ENANTIOSELECTIVE TOTAL SYNTHESIS OF MARINE MERODITERPENES WITH ANTI-INFLAMMATORY AND ANTI-TUMOR ACTIVITY

Inaugural-Dissertation

zur

Erlangung des Doktorgrades

der Mathematisch-Naturwissenschaftlichen Fakultät der

Universität zu Köln

vorgelegt von

Isabelle Grimm

aus Birkenfeld

Köln, 2023

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

Berichterstatter:	Prof. Dr. Hans-Günther Schmalz Prof.'in Dr. Stephanie Kath-Schorr
Vorsitzender:	Prof. Dr. Axel Klein
Beisitzer:	PD Dr. Dirk Blunk
Tag der Disputation:	14. Juli 2023

„It was the best of times, it was the worst of times. “

Charles Dickens

ABSTRACT

During the past decade an increasing number of meroterpenoids have emerged from marine organism that became the main source for interesting, biologically active natural products. Five compounds, dysiherbols A-E, were isolated from marine sponges of genus *Dysidea* and shown to exhibit cytotoxicity, NF-κB inhibitory and anti-inflammatory activities. Their structures were proposed to display a tetracyclic 6/6/5/6 carbon skeleton with five adjacent stereocenters.

This work comprises the first enantioselective total synthesis of dysiherbol A together with the revision of its absolute configuration and its constitution, that was proven to be pentacyclic. Dysiherbol A was synthesized over 12 steps via an enantioselective Cu-catalyzed 1,4-addition/ enolate trapping as asymmetric opening step and a gold-catalyzed twofold cyclization as key step to construct the tetracyclic carbon skeleton. In the final step an acidic-mediated deprotection/ cyclopropane opening occurred under oxy-cyclization to deliver the pentacyclic target molecule. Comparison of both synthesized enantiomers in biological studies revealed naturally occurring (+)-dysiherbol A to show superior apoptosis-inducing potency in lymphoma and leukemia cell lines, even overcoming resistances to conventional cytostatics. Thus, this work highlights the role of total synthesis for structural elucidation and pharmacological investigation.

Furthermore, contributions to the enantioselective total syntheses of dysiherbol B, C and E are reported from common intermediates. (+)-Dysiherbol E was synthesized via carbonylative cross coupling, proton-induced formation of the ether bridge and final ozonolysis.

Moreover, the gold-catalyzed twofold cyclization was further investigated, and the observations support the proposed mechanism via an allylic cation intermediate.

KURZFASSUNG

Im letzten Jahrzehnt wurde eine zunehmende Anzahl von Meroterpenen aus marinen Organismen gewonnen, die eine Hauptquelle für interessante, biologisch aktive Naturstoffe darstellen. Fünf Verbindungen, Dysiherbol A-E, die aus Meeresschwämmen der Gattung *Dysidea* isoliert wurden, zeigten zytotoxische, NF-κB-hemmende und entzündungshemmende Eigenschaften. Für die Strukturen wurde ursprünglich ein tetracyclisches 6/6/5/6 Ringsystem mit fünf benachbarten Stereozentren vorgeschlagen.

Diese Arbeit beschreibt die erste enantioselektive Totalsynthese von Dysiherbol A zusammen mit der Revision seiner absoluten Konfiguration und seiner Konstitution, die sich als pentacyclisch erwiesen hat. Dysiherbol A wurde in 12 Schritten, über eine enantioselektive Cu-katalysierte 1,4-Addition unter Abfangen des Enolats als asymmetrischen Einstieg in die Synthese und eine Gold-katalysierte zweifache Zyklisierung als Schlüsselschritt zum Aufbau des tetrazyklischen Kohlenstoffgerüsts synthetisiert. Im letzter Schritt lieferte eine säure-vermittelte Entschützung/ Cyclopropan-Öffnung unter Oxycyclisierung des resultierenden Kations das pentacyclische Zielmolekül. Der Vergleich der beiden synthetisierten Enantiomere in biologischen Studien ergab, dass das natürlich vorkommende (+)-Dysiherbol A eine überlegene Apoptose-induzierende Wirkung in Lymphom- und Leukämie-Zelllinien, sowie Resistenzüberwindung gegenüber herkömmlichen Zytostatika aufweist. Damit unterstreicht diese Arbeit die Bedeutung der Totalsynthese für sowohl Strukturaufklärung als auch pharmakologische Untersuchung.

Darüber hinaus wird über Beiträge zu den enantioselektiven Totalsynthesen von Dysiherbol B, C und E über gemeinsame Intermediate berichtet. (+)-Dysiherbol E konnte über carbonylierende Kreuzkupplung, protoneninduzierte Bildung der Etherbrücke und abschließende Ozonolyse synthetisiert werden.

Darüber hinaus wurde die Gold-katalysierte Zweifach-Cyclisierung weiter untersucht, wobei die Beobachtungen den vorgeschlagenen Mechanismus über ein Allylkation unterstützen.

VORWORT

An dieser Stelle möchte ich mich bedanken und anfangen möchte ich mit dem Mann, durch dessen Unterstützung ich diese Arbeit trotz widriger Umstände anfertigen konnte. Ich danke Prof. Schmalz von Herzen für ganz viel Verständnis und Rückendeckung. Ich hätte mir keinen besseren Doktorvater wünschen können.

Frau Prof.'in Kath-Schorr möchte ich ganz herzlich für die Zweitbetreuung während meiner Promotion danken und darüber hinaus für die Übernahme des Zweitgutachtens. Herrn Prof. Klein danke ich für die Übernahme des Prüfungsvorsitzes. Dirk danke ich für die Übernahme der Schriftführung und außerdem für die Unterstützung und die liebenswerte Art.

Außerdem danke ich natürlich allen Mitarbeitern des Instituts, ohne die wir alle aufgeschmissen wären. Anja Bitners (für Organisation im Arbeitskreis und die Korrekturen), Dr. Jörg-Neudörfl (für die Kristallstrukturen), Dietmar Rutsch, Andreas Wallraf, Andreas Adler (für die HPLC Messungen), Kathrin König, Daniela Naumann, Daniel Friedrich, Philipp Hegemann, Michael Neihs, Wen, Astrid Baum und vielen mehr.

Als Nächstes möchte ich gerne meinen Kollegen danken, ganz besonders der aktuellen und alten Besetzung von Labor 311. Es war mir eine Freude mit euch. Vor allem Pascal, beiden Julians und Finn möchte ich danken. Wie in jeder guten Familie kann man sich auch mal streiten, solange man am Ende wieder an einem Tisch zusammenkommt (am besten mit einem Glas Wein oder einem Kölsch). Ich danke außerdem Mira für die wundervolle Zusammenarbeit im Rahmen der Mediziner Oberassistenz (hier sei auch noch Judith Bruns gedankt!), sowie für deine Hilfe und dein Verständnis. Das werd ich dir nicht vergessen. Außerdem danke ich Pepe, einfach dafür, dass du immer da warst. An dieser Stelle auch danke an Niclas, du hast meine Promotionszeit durch dein Auftauchen extrem bereichert. Und danke an Martin, einfach danke.

Für das Korrekturlesen danke ich beiden Julians, Dominik, Bernhard, Alicia und Pepe.

Außerdem danke ich all meinen Praktikanten und Bacheloranden für die Beiträge zu dieser Arbeit. Hier besonders zu erwähnen sind Finn Dicke, Steffen Schwammborn und Julius Wiener.

Zu guter Letzt danke ich den Menschen, die mich durch die letzten drei Jahre getragen haben. Ohne euch würde ich gerade nicht hier sitzen und als letzten Akt einer Dissertation diese Danksagung schreiben. Mama und Papa, ihr habt mir alles mitgegeben, was ich brauche, um meinen Weg zu gehen, egal was kommt. Meiner ganzen Familie möchte ich danken, den Rückhalt und die Liebe, die ich durch euch erfahre, kann man sich nicht ausdenken. Außerdem danke ich meinen Freunden und wenn ich sage „Freunde" meine ich meine Köln-Familie, die über meine zehn Jahre hier stetig gewachsen ist, besonders in Punkto Zusammenhalt. Ohne euch wäre Alles Nichts. Ich würde euch gerne alle aufzählen, aber da ich nur eine Seite schreiben wollte erwähne ich hier stellvertretend (natürlich) Anna und Daria, die beiden Frauen, mit denen mir die Welt gehört!

TABLE OF CONTENTS

1 INTRODUCTION AND BACKGROUND

1.1 INTRODUCTION

NATURAL PRODUCTS AND THE ROLE OF TOTAL SYNTHESIS

The existence of all organisms is based on the transformation of a huge number of organic compounds utilizing a variety of enzyme-regulated chemical reactions. To ensure fecundity and survivability, carbohydrates, proteins, fats as well as nucleic acids are of crucial importance, thus considered "*primary* metabolites". When talking about natural products associated with pharmacologically interesting activity, we usually refer to "*secondary* metabolites". These compounds are specific to certain organisms, or groups of organisms and not directly involved in growth and reproduction but come with particular advantages in defense or well-being – although in most cases the exact function is yet unknown.[1]

Since ancient times, people all over the world have recognized and used the biological activities of natural products in traditional medicine. Different plant extracts already appear in the 3500 years old Ebers Papyrus, e.g. willow bark was used as a remedy for fever and pain.[2] In 1828, salicin, a chemical precursor of salicylic acid, was isolated from its extract.[3] It provided the basis for the development of acetylsalicylic acid (ASA), better known as Bayer's *Aspirin*.[1] There are many more examples of such "*Molecules that Changed the World*" through their discovery. Famous and valued for their outstanding medicinal properties are e.g. quinine (**1**, anti-malaria), penicillin G (**2**, antibiotic) and morphine (**3**, painkiller) (*Figure 1*).[4]

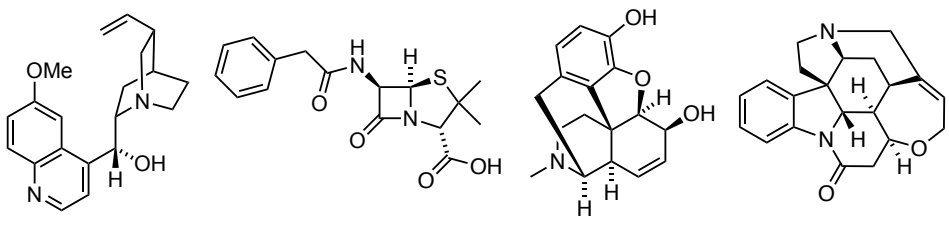


FIGURE 1 SELECTED NATURAL PRODUCTS TOGETHER WITH THEIR BIOLOGICAL ACTIVITY.[4]

Although the hypothesis of *Paracelsus* (1493-1541) describing the human body as 'chemical laboratory' already indicated the importance of single active components in traditional medicine, it took until the beginning of the 19th century for pure organic compounds to become the main interest in pharmacology. This was the time when the field of organic chemistry arose and the era of natural product-derived medical agents begun.[5] The elucidation of chemical structures is a critical aspect of both, as the knowledge of constitution, conformation and stereochemistry of bioactive agents is necessary. This process is not always easy, e.g. it took a century to decipher the architecture of morphine (**3**) and strychnine (**4**) after their isolation in the beginning of the 19th century. Even though great progress has been made in the field of analytical methods, the correct assignment of a newly discovered compound is still not trivial and misassignments are no exception. This is why structural revision is an significant part of natural product research and

the fifty different structures proposed for strychnine are an impressive example.[6] Many cases can be found in literature where total synthesis not only revealed errors but furthermore delivered the correct structures, emphasizing its importance in the context of structural elucidation.[6-7]

Total synthesis of natural products also played and still plays an major role in the development of organic chemistry by providing challenging synthetic targets and research opportunities.[8] One of the most famous examples are the *Woodward-Hoffmann* rules[9] discovered in the course of the synthesis of Vitamin B_{12},[10] for which *Hoffmann* and *Fukui* received the Nobel Prize in 1981.

The field of pharmacology has evolved tremendously in the last century. Between 1980 and 2006, 63% of the newly developed drugs were naturally derived or semisynthetic derivatives of natural products.[11] Even if other approaches like protein structure-based drug design have gained importance since then, natural products still play a major role as starting point for new therapeutics.[12]

1.2 SESQUITERPENE QUINONES

1.2.1 CLASSIFICATION

Sesquiterpene (hydro-)quinones represent the most common meroterpenoids found in nature and are characterized by a sesquiterpene unit (C_{15}) connected to a (hydro-)quinone moiety (C_6). Various possible connections between the two parts, differences in the sesquiterpene skeleton, as well as versatile substitutions of the benzoquinone/quinol result in a vast number of unprecedented compounds. With this diversity in structure comes a diversity in biological activities, presumably connected to the redox reactivity and electron transfer capacity of the quinone group in combination with the adaptable hydrophobic/hydrophilic properties of the terpene part.[13]

Most natural products of this type are found in marine sponges. These invertebrates lack an immune system, a protective shell, or mobility and therefore produce a multitude of chemically unique compounds ensuring their survival and representing potential bioactive agents.[14] Due to the rapid progress made in structural analysis and discovery methods, over 500 new sesquiterpene quinones have emerged in the past decade.[13] The majority of them contain a bicyclic terpenoid system possessing a drimane or rearranged drimane skeleton (*Figure 2*).[15] This rearrangement occurs by migration of two methyl groups, leading to so called 4,9-friedodrimane structures, sometimes also referred to as avaranes to be distinguished from the so called aureanes emerging from only one methyl shift.[15-16]

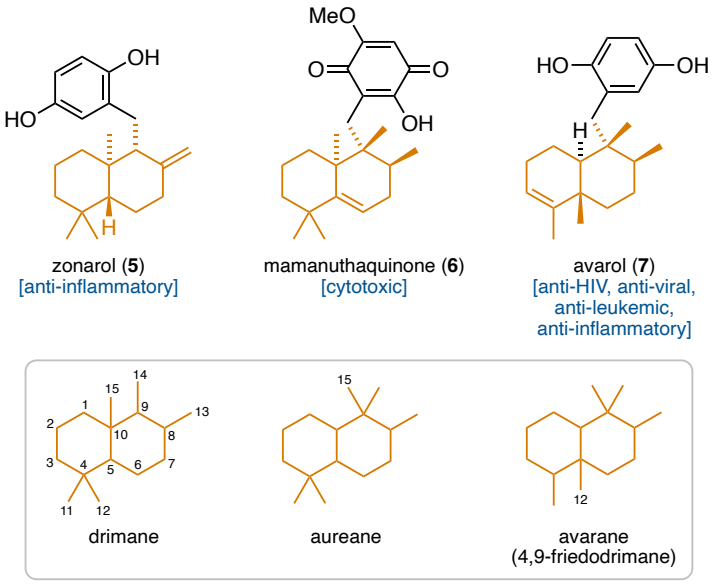


FIGURE 2 BICYCLIC SESQUITERPENE SKELETONS FOUND IN MARINE PRODUCTS AND REPRESENTATIVES THEREOF WITH THEIR BIOLOGICAL ACTIVITIES.[16-17]

The term avaranes originates from the first in 1974 discovered representative avarol *(Figure 2)*,[18] which is to date still intensely studied as potential anti-HIV (stage of clinical the phase II), anti-leukemic and anti-parasitic therapeutic agent and has already found application as medicine against psoriasis, to name only a few of its biological activities.[13]

Most commonly, the decalin system (*trans*- and less common *cis*-fused ring junction) is bound via a methylene group to the differently functionalized *p*-benzoquinone or hydroquinone ring at C14 via a C–C bond. Additionally, C–O bonding of C-8, C-9 or C-10 to a hydroxy group of the aromatic ring forming dihydropyran or -furan rings (*Figure 3*, **8-11**) is regularly observed.

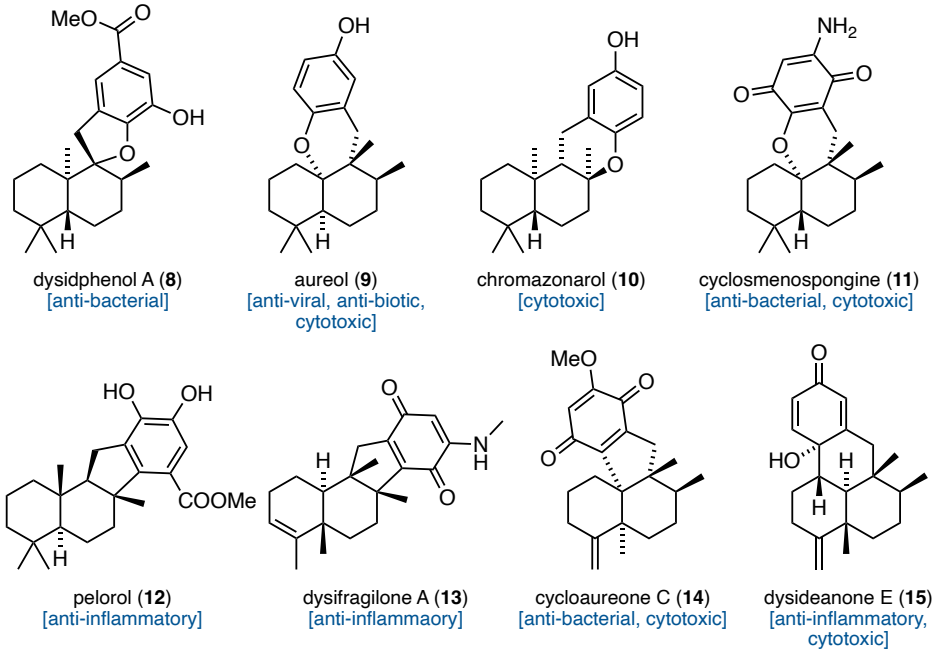


FIGURE 3 TETRACYCLIC SESQUITERPENE (HYDRO)QUINONES FEATURING AN ADDITIONAL C–O (TOP) OR C–C BOND (BOTTOM) BETWEEN THE AROMATIC RING AND THE DECALIN SYSTEM TOGETHER WITH THEIR BIOLOGICAL ACTIVITIES.[19]

Since the first member of this family of tetracyclic meroterpenes, aureol (name-giving for the group of aureanes), was isolated in 1980 by the group of *Faulkner*,[20] many related compounds bearing one heterocycle have been discovered. Less common are metabolites in which the fourth ring is formed via another carbon-carbon bond between the aromatic moiety and the decalin system (*Figure 3*, **12**-**15**). The first example, the drimane derivative pelorol (**12**), was isolated in 2000.[21] The aminoquinone/avarone dysifragilone A (**13**) was discovered in 2015 by *Lin* and coworkers.[19d] In the same year, *Kim et al.* isolated three new meroterpenoids, cycloaurenone A-C (**14**), showing a novel 6/6/5/6-tetracyclic carbon skeleton (*Figure 3*).[19e] [19f]

One year later, *Lin* and coworkers in turn isolated three additional meroterpenes with this intriguing structural feature and, in 2021, two more of the dysiherbols (see *Figure 5*, p. 15).[19f, 22] These avaranes can be counted to the subgroup of dysideanones, sharing the two-point C-C connection resulting in a tetracyclic skeleton with a central five- or six-membered ring. The dysideanones are closely related congeners derived from the same marine sponge *Dysidea* sp. as the dysiherbols and were also first obtained during the past decade by the *Lin* group.[23] Since 2012 they have isolated over 120 new sesquiterpene quinones, accounting for 80% of all avaranes, and discovered eight new carbon skeletons.[13]

An example for a merosesquiterpenoid bearing an unusual carbon skeleton is shown in *Figure 4*. Septosone A (**16**), which was isolated only recently from marine sponge *Dysidea septosa*, exhibits a novel pentacyclic structure.[24] Since the precedent bispuupehenone in 1983, there have also been reports of dimeric meroterpenoids.[25] One of the latest examples is dysiarenone (**17**), isolated in 2018.[26] There are many other examples of rearrangements of the sesquiterpenoid carbon skeleton and even more opportunities of modifications of the aromatic group thus resulting in a seemingly endless number of interesting natural products.

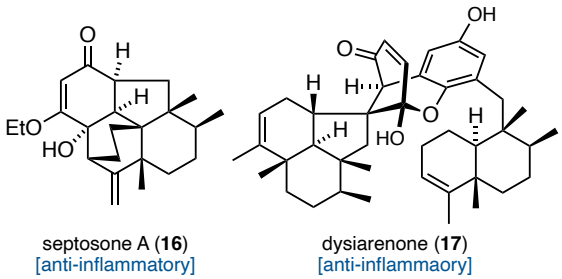


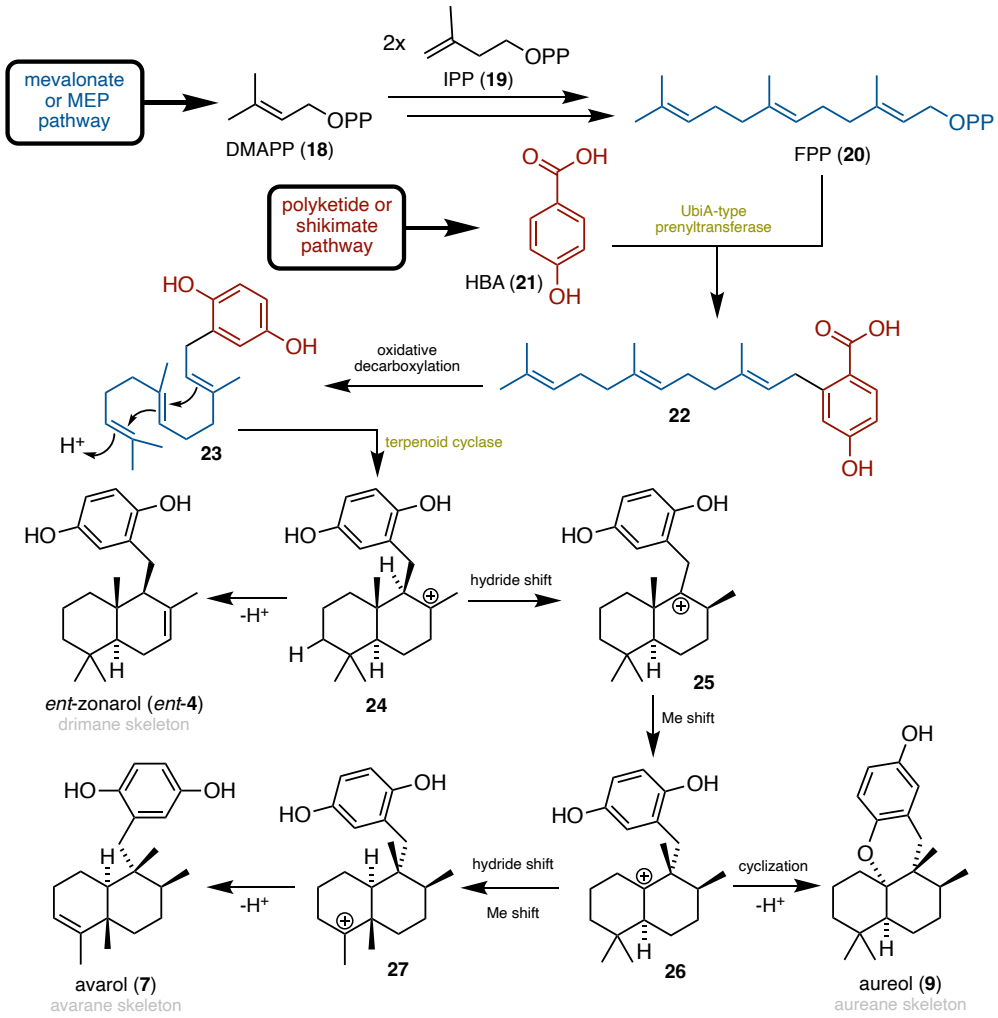
FIGURE 4 MEROSESQUITERPENOIDS WITH UNUSUAL STRUCTURAL FEATURES TOGETHER WITH THEIR BIOLOGICAL ACTIVITIES.[24]

Meroterpenes have not only gained attention because of their chemical diversity, but also due to their variety of biological activities. In particular sponges of the order *Dictyceratida* deliver a manifold of bioactive meroterpenoids, the majority of which are sesquiterpene quinones/hydroquinones.[19a] The observed biological effects comprise for example anti-bacterial,[19a, 27] anti-inflammatory,[24, 28] anti-microbial,[19e, 29] anti-HIV[30] activity, as inhibitory

activity against protein tyrosine kinase[17b, 31] and protein tyrosine phosphatase.[31b] Furthermore, a range of compounds displayed cytotoxic[19e, 27c, 28b, 29a, 32] and anti-proliferative[32c, 33] properties, thus offering promising opportunities for the development of new anti-tumor agents.[32c] It is believed that these anti-cancer activities are caused by the aromatic moiety, as quinones/ hydroquinones are known to be susceptible to redox cycling, forming reactive oxygen species (ROS).[34] But also the oxidation pattern of the decalin system seems to have an important impact on the biological activity.[32e]

1.2.2 BIOSYNTHESIS

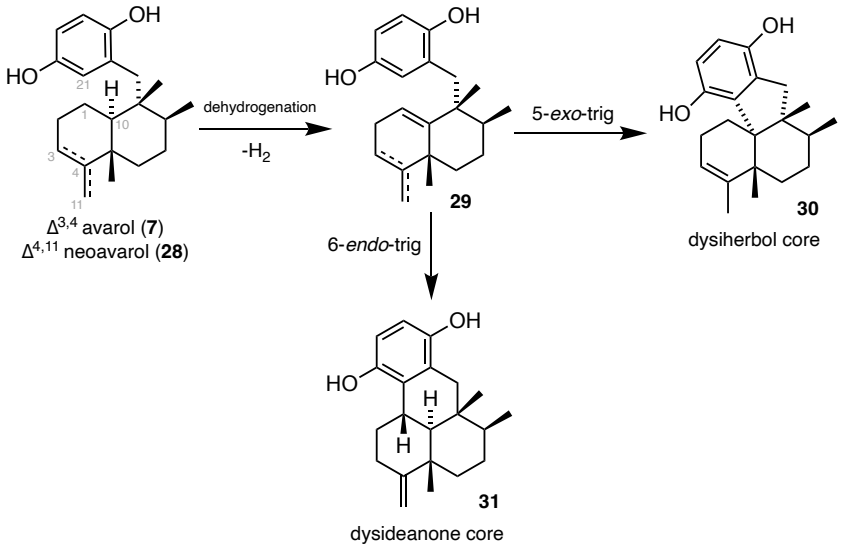
The sesquiterpene quinones belong to a class of large variety called meroterpenes that are of mixed biosynthetic origin, partially derived from terpenoids.[29b] When thinking about the biosynthesis of meroterpenoids, one has to consider the hybrid nature of these natural products. Their biogenesis incorporates two different building blocks originating from two different pathways.[35]



SCHEME 1 PROPOSED MIXED BIOSYNTHETIC ORIGIN FOR SESQUITERPENE QUINONES AND POSSIBLE REARRANGEMENTS YIELDING DIFFERENT CARBON SKELETONS.[17B, 36]

One is the sesquiterpene subunit belonging to the class of terpenes that consist of a certain number of C_5 units. *Iso*pentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP) are suitable C_5 units, coming from the mevalonate or the deoxyxylulose phosphate pathway (MEP pathway) and delivering farnesyl pyrophosphate (FPP, C_{15}), the central precursor of sesquiterpenes.[1, 37] The second part is an aromatic core that might be provided by the polyketide pathway,[20, 35-36] or the shikimate pathway that produces amino acids and 4-hydroxybenzoic acid (HBA).[1, 17b, 18] Different studies on biosyntheses lead to the assumption that HBA, upon oxidative decarboxylation, delivers a hydroquinone moiety (*Scheme 1*).[38]

The connection between the two building blocks might be enabled by the enzyme UbiA-type prenyltransferase, which catalyzes a S_EAr reaction.[38a, 38c] The thus formed aromatic polyene chain can undergo a cationic cyclization cascade to form the key biosynthetic intermediate **24**, most probably catalyzed by a terpenoid cyclase.[18, 35] Deprotonation at the resulting decalin scaffold yields the drimane skeleton. A series of stereospecific [1,2]-hydride and methyl shifts can lead to further rearranged carbon skeletons, the aureanes or the avaranes, e.g. avarol (**7**).[17b, 18] The possibly formed aureane-like cation **26** could be trapped by the adjacent phenolic oxygen (or the electrons of the aromatic ring) to form a tetracyclic structure with a *cis*-fused decalin ring system, as in aureol (**9**).[39] Deprotonation would lead to the respective bridgehead olefine, considered to be the biosynthetic precursor of *trans*-fused tetracyclic decalin systems.[35-36]



SCHEME 2 POSSIBLE BIOSYNTHETIC TRANSFORMATION OF (NEO)AVAROL TO THE CARBON SKELETON OF THE DYSIHERBOLS OR THE DYSIDEANONES.[24, 40]

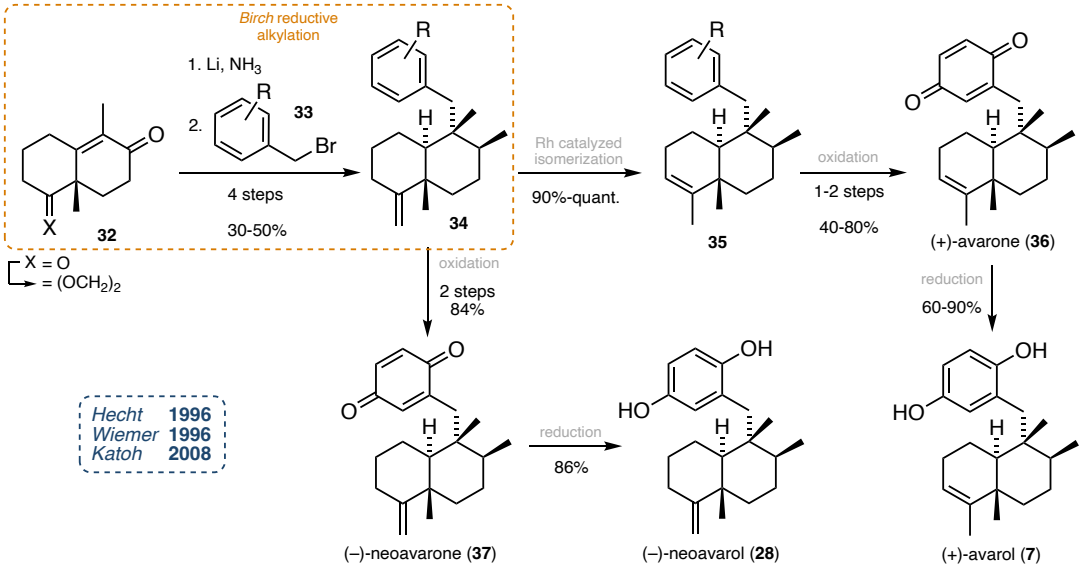
Bicyclic avarol is believed to be a biosynthetic precursor for more complex tetra- or pentacyclic sesquiterpene quinones with another C–C bond between the two units (*Scheme 2*).[24, 40] Dehydrogenation at the decalin bridgehead would lead to an unconjugated diene (**29**), which could undergo a 5-exo-trig *Friedel-Crafts* cyclization (C21 -> C10) delivering the 6/6/5/6 carbon skeleton of the dysiherbols. The corresponding diene resulting from neoavarol could deliver the

6/6/6/6 fused ring system of the dysideanones as product of a 6-endo-trig cyclization (C-21 -> C-1). Final oxidation of the hydroquinone moiety of **31** would lead to dysideanones, whereas the dysiherbols could result from **30** by further hydration, dihydroxylation, oxidation and isomerization processes.[40]

1.2.3 TOTAL SYNTHESIS

Meroterpenoid sesquiterpenes exhibit a broad range of pharmacologically promising bioactivities and at the same time unique and diverse structural features, rendering a total synthesis a real challenge, thus attracting the attention of many natural product chemists. In the early days two strategies evolved for the construction of the skeleton which most members have in common.[41] A biomimetic strategy with sequential cyclizations of prenylated hydroquinones as key step evolved, which was already applied in 1973 by *Gonzalez et al.* for the synthesis of taondiol,[42] as did a two-synthon strategy consecutively building up the different rings, first reported by *Corey* and *Das* in 1982.[43]

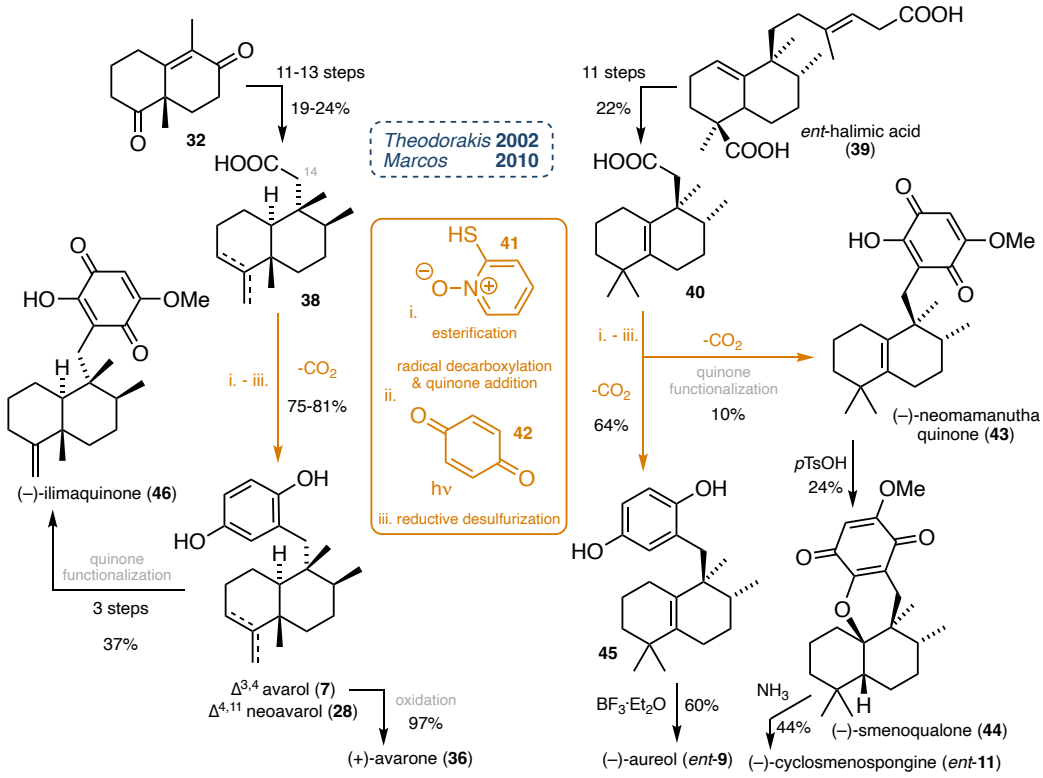
Two targets of the natural product family many researchers were interested in are avarol (**36**) and avarone (**7**). The first racemic synthesis of (±)-avarol (**7**) was published in 1982 by *Sarma et al.*[44] and the following enantioselective syntheses (*Scheme 3*) are all starting from the same building block **32**, a known derivative of the *Wieland-Miescher* ketone, which in turn is a common precursor in the synthesis of terpenes. In these approaches, the bond between the decalin system and the quinone unit is introduced via a "reductive alkylation" under *Birch* conditions, delivering key intermediate **34** as single diastereomer.[45] High yielding Rh-catalyzed isomerization provided the double bond in the adequate position to obtain avarone (**36**) and avarol (**7**) by oxidation and additional reduction, respectively.



SCHEME 3 TOTAL SYNTHETIC APPROACHES TOWARDS AVAROLS AND AVARONES UTILIZING A BIRCH REDUCTIVE ALKYLATION TO CONNECT THE AROMATIC RING AND THE DECALIN SYSTEM.[45]

The same key step was employed in 2010 in *Katoh's* synthesis for (+)-stachyflin,[46] a first racemic total synthesis was reported in 1998 by *Mori et al.*[47] In 2002 *Katoh* already published a methodology for the synthesis of the stachyflin core[48] and in 2011 an alternative synthesis for (+)-stachyflin.[49]

Another strategy for the coupling of the aromatic building block to the bicyclic system was introduced in 2002 by *Theodorakis* and co-workers as a unified synthetic approach based on a radical decarboxylation followed by the addition of a quinone to the C-14 centered radical (*Scheme 4*).[50] The thus achieved total syntheses of (–)-ilimaquinone (**46**) (first total synthesis by *Snapper* in 1995),[30] (+)-avarol (**7**) and (+)-avarone (**36**) also utilize ketone **32** as starting material.

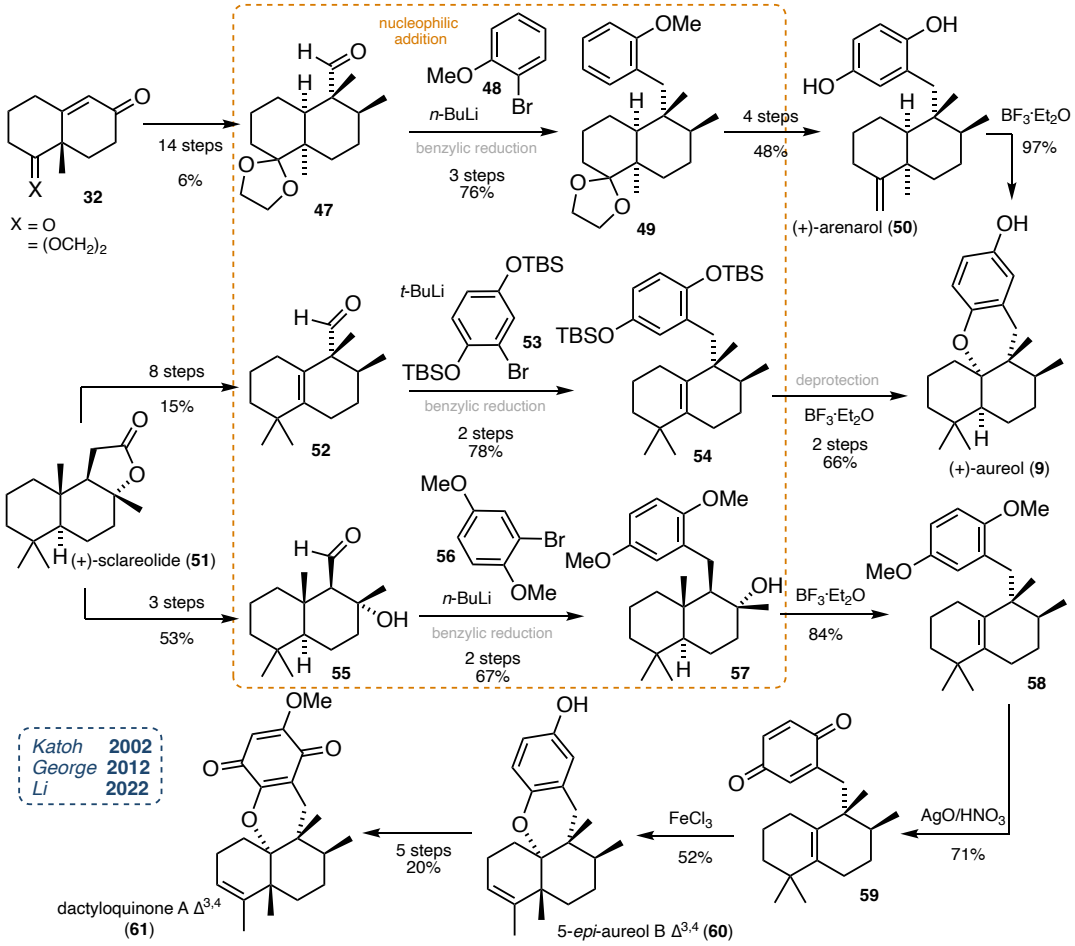


SCHEME 4 TOTAL SYNTHESIS OF A VARIETY OF QUINONE SESQUITERPENES VIA RADICAL DECARBOXYLATION AND QUINONE ADDITION.[50A, 51]

In 2010 *Marcos et al.* applied the methodology for the synthesis of four different tetracyclic sesquiterpene (hydro-)quinones (*Scheme 4*, right). Esterification of carboxylic acids **38** or **40** with 2-mercaptopyridine *N*-oxide **41** leads to a photolabile intermediate, subsequently employed in the radical decarboxylation and the addition of quinone **42**. The aromatic moiety of the coupling products can be further functionalized, thus allowing access to a wide range of family members (*Scheme 4*).[51] In contrast to the already discussed approaches, *Marcos et al.* employed a chiral pool starting material, *ent*-halimic acid (**39**). After quinone addition and desulfurization, they either obtained quinol **45** or (–)-neomamanuthaquinone (**43**) upon additional functionalization

of the quinone. The latter gave tetracyclic (–)-aureol (*ent*-**9**) by *Lewis* acid-mediated cyclization, based on seminal work by *Capon* and *van der Helm*.[52]

The same conditions were already used by *Katoh et al.* to convert (–)-neoavarol (**28**), (+)-avarol (**7**) (compare *Scheme 3*)[45c] and (+)-arenarol (**50**) (*Scheme 5*),[53] into (+)-aureol (**9**) via a boron-mediated rearrangement/cyclization reaction.



SCHEME 5 TOTAL SYNTHETIC APPROACHES TOWARDS AUREOL AND DACTYLOQUINONE A UTILIZING A NUCLEOPHILIC ADDITION TO CONNECT THE AROMATIC RING AND THE DECALIN SYSTEM.[35, 53-54]

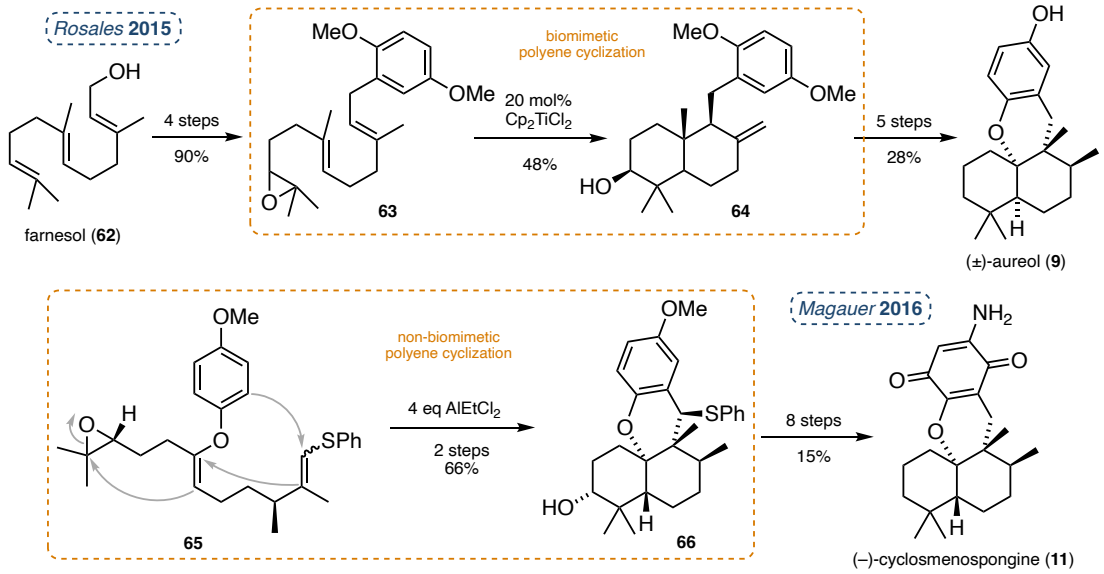
In the total syntheses depicted in *Scheme 5* the connection between the hydroquinone and the decalin bicycle was achieved by nucleophilic addition of a lithiated arene to an aldehyde. Benzylic reduction delivers the key intermediates, in the case of *Katoh's* synthesis compound **49**, that could be converted into (+)-arenarol (**50**) over four steps.

A similar synthesis exhibiting the same key transformation was reported in 2012 by *George et al.* starting from (+)-sclareolide (**51**).[35] Cyclization of aureane **54** also delivered tetracyclic (+)-aureol (**9**). In contrast to the *Katoh* synthesis from 2002, there is no rearrangement taking place in the final cyclization step.

Only recently *Li* and coworkers published a total synthesis for the double bond isomer of dactyloquinone A (**61**) using the same coupling strategy. The synthesis also features a *Lewis* acid-mediated cyclization/rearrangement step delivering 5-*epi*-aureol B $\Delta^{3,4}$ (**60**). Employing AgOTf instead of $FeCl_3$, an inseparable mixture of double bond isomers and epimers was obtained, subsequently leading to the respective mixture containing dactyloquinone A, which could not be separated.[54]

In the course of a bioinspired total synthesis of racemic aureol by *Rosales* an Ti^{III}-mediated reductive epoxide cyclization cascade was used (*Scheme 6*).[39] Cyclization precursor in this sequence was a racemic mixture of **63**. Applying this methodology to a general approach towards the core structure of several polycyclic meroterpenoids, as for example pelorol (**12**), was already reported by *Cuerva et al*. in 2004. [41]

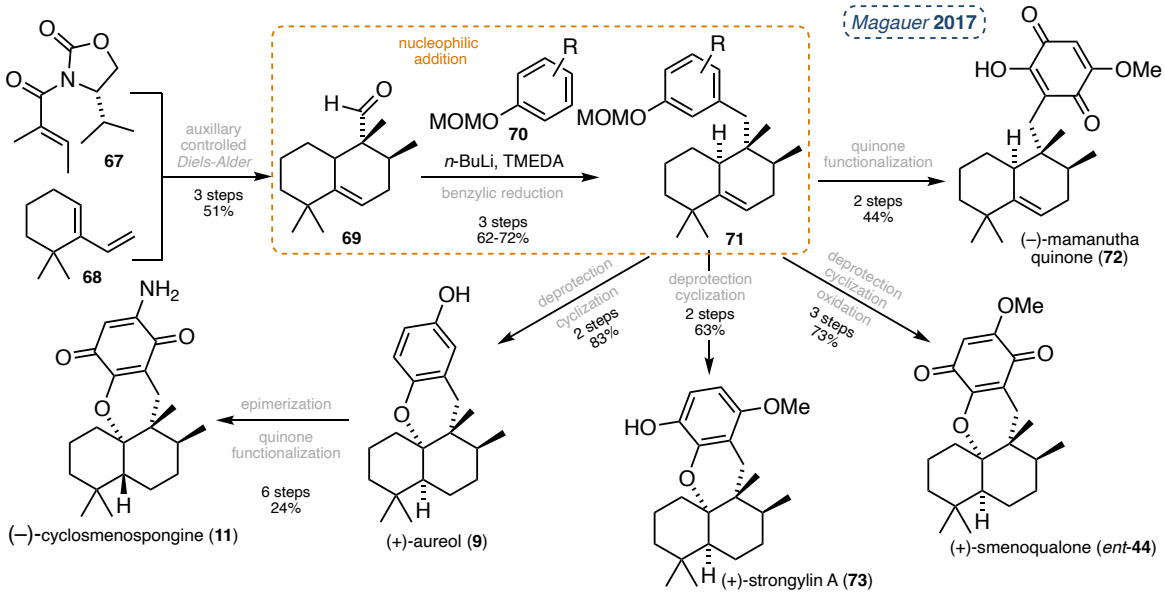
Deviating from mother nature's prototype of a cyclization precursor, *Magauer* and coworkers developed an intriguing polyene cyclization cascade (depicted in *Scheme 6*) by establishing three rings and setting four consecutive stereocenters in one single step.[36, 55] Contrary to the other strategies, the central dihydropyran ring is not constructed in a late-stage cyclization.



SCHEME 6 DIFFERENT APPROACHES UTILIZING CYCLIZATION CASCADES IN THE TOTAL SYNTHESIS OF *rac*-AUREOL (**9**) AND (–)-CYCLOSMENOSPONGINE.[39, 55]

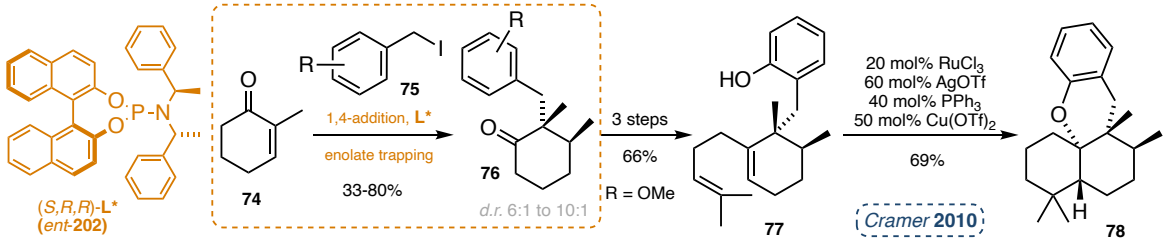
Precursor **65** was synthesized via a convergent three-component coupling utilizing a phenol-alkyne addition and a *Suzuki-Miyaura* cross coupling. The authors originally aimed to synthesize the *cis*-fused decalin system present in aureol (**9**), but the threefold cyclization gave exclusively the *trans*-decalin framework, as in (–)-cyclosmenospongine (**11**). One year later, the group published another synthesis for (+)-stachyflin with the *cis*-fused ring system, employing a different sequence of *Negishi* cross coupling for the formation of the arene-decalin bond and common late-stage $BF_3{\cdot}Et_2O$ cyclization.[56]

In 2017 the *Magauer* group published a divergent approach for the synthesis of several aureanes.[57] The innovative part thereof is the stereoselective construction of the decalin system using an auxiliary-controlled, *exo*-selective *Diels-Alder* reaction between dienophile **67** and diene **68** (*Scheme 7*). For the coupling of the two building blocks the common, already discussed nucleophilic addition was applied.[19b]



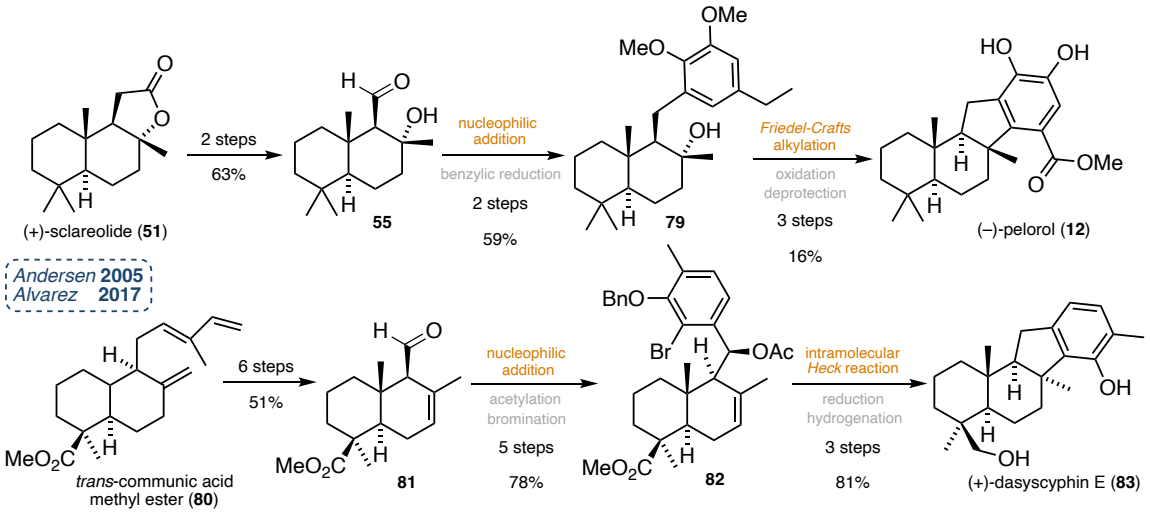
SCHEME 7 UNIFIED TOTAL SYNTHESIS OF SEVERAL AUREANE TYPE SESQUITERPENE HYDROQUINONES BY MAGAUER *ET. AL* FROM 2017.[19B]

A new enantioselective approach was disclosed in 2010 by Cramer coming up with a route for the formation of the tetracyclic core of the oxygen-bridged sesquiterpene (hydro)quinones (**78**), reportedly providing access to the majority of the so-called benzo[d]xanthenes.[58] The key steps of the synthesis are depicted in *Scheme 8.* The coupling between the substituted arene and the decalin precursor is enantioselective, deploying chiral ligand *ent*-**202** and introducing one methyl group via a 1,4-addition. The resulting enolate is trapped with an electrophile (**75**). The second key step of the reported sequence is the Ru^{III}-mediated twofold cyclization, affording exclusively the trans-fused ring system as in compound **78**.



SCHEME 8 ENANTIO- AND DIASTEREOSELECTIVE CONSTRUCTION OF THE TETRACYCLIC CORE OF SESQUITERPENE QUINONES VIA A 1,4-ADDITION/ENOLATE TRAPPING ONE POT REACTION BY CRAMER.[58]

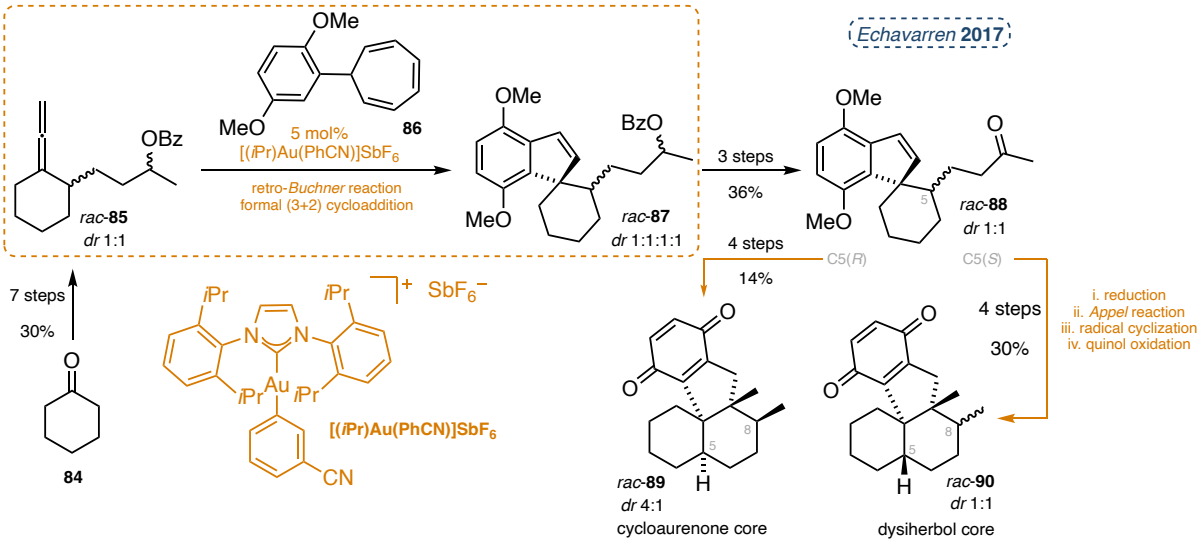
To date, there are fewer publications dealing with the establishment of a fourth ring via a second carbon-carbon bond between the two entities of the sesquiterpene quinones. Two examples of such total syntheses are shown in *Scheme 9.*[19c, 59]



SCHEME 9 TOTAL SYNTHESIS OF TETRACYCLIC (+)-DASYSCYPHIN E (**83**) AND (–)-PELOROL (**12**) USING DIFFERENT STRATEGIES TO ESTABLISH THE SECOND C–C BOND BETWEEN THE AROMATIC MOIETY AND THE DECALIN.[19c, 59]

The first connection between the arene and the decalin was in both cases achieved by a nucleophilic addition of the lithiated aromatic ring to aldehyde **55** or **81**, as seen in previous examples. In the case of dasyscyphin E (**83**), the key step for the closing of the fourth ring is an intramolecular Pd-catalyzed *Heck* reaction of compound **82**, assisted by a remote acetate group. In the upper example the cyclopentane ring of pelorol (**12**) was constructed by an *Lewis* acid-mediated intramolecular *Friedel-Crafts* reaction of alcohol **79**.[19c]

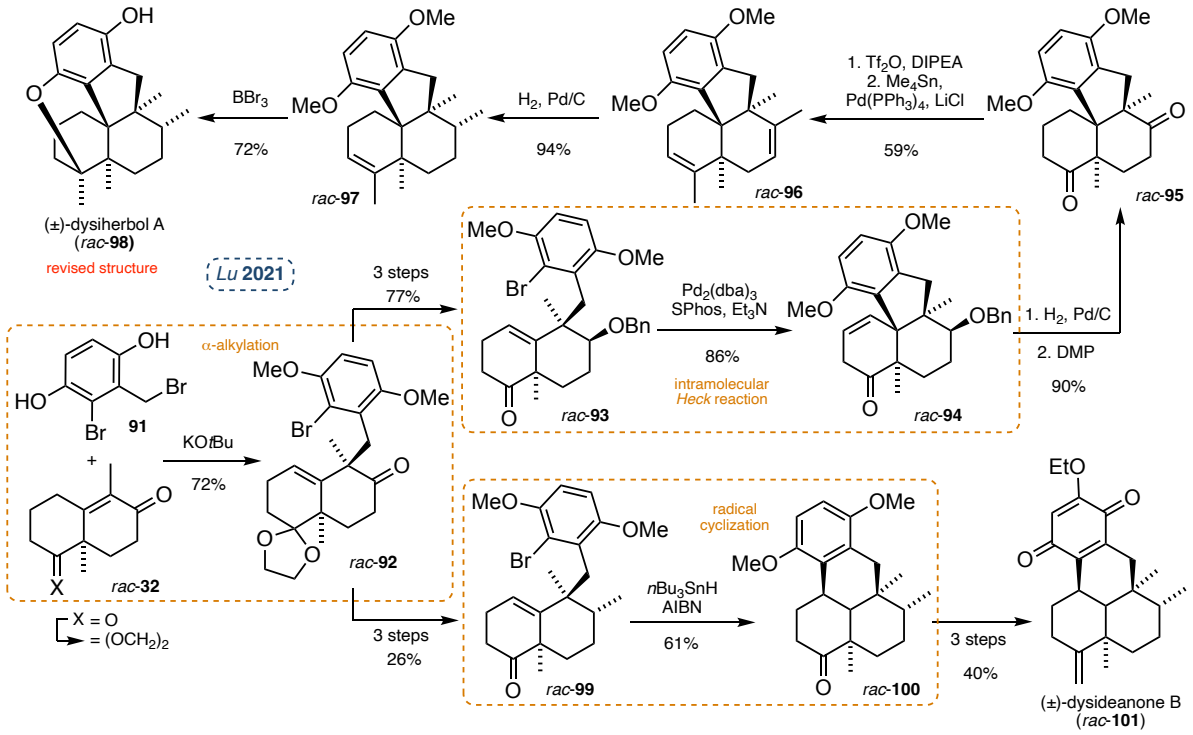
Another publication addressing the challenging synthesis of such carbon skeletons was published in 2017 by *Echavarren* (*Scheme 10*).[60] They developed a formal (3+2) cycloaddition between terminal allenes and aryl-Au^{I}-carbenes generated by a retro-*Buchner* reaction of 7-substituted 1,3,5-cycloheptatrienes (**86**).



SCHEME 10 AU^{I}-CATALYZED SYNTHESIS OF INDENES GIVING ACCESS TO CYLOAURENONE AND DYSIHERBOL CORE STRUCTURES. A NOVEL CYCLOADDITION REACTION IS USED TO ESTABLISH THE FIRST C–C BOND BETWEEN THE TWO SESQUITERPENE SUBUNITS AND A RADICAL CYCLIZATION TO BUILD UP THE DECALIN SYSTEM.[60]

This novel methodology enables the construction of indenes such as *rac*-**87** and was applied for the synthesis of the *cis*-decalin core structure of cycloaureones as in quinone *rac*-**89** and the *trans*-fused carbon skeletons found in the dysiherbols (compound *rac*-**90**).

In 2021, *Lu* published the first racemic total synthesis of dysiherbol A (*rac*-**98**) and dysideanone B (*rac*-**101**), featuring a central five- or six-membered ring (*Scheme* 11).[40] For the attachment of the aromatic ring they used an α-alkylation of common *Wieland-Miescher* analogue *rac*-**32**. As key step towards dysiherbol A (*rac*-**98**) an intramolecular *Heck* reaction of olefin *rac*-**93** was utilized. The installation of two of the four methyl groups providing the decalin system was achieved via a double *Stille* coupling of the enol triflate resulting from compound *rac*-**95**.



SCHEME 11 RACEMIC TOTAL SYNTHESIS OF (±)-DYSIHERBOL A VIA α-ALKYLATION AND INTRAMOLECULAR *HECK* REACTION, LEADING TO ITS STRUCTURAL REVISION PUBLISHED TOGETHER WITH THE SYNTHESIS OF (±)-DYSIDEANONE B VIA THE SAME INTERMEDIATE **92** AND SUBSEQUENT RADICAL CYCLIZATION.[40]

The final deprotection step led to pentacyclic *rac*-**98** displaying the revised constitution of dysiherbol A (**98**). The core structure of dysideanone B was synthesized by methylenation and stereoselective hydrogenation of the common intermediate *rac*-**92** followed by radical cyclization to build up the fourth ring (*rac*-**100**). Oxidation and functionalization of the aromatic ring gives the natural product as racemic mixture (*rac*-**101**).

1.2.4 THE DYSIHERBOLS

1.2.4.1 STRUCTURE AND ACTIVITY

In 2016 three new tetracyclic avarane hydroquinones were isolated, dysiherbols A-C (*Figure 5*) from a *Dysidea sp.* marine sponge found in the South China Sea.[32e] All three showed interesting

biological activities, but dysiherbol A turned out to be the most potent compound in terms of cytotoxicity against the human myeloma cancer cell line NCI H-929 (IC_{50} = 0.58 µM) and NF-κB inhibitory activity (IC_{50} = 0.49 µM).[32e] This transcription factor protein complex is of importance for immune response and suspected to be involved in several types of carcinogenic processes as in the process of inflammation.[61] Therefore, dysiherbol A might be a potent precursor for anti-cancer or anti-inflammatory drugs, what makes it a highly interesting natural product for total synthesis.

Their structures were proposed to be as displayed in the top row of *Figure 5* (**102**-**104**), based on 2D-NMR experiments and HR-MS. The absolute configuration was determined by the comparison of experimental and computationally calculated CD spectra.

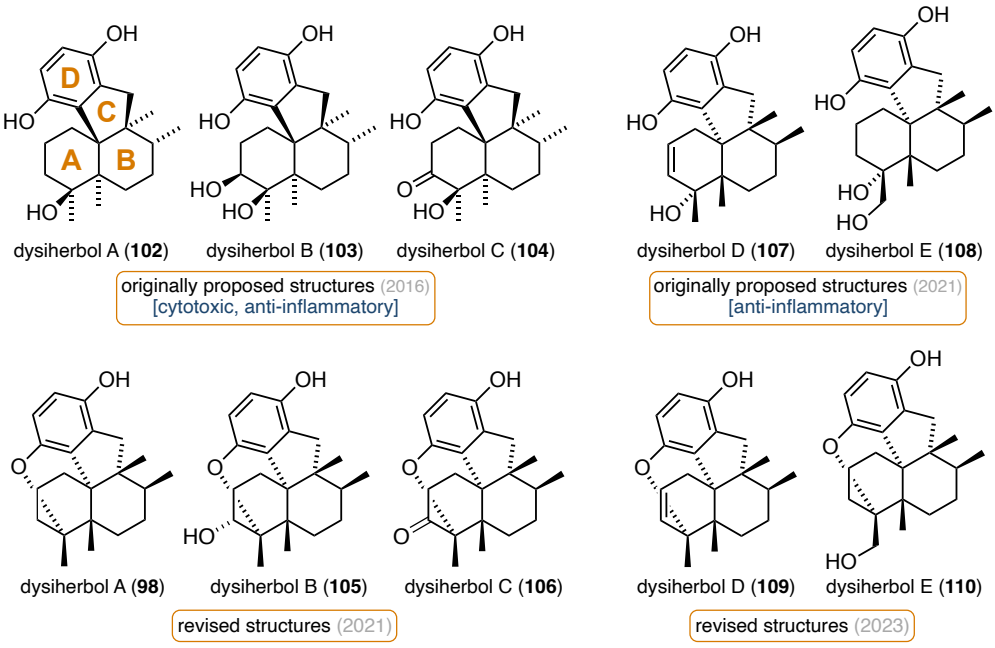


FIGURE 5 DYSIHERBOL A-E AND BIOLOGICAL ACTIVITIES TOGETHER WITH THE ORIGINALLY PROPOSED AND REVISED STRUCTURES FOR DYSIHERBOL A-C.[19F, 22, 40, 62]

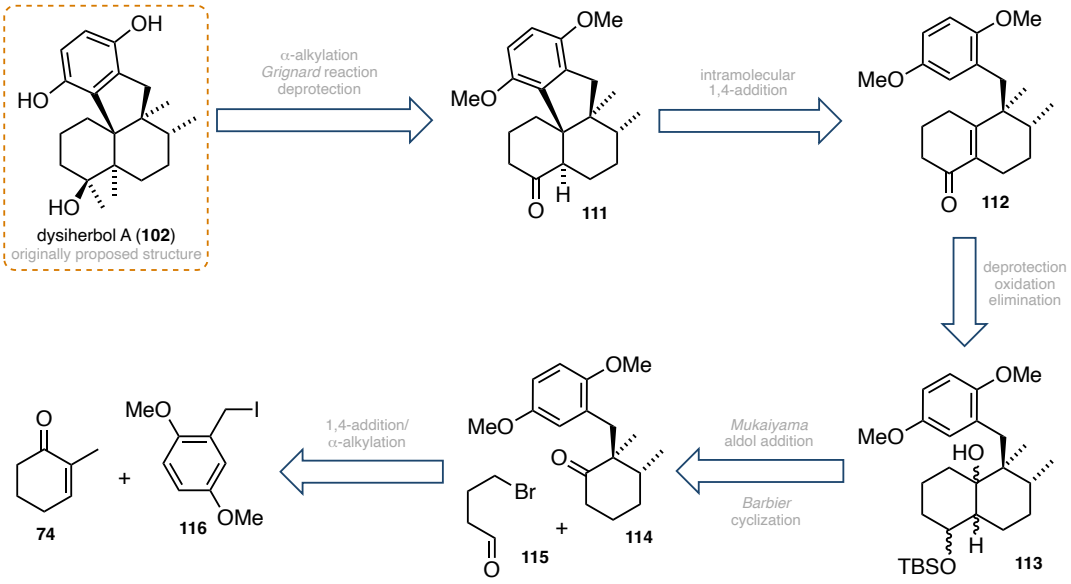
As already discussed in the previous chapter, the first racemic total synthesis of dysiherbol A resulted in the revision of its constitution in 2021 (*Scheme 11*).[40] Moreover, in the course of this work and the development of the first enantioselective total synthesis of dysiherbol A, the absolute configuration of compound **102** was proven to be opposite to the natural product.[62] Thus, the dysiherbols were elucidated to be pentacyclic exhibiting two C–C bonds and one C–O bond between the sesquiterpene and the hydroquinone and featuring the absolute configuration indicated in the structures in the bottom row of *Figure 5* (**98**, **105** + **106**).

Two more dysiherbols (D and E) were isolated in 2021, also showing anti-inflammatory activities from marine sponge *Dysidea avara*.[22] The absolute configuration was proposed to be identical with the revised dysiherbol A (**98**), but the constitution was again suggested to be tetracyclic

(structures **107** and **108**), but were found to be also characterized by the additional C–O bond in the course of their total synthesis (**109** + **110**).[63]

1.2.4.2 SYNTHETIC STRATEGY

The originally proposed, novel three-dimensional structure of dysiherbol A (**102**), with five adjacent stereocenters, renders a total synthesis a real challenge and potential grounding for scientific advance in the field of organic chemistry. Based on the retrosynthetic analysis depicted in *Scheme 12*, *Julian Baars* was able to establish a sophisticated synthesis to build up the novel tetracyclic 6/6/5/6 fused carbon skeleton of dysiherbol A (*Scheme 13*).[64]

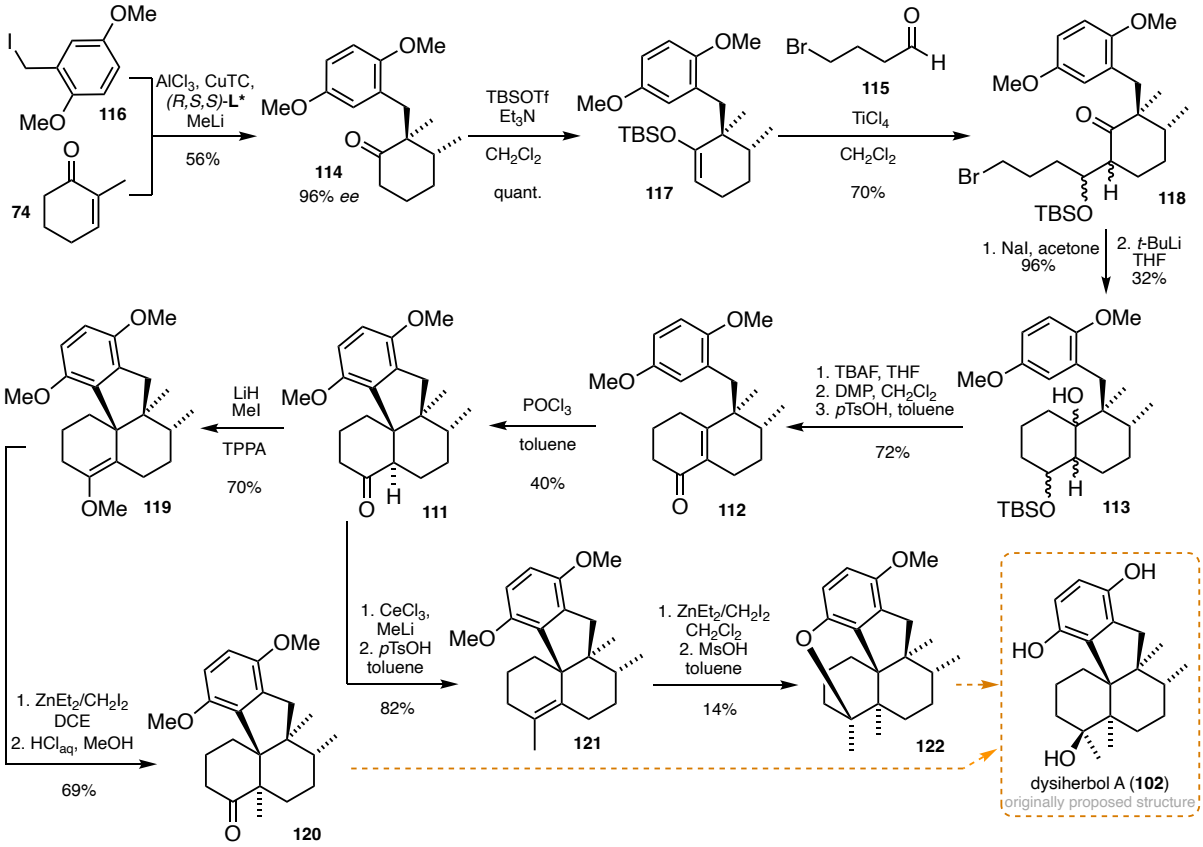


SCHEME 12 RETROSYNTHETIC ANALYSIS OF THE ORIGINALLY PROPOSED DYSIHERBOL A BY *BAARS* AND *SCHMALZ*.[64]

Introducing the five adjacent stereocenters, with three of them being quaternary, is another challenge of the target. With the first key step of the developed route, both challenges are addressed: a one-pot reaction comprising a copper-catalyzed, stereoselective 1,4-addition, employing a chiral ligand (*Scheme 8, p. 12*) with subsequent enolate trapping with iodide **116** based on the work of *Cramer et al.* from 2010.[58] Thus already half of the fused rings composing the dysiherbol A core as well as two of five stereogenic centers can be established. After TBS-protection of ketone **114**, the next step in the current synthetic approach employs a *Mukaiyama* aldol addition to aldehyde **115** (*Scheme 13*). Subsequent halogen exchange via *Finkelstein* reaction and *t*-BuLi-mediated *Babier*-like cyclization build up the decalin system of compound **113**.[64]

Thereby, only one diastereomer is formed, although control of stereochemistry is not necessary in these reactions because the three newly formed stereocenters are destroyed in the following functional group interconversion (deprotection, oxidation, elimination) towards enone **112**. Intramolecular *Friedel-Crafts* type 1,4-addition, resulting in the desired tetracyclic carbon

skeleton (**111**), can be mediated by $POCl_3$. This reaction also establishes two stereocenters, delivering *trans*-decalin **111** as single diastereomer.



SCHEME 13 SYNTHETIC APPROACHES TOWARDS ORIGINALLY PROPOSED DYSIHERBOL A (**102**) BY *BAARS*.[62, 64]

From this key intermediate, *Baars* developed two possible approaches for the introduction of the two missing methyl groups of the assumed natural product **102**. An α-alkylation can be achieved via three steps by formation of enol ether **119**, followed by cyclopropanation utilizing the *Furukawa* variant of the *Simmons-Smith* reaction, occurring from the α-site of the molecule due to steric hinderance of the β-site. Subsequent acidic cyclopropane opening delivers compound **120**. Introducing the last stereocenter by methyl-1,2-addition at the ketone and final deprotection of the quinol moiety might deliver the desired dysiherbol A structure **102**.

As intermediate **120** appeared to be sterically and electronically too hindered towards a 1,2-addition, the second approach aimed to introduce the two methyl groups at the bottom of **102** the other way around. Ketone **111** is a suitable substrate for a *Grignard* type addition, yielding olefine **121** upon subsequent elimination. *Simmons-Smith* cyclopropanation and addition of acid to the resulting cyclopropane delivers mono-deprotected anhydrate of **102**, pentacyclic **122**, which displays the complete carbon skeleton of the desired natural product.[62, 64] At the beginning of the present work the conversion to triol **102** was still under investigation, as the structural revision of the constitution was not published (compare *Scheme 11*, p. 14 and *Figure 5*, p. 15)

1.3 CATIONIC TWOFOLD CYCLIZATIONS

The design of cascade reactions is a challenging aspect of organic chemistry, and reaching applicability of such reactions to natural product synthesis is a desirable goal due to their elegance, efficiency, and highly step-economic character. Hence, a manifold of examples of cascade reactions as key steps in total syntheses can be found in the literature. A detailed review on this topic was published in 2006 by *Nicolaou*.[65]

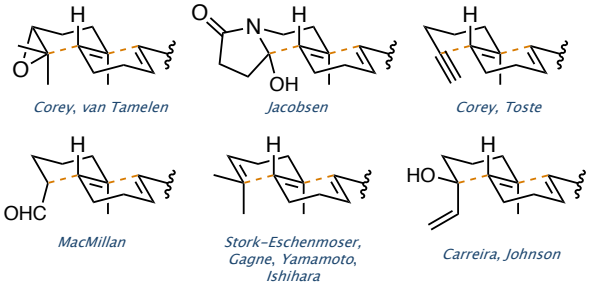
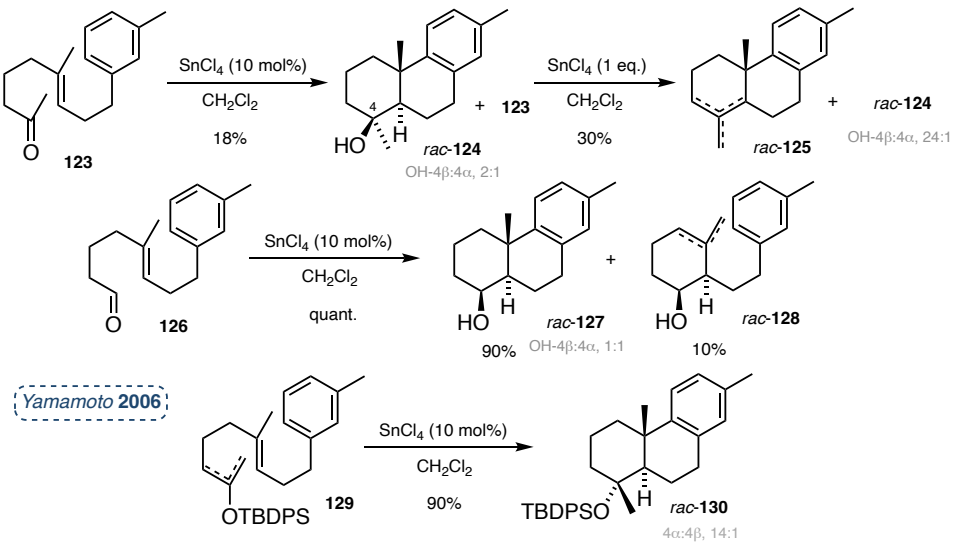


FIGURE 6 OVERVIEW OF PREVIOUS STUDIES BY DIFFERENT CHEMISTS TOWARDS (TWOFOLD) POLYENE CYCLIZATIONS USING BIOMIMETIC PRECURSORS.[55, 66]

As already indicated in the previous chapter, chemists aim to mimic nature's cationic cyclization for the construction of complex polycyclic terpenoids (compare *Scheme 1* and *Scheme 6).* Studies towards the implementation of such reactions often comprise the use of biomimetic precursors activated by *Lewis* or *Brønsted* acids. Due to the substitution pattern of most terpenoids, cyclization precursors with methyl-substituents are the most common substrates. A brief overview of previous studies is shown in *Figure 6*.[66] Usually a multiple bond or a functional group containing an oxygen is addressed to initiate the reaction.

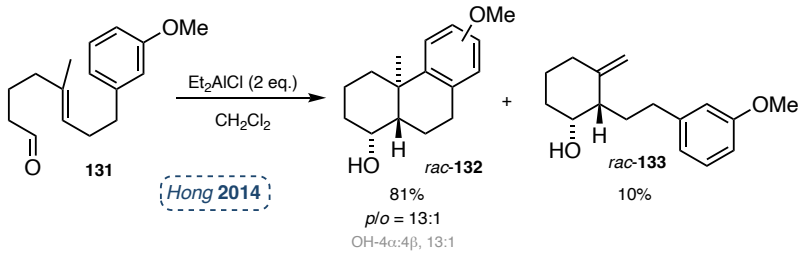
In 2006, *Yamamoto et al.* reported a catalytic diastereoselective polycyclization of homo- and polyprenyl analogues bearing terminal siloxyvinyl groups (*Scheme 14*).[67]



SCHEME 14 EVOLUTION OF A CATALYTIC DIASTEREOSELECTIVE TWOFOLD CYCLIZATION OF POLYPRENYL ARENE ANALOGUES BEARING TERMINAL SILOXYVINYL GROUPS.[67]

They found that δ,ε-unsaturated ketones as **123** are too unreactive for catalytic *Lewis* acid cyclization to alcohol *rac*-**124** with good conversions. However, adding stoichiometric amounts of $SnCl_4$ to the mixture of starting material **123** and product *rac*-**124** lead to dehydrated alkenes of type *rac*-**125**, while alcohol *rac*-**124** was stable under these conditions (despite epimerization at C-4). They further found aldehydes as **126** capable of this transformation with catalytic amounts of $SnCl_4$, giving secondary alcohol *rac*-**127** in excellent yield. Additionally, monocyclized *rac*-**128** was formed as minor product as mixture of double bond isomers. With aldehydes, there was no selectivity for the stereocenter at C-4 observed. Employing the corresponding silyl, dienol ethers gave the β-isomer almost exclusively. In general, they found the α/β selectivity to be controllable by adjusting the steric hinderance of the silyl group in **129** and by changing the substitution pattern of the aromatic ring. In addition to *rac*-α-**130**, only small amounts of the corresponding elimination product *rac*-**125** were obtained.

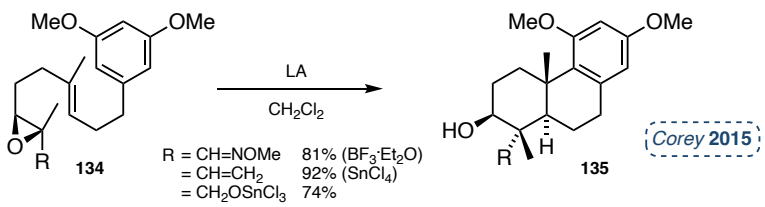
Based on these preliminary results, *Hong* and coworkers employed a similar twofold cyclization of aldehyde **131** (*Scheme 15*) in their 2014 total synthesis of (±)-cafestol.[68] They also observed a monocyclized side product *rac*-**133** along with undesired *ortho*-methoxylated *rac*-**132**.



SCHEME 15 *LEWIS* ACID-PROMOTED ALDEHYDE-ENE CYCLIZATION WITH SUBSEQUENT *FRIEDEL-CRAFTS* REACTION INCORPORATED IN THE TOTAL SYNTHESIS OF (±)-CAFESTOL.[68]

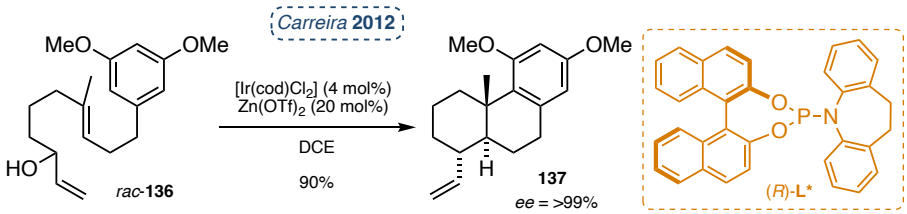
Aiming at the formation of *rac*-**132**, they screened for several *Lewis* acids and achieved the best results with stoichiometric amounts of Et_2AlCl. In contrast to *Yamamoto*, they reported a selectivity for the formation of the C-4 stereocenter with an aldehyde as cyclization precursor. They proposed an aldehyde-ene cyclization and subsequent *Friedel-Crafts* reaction as the underlying mechanism.

In 2015, *Corey* investigated the applicability of functionalized chiral oxiranes of type **134** as starting point for polycyclization reactions.[66c] They found different *Lewis* acids to be suitable for the activation of cationic twofold π-cyclizations. Selected results are shown in *Scheme 16*.



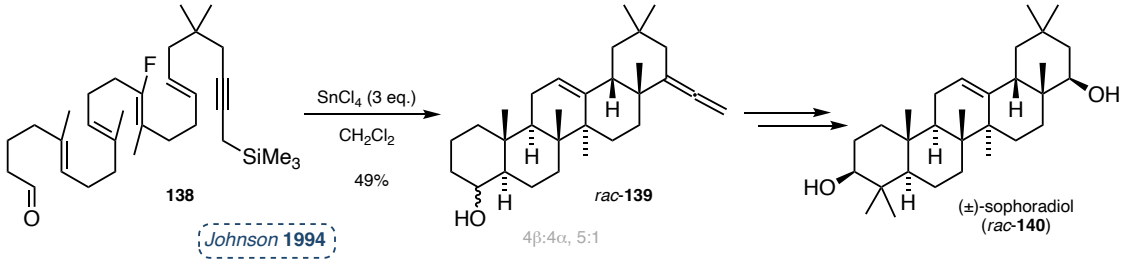
SCHEME 16 STUDY OF FUNCTIONALIZED CHIRAL OXIRANES AS INITIATING GROUPS FOR CATIONIC TWOFOLD CYCLIZATIONS BY *COREY*.[66c]

An unprecedented combination of *Lewis* acid activation and iridium-catalyzed allylic substitution is depicted in *Scheme 17*. This method enables a highly enantioselective polycyclization using racemic mixtures of branched allylic alcohols by employing a chiral phosphoramidite ligand. It was applied to a variety of different aromatic moieties, as in a tricyclization.[66h]



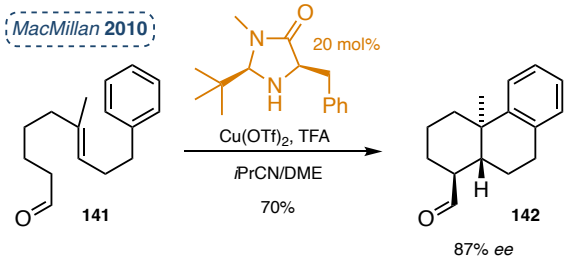
SCHEME 17 HIGHLY ENANTIOSELECTIVE TWOFOLD CYCLIZATION USING A COMBINATION OF *LEWIS* ACID ACTIVATION AND IRIDIUM-CATALYZED ALLYLIC SUBSTITUTION.[66H]

Most polyene-type cyclizations feature epoxides as activating group, but there are also aldehydes employed. One early example is the first nonenzymatic, biomimetic pentacyclization used in the total synthesis of triterpenoid (±)-sophoradiol (*rac*-**140**), see *Scheme 18*.[69] During these studies, corresponding acetals were tested as well, giving similar results.



SCHEME 18 LEWIS ACID INDUCED PENTACYCLIZATION IN THE TOTAL SYNTHESIS OF SOPHORADIOL (**140**).[69]

A different mode of activation was used by the *MacMillan* group in the twofold cyclization shown in *Scheme 19*. Here, an aldehyde is employed in a radical organo-SOMO catalysis. The process can be performed enantioselectively on account of the applied chiral organocatalyst, condensed to enal **141**.



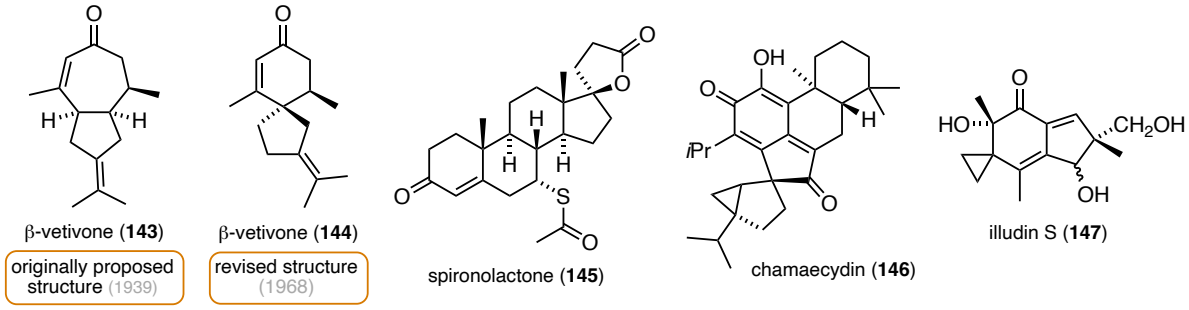
SCHEME 19 ENANTIOSELECTIVE TWOFOLD CYCLIZATION VIA ORGANO-SOMO CATALYSIS.[66I]

Single-electron oxidation of the resulting enamine by a Cu^{II} oxidant initiates the cascade by α-alkylation of the aldehyde.[66i] This strategy was also applied to pentacyclic systems, giving comparable results.

1.4 SPIROCYCLIZATIONS

Spirocycles are structural features characterized by a unique balance of conformational rigidity and flexibility, which enhances the sphericity of corresponding compounds. These scaffolds can be found in many biologically active natural products from a variety of sources and are becoming more and more prevalent in medicinal research and application.[70] Consequently, many divergent strategies have emerged for the synthesis of these motives, including general methods as well as total synthetic approaches.[71]

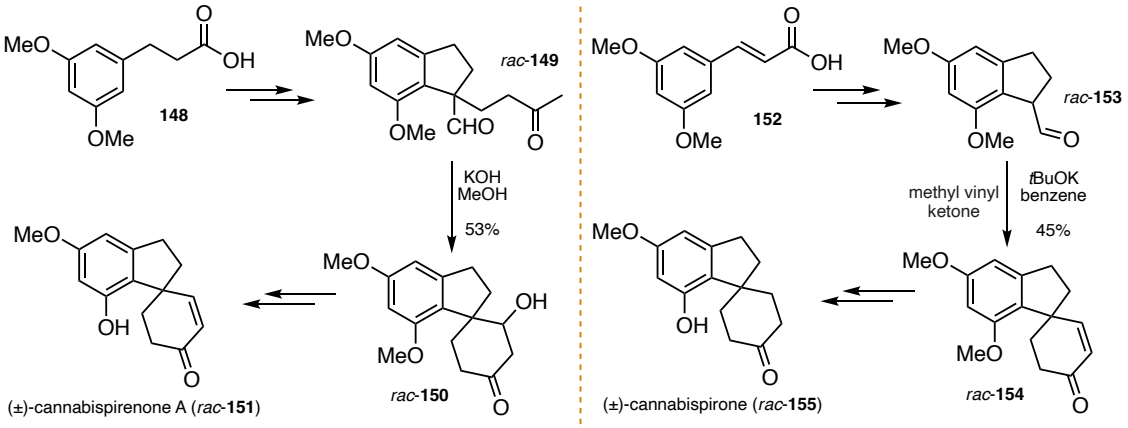
One of the earliest examples of a spirocyclic natural product is β-vetivone (**144**) (*Scheme 20*) isolated in 1939,[72] long mistaken for hydroazulenic compound **143** and structurally revised based on its first total synthesis by *Marshall et al.* in 1968.[73]



SCHEME 20 DIFFERENT COMPOUNDS CONTAINING A SPIROCYCLIC MOIETY.

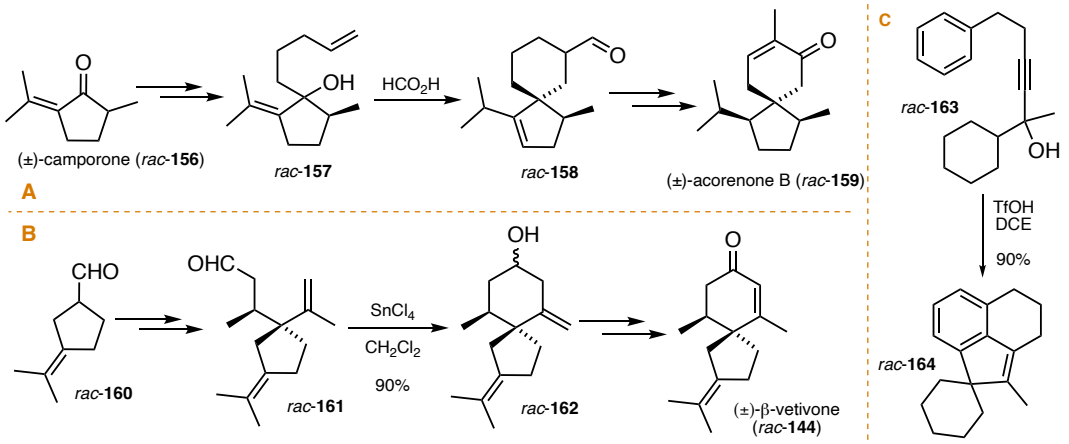
The next example depicted in *Scheme 20*, spironolactone (**145**), can be found on the WHO's list of essential medicines and used as a diuretic and anti-hypertensive drug.[71d] Chamaecydin (**146**) is a spiro polycyclic natural product found in a specific family of conifers, the swamp cypress subfamily.[74] The illudins, like illudin S (**147**), are sesquiterpenoids isolated from fungi and are being investigated for their promising cytotoxic activities. Illudin S was first synthesized by *Matsumoto et al.* using a basic aldol ring-closing reaction, a strategy often employed for the construction of spiro cycles.[75]

The spiroindane natural products cannabispirenone A (**151**) and cannabispirone (**155**), shown in *Scheme 21,* have been isolated from the marijuana plant *Cannabis sativa.*[76] *Crombie et al.* likewise applied a basic aldol reaction to intramolecularly close the ring of these compounds (*Scheme 21*, left side), e.g. (±)-cannabispirenone A (*rac*-**151**).[77] An asymmetric synthesis was published in 1984 by *Natale et al.* using a chiral amine and methyl vinyl ketone to establish the stereocenter as in compound *rac*-**149** enantioselectively and subsequently close the spiro cycle by condensation.[78] (±)-Cannabispirone (*rac*-**155**) was also obtained via an aldol condensation between methyl vinyl ketone and aldehyde *rac*-**153** as key cyclization step in 1981 by *El-Feraly et al.*[79]



SCHEME 21 SYNTHESES OF SPIROINDANE NATURAL PRODUCTS UTILIZING ALDOL REACTIONS TO CONSTRUCT THE SPIRO CENTER.[77, 79]

Despite aldol reactions other acid- or base-promoted spirocyclizations are frequently used. In the total synthesis of (±)- acorenone B (*rac*-**159**) (*Scheme 22,* section **A**) starting from (±)-camporone (*rac*-**156**) intermediate alcohol *rac*-**157** can be synthesized and converted into spiro compound *rac*-**158** by the addition of formic acid.[80] In a *Prins* cyclization of aldehyde *rac*-**161** a *Lewis* acid was employed, delivering both diastereomers of alcohol *rac*-**162** as intermediate in the racemic total synthesis of (±)-β-vetivone (*rac*-**144**) (*Scheme 22*,section **B**).[81]



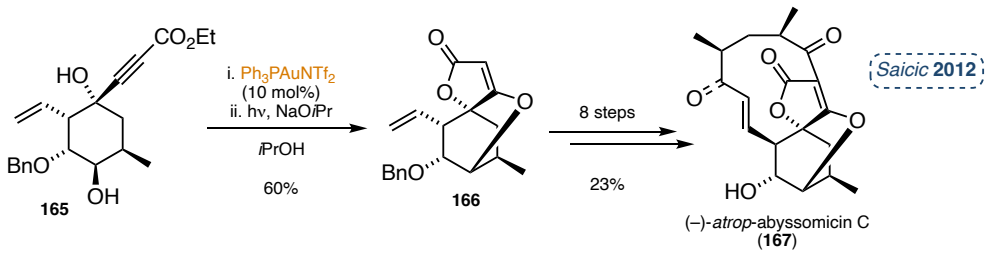
SCHEME 22 TOTAL SYNTHESIS OF (±)-ACORENONE B (**159**) (SECTION **A**), β-VETIVONE (**163**) (SECTION **B**) AND POLYCYCLIZATION APPROACH TOWARDS SPIRO TETRACYCLIC FRAMEWORKS AS **164** (SECTION **C**).[80-82]

In section **C** a more complex acid-catalyzed domino cyclization for the establishment of spirocyclic frameworks as in tetracyclic *rac*-**164** is illustrated. This approach using propagylic alcohols like *rac*-**163** as cyclization precursor was extended to a wide substrate scope and spiro polycycles like chamaecydin (**146**) (*Scheme 20*) natural products.[82]

1.5 GOLD-CATALYZED CYCLIZATIONS IN TOTAL SYNTHESIS

The days of gold compounds being considered too precious and inert for the regular use in research, synthesis or even industrial applications are long gone.[83] During the last decades, homogenous gold catalysis evolved as one of the fastest growing areas of organic chemistry due to a range of beneficial properties.[84] Gold complexes are generally air- and moisture-tolerant, often show orthogonal reactivities compared to other transition metal catalysts and have a high functional group tolerance owing to mild reaction conditions and excellent chemoselectivity.[85] Numerous new methodologies emerged exploiting their ability to catalyze a variety of powerful, highly atom economic transformations, often coming along with a tremendous increase in molecular complexity.[86] Advances have been made both in the development of new reactions and in improving known ones, e.g. oxidation, hydroamination, epoxidation and substitution reactions of allylic alcohols.[87] The exceptionally carbophilic and soft *Lewis* acidic character renders Gold salts extremely efficient in the electrophilic activation of π-bonds.[88] Consideration of relativistic effects is one major aspect in rationalizing the reaction manifold that can be catalyzed by different gold species.[89]

Until today, gold catalysis is a prosperous field of organic chemistry with ongoing research and wide-ranging achievements, also in the development of asymmetric variants.[90] It is not surprising that many organic chemists in total synthesis recognized the highly valuable features of gold complexes and increasingly utilized them in key steps towards many different natural products, often comprising cyclization steps to establish new C–C or C–O bonds.[91]

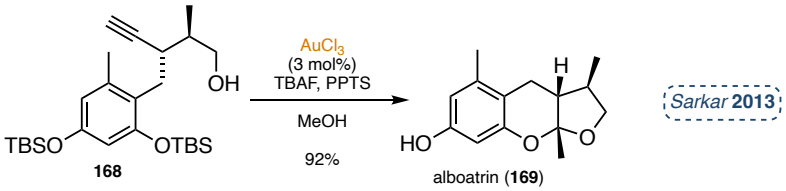


SCHEME 23 PART OF THE TOTAL SYNTHESIS OF (–)-*ATROP*-ABYSSOMICIN C (**167**) VIA A GOLD-CATALYZED CASCADE CYCLIZATION KEY STEP.[92]

In the total synthesis of (–)-*atrop*-abyssomicin C (**167**), *Saicic* and *Bihelovic* established two of the four rings via a gold(I)-catalyzed cyclization cascade (*Scheme 23*). Initially, the catalyst might activate the triple bond towards an *oxa-Michael* addition, followed by photo-induced *cis*/*trans* isomerization. Final addition of a base led to ester hydrolysis and lactonization. Resulting tricyclic **166** can be converted to the natural product in eight additional steps.[92]

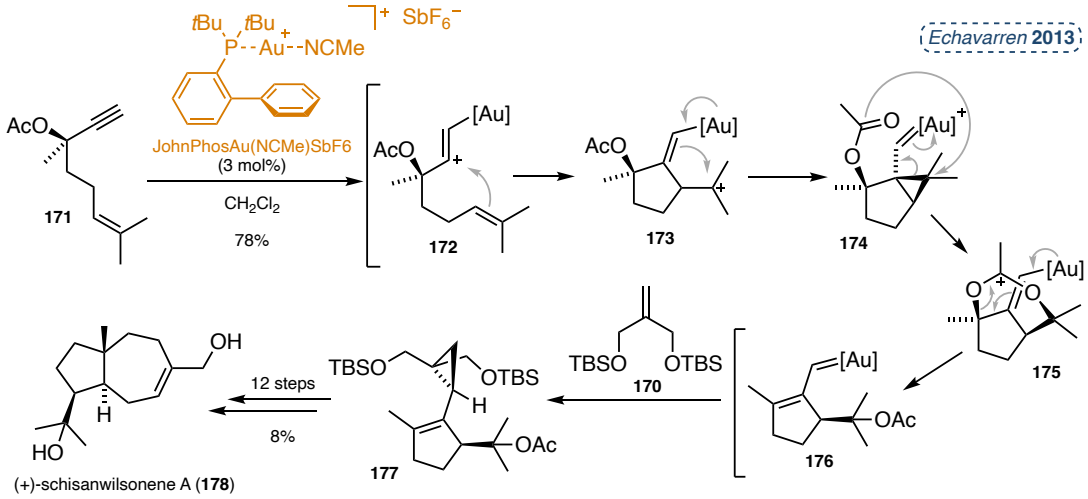
In 2013, *Sarkar* and coworkers employed $AuCl_3$ as catalyst in a one-pot procedure in the presence of TBAF (tetra-*n*-butylammonium fluoride) and PPTS (pyridinium *p*-toluenesulfonate). After deprotection gold activated the triple bond to facilitate its reaction with the two hydroxy groups

to consecutively build up two rings.[93] This approach has been applied for the regio- and stereoselective total synthesis of alboatrin (**169**) (*Scheme 24*).



SCHEME 24 FINAL KEY TRANSFORMATION IN THE TOTAL SYNTHESIS OF ALBOATRIN (**169**) CONSISTING OF AN ONE-POT DESILYLATION/GOLD-CATALYZED CYCLOISOMERIZATION.[93]

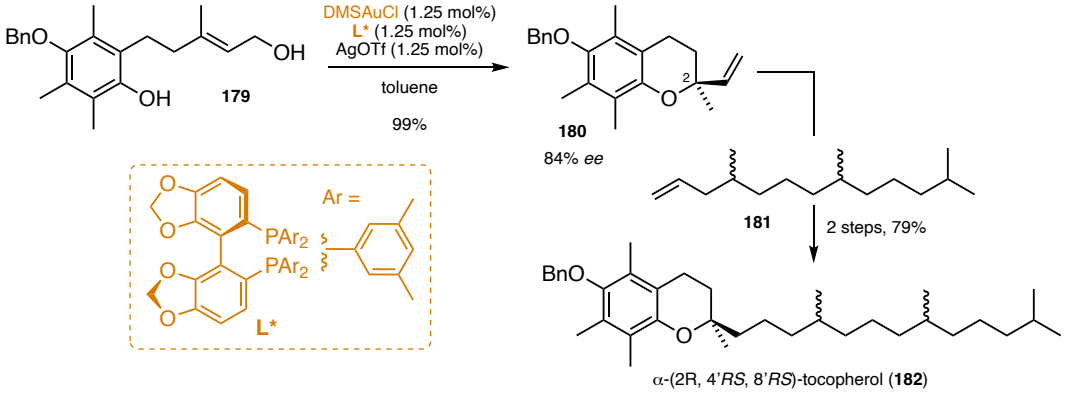
In the same year the group of Echavarren developed a novel tandem cyclization/migration/ cyclopropanation reaction facilitated by a gold (I) complex (*Scheme 25*).



SCHEME 25 COMPLEX GOLD (I) CATALYZED KEY STEP IN THE FIRST ENANTIOSELECTIVE TOTAL SYNTHESIS OF (+)-SCHISANWILSONENE A (**178**).[94]

The triple bond of chiral propagylic ester **171** is activated by the metal complex and a 1,6-enyne cyclization takes place, yielding bicyclic intermediate **174**. After 1,5-migration of the acetate group towards intermediate **176**, this α,β-unsaturated gold carbene species presumably reacts in a cyclopropanation with disilylether **170**. This transformation was employed as the opening key step of the first enantioselective total synthesis of (+)-schisanwilsonene A (**178**).[94]

Many examples can be found where the stereoselectivity of a gold-catalyzed key step in total syntheses is based on substrate control by employing a chiral starting material. Despite the fact that there is an increasing number of enantioselective gold-catalyzed transformations available,[90a] the application to total synthesis is currently still limited.[91] One example is shown in *Scheme 26* where *Rueping* and coworkers used a gold (I) complex with a chiral ligand for the enantioselective installation of a quaternary carbon center C-2 by an intramolecular allylic substitution of alcohol **179**.[95] Resulting chromane **180** can be converted to the target molecule over two additional steps.



SCHEME 26 TOTAL SYNTHESIS OF α-(2*R*, 4'*RS*, 8'*RS*)-TOCOPHEROL(**182**) VIA AN INTRAMOLECULAR ALLYLIC SUBSTITUTION MEDIATED BY GOLD (I).[95]

Although the stereo information at C-4' and C-8' is undefined, this work can be seen as formal enantioselective total synthesis of α-tocopherol since the phytyl side chain **181** is available in an enantiopure fashion starting from farnesol following *Pfaltz's* procedure from 2008.[96]

2 MOTIVATION AND CONCEPTION

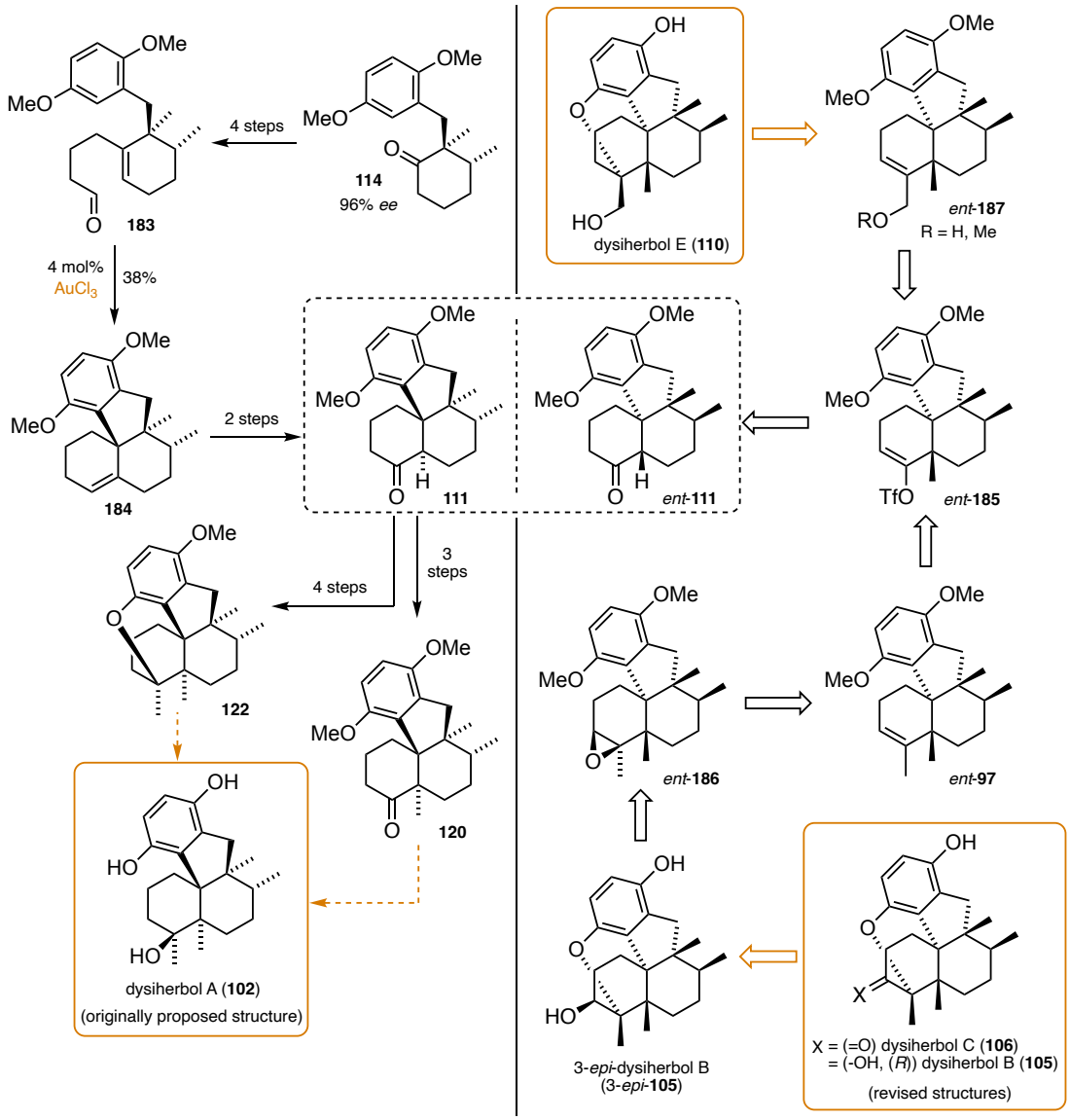
2.1 TOTAL SYNTHESIS OF THE DYSIHERBOLS

Natural product synthesis is the art of mimicking mother nature's molecules in the laboratory, where synthetic organic chemists find ways to provide interesting biologically active agents, not only for the sake of drug development. The research field of organic chemistry highly benefits from the discoveries made in the course of total syntheses, as already outlined in chapter **1.1**. This involves not only newly discovered methods and reactions, but also structural elucidations, as the synthesis of a molecule is often the only way to gain certainty about its constitution and configuration.[6-7, 8]

In particular, marine environments have shown promise for the discovery of novel, interesting compounds. Marine sponges are the main source of sesquiterpene quinones, a natural product class of huge structural diversity showing a multitude of different bioactivities (see chapter **1.2.1**).[13] For example, the dysiherbols (chapter **1.2.4**) all exhibit anti-inflammatory activities. Notably, dysiherbol A showed auspicious sub-micromolar IC_{50} values towards cancer cell line NCI H-929 and protein complex NF-κB involved in the process of inflammation.[19f] Additionally, the intriguing structures of dysiherbols A-E render them all attractive targets for total synthesis.

In this work, the first goal was the completion and optimization of the total synthesis towards dysiherbol A together with *Julian Baars*. Based on his seminal work displayed in *Scheme 13* (p. 17), an improved synthetic route for the construction of tetracyclic **184** via a twofold cyclization of aldehyde **183** was already developed during my master's thesis.[97] Central tetracyclic ketone **111** can be converted into advanced intermediates **120** or **122** over three or four steps. As the revised constitution and absolute configuration of dysiherbol A (**98**, *Figure 5*) was not known at the beginning of this work, their conversion into tetracyclic triol **102** was the goal at this point (indicated with orange dashed lines on the left side of *Scheme 27*).

Subsequently, the total syntheses of congeners dysiherbol B (**105**) and C (**106**) in revised constitution and absolute configuration were targeted (*Scheme 27*). From a retrosynthetic point of view dysiherbol B (**105**) might be accessible via diastereoselective reduction of dysiherbol C (**106**). The epimer of dysiherbol B (3-*epi*-**105**) might result from an envisioned deprotection, (acidic) epoxide opening, cyclization cascade employing epoxide *ent*-**186**. This diastereomer is believed to be formed based on substate control in the epoxidation of olefin *ent*-**97**. This olefin in turn is accessible via *Stille* coupling of triflate *ent*-**185** (compare *Scheme 11*),[40] which can be traced back to central ketone *ent*-**111** again.



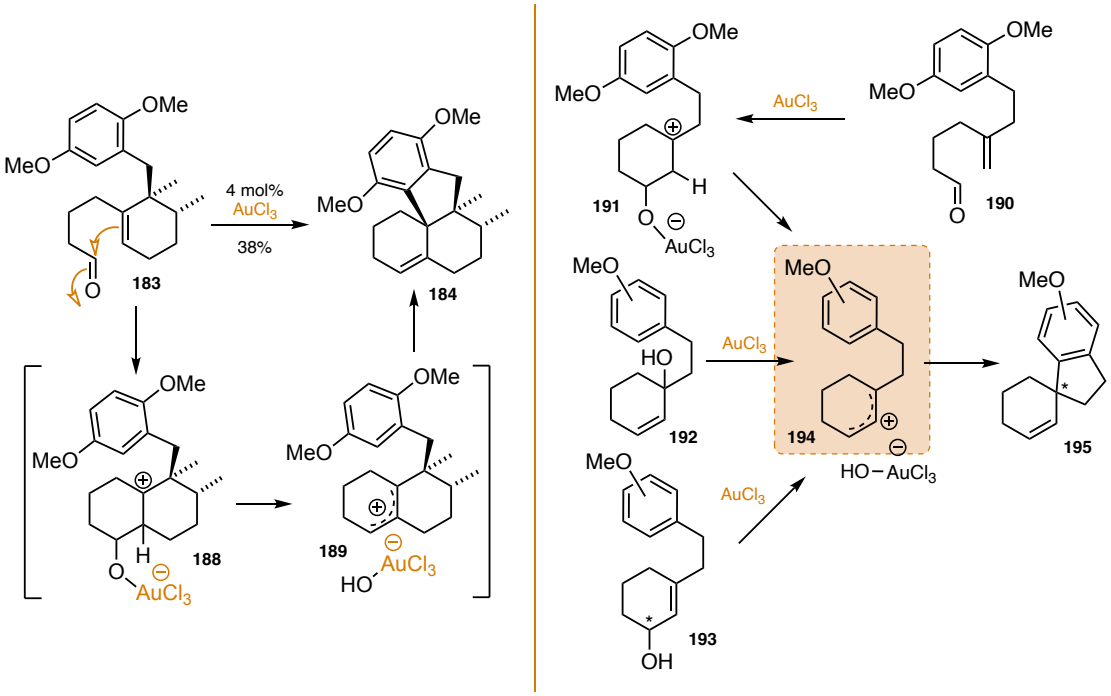
SCHEME 27 TOTAL SYNTHETIC APPROACH TOWARDS THE ORIGINALLY PROPOSED STRUCTURE OF DYSIHERBOL A (**102**) (LEFT; REMAINING CHALLENGES IN ORANGE DASHED LINES) AND RETROSYNTHETIC ANALYSIS OF DYSIHERBOL B (**105**), C (**106**) AND E (**110**) (RIGHT) WITH COMMON INTERMEDIATE KETONE (*ent*-)**111**.

For the total synthesis of dysiherbol E (**110**) triflate *ent*-**185** was again considered as a precursor for a cross coupling reaction to introduce the –(CH_2OR) group. Subsequently, deprotection and protonation of the double bond of *ent*-**187** might result in the closure of the last ring and thereby lead directly to the desired natural product.

2.2 STUDIES ON A GOLD-CATALYZED CYCLIZATION

In the course of the studies towards the total synthesis of dysiherbol A, a novel twofold cyclization was developed as already depicted in *Scheme 27*. Among several *Lewis* acids tested, $AuCl_3$ was the only one capable of catalyzing (4 mol%) the desired transformation and thereby building up the tetracyclic carbon skeleton of the dysiherbols as in olefin **184**, under the elimination of water. Another goal of this work was to further investigate this interesting reaction and gain deeper

insights into the mechanism. For that purpose, different cyclization precursors should be synthesized and treated with $AuCl_3$, as shown in *Scheme 28.*



SCHEME 28 STUDIES ON THE $AuCl_3$-CATALYZED TWOFOLD CYCLIZATION DEVELOPED FOR THE TOTAL SYNTHESIS OF THE DYSIHERBOLS (LEFT, WITH PROPOSED MECHANISM) CONDUCTED ON SIMPLIFIED PRECURSORS AND RESULTING IN A SPIRO CYCLIZATION (RIGHT).

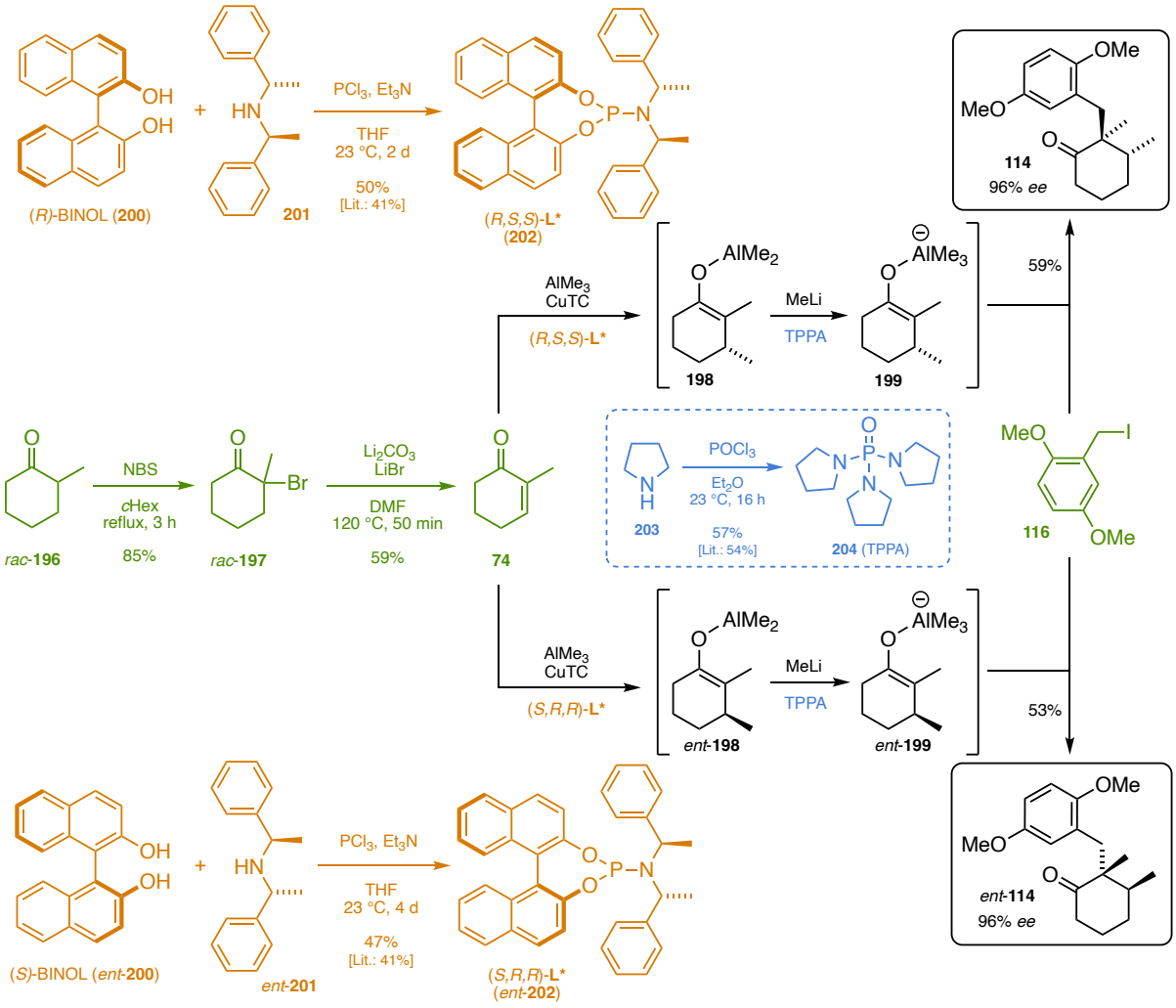
Most of the tested *Lewis* acids afforded the first cyclization to create the *trans*-decalin system, but not the subsequent S_EAr type connection to the electron rich aromatic ring. As $AuCl_3$ is known to catalyze substitutions of allylic alcohols (see chapter **1.5**) the mechanism depicted in *Scheme 28* was proposed as explanation for its unique performance in the observed transformation. The gold (III) salt is supposed to rapidly convert the primary cyclization intermediate **188** into the more stable allylic cation **189** under the formation of known anion $AuCl_3(OH)^-$. The allylic cation in turn can then be attacked by the aromatic ring at the bridgehead position, whereas **188** is more prone to result in primary cyclization or benzyl shift products, as observed for other *Lewis* acids.

To support this hypothesis, allylic alcohols **192** and **193** should be treated with $AuCl_3$, both expected to deliver allylic cation **194** which upon cyclization probably give spirocyclic compound **195**. Additionally, allylic alcohol **193** is planned to be synthesized in an enantiopure fashion to test if the stereochemical information is conserved during the reaction. Furthermore, the role of the substitution of the aromatic moiety should be examined by testing different Me-protected phenols. The reaction of simplified aldehyde **190** might provide evidence if the preorganization within aldehyde **183** is necessary for successful cyclization.

3 RESULTS AND DISCUSSION

3.1 TOTAL SYNTHESIS OF THE DYSIHERBOLS

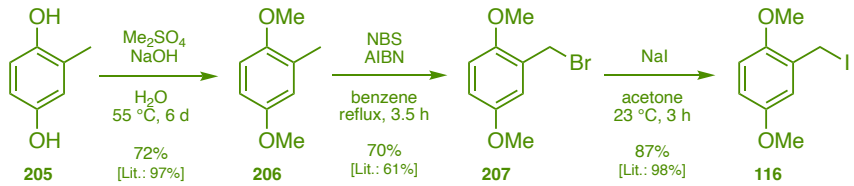
As first key step of the discussed total synthesis the one-pot 1,4-addition enolate trapping sequence developed by *Cramer et al.* was applied, as already mentioned in the previous chapter (compare *Scheme 8*).[58] *Julian Baars* was able to transfer this method to 2,5-dimethoxy benzyl iodide **116**, furthermore replacing the originally employed, highly carcinogenic solvent HMPA by related TPPA (**204**),[64] which was synthesized according to a published protocol.[98] Based on his seminal work the synthesis of ketone **114** depicted in *Scheme 29* was conducted and additionally applied to the synthesis of *ent*-**114**. The chiral information is introduced by employing *Feringa's* phosphor amidite ligand **202**,[99] both enantiomers were synthesized following a literature known protocol.[100] This ligand is used together with CuTC (copper(I) thiophene-2-carboxylate) as catalyst to enantioselectively introduce a methyl group in an 1,4-addition on enone **74**, resulting in enolate (*ent*-)**198**. To facilitate the nucleophilic substitution reaction of this enolate on iodide **116**, it was treated with MeLi before the iodide was added to the reaction mixture.



SCHEME 29 SYNTHETIC TRANSFORMATIONS FOR THE SYNTHESIS OF KETONE **114** - ENANTIOSELECTIVE ENTRY OF THE TOTAL SYNTHESIS OF THE DYSIHERBOLS.[64]

Enone **74** was synthesized from *rac*-2-methylcyclohexanone (*rac*-**196**) applying a literature protocol for α-bromination and elimination, but exchanging CCl_4 for *c*-Hex as a less toxic solvent in the bromination step.[101]

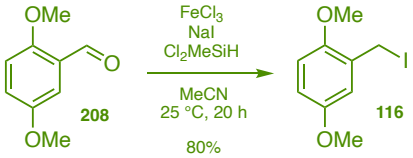
Benzyl iodide **116** might be prepared starting from methylhydroquinone (**205**) based on a literature sequence. Starting off with double protection of the hydroquinone the benzylic position is functionalized in the second step via a radical bromination.[102] Subsequent *Finkelstein* reaction transforms benzylic bromide **207** into benzylic iodide **116**.[103] Remarkably, this iodide is prone to decomposition during the purification process due to different side reactions such as polymerization under formation of a black solid mass. Another drawback of this sequence is the work- and time load, especially when considering potentially losing the product in the purification of the last step.



SCHEME 30 SYNTHESIS OF IODINE BUILDING BLOCK **116** STARTING FROM HYDROQUINONE **205**.

Therefore, an alternative synthesis for this building block was developed, based on a literature protocol applying a reductive halogenation to 2,5-dimethoxybenzaldehyde (**208**) using $FeCl_3$ as a catalyst.[104] In the cited publication this method was used to synthesize mono-methoxylated benzyl iodide, apparently showing a higher stability as the reaction was conducted in refluxing MeCN, causing decomposition in the case of the more electron rich aromatic compounds (*Table 1*, *entry 1*). Lowering the temperature required longer reaction times and higher amounts of reagents (*entry 1 & 2*), but eventually led to full conversion of the starting material (*entry 3*).

TABLE 1 CONDITIONS SCREENING FOR REDUCTIVE HALOGENATION OF BENZYLIC ALDEHYDE **208**.



entry	$FeCl_3$ [eq]	Cl_2MeSiH [eq]	NaI [eq]	T	t	purification	result
1[104]	0.05	1.5	1.5	reflux	1 d	-	decomposition
2	0.05	1.5	1.5	25 °C	1 w	-	<50% conversion
3	0.1	3.0	3.0	25 °C	20 h	extraction	mixture (side products/impurities)
4	0.1	3.0	3.0	25 °C	20 h	column	decomposition
5	0.1	3.0	3.0	25 °C	20 h	crystallization	mixture (insoluble polymer)
6	0.1	3.0	3.0	25 °C	20 h	filtration crystallization MeOH wash	70-80% isolated yield for **116**

Purification via extraction yielded **116** in a mixture with side products, and separation using column chromatography was not feasible due to decomposition. Crystallization by adding water gave **116** together with an insoluble silicon polymer, which could be separated by filtration before crystallization. Thereby, the desired building block **116** is accessible via one single step from benzylic aldehyde **208** in yields ranging from 70-80%. Polymerization was not observed during the purification process.

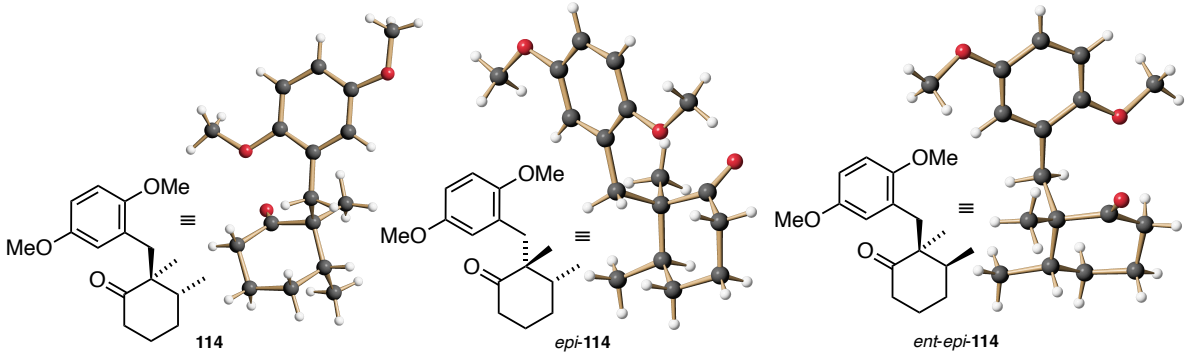
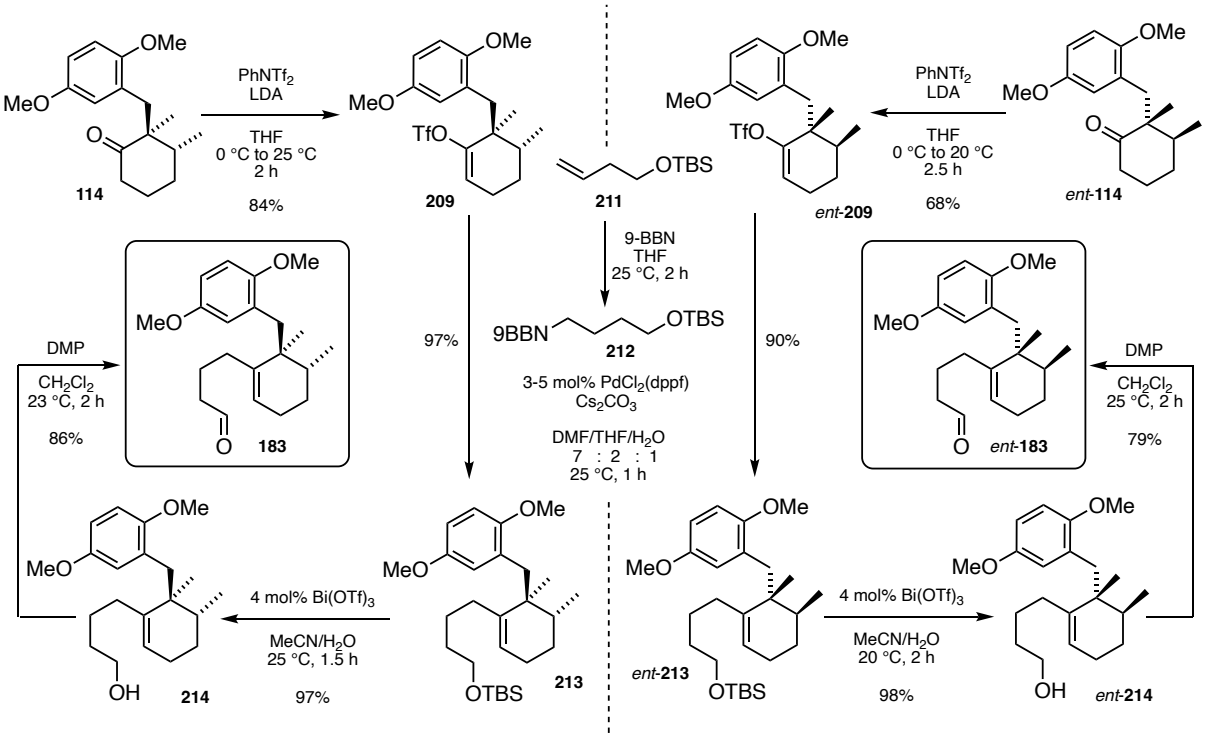


FIGURE 7 PRODUCTS OF THE 1,4-ADDITION/α-ALKYLATION SHOWN IN *SCHEME 29*.

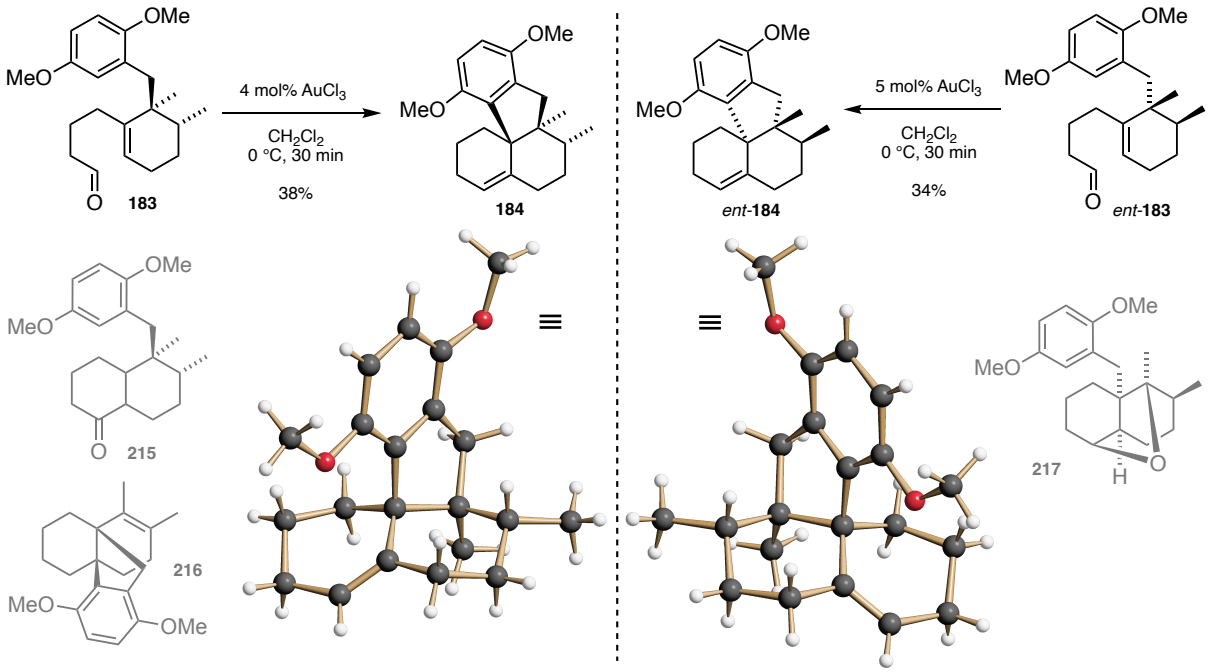
The reaction with enolate **199** was performed with a good yield of 59% for **114** and 53% for enantiomer *ent*-**114**, both obtained with an enantiomeric excess of 96% (determined by chiral HPLC). Additionally, diastereomers *epi*-**114** and *ent-epi*-**114** were formed during the reaction and separated via column chromatography. The diastereoselectivity for the desired *trans*-products was approximately 5:1 (according to GC-MS). Measured crystal structures of the products are shown in *Figure 7* and confirm the assigned absolute configuration.



SCHEME 31 SYNTHESIS OF CYCLIZATION PRECURSOR **183** FROM KETONE **114**.

As already outlined in the previous chapter, an alternative approach (compared to that shown in *Scheme 13*) for the construction of the tetracyclic carbon skeleton of the dysiherbols was developed during my master's thesis.[97] The key step of this strategy is the double cyclization of aldehyde **183** (*Scheme 32*). An optimized route towards this cyclization precursor starting from ketone **114** is displayed in *Scheme 31*. For the introduction of the C_4-unit, TBS-protected homoallylic alcohol **211** is reacted with 9-BBN to be subsequently coupled to enol triflate **209** in a *Suzuki-Miyaura* cross coupling applying literature known conditions[105] to deliver **213** in excellent yield. The outcome of this reaction depends on the purity of triflate **209** as residual triflation agent was difficult to separate from the product due to similar polarity on column, yields ranging from 78% (amount of $PhNTf_2$ in a mixture with **209** > 15%) to 97% (amount of $PhNTf_2$ in a mixture with **209** <5%). The cleavage of the TBS group was achieved in excellent yield using a very mild and atom economic method with catalytic amounts of $Bi(OTf)_3$ together with water.[106] The resulting alcohol was directly subjected to oxidation using DMP (*Dess-Martin* periodinane). With this scalable synthesis, up to 15 g of bench-stable aldehyde **183** can be synthesized. The route was also applied to the enantiomeric ketone *ent*-**114**, giving comparable yields for all reactions and delivering *ent*-**183**, as expected (*Scheme 31*, right).

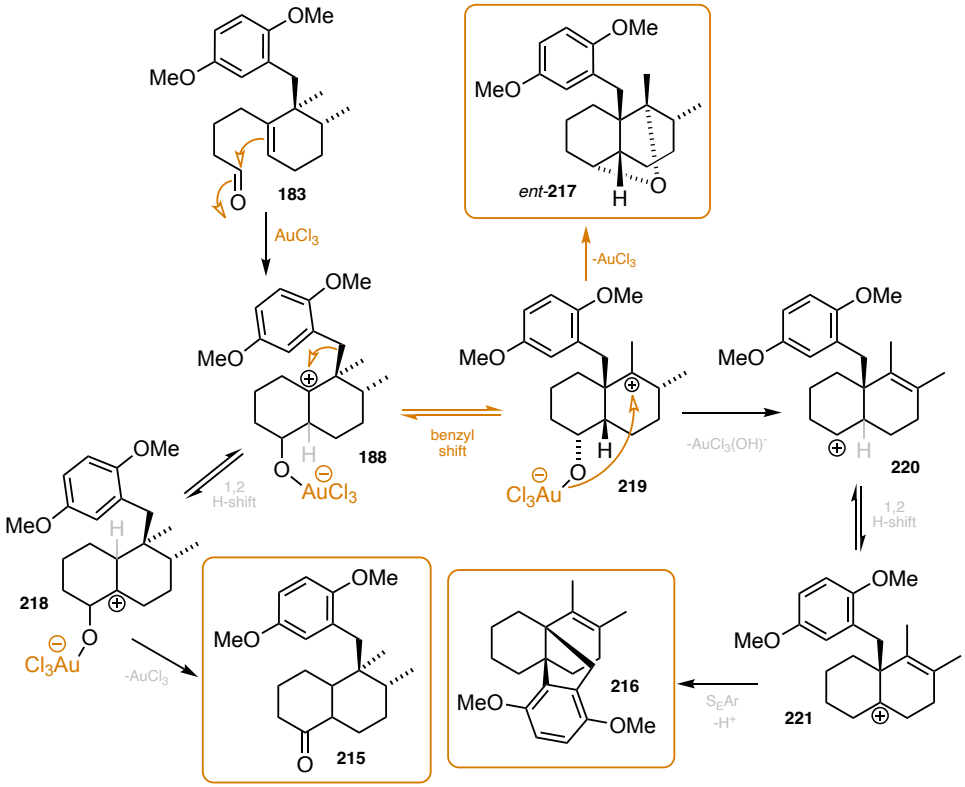
With cyclization precursor **183** the gold-catalyzed twofold cyclization depicted in *Scheme 32* was elaborated. $AuCl_3$ was the only *Lewis* acid tested that delivered the desired tetracyclic carbon skeleton of olefin **184** as sole major product, transformation proceeding under the elimination of water (for a detailed discussion concerning the mechanism see chapter **3.2**). Optimization attempts, e.g. solvent screening,[64] testing of other Au(III)-based catalysts and trapping of water did not result in higher selectivity and isolated yield. The best result of 38% isolated yield was achieved on high dilution in CH_2Cl_2. Under these conditions, up-scaling was feasible to gram scale without a significant loss in yield.



SCHEME 32 GOLD-CATALYZED TWOFOLD CYCLIZATION OF ALDEHYDE **183** FOR THE CONSTRUCTION OF THE TETRACYCLIC DYSIHERBOL SKELETON (**184**) TOGETHER WITH ISOLATED SIDE PRODUCTS.

Olefin **184** was obtained together with numerous side products, some of them were isolated and characterized (*Scheme 32*). Bicyclic ketone **215** is the product of the onefold cyclization of aldehyde **183**, a possible mechanism of formation is depicted in *Scheme 33.* This compound was obtained in almost all cases during the screening for a suitable *Lewis* acid to build up the 6/6/5/6 tetracyclic carbon skeleton. A possible explanation for the outstanding role of $AuCl_3$ might be the formation of an allylic cation (**189**, see *Scheme 28*) that is stable enough to undergo the seemingly tricky S_EAr connection between the decalin bridgehead and the electron rich aromatic moiety preferentially over side reactions such as benzyl shifts. Nevertheless, such shifts also occur with the gold catalyst. Two resulting side products are also shown in *Scheme 32*.

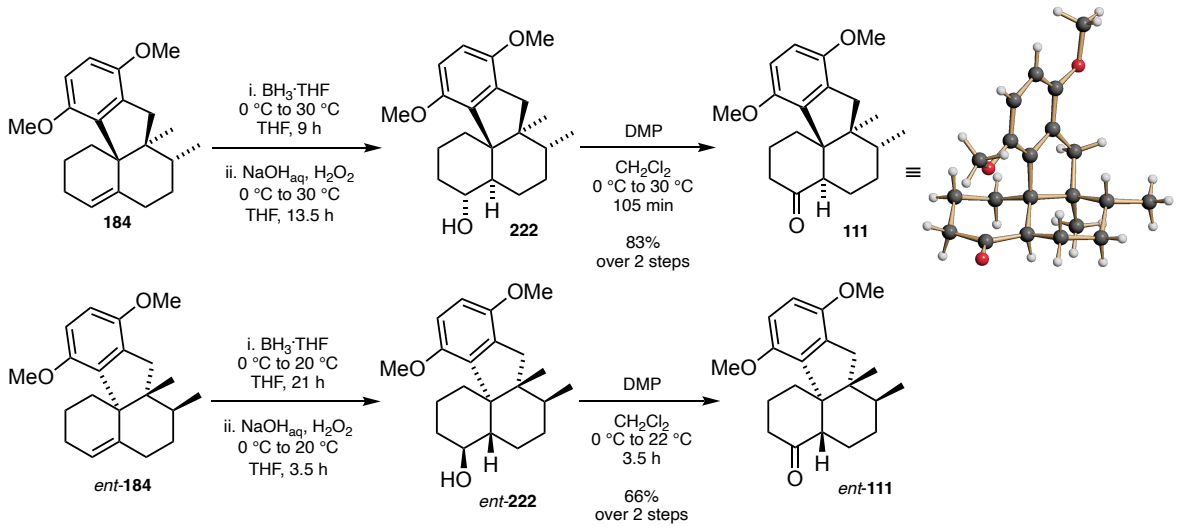
Cis-decalin **217** is also a product of a onefold cyclization and probably results from a benzyl shift after the initial cyclization to cation **188** and trapping of the resulting cation **219** by the oxygen, building up an ether bridge (*Scheme 33*). The decalin system of product **217** is supposed to be forced into its thermodynamically unfavored *cis* configuration by this additional bond. It was isolated as side product (4% yield) of the cyclization of aldehyde *ent*-**183**. A possible mechanism for the formation of its enantiomer *ent*-**217** is also given in *Scheme 33.*



SCHEME 33 ISOLATED SIDE PRODUCTS OF THE GOLD-CATALYZED TWOFOLD CYCLIZATION OF ALDEHYDE **183** TOGETHER WITH POSSIBLE MECHANISMS OF FORMATION.

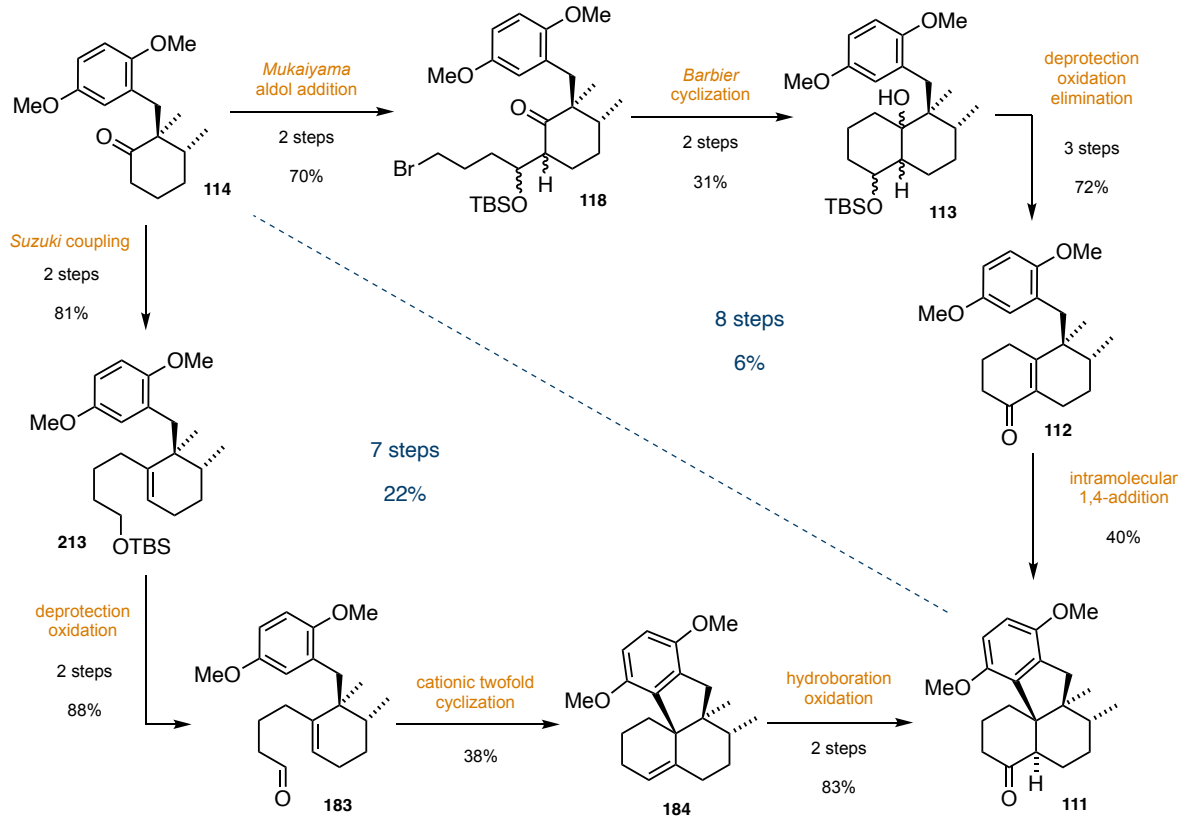
Another isolated side product **216** emerges under the elimination of water and a S_EAr reaction, similar to olefin **184**. In contrast to **184** it is the product of an additional benzyl and a 1,2 H-shift. By trapping the resulting cation **221** the aromatic ring forms another 6/6/5/6 carbon skeleton (**216**), with both connections to the bridgehead carbon atoms of the decalin system.

As the discussed formation of the tetracyclic core motif proceeded under elimination of water, two additional steps were necessary to synthesize ketone **111**, the common intermediate for the envisioned total syntheses of the dysiherbols (compare *Scheme 27*). The sequence shown in *Scheme 34* proceeded smoothly with a very good yield of 83%, given over two steps as the crude product was directly employed in the DMP oxidation (66% over two steps for the enantiomeric series). After hydroboration/oxidation of olefin **184**, a sample of the resulting secondary alcohol **222** was purified to determine the configuration of the two newly formed stereocenters by ^{1}H,^{1}H-NOESY NMR experiments. A crystal structure of desired ketone **111** is also shown in *Scheme 34*.



SCHEME 34 OXIDATION OF TETRACYCLIC OLEFIN **184** TO PROVIDE COMMON INTERMEDIATE KETONE **111** FOR THE TOTAL SYNTHESIS OF THE DYSIHERBOLS.

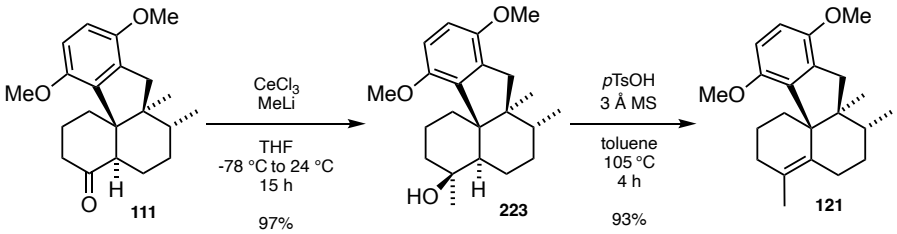
In summary, the developed synthetic strategy delivers ketone **111** within seven steps in an overall yield of 22%. In comparison, the previous route counted one step more with a yield of 6%. The difference is the application of the twofold cyclization to construct the tetracyclic core structure versus two single cyclizations in the old route, a *Barbier* cyclization and an intramolecular 1,4-addition (*Scheme 35*).



SCHEME 35 COMPARISON OF THE TWO SYNTHETIC STRATEGIES FOR THE SYNTHESIS OF KETONE **111**.

3.1.1 DYSIHERBOL A

The finalization of the first enantioselective total synthesis of dysiherbol A was further pursued together with *Julian Baars* based on his seminal results shown in *Scheme 13*. During the preparative work presented here, he discovered that the constitution of targeted natural product needs to be revised,[64] independently from the findings of *Chong et al.* published in 2021 (*Scheme 11*).[40] Pentacyclic **98**, an anhydride of the originally proposed triol **102**, turned out to be the correct structure of the natural product isolated in 2016 (*Figure 5*, *p. 15*). Thus, *Baars* total synthesis depicted in *Scheme 13* was completed by simple deprotection of compound **122**, but further optimizations of the protocols and analytical characterizations of the synthesized products were still pending.

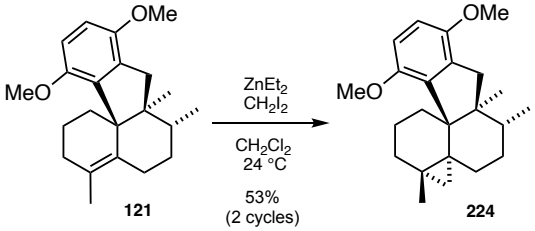


SCHEME 36 SYNTHESIS OF OLEFIN **121** FROM KETONE **111** VIA *GRIGNARD* ADDITION/ELIMINATION.

Ketone **111** was converted over two steps into olefine **121** via *Grignard* addition and subsequent elimination with excellent yields. Between the two reactions no purification was necessary.

The following *Simmon-Smith* cyclopropanation under *Furukawa* conditions (*Scheme 11*) is rather challenging as the methylenation of all-carbon tetrasubstituted olefines is not that common.[107] The reaction gave room for improvement as the conversion of **121** to **224** always stopped after approximately 30 min at around 50% (based on GC-MS data), even though the reagents were applied in huge excess. It was hypothesized that this might be explained by the decomposition of the active carbenoid species ("$EtZnCH_2I$"). Therefore, $ZnEt_2$ (in hexanes) was successively added to a solution of **121** together with CH_2I_2 in CH_2Cl_2, to ensure a continuous generation of the active species, and indeed the SM/product ratio was shifted to 75% at a point of equimolar amounts of the two reagents and even over 80% when more $ZnEt_2$ was applied (*Table 2, entry 1)*. Successive simultaneous addition of equimolar amounts of both reagents gave similar results (1.2 equivalents every 20 minutes) and inverting the procedure by successively adding CH_2I_2 worsened the result significantly. At higher concertation it was possible to increase the conversion to over 90% and stopped to further proceed at twelve equivalents of the reagents (*Table 2, entry 2)*.

TABLE 2 CONDITIONS SCREENING FOR THE *SIMMON-SMITH* CYCLOPROPANATION OF OLEFIN **121**.



121 **224**

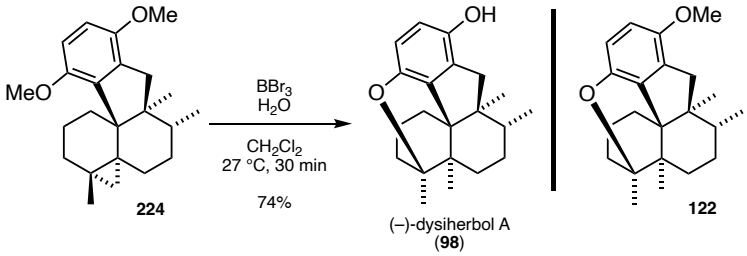
entry	$ZnEt_2$ [eq]	CH_2I_2 [eq]	c [M]	CH_2Cl_2/ hexanes	**121**[a]	**224**[a]	side products[a]	note
1	8 12	8 8	0.045	2.9 : 1 1.4 : 1	25% 20%	75% 80%		$ZnEt_2$ successively added
2[b]	5 12	5 12	0.45	1 : 2.5 1 : 5	40% 5%	60% 95%		Simultaneous addition of $ZnEt_2$ and CH_2I_2
3[b]	5 16 18	5 16 18	0.45	1 : 2.5	40% 5% -	55% 65% 40%	5% 30% 60%	Solvent ratio adjusted, 16% isolated yield
4-1[b]	5	5	0.45	1 : 2.2	40%	50%	10%	Extraction at 50% conversion
4-2[b]	5	5	0.45	1 : 2.2	15%	65%	20%	2nd cycle with crude 4-1
5-1[b]	5	5	0.45	1 : 2.3	45%	50%	5%	1st cycle, 44% isolated yield
5-2[b]	5	5	0.45	1 : 2.3	30%	50%	20%	2nd cycle, 24% isolated yield

$ZnEt_2$ was added as a solution in hexanes. [a] Ratio of **121** to **224** was determined via integration of suitable GC (TIC) signals. [b] Addition of both reagents was performed simultaneously, 1.2 eq. each, every 20 min.

As the diminished concentration resulted in a changed ratio of solvents CH_2Cl_2/hexanes, the speculation arose that the reaction is not proceeding if the amount of hexane exceeds a certain point (CH_2Cl_2/hexanes = 1:5 for *entry 2*). Therefore, in the following experiments the ratio of the solvents was adjusted by adding CH_2Cl_2 when adding $ZnEt_2$ (in hexanes). Thereby full conversion was achieved, but numerous side products were observed via GC-MS and NMR analysis (*Table 2, entry 3*, for *entry 1* and *entry 2* the amount of side products was not determined), also reflected in the poor isolated yield of 16% for cyclopropane **224**. Two compounds were isolated but not fully characterized due to rapid decomposition. NMR analysis indicated the reaction of the electron rich aromatic moiety in a cyclopropanation and a *Buchner* ring expansion reaction as occurring side processes. As the number of undesired products is increasing with time, conversion and amount of reagent added, an additional experiment was performed (*entry 4*), stopping the reaction at 50% conversion with five equivalents of reagents after 30 minutes. The crude product, a mixture of approximately 40% olefin **121**, 50% cyclopropane **224** and 10% side products, was subjected to the same conditions a second time. Unfortunately, no full conversion was achieved, but the previously observed significantly increased side product formation was still a problem. To circumvent this drawback, the best solution was to separate the desired product from the starting material and the side products via column chromatography and employing **121** in another round of cyclopropanation (*entry 5*), best result over two cycles 53% on a 100 mg scale. The drop in yield between the first and the second cycle might be explained by the halving of the scale size, as exact additions on the smaller size are more difficult.

Since pentacyclic **98** is believed to be the actual structure of the natural product, a final three-in-one reaction was envisioned. Deprotection of **224** under acidic conditions should lead to opening of the cyclopropane and the resulting cation might be trapped by the subjacent phenolic oxygen.

TABLE 3 CONDITIONS SCREENING FOR THE FINAL DEPROTECTION/CYCLOPROPANE OPENING/CYCLIZATION REACTION IN THE TOTAL SYNTHESIS OF REVISED, PENTACYCLIC DYSIHERBOL A (**98**).

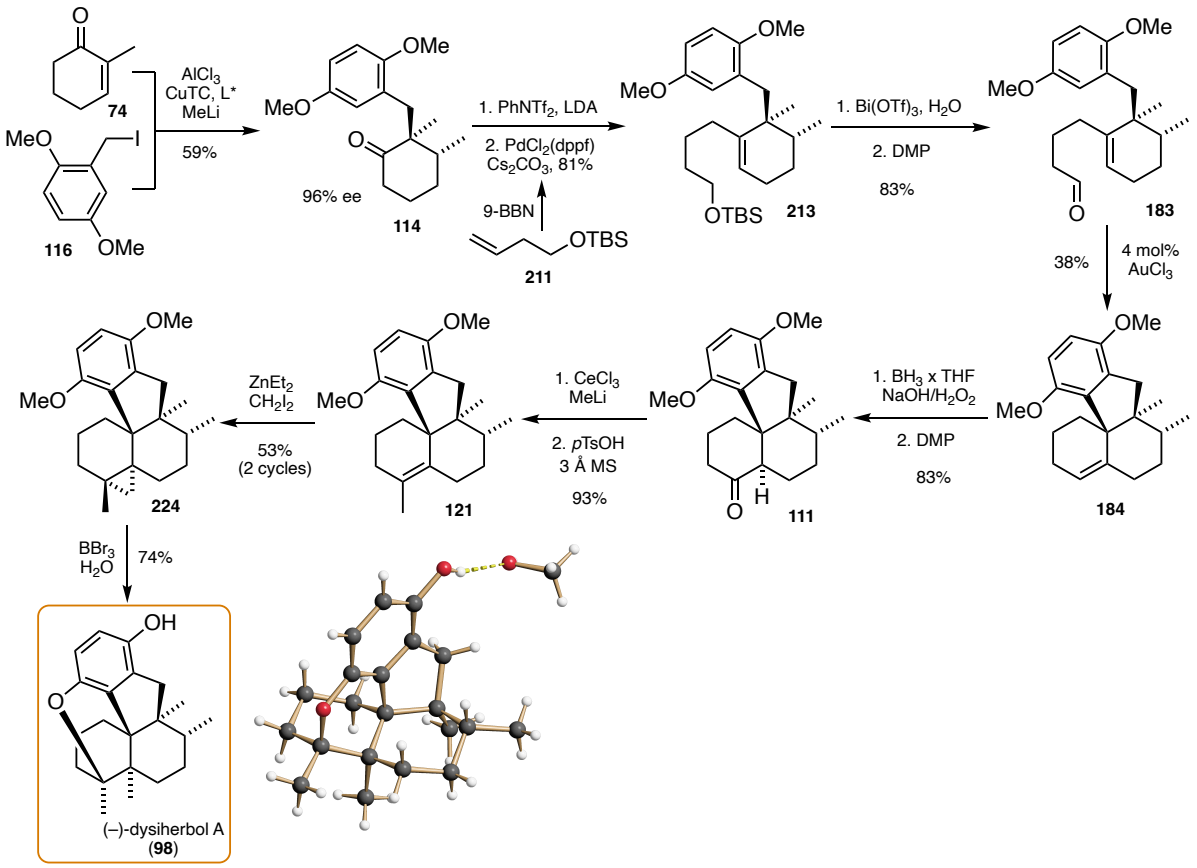


entry	BBr_3 [eq]	H_2O [eq]	t [h]	**98**[a]	**122**[a]	uncyclized olefin[a]	other side products[a]	note
1	3	-	1	30%	20%	20%	30%	
2	3	10	0.5	25%	75%	-	-	
3	4	10	0.5	85%	15%	-	-	
4	5	10	1	85%	-	15%	-	
5	8	20	0.5	85%	5%	10%	-	
6	10	20	0.5	75%	15%	-	10%	BBr_3 added first
7	10	10	1	80%	-	10%	10%	
8	10	10	0.5	90%	-	10%	-	74% isolated yield

All reactions were performed by adding H_2O first and subsequently BBr_3 (except entry 1 and 7). [a] Ratio of **98** and observed side products was determined via integration of suitable GC (TIC) signals and characteristic NMR signals.

Similar reactivities were already observed by *Julian Baars*, and if instead of MsOH (see *Scheme 13*) BBr_3 is used directly, full demethylation should be possible to deliver dysiherbol A (**98**) instead of cyclic ether **122**, a comparable reaction was also previously observed for alcohol **223**.

In *Table 3* the results of the screening for this reaction are summarized. With three equivalents of BBr_3 (*entry 1*) a mixture of many different products was obtained, containing desired **98** as main product. However, substantial amounts of still mono-methylated dysiherbol A (methyl ether **122**) and other unknown side products remained. Based on NMR analysis of the crude product, one prominent side product seemed to be a demethylated but uncyclized olefin, indicating the necessity of more acidic conditions for the generation of a cation to achieve the final cyclization. Thus, water was added to generate HBr and indeed, the olefinic side product was avoided, but with increased equivalents of water over equivalents of BBr_3 the second deprotection was difficult (*entry 2 & 3*). However, if in turn the ratio BBr_3/H_2O exceeds a certain point the olefinic side product is again observed (*entry 4*). Doubling the equivalents of both reagents did not make much difference (compare *entry 3 & 5*). Adding BBr_3 first instead of water raised the formation of the undesired compounds (*entry 6*). The best reproducible result was achieved with equimolar amounts of water and BBr_3 with shorter reaction time reducing the amount of side products (*entry 7 & 8*).



SCHEME 37 ENANTIOSELECTIVE TOTAL SYNTHESIS OF (–)-DYSIHERBOL A (**98**) TOGETHER WITH ITS CRYSTAL STRUCTURE CO-CRYSTALLIZED WITH A METHANOL MOLECULE.

Dysiherbol A (**98**) could thereby be synthesized from precursor **224** in a three-in-one transformation involving an acidic cyclopropane opening at the decalin system, a demethylation of the hydroquinone and subsequent cyclization between the two moieties. Thus, the first enantioselective total synthesis of dysiherbol A (**98**) was accomplished within twelve steps with an overall yield of 5% (*Scheme 37*).

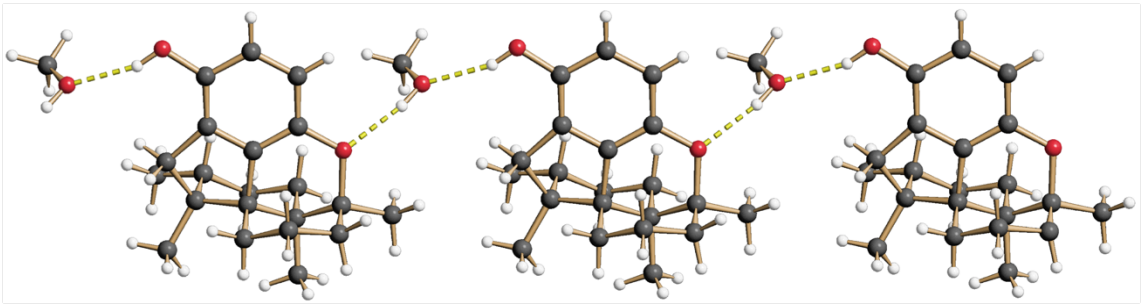


FIGURE 8 CRYSTAL STRUCTURE OF SYNTHESIZED DYSIHERBOL A (**98**), THREE MOLECULES CONNECTED VIA HYDROGEN BONDS TO CO-CRYSTALLIZED METHANOL MOLECULES.

Surprisingly, the specific rotation of synthesized dysiherbol A (**98**) ($[\alpha]^{20}_D$ = –23°; *c* = 0.5 in MeOH) did not match the one reported for the isolated natural product ($[\alpha]^{22}_D$ = +23°; *c* = 0.1 in MeOH).[19f] Since the absolute configuration of synthesized (–)-dysiherbol A (**98**) was ensured by X-ray crystal structures (*Figure 8*), the assigned absolute configuration (*Figure 5*, **102**) proved to be

wrong. The original configurational assignment was based on the comparison of computational ECD spectra with a measured one of the isolated natural product. That this method led to the false assignment is not surprising, since the computational calculations were based on the wrong constitution of **102** instead of pentacyclic **98**. To further validate this theory, an ECD spectrum of synthesized (–)-dysiherbol A (**98**) was measured, the comparison with the reported one clearly confirmed it being the enantiomer of natural (+)-dysiherbol A (*ent*-**98**) (*Figure 9*).

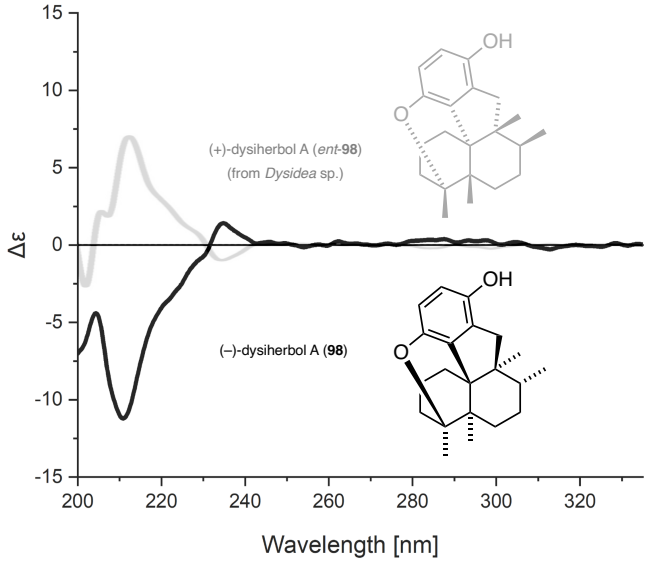
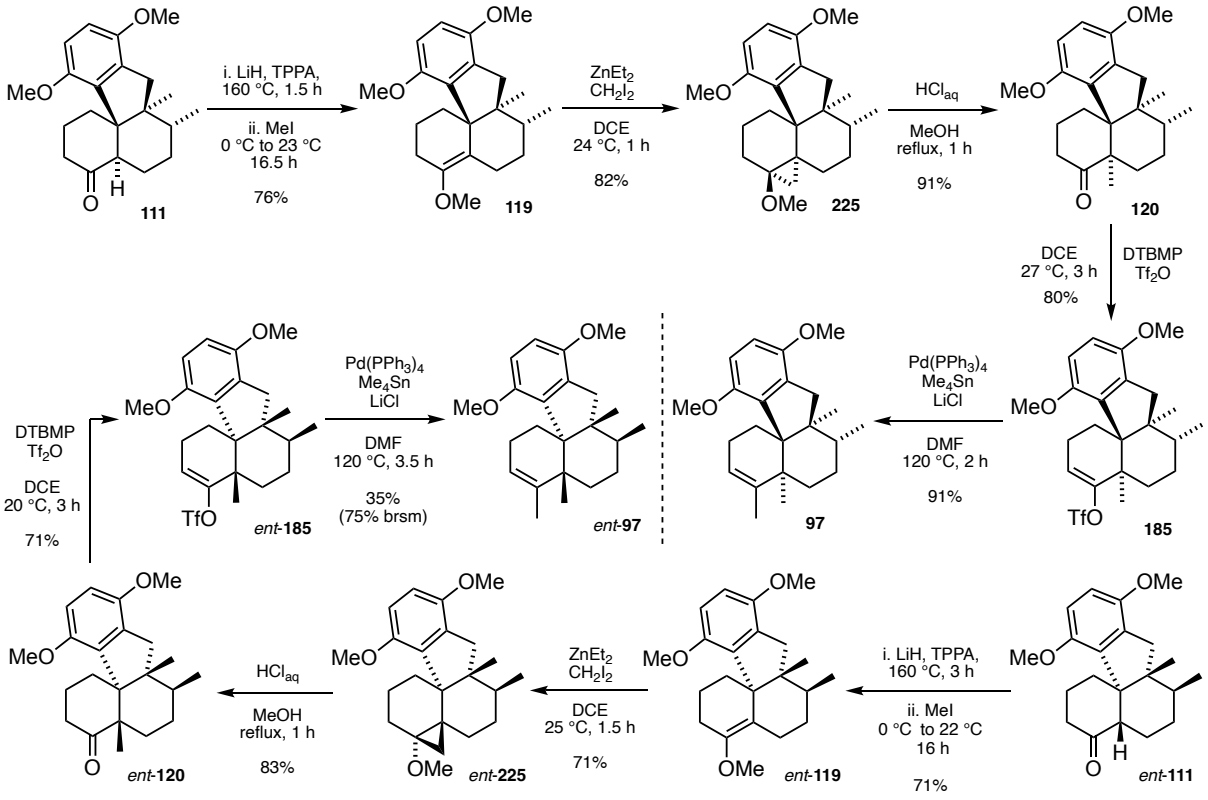


FIGURE 9 COMPARISON OF EXPERIMENTAL ECD SPECTRA OF NATURAL OCCURRING (+)-DYSIHERBOL A (*ent*-**98**, GREY)[19F] AND SYNTHESIZED (–)-DYSIHERBOL A (**98**, BLACK).

As described earlier in this chapter, the enantioselective total synthesis of (–)-dysiherbol A can be easily transferred to (+)-dysiherbol A by just using the opposite enantiomer of ligand **202** in the first key step (compare *Scheme 29*), since all subsequent reactions proceed substrate controlled (*Scheme 37*). Nevertheless, the synthesis of (+)-dysiherbol A was pursued because the comparison of the two enantiomers in biological tests might reveal interesting (differing) properties.

As depicted in chapter **0**, *p. 27* in *Scheme 27* olefin *ent*-**97** might be a suitable precursor for the envisioned total synthesis of dysiherbol B & C. This olefin should be accessible from triflate **185** by utilizing a *Stille* cross coupling based on the seminal work by *Lu* and coworkers on a double methylation at the end of their racemic total synthesis for dysiherbol A (*Scheme 11*). This triflate in turn is considered a good starting point for the synthesis of dysiherbol E (see also chapter **0**, *p. 27* in *Scheme 27*). All dysiherbols are believed to be naturally occurring with the same absolute configuration as (+)-dysiherbol A (*ent*-**98**). Thus, for its synthesis the alternative dysiherbol A-route towards α-methyl ketone **120** developed by *Julian Baars* (*Scheme 13*)[64] was used, since triflate *ent*-**185** and olefin *ent*-**97** are accessible from this intermediate and the latter can be transferred into (+)-dysiherbol (*ent*-**98**), as already investigated by *Lu* (*Scheme 11*).[40]



SCHEME 38 SYNTHESIS OF OLEFIN (*ent*-)**97** FROM COMMON KETONE INTERMEDIATE (*ent*-)**111**.

For supply reasons, the described route (*Scheme 38*) was again performed in both enantiomeric configurations, since precious ketone **111** was still in stock and investigations on advanced intermediates can be performed in either configuration. The three step process (*O*-methylation, cyclopropanation, acidic cyclopropane opening) for the introduction of the α-methyl group in ketone **120** was performed according to *Scheme 13* under minor optimizations regarding procedure and purification, coming with slightly improved yields (57% instead of 48% over three steps).

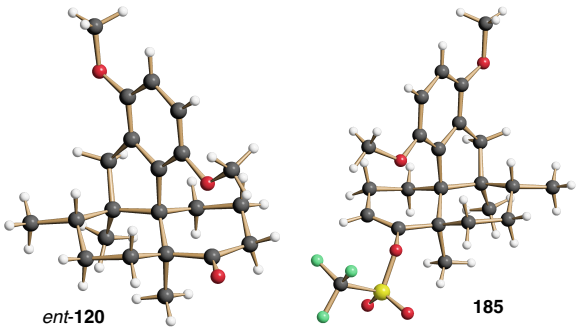
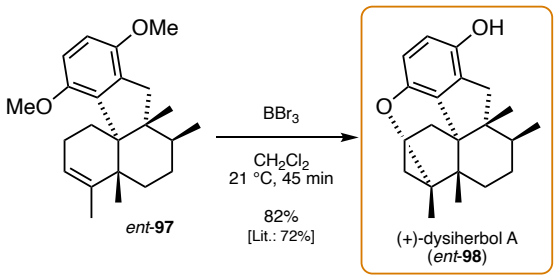


FIGURE 10 CRYSTAL STRUCTURES OF α-METHYL KETONE *ent*-**120** AND TRIFLATE **185**.

After formation of enol triflate **185** in a very good yield of 80%, this intermediate was subjected to the already discussed *Stille* coupling conditions, delivering desired olefin **97** with an excellent yield of 91%. In the enantiomeric series, all yields were in a comparable range, although slightly

diminished, especially in the case of the *Stille* coupling, presumably due to the degraded quality of the tin reagent. However, 40% of the starting material *ent*-**185** could be reisolated.

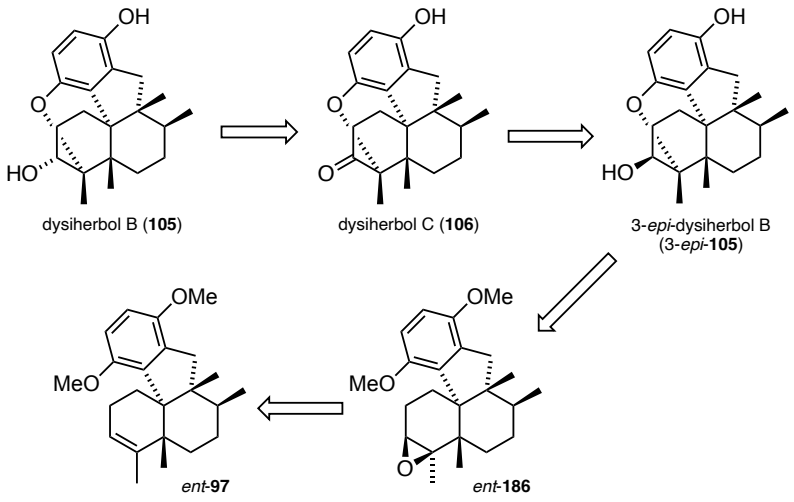


SCHEME 39 DEPROTECTION/CYCLIZATION REACTION OF OLEFIN *ent*-**97** TO OBTAIN NATURALLY OCCURRING ENANTIOMER (+)-DYSIHERBOL A (*ent*-**98**).[40]

To finally obtain (+)-dysiherbol A (*ent*-**98**) in its natural absolute configuration, olefin *ent*-**97** was subjected to the deprotection/cyclization conditions depicted in *Scheme 11* delivering the desired pentacyclic product with a very good yield of 82% (Lit.: 72%).[40]

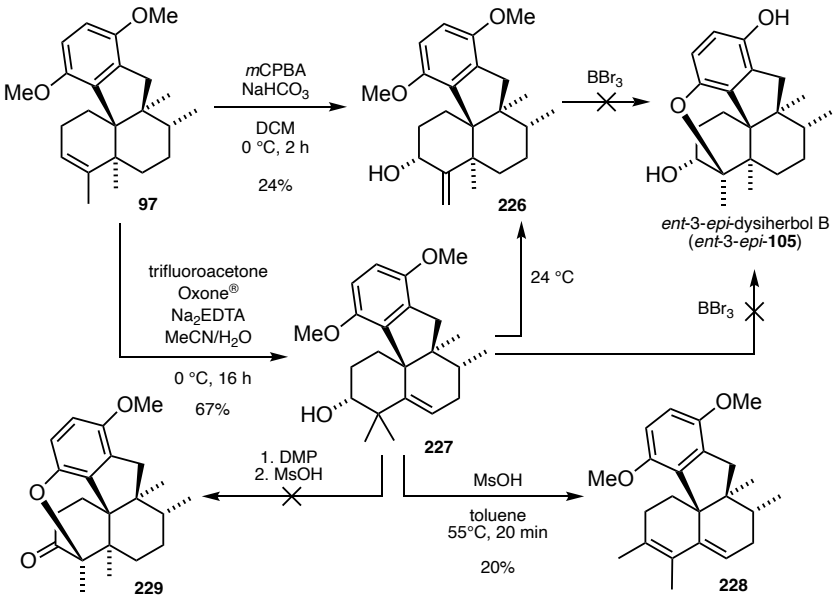
3.1.2 DYSIHERBOL B & C

Having olefin (*ent*)-**97** in hand, which has already the desired carbon skeleton of the dysiherbols, the total synthesis of dysiherbol B and C was targeted (*Scheme 40*). Compound *ent*-**186** was envisioned to be easily accessible by epoxidation of this olefin. Subsequently, a cascade reaction similar to the one developed for dysiherbol A (**98**) (compare *Table 3*) would lead directly to 3-*epi*-dysiherbol B (3-*epi*-**105**) via a sequence of epoxide opening, deprotection and cyclization of the ether ring. Oxidation of this pentacyclic alcohol would yield dysiherbol C (**106**). As the epoxidation of **97** is suspected to occur from the side opposite to the aromatic ring, dysiherbol B (**105**) in its correct epimeric form might be accessible via reduction of dysiherbol C, as this presumably occurs from the less hindered side as well.



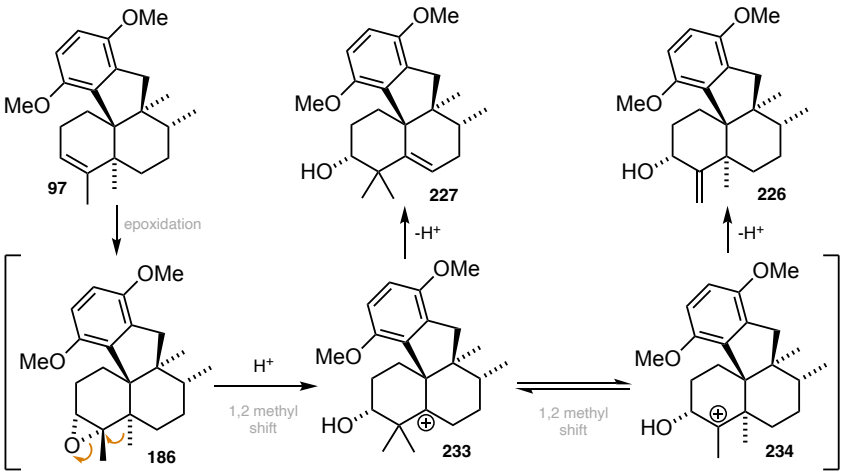
SCHEME 40 RETROSYNTHETIC ANALYSIS OF DYSIHERBOL B & C GOING BACK TO OLEFIN *ent*-**97**.

The following investigations were conducted in the not-naturally occurring enantiomeric series for supply reasons. However, the epoxidation of olefin *ent*-**97** proved to be surprisingly challenging. As depicted in *Scheme 41*, different tested epoxidation methods did not lead to the expected epoxide **186**. Employing *m*CPBA as oxidation agent delivered allylic alcohol **226** as main product, whereas a dioxirane (*in situ* generated using trifluoroacetone and Oxone) yielded the rearranged homoallylic alcohol **227** with 67% when stirring at 0 °C for 16 h. If the reaction was allowed to reach 24 °C, again allylic alcohol **226** was obtained. A putative mechanism for the formation of the two undesired products is drawn in *Scheme 42*. The initially formed epoxide **186** might open up rapidly under migration of the adjacent methyl group resulting in cation **233**, which probably is in equilibrium with the 1,2-methyl shifted cation **234**. Proton elimination delivers either allylic alcohol **226** or homoallylic alcohol **227**.

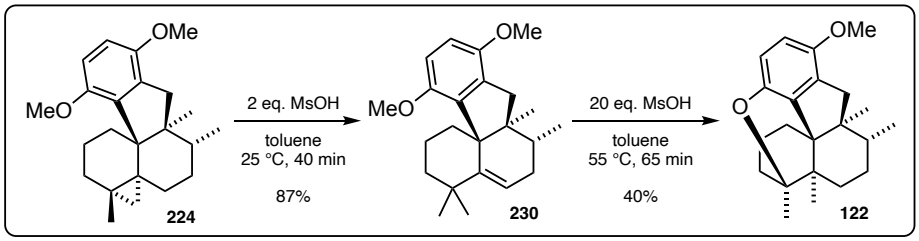


SCHEME 41 SYNTHESIS OF UNDESIRED INTERMEDIATES **226** & **227** AND ATTEMPTS OF THEIR (REARRANGEMENT)/CYCLIZATION TO PROVIDE *ent*-3-*epi*-DYSIHERBOL B (*ent*-3-*epi*-**105**).

A similar 1,2-methyl shift was previously studied by *Julian Baars* for cyclopropane **224** (*Scheme 43*). These results indicated a reversibility of this process and led to the assumption that under acidic conditions the undesired intermediate **227** might undergo the envisioned ether cyclization. Unfortunately, the conditions shown in *Scheme 43* gave elimination product diene **228**. To avoid elimination of the alcohol, oxidation prior to treatment with MsOH was considered. Although the desired intermediate ketone was observed via GC-MS and NMR analysis of the crude product, the subsequent reaction with MsOH did not result in rearrangement and cyclization but in a mixture of many different products, neither isolated nor characterized. Deprotection/*Lewis* acidic conditions adding BBr_3 delivered comparably unsatisfactory results. The same holds true for allylic alcohol **226** when subjected to these conditions.

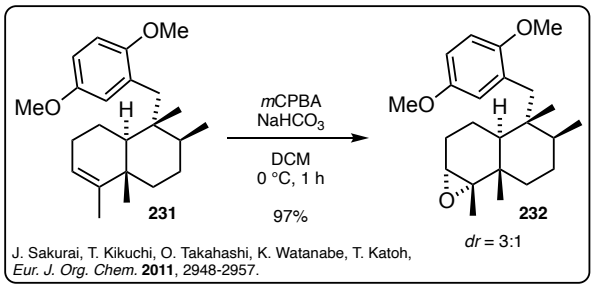


SCHEME 42 PUTATIVE MECHANISM FOR THE FORMATION OF ALLYLIC ALCOHOL **226** AND HOMOALLYLIC ALCOHOL **227** FROM OLEFIN **97**.



SCHEME 43 OBSERVATIONS MADE BY *JULIAN BAARS* FOR A REVERSIBLE ACID MEDIATED 1,2-METHYL SHIFT.[62]

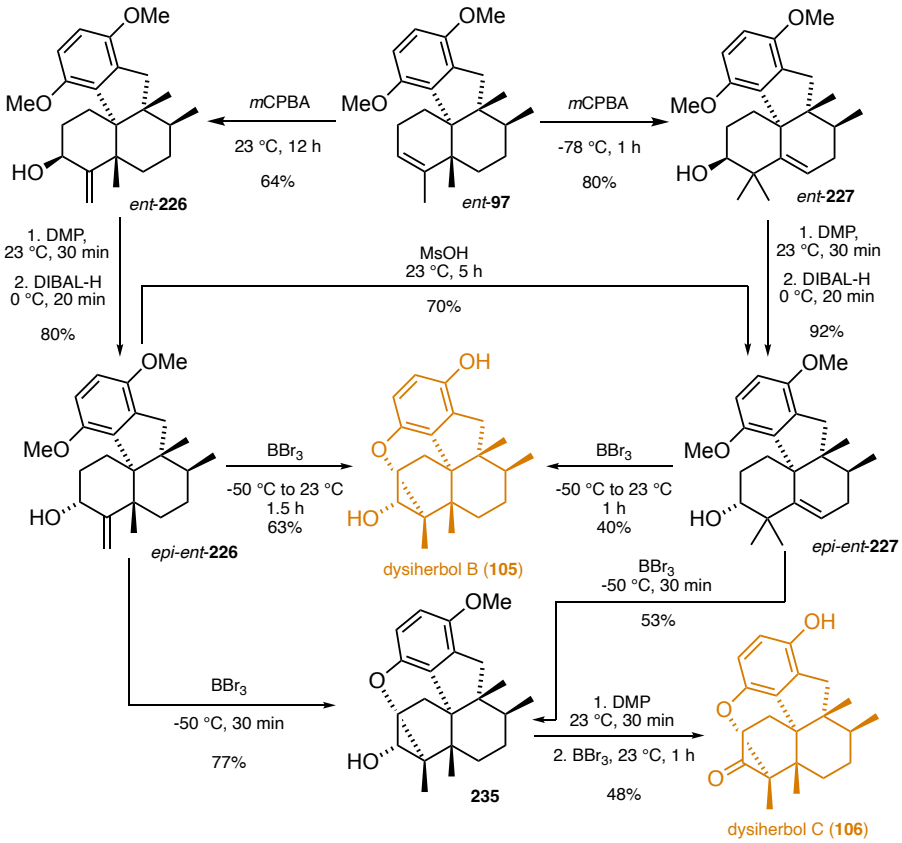
Interestingly, when looking at the literature known epoxidation in *Scheme 44* used for the total synthesis of (+)-stachyflin, the tetracyclic structure of olefin **97** seems to have a huge impact on its reactivity. Olefin **231** has a very similar structure, but with the additional connection to the aromatic moiety, epoxide **186** is apparently way more prone to rearrangement compared to **232**.



SCHEME 44 LITERATURE KNOWN EPOXIDATION OF OLEFIN **231** USING A PEROXIDE WITHIN THE TOTAL SYNTHESIS OF (+)-STACHYFLIN.[49]

The solution for the synthesis of dysiherbol B and C was discovered by cooperation partners from the Nankai University in China simultaneously working on the same topic. *Lu* and coworkers found that changing the configuration of the C-3 hydroxy group is crucial for the subsequent ether cyclization to be feasible (*Scheme 45*), maybe due to a change in the conformational bias of the cationic intermediates. They also obtained allylic alcohol *ent*-**226** and homoallylic alcohol *ent*-**227** when aiming for the epoxidation of olefin *ent*-**97** under differing reaction time and temperature with *m*CPBA. Oxidation and subsequent reduction delivered the epimers 3-*epi*-*ent*-**226** and 3-*epi*-*ent*-**227**, as suspected for the cyclized congener 3-*epi*-**105** in the retrosynthetic analysis shown in *Scheme 40*. Additionally, they observed that transformation between the two alcohols is possible under acidic conditions. With the correct configuration at C-3, as found in dysiherbol B, the ether ring formation proceeded smoothly with *epi*-*ent*-**226** and *epi*-*ent*-**227** under common BBr_3 conditions. The obtained synthetic dysiherbol B (**105**) exhibited the same analytical data compared to those reported for the natural product, thus confirming the anticipated revised structure.[22] Converting dysiherbol B into dysiherbol C gave poor yields, but mono methyl protected congener **235** gave dysiherbol C upon oxidation and final deprotection with a yield of 48% over two steps. Spectroscopic and optical rotation data again fitted the reported ones. Noteworthy, they observed diene *ent*-**228** as well when subjecting homo allylic alcohol *ent*-**227**

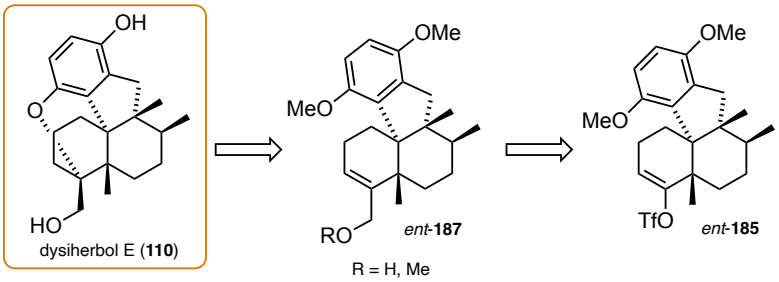
to *Brønsted* or *Lewis* acidic conditions, also explaining the diminished yield for the BBr_3 reactions in comparison to those of *ent*-**226**.



SCHEME 45 SYNTHESIS OF DYSIHERBOL B & C DEVELOPED BY COOPERATION PARTNERS AROUND *LU* FROM THE NANKAI UNIVERSITY IN CHINA.[63]

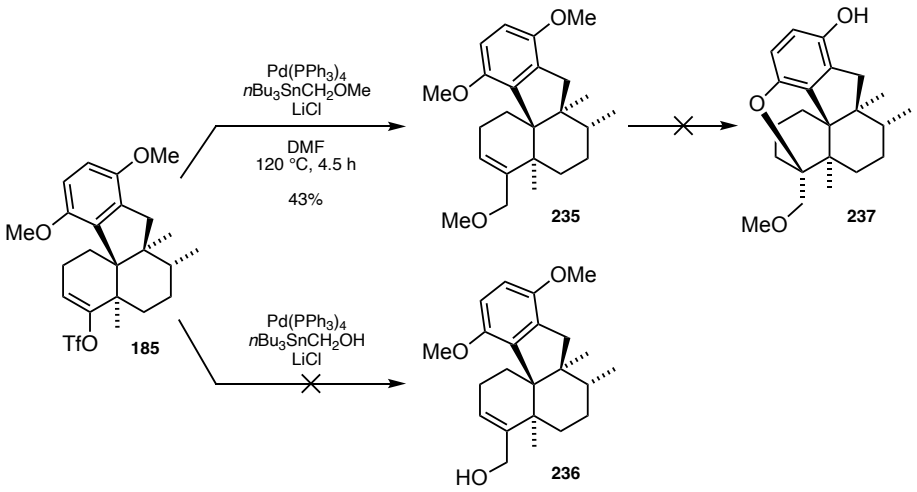
3.1.3 DYSIHERBOL E

For the total synthesis of dysiherbol E (**110**) triflate (*ent*-)**185** was considered as a suitable starting point to create the (protected) allylic alcohol *ent*-**187** as cyclization precursor accessible via a cross coupling reaction. Subsequently, under treatment with acidic deprotection conditions, this precursor might give the targeted natural product, as already studied for its congeners.



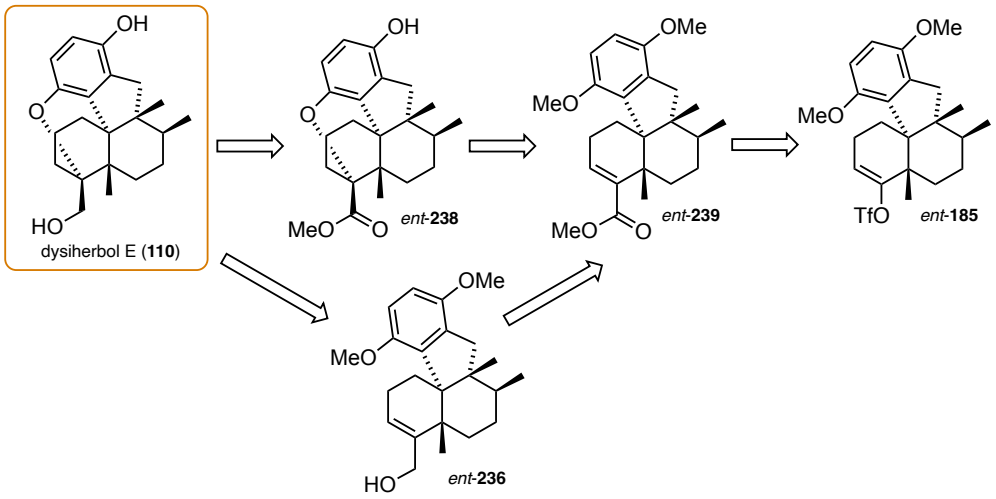
SCHEME 46 RETROSYNTHETIC ANALYSIS OF DYSIHERBOL E (**110**) STARTING FROM KNOWN TRIFLATE *ent*-**185** VIA (PROTECTED) ALLYLIC ALCOHOL *ent*-**187**.

The following studies were again conducted in the enantiomeric series. Initial attempts focused on the synthesis of the unprotected allylic alcohol **236**. Literature research revealed a *Stille*-type cross coupling as promising conditions for the desired transformation of olefin **185** into **236**. Unfortunately, various conditions failed in the coupling, showing no conversion of the starting material. The *Stille* reagent was synthesized following a literature protocol,[108] seemingly decomposing upon the high temperatures necessary for the reaction of triflate **185**. Thus, microwave-assisted conditions were applied to eventually enable its conversion at lower temperatures, but to no avail. On the contrary, the analogous methoxy-tin reagent underwent the desired reaction under standard Stille conditions, resisting the elevated temperatures, thereby yielding the methyl protected allylic alcohol **235** with a yield of 43% (*Scheme 47*).



SCHEME 47 SYNTHESIS OF PROTECTED ALLYLIC ALCOHOL **235** AND ITS UNSUCCESSFUL CYCLIZATION TOGETHER WITH UNSUCCESSFUL SYNTHESIS OF ALLYLIC ALCOHOL **236**.

Two side products were observed, the minor related to the coupling of one *n*-butyl residue and the major to that of a hydrogen atom, presumably resulting from residual nBu$_3$SnH, the precursor of the synthesized tin reagent.[108] A second approach for the synthesis of **235** employing *Molander* conditions with the respective trifluoroborate salt (KF_3BCH_2OMe) as coupling reagent, synthesized according to published protocols,[109] failed. Unfortunately, subsequent efforts to facilitate the envisioned cyclization of **235** remained unsuccessful. Analysis of the performed experiments indicated the formation of several products related to elimination of the newly introduced -CH_2OMe group, rearrangements or bromination, likewise decomposition was observed. Comparable results were received under the previously developed conditions for dysiherbol A using MsOH, in the case of olefin **230** resulting in mono deprotection and cyclization (compare *Scheme 43*). Consequently, allyl methyl ether **235** was considered too unstable under common cyclization conditions.

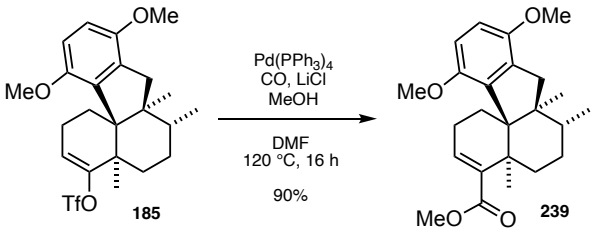


SCHEME 48 RETROSYNTHETIC ANALYSIS OF DYSIHERBOL E (**110**) STARTING FROM KNOWN TRIFLATE *ent*-**185** VIA ESTER *ent*-**239**.

Thus, a new strategy was developed utilizing the presumably more stable ester (*ent*-)**239** in a similar fashion. Despite the opposed polarity present in α,β-unsaturated ester **239**, the driving force of the ether cyclization was suspected to potentially overcome this bias. However, ester **239** could also deliver the unprotected allylic alcohol **236** upon reduction.

For the synthesis of ester **239** a carbonylative cross coupling was performed. Initial attempts using amine bases being most prevalent in corresponding literature gave no conversion of the starting material **185** under the literature reported conditions (*Table 4, entry 1 & 2*). When switching to LiCl instead of a base, traces of the desired product could be detected via GC-MS (*entry 3*). The versatile optimization of the reaction set up turned out to be crucial for the successful reaction. Evacuating the balloon filled with CO prior to filling increased the conversion (*entry 5*), as does extending the reaction surface in contact with the supernatant gas (*entry 4*).

TABLE 4 SCREENING OF THE CARBONYLATIVE CROSS COUPLING FOR THE SYNTHESIS OF ESTER **239**.

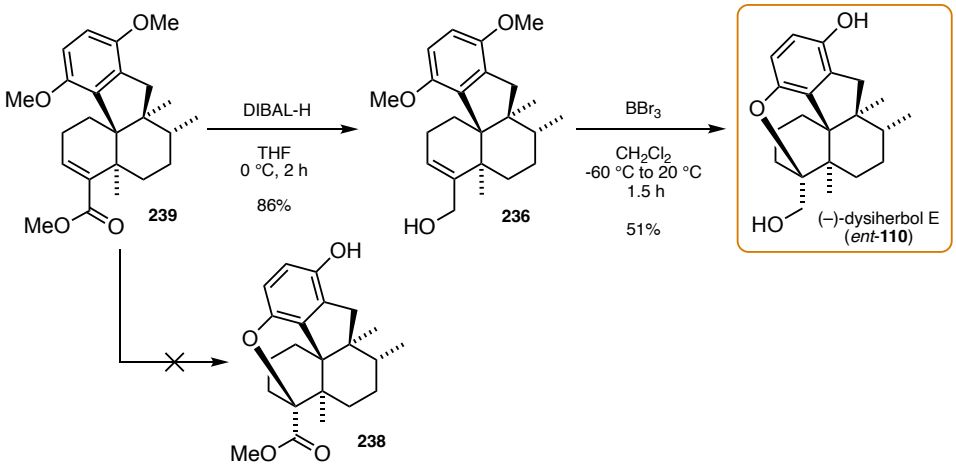


entry	additive	MeOH/DMF	T [°C]	t [h]	Change in set up	result[a]
1	Et_3N	5:1	65	16	*Schlenk* tube	no conversion
2	DIPEA	3:1	120	6		no conversion
3	LiCl	1:1	120	64		traces of **239**
4	LiCl	1:1	120	3	larger surface	25% conv. to **239**
5	LiCl	1:1	120	8	balloon evacuated	65% isolated yield
6	LiCl	2:1	120	16		45% isolated yield
7	LiCl	1:1	120	16	MeOH reflux assured	90% isolated yield

All reactions were degassed with three freeze-pump-thaw cycles and the atmosphere exchanged with CO. Stirring was continued until no further conversion was observed. [a] Conversion was tracked via GC-MS.

Even more improvement in yield was observed when additionally ensuring the condensation of MeOH on the wall of the wide tube by shielding the oil bath with aluminum foil (*entry 7*). Surprisingly, applying a vigreux column worsened the results, the same holds true when adding more MeOH to the reaction (*entry 6*). Under steady reflux of MeOH (in a 1:1 mixture with DMF) the conditions depicted in *Table 4* delivered desired ester **239** in excellent yield of 90% after 16 h.

Employing synthesized ester **239** in the intended cyclization towards pentacyclic **238** resulted in different products, but the desired transformation was not viable. Several test experiments with BBr_3 were conducted with variations in temperature, time and equivalents added.

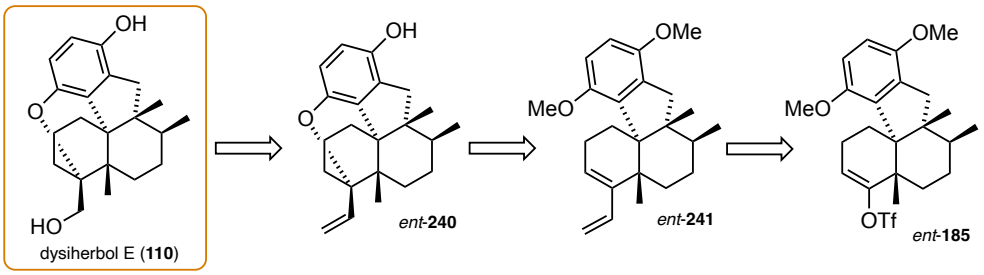


SCHEME 49 SYNTHESIS OF DYSIHERBOL E VIA ALLYLIC ALCOHOL **236**, SYNTHESIZED FROM ESTER **239** AND UNSUCCESSFUL CYCLIZATION OF THE LATTER.

Taking together the obtained results, three different products were observed according to GC-MS: Presumably the mono demethylated ester ($m/z = 370$), the double demethylated ester

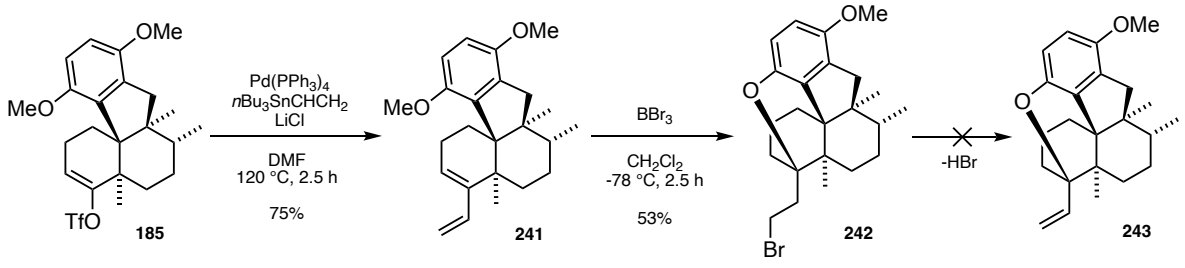
(*m/z* = 356) and mono deprotected free acid (*m/z* = 356). This assumption was further supported by observations during acid-base extraction, proving the suspected compound to be a free acid. As the second species with the same mass (*m/z* = 356) in contrast was not transferred into the aqueous phase upon treatment with NaOH, this species was assumed to be the double deprotected ester. NMR analysis of a crude sample containing this species as major component clearly showed the characteristic double bond signal of **239** still present. This observation led to the conclusion that the cyclization of the α,β-unsaturated ester is not favored. This demethylated compound as well as ester **239** were subjected to *Brønsted* acidic conditions (MsOH), only resulting in cleavage of the ester. Another side product detected shows the mass of the species corresponding to decarboxylation. These results demonstrate ester **239** being no suitable precursor for the desired cyclization.

Nevertheless, it could be converted into allylic alcohol **236** (*Scheme 49*), which turned out to be suitable for the desired transformation into (–)-dysiherbol E (*ent*-**110**) as independently discovered for naturally occurring (+)-dysiherbol E (**110**) by cooperation partners from the *Lu* group. As entry to allylic alcohol *ent*-**236** they used an allylic oxidation of known olefin *ent*-**97**.[63]



SCHEME 50 RETROSYNTHETIC ANALYSIS OF DYSIHERBOL E (**110**) STARTING FROM KNOWN TRIFLATE *ent*-**185** VIA DIENE *ent*-**241**.

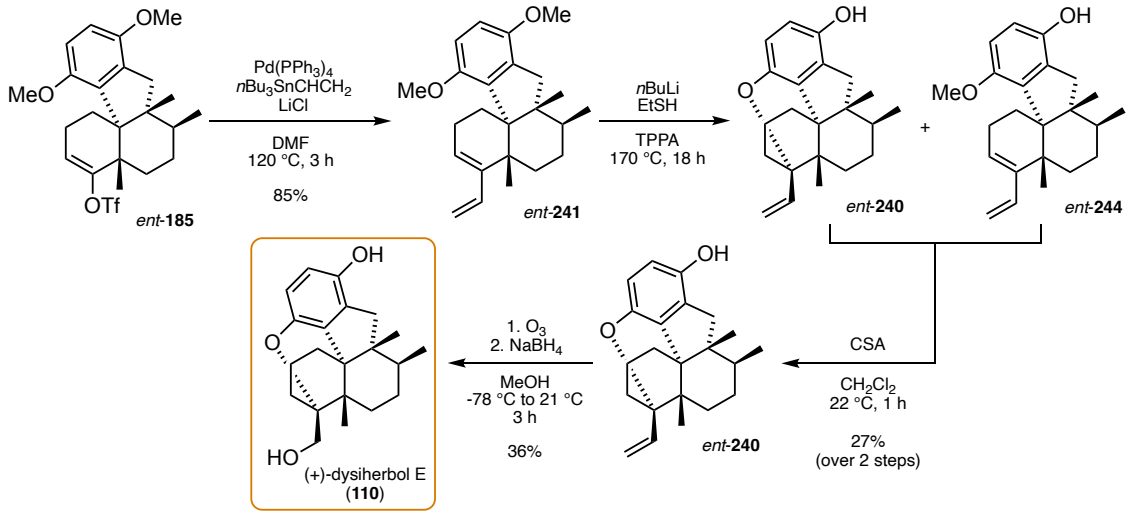
Concurrent to the findings by *Lu* and coworkers, an additional approach towards dysiherbol E (**110**) was developed, shown in *Scheme 50*. *Stille* coupling with the respective tin reagent might introduce a vinyl residue to triflate **185**. Resulting **241** upon treatment with common cyclization conditions may give pentacyclic primary olefin **240**, a potential substrate for a (reductive) ozonolysis, introducing the primary alcohol of the natural product **110**.



SCHEME 51 SYNTHESIS OF DIENE **241**, UNDESIRED HBr ADDITION TO THE TERMINAL DOUBLE BOND UNDER CYCLIZATION WITH BBr_3 AND UNSUCCESSFUL ELIMINATION.

The *Stille* coupling for the synthesis of diene **241** (*Scheme 51*) proceeded smoothly under standard conditions, with a yield of 75%. Subsequent treatment with BBr_3 delivered cyclized **242** under addition of HBr to the terminal double bond. Various changes in the reaction conditions and especially in the quenching procedure could not avoid this undesired reaction. Unfortunately, elimination of HBr from **242** was not feasible, presumably due to steric hinderance of this position.

Thus, the idea arose to deprotect diene **241** in the first place, thereby rendering the subsequent cyclization possible under mild acidic conditions, to avoid side reactions. The *Stille* vinyl coupling was also performed for the enantiomer *ent*-**241** (*Scheme 52*), and subsequently demethylation conditions developed for dysiherbol A related compounds were applied.[64]

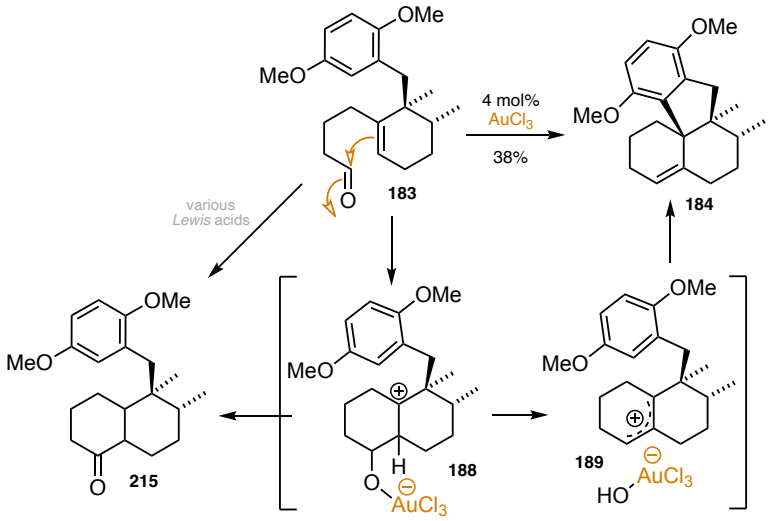


SCHEME 52 ALTERNATIVE SYNTHESIS ROUTE TO (+)-DYSIHERBOL E (**110**) VIA DIENE *ent*-**241** WITH A REDUCTIVE OZONOLYSIS AS FINAL STEP.

In situ-generated LiSEt in TPPA gave full conversion of the starting material, but still the mono-methylated compound *ent*-**244** remained and further conversion stopped at a ratio of approximately 1:1 mono-deprotected to fully deprotected. Fortunately, the fully deprotected species turned out to be the already cyclized desired olefin *ent*-**240**. Separation of the two compounds via silica column chromatography was rather difficult due to similar polarity. Therefore, a mixture of *ent*-**240** and *ent*-**244** was applied to mild acidic conditions utilizing camphorsulfonic acid (CSA) mediating the cyclization accompanied by the second demethylation of diene *ent*-**244** and thereby delivering olefin *ent*-**240** in 27% yield over two steps. This terminal olefin was subjected to reductive ozonolysis conditions, yielding (+)-dysiherbol E (**110**) with a yield of 36%.

3.2 STUDIES ON A GOLD-CATALYZED CYCLIZATION

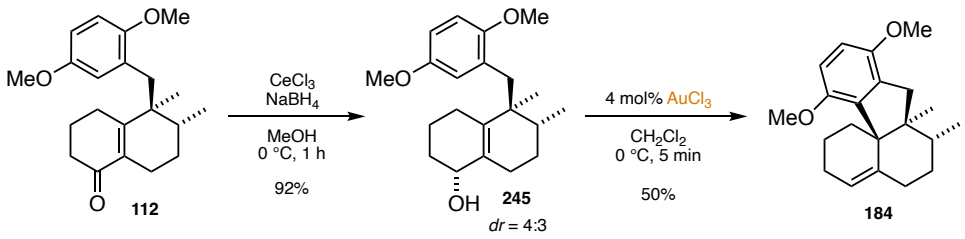
The observations made for the key twofold cyclization in the total synthesis of dysiherbol A (*Scheme 53*), already briefly addressed in chapter **3.1**, render this reaction an interesting objective for further investigations. Treatment of cyclization precursor **183** with a variety of different *Lewis* acids only resulted in complex product mixtures, usually containing ketone **215** as a major component. This compound corresponds to the single cyclization of the cationically-activated aldehyde attacked by the electrons of the central double bond, with cation **188** as presumptive intermediate (for a more detailed mechanistic proposal see *Scheme 33*). $AuCl_3$ turned out to be the only catalyst capable of building up the desired tetracyclic carbon skeleton of **184** as a major product under the elimination of water, although still giving a vast number of side products (see *Scheme 33*) including ketone **215**.



SCHEME 53 TWOFOLD CYCLIZATION OF ALDEHYDE **183** TO OLEFIN **184** USING $AuCl_3$ AS A CATALYST TOGETHER WITH A MECHANISTIC PROPOSAL AND UNDESIRED ONEFOLD CYCLIZATION PRODUCT **215**.

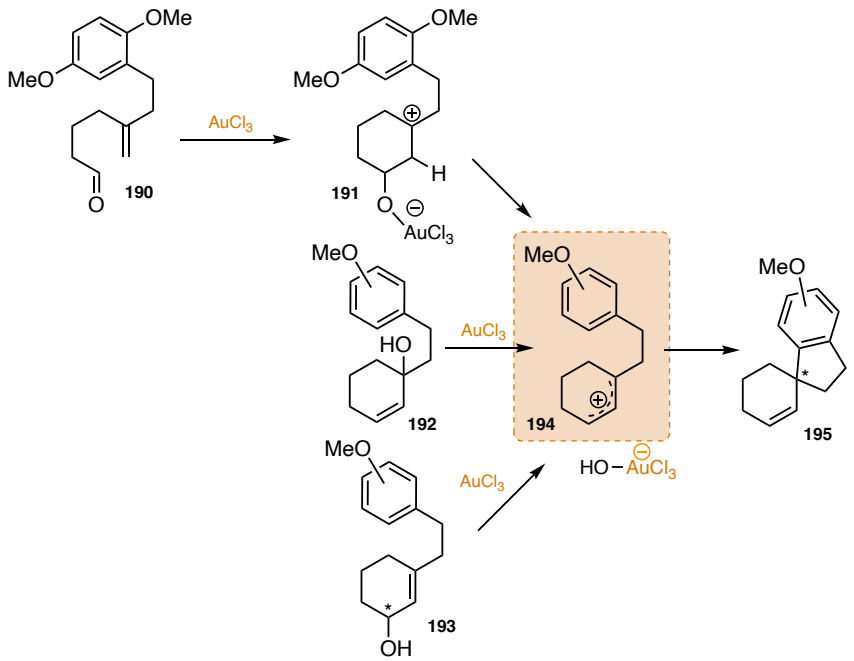
This and other undesired side products indicate that the S_EAr reaction is the rate-determining step in the formation of **184**. The unique role of $AuCl_3$ lead to the assumption that, in contrast to other *Lewis* acids it seems to be able to convert primary cyclization intermediate **188** into a more stable allylic cation **189**, thus preventing alternative reactions like benzyl and hydride shifts, presumably being faster than the desired S_EAr. The reason for $AuCl_3$ being unique in this transformation might be the formation of the known aurate anion $AuCl_3(OH)^-$, also explaining the concomitant elimination of water. This ion is also suspected to be formed in substitution reactions of allylic alcohols, a reaction for which $AuCl_3$ is known to be a suitable catalyst.[87] Upon protonation the anion releases a water molecule under the regeneration of the catalyst.

Treatment of allylic alcohol **245**, synthesized from enone **112** employing *Luche* reduction conditions as depicted in *Scheme 54*,[110] with catalytic amounts of $AuCl_3$ supposably also results in olefin **184** via allylic cation **189**. And indeed, the expected cyclization proceeded, even in an improved yield of 50%, supporting the mechanistic proposal in *Scheme 53*.



SCHEME 54 SYNTHESIS OF ALLYLIC ALCOHOL **245** AND SUBSEQUENT CYCLIZATION CATALYZED BY $AuCl_3$.

To investigate on the possibilities and limitations of such gold-catalyzed reactions, additional cyclization experiments using $AuCl_3$ were conducted, the conception is depicted in *Scheme 55*. One possible substrate is aldehyde **190**, the simplified version of the originally designed cyclization precursor **183** broken down to the key functionalities involved in the transformation. Two general onefold cyclization substrates were considered, allylic alcohols **192** and **193**. All three precursors are suspected to give the same allylic cation **194** upon treatment with $AuCl_3$. Subsequent S_EAr reaction with the superjacent aromatic ring might result in spirocyclic olefins of type **195**, as racemates.

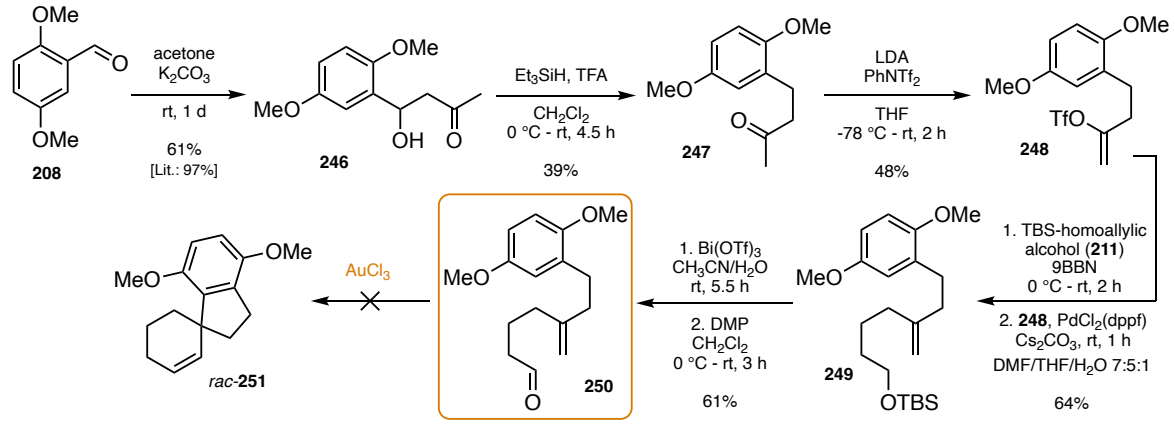


SCHEME 55 SIMPLIFIED TWOFOLD (**190**, TOP) AND DESIGNED ONEFOLD CYCLIZATION PRECURSORS (**192**, **193**) TO STUDY THE GOLD-CATALYZED CYCLIZATION PRESUMABLY PROCEEDING VIA COMMON ALLYLIC CATION **194**.

Moreover, different substitution patterns of the aromatic moiety should be employed in the reaction. Another interesting experiment is to transfer the conditions to an enantiopure compound, for example allylic alcohol **193**, to check if the stereo information is conserved during the reaction.

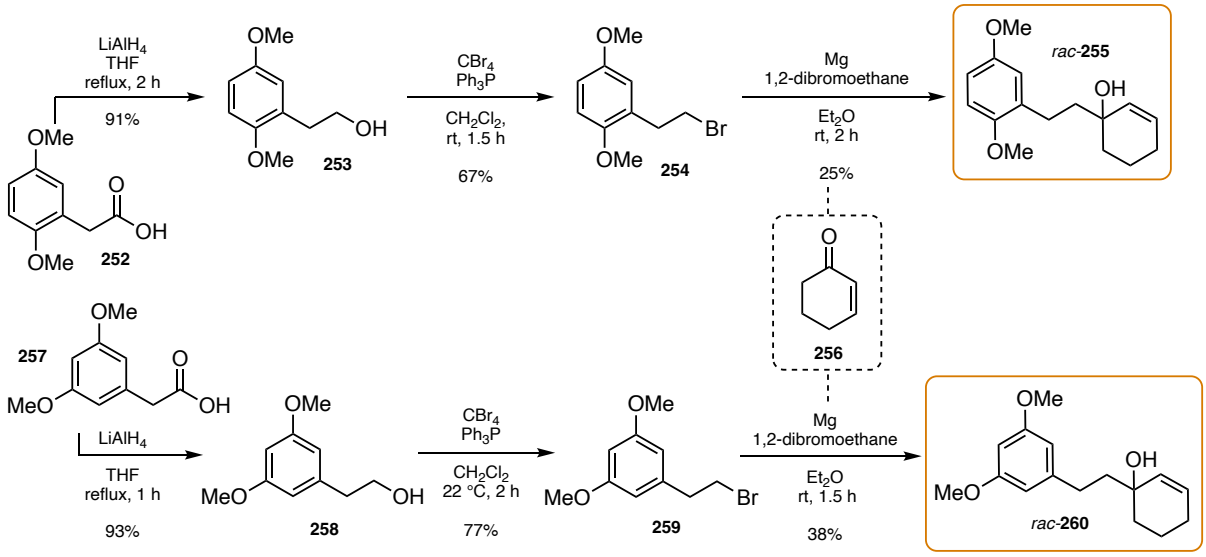
The synthesis of the simplified aldehyde **190** is shown in *Scheme 56*. Starting from 2,5-dimethoxybenzaldehyde (**208**) aldol reaction with acetone gave β-hydroxy ketone **246**, following

a literature protocol.[111] After benzylic reduction utilizing a silane and trifluoracetic acid (TFA) ketone **247** was obtained.[110] The following sequence of enol triflate formation, *Suzuki* coupling, deprotection and oxidation was performed in analogy to the conditions developed for the total synthesis of the dysiherbols (chapter **3.1**) finally delivering the desired aldehyde **250**. When this precursor was subjected to $AuCl_3$, no cyclization could be observed, neither with catalytic nor with stochiometric amounts of the *Lewis* acid. The preorganization in **183** (*Scheme 53*) with the six membered ring seems to be crucial for the success of the cyclization, and **250** seems to have too many degrees of freedom, resulting in degradation and formation of a complex product mixture.



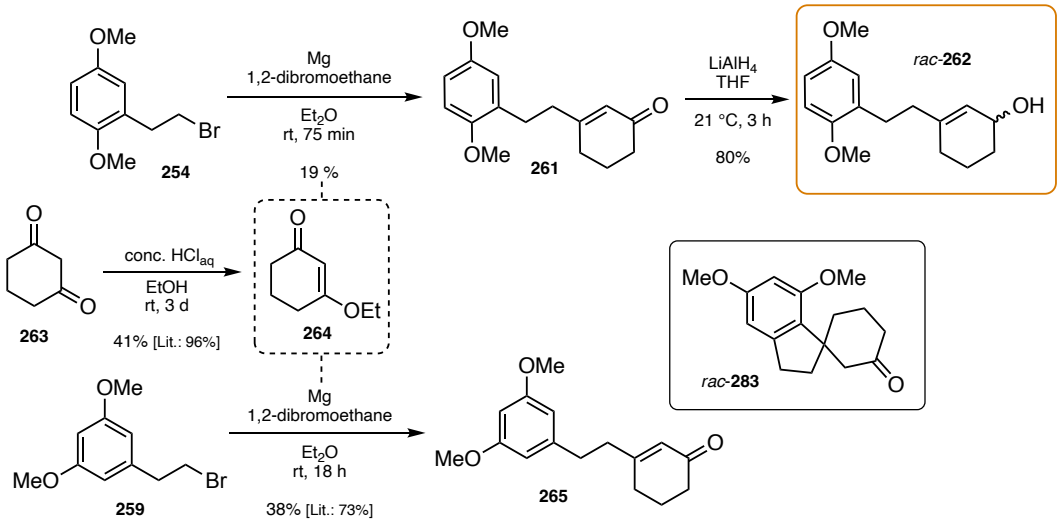
SCHEME 56 SYNTHESIS OF SIMPLIFIED TWOFOLD CYCLIZATION PRECURSOR ALDEHYDE **250** STARTING FROM BENZALDEHYDE **208** AND UNSUCCESSFUL GOLD-CATALYZED CYCLIZATION THEREOF.

The synthesis of allylic alcohols of type **192** (*Scheme 55*) is feasible via *Grignard* addition of the respective bromides to enone **256**. Based on a literature known procedure,[112] allylic alcohols *rac*-**255** and *rac*-**260** could be obtained, albeit in poor yields due to the formation of side products resulting from reduction and *Wurtz* coupling of the bromides, also previously reported.[113]



SCHEME 57 SYNTHESIS OF ALLYLIC ALCOHOLS OF TYPE **192** VIA GRIGNARD ADDITION OF THE RESPECTIVE BROMIDES SYNTHESIZED FROM THE CARBOXYLIC ACIDS.

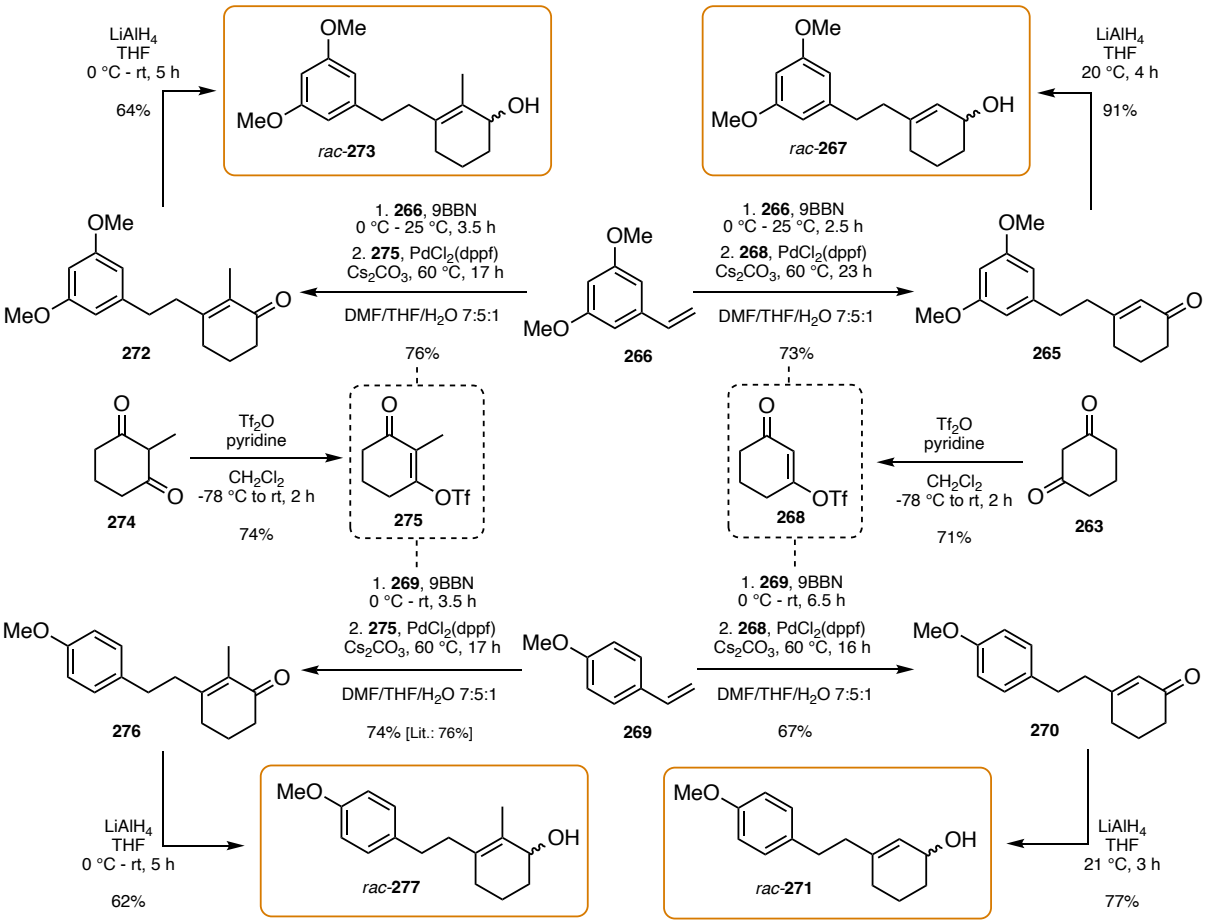
The employed bromides were synthesized over two steps by reduction and *Appel* reaction starting from the respective carboxylic acids following literature protocols (*Scheme 57*).[114] The cited protocol was originally developed for the 1,4-*Grignard* type addition to vinylogous ester **264**, synthesized according to a known protocol.[115] Thus, it was also utilized for the synthesis of cyclization precursors of type **193** (*Scheme 55*). Unfortunately, the literature yield of 73% for the 3,5-dimethoxy derivative **265** could not be reproduced. Moreover, the reaction gave unreliable yields ranging from 9% to 38%, with the best result obtained at tenfold dilution compared to the literature.[112] Diluting the reaction mixture further yielded the cyclized side product *rac*-**283** in 15% yield. For the 2,5-dimethoxy congener the best yield achieved was 19%. Under several tested reduction methods, $LiAlH_4$ turned out to be best suited for the reduction of enone **261**, thereby yielding cyclization precursor *rac*-**262** in 80% yield.



SCHEME 58 SYNTHESIS OF ENONES **261** AND **265** BY GRIGNARD ADDITION TO VINYLOGOUS ESTER **264**, SUBSEQUENT REDUCTION OF **261** AND SIDE PRODUCT IN THE SYNTHESIS OF **265**, CYCLIZED **284**.

As the poor, unreliable yields for the synthesis of this type of cyclization precursors made further investigations challenging, an alternative protocol for their synthesis was considered. As depicted in *Scheme 59*, *Suzuki-Miyaura* cross coupling between styrenes **266** or **269** and triflates **268** or **275** turned out to reliably deliver good yields of the desired coupling products. Thus, four different enones (**265**, **270**, **272** and **276**) could be synthesized in good yields of around 70%, which is in accordance with the cited literature, reporting 76% for the synthesis of enone **276**.[105] Transferring the developed protocol to the synthesis of compound **261** (*Scheme 58*) gave quantitative yield when using an excess of 2,5-dimethoxy styrene (see chapter **5.3.16**). It turned out to be crucial to degas all solvents before usage, otherwise side products resulting from the styrene building blocks were obtained and the desired coupling was inhibited. The involved building blocks were synthesized following common protocols via enol triflate formation to obtain **268** or **275**,[116] and styrene **266** via *Wittig* reaction of the respective aldehyde (96% yield in accordance with literature).[117]

Subsequently, the reduction using $LiAlH_4$ was performed to obtain the cyclization precursors, allylic alcohols *rac*-**267**, *rac*-**271**, *rac*-**273** and *rac*-**277** as racemic mixtures in good to excellent yields.



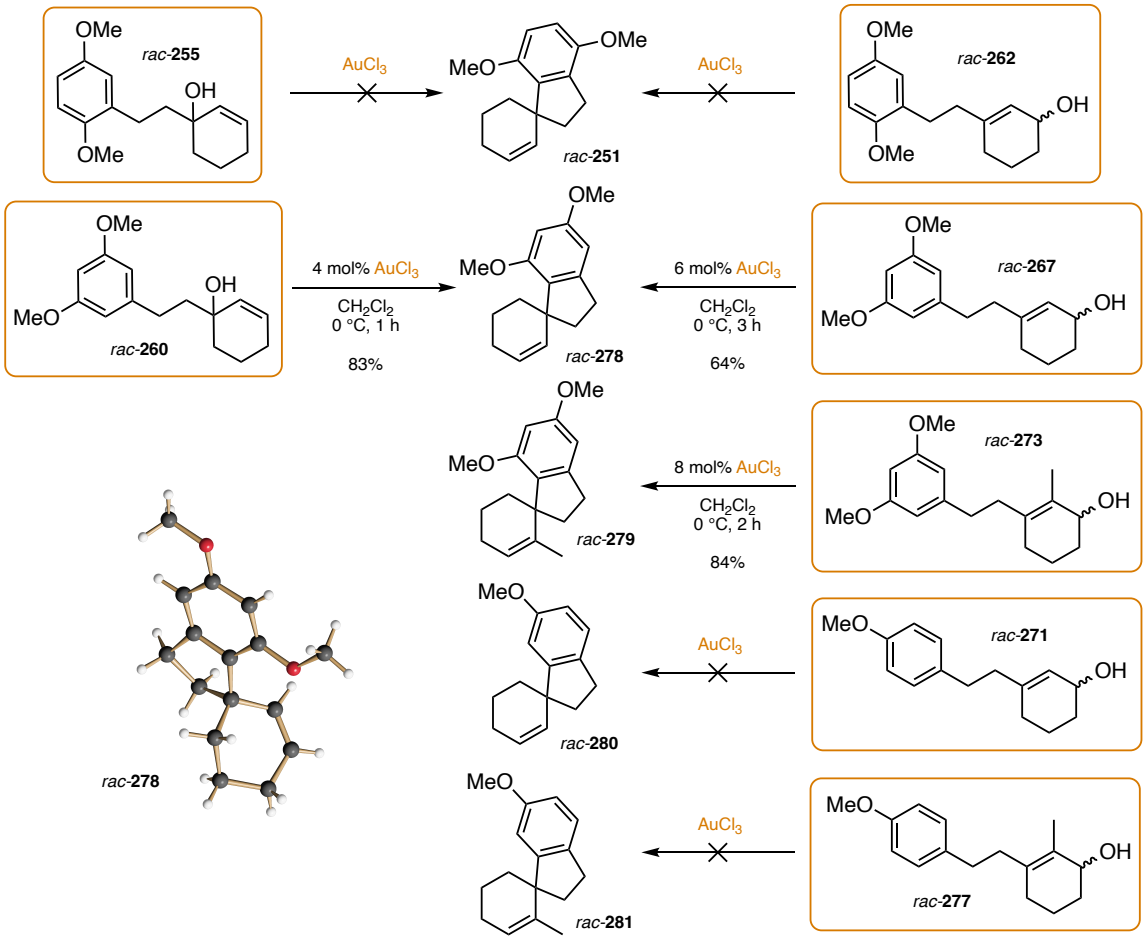
SCHEME 59 SUZUKI COUPLING BETWEEN STYRENES AND ENOL TRIFLATES WITH SUBSEQUENT REDUCTION FOR THE SYNTHESIS OF CYCLIZATION PRECURSORS OF TYPE **193**.

The results of the tested $AuCl_3$-catalyzed cyclization reactions are summarized in *Scheme 60*. Surprisingly, precursor *rac*-**262**, representing the simplified form of the already tested allylic alcohol **245** (*Scheme 54*) gave expected spirocyclic olefin *rac*-**251** in only very low yield and an inseparable mixture of unknown isomers. Same observations were made for the second 2,5-dimethoxy substituted precursor of type **192**, *rac*-**255**.

In contrast to that, all 3,5-dimethoxy substituted precursors underwent the suspected cyclization upon treatment with catalytic amounts of $AuCl_3$. Allylic alcohol *rac*-**267** delivered spirocyclic olefin *rac*-**278** with a yield of 64%, so does the constitutionally different allylic alcohol *rac*-**260** giving even higher yields for the cyclization towards *rac*-**278**, of which a crystal structure was obtained (*Scheme 60*). These results support the suggested mechanism, as for the different positions of the hydroxy group within the six membered ring, the same cation can be formed under the treatment with catalytic amounts of $AuCl_3$. For the discussed onefold cyclization the

yield was remarkably higher compared to the cyclization of **183** in the synthesis of dysiherbol A, certainly due to less possibilities for undesired side reactions, the excluded first cyclization and less steric hinderance. Introducing a methyl group next to the hydroxygroup in the 3,5-dimethoxy cyclization precursor of type **193** resulted in a higher yield for the cyclization of *rac*-**273** to form spirocyclic olefin *rac*-**279**, maybe due to higher stability of the intermediate allylic cation.

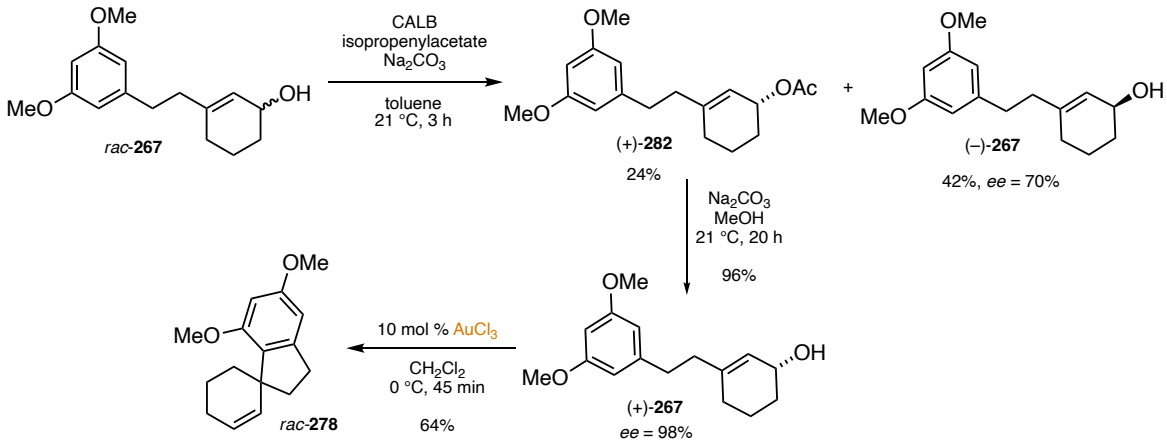
However, the substitution pattern of the aromatic ring seems to strongly influence the ability to undergo the desired spiro cyclization, as all 2,5-dimethoxy substituted precursors delivered the expected spirocycle *rac*-**251** either in small amounts and inseparable isomeric mixtures or not at all. On the contrary, the 3,5-dimethoxy precursors showed formation of only minor amounts of (isomeric) side products together with good yields for the envisioned S_EAr. The reason might be the higher reactivity of the 3,5-substituted aromatic ring due to better resonance stabilization with the two methoxy groups in *meta* position. Furthermore, for the symmetrically substituted 3,5-dimethoxylated precursors, the S_EAr at both possible positions lead to the same product, presumably explaining the enhanced selectivity.



SCHEME 60 CYCLIZATION EXPERIMENTS OF DIFFERENT ALLYLIC ALCOHOLS USING CATALYTIC AMOUNTS OF $AuCl_3$.

Diminishing the electron density by using mono-methoxylated cyclization precursors as in *rac*-**271** and *rac*-**277** again resulted in a mixture of inseparable isomers, containing spirocyclic compounds *rac*-**280** and *rac*-**281**. This might be explained by the lower reactivity in the desired transformation resulting from the reduced electron density within the aromatic ring. For the 4-methoxy and 2,5-dimethoxy cyclization precursors there are many competing side reactions occurring, whereas the 3,5-substitution pattern almost exclusively resulted in the formation of the five-membered ring delivering spirocyclic *rac*-**278**.

Racemic 3,5-methoxy-substituted allylic alcohol *rac*-**267** was chosen to investigate the possible retention of stereoinformation during the reaction. The racemic mixture *rac*-**267** was employed in a kinetic resolution using enzyme CALB (*Candida Antarctica* lipase B) in combination with an acetylation agent, based on a modified literature procedure (*Scheme 61*).[118] The assigned absolute configuration is based on the results reported in the cited literature.



SCHEME 61 KINETIC RESOLUTION UTILIZING ENZYME CALB AND SUBSEQUENT $AuCl_3$ CYCLIZATION RESULTING IN RACEMIZATION REFLECTED IN PRODUCT *rac*-**278**.

Afterwards, the two products could be easily separated by column chromatography. The unreacted allylic alcohol (–)-**267** showed an *ee* of 70% (determined by chiral HPLC), indicating incomplete conversion of *rac*-**267** in the reaction. The acetate (+)-**282** was saponified using Na_2CO_3 and the enantiomeric allylic alcohol (+)-**267** was obtained with 96% and an excellent *ee* of 98%. This enantiopure compound was subjected to the $AuCl_3$ cyclization conditions, delivering spirocyclic olefin *rac*-**278** as a racemic mixture. This result further supports the proposed mechanism in *Scheme 53* as the pathway via allylic cation **189** as reactive intermediate would be accompanied by the loss of chiral information.

3.3 BIOLOGICAL TESTING

The following biological data for the synthesized compounds (+)-dysiherbol A (*ent*-**98**) and (–)-dysiherbol A (**98**) were provided by *Prof. Dr. Aram Prokop* and coworkers from the Medical School Hamburg. Antiproliferative and apoptotic activities of dysiherbol A were tested in leukemia (K562, NALM-6) and lymphoma cell lines (BJAB). In anti-tumor therapy the development of resistances against commercial cytostatic drugs limits the efficacy and newly developed drugs need to overcome these resistances. This ability was investigated in cell lines resistant to the anthracyclines doxorubicin (7CCA) and daunorubicin (NiWi, NALM-6/Dau), the *Vinca* alkaloid vincristine (BiBo, NALM-6/Vcr) and the antimetabolite cytarabine (K562/AraC) as well as in one multiple drug-resistant cell line resistant against both daunorubicin and prednisolone (NaKu).

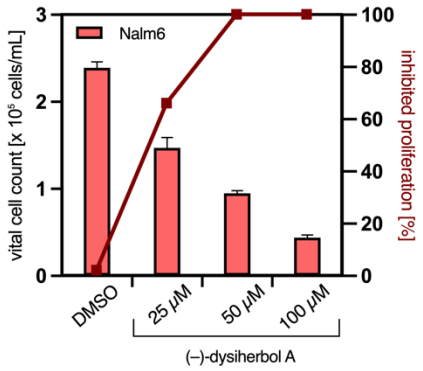


FIGURE 11 INHIBITION OF CELL PROLIFERATION BY (–)-DYSIHERBOL A (**98**) IN NALM-6 CELLS. CELLS WERE EITHER LEFT UNTREATED AS CONTROL OR INCUBATED WITH DIFFERENT CONCENTRATIONS OF **98**. CELL PROLIFERATION WAS DETERMINED AFTER 24 H. INHIBITION OF PROLIFERATION IS GIVEN IN % OF CONTROL ± SD (*N* = 3).

To investigate the antiproliferative activity of (–)-dysiherbol A (**98**), viability and cell count of leukemia cell lines NALM-6 was measured after incubation for 24 h with different concentrations of the agent. (–)-dysiherbol A decreases tumor cell proliferation in a concentration-dependent manner (*Figure 11*). Inhibition appeared at a concentration of < 25 µM, was 66% at 25 µM, and the effect increased to 100% inhibition at 50 µM in NALM-6.

Apoptotic cells undergo characteristic morphological changes, such as cell shrinkage, coalescence and margination of chromatin, fragmentation of the cell and the nucleus. After incubation with varying concentrations of (–)-dysiherbol A (**98**) for 72 h, treated cells showed several apoptotic features. To quantify induction of apoptosis, DNA fragmentation (an accepted hallmark of apoptosis) was determined by flow cytometric measurement of hypodiploid DNA. (–)-dysiherbol A (**98**) effectively induced apoptosis in lymphoma cell line BJAB, with over 70% apoptotic cells at 50 µM concentration (*Figure 12*). Moreover, it overcomes resistance against different cytostatics. In vincristine-resistant BJAB cells (BiBo) it shows comparable activity to that in non-resistant parental cells, in doxorubicin-resistant BJAB cells (7CCA) comparable apoptotic effects were observed at 100 µM concentration.

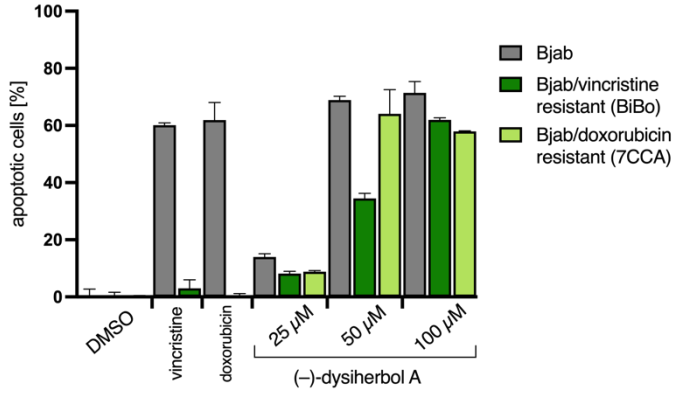


FIGURE 12 (–)-DYSIHERBOL A INDUCES DNA FRAGMENTATION IN DIFFERENT BJAB CELLS. CELLS WERE EITHER LEFT UNTREATED AS CONTROL OR INCUBATED WITH DIFFERENT CONCENTRATIONS OF **98**. DNA FRAGMENTATION WAS MEASURED AFTER 72 H. VALUES OF DNA FRAGMENTATION ARE GIVEN IN % ±SD (*N* = 3).

The capacity of (–)-dysiherbol A (**98**) to overcome drug resistances was also investigated in leukemia cell line K562 (*Figure 13*, left). For cytarabine (AraC)- and daunorubicin-resistant cells (NiWi), as well as for the non-resistant parental cells, (–)-dysiherbol A (**98**) showed similar apoptotic effects (LC_{50} = 50 µM). For the NiWi cell line (*Figure 13*, orange bars) it shows to be even more effective in the resistant cells than in the non-resistant parental cells. These cell lines were also subjected to the enantiomer (+)-dysiherbol A (*ent*-**98**).

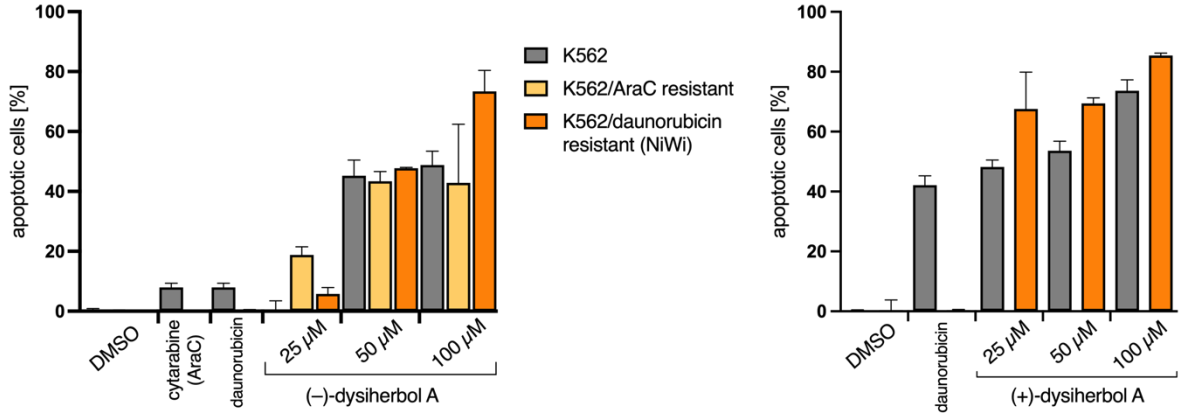


FIGURE 13 COMPARISON OF (+) AND (–)-DYSIHERBOL A INDUCING DNA FRAGMENTATION IN DIFFERENT K562 CELLS. CELLS WERE EITHER LEFT UNTREATED AS CONTROL OR INCUBATED WITH DIFFERENT CONCENTRATIONS OF (*ent*-)**98** OR THE RESPECTIVE CYTOSTATICS. DNA FRAGMENTATION WAS MEASURED AFTER 72 H. VALUES OF DNA FRAGMENTATION ARE GIVEN IN % ±SD (*N* = 3).

In comparison, naturally occurring (+)-dysiherbol A (*ent*-**98**) showed remarkably higher activity with induced apoptosis in up to 80% of cells already at 25 µM concentration (LC_{50} < 25 µM), while the cells did not respond to daunorubicin (*Figure 13*, right). With (–)-dysiherbol A (**98**) similar rates were observed at four times the concentration. (+)-Dysiherbol A (*ent*-**98**) was more potent in the daunorubicin-resistant cells than in the non-resistant parental cells as well.

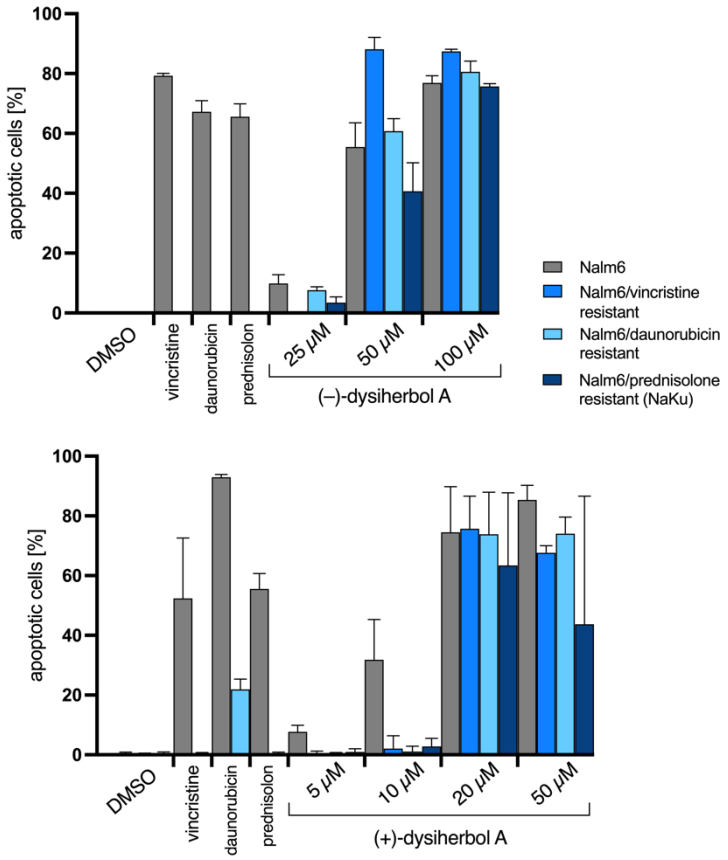


FIGURE 14 COMPARISON OF (+) AND (–)-DYSIHERBOL A INDUCING DNA FRAGMENTATION IN DIFFERENT NALM-6 CELLS. CELLS WERE EITHER LEFT UNTREATED AS CONTROL OR INCUBATED WITH DIFFERENT CONCENTRATIONS OF (*ent*-)**98** OR THE RESPECTIVE CYTOSTATICS. DNA FRAGMENTATION WAS MEASURED AFTER 72 H. VALUES OF DNA FRAGMENTATION ARE GIVEN IN % ±SD (N = 3).

When treating cells of the leukemia cell line NALM-6 in comparison with corresponding cell lines resistant against different commercial cytostatics (and the multiple drug-resistant cell line NaKu resistant against daunorubicin and prednisolone), the superior effect of natural (+)-dysiherbol A (*ent*-**98**) was again observed (*Figure 14*). Both enantiomers not only showed apoptotic effects in the non-resistant parental cells but overcame drug resistances against vincristine, daunorubicin and prednisolone. (+)-Dysiherbol A (*ent*-**98**) turned out to be more effective in all cell lines with LC_{50} values between 10 µM and 20 µM concentration (*Figure 14*, bottom), whereas (–)-dysiherbol A (**98**) exhibited no significant effects at 25 µM concentration (*Figure 14*, top).

Leukemia cell line NALM-6 was also used to further study the apoptotic effect of (–)-dysiherbol A (**98**). In a concentration-dependent manner, the applied agent led to reduced mitochondrial potential in up to 50% of the cells (*Figure 15*). Healthy cells show a high mitochondrial membrane potential and its decline is evidence for the early stage of apoptosis.

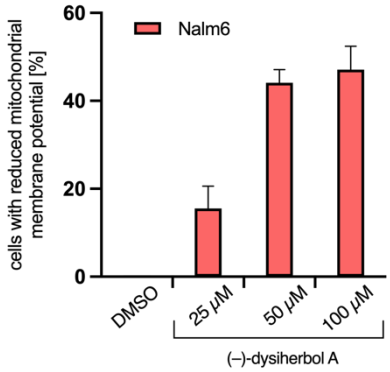


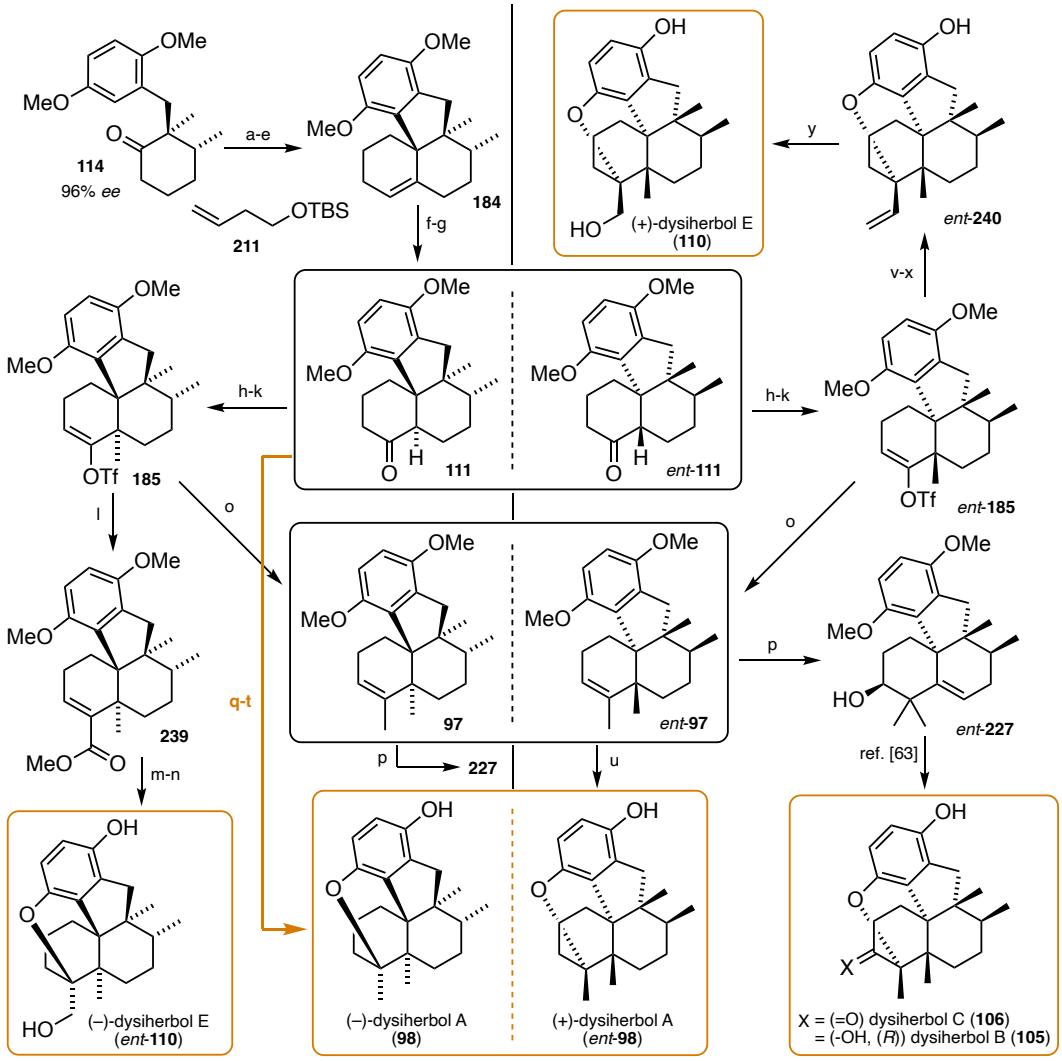
FIGURE 15 (–)-DYSIHERBOL A INDUCES APOPTOSIS IN DIFFERENT NALM-6 CELLS. CELLS WERE EITHER LEFT UNTREATED AS CONTROL OR INCUBATED WITH DIFFERENT CONCENTRATIONS OF **98**. FLUORESCENCE WAS MEASURED AFTER 48 H. JC-1 WAS USED AS DYE TO INDICATE DEPOLARIZED MEMBRANE POTENTIAL. CELLS WITH REDUCED MEMBRANE POTENTIAL ARE GIVEN IN % ±SD (N = 3).

Taking together these biological results, the synthesized compounds (–)-dysiherbol A (**98**) and (+)-dysiherbol A (*ent*-**98**) showed the ability to initiate apoptosis *in vitro* in tumor cells and to overcome resistances to conventional cytostatics in different leukemia and lymphoma cell lines. Moreover, (–)-dysiherbol A (**98**) turned out to effectively inhibit tumor cell proliferation in NALM-6 cells. In comparison, naturally occurring (+)-dysiherbol A (*ent*-**98**) showed superior apoptosis-inducing potency in all cell lines examined and a remarkable ability to overcome drug resistances. Additional experiments are ongoing to study its potential as drug candidate for the treatment of drug-refractory malignancies in leukemia.

4 SUMMARY

4.1 TOTAL SYNTHESIS OF THE DYSIHERBOLS

In this thesis, the enantioselective total syntheses of the revised structures of marine natural products dysiherbols A-C and E are described, together with contributions to their structural revision. Studies were conducted in both enantiomeric series. Tetracyclic ketone (*ent*-)**111** served as common intermediate, which is accessible starting from ketone (*ent*-)**114** via *Suzuki-Miyaura* coupling and a novel gold-catalyzed twofold cyclization (see *Scheme 63*) as key steps. Ketone (*ent*-)**114** in turn was synthesized in analogy to *Cramer*,[58] employing a chiral ligand in an one-pot 1,4-addition/enolate trapping sequence for the asymmetric entry into the total synthesis.



SCHEME 62 OVERVIEW OF THE HERE DISCUSSED TOTAL SYNTHESES OF DYSIHERBOLS A-C AND E. REAGENTS AND YIELDS (FOR THE ENANTIOMERIC SERIES IN PARENTHESIS): a) LDA, $PhNTf_2$, THF, 84% (68%); b) $Pd(dppf)Cl_2$ (3 mol%), Cs_2CO_3, DMF, **211**, 9-BBN, THF/H_2O, 97% (90%); c) $Bi(OTf)_3$ (4 mol%), CH_3CN/H_2O, 97% (98%); d) DMP, CH_2Cl_2, 86% (79%); e) $AuCl_3$ (4 mol%), CH_2Cl_2, 38% (34%); f) BH_3·THF, THF, then NaOH, H_2O_2, THF/H_2O; g) DMP, CH_2Cl_2, 83% (66%); h) LiH, 160 °C, then MeI, 23 °C, TPPA, 76% (71%); i) $ZnEt_2$, CH_2I_2, DCE, 82% (71%); j) aq. HCl, MeOH, reflux, 91% (83%); k) DTBMP, Tf_2O, DCE, 80% (71%); l) $Pd(PPh_3)_4$, LiCl, CO, DMF, 120 °C, 90%; m) DIBAL-H, THF, 86%; n) BBr_3, CH_2Cl_2, 51%; o) $Pd(PPh_3)_4$, Me_4Sn, LiCl, DMF, 120 °C, 91% (35%); p) trifluoroacetone, Oxone®, Na_2EDTA, $NaHCO_3$, $MeCN/H_2O$, 67%; q) $CeCl_3$, MeLi, THF, 97%; r) *p*TsOH, toluene, 105 °C, 93%; s) $ZnEt_2$, CH_2I_2, CH_2Cl_2, 2 cycles, 53%; t) BBr_3, H_2O, CH_2Cl_2, 74%; u) BBr_3, CH_2Cl_2, 82%; v) $Pd(PPh_3)_4$, $nBu_3SnCHCl_2$, LiCl, DMF, 120 °C, 75%; w) LiSEt, TPPA, 170 °C; x) CSA, CH_2Cl_2, 27%; y) O_3, then $NaBH_4$, MeOH, 36%.

Unnatural (–)-dysiherbol A (**98**) was synthesized from ketone **111** over four steps for the introduction of the two missing methyl groups followed by final deprotection/cyclization.

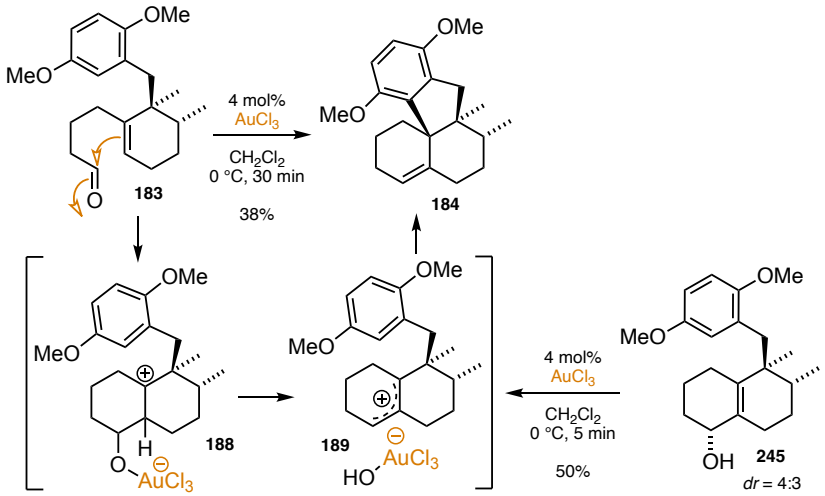
Natural occurring (+)-dysiherbol A (*ent*-**98**) was obtained using another route via triflate *ent*-**185** by *Stille* cross coupling and similar deprotection/cyclization.[40] Both enantiomers were tested in biological essays, showing cytotoxic activity in lymphoma and leukemia cell lines, while also overcoming resistances to conventional cytostatics. In comparison, naturally occurring (+)-dysiherbol A (*ent*-**98**) showed superior apoptosis-inducing potency in all examined cell lines.

Studies towards the synthesis of congeners dysiherbol B (**105**) and C (**106**) from *Stille* coupling product (*ent*-)**97** delivered rearranged homoallylic alcohol (*ent*)-**227** under epoxidation conditions. The transformation into natural product **105** turned out to be rather challenging, but could be achieved by cooperation partners from the group of *Prof. Z. Lu* (Nankai University) by inverting the configuration of the hydroxy group and exploiting a 1,2-methyl shift[64] under known deprotection/cyclization conditions.[63]

Studies concerning the total synthesis of dysiherbol E (**110**) revealed two different approaches, both utilizing palladium-catalyzed cross couplings starting from (*ent*-)**185**. Naturally occurring (+)-dysiherbol E (**110**) was obtained by ozonolysis of pentacyclic terminal olefin *ent*-**240**. This intermediate in turn was accessible via introduction of a vinyl residue to triflate *ent*-**185** by *Stille* cross coupling, deprotection of the hydroquinone moiety and subsequent acid-mediated oxy-cyclization. The enantiomer (–)-dysiherbol E (*ent*-**110**) was prepared starting from methyl ester **239**, obtained in excellent yield by carbonylative cross coupling. Reduction gave the respective homoallylic alcohol, which in turn delivered the target molecule under known deprotection/ cyclization conditions using BBr_3.[63]

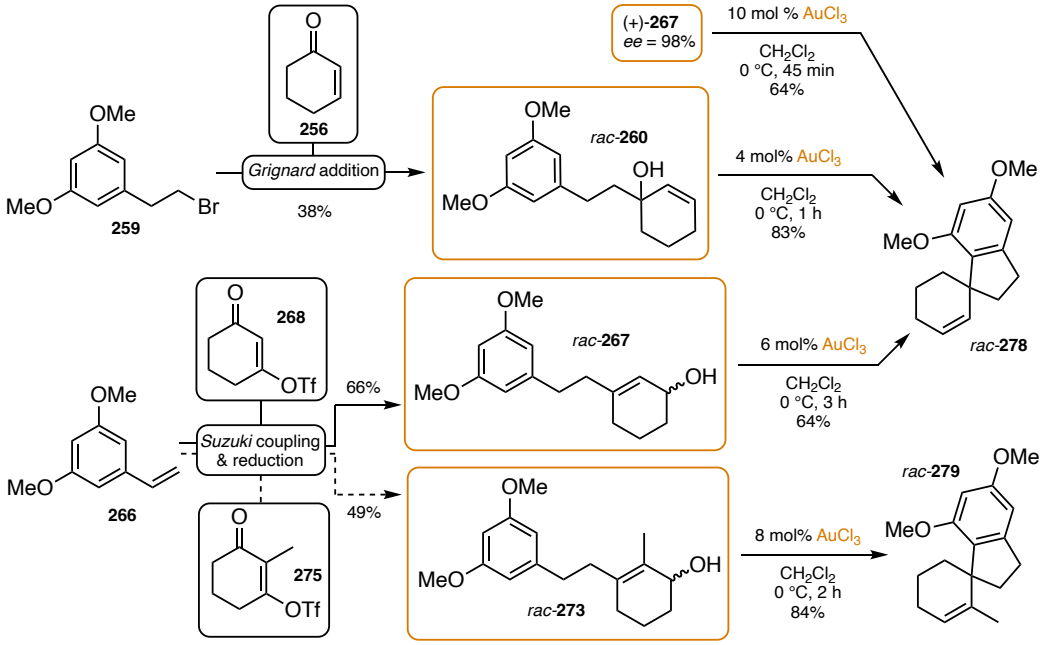
4.2 STUDIES ON A GOLD-CATALYZED CYCLIZATION

In the course of the studies towards the total synthesis of dysiherbol A (**98**) a gold-catalyzed twofold cyclization was developed (including a mechanistic rationale) (*Scheme 63*).



SCHEME 63 GOLD-CATALYZED TWOFOLD CYCLIZATION DEVELOPED WITHIN THE TOTAL SYNTHESIS OF THE DYSIHERBOLS TOGETHER WITH A PROPOSED MECHANISM.

Additional experiments were conducted to further study this transformation and to verify the supposed mechanism, which involves the formation of allylic cation **189** as a central intermediate. The reaction of allylic alcohol **245** to form tetracyclic olefin **184** in a onefold cyclization upon treatment with catalytic amounts of $AuCl_3$ supported the hypothesis.



SCHEME 64 SYNTHESIZED 3,5-DIMETHOXY SUBSTITUTED CYCLIZATION PRECURSORS (IN ORANGE BOXES) AND RESULTS OF GOLD-CATALYZED CYCLIZATION.

In addition, different simplified cyclization precursors were designed, which also could form respective allylic cations upon reaction with $AuCl_3$.These cationic intermediates might be trapped by the aromatic moiety in a S_EAr, delivering spirocyclic compounds.

The 3,5-dimethoxy congeners *rac*-**260** and *rac*-**267** underwent the suspected spiro cyclization delivering *rac*-**278** in good to very good yields (*Scheme 64*). These results supported the supposed mechanism, as despite differing positions of the hydroxy group the precursors gave comparable results. Introducing an additional methyl group next to the hydroxy group resulted in higher yield for spirocyclic compound *rac*-**279**, maybe due to higher stability of the intermediate allylic cation. Subjecting enantiopure allylic alcohol (+)-**267** to the developed cyclization conditions resulted in *rac*-**278**. This observation is also in agreement with the mechanistic proposal, as the chiral information is lost during the reaction via a cationic intermediate.

While other related substrates with less nucleophilic aryl substituents failed to undergo the gold-catalyzed cyclization, the results summarized in *Scheme 64* clearly support the mechanistic rationale of the AuCl3-catalyzed double cyclization as the most remarkable key step in the developed total synthesis of the dysiherbols.

5 EXPERIMENTAL

5.1 GENERAL INFORMATION

MATERIALS

All used chemicals were provided by commercial suppliers *Acros Organics*, *Carbolution, Merck*, *TCI*, *ABCR*, *Alfa-Aesar, BLDPharm and Sigma-Aldrich* with purities of ≥95 % and applied without further purification, unless otherwise noticed. Absolute CH_2Cl_2 was distilled over $CaCl_2$. Absolute THF/Et_2O/toluene was prepared by distillation over Na/benzophenone. Other dry solvents were used as provided by commercial suppliers, in septum bottles over molecular sieve. Other solvents were bought in technical quality and distilled before use. Synthesized compounds were stored in a freezer at -25°C. The molarity of MeLi, *n*-BuLi and *t*-BuLi solutions was determined by titration vs *N*-benzylbenzamide as an indicator. CAL-B (Lipase on acrylic resin, Novozym435®), recombinant, from *Aspergillus niger* (>5000 U/g, Lot-No. SLBZ9898) was obtained from *Merck* (*Aldrich*).

WORKING TECHNIQUES

Air and moisture sensible reactions were performed applying inert gas technique by flame-drying the evacuated glass ware and adding Ar-atmosphere (BIP argon from Air Products with a purity of 5.7 (99.9997 %). Sensible chemicals were stored and weighted in an Unilab glovebox by M. Braun Inertgas-Systeme GmbH. O2 and H2O concentration in the glovebox were kept under 1 ppm each. Substances were added through argon-flushed syringes via septa or by addition with reverse argon stream. Solvent evaporation was conducted using a Büchi Rotavapor RE 114 rotary evaporator at 40 °C unless otherwise noted. Room temperature (rt) corresponds to 25 ± 2 °C. Low-temperature reactions were performed in a Dewar vessel filled with a cooling mixture: H2O/ice (0 °C), acetone/CO2(s) (−78 °C). The ozonolysis was carried out using an ozone generator model 500 of the company Fischer. The required ozone was generated for each experiment at a current of 110 mA and an oxygen flow of 60 L/h.

COLUMN AND THIN LAYER CHROMATOGRAPHY (TLC)

Purifications using column chromatography were performed using silica gel 60 (0.020-0.035 mm) provided by Machery Nagel. Ultra pure silica gel was provided by Acros Organics (40-60 µM, 60A). For TLC, 60-F254 silica aluminum plates provided by Merck (0.20 mm silica gel) were used. Visualization was accomplished by UV light (at 254 nm) with an aqueous KMnO4 solution or with ceric ammonium molybdate as dying agent. Unless otherwise stated, reaction control was performed using TLC or GC-MS before terminating a reaction.

5.1.1 ANALYTICAL METHODS

NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY (NMR)

^{1}H, ^{13}C (APT or DEPTQ), ^{31}P and ^{19}F NMR spectra were measured in $CDCl_3$ at room temperature on a Bruker Avance 300 (300 MHz), *Bruker* Avance II 300 (300 MHz), *Bruker* Avance II 500 (500 MHz), *Bruker* Avance III 500 (500 MHz) or *Bruker* Avance II+ 600 (600 MHz) spectrometers. Deuterated chloroform with TMS as a standard was used as a solvent. Chemical shifts are given relatively to TMS (^{1}H, 0 ppm) or $CDCl_3$ (^{1}H 7.26 ppm, ^{13}C, 77.16 ppm). The multiplicity was assigned with singulet (s), dublet (d), triplet (t), quartet (q), quintet (quin) and multiplet (m). The assignments were carried out using 2D NMR spectra (H,H-COSY, H,C-HSQC, H,C-HMBC). The atom numbering shown for signal assignment does not correspond to IUPAC nomenclature.

HIGH RESOLUTION MASS SPECTROMETRY (HR-MS)

HR-MS spectra were measured at a *THERMO Scientific* LTQ Orbitrap XL mass spectrometer via electron spray ionization and a FTMS Analyzer. ESI conditions were set as 3.4 kV (spray voltage), 3.0 V (capillary voltage), 3.0 V (tube lens voltage) and 275 °C (capillary temperature). For a stable electrospray, sheath gas and sweep gas were used (Nitrogen 5.0, ≥ 99.999%, Linde). In some cases, high resolution mass spectra were obtained using a Thermo Scientific Exactive GC Orbitrap GC-MS system (EI mode).

GAS CHROMATOGRAPHY WITH MASS SPECTROSCOPY (GC-MS)

GC-MS spectra were measured at the *Aglient* HP6890N gas chromatograph using a 5937N mass detector and an electron ionization chamber. For detection a TIC detector was employed. H_2 was used as carrier gas and an *Optima* 1 MS (30 mm x 0.25 mm) column provided by *Machery Nagel* was applied. Unless otherwise stated, reaction control was performed using TLC or GC-MS before terminating a reaction.

CHIRAL HIGH PERFORMANCE LIQUID CHROMATOGRAPHY (CHIRAL HPLC)

The enantiomeric excess (*ee*) was determined using a racemic standard on a *VWR Hitachi* Chromaster HPLC system with a CHIRALPAK AD-H column (column temperature: 18 °C, detection at 250 nm) or on a HPLC system from *Knauer* on a *Macherey-Nagel* Nucleocell column.

FOURIER TRANSFORM INFRARED SPECTROSCOPY (FT-IR)

FT-IR (ATR): $\tilde{\nu}$ spectra were measured at a *Perkin Elmer* FTIR-ATR (UATR TWO) at room temperature. Absorption bands are given in cm^{-1} and assigned with broad (br), weak (w), medium (m) and strong (s).

SPECIFIC ROTATION

Specific rotation was measured at 20 °C in $CHCl_3$ or MeOH with an MCP 200 polarimeter from *Anton Paar* at different wavelengths with a cell length of 10 cm.

MELTING POINT

Melting points were determined on a *Büchi* B-545 instrument in open capillary tubes and are uncorrected.

X-RAY CRYSTALLOGRAPHY

X-ray data were obtained using a *Bruker* D8 VENTURE (Kappa geometry, microfocus source (Cu anode), λ = 1.54178 Å) apparatus with a PHOTON III M14 or PHOTON 100 detector. Structure solution and refinement were performed using SHELXT software. If applicable, supplementary crystallographic data can be obtained free of charge from the Cambridge Crystallographic Data Centre (CCDC) under the indicated deposition numbers shown at the respective crystal structures. The measurements and evaluations were carried out by *Dr. J.-M. Neudörfl*.

ECD SPECTROSCOPY

The ECD spectrum of (–)-dysiherbol A was measured on a *Jasco* j-715 CD spectropolarimeter in methanol (10^{-3} M solution).

5.1.2 BIOLOGICAL STUDIES

MATERIALS AND METHODS

Doxorubicine (Doxo), vincristine (Vcr) and cytarabine (AraC) were provided by the Charité, Berlin, Germany. Drugs were freshly dissolved in DMSO prior to the experiments and diluted with the appropriate medium or buffer during the assay procedures. For each experiment, dysiherbol A was freshly dissolved in 0.4% NaCl solution to give a 1 mM stock solution.

CELL LINES AND CELL CULTURE

Doxorubicin-resistant BJAB cells (7CCA) were generated by exposing BJAB cells to increasing doxorubicin concentrations of up to 1 µg/mL. NALM-6 cells (human B-cell precursor leukemia) were provided by AG Henze, Charité, Berlin. To generate a vincristine-resistant Nalm-6 cell line (NALM-6/Vcr), Nalm-6 cells were exposed to increasing concentrations of vincristine up to 30 nM. Cell lines were maintained in 250-mL cell culture flasks at 37 °C. Suspension cells were grown in RPMI 1640 medium (Gibco, Invitrogen, Karlsruhe, Germany) supplemented with heat-inactivated fetal calf serum (FCS, 10%, v/v), L-glutamine (0.56 g/l), penicillin (100,000 i.u.) and streptomycin (0.1 g/l). Adherent cells were grown in Dulbecco's modified minimal essential medium (DMEM) supplemented with FCS (10%, v/v) and geniticine (0.4 g/l). Cells were passaged 2–3 times per week by dilution to 1 × 105 cells/mL. 24 h before the assay setup, cells were adjusted to 3 × 105 cells/mL to ascertain standardized growth conditions. For proliferation and apoptosis assays, cells were diluted to 1 × 105 cells/mL immediately before treatment.

DETERMINATION OF CELL DENSITY AND CELL VIABILITY

Cell count and viability were measured with a CASY® Counter and Analyzer System (Innovatis, Bielefeld, Germany) as described in literature.[119] Parameters measured were adjusted to the requirements of the cells used. With this system, cell density can be analyzed simultaneously in different size ranges: cell debris, dead cells, and viable cells. Cells were seeded at a density of 1 × 105 cells/ mL in 6-well plates and treated with the respective agent in comparison to untreated and DMSO controls. After 24 h incubation at 37 °C, cells were resuspended properly and 100 µL from each well were diluted in CASYton (ready-to-use isotonic saline solution, 10 mL) for immediate cell counting. The frequency of cells in untreated controls was defined as 100% growth. Maximal inhibition of proliferation was achieved when the cell density was not higher than at the beginning of the experiment.

MEASUREMENT OF APOPTOSIS

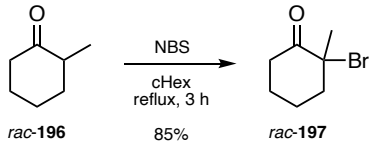
DNA fragmentation during the late phase of apoptosis was measured by a modified cell cycle analysis as described in literature.[120] After incubation for 72 h or 60 h at 37 °C in 6-well plates, cells were collected by centrifugation at 1500 rpm for 5 min, washed with PBS at 4 °C and fixed in PBS/2% (v/v) formaldehyde on ice for 30 min. After fixation, cells were pelleted, incubated with ethanol/PBS (2:1, v/v) for 15 min, pelleted and resuspended in PBS containing RNase A (40 µg/mL). RNA was digested for 30 min at 37 °C; cells were pelleted again and resuspended in PBS containing propidium iodide (50 µg/mL). Nuclear DNA fragmentation was quantified by flow cytometric determination of hypodiploid DNA. Data were collected and analyzed with FACScan (Becton Dickinson, Heidelberg, Germany) instrument with CellQuest software.

STATISTICAL ANALYSIS

The data in the diagrams are shown as mean values from three independent samples of one approach, and standard deviations are given by the error indicators. Data evaluation and statistical calculations were carried out with Microsoft Excel. The evaluation of the flow-cytometric measurements was carried out with the CellQuest Pro software.

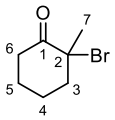
5.2 SYNTHETIC PROCEDURES AND ANALYTICAL DATA – TOTAL SYNTHESIS OF THE DYSIHERBOLS

5.2.1 SYNTHESIS OF *rac*-2-BROMO-2-METHYLCYCLOHEXANONE (*rac*-**197**)[101]



According to a literature procedure,[101] 35.0 mL (32.4 g, 289 mmol, 1.0 eq.) of 2-methyl cyclohexanone (*rac*-**196**) were added to a suspension of 51.4 g (289 mmol, 1.0 eq.) of NBS in 1400 mL of *c*-Hex. After refluxing for 3 h, the reaction mixture was allowed to cool to rt. The colorless precipitate was filtered off and washed with *c*-Hex. The filtrate was washed with 400 mL of H_2O, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (*c*-Hex/EtOAc 33:1) to provide 47.0 g (246 mmol, 85%) of *rac*-2-bromo-2-methylcyclohexanone (*rac*-**201**) as a pale yellow oil.

M ($C_7H_{11}BrO$) = 191.07 g/mol



R_f (*c*-Hex/EtOAc 9:1) = 0.43

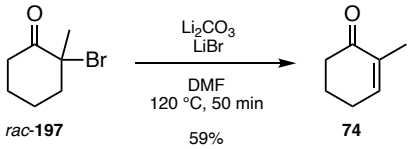
^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 3.20 (td, J = 14.4, 6.2 Hz, 1H, H-6), 2.40 – 2.31 (m, 2H, H-3, H), 2.12 – 2.02 (m, 2H, H-4, H-5), 1.81 (s, 3H, H-7), 1.81 – 1.73 (m, 2H, H-3', 4-H'), 1.66 – 1.55 (m, 1H, H-5').

^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 204.7 (C-1), 65.9 (C-2), 43.6 (C-3), 36.7 (C-6), 28.1 (C-7), 26.9 (C-5), 22.3 (C-4).

FT (ATR): $\tilde{\nu}$ [cm^{-1}] = 2998 (w), 2939 (m), 2867 (w), 2834 (w), 1713 (s), 1447 (m), 1427 (m), 1378 (w), 1349 (w), 1339 (w), 1317 (w), 1283 (w), 1256 (w), 1235 (w), 1181 (w), 1137 (w), 1126 (w), 1109 (w), 1084 (m), 1067 (w), 1018 (w), 991 (w), 938 (w), 902 (w), 866 (w), 843 (w), 836 (w), 709 (w), 667 (w), 581 (m), 514 (w).

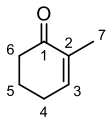
GC-MS (70 eV): *m/z* (%) = 190 (23, $[M]^+$), 146 (70), 111 (60), 83 (33), 55 (100), 39 (43).

5.2.2 SYNTHESIS OF 2-METHYL-2-CYCLOHEXENONE (74)[101]



According to a literature procedure,[101] to a solution of 42.4 g (222 mmol, 1.0 eq.) of *rac*-2-bromo-2-methylcyclohexanone (*rac*-**197**) in 670 mL of DMF were added 54.2 g (733 mmol, 3.3 eq.) of Li_2CO_3 and 38.6 g (444 mmol, 2.0 eq.) of LiBr. The stirred reaction mixture was heated to 120 °C for 50 min before it was allowed to cool to rt. The solids were filtered off, the filtrate was diluted with 400 mL of H_2O and 300 mL of MTBE and the phases were separated. The aqueous phase was extracted with 3 x 300 mL of MTBE, the combined organic phases were washed with 2 x 200 mL of H_2O and dried over Na_2SO_4. The crude product was purified by column chromatography (*n*-pentane/MTBE 50:1 to 10:1). The solvent was removed under reduced pressure to give 15.7 g (131 mmol, 59%) of 2-methyl-2-cyclohexenone (**74**) as a yellow oil. Due to the volatility of the product, the rotary evaporator was used at a minimum of 300 mbar at 40 °C bath temperature until constant loss in mass was reached.

M ($C_7H_{10}O$) = 110.16 g/mol



R_f (*c*-Hex/EtOAc 9:1) = 0.20

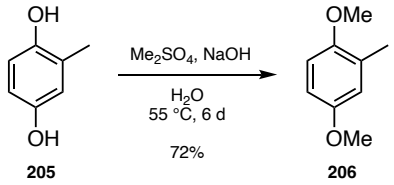
^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.74 (s, 1H, 3-H), 2.44 – 2.38 (m, 2H, 6-H), 2.34 – 2.28 (m, 2H, 4-H), 1.97 (quint, J = 6.4 Hz, 2H, 5-H), 1.77 – 1.76 (m, 3H, 7-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 200.1 (C-1), 145.7 (C-3), 135.8 (C-2), 38.4 (C-6), 26.1 (C-4), 23.4 (C-5), 16.1 (C-7).

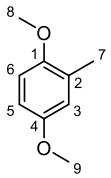
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2950 (m), 2925 (m), 2885 (w), 2868 (w), 2834 (w), 1664 (s), 1453 (m), 1432 (m), 1359 (m), 1255 (w), 1174 (m), 1139 (w), 1106 (m), 1082 (m), 1022 (m), 902 (m), 880 (m), 860 (w), 801 (w), 708 (w), 685 (w), 524 (m), 472 (w), 411 (m).

GC-MS (70 eV): *m/z* (%) = 110 (70, $[M]^+$), 82 (100), 54 (50), 39 (31).

5.2.3 SYNTHESIS OF 1,4-DIMETHOXY-2-METHYLBENZENE (**206**)[102]



According to a literature procedure,[102] in a 2000 mL three-necked round flask equipped with a reflux condenser connected to a gas washing bottle containing 25% aqueous NH_4OH, 116 g (2.90 mol, 8.0 eq.) of NaOH were dissolved in 420 mL of H_2O. To the solution were added 45.0 g (362 mmol, 1.0 eq.) of 2-methyl-hydroquinone (**205**) causing a green to brown coloring. Then, 170 mL (226 g, 1.79 mol, 4.9 eq.) of Me_2SO_4 were added. The reaction mixture was very carefully heated to 55 °C (CAUTION: the exothermic reaction will start spontaneously and has to be thermally controlled by cooling with an ice bath). Once the reaction was not self-heating anymore, it was stirred at 55 °C for 6 d, forming an oil film as an upper layer. The reaction was quenched with 500 mL of 25% aqueous NH_4OH at rt and the suspension was extracted with 3 x 300 mL of MTBE. The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (*c*-Hex/EtOAc 10:1) to provide 39.6 g (260 mmol, 72%; Lit.: 97%) of 1,4-dimethoxy-2-methylbenzene (**206**) as a pale yellow oil.



M ($C_9H_{12}O_2$) = 152.19 g/mol

R_f (*c*-Hex/EtOAc 9:1) = 0.53

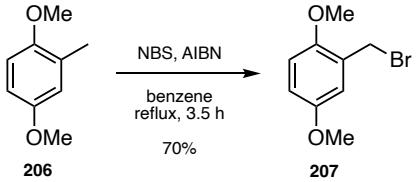
^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.77 (d, J = 6.7 Hz, 1H, 6-H), 6.76 (s, 1H, 3-H), 6.70 (dd, J = 8.6, 3.1 Hz, 1H, 5-H), 3.80 (s, 3H, 8-H), 3.77 (s, 3H, 9-H), 2.24 (s, 3H, 7-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 153.5 (C-4), 152.2 (C-1), 128.0 (C-2), 117.2 (C-3), 111.0 (C-6), 110.8 (C-5), 56.0 (C-8), 55.8 (C-9), 16.5 (C-7).

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2996 (w), 2947 (w), 2907 (w), 2833 (w), 1612 (w), 1593 (w), 1499 (s), 1465 (m), 1442 (w), 1419 (w), 1410 (w), 1378 (w), 1305 (w), 1280 (m), 1219 (s), 1190 (w), 1180 (m), 1157 (m), 1130 (w), 1047 (s), 1031 (m), 997 (w), 923 (w), 866 (w), 851 (w), 795 (m), 752 (w), 711 (m), 699 (m), 584 (w), 555 (w).

GC-MS (70 eV): *m/z* (%) = 152 (79, $[M]^+$), 137 (100), 109 (14), 94 (11), 77 (14).

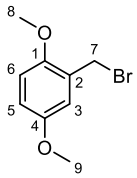
5.2.4 SYNTHESIS OF 2-(BROMOMETHYL)-1,4-DIMETHOXYBENZENE (**207**)[102]



According to a literature procedure,[102] 20.0 g (131 mmol, 1.0 eq.) of 1,4-dimethoxy-2-methylbenzene (**206**) were dissolved in 470 mL of benzene and 23.4 g (131 mmol, 1.0 eq.) of NBS were added. The stirred suspension was heated to 60°C, 533 mg (3.25 mmol, 0.025 eq.) of AIBN were added in portions and the reaction mixture was refluxed for 3.5 h. After the mixture was cooled to 0 °C, the precipitate was separated by filtration and washed with MTBE. The filtrate was washed with 2 x 200 mL of H_2O, 2 x 100 mL of sat. aqueous $Na_2S_2O_3$ and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was recrystallized with 50 mL of *c*-Hex overnight at 5 °C. The resulting solid was washed with *c*-Hex to obtain 21.1 g (91.3 mmol, 70 %; Lit.: 61%) of 2-(bromomethyl)-1,4-dimethoxybenzene (**207**) as off-white needles.

M ($C_9H_{11}BrO_2$) = 231.09 g/mol

R_f (*c*-Hex/EtOAc 9:1) = 0.47



m.p.= 72 °C – 72 °C

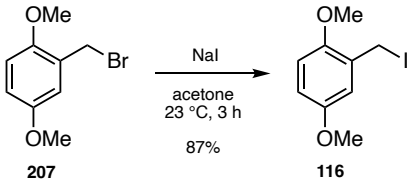
^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.90 (d, *J* = 2.6 Hz, 1H, 3-H), 6.85 – 6.82 (m, 1H, 5-H), 6.81 (d, *J* = 8.8 Hz, 1H, 6-H), 4.54 (s, 2H, 7-H), 3.85 (s, 3H, 8-H), 3.77 (s, 3H, 9-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 153.5 (C-4), 151.8 (C-1), 127.0 (C-2), 116.5 (C-3), 115.1 (C-5), 112.3 (C-6), 56.3 (C-8), 55.9 (C-9), 29.0 (C-7).

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3008 (w), 2936 (w), 2835 (w), 1974 (w), 1839 (w), 1720 (w), 1587 (m), 1497 (s), 1458 (m), 1420 (m), 1283 (m), 1223 (s), 1207 (s), 1191 (m), 1044 (s), 1021 (s), 930 (m), 870 (m), 809 (s), 712 (m), 638 (w), 582 (m), 538 (s), 508 (m).

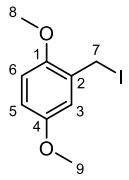
GC-MS (70 eV): *m/z* (%) = 230 (8, $[M]^+$), 152 (72), 137 (100), 121 (29), 109 (11), 94 (11), 77 (23), 66 (15), 39 (10).

5.2.5 SYNTHESIS OF 2-(IODOMETHYL)-1,4-DIMETHOXYBENZENE (**116**)[103]



According to a literature procedure,[103] to a solution of 30.0 g (130 mmol, 1.0 eq.) of 2-(bromomethyl)-1,4-dimethoxybenzene (**207**) in 185 mL of acetone were added 38.9 g (260 mmol, 2.0 eq.) of NaI. The suspension was stirred at 23 °C for 3 h, before the precipitate was separated by filtration. The solvent was removed under reduced pressure (flask wrapped in aluminum foil, 30°C bath temperature) to obtain a pale yellow solid, which was immediately quenched with 200 mL of sat. aqueous $Na_2S_2O_3$ (CAUTION: Upon solidification, an accelerating and exothermic decomposition process can occur). 400 mL of CH_2Cl_2 were added and the phases were separated. The solvent of the organic layer was removed under reduced pressure (flask wrapped in aluminum foil, 30°C bath temperature) and the resulting solid washed with sat. aqueous $Na_2S_2O_3$ and H_2O to give 31.5 g (113 mmol, 87%; Lit.: 98%) of 2-(iodomethyl)-1,4-dimethoxybenzene (**116**) as a yellow solid.

M ($C_9H_{11}IO_2$) = 278.09 g/mol



R_f (*c*-Hex/EtOAc 9:1) = 0.53

decomposition point = 59 °C – 60 °C

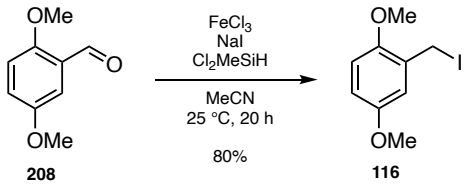
^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.87 (d, *J* = 2.9 Hz, 1H, 3-H), 6.80 (dd, *J* = 8.9, 2.9 Hz, 1H, 5-H), 6.76 (d, *J* = 8.9 Hz, 1H, 6-H), 4.46 (s, 2H, 7-H), 3.87 (s, 3H, 8-H), 3.76 (s, 3H, 9-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 153.5 (C-4), 151.5 (C-1), 128.5 (C-2), 115.8 (C-3), 114.6 (C-5), 112.3 (C-6), 56.1 (C-8), 55.9 (C-9), 1.3 (C-7).

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3003 (w), 2988 (w), 2959 (w), 2934 (w), 2902 (w), 2832 (w), 1824 (w), 1605 (w), 1586 (w), 1491 (s), 1467 (m), 1439 (w), 1414 (m), 1318 (w), 1278 (m), 1263 (w), 1225 (s), 1185 (m), 1180 (m), 1148 (m), 1134 (m), 1084 (m), 1043 (s), 1019 (s), 927 (w), 875 (m), 825 (w), 801 (s), 757 (w), 730 (w), 714 (m), 576 (w), 550 (w).

GC-MS (70 eV): *m/z* (%) = 278 (4, $[M]^+$), 151 (100), 137 (99), 121 (38), 91 (18), 77 (22), 66 (16), 39 (9).

5.2.6 ALTERNATIVE SYNTHESIS OF 2-(IODOMETHYL)-1,4-DIMETHOXYBENZENE (116)[104]

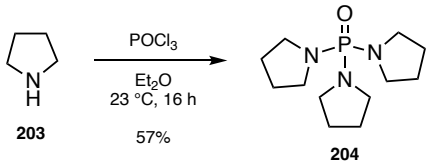


According to a literature procedure,[104] an orange-colored solution of 488 mg (3.01 mmol, 0.1 eq.) of $FeCl_3$ in 150 mL of acetonitrile was vigorously stirred at 25 °C for 2 h before 5 g (30.1 mmol, 1.0 eq.) of 2,5-dimethoxybenzaldehyde (**208**) were added. The dark-brown solution was stirred for 35 min and 9.4 mL (10.3 g, 89.5 mmol, 3.0 eq.) of Cl_2MeSiH were added. The orange-colored solution was stirred at 25 °C for 10 min before 13.5 g (90.1 mmol, 3.0 eq) of NaI were added. The dark brown-greenish suspension was stirred at 23 °C for 20 h, cooled to 0 °C and quenched with 15 mL of diluted HCl and 50 mL of sat. aqueous $Na_2S_2O_3$. Subsequently, 50 mL of sat. aqueous $NaHCO_3$ were added and the phases were separated. Crystallization was achieved by adding 50 mL of H_2O to the organic layer. After addition of 50 mL of sat. aqueous $Na_2S_2O_3$, the solid was separated by filtration, washed with H_2O and resolved with EtOAc to separate the product from an insoluble polymer. EtOAc was removed carefully under reduced pressure (flask wrapped in aluminum foil, 30°C bath temperature) until crystallization started and 6.68 g (24.9 mmol, 80%) of 2-(iodomethyl)-1,4-dimethoxybenzene (**116**) were obtained as a yellow solid.

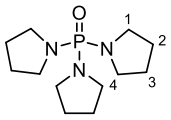
M ($C_9H_{11}IO_2$) = 278.09 g/mol

See chapter **5.2.5** for analytical data.

5.2.7 SYNTHESIS OF TRIS-(PYRROLIDINYL)-PHOSPHORAMIDE (TPPA, **207**)[98]



According to a literature procedure,[98] in an argon flushed 1000 mL three-necked round flask equipped with a 300 mL dropping funnel and reflux condenser connected to a bubble counter containing 1 M $NaOH_{(aq)}$, 48.0 mL (79.0 g, 515 mmol, 1.0 eq.) of $POCl_3$ were dissolved in 250 mL of dry Et_2O. The stirred solution was cooled in an ice bath and 250 mL (215 g, 3.0 mol, 5.8 eq.) of pyrrolidine (**203**) were added slowly over 2 h through the dropping funnel. Upon addition a white precipitate/fume formed immediately (pyrrolidine hydrochloride) and the reaction proceeded in an exothermic fashion. Therefore, the dropping speed was adapted carefully. After complete addition, the white suspension was allowed to reach 23 °C overnight. Afterwards, the white precipitate was separated by filtration, washed with Et2O and the solvent was removed under reduced pressure to obtain a yellow oil. The crude product was purified by fractional vacuum distillation over CaH_2 (0.018 mbar, head temperature: 140°C) to provide 75.6 g (294 mmol, 57%; Lit.: 54%) of TPPA (**204**) as a colorless, viscous oil.



M ($C_{12}H_{24}N_3OP$) = 257.32 g/mol

^{1}**H NMR** (500 MHz, $CDCl_3$): δ [ppm] = 3.14 (td, J = 6.6, 4.2 Hz, 12H, 1-H, 4-H), 1.81 – 1.78 (m, 12H, 2-H, 3-H).

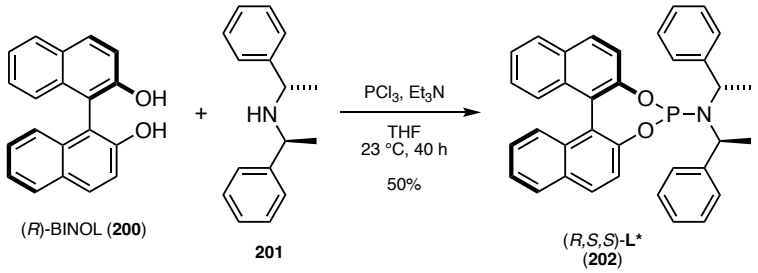
^{13}**C NMR** (75 MHz, $CDCl_3$): δ [ppm] = 46.3 (d, $J_{C,P}$ = 4.4 Hz, C-1, C-4), 26.5 (d, $J_{C,P}$ = 8.0 Hz, C-2, C-3).

^{31}**P NMR** (121 MHz, $CDCl_3$): δ [ppm] = 14.3.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2960 (m), 2864 (m), 1490 (w), 1449 (w), 1345 (w), 1292 (w), 1222 (s), 1202 (s), 1126 (m), 1076 (s), 1008 (s), 956 (w), 912 (m), 873 (w), 765 (m), 573 (s), 512 (w).

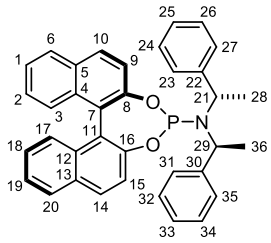
GC-MS (70 eV): m/z (%) = 257 (25, [M]+), 187 (54), 145 (8), 118 (9), 89 (7), 70 (100), 41 (11).

5.2.8 SYNTHESIS OF PHOSPHORAMIDITE LIGAND (*R,S,S*)-L* (202)[100]



According to a literature procedure,[100] in a flame dried *Schlenk* flask 1.40 mL (2.20 g, 16.0 mmol, 1.0 eq.) of PCl_3 were added to 11.0 mL (8.03 g, 79.0 mmol, 4.9 eq.) of Et_3N. The resulting suspension was cooled to 0 °C and a solution of 3.65 g (16.2 mmol, 1.0 eq.) of amine **201** in 7.0 mL of dry THF was added over 15 min. The mixture was allowed to reach 23 °C and stirred for 2.5 h. The suspension was cooled to 0 °C and a solution of 4.58 g (16.0 mmol, 1.0 eq.) of (*R*)-BINOL (**208**) in 2.5 mL of dry THF was added. The reaction mixture was allowed to reach 23 °C again and stirred for 40 h. Afterwards, the white precipitate was filtered off and washed with EtOAc. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (*c*-Hex/EtOAc 50:1) to provide 4.34 g (8.04 mmol, 50%; Lit.: 41%) of phosphoramidite ligand (*R,S,S*)-**L*** (**202**) as a colorless foam.

M ($C_{36}H_{30}NO_2P$) = 539.61 g/mol



R_f (*c*-Hex/EtOAc 9:1) = 0.46

m.p.: > 250°C

^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.94 (d, J = 8.7 Hz, 2H, H-10, H-14), 7.92 – 7.87 (m, 2H, H-6, H-20), 7.58 (d, J = 8.7 Hz, 1H, H-9/15), 7.42 (d, J = 8.7 Hz, 1H, H-9/15), 7.43 – 7.36 (m, 3H, H-1, H-19, H-3/17), 7.27 (d, J = 8.5 Hz, 1H, 3/17-H), 7.25 – 7.19 (m, 2H, H-2, H-18), 7.11 (s, 10H, H-23, H-24, H-25, H-26, H-27, H-31, H-32, H-33, H-34, H-35), 4.56 – 4.43 (m, 2H, H-21, H-29), 1.72 (d, J = 6.6 Hz, 6H, H-28, H-36).

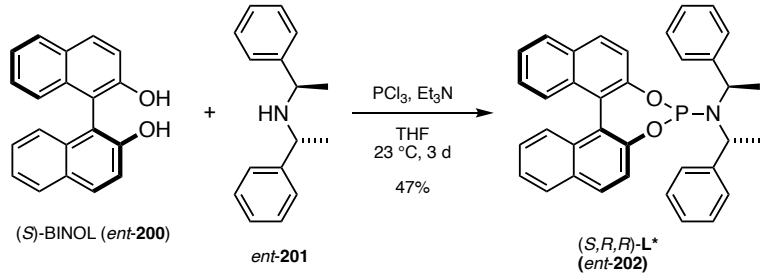
^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 150.2 (d, $J_{C,P}$ = 7.4 Hz, C-8/16), 149.7 (C-8/16), 143.0 (C-22, C-30), 132.94 (d, $J_{C,P}$ = 1.3 Hz, C-4/12), 132.89 (d, $J_{C,P}$ = 1.8 Hz, C-4/12), 131.5 (d, $J_{C,P}$ = 1.1 Hz, C-7/11), 130.6 (d, $J_{C,P}$ = 0.7 Hz, C-7/11), 130.4 (d, $J_{C,P}$ = 0.9 Hz, C-10/14), 129.6 (d, $J_{C,P}$ = 1.1 Hz, C-10/14), 128.4 (C-6/20), 128.2 (C-6/20), 128.1 (C-23/31, C-27/35), 128.0 (C-23/31, C-27/35), 127.9 (C-24, C-26, C-32, C-34), 127.3 (C-3/17), 127.2 (C-3/17), 126.8 (C-25, C-33), 126.12 (C-2/18), 126.09 (C-2/18), 124.9 (C-1/19), 124.6 (C-1/19), 124.2 (d, $J_{C,P}$ = 5.3 Hz, C-5/13), 122.6 (C-5/13), 122.5 (d, $J_{C,P}$ = 2.3 Hz, C-9/15), 121.9 (d, $J_{C,P}$ = 2.5 Hz, C-9/15), 52.5 (C-21/29), 52.3 (C-21/29), 22.2 (C-28/36), 22.1 (C-28/36).

^{31}P NMR (121 MHz, $CDCl_3$): δ [ppm] = 145.3.

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3061 (w), 3027 (w), 2985 (w), 2971 (w), 2923 (w), 2902 (w), 2849 (w), 1619 (w), 1590 (w), 1505 (w), 1495 (w), 1463 (w), 1450 (w), 1375 (w), 1327 (w), 1271 (w), 1256 (w), 1230 (m), 1203 (w), 1156 (w), 1134 (w), 1120 (w), 1070 (m), 1050 (w), 1032 (w), 1020 (w), 983 (w), 969 (w), 948 (m), 924 (m), 864 (w), 851 (w), 820 (m), 799 (w), 779 (m), 763 (m), 747 (s), 695 (s), 653 (w), 626 (w), 607 (w), 590 (w), 571 (w), 555 (w), 524 (w).

[α]$^{20}_{\lambda}$ (c = 0.50 g/100 mL, $CHCl_3$): – 870° (436 nm), – 541° (546 nm), – 473° (579 nm), – 453° (589 nm).

5.2.9 SYNTHESIS OF PHOSPHORAMIDITE LIGAND (*S,R,R*)-**L***(*ent*-**202**)[100]



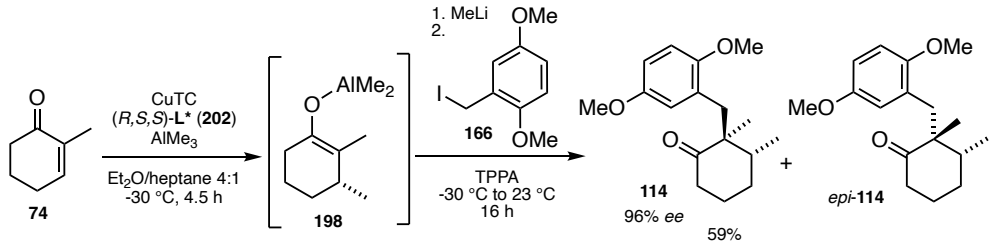
According to a literature procedure,[100] in a flame-dried *Schlenk* flask 840 µL (1.32 g, 9.61 mmol, 1.0 eq.) of PCl_3 were added to 6.7 mL (4.89 g, 48.3 mmol, 5.0 eq.) of Et_3N. The resulting suspension was cooled to 0 °C and a solution of 2.16 g (9.58 mmol, 1.0 eq.) of amine *ent*-**209** in 7.0 mL of dry THF was added over 15 min. The mixture was allowed to reach 23 °C and stirred for 5 h. The suspension was cooled back to 0°C and a solution of 2.75 g (9.59 mmol, 1.0 eq.) of (*S*)-BINOL (*ent*-**208**) and additional 7 mL of dry THF were added. The reaction mixture was allowed to reach 23 °C again and stirred for 3 d. Afterwards, the white precipitate was separated by filtration and washed with EtOAc. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (*c*-Hex/toluene 8:1 to 4:1) to provide 2.43 g (4.50 mmol, 47%; Lit.: 41%) of phosphoramidite ligand (*S,R,R*)-**L*** (*ent*-**202**) as a colorless foam.

M ($C_{36}H_{30}NO_2P$) = 539.61 g/mol

[α]$^{20}_{\lambda}$ (c = 0.56 g/100 mL, $CHCl_3$): 763° (436 nm), 464° (546 nm), 405° (579 nm), 387° (589 nm).

Additional analytical data was in accordance with that recorded for (*R,S,S*)-**L*** (**202**) (see chapter **5.2.8**).

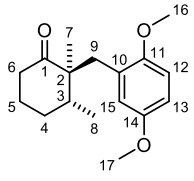
5.2.10 SYNTHESIS OF (2*S*,3*R*)-2-(2,5-DIMETHOXYBENZYL)-2,3-DIMETHYL-CYCLOHEXANONE (**114**)[58]



Based on a literature procedure,[58] in a flame dried *Schlenk* flask 173 mg (0.908 mmol, 0.024 eq.) CuTC and 980 mg (1.82 mmol, 0.047 eq.) of phosphoramidite ligand (*R,S,S*)-**L*** (see chapter **5.3.8**) in 100 mL of dry Et_2O were stirred at 23 °C for 20 min. The salmon-colored solution was cooled to -30 °C and 4.24 g (38.5 mmol, 1.0 eq.) of enone **74** were added. Then, 27.2 mL (54.5 mmol, 1.4 eq.) of $AlMe_3$ (2.0 M in heptane) were added via syringe over a period of 10 min. The reaction mixture was stirred at -30 °C for 4.5 h. The solvents were removed *in vacuo* at -30 °C (using the *Schlenk* line) until a small volume remained, which was dissolved in 40 mL of TPPA before 34.1 mL (54.5 mmol, 1.4 eq.) of methyllithium (1.6 M in Et_2O) were added over a period of 5 min (at -30 °C). Finally, 20.2 g (72.6 mmol, 1.9 eq.) of iodide **166** were added and the stirred suspension was allowed to slowly warm up to 23 °C overnight. At this point, GC-MS analysis indicated full conversion of the 1,4-addition intermediate and a diastereoselectivity of *dr* = 5:1. The reaction mixture was carefully quenched by addition of 20 mL of sat. aqueous NH_4Cl at 0 °C before 200 mL of H_2O and 100 mL of sat. aqueous Na K tartrate solution were added (to facilitate phase separation). The aqueous phase was extracted with 4 x 200 mL of *c*-Hex, the combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (*c*-Hex/EtOAc 33:1) to give 6.34 g (22.9 mmol, 59%) of the pure *trans*-product **114** as a pale yellow crystals. This product showed an enantiomeric excess of 96% *ee* as determined by chiral HPLC using a racemic standard (for details see chapter **6.3**). In addition, a sample of the separated *cis*-byproduct *epi*-**114** was obtained and used for analytical characterization.

<u>*trans*-product **114**:</u>

M ($C_{17}H_{24}O_3$) = 276.38 g/mol



R_f (*c*-Hex/EtOAc 9:1) = 0.32

m.p.: 50 °C – 53 °C

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.74 – 6.72 (m, 1H, H-12), 6.70 – 6.68 (m, 2H, H-13, H-15), 3.73 (s, 3H, H-17), 3.69 (s, 3H, H-16), 3.18 (d, *J* = 13.6 Hz, 1H, H-9), 2.90 (d, *J* = 13.6 Hz, 1H, H-9'),

2.73 (ddd, *J* = 14.5, 9.9, 6.6 Hz, 1H, H-6), 2.33 (dt, *J* = 14.5, 5.8 Hz, 1H, H-6'), 2.09 (ddt, *J* = 13.7, 9.1, 4.4 Hz, 1H, H-4), 2.01 – 1.93 (m, 1H, H-3), 1.89 (dtt, *J* = 14.6, 9.8, 5.0 Hz, 1H, H-5), 1.82 – 1.74 (m, 1H, H-5'), 1.50 (dtd, *J* = 13.4, 6.5, 4.5 Hz, 1H, H-4'), 0.91 (d, *J* = 7.0 Hz, 3H, H-8), 0.89 (s, 3H, H-7).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 216.2 (C-1), 153.1 (C-14), 152.3 (C-11), 128.2 (C-10), 118.5 (C-15), 111.8 (C-13), 111.2 (C-12), 55.7 (C-17), 55.5 (C-16), 53.6 (C-2), 40.2 (C-3), 38.4 (C-6), 37.2 (C-9), 28.7 (C-4), 23.0 (C-5), 18.9 (C-7), 16.4 (C-8).

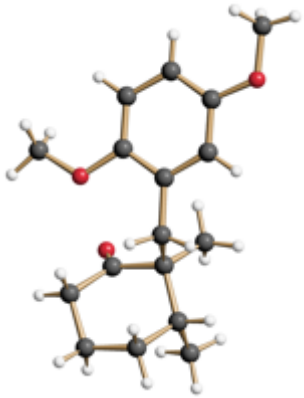
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2988 (w), 2935 (m), 2871 (w), 2833 (w), 1700 (s), 1610 (w), 1589 (w), 1498 (s), 1462 (m), 1426 (w), 1382 (w), 1351 (w), 1313 (w), 1222 (s), 1179 (w), 1158 (w), 1122 (w), 1107 (w), 1091 (w), 1048 (s), 1027 (w), 946 (w), 918 (w), 874 (w), 800 (m), 716 (m), 623 (w), 588 (w), 557 (w), 532 (w).

GC-MS (70 eV): m/z (%) = 276 (29, [M]+), 151 (100), 121 (22), 91 (12), 77 (9), 65 (6), 55 (9).

HRMS (ESI):	Calc. [amu]	Found [amu]
	277.17982 $[M+H]^+$	277.18007 $[M+H]^+$
	299.16177 $[M+Na]^+$	299.16179 $[M+Na]^+$

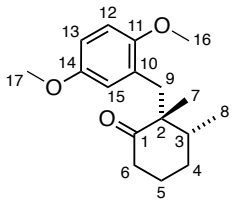
$[\alpha]^{20}_{\lambda}$ (c = 0.65 g/100 mL, $CHCl_3$): + 76° (436 nm), + 35° (546 nm), + 29° (579 nm), + 27° (589 nm).

X-ray crystal structure (CCDC 2077905):



cis-byproduct *epi*-**114**:

M ($C_{17}H_{24}O_3$) = 276.38 g/mol



R_f (*c*-Hex/EtOAc 9:1) = 0.25

m.p.: 61 °C – 63 °C

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.69 – 6.65 (m, 2H, H-12, H-13), 6.57 (d, *J* = 2.6 Hz, 1H, H-15), 3.71 (s, 3H, H-17), 3.64 (s, 3H, H-16), 3.22 (d, *J* = 13.5 Hz, 1H, H-9), 3.06 (td, *J* = 13.4, 6.4 Hz, 1H, H-6), 2.60 (d, *J* = 13.5 Hz, 1H, H-9'), 2.36 – 2.30 (m, 1H, H-6'), 2.02 (ddq, *J* = 9.3, 6.1, 3.1 Hz, 1H, H-5), 1.84 – 1.75 (m, 1H, H-4), 1.75 – 1.68 (m, 1H, H-3), 1.68 – 1.61 (m, 2H, H-4', H-5'), 1.10 (d, *J* = 6.4 Hz, 3H, H-8), 0.88 (s, 3H, H-7).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 214.9 (C-1), 153.0 (C-14), 152.1 (C-11), 127.5 (C-10), 118.5 (C-15), 111.6 (C-13), 110.9 (C-12), 55.7 (C-17), 55.2 (C-16), 53.1 (C-2), 44.7 (C-3), 38.5 (C-6), 31.8 (C-9), 29.8 (C-4), 26.4 (C-5), 19.9 (C-7), 16.1 (C-8).

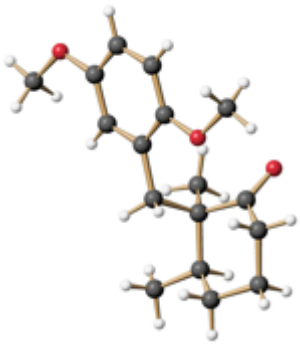
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2964 (m), 2919 (m), 2859 (w), 2834 (w), 1696 (s), 1607 (w), 1501 (s), 1465 (m), 1450 (m), 1417 (w), 1382 (w), 1371 (w), 1356 (w), 1339 (w), 1323 (w), 1313 (w), 1297 (w), 1267 (w), 1222 (s), 1194 (w), 1179 (m), 1159 (w), 1125 (w), 1099 (w), 1089 (w), 1068 (w), 1037 (s), 1017 (m), 947 (w), 915 (w), 874 (m), 855 (w), 832 (w), 803 (m), 742 (w), 708 (m), 629 (w), 595 (w), 573 (w), 538 (w).

GC-MS (70 eV): m/z (%) = 276 (27, [M]+), 151 (100), 121 (24), 91 (14), 77 (11), 65 (8), 55 (12).

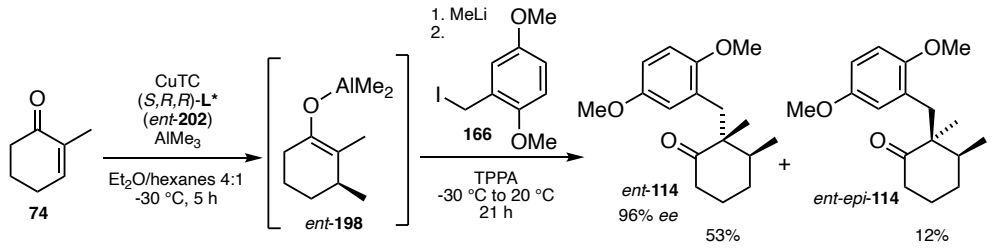
HRMS (ESI):	Calc. [amu]	Found [amu]
	277.17982 $[M+H]^+$	277.18007 $[M+H]^+$
	299.16177 $[M+Na]^+$	299.16179 $[M+Na]^+$

$[\alpha]^{20}_{\lambda}$ (c = 0.53 g/100 mL, $CHCl_3$): – 111° (436 nm), – 62° (546 nm), – 54° (579 nm), – 53° (589 nm).

X-ray crystal structure (CCDC 2077912):



5.2.11 SYNTHESIS OF (2*R*,3*S*)-2-(2,5-DIMETHOXYBENZYL)-2,3-DIMETHYL-CYCLOHEXANONE (*ent*-**114**)[58]



Based on a literature procedure,[58] in a flame dried *Schlenk* flask 145 mg (0.760 mmol, 0.022 eq.) CuTC and 821 mg (1.52 mmol, 0.071 eq.) of phosphoramidite ligand (*S,R,R*)-**L*** (see chapter **5.3.9**) in 95 mL of dry Et_2O was stirred at 20 °C for 35 min. The salmon-colored solution was cooled to -30 °C and 2.35 g (21.3 mmol, 1.0 eq.) of enone **74** were added. Then, 23.0 mL (46.0 mmol, 2.2 eq.) of $AlMe_3$ (2.0 M in hexanes) were added via syringe over a period of 10 min. The reaction mixture was stirred at -30 °C for 5 h. The solvents were removed *in vacuo* at -30 °C (using the *Schlenk* line) until a small volume remained, which was dissolved in 35 mL of TPPA before 32.0 mL (44.8 mmol, 2.1 eq.) of methyllithium (1.4 M in Et_2O) were added over 5 min (still at -30 °C). Finally, 16.8 g (60.4 mmol, 2.8 eq.) of iodide **166** were added and the stirred suspension was allowed to slowly warm up to 20 °C and stirred for 21 h. At this point, GC-MS analysis indicated full conversion of the 1,4-addition intermediate and a diastereoselectivity of *dr* = 5:1. The reaction mixture was carefully quenched by addition of 20 mL of sat. aqueous NH_4Cl at 0°C before 200 mL of H_2O and 100 mL of sat. aqueous Na K tartrate solution were added to facilitate phase separation. The aqueous phase was extracted with 4 x 200 mL of *c*-Hex, the combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (*c*-Hex/EtOAc 33:1) to give 3.11 g (11.3 mmol, 53%) of *trans*-product *ent*-**114** as a pale yellow solid. This product showed an enantiomeric excess of 96% *ee* as determined by chiral HPLC using a racemic standard (for details see **6.3**). In addition, 704 mg (2.55 mmol, 12%) of cis-byproduct *ent-epi*-**114** was obtained as yellow crystals

<u>*trans*-product *ent*-**114**:</u>

M ($C_{17}H_{24}O_3$) = 276.38 g/mol

[α]$^{20}_{\lambda}$ (c = 0.64 g/100 mL, $CHCl_3$): – 59° (436 nm), – 27° (546 nm), – 24° (579 nm), – 23° (589 nm).

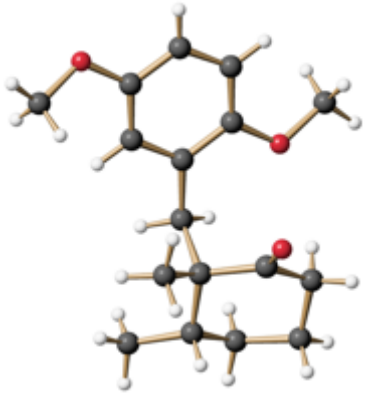
Additional analytical data was in accordance with that recorded for **114** (see chapter **5.2.10**).

cis-byproduct *ent-epi*-**114**:

M ($C_{17}H_{24}O_3$) = 276.38 g/mol

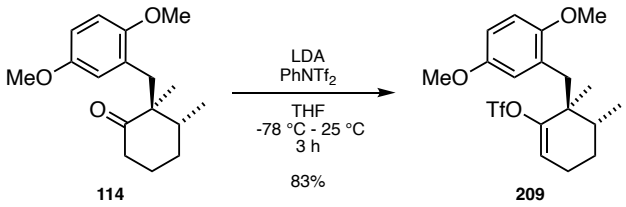
[α]$^{20}_{\lambda}$ (c = 0.53 g/100 mL, $CHCl_3$): + 111° (436 nm), + 64° (546 nm), + 56° (579 nm), + 53° (589 nm).

X-ray crystal structure:



Additional analytical data was in accordance with that recorded for *epi*-**114** (see chapter **5.2.10**).

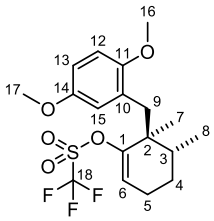
5.2.12 SYNTHESIS OF ENOL TRIFLATE **209**



In a flame dried *Schlenk* flask 5.78 g (54.0 mmol, 1.7 eq.) of LDA were partially dissolved in 250 mL of dry THF. The suspension was cooled to -78 °C and 8.77 g (31.7 mmol, 1.0 eq.) of ketone **114** in 100 mL of dry THF were added. After stirring for 10 min at -78 °C, 19.3 g (54.0 mmol, 1.7 eq.) of $PhNTf_2$ were added portion wise at that temperature. The reaction mixture was then stirred at 0 °C for 50 min and at 25 °C for 2 h. After quenching with sat. aqueous NH4Cl, the aqueous phase was extracted with 3 x 200 mL of EtOAc. The combined organic phases were washed with H_2O, dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification of the crude product by silica gel column chromatography (*c*-Hex/EtOAc 30:1 to 20:1) afforded 10.7 g (26.2 mmol, 83%) of enol triflate **209** as a yellow, viscous oil.

M ($C_{18}H_{23}F_3O_5S$) = 408.43 g/mol

R_f (*c*-Hex/EtOAc 20:1) = 0.29



^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.77 – 6.75 (m, 1H, H-12), 6.74 – 6.72 (m, 2H, H-13, H-15), 5.77 (dd, *J* = 5.3, 3.0 Hz, 1H, H-6), 3.74 (s, 3H, H-16), 3.73 (s, 3H, H-17), 3.00 (d, *J* = 13.9 Hz, 1H, H-9), 2.70 (d, *J* = 13.8 Hz, 1H, H-9'), 2.08 (dtd, *J* = 17.8, 5.4, 4.3 Hz, 1H, H-5), 1.94 (dddd, *J* = 17.8, 8.8, 5.6, 3.0 Hz, 1H, H-5'), 1.64 (dqd, *J* = 9.8, 6.8, 3.0 Hz, 1H, H-3), 1.60 – 1.53 (m, 1H, H-4), 1.42 – 1.33 (m, 1H, H-4'), 1.11 (s, 3H, H-7), 0.97 (d, *J* = 6.8 Hz, 3H, H-8).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 154.5 (C-1), 153.3 (C-14), 152.7 (C-11), 127.2 (C-10), 118.6 (q, $J_{C,F}$ = 319.3 Hz, C-18), 118.0 (C-6), 117.1 (C-15), 112.7 (C-13), 111.3 (C-12), 55.74 (C-16), 55.65 (C-17), 43.9 (C-2), 35.2 (C-9), 34.6 (C-3), 26.2 (C-4), 23.3 (C-5), 20.1 (C-7), 16.2 (C-8).

^{19}F NMR (282 MHz, CDCl3): δ [ppm] = –75.0.

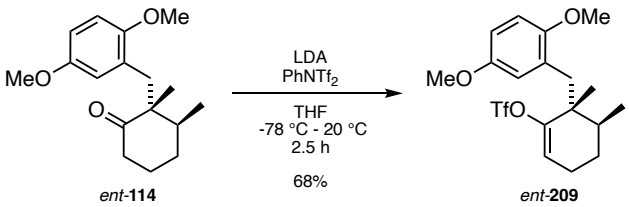
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2935 (br), 2835 (w), 1674 (w), 1609 (w), 1589 (w), 1501 (m), 1465 (m), 1408 (m), 1386 (m), 1347 (w), 1314 (w), 1301 (w), 1284 (w), 1270 (w), 1245 (m), 1208 (s), 1189 (m), 1141 (m), 1103 (w), 1081 (w), 1049 (m), 1029 (m), 1012 (m), 983 (s), 959 (w), 918 (m), 904 (m), 869 (s), 855 (s), 802 (m), 773 (w), 756 (m), 737 (w), 716 (m), 709 (m), 689 (m), 689 (w), 648 (w), 605 (s).

GC-MS (70 eV): m/z (%) = 408 (20, [M]+), 151 (100), 121 (19), 91 (9), 69 (9), 55 (5).

HRMS (ESI):	Calc. [amu]	Found [amu]
	431.11105 $[M+Na]^+$	431.11125 $[M+Na]^+$

$[\alpha]^{20}_{\lambda}$ (c = 0.59 g/100 mL, $CHCl_3$): + 44° (436 nm), + 26° (546 nm), + 23° (579 nm), + 23° (589 nm).

5.2.13 SYNTHESIS OF ENOL TRIFLATE *ent*-**209**



ent-**114** *ent*-**209**

In a flame dried *Schlenk* flask, 2.70 mL (1.94 g, 19.2 mmol, 1.7 eq.) of di*iso*propylamine were dissolved in 31 mL of dry THF. The suspension was cooled to -78 °C and 7.8 mL (19.1 mmol, 1.7 eq.) of *n*BuLi (2.47 M in THF) were added over 10 min and the resulting mixture stirred for 20 min at 0 °C. After cooling to -78 °C, 3.11 g (11.3 mmol, 1.0 eq.) of ketone *ent*-**114** in 15 mL of

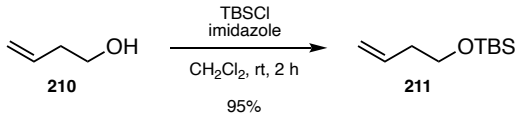
dry THF were added. After stirring for 20 min at -78°C, 6.83 g (19.1 mmol, 1.7 eq.) of $PhNTf_2$ were added portion wise at that temperature. The reaction mixture was stirred at 0 °C for 30 min and at 20 °C for 2 h. After quenching with 10 mL of sat. aqueous NH_4Cl and addition of 20 mL H_2O, the aqueous phase was extracted with 3 x 100 mL of EtOAc. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification of the crude product by silica gel column chromatography (*c*-Hex/EtOAc 30:1 to 20:1) afforded 3.11 g (7.61 mmol, 68%) of enol triflate *ent*-**209** as a yellow, viscous oil.

M ($C_{18}H_{23}F_3O_5S$) = 408.43 g/mol

[α]$^{20}_{\lambda}$ (c = 0.54 g/100 mL, $CHCl_3$): – 38° (436 nm), – 22° (546 nm), – 19° (579 nm), – 18° (589 nm).

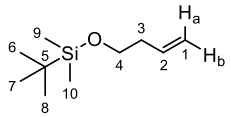
Additional analytical data was in accordance with that recorded for **209** (see chapter **5.2.12**).

5.2.14 SYNTHESIS OF TBS-HOMOALLYLIC ALCOHOL (211)[121]



According to a literature procedure,[121] in an argon-flushed flask 5.89 mL (4.94 g, 69.3 mmol, 1.00 eq.) of homoallylic alcohol (**212**) were dissolved in 150 mL of dry CH_2Cl_2 and 9.44 g (139 mmol, 2.00 eq.) of imidazole were added. The suspension was stirred until a clear solution was obtained. Then, 11.5 g (76.3 mmol, 1.10 eq.) of TBSCl were added and the reaction mixture was stirred for at rt for 2 h. 200 mL of H_2O were added, phases were separated and the aqueous phase was extracted with 2 x 100 mL of CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Filtration through a short plug of silica gel (*c*-Hex/EtOAc 5:1) afforded 12.3 g (66.0 mmol, 95%) of but-3-en-1-yloxy(*tert*-butyl) dimethylsilane (**213**) as a volatile, colorless liquid.

M ($C_{10}H_{22}OSi$) = 186.37 g/mol



R_f (*c*-Hex/EtOAc 3:1) = 0.90

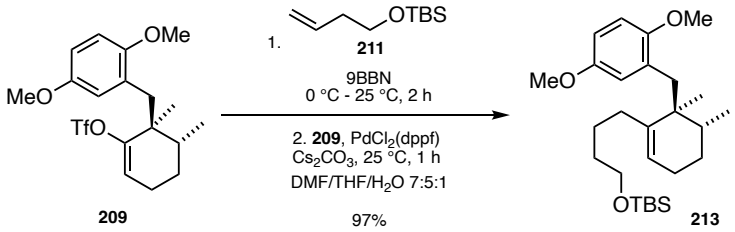
^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 5.81 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H, H-2), 5.07 (dq, *J* = 17.2, 1.5 Hz, 1H, H-1), 5.03 – 5.00 (m, 1H, H-1'), 3.66 (t, *J* = 6.8 Hz, 2H, H-4), 2.28 (qt, *J* = 6.8, 1.2 Hz, 2H, H-3), 0.90 (s, 9H, H-6, H-7, H-8), 0.05 (s, 6H, H-9, H-10).

^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 135.5 (C-2), 116.4 (C-1), 62.9 (C-4), 37.6 (C-3), 26.1 (C-6, C-7, C-8), –5.1 (C-9, C-10).

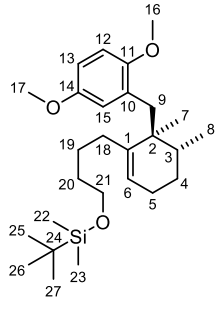
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3080 (w), 2955 (w), 2929 (m), 2897 (w), 2858 (m), 1642 (w), 1472 (w), 1463 (w), 1432 (w), 1408 (w), 1384 (w), 1361 (w), 1254 (m), 1228 (w), 1096 (s), 1005 (w), 986 (m), 938 (w), 909 (m), 833 (s), 810 (m), 733 (w), 678 (w), 664 (w), 626 (w).

GC-MS (70 eV): m/z (%) = 129 (66), 101 (100), 89 (18), 73 (30), 59 (16), 41 (18).

5.2.15 SYNTHESIS OF SILYL ETHER **213**



Based on a literature protocol,[105] in a *Schlenk* flask, a solution of 7.14 g (38.3 mmol, 1.5 eq.) of olefin **211** in 55 mL of dry THF was cooled to 0 °C. Then, 92.0 mL (46.0 mmol, 1.8 eq.) of 9-BBN (0.5 M in THF) were added and the mixture was stirred at 25 °C for 2 h. The solution was then cooled to 0 °C before 27.5 mL of H_2O were added and stirring was continued at 0 °C for 1 h. This borane solution was then transferred via needle to a second *Schlenk* flask charged with a solution of 625 mg (765 µmol, 0.03 eq.) of $PdCl_2$(dppf) x CH_2Cl_2, 20.8 g (63.8 mmol, 2.5 eq.) of Cs_2CO_3 and 10.4 g (25.5 mmol, 1.0 eq.) of the enol triflate **209** in 190 mL of dry DMF at 25 °C. The black reaction mixture was stirred at that temperature for 60 min before 0.40 g of QuadraSil AP® were added as a metal scavenger and the suspension was stirred for further 30 min. Then the solvent was separated by decantation and H_2O and brine were added to the product solution. After extraction with EtOAc (4x) the combined organic layers were washed with H_2O, dried over Na_2SO_4 and the solvents were removed under reduced pressure. The residue was purified by silica gel column chromatography (*c*-Hex/EtOAc 20:1) to yield 11.1 g (24.8 mmol, 97%) of silyl ether **213** as a yellow, viscous oil.



M ($C_{27}H_{46}O_3Si$) = 446.75 g/mol

R_f (*c*-Hex/EtOAc 15:1) = 0.42

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.78 (d, J = 3.1 Hz, 1H, H-15), 6.75 (d, J = 8.8 Hz, 1H, H-12), 6.68 (dd, J = 8.8, 3.1 Hz, 1H, H-13), 5.46 (t, J = 3.8 Hz, 1H, H-6), 3.75 (s, 3H, H-16), 3.72 (s, 3H, H-17), 3.62 (t, J = 6.3 Hz, 2H, H-21), 2.93 (d, J = 14.6 Hz, 1H, H-9), 2.66 (d, J =

14.6 Hz, 1H, H-9'), 2.04 (t, *J* = 7.1 Hz, 2H, H-18), 2.02 – 1.91 (m, 2H, H-5), 1.78 (dtd, *J* = 12.9, 6.5, 3.2 Hz, 1H, H-4), 1.70 (quind, *J* = 7.0, 3.1 Hz, 1H, H-3), 1.59 – 1.53 (m, 2H, H-20), 1.53 – 1.42 (m, 2H, H-19), 1.40 – 1.32 (m, 1H, H-4'), 0.93 (s, 3H, H-7), 0.90 (s, 9H, H-25, H-26, H-27), 0.80 (d, *J* = 6.8 Hz, 3H, H-8), 0.05 (s, 6H, H-22, H-23).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 153.1 (C-14), 152.6 (C-11), 143.3 (C-1), 129.6 (C-10), 121.4 (C-6), 117.3 (C-15), 111.24 (C-12), 111.19 (C-13), 63.5 (C-21), 56.0 (C-16), 55.7 (C-17), 42.0 (C-2), 36.3 (C-9), 33.8 (C-3), 33.3 (C-20), 31.3 (C-18), 26.5 (C-4), 26.1 (C-25, C-26, C-27), 25.5 (C-19), 23.9 (C-5), 21.8 (C-7), 18.5 (C-24), 16.1 (C-8), –5.1 (C-22, C-23).

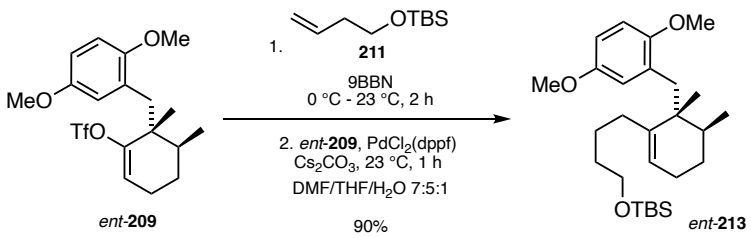
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2951 (br), 2929 (m), 2906 (w), 2857 (w), 2833 (w), 1609 (w), 1588 (w), 1498 (m), 1463 (m), 1426 (w), 1380 (w), 1360 (w), 1298 (w), 1282 (w), 1254 (m), 1219 (s), 1179 (w), 1158 (w), 1099 (m), 1051 (m), 1030 (m), 1005 (w), 964 (w), 939 (w), 901 (w), 834 (s), 804 (m), 795 (m), 773 (s), 732 (w), 714 (m), 686 (w), 661 (w), 606 (w).

GC-MS (70 eV): m/z (%) = 446 (17, [M]+), 389 (17), 295 (8), 237 (7), 163 (100), 152 (48), 147 (10), 121 (22), 107 (16), 91 (15), 75 (14).

HRMS (ESI):	Calc. [amu]	Found [amu]
	447.32889 $[M+H]^+$	447.32930 $[M+H]^+$
	469.31084 $[M+Na]^+$	469.31088 $[M+Na]^+$

$[\alpha]^{20}_{\lambda}$ (c = 0.51 g/100 mL, $CHCl_3$): – 51° (436 nm), – 27° (546 nm), – 24° (579 nm), – 21° (589 nm).

5.2.16 SYNTHESIS OF SILYL ETHER *ent*-**213**



Based on a literature protocol,[105] in a *Schlenk* flask, a solution of 960 mg (5.15 mmol, 2.3 eq.) of olefin **211** in 7.4 mL of dry THF was cooled to 0 °C. Then, 12.4 mL (6.20 mmol, 2.8 eq.) of 9-BBN (0.5 M in THF) were added and the mixture was stirred at 23 °C for 2 h. The solution was then cooled to 0 °C before 3.7 mL of H_2O were added and stirring was continued for 60 min at 0 °C. This

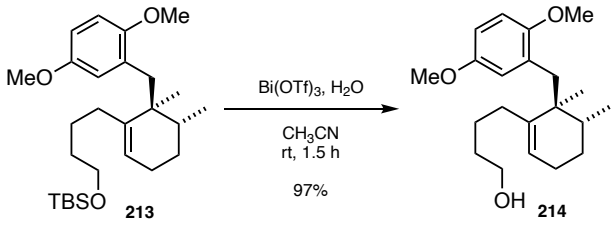
borane solution was then transferred via needle to a second *Schlenk* flask charged with a solution of 84.0 mg (103 µmol, 0.05 eq.) of $PdCl_2$(dppf) x CH_2Cl_2, 2.70 g (8.29 mmol, 3.7 eq.) of Cs_2CO_3 and 914 g (2.24 mmol, 1.0 eq.) of the enol triflate *ent*-**209** in 30 mL of dry DMF at 23 °C. The black reaction mixture was stirred at that temperature for 60 min before 54.0 mg of QuadraSil AP® were added as a metal scavenger and the suspension was stirred for further 30 min. Then the solids were separated by decantation and 50 mL of H_2O and brine were added to the product solution. After extraction with 3x 50 mL of EtOAc the combined organic layers were washed with H_2O, dried over $MgSO_4$ and the solvents were removed under reduced pressure. The residue was purified by silica gel column chromatography (*c*-Hex/EtOAc 20:1) to yield 930 mg (202 mmol, 90%) of silyl ether *ent*-**213** as a yellow, viscous oil.

M ($C_{27}H_{46}O_3Si$) = 446.75 g/mol

[α]$^{20}_{λ}$ (c = 0.45 g/100 mL, $CHCl_3$): + 57° (436 nm), + 30° (546 nm), + 26° (579 nm), + 25° (589 nm).

Additional analytical data was in accordance with that recorded for **213** (see chapter **5.2.15**).

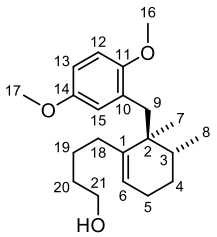
5.2.17 SYNTHESIS OF ALCOHOL **214**



Based on a literature protocol,[106] in an argon-flushed flask 11.1 g (24.8 mmol, 1.0 eq.) of silyl ether **214** were dissolved in 400 mL of CH_3CN and 4.5 mL (4.5 g, 250 mmol, 10 eq.) of H_2O. Then, 650 mg (0.99 mmol, 0.04 eq.) of $Bi(OTf)_3$ were added and the reaction mixture was stirred at rt for 90 min. 200 mL of H_2O were added and the aqueous phase was extracted with 3 x 200 mL of CH_2Cl_2. The combined organic phases were washed with H_2O, dried over $MgSO_4$ and the solvent was removed under reduced pressure. 7.98 g (24.0 mmol, 97%) of alcohol **214**, together with 1.48 g of TBSOH/TBSOTBS were obtained as a pale yellow, viscous oil. The crude alcohol **214** was used for the following reaction without further purification. For analytical characterization, a sample of was purified by silica gel column chromatography (*c*-Hex/MTBE 2:1).

M ($C_{21}H_{32}O_3$) = 332.48 g/mol

R_f (*c*-Hex/EtOAc 4:1) = 0.22



^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.77 – 6.75 (m, 2H, H-12, H-15), 6.68 (dd, *J* = 8.8, 3.1 Hz, 1H, H-13), 5.47 (t, *J* = 3.6 Hz, 1H, H-6), 3.75 (s, 3H, H-16), 3.73 (s, 3H, H-17), 3.65 (t, *J* = 6.4 Hz, 2H, H-21), 2.92 (d, *J* = 14.6 Hz, 1H, H-9), 2.66 (d, *J* = 14.5 Hz, 1H, H-9'), 2.07 – 2.02 (m, 2H, H-18), 2.02 – 1.92 (m, 2H, H-5), 1.79 (dtd, *J* = 13.0, 6.6, 3.2 Hz, 1H, H-4), 1.71 (quind, *J* = 7.0, 3.2 Hz, 1H, H-3), 1.65 – 1.57 (m, 2H, H-20), 1.57 – 1.44 (m, 2H, H-19), 1.36 (td, *J* = 13.5, 6.3 Hz, 1H, H-4'), 0.93 (s, 3H, H-7), 0.81 (d, *J* = 6.9 Hz, 3H, H-8).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 153.1 (C-14), 152.6 (C-11), 143.0 (C-1), 129.6 (C-10), 121.5 (C-6), 117.5 (C-15), 111.2 (C-12), 111.1 (C-13), 63.2 (C-21), 56.0 (C-16), 55.7 (C-17), 42.0 (C-2), 36.4 (C-9), 33.8 (C-3), 33.2 (C-20), 31.2 (C-18), 26.4 (C-4), 25.4 (C-19), 23.8 (C-5), 21.8 (C-7), 16.0 (C-8).

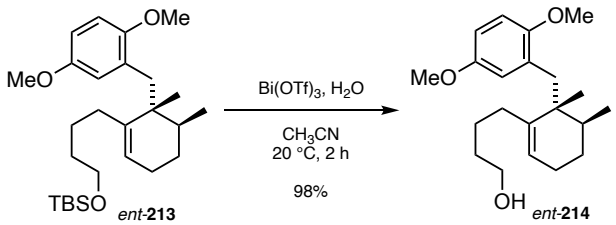
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3354 (br), 2933 (br), 2834 (w), 1611 (w), 1592 (w), 1499 (s), 1463 (m), 1379 (w), 1282 (w), 1271 (w), 1221 (s), 1179 (w), 1159 (w), 1126 (w), 1051 (m), 1045 (m), 1029 (m), 878 (w), 800 (w), 717 (w).

GC-MS (70 eV): m/z (%) = 332 (40, $[M]^+$), 181 (43), 152 (79), 151 (65), 137 (29), 121 (100), 107 (56), 91 (73), 79 (47), 71 (29), 55 (40).

HRMS (ESI):	Calc. [amu]	Found [amu]
	355.22437 $[M+Na]^+$	355.22478 $[M+Na]^+$

$[\alpha]^{20}_{\lambda}$ (c = 0.67 g/100 mL, $CHCl_3$): – 59° (436 nm), – 30° (546 nm), – 26° (579 nm), – 25° (589 nm).

5.2.18 SYNTHESIS OF ALCOHOL *ent*-**214**



Based on a literature protocol,[106] in an argon-flushed flask 2.84 g (6.36 mmol, 1.0 eq.) of silyl ether *ent*-**213** were dissolved in 100 mL of CH_3CN and 1.2 mL of H_2O. Then, 167 mg (254 µmol, 0.04 eq.) of $Bi(OTf)_3$ were added and the reaction mixture was stirred at rt for 2 h. 50 mL of H_2O

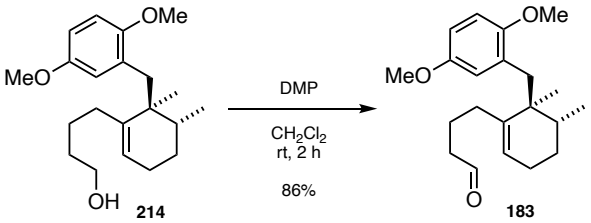
were added and the aqueous phase was extracted with 3 x 50 mL of CH_2Cl_2. The combined organic phases were washed with H_2O, dried over $MgSO_4$ and the solvent was removed under reduced pressure. 2.07 g (6.23 mmol, 98%) of alcohol *ent*-**214**, together with 230 mg of TBSOH/TBSOTBS were obtained as a pale yellow, viscous oil. The crude alcohol *ent*-**214** was used for the following reaction without further purification. For analytical characterization, a sample was purified by silica gel column chromatography (*c*-Hex/MTBE 2:1).

M ($C_{21}H_{32}O_3$) = 332.48 g/mol

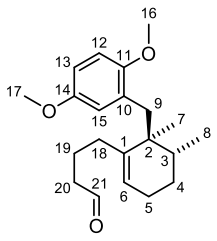
[α]$^{20}_{\lambda}$ (c = 0.67 g/100 mL, $CHCl_3$): + 52° (436 nm), + 24° (546 nm), + 17° (579 nm), + 12° (589 nm).

Additional analytical data was in accordance with that recorded for **214** (see chapter **5.2.17**).

5.2.19 SYNTHESIS OF ALDEHYDE **183**



A solution of 7.98 g (24.0 mmol, 1.0 eq.) of crude alcohol **214** (in a mixture with 1.48 g of TBSOH/TBSOTBS) were dissolved in 630 mL of dry CH_2Cl_2. The solution was cooled to 0 °C and 21.0 g (49.6 mmol, 2.0 eq.) of *Dess-Martin* periodinane were added over 5 min and stirring was continued at 0 °C for 15 min and at rt for 2 h. Then, the mixture was cooled to 0 °C before 200 mL of H_2O were added. The phases were separated and the aqueous phase was extracted with 3 x 200 mL of CH_2Cl_2. The combined organic phases were washed with H_2O, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (ultrapure SiO_2, *c*-Hex/EtOAc 9:1) to provide 6.83 g (20.7 mmol, 86%) of aldehyde **183** as a yellowish viscous oil.



M ($C_{21}H_{30}O_3$) = 330.47 g/mol

R_f (*c*-Hex/EtOAc 9:1) = 0.27

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 9.77 (t, *J* = 1.8 Hz, 1H, 21-H), 6.76 – 6.74 (m, 2H, 12-H, 15-H), 6.68 (dd, *J* = 8.9, 3.0 Hz, 1H, 13-H), 5.48 (t, *J* = 3.7 Hz, 1H, 6-H), 3.75 (s, 3H, 16-H), 3.73 (s, 3H, 17-H), 2.90 (d, J = 14.5 Hz, 1H, 9-H), 2.64 (d, *J* = 14.4 Hz, 1H, 9-H'), 2.46 (td,

J = 7.2, 1.6 Hz, 2H, 20-H), 2.09 – 2.02 (m, 2H, 18-H), 2.02 – 1.92 (m, 2H, 5-H), 1.90 – 1.77 (m, 3H, 4-H, 19-H), 1.73 (mnm,.-, 1H, 3-H), 1.37 (ddt, *J* = 13.4, 7.5, 6.1 Hz, 1H, 4-H'), 0.92 (s, 3H, 7-H), 0.81 (d, *J* = 6.9 Hz, 3H, 8-H).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 203.0 (C-21), 153.1 (C-11), 152.6 (C-14), 142.3 (C-1), 129.4 (C-10), 122.1 (C-6), 117.6 (C-15), 111.2 (C-12/13), 111.1 (C-12/13), 56.0 (C-16), 55.7 (C-17), 44.1 (C-20), 42.0 (C-2), 36.6 (C-9), 33.8 (C-3), 30.9 (C-18), 26.3 (C-4), 23.7 (C-5), 21.8 (C-19), 21.7 (C-7), 16.0 (C-8).

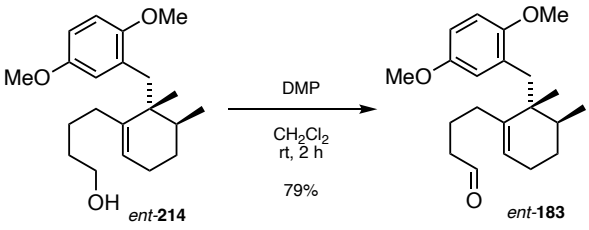
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2932 (br), 2833 (w), 2718 (w), 1723 (m), 1608 (w), 1588 (w), 1497 (s), 1463 (m), 1425 (w), 1379 (w), 1283 (w), 1268 (w), 1218 (s), 1179 (m), 1158 (w), 1127 (w), 1074 (w), 1048 (s), 1028 (m), 952 (w), 940 (w), 909 (w), 873 (w), 849 (w), 799 (m), 757 (w), 732 (w), 714 (m), 687 (w), 637 (w).

GC-MS (70 eV): m/z (%) = 330 (30, [M]+), 207 (8), 179 (13), 161 (83), 151 (85), 135 (36), 121 (100), 105 (56), 91 (96), 77 (60), 55 (37).

HRMS (ESI):	Calc. [amu]	Found [amu]
	353.20871 $[M+Na]^+$	353.20897 $[M+Na]^+$

$[\alpha]^{20}_{\lambda}$ (c = 0.57 g/100 mL, $CHCl_3$): – 80° (436 nm), – 41° (546 nm), – 34° (579 nm), – 32° (589 nm).

5.2.20 SYNTHESIS OF ALDEHYDE *ent*-**216**



A solution of 1.42 g (4.26 mmol, 1.0 eq.) of alcohol *ent*-**215** (in a mixture with 150 mg of TBSOH/TBSOTBS) were dissolved in 105 mL of dry CH_2Cl_2. The solution was cooled to 0 °C and 3.62 g (8.53 mmol, 2.0 eq.) of *Dess-Martin* periodinane were added over 5 min and stirring was continued for 15 min at 0 °C and at rt for 2 h. Then, the mixture was cooled to 0 °C before 30 mL of H_2O and 30 mL of sat. aqueous $NaHCO_3$ were added. The phases were separated and the aqueous phase was extracted with 3 x 30 mL of CH_2Cl_2. The combined organic phases were washed with H_2O, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The

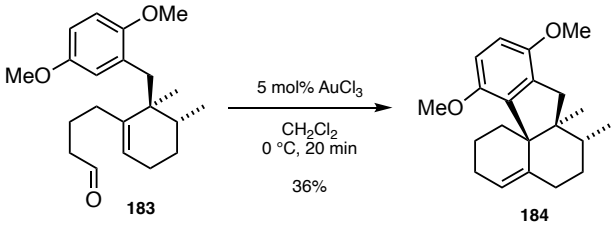
residue was purified by silica gel column chromatography (ultrapure SiO_2, *c*-Hex/EtOAc 9:1) to provide 1.11 g (3.35 mmol, 79%) of aldehyde *ent*-**216** as a yellow viscous oil.

M ($C_{21}H_{30}O_3$) = 330.47 g/mol

[α]$^{20}_{\lambda}$ (c = 0.57 g/100 mL, $CHCl_3$): + 66° (436 nm), + 36° (546 nm), + 31° (579 nm), + 29° (589 nm).

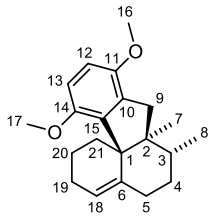
Additional analytical data was in accordance with that recorded for **183** (see chapter **5.2.19**).

5.2.21 SYNTHESIS OF TETRACYCLIC OLEFIN **184**



A solution of 2.00 g (6.05 mmol, 1.0 eq.) of aldehyde **183** in 605 mL of CH_2Cl_2 (HPLC grade) was cooled to 0 °C and 100 mg (330 µmol, 0.05 eq.) of $AuCl_3$ were added. The dark green mixture was stirred for 20 min at 0 °C before 400 mL of H_2O were added (discoloration). The aqueous phase was extracted with 3 x 400 mL of CH_2Cl_2 and the resulting organic layer dried over $MgSO_4$. The resulting pale brown, viscous oil was purified by silica gel filtration (*c*-Hex/EtOAc 30:1) to give 1.12 g of a colorless sticky oil, containing approximately 672 mg (2.15 mmol, 36%) of tetracyclic olefin **184** along with (at this stage) inseparable side products, as determined by integration of suitable ^{1}H NMR signals. On a 100 mg scale a yield of 38% of **184** was obtained (37% for a 300 mg scale). The oil crystallizes very slowly at rt. Samples of different side products were also obtained and characterized, but no yield was determined.

olefin **184**:



M ($C_{21}H_{28}O_2$) = 312.45 g/mol

R_f (*c*-Hex/EtOAc 20:1) = 0.27

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.63 (s, 2H, 12-H, 13-H), 5.61 (td, *J* = 3.9, 1.7 Hz, 1H, 18-H), 3.78 (s, 3H, 16-H), 3.68 (s, 3H, 17-H), 2.83 (d, *J* = 15.8 Hz, 1H, 9-H), 2.54 (d, *J* = 15.8 Hz, 1H, 9-H'), 2.09 (dt, *J* = 13.1, 3.3 Hz, 1H, 5-H), 2.05 – 2.01 (m, 2H, 19-H), 2.01 – 1.95 (m, 1H, 5-H'), 1.92 (ddd, *J* = 12.8, 9.5, 2.9 Hz, 1H, 21-H), 1.64 (ddtd, *J* = 12.6, 9.4, 6.4, 2.9 Hz, 1H, 20-H), 1.57 – 1.49 (m, 1H,

20-H'), 1.49 – 1.42 (m, 2H, 3-H, 21-H'), 1.36 (dq, *J* = 12.7, 3.5 Hz, 1H, 4-H), 1.18 (dq, *J* = 12.9, 3.9 Hz, 1H, 4-H'), 1.00 (s, 3H, 7-H), 0.83 (d, *J* = 6.7 Hz, 3H, 8-H).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 151.6 (C-14), 150.9 (C-11), 141.2 (C-15), 138.3 (C-6), 131.8 (C-10), 122.5 (C-18), 110.3 (C-13), 108.8 (C-12), 56.0 (C-17), 55.8 (C-16), 55.4 (C-1), 52.2 (C-2), 38.4 (C-9), 36.3 (C-3), 35.0 (C-5), 32.5 (C-21), 32.3 (C-4), 25.9 (C-19), 20.3 (C-20), 18.2 (C-8), 14.2 (C-7).

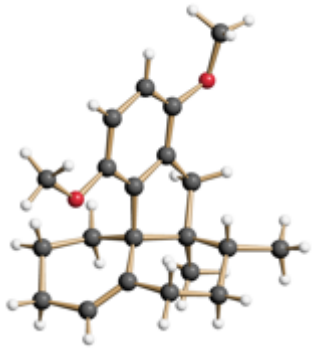
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2924 (br), 2851 (m), 2830 (m), 1596 (w), 1491 (s), 1462 (m), 1437 (m), 1379 (w), 1323 (w), 1278 (w), 1254 (s), 1189 (w), 1157 (w), 1141 (w), 1110 (w), 1095 (m), 1070 (m), 1055 (m), 1012 (w), 972 (w), 914 (w), 883 (w), 865 (w), 788 (m), 715 (w), 669 (w), 638 (w).

GC-MS (70 eV): m/z (%) = 312 (100, [M]+), 297 (38), 255 (16), 241 (15), 227 (16), 165 (17), 115 (16), 55 (15).

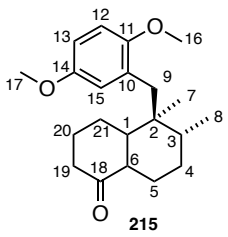
HRMS (ESI):	Calc. [amu]	Found [amu]
	313.21620 $[M+H]^+$	313.21688 $[M+H]^+$

$[\alpha]^{20}_{\lambda}$ (c = 0.45 g/100 mL, $CHCl_3$): + 249° (436 nm), + 131° (546 nm), + 113° (579 nm), + 107° (589 nm).

X-ray crystal structure (CCDC 207790):



ketone side product **215**:



M ($C_{21}H_{30}O_3$) = 330.47 g/mol

R_f (*c*-Hex/EtOAc 5:1) = 0.36

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.74 (d, *J* = 8.8 Hz, 1H, 12-H), 6.71 (dd, *J* = 8.8, 2.9 Hz, 1H, 13-H), 6.68 (d, *J* = 2.8 Hz, 1H, 15-H), 3.74 (s, 3H, 17-H), 3.71 (s, 3H, 16-H), 2.82 (d, *J* = 14.0 Hz, 1H, 9-H), 2.62 (d, *J* = 14.0 Hz, 1H, 9-H'), 2.46 – 2.41 (m, 1H, 21-H), 2.35 (ddt, *J* = 13.6, 4.2, 2.1 Hz, 1H, 19-H), 2.30 – 2.22 (m, 1H, 19-H'), 2.15 – 2.07 (m, 2H, 6-H, 20-H), 1.73 (dq, *J* = 13.5, 3.1 Hz, 1H, 5-H),

1.53 – 1.49 (m, 1H, 20-H'), 1.49 – 1.43 (m, 2H, 4-H, 21-H'), 1.38 – 1.30 (m, 1H, 3-H), 1.23 – 1.18 (m, 1H, 1-H), 1.18 – 1.10 (m, 1H, 4-H'), 1.10 – 1.04 (m, 1H, 5-H'), 1.02 (d, *J* = 6.5 Hz, 3H, 8-H), 0.89 (s, 3H, 7-H).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 214.2 (C-18), 152.9 (C-14), 152.8 (C-11), 127.9 (C-10), 119.0 (C-15), 111.3 (C-13), 110.9 (C-12), 55.7 (C-17), 55.5 (C-16), 51.3 (C-6), 47.7 (C-1), 42.1 (C-19), 41.8 (C-2), 35.6 (C-9), 35.3 (C-3), 29.9 (C-4), 27.6 (C-21), 26.1 (C-20), 25.2 (C-5), 17.6 (C-8), 14.9 (C-7).

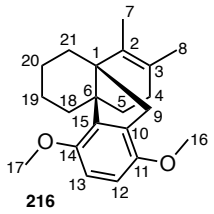
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2927 (s), 2855 (m), 2837 (w), 1734 (w), 1709 (m), 1590 (w), 1498 (s), 1464 (s), 1400 (w), 1379 (w), 1260 (s), 1221 (s), 1179 (w), 1159 (w), 1090 (m), 1049 (s), 1028 (m), 870 (w), 799 (s), 715 (w).

GC-MS (70 eV): m/z (%) = 330 (72, [M]+), 161 (15), 151 (100), 121 (24), 105 (13), 91 (27), 77 (17).

HRMS (ESI):	Calc. [amu]	Found [amu]
	353.20872 $[M+Na]^+$	353.20896 $[M+Na]^+$

$[\alpha]^{20}_{\lambda}$ (c = 0.25 g/100 mL, $CHCl_3$): – 2.7° (436 nm), + 4.7° (546 nm), + 2.7° (579 nm), – 2.7° (589 nm).

Olefin side product **216**:



216

M ($C_{21}H_{28}O_2$) = 312.45 g/mol

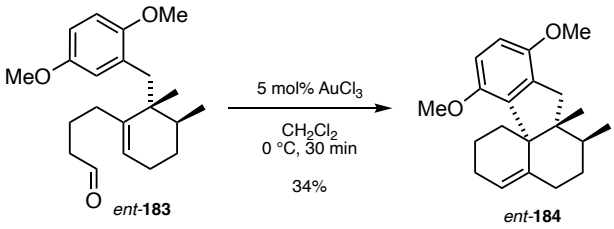
R_f (*c*-Hex/EtOAc 9:1) = 0.85

1H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.63 (d, *J* = 8.7 Hz, 1H, 13-H), 6.59 (d, *J* = 8.7 Hz, 1H, 12-H), 3.76 (s, 3H, 16-H), 3.75 (s, 3H, 17-H), 2.77 (d, *J* = 15.7 Hz, 1H, 9-H), 2.72 (d, *J* = 15.7 Hz, 1H, 9-H'), 2.06 – 1.99 (m, 1H, 4-H), 1.91 – 1.81 (m, 2H, 4-H', 5-H), 1.75 – 1.70 (m, 1H, 5-H'), 1.69 – 1.62 (m, 1H, 21-H), 1.60 (s, 3H, 7-H), 1.58 – 1.52 (m, 1H, 21-H'), 1.56 (s, 3H, 8-H), 1.47 – 1.42 (m, 1H, 19-H), 1.37 – 1.32 (m, 1H, 20-H), 1.32 – 1.26 (m, 4H, 18-H, 19-H', 20-H').

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 151.4 (C-14), 151.2 (C-11), 140.1 (C-15), 131.3 (C-10), 130.1 (C-2), 126.9 (C-3), 109.7 (C-13), 108.4 (C-12), 55.9 (C-17), 55.7 (C-16), 50.6 (C-6), 50.0 (C-1), 37.0 (C-9), 31.7 (C-21), 30.1 (C-4), 29.5 (C-18), 28.9 (C-5), 23.1 (C-20), 22.6 (C-19), 20.3 (C-8), 14.8 (C-7).

GC-MS (70 eV): m/z (%) = 312 (100, $[M]^+$), 297 (17), 257 (20), 255 (44), 242 (20), 240 (16), 230 (71), 225 (13), 215 (11), 204 (14), 165 (10), 119 (10).

5.2.22 SYNTHESIS OF TETRACYCLIC OLEFIN *ent*-**184**



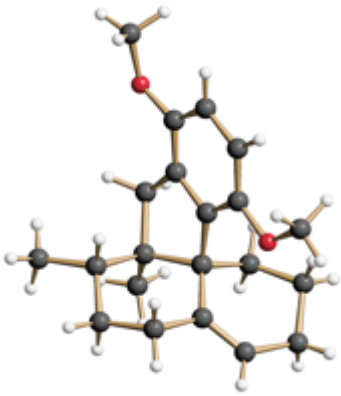
A solution of 1.11 g (3.36 mmol, 1.0 eq.) of aldehyde *ent*-**183** in 335 mL of CH_2Cl_2 (HPLC grade) was cooled to 0 °C and 52 mg (168 µmol, 0.05 eq.) of $AuCl_3$ were added. The dark green mixture was stirred at 0 °C for 30 min before 200 mL of H_2O were added (discoloration). The aqueous phase was extracted with 3 x 100 mL of CH_2Cl_2 and the combined organic layer dried over $MgSO_4$. The resulting pale brown, viscous oil was purified by silica gel filtration (*c*-Hex/EtOAc 30:1) to give 1.12 g of a colorless sticky oil, containing approximately 672 mg (2.15 mmol, 36%) of tetracyclic olefin *ent*-**184** along with (at this stage) inseparable side products, as determined by integration of suitable ^{1}H NMR signals. The oil crystallizes very slowly at rt. Additionally, 44 mg (133 µmol, 4%) of side product **217** were isolated and characterized.

olefin *ent*-**184**:

M ($C_{21}H_{28}O_2$) = 312.45 g/mol

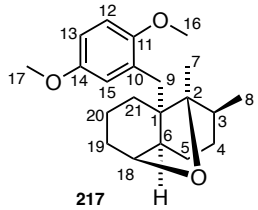
[α]$^{20}_{\lambda}$ (c = 0.45 g/100 mL, $CHCl_3$): – 240° (436 nm), – 128° (546 nm), – 109° (579 nm), – 105° (589 nm).

X-ray crystal structure:



Additional analytical data was in accordance with that recorded for **184** (see chapter **5.2.21**).

side product **217**:



217

M ($C_{21}H_{30}O_3$) = 330.47 g/mol

R_f (*c*-Hex/EtOAc 9:1) = 0.50

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.79 – 6.75 (m, 1H, H-12), 6.72 – 6.69 (m, 2H, H-13, H-15), 4.12 (d, *J* = 4.9 Hz, 1H, H-18), 3.76 (d, *J* = 3.8 Hz, 6H, H-16, H-17), 2.88 (d, *J* = 13.5 Hz, 1H, H-9), 2.58 (d, *J* = 13.4 Hz, 1H, H-9‘), 2.24 (tdd, *J* = 13.5, 6.7, 2.2 Hz, 1H, H-19), 1.86 (ddq, *J* = 25.0, 11.9, 6.3 Hz, 2H, H-3, H-20), 1.75 (dt, *J* = 12.2, 5.7 Hz, 1H, H-5), 1.71 (t, 1H, H-6), 1.63 (dd, *J* = 14.3, 6.2 Hz, 1H, H-21), 1.53 (ddd, *J* = 20.0, 10.2, 4.7 Hz, 2H, H-4, H-19‘), 1.48 – 1.40 (m, 1H, H-4‘), 1.34 (dt, *J* = 12.4, 6.2 Hz, 1H, H-20‘), 1.25 (dd, *J* = 24.5, 6.0 Hz, 1H, H-5‘), 1.20 (s, 3H, H-7), 0.92 – 0.85 (m, 1H, H-21‘), 0.84 (d, *J* = 6.5 Hz, 3H, H-8).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 153.1 (C-14), 152.4 (C-11), 130.0 (C-10), 118.0 (C-15), 111.1 (C-12), 110.6 (C-13), 87.1 (C-2), 79.3 (C-18), 55.7 (C-17), 55.6 (C-16), 48.2 (C-1), 47.3 (C-6), 34.4 (C-3), 31.7 (C-21), 31.4 (C-5), 29.9 (C-9), 28.4 (C-4), 24.6 (C-19), 19.2 (C-20), 16.6 (C-8), 14.9 (C-7).

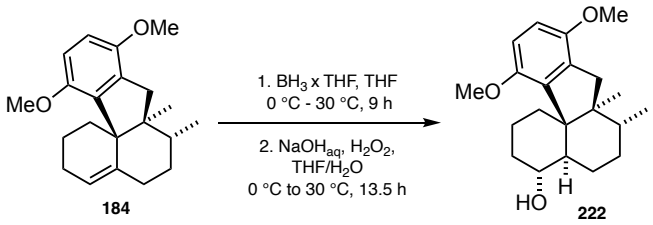
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2929 (m), 2867 (w), 2832 (w), 1727 (w), 1611 (w), 1590 (w), 1499 (s), 1463 (m), 1444 (m), 1427 (w), 1377 (w), 1355 (w), 1342 (w), 1330 (w), 1312 (w), 1279 (w), 1264 (w), 1242 (m), 1221 (s), 1193 (w), 1179 (m), 1159 (w), 1121 (w), 1099 (w), 1080 (w), 1051 (m), 1031 (m), 1022 (w), 981 (w), 958 (w), 939 (m), 888 (w), 879 (w), 859 (w), 840 (w), 799 (w), 735 (w), 715 (w), 706 (w), 524 (w).

GC-MS (70 eV): m/z (%) = 330 (45, [M]+), 312 (5), 161 (30), 152 (100), 121 (24), 105 (13), 91 (27), 77 (17).

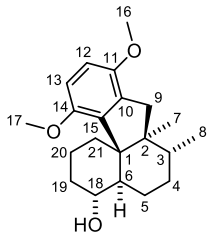
HRMS (EI):	Calc. [amu]	Found [amu]
	330.21895 $[M]^{\bullet+}$	330.2189 $[M]^{\bullet+}$

$[\alpha]^{20}_{\lambda}$ (c = 0.55 g/100 mL, $CHCl_3$): + 3.2° (436 nm), + 1.5° (546 nm), + 1.1° (579 nm), + 0.2° (589 nm).

5.2.23 SYNTHESIS OF TETRACYCLIC ALCOHOL **222**



A solution of 644 mg (2.06 mmol, 1.0 eq.) of olefin **184** in 60 mL of dry THF was cooled to 0 °C and 13.5 mL (13.5 mmol, 6.55 eq.) of BH_3 x THF (1.0 M in THF) were added. The mixture was stirred at 0 °C for 2 h and at 30 °C for 7.5 h. Then, the solution was cooled to 0 °C before 20 mL of 10% (w/w) aqueous NaOH and 40 mL of aqueous 30% (w/V) H_2O_2 were slowly added successively (CAUTION: The reaction with NaOH is exothermic!). The stirred mixture was left in the cooling bath overnight to slowly reach 25 °C (14 h). After cooling to 0 °C and careful addition of sat. aqueous $Na_2S_2O_3$ the mixture was allowed to reach 30 °C before the aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were washed with water and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure to give a colorless, viscous oil. The crude alcohol **222** was used for the following reaction without further purification. For analytical characterization, a sample of the crude product was purified by silica gel column chromatography (CH_2Cl_2/*c*-Hex 4:1). The configuration of the two newly formed stereocenters was verified by ^{1}H,^{1}H-NOESY NMR analysis.



M ($C_{21}H_{30}O_3$) = 330.47 g/mol

R$_f$ (*c*-Hex/EtOAc 4:1) = 0.41

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.67 (s, 2H, H-12, H-13), 4.50 (td, *J* = 10.0, 5.9 Hz, 1H, H-18), 3.77 (s, 3H, H-16), 3.75 (s, 3H, H-17), 2.77 (d, *J* = 15.9 Hz, 1H, H-9), 2.43 (d, *J* = 15.9 Hz, 1H, H-9'), 2.17 – 2.10 (m, 1H, H-19), 1.97 – 1.92 (m, 1H, H-5), 1.53 – 1.46 (m, 1H, H-21), 1.46 – 1.39 (m, 3H, H-4, H-20, H-21'), 1.35 – 1.28 (m, 3H, H-3, H-6, H-20'), 1.22 – 1.10 (m, 3H, H-4', H-5', H-19'), 1.02 (s, 3H, H-7), 0.77 (d, *J* = 6.7 Hz, 3H, H-8).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 151.3 (C-11), 150.8 (C-14), 138.8 (C-15), 132.9 (C-10), 109.7 (C-12), 109.2 (C-13), 71.1 (C-18), 59.4 (C-1), 55.8 (C-16), 55.1 (C-17), 50.9 (C-2), 47.4 (C-6), 37.7 (C-9), 36.5 (C-19), 35.2 (C-3), 35.1 (C-21), 32.0 (C-4), 25.6 (C-5), 20.9 (C-20), 18.1 (C-8), 13.3 (C-7).

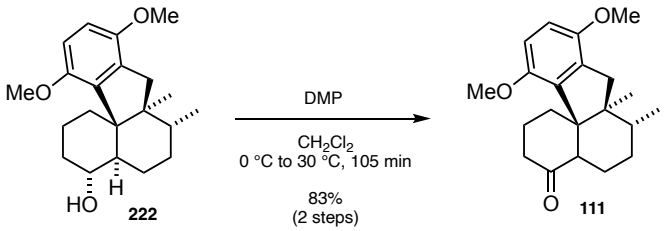
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3363 (br), 2931 (s), 2854 (m), 2043 (w), 1971 (w), 1735 (br), 1594 (w), 1492 (s), 1462 (m), 1380 (w), 1324 (w), 1281 (w), 1255 (s), 1171 (w), 1148 (w), 1071 (m), 1047 (w), 1034 (w), 1004 (w), 968 (w), 941 (w), 873 (w), 848 (w), 790 (w), 719 (w).

GC-MS (70 eV): m/z (%) = 330 (52, $[M]^+$), 312 (100), 297 (34), 258 (18), 255 (22), 243 (25), 227 (18), 203 (23), 189 (21).

HRMS (ESI):	Calc. [amu]	Found [amu]
	353.20872 $[M+Na]^+$	353.20865 $[M+Na]^+$

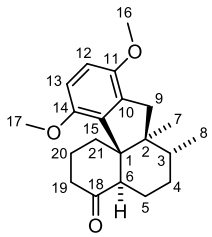
$[\alpha]^{20}_{\lambda}$ (c = 0.76 g/100 mL, $CHCl_3$): – 75° (436 nm), – 44° (546 nm), – 39° (579 nm), – 37° (589 nm).

5.2.24 SYNTHESIS OF TETRACYCLIC KETONE **111**



A solution of the crude alcohol **222** of the previous reaction (≤2.06 mmol) in 72 mL of CH_2Cl_2 (HPLC grade) was cooled to 0 °C before 2.46 g (5.80 mmol, 2.82 eq.) of DMP were added over 5 min. The mixture was stirred at 0 °C for 30 min and at 30 °C for 75 min. After addition of H_2O, the phases were separated and the aqueous phase was extracted with 3x 50 mL CH_2Cl_2. The combined organic layers were washed with sat. $NaHCO_3$ and H_2O, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (*c*-Hex/EtOAc 9:1) to provide 559 mg (1.70 mmol, 83% over 2 steps) of tetracyclic ketone **111** as a yellow sticky oil, which crystallized very slowly at rt.

M ($C_{21}H_{28}O_3$) = 328.45 g/mol



R_f (*c*-Hex/EtOAc 9:1) = 0.24

m.p.: 126.5°C – 128.2°C

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.65 (d, *J* = 8.7 Hz, 1H, H-12), 6.61 (d, *J* = 8.8 Hz, 1H, H-13), 3.77 (s, 3H, H-16/17), 3.56 (s, 3H, H-16/17), 2.82 (d, *J* = 15.8 Hz, 1H, H-9), 2.53 (d, *J* = 15.8 Hz, 1H, H-9'), 2.47 (ddt, *J* = 16.6, 5.0, 1.7 Hz, 1H, H-19), 2.24 – 2.19 (m, 1H, H-5), 2.19 – 2.13 (m, 1H, H-19'), 2.09 – 2.05 (m, 1H, H-6), 1.81 – 1.74 (m, 1H, H-21), 1.74 – 1.65 (m, 2H, H-20, H-21'), 1.63 – 1.53 (m, 1H, H-20'), 1.47 – 1.41 (m, 1H, H-4), 1.28 – 1.20 (m, 1H, H-3), 1.13 – 1.06 (m, 1H, H-4'), 1.05 (s, 3H, H-7), 1.04 – 0.98 (m, 1H, H-5'), 0.81 (d, *J* = 6.7 Hz, 3H, H-8).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 209.6 (C-18), 151.3 (C-11/14), 151.2 (C-11/14), 136.7 (C-15), 131.8 (C-10), 109.4 (C-12), 109.2 (C-13), 58.4 (C-1), 55.8 (C-16/17), 53.8 (C-16/17), 51.9 (C-6), 50.9 (C-2), 40.4 (C-19), 38.0 (C-9), 35.2 (C-3), 33.4 (C-21), 30.9 (C-4), 22.6 (C-5), 21.1 (C-20), 18.1 (C-8), 12.7 (C-7).

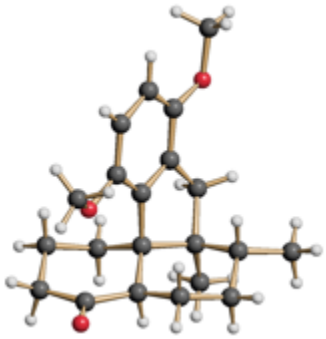
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2924 (br), 2851 (m), 1706 (s), 1597 (w), 1493 (s), 1460 (m), 1381 (w), 1354 (w), 1320 (w), 1293 (w), 1279 (m), 1259 (s), 1251 (s), 1187 (w), 1171 (w), 1146 (w), 1129 (w), 1094 (m), 1083 (m), 1068 (m), 1051 (m), 1024 (w), 1007 (w), 967 (w), 954 (w), 898 (w), 879 (w), 842 (w), 792 (m), 738 (w), 716 (w), 678 (w), 648 (w).

GC-MS (70 eV): m/z (%) = 328 (100, $[M]^+$), 297 (97), 285 (100), 258 (31), 243 (49), 227 (18), 201 (22), 189 (20), 115 (21), 91 (12), 55 (16).

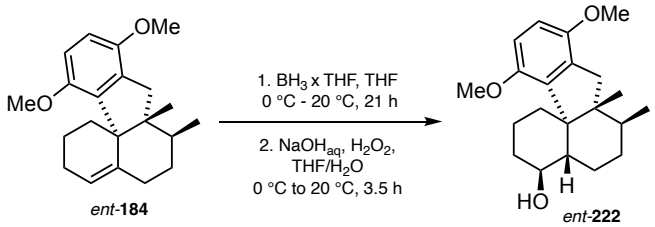
HRMS (ESI):	Calc. [amu]	Found [amu]
	329.21112 $[M+H]^+$	329.21094 $[M+H]^+$
	351.19307 $[M+Na]^+$	351.19257 $[M+Na]^+$

$[\alpha]^{20}_{\lambda}$ (c = 0.55 g/100 mL, $CHCl_3$): – 39° (436 nm), – 20° (546 nm), – 17° (579 nm), – 17° (589 nm).

X-ray crystal structure (CCDC 2077914):



5.2.25 SYNTHESIS OF TETRACYCLIC ALCOHOL *ent*-**222**



ent-**184** *ent*-**222**

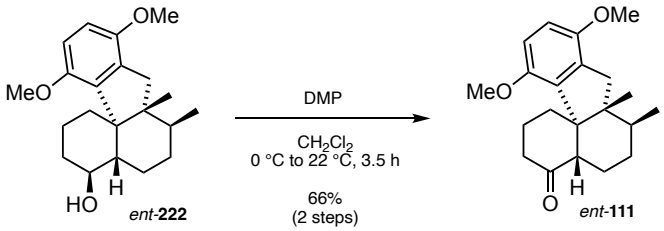
A solution of 189 mg (605 µmol, 1.0 eq.) of olefin *ent*-**184** in 18 mL of dry THF was cooled to 0 °C and 4.0 mL (4.0 mmol, 6.6 eq.) of BH_3 x THF (1.0 M in THF) were added. The mixture was stirred at 0 °C for 2 h and at 20 °C for 19 h. Then, the solution was cooled to 0 °C before 8 mL of 10% (w/w) aqueous NaOH and 16 mL of aqueous 30% (w/V) H_2O_2 were slowly added successively (CAUTION: The reaction with NaOH is exothermic!). The stirred mixture was stirred at 0 °C for 20 min and 3 h at 20 °C. After re-cooling to 0 °C and careful addition of 20 mL of sat. aqueous $Na_2S_2O_3$ the mixture was allowed to reach 20 °C again before the aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were washed with water and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure to give a colorless, viscous oil. The crude alcohol *ent*-**222** was used for the following reaction without further purification. For analytical characterization, a sample of the crude product was purified by silica gel column chromatography (CH_2Cl_2/*c*-Hex 4:1). The configuration of the two newly formed stereocenters was verified by ^{1}H,^{1}H-NOESY NMR analysis.

M ($C_{21}H_{30}O_3$) = 330.47 g/mol

[α]$^{20}_{\lambda}$ (c = 0.36 g/100 mL, $CHCl_3$): + 13° (436 nm), + 12° (546 nm), + 10° (579 nm), + 9.3° (589 nm).

Additional analytical data was in accordance with that recorded for **222** (see chapter **5.3.23**).

5.2.26 SYNTHESIS OF TETRACYCLIC KETONE *ent*-**111**



ent-**222** *ent*-**111**

A solution of the crude alcohol *ent*-**222** of the previous reaction (≤605 mmol) in 18 mL of CH_2Cl_2 (HPLC grade) was cooled to 0 °C before 536 mg (1.26 mmol, 2.08 eq.) of DMP were added over 5 min. The mixture was stirred at 0 °C for 2 h and at 22 °C for 1.5 h. After addition of 10 mL of H_2O,

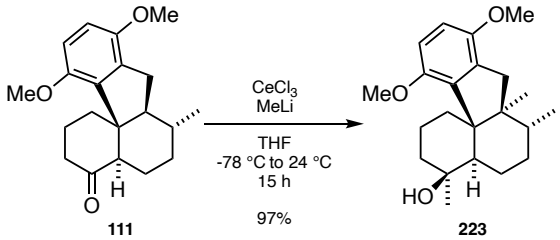
the phases were separated and the aqueous phase was extracted with 3 x 10 mL CH_2Cl_2. The combined organic layers were washed with 10 mL of sat. aqueous $NaHCO_3$ and 10 mL of H_2O, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (*c*-Hex/EtOAc 9:1) to provide 131 mg (399 µmol, 66% over 2 steps) of tetracyclic ketone *ent*-**111** as a yellow sticky oil.

M ($C_{21}H_{28}O^3$) = 328.45 g/mol

[α]$^{20}_{\lambda}$ (c = 0.46 g/100 mL, $CHCl_3$): + 51° (436 nm), + 26° (546 nm), + 23° (579 nm), + 22° (589 nm).

Additional analytical data was in accordance with that recorded for **111** (see chapter **5.2.24**).

5.2.27 SYNTHESIS OF TERTIARY ALCOHOL **223**

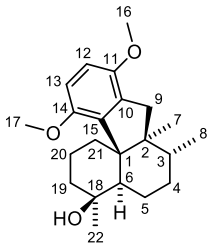


Based on a literature protocol,[122] a suspension of 880 mg (3.57 mmol, 2.3 eq.) of $CeCl_3$ in 20 mL of dry THF was stirred at 24 °C for 2.5 h. Then, the mixture was cooled to -78 °C and 2.2 mL (3.1 mmol, 2.0 eq.) of MeLi (1.3 M in Et_2O) were added over 1 min. After stirring at -78 °C for 1 h, 493 mg (1.50 mmol, 1.0 eq.) of ketone **111** in 4.5 mL of dry THF were added and the mixture was stirred for 17 h and allowed to slowly reach 24 °C. Excess reagent was quenched by addition of 20 mL of sat. aqueous NH_4Cl and 40 mL of H_2O. After extraction with 3 x 50 mL of MTBE the combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure to give 504 mg (1.46 mmol, 97%) of tertiary alcohol **223** as a colorless, crystalline solid.

M ($C_{22}H_{32}O$) = 344.50 g/mol)

R_f (*c*-Hex/EtOAc 3:1) = 0.35

m.p.: 149 °C – 151 °C



^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.74 (d, *J* = 8.9 Hz, 1H, H-13), 6.70 (d, *J* = 8.8 Hz, 1H, H-12), 6.33 (s, 1H, OH), 3.85 (s, 3H, H-17), 3.78 (s, 3H, H-16), 2.76 (d, *J* = 16.0 Hz, 1H, H-9), 2.40 (d, *J* = 16.0 Hz, 1H, H-9'), 1.92 – 1.83 (m, 2H, H-5, H-19), 1.60 – 1.55 (m, 1H, H-6), 1.54 – 1.49 (m, 1H, H-

4), 1.49 – 1.44 (m, 3H, H-19', H-21), 1.44 – 1.37 (m, 1H, H-20), 1.37 – 1.28 (m, 2H, 3-H, H-20'), 1.25 (d, *J* = 1.1 Hz, 3H, H-22), 1.24 – 1.16 (m, 2H, H-4', H-5'), 0.99 (s, 3H, H-7), 0.76 (d, *J* = 6.7 Hz, 3H, H-8).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 152.0 (C-11), 149.5 (C-14), 139.6 (C-15), 133.6 (C-10), 110.2 (C-13), 109.2 (C-12), 69.8 (C-18), 59.5 (C-1), 56.2 (C-17), 55.8 (C-16), 52.2 (C-2), 47.5 (C-6), 42.7 (C-19), 37.2 (C-9), 35.8 (C-21), 35.3 (C-3), 33.5 (C-4), 31.2 (C-22), 24.6 (C-5), 19.1 (C-20), 18.0 (C-8), 13.6 (C-7).

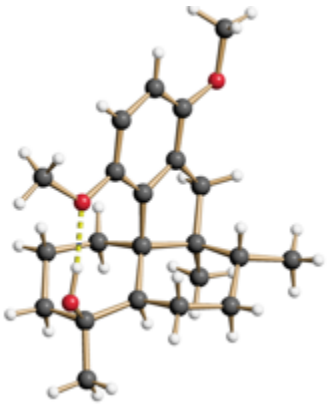
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3462 (br), 2930 (s), 2873 (w), 2848 (w), 1588 (w), 1490 (s), 1462 (m), 1385 (w), 1374 (w), 1359 (w), 1317 (w), 1298 (w), 1266 (w), 1253 (s), 1190 (w), 1171 (w), 1162 (w), 1149 (w), 1077 (m), 1047 (m), 997 (w), 962 (m), 923 (w), 898 (w), 863 (w), 789 (m), 726 (m), 665 (w), 647 (w), 580 (w), 537 (w).

GC-MS (70 eV): m/z (%) = 344 (21, [M]+), 326 (11), 269 (19), 259 (100), 243 (8), 203 (22), 189 (16), 71 (9), 55 (13).

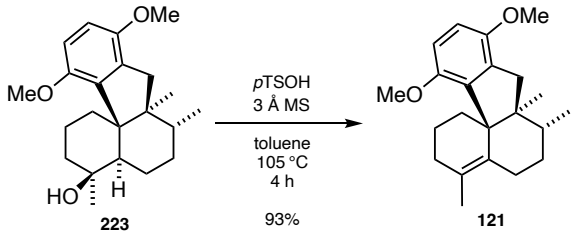
HRMS (ESI):	Calc. [amu]	Found [amu]
	367.22437 $[M+Na]^+$	367.22418 $[M+Na]^+$

$[\alpha]^{20}_{\lambda}$ (c = 0.40 g/100 mL, $CHCl_3$): – 72° (436 nm), – 42° (546 nm), – 36° (579 nm), – 35° (589 nm).

X-ray crystal structure (CCDC 2077910):

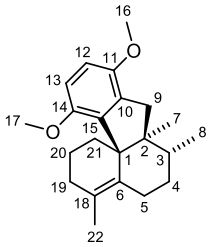


5.2.28 SYNTHESIS OF TETRASUBSTITUTED OLEFIN **121**



A *Schlenk* flask was charged with 2.2 g of freshly activated MS 3 Å powder before a solution of 504 mg (1.46 mmol, 1.0 eq.) of tertiary alcohol **223** in 42 mL of toluene (HPLC grade) and 2.93 g (15.4 mmol, 11 eq.) of *p*TsOH x H_2O were added. Then, the mixture was stirred at 105 °C for 4 h. After cooling to rt and addition of sat. aqueous $NaHCO_3$ the phases were separated and the aqueous phase was extracted twice with EtOAc. The combined organic phases were washed with H_2O, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (*c*-Hex/EtOAc 50:1) to afford 442 mg (1.35 mmol, 93%) of tetrasubstituted olefin **121** as a colorless, crystalline solid.

M ($C_{22}H_{30}O_2$) = 326.48 g/mol



R_f (*c*-Hex/EtOAc 49:1) = 0.39

m.p.: 77.9 °C – 80.3 °C

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.61 (s, 2H, 12-H, H-13), 3.77 (s, 3H, H-16), 3.64 (s, 3H, H-17), 2.80 (d, *J* = 15.8 Hz, 1H, H-9), 2.61 (dt, *J* = 13.8, 3.3 Hz, 1H, H-5), 2.52 (d, *J* = 15.8 Hz, 1H, H-9), 2.08 – 1.99 (m, 1H, H-19), 1.99 – 1.92 (m, 1H, H-19'), 1.88 (ddd, *J* = 13.0, 10.1, 3.1 Hz, 1H, H-21), 1.71 (s, 3H, H-22), 1.65 – 1.59 (m, 1H, H-5'), 1.59 – 1.56 (m, 1H, H-20), 1.55 – 1.47 (m, 1H, H-20'), 1.47 – 1.39 (m, 2H, 3-H, H-21'), 1.33 (dq, *J* = 12.8, 3.5 Hz, 1H, H-4), 1.10 (dtd, *J* = 13.9, 12.6, 3.4 Hz, 1H, H-4'), 0.96 (s, 3H, H-7), 0.82 (d, *J* = 6.8 Hz, 3H, H-8).

13C NMR (126 MHz, $CDCl_3$): δ [ppm] = 151.7 (C-14), 150.9 (C-11), 142.0 (C-15), 131.7 (C-10), 130.0 (C-6), 126.8 (C-18), 110.4 (C-13), 108.7 (C-12), 56.3 (C-17), 56.1 (C-1), 55.8 (C-16), 52.1 (C-2), 38.5 (C-9), 36.4 (C-3), 33.1 (C-19), 32.9 (C-21), 31.5 (C-4), 27.9 (C-5), 20.3 (C-20), 20.2 (C-22), 18.2 (C-8), 14.3 (C-7).

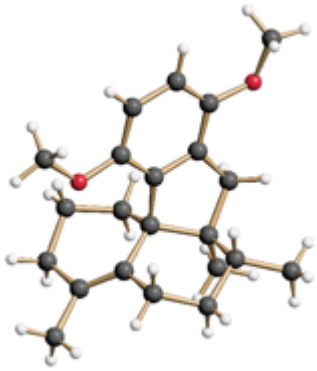
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2951 (w), 2931 (m), 2908 (m), 2871 (w), 2852 (m), 2829 (m), 2044 (w), 1973 (w), 1595 (w), 1492 (s), 1463 (m), 1437 (m), 1379 (w), 1325 (w), 1255 (s), 1194 (w), 1172 (w), 1157 (w), 1142 (w), 1125 (w), 1094 (m), 1074 (m), 1057 (m), 1011 (w), 971 (w), 945 (w), 897 (w), 866 (w), 789 (m), 715 (m), 665 (w).

GC-MS (70 eV): *m/z* (%) = 326 (100, $[M]^+$), 311 (69), 267 (19), 258 (24), 241 (27), 227 (11), 225 (11), 211 (13), 175 (15), 165 (11), 152 (10), 115 (11), 91 (11), 71 (13), 55 (15).

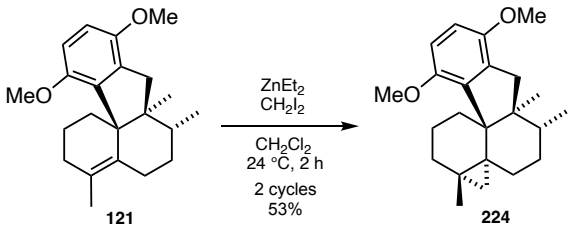
HRMS (ESI):	Calc. [amu]	Found [amu]
	327.23186 $[M+H]^+$	327.23177 $[M+H]^+$
	349.21380 $[M+Na]^+$	349.21378 $[M+Na]^+$

$[\alpha]^{20}_{\lambda}$ (c = 0.49 g/100 mL, $CHCl_3$): + 338° (436 nm), + 180° (546 nm), + 156° (579 nm), + 149° (589 nm).

X-ray crystal structure (CCDC 2077904):

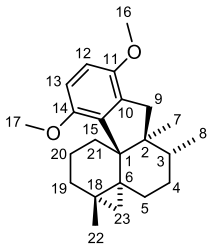


5.2.29 SYNTHESIS OF CYCLOPROPANE **224**



In a flame dried *Schlenk* flask 105 mg (0.322 mmol, 1.0 eq.) of tetrasubstituted olefin **121** were dissolved in 750 µL of CH_2Cl_2 (HPLC grade). Then, 430 µL (0.387 mmol, 1.2 eq.) of $ZnEt_2$ (0.9 M in hexane) and 32.0 µL (106 mg, 396 µmol, 1.2 eq.) of CH_2I_2 were simultaneously added at 24 °C and the addition procedure (same amounts) was repeated 3 more times with an interval of 20 minutes. The mixture was stirred at 24 °C for 1 h before excess reagent was quenched by addition of H_2O and sat. aqueous $NaHCO_3$. After extraction with EtOAc (2x) and CH_2Cl_2 the combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (*c*-Hex/toluene 8:1 to 4:1) to provide 48 mg (0.14 mmol, 44%) of cyclopropane **224** besides 40 mg (0.12 mmol, 38%) of reisolated olefin **121** which again subjected to the same cyclopropanation procedure. After the two cycles, 58 mg (0.17 mmol, 53%) of cyclopropane **224** were obtained as a colorless sticky oil, which solidified very slowly at rt.

M ($C_{23}H_{32}O_2$) = 340.51 g/mol



R_f (*c*-Hex/toluene 1:1) = 0.62

m.p.: 76.1 °C – 79.9 °C

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.66 (d, *J* = 8.9 Hz, 1H, H-13), 6.64 (d, *J* = 8.8 Hz, 1H, H-12), 3.78 (s, 3H, H-17), 3.77 (s, 3H, H-16), 2.70 (d, *J* = 15.7 Hz, 1H, H-9), 2.46 (d, *J* = 15.7 Hz, 1H, H-9'), 1.73 (ddd, *J* = 13.9, 11.1, 8.6 Hz, 1H, H-19), 1.62 (dd, *J* = 13.8, 8.7 Hz, 1H, H-19'), 1.58 – 1.47 (m, 2H, H-5, H-21), 1.41 – 1.23 (m, 4H, 3-H, H-4, H-5', H-20), 1.20 (ddd, *J* = 9.8, 4.6, 3.5 Hz, 1H, H-20'), 1.14 (s, 3H, H-22), 1.13 – 1.06 (m, 2H, H-4', H-21'), 1.01 (s, 3H, H-7), 0.81 (d, *J* = 6.2 Hz, 3H, H-8), 0.72 (dd, *J* = 4.3, 1.7 Hz, 1H, H-23), –0.01 (d, *J* = 4.4 Hz, 1H, H-23').

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 152.4 (C-14), 151.1 (C-11), 139.7 (C-15), 132.3 (C-10), 108.8 (C-12), 108.7 (C-13), 55.7 (C-17), 55.6 (C-16), 55.0 (C-1), 51.0 (C-2), 38.5 (C-9), 36.1 (C-3), 31.4 (C-19), 30.5 (C-5), 30.3 (C-4), 28.5 (C-6), 28.1 (C-21), 23.6 (C-23), 23.4 (C-22), 20.7 (C-18), 18.6 (C-20), 18.2 (C-8), 14.0 (C-7).

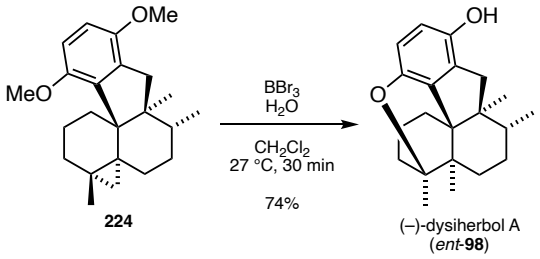
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3676 (br), 3053 (w), 2946 (w), 2928 (s), 2904 (w), 2849 (w), 2830 (w), 1594 (w), 1492 (s), 1462 (m), 1438 (w), 1407 (w), 1395 (w), 1380 (w), 1322 (w), 1255 (s), 1175 (w), 1147 (w), 1085 (m), 1062 (m), 978 (w), 893 (br), 808 (w), 788 (w), 716 (w), 649 (w).

GC-MS (70 eV): *m/z* (%) = 340 (100, $[M]^+$), 272 (26), 258 (40), 257 (51), 255 (37), 243 (27), 215 (31), 201 (29), 189 (38), 55 (30).

HRMS (EI):	Calc. [amu]	Found [amu]
	340.23968 $[M]^{\bullet+}$	340.23914 $[M]^{\bullet+}$

$[\alpha]^{20}_{\lambda}$ (*c* = 1.00 g/100 mL, $CHCl_3$): + 132° (436 nm), + 73° (546 nm), + 63° (579 nm), + 60° (589 nm).

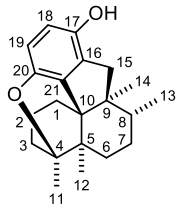
5.2.30 SYNTHESIS OF (–)-DYSIHERBOL A (*ent*-**98**)



To solution of 43 mg (0.13 mmol, 1.0 eq.) of cyclopropane **224** in 1.6 mL of CH_2Cl_2 were added 23 µL (23 mg, 1.3 mmol, 10 eq.) of H_2O and 1.6 mL (1.3 mmol, 10 eq.) of BBr_3 (0.78 M in heptane) and the mixture was stirred at rt for 40 min. After addition of H_2O the aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (*c*-Hex/EtOAc 20:1) to provide 29 mg (0.092 mmol, 74%) of (–)-dysiherbol A (*ent*-**98**) as a yellow, sticky oil. Slow evaporation of an Et_2O/MeOH solution of *ent*-**98** at rt delivered crystalline (–)-dysiherbol A (as MeOH complex) as a yellowish, crystalline solid.

M ($C_{21}H_{28}O_2$) = 312.45 g/mol

R$_f$ (*c*-Hex/EtOAc 9:1) = 0.31



m.p. of *ent*-Dysiherbol A – MeOH complex: 96.7 °C – 99.9 °C

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.49 (d, *J* = 8.5 Hz, 1H, H-18), 6.43 (d, *J* = 8.5 Hz, 1H, H-19), 4.20 (br, 1H, OH), 2.57 (d, *J* = 15.2 Hz, 1H, H-15), 2.54 (d, *J* = 15.0 Hz, 1H, H-15'), 1.96 (td, *J* = 14.1, 6.5 Hz, 1H, H-3), 1.85 (td, *J* = 12.7, 4.4 Hz, 1H, H-1), 1.68 (dd, *J* = 14.6, 5.8 Hz, 1H, H-3'), 1.54 – 1.47 (m, 1H, H-2), 1.41 – 1.37 (m, 1H, H-6), 1.37 – 1.27 (m, 4H, H-1', H-2', H-6', H-7), 1.25 – 1.17 (m, 2H, H-7', H-8), 1.22 (s, 3H, H-11), 1.21 (s, 3H, H-12), 1.08 (s, 3H, H-14), 0.83 (d, *J* = 6.6 Hz, 3H, H-13).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 148.5 (C-20), 145.7 (C-17), 133.2 (C-21), 126.0 (C-16), 114.4 (C-18), 111.2 (C-19), 82.6 (C-4), 52.0 (C-9), 49.3 (C-10), 39.5 (C-15), 37.4 (C-5), 35.8 (C-3), 35.6 (C-8), 30.1 (C-6), 26.6 (C-7), 26.5 (C-1), 22.1 (C-11), 19.9 (C-2), 18.6 (C-12), 17.9 (C-13), 15.0 (C-14).

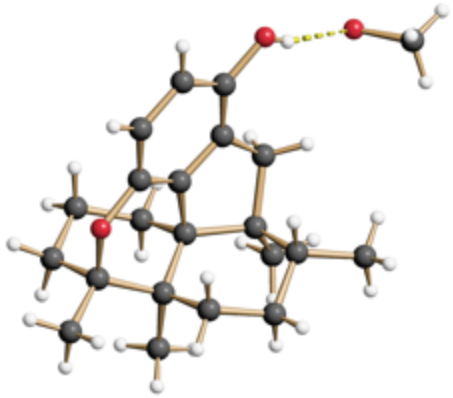
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3389 (br), 2929 (s), 2870 (m), 2856 (m), 1710 (br), 1633 (w), 1489 (s), 1461 (s), 1382 (m), 1349 (w), 1324 (w), 1312 (w), 1263 (s), 1196 (m), 1183 (s), 1164 (m), 1131 (w), 1106 (s), 1087 (w), 1061 (w), 1045 (w), 1027 (w), 1010 (w), 988 (w), 959 (s), 937 (w), 911 (w), 887 (w), 869 (s), 800 (s), 763 (w), 738 (m), 704 (w), 594 (w).

GC-MS (70 eV): *m/z* (%) = 312 (100, $[M]^+$), 243 (9), 225 (9), 213 (8), 199 (8), 187 (10), 173 (33), 161 (8), 119 (15), 115 (8), 55 (14).

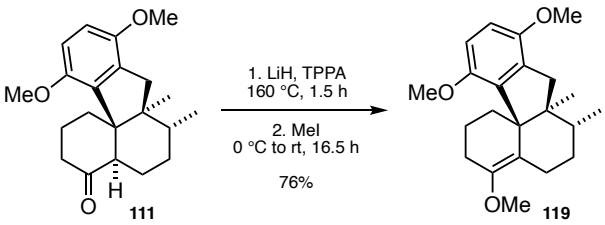
HRMS (ESI):	Calc. [amu]	Found [amu]
	313.21620 $[M+H]^+$	313.21688 $[M+H]^+$

$[\alpha]^{20}_{\lambda}$ (*c* = 0.50 g/100 mL, MeOH): – 27° (546 nm), – 24° (579 nm), – 23° (589 nm).

X-ray crystal structure (*ent*-Dysiherbol A – MeOH complex, CCDC 2077913):



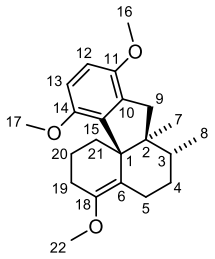
5.2.31 SYNTHESIS OF METHYL ENOL ETHER **119**



In a flame dried *Schlenk* flask 195 mg (595 µmol, 1.0 eq.) of ketone **111** were dissolved in 2.8 mL of TPPA. 107 mg (13.5 mmol, 23.1 eq.) of LiH were added and the stirred suspension was heated to 160 °C for 90 min. Then, the mixture was cooled to 0 °C and 760 µL (1.73 g, 12.2 mmol, 20.9 eq.) of MeI were added. The mixture was allowed to reach rt and stirred for 16.5 h, before excess LiH was carefully quenched with 5 mL of 25% aqueous NH_4OH. After addition of 60 mL H_2O and extraction with 3 x 40 mL of MTBE the combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (*c*-Hex/EtOAc 20:1) to provide 155 mg (453 µmol, 76%) of enol ether **119** as colorless, crystalline solid.

M $C_{22}H_{30}O_3$ = 342.48 g/mol

R_f (*c*-Hex/EtOAc 9:1) = 0.64



m.p.: 77.6 °C – 80.3 °C

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.62 (s, 2H, H-12, H-13), 3.77 (s, 3H, H-16), 3.66 (s, 3H, H-17), 3.53 (s, 3H, H-22), 2.89 (dt, *J* = 13.6, 3.2 Hz, 1H, H-5), 2.83 (d, *J* = 15.8 Hz, 1H, H-9), 2.51 (d, *J* = 15.8 Hz, 1H, H-9'), 2.20 – 2.10 (m, 2H, H-19), 1.84 (ddd, *J* = 13.2, 10.0, 3.6 Hz, 1H, H-21), 1.70 – 1.59 (m, 2H, H-20), 1.49 (tq, *J* = 13.6, 2.9 Hz, 1H, H-5'), 1.41 – 1.37 (m, 2H, 3-H, H-21'), 1.33 (dt, *J* = 12.8, 3.5 Hz, 1H, H-4), 1.11 (qd, *J* = 12.7, 3.6 Hz, 1H, H-4'), 0.97 (s, 3H, H-7), 0.82 (d, *J* = 6.7 Hz, 3H, H-8).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 151.7 (C-14), 150.8 (C-11), 149.0 (C-18), 140.7 (C-15), 131.7 (C-10), 120.3 (C-6), 109.9 (C-13), 108.8 (C-12), 56.8 (C-22), 55.8 (C-16), 55.7 (C-1), 55.6 (C-17), 51.7 (C-2), 38.5 (C-9), 36.0 (C-3), 32.2 (C-21), 31.0 (C-4), 25.7 (C-19), 24.1 (C-5), 20.1 (C-20), 18.2 (C-8), 14.1 (C-7).

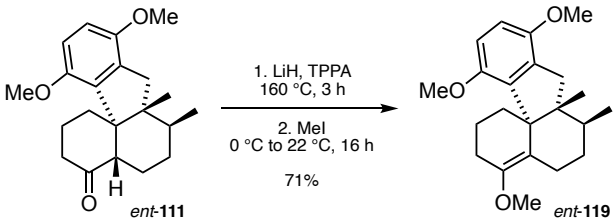
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2930 (m), 2909 (w), 2874 (w), 2850 (w), 2830 (m), 1708 (w), 1673 (m), 1595 (w), 1491 (s), 1462 (m), 1437 (m), 1380 (w), 1360 (w), 1326 (w), 1305 (w), 1282 (w), 1253 (s), 1208 (m), 1170 (m), 1149 (m), 1125 (m), 1111 (w), 1093 (m), 1070 (m), 1056 (m), 1022 (m), 971 (m), 945 (w), 936 (w), 907 (w), 871 (w), 854 (w), 789 (m), 737 (w), 715 (m), 666 (w), 646 (w), 518 (w).

GC-MS (70 eV): *m/z* (%) = 342 (30, $[M]^+$), 311 (100), 295 (22), 285 (9), 283 (9), 255 (4), 241 (9), 227 (4).

HRMS (ESI):	Calc. [amu]	Found [amu]
	343.22677 $[M+H]^+$	343.22754 $[M+H]^+$
	365.20872 $[M+Na]^+$	365.20848 $[M+Na]^+$

$[\alpha]^{20}_{\lambda}$ (*c* = 0.50 g/100 mL, $CHCl_3$): + 346° (436 nm), + 185° (546 nm), + 159° (579 nm), + 152° (589 nm).

5.2.32 SYNTHESIS OF METHYL ENOL ETHER *ent*-**119**



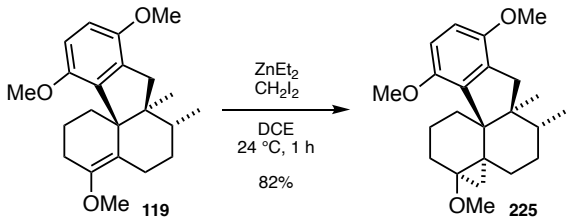
In a flame dried *Schlenk* 131 mg (399 µmol, 1.0 eq.) of ketone *ent*-**111** were dissolved in 1.8 mL of TPPA. 65 mg (8.18 mmol, 20 eq.) of LiH were added and the stirred suspension was heated to 160 °C for 3 h. Then, the mixture was cooled to 0 °C and 497 µL (1.13 g, 7.98 mmol, 20 eq.) of MeI were added. The mixture was allowed to reach 22 °C and stirred for 16 h, before excess LiH was carefully quenched with 5 mL of 25% aqueous NH_4OH. After addition of 10 mL H_2O and extraction with 3 x 10 mL of MTBE the combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (*c*-Hex/EtOAc 20:1) to provide 97 mg (283 µmol, 71%) of enol ether *ent*-**119** as colorless, crystalline solid.

M $C_{22}H_{30}O_3$ = 342.48 g/mol

[α]$^{20}_{\lambda}$ (*c* = 0.40 g/100 mL, $CHCl_3$): – 270° (436 nm), – 142° (546 nm), – 122° (579 nm), – 117° (589 nm).

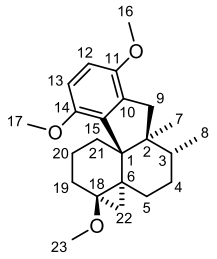
Additional analytical data was in accordance with that recorded for **119** (see chapter **5.2.31**).

5.2.33 SYNTHESIS OF CYCLOPROPANE **225**



In an argon flushed flask 155 mg (453 µmol, 1.0 eq.) of methyl enol ether **119** were dissolved in 9.8 mL of dry DCE. The solution was cooled to 0 °C and 1.80 mL (1.62 mmol, 3.58 eq.) of $ZnEt_2$ (0.9 M in hexane) were added slowly. Then, 0.30 mL (1.0 g, 3.7 mmol, 8.2 eq.) of CH_2I_2 were added and the arising colorless, cloudy suspension was allowed to reach rt and stirred for 1 h. Excess reagent was quenched with 3 mL of sat. aqueous $NaHCO_3$. After addition of 35 mL of H_2O and extraction with 3 x 25 mL of MTBE the combined organic phases were dried over $MgSO_4$ and the

solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (*c*-Hex/EtOAc 50:1) to provide 132 mg (0.370 mmol, 82%) of cyclopropane **225** as a colorless sticky oil, crystallizing upon repetitive dissolving in CH_2Cl_2 and solvent removal *in vacuo*.



M ($C_{23}H_{32}O_3$) = 356.51 g/mol

R_f (*c*-Hex/EtOAc 19:1) = 0.37

m.p.: 87.1 °C – 90.4 °C

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.65 (s, 1H, H-12, H-13), 3.78 (s, 3H, H-17), 3.77 (s, 3H, H-16), 3.32 (s, 3H, H-23), 2.72 (d, *J* = 15.7 Hz, 1H, H-9), 2.44 (d, *J* = 15.7 Hz, 1H, H-9'), 2.08 – 2.01 (m, 2H, H-19), 1.56 – 1.50 (m, 1H, H-5), 1.39 – 1.33 (m, 6H, H-3, H-4, H-5', H-20, H-21), 1.27 – 1.25 (m, 1H, H-20'), 1.12 (dd, *J* = 9.4, 3.2 Hz, 1H, H-21'), 1.00 (s, 3H, H-7), 0.82 (d, *J* = 6.0 Hz, 3H, H-8), 0.65 (dd, *J* = 5.1, 1.7 Hz, 1H, H-22), 0.41 (d, *J* = 4.3 Hz, 1H, H-22').

^{13}C NMR (151 MHz, $CDCl_3$): δ [ppm] = 152.4 (C-14), 151.1 (C-11), 139.0 (C-15), 132.1 (C-10), 109.0 (C-13), 108.9 (C-12), 65.1 (C-18), 55.8 (C-17), 55.5 (C-16), 54.7 (C-1), 53.8 (C-23), 50.9 (C-2), 38.5 (C-9), 36.1 (C-3), 32.3 (C-6), 30.4 (C-4), 29.0 (C-5), 27.9 (C-19), 27.5 (C-21), 21.3 (C-22), 18.2 (C-8), 17.1 (C-20), 14.0 (C-7).

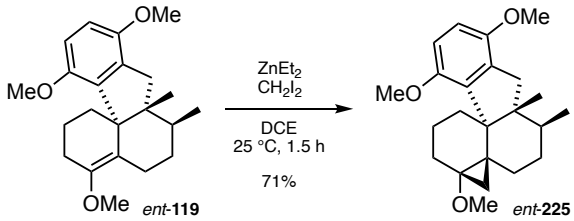
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3061 (w), 2991 (w), 2931 (m), 2902 (w), 2874 (w), 2847 (w), 2829 (w), 1595 (w), 1492 (s), 1459 (m), 1437 (w), 1379 (w), 1353 (w), 1324 (w), 1300 (w), 1282 (w), 1255 (s), 1214 (w), 1201 (w), 1174 (m), 1160 (w), 1135 (w), 1097 (m), 1081 (w), 1049 (m), 1016 (w), 998 (w), 985 (w), 970 (w), 951 (w), 915 (w), 886 (w), 838 (w), 822 (w), 789 (m), 759 (w), 738 (w), 716 (m), 649 (w), 635 (w), 510 (w).

GC-MS (70 eV): *m/z* (%) = 356 (100, $[M]^+$), 324 (28), 309 (26), 271 (51), 257 (25), 255 (26), 216 (29), 215 (42), 201 (26), 189 (26), 85 (18).

HRMS (ESI):	Calc. [amu]	Found [amu]
	379.22437 [M+Na]+	379.22467 $[M+Na]^+$

$[\alpha]^{20}_{\lambda}$ (*c* = 1.00 g/100 mL, $CHCl_3$): + 71° (436 nm), + 38° (546 nm), + 34° (579 nm), + 30° (589 nm).

5.2.34 SYNTHESIS OF CYCLOPROPANE *ent*-**225**



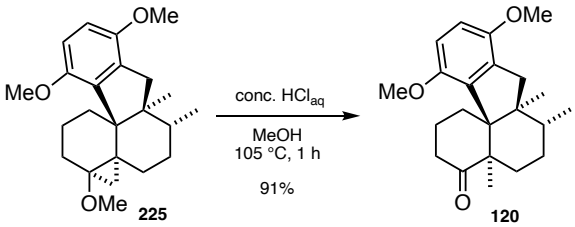
In an argon flushed flask 78 mg (228 µmol, 1.0 eq.) of enol ether *ent*-**119** were dissolved in 4.9 mL of dry DCE. The solution was cooled to 0 °C and 910 µL (910 µmol, 4.0 eq.) of $ZnEt_2$ (1.0 M in hexane) were added slowly. Then, 150 µL (470 mg, 1.86 mmol, 8.2 eq.) of CH_2I_2 were added and the arising colorless, cloudy suspension was allowed to reach 25 °C and stirred for 1.5 h. Excess reagent was quenched with 2 mL of sat. aqueous $NaHCO_3$ at 0 °C. After addition of 2 mL of H_2O and extraction with 3 x 5 mL of EtOAc the combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (*c*-Hex/EtOAc 50:1) to provide 58 mg (163 µmol, 71%) of cyclopropane *ent*-**225** as a colorless sticky oil.

M ($C_{23}H_{32}O_3$) = 356.51 g/mol

[α]$^{20}_{\lambda}$ (*c* = 1.00 g/100 mL, $CHCl_3$): – 55° (436 nm), – 28° (546 nm), – 26° (579 nm), – 24° (589 nm).

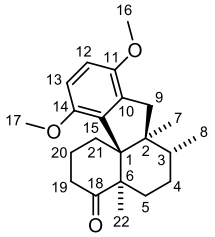
Additional analytical data was in accordance with that recorded for **225** (see chapter **5.3.33**).

5.2.35 SYNTHESIS OF α-METHYL KETONE **120**



In an argon-flushed flask 132 mg (370 µmol, 1.0 eq.) of cyclopropane **225** were dissolved in 4.5 mL MeOH (under gentle warming), 4.0 mL of conc. $HCl_{(aq)}$ were added and the mixture was refluxed for 45 min. The solution was allowed to cool to rt before it was neutralized with 20 mL of sat. aqueous $NaHCO_3$. The aqueous phase was extracted with 3 x 40 mL of MTBE, the combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure to provide 115 mg (336 µmol, 91%) of ketone **120**.

M ($C_{22}H_{30}O_3$) = 342.48 g/mol



R_f (*c*-Hex/EtOAc 9:1) = 0.24

m.p.: 124.8°C – 128.0°C

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.64 (d, *J* = 8.7 Hz, 1H, H-12), 6.59 (d, *J* = 8.7 Hz, 1H, H-13), 3.76 (s, 3H, H-16), 3.55 (s, 3H, H-17), 2.72 (d, *J* = 15.9 Hz, 1H, H-9), 2.55 – 2.47 (m, 1H, H-19), 2.51 (d, *J* = 15.9 Hz, 1H, H-9'), 2.27 (dd, *J* = 17.1, 6.0 Hz, 1H, H-19'), 2.17 (td, *J* = 13.4, 4.2 Hz, 1H, H-21), 1.97 – 1.91 (m, 1H, H-5), 1.75 – 1.69 (m, 1H, H-20), 1.56 – 1.48 (m, 1H, H-20'), 1.45 – 1.37 (m, 4H, H-4, H-5', H-21'), 1.37 – 1.33 (m, 1H, H-3), 1.31 (s, 3H, H-22), 1.15 (s, 3H, H-7), 0.84 (d, *J* = 6.5 Hz, 3H, H-8).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 212.2 (C-18), 151.4 (C-14), 151.1 (C-11), 138.3 (C-15), 131.7 (C-10), 109.2*0* (C-12), 109.1*8* (C-13), 59.7 (C-1), 55.7 (C-16), 53.2 (C-17), 50.7 (C-2), 50.3 (C-6), 40.1 (C-9), 36.4 (C-19), 35.1 (C-3), 28.8 (C-5), 27.3 (C-21), 27.2 (C-4), 22.8 (C-22), 20.7 (C-20), 17.7 (C-8), 17.4 (C-7).

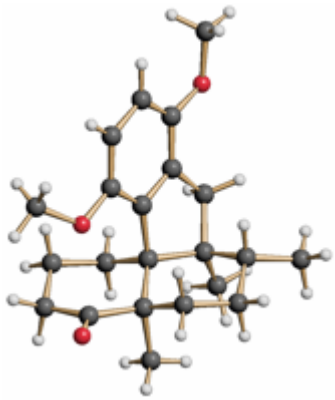
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3028 (w), 2935 (m), 2881 (w), 2833 (w), 1701 (s), 1595 (w), 1493 (s), 1460 (m), 1415 (w), 1386 (w), 1347 (w), 1321 (w), 1277 (w), 1256 (s), 1194 (w), 1172 (w), 1151 (w), 1128 (w), 1115 (w), 1091 (m), 1065 (w), 1056 (w), 1045 (m), 1023 (w), 1005 (w), 974 (m), 957 (w), 927 (w), 853 (w), 827 (w), 798 (m), 720 (m), 676 (w), 648 (w), 578 (w), 560 (w), 523 (w).

GC-MS (70 eV): *m/z* (%) = 342 (100, $[M]^+$), 286 (12), 271 (8), 257 (11), 232 (10), 217 (9), 203 (8), 189 (8), 175 (7), 109 (7).

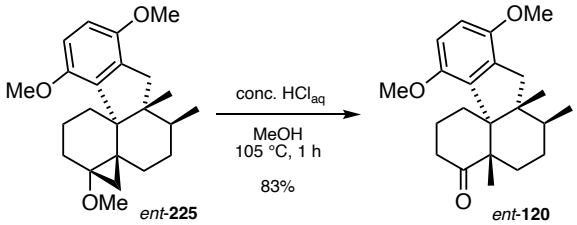
HRMS (ESI):	Calc. [amu]	Found [amu]
	343.22677 $[M+H]^+$	343.22720 $[M+H]^+$
	365.20872 $[M+Na]^+$	365.20884 $[M+Na]^+$

$[\alpha]^{20}_{\lambda}$ (*c* = 0.50 g/100 mL, $CHCl_3$): + 8.6° (436 nm), + 0.9° (546 nm), + 0.4° (579 nm), + 0.0° (589 nm).

X-ray crystal structure (CCDC 2077908):



5.2.36 SYNTHESIS OF α-METHYL KETONE *ent*-**120**

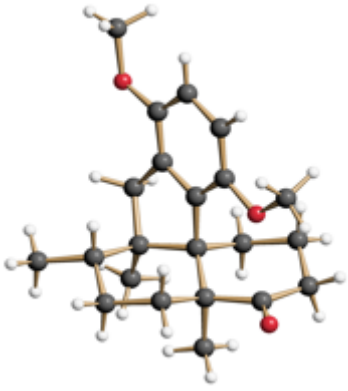


In an argon-flushed flask 66 mg (186 µmol, 1.0 eq.) of cyclopropane *ent*-**225** were dissolved in 6.5 mL MeOH (under gentle warming), 2.3 mL of conc. aqueous HCl were added and the mixture was refluxed for 50 min. The solution was allowed to cool to rt before it was neutralized with 30 mL of sat. aqueous $NaHCO_3$. The aqueous phase was extracted with 3 x 20 mL of MTBE, the combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (*c*-Hex/EtOAc 15:1) to provide 53 mg (115 µmol, 83%) of ketone *ent*-**120**.

M ($C_{22}H_{30}O_3$) = 342.48 g/mol

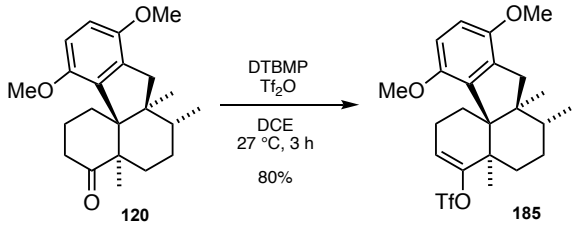
[α]$^{20}_{\lambda}$ (*c* = 0.41 g/100 mL, $CHCl_3$): – 11° (436 nm), – 0.7° (546 nm), – 0.0° (579 nm), – 0.5° (589 nm).

X-ray crystal structure:

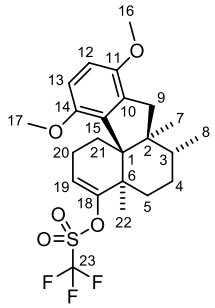


Additional analytical data was in accordance with that recorded for **120** (see chapter **5.2.35**).

5.2.37 SYNTHESIS OF ENOL TRIFLATE **185**



In a flame dried *Schlenk* flask 115 mg (336 µmol, 1.0 eq.) of ketone **120** were dissolved in 1.6 mL of dry DCE. After the addition of 196 mg (955 µmol, 2.8 eq.) of DTBMP, the solution was cooled to 0 °C and 120 µL (202 mg, 717 µmol, 2.1 eq.) of Tf_2O were added. The arising suspension was allowed to reach 27 °C and stirred for 3 h. After quenching with 2 mL of sat. aqueous $NaHCO_3$ and addition of 25 mL of H_2O the aqueous phase was extracted with 3 x 25 mL of MTBE. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification of the crude product by silica gel column chromatography (*c*-Hex/EtOAc 50:1) afforded 127 mg (268 µmol, 80%) of enol triflate **185**.



M ($C_{23}H_{29}F_3O_5S$) = 474.54 g/mol

R_f (*c*-Hex/EtOAc 9:1) = 0.80

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.66 (s, 2H, H-12, H-13), 5.38 (t, J = 3.9 Hz, 1H, H-19), 3.77 (s, 3H, H-16), 3.66 (s, 3H, H-17), 2.67 (d, J = 16.2 Hz, 1H, H-9), 2.57 (d, J = 16.2 Hz, 1H, H-9'), 2.13 – 2.02 (m, 2H, H-20, H-21), 1.81 – 1.74 (m, 1H, H-5), 1.74 – 1.67 (m, 1H, H-20'), 1.60 – 1.55 (m, 1H, H-5'), 1.50 – 1.44 (m, 1H, H-21'), 1.42 – 1.34 (m, 3H, H-3, H-4), 1.40 (s, 3H, H-22), 1.10 (s, 3H, H-7), 0.81 (d, J = 6.0 Hz, 3H, H-8).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 157.3 (C-18), 151.8 (C-14), 151.1 (C-11), 137.7 (C-15), 131.6 (C-10), 118.6 (q, $J_{C,F}$ = 319.2 Hz, C-23), 110.5 (C-12), 110.0 (C-19), 109.5 (C-13), 61.4 (C-1), 55.7 (C-16), 55.1 (C-17), 49.5 (C-2), 40.2 (C-9), 40.1 (C-6), 34.5 (C-3), 28.9 (C-5), 27.3 (C-4), 25.2 (C-21), 23.6 (C-22), 22.1 (C-20), 17.4 (C-8), 17.0 (C-7).

^{19}F NMR (471 MHz, $CDCl_3$): δ [ppm] = –75.1.

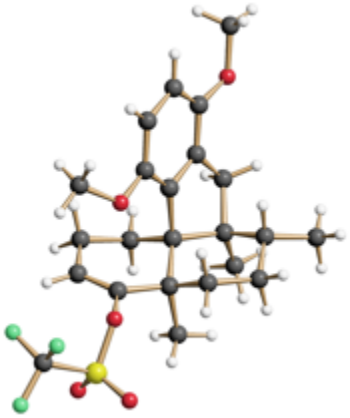
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3025 (w), 2956 (br), 2913 (w), 2836 (w), 1683 (w), 1586 (w), 1491 (s), 1463 (m), 1439 (w), 1407 (m), 1345 (w), 1313 (w), 1256 (s), 1208 (s), 1177 (w), 1144 (s), 1079 (m), 1063 (w), 1041 (w), 1023 (m), 1000 (m), 981 (m), 944 (m), 910 (w), 885 (m), 792 (m), 740 (w), 720 (w), 687 (w), 652 (w), 616 (w), 600 (m), 516 (w).

GC-MS (70 eV): *m/z* (%) = 474 (18, $[M]^+$), 342 (100), 324 (16), 309 (15), 297 (16), 286 (16), 271 (15), 257 (23), 241 (16), 231 (15), 217 (20), 203 (19), 189 (18), 173 (17), 151 (18), 128 (9), 109 (11).

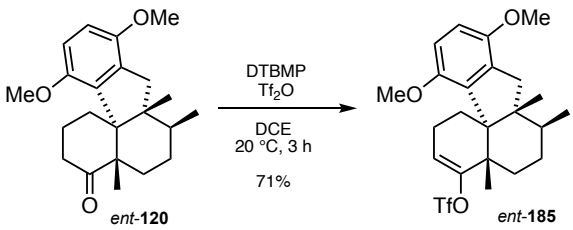
HRMS (ESI):	Calc. [amu]	Found [amu]
	497.15800 $[M+Na]^+$	497.15874 $[M+Na]^+$

[α]$^{20}_{\lambda}$ (*c* = 0.50 g/100 mL, $CHCl_3$): + 21° (436 nm), + 3.1° (546 nm), + 1.3° (579 nm), + 0.5° (589 nm).

X-ray crystal structure:



5.2.38 SYNTHESIS OF ENOL TRIFLATE *ent*-**185**



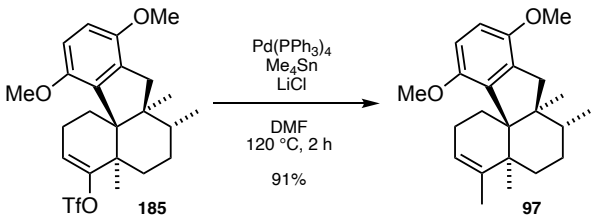
In a flame dried *Schlenk* flask 58.5 mg (172 µmol, 1.0 eq.) of ketone *ent*-**120** were dissolved in 819 µL of dry DCE. After the addition of 99.0 mg (482 µmol, 2.8 eq.) of DTBMP, the solution was cooled to 0 °C and 61.0 µL (102 mg, 362 µmol, 2.1 eq.) of Tf_2O were added. The arising suspension was allowed to reach 20 °C and stirred for 3 h. After quenching with 2 mL of sat. aqueous $NaHCO_3$ and addition of 10 mL of H_2O the aqueous phase was extracted with 3 x 10 mL of EtOAc. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification of the crude product by silica gel column chromatography (*c*-Hex/EtOAc 50:1) afforded 58.0 mg (122 µmol, 71%) of enol triflate *ent*-**185**.

M ($C_{23}H_{29}F_3O_5S$) = 474.54 g/mol

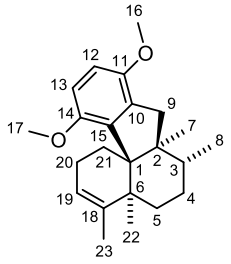
[α]$^{20}_{\lambda}$ (c = 0.29 g/100 mL, $CHCl_3$): – 15° (436 nm), + 2.1° (546 nm), + 3.6° (579 nm), + 3.7° (589 nm).

Additional analytical data was in accordance with that recorded for **185** (see chapter **5.2.37**).

5.2.39 SYNTHESIS OF OLEFIN **97** (PREDYSIHERBOL)



The reaction was performed in analogy to a literature procedure.[40] In a flame dried *Schlenk* flask 123 mg (259 µmol, 1.0 eq.) of enol triflate **225** were dissolved in 2.0 mL of dry DMF. 57 mg (1.3 mmol, 5.0 eq.) of LiCl, 62 mg (54 µmol, 0.21 eq.) of $Pd(PPh_3)_4$ and 74 µL (95 mg, 53 µmol, 2.0 eq.) of Me_4Sn were added and the reaction mixture was heated to 120 °C for 2 h. After cooling to 25 °C, excess reagent was quenched with 10 mL of sat. aqueous NH_4Cl and the aqueous phase was extracted with 3 x 10 mL of EtOAc. The combined organic phases were washed with 10 mL of brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification of the crude product by silica gel column chromatography (*c*-Hex/toluene 5:1) afforded 80.0 mg (235 µmol, 91%) of olefin **121**.



M ($C_{23}H_{32}O_2$) = 340.51 g/mol

R_f (*c*-Hex/EtOAc 4:1) = 0.41

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.66 (d, J = 8.8 Hz, 1H, H-13), 6.63 (d, J = 8.8 Hz, 1H, H-12), 5.04 (s, 1H, H-19), 3.76 (s, 3H, H-16), 3.62 (s, 3H, H-17), 2.62 (d, J = 16.1 Hz, 1H, H-9), 2.57 (d, J = 16.1 Hz, 1H, H-9'), 2.10 (td, J = 12.5, 6.1 Hz, 1H, H-21), 1.93 – 1.85 (m, 1H, H-20), 1.72 – 1.66 (m, 1H, H-5), 1.69 – 1.67 (m, 3H, H-23), 1.60 – 1.54 (m, 1H, H-20'), 1.54 – 1.49 (m, 1H, H-5'), 1.49 – 1.43 (m, 1H, H-4), 1.42 – 1.37 (m, 2H, H-3, H-21'), 1.35 – 1.29 (m, 1H, H-4'), 1.24 (s, 3H, H-22), 1.10 (s, 3H, H-7), 0.79 (d, J = 6.4 Hz, 3H, H-8).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 152.4 (C-14), 151.0 (C-11), 144.9 (C-18), 140.3 (C-15), 131.9 (C-10), 116.2 (C-19), 111.4 (C-13), 108.9 (C-12), 60.1 (C-1), 55.6 (C-16), 55.6 (C-17), 49.4 (C-2), 40.0 (C-9), 39.2 (C-6), 34.7 (C-3), 30.8 (C-5), 27.9 (C-4), 26.1 (C-21), 24.0 (C-22), 23.9 (C-20), 19.2 (C-23), 17.5 (C-8), 17.0 (C-7).

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3014 (w), 2940 (s), 2909 (m), 2831 (m), 1585 (w), 1489 (s), 1463 (m), 1450 (m), 1437 (m), 1385 (w), 1377 (w), 1314 (w), 1254 (s), 1176 (w), 1162 (w), 1149 (w), 1123

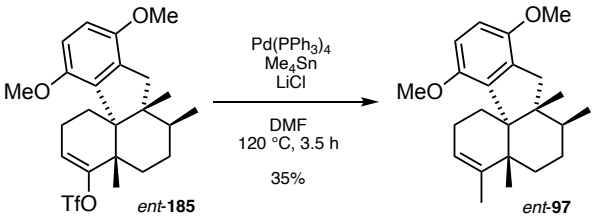
(w), 1090 (m), 1074 (m), 1045 (m), 1035 (m), 1017 (w), 997 (w), 988 (w), 969 (w), 904 (w), 878 (w), 790 (m), 742 (w), 720 (w), 663 (w), 651 (w), 515 (w).

GC-MS (70 eV): *m/z* (%) = 340 (100, $[M]^+$), 297 (64), 271 (35), 255 (15), 204 (21), 199 (70), 189 (37), 152 (16).

HRMS (ESI):	Calc. [amu]	Found [amu]
	341.24751 $[M+H]^+$	341.24774 $[M+H]^+$

$[\alpha]^{20}_{\lambda}$ (*c* = 0.40 g/100 mL, $CHCl_3$): – 41° (436 nm), – 26° (546 nm), – 22° (579 nm), – 24° (589 nm).

5.2.40 SYNTHESIS OF OLEFIN *ent*-**97**



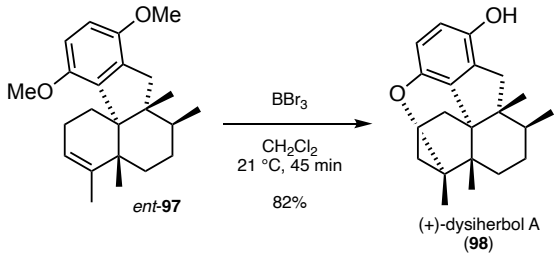
The reaction was performed in analogy to a literature procedure.[40] In a flame dried *Schlenk* flask 44.0 mg (92.7 µmol, 1.0 eq.) of enol triflate *ent*-**225** were dissolved in 700 µL of dry DMF. 19.7 mg (465 µmol, 5.0 eq.) of LiCl, 21.6 mg (18.7 µmol, 0.20 eq.) of $Pd(PPh_3)_4$ and 25.7 µL (33.2 mg, 185 µmol, 2.0 eq.) of Me_4Sn were added and the reaction mixture was heated to 120 °C for 3.5 h. After cooling to 21 °C, excess reagent was quenched with 3 mL of sat. aqueous NH_4Cl and the aqueous phase was extracted with 3 x 5 mL of EtOAc. The combined organic phases were washed with 5 mL of brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification of the crude product by silica gel column chromatography (*c*-Hex/toluene 5:1) afforded 11.0 mg (32.3 µmol, 35%) of olefin *ent*-**97**.

M ($C_{23}H_{32}O_2$) = 340.51 g/mol

$[\alpha]^{20}_{\lambda}$ (*c* = 0.55 g/100 mL, $CHCl_3$): + 44° (436 nm), + 33° (546 nm), + 28° (579 nm), + 26° (589 nm).

Additional analytical data was in accordance with that recorded for **97** (see chapter **5.2.28**).

5.2.41 SYNTHESIS OF (+)-DYSIHERBOL A (98)[40]



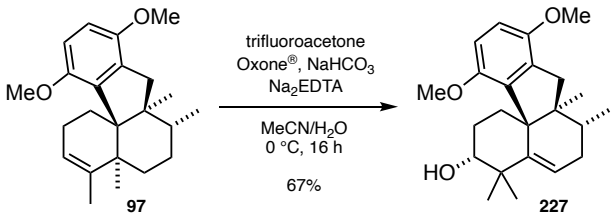
According to a literature procedure,[40] a solution of 11.0 mg (32.3 µmol, 1.0 eq.) of olefin *ent*-**97** in 1.4 mL of CH_2Cl_2 was cooled to -78 °C and 162 µL (162 µmol, 5.0 eq.) of BBr_3 (1.0 M in CH_2Cl_2) and the mixture was stirred at 21 °C for 45 min. After quenching with 8 mL of sat. aqueous $NaHCO_3$ the aqueous phase was extracted with 3 x 5 mL of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (*c*-Hex/EtOAc 20:1) to provide 8.30 mg (26.6 µmol, 82%; Lit.: 72%) of (+)-dysiherbol A (**98**) as a yellow, sticky oil.

M ($C_{21}H_{28}O_2$) = 312.45 g/mol

[α]$^{20}_{\lambda}$ (*c* = 0.67 g/100 mL, MeOH): + 31° (546 nm), + 25° (579 nm), + 24° (589 nm).

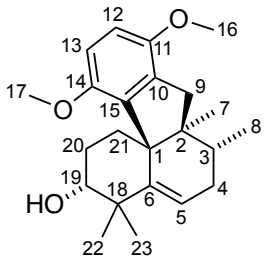
Additional analytical data was in accordance with that recorded for *ent*-**98** (see chapter **5.2.30**).

5.2.42 SYNTHESIS OF HOMOALLYLIC ALCOHOL 227



To a solution of 10 mg (0.029 mmol, 1.0 eq.) of olefin **97** in 0.30 mL of acetonitrile was added a mixture of 0.22 mg (0.59 µmol, 0.020 eq.) of Na_2EDTA, 6.0 µL of H_2O and 26 µL (33 mg, 0.29 mmol, 9.9 eq.) of 1,1,1-trifluoroacetone at 0 °C. Then, a solid mixture of 41 mg (0.13 mmol, 4.5 eq.) of Oxone® and 17 mg (0.20 mmol, 6.9 eq.) of $NaHCO_3$ was added at 0 °C over a period of 20 min. The reaction mixture was stirred at 0 °C for 16 h, before the solid was filtered off, the filtrate was diluted with 2 mL of H_2O and the aqueous phase was extracted with 3 x 3 mL CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (*c*-Hex/EtOAc 9:1) to provide 7 mg (0.02 mmol, 67%) of homoallylic alcohol **227** as pale yellow, viscous oil.

M ($C_{23}H_{32}O_3$) = 356.51 g/mol



R_f (*c*-Hex/EtOAc 4:1) = 0.23

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.61 (d, *J* = 2.4 Hz, 2H, H-12, H-13), 5.77 (t, *J* = 3.7 Hz, 1H, H-5), 4.48 (dd, *J* = 9.3, 6.8 Hz, 1H, H-19), 3.77 (s, 3H, H-16), 3.66 (s, 3H, H-17), 2.83 (d, *J* = 16.1 Hz, 1H, H-9), 2.59 (d, *J* = 16.1 Hz, 1H, H-9'), 2.08 – 2.01 (m, 1H, H-4), 2.00 – 1.94 (m, 1H, H-21), 1.93 – 1.85 (m, 1H, H-20), 1.67 (ddd, *J* = 18.5, 11.3, 3.3 Hz, 1H, H-4'), 1.59 – 1.50 (m, 2H, 3-H, H-21'), 1.44 – 1.37 (m, 1H, H-20'), 1.32 (s, 3H, H-22), 1.12 (s, 3H, H-23), 0.85 (s, 3H, H-7), 0.78 (d, *J* = 6.7 Hz, 3H, H-8).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 151.4 (C-14), 151.2 (C-11), 144.8 (C-6), 142.2 (C-15), 131.1 (C-10), 121.7 (C-5), 110.4 (C-12), 109.2 (C-13), 70.93 (C-19), 56.0 (C-17), 55.8 (C-16), 55.0 (C-1), 50.5 (C-2), 40.8 (C-18), 36.6 (C-9), 32.9 (C-4), 30.1 (C-3), 28.05 (C-20), 27.5 (C-23), 27.4 (C-22), 27.2 (C-21), 16.8 (C-8), 12.3 (C-7).

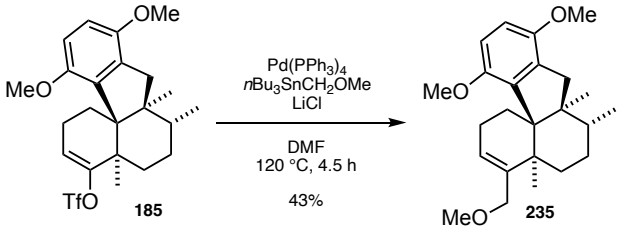
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3412 (br), 2958 (m), 2925 (s), 2855 (m), 1673 (w), 1492 (s), 1463 (m), 1380 (w), 1253 (s), 1176 (w), 1150 (w), 1091 (m), 1062 (m), 1026 (m), 999 (m), 967 (w), 790 (m), 718 (w).

GC-MS (70 eV): *m/z* (%) = 356 (30, $[M]^+$), 338 (29), 323 (11), 307 (32), 269 (100), 239 (23), 201 (65), 187 (40), 152 (29).

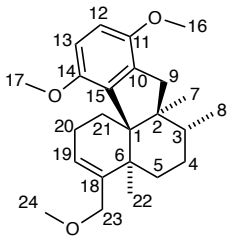
HRMS (EI):	Calc. [amu]	Found [amu]
	356.23460 $[M]^{\bullet+}$	356.23389 $[M]^{\bullet+}$

$[\alpha]^{20}_{\lambda}$ (*c* = 0.50 g/100 mL, $CHCl_3$): + 58° (436 nm), + 30° (546 nm), + 26° (579 nm), + 23° (589 nm).

5.2.43 SYNTHESIS OF ALLYL METHYL ETHER **235**



In a flame dried *Schlenk* flask 12.0 mg (25.3 µmol, 1.0 eq.) of enol triflate **185** were dissolved in 390 µL of dry DMF. 16.3 mg (38.5 mmol, 15 eq.) of LiCl, 17.5 mg (15.1 µmol, 0.60 eq.) of $Pd(PPh_3)_4$ and 32.0 mg (95.5 µmol, 3.8 eq.) of $n$$Bu_3SnCH_2OMe$ were added and the reaction mixture was heated to 120 °C for 4.5 h. After cooling to 25 °C, excess reagent was quenched with 0.5 mL of H_2O and the aqueous phase was extracted with 4 x 0.5 mL of EtOAc. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification of the crude product by silica gel column chromatography (*c*-Hex/EtOAc 50:1) afforded 4.0 mg (11 µmol, 43%) of allyl methyl ether **235**.



M ($C_{24}H_{34}O_3$) = 370.53 g/mol

R_f (*c*-Hex/EtOAc 20:1) = 0.37

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.63 (s, 2H, H-12, H-13), 5.38 (s, 1H, H-19), 4.10 (d, J = 12.2 Hz, 1H, H-23), 3.81 (d, J = 12.2 Hz, 1H, H-23‘), 3.76 (s, 3H, H-16), 3.57 (s, 3H, H-17), 3.37 (s, 3H, H-24), 2.63 (d, J = 16.2 Hz, 1H, H-9), 2.57 (d, J = 16.2 Hz, 1H, H-9‘), 2.13 (td, J = 12.4, 6.3 Hz, 1H, H-21), 2.02 (dt, J = 18.4, 5.1 Hz, 1H, H-20), 1.71 (td, J = 13.0, 3.9 Hz, 1H, H-5), 1.62 (ddd, J = 11.7, 5.8, 2.4 Hz, 1H, H-20‘), 1.59 – 1.57 (m, 1H, H-5‘), 1.52 – 1.49 (m, 1H, H-4), 1.48 – 1.43 (m, 1H, H-21‘), 1.40 (d, J = 6.3 Hz, 1H, H-3), 1.39 – 1.35 (m, 1H, H-4‘), 1.33 (s, 3H, H-22), 1.11 (s, 3H, H-7), 0.80 (d, J = 6.5 Hz, 3H, H-8).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 152.2 (C-14), 151.0 (C-11), 144.2 (C-18), 139.8 (C-15), 131.8 (C-10), 118.3 (C-19), 111.1 (C-13), 108.9 (C-12), 74.6 (C-23), 60.2 (C-1), 58.0 (C-24), 55.6 (C-16), 55.4 (C-17), 49.4 (C-2), 40.1 (C-9), 38.5 (C-6), 34.6 (C-3), 30.1 (C-5), 27.7 (C-4), 26.0 (C-21), 25.2 (C-22), 23.8 (C-20), 17.4 (C-8), 17.2 (C-7).

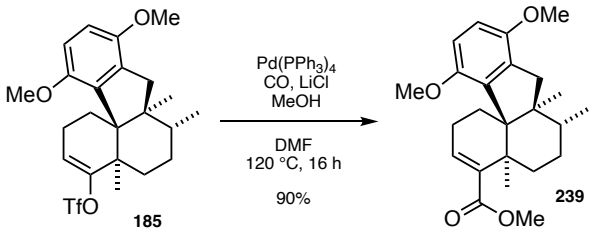
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2955 (s), 2925 (s), 2854 (s), 2160 (s), 2053 (s), 1974 (s), 1669 (s), 1490 (s), 1463 (s), 1378 (s), 1255 (s), 1177 (s), 1138 (s), 1092 (s), 1040 (s), 966 (s), 793 (s), 721 (s), 649 (s), 562 (s), 541 (s).

GC-MS (70 eV): *m/z* (%) = 370 (60, $[M]^+$), 338 (100), 323 (75), 307 (40), 281 (40), 241 (40), 187 (70), 151 (30), 115 (20), 91 (20), 55 (20).

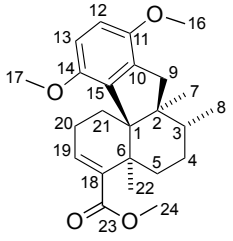
HRMS (EI):	Calc. [amu]	Found [amu]
	370.25025 $[M]^{\bullet+}$	370.2503 $[M]^{\bullet+}$

[α]$^{20}_{\lambda}$ (c = 0.10 g/100 mL, $CHCl_3$): – 41° (436 nm), – 25° (546 nm), – 25° (579 nm), – 27° (589 nm).

5.2.44 SYNTHESIS OF METHYL ESTER **239**



To a solution of 10 mg (21 µmol, 1.0 eq.) of enol triflate **185** in 0.28 mL of DMF were successively added 11 mg (9.5 µmol, 0.45 eq.) of $Pd(PPh_3)_4$, 10 mg (0.24 mmol, 11 eq.) LiCl and 0.28 mL of MeOH. The suspension was degassed with 3 freeze-pump-thaw cycles and stirred under CO atmosphere at 120 °C for 16 h. The mixture was allowed to reach rt before it was quenched with 0.5 mL of H_2O and the aqueous phase was extracted with 3 x 1 mL EtOAc. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (*c*-Hex/EtOAc 100:1 to 50:1) to provide 7.3 mg (0.019 mmol, 90%) of methyl ester **239** as a pale yellow, viscous oil.



M ($C_{24}H_{32}O_4$) = 384.52 g/mol

R_f (*c*-Hex/EtOAc 20:1) = 0.20

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.64 (d, J = 8.8 Hz, 1H, H-12), 6.61 (d, J = 8.9 Hz, 1H, H-13), 6.53 (dd, J = 4.4, 2.6 Hz, 1H, H-19), 3.76 (s, 3H, H-16), 3.74 (s, 3H, H-24), 3.60 (s, 3H, H-17), 2.65 (d, J = 16.1 Hz, 1H, H-9), 2.58 (d, J = 16.2 Hz, 1H, H-9'), 2.29 (dt, J = 12.6, 3.2 Hz, 1H, H-5), 2.14 – 2.03 (m, 2H, 20-H, H-21), 1.75 – 1.65 (m, 1H, H-20'), 1.58 (qd, J = 13.2, 3.4 Hz, 1H, H-5'), 1.52 – 1.47 (m, 2H, H-4, H-21'), 1.45 (s, 3H, H-22), 1.42 – 1.36 (m, 1H, H-3), 1.36 – 1.34 (m, 1H, H-4'), 1.11 (s, 3H, H-7), 0.80 (d, J = 6.5 Hz, 3H, H-8).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 168.1 (C-23), 152.4 (C-14), 150.9 (C-11), 141.9 (C-18), 139.1 (C-15), 134.0 (C-19), 131.9 (C-10), 110.3 (C-13), 109.1 (C-12), 60.6 (C-1), 55.7 (C-16), 55.5

(C-17), 51.1 (C-24), 49.8 (C-2), 40.3 (C-9), 38.7 (C-6), 34.6 (C-3), 29.7 (C-5), 28.0 (C-4), 25.2 (C-21), 24.9 (C-22), 24.5 (C-20), 17.5 (C-8), 17.3 (C-7).

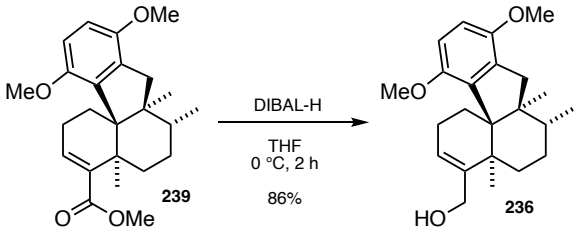
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3019, 2947, 2858, 2831, 1709, 1638, 1586, 1488, 1461, 1436, 1385, 1377, 1355, 1315, 1291, 1253, 1224, 1174, 1158, 1126, 1081, 1061, 1036, 1015, 999, 989, 972, 958, 948, 934, 912, 885, 866, 852, 823, 790, 772, 761,739, 720, 711, 652, 599, 530, 453.

GC-MS (70 eV): *m/z* (%) = 340 (100, [M]$^+$), 297 (64), 271 (35), 255 (15), 204 (21), 199 (70), 189 (37), 152 (16).

HRMS (ESI):	Calc. [amu]	Found [amu]
	407.21928 [M+Na]$^+$	407.21946 [M+Na]$^+$

[α]$^{20}_{\lambda}$ (*c* = 0.48 g/100 mL, $CHCl_3$): – 31° (436 nm), – 17° (546 nm), – 15° (579 nm), – 14° (589 nm).

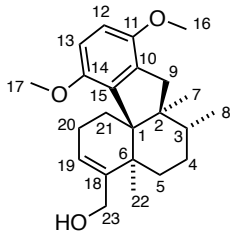
5.2.45 SYNTHESIS OF ALLYLIC ALCOHOL **236**



A solution of 5.3 mg (0.014 mmol, 1.0 eq.) of ester **239** in 0.16 mL of THF was cooled to 0 °C and 85 µL (0.085 mmol, 6.2 eq.) of DIBAL-H (1.0 M in hexanes) were added dropwise. The solution was stirred for 1.5 h and the reaction was quenched with 0.3 mL of MeOH. After addition of 0.3 mL of aqueous Rochelle's salt solution and 0.3 mL of H_2O the aqueous phase was extracted with 3 x 1 mL EtOAc. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (*c*-Hex/EtOAc 20:1 to 9:1) to provide 4.1 mg (0.012 mmol, 86%) of allylic alcohol **236** as colorless, viscous oil.

M ($C_{23}H_{32}O_2$) = 356.51 g/mol

R$_f$ (*c*-Hex/EtOAc 9:1) = 0.08



^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.72 (d, J = 8.8 Hz, 1H, H-13), 6.67 (d, J = 8.8 Hz, 1H, H-12), 5.46 (dt, J = 3.4, 2.1 Hz, 1H, H-19), 4.28 – 4.25 (m, 1H, H-23), 4.18 – 4.14 (m, 1H, H-23'), 3.79 (s, 3H, H-16), 3.67 (s, 3H, H-17), 2.68 (d, J = 16.2 Hz, 1H, H-9), 2.59 (d, J = 16.2 Hz, 1H. H-9'), 2.14 (td, J = 12.6, 6.2 Hz, 1H, H-21), 2.06 – 2.01 (m, 1H, H-20), 1.76 (td, J = 13.1, 3.7 Hz, 1H, H-5), 1.68 – 1.65 (m, 2H, H-5', H-20'), 1.52 – 1.49 (m, 1H, H-4), 1.47 – 1.44 (m, 1H, H-21'), 1.43 – 1.40 (m, 1H, H-3), 1.38 – 1.35 (m, 1H, H-4'), 1.33 (s, 3H, H-22), 1.13 (s, 3H, H-7), 0.83 (d, J = 6.5 Hz, 3H, H-8).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 152.3 (C-14), 151.4 (C-11), 146.9 (C-18), 139.8 (C-15), 132.0 (C-10), 119.2 (C-19), 112.2 (C-13), 109.2 (C-12), 64.9 (C-23), 60.6 (C-1), 56.2 (C-17), 55.7 (C-16), 49.5 (C-2), 40.2 (C-9), 38.9 (C-6), 34.7 (C- 3), 30.9 (C-5), 27.8 (C-4), 25.9 (C-22), 25.5 (C-21), 23.8 (C-20), 17.5 (C-8), 17.4 (C-7).

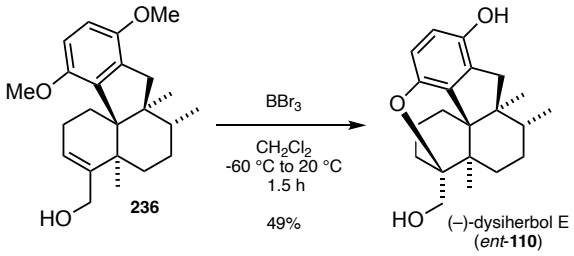
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2955 (m), 2925 (m), 2854 (m), 2160 (w), 2053 (w), 1974 (w), 1669 (w), 1490 (m), 1463 (m), 1378 (w), 1255 (m), 1177 (w), 1138 (w), 1092 (w), 1040 (w), 966 (w), 793 (w), 721 (w), 649 (w), 562 (w), 541 (w)

GC-MS (70 eV): m/z (%) = 356 $[M]^+$, 338, 323, 297, 269, 255, 241, 217, 204, 187, 165, 151, 128, 115, 91, 69, 55.

HRMS (EI):	Calc. [amu]	Found [amu]
	356.23460 $[M]^{\bullet+}$	356.23480 $[M]^{\bullet+}$

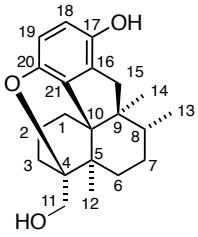
$[\alpha]^{20}_{\lambda}$ (c = 0.37 g/100 mL, $CHCl_3$): – 0.3° (436 nm), – 5.1° (546 nm), – 4.4° (579 nm), – 4.7° (589 nm).

5.2.46 SYNTHESIS OF (–)-DYSIHERBOL E (*ent*-**110**)



According to *Lu* and coworkers,[63] a solution of 4.0 mg (11.2 µmol, 1.0 eq.) of olefin **236** in 750 µL of CH_2Cl_2 was cooled to -60 °C and 56 µL (56 µmol, 5.0 eq.) of BBr_3 (1.0 M in CH_2Cl_2) and the mixture was stirred at 20 °C for 1.5 h. After quenching with 5 mL of sat. aqueous $NaHCO_3$ the

aqueous phase was extracted with 3 x 5 mL of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (*c*-Hex/EtOAc 20:1) to provide 1.8 mg (5.5 µmol, 49%; Lit.: 55%) of (–)-dysiherbol E (*ent*-**110**) as a yellow, sticky oil.



M ($C_{21}H_{28}O_3$) = 328.45 g/mol

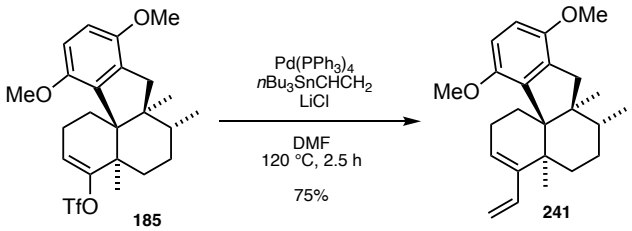
R_f (*c*-Hex/EtOAc 9:1) = 0.22

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 6.53 (d, *J* = 8.4 Hz, 1H, H-18), 6.51 (d, *J* = 8.5 Hz, 1H, H-19), 4.37 (br, 1H, OH), 3.82 (d, *J* = 10.6 Hz, 1H, H-11), 3.58 (d, *J* = 10.6 Hz, 1H, H-11‘), 2.57 (s, 2H, H-15), 2.25 (dd, *J* = 14.7, 5.9 Hz, 1H, H-3), 1.88 – 1.82 (m, 2H, H-3‘, H-1), 1.63 – 1.59 (m, 2H, H-2), 1.40–1.25 (m, 5H, H-1‘, H-6, H-7), 1.27 (s, 3H, H-12), 1.23 – 1.22 (m , 1H, H-8), 1.09 (s, 3H, H-14), 0.83 (d, *J* = 6.7 Hz, 3H, H-13).

^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 147.52 (C-20), 146.2 (C-17), 132.5 (C-21), 125.6 (C-16), 114.5 (C-18), 111.7 (C-19), 81.2 (C-4), 52.0 (C-9) , 49.4 (C-10), 39.4 (C-11), 38.3 (C-5), 35.4 (C-8), 31.9 (C-3), 30.2 (C-6), 26.2 (C-7, C-1), 19.1 (C-2), 19.0 (C-12), 17.7 (C-13), 14.9 (C-14).

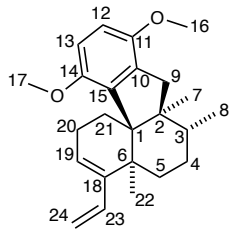
GC-MS (70 eV): *m/z* (%) = 328 (5, $[M]^+$), 312 (100), 296 (14), 283 (14), 269 (18), 227 (14), 187 (11), 173 (41), 156 (11), 119 (14), 91 (14).

5.2.47 SYNTHESIS OF DIENE **241**



In a flame dried *Schlenk* flask 19.8 mg (41.7 µmol, 1.0 eq.) of enol triflate **185** were dissolved in 200 µL of dry DMF. 8.7 mg (0.21 mmol, 5.0 eq.) of LiCl, 10.2 mg (8.83 µmol, 0.21 eq.) of $Pd(PPh_3)_4$ and 50.0 µL (54.3 mg, 171 µmol, 4.1 eq.) of $n$$Bu_3SnCHCH_2$ were added and the reaction mixture was heated to 120 °C for 2.5 h. After cooling to rt, excess reagent was quenched with 0.5 mL of H_2O and the aqueous phase was extracted with 4 x 0.5 mL of EtOAc. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification of the crude product by silica gel column chromatography (*c*-Hex/toluene 8:1) afforded 11.0 mg (31.2 µmol, 75%) of diene **241**.

M ($C_{24}H_{32}O_2$) = 352.52 g/mol



R_f (*c*-Hex/EtOAc 20:1) = 0.52

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.66 (s, 2H, H-12, H-13), 6.46 – 6.39 (m, 1H, H-23), 5.53 – 5.51 (m, 1H, H-19), 5.34 (dd, *J* = 17.1, 2.6 Hz, 1H, H-24), 4.97 (dd, *J* = 10.7, 2.6 Hz, 1H, H-24'), 3.79 (s, 3H, H-17), 3.62 (s, 3H, H-16), 2.66 (d, *J* = 16.1 Hz, 1H, H-9), 2.61 (d, *J* = 16.1 Hz, 1H, H-9'), 2.11 (td, *J* = 12.5, 6.0 Hz, 1H, H-21), 2.01 (dt, *J* = 18.4, 5.4 Hz, 1H, H-20), 1.76 (td, *J* = 12.9, 3.8 Hz, 1H, H-5), 1.68 (dddt, *J* = 16.1, 9.5, 6.7, 3.2 Hz, 1H, H-20'), 1.61 (dt, *J* = 13.0, 3.2 Hz, 1H, H-5'), 1.55 – 1.44 (m, 2H, H-4, H-21'), 1.43 – 1.34 (m, 2H, H-3, H-4'), 1.27 (s, 3H, H-22), 1.12 (s, 3H, H-7), 0.83 (d, *J* = 6.4 Hz, 3H, H-8).

^{13}C NMR (151 MHz, $CDCl_3$): δ [ppm] = 152.5 (C-14), 151.0 (C-11), 148.6 (C-18), 139.9 (C-15), 137.4 (C-23), 131.9 (C-10), 117.3 (C-19), 112.8 (C-24), 111.0 (C-12), 109.0 (C-13), 60.0 (C-1), 55.8 (C-17), 55.7 (C-16), 49.6 (C-2), 40.1 (C-9), 38.9 (C-6), 34.7 (C-3), 31.0 (C-5), 27.9 (C-4), 25.9 (C-21), 25.0 (C-22), 24.1 (C-20), 17.6 (C-8), 17.1 (C-7).

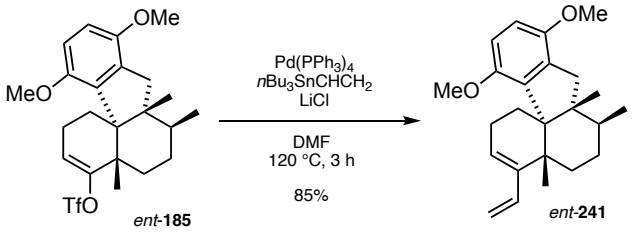
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3077 (w), 2941 (m), 2907 (m), 2871 (m), 2830 (m), 1607 (w), 1586 (w), 1489 (s), 1461 (m), 1436 (m), 1385 (m), 1349 (w), 1314 (m), 1253 (s), 1175 (m), 1161 (w), 1149 (m), 1133 (m), 1122 (w), 1089 (m), 1077 (m), 1060 (m), 1038 (m), 997 (m), 971 (m), 956 (w), 902 (m), 851 (w), 790 (m), 734 (m), 720 (m), 651 (w), 518 (w).

GC-MS (70 eV): *m/z* (%) = 352 (70, $[M]^+$), 337 (15), 297 (15), 257 (20), 241 (15), 199 (100), 171 (30), 151 (15), 91 (30), 55 (15).

HRMS (EI):	Calc. [amu]	Found [amu]
	352.23968 $[M]^{\bullet+}$	352.23929 $[M]^{\bullet+}$

$[\alpha]^{20}_{\lambda}$ (*c* = 0.55 g/100 mL, $CHCl_3$): – 47° (436 nm), – 31° (546 nm), – 28° (579 nm), – 27° (589 nm).

5.2.48 SYNTHESIS OF DIENE *ent*-**241**



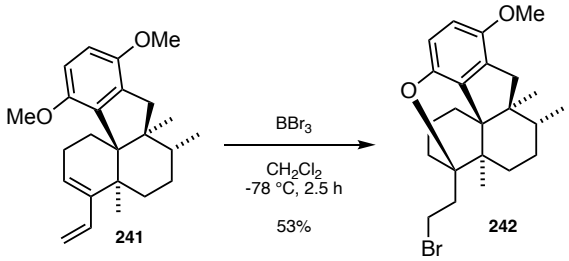
In a flame dried *Schlenk* flask 20.0 mg (42.1 µmol, 1.0 eq.) of enol triflate *ent*-**185** were dissolved in 200 µL of dry DMF. 10.7 mg (0.25 mmol, 5.9 eq.) of LiCl, 10.4 mg (9.00 µmol, 0.21 eq.) of $Pd(PPh_3)_4$ and 49.0 µL (53.2 mg, 168 µmol, 4.0 eq.) of $n Bu_3SnCHCH_2$ were added and the reaction mixture was heated to 120 °C for 3 h. After cooling to rt, excess reagent was quenched with 0.3 mL of H_2O, NaCl was added and the aqueous phase was extracted with 4 x 0.5 mL of EtOAc. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification of the crude product by silica gel column chromatography (*c*-Hex/toluene 5:1) afforded 12.6 mg (35.7 µmol, 85%) of diene *ent*-**241**.

M ($C_{24}H_{32}O_2$) = 352.52 g/mol

[α]$^{20}_{\lambda}$ (*c* = 0.57 g/100 mL, $CHCl_3$): + 24° (436 nm), + 19° (546 nm), + 17° (579 nm), + 16° (589 nm).

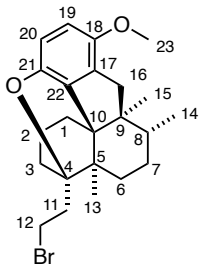
Additional analytical data was in accordance with that recorded for **241** (see chapter **5.2.47**).

5.2.49 SYNTHESIS OF PENTACYCLIC BROMIDE **242**



A solution of 2.4 mg (6.8 µmol, 1.0 eq.) of diene **241** in 190 µL of CH_2Cl_2 was cooled to -78 °C and 34 µL (34 µmol, 5.0 eq.) of BBr_3 (1.0 M in CH_2Cl_2) and the dark brown mixture was stirred at -78 °C for 1.5 h. After quenching with solid $NaHCO_3$ at this temperature the mixture was allowed to warm to 0 °C and sat. aqueous $NaHCO_3$ and H_2O were added (decolorization). The aqueous phase was extracted with 3 x 0.5 mL of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by silica gel

column chromatography (*c*-Hex/EtOAc 100:1) to provide 1.5 mg (3.6 µmol, 53%) of bromide **242** as a yellow, sticky oil.



M ($C_{23}H_{31}BrO_2$) = 419.40 g/mol

R_f (*c*-Hex/EtOAc 20:1) = 0.33

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.55 (d, *J* = 8.6 Hz, 1H, H-19), 6.46 (d, *J* = 8.6 Hz, 1H, H-20), 3.77 (m, 1H, H-12), 3.75 (s, 3H, H-23), 3.57 (ddd, *J* = 12.2, 9.2, 5.2 Hz, 1H, H-12‘), 2.62 (d, *J* = 15.3 Hz, 1H, H-16), 2.56 (d, *J* = 15.5 Hz, 1H, H-16’), 2.40 – 2.33 (m, 1H, H-11), 2.00 (ddd, *J* = 13.7, 12.3, 5.4 Hz, 1H, H-11’), 1.89 – 1.80 (m, 2H, H-3), 1.83 (td, *J* = 12.9, 5.2 Hz, 3H, H-1, H-3), 1.59 – 1-54 (m, 2H, H-2), 1.37 (m, 1H, H-1’), 1.21 (s, 3H, H-13), 1.20 (m, 1H, H-8), 1.06 (s, 3H, H-15), 0.82 (d, *J* = 6.7 Hz, 3H, H-14).

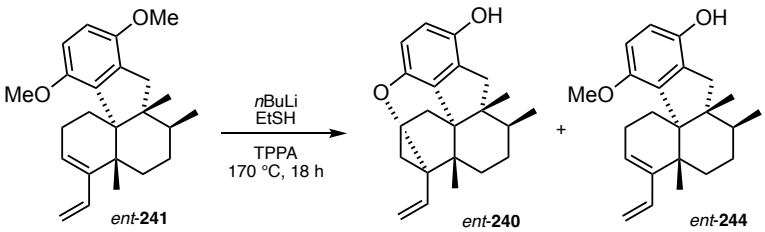
^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 150.2 (C-18), 147.9 (C-21), 133.0 (C-22), 128.1 (C-17), 110.4 (C-20), 110.2 (C-19), 83.7 (C-4), 55.9 (C-23), 51.7 (C-9), 48.9 (C-10), 39.9 (C-16), 38-3 (C-11), 37.5 (C-5), 35.3 (C-8) ,31.7 (C-3), 29.8 (C-6), 26.4 (C-7), 26.2 (C-1), 19.3 (C-2), 18.4 (C-13), 17.8 (C-14), 14.9 (C-15).

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3383 (w), 2925 (s), 2854 (s), 1735 (m), 1492 (w), 1464 (m), 1378 (w), 1263 (m), 1177 (w), 1108 (w), 1075 (w), 796 (w), 731 (w), 663 (w).

GC-MS (70 eV): *m/z* (%) = 420 (100,[M]$^+$), 338 (10), 269 (10), 241 (10), 227 (10), 201 (15), 187 (90), 173 (10), 107 (15), 91 (10), 69 (10), 55 (20).

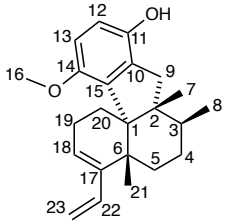
HRMS (EI):	Calc. [amu]	Found [amu]
	418.15019 [M]$^+$	418.1503 [M]$^+$

5.2.50 SYNTHESIS OF PENTACYCLIC OLEFIN *ent*-**240** AND METHYL ETHER *ent*-**244**



Based on a literature known procedure,[123] in a flame dried *Schlenk* flask 170 µL (578 µmol, 14 eq.) of *n*BuLi (3.4 M in hexane) were diluted with 780 µL heptane. The solution was cooled to

0 °C and 52.0 µL (43.7 mg, 710 µmol, 18 eq.) of EtSH were added. The arising suspension was stirred at 0 °C for 10 min and at 21 °C for 30 min. Then, the solvents were removed *in vacuo* (using *Schlenk* line) and the residual colorless solid was dried for 1.5 h. 14.2 mg (40.3 µmol, 1.0 eq.) of diene *ent*-**241** in heptane were added before the solvent was again removed and the resulting solid dried *in vacuo* for 1 h. 300 µL of TPPA were added and the reaction mixture was stirred at 170 °C for 18 h. After cooling back to 21 °C, the reaction was quenched with 2 mL of sat. aqueous NH_4Cl, 0.3 mL of H_2O were added and the aqueous phase was extracted with 3 x 0.5 mL of EtOAc. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification of the crude product by silica gel column chromatography (*c*-Hex/EtOAc 20:1) afforded 11 mg of an approximately 1:1 mixture of pentacyclic olefin *ent*-**240** and methyl ether *ent*-**244** that was used in the following reaction. An aliquot was again subjected to silica gel column chromatography (*c*-Hex/EtOAc 20:1) to separate methyl ether *ent*-**244** for analytical characterization.



M ($C_{23}H_{30}O_2$) = 338.49 g/mol

R_f (*c*-Hex/EtOAc 9:1) = 0.26

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 6.60 (s, 2H, H-12, H-13), 6.42 – 6.36 (m, 1H, H-22), 5.50 – 5.47 (m, 1H, H-18), 5.31 (dd, *J* = 17.1, 2.6 Hz, 1H, H-23), 4.95 (dd, *J* = 10.7, 2.6 Hz, 1H, H-23'), 3.58 (s, 3H, H-16), 2.60 (d, *J* = 15.4 Hz, 1H, H-9), 2.53 (d, *J* = 15.4 Hz, 1H, H-9'), 2.09 (td, *J* = 12.5, 6.0 Hz, 1H, H-20), 1.99 (dt, *J* = 18.4, 5.4 Hz, 1H, H-19), 1.74 (td, *J* = 12.9, 3.8 Hz, 1H, H-5), 1.71 – 1.63 (m, 1H, H-19), 1.58 (dt, *J* = 13.0, 3.1 Hz, 1H, H-5'), 1.52 – 1.44 (m, 1H, H-4), 1.44 – 1.39 (m, 2H, H-3, H-20'), 1.39 – 1.33 (m, 1H, H-4'), 1.24 (s, 3H, H-21), 1.11 (s, 3H, H-7), 0.80 (d, *J* = 6.5 Hz, 3H, H-8).

^{13}C NMR (151 MHz, $CDCl_3$): δ [ppm] = 152.3 (C-14), 148.4 (C-17), 146.5 (C-11), 139.4 (C-15), 137.1 (C-22), 129.0 (C-10), 117.0 (C-18), 112.7 (C-23), 111.9 (C-12,C-13), 59.8 (C-1), 55.7 (C-16), 49.8 (C-2), 39.2 (C-9), 38.7 (C-6), 34.4 (C-3), 30.7 (C-5), 27.7 (C-4), 25.7 (C-20), 24.8 (C-21), 23.8 (C-19), 17.3 (C-8), 16.9 (C-7).

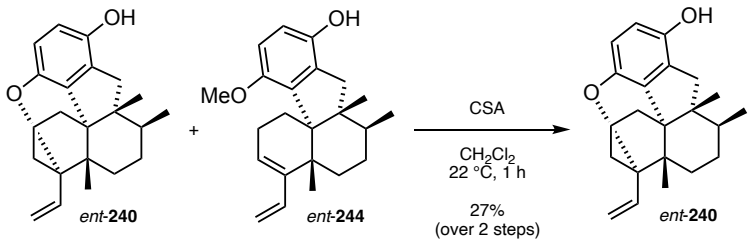
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3676 (w), 3363 (w), 2954 (m), 2926 (m), 2195 (w), 2156 (w), 2025 (w), 1973 (w), 1669 (w), 1490 (m), 1461 (m), 1409 (w), 1385 (w), 1257 (m), 1076 (m), 1048 (m), 903 (w), 802 (w), 729 (w), 649 (w).

GC-MS (70 eV): *m/z* (%) = 338 (90, $[M]^+$), 323 (20), 283 (20), 243 (30), 227 (20) 201 (35), 185 (100) 157 (40), 115 (20), 91 (30), 77 (20), 55 (25).

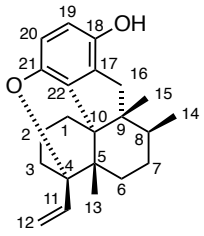
HRMS (EI):	Calc. [amu]	Found [amu]
	338.22403 $[M]^{\bullet+}$	338.2240 $[M]^{\bullet+}$

[α]$^{20}_{\lambda}$ (c = 0.20 g/100 mL, $CHCl_3$): + 35° (436 nm), + 22° (546 nm), + 16° (579 nm), + 16° (589 nm).

5.2.51 SYNTHESIS OF PENTACYCLIC DIENE *ent*-**240**



In an argon flushed flask 11 mg of an approximately 1:1 mixture of pentacyclic olefin *ent*-**240** and methyl ether *ent*-**244** were dissolved in 850 µL of CH_2Cl_2. At 22 °C 52.5 mg (226 µmol, 7 eq.) of CSA were added and the arising green suspension was stirred for 1 h. The reaction was quenched with 1 mL of sat. aqueous $NaHCO_3$ and the aqueous phase was extracted with 3 x 0.5 mL of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification of the crude product by silica gel column chromatography (*c*-Hex/EtOAc 50:1) afforded 3.5 mg (10.8 µmol, 27% over 2 steps) of pentacyclic diene *ent*-**240** as a yellowish viscous oil.



M ($C_{23}H_{30}O_2$) = 324.46 g/mol

R_f (*c*-Hex/EtOAc 9:1) = 0.24

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 6.51 (d, J = 1.2 Hz, 2H, H-19, H-20), 5.93 (dd, J = 17.4, 11.0 Hz, 1H, H-11), 5.36 (dd, J = 17.4, 1.7 Hz, 1H, H-12), 5.21 (dd, J = 11.0, 1.8 Hz, 1H, H-12‘), 2.56 (d, J = 2.2 Hz, 2H, H-16), 1.92 – 1.86 (m, 1H, H-1), 1.61 – 1.58 (m, 2H, H-1‘, H-2), 1.36 – 1.33 (m, 1H, H-2‘), 1.25 – 1.20 (m, 3H, H-3, H-8), 1.20 (s, 3H, H-13), 1.08 (s, 3H, H-15), 0.83 (d, J = 6.6 Hz, 3H, H-14).

^{13}C NMR (151 MHz, $CDCl_3$): δ [ppm] = 145.9 (C-18), 141.0 (C-21), 138.8 (C-11), 132.6 (C-22), 125.6 (C-17), 115.3 (C-12), 114.2 (C-20), 111.4 (C-19), 83.8 (C-11), 52.0 (C-9), 49.0 (C-10), 37.2 (C-5), 35.7 (C-8), 30.2 (C-3), 26.6 (C-1), 26.2 (C-7), 19.3 (C-2), 18.0 (C-13), 17.6 (C-14), 15.7 (C-15).

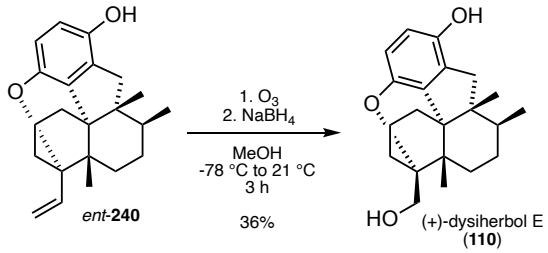
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3357 (w), 2929 (s), 2856 (m), 2153 (w), 1719 (w), 1631 (w), 1491 (m), 1462 (m), 1384 (w), 1323 (w), 1261 (s), 1195 (w), 1156 (w), 1103 (w), 1083 (w), 1056 (w), 957 (w), 924 (w), 870 (w), 802 (m), 741 (w), 576 (w), 552 (w), 527 (w), 519 (w).

GC-MS (70 eV): *m/z* (%) = 324 (100, [M]$^+$), 309 (39), 295 (71), 253 (32), 236 (52), 225 (66), 187 (33), 165 (21), 115 (30), 91 (42), 55 (47).

HRMS (EI):	Calc. [amu]	Found [amu]
	324.20838 [M]$^{\cdot+}$	324.2080 [M]$^{\cdot+}$

[α]$^{20}_{\lambda}$ (*c* = 0.10 g/100 mL, $CHCl_3$): + 92° (436 nm), + 51° (546 nm), + 43° (579 nm), + 34° (589 nm).

5.2.52 SYNTHESIS OF (+)-DYSIHERBOL E (**110**)



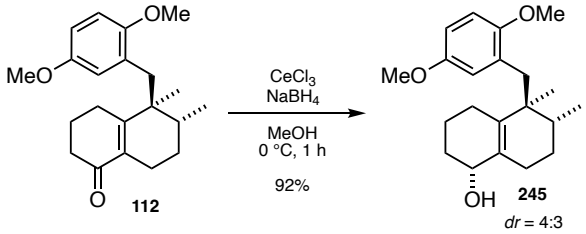
In *Schlenk* tube 5.2 mg (16.0 µmol, 1.0 eq.) of pentacyclic olefin *ent*-**240** were dissolved in 50 µL of MeOH and the solution was cooled to -78 °C. The yellowish solution was ozonized for 20 min until discoloration was observed. Residual O_3 was removed by directing O_2 through the solution for 15 min. Subsequently, 1.8 mg (47.6 µmol, 3.0 eq.) of $NaBH_4$ were added and the solution allowed to stir at 21 °C for 2.5 h. After adding 100 µL of MeOH the solution was again treated with O_2. H_2O was added, the aqueous phase extracted with 3 x EtOAc and the combined organic layers dried over $MgSO_4$. The crude product was purified by silica gel column chromatography (*c*-Hex/EtOAc 20:1) to provide 1.9 mg (5.8 µmol, 36%) of (+)-dysiherbol E (**110**) as a yellow, sticky oil.

M ($C_{21}H_{28}O_3$) = 328.45 g/mol

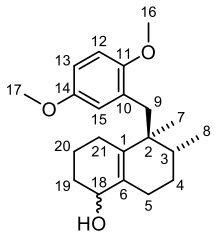
Analytical data was in accordance with that recorded for *ent*-**110** (see chapter **5.2.46**) and with that reported by *Lu* and coworkers.[63]

5.3 SYNTHETIC PROCEDURES AND ANALYTICAL DATA – STUDIES ON A GOLD-CATALYZED CYCLIZATION

5.3.1 SYNTHESIS OF ALLYLIC ALCOHOL **245**



In an argon-flushed flask 27 mg (0.082 mmol, 1.0 eq.) of enone **112** were dissolved in 0.80 mL of MeOH and the solution was cooled to 0 °C. 37 mg (0.099 mmol, 1.2 eq.) of $CeCl_3$ x $7H_2O$ were added and 8.0 mg (0.21 mmol, 2.6 eq.) $NaBH_4$ were added over 5 min and the reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched with H_2O and the aqueous phase was extracted 3x with EtOAc. The combined organic phases were washed with H_2O, dried over $MgSO_4$ and the solvent was removed under reduced pressure to give 25 mg (0.076 mmol, 92%) of a diastereomeric mixture (*dr* = 4:3) of allylic alcohol **245** as a pale yellow oil.



M ($C_{21}H_{30}O_3$) = 330.47 g/mol

R_f (*c*-Hex/EtOAc 1:1) = 0.61

^{1}H NMR (500 MHz, $CDCl_3$): Major diastereomer: δ [ppm] = 6.77 (d, *J* = 3.6 Hz, 1H, H-15), 6.77 – 6.75 (m, 1H, H-12), 6.70 – 6.66 (m, 1H, H-13), 3.97 (t, *J* = 4.0 Hz, 1H, H-18), 3.76 (s, 3H, H-17), 3.69 (s, 3H, H-16), 2.96 (d, *J* = 15.5 Hz, 1H, H-9), 2.64 (d, *J* = 15.5 Hz, 1H, H-9'), 2.43 – 2.37 (m, 1H, H-5), 2.17 – 2.14 (m, 1H, H-4), 2.06 – 1.98 (m, 1H, H-4')*, 1.91 – 1.85 (m, 1H, H-21)*, 1.77 – 1.68 (m, 2H, H-19), 1.74 – 1.70 (m, 2H, 3-H, H-5'), 1.67 – 1.54 (m, 2H, H-20), 1.42 – 1.37 (m, 1H, H-21')*, 0.96 (s, 3H, H-7), 0.81 (d, *J* = 6.4 Hz, 3H, H-8). Minor diastereomer: δ [ppm] = 6.77 – 6.75 (m, 0.8H, H-12), 6.75 (d, *J* = 3.5 Hz, 0.8H, H-15), 6.70 – 6.66 (m, 0.8H, H-13), 3.90 (t, *J* = 4.0 Hz, 0.8H, H-18), 3.75*3* (s, 2.3H, H-17), 3.74*9* (s, 2.3H, H-16), 2.95 (d, *J* = 14.3 Hz, 0.8H, H-9), 2.61 (d, *J* = 14.3 Hz, 0.8H, H-9'), 2.06 – 1.98 (m, 0.8H, H-4)*, 1.95 – 1.89 (m, 0.8H, H-4')*, 1.91 – 1.85 (m, 0.8H, H-21)*, 1.77 – 1.68 (m, 1.6H, H-19), 1.71 – 1.66 (m, 0.8H, H-5)*, 1.70 – 1.67 (m, 0.8H, H-3), 1.67 – 1.54 (m, 1.6H, H-20), 1.46 – 1.42 (m, 0.8H, H-5')*, 1.42 – 1.37 (m, 0.8H, H-21')*, 0.92 (s, 2.3H, H-7), 0.80 (d, *J* = 6.5 Hz, 2.3H, H-8). *Assignments possibly interconvertible.

^{13}C NMR (126 MHz, CDCl3): Major diastereomer: δ [ppm] = 153.2 (C-14), 152.5 (C-11), 138.9 (C-1), 131.1 (C-6), 129.5 (C-10), 116.1 (C-15), 111.33 (C-12), 111.31 (C-13), 69.3 (C-18), 56.1 (C-17), 55.7 (C-16), 41.4 (C-2), 34.4 (C-9), 33.6 (C-3), 32.3 (C-19), 26.7 (C-5), 26.6 (C-21), 25.6 (C-4), 22.2 (C-7), 19.1 (C-20), 16.2 (C-8). Minor diastereomer: δ [ppm] = 153.1*6* (C-14), 152.6

(C-11), 138.1 (C-1), 130.7 (C-6), 129.6 (C-10), 117.4 (C-15), 111.6 (C-12), 111.2 (C-13), 69.7 (C-18), 56.2 (C-17), 55.8 (C-16), 41.8 (C-2), 36.8 (C-9), 34.0 (C-3), 32.1 (C-19), 26.2 (C-5), 26.1 (C-21), 25.8 (C-4), 21.5 (C-7), 19.0 (C-20), 16.1 (C-8).

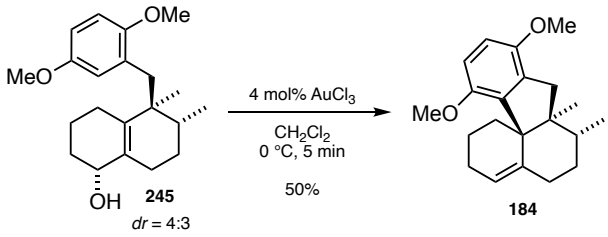
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3407 (br), 2926 (s), 2856 (w), 2834 (w), 1730 (br), 1607 (w), 1589 (w), 1499 (s), 1464 (m), 1380 (m), 1346 (w), 1325 (w), 1274 (w), 1222 (s), 1179 (m), 1159 (w), 1123 (w), 1050 (m), 1030 (w), 996 (w), 926 (w), 880 (w), 868 (w), 803 (m), 715 (m).

GC-MS (70 eV): *m/z* (%) = 330 (1, [M]$^+$), 312 (15), 179 (45), 161 (100), 152 (62), 137 (61), 119 (38), 105 (38), 91 (52).

HRMS (ESI):	Calc. [amu]	Found [amu]
	353.20872 [M+Na]$^+$	353.20907 [M+Na]$^+$

[α]$^{20}_{\lambda}$ (*c* = 0.50 g/100 mL, $CHCl_3$): + 0.3° (436 nm), + 0.7° (546 nm), + 0.4° (579 nm), + 0.1° (589 nm).

5.3.2 SYNTHESIS OF OLEFIN **184** FROM ALLYLIC ALCOHOL **245**

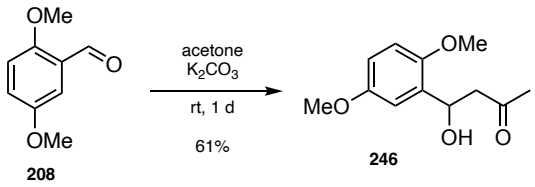


In an argon-flushed flask 20 mg (0.061 mmol, 1.0 eq.) of a diastereomeric mixture (*dr* = 4:3) of allylic alcohol **245** were dissolved in 6.0 mL of CH_2Cl_2. The solution was cooled to 0 °C, 0.73 mg (0.0024 mmol, 0.039 eq.) of $AuCl_3$ in 0.66 mL CH_2Cl_2 were added and the green reaction mixture was stirred for 5 min at that temperature. 5 mg of QuadraSil TA® were added and the suspension was stirred for further 15 min at 0 °C. The solids were separated by filtration and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (*c*-Hex/EtOAc 30:1) to give 11 mg of a colorless sticky oil, containing approximately 9.4 mg (0.030 mmol, 50%) of olefin **184** along with inseparable side products, which was determined by integration of suitable ^{1}H-NMR signals.

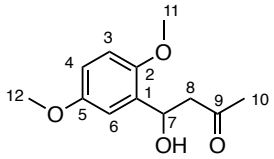
M ($C_{21}H_{28}O_2$) = 312.45 g/mol

See chapter **5.2.21** for analytical characterization.

5.3.3 SYNTHESIS OF 4-(2,5-DIMETHOXYPHENYL)-4-HYDROXYBUTAN-2-ONE (246)[124]



According to a literature procedure,[124] a round bottom flask was charged with 1.00 g (6.02 mmol, 1.0 eq.) of dimethoxybenzaldehyde **208** together with 1.58 g (11.4 mmol, 1.9 eq.) of K_2CO_3 and the solids were dissolved in 2.00 mL (27.2 mmol, 4.5 eq.) of acetone. The suspension was stirred for 2 d at rt. The reaction was quenched with H_2O and the aqueous phase was extracted 3x with MTBE. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification of the crude product by silica gel column chromatography (*c*-Hex/EtOAc 4:1 to 2:1) afforded 835 mg (3.72 mmol, 62%; Lit.: 97%) *β*-hydroxyketone **246** as a pale yellow oil.



M ($C_{12}H_{16}O_4$) = 224.26 g/mol

R_f (cHex/EtOAc 4:1) 0.07

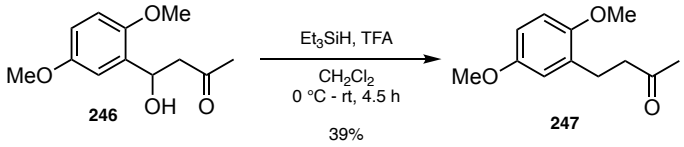
^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 7.05 (d, J = 2.8 Hz, 1H, H-6), 6.82 – 6.74 (m, 2H, H-3, H-4), 5.40 – 5.35 (m, 1H, H-7), 3.79 (s, 3H, H-11), 3.78 (s, 3 H, H-12), 3.43 (d, J = 4.3 Hz, 1H, OH), 2.93 (dd, J = 17.3, 2.9 Hz, 1H, H-8), 2.76 (dd, J = 17.3, 9.4 Hz, 1H, H-8'), 2.19 (s, 3H, H-10).

^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 209.6 (C-9), 154.1 (C-5), 150.0 (C-2), 132.1 (C-1), 113.1 (C-3, C-4), 112.5 (C-6), 65.7 (C-7), 55.9 (C-11, C-12), 50.5 (C-8), 30.8 (C-10).

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3443 (br), 2999 (w), 2941 (m), 2835.7 (m), 2063 (w), 1705 (s), 1610 (w), 1591 (w), 1493 (vs), 1464 (m), 1428 (m), 1359 (m), 1276 (m), 1213 (vs), 1178 (s), 1156 (s), 1124 (w), 1068 (m), 1042 (vs), 1023 (s), 957 (m), 926 (w), 877 (m), 803 (m), 778 (w), 713 (m), 704 (m), 604 (m), 558 (m), 527 (m), 504 (m).

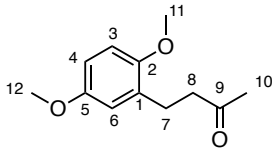
$[\alpha]^{20}_{\lambda}$ (c = 0.51 g/100cm^3, $CHCl_3$): -0.06° (436 nm), 0.46° (546 nm), 0.20° (579 nm), 0.39° (589 nm).

5.3.4 SYNTHESIS OF 4-(2,5-DIMETHOXYPHENYL)BUTAN-2-ONE (**247**)



Based on a literature protocol,[125] in an argon flushed *Schlenk* flask 402 mg (1.79 mmol, 1.0 eq.) of **246** were dissolved in 34 mL of CH_2Cl_2. 2.80 mL (2.04 g, 17.5 mmol, 9.8 eq.) Et_3SiH were added, the mixture was cooled to 0 °C and 0.69 mL (1.02 g, 8.95 mmol, 5.0 eq.) of TFA were added over 10 min. After stirring at 0 °C for 4.5 h the reaction was quenched with sat. aqueous $NaHCO_3$ the aqueous phase was extracted 3x with CH_2Cl_2. The combined organic phases dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification of the crude product by silica gel column chromatography (*c*-Hex/EtOAc 9:1 to 4:1) afforded 147 mg (706 µmol, 39%) of ketone **247** as a yellowish oil.

M ($C_{12}H_{16}O_3$) = 208.26 g/mol



R_f (cHex/EtOAc 4:1) = 0.37

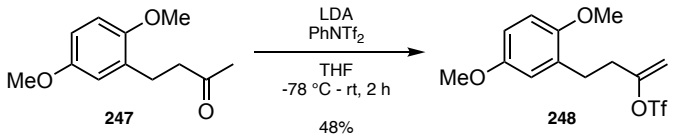
^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 6.78 – 6.68 (m, 3H, H-3, H-4, H-6), 3.78 (s, 3H, H-11), 3.75 (s, 3H, H-12), 2.87 – 2.82 (m, 2H, H-7), 2.74 – 2.69 (m, 2H, H-8), 2.14 (s, 3H, H-10').

^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 208.7 (C-9), 153.58 (C-5), 151.8 (C-2), 130.6 (C-1), 116.5 (C-6), 111.5 (C-3, C-4), 55.9 (C-11, C-12), 43.9 (C-8), 30.1 (C-10), 25.3 (C-7).

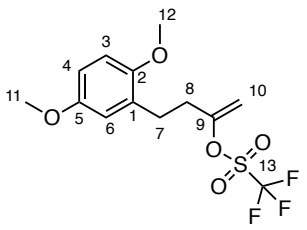
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2997 (w), 2939 (m), 2834 (m), 1970 (w), 1712 (s), 1609.15 (w), 1590 (w), 1497 (vs), 1464 (m), 1444 (m), 1427 (m), 1358 (m), 1279 (m), 1219 (vs), 1179 (s), 1158 (s), 1124 (m), 1039 (s), 1022 (s), 967 (w), 926 (w), 872 (w), 840 (w), 800 (m), 759 (w), 743 (w), 728 (w), 712 (m), 631 (w), 601 (w), 552 (w), 527 (w), 514 (w).

GC-MS (70 eV): *m/z* (%) = 208 (M^+, 100), 165 (33), 151 (56), 138 (12), 121 (25), 91 (17), 77 (17), 43 (26).

5.3.5 SYNTHESIS OF ENOL TRIFLATE **248**



In a flame dried *Schlenk* flask 115 mg (1.01 mmol, 1.6 eq.) of LDA were dissolved in 2.9 mL of dry THF. The suspension was cooled to -78 °C and 124 mg (629 µmol, 1.0 eq.) of ketone **247** in 1.7 mL of dry THF were added over 10 min. After stirring for 10 min at -78°C, 364 mg (1.02 mmol, 1.7 eq.) of $PhNTf_2$ were added portion wise. The reaction mixture was stirred at 0 °C for 50 min and at rt for 1 h. After quenching with sat. aqueous NH_4Cl the aqueous phase was extracted 3x with EtOAc. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification of the crude product by silica gel column chromatography (*c*-Hex/EtOAc 20:1) afforded 103 mg (303 µmol, 48%) of enol triflate **248** as a yellow, viscous oil.



M ($C_{13}H_{15}F_3O_5S$) = 340.31 g/mol

R_f (cHex/EtOAc 9:1) = 0.53

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 6.78(d, *J* = 8.6 Hz, 1H, H-3), 6.74 – 6.70 (m, 2H, H-4, H-6), 6.72 – 6.70 (m, 1H, H-6), 5.08 (d, *J* = 3.6 Hz, 1H H-10), 4.92 (dt, *J* = 3.6, 1.1 Hz, 1H, H-10'), 3.78 (s, 3H, H-12), 3.76 (s, 3H, H-11), 2.85 – 2.80 (m, 2H, H-7), 2.64 – 2.60 (m, 2H, H-8).

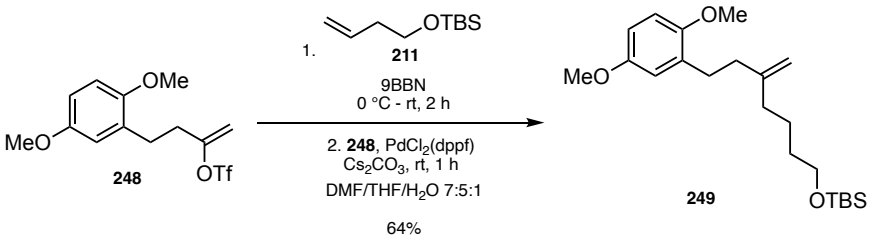
^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 156.6 (C-9), 153.6 (C-5), 151.8 (C-2), 129.1 (C-1), 116.5 (C-6), 111.3 (C-3), 111.9 (C-4), 104.7 (C-10), 55.9 (C-11, C-12), 34.1 (C-8), 27.7 (C-7).

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3671, 3000 ,2942, 2836, 1972, 1670, 1592, 1501, 1466, 1415, 1303, 1282, 1248, 1208, 1145, 1050, 1030, 929, 898, 838, 800, 707, 612.

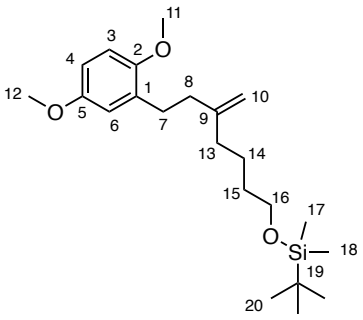
GC-MS (70 eV): *m/z* (%) = 340 (M^+, 20), 151 (100), 121 (35), 91 (18), 69 (23), 51 (8).

HRMS (EI):	Calc. [amu]	Found [amu]
	340.05868 $[M]^{\bullet+}$	340.05835 $[M]^{\bullet+}$

5.3.6 SYNTHESIS OF SILYL ETHER **249**



Based on a literature protocol[105] in a *Schlenk* flask, a solution of 79 mg (434 µmol, 1.6 eq.) of olefin **211** in 0.3 mL of dry THF was cooled to 0 °C. Then, 1.0 mL (0.5 mmol, 1.9 eq.) of 9-BBN (0.5 M in THF) were added and the mixture was stirred at rt for 2 h. The solution was then cooled to 0 °C before 0.3 mL of H_2O were added and stirring was continued at 0 °C for 1 h. This borane solution was then transferred via needle to a second *Schlenk* flask charged with a solution of 11.6 mg (14.2 µmol, 0.05 eq.) of $PdCl_2$(dppf) x CH_2Cl_2, 218 mg (669 µmol, 2.5 eq.) of Cs_2CO_3 and 91.0 mg (267 µmol, 1.0 eq.) of the enol triflate **248** in 2.0 mL of dry DMF at rt. The black reaction mixture was stirred at that temperature for 1 h before 7.7 mg of QuadraSil AP® were added as a metal scavenger and the suspension was stirred for further 30 min. Then the solids were separated by decantation and H_2O and brine were added to the product solution. After extracting 4x with EtOAc the combined organic layers were washed with H_2O, dried over Na_2SO_4 and the solvents were removed under reduced pressure. The residue was purified by silica gel column chromatography (*c*-Hex/EtOAc 20:1) to yield 65 mg (172 µmol, 64%) of silyl ether **249** as a colorless oil.



M ($C_{22}H_{38}O_3Si$) = 378.63 g/mol

R_f (cHex/EtOAc 9:1) = 0.5

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 6.76 (d, J = 8.8 Hz, 1H, H-3), 6.73 (d, J = 3.1 Hz, 1H, H-6), 6.69 (dd, J = 8.7, 3.1 Hz, 1H, H-4), 4.76 (d, J = 8.7 Hz, 2H, H-10), 3.78 (s, 3H, H-11), 3.76 (s, 3H, H-12), 3.64 – 3.60 (m, 2H, H-16), 2.74 – 2.69 (m, 2H, H-7), 2.30 – 2.24 (m, 2H, H-8), 2.08 (t, J = 7.1 Hz, 2H, H-13), 1.56 – 1.46 (m, 4H, H-14, H-15), 0.89 (s, 9H, H-20), 0.05 (s, 6H, H-17, H-18).

^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 153.6 (C-2), 151.9 (C-5), 149.8 (C-9), 132.2 (C-1), 116.3 (C-6), 111.3 (C-3), 110.9 (C-4), 109.1 (C-10), 63.3 (C-16), 56.1 (C-11, C-12), 36.2 (C-8), 36.2 (C-13), 32.7 (C-15), 29.1 (C-7), 26.1 (C-20, C-21, C-22), 24.1 (C-14), -5.1 (C-17, C-18).

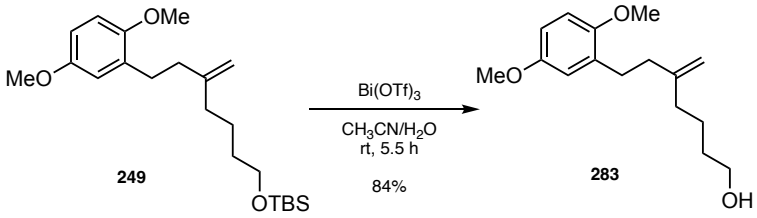
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3073 (w), 2992 (w), 2949 (m), 2929 (s), 2903 (m), 2857 (m), 2833 (w), 1734 (w), 1644 (w), 1591 (w), 1499 (s), 1463 (m), 1428 (m), 1388 (w), 1360 (w), 1326 (w), 1299

(w), 1279 (m), 1253 (m), 1221 (vs), 1179 (m), 1157 (w), 1100 (s), 1051 (s), 1031 (m), 1006 (m), 977 (w), 938 (w), 887 (m), 834 (vs), 807 (m), 774 (vs), 713 (m), 678 (w), 661 (w), 571 (w).

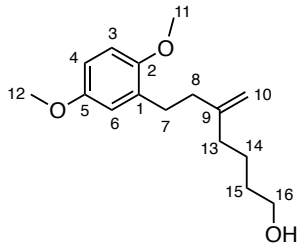
GC-MS (70 eV): *m/z* (%) = 378 (M^+, 6), 321 (42), 306 (29), 207 (18), 151 (100), 121 (22), 91 (12), 75 (22), 59 (8).

HRMS (EI):	Calc. [amu]	Found [amu]
	378.25847 $[M]^{\bullet+}$	378.25790 $[M]^{\bullet+}$

5.3.7 SYNTHESIS OF PRIMARY ALCOHOL **283**



Based on a literature protocol,[106] in an argon flushed flask 55 mg (145 µmol, 1.0 eq.) of silyl ether **249** were dissolved in 2.3 mL of CH_3CN and 0.03 mL of H_2O. Then, 4.0 mg (6.0 µmol, 0.04 eq.) of $Bi(OTf)_3$ were added and the reaction mixture was stirred at rt for 5.5 h. H_2O was added and the aqueous phase was extracted 3x with CH_2Cl_2. The combined organic phases were washed with H_2O, dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford 33.0 mg (125 µmol, 84%) of alcohol **283** as a colorless oil.



M ($C_{16}H_{24}O_3$) = 264.37 g/mol

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 6.79 (d, *J* = 8.8 Hz, 1H, H-3), 6.76 (d, *J* = 3.1 Hz, 1H, H-6), 6.71 (dd, *J* = 8.7, 3.1 Hz, 1H, H-4), 4.79 (d, *J* = 10.6 Hz, 2H, H-10), 3.81 (s, 3H, H-11), 3.78 (s, 3H, H-12), 3.68 (t, *J* = 6.3 Hz, 2H, H-16), 2.76 – 2.71 (m, 2H, H-7), 2.33 – 2.27 (m, 2H, H-8), 2.13 (t, *J* = 7.3 Hz, 2H, H-13), 1.66 – 1.51 (m, 4H, H-14, H-15).

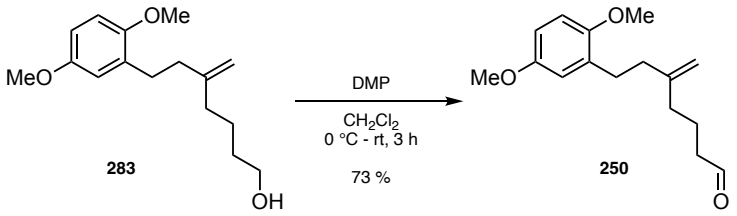
^{13}C NMR (126 MHz, $CDCl_3$) *δ* [ppm] = 153.6 (C-2), 151.9 (C-5), 149.6 (C-9), 132.1 (C-1), 116.4 (C-6), 111.3 (C-3), 110.9 (C-4), 109.3 (C-10), 63.1 (C-16), 56.1 (C-11, C-12), 36.2 (C-8), 36.1 (C-13), 32.6 (C-15), 29.1 (C-7), 24.0 (C-14).

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3361 (br), 3073 (w), 2993 (w), 2933 (m), 2861 (m), 2833 (m), 1716 (w), 1644 (w), 1608 (w), 1591 (w), 1498 (s), 1464 (m), 1427 (m), 1357 (w), 1325 (w), 1279 (m), 1220 (vs), 1179 (m), 1156 (m), 1121 (m), 1048 (s), 1029 (s), 931 (w), 886 (m), 798 (m), 713 (m), 555 (w).

GC-MS (70 eV): *m/z* (%) = 264 (M^+, 18), 191 (6), 151 (100), 121 (35), 91 (14), 65 (6).

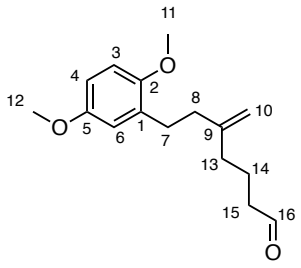
HRMS (EI):	Calc. [amu]	Found [amu]
	264.17200 $[M]^{\bullet+}$	264.17178 $[M]^{\bullet+}$

5.3.8 SYNTHESIS OF ALDEHYDE **250**



A solution of 28.0 mg (106 µmol, 1.0 eq.) of primary alcohol **283** in 2.8 mL of dry CH_2Cl_2 was cooled to 0 °C and 91 mg (215 µmol, 2.0 eq.) of *Dess-Martin* periodinane were added slowly and stirring was continued at rt for 3 h. Then, the mixture was cooled to 0 °C before H_2O was added. The phases were separated and the aqueous phase was extracted 3x with CH_2Cl_2. The combined organic phases were washed with H_2O, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (ultrapure SiO_2, *c*-Hex/EtOAc 5:1) to provide 20.0 mg (76.2 µmol, 73%) of aldehyde **250** as a colorless oil.

M ($C_{16}H_{22}O_3$) = 262.35 g/mol



R$_f$ (cHex/EtOAc 9:1) = 0.25

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 9.78 (t, *J* = 1.7 Hz, 1H, H-16), 6.77 (d, *J* = 8.7 Hz, 1H, H-3), 6.73 (d, *J* = 3.1 Hz, 1H, H-6), 6.69 (dd, *J* = 8.7, 3.1 Hz, 1H, H-4), 4.79 (d, *J* = 25.6 Hz, 2H, H-10), 3.78 (s, 3H, H-11), 3.76 (s, 3H, H-12), 2.73 – 2.68 (m, 2H, H-7), 2.44 (td, *J* = 7.3, 1.7 Hz, 2H, H-15), 2.30 – 2.24 (m, 2H, H-8), 2.11 (t, *J* = 7.7 Hz, 2H, H-13), 1.81 (quin, *J* = 7.5 Hz, 2H, H-14).

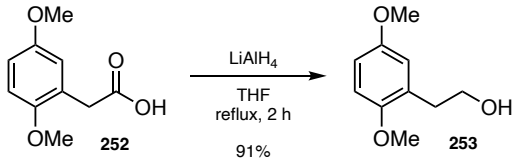
^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 202.7 (C-16), 153.6 (C-5), 151.9 (C-2), 148.5 (C-9), 131.8 (C-1), 116.4 (C-6), 111.3 (C-3), 110.9 (C-4), 110.1 (C-10), 56.0 (C-11, C-12), 43.5 (C-15), 35.9 (C-8), 35.6 (C-13), 31.1 (C-7), 20.1 (C-14).

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3073 (w), 2989 (w), 2935 (m), 2833 (m), 2721 (w), 1722 (m), 1644 (w), 1610 (w), 1590 (w), 1498 (s), 1464 (m), 1454 (m), 1428 (m), 1391 (w), 1279 (m), 1221 (vs), 1179 (m), 1157 (m), 1121 (m), 1048 (s), 1028 (m), 930 (w), 890 (m), 800 (m), 713 (m), 518 (w).

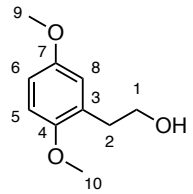
GC-MS (70 eV): *m/z* (%) = 262 (M^+, 18), 244 (8), 151 (100), 137 (12), 121 (38), 91 (18), 77 (15).

HRMS (EI):	Calc. [amu]	Found [amu]
	262.15635 $[M]^{\bullet+}$	262.15604 $[M]^{\bullet+}$

5.3.9 SYNTHESIS OF 2-(2,5-DIMETHOXYPHENYL)ETHANOL (**253**)



Based on a literature protocol,[114a] 2.32 g (61.2 mmol, 2.5 eq) of $LiAlH_4$ were suspended in 20 mL of dry THF under argon atmosphere and cooled to 0 °C. In another flask, 4.8 g (24.5 mmol, 1.0 eq.) of 2-(2,5-dimethoxyphenyl)acetic acid (**252**) was dissolved in 10 mL of dry THF, under argon atmosphere. This solution was slowly added to the stirred $LiAlH_4$ suspension and the mixture was refluxed for 2 h. The reaction was cooled to 0 °C and quenched by carefully adding 40 mL of H_2O. The mixture was brought to pH ~7 by addition of 1 M aqueous HCl and the aqueous phase was extracted with 3 x 100 mL of EtOAc. The combined organic layers were washed with 100 mL of sat. aqueous NaCl, dried over Na_2SO_4, and the solvent was removed under reduced pressure to obtain 4.07 g (22.3 mmol, 91%) of alcohol **253** as a yellowish oil.



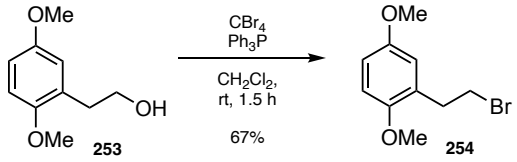
M ($C_{10}H_{14}O_3$) = 182.22 g/mol

R_f (cHex/EtOAc 2:1) = 0.25

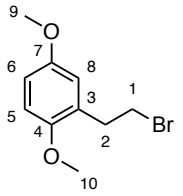
^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 6.81 – 6.70 (m, 3H, H-5, H-6, H-8), 3.83 (q, *J* = 6.0 Hz, 2H, H-1), 3.79 (s, 3H, H-9/10), 3.76 (s, 3H, H-9/10), 2.88 (t, *J* = 6.4 Hz, 2H, H- 2), 1.80 (s, 1H, OH).

GC-MS (70 eV): *m/z* (%) = 82 (M^+, 94), 151 (100), 137 (38), 121 (57), 107 (6), 91 (25), 77 (29), 66 (12).

5.3.10 SYNTHESIS OF 1-BROMO-2-(2,5-DIMETHOXYPHENYL)ETHANE (**254**)



Based on a literature protocol, 4.07 g (22.3 mmol, 1.0 eq) of alcohol **253** were dissolved in 50 mL of dry CH_2Cl_2 under argon atmosphere. 9.61 g (29.0 mmol, 1.3 eq.) of CBr_4 was added and the solution was cooled to 0 °C. 7.61 g (29.0 mmol, 1.3 eq.) of PPh_3 were added over 10 min upon which the colorless solution turned yellow. The reaction was stirred at rt for1.5 h before the reaction was poured into 50 mL of H_2O. The mixture was extracted with 3 x 50 mL of EtOAc, and the combined organic layers were washed with sat. aqueous NaCl and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the crude product was purified by silica gel column chromatography (*c*-Hex/EtOAc 20:1) to yield 3.65 g (14.9 mmol, 67%) of bromide **254** as a colorless oil.



M ($C_{10}H_{13}O_2$) = 245.12 g/mol

R_f (cHex/EtOAc 2:1) = 0.83

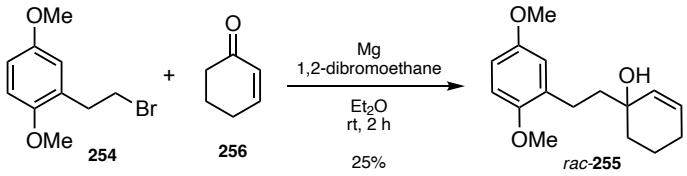
^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 6.81 – 6.73 (m, 3H, H-5, H-6, H-8), 3.79 (s, 3H, H-10), 3.77 (s, 3H, H-9), 3.57 (dd, *J* = 8.1, 7.3 Hz, 2H, H-1), 3.15 (t, *J* = 7.7 Hz, 2H, H-2).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] = 153.5 (C-7), 151.9 (C-4), 128.3 (C-3), 117.1 (C-8), 112.4 (C-6), 111.3 (C-5), 55.9 (C-10), 55.8 (C-9), 34.9 (C-2), 32.1 (C-1).

GC-MS (70 eV): *m/z* (%) = 246 (M^+ (81Br), 95), 246 (M^+ (79Br), 100), 231 (12), 229 (11), 166 (20), 151 (66), 135 (21), 121 (27), 91 (17), 77 (10).

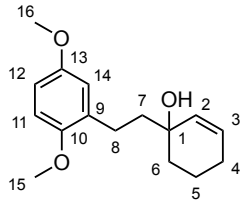
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2998 (w), 2948 (w), 2908 (w), 2833 (w), 1611 (w), 1591 (w), 1498 (s), 1464 (m), 1428 (m), 1272 (m), 1220 (s), 1179 (s), 1158 (m), 1138 (w), 1106 (m), 1046 (s), 1026 (m), 912 (w), 873 (w), 741 (w), 799 (m), 772 (w), 741 (w), 710 (w), 660 (m), 577 (w), 553 (w), 531 (w), 508 (w), 459 (w).

5.3.11 SYNTHESIS OF ALLYLIC ALCOHOL *rac*-**255**



Based on a literature protocol,[112] a *Schlenk* flask charged with Mg turnings (25 mg, 1.02 mmol, 12 eq) was heated under vacuum with a gas torch. The Mg was soaked in 0.5 mL of dry Et_2O. In a separate flask, 50 mg (0.20 mmol, 2.3 eq.) of bromide **254** were dissolved 2.5 mL of dry Et_2O and 75 mg (0.4 mmol, 4.4 eq.) of 1,2-dibromoethane were added. This mixture was added to the Mg suspension over 10 min. The slowly darkening mixture was stirred at rt for 100 min. The suspension was cooled to 0 °C and a solution of 9 µL (9 mg, 0.09 mmol, 1.0 eq.) of cyclohex-2-enone (**256**) in 1.5 mL of dry Et_2O was added. The reaction was stirred at rt for 2 h and quenched with H_2O and extracted 3 x with MTBE. The combined organic layers were washed with H_2O and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the crude product was purified by silica gel column chromatography (*c*-Hex/EtOAc 15:1 to 2:1) to yield 6.0 mg (23 µmol, 25%) of allylic alcohol *rac*-**255** as a colorless oil. Additionally, as undesired side products 10 mg (60 µmol, 30% respective to **254**) of (2,5-dimethoxy-phenyl)ethane (**284**) and 4 mg (12 µmol, 12% respective to **254**) of 1,4-di(2,5-dimethoxy-phenyl)butane (**283**) were isolated as yellow oils.

alcohol *rac*-**255**:



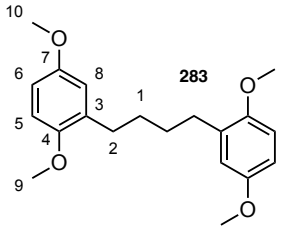
M ($C_{16}H_{22}O_3$) = 262.35 g/mol

R$_f$ (cHex/EtOAc 3:1) = 0.31

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 6.78 – 6.73 (m, 2H, H-11, H-14), 6.69 (dd, *J* = 8.8, 3.1 Hz, 1H, H-12), 5.86 – 5.79 (m, 1H, H-3), 5.69 (d, *J* = 10.1 Hz, 1H, H-2), 3.78 (s, 3H, H-15), 3.76 (s, 3H, H-16), 2.68 (t, *J* = 8.4 Hz, 2H, H-8), 2.06 – 1.93 (m, 2H, H-4), 1.83 – 1.68 (m, 6H, H-5, H-6, H-7).

^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 153.7 (C-13), 151.8 (C-10), 132.7 (C-2), 132.5 (C-9), 130.1 (C-3), 116.2 (C-14), 111.4 (C-11), 111.1 (C-12), 69.9 (C-1), 56.1 (C-15), 55.8 (C-16), 42.5 (C-7), 35.5 (C-6), 25.4 (C-4), 24.7 (C-8), 19.2 (C-5).

1,4-di(2,5-dimethoxyphenyl)butane (**283**):



M ($C_{20}H_{26}O_4$) = 330.42 g/mol

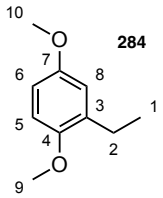
R$_f$ (cHex/EtOAc 2:1) = 0.73

^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 6.76 (d, *J* = 8.8 Hz, 1H, H-5), 6.72 (d, *J* = 3.1 Hz, 1H, H-8), 6.67 (dd, *J* = 8.8, 3.1 Hz, 1H, H-6), 3.77 (s, 3H, H-9), 3.75 (s, 3H, H-10), 2.61 (t, *J* = 7.1 Hz, 2H, H-2), 1.66 – 1.61 (m, 2H, H-1).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] = 153.6 (C-4), 152.0 (C-7), 132.7 (C-3), 116.4 (H-8), 111.4 (C-5), 110.8 (C-6), 56.1 (C-9), 55.8 (C-10), 30.2 (C-2), 29.8 (C-1).

GC-MS (70 eV): *m/z* (%) = 330 (M^+, 100), 165 (12), 151 (28), 121 (15).

(2,5-dimethoxyphenyl)ethane (**284**):



M ($C_{10}H_{14}O_2$) = 166.22 g/mol

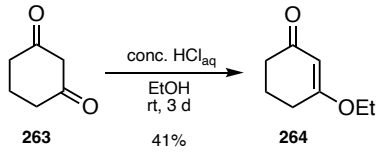
R$_f$ (cHex/EtOAc 2:1) = 0.88

^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 6.78 – 6.75 (m, 2H, H-5, H-8), 6.68 (dd, *J* = 8.7, 3.1 Hz, 1H, H-6), 3.79 (s, 3H, H-9), 3.77 (s, 3H, H-10), 2.62 (q, *J* = 7.5 Hz, 2H, H-2), 1.19 (t, *J* = 7.6 Hz, 3H, H-1).

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] = 153.7 (C-4), 151.8 (C-7), 134.1 (C-3), 115.7 (C-8), 111.3 (C-5), 110.6 (C-6), 56.1 (C-9), 55.8 (C-10), 23.5 (C-2), 14.3 (C-1).

GC-MS (70 eV): *m/z* (%) = 166 (M^+, 89), 151 (100), 136 (18), 121 (17), 108 (17), 91 (25), 77 (18).

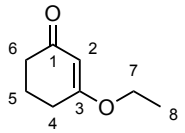
5.3.12 SYNTHESIS OF 3-ETHOXYCYCLOHEX-2-ENONE (**264**)[115]



According to a literature protocol,[115] 2.0 g (18 mmol, 1.0 eq.) of 1,3-cyclohexadione (**263**) was dissolved in 20 mL of EtOH and 1.2 mL of conc. aqueous HCl were added. After stirring for 2 d at rt the reaction was quenched with 30 mL of sat. aqueous $NaHCO_3$, despite incomplete conversion indicated by TLC. The mixture was extracted with 3 × 20 mL of CH_2Cl_2, and the combined organic layers were washed with 2 × 20 mL H_2O and 2 × 20 mL of sat. aqueous NaCl and dried over $MgSO_4$.

Evaporation of the solvent under reduced pressure yielded product 1.04 g (7.40 mmol, 41%; Lit.: 96%) of **264** as an slightly orange oil.

M ($C_8H_{12}O_2$) = 140.18 g/mol



R_f (cHex/EtOAc 2:1) = 0.22

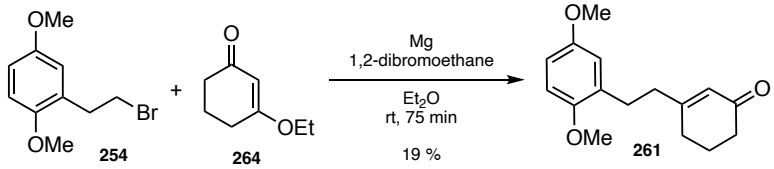
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 5.34 (s, 1H, H-2), 3.89 (q, *J* = 7.0 Hz, 2H, H-7), 2.39 (t, *J* = 6.3 Hz, 2H, H-6), 2.36 – 2.31 (m, 2H, H-4), 1.97 (p, *J* = 6.4 Hz, 2H, H-5), 1.35 (t, *J* = 7.0 Hz, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 200.0 (C-1), 178.0 (C-3), 102.9 (C-2), 64.3 (C-7), 36.9 (C-6), 29.2 (C-4), 21.4 (C-5), 14.3 (C-8).

GC-MS (70 eV): *m/z* (%) = 140 (M^+, 76), 112 (54), 84 (100), 68 (52), 43 (18).

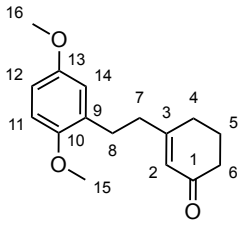
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2982 (w), 2944 (w), 2894 (w), 2834 (w), 1730 (w), 1647 (s), 1596 (s), 1476 (w), 1403 (w), 1429 (w), 1377 (s), 1348 (m), 1328 (m), 1217 (s), 1180 (s), 1135 (s), 1111 (m), 1059 (w), 1029 (m), 967 (w), 929 (m), 869 (w), 814 (m), 759 (w), 658 (w), 606 (m), 549 (w), 510 (m), 485 (w), 447 (w), 429 (w).

5.3.13 SYNTHESIS OF ENONE **261** VIA *GRIGNARD* ADDITION



Based on a literature procedure,[112] a flame dried *Schlenk* flask was charged with 50 mg (2.02 mmol, 12 eq.) of Mg turnings and heated under vacuum with a gas torch. The Mg was soaked in 1 mL of dry Et_2O under argon atmosphere. In a second flask, 100 mg (0.40 mmol, 2.3 eq.) of bromide **254** were dissolved in 5 mL of abs. Et_2O and 68 µL (150 mg, 0.80 mmol, 4.5 eq.) of 1,2-dibromoethane were added. This mixture was added to the Mg suspension over 15 min. The mixture was stirred for 30 min at rt resulting in a grey suspension, which was cooled to 0 °C and a solution of 26 mg (0.18 mmol, 1.0 eq.) of 3-ethoxycyclohex-2-enone (**264**) in 3 mL of dry Et_2O was added upon which the mixture turned yellow. The reaction was stirred for 75 min at rt. The reaction was quenched with H_2O and extracted 3 x with MTBE. The combined organic layers were washed with H_2O and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the crude product was purified by silica gel column chromatography (*c*-Hex/EtOAc 9:1 to 2:1) to yield 9.0 mg (35 µmol, 19%) of enone **261** as a colorless oil. Additionally, 32 mg (0.19 mmol, 48%

respective to **254**) of (2,5-dimethoxyphenyl)ethane (**284**) was obtained as undesired major product as well as 6 mg (18 µmol, 9% respective to **254**) of 1,4-di(2,5-dimethoxyphenyl)butane (**283**) (for analytical data see **5.3.11**).



M ($C_{16}H_{20}O_3$) = 260.33 g/mol

R_f (cHex/EtOAc 2:1) = 0.42

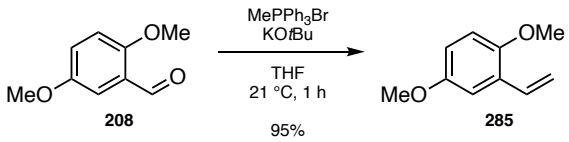
^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 6.77 (d, J = 8.6 Hz, 1H, H-11), 6.73 – 6.67 (m, 1H, H-12), 5.89 (t, J = 1.4 Hz, 1H, H-14), 3.78 (s, 3H, H-15), 3.75 (s, 3H, H-16), 2.81 – 2.75 (m, 2H, H-8), 2.51 – 2.45 (m, 2H, H-7), 2.38 – 2.33 (m, 2H, H-6), 2.32 (t, J = 5.8 Hz, 2H, H-4), 1.99 (dt, J = 12.4, 6.2 Hz, 2H, H-5).

^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] =200.1 (C-1), 166.3 (C-3), 153.6 (C-13), 151.8 (C-10), 130.5 (C-9), 126.0 (C-2), 116.4 (C-14), 111.4 (C-12), 111.3 (C-11), 55.9 (C-15), 55.8 (C-16), 38.3 (C-7), 37.5 (C-6), 30.0 (C-4), 28.4 (C-8), 22.9 (C-5).

GC-MS (70 eV): *m/z* (%) = 260 (M^+, 43), 242 (40), 151 (100), 121 (32), 91 (15), 77 (10).

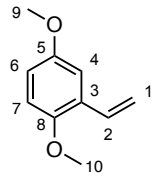
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3475 (w), 2996 (w), 2935 (m), 2867 (w), 2833 (m), 1971 (w), 1664 (s), 1624 (m), 1591 (m), 1499 (s), 1465 (m), 1453 (m), 1427 (m), 1373 (m), 1347 (m), 1325 (m), 1301 (m), 1280 (m), 1221 (s), 1192 (m), 1180 (m), 1157 (m), 1131 (m), 1118 (m), 1046 (m), 1028 (m), 965 (m), 932 (w), 886 (m), 803 (m), 756 (m), 732 (w), 712 (m), 673 (w), 626 (w), 594 (w), 554 (w), 488 (m), 464 (w), 426 (w).

5.3.14 SYNTHESIS OF 2,5-DIMETHOXY STYRENE **285**



Based on a literature protocol,[117] 2.73 g (7.28 mmol, 1.2 eq.) of $MePPh_3Br$ were dissolved in 11.5 mL of dry THF. 950 mg (8.47 mmol, 1.4 eq.) of KO*t*Bu were added, the arising yellow suspension was stirred for 30 min at 21 °C and cooled to -60 °C. 1.00 g (6.02 mmol, 1.0 eq.) of aldehyde **208** dissolved in 6.0 mL dry THF were added over 5 min and the mixture warmed up to 21 °C. After 1 h the reaction was quenched with 2.0 mL of MeOH. After evaporation of the solvents, the crude product was purified by silica column chromatography (*c*-Hex/EtOAc 20:1) and 934 mg (5.69 mmol, 95%) of olefin **285** were obtained.

M ($C_{10}H_{12}O_2$) = 164.20 g/mol



R_f (*c*-Hex/EtOAc 9:1) =0.48

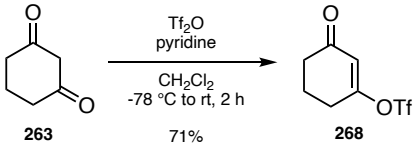
^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 7.07 – 6.99 (m, 2H, H-2, H-7), 6.84 – 6.77 (m, 2H, H-4, H-6), 5.73 (dd, *J* = 17.7, 1.2 Hz, 1H, H-1), 5.28 (dd, *J* = 11.1, 1.2 Hz, 1H, H-1‘), 3.81 (s, 3H, H-10), 3.79 (s, 3H, H-9).

^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 153.8 (C-5), 151.4 (C-8), 131.6 (C-2), 127.7 (C-3), 114.8 (C-1), 113.9 (C-4/6/7), 112.4 (C-6/7), 112.0 (C-4/6/7), 56.4 (C-9/10), 55.9 (C-9/10).

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2998 (w), 2942 (w), 2907 (w), 2833 (m), 1626 (w), 1581 (m), 1491 (s), 1463 (m), 1427 (m), 1418 (m), 1307 (m), 1282 (m), 1248 (m), 1216 (s), 1192 (m), 1179 (m), 1161 (m), 1120 (m), 1059 (m), 1038 (s), 1024 (m), 996 (m), 908 (m), 874 (m), 857 (m), 801 (m), 756 (m), 709 (m), 697 (m), 662 (m), 543 (m), 503 (w), 432 (m).

GC-MS (70 eV): *m/z* (%) = 164 (M^+, 100), 149 (55), 121 (56), 106 (9), 91 (41), 77 (2), 63 (5).

5.3.15 SYNTHESIS OF 3-OXOCYCLOHEX-1-EN-1-YL TRIFLUOROMETHANE SULFONATE (268)

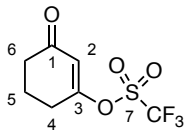


According to a literature protocol,[116] in a flame dried *Schlenk* flask 501 mg (4.47 mmol, 1.0 eq.) of dione **263** were dried *in vacuo* over 5 min and dissolved in 20 mL of dry CH_2Cl_2. 0.72 mL (707 mg, 8.94 mmol, 2.0 eq.) of dry pyridine were added, the mixture was cooled to -78 °C and 1.0 mL (1.7 g, 6.0 mmol, 1.3 eq.) of Tf_2O was added. After stirring at rt for 2 h the reaction was quenched with 1 M aqueous HCl. The aqueous phase was extracted with 3 x 30 mL of EtOAc, the combined organic layers washed with sat. aqueous $NaHCO_3$ and sat. aqueous NaCl and dried over MgSO4. After removal of the solvent under reduced pressure the crude product was purified by silica column chromatography (*c*-Hex/EtOAc 5:1) to yield 778 mg (3.19 mmol, 71%) of enol triflate **268** as pale yellow oil.

M ($C_7H_7F_3O_4S$) = 244.18 g/mol

R_f (*c*-Hex/EtOAc 5:1) =0.24

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 6.06 (t, J = 1.4 Hz, 1H, H-2), 2.69 (td, J = 6.2 Hz, J = 1.4 Hz, 2H, H-6), 2.45 (t, J=7.1 Hz, 2H, H-4), 2.13 (p, J=6.3 Hz, 2H, H-5).

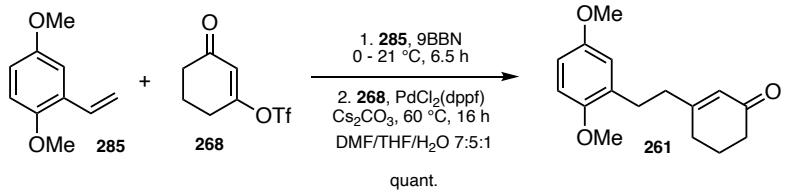


^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 197.5 (C-1), 167.5 (C-3), 119.4 (C-2), 36.4 (C-6), 28.6 (C-4), 20.9 (C-5).

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 1362 (m), 1346 (m), 1328 (m), 1302 (m), 1246 (m), 1206 (s), 1134 (s), 1069 (s), 1037 (s), 972 (w), 908 (s), 891 (s), 853 (m), 798 (s), 763 (s), 752 (s), 698 (w), 601 (s), 575 (m), 519 (m), 506 (m), 460 (m), 429 (m).

GC-MS (70 eV): *m/z* (%) = 244 (M^+, 9), 216 (24), 86 (18), 69 (100), 55 (10).

5.3.16 SYNTHESIS OF ENONE **261** VIA *SUZUKI* COUPLING

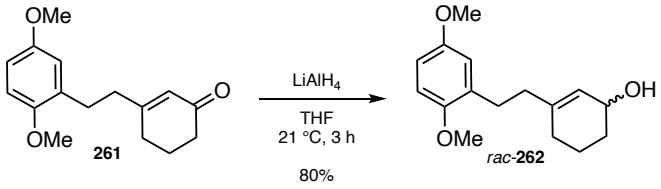


Based on a literature protocol,[105] in a *Schlenk* flask, a solution of 340 mg (2.07 mmol, 1.0 eq.) of olefin **285** in 4.1 mL of dry, degassed THF was cooled to 0 °C. Then, 8.20 mL (4.10 mmol, 3.3 eq.) of 9-BBN (0.5 M in THF) were added and the mixture was stirred at 21 °C for 6.5 h. The solution was then cooled to 0 °C before 1.8 mL of degassed H_2O were added and stirring was continued for 60 min at 0 °C. This borane solution was then transferred via needle to a second *Schlenk* flask charged with a solution of 86 mg (0.11 µmol, 0.09 eq.) of $PdCl_2$(dppf) x CH_2Cl_2, 1.33 g (4.08 mmol, 3.3 eq.) of Cs_2CO_3 and 300 mg (1.23 mmol, 1.0 eq.) of the enol triflate **268** in 14.5 mL of dry, degassed DMF at 21 °C. The reaction mixture was stirred at 60 °C for 16 h before 30 mg of QuadraSil AP® were added and the suspension was stirred for further 60 min. Then the solids were separated by decantation and H_2O was added to the product solution. After extraction with EtOAc (4x) the combined organic layers were washed with H_2O and sat. aqueous NaCl, dried over $MgSO_4$ and the solvents were removed under reduced pressure. The residue was purified by silica gel column chromatography (*c*-Hex/EtOAc 10:1 to 5:1) to yield 320 mg (1.23 mmol, 100%) of enone **261** as a pale yellow oil.

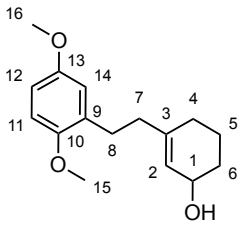
M ($C_{16}H_{20}O_3$) = 260.33 g/mol

See chapter **5.3.13** for analytical data.

5.3.17 SYNTHESIS OF ALLYLIC ALCOHOL *rac*-**262**



In a flame dried *Schlenk* flask, 132 mg (3.48 mmol, 4.5 eq.) of $LiAlH_4$ were suspended in 17 mL of dry THF and cooled to 0 °C. To this suspension, a solution of 202 mg (776 µmol, 1.0 eq.) of enone **261** in 7 mL of dry THF was added. The reaction was stirred at 21 °C for 3 h before the reaction was terminated by carefully adding 25 mL of H_2O. The mixture was extracted with 3 x 25 mL EtOAc and the combined organic layers were dried over $MgSO_4$. Removal of the solvent under reduced pressure gave 162 mg (617 µmol, 80%) of allylic alcohol *rac*-**262** as pale yellow oil.



M ($C_{16}H_{22}O_3$) = 262.35 g/mol

R_f (*c*-Hex/EtOAc 3:1) =0.23

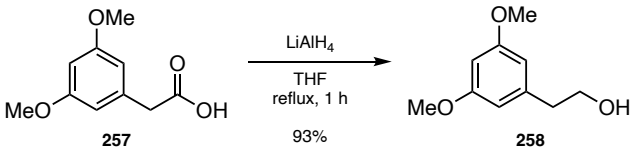
^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 6.76 (d, J = 8.4 Hz, 1H, H-11), 6.72 – 6.66 (m, 2H, H-12, H-14), 5.52 – 5.47 (m, 1H, H-2), 4.17 (s, 1H, H-1), 3.78 (s, 3H, H-15), 3.76 (s, 3H, H-16), 2.72 – 2.69 (m, 2H, H-8), 2.24 – 2.21 (m, 2H, H-7), 2.10 – 1.92 (m, 2H, H-4), 1.82 – 1.71 (m, 2H, H-5, H-6), 1.63 – 1.55 (m, 2H, H-5', H-6').

^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 153.5 (C-13), 151.9 (C-10), 142.4 (C-3), 131.9 (C-9), 124.0 (C-2), 116.4 (C-14), 111.3 (C-11), 111.0 (C-12), 66.0 (C-1), 56.1 (C-15), 55.8 (C-16), 37.7 (C-7), 32.0 (C-8), 28.8 (C-6, C-4), 19.2 (C-5).

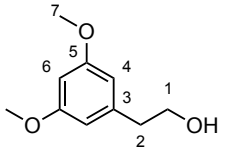
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3366 (br), 2995 (w), 2930 (m), 2859 (m), 2832 (m), 1665 (w), 1609 (w), 1591 (w), 1498 (s), 1464 (m), 1452 (m), 1428 (m), 1342 (w), 1279 (m), 1220 (s), 1179 (m), 1157 (m), 1121 (m), 1047 (s), 1028 (m), 958 (m), 932 (w), 906 (m), 870 (m), 800 (m), 769 (w), 731 (w), 712 (m), 554 (w), 486 (m), 466 (m), 405 (w).

HRMS (EI):	Calc. [amu]	Found [amu]
	262.15635 $[M]^{\bullet+}$	262.1562 $[M]^{\bullet+}$

5.3.18 SYNTHESIS OF 2-(3,5-DIMETHOXYPHENYL)ETHANOL (**258**)[114a]



According to a literature protocol,[114a] 2.31 g (60.9 mmol, 2.7 eq.) of $LiAlH_4$ were suspended in 20 mL of dry THF under argon atmosphere and cooled to 0 °C. In a second flask, 4.50 g (22.9 mmol, 1.0 eq.) of 2-(3,5-dimethoxyphenyl)acetic acid (**257**) were dissolved in 10 mL of dry THF, under argon atmosphere. This solution was slowly added to the stirred $LiAlH_4$ suspension and the mixture refluxed for 1 h. The reaction was cooled to 0 °C and quenched by carefully adding 30 mL of H_2O. The mixture was acidified to pH ~3 by addition of 1 M aqueous HCl. The aqueous phase was extracted with 2 × 100 mL and 1 × 50 mL of EtOAc. The combined organic layers were washed with 100 mL of H_2O, dried over Na_2SO_4 and removed under reduced pressure to obtain 3.86 g (21.2 mmol, 93%; Lit.: 93%) of alcohol **258** as a colorless oil.



M ($C_{10}H_{14}O_3$) = 182.22 g/mol

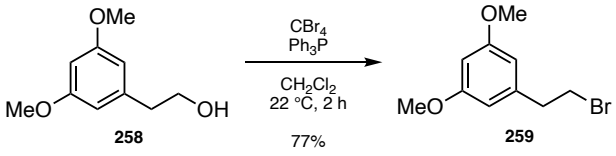
R_f (cHex/EtOAc 2:1) = 0.25

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 6.38 (d, J = 2.3 Hz, 2H, H-4), 6.34 (t, J = 2.3 Hz, 1H, H-6), 3.84 (t, J = 6.5 Hz, 2H, H-1), 3.78 (s, 6H, H-7), 2.80 (t, J = 6.5 Hz, 2H, H-2), 1.65 (s, 1H, OH).

^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 161.1 (C-5), 140.9 (C-3), 107.2 (C-4), 98.5 (C-6), 63.6 (C-1), 55.4 (C-7), 39.6 (C-2).

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3545.70 (br), 3378.22 (br), 3000 (w), 2940.22 (m), 2839.01 (m), 2079.86 (w), 1595.46 (vs), 1461.29 (s), 1429.54 (s), 1347.02 (m), 1324.83 (m), 1309.27 (m), 1293.14 (m), 1205.08 (s), 1149.27 (vs), 1067.98 (s), 1056.28 (s), 993.79 (w), 939.36 (w), 924.79 (w), 891.83 (w), 831.39 (m), 696.94 (m), 658.19 (w), 595.04 (w), 540.06 (w).

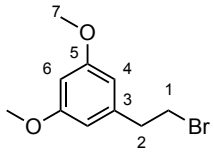
5.3.19 SYNTHESIS OF 1-BROMO-2-(3,5-DIMETHOXYPHENYL)ETHANE (**259**)[114b]



According to a literature protocol,[114b] 4.22 g (23.1 mmol, 1.0 eq.) of alcohol **258** were dissolved in 55 mL of dry CH_2Cl_2 under argon atmosphere. 9.97 g (30.1 mmol, 1.3 eq.) of CBr_4 were added

and the solution was cooled to 0 °C. 7.89 g (30.1 mmol, 1.3 eq.) of PPh_3 were added over 10 min upon which the colorless solution turned yellow. The reaction was stirred at rt for 1 h and the reaction was poured into 70 mL of H_2O. The mixture was extracted with 3 × 70 mL of EtOAc, and the combined organic layers were washed with 70 mL of sat. aqueous NaCl and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the crude product was purified by silica gel column chromatography (*c*-Hex/EtOAc 20:1 to 5:1) to obtain 3.84 g (15.7 mmol, 77%) of bromide **259** as a colorless oil.

M ($C_{10}H_{13}BrO_2$) = 245.12 g/mol



R_f (cHex/EtOAc 20:1) = 0.24

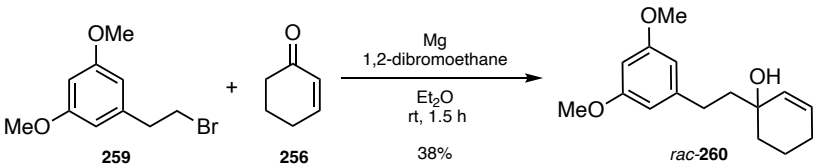
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 6.37 (s, 3H, H-4, H-6), 3.79 (s, 6H, H-7), 3.56 (t, J = 7.7 Hz, 2H, H-1), 3.14 – 3.07 (m, 2H, H-2).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 161.1 (C-5), 141.3 (C-3), 106.9 (C-4), 98.9 (C-6), 55.4 (C-7), 39.8 (C-2), 32.7 (C-1).

GC-MS (70 eV): *m/z* (%) = 246 (M^+ (^{81}Br), 48), 246 (M^+ (^{79}Br), 49), 165 (100), 151 (28), 135 (10), 121 (10), 105 (13), 91 (13), 77 (13).

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3000 (w), 2958 (w), 2938 (w), 2837 (w), 1594 (s), 1460 (m), 1429 (m), 1348 (m), 1308 (m), 1293 (m), 1251 (w), 1204 (s), 1147 (s), 1057 (s), 993 (w), 969 (w), 922 (w), 830 (m), 712 (m), 690 (m), 624 (w), 589 (w), 536 (w), 485 (w), 422 (w).

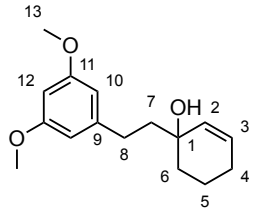
5.3.20 SYNTHESIS OF ALLYLIC ALCOHOL *rac*-260



Based on a literature protocol,[112] a flame dried *Schlenk* flask was charged with 25 mg (1.02 mmol, 12 eq.) of Mg turnings and heated under vacuum with a gas torch. The Mg was soaked in 0.5 mL of dry Et_2O under argon atmosphere. In a second flask, 50 mg (0.20 mmol, 2.3 eq.) of bromide **259** were dissolved 2.5 mL of dry Et_2O and 34 µL (75 mg, 0.4 mmol, 4.5 eq.) of 1,2-dibromoethane were added. This mixture was added to the Mg over 10 min. The mixture was stirred for 90 min at rt resulting in darkened suspension which was cooled to 0 °C and a solution of 9 mg (9 µL, 0.09 mmol, 1.0 eq.) of cyclohex-2-enone (**256**) in 1.5 mL of dry Et_2O was added. The reaction was

stirred for 75 min at rt, cooled to 0 °C and quenched with H_2O. The aqueous phase was extracted 3 x with MTBE and the combined organic layers were washed with H_2O and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the crude product was purified by silica gel column chromatography (*c*-Hex/EtOAc 15:1 to 2:1) to obtain 9 mg (34 µmol, 38%) of allylic alcohol *rac*-**260** as a yellow oil. Additionally, as undesired side products 14 mg (84 µmol, 42% respective to **259**) of (3,5-dimethoxyphenyl)ethane (**287**) and 3 mg (9 µmol, 9% respective to **259**) of 1,4-di(3,5-dimethoxyphenyl)butane (**286**) were isolated as yellow oils.

allylic alcohol **255**:



M ($C_{16}H_{22}O_3$) = 262.35 g/mol

R$_f$ (cHex/EtOAc 3:1) = 0.29

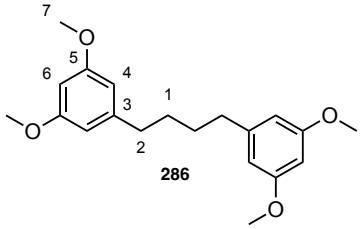
^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 6.37 (d, *J* = 2.3 Hz, 2H, H-10), 6.30 (t, *J* = 2.3 Hz, 1H, H-12), 5.84 (ddd, *J* = 10.0, 4.5, 2.9 Hz, 1H, H-3), 5.69 (d, *J* = 10.0 Hz, 2H, H-2), 3.78 (s, 6H, H-13), 2.70 – 2.63 (m, 2H, H-8), 2.11 – 1.93 (m, 2H, H-4), 1.91 – 1.66 (m, 6H, H-5, H-6, H-7).

^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 160.9 (C-11), 145.3 (C-9), 132.5 (C-2), 130.4 (C-3), 106.5 (C-10), 98.0 (C-12), 69.7 (C-1), 55.4 (C-13), 44.1 (C-7), 35.8 (C-6), 30.4 (C-8), 25.4 (C-4), 19.2 (C-5).

GC-MS (70 eV): *m/z* (%) = 262 (M^+, 3), 244 (63), 216 (100), 201 (28), 185 (8), 180 (11), 166 (26), 152 (47), 139 (42), 129 (12), 115 (14), 105 (12), 97 (46), 91 (26), 77 (17), 65 (11), 55 (6).

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3531 (br), 3431 (br), 3014 (w), 2998 (w), 2934 (m), 2865.23 (w), 2836(w), 2075 (w), 1705 (w), 1682 (w), 1594 (vs), 1458 (s), 1428 (s), 1344 (m), 1321 (m), 1294 (m), 1273 (w), 1203 (s), 1147 (vs), 1111 (w), 1057 (s), 1005 (w), 992 (w), 963 (m), 939 (m), 925 (m), 830 (m), 733 (m), 686 (m), 640 (w), 598 (w), 572 (w), 533 (w), 512 (w).

1,4-di(3,5-dimethoxyphenyl)butane (**286**):



M ($C_{20}H_{26}O_4$) = 330.42 g/mol

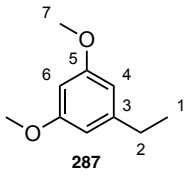
R$_f$ (cHex/EtOAc 2:1) = 0.73

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 6.33 (d, *J* = 2.3 Hz, 4H, H-4), 6.29 (t, *J* = 2.3 Hz, 2H, H-6), 3.77 (s, 12H, H-7), 2.61 – 2.54 (m, 4H, H-2), 1.68 – 1.62 (m, 4H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 160.8 (C-5), 145.1 (C-3), 106.6 (C-4), 97.8 (C-6), 55.4 (C-7), 36.3 (C-2), 30.9 (C-1).

GC-MS (70 eV): *m/z* (%) = 330 (M^+, 39), 165 (31), 152 (100).

(3,5-dimethoxyphenyl)ethane (**287**):



M ($C_{10}H_{14}O_2$) = 166.22 g/mol

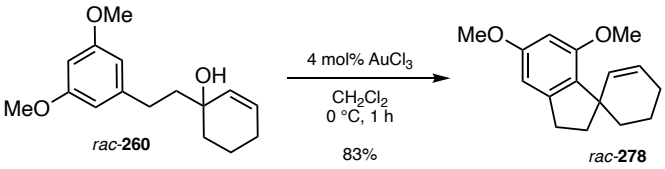
R$_f$ (cHex/EtOAc 2:1) = 0.77

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 6.38 (dt, *J* = 2.3, 0.6 Hz, 2H, H-4), 6.31 (t, *J* = 2.3 Hz, 1H, H-6), 3.79 (s, 6H, H-7), 2.61 (q, *J* = 7.6 Hz, 2H, H-2), 1.24 (t, *J* = 7.6 Hz, 3H, H-1).

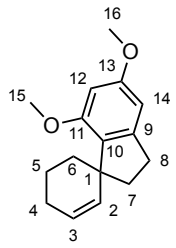
^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 160.9 (C-5), 146.8 (C-3), 106.1 (C-4), 97.7 (C-6), 55.3 (C-7), 29.3 (C-2), 15.5 (C-1).

GC-MS (70 eV): *m/z* (%) = 166 (M^+, 100), 151 (31), 137 (12), 121 (27), 108 (15), 91 (13), 78 (9).

5.3.21 GOLD-CATALYZED CYCLIZATION OF ALLYLIC ALCOHOL *rac*-**260**



In a flame dried *Schlenk* flask, a solution of 11.0 mg (39.6 µmol, 1.0 eq.) of allylic alcohol **255** in 3.8 mL of CH_2Cl_2 (HPLC grade) was cooled to 0 °C and 10 µL (2.0 µmol, 0.04 eq.) of a $AuCl_3$ solution (138 mM in CH_2Cl_2) were added. The mixture was stirred at 0 °C for 1 h before 4.1 mg of QuadraSil TA® were added, the mixture stirred for further 30 min and the solids were removed by filtration. After evaporation of the solvent, the resulting pale brown, viscous oil was purified by silica gel filtration (*c*-Hex/EtOAc 30:1) to give 8.0 mg (33 µmol, 83%) of spirocycle *rac*-**278** as colorless oil.



M ($C_{16}H_{20}O_2$) = 244.33 g/mol

R$_f$ (cHex/EtOAc 9:1) =0.79

^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 6.36 (d, *J* = 2.1 Hz, 21, H-14), 6.27 (d, *J* = 2.2 Hz, 1H, H-12), 5.70 – 5.64 (m, 1H, H-3), 5.64 – 5.59 (m, 1H, H-2), 3.78 (s, 3H, H-16), 3.74 (s, 3H, H- 15), 2.91 – 2.76 (m, 2H, H-8), 2.08 – 2.00 (m, 3H, H- 4, H-7), 1.97 – 1.88 (m, 2H, H-6, H-7'), 1.77 (d, *J* = 13.3 Hz, 1H, H-5), 1.64 – 1.59 (m, 2H, H-5', H-6').

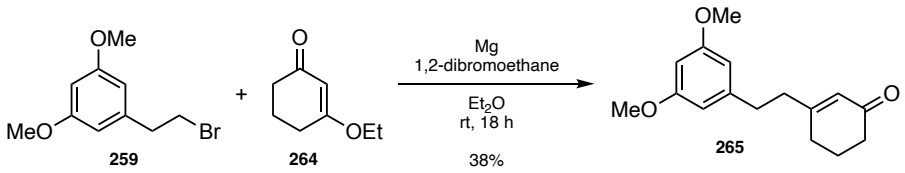
^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] = 160.6 (C-13), 157.6 (C-11), 146.5 (C-9), 135.8 (C-2), 124.4 (C-3), 100.8 (C-14), 97.5 (C-12), 55.7 (C-16), 55.5 (C-15), 48.3 (C-1), 39.6 (C-7), 31.9 (C-6), 31.2 (C-8), 24.9 (C-4), 20.9 (C-5).

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3012 (m), 2995 (m), 2927 (s), 2855 (m), 2834 (m), 2253 (w), 1722 (w),1646 (w), 1593 (s), 1487 (m), 1464 (m), 1455 (m), 1425 (m), 1392 (w), 1379 (w), 1331 (m), 1311 (m), 1276 (m), 1221 (m), 1211 (m), 1197 (m), 1147 (vs), 1098 (m), 1079 (m), 1053 (m), 1018 (w), 985 (w), 967 (w), 932 (w), 913 (w), 864 (w), 826 (m), 741 (w), 729 (w), 699 (w), 673 (w), 662 (w), 635 (w), 547 (w).

GC-MS (70 eV): *m/z* (%) = 244 (M^+, 78), 216 (100), 201 (57), 175 (34), 158 (9), 141 (18), 115 (38), 91 (15), 63 (8).

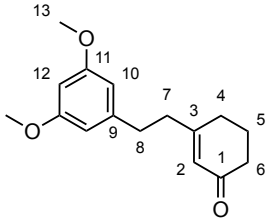
HRMS (EI):	Calc. [amu]	Found [amu]
	244.14578 $[M]^{\bullet+}$	244.14531 $[M]^{\bullet+}$

5.3.22 SYNTHESIS OF ENONE **265** VIA *GRIGNARD* ADDITION[112]



Based on a literature procedure,[112] a flame dried *Schlenk* flask was charged with 25 mg (1.02 mmol, 12 eq.) of Mg turnings and heated under vacuum with a gas torch. The Mg was soaked in 0.5 mL of dry Et_2O under argon atmosphere. In a second flask, 50 mg (0.20 mmol, 2.3 eq.) of bromide **259** were dissolved 2.5 mL of dry Et_2O and 34 µL (75 mg, 0.4 mmol, 4.5 eq.) of 1,2-dibromoethane were added. This mixture was added to the Mg over 10 min. The mixture was stirred at rt for 1 h and cooled to 0 °C and a solution of 13 mg (0.09 mmol, 1,0 eq.) of 3-ethoxycyclohex-2-enone (**264**) in 1.5 mL of dry Et_2O was added. The reaction was stirred at rt for 18 h, cooled to 0 °C and quenched with 1 M aqueous HCl. The aqueous phase was extracted 3 x with MTBE and the combined organic layers were washed with H_2O and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the crude product was purified by silica gel column chromatography (*c*-Hex/EtOAc 9:1 to 2:1) to obtain 9 mg (35 µmol, 38%; Lit.: 73%) of enone **265** as a yellow oil. Additionally, as undesired side products 3 mg (18 µmol, 9% respective to **259**) of (3,5-dimethoxyphenyl)ethane (**287**) and 3 mg (9 µmol, 9% respective to **259**) of

1,4-di(3,5-dimethoxyphenyl)butane (**286**) were isolated as yellow oils (for analytical data see chapter **5.3.20**)



M ($C_{16}H_{20}O_3$) = 260.33 g/mol

R$_f$ (cHex/EtOAc 2:1) =0.40

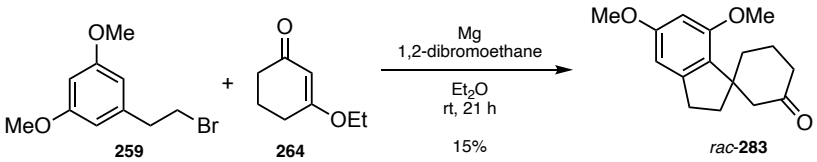
^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 6.34 – 6.31 (m, 3H, H-10, H-12), 5.90 (t, J = 1.4 Hz, 1H, H-2), 3.78 (s, 6H, H-13), 2.78 – 2.73 (m, 2H, H-8), 2.54 – 2.49 (m, 2H, H-7), 2.38 – 2.34 (m, 2H, H-6), 2.30 (t, J = 5.9 Hz, 2H, H-4), 1.99 (p, J = 6.2 Hz, 2H, H-5).

^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 200.0 (C-1), 165.4 (C-3), 161.0 (C-11), 143.3 (C-9), 126.1 (C-2), 106.5 (C-10), 98.2 (C-12), 55.4 (C-13), 39.6 (C-7), 37.5 (C-6), 33.8 (C-8), 30.0 (C-4), 22.8 (C-5).

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3672 (w), 3501 (w), 2988 (m), 2935 (m), 2838 (m), 2223 (w), 1709 (m), 1666 (m), 1595 (vs), 1460 (m), 1428 (m), 1347.26 (m), 1324 (m), 1294 (m), 1256 (m), 1204 (s), 1150 (vs), 1065 (s), 966 (w), 938 (w), 923 (w), 888 (w), 832 (m), 759 (w), 695 (w), 599 (w), 538 (w).

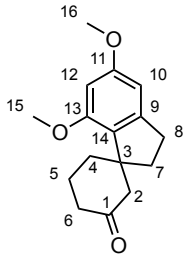
GC-MS (70 eV): m/z (%) = 260 (M$^+$, 58), 242 (18), 227 (9), 189 (25), 165 (62), 151 (100), 121 (15), 106 (9), 91 (28), 77 (28), 65 (19).

5.3.23 UNDESIRED *GRIGNARD* ADDITION PRODUCT ON HIGH DILUTION (*rac*-**283**)



Based on a literature procedure,[112] a flame dried *Schlenk* flask was charged with 25 mg (1.02 mmol, 12 eq.) of Mg turnings and heated under vacuum with a gas torch. The Mg was soaked in 1.0 mL of dry Et_2O under argon atmosphere. In a second flask, 50 mg (0.20 mmol, 2.3 eq.) of bromide **259** were dissolved 5.0 mL of dry Et_2O and 34 µL (75 mg, 0.4 mmol, 4.5 eq.) of 1,2-dibromoethane were added. This mixture was added to the Mg over 10 min. The mixture was stirred at rt for 1 h and cooled to 0 °C and a solution of 13 mg (0.09 mmol, 1,0 eq.) of 3-ethoxycyclohex-2-enone (**264**) in 3.0 mL of dry Et_2O was added. The reaction was stirred at rt for 21 h, cooled to 0 °C and quenched with 1 M aqueous HCl. The aqueous phase was extracted 3 x with MTBE and the combined organic layers were washed with H_2O and dried over $MgSO_4$. After

evaporation of the solvent under reduced pressure, the crude product was purified by silica gel column chromatography (*c*-Hex/EtOAc 9:1 to 2:1) to obtain desired *Grignard* coupling product **265** (see chapter **5.3.22**) in a yield of 2 mg (8 µmol, 9%) and cyclization product *rac*-**283** was obtained in a yield of 3 mg (12 µmol, 15%) as a colorless oil.



M ($C_{16}H_{20}O_3$) = 260.33 g/mol

R_f (cHex/EtOAc 2:1) =0.56

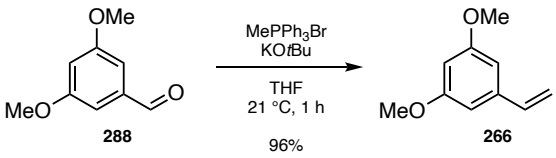
^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 6.36 (d, *J* = 2.3 Hz, 1H, H-10), 6.29 (d, *J* = 2.1 Hz, 1H, H-12), 3.78 (s, 3H, H-16), 3.76 (s, 3H, H-15), 3.02 (dd, *J* = 14.2, 1.2 Hz, 1H, H-2), 2.93 – 2.78 (m, 2H, H-8), 2.48 (ddd, *J* = 13.7, 11.4, 4.1 Hz, 1H, H-5), 2.45 – 2.30 (m, 2H, H-6), 2.24 (dt, *J* = 14.3, 1.8 Hz, 1H, H-2'), 1.98 (dp, *J* = 15.0, 5.0 Hz, 1H, H-4), 1.90 (t, *J* = 7.4 Hz, 2H, H-7), 1.88 – 1.77 (m, 1H, H-5').

^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 211.9 (C-1), 160.9 (C-11), 157.4 (C-13), 145.9 (C-9), 128.1 (C-14), 101.1 (C-10), 97.3 (C-12), 55.6 (C-16), 54.9 (C-15), 52.2 (C-3), 50.9 (C-2), 41.3 (C-6), 37.9 (C-7), 34.6 (C-4), 31.0 (C-8), 23.1 (C-5).

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3672 (w), 3501 (w), 2988 (m), 2935 (m), 2838 (m), 2223 (w), 1709 (m), 1666 (m), 1595 (vs), 1460 (m), 1428 (m), 1347.26 (m), 1324 (m), 1294 (m), 1256 (m), 1204 (s), 1150 (vs), 1065 (s), 966 (w), 938 (w), 923 (w), 888 (w), 832 (m), 759 (w), 695 (w), 599 (w), 538 (w).

GC-MS (70 eV): *m/z* (%) = 260 (M^+, 85), 245 (25), 217 (82), 203 (100), 190 (60), 175 (46), 161 (18), 145 (15), 115 (23), 91 (11).

5.3.24 SYNTHESIS OF 3,5-DIMETHOXY STYRENE (266)[117]

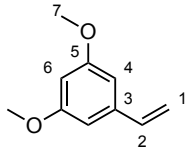


According to a literature protocol,[117] 8.20 g (21.0 mmol, 1.2 eq.) of $MePPh_3Br$ were dissolved in 33.5 mL of dry THF. 2.86 g (25.5 mmol, 1.4 eq.) of KO*t*Bu were added, the arising yellow suspension was stirred at 21 °C for 30 min and cooled to -60 °C. 3.01 g (18.1 mmol, 1.0 eq.) of aldehyde **288** dissolved in 16.5 mL dry THF were added over 5 min and the mixture was allowed to warm up to 21 °C. After 1 h the reaction was quenched with 5.0 mL of MeOH. After evaporation

of the solvents, the crude product was purified by silica column chromatography (*c*-Hex/EtOAc 20:1) and 2.84 g (17.3 mmol, 96%; Lit.: 96%) of olefin **266** were obtained.

M ($C_{10}H_{12}O_2$) = 164.20 g/mol

R$_f$ (*c*-Hex/toluene 5:1) =0.13



m.p. = 80-81 °C

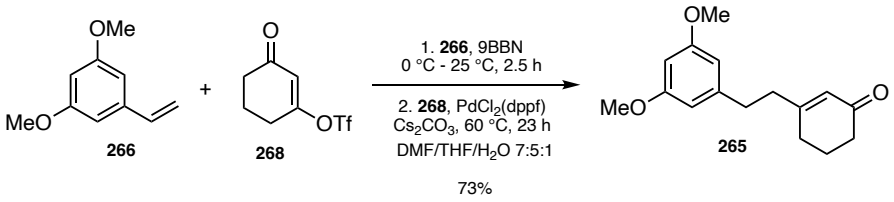
^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 6.65 (dd, *J* = 17.5 Hz, *J* = 10.8 Hz, 2H, H-5), 6.57 (d, *J* = 2.3 Hz, 2H, H-3), 6.39 (t, *J* = 2.3 Hz, 1H, H-2), 5.67 – 5.79 (d, *J* = 17.4 Hz, 1H, H-4‘), 5.20 – 5.31 (d, *J* = 10.7 Hz, 1H, H-4), 3.81 (s, 6H, H-1).

^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm] = 161.0 (C-7), 139.8 (C-6), 137.0 (C-5), 114.5 (C-4), 104.5 (C-3), 100.2 (C-2), 55.5 (C-1).

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3088 (w), 3002 (w), 2958 (w), 2937 (w), 2836 (w), 2225 (w), 2091 (w), 1589 (s), 1456 (m), 1428 (m), 1409 (m), 1342 (m), 1314 (m), 1294 (m), 1254 (w), 1204 (s), 1149 (s), 1073 (m), 1058 (m), 1032 (m), 989 (m), 931 (m), 909 (m), 831 (m), 718 (w), 665 (m), 633 (w), 589 (w), 538 (w), 508 (w), 480 (w), 441 (w), 411 (w).

GC-MS (70 eV): *m/z* (%) = 164 (M$^+$, 100), 135 (28), 121 (9), 105 (11), 91 (23), 77 (17), 63 (8).

5.3.25 SYNTHESIS OF ENONE **265** VIA *SUZUKI* COUPLING



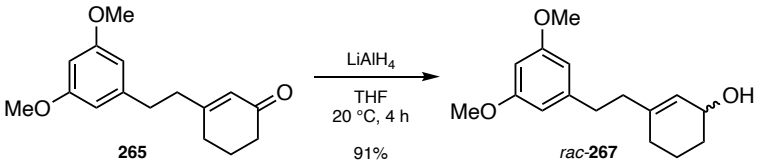
Based on a literature protocol,[105] in a *Schlenk* flask, a solution of 146 mg (889 µmol, 1.0 eq.) of olefin **266** in 1.8 mL of dry, degassed THF was cooled to 0 °C. Then, 3.7 mL (1.9 mmol, 2.1 eq.) of 9-BBN (0.5 M in THF) were added and the mixture was stirred at rt for 2.5 h. The solution was then cooled to 0 °C before 0.8 mL of degassed H_2O were added and stirring was continued for 60 min at 0 °C. This borane solution was then transferred via needle to a second *Schlenk* flask charged with a solution of 35 mg (43 µmol, 0.05 eq.) of $PdCl_2$(dppf) x CH_2Cl_2, 574 mg (1.76 mmol, 2.0 eq.) of Cs_2CO_3 and 211 mg (864 µmol, 1.0 eq.) of the enol triflate **268** in 6.0 mL of dry, degassed DMF at 25 °C. The reaction mixture was stirred at 60 °C for 23 h before 10 mg of QuadraSil AP® were added as a metal scavenger and the suspension was stirred for further 50 min. Then the

solids were separated by decantation and H_2O was added to the product solution. After extraction with EtOAc (4x) the combined organic layers were washed with H_2O and sat. aqueous $NaHCO_3$, dried over Na_2SO_4 and the solvents were removed under reduced pressure. The residue was purified by silica gel column chromatography (*c*-Hex/EtOAc 30:1 to 10:1) to yield 163 mg (630 µmol, 73%) of enone **265** as a pale yellow oil.

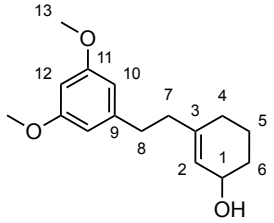
M ($C_{16}H_{20}O_3$) = 260.33 g/mol

See chapter **5.3.22** for analytical data.

5.3.26 SYNTHESIS OF ALLYLIC ALCOHOL *rac*-**267**



In a flame dried *Schlenk* flask, 180 mg (4.74 mmol, 5.9 eq.) of $LiAlH_4$ were suspended in 11 mL of dry THF and cooled to 0 °C. To this suspension, a solution of 210 mg (807 µmol, 1.0 eq.) of enone **265** in 22 mL of dry THF was added. The reaction was stirred at 20 °C for 4 h before the reaction was terminated by carefully adding 25 mL of H_2O. The mixture was extracted with 3 x 25 mL EtOAc and the combined organic layers were washed with sat. aqueous NaCl and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave 192 mg (732 µmol, 91%) of allylic alcohol *rac*-**267** as colorless solid.



M ($C_{16}H_{22}O_3$) = 262.35 g/mol

R$_f$ (*c*-Hex/EtOAc 3:1) = 0.23

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 6.34 (d, J = 2.3 Hz, 2H, H-10), 6.30 (t, J = 2.3 Hz, 1H, H-12), 5.52 (s, 1H, H-2), 4.19 (s, 1H, H-1), 3.78 (s, 6H, H-13), 2.72 – 2.64 (m, 2H, H-8), 2.32 – 2.23 (m, 2H, H-7), 2.07 – 1.89 (m, 2H, H-4), 1.85 – 1.71 (m, 2H, H-5, H-6), 1.63 – 1.55 (m, 2H, H-5', H-6').

^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 160.9 (C-11), 144.6 (C-9), 141.9 (C-3), 124.4 (C-2), 106.6 (C-10), 97.9 (C-12), 66.0 (C-1), 55.4 (C-13), 39.3 (C-7), 34.6 (C-8), 32.0 (C-6), 28.8 (C-4), 19.3 (C-5).

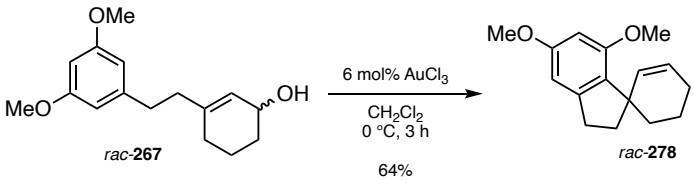
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3402 (br), 2999 (w), 2923 (m), 2860 (w), 2835 (w), 1608 (m), 1593 (m), 1462 (m), 1427 (m), 1342 (m), 1293 (m), 1270 (w), 1203 (s), 1146 (s), 1107 (w), 1058 (m),

1010 (m), 993 (m), 968 (m), 955 (m), 923 (m), 906 (m), 883 (w), 872 (m), 822 (m), 775 (w), 720 (w), 694 (m), 657 (w), 614 (w), 540 (m), 494 (m), 447 (m), 412 (m

GC-MS (70 eV): *m/z* (%) = 262 (M^+, 1), 244 (62), 229 (8), 216 (100), 201 (25), 171 (12), 152 (94), 139 (23), 115 (12), 91 (20), 77 (18).

HRMS (EI):	Calc. [amu]	Found [amu]
	244.14578 $[M-H_2O]^{\bullet+}$	244.1459 $[M-H_2O]^{\bullet+}$

5.3.27 GOLD-CATALYZED CYCLIZATION OF ALLYLIC ALCOHOL *rac*-**267**

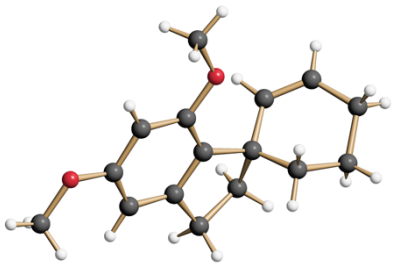


A solution of 40 mg (152 µmol, 1.0 eq.) of allylic alcohol *rac*-**267** in 17 mL of CH_2Cl_2 (HPLC grade) was cooled to 0 °C and 3.0 mg (9.89 µmol, 0.06 eq.) of $AuCl_3$ dissolved in 0.5 mL of CH_2Cl_2 were added. The yellow solution was stirred at 0 °C for 3 h before 5 mL of H_2O were added (discoloration). The aqueous phase was extracted with 3 x 10 mL of CH_2Cl_2 and the combined organic layers dried over $MgSO_4$. The resulting pale brown, viscous oil was purified by silica gel filtration (*c*-Hex/EtOAc 30:1) to give 24 mg (98 µmol, 64%) of spiro cycle *rac*-**278** as a colorless sticky oil, crystallizing slowly at rt.

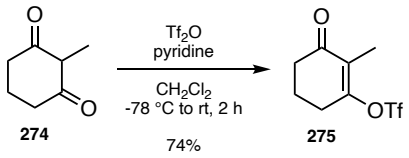
M ($C_{16}H_{20}O_2$) = 244.33 g/mol

See chapter **5.3.21** for analytical data.

X-ray crystal structure:

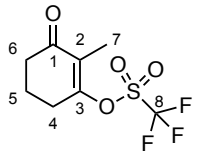


5.3.28 SYNTHESIS OF 2-METHYL-3-OXO-1-CYCLOHEXEN-1-YL-TRIFLUOROMETHANESULFONATE (275)



According to a literature protocol,[116] in a flame dried *Schlenk* flask 390 mg (3.48 mmol, 1.0 eq.) of dione **274** were dried *in vacuo* over 5 min and dissolved in 14 mL of dry CH_2Cl_2. 0.51 mL (501 mg, 6.34 mmol, 1.8 eq.) of dry pyridine were added, the mixture was cooled to -78 °C and 0.69 mL (1.2 g, 4.3 mmol, 1.2 eq.) of Tf_2O was added. After stirring at rt for 2 h the reaction was quenched with 1 M aqueous HCl. The aqueous phase was extracted with 3 x 20 mL of EtOAc, the combined organic layers washed with sat. aqueous $NaHCO_3$ and NaCl and dried over Na_2SO_4. After removal of the solvent under reduced pressure the crude product was purified by silica column chromatography (*c*-Hex/EtOAc 5:1) to yield 592 mg (2.29 mmol, 74%) of enol triflate **275** as colorless oil.

M ($C_8H_9F_3O_4S$) = 258.21 g/mol



R_f (*c*-Hex/EtOAc 5:1) = 0.43

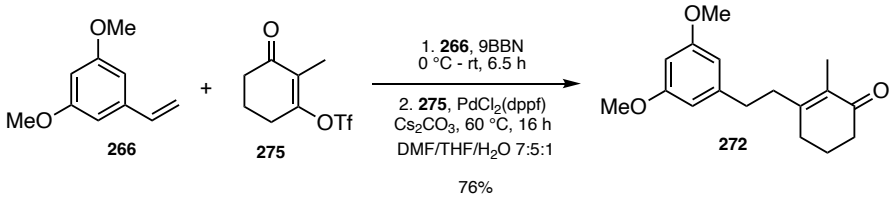
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] = 2.74 (tq, J = 6.2 Hz, J = 2.1 Hz, 2H, H-4), 2.49 (t, J = 7.1 Hz, 2H, H-6), 2.09 (p, J = 6.6 Hz, 2H, H-5), 1.87 (t, J = 2.1 Hz, 3H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm] = 197.9 (C-1), 162.2 (C-3), 128.4 (C-2), 118.28 ($J_{C,F}$ = 320 Hz, C-8), 36.8 (C-6), 28.9 (C-4), 20.8 (C-5), 9.3 (C-7).

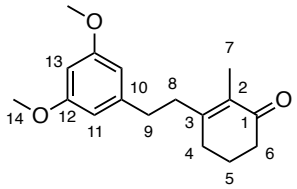
FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3363 (w), 2965 (w), 2879 (w), 1689 (m), 1669 (m), 1554 (w), 1416 (m), 1382 (w), 1345 (m), 1330 (w), 1298 (w), 1242 (m), 1206 (s), 1135 (s), 1109 (w), 1056 (m), 1024 (s), 912 (s), 891 (s), 860 (w), 793 (s), 759 (s), 693 (w), 659 (m), 630 (m), 595 (m), 571 (m), 545 (w), 527 (m), 493 (m), 470 (w), 436 (w), 411 (w).

GC-MS (70 eV): *m/z* (%) = 258 (M^+, 1), 230 (7), 125 (31), 69 (100), 55 (21).

5.3.29 SYNTHESIS OF ENONE **272** VIA *SUZUKI* COUPLING



Based on a literature protocol,[105] in a *Schlenk* flask, a solution of 151 mg (919 µmol, 1.0 eq.) of olefin **266** in 1.8 mL of dry, degassed THF was cooled to 0 °C. Then, 3.7 mL (1.9 mmol, 2.1 eq.) of 9-BBN (0.5 M in THF) were added and the mixture was stirred at rt for 3.5 h. The solution was then cooled to 0 °C before 0.8 mL of degassed H_2O were added and stirring was continued for 60 min at 0 °C. This borane solution was then transferred via needle to a second *Schlenk* flask charged with a solution of 38 mg (47 µmol, 0.05 eq.) of $PdCl_2$(dppf) x CH_2Cl_2, 595 mg (1.83 mmol, 2.0 eq.) of Cs_2CO_3 and 236 mg (914 µmol, 1.0 eq.) of the enol triflate **275** in 6.0 mL of dry, degassed DMF at rt. The reaction mixture was stirred at 60 °C for 17 h before 10 mg of QuadraSil AP® were added and the suspension was stirred for further 45 min. Then the solids were separated by decantation and H_2O was added to the product solution. After extraction with 4 x 20 mL of EtOAc the combined organic layers were washed with brine and sat. aqueous $NaHCO_3$, dried over Na_2SO_4 and the solvents were removed under reduced pressure. The residue was purified by silica gel column chromatography (*c*-Hex/EtOAc 20:1 to 5:1) to yield 190 mg (690 µmol, 76%) of enone **272** as a pale yellow oil.



M ($C_{17}H_{22}O_3$) = 274.36 g/mol

R_f (*c*-Hex/EtOAc 5:1) = 0.25

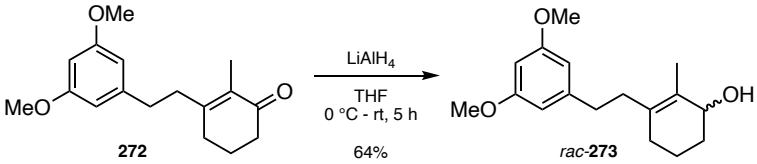
^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 6.30 – 6.36 (m, 3H, H-11,H-13), 3.78 (s, 6H, H-14), 2.70 (t, *J* = 8.2 Hz, 2H, H-9), 2.54 (t, *J* = 8.3 Hz, 2H, H-8), 2.38 (t, *J* = 6.7 Hz, 2H, H-6), 2.31 (ddd, *J* = 8.2 Hz, *J* = 4.2 Hz, *J* = 1.7 Hz, 2H, H-4), 1.91 (p, *J* = 6.2 Hz, 2H, H-5), 1.75 (t, *J* = 1.8 Hz, 3H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm] = 199.6 (C-1), 161.0 (C-12), 157.9 (C-3), 143.5 (C-10), 131.6 (C-2), 106.6 (C-11), 98.1 (C-13), 55.4 (C-14), 37.9 (C-6), 37.2 (C-8), 34.0 (C-9), 31.2 (C-4), 22.6 (C-5), 10.7 (C-7).

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3005 (w), 1659 (m), 1594 (s), 1460 (m), 1428 (m), 1379 (w), 1349 (m), 1326 (m), 1295 (m), 1204 (m), 1148 (s), 1060 (m), 1041 (m), 991 (w), 974 (w), 942 (w), 923 (w), 862 (w), 851 (m), 832 (m), 808 (m), 714 (w), 709 (w), 691 (m), 675 (m), 670 (m), 662 (w), 636 (w), 611 (w), 592 (w), 578 (m), 572 (m), 563 (w), 546 (m), 528 (m), 522 (w), 513 (w).

GC-MS (70 eV): *m/z* (%) = 274 (M^+, 100), 259 (37), 231 (2).

5.3.30 SYNTHESIS OF ALLYLIC ALCOHOL *rac*-**273**



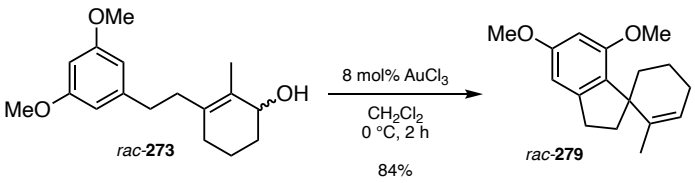
In a flame dried *Schlenk* flask, 60 mg (1.6 mmol, 6.1 eq.) of $LiAlH_4$ were suspended in 3.7 mL of dry THF and cooled to 0 °C. To this suspension, a solution of 70 mg (260 µmol, 1.0 eq.) of enone **272** in 7.3 mL of dry THF were added. The reaction was stirred for 5 h in the thawing ice bad before the reaction was terminated by carefully adding H_2O. The mixture was extracted with 3 x 20 mL EtOAc and the combined organic layers were washed with H_2O and dried over $MgSO_4$. Purification by silica column chromatography (*c*-Hex/EtOAc 10:1 to 5:1) gave 46 mg (170 µmol, 64%) of allylic alcohol *rac*-**273** as pale yellow solid in a mixture of inseparable side products. As separation was not feasible, this mixture was used in the following cyclization experiment without further purification and characterization of *rac*-**273**.

M ($C_{17}H_{24}O_3$) = 276.38 g/mol

R$_f$ (*c*-Hex/EtOAc 5:1) = 0.17

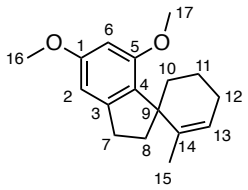
GC-MS (70 eV): *m/z* (%) = 276 (M^+, 1), 258 (61), 244 (24), 230 (27), 215 (10), 199 (21), 175 (19), 152 (100), 139 (33), 128 (9), 107 (42), 91 (49), 77 (37), 55 (22).

5.3.31 GOLD-CATALYZED CYCLIZATION OF ALLYLIC ALCOHOL *rac*-**273**



A solution of 25 mg (90 µmol, 1.0 eq.) of allylic alcohol *rac*-**273** in 14 mL of CH_2Cl_2 (HPLC grade) was cooled to 0 °C and 2.2 mg (7.3 µmol, 0.08 eq.) of $AuCl_3$ dissolved in 2.0 mL of CH_2Cl_2 were added. The yellow solution was stirred at 0 °C for 2 h before 15 mL of H_2O were added (discoloration). The aqueous phase was extracted with 3 x 20 mL of CH_2Cl_2 and the combined organic layers dried over $MgSO_4$. The resulting pale brown, viscous oil was purified by silica gel filtration (*c*-Hex/EtOAc 50:1 to 40.1) to give 20 mg (76 µmol, 84%) of spiro cycle *rac*-**279** as a colorless oil.

M ($C_{17}H_{22}O_2$) = 258.36 g/mol



R_f (*c*-Hex/EtOAc 30:1) = 0.59

^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm] = 6.41 – 6.30 (m, 1H, H-2), 6.26 (d, *J* = 2.0 Hz, 1H, H-6), 5.44 (ddt, *J* = 5.3 Hz, 2.6 Hz, 1.2, 1H, H-13), 3.78 (s, 3H, H-16), 3.73 (s, 3H, H-17), 2.96 – 2.86 (m, 1H, H-7), 2.87 – 2.79 (m, 1H, H-7'), 2.14 – 1.94 (m, 4H, H-12, H-8), 1.93 – 1.84 (m, 1H, H-11), 1.74 – 1.67 (m, 1H, H-10), 1.68 – 1.54 (m, 2H, H-10', H-11'), 1.44 (dt, *J* = 2.7 Hz, 1.4 Hz, 3H, H-15).

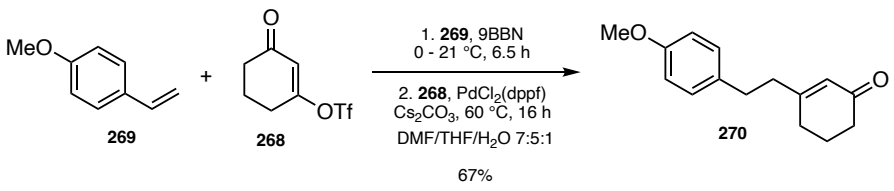
^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] = 160.5 (C-1), 157.0 (C-5), 146.6 (C-3), 139.2 (C-14), 129.5 (C-4), 121.4 (C-13), 100.6 (C-2), 97.0 (C-6), 55.5 (C-16), 55.3 (C-17), 51.6 (C-9), 36.8 (C-8), 33.0 (C-11), 31.4 (C-7), 25.6 (C-12), 20.6 (C-10), 20.1 (C-15).

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3428 (w), 3006 (w), 2942 (m), 2924 (m), 2842 (m), 2660 (w), 2464 (w), 2080 (w), 1721 (w), 1660 (w), 1604 (m), 1586 (s), 1512 (w), 1488 (m), 1471 (m), 1455 (m), 1443 (m), 1429 (m), 1370 (w), 1327 (s), 1297 (m), 1277 (m), 1246 (m), 1219 (m), 1200 (m), 1177 (m), 1171 (m), 1137 (s), 1089 (m), 1080 (m), 1071 (m), 1045 (m), 1023 (w), 1010 (m), 982 (w), 962 (m), 942 (m), 922 (w), 879 (w), 863 (w), 831 (s), 802 (s), 734 (w), 679 (w), 632 (m), 579 (m), 559 (w), 544 (w), 514 (m).

GC-MS (70 eV): *m/z* (%) = 258 (M^+, 100), 244 (35), 230 (48), 215 (23), 190 (53), 175 (27), 161 (11), 145 (11), 129 (17), 115 (27), 91 (24), 68 (71), 53 (30).

HRMS (EI):	Calc. [amu]	Found [amu]
	258.16143 $[M]^{\bullet+}$	258.16144 $[M]^{\bullet+}$

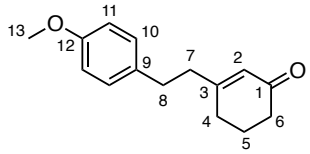
5.3.32 SYNTHESIS OF ENONE **270** VIA *SUZUKI* COUPLING



Based on a literature protocol,[105] in a *Schlenk* flask, a solution of 280 mg (2.07 mmol, 1.0 eq.) of olefin **269** in 4.1 mL of dry, degassed THF was cooled to 0 °C. Then, 8.20 mL (4.10 mmol, 3.3 eq.) of 9-BBN (0.5 M in THF) were added and the mixture was stirred at 21 °C for 6.5 h. The solution was then cooled to 0 °C before 1.8 mL of degassed H_2O were added and stirring was continued for

60 min at 0 °C. This borane solution was then transferred via needle to a second *Schlenk* flask charged with a solution of 86 mg (0.11 µmol, 0.09 eq.) of $PdCl_2$(dppf) x CH_2Cl_2, 1.33 g (4.08 mmol, 3.3 eq.) of Cs_2CO_3 and 300 mg (1.23 mmol, 1.0 eq.) of the enol triflate **268** in 14.5 mL of dry, degassed DMF at 21 °C. The reaction mixture was stirred at 60 °C for 16 h before 30 mg of QuadraSil AP® were added and the suspension was stirred for further 60 min. Then the solids were separated by decantation and H_2O was added to the product solution. After extraction with EtOAc (4x) the combined organic layers were washed with H_2O and sat. aqueous NaCl, dried over $MgSO_4$ and the solvents were removed under reduced pressure. The residue was purified by silica gel column chromatography (*c*-Hex/EtOAc 10:1 to 5:1) to yield 191 mg (829 µmol, 67%) of enone **270** as a pale yellow oil.

M ($C_{15}H_{18}O_2$) = 230.31 g/mol



R_f (*c*-Hex/EtOAc 5:1) =0.18

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 7.12 – 7.05 (m, 2H, H-10), 6.86 – 6.79 (m, 2H, H-11), 5.89 (p, *J* = 1.4 Hz, 1H, H-2), 3.79 (s, 3H, H-13), 2.77 (t, *J* = 7.8 Hz, 2H, H-8), 2.48 (t, *J* = 7.5 Hz, 2H, H-7), 2.35 (t, *J* = 6.9 Hz, 2H, H-6), 2.28 (t, *J* = 6.9 Hz, 2H, H-8), 1.96 – 1.99 (m, 2H, H-5).

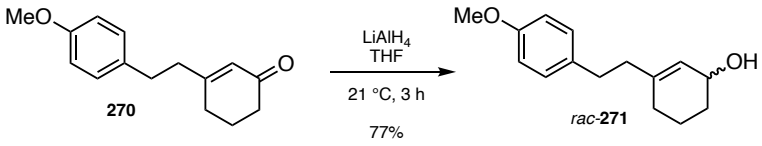
^{13}C NMR (125 MHz, $CDCl_3$) δ [ppm] = 200.0 (C-1), 165.6 (C-3), 158.2 (C-12), 132.9 (C-9), 129.3 (C-10), 126.2 (C-2), 114.1 (C-11), 55.4 (C-4), 40.1 (C-7), 37.5 (C-6), 32.7 (C-8), 30.1 (C-4), 22.8 (C-5).

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3483 (w), 2931 (w), 2836 (w), 1664 (s), 1624 (m), 1612 (m), 1584 (w), 1511 (s), 1455 (m), 1427 (w), 1374 (w), 1347 (w), 1325 (m), 1301 (m), 1242 (s), 1191 (m), 1177 (m), 1128 (m), 1105 (w), 1033 (m), 965 (m), 885 (m), 829 (m), 753 (w), 701 (w), 661 (w), 638 (w), 591 (w), 535 (m).

GC-MS (70 eV): *m/z* (%) = 230 (M^+, 4), 200 (3), 172 (1), 147 (1), 121 (100), 107 (3), 91 (12), 78 (15), 53 (8).

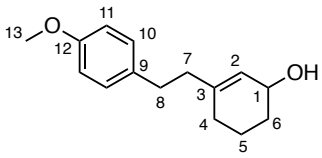
HRMS (EI):	Calc. [amu]	Found [amu]
	230.13013 $[M]^{\bullet+}$	230.13013 $[M]^{\bullet+}$

5.3.33 SYNTHESIS OF ALLYLIC ALCOHOL *rac*-**271**



In a flame dried *Schlenk* flask, 100 mg (2.64 mmol, 6.1 eq.) of $LiAlH_4$ were suspended in 6.0 mL of dry THF and cooled to 0 °C. To this suspension, a solution of 100 mg (434 µmol, 1.0 eq.) of enone **257** in 22 mL of dry THF was added. The reaction was stirred at 21 °C for 3 h before the reaction was terminated by carefully adding 20 mL of H_2O. The mixture was extracted with 3 x 20 mL EtOAc and the combined organic layers were dried over $MgSO_4$. Removal of the solvent under reduced pressure gave 78 mg (336 µmol, 77%) of allylic alcohol *rac*-**271** as colorless solid.

M ($C_{15}H_{20}O_2$) = 232.32 g/mol



R$_f$ (*c*-Hex/EtOAc 3:1) =0.30

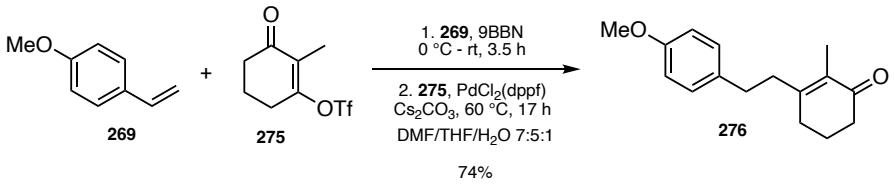
^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 7.09 (d, J = 8.6 Hz, 2H, H-11), 6.82 (t, J = 8.6 Hz, 1H, H-10), 5.51 – 5.48 (m, 1H, H-2), 4.21 – 4.16 (m, 1H, H-1), 3.79 (s, 3H, H-13), 2.71 – 2.65 (m, 2H, H-8), 2.27 – 2.22 (m, 2H, H-7), 2.09 – 1.90 (m, 2H, H-4), 1.82 – 1.69 (m, 2H, H-5, H-6). 1.61 – 1.55 (m, 2H, H-5', H-6').

^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 157.9 (C-12), 142.0 (C-3), 134.3 (C-9), 129.4 (C-11), 124.3 (C-2), 113.9 (C-10), 66.0 (C-1), 55.4 (C-13), 39.8 (C-7), 33.4 (C-8), 32.0 (C-6), 28.8 (C-4), 19.2 (C-5).

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3351 (w), 2996 (w), 2929 (m), 2858 (m), 2834 (w), 1876 (w), 1759 (w), 1665 (w), 1612 (m), 1584 (w), 1511 (s), 1464 (m), 1453 (m), 1441 (m), 1342 (w), 1321 (w), 1300 (m), 1243 (s), 1177 (m), 1106 (w), 1059 (m), 1035 (s), 959 (m), 907 (m), 863 (w), 826 (m), 785 (w), 752 (w), 704 (w), 675 (w), 638 (w), 577 (w), 526 (m), 450 (w), 428 (w).

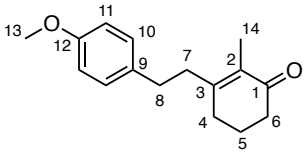
HRMS (EI):	Calc. [amu]	Found [amu]
	232.14578 $[M]^{\bullet+}$	232.1456 $[M]^{\bullet+}$

5.3.34 SYNTHESIS OF ENONE **276** VIA *SUZUKI* COUPLING[105]



According to a literature protocol,[105] in a *Schlenk* flask, a solution of 153 mg (1.14 mmol, 1.1 eq.) of olefin **269** in 2.2 mL of dry, degassed THF was cooled to 0 °C. Then, 4.5 mL (2.3 mmol, 2.0 eq.) of 9-BBN (0.5 M in THF) were added and the mixture was stirred at rt for 3.5 h. The solution was then cooled to 0 °C before 1.0 mL of degassed H_2O were added and stirring was continued for 40 min at 0 °C. This borane solution was then transferred via needle to a second *Schlenk* flask charged with a solution of 46 mg (56 µmol, 0.05 eq.) of $PdCl_2$(dppf) x CH_2Cl_2, 730 mg (2.24 mmol, 2.0 eq.) of Cs_2CO_3 and 289 mg (1.12 mmol, 1.0 eq.) of the enol triflate **275** in 7.5 mL of dry, degassed DMF at rt. The reaction mixture was stirred at 60 °C for 17 h before 12 mg of QuadraSil AP® were added as a metal scavenger and the suspension was stirred for further 45 min. Then the solids were separated by decantation and H_2O was added to the product solution. After extraction with 4 x 20 mL of EtOAc the combined organic layers were washed with brine and sat. aqueous $NaHCO_3$, dried over Na_2SO_4 and the solvents were removed under reduced pressure. The residue was purified by silica gel column chromatography (*c*-Hex/EtOAc 20:1 to 5:1) to yield 202mg (826 µmol, 74%; Lit.: 76%) of enone **276** as a pale yellow oil.

M ($C_{16}H_{20}O_2$) = 244.33 g/mol



R_f (*c*-Hex/EtOAc 5:1) =0.29

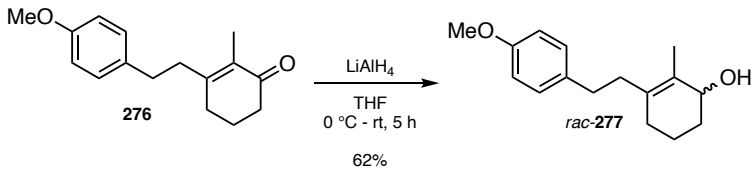
^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 7.09 (d, J = 8.5 Hz, 2H, H-10), 6.83 (d, J = 8.5 Hz, 2H, H-11), 3.79 (s, 3H, H-13), 2.72 (t, J = 8.7 Hz, 2H, H-8), 2.51 (t, J = 7.9 Hz, 2H, H-7), 2.37 (t, J = 6.4 Hz, 2H, H-6), 2.31 – 2.26 (m, 2H, H-4), 1.87 – 1.93 (m, 2H, H-5), 1.71 (s, 3H, H-14).

^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm] = 199.7 (C-1), 158.1 (C-12, C-3), 133.2 (C-9), 131.6 (C-2), 129.3 (C-10), 114.0 (C-11), 55.4 (C-13), 37.9 (C-6), 37.7 (C-7), 32.9 (C-8), 31.3 (C-4), 22.6 (C-5), 10.7 (C-14).

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3379 (w), 2922 (m), 2861 (w), 2056 (w), 1739 (w), 1661 (m), 1625 (w), 1613 (w), 1584 (w), 1512 (m), 1466 (w), 1451 (m), 1412 (m), 1385 (m), 1360 (m), 1340 (m), 1326 (m), 1300 (m), 1244 (m), 1210 (w), 1176 (m), 1110 (w), 1082 (m), 1035 (m), 1008 (m), 978 (m), 954 (w), 937 (w), 915 (w), 876 (m), 845 (w), 819 (m), 809 (m), 756 (w), 727 (w), 700 (m), 675 (m), 656 (w), 593 (w), 540 (m), 527 (m).

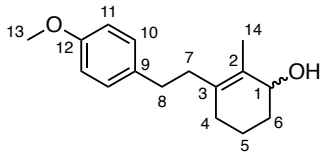
GC-MS (70 eV): *m/z* (%) = 244 (M^+, 9), 121 (100), 91 (12), 77 (13), 55 (3).

5.3.35 SYNTHESIS OF ALLYLIC ALCOHOL *rac*-**277**



In a flame dried *Schlenk* flask, 73 mg (1.9 mmol, 7.3 eq.) of $LiAlH_4$ were suspended in 12.3 mL of dry THF and cooled to 0 °C. To this suspension, a solution of 63 mg (260 µmol, 1.0 eq.) of enone **276** in 7.3 mL of dry THF was added. The reaction was stirred for 5 h in the thawing ice bad before the reaction was terminated by carefully adding H_2O. The mixture was extracted with 3 x 20 mL EtOAc and the combined organic layers were washed with H_2O and dried over $MgSO_4$. Removal of the solvent under reduced pressure and purification by silica column chromatography (*c*-Hex/EtOAc 30:1 to 15:1) gave 39 mg (0.16 mmol, 62%) of allylic alcohol *rac*-**277** as pale yellow solid.

M ($C_{16}H_{22}O_2$) = 246.35 g/mol



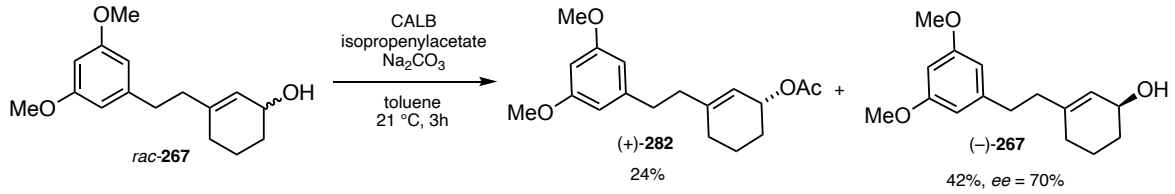
R_f (*c*-Hex/EtOAc 5:1) =0.18

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 7.00 (dd, *J* = 133.2, 8.6 Hz), 3.94 (t, *J* = 4.2 Hz, 1H, H-1), 3.79 (s, 3H, H-13), 2.61 (m, 2H, H-8), 2.26 (td, *J* = 7.5 Hz, 2.7 Hz, 2H, H-7), 2.03 – 1.89 (m, 2H, H-4), 1.83 – 1.73 (m, 2H, H-5), 1.67 (s, 3H, H-14), 1.61 – 1.52 (m, 2H, H-6).

^{13}C NMR (125 MHz, $CDCl_3$) δ [ppm] = 157.8 (C-12), 134.5 (C-9), 130.7 (C-2), 129.3 (C-10), 128.7 (C-3), 113.7 (C-11), 70.0 (C-1), 55.2 (C-13), 35.8 (C-7), 33.3 (C-8), 32.4 (C-5), 29.9 (C-4), 18.5 (C-6), 16.3 (C-14).

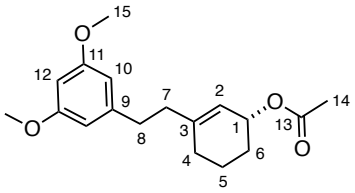
GC-MS (70 eV): *m/z* (%) = 246 (M^+, 3), 228 (9), 213 (3), 134 (7), 121 (100), 107 (4), 91 (19), 77 (15), 64 (3), 51 (4).

5.3.36 KINETIC RESOLUTION OF ALLYLIC ALCOHOL **267**



Based on a literature protocol,[118] in a flame dried *Schlenk* flask 25 mg (95.3 µmol, 1.0 eq) of a racemic mixture of allylic alcohol *rac*-**267** together with 3.8 mg (35.0 µmol, 0.4 eq.) of Na_2CO_3, 4.8 mg of CAL-B and 21.0 µL (191 µmol, 2.0 eq.) of *iso*propenylacetate were dissolved in 0.4 mL of dry toluene. The colorless suspension was stirred at 21 °C for 3 h before the solid parts were filtered off and the solvent was evaporated. Purification via silica column chromatography (*c*-Hex/EtOAc 2:1) delivered 7.3 mg (23.1 µmol, 24%) of acetate (+)-**282** and 10.4 mg (39.6 µmol, 42% of enantioenriched alcohol (–)-**267** with an enantiomeric excess of 70% *ee* determined by chiral HPLC using a racemic standard (see chapter **6.3**). The latter crystalized slowly at rt.

acetate (+)-**282**:



M ($C_{18}H_{24}O_4$) = 304.39 g/mol

R$_f$ (*c*-Hex/EtOAc 2:1) =0.51

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] = 6.33 (d, *J* = 2.2 Hz, 2H, H-10), 6.30 (t, *J* = 2.2 Hz, 1H, H-12), 5.52 – 5.49 (m, 1H, H-2), 5.26 (d, *J* = 3.6 Hz, 1H, H-1), 3.78 (s, 6H, H-15), 2.67 (t, *J* = 8.1 Hz, 2H, H-8), 2.31 – 2.25 (t, *J* = 8.1 Hz, 2H, H-7), 2.07 – 1.94 (m, 2H, H-4), 2.04 (s, 3H, H-14), 1.83 – 1.61 (m, 4H, H-5, H-6).

^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] = 171.0 (C-13), 160.9 (C-11), 144.6 (C-9), 141.9 (C-3), 124.4 (C-2), 106.6 (C-10), 97.9 (C-12), 66.0 (C-1), 55.4 (C-15), 39.3 (C-7), 34.6 (C-8), 32.0 (C-6), 28.8 (C-4), 19.3 (C-5).

FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2937 (m), 2862 (w), 2837 (w), 1726 (m), 1596 (s), 1461 (m), 1429 (m), 1370 (m), 1322 (w), 1293 (w), 1241 (s), 1205 (m), 1151 (s), 1061 (m), 1019 (m), 954 (w), 909 (w), 830 (w), 691 (w), 608 (w).

GC-MS (70 eV): *m/z* (%) = 306 (M^++H_2, 5), 246 (5), 203 (15), 165 (5), 152 (100), 121 (4), 91 (10), 77 (10).

[α]$^{20}_{\lambda}$ (*c* = 0.34 g/100 mL, $CHCl_3$): + 234° (436 nm), + 129° (546 nm), + 112° (579 nm), + 107° (589 nm).

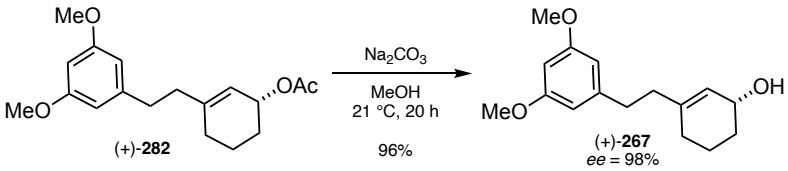
allylic alcohol (–)-**265**:

M ($C_{16}H_{22}O_3$) = 262.35 g/mol

[α]$^{20}_{\lambda}$ (*c* = 0.49 g/100 mL, $CHCl_3$): – 39° (436 nm), – 22° (546 nm), – 19° (579 nm), – 19° (589 nm).

See chapter **5.3.26** for additional analytical data.

5.3.37 SAPONIFICATION OF ACETATE (+)-282



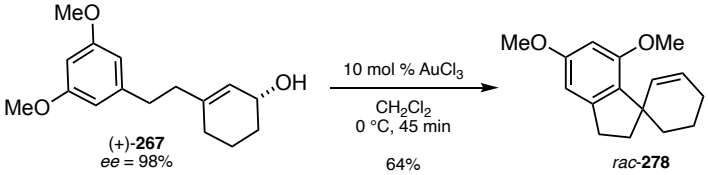
Acetate **278** (7.0 mg, 23 µmol, 1.0 eq.) was dissolved in MeOH (HPLC grade) and 10 mg (94 µmol, 4.1 eq.) Na_2CO_3 were added. After stirring at 21 °C for 20 h H_2O was added and the aqueous phase was extracted with 4 x EtOAc. After removal of the solvent 5.8 mg (22.1 µmol, 96%) of enantiopure allylic alcohol (+)-**265** was obtained with an enantiomeric excess of 98% *ee* determined by chiral HPLC using a racemic standard (see chapter **6.3**) as colorless oil.

M ($C_{16}H_{22}O_3$) = 262.35 g/mol

[α]$^{20}_{\lambda}$ (*c* = 0.44 g/100 mL, $CHCl_3$): + 42° (436 nm), + 26° (546 nm), + 22° (579 nm), + 20° (589 nm).

See chapter **5.3.26** for additional analytical data.

5.3.38 GOLD-CATALYZED CYCLIZATION OF ENANTIOPURE ALLYLIC ALCOHOL (+)-267



A solution of 3.5 mg (13 µmol, 1.0 eq.) of enantiopure allylic alcohol (+)-**267** in 1.3 mL of CH_2Cl_2 (HPLC grade) was cooled to 0 °C and 0.4 mg (1.3 µmol, 0.1 eq.) of $AuCl_3$ dissolved in 0.3 mL of

CH_2Cl_2 were added. The yellow solution was stirred for 45 min at 0 °C before H_2O was added (discoloration). The aqueous phase was extracted 3 x with CH_2Cl_2 and the combined organic layers dried over $MgSO_4$. The resulting brown, viscous oil was purified by silica gel filtration (*c*-Hex/EtOAc 50:1) to give 2.0 mg (8.2 µmol, 64%) of spiro cycle *rac*-**278** as a racemic mixture.

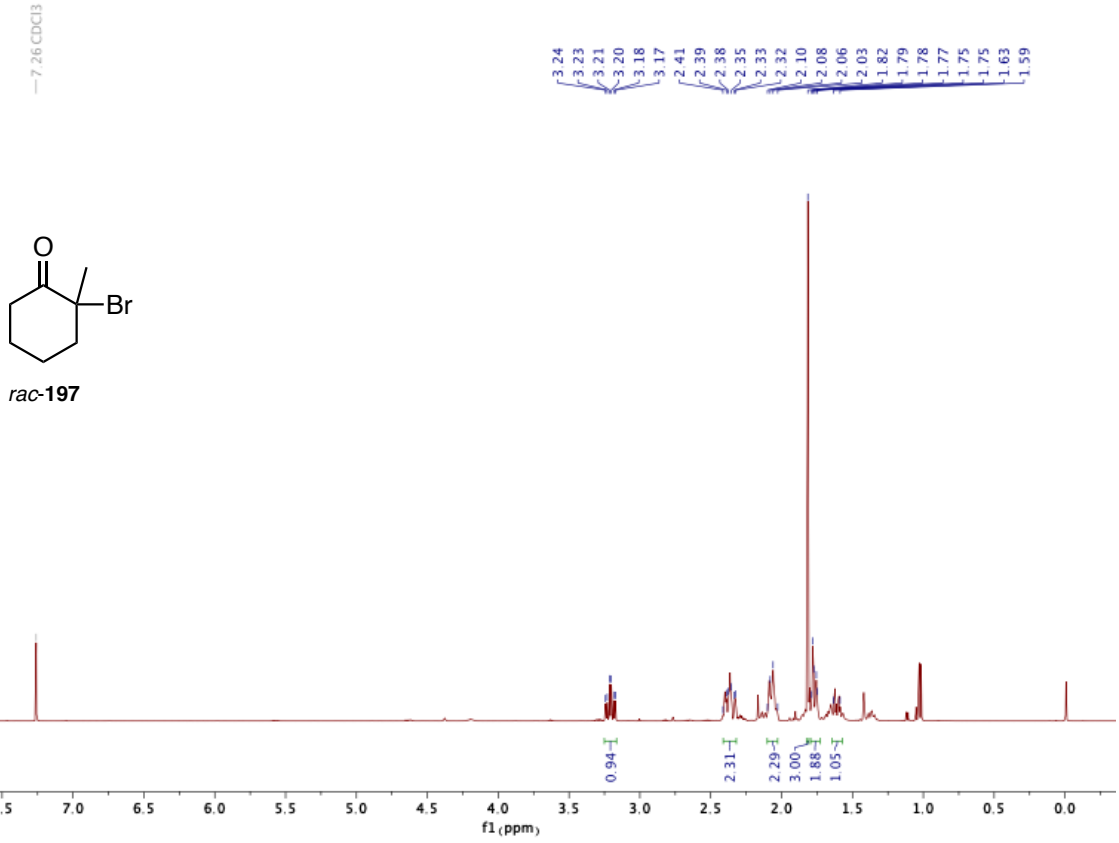
M ($C_{16}H_{20}O_2$) = 244.33 g/mol

See chapter **5.3.21** for analytical data.

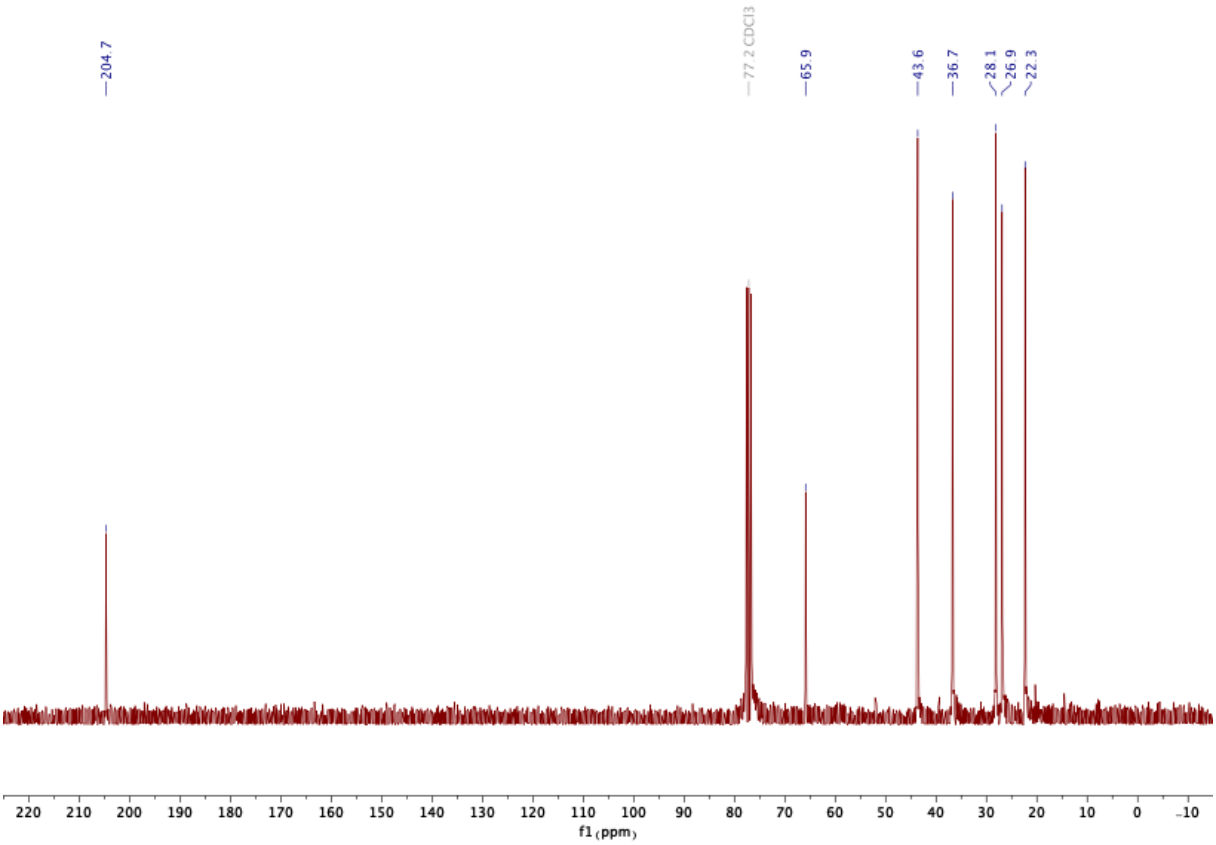
6 APPENDIX

6.1 NMR SPECTRA

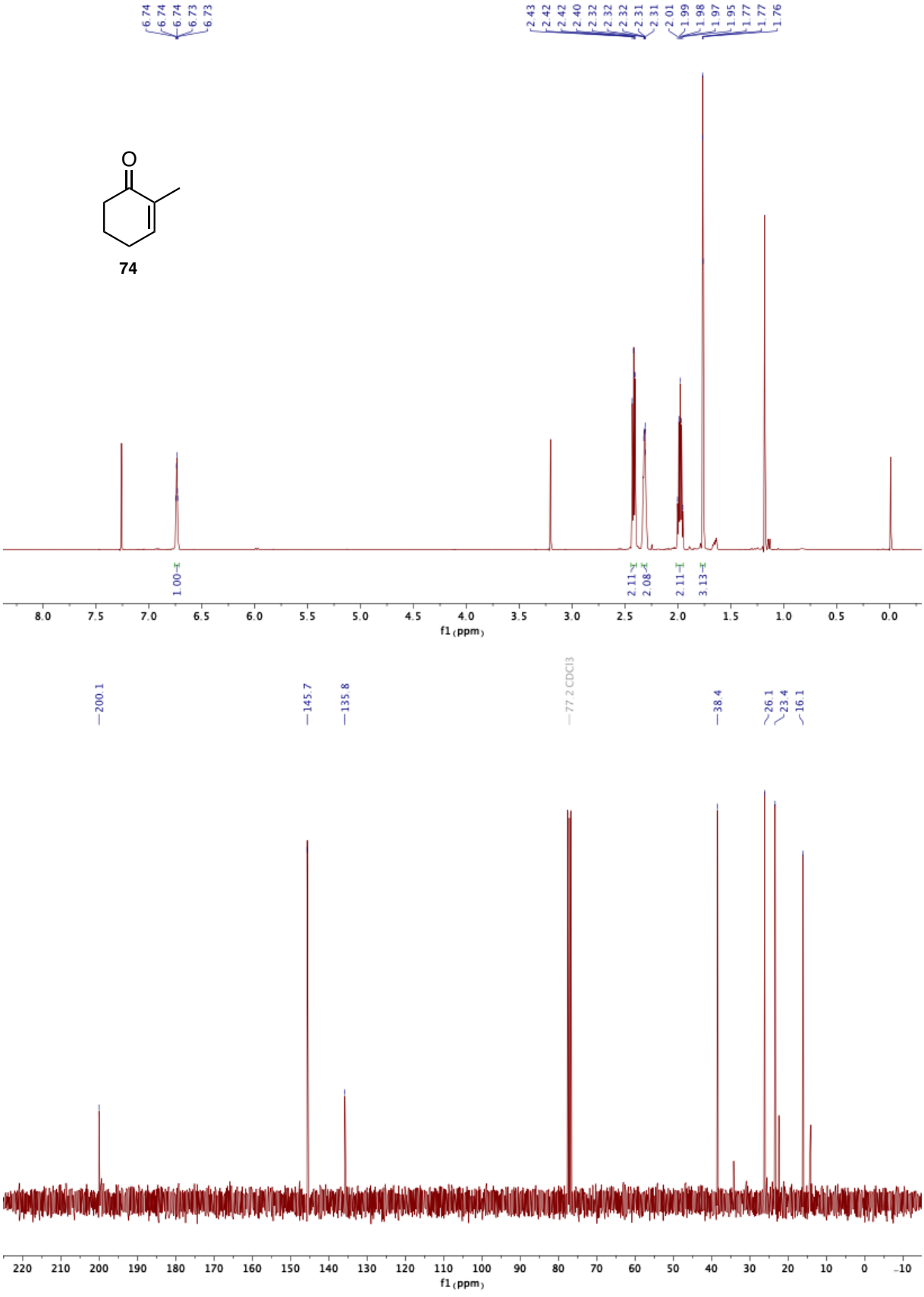
6.1.1 ^{1}H AND ^{13}C NMR SPECTRA OF *rac*-2-BROMO-2-METHYLCYCLOHEXANONE (*rac*-**197**)



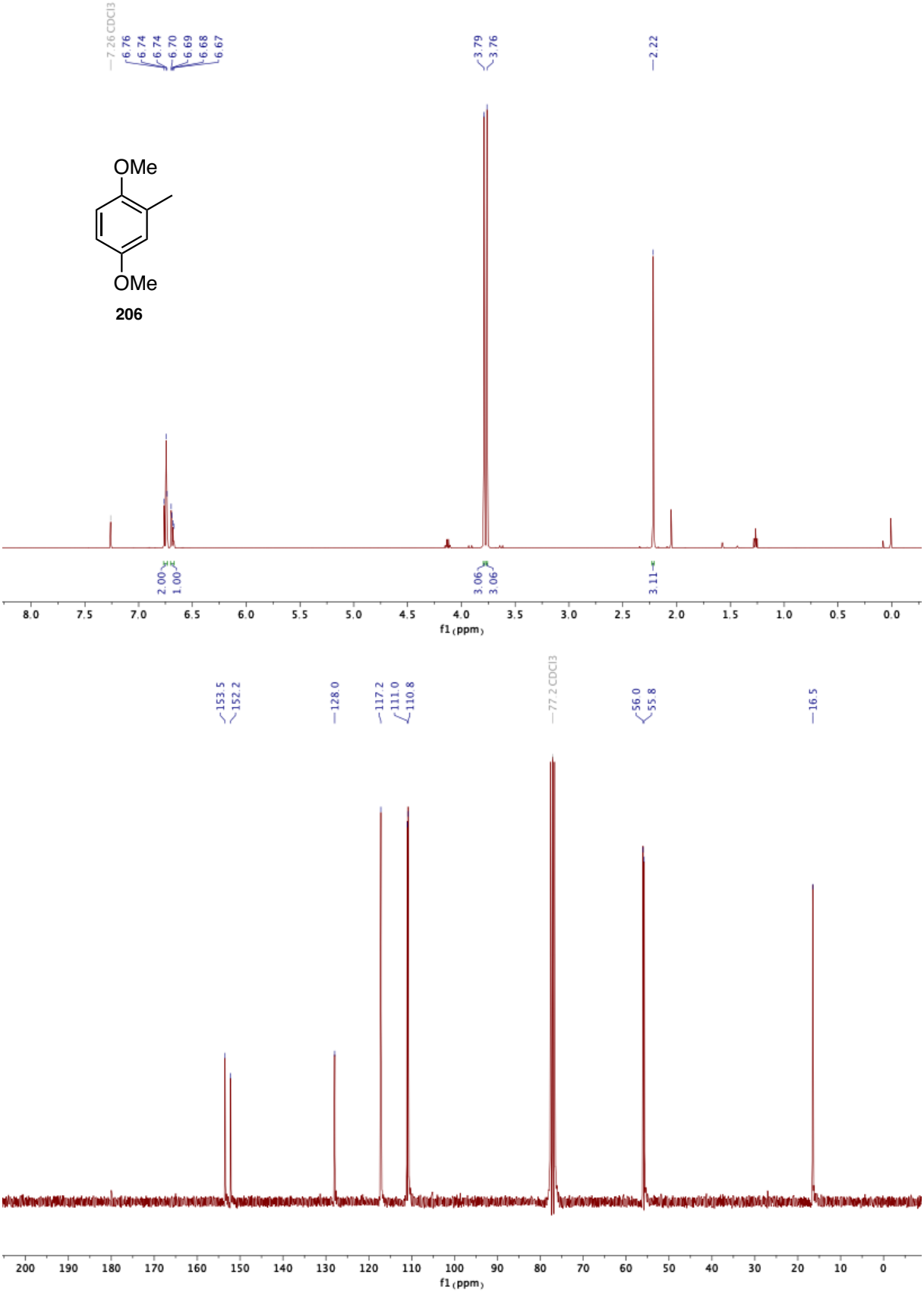
rac-**197**



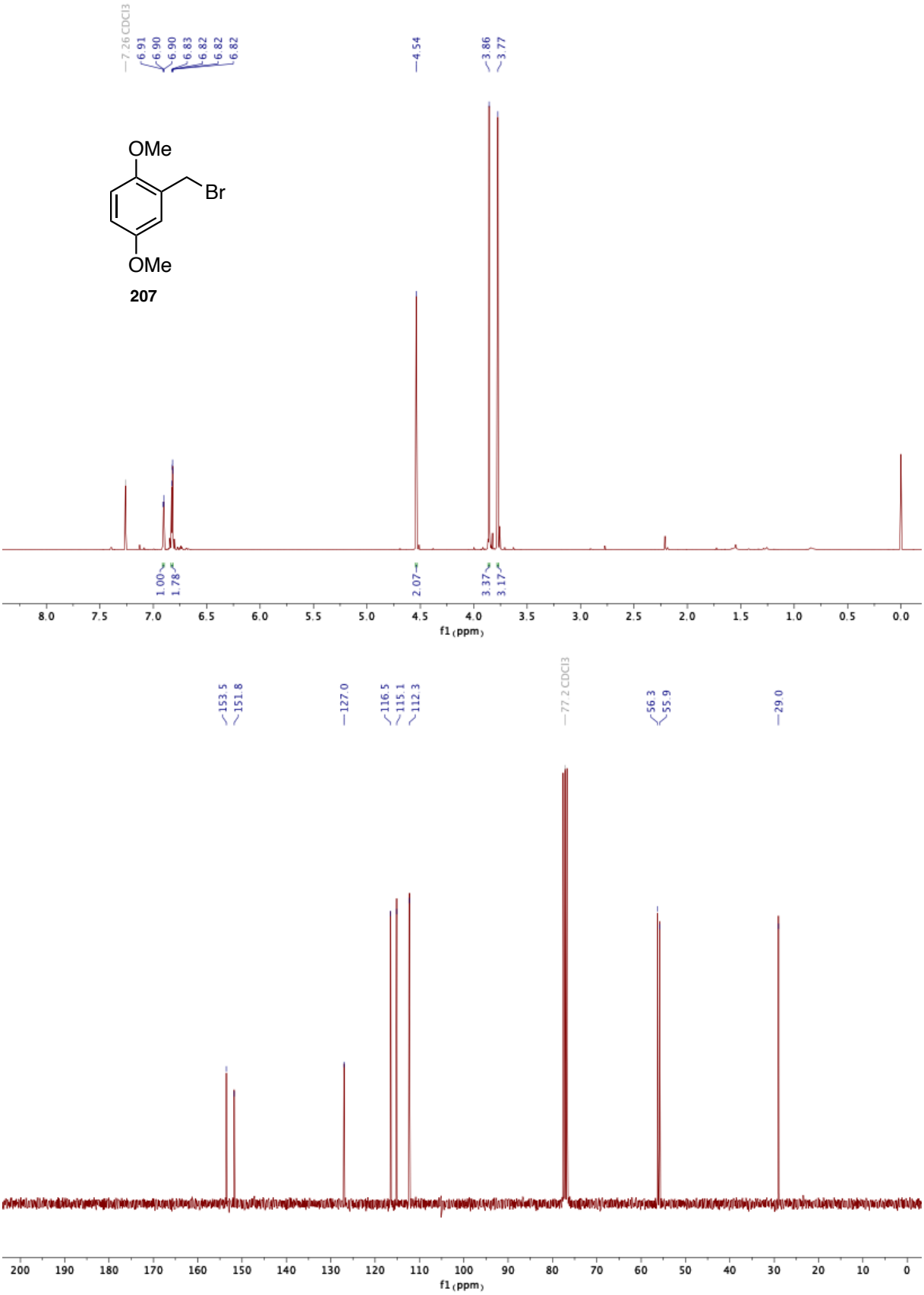
6.1.2 ^{1}H AND ^{13}C NMR SPECTRA OF ENONE **74**



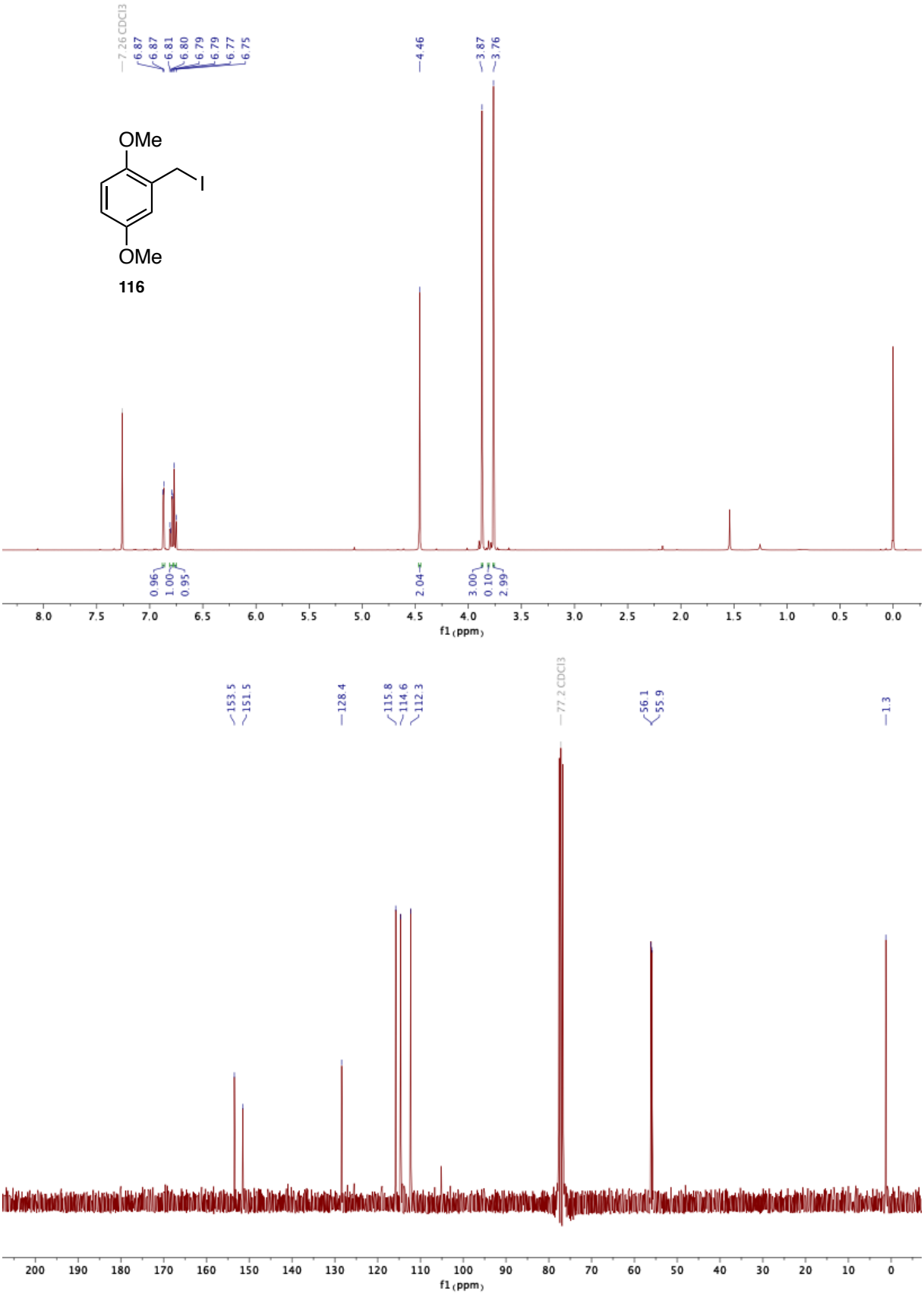
6.1.3 ^{1}H AND ^{13}C NMR SPECTRA OF 1,4-DIMETHOXY-2-METHYLBENZENE (**206**)



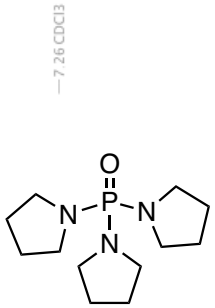
6.1.4 ^{1}H AND ^{13}C NMR SPECTRA OF 2-(BROMOMETHYL)-1,4-DIMETHOXYBENZENE (**207**)



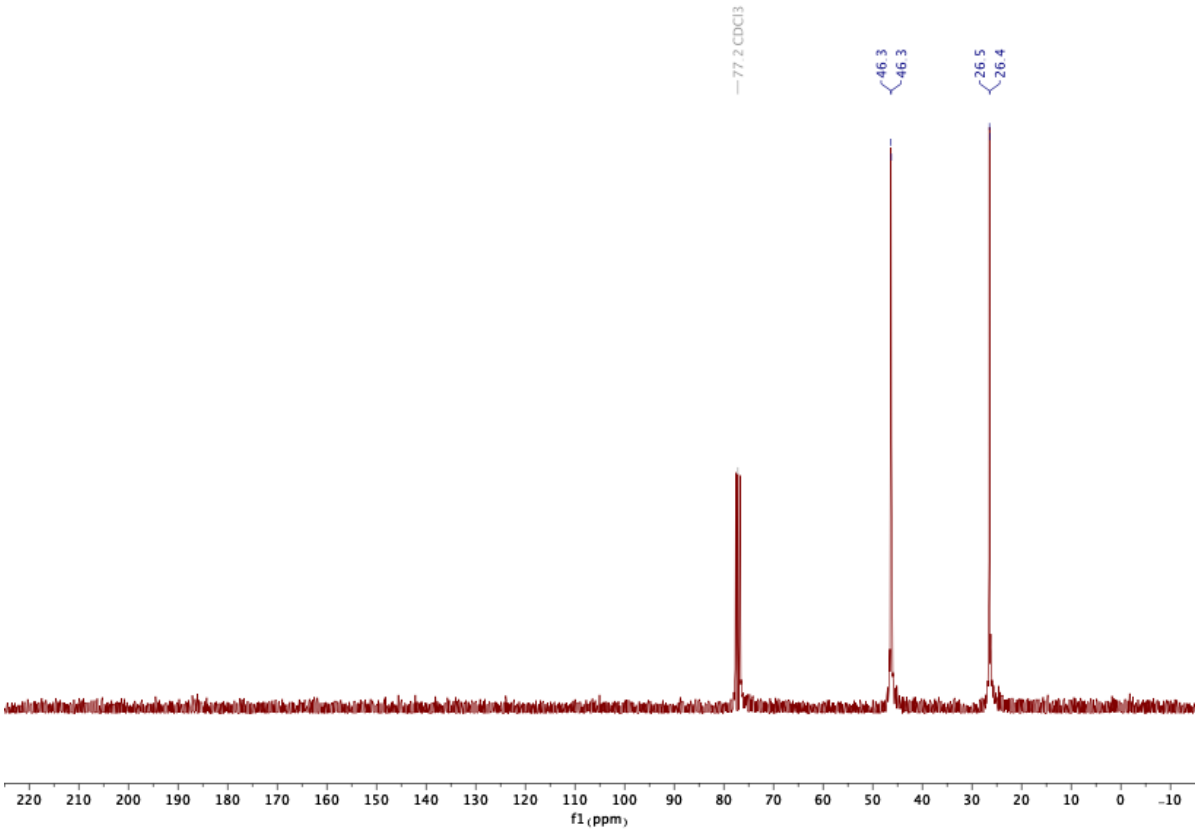
6.1.5 ^{1}H AND ^{13}C NMR SPECTRA OF 2-(IODOMETHYL)-1,4-DIMETHOXYBENZENE (**116**)

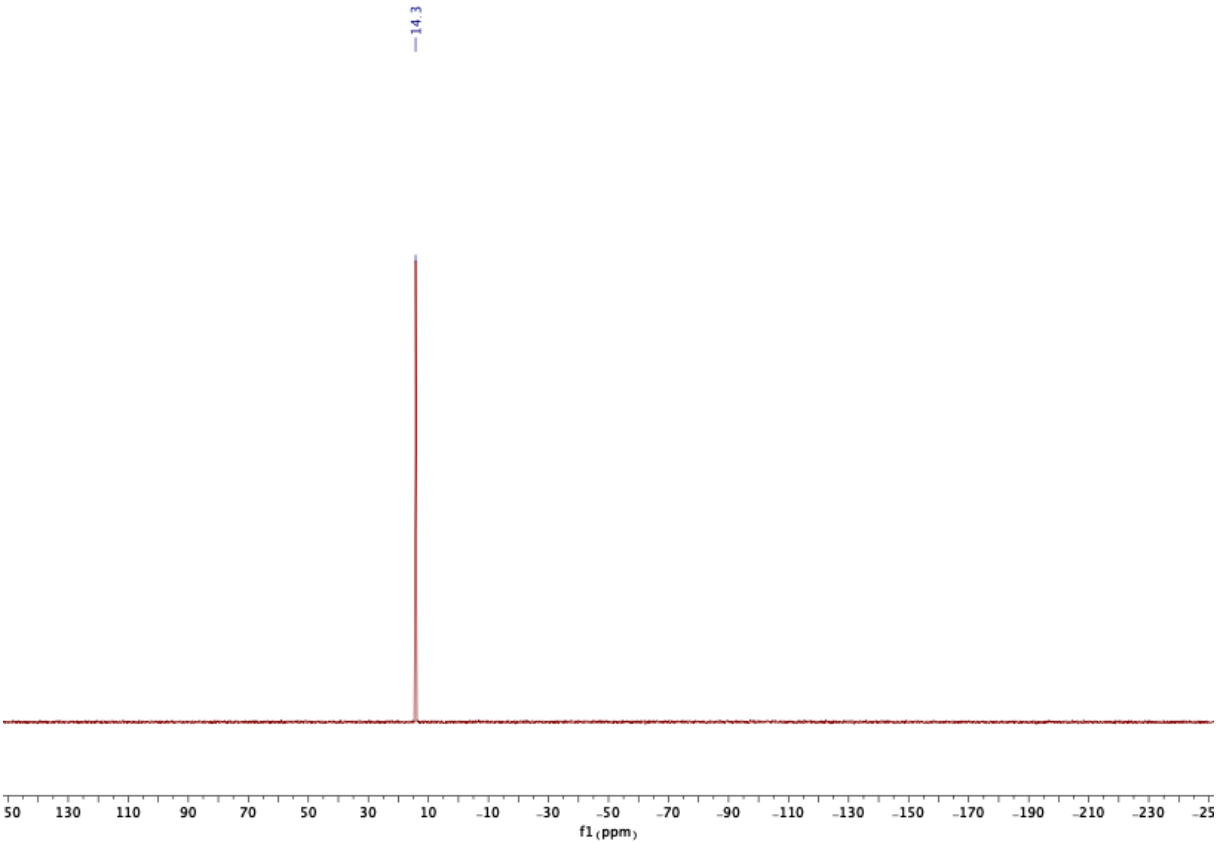


6.1.6 ^{1}H, ^{13}C AND ^{31}P NMR SPECTRA OF TPPA (**204**)

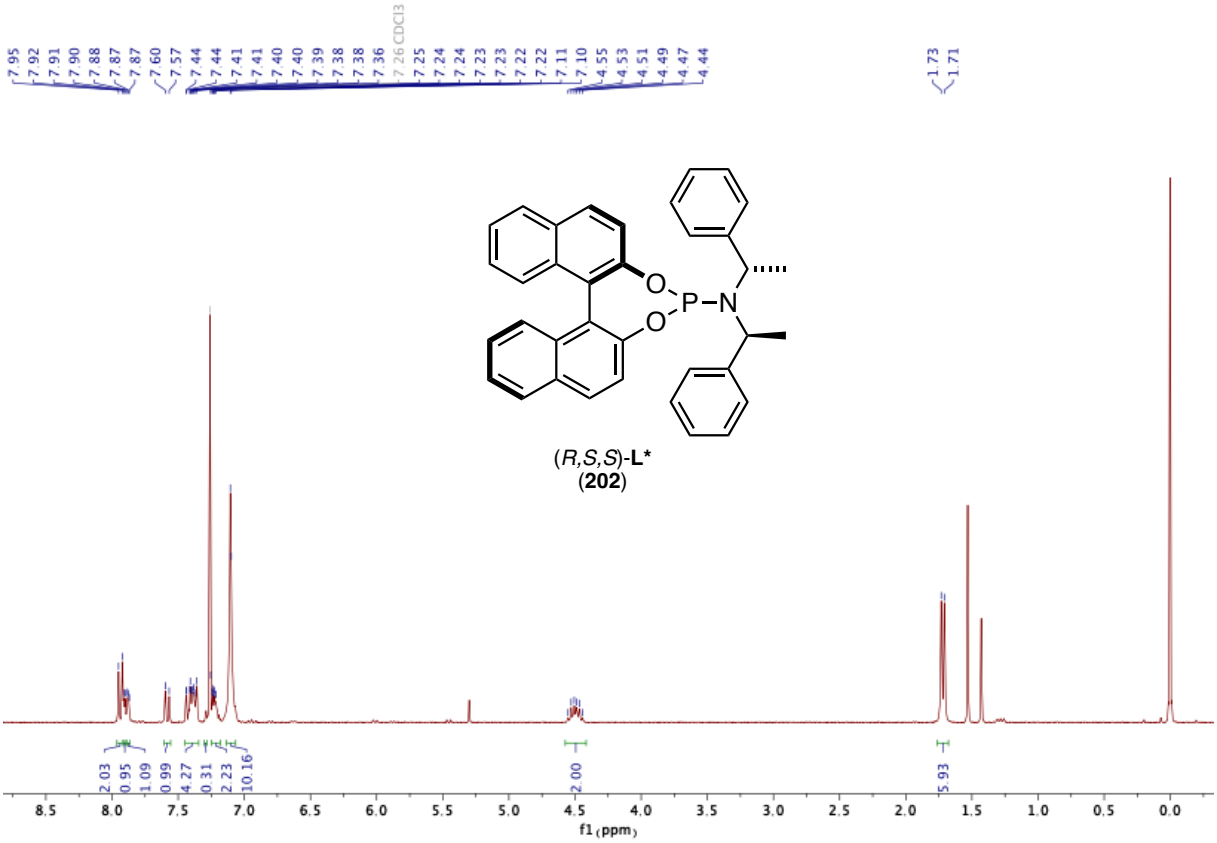


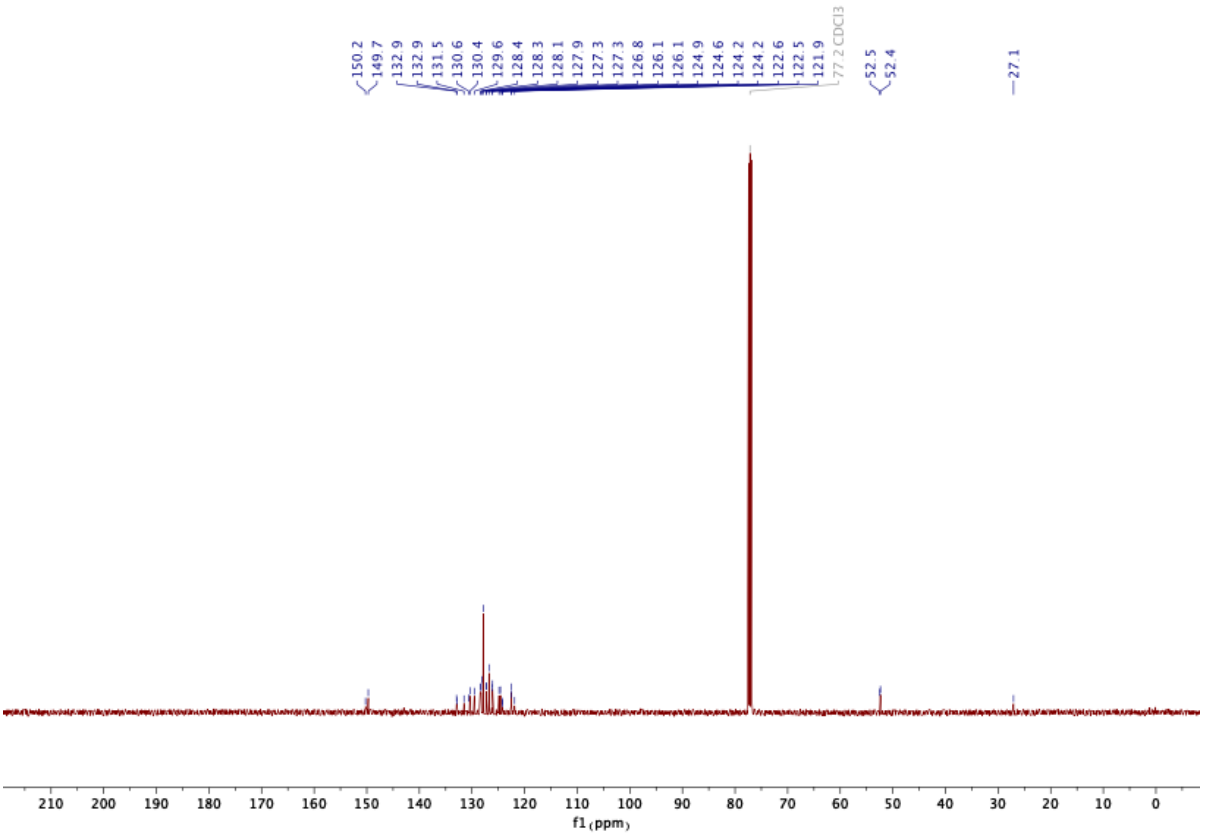
204

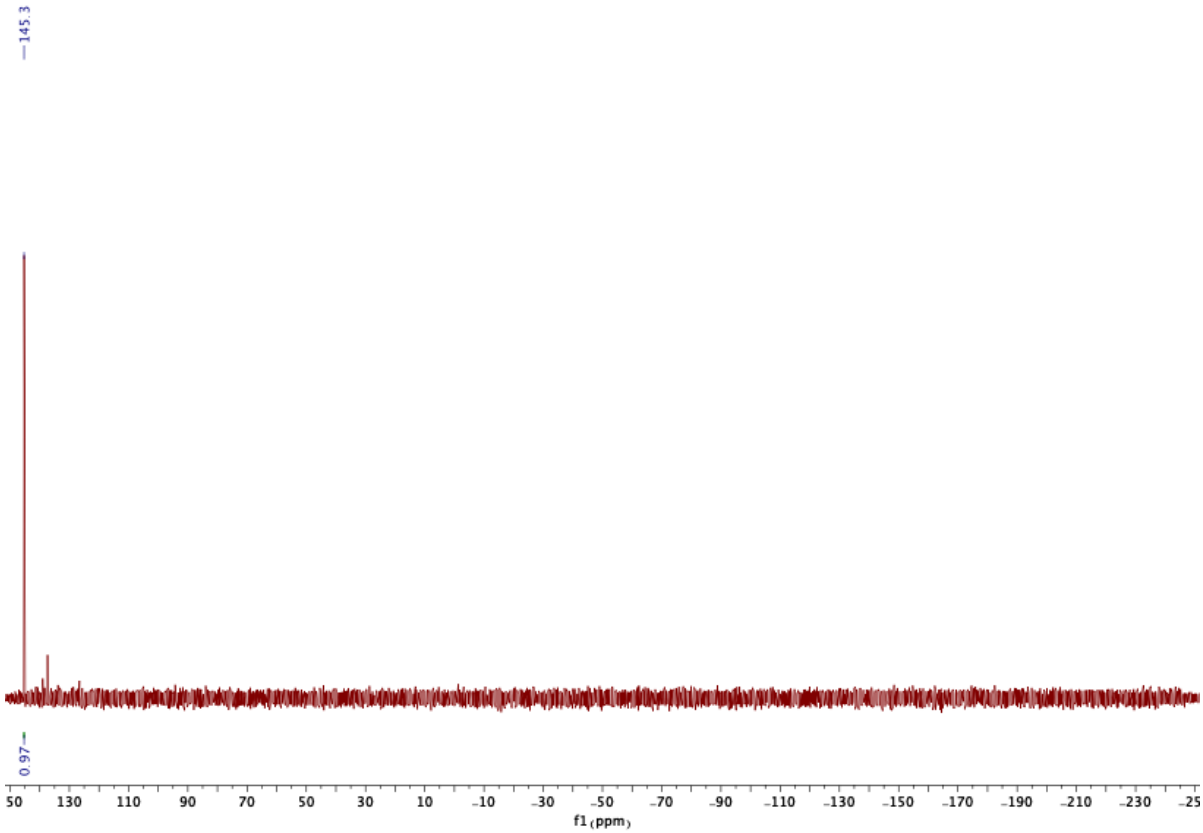



14.3
50
130
110
90
70
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
-25
f1 (ppm)

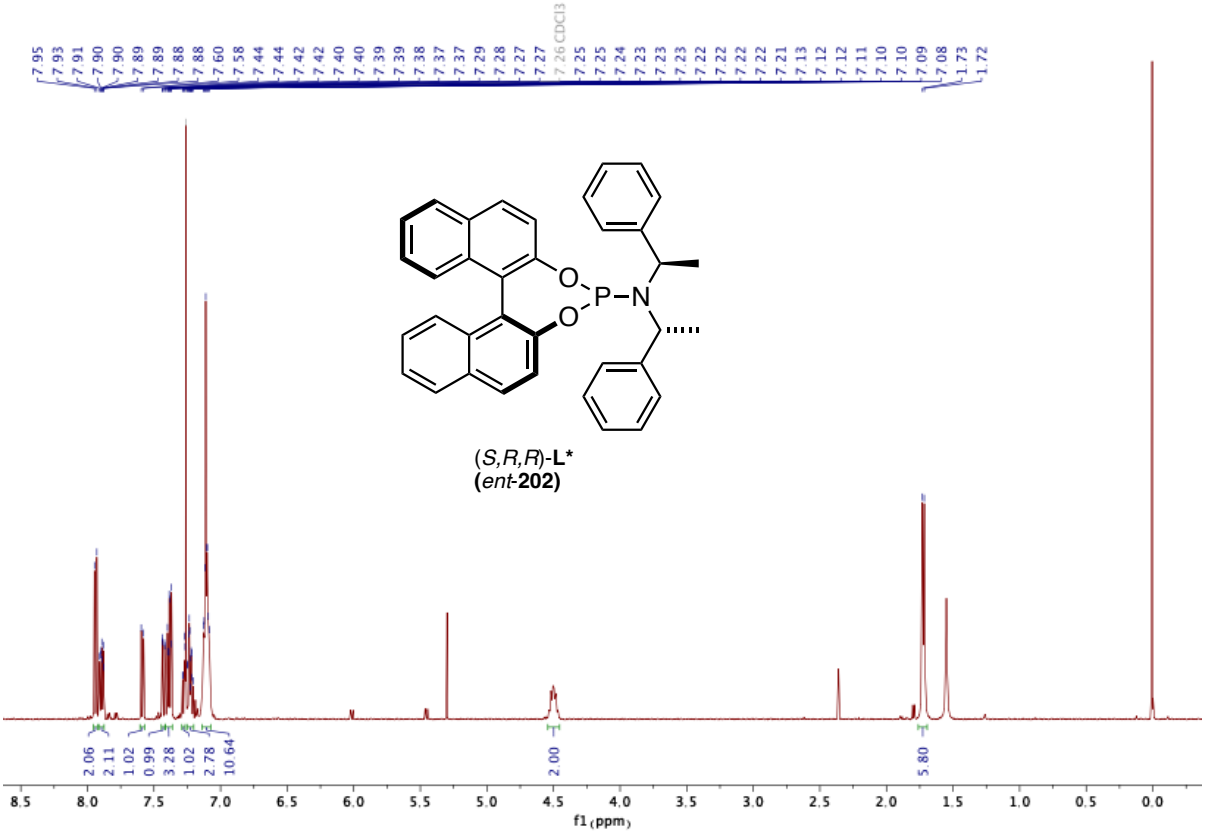
6.1.7 ^{1}H, ^{13}C NMR AND ^{31}P SPECTRA OF PHOSPHORAMIDITE LIGAND **202**

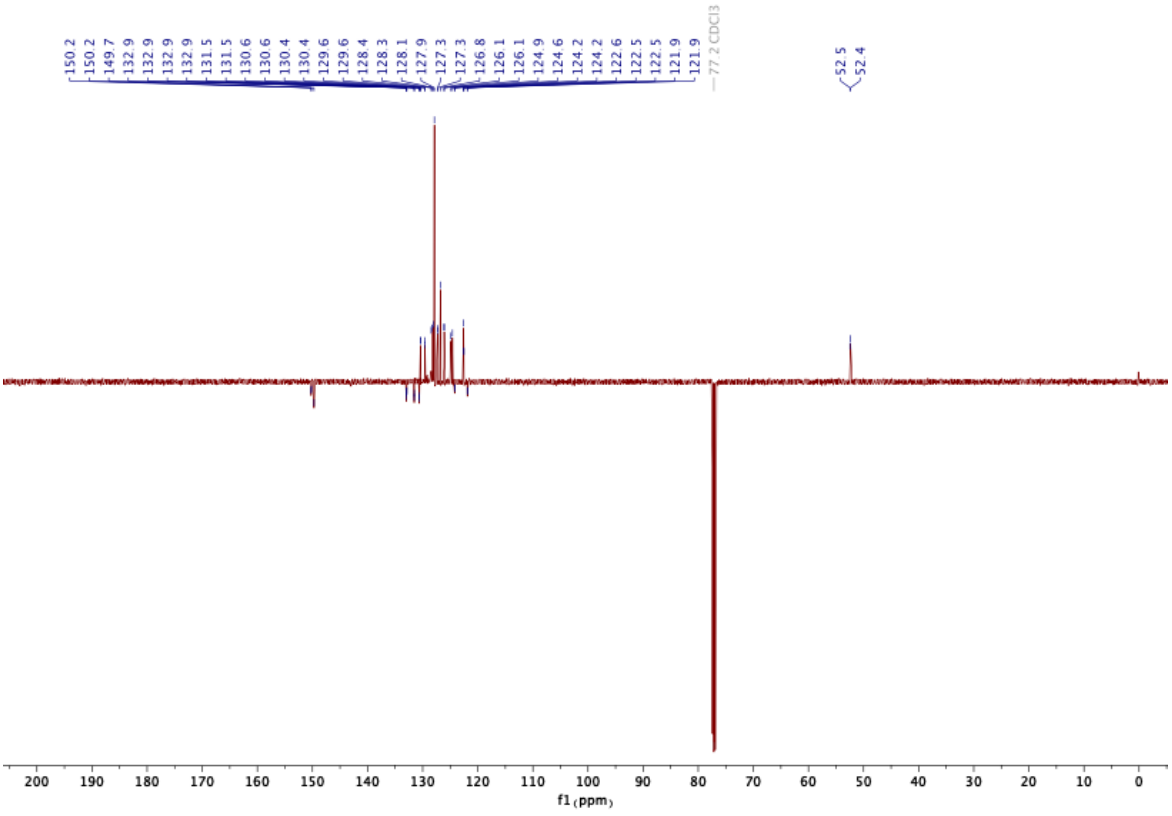


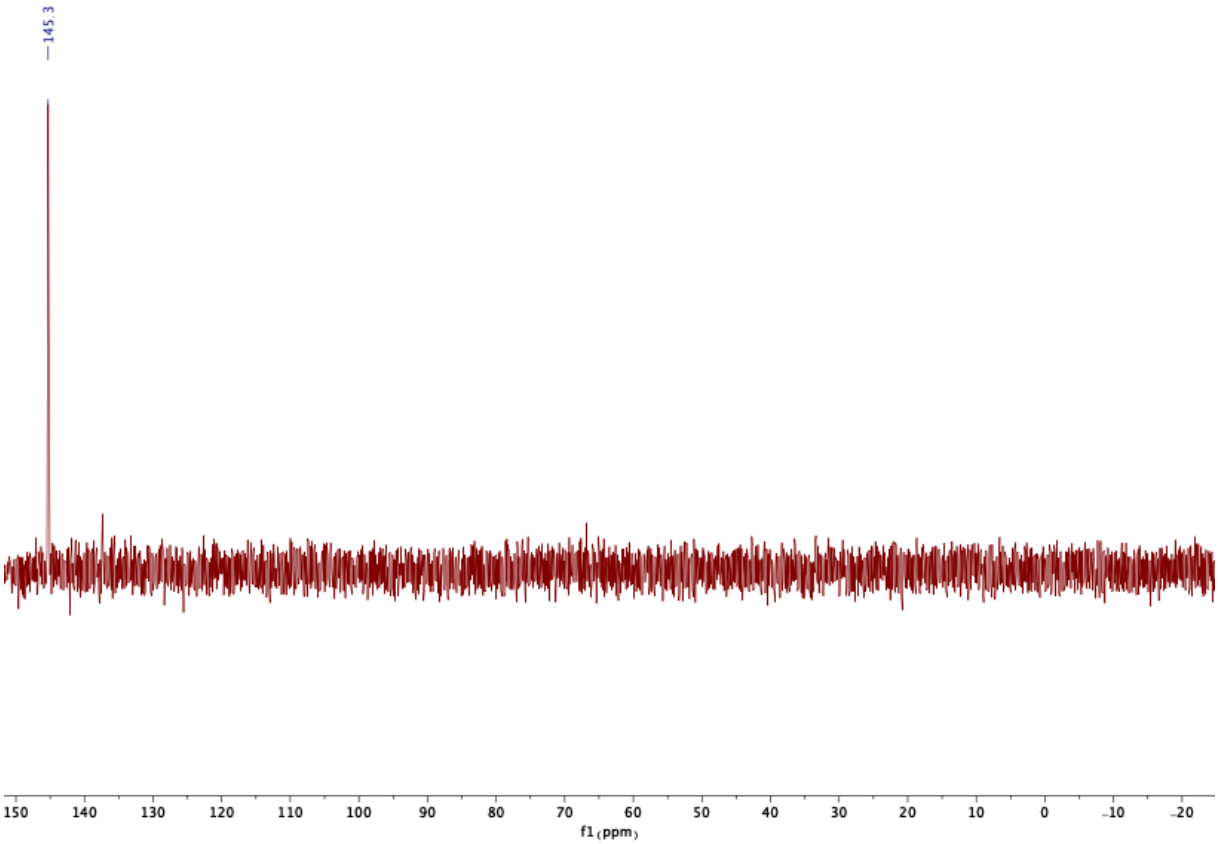



145.3
0.97
50
130
110
90
70
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
-25
f1 (ppm)

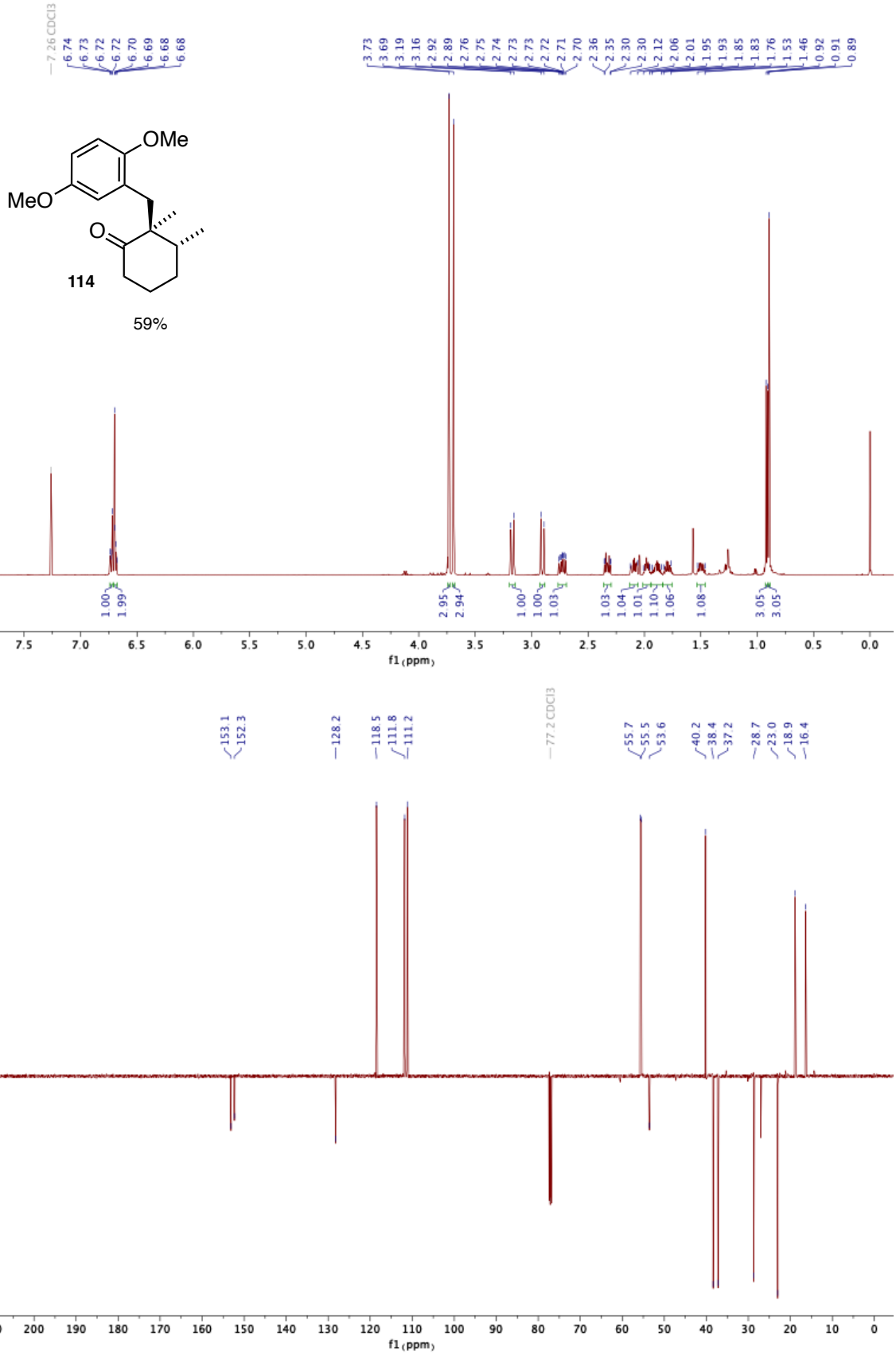
6.1.8 ^{1}H, ^{13}C AND ^{31}P NMR SPECTRA OF PHOSPHORAMIDITE LIGAND (*ent*-**202**)



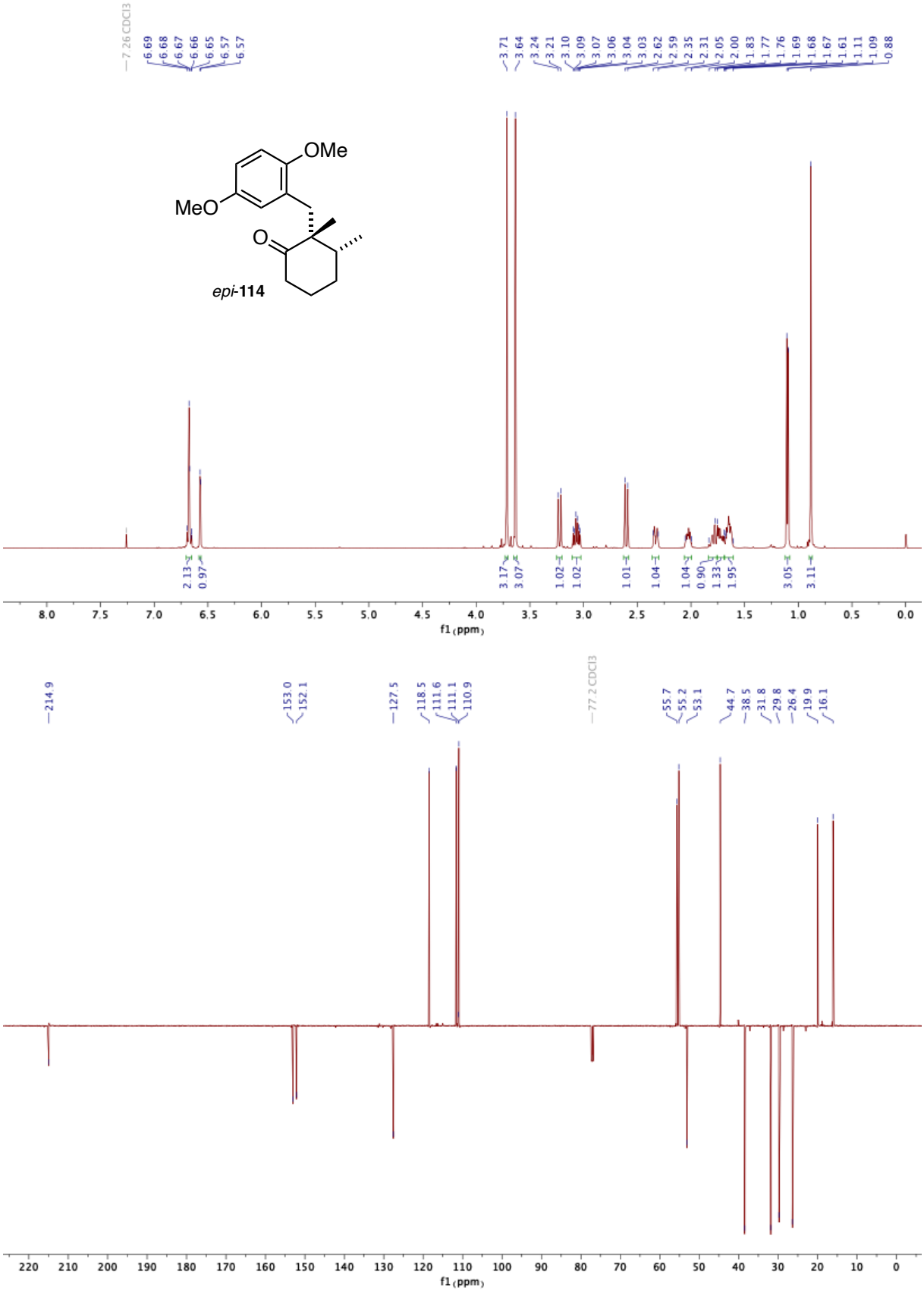



145.3
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

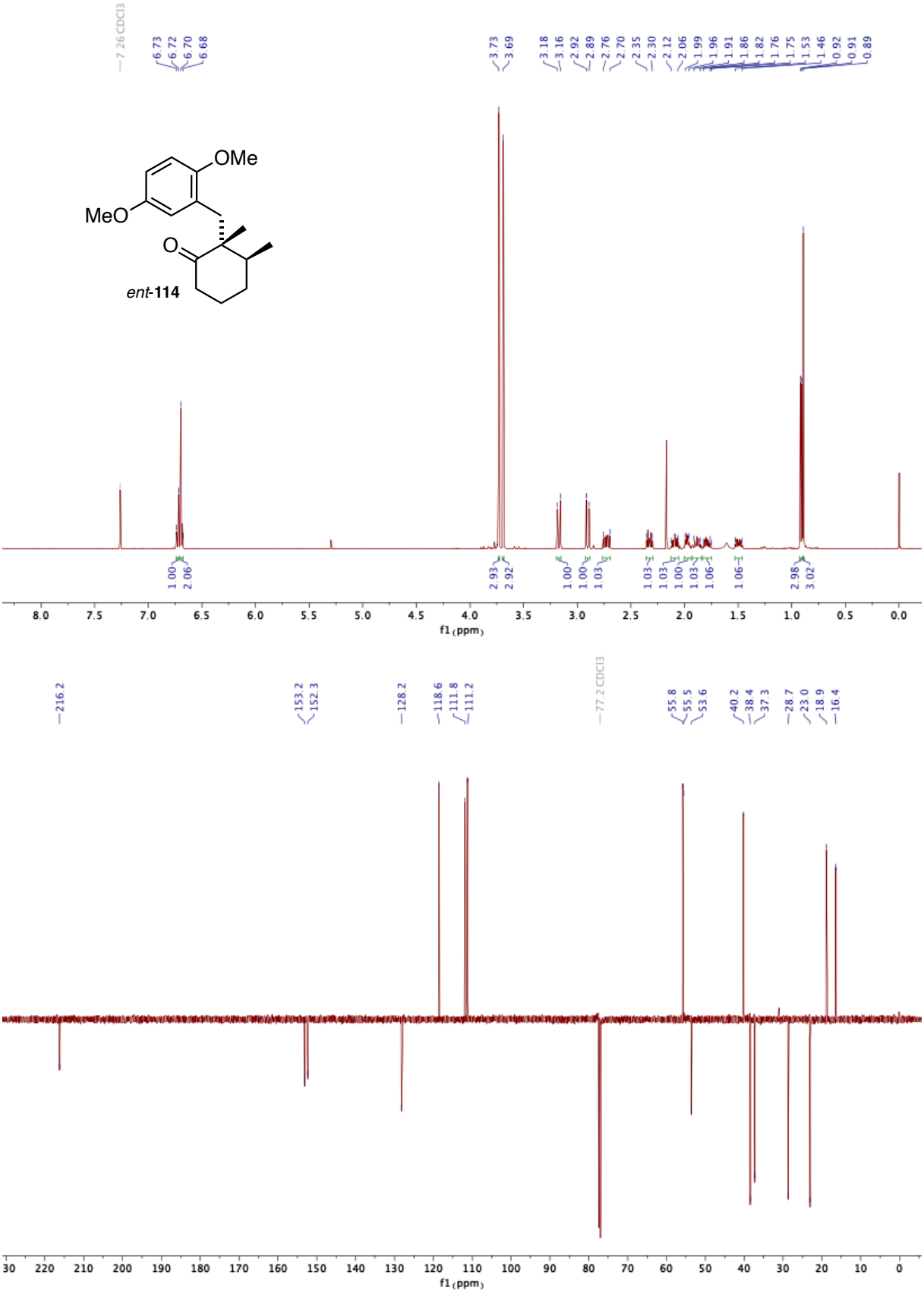
6.1.9 ^{1}H AND ^{13}C NMR SPECTRA OF KETONE **114**



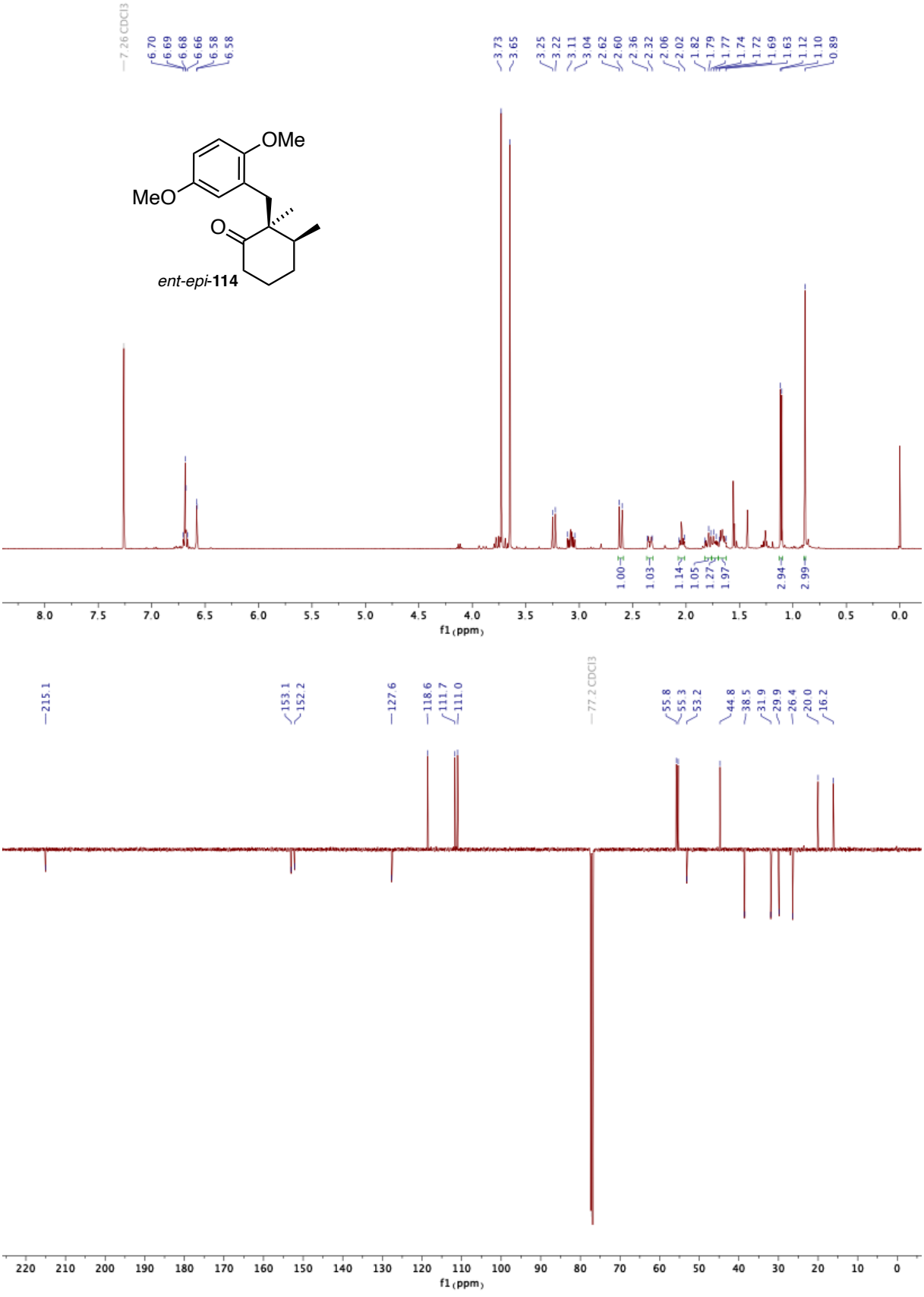
6.1.10 ^{1}H AND ^{13}C NMR SPECTRA OF KETONE *epi*-**114**



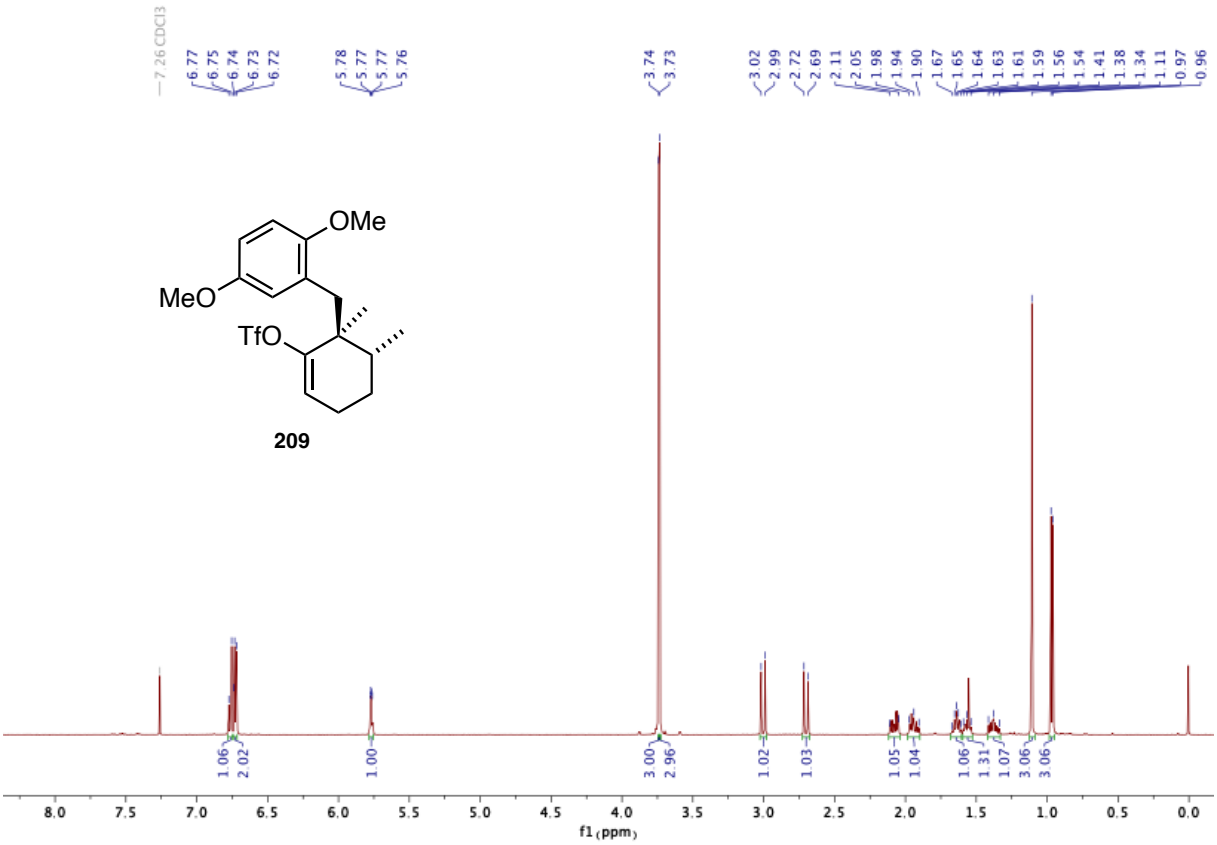
6.1.11 ^{1}H AND ^{13}C NMR SPECTRA OF KETONE *ent*-**114**

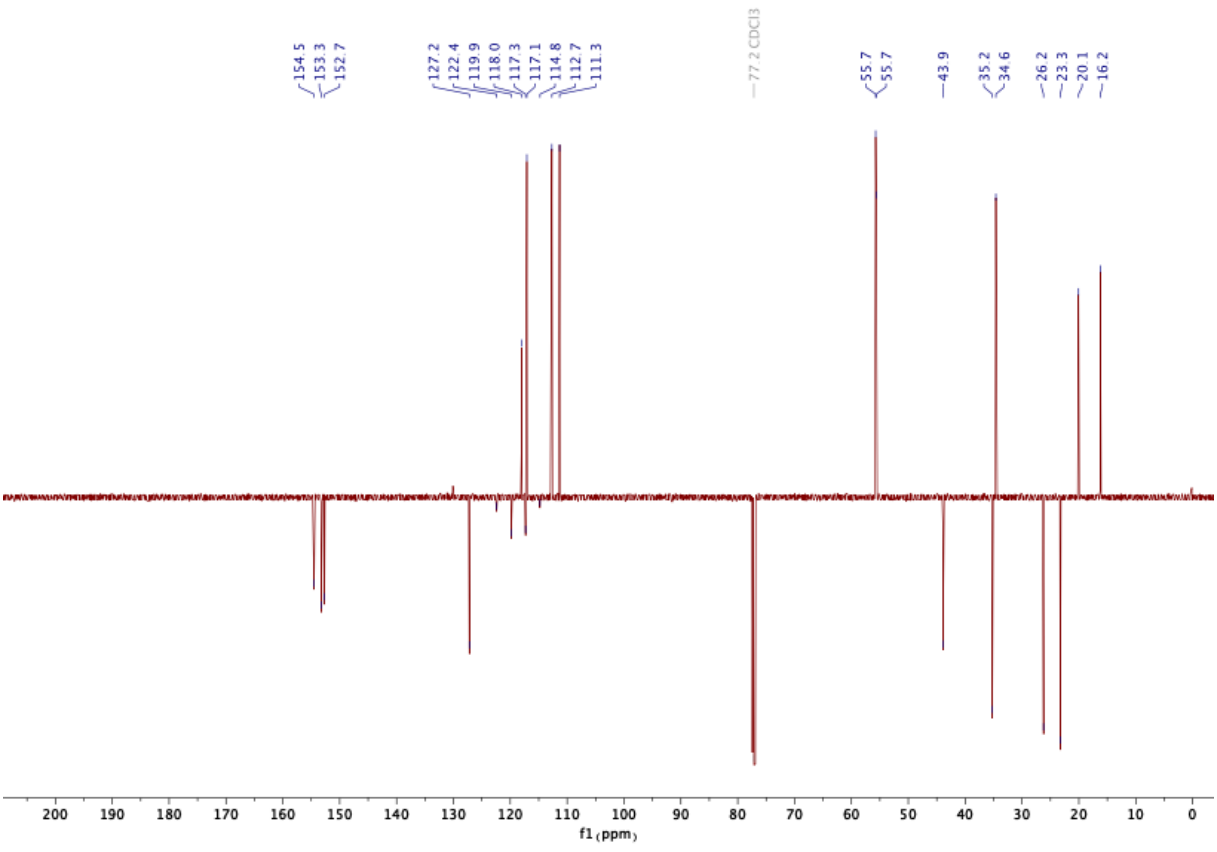


6.1.12 ^{1}H AND ^{13}C NMR SPECTRA OF KETONE *ent-epi*-**114**

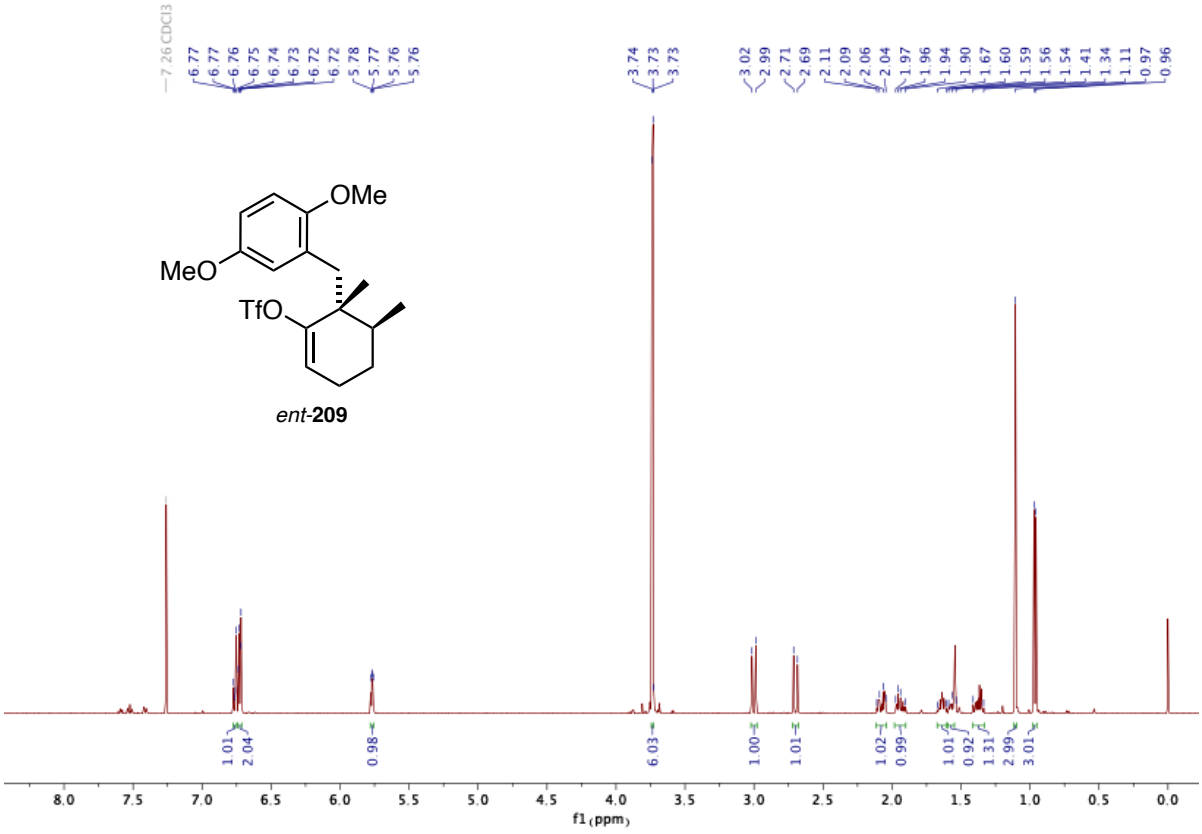


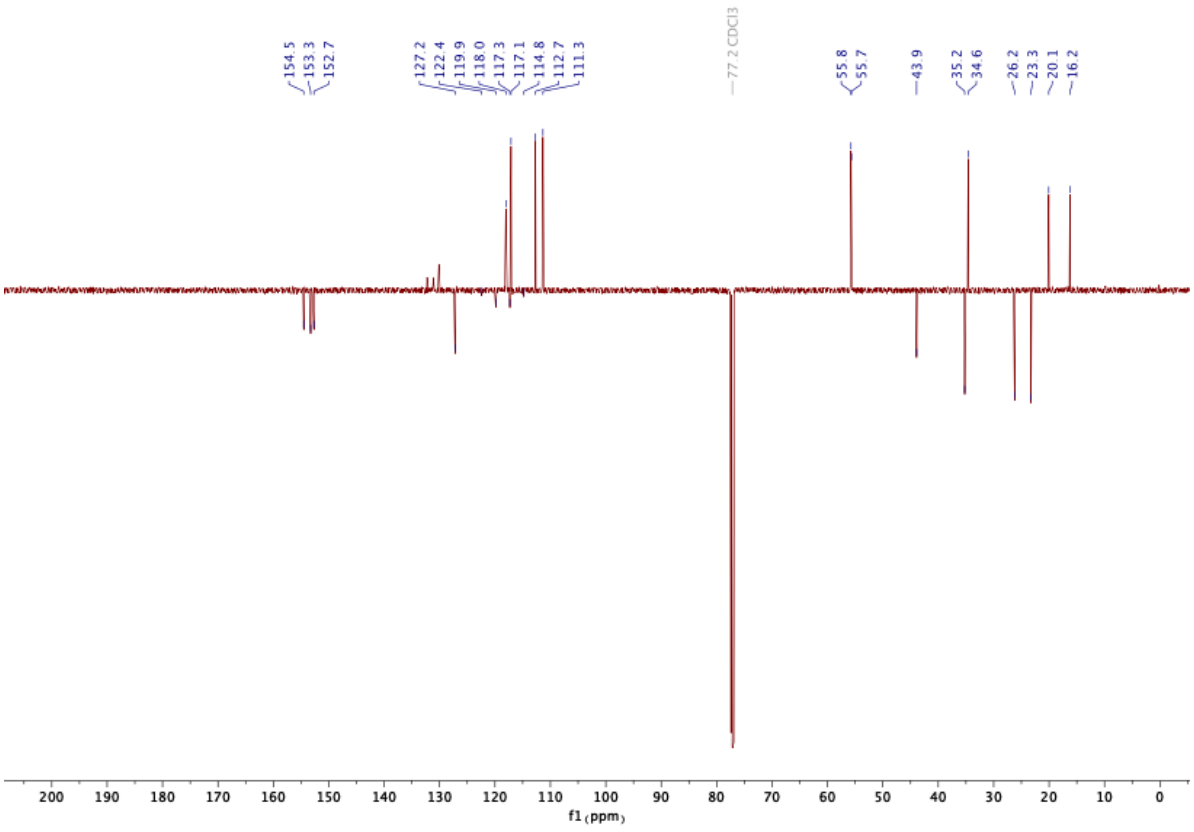
6.1.13 ^{1}H AND ^{13}C NMR SPECTRA OF ENOL TRIFLATE **209**

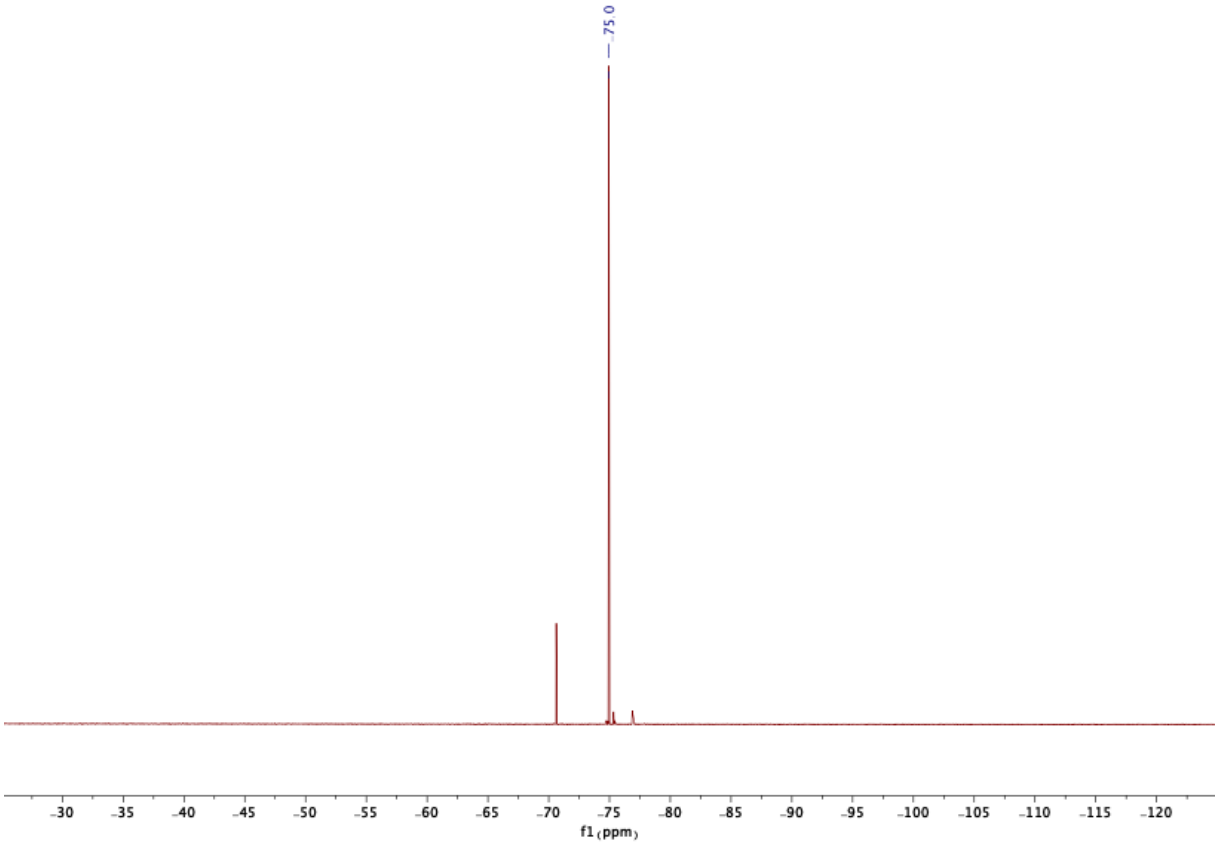




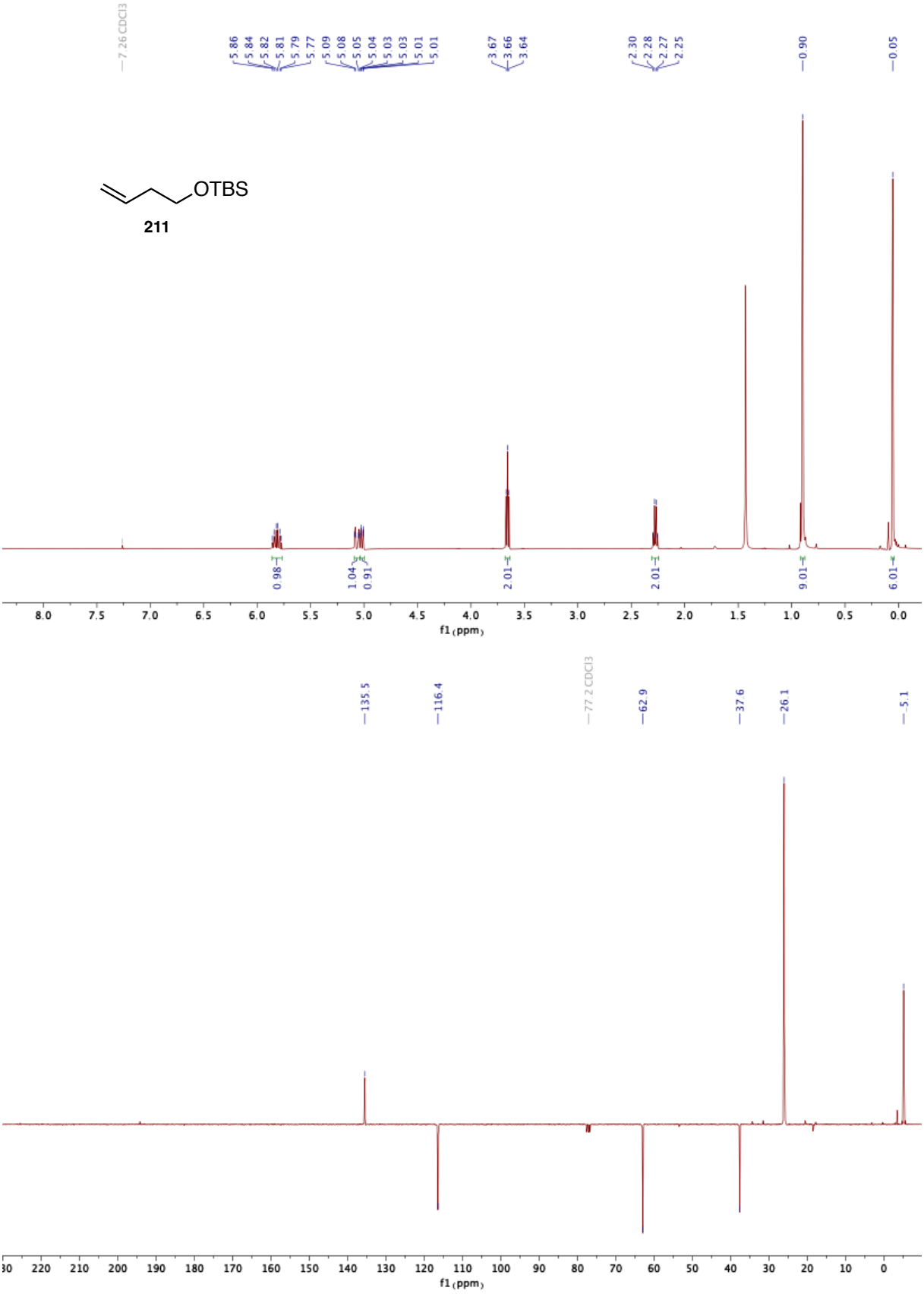
6.1.14 ^{1}H, ^{13}C NMR AND ^{19}F SPECTRA OF ENOL TRIFLATE *ent*-**209**



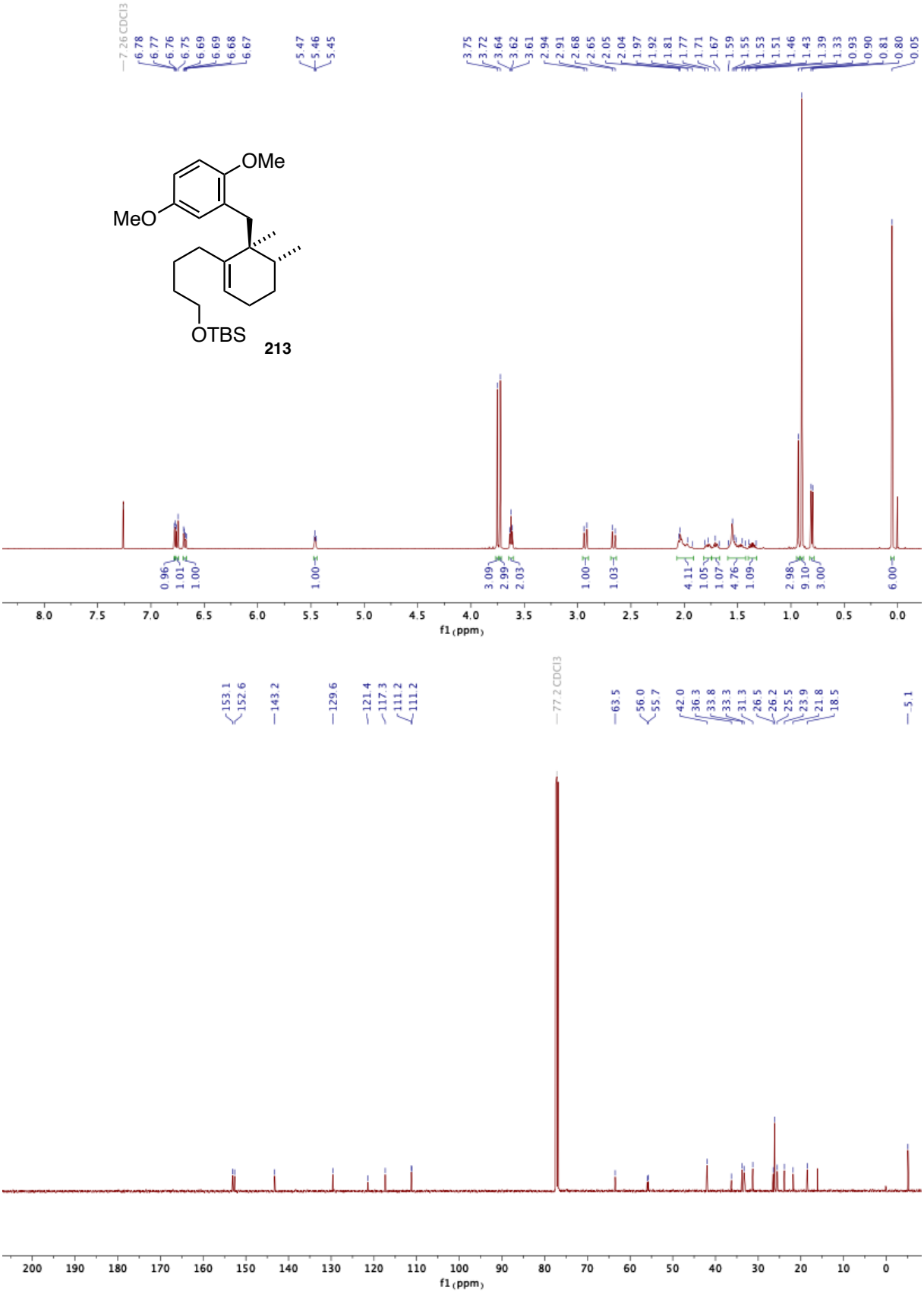



-75.0
-30
-35
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
f1 (ppm)

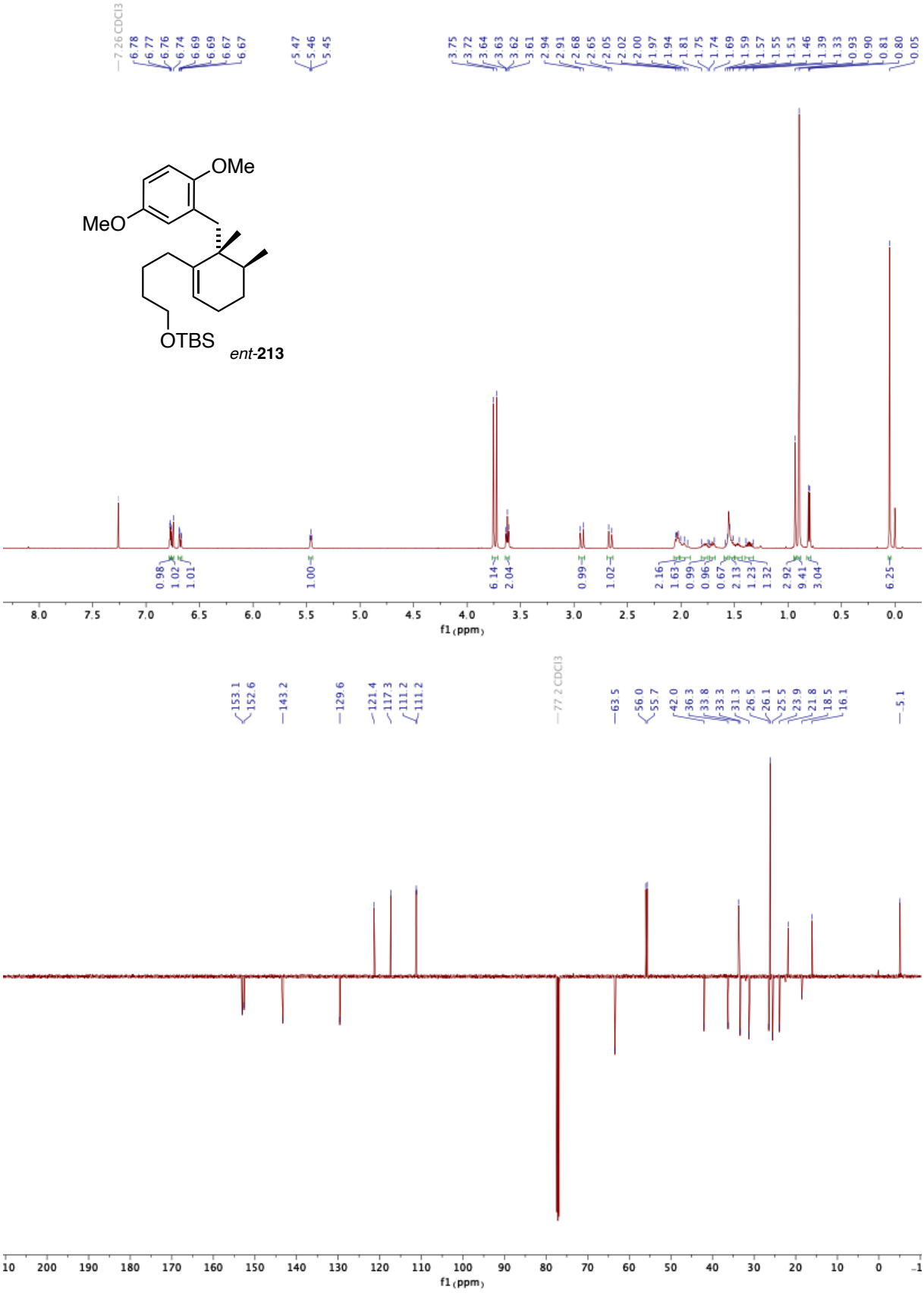
6.1.15 ^{1}H AND ^{13}C NMR SPECTRA OF HOMOALLYLIC ALCOHOL **211**



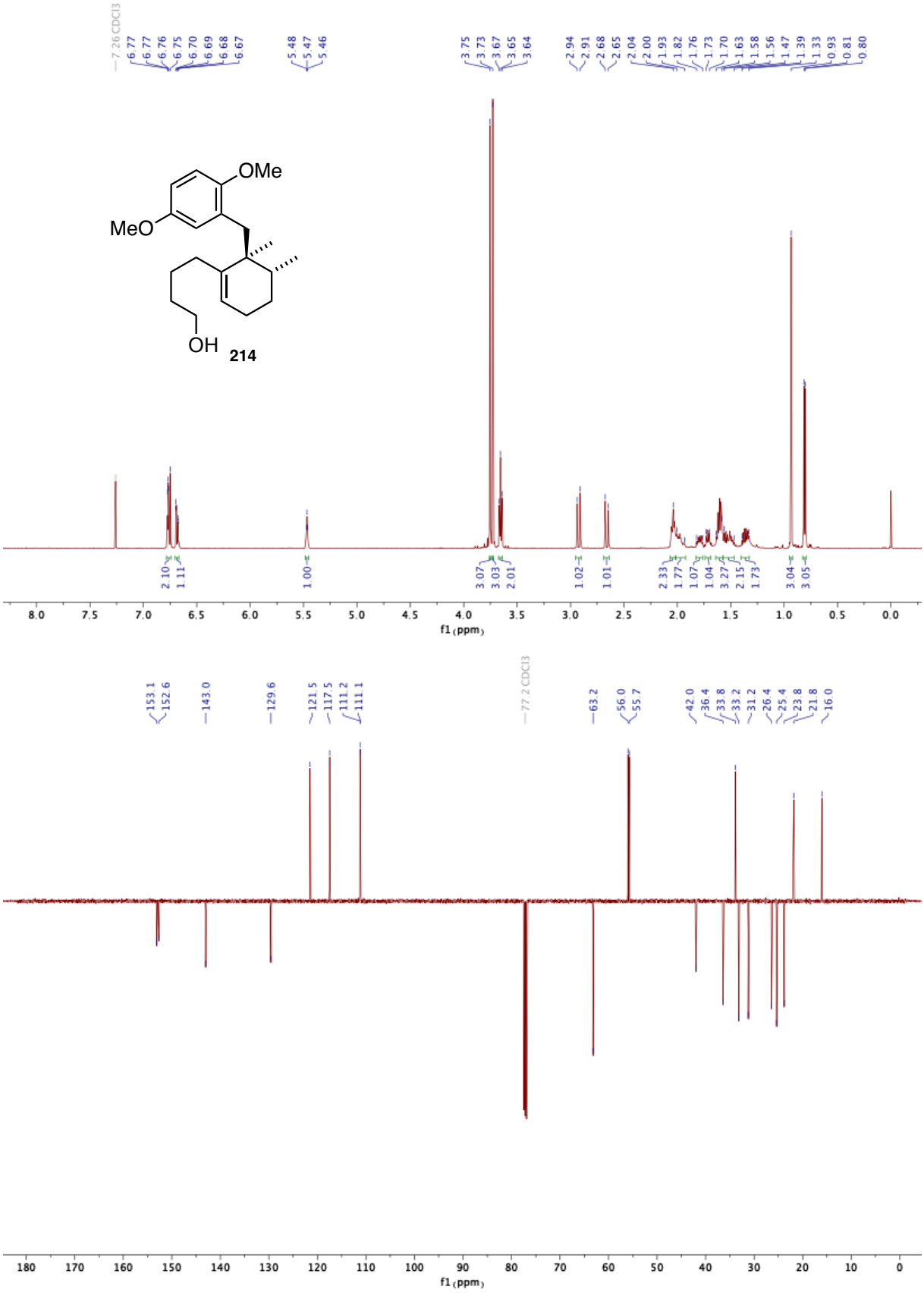
6.1.16 ^{1}H AND ^{13}C NMR SPECTRA OF SILYL ETHER **213**



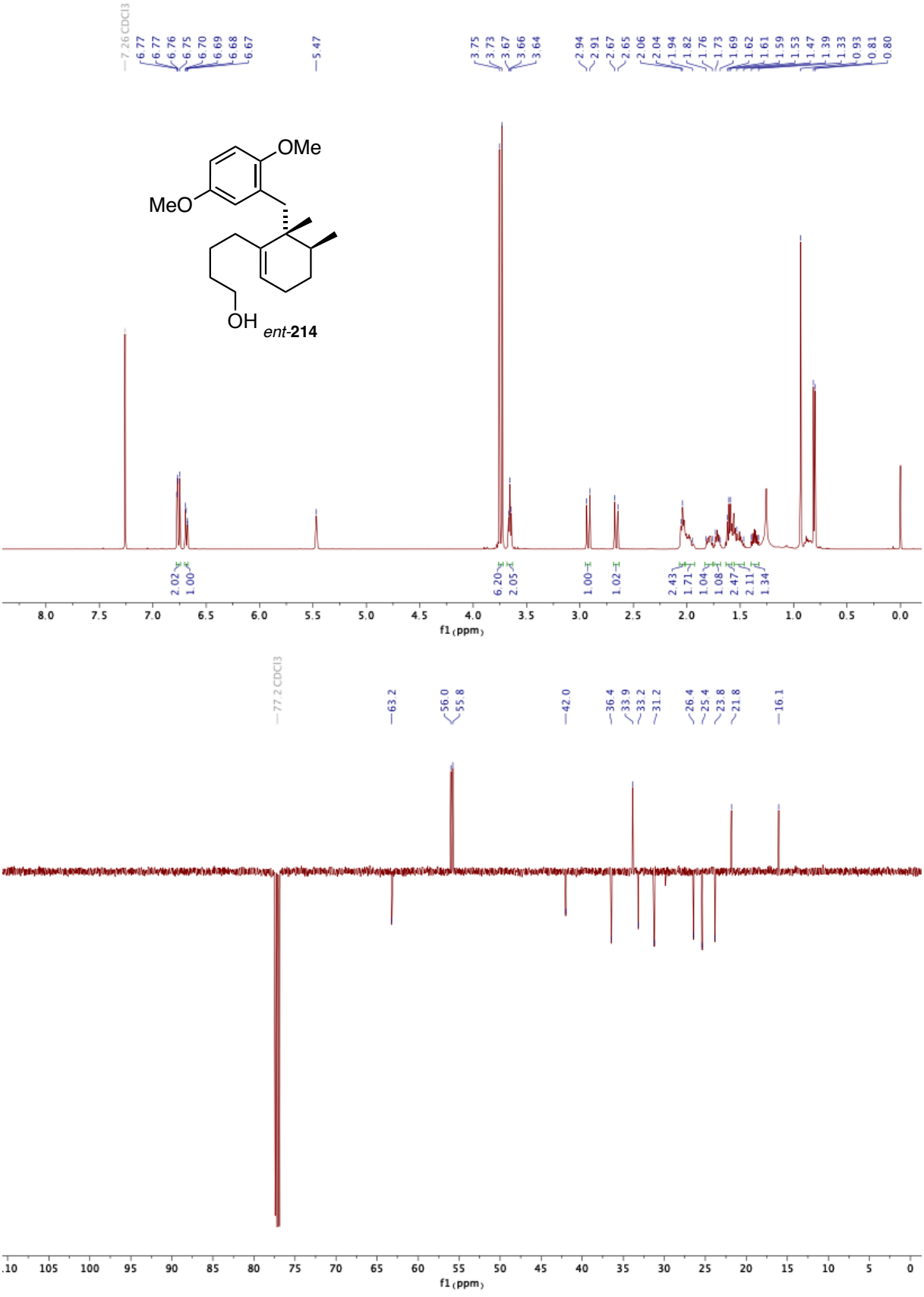
6.1.17 ^{1}H AND ^{13}C NMR SPECTRA OF SILYL ETHER *ent*-**213**



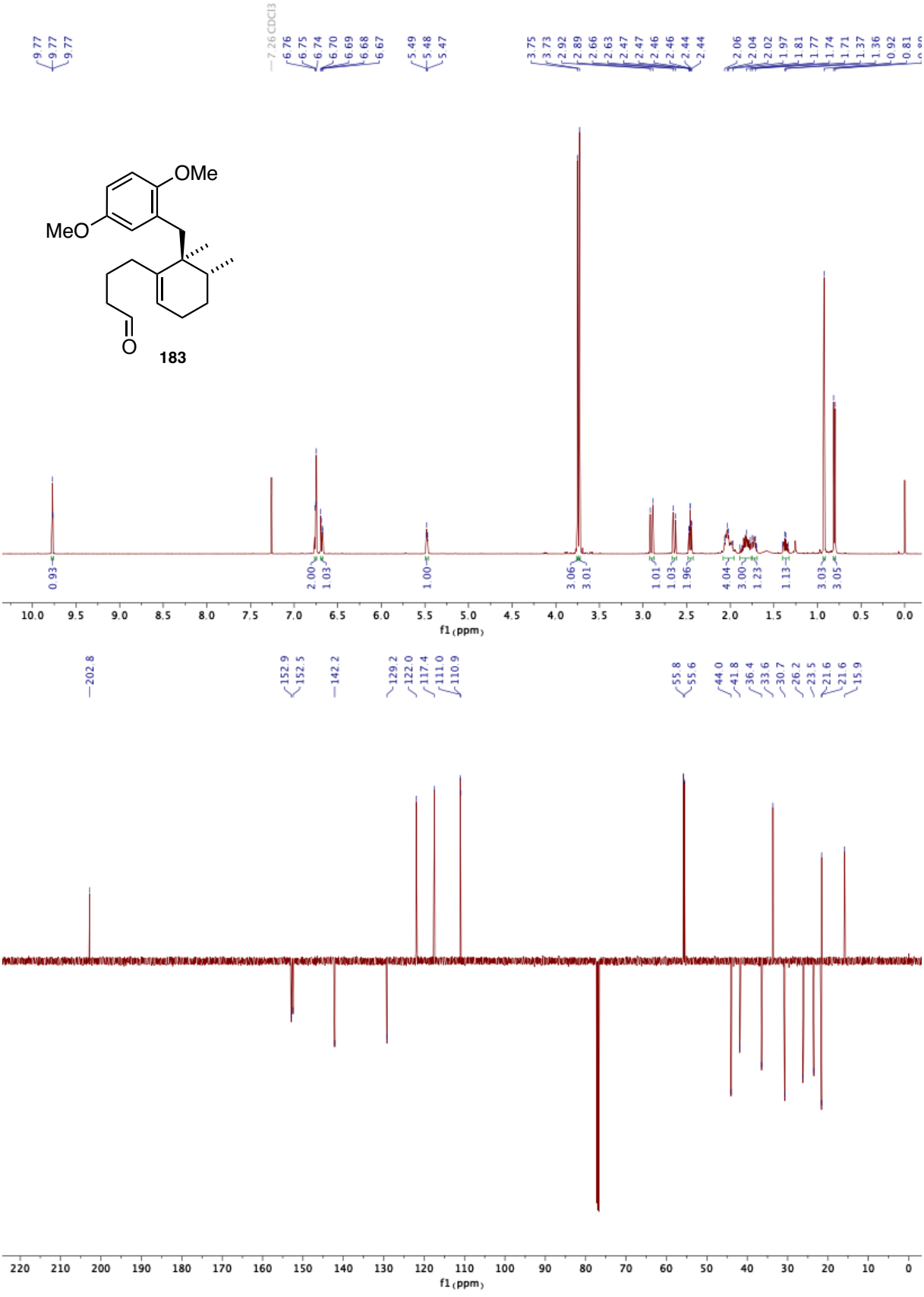
6.1.18 ^{1}H AND ^{13}C NMR SPECTRA OF PRIMARY ALCOHOL **214**



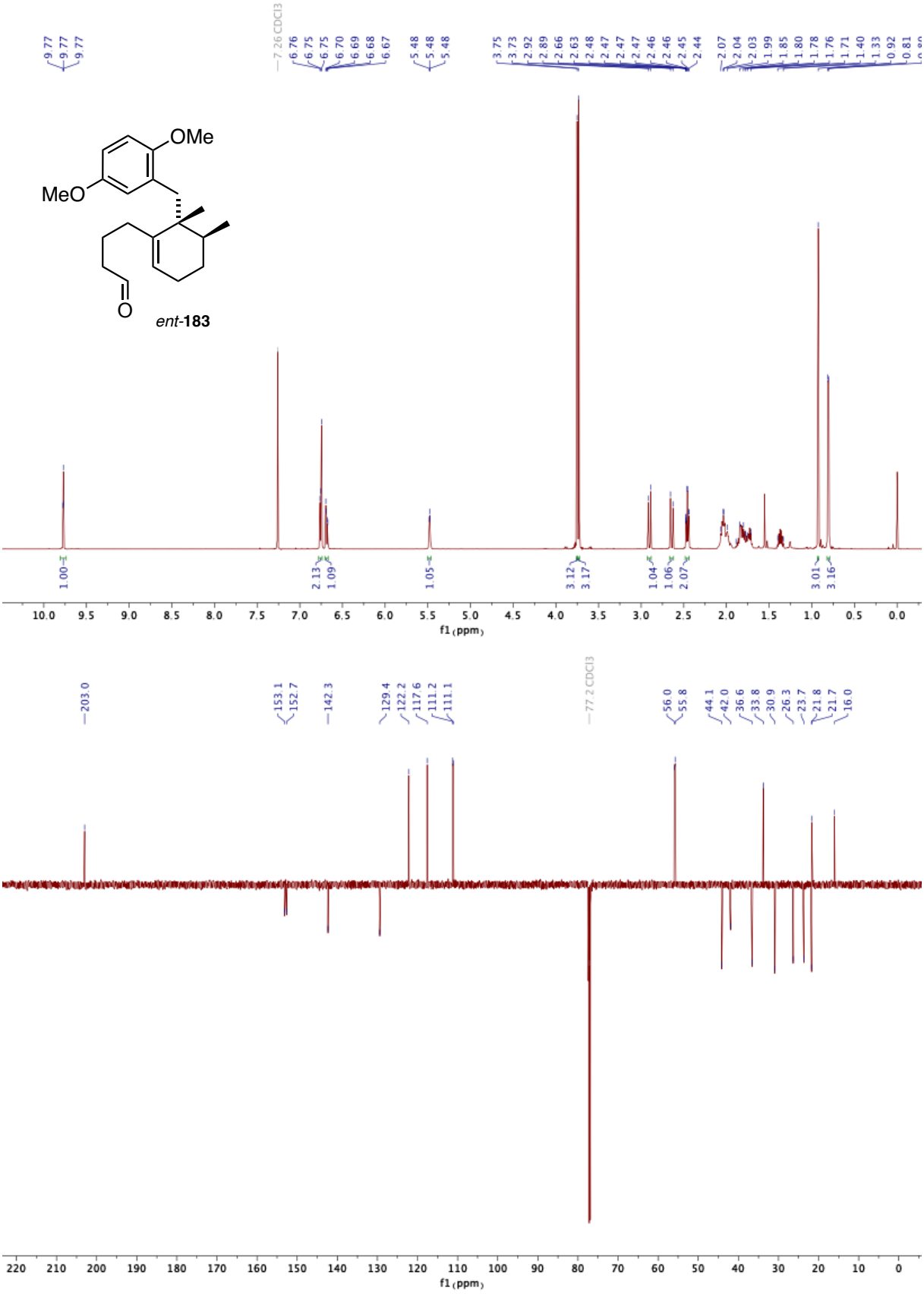
6.1.19 ^{1}H AND ^{13}C NMR SPECTRA OF PRIMARY ALCOHOL *ent*-**214**



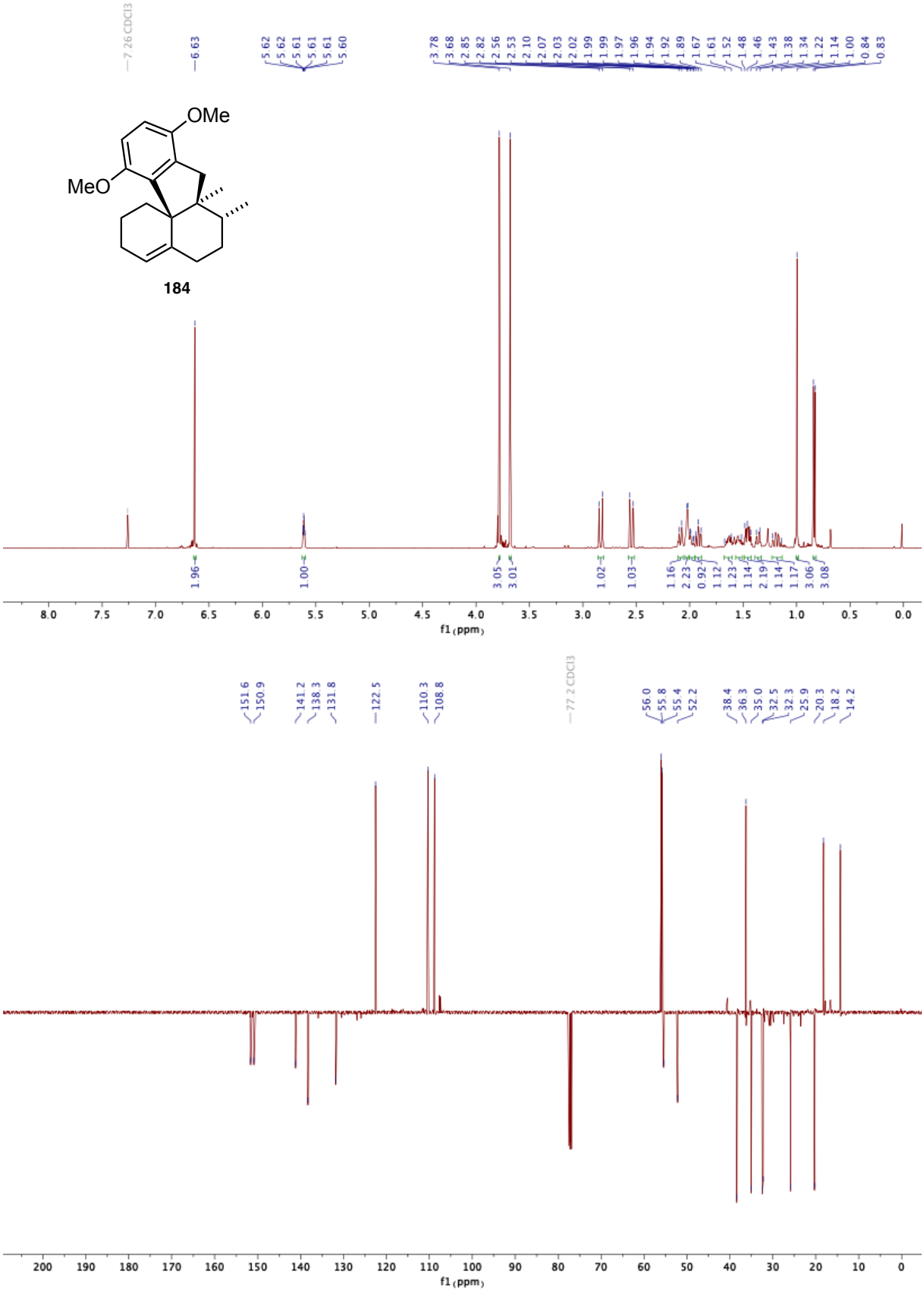
6.1.20 ^{1}H AND ^{13}C NMR SPECTRA OF ALDEHYDE **183**



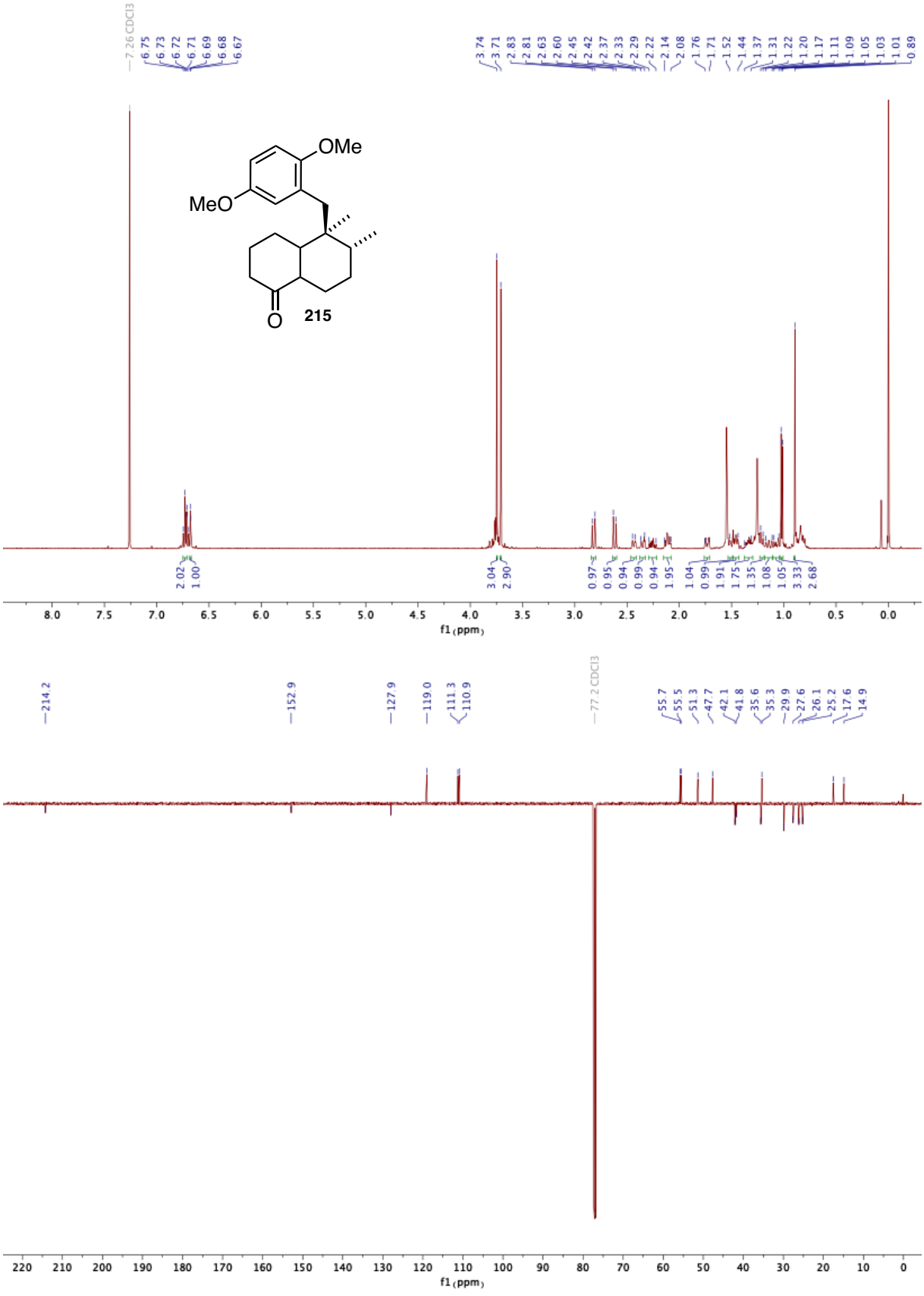
6.1.21 ^{1}H AND ^{13}C NMR SPECTRA OF ALDEHYDE *ent*-**183**



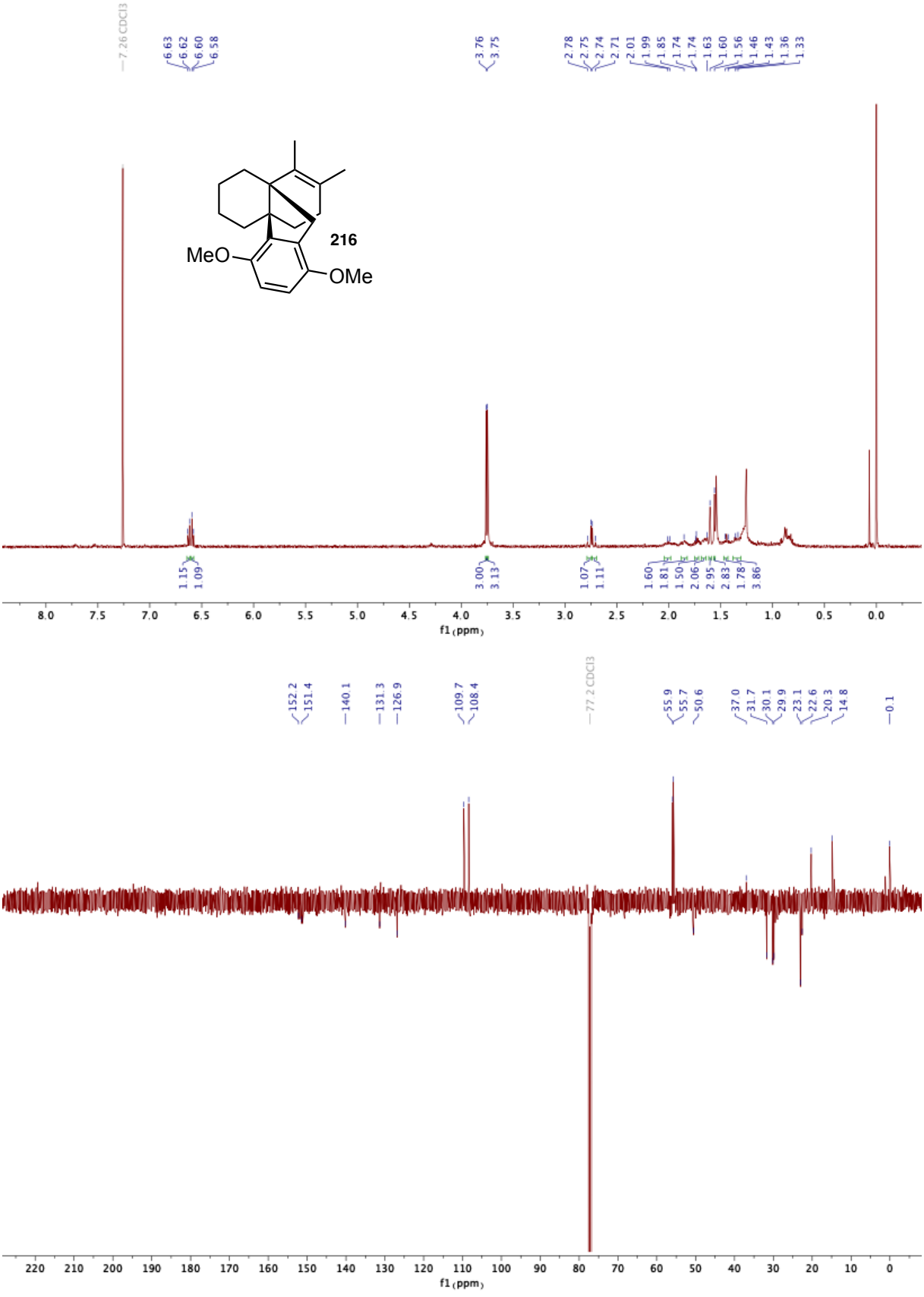
6.1.22 ^{1}H AND ^{13}C NMR SPECTRA OF OLEFIN **184**



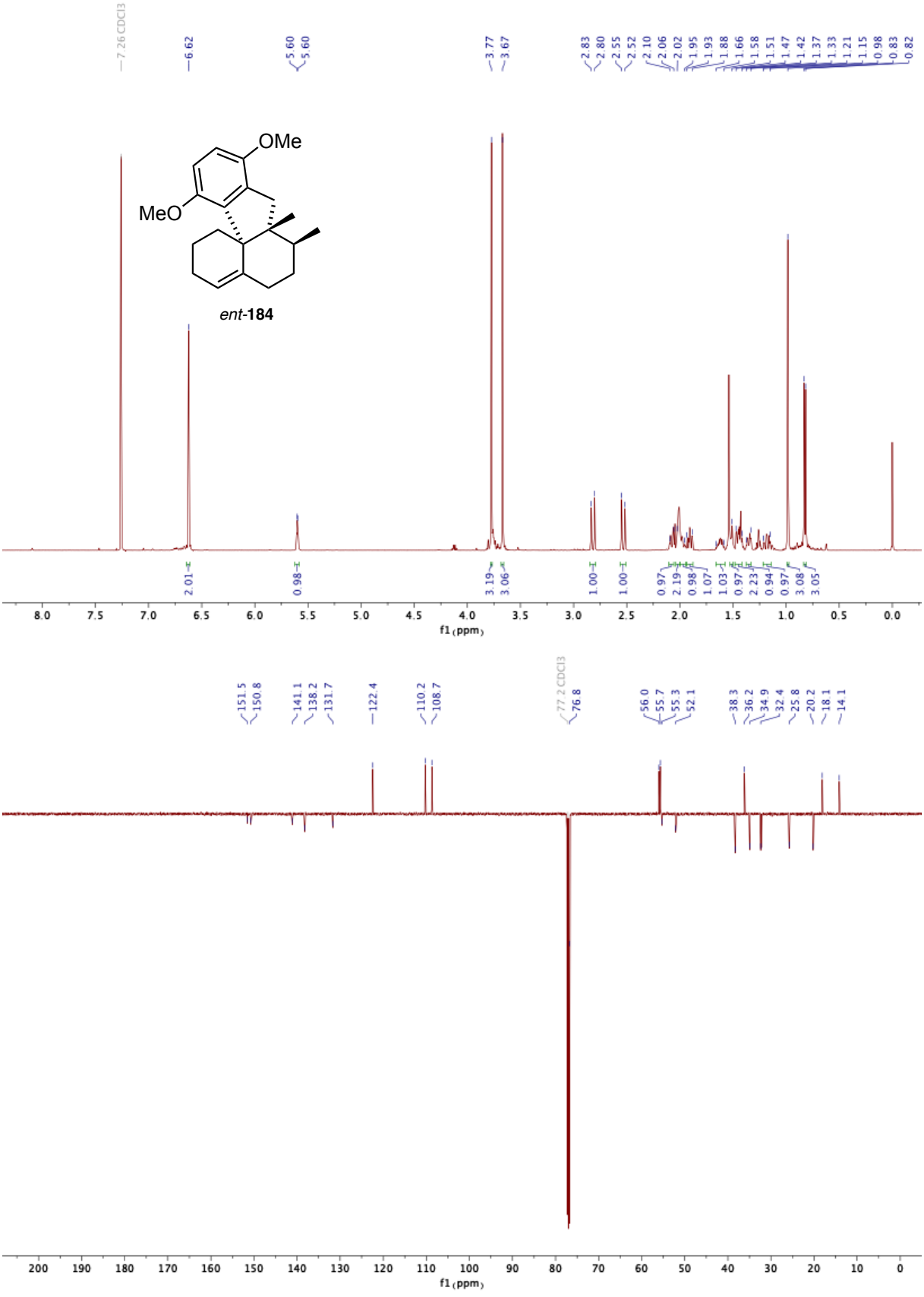
6.1.23 ^{1}H AND ^{13}C NMR SPECTRA OF KETONE **215**



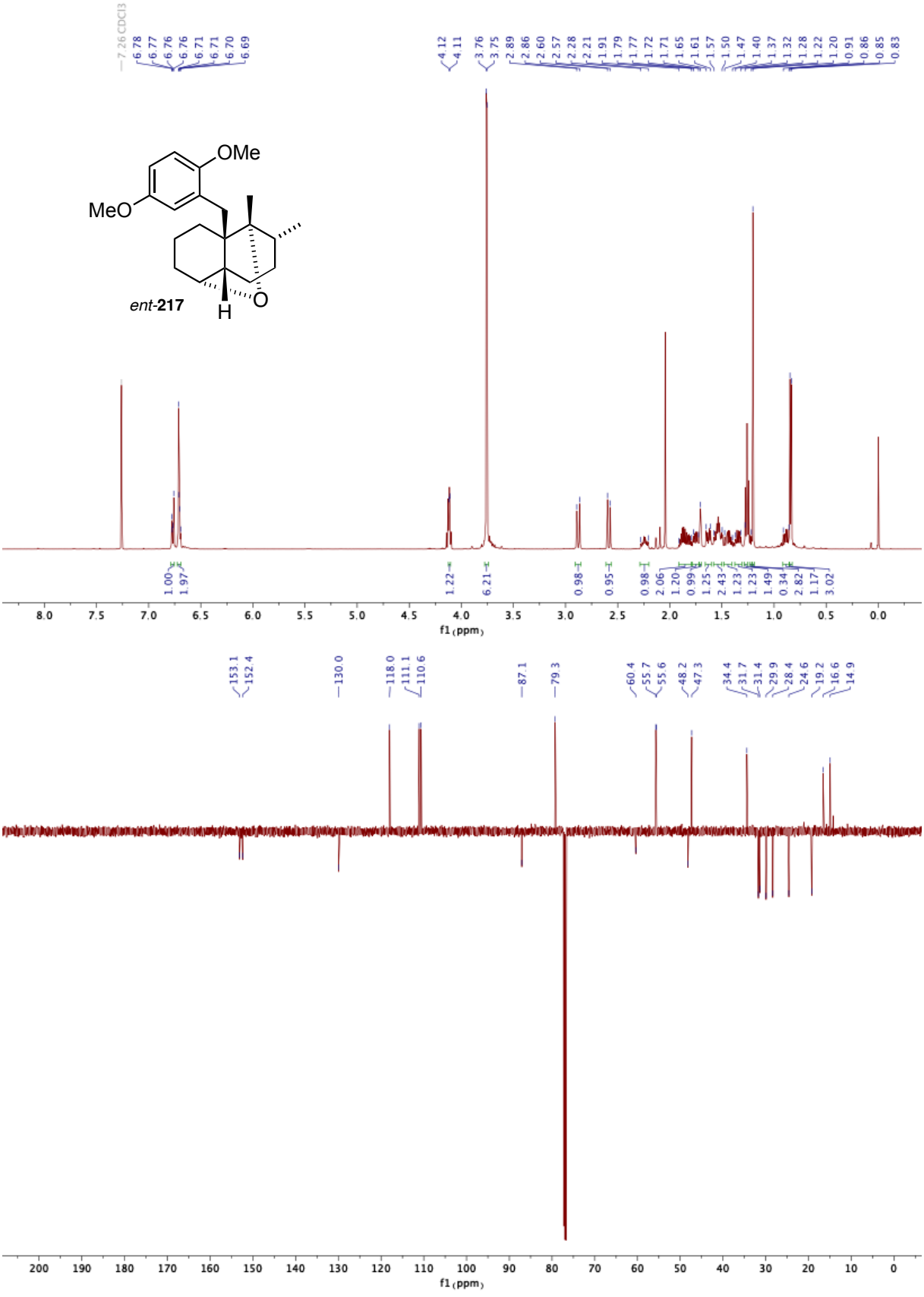
6.1.24 ^{1}H AND ^{13}C NMR SPECTRA OF OLEFIN **216**



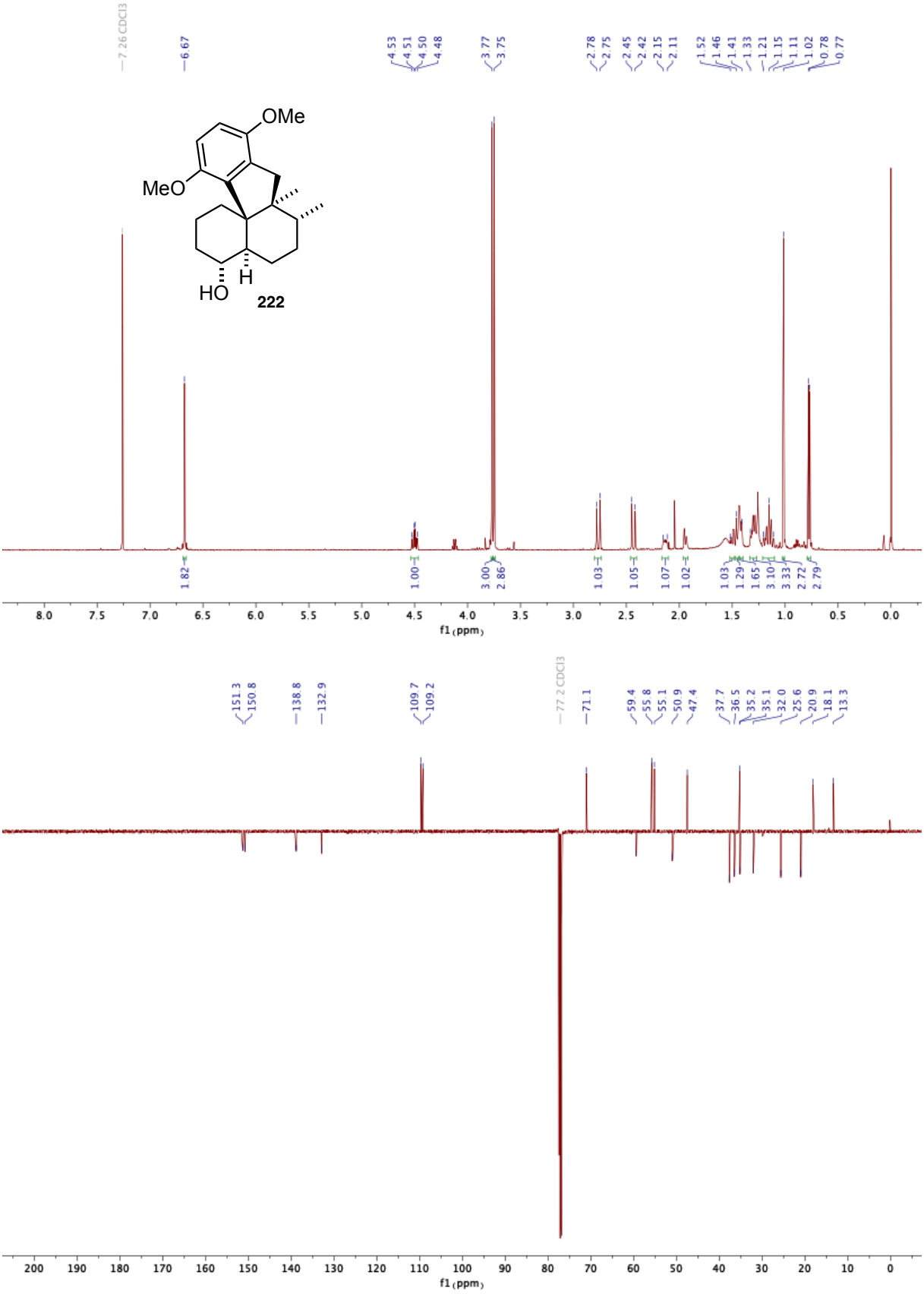
6.1.25 ^{1}H AND ^{13}C NMR SPECTRA OF OLEFIN *ent*-**184**



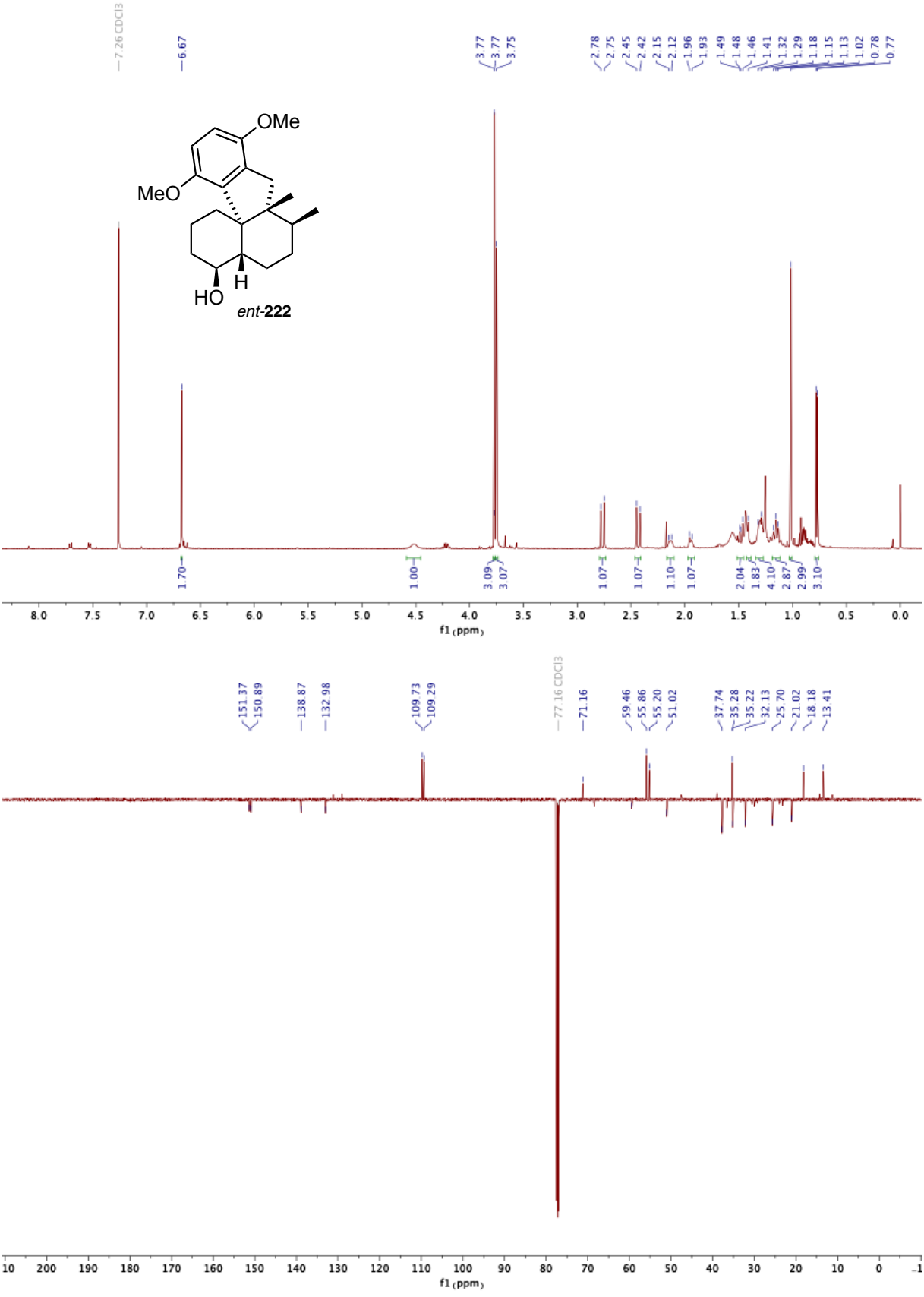
6.1.26 ^{1}H AND ^{13}C NMR SPECTRA OF ETHER *ent*-**217**



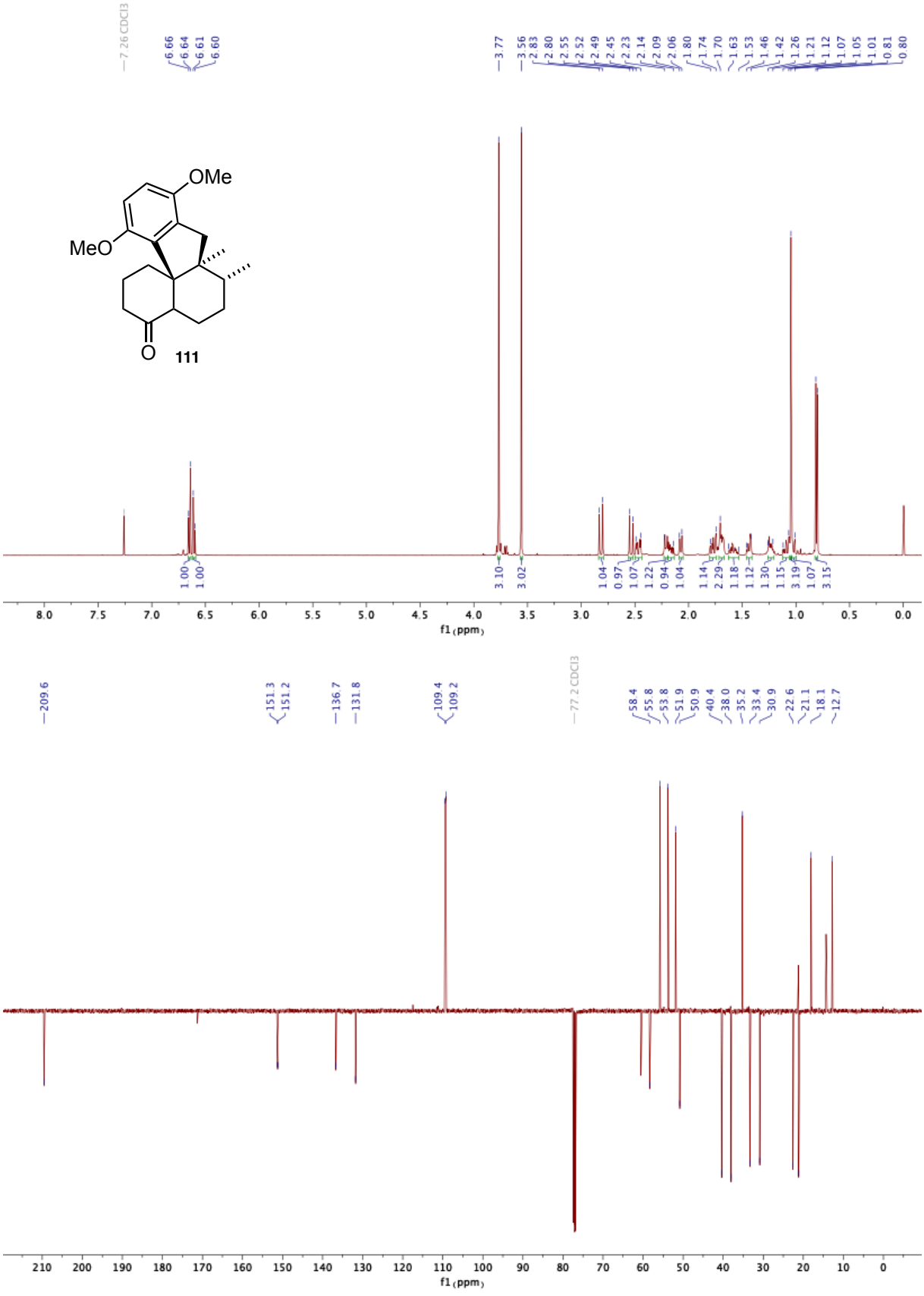
6.1.27 ^{1}H AND ^{13}C NMR SPECTRA OF TETRACYCLIC ALCOHOL **222**



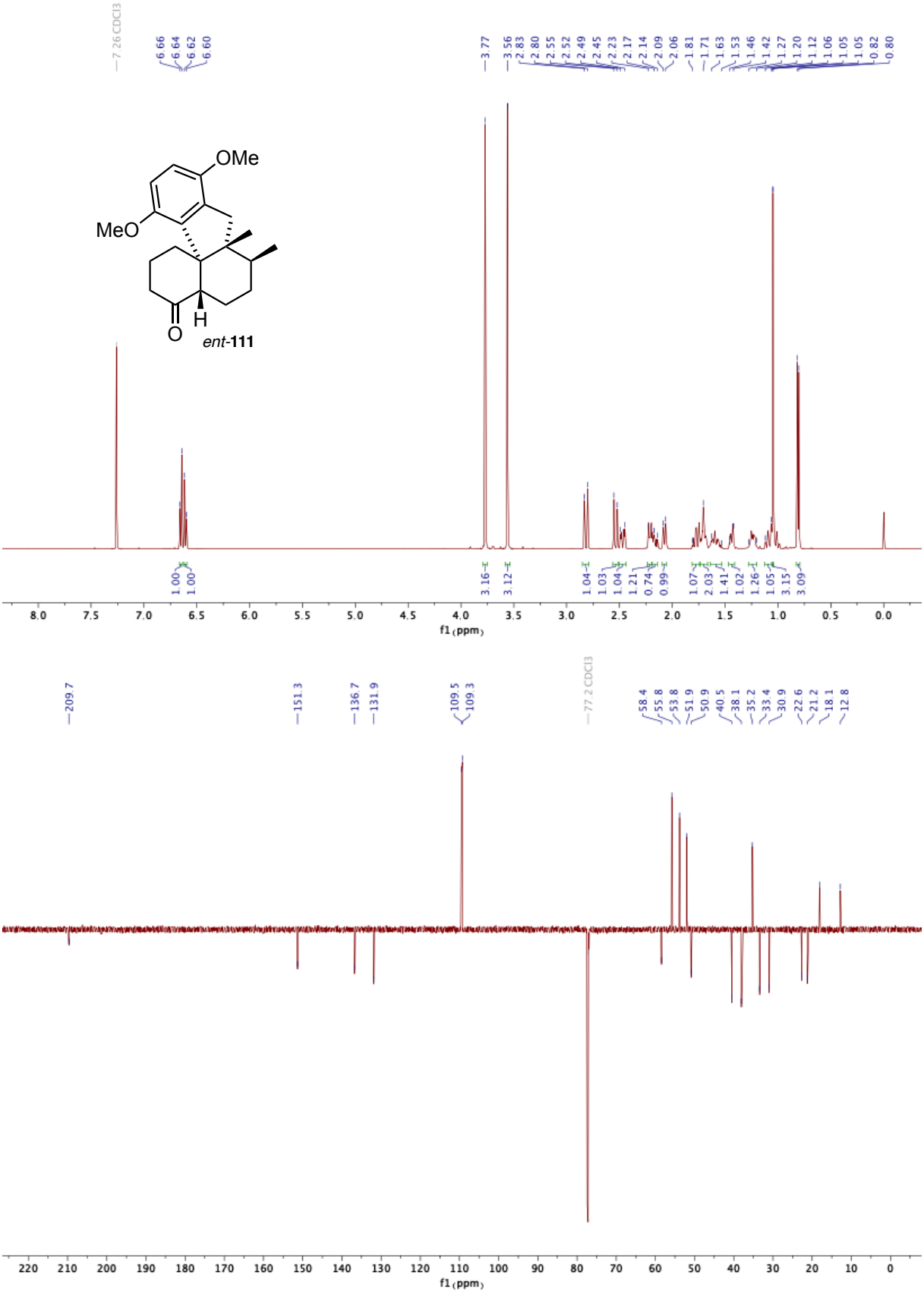
6.1.28 ^{1}H AND ^{13}C NMR SPECTRA OF TETRACYCLIC ALCOHOL *ent*-**222**



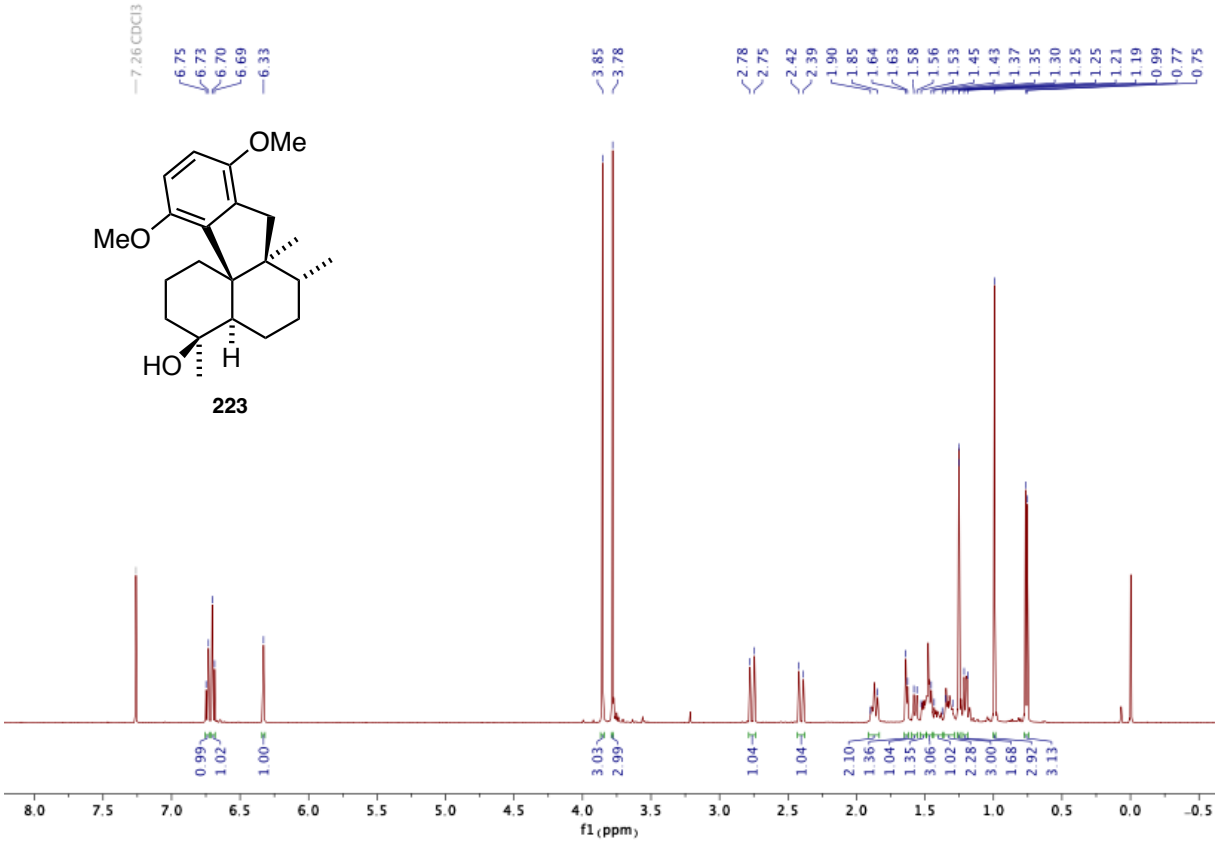
6.1.29 ^{1}H AND ^{13}C NMR SPECTRA OF KETONE **111**



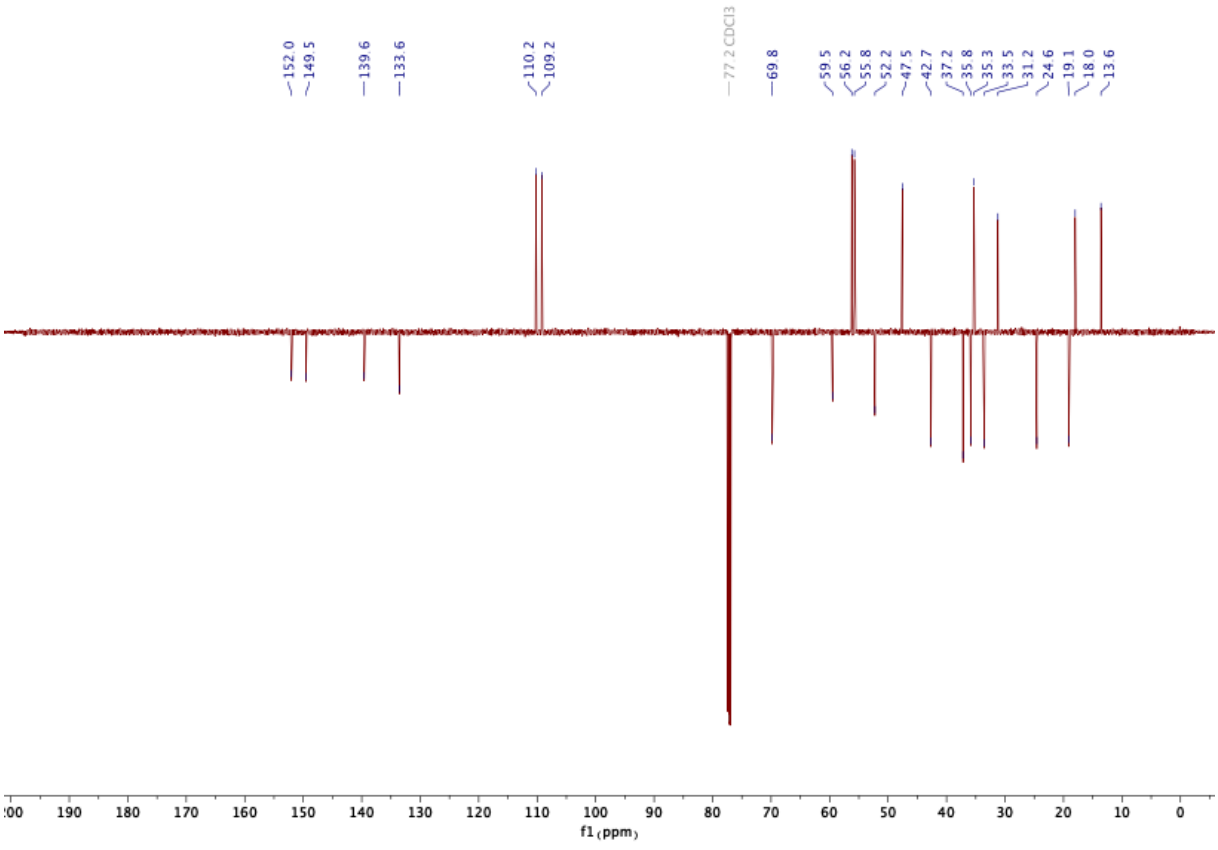
6.1.30 ^{1}H AND ^{13}C NMR SPECTRA OF KETONE *ent*-**111**



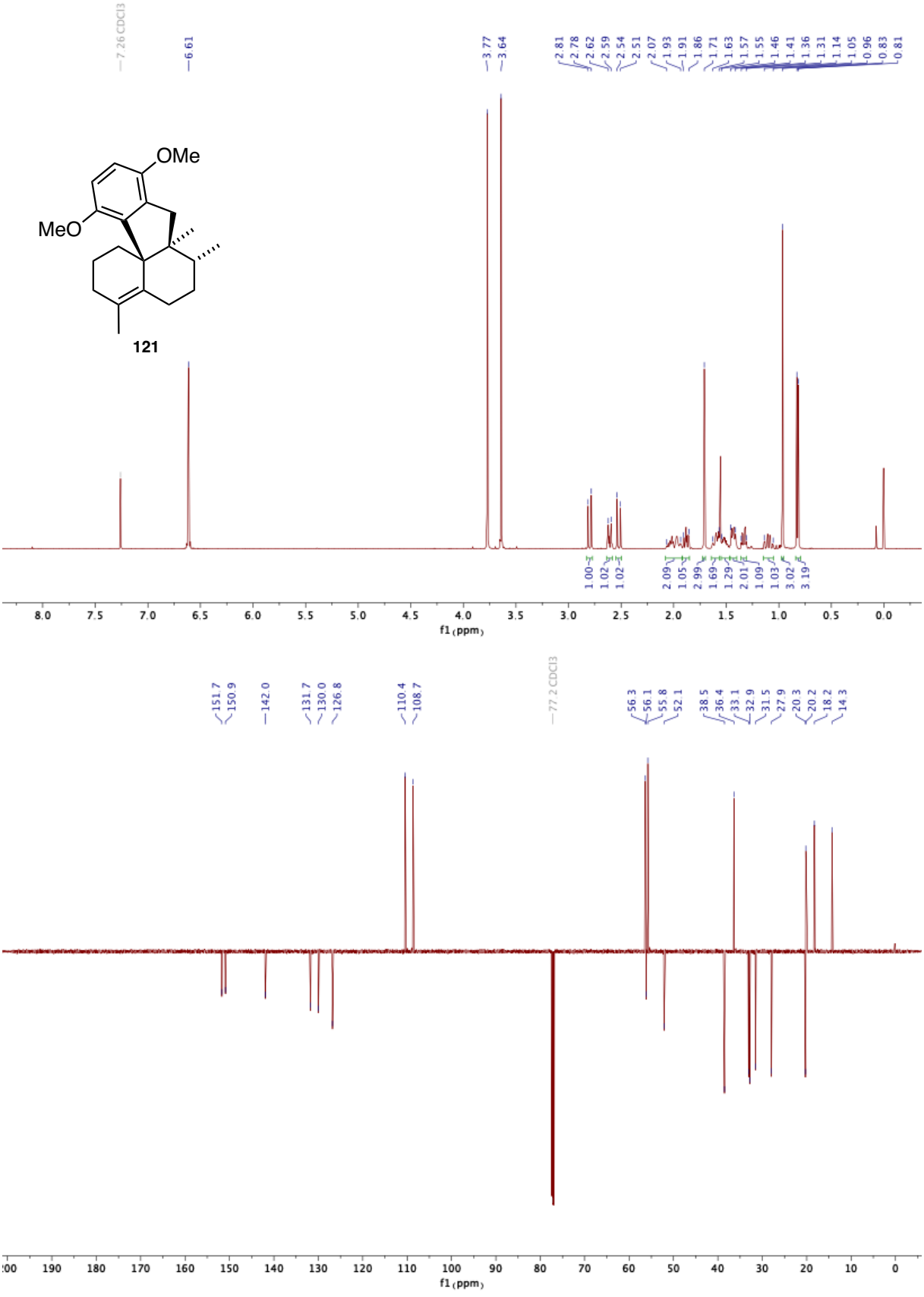
6.1.31 ^{1}H AND ^{13}C NMR SPECTRA OF TERTIARY ALCOHOL **223**



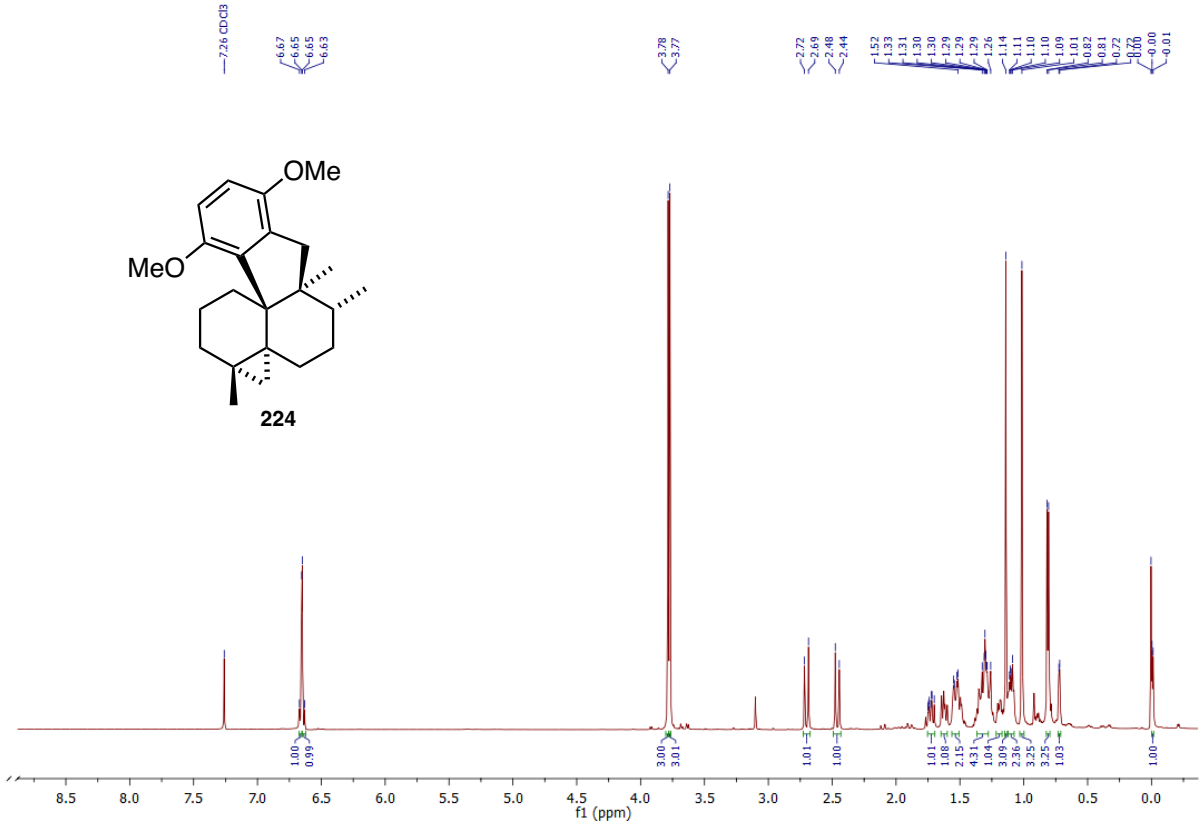
223

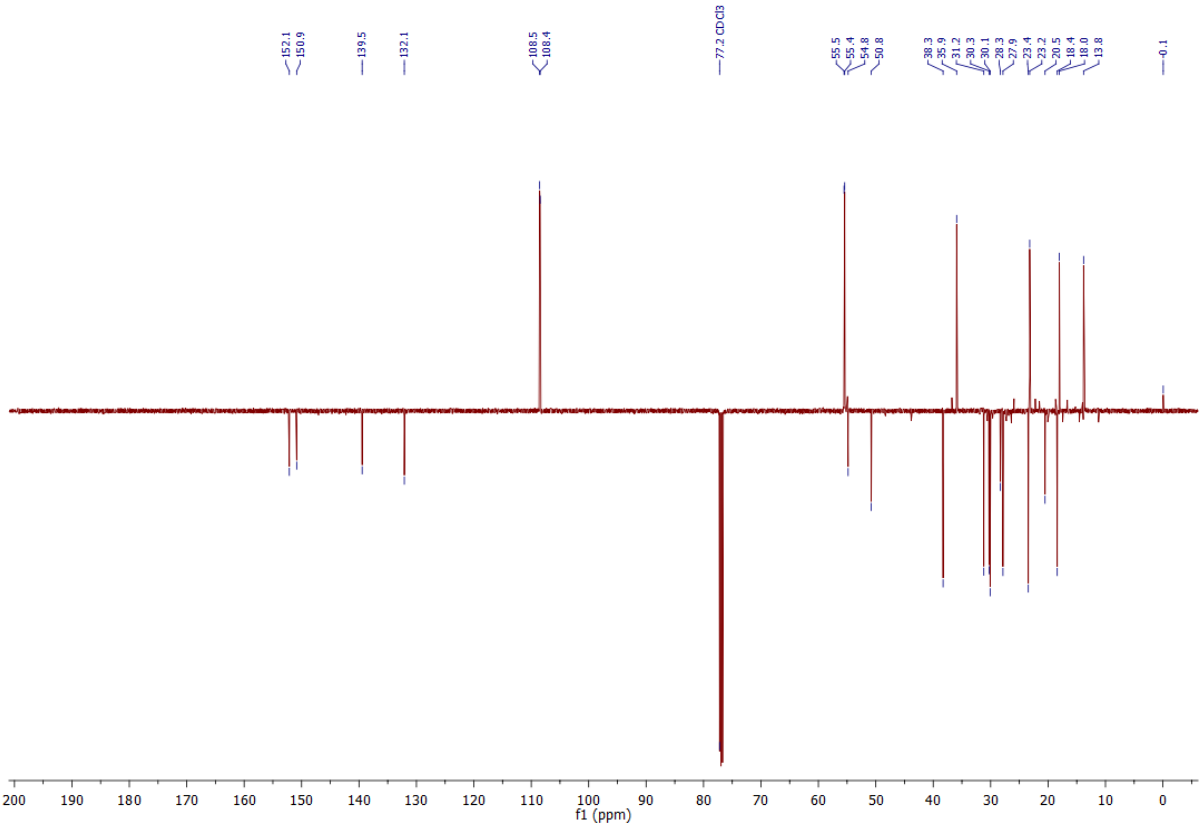


6.1.32 ^{1}H AND ^{13}C NMR SPECTRA OF OLEFIN **121**

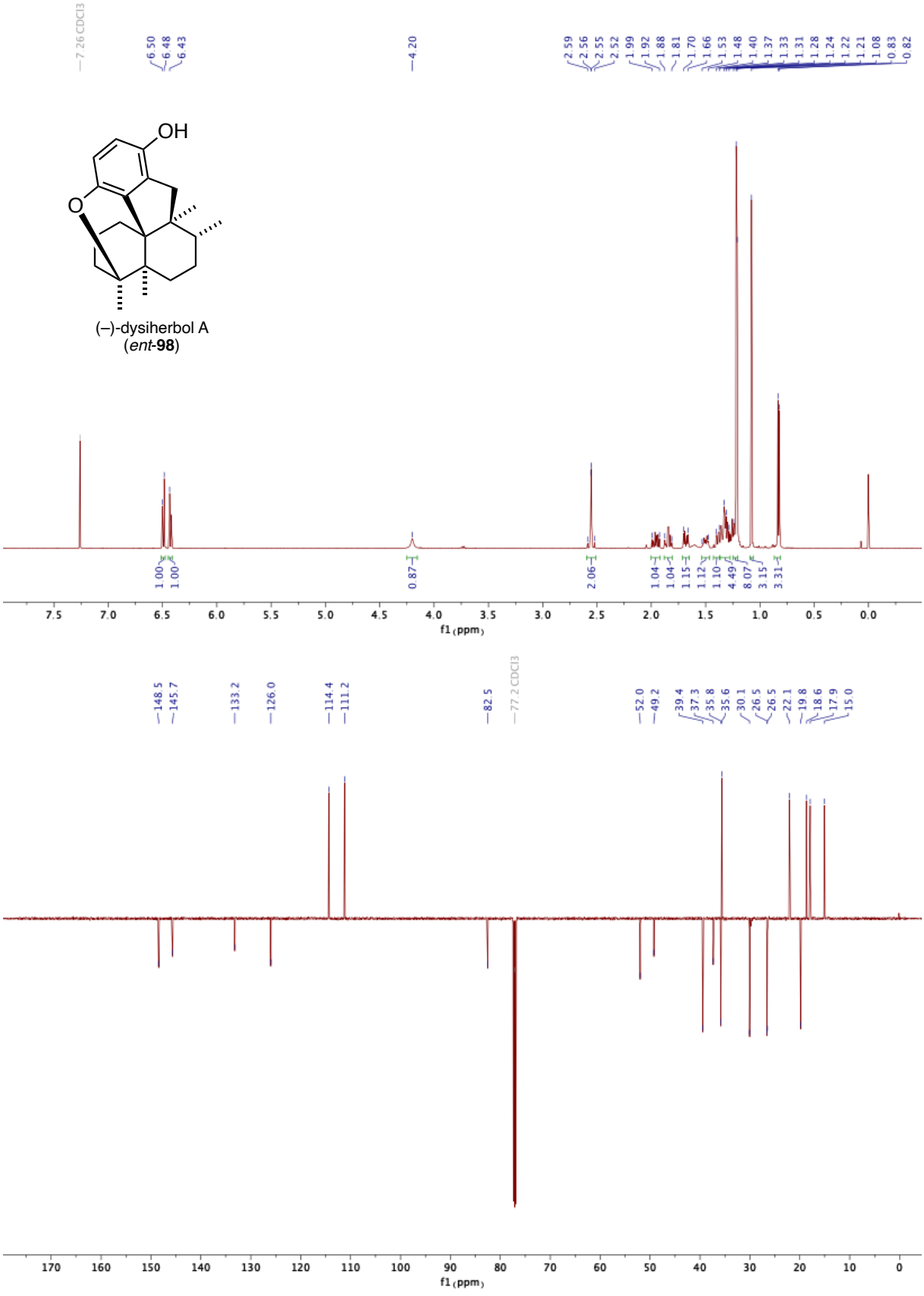


6.1.33 ^{1}H AND ^{13}C NMR SPECTRA OF CYCLOPROPANE **224**

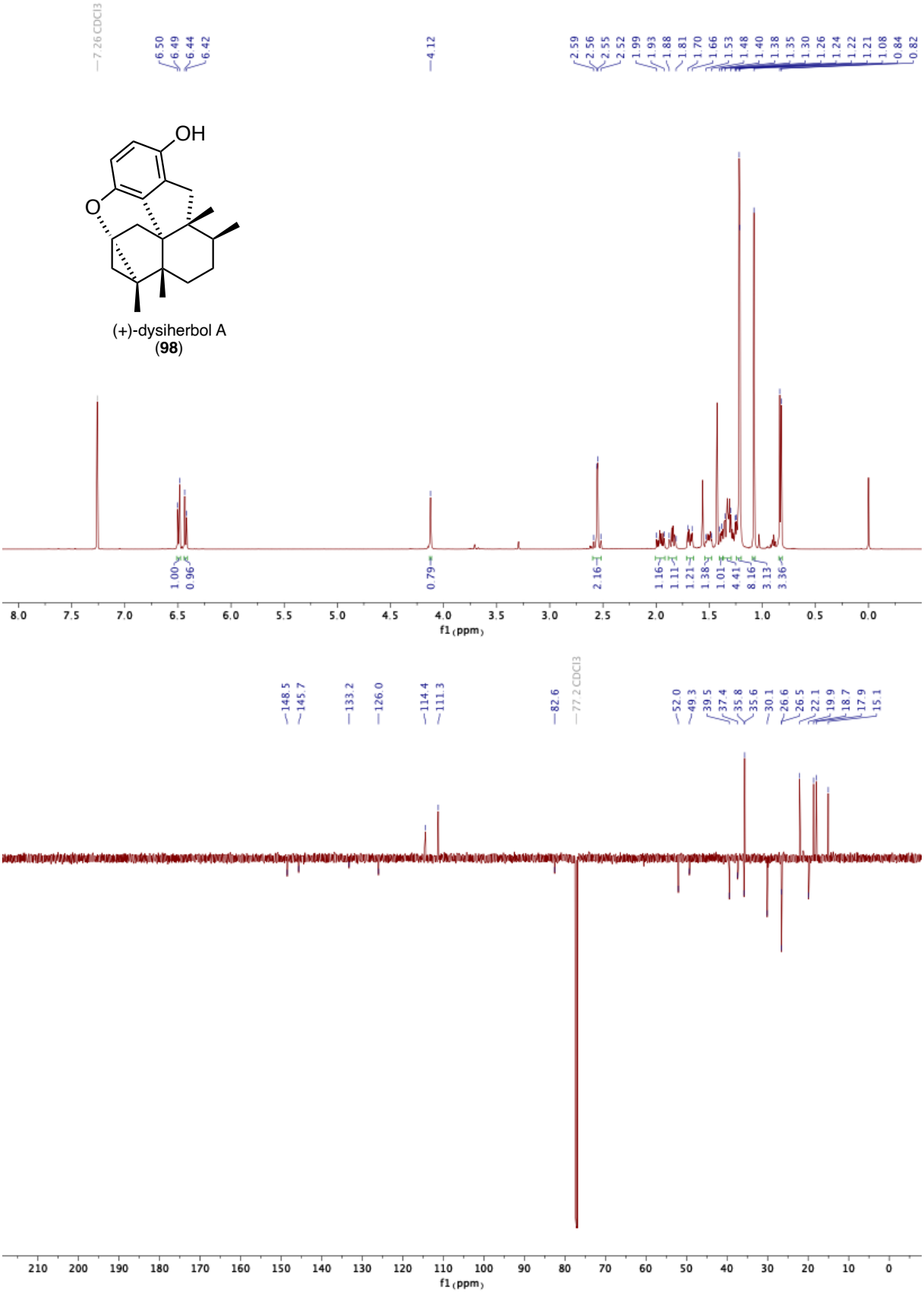




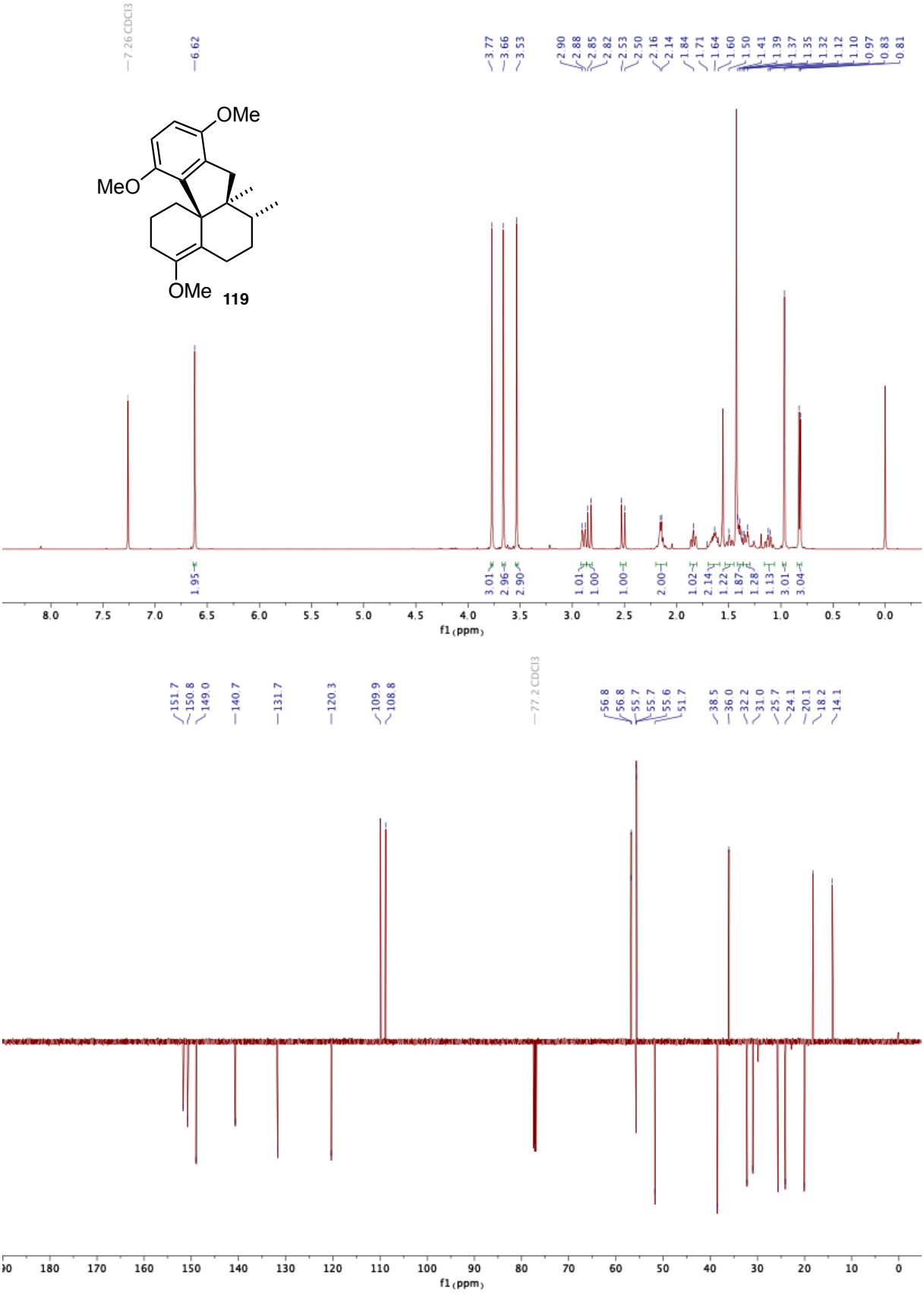
6.1.34 ^{1}H AND ^{13}C NMR SPECTRA OF (–)-DYSIHERBOL A (*ent*-**98**)



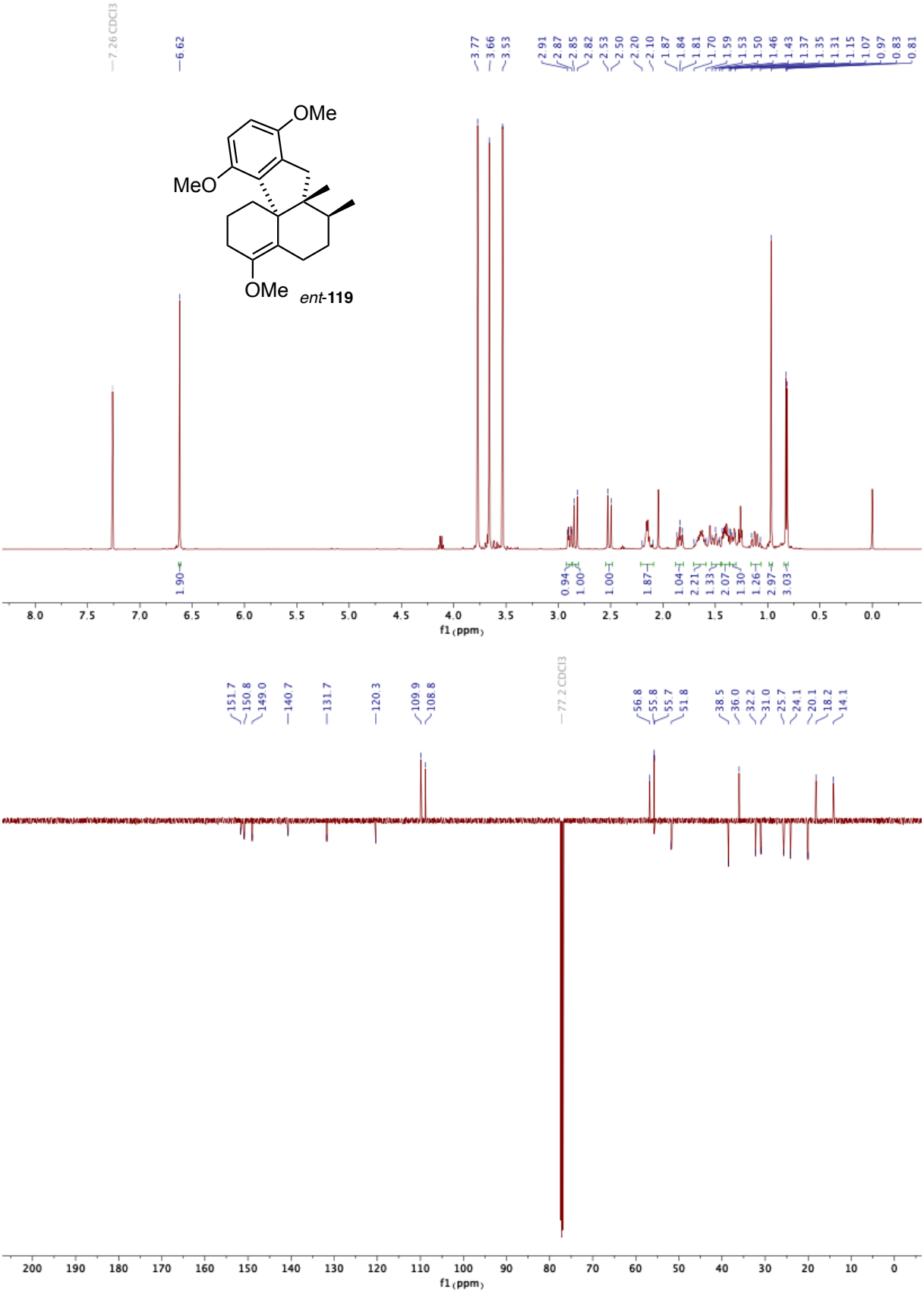
6.1.35 ^{1}H AND ^{13}C NMR SPECTRA OF (+)-DYSIHERBOL A (**98**)



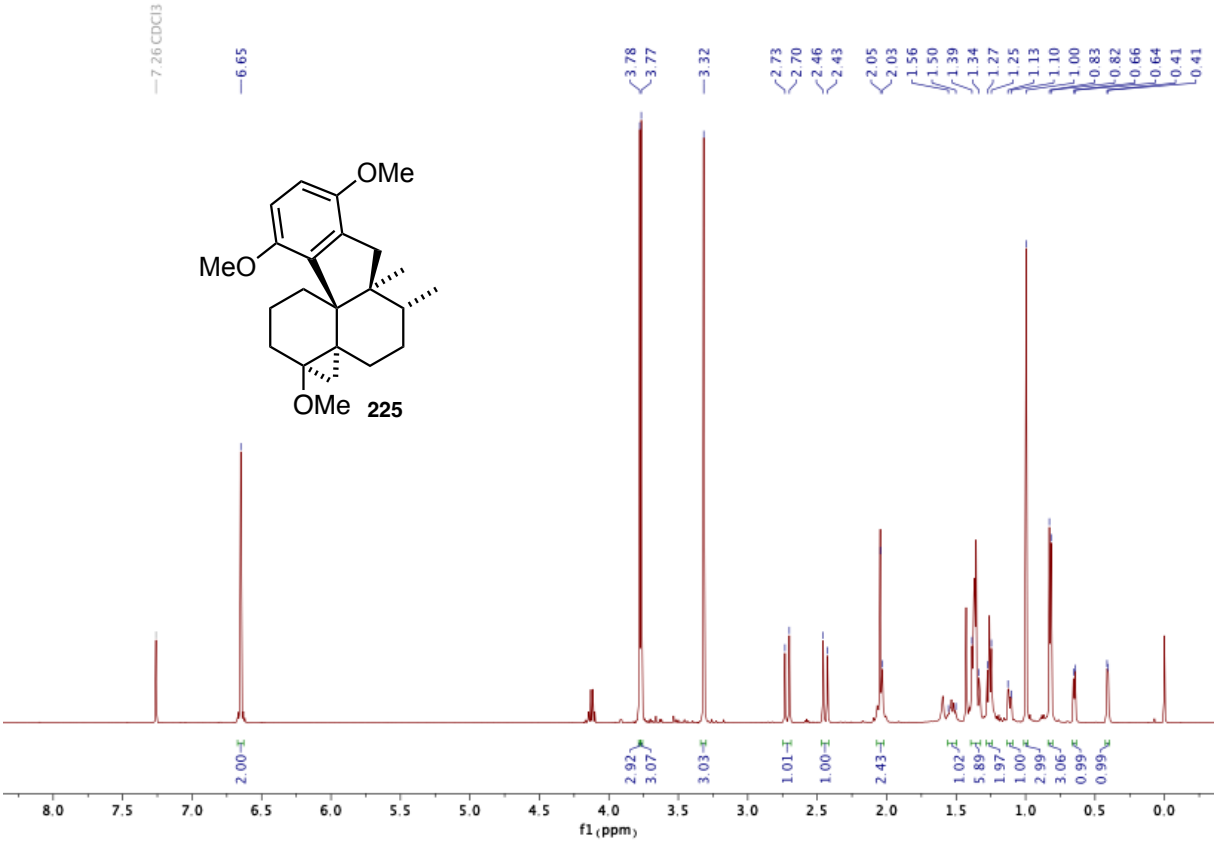
6.1.36 ^{1}H AND ^{13}C NMR SPECTRA OF METHYL ENOL ETHER **119**

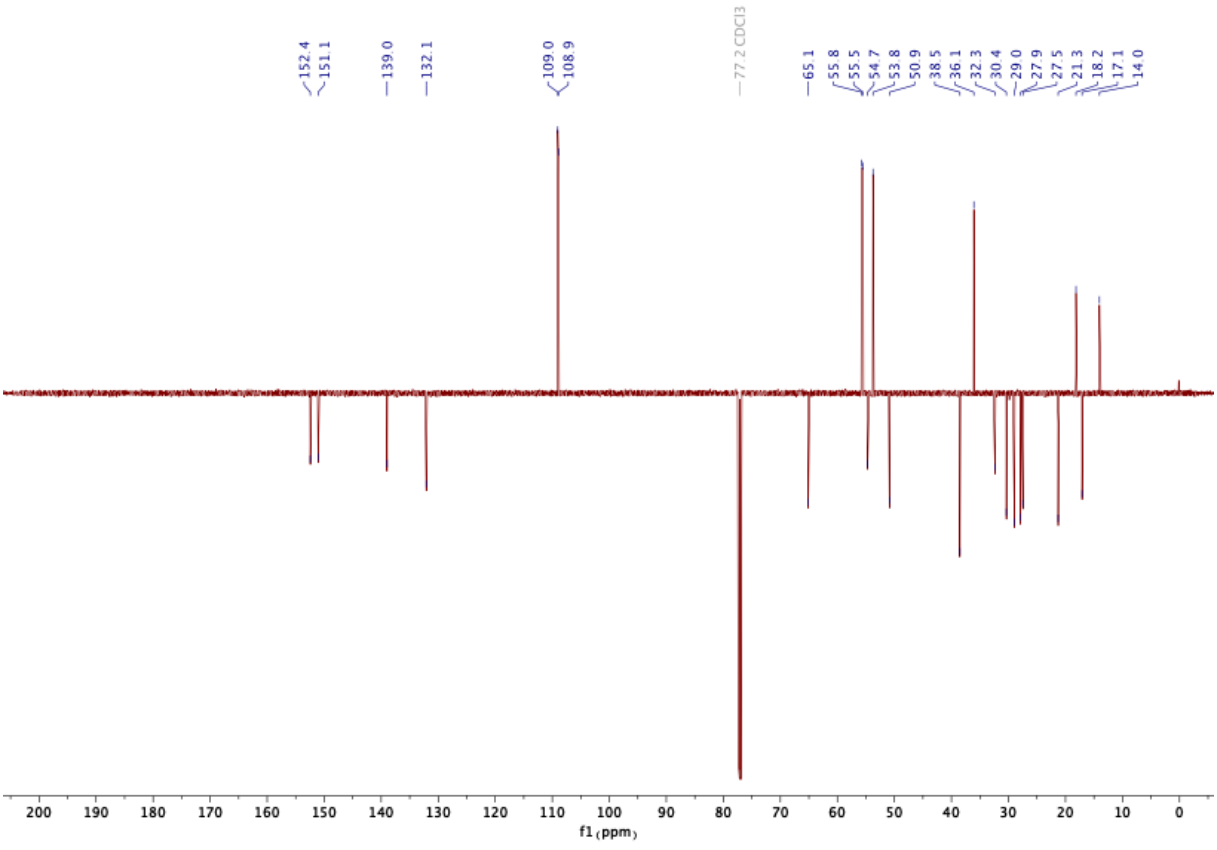


6.1.37 ^{1}H AND ^{13}C NMR SPECTRA OF METHYL ENOL ETHER *ent*-**119**

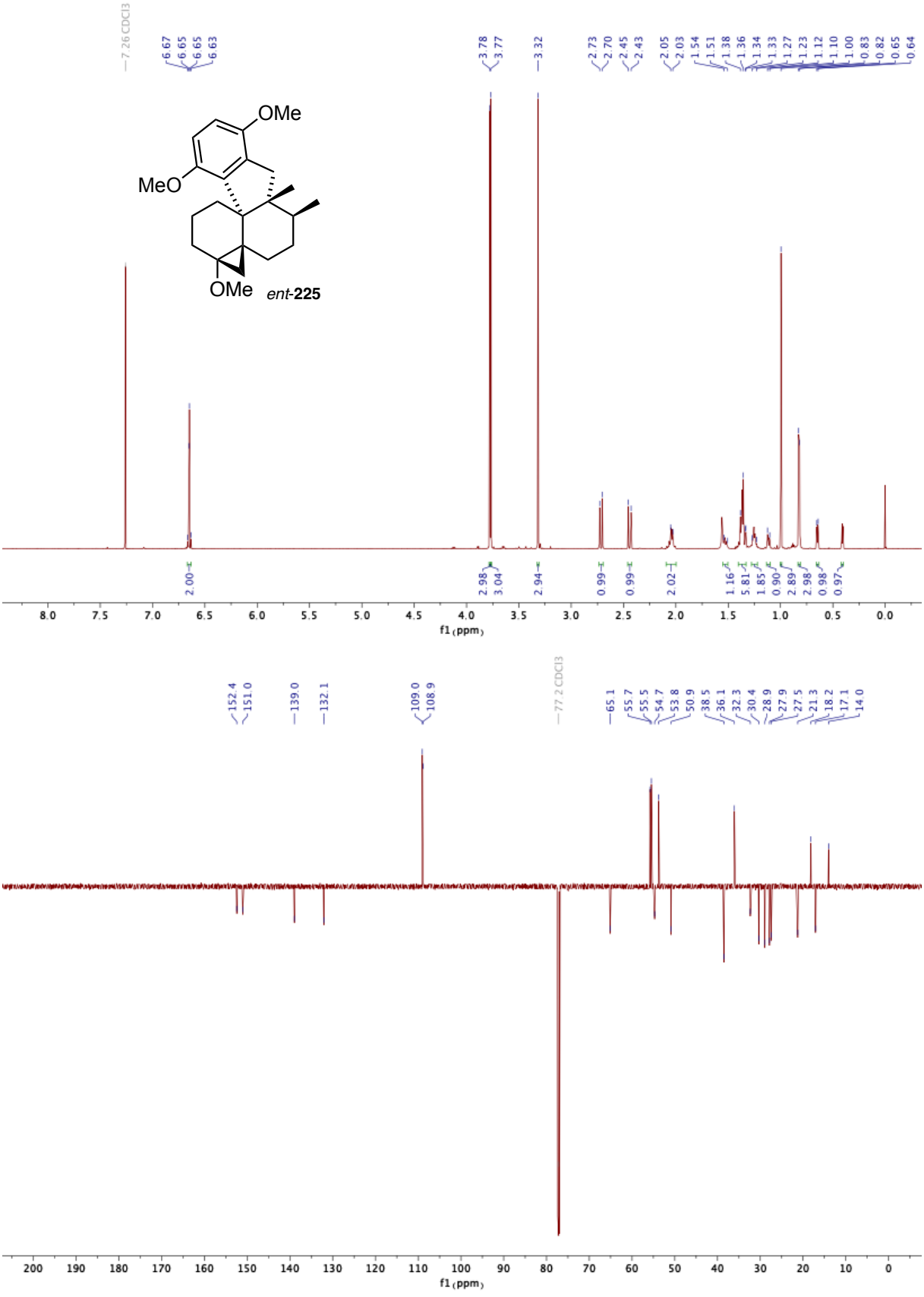


6.1.38 ^{1}H AND ^{13}C NMR SPECTRA OF CYCLOPROPANE **225**

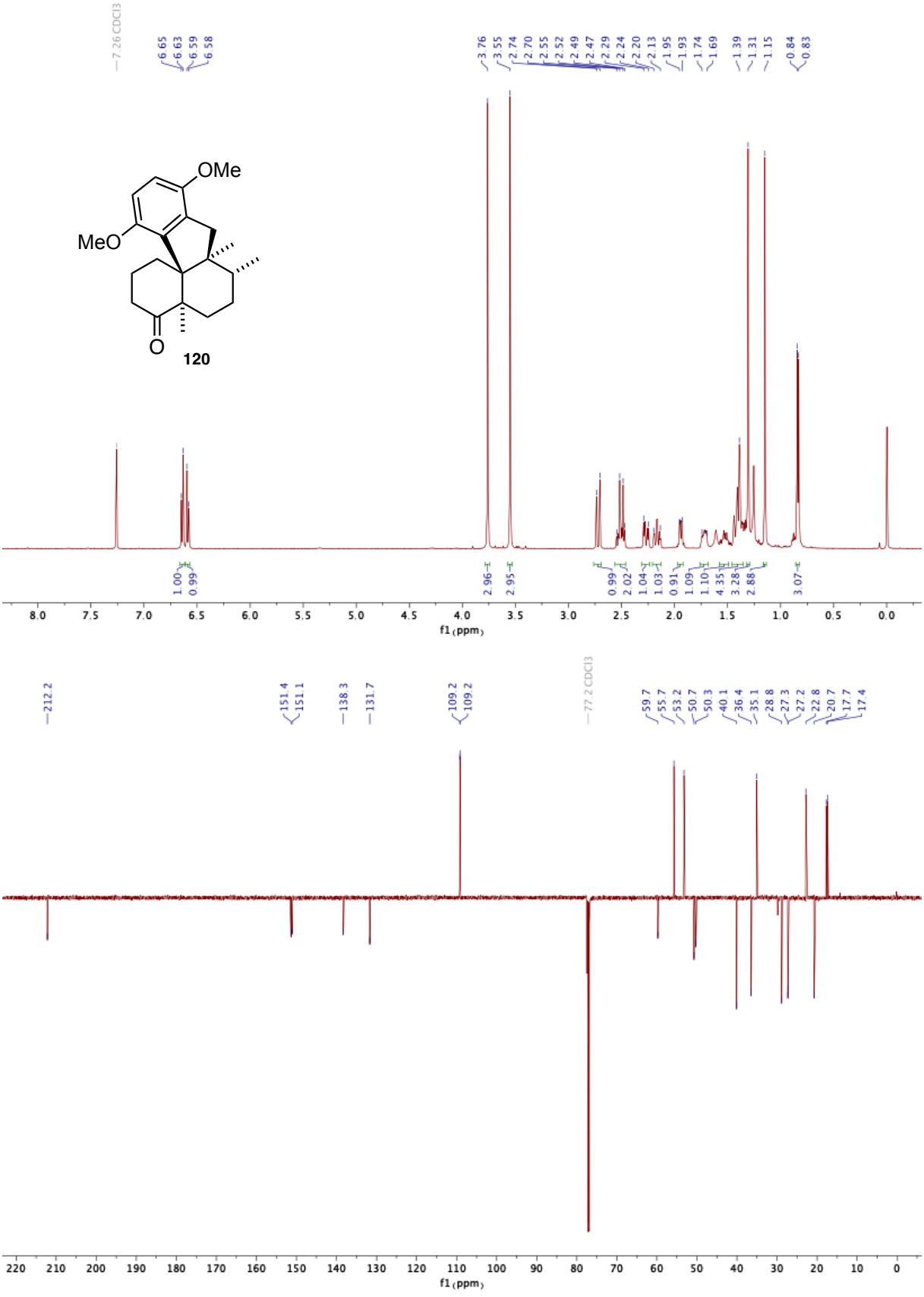




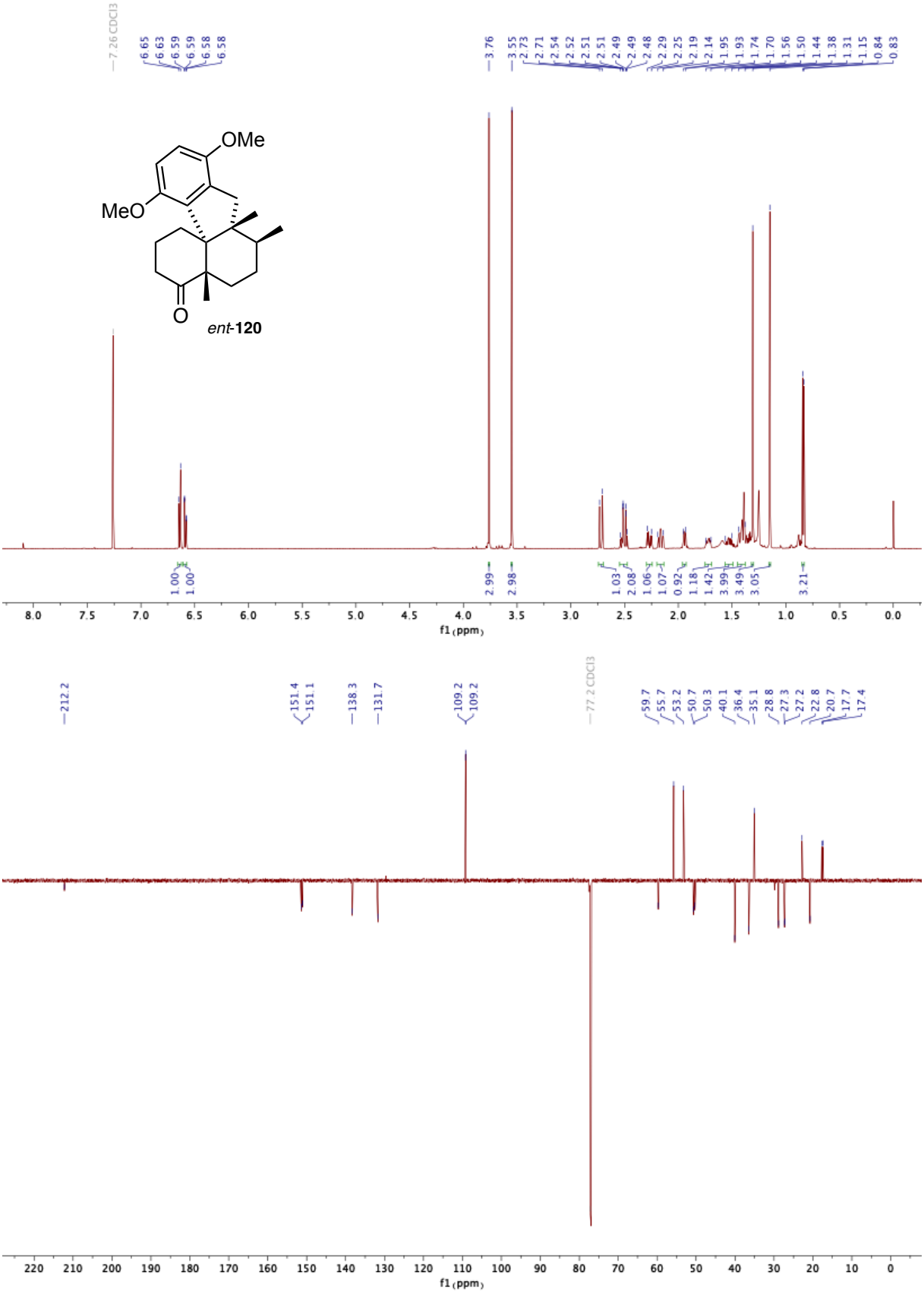
6.1.39 ^{1}H AND ^{13}C NMR SPECTRA OF CYCLOPROPANE *ent*-**225**



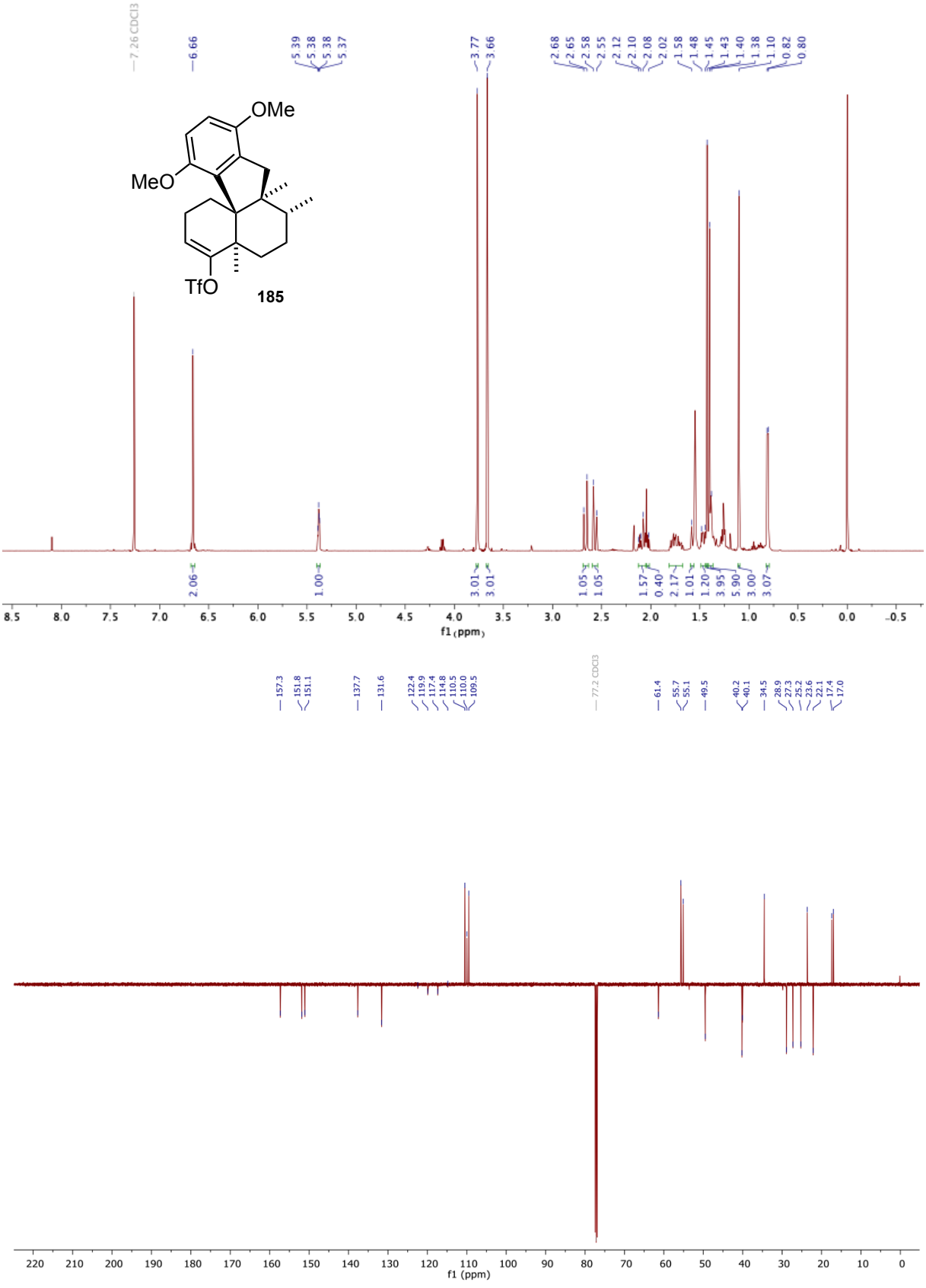
6.1.40 ^{1}H AND ^{13}C NMR SPECTRA OF α-METHYL KETONE **120**

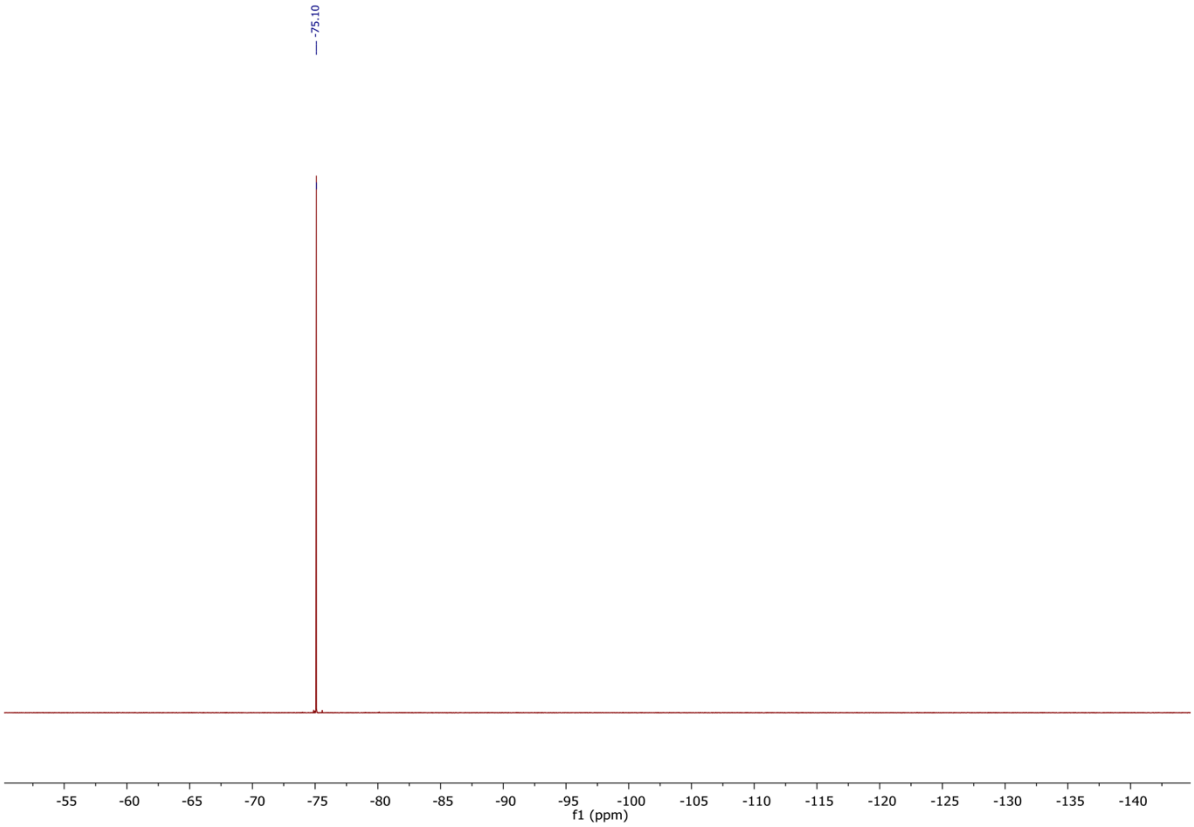


6.1.41 ^{1}H AND ^{13}C NMR SPECTRA OF α-METHYL KETONE *ent*-**120**

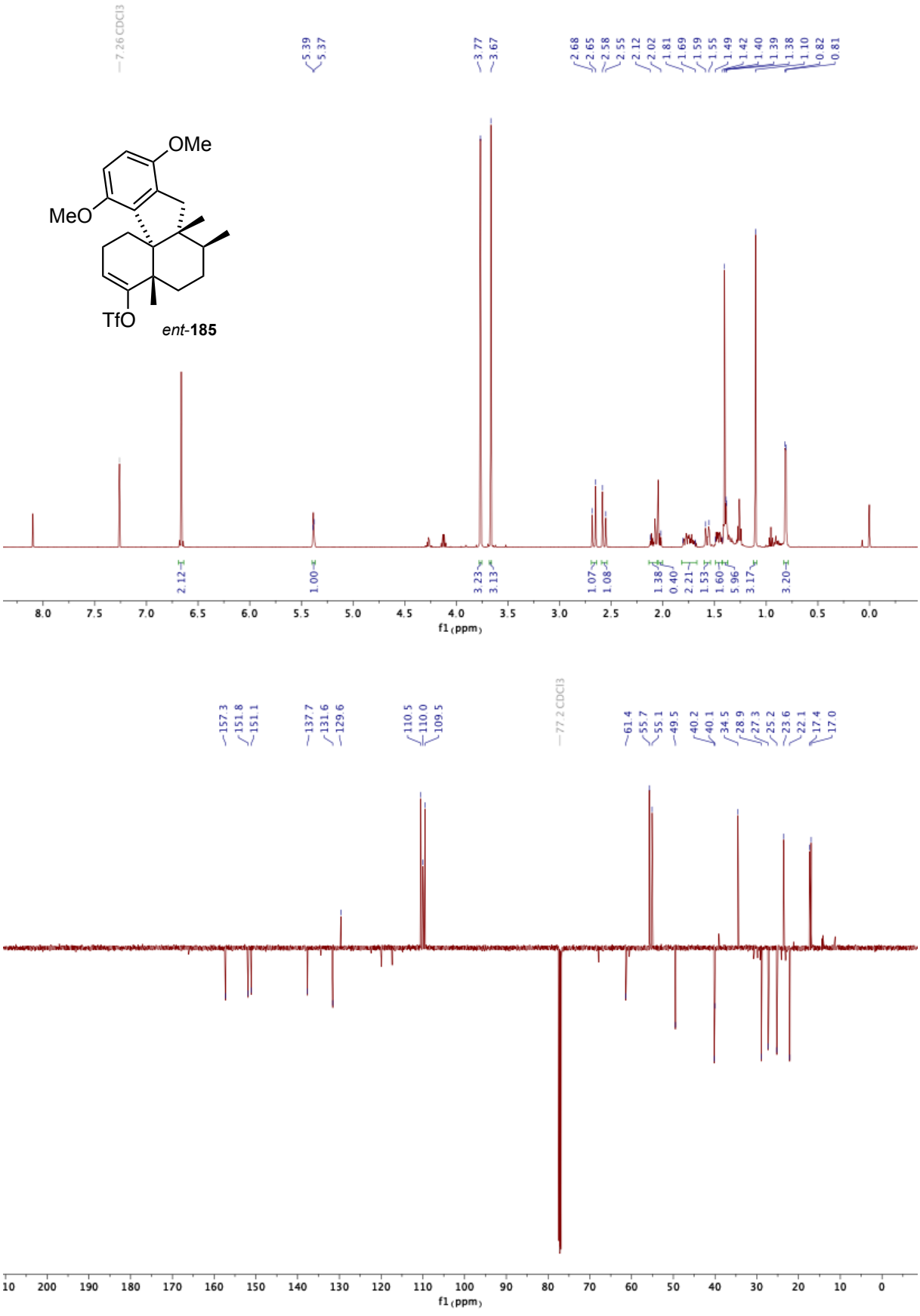


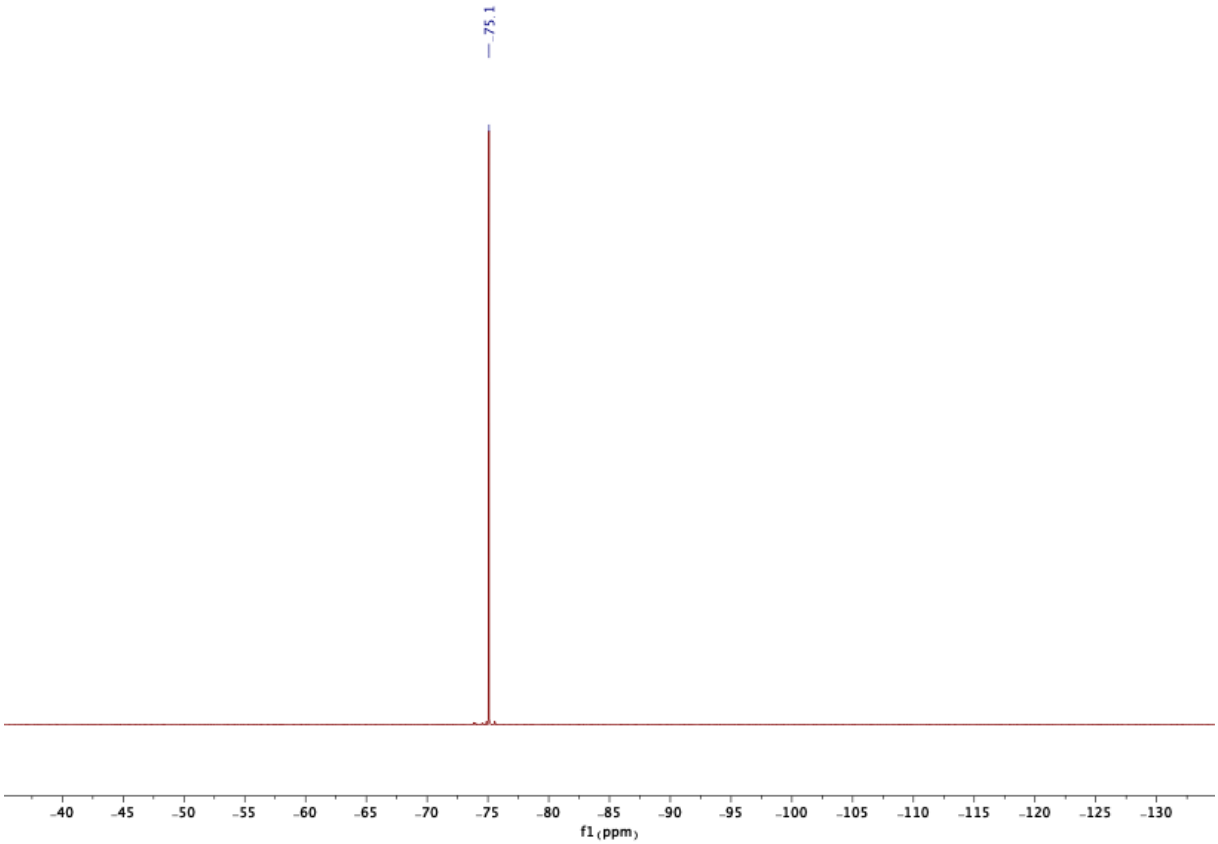
6.1.42 ^{1}H, ^{13}C AND ^{19}F NMR SPECTRA OF ENOL TRIFLATE **185**



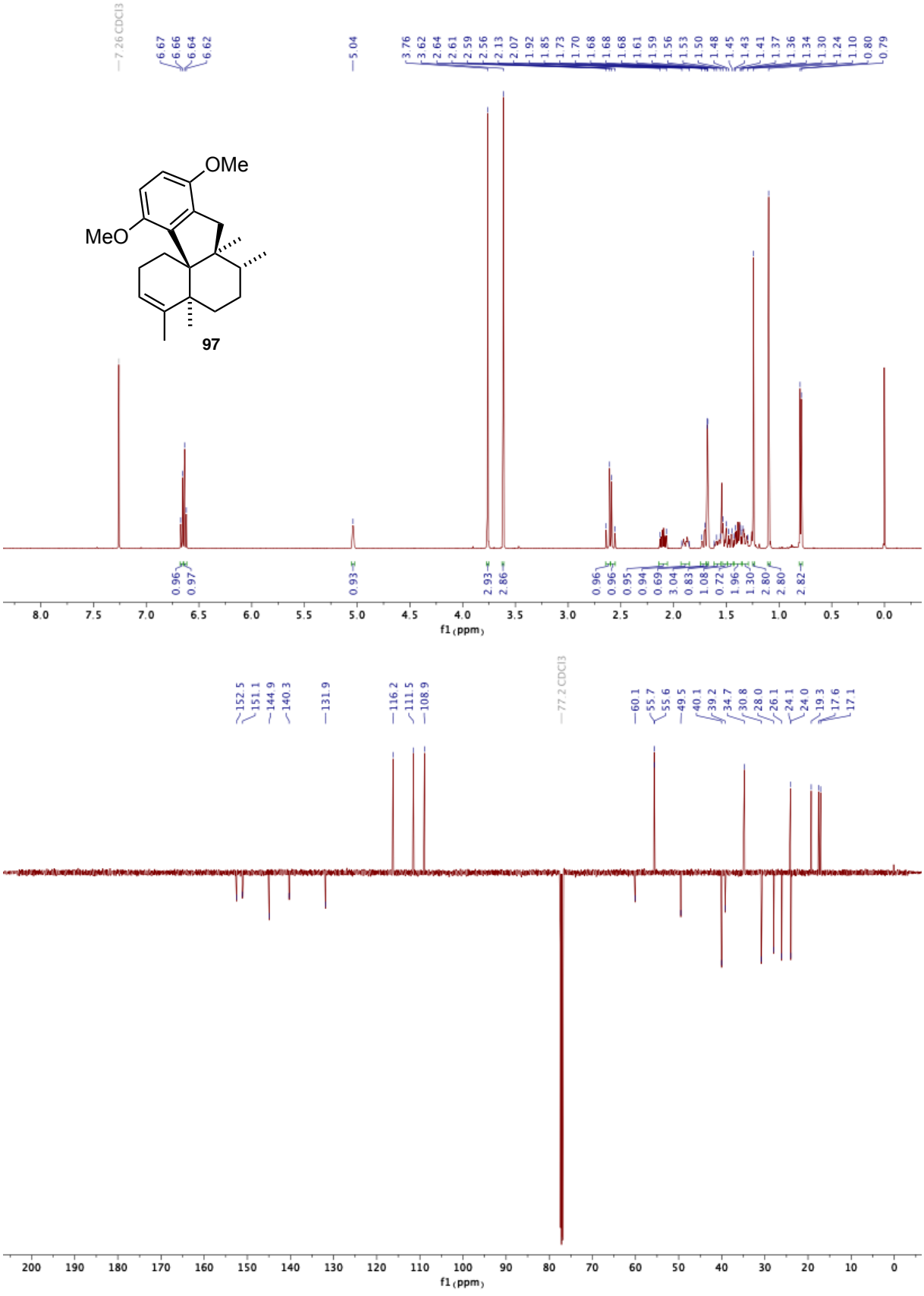

-75.10
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
f1 (ppm)

6.1.43 ^{1}H, ^{13}C AND ^{19}F NMR SPECTRA OF ENOL TRIFLATE *ent*-**185**

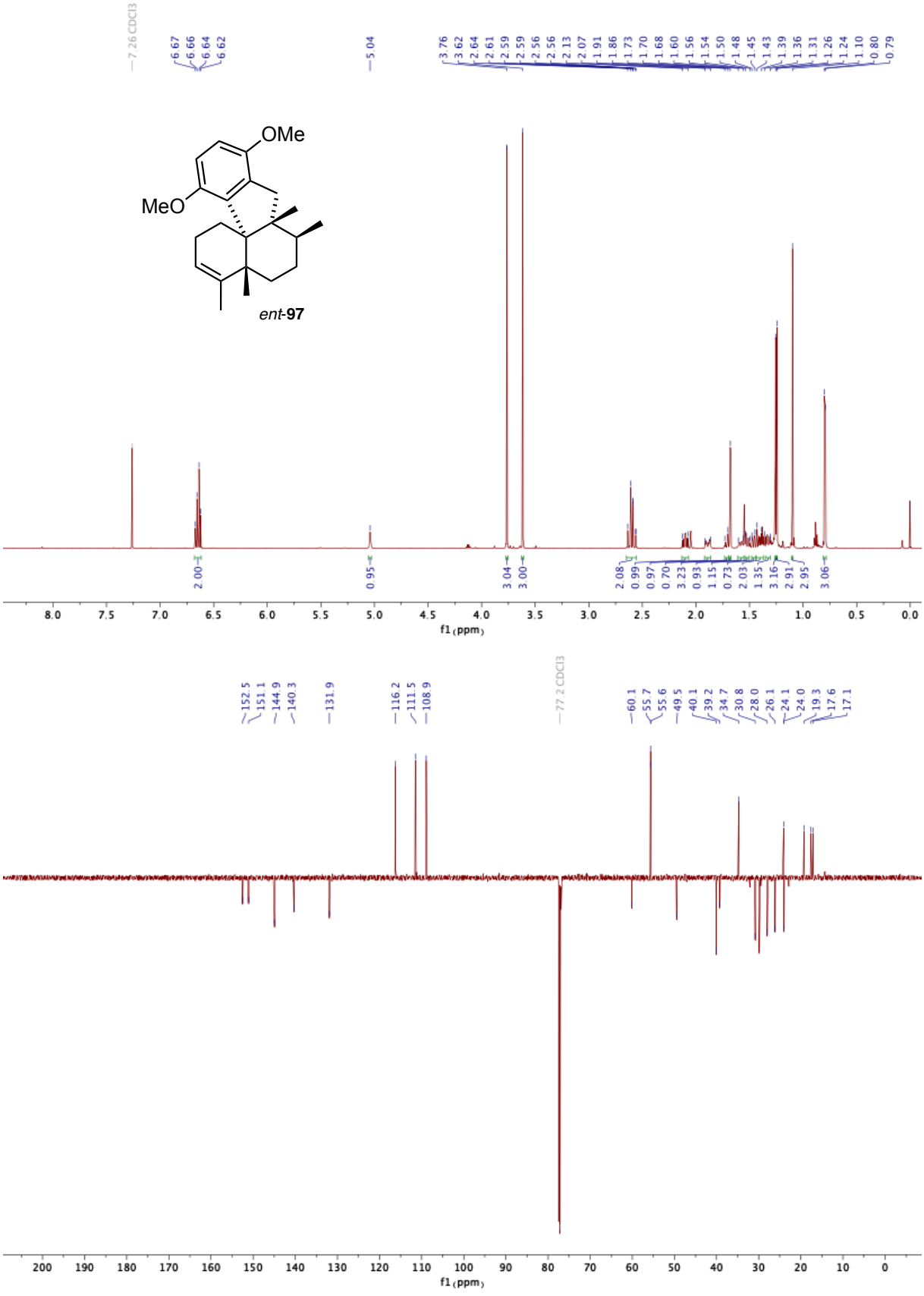



-75.1
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
f1 (ppm)

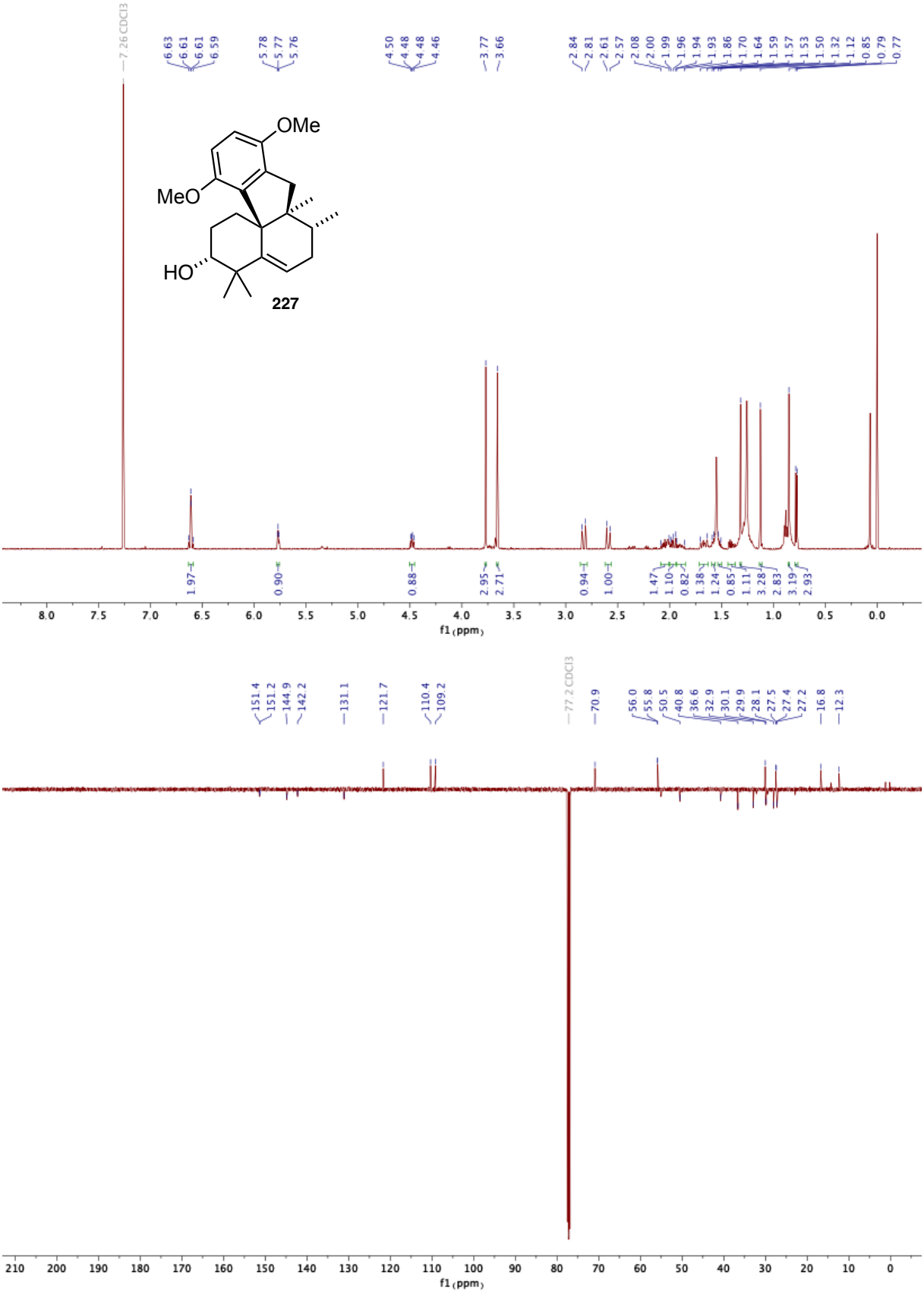
6.1.44 ^{1}H AND ^{13}C NMR SPECTRA OF OLEFIN **97**



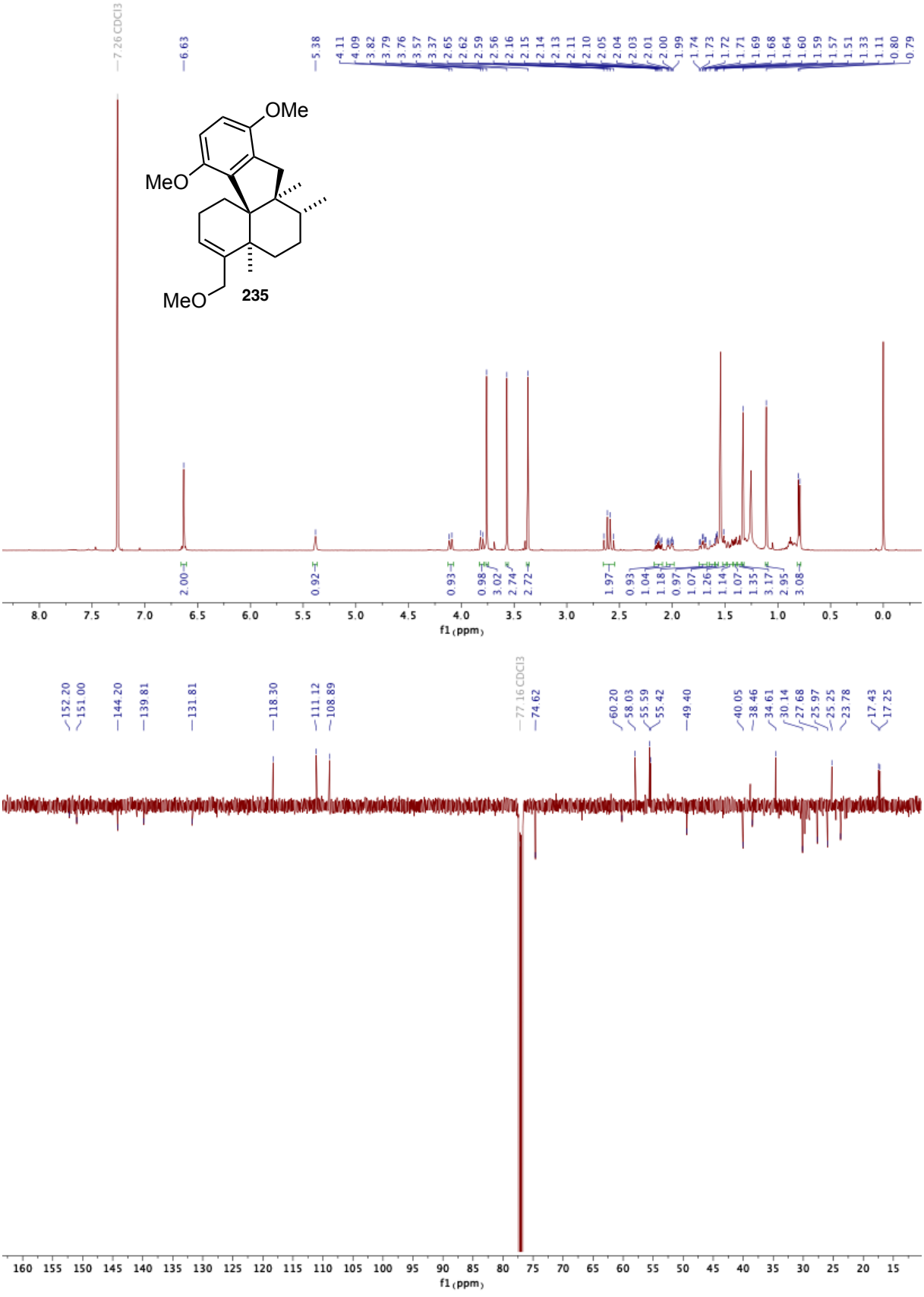
6.1.45 ^{1}H AND ^{13}C NMR SPECTRA OF OLEFIN *ent*-**97**



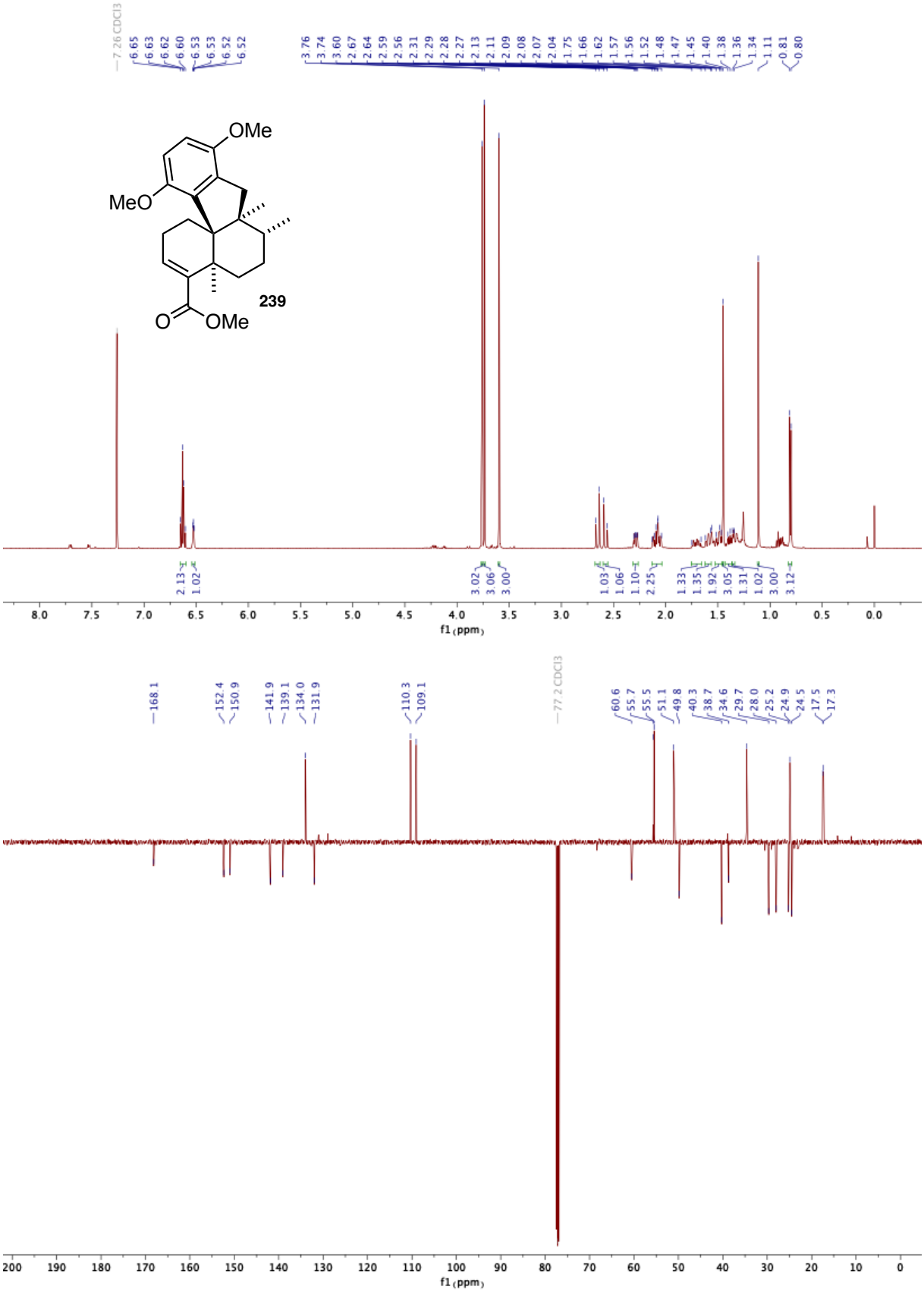
6.1.46 ^{1}H AND ^{13}C NMR SPECTRA OF HOMOALLYLIC ALCOHOL **227**



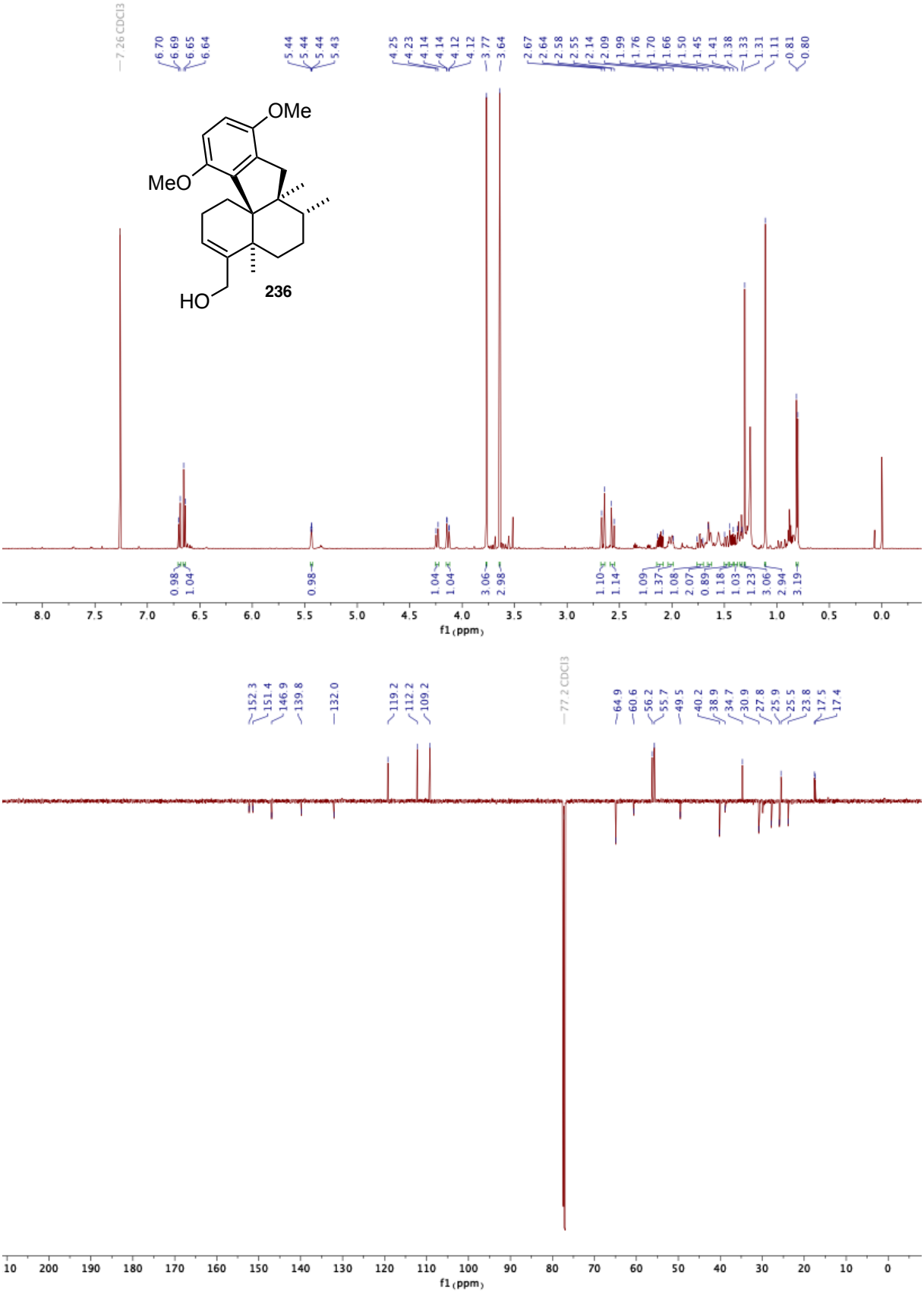
6.1.47 ^{1}H AND ^{13}C NMR SPECTRA OF ALLYL METHYL ETHER **235**



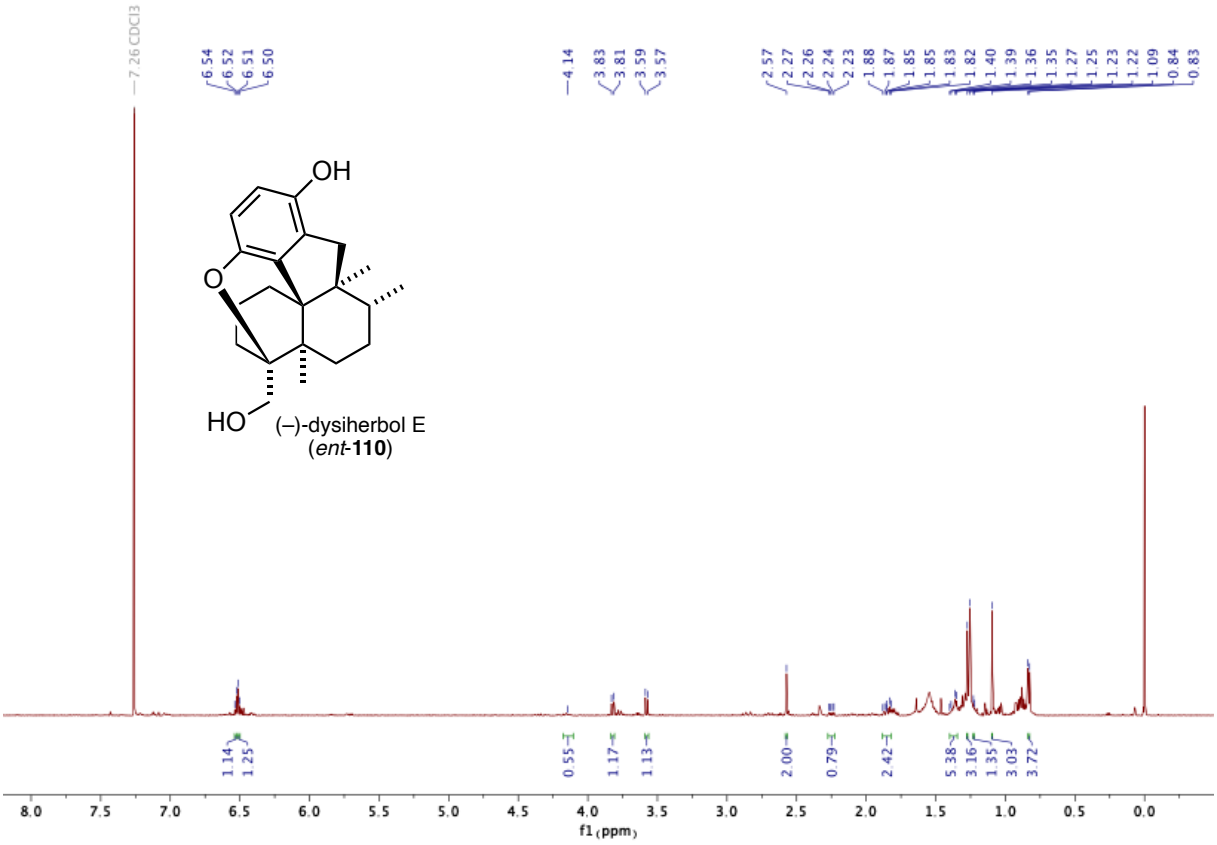
6.1.48 ^{1}H AND ^{13}C NMR SPECTRA OF METHYL ESTER **239**

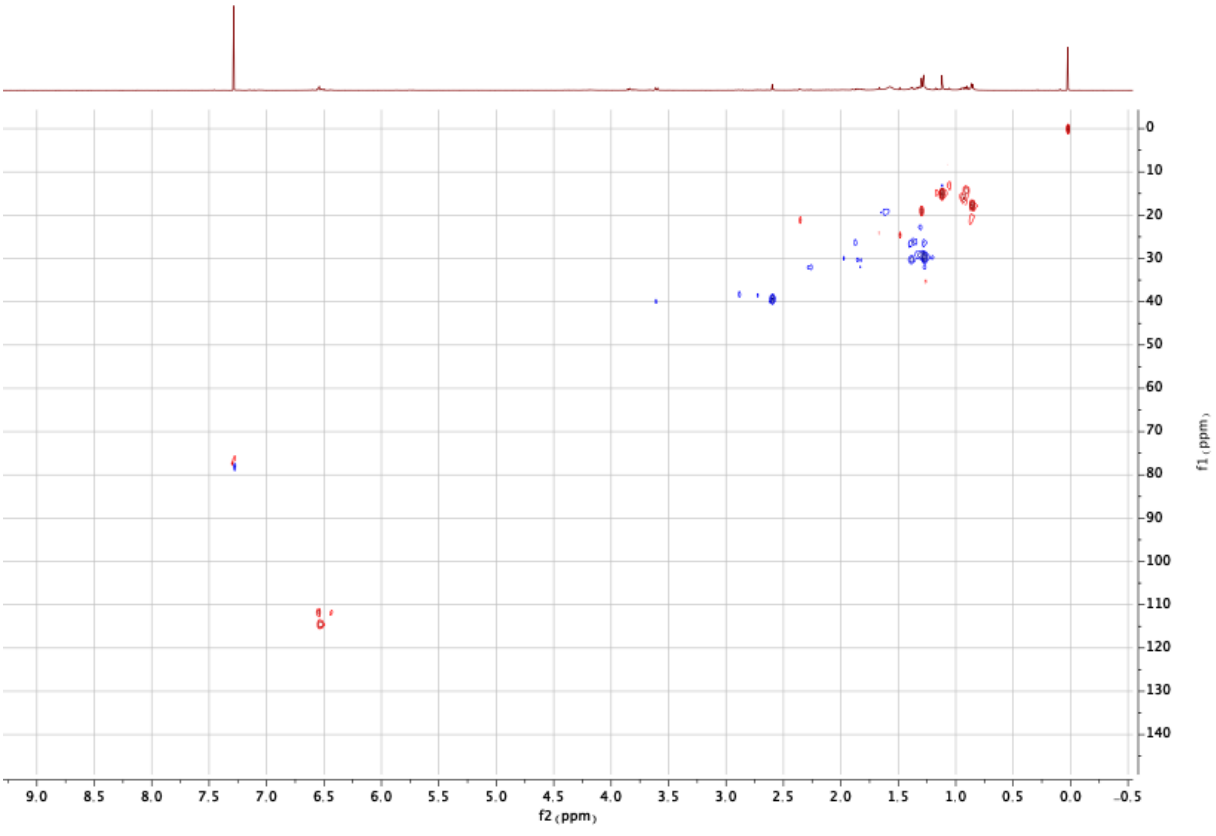


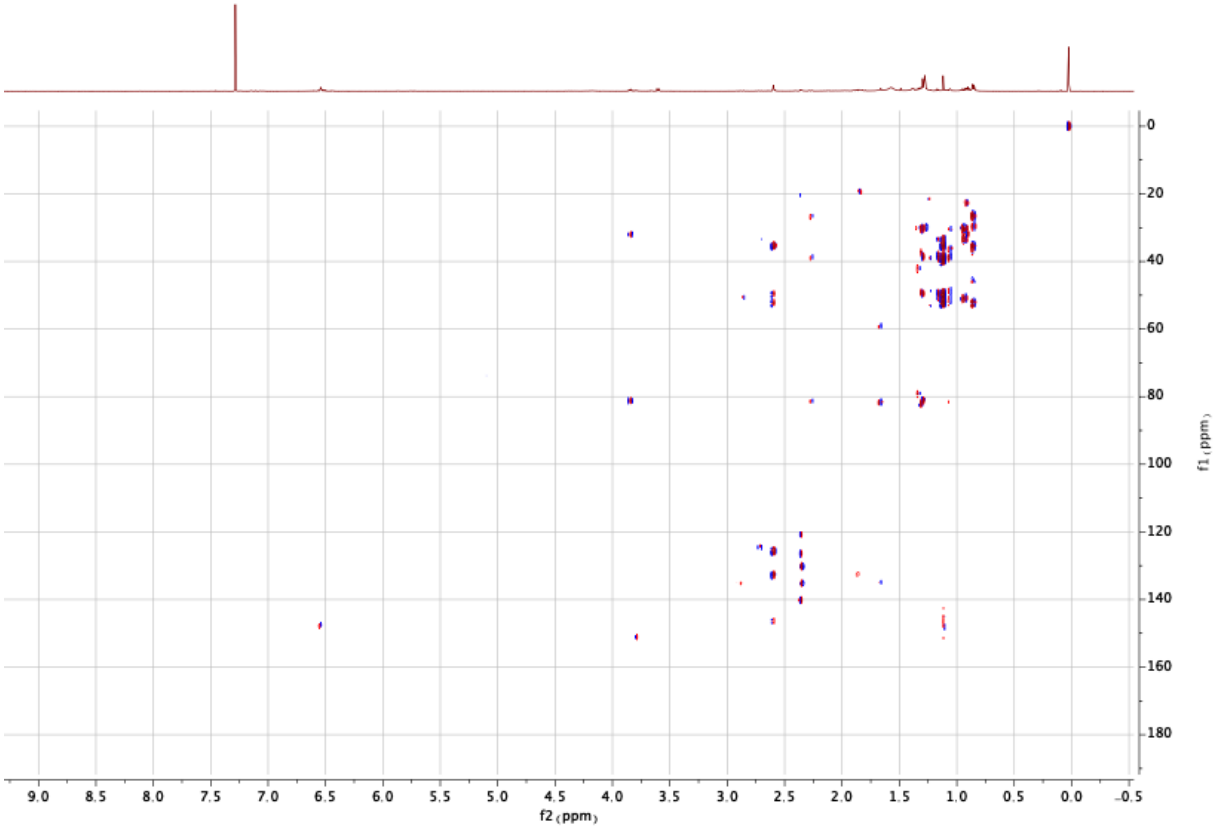
6.1.49 ^{1}H AND ^{13}C NMR SPECTRA OF ALLYLIC ALCOHOL **236**



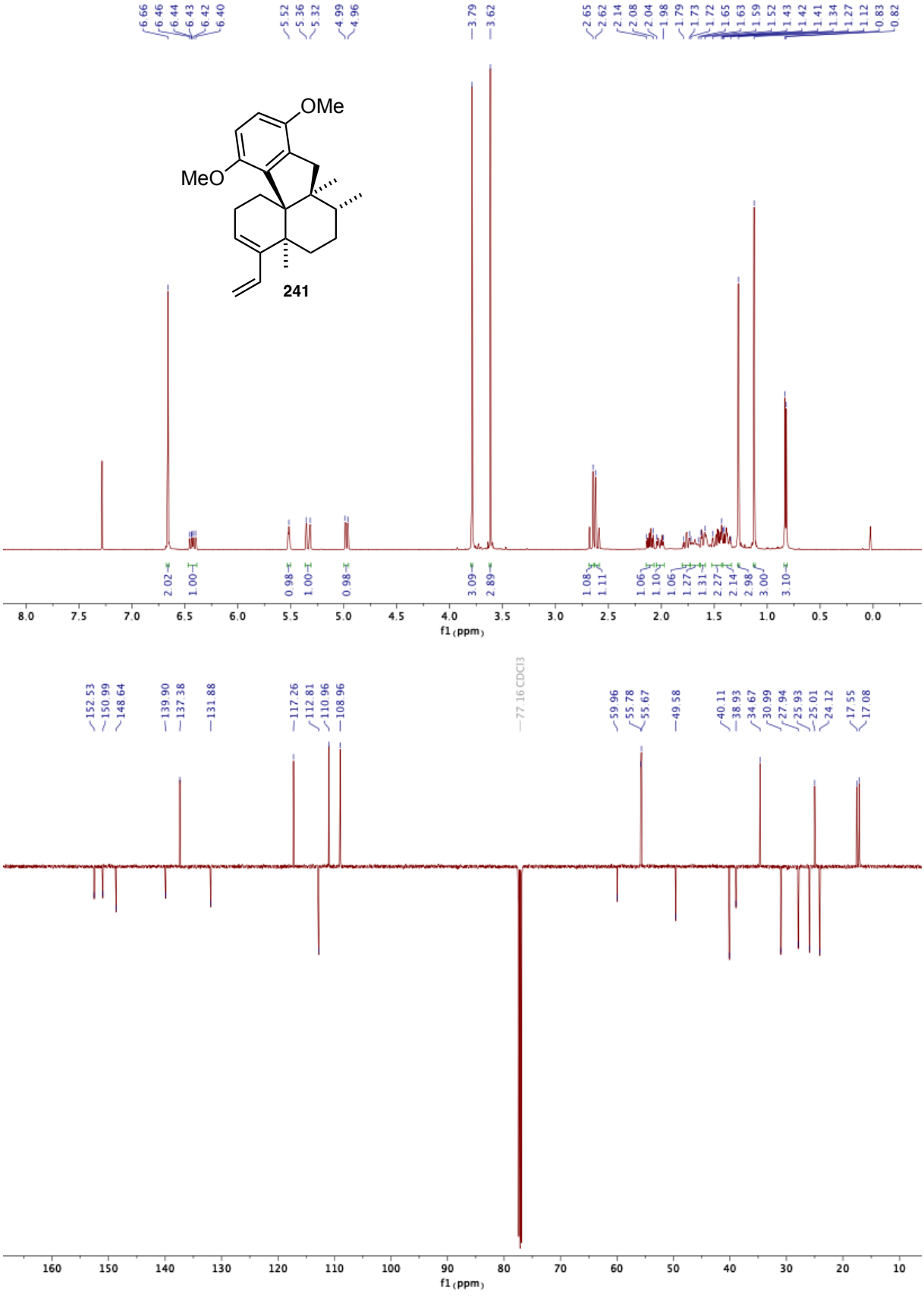
6.1.50 ^{1}H, H,C-HSQC AND HMBC NMR SPECTRA OF (–)-DYSIHERBOL E (*ent*-**110**)



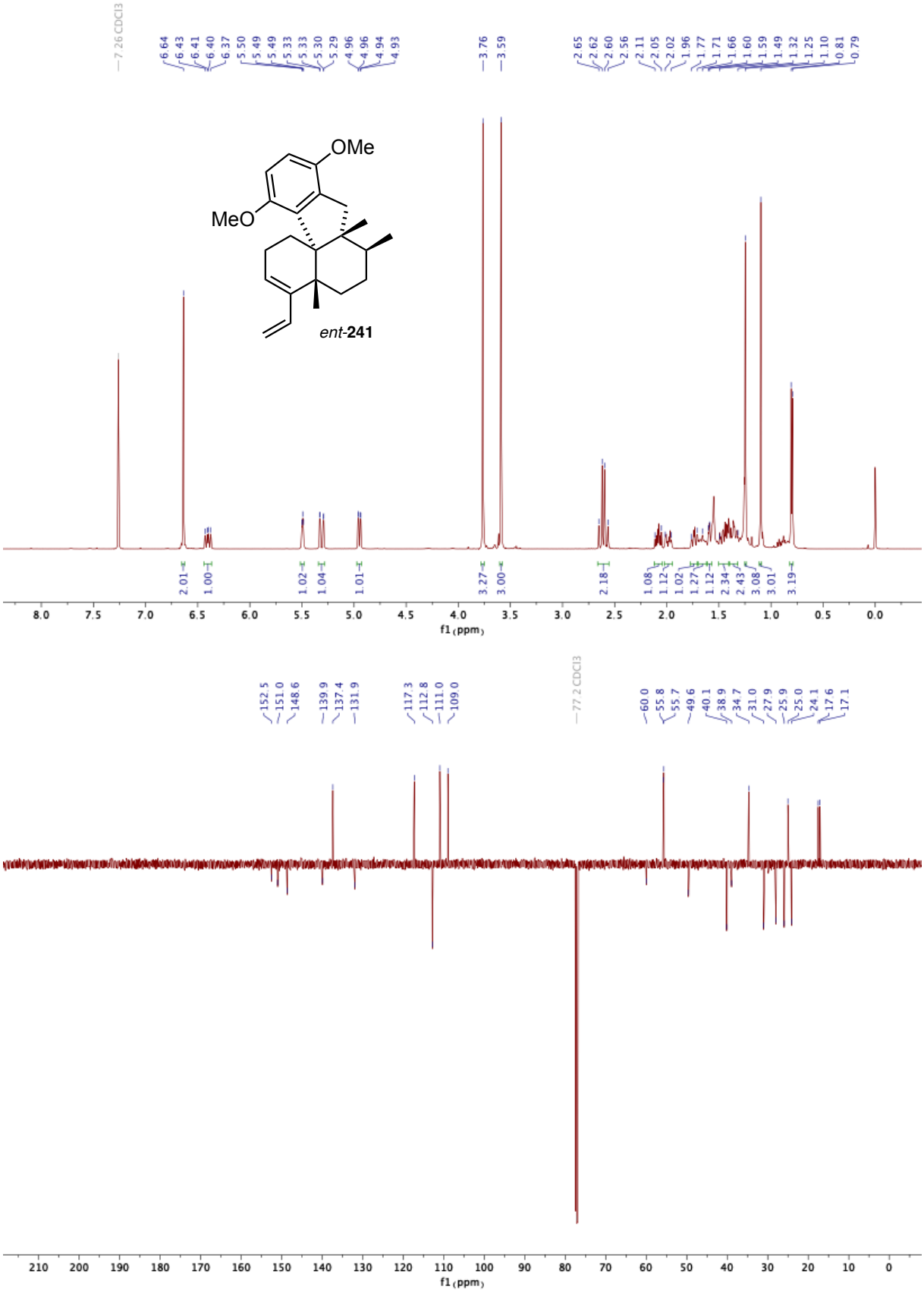



0
20
40
60
80
100
120
140
160
180
f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f2 (ppm)

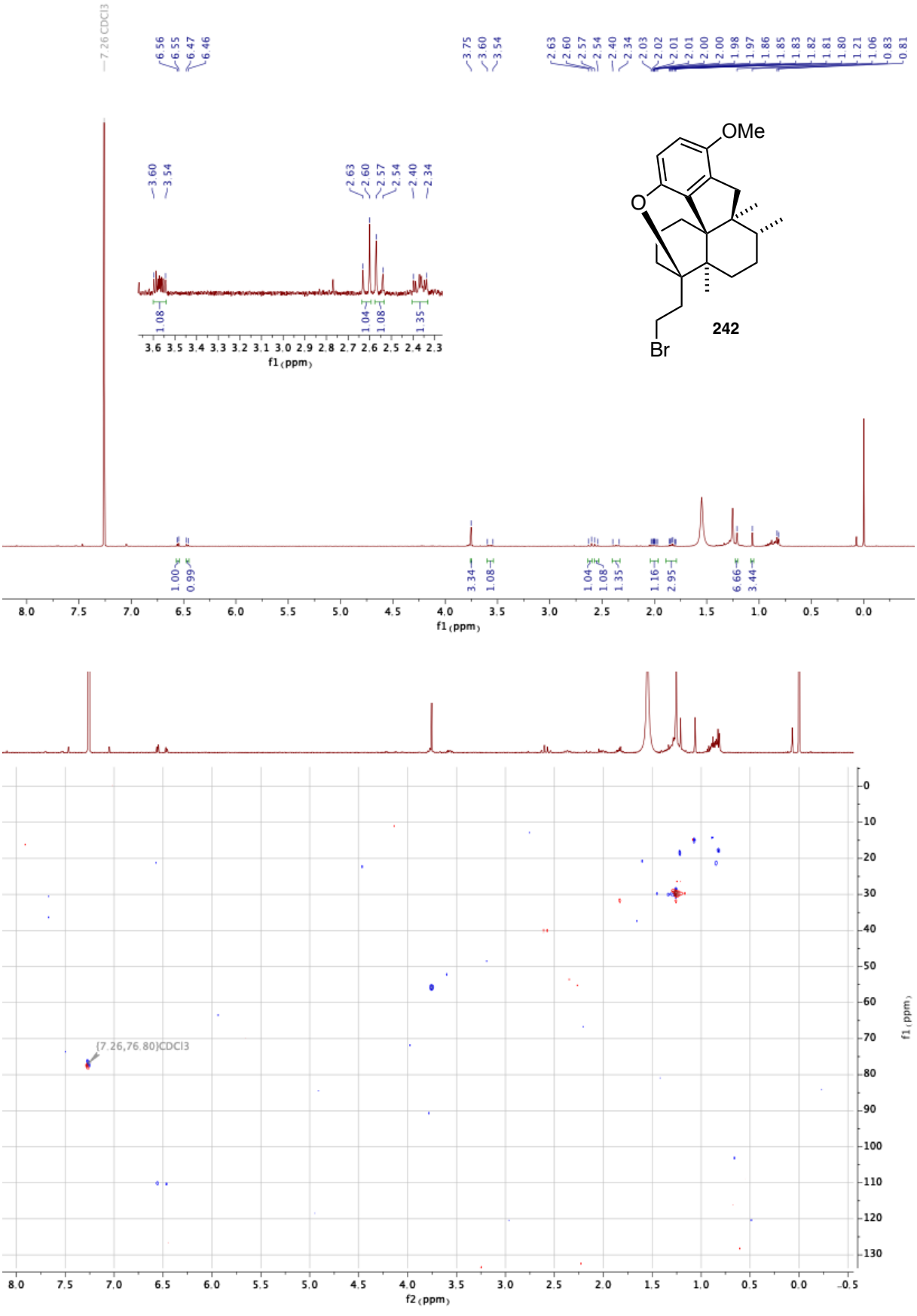
6.1.51 ^{1}H AND ^{13}C NMR SPECTRA OF DIENE **241**

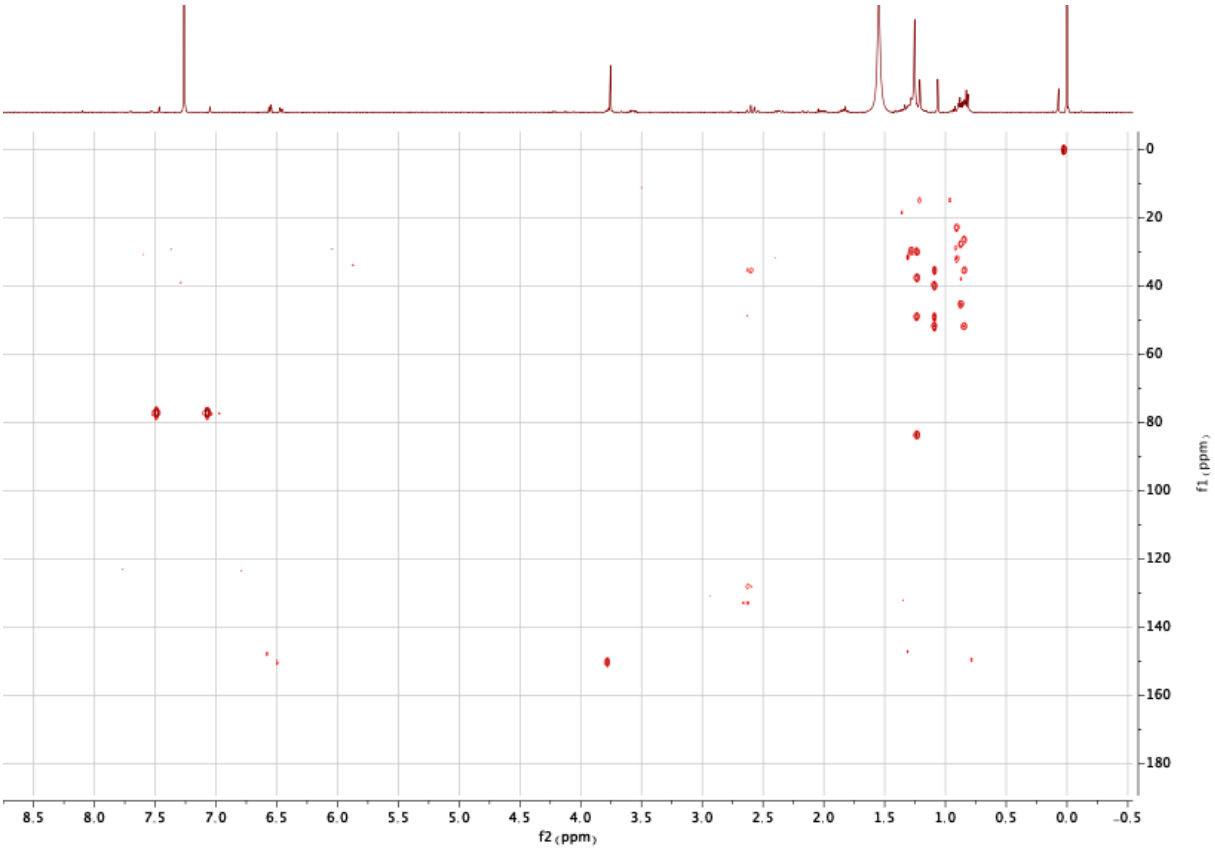


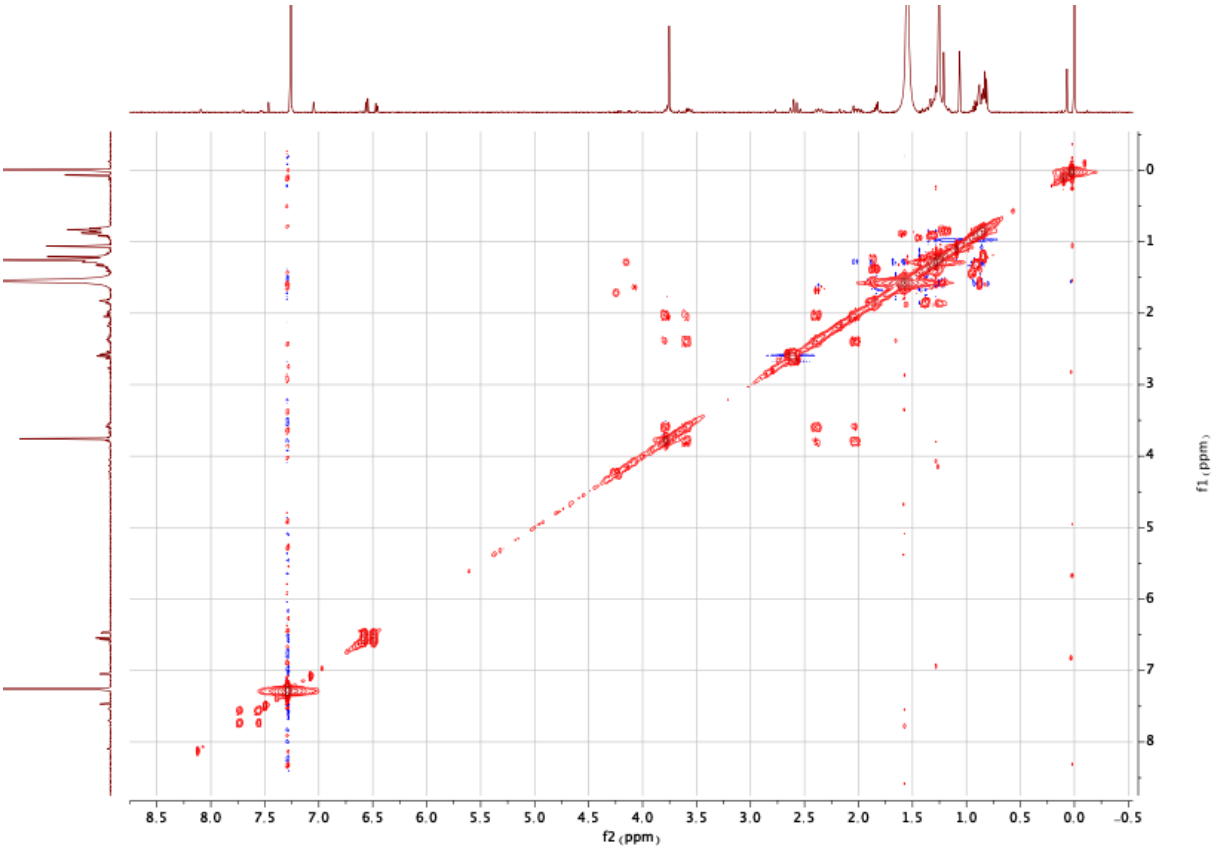
6.1.52 ^{1}H AND ^{13}C NMR SPECTRA OF DIENE *ent*-**241**



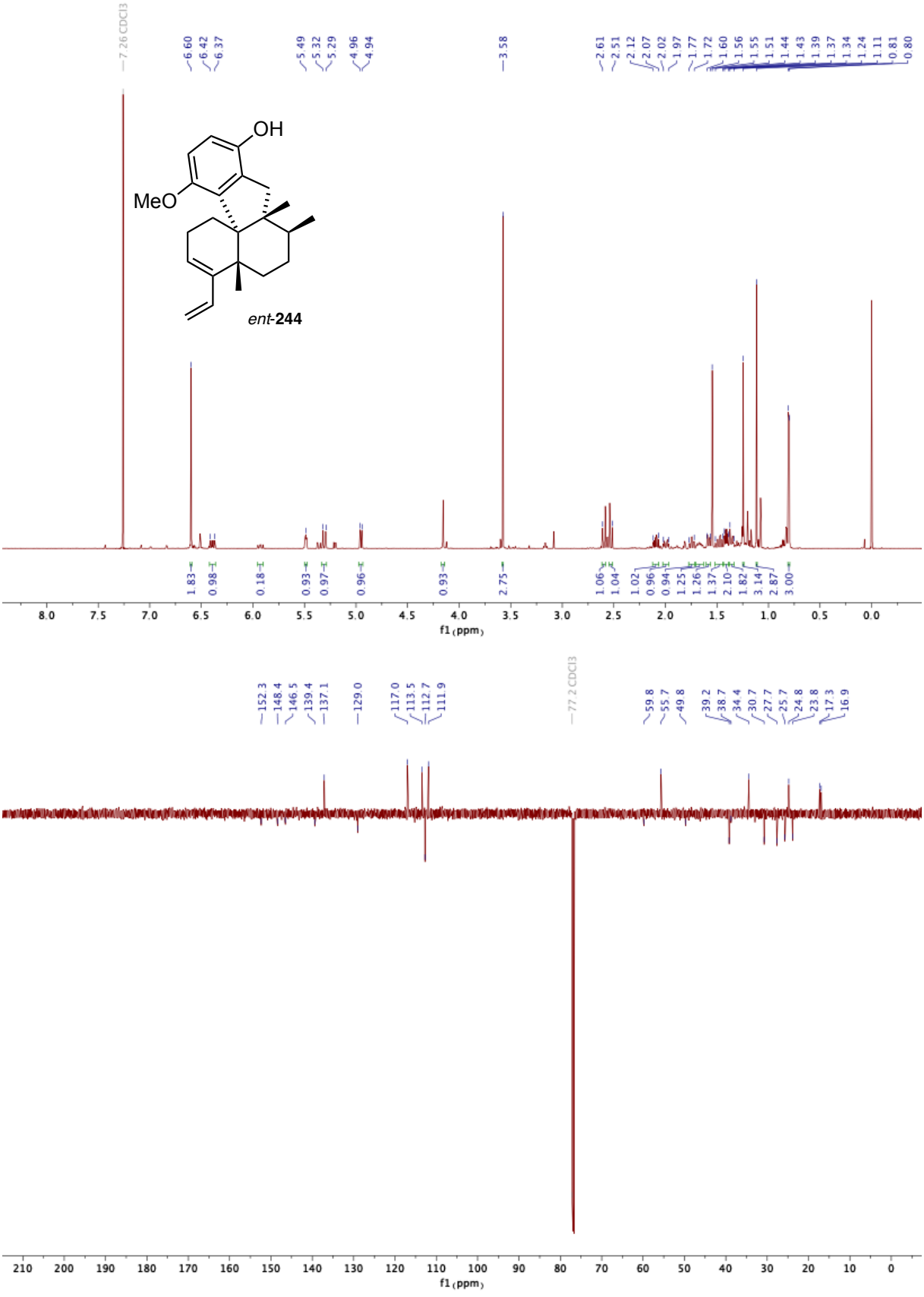
6.1.53 ^{1}H, H,C-HSQC AND HMBC AND H,H-COSY NMR SPECTRA OF PENTACYCLIC BROMIDE **242**



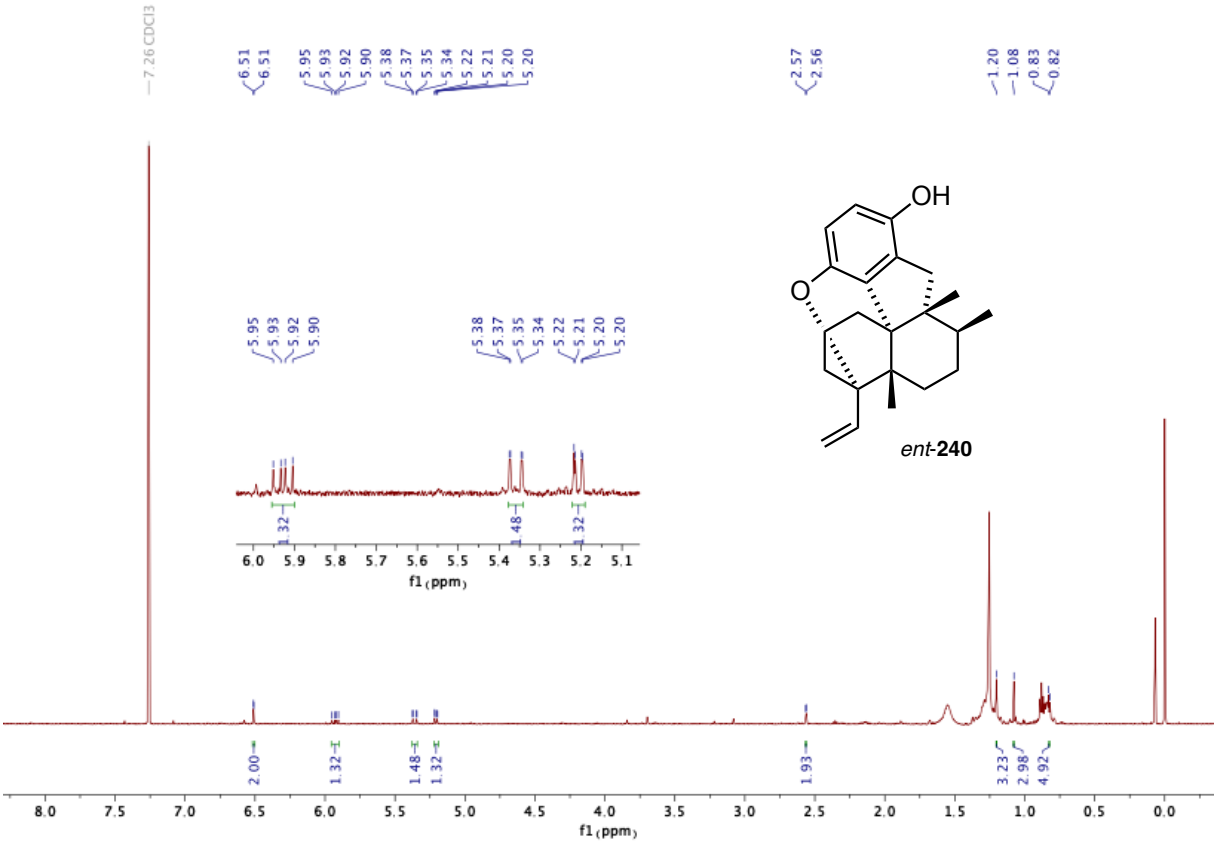

f2 (ppm)
f1 (ppm)

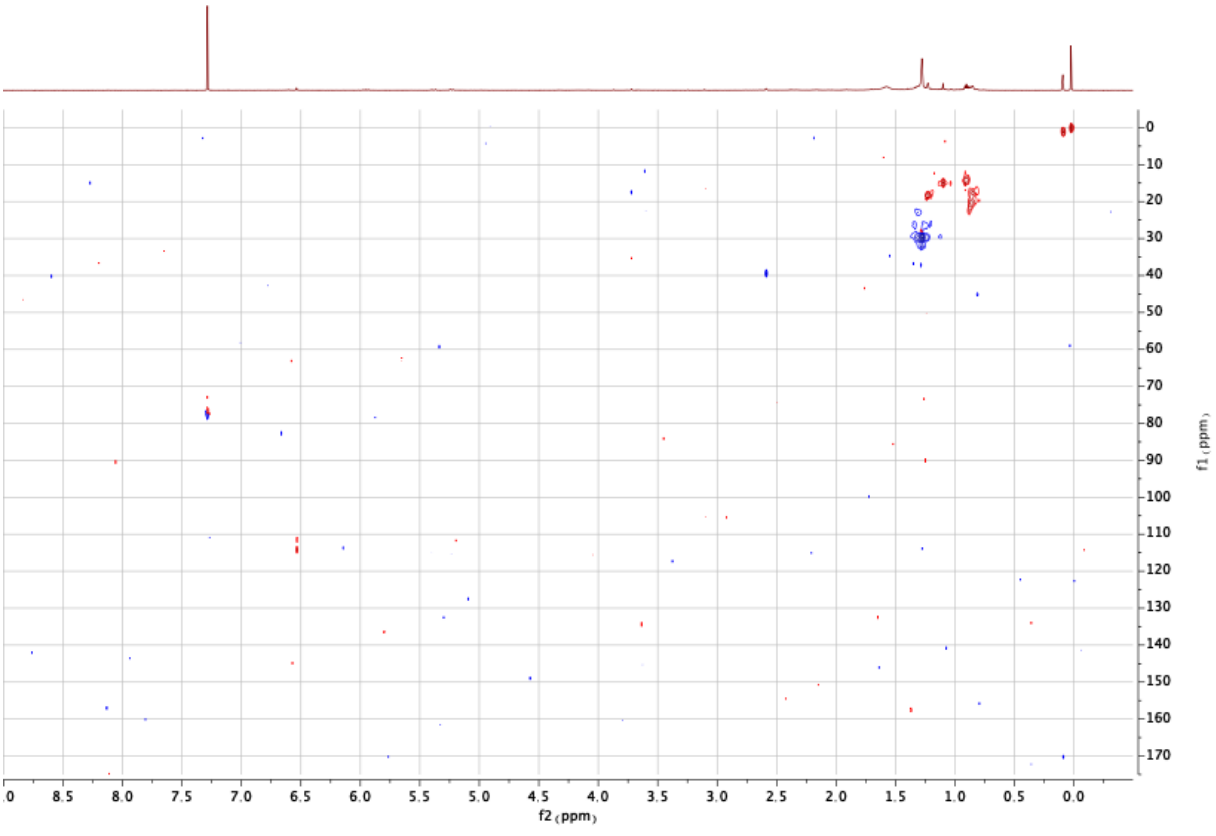

f2 (ppm)
f1 (ppm)

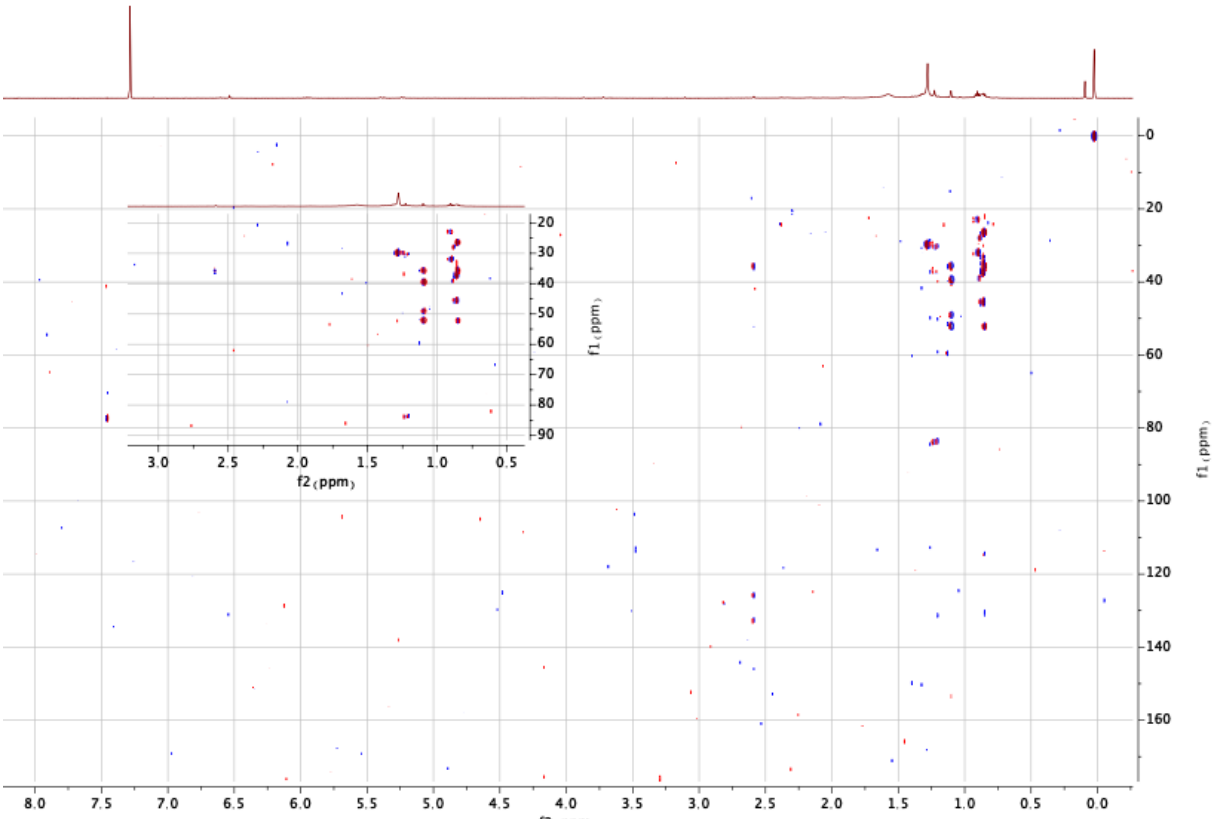
6.1.54 ^{1}H AND ^{13}C NMR SPECTRA OF METHYL ETHER *ent*-**244**

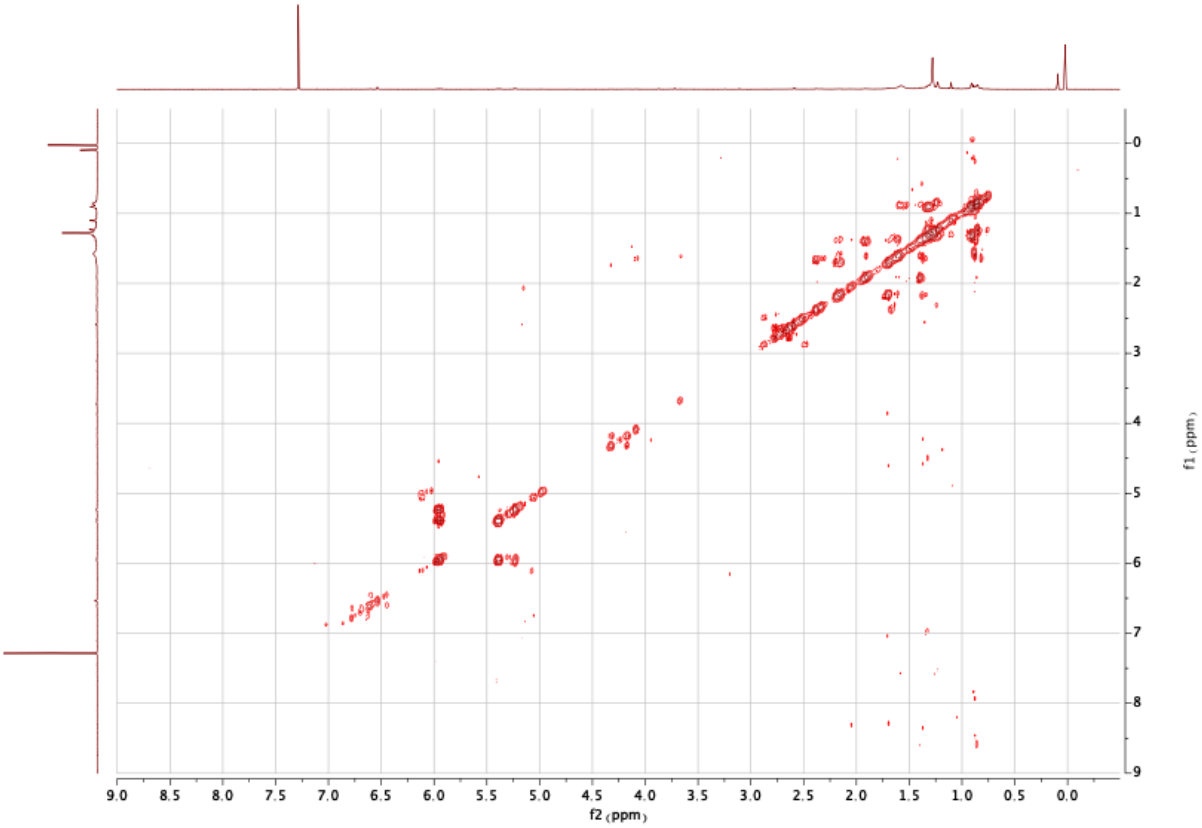


6.1.55 ^{1}H, H,C-HSQC AND HMBC AND H,H-COSY NMR SPECTRA OF PENTACYCLIC OLEFIN *ent*-**240**

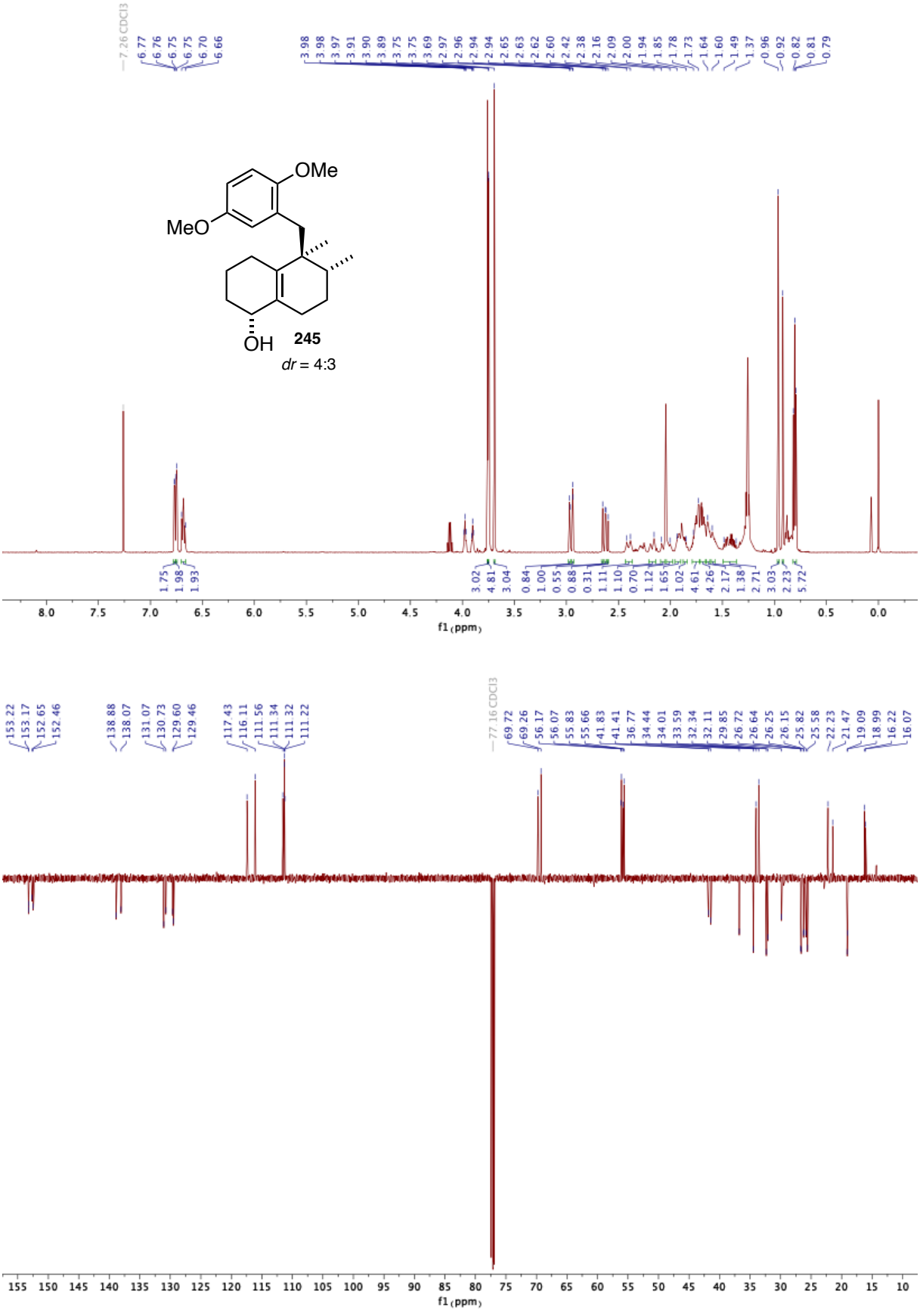




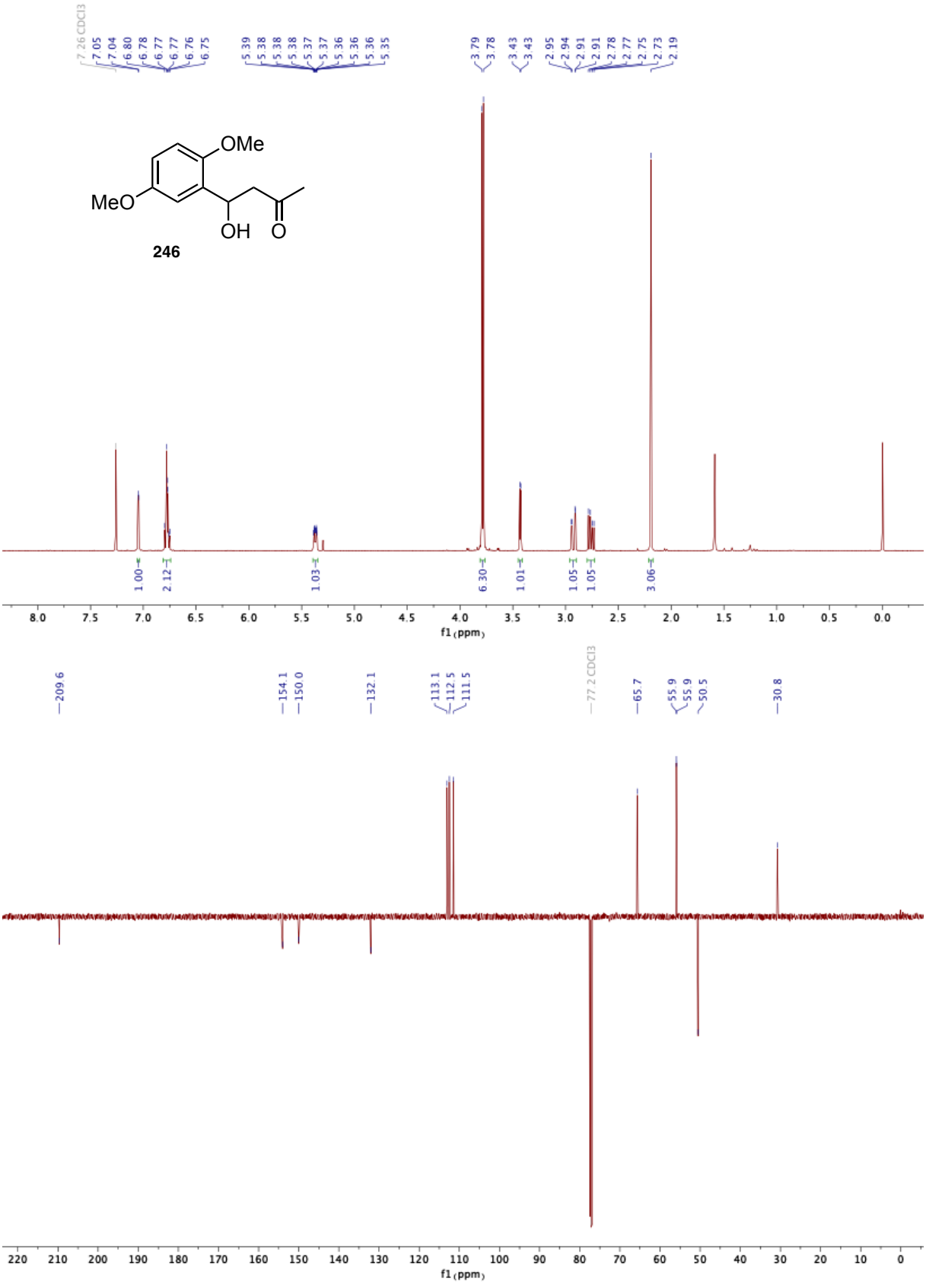

f2 (ppm)
f1 (ppm)


f2 (ppm)
f1 (ppm)

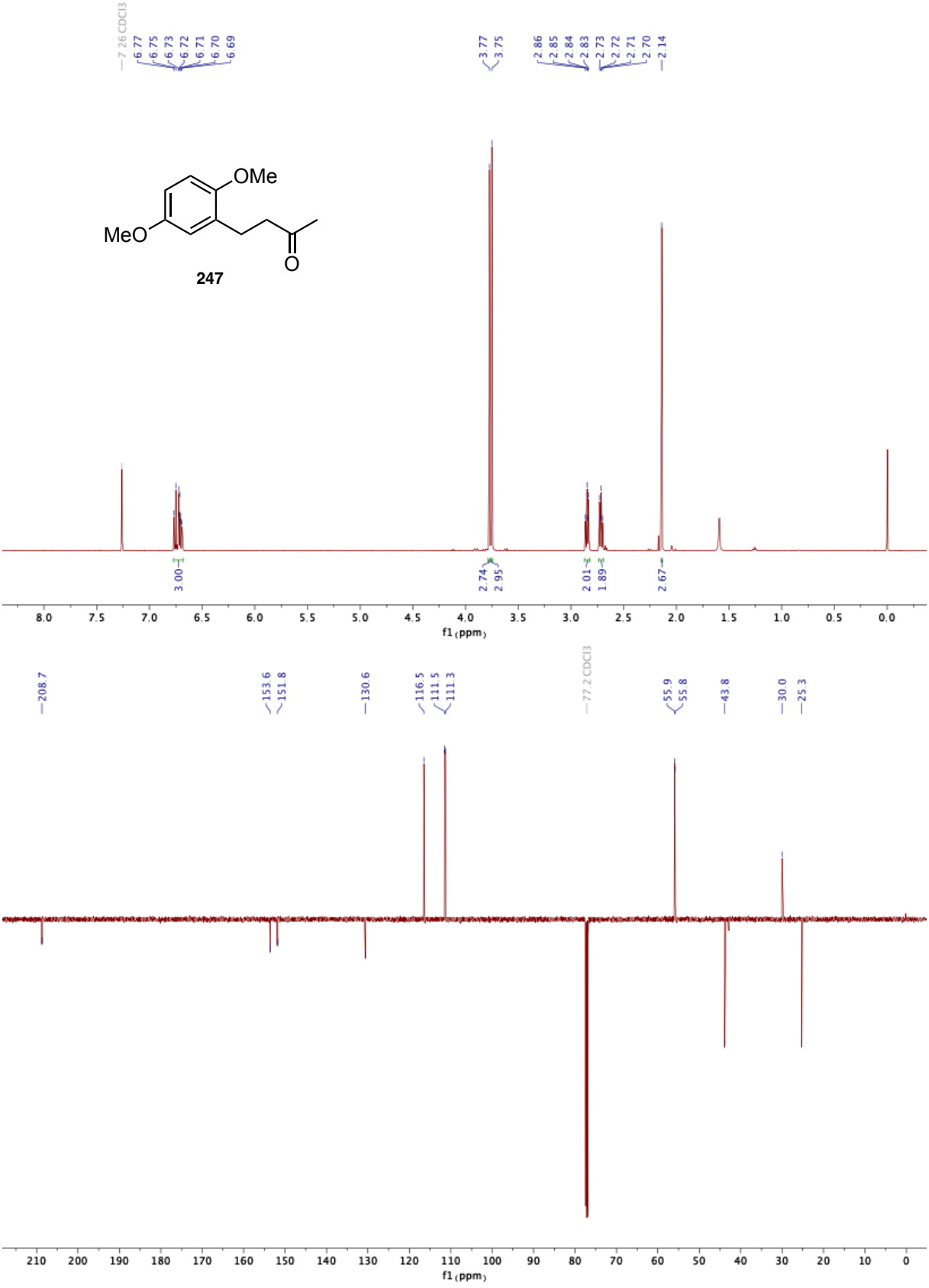
6.1.56 ^{1}H AND ^{13}C NMR SPECTRA OF ALLYLIC ALCOHOL **245**



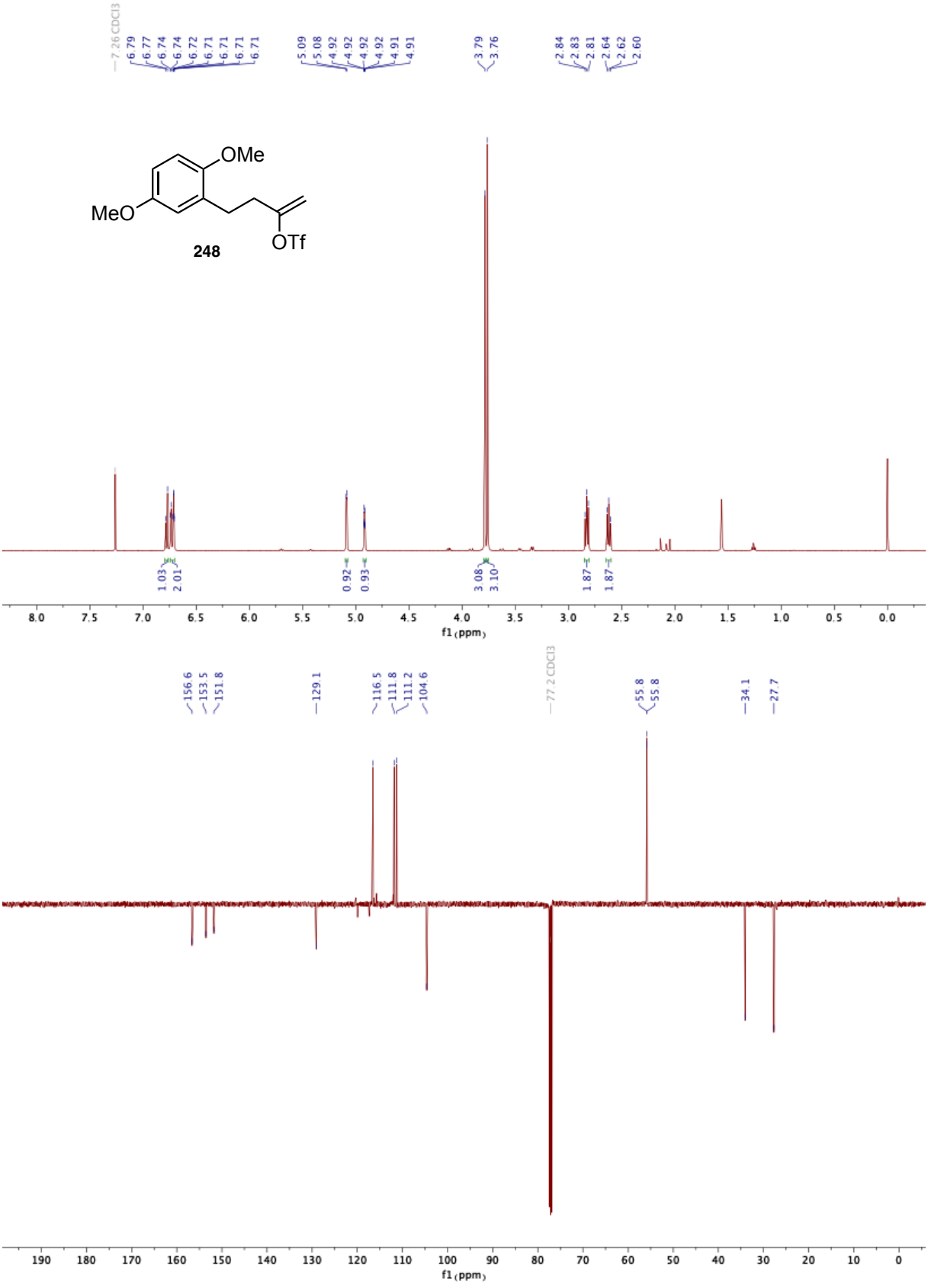
6.1.57 ^{1}H AND ^{13}C NMR SPECTRA OF 4(2,5-DIMETHOXYPHENYL)-4-HYDROXYBUTAN-2-ONE (**246**)



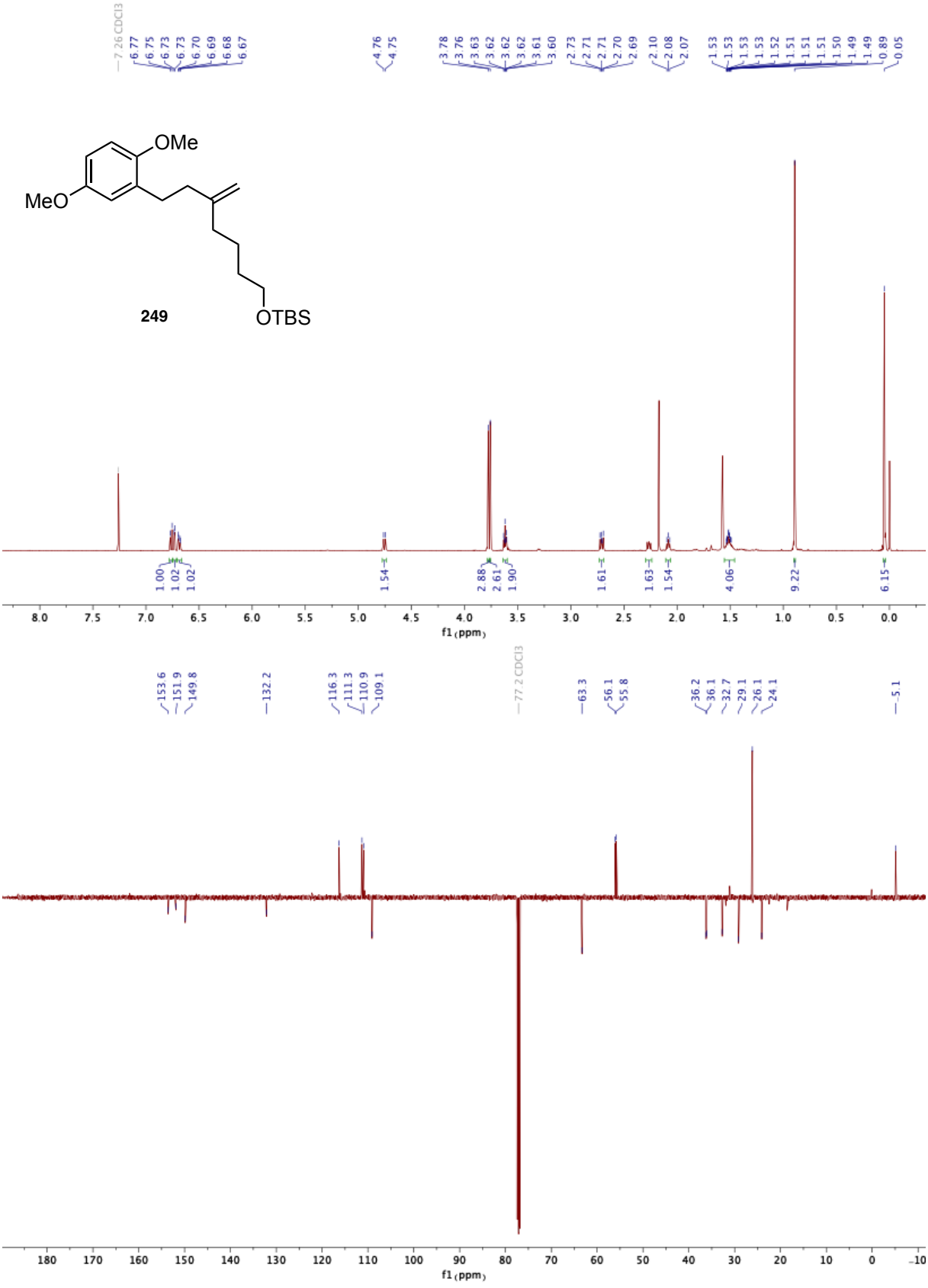
6.1.58 ^{1}H AND ^{13}C NMR SPECTRA OF 4-(2,5-DIMETHOXYPHENYL) BUTAN-2-ONE (**247**)



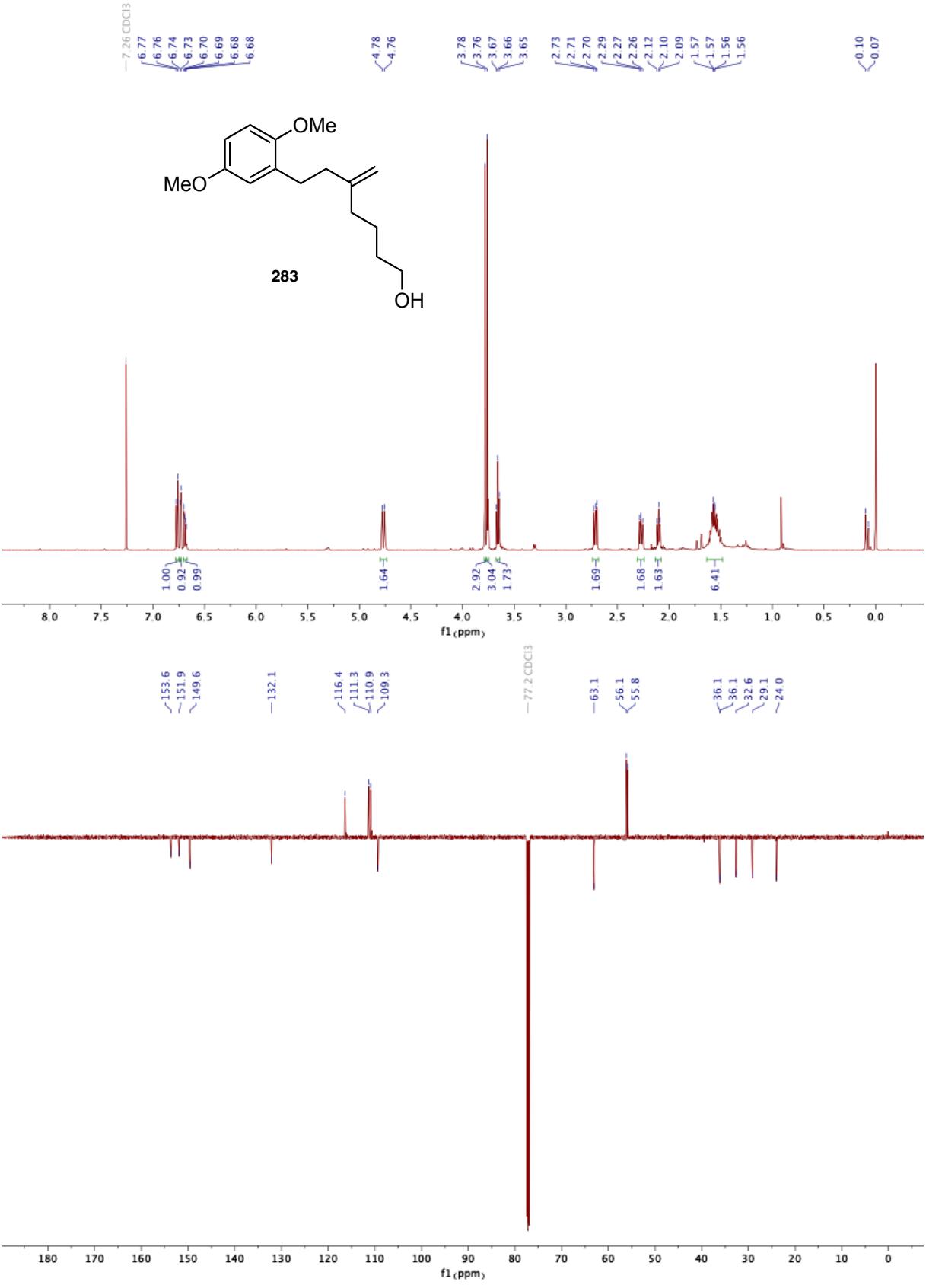
6.1.59 ^{1}H AND ^{13}C NMR SPECTRA OF ENOL TRIFLATE **248**



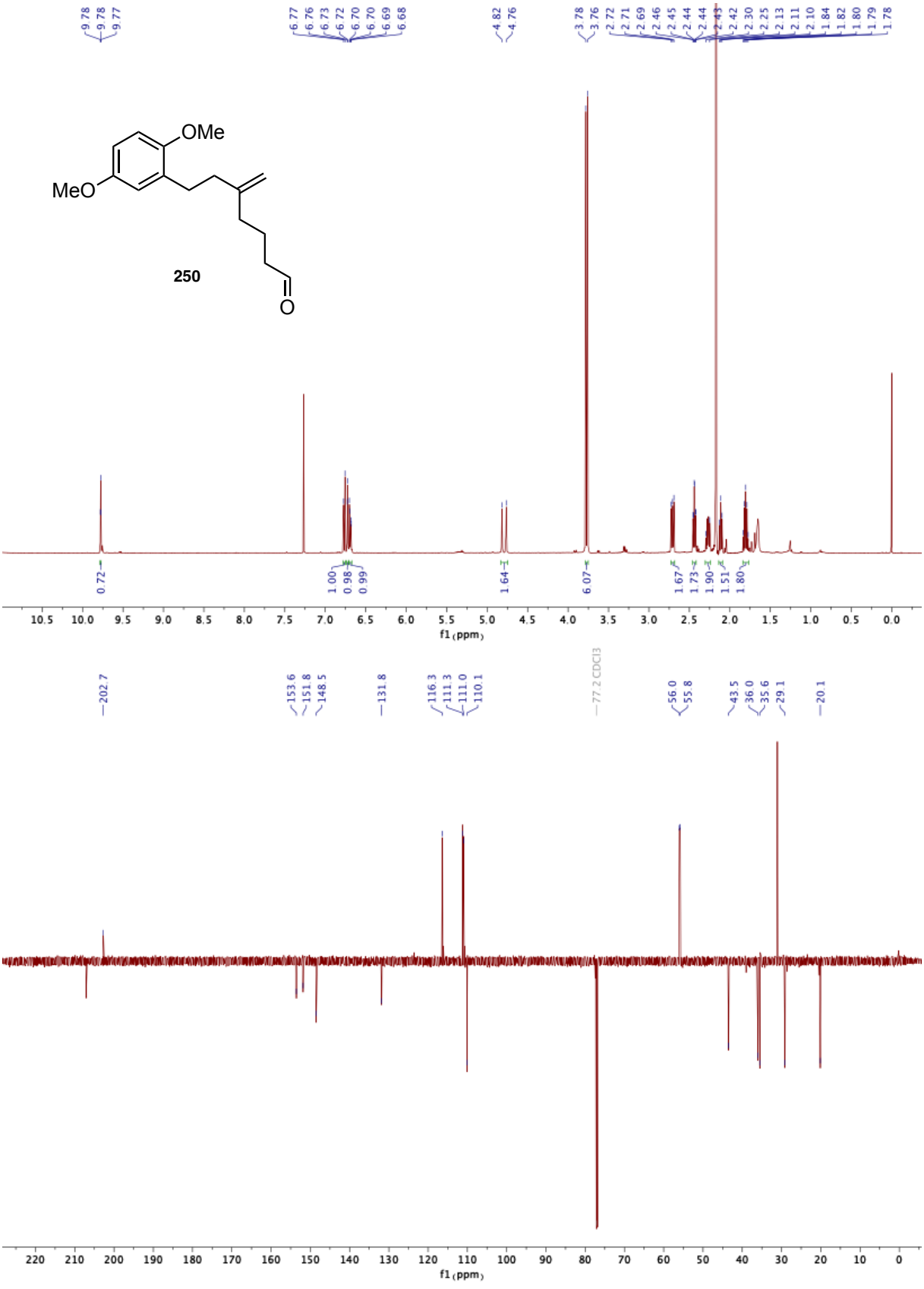
6.1.60 ^{1}H AND ^{13}C NMR SPECTRA OF SILYL ETHER **249**



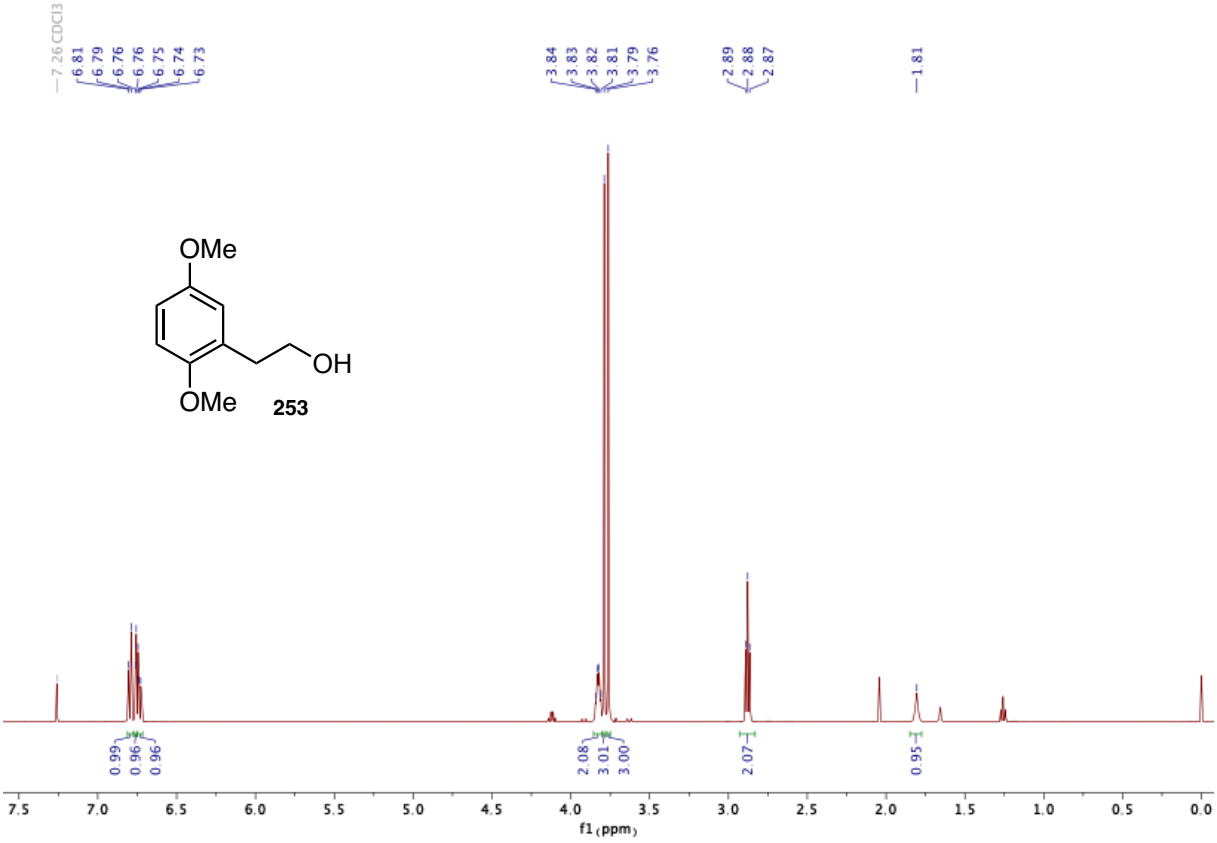
6.1.61 ^{1}H AND ^{13}C NMR SPECTRA OF PRIMARY ALCOHOL **283**



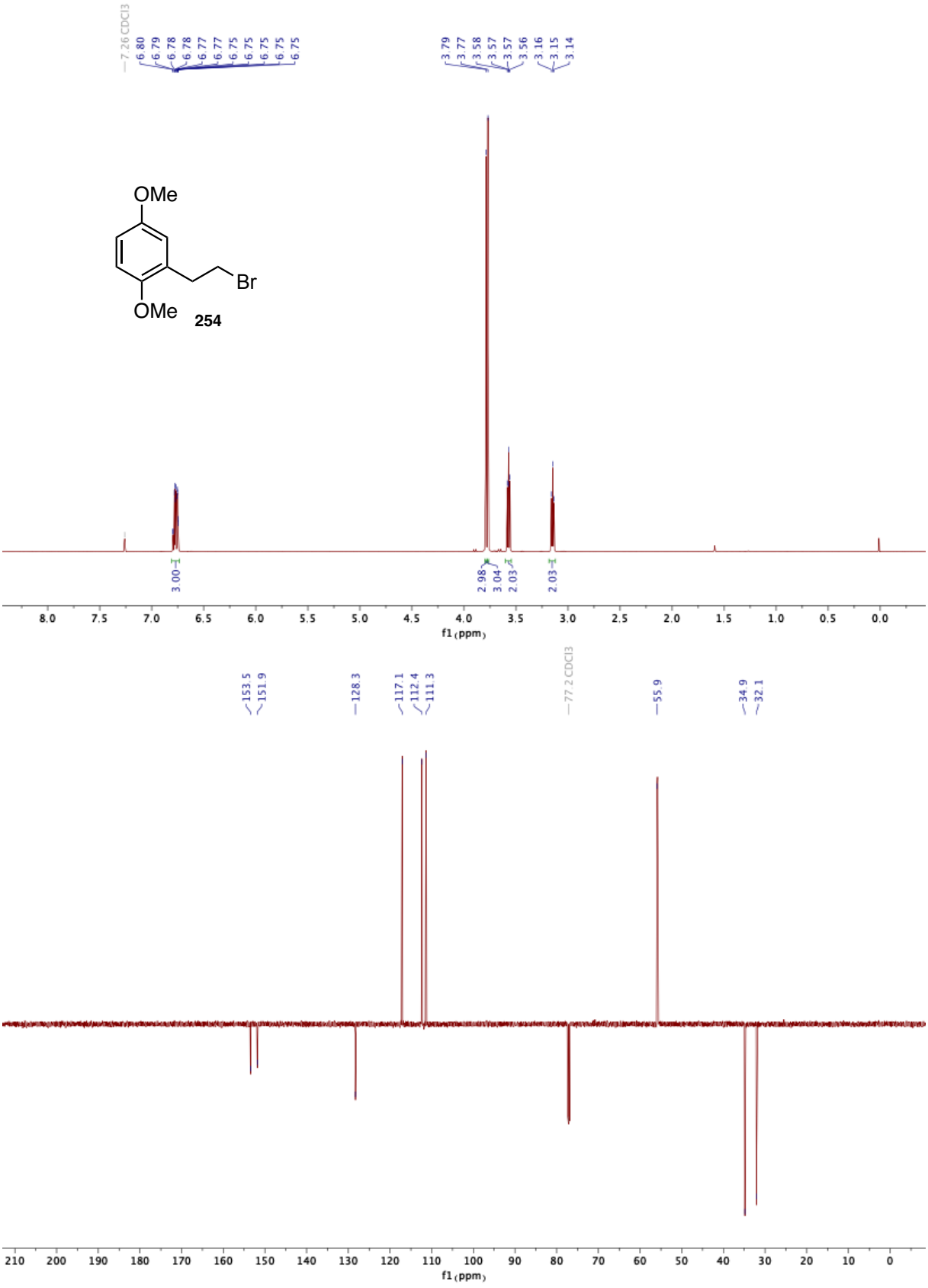
6.1.62 ^{1}H AND ^{13}C NMR SPECTRA OF ALDEHYDE **250**



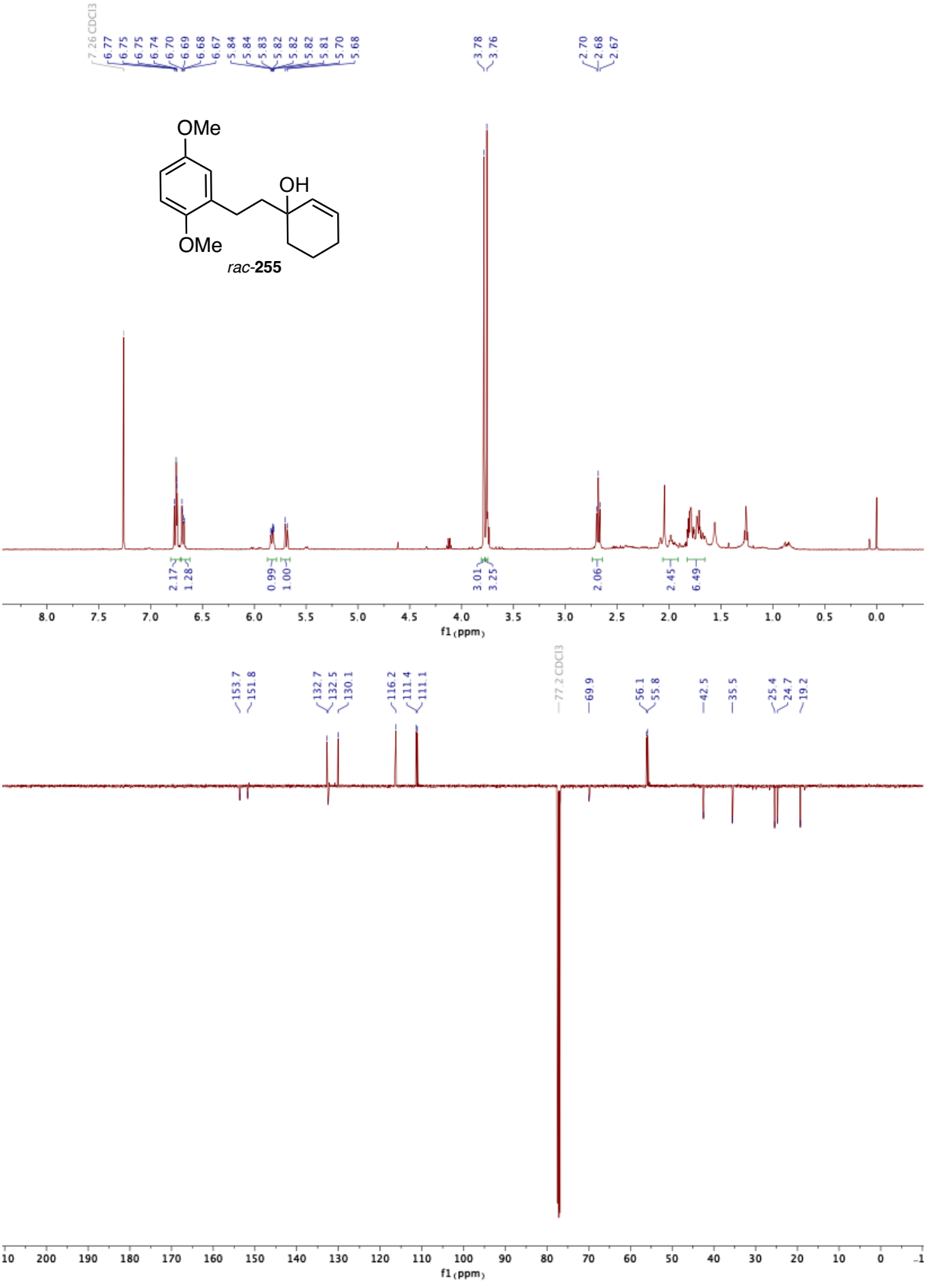
6.1.63 ^{1}H NMR SPECTRUM OF 2-(2,5-DIMETHOXYPHENYL) ETHANOL (**253**)



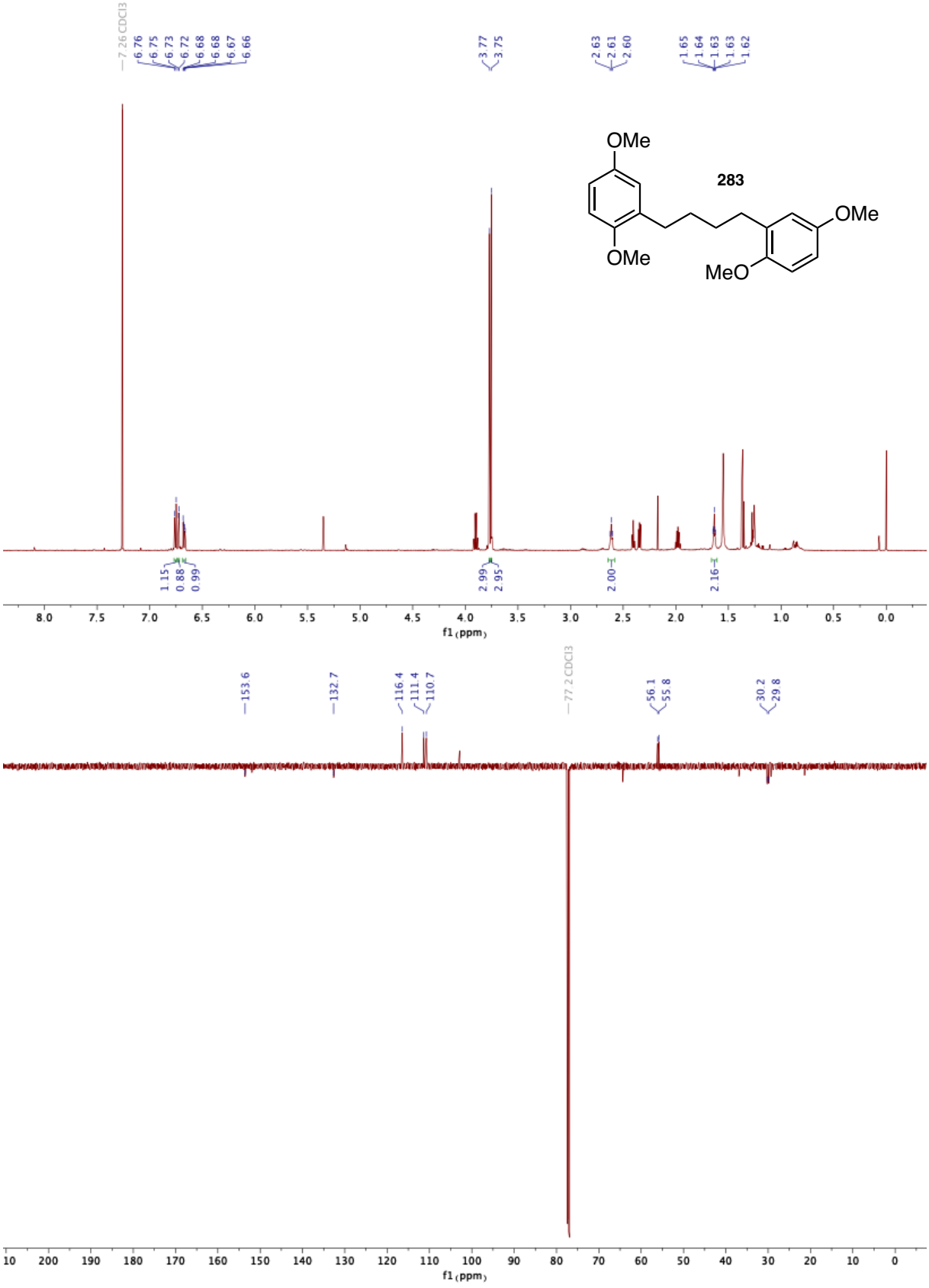
6.1.64 ^{1}H AND ^{13}C NMR SPECTRA OF 1-BROMO-2-(2,5-DIMETHOXY PHENYL)ETHANE (**254**)



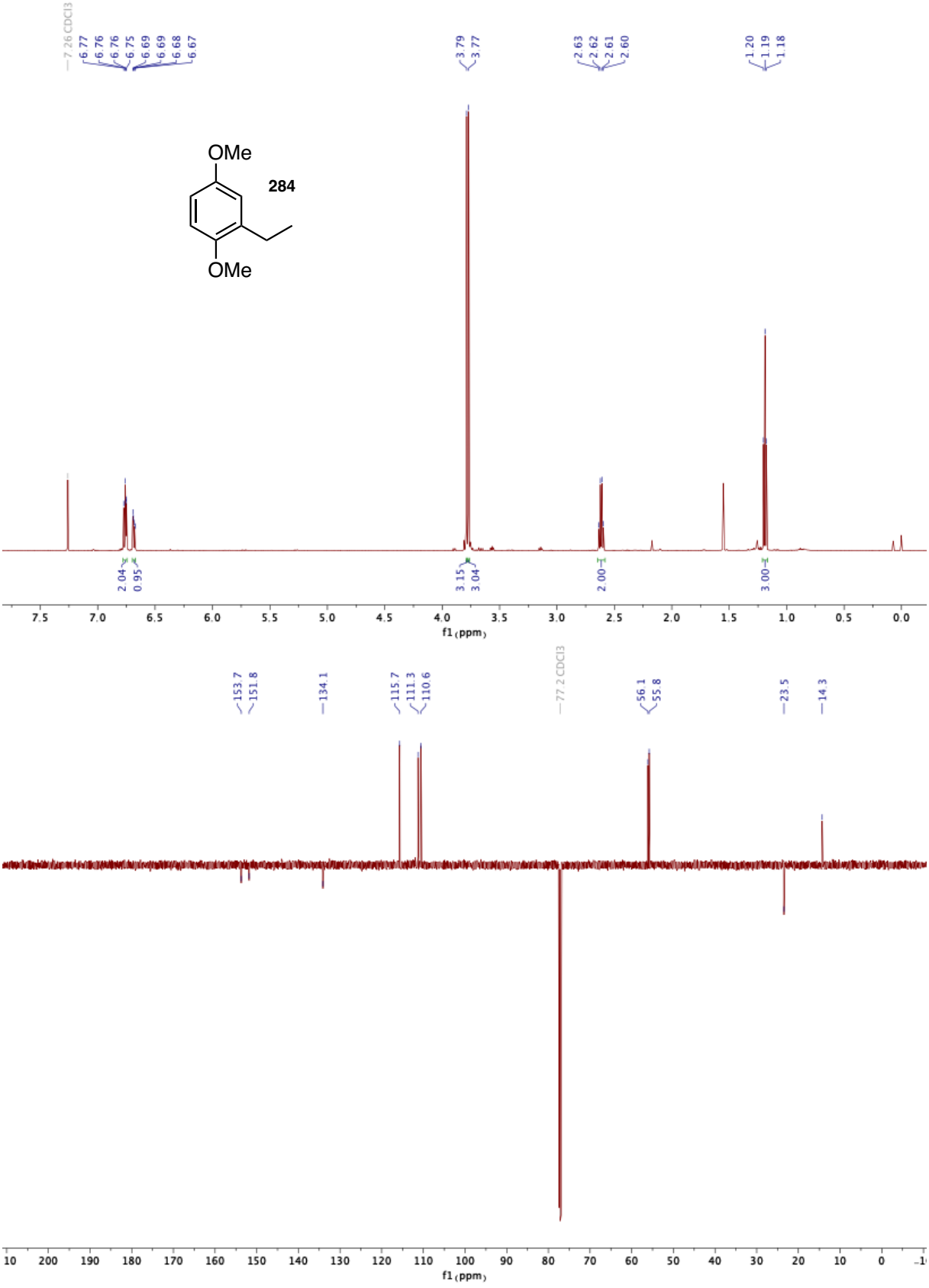
6.1.65 ^{1}H AND ^{13}C NMR SPECTRA OF ALLYLIC ALCOHOL *rac*-**255**



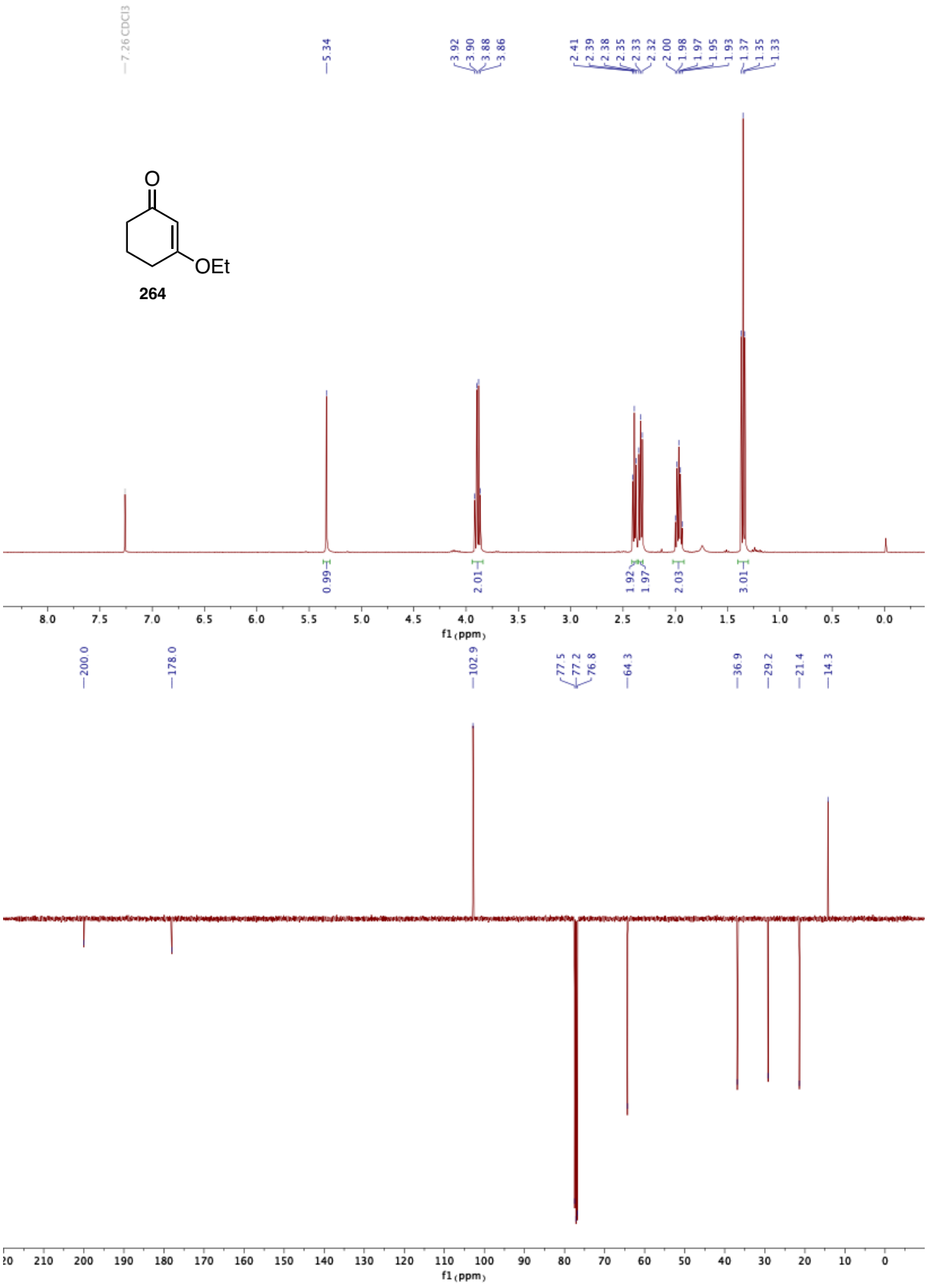
6.1.66 ^{1}H AND ^{13}C NMR SPECTRA OF 1,4-DI(2,5-METHOXYPHENYL) BUTANE (**283**)



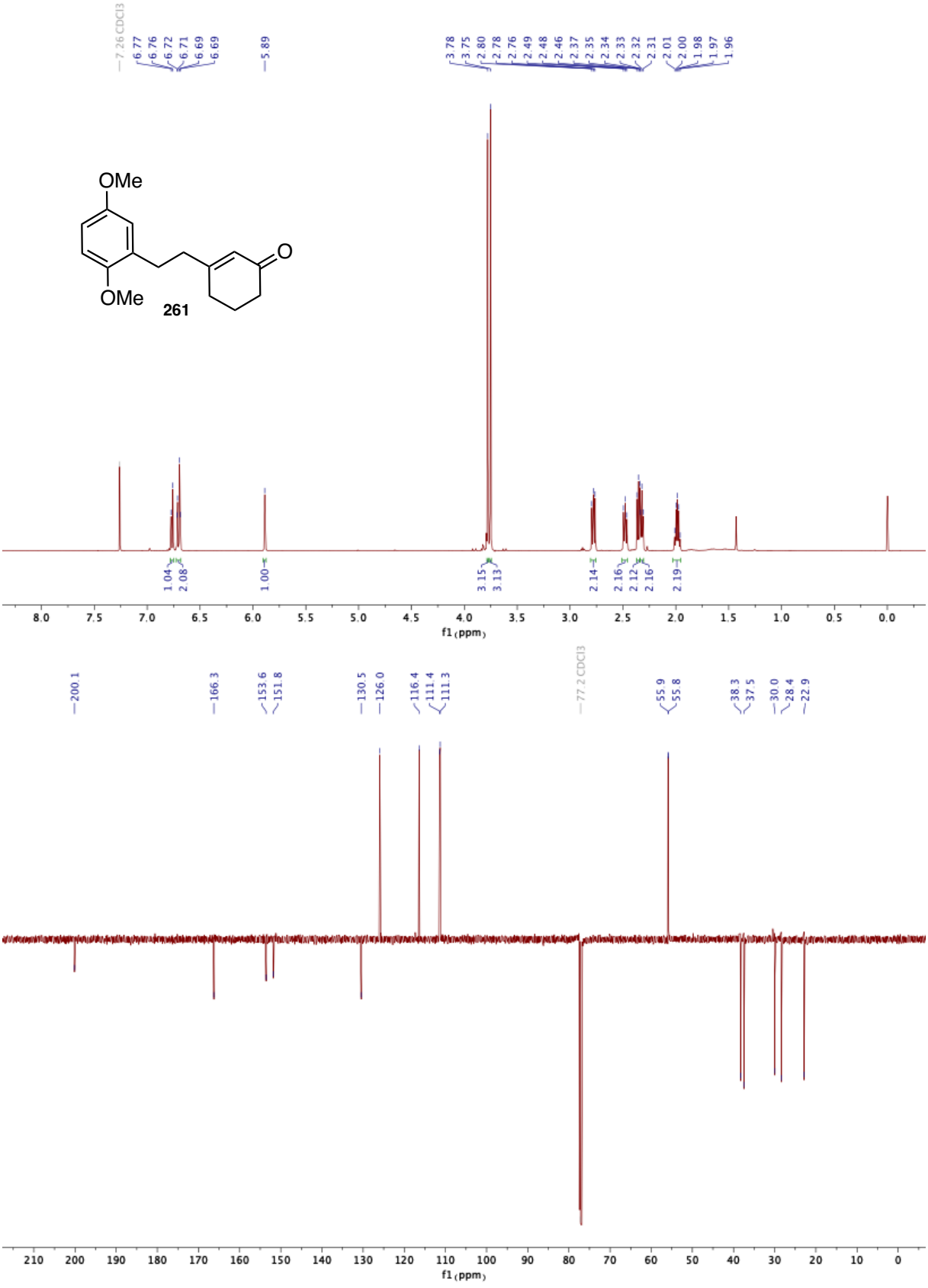
6.1.67 ^{1}H AND ^{13}C NMR SPECTRA OF (2,5-DIMETHOXYPHENYL) ETHANE (**284**)



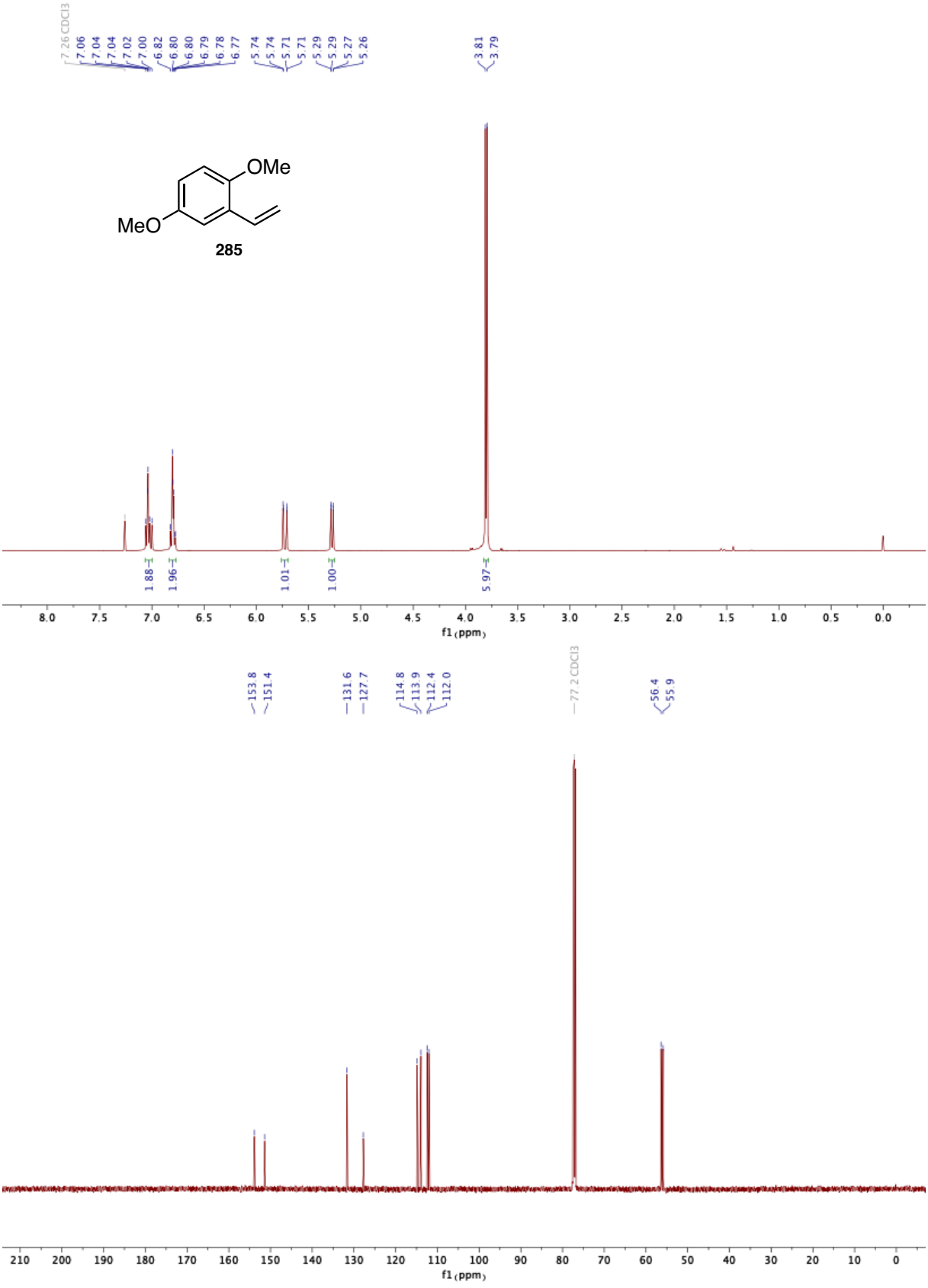
6.1.68 ^{1}H AND ^{13}C NMR SPECTRA OF 3-ETHOXYCYCLOHEX-2-ENONE (**264**)



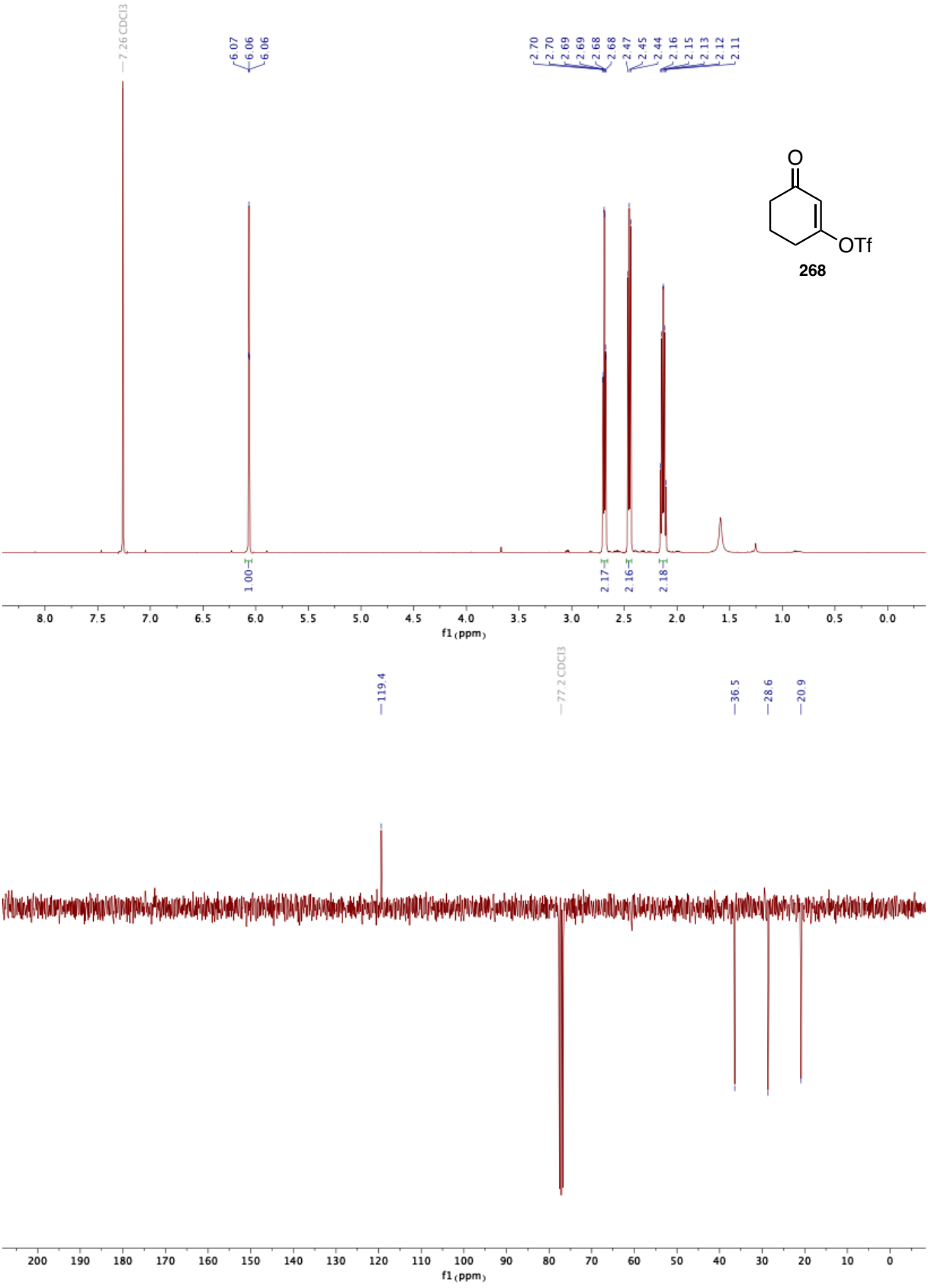
6.1.69 ^{1}H AND ^{13}C NMR SPECTRA OF ENONE **261**



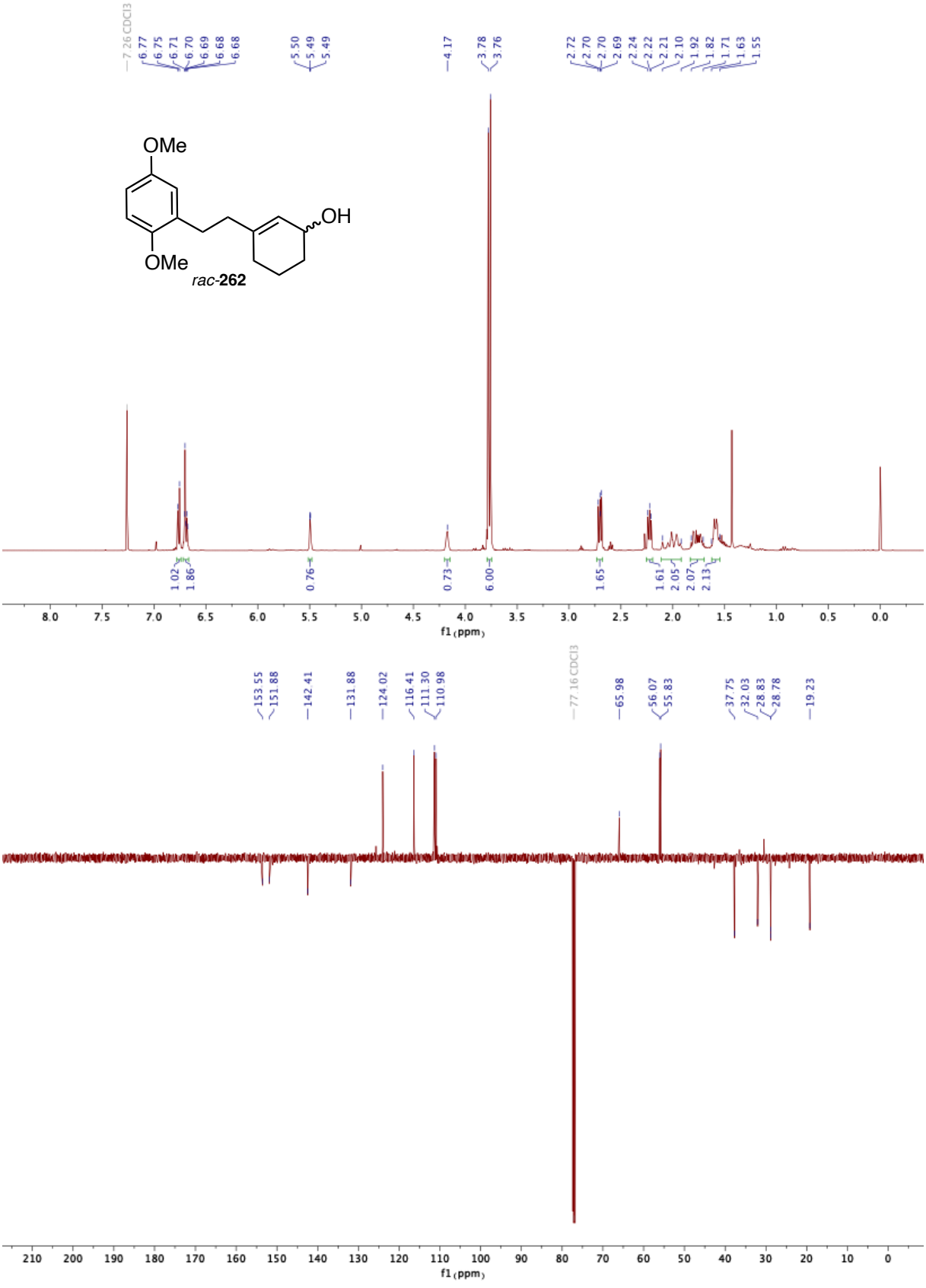
6.1.70 ^{1}H AND ^{13}C NMR SPECTRA OF 2,5-DIMETHOXYSTYRENE (**285**)



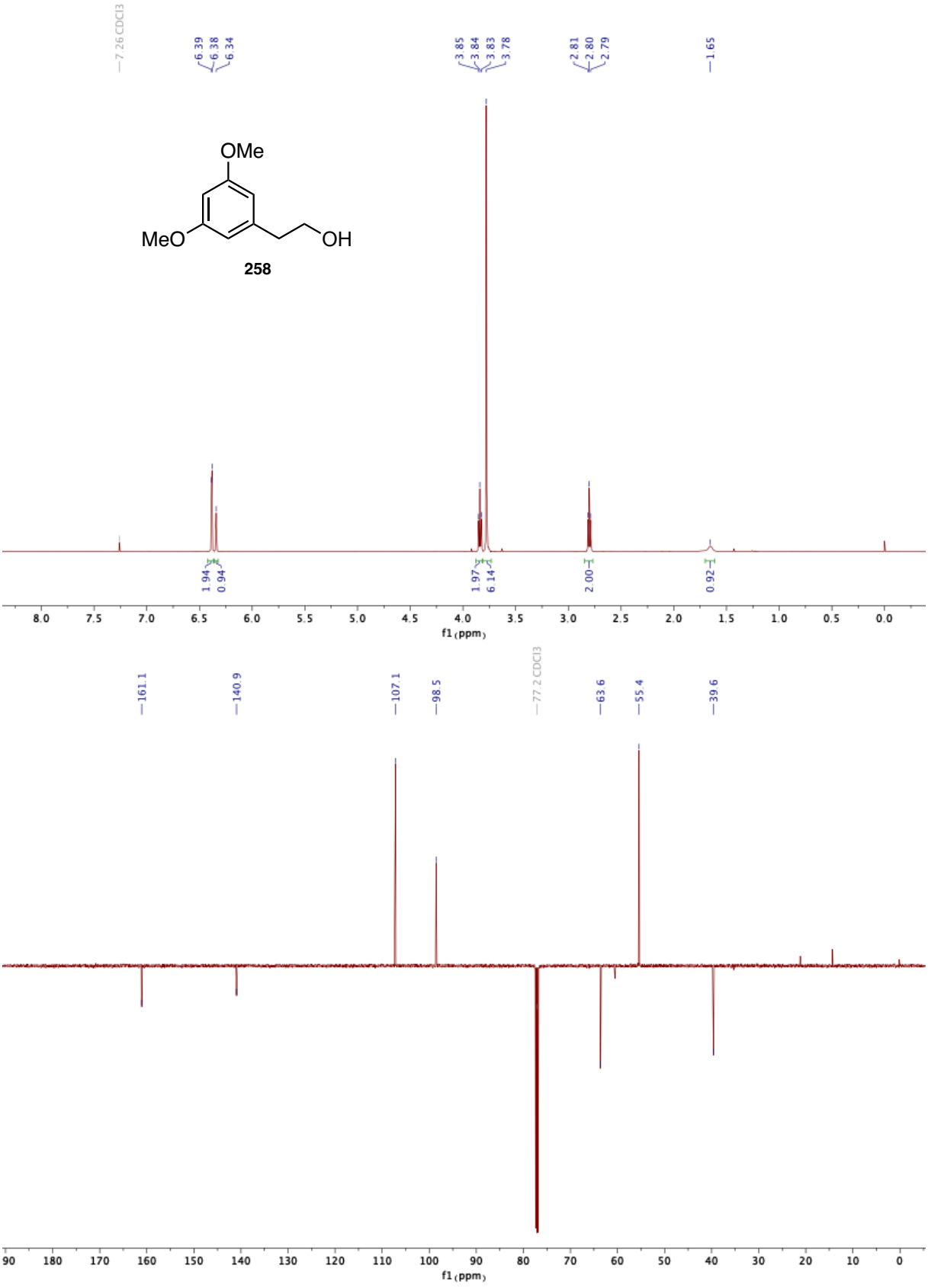
6.1.71 ^{1}H AND ^{13}C NMR SPECTRA OF 3-OXOCYCLOHEX-1-EN-1-YL TRIFLUOROMETHANE SULFONATE (**268**)



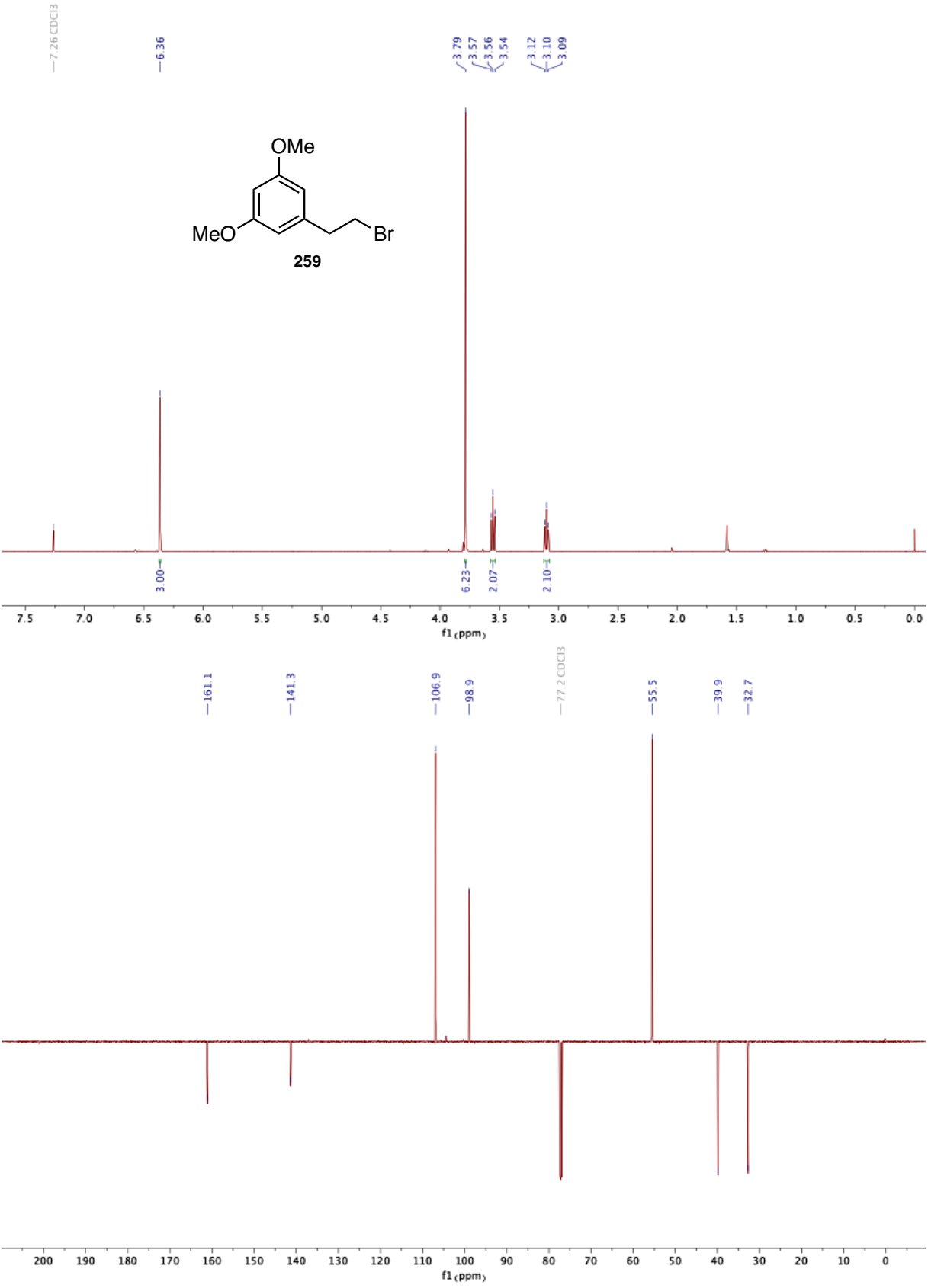
6.1.72 ^{1}H AND ^{13}C NMR SPECTRA OF ALLYLIC ALCOHOL *rac*-**262**



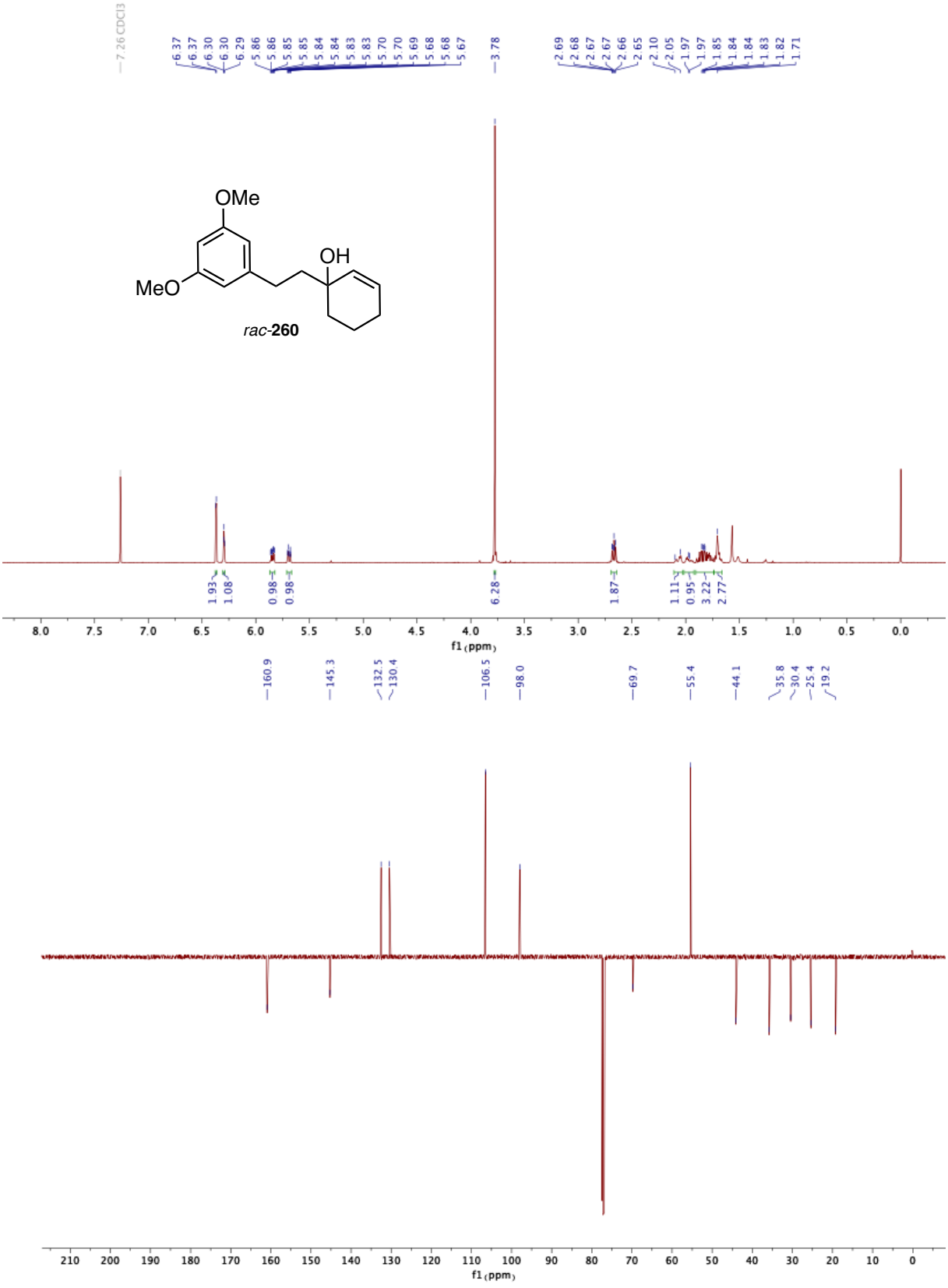
6.1.73 ^{1}H AND ^{13}C NMR SPECTRA OF 2-(3,5-DIMETHOXYPHENYL) ETHANOL (**258**)



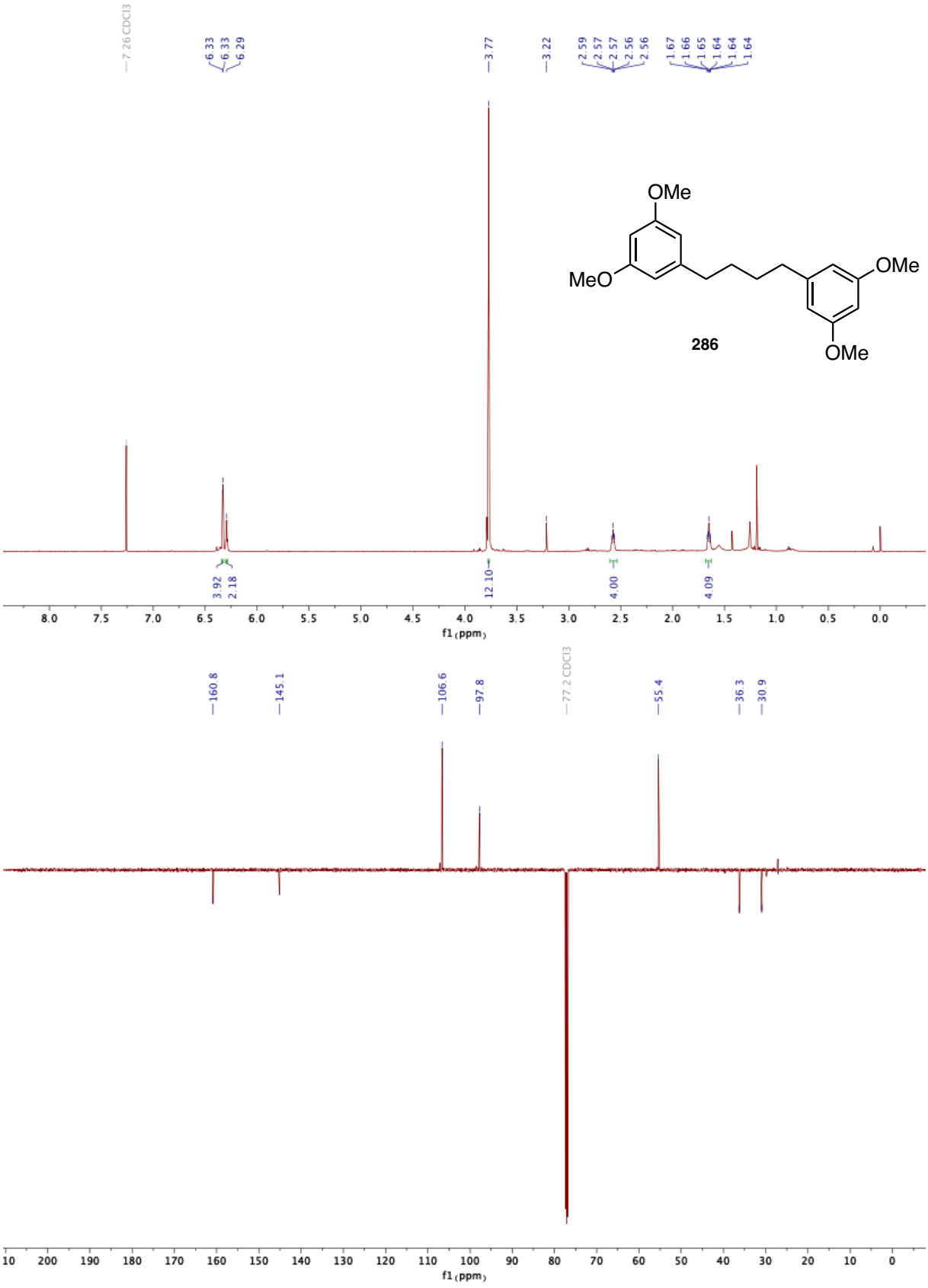
6.1.74 ^{1}H AND ^{13}C NMR SPECTRA OF 1-BROMO-2-(3,5-DIMETHOXYPHENYL) ETHANANE (**259**)



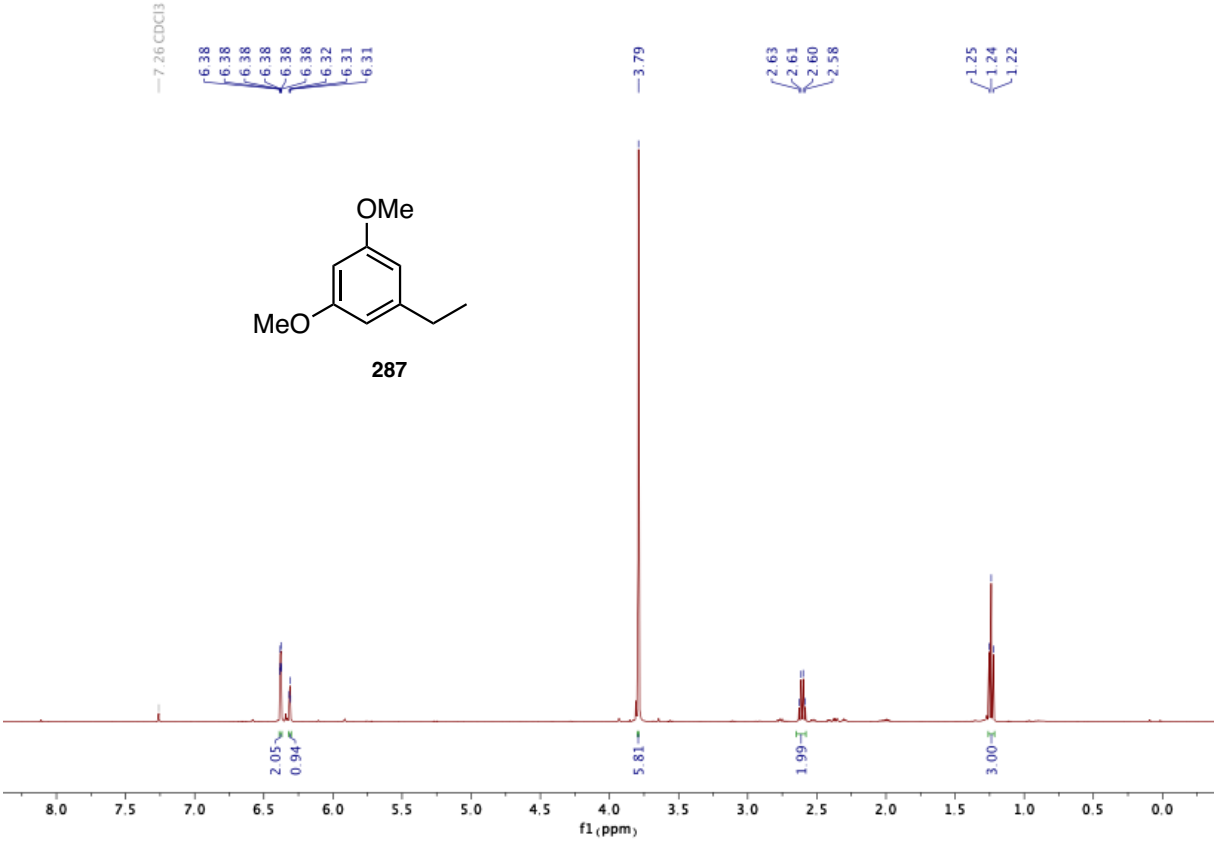
6.1.75 ^{1}H AND ^{13}C NMR SPECTRA OF ALLYLIC ALCOHOL *rac*-**260**

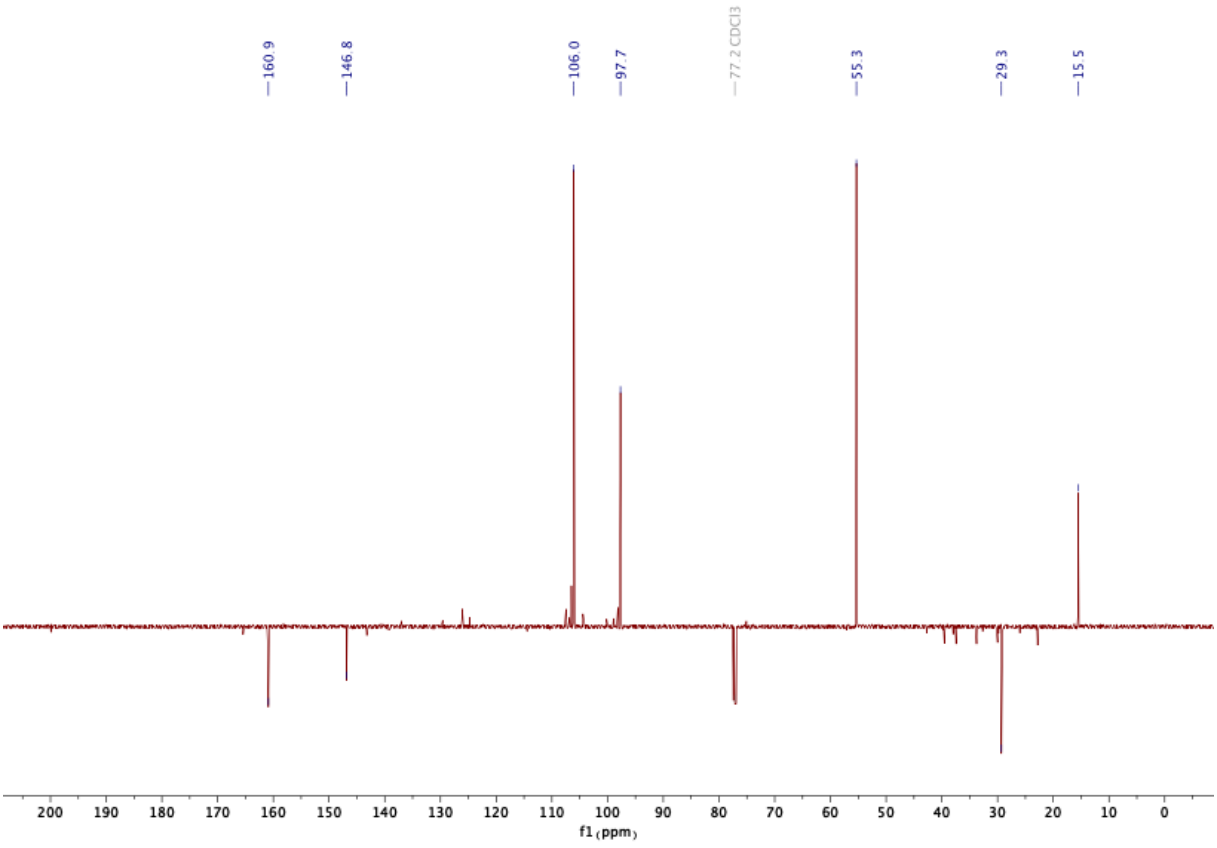


6.1.76 ^{1}H AND ^{13}C NMR SPECTRA OF 1,4-DI(3,5-METHOXYPHENYL) BUTANE (**286**)

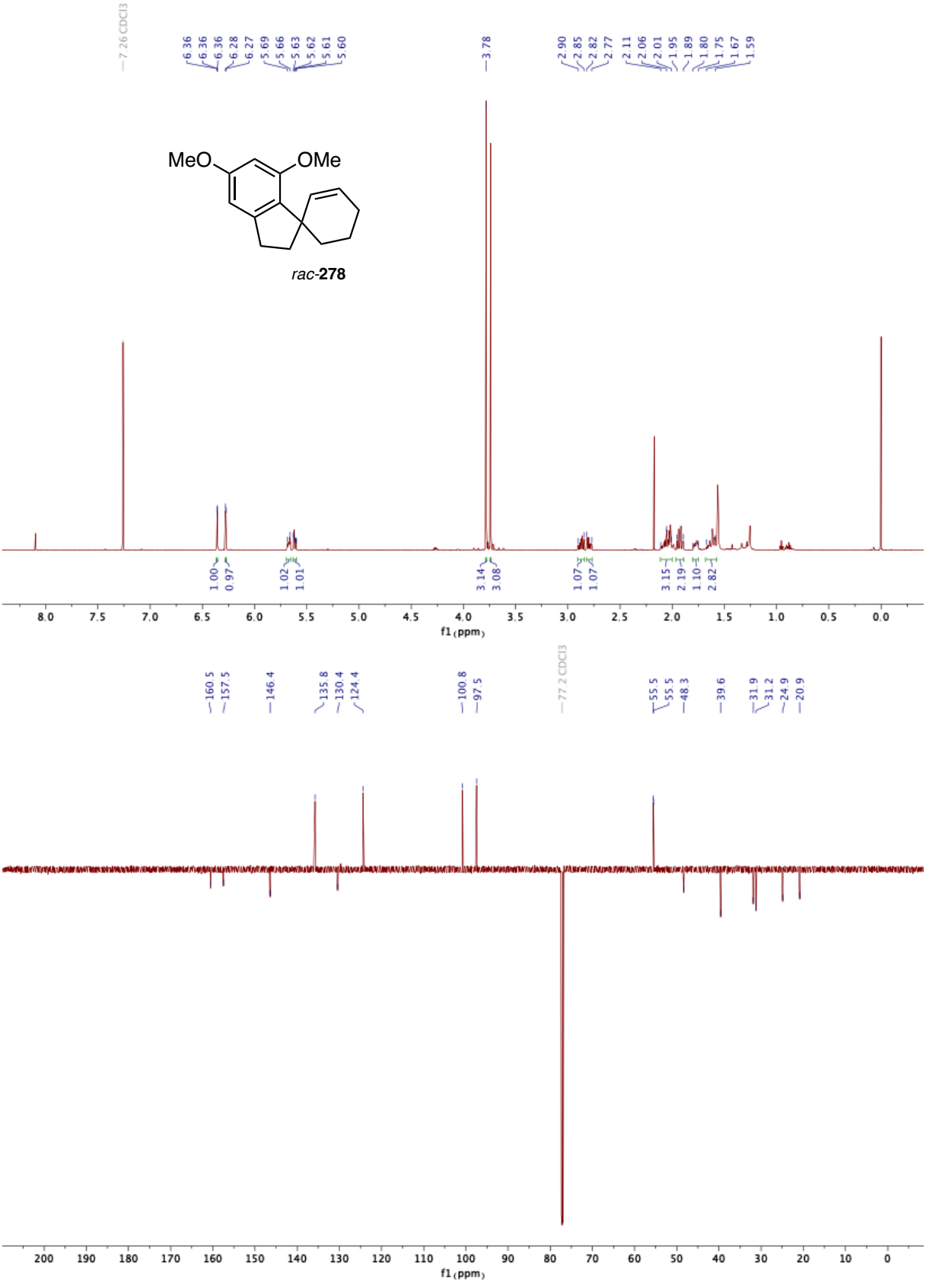


6.1.77 ^{1}H AND ^{13}C NMR SPECTRA OF (3,5-DIMETHOXYPHENYL) ETHANE (**287**)

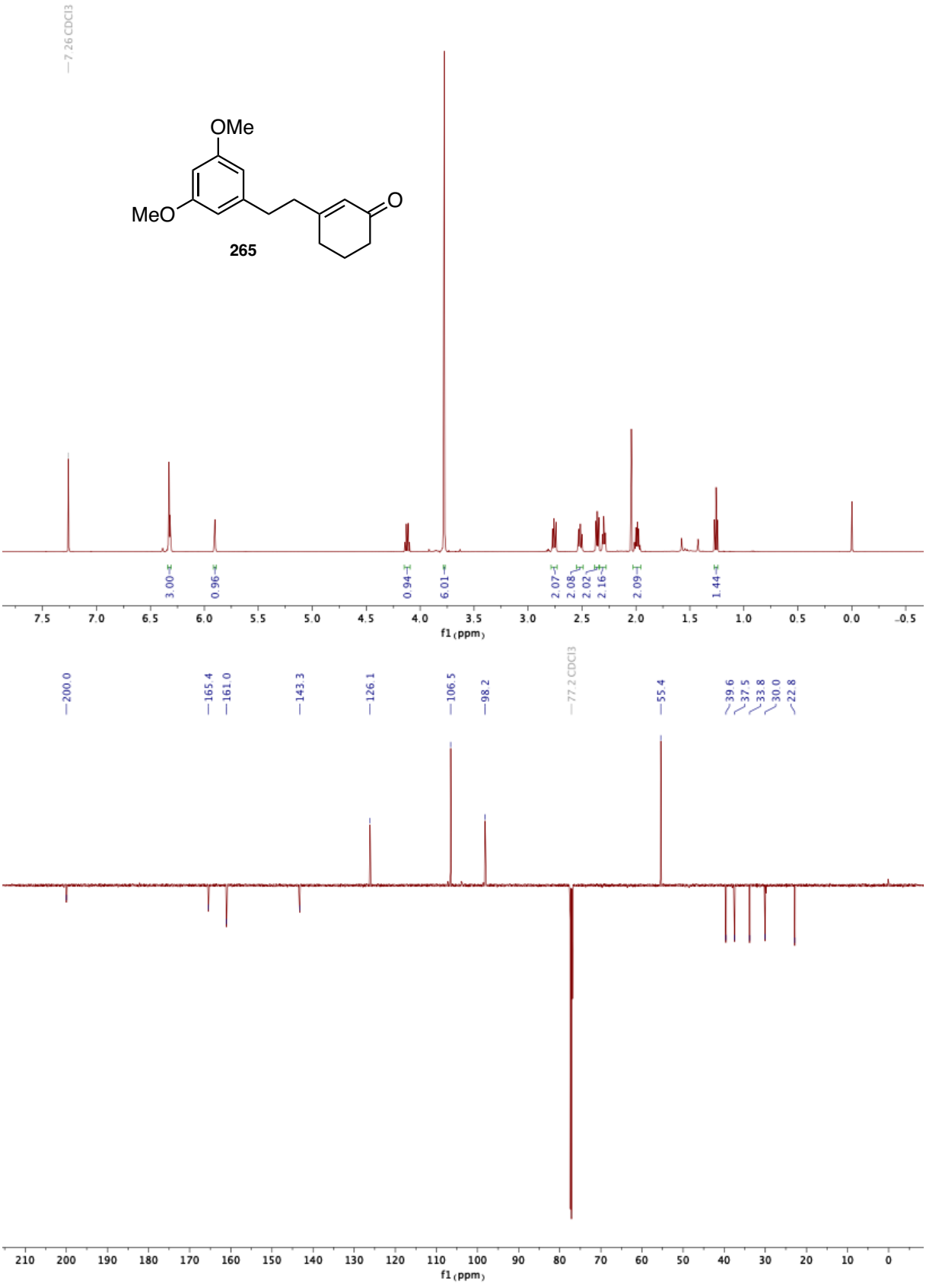




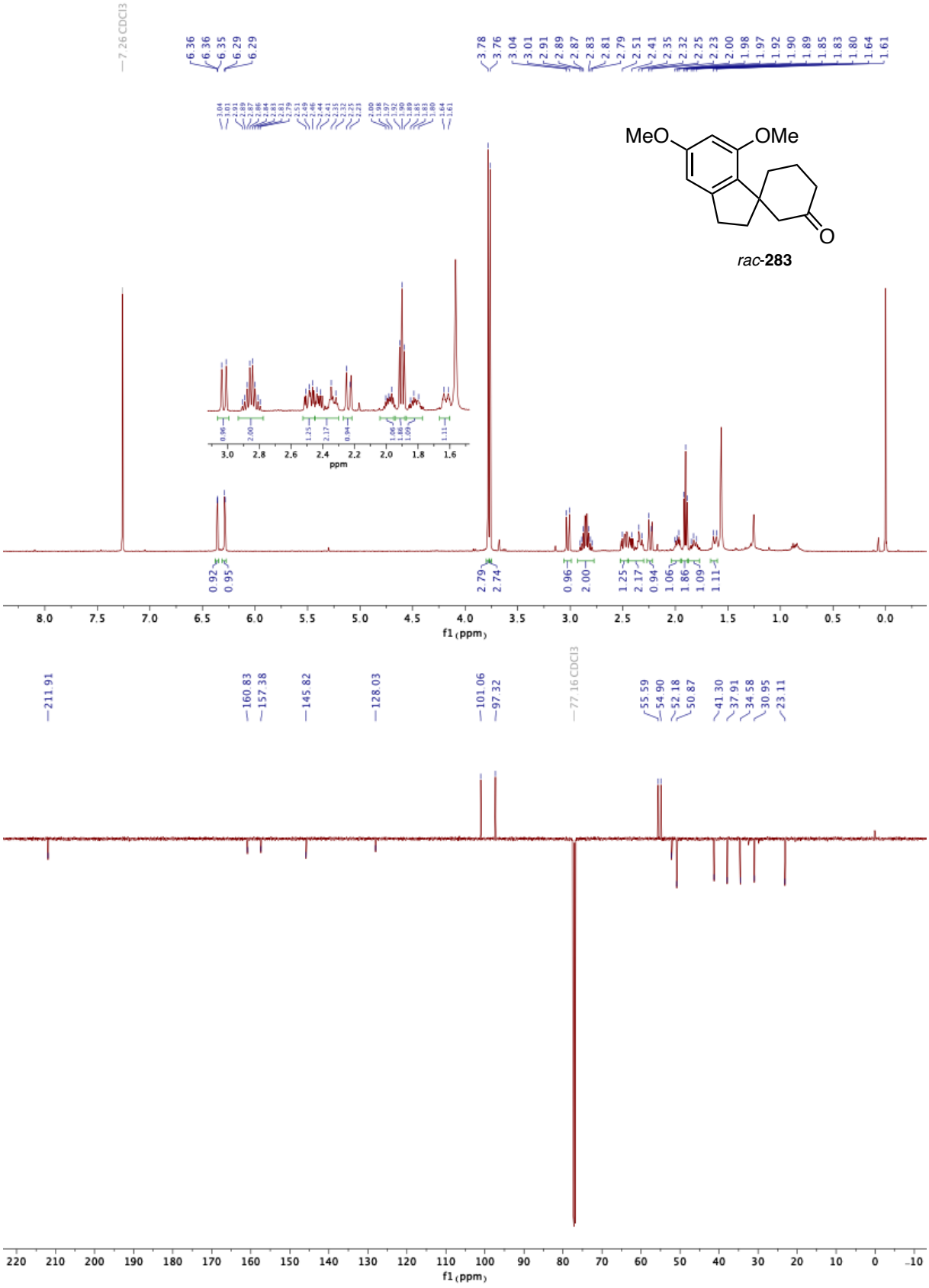
6.1.78 ^{1}H AND ^{13}C NMR SPECTRA OF SPIROCYCLIC *rac*-**278**



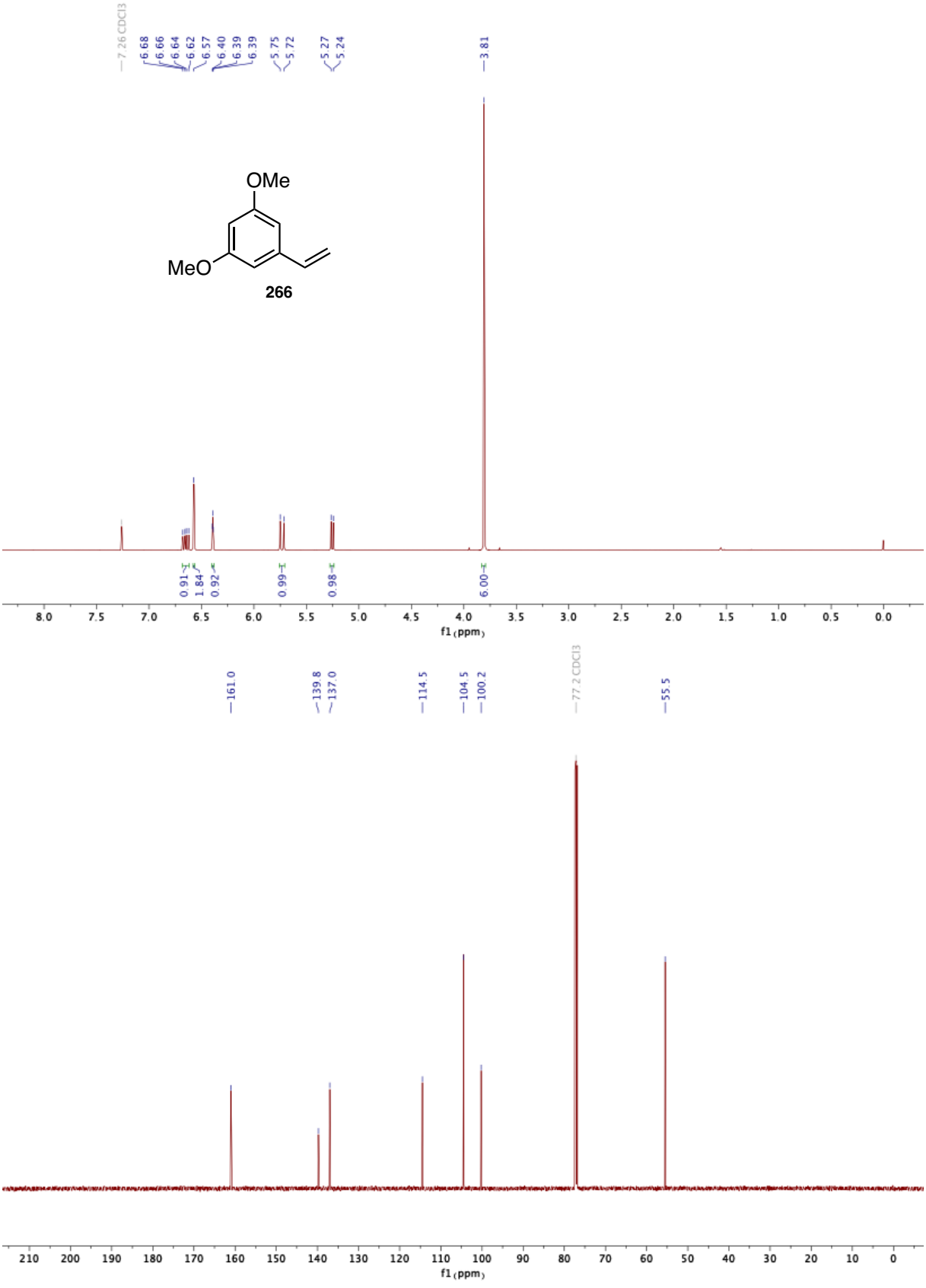
6.1.79 ^{1}H AND ^{13}C NMR SPECTRA OF ENONE **265**



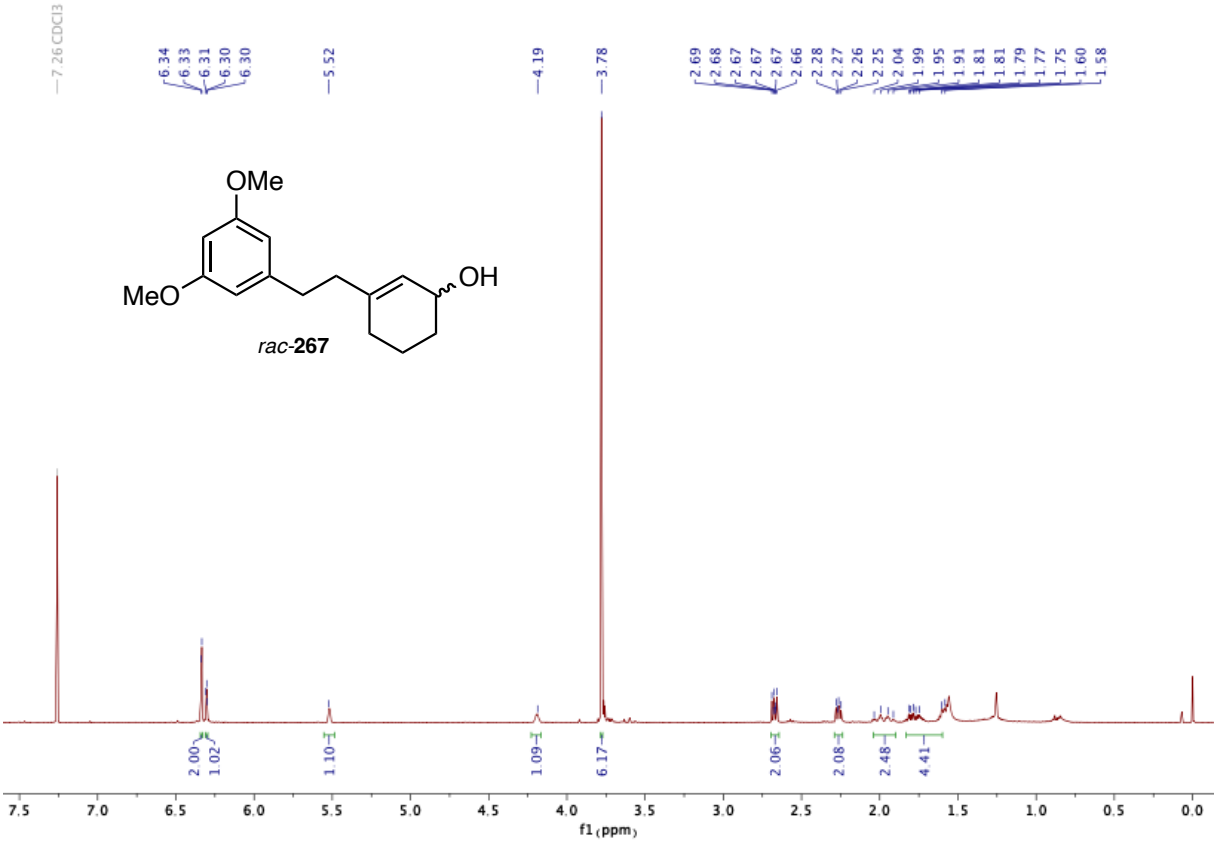
6.1.80 ^{1}H AND ^{13}C NMR SPECTRA OF SPIROCYCLIC KETONE *rac*-**283**

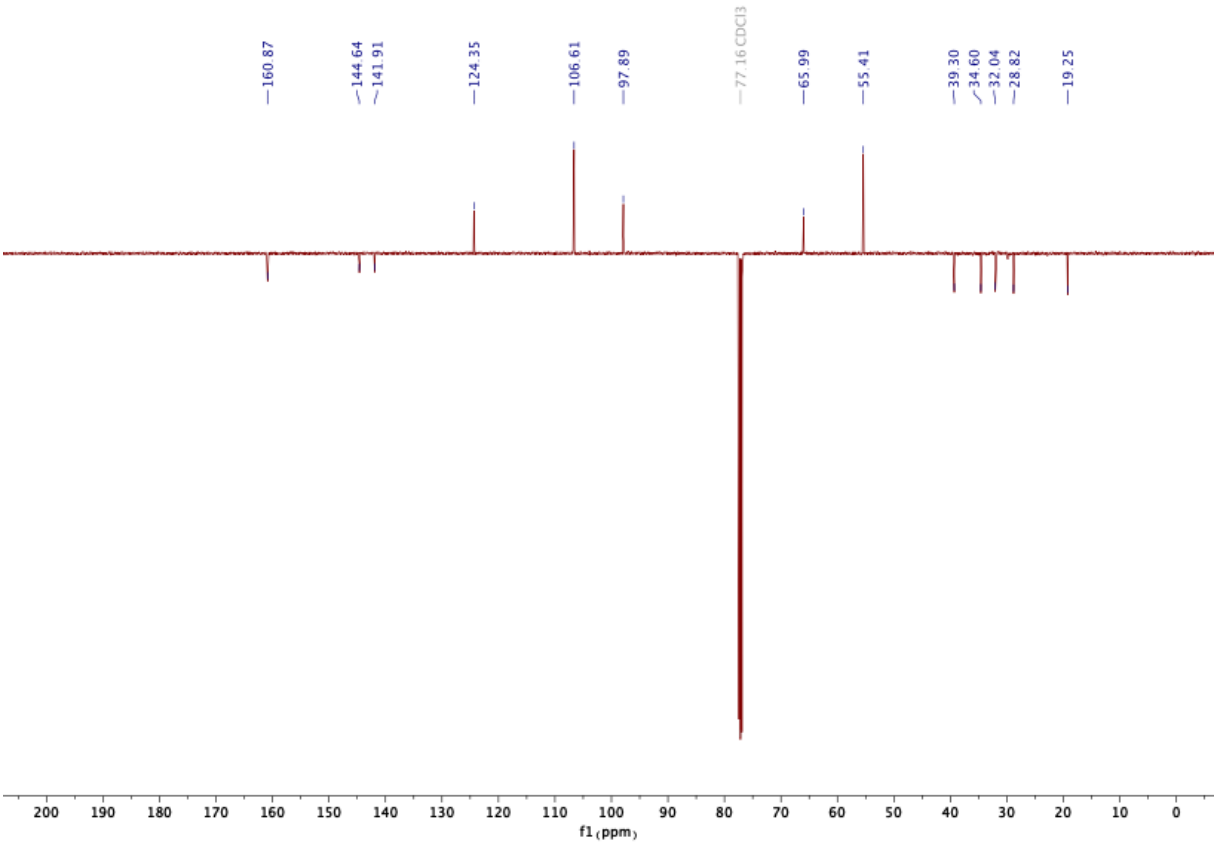


6.1.81 ^{1}H AND ^{13}C NMR SPECTRA OF 3,5-DIMETHOXYSTYRENE (**266**)

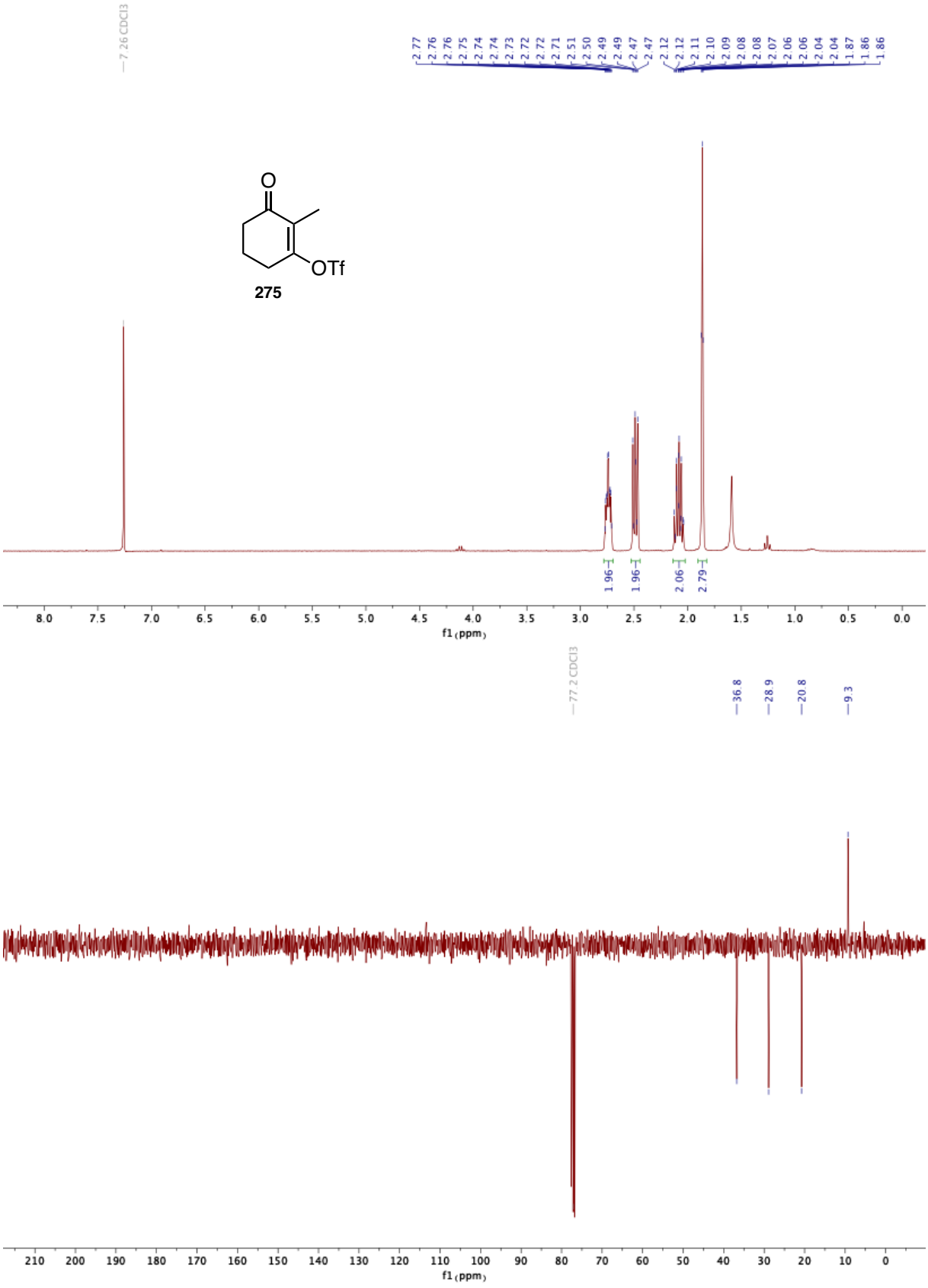


6.1.82 ^{1}H AND ^{13}C NMR SPECTRA OF ALLYLIC ALCOHOL *rac*-**267**

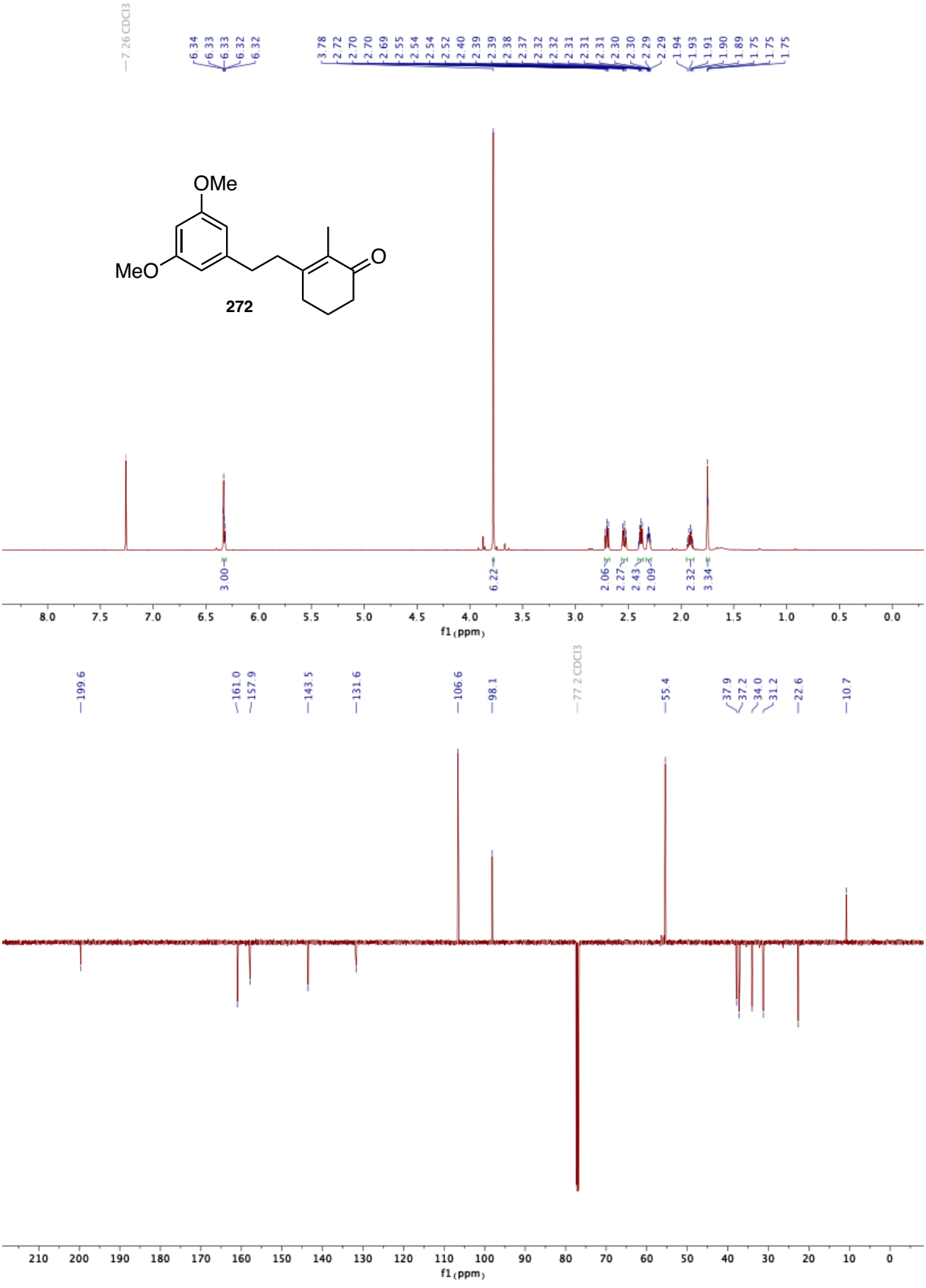




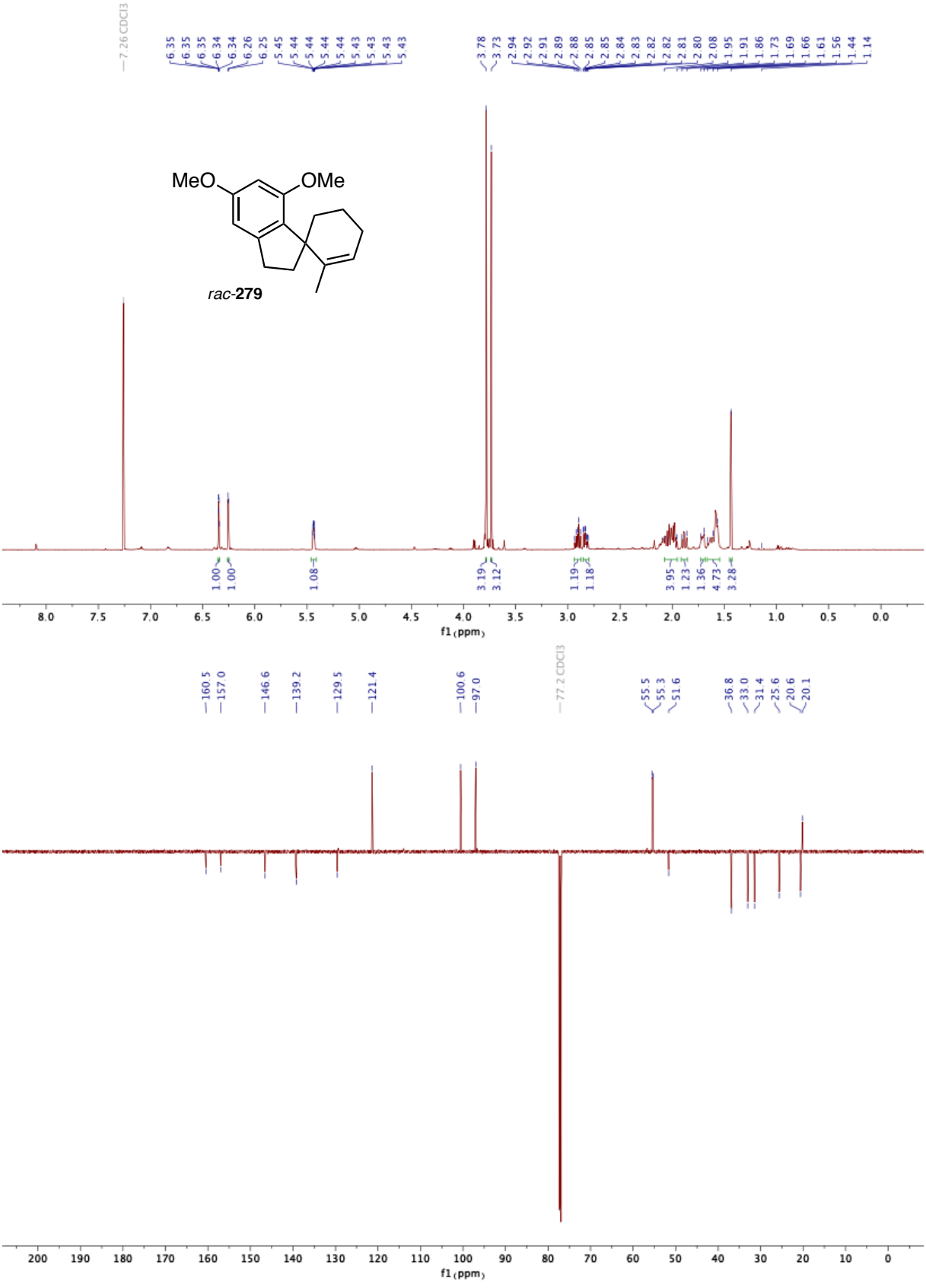
6.1.83 ^{1}H AND ^{13}C NMR SPECTRA OF 2-METHYL-3-OXO-1-CYCLOHEXEN-1-YL-TRIFLUOROMETHANESULFONATE (**275**)



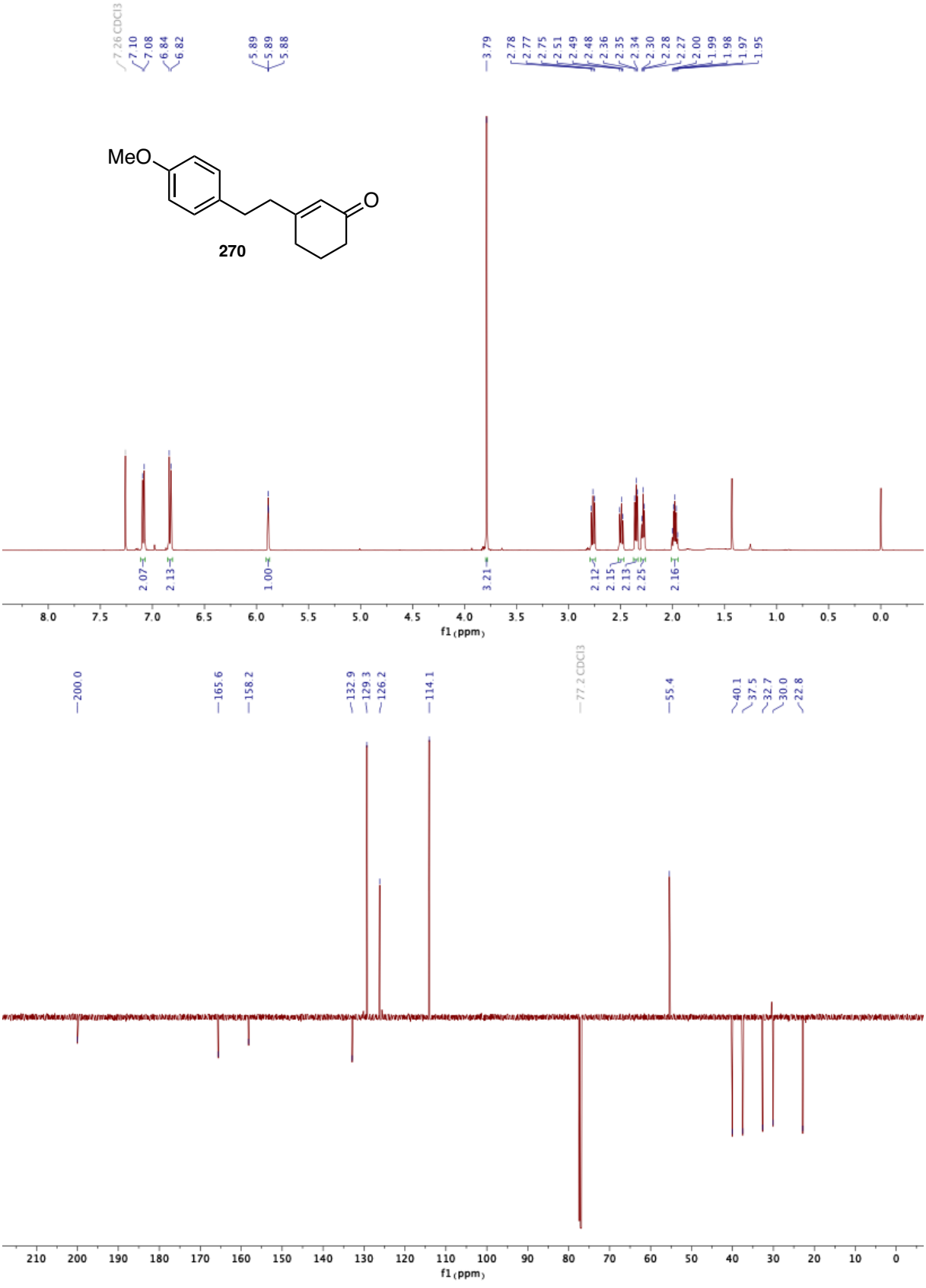
6.1.84 ^{1}H AND ^{13}C NMR SPECTRA OF ENONE **272**



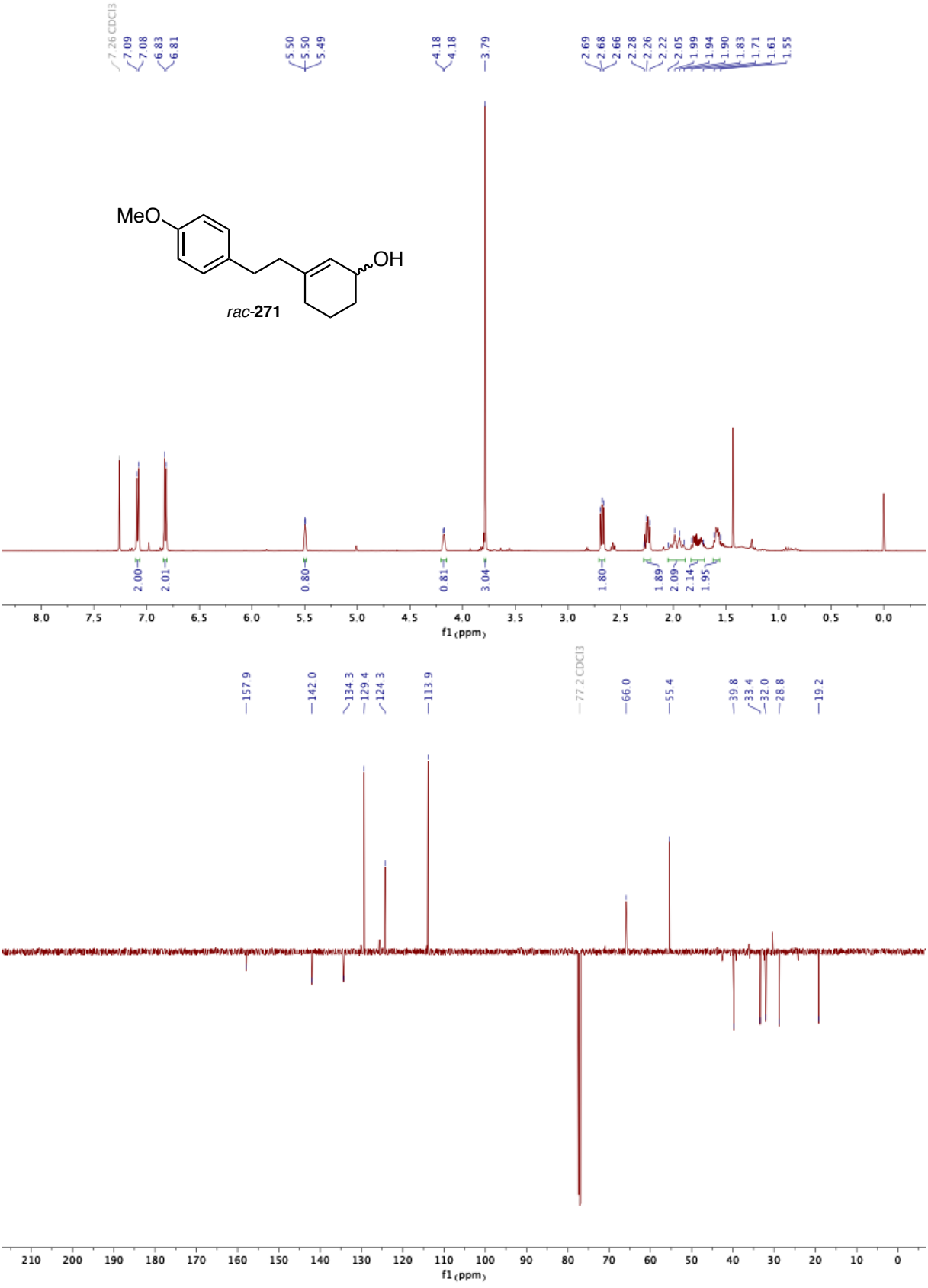
6.1.85 ^{1}H AND ^{13}C NMR SPECTRA OF SPIROCYCLIC *rac*-**279**



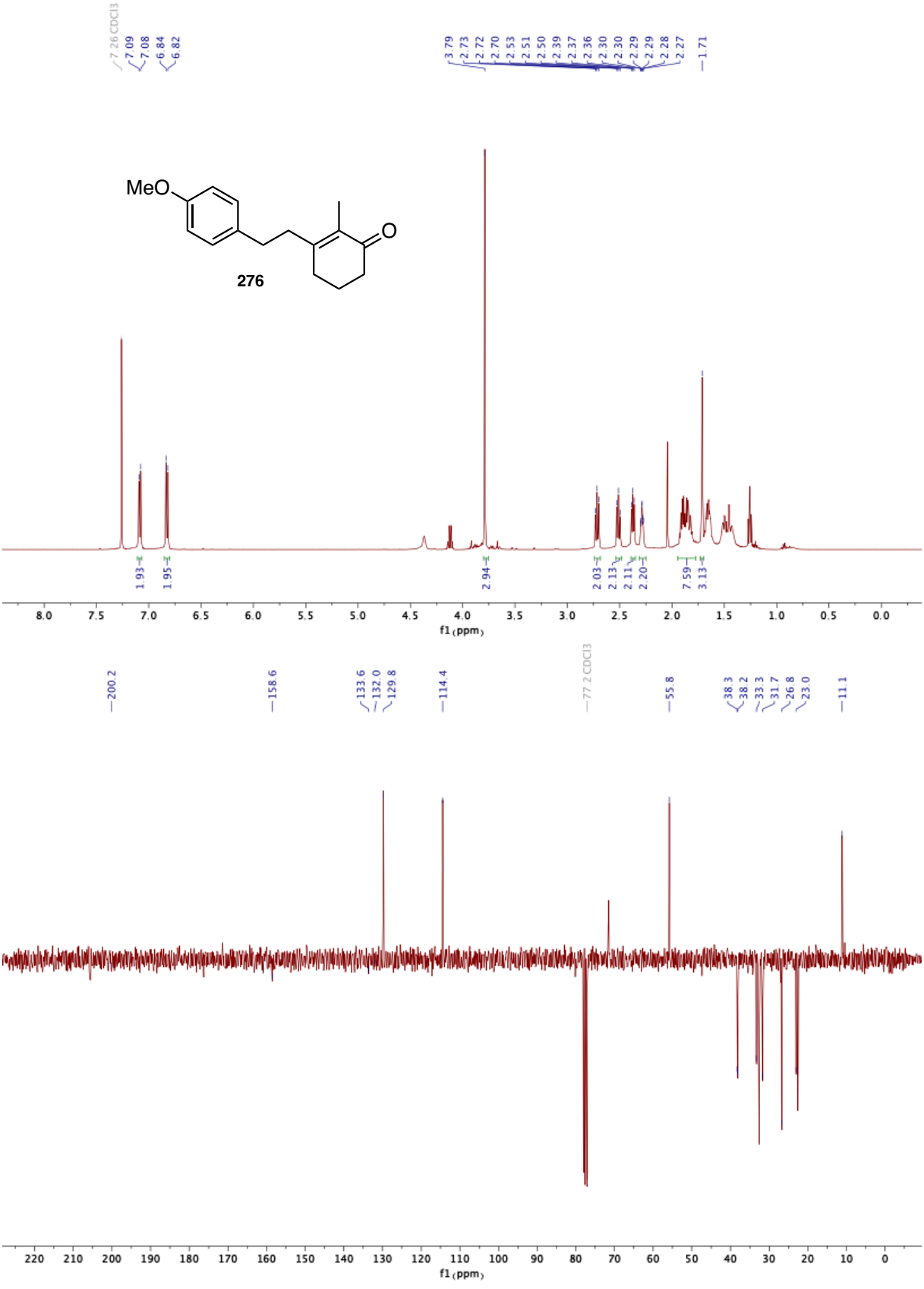
6.1.86 ^{1}H AND ^{13}C NMR SPECTRA OF ENONE **270**



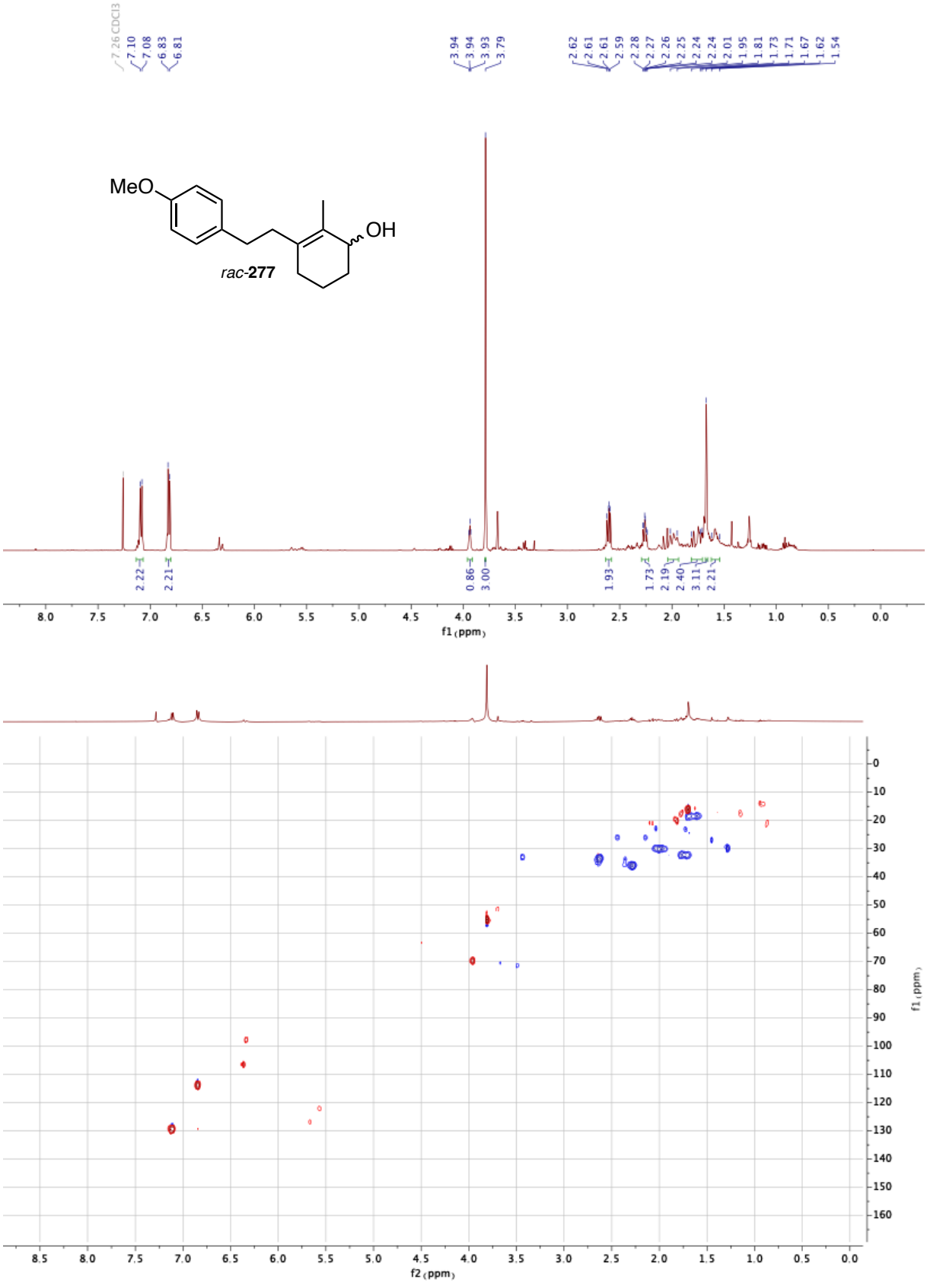
6.1.87 ^{1}H AND ^{13}C NMR SPECTRA OF ALLYLIC ALCOHOL *rac*-**271**



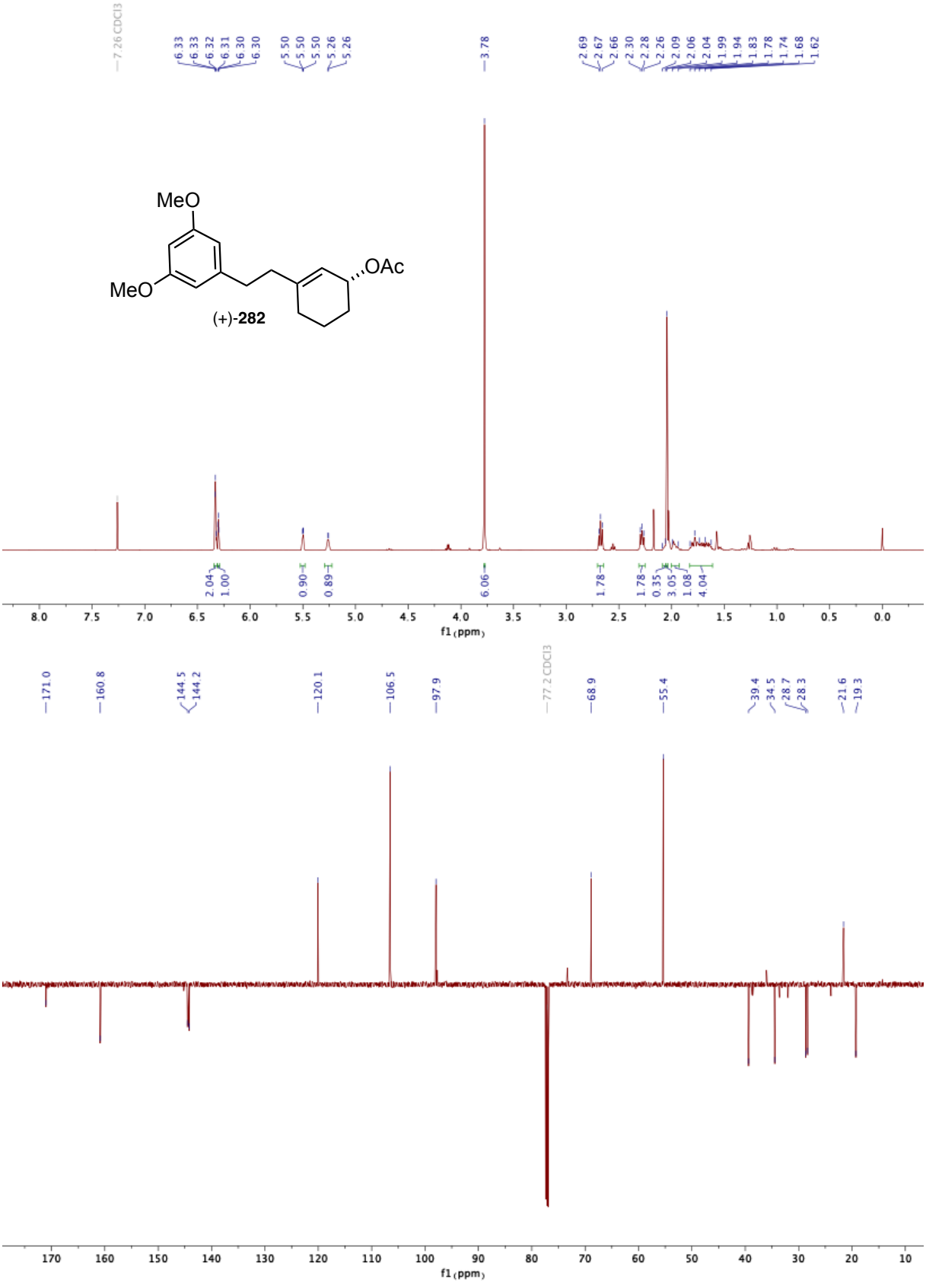
6.1.88 ^{1}H AND ^{13}C NMR SPECTRA OF ENONE **276**



6.1.89 ^{1}H AND ^{13}C NMR SPECTRA OF ALLYLIC ALCOHOL *rac*-**277**



6.1.90 ^{1}H AND ^{13}C NMR SPECTRA OF ACETATE (+)-**282**



6.2 X-RAY CRYSTALLOGRAPHIC DATA

6.2.1 DATA OF KETONE **114**

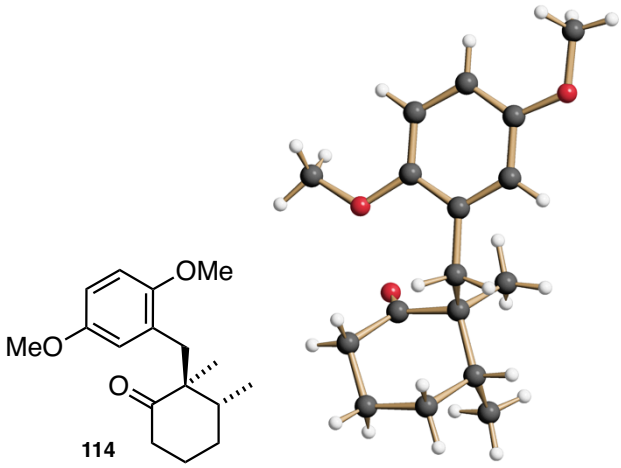


TABLE 5 CRYSTAL DATA AND STRUCTURE REFINEMENT FOR KETONE **114**.

Empirical formula	**C17 H24 O3**
Moiety formula	C17 H24 O3
Formula weight	276.36
Temperature	100(2) K
Wavelength	1.54178 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 7.0055(3) Å a = 90°
	b = 12.6745(5) Å b = 90°
	c = 17.0091(6) Å g = 90°
Volume	1510.26(10) $Å^3$
Z	4
Density (calculated)	1.215 Mg/m^3
Absorption coefficient	0.650 mm^{-1}
F(000)	600
Crystal size	0.200 x 0.200 x 0.060 mm^3
□□range for data collection	4.350 to 72.086°.
Index ranges	-8<=h<=8, -15<=k<=15, -20<=l<=20
Reflections collected	45975
Independent reflections	2980 [R(int) = 0.0348]
Completeness to □ = 67.679°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7536 and 0.6732
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2980 / 0 / 186
Goodness-of-fit on F^2	1.072
Final R indices [I>2□(I)]	R1 = 0.0251, wR2 = 0.0667
R indices (all data)	R1 = 0.0253, wR2 = 0.0668
Absolute structure parameter	0.030(18)
Extinction coefficient	0.0069(7)
Largest diff. peak and hole	0.215 and -0.166 $e.Å^{-3}$

6.2.2 DATA OF KETONE *epi*-**114**

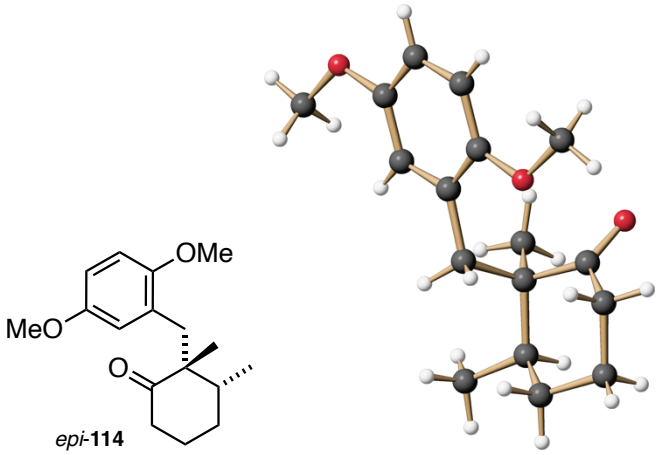


TABLE 6 CRYSTAL DATA AND STRUCTURE REFINEMENT FOR KETONE *epi*-**114**.

Empirical formula	**C17 H24 O3**
Moiety formula	C17 H24 O3
Formula weight	276.36
Temperature	100(2) K
Wavelength	1.54178 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 7.0055(3) Å a = 90°
	b = 12.6745(5) Å b = 90°
	c = 17.0091(6) Å g = 90°
Volume	1510.26(10) $Å^3$
Z	4
Density (calculated)	1.215 Mg/m^3
Absorption coefficient	0.650 mm^{-1}
F(000)	600
Crystal size	0.200 x 0.200 x 0.060 mm^3
□□range for data collection	4.350 to 72.086°.
Index ranges	-8<=h<=8, -15<=k<=15, -20<=l<=20
Reflections collected	45975
Independent reflections	2980 [R(int) = 0.0348]
Completeness to □ = 67.679°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7536 and 0.6732
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2980 / 0 / 186
Goodness-of-fit on F^2	1.072
Final R indices [I>2□(I)]	R1 = 0.0251, wR2 = 0.0667
R indices (all data)	R1 = 0.0253, wR2 = 0.0668
Absolute structure parameter	0.030(18)
Extinction coefficient	0.0069(7)
Largest diff. peak and hole	0.215 and -0.166 e.$Å^{-3}$

6.2.3 DATA OF KETONE *ent-epi*-**114**

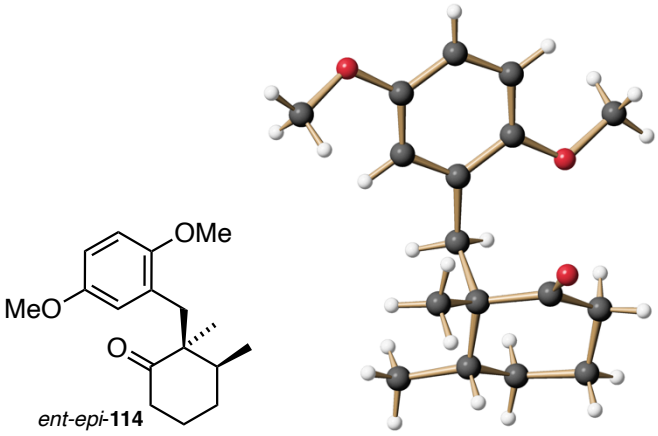


TABLE 7 CRYSTAL DATA AND STRUCTURE REFINEMENT FOR KETONE *ent-epi*-**114**.

Empirical formula	**C17 H24 O3**
Moiety formula	C17 H24 O3
Formula weight	276.36
Temperature	100(2) K
Wavelength	1.54178 Å
Crystal system	Triclinic
Space group	P1
Unit cell dimensions	a = 7.3352(7) Å
	b = 9.8566(7) Å
	c = 10.8535(7) Å
Volume	762.70(10) $Å^3$
Z	2
Density (calculated)	1.203 Mg/m^3
Absorption coefficient	0.644 mm^{-1}
F(000)	300
Crystal size	0.150 x 0.150 x 0.020 mm^3
Theta range for data collection	4.190 to 72.250°.
Index ranges	-9<=h<=9, -12<=k<=12, -13<=l<=12
Reflections collected	23278
Independent reflections	5653 [R(int) = 0.0940]
Completeness to theta = 67.679°	98.1 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7535 and 0.5928
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5653 / 3 / 369
Goodness-of-fit on F^2	1.050
Final R indices [I>2sigma(I)]	R1 = 0.0476, wR2 = 0.1080
R indices (all data)	R1 = 0.0644, wR2 = 0.1178
Absolute structure parameter	0.02(18)
Extinction coefficient	n/a
Largest diff. peak and hole	0.229 and -0.230 $e.Å^{-3}$

6.2.4 DATA OF OLEFIN **184**

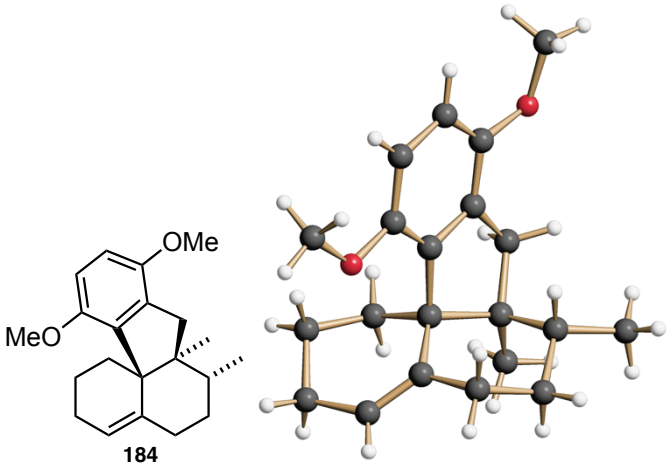
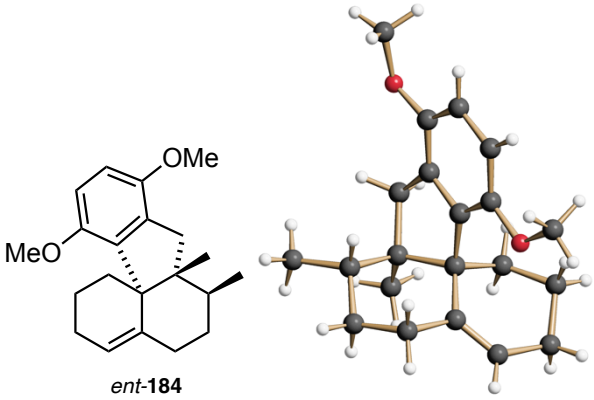


TABLE 8 CRYSTAL DATA AND STRUCTURE REFINEMENT FOR OLEFIN **184**.

Empirical formula	C21 H28 O2	
Moiety formula	C21 H28 O2	
Formula weight	312.43	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Hexagonal	
Space group	$P6_3$	
Unit cell dimensions	a = 13.3520(4) Å	a = 90°
	b = 13.3520(4) Å	b = 90°
	c = 17.1138(7) Å	g = 120°
Volume	2642.22(19) $Å^3$	
Z	6	
Density (calculated)	1.178 Mg/m^3	
Absorption coefficient	0.571 mm^{-1}	
F(000)	1020	
Crystal size	0.200 x 0.100 x 0.070 mm^3	
□-range for data collection	3.823 to 72.044°.	
Index ranges	-16<=h<=16, -16<=k<=16, -21<=l<=21	
Reflections collected	32133	
Independent reflections	3489 [R(int) = 0.0798]	
Completeness to □ = 67.679°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7536 and 0.5950	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3489 / 1 / 212	
Goodness-of-fit on F^2	1.045	
Final R indices [I>2□(I)]	R1 = 0.0444, wR2 = 0.1030	
R indices (all data)	R1 = 0.0490, wR2 = 0.1066	
Absolute structure parameter	0.17(12)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.487 and -0.212 $e.Å^{-3}$	

6.2.5 DATA OF OLEFIN *ent*-184



ent-184

TABLE 9 CRYSTAL DATA AND STRUCTURE REFINEMENT FOR OLEFIN *ent*-184.

Empirical formula	**C21 H28 O2**
Moiety formula	C21 H28 O2
Formula weight	312.43
Temperature	100(2) K
Wavelength	1.54178 Å
Crystal system	Hexagonal
Space group	$P6_3$
Unit cell dimensions	a = 13.3658(3) Å
	b = 13.3658(3) Å
	c = 17.1449(7) Å
Volume	2652.50(16) $Å^3$
Z	6
Density (calculated)	1.174 Mg/m^3
Absorption coefficient	0.569 mm^{-1}
F(000)	1020
Crystal size	0.070 x 0.030 x 0.030 mm^3
Theta range for data collection	3.819 to 72.203°.
Index ranges	-16<=h<=16, -16<=k<=16, -21<=l<=21
Reflections collected	92727
Independent reflections	3505 [R(int) = 0.1061]
Completeness to theta = 67.679°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7536 and 0.6557
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3505 / 1 / 212
Goodness-of-fit on F^2	1.032
Final R indices [I>2sigma(I)]	R1 = 0.0372, wR2 = 0.0980
R indices (all data)	R1 = 0.0389, wR2 = 0.0996
Absolute structure parameter	0.04(9)
Extinction coefficient	n/a
Largest diff. peak and hole	0.318 and -0.163 e.$Å^{-3}$

6.2.6 DATA OF KETONE **111**

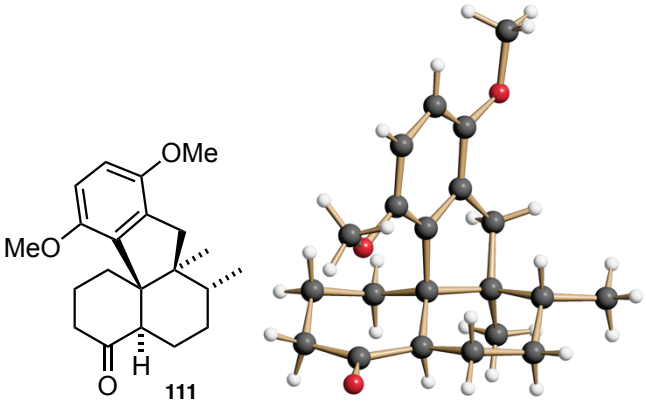


TABLE 10 CRYSTAL DATA AND STRUCTURE REFINEMENT FOR KETONE **111**.

Empirical formula	**C21 H28 O3**
Formula weight	328.43
Temperature	295(2) K
Wavelength	1.54178 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 10.6575(2) Å
	b = 11.2368(3) Å
	c = 15.3203(4) Å
Volume	1834.70(8) $Å^3$
Z	4
Density (calculated)	1.189 Mg/m^3
Absorption coefficient	0.614 mm^{-1}
F(000)	712
Crystal size	0.100 x 0.070 x 0.050 mm^3
Theta range for data collection	4.881 to 72.208°.
Index ranges	-13<=h<=11, -13<=k<=13, -18<=l<=18
Reflections collected	40088
Independent reflections	3616 [R(int) = 0.0534]
Completeness to theta = 67.679°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7536 and 0.5789
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3616 / 0 / 221
Goodness-of-fit on F^2	1.111
Final R indices [I>2sigma(I)]	R1 = 0.0310, wR2 = 0.0886
R indices (all data)	R1 = 0.0386, wR2 = 0.0980
Absolute structure parameter	0.01(7)
Extinction coefficient	n/a
Largest diff. peak and hole	0.296 and -0.331 $e.Å^{-3}$
Empirical formula	C21 H28 O3

6.2.7 DATA OF A-METHYL KETONE *ent*-120

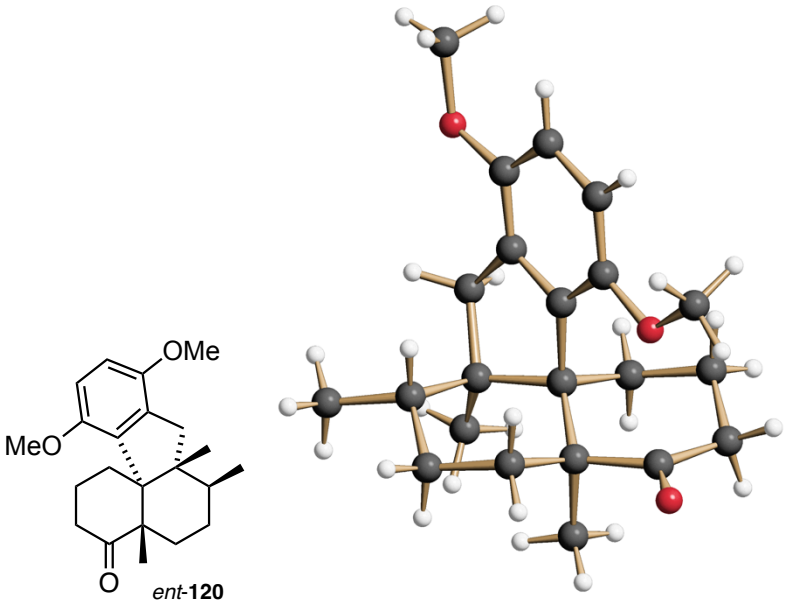


TABLE 11 CRYSTAL DATA AND STRUCTURE REFINEMENT FOR α-METHYL KETONE *ent*-**120**.

Empirical formula	**C22 H30 O3**
Moiety formula	C22 H30 O3
Formula weight	342.46
Temperature	100(2) K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 9.256(2) Å
	b = 12.765(3) Å
	c = 15.556(4) Å
Volume	1820.4(8) $Å^3$
Z	4
Density (calculated)	1.250 Mg/m^3
Absorption coefficient	0.639 mm^{-1}
F(000)	744
Crystal size	0.070 x 0.010 x 0.005 mm^3
Theta range for data collection	2.868 to 72.874°.
Index ranges	-11<=h<=11, -15<=k<=14, -19<=l<=18
Reflections collected	30701
Independent reflections	7014 [R(int) = 0.2085]
Completeness to theta = 67.679°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7536 and 0.6178
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7014 / 1 / 462
Goodness-of-fit on F^2	0.949
Final R indices [I>2sigma(I)]	R1 = 0.0794, wR2 = 0.1620
R indices (all data)	R1 = 0.1583, wR2 = 0.2014
Absolute structure parameter	0.1(4)
Extinction coefficient	0.0117(13)
Largest diff. peak and hole	0.307 and -0.259 $e.Å^{-3}$

6.2.8 DATA OF TRIFLATE **185**

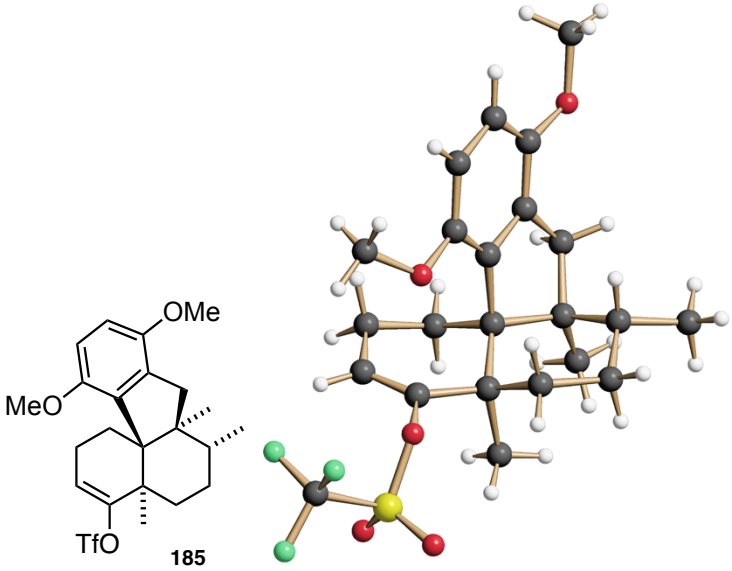


TABLE 12 CRYSTAL DATA AND STRUCTURE REFINEMENT FOR TRIFLATE **185**.

Empirical formula	**C23 H29 F3 O5 S**
Moiety formula	C23 H29 F3 O5 S
Formula weight	474.52
Temperature	100(2) K
Wavelength	1.54178 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 7.5398(2) Å
	b = 13.1822(4) Å
	c = 22.8490(7) Å
Volume	2270.99(11) $Å^3$
Z	4
Density (calculated)	1.388 Mg/m^3
Absorption coefficient	1.774 mm^{-1}
F(000)	1000
Crystal size	0.070 x 0.030 x 0.010 mm^3
Theta range for data collection	3.869 to 72.383°.
Index ranges	-9<=h<=9, -16<=k<=16, -28<=l<=28
Reflections collected	96673
Independent reflections	4251 [R(int) = 0.0827]
Completeness to theta = 67.679°	95.2 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7536 and 0.5978
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4251 / 0 / 294
Goodness-of-fit on F^2	1.045
Final R indices [I>2sigma(I)]	R1 = 0.0352, wR2 = 0.0904
R indices (all data)	R1 = 0.0371, wR2 = 0.0915
Absolute structure parameter	0.031(6)
Extinction coefficient	n/a
Largest diff. peak and hole	0.317 and -0.319 e.$Å^{-3}$

6.2.9 DATA OF (–)-DYSIHERBOL A (98) — MeOH COMPLEX

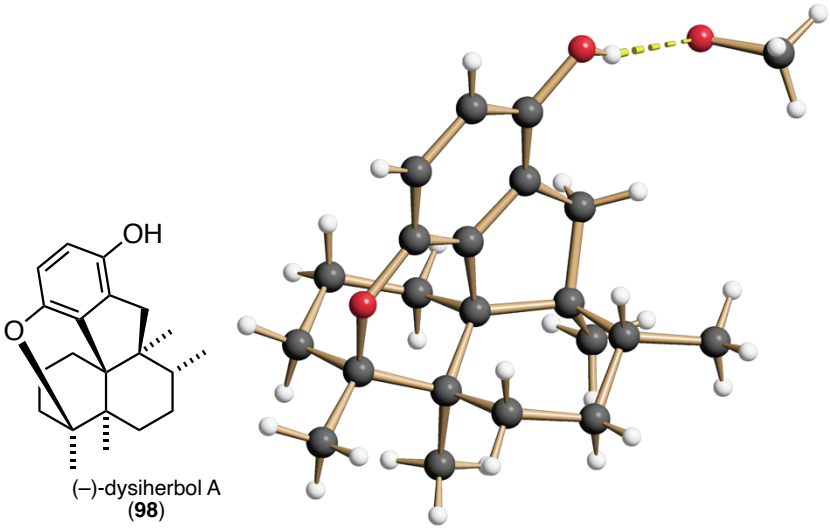


TABLE 13 CRYSTAL DATA AND STRUCTURE REFINEMENT FOR (–)-DYSIHERBOL A (98) — MeOH COMPLEX.

Empirical formula	**C22 H32 O3**
Moiety formula	C21 H28 O2, C H4 O
Formula weight	344.47
Temperature	100(2) K
Wavelength	1.54178 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 9.4931(5) Å
	b = 12.8945(7) Å
	c = 15.0694(9) Å
Volume	1844.63(18) $Å^3$
Z	4
Density (calculated)	1.240 Mg/m^3
Absorption coefficient	0.631 mm^{-1}
F(000)	752
Crystal size	0.150 x 0.080 x 0.080 mm^3
Crystal colour	yellowish
Theta range for data collection	4.513 to 72.088°.
Index ranges	-11<=h<=11, -14<=k<=15, -18<=l<=18
Reflections collected	108102
Independent reflections	3629 [R(int) = 0.0575]
Completeness to theta = 67.679°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7536 and 0.6407
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3629 / 0 / 239
Goodness-of-fit on F^2	1.081
Final R indices [I>2sigma(I)]	R1 = 0.0283, wR2 = 0.0770
R indices (all data)	R1 = 0.0289, wR2 = 0.0777
Absolute structure parameter	0.04(3)
Extinction coefficient	n/a

6.2.10 DATA OF SPIROCYCLIC OLEFIN *rac*-278

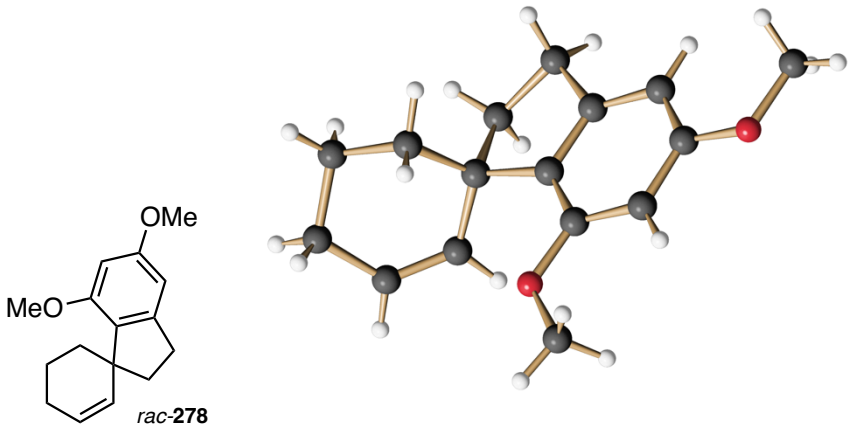


TABLE 14 CRYSTAL DATA AND STRUCTURE REFINEMENT FOR SPIROCYCLIC OLEFIN *rac*-278.

Empirical formula	**C16 H20 O2**
Moiety formula	C16 H20 O2
Formula weight	244.32
Temperature	100(2) K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 9.6883(12) Å
	b = 21.748(3) Å
	c = 6.4103(8) Å
Volume	1321.8(3) $Å^3$
Z	4
Density (calculated)	1.228 Mg/m^3
Absorption coefficient	0.623 mm^{-1}
F(000)	528
Crystal size	0.100 x 0.020 x 0.005 mm^3
Theta range for data collection	4.065 to 72.320°.
Index ranges	-11<=h<=11, -26<=k<=26, -6<=l<=7
Reflections collected	26751
Independent reflections	2588 [R(int) = 0.1216]
Completeness to theta = 67.679°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7536 and 0.5857
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2588 / 0 / 166
Goodness-of-fit on F^2	1.039
Final R indices [I>2sigma(I)]	R1 = 0.0635, wR2 = 0.1612
R indices (all data)	R1 = 0.0826, wR2 = 0.1757
Extinction coefficient	0.0029(9)
Largest diff. peak and hole	0.676 and -0.307 $e.Å^{-3}$
Empirical formula	C16 H20 O2

6.3 CHIRAL HPLC ANALYSIS

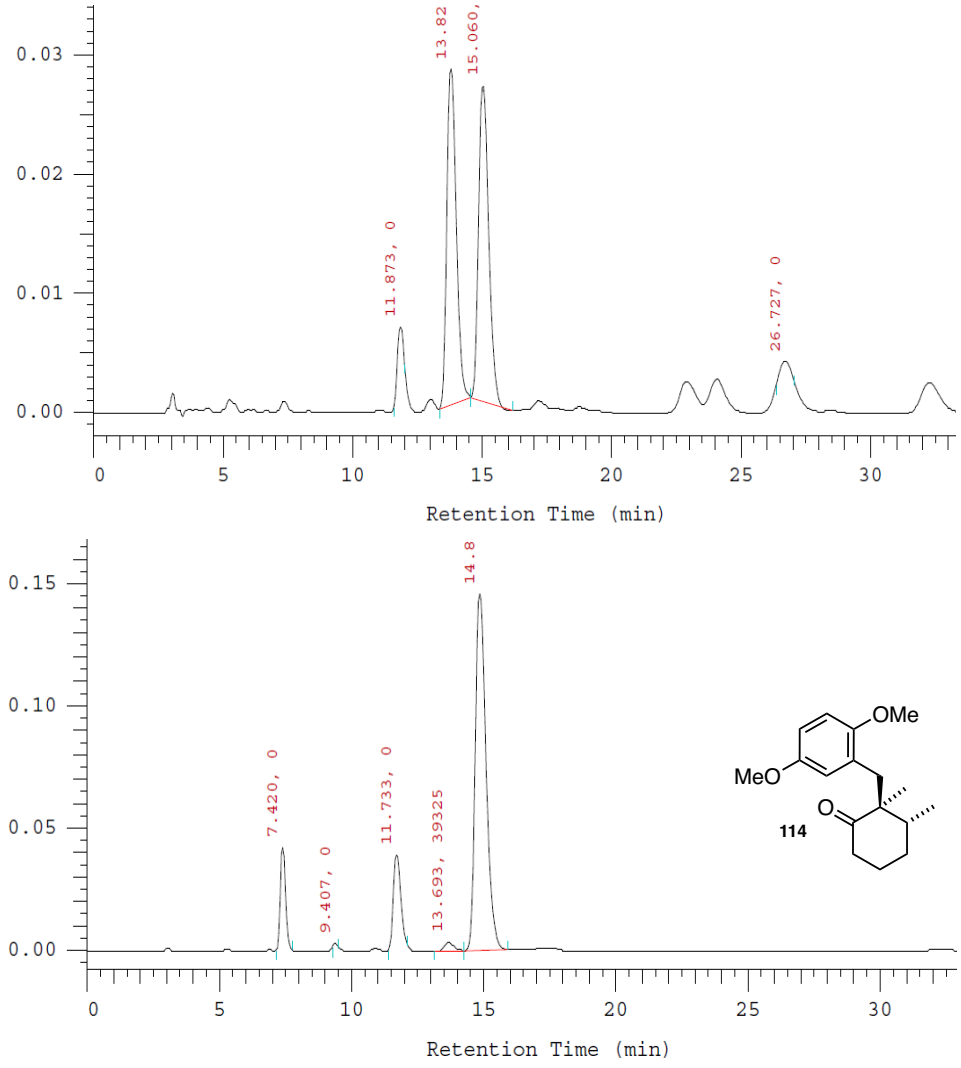


FIGURE 16 HPLC CHROMATOGRAM OF A RACEMIC SAMPLE OF (±)-**114** (TOP) AND AN ENANTIOENRICHED SAMPLE OF **114** (BOTTOM) ON CHIRAL STATIONARY PHASE.

Column: CHIRALPAK AD-H

Column temperature: 18 °C

Solvent: *n*-hexane/2-propanol 99:1

Flow: 1 mL/min

Detection: 250 nm

Enantiomeric excess: 96%

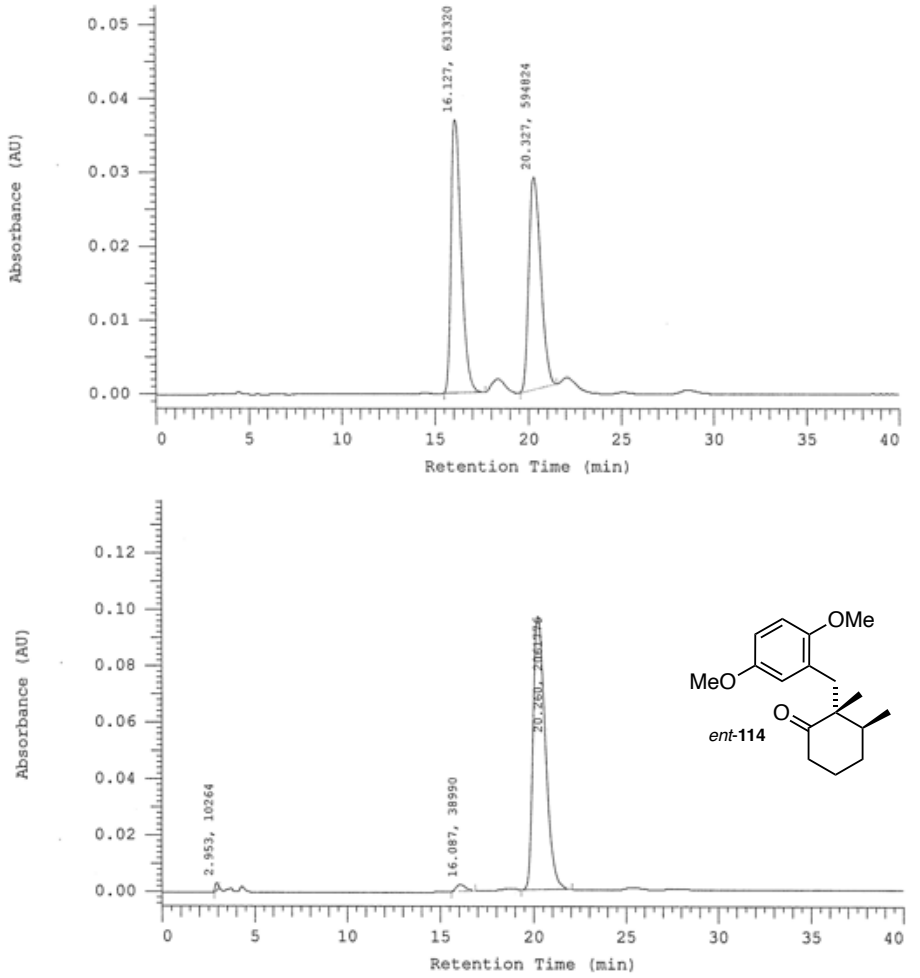


FIGURE 17 HPLC CHROMATOGRAM OF *rac*-**114** (TOP) AND ENANTIOENRICHED *ent*-**114** (BOTTOM) ON CHIRAL STATIONARY PHASE.

Column: CHIRALPAK AD-H

Column temperature: 18 °C

Solvent: *n*-hexane/2-propanol 99:1

Flow: 1 mL/min

Detection: 250 nm

Enantiomeric excess: 96%

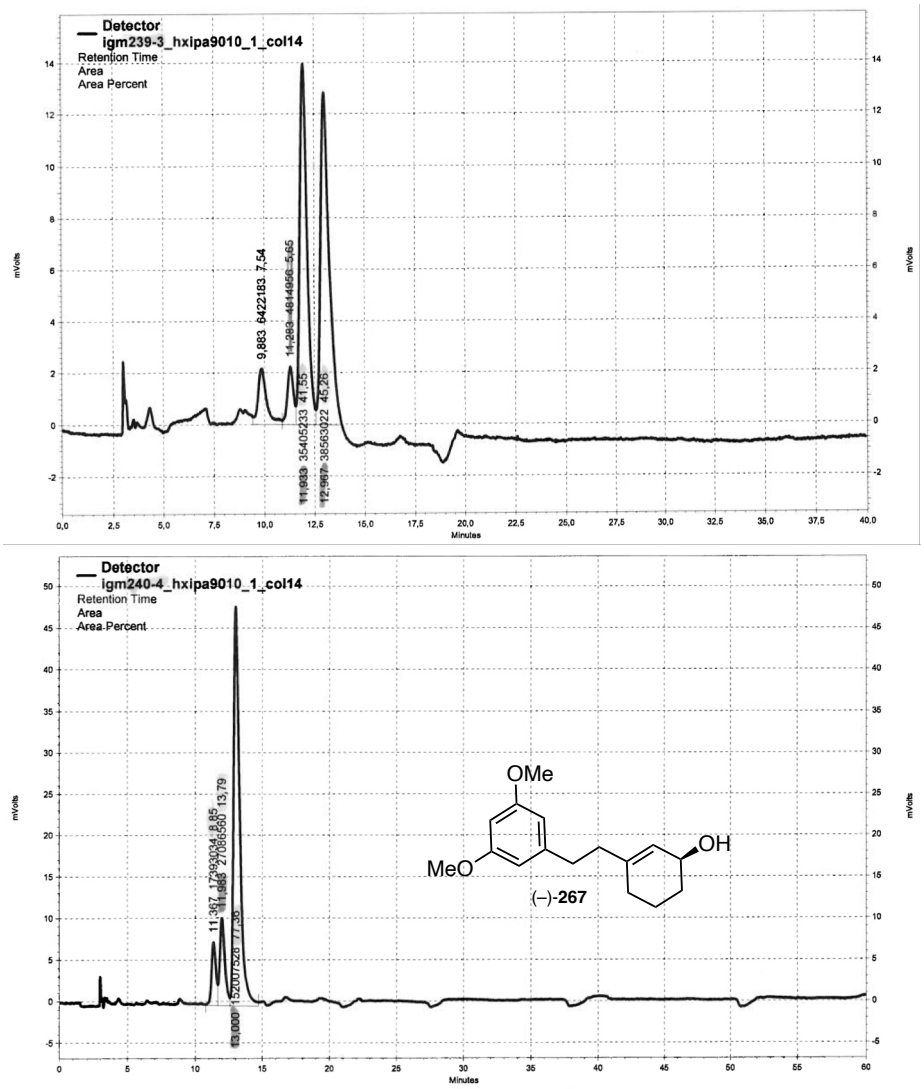


FIGURE 18 HPLC CHROMATOGRAM OF *rac*-**267** (TOP) AND ENANTIOENRICHED (–)-**267** (BOTTOM) ON STATIONARY PHASE.

Column: Diacel CHIRALPAK AD-H

Column temperature: rt

Solvent: *n*-hexane/2-propanol 90:10

Flow: 1 mL/min

Detection: 254 nm

Enantiomeric excess: 70%

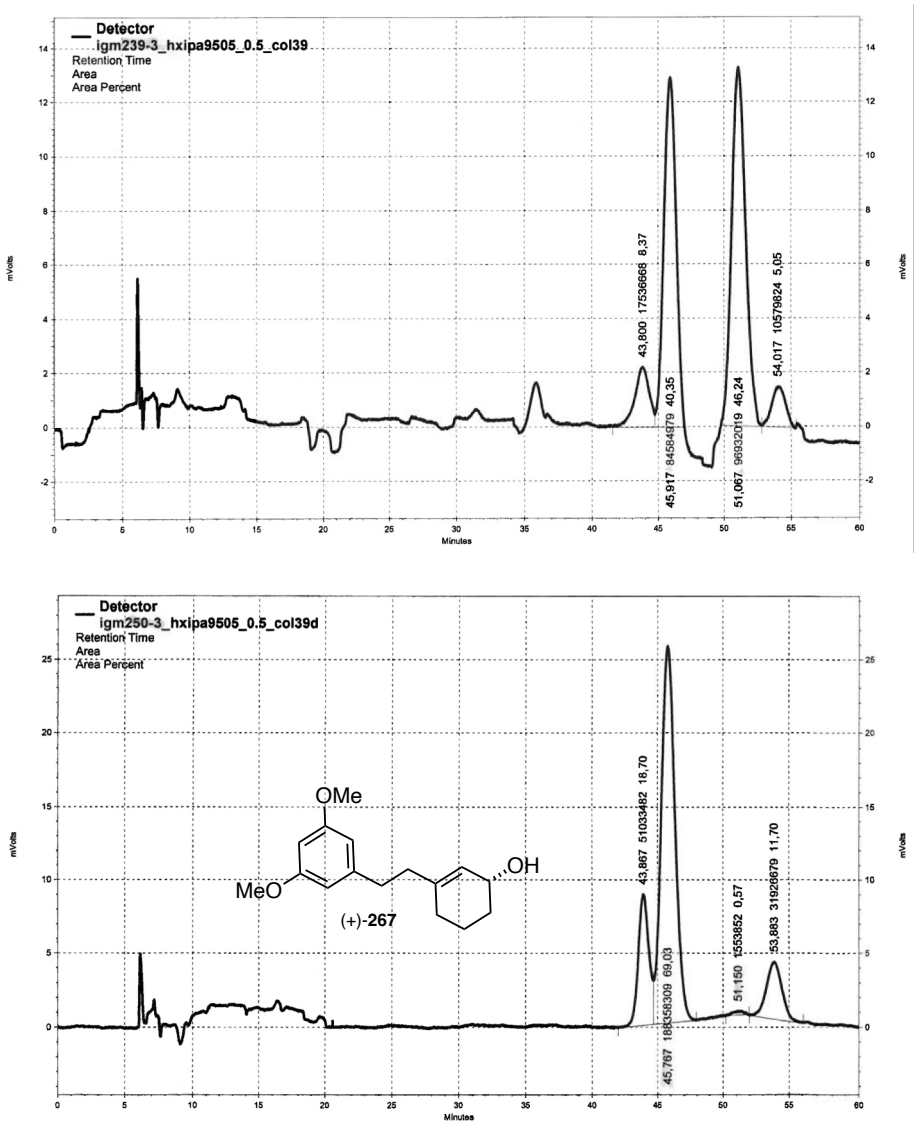


FIGURE 19 HPLC CHROMATOGRAM OF *rac*-**267** (TOP) AND ENANTIOENRICHED (+)-**267** (BOTTOM) ON STATIONARY PHASE.

Column: Diacel CHIRALPAK AD-H

Column temperature: rt

Solvent: *n*-hexane/2-propanol 95:05

Flow: 0.5 mL/min

Detection: 254 nm

Enantiomeric excess: 98 %

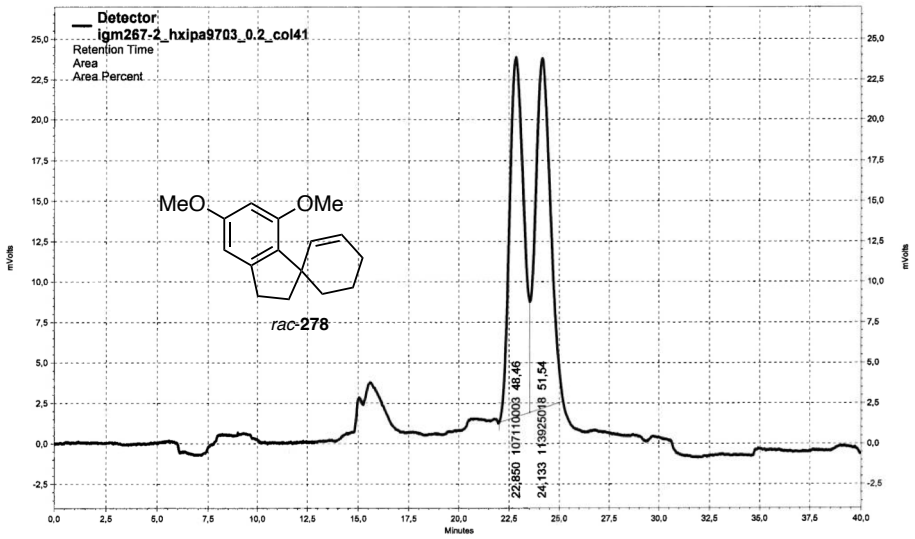


FIGURE 20 HPLC CHROMATOGRAM OF *rac*-**278** AFTER CYCLIZATION OF ENANTIOENRICHED (+)-**267** (*ee* = 98%) WITH $AuCl_3$.

Column: *Macherey-Nagel* Nucleocell

Column temperature: rt

Solvent: *n*-hexane/2-propanol 98:02

Flow: 0.1 mL/min

Detection: 254 nm

6.4 LIST OF ABBREVIATIONS

AIBN	azobisisobutyronitril
9-BBN	9-borobicyclo[3.3.1]nonane
Ac	acetyl
AcOH	acetic acid
APT	attached proton test
aq.	aqueous
AraC	cytarabine
ASA	acetylsalicylic acid
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Br	broad (NMR and IR spectra)
brsm	based on reisolation of starting material
Bu	butyl
CALB	*Candida antarctica* Lipase B
calc.	calculated
CoA	coenzyme A
cod	cycloocta-1,5-diene
conc.	concentrated
conv.	conversion
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
d	doublet (NMR spectra) or day(s) (reaction time)
DABCO	1,4-diazabicyclo[2.2.2] octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DEPTQ	distorsionless enhancement by polarisation transfer including the detection of quaternary nuclei
dia	diastereomer
DIBAL-H	diisobutylaluminum hydride
DIPEA	*N*,*N*-di*iso*propylethylamine
DMAPP	dimethylallyl pyrophosphate
DME	1,2-Dimethoxyethane
DMEM	Dulbecco's modified minimal essential medium
DMF	*N*,*N*-dimethylformamide
DMP	*Dess-Martin* periodinane
DMS	dimethyl sulfide
DMSO	dimethylsulfoxide
Doxo	doxorubicin
dppe	1,2-bis(diphenylphosphino) ethane
dppf	1,1'-bis(diphenylphosphino) ferrocene
dr	diastereomeric ratio
DTBMP	2,6-Di-*tert*-butylpyridine
ECD	electronic circular dichroism

EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
EI	electron impact ionisation
ent	enantiomer
epi	epimeric
eq.	equivalent(s)
ESI	electron spray ionisation
Et	ethyl
et al.	*et altera*
FCS	fetal calf serum
FPP	farnesyl pyrophosphate
FT-IR	*Fourier*-transform infrared spectroscopy
GC	gas chromatography
h	hour(s)
HBA	4-hydroxybenzoic acid
HIV	human immunodeficiency viruses
HMBC	heteronuclear multiple bond correlation
HMBC	heteronuclear multiple bond MS correlation
HMPA	hexamethylphosphoramide
HPLC	high performance liquid MTBE chromatography
HR	high resolution
HSQC	heteronuclear single quantum coherence
HSQC	heteronuclear single quantum coherence
IC50	half maximal inhibitory concentration
IPP	*iso*pentenyl diphosphate
*i*Pr	*iso*-propy*l*
IR	infrared
LDA	lithium *N*,*N*-di*iso*propylamide
lit.	literature
m	medium (IR spectra) *or* multiplet (NMR spectra)
m.p.	melting point
mCPBA	meta-chloroperbenzoic acid
Me	methyl
MEP	2-*C*-methyl-D-erythritol 4-phosphate
MRSA	methicillin-resistant *Staphylococcus aureus*
MS	mass spectrometry or molecular sieves
Ms	methanesulfonyl
MTBE	*tert*-butyl methyl ether
NBS	*N*-bromosuccinimide
NF-κB	nuclear factor kappa B
NMR	nuclear magnetic resonance
NOESY	nuclear *Overhauser* effect correlation spectroscopy
o	*ortho*
o/n	overnight

p	*para*
PBS	Phosphate-buffered saline
Ph	phenyl
PPTS	pyridinium p-toluenesulfonate
*p*TsOH	*para*-toluenesulfonic acid
q	quartet (NMR spectra)
quint	quintet (NMR spectra)
R	non-defined substituent
rac	racemic
RCM	ring-closing metathesis
ref.	reference
R_f	retardation factor
ROS	reactive oxygen species
rt	room temperature
s	strong (IR spectra) *or* singlet (NMR spectra)
SAR	structure-activity relationship
sat.	saturated
SEAr	electrophilic aromatic substitution
SM	starting material
Sphos	2-dicyclohexylphosphino- 2',6'-dimethoxybiphenyl
t	triplet (NMR spectra)
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tertiary*-butyldimethylsilyl
*t*Bu	*tertiary*-butyl
TC	thiophene-2-carboxylate
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIC	total ion current
TLC	thin layer chromatography
TMS	trimethylsilyl
TPPA	tris(pyrrolidinyl)-phosphoramide
UbiA	4-hydroxybenzoate polyprenyltransferase
UV	ultraviolet
VCr	vincristine
w	weak (IR spectra)
WHO	World Health Organization

6.5 REFERENCES

[1] P. M. Dewick, *Medicinal Natural Products: A Biosynthetic Approach*, 3rd ed., John Wiley & Sons, Ltd., **2009**.

[2] P. E. H. Gerhard Habermehl, Hans C. Krebs, W. Ternes, *Naturstoffchemie, Eine Einführung, Vol. 3*, Springer-Verlag Berlin Heidelberg, **2008**.

[3] A. Jones, *Chemistry, An Introduction for Medical and Health Sciences*, John Wiley & Sons, Ltd., Chichester, **2005**.

[4] T. M. K. C. Nicolaou, *Molecules that Changed the World*, Wiley-VCH, Weinheim, **2008**.

[5] G. Klebe, *Wirkstoffdesign*, 2nd ed., Spektrum Akademischer Verlag, Heidelberg, **2009**.

[6] S.-M. Shen, G. Appendino, Y.-W. Guo, *Nat. Prod. Rep.* **2022**, *39*, 1803-1832.

[7] a) K. C. Nicolaou, *Proc. Math. Phys. Eng. Sci.* **2014**, *470*, 20130690; b) M. E. Maier, *Nat. Prod. Rep.* **2009**, *26*, 1105-1124.

[8] K. C. Nicolaou, S. A. Snyder, *Proceedings of the National Academy of Sciences of the United States of America* **2004**, *101*, 11929-11936.

[9] R. B. Woodward, R. Hoffmann, *J. Am. Chem. Soc.* **1965**, *87*, 395-397.

[10] R. B. Woodward, *Pure Appl. Chem.* **1973**, *33*, 145-178.

[11] D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2007**, *70*, 461-477.

[12] M. Feher, J. M. Schmidt, *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 218-227.

[13] X.-H. Tian, L.-L. Hong, W.-H. Jiao, H.-W. Lin, *Nat. Prod. Rep.* **2023**.

[14] a) D. Varijakzhan, J.-Y. Loh, W.-S. Yap, K. Yusoff, R. Seboussi, S.-H. E. Lim, K.-S. Lai, C.-M. Chong, *Mar. Drugs* **2021**, *19*, 246; b) R. J. Capon, in *Stud. Nat. Prod. Chem., Vol. 15* (Ed.: R. Atta ur), Elsevier, **1995**, pp. 289-326.

[15] I. S. Marcos, A. Conde, R. F. Moro, P. Basabe, D. Diez, J. G. Urones, *Mini-Rev. Org. Chem.* **2010**, *7*, 230-254.

[16] P. A. Garcia, A. P. Hernandez, A. San Feliciano, M. A. Castro, *Mar. Drugs* **2018**, *16*.

[17] a) T. Yoon, S. J. Danishefsky, S. de Gala, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 853-855; b) D. Sladic, M. J. Gasic, *Molecules* **2006**, *11*, 1-33; c) T. Namba, R. Kodama, *Mar. Drugs* **2015**, *13*, 2376-2389.

[18] L. Minale, R. Riccio, G. Sodano, *Tetrahedron Lett.* **1974**, *15*, 3401-3404.

[19] a) X. Zhang, H.-Y. Xu, A.-M. Huang, L. Wang, Q. Wang, P.-Y. Cao, P.-M. Yang, *Chem. Pharm. Bull.* **2016**, *64*, 1036-1042; b) R. Wildermuth, K. Speck, F. L. Haut, P. Mayer, B. Karge, M. Bronstrup, T. Magauer, *Nat. Commun.* **2017**, *8*, 2083; c) L. Yang, D. E. Williams, A. Mui, C. Ong, G. Krystal, R. van Soest, R. J. Andersen, *Org. Lett.* **2005**, *7*, 1073-1076; d) W.-H. Jiao, T.-T. Xu, F. Zhao, H. Gao, G.-H. Shi, J. Wang, L.-L. Hong, H.-B. Yu, Y.-S. Li, F. Yang, H.-W. Lin, *Eur. J. Org. Chem.* **2015**, *2015*, 960-966; e) C. K. Kim, J. K. Woo, S. H. Kim, E. Cho, Y. J. Lee, H. S. Lee, C. J. Sim, D. C. Oh, K. B. Oh, J. Shin, *J. Nat. Prod.* **2015**, *78*, 2814-2821; f) W. H. Jiao, G. H. Shi, T. T.

Xu, G. D. Chen, B. B. Gu, Z. Wang, S. Peng, S. P. Wang, J. Li, B. N. Han, W. Zhang, H. W. Lin, *J. Nat. Prod.* **2016**, *79*, 406-411.

[20] P. Djura, D. B. Stierle, B. Sullivan, D. J. Faulkner, E. V. Arnold, J. Clardy, *J. Org. Chem.* **1980**, *45*, 1435-1441.

[21] E. Goclik, G. M. König, A. D. Wright, R. Kaminsky, *J. Nat. Prod.* **2000**, *63*, 1150-1152.

[22] L. I. U. Hong-Yan, Z. Mi, S. Ru-Yi, H. Li-Li, W. Guang-Hui, T. Wen-Jing, J. Wei-Hua, C. Hai-Feng, L. I. N. Hou-Wen, *Chin. J. Nat. Med.* **2021**.

[23] W. H. Jiao, T. T. Xu, H. B. Yu, G. D. Chen, X. J. Huang, F. Yang, Y. S. Li, B. N. Han, X. Y. Liu, H. W. Lin, *J. Nat. Prod.* **2014**, *77*, 346-350.

[24] Y. H. Gui, W. H. Jiao, M. Zhou, Y. Zhang, D. Q. Zeng, H. R. Zhu, K. C. Liu, F. Sun, H. F. Chen, H. W. Lin, *Org. Lett.* **2019**, *21*, 767-770.

[25] P. Amade, L. Chevelot, H. P. Perzanowski, P. J. Scheuer, *Helv. Chim. Acta* **1983**, *66*, 1672-1675.

[26] W. H. Jiao, B. H. Cheng, G. D. Chen, G. H. Shi, J. Li, T. Y. Hu, H. W. Lin, *Org. Lett.* **2018**, *20*, 3092-3095.

[27] a) W. H. Jiao, J. Li, Q. Liu, T. T. Xu, G. H. Shi, H. B. Yu, F. Yang, B. N. Han, M. Li, H. W. Lin, *Molecules* **2014**, *19*, 18025-18032; b) D. Lee, J. Shin, K.-M. Yoon, T.-I. Kim, S.-H. Lee, H.-S. Lee, K.-B. Oh, *Bioorganic & Medicinal Chemistry Letters* **2008**, *18*, 5377-5380; c) H. M. Nguyen, T. Ito, S. I. Kurimoto, M. Ogawa, N. N. Win, V. Q. Hung, H. T. Nguyen, T. Kubota, J. Kobayashi, H. Morita, *Bioorg. Med. Chem. Lett.* **2017**, *27*, 3043-3047.

[28] a) D.-S. Lee, I. H. Hwang, N.-K. Im, G.-S. Jeong, M. Na, *Nat. Prod. Sci.* **2015**, *21*; b) J. Li, F. Yang, Z. Wang, W. Wu, L. Liu, S.-P. Wang, B.-X. Zhao, W.-H. Jiao, S.-H. Xu, H.-W. Lin, *Org. Biomol. Chem.* **2018**, *16*, 6773-6782.

[29] a) S. S. Ebada, N. de Voogd, R. Kalscheuer, W. E. G. Müller, Chaidir, P. Proksch, *Phytochem. Lett.* **2017**, *22*, 154-158; b) M. Menna, C. Imperatore, F. D'Aniello, A. Aiello, *Mar. Drugs* **2013**, *11*, 1602-1643; cH. Suzuki, T. Kubota, A. Takahashi-Nakaguchi, J. Fromont, T. Gonoi, J. Kobayashi, *Chem Pharm Bull (Tokyo)* **2014**, *62*, 209-212.

[30] S. D. Bruner, H. S. Radeke, J. A. Tallarico, M. L. Snapper, *J. Org. Chem.* **1995**, *60*, 1114-1115.

[31] a) K. A. Alvi, M. C. Diaz, P. Crews, D. L. Slate, R. H. Lee, R. Moretti, *J. Org. Chem.* **1992**, *57*, 6604-6607; b) J. Wang, F. R. Mu, W. H. Jiao, J. Huang, L. L. Hong, F. Yang, Y. Xu, S. P. Wang, F. Sun, H. W. Lin, *J. Nat. Prod.* **2017**, *80*, 2509-2514.

[32] a) A. Boufridi, S. Petek, L. Evanno, M. A. Beniddir, C. Debitus, D. Buisson, E. Poupon, *Tetrahedron Lett.* **2016**, *57*, 4922-4925; b) J. R. Carney, P. J. Scheuer, *Tetrahedron Lett.* **1993**, *34*, 3727-3730; c) M. Gordaliza, *Mar. Drugs* **2010**, *8*, 2849-2870; d) L. T. Huyen, D. T. Hang, N. X. Nhie, B. H. Tai, H. L. T. Anh, T. H. Quang, P. H. Yen, C. Van Minh, N. Van Dau, P. Van Kiem, *Nat Prod Commun* **2017**, *12*, 477-478; e) W. H. Jiao, G. H. Shi, T. T. Xu, G. D. Chen, B. B. Gu, Z. Wang, S. Peng, S. P. Wang, J. Li, B. N. Han, W. Zhang, H. W. Lin, *J. Nat. Prod.* **2016**, *79*, 406-411; f) S. P. Ovenden, J. L. Nielson, C. H. Liptrot, R. H. Willis, D. M. Tapiolas, A. D. Wright, C. A. Motti, *J. Nat. Prod.* **2011**, *74*, 65-68.

[33] a) M. Arai, T. Kawachi, H. Sato, A. Setiawan, M. Kobayashi, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3155-3157; b) P. H. Lu, S. C. Chueh, F. L. Kung, S. L. Pan, Y. C. Shen, J. H. Guh, *Eur. J. Pharmacol.* **2007**, *556*, 45-54.

[34] D. M. Pereira, P. Valentão, P. B. Andrade, in *Handbook of Anticancer Drugs from Marine Origin* (Ed.: S.-K. Kim), Springer International Publishing, Cham, **2015**, pp. 423-437.

[35] K. K. W. Kuan, H. P. Pepper, W. M. Bloch, J. H. George, *Org. Lett.* **2012**, *14*, 4710-4713.

[36] K. Speck, T. Magauer, *Chem. - Eur. J.* **2017**, *23*, 1157-1165.

[37] a) D. J. McGarvey, R. Croteau, *The Plant Cell* **1995**, *7*, 1015-1026; b) R. J. Sowden, S. Yasmin, N. H. Rees, S. G. Bell, L.-L. Wong, *Org. Biomol. Chem.* **2005**, *3*, 57-64.

[38] a) J. A. Stefely, D. J. Pagliarini, *Trends Biochem. Sci.* **2017**, *42*, 824-843; b) Y.-L. Yang, H. Zhou, G. Du, K.-N. Feng, T. Feng, X.-L. Fu, J.-K. Liu, Y. Zeng, *Angew. Chem., Int. Ed.* **2016**, *55*, 5463-5466; c) J. M. Lv, Y. H. Gao, H. Zhao, T. Awakawa, L. Liu, G. D. Chen, X. S. Yao, D. Hu, I. Abe, H. Gao, *Angew. Chem., Int. Ed. Engl.* **2020**, *59*, 13531-13536.

[39] A. Rosales, J. Muñoz-Bascón, E. Roldan-Molina, N. Rivas-Bascón, N. M. Padial, R. Rodríguez-Maecker, I. Rodríguez-García, J. E. Oltra, *J. Org. Chem.* **2015**, *80*, 1866-1870.

[40] C. Chong, Q. Zhang, J. Ke, H. Zhang, X. Yang, B. Wang, W. Ding, Z. Lu, *Angew. Chem., Int. Ed.* **2021**, *60*, 13807-13813.

[41] J. Justicia, J. E. Oltra, J. M. Cuerva, *J. Org. Chem.* **2004**, *69*, 5803-5806.

[42] A. G. González, J. D. Martín, M. L. Rodríguez, *Tetrahedron Lett.* **1973**, *14*, 3657-3660.

[43] E. J. Corey, J. Das, *J. Am. Chem. Soc.* **1982**, *104*, 5551-5553.

[44] A. S. Sarma, P. Chattopadhyay, *J. Org. Chem.* **1982**, *47*, 1727-1731.

[45] a) E. P. Locke, S. M. Hecht, *Chem. Commun.* **1996**, 2717-2718; b) J. An, D. F. Wiemer, *J. Org. Chem.* **1996**, *61*, 8775-8779; c) J. Sakurai, T. Oguchi, K. Watanabe, H. Abe, S.-i. Kanno, M. Ishikawa, T. Katoh, *Chemistry – A European Journal* **2008**, *14*, 829-837.

[46] K. Watanabe, J. Sakurai, H. Abe, T. Katoh, *Chem. Commun. (Cambridge, U. K.)* **2010**, *46*, 4055-4057.

[47] T. Taishi, S. Takechi, S. Mori, *Tetrahedron Lett.* **1998**, *39*, 4347-4350.

[48] M. Nakatani, M. Nakamura, A. Suzuki, M. Inoue, T. Katoh, *Org. Lett.* **2002**, *4*, 4483-4486.

[49] J. Sakurai, T. Kikuchi, O. Takahashi, K. Watanabe, T. Katoh, *Eur. J. Org. Chem.* **2011**, *2011*, 2948-2957.

[50] a) T. Ling, E. Poupon, E. J. Rueden, S. H. Kim, E. A. Theodorakis, *J. Am. Chem. Soc.* **2002**, *124*, 12261-12267; b) T. Ling, E. Poupon, E. J. Rueden, E. A. Theodorakis, *Org. Lett.* **2002**, *4*, 819-822.

[51] I. S. Marcos, A. Conde, R. F. Moro, P. Basabe, D. Díez, J. G. Urones, *Tetrahedron* **2010**, *66*, 8280-8290.

[52] a) R. J. Capon, *J. Nat. Prod.* **1990**, *53*, 753-756; b) S. Urban, R. Capon, *Aust. J. Chem.* **1994**, *47*, 1023-1029; cV. Lakshmi, S. P. Gunasekera, F. J. Schmitz, X. Ji, D. Van der Helm, *J. Org. Chem.* **1990**, *55*, 4709-4711.

[53] M. Nakamura, A. Suzuki, M. Nakatani, T. Fuchikami, M. Inoue, T. Katoh, *Tetrahedron Lett.* **2002**, *43*, 6929-6932.

[54] Y. Wu, X. Du, X. Wang, H. Liu, L. Zhou, Y. Tang, D. Li, *Org. Chem. Front.* **2022**, *9*, 4705-4711.

[55] K. Speck, R. Wildermuth, T. Magauer, *Angew. Chem., Int. Ed. Engl.* **2016**, *55*, 14131-14135.

[56] F.-L. Haut, K. Speck, R. Wildermuth, K. Möller, P. Mayer, T. Magauer, *Tetrahedron* **2018**, *74*, 3348-3357.

[57] R. Wildermuth, K. Speck, F. L. Haut, P. Mayer, B. Karge, M. Bronstrup, T. Magauer, *Nat Commun* **2017**, *8*, 2083.

[58] D. T. Ngoc, M. Albicker, L. Schneider, N. Cramer, *Org. Biomol. Chem.* **2010**, *8*, 1781-1784.

[59] F. Jiménez, A. Fernández, E. Boulifa, A. I. Mansour, R. Alvarez-Manzaneda, R. Chahboun, E. Alvarez-Manzaneda, *J. Org. Chem.* **2017**, *82*, 9550-9559.

[60] X. Yin, M. Mato, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2017**, *56*, 14591-14595.

[61] D. Faustman, M. Davis, *Nat. Rev. Drug Discovery* **2010**, *9*, 482.

[62] J. Baars, I. Grimm, D. Blunk, J.-M. Neudörfl, H.-G. Schmalz, *Angew. Chem., Int. Ed.* **2021**, *60*, 14915-14920.

[63] C. Chong, L. Chang, I. Grimm, Q. Zhang, Y. Kuang, B. Wang, J. Kang, W. Liu, J. Baars, Y. Guo, H. G. Schmalz, Z. Lu, *Chemical Science* **2023**.

[64] J. L. Baars, PhD thesis, University of Cologne **2022**.

[65] K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem., Int. Ed. Engl.* **2006**, *45*, 7134-7186.

[66] a) O. F. Jeker, A. G. Kravina, E. M. Carreira, *Angew. Chem., Int. Ed.* **2013**, *52*, 12166-12169; b) Y. Tian, X. Xu, L. Zhang, J. Qu, *Org. Lett.* **2016**, *18*, 268-271; c) G. Rajendar, E. J. Corey, *J. Am. Chem. Soc.* **2015**, *137*, 5837-5844; d) S. V. Pronin, R. A. Shenvi, *Nat. Chem.* **2012**, *4*, 915; e) Q. Zhang, K. Tiefenbacher, *Nat. Chem.* **2015**, *7*, 197; f) M. J. Geier, M. R. Gagné, *J. Am. Chem. Soc.* **2014**, *136*, 3032-3035; g) Z. Yang, H. Li, L. Zhang, M.-T. Zhang, J.-P. Cheng, S. Luo, *Chem. - Eur. J.* **2015**, *21*, 14723-14727; h) M. A. Schafroth, D. Sarlah, S. Krautwald, E. M. Carreira, *J. Am. Chem. Soc.* **2012**, *134*, 20276-20278; i) S. Rendler, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 5027-5029; j) S. G. Sethofer, T. Mayer, F. D. Toste, *J. Am. Chem. Soc.* **2010**, *132*, 8276-8277; k) K. Surendra, E. J. Corey, *J. Am. Chem. Soc.* **2012**, *134*, 11992-11994; l) R. R. Knowles, S. Lin, E. N. Jacobsen, *J. Am. Chem. Soc.* **2010**, *132*, 5030-5032.

[67] M. Uyanik, K. Ishihara, H. Yamamoto, *Org. Lett.* **2006**, *8*, 5649-5652.

[68] L. Zhu, J. Luo, R. Hong, *Org. Lett.* **2014**, *16*, 2162-2165.

[69] P. V. Fish, W. S. Johnson, *J. Org. Chem.* **1994**, *59*, 2324-2335.

[70] a) E. Chupakhin, O. Babich, A. Prosekov, L. Asyakina, M. Krasavin, *Molecules* **2019**, *24*, 4165; b) Y. Zheng, C. M. Tice, S. B. Singh, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3673-3682; c) K. Hiesinger, D. Dar'in, E. Proschak, M. Krasavin, *J. Med. Chem.* **2021**, *64*, 150-183; d) P. Saraswat, G. Jeyabalan, M. Z. Hassan, M. U. Rahman, N. K. Nyola, *Synth. Commun.* **2016**, *46*, 1643-1664.

[71] a) R. Rios, *Chem. Soc. Rev.* **2012**, *41*, 1060-1074; b) K. Babar, A. F. Zahoor, S. Ahmad, R. Akhtar, *Mol. Diversity* **2021**, *25*, 2487-2532; c) C. Marti, Erick M. Carreira, *Eur. J. Org. Chem.* **2003**, *2003*, 2209-2219; dL. K. Smith, I. R. Baxendale, *Org. Biomol. Chem.* **2015**, *13*, 9907-9933.

[72] A. St. Pfau, P. A. Plattner, *Helv. Chim. Acta* **1939**, *22*, 640-654.

[73] aJ. A. Marshall, P. C. Johnson, *J. Am. Chem. Soc.* **1967**, *89*, 2750-2751; bJ. A. Marshall, P. C. Johnson, *Chem. Commun. (London)* **1968**, 391-392.

[74] W.-C. Su, J.-M. Fang, Y.-S. Cheng, *Phytochemistry* **1993**, *34*, 779-782.

[75] a) T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin, S. Kagawa, F. Sakan, S. Matsumoto, S. Nishida, *J. Am. Chem. Soc.* **1968**, *90*, 3280-3281; b) T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin, S. Kagawa, F. Sakan, K. Miyano, *Tetrahedron Lett.* **1971**, *12*, 2049-2052.

[76] C. A. L. Bercht, J. P. C. M. van Dongen, W. Heerma, R. J. J. Ch. Lousberg, F. J. E. M. Küppers, *Tetrahedron* **1976**, *32*, 2939-2943.

[77] L. Crombie, P. Tuchinda, M. J. Powell, *J. Chem. Soc., Perkin Trans. 1* **1982**, 1477-1484.

[78] N. R. Natale, B. E. Marron, E. J. Evain, C. D. Dodson, *Synth. Commun.* **1984**, *14*, 599-603.

[79] F. S. El-Feraly, Y.-M. Chan, *J. Nat. Prod.* **1981**, *44*, 557-561.

[80] H. Wolf, M. Kolleck, *Synth. Commun.* **1975**, *16*, 451-454.

[81] P. M. McCurry, R. K. Singh, *Tetrahedron Lett.* **1973**, *14*, 3325-3328.

[82] B. Yadav, B. Baire, *Adv. Synth. Catal.* **2022**, *364*, 4305-4309.

[83] R. Ciriminna, E. Falletta, C. Della Pina, J. H. Teles, M. Pagliaro, *Angew. Chem., Int. Ed.* **2016**, *55*, 14210-14217.

[84] Z. Li, C. Brouwer, C. He, *Chem. Rev.* **2008**, *108*, 3239-3265.

[85] S. A. Shahzad, M. A. Sajid, Z. A. Khan, D. Canseco-Gonzalez, *Synth. Commun.* **2017**, *47*, 735-755.

[86] R. Dorel, A. M. Echavarren, *Chem. Rev.* **2015**, *115*, 9028-9072.

[87] a) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180-3211; b) A. Quintavalla, M. Bandini, *ChemCatChem* **2016**, *8*, 1437-1453.

[88] A. Fürstner, P. W. Davies, *Angew. Chem., Int. Ed.* **2007**, *46*, 3410-3449.

[89] D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395-403.

[90] a) W. Zi, F. Dean Toste, *Chem. Soc. Rev.* **2016**, *45*, 4567-4589; b) L. Rocchigiani, M. Bochmann, *Chem. Rev.* **2021**, *121*, 8364-8451; cX. Zhao, M. Rudolph, A. S. K. Hashmi, *Chem. Commun.* **2019**, *55*, 12127-12135.

[91] D. Pflästerer, A. S. K. Hashmi, *Chem. Soc. Rev.* **2016**, *45*, 1331-1367.

[92] F. Bihelovic, R. N. Saicic, *Angew. Chem., Int. Ed.* **2012**, *51*, 5687-5691.

[93] B. Panda, T. K. Sarkar, *J. Org. Chem.* **2013**, *78*, 2413-2421.

[94] M. Gaydou, R. E. Miller, N. Delpont, J. Ceccon, A. M. Echavarren, *Angew. Chem., Int. Ed.* **2013**, *52*, 6396-6399.

[95] U. Uria, C. Vila, M.-Y. Lin, M. Rueping, *Chem. - Eur. J.* **2014**, *20*, 13913-13917.

[96] A. Wang, B. Wüstenberg, A. Pfaltz, *Angew. Chem., Int. Ed.* **2008**, *47*, 2298-2300.

[97] I. Grimm, Master thesis, University of Cologne **2019**.

[98] S. R. Wilson, R. N. Misra, G. M. Georgiadis, *J. Org. Chem.* **1980**, *45*, 2460-2468.

[99] L. A. Arnold, R. Imbos, A. Mandoli, A. H. M. de Vries, R. Naasz, B. L. Feringa, *Tetrahedron* **2000**, *56*, 2865-2878.

[100] M. Vuagnoux-d'Augustin, A. Alexakis, *Chem. - Eur. J.* **2007**, *13*, 9647-9662.

[101] D. H. Hua, Y. Chen, H.-S. Sin, M. J. Maroto, P. D. Robinson, S. W. Newell, E. M. Perchellet, J. B. Ladesich, J. A. Freeman, J.-P. Perchellet, P. K. Chiang, *J. Org. Chem.* **1997**, *62*, 6888-6896.

[102] U. Sudhir, B. James, S. Joly, M. S. Nair, *Res. Chem. Intermed.* **2003**, *29*, 523-532.

[103] H. Z. Kaplan, V. L. Rendina, J. S. Kingsbury, *J. Org. Chem.* **2013**, *78*, 4620-4626.

[104] Z. Li, C. Sheng, C. Yang, H. Qiu, *Org. Prep. Proced.* **2007**, *39*, 608-611.

[105] D. E. Kim, Y. Zhu, T. R. Newhouse, *Org. Biomol. Chem.* **2019**, *17*, 1796-1799.

[106] B. Barnych, J.-M. Vatèle, *Synlett* **2011**, *22*, 2048-2052.

[107] J. Furukawa, N. Kawabata, J. Nishimura, *Tetrahedron* **1968**, *24*, 53-58.

[108] K. R. R. Rick L. Danheiser, Hiroo Koyama, Stephen K. Gee, Carl R. Johnson, John R. Medich, *Org. Synth.* **1993**, *71*.

[109] H. Huo, K. Harms, E. Meggers, *J. Am. Chem. Soc.* **2016**, *138*, 6936-6939.

[110] D. L. J. Clive, S. R. Magnuson, H. W. Manning, D. L. Mayhew, *J. Org. Chem.* **1996**, *61*, 2095-2108.

[111] C. Sate B, J. A. Valderrama, R. Tapia, F. Farifia, M. C. Paredes, *Synth. Commun.* **1992**, *22*, 955-960.

[112] K. Yoshida, Y. Itatsu, Y. Fujino, H. Inoue, K.-i. Takao, *Angew. Chem., Int. Ed.* **2016**, *55*, 6734-6738.

[113] L. Crombie, W. M. L. Crombie, S. V. Jamieson, P. Tuchinda, A. J. Whitaker, *J. Chem. Soc., Perkin Trans. 1* **1982**, 1485-1491.

[114] aR. Sunnapu, S. N. Banoth, R. R. S, A. Thomas, N. Venugopal, G. Rajendar, *J. Org. Chem.* **2020**, *85*, 4103-4113; bS. D. Holmbo, S. V. Pronin, *J. Am. Chem. Soc.* **2018**, *140*, 5065-5068.

[115] M. J. Petersson, C. Marchal, W. A. Loughlin, I. D. Jenkins, P. C. Healy, A. Almesåker, *Tetrahedron* **2007**, *63*, 1395-1401.

[116] C. Kong, N. Jana, C. Jones, T. G. Driver, *J. Am. Chem. Soc.* **2016**, *138*, 13271-13280.

[117] N. Jana, S. Nanda, *Eur. J. Org. Chem.* **2012**, *2012*, 4313-4320.

[118] R. Lihammar, R. Millet, J.-E. Baeckvall, *J. Org. Chem.* **2013**, *78*, 12114-12120.

[119] a) J. Tillner, T. Winckler, T. Dingermann, *Pharmazie* **1994**, *49*, 759-761; b) R. Voisard, P. C. Dartsch, U. Seitzer, D. Roth, M. Kochs, V. Hombach, *Vasa Suppl.* **1991**, *33*, 140-141.

[120] a) I. Nicoletti, G. Migliorati, M. C. Pagliacci, F. Grignani, C. Riccardi, *J. Immunol. Methods* **1991**, *139*, 271-279; b) F. Essmann, T. Wieder, A. Otto, E.-C. Müller, B. Dörken, P. T. Daniel, *Biochem. J* **2000**, *346*, 777-783.

[121] S. L. Rössler, B. S. Schreib, M. Ginterseder, J. Y. Hamilton, E. M. Carreira, *Org. Lett.* **2017**, *19*, 5533-5536.

[122] T. Imamoto, Y. Sugiura, N. Takiyama, *Synth. Commun.* **1984**, *25*, 4233-4236.

[123] J. Cvengroš, S. Neufeind, A. Becker, H.-G. Schmalz, *Synlett* **2008**, *2008*, 1993-1998.

[124] M. Hofmann, N. Hampel, T. Kanzian, H. Mayr, *Angew. Chem., Int. Ed.* **2004**, *43*, 5402-5405.

[125] S. A. Snyder, D. S. Treitler, A. P. Brucks, *J. Am. Chem. Soc.* **2010**, *132*, 14303-14314.

6.6 EIDESSTATTLICHE ERKLÄRUNG

„Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertation mit dem Titel "**Enantioselective total synthesis of marine meroditerpenes with anti-inflammatory and anti-tumor activity**" 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:

J. Baars, I. Grimm, D. Blunk, J.-M. Neudörfl, H.-G. Schmalz, *Angew. Chem., Int. Ed.* **2021**, *60*, 14915-14920.

C. Chong, L. Chang, I. Grimm, Q. Zhang, Y. Kuang, B. Wang, J. Kang, W. Liu, J. Baars, Y. Guo, H.-G. Schmalz, Z. Lu, *Chem. Sci.* **2023**, *14*, 3302-3310.

28.04.2023, Isabelle Grimm 

6.7 CURRICULUM VITAE

Name	Isabelle Grimm
Date of birth	09.05.1994
Place of birth	Birkenfeld (Germany)
Nationality	German

Education

12/2019 – 07/2023	PhD Studies in organic chemistry under supervision of Prof. Dr. Hans-Günther Schmalz, University of Cologne
10/2017 – 09/2019	Master studies, University of Cologne Master's thesis: „Studies towards the total synthesis of dysiherbol A via cationic twofold cyclization"
10/2013 – 08/2017	Bachelor studies, University of Cologne Bachelor's thesis: „Synthese eines oxiranverbrückten Peptidmimetikums mit PPII-Helix-Konformation"
08/2004 – 06/2010	Abitur, Gymnasium Birkenfeld
08/2004 – 06/2010	Secondary education, Realschule Baumholder

Scholarships

03/2020 – 03/2023	Jürgen Manchot Foundation
10/2013 – 09/2019	Kalyandjian-Conrad foundation