323 (bw), 2952 (w), 2926 (m), 2855 (w), 1726 (m), 1697 (s), 1601 (m), 1525 (s), 1501 (m), 1442 (s), 1379 (w), 1357 (w), 1311 (m), 1215 (s), 1157 (m), 1082 (m), 1045 (s), 1026 (s), 997 (w), 965 (m), 925 (m), 898 (w), 824 (w), 752 (s), 691 (s), 570 (w), 505 (m).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{21}H_{29}NO_2Na$ $[M+Na]^+$ 350.2091 u, found: 350.2089 u.

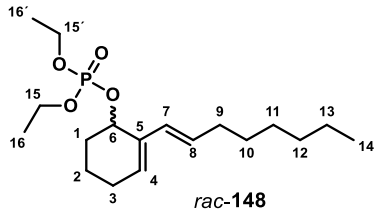
4.2.21. rac-Diethyl 2-((*E*)-oct-1-en-1-yl)-cyclohex-2-en-1-yl phosphate



rac-**112** *rac*-**148**

A solution of dienol *rac*-**112** (199 mg, 0.955 mmol, 1.0 eq.) and pyridine (0.39 ml, 4.8 mmol, 5.1 eq.) in 1.0 ml CH_2Cl_2 was cooled to 0 °C under an argon atmosphere. Then, diethyl chlorophosphate (0.15 ml, 1.0 mmol, 1.05 eq.) was added and the reaction mixture was stirred for 1 h. It was subsequently warmed to r.t. and stirred for further 2 h. Then, another portion of diethyl chlorophosphate (0.05 ml, 0.3 mmol, 0.3 eq.) was added and the reaction mixture was stirred for 1 h at r.t. After

confirmation of full conversion of the starting material (TLC), the reaction mixture was diluted with MTBE. The org. phase was washed thrice with 1M aq. HCl, once with a sat. aq. NaCl solution and with a sat. aq. $NaHCO_3$ solution. The org. phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 1:4) and the desired diethyl phosphate *rac*-**148** was obtained as a pale-yellow oil (155 mg, 0.455 mmol, 47%).



rac-**148**

Formula: $C_{18}H_{33}O_4P$

M: 344.43 g/mol

R_f: 0.30 (SiO_2, 2:1, *c*Hex/EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 6.00 – 5.91 (m, 2H, H-8, H-7), 5.87 (dd, *J* = 5.2, 3.0 Hz, 1H, H-4), 5.18 (dt, *J* = 6.7, 3.2 Hz, 1H, H-6), 4.14 – 4.04 (m, 4H, H-15, H-15´), 2.27 – 2.19 (m, 2H, H-1, H-3), 2.13 – 2.04 (m, 3H, H-3, H-9), 1.83 – 1.61 (m, 3H, H-1, H-2), 1.42 – 1.23 (m, 14H, H-10, H-11, H-12, H-13, H-16, H-16´), 0.88 (t, *J* = 6.9 Hz, 3H, H-14).

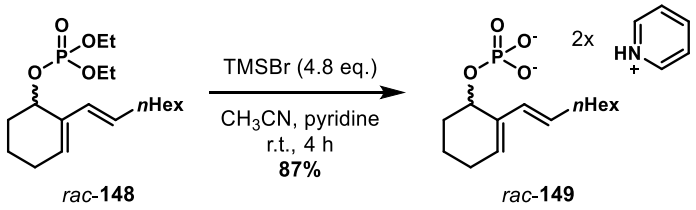
^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 134.1 (d, C-5), 131.5 (C-4), 130.1 (C-7), 129.3 (C-8), 70.9 (d, C-6), 63.6 (dd, C-15, C-15´), 33.3 (C-9), 31.9 (C-10), 29.8 (C-1), 29.6 (C-11), 29.1 (C-12), 25.7 (C-3), 22.8 (C-13), 16.8 (C-2), 16.2 (dd, C-16, C-16´), 14.3 (C-14).

^{31}P NMR: (202 MHz, $CDCl_3$): δ [ppm] = -1.98.

FT-IR (ATR): ν [cm^{-1}] = 3475 (bw), 3028 (w), 2980 (w), 2952 (w), 2927 (m), 2856 (w), 1626 (w), 1479 (w), 1455 (w), 1442 (w), 1393 (w), 1259 (m), 1163 (w), 1033 (s), 983 (s), 906 (w), 879 (w), 819 (w), 753 (w), 675 (w), 617 (w), 570 (w).

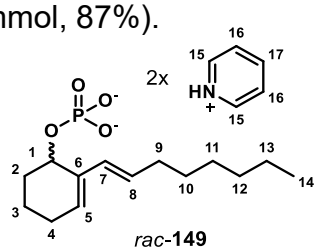
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{18}H_{33}O_4PNa$ $[M+Na]^+$ 367.2012 u, found: 367.2012 u.

4.2.22. *rac*-Dipyridinium 2-((*E*)-oct-1-ene-1-yl)cyclohex-2-ene-1-yl phosphate



rac-**148** *rac*-**149**

To a solution of diethylphosphate *rac*-**148** (1.16 g, 3.35 mmol, 1.0 eq.) and pyridine (19 ml) in 17 ml CH_3CN was added TMSBr (2.2 ml, 16 mmol, 4.8 eq.) under an argon atmosphere. The reaction mixture was stirred for 4 h at r.t. After full conversion of the starting material (TLC), excess of TMSBr was inactivated upon addition of MeOH. Then, all volatiles were removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc/MeOH, 2:2:1). The desired product *rac*-**149** was obtained as an orange viscous oil (1.30 g, 2.92 mmol, 87%).



rac-**149**

Formula: $C_{24}H_{35}N_2O_4P$

M: 446.53 g/mol

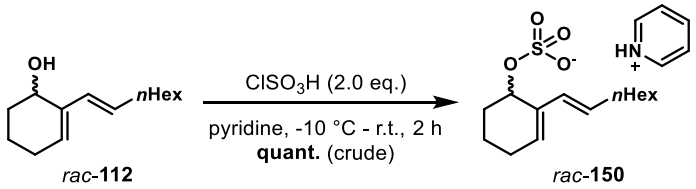
R_f: 0.10 (SiO_2, 2:2:1, *c*Hex/EtOAc/MeOH).

^{1}H NMR: (300 MHz, MeOD-d_4): δ [ppm] = 9.18 – 9.05 (m, 2H, H-15), 9.00 – 8.87 (m, 2H, H-15), 8.69 (tt, *J* = 7.7, 1.5 Hz, 2H, H-16), 8.30 – 8.09 (m, 4H, H-16, H-17), 6.52 (t, *J* = 4.2 Hz, 1H, H-5), 6.08 (d, *J* = 16.1 Hz, 1H, H-7), 5.84 (t, *J* = 4.7 Hz, 1H, H-1), 5.32 (dt, *J* = 16.1, 7.0 Hz, 1H, H-8), 2.51 (dq, *J* = 19.6, 4.7 Hz, 1H, H-4), 2.44 – 2.25 (m, 2H, H-3, H-4), 2.18 (ddt, *J* = 14.6, 6.2, 3.4 Hz, 1H, H-3), 1.97 (ddq, *J* = 20.9, 14.4, 7.0 Hz, 2H, H-9), 1.76 (m, 1H, H-2), 1.48 (m, 1H, H-2), 1.31 – 1.01 (m, 8H, H-10, H-11, H-12, H-13), 0.87 (t, *J* = 7.0 Hz, 3H, H-14).

^{13}C NMR: (126 MHz, MeOD-d_4): δ [ppm] = 145.9 (C-15), 145.3 (C-16), 141.8 (C-17), 137.8 (C-5), 130.3 (C-8), 128.7 (C-6), 128.3 (C-7), 65.8 (C-1), 32.2 (C-3), 31.3 (C-4), 31.1 (C-2), 28.8 (C-9), 28.3 (C-10), 24.9 (C-11), 22.2 (C-12), 16.0 (C-13), 13.0 (C-14).

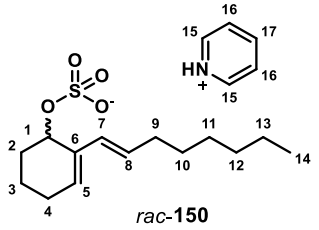
FT-IR (ATR): ν [cm^{-1}] = 3362 (bw), 3121 (w), 3027 (w), 2951 (m), 2925 (m), 2855 (m), 2673 (w, b), 2071 (w), 1844 (w), 1715 (w), 1674 (w), 1627 (m), 1536 (w), 1477 (s), 1378 (w), 1252 (w), 1212 (w), 1163 (m), 1078 (w), 1052 (m), 1026 (w), 968 (m), 934 (w), 901 (w), 875 (w), 781 (m), 756 (m), 727 (w), 683 (s), 643 (w), 608 (w), 562 (w).

4.2.23. *rac*-pyridinium 2-((*E*)-oct-1-ene-1-yl)cyclohex-2-ene-1-yl sulfate



rac-**112** *rac*-**150**

A solution of dienylic alcohol *rac*-**112** (100 mg, 0.48 mmol, 1.0 eq.) in pyridine (5.0 ml) was cooled to -10 °C under an argon atmosphere. To this solution chlorosulfonic acid (0.04 ml, 0.5 mmol, 1.1 eq.) was added and the mixture was stirred for 45 min at -10 °C. Then, the reaction mixture was warmed to r.t. and stirred for further 30 min. After confirmation of full conversion of the starting material (TLC), the solvent was removed under reduced pressure and the crude product *rac*-**150** was obtained as a yellow oil (285 mg, 0.471, quant.). The crude product *rac*-**150** was directly used in following reactions.



rac-**150**

Formula: $C_{19}H_{29}NO_4S$

M: 367.50 g/mol

R_f: 0.60 (SiO_2, 2:1, *c*Hex/EtOAc).

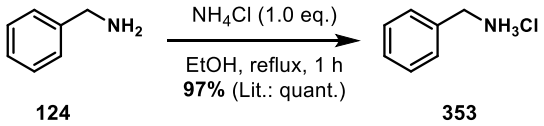
^{1}H NMR: (300 MHz, $CDCl_3$): δ [ppm] = 8.97 – 8.85 (m, 4H, remaining pyridine), 8.69 (tt, *J* = 7.9, 1.6 Hz, 2H, remaining pyridine), 8.23 – 8.04 (m, 4H, remaining pyridine), 6.11 (dt, *J* = 15.9, 6.8 Hz, 1H, H-8), 5.90 (d, *J* = 16.0 Hz, 1H, H-7), 5.82 (t, , 4.1 Hz, 1H, H-5), 5.03 (t, *J* = 2.9 Hz, 1H, H-1), 2.63 – 2.50 (m, 1H, H-4), 2.18 – 1.95 (m, 5H, H-4,H-9,H-2), 1.76 (tdd, *J* = 13.5, 6.3, 3.0 Hz, 2H, H-3), 1.55 (m, *J* = 14.2, 10.1, 3.2 Hz, 2H, H-10), 1.44 – 1.22 (m, 11H, H-11, H-12, H-13), 0.89 (td, *J* = 6.7, 3.6 Hz, 3H, H-14).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 147.2 (C-Pyr.), 141.6 (C-Pyr.), 135.6 (CPyr.), 131.3 (C-5), 129.9 (C-8), 127.6 (C-6), 127.5 (C-7), 72.6 (C-1), 32.7 (C-2), 31.5 (C-4), 29.3 (C-9), 28.6 (C-10), 25.5 (C-11, C-3), 22.3 (C-12), 16.8 (C-13), 13.1 (C-14).

FT-IR (ATR): ν [cm^{-1}] = 3423 (bw), 3053 (w), 2927 (m), 2850 (w), 2561 (bw), 2112 (w), 2004 (w), 1633 (w), 1607 (m), 1536 (m), 1486 (m), 1248 (s), 1180 (s), 1160 (s), 1029 (s), 977 (s), 938 (m), 912 (s), 877 (s), 768 (s), 753 (s), 690 (s), 635 (s), 607 (s), 584 (s).

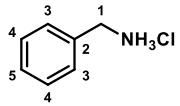
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{14}H_{23}O_4S$ $[M]^-$ 287.1323 u, found: 287.1305 u.

4.2.24. Benzylamine hydrochloride



124 353

According to a procedure by Saba *et al.*[169], a solution of benzylamine (**124**) (5.00 g, 46.7 mmol, 1.0 eq.) and ammonium chloride (2.51 g, 46.9 mmol, 1.0 eq.) in ethanol (50 ml) was warmed to reflux and stirred for 1 h. Then, the solvent was removed under reduced pressure, the residue was washed with toluene and the resulting solid was dried under reduced pressure. The benzylamine hydrochloride (**353**) was obtained as a colorless solid (6.52 g, 45.4 mmol, 97%, Lit.[169]: quant.).



353

Formula: $C_7H_{10}ClN$

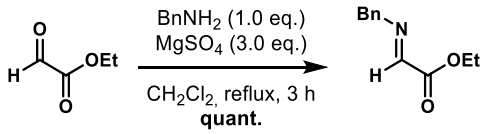
M: 143.61 g/mol

^{1}H NMR: (300 MHz, D_2O): δ [ppm] = 7.49 (s, 5H, H-3, H-4, H-5), 4.20 (s, 2H, H-1).

^{13}C NMR: (75 MHz, D_2O): δ [ppm] = 132.6 (C-2), 129.2 (C-3, C-5), 128.8 (C-4), 43.1 (C-1).

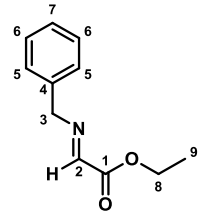
The analytical data are in accordance with the literature[170].

4.2.25. Ethyl 2-(benzylimino)acetate



139 140

According to a procedure reported by Sebesta *et al.*[171], to a solution of benzylamine **124** (0.87 ml, 8.0 mmol, 1.0 eq.) in 8.0 ml CH_2Cl_2 was added $MgSO_4$ (2.86 g, 23.7 mmol, 3.0 eq.) and a solution of ethyl glyoxylate (**139**) in toluene (50 w%, 1.55 g, 8.0 mmol, 1.0 eq.) under an argon atmosphere. The reaction mixture was warmed to reflux and stirred for 3 h until full conversion of the starting material was observed (TLC). The reaction mixture was cooled to r.t. and filtered through a plug of celite. The solvent was removed under reduced pressure and the imine **140** was obtained as a slightly yellow oil (1.65 g, 8.63 mmol, quant.).



Formula: $C_{11}H_{13}NO_2$

M: 191.23 g/mol

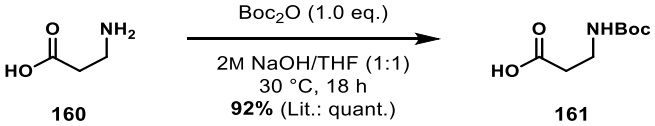
140

^{1}H NMR: (300 MHz, $CDCl_3$): δ [ppm] = 7.72 (t, *J* = 1.7 Hz, 1H, H-2), 7.38 – 7.22 (m, 5H, H-5, H-6, H-7), 4.86 (d, *J* = 1.7 Hz, 2H, H-3), 4.34 (q, *J* = 7.1 Hz, 2H, H-8), 1.36 (t, *J* = 7.1 Hz, 3H, H-9).

The analytical data are in accordance with the literature.[171]

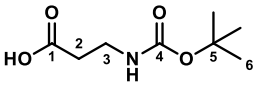
4.3. Synthesis of Compounds Regarding the Intramolecular Imino Diels Alder (Northern Route)

4.3.1. *N*-Boc-β-Alanine



160 **161**

According to a procedure reported by Laughlin *et al.*[93], to a solution of β-alanine 160 (10.0 g, 112 mmol, 1.0 eq.) and aq. NaOH (2M, 100 ml, 200 mmol, 1.8 eq.) in 100 ml THF was added Boc_2O (24.5 ml, 115 mmol, 1.0 eq.). The reaction mixture was stirred at 30 °C for 18 h. Then, the solvent was removed under reduced pressure and the aq. residue was washed with CH_2Cl_2. The aq. phase was acidified by addition of an aq. 2M HCl solution (100 ml) and the aq. phase was extracted thrice with EtOAc. The combined org. phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The desired *N*-Boc-β-alanine **161** was obtained as a colorless solid (19.6 g, 103 mmol, 92%, Lit.[93]: quant.).



Formula: $C_8H_{15}NO_4$

M: 189.21 g/mol

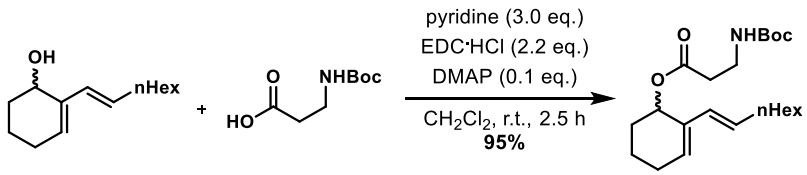
161

^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 11.07 (s, 1H, CO_2H), 6.30 (s, 0.3H, NH), 5.12 (s, 0.7H, NH), 3.42 – 3.30 (m, 2H, H-3), 2.61 – 2.47 (m, 2H, H-2), 1.60 – 1.31 (m, 9H, H-6).

^{13}C NMR: (126 MHz, $CDCl_3$, mixture of rotamers): δ [ppm] = 177.7 (C-1_{rot1}), 176.5 (C-1_{rot2}), 157.7 (C-4_{rot1}), 156.1 (C-4_{rot2}), 81.2 (C-5_{rot1}), 79.8 (C-5_{rot2}), 37.3 (C-3_{rot1}), 36.0 (C-3_{rot2}), 34.7 (C-2_{rot1}), 34.6 (C-2_{rot2}), 28.5 (C-6).

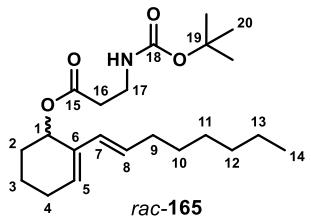
The analytical data are in accordance with the literature.[93]

4.3.2. *rac*-*N*-Boc-β-Alanine 2-(1-octen-1-yl)-cyclohex-1-yl ester



rac-**112** **161** *rac*-**165**

To a solution of dienol *rac*-**112** (825 mg, 3.96 mmol, 1.0 eq.) in CH_2Cl_2 (40 ml) was added pyridine (0.92 ml, 12 mmol, 3.0 eq.), EDC·HCl (1.68 g, 8.76 mmol, 2.2 eq.), DMAP (148 mg, 0.363 mmol, 0.10 eq.) and *N*-Boc-β-alanine (**161**) (802 mg, 4.24 mmol, 1.1 eq.) under an argon atmosphere. The solution was stirred for 2.5 h at r.t. After full conversion of the starting material (TLC), the reaction mixture was diluted with EtOAc and the org. phase was washed with a sat. aq. $NaHCO_3$ solution, water and a sat. aq. NaCl solution. The org. phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 9:1) and the desired product *rac*-**165** was obtained as a colorless oil (1.44 g, 3.79 mmol, 95%).



rac-**165**

Formula: $C_{22}H_{37}NO_4$

M: 379.54 g/mol

R_f: 0.25 (SiO_2, 6:1, *c*Hex/EtOAc).

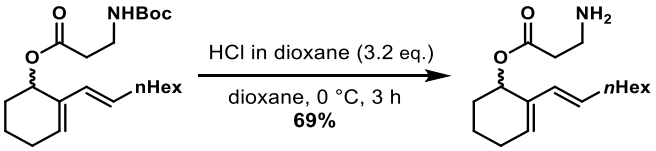
^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 5.94 – 5.89 (m, 2H, H-5, H-7), 5.65 (s, 1H, H-1), 5.52 (dt, *J* = 15.8, 7.0 Hz, 1H, H-8), 4.98 (s, 1H, NH), 3.46 – 3.30 (m, 2H, H-17), 2.54 – 2.47 (m, 2H, H-16), 2.28 – 2.19 (m, 1H, H-4), 2.15 – 2.01 (m, 3H, H-4, H-9), 1.97 – 1.88 (m, 1H, H-2), 1.74 – 1.61 (m, 3H, H-2, H-3), 1.43 (s, 9H, H-20), 1.38 – 1.22 (m, 8H, H-10, H-11, H-12, H-13), 0.87 (t, *J* = 6.9 Hz, 3H, H-14).

^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 172.2 (C-15), 155.9 (C-18), 133.5 (C-6), 132.2 (C-5), 130.4 (C-7), 128.6 (C-8), 79.4 (C-19), 66.3 (C-1), 36.4 (C-17), 35.2 (C-16), 33.0 (C-9), 31.8 (C-12), 29.5 (C-10), 29.0 (C-11), 28.8 (C-2), 28.5 (C-20), 25.7 (C-4), 22.8 (C-13), 17.5 (C-3), 14.2 (C-14).

FT-IR (ATR): ν [cm^{-1}] = 3376 (bw), 2927 (m), 2856 (w), 1717 (s), 1503 (m), 1454 (w), 1390 (w), 1365 (m), 1337 (w), 1246 (m), 1168 (s), 1053 (m), 965 (m), 917 (m), 872 (w), 861 (w), 780(w), 759 (w), 724 (w), 563 (w).

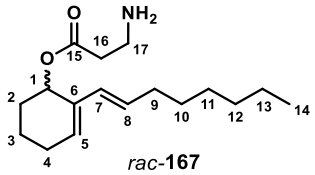
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{22}H_{37}NO_4Na$ $[M+Na]^+$ 402.2615 u, found: 402.2616 u.

4.3.3. *rac*-*β*-Alanine 2-(1-octen-1-yl)-cyclohex-1-yl ester



rac-**165** *rac*-**167**

To a solution of the *N*-Boc-amine *rac*-**165** (379 mg, 1.00 mmol, 1.0 eq.) in 0.60 ml dioxane was slowly added a solution of HCl in dioxane (4.0 M, 0.80 ml, 3.2 mmol, 3.2 eq.) at 0 °C under an argon atmosphere and stirred for 2 h. After full conversion of the starting material (TLC), the reaction mixture was diluted with EtOAc and basified upon addition of a sat. aq. $NaHCO_3$ solution. The aq. phase was extracted four times with EtOAc, the combined org. phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 1:1 +1% Et_3N) and the desired amine *rac*-**167** was obtained as a colorless oil (193 mg, 0.691 mmol, 69%).



rac-**167**

Formula: $C_{17}H_{29}NO_2$

M: 279.42 g/mol

R_f: 0.08 (SiO_2, 1:1, *c*Hex/EtOAc +1% Et_3N).

^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 5.95 – 5.87 (m, 2H, H-5, H-7), 5.66 (s, 1H, H-1), 5.53 (dt, *J* = 15.8, 7.0 Hz, 1H, H-8), 2.98 (q, *J* = 6.3 Hz, 2H, H-17), 2.46 (t, *J* = 6.2 Hz, 2H, H-16), 2.26 – 2.19 (m, 1H, H-4), 2.14 – 2.00 (m, 3H, H-3, H-9), 1.96 – 1.89 (m, 1H, H-2), 1.76 (s, 2H, NH_2), 1.69 – 1.61 (m, 3H, H-2, H-3), 1.37 – 1.20 (m, 8H, H-10, H-11, H-12, H-13), 0.87 (t, *J* = 6.8 Hz, 3H, H-14).

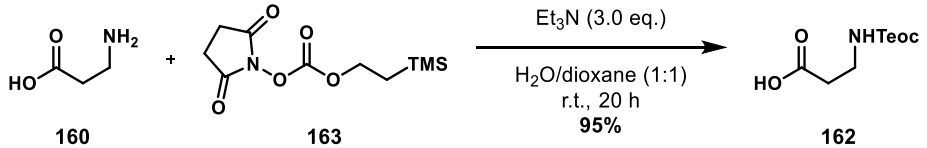
^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 172.4 (C-15), 133.6 (C-6), 132.1 (C-7), 130.4 (C-5), 128.6 (C-8), 66.1 (C-1), 38.6 (C-17), 38.2 (C-16), 33.1 (C-9), 31.9 (C-12/13), 29.6 (C-10), 29.0 (C-11), 28.8 (C-2), 25.7 (C-4), 22.8 (C-12/13), 17.5 (C-3), 14.2 (C-14).

FT-IR (ATR): ν [cm^{-1}] = 3381 (bw), 2925 (m), 2855 (m), 1723 (s), 1670 (w), 1586 (w), 1455 (w), 1439 (w), 1371 (w), 1356 (m), 1338 (m), 1246 (m), 1198 (m),

1156 (m), 1141 (m), 1087 (w), 1053 (m), 988 (m), 965 (s), 917 (s), 866 (m), 825 (m), 796 (m), 724 (w), 591 (w), 563 (w).

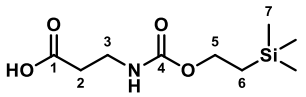
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{17}H_{30}NO_2$ $[M+H]^+$ 280.2271 u, found: 280.2275 u; $C_{17}H_{29}NO_2Na$ $[M+Na]^+$ 302.2091 u, found: 302.2095 u.

4.3.4. *N*-Teoc-β-Alanine



160 163 162

According to a modified procedure reported by Shute *et al*[94], to a solution of β-alanine **160** (180 mg, 2.02 mmol, 1.0 eq.) in 2.0 ml water was added a solution of triethylamine (0.42 ml, 3.0 mmol, 1.5 eq.) in 2.0 ml dioxane and Teoc-OSu **163** (581 mg, 2.24 mmol, 1.1 eq.). The reaction mixture was stirred at r.t. for 20 h. Then, it was diluted with water (10 ml) and the aq. phase was extracted with diethylether (4 x 30 ml). The combined org. phases were washed with water (4 x 50 ml), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The desired product **162** was obtained as a colorless solid (452 mg, 1.94 mmol, 95%).



162

Formula: $C_9H_{19}NO_4Si$

M: 233.34 g/mol

R_f: 0.05 (SiO_2, 1:1, *c*Hex/EtOAc).

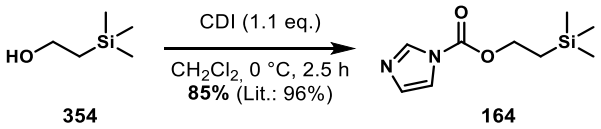
^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 10.41 (s, 1H, CO_2H), 6.42 and 5.24 (s, 1H, NH), 4.24-4.09 (m, 2H, H-5), 3.47-3.37 (m, 2H, H-3), 2.61-2.50 (m, 2H, H-2) 1.04-0.91 (m, 2H, H-6), 0.02 (s, 9H, H-7).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 177.5 (C-1), 157.0 (C-4), 63.4 (C-5), 36.3 (C-3), 34.4 (C-2) 17.8 (C-6), –1.4 (C-7).

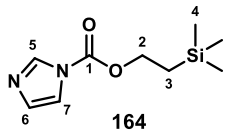
FT-IR (ATR): ν [cm^{-1}] = 3456 (w), 3334 (w), 2954 (m), 2899 (w), 1707 (s), 1523 (m), 1478 (w), 1412 (m), 1340 (m), 1249 (s), 1178 (m), 1064 (m), 984 (w), 858 (s), 835 (s), 770 (m), 694 (m), 663 (w), 609 (w), 587 (w).

The analytical data are in accordance with the literature.[172]

4.3.5. 1-(*O*-(2-(Trimethylsilyl)ethyl)-oxycarbonyl)imidazole



According to a procedure reported by Herzon *et al.*[173], to a cooled solution (0 °C) of CDI (1.66 g, 10.2 mmol, 1.1 eq.) in 13.5 ml CH_2Cl_2 was added 2-trimethylsilylethanol **354** (1.14 g, 9.61 mmol, 1.0 eq.) under an argon atmosphere. The reaction mixture was stirred at 0 °C for 2.5 h and after confirmation of full conversion of the starting material (TLC), water (6 ml) was added. The mixture was stirred for 15 min at r.t. Then, the org. phase was washed with water thrice, once with a sat. aq. NaCl solution and was dried over Na_2SO_4. The solvent was removed under reduced pressure and the desired product **164** was obtained as a colorless solid (1.73 g, 8.15 mmol, 85%, Lit.[173]: 96%).



Formula: $C_9H_{16}N_2O_2Si$

M: 212.32 g/mol

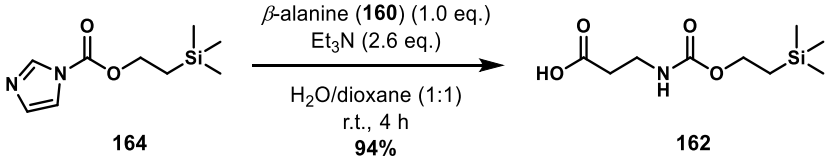
R_f: 0.81 (SiO_2, 1:1, *c*Hex/EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 8.13 (s, 1H, H-5), 7.43-7.41 (m, 1H, H-6), 7.06 (dd, *J* = 1.7, 0.8 Hz, 1H, H-7), 4.53-4.48 (m, 2H, H-2), 1.21-1.14 (m, 2H, H-3), 0.09 (s, 9H, H-4).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 148.9 (C-1), 137.2 (C-5), 130.7 (C-7), 117.2 (C-6), 67.3 (C-2), 17.7 (C-3), –1.4 (C-4).

The analytical data are in accordance with the literature.[174]

4.3.6. *N*-Teoc-β-Alanine

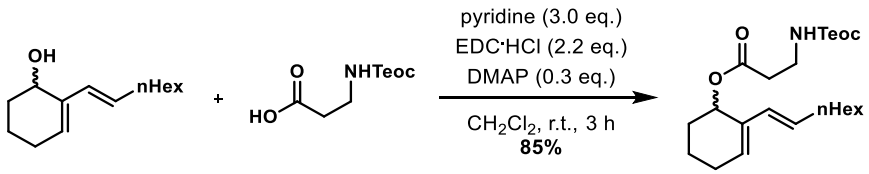


According to a slightly modified procedure reported by Shute *et al.*[94], to a solution of β-alanine (**160**) (287 mg, 3.22 mmol, 1.0 eq.) in 3.2 ml water was added a solution of Et_3N in dioxane (2.6 M, 3.2 ml, 8.3 mmol, 2.6 eq.) and freshly prepared **164** (759 mg, 3.57 mmol, 1.1 eq.). The reaction mixture was stirred for 4 h at r.t. After full conversion of the starting material (TLC), water was added and the mixture was

acidified by addition of a sat. aq. $KHSO_4$ solution. The aq. phase was extracted thrice with MTBE, the combined org. phases were washed twice with water, once with a sat. aq. NaCl solution and it was dried over $MgSO_4$. The solvent was removed under reduced pressure and the *N*-Teoc-β-alanine **162** was obtained as a colorless solid (706 mg, 3.03 mmol, 94%).

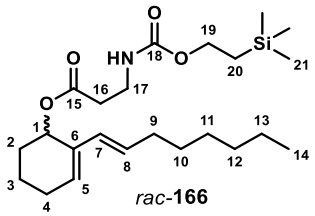
The analytical data are in accordance with the *N*-Teoc-β-alanine **162** reported previously (see 4.3.4).

4.3.7. *rac*-*N*-Teoc-β-Alanine 2-(1-octen-1-yl)-cyclohex-1-yl ester



rac-**112** **162** *rac*-**166**

To a solution of dienol *rac*-**112** (208 mg, 1.00 mmol, 1.0 eq.) in 10 ml CH_2Cl_2 was added pyridine (0.23 ml, 3.0 mmol, 3.0 eq.), EDC·HCl (422 mg, 2.20 mmol, 2.2 eq.), DMAP (37 mg, 0.30 mmol, 0.3 eq.) and *N*-Teoc-β-alanine **162** (259 mg, 1.11 mmol, 1.1 eq.) under an argon atmosphere. The solution was stirred for 3 h at r.t. and after full conversion of the starting material (GC-MS), the reaction mixture was diluted with EtOAc and the org. phase was washed with a sat. aq. $NaHCO_3$ solution, water and a sat. aq. NaCl solution. The org. phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 9:1) and the desired product *rac*-**166** was obtained as a colorless oil (362 mg, 0.854 mmol, 85%).



rac-**166**

Formula: $C_{23}H_{41}NO_4Si$

M: 423.67 g/mol

R_f: 0.21 (SiO_2, 9:1, *c*Hex/EtOAc +1% Et_3N).

^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 5.95 – 5.89 (m, 2H, H-5, H-7), 5.67 – 5.64 (m, 1H,H-1), 5.51 (dt, *J* = 15.9, 6.9 Hz, 1H, H-8), 5.08 (s, 1H, NH), 4.16 – 4.10 (m, 2H, H-19), 3.51 – 3.37 (m, *J* = 6.6, 6.1 Hz, 2H, H-17), 2.58 – 2.46 (m, 2H, H-16), 2.28 – 2.18 (m, 1H, H-4), 2.14 – 2.00 (m, 3H, H-4´, H-9), 1.96 – 1.89 (m, 1H, H-2), 1.75 – 1.60 (m, 3H, H-2´, H-3), 1.37 –

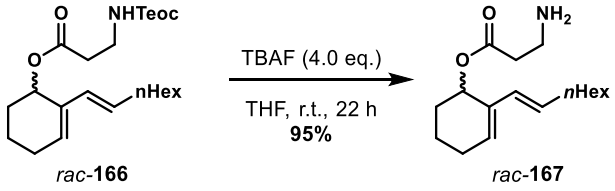
1.31 (m, 2H, H-10), 1.29 – 1.23 (m, 6H, H-11, H-12, H-13), 0.96 (t, *J* = 8.5 Hz, 2H, H-20), 0.87 (t, *J* = 6.9 Hz, 3H, H-14), 0.03 (s, 9H, H-21).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 172.1 (C-15), 156.8 (C-18), 133.5 (C-6), 132.3 (C-5), 130.4 (C-7), 128.6 (C-8), 66.4 (C-1), 63.1 (C-19), 36.7 (C-17), 35.2 (C-16), 33.0 (C-9), 31.9 (C-12), 29.5 (C-10), 29.0 (C-11), 28.8 (C-2), 25.7 (C-4), 22.8 (C-13), 17.9 (C-20), 17.5 (C-3), 14.3 (C-14), -1.3 (C-21).

FT-IR (ATR): ν [cm^{-1}] = 3355 (bw), 3028 (w), 2952 (m), 2927 (m), 2855 (w), 1723 (s), 1513 (m), 1455 (w), 1440 (w), 1375 (w), 1336 (w), 1249 (s), 1180 (s), 1157 (m), 1140 (m), 1056 (m), 967 (m), 944 (w), 918 (m), 859 (m), 837 (s), 778 (w), 694 (w).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{20}H_{30}Cl_3NO_4Na$ $[M+Na]^+$ 446.2698 u, found: 446.2698 u.

4.3.8. *rac*-*β*-Alanine 2-(1-octen-1-yl)-cyclohex-1-yl ester

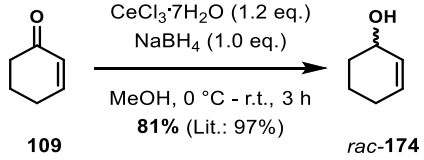


rac-**166** *rac*-**167**

To a solution of the Teoc-protected amine *rac*-**166** (245 mg, 0.578 mmol, 1.0 eq.) in 0.60 ml THF was added a solution of TBAF in THF (1 M, 2.3 ml, 2.3 mmol, 4.0 eq.) under an argon atmosphere. The reaction mixture was stirred for 22 h at r.t. until full conversion of the starting material was observed (TLC). The reaction mixture was diluted with EtOAc and with a sat. aq. $NaHCO_3$ solution. The aq. phase was extracted thrice with EtOAc, the combined org. phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc/MeOH, 10:10:1 +1% Et_3N) and the desired amine *rac*-**167** was obtained as a colorless oil (153 mg, 0.548 mmol, 95%).

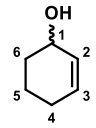
The literature is in accordance with the previously synthesized product from procedure 4.3.3.

4.3.9. *rac*-Cyclohex-2-en-1-ol



109 *rac*-**174**

According to a procedure reported by Csatayová *et al.*[95], to a cooled (0 °C) solution of cyclohexenone **109** (2.00 g, 20.8 mmol, 1.0 eq.) and $CeCl_3 \cdot 7H_2O$ (9.30 g, 25.0 mmol, 1.2 eq.) 55 ml in MeOH was added $NaBH_4$ (790 mg, 20.8 mmol, 1.0 eq.). The reaction mixture was stirred for 30 min at 0 °C and further 2.5 h at r.t. After confirmation of full conversion of the starting material (TLC), the reaction was terminated by the addition of an aq. 1M HCl solution (20 ml). The aq. phase was extracted thrice with CH_2Cl_2, the combined org. phases were washed with a sat. aq. NaCl solution and dried over $MgSO_4$. The solvent was removed under reduced pressure and the desired *rac*-1-hydroxy-cyclohexene *rac*-**174** was obtained as a colorless oil (1.66 g, 16.9 mmol, 81%, Lit.[95]: 97%).



rac-**174**

Formula: $C_6H_{10}O$

M: 98.15 g/mol

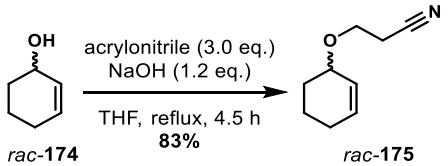
R_f: 0.19 (SiO_2, 1:3, *c*Hex/EtOAc).

^{1}H NMR: (300 MHz, $CDCl_3$): δ [ppm] = 5.89 – 5.81 (dt, *J* = 10.1, 3.3 Hz, 1H, H-2), 5.78 – 5.72 (m, 1H, H-3), 4.19 (s, 1H, H-1), 2.08 – 1.59 (m, 7H, H-4, H-5, H-6, OH).

^{13}C NMR: (76 MHz, $CDCl_3$): δ [ppm] = 130.5 (C-2), 129.9 (C-3), 65.5 (C-1), 32.0 (C-6), 25.0 (C-4), 18.9 (C-5).

The analytical data are in accordance with the literature.[95]

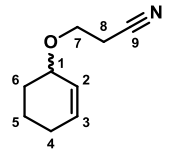
4.3.10. *rac*-3-(Cyclohex-2-en-1-yloxy)propionitrile



rac-**174** *rac*-**175**

According to a modified procedure reported by Walton *et al*[175], to a solution of *rac*-1-hydroxycyclohex-2-ene *rac*-**174** (1.20 g, 12.2 mmol, 1.0 eq.) and NaOH (587 mg, 14.7 mmol, 1.2 eq.) in 120 ml THF was added acrylonitrile (2.4 ml, 37 mmol, 3.0 eq.)

under an argon atmosphere. The reaction mixture was warmed to reflux and stirred for 4.5 h. After confirmation of full conversion of the starting material (TLC), the reaction mixture was cooled to r.t. and diluted with an aq. 1M HCl solution. The aq. phase was extracted thrice with CH_2Cl_2, the combined org. phases were washed with a sat. aq. NaCl solution and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 3:1). The desired nitrile *rac*-**175** was obtained as a colorless amorphous solid (1.54 g, 10.2 mmol, 83%).



rac-**175**

Formula: $C_9H_{13}NO$

M: 151.21 g/mol

R_f: 0.26 (SiO_2, 3:1, *c*Hex/EtOAc).

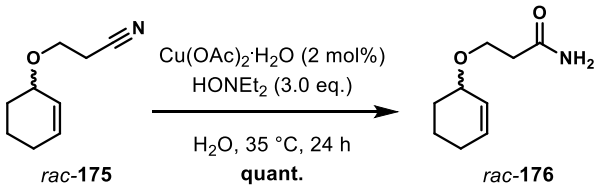
^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 5.90 (ddt, *J* = 8.6, 3.7, 1.8 Hz, 1H, H-3), 5.75 (dq, *J* = 10.1, 2.3 Hz, 1H, H-2), 3.95 – 3.90 (m, 1H, H-1), 3.72 (ddt, *J* = 25.8, 9.3, 6.5 Hz, 2H, H-7), 2.60 (t, *J* = 6.5 Hz, 2H, H-8), 2.11 – 2.02 (m, 1H, H-4), 2.00 – 1.92 (m, 1H, H-4´), 1.87 – 1.67 (m, 3H, H-6, H-5), 1.57 (ddt, *J* = 13.2, 6.7, 3.5 Hz, 1H, H-5´).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 131.9 (C-3), 126.9 (C-2), 118.1 (C-9), 73.7 (C-1), 62.9 (C-7), 28.3 (C-6), 25.3 (C-4), 19.5 (C-8), 19.1 (C-5).

FT-IR (ATR): ν [cm^{-1}] = 3028 (w), 2934 (w), 2867 (w), 2837 (w), 2250 (w), 1650 (w), 1478 (w), 1450 (w), 1436 (w), 1413 (w), 1389 (w), 1347 (w), 1321 (w), 1254 (w), 1220 (w), 1162 (w), 1139 (w), 1096 (s), 1035 (w), 959 (m), 928 (w), 900 (w), 870 (w), 842 (w), 809 (w), 726 (m), 672 (w), 588 (w), 568 (w), 555 (w).

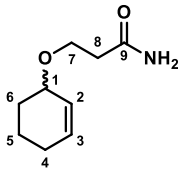
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_9H_{13}NONa$ $[M+Na]^+$ 174.0889 u, found: 174.0890 u.

4.3.11. *rac*-3-(Cyclohex-2-en-1-yloxy)propenamide



rac-**175** *rac*-**176**

According to a modified procedure reported by Williams et al.[98], a solution of $Cu(OAc)_2{\cdot}H_2O$ (2.4 mg, 0.012 mmol, 2 mol%), $HONEt_3$ (0.20 ml, 1.98 mmol, 3.0 eq.) and nitrile *rac*-**175** (100 mg, 0.66 mmol, 1.0 eq.) in 1.0 ml degassed water was heated to 35 °C for 24 h under an argon atmosphere. After confirmation of full conversion of the starting material (TLC), the reaction mixture was filtered through a short pad of silica and the aq. phase was extracted thrice with EtOAc. The combined org. phases were washed with a sat. aq. NaCl solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc/MeOH, 10:10:1) and the desired amide *rac*-**176** was obtained as a colorless amorphous solid (120 mg, 0.709 mmol, quant.).



rac-**176**

Formula: $C_9H_{15}NO_2$

M: 169.22 g/mol

R_f: 0.11 (SiO_2, 10:10:1, *c*Hex/EtOAc/MeOH).

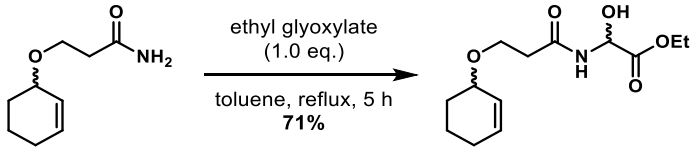
^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 6.44 (s, 1H, NH), 5.89 (dtd, *J* = 10.0, 3.6, 1.2 Hz, 1H, H-3), 5.77 (dq, *J* = 10.1, 2.2 Hz, 1H, H-2), 5.61 (s, 1H, NH), 3.91 (dddp, *J* = 6.6, 4.7, 3.3, 1.8 Hz, 1H, H-1), 3.80 (dt, *J* = 9.6, 5.5 Hz, 1H, H-7), 3.76 – 3.71 (m, 1H, H-7´), 2.51 (t, *J* = 5.8 Hz, 2H, H-8), 2.11 – 2.03 (m, 1H, H-4), 2.02 – 1.94 (m, 1H, H-4´), 1.89 – 1.81 (m, 1H, H-6), 1.79 – 1.66 (m, 2H, H-6´, H-5), 1.63 – 1.54 (m, 1H, H-5´).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 174.5 (C-9), 131.6 (C-3), 127.2 (C-2), 73.4 (C-1), 64.1 (C-7), 37.1 (C-8), 28.3 (C-6), 25.3 (C-4), 19.2 (C-5).

FT-IR (ATR): ν [cm^{-1}] = 3351 (m), 3177 (m), 3027 (w), 2931 (m), 2904 (m), 2870 (m), 2830 (w), 1650 (s), 1467 (w), 1420 (s), 1394 (s), 1341 (m), 1303 (s), 1255 (m), 1217 (m), 1162 (m), 1135 (m), 1092 (s), 1059 (s), 1048 (s), 1000 (m), 965 (m), 901 (w), 887 (m), 814 (m), 719 (s), 671 (s), 577 (s), 566 (m), 553 (s).

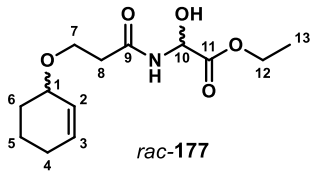
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_9H_{15}NO_2Na$ $[M+Na]^+$ 192.0995 u, found: 192.0995 u.

4.3.12. *rac*-Ethyl 2-(3-(cyclohex-2-en-1-yloxy)propanamido)-2-hydroxyacetate



rac-**176** *rac*-**177**

To a solution of amide *rac*-**176** (300 mg, 1.77 mmol, 1.0 eq.) in 10 ml toluene was added a solution of ethylglyoxylate in toluene (40.5 w%, 0.45 ml, 1.77 mmol, 1.0 eq.) and the reaction mixture was heated to reflux under *Dean-Stark* conditions for 5 h. After confirmation of full conversion of the starting material (TLC), the reaction mixture was cooled to r.t. and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 3:7) and the desired product *rac*-**177** was obtained as a colorless oil (340 mg, 1.25 mmol, 71%).



rac-**177**

Formula: $C_{13}H_{21}NO_5$

M: 271.31 g/mol

R_f: 0.20 (SiO_2, 3:7, *c*Hex/EtOAc).

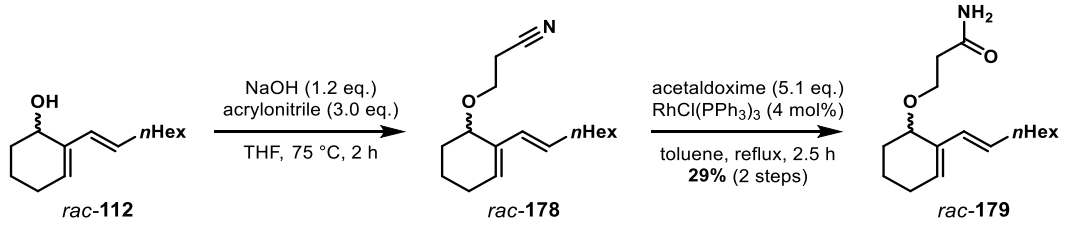
^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 7.82 – 7.81 (d, *J* = 6.0 Hz, 1H, NH), 5.89 – 5.87 (m, 1 H, H-3), 5.79 – 5.77 (m, 1H, H-2), 5.61 – 5.58 (m, 1H, H-10), 4.68 – 4.63 (m, 1H, OH), 4.30 – 4.25 (q, *J* = 7.1 Hz, 2H, H-12), 3.91 (s, 1H, H-1), 3.80 – 3.70 (m, 2H, H-7), 2.55 – 2.52 (t, *J* = 5.8 Hz, 2H, H-8), 2.07 – 1.97 (m, 2H, H-4), 1.87 – 1.53 (m, 4H, H-5, H-6), 1.33 – 1.30 (m, 3H, H-13).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 172.9 (C-9), 169.4 (C-11), 131.5 (C-3), 127.0 (C-2), 73.4 (C-1), 72.0 (C-10), 63.6 (C-7), 62.3 (C-12), 37.0 (C-8), 28.1 (C-5), 25.1 (C-4), 19.1 (C-6), 14.0 (C-13).

FT-IR (ATR): ν [cm^{-1}] = 3321 (bw), 3028 (w), 2936 (w), 2867 (w), 1744 (m), 1662 (m), 1527 (m), 1372 (w), 1393 (w), 1321 (w), 1205 (m), 1086 (vs), 1022 (m), 961 (w), 901 (w), 727 (w), 671 (w), 555 (w).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{13}H_{21}NO_5Na$ $[M+Na]^+$ 294.1312 u, found: 294.1314 u.

4.3.13. *rac*-(*E*)-3-((2-(Oct-1-en-1-yl)cyclohex-2-en-1-yl)oxy)propan-amide



rac-**112** *rac*-**178** *rac*-**179**

To solution of dienol *rac*-**112** (605 mg, 2.09 mmol, 1.0 eq.) and NaOH (140 mg, 3.46 mmol, 1.2 eq.) in 29 ml THF was added acrylonitrile (0.57 ml, 8.64 mmol, 3.0 eq.) under an argon atmosphere. The reaction mixture was warmed to 75 °C and stirred for 2 h. Then, the reaction mixture was cooled to r.t. and diluted with CH_2Cl_2 (70 ml) and with a 0.5M aq. HCl solution (100 ml). The aq. phase was extracted with CH_2Cl_2 (2x 50 ml), the combined org. phases were washed with water (100 ml) and with a sat. aq. NaCl solution (100 ml). The org. phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 5:1) and the desired product *rac*-1**78** was obtained as a mixture with the starting material *rac*-**112** (447 mg, 40:60, product *rac*-**178**/starting material *rac*-**112**). This mixture was directly used in the following hydrolysis of the nitrile.

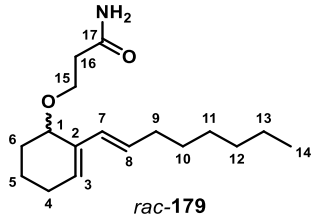
To a solution of the previously synthesized nitrile *rac*-**178** (44 w%, 0.76 mmol, 1.0 eq.) in 0.80 ml toluene was added $RhCl(PPh_3)_3$ (29 mg, 0.031 mmol, 4 mol%) and acetaldoxime (230 mg, 3.89 mmol, 5.1 eq.) under an argon atmosphere. The reaction mixture was warmed to reflux and stirred for 2.5 h until full conversion of the starting material was observed (GC-MS). The reaction mixture was diluted with EtOAc, filtered through a pad of silica and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 19:1 → 1:1) and the desired amide *rac*-**179** was obtained as a slightly yellow solid (169 mg, 0.605 mmol, 29% over 2 steps).

Formula: $C_{17}H_{29}NO_2$

M: 279.42 g/mol

m.p.: 25-35 °C

R_f: 0.21 (SiO_2, 10:10:1, *c*Hex/EtOAc/MeOH).



rac-**179**

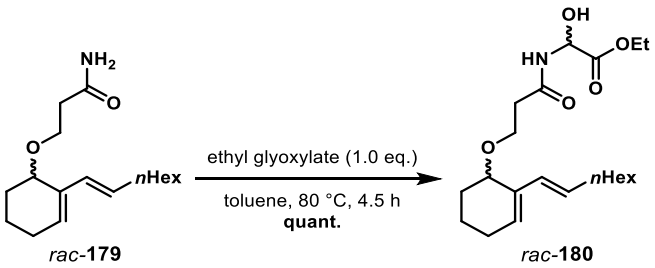
^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 6.44 (s, 1H, NH), 5.95 (d, *J* = 15.9 Hz, 1H, H-7), 5.84 – 5.75 (m, 1H, H-3), 5.65 (dt, *J* = 15.3, 6.8 Hz, 1H, H-8), 5.27 (s, 1H, NH), 4.07 (s, 1H, H-1), 3.87 (ddd, *J* = 10.5, 6.3, 4.4 Hz, 1H, H-15), 3.65 (ddd, *J* = 9.2, 7.7, 4.3 Hz, 1H, H-15´), 2.57 – 2.45 (m, 2H, H-16), 2.18 (dt, *J* = 18.5, 6.1 Hz, 1H, H-4), 2.07 (q, *J* = 9.6, 8.4 Hz, 4H, H-9, H-6, H-4´), 1.74 – 1.54 (m, 2H, H-5), 1.46 (tt, *J* = 15.9, 4.4 Hz, 1H, H-6), 1.40 – 1.34 (m, 2H, H-10), 1.34 – 1.23 (m, 6H, H-11, H-12, H-13), 0.88 (t, *J* = 6.9 Hz, 3H, H-14).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 174.4 (C-17), 135.3 (C-2), 131.3 (C-7), 130.9 (C-3), 128.1 (C-8), 71.7 (C-1), 64.5 (C-15), 37.1 (C-16), 33.1 (C-9), 31.9 (C-12), 29.7 (C-10), 29.1 (C-11), 26.2 (C-6), 25.9 (C-4), 22.8 (C-13), 17.3 (C-5), 14.2 (C-14).

FT-IR (ATR): ν [cm^{-1}] = 3423 (w), 3347 (w), 3193 (w), 2951 (m), 2926 (vs), 2857 (m), 1674 (vs), 1621 (w), 1395 (w), 1253 (w), 1210 (w), 1160 (w), 1089 (m), 1058 (m), 964 (m), 904 (s), 728 (s), 650 (m), 565 (w).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{17}H_{29}NO_2Na$ $[M+Na]^+$ 302.2091 u, found: 302.2093 u.

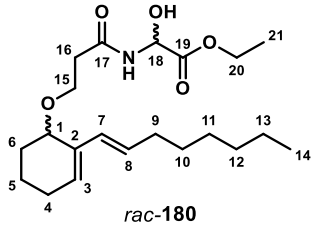
4.3.14. *rac*-Ethyl-(*E*)-2-(3-((2-(oct-1-en-1-yl)cyclohex-2-en-1-yl)oxy)-propanamido)-2-hydroxyacetate



rac-**179** *rac*-**180**

To a solution of amide *rac*-**179** (131 mg, 0.469 mmol, 1.0 eq.) in 2.4 ml toluene was added a solution of ethyl glyoxylate in toluene (15 w%, 319 mg, 0.469 mmol, 1.0 eq.)

under an argon atmosphere. The reaction mixture was warmed to 80 °C for 4.5 h. After confirmation of full conversion of the starting material (TLC), the reaction mixture was cooled to r.t. and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 2:1) and the desired product *rac*-**180** was obtained as a colorless oil (180 mg, 471 mmol, quant.).



rac-**180**

Formula: $C_{21}H_{35}NO_5$

M: 381.51 g/mol

R_f: 0.29 (SiO_2, 10:10:1, *c*Hex/EtOAc/MeOH).

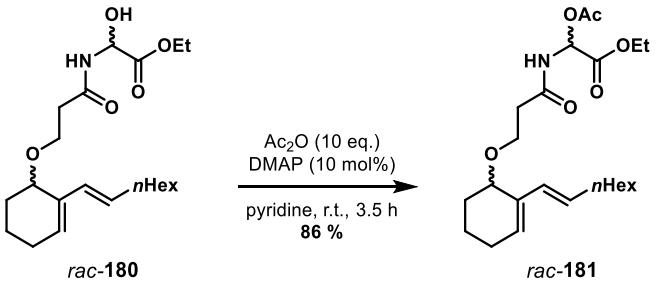
^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 7.62 – 7.56 (dd, *J* = 20.5, 6.9 Hz, 1 H, NH), 5.97 (d, *J* = 15.9 Hz, 1 H, H-7), 5.82 (s, 1 H, H-3), 5.71 – 5.65 (m, 1 H, H-8), 5.47 – 5.42 (m, 1 H, H-18), 4.30 – 4.26 (q, *J* = 7.4 Hz, 2 H, H-20), 4.08 (d, *J* = 7.4 Hz, 1 H, H-1), 3.90 – 3.86 (m, 1 H, H-15), 3.71 – 3.66 (m, 1 H, H-15), 2.56 – 2.53 (m, 2 H, H-16), 2.21 – 2.17 (m, 1 H, H-4), 2.14 – 2.05 (m, 3 H, H-4, H-9), 1.76 – 1.66 (m, 1 H, H-5), 1.60 – 1.58 (m, 1 H, H-5), 1.51 – 1.34 (m, 4 H, H-6, H-10), 1.32 – 1.25 (m, 9 H, H- 11, H-12, H-13, H-21), 0.91 – 0.88 (t, *J* = 4.4 Hz, 3 H, H-14).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 172.7 (C-17), 169.5 (C-19), 135.1 (C-2), 131.2 (C-7), 130.8 (C-3), 128.1 (C-8), 72.3 (C-18), 71.8 (C-1), 64.0 (C-15), 62.4 (C-20), 37.2 (C-16), 32.9 (C-9), 31.7 (C-12), 29.5 (C-10), 29.0 (C-11), 26.3 (C-6), 25.8 (C-4), 22.6 (C-13), 17.2 (C-5), 14.1 (C-14), 14.0 (C-21).

FT-IR (ATR): ν [cm^{-1}] = 3334 (bw), 2926 (s), 2857 (m), 1746 (s), 1666 (s), 1526 (m), 1467 (w), 1373 (w), 1334 (w), 1200 (m), 1086 (vs), 964 (m), 927 (w), 862 (w), 796 (w), 724 (w), 566 (w).

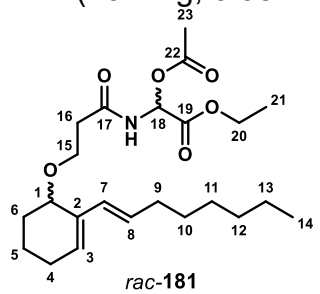
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{21}H_{35}NO_5Na$ $[M+Na]^+$ 404.2407 u, found: 404.2409 u.

4.3.15. *rac*-Ethyl-(*E*)-2-(3-((2-(oct-1-en-1-yl)cyclohex-2-en-1-yl)oxy)-propanamido)-2-acetoxyacetate



rac-**180** *rac*-**181**

To a solution of the hemiaminal *rac*-**180** (170 mg, 0.446 mmol, 1.0 eq.) and DMAP (6 mg, 0.05 mmol, 10 mol%) in 1.1 ml pyridine was added acetic anhydride (0.42 ml, 4.5 mmol, 10 eq.). The reaction mixture was stirred at r.t. for 3.5 h until full conversion of the starting material was observed (TLC). The reaction mixture was diluted with EtOAc (15 ml) and washed with an aq. 1M HCl solution (3 x 10 ml). The org. phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 3:1) and the desired acetate *rac*-**181** was obtained as an amorphous solid (162 mg, 0.382 mmol, 86%).



rac-**181**

Formula: $C_{23}H_{37}NO_6$

M: 423.55 g/mol

m.p.: 25-35 °C

R_f: 0.23 (SiO_2, 6:1, *c*Hex/EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 7.59 – 7.44 (dd, *J* = 64.0, 8.9 Hz, 1 H, NH), 6.43 – 6.40 (m, 1 H, H-18), 5.97 (d, *J* = 15.9 Hz, 1 H, H-7), 5.83 – 5.82 (t, *J* = 3.9 Hz, 1 H, H-3), 5.71 – 5.64 (m, 1 H, H-8), 4.29 – 4.22 (m, 2 H, H-20), 4.09 (s, 1 H, H-1), 3.92 – 3.86 (m, 1 H, H-15), 3.73 – 3.68 (m, 1 H, H-15), 2.62 – 2.51 (m, 2 H, H-16), 2.21 – 2.18 (m, 1 H, H-4), 2.11 – 2.06 (m, 6 H, H-4, H-9, H-23), 1.74 – 1.70 (m, 1 H, H-5), 1.60 – 1.57 (m, 1 H, H-5), 1.53 – 1.34 (m, 4 H, H-6, H-10), 1.31 – 1.28 (m, 9 H, H-11, H-12, H-13, H-21), 0.91 – 0.88 (t, *J* = 6.9 Hz, 3 H, H-14).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 171.6 (C-17), 170.0 (C-22), 166.6 (C-19), 135.1 (C-2), 131.2 (C-7), 130.8 (C-3), 128.1 (C-8), 72.2 (C-18), 71.8 (C-1), 64.0 (C-15), 62.5 (C-20), 37.2 (C-16), 33.0 (C-9), 31.8 (C-12), 29.5

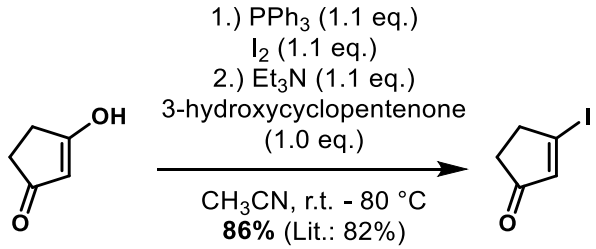
(C-10), 29.0 (C-11), 26.5 (C-6), 25.8 (C-4), 22.6 (C-13), 20.6 (C-23), 17.2 (C-5), 14.1 (C-14), 14.0 (C-21).

FT-IR (ATR): ν [cm^{-1}] = 3670 (w), 3328 (bw), 2926 (s), 2857 (m), 1748 (vs), 1698 (m), 1521 (m), 1454 (w), 1373 (m), 1322 (w), 1195 (vs), 1158 (m), 1090 (s), 1038 (s), 964 (s), 927 (w), 859 (w), 607 (w), 568 (w), 536 (w).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{23}H_{37}NO_6Na$ $[M+Na]^+$ 446.2513 u, found: 446.2513 u.

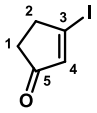
4.4. Synthesis of Compounds Regarding the Intramolecular Imino DA Approach (Southern Route)

4.4.1. 3-Iodo-cyclopent-2-enone



188 **189**

According to a procedure by Lemiére *et al*[99], to a solution of triphenylphosphine (3.50 g, 13.3 mmol, 1.1 eq.) in 120 ml CH_3CN was added iodine (3.40 g, 13.3 mmol, 1.1 eq.) under an argon atmosphere and the mixture was stirred for 2 h at r.t. Then, cyclopenta-1,3-dione (**188**) (1.16 g, 11.8 mmol, 1.0 eq.) and triethylamine (1.8 ml, 13 mmol, 1.1 eq.) were added and the former suspension turned clear. The reaction mixture was stirred at reflux for 1 h, then at r.t. for 20 h and finally again at reflux for 1 h. Afterwards, the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 and diethylether was added, which led to the formation of a colorless solid. The suspension was filtered and the solvent was removed from the filtrate under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 4:1) and the desired product **189** was obtained as a slightly yellow solid (2.11 g, 10.2 mmol, 86%, Lit.[99]: 82%).



189

Formula: C_5H_5IO

M: 208.00 g/mol

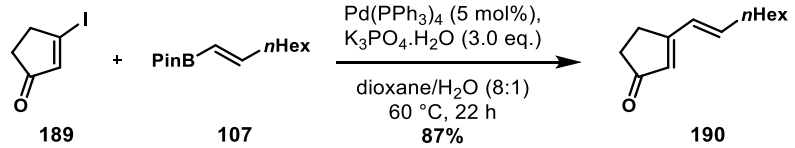
R_f: 0.39 (SiO_2, 3:1, *c*Hex/EtOAc).

^{1}H NMR: (300 MHz, $CDCl_3$): δ [ppm] = 6.69 (t, *J* = 1.9 Hz, 1H, H-4), 3.07 (dt, *J* = 7.1, 2.0 Hz, 2H, H-1), 2.52-2.47 (m, 2H, H-2).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 205.3 (C-5), 197.6 (C-3), 143.7 (C-4), 41.8 (C-1), 37.6 (C-2).

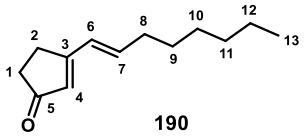
The analytical data are in accordance with the literature.[99]

4.4.2. 3-((*E*)-Oct-1-en-1-yl)-cyclopent-2-enone



189 **107** **87%** **190**

To a solution of 3-iodocyclopentenone **189** (1.39 g, 6.68 mmol, 1.0 eq.) in 18 ml degassed dioxane and 3.6 ml degassed water was added pinacolboronate **107** (1.92 g, 8.08 mmol, 1.2 eq.), $Pd(PPh_3)_4$ (396 mg, 0.343 mmol, 5 mol%) and $K_3PO_4 \cdot H_2O$ (4.70 g, 20.4 mmol, 3.1 eq.) under an argon atmosphere. The solution was heated to 60 °C and stirred for 20 h. After confirmation of full conversion (GC-MS), the reaction mixture was cooled to r.t. and filtered through a plug of celite. The phases were separated and the aq. phase was extracted thrice with EtOAc. The combined org. phases were washed with a sat. aq. NaCl solution and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 7:1). The desired product **190** was obtained as a colorless oil (1.12 g, 5.81 mmol, 87%).



190

Formula: $C_{13}H_{20}O$

M: 192.30 g/mol

R_f: 0.49 (SiO_2, 1:1, *c*Hex/EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 6.53 (d, *J* = 15.7 Hz, 1H, H-6), 6.33 (dt, *J* = 15.7, 6.9 Hz, 1H, H-7), 5.96 (s, 1H, H-4), 2.77 – 2.71 (m, 2H, H-1), 2.47 – 2.42 (m, 2H, H-2), 2.23 (m, 2H, H-8), 1.47 (m, 2H, H-9), 1.31 (td, *J* = 9.7, 4.8 Hz, 6H, H-10, H-11, H-12), 0.89 (t, *J* = 6.9 Hz, 3H, H-13).

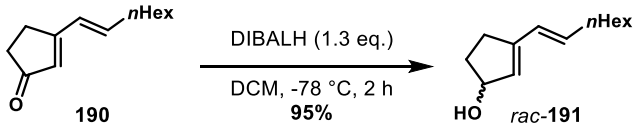
^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 209.8 (C-5), 172.9 (C-3), 141.4 (C-7), 129.2 (C-4), 126.7 (C-6), 34.9 (C-2), 33.3 (C-8), 31.7 (C-10), 29.0 (C-11), 28.7 (C-9), 27.2 (C-1), 22.7 (C-12), 14.2 (C-13).

FT-IR (ATR): ν [cm^{-1}] = 3486 (bw), 2955 (w), 2925 (m), 2855 (w), 1699 (s), 1673 (s), 1638 (s), 1578 (s), 1465 (w), 1439 (w), 1410 (w), 1378 (w), 1346 (m), 1283 (m), 1237 (w), 1172 (m), 1119 (w), 992 (m), 965 (m), 867 (w), 841 (m), 816 (w), 724 (w), 626 (w), 540 (w), 505 (m).

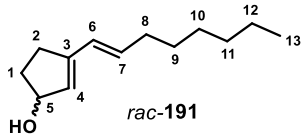
HR-MS: (GC-EI-MS, 70 eV) *m/z* (%): 192.1505 (10, $[M]^+$), 163.0958 (5, $[M\text{-}C_2H_5]^+$), 149.0958 (14, $[M\text{-}C_3H_7]^+$), 135.0802 (19, $[M\text{-}C_4H_9]^+$),

109.0646 (100), 107.0490 (78, $[M-C_6H_{13}]^+$), 96.0568 (26), 91.0541 (40), 79.0541 (74).

4.4.3. *rac*-3-((*E*)-Oct-1-enyl)-cyclopent-2-en-1-ol



To a cooled solution (-78 °C) of dienone **190** (1.00 g, 5.20 mmol, 1.0 eq.) in 26 ml CH_2Cl_2 was added DIBAL-H (6.5 ml, 6.5 mmol, 1.25 eq., 1 M) under an argon atmosphere and the reaction mixture was stirred for 2 h at -78 °C. After confirmation of full conversion of the starting material (GC-MS), excess DIBALH was desactivated by the addition of MeOH to the reaction mixture and it was stirred for 10 min, until it was slowly warmed to r.t. A sat. aq. sodium potassium tartrate solution was added and the mixture was stirred for another 1 h at r.t. Then, the aq. phase was extracted four times with CH_2Cl_2, the combined org. phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 7:1 → 5:1) and the desired dienylic alcohol *rac*-**191** was obtained as a colorless oil (955 mg, 4.91 mmol, 95%).



Formula: $C_{13}H_{22}O$

M: 194.32 g/mol

R_f: 0.60 (SiO_2, 1:1, *c*Hex/EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 6.25 (d, *J* = 15.7 Hz, 1H, H-6), 5.75 (dt, *J* = 15.6, 7.0 Hz, 1H, H-7), 5.66 (d, *J* = 2.1 Hz, 1H, H-4), 4.87 (s, 1H, H-5), 2.68-2.58 (m, 1H, H-2), 2.38-2.31 (m, 2H, H-1, H-2´), 2.14-2.08 (m, 2H, H-8), 1.82-1.73 (m, 1H, H-1'), 1.46-1.34 (m, 3H, H-9, OH), 1.34-1.27 (m, 6H, H-10, H-11, H-12), 0.91 (t, *J* = 7.0 Hz, 3H, H-13).

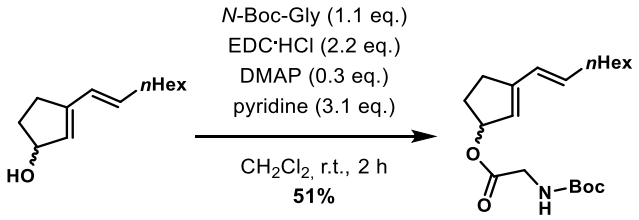
^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 146.1 (C-3), 134.8 (C-7), 129.3 (C-4), 126.5 (C-6), 77.6 (C-5), 33.8 (C-1), 33.0 (C-8), 31.9 (C-11), 29.8 (C-10), 29.4 (C-9), 29.0 (C-1), 22.7 (C-12), 14.2 (C-13).

FT-IR (ATR): ν [cm^{-1}] = 3309 (bw), 2956 (m), 2923 (m), 2853 (m), 1742 (w), 1652 (w), 1605 (w), 1455 (w), 1378 (w), 1351 (w), 1319 (w), 1266 (w), 1221 (w),

1157 (w), 1111 (w), 1035 (s), 961 (s), 876 (w), 847 (w), 809 (w), 724 (w), 548 (w), 510 (w).

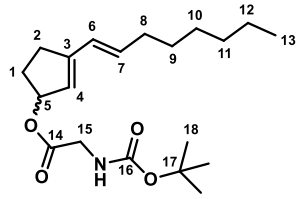
HR-MS: (GC-EI-MS, 70 eV) *m/z* (%): 176.1559 (54, $[M\text{-}H_2O]^+$), 147.1168 (1, $[M\text{-}C_2H_7O]^+$), 133.1012 (54, $[M\text{-}C_3H_9O]^+$), 119.0856 (20, $[M\text{-}C_4H_{11}O]^+$), 105.0699 (100, $[M\text{-}C_5H_{13}O]^+$), 91.0543 (95, $[M\text{-}C_6H_{15}O]^+$), 79.0543 (45), 77.0386 (27).

4.4.4. *rac-N*-Boc-Glycine 3-(oct-1-en-1-yl)-cyclopent-2-en-1-yl ester



rac-**191** *rac*-**197**

A solution of EDC·HCl (218 mg, 1.14 mmol, 2.2 eq.), DMAP (19 mg, 0.16 mmol, 0.3 eq.), pyridine (0.13 ml, 1.6 mmol, 3.1 eq.), dienol *rac*-**191** (100 mg, 0.516 mmol, 1.0 eq.) and *N*-Boc-glycine (100 mg, 0.571 mmol, 1.1 eq.) in 5.0 ml CH_2Cl_2 was stirred for 2 h at r.t. under an argon atmosphere. After confirmation of full conversion of the starting material (crude NMR), the reaction mixture was diluted with EtOAc. The organic phase was washed with a sat. aq. $NaHCO_3$ solution, water and a sat. aq. NaCl solution. The org. phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 6:1 +1% Et_3N) and the desired ester *rac*-**197** was obtained as a pale-yellow oil (103 mg, 0.293 mmol, 51%).



rac-**197**

Formula: $C_{20}H_{33}NO_4$

M: 351.49 g/mol

R_f: 0.14 (SiO_2, 6:1 +1% Et_3N, *c*Hex/EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 6.26 (d, *J* = 15.8 Hz, 1H, H-4), 5.81-5.73 (m, 2H, H-5, H-7), 5.61 (s, 1H, H-6), 4.99 (s, 1H, NH), 3.92-3.77 (m, 2H, H-15), 2.66-2.56 (m, 1H, H-2), 2.44-2.31 (m, 2H, H-1, H-2´), 2.12 (q, *J* = 6.9 Hz, 2H, H-8), 1.96-1.88 (m, 1H, H-1´), 1.45 (s, 9H, H-18), 1.43-

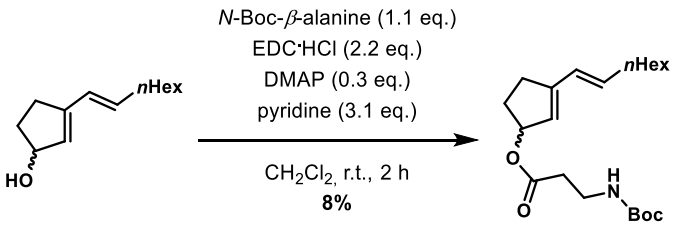
1.36 (m, 2H, H-9), 1.32-1.26 (m, 6H, H-12, H-11, H-10), 0.88 (t, *J* = 7.1 Hz, 3H, H-13).

^{13}C NMR: (126 MHz, $CDCl_3$, mixture of rotamers): δ [ppm] = 170.3 (C-16), 155.7 (C-14), 149.0 (C-3), 135.9 (C-7), 126.1 (C-4_{rot1}), 125.9 (C-4_{rot2}), 124.9 (C-6), 124.2 (C-7), 81.9 (C-5), 80.0 (C-17), 42.7 (C-15), 33.0 (C-8_{rot1}), 32.9 (C-8_{rot2}), 31.8 (C-10_{rot1}), 31.7 (C-10_{rot2}), 30.0 (C-1), 29.7 (C-2), 29.5 (C-9_{rot1}), 29.4 (C-9_{rot2}), 29.1 (C-11), 28.3 (C-19), 22.6 (C-12), 14.1 (C-13).

FT-IR (ATR): ν [cm^{-1}] = 3364 (b), 2954 (m), 2930 (s), 2858 (m), 1718 (s), 1518 (m), 1454 (w), 1393 (m), 1368 (m), 1288 (w), 1252 (m), 1164 (s), 1055 (m), 1030 (w), 953 (w), 860 (w), 782 (w).

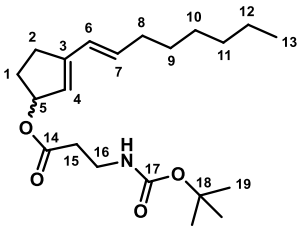
HR-MS: (DIP-EI, 70 eV) τ_R= 8.2 – 8.5 min; *m/z* (%) = 265.1982 (4, [M-C_6H_{14}]$^+$), 193.1586 (26, [M-$C_7H_{12}NO_3$]$^+$), 176.1559 (47, [M-$C_7H_{13}NO_4$]$^+$), 146.0631 (20), 117.0366 (31, [M-$C_{17}H_{30}$]$^+$), 105.0699 (86, [M-$C_{12}H_{24}NO_4$]$^+$), 91.0543 (100, [M-$C_{13}H_{26}NO_4$]$^+$), 75.0261 (63), 73.0468 (31).

4.4.5. *rac*-*N*-Boc-β-Alanine 3-((*E*)-oct-1-en-1-yl)-cyclopent-2-en-1-yl ester



rac-**191** *rac*-**198**

A solution of EDC·HCl (218 mg, 1.14 mmol, 2.2 eq.), DMAP (19 mg, 0.16 mmol, 0.3 eq.), pyridine (0.13 ml, 1.6 mmol, 3.1 eq.), dienol *rac*-**191** (99 mg, 0.510 mmol, 1.0 eq.) and *N*-Boc-β-alanine (106 mg, 0.571 mmol, 1.1 eq.) in 5.0 ml CH_2Cl_2 was stirred for 1.5 h at r.t under an argon atmosphere. After confirmation of full conversion of the starting material (crude NMR), the reaction mixture was diluted with EtOAc. The solution was washed with a sat. aq. $NaHCO_3$ solution, water and a sat. aq. NaCl solution. The org. phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 20:1 +1% Et_3N) and the desired ester *rac*-**198** was obtained as a pale-yellow oil (16 mg, 0.042 mmol, 8%).



rac-**198**

Formula: $C_{21}H_{35}NO_4$

M: 365.51 g/mol

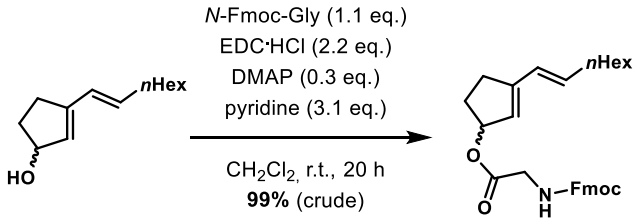
R_f: 0.11 (SiO_2, 6:1 +1% Et_3N, *c*Hex/EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 6.26 (d, *J* = 15.7 Hz, 1H, H-4), 5.81-5.69 (m, 2H, H-5, H-7), 5.62 (d, *J* = 16.4 Hz, 1H, H-6), 5.03 (s, 1H, NH), 3.44-3.32 (m, 2H, H-16), 2.64-2.58 (m, 1H, H-2'), 2.48 (t, *J* = 6.1 Hz, 2H, H-15) 2.43-2.29 (m, 2H, H-1´, H-2´), 2.15-2.07 (m, 2H, H-8), 1.92-1.86 (m, 1H, H-1´), 1.49-1.37 (m, 11H, H-9, H-19), 1.32-1.25 (m, 6H, H-10, H-11, H-12), 0.88 (t, *J* = 7.1 Hz, 3H, H-13).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 172.6 (C-14), 155.9 (C-17), 148.7 (C-3), 135.8 (C-7_{rot1}), 134.8 (C-7_{rot2}), 126.4 (C-4_{rot1}), 126.0 (C-4_{rot2}), 124.7 (C-6), 81.1 (C-5), 79.4 (C-18), 36.2 (C-16), 34.9 (C-15), 33.8 (C-2) 33.0 (C-8), 31.8 (C-10), 29.9 (C-1_{rot1}), 29.8 (C-1_{rot2}), 29.3 (C-19) 29.0 (C-11), 28.5 (C-9), 22.7 (C-12), 14.2 (C-13).

FT-IR (ATR): ν [cm^{-1}] = 3457 (w), 3384 (b), 3025 (w), 2956 (m), 2955 (m), 1717 (s), 1605 (w), 1505 (m), 1456 (m), 1391 (w), 1366 (m), 1278 (m), 1248 (m), 1169 (s), 1064 (m), 1023 (m), 963 (s), 886 (w), 871 (w), 781 (w), 725 (w).

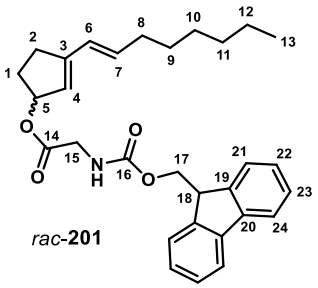
4.4.6. *rac-N*-Fmoc-Glycine 3-(oct-1-en-1-yl)-cyclopent-2-en-1-yl ester



rac-**191** *rac*-**201**

A solution of EDC·HCl (218 mg, 1.14 mmol, 2.2 eq.), DMAP (20 mg, 0.16 mmol, 0.3 eq.), pyridine (0.13 ml, 1.6 mmol, 3.1 eq.), dienol *rac*-**191** (99 mg, 0.510 mmol, 1.0 eq.) and *N*-Fmoc-glycine (168 mg, 0.565 mmol, 1.1 eq.) in 5.0 ml CH_2Cl_2 was stirred for 20 h at r.t. under an argon atmosphere. After confirmation of full conversion of the starting material (crude NMR), the reaction mixture was diluted with EtOAc. The solution was washed with a sat. aq. $NaHCO_3$ solution, water and a sat. aq. NaCl solution. The org. phase was dried over $MgSO_4$ and the solvent was removed under

reduced pressure. The desired ester *rac*-**201** was obtained as an orange solid and was directly used in following experiments (239 mg, 0.505 mmol, 99%).



rac-**201**

Formula: $C_{30}H_{35}NO_4$

M: 473.61 g/mol

R_f: 0.14 (SiO_2, 6:1, *c*Hex/EtOAc, decomposition on TLC).

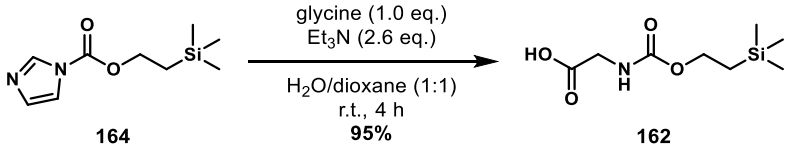
^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 7.79 (d, *J* = 7.5 Hz, 2H, H-21), 7.63 (d, *J* = 7.5 Hz, 2H, H-24), 7.40 (t, *J* = 7.4 Hz, 2H, H-22), 7.31 (td, *J* = 7.4, 1.2 Hz, 2H, H-23), 6.25 (d, *J* = 15.7 Hz, 1H, H-4), 5.84-5.73 (m, 2H, H-7, H-5), 5.61 (s, 1H, H-6), 5.28 (s, 1H, NH), 4.42-4.34 (m, 2H, H-17), 4.27-4.19 (m, 1H, H-18), 3.98-3.87 (m, 2H, H-15), 2.65-2.58 (m, 1H, H-2), 2.44-2.29 (m, 2H, H-1, H-2´), 2.18-2.07 (m, 2H, H-8), 1.98-1.89 (m, 1H, H-1´), 1.43-1.36 (m, 2H, H-9), 1.35-1.21 (m, 6H, H-10, H-11, H-12), 0.92-0.79 (m, H-13).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 170.1 (C-14), 156.4 (C-16), 149.3 (C-3), 144.0 (C-19), 141.4 (C-20), 136.1 (C-7), 127.8 (C-22), 127.0 (C-23), 126.2 (C-4), 125.1 (C-24), 124.2 (C-6), 120.1 (C-21), 82.3 (C-5), 67.3 (C-17), 47.3 (C-18), 43.1 (C-15), 33.0 (C-8), 31.9 (C-10), 30.1 (C-1), 29.9 (C-2), 29.3 (C-9), 29.0 (C-11), 22.7 (C-12), 14.2 (C-13).

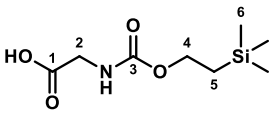
FT-IR (ATR): ν [cm^{-1}] = 3413 (w), 3333 (w), 3065 (w), 3041 (w), 3015 (w), 2954 (m), 2927 (s), 2855 (m), 1715 (s), 1611 (w), 1524 (m), 1450 (s), 1407 (m), 1347 (m), 1245 (m), 1204 (s), 1104 (m), 1051 (s), 1007 (m), 966 (m), 876 (w), 759 (m), 740 (s), 621 (m), 539 (w), 427 (w).

HR-MS: (DIP-EI, 70 eV) τ_R = 4.25 – 4.50 min; *m/z* (%) = 177.1590 (8, $[M-C_{17}H_{14}NO_4]^+$), 176.1557 (48), 133.1010 (8), 119.0854 (20), 105.0697 (100), 91.0541 (100), 79.0541 (49).

4.4.7. *N*-Teoc-Glycine



According to a slightly modified procedure reported by Shute *et al.*[94], to a solution of glycine (242 mg, 3.22 mmol, 1.0 eq.) in 3.2 ml water was added a solution of Et_3N in dioxane (2.6 M, 3.2 ml, 8.3 mmol, 2.6 eq.) and freshly prepared **164** (747 mg, 3.52 mmol, 1.1 eq.). The reaction mixture was stirred for 4 h at r.t. After full conversion of the starting material (TLC), water was added and the mixture was acidified upon addition of a sat. aq. $KHSO_4$ solution. The aq. phase was extracted thrice with MTBE, the combined org. phases were washed twice with water, once with a sat. aq. NaCl solution and it was dried over $MgSO_4$. The solvent was removed under reduced pressure and *N*-Teoc-glycine **162** was obtained as a colorless oil (672 mg, 3.06 mmol, 95%).



Formula: $C_8H_{17}NO_4Si$

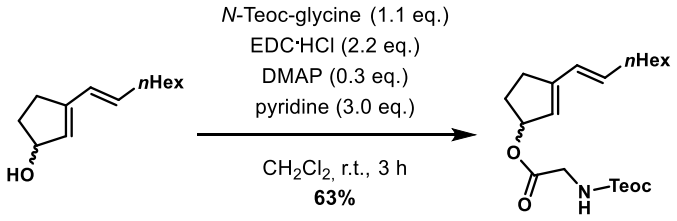
M: 219.31 g/mol

^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 9.50 (s, 1H, CO_2H), 7.03 and 5.29 (s, 1H, NH*), 4.27-4.11 (2H, H-4), 4.01 (d, *J* = 5.6 Hz, 2H, H-2), 1.03-0.95 (m, 2H, H-5), 0.03 (s, 9H, H-6).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 174.6 (C-1_{rot1}), 173.6 (C-1_{rot2}), 157.1 (C-3), 64.8 (C-2_{rot1}), 64.0 (C-2_{rot2}), 43.2 (C-4_{rot1}), 42.6 (C-4_{rot2}), 17.8 (C-5), –1.4 (C-6).

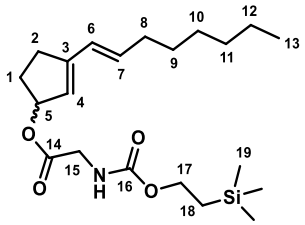
The analytical data are in accordance with the literature.[176]

4.4.8. *rac-N*-Teoc-Glycine 3-(oct-1-en-1-yl)-cyclopent-2-en-1-yl ester



rac-**191** *rac*-**199**

A solution of EDC·HCl (977 mg, 5.10 mmol, 2.2 eq.), DMAP (91 mg, 0.74 mmol, 0.3 eq.), pyridine (0.56 ml, 7.0 mmol, 3.0 eq.), dienol *rac*-**191** (444 mg, 2.29 mmol, 1.0 eq.) and *N*-Teoc-glycine (548 mg, 2.50 mmol, 1.1 eq.) in 23 ml CH_2Cl_2 was stirred for 3 h at r.t. under an argon atmosphere. Afterwards the reaction mixture was diluted with EtOAc and washed with a sat. aq. $NaHCO_3$ solution, water and a sat. aq. NaCl solution. The org. phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 9:1 +3% Et_3N) and the desired ester *rac*-**199** was obtained as a pale-yellow oil (574 mg, 1.45 mmol, 63%).



rac-**199**

Formula: $C_{21}H_{37}NO_4Si$

M: 395.62 g/mol

R_f: 0.72 (SiO_2, 1:1 +3% Et_3N, *c*Hex/EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 6.26 (d, *J* = 15.7 Hz, 1H, H-4), 5.82-5.73 (m, 2H, H-5, H-7), 5.61 (s, 1H, H-6), 5.08 (s, 1H, NH), 4.17 (t, *J* = 8.4 Hz, 2H, H-17), 3.91 (d, *J* = 4.8 Hz, 2H, H-15), 2.66-2.57 (m, 1H, H-2), 2.44-2.30 (m, 2H, H-1, H-2´), 2.12 (q, *J* = 7.2 Hz, 2H, H-8), 1.96-1.88 (m, 1H, H-1´), 1.43-1.36 (m, 2H, H-9), 1.32-1.23 (m, 6H, H-12, H-11, H-10), 1.02-0.96 (m, 2H, H-18), 0.88 (t, *J* = 7.0 Hz, 3H, H-13), 0.03 (s, 9H, H-19).

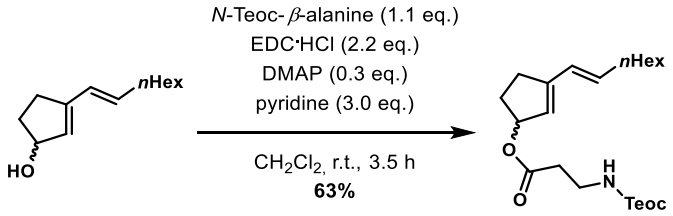
^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 170.3 (C-14), 156.8 (C-16), 149.2 (C-3), 136.1 (C-7), 126.0 (C-4_{rot1}), 125.1 (C-4_{rot2}), 124.3 (C-6), 82.2 (C-5), 64.0 (C-17_{rot1}), 63.7 (C-17_{rot2}), 43.0 (C-15), 33.1 (C-8), 31.9 (C-10), 30.1 (C-2), 29.9 (C-1), 29.3 (C-9), 29.0 (C-11), 22.8 (C-12), 17.9 (C-18), 14.2 (C-13), –1.3 (C-19).

FT-IR (ATR): ν [cm^{-1}] = 3364 (b), 3029 (w), 2954 (m), 2926 (m), 2954 (m), 2855 (w), 1723 (s), 1604 (w) 1517 (m), 1454 (w), 1381 (w), 1357 (m), 1249 (s),

1192 (s), 1160 (m), 1050 (m), 1023 (w), 964 (m), 859 (s), 835 (s), 769 (m), 694 (m), 608 (w), 486 (w).

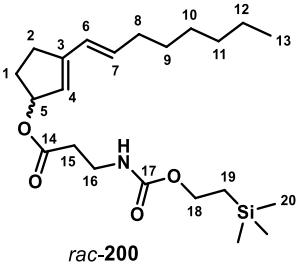
HR-MS: (DIP-EI, 70 eV) τ_R = 4.8 – 5.0 min; *m/z* (%) = 265.1617 (5), 213.0940 (14), 176.0372 (21, [M-$C_8H_{16}NO_4Si$]$^+$), 146.0631 (18), 123.0440 (26), 102.0733 (43), 95.0491 (58), 81.0699 (60), 75.0261 (88), 73.0468 (100, $SiMe_3^+$),

4.4.9. *rac*-*N*-Teoc-β-Alanine 3-((*E*)-oct-1-en-1-yl)-cyclopent-2-en-1-yl ester



rac-**191** *rac*-**200**

A solution of EDC·HCl (986 mg, 5.14 mmol, 2.2 eq.), DMAP (90 mg, 0.74 mmol, 0.3 eq.), pyridine (0.57 ml, 7.1 mmol, 3.0 eq.), dienol *rac*-**191** (456 mg, 2.35 mmol, 1.0 eq.) and *N*-Teoc-β-alanine (600 mg, 2.57 mmol, 1.1 eq.) in 23 ml CH_2Cl_2 was stirred for 3.5 h at r.t. under an argon atmosphere. Afterwards the reaction mixture was diluted with EtOAc and it was washed with a sat. aq. $NaHCO_3$ solution, water and a sat. aq. NaCl solution. The org. phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 6:1 +3% Et_3N) and the desired ester *rac*-**200** was obtained as a colorless oil (607 mg, 1.48 mmol, 63%).



rac-**200**

Formula: $C_{22}H_{39}NO_4Si$

M: 409.64 g/mol

R_f: 0.23 (SiO_2, 6:1 +3% Et_3N, *c*Hex/EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 6.26 (d, *J* = 15.6 Hz, 1H, H-4), 5.77 (dt, *J* = 15.6, 7.0 Hz, 1H, H-7), 5.74-5.71 (m, 1H, H-5), 5.61 (s, 1H, H-6), 5.11 (s, 1H, NH), 4.16-4.10 (m, 2H, H-18), 3.46-3.38 (m, 2H, H-16), 2.65-2.58 (m, 1H, H-2), 2.49 (t, *J* = 6.0 Hz, 2H, H-15), 2.42-2.31 (m, 2H, H-1, H-2´), 2.12 (q, *J* = 7.34 Hz, 2H, H-8), 1.91-1.85 (m, 1H, H-1´), 1.42-1.36

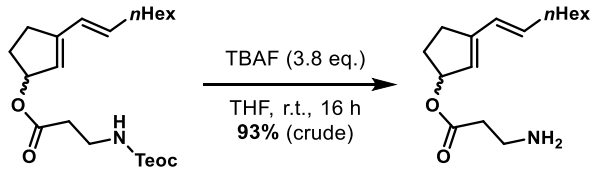
(m, 2H, H-9), 1.31-1.24 (m, 6H, H-12, H-11, H-10), 0.97 (t, *J* = 8.5 Hz, 2H, H-19), 0.88 (t, *J* = 7.1 Hz, 3H, H-13), 0.03 (s, 9H, H-20).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 172.8 (C-14), 157.0 (C-17), 149.0 (C-3), 136.0 (C-7), 126.3 (C-4), 124.9 (C-6), 81.4 (C-5), 63.4 (C-18), 36.8 (C-16), 35.1 (C-15), 33.3 (C-8), 32.1 (C-10), 30.4 (C-1), 30.1 (C-2), 29.5 (C-9), 29.3 (C-11), 23.0 (C-12), 18.1 (C-19), 14.5 (C-13), –1.1 (C-20).

FT-IR (ATR): ν [cm^{-1}] = 3451 (w), 3359 (b), 3056 (w), 3025 (w), 2954 (m), 2927 (m), 2856 (s), 1725 (s), 1513 (m), 1468 (w), 1454 (w), 1378 (w), 1358 (w), 1250 (s), 1181 (s), 1140 (m), 1062 (w), 1023 (w), 964 (m), 895 (w), 860 (m), 834 (m), 778 (w), 695 (w).

HR-MS: (DIP-EI, 70 eV) τ_R = 5.4 – 5.6 min; *m/z* (%) = 208.1459 (15), 192.1510 (46, [M-$C_9H_{19}NO_3Si$]$^+$), 149.0962 (17, [M-$C_{12}H_{26}NO_3Si$]$^+$), 135.0806 (31, [M-$C_{13}H_{28}NO_3Si$]$^+$), 121.0649 (100, [M-$C_{14}H_{30}NO_3Si$]$^+$), 107.0493 (56, [M-$C_{15}H_{32}NO_3Si$]$^+$), 95.0493 (71), 79.0543 (90).

4.4.10. *rac*-*β*-Alanine 3-((*E*)-oct-1-en-1-yl)-cyclopent-2-en-1-yl ester



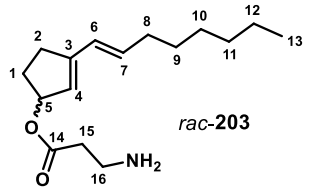
rac-**200** *rac*-**203**

To a solution of the Teoc protected amine *rac*-**200** (53 mg, 0.13 mmol, 1.0 eq.) in 0.6 ml THF was added a 1M solution of TBAF in THF (0.50 ml, 0.50 mmol, 3.8 eq.) and the reaction mixture was stirred for 16 h at r.t. After confirmation of full conversion of the starting material (TLC), the reaction mixture was diluted with EtOAc and washed thrice with a sat. aq. $NaHCO_3$ solution. The combined aq. phases were extracted thrice with EtOAc and all combined org. phases were washed with a sat. aq. NaCl solution. The org. phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product *rac*-**203** was obtained as a brown oil and was directly used in following reactions (32 mg, 0.12 mmol, 93%).

Formula: $C_{16}H_{27}NO_2$

M: 265.40 g/mol

R_f: 0.11 (SiO_2, 1:1 +3% Et_3N, *c*Hex/EtOAc, decomposition on TLC).



rac-**203**

^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 6.25 (d, *J* = 15.6 Hz, 1H, H-4), 5.79-5.66 (m, 2H, H-5, H-7), 5.60 (s, 1H, H-6), 2.95 (t, *J* = 6.3 Hz, 2H, H-16), 2.67-2.55 (m, 1H, H-2), 2.42 (t, *J* = 6.3 Hz, 2H, H-15), 2.39-2.26 (m, 2H, H-1, H-2´), 2.10 (q, *J* = 6.0 Hz, 2H, H-8), 1.90-1.83 (m, 1H, H-1´), 1.40-1.34 (m, 2H, H-9), 1.30-1.22 (m, 6H, H-12, H-11, H-10), 0.86 (t, *J* = 7.1 Hz, 3H, H-13).

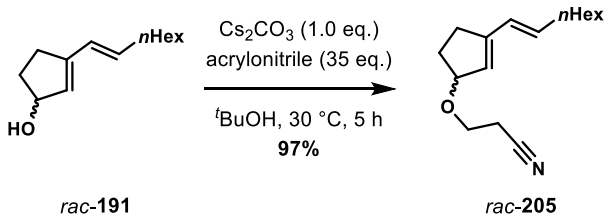
^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 172.7 (C-14), 148.8 (C-3), 135.8 (C-7), 126.2 (C-4), 125.0 (C-6), 83.0 (C-5), 41.6 (C-15), 39.9 (C-16), 33.1 (C-8_{rot1}), 33.0 (C-8_{rot2}), 31.9 (C-10), 29.9 (C-2), 29.8 (C-1), 29.4 (C-9), 29.1 (C-11_{rot1}), 29.0 (C-11_{rot2}), 22.8 (C-12_{rot1}), 22.7 (C-12_{rot2}), 14.3 (C-13_{rot1}), 14.2 (C-13_{rot2}).*

FT-IR (ATR): ν [cm^{-1}] = 3378 (b), 2957 (m), 2925 (s), 2871 (m), 2855 (m), 1726 (s), 1650 (m), 1572 (m), 1457 (m), 1378 (m), 1355 (s), 1206 (s), 1181 (s), 1159 (s), 1066 (m), 1024 (s), 963 (s), 891 (m), 800 (s), 725 (m), 662 (s), 592 (m), 471 (m).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{16}H_{27}NO_2$ $[M+H]^+$ 266.2115 u, found: 266.2118 u.

*Major decomposition is visible in the spectrum, due to instability in $CDCl_3$.

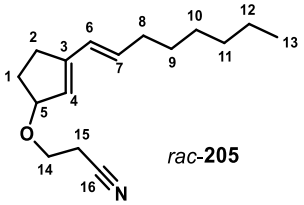
4.4.11. *rac*-3-((3-((*E*)-Oct-1-en-1-yl)-cyclopent-2-en-1-yl)oxy)propionitrile



rac-**191** *rac*-**205**

To a solution of alcohol *rac*-**191** (399 mg, 2.06 mmol, 1.0 eq.) in 10.5 ml ^{t}BuOH was added Cs_2CO_3 (676 mg, 2.07 mmol, 1.0 eq.) and acrylonitrile (4.8 ml, 72 mmol, 35 eq.). The reaction mixture was stirred at 30 °C for 5 h until full conversion of the starting material was observed (TLC). Then, water (10 ml) was added and the aq. phase was extracted with EtOAc (3 x 20 ml). The combined org. phases were washed

with a sat. aq. NaCl solution (25 ml), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 4:1 +1% Et_3N) and the desired ether *rac*-**205** was obtained as a colorless oil (490 mg, 1.98 mmol, 97%).



rac-**205**

Formula: $C_{16}H_{25}NO$

M: 247.38 g/mol

R_f: 0.49 (SiO_2, 2:1, *c*Hex/EtOAc).

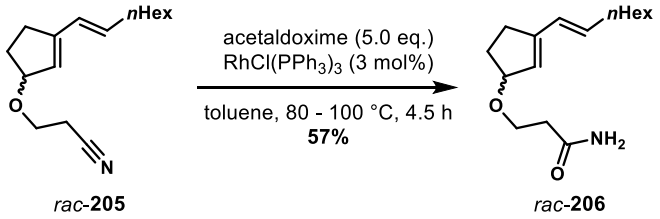
^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 6.26 (d, *J* = 15.7 Hz, 1H, H-6), 5.73 (dt, *J* = 15.5, 7.0 Hz, 1H, H-7), 5.64 (q, *J* = 1.9 Hz, 1H, H-4), 4.64 (dd, *J* = 6.9, 2.5 Hz, 1H, H-5), 3.65 (td, *J* = 6.6, 3.6 Hz, 2H, H-14), 2.64 – 2.55 (m, 3H, H-1, H-15), 2.38 – 2.31 (m, 1H, H-1), 2.22 (dddd, *J* = 13.9, 9.1, 7.3, 4.9 Hz, 1H, H-2), 2.11 (q, *J* = 6.8 Hz, 2H, H-8), 1.87 (dddd, *J* = 13.6, 8.8, 4.4, 3.5 Hz, 1H, H-2), 1.43 – 1.36 (m, 2H, H-9), 1.33 – 1.24 (m, 6H, H-10, H-11, H-12), 0.88 (d, *J* = 6.9 Hz, 3H, H-13).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 147.5 (C-3), 135.2 (C-7), 126.3 (C-6), 125.8 (C-4), 118.1 (C-16), 85.4 (C-5), 62.8 (C-14), 33.0 (C-8), 31.8 (C-11), 30.0 (C-2), 29.9 (C-1), 29.3 (C-9), 29.0 (C-10), 22.7 (C-12), 19.4 (C-15), 14.2 (C-13).

FT-IR (ATR): ν [cm^{-1}] = 2955 (m), 2924 (m), 2854 (m), 2251 (w), 1721 (w), 1651 (w), 1605 (w)1456 (w), 1358 (m), 1331 (w), 1302 (w), 1270 (w), 1221 (w), 1162 (w), 1095 (s), 1035 (m), 963 (s), 883 (w), 859 (w), 812 (w), 731 (w).

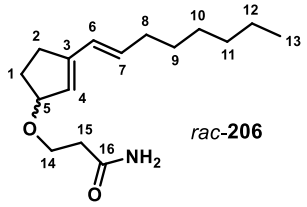
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{16}H_{25}NONa$ $[M+Na]^+$ 270.1828 u, found: 270.1831 u.

4.4.12. *rac*-3-((3-((*E*)-Oct-1-en-1-yl)-cyclopent-2-en-1-yl)oxy)propan-amide



rac-**205** *rac*-**206**

To a solution of nitrile *rac*-**205** (99 mg, 0.40 mmol, 1.0 eq.) in 0.40 ml toluene was added $RhCl(PPh_3)_3$ (10.4 mg, 0.0112 mmol, 0.3 eq.) and acetaldoxime (120 mg, 2.03 mmol, 5.0 eq.). The reaction mixture was stirred for 2 h at 80 °C and for further 2.5 h at 100 °C, until full conversion of the starting material was observed (TLC). Then, the reaction mixture was cooled to r.t, diluted with EtOAc and filtered through a plug of silica. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 1:1 → 5:5:1, *c*Hex/EtOAc/MeOH). The desired amide *rac*-**206** was obtained as a slightly yellow solid (60 mg, 0.23 mmol, 57%).



rac-**206**

Formula: $C_{16}H_{27}NO_2$

M: 265.40 g/mol

m.p.: 71-72 °C

R_f: 0.14 (SiO_2, 5:5:1, *c*Hex/EtOAc/MeOH).

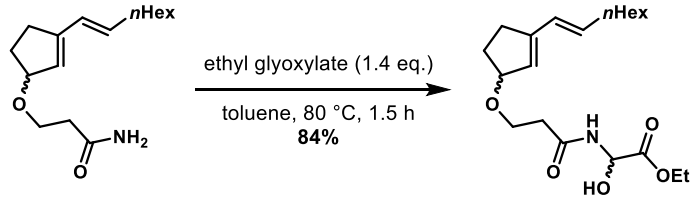
^{1}H NMR: (500 MHz, toluene-d_8): δ [ppm] = 6.24 (d, *J* = 15.4 Hz, 1H, H-6), 5.92 (s, 1H, NH), 5.65 – 5.50 (m, 3H, H-4, H-7, NH´), 4.35 – 4.31 (m, 1H, H-5), 3.45 – 3.35 (m, 2H, H-14), 2.45 (dddt, *J* = 13.4, 8.9, 4.4, 2.2 Hz, 1H, H-1), 2.19 – 2.11 (m, 3H, H-1´, H-15), 2.03 (qd, *J* = 7.0, 1.4 Hz, 2H, H-8), 1.96 (dddd, *J* = 13.6, 9.0, 7.3, 4.7 Hz, 1H, H-2), 1.74 (dddd, *J* = 13.9, 9.0, 5.1, 3.8 Hz, 1H, H-2), 1.37 – 1.19 (m, 8H, H-9, H-10, H-11, H-12), 0.90 (t, *J* = 7.0 Hz, 3H, H-13).

^{13}C NMR: (126 MHz, toluene-d_8): δ [ppm] = 173.7 (C-16), 146.6 (C-3), 134.4 (C-7), 127.9 (C-4), 127.6 (C-6), 85.5 (C-5), 64.8 (C-14), 37.5 (C-15), 33.7 (C-8), 32.6 (C-11), 30.8 (C-2), 30.4 (C-1), 30.1 (C-9), 29.8 (C-10), 23.5 (C-12), 14.7 (C-13).

FT-IR (ATR): ν [cm^{-1}] = 3359 (m), 3183 (m), 2959 (m), 2920 (m), 2876 (m), 2851 (m), 1708 (w), 1657 (s), 1630 (s), 1432 (s), 1422 (s), 1391 (m), 1358 (m), 1329 (m), 1307 (m), 1259 (m), 1227 (w), 1166 (w), 1138 (w), 1077 (s), 1054 (m), 1031 (m), 966 (s), 877 (m), 808 (m), 695 (s), 630 (s), 555 (m), 541 (m), 525 (m).

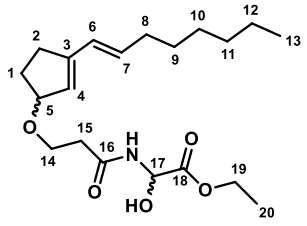
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{16}H_{27}NO_2Na$ $[M+Na]^+$ 288.1934 u, found: 288.1937 u.

4.4.13. *rac*-Ethyl 2-(3-((3-((*E*)-oct-1-en-1-yl)-cyclopent-2-en-1-yl)oxy)propanamido)-2-hydroxyacetate



rac-**206** *rac*-**207**

To a solution of amide *rac*-**206** (145 mg, 0.554 mmol, 1.0 eq.) in 2.8 ml toluene was added a solution of ethyl glyoxylate in toluene (19 w%, 330 mg, 0.615 mmol, 1.1 eq.) under an argon atmosphere. The reaction mixture was stirred for 50 min at 80 °C and subsequently another portion of ethyl glyoxylate in toluene (19 w%, 90 mg, 0.17 mmol, 0.3 eq.) was added. The reaction mixture was continued to stir at 80 °C for 45 min, until full conversion of the starting material was observed (TLC). Then, the solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 1:1). The desired product *rac*-**207** was obtained as a slightly yellow solid (172 mg, 0.468 mmol, 84%).



rac-**207**

Formula: $C_{20}H_{33}NO_5$

M: 367.49 g/mol

m.p.: 60-61 °C

R_f: 0.36 (SiO_2, 5:5:1, *c*Hex/EtOAc/MeOH).

^{1}H NMR: (500 MHz, toluene-d_8): δ [ppm] = 7.63 – 7.53 (m, 1H, NH), 6.26 (dd, *J* = 15.7, 2.2 Hz, 1H, H-6), 5.69 (dd, *J* = 4.4, 1.8 Hz, 1H, H-4), 5.67 – 5.58 (m, 2H, H-7, H-17), 4.86 (s, 1H, OH), 4.39 (dd, *J* = 5.6, 2.8 Hz, 1H,

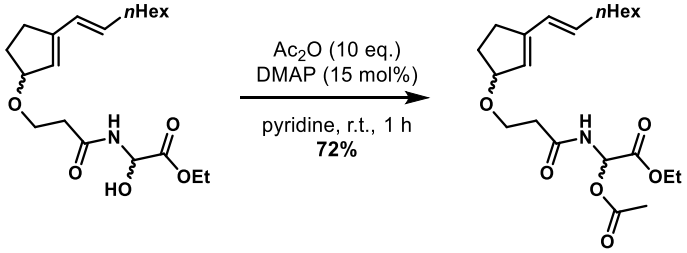
H-5), 3.92 (qt, *J* = 7.1, 1.4 Hz, 2H, H-19), 3.45 – 3.32 (m, 2H, H-14), 2.53 (dddd, *J* = 13.8, 8.8, 4.7, 2.3 Hz, 1H, H-2), 2.25 – 2.14 (m, 3H, H-2, H-15), 2.06 – 1.98 (m, 3H, H-1, H-8), 1.86 (tdd, *J* = 13.5, 4.8, 3.9 Hz, 1H, H-1´), 1.35 – 1.20 (m, 8H, H-9, H-10, H-11, H-12), 0.95 (td, *J* = 7.2, 1.1 Hz, 3H, H-20), 0.90 (t, *J* = 7.1 Hz, 3H, H-13).

^{13}C NMR: (126 MHz, toluene-d_8, mixture of rotamers): δ [ppm] = 172.2 (C-16), 169.8 (C-18), 146.6 (C-3), 134.1 (C-7_{rot1}), 134.1 (C-7_{rot2}), 127.3 (C-6_{rot1}), 127.3 (C-6_{rot2}), 127.2 (C-4_{rot1}), 127.2 (C-4_{rot2}), 85.2 (C-5), 72.4 (C-17_{rot1}), 72.4 (C-17_{rot2}), 63.9 (C-14), 61.7 (C-19), 37.2 (C-15), 33.3 (C-8), 32.2 (C-11), 30.3 (C-1), 30.0 (C-2), 29.7 (C-9), 29.4 (C-10), 23.1 (C-12), 14.3 (C-13), 13.9 (C-20).

FT-IR (ATR): ν [cm^{-1}] = 3327 (m), 2956 (w), 2923 (m), 2853 (w), 1745 (s), 1652 (s), 1546 (s), 1448 (w), 1424 (w), 1365 (m), 1239 (m), 1206 (m), 1162 (w), 1086 (s), 1028 (m), 991 (w), 959 (m), 881 (w), 867 (w), 806 (w), 660 (m), 624 (m), 592 (m).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{20}H_{33}NO_5Na$ $[M+Na]^+$ 390.2251 u, found: 390.2253 u.

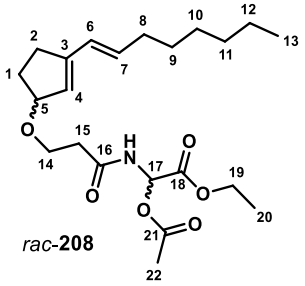
4.4.14. *rac*-Ethyl 2-(3-((3-((*E*)-oct-1-en-1-yl)-cyclopent-2-en-1-yl)oxy)-propanamido)-2-acetoxyacetate



rac-**207** *rac*-**208**

To a solution of the hemiaminal *rac*-**207** (124 mg, 0.337 mmol, 1.0 eq.) in 0.85 ml pyridine was added acetic anhydride (0.33 ml, 3.5 mmol, 10 eq.) and DMAP (6 mg, 0.05 mmol, 0.15 eq.). The reaction mixture was stirred for 1 h at r.t, until full conversion of the starting materials was observed (TLC). Then, the reaction mixture was diluted with EtOAc (15 ml) and the org. phase was washed with an aq. 1M HCl solution (3x 10 ml) and water (10 ml). The org. phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column

chromatography (SiO_2, *c*Hex/EtOAc, 2:1) and the desired acetate *rac*-**208** was obtained as a colorless oil (100 mg, 0.244, 72%).



rac-**208**

Formula: $C_{22}H_{35}NO6$

M: 409.52 g/mol

R_f: 0.25 (SiO_2, 2:1, *c*Hex/EtOAc).

^{1}H NMR: (500 MHz, toluene-d_8, mixture of diastereomers): δ [ppm] = 7.80 (d, *J* = 9.1 Hz, 1H, NH), 6.65 (dd, *J* = 9.2, 1.6 Hz, 1H, H-17), 6.25 (dd, *J* = 15.7, 3.6 Hz, 1H, H-6), 5.72 – 5.58 (m, 2H, H-4, H-7), 4.39 (s, 1H, H-5), 3.90 (qqd, *J* = 10.5, 7.1, 3.6 Hz, 2H, H-19), 3.36 – 3.26 (m, 2H, H-14), 2.58 – 2.48 (m, 1H, H-2), 2.22 – 2.13 (m, 3H, H-2, H-15), 2.01 (q, *J* = 7.0 Hz, 3H, H-1, H-8), 1.94 – 1.79 (m, 1H, H-1), 1.64 (d, *J* = 1.1 Hz, 3H, H-22), 1.27 (ddd, *J* = 24.8, 13.3, 5.7 Hz, 8H), 0.95 – 0.87 (m, 6H, H-13, H-20).

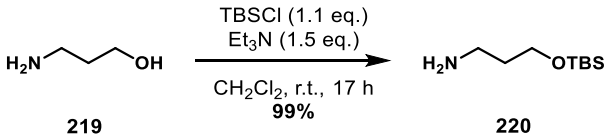
^{13}C NMR: (126 MHz, toluene-d_8, mixture of diastereomers): δ [ppm] = 170.8 (C-16), 169.8 (C-21_{dia1}), 169.8 (C-21_{dia2}), 167.1 (C-18_{dia1}), 167.0 (C-18_{dia2}), 146.7 (C-3_{dia1}), 146.6 (C-3_{dia2}), 134.1 (C-7_{dia1}), 134.1 (C-7_{dia2}), 127.2 (C-6), 127.1 (C-4_{dia1}), 127.0 (C-4_{dia2}), 85.3 (C-5_{dia1}), 85.3 (C-5_{dia2}), 72.9 (C-17_{dia1}), 72.9 (C-17_{dia2}), 63.7 (C-14), 61.9 (C-19), 37.1 (C-15_{dia1}), 37.1 (C-15_{dia2}), 33.3 (C-11), 32.2 (C-8), 30.3, 30.2 (C-1), 30.0 (C-2), 29.7 (C-9), 29.4 (C-10), 23.1 (C-12), 20.0 (C-22_{dia1}), 20.0 (C-22_{dia2}), 14.3 (C-13), 13.9 (C-20_{dia1}), 13.9 (C-20_{dia2}).

FT-IR (ATR): ν [cm^{-1}] = 3319 (bw), 2956 (w), 2925 (m), 2855 (w), 1746 (s), 1696 (m), 1678 (m), 1522 (m), 1466 (w), 1372 (m), 1328 (m), 1203 (s), 1156 (m), 1089 (s), 1031 (s), 963 (s), 930 (m), 861 (w), 810 (w), 723 (w), 605 w).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{22}H_{35}NO_6Na$ $[M+Na]^+$ 432.2357 u, found: 432.2360 u.

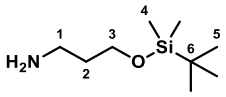
4.5. Synthesis of Compounds Regarding the Aza-Michael/Aldol Approach

4.5.1. 3-Aminopropoxy-1-*tert*-butyldimethylsilane



219 **220**

According to a procedure by van de Winckel *et al.*[109], to a solution of 3-aminopropanol **219** (2.30 ml, 30.3 mmol, 1.0 eq.) and Et_3N (6.5 ml, 47 mmol, 1.5 eq.) in 50 ml CH_2Cl_2 was added TBSCl (5.05 g, 33.7 mmol, 1.1 eq.) and the reaction mixture was stirred for 17 h at r.t. After confirmation of full conversion of the starting material (TLC), the reaction mixture was washed with water (3x 50 ml) and the org. phase was dried over $MgSO_4$. The solvent was removed under reduced pressure and the desired product **220** was obtained as a colorless oil (5.70 g, 30.1 mmol, 99%, Lit.[109]: 98%).



220

Formula: $C_9H_{23}NOSi$

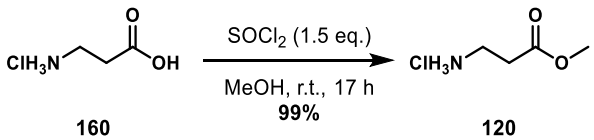
M: 189.37 g/mol

^{1}H NMR: (300 MHz, $CDCl_3$): δ [ppm] = 3.70 (t, *J* = 3.70 Hz, 2H, H-3), 2.81 (t, *J* = 2.81 Hz, 2H, H-1), 1.69 (m, 4H, H-2, NH2), 0.89 (s, 9H, H-5), 0.06 (s, 6H, H-4).

^{13}C NMR: (75 MHz, $CDCl_3$): δ [ppm] = 61.5 (C-3), 39.6 (C-1), 36.3 (C-2), 26.1 (C-5), -5.2 (C-4).

The analytical data are in accordance with the literature.[109]

4.5.2. β-Alanine methylester hydrochloride

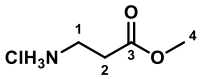


160 **120**

According to a procedure by Dekker *et al.*[110], to a solution of β-alanine hydrochloride **160** (5.97 g, 67.0 mmol, 1.0 eq.) in 150 ml MeOH was added $SOCl_2$ (7.5 ml, 103 mmol, 1.5 eq.) dropwise and the solution was stirred for 17 h at r.t. Then, the solvent was removed under reduced pressure and the desired product **120** was obtained as a colorless solid (9.29 g, 66.5 mmol, 99%, Lit.[110]: 99%).

Formula: $C_4H_{10}ClNO_2$

M: 139.58 g/mol



120

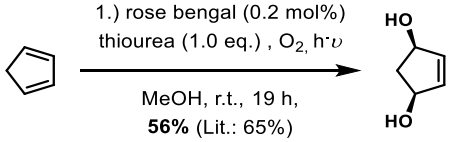
m.p.: 102-104 °C (Lit.[110]: 101 °C).

^{1}H NMR: (300 MHz, MeOD-d_4): δ [ppm] = 4.86 (s, 3H, NH_3), 3.74 (s, 3H, H-4), 3.21 (t, J = 3.21 Hz, 2H, H-1), 2.76 (t, J = 2.76 Hz, 2H, H-2).

^{13}C NMR: (75 MHz, MeOD-d_4): δ [ppm] = 174.6 (C-3), 52.7 (C-4), 36.5 (C-1), 31.1 (C-2).

The analytical data are in accordance with the literature.[110]

4.5.3. *cis*-4-Cyclopentene-1,3-diol

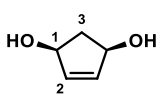


115 **213**

According to a procedure by Tietze *et al*.[105], cyclopentadiene **115** (3.0 ml, 36 mmol, 1.0 eq.), rose Bengal (69 mg, 0.071 mmol, 0.2 mol%) and thiourea (2.73 g, 35.6 mmol, 1.0 eq.) were dissolved in 600 ml MeOH. The reaction mixture and the air volume in the reaction flask was flushed with oxygen through a gas inlet. Subsequently, the reaction mixture was irradiated with a 150 W mercury vapor lamp at r.t. for 4 h and then stirred for further 15 h without irradiation. Afterwards, the reaction mixture was concentrated under reduced pressure and the residue was dissolved in water (250 ml). The aq. phase was washed with MTBE (3x 200 ml) and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, EtOAc/MeOH, 99:1) and the desired diol **213** was obtained as a red-brown oil (2.00 g, 20.0 mmol, 56%, Lit.[105]: 65%).

Formula: $C_5H_8O_2$

M: 100.12 g/mol



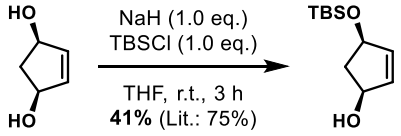
213

R_f: 0.18 (SiO_2, 99:1, EtOAc/MeOH).

^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 5.89 (s, 2H, H-2), 4.58 (dd, J = 7.24 Hz, 4.59 Hz, 2H, H-1), 2.73 (m, 1H, H-3), 1.42 (m, 1H, H-3').

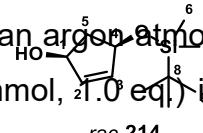
The analytical data are in accordance with the literature.[105]

4.5.4. *rac-cis*-4-(*tert*-Butyldimethylsilanyloxy)-cyclopenten-2-ol



213 rac-**214**

According to a procedure by Ouyang *et al*.[106], NaH (747 mg, 18.7 mmol, 1.0 eq., 60 w% in mineral oil) was washed with pentane (5 ml) under an argon atmosphere. Then, THF (40 ml) and a solution of diol **213** (1.87 g, 18.7 mmol, 1.0 eq.) in 20 ml THF was added. The resulting suspension was stirred for 1 h at r.t., followed by the addition of TBSCl (2.83 g, 18.8 mmol, 1.0 eq.). The reaction mixture was stirred for another 2 h. After confirmation of full conversion of the starting material (TLC), the reaction mixture was washed with a sat. aq. $NaHCO_3$ solution (20 ml) and with a sat. aq. NaCl solution (20 ml). The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 5:1). The desired product *rac*-**214** was obtained as a slightly yellow oil (1.64 g, 7.67 mmol, 41%, Lit.[106]: 75%).



rac-**214**

Formula: $C_{11}H_{22}O_2Si$

M: 214.38 g/mol

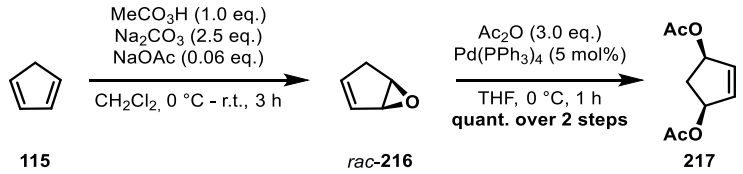
R_f: 0.36 (SiO_2, 22:3, EtOAc/MeOH).

^{1}H NMR: (300 MHz, $CDCl_3$): δ [ppm] = 5.93 (ddt, *J* = 16.5 Hz, 10.9 Hz, 5.63 Hz, 2H, H-2, H-3), 4.64 (m, 2H, H-1, -OH), 2.74 (m, 1H, H-4), 1.56 (m, 2H, H-5), 0.92 (s, 9H, H-7), 0.11 (s, 6H, H-6).

^{13}C NMR: (75 MHz, $CDCl_3$): δ [ppm] = 137.1 (C-2), 135.6 (C-3), 75.3 (C-1), 75.1 (C-4), 26.9 (C-5), 25.9 (C-7), -4.6 (C-6).

The analytical data are in accordance with the literature.[106]

4.5.5. *cis*-1,4-Diacetoxy-cyclopent-2-en

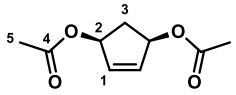


115 *rac*-**216** **217**

According to a slightly modified procedure by Tietze *et al*.[105], a solution of NaOAc (610 mg, 7.44 mmol, 0.07 eq.), Na_2CO_3 (31.0 g, 296 mmol, 2.7 eq.) and cycopentadiene **115** (11.0 ml, 132 mmol, 1.2 eq.) in 160 ml CH_2Cl_2 was cooled to 0 °C in an ice bath followed by the addition of peracetic acid (23 ml, 110 mmol, 1.0 eq.) in four portions over 30 min. After complete addition of peracetic acid, the reaction mixture was warmed to r.t. and stirred for 2.5 h. Then, the reaction mixture was filtrated and the solvent was carefully removed under reduced pressure at r.t. In a separate flask a solution of $Pd(PPh_3)_4$ (706 mg, 0.611 mmol, 0.56 mol%) and Ac_2O (34 ml, 360 mmol, 3.3 eq.) in 90 ml THF was cooled to 0 °C in an ice bath under an argon atmosphere. The residue, containing the crude epoxide *rac*-**216,** was slowly added to the catalyst solution over 5 min. After 40 min, DMAP (80 mg, 0.66 mmol, 0.60 mol%) was added and it was stirred for 10 min at r.t. After full conversion of the epoxide *rac*-**216**, water (100 ml) was added to the reaction mixture and the aq. phase was extracted with EtOAc (3x 100 ml). The combined org. phases were washed with a sat. aq. $NaHCO_3$ solution (70 ml), with a sat. aq. NaCl solution (2x 70 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 4:1 → 2:1). The desired product **217** was obtained as a slightly yellow oil (20.4 g, 111 mmol, quant., Lit.[105]: 56%).

Formula: $C_9H_{12}O_4$

M: 184.19 g/mol



217

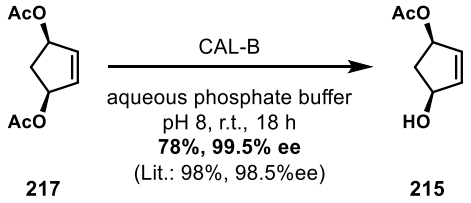
R_f: 0.48 (SiO_2, 1:1, *c*Hex/EtOAc).

^{1}H NMR: (300 MHz, $CDCl_3$): δ [ppm] = 6.10 (m, 2H, H-1), 5.55 (m, 2H, H-2), 2.88 (m, 1H, H-3), 2.07 (s, 6H, H-5), 1.74 (m, 1H, H-3‘).

^{13}C NMR: (75 MHz, $CDCl_3$): δ [ppm] = 170.7 (C-4), 134.7 (C-1), 60.4 (C-2), 37.2 (C-3), 21.1 (C-5).

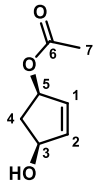
The analytical data are in accordance with the literature.[105]

4.5.6. (1*S*,4*R*)-4-Acetoxycyclopent-2-en-1-ol



217 **215**

According to a procedure by Specklin *et al*.[108], an emulsion of *cis*-1,4-diacetoxy-2-cyclopentene **217** (513 mg, 2.79 mmol, 1.0 eq.) and immobilized CAL-B (27 mg, 5000 units/g) in an aq. NaH_2PO_4/Na_2HPO_4 buffer (13.5 ml, 0.1 M, pH 8.0) was shaken for 18 h at r.t. After confirmation of full conversion of the starting material (TLC), the reaction mixture was filtrated over a short pad of celite and the pad was washed with water (50 ml) and EtOAc (50 ml). The aq. phase was extracted with EtOAc (4x 50 ml) and the combined org. phases were dried over $MgSO_4$. The solvent was removed under reduced pressure and the desired product **215** was obtained as a slightly yellow solid (309 mg, 278 mmol, 78%, 99.5%ee, Lit.[108]: 98%, 98.5%ee).



215

Formula: $C_7H_{10}O_3$

M: 142.15 g/mol

m.p.: 40-44 °C (Lit.[177]: 49-51 °C)

R_f: 0.21 (SiO_2, 1:1, *c*Hex/EtOAc).

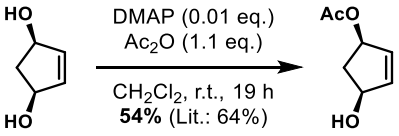
^{1}H NMR: (300 MHz, $CDCl_3$): δ [ppm] = 6.05 (m, 2H, H-1, H-2), 5.50 (m, 1H, H-5), 4.73 (m, 1H, H-3), 2.81 (dt, *J* = 14.5 Hz, 7.37 Hz, 1H, H-4), 2.06 (s, 3H, H-7), 1.66 (dt, *J* = 14.6 Hz, 3.79 Hz, 1H, H-4).

^{13}C NMR: (75 MHz, $CDCl_3$): δ [ppm] = 170.9 (C-6), 138.6 (C-1), 132.4 (C-2), 74.6 (C-3, C-5), 40.5 (C-4), 21.2 (C-7).

$[\alpha]_\lambda^{20}$: c = 1.18 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = 248.0° (± 0.3°), $[\alpha]_{436}^{20}$ = 143.1° (± 0.1°), $[\alpha]_{546}^{20}$ = 77.5° (± 0.0°), $[\alpha]_{579}^{20}$ = 66.8° (± 0.1°), $[\alpha]_{589}^{20}$ = 63.4° (± 0.0°).

The analytical data are in accordance with the literature.[177]

4.5.7. *rac-cis*-4-Acetoxycyclopent-2-ene-1-ol



213 *rac*-**215**

According to a procedure by Maguire *et al*.[107], to a solution of *cis*-4-cyclopentene-1,3-diol **213** (189 mg, 1.89 mmol, 1.0 eq.) and DMAP (3 mg, 0.03 mmol, 0.01 eq.) in 5.0 ml CH_2Cl_2 was added Ac_2O (0.20 ml, 2.1 mmol, 1.1 eq.) and stirred for 19 h at r.t. After confirmation of full conversion of the starting material (TLC), the solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 1:1). The desired product *rac*-**215** was obtained as a colorless oil (146 mg, 1.02 mmol, 54%, Lit.[107]: 64%).

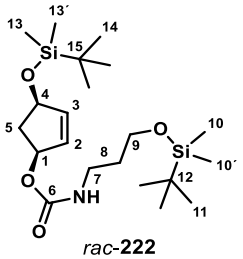
The analytical data are in accordance with the data for the enantiomerically enriched compound **215** reported previously (See 4.5.6).

4.5.8. *rac-cis*-4-(*tert*-Butyldimethylsilanyloxy)cyclopent-2-en-1-yl 3-((*tert*-butyldimethylsilanyloxy)prop-1-yl carbamate

rac-**214** *rac*-**222**

To a solution of CDI (78 mg, 0.48 mmol, 1.0 eq.) in 0.94 ml CH_2Cl_2 was added alcohol *rac*-**214** (98 mg, 0.46 mmol, 1.0 eq.) under an argon atmosphere. The reaction mixture was stirred for 7 h and after confirmation of full conversion of the starting material (TLC), the amine **220** (0.11 ml, 0.46 mmol, 1.0 eq.) was added. The reaction mixture was stirred for 17 h at r.t. and after confirmation of full conversion of the intermediate (TLC), the reaction mixture was diluted with water (20 ml). The aq. phase was extracted with EtOAc (3x 30 ml), the combined org. phases were washed with a sat. aq. NaCl solution (20 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 5:1). The desired carbamate *rac*-**222** was obtained as a colorless oil (123 mg, 0.290 mmol, 61%).

Formula: $C_{21}H_{43}NO_4Si_2$



rac-**222**

M: 429.75 g/mol

R_f: 0.36 (SiO_2, 5:1, *c*Hex/EtOAc).

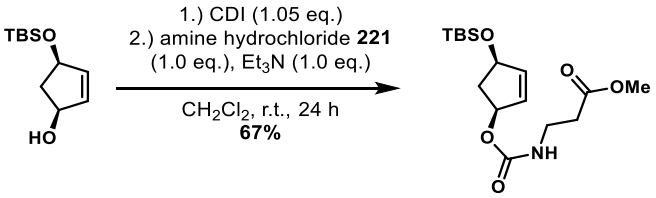
^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 5.91 (dd, *J* = 14.4 Hz, 5.60 Hz, 2H, H-2, H-3), 5.42 (t, *J* = 5.42 Hz, 1H, H-1), 5.13 (s, 1H, NH), 4.70 (t, 1H, *J* = 4.70 Hz, H-4), 3.70 (t, 2H, H-9), 3.30 (q, *J* = 3.29 Hz, 2H, H-7), 2.79 (m, 1H, H-5), 1.71 (m, 2H, H-8), 1.57 (m, 1H, H-5‘), 0.90 (s, 9H, H-14), 0.89 (s, 9H, H-11), 0.08 (d, 6H, H-13), 0.05 (s, 6H, H-10).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 156.3 (C-6), 138.3 (C-2), 132.0 (C-3), 76.9 (C-1), 74.9 (C-4), 61.8 (C-9), 41.5 (C-5), 39.2 (C-7), 32.0 (C-8), 25.9 (C-11, C-14), 18.2 (C-12, C-15), -4.6 (C-13), -5.4 (C-10).

FT-IR (ATR): ν [cm^{-1}] = 3338 (w), 3065 (w), 2953 (m), 2929 (m), 2886 (m), 2857 (m), 1723 (m), 1699 (s), 1515 (m), 1472 (m), 1463 (m), 1443 (w), 1406 (w), 1389 (w), 1370 (m), 1250 (s), 1097 (s), 1065 (s), 1047 (s), 1005 (m), 978 (m), 939 (m), 906 (m), 833 (vs), 773 (vs), 666 (m), 579 (w).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{21}H_{43}NO_4Si_2Na$ $[M+Na]^+$ 452.2623 u, found: 452.2625 u.

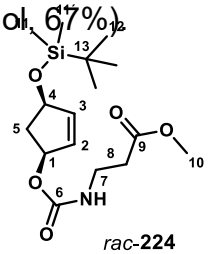
4.5.9. *rac*-*cis*-Methyl 3-(((4-((*tert*-butyldimethylsilanyloxy)cyclopent-2-en-1-yl)oxy)carbonyl)amino)propanoate



rac-**214** *rac*-**224**

To a solution of CDI (258 mg, 2.21 mmol, 1.05 eq.) in 5.0 ml CH_2Cl_2 was added alcohol *rac*-**214** (450 mg, 2.10 mmol, 1.0 eq.) under an argon atmosphere. The reaction mixture was stirred for 7 h and after confirmation of full conversion of the starting material (TLC), amine **221** (253 mg, 2.10 mmol, 1.0 eq.) and Et_3N (0.35 ml, 2.1 mmol, 1.0 eq.) were added. The reaction mixture was stirred for 17 h at r.t. and after confirmation of full conversion of the intermediate (TLC), the reaction mixture

was diluted with water (70 ml). The aq. phase was extracted with EtOAc (3x 50 ml), the combined org. phases were washed with a sat. aq. NaCl solution (30 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 5:1). The desired carbamate *rac*-**224** was obtained as a colorless oil (483 mg, 1.41 mmol, 67%).



rac-**224**

Formula: $C_{16}H_{29}NO_5Si$

M: 343.50 g/mol

R_f: 0.11 (SiO_2, 3:1, *c*Hex/EtOAc).

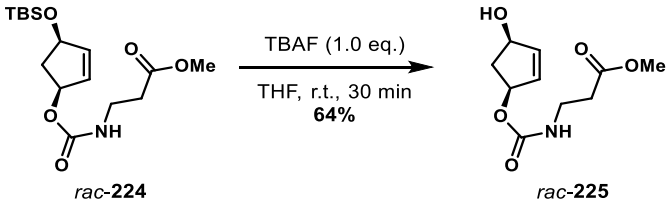
^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 5.94 (d, *J* = 5.93 Hz, 1H, H-2), 5.94 (d, *J* = 5.93 Hz, 1H, H-3), 5.42 (t, *J* = 5.74 Hz, 1H, H-1), 5.16 (s, 1H, NH), 4.70 (t, *J* = 5.68 Hz, 1H, H-4), 3.70 (s, 3H, H-10), 3.46 (m, 2H, H-7), 2.79 (m, 1H, H-5), 2.55 (t, *J* = 5.93 Hz, 2H, H-8), 1.59 (m, 1H, H-5‘), 0.90 (s, 9H, H-12), 0.09 (d, 6H, H-11).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 172.8 (C-9), 156.1 (C-6), 138.5 (C-2), 131.7 (C-3), 76.8 (C-1), 74.9 (C-4), 51.9 (C-10), 41.7 (C-5), 36.6 (C-7), 34.2 (C-8), 26.0 (C-12), 18.3 (C-13), -4.6 (C-11).

FT-IR (ATR): ν [cm^{-1}] = 3349 (w), 2918 (vs), 2850 (vs), 1738 (vs), 1523 (m), 1471 (s), 1464 (s), 1439 (m), 1371 (s), 1318 (m), 1239 (vs), 1196 (s), 1177 (s), 1124 (m), 1102 (s), 1064 (s), 1046 (s), 1000 (s), 940 (m), 906 (s), 836 (vs), 776 (vs), 719 (s), 669 (m), 608 (w).

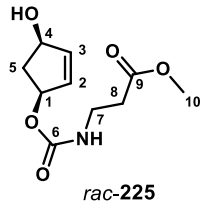
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{16}H_{29}NO_5SiNa$ $[M+Na]^+$ 366.1707 u, found: 366.1707 u.

4.5.10. *rac-cis*-3-(((4-Hydroxy-cyclopent-2-ene-1-yloxy)carbonyl)-amino)propionic acid methylester



rac-**224** *rac*-**225**

To a solution of carbamate *rac*-**224** (317 mg, 0.920 mmol, 1.0 eq.) in 2.0 ml THF was added TBAF (0.92 ml, 0.92 mmol, 1.0 eq., 1M in THF). The reaction mixture was stirred for 30 min at r.t. Then, a sat. aq. $NaHCO_3$ solution was added and the aq. phase was extracted with EtOAc (3x 50 ml). The combined org. phases were washed with a sat. aq. NaCl solution and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc/MeOH, 2:2:1). The desired allylic alcohol *rac*-**225** was obtained as a colorless oil (135 mg, 0.590 mmol, 64%).



rac-**225**

Formula: $C_{10}H_{15}NO_5$

M: 229.23 g/mol

R_f: 0.37 (SiO_2, 2:2:1, *c*Hex/EtOAc/MeOH).

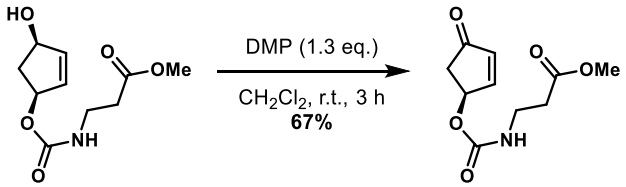
^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 6.09 (d, *J* = 5.16 Hz, 1H, H-2), 6.00 (d, *J* = 5.16 Hz, 1H, H-3), 5.44 (m, 1H, H-1), 5.21 (s, 1H, -NH), 4.70 (m, 1H, H-4), 3.70 (s, 3H, H-10), 3.46 (m, 2H, H-7), 2.78 (m, 1H, H-5), 2.55 (t, *J* = 5.70 Hz, 2H, H-8), 1.91 (s, 1H, -OH), 1.68 (m, 1H, H-5').

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 172.8 (C-9), 156.0 (C-6), 138.2 (C-2), 133.1 (C-3), 77.5 (C-1), 74.9 (C-4), 51.9 (C-10), 40.7 (C-5), 36.4 (C-7), 34.2 (C-8).

FT-IR (ATR): ν [cm^{-1}] = 3347 (br), 3064 (w), 2953 (m), 2087 (w), 1693 (vs), 1526 (vs), 1439 (s), 1412 (m), 1365 (s), 1323 (m), 1248 (vs), 1198 (vs), 1178 (vs), 1140 (s), 1058 (vs), 1024 (s), 990 (vs), 879 (m), 842 (m), 776 (s), 583 (s), 543 (vs).

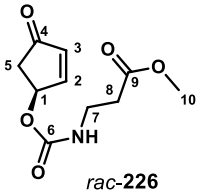
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{10}H_{15}NO_5Na$ $[M+Na]^+$ 252.0842 u, found: 252.0845 u.

4.5.11. *rac*-3-((4-Oxo-cyclopent-2-ene-1-yl)oxy)carbonyl)amino-propionic acid methylester



rac-**225** *rac*-**226**

To a solution of allylic alcohol *rac*-**225** (66 mg, 0.29 mmol, 1.0 eq.) in 0.90 ml CH_2Cl_2 was added DMP (159 mg, 0.374 mmol, 1.3 eq.) under an argon atmosphere. The reaction mixture was stirred at r.t. for 3 h. After confirmation of full conversion of the starting material (TLC), water (20 ml) was added to the reaction mixture and the aq. phase was extracted with EtOAc (3x 20 ml). The combined org. phases were washed with a sat. aq. NaCl solution and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 1.5:1). The desired enone *rac*-**226** was obtained as a colorless oil (44 mg, 0.194 mmol, 67%).



rac-**226**

Formula: $C_{10}H_{13}NO_5$

M: 227.22 g/mol

R_f: 0.19 (SiO_2, 1:1, *c*Hex/EtOAc).

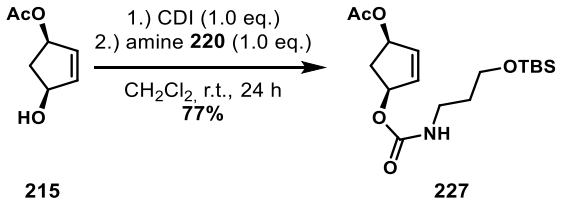
^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 7.58 (d, *J* = 5.54 Hz, 1H, H-2), 6.31 (d, *J* = 5.54 Hz, 1H, H-3), 5.81 (m, 1H, H-1), 3.71 (s, 3H, H-10), 3.48 (m, 2H, H-7), 2.82 (dd, *J* = 19.0 Hz, 6.35 Hz, 1H, H-5), 2.59 (t, *J* = 5.9 Hz, 2H, H-8), 2.33 (dd, *J* = 19.0 Hz, 2.11 Hz, 1H, H-5).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 205.4 (C-4), 172.8 (C-9), 159.8 (C-2), 155.5 (C-6), 136.7 (C-3), 72.4 (C-1), 51.9 (C-10), 41.3 (C-5), 36.5 (C-7), 34.1 (C-8).

FT-IR (ATR): ν [cm^{-1}] = 3347 (br), 3001 (w), 2956 (w), 2339 (w), 2098 (w), 1818 (w), 1767 (w), 1711 (vs), 1589 (w), 1525 (s), 1440 (m), 1407 (m), 1370 (m), 1348 (m), 1327 (m), 1246 (s), 1198 (s), 1178 (s), 1136 (s), 1101 (m), 1075 (s), 1051 (s), 1015 (s), 866 (w), 844 (m), 801 (m), 730 (s), 650 (m), 557 (s).

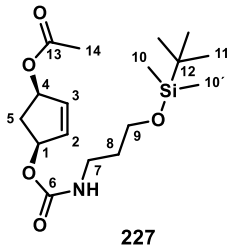
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{10}H_{13}NO_5$ $[M+Na]^+$ 250.0686 u, found: 250.0687 u.

4.5.12. (1*R*,4*S*)-4-(((3-((*tert*-Butyl(dimethyl)silyl)oxy)propyl)-carbamoyl)oxy)-cyclopent-2-en-1-yl acetate



215 227

To a solution of (1*R*,4*S*)-4-acetoxycyclopent-2-ene-1-ol (**215**) (1.35 g, 9.49 mmol, 1.0 eq.) in 20 ml CH_2Cl_2 was added CDI (1.61 g, 9.96 mmol, 1.05 eq.) under an argon atmosphere. The reaction mixture was stirred for 2.5 h at r.t. and after confirmation of full conversion of the starting material (TLC), (3-aminopropoxy)(*tert*-butyl)dimethylsilane **220** (1.80 g, 9.49 mmol, 1.0 eq.) was added. The reaction mixture was stirred for 22 h at r.t. and after confirmation of full conversion of the intermediate (TLC), the reaction mixture was diluted with water (70 ml). The aq. phase was extracted with EtOAc (3x 50 ml), the combined org. phases were washed with a sat. aq. NaCl solution (50 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 3.5:1). The desired carbamate **227** was obtained as a colorless oil (2.62 g, 7.32 mmol, 77%).



227

Formula: $C_{17}H_{31}NO_5Si$

M: 357.52 g/mol

R_f: 0.28 (SiO_2, 3:1, *c*Hex/EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 6.10 (d, *J* = 5.48 Hz, 1H, H-2), 6.05 (d, *J* = 5.48 Hz, 1H, H-3), 5.52 (m, 2H, H-1, H-4), 5.21 (br, 1H, NH), 3.71 (t, *J* = 5.67 Hz, 2H, H-9), 3.30 (q, *J* = 6.00 Hz, 2H, H-7), 2.85 (dt, *J* = 14.9 Hz, 7.51 Hz, 1H, H-5), 2.05 (s, 3H, H-14), 1.72 (m, 3H, H-5, H-8), 0.90 (s, 9H, H-11), 0.06 (s, 6H, H-10).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 170.7 (C-13), 155.0 (C-5), 135.4 (C-2), 133.9 (C-3), 76.7 (C-1), 61.9 (C-9), 39.5 (C-7), 37.4 (C-5), 31.9 (C-8), 25.9 (C-11), 21.2 (C-14), 18.2 (C-12), -5.5 (C-10).

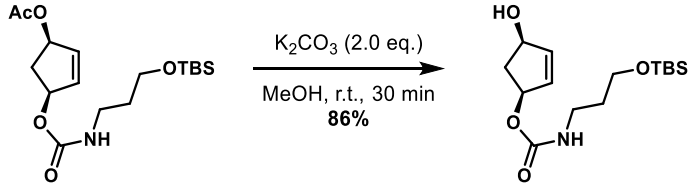
FT-IR (ATR): ν [cm^{-1}] = 3344 (br), 3071 (w), 2953 (m), 2930 (m), 2885 (w), 2858 (m), 1723 (s), 1699 (s), 1528 (m), 1472 (m), 1463 (m), 1441 (w), 1366 (s),

1232 (vs), 1140 (m), 1091 (s), 1072 (s), 1011 (s), 956 (m), 939 (m), 909 8w), 834 (vs), 774 (vs), 729 (m), 662 (m), 632 (m), 607 (m), 572 (m).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{17}H_{31}NO_5Si$ $[M+Na]^+$ 380.1864 u, found: 380.1865 u.

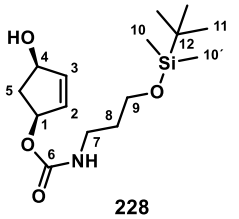
$[\alpha]_\lambda^{20}$: c = 1.05 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = -69.3° (± 0.1°), $[\alpha]_{436}^{20}$ = -41.7° (± 0.0°), $[\alpha]_{546}^{20}$ = -23.1° (± 0.0°), $[\alpha]_{579}^{20}$ = -20.4° (± 0.0°), $[\alpha]_{589}^{20}$ = -20.0° (± 0.1°).

4.5.13. (1*S*,4*R*)-4-Hydroxycyclopent-2-en-1-yl (3-((*tert*-butyl(dimethyl)silyl)-oxy)propyl)carbamate



227 228

To a solution of acetate **227** (2.45 g, 6.85 mmol, 1.0 eq.) in 69 ml MeOH was added K_2CO_3 (1.89 g, 13.7 mmol, 2.0 eq.) at r.t. and the reaction mixture was stirred for 30 min. After confirmation of full conversion of the starting material (TLC), EtOAc (50 ml) and a sat. aq. NH_4Cl solution (50 ml) were added to the reaction mixture. The aq. phase was extracted with EtOAc (3x 50 ml). The combined org. phases were washed with a sat. aq. NaCl solution (50 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 1:1). The desired allylic alcohol **228** was obtained as a colorless oil (2.13 g, 5.95 mmol, 86%).



228

Formula: $C_{15}H_{29}NO_4Si$

M: 315.49 g/mol

R_f: 0.14 (SiO_2, 1:1, *c*Hex/EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 6.08 (d, *J* = 6.28 Hz, 1H, H-2), 6.01 (d, *J* = 6.28 Hz, 1H, H-3), 5.43 (m, 1H, H-1), 5.20 (br, 1H, NH), 4.69 (m, 1H, H-4), 3.71 (t, 2H, H-9), 3.30 (q, 2H, H-7), 2.77 (dt, *J* = 14.3 Hz, 7.33 Hz,

1H, H-5), 1.72 (m, 2H, H-8), 1.65 (dt, *J* = 14.5 Hz, 3.69 Hz, 1H, H-5), 0.90 (s, 9H, H-11), 0.06 (s, 6H, H-10).

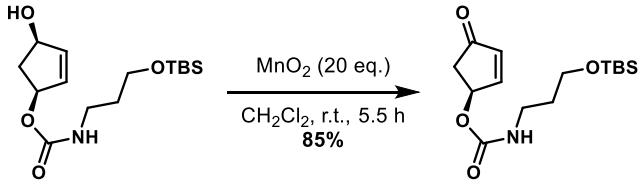
^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 156.1 (C-6), 137.9 (C-2), 133.4 (C-3), 77.2 (C-1), 75.0 (C-4), 62.0 (C-9), 40.8 (C-5), 39.5 (C-7), 31.9 (C-8), 25.9 (C-11), 18.2 (C-12), -5.45 (C-10).

FT-IR (ATR): ν [cm^{-1}] = 3332 (br), 3065 (w), 2953 (m), 2923 (m), 2885 (w), 2857 (m), 1693 (s), 1525 (m), 1471 (m), 1464 (m), 1443 (w), 1407 (w), 1389 (w), 1335 (w), 1319 (w), 1292 (s), 1142 (m), 1093 (s), 1061 (s), 1005 (s), 940 (m), 834 (vs), 814 (m), 774 (vs), 736 (s), 663 (m), 586 (m).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{15}H_{29}NO_4Si$ $[M+Na]^+$ 338.1758 u, found: 338.1760 u.

$[\alpha]_\lambda^{20}$: c = 1.01 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = -887.5° (± 23.0°), $[\alpha]_{436}^{20}$ = -75.5° (± 1.2°), $[\alpha]_{546}^{20}$ = -39.5° (± 0.1°), $[\alpha]_{579}^{20}$ = -34.1° (± 0.1°), $[\alpha]_{589}^{20}$ = -33.1° (± 0.1°).

4.5.14. (1*R*)-4-Oxocyclopent-2-en-1-yl (3-((*tert*-butyl(dimethyl)silyl)-oxy)propyl)carbamate with MnO_2

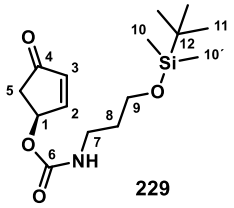


228 **229**

To a solution of the allylic alcohol **228** (1.52 g, 4.75 mmol, 1.0 eq.) in 20 ml CH_2Cl_2 was added MnO_2 (6.24 g, 71.3 mmol, 15 eq.) at r.t. The resulting suspension was stirred for 5 h until a second charge of MnO_2 (2.06 g, 23.8 mmol, 5.0 eq.) was added and the suspension was continued to stir for further 30 min. After confirmation of full conversion of the starting material (TLC), the reaction mixture was filtered through a short pad of celite and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 3:1) and the desired enone **229** was obtained as a colorless oil (1.26 g, 4.03 mmol, 85%).

Formula: $C_{15}H_{27}NO_4Si$

M: 313.47 g/mol



229

R_f: 0.36 (SiO_2, 1:1, *c*Hex/EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 7.58 (dd, *J* = 5.67 Hz, 2.30 Hz, 1H, H-2), 6.30 (dd, *J* = 5.78 Hz, 0.89 Hz, 1H, H-3), 5.81 (m, 1H, H-1), 5.43 (br, 1H, NH), 3.73 (t, 2H, H-9), 3.34 (q, 2H, H-7), 2.81 (dd, *J* = 18.6 Hz, 6.37 Hz, 1H, H-5), 2.30 (dd, *J* = 18.7 Hz, 2.17 Hz, 1H, H-5), 1.73 (p, 2H, H-8), 0.89 (s, 9H, H-11), 0.06 (s, 6H, H-10).

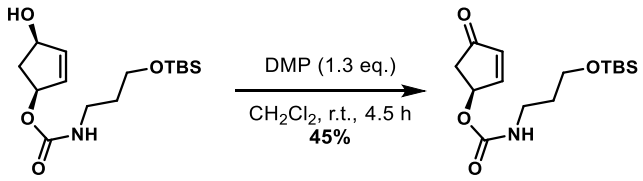
^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 205.5 (C-4), 160.0 (C-2), 155.5 (C-6),136.5 (C-3), 72.0 (C-1), 62.0 (C-9), 41.4 (C-5), 40.0 (C-7), 31.6 (C-8), 25.9 (C-11), 18.1 (C-12), -5.49 (C-10).

FT-IR (ATR): ν [cm^{-1}] = 3342 (br), 3072 (w), 2953 (m), 2929 (m), 2885 (m), 2857 (m), 2097 (w), 1717 (vs), 1589 (w), 1525 (m), 1472 (m), 1444 (m), 1403 (m), 1390 (m), 1349 (m), 1331 (m), 1295 (m), 1249 (vs), 1182 (m), 1096 (vs), 1060 (s), 1020 (m), 1007 (m), 975 (m), 938 (m), 834 (vs), 798 (s), 774 (vs), 735 (m), 662 (m).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{15}H_{27}NO_4Si$ $[M+Na]^+$ 314.1782 u, found: 314.1785 u.

$[\alpha]_\lambda^{20}$: c = 0.99 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = 502.1° (± 0.9°), $[\alpha]_{436}^{20}$ = -87.1° (± 0.1°), $[\alpha]_{546}^{20}$ = -83.5° (± 0.4°), $[\alpha]_{579}^{20}$ = -75.9° (± 0.1°), $[\alpha]_{589}^{20}$ = -74.0° (± 0.1°).

4.5.15. (1*R*)-4-Oxocyclopent-2-en-1-yl (3-((*tert*-butyl(dimethyl)silyl)-oxy)propyl)carbamate with DMP



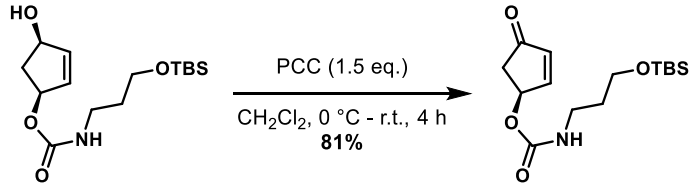
228 **229**

To a solution of the allylic alcohol **228** (200 mg, 0.634 mmol, 1.0 eq.) in 1.0 ml CH_2Cl_2 was added DMP (348 mg, 0.820 mmol, 1.3 eq.) and the reaction mixture was stirred for 4.5 h at r.t. After confirmation of full conversion of the starting material (TLC), water (50 ml) was added to the reaction mixture. The aq. phase was extracted with EtOAc

(3x 50 ml), the combined org. phases were washed with a sat. aq. NaCl solution (50 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 3:1). The desired enone **229** was obtained as a colorless oil (106 mg, 0.339 mmol, 45%).

The analytical data are in accordance with the data for the same compound **229** reported previously (See 4.5.14).

4.5.16. (1*R*)-4-Oxocyclopent-2-en-1-yl (3-((*tert*-butyl(dimethyl)silyl)oxy)propyl)-carbamate with PCC

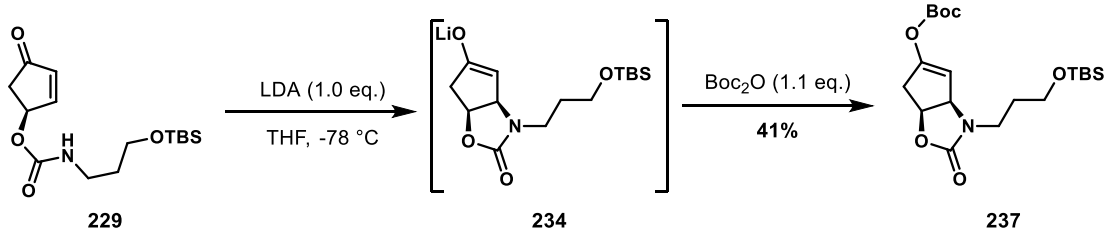


228 **229**

To a solution of allylic alcohol **228** (100 mg, 0.317 mmol, 1.0 eq.) in 3.2 ml CH_2Cl_2 was added PCC (104 mg, 0.482 mmol, 1.5 eq.) at 0 °C. The reaction mixture was subsequently warmed to r.t. and stirred for 4 h. After confirmation of full conversion of the starting material (TLC), the reaction mixture was filtered over a pad of celite and washed with CH_2Cl_2. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 3:1). The desired enone **229** was obtained as a colorless oil (80 mg, 0.26 mmol, 81%).

The analytical data are in accordance with the data for the same compound **229** reported previously (See 4.5.14).

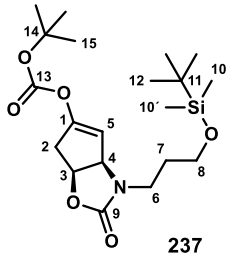
4.5.17. *tert*-Butyl 3-(3-((*tert*-butyl(dimethyl)silyl)oxy)propyl)-2-oxo-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*d*][1,3]oxazol-5-yl carbonate



229 **234** **237**

A solution of enone **229** (1.00 g, 3.19 mmol, 1.0 eq.) in 32 ml THF was cooled to -78 °C in an acetone/dry ice bath and subsequently a freshly prepared solution of 1M

LDA in THF (3.2 ml, 3.2 mmol, 1.0 eq.) was added dropwise to the reaction mixture. The solution was stirred for 2 h at -78 °C. Then, Boc_2O (775 mg, 3.55 mmol, 1.1 eq.) was added and the reaction mixture was stirred at -78 °C for 4 h, subsequently warmed to r.t. and stirred for another 13 h. Afterwards, the solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 3:1). The desired enol-carbonate **237** was obtained as a pale-yellow semisolid oil (537 mg, 1.30 mmol, 41%).



237

Formula: $C_{20}H_{35}NO_6Si$

M: 413.59 g/mol

R_f: 0.59 (SiO_2, 2:1, *c*Hex/EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 5.75 (d, *J* = 1.7 Hz, 1H, H-5), 4.99 (td, *J* = 7.7, 1.2 Hz, 1H, H-3), 4.70 (d, *J* = 7.6 Hz, 1H, H-4), 3.66 (t, *J* = 6.0 Hz, 2H, H-8), 3.51 (ddd, *J* = 14.5, 8.1, 6.6 Hz, 1H, H-6), 3.17 (ddd, *J* = 14.2, 8.0, 6.1 Hz, 1H, H-6´), 2.99 (ddd, *J* = 17.9, 6.9, 2.1 Hz, 1H, H-2), 2.82 (dd, *J* = 17.9, 1.6 Hz, 1H, H-2), 1.88 – 1.73 (m, 2H, H-7), 1.52 (s, 9H, H-15), 0.89 (s, 9H, H-12), 0.05 (d, *J* = 1.8 Hz, 6H, H-10).

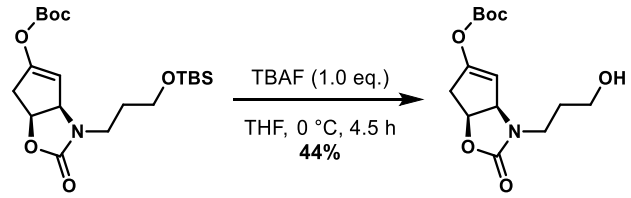
^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 157.4 (C-9), 152.6 (C-1), 149.8 (C-13), 107.5 (C-5), 84.3 (C-14), 72.8 (C-3), 63.1 (C-4), 60.5 (C-8), 40.4 (C-6), 38.9 (C-2), 31.0 (C-7), 27.7 (C-15), 26.1 (C-12), 18.4 (C-11), -5.2 (C-10).

FT-IR (ATR): ν [cm^{-1}] = 2954 (w), 2930 (w), 2886 (w), 2857 (w), 1758 (s), 1664 (w), 1646 (w), 1472 (w), 1416 (w), 1396 (w), 1371 (m), 1239 (s), 1147 (s), 1100 (m), 1063 (m), 1006 (w), 971 (w), 837 (m), 777 (m), 759 (m), 688 (w), 662 (w).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{20}H_{36}NO_6Si$ $[M+H]^+$ 414.2306 u, found: 414.2308; $C_{20}H_{35}NO_6SiNa$ $[M+Na]^+$ 436.2126 u, found: 436.2127 u.

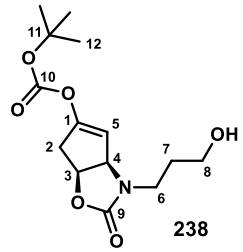
$[\alpha]_\lambda^{20}$: c = 0.99 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = 173.6° (± 0.6°), $[\alpha]_{436}^{20}$ = 50.5° (± 0.2°), $[\alpha]_{546}^{20}$ = 25.4° (± 0.1°), $[\alpha]_{579}^{20}$ = 22.3° (± 0.2°), $[\alpha]_{589}^{20}$ = 22.2° (± 0.1°).

4.5.18. *tert*-Butyl (6a*S*)-3-(3-hydroxypropyl)-2-oxo-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*d*][1,3]oxazol-5-yl carbonate



237 238

To a solution of the TBS-ether **237** (451 mg, 1.09 mmol, 1.0 eq.) in 11 ml THF was added TBAF in THF (1 M, 1.1 ml, 1.1 mmol, 1.0 eq.) at 0 °C. After 3.5 h, additional TBAF in THF (1 M, 0.10 ml, 0.10 mmol, 0.1 eq.) was added and the reaction mixture was stirred 1 h at 0 °C. After confirmation of full conversion of the starting material (TLC), a sat. aq. $NaHCO_3$ solution was added and the aq. phase was extracted with EtOAc (3 x 20 ml). The combined org. phases were washed with a sat. aq. NaCl solution (20 ml), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 1:10 → 100% EtOAc) and the desired product **238** was obtained as a colorless oil (142 mg, 0.475 mmol, 44%).



Formula: $C_{14}H_{21}NO_6$

M: 299.32 g/mol

R_f: 0.30 (SiO_2, 100% EtOAc).

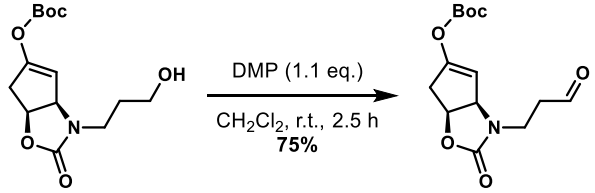
^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 5.76 (q, *J* = 2.0 Hz, 1H, H-5), 5.05 (td, *J* = 7.3, 1.6 Hz, 1H, H-3), 4.70 (dt, *J* = 7.7, 1.7 Hz, 1H, H-4), 3.66 (t, *J* = 5.8 Hz, 2H, H-8), 3.52 (dt, *J* = 14.5, 6.6 Hz, 1H, H-6), 3.34 (dt, *J* = 14.6, 6.3 Hz, 1H, H-6´), 3.01 (ddd, *J* = 18.0, 7.0, 2.2 Hz, 1H, H-2), 2.84 (dq, *J* = 17.9, 1.7 Hz, 1H, H-2´), 1.78 (p, *J* = 6.3 Hz, 2H, H-7), 1.52 (s, 9H, H-12).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 158.5 (C-10), 152.8 (C-9), 149.8 (C-1), 107.4 (C-5), 84.5 (C-11), 73.3 (C-3), 63.5 (C-4), 58.9 (C-8), 39.7 (C-6), 38.7 (C-2), 30.7 (C-7), 27.7 (C-12).

FT-IR (ATR): ν [cm^{-1}] = 3441 (bw), 2979 (w), 2935 (w), 2877 (w), 1728 (s), 1663 (w), 1646 (w), 1455 (w), 1421 (m), 1396 (w), 1370 (m), 1285 (m), 1233 (s), 1139 (s), 1038 (s), 1003 (m), 948 (w), 927 (w), 851 (m), 809 (w), 779 (m), 758 (m), 688 (w), 667 (w), 649 (w), 508 (w).

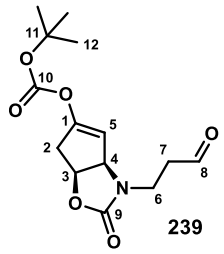
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{14}H_{22}NO_6$ $[M+H]^+$ 300.1442 u, found: 300.1444 u; $C_{14}H_{21}NO_6Na$ $[M+Na]^+$ 322.1261 u, found: 322.1259 u.

4.5.19. *tert*-Butyl (6a*S*)-2-oxo-3-(3-oxopropyl)-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*d*][1,3]oxazol-5-yl carbonate



238 **239**

To a solution of alcohol **238** (104 mg, 0.347 mmol, 1.0 eq.) in 3.4 ml CH_2Cl_2 was added DMP (162 mg, 0.382 mmol, 1.1 eq.) and the suspension was stirred for 2.5 h at r.t. Then, the suspension was filtered through a plug of celite and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 1:1) and the desired aldehyde **239** was obtained as a colorless oil (77 mg, 0.26 mmol, 75%).



239

Formula: $C_{14}H_{19}NO_6$

M: 297.31 g/mol

R_f: 0.35 (SiO_2, 1:2, *c*Hex/EtOAc).

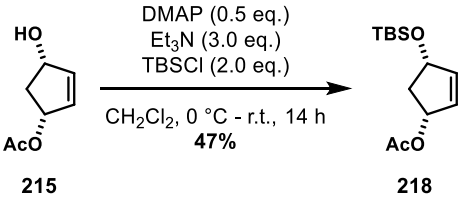
^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 9.83 (t, *J* = 1.0 Hz, 1H, H-8), 5.79 (qd, *J* = 1.9, 0.6 Hz, 1H, H-5), 4.99 (dddd, *J* = 7.6, 6.9, 1.5, 0.6 Hz, 1H, H-3), 4.74 (dt, *J* = 7.6, 1.4 Hz, 1H, H-4), 3.68 (dt, *J* = 14.5, 6.0 Hz, 1H, H-6), 3.44 (ddd, *J* = 14.5, 7.7, 5.5 Hz, 1H, H-6´), 3.04 – 2.90 (m, 2H, H-7, H-2), 2.85 – 2.72 (m, 2H, H-7´, H-2´), 1.53 (s, 9H, H-12).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 200.4 (C-8), 157.4 (C-9), 152.8 (C-10), 149.8 (C-1), 107.2 (C-5), 84.5 (C-11), 73.1 (C-3), 63.6 (C-4), 42.8 (C-7), 38.9 (C-2), 36.6 (C-6), 27.7 (C-12).

FT-IR (ATR): ν [cm^{-1}] = 3483 (bw), 2981 (w), 2934 (w), 2845 (w), 2732 (w), 1739 (s), 1663 (w), 1646 (w), 1449 (w), 1419 (w), 1396 (w), 1370 (m), 1284 (m), 1233 (s), 1139 (s), 1038 (m), 1003 (w), 923 (w), 851 (m), 810 (w), 779 (m), 759 (m), 721 (w), 661 (w), 526 (w).

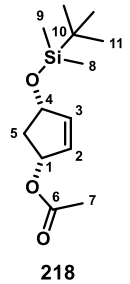
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{14}H_{20}NO_6$ $[M+H]^+$ 298.1285 u, found: 298.1289 u; $C_{14}H_{19}NO_6Na$ $[M+Na]^+$ 320.1105 u, found: 320.1104 u.

4.5.20. (1*R*,4*S*)-4-((*tert*-Butyldimethylsilyl)oxy)cyclopent-2-en-1-yl acetate



215 **218**

According to a slightly modified procedure reported by Delayre *et al.*[178], a solution of monoacetate **215** (962 mg, 6.77 mmol, 1.0 eq.) and DMAP (411 mg, 3.37 mmol, 0.5 eq.) in 62 ml CH_2Cl_2 was cooled to 0 °C. Subsequently, Et_3N (2.8 ml, 20 mmol, 3.0 eq.) and TBSCl (2.03 g, 13.5 mmol, 2.0 eq.) were added. The cooling bath was removed after 15 min and the reaction mixture was stirred for further 14 h at r.t. After confirmation of the full conversion of the starting material (TLC), the reaction mixture was diluted with CH_2Cl_2 (60 ml) and the org. phase was washed with 0.5M HCl (2x 40 ml), sat. aq. $NaHCO_3$ (50 ml) and sat. aq. NaCl solution (50 ml). The org. phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 24:1) and the desired product **218** was obtained as colorless, slightly volatile oil (811 mg, 3.16 mmol, 47%, Lit.[178]: 96%).



218

Formula: $C_{13}H_{24}O_3Si$

M: 256.42 g/mol

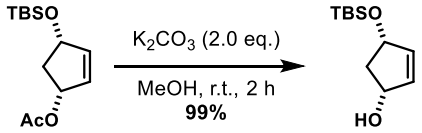
R_f: 0.43 (SiO_2, 6:1, *c*Hex/EtOAc).

^{1}H NMR: (300 MHz, $CDCl_3$) δ [ppm]: 5.97 (dt, *J* = 5.6, 1.6 Hz, 1H, H-3), 5.88 (dt, *J* = 5.6, 1.6 Hz, 1H, H-2), 5.46 (t, *J* = 6.2 Hz, 1H, H-1), 4.71 (t, *J* = 6.0 Hz, 1H, H-4), 2.80 (dt, *J* = 13.8, 7.3 Hz, 1H, H-5), 2.04 (s, 3H, H-7), 1.60 (dt, *J* = 13.8, 5.1 Hz, 1H, H-5), 0.90 (s, 9H, H-11), 0.09 (d, *J* = 1.7 Hz, 6H, H-8, H-9).

^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 171.1 (C-6), 139.1 (C-2), 131.3 (C-3), 77.1 (C-1), 75.0 (C-4), 41.3 (C-5), 26.0 (C-11), 21.3 (C-7), 18.3 (C-10), -4.5 (C-8, C-9).

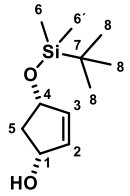
The analytical data are in accordance with the literature.[178,179]

4.5.21. (1*R*,4*S*)-4-((*tert*-Butyldimethylsilyl)oxy)cyclopent-2-en-1-ol



218 214

According to a procedure reported by Holec *et al*.[180], to a solution of acetate **218** (498 mg, 1.94 mmol, 1.0 eq.) in 20 ml MeOH was added K_2CO_3 (539 mg, 3.90 mmol, 2.0 eq.) and it was stirred at r.t. for 2 h. After confirmation of full conversion of the starting material (TLC), the reaction mixture was diluted by addition of water and EtOAc. The aq. phase was extracted thrice with EtOAc (3x 30 ml), the combined org. phases were washed with sat. aq. NaCl solution (20 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, 3:1, *c*Hex/EtOAc). The desired alcohol **214** was obtained as a colorless oil (408 mg, 1.90 mmol, 99%, Lit.[180]: quant.).



214

Formula: $C_{11}H_{22}O_2Si$

M: 214.38 g/mol

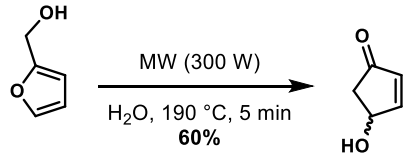
R_f: 0.19 (SiO_2, 3:1, *c*Hex/EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 5.94 (ddd, *J* = 5.6, 2.0, 1.2 Hz, 1H, H-3), 5.89 (ddd, *J* = 5.6, 1.9, 1.3 Hz, 1H, H-2), 4.70 – 4.63 (m, 1H, H-1), 4.62 – 4.56 (m, 1H, H-4), 2.68 (dt, *J* = 13.9, 7.0 Hz, 1H, H-5), 1.81 (s, 1H, OH), 1.51 (dt, *J* = 13.7, 4.5 Hz, 1H, H-5), 0.89 (s, 9H, H-9), 0.09 (s, 6H, H-6).

^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 137.1 (C-2), 135.7 (C-3), 75.3 (C-4), 75.3 (C-1), 44.9 (C-5), 26.0 (C-8), 18.3 (C-7), -4.5 (C-6), -4.5 (C-6´).

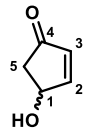
The analytical data are in accordance with the literature.[180]

4.5.22. *rac*-4-Hydroxycyclopentenone



233 *rac*-**231**

According to a slightly modified procedure reported by Ulbrich *et al*.[112], a solution of furfuryl alcohol **233** (0.22 ml, 2.5 mmol, 1.0 eq.) in 5.0 ml water was heated in a microwave reactor to 190 °C (300 W) for 5 min. After cooling to r.t., the aq. phase was washed with MTBE (3 x 5 ml) and the solvent was removed under reduced pressure. *rac*-4-Hydroxycyclopentenone *rac*-**231** was obtained as a slightly yellow oil (148 mg, 1.51 mmol, 60%, Lit.[112]: 70%).



rac-**231**

Formula: $C_5H_6O_2$

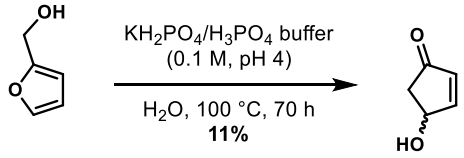
M: 98.10 g/mol

^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 7.57 (dd, *J* = 5.7, 2.4 Hz, 1H, H-2), 6.22 (dd, *J* = 5.7, 1.3 Hz, 1H, H-3), 5.04 (dtd, *J* = 6.0, 2.3, 1.3 Hz, 1H, H-1), 2.77 (dd, *J* = 18.5, 6.1 Hz, 1H, H-5), 2.57 (bs, 1H, OH), 2.27 (dd, *J* = 18.5, 2.2 Hz, 1H, H-5´).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 206.9 (C-4), 163.5 (C-2), 135.3 (C-3), 70.6 (C-1), 44.4 (C-5).

The analytical data are in accordance with the literature.[181]

4.5.23. *rac*-4-Hydroxycyclopentenone



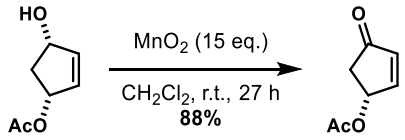
233 *rac*-**231**

According to a slightly modified procedure reported by Watson *et al*.[113], a solution of furfuryl alcohol **233** (52 ml, 560 mmol, 1.0 eq.) in 1.15 l of an aq. KH_2PO_4/H_3PO_4 buffer (0.1 M, pH 4) was stirred at reflux for 70 h. After cooling to r.t., the aq. phase was washed with EtOAc (2 x 250 ml) and the solvent was removed under reduced pressure. The combined org. phases were extracted with water (2 x 200 ml), the combined aq. phases were washed with MTBE (100 ml) and the solvent was removed under reduced pressure. Both aq. residues were combined, dissolved in THF, dried

over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH, 40:1 → 30:1) and *rac*-4-hydroxycyclopentenone *rac*-**231** was obtained as a colorless oil (5.78 g, 58.9 mmol, 11%, Lit.[113]: 17%).

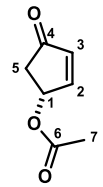
The analytical data are in accordance with the data for the same compound **231** reported previously (See 4.5.22).

4.5.24. (4*R*)-4-Acetoxycyclopentenone



212 **230**

To a solution of allylic alcohol **212** (500 mg, 3.54 mmol, 1.0 eq.) in 18 ml CH_2Cl_2 was added MnO_2 (3.07 g, 35.4 mmol, 10 eq.) and the suspension was stirred for 3.5 h at r.t. Then, additional MnO_2 (1.50 g, 17.3 mmol, 5 eq.) was added and the suspension was stirred for 24 h at r.t. After confirmation of full conversion of the starting material (TLC), the reaction mixture was filtered through a plug of celite and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 2:1) and the desired enone **230** was obtained as a slightly yellow oil (435 mg, 3.11 mmol, 88%).



231

Formula: $C_7H_8O_3$

M: 140.14 g/mol

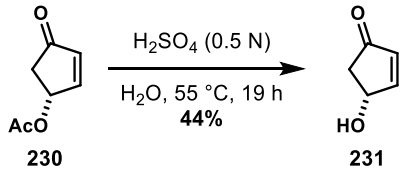
R_f: 0.37 (SiO_2, 1:1, *c*Hex/EtOAc).

^{1}H NMR: (400 MHz, $CDCl_3$): δ [ppm] = 7.56 (dd, *J* = 5.7, 2.4 Hz, 1H, H-2), 6.33 (dd, *J* = 5.7, 1.3 Hz, 1H, H-3), 5.85 (dtd, *J* = 6.1, 2.3, 1.3 Hz, 1H, H-1), 2.82 (dd, *J* = 18.7, 6.4 Hz, 1H, H-5), 2.32 (dd, *J* = 18.7, 2.2 Hz, 1H, H-5´), 2.10 (s, 3H, H-7).

^{13}C NMR: (101 MHz, $CDCl_3$): δ [ppm] = 204.9 (C-4), 170.4 (C-6), 158.9 (C-2), 137.0 (C-3), 71.9 (C-1), 41.0 (C-5), 20.9 (C-7).

The analytical data are in accordance with the literature.[180]

4.5.25. (4*R*)-4-hydroxycyclopentenone

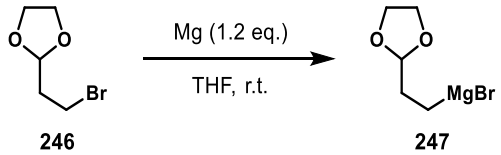


According to a procedure reported by Gerdil *et al*.[182], a solution of allylic acetate **230** (50 mg, 0.51 mmol, 1.0 eq.) in 0.25 ml 0.5N an aq. H_2SO_4 was stirred for 24 h at 55 °C. After confirmation of full conversion of the starting material (TLC), the reaction mixture was cooled to r.t. and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH, 40:1) and the desired allylic alcohol **231** was obtained as a colorless oil (22 mg, 0.22 mmol, 44%, Lit.[182]: 66%).

The analytical data are in accordance with the data for the same compound **231** reported previously (See 4.5.22).

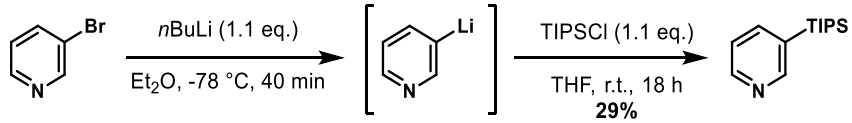
4.6. Synthesis of Compounds Regarding the 1,3-Dipolar Cycloaddition Approach

4.6.1. General procedure for the 1,3-dioxolane-2-ylethylmagnesium bromide



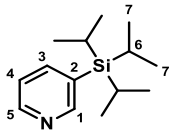
Magnesium turnings (1.2 eq.) were suspended in a solution of a small amount of I_2 (<0.05 eq.) in THF under an argon atmosphere. Then, a solution of 2-(2-bromoethyl)-1,3-dioxolane (**246**) (1.1 eq.) in anhydrous THF was added dropwise to the suspension. The reaction mixture was stirred for 60 min at r.t. and the concentration of the Grignard reagent **247** was determined by titration against iodine. The solution was used directly after preparation in the individual experiments.

4.6.2. 3-(Triisopropylsilyl)pyridine



243 244 245

According to a modified procedure by Wanner *et al.*[114], a solution of 3-bromopyridine **243** (8.4 ml, 86 mmol, 1.0 eq.) in 200 ml anhydrous Et_2O was cooled to -78 °C under an argon atmosphere. Then, *n*BuLi (38 ml, 94 mmol, 2.53M in hexane, 1.1 eq.) was added dropwise to the solution and it was stirred for 50 min at -78 °C, until a yellow precipitate formed. Then, anhydrous THF (120 ml) and TIPSCl (20 ml, 94 mmol, 1.1 eq.) were added, which led to the formation of a brown-green reaction mixture. The reaction mixture was slowly warmed to r.t. and stirred for 63 h, which led to a color change to orange. Afterwards, the reaction mixture was neutralized by addition of a sat. aq. NH_4Cl solution and the aq. phase was extracted thrice with CH_2Cl_2. The combined org. phases were washed with water, with a sat. aq. NaCl solution and it was dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by distillation (140 °C, 0.2 mbar) and subsequently by column chromatography (SiO_2, *c*Hex/EtOAc, 9:1 → 7:1). The desired product **245** was obtained as a slightly yellow oil (6.06 g, 24.7 mmol, 29%, Lit.[114]: 67%).



245

Formula: $C_{14}H_{25}NSi$

M: 235.45 g/mol

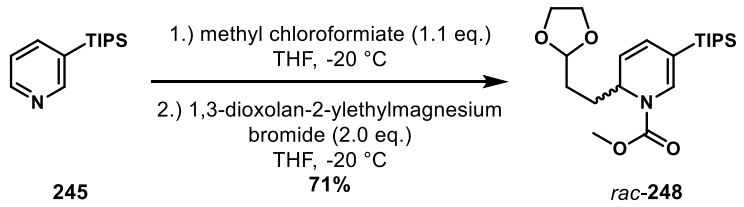
R_f: 0.28 (SiO_2, 6:1, *c*Hex/EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 8.67 (s, 1H, H-1), 8.57 (d, *J* = 4.9 Hz, 1H, H-5), 7.77 (d, *J* = 7.6 Hz, 1H, H-3), 7.27 (m, 1H, H-4), 1.40 (m, 3H, H-6), 1.10 (d, *J* = 7.4 Hz, 18H, H-7).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 155.6 (C-1), 149.8 (C-5), 143.0 (C-3), 130.1 (C-2), 123.2 (C-4), 18.6 (C-7), 10.7 (C-6).

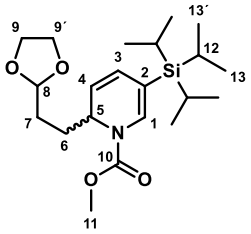
The analytical data are in accordance with the literature.[31]

4.6.3. *rac*-2-(2-Ethyl-1,3-dioxolane)-(methoxycarbonyl)-5-(triiso-propylsilyl)-1,2-dihydropyridine



245 *rac*-**248**

According to a modified procedure by Commins *et al*.[31], a solution of 3-TIPS pyridine **245** (123 mg, 0.500 mmol, 1.0 eq.) in 2.0 ml anhydrous THF was cooled to -20 °C. Subsequently, methyl chloroformate (0.04 ml, 0.55 mmol, 1.1 eq.) was added and a colorless precipitate formed. Then, the previously synthesized 1,3-dioxolan-2-ylethylmagnesium bromide **247** (3.23 ml, 0.31 M, 1.00 mmol, 2.0 eq.) (see General procedure 4.6.1) was added carefully and the reaction mixture was stirred for 30 min at -20 °C. Then, the reaction mixture was warmed to r.t. and stirred for further 30 min. The reaction mixture was treated with a sat. aq. NH_4Cl solution and the aq. phase was extracted thrice with EtOAc. The combined org. phases were washed with water, sat. aq. NaCl solution and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica, *c*Hex/EtOAc, 6:1). The desired product *rac*-**248** was obtained as a colorless oil (140 mg, 0.350 mmol, 71%).



rac-**248**

Formula: $C_{21}H_{37}NO_4Si$

M: 395.62 g/mol

R_f: 0.17 (SiO_2, 4:1, *c*Hex/EtOAc).

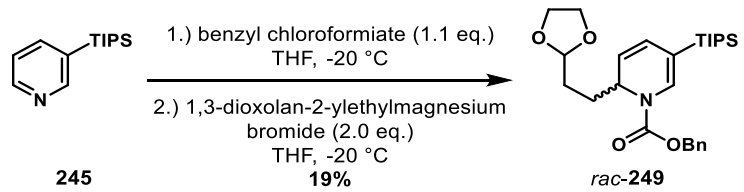
^{1}H NMR: (500 MHz, $CDCl_3$, mixture of rotamers): δ [ppm] = 6.85 and 6.69 (pair of s due to rotamers, 1H, H-1), 5.94 (m, 1H, H-3), 5.59 (m, 1H, H-4), 4.84 (m, 1H, H-8), 4.84 and 4.71 (pair of m due to rotamers, 1H, H-5), 3.93 (m, 2H, H-9/H-9´), 3.83 (m, 2H, H-9/H-9´), 3.79 (s, 3H, H-11), 1.72 and 1.57 (pair of m, 4H, H-6, H-7), 1.18 - 1.16 (m, 3H, H-12), 1.07 - 1.05 (m, 18H, H-13).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 154.1 (C-10), 131.6 (C-1), 125.5 (C-3), 121.4 (C-4), 108.8 (C-2), 104.5 (C-8), 65.0 (C-9/C-9´), 65.0 (C-9/C-9´), 53.4 (C-11), 51.2 (C-5), 28.9 (C-6), 27.9 (C-7), 18.7 (C-13), 10.8 (C-12).

FT-IR (ATR): ν [cm^{-1}] = 3040 (w), 2943 (m), 2889 (w), 2864 (m), 1714 (s), 1625 (w), 1557 (m), 1441 (s), 1383 (m), 1343 (m), 1311 (s), 1254 (w), 1234 (w), 1189 (m), 1125 (s), 1072 (m), 1041 (m), 1016 (m), 991 (m), 963 (w), 944 (w), 920 (w), 883 (m), 858 (w), 769 (w), 749 (w), 710 (w), 678 (m), 664 (w), 644 (m), 611 (w), 558 (w), 508 (m), 479 (w).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{21}H_{37}NO_4Si$ $[M+H]^+$ 396.2565 u, found: 396.2564 u.

4.6.4. *rac*-2-(2-Ethyl-1,3-dioxolane)-(benzyloxycarbonyl)-5-(triiso-propylsilyl)-1,2-dihydropyridine



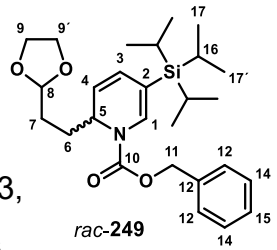
245 **19%** *rac*-**249**

According to a modified procedure by Commins *et al*.[31], a solution of 3-TIPS pyridine **245** (129 mg, 0.530 mmol, 1.0 eq.) in 2.0 ml anhydrous THF was cooled to -20 °C. Subsequently, benzyl chloroformate (0.08 ml, 0.55 mmol, 1.1 eq.) and 1,3-dioxolan-2-ylethylmagnesium bromide **247** (4.0 ml, 0.25 M, 1.00 mmol, 2.0 eq.), which was prepared according to general procedure 4.6.1, were added carefully to the suspension and the reaction mixture. It was stirred for 30 min at -20 °C and further 45 min at r.t. Afterwards, the reaction mixture was treated with a sat. aq. NH_4Cl solution and the aq. phase was extracted thrice with EtOAc. The combined org. phases were washed with water, sat. aq. NaCl solution and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 6:1). The desired product *rac*-**249** was obtained as a colorless oil (49 mg, 0.10 mmol, 19%).

Formula: $C_{27}H_{41}NO_4Si$

M: 471.71 g/mol

R_f: 0.29 (SiO_2, 4:1, *c*Hex/EtOAc).



rac-**249**

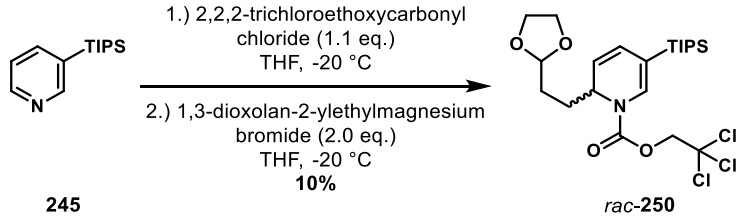
^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 7.40 - 7.30 (m, 5H, H-13, H-14, H-15), 6.87 and 6.78 (pair of s due to rotamers, 1H, H-1), 5.94 (m, 1H, H-3), 5.58 (m, 1H, H-4), 5.29 - 5.16 (m, 2H, H-11), 4.86 (m, 1H, H-8), 4.86 and 4.78 (pair of m due to rotamers, 1H, H-5), 3.96 - 3.76 (m, 4H, H-9, H-9´), 1.76 - 1.66 and 1.62 - 1.56 (pair of m, 4H, H-6, H-7), 1.22 - 1.13 (m, 3H, H-16), 1.10 - 1.02 (m, 18H, H-17).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 153.4 (C-10), 136.3 (C-12), 131.6 (C-1), 128.1 - 128.7 (C-13, C-14, C-15), 125.4 (C-3), 121.6 (C-4), 109.1 (C-2), 104.5 (C-8), 67.8 (C-11), 65.0 (C-9/C-9´), 65.0 (C-9/C-9´), 51.3 (C-5), 29.0 (C-6), 27.9 (C-7), 18.7 (C-17), 10.8 (C-16).

FT-IR (ATR): ν [cm^{-1}] = 3037 (w), 2943 (m), 2889 (w), 2865 (m), 1710 (s), 1626 (w), 1559 (w), 1498 (w), 1463 (w), 1401 (m), 1390 (m), 1301 (s), 1254 (w), 1232 (w), 1189 (w), 1119 (s), 1072 (m), 1029 (m), 1016 (m), 988 (m), 920 (w), 883 (m), 766 (w), 747 (w), 697 (m), 678 (m), 645 (m), 603 (w), 572 (w), 509 (w).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{27}H_{41}NO_4Si$ $[M+H]^+$ 472.2878 u, found: 472.2881 u.

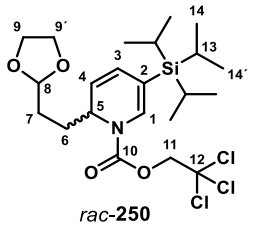
4.6.5. *rac*-2-(2-Ethyl-1,3-dioxolane)-(2,2,2-trichloroethoxycarbonyl)-5-(triisopropylsilyl)-1,2-dihydropyridine



245 *rac*-**250**

According to a modified procedure by Commins *et al*.[31], a solution of 3-TIPS pyridine **245** (128 mg, 0.530 mmol, 1.0 eq.) in 2.0 ml anhydrous THF was cooled to -20 °C. Subsequently, 2,2,2-trichloroethoxycarbonyl chloride (0.08 ml, 0.55 mmol, 1.1 eq.) and freshly prepared 1,3-dioxolan-2-ylethylmagnesium bromide **247** (4.0 ml, 0.25 M, 1.00 mmol, 2.0 eq.) (see general procedure 4.6.1) was added carefully to the

suspension. The reaction mixture was stirred for 30 min at -20 °C further 80 min at r.t. Afterwards, the reaction mixture was treated with a sat. aq. NH_4Cl solution and the aq. phase was extracted thrice with EtOAc. The combined org. phases were washed with water, sat. aq. NaCl solution and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 6:1). The desired product *rac*-**250** was obtained as a colorless oil (27 mg, 0.053 mmol, 10%).



rac-**250**

Formula: $C_{22}H_{36}Cl_3NO_4Si$

M: 512.97 g/mol

R_f: 0.37 (SiO_2, 4:1, *c*Hex/EtOAc).

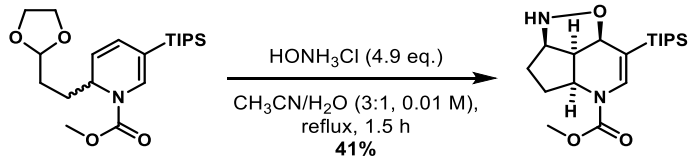
^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 6.83 and 6.79 (pair of s due to rotamers, 1H, H-1), 5.96 (m, 1H, H-3), 5.64 (m, 1H, H-4), 4.86 (m, 1H, H-8), 4.86 and 4.78 (pair of m due to rotamers, 1H, H-5), 4.84 (m, 1H, H-11), 3.95 - 3.79 (m, 4H, H-9, H-9´), 1.78 - 1.69 and 1.67 - 1.57 (pair of m, 4H, H-6, H-7), 1.22 - 1.13 (m, 3H, H-13), 1.09 - 1.04 (m, 18H, H-14).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 151.8 (C-10), 130.7 (C-1), 125.3 (C-3), 121.9 (C-4), 110.6 (C-2), 104.3 (C-8), 95.3 (C-12), 75.6 (C-11), 65.0 (C-9/C-9´), 65.0 (C-9/C-9´), 51.7 (C-5), 28.9 (C-6), 27.7 (C-7), 18.7 (C-14), 10.8 (C-13).

FT-IR (ATR): ν [cm^{-1}] = 3042 (w), 2944 (m), 2889 (w), 2865 (m), 1721 (s), 1627 (w), 1560 (w), 1462 (w), 1402 (m), 1390 (m), 1307 (s), 1253 (w), 1233 (w), 1189 (w), 1128 (s), 1073 (m), 1016 (w), 994 (w), 971 (w), 943 (w), 921 (w), 883 (m), 806 (w), 751 (w), 722 (m), 678 (w), 665 (w), 645 (m), 614 (w), 570 (w), 509 (w).

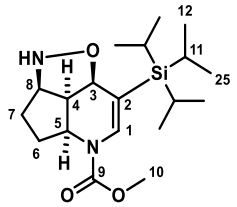
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{22}H_{36}Cl_3NO_4Si$ $[M+H]^+$ 512.1552 u, found: 512.1558 u.

4.6.6. *rac*-Methyl 5-(triisopropylsilyl)-1,2a,2a1,3,4a,7a-hexahydro-4-oxa-3,7-diazacyclopenta[*cd*]indene-7,3-carboxylate



rac-**248** *rac*-**252**

A solution of acetal *rac*-**248** (918 mg, 2.32 mmol, 1.0 eq.) and hydroxylamine hydrochloride (791 mg, 11.4 mmol, 4.9 eq.) in 180 ml CH_3CN and 60 ml water stirred at reflux for 1.5 h. After full conversion of the starting material (TLC), the reaction mixture was cooled to r.t. and diluted with a mixture of water, sat. aq. $NaHCO_3$ solution and sat. aq. NaCl solution. The aq. phase was extracted with EtOAc (3x 200 ml), the combined org. phases were washed with water (300 ml) and with a sat. aq. NaCl solution (200 ml). The org. phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 3:1) and the desired product *rac*-**252** was obtained as a colorless oil (338 mg, 0.922 mmol, 41%).



rac-**252**

Formula: $C_{19}H_{34}N_2O_3Si$

M: 395.62 g/mol

R_f: 0.33 (SiO_2, 1:1, *c*Hex/EtOAc).

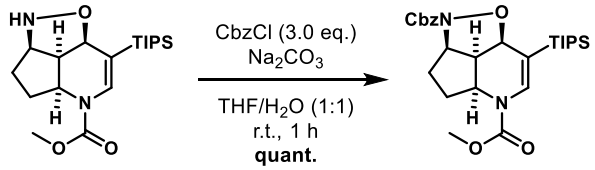
^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 7.21 and 7.04 (pair of s, 1H, H-1*), 4.39 and 4.27 (pair of m, 1H, H-5*), 4.11 (m, 1H, H-8), 3.90 (m, 1H, H-3), 3.82 (s, 3H, H-10), 2.68 (q, *J* = 7.0 Hz, 1H, H-4), 1.90-1.79 and 1.64-1.59 (m, 4H, H-6 and H-7), 1.24 (m, 3H, H-11), 1.08 (m, 18H, H-12).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 153.8 (C-9), 132.9 (C-1), 103.8 (C-2), 79.2 (C-3), 65.6 (C-8), 53.6 (C-10), 51.8 (C-5), 44.5 (C-4), 32.1 (C-6/C-7), 28.8 (C-6/C-7), 18.9 (C-12), 11.1 (C-11).

FT-IR (ATR): ν [cm^{-1}] = 2944 (m), 2865 (m), 1718 (s), 1609 (s), 1441 (s), 1394 (m), 1359 (m), 1322 (s), 1284 (m), 1239 (m), 1193 (w), 1126 (s), 1086 (m), 1052 (w), 1017 (m), 997 (m), 939 (m), 905 (m), 883 (m), 831 (w), 769 (m), 720 (w), 677 (m), 644 (m), 567 (w), 505 (m).

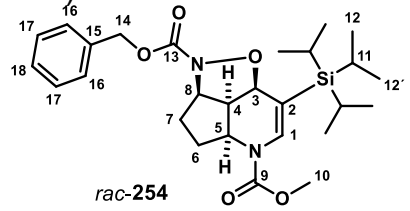
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{19}H_{34}N_2O_3Si$ $[M+H]^+$ 367.2411 u, found: 367.2407 u.

4.6.7. *rac*-3-Benzyl 7-methyl 5-(triisopropylsilyl)-1,2a,2a1,3,4a,7a-hexahydro-4-oxa-3,7-diazacyclopenta[*cd*]indene-7,3-dicarboxylate



rac-**252** *rac*-**254**

To a solution of the amine *rac*-**252** (195 mg, 0.532 mmol, 1.0 eq.) in 1.8 ml THF and 0.60 ml water was added CbzCl (0.23 ml, 1.6 mmol, 3.0 eq.) and a sat. aq. Na_2CO_3 solution (1.2 ml). The reaction mixture was stirred for 30 min at 0 °C and further 1 h at r.t.. After confirmation of full conversion of the starting material (TLC), the reaction mixture was diluted with water (5 ml). The aq. phase was extracted with EtOAc (4x 5 ml), the combined org. phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 6:1) and the desired product *rac*-**254** was obtained as a colorless oil (270 mg, 0.539 mmol, quant.).



rac-**254**

Formula: $C_{27}H_{40}N_2O_5Si$

M: 500.71 g/mol

R_f: 0.33 (SiO_2, 3:1, *c*Hex/EtOAc).

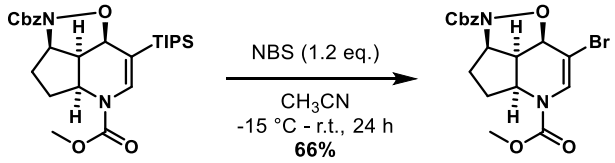
^{1}H NMR: (600 MHz, $CDCl_3$, mixture of rotamers): δ [ppm] = 7.38 – 7.31 (m, 5H, H-16, H-17, H-18), 7.18 (d, *J* = 107.8 Hz, 1H, H-1*), 5.15 (dd, *J* = 13.7, 12.0 Hz, 2H, H-14), 4.99 (t, *J* = 7.1 Hz, 1H, H-8), 4.27 (d, *J* = 67.4 Hz, 1H, H-5), 4.05 (s, 1H, H-3), 3.83 (s, 3H, H-10), 2.73 (dt, *J* = 8.5, 6.8 Hz, 1H, H-4), 2.04 – 1.91 (m, 2H, H-7, H-6), 1.84 (s, 1H, H-7´), 1.69 – 1.55 (m, 1H, H-6´), 1.23 – 1.12 (m, 3H, H-11), 1.03 (d, *J* = 7.5 Hz, 9H, H-12), 0.98 (d, *J* = 7.5 Hz, 9H, H-12´).

^{13}C NMR: (151 MHz, $CDCl_3$, mixture of rotamers): δ [ppm] = 158.4 (C-13), 154.6 (C-9_{rot1}), 153.7 (C-9_{rot2}), 135.8 (C-15), 135.1 (C-1_{rot1}), 134.3 (C-1_{rot2}), 128.7 (C-16), 128.6 (C-17), 128.5 (C-18), 101.8 (C-2), 76.8 (C-3_{rot1}), 76.5 (C-3_{rot2}), 68.4 (C-14), 64.7 (C-8_{rot1}), 64.6 (C-8_{rot2}), 53.8 (C-10_{rot1}), 53.6 (C-10_{rot2}), 52.9 (C-5_{rot1}), 52.6 (C-5_{rot2}), 43.4 (C-4), 30.9 (C-7), 29.4 (C-6_{rot1}), 28.7 (C-6_{rot2}), 18.9 (C-12), 18.6 (C-12´), 11.0 (C-11).

FT-IR (ATR): ν [cm^{-1}] = 2960 (w), 2944 (w), 2866 (w), 1720 (m), 1704 (s), 1615 (m), 1463 (w), 1445 (m), 1391 (m), 1336 (m), 1316 (m), 1297 (s), 1284 (s), 1258 (s), 1244 (s), 1199 (w), 1158 (w), 1149 (w), 1129 (m), 1114 (m), 1070 (m), 1041 (w), 1018 (m), 978 (s), 961 (m), 941 (m), 924 (m), 881 (m), 863 (w), 834 (w), 785 (w), 767 (m), 747 (s), 723 (m), 699 (m), 679 (s), 648 (m), 626 (m), 604 (m), 591 (m), 564 (m), 553 (w), 514 (w), 502 (m).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{27}H_{41}N_2O_5Si$ $[M+H]^+$ 501.2779 u, found: 501.2782 u; $C_{27}H_{40}N_2O_5SiNa$ $[M+Na]^+$ 523.2599 u, found: 523.2595 u.

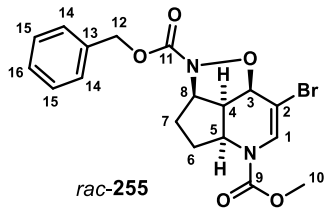
4.6.8. *rac*-3-Benzyl 7-methyl (2a*R*,2a1*S*,4a*R*,7a*S*)-5-bromo-1,2a,2a1,3,4a,7a-hexahydro-4-oxa-3,7-diazacyclopenta-[*cd*]indene-3,7-dicarboxylate



rac-**254** *rac*-**255**

To a solution of the starting material *rac*-**254** (260 mg, 0.519 mmol, 1.0 eq.) in 5.4 ml dry CH_3CN was added NBS (109 mg, 0.612 mmol, 1.2 eq.) at -15 °C (ice bath with NH_4Cl). The reaction mixture was stirred for 7 h at -15 °C and further 16 h at r.t. After confirmation of full conversion of the starting material (TLC), a sat. aq. $Na_2S_2O_3$ solution (1 ml) and water (10 ml) were added and the resulting mixture was stirred vigorously for 5 min. The aq. phase was extracted with EtOAc (4x 10 ml), the combined org. phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatograph (SiO_2, *c*Hex/EtOAc, 4:1) and the desired product *rac*-**255** was obtained as a colorless amorphous solid (145 mg, 0.343 mmol, 66%).

Formula: $C_{18}H_{19}BrN_2O_5$



rac-**255**

M: 423.26 g/mol

m.p.: 135-136 °C

R_f: 0.50 (SiO_2, 1:1, *c*Hex/EtOAc).

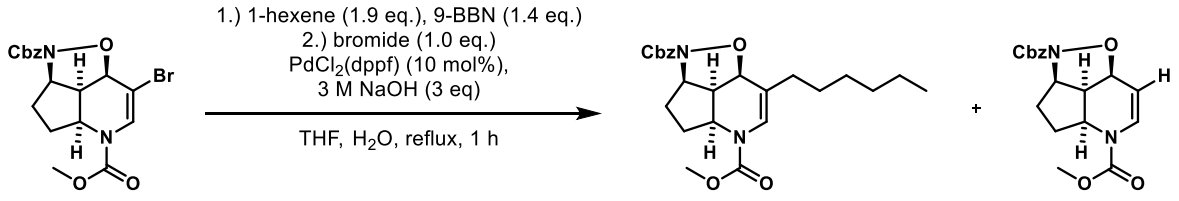
^{1}H NMR: (500 MHz, $CDCl_3$, mixture of rotamers): δ [ppm] = 7.56 – 7.29 (m, 6H, H-16, H-15, H-14, H-1), 5.27 (d, *J* = 12.4 Hz, 1H, H-12), 5.19 (d, *J* = 12.4 Hz, 1H, H-12´), 5.04 (t, *J* = 7.1 Hz, 1H, H-8), 4.44 – 4.21 (m, 2H, H-5, H-3), 3.83 (s, 3H, H-10), 2.90 (q, *J* = 7.3 Hz, 1H, H-4), 2.02 – 1.82 (m, 3H, H-7, H-6), 1.76 – 1.63 (m, 1H, H-6´).

^{13}C NMR: (126 MHz, $CDCl_3$ mixture of rotamers): δ [ppm] = 158.0 (C-11), 153.4 (C-9_{rot1}), 152.7 (C-9_{rot2}), 135.9 (C-13), 129.0 (C-1), 128.7 (C-14), 128.4 (C-15), 128.0 (C-16), 94.8 (C-2_{rot1}), 94.4 (C-2_{rot2}), 79.1 (C-3_{rot1}), 78.8 (C-3_{rot2}), 68.2 (C-12), 65.1 (C-8_{rot1}), 64.9 (C-8_{rot2}), 54.0 (C-10), 53.1 (C-5_{rot1}), 52.7 (C-5_{rot2}), 45.2 (C-4_{rot1}), 45.0 (C-4_{rot2}), 30.9 (C-7), 28.8 (C-6_{ro1}), 28.2 (C-6_{rot2}).

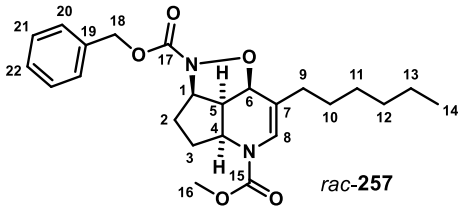
FT-IR (ATR): ν [cm^{-1}] = 3092 (w), 3033 (w), 2956 (w), 2880 (w), 1711 (s), 1648 (m), 1497 (w), 1440 (s), 1402 (m), 1384 (m), 1340 (s), 1297 (s), 1277 (s), 1254 (s), 1241 (s), 1193 (m), 1116 (s), 1075 (m), 995 (m), 982 (m), 936 (m), 913 (m), 888 (m), 824 (w), 786 (w), 764 (m), 729 (s), 696 (s), 647 (w), 632 (w), 598 (w), 575 (w), 553 (w).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{18}H_{19}BrN_2O_5Na$ $[M+Na]^+$ 445.0370 u, found: 445.0372 u; $C_{18}H_{20}BrN_2O_5$ $[M+H]^+$ 423.0550 u, found: 423.0554 u.

4.6.9. *rac*-3-Benzyl 7-methyl (2a*R*,2a1*S*,4a*R*,7a*S*)-5-hexyl-1,2a,2a1,-3,4a,7a-hexahydro-4-oxa-3,7-diazacyclopenta-[*cd*]indene-3,7-dicarboxylate



To a 0.5M solution of 9-BBN (0.80 ml, 0.40 mmol, 1.4 eq.) in THF was added 1-hexyne (67 μl, 0.53 mmol, 1.9 eq.) under an argon atmosphere at r.t. After stirring for 3.5 h, a 3M aq. NaOH solution (0.28 ml, 0.851 mmol, 3.0 eq.) was added and the reaction mixture was stirred for further 30 min. Then, $PdCl_2$(dppf) (21 mg, 0.29 mmol, 0.10 eq.) was added, the solution turned dark red and subsequently vinylbromide *rac*-**255** (120 mg, 0.284 mmol, 1.0 eq.) was added to the mixture. After stirring for 1 h at reflux, the reaction mixture was diluted by addition of 1M aq. HCl (1.0 ml) and EtOAc (10 ml). The aq. phase was extracted with EtOAc (3x 10 ml), the combined org. phases were washed with a sat. aq. NaCl solution (15 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, 6:1 → 2:1, *c*Hex/EtOAc). The desired product *rac*-**257** was obtained as a slightly yellow oil (50 mg, 0.12 mmol, 41%) and the undesired sideproduct *rac*-**258** was obtained as a slightly yellow oil (57 mg, 0.17 mmol, 58%)



The analytical data for compound **257**:

Formula: $C_{24}H_{32}N_2O_5$

M: 428.53 g/mol

R_f: 0.48 (SiO_2, 1:1, *c*Hex/EtOAc).

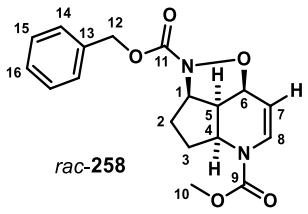
^{1}H NMR: (500 MHz, $CDCl_3$, mixture of rotamers): δ [ppm] = 7.41 – 7.30 (m, 5H, H-20, H-21, H-22), 6.94 (s, 0.4H, H-8$_{rot1}$), 6.78 (s, 0.6H, H-8$_{rot2}$), 5.26 (d, *J* = 12.3 Hz, 1H, H-18), 5.16 (d, *J* = 12.4 Hz, 1H, H-18), 5.01 – 4.94 (m, 1H, H-1), 4.40 – 4.17 (m, 1H, H-4), 4.02 (d, *J* = 6.8 Hz, 1H, H-6), 3.80 (d, *J* = 4.4 Hz, 3H, H-16), 2.79 (q, *J* = 7.2 Hz, 1H, H-5), 2.29 – 2.10 (m, 2H, H-9), 1.99 – 1.79 (m, 4H, H-2, H-3), 1.51 – 1.40 (m, 2H, H-10), 1.34 – 1.21 (m, 6H, H-11, H-12, H-13), 0.92 – 0.86 (m, 3H, H-14).

^{13}C NMR: (125 MHz, $CDCl_3$, mixture of rotamers): δ [ppm] = 158.2 (C-17), 154.3 (C-15$_{rot1}$), 153.7 (C-15$_{rot2}$), 136.0 (C-19), 128.7 (C-20/21/22), 128.4 (C-20/21/22), 128.1 (C-20/21/22), 123.3 (C-8$_{rot1}$), 122.6 (C-8$_{rot2}$), 112.5 (C-7$_{rot1}$), 112.5 (C-7$_{rot2}$), 77.0 (C-6$_{rot1}$), 76.7 (C-6$_{rot2}$), 71.1 (C-16$_{rot1}$), 68.0 (C-18), 64.5 (C-1$_{rot2}$), 64.4 (C-1$_{rot1}$), 53.5 (C-16$_{rot2}$), 53.1 (C-4$_{rot1}$), 52.8 (C-4$_{rot2}$), 44.3 (C-5$_{rot1}$), 44.1 (C-5$_{rot2}$), 33.5 (C-9$_{rot2}$), 33.4 (C-9$_{rot1}$), 32.2 (C-), 31.8 (C-12), 31.1 (C-2$_{rot2}$), 31.0 (C-2$_{rot1}$), 29.2 (C-11), 28.7 (C-3$_{rot1}$), 28.3 (C-10), 28.1 (C-3$_{rot2}$), 26.4, 22.8 (C-13), 22.1, 14.3 (C-14).

FT-IR (ATR): ν [cm^{-1}] = 3454 (bw), 2954 (w), 2927 (m), 2857 (w), 1714 (s), 1671 (m), 1443 (m), 1397 (m), 1322 (s), 1300 (m), 1280 (m), 1253 (m), 1196 (m), 1152 (w), 1116 (w), 1093 (w), 1075 (w), 1029 (w), 1009 (w), 979 (w), 933 (w), 880 (w), 849 (w), 767 (w), 698 (w).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{24}H_{33}N_2O_5Na$ $[M+H]^+$ 429.2384 u, found: 429.2386 u; $C_{24}H_{32}N_2O_5Na$ $[M+Na]^+$ 451.2203 u, found: 451.2205 u.

The analytical data for compound **258**:



rac-**258**

Formula: $C_{18}H_{20}N_2O_5$

M: 344.37 g/mol

R_f: 0.33 (SiO_2, 2:1, *c*Hex/EtOAc).

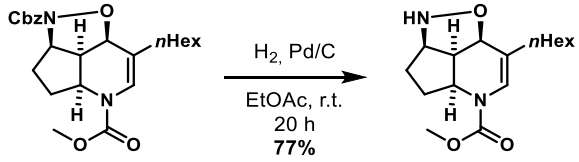
^{1}H NMR: (400 MHz, $CDCl_3$, mixture of rotamers): δ [ppm] = 7.42 – 7.30 (m, 5H, H-14, H-15, H-16), 7.13 (dd, *J* = 61.7, 8.1 Hz, 1H, H-8), 5.29 – 5.12 (m, 3H, H-7, H-12), 4.98 (t, *J* = 7.0 Hz, 1H, H-1), 4.43 – 4.15 (m, 2H, H-4, H-6), 3.82 (s, 3H, H-10), 2.81 (q, *J* = 7.1 Hz, 1H, H-5), 1.99 – 1.63 (m, 4H, H-2, H-3).

^{13}C NMR: (125 MHz, $CDCl_3$, mixture of rotamers): δ [ppm] = 157.7 (C-11), 153.6 (C-9), 136.0 (C-13), 128.7 (C-14/15/16), 128.5 (C-14/15/16), 128.4 (C-14/15/16), 128.0 (C-8), 99.0 (C-7), 74.1 (C-6$_{dia1}$), 73.8 (C-6$_{dia2}$), 68.2 (C-12), 64.4 (C-1$_{rot1}$), 64.3 (C-1$_{rot2}$), 53.6 (C-10), 53.3 (C-4$_{rot1}$), 52.9 (C-4$_{rot2}$), 43.8 (C-5), 30.9 (C-2$_{rot1}$), 30.8 (C-2$_{rot2}$), 28.7 (C-3$_{rot1}$), 28.0 (C-3$_{rot2}$).

FT-IR (ATR): ν [cm^{-1}] = 3457 (bw), 3033 (w), 2956 (w), 2926 (w), 2873 (w), 2857 (w), 1712 (s), 1653 (m), 1441 (m), 1385 (m), 1335 (s), 1327 (s), 1317 (s), 1294 (s), 1277 (s), 1251 (s), 1192 (m), 1152 (w), 1109 (s), 1073 (m), 1048 (m), 1028 (m), 992 (m), 971 (m), 932 (m), 877 (m), 831 (w), 807 (w), 791 (w), 767 (m), 749 (m), 718 (m), 697 (m), 611 (w), 579 (w), 536 (m).

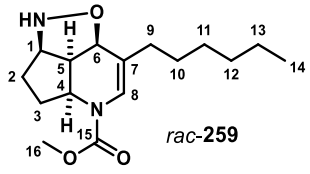
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{18}H_{21}N_2O_5$ $[M+H]^+$ 345.1445 u, found: 345.1452 u; $C_{18}H_{20}N_2O_5Na$ $[M+Na]^+$ 367.1264 u, found: 367.1263 u.

4.6.10. *rac*-7-Methyl (2a*R*,2a1*S*,4a*R*,7a*S*)-5-*n*hexyl-1,2a,2a1,3,4a,7a-hexahydro-4-oxa-3,7-diazacyclopenta[*cd*]indene-7-carboxylate



rac-**257** *rac*-**259**

To a solution of the Cbz-protected amine *rac*-**257** (19 mg, 0.044 mmol, 1.0 eq.) in 2.0 ml EtOAc was added a tip of a spatula of palladium on charcoal (10 w%) and subsequently an atmosphere of hydrogen was established. The reaction mixture was stirred for 20 h at r.t. until full conversion of the starting material was observed (TLC). The reaction mixture was filtered through a pad of celite and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 2:1) and the desired product *rac*-**259** was obtained as a colorless oil (10 mg, 0.034 mmol, 77%).



rac-**259**

Formula: $C_{16}H_{26}N_2O_3$

M: 294.40 g/mol

R_f: 0.14 (SiO_2, 2:1, *c*Hex/EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$, mixture of rotamers): δ [ppm] = 6.86 (s, 1H, H-8$_{rot1}$), 6.69 (s, 1H, H-8$_{rot2}$), 4.48 – 4.23 (m, 1H, H-4), 4.12 (m, 1H, H-1), 3.87 (m, 1H, H-6), 3.80 (m, 3H, H-16), 2.88 – 2.71 (m, 1H, H-5), 2.26 – 2.09 (m, 2H, H-9), 1.91 – 1.71 (m, 3H, H-2, N-H), 1.64 – 1.43 (m, 4H, H-3, H-10), 1.35 – 1.22 (m, 6H, H-11, H-12, H-13), 0.92 – 0.85 (m, 3H, H-14).

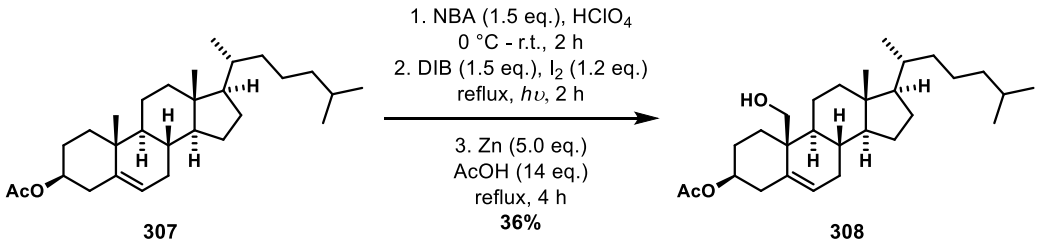
^{13}C NMR: (126 MHz, $CDCl_3$, mixture of rotamers): δ [ppm] = 154.4 (C-15_{rot1}), 153.8 (C-15_{rot2}), 121.9 (C-8_{rot1}), 121.2 (C-8_{rot2}), 114.5 (C-7), 79.5 (C-6_{rot1}), 79.2 (C-6_{rot2}), 65.8 (C-1_{rot1}), 65.6 (C-1_{rot2}), 53.6 (C-4_{rot1}), 53.3 (C-16), 53.3 (C-4_{rot2}), 45.6 (C-5_{rot1}), 45.5 (C-5_{rot2}), 33.5 (C-9), 32.3 (C-2), 31.8 (C-12), 29.2 (C-11), 28.5 (C-3_{rot1}), 28.5 (C-10_{rot1}), 28.3 (C-3_{rot2}), 28.0 (C-10_{rot2}), 22.8 (C-13), 14.2 (C-14).

FT-IR (ATR): ν [cm^{-1}] = 3216 (bw), 2955 (m), 2925 (m), 2855 (m), 1707 (s), 1668 (s), 1442 (s), 1406 (m), 1321 (s), 1281 (s), 1241 (s), 1193 (m), 1168 (m), 1116 (m), 1096 (m), 1007 (m), 983 (m), 938 (m), 876 (m), 845 (m), 808 (w), 766 (s) ,726 (m), 645 (w), 610 (w), 562 (w), 526 (w).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{16}H_{27}N_2O_3$ $[M+H]^+$ 295.2016 u, found: 295.2017 u; calc. for: $C_{16}H_{27}N_2O_3Na$ $[M+Na]^+$ 317.1836 u, found: 317.1835 u.

4.7. Synthesis of 7,19-Epoxysteroids

4.7.1. 3β-Acetoxy-cholest-Δ^5-en-19β-ol



According to our published procedure[140], to a solution of cholesteryl acetate **307** (200 g, 467 mmol, 1.0 eq.) in 1.6 l dioxane were added *N*-bromoacetamide (96.0 g, 696 mmol, 1.5 eq.) and aq. $HClO_4$ (320 ml, 0.5 N). The reaction mixture stirred for 1 h at 0 °C under exclusion of light. Afterwards, the reaction mixture was stirred for 1 h at r.t. The reaction was stopped upon addition of a sat. aq. Na_2SO_3 solution and water. The reaction mixture was stirred until full discoloration was visible. Then, the aq. phase was extracted with MTBE, the combined org. phases were washed with a sat. aq. NaCl solution and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude bromohydrine **312** (>40% regioisomeric bromohydrine present) was used without further purification in the following reaction step.

To a solution of ~25 g crude bromohydrine **312** in 1.5 l cyclohexane were added diacetoxyiodobenzene (27.6 g, 85.8 mmol, 1.5 eq) and iodine (8.76 g, 68.6 mmol, 1.2 eq.). The reaction mixture was irradiated with a 150 W mercury vapor lamp at reflux for 1 h. The violet reaction mixture was cooled to r.t. and unreacted iodine was desactivated upon treatment with a sat. aq. Na_2SO_3 solution until the color disappeared. Then, the reaction mixture was extracted with EtOAc, the combined org. phases were washed with a sat. aq. NaCl solution and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude oil **313** was used in the next reaction step without further purification. This reaction was repeated six times to react all the crude product **313** from the first step.

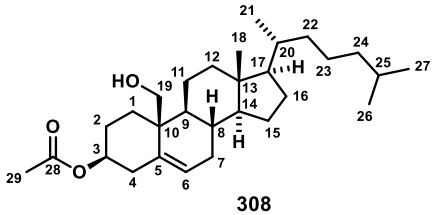
To a solution of bromoether **313** (~50 g) in 1.6 l isopropanol were added Zn powder (37.8 g, 578 mmol, 5.0 eq.) and AcOH (94 ml, 1.64 mol, 14.0 eq.). The reaction mixture was stirred at reflux for 3 h, then cooled to r.t. and filtered over Celite. The clear yellow solution was concentrated to a volume of 100 ml, water was added and the aq. phase was extracted with MTBE. The combined org. phases were washed with a sat. aq. NaCl solution and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield the crude product. This procedure was carried out a total of four times to react all the crude starting material **313** from the previous step. Alcohol **308** was obtained after purification by column chromatography (SiO_2, *c*Hex/EtOAc, 10:1) as a beige solid (74.0 g, 166 mmol, 36% over three steps, Lit.[140]: 43% over three steps).

Formula: $C_{29}H_{48}O_3$

M: 444.70 g/mol

m.p.: 112-114 °C.

R_f: 0.35 (SiO_2, 3:1, *c*Hex/EtOAc).



308

^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 5.76 (d, *J* = 5.0 Hz, 1H, H-6), 4.66 – 4.60 (m, 1H, H-3), 3.82 (d, *J* = 11.2 Hz, 1H, H-19), 3.61 (dd, *J* = 11.4, 9.1 Hz, 1H, H-19α), 2.41 (ddd, *J* = 13.0, 4.9 Hz, 2.1 Hz, 1H, H-4α), 2.28 – 2.23 (m, 1H, H-4β), 2.02 (s, 3H, H-29), 1.95 (dt, *J* = 13.8, 3.4 Hz, 1H, H-1α), 1.90 – 0.93 (m, 26H), 0.90 (d, *J* = 6.5 Hz, 3H, H-21), 0.85 (dd, *J* = 6.6, 2.2 Hz, 6H, H-26, H-27), 0.72 (s, 3H, H-18).

^{13}C NMR: (125 MHz, $CDCl_3$): δ [ppm] = 170.6 (C-28), 134.7 (C-5), 128.4 (C-6), 73.6 (C-3), 62.9 (C-19), 57.7 (C-14), 56.2 (C-17), 50.4 (C-9), 42.7 (C-13), 41.7 (C-10), 40.1 (C-12), 39.6 (C-24), 38.4 (C-4), 36.3 (C-22), 35.9 (C-20), 33.5 (C-8), 33.2 (C-1), 31.4 (C-7), 28.4 (C-16), 28.2 (C-2), 28.2 (C-25), 24.2 (C-15), 24.0 (C-23), 23.0 (C-27), 22.7 (C-26), 21.9 (C-11), 21.5 (C-29), 18.8 (C-21), 12.4 (C-18).

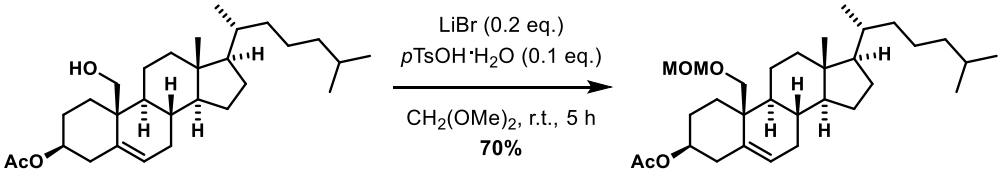
FT-IR (ATR): ν [cm^{-1}] = 3507 (bw), 2944 (s), 2934 (s), 2870 (m), 1734 (m), 1713 (s), 1469 (m), 1444 (m), 1381 (m), 1370 (m), 1254 (s), 1245 (vs), 1029 (vs), 977 (m), 961 (m), 911 (w), 886 (w), 824 (w), 807 (w), 742 (w), 670 (w), 610 (w).

HR-MS: (ESI, 70 eV) = m/z calc. for: $C_{29}H_{48}O_3Na^+$ $[M+Na]^+$ = 467.3469 u, found: 467.3493 u.

$[\alpha]_\lambda^{20}$: c = 0.58 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = -77.7° (± 0.0°), $[\alpha]_{436}^{20}$ = -49.9° (± 0.1°), $[\alpha]_{546}^{20}$ = -28.6° (± 0.1°), $[\alpha]_{579}^{20}$ = -25.2° (± 0.1°), $[\alpha]_{589}^{20}$ = -25.2° (± 0.1°).

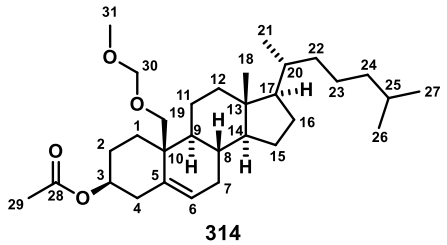
The analytical data are in accordance with the literature.[140]

4.7.2. 3β-Acetoxy-19-(methoxymethyloxy)-cholestan-Δ^5-en



308 **314**

According to our published procedure[140], to a solution of 19-hydroxycholesteryl acetate **308** (42.0 g, 78.7 mmol, 1.0 eq.) in $CH_2(OMe)_2$ (315 ml) were added lithium bromide (1.64 g, 18.9 mmol, 0.2 eq.) and *p*TsOH·H_2O (1.80 g, 9.44 mmol, 0.1 eq.). The reaction mixture was stirred for 5 h at r.t. Afterwards, the reaction was stopped by addition of a sat. aq. NaCl solution and the aq. phase was extracted with MTBE. The combined org. phases were washed with a sat. aq. $NaHCO_3$ solution as well as a sat. aq. NaCl solution and dried over $MgSO_4$. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 5:1) and product **314** was obtained as a white solid (26.9 g, 55.0 mmol, 70%, Lit.[140]: 82%).



314

Formula: $C_{31}H_{52}O_4$

M: 488.75 g/mol

m.p.: 84-85 °C.

R_f: 0.65 (SiO_2, 3:1, *c*Hex/EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 5.60 (d, *J* = 5.4 Hz, 1H, H-6), 4.69 – 4.57 (m, 3H, H-3, H-30), 3.73 (d, *J* = 10.3 Hz, 1H, H-19), 3.48 (d, *J* = 10.3 Hz, 1H, H-19), 3.37 (s, 3H, H-31), 2.40 (ddd, *J* = 13.0, 5.2, 2.2 Hz, 1H, H-4α), 2.33 (t, *J* = 12.2 Hz, 1H, H-4β), 2.11 (dt, *J* = 13.8, 3.7 Hz, 1H, H-1), 2.03 (s, 3H, H-29), 2.02 – 0.96 (m, 25H), 0.91 (d, *J* = 6.5 Hz, 3H, H-21), 0.86 (dd, *J* = 6.6, 2.3 Hz, 6H, H-26, H-27), 0.70 (s, 3H, H-18).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 170.7 (C-28), 135.8 (C-5), 126.3 (C-6), 97.0 (C-30), 73.8 (C-3), 69.1 (C-19), 57.4 (C-14), 56.2 (C-17), 55.6 (C-31), 50.5 (C-9), 42.6 (C-13), 40.5 (C-10), 40.2 (C-12), 39.7 (C-24), 38.5 (C-4), 36.3 (C-22), 36.0 (C-20), 33.4 (C-1), 32.9 (C-8), 31.7 (C-7), 28.4 (C-16), 28.2 (C-2), 28.2 (C-25), 24.3 (C-23), 24.0 (C-15), 23.0 (C-26/27), 22.7 (C-26/27), 22.0 (C-11), 21.6 (C-29), 18.9 (C-21), 12.2 (C-18).

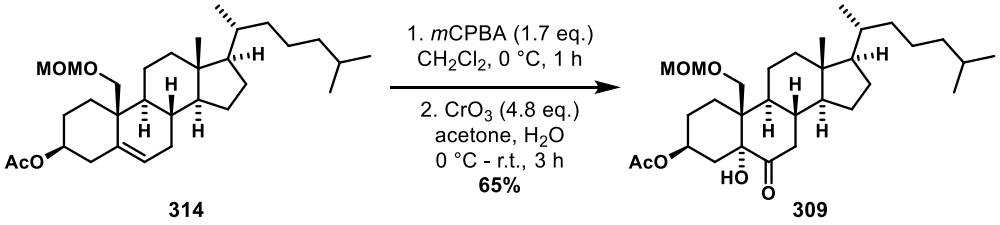
FT-IR (ATR): ν [cm^{-1}] = 3419 (br w), 2932 (m), 2868 (m), 1733 (m), 1498 (w), 1467 (w), 1444 (w), 1366 (m), 1242 (s), 1144 (m), 1112 (m), 1096 (m), 1046 (s), 1033 (s), 986 (m), 962 (m), 943 (m), 915 (m), 881 (w), 845 (w), 824 (w), 814 (w), 727 (w), 703 (w), 679 (w), 630 (w), 607 (m), 580 (w).

MS: (GC-MS, 70eV): m/z (%): 428 (2), 396 (24), 366 (26), 353 (100).

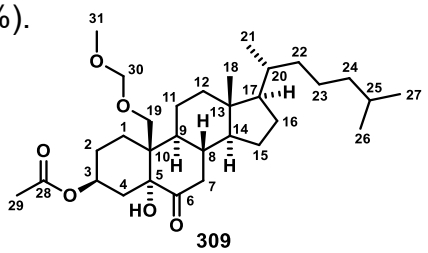
$[\alpha]_\lambda^{20}$: c = 0.63 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = -136.7° (± 0.1°), $[\alpha]_{436}^{20}$ = -82.7° (± 0.1°), $[\alpha]_{546}^{20}$ = -46.6° (± 0.2°), $[\alpha]_{579}^{20}$ = -41.0° (± 0.2°), $[\alpha]_{589}^{20}$ = -41.6° (± 0.1°).

The analytical data are in accordance with the literature.[140]

4.7.3. of 3β-Acetoxy-5α-hydroxy-19-(methoxymethyloxy)-cholestan-6-one



According to our published procedure[140], to a solution of alkene **314** (32.4 g, 66.3 mmol, 1.0 eq.) in CH_2Cl_2 (400 ml) was added *m*CPBA (70w%, 25.3 g, 113 mmol, 1.7 eq.). The reaction mixture was stirred at r.t. for 1 h (the formation of a white precipitate was observed) and then it was cooled to 0 °C. The resulting white precipitate was dissolved by the addition of acetone (950 ml) and subsequently a solution of CrO_3 (24.0 g, 239 mmol, 3.6 eq.) in 80 ml water was added to the reaction mixture. After 10 min at 0 °C, the reaction mixture was stirred for 1 h at r.t. Then, the previously described procedure was repeated with CrO_3 (7.82 g, 78.2 mmol, 1.18 eq.) in 35 ml water. After 2 h, the reaction mixture was stopped by addition of a sat. aq. $NaHCO_3$ solution and the aq. phase was extracted with EtOAc. The combined org. phases were washed with water, a sat. aq. $NaHCO_3$ solution and a sat. aq. NaCl solution. The clear yellow org. phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 8:1) and the desired product **309** was obtained as a white foam (22.3 g, 42.8 mmol, 65%, Lit.[140]: 63%).


309

Formula: $C_{31}H_{52}O_6$

M: 520.75 g/mol

m.p.: 143-144 °C.

R_f: 0.37 (SiO_2, 3:1, *c*Hex/EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 5.11 (tt, *J* = 11.4, 5.3 Hz, 1H, H-3), 4.50 (s, 2H, H-30), 3.64 (d, *J* = 10.6 Hz, 1H, H-19), 3.57 (d, *J* = 10.6 Hz, 1H, H-19), 3.34 (s, 3H, H-31), 2.75 (s, 1H, *O*H), 2.57 (dd, *J* = 14.6, 11.6 Hz, 1H, H-7), 2.20 – 2.13 (m, 2H, H-4, H-7), 2.09 – 2.03 (m, 2H, H-8, H-12), 2.02 (s, 3H, H-29), 1.96 – 1.82 (m, 3H, H-2, H-9, H-23), 1.76 – 1.63 (m, 3H, H-1, H-4), 1.59 – 1.43 (m, 5H), 1.39 – 0.96 (m, 12H), 0.91 (d, *J* = 6.5 Hz, 3H, H-21), 0.86 (dd, *J* = 6.6, 2.1 Hz, 6H, H-26, H-27), 0.68 (s, 3H, H-18).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 209.6 (C-6), 171.1 (C-28), 97.1 (C-30), 77.9 (C-5), 70.4 (C-3), 67.1 (C-19), 57.1 (C-14), 56.3 (C-17), 56.1 (C-31), 45.7 (C-10), 44.1 (C-9), 43.2 (C-13), 41.5 (C-7), 40.0 (C-12), 39.6 (C-24), 37.2 (C-8), 36.3 (C-22), 35.9 (C-20), 32.5 (C-4), 28.3 (C-23), 28.2 (C-25), 26.6 (C-2), 26.1 (C-1), 24.1 (C-16), 23.0 (C-26/27), 22.7 (C-26/27), 21.9 (C-11), 21.5 (C-29), 18.8 (C-21), 12.3 (C-18).

FT-IR (ATR): ν [cm^{-1}] = 3384 (br w), 2939 (m), 2869 (m), 1730 (m), 1713 (s), 1467 (w), 1401 (w), 1382 (m), 1365 (m), 1236 (s), 1150 (m), 1106 (m), 1034 (s), 1012 (s), 967 (m), 940 (m), 920 (m), 904 (m), 871 (w), 834 (w), 734 (w), 664 (w), 941 (w), 609 (w), 553 (w).

MS: (GC-MS, 70eV): m/z (%): 520 (1, $[M]^+$), 460 (4), 415 (29), 397 (29), 369 (49).

$[\alpha]_\lambda^{20}$: c = 0.50 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = -253.0° (± 0.3°), $[\alpha]_{436}^{20}$ = -120.5° (± 0.1°), $[\alpha]_{546}^{20}$ = -62.8° (± 0.4°), $[\alpha]_{579}^{20}$ = -54.6° (± 0.0°), $[\alpha]_{589}^{20}$ = -55.1° (± 0.1°).

The analytical data are in accordance with the literature.[140]

4.7.4. 3β-Acetoxy-7α-bromo-6β,19-epoxy-cholestan- 5α,6α-diol

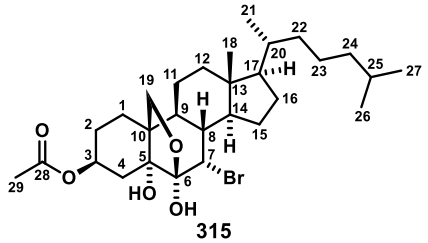
According to our published procedure[140], to a solution of ketone **309** (22.3 g, 42.8 mmol, 1.0 eq.) in AcOH (400 ml) was added bromine (6.6 ml, 130 mmol, 3.5 eq.) in AcOH (65 ml) and a few drops of aq. HBr (48%). The reaction mixture was stirred at 60 °C for 5 h and then cooled to r.t. Excess bromine was neutralized with a sat. aq. Na_2SO_3 solutionn and the aq. phase was extracted with EtOAc. The combined org. phases were washed with water, sat. aq. NaCl solution and dried over $MgSO_4$. Then, the solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 6:1). The desired bromide **315** was obtained as a white solid (13.4 g, 24.2 mmol, 57%, Lit.[140]: 56%).

Formula: $C_{29}H_{47}BrO_5$

M: 555.59 g/mol

m.p.: 124-125 °C.

R_f: 0.35 (SiO_2, 2:1, *c*Hex:EtOAc).



315

^{1}H NMR: (600 MHz, $CDCl_3$): δ [ppm] = 5.02 (tt, *J* = 11.0, 4.6 Hz, 1H, H-3), 4.12 (d, *J* = 4.9 Hz, 1H, H-7), 4.02 (d, *J* = 9.0 Hz, 1H, H-19), 3.73 (d, *J* = 9.0 Hz, 1H, H-19), 3.09 (s, 1H, OH-6), 2.89 (s, 1H, OH-5), 2.19 (ddd, *J* = 12.9, 4.5, 2.2 Hz, 1H, H-4), 2.04 (s, 3H, H-29), 2.05 – 1.99 (m, 1H, H-12), 1.97 – 1.83 (m, 5H, H-8, H-9, H-16, H-2, H-15), 1.74 (t, *J* = 12.4 Hz, 1H, H-4), 1.62 (s, 2H), 1.59 – 0.98 (m, 19H), 0.91 (d, *J* = 6.5 Hz, 3H, H-21), 0.87 (dd, *J* = 6.6, 3.0 Hz, 6H, H-26, H-27), 0.74 (s, 3H, H-18).

^{13}C NMR: (151 MHz, $CDCl_3$): δ [ppm] = 170.7 (C-28), 101.7 (C-6), 79.4 (C5), 69.9 (C-3), 66.8 (C-19), 59.4 (C-7), 55.7 (C-17), 52.9 (C-14), 45.4 (C-10), 43.5 (C-13), 39.6 (C-24), 39.0 (C-12), 38.7 (C-8), 38.6 (C-9), 36.2 (C-22), 35.8 (C-20), 35.0 (C-4), 28.2 (C-25), 28.1 (C-16), 27.2 (C-2), 24.0 (C-1), 24.0 (C-23), 23.3, (C-15), 23.0 (C-26/27), 22.7 (C-26/27), 21.6 (C-11), 21.5 (C-29), 18.8 (C-21), 13.1 (C-18).

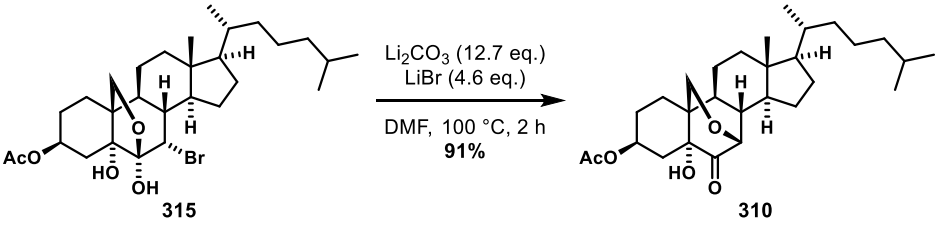
FT-IR (ATR): ν [cm^{-1}] = 3418 (br w), 2933 (m), 2868 (m), 1726 (s), 1714 (s), 1498 (w), 1466 (w), 1382 (m), 1366 (m), 1244 (s), 1154 (m), 1131 (m), 1096 (m), 1042 (s), 984 (m), 965 (s), 942 (s), 906 (m), 846 (m), 814 (w), 727 (w), 703 (m), 680 (m), 666 (m), 629 (m), 609 (m), 583 (m).

MS: (GC-MS, 70eV): m/z (%): 474 (1), 446 (5), 414 (2), 386 (24), 368 (14).

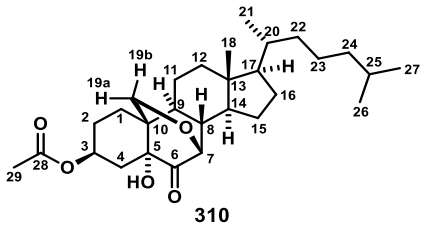
$[\alpha]_\lambda^{20}$: c = 0.51 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = -187.2° (± 0.4°), $[\alpha]_{436}^{20}$ = -86.2° (± 0.2°), $[\alpha]_{546}^{20}$ = -50.6° (± 0.5°), $[\alpha]_{579}^{20}$ = -44.8° (± 0.2°), $[\alpha]_{589}^{20}$ = -131.5° (± 0.2°).

The analytical data are in accordance with the literature.[140]

4.7.5. 3β-Acetoxy-5α-hydroxy-7β,19-epoxy-cholestan-6-one



According to our published procedure[140], to a solution of bromide **315** (22.6 g, 40.7 mmol, 1.0 eq.) in DMF (1.8 l) were added Li_2CO_3 (38.3 g, 0.52 mol, 12.7 eq.) and LiBr (16.3 g, 188 mmol, 4.6 eq.). The reaction mixture was stirred at 100 °C for 2 h. Then, it was cooled to r.t. and diluted with water. The aq. phase was extracted with EtOAc, the combined org. phases were washed with water and with a sat. aq. NaCl solution and dried over $MgSO_4$. Subsequently, the solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 6:1). The desired product **310** was obtained as a white solid (17.5 g, 37.0 mmol, 91%, Lit.[140]: 92%).



Formula: $C_{29}H_{46}O_5$

M: 474.68 g/mol

m.p.: 146-147 °C.

R_f: 0.48 (SiO_2, 3:1, *c*Hex/EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 5.22 (tt, *J* = 11.1, 5.4 Hz, 1H, H-3), 4.14 (dd, *J* = 10.2, 1.7 Hz, 1H, H-19a), 3.91 (d, *J* = 10.2 Hz, 1H, H-19b), 3.82 (d, *J* = 1.7 Hz, 1H, H-7), 2.61 (s, 1H, OH), 2.12 – 2.03 (m, 3H, H-4, H-8, H-12), 2.03 (s, 3H, H-29), 2.00 – 1.94 (m, 2H, H-2, H-4), 1.86 (dtd, *J* = 13.0, 9.4, 5.8 Hz, 1H, H-16), 1.73 (td, *J* = 13.8, 4.7 Hz, 1H, H-1), 1.65 – 1.48 (m, 5H), 1.42 – 1.04 (m, 13H), 0.98 (dt, *J* = 10.2, 8.7 Hz, 1H, H-22), 0.89 (d, *J* = 6.5 Hz, 3H, H-21), 0.86 (dd, *J* = 6.6, 2.4 Hz, 6H, H-26, H-27), 0.74 (s, 3H, H-18).

^{13}C NMR: (125 MHz, $CDCl_3$): δ [ppm] = 212.9 (C-6), 170.6 (C-28), 78.7 (C-5), 76.2 (C-7), 69.2 (C-3), 63.6 (C-19), 55.7 (C-17), 52.0 (C-14), 45.5 (C-13), 45.1 (C-8), 43.2 (C-9), 40.5 (C-10), 40.2 (C-12), 39.6 (C-24), 36.2 (C-22), 35.8 (C-20), 35.2 (C-4), 28.6 (C-16), 28.1 (C-25), 26.2 (C-2), 23.9 (C-23), 22.9

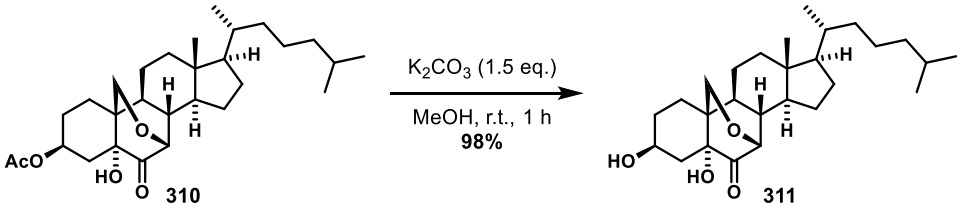
(C-26/27), 22.9 (C-15), 22.7 (C-26/27), 21.7 (C-11), 21.5 (C-29), 21.3 (C-1), 18.7 (C-21), 13.1 (C-18).

FT-IR (ATR): ν [cm^{-1}] = 3507 (br w), 2944 (s), 2934 (s), 2870 (m), 1734 (m), 1713 (s), 1469 (m), 1444 (m), 1381 (m), 1370 (m), 1254 (s), 1245 (vs), 1029 (vs), 977 (m), 961 (m), 911 (w), 886 (w), 824 (w), 807 (w), 742 (w), 670 (w), 610 (w).

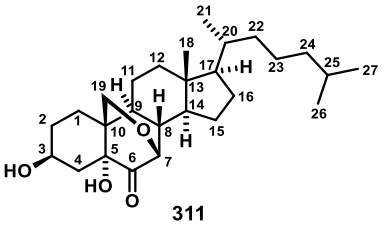
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{29}H_{46}O_5Na^+$ $[M+Na]^+$ 497.3238 u, found: 497.3234 u.

The analytical data are in accordance with the literature.[140]

4.7.6. 3β,5α-Dihydroxy-7β,19-epoxy-cholestan-6-one



According to our published procedure[140], to a solution of acetate **310** (12.7 g, 26.7 mmol, 1.0 eq.) in MeOH (890 ml) was added K_2CO_3 (5.54 g, 40.1 mmol, 1.5 eq.) and the reaction mixture was stirred for 1 h at r.t. The reaction mixture was diluted with water and the aq. phase was extracted with EtOAc. The combined org. phases were washed with a sat. aq. NaCl solution and dried over $MgSO_4$. Subsequently, the solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2,*c*Hex/EtOAc, 1:1). The desired product **311** (**WIL-071**) was obtained as a white solid (11.3 g, 26.1 mmol, 98%, Lit.[140]: 92%) and recrystallization from 400 ml (EtOH/H_2O, 1:1) gave rise to a batch of highly pure substance (9.7 g, 22.4 mmol).



Formula: $C_{27}H_{44}O_4$

M: 432.65 g/mol

m.p.: 178-180 °C.

R_f: 0.19 (SiO_2, 1:1, *c*Hex/EtOAc).

^{1}H NMR: (600 MHz, $CDCl_3$): δ [ppm] = 4.19 – 4.13 (m, 2H, H-3, H-19), 3.88 (d, *J* = 10.2 Hz, 1H, H-19´), 3.81 (s, 1H, H-7), 2.71 (s, 1H, OH-5), 2.11 – 2.00 (m, 3H, H-4, H-8, H-12), 1.96 – 1.82 (m, 3H, H-2, H-4´, H-16), 1.75

(s, 1H, OH-3), 1.65 – 0.94 (m, 20H), 0.88 (d, *J* = 6.5 Hz, 3H, H-21), 0.85 (dd, *J* = 6.6, 2.9 Hz, 6H, H-26, H-27), 0.73 (s, 3H, H-18).

^{13}C NMR: (150 MHz, $CDCl_3$): δ [ppm] = 213.6 (C-6), 79.2 (C-5), 76.2 (C-7), 66.2 (C-3), 63.7 (C-19), 55.7 (C-17), 52.1 (C-14), 45.5 (C-13), 45.2 (C-8), 43.3 (C-9), 40.6 (C-10), 40.3 (C-12), 39.6 (C-24), 38.8 (C-2), 36.2 (C-22), 35.8 (C-20), 30.2 (C-4), 28.6 (C-16), 28.1 (C-25), 23.9 (C-23), 22.9 (C-15), 22.9 (C-27), 22.7 (C-26), 21.8 (C-11), 21.5 (C-1), 18.7 (C-21), 13.1 (C-18).

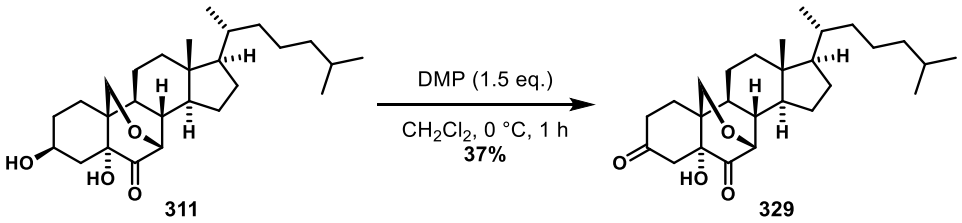
FT-IR (ATR): ν [cm^{-1}] = 3463 (br w), 2948 (s), 2868 (m), 1733 (vs), 1497 (w), 1466 (m), 1414 (w), 1382 (m), 1365 (w), 1340 (w), 1296 (w), 1248 (m), 1225 (w), 1153 (m), 1051 (vs), 968 (m), 958 (m), 887 (w), 818 (w), 779 (w), 756 (m), 713 (w), 637 (w), 558 (m), 539 (w).

MS: (ESI, 70 eV) = *m/z* calc. for: $C_{27}H_{44}O_4Na^+$ $[M+Na]^+$ 455.3132 u, found: 455.3137 u.

$[\alpha]_\lambda^{20}$: c = 0.99 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = 261.2°, $[\alpha]_{436}^{20}$ = 125.1°, $[\alpha]_{546}^{20}$ = 66.9°, $[\alpha]_{579}^{20}$ = 58.0°, $[\alpha]_{589}^{20}$ = 55.2°.

The analytical data are in accordance with the literature.[140]

4.7.7. 7*β*,19-Epoxy-cholest-4-en-3,6-dione



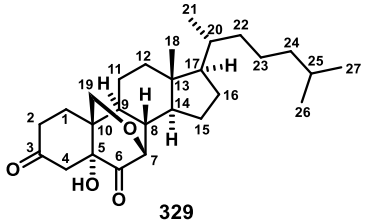
To a solution of alcohol **311** (400 mg, 0.925 mmol. 1.0 eq.) in CH_2Cl_2 (11.5 ml) was added DMP (588 mg, 1.39 mmol, 1.5 eq.) at 0 °C. The solution was subsequently stirred at r.t. for 1 h and afterwards diluted upon addition of a sat. aq. solution of $NaHCO_3$ and a sat. aq. solution of $Na_2S_2O_3$. The aq. phase was extracted with CH_2Cl_2, the combined org. phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, *c*Hex/EtOAc, 5:1) and product **329** was obtained as a colorless solid (148 mg, 0.344 mmol, 37%).

Formula: $C_{27}H_{42}O_4$

M: 430.63 g/mol

m.p.: 204-205 °C.

R_f: 0.56 (SiO_2, 1:1, cHex:EtOAc).



329

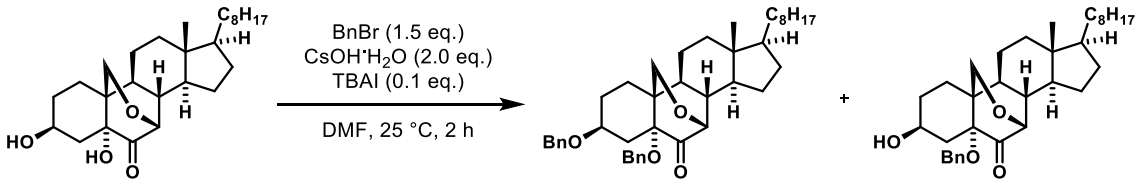
^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 4.12 (q, *J* = 10.5 Hz, 2H, H-19), 3.93 (d, *J* = 1.6 Hz, 1H, H-7), 2.99 (d, *J* = 15.6 Hz, 1H, H-4), 2.92 – 2.87 (m, 1H, OH), 2.48 (m, *J* = 16.3, 8.0 Hz, 2H, H-2, H-4), 2.43 – 2.34 (m, 1H, H-2), 2.19 (t, *J* = 10.6 Hz, 1H, H-8), 2.11 – 2.00 (m, 2H, H-1, H-12), 1.93 – 1.84 (m, 1H, H-16), 1.65 – 1.56 (m, 3H, H-1, H-9, H-15), 1.55 – 1.06 (m, 14H, H-11, H-12, H-14, H-15, H-16, H-17, H-20, H-22, H-23, H-24, H-25), 1.03 – 0.95 (m, 1H, H-22), 0.90 (d, *J* = 6.5 Hz, 3H, H-21), 0.86 (dd, *J* = 6.6, 2.5 Hz, 6H, H-26, H-27), 0.77 (s, 3H, H-18).

^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 211.5 (C6), 206.5 (C3), 80.0 (C5), 76.8 (C7), 63.6 (C19), 55.7 (C17), 51.9 (C14), 47.1 (C4), 45.4 (C13), 45.1 (C8), 43.4 (C9), 40.9 (C10), 40.2 (C12), 39.6 (C24), 36.9 (C2), 36.2 (C22), 35.8 (C20), 28.6 (C16), 28.1 (C25), 23.9 (C23), 22.9 (C26/C27), 22.9 (C15), 22.7 (C26/C27), 22.4 (C1), 21.8 (C11), 18.7 (C21), 13.1 (C18).

FT-IR (ATR): ν [cm^{-1}] = 3459 (bw), 2952 (m), 2940 (m), 2918 (m), 2859 (m), 1742 (s), 1714 (s), 1466 (m), 1382 (m), 1345 (w), 1298 (w), 1252 (w), 1238 (m), 1195 (w), 1163 (m), 1145 (m), 1102 (w), 1079 (w), 1051 (s), 980 (w), 948 (m), 913 (w), 903 (w), 891 (w), 854 (w), 822 (w), 797 (w), 752 (m), 723 (m), 663 (w), 631 (m), 594 (w), 559 (m), 525 (m).

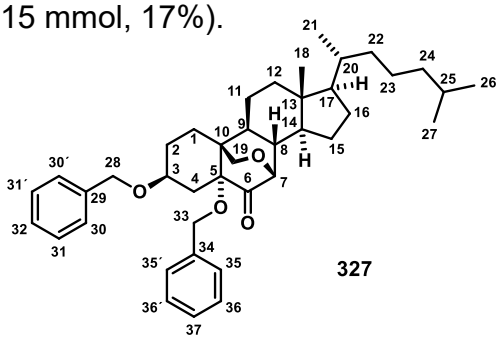
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{27}H_{43}O_4^+$ $[M+H]^+$ 431.3156 u, found: 431.3154 u;
m/z calc. for: $C_{27}H_{42}O_4Na^+$ $[M+Na]^+$ 453.29753 u, found: 453.29761 u.

4.7.8. 3β,5α-Dibenzyloxy-7β,19-epoxy-cholestan-6-one and 5α-benzyloxy-3β-hydroxy-7β,19-epoxy-cholestan-6-one



311 327: 40% 328: 17%

To a solution of alcohol **311** (39 mg, 0.090 mmol, 1.0 eq.) in DMF (0.92 ml) were added $CsOH{\cdot}H_2O$ (35 mg, 0.19 mmol, 2.0 eq.), BnBr (16.2 ml, 0.139 mmol, 1.5 eq.) and Bu_4NI (4 mg, 0.011 mmol, 0.1 eq.) at r.t. The reaction mixture was stirred for 2 h at r.t. and afterwards diluted with MTBE and sat. aq. NH_4Cl solution. The aq. phase was extracted with MTBE, the combined org. phases were washed with water, sat. aq. NaCl solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *c*Hex/EtOAc, 9:1 to 3:1). The double benzylated product **327** was obtained as a colorless oil (22 mg, 0.036 mmol, 40%) and the single benzylated product **328** was as well obtained as a colorless oil (7.9 mg, 0.015 mmol, 17%).



327

Formula: $C_{41}H_{56}O_4$

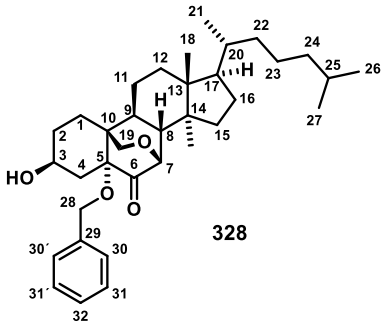
M: 612.90 g/mol

^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 7.38 – 7.23 (m, 8H, H-30, H-31, H-35, H-36), 7.16 (d, *J* = 6.9 Hz, 2H, H-32, H-37), 5.07 (d, *J* = 11.6 Hz, 1H, H-33), 4.58 – 4.51 (m, 3H, H-28, H-33), 4.15 (d, *J* = 9.9 Hz, 1H, H-19), 3.86 (d, *J* = 10.1 Hz, 1H, H-19), 3.66 (s, 1H, H-7), 3.64 – 3.55 (m, 1H, H-3), 2.72 (dd, *J* = 14.2, 3.4 Hz, 1H, H-4), 2.08 – 1.93 (m, 4H, H-2, H-8, H-9, H-12), 1.91 – 1.83 (m, 1H, H-16), 1.79 (dd, *J* = 14.1, 11.4 Hz, 1H, H-4), 1.72 (td, *J* = 13.8, 4.7 Hz, 1H, H-1), 1.62 – 1.46 (m, 4H, H-2, H-15, H-25), 1.41 – 1.06 (m, 13H, H-1, H-11, H-12, H-14, H-15, H-16, H-17, H-20, H-22, H-23, H-24), 1.02 – 0.94 (m, 1H, H-22), 0.89 (d, *J* = 6.4 Hz, 3H, H-21), 0.86 (dd, *J* = 6.6, 2.5 Hz, 6H, H-26, H-27), 0.73 (s, 3H, H-18).

^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 208.7 (C-6), 139.2 (C-34), 138.7 (C-29), 128.6 (C-30/35), 128.4 (C-30/35), 127.8 (C-31, C-36), 127.3 (C-32/37), 127.3 (C-32/37), 80.6 (C-5), 77.1 (C-7), 72.3 (C-3), 70.6 (C-28), 65.5 (C-33), 63.7 (C-19), 55.8 (C-17), 52.6 (C-14), 45.6 (C-13), 44.1 (C-8), 43.1 (C-9), 41.6, (C-10), 40.6 (C-12), 39.6 (C-24), 36.3 (C-22), 35.8 (C-20), 30.2 (C-4), 28.7 (C-16), 28.2 (C-25), 27.3 (C-2), 23.9 (C-23), 23.0 (C-26/27), 22.9 (C-15), 22.7 (C-26/27), 21.9 (C-11), 21.8 (C-1), 18.7 (C-21), 13.1 (C-18).

FT-IR (ATR): ν [cm^{-1}] = 3064 (w), 3031 (w), 2949 (s), 2867 (s), 1733 (s), 1496 (w), 1454 (m), 1382 (w), 1364 (w), 1307 (w), 1262 (w), 1228 (w), 1206 (w), 1179 (w), 1142 (w), 1090 (s), 1054 (m), 1001 (w), 953 (w), 873 (w), 842 (w), 803 (w), 734 (s), 693 (s), 557 (w).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{41}H_{56}O_4Na^+$ $[M+Na]^+$ 635.4071 u, found: 635.4075 u.



328

Formula: $C_{35}H_{52}O_4$

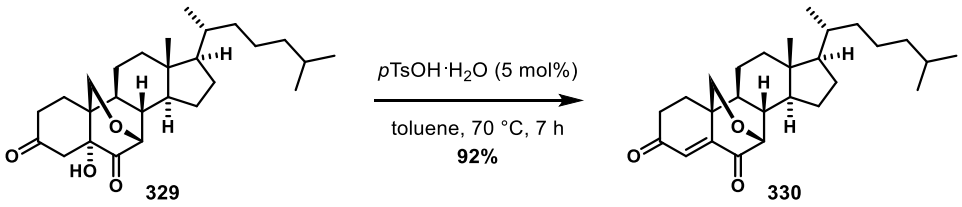
M: 536.80 g/mol

^{1}H NMR: (500 MHz, $CDCl_3$): δ [ppm] = 7.38 – 7.25 (m, 5H, H-30, H-31, H-32), 5.15 (d, *J* = 11.9 Hz, 1H, H-28), 4.79 (d, *J* = 12.0 Hz,1H, H-28), 4.13 (d, *J* = 10.3 Hz, 1H, H-19), 3.88 (m, 2H, H-3, H-19), 3.67 (s, 1H, H-7), 2.65 (dd, *J* = 14.2, 3.5 Hz, 1H, H-4), 2.09 – 1.97 (m, 3H, H-8, H-9, H-12), 1.96 – 1.73 (m, 4H, H-1, H-2, H-4, H-16), 1.63 – 1.06 (m, 18H, H-1, H-2, H-4, H-11, H-12, H-14, H-15, H-16, H-17, H-20, H-22, H-24, H-25,), 1.02 – 0.95 (m, 1H, H-22), 0.89 (d, *J* = 6.5 Hz, 3H, H-21), 0.86 (dd, *J* = 6.6, 2.5 Hz, 6H, H-26, H-27), 0.74 (s, 3H, H-18).

^{13}C NMR: (126 MHz, $CDCl_3$): δ [ppm] = 208.4 (C-6), 139.3 (C-29), 128.4 (C-31), 127.3 (C-32), 127.1 (C-30) 80.7 (C-5), 77.2 (C-7), 66.1 (C-3), 65.5 (C-28), 63.7 (C-19), 55.7 (C-17), 52.6 (C-14), 45.6 (C-13), 44.1 (C-8), 43.0 (C-9), 41.4 (C-10), 40.6 (C-12), 39.6 (C-24), 36.3 (C-22), 35.8 (C-20), 33.2 (C-4), 30.5 (C-2), 28.7 (C-16), 28.2 (C-25), 23.9 (C-23), 23.0 (C-26/27), 22.9 (C-15), 22.7 (C-26/27), 22.0 (C-11), 21.9 (C-1), 18.7 (C-21), 13.1 (C-18).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{34}H_{50}O_4Na^+$ $[M+Na]^+$ 545.3601 u, found: 545.3602 u.

4.7.9. 7β,19-Epoxycholest-4-ene-3,6-dione



To a solution of alcohol **329** (50 mg, 0.12 mmol, 1.0 eq.) in toluene (1.2 ml) was added *p*TsOH·H_2O (1.8 mg, 5.8 μmol, 0.05 eq.) at r.t. The reaction mixture was stirred at 70 °C for 7 h. After full the conversion of the starting material **329** was confirmed by TLC, the reaction mixture was diluted by addition of CH_2Cl_2 and aq. $NaHCO_3$ solution. The aq. phase was extracted four times with CH_2Cl_2, the combined org. phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *c*Hex/EtOAc, 6:1) and the desired endione **330** was obtained as a colorless solid (44 mg, 0.11 mmol, 92%).

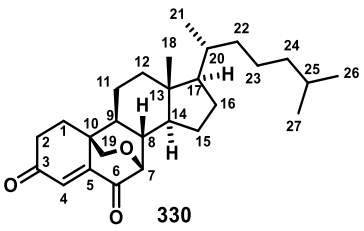
Formula: $C_{27}H_{40}O_3$

M: 412.61 g/mol

Yield: 92% (44 mg, 0.11 mmol).

M.p.: 127-128 °C.

R_f: 0.43 (SiO_2, 2:1, *c*Hex:EtOAc).



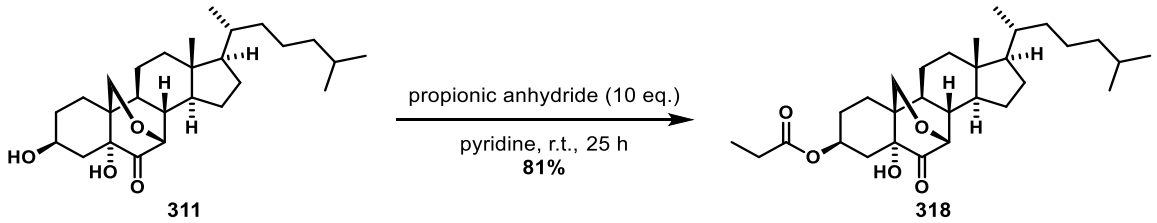
^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 6.42 (s, 1H, H-4), 4.03 (d, *J* = 8.9 Hz, 1H, H-19), 3.95 (s, 1H, H-7), 3.91 (d, *J* = 8.9 Hz, 1H, H-19), 2.50 – 2.43 (m, 2H, H-2), 2.23 (t, *J* = 10.9 Hz, 1H, H-8), 2.13 (dt, *J* = 13.2, 3.1 Hz, 1H, H-12), 2.06 – 1.96 (m, 1H, H-1), 1.95 – 1.83 (m, 2H, H-1, H-16), 1.70 – 1.62 (m, 1H, H-15), 1.62 – 1.47 (m, 3H, H-11, H-25), 1.44 – 1.06 (m, 12H, H-9, H-12, H-14, H-15, H-16, H-17, H-20, H-22, H-23, H-24), 1.03 – 0.96 (m, 1H, H-22), 0.90 (d, *J* = 6.5 Hz, 3H, H-21), 0.86 (dd, *J* = 6.6, 2.4 Hz, 6H, H-26, H-27), 0.78 (s, 3H, H-18).

^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 198.6 (C-3), 197.7 (C-6), 156.4 (C-5), 122.7 (C-4), 77.0 (C-7), 64.3 (C-19), 55.7 (C-17), 52.4 (C-14), 49.3 (C-9), 45.4 (C-13), 43.5 (C-8), 40.3 (C-12), 39.6 (C-24), 38.4 (C-10), 36.2 (C-22), 35.8 (C-20), 34.7 (C-2), 28.7 (C-16), 28.1 (C-25), 24.2 (C-1), 23.9 (C-23), 22.9 (C-26/27), 22.9 (C-15), 22.7 (C-26/27), 21.9 (C-11), 18.7 (C-21), 13.1 (C-18).

FT-IR (ATR): ν [cm^{-1}] = 2954 (m), 2933 (m), 2857 (m), 1724 (m), 1688 (s), 1632 (w), 1465 (m), 1453 (m), 1383 (w), 1366 (w), 1328 (w), 1274 (w), 1245 (w), 1231 (m), 1185 (m), 1113 (w), 1074 (w), 1035 (s), 974 (w), 932 (w), 904 (s), 879 (w), 857 (w), 828 (m), 811 (w), 780 (m), 766 (w), 720 (w), 653 (w), 634 (w), 571 (w), 548 (m), 529 (m), 507 (w).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{27}H_{41}O_3^+$ $[M+H]^+$ 413.3050 u, found: 413.3051 u;
m/z calc. for: $C_{27}H_{40}O_3Na^+$ $[M+Na]^+$ 435.28697 u, found: 435.28720 u.

4.7.10. 7β,19-Epoxy-5α-hydroxy-6-one-3β-cholesteryl-propionate



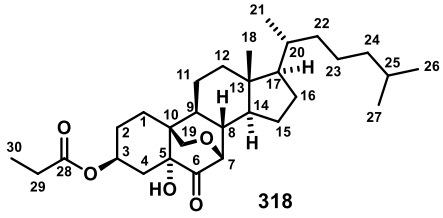
To a solution of alcohol **311** (100 mg, 0.232 mmol, 1.0 eq.) in pyridine (0.58 ml) was added propionic anhydride (0.30 ml, 2.32 mmol, 10 eq.) at r.t. The reaction mixture was stirred for 25 h and after confirmation of full conversion of the starting material it was diluted with EtOAc. The org. phase was washed twice with an aq. 1M HCl solution and once with water. The org. phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 10:1). The desired product **318** was obtained as a colorless solid in a yield of 92 mg (0.19 mmol, 81%).

Formula: $C_{30}H_{48}O_5$

M: 488.71 g/mol

M.p.: 50-55 °C.

R_f: 0.50 (SiO_2, 3:1, *c*Hex:EtOAc).



318

^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 5.23 (tt, *J* = 11.1, 5.5 Hz, 1H, H-3), 4.15 (dd, *J* = 10.1, 1.1 Hz, 1H, H-19), 3.91 (d, *J* = 10.2 Hz, 1H, H-19), 3.82 (d, *J* = 1.5 Hz, 1H, H-7), 2.61 (s, 1H, OH), 2.29 (q, *J* = 7.5 Hz, 2H, H-29), 2.13 – 2.03 (m, 3H, H-4, H-8, H-12), 2.00 – 1.93 (m, 2H, H-2, H-4), 1.91 – 1.82 (m, 1H, H-16), 1.73 (td, *J* = 13.9, 4.7 Hz, 1H, H-1), 1.65 – 1.47 (m, 4H, H-2, H-9, H-15, H-25), 1.44 – 1.07 (m, 17H, H-1, H-11, H-12, H-14, H-15, H-16, H-17, H-20, H-22, H-23, H-24, H-30), 1.02 – 0.95 (m, 1H, H-22), 0.89 (d, *J* = 6.6 Hz, 3H, H-21), 0.86 (dd, *J* = 6.7, 2.4 Hz, 6H, H-26, H-27), 0.74 (s, 3H, H-18).

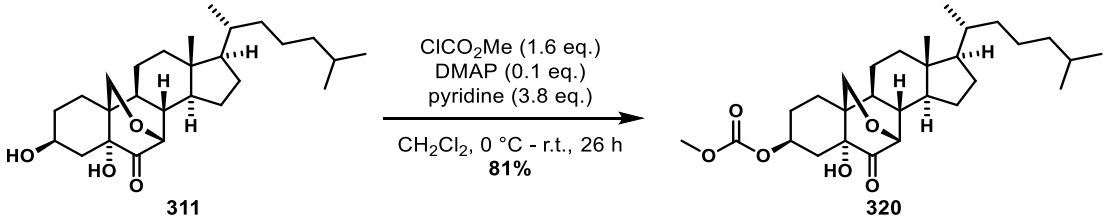
^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 212.9 (C-6), 174.0 (C-28), 78.7 (C-5), 76.2 (C-7), 68.9 (C-3), 63.6 (C-19), 55.7 (C-17), 52.0 (C-14), 45.5 (C-13), 45.1 (C-8), 43.2 (C-9), 40.5 (C-10), 40.2 (C-12), 39.6 (C-24), 36.2 (C-22), 35.8 (C-20), 35.3 (C-4), 28.6 (C-16), 28.1 (C-25), 28.0 (C-29), 26.2 (C-2), 23.9 (C-23), 22.9 (C-26/27), 22.9 (C-15), 22.7 (C-26/27), 21.7 (C-11), 21.3 (C-1), 18.7 (C-21), 13.1 (C-18), 9.3 (C-30).

FT-IR (ATR): ν [cm^{-1}] = 3444 (bw), 2947 (m), 2868 (m), 1737 (s), 1463 (m), 1381 (m), 1350 (m), 1275 (w), 1261 (w), 1181 (s), 1155 (m), 1082 (m), 1046 (m), 1022 (m), 975 (w), 952 (m), 889 (w), 869 (m), 824 (w), 808 (w), 757 (m), 711 (w), 663 (w), 637 (w), 559 (m).

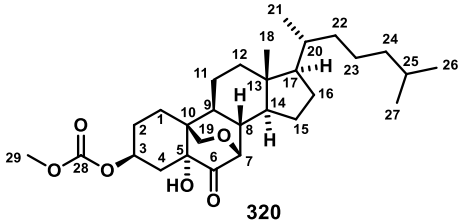
HR-MS: (GC-EI-MS, 70 eV) = *m/z* calc. for: $C_{30}H_{48}O_5$ $[M]^+$ 488.3496 u, found: 488.3490 u.

$[\alpha]_\lambda^{20}$: c = 0.56 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = 108.8° (± 0.2°), $[\alpha]_{436}^{20}$ = 64.4° (± 0.2°), $[\alpha]_{546}^{20}$ = 37.5° (± 0.0°), $[\alpha]_{579}^{20}$ = 32.4° (± 0.2°), $[\alpha]_{589}^{20}$ = 30.5° (± 0.0°).

4.7.11. 7β,19-Epoxy-5α-hydroxy-6-on-cholestan-3β-yl methyl-carbonate



To a solution of alcohol **311** (99 mg, 0.231 mmol, 1.0 eq.) in CH_2Cl_2 (0.49 ml) were added pyridine (0.07 ml, 8.8 mmol, 3.8 eq.), DMAP (3 mg, 0.025 mmol, 0.1 eq.) and methylchloroformiate (0.03 ml, 0.38 mmol, 1.6 eq.) at 0 °C. After 1.5 h at 0 °C, the reaction mixture was warmed to r.t. and continued to stir for further 24 h. After full conversion of the starting material, the reaction mixture was diluted with a aq. NaCl solution. The aq. phase was extracted twice with CH_2Cl_2. The combined org. phases were washed with an aq. 1M HCl solution, with a sat. aq. NaCl solution and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 10:1). The desired product **320** was obtained as a colorless solid (93 mg, 0.19 mmol, 81%).



Formula: $C_{29}H_{46}O_6$

M: 490.68 g/mol

M.p.: 64-65 °C.

R_f: 0.67 (SiO_2, 1:1, cHex:EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 5.09 (tt, *J* = 11.1, 5.4 Hz, 1H, H-3), 4.12 (dd, *J* = 10.4, 1.6 Hz, 1H, H-19), 3.90 (d, *J* = 10.3 Hz, 1H, H-19), 3.82 (d, *J* = 1.7 Hz, 1H, H-7), 3.77 (s, 3H, H-29), 2.63 (s, 1H, OH), 2.17 (ddd, *J* = 13.0, 5.2, 1.6 Hz, 1H, H-4), 2.13 – 1.99 (m, 4H, H-2, H-4, H-8, H-12), 1.86 (dtd, *J* = 13.1, 9.5, 5.9 Hz, 1H, H-16), 1.73 (td, *J* = 13.7, 4.5 Hz, 1H, H-1), 1.66 – 1.55 (m, 3H, H-2, H-9, H-15), 1.51 (dt, *J* = 13.2, 6.6 Hz, 1H, H-25), 1.43 – 1.07 (m, 14H, H-1, H-11, H-12, H-14, H-15, H-16, H-17, H-20, H-22, H-23, H-24), 1.02 – 0.95 (m, 1H, H-22), 0.89 (d, *J* = 6.5 Hz, 3H, H-21), 0.86 (dd, *J* = 6.6, 2.5 Hz, 6H, H-26, H-27), 0.74 (s, 3H, H-18).

^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 212.7 (C-6), 155.2 (C-28), 78.7 (C-5), 76.1 (C-7), 73.3 (C-3), 63.5 (C-19), 55.7 (C-17), 54.8 (C-29), 52.0 (C-14), 45.5 (C-13), 45.1 (C-8), 43.2 (C-9), 40.5 (C-10), 40.2 (C-12), 39.6 (C-24), 36.2

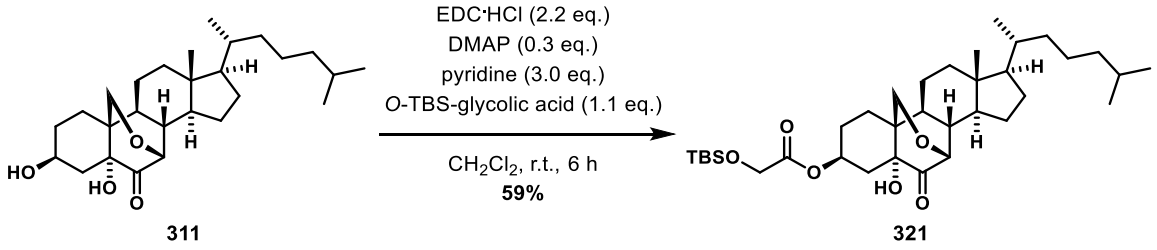
(C-22), 35.8 (C-20), 35.2 (C-4), 28.6 (C-16), 28.1 (C-25), 26.2 (C-2), 23.9 (C-23), 22.9 (C-26/27), 22.9 (C-15), 22.7 (C-26/27), 21.7 (C-11), 21.2 (C-1), 18.7 (C-21), 13.1 (C-18).

FT-IR (ATR): ν [cm^{-1}] = 3457 (bw), 2950 (m), 2867 (w), 1743 (s), 1443 (m), 1383 (w), 1320 (w), 1269 (s), 1258 (s), 1227 (m), 1171 (w), 1154 (w), 1046 (m), 1018 (m), 952 (m), 935 (m), 877 (w), 825 (w), 792 (m), 757 (w), 721 (w), 664 (w), 625 (w), 559 (w), 530 (w).

HR-MS: (GC-EI-MS, 70 eV) = *m/z* calc. for: $C_{27}H_{46}O_6$ $[M]^+$ 490.3289 u, found: 490.3283 u.

$[\alpha]_\lambda^{20}$: c = 0.58 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = 105.1° (± 0.1°), $[\alpha]_{436}^{20}$ = 61.2° (± 0.0°), $[\alpha]_{546}^{20}$ = 35.3° (± 0.0°), $[\alpha]_{579}^{20}$ = 30.5° (± 0.1°), $[\alpha]_{589}^{20}$ = 28.8° (± 0.0°).

4.7.12. (*tert*-Butyldimethylsilanyloxy)acetic acid (7β,19-epoxy-5α-hydroxy-6-one-cholestane-3β-yl) ester



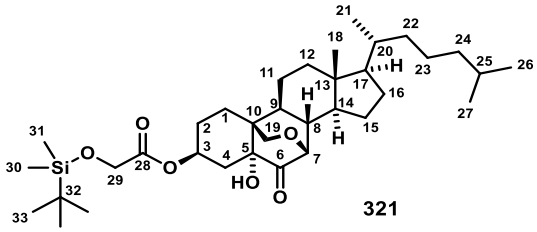
To a solution of alcohol **311** (198 mg, 0.458 mmol, 1.0 eq.) in 4.6 ml CH_2Cl_2 was added pyridine (0.12 ml, 1.5 mmol, 3.4 eq.), EDC·HCl (197 mg, 1.02 mmol, 2.2 eq.), DMAP (18 mg, 0.14 mmol, 0.3 eq.) and 2-(*tert*-butyldimethylsilyloxy)AcOH (98 mg, 0.51 mmol, 1.1 eq.) under an argon atmosphere. The reaction mixture was stirred for 6 h at r.t. and it was diluted with EtOAc after full conversion of the starting material (TLC). The org. phase was washed with a sat. aq. $NaHCO_3$ solution, water and a sat. aq. NaCl solution. The org. phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 20:1) and the desired product **321** was obtained as a colorless solid (165 mg, 0.273 mmol, 59%). Additionally, the undesired sideproduct **351** was isolated as a colorless solid (53 mg, 0.080 mmol, 17%).

Formula: $C_{35}H_{60}O_6Si$

M: 604.94 g/mol

M.p.: 139-140 °C.

R_f: 0.59 (SiO_2, 3:1, cHex:EtOAc).



321

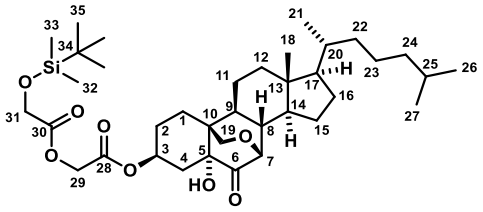
^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 5.29 (dt, *J* = 11.3, 5.6 Hz, 1H, H-3), 4.20 (s, 2H, H-29), 4.12 (d, *J* = 9.3 Hz, 1H, H-19), 3.90 (d, *J* = 10.2 Hz, 1H, H-19), 3.81 (d, *J* = 1.5 Hz, 1H, H-7), 2.60 (s, 1H, OH), 2.13 – 1.94 (m, 5H, H-2, H-4, H-8, H-12), 1.91 – 1.81 (m, 1H, H-16), 1.73 (td, *J* = 13.9, 4.7 Hz, 1H, H-1), 1.64 – 1.46 (m, 4H, H-2, H-9, H-15, H-25), 1.43 – 1.06 (m, 14H, H-1, H-11, H-12, H-14, H-15, H-16, H-17, H-20, H-22, H-23, H-24), 1.02 – 0.95 (m, 1H, H-22), 0.91 (s, 9H, H-33), 0.89 (d, *J* = 6.6 Hz, 3H, H-21), 0.85 (dd, *J* = 6.6, 2.4 Hz, 6H, H-26, H-27), 0.74 (s, 3H, H-18), 0.09 (d, *J* = 1.3 Hz, 6H, H-30, H-31).

^{13}C NMR: (151 MHz, $CDCl_3$) δ [ppm]: 212.7 (C-6), 171.3 (C-28), 78.6 (C-5), 76.2 (C-7), 69.8 (C-3), 63.5 (C-19), 62.1 (C-29), 55.7 (C-17), 52.0 (C-14), 45.5 (C-13), 45.1 (C-8), 43.2 (C-9), 40.5 (C-10), 40.2 (C-12), 39.6 (C-24), 36.2 (C-22), 35.8 (C-20), 35.2 (C-4), 28.6 (C-16), 28.1 (C-25), 26.2 (C-2), 25.9 (C-33), 23.9 (C-23), 22.9 (C-26/27), 22.9 (C-15), 22.7 (C-26/27), 21.7 (C-11), 21.2 (C-1), 18.7 (C-21), 18.5 (C-32), 13.1 (C-18), -5.3 (C-30/31), -5.3 (C-30/31).

FT-IR (ATR): ν [cm^{-1}] = 3494 (w), 2952 (m), 2931 (m), 2896 (w), 2858 (w), 1741 (m), 1495 (w), 1463 (w), 1441 (w), 1383 (w), 1361 (w), 1252 (m), 1221 (m), 1187 (w), 1147 (s), 1085 (w), 1048 (m), 1021 (m), 977 (w), 961 (w), 888 (w), 835 (s), 780 (s), 755 (m), 712 (m), 663 (w), 636 (w), 602 (w), 559 (w), 474 (w), 434 (w).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{35}H_{60}O_6SiNa$ $[M+Na]^+$ 627.4051 u, found: 627.4056 u.

$[\alpha]_\lambda^{20}$: c = 0.53 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = 97.9° (± 0.1°), $[\alpha]_{436}^{20}$ = 58.6° (± 0.1°), $[\alpha]_{546}^{20}$ = 34.5° (± 0.2°), $[\alpha]_{579}^{20}$ = 30.3° (± 0.4°), $[\alpha]_{589}^{20}$ = 28.3° (± 0.2°).



351

Formula: $C_{37}H_{62}O_8Si$

M: 662.98 g/mol

M.p.: 170-171 °C.

R_f: 0.48 (SiO_2, 3:1, *c*Hex:EtOAc).

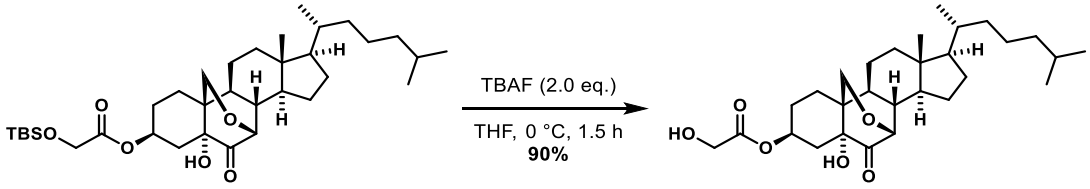
^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 5.33 (tt, *J* = 11.1, 5.5 Hz, 1H, H-3), 4.69 – 4.60 (m, 2H, H-29), 4.38 (s, 2H, H-31), 4.14 (dd, *J* = 10.3, 1.8 Hz, 1H, H-19), 3.93 (d, *J* = 10.2 Hz, 1H, H-19), 3.84 (d, *J* = 1.7 Hz, 1H, H-7), 2.63 (s, 1H, OH), 2.15 – 1.98 (m, 5H, H-2, H-4, H-8, H-12), 1.93 – 1.84 (m, 1H, H-16), 1.75 (td, *J* = 13.8, 4.7 Hz, 1H, H-1), 1.65 – 1.49 (m, 4H, H-2, H-9, H-15, H-25), 1.44 – 1.08 (m, 14H, H-1, H-11, H-12, H-14, H-15, H-16, H-17, H-20, H-22, H-23, H-24), 1.04 – 0.97 (m, 1H, H-22), 0.94 (s, 9H, H-35), 0.91 (d, *J* = 6.5 Hz, 3H, H-21), 0.88 (dd, *J* = 6.6, 2.4 Hz, 6H, H-26, H-27), 0.76 (s, 3H, H-18), 0.14 (s, 6H, H-32, H-33).

^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 212.6 (C-6), 171.3 (C-30), 167.0 (C-28), 78.6 (C-5), 76.1 (C-7), 70.8 (C-3), 63.5 (C-19), 61.6 (C-31), 61.0 (C-29), 55.7 (C-17), 52.0 (C-14), 45.5 (C-13), 45.1 (C-8), 43.2 (C-9), 40.5 (C-10), 40.2 (C-12), 39.6 (C-24), 36.2 (C-22), 35.8 (C-20), 35.1 (C-4), 28.6 (C-16), 28.1 (C-25), 26.1 (C-2), 25.9 (C-35), 23.9 (C-23), 22.9 (C-26/27), 22.9 (C-15), 22.7 (C-26/27), 21.7 (C-11), 21.2 (C-1), 18.7 (C-21), 18.5 (C-34), 13.1 (C-18), -5.3 (C-32, C-33).

FT-IR (ATR): ν [cm^{-1}] = 3523 (w), 2950 (m), 2930 (m), 2885 (w), 2858 (w), 1771 (m), 1754 (m), 1739 (m), 1470 (w), 1444 (w), 1389 (w), 1367 (w), 1255 (w), 1223 (w), 1180 (m), 1141 (s), 1040 (m), 1018 (w), 975 (w), 956 (w), 891 (w), 880 (w), 836 (s), 782 (m), 760 (m), 729 (w), 693 (w), 663 (w), 635 (w), 561 (w), 545 (w), 454 (w), 408 (w).

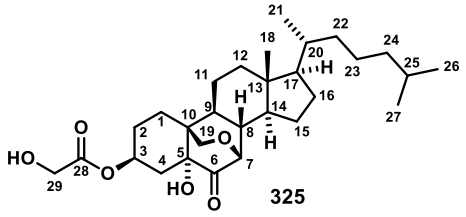
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{37}H_{62}O_8SiNa$ $[M+Na]^+$ 685.4106 u, found: 685.4103 u.

4.7.13. 7β,19-Epoxy-5α-hydroxy-6-on-cholestan-3β-glycolate



321 325

A solution of the TBS-ether **321** (104 mg, 0.172 mmol, 1.0 eq.) in 1.7 ml THF was cooled to 0 °C and subsequently TBAF (0.34 ml, 0.34 mmol, 2.0 eq., 1M in THF) was added. The reaction mixture was stirred for 1.5 h and after full conversion of the starting material (TLC) a sat. aq. NaCl solution (1 ml) was added. The aq. phase was extracted thrice with EtOAc (3x 15 ml), the combined org. phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 3:1) and the desired product **325** was obtained as a colorless solid (76 mg, 0.15 mmol, 90%).


325

Formula: $C_{29}H_{46}O_6$

M: 490.68 g/mol

M.p.: 164-166 °C.

R_f: 0.17 (SiO_2, 2:1, *c*Hex:EtOAc).

^{1}H NMR: (600 MHz, $CDCl_3$) δ [ppm]: 5.36 (tt, *J* = 11.2, 5.5 Hz, 1H, H-3), 4.15 – 4.09 (m, 3H, H-19, H-29), 3.92 (d, *J* = 10.3 Hz, 1H, H-19), 3.83 (d, *J* = 1.7 Hz, 1H, H-7), 2.80 (s, 1H, OH-5), 2.49 (t, *J* = 5.4 Hz, 1H, OH-29), 2.15 – 2.04 (m, 3H, H-4, H-8, H-12), 2.03 – 1.97 (m, 2H, H-2, H-4), 1.87 (dtd, *J* = 13.1, 9.4, 6.0 Hz, 1H, H-16), 1.75 (td, *J* = 13.9, 4.7 Hz, 1H, H-1), 1.64 – 1.55 (m, 3H, H-2, H-9, H-15), 1.54 – 1.48 (m, 1H, H-25), 1.42 – 1.05 (m, 14H, H-1, H-11, H-12, H-14, H-15, H-16, H-17, H-20, H-22, H-23, H-24), 1.02 – 0.95 (m, 1H, H-22), 0.89 (d, *J* = 6.5 Hz, 3H, H-21), 0.86 (dd, *J* = 6.6, 2.9 Hz, 6H, H-26, H-27), 0.74 (s, 3H, H-18).

^{13}C NMR: (151 MHz, $CDCl_3$) δ [ppm]: 212.8 (C-6), 173.0 (C-28), 78.6 (C-5), 76.2 (C-7), 70.9 (C-3), 63.5 (C-19), 60.9 (C-29), 55.7 (C-17), 52.0 (C-14), 45.5 (C-13), 45.1 (C-8), 43.2 (C-9), 40.5 (C-10), 40.2 (C-12), 39.6 (C-24), 36.2 (C-22), 35.8 (C-20), 35.2 (C-4), 28.6 (C-16), 28.1 (C-25), 26.2 (C-2), 23.9

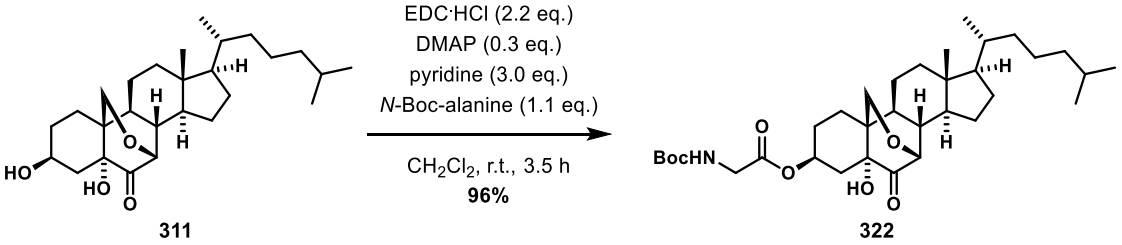
(C-23), 22.9 (C-26/27), 22.9 (C-15), 22.7 (C-26/27), 21.7 (C-11), 21.2 (C-1), 18.7 (C-21), 13.1 (C-18).

FT-IR (ATR): ν [cm^{-1}] = 3454 (bw), 2949 (m), 1932 (m), 2867 (m), 1738 (s), 1465 (m), 1446 (m), 1383 (m), 1366 (w), 1223 (s), 1208 (s), 1155 (m), 1097 (s), 1087 (s), 1045 (s), 1020 (m), 973 (m), 961 (m), 920 (w), 888 (w), 824 (m), 780 (w), 757 (m), 716 (w), 663 (w), 637 (w), 559 (m), 522 (m), 477 (m), 431 (m).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{29}H_{46}O_6Na$ $[M+Na]^+$ 513.3187 u, found: 513.3186 u.

$[\alpha]_\lambda^{20}$: c = 0.56 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = 95.6° (± 0.3°), $[\alpha]_{436}^{20}$ = 58.0° (± 0.1°), $[\alpha]_{546}^{20}$ = 34.2° (± 0.2°), $[\alpha]_{579}^{20}$ = 30.1° (± 0.2°), $[\alpha]_{589}^{20}$ = 28.2° (± 0.1°).

4.7.14. *N*-Boc-Glycine (7β,19-epoxy-5α-hydroxy-6-one-cholestan-3β-yl) ester



To a solution of alcohol **311** (199 mg, 0.460 mmol, 1.0 eq.) in 4.6 ml CH_2Cl_2 was added pyridine (0.12 ml, 1.5 mmol, 3.4 eq.), EDC·HCl (195 mg, 1.02 mmol, 2.2 eq.), DMAP (18 mg, 0.14 mmol, 0.3 eq.) and *N*-Boc-glycine (89 mg, 0.51 mmol, 1.1 eq.) under an argon atmosphere. The solution was stirred at r.t. for 3.5 h and diluted with EtOAc (20 ml) after full conversion of the starting material **311** (TLC). The org. phase was washed with a sat. aq. $NaHCO_3$ solution, water and with a sat. aq. NaCl solution. The org. phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 10:1) and the desired product **322** was obtained as a colorless solid (262 mg, 0.444 mmol, 96%).

Formula: $C_{34}H_{55}NO_7$

M: 589.81 g/mol

M.p.: 76-77 °C.

R_f: 0.42 (SiO_2, 3:1, *c*Hex:EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 5.29 (tt, *J* = 11.1, 5.5 Hz, 1H, H-3), 5.04 – 4.71 (m, 1H, NH), 4.12 (d, *J* = 10.8 Hz, 1H, H-19), 3.94 – 3.78 (m, 4H, H-29, H-19, H-7), 2.64 (s, 1H, OH), 2.12 – 1.95 (m, 5H, H-2, H-4, H-7, H-12), 1.91 – 1.81 (m, 1H, H-16), 1.73 (td, *J* = 13.7, 4.6 Hz, 1H, H-1), 1.63 – 1.54 (m, 4H, H-2, H-9, H-15), 1.50 (dt, *J* = 13.3, 6.6 Hz, 1H, H-25), 1.45 (s, 9H, H-32), 1.41 – 1.05 (m, 13H, H-1, H-11, H-12, H-14, H-16, H-17, H-20, H-22, H-23, H-24), 0.98 (q, *J* = 9.1 Hz, 1H, H-22), 0.89 (d, *J* = 6.6 Hz, 3H, H-21), 0.85 (dd, *J* = 6.6, 2.4 Hz, 6H, H-26, H-27), 0.74 (s, 3H, H-18).

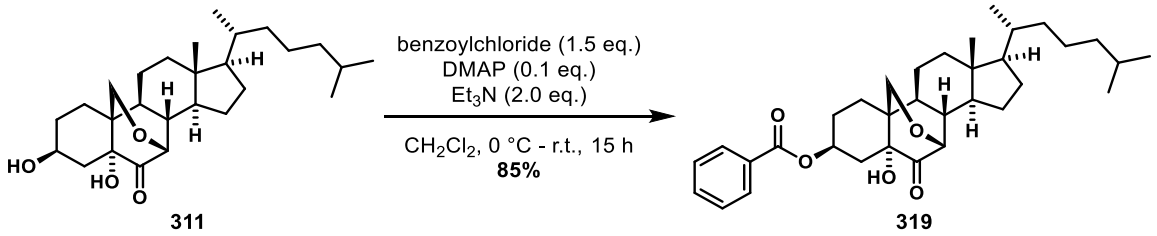
^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 212.7 (C-6), 169.9 (C-28), 155.8 (C-30), 80.1 (C-31), 78.6 (C-5), 76.2 (C-7), 70.5 (C-3), 63.5 (C-19), 55.7 (C-17), 52.0 (C-14), 45.5 (C-13), 45.1 (C-8), 43.2 (C-9), 42.8 (C-29), 40.5 (C-10), 40.2 (C-12), 39.6 (C-24), 36.2 (C-22), 35.8 (C-20), 35.2 (C-4), 28.6 (C-16), 28.5 (C-32), 28.1 (C-25), 26.2 (C-2), 23.9 (C-23), 22.9 (C-26/27), 22.9 (C-15), 22.7 (C-26/27), 21.7 (C-11), 21.2 (C-1), 18.7 (C-21), 13.1 (C-18).

FT-IR (ATR): ν [cm^{-1}] = 3387 (bw), 2951 (m), 2869 (m), 1740 (s), 1720 (s), 1513 (m), 1467 (w), 1384 (m), 1366 (m), 1282 (w), 1251 (m), 1204 (m), 1169 (s), 1051 (m), 970 (w), 918 (w), 867 (w), 825 (w), 757 (w), 734 (w), 559 (w).

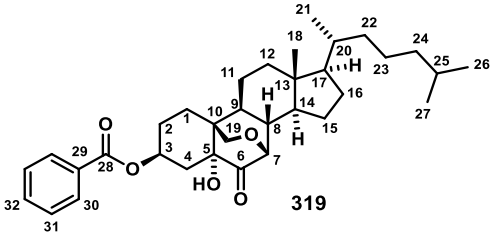
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{34}H_{55}NO_7Na$ $[M+Na]^+$ 612.3871 u, found: 612.3875 u.

$[\alpha]_\lambda^{20}$: c = 0.575 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = 94.9° (± 0.2°), $[\alpha]_{436}^{20}$ = 56.9° (± 0.0°), $[\alpha]_{546}^{20}$ = 33.4° (± 0.0°), $[\alpha]_{579}^{20}$ = 29.0° (± 0.1°), $[\alpha]_{589}^{20}$ = 27.4° (± 0.1°).

4.7.15.Benzoic acid (7β,19-epoxy-5α-hydroxy-6-one-cholestan-3β-yl) ester



To a solution of alcohol **311** (150 mg, 0.347 mmol, 1.0 eq.), DMAP (6 mg, 0.05 mmol, 0.1 eq.) and triethylamine (0.10 ml, 0.69 mmol, 2.0 eq.) in 2.3 ml CH_2Cl_2 was added benzoylchloride (0.06 ml, 0.52 mmol, 1.5 eq.) at 0 °C under an argon atmosphere. The solution was stirred for 15 min at 0 °C, subsequently warmed to r.t. and stirred for further 15 h at r.t. After full conversion of the starting material **311** (TLC), the reaction mixture was diluted with CH_2Cl_2 (10 ml) and water (15 ml). The aq. phase was extracted thrice with CH_2Cl_2 (3x 10 ml), the combined org. phases were washed with a sat. aq. NaCl solution (15 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 40:1 → 15:1). The desired product **319** was isolated as a colorless solid (158 mg, 0.294 mmol, 85%).



Formula: $C_{34}H_{48}O_5$

M: 536.75 g/mol

M.p.: 151-152 °C.

R_f: 0.55 (SiO_2, 3:1, *c*Hex:EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 8.04 – 7.99 (m, 2H, H-30), 7.58 – 7.52 (m, 1H, H-32), 7.43 (t, *J* = 7.8 Hz, 2H, H-31), 5.48 (tt, *J* = 11.0, 5.5 Hz, 1H, H-3), 4.23 (dd, *J* = 10.3, 1.7 Hz, 1H, H-19), 3.95 (d, *J* = 10.3 Hz, 1H, H-19), 3.84 (d, *J* = 1.7 Hz, 1H, H-7), 2.68 (s, 1H, OH), 2.23 (ddd, *J* = 13.0, 5.3, 1.5 Hz, 1H, H-4), 2.17 – 2.04 (m, 4H, H-2, H-4, H-8, H-12), 1.93 – 1.76 (m, 2H, H-1, H-16), 1.76 – 1.56 (m, 3H, H-2, H-9, H-15), 1.51 (dt, *J* = 13.1, 6.6 Hz, 1H, H-25), 1.46 – 1.06 (m, 14H, H-1, H-11, H-12, H-14, H-15, H-16, H-17, H-20, H-22, H-23, H-24), 1.03 – 0.96 (m, 1H, H-22), 0.90 (d, *J* = 6.5 Hz, 3H, H-21), 0.86 (dd, *J* = 6.6, 2.4 Hz, 6H, H-26, H-27), 0.75 (s, 3H, H-18).

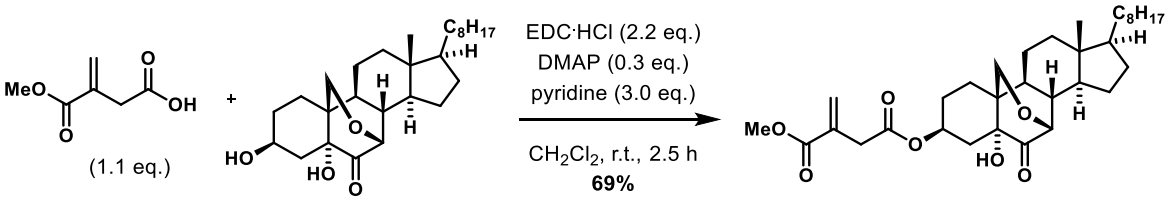
^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 212.9 (C-6), 166.0 (C-28), 133.0 (C-32), 130.6 (C-29), 129.7 (C-30), 128.5 (C-31), 78.7 (C-5), 76.2 (C-7), 69.8 (C-3), 63.6 (C-19), 55.7 (C-17), 52.0 (C-14), 45.5 (C-13), 45.1 (C-8), 43.3 (C-9), 40.6 (C-10), 40.3 (C-12), 39.6 (C-24), 36.2 (C-22), 35.8 (C-20), 35.4 (C-4), 28.7 (C-16), 28.1 (C-25), 26.4 (C-2), 23.9 (C-23), 22.9 (C-26/27), 22.9 (C-15), 22.7 (C-26/27), 21.7 (C-11), 21.3 (C-1), 18.8 (C-21), 13.1 (C-18).

FT-IR (ATR): ν [cm^{-1}] = 3423 (bw), 2949 (m), 2867 (m), 1739 (m), 1717 (m), 1603 (w), 1585 (w), 1493 (w), 1451 (w), 1382 (w), 1316 (w), 1273 (s), 1227 (m), 1175 (w), 1152 (w), 1112 (m), 1069 (m), 1046 (m), 1027 (m), 954 (m), 887 (w), 856 (w), 822 (w), 757 (w), 710 (s), 686 (m), 663 (w), 637 (w), 600 (w), 559 (m), 524 (w).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{34}H_{49}O_5$ $[M+H]^+$ 537.3575 u, found: 537.3577 u; $C_{34}H_{48}O_5Na$ $[M+Na]^+$ 559.3394 u, found: 559.3394.

$[\alpha]_\lambda^{20}$: c = 0.56 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = 201.6° (± 0.3°), $[\alpha]_{436}^{20}$ = 111.6° (± 0.2°), $[\alpha]_{546}^{20}$ = 63.6° (± 0.4°), $[\alpha]_{579}^{20}$ = 55.4° (± 0.3°), $[\alpha]_{589}^{20}$ = 52.7° (± 0.4°).

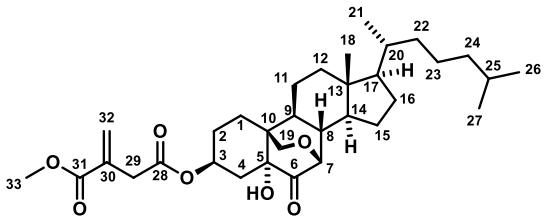
4.7.16. Itaconic acid 4-(7β,19-epoxy-5α-hydroxy-6-one-cholestane-3β-yl)-1-methyl ester



311 323

To a solution of alcohol **311** (73 mg, 0.169 mmol, 1.0 eq.) in 1.7 ml CH_2Cl_2 was added pyridine (0.042 ml, 0.54 mmol, 3.2 eq.), EDC·HCl (74 mg, 0.39 mmol, 2.3 eq.), DMAP (8 mg, 0.07 mmol, 0.4 eq.) and itaconic acid methylester (28 mg, 0.19 mmol, 1.1 eq.) under an argon atmosphere. The reaction mixture was stirred for 2.5 h at r.t. and after full conversion of the starting material (TLC), the solution was diluted with EtOAc (10 ml). The org. phase was washed with a sat. aq. $NaHCO_3$ solution, water and a sat. aq. NaCl solution (each time 5 ml). Afterwards, the org. phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was

purified by column chromatography (SiO_2, *c*Hex/EtOAc, 10:1 – 8:1) and the desired product **323** was obtained as a colorless solid (65 mg, 0.12 mmol, 69%).



323

Formula: $C_{33}H_{50}O_7$

M: 558.76 g/mol

M.p.: 132-134 °C.

R_f: 0.39 (SiO_2, 3:1, *c*Hex:EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 6.31 (d, *J* = 1.0 Hz, 1H, H-32), 5.69 (d, *J* = 1.1 Hz, 1H, H-32), 5.25 (tt, *J* = 11.1, 5.4 Hz, 1H, H-3), 4.13 (d, *J* = 10.5 Hz, 1H, H-19), 3.90 (d, *J* = 10.2 Hz, 1H, H-19), 3.81 (d, *J* = 1.7 Hz, 1H, H-7), 3.76 (s, 3H, H-33), 3.30 (d, *J* = 1.1 Hz, 2H, H-29), 2.57 (s, 1H, OH), 2.12 – 2.02 (m, 3H, H-8, H-12, H-4), 2.00 – 1.94 (m, 2H, H-1, H-4), 1.91 – 1.82 (m, 1H, H-16), 1.72 (td, *J* = 13.8, 4.7 Hz, 1H, H-1), 1.63 – 1.47 (m, 4H, H-9, H-15, H-25), 1.42 – 1.06 (m, 14H, H-1, H-11, H-12, H-14, H-15, H-16, H-17, H-20, H-22, H-23, H-24), 1.02 – 0.95 (m, 1H, H-22), 0.89 (d, *J* = 6.5 Hz, 3H, H-21), 0.86 (dd, *J* = 6.6, 2.4 Hz, 6H, H-26, H-27), 0.74 (s, 3H, H-18).

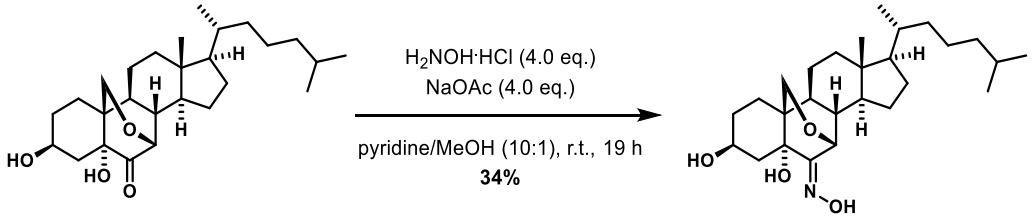
^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 212.8 (C-6), 170.1 (C-28), 166.8 (C-31), 133.9 (C-30), 128.6 (C-32), 78.7 (C-5), 76.2 (C-7), 69.8 (C-3), 63.5 (C-19), 55.7 (C-17), 52.3 (C-33), 52.0 (C-14), 45.5 (C-13), 45.1 (C-8), 43.2 (C-9), 40.5 (C-10), 40.2 (C-12), 39.6 (C-24), 38.2 (C-29), 36.2 (C-22), 35.8 (C-20), 35.1 (C-4), 28.6 (C-16), 28.1 (C-25), 26.1 (C-2), 23.9 (C-23), 22.9 (C-26/27), 22.9 (C-15), 22.7 (C-26/27), 21.7 (C-11), 21.2 (C-1), 18.7 (C-21), 13.1 (C-18).

FT-IR (ATR): ν [cm^{-1}] = 3422 (bw), 2951 (w), 2930 (w), 2866 (w), 1731 (s), 1644 (w), 1457 (w), 1434 (w), 1375 (w), 1333 (m), 1301 (w), 1201 (s), 1178 (s), 1146 (m), 1097 (w), 1040 (m), 1033 (m), 1023 (m), 975 (w), 956 (m), 936 (w), 920 (w), 884 (w), 826 (m), 813 (m), 783 (w), 754 (m), 712 (w), 644 (w), 584 (w), 562 (m), 545 (w), 459 (w).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{34}H_{50}O_7$ $[M+H]^+$ 559.36293 u, found: 559.36329 u; $C_{33}H_{50}O_7Na$ $[M+Na]^+$ 581.3449 u, found: 581.3451 u.

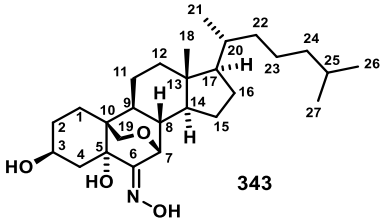
$[\alpha]_\lambda^{20}$: c = 0.52 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = 75.0°, $[\alpha]_{436}^{20}$ = 64.8°, $[\alpha]_{546}^{20}$ = 38.1°, $[\alpha]_{579}^{20}$ = 33.7°, $[\alpha]_{589}^{20}$ = 33.8°.

4.7.17. 7β,19-Epoxy-3β,5α-hydroxy-cholestane-6-one oxime



311 343

To a solution of ketone **311** (101 mg, 0.231 mmol, 1.0 eq.) in 2.3 ml pyridine was added hydroxylamine hydrochloride (64 mg, 0.93 mmol, 4.0 eq.) and a solution of sodium acetate (78 mg, 0.93 mmol, 4.0 eq.) in 0.5 ml MeOH at r.t. The reaction mixture was stirred for 19 h at r.t. and after full conversion of the starting material (TLC) EtOAc (5 ml) was added. The org. phase was washed with a diluted aq. NaCl solution (3 ml), water (3 ml), a sat. aq. $CuSO_4$ solution (3 ml) and a sat. aq. NaCl solution (3 ml). The org. phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was recrystallized from MeOH and traces of EtOAc and water. The desired product **343** was obtained as a colorless solid (35 mg, 0.078 mmol, 34%).



343

Formula: $C_{27}H_{45}NO_4$

M: 447.66 g/mol

M.p.: 266-267 °C (decomposition).

R_f: 0.09 (SiO_2, 1:1, *c*Hex:EtOAc); 0.45 (SiO_2, 5:5:1, *c*Hex:EtOAc:MeOH)

^{1}H NMR: (600 MHz, DMSO-d_6) δ [ppm]: 11.02 (s, 1H, OH-*N*), 4.62 (s, 1H, OH-5), 4.36 (d, *J* = 5.9 Hz, 1H, OH-3), 3.84 (d, *J* = 9.5 Hz, 2H, H-3, H-19), 3.69 (s, 1H, H-7), 3.59 (d, *J* = 9.9 Hz, 1H, H-19), 1.95 (d, *J* = 12.7 Hz, 1H, H-12), 1.82 – 1.65 (m, 3H, H-8, H-9, H-2), 1.65 – 1.57 (m, 1H, H-16), 1.55 – 1.43 (m, 3H, H-1, H-4, H-25), 1.42 – 1.17 (m, 8H, H-1, H-2, H-11, H-15, H-16, H-20, H-22, H-23), 1.17 – 0.99 (m, 8H, H-7, H-11, H-12, H-14, H-15, H-23, H-24), 0.97 – 0.90 (m, 1H, H-22), 0.85 (d, *J* = 6.5 Hz, 3H, H-21), 0.81 (dd, *J* = 6.6, 2.9 Hz, 6H, H-26, H-27), 0.67 (s, 3H, H-18).

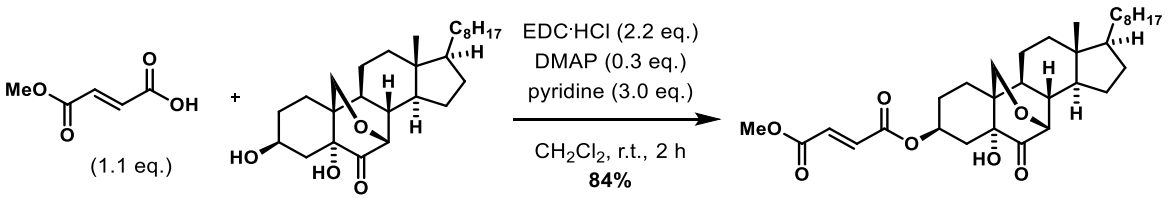
^{13}C NMR: (151 MHz, DMSO-d_6) δ [ppm]: 158.8 (C-6), 74.7 (C-5), 71.5 (C-7), 63.8 (C-3), 62.8 (C-19), 55.2 (C-17), 52.2 (C-14), 44.8 (C-13), 44.3 (C-8), 42.5 (C-9), 40.2 (C-12), 38.9 (C-24), 38.8 (C-10), 38.0 (C-4), 35.7 (C-22), 35.1 (C-20), 29.9 (C-16), 28.2 (C-2), 27.4 (C-25), 23.2 (C-23), 22.7 (C-26/27),

22.4 (C-15), 22.4 (C-26/27), 21.1 (C-1/11), 21.1 (C-1/11), 18.5 (C-21), 12.8 (C-18).

FT-IR (ATR): ν [cm^{-1}] = 3511 (bw), 3290 (bw), 3197 (bw), 3111 (bw), 2954 (m), 2939 (m), 2921 (m), 2867 (m), 1493 (w), 1469 (m), 1444 (w), 1418 (w), 1384 (w), 1375 (w), 1362 (w), 1337 (w), 1307 (w), 1251 (w), 1208 (w), 1181 (w), 1157 (m), 1131 (w), 1098 (w), 1069 (w), 1042 (m), 1018 (m), 986 (m), 944 (s), 906 (m), 894 (w), 873 (w), 838 (w), 811 (m), 789 (m), 733 (m), 712 (w), 666 (w), 605 (w), 593 (w), 578 (w), 562 (m), 488 (w), 462 (w), 443 (w).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{27}H_{46}NO_4$ $[M+H]^+$ 448.3421 u, found: 448.3420 u.

4.7.18. Fumaric acid 4-(7β,19-epoxy-5α-hydroxy-6-one-cholestane-3β-yl) 1-methyl ester



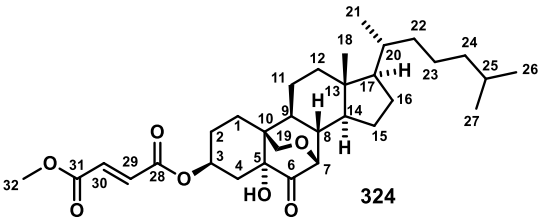
To a solution of alcohol **311** (100 mg, 0.23 mmol, 1.0 eq.) in 2.3 ml CH_2Cl_2 was added pyridine (0.06 ml, 0.69 mmol, 3.0 eq.), EDC·HCl (97 mg, 0.051 mmol, 2.2 eq.), DMAP (8 mg, 0.07 mmol, 0.3 eq.) and fumaric acid monomethylester (37 mg, 0.25 mmol, 1.1 eq.) under an argon atmosphere. The resulting reaction mixture was stirred for 2 h at r.t. After full conversion of the starting material (TLC), the reaction mixture was diluted with EtOAc (20 ml). The org. phase was washed with a sat. aq. $NaHCO_3$ solution (10 ml), water (10 ml) and a sat. aq. NaCl solution (10 ml). The org. phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 8:1 → 6:1) and the desired product **324** was obtained as a colorless solid (106 mg, 0.195 mmol, 84%).

Formula: $C_{32}H_{48}O_7$

M: 544.73 g/mol

M.p.: 153-154 °C.

R_f: 0.20 (SiO_2, 6:1, *c*Hex:EtOAc).



324

^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 6.85 (d, *J* = 1.1 Hz, 2H, H-29, H-30), 5.36 (tt, *J* = 11.1, 5.5 Hz, 1H, H-3), 4.17 (dd, *J* = 10.3, 1.7 Hz, 1H, H-19), 3.94 (d, *J* = 10.3 Hz, 1H, H-19), 3.85 (d, *J* = 1.7 Hz, 1H, H-7), 3.83 (s, 3H, H-32), 2.67 (s, 1H, OH-5), 2.18 – 2.01 (m, 5H, H-2, H-4, H-8, H-12), 1.94 – 1.84 (m, 1H, H-16), 1.77 (td, *J* = 13.8, 4.6 Hz, 1H, H-1), 1.69 – 1.57 (m, 3H, H-2, H-9, H-15), 1.53 (dt, *J* = 13.1, 6.6 Hz, 1H, H-20), 1.45 – 1.08 (m, 14H, H-1, H-11, H-12, H-14, H-15, H-16, H-17, H-22, H-23, H-24, H-25), 1.04 – 0.97 (m, 1H, H-22), 0.91 (d, *J* = 6.5 Hz, 3H, H-21), 0.88 (dd, *J* = 6.6, 2.4 Hz, 6H, H-26, H-27), 0.76 (s, 3H, H-18).

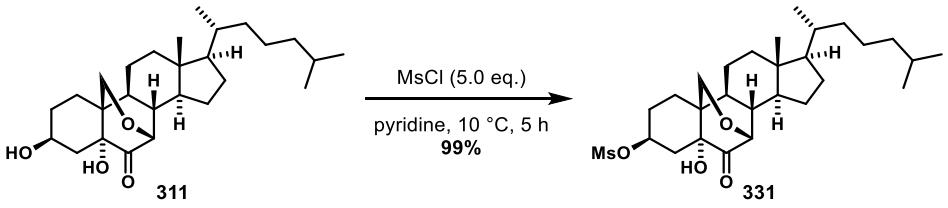
^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 212.7 (C-6), 165.5 (C-31), 164.4 (C-28), 134.1 (C-29), 133.4 (C-30), 78.6 (C-5), 76.2 (C-7), 70.5 (C-3), 63.5 (C-19), 55.7 (C-17), 52.5 (C-32), 52.0 (C-14), 45.5 (C-13), 45.1 (C-8), 43.2 (C-9), 40.5 (C-10), 40.2 (C-12), 39.6 (C-24), 36.2 (C-22), 35.8 (C-20), 35.2 (C-4), 28.6 (C-16), 28.1 (C-25), 26.1 (C-2), 23.9 (C-23), 22.9 (C-26/27), 22.9 (C-15), 22.7 (C-26/27), 21.7 (C-11), 21.2 (C-1), 18.7 (C-21), 13.1 (C-18).

FT-IR (ATR): ν [cm^{-1}] = 3453 (bw), 2951 (m), 2868 (m), 1722 (s), 1645 (w), 1495 (w), 1437 (w), 1383 (w), 1302 (s), 1260 (m), 1227 (w), 1155 (s), 1100 (w), 1086 (w), 1033 (m), 1021 (m), 977 (m), 910 (w), 889 (w), 825 (w), 775 (w), 757 (w), 734 (w), 676 (w), 593 (w), 559 (w), 529 (w).

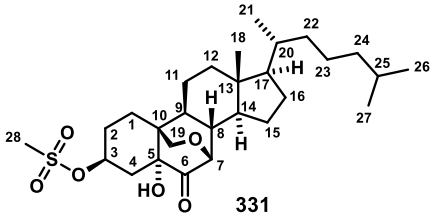
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{33}H_{48}O_7$ $[M+H]^+$ 545.3473 u, found: 545.3476 u; $C_{32}H_{48}O_7Na$ $[M+Na]^+$ 567.3292 u, found: 567.3294 u.

$[\alpha]_\lambda^{20}$: c = 0.59 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = 141.1° (± 0.2°), $[\alpha]_{436}^{20}$ = 84.6° (± 0.0°), $[\alpha]_{546}^{20}$ = 48.4° (± 0.1°), $[\alpha]_{579}^{20}$ = 41.6° (± 0.2°), $[\alpha]_{589}^{20}$ = 38.0° (± 0.2°).

4.7.19. Methanesulfonic acid (7β,19-epoxy-5α-hydroxy-6-one-cholestane-3β-yl) ester



To a solution of alcohol **311** (150 mg, 0.347 mmol, 1.0 eq.) in 8 ml pyridine was added mesylchloride (138 μl, 1.75 mmol, 5.0 eq.) at 10 °C and the reaction mixture was stirred at 10 °C for 5 h. The reaction mixture was diluted with water (10 ml) and the aq. phase was extracted thrice with EtOAc (3x 10 ml). The combined org. phases were washed with water (10 ml), 1 N aq. HCl (10 ml) and sat. aq. NaCl solution (10 ml). The org. phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 2:1) and the desired product **331** was obtained as a colorless solid (175 mg, 0.343 mmol, 99%).



Formula: $C_{28}H_{46}O_6S$

M: 510.73 g/mol

M.p.: 173-176 °C.

R_f: 0.35 (SiO_2, 2:1, cHex:EtOAc).

^{1}H NMR: (600 MHz, $CDCl_3$) δ [ppm]: 5.12 (dp, *J* = 11.0, 5.7 Hz, 1H, H-3), 4.14 – 4.08 (m, 1H, H-19), 3.92 (d, *J* = 10.3 Hz, 1H, H-19), 3.84 (d, *J* = 1.7 Hz, 1H, H-7), 3.01 (s, 3H, H-28), 2.77 (s, 1H, OH), 2.24 (ddd, *J* = 13.0, 5.4, 1.6 Hz, 1H, H-4), 2.21 – 2.07 (m, 3H, H-2, H-4, H-8), 2.09 – 2.03 (m, 1H, H-12), 1.91 – 1.82 (m, 1H, H-16), 1.81 – 1.70 (m, 2H, H-1, H-2), 1.62 – 1.47 (m, 3H, H-9, H-15, H-25), 1.42 – 1.05 (m, 14H, H-1, H-11, H-12, H-14, H-15, H-16, H-17, H-20, H-22, H-23, H-24), 1.02 – 0.95 (m, 1H, H-22), 0.89 (d, *J* = 6.5 Hz, 3H, H-21), 0.86 (dd, *J* = 6.6, 2.9 Hz, 6H, H-26, H-27), 0.75 – 0.73 (m, 3H, H-18).

^{13}C NMR: (151 MHz, $CDCl_3$) δ [ppm]: 212.2 (C-6), 78.7 (C-5), 77.5 (C-3), 76.1 (C-7), 63.4 (C-19), 55.7 (C-17), 52.0 (C-14), 45.5 (C-13), 45.0 (C-8), 43.1 (C-9), 40.4 (C-10), 40.2 (C-12), 39.6 (C-24), 38.7 (C-28), 36.5 (C-4), 36.2 (C-22), 35.7 (C-20), 28.6 (C-16), 28.1 (C-25), 27.6 (C-2), 23.9 (C-23),

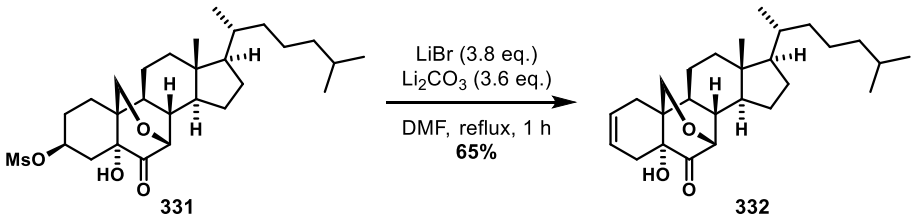
22.9 (C-26/27), 22.9 (C-15), 22.7 (C-26/27), 21.7 (C-11), 21.4 (C-1), 18.7 (C-21), 13.1 (C-18).

FT-IR (ATR): ν [cm^{-1}] = 3499 (w), 2947 (w), 2921 (w), 2865 (w), 1733 (m), 1496 (w), 1467 (w), 1455 (w), 1417 (w), 1363 (m), 1356 (m), 1334 (m), 1302 (m), 1262 (w), 1229 (w), 1181 (m), 1169 (s), 1151 (m), 1100 (w), 1087 (w), 1045 (m), 1019 (w), 981 (m), 945 (s), 885 (m), 861 (s), 821 (m), 764 (m), 748 (m), 720 (w), 662 (w), 638 (w), 592 (w), 559 (w), 531 (m), 507 (m), 497 (m), 434 (w).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{28}H_{46}O_6SNa$ $[M+Na]^+$ 533.2907 u, found: 533.2909 u.

$[\alpha]_\lambda^{20}$: c = 0.54 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = 131.6° (± 0.2°), $[\alpha]_{436}^{20}$ = 75.8° (± 0.1°), $[\alpha]_{546}^{20}$ = 43.5° (± 0.1°), $[\alpha]_{579}^{20}$ = 38.1° (± 0.2°), $[\alpha]_{589}^{20}$ = 36.3° (± 0.0°).

4.7.20. 7β,19-Epoxy-5α-hydroxy-cholest-2-en-6-on



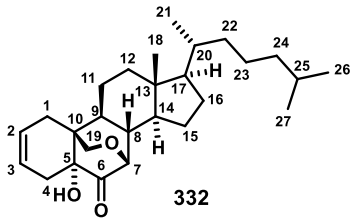
To a solution of mesylate **331** (143 mg, 0.280 mmol, 1.0 eq.) in 5.0 ml DMF was added LiBr (92 mg, 1.06 mmol, 3.8 eq.) and Li_2CO_3 (99 mg, 1.01 mmol, 3.6 eq.). The reaction mixture was heated at reflux for 1 h and the solvent was removed under reduced pressure after subsequent cooling to r.t. The residue was dissolved in water and CH_2Cl_2. After phase separation, the aq. phase was extracted with CH_2Cl_2. The combined org. phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 15:1) and the desired product **332** was obtained as a colorless solid (75 mg, 0.18 mmol, 65%).

Formula: $C_{27}H_{42}O_3$

M: 414.63 g/mol

M.p.: 78-80 °C.

R_f: 0.56 (SiO_2, 2:1, cHex:EtOAc).



332

^{1}H NMR: (600 MHz, $CDCl_3$) δ [ppm]: 5.76 – 5.66 (m, 2H, H-2, H-3), 3.91 – 3.80 (m, 3H, H-19, H-7), 2.76 – 2.64 (m, 2H, H-4, OH-5), 2.19 – 2.08 (m, 3H, H-1, H-4, H-8), 2.06 (dt, *J* = 13.1, 3.1 Hz, 1H, H-12), 1.87 (dtd, *J* = 13.1, 9.4, 5.9 Hz, 1H, H-16), 1.72 – 1.36 (m, 8H, H-1, H-9, H-11, H-15, H-22, H-25), 1.35 – 1.05 (m, 9H, H-12, H-14, H-15, H-16, H-17, H-22, H-23, H-24), 1.02 – 0.95 (m, 1H, H-22), 0.89 (d, *J* = 6.5 Hz, 3H, H-21), 0.85 (dd, *J* = 6.6, 3.0 Hz, 6H, H-26, H-27), 0.75 (s, 3H, H-18).

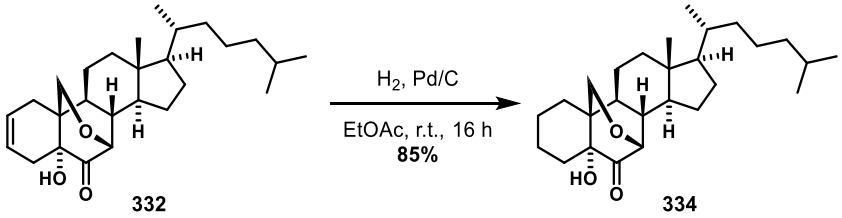
^{13}C NMR: (151 MHz, $CDCl_3$) δ [ppm]: 214.9 (C-6), 125.5 (C-2/3), 123.7 (C-2/3), 77.2 (C-5), 77.1 (C-7), 65.1 (C-19), 55.7 (C-17), 51.9 (C-14), 45.5 (C-13), 45.4 (C-8), 43.6 (C-9), 40.4 (C-10), 40.3 (C-12), 39.6 (C-24), 36.2 (C-22), 35.8 (C-20), 33.5 (C-4), 28.7 (C-16), 28.1 (C-25), 24.7 (C-1), 23.9 (C-23), 22.9 (C-26/27), 22.9 (C-15), 22.7 (C-26/27), 21.5 (C-11), 18.7 (C-21), 13.1 (C-18).

FT-IR (ATR): ν [cm^{-1}] = 3568 (bw), 3464 (bw), 3399 (bw), 3023 (w), 2949 (s), 2933 (m), 1895 (m), 2865 (m), 1742 (s), 1646 (w), 1615 (w), 1490 (w), 1464 (m), 1425 (m), 1380 (m), 1366 (w), 1336 (w), 1314 (w), 1285 (w), 1257 (w), 1232 (w), 1207 (w), 1178 (m), 1128 (w), 1099 (w), 1077 (m), 1039 (s), 979 (w), 966 (w), 932 (w), 908 (m), 899 (m), 876 (w), 861 (w), 820 (w), 801 (w), 770 (w), 738 (m), 657 (s), 608 (m), 565 (m), 488 (w), 463 (w), 429 (w).

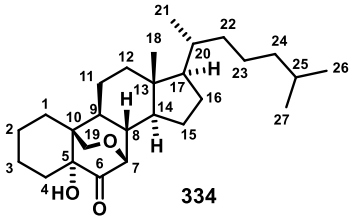
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{27}H_{43}O_3$ $[M+H]^+$ 415.3207 u, found: 415.3209 u; $C_{27}H_{42}O_3Na$ $[M+Na]^+$ 437.3026 u, found: 437.3027 u.

$[\alpha]_\lambda^{20}$: c = 0.55 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = 663.9° (± 0.3°), $[\alpha]_{436}^{20}$ = 291.0° (± 0.1°), $[\alpha]_{546}^{20}$ = 146.7° (± 0.2°), $[\alpha]_{579}^{20}$ = 125.9° (± 0.1°), $[\alpha]_{589}^{20}$ = 119.9° (± 0.2°).

4.7.21. 7β,19-Epoxy-5α-hydroxy-cholestane-6-one



To a solution of alkene **332** (70 mg, 0.17 mmol, 1.0 eq.) in 4 ml EtOAc was added Pd/C (20 mg, 10 w%) and the reaction mixture was stirred for 16 h at r.t. under an atmosphere of hydrogen. Subsequently, the reaction mixture was filtered through a pad of Celite and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 5:1) and the desired product **334** was obtained as a colorless solid (60 mg, 0.14 mmol, 85%).



Formula: $C_{27}H_{44}O_3$

M: 416.65 g/mol

M.p.: 50 °C.

R_f: 0.58 (SiO_2, 3:1, cHex:EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 4.15 (dd, *J* = 10.1, 1.6 Hz, 1H, H-19), 3.86 (d, *J* = 10.1 Hz, 1H, H-19), 3.79 (d, *J* = 1.7 Hz, 1H, H-7), 2.43 – 2.36 (m, 1H, OH-5), 2.07 (m, 2H, H-8, H-12), 1.94 (dd, *J* = 13.8, 4.5 Hz, 1H, H-3), 1.92 – 1.75 (m, 2H, H-2, H-16), 1.64 – 1.55 (m, 6H, H-2, H-3, H-4, H-9, H-15), 1.51 (ddt, *J* = 16.5, 6.6, 3.2 Hz, 2H, H-25), 1.44 – 1.06 (m, 14H, H-1, H-11, H-12, H-14, H-15, H-16, H-17, H-20, H-22, H-23, H-24), 1.03 – 0.95 (m, 1H, H-22), 0.89 (d, *J* = 6.5 Hz, 3H, H-21), 0.86 (dd, *J* = 6.6, 2.5 Hz, 6H, H-26, H-27), 0.74 (s, 3H, H-18).

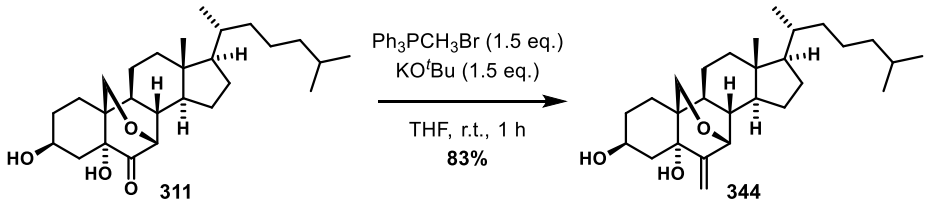
^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 215.5 (C-6), 77.9 (C-5), 76.5 (C-7), 63.8 (C-19), 55.8 (C-17), 52.1 (C-14), 45.6 (C-13), 45.1 (C-8), 44.1 (C-9), 40.8 (C-10), 40.3 (C-12), 39.6 (C-24), 36.2 (C-22), 35.8 (C-20), 30.1 (C-3), 28.7 (C-16), 28.1 (C-25), 23.9 (C-23), 22.9 (C-26/27), 22.9 (C-15), 22.7 (C-26/27), 22.2 (C-11), 21.4 (C-1), 20.3 (C-4), 19.1 (C-2), 18.8 (C-21), 13.1 (C-18).

FT-IR (ATR): ν [cm^{-1}] = 3474 (bw), 2932 (s), 2866 (s), 1734 (s), 1492 (w), 1465 (m), 1449 (m), 1382 (m), 1346 (w), 1261 (w), 1237 (w), 1205 (w), 1153 (m), 1132 (w), 1103 (w), 1085 (w), 1043 (s), 1006 (m), 988 (m), 962 (w), 946 (w), 906 (w), 879 (m), 825 (w), 804 (w), 749 (s), 689 (w), 660 (w), 632 (w), 558 (s), 538 (w), 473 (w), 463 (w), 453 (w).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{27}H_{45}O_3$ $[M+H]^+$ 417.3363 u, found: 417.3366 u; $C_{27}H_{44}O_3Na$ $[M+Na]^+$ 439.3183 u, found: 439.3184 u.

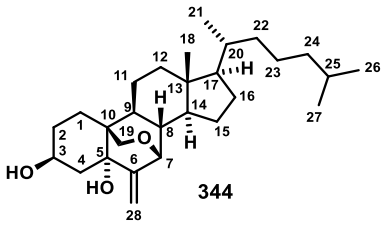
$[\alpha]_\lambda^{20}$: c = 0.49 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = 338.2° (± 0.2°), $[\alpha]_{436}^{20}$ = 153.7° (± 0.1°), $[\alpha]_{546}^{20}$ = 80.1° (± 0.1°), $[\alpha]_{579}^{20}$ = 69.2° (± 0.2°), $[\alpha]_{589}^{20}$ = 65.8° (± 0.1°).

4.7.22. 7β,19-Epoxy-6-methylene-cholest-3β,5α-diol



To a solution of Ph_3PCH_3Br (125 mg, 0.350 mmol, 1.5 eq.) in 2 ml THF was added KO*t*Bu (39 mg, 0.35 mmol, 1.5 eq.) at 0 °C under an argon atmosphere. The reaction mixture was warmed to r.t., stirred for 30 min and cooled to 0 °C. Subsequently, a solution of alcohol **311** (100 mg, 0.231 mmol, 1.0 eq.) in 3.0 ml THF was added to the reaction mixture and the mixture was stirred at r.t. for 1 h. Then, the reaction was stopped upon addition of water and the aq. phase was extracted with EtOAc. The combined org. phases were washed with a sat. aq. NaCl solution and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 1:1). The desired alkene **344** was obtained as a colorless solid (82 mg, 0.19 mmol, 83%).

Formula: $C_{28}H_{46}O_3$



344

M: 430.67 g/mol

M.p.: 171-174 °C.

R_f: 0.20 (SiO_2, 1:2, cHex:EtOAc).

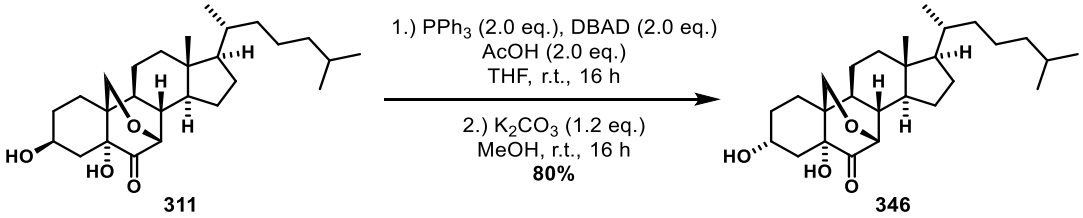
^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 5.23 (s, 1H, H-28), 4.97 (s, 1H, H-28), 4.10 (tt, *J* = 11.0, 5.2 Hz, 1H, H-3), 3.98 (dd, *J* = 10.0, 1.7 Hz, 1H, H-19), 3.91 (s, 1H, H-7), 3.71 (d, *J* = 9.9 Hz, 1H, H-19), 2.11 – 2.03 (m, 2H, H-4, H-12), 1.93 – 1.80 (m, 4H, H-2, H-4, H-8, H-16), 1.69 – 1.61 (m, 3H, H-1, OH-3, OH-5), 1.54 – 1.47 (m, 2H, H-15, H-25), 1.45 – 1.06 (m, 16H, H-1, H-2, H-9, H-11, H-12, H-14, H-15, H-16, H-17, H-20, H-22, H-23, H-24), 1.02 – 0.95 (m, 1H, H-22), 0.90 (d, *J* = 6.5 Hz, 3H, H-21), 0.86 (dd, *J* = 6.6, 2.1 Hz, 6H, H-26, H-27), 0.75 (s, 3H, H-18).

^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 155.4 (C-6), 109.5 (C-28), 75.7 (C-5), 75.2 (C-7), 66.8 (C-3), 63.8 (C-19), 55.9 (C-17), 53.0 (C-14), 45.4 (C-13), 44.9 (C-8), 43.9 (C-9), 43.4 (C-4), 40.8 (C-12), 39.6 (C-24), 39.1 (C-10), 36.3 (C-22), 35.8 (C-20), 30.2 (C-2), 28.8 (C-16), 28.2 (C-25), 23.9 (C-23), 23.0 (C-15), 22.9 (C-26/27), 22.7 (C-26/27), 21.9 (C-1), 21.7 (C-11), 18.8 (C-21), 13.4 (C-18).

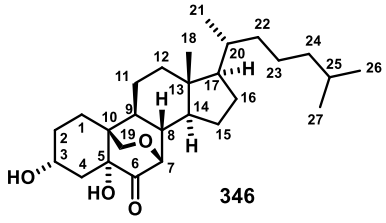
FT-IR (ATR): ν [cm^{-1}] = 3436 (bw), 1934 (s), 1906 (s), 2865 (s), 1657 (w), 1489 (w), 1462 (m), 1450 (m), 1437 (m), 1415 (w), 1382 (m), 1365 (m), 1310 (m), 1263 (m), 1222 (m), 1171 (w), 1151 (w), 1122 (w), 1073 (s), 1039 (s), 1029 (s), 1013 (s), 1001 (m), 956 (s), 926 (m), 892 (m), 875 (m), 852 (m), 818 (m), 767 (w), 749 (w), 710 (w), 693 (m), 660 (w), 531 (m), 491 (m), 454 (m).

$[\alpha]_\lambda^{20}$: c = 0.57 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = 85.7° (± 0.3°), $[\alpha]_{436}^{20}$ = 56.8° (± 0.1°), $[\alpha]_{546}^{20}$ = 34.5° (± 0.2°), $[\alpha]_{579}^{20}$ = 30.4° (± 0.2°), $[\alpha]_{589}^{20}$ = 29.1° (± 0.0°).

4.7.23. 3α,5α-Dihydroxy-7β,19-epoxy-cholestane-6-one



To a solution of PPh_3 (121 mg, 0.46 mmol, 2.0 eq.) and DBAD (106 mg, 0.46 mmol, 2.0 eq.) in 2.0 ml dry THF was added a solution of alcohol **311** (100 mg, 0.23 mmol, 1.0 eq.) in 3.0 ml dry THF. AcOH (26 μl, 0.46 mmol, 2.0 eq.) was added after formation of a yellow solution and the reaction mixture was stirred at r.t. for 16 h. Then, the reaction mixture was adsorbed on SiO_2, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 20:1 → 6:1). The obtained acetate **347** (97 mg, 0.20 mmol, 1.0 eq.) was directly dissolved in 5.0 ml MeOH. K_2CO_3 (34 mg, 0.25 mmol,1.2 eq.) weas added to the solution and the reaction mixture was stirred at r.t. for 16 h. Then, the reaction mixture was diluted with water and the aq. phase was extracted with EtOAc. The combined org. phases were washed with a sat. aq. NaCl solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 2:1) and the desired product **346** was isolated as a colorless solid (80 mg, 0.18 mmol, 80%).



Formula: $C_{27}H_{44}O_4$

M: 432.65 g/mol

M.p.: 148-150 °C.

R_f: 0.11 (SiO_2, 2:1, *c*Hex:EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 4.18 (p, *J* = 2.9 Hz, 1H, H-3), 3.97 (dd, *J* = 10.3, 1.6 Hz, 1H, H-19), 3.92 (d, *J* = 10.2 Hz, 1H, H-19), 3.81 (d, *J* = 1.6 Hz, 1H, H-7), 3.62 (bs, 2H, OH-3, OH-5), 2.13 – 2.04 (m, 4H, H-4, H-8, H-12), 1.92 – 1.76 (m, 4H, H-1, H-2, H-16), 1.69 – 1.55 (m, 2H, H-9, H-15), 1.51 (dt, *J* = 13.1, 6.6 Hz, 1H, H-25), 1.47 – 1.07 (m, 14H, H-1, H-11, H-12, H-14, H-15, H-16, H-17, H-20, H-22, H-23, H-24), 1.03 – 0.94 (m, 1H, H-22), 0.90 (d, *J* = 6.5 Hz, 3H, H-21), 0.86 (dd, *J* = 6.6, 2.5 Hz, 6H, H-26, H-27), 0.74 (s, 3H, H-18).

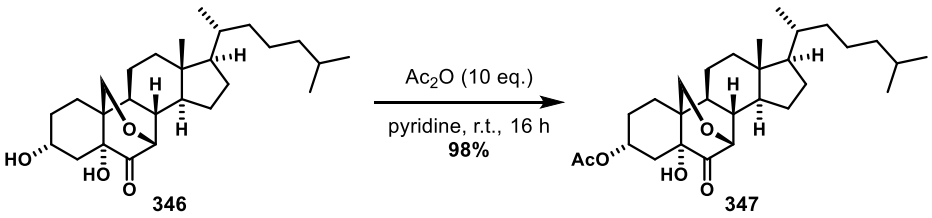
^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 212.4 (C-6), 79.6 (C-5), 76.6 (C-7), 66.5 (C-3), 63.6 (C-19), 55.7 (C-17), 52.0 (C-14), 45.6 (C-13), 45.1 (C-8), 43.6 (C-9), 41.4 (C-10), 40.2 (C-12), 39.6 (C-24), 36.2 (C-22), 35.8 (C-20), 35.0 (C-4), 28.7 (C-2), 28.6 (C-16), 28.1 (C-25), 23.9 (C-23), 22.9 (C-26/27), 22.9 (C-15), 22.7 (C-26/27), 21.5 (C-11), 18.7 (C-21), 17.6 (C-1), 13.1 (C-18).

FT-IR (ATR): ν [cm^{-1}] = 3428 (bw), 3287 (bw), 2946 (s), 2867 (m), 1735 (s), 1459 (m), 1439 (m), 1377 (m), 1344 (w), 1327 (w), 1297 (w), 1244 (m), 1211 (m), 1119 (m), 1089 (m), 1079 (m), 1044 (s), 949 (m), 934 (m), 921 (m), 897 (m), 860 (m), 821 (w), 766 (w), 730 (w), 714 (w), 667 (m), 632 (m), 597 (m), 581 (m), 526 (w), 492 (w), 453 (w).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{27}H_{45}O_4$ $[M+H]^+$ 433.3312 u, found: 433.3315 u; $C_{27}H_{44}O_4Na$ $[M+Na]^+$ 455.3132 u, found: 455.3133 u.

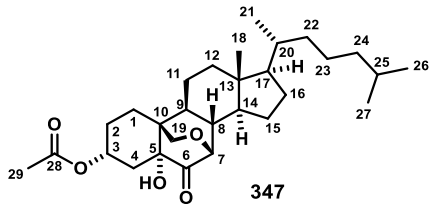
$[\alpha]_\lambda^{20}$: c = 0.53 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = 181.7° (± 0.7°), $[\alpha]_{436}^{20}$ = 82.5° (± 0.5°), $[\alpha]_{546}^{20}$ = 42.9° (± 0.3°), $[\alpha]_{579}^{20}$ = 36.2° (± 0.3°), $[\alpha]_{589}^{20}$ = 32.2° (± 0.3°).

4.7.24. 3α-Acetoxy-5α-hydroxy-7β,19-epoxy-cholestane-6-one



To a solution of alcohol **346** (50 mg, 0.116 mmol, 1.0 eq.) in 2.0 ml pyridine were added 110 μl (1.16 mmol, 10 eq.) Ac_2O at r.t. The reaction mixture was stirred for 16 h and afterwards water was added. The mixture was extracted with EtOAc, the combined org. phases were washed with a 1M aq. HCl solution and with a sat. aq. NaCl solution. The org. phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 2:1) and the desired product **347** was obtained as a colorless solid (54 mg, 0.114 mmol, 98%).

Formula: $C_{29}H_{46}O_5$



M: 474.68 g/mol

M.p.: 122-114 °C.

R_f: 0.43 (SiO_2, 2:1, *c*Hex:EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 5.31 – 5.26 (m, 1H, H-3), 3.94 (s, 2H, H-19), 3.77 (d, *J* = 1.6 Hz, 1H, H-7), 3.33 (s, 1H, OH-5), 2.23 – 2.11 (m, 2H, H-4), 2.13 – 2.03 (m, 5H, H-8, H-12, H-29), 1.92 – 1.75 (m, 5H, H-1, H-2, H-9, H-16), 1.66 – 1.56 (m, 1H, H-15), 1.51 (dt, *J* = 13.1, 6.6 Hz, 1H, H-25), 1.46 – 1.23 (m, 9H, H-1, H-11, H-12, H-14, H-16, H-20, H-22, H-23), 1.22 – 1.05 (m, 5H, H-15, H-17, H-23, H-24), 1.03 – 0.95 (m, 1H, H-22), 0.90 (d, *J* = 6.5 Hz, 3H, H-21), 0.86 (dd, *J* = 6.6, 2.5 Hz, 6H, H-26, H-27), 0.75 (s, 3H, H-18).

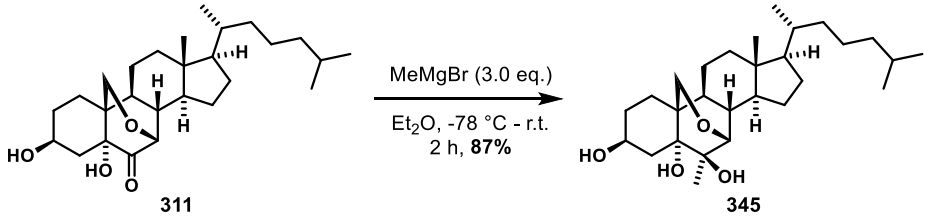
^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 210.3 (C-6), 169.4 (C-28), 77.2 (C-5), 76.7 (C-7), 68.8 (C-3), 63.4 (C-19), 55.7 (C-17), 52.0 (C-14), 45.6 (C-13), 44.6 (C-8), 43.3 (C-9), 41.1 (C-10), 40.3 (C-12), 39.6 (C-24), 36.2 (C-22), 35.8 (C-20), 33.2 (C-4), 28.7 (C-16), 28.1 (C-25), 25.5 (C-2), 23.9 (C-23), 22.9 (C-26/27), 22.9 (C-15), 22.7 (C-26/27), 21.6 (C-29), 21.5 (C-11), 18.8 (C-21), 18.1 (C-1), 13.1 (C-18).

FT-IR (ATR): ν [cm^{-1}] = 3484 (bw), 2948 (m), 2932 (m), 2866 (m), 1737 (s), 1465 (w), 1441 (w), 1375 (m), 1248 (m), 1224 (m), 1157 (m), 1119 (w), 1094 (m), 1083 (m), 1043 (s), 969 (w), 914 (w), 893 (w), 852 (w), 832 (m), 769 (w), 749 (m), 713 (w), 657 (w), 631 (w), 606 (w), 563 (m), 524 (w), 494 (w), 427 (w).

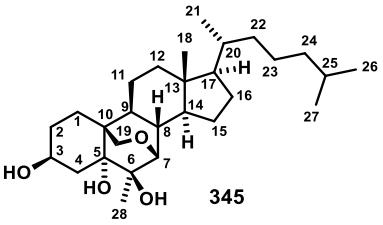
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{29}H_{47}O_5$ $[M+H]^+$ 475.2418 u, found: 475.3418 u; $C_{29}H_{46}O_5Na$ $[M+Na]^+$ 497.3237 u, found: 497.3237 u.

$[\alpha]_\lambda^{20}$: c = 0.55 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = 87.2° (± 0.2°), $[\alpha]_{436}^{20}$ = 52.9° (± 0.1°), $[\alpha]_{546}^{20}$ = 31.0° (± 0.2°), $[\alpha]_{579}^{20}$ = 27.8° (± 0.3°), $[\alpha]_{589}^{20}$ = 26.1° (± 0.2°).

4.7.25. 7β,19-Epoxy-6α-methylcholestane-3β-5α,6β-triol



To a solution of ketone **311** (100 mg, 0.230 mmol, 1.0 eq.) in 5.0 ml dry Et_2O was added MeMgBr (0.23 ml, 0.69 mmol, 3.0 eq., 3.0M in Et_2O) at -78 °C. Subsequently, the reaction mixture was slowly warmed to r.t. and at r.t. stirred for 2 h. The reaction was stopped upon addition of a sat. aq. NH_4Cl solution after full conversion of the starting material (TLC). The aq. phase was extracted with EtOAc, the combined org. phases were washed with a sat. aq. NaCl solution and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 1:5). The desired product **345** was obtained as a colorless solid (90 mg, 0.20 mmol, 87%).



Formula: $C_{28}H_{48}O_4$

M: 448.69 g/mol

M.p.: 218-221 °C.

R_f: 0.16 (SiO_2, 1:5, *c*Hex:EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 4.04 (tt, *J* = 10.9, 5.1 Hz, 1H, H-3), 3.87 (dd, *J* = 10.0, 1.6 Hz, 1H, H-19), 3.63 (d, *J* = 10.0 Hz, 1H, H-19), 3.34 (d, *J* = 1.2 Hz, 1H, H-7), 2.49 (s, 3H, OH-3, OH-5, OH-6), 2.07 – 1.98 (m, 2H, H-2, H-12), 1.90 – 1.75 (m, 3H, H-4, H-8, H-16), 1.69 – 1.46 (m, 6H, H-1, H-2, H-9, H-14, H-15, H-25), 1.43 – 1.23 (m, 11H, H-4, H-11, H-12, H-16, H-20, H-22, H-23, H-28), 1.21 – 1.07 (m, 6H, H-1, H-15, H-17, H-23, H-24), 1.03 – 0.96 (m, 1H, H-22), 0.90 (d, *J* = 6.5 Hz, 3H, H-21), 0.86 (dd, *J* = 6.6, 2.3 Hz, 6H, H-26, H-27), 0.71 (s, 3H, H-18).

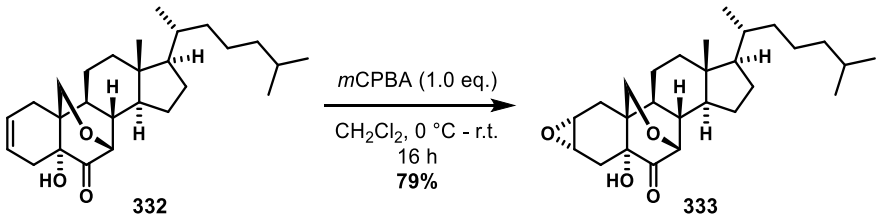
^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 76.8 (C-7), 74.9 (C-5/6), 74.9 (C-5/6), 67.9 (C-3), 64.1 (C-19), 55.9 (C-17), 54.4 (C-14), 45.4 (C-13), 43.0 (C-8), 40.8 (C-12), 40.7 (C-9), 40.0 (C-2), 39.6 (C-24), 39.3 (C-10), 36.3 (C-22), 35.9 (C-20), 30.2 (C-4), 28.8 (C-16), 28.2 (C-25), 24.1 (C-28), 23.9 (C-23), 23.0 (C-26/27), 22.9 (C-15), 22.7 (C-26/27), 22.6 (C-1), 22.1 (C-11), 18.8 (C-21), 12.7 (C-18).

FT-IR (ATR): ν [cm^{-1}] = 3449 (bw), 2930 (m), 2847 (m), 1492 (w), 1463 (w), 1438 (w), 1378 (m), 1365 (w), 1325 (w), 1279 (w), 1226 (w), 1171 (w), 1125 (w), 1107 (m), 1067 (m), 1043 (s), 982 (w), 960 (w), 935 (m), 920 (w), 881 (w), 852 (w), 819 (w), 757 (w), 646 (m), 523 (m).

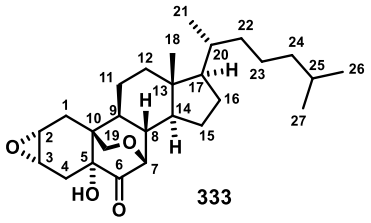
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{28}H_{48}O_4Na$ $[M+Na]^+$ 471.3445 u, found: 471.3446 u.

$[\alpha]_\lambda^{20}$: c = 0.54 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = 252.1° (± 0.2°), $[\alpha]_{436}^{20}$ = 157.4° (± 0.8°), $[\alpha]_{546}^{20}$ = 92.3° (± 0.6°), $[\alpha]_{579}^{20}$ = 81.1° (± 0.1°), $[\alpha]_{589}^{20}$ = 77.1° (± 0.1°).

4.7.26. 5α-Hydroxy-2,3-7β,19-diepoxy-cholestane-6-one



To a solution of alkene **332** (117 mg, 0.28 mmol, 1.0 eq.) in 5.0 ml CH_2Cl_2 was added *m*CPBA (58 mg, 0.34 mmol, 1.2 eq.) at 0 °C. The reaction mixture was stirred at r.t. for 16 h and afterwards water was added. The aq. phase was extracted with CH_2Cl_2 and the combined org. phases were washed with sat. aq. solutions of Na_2SO_3, $NaHCO_3$ and NaCl. The org. phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 3:1) and the desired epoxide **333** was obtained as a colorless solid (95 mg, 0.22 mmol, 79%).



Formula: $C_{27}H_{42}O_4$

M: 430.63 g/mol

M.p.: 189-191 °C.

R_f: 0.20 (SiO_2, 2:1, *c*Hex:EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 3.96 (d, *J* = 10.1 Hz, 1H, H-19), 3.77 (d, *J* = 1.6 Hz, 1H, H-7), 3.68 (dd, *J* = 10.1, 1.6 Hz, 1H, H-19), 3.52 (s, 1H, OH-5), 3.46 (dt, *J* = 3.8, 1.9 Hz, 1H, H-3), 3.31 (dd, *J* = 5.6, 3.8 Hz, 1H, H-2), 2.52 – 2.40 (m, 2H, H-4), 2.10 – 2.03 (m, 3H, H-8, H-12), 1.86 (dtd,

J = 13.2, 9.4, 6.2 Hz, 1H, H-16), 1.68 – 1.56 (m, 3H, H-1, H-9, H-15), 1.50 (dq, *J* = 13.2, 6.6 Hz, 1H, H-25), 1.45 – 1.22 (m, 8H, H-11, H-12, H-14, H-16, H-20, H-22, H-23), 1.19 – 1.04 (m, 5H, H-15, H-17, H-23, H-24), 1.01 – 0.94 (m, 1H, H-22), 0.89 (d, *J* = 6.5 Hz, 3H, H-21), 0.86 (dd, *J* = 6.6, 2.5 Hz, 6H, H-26, H-27), 0.74 (s, 3H, H-18).

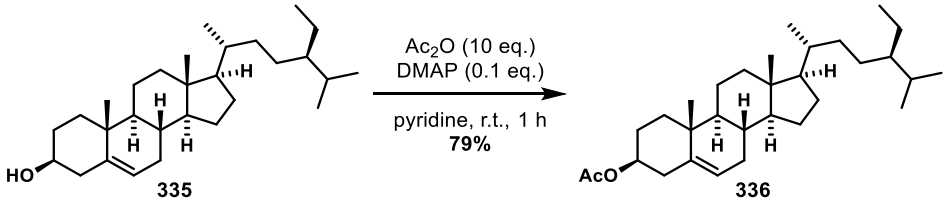
^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 209.3 (C-6), 77.7 (C-7), 77.6 (C-5), 65.2 (C-19), 55.7 (C-17), 54.1 (C-3), 51.7 (C-14), 51.3 (C-2), 45.4 (C-13), 44.8 (C-8), 43.7 (C-9), 40.1 (C-10), 40.0 (C-12), 39.6 (C-24), 36.2 (C-22), 35.8 (C-20), 29.6 (C-4), 28.6 (C-16), 28.1 (C-25), 23.9 (C-23), 23.6 (C-1), 22.9 (C-26/27), 22.8 (C-15), 22.7 (C-26/27), 21.3 (C-11), 18.7 (C-21), 13.0 (C-18).

FT-IR (ATR): ν [cm^{-1}] = 3460 (w), 2977 (m), 2943 (m), 2932 (m), 2922 (m), 2864 (m), 1746 (s), 1466 (m), 1435 (w), 1382 (w), 1374 (m), 1326 (w), 1304 (w), 1264 (w), 1245 (w), 1234 (w), 1142 (m), 1130 (m), 1096 (m), 1051 (s), 1034 (m), 978 (w), 937 (m), 903 (s), 870 (m), 803 (s), 792 (m), 776 (m), 750 (m), 723 (m), 681 (w), 651 (w), 610 (m), 590 (m), 566 (m), 487 (w), 470 (m), 450 (s), 414 (w).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{27}H_{43}O_4$ $[M+H]^+$ 431.3156 u, found: 431.3157 u; $C_{27}H_{42}O_4Na$ $[M+Na]^+$ 453.2975 u, found: 453.2976 u.

$[\alpha]_\lambda^{20}$: c = 0.60 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = 376.0° (± 0.1°), $[\alpha]_{436}^{20}$ = 161.2° (± 0.1°), $[\alpha]_{546}^{20}$ = 81.4° (± 0.1°), $[\alpha]_{579}^{20}$ = 70.1° (± 0.0°), $[\alpha]_{589}^{20}$ = 66.6° (± 0.0°).

4.7.27. β-Sitosteryl acetate



To a solution of alcohol **335** (9.50 g, 22.9 mmol, 1.0 eq.) in 57 ml pyridine was added acetic acid anhydride (23.4 g, 230 mmol, 10 eq.) and DMAP (280 mg, 2.30 mmol, 0.1 eq.) at r.t. The reaction mixture was stirred at r.t. for 1 h. After full conversion of the starting material (TLC), the reaction was stopped by the addition of 200 ml 1M aq. HCl solution. The aq. phase was extracted with EtOAc. The combined org. phases were washed with 1M hydrochloric acid, sat. aq. $NaHCO_3$ solution and sat. aq. NaCl solution. The org. phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 29:1) and the desired product **336** was obtained as a colorless solid (8.23 g, 18.0 mmol, 79%).

Formula: $C_{31}H_{52}O_2$

M: 456.76 g/mol

M.p.: 125-126 °C.

R_f: 0.17 (SiO_2, 29:1, *c*Hex:EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 5.40 – 5.36 (m, 1H), 4.61 (dddd, *J* = 14.3, 10.7, 6.8, 4.2 Hz, 1H), 2.34 – 2.30 (m, 2H), 2.03 (s, 5H), 1.85 (tq, *J* = 9.4, 3.4 Hz, 3H), 1.71 – 1.40 (m, 7H), 1.39 – 0.89 (m, 21H), 0.87 – 0.76 (m, 9H), 0.68 (s, 3H).

^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 170.7, 139.8, 122.8, 74.1, 56.8, 56.2, 50.2, 46.0, 42.5, 39.9, 38.3, 37.1, 36.7, 36.3, 34.1, 32.1, 32.0, 29.3, 28.4, 27.9, 26.2, 24.4, 23.2, 21.6, 21.2, 20.0, 19.5, 19.2, 18.9, 12.1, 12.0.

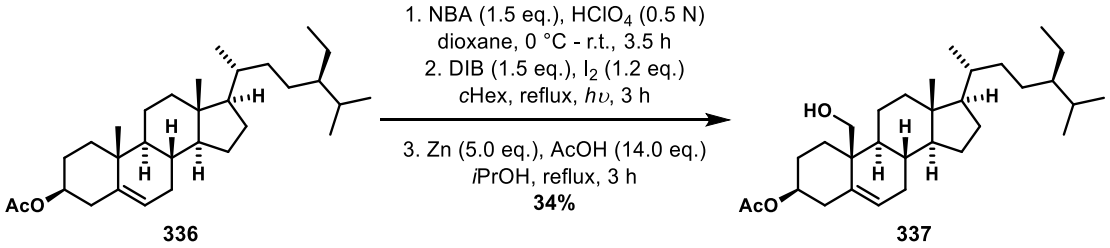
FT-IR (ATR): ν [cm^{-1}] = 2960 (bs), 2937 (s), 2905 (s), 2870 (m), 2892 (s), 1730 (m), 1465 (w), 1441 (s), 1367 (m), 1248 (m), 1198 (s), 1037 (m), 959 (s), 940 (s), 841 (s), 737 (s), 625 (s), 610 (s).

HR-MS: (GC-EI/MS, 70 eV, 50-300 °C) m/z (%) = 145.1011 (70), 147.1163 (100), 255.2106 (40), 367.3354 (10), 381.3512 (35), 396.3747 (65), 456.3954 (<1).

$[\alpha]_{\lambda}^{20}$: c = 0.93 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = -138.2° (± 0.1°), $[\alpha]_{436}^{20}$ = -84.8° (± 0.1°), $[\alpha]_{546}^{20}$ = -48.1° (± 0.1°), $[\alpha]_{579}^{20}$ = -42.0° (± 0.0°), $[\alpha]_{589}^{20}$ = -40.3° (± 0.0°).

The analytical data are in accordance with the literature.[183]

4.7.28. 3β-Acetoxy-19-hydroxy-stigmast-Δ^5-ene

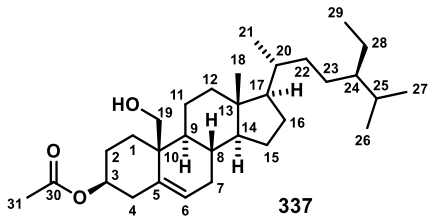


To a solution of sitosterylacetate (**336**) (7.49 g, 16.4 mmol, 1.0 eq.) in 200 ml dioxane was added *N*-bromoacetamide (NBA) (3.39 g, 23.6 mmol, 1.5 eq.) and 40 ml of an aq. 0.5N $HClO_4$ solution at 0 °C. The reaction mixture was stirred for 1 h at 0 °C under exclusion of light and further 2.5 h at r.t. Then, the reaction was stopped upon addition of a sat. aq. Na_2SO_3 solution and water. The aq. phase was extracted with MTBE, the combined org. phases were washed with a sat. aq. NaCl solution and dried over $MgSO_4$. The solvent was removed under reduced pressure and the obtained crude bromohydrine (beige solid, 9.06 g) was used in the next reaction step without further purification.

To a solution of bromohydrine (9.06 g of the crude product from the previous step) in 500 ml cyclohexane was added diacetoxyiodobenzene (DIB) (7.92 g, 24.5 mmol, 1.5 eq.) and iodine (4.99 g, 19.6 mmol, 1.2 eq.). The reaction mixture was stirred under irradiation of a 150 watts mercury vapour lamp for 3 h at reflux. Then, the violet reaction mixture was cooled to r.t. and a diluted aq. N_2SO_3 solution was added. The aq. phase was extracted with MTBE, the combined org. phases were washed with water, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The obtained crude product (brown, highly viscous oil, 13.6 g) was used in the next reaction step without further purification.

To a solution of this crude product (13.6 g) in 400 ml *i*PrOH was added zinc powder (5.35 g, 8.19 mmol, 5.0 eq.) and AcOH (13.8 g, 22.9 mmol, 14 eq.). The reaction mixture was stirred for 3 h at reflux, subsequently cooled to r.t. and filtered through a pad of Celite. The clear, yellow solution was concentrated to a total volume of 100 ml

under reduced pressure. Then, water was added and the aq. phase was extracted with MTBE. The combined org. phases were washed with water, a sat. aq. NaCl solution and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 4:1) to obtain the desired product **337** as a beige solid (2.67 g, 5.65 mmol, 34% over 3 steps).



337

Formula: $C_{31}H_{52}O_3$

M: 472.75 g/mol

M.p.: 115-118 °C.

R_f: 0.33 (SiO_2, 4:1, *c*Hex:EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 5.78 (dd, *J* = 4.8, 2.4 Hz, 1H, H-6), 4.64 (m, 1H, H-3), 3.83 (d, *J* = 11.4 Hz, 1H, H-19), 3.62 (d, *J* = 11.4 Hz, 1H, H-19), 2.42 (ddd, *J* = 13.0, 4.9, 2.3 Hz, 1H, H-4), 2.31 – 2.23 (m, 1H, H-4), 2.07 – 1.99 (m, 5H, H-7, H-12, H-31), 1.96 (dt, *J* = 13.9, 3.7 Hz, 1H, H-1), 1.90 – 1.77 (m, 3H, H-2, H-8, H-16), 1.70 – 1.46 (m, 7H, H-2, H-7, H-11, H-15, H-25), 1.40 – 0.98 (m, 11H, H-1, H-12, H-15, H-16, H-17, H-20, H-22, H-26, H-28), 0.95 – 0.89 (m, 6H, H-9, H-14, H-21, H-24), 0.86 – 0.80 (m, 9H, H-29, H-26, H-27), 0.80 – 0.76 (m, 1H), 0.73 (s, 3H, H-18).

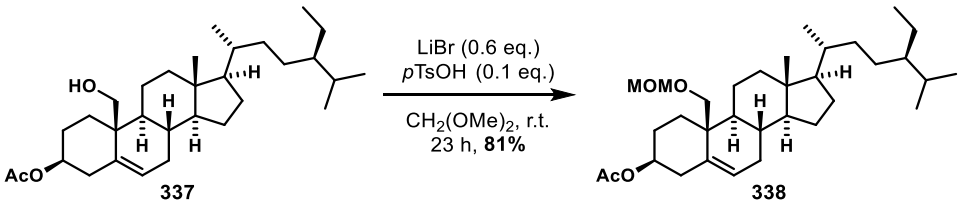
^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 170.7 (C-30), 134.7 (C-5), 128.5 (C-6), 73.6 (C-3), 62.9 (C-19), 57.7 (C-14), 56.1 (C-17), 50.5 (C-9), 46.0 (C-24), 42.7 (C-13), 41.8 (C-10), 40.1 (C-12), 38.4 (C-4), 36.3 (C-20), 34.1 (C-22), 33.5 (C-8), 33.2 (C-1), 31.4 (C-7), 29.3 (C-25), 28.4 (C-16), 28.3 (C-2), 26.2 (C-23), 24.2 (C-15), 23.2 (C-28), 21.9 (C-11), 21.5 (C-31), 20.0 (C-26/27), 19.2 (C-26/27), 18.9 (C-21), 12.4 (C-18), 12.1 (C-29).

FT-IR (ATR): ν [cm^{-1}] = 3497(bs), 2956 (s), 2932 (s), 2866 (s), 1728 (m), 1464 (s), 1441 (S), 1377 (m), 1255 (m), 1133 (s), 1088 (s), 1033 (m), 960 (s), 916 (s), 883 (s), 841 (s), 810 (s), 798 (s), 623 (s), 585 (s).

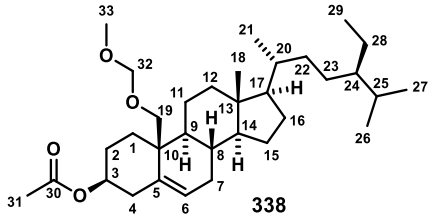
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{31}H_{52}O_3Na$ $[M+Na]^+$ 481.3652 u, found: 481.3653 u.

$[\alpha]_\lambda^{20}$: c = 0.95 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = -87.4° (± 0.4°), $[\alpha]_{436}^{20}$ = -53.2° (± 0,1°), $[\alpha]_{546}^{20}$ = -30.5° (± 0.1°), $[\alpha]_{579}^{20}$ = -27.0° (± 0.1°), $[\alpha]_{589}^{20}$ = -27.0° (± 0.0°).

4.7.29. 3β-Acetoxy-19-(methoxymethyloxy)-stigmast-Δ^5-ene



To a solution of 19-hydroxystigmastylacetate (**337**) (2.67 g, 5.65 mmol, 1.0 eq.) in 34 ml $CH_2(OMe)_2$ was added LiBr (300 mg, 2.31 mmol, 0.6 eq.) and *p*TsOH·H_2O (0.11 g, 0.57 mmol, 0.1 eq.). The reaction mixture was stirred for 23 h at r.t. and after full conversion of the starting material (TLC), water was added. The aq. phase was extracted with MTBE and the combined org. phases were washed with water, sat. aq. NaCl solution and finally dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 10:1). The desired product **338** was obtained as a brown solid (2.37 g, 4.59 mmol, 81%).



Formula: $C_{33}H_{56}O_4$

M: 516.81 g/mol

M.p.: 83-84 °C.

R_f: 0.39 (SiO_2, 10:1, *c*Hex:EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 5.60 (dt, *J* = 4.4, 1.9 Hz, 1H, H-6), 4.69 – 4.57 (m, 3H, H-3, H-32), 3.73 (d, *J* = 10.3 Hz, 1H, H-19), 3.48 (d, *J* = 10.3 Hz, 1H, H-19), 3.37 (s, 3H, H-33), 2.40 (ddd, *J* = 13.1, 5.2, 2.2 Hz, 1H, H-4), 2.36 – 2.27 (m, 1H, H-4), 2.19 – 2.15 (m, 1H), 2.11 (dt, *J* = 13.5, 3.5 Hz, 1H, H-1), 2.07 – 1.96 (m, 5H, H-7, H-12, H-31), 1.84 (m, 2H, H-2, H-16), 1.79 – 1.61 (m, 2H, H-8, H-25), 1.64 – 1.45 (m, 6H, H-2, H-7, H-11, H-15), 1.39 – 0.98 (m, 15H, H-1, H-12, H-15, H-16, H-17, H-20, H-22, H-23, H-28), 0.97 – 0.86 (m, 6H, H-9, H-14, H-21, H-24), 0.88 – 0.79 (m, 9H, H-26, H-27, H-29), 0.70 (s, 3H, H-18).

^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 170.7 (C-30), 135.8 (C-5), 126.3 (C-6), 97.1 (C-32), 73.8 (C-3), 69.1 (C-19), 57.4 (C-14), 56.1 (C-17), 55.6 (C-33), 50.5 (C-9), 46.0 (C-24), 42.6 (C-13), 40.5 (C-10), 40.2 (C-12), 38.5 (C-4), 36.3 (C-20), 34.1 (C-22), 33.5 (C-1), 32.9 (C-8), 31.7 (C-7), 29.3 (C-25), 28.4 (C-16), 28.2 (C-2), 26.2 (C-23), 24.4 (C-15), 23.2 (C-28), 22.0

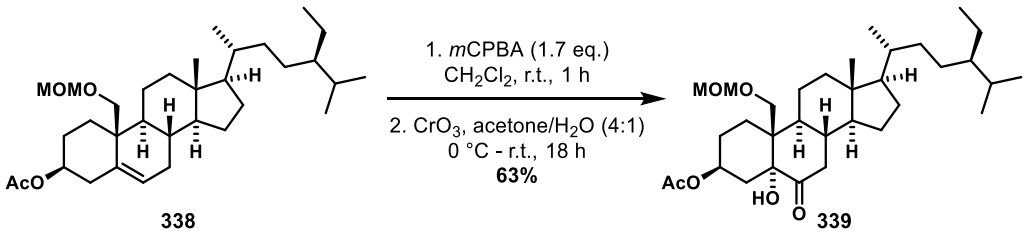
(C-11), 21.6 (C-31), 20.0 (C-26/27), 19.2 (C-26/27), 18.9 (C-21), 12.2 (C-18), 12.1 (C-29).

FT-IR (ATR): ν [cm^{-1}] = 2952 (bs), 2933 (s), 2869 (s), 1728 (m), 1463 (s), 1443 (s), 1379 (m), 1369 (s), 1243 (m), 1140 (s), 1112 (s), 1045 (m), 1027 (m), 917 (s), 916 (s), 881 (s), 839 (s), 802 (s), 736 (s), 611 (s), 578 (s).

HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{33}H_{56}O_4Na$ $[M+Na]^+$ 539.4071 u, found: 539.4067 u.

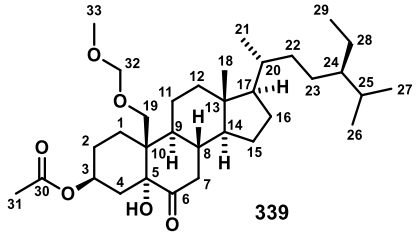
$[\alpha]_\lambda^{20}$: c = 0.85 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = -87.4° (± 0.4°), $[\alpha]_{436}^{20}$ = -53.2° (± 0.1°), $[\alpha]_{546}^{20}$ = -30.5° (± 0.1°), $[\alpha]_{579}^{20}$ = -27.0° (± 0.1°), $[\alpha]_{589}^{20}$ = -27.0° (± 0.0°).

4.7.30. 3β-Acetoxy-5α-hydroxy-19-(methoxymethyloxy)-sitgmastane-6-one



To a solution of alkene **338** (2.27 g, 4.39 mmol, 1.0 eq.) in 33 ml CH_2Cl_2 was added *m*CPBA (70w%, 1.28 g, 7.47 mmol, 1.7 eq.). The reaction mixture was stirred 1 h at r.t. and cooled to 0 °C afterwards. The resulting white precipitate was dissolved upon addition of 81 ml acetone and a solution of CrO_3 (2.37 g, 23.4 mmol, 5.4 eq.) in 8.0 ml water was added. The solution was stirred for 10 min at 0 °C and further 18 h at r.t. Then, a sat. aq. $NaHCO_3$ solution was added and the aq. phase was extracted with EtOAc. The combined org. phases were washed with water as well as a sat. aq. NaCl solution and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 3:1). The desired product **339** was obtained as a colorless gel (1.51 g, 2.75 mmol, 63%).

Formula: $C_{33}H_{56}O_6$



M: 548.81 g/mol

R_f: 0.19 (SiO_2, 3:1, *c*Hex:EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 5.11 (m, 1H, H-3), 4.50 (s, 2H, H-32), 3.64 (d, *J* = 10.7 Hz, 1H, H-19), 3.57 (d, *J* = 10.6 Hz, 1H, H-19), 3.34 (s, 3H, H-33), 2.83 (s, 1H, OH-5), 2.57 (dd, *J* = 14.6, 11.5 Hz, 1H, H-7), 2.21 – 2.12 (m, 2H, H-4, H-7), 2.08 – 1.99 (m, 5H, H-8, H-12, H-31), 1.96 – 1.82 (m, 3H, H-2, H-9, H-16), 1.77 – 1.63 (m, 3H, H-1, H-4, H-25), 1.59 – 1.43 (m, 4H, H-2, H-11, H-15), 1.39 – 0.98 (m, 12H, H-12, H-14, H-15, H-16, H-17, H-20, H-22, H-23, H-28), 0.92 (m, 4H, H-21, H-24), 0.88 – 0.76 (m, 9H, H-26, H-27, H-29), 0.68 (s, 3H, H-18).

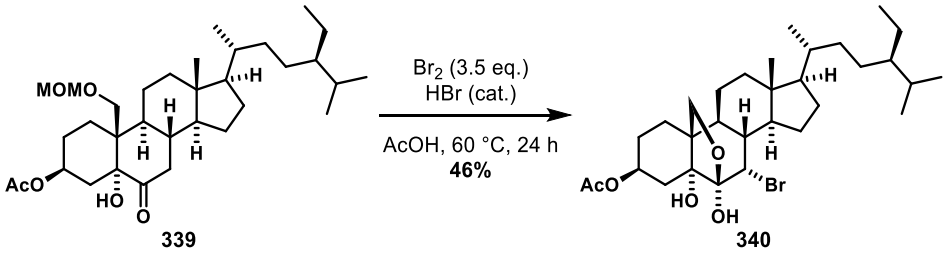
^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 209.6 (C-6), 171.1 (C-30), 97.1 (C-32), 77.8 (C-5), 70.5 (C-3), 67.1 (C-19), 57.1 (C-14), 56.2 (C-17), 56.1 (C-33), 45.9 (C-24), 45.7 (C-10), 44.1 (C-9), 43.2 (C-13), 41.5 (C-7), 40.0 (C-12), 37.2 (C-8), 36.3 (C-20), 34.0 (C-22), 32.5 (C-4), 29.3 (C-25), 28.3 (C-16), 26.6 (C-2), 26.3 (C-23), 26.1 (C-1), 24.1 (C-15), 23.2 (C-28), 21.9 (C-11), 21.5 (C-31), 20.0 (C-26/27), 19.2 (C-26/27), 18.8 (C-21), 12.3 (C-18), 12.1 (C-29).

FT-IR (ATR): ν [cm^{-1}] = 3417 (bs), 2936 (m), 2870 (s), 1713 (m), 1463 (s), 1443 (s), 1379 (m), 1365 (s), 1236 (m), 1150 (s), 1106 (s), 1034 (m), 1012 (s), 967 (s), 941 (s), 919 (s), 835 (s), 666 (s), 608 (s), 581 (s), 552 (s).

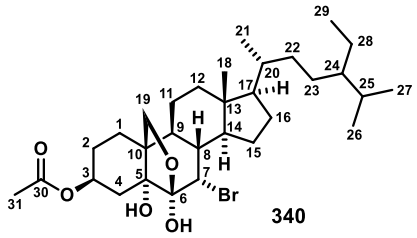
HR-MS: (ESI, 70 eV) = *m/z* calc. for: $C_{33}H_{56}O_6Na$ $[M+Na]^+$ 571.3969 u, found: 571.3968 u.

$[\alpha]_\lambda^{20}$: c = 0.90 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = -243.2° (± 0.1°), $[\alpha]_{436}^{20}$ = -116.3° (± 0.1°), $[\alpha]_{546}^{20}$ = -60.2° (± 0.1°), $[\alpha]_{579}^{20}$ = -52.0° (± 0.1°), $[\alpha]_{589}^{20}$ = -49.9° (± 0.1°).

4.7.31. 3*β*-Acetoxy-7*α*-bromo-6*β*,19-epoxy-stigmastane-5*α*,6*α*-diol



To a solution of hemiacetal **339** (1.34 g, 2.44 mmol, 1.0 eq.) in 25 ml AcOH was added bromine (1.37 ml, 8.57 mmol, 3.5 eq.) and 8 drops aq. HBr (48%). The reaction mixture was warmed to 60 °C and stirred for 24 h. The reaction mixture was subsequently cooled to r.t. and the reaction was stopped by addition of a sat. aq. $N_2S_2O_3$ solution. The aq. phase was extracted with EtOAc and the combined org. phases were washed with water and sat. aq. NaCl solution. The org. phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 5:1) and the desired product **340** was obtained as a colorless solid (657 mg, 1.13 mmol, 46%).



Formula: $C_{31}H_{51}BrO_5$

M: 583.65 g/mol

M.p.: 93-94 °C.

R_f: 0.21 (SiO_2, 5:1, *c*Hex:EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 5.03 (m, 1H, H-3), 4.13 (d, *J* = 4.7 Hz, 1H, H-7), 4.06 – 4.01 (m, 1H, H-19), 3.73 (d, *J* = 8.9 Hz, 1H, H-19), 2.20 (ddd, *J* = 12.9, 4.4, 2.2 Hz, 1H, H-4), 2.10 (s, 1H, OH-6), 2.07 – 2.00 (m, 4H, H-12, H-31), 1.97 – 1.83 (m, 5H, H-2, H-8, H-9, H-15, H-16), 1.75 (dd, *J* = 12.9, 11.9 Hz, 1H, H-4), 1.70 – 1.64 (m, 1H, H-25), 1.60 – 1.00 (m, 17H, H-1, H-2, H-11, H-12, H-14, H-15, H-16, H-17, H-20, H-22, H-23, H-28), 0.96 – 0.89 (m, 4H, H-21, H-24), 0.88 – 0.76 (m, 9H, H-26, H-27, H-29), 0.75 (s, 3H, H-18).

^{13}C NMR: (151 MHz, $CDCl_3$) δ [ppm]: 170.8 (C-30), 101.8 (C-6), 79.3 (C-5), 69.9 (C-3), 66.9 (C-19), 59.4 (C-7), 55.6 (C-17), 52.9 (C-14), 45.9 (C-24), 45.4 (C-10), 43.4 (C-13), 39.0 (C-12), 38.6 (C-8), 38.5 (C-9), 36.2 (C-20), 35.0 (C-4), 34.0 (C-22), 29.3 (C-25), 28.1 (C-16), 27.2 (C-2), 26.2 (C-23), 24.0

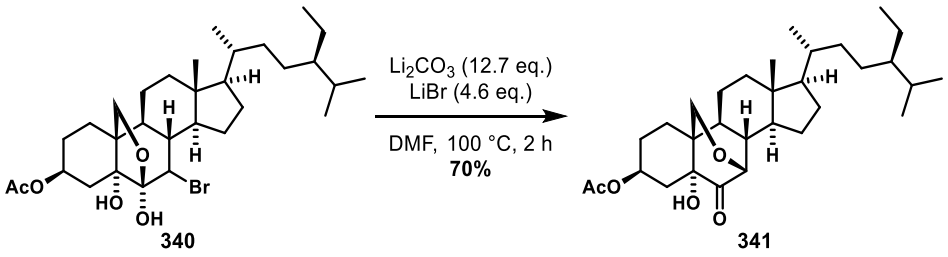
(C-1), 23.3 (C-15), 23.2 (C-28), 21.6 (C-11), 21.5 (C-31), 20.0 (C-26/27), 19.2 (C-26/27), 18.9 (C-21), 13.1 (C-18), 12.1 (C-29).

FT-IR (ATR): ν [cm^{-1}] = 3413 (bs), 2954 (m), 2936 (m), 2869 (s), 2050 (s), 1713 (m), 1497 (s), 1457 (s), 1377 (m), 1365 (s), 1243 (m), 1153 (s), 1129 (s), 1036 (m), 1095 (s), 985 (s), 945 (s), 906 (s), 844 (s), 702 (s), 677 (s), 628 (s), 608 (s), 528 (s).

HR-MS: (GC-EI/MS, 70 eV, 50-250 °C) m/z (%) = 81.0698 (88), 109.0647 (100), 255.1739 (55), 396.3380 (30), 414.3487 (45), 474.3693 (10), 502.3643 (<5).

$[\alpha]_{\lambda}^{20}$: c = 1.00 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = -137.9° (± 3.7°), $[\alpha]_{436}^{20}$ = -85.0° (± 0.1°), $[\alpha]_{546}^{20}$ = -50.1° (± 0.2°), $[\alpha]_{579}^{20}$ = -43.8° (± 0.1°), $[\alpha]_{589}^{20}$ = -42.3° (± 0.3°).

4.7.32. 3β-Acetoxy-5α-hydroxy-7β,19-epoxy-stigmastane-6-one



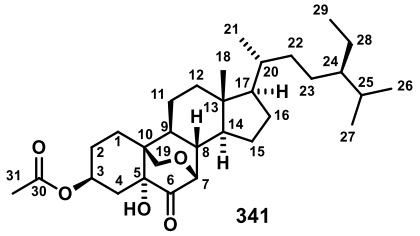
To a solution of bromide **340** (533 mg, 0.913 mmol, 1.0 eq.) in 46 ml DMF was added Li_2CO_3 (858 mg, 11.6 mmol, 12.7 eq.) and LiBr (365 mg, 4.20 mmol, 4.6 eq.). The reaction mixture was stirred for 2 h at 100 °C, subsequently cooled to r.t. and diluted by addition of water. The aq. phase was extracted with EtOAc and the combined org. phases were washed with water and a sat. aq. NaCl solution. The org. phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 2.5:1) and the desired product **341** was obtained as a colorless solid (321 mg, 0.639 mmol, 70%).

Formula: $C_{31}H_{50}O_5$

M: 502.74 g/mol

M.p.: 142-143 °C.

R_f: 0.33 (SiO_2, 2.5:1, *c*Hex:EtOAc).



341

^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 5.22 (m, 5.5 Hz, 1H, H-3), 4.14 (dd, *J* = 10.3, 1.7 Hz, 1H, H-19), 3.91 (d, *J* = 10.2 Hz, 1H, H-19), 3.82 (d, *J* = 1.7 Hz, 1H, H-7), 2.63 (s, 1H, OH-5), 2.13 – 2.01 (m, 6H, H-4, H-8, H-12, H-31), 2.00 – 1.93 (m, 2H, H-2, H-4), 1.88 (dtd, *J* = 13.0, 9.4, 5.9 Hz, 1H, H-16), 1.77 – 1.49 (m, 5H, H-1, H-2, H-9, H-15, H-25), 1.42 – 1.11 (m, 14H, H-1, H-11, H-12, H-14, H-15, H-16, H-17, H-20, H-22, H-23, H-28), 1.05 – 0.97 (m, 1H, H-22), 0.95 – 0.87 (m, 4H, H-21, H-24), 0.87 – 0.75 (m, 9H, H-26, H-27, H-29), 0.74 (s, 3H, H-18).

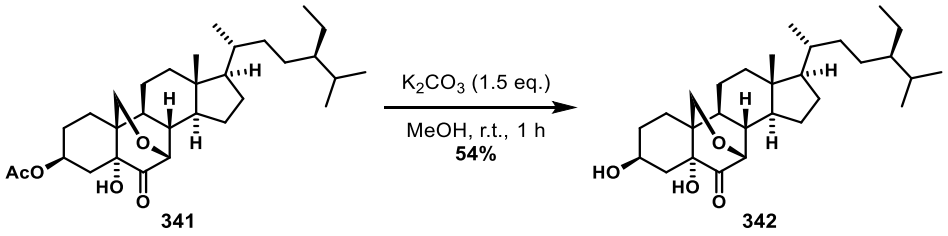
^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 212.9 (C-6), 170.6 (C-30), 78.7 (C-5), 76.2 (C-7), 69.2 (C-3), 63.6 (C-19), 55.6 (C-17), 52.0 (C-14), 45.9 (C-24), 45.5 (C-13), 45.1 (C-8), 43.2 (C-9), 40.5 (C-10), 40.2 (C-12), 36.1 (C-20), 35.2 (C-4), 34.0 (C-22), 29.2 (C-25), 28.7 (C-16), 26.2 (C-2), 26.1 (C-23), 23.2 (C-28), 22.9 (C-15), 21.7 (C-11), 21.5 (C-31), 21.3 (C-1), 19.9 (C-26/27), 19.1 (C-26/27), 18.8 (C-21), 13.1 (C-18), 12.1 (C-29).

FT-IR (ATR): ν [cm^{-1}] = 3533 (bs), 2953 (m), 2863 (s), 2112 (s), 1733 (m), 1499 (s), 1463 (s), 1375 (m), 1332 (s), 1253 (m), 1151 (s), 1097 (s), 1042 (m), 1024 (s), 963 (s), 945 (s), 910 (s), 892 (s), 870 (s), 753 (s), 710 (s), 655 (s), 635 (s), 606 (s), 574 (s).

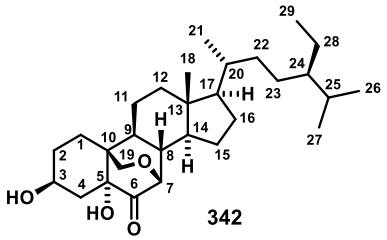
HR-MS: (GC-EI/MS, 70 eV, 50-250 °C) m/z (%) = 81.0698 (100), 109.0647 (100), 255.1741 (65), 396.3380 (35), 414.3487 (50), 474.3696 (10), 502.3645 (<1).

$[\alpha]_{\lambda}^{20}$: c = 0.91 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = 111.6° (± 0.3°), $[\alpha]_{436}^{20}$ = 66.7° (± 0.2°), $[\alpha]_{546}^{20}$ = 39.4° (± 0.2°), $[\alpha]_{579}^{20}$ = 34.4° (± 0.2°), $[\alpha]_{589}^{20}$ = 33.1° (± 0.1°).

4.7.33. 3*β*,5*α*-Dihydroxy-7*β*,19-epoxy-stigmastane-6-one



To a solution of acetate **341** (222 mg, 0.442 mmol, 1.0 eq.) in 30 ml MeOH was added K_2CO_3 (91 mg, 0.66 mmol, 1.5 eq.). The reaction mixture was stirred for 1 h at r.t. and after confirmation of full conversion of the starting material (TLC), the reaction mixture was diluted by addition of water. The aq. phase was extracted with EtOAc and the combined org. phases were washed with a sat. aq. NaCl solution. The org. phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, *c*Hex/EtOAc, 1:1) and subsequently by recrystallization from EtOH/H_2O. The desired product **342** was obtained as a colorless solid (110 mg, 0.239 mmol, 54%).



Formula: $C_{29}H_{48}O_4$

M: 460.70 g/mol

M.p.: 175-176 °C.

R_f: 0.17 (SiO_2, 1:1, *c*Hex:EtOAc).

^{1}H NMR: (500 MHz, $CDCl_3$) δ [ppm]: 4.22 – 4.12 (m, 2H, H-3, H-19), 3.89 (d, *J* = 10.2 Hz, 1H, H-19), 3.82 (d, *J* = 1.7 Hz, 1H, H-7), 2.14 – 2.01 (m, 3H, H-2, H-8, H-12), 1.97 – 1.84 (m, 3H, H-2, H-4, H-16), 1.71 – 1.54 (m, 4H, H-1, H-9, H-15, H-25), 1.48 (tdd, *J* = 13.4, 11.2, 4.9 Hz, 1H, H-4), 1.42 – 1.11 (m, 14H, H-1, H-11, H-12, H-14, H-15, H-16, H-17, H-20, H-22, H-23, H-28), 1.05 – 0.98 (m, 1H, H-22), 0.94 – 0.88 (m, 4H, H-21, H-24), 0.86 – 0.75 (m, 9H, H26, H-27, H-29), 0.74 (s, 3H, H-18).

^{13}C NMR: (126 MHz, $CDCl_3$) δ [ppm]: 213.7 (C-6), 79.2 (C-5), 76.2 (C-7), 66.2 (C-3), 63.7 (C-19), 55.6 (C-17), 52.1 (C-14), 45.9 (C-24), 45.5 (C-13), 45.2 (C-8), 43.3 (C-9), 40.6 (C-10), 40.3 (C-12), 38.9 (C-2), 36.1 (C-20), 34.0 (C-22), 30.2 (C-4), 29.2 (C-25), 28.7 (C-16), 26.1 (C-23), 23.2 (C-28), 22.9 (C-15), 21.8 (C-11), 21.5 (C-1), 19.9 (C-26/27), 19.1 (C-26/27), 18.8 (C-21), 13.1 (C-18), 12.1 (C-29).

FT-IR (ATR): ν [cm^{-1}] = 3353 (bs), 2955 (m), 2861 (s), 2050 (s), 1732 (m), 1495 (s), 1463 (s), 1376 (m), 1365 (s), 1250 (m), 1225 (s), 1154 (s), 1070 (s), 1049 (m), 969 (s), 914 (s), 88 (s), 872 (s), 853 (s), 818 (s), 754 (s), 710 (s), 6635 (s), 637 (s), 583 (s), 559 (s).

HR-MS: (GC-EI/MS, 70 eV, 50-300 °C) m/z (%) = 81.0698 (100), 109.0647 (60), 133.1011 (55), 273.1846 (35), 414.3488 (25), 432.3590 (15), 460.3541 (<1).

$[\alpha]_{\lambda}^{20}$: c = 0.86 g/100 ml, $CHCl_3$: $[\alpha]_{365}^{20}$ = 248.0° (± 0.2°), $[\alpha]_{436}^{20}$ = 120.9° (± 0.3°), $[\alpha]_{546}^{20}$ = 63.8° (± 0.6°), $[\alpha]_{579}^{20}$ = 56.5° (± 0.5°), $[\alpha]_{589}^{20}$ = 53.8° (± 0.7°).

5. Appendix

5.1. List of Abbreviations

Ac	Acetate
9BBN	9-Borabicyclo(3.3.1)nonan
ADME	Absorption, Distribution, Metabolism and Excretion
ALL	Acute Lymphoblastic Leucemia
aq.	aqueous
CA	Cycloaddition
CBS-reduction	Corey-Bakshi-Shibata-reduction
CDI	Carbonyldiimidazole
DA	Diels-Alder
DFT	Density Functional Theory
DIB	Diacetoxyiodobenzene
DIBALH	Diisobutyl aluminum hydride
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMP	Dess-Martin periodinan
DMSO	Dimethylsulfoxide
DPP II	Dipeptidyl peptidase II
dppf	1,1'-Bis(diphenylphosphino)ferrocene
E. coli	Escherichia coli
e.g.	esxempli gratia
EDCHCl	N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimid hydrochlorid
ee	enantiomeric excess
et. al.	et alii
etc.	et cetera
GC-MS	Gas chromatography - Mass spectrometry
HBPin	Pinacolborane
HOMO	Highest occupied molecular orbital
HPLC	High-performance liquid chromatography
IBX	2-Iodobenzoesäure
LDA	Lithium diisopropylamine

LUMO	Lowest unoccupied molecular orbital
mCPBA	*meta* Chloroperbenzoic acid
MOM	Methoxymethyl
MS	Mass spectrometry
MW	Microwave
NBA	*N*-Bromacetamide
NBS	*N*-Bromsuccinimide
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
PCC	Pyridiunium chlorochromate
r.t.	room temperature
sat.	saturated
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*Butyldiphenylsilyl
TBS	*tert* Butyldimethylsilyl
Teoc	2-(trimethylsilyl)ethoxycarbonyl
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMS	trimethylsily

5.2. Literature

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5.3. NMR Spectra of Selected Compounds

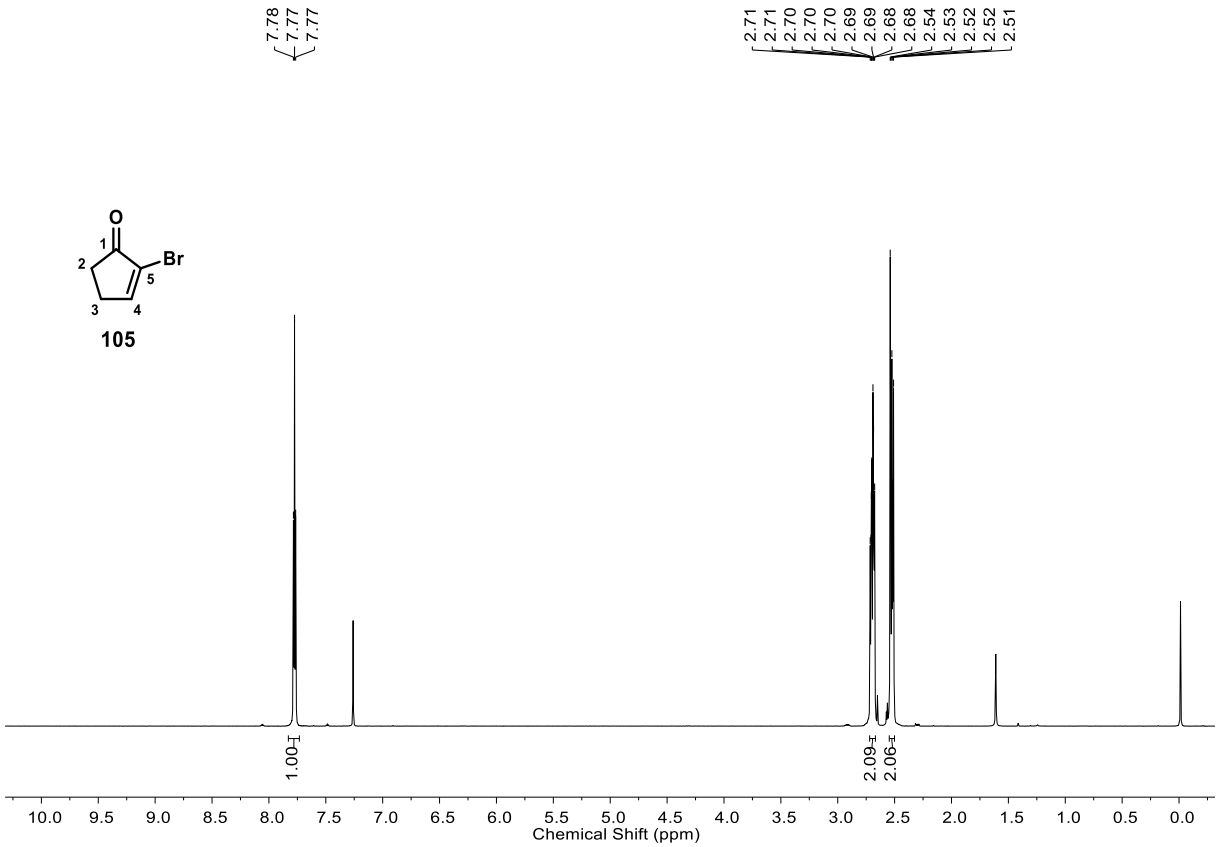


Figure 20: ^{1}H NMR (300 MHz, $CDCl_3$) of 2-bromo-cyclopent-2-ene-1-one (**105**).

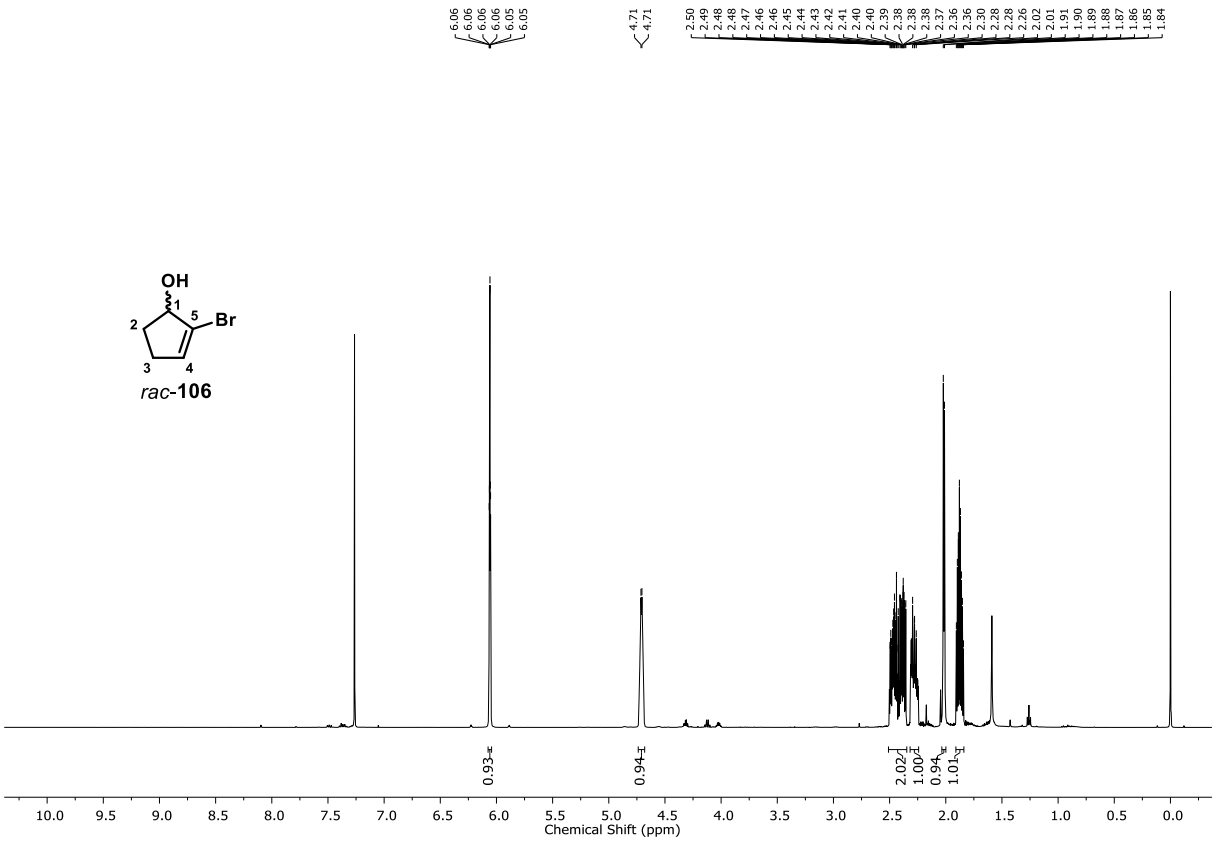


Figure 21: ^{1}H NMR (300 MHz, $CDCl_3$) of *rac*-2-bromo-cyclopent-2-ene-1-ol (**106**).

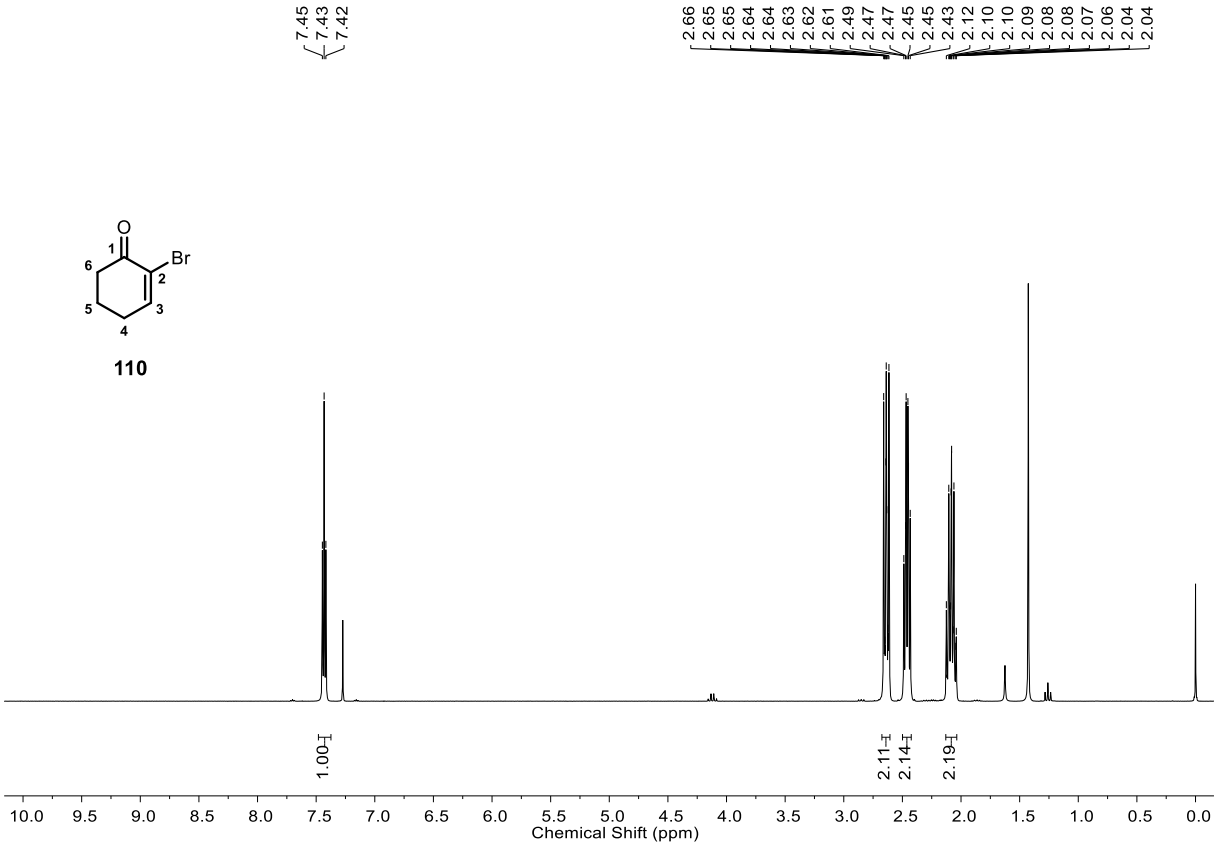


Figure 22: ^{1}H NMR (300 MHz, $CDCl_3$) of 2-bromo-cyclohex-2-ene-1-one (**110**).

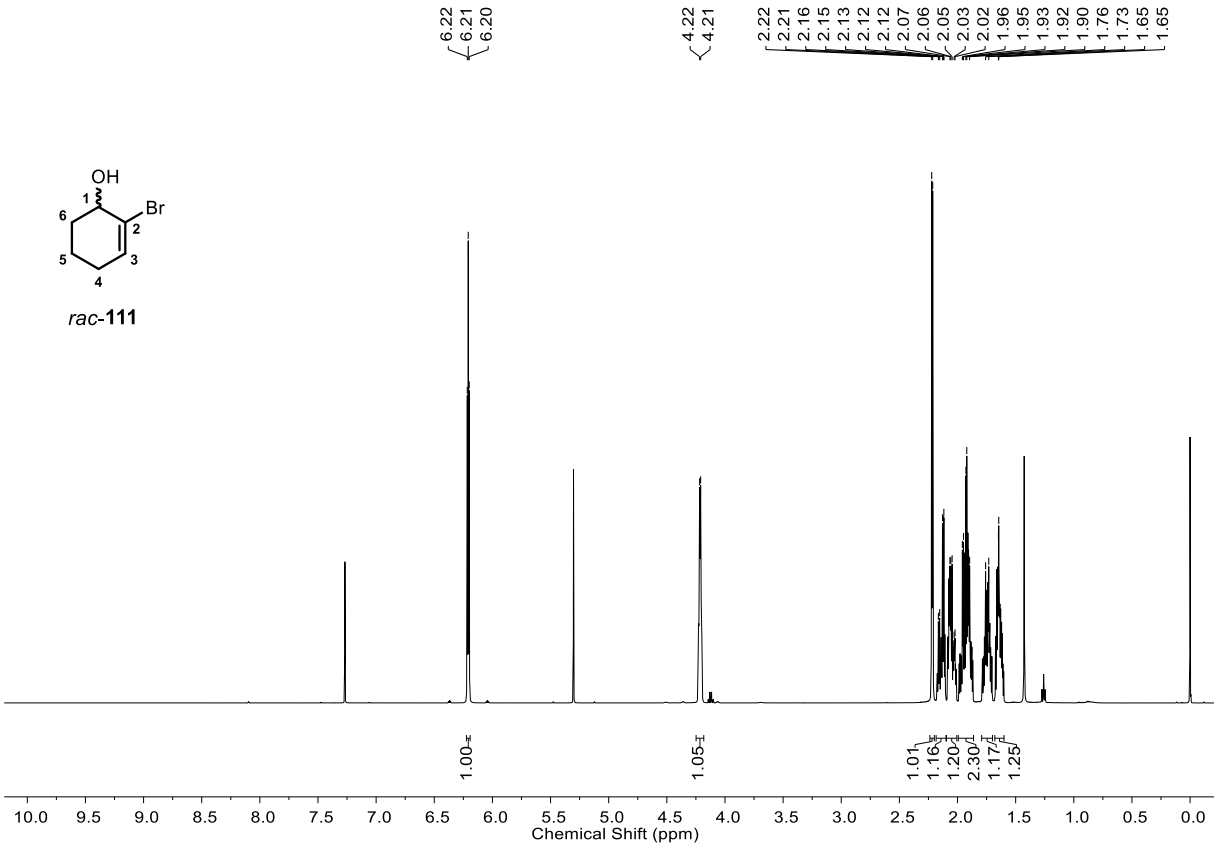


Figure 23: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-2-bromocyclohex-2-ene-1-ol (*rac*-**111**).

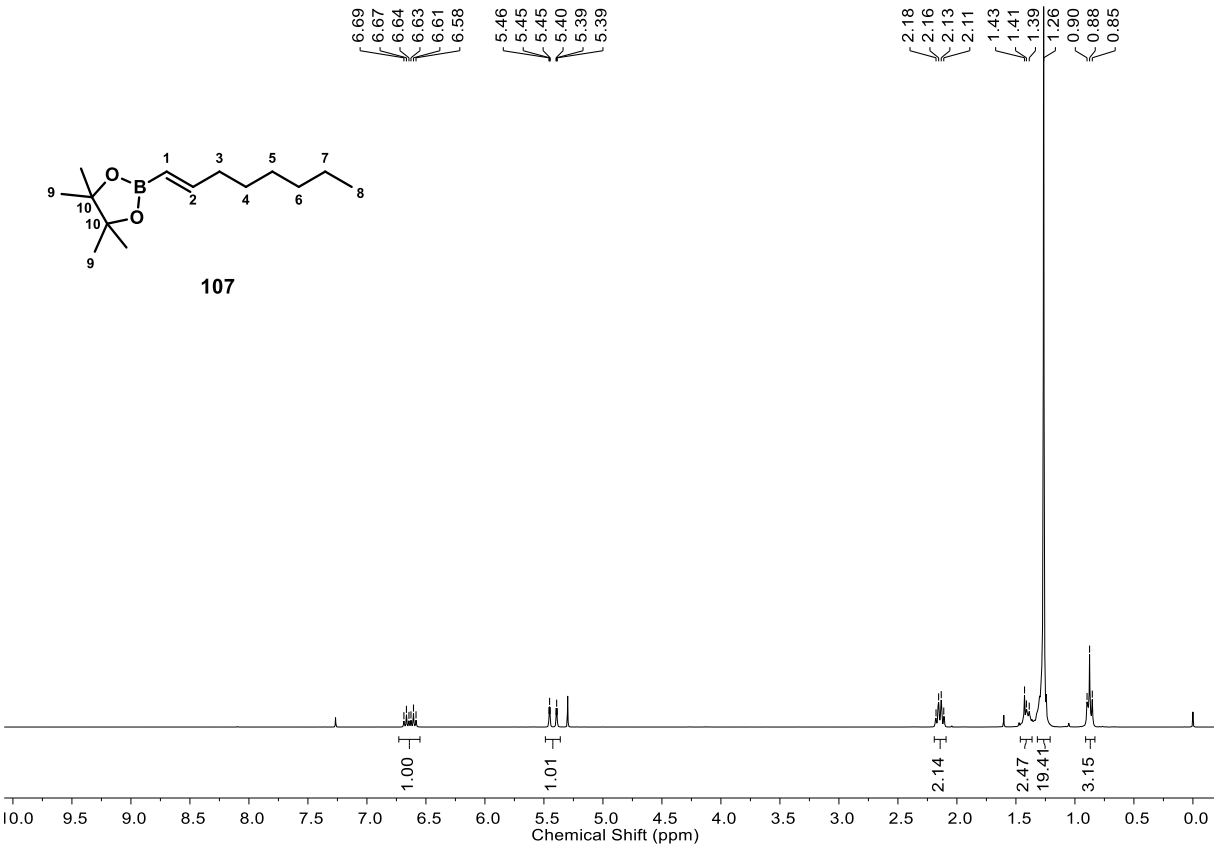


Figure 24: ^{1}H NMR (300 MHz, $CDCl_3$) of (*E*)-4,4,5,5-Tetramethyl-2-(oct-1-enyl)-1,3,2-dioxaborolane (**107**).

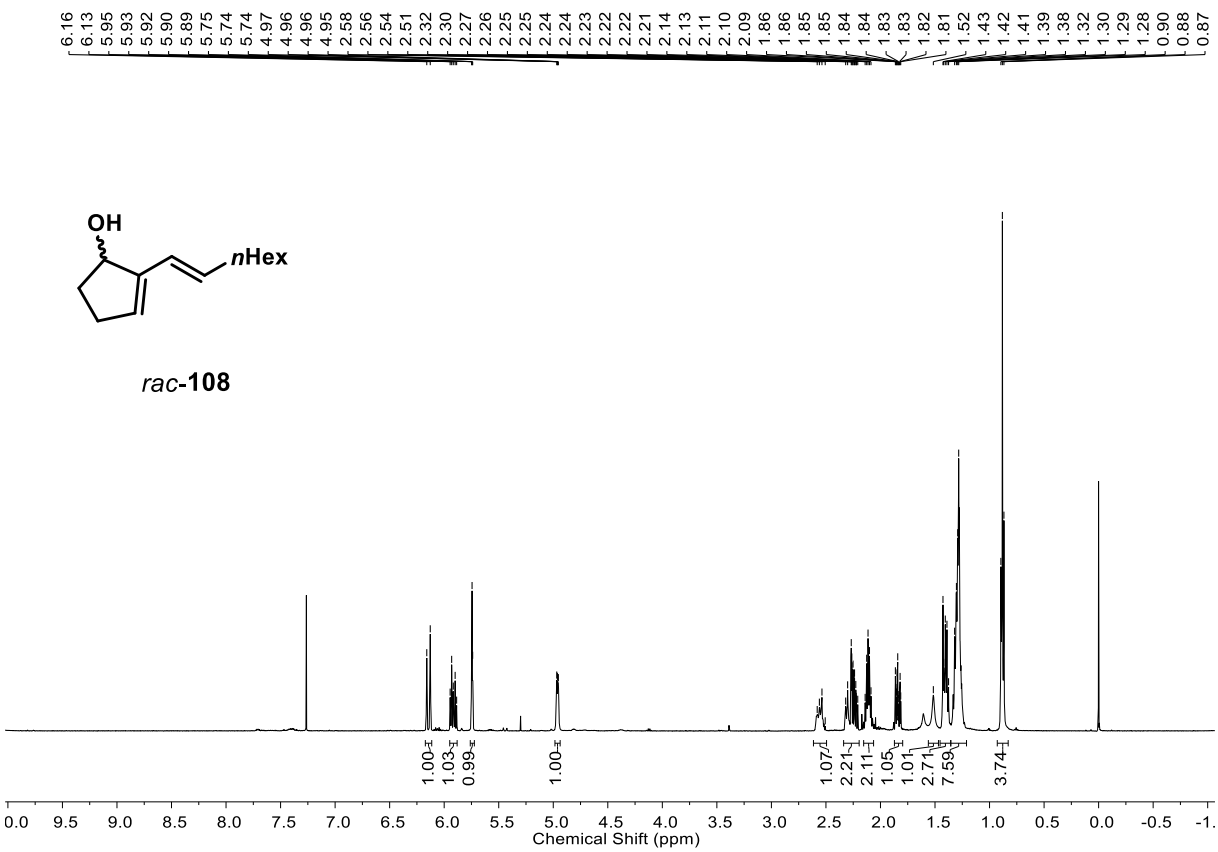


Figure 25: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-1-hydroxy-2-(1-octen-1-yl)-cyclopent-2-ene (*rac*-**108**).

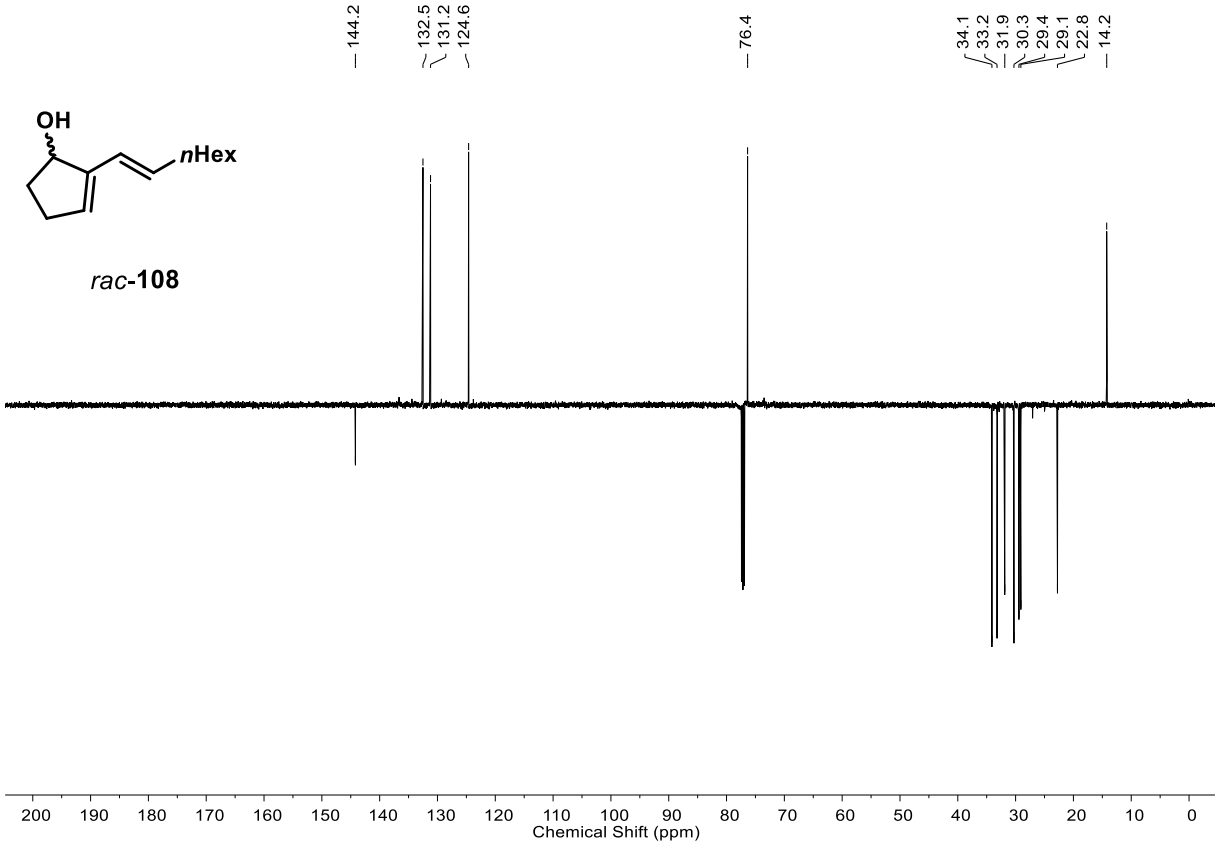


Figure 26: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-1-hydroxy-2-(1-octen-1-yl)-cyclopent-2-ene (*rac*-**108**).

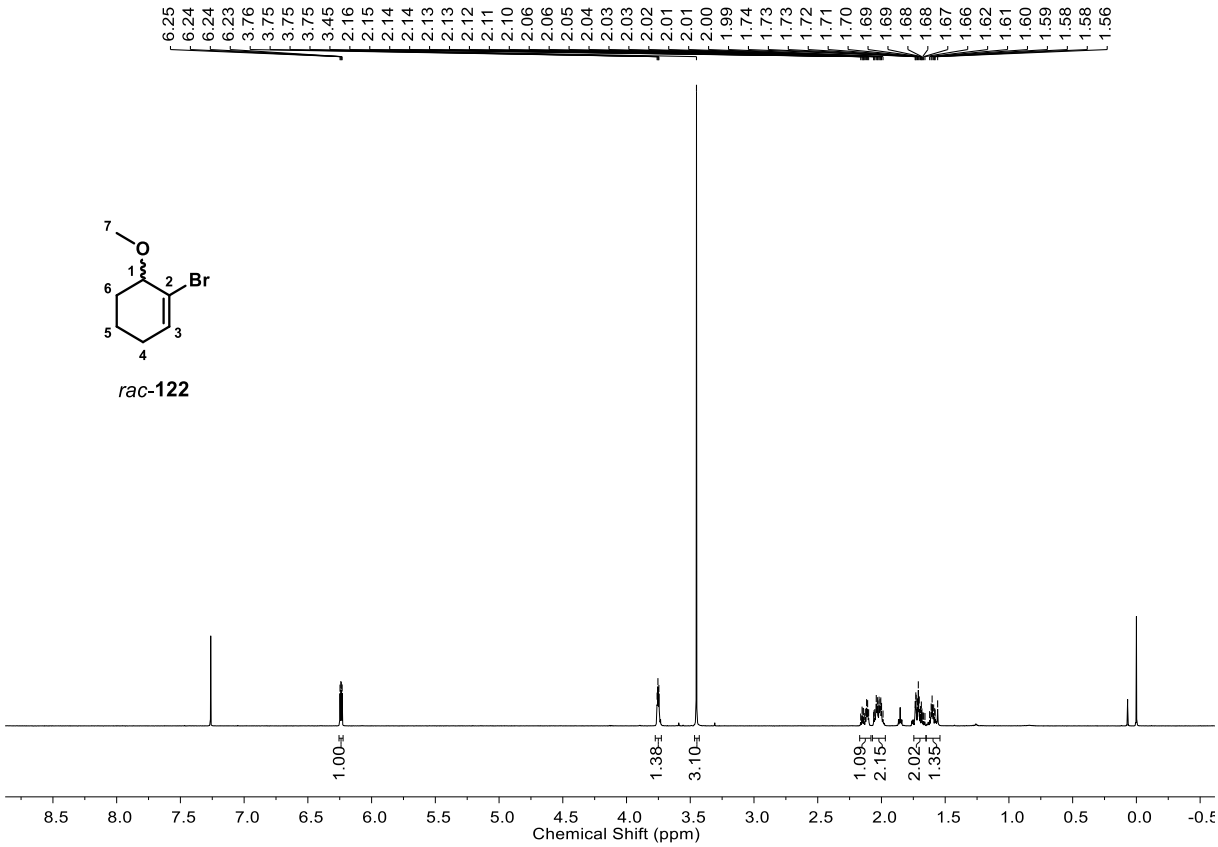


Figure 27: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-2-bromo-1-methoxycyclohex-2-ene (*rac*-**122**).

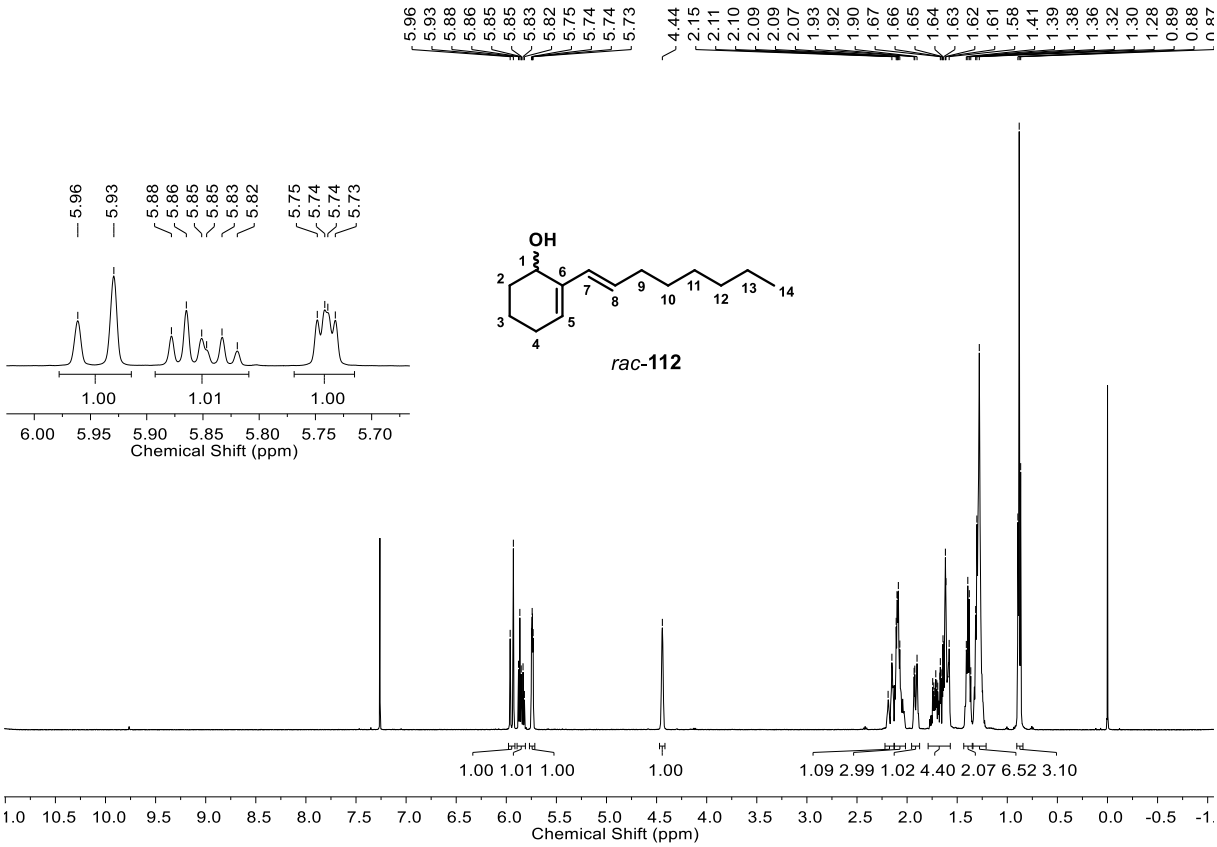


Figure 28: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-1-hydroxy-2-(1-octen-1-yl)-cyclohex-2-ene (*rac*-**112**).

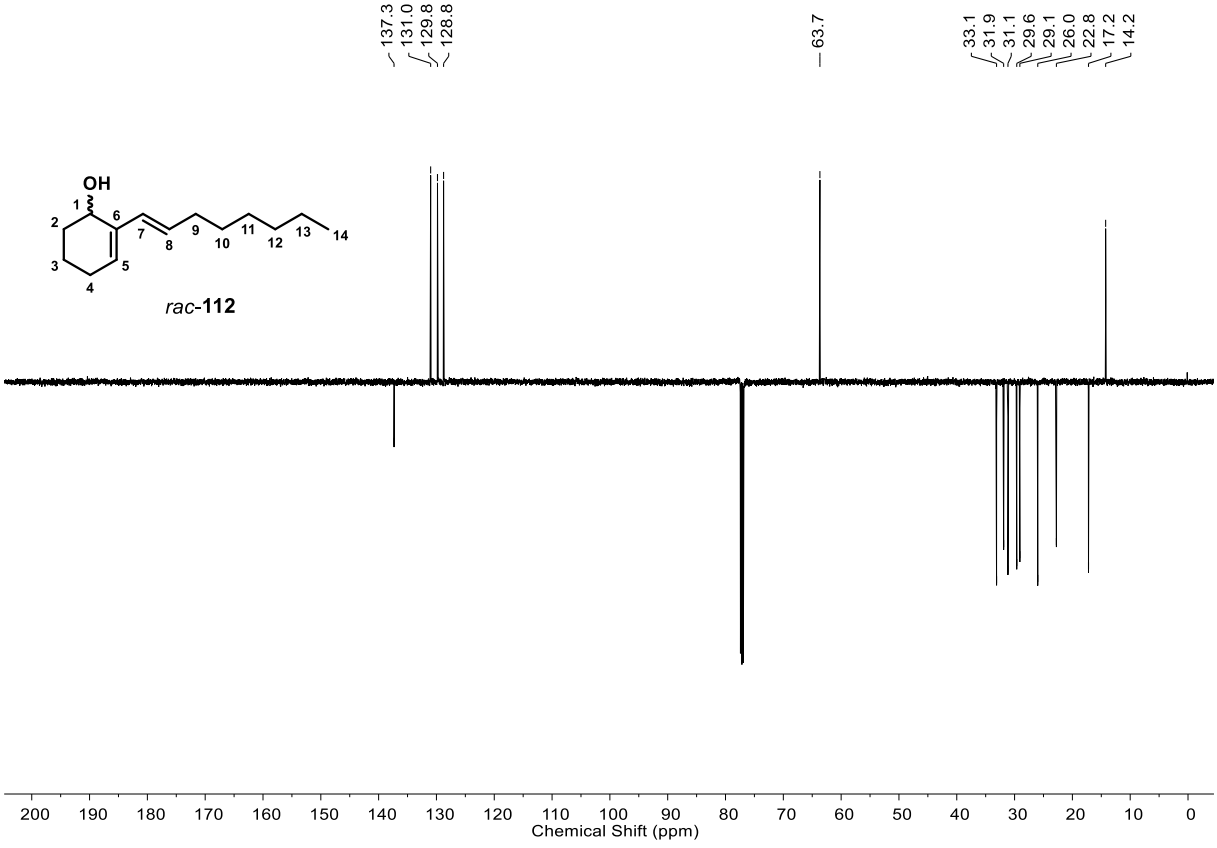


Figure 29: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-1-hydroxy-2-(1-octen-1-yl)-cyclohex-2-ene (*rac*-**112**).

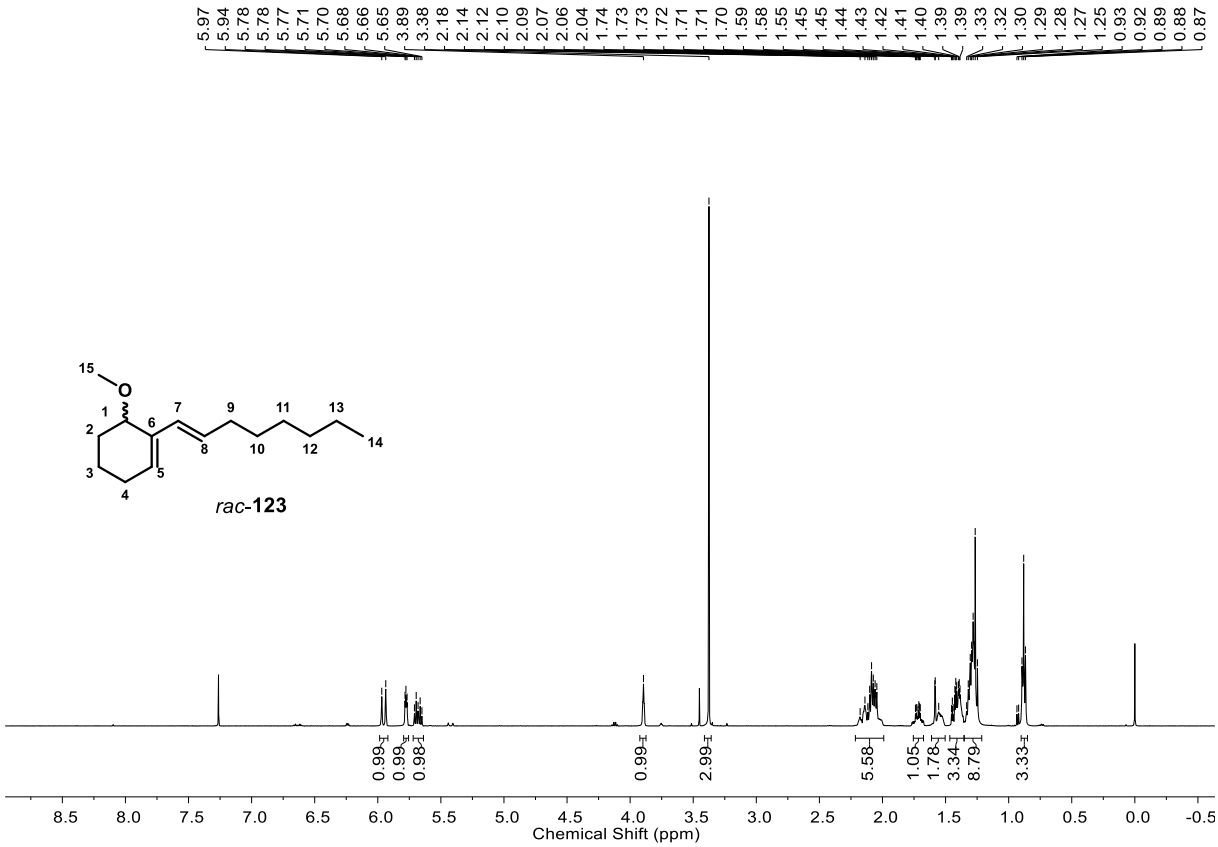


Figure 30: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-1-methoxy-2-(1-octen-1-yl)-cyclohex-2-ene (*rac*-**123**).

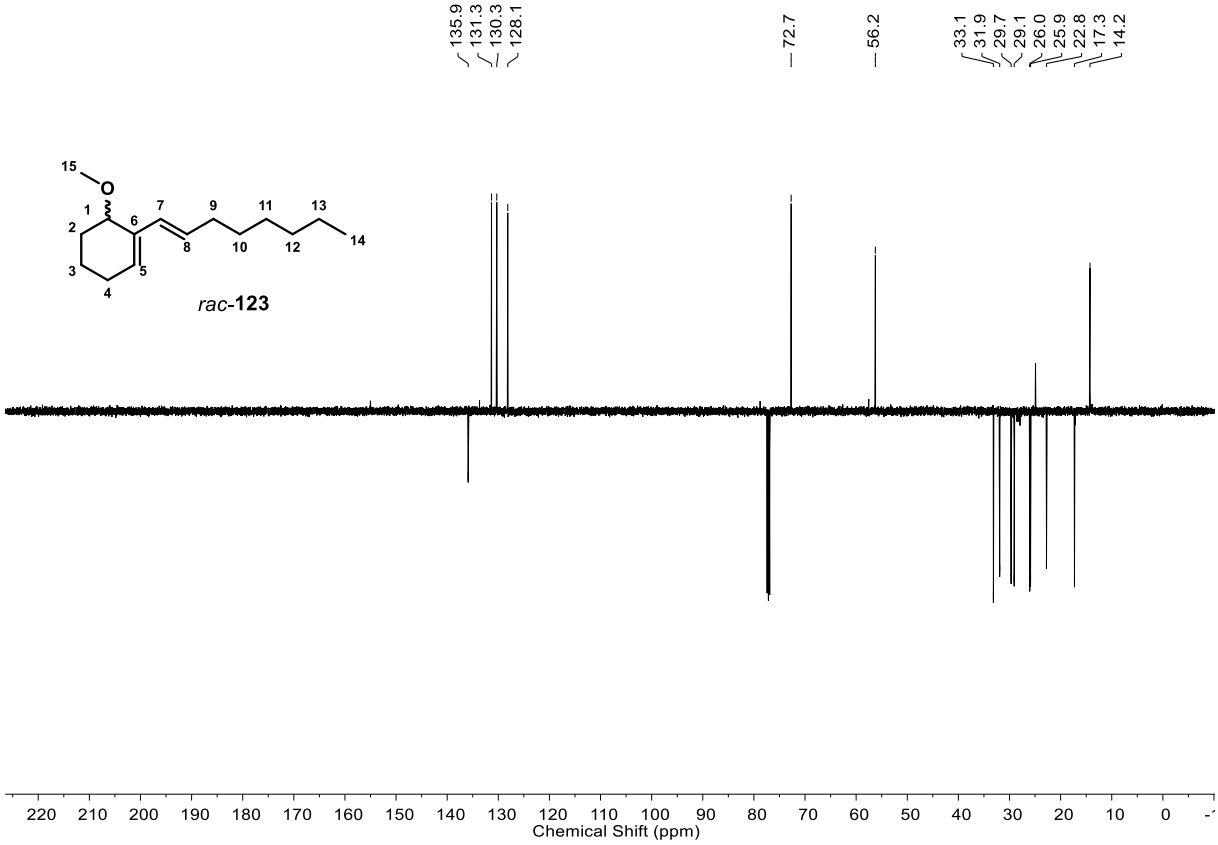


Figure 31: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-1-methoxy-2-(1-octen-1-yl)-cyclohex-2-ene (*rac*-**123**).

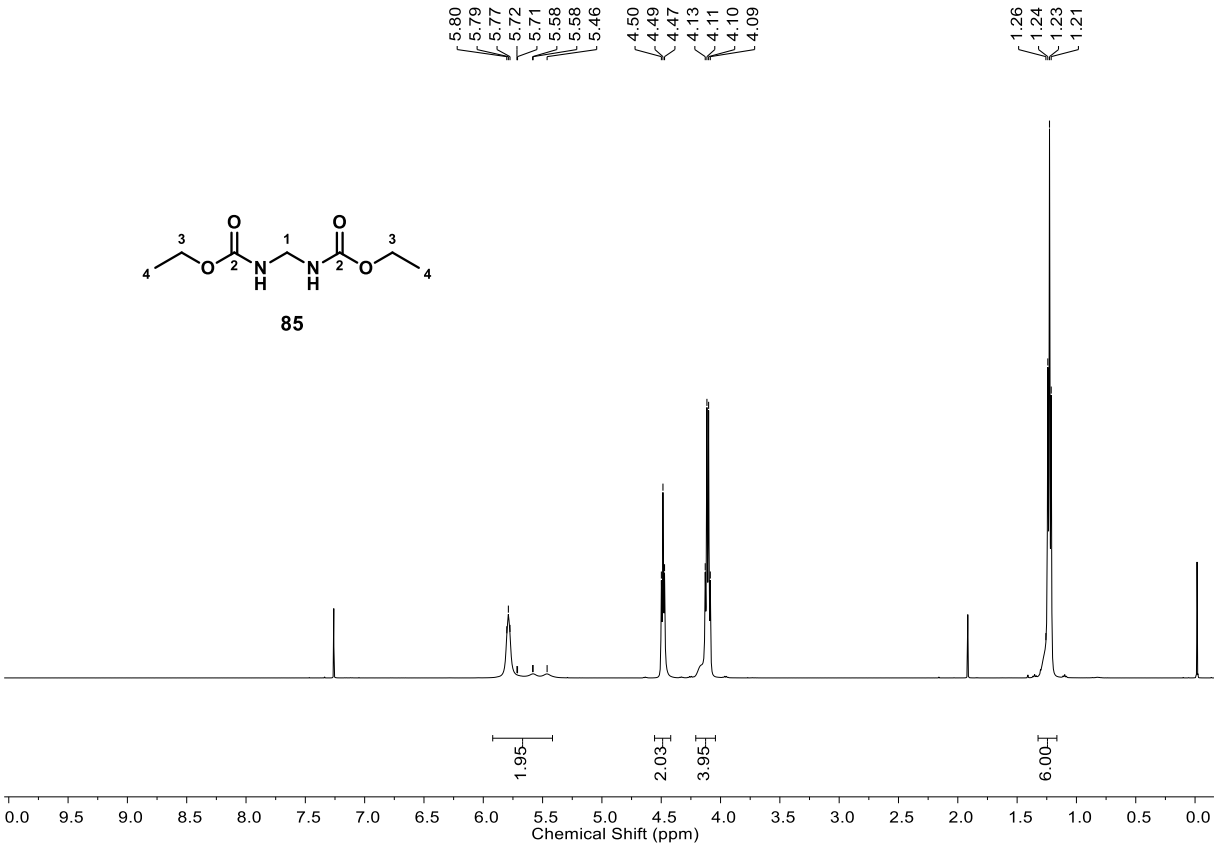


Figure 32: ^{1}H NMR (500 MHz, $CDCl_3$) of diethyl methylenedicarbamate (**85**).

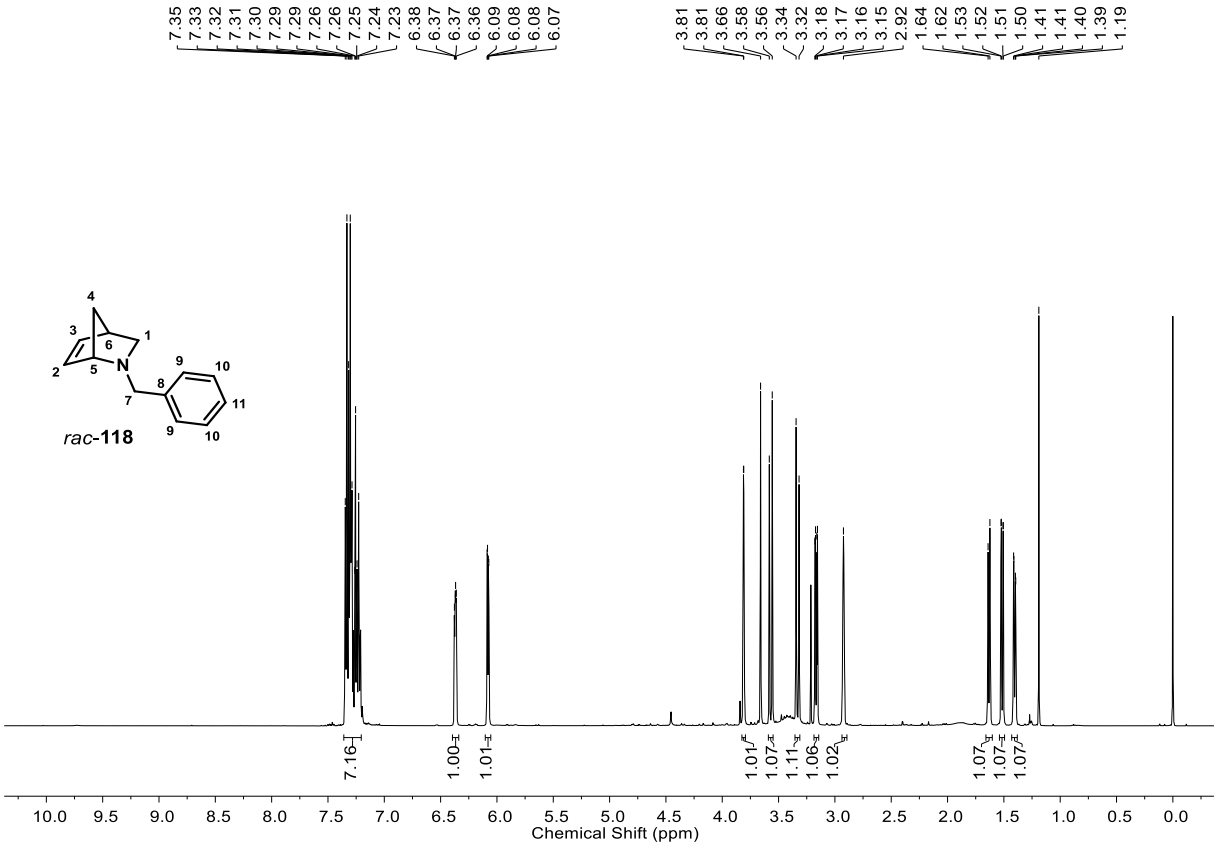


Figure 33: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-*N*-benzyl-2-azanorbornene (*rac*-**118**).

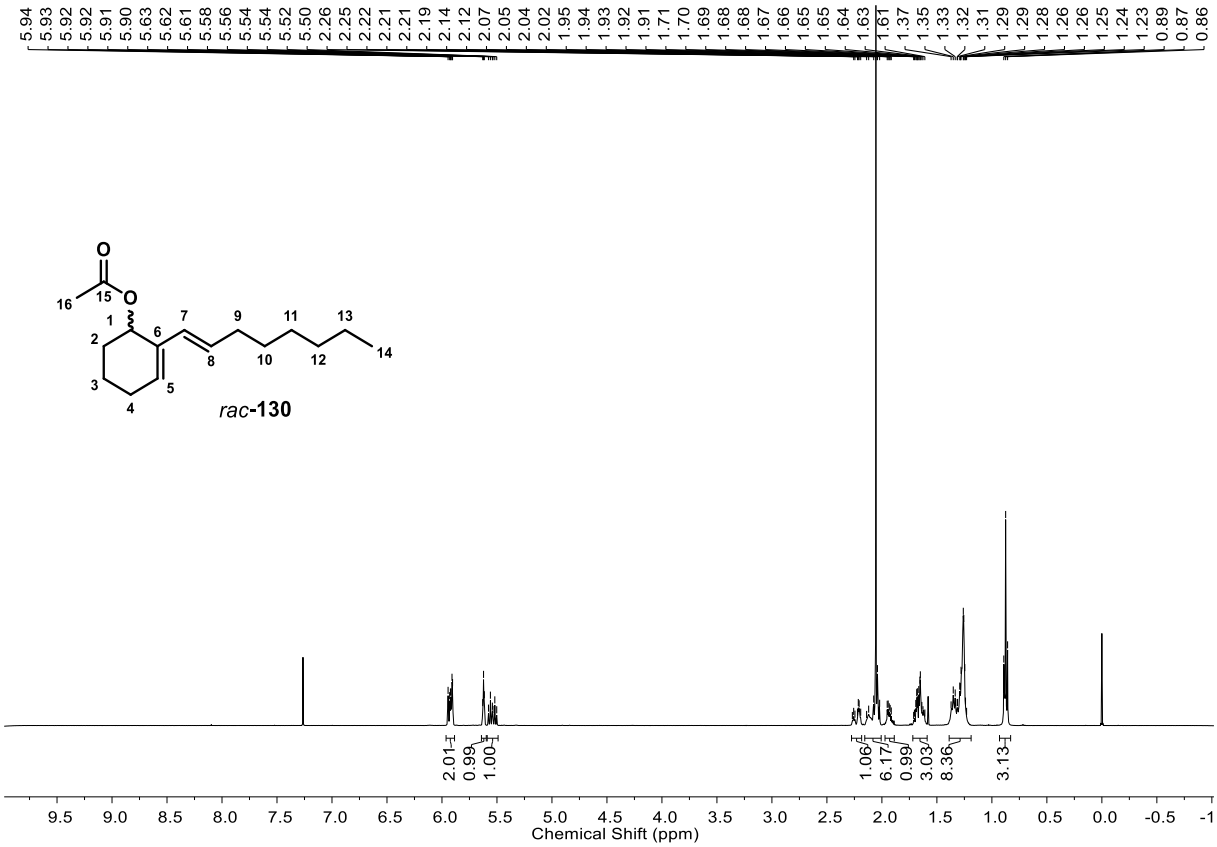


Figure 34: ^{1}H NMR (400 MHz, $CDCl_3$) of *rac*-1-acetoxy-2-(1-octen-1-yl)-cyclohex-2-ene (*rac*-**130**).

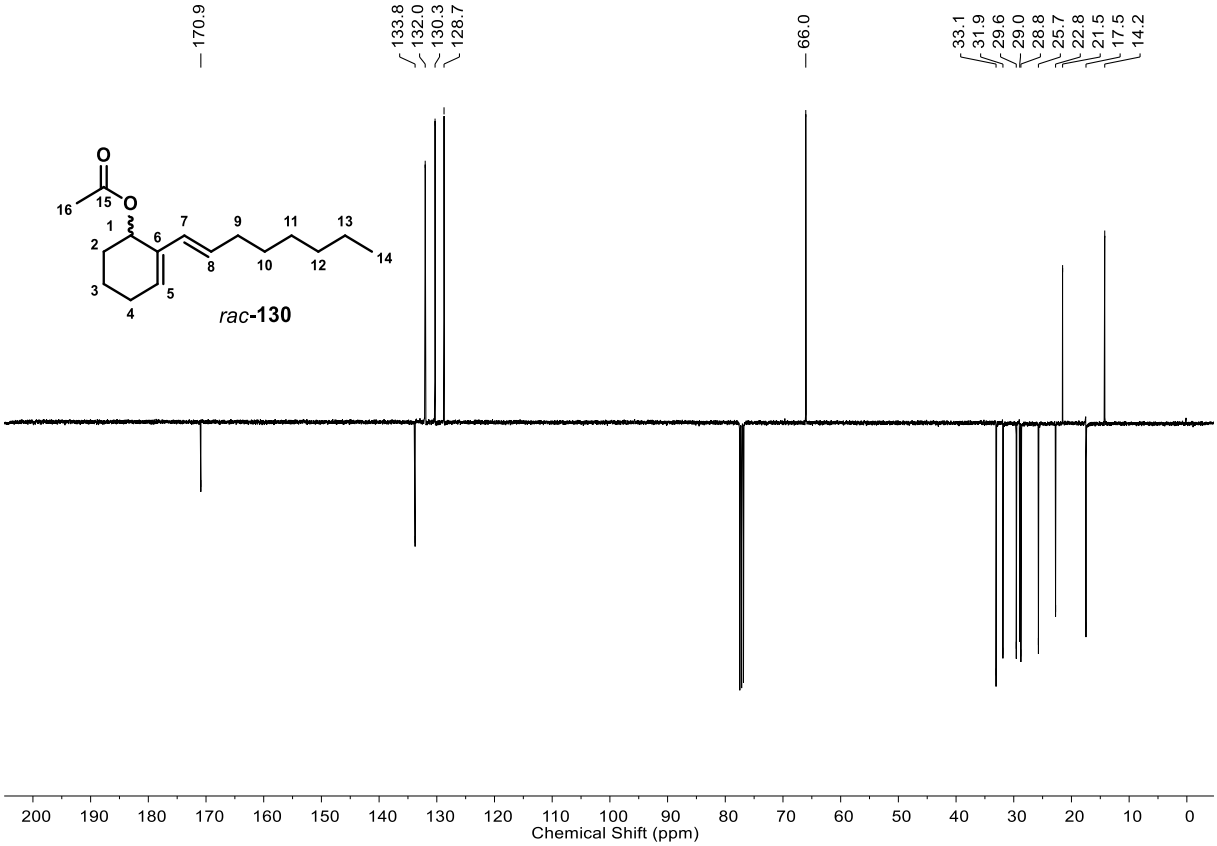


Figure 35: ^{13}C NMR (101 MHz, $CDCl_3$) of *rac*-1-acetoxy-2-(1-octen-1-yl)-cyclohex-2-ene (*rac*-**130**).

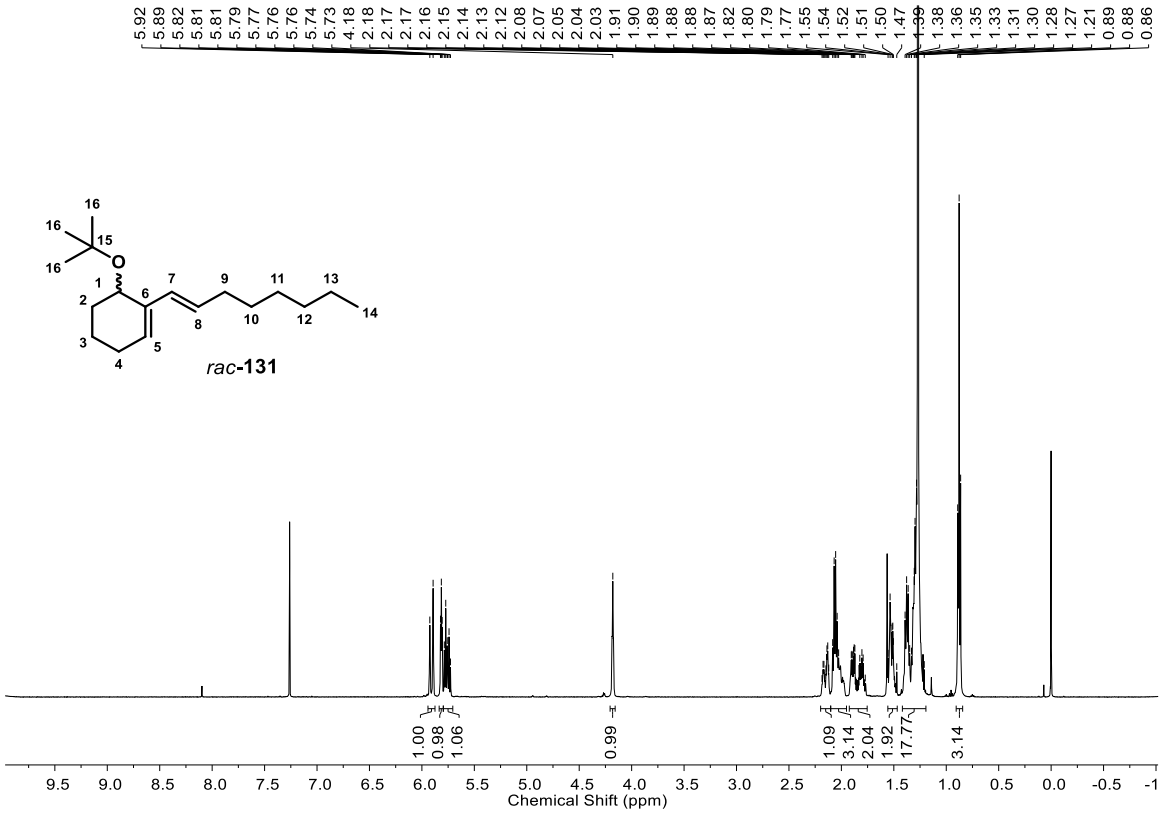


Figure 36: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-1-(1,1-Dimethylethoxy)-2-(1-octen-1-yl)-cyclohex-2-ene (*rac*-**131**).

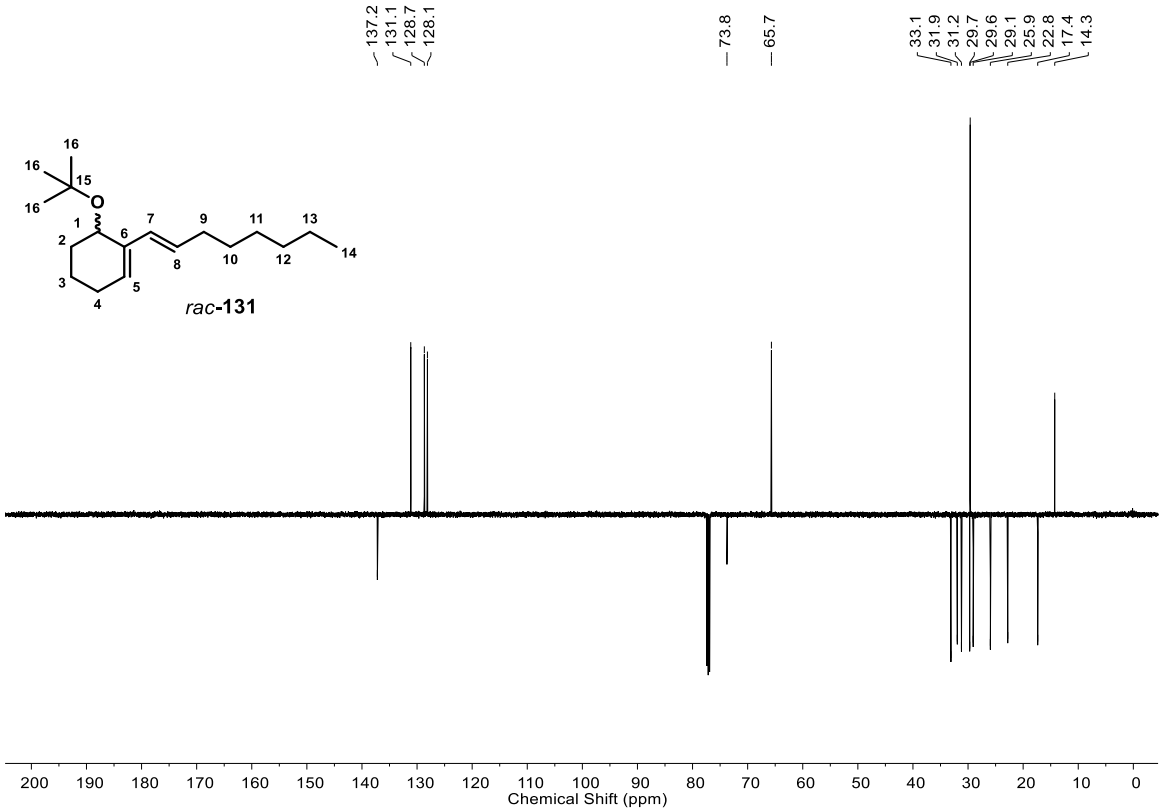


Figure 37: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-1-(1,1-Dimethylethoxy)-2-(1-octen-1-yl)-cyclohex-2-ene (*rac*-**131**).

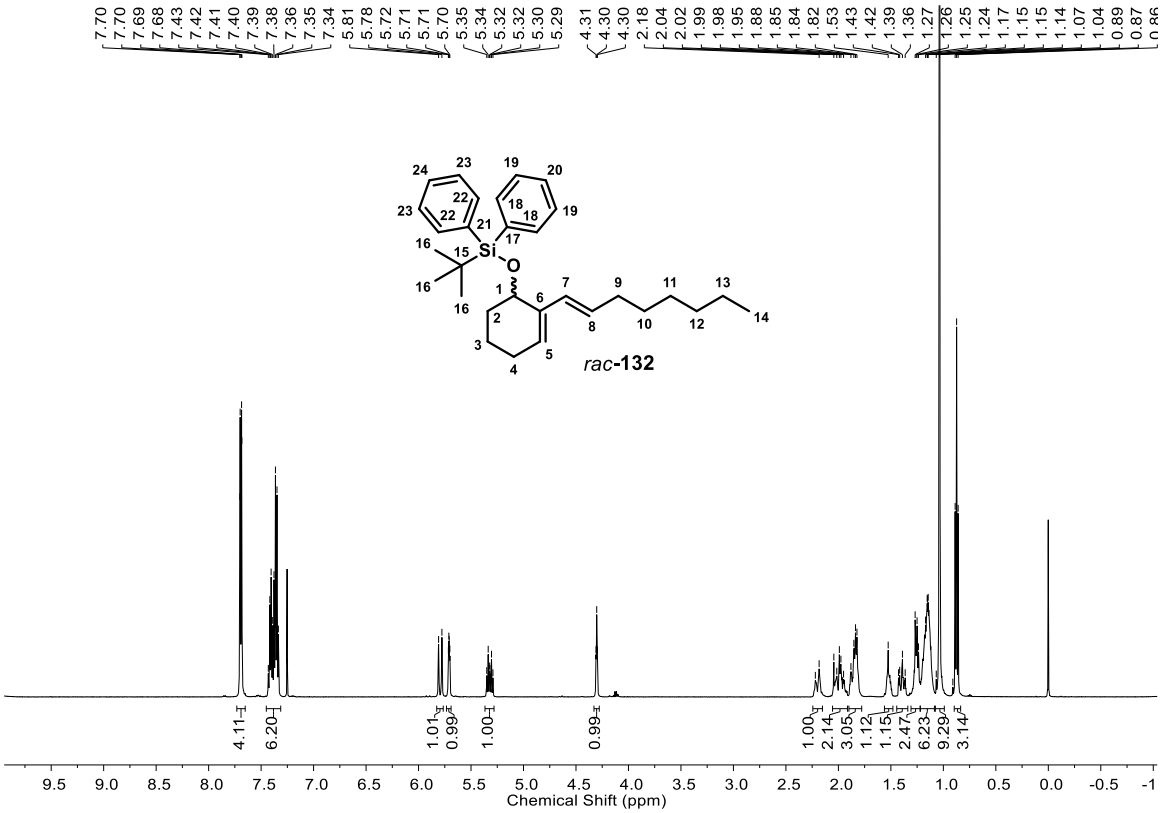


Figure 38: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-1-(*tert*-Butyldiphenylsilyloxy)-2-(1-octen-1-yl)-cyclohex-2-ene (*rac*-**132**).

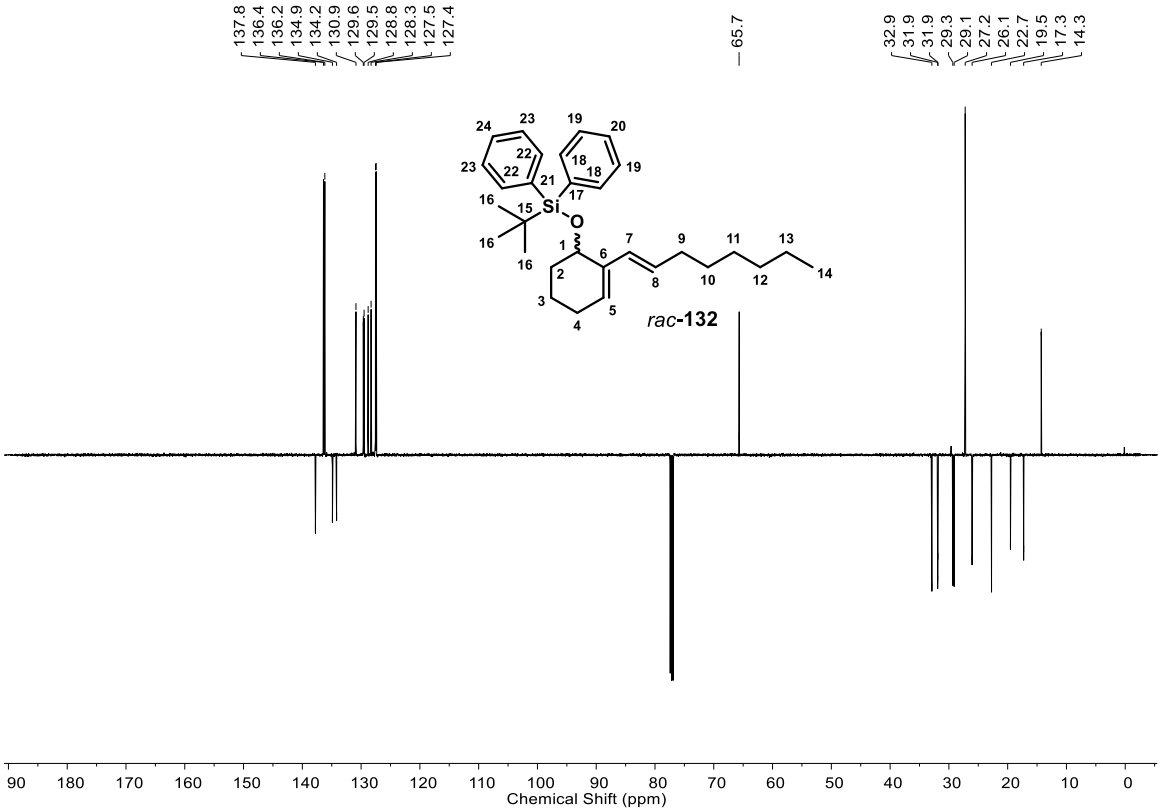


Figure 39: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-1-(*tert*-Butyldiphenylsilyloxy)-2-(1-octen-1-yl)-cyclohex-2-ene (*rac*-**132**).

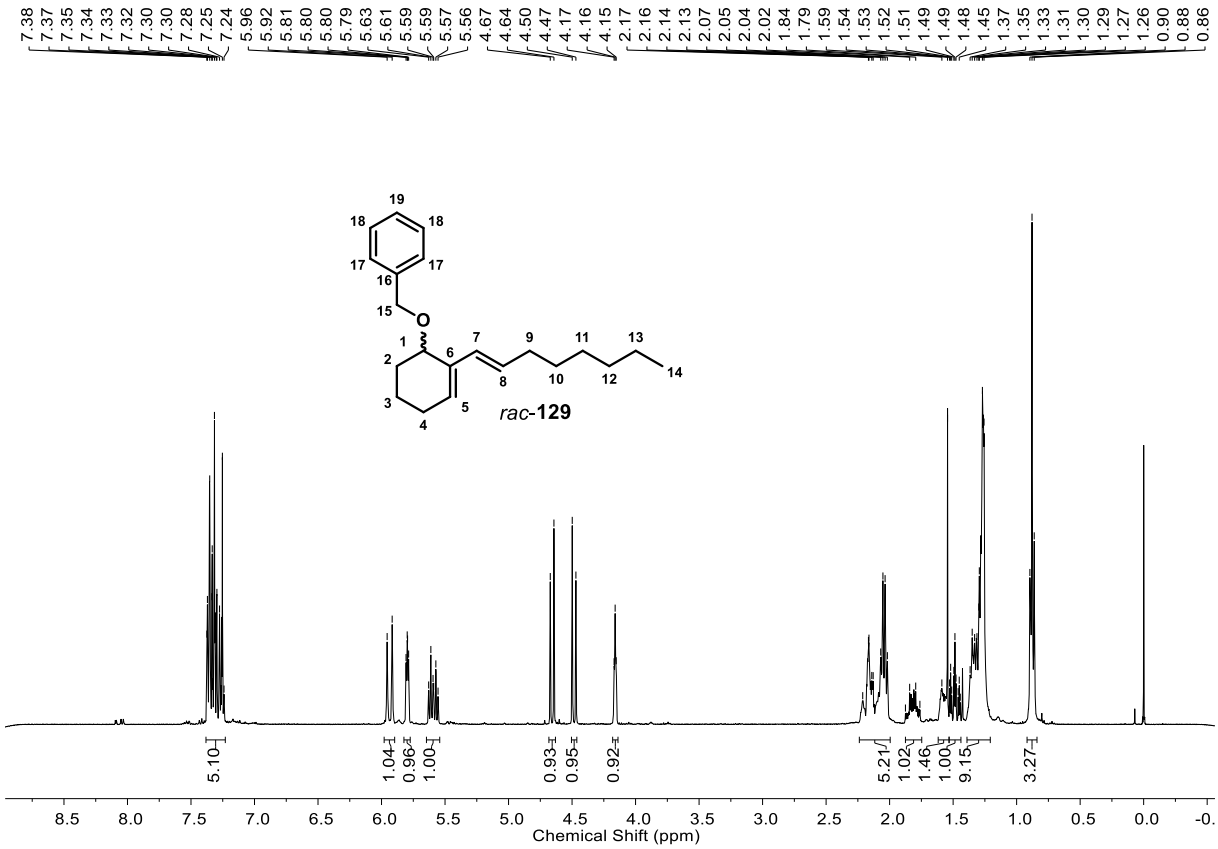


Figure 40: ^{1}H NMR (400 MHz, $CDCl_3$) of *rac*-1-(benzyloxy)-2-(1-octen-1-yl)-cyclohex-2-ene (*rac*-**129**).

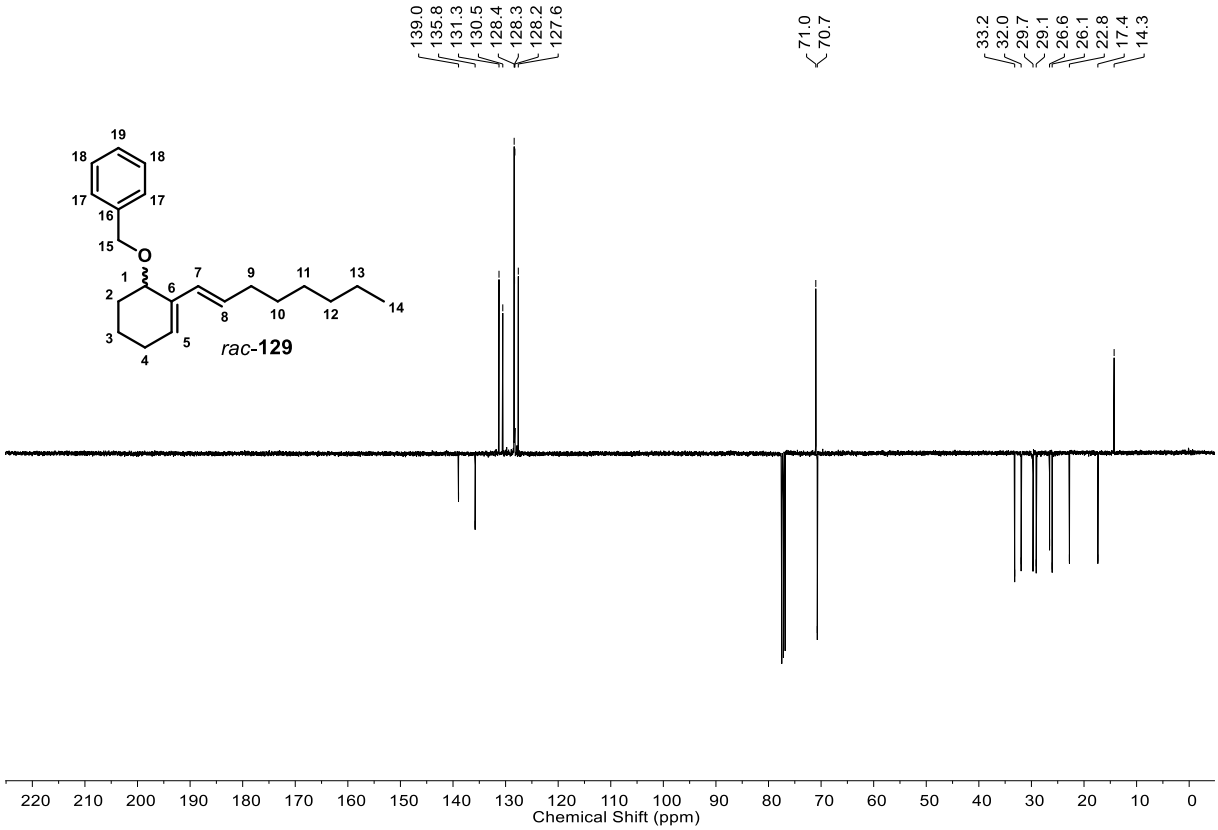


Figure 41: ^{13}C NMR (101 MHz, $CDCl_3$) of *rac*-1-(benzyloxy)-2-(1-octen-1-yl)-cyclohex-2-ene (*rac*-**129**).

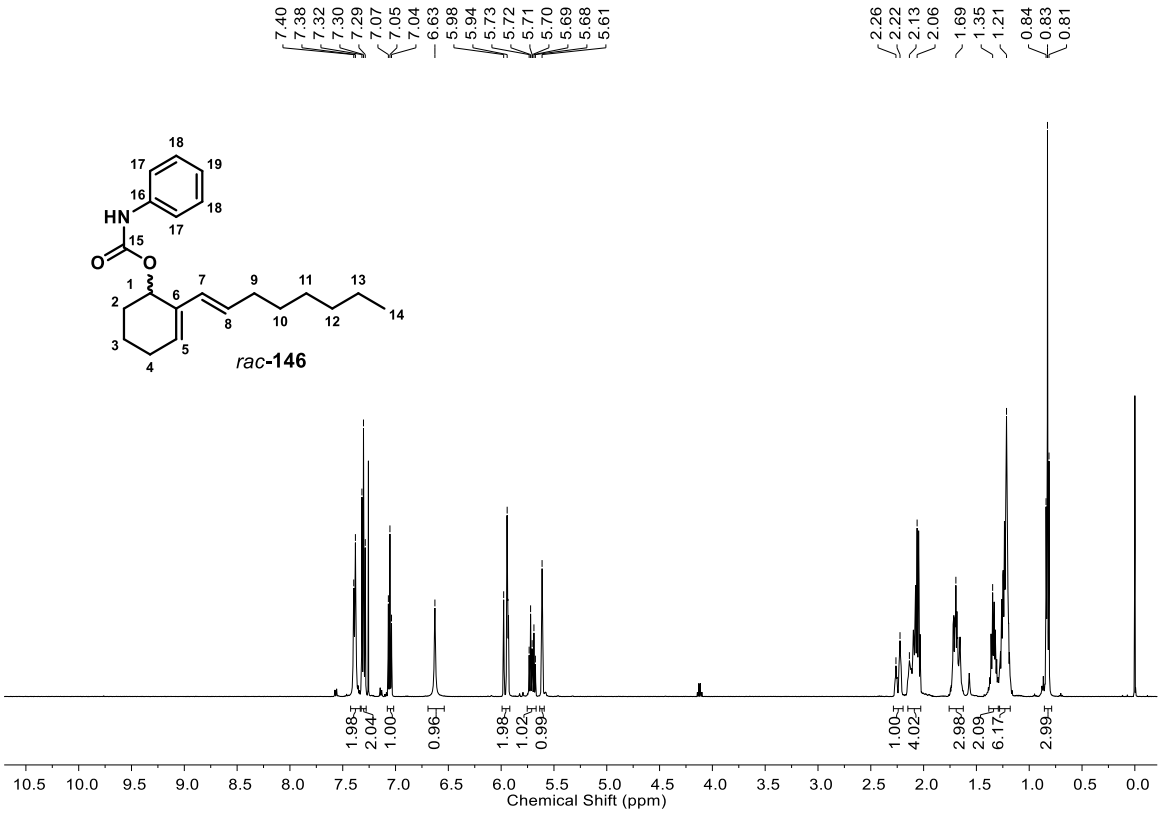


Figure 42: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-2-((*E*)-1-octen-1-yl)-cyclohex-2-en-1-yl phenylcarbamate (*rac*-**146**).

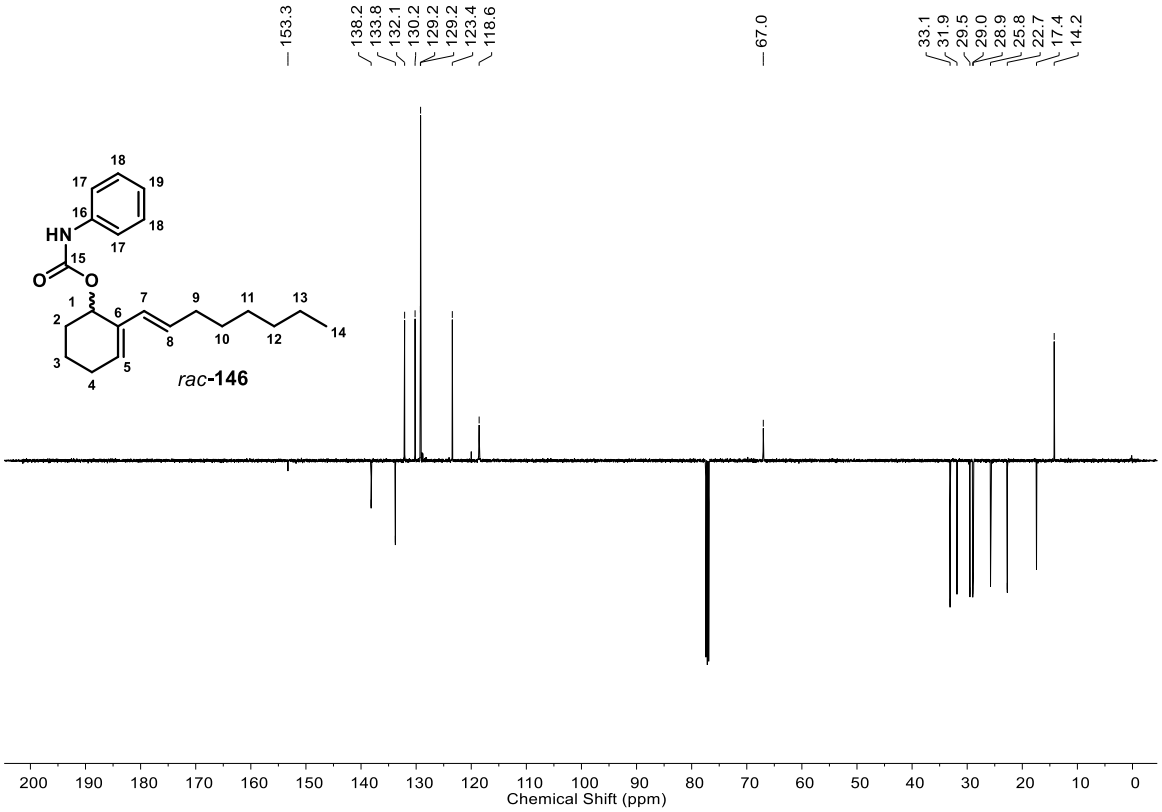


Figure 43: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-2-((*E*)-1-octen-1-yl)-cyclohex-2-en-1-yl phenylcarbamate (*rac*-**146**).

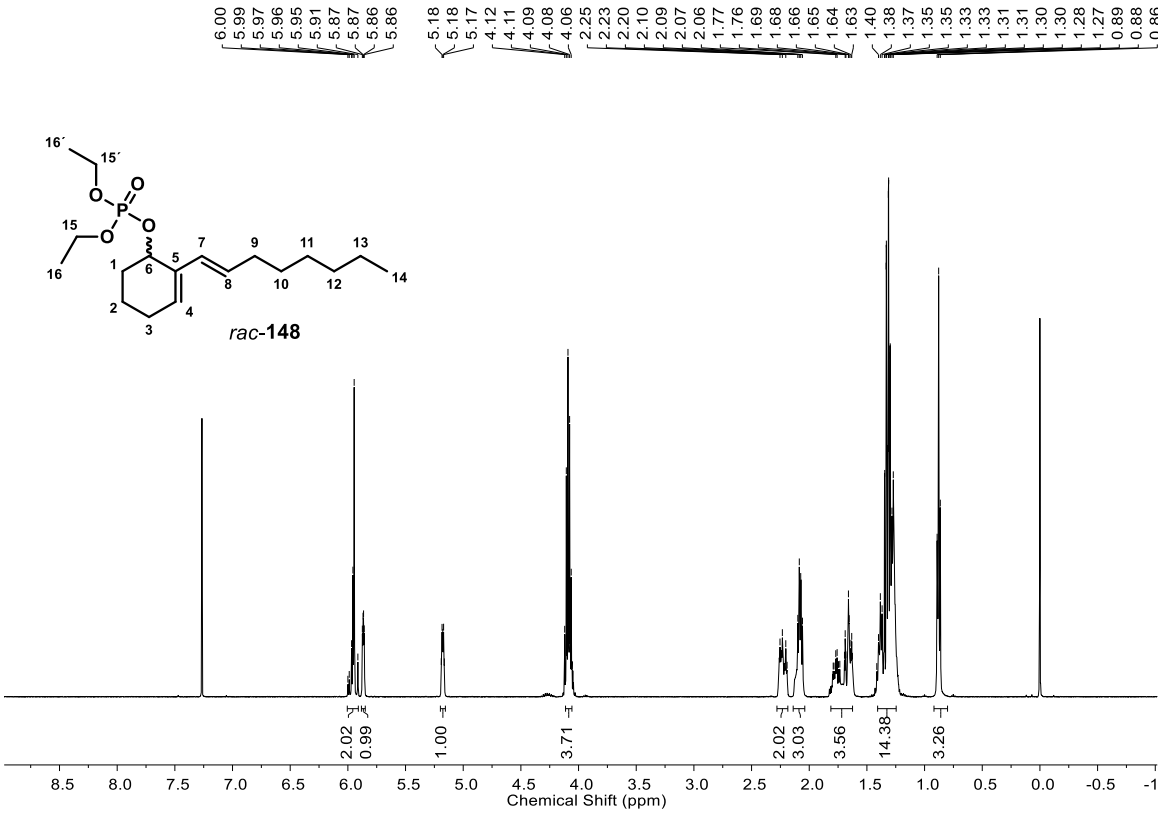


Figure 44: ^{1}H NMR (500 MHz, $CDCl_3$) of rac-diethyl 2-((*E*)-oct-1-en-1-yl)-cyclohex-2-en-1-yl phosphate (*rac*-**148**).

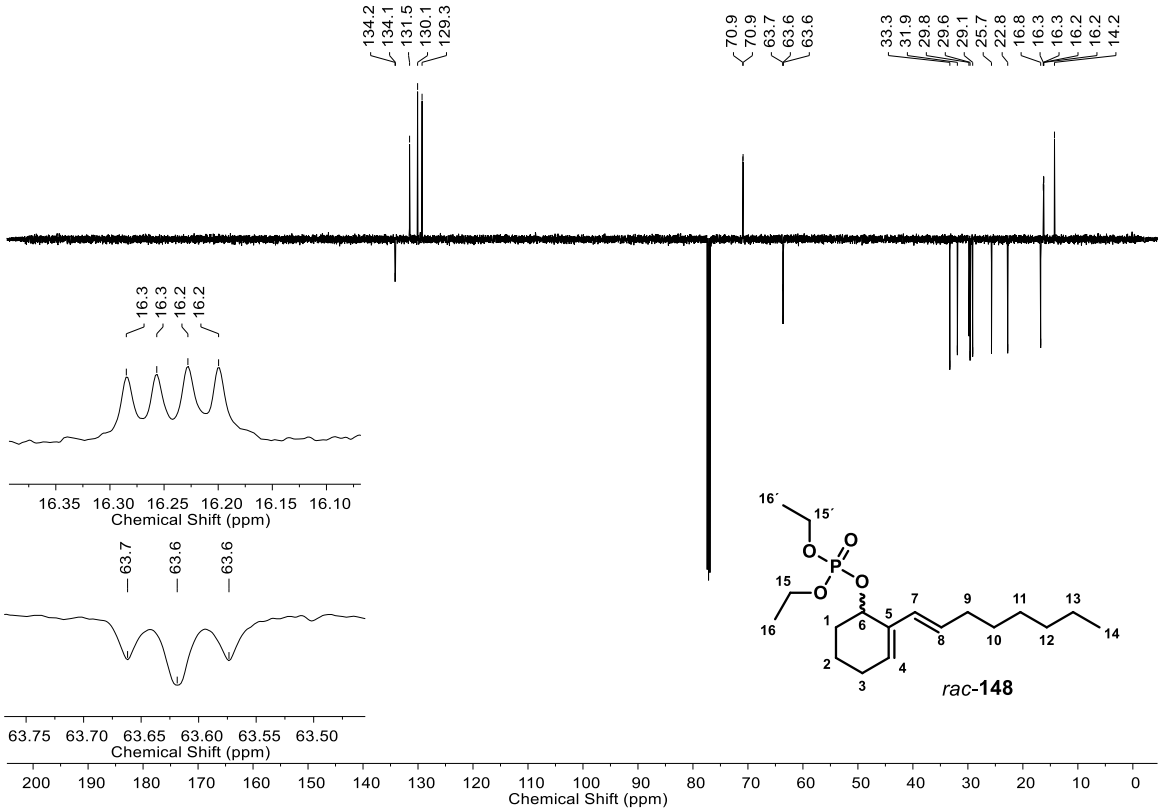


Figure 45: ^{13}C NMR (126 MHz, $CDCl_3$) of rac-diethyl 2-((*E*)-oct-1-en-1-yl)-cyclohex-2-en-1-yl phosphate (*rac*-**148**).

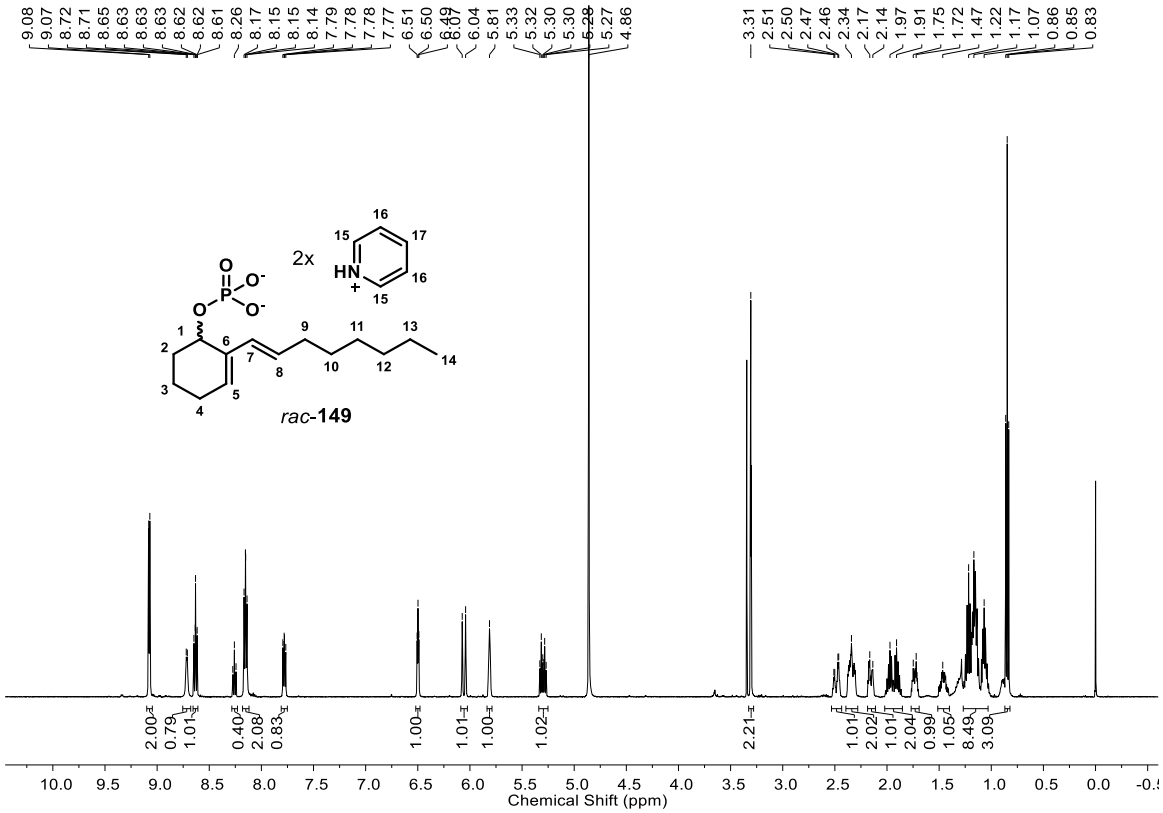


Figure 46: ^{1}H NMR (500 MHz, MeOD-d$_4$) of *rac*-dipyridinium 2-((*E*)-oct-1-ene-1-yl)cyclohex-2-ene-1-yl phosphate (*rac*-**149**).

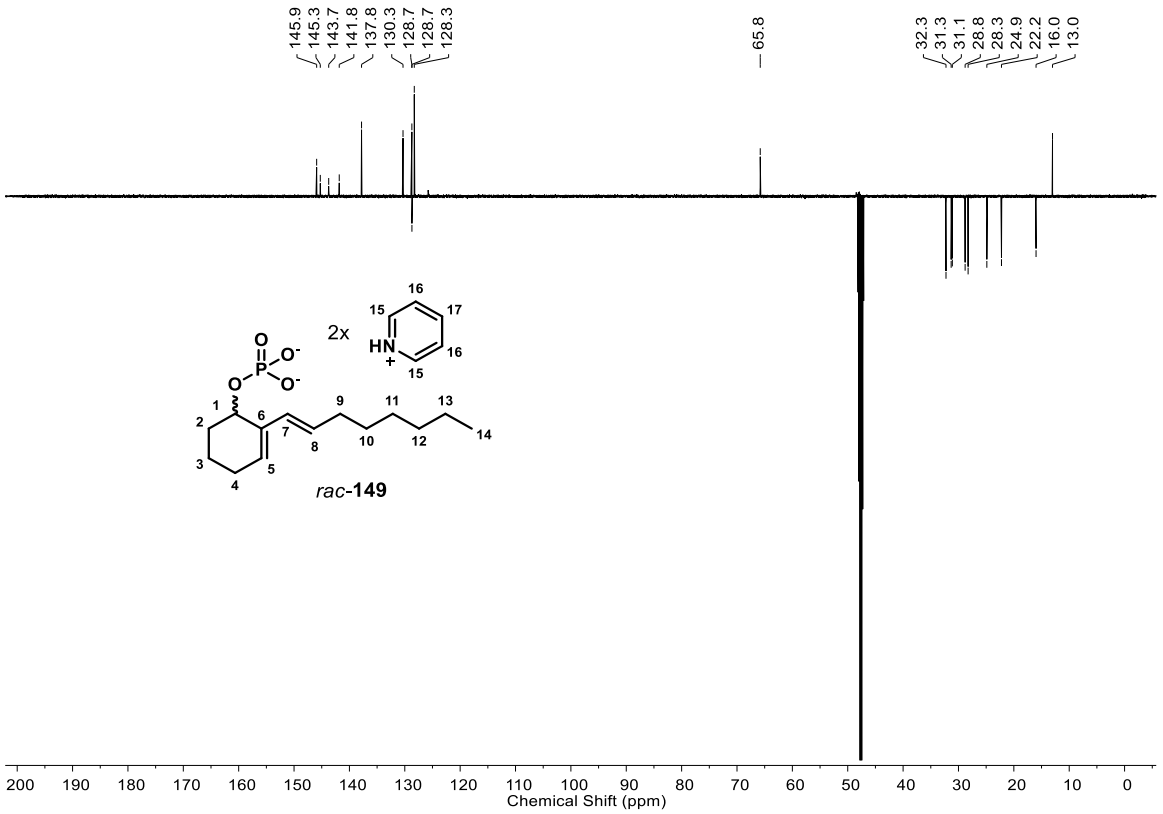


Figure 47: ^{13}C NMR (126 MHz, MeOD-d$_4$) of *rac*-dipyridinium 2-((*E*)-oct-1-ene-1-yl)cyclohex-2-ene-1-yl phosphate (*rac*-**149**).

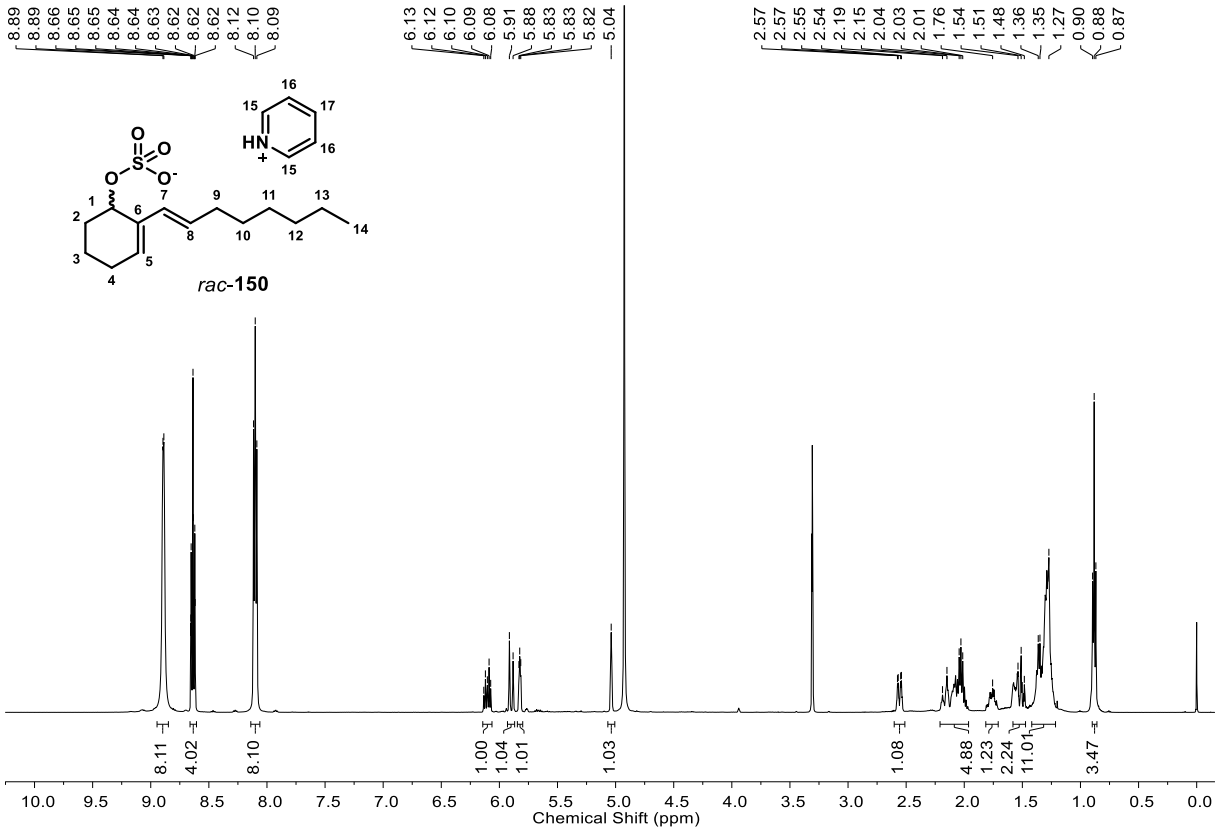


Figure 48: ^{1}H NMR (500 MHz, MeOD-d_4) of *rac*-pyridinium 2-((*E*)-oct-1-ene-1-yl)cyclohex-2-ene-1-yl sulfate (*rac*-**150**).

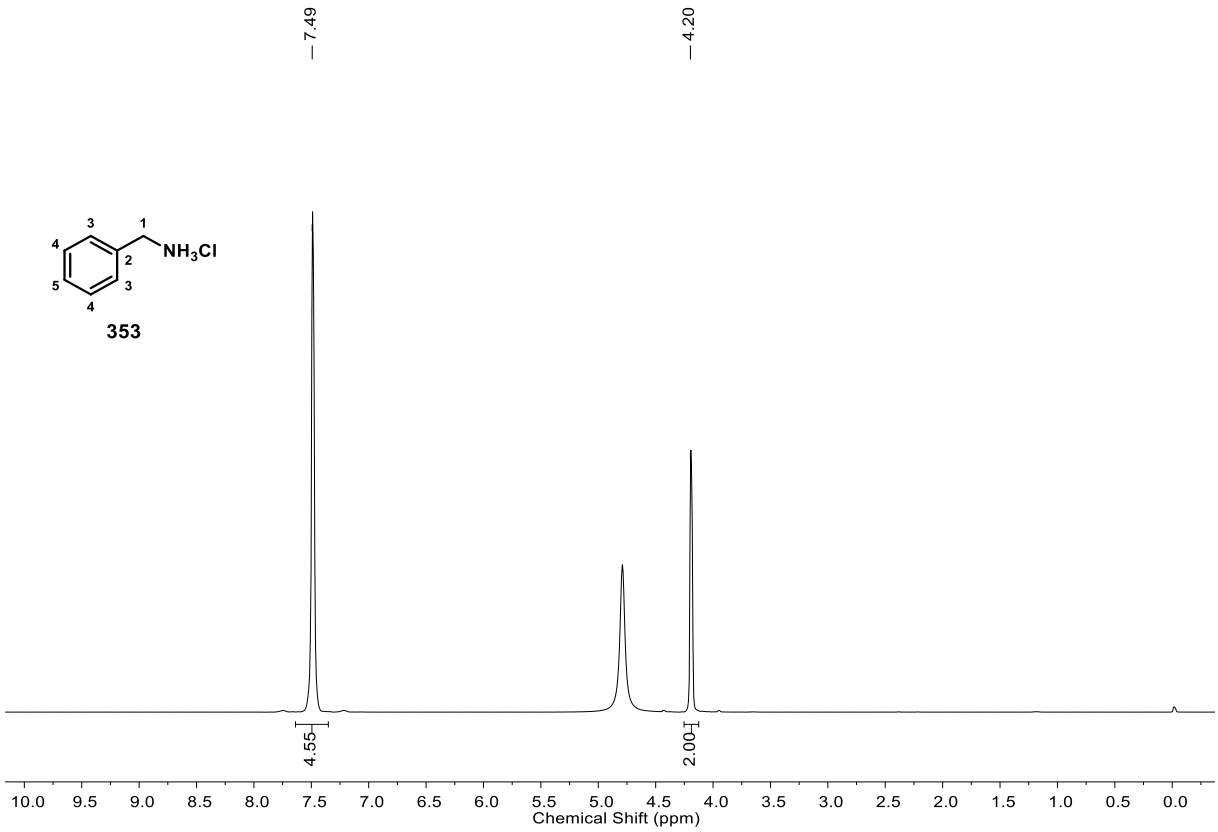


Figure 49: ^{1}H NMR (500 MHz, D_2O) benzylamine hydrochloride (**353**).

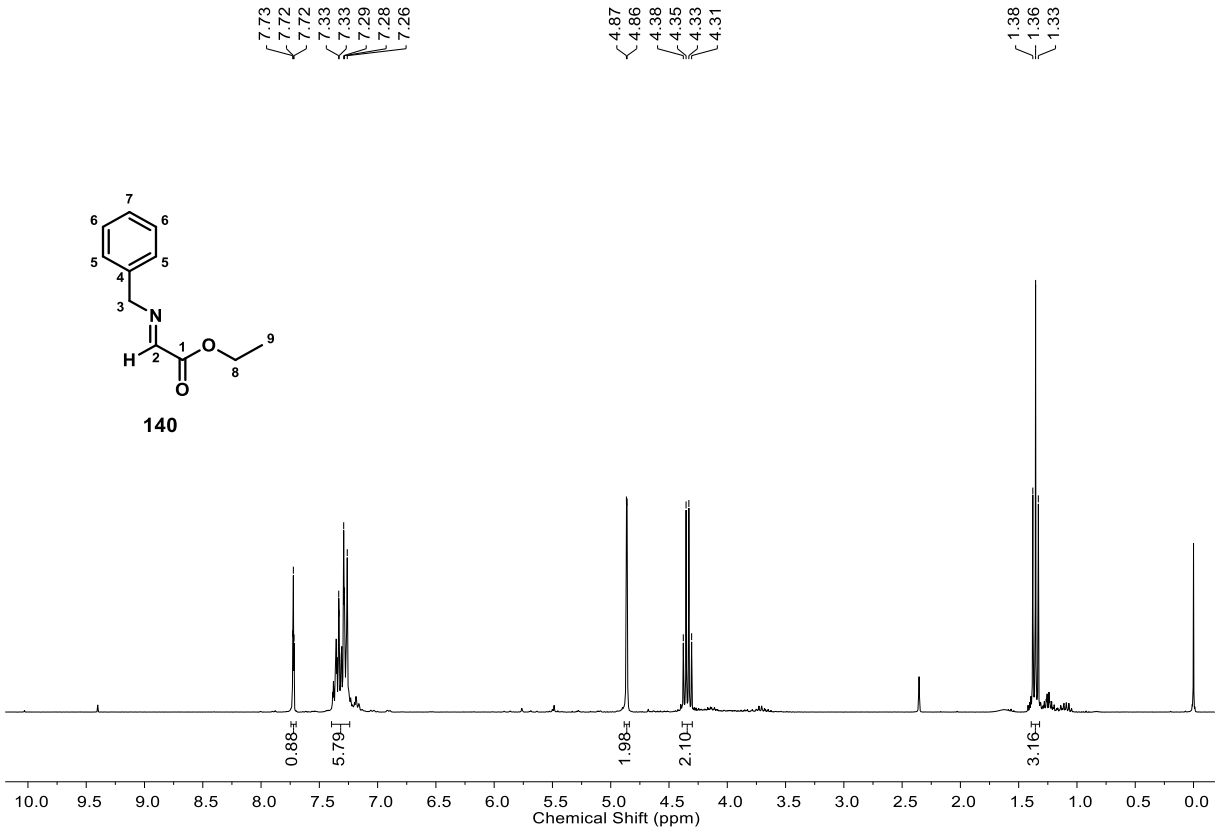


Figure 50: ^{1}H NMR (300 MHz, $CDCl_3$) of ethyl 2-(benzylimino)acetate (**140**).

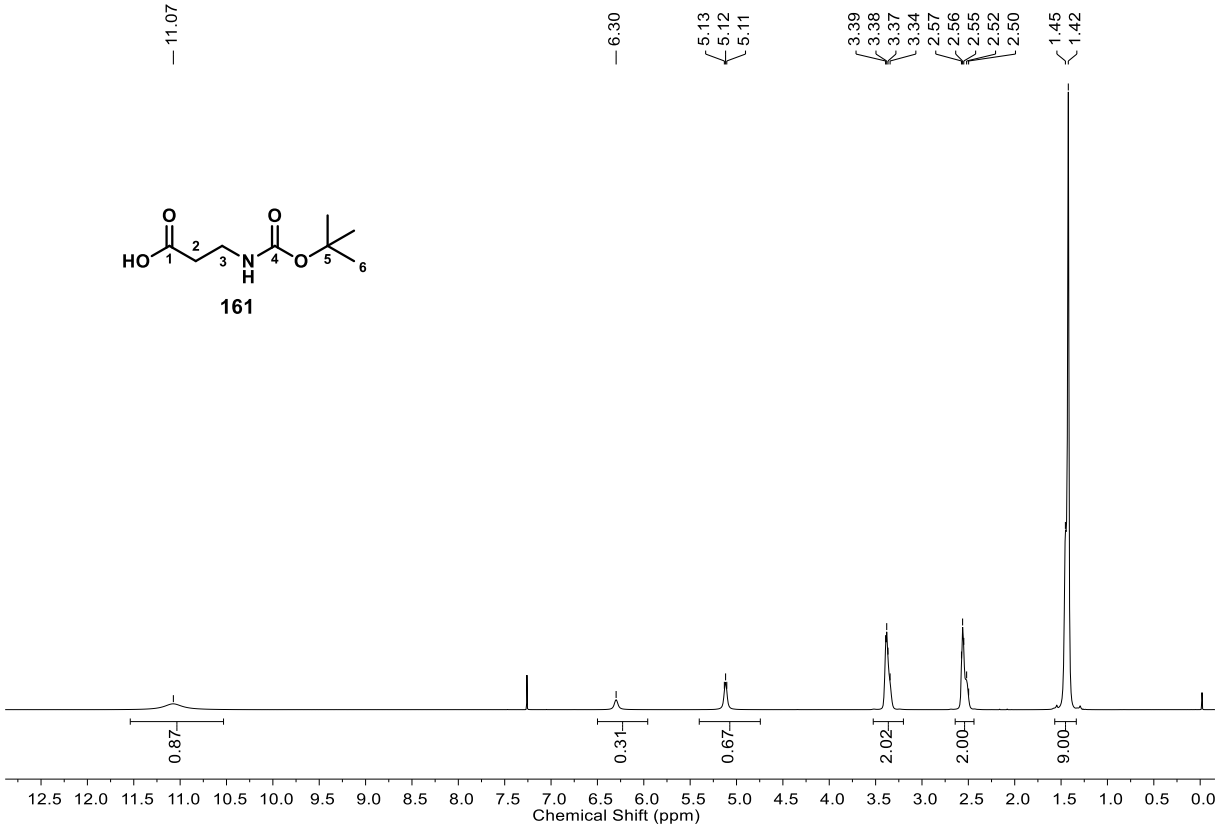


Figure 51: ^{1}H NMR (500 MHz, $CDCl_3$) of *N*-Boc-β-alanine (**161**).

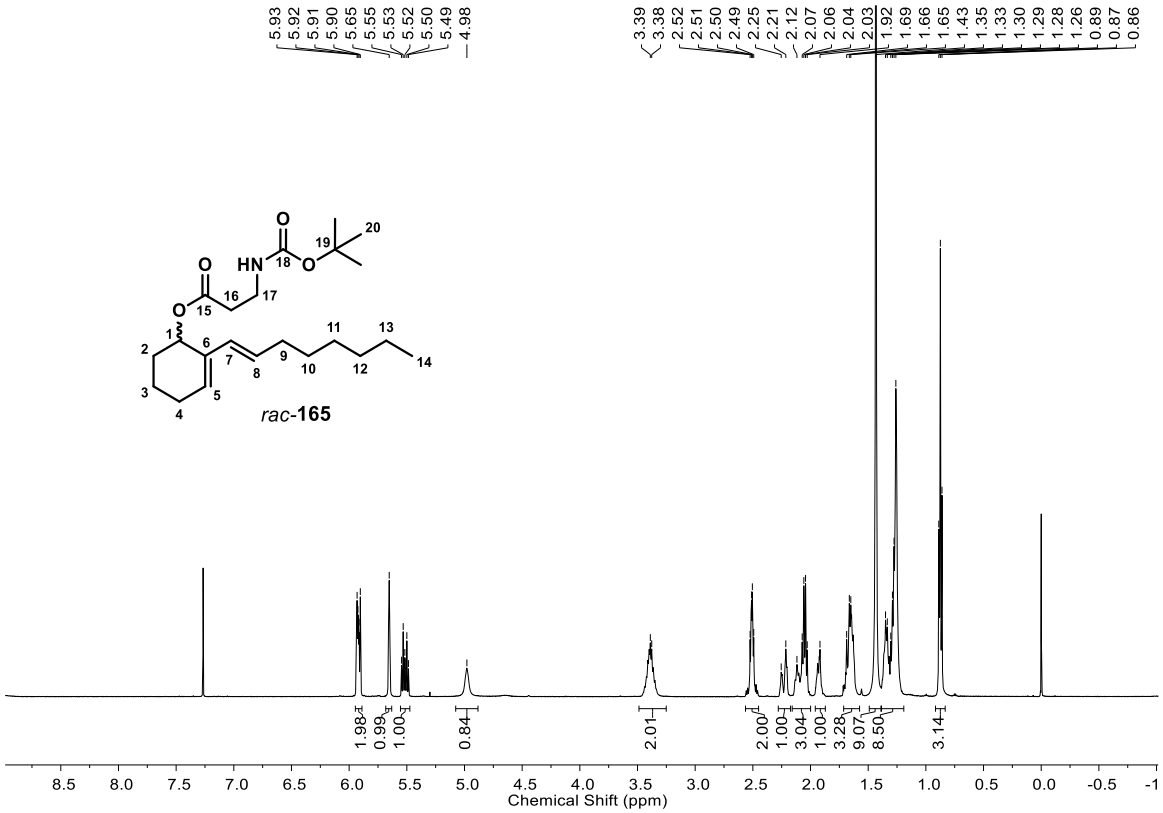


Figure 52: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-*N*-Boc-β-alanine 2-(1-octen-1-yl)-cyclohex-1-yl ester (*rac*-**165**).

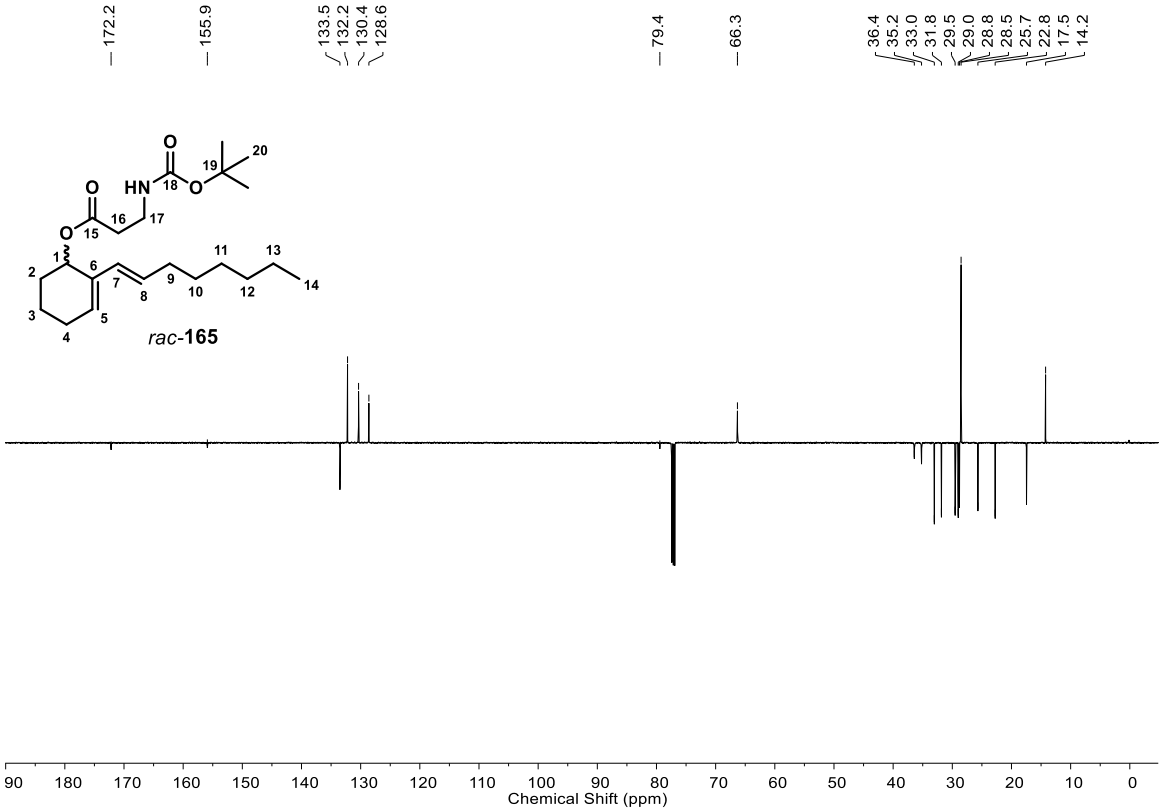


Figure 53: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-*N*-Boc-β-alanine 2-(1-octen-1-yl)-cyclohex-1-yl ester (*rac*-**165**).

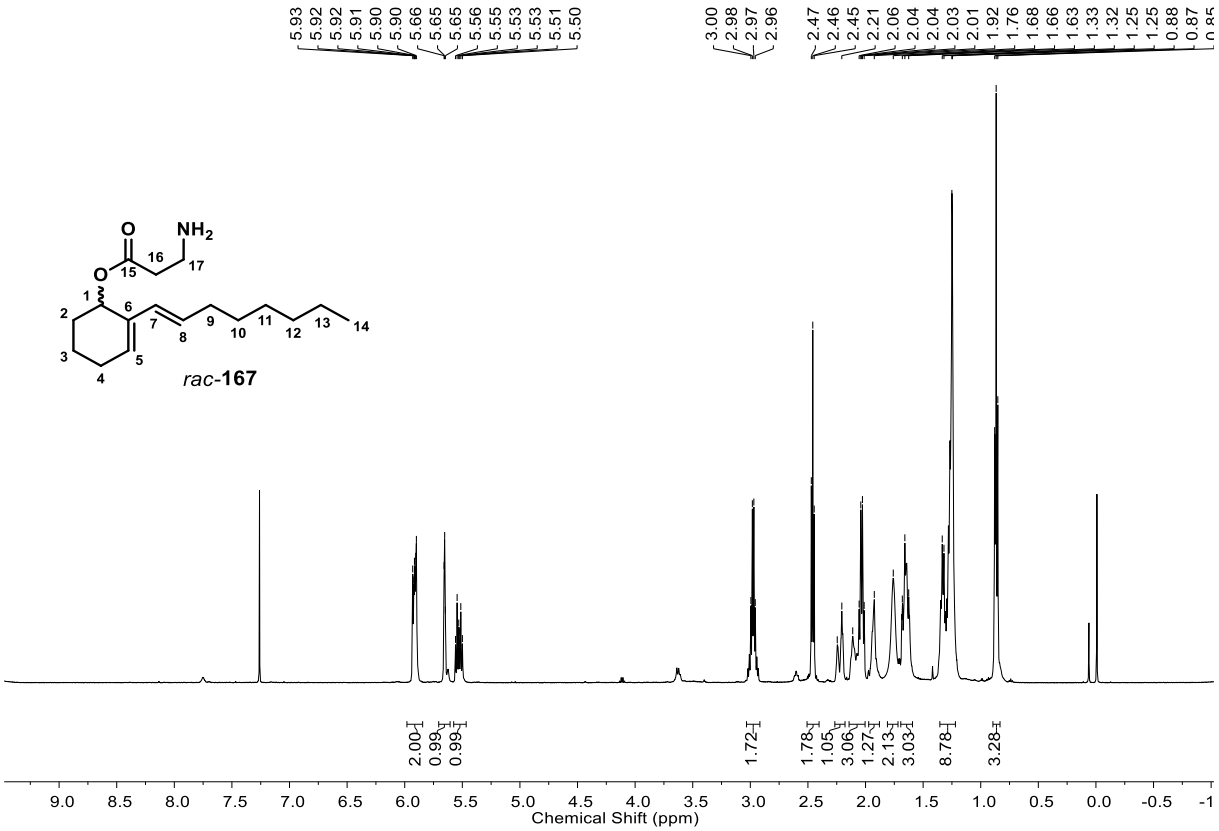


Figure 54: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-*β*-alanine 2-(1-octen-1-yl)-cyclohex-1-yl ester (*rac*-**167**).

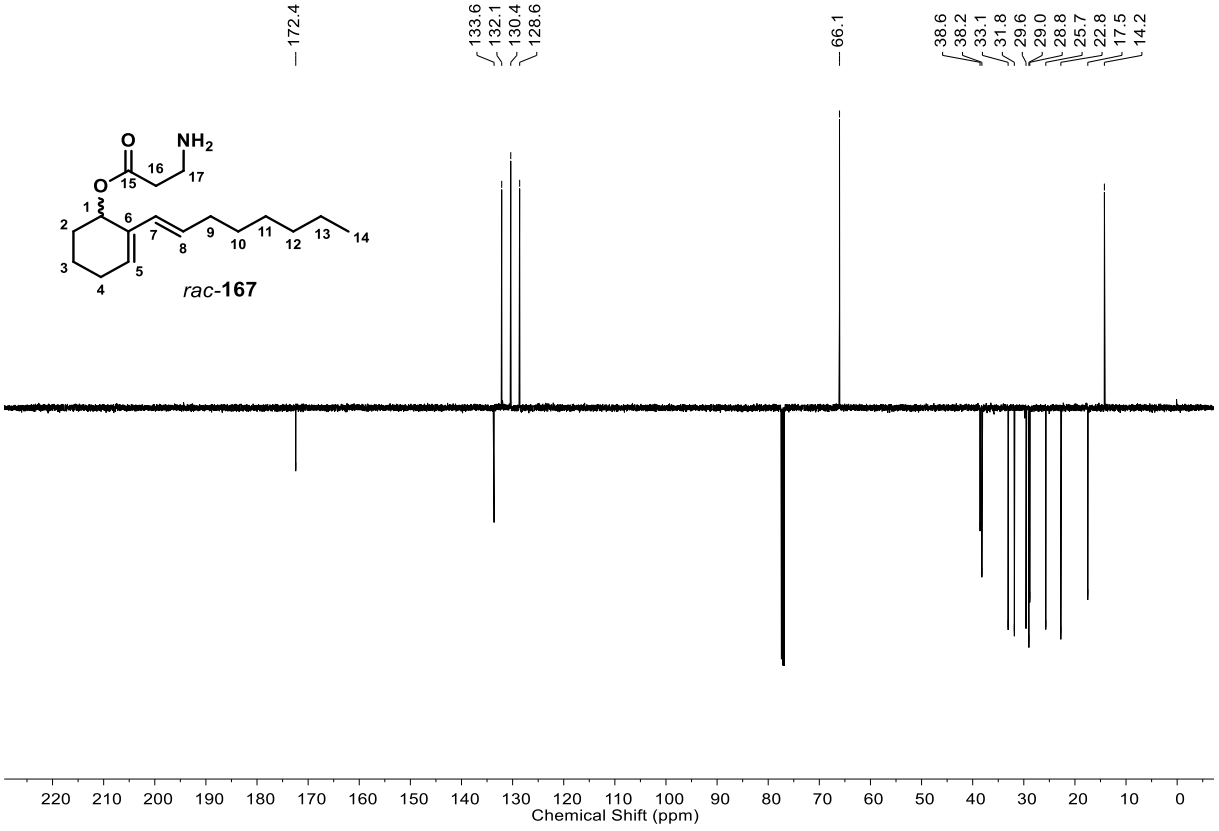
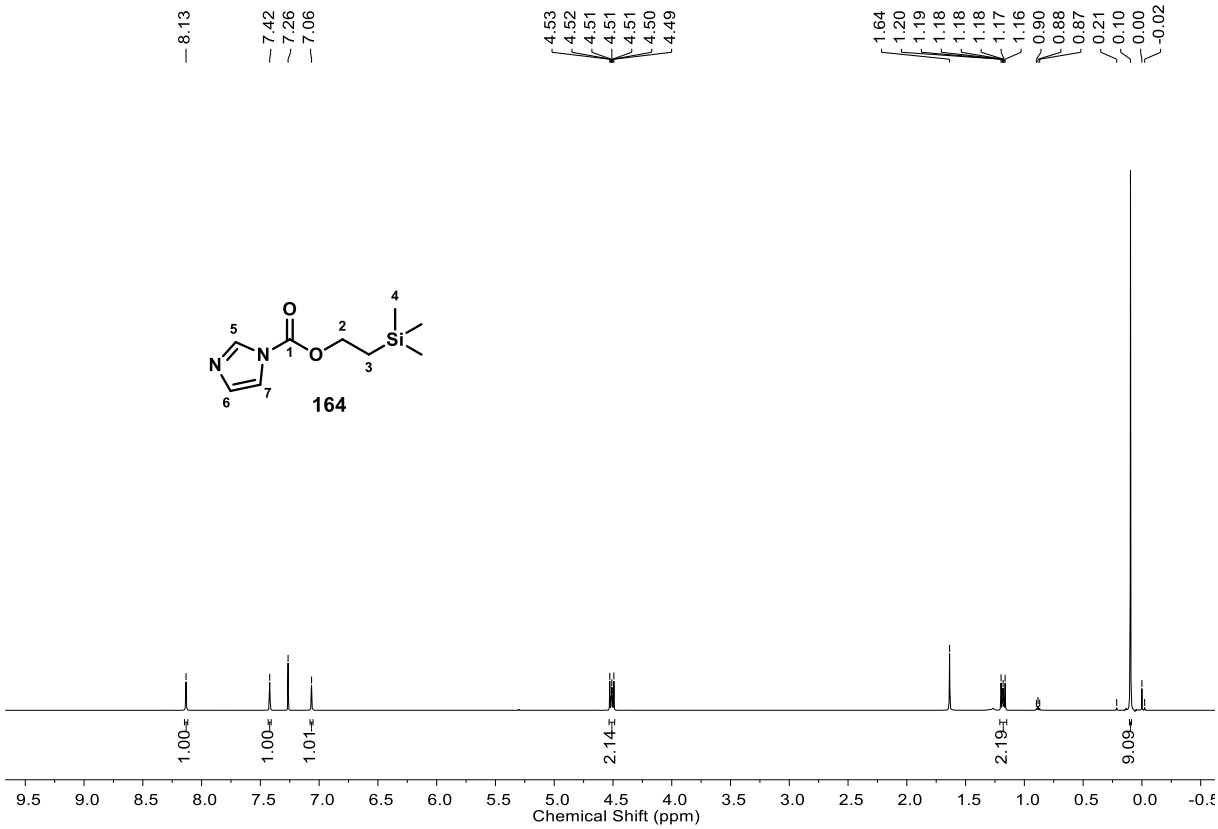
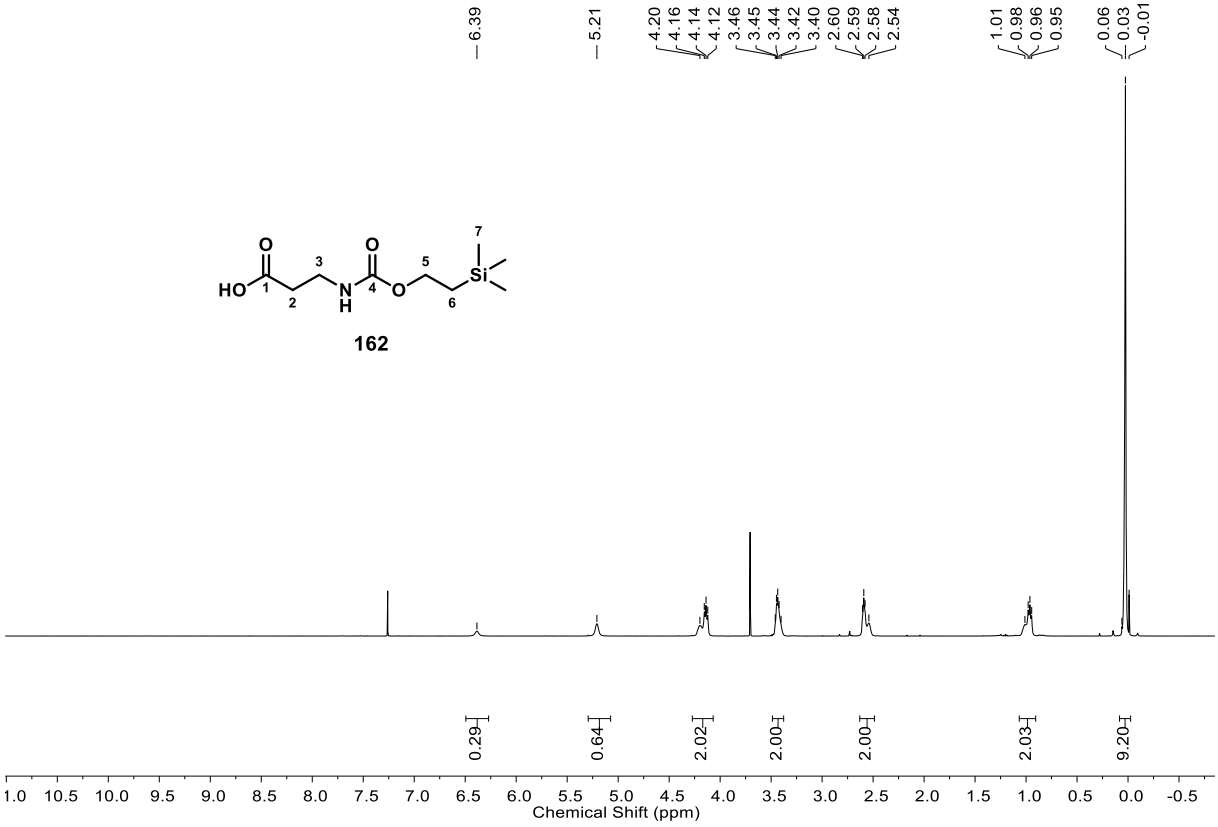


Figure 55: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-*β*-alanine 2-(1-octen-1-yl)-cyclohex-1-yl ester (*rac*-**167**).



164

Figure 56: ^{1}H NMR (500 MHz, $CDCl_3$) of 1-(*O*-(2-(Trimethylsilyl)ethyl)-oxycarbonyl)imidazole (**164**).



162

Figure 57: ^{1}H NMR (500 MHz, $CDCl_3$) of *N*-Teoc-β-alanine (**162**).

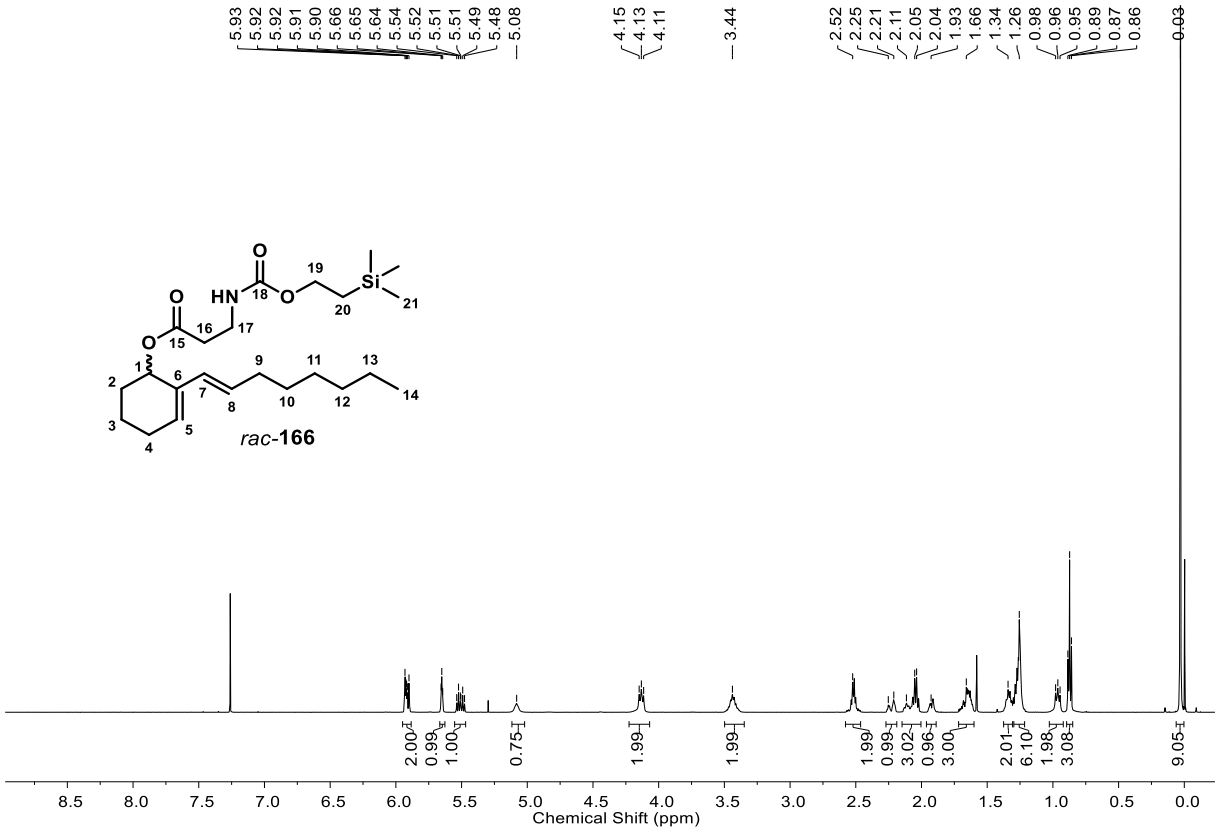


Figure 58: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-*N*-Teoc-β-alanine 2-(1-octen-1-yl)-cyclohex-1-yl ester (*rac*-**166**).

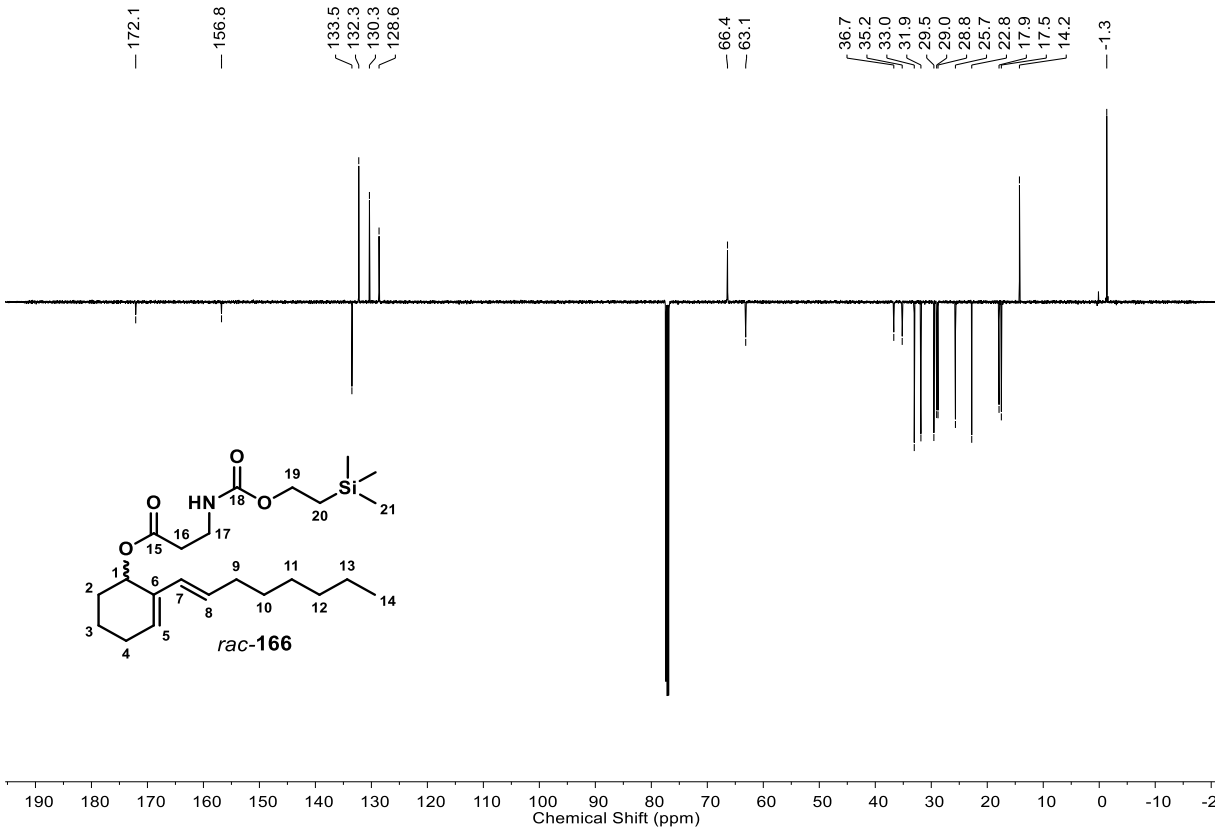


Figure 59: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-*N*-Teoc-β-alanine 2-(1-octen-1-yl)-cyclohex-1-yl ester (*rac*-**166**).

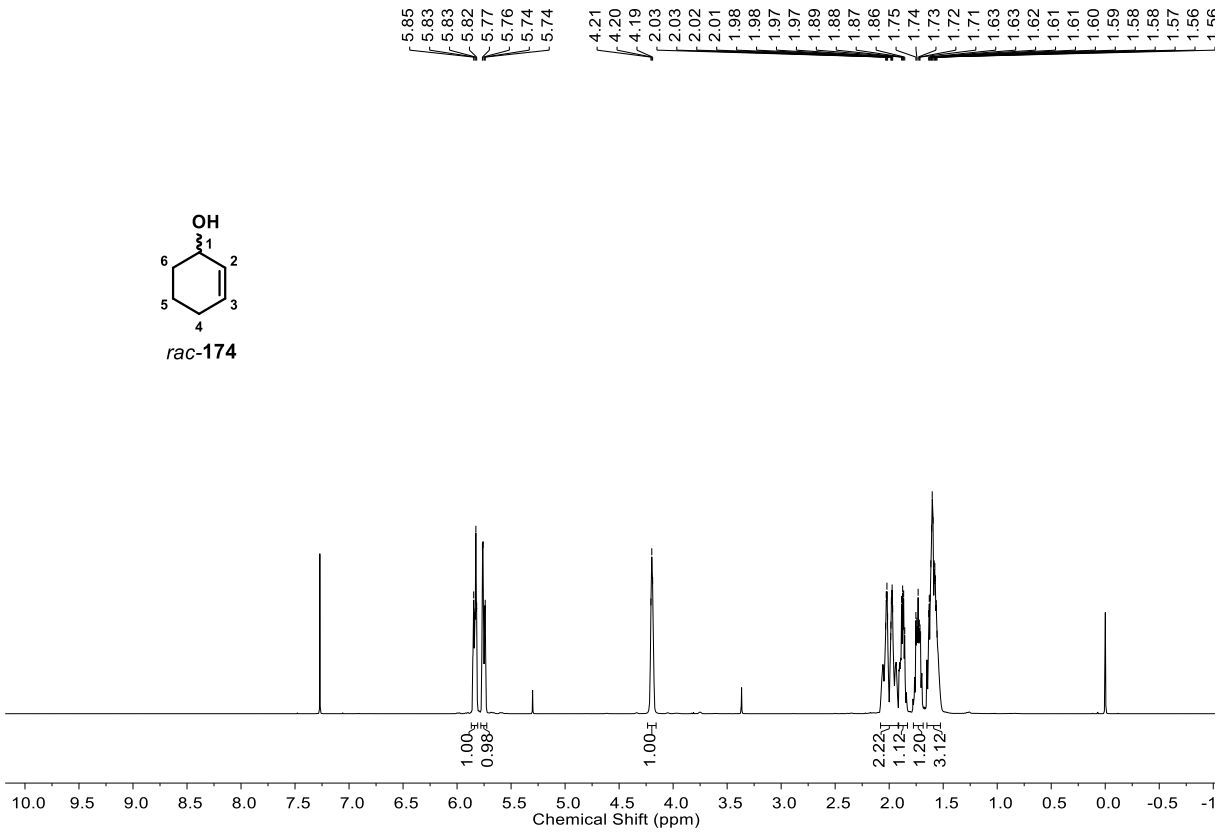


Figure 60: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-cyclohex-2-en-1-ol (*rac*-**174**).

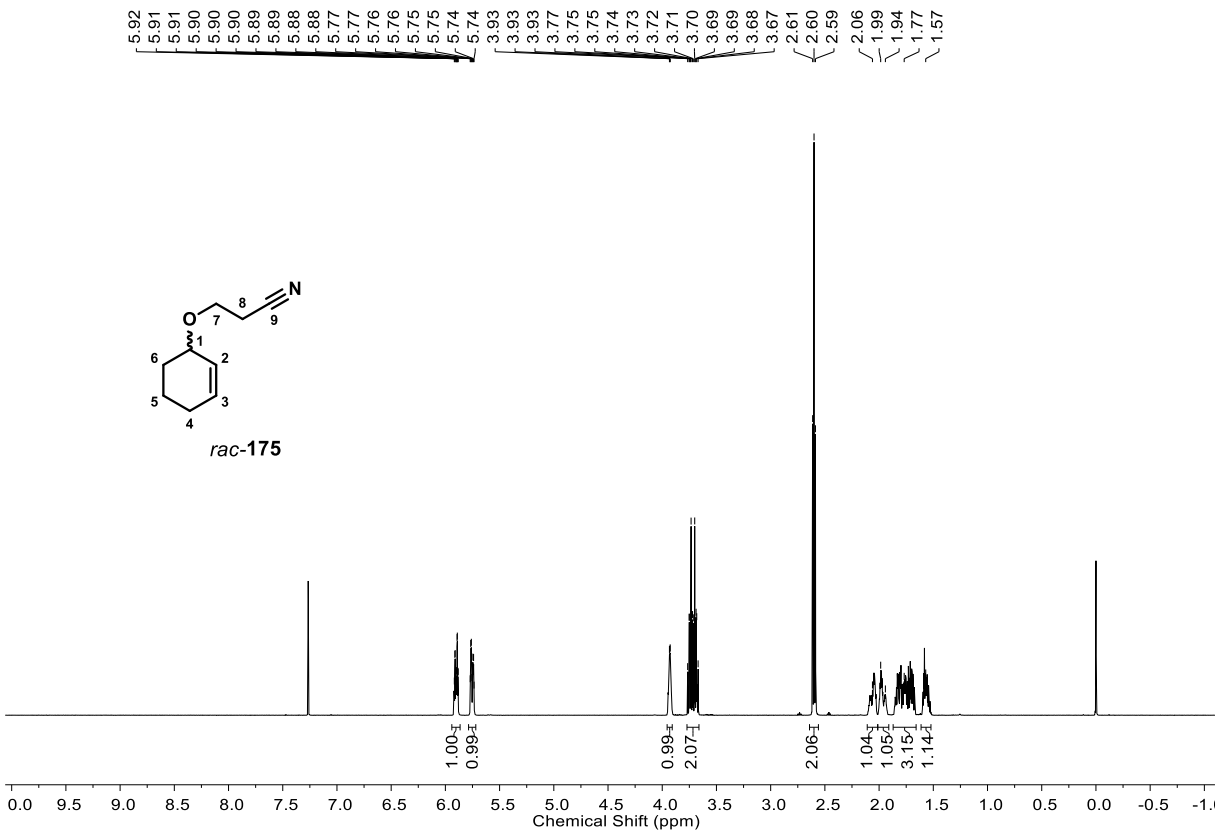


Figure 61: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-3-(cyclohex-2-en-1-yloxy)propionitrile (*rac*-**175**).

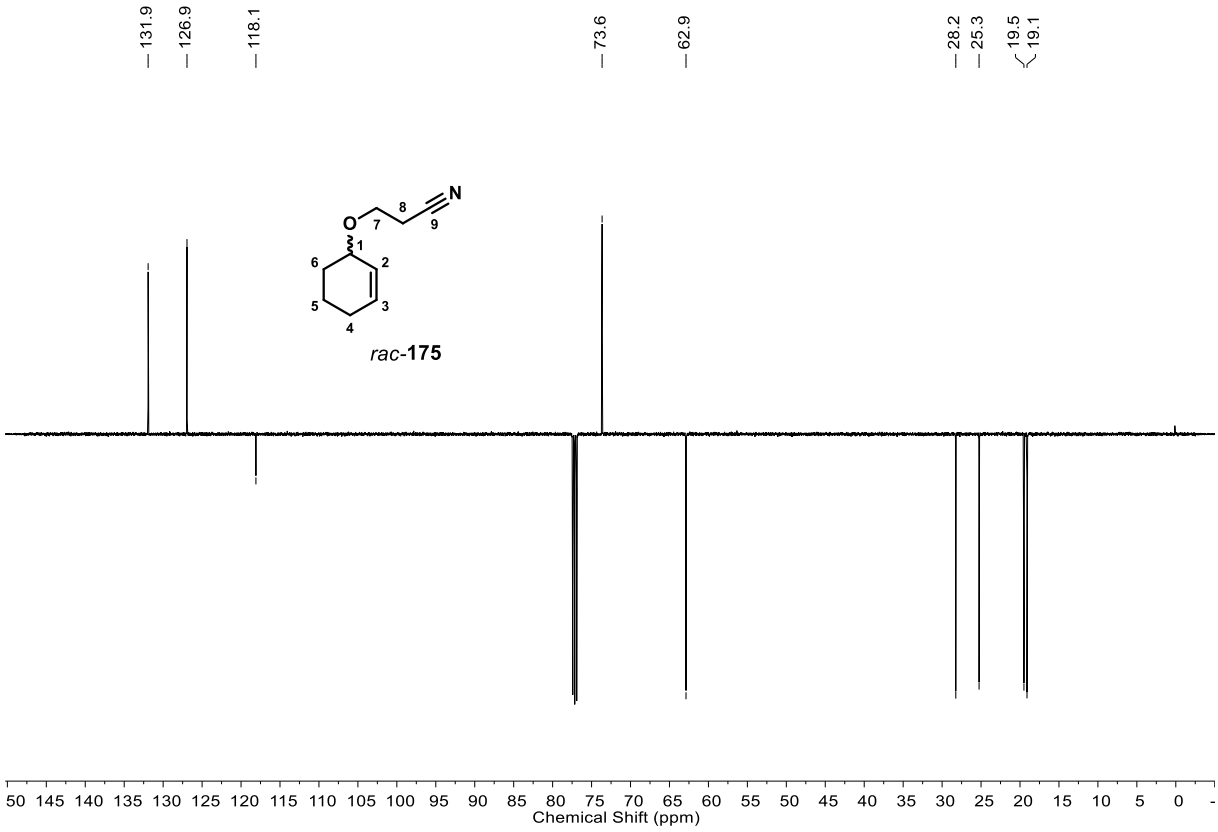


Figure 62: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-3-(cyclohex-2-en-1-yloxy)propionitrile (*rac*-**175**).

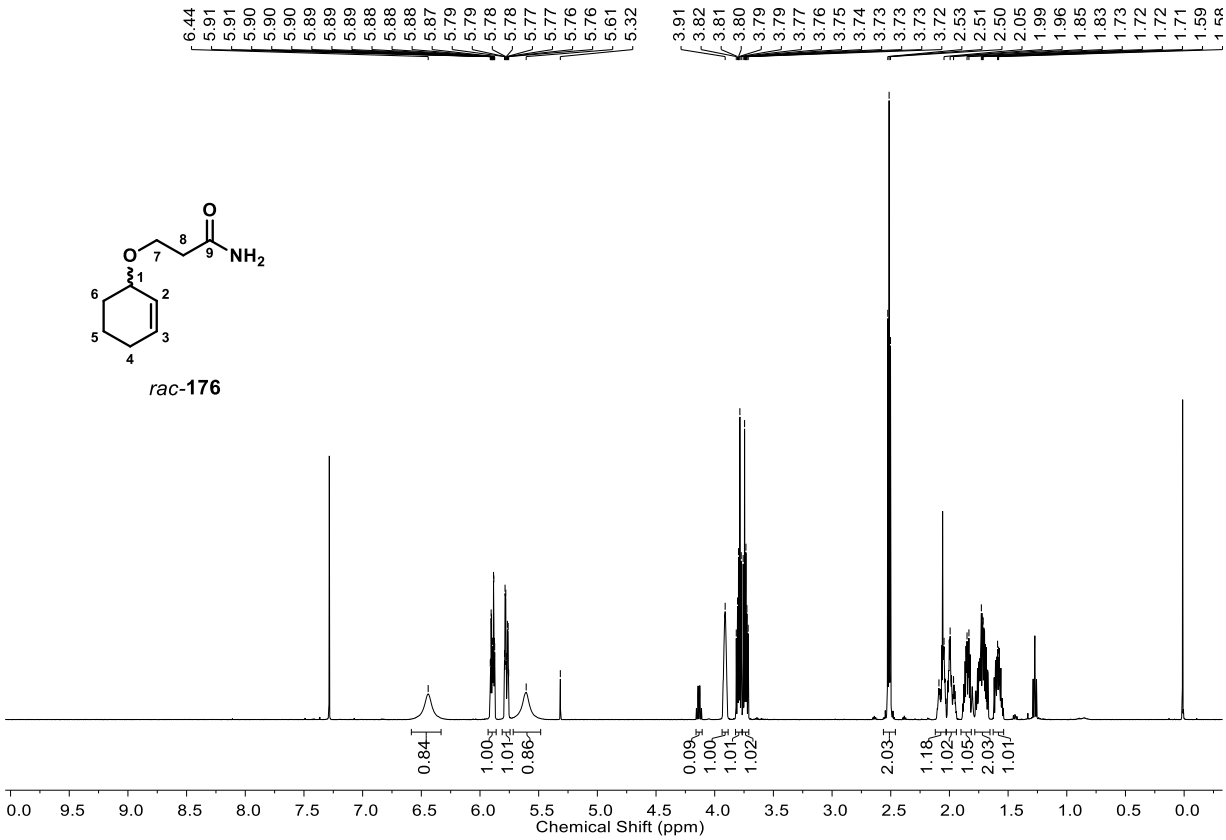


Figure 63: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-3-(cyclohex-2-en-1-yloxy)propenamide (*rac*-**176**).

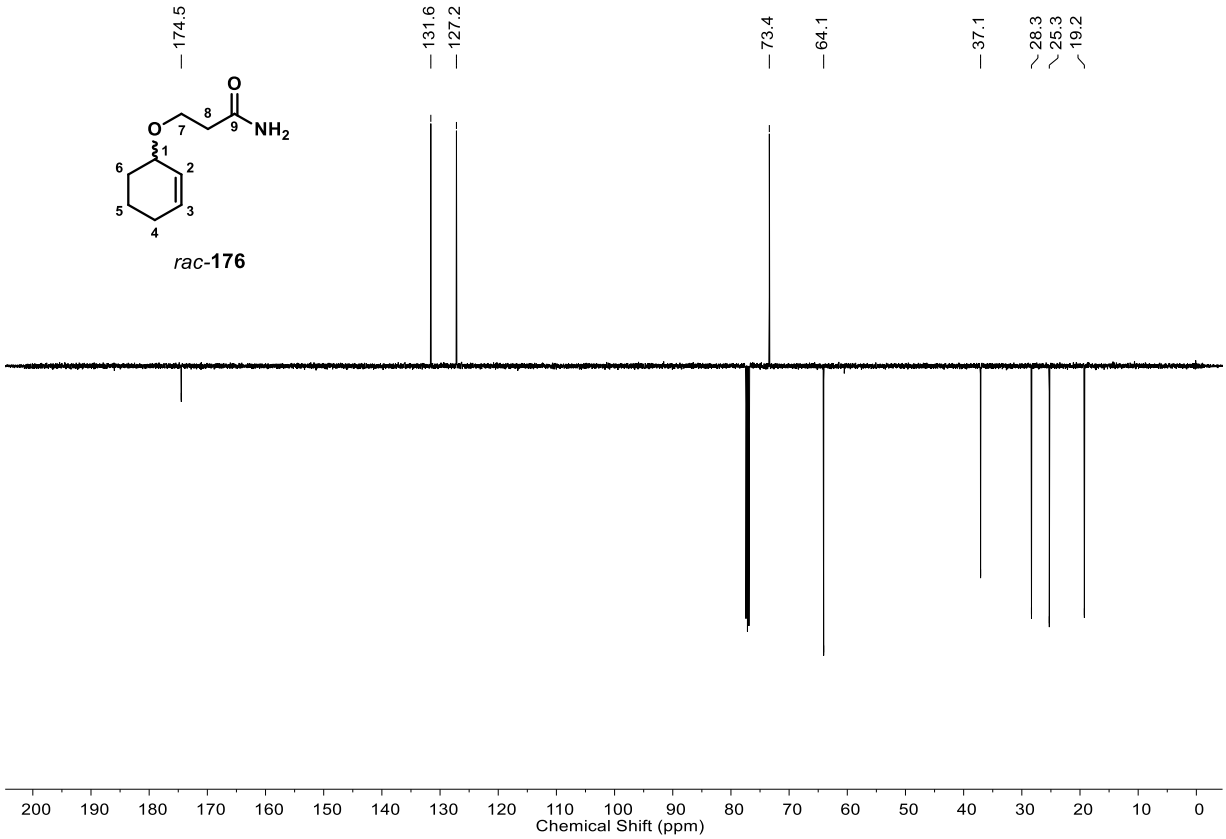


Figure 64: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-3-(cyclohex-2-en-1-yloxy)propenamide (*rac*-**176**).

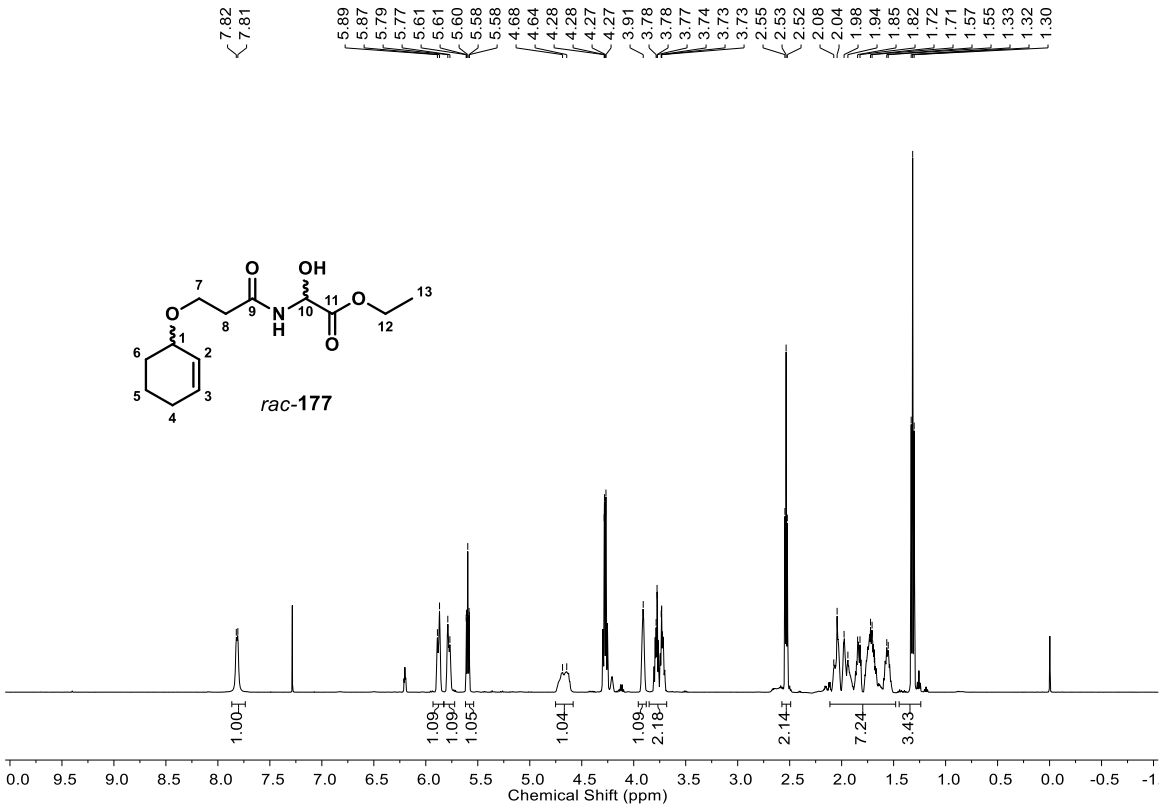


Figure 65: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-ethyl 2-(3-(cyclohex-2-en-1-yloxy)propanamido)-2-hydroxyacetate (*rac*-**177**).

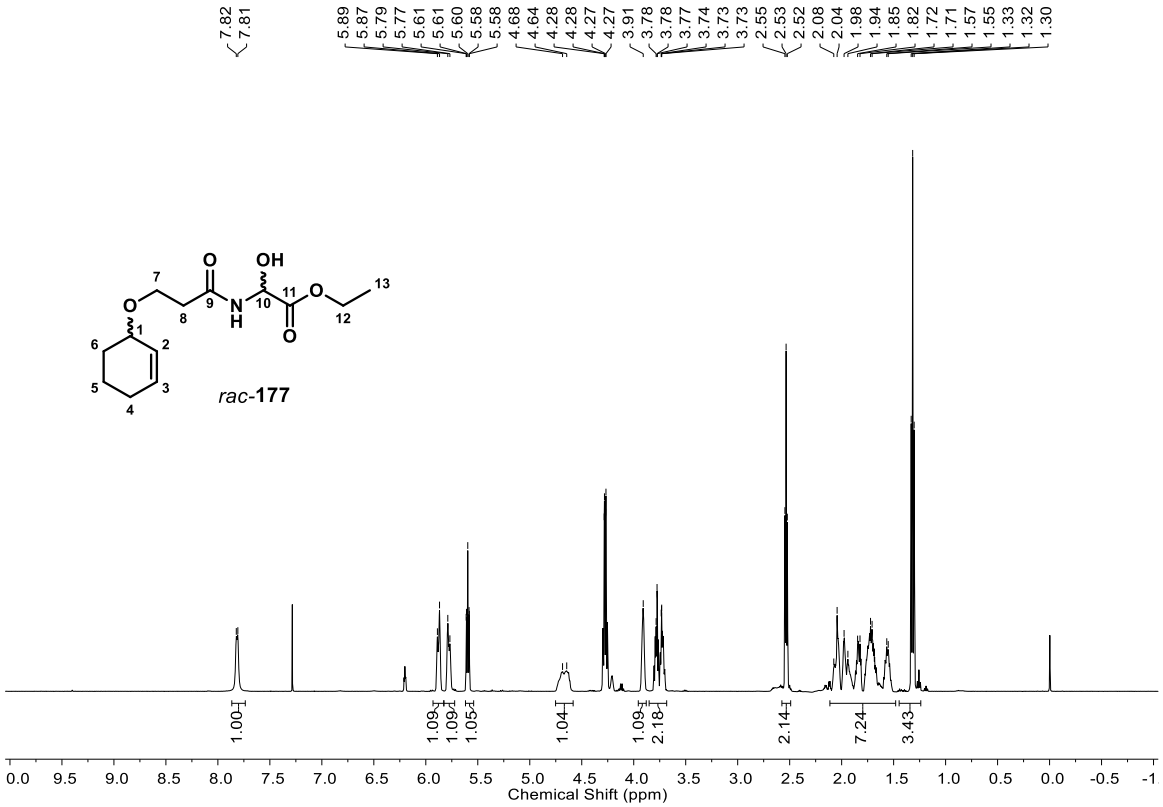


Figure 66: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-ethyl 2-(3-(cyclohex-2-en-1-yloxy)propanamido)-2-hydroxyacetate (*rac*-**177**).

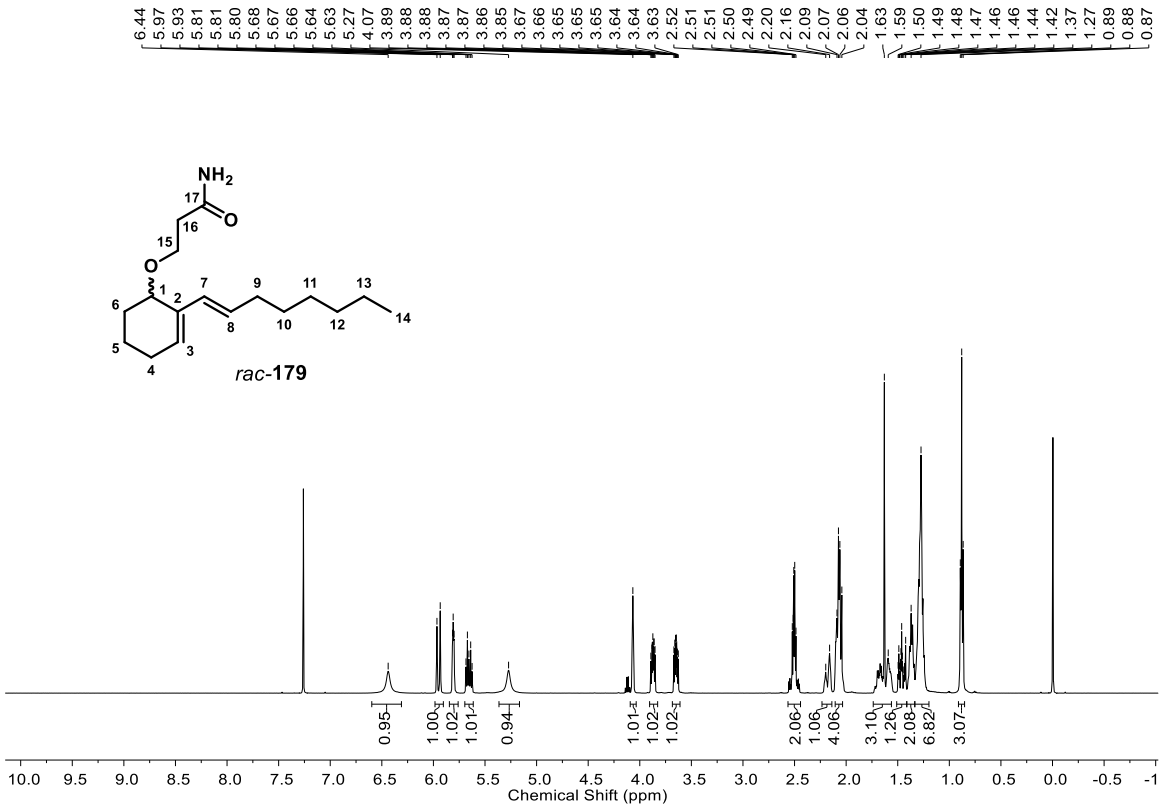


Figure 67: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-(*E*)-3-((2-(Oct-1-en-1-yl)cyclohex-2-en-1-yl)oxy)propanamide (*rac*-**179**).

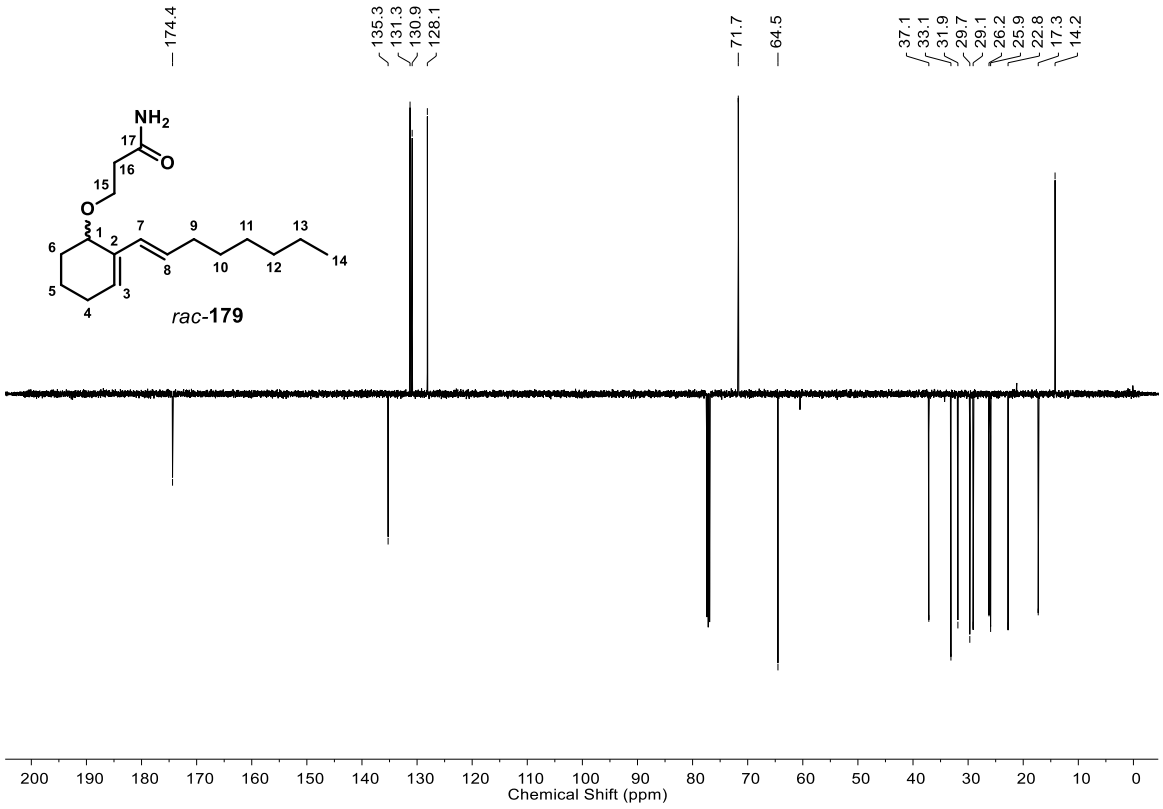


Figure 68: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-(*E*)-3-((2-(Oct-1-en-1-yl)cyclohex-2-en-1-yl)oxy)propanamide (*rac*-**179**).

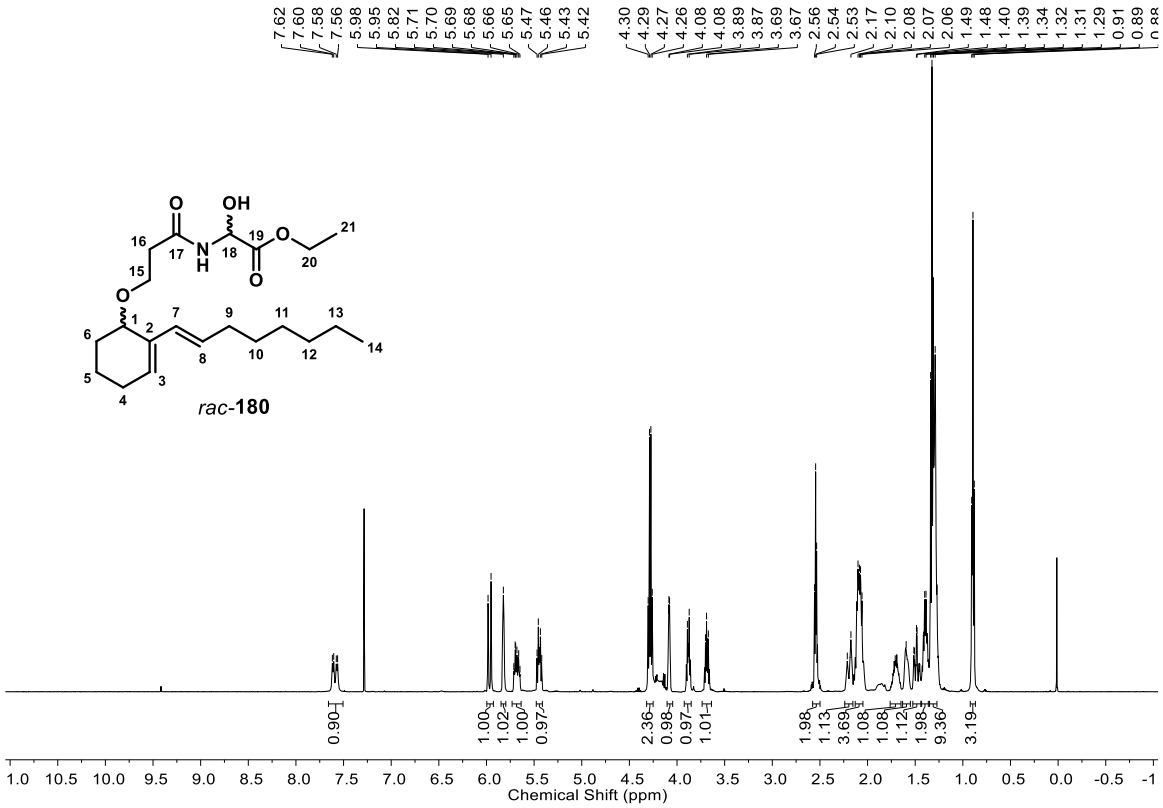


Figure 69: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-ethyl (*E*)-2-(3-((2-(oct-1-en-1-yl)cyclohex-2-en-1-yl)oxy)-propanamido)-2-hydroxyacetate (*rac*-**180**).

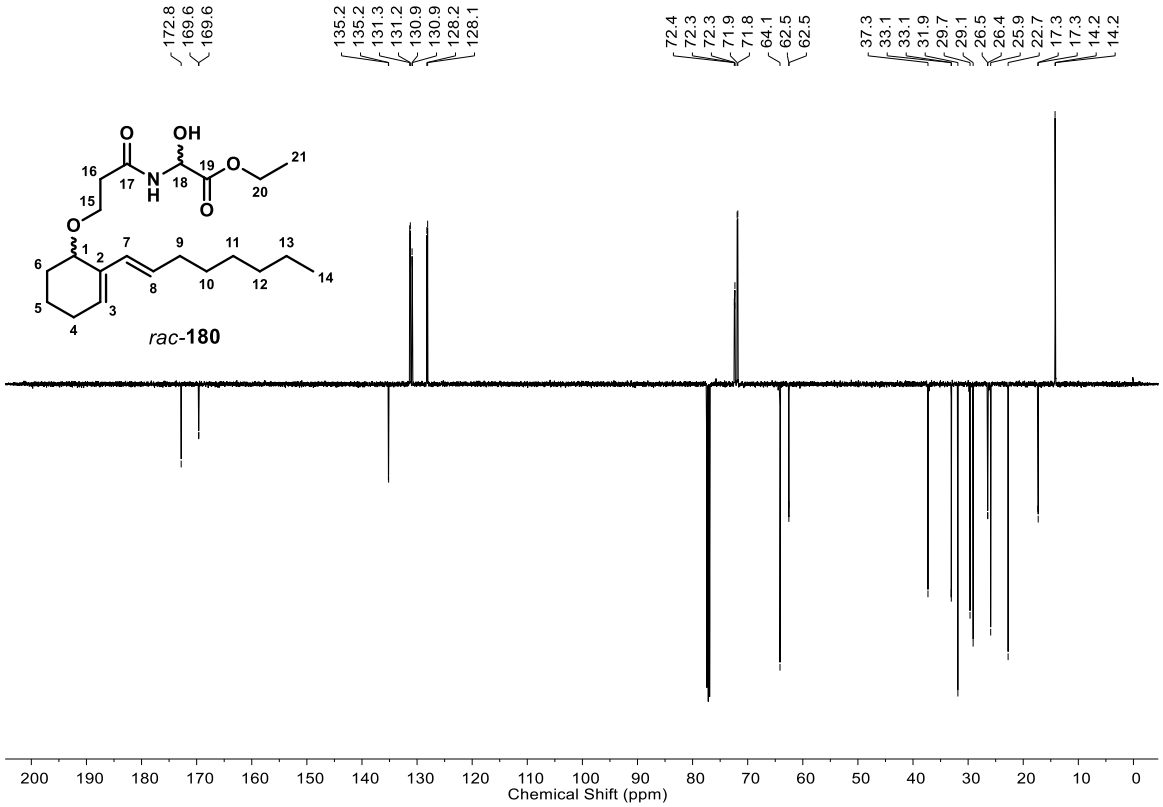


Figure 70: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-ethyl (*E*)-2-(3-((2-(oct-1-en-1-yl)cyclohex-2-en-1-yl)oxy)-propanamido)-2-hydroxyacetate (*rac*-**180**).

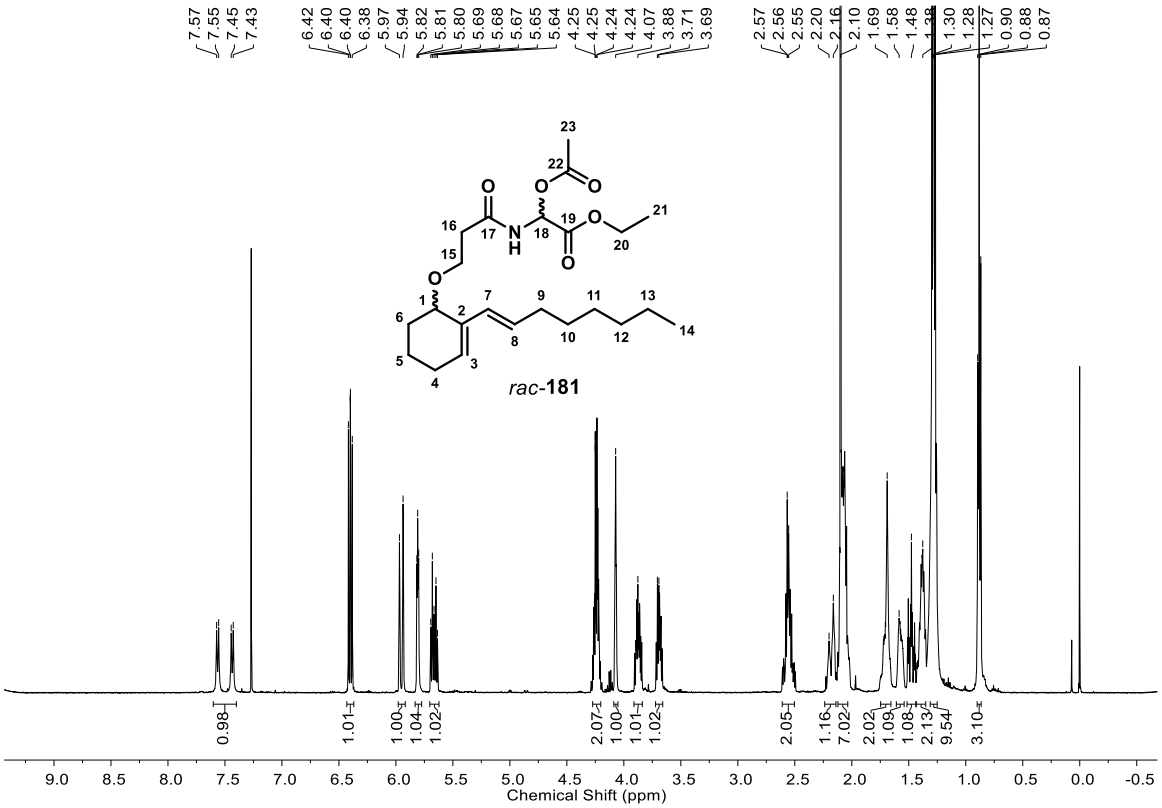


Figure 71: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-ethyl (*E*)-2-(3-((2-(oct-1-en-1-yl)cyclohex-2-en-1-yl)oxy)-propanamido)-2-acetoxyacetate (*rac*-**181**).

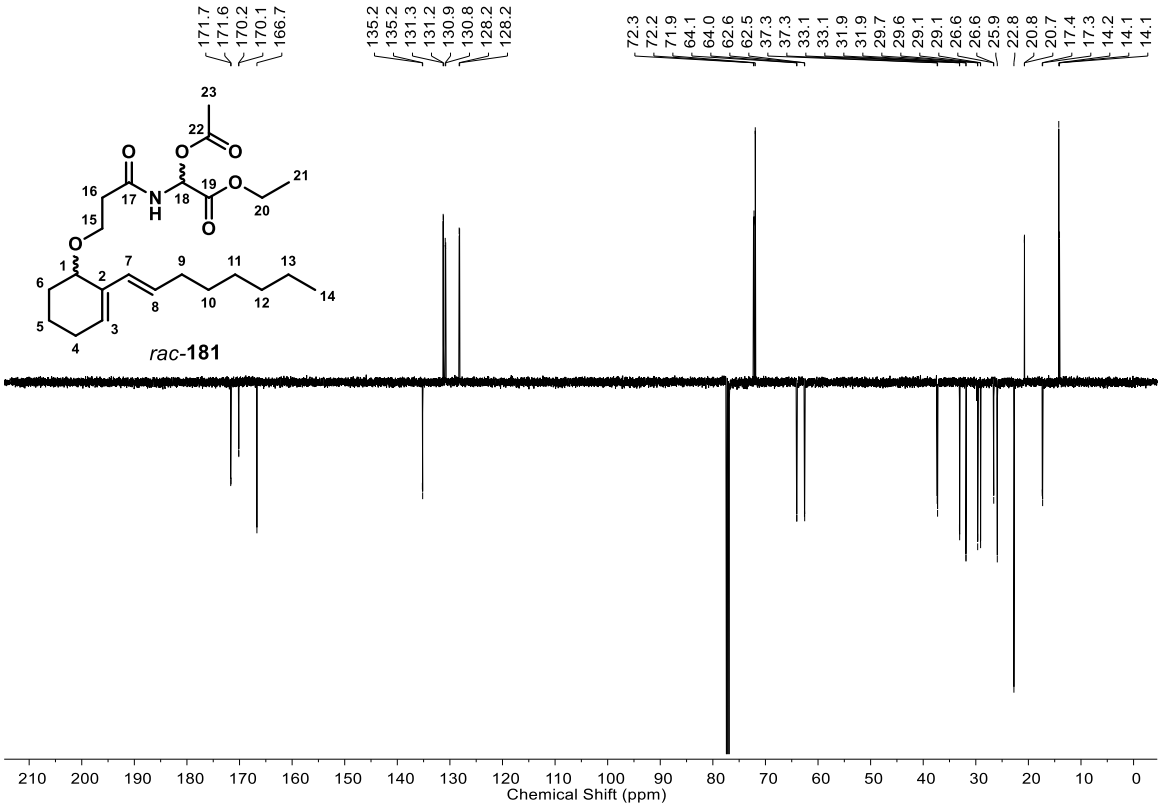


Figure 72: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-ethyl (*E*)-2-(3-((2-(oct-1-en-1-yl)cyclohex-2-en-1-yl)oxy)-propanamido)-2-acetoxyacetate (*rac*-**181**).

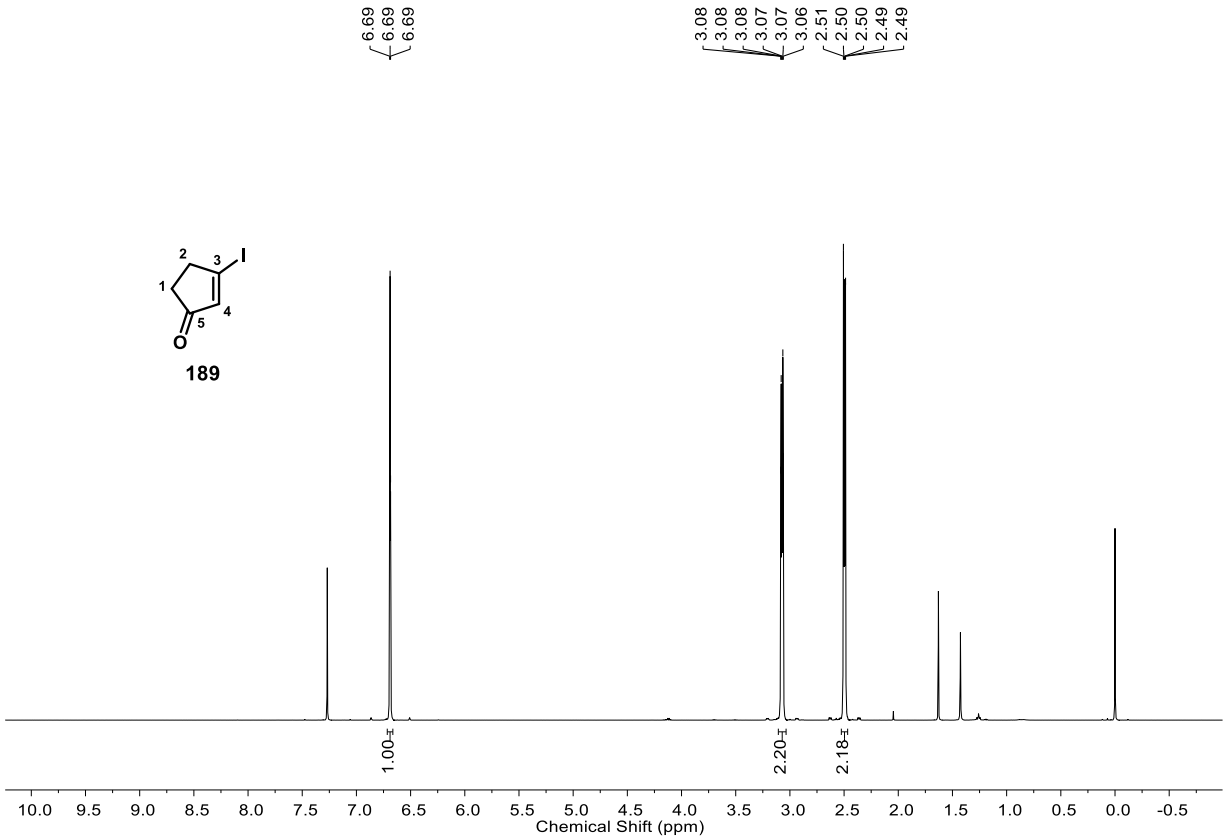


Figure 73: ^{1}H NMR (500 MHz, $CDCl_3$) of 3-Iodo-cyclopent-2-enone (**189**).

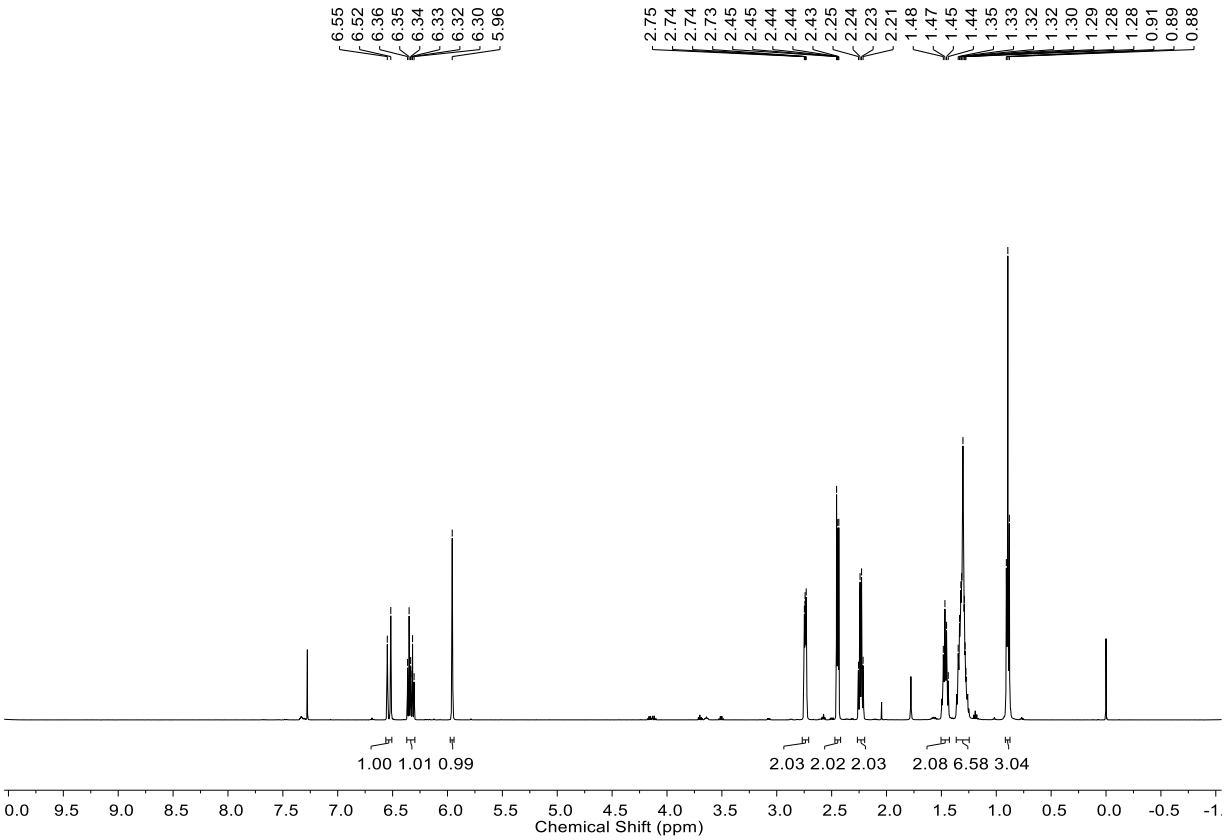


Figure 74: ^{1}H NMR (500 MHz, $CDCl_3$) of 3-((*E*)-oct-1-en-1-yl)-cyclopent-2-enone (**190**).

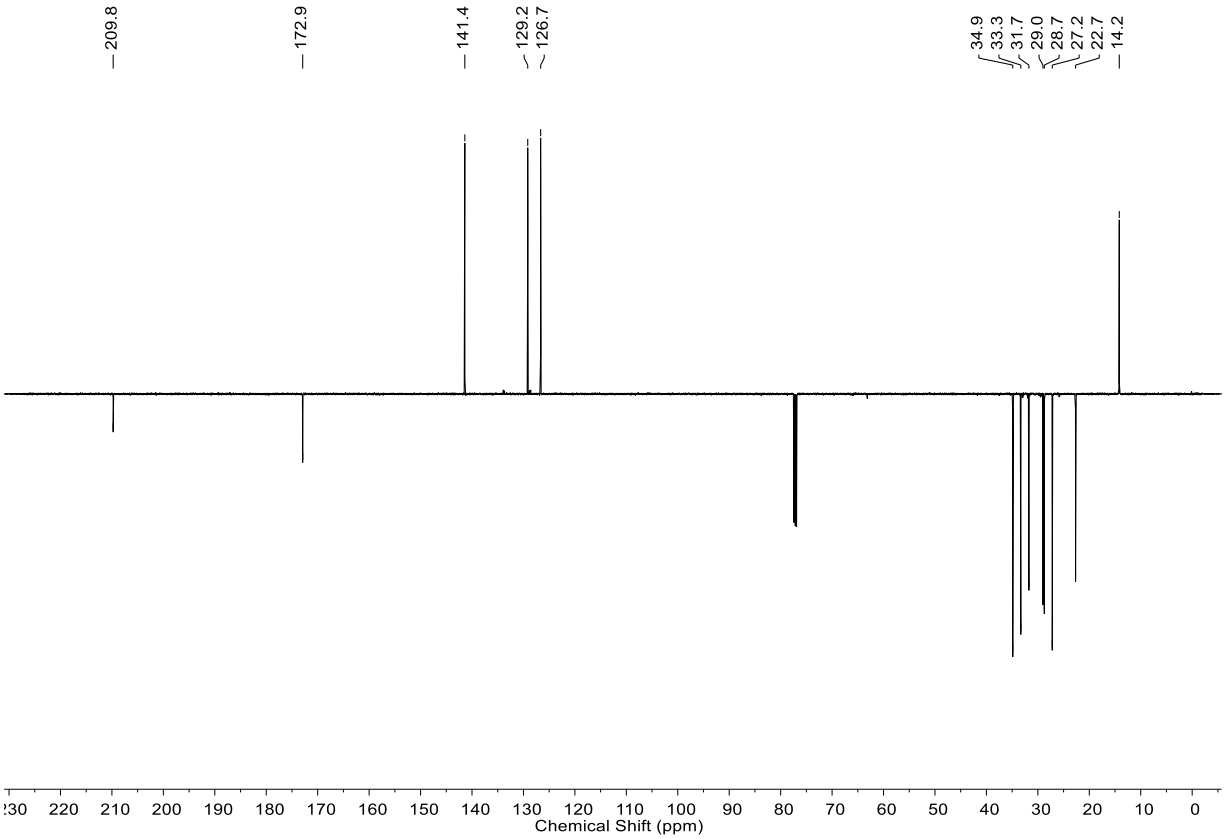


Figure 75: ^{13}C NMR (126 MHz, $CDCl_3$) of 3-((*E*)-oct-1-en-1-yl)-cyclopent-2-enone (**190**).

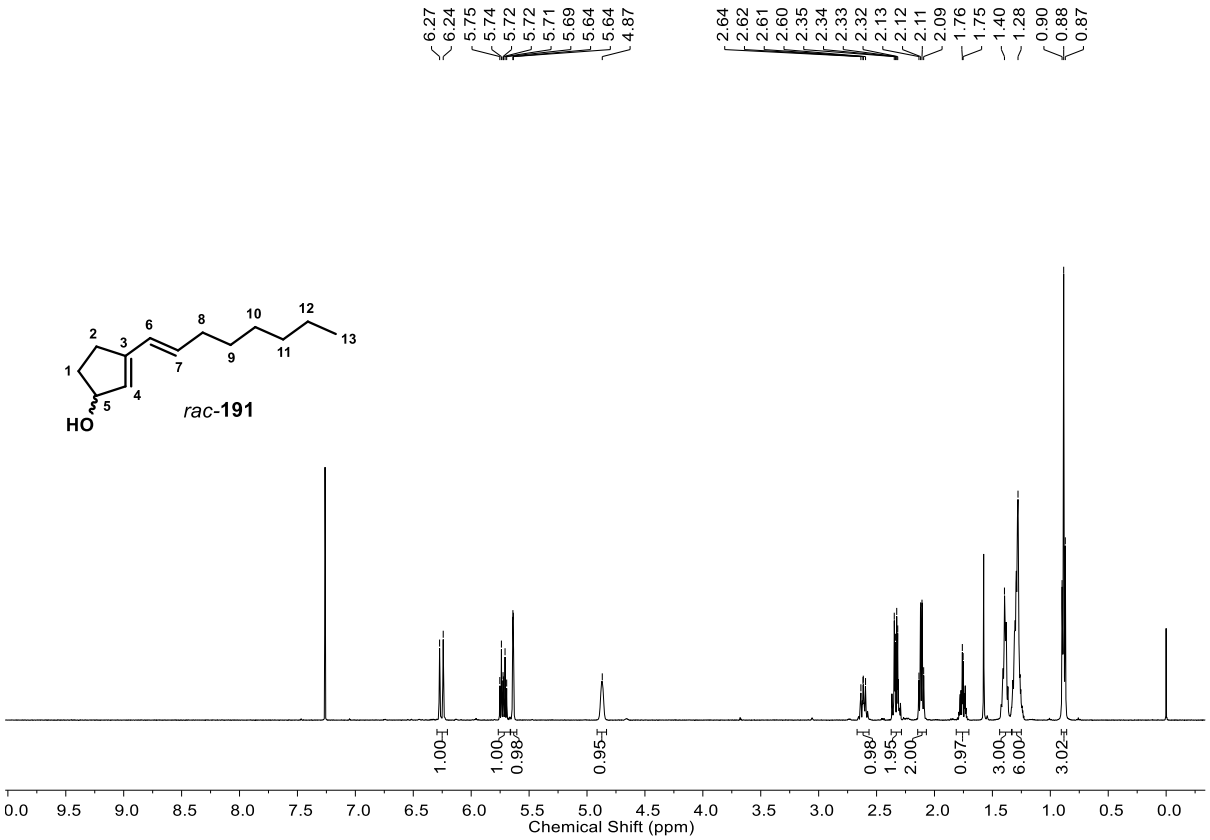


Figure 76: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-3-((*E*)-oct-1-enyl)-cyclopent-2-en-1-ol (*rac*-**191**).

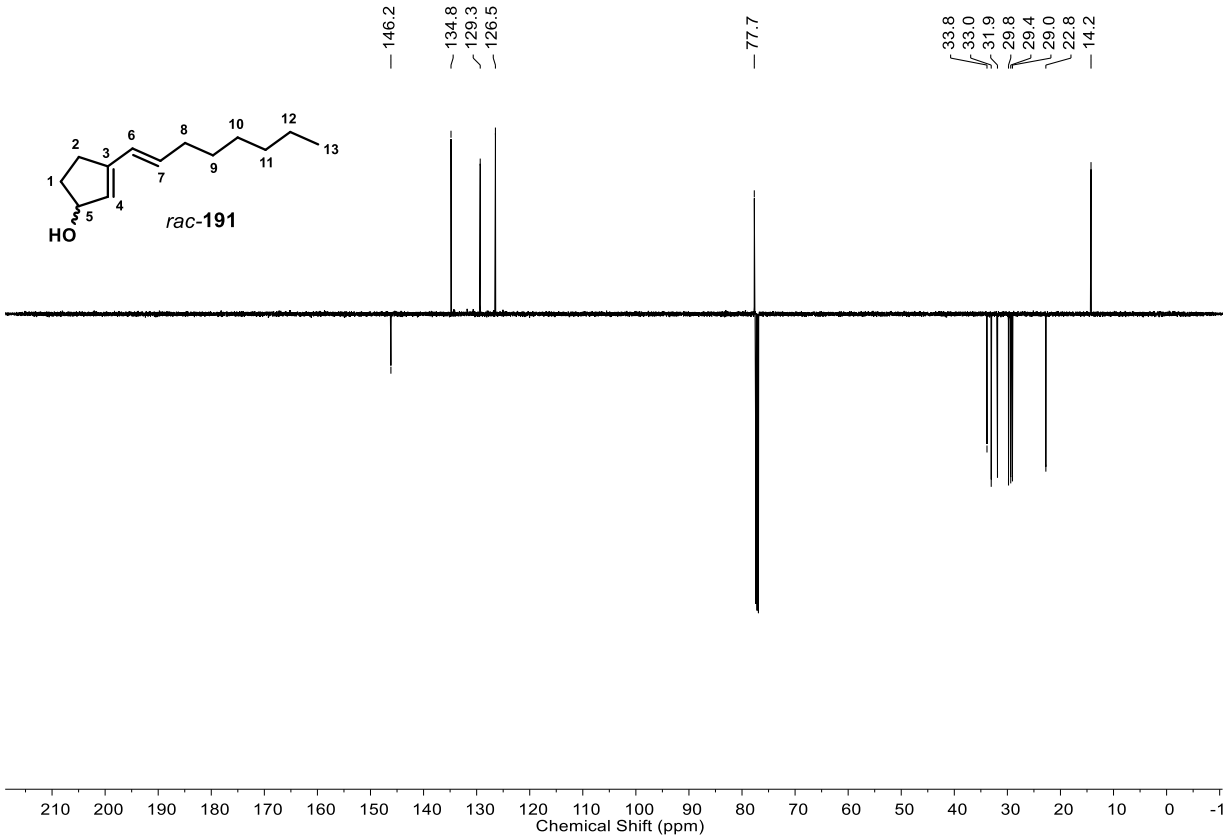


Figure 77: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-3-((*E*)-oct-1-enyl)-cyclopent-2-en-1-ol (*rac*-**191**).

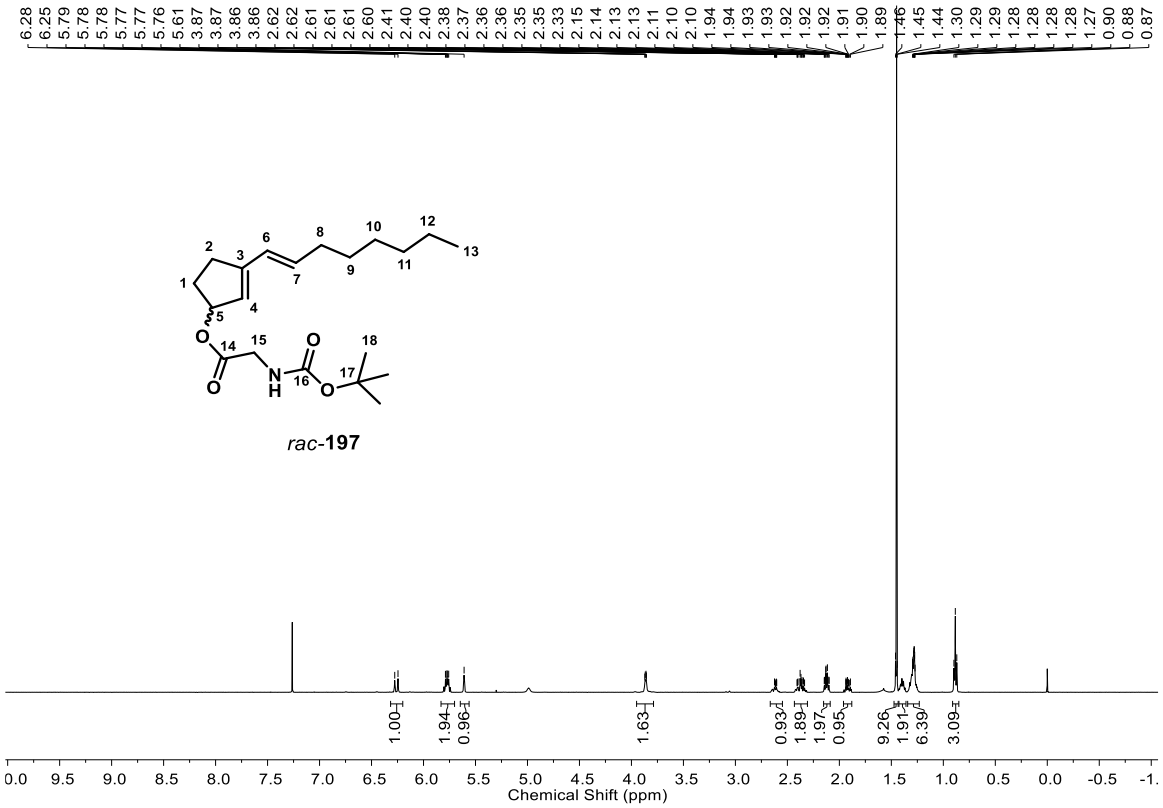


Figure 78: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-*N*-Boc-glycine 3-(oct-1-en-1-yl)-cyclopent-2-en-1-yl ester (*rac*-**197**).

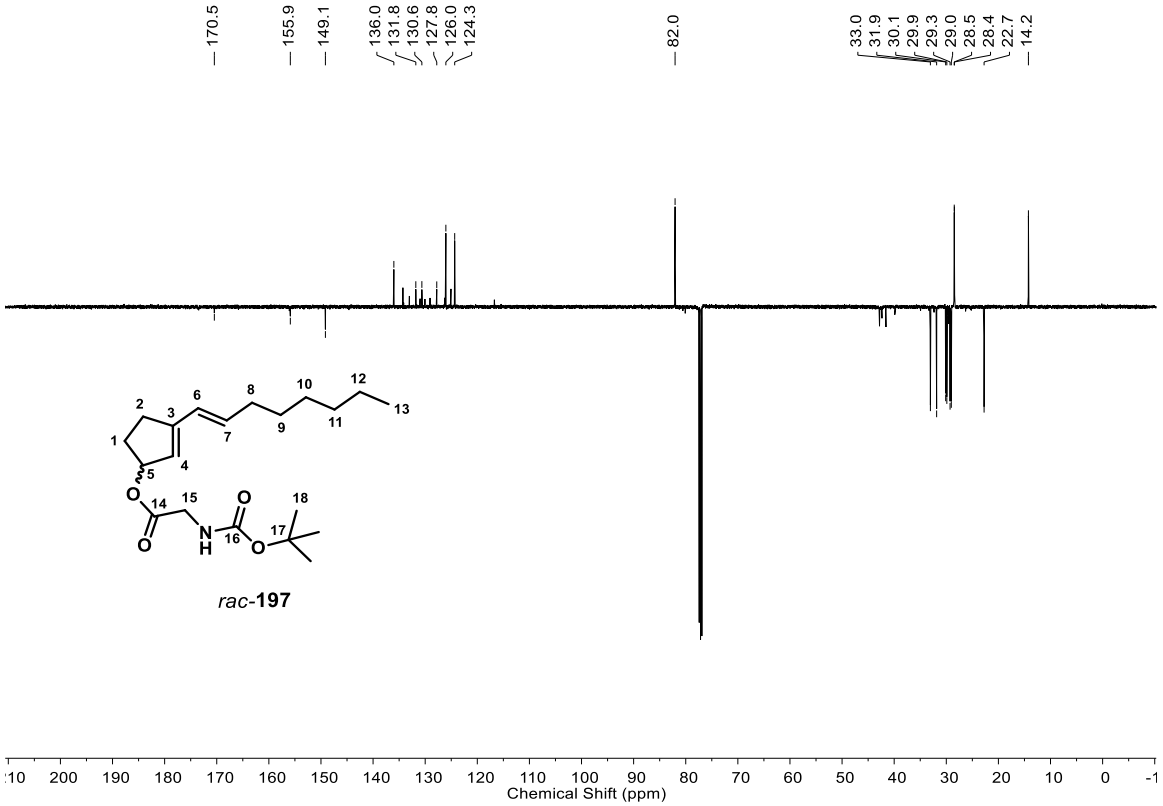
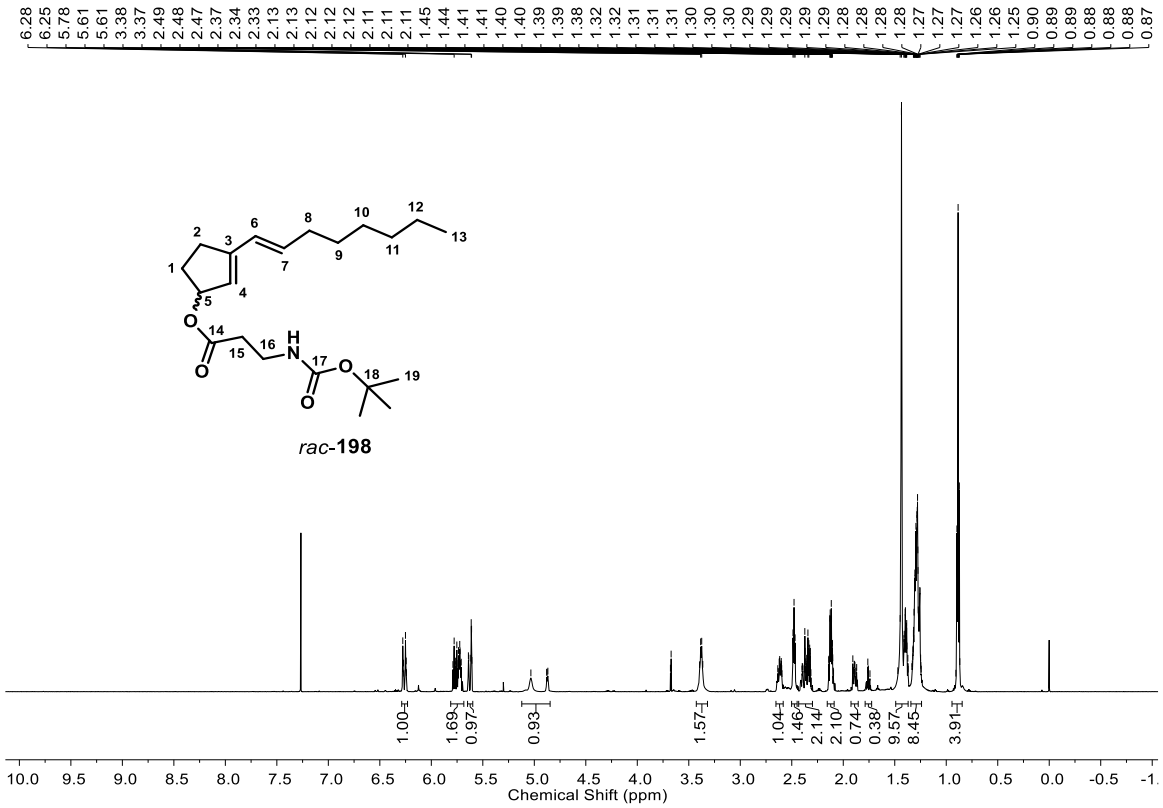
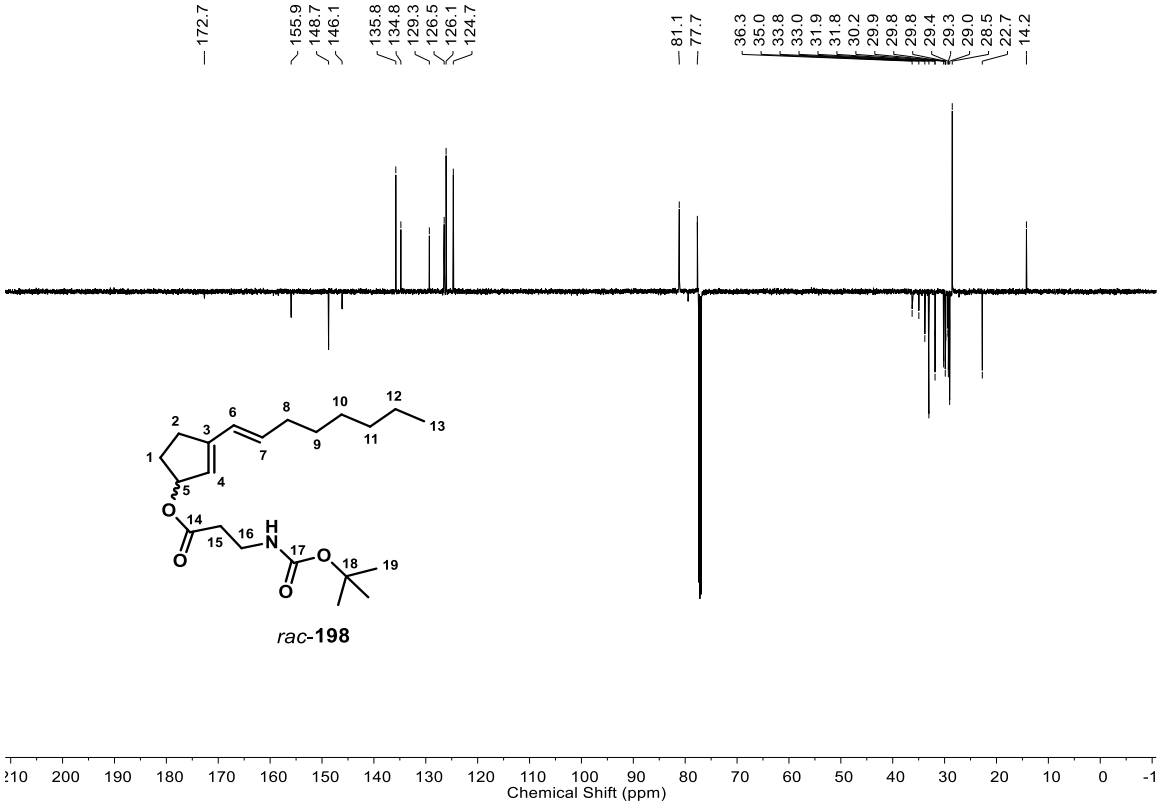


Figure 79: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-*N*-Boc-glycine 3-(oct-1-en-1-yl)-cyclopent-2-en-1-yl ester (*rac*-**197**).



rac-**198**

Figure 80: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-*N*-Boc-β-alanine 3-((*E*)-oct-1-en-1-yl)-cyclopent-2-en-1-yl ester (*rac*-**198**).



rac-**198**

Figure 81: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-*N*-Boc-β-alanine 3-((*E*)-oct-1-en-1-yl)-cyclopent-2-en-1-yl ester (*rac*-**198**).

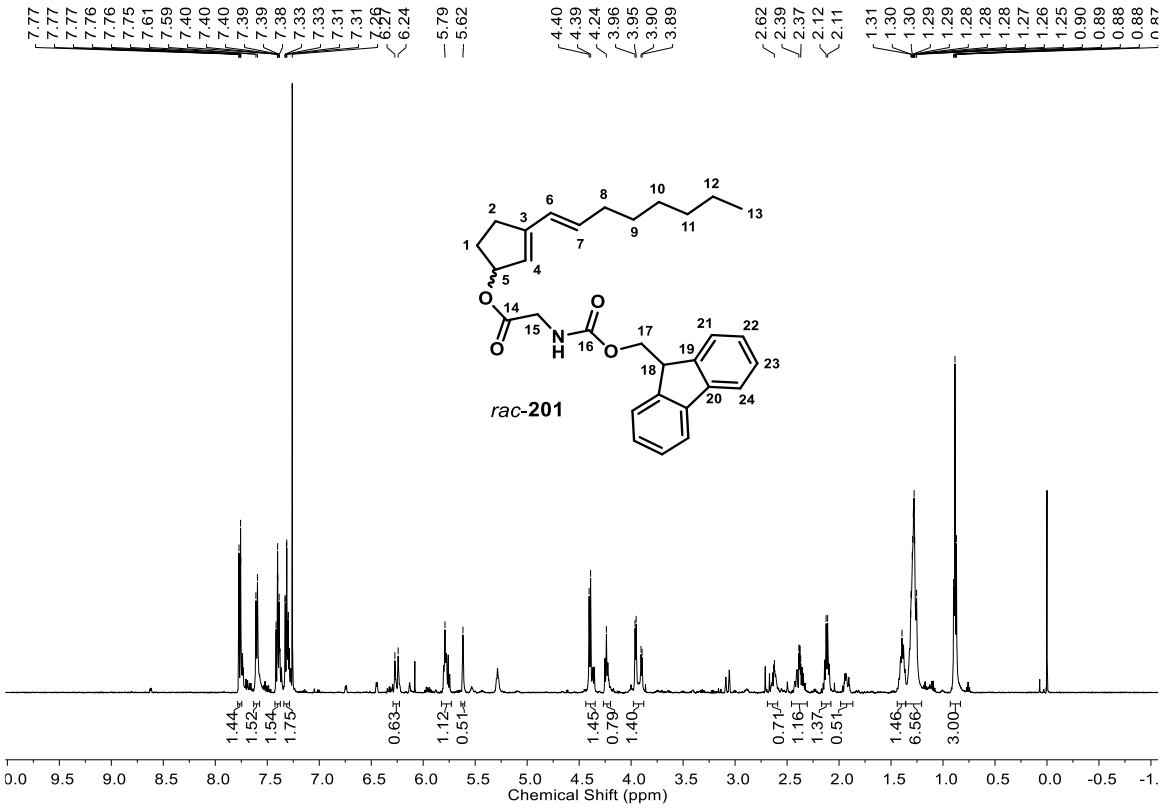


Figure 82: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-*N*-Fmoc-glycine 3-(oct-1-en-1-yl)-cyclopent-2-en-1-yl ester (*rac*-**201**).

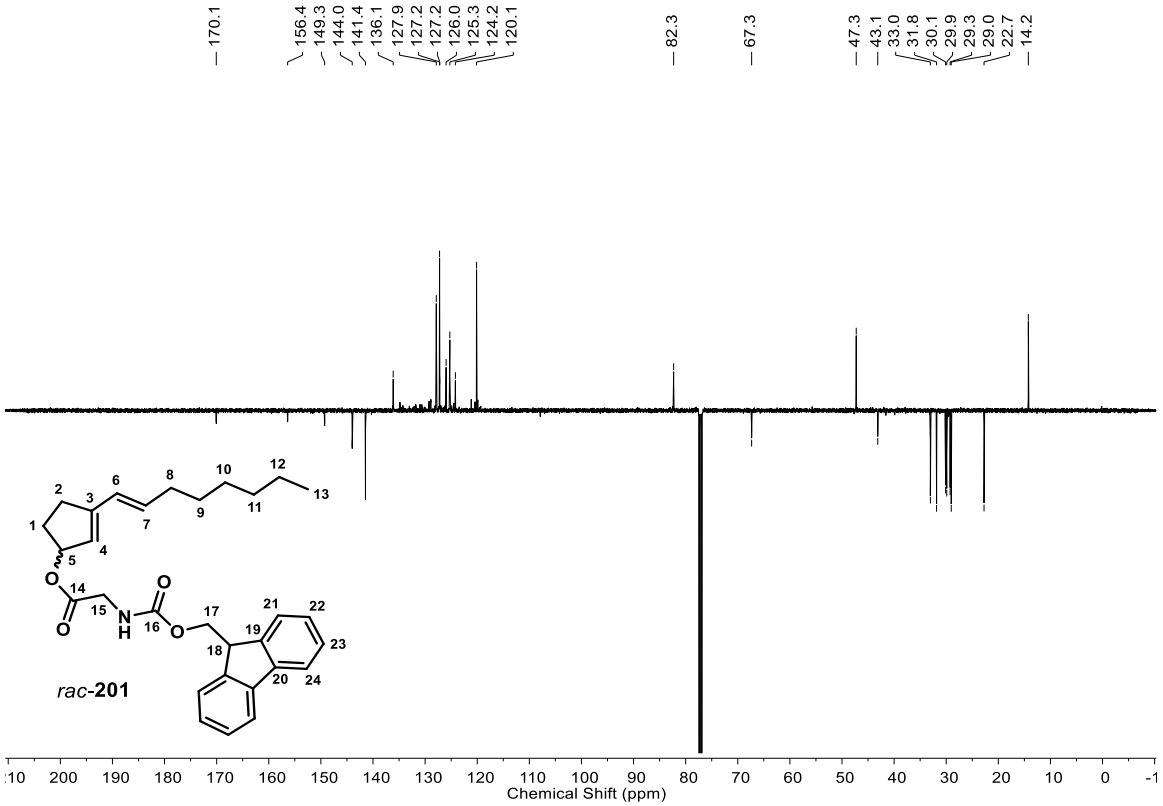


Figure 83: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-*N*-Fmoc-glycine 3-(oct-1-en-1-yl)-cyclopent-2-en-1-yl ester (*rac*-**201**).

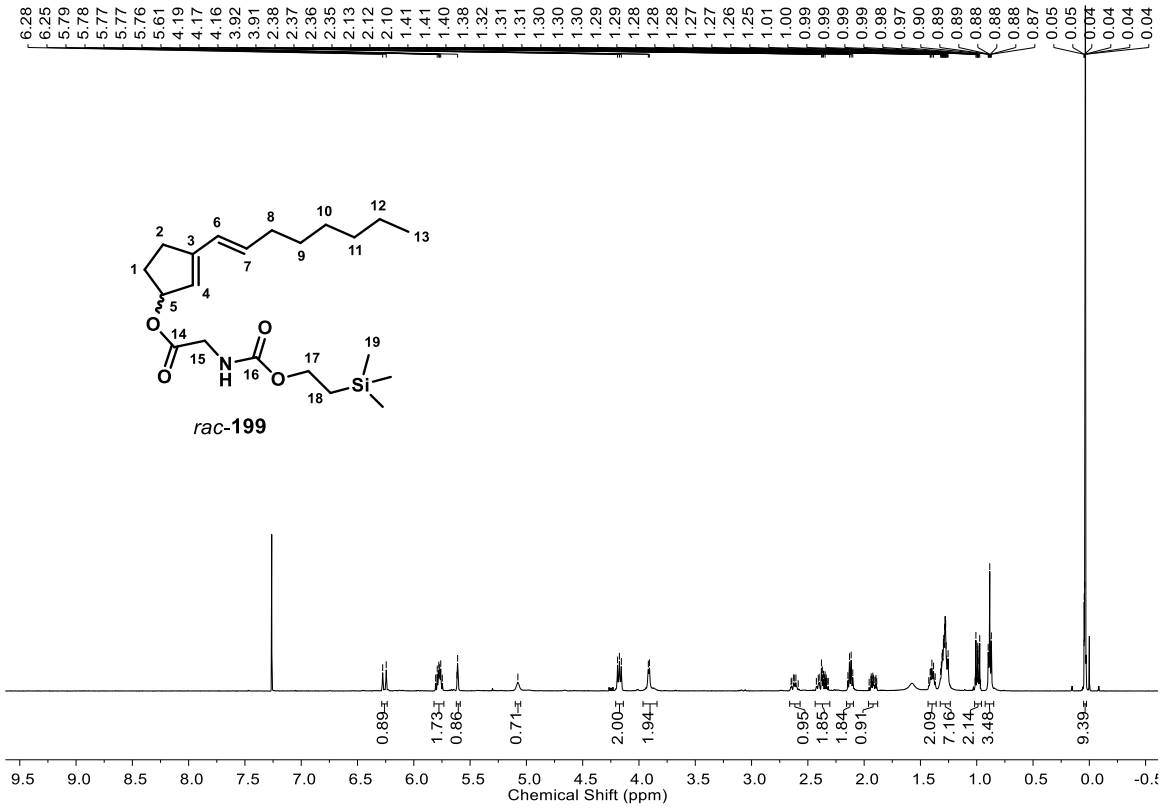


Figure 84: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-*N*-Teoc-Glycine 3-(oct-1-en-1-yl)-cyclopent-2-en-1-yl ester (*rac*-**199**).

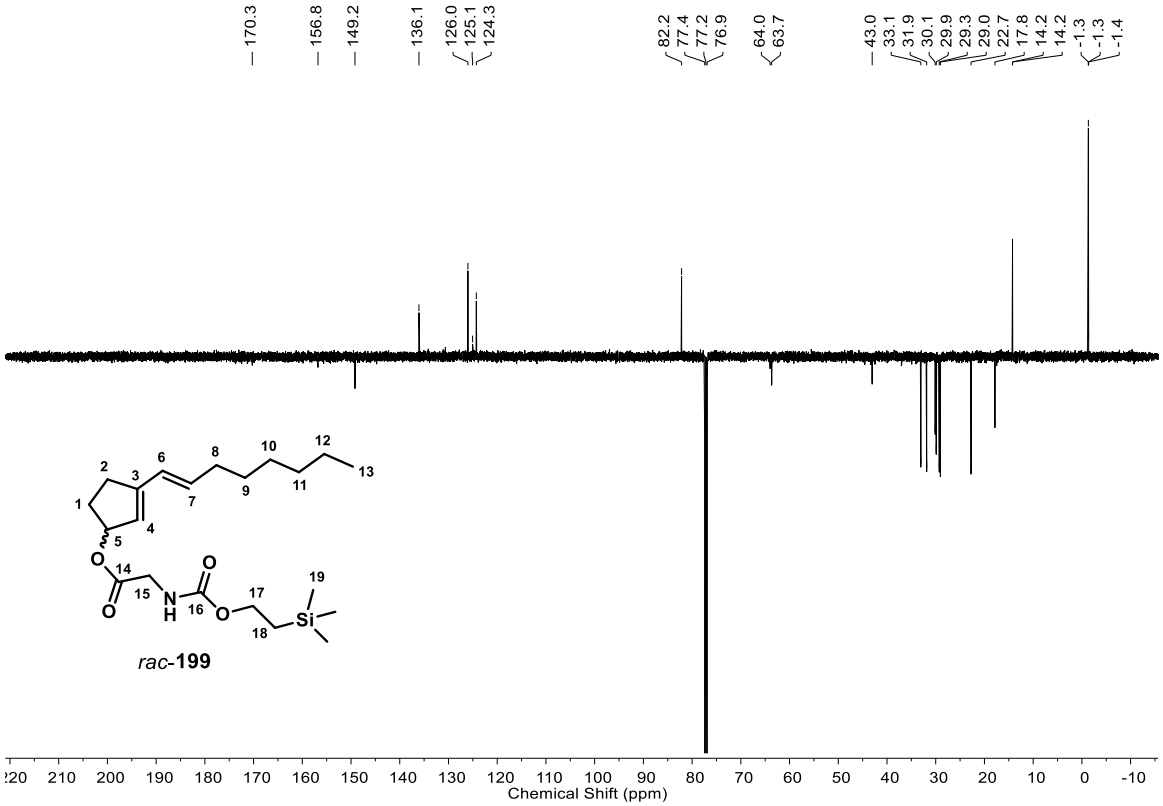
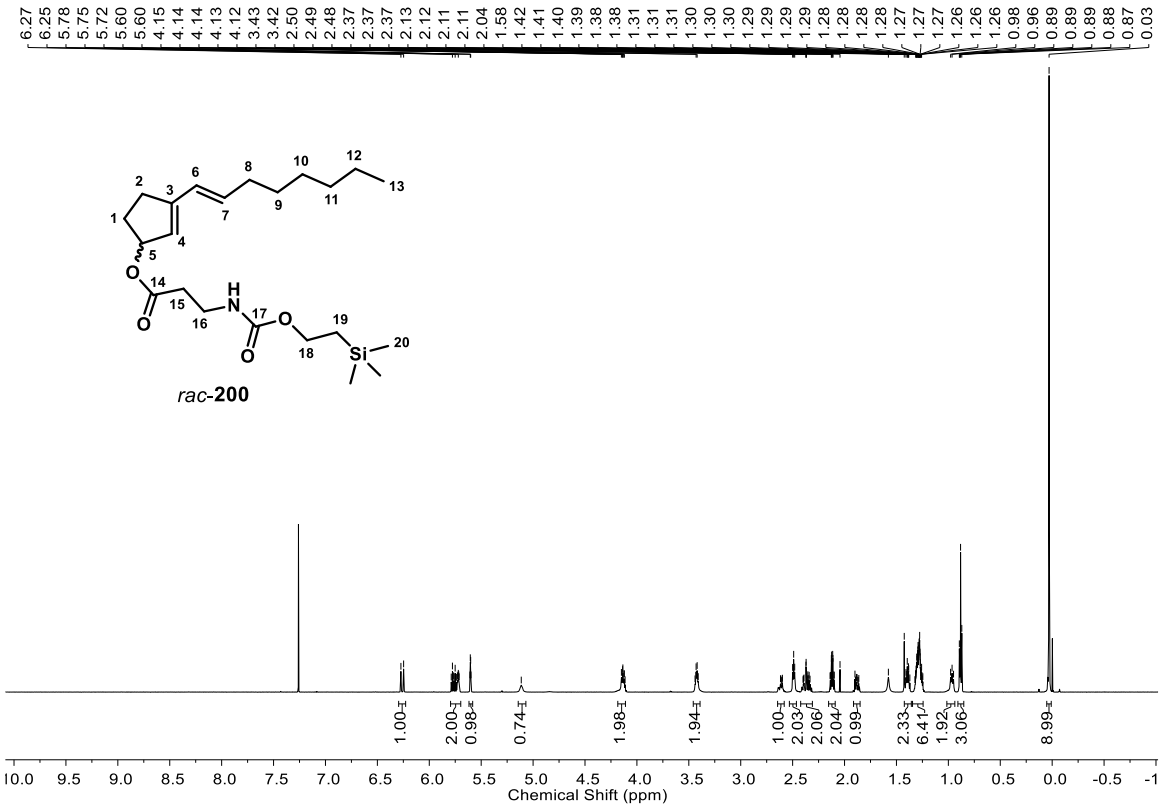
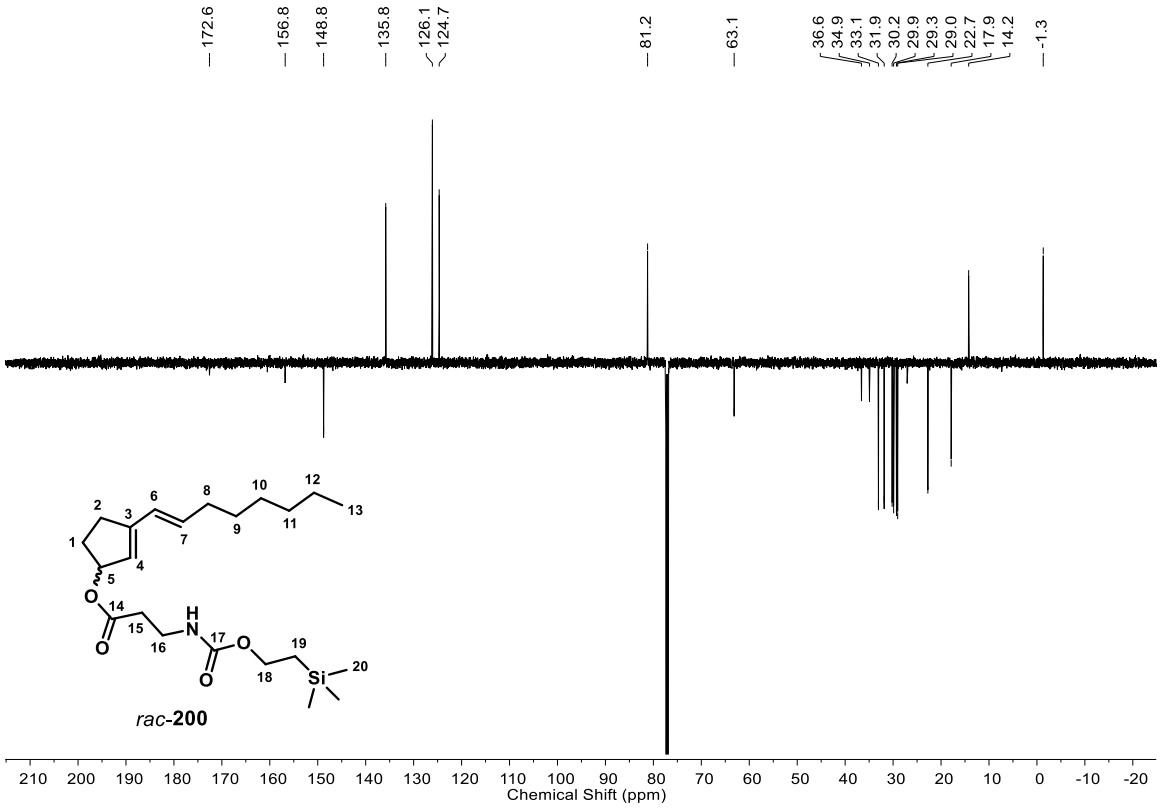


Figure 85: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-*N*-Teoc-Glycine 3-(oct-1-en-1-yl)-cyclopent-2-en-1-yl ester (*rac*-**199**).



rac-**200**

Figure 86: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-*N*-Teoc-β-alanine 3-((*E*)-oct-1-en-1-yl)-cyclopent-2-en-1-yl ester (*rac*-**200**).



rac-**200**

Figure 87: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-*N*-Teoc-β-alanine 3-((*E*)-oct-1-en-1-yl)-cyclopent-2-en-1-yl ester (*rac*-**200**).

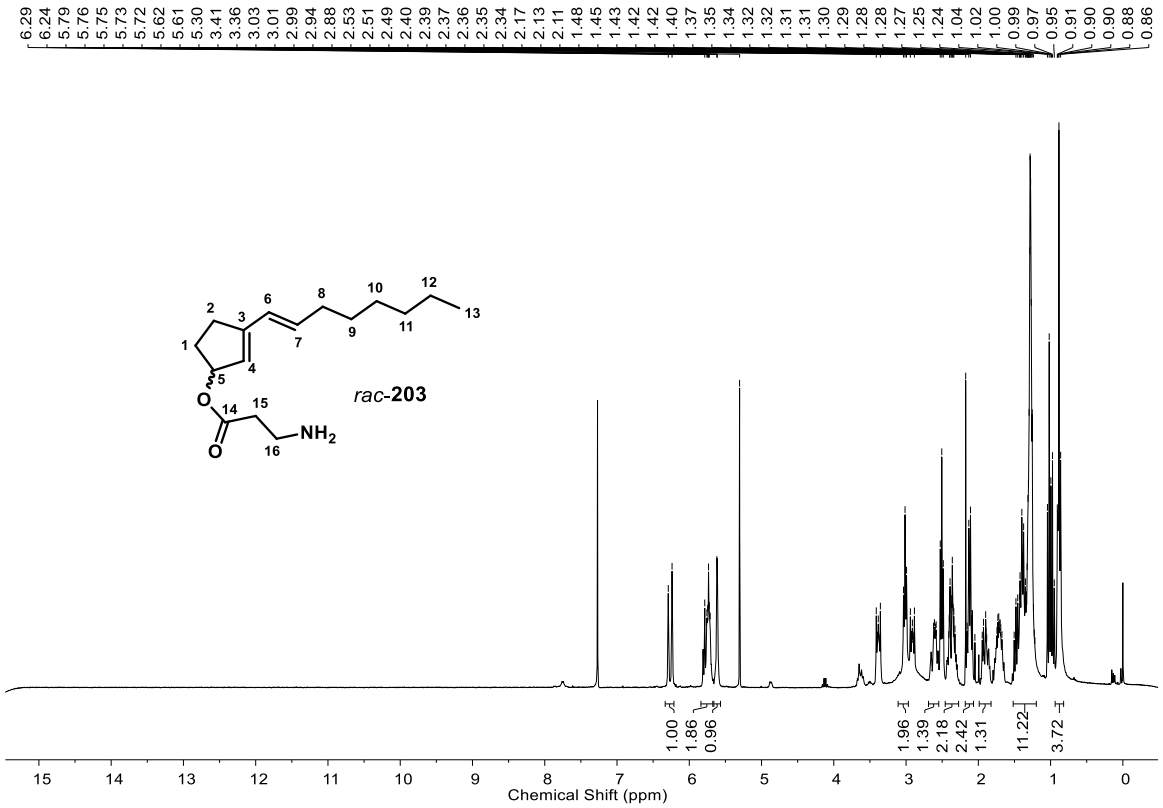


Figure 88: : ^{1}H NMR (300 MHz, $CDCl_3$) of *rac*-*β*-alanine 3-((*E*)-oct-1-en-1-yl)-cyclopent-2-en-1-yl ester (*rac*-**200**). (Major impurities are visible, due to decomposition.)

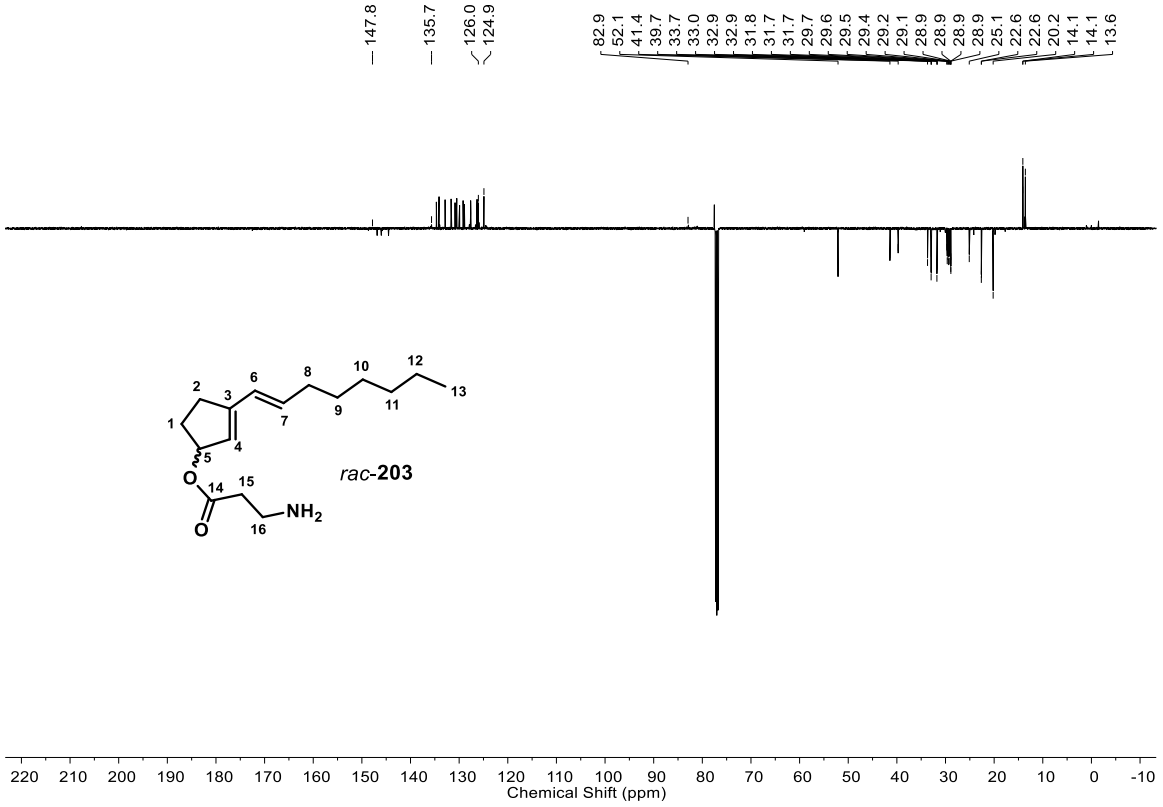


Figure 89: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-*β*-alanine 3-((*E*)-oct-1-en-1-yl)-cyclopent-2-en-1-yl ester (*rac*-**200**). (Major impurities are visible, due to decomposition.)

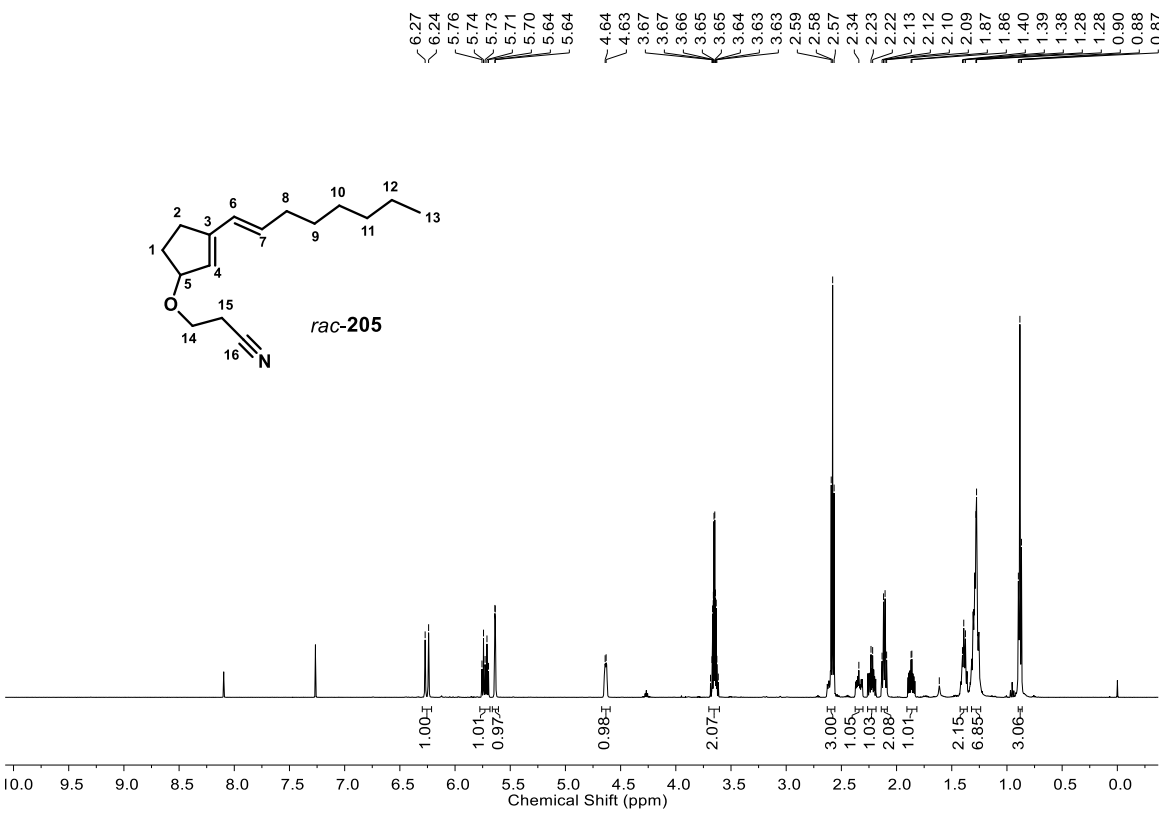


Figure 90: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-3-((3-((*E*)-Oct-1-en-1-yl)-cyclopent-2-en-1-yl)oxy)propionitrile (*rac*-**205**).

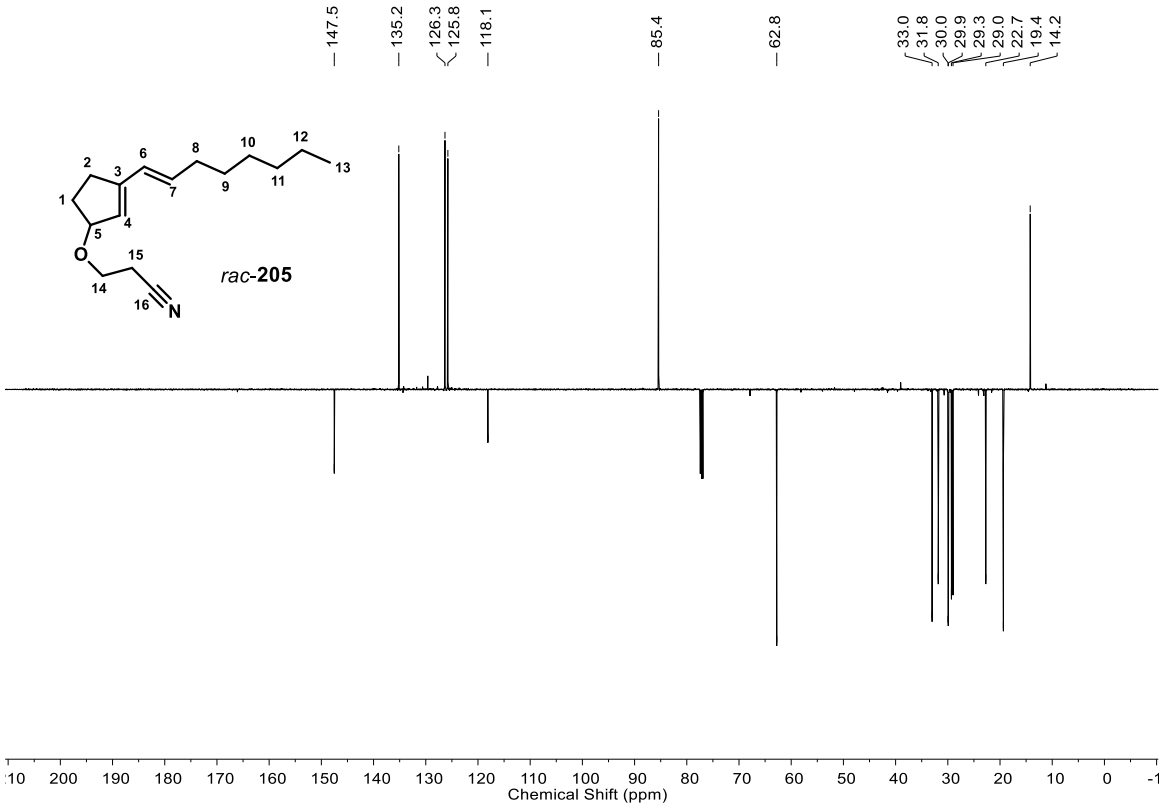


Figure 91: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-3-((3-((*E*)-Oct-1-en-1-yl)-cyclopent-2-en-1-yl)oxy)propionitrile (*rac*-**205**).

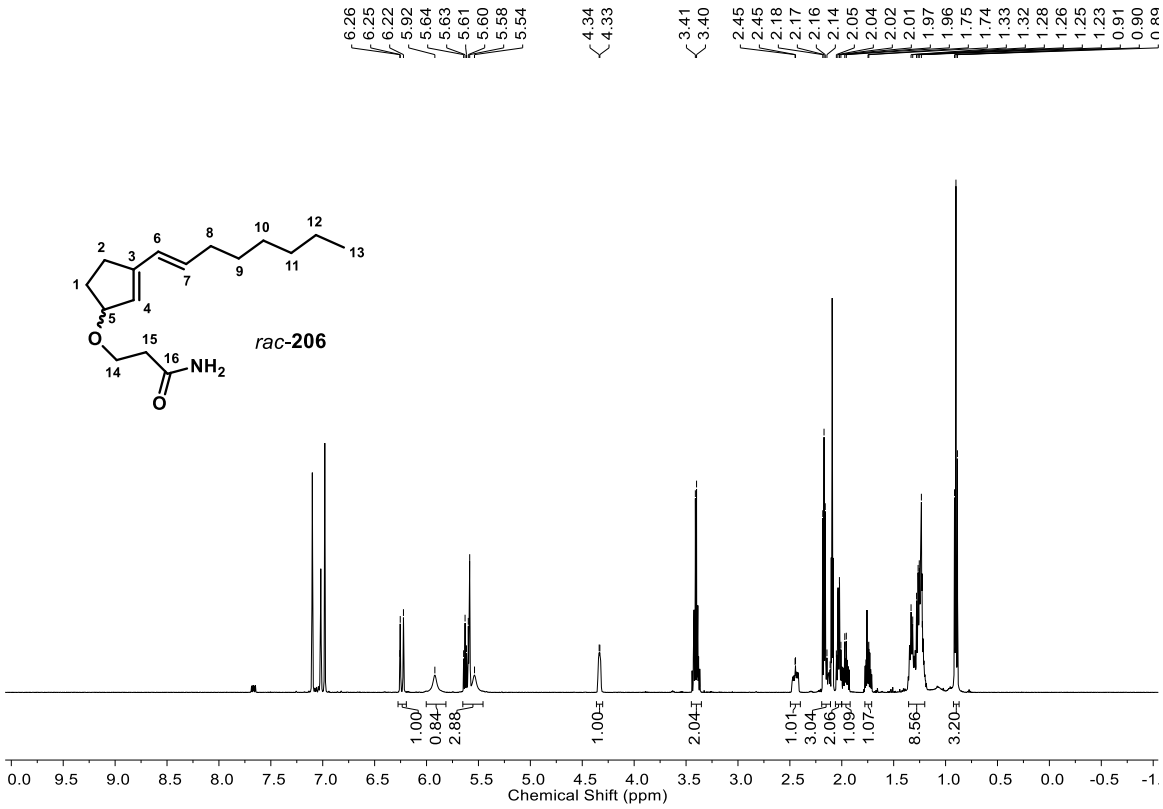


Figure 92: ^{1}H NMR (500 MHz, toluene-d$_8$) of *rac*-3-((3-((*E*)-oct-1-en-1-yl)-cyclopent-2-en-1-yl)oxy)propan-amide (*rac*-**206**).

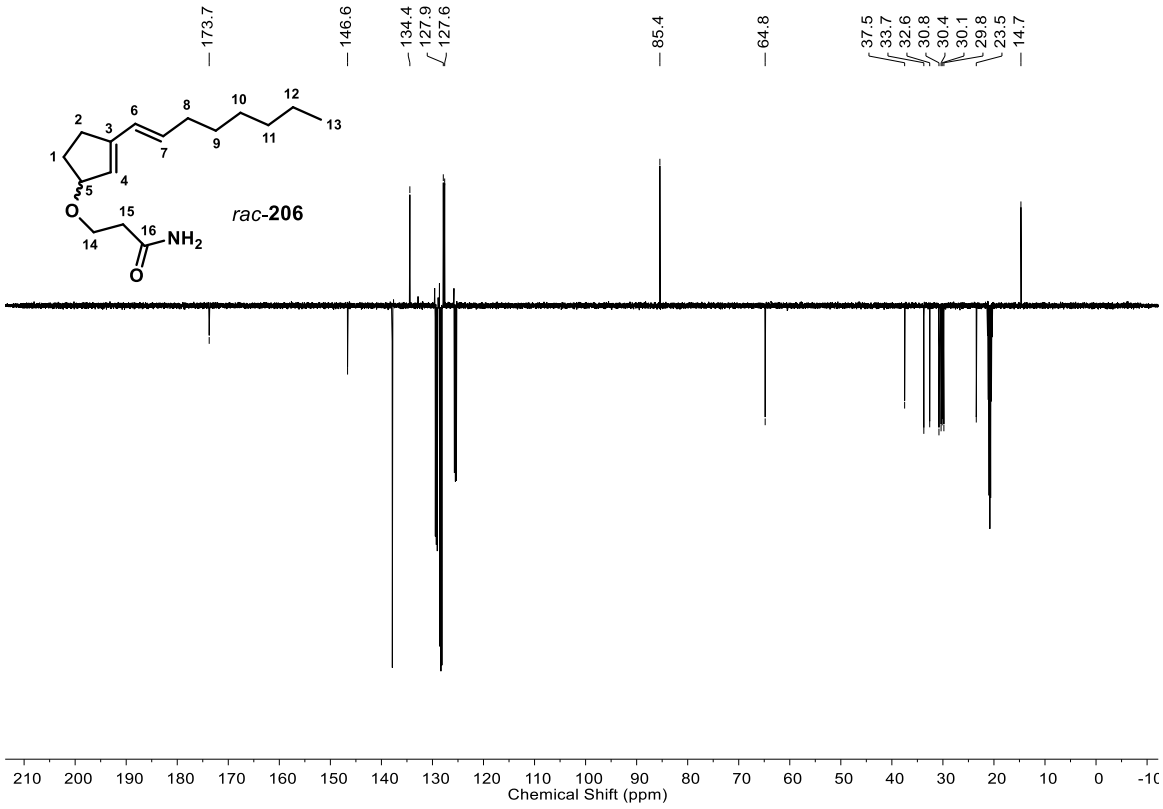


Figure 93: ^{13}C NMR (126 MHz, toluene-d$_8$) of *rac*-3-((3-((*E*)-oct-1-en-1-yl)-cyclopent-2-en-1-yl)oxy)propan-amide (*rac*-**206**).

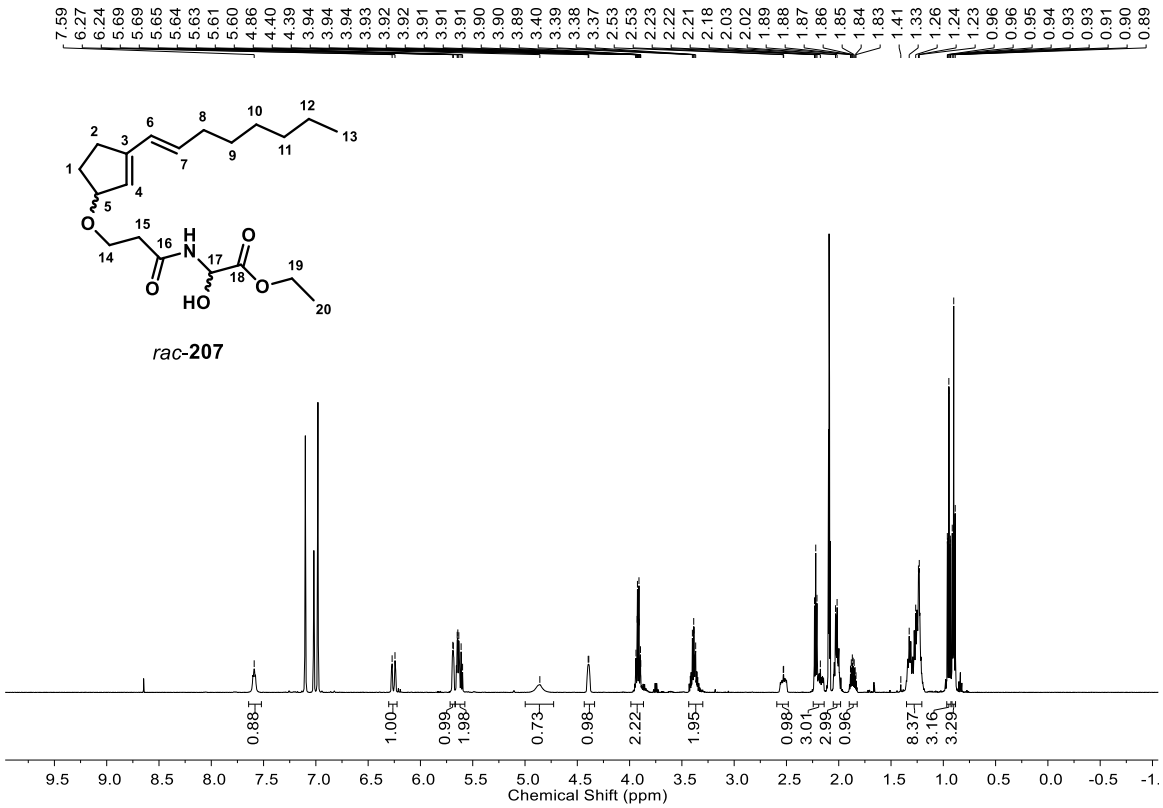


Figure 94: ^{1}H NMR (500 MHz, toluene-d_8) of *rac*-ethyl 2-(3-((3-((*E*)-oct-1-en-1-yl)-cyclopent-2-en-1-yl)oxy)propanamido)-2-hydroxyacetate (*rac*-**207**).

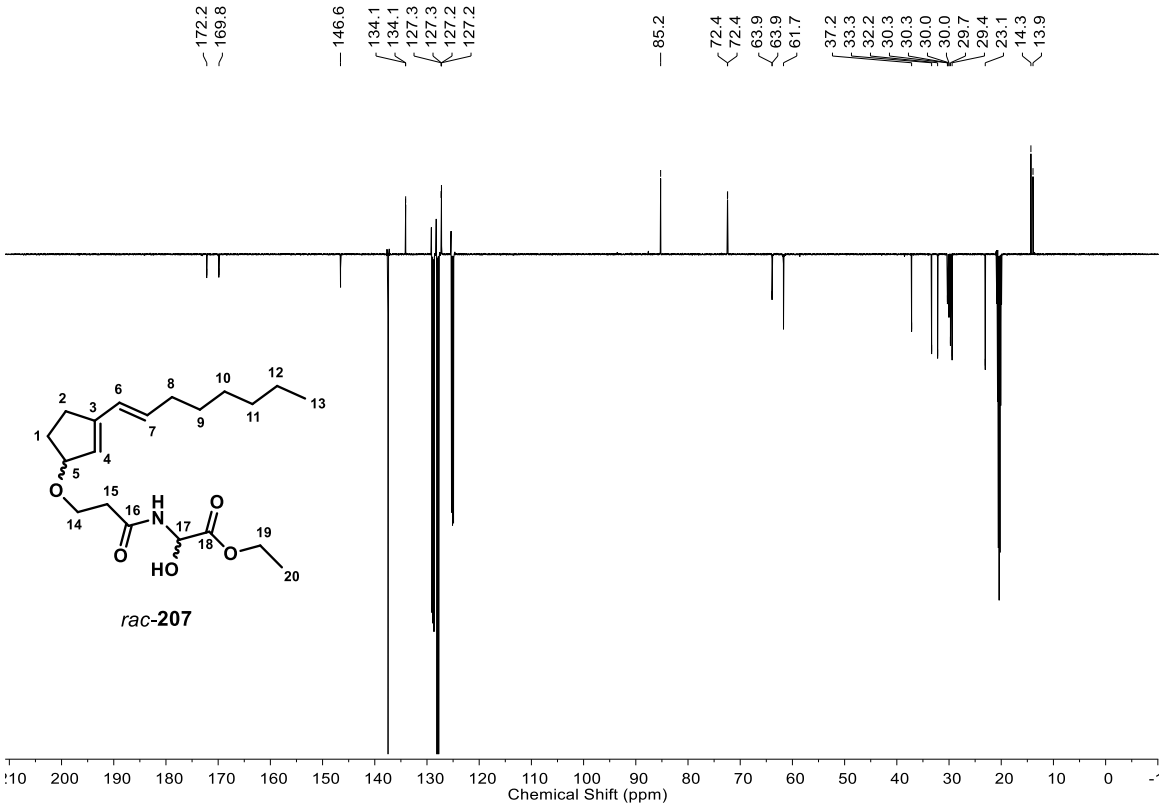


Figure 95: ^{13}C NMR (126 MHz, toluene-d_8) of *rac*-ethyl 2-(3-((3-((*E*)-oct-1-en-1-yl)-cyclopent-2-en-1-yl)oxy)propanamido)-2-hydroxyacetate (*rac*-**207**).

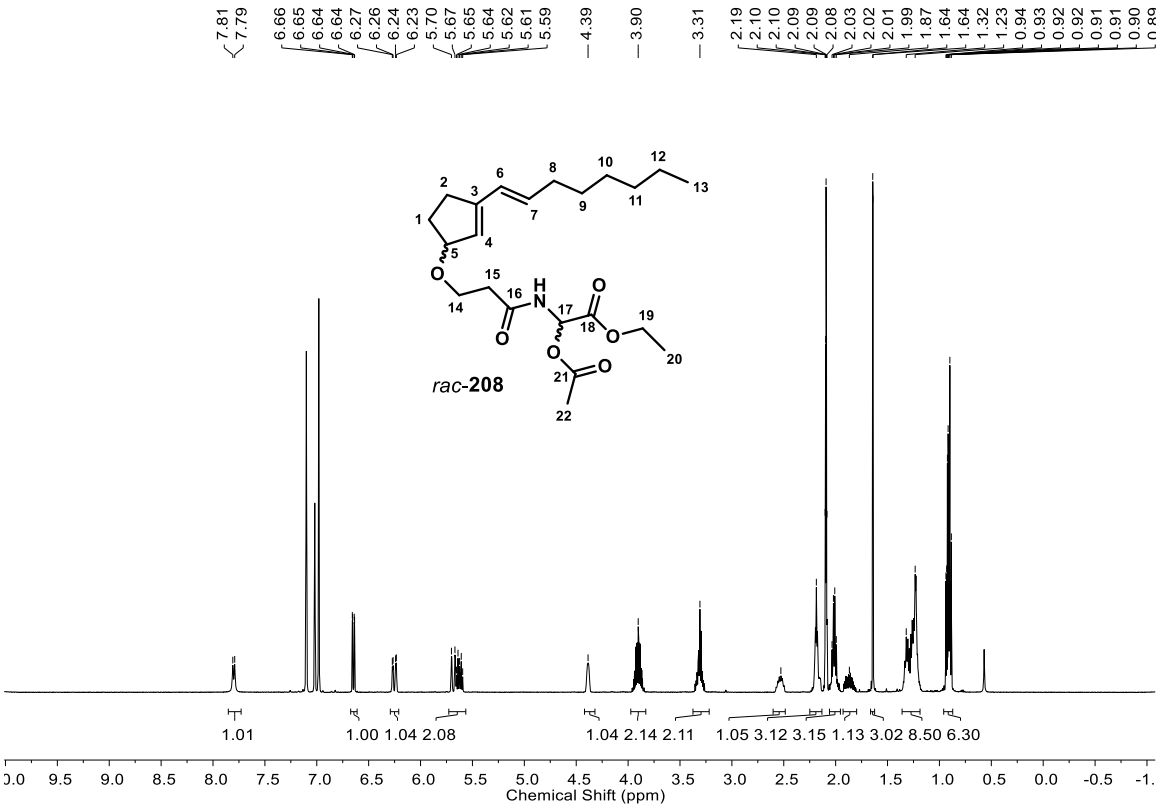


Figure 96: ^{1}H NMR (500 MHz, toluene-d_8) of *rac*-ethyl 2-(3-((3-((*E*)-oct-1-en-1-yl)-cyclopent-2-en-1-yl)oxy)-propanamido)-2-acetoxyacetate (*rac*-**208**).

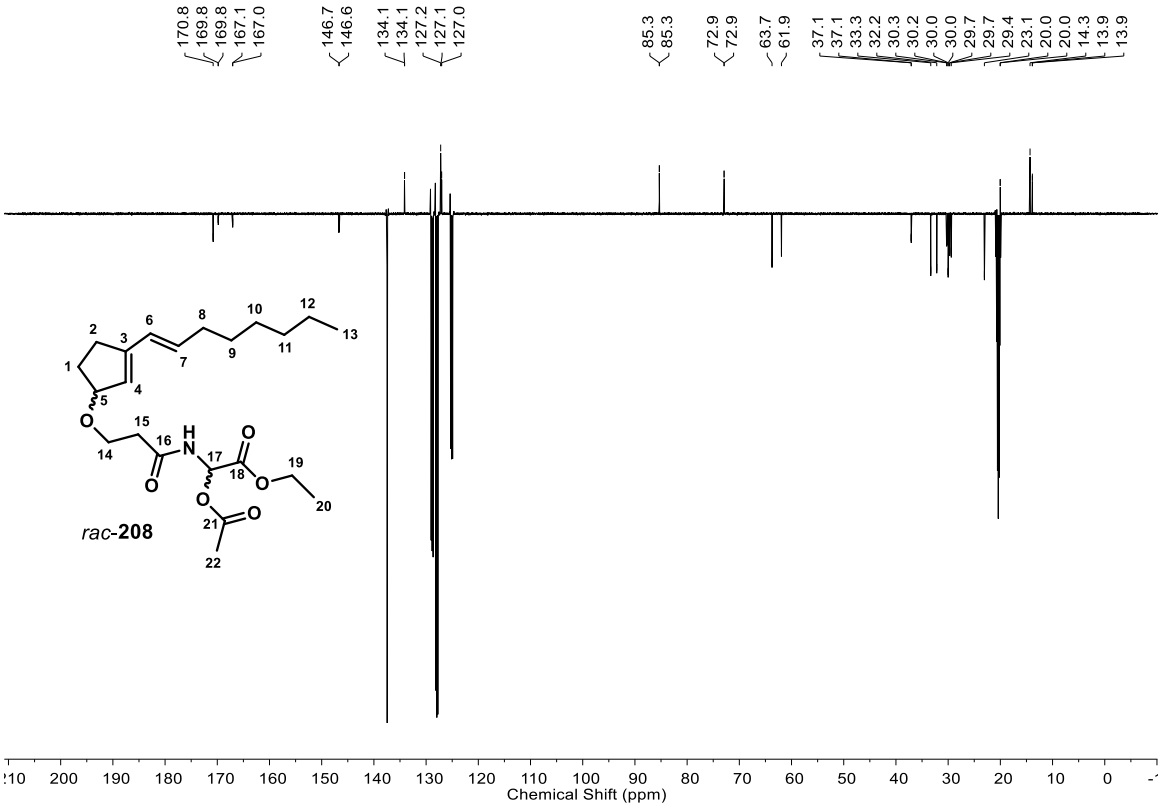
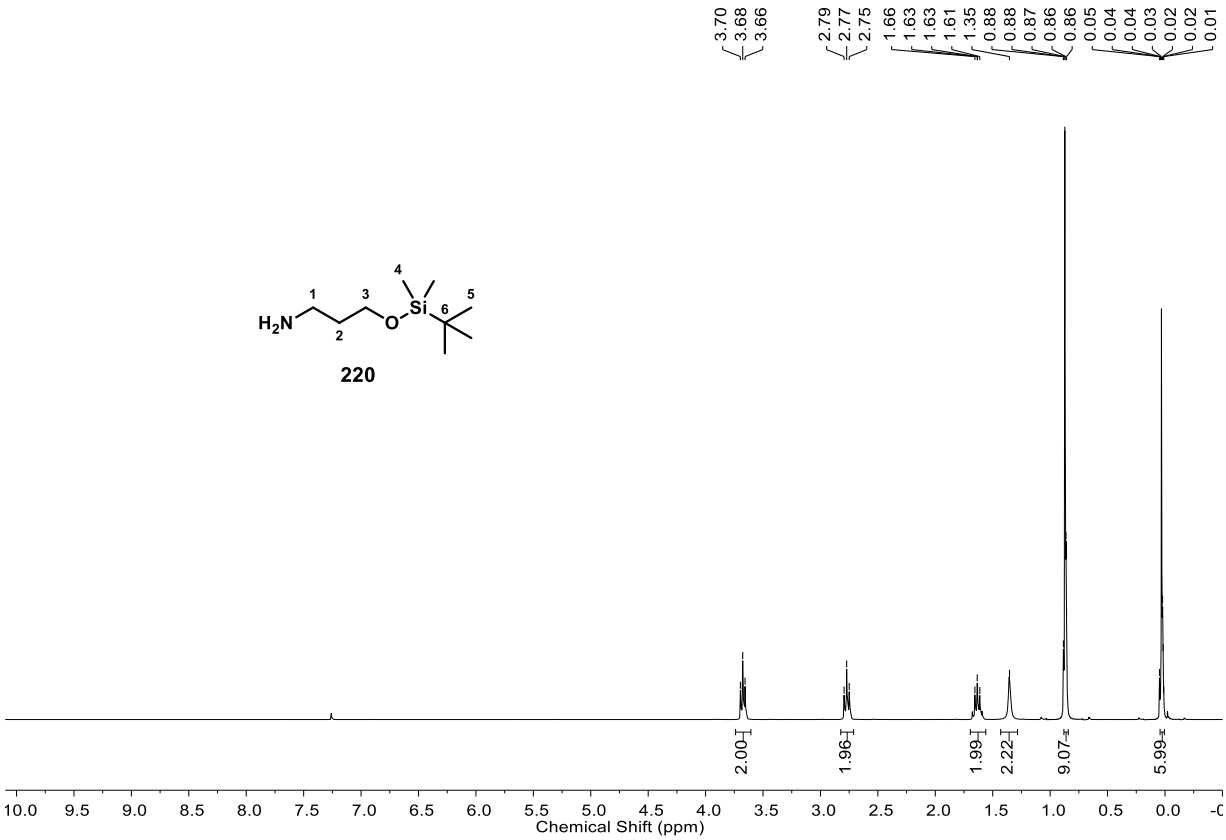
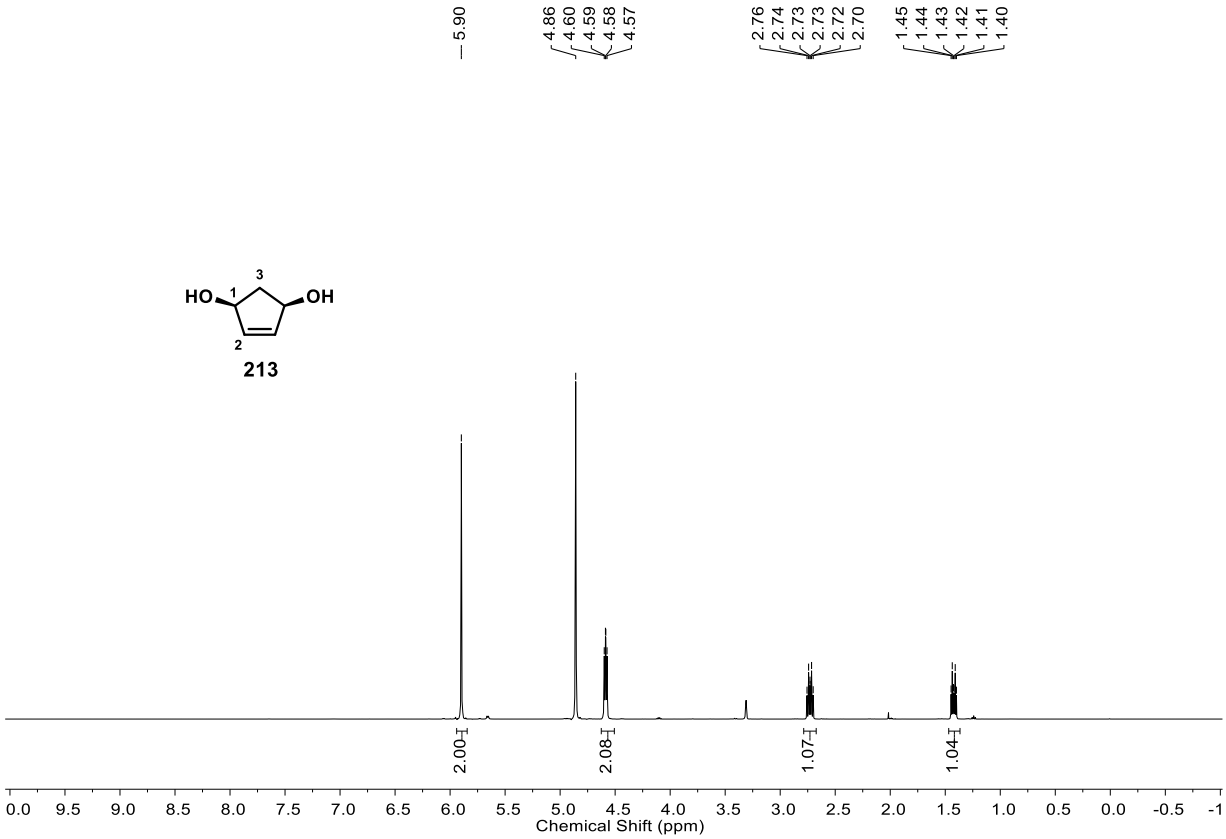


Figure 97: ^{13}C NMR (126 MHz, toluene-d_8) of *rac*-ethyl 2-(3-((3-((*E*)-oct-1-en-1-yl)-cyclopent-2-en-1-yl)oxy)-propanamido)-2-acetoxyacetate (*rac*-**208**).



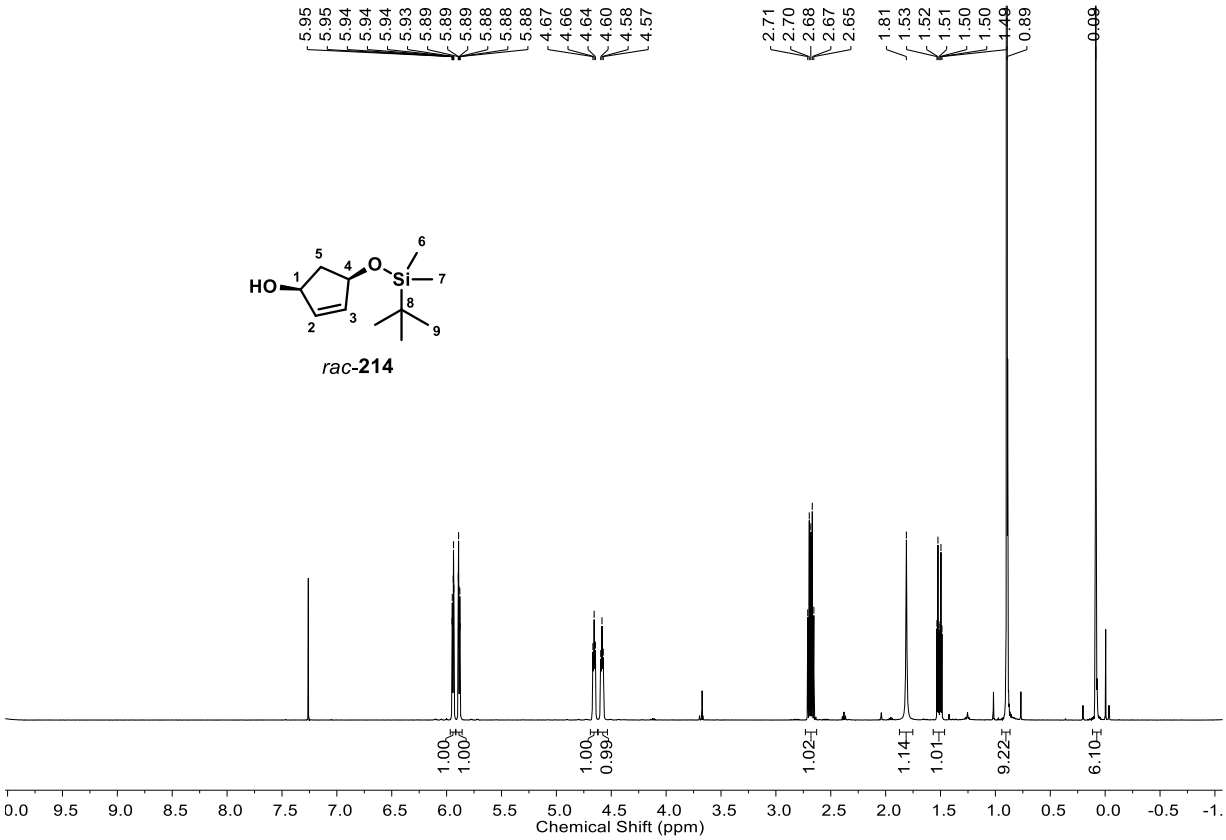
220

Figure 98: ^{1}H NMR (300 MHz, $CDCl_3$) of 3-aminopropoxy-1-*tert*-butyldimethylsilane (**220**).



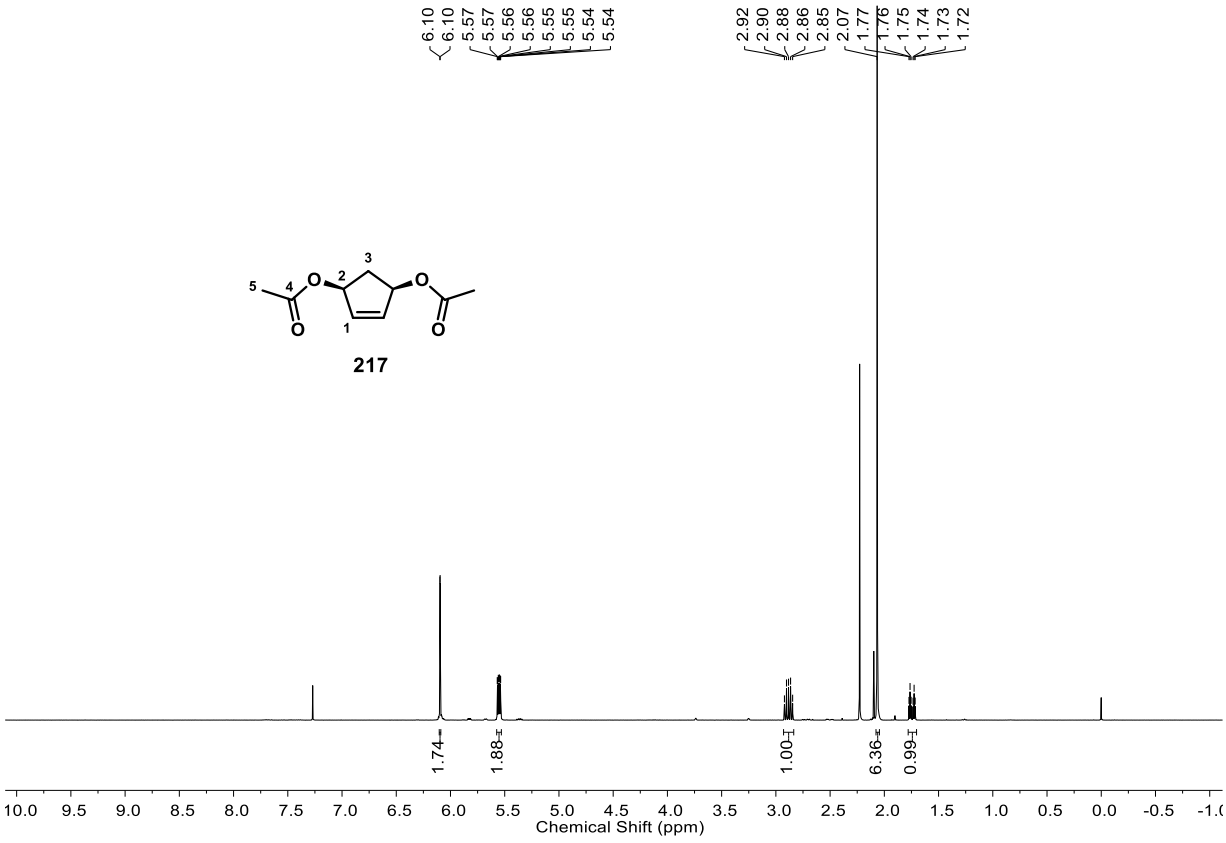
213

Figure 99: ^{1}H NMR (500 MHz, MeOD-d_4) of *cis*-4-cyclopentene-1,3-diol (**213**).



rac-**214**

Figure 100: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-*cis*-4-(*tert*-butyldimethylsilanyloxy)-cyclopenten-2-ol (*rac*-**214**).



217

Figure 101: ^{1}H NMR (400 MHz, $CDCl_3$) of *cis*-1,4-diacetoxy-cyclopent-2-en (**217**).

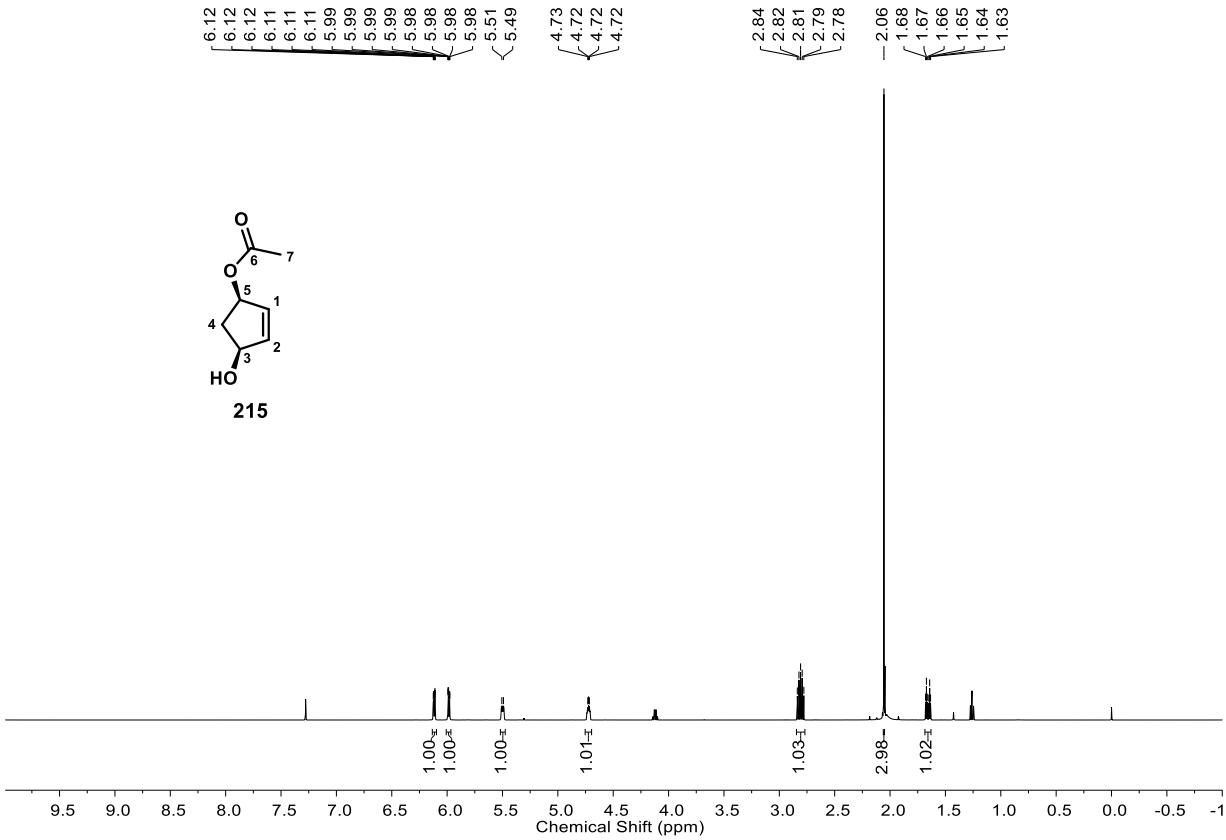


Figure 102: ^{1}H NMR (500 MHz, $CDCl_3$) of 4-acetoxycyclopent-2-en-1-ol (**215**).

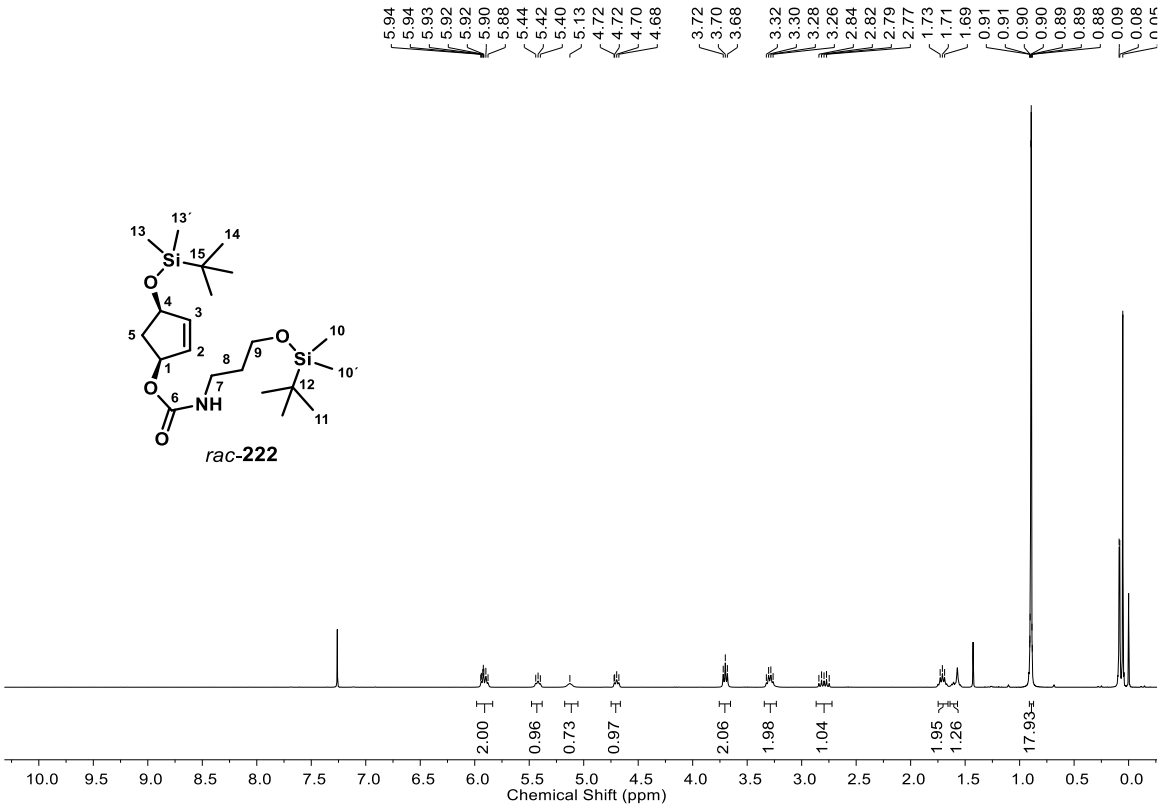


Figure 103: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac-cis*-4-(*tert*-butyldimethylsilanyloxy)cyclopent-2-en-1-yl 3-((*tert*-butyldimethylsilanyloxy)prop-1-yl carbamate (**222**).

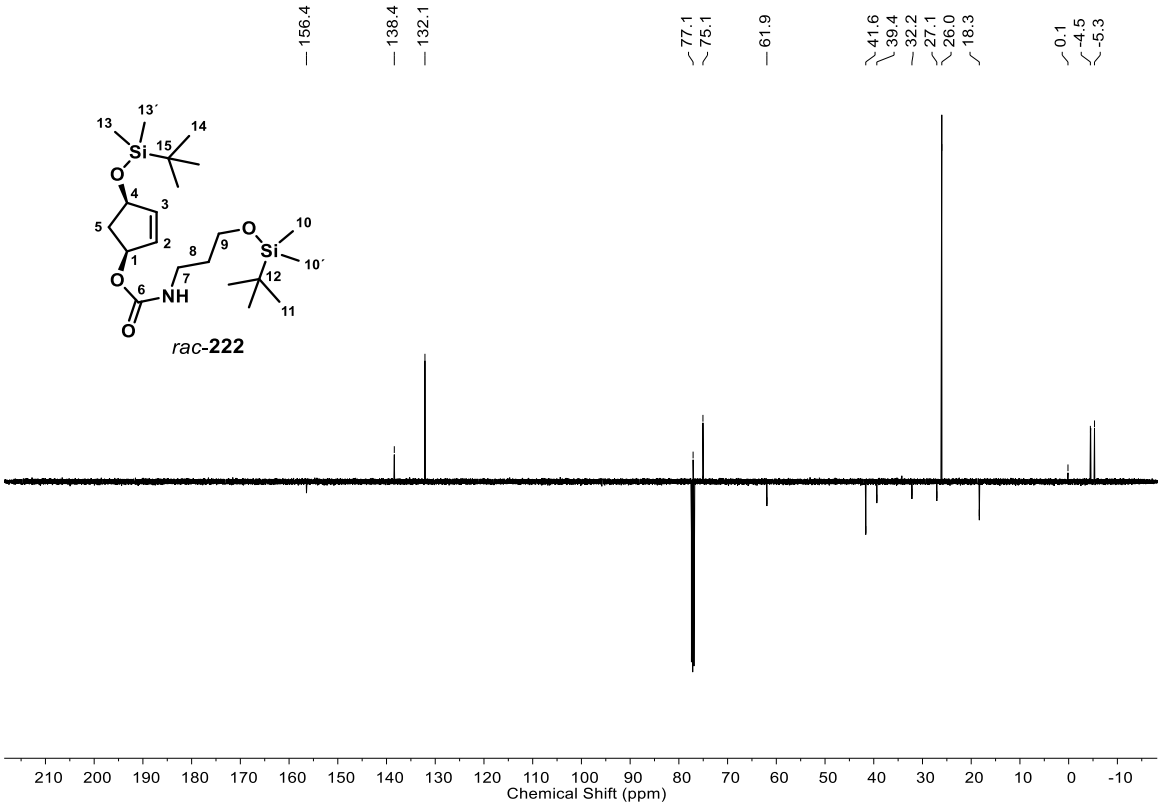


Figure 104: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac-cis*-4-(*tert*-butyldimethylsilanyloxy)cyclopent-2-en-1-yl 3-((*tert*-butyldimethylsilanyloxy)prop-1-yl carbamate (**222**).

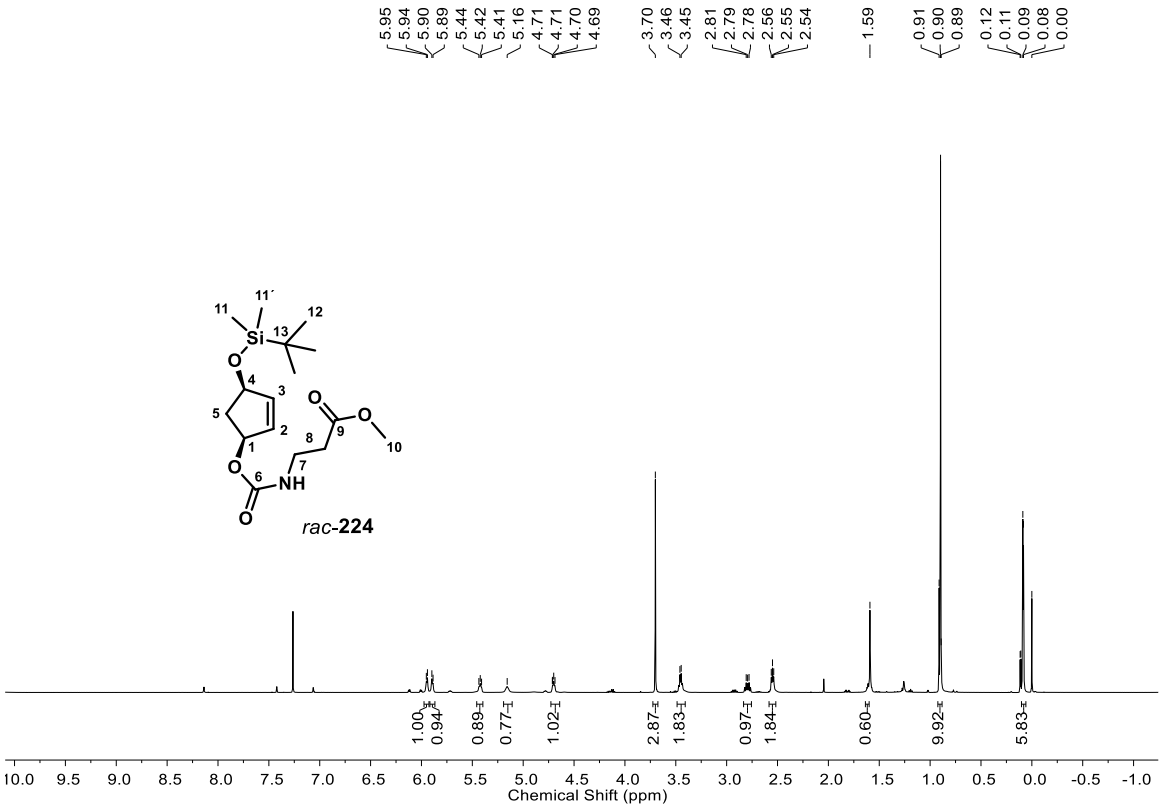


Figure 105: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-*cis*-methyl 3-(((4-((*tert*-butyldimethylsilanyloxy)cyclopent-2-en-1-yl)oxy)carbonyl)amino)propanoate (*rac*-**224**).

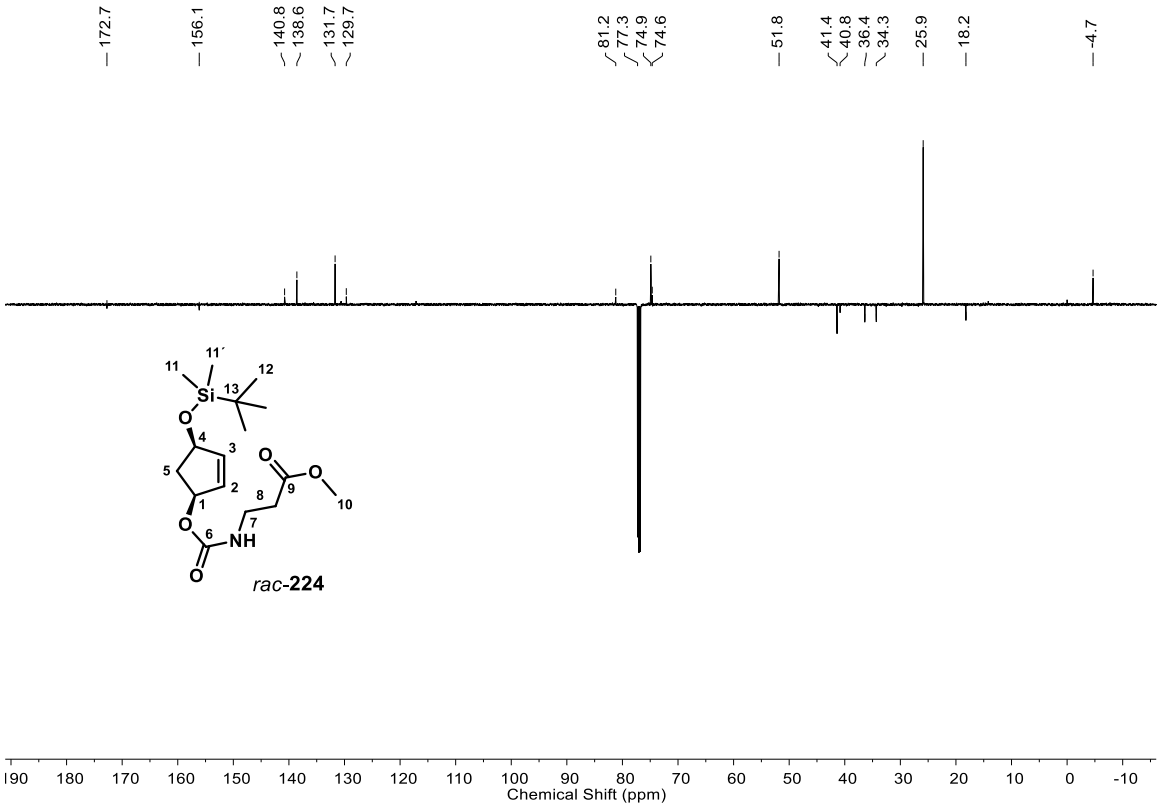


Figure 106: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-*cis*-methyl 3-(((4-((*tert*-butyldimethylsilanyloxy)cyclopent-2-en-1-yl)oxy)carbonyl)amino)propanoate (*rac*-**224**).

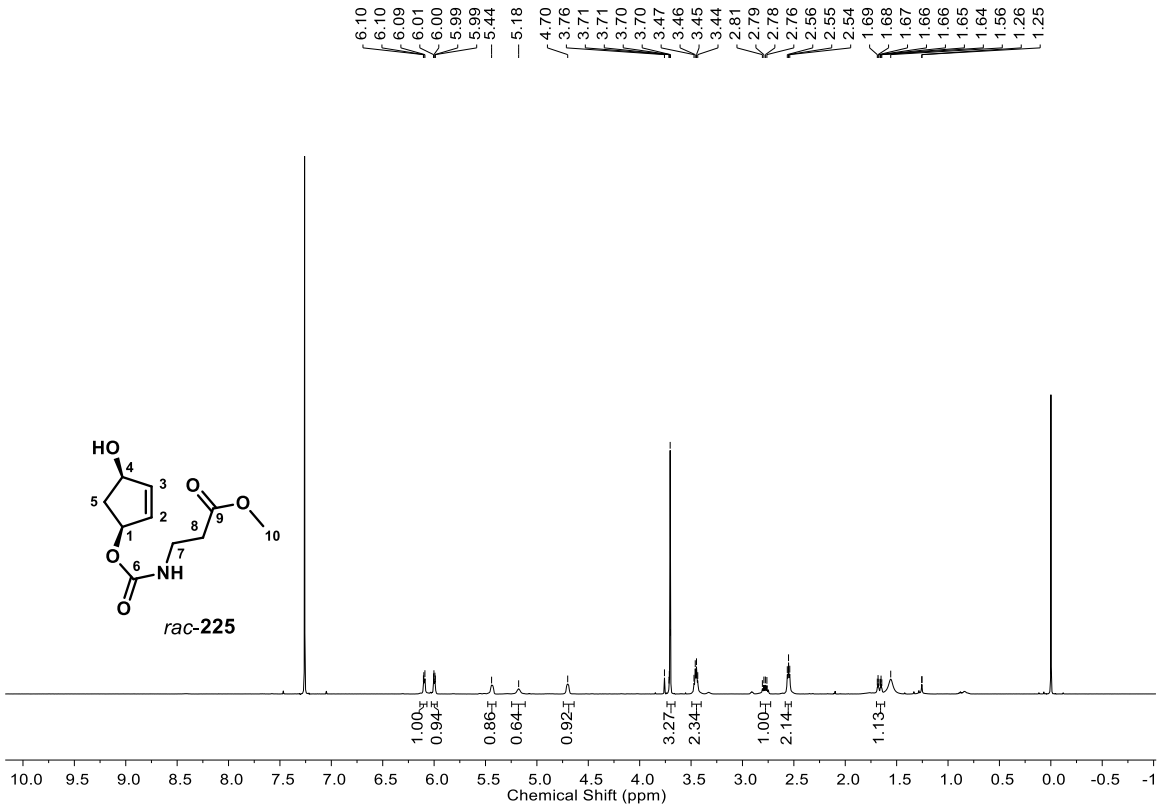


Figure 107: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac-cis*-3-(((4-hydroxy-cyclopent-2-ene-1-yloxy)carbonyl)-amino)propionic acid methylester (*rac*-**225**).

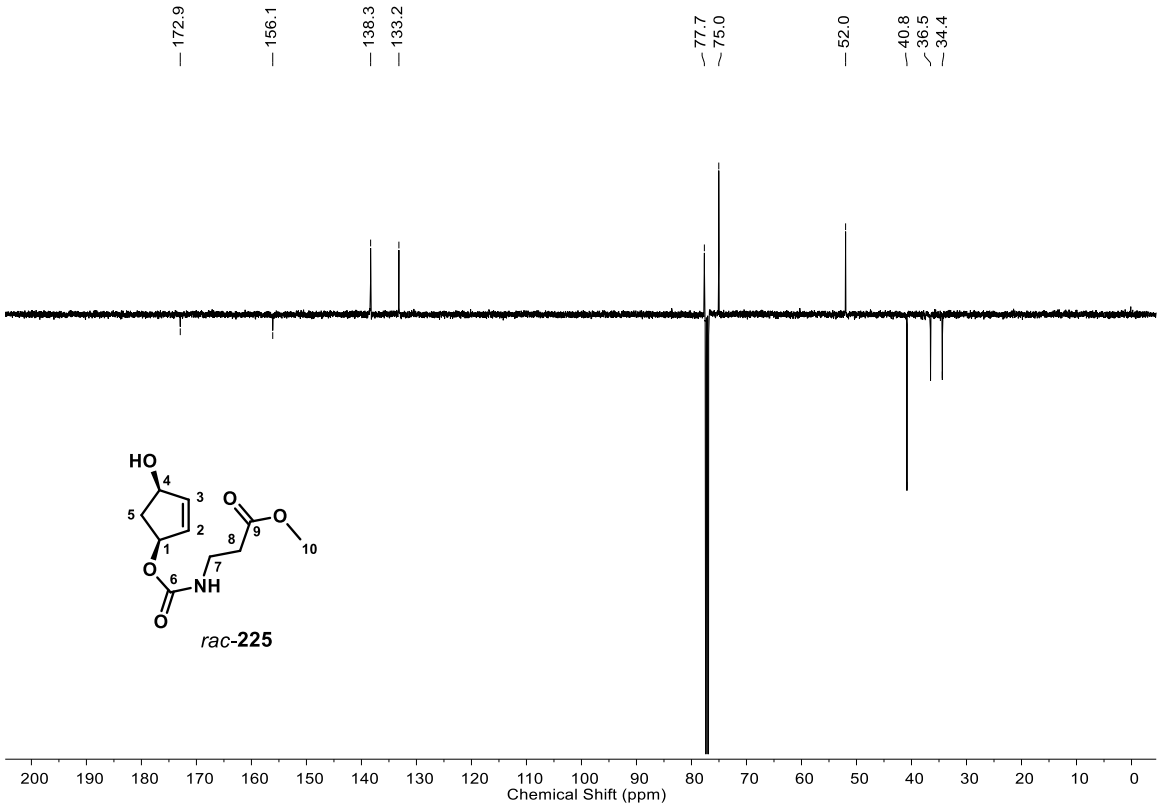


Figure 108: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac-cis*-3-(((4-hydroxy-cyclopent-2-ene-1-yloxy)carbonyl)-amino)propionic acid methylester (*rac*-**225**).

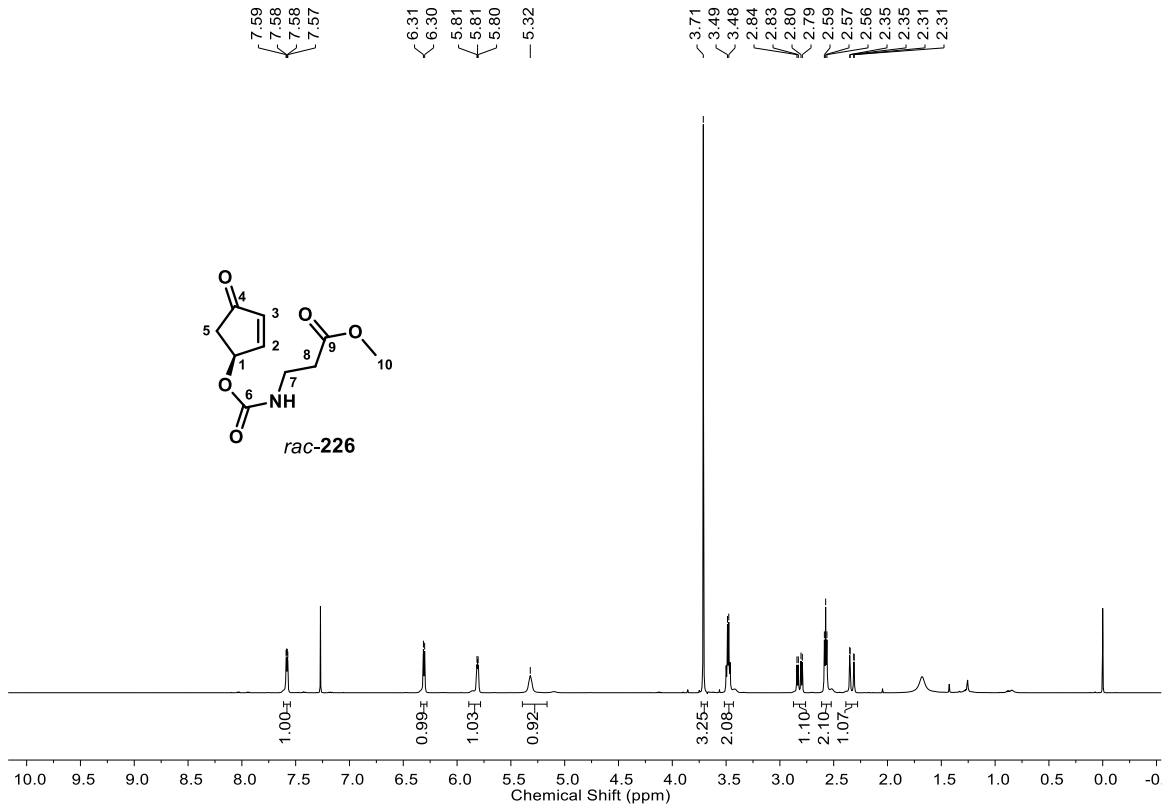


Figure 109: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-3-((4-oxo-cyclopent-2-ene-1-yl)oxy)carbonyl)amino-propionic acid methylester (*rac*-**226**).

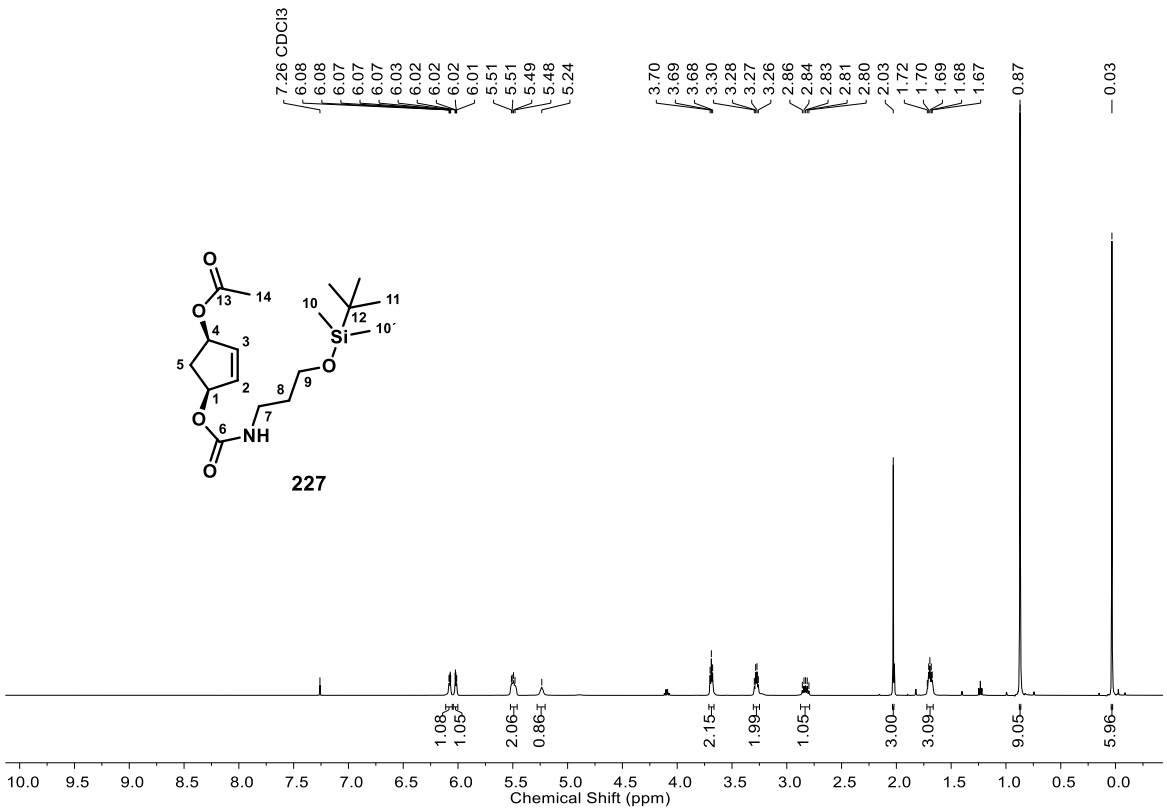


Figure 110: ^{1}H NMR (500 MHz, $CDCl_3$) of (1*R*,4*S*)-4-(((3-((*tert*-butyl(dimethyl)silyl)oxy)propyl)-carbamoyl)oxy)cyclopent-2-en-1-yl acetate (**227**).

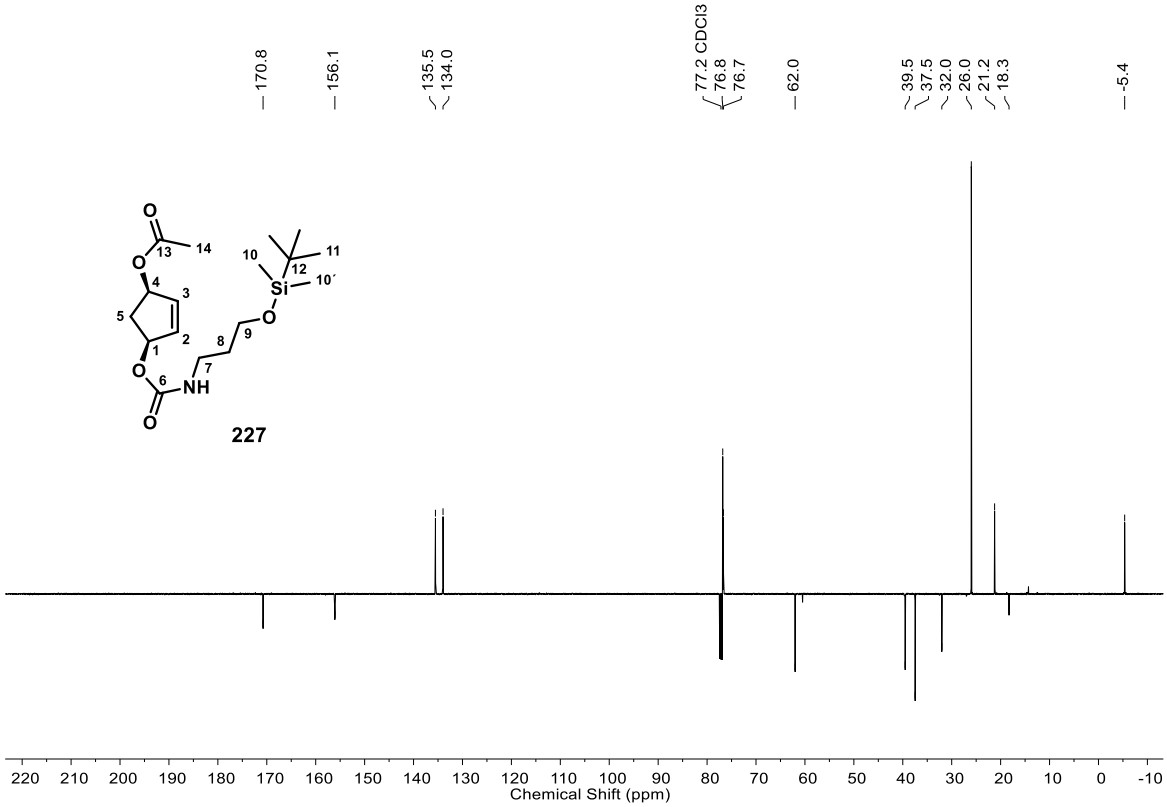


Figure 111: ^{13}C NMR (126 MHz, toluene-d_8) of (1*R*,4*S*)-4-(((3-((*tert*-butyl(dimethyl)silyl)oxy)propyl)-carbamoyl)oxy)cyclopent-2-en-1-yl acetate (**227**).

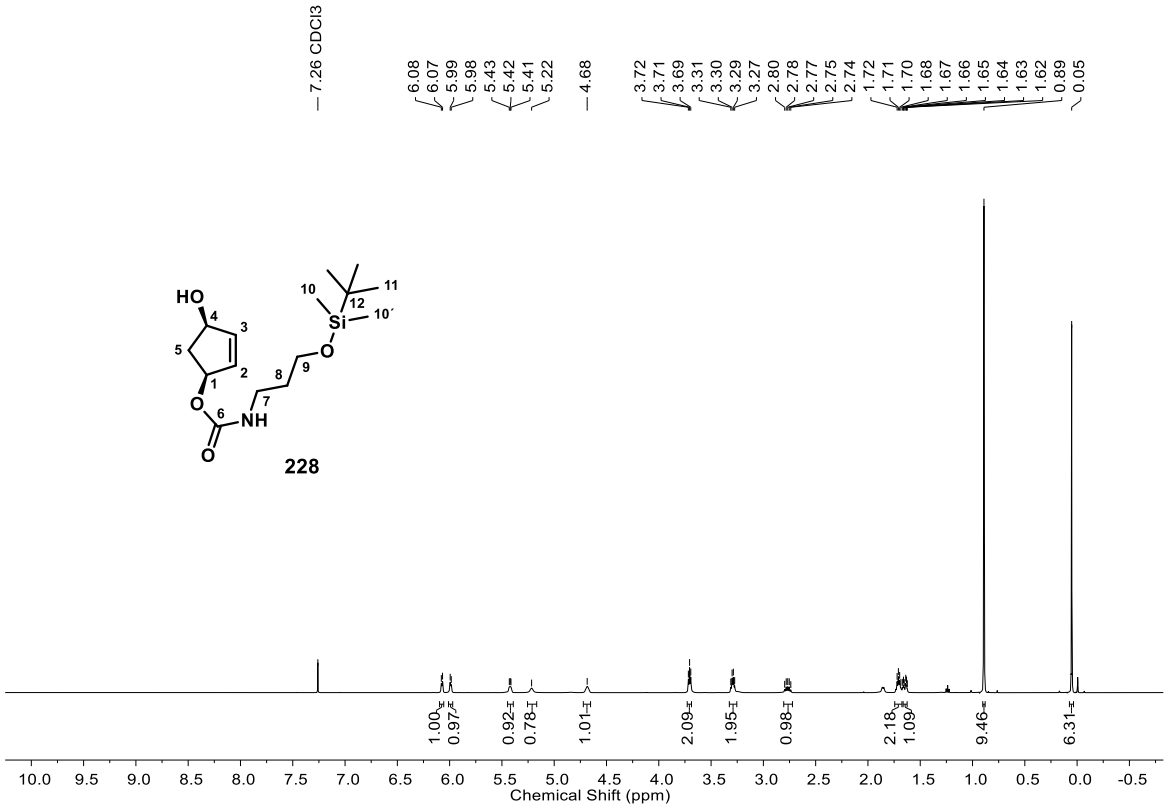


Figure 112: ^{1}H NMR (500 MHz, $CDCl_3$) of (1*S*,4*R*)-4-hydroxycyclopent-2-en-1-yl (3-((*tert*-butyl(dimethyl)-silyl)oxy)propyl)carbamate (**228**).

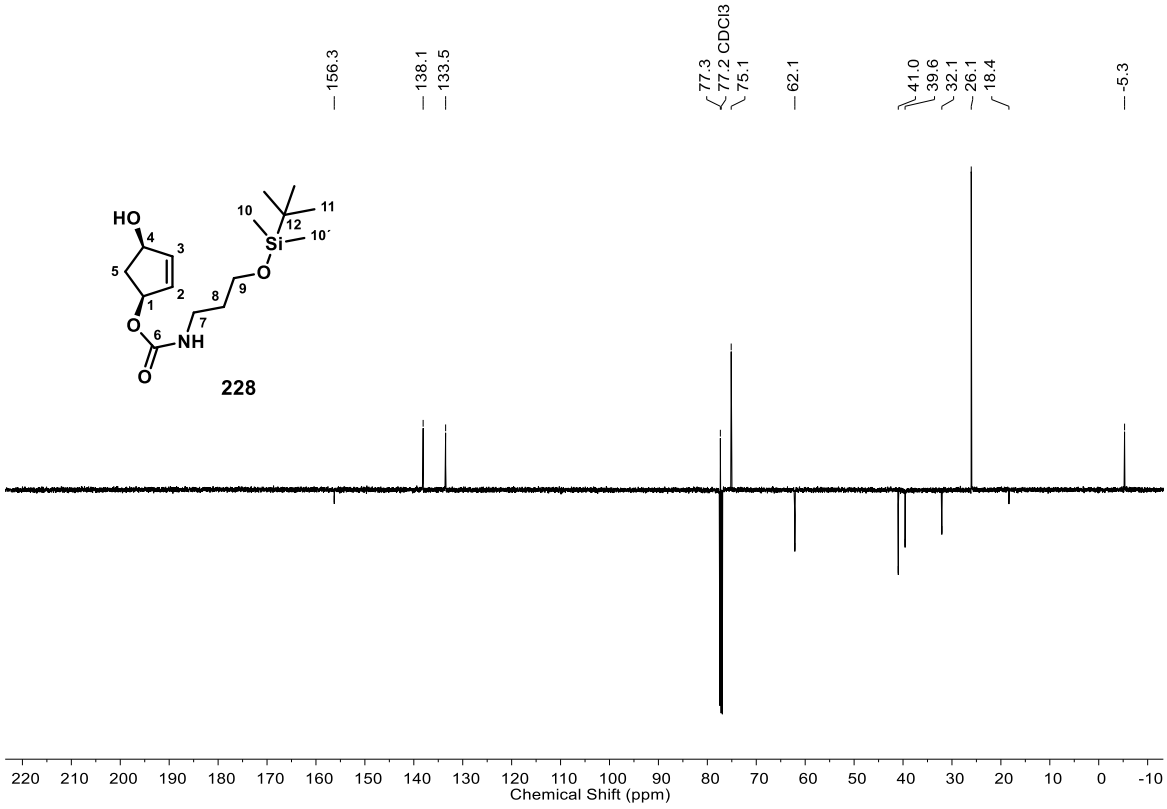


Figure 113: ^{13}C NMR (126 MHz, $CDCl_3$) of (1*S*,4*R*)-4-hydroxycyclopent-2-en-1-yl (3-((*tert*-butyl(dimethyl)-silyl)oxy)propyl)carbamate (**228**).

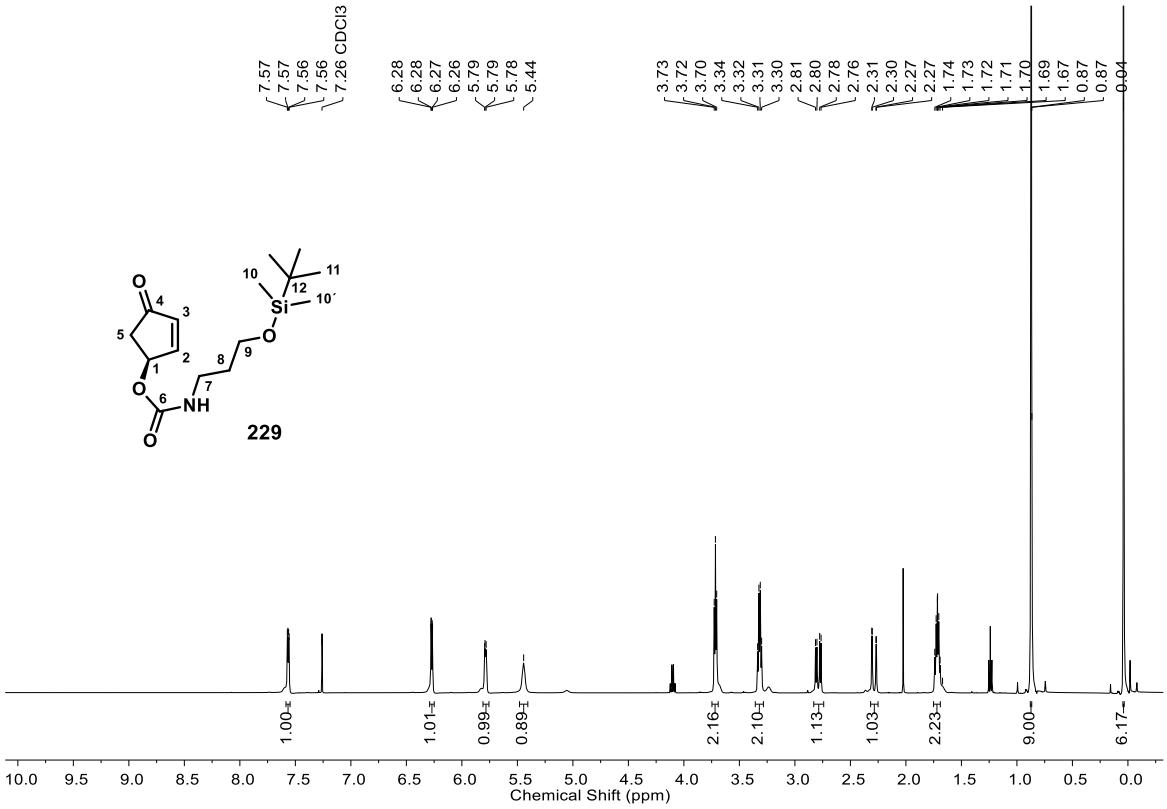


Figure 114: ^{1}H NMR (500 MHz, $CDCl_3$) of (1*R*)-4-oxocyclopent-2-en-1-yl (3-((*tert*-butyl(dimethyl)silyl)-oxy)propyl)carbamate (**229**).

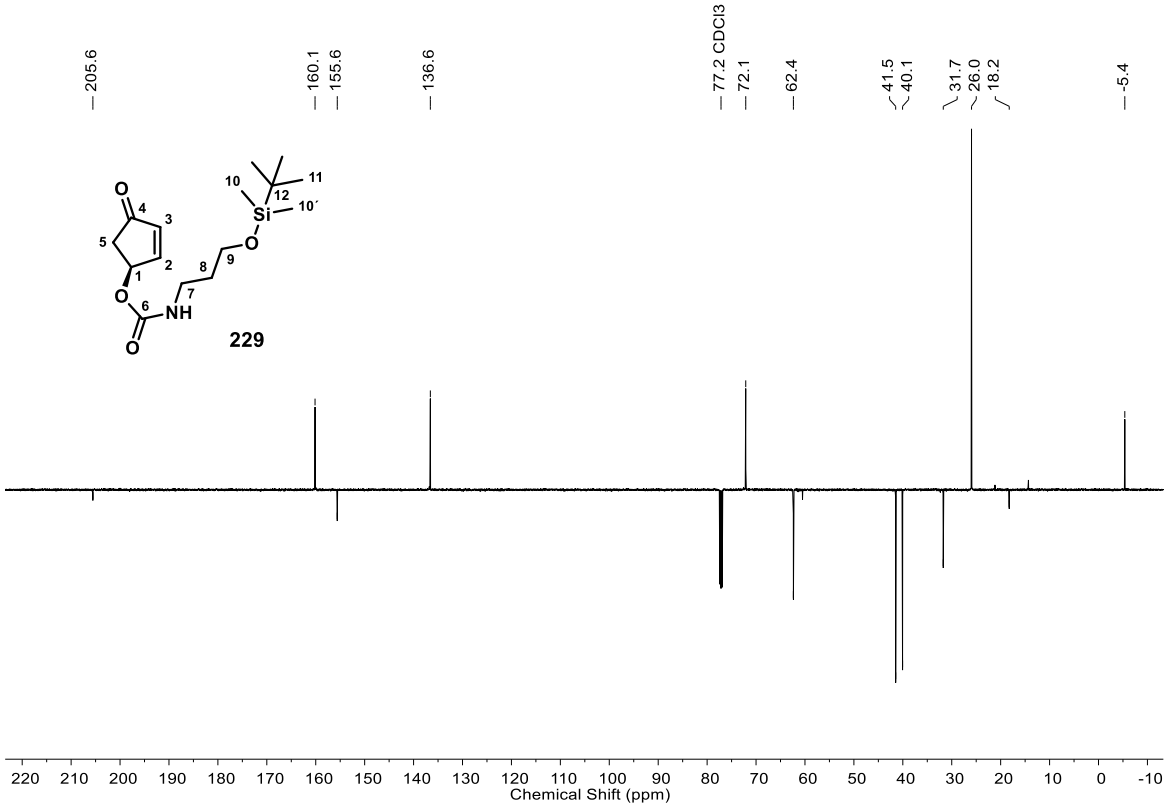


Figure 115: ^{13}C NMR (126 MHz, $CDCl_3$) of (1*R*)-4-oxocyclopent-2-en-1-yl (3-((*tert*-butyl(dimethyl)silyl)-oxy)propyl)carbamate (**229**).

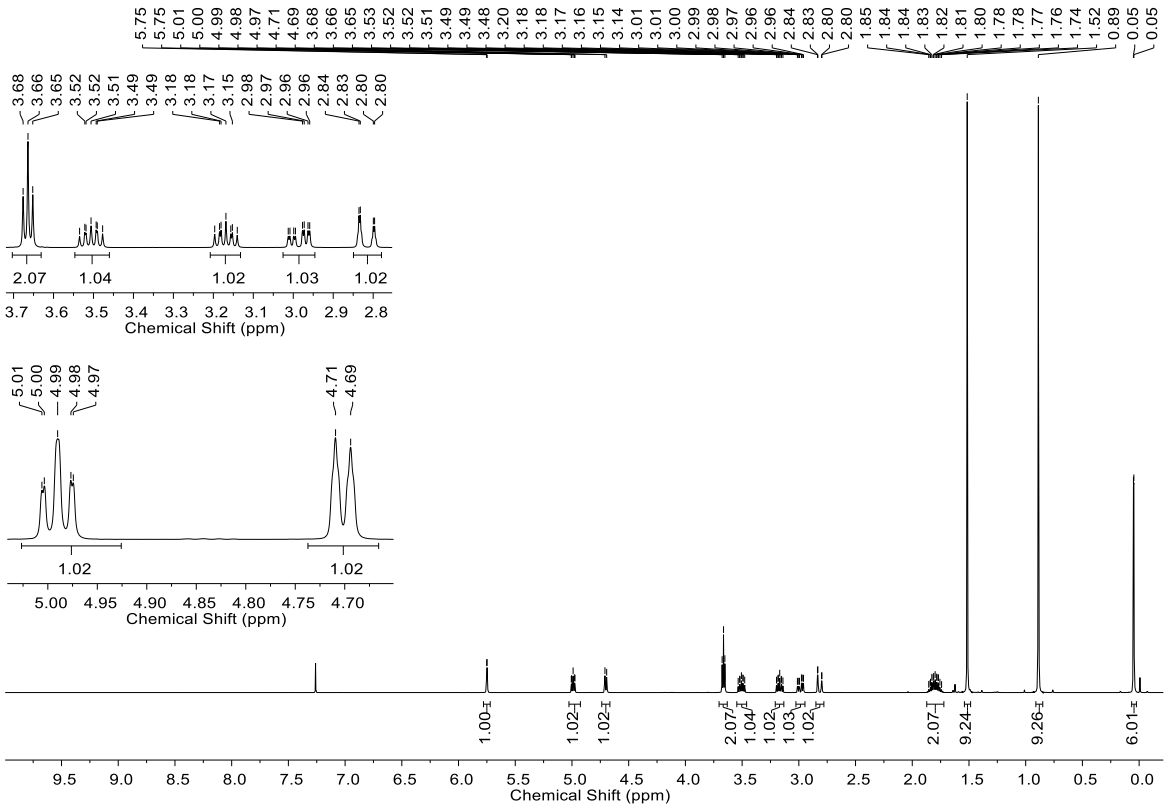


Figure 116: ^{1}H NMR (500 MHz, $CDCl_3$) of *tert*-butyl 3-(3-((*tert*-butyl(dimethyl)silyl)oxy)propyl)-2-oxo-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*d*][1,3]oxazol-5-yl carbonate (**237**).

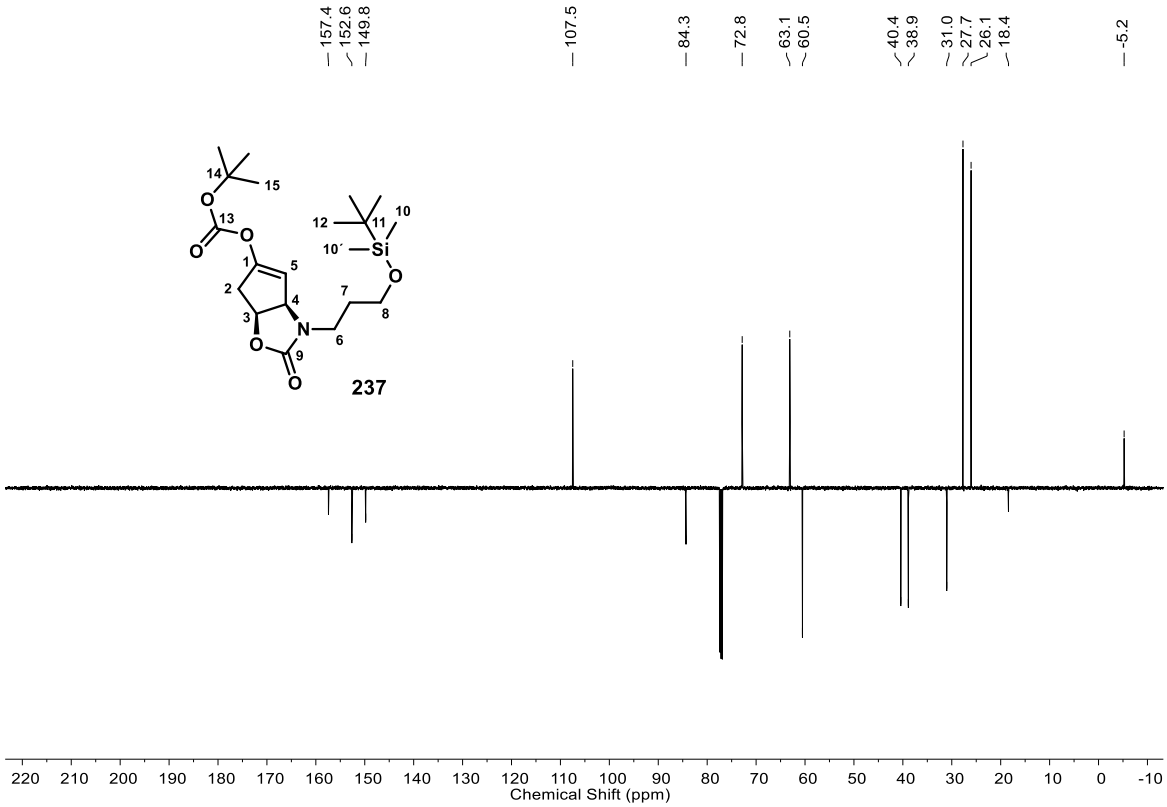


Figure 117: ^{13}C NMR (126 MHz, $CDCl_3$) of *tert*-butyl 3-(3-((*tert*-butyl(dimethyl)silyl)oxy)propyl)-2-oxo-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*d*][1,3]oxazol-5-yl carbonate (**237**).

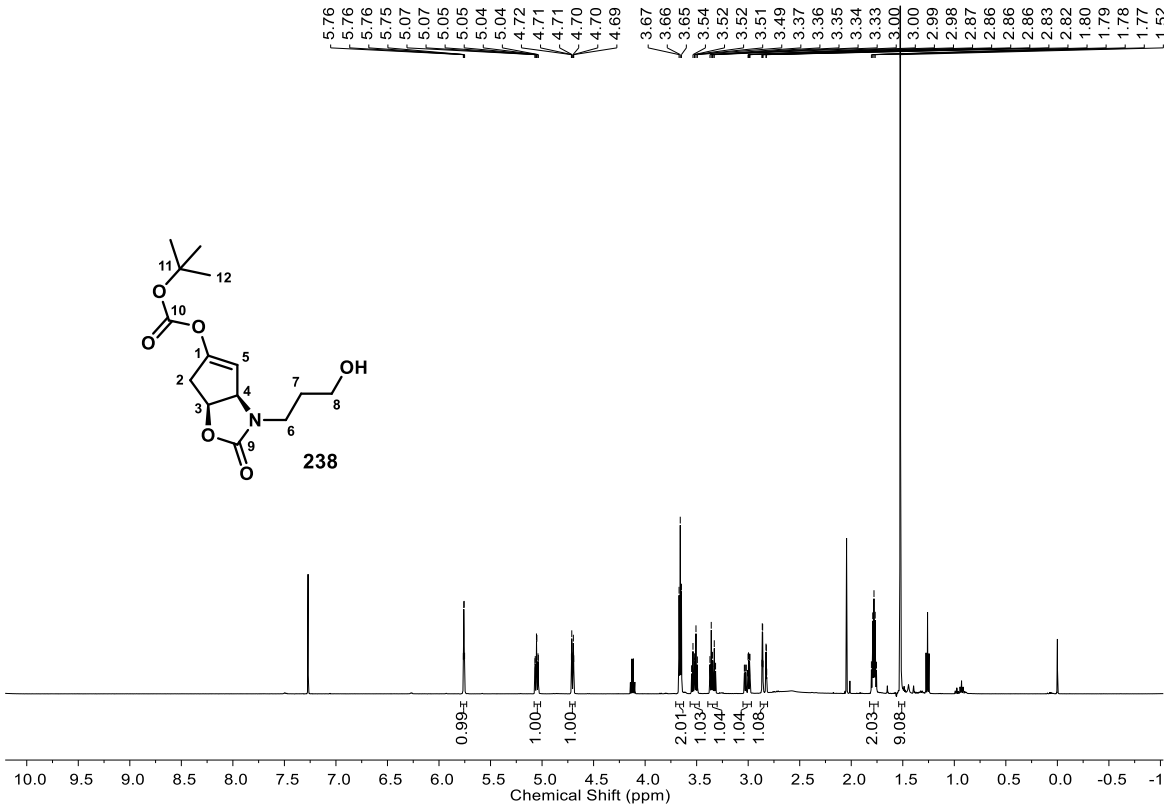


Figure 118: ^{1}H NMR (500 MHz, $CDCl_3$) of *tert*-butyl (6a*S*)-3-(3-hydroxypropyl)-2-oxo-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*d*][1,3]oxazol-5-yl carbonate (**238**).

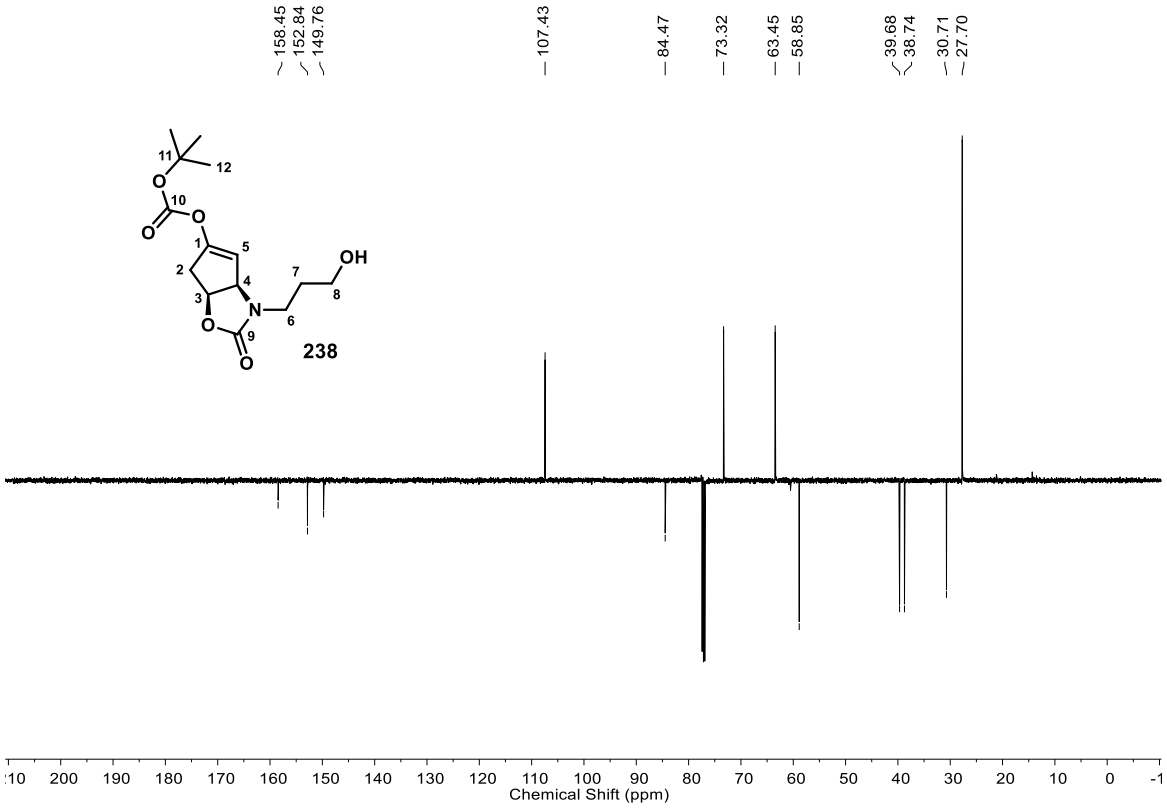


Figure 119: ^{13}C NMR (126 MHz, $CDCl_3$) of *tert*-butyl (6a*S*)-3-(3-hydroxypropyl)-2-oxo-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*d*][1,3]oxazol-5-yl carbonate (**238**).

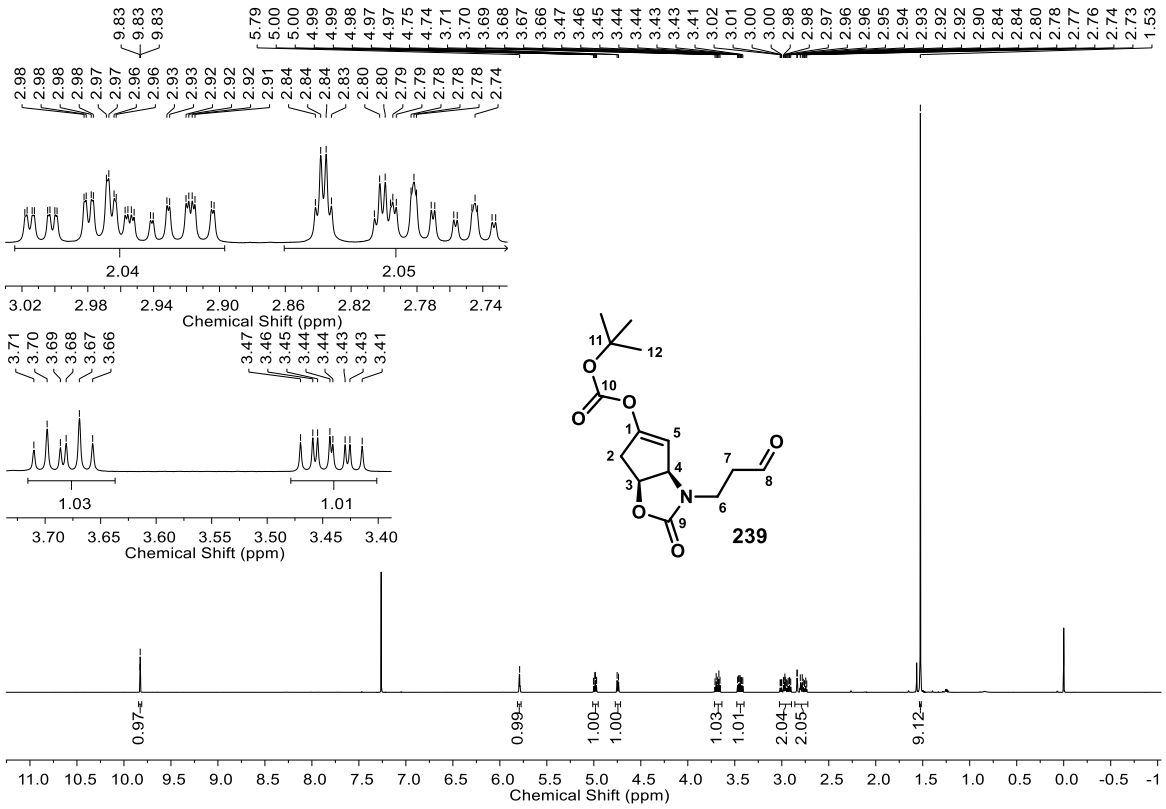


Figure 120: ^{1}H NMR (500 MHz, $CDCl_3$) of *tert*-butyl (6a*S*)-2-oxo-3-(3-oxopropyl)-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*d*][1,3]oxazol-5-yl carbonate (**239**).

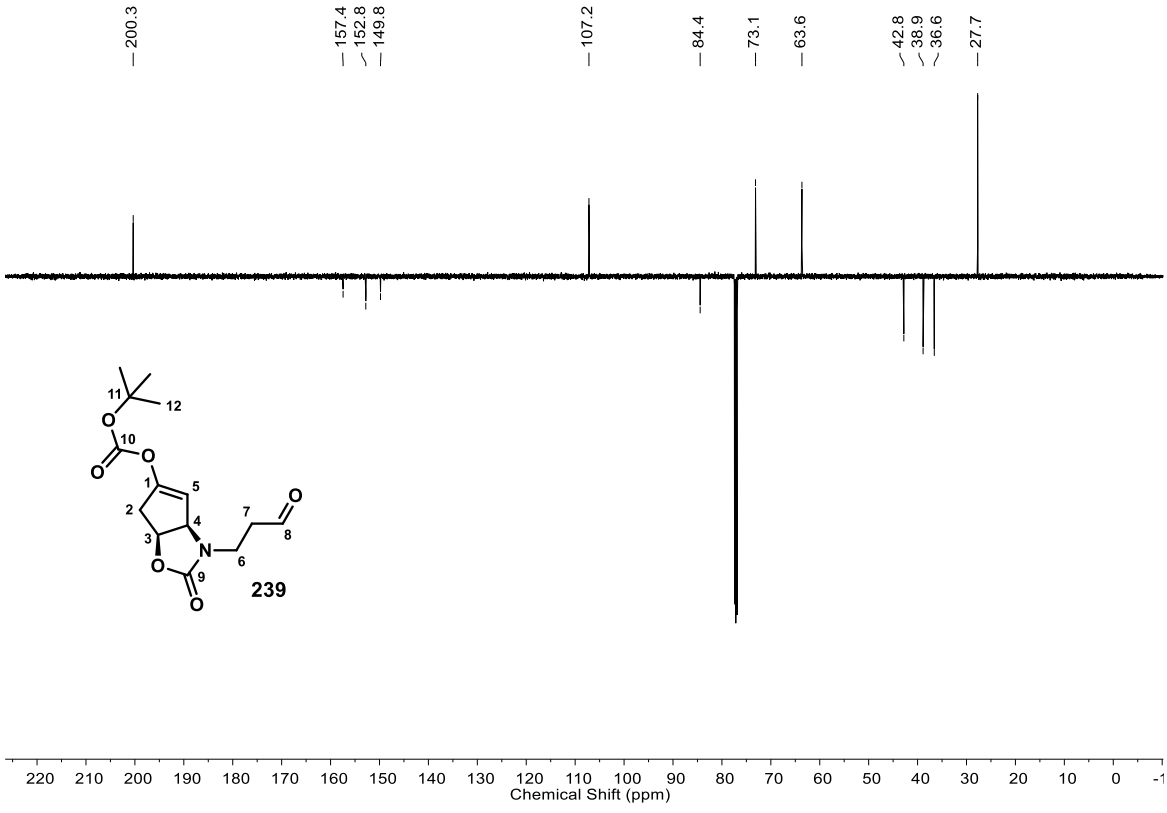


Figure 121: ^{13}C NMR (126 MHz, $CDCl_3$) of *tert*-butyl (6a*S*)-2-oxo-3-(3-oxopropyl)-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*d*][1,3]oxazol-5-yl carbonate (**239**).

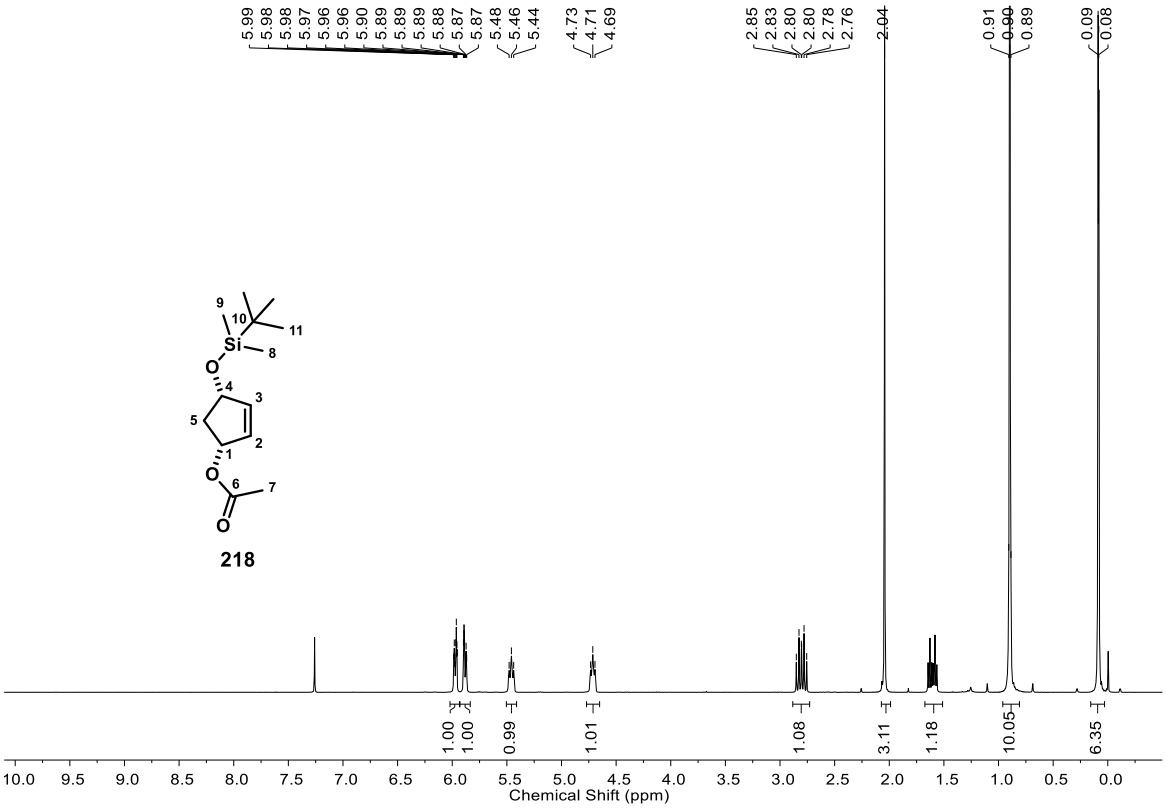


Figure 122: ^{1}H NMR (300 MHz, $CDCl_3$) of (1*R*,4*S*)-4-((*tert*-Butyldimethylsilyl)oxy)cyclopent-2-en-1-yl acetate (**218**).

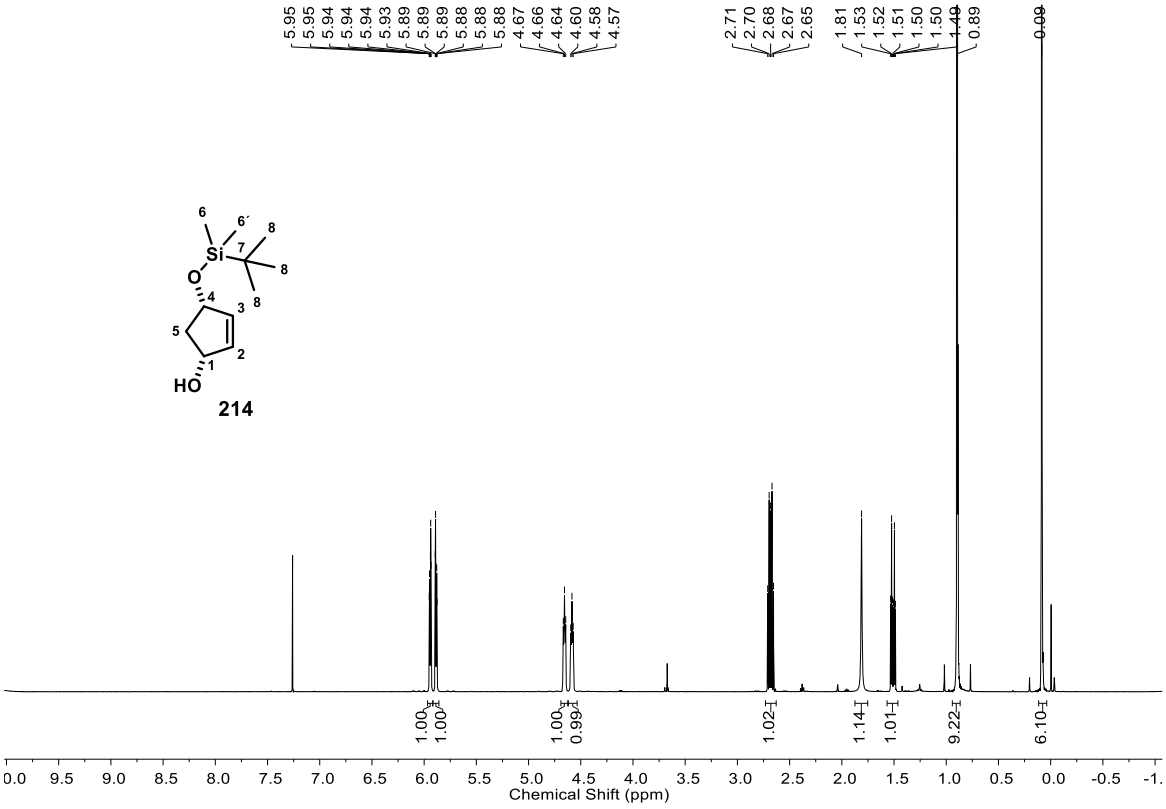


Figure 123: ^{1}H NMR (500 MHz, $CDCl_3$) of (1*R*,4*S*)-4-((*tert*-Butyldimethylsilyl)oxy)cyclopent-2-en-1-ol (**214**).

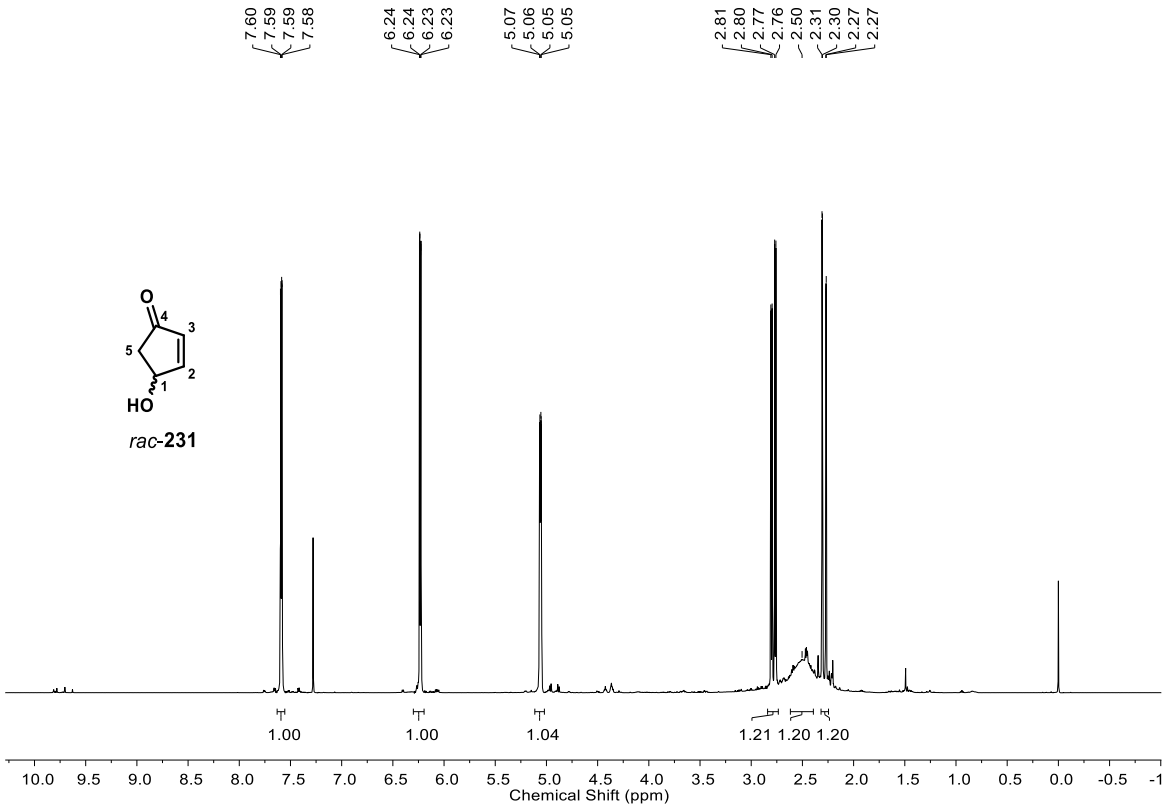


Figure 124: ^{1}H NMR (500 MHz, $CDCl_3$) of 4-hydroxycyclopentenone (**231**).

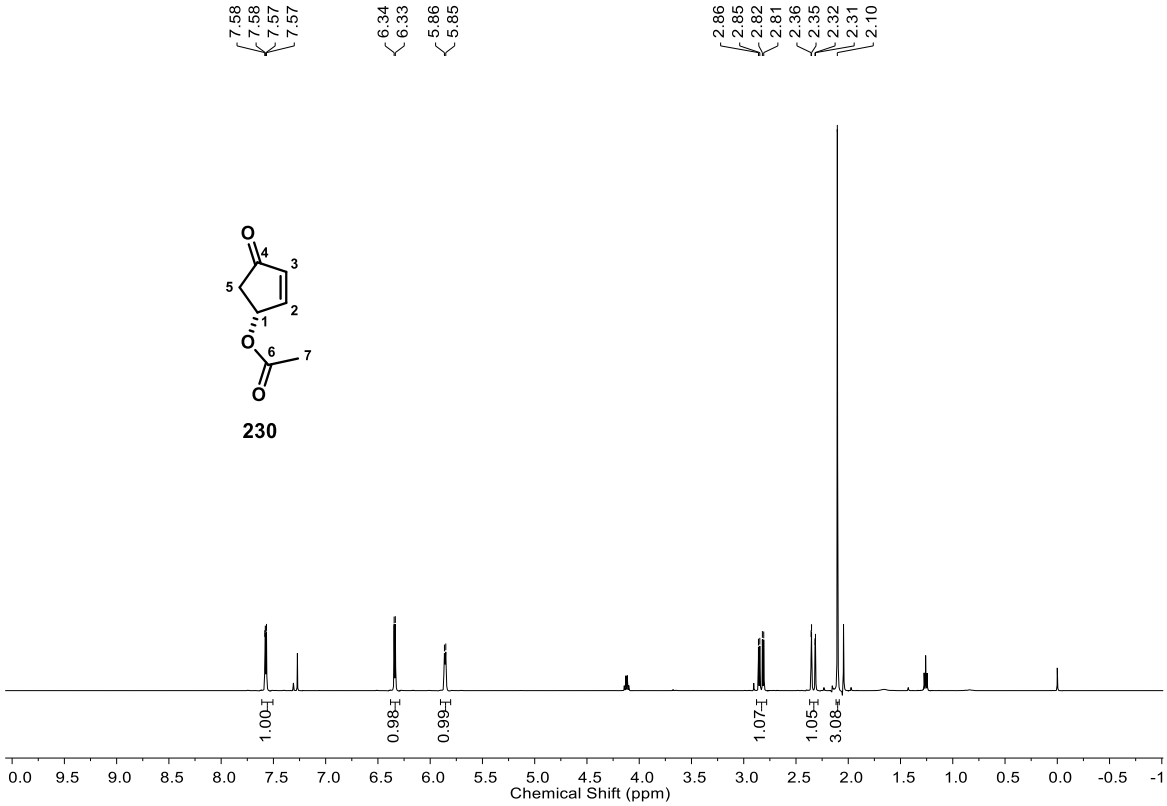


Figure 125: ^{1}H NMR (500 MHz, $CDCl_3$) of (4*R*)-4-acetoxycyclopentenone (**230**).

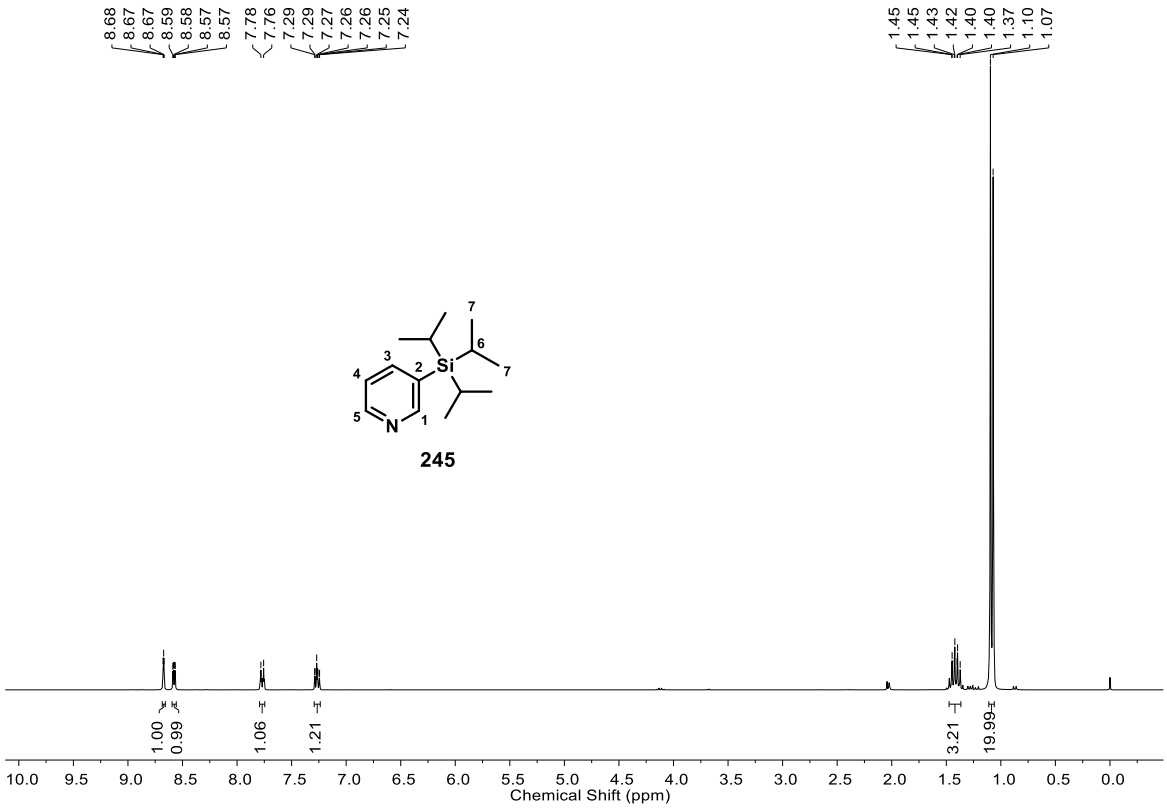


Figure 126: ^{1}H NMR (300 MHz, $CDCl_3$) of 3-(Triisopropylsilyl)pyridine (**245**).

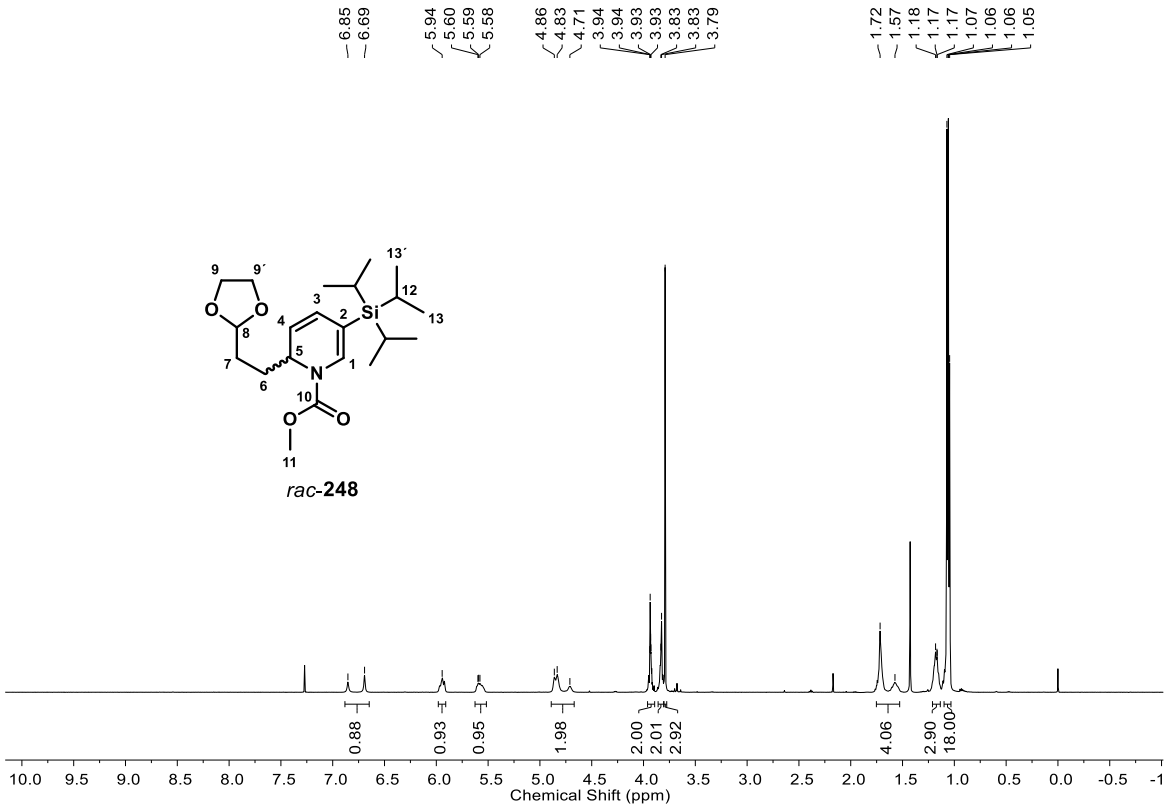


Figure 127: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-2-(2-ethyl-1,3-dioxolane)-(methoxycarbonyl)-5-(triisopropylsilyl)-1,2-dihydropyridine (*rac*-**248**).

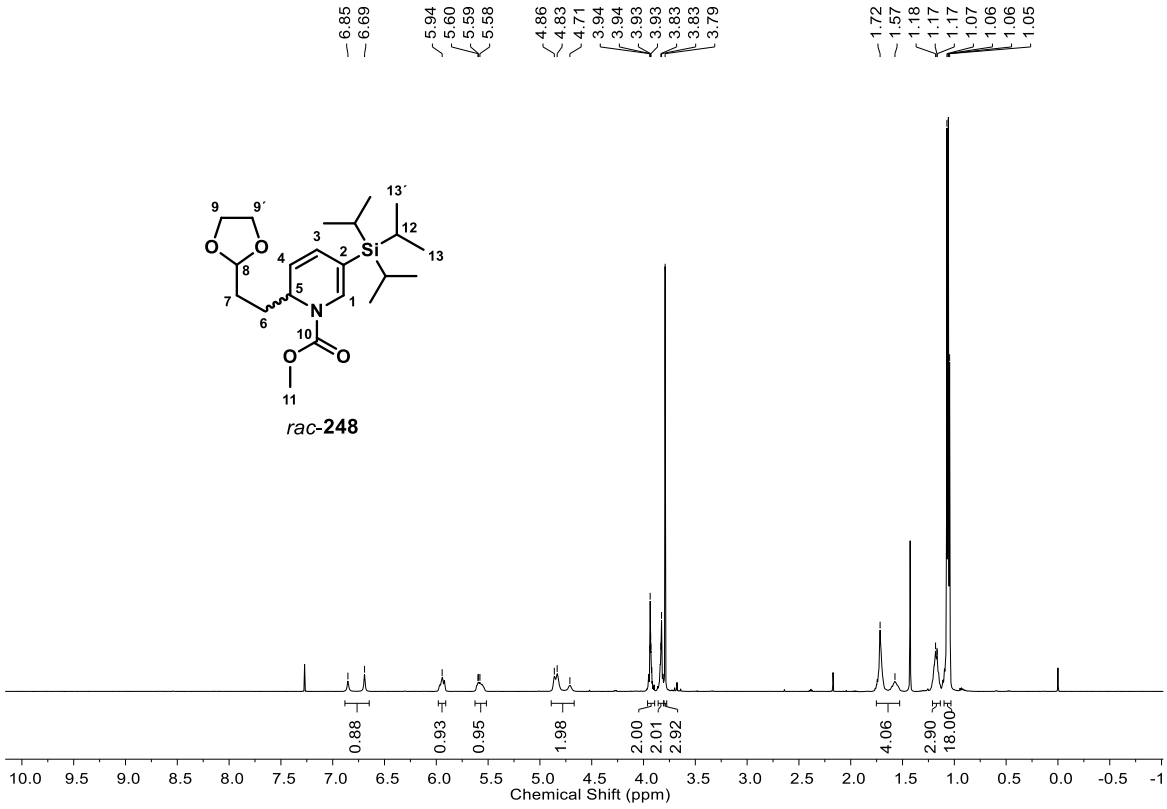


Figure 128: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-2-(2-ethyl-1,3-dioxolane)-(methoxycarbonyl)-5-(triisopropylsilyl)-1,2-dihydropyridine (*rac*-**248**).

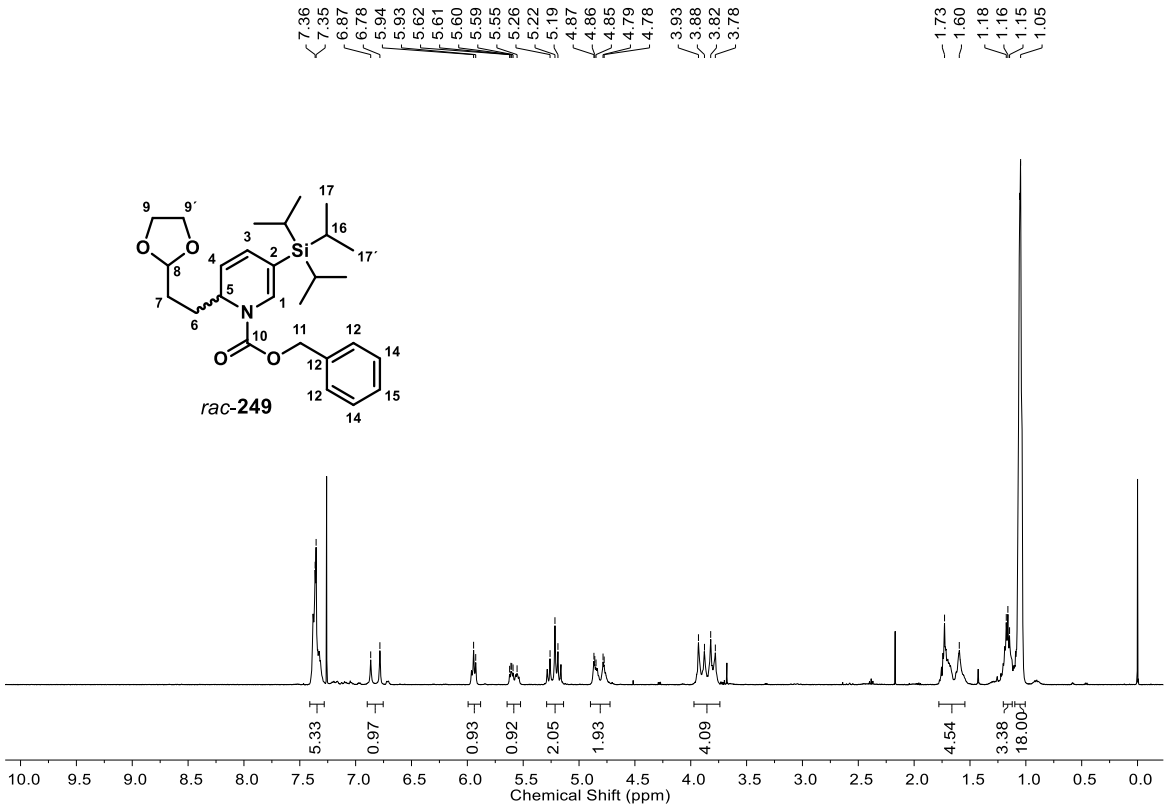


Figure 129: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-2-(2-ethyl-1,3-dioxolane)-(benzyloxycarbonyl)-5-(triisopropylsilyl)-1,2-dihydropyridine (*rac*-**249**).

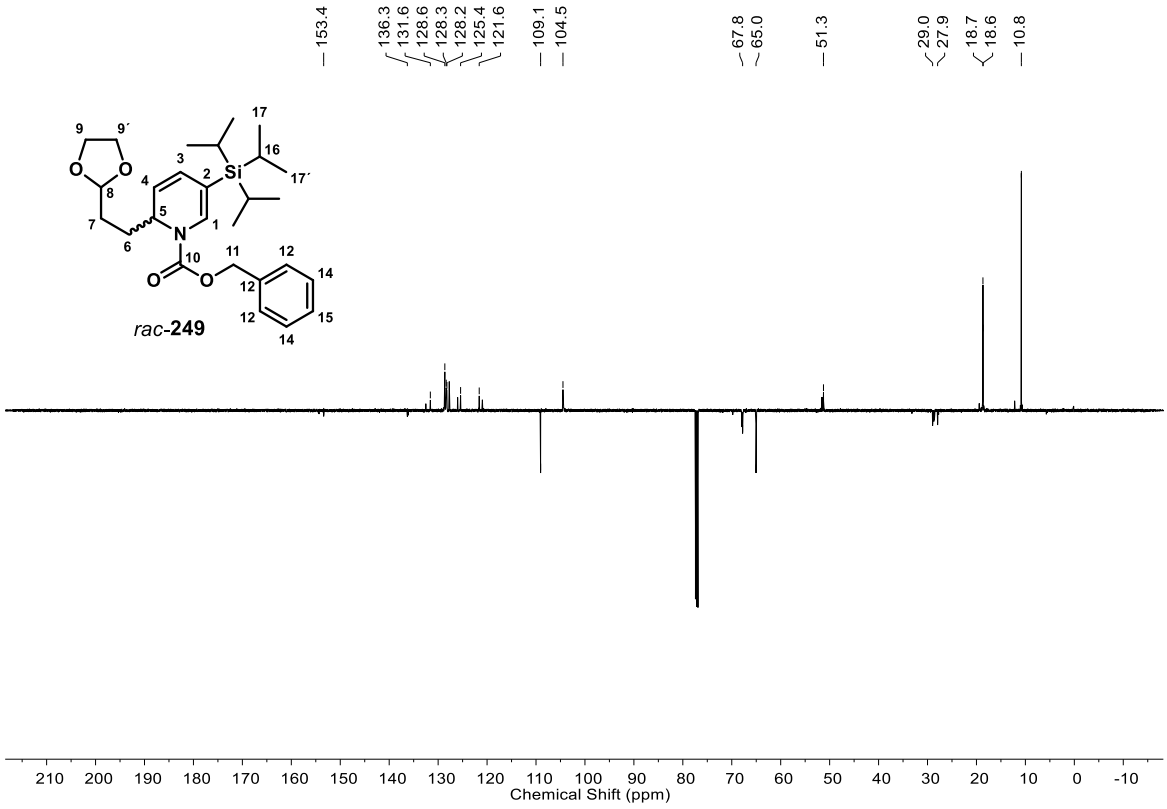


Figure 130: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-2-(2-ethyl-1,3-dioxolane)-(benzyloxycarbonyl)-5-(triisopropylsilyl)-1,2-dihydropyridine (*rac*-**249**).

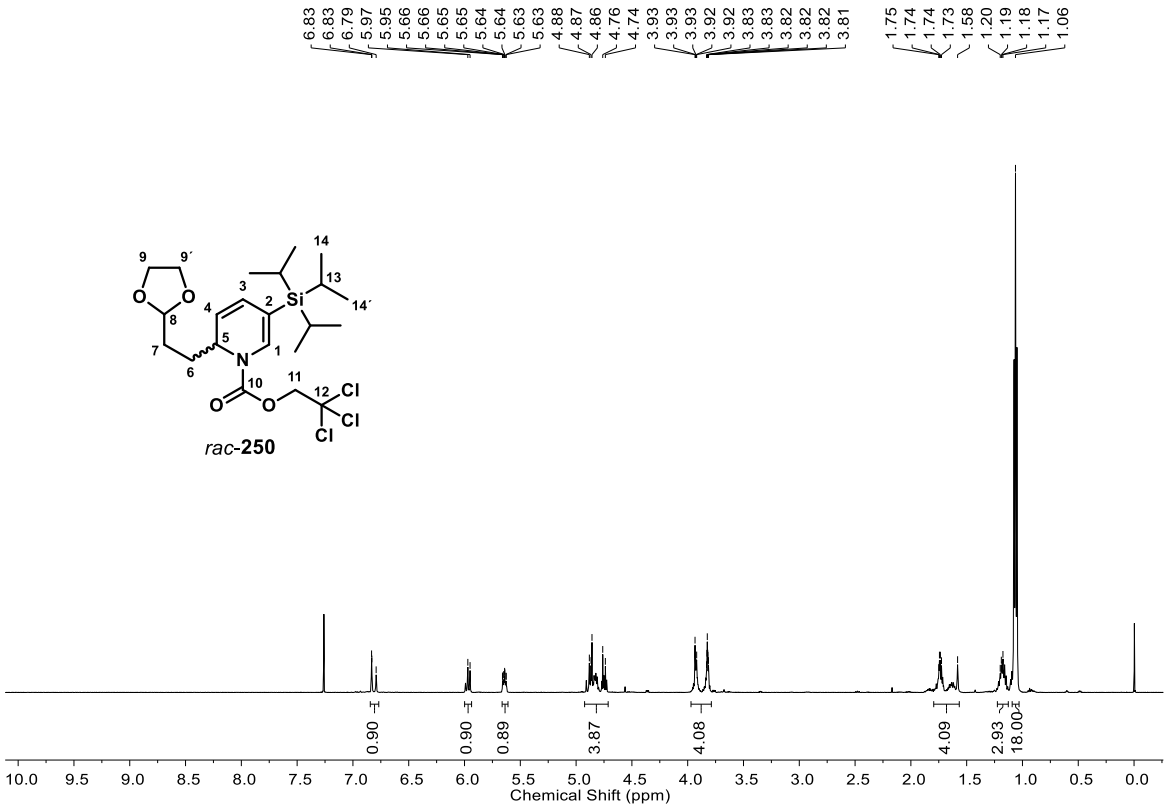


Figure 131: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-2-(2-ethyl-1,3-dioxolane)-(2,2,2-trichloroethoxycarbonyl)-5-(triisopropylsilyl)-1,2-dihydropyridine (*rac*-**250**).

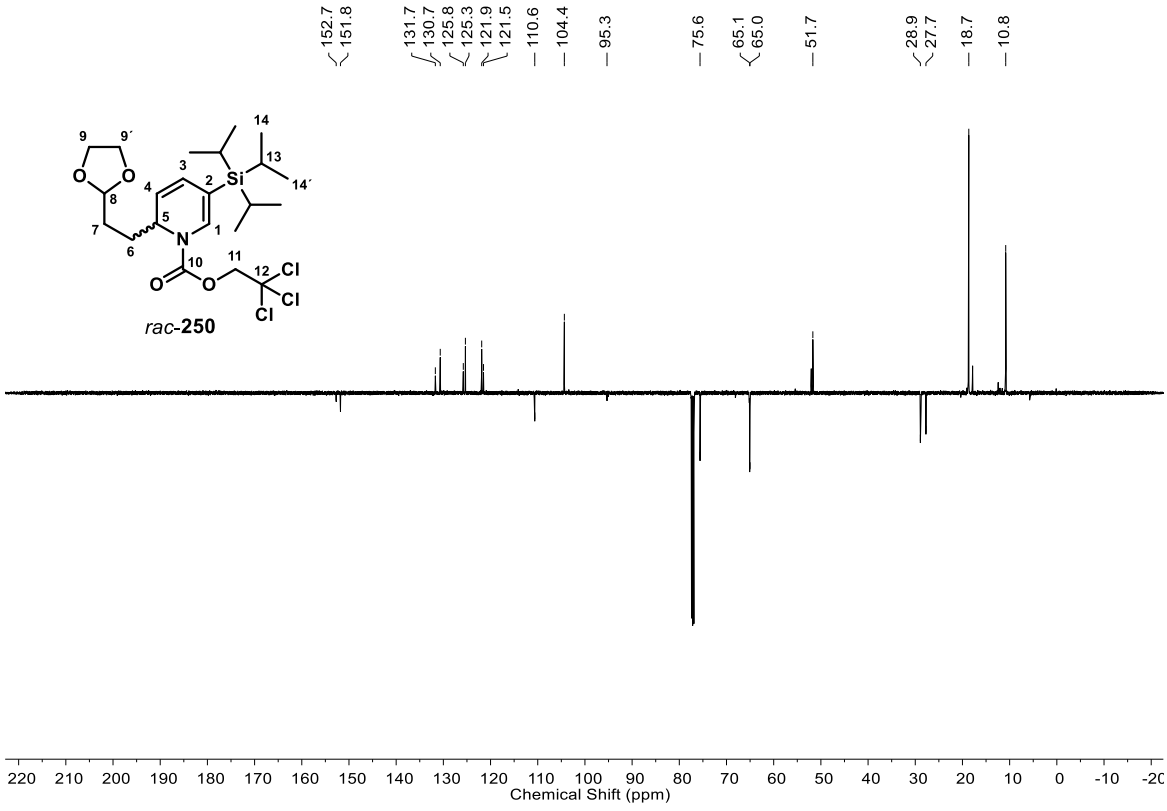


Figure 132: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-2-(2-ethyl-1,3-dioxolane)-(2,2,2-trichloroethoxycarbonyl)-5-(triisopropylsilyl)-1,2-dihydropyridine (*rac*-**250**).

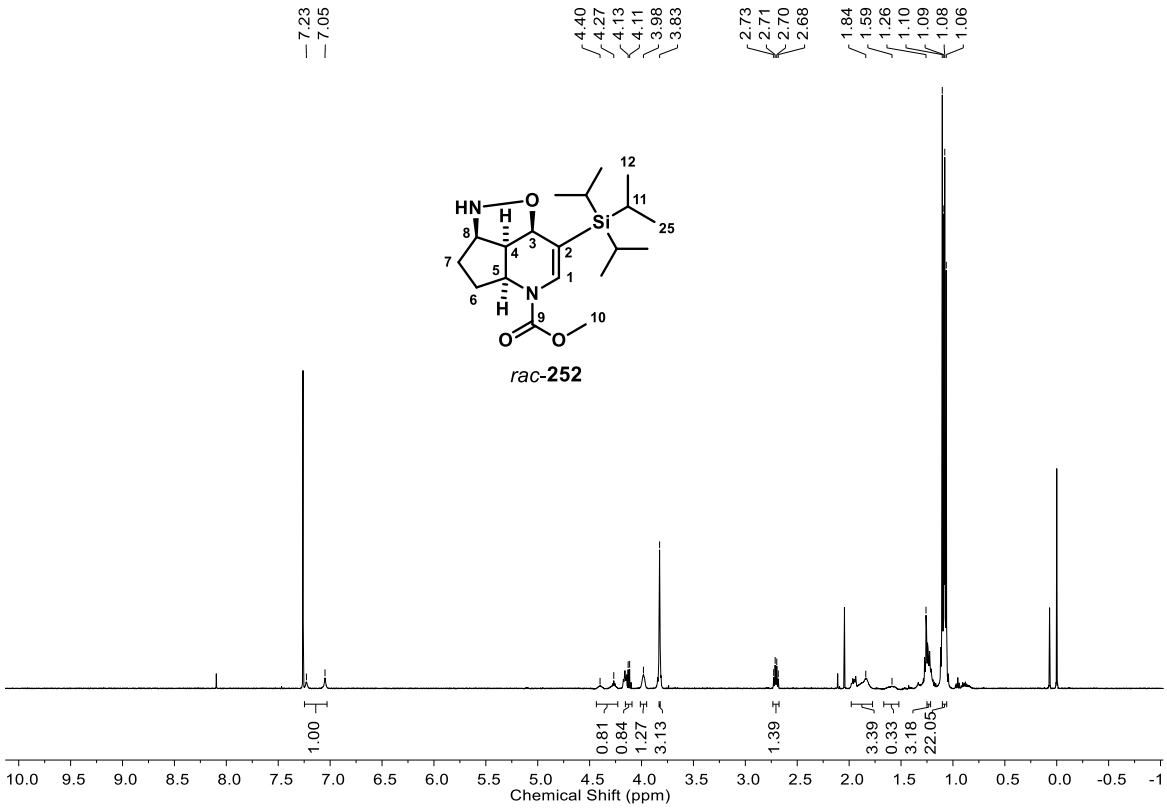


Figure 133: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-methyl 5-(triisopropylsilyl)-1,2a,2a1,3,4a,7a-hexahydro-4-oxa-3,7-diazacyclopenta-[*cd*]indene-7,3-carboxylate (*rac*-**252**).

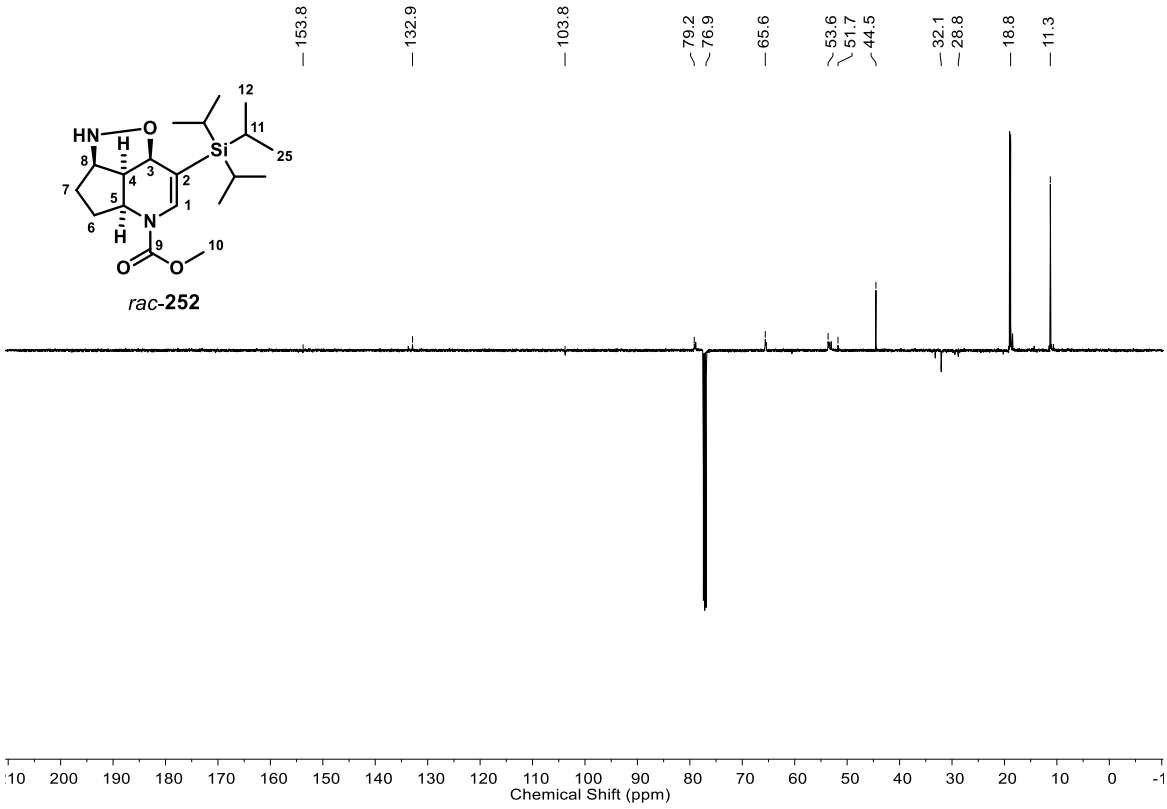


Figure 134: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-methyl 5-(triisopropylsilyl)-1,2a,2a1,3,4a,7a-hexahydro-4-oxa-3,7-diazacyclopenta-[*cd*]indene-7,3-carboxylate (*rac*-**252**).

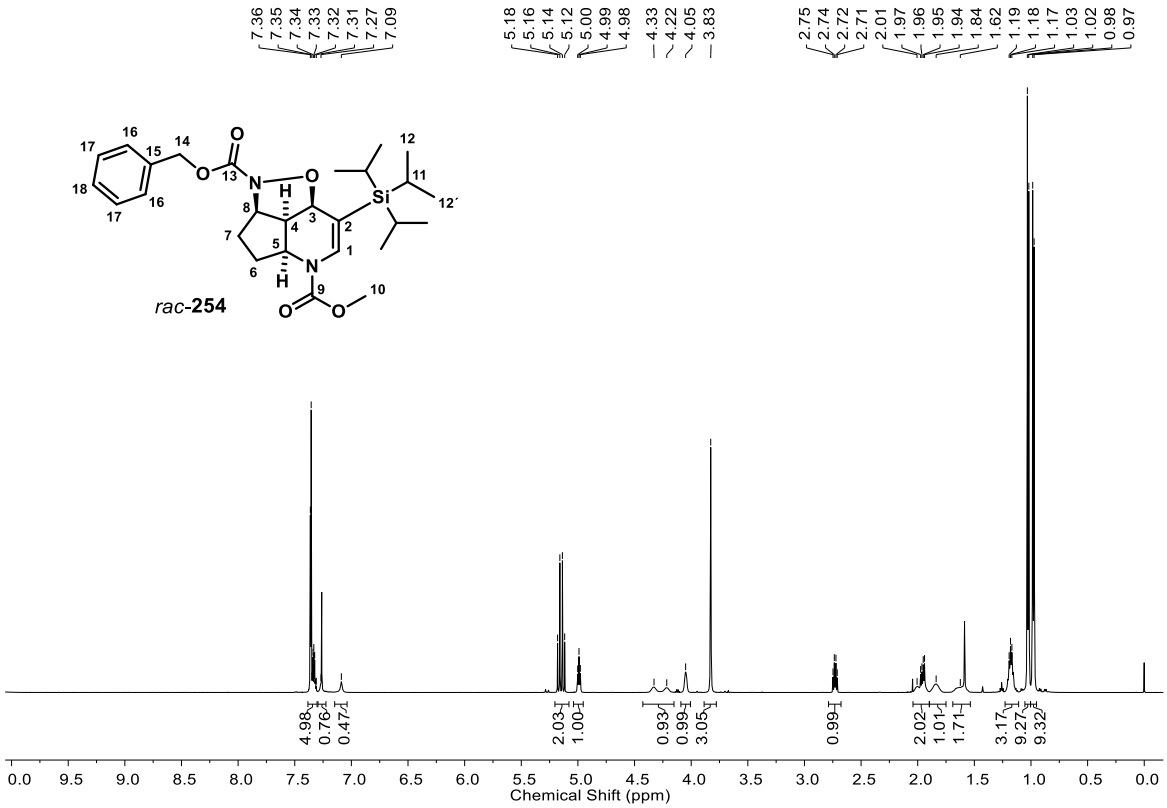


Figure 135: ^{1}H NMR (600 MHz, $CDCl_3$) of *rac*-3-benzyl 7-methyl 5-(triisopropylsilyl)-1,2a,2a1,3,4a,7a-hexahydro-4-oxa-3,7-diazacyclopenta[*cd*]indene-7,3-dicarboxylate (*rac*-**254**).

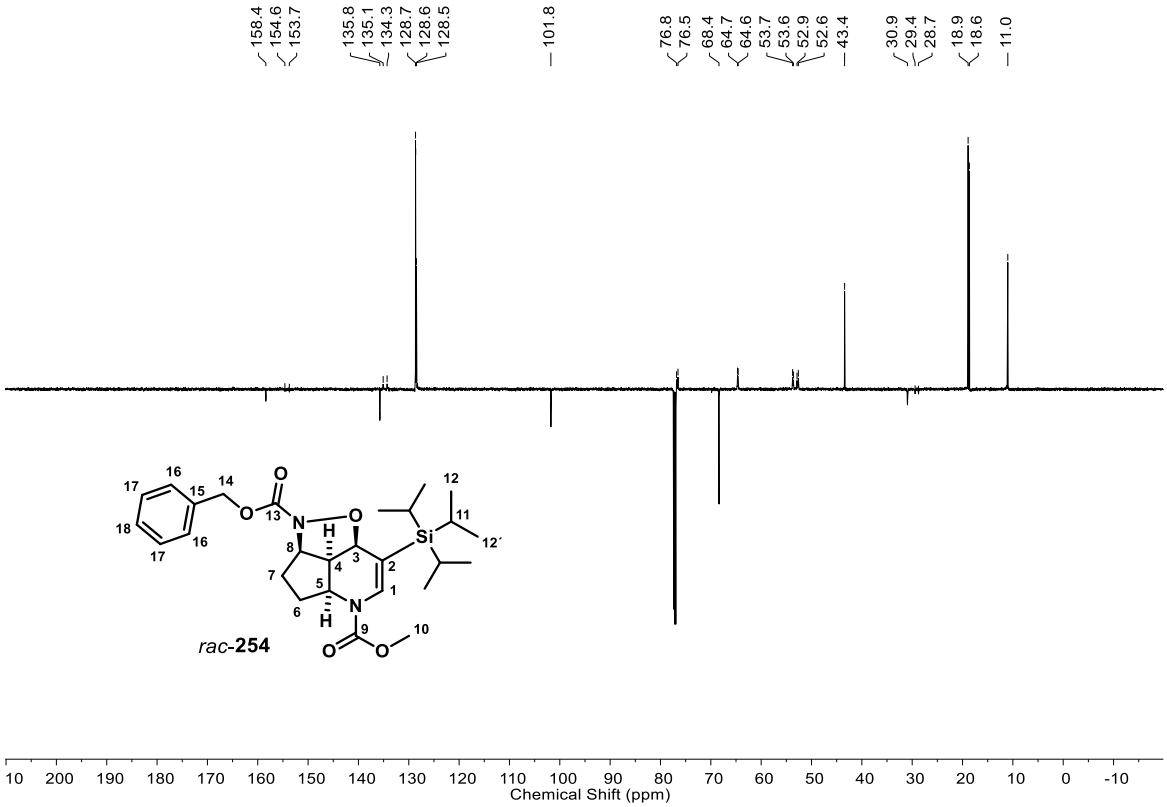


Figure 136: ^{13}C NMR (151 MHz, $CDCl_3$) of *rac*-3-benzyl 7-methyl 5-(triisopropylsilyl)-1,2a,2a1,3,4a,7a-hexahydro-4-oxa-3,7-diazacyclopenta[*cd*]indene-7,3-dicarboxylate (*rac*-**254**).

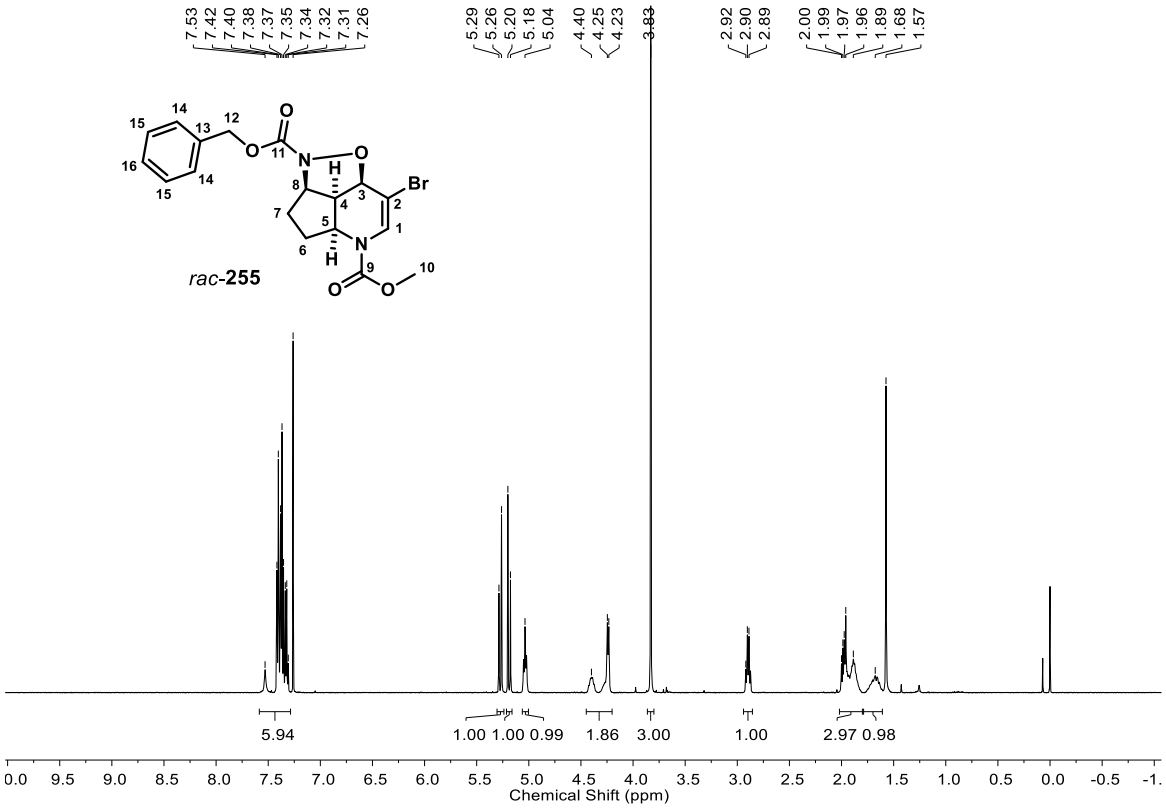


Figure 137: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-3-benzyl 7-methyl (2a*R*,2a1*S*,4a*R*,7a*S*)-5-bromo-1,2a,2a1,3,4a,7a-hexahydro-4-oxa-3,7-diazacyclopenta-[*cd*]indene-3,7-dicarboxylate (*rac*-**255**).

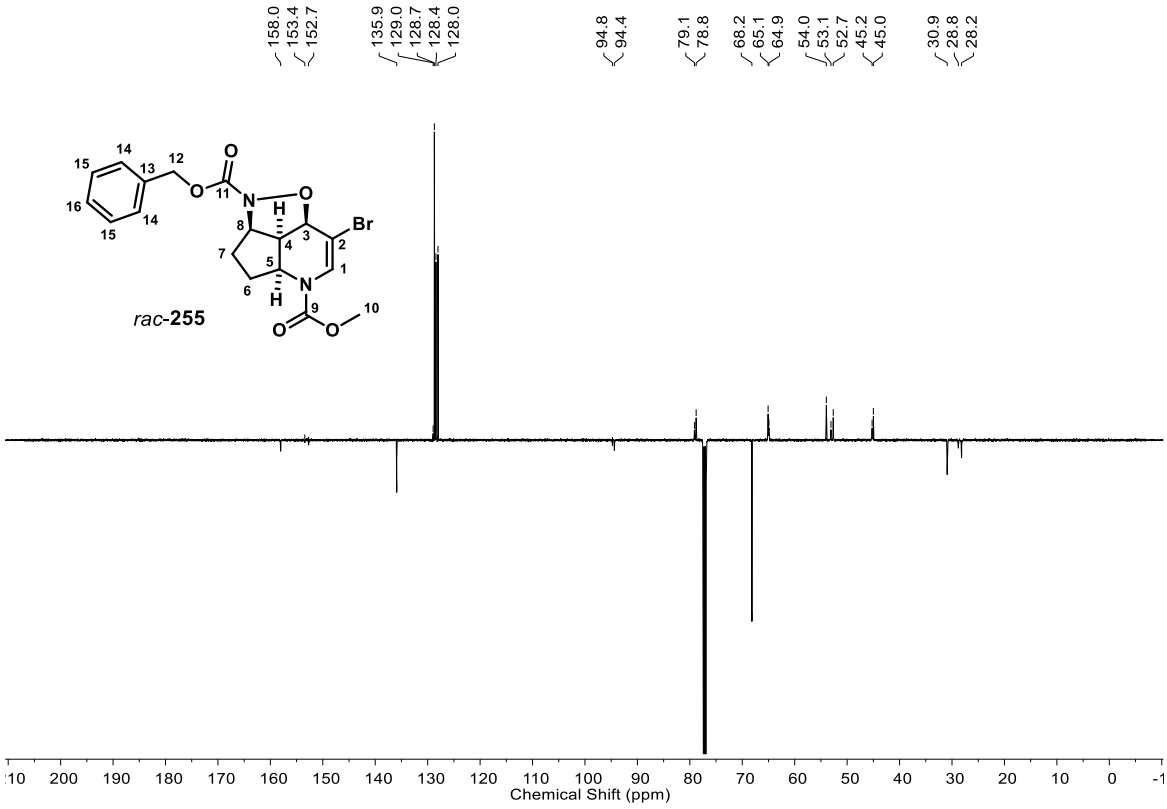


Figure 138: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-3-benzyl 7-methyl (2a*R*,2a1*S*,4a*R*,7a*S*)-5-bromo-1,2a,2a1,3,4a,7a-hexahydro-4-oxa-3,7-diazacyclopenta-[*cd*]indene-3,7-dicarboxylate (*rac*-**255**).

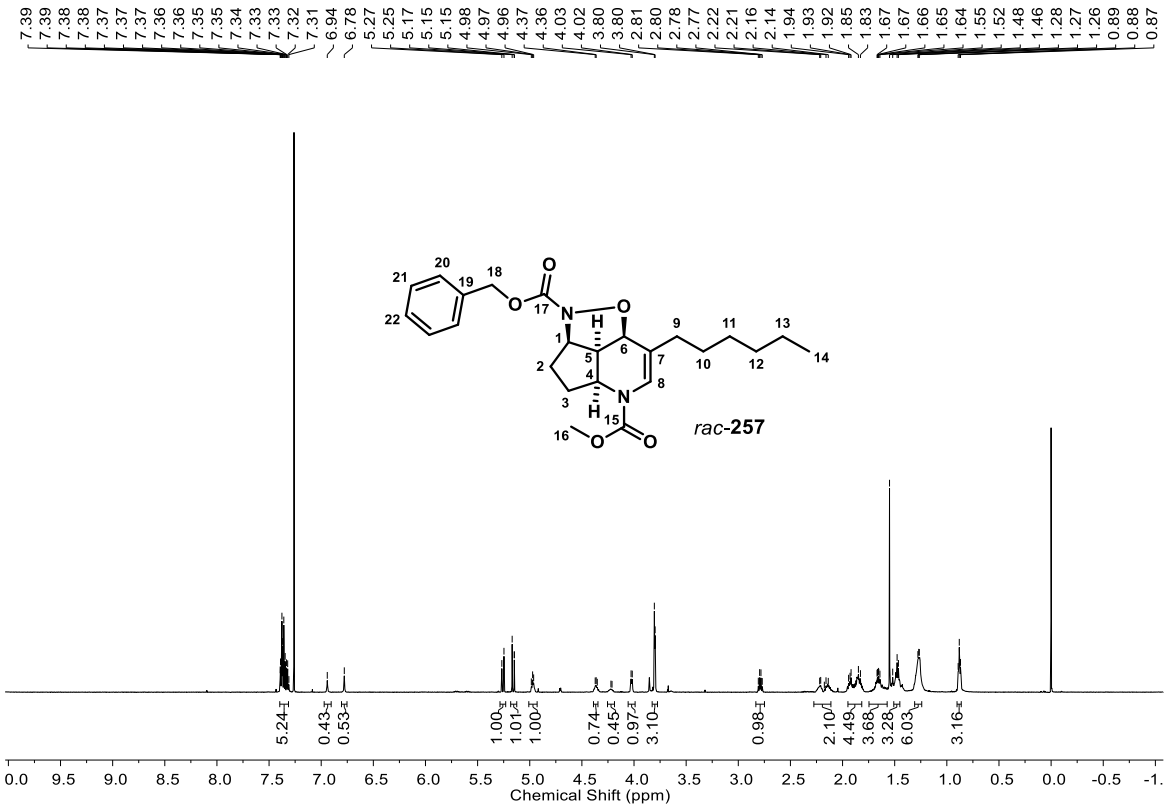


Figure 139: ^{1}H NMR (600 MHz, $CDCl_3$) of *rac*-3-benzyl 7-methyl (2a*R*,2a1*S*,4a*R*,7a*S*)-5-hexyl-1,2a,2a1,-3,4a,7a-hexahydro-4-oxa-3,7-diazacyclopenta-[*cd*]indene-3,7-dicarboxylate (*rac*-**257**).

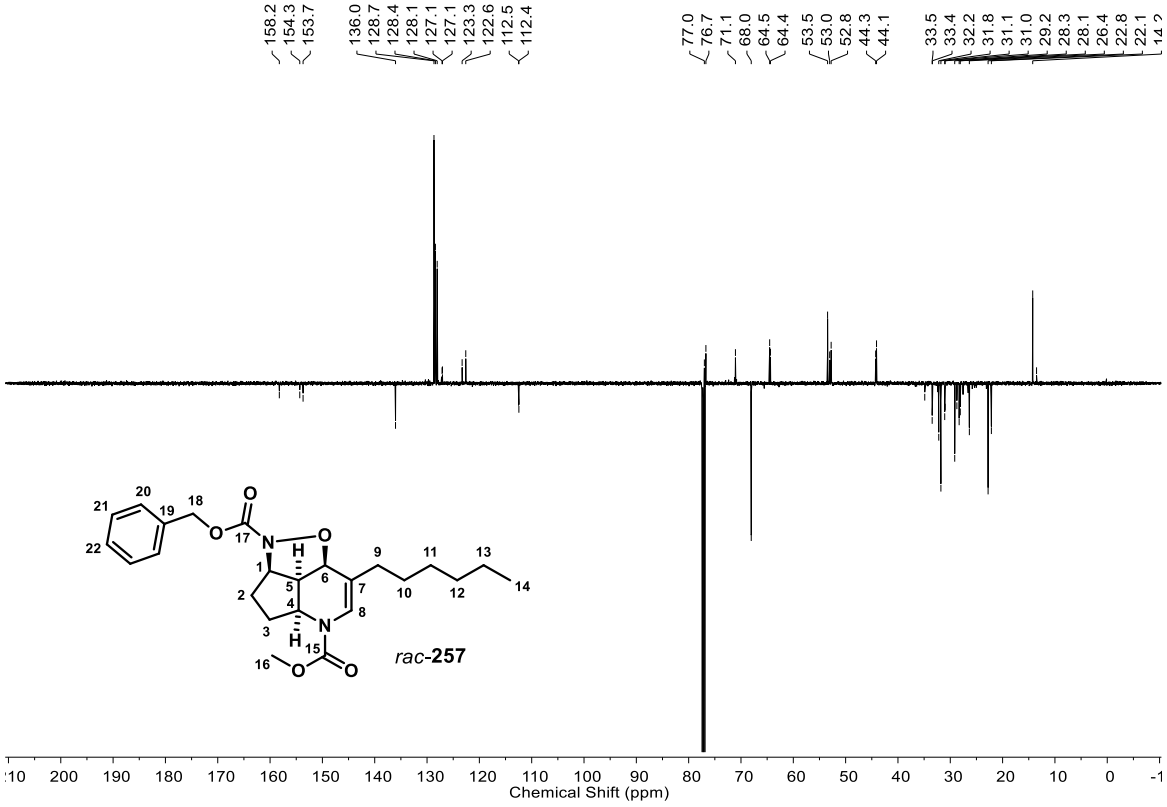


Figure 140: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-3-benzyl 7-methyl (2a*R*,2a1*S*,4a*R*,7a*S*)-5-hexyl-1,2a,2a1,-3,4a,7a-hexahydro-4-oxa-3,7-diazacyclopenta-[*cd*]indene-3,7-dicarboxylate (*rac*-**257**).

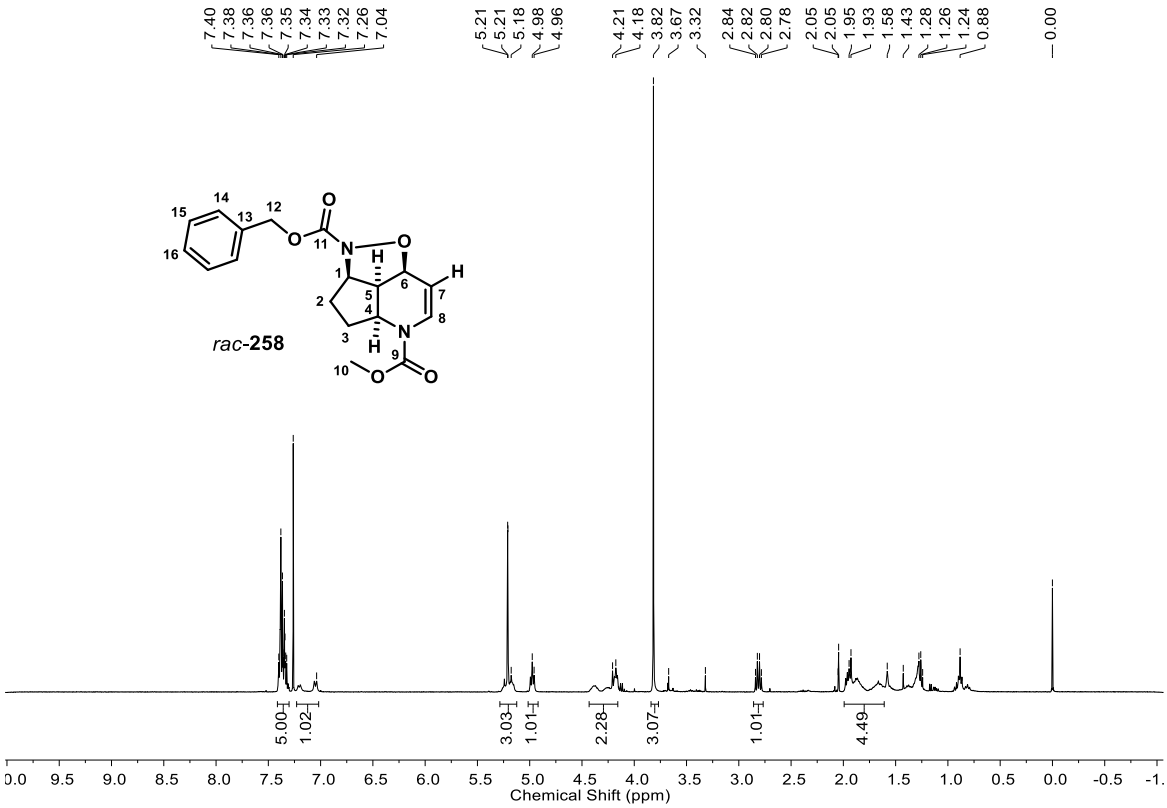


Figure 141: ^{1}H NMR (400 MHz, $CDCl_3$) of compound *rac*-**258**.

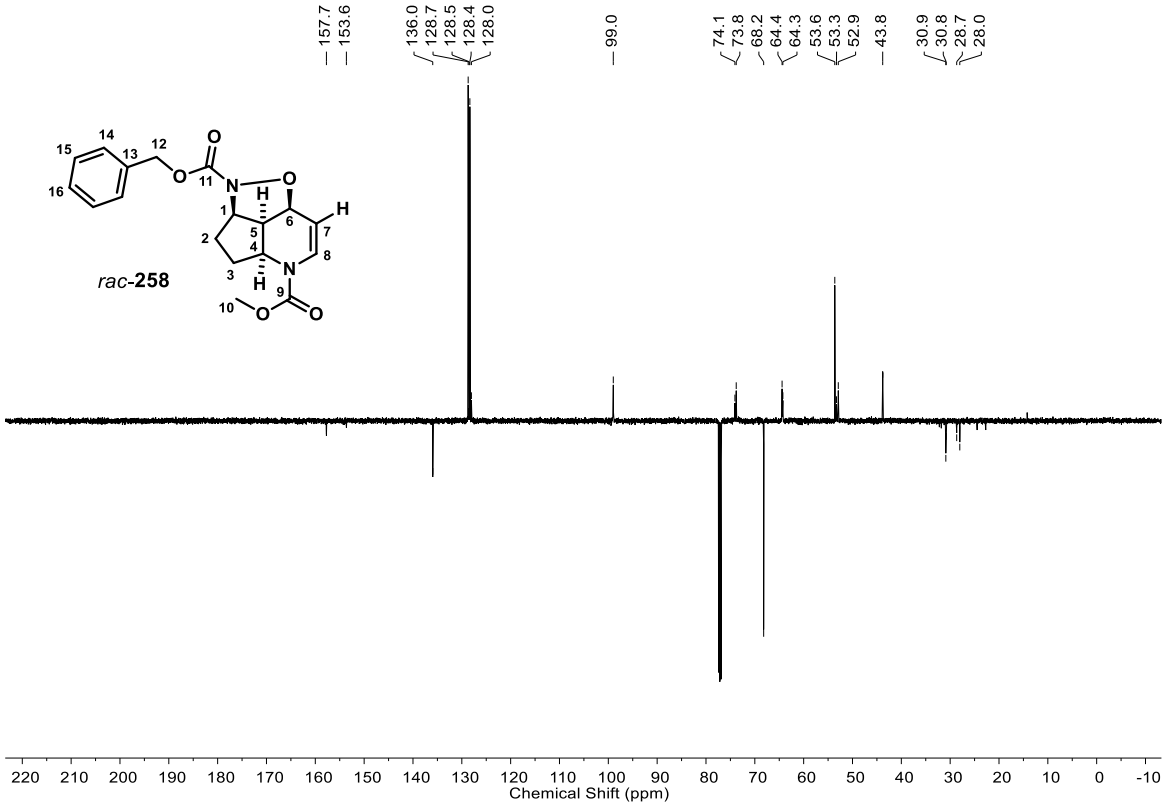


Figure 142: ^{13}C NMR (126 MHz, $CDCl_3$) of compound *rac*-**258**.

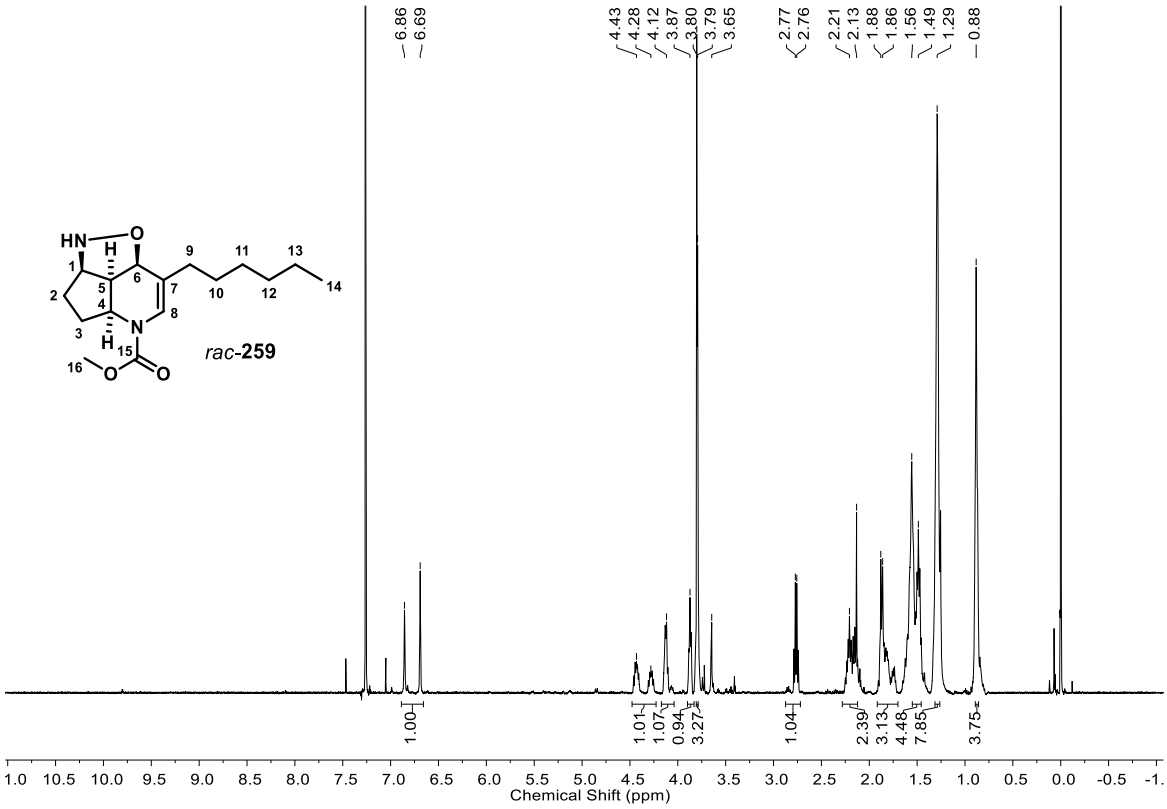


Figure 143: ^{1}H NMR (500 MHz, $CDCl_3$) of *rac*-7-methyl (2a*R*,2a1*S*,4a*R*,7a*S*)-5-*n*hexyl-1,2a,2a1,3,4a,7a-hexahydro-4-oxa-3,7-diazacyclopenta[*cd*]indene-7-carboxylate (*rac*-**259**).

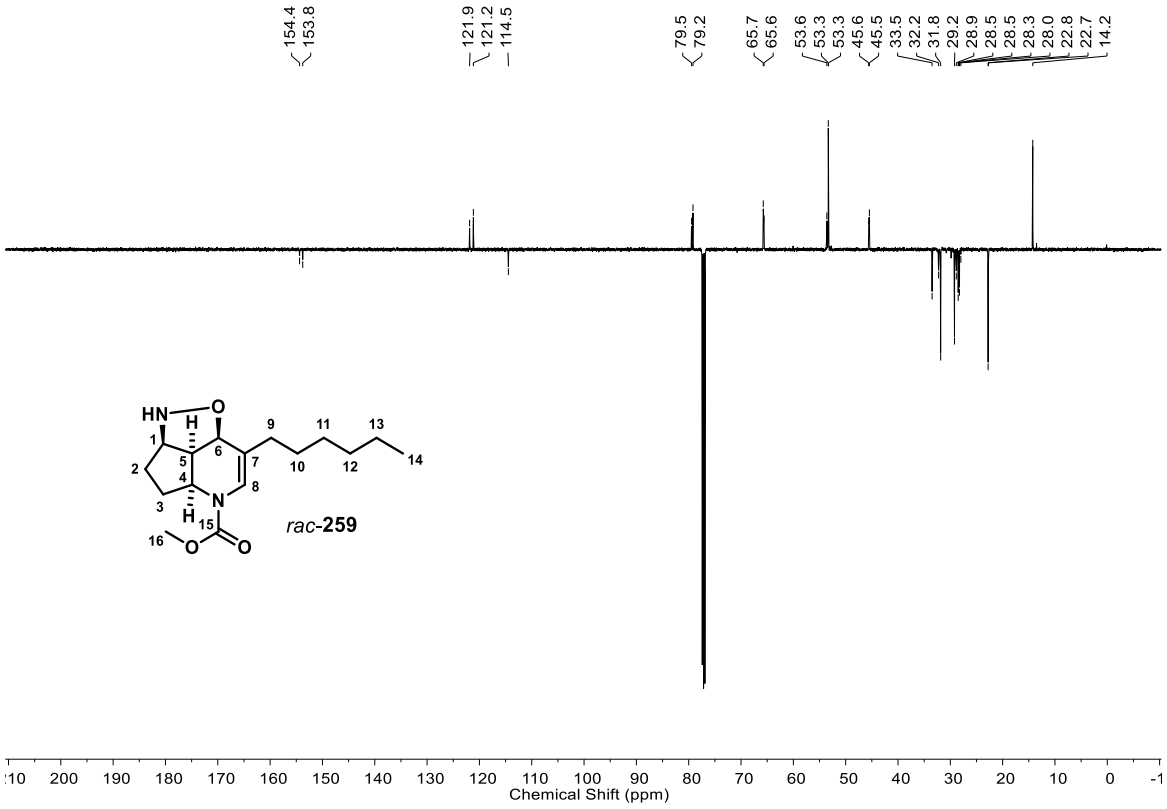


Figure 144: ^{13}C NMR (126 MHz, $CDCl_3$) of *rac*-7-methyl (2a*R*,2a1*S*,4a*R*,7a*S*)-5-*n*hexyl-1,2a,2a1,3,4a,7a-hexahydro-4-oxa-3,7-diazacyclopenta[*cd*]indene-7-carboxylate (*rac*-**259**).

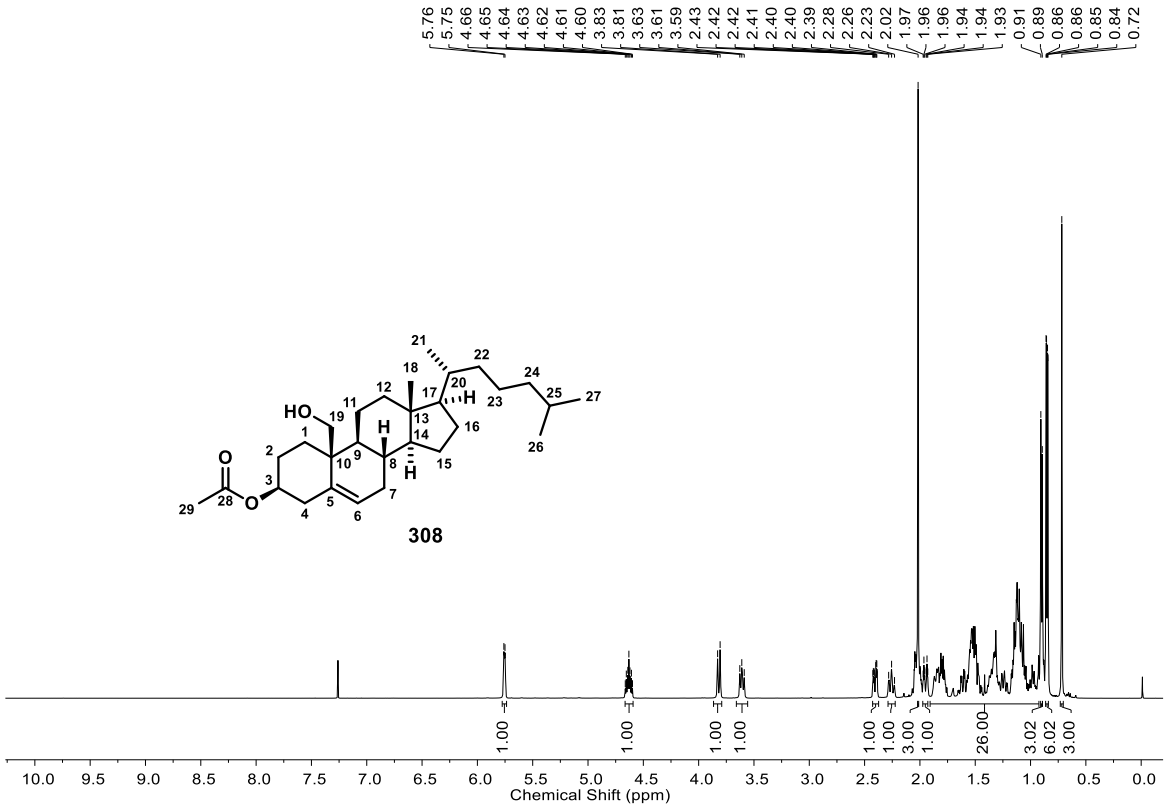


Figure 145: ^{1}H NMR (500 MHz, $CDCl_3$) of 3β-acetoxy-cholest-Δ^5-en-19β-ol (**308**).

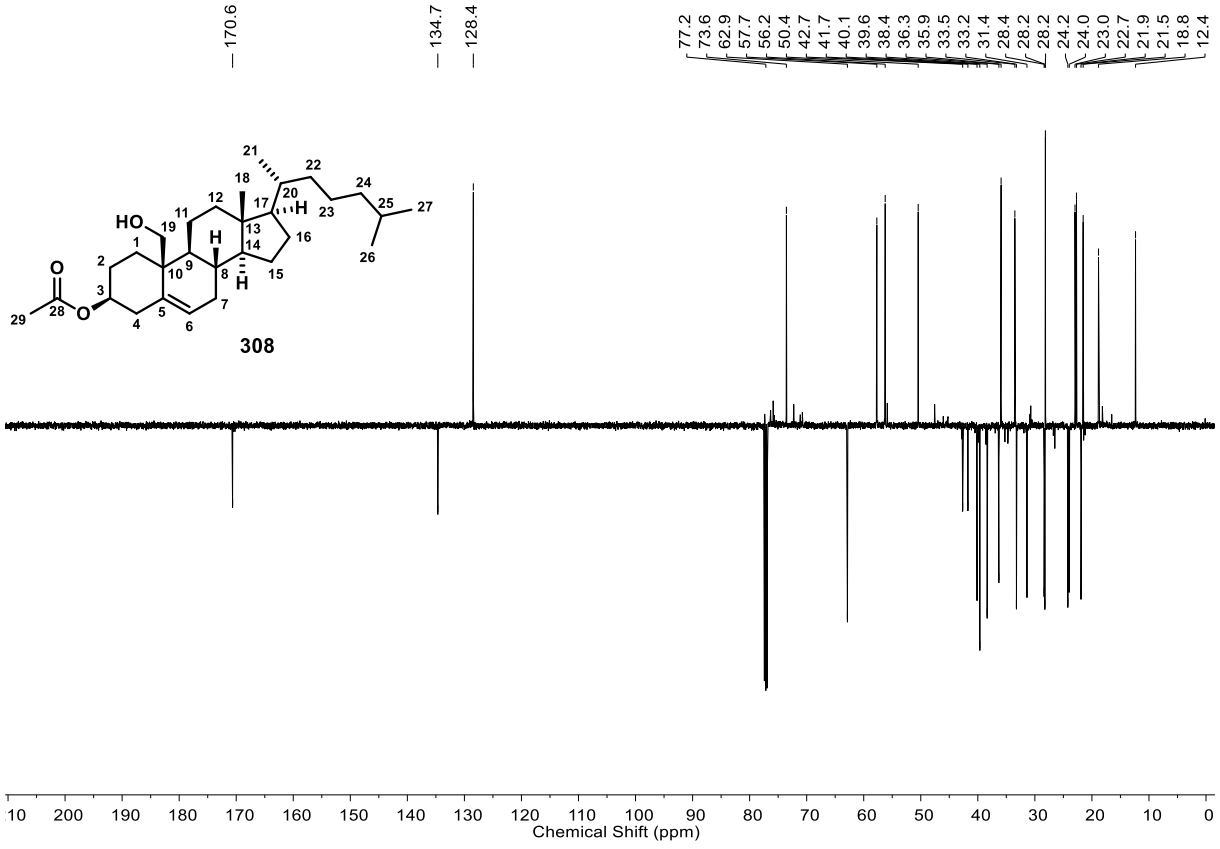


Figure 146: ^{13}C NMR (126 MHz, $CDCl_3$) of 3β-acetoxy-cholest-Δ^5-en-19β-ol (**308**).

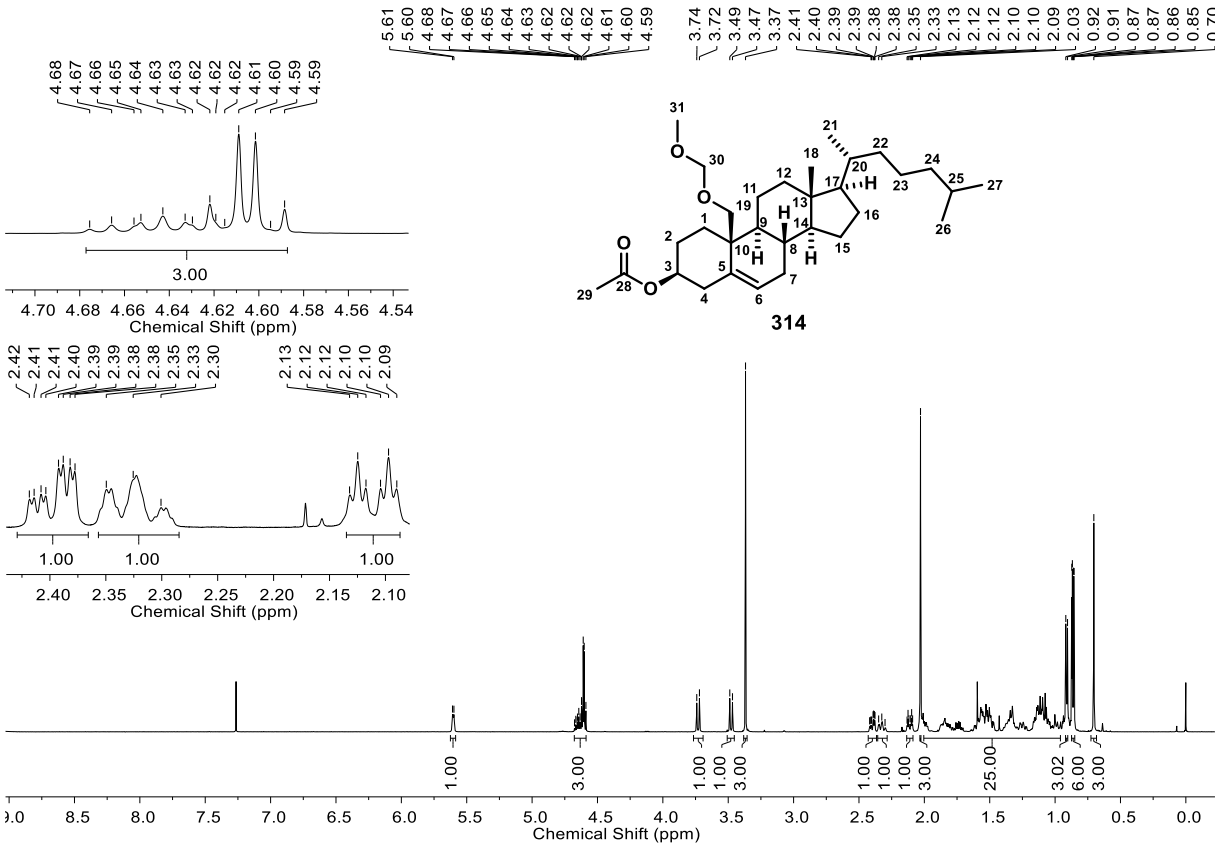


Figure 147: ^{1}H NMR (500 MHz, $CDCl_3$) of 3β-acetoxy-19-(methoxymethyloxy)-cholestan-Δ^5-en (**314**).

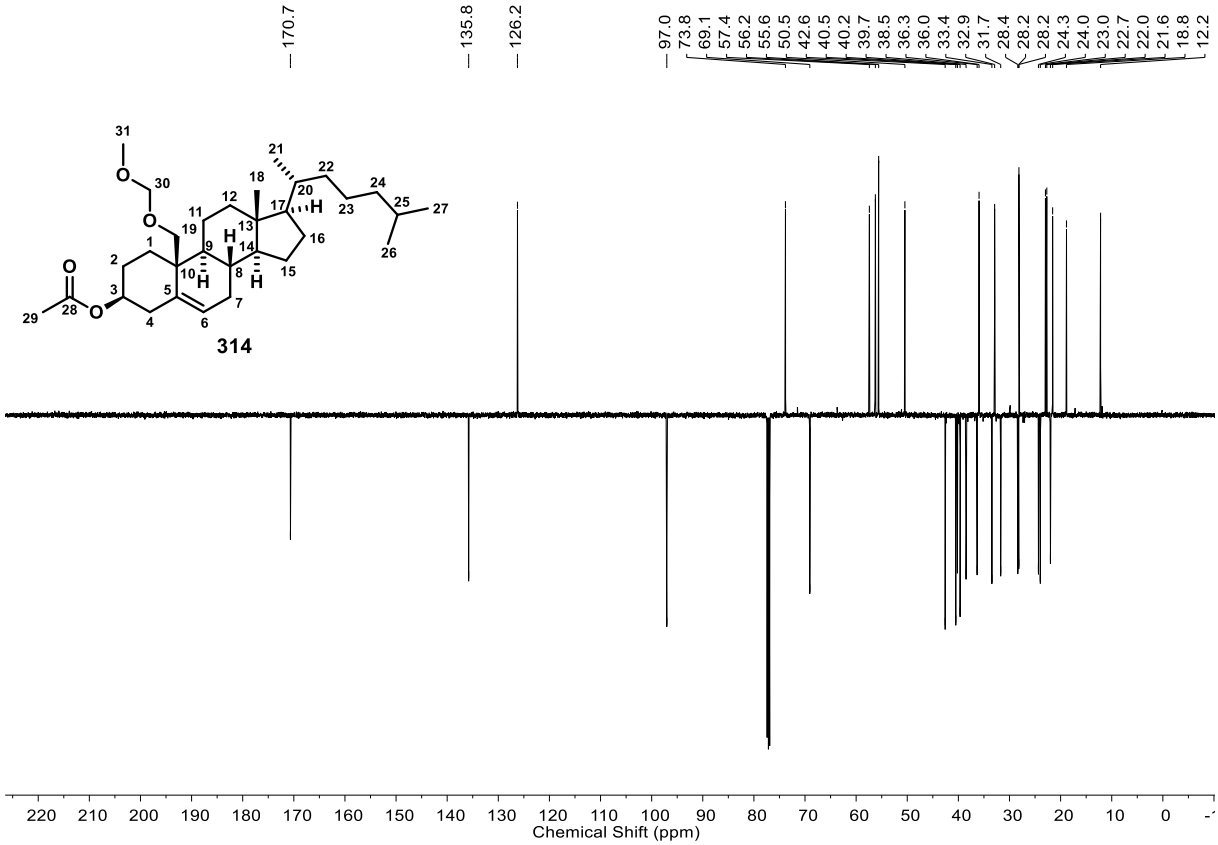


Figure 148: ^{13}C NMR (126 MHz, $CDCl_3$) of 3β-acetoxy-19-(methoxymethyloxy)-cholestan-Δ^5-en (**314**).

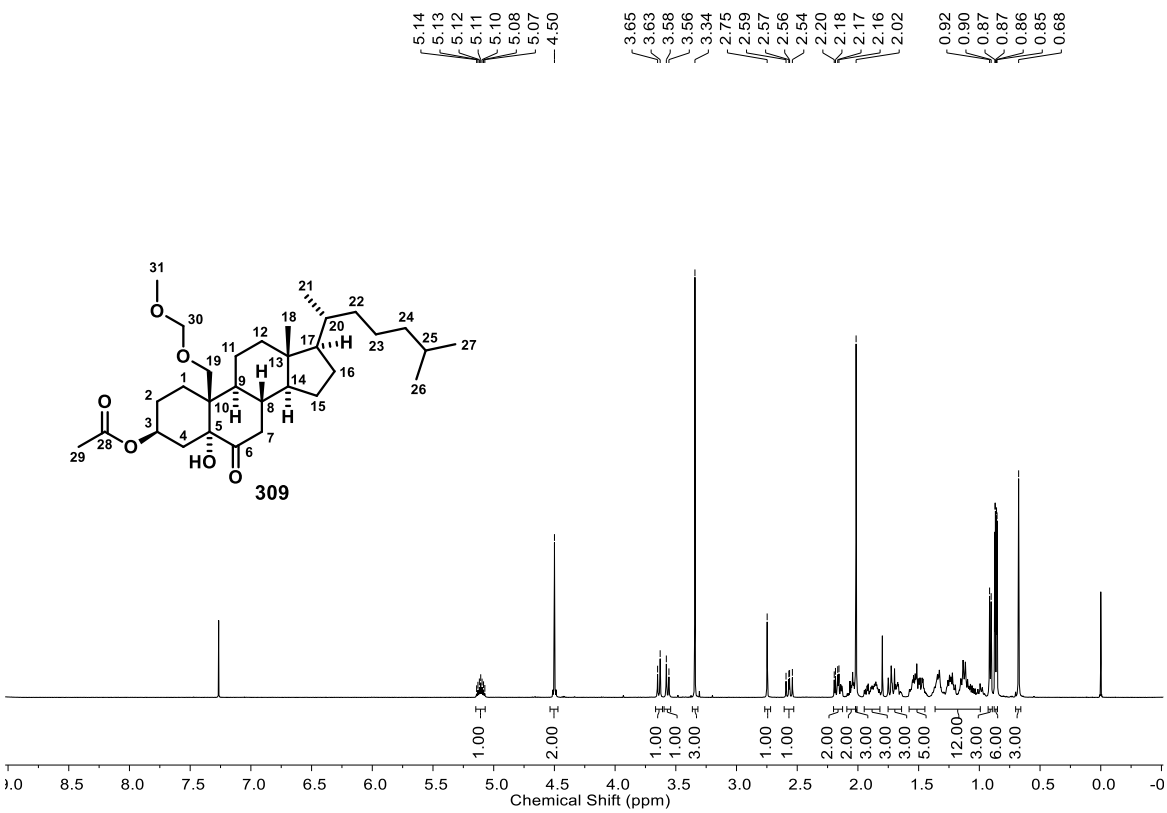


Figure 149: ^{1}H NMR (500 MHz, $CDCl_3$) of 3β-acetoxy-5α-hydroxy-19-(methoxymethyloxy)-cholestan-6-one (**309**).

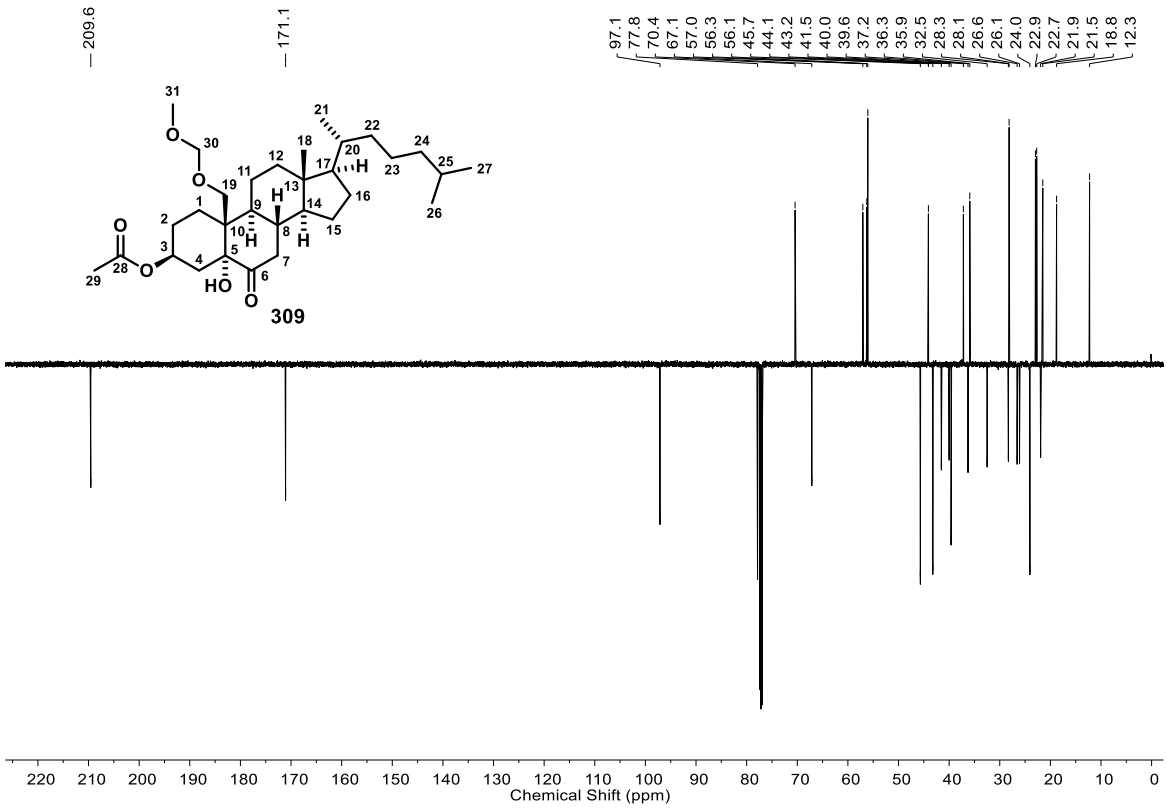


Figure 150: ^{13}C NMR (126 MHz, $CDCl_3$) of 3β-acetoxy-5α-hydroxy-19-(methoxymethyloxy)-cholestan-6-one (**309**).

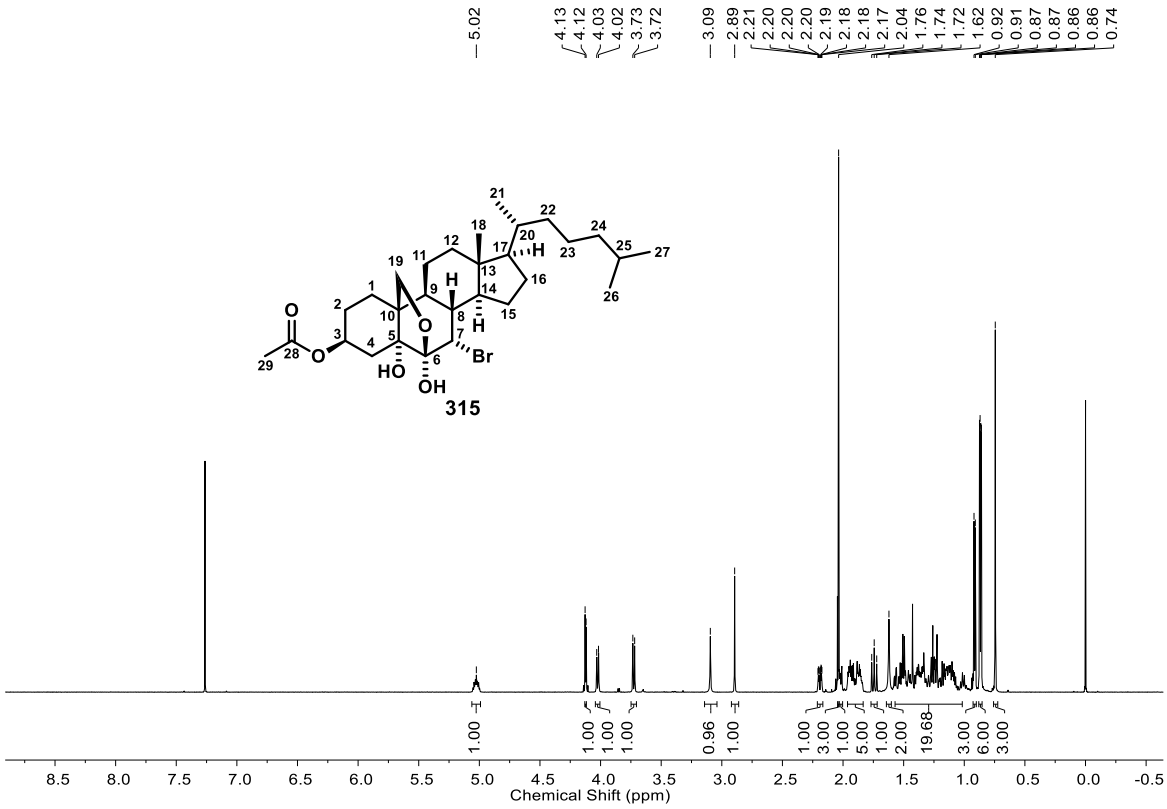


Figure 151: ^{1}H NMR (600 MHz, $CDCl_3$) of 3β-acetoxy-7α-bromo-6β,19-epoxy-cholestan- 5α,6α-diol (**315**).

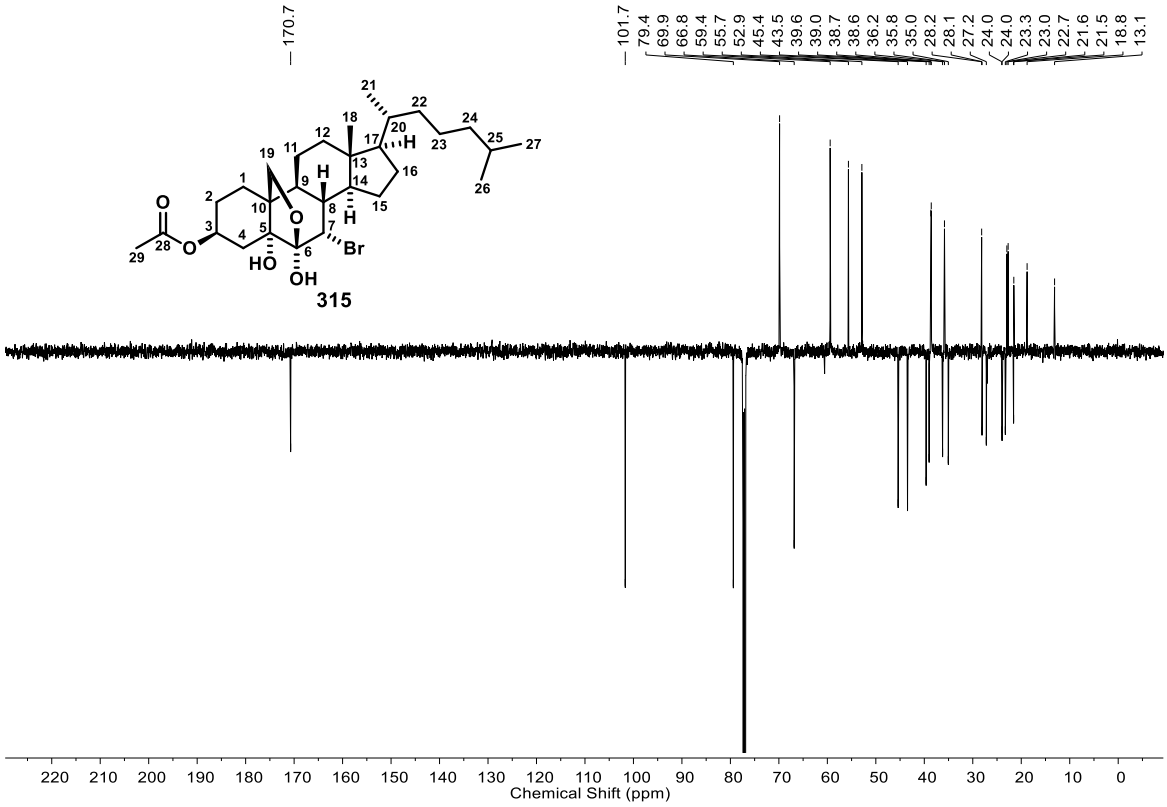


Figure 152: ^{13}C NMR (151 MHz, $CDCl_3$) of 3β-acetoxy-7α-bromo-6β,19-epoxy-cholestan- 5α,6α-diol (**315**).

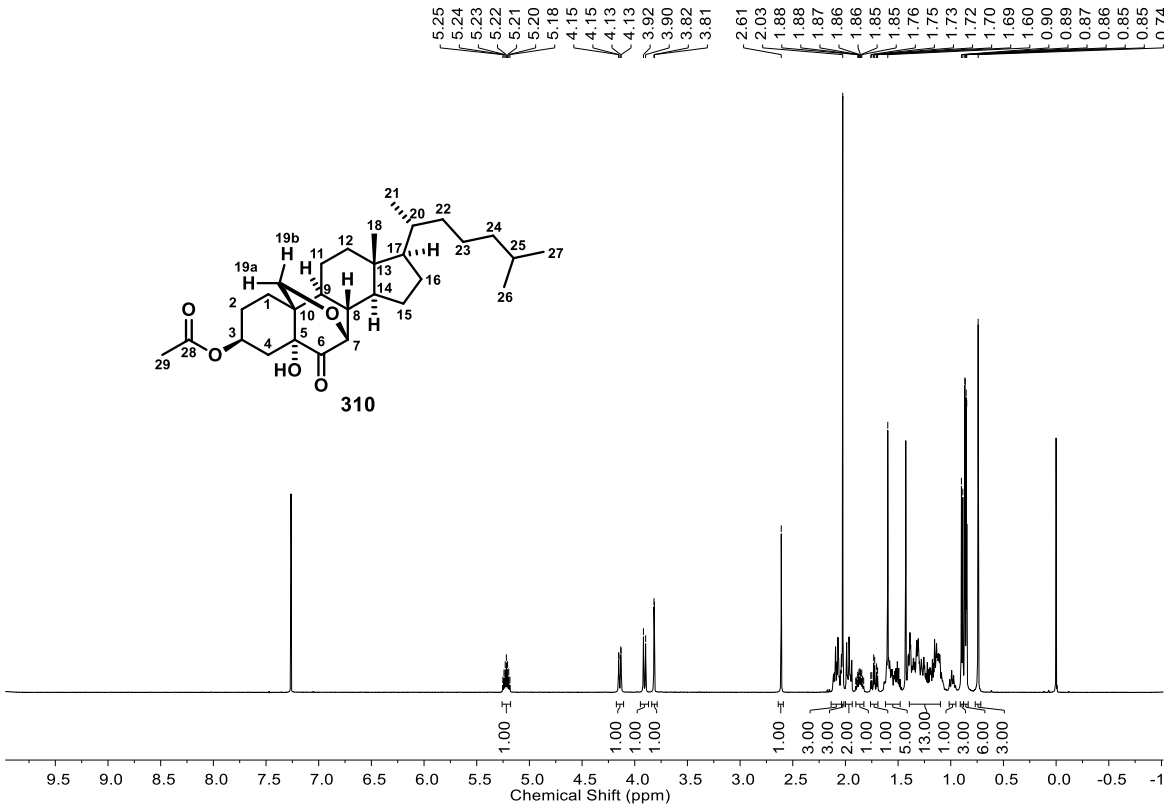


Figure 153: ^{1}H NMR (500 MHz, $CDCl_3$) of 3β-acetoxy-5α-hydroxy-7β,19-epoxy-cholestan-6-one (**310**).

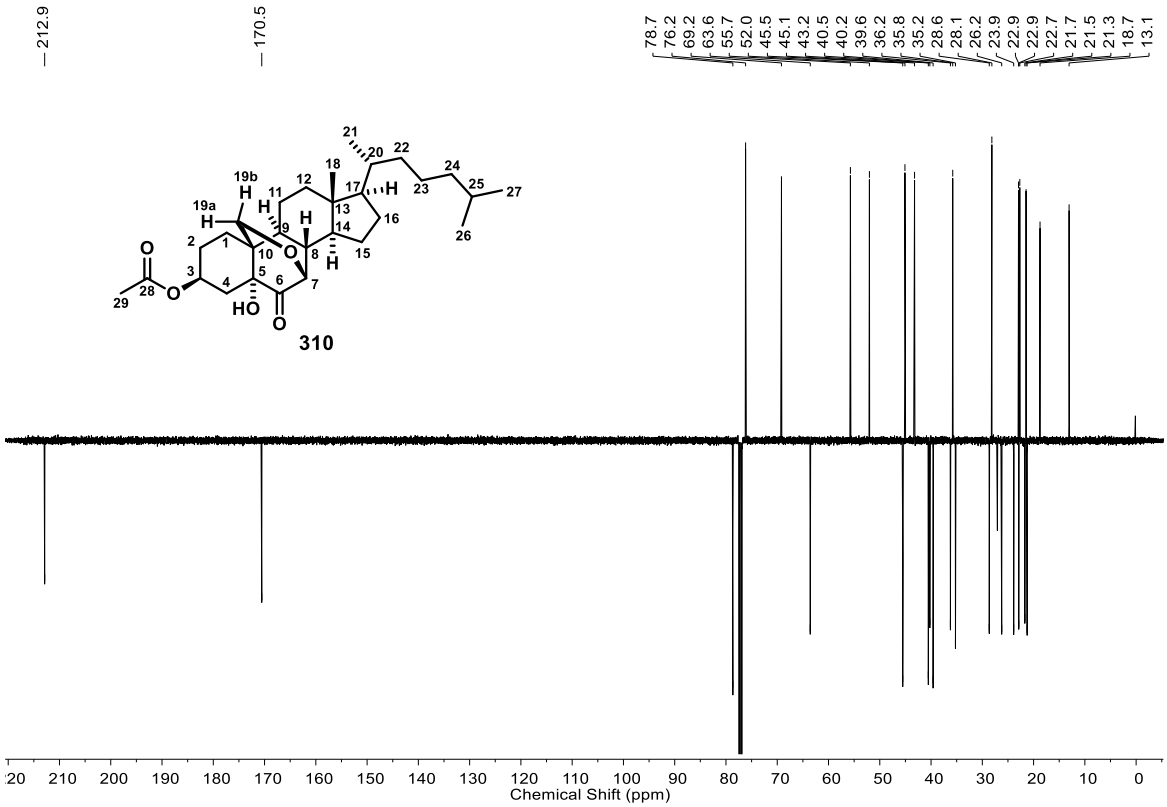


Figure 154: ^{13}C NMR (126 MHz, $CDCl_3$) of 3β-acetoxy-5α-hydroxy-7β,19-epoxy-cholestan-6-one (**310**).

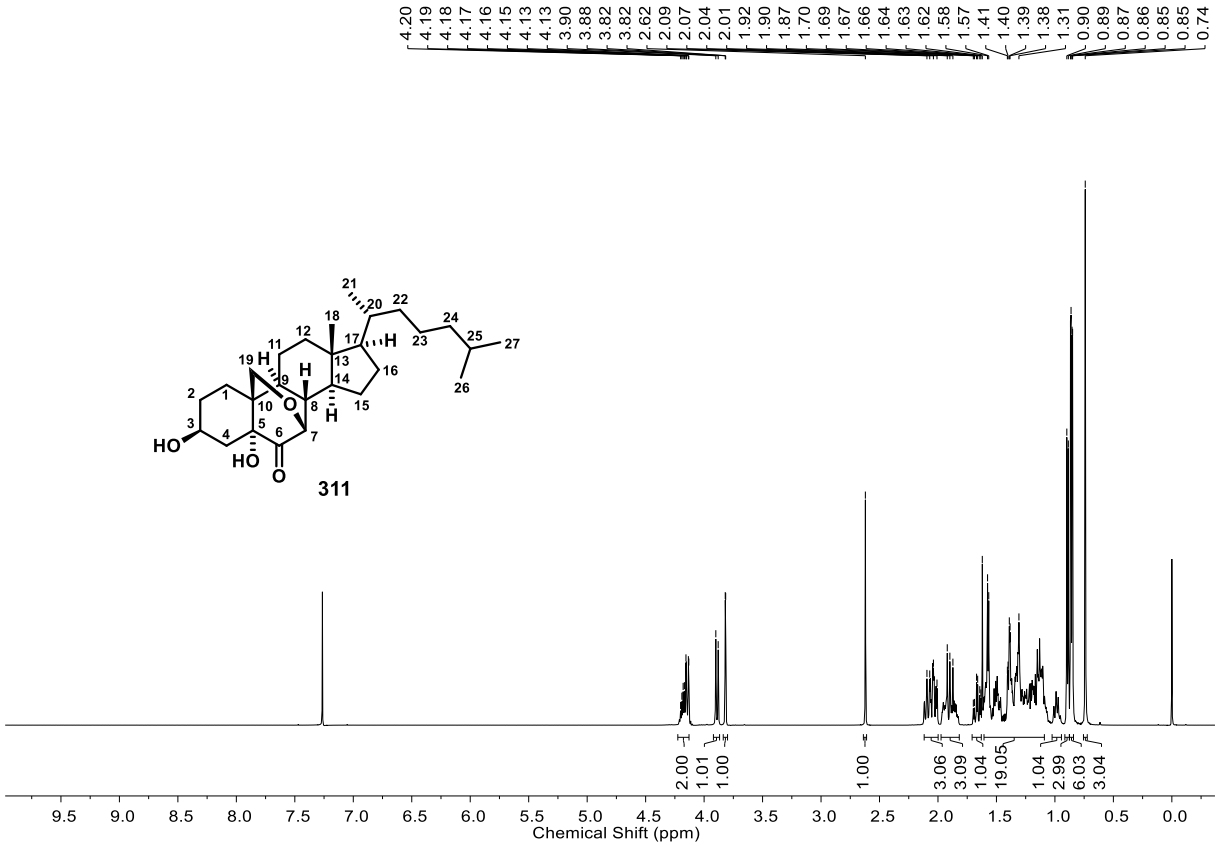


Figure 155: ^{1}H NMR (600 MHz, $CDCl_3$) of 3β,5α-dihydroxy-7β,19-epoxy-cholestan-6-one (**311**).

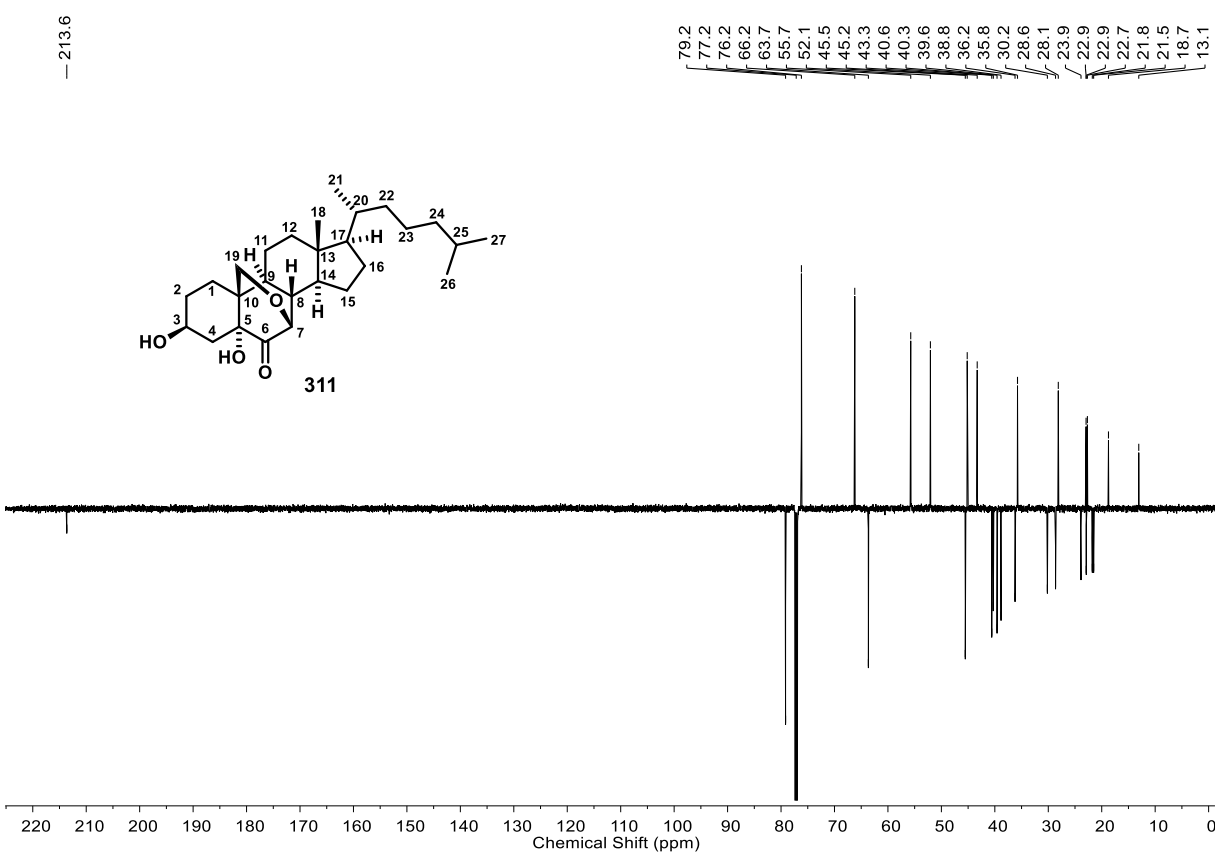


Figure 156: ^{13}C NMR (151 MHz, $CDCl_3$) of 3β,5α-dihydroxy-7β,19-epoxy-cholestan-6-one (**311**).

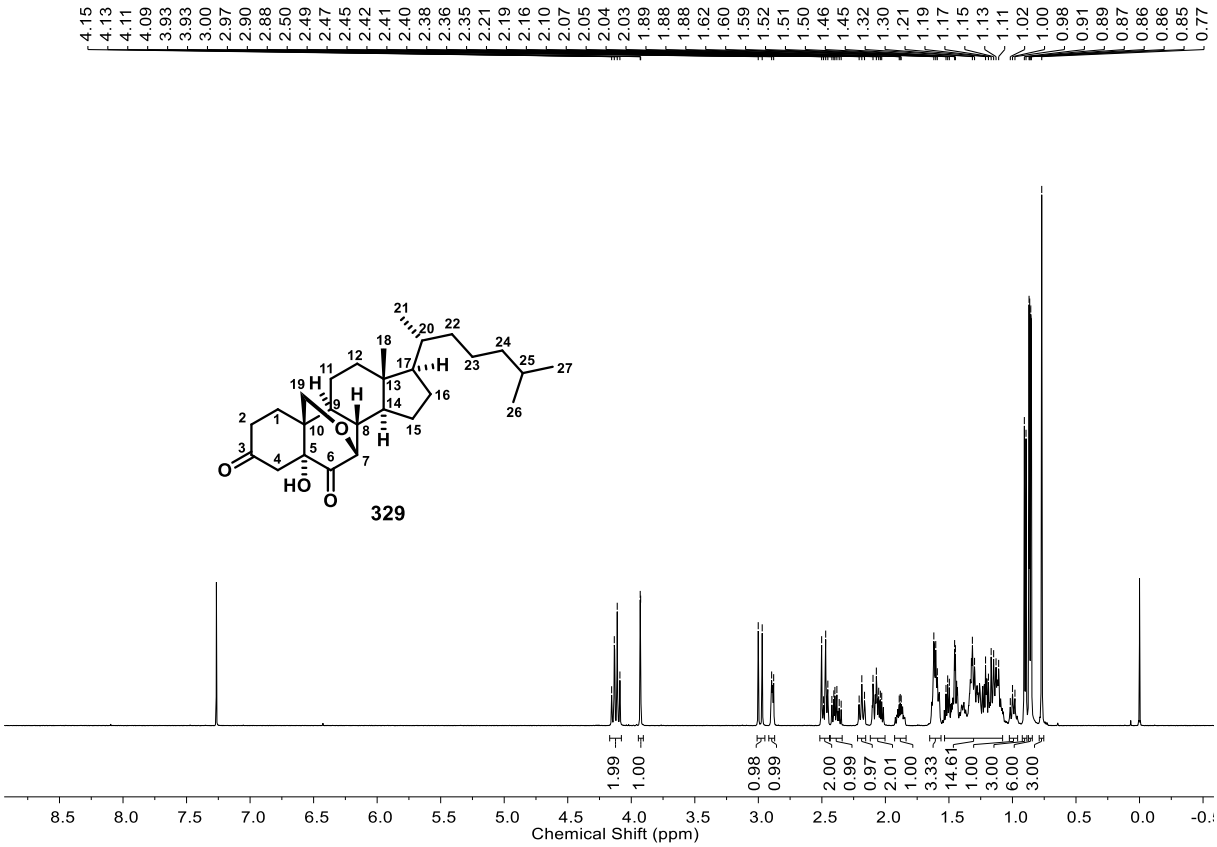


Figure 157: ^{1}H NMR (500 MHz, $CDCl_3$) of 7β,19-Epoxy-cholest-4-en-3,6-dione (**329**).

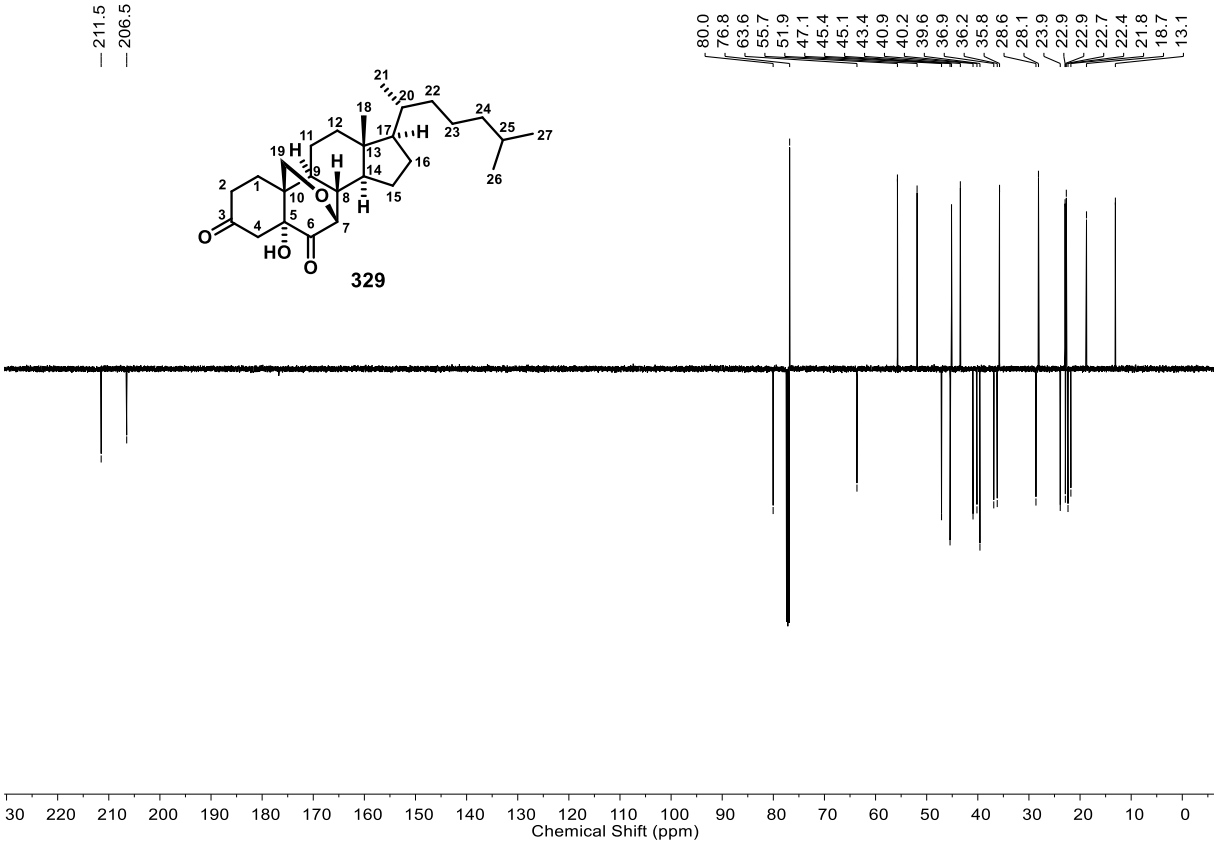


Figure 158: ^{13}C NMR (126 MHz, $CDCl_3$) of 7β,19-Epoxy-cholest-4-en-3,6-dione (**329**).

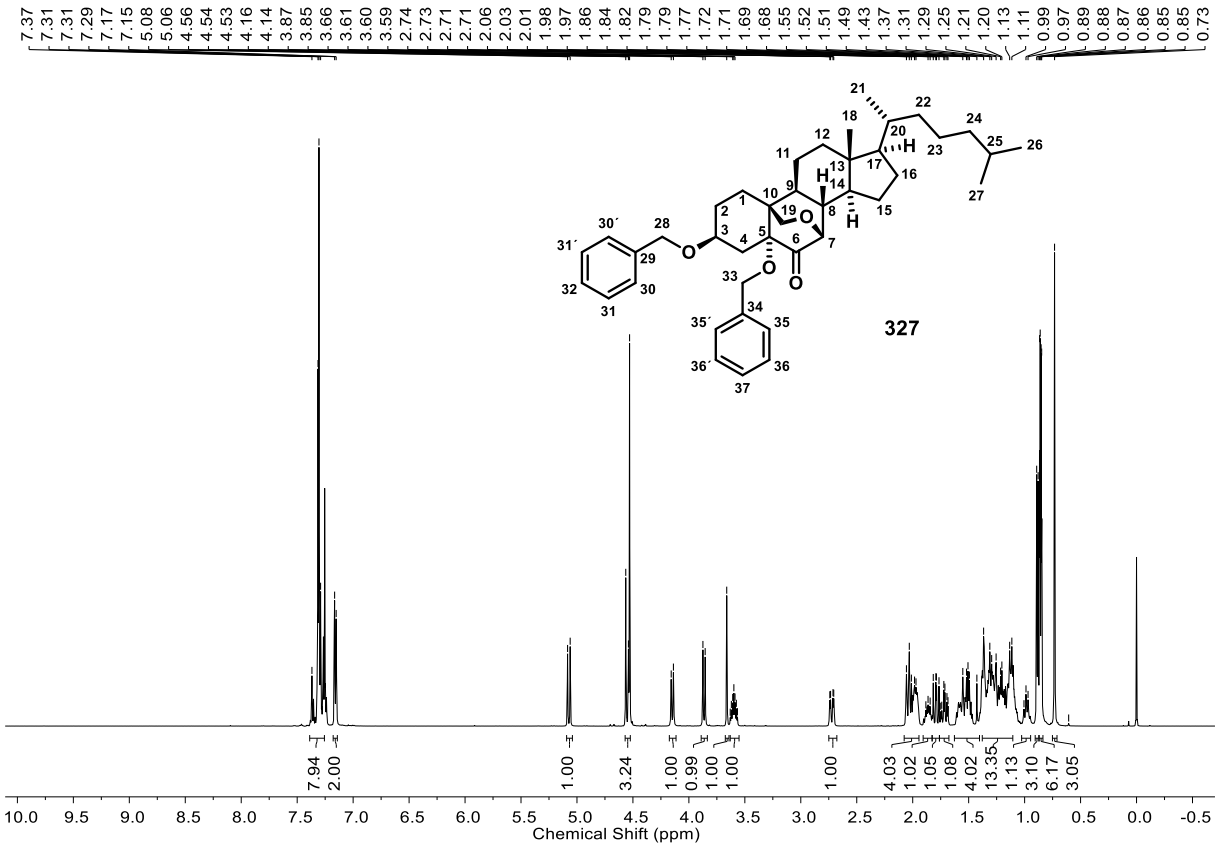


Figure 159: ^{1}H NMR (500 MHz, $CDCl_3$) of 3β,5α-Dibenzyloxy-7β,19-epoxy-cholestan-6-one (**327**).

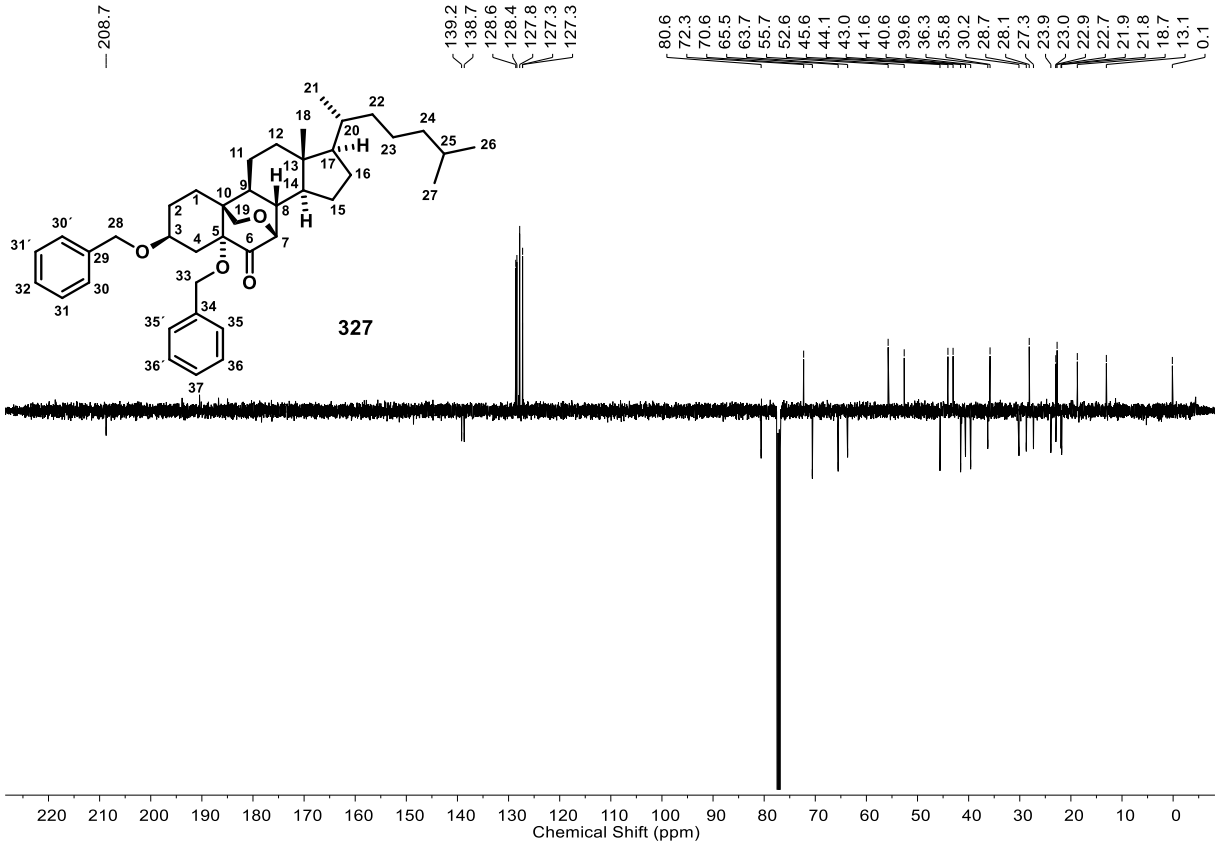


Figure 160: ^{13}C NMR (126 MHz, $CDCl_3$) of 3β,5α-Dibenzyloxy-7β,19-epoxy-cholestan-6-one (**327**).

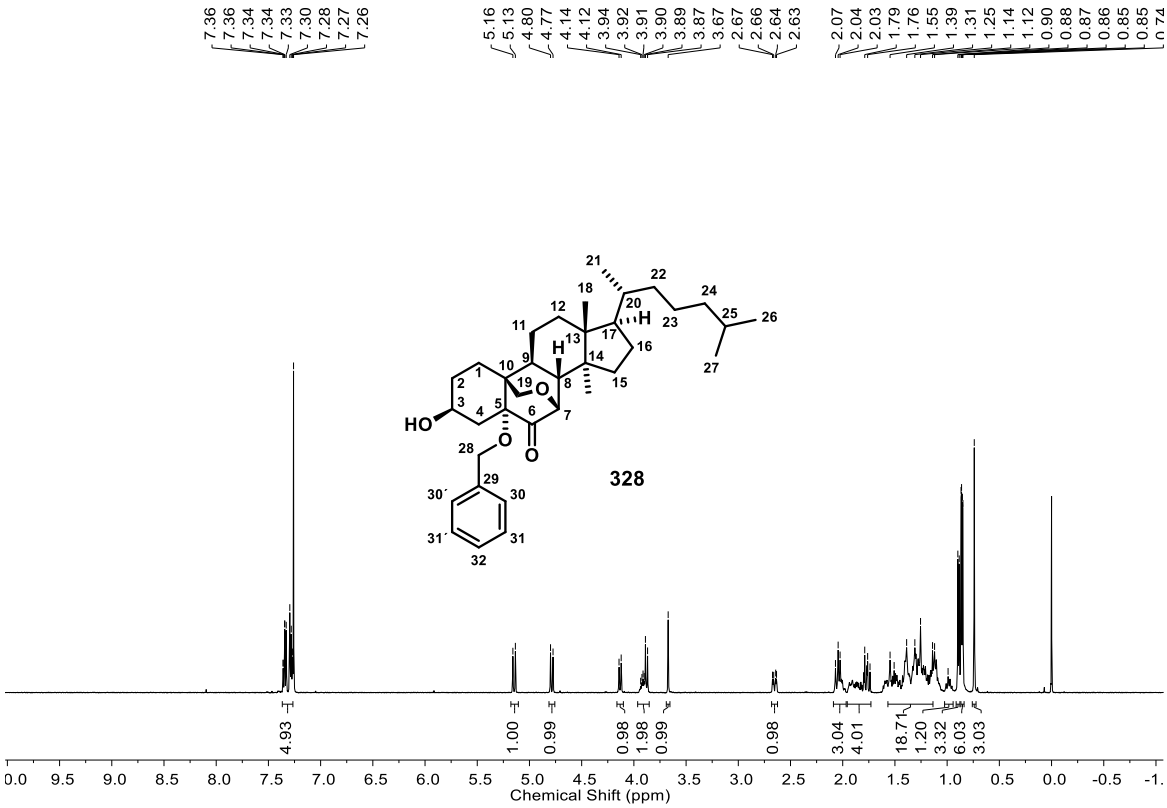


Figure 161: ^{1}H NMR (500 MHz, $CDCl_3$) of 5α-benzyloxy-3β-hydroxy-7β,19-epoxy-cholestan-6-one (**328**).

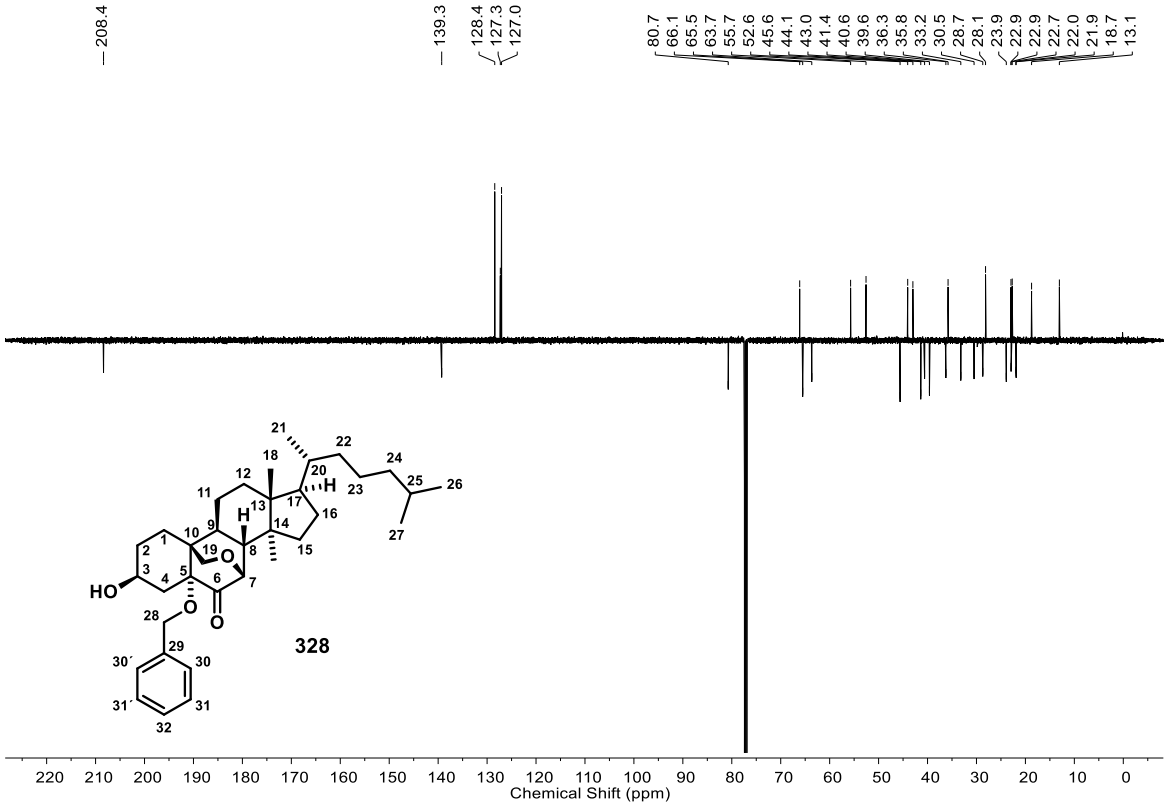


Figure 162: ^{13}C NMR (126 MHz, $CDCl_3$) of 5α-benzyloxy-3β-hydroxy-7β,19-epoxy-cholestan-6-one (**328**).

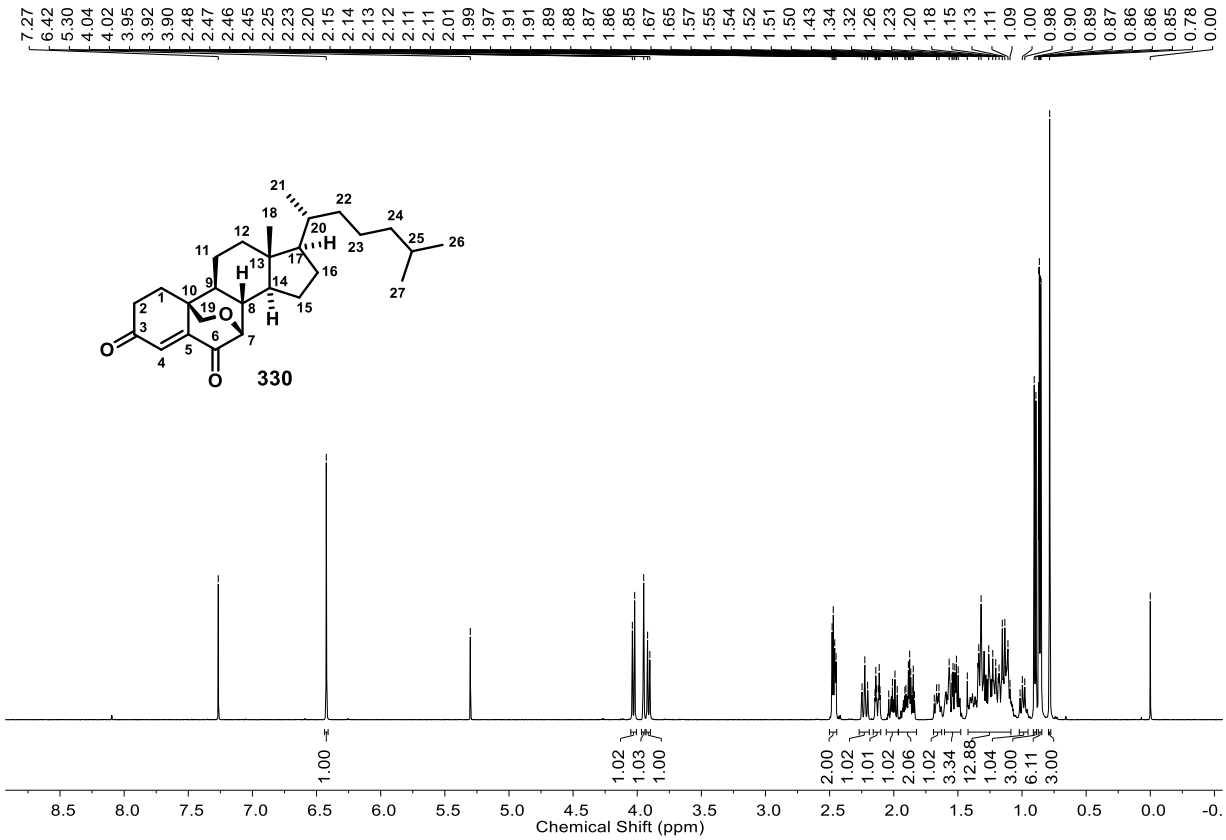


Figure 163: ^{1}H NMR (500 MHz, $CDCl_3$) of 7β,19-epoxycholest-4-ene-3,6-dione (**330**).

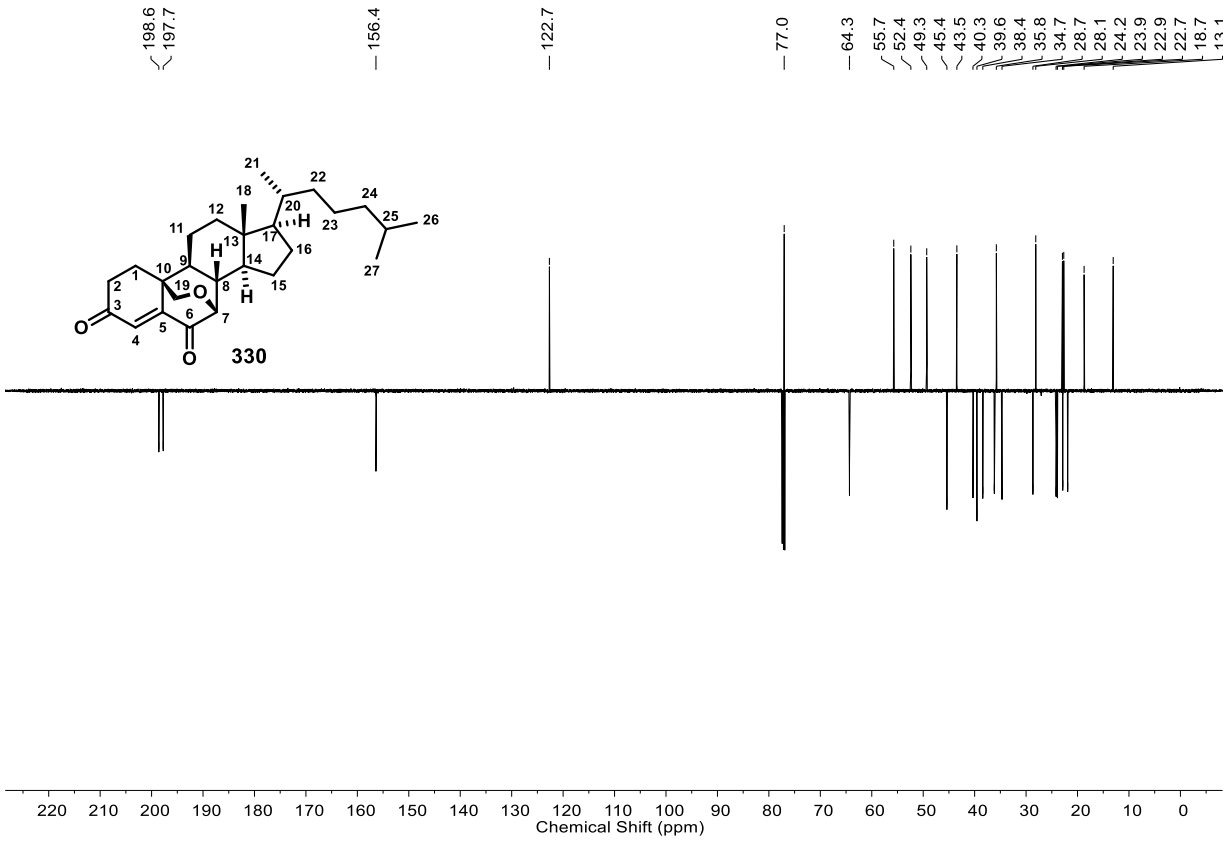


Figure 164: ^{13}C NMR (126 MHz, $CDCl_3$) of 7β,19-epoxycholest-4-ene-3,6-dione (**330**).

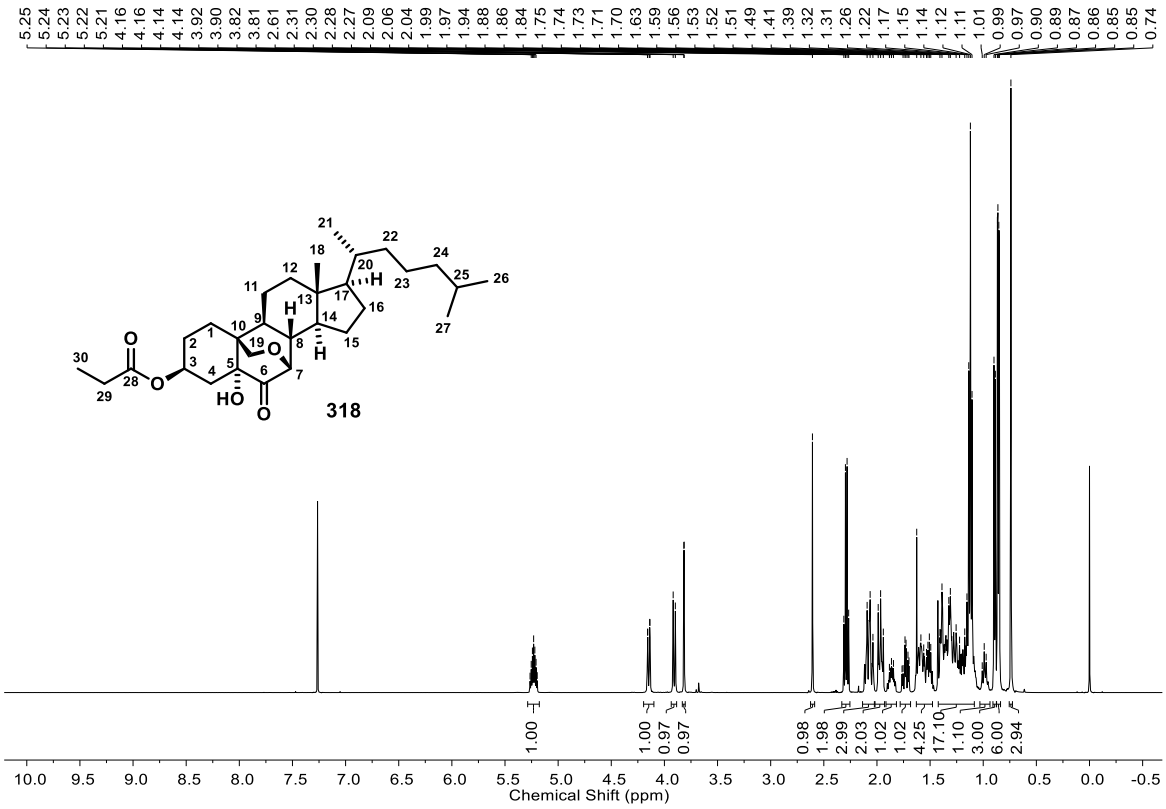


Figure 165: ^{1}H NMR (500 MHz, $CDCl_3$) of 7β,19-epoxy-5α-hydroxy-6-one-3β -cholesteryl-propionate (**318**).

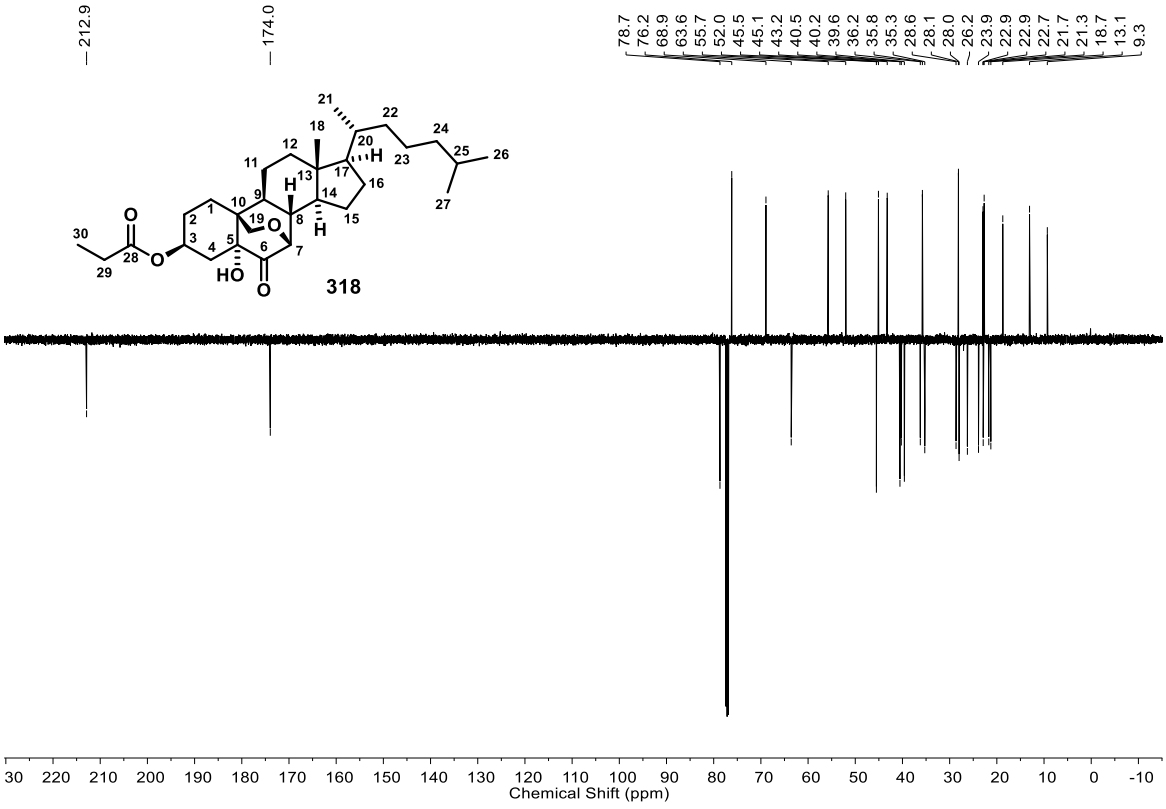


Figure 166: ^{13}C NMR (126 MHz, $CDCl_3$) of 7β,19-epoxy-5α-hydroxy-6-one-3β -cholesteryl-propionate (**318**).

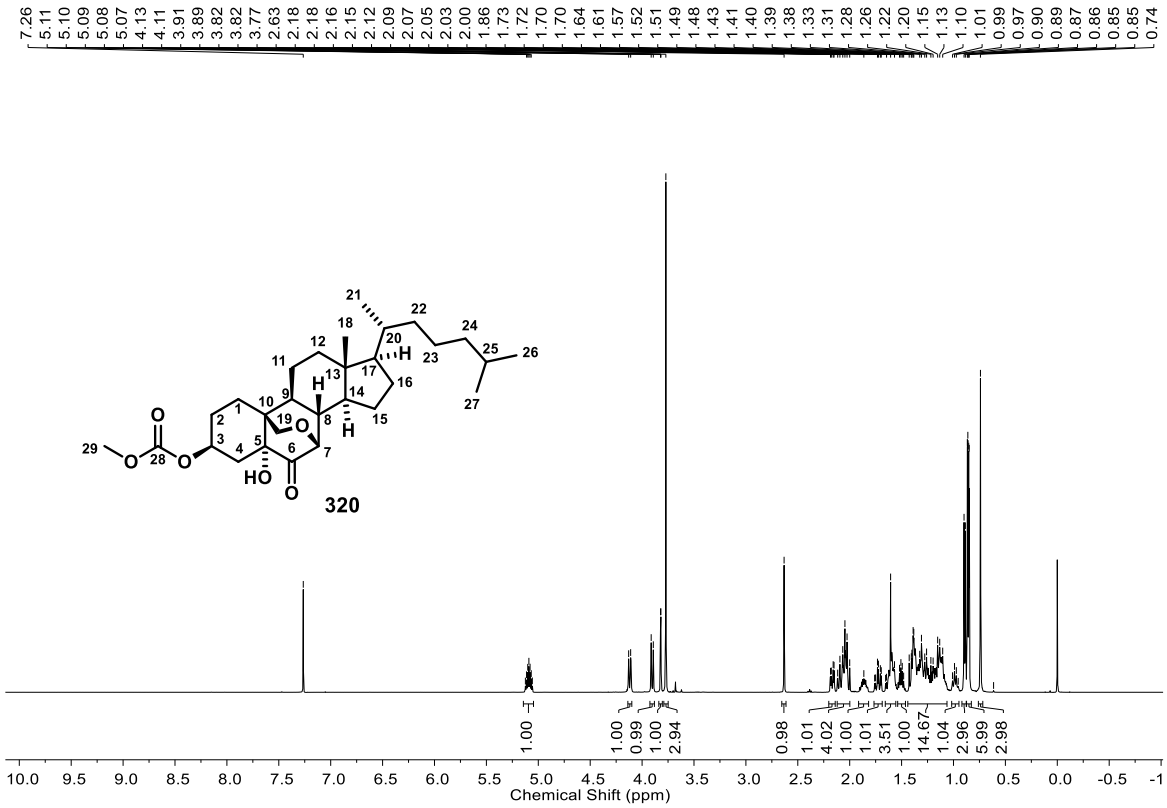


Figure 167: ^{1}H NMR (500 MHz, $CDCl_3$) of 7β,19-epoxy-5α-hydroxy-6-on-cholestan-3β-yl methyl-carbonate (**320**).

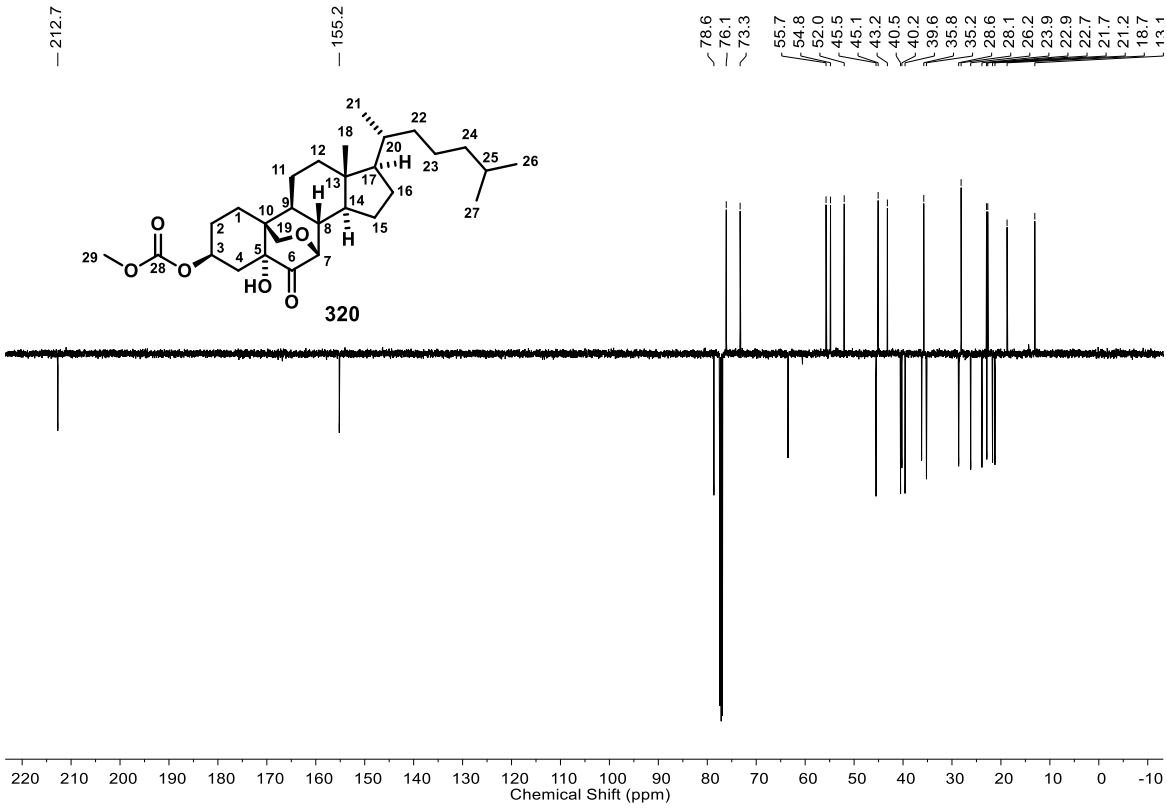


Figure 168: ^{13}C NMR (126 MHz, $CDCl_3$) of 7β,19-epoxy-5α-hydroxy-6-on-cholestan-3β-yl methyl-carbonate (**320**).

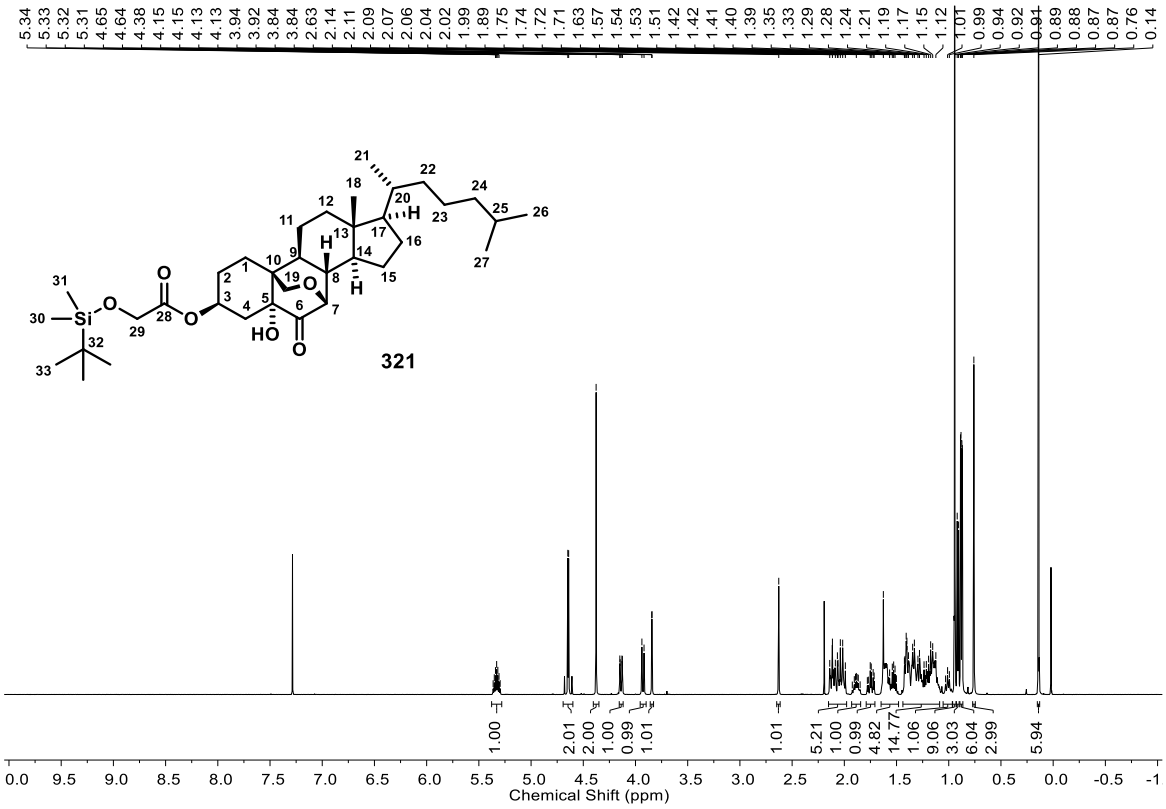


Figure 169: ^{1}H NMR (500 MHz, $CDCl_3$) of (*tert*-Butyldimethylsilanyloxy)acetic acid (7β,19-epoxy-5α-hydroxy-6-one-cholestane-3β-yl) ester (**321**).

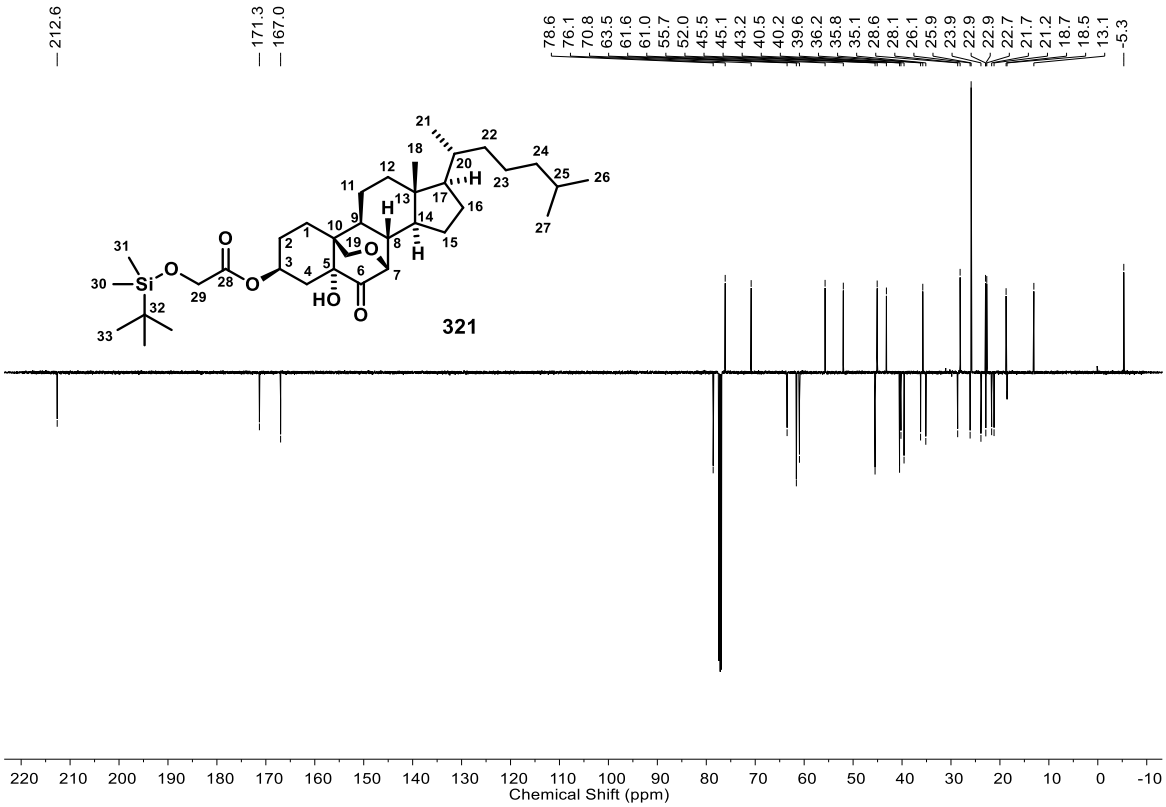


Figure 170: ^{13}C NMR (126 MHz, $CDCl_3$) of (*tert*-Butyldimethylsilanyloxy)acetic acid (7β,19-epoxy-5α-hydroxy-6-one-cholestane-3β-yl) ester (**321**).

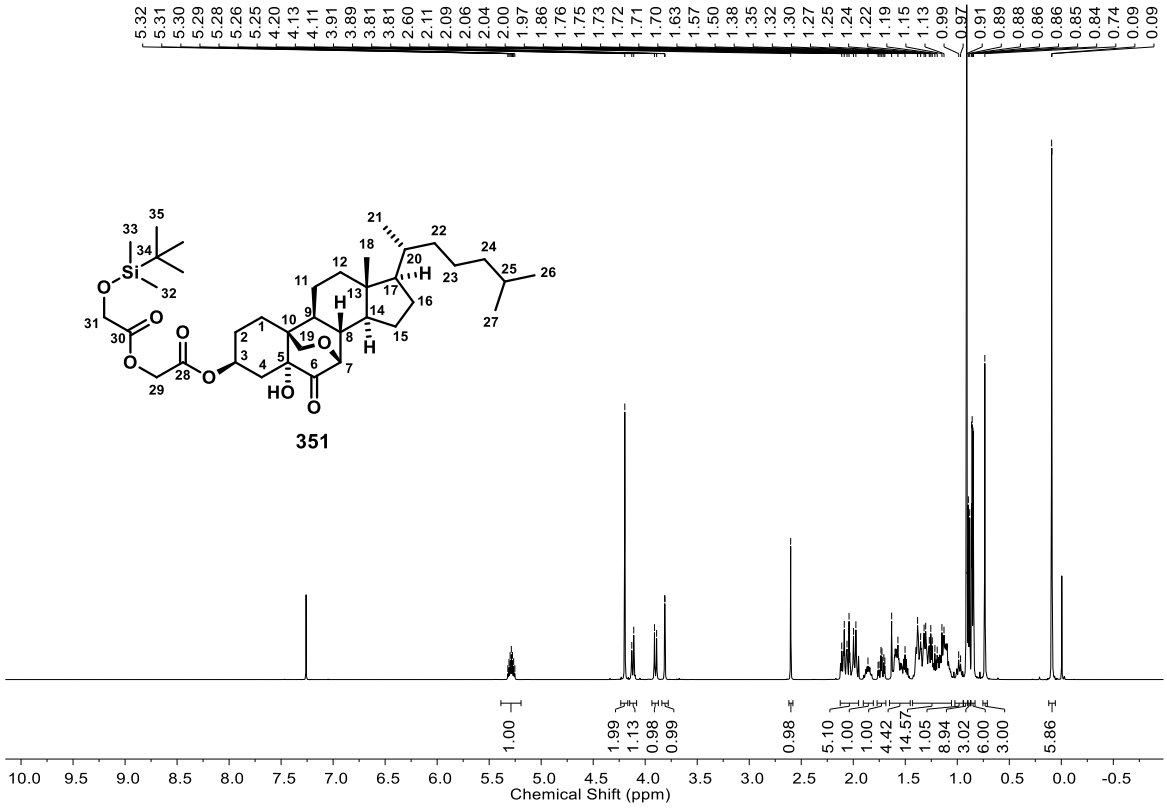


Figure 171: ^{1}H NMR (500 MHz, $CDCl_3$) of compound (**351**).

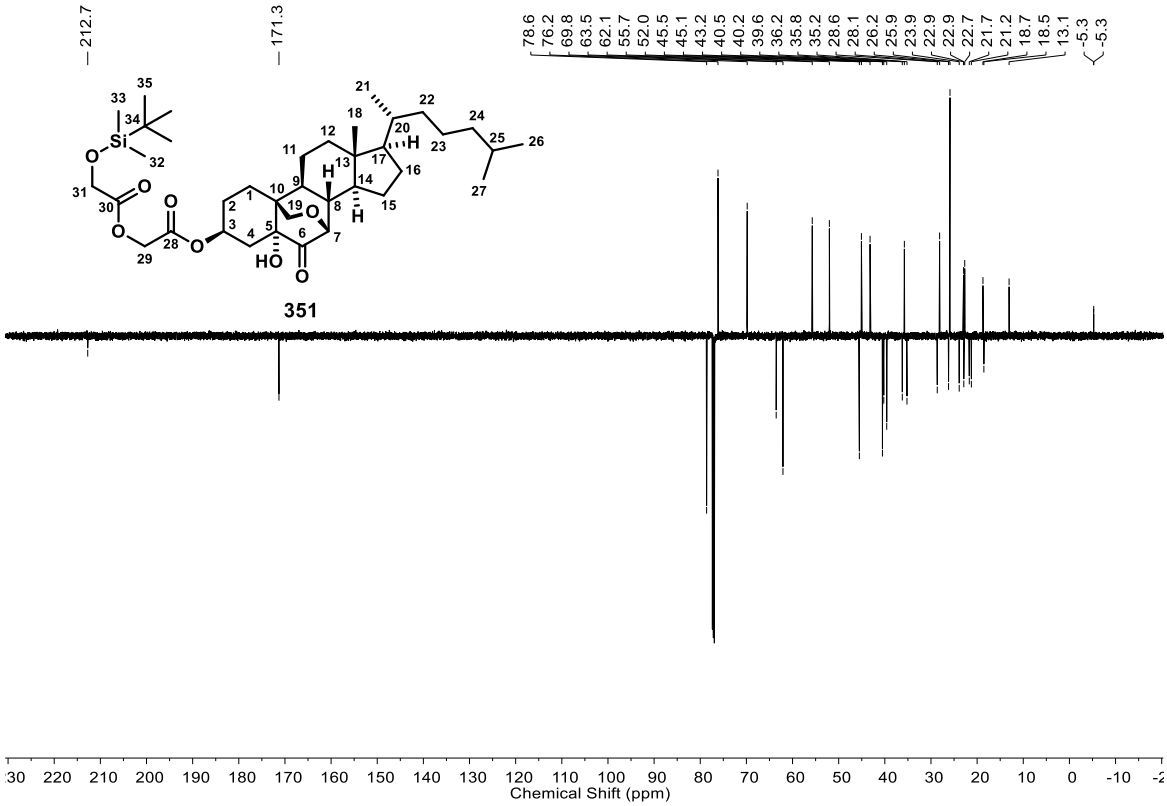


Figure 172: ^{13}C NMR (126 MHz, $CDCl_3$) of compound (**351**).

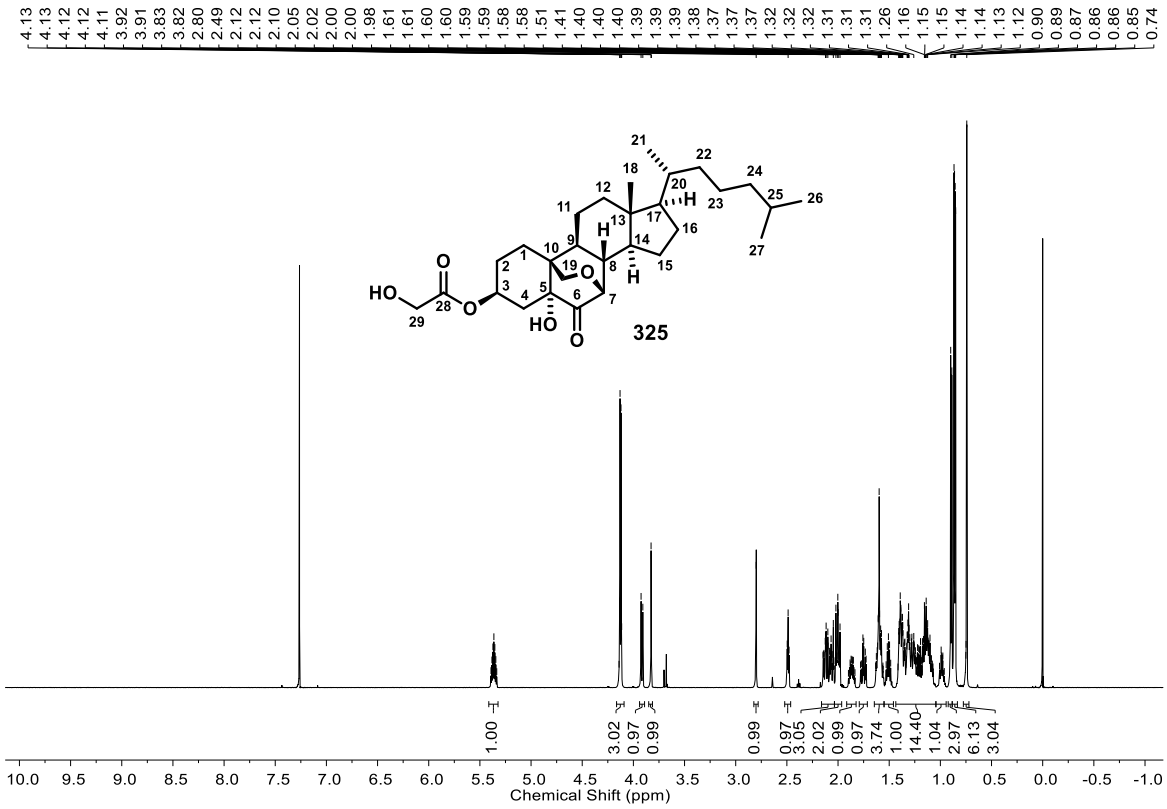


Figure 173: ^{1}H NMR (600 MHz, $CDCl_3$) of 7β,19-Epoxy-5α-hydroxy-6-on-cholestan-3β -glycolate (**325**).

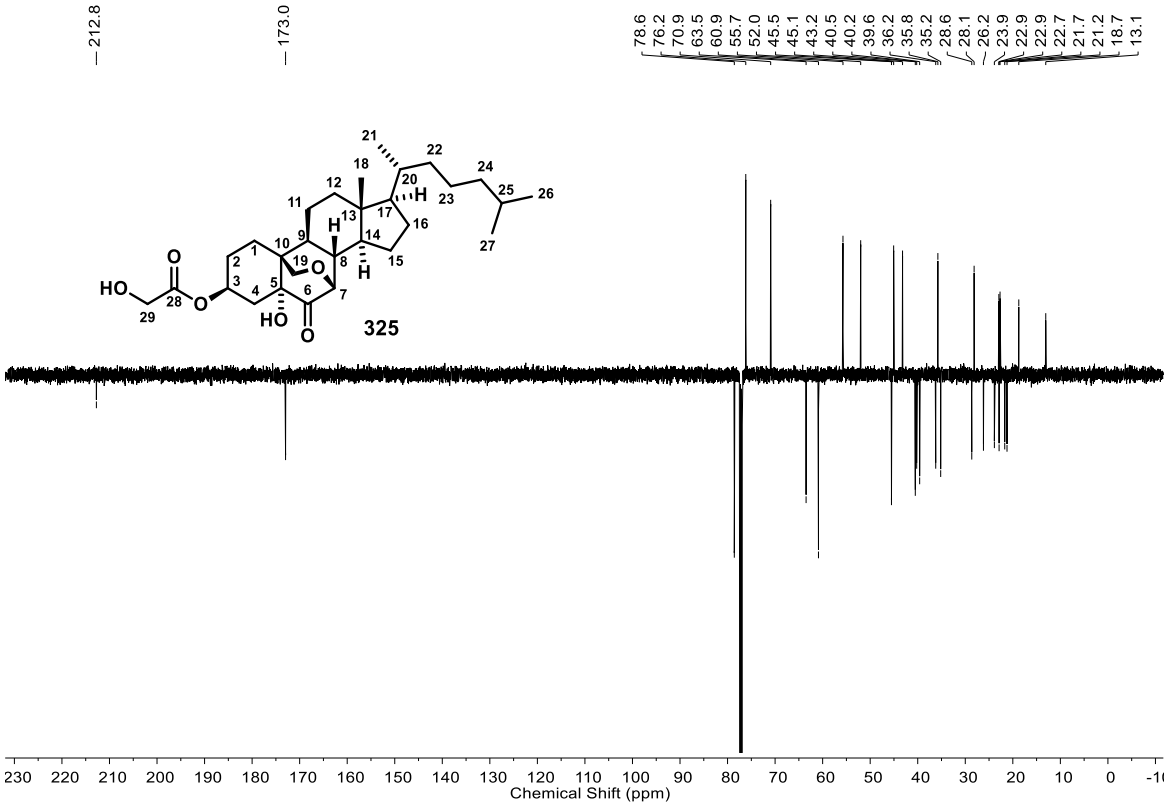


Figure 174: ^{13}C NMR (151 MHz, $CDCl_3$) of 7β,19-Epoxy-5α-hydroxy-6-on-cholestan-3β -glycolate (**325**).

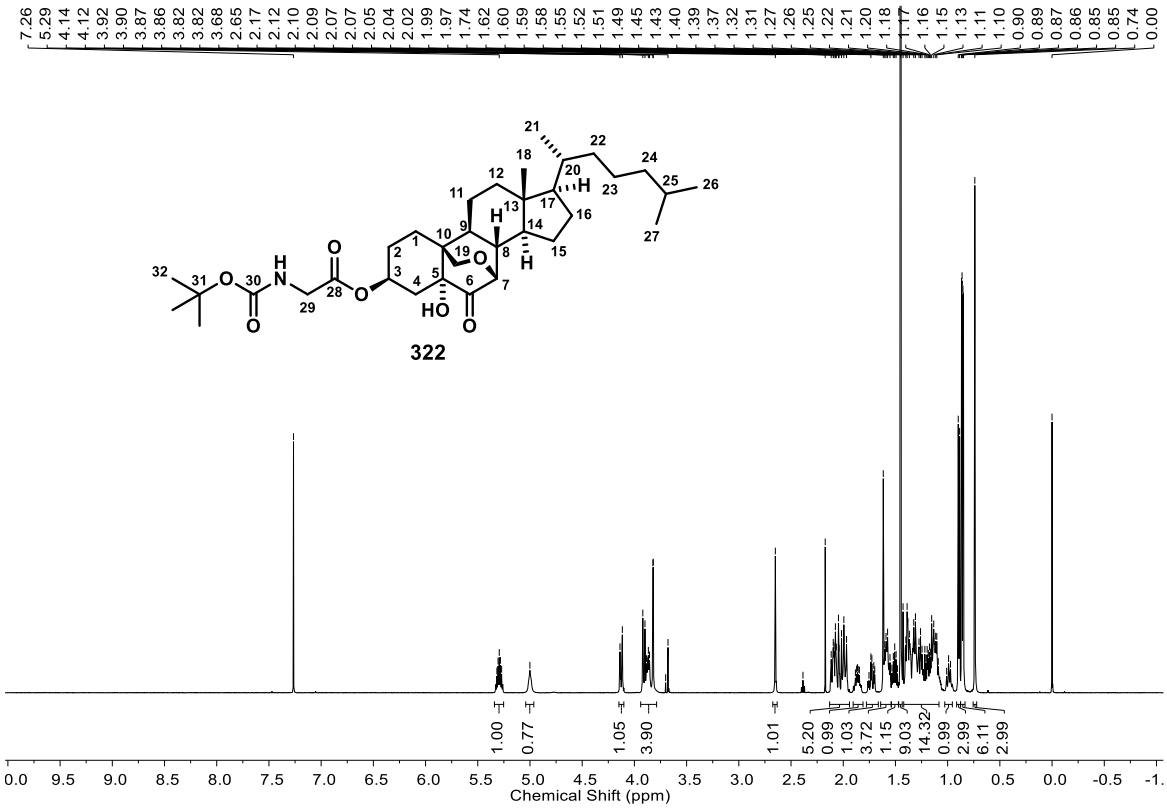


Figure 175: ^{1}H NMR (500 MHz, $CDCl_3$) of *N*-Boc-glycine (7β,19-epoxy-5α-hydroxy-6-one-cholestan-3β-yl) ester (**322**).

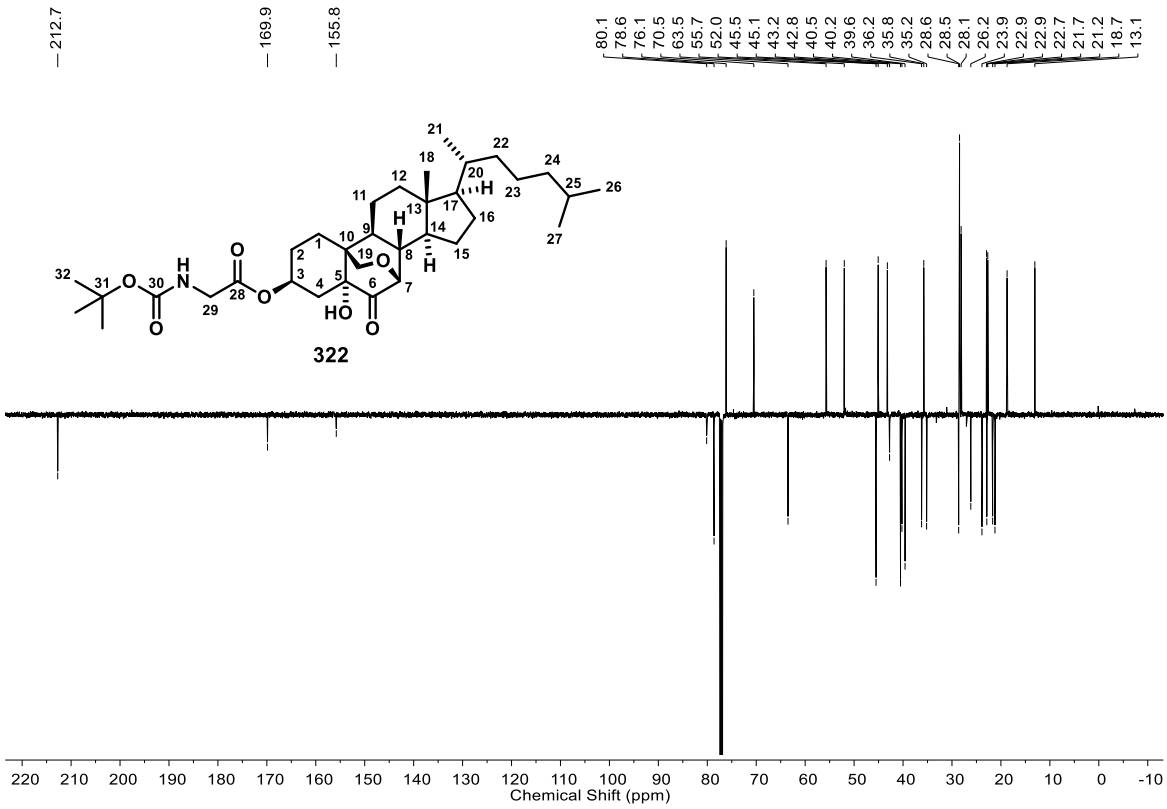


Figure 176: ^{13}C NMR (126 MHz, $CDCl_3$) of *N*-Boc-glycine (7β,19-epoxy-5α-hydroxy-6-one-cholestan-3β-yl) ester (**322**).

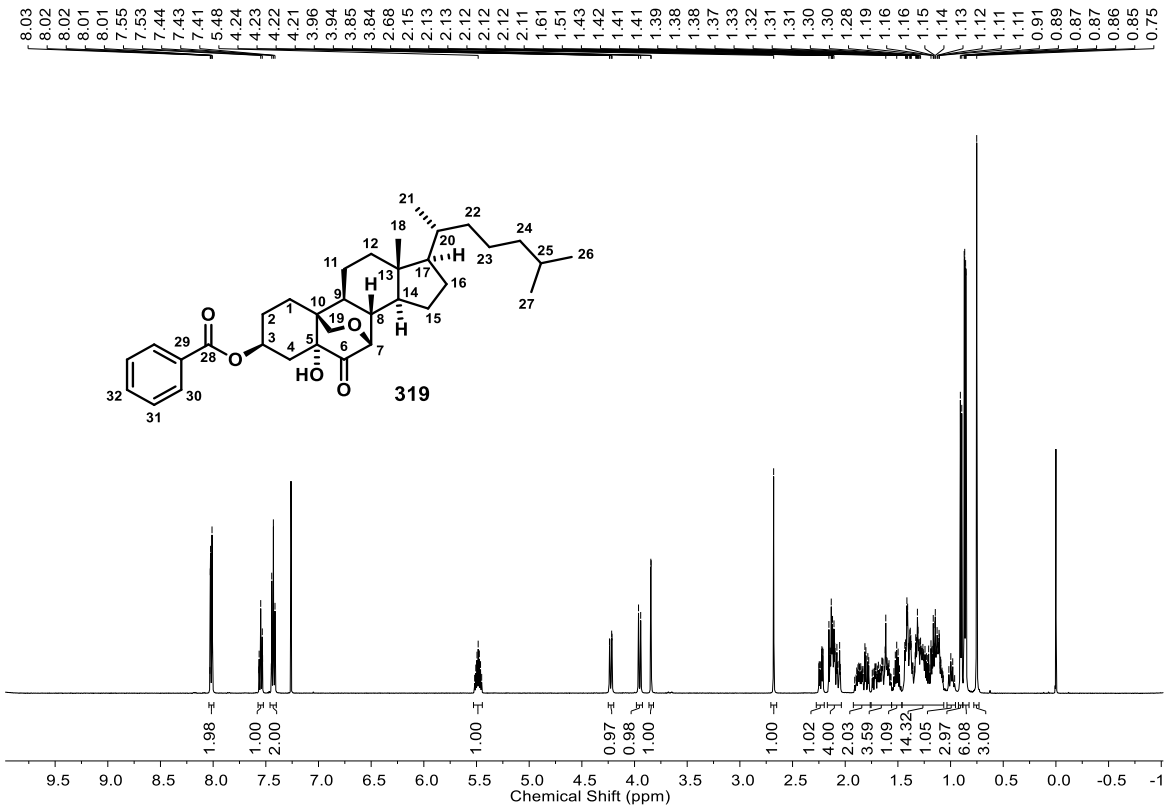


Figure 177: ^{1}H NMR (500 MHz, $CDCl_3$) of benzoic acid (7β,19-epoxy-5α-hydroxy-6-one-cholestan-3β-yl) ester (**319**).

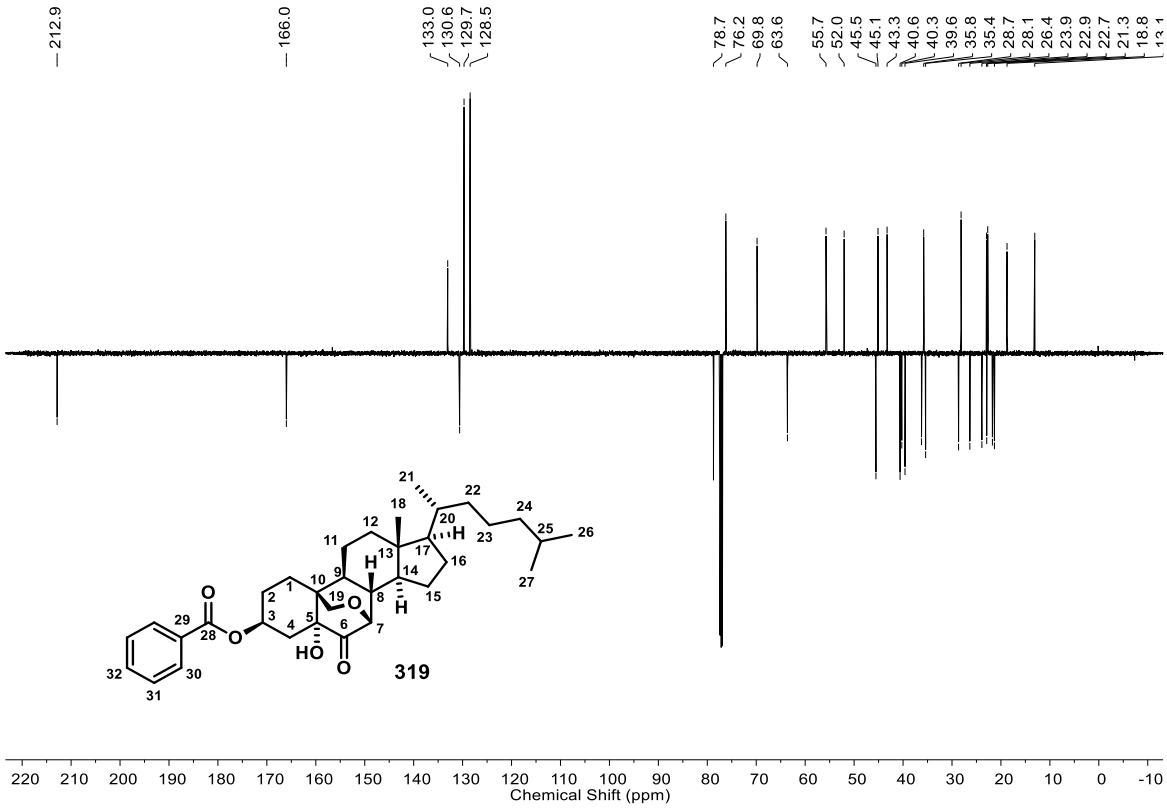


Figure 178: ^{13}C NMR (126 MHz, $CDCl_3$) of benzoic acid (7β,19-epoxy-5α-hydroxy-6-one-cholestan-3β-yl) ester (**319**).

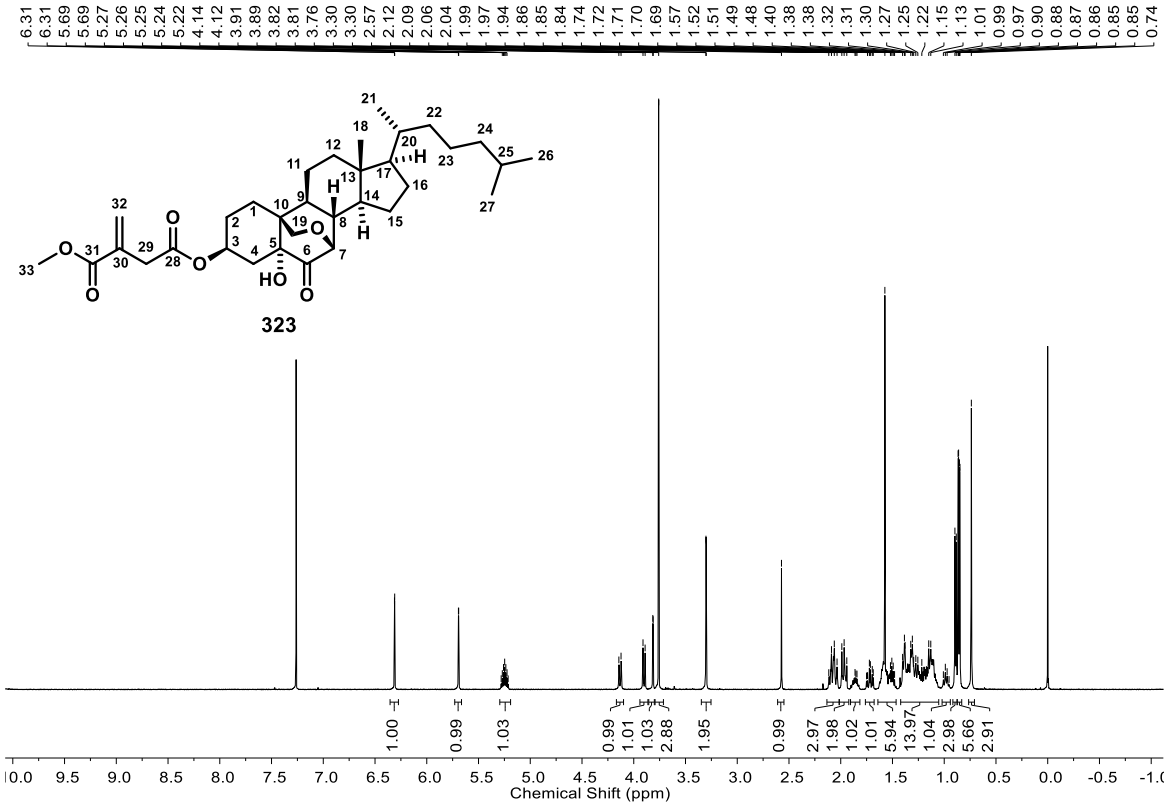


Figure 179: ^{1}H NMR (500 MHz, $CDCl_3$) of itaconic acid 4-(7β,19-epoxy-5α-hydroxy-6-one-cholestane-3β-yl)-1-methyl ester (**323**).

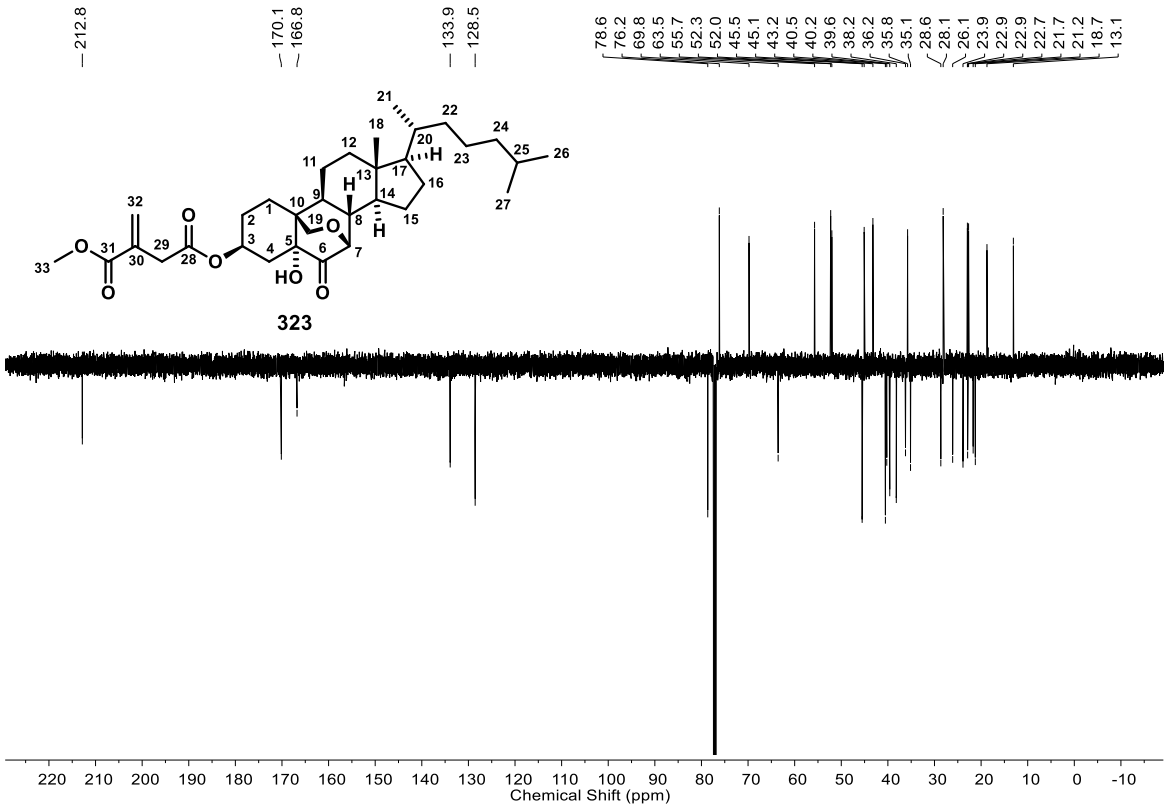


Figure 180: ^{13}C NMR (126 MHz, $CDCl_3$) of itaconic acid 4-(7β,19-epoxy-5α-hydroxy-6-one-cholestane-3β-yl)-1-methyl ester (**323**).

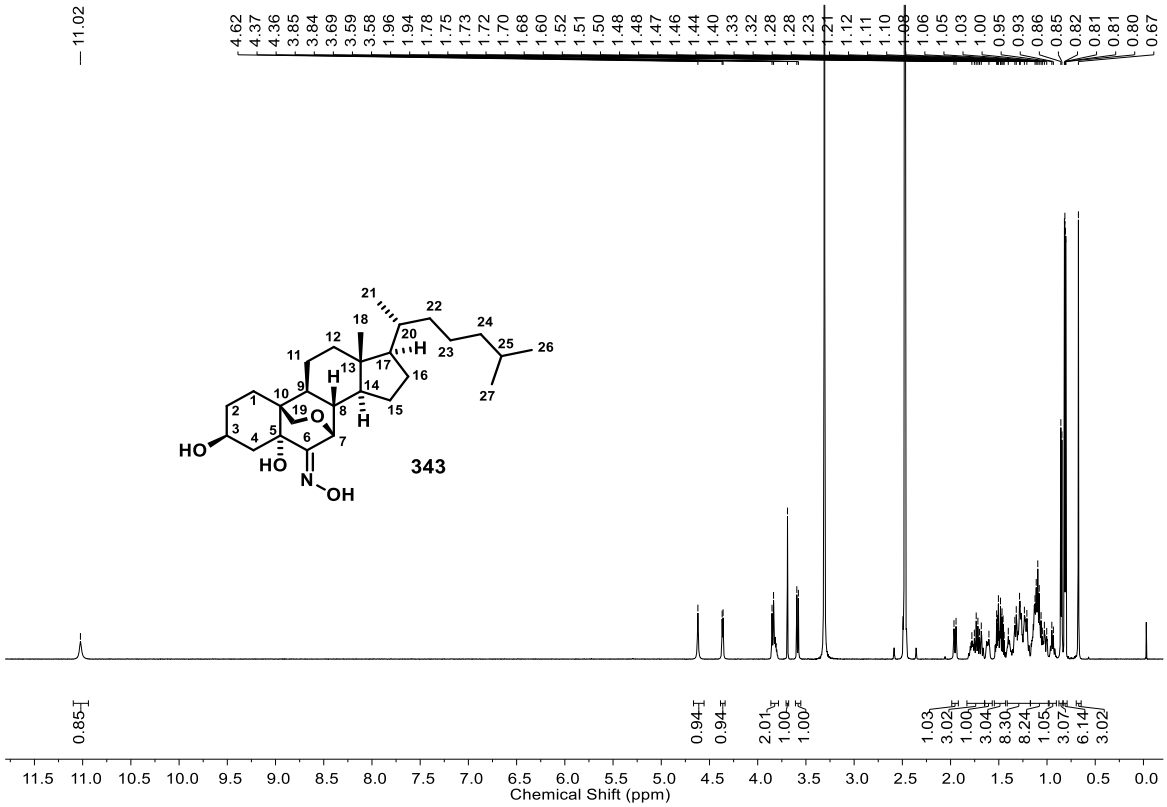


Figure 181: ^{1}H NMR (600 MHz, DMSO-d_6) of 7β,19-epoxy-3β,5α-hydroxy-cholestane-6-one oxime (**343**).

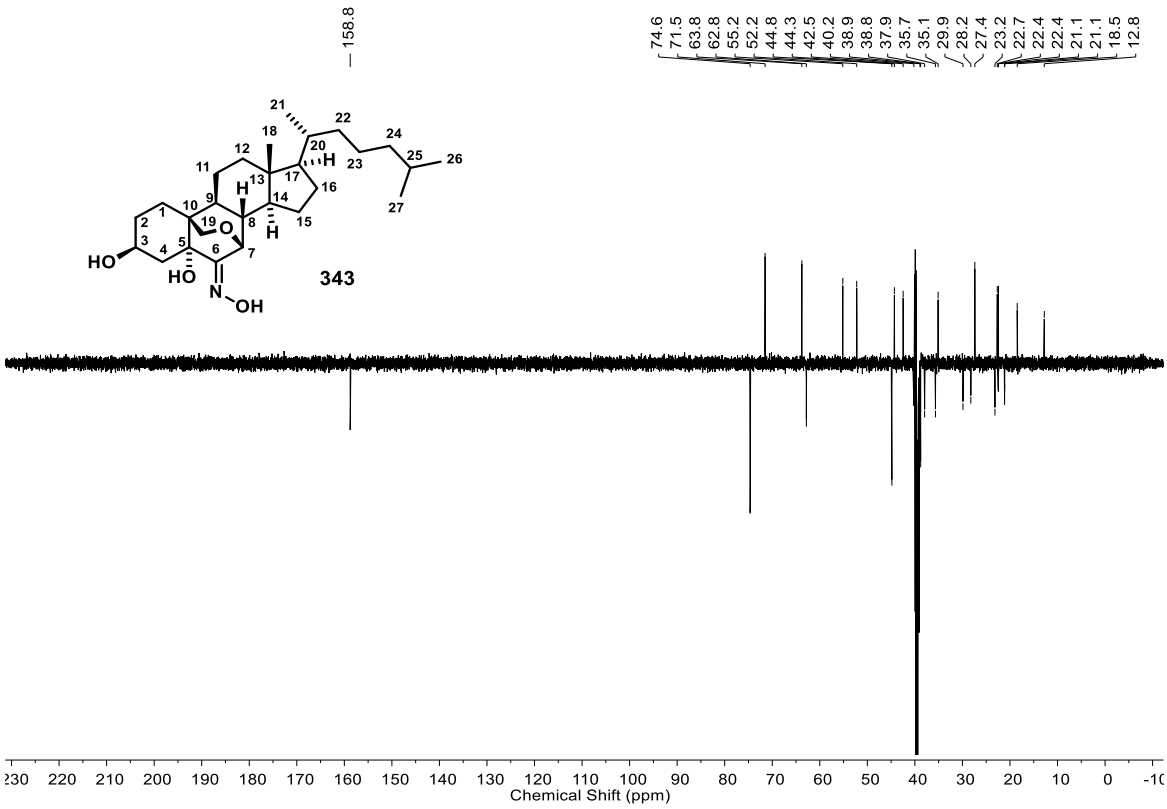


Figure 182: ^{13}C NMR (151 MHz, DMSO-d_6) of 7β,19-epoxy-3β,5α-hydroxy-cholestane-6-one oxime (**343**).

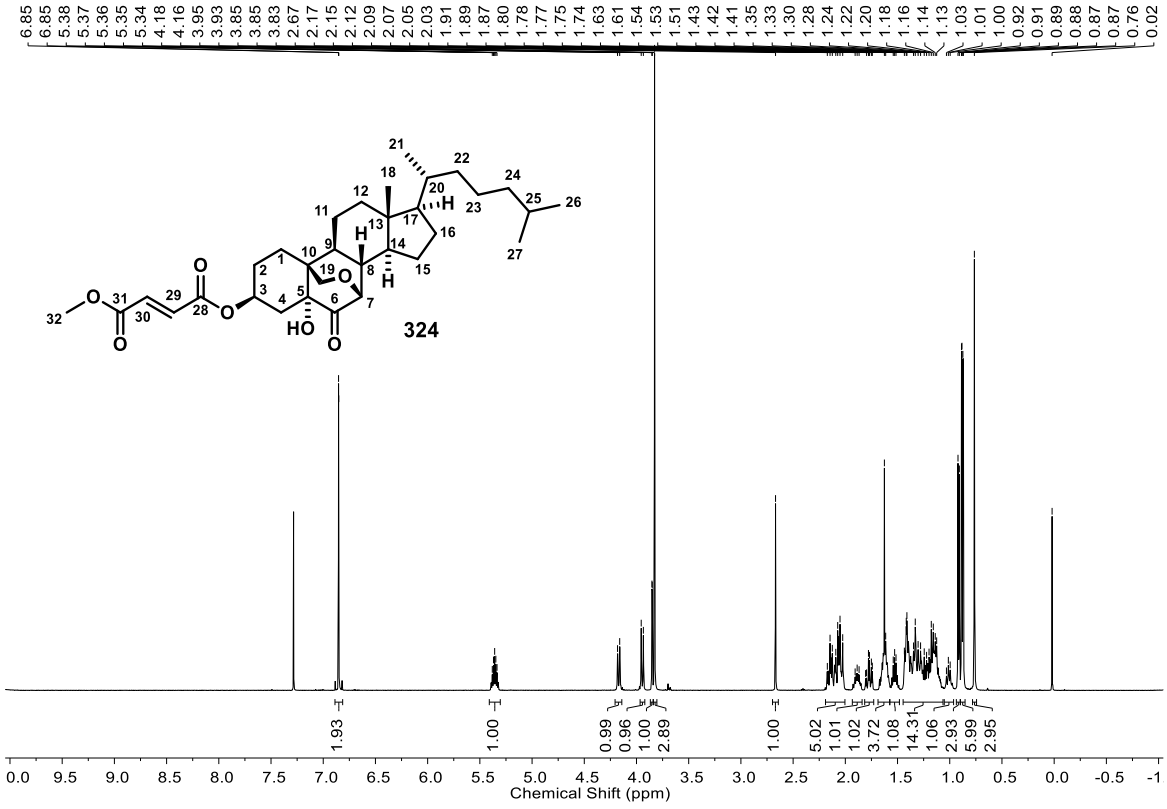


Figure 183: ^{1}H NMR (500 MHz, $CDCl_3$) of fumaric acid 4-(7β,19-epoxy-5α-hydroxy-6-one-cholestane-3β-yl) 1-methyl ester (**324**).

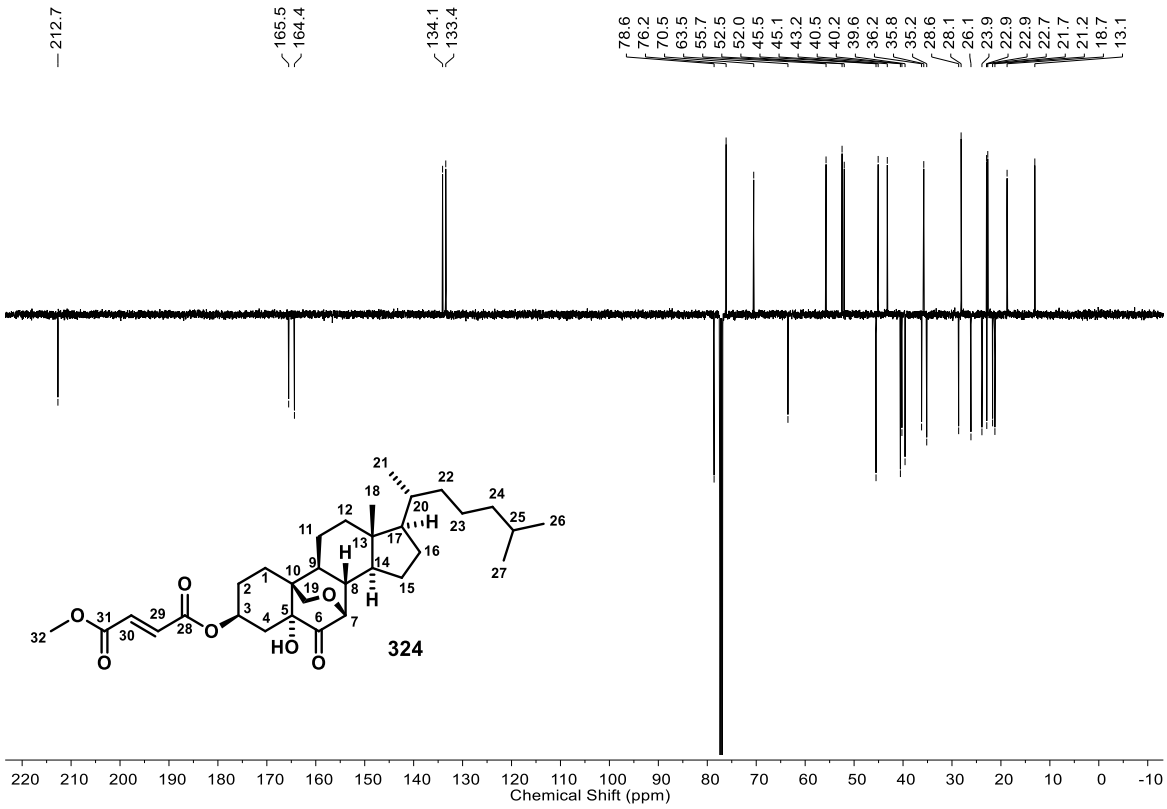


Figure 184: ^{13}C NMR (126 MHz, $CDCl_3$) of fumaric acid 4-(7β,19-epoxy-5α-hydroxy-6-one-cholestane-3β-yl) 1-methyl ester (**324**).

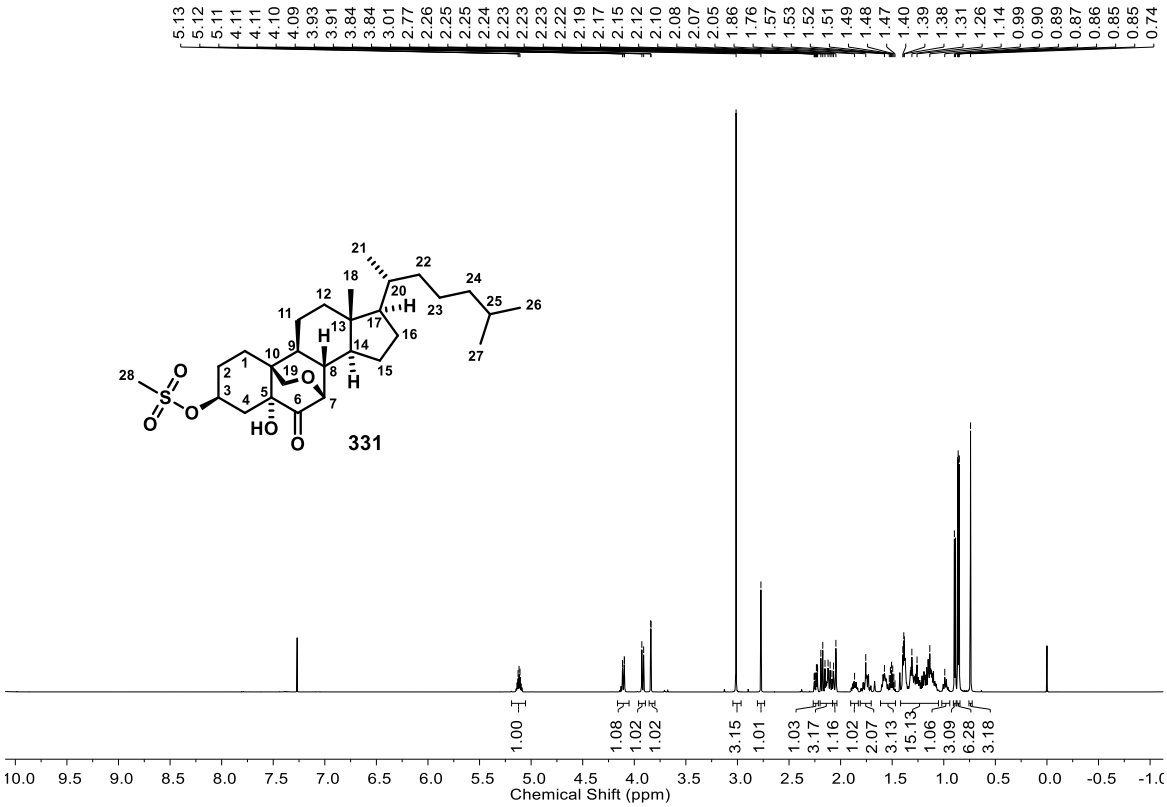


Figure 185: ^{1}H NMR (600 MHz, $CDCl_3$) of methanesulfonic acid (7β,19-epoxy-5α-hydroxy-6-one-cholestane-3β-yl) ester (**331**).

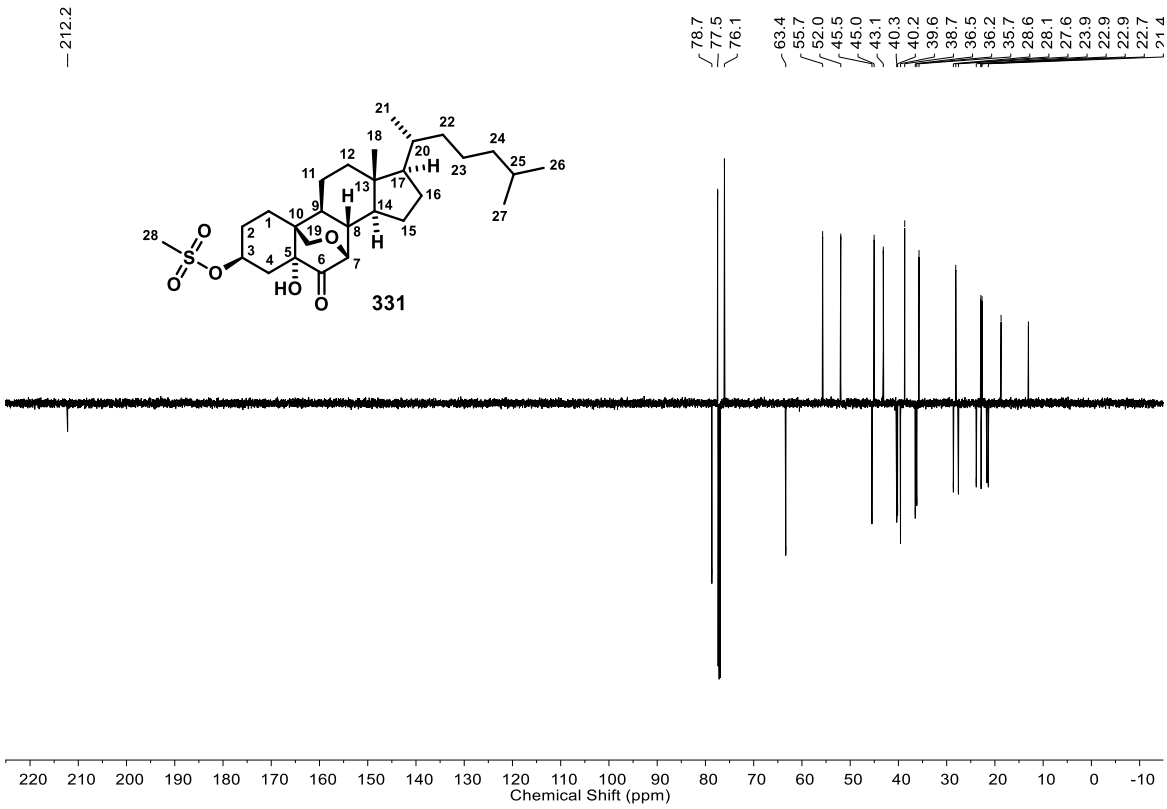


Figure 186: ^{13}C NMR (151 MHz, $CDCl_3$) of methanesulfonic acid (7β,19-epoxy-5α-hydroxy-6-one-cholestane-3β-yl) ester (**331**).

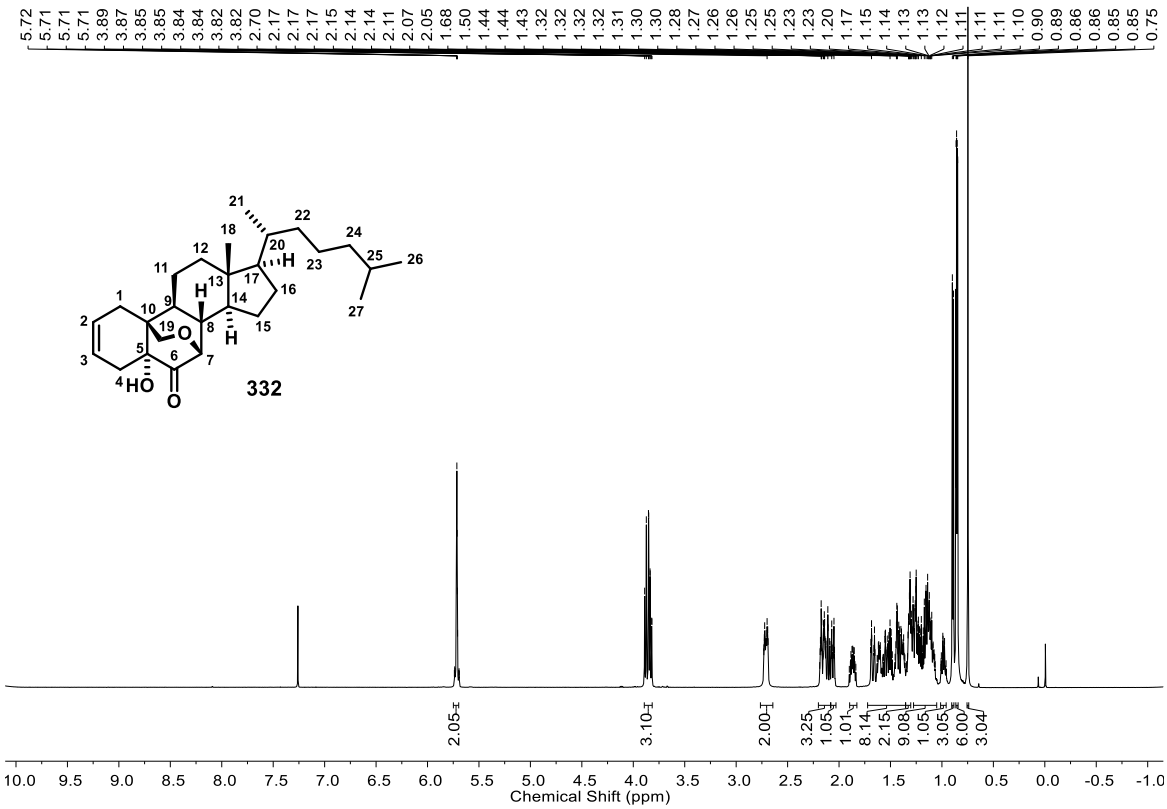


Figure 187: ^{1}H NMR (600 MHz, $CDCl_3$) of 7β,19-Epoxy-5α-hydroxy-cholest-2-en-6-on (**332**).

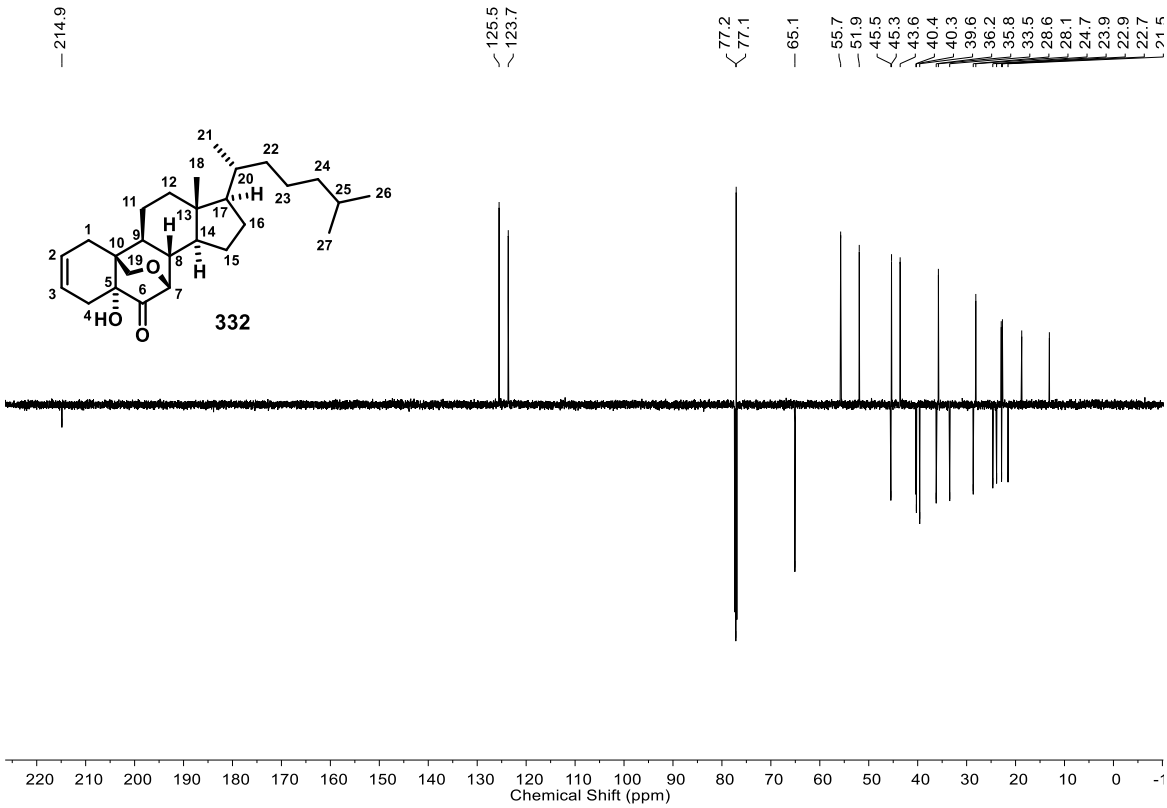


Figure 188: ^{13}C NMR (151 MHz, $CDCl_3$) of 7β,19-Epoxy-5α-hydroxy-cholest-2-en-6-on (**332**).

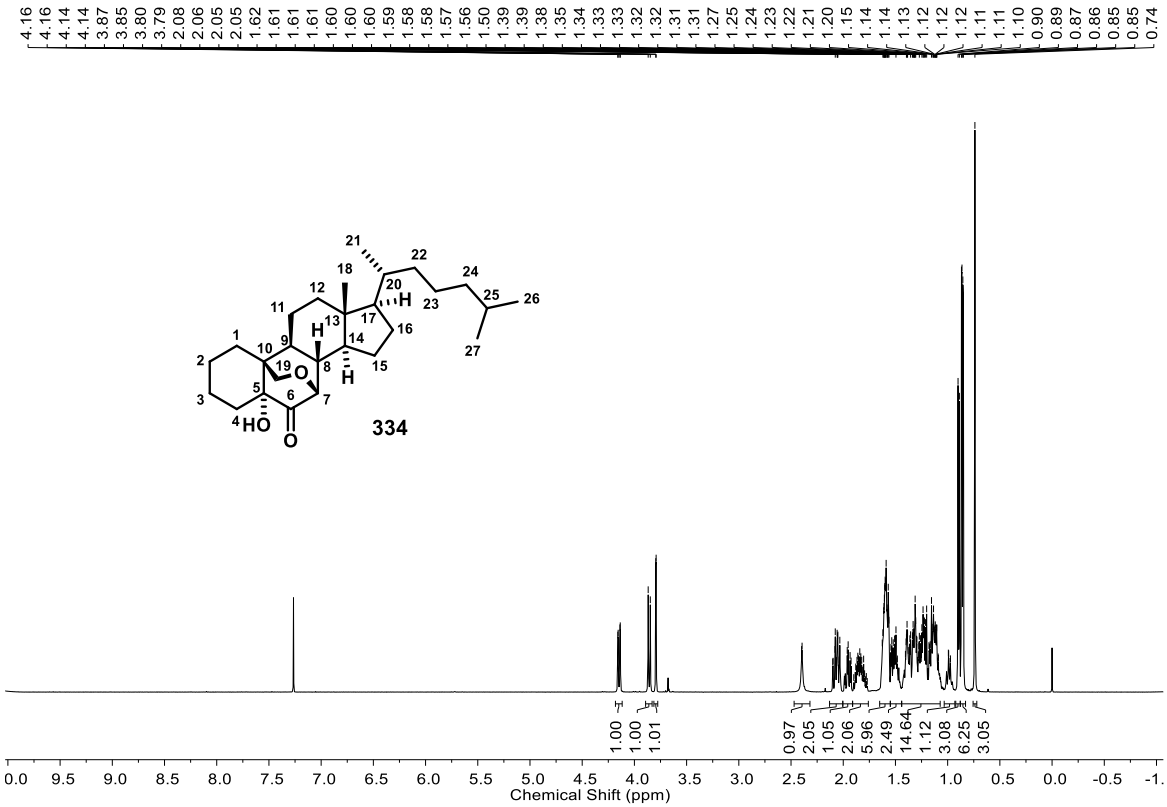


Figure 189: ^{1}H NMR (500 MHz, $CDCl_3$) of 7β,19-Epoxy-5α-hydroxy-cholestane-6-one (**334**).

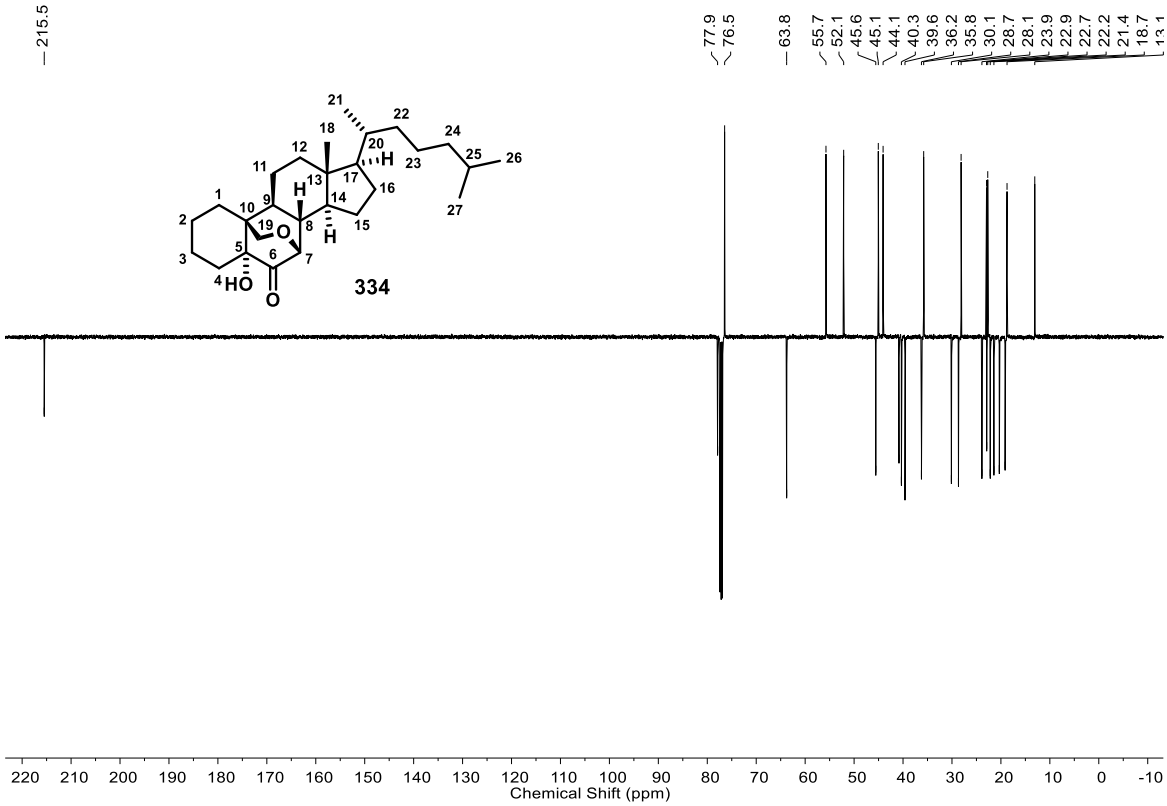


Figure 190: ^{13}C NMR (126 MHz, $CDCl_3$) of 7β,19-Epoxy-5α-hydroxy-cholestane-6-one (**334**).

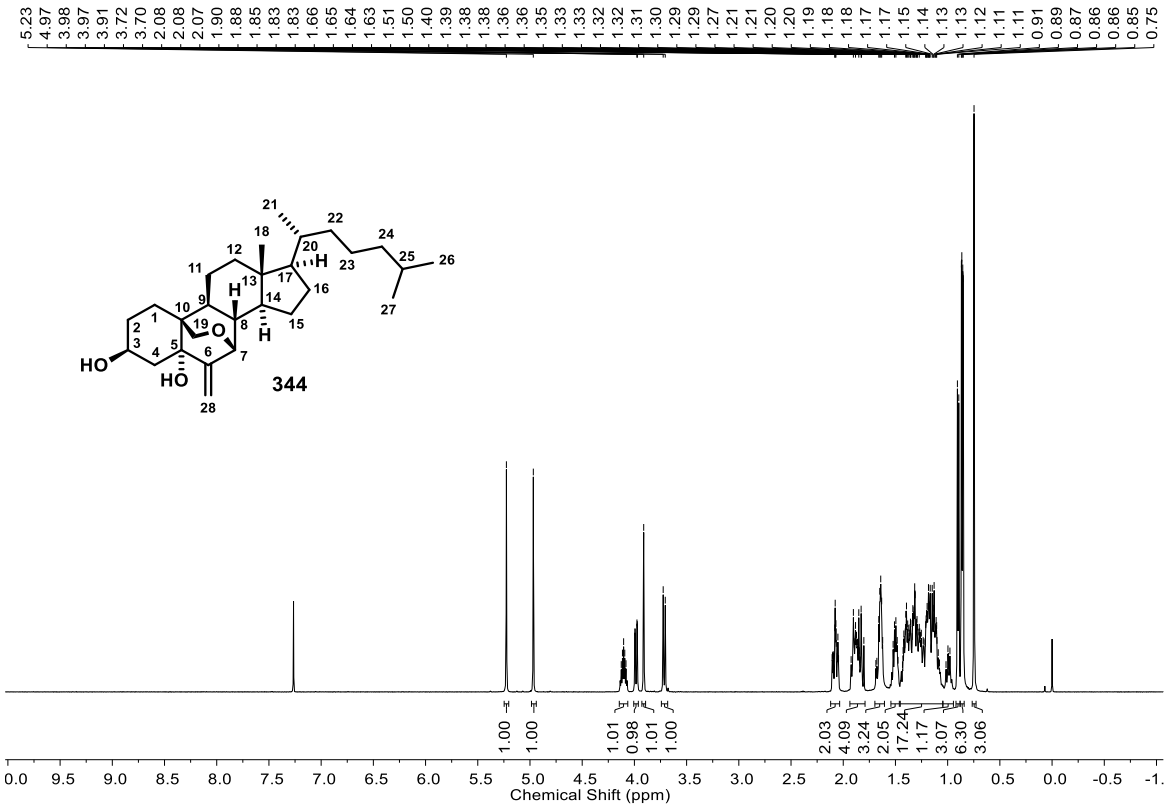


Figure 191: ^{1}H NMR (500 MHz, $CDCl_3$) of 7β,19-epoxy-6-methylene-cholest-3β,5α-diol (**344**).

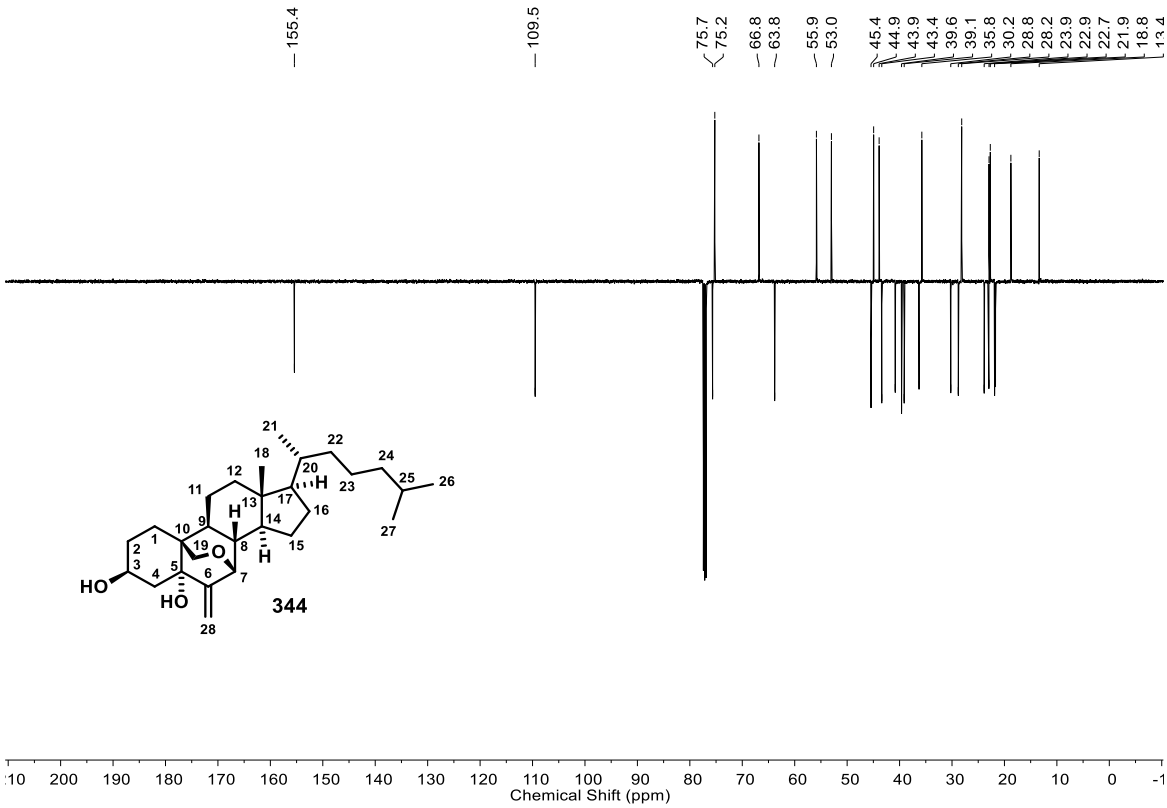


Figure 192: ^{13}C NMR (126 MHz, $CDCl_3$) of 7β,19-epoxy-6-methylene-cholest-3β,5α-diol (**344**).

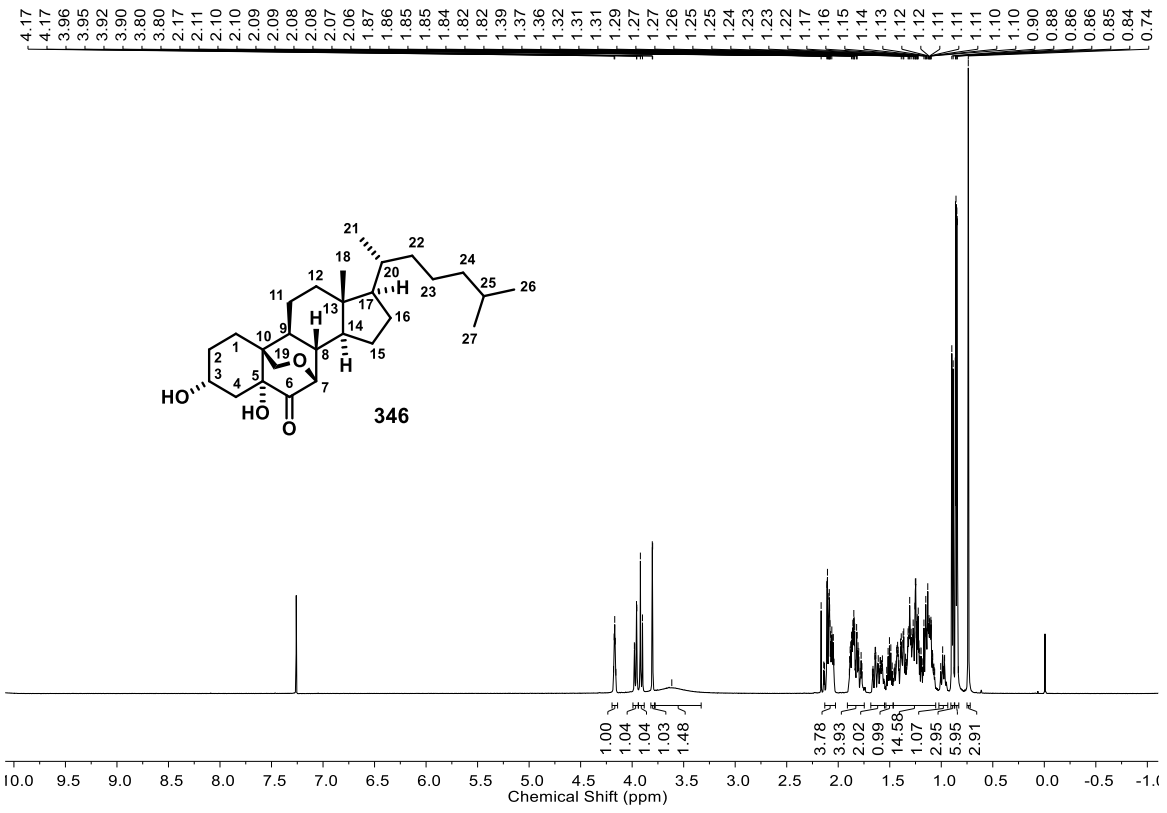


Figure 193: ^{1}H NMR (500 MHz, $CDCl_3$) of 3α,5α-dihydroxy-7β,19-epoxy-cholestane-6-one (**346**).

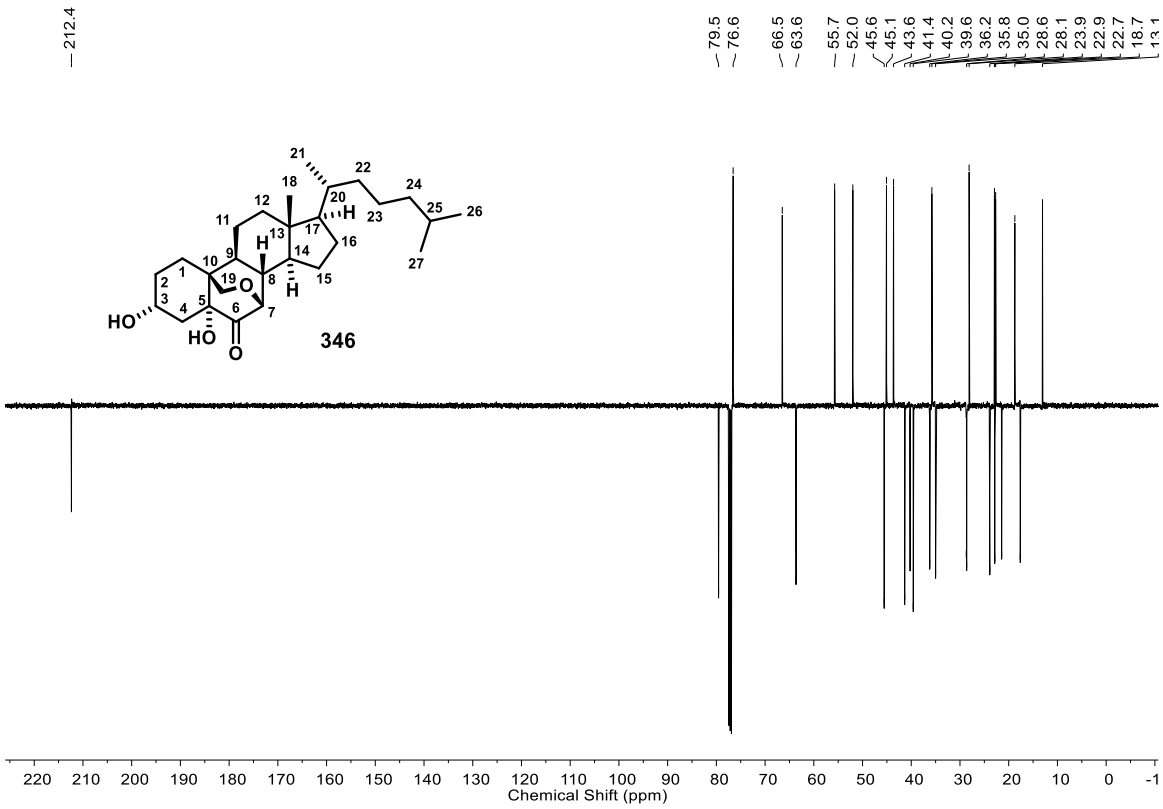


Figure 194: ^{13}C NMR (126 MHz, $CDCl_3$) of 3α,5α-dihydroxy-7β,19-epoxy-cholestane-6-one (**346**).

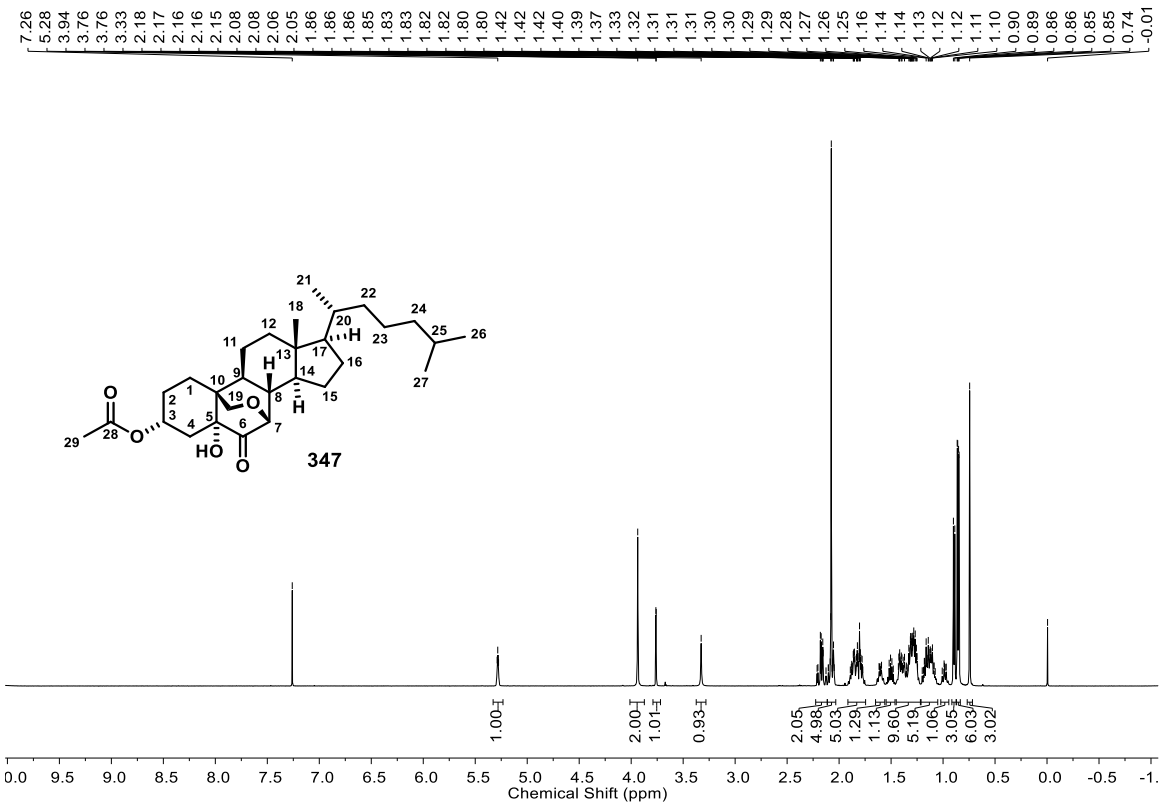


Figure 195: ^{1}H NMR (500 MHz, $CDCl_3$) of 3α-acetoxy-5α-hydroxy-7β,19-epoxy-cholestane-6-one (**347**).

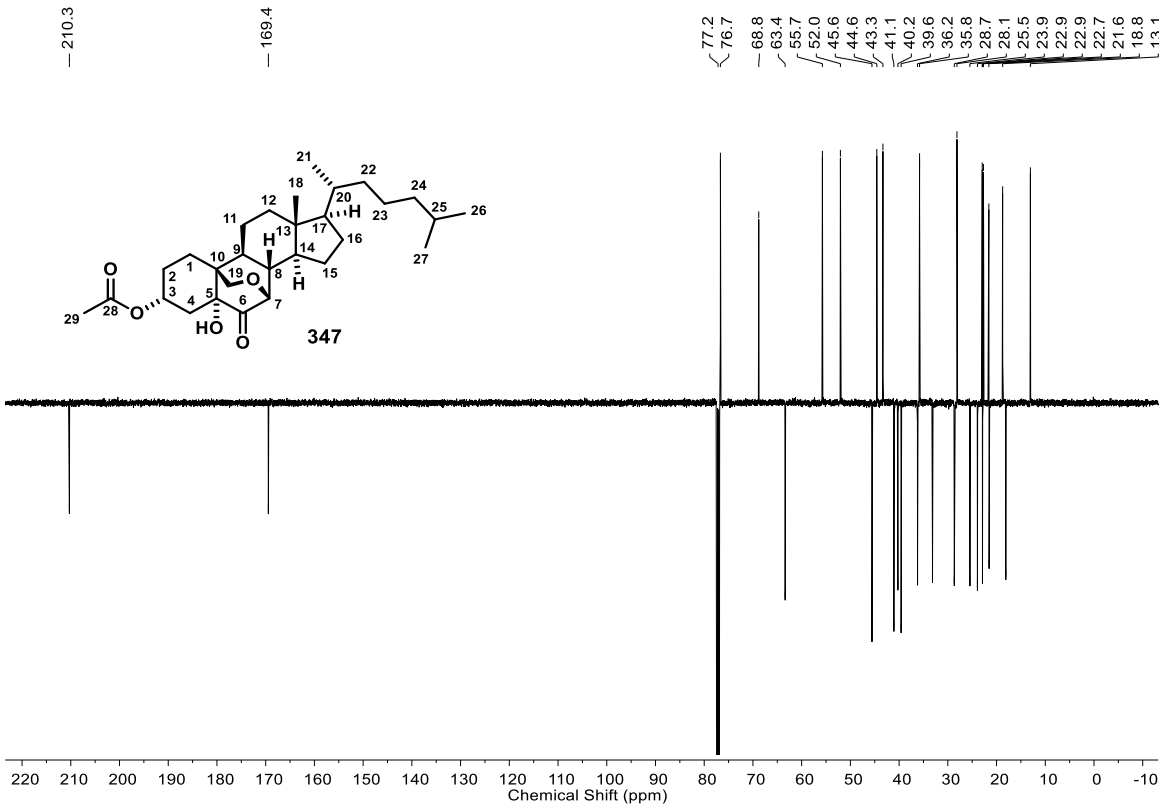


Figure 196: ^{13}C NMR (126 MHz, $CDCl_3$) of 3α-acetoxy-5α-hydroxy-7β,19-epoxy-cholestane-6-one (**347**).

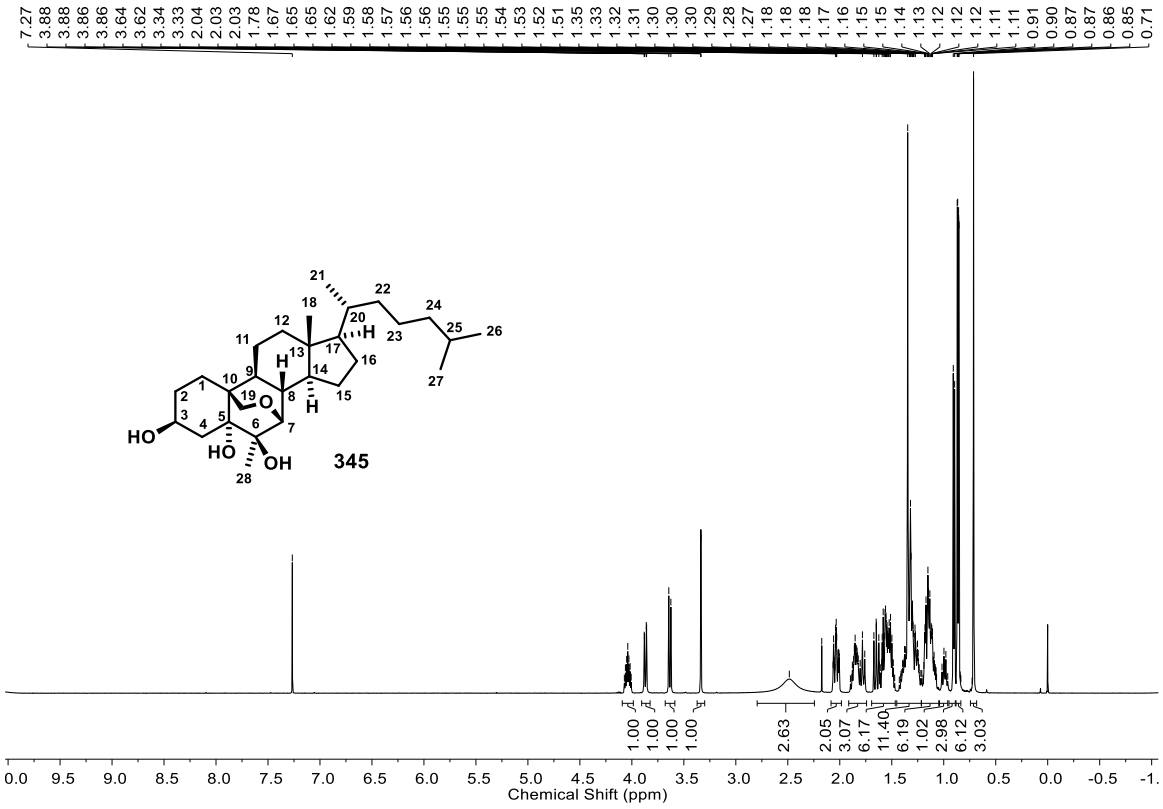


Figure 197: ^{1}H NMR (500 MHz, $CDCl_3$) of 7β,19-epoxy-6α-methylcholestane-3β-5α,6β-triol (**345**).

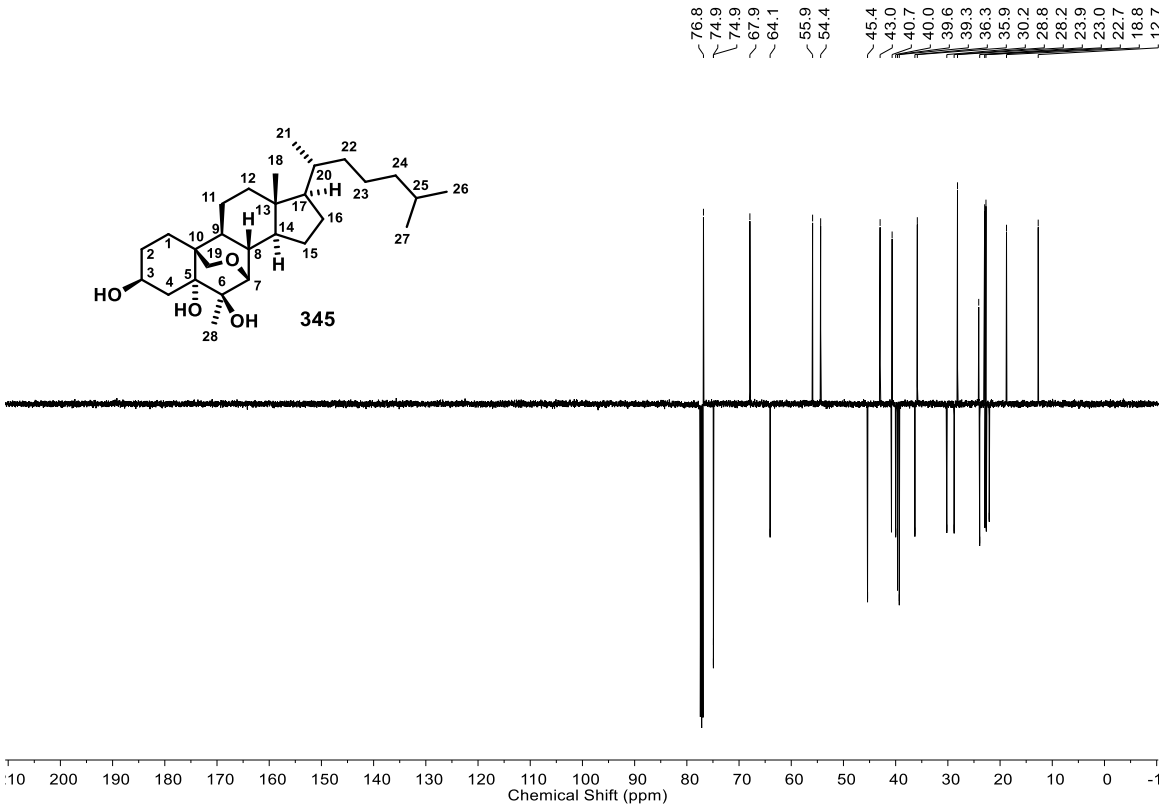


Figure 198: ^{13}C NMR (126 MHz, $CDCl_3$) of 7β,19-epoxy-6α-methylcholestane-3β-5α,6β-triol (**345**).

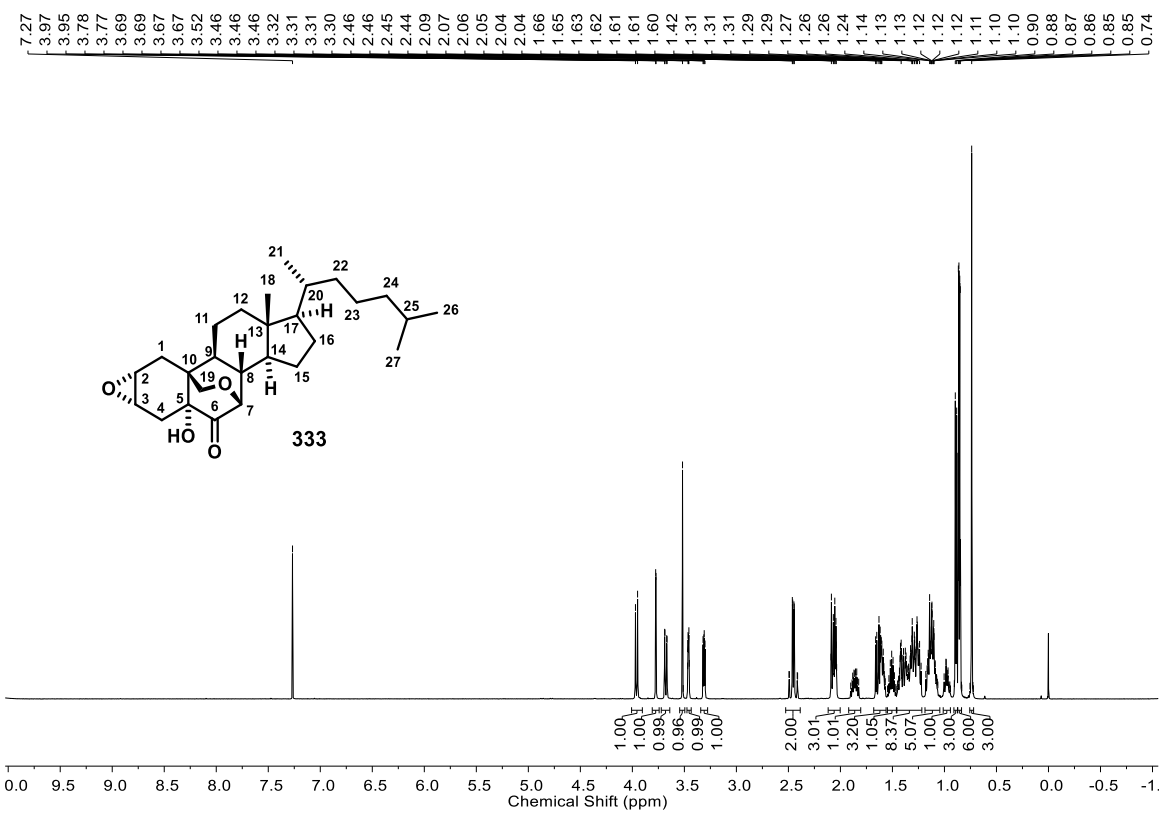


Figure 199: ^{1}H NMR (500 MHz, $CDCl_3$) of 5***α***-Hydroxy-2,3-7***β***,19-diepoxy-cholestane-6-one (**333**).

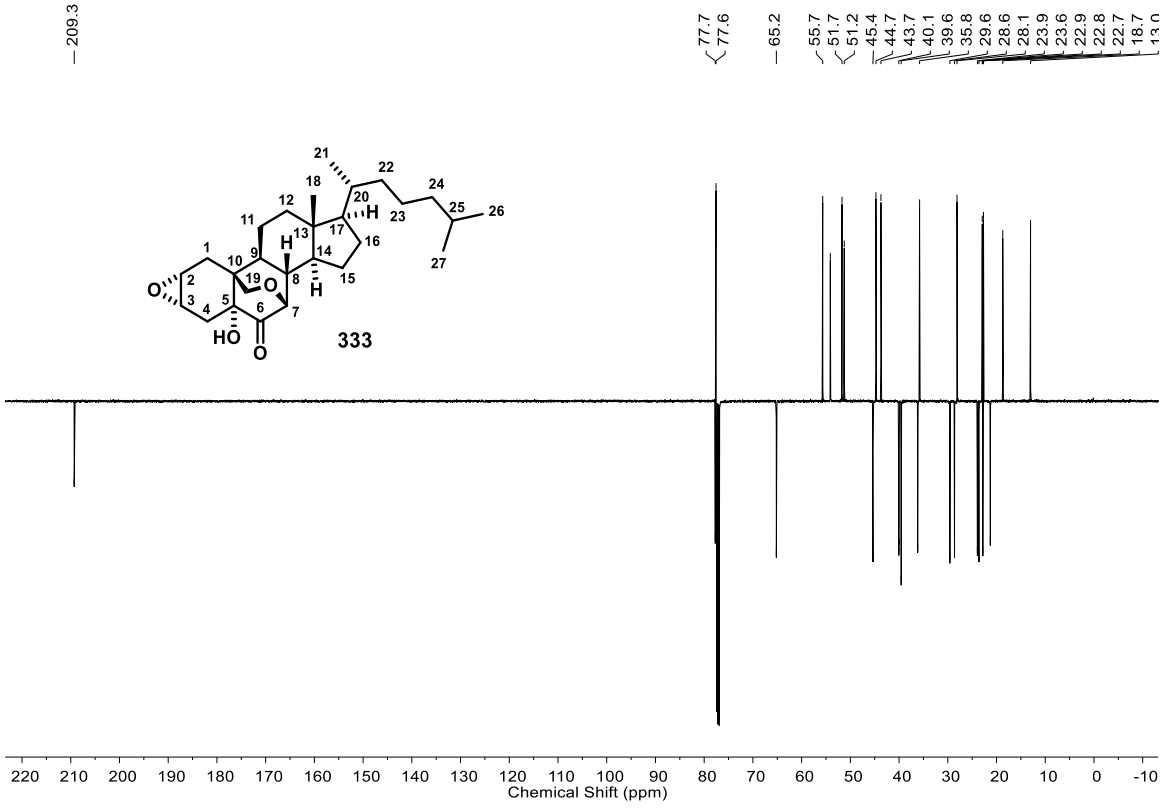


Figure 200: ^{13}C NMR (126 MHz, $CDCl_3$) of 5***α***-Hydroxy-2,3-7***β***,19-diepoxy-cholestane-6-one (**333**).

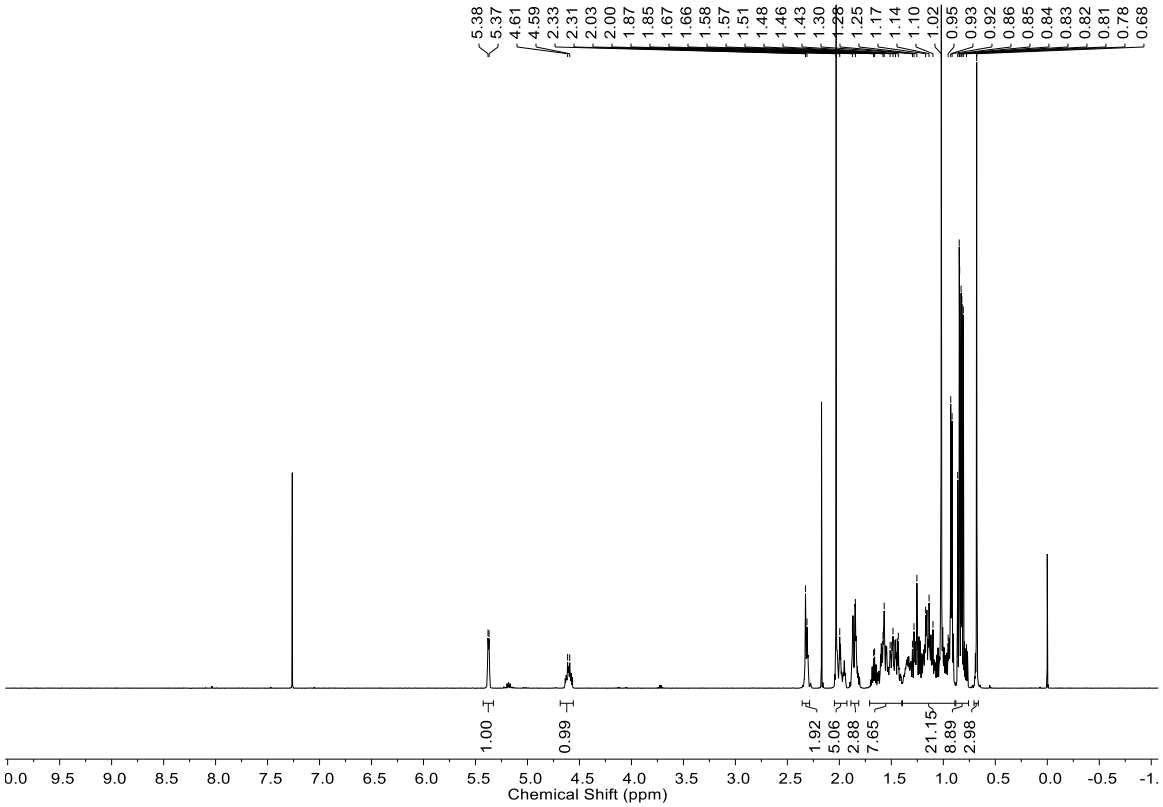


Figure 201: ^{1}H NMR (500 MHz, $CDCl_3$) of β-Sitosteryl acetate (**336**).

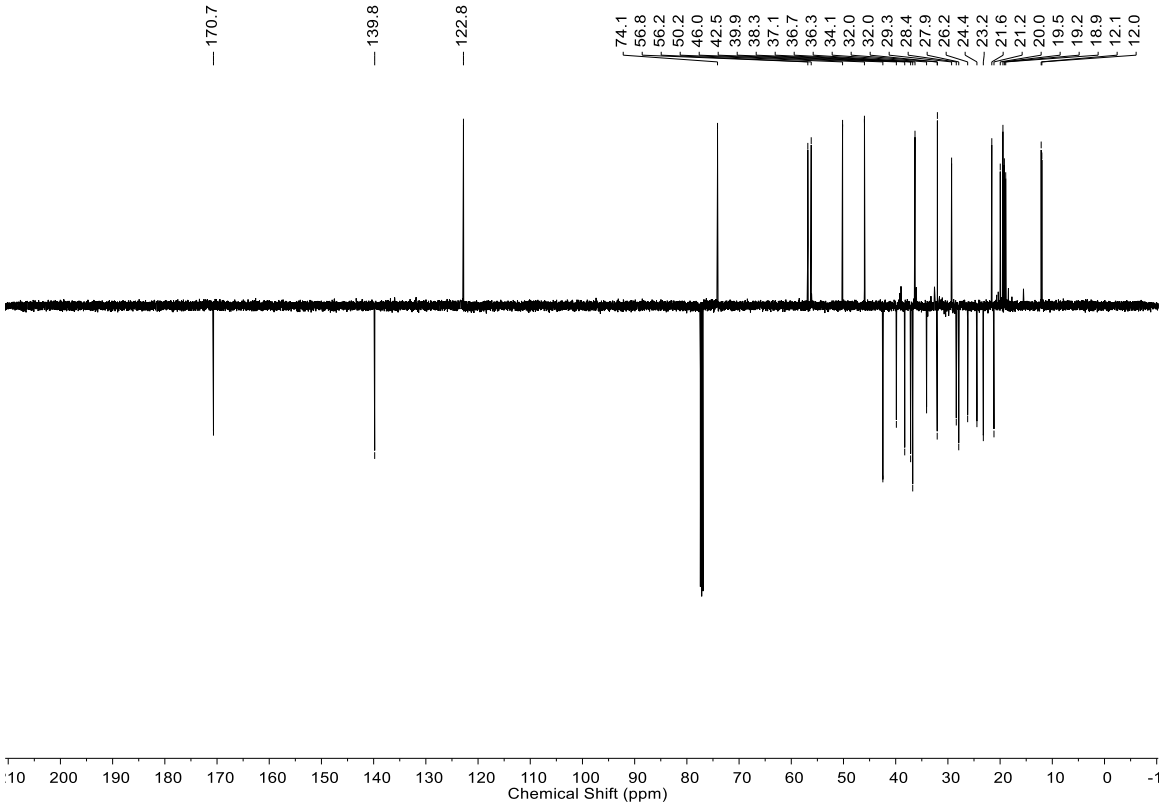


Figure 202: ^{13}C NMR (126 MHz, $CDCl_3$) of β-Sitosteryl acetate (**336**).

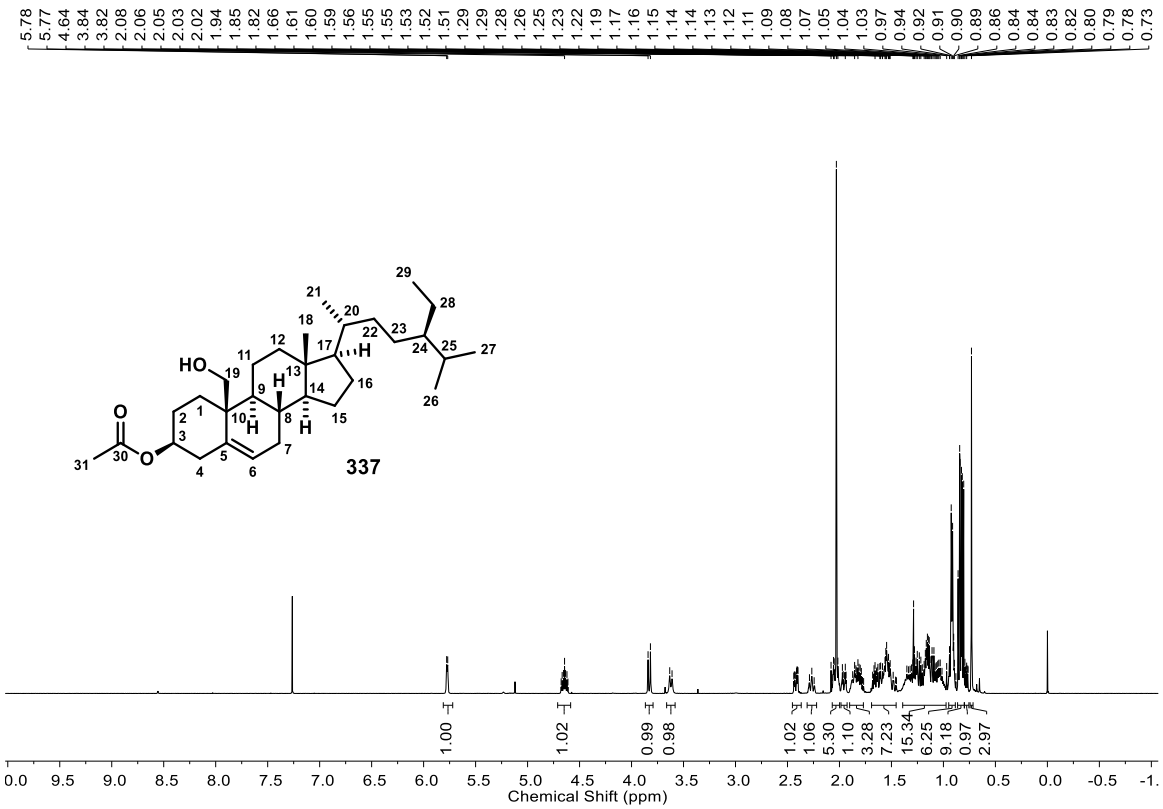


Figure 203: ^{1}H NMR (500 MHz, $CDCl_3$) of 3$\boldsymbol{\beta}$-acetoxy-19-hydroxy-stigmast-Δ^5-ene (**337**).

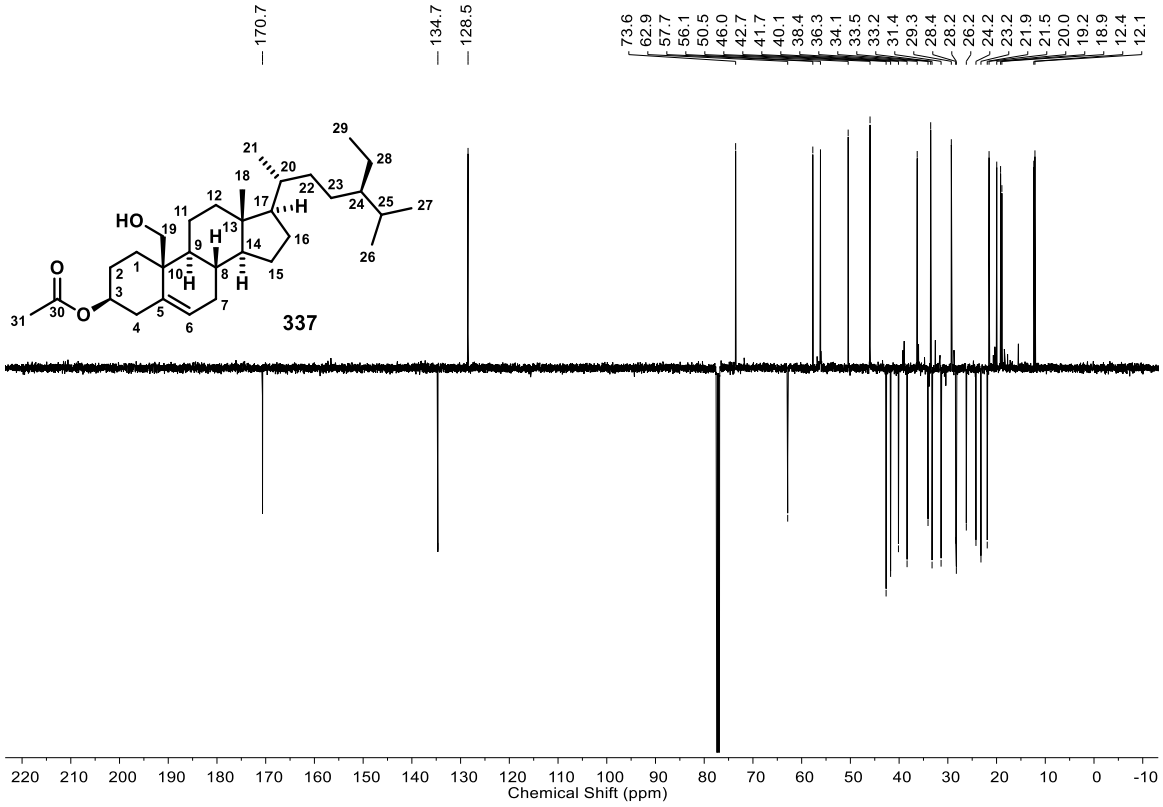


Figure 204: ^{13}C NMR (126 MHz, $CDCl_3$) of 3$\boldsymbol{\beta}$-acetoxy-19-hydroxy-stigmast-Δ^5-ene (**337**).

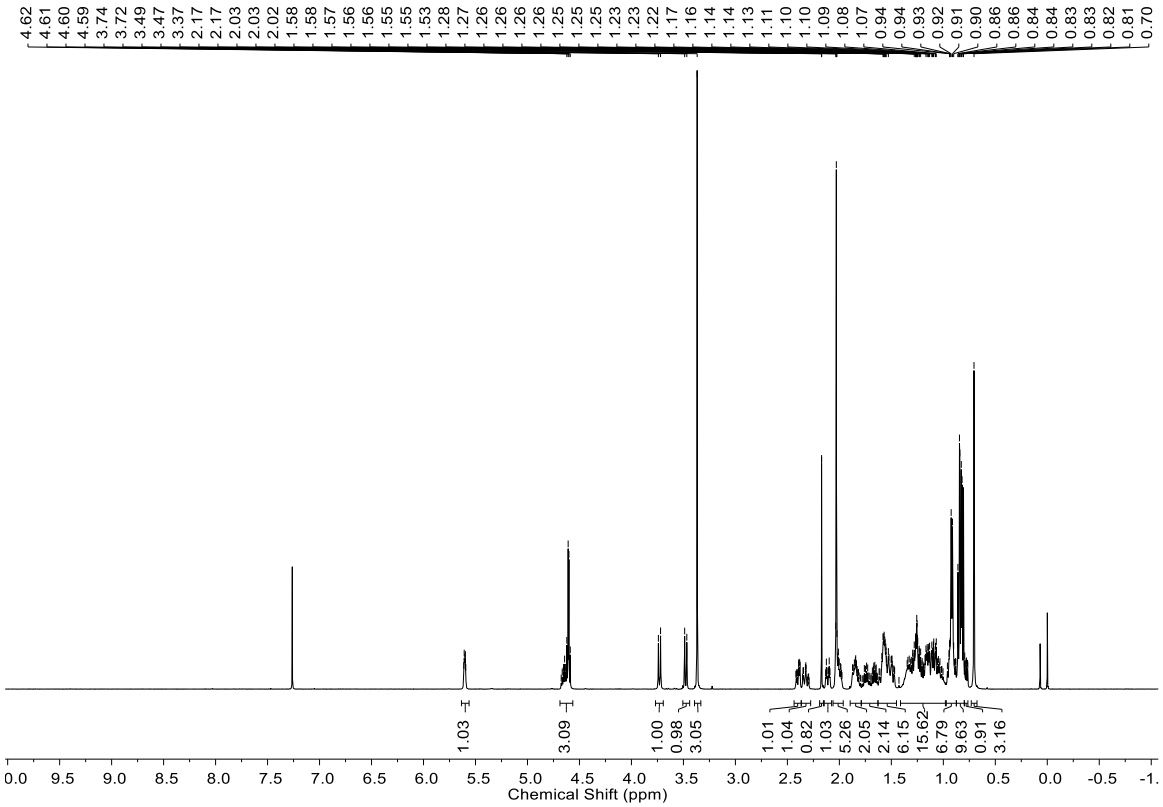


Figure 205: ^{1}H NMR (500 MHz, $CDCl_3$) of 3$\boldsymbol{\beta}$-acetoxy-19-(methoxymethyloxy)-stigmast-Δ^5-ene (**338**).

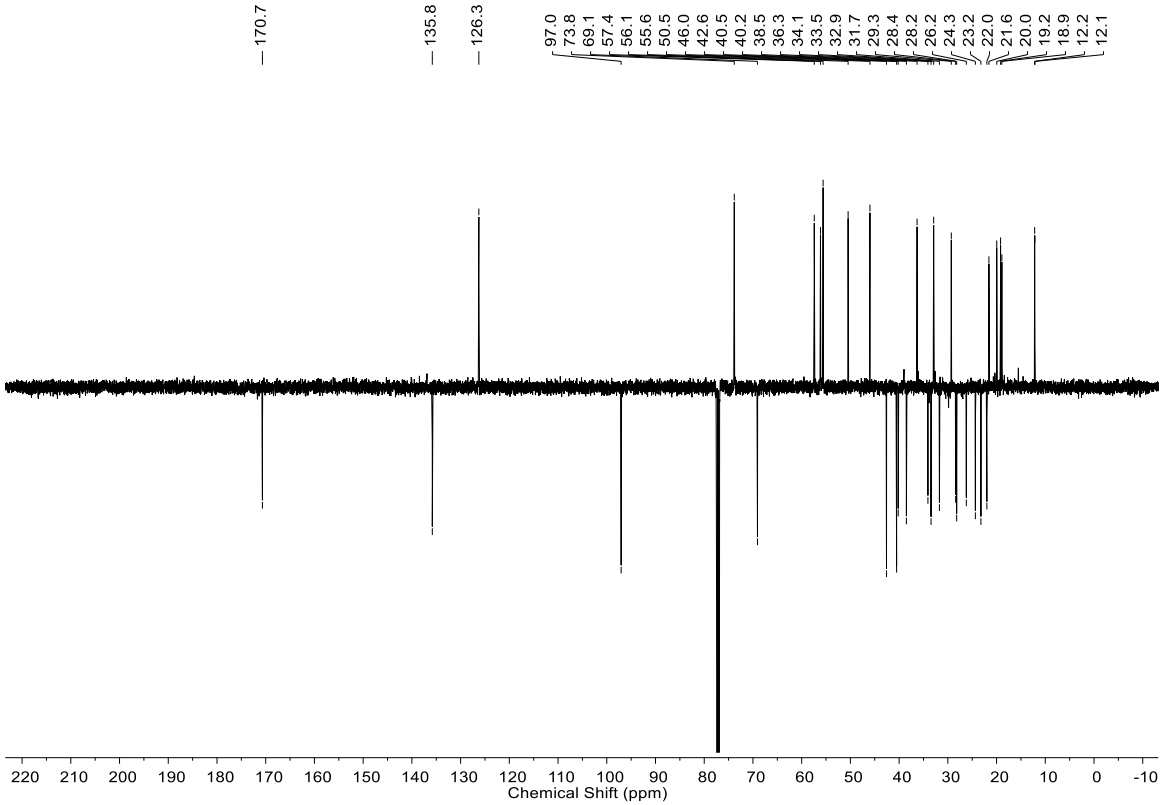


Figure 206: ^{13}C NMR (126 MHz, $CDCl_3$) of 3$\boldsymbol{\beta}$-acetoxy-19-(methoxymethyloxy)-stigmast-Δ^5-ene (**338**).

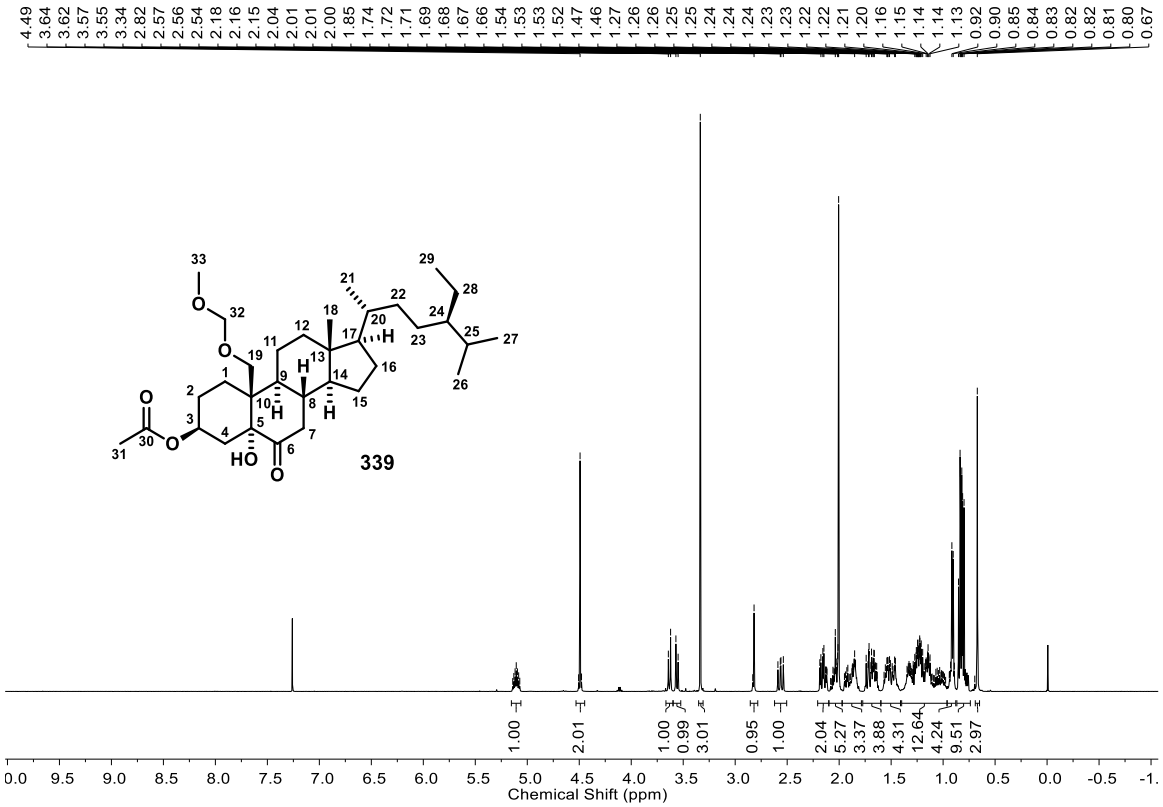


Figure 207: ^{1}H NMR (500 MHz, $CDCl_3$) of 3***β***-acetoxy-5*α*-hydroxy-19-(methoxymethyloxy)-sitgmastane-6-one (**339**).

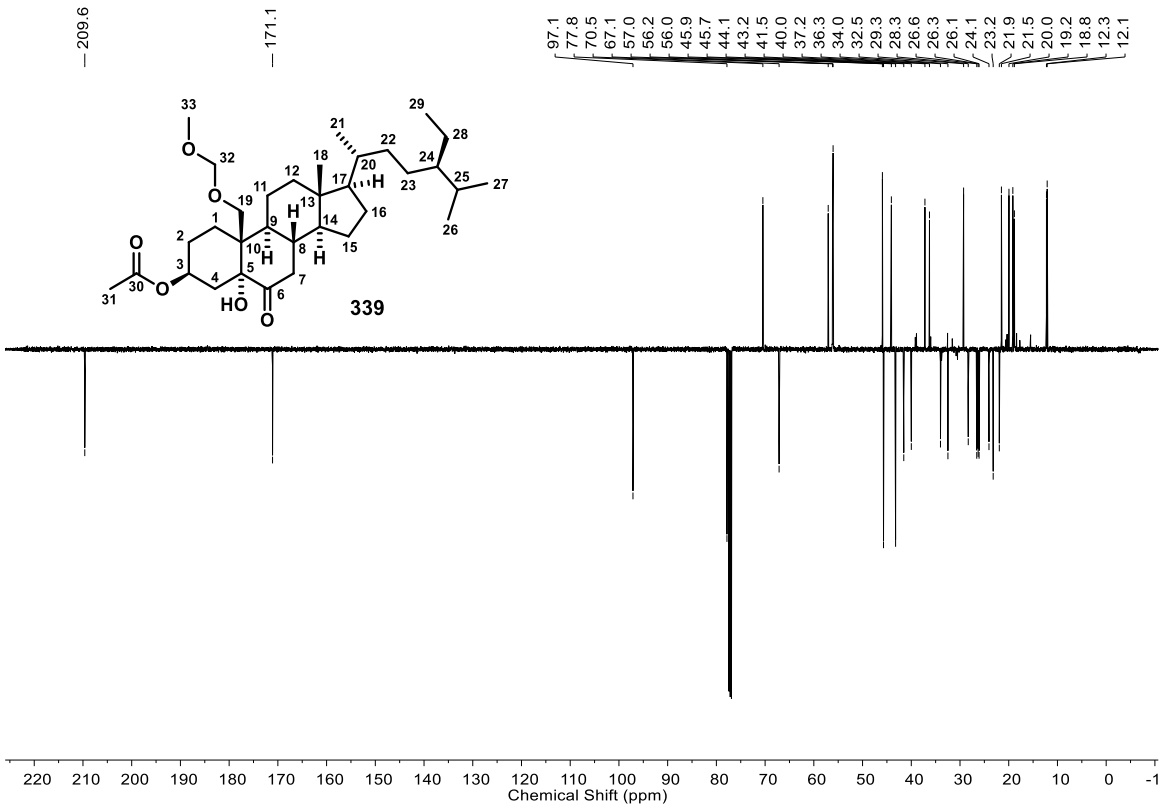


Figure 208: ^{13}C NMR (126 MHz, $CDCl_3$) of 3***β***-acetoxy-5*α*-hydroxy-19-(methoxymethyloxy)-sitgmastane-6-one (**339**).

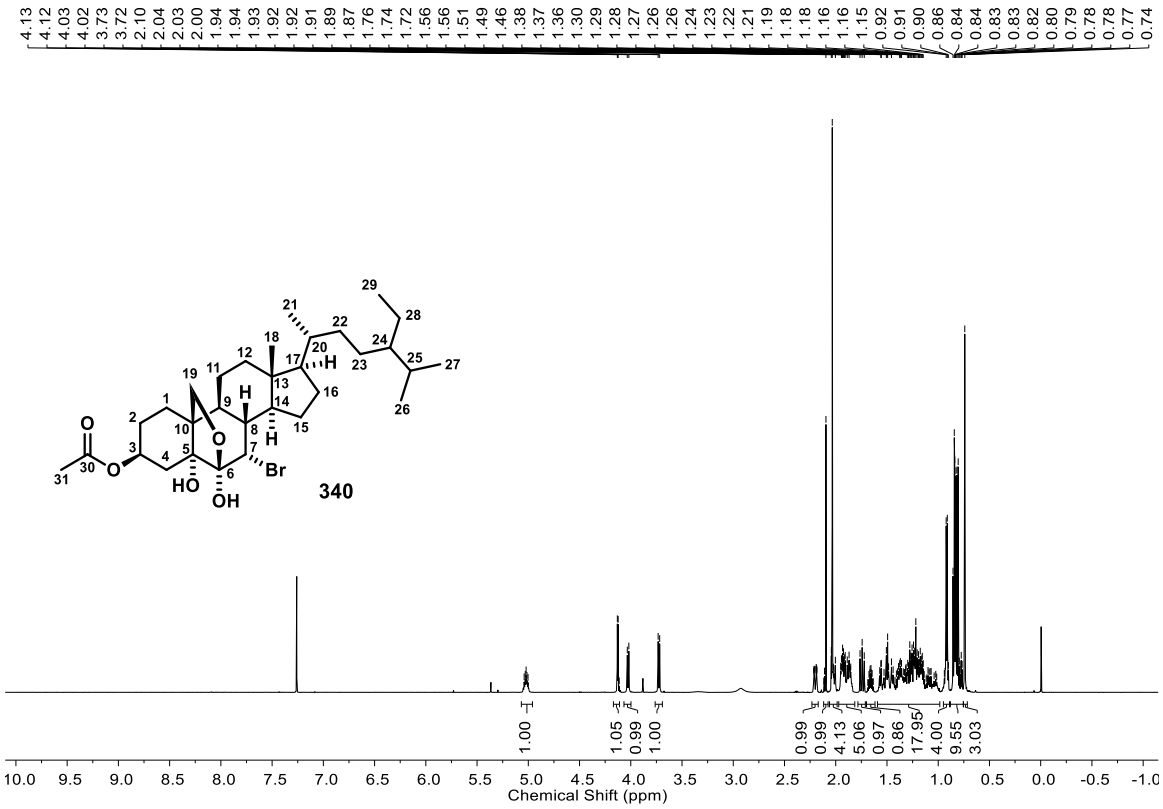


Figure 209: ^{1}H NMR (500 MHz, $CDCl_3$) of 3***β***-acetoxy-7*α*-bromo-6*β*,19-epoxy-stigmastane-5*α*,6*α*-diol (**340**).

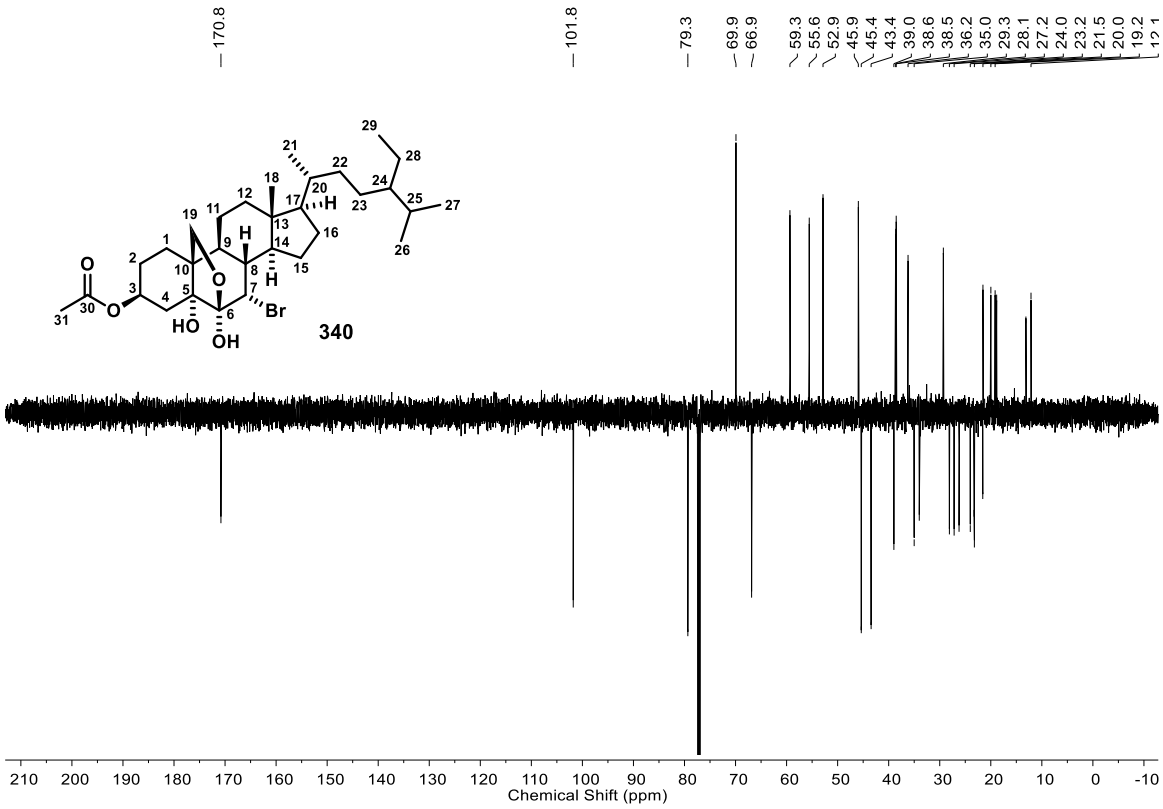


Figure 210: ^{13}C NMR (126 MHz, $CDCl_3$) of 3***β***-acetoxy-7*α*-bromo-6*β*,19-epoxy-stigmastane-5*α*,6*α*-diol (**340**).

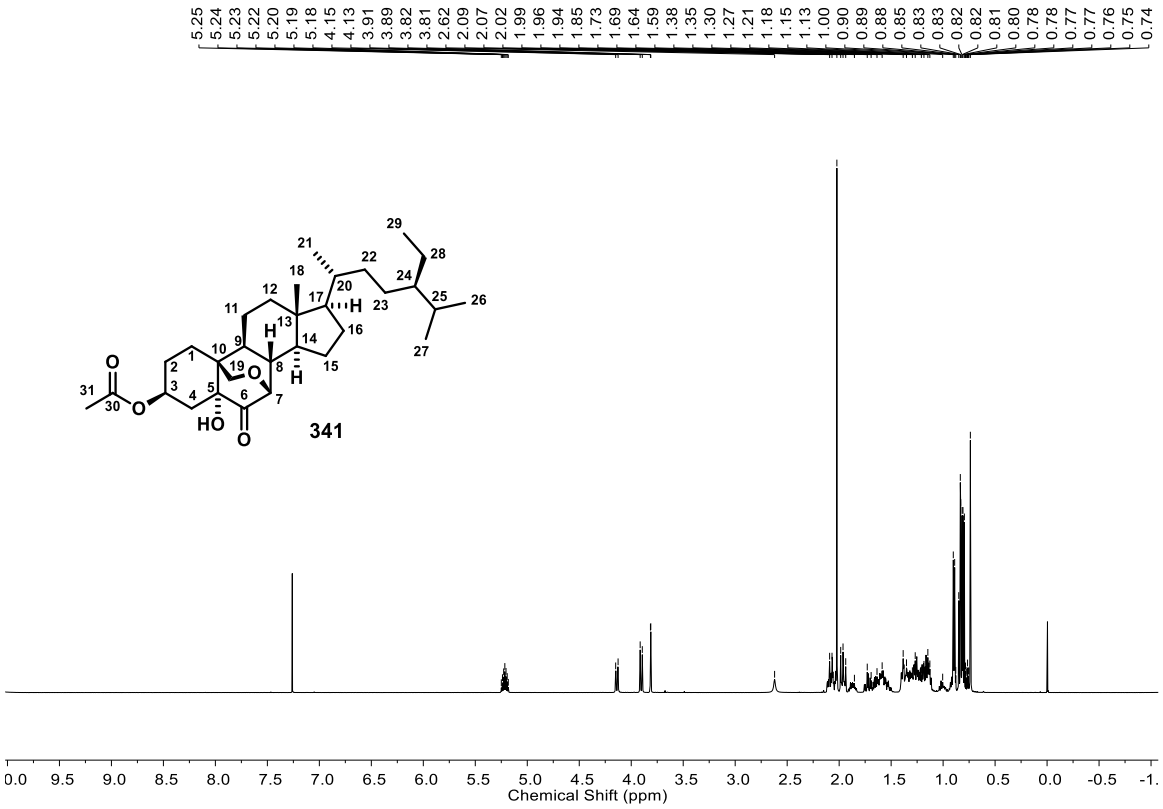


Figure 211: ^{1}H NMR (500 MHz, $CDCl_3$) of 3**β**-acetoxy-5α-hydroxy-7β,19-epoxy-stigmastane-6-one (**341**).

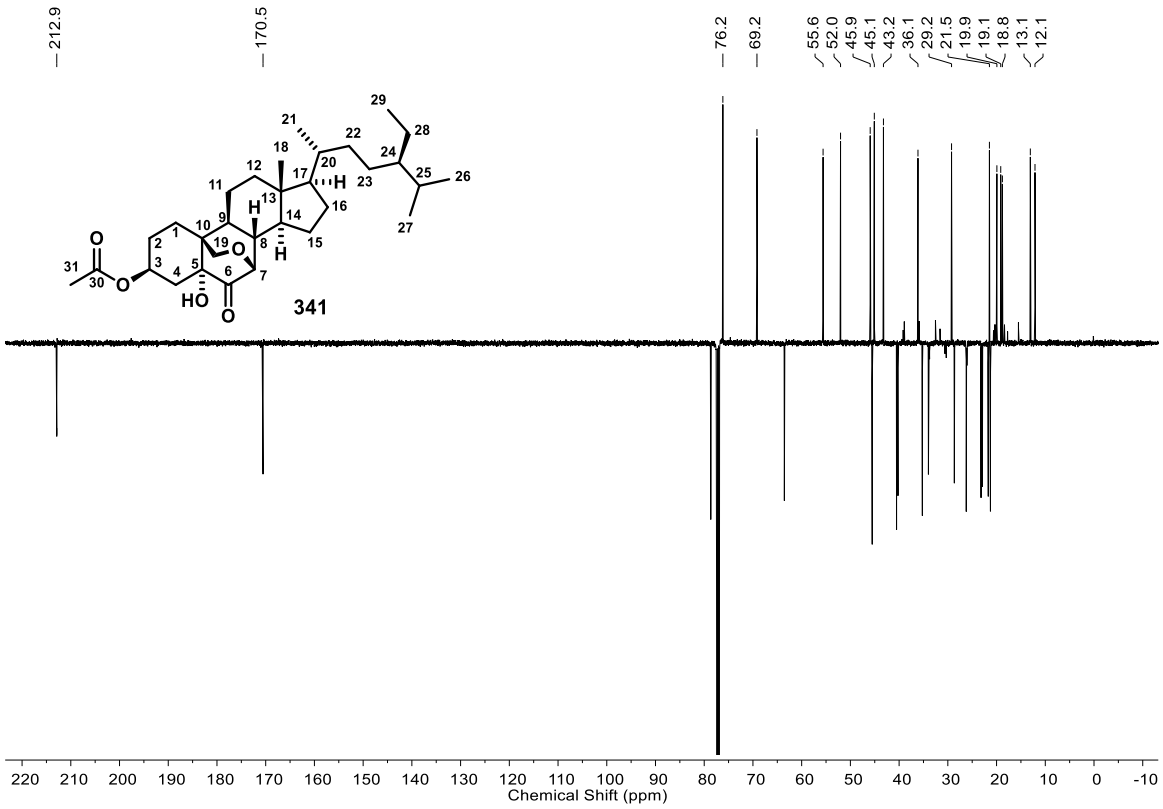


Figure 212: ^{13}C NMR (126 MHz, $CDCl_3$) of 3**β**-acetoxy-5α-hydroxy-7β,19-epoxy-stigmastane-6-one (**341**).

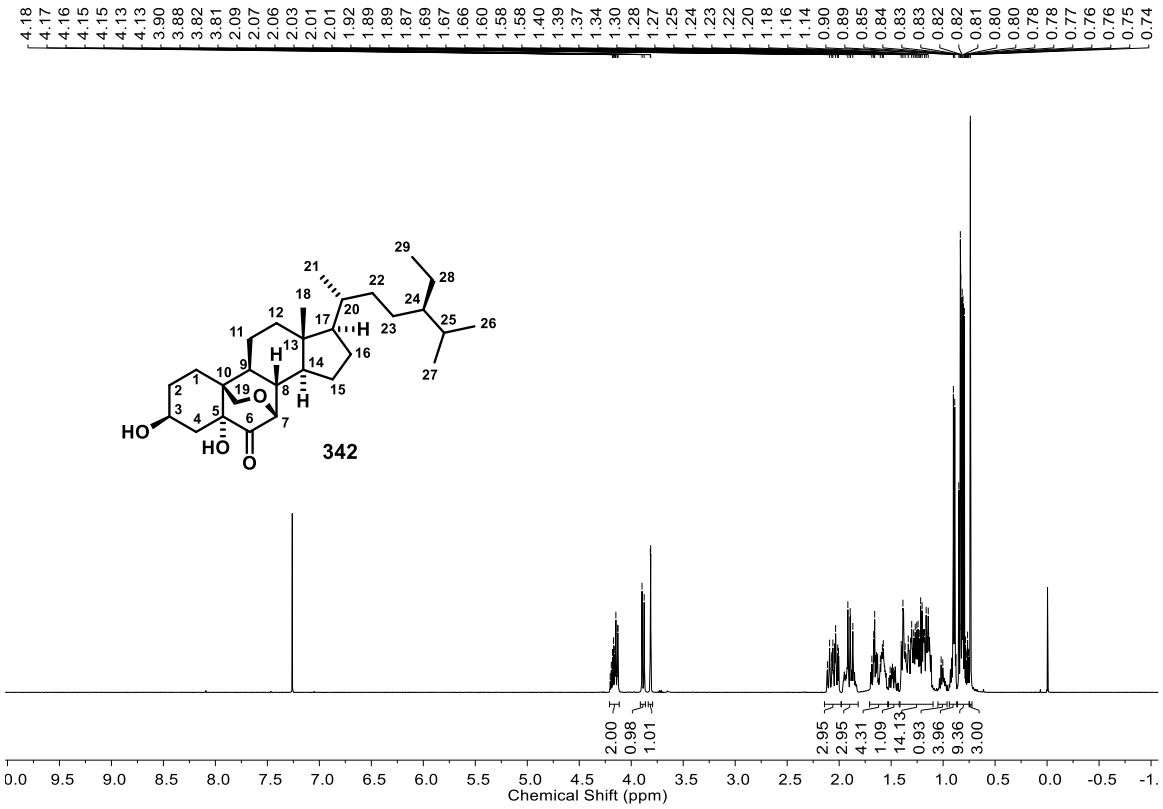


Figure 213: ^{1}H NMR (500 MHz, $CDCl_3$) of 3*β*,5*α*-Dihydroxy-7*β*,19-epoxy-stigmastane-6-one (**342**).

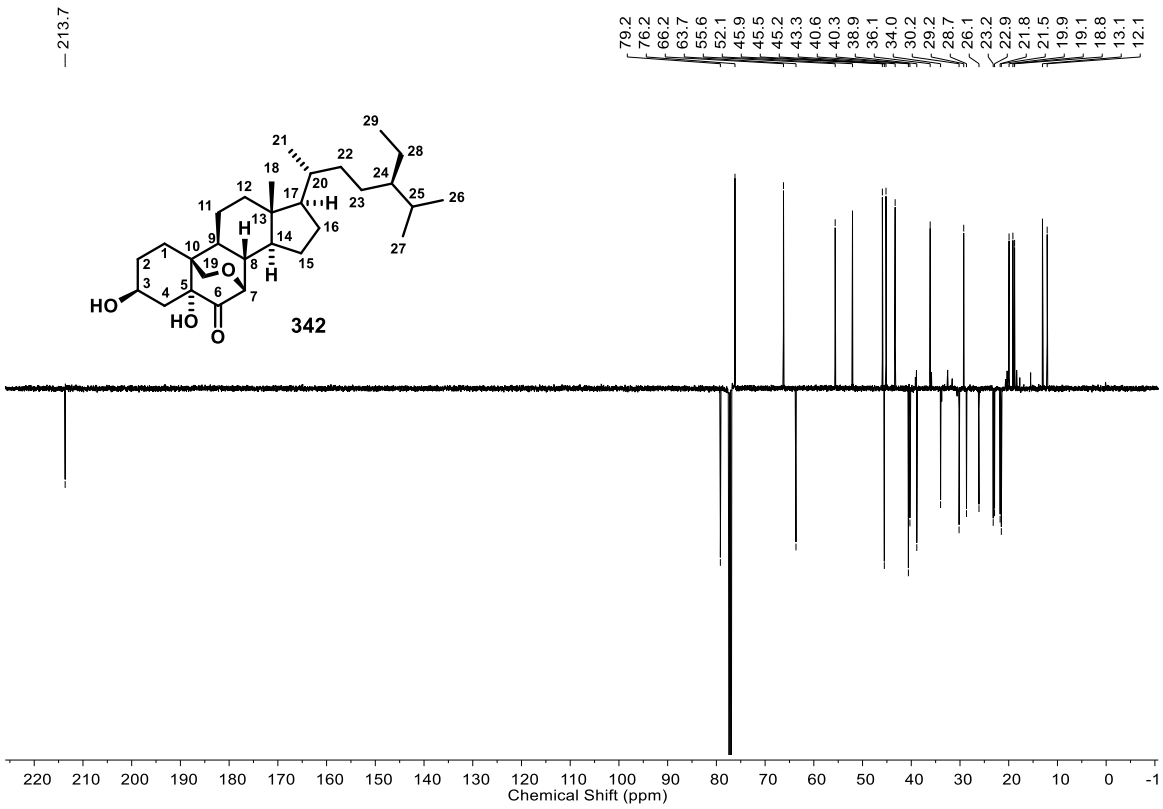
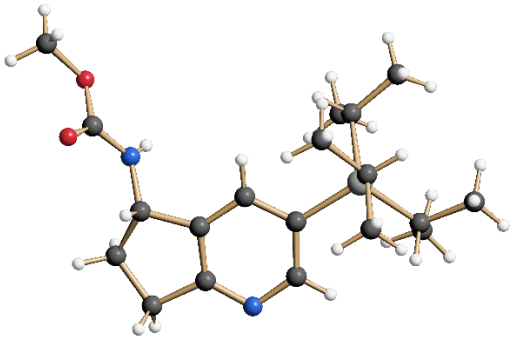


Figure 214: ^{13}C NMR (126 MHz, $CDCl_3$) of 3*β*,5*α*-Dihydroxy-7*β*,19-epoxy-stigmastane-6-one (**342**).

5.4. X-Ray Crystallography



Empirical formula	C20 H36 N2 O3 Si	
Moiety formula	C19 H32 N2 O2 Si, C H4 O	
Formula weight	380.60	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 11.4592(6) Å	α= 105.819(2)°.
	b = 13.3808(8) Å	β= 95.868(2)°.
	c = 16.3369(9) Å	γ = 111.653(2)°.
Volume	2181.7(2) $Å^3$	
Z	4	
Density (calculated)	1.159 Mg/m^3	
Absorption coefficient	1.109 mm^{-1}	
F(000)	832	
Crystal size	0.100 x 0.100 x 0.060 mm^3	
Theta range for data collection	2.886 to 72.118°.	
Index ranges	-12<=h<=14, -16<=k<=16, -20<=l<=20	
Reflections collected	97764	
Independent reflections	8588 [R(int) = 0.0422]	
Completeness to theta = 67.679°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7536 and 0.6576	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8588 / 0 / 501	
Goodness-of-fit on F^2	1.037	
Final R indices [I>2sigma(I)]	R1 = 0.0332, wR2 = 0.0884	
R indices (all data)	R1 = 0.0342, wR2 = 0.0891	

Extinction coefficient	n/a
Largest diff. peak and hole	0.595 and -0.210 e.Å^{-3}

5.5. Statutory Declaration

Erklärung zur Dissertationgemäß der Promotionsordnung vom 12. März 2020:

„Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertation selbstständig und ohne die Benutzung anderer als der angegebenen Hilfsmittel und Literatur angefertigt habe. Alle Stellen, die wörtlich oder sinngemäß aus veröffentlichten und nicht veröffentlichten Werken dem Wortlaut oder dem Sinn nach entnommen wurden, sind als solche kenntlich gemacht. Ich versichere an Eides statt, dass diese Dissertation noch keiner anderen Fakultät oder Universität zur Prüfung vorgelegen hat; dass sie - abgesehen von unten angegebenen Teilpublikationen und eingebundenen Artikeln und Manuskripten - noch nicht veröffentlicht worden ist sowie, dass ich eine Veröffentlichung der Dissertation vor Abschluss der Promotion nicht ohne Genehmigung des Promotionsausschusses vornehmen werde. Die Bestimmungen dieser Ordnung sind mir bekannt. Darüber hinaus erkläre ich hiermit, dass ich die Ordnung zur Sicherung guter wissenschaftlicher Praxis und zum Umgang mit wissenschaftlichem Fehlverhalten der Universität zu Köln gelesen und sie bei der Durchführung der Dissertation zugrundeliegenden Arbeiten und der schriftlich verfassten Dissertation beachtet habe und verpflichte mich hiermit, die dort genannten Vorgaben bei allen wissenschaftlichen Tätigkeiten zu beachten und umzusetzen. Ich versichere, dass die eingereichte elektronische Fassung der eingereichten Druckfassung vollständig entspricht."

Teilpublikationen:
-Ö. Taspinar, T. Wilczek, J. Erver, M. Breugst, J.-M. Neudörfl, H.-G. Schmalz, *Chem. Eur. J.* **2020**, *26*, 4256-4260.
-Europäische Patentanmeldung: EP21217028.6 – Epoxysteroide.

Datum, Name und Unterschrift