Stereoselective C–C Bond Formations: Syntheses and Applications of Dendritic Organocatalysts and Polycyclic Hydrocarbon Scaffolds

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Synthesis of Highly Enantioenriched Propelladienes and their Application as Ligands in Asymmetric Rh-Catalyzed 1,4-Additions. **T. Pecchioli** and M. Christmann, *Org. Lett.* **2018**, *20*, 5256–5259.

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Abstract

The present work consists of two different parts in which the synthesis and application of a dendritic hyperbranched polyglycerol supported organocatalysts and of enantioenriched polycyclic hydrocarbon scaffolds are described.

In the first part, the efficiency of hyperbranched polyglycerol (PG) as a dendritic high loading platform for catalyst immobilization was evaluated in a study carried out in collaboration with Dr. MANOJ KUMAR MUTHYALA. Three different multivalent organocatalysts, characterized by a low (PG-30), an intermediate (PG-57) and a high degree (PG-95) of peripheral functionalization of the polymeric support, were synthesized using copper-catalyzed alkyne-azide cycloadditions. Their application in the asymmetric FRIEDEL–CRAFTS alkylation of *N*-methylpyrrole showed that multivalent PG-57 was the most active catalyst. The final recycling of PG-57 demonstrated that hyperbranched polyglycerol is an efficient and convenient support for organocatalysts immobilization.

In the second part, the synthesis of large-ring propellanes and of a bridgehead bicyclo[4.4.4]tetradecadiene starting from closely related bicyclic frameworks are reported.

The preparation of propellanes was carried out in collaboration with Dr. LISA M. SCHNEIDER and Dr. VOLKER M. SCHMIEDEL. Conjugate additions of vinyl cuprates to HAJOS–PARRISH and WIELAND–MIESCHER ketone derivatives, followed by ring-closing metathesis, gave access to the propellanes. This methodology was applied for obtaining highly enantioenriched (>99% *ee*) propelladienes as new chiral steering ligands for metal-catalyzed transformations. It was observed that the application of rigid polycyclic scaffolds in the asymmetric Rh-catalyzed arylation of cyclic enones led to a high turnover frequency of the active catalyst.

The highly strained bridgehead bicyclo[4.4.4]tetradecadiene was prepared through skeletal rearrangement of a bicyclic WIELAND–MIESCHER derivative. A tandem sigmatropic reaction was used to install the two bridgehead double bonds. Finally, strain-driven intramolecular C–C bond formations permitted the synthesis of bridged medium-sized carbocycles from the caged diene in a diversity-oriented fashion.

Acknowledgements

Firstly, I would like to express my gratitude to Professor Mathias Christmann for giving me the opportunity to carry out my doctoral studies in his research group and for his guidance and prolific insights provided during these years. I am truly grateful to Professors Hans-Ulrich Reißig and Andrea Goti for giving me the possibility to do research at the Freie Universität Berlin, without their support I would not be able to comprehend unique features that this amazing city has to offer.

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Kurzfassung

Die vorliegende Arbeit ist aus zwei verschiedenen Teilen zusammengesetzt. Zum Einen wird die Synthese und Anwendung von an dendritisch Polyglycerol immobilisierten konjugierten Organokatalysatoren beschrieben und zum Anderen die Darstellung von enantiomerenangereicherten polycyclischen Kohlenwasserstoffgerüsten untersucht.

Im ersten Projekt wurde in Zusammenarbeit mit Dr. MANOJ KUMAR MUTHYALA die Effizienz von hochverzweigtem Polyglycerin (PG) als dendritisch Trägermaterial für die Katalysatorimmobilisierung untersucht. Drei verschiedene multivalente Organokatalysatoren wurden *via* kupferkatalysierter Alkin-Azid-Cycloaddition synthetisiert. Sie unterschieden sich durch ein niedriges (PG-30), ein mittleres (PG-57) und ein hohes Maß (PG-95) der peripheren Funktionalisierung des polymeren Trägers. Bei deren Anwendung in der asymmetrischen FRIEDEL–CRAFTS-Alkylierung von *N*-Methylpyrrol zeigte sich, dass das multivalente PG-57 am aktivsten war. Zudem konnte gezeigt werden, dass die immobilisierten Organokatalysatoren leicht abgetrennt und recycelt werden können für zwei Zyklen. Die Ergebnisse demonstrieren, dass hochverzweigtes Polyglycerin eine effizientes Trägermaterial für die Immobilisierung von Organokatalysatoren darstellt.

Im zweiten Teil sind die Synthesen von Großring-Propellanen und von einem Brückenkopf-Bicyclo[4.4.4]tetradecadien ausgehend von eng verwandten bicyclischen Gerüsten beschrieben.
Die Herstellung der Propellane erfolgte in Zusammenarbeit mit Dr. LISA M. SCHNEIDER und Dr. VOLKER M. SCHMIEDEL. Die konjugierte Addition von Vinylcupraten an hajos–parrish- und wieland–miescher-Ketonderivaten, gefolgt von einer Ringschlussmetathese ermöglichte die Darstellung von Propellanen. Diese Methode wurde ebenfalls angewendet, um hoch enantiomerenangereicherte (>99% ee) Propelladiene als neue chirale Dienliganden für metallkatalysierte Reaktionen zu erhalten. Es wurde beobachtet, dass die Anwendung von starren polycyclischen Gerüsten in der asymmetrischen Rh-katalysierten Arylierung von cyclischen Enonen zu einer hohen Umsatzfrequenz des aktiven Katalysators führte.

Die hoch gespanntes Brückenkopf-Bicyclo[4.4.4]tetradecadien konnte durch die Gerüstumlagerung eines bicyclischen WIELAND–MIESCHER-Decalins erreicht werden. Die spannungsgesteuerte intrinsische C–C-Brückenbindungsbildung generierte in einer Diversitäts-orientierten Weise verbrückten, mittelgroßen Carbocyclen aus dem Käfig-Dien.

I would like to thank Dr. Matthias Henrot, Dr. Timon Kurzawa, Dr. Martina Menger and Dr. Reinhold Zimmer for the correction and proofreading of this thesis.

I would like to express my gratitude to Dr. Mathias Henrot and Matteo Accorsi for the time spent together in these years in both scientific and leisure contexts. In particular, I acknowledge Matteo for all the prolific discussion we enjoyed.

Ringrazio con tutto il cuore i miei più cari amici che ho avuto fortuna di apprezzare nella mia vita italiana. Vi ringrazio per aver sopportato la mia irritabilità e mancanza di pazienza. Mi dispiace di essere stato assente in molte occasioni e di non aver contribuito abbastanza nel corso di questi anni. Grazie mille.

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Contents

Abbreviations and Symbols

$[\alpha]_d^{26}$	specific rotation, d = sodium lamp, 26 = temperature in °C
°C	degree Celsius
Ac	acetyl
Acac	acetylacetonate
anhydr.	anhydrous
Ar	aryl
Bn	benzyl
c	concentration in g/mL
cal	calorie
cat.	catalyst
COSY	correlation spectroscopy
CuAAC	copper-catalyzed alkyne-azide cycloaddition
Cy	cyclohexyl
d	days
d.r.	diastereomeric ratio
Da	Dalton
DB	degree of branching
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
ee	enantiomeric excess

ESI	electrospray ionization
Et	ethyl
FG	functional group
g	gram
G	polymer generation
h	hours
HMBC	heteronuclear multiple bond correlation
HPG	hyperbranched polyglycerol
HRMS	high resolution mass spectrometry
Hz	Hertz
^{i}Bu	*iso*-butyl
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
$LiAlH_4$	lithium aluminum hydride
LiHMDS	lithium bis(trimethylsilyl)amide
M	molar concentration: mol/L
m.p.	melting point
m/z	mass-to-charge ratio
Me	methyl
MI	multivalent interactions
min	minutes
mol	mole
MOM	methoxymethyl ether
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine *N*-oxide

NMR	nuclear magnetic resonance
PAMAM	polyamido amine
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PDI	polydispersity index
PG	polyglycerol
Ph	phenyl
PPD	propelladiene
PPI	polypropylene imine
ppm	parts per million
PS	polystyrene
p-tol	*p*-tolyl
PTSA	*p*-toluenesulfonic acid
Py	pyridine
quant.	quantitative yield
R	general organic rest
r.t.	room temperature
RCM	ring-closing metathesis
R_f	retardation factor
ROMBP	ring-opening multi-branching polymerization
TBAF	tetrabutylammonium fluoride
^{t}Bu	*tert*-butyl
Tf	triflyl
THF	tetrahydrofuran
TLC	thin-layer chromatography

TMS	trimethylsilyl
TS	transition state
δ	chemical shift

Part I

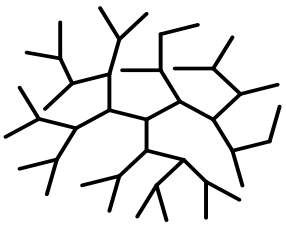
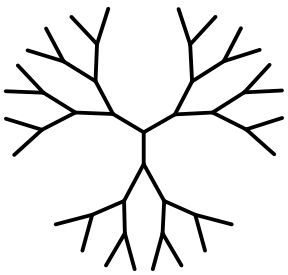
Dendritic Organocatalysts

1 Introduction

1.1 Dendritic Polymers

Dendritic polymers are globular macromolecules characterized by a radial evolution of a common structural element or monomer.[1] The periphery of these high loading platforms can be decorated with several molecular entities to prepare multivalent systems. These macromolecules are particularly appealing for catalysts immobilization since they combine the advantages of hetero- and homogeneous catalysis: efficient recovering using selective precipitation, dialysis or filtration techniques and high solubility in organic solvents, respectively. These globular polymers are divided in two main groups: structurally defined dendrimers and irregular hyperbranched polymers, whose main features are summarized in Table 1.[2] The degree of uniformity of these two supports is indicated using the branching degrees (DB), and the polydispersity index (PDI).

Table 1. Comparison between hyperbranched polymers and dendrimers.

polymer	hyperbranched	dendrimer
structure		
topology	3D, irregular	3D, regular
synthesis	one-step, relatively facile	multi-step, laborious
purification	Precipitation, dialysis or filtration	chromatography
scaling-up	easy	difficult
PDI	>1.1	1.0 (<1.05)
DB	0.4–0.6	1.0
organic solvents	high solubility	high solubility

DB is defined as ratio in percent of the sum of dendritic and terminal units to the total of units (dendritic, terminal and linear).[3] The values are ranging from 40% for the uneven hyperbranched polymers to 100% in case of the ideal dendrimers.[4, 2] The PDI is low for uniform macromolecules.[5] In dendrimers the PDI is usually below 1.05, due to the high regularity obtained using time-consuming multistep syntheses.[a] In the case of hyperbranched polymers, the PDI is higher due to lower control in the synthesis of this platform, which can be readily prepared on a large scale maintaining the high loading capacity and solubility characteristics of dendrimers.

1.1.1 Dendrimers

Dendrimers are highly ordered branched oligomers characterized by a "tree like" architecture. The number of peripheral groups of these macromolecules are directly related to the size and number of layered branched units, which are called generations (Figure 1).

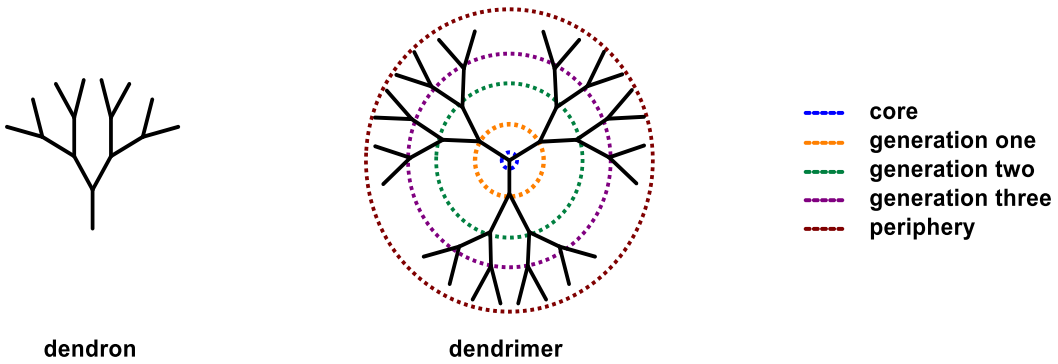


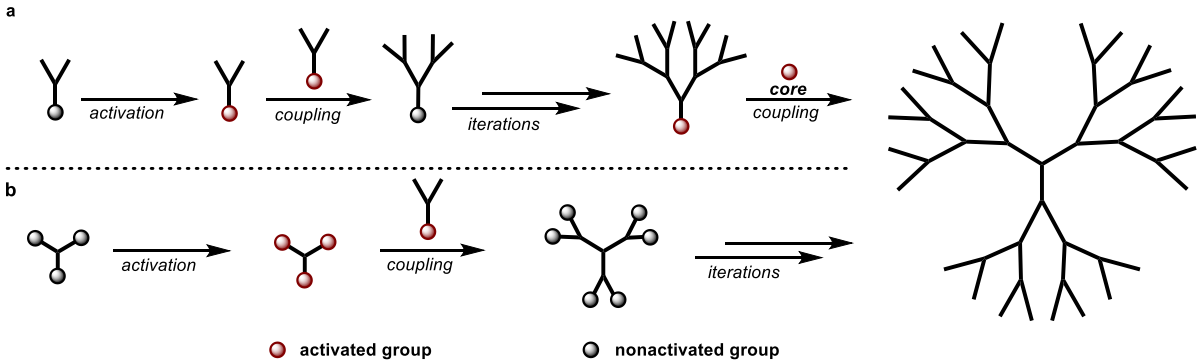
Figure 1. Macromolecular architecture of dendrimers.[6]

The preparation of these well-defined macromolecules requires high levels of control. For this reason, their synthesis is carried out using iterative synthetic procedures, either in a divergent or in a convergent approach. In both synthetic approaches, iterations of coupling and activation are used to avoid uncontrolled polymerizations.

In the convergent approach the single dendrons are assembled from the periphery toward the final central core (Scheme 1a). After completion, the obtained branches are attached to a polyfunctional core to give the final dendrimer. This method permits purification using chromatographic methods, thus giving monodisperse macromolecules. However, steric

[a] The polydispersity index (PDI) is defined as M_w/M_n, where M_w is the weight average (total sum of weight fraction x molecular weight of each type of macromolecule) and M_n is the number average molecular weight (total weight of the sample divided by the number of macromolecules).

inhibitions at the focal point limits this method to the synthesis of small polymers. On the other hand, the divergent approach requires construction of the polymers starting from the central core toward the periphery (Scheme 1b).

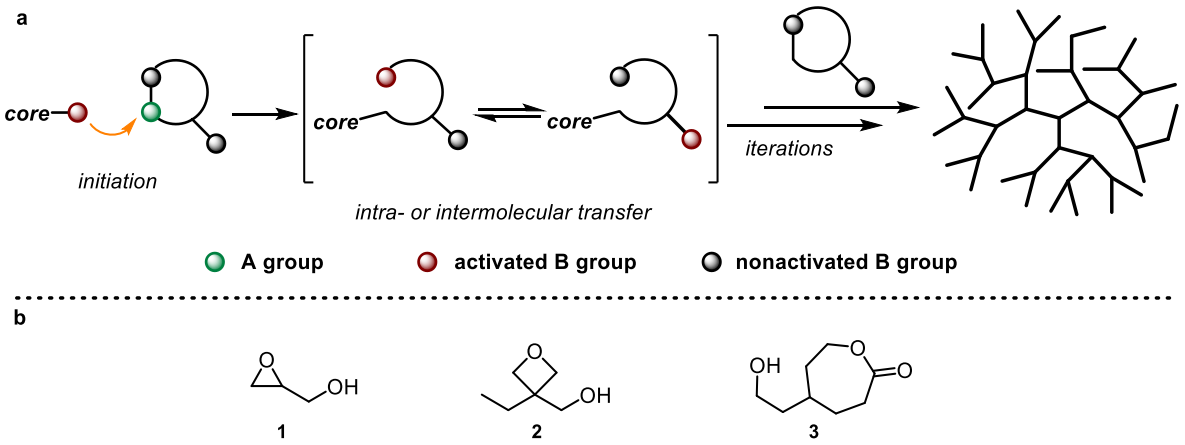


Scheme 1. Dendrimer syntheses. a) Convergent and b) divergent approaches.[7]

A large excess of reagents is needed to limit the incomplete growing, which enhance the degree of polydispersity. This method is convenient for practical syntheses on a large scale. The commercially available PPI (polypropylene imine) and PAMAM (polyamido amine) dendrimers are prepared on kilogram scale using a scalable divergent approach based on "click" 1,4-additions as coupling strategy.[8]

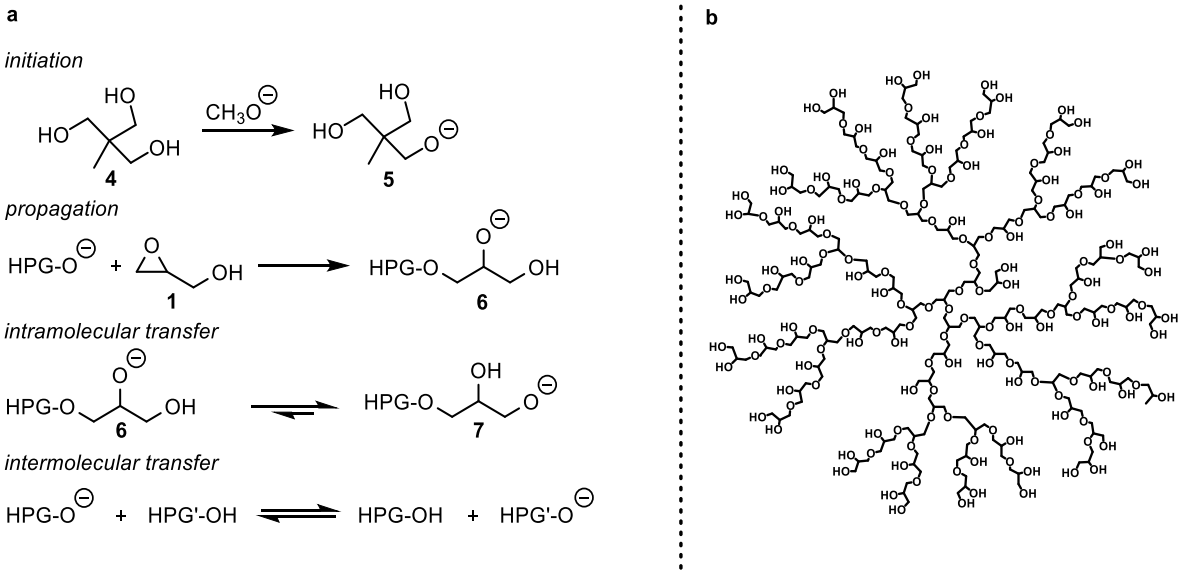
1.1.2 Hyperbranched Polymers

Hyperbranched polymers are a convenient alternative to the structurally perfect dendrimers. As previously mentioned, these dendritic architectures possess higher polydispersity ($1.1 < PDI < 7.01$) than the dendrimers while maintaining the advantages of solubility in organic solvents and high-loading capacity. They are easily synthesized starting from small monomers using one-pot polymerizations.[4a] The short procedure facilitates kilogram-scale production at lower manufacturing costs, thus making the hyperbranched polymers more appealing than the dendrimers for industrial applications. In particular, the use of a ring-opening multi-branching polymerization (ROMBP) of AB_m monomers allows for the synthesis of high-quality polymers with PDI often below 2.7.[9] In the case of AB_2 monomers, an initiator starts the polymerization by opening a cyclic monomer, such as epoxide **1**, oxetane **2** or lactone **3** (Scheme 2). Consequently, the activated acyclic monomer propagates the polymerization. Intra- and intermolecular transfers permit equilibration between the B groups, thus leading to branching of the growing polymer.



Scheme 2. ROMBP of AB_2 monomers. a) General mechanism. b) Common monomers.

For instance, hyperbranched polyglycerol (HPG) is prepared by anionic ring-opening polymerization using glycidol (**1**) as AB_2 monomer (Scheme 3).[10] Initially, the core triol **4** is deprotonated using catalytic amounts of alkoxides. In the propagation phase, the glycidol monomers are opened by the terminal alkoxides of the growing polymer. Intra- and intermolecular transfers activate the hydroxyl groups potentially suitable for branching.



Scheme 3. Hyperbranched polyglycerol. a) Synthesis. b) Macromolecular architecture.[10]

This method gives high-quality polymers with PDI up to 1.3. Moreover, the high density of hydroxyl groups located at the periphery of HPG makes this polymer an attractive hydrophilic platform for catalyst immobilization.

1.2 Multivalent Organocatalysts

In nature, multivalent interactions (MIs) are essential for the modulation of biological processes based on weak and reversible multiple bindings between two surfaces.[11] MIs are the result of cooperativity between the numerous molecular entities present at the surfaces.[12] The recent progress in the synthesis of high-loading platforms has stimulated investigation on multivalent effects in catalysis.[13] As introduced previously, dendritic architectures, such as hyperbranched polymers and regular dendrimers are soluble in a wide range of organic solvents, topologically globular, and rich in peripheral functional groups (Figure 2).[14] These features could promote cooperativity between the catalysts, reagents, and reactants which are in close proximity at the surface of the macromolecular support.[15]

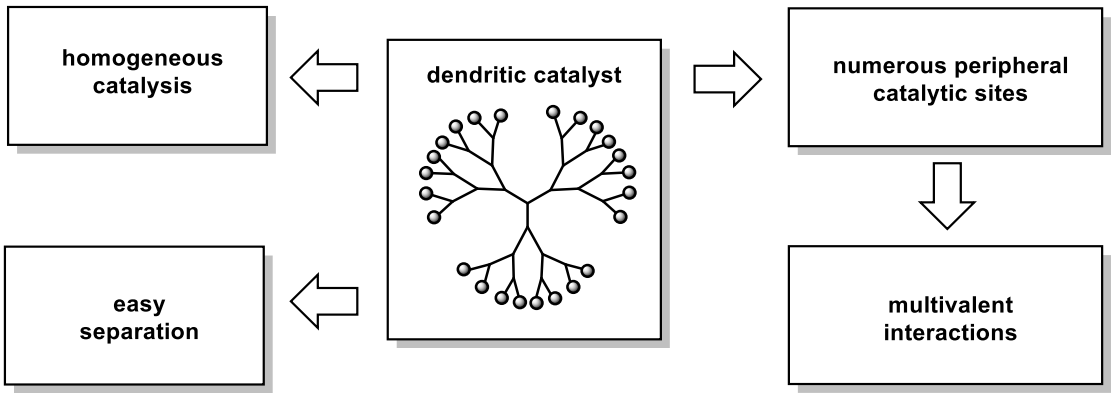
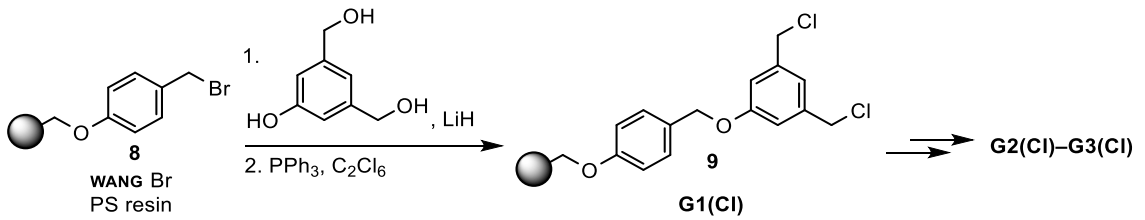


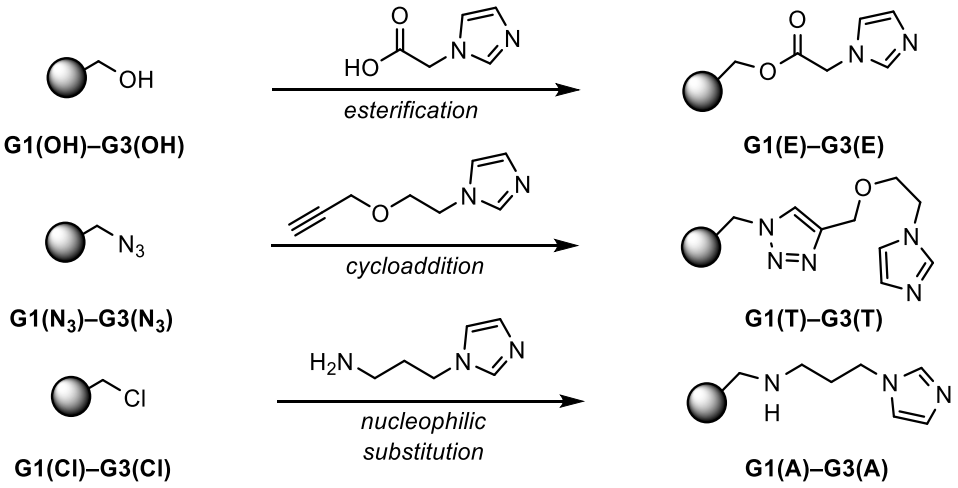
Figure 2. The benefit of dendritic supports for multivalent catalysts.[14]

Numerous dendritic architectures for metal catalyzed transformations have been extensively reviewed.[16, 13b] Nevertheless, dendritic supports and derivates have been seldom used for organocatalytic transformations, but are currently receiving increasing attention.[17] Recently, a collaboration between the groups of PORTNOY and MILLER led to the synthesis of dendritic *N*-alkylated imidazole catalysts immobilized on a polystyrene core (WANG resin).[17e] This type of multivalent support is a hybrid constituted by a central resin on which dendrons are coupled. Although the central polymeric unit makes this macromolecule not suitable for homogeneous catalysis, the presence of dendrons allowed dense functionalization at its periphery and investigation on dendritic effects. Different generations of polyether dendrons having a terminal activated benzyl chloride group, namely **G1(Cl)** to **G3(Cl)** in Scheme 4, were grafted from the polystyrene core **8** in a divergent fashion to produce multivalent platforms of different sizes.



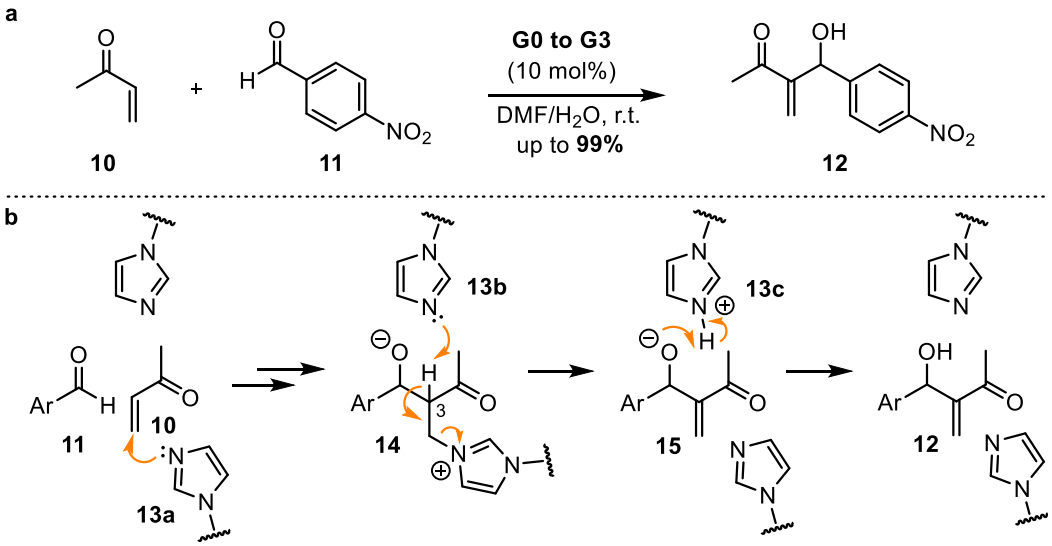
Scheme 4. Representative example of the preparation of dendronized polymers (**G1(Cl)** to **G3(Cl)**) by the groups of MILLER and PORTNOY.

The imidazole catalysts were immobilized using highly efficient ("click") alternative strategies: esterification, copper catalyzed azide-alkyne cycloaddition and nucleophilic substitution (Scheme 5).[8c] In this way, different series of **G1–G3** ester (**E**), triazole (**T**) and amine (**A**) based multivalent catalysts were prepared. The **G0** analogs were obtained by direct immobilization of the catalyst on the WANG PS followed by removal of the PS residue.



Scheme 5. Immobilization of *N*-alkylimidazole units onto dendronized polymers.

The three series of multivalent catalysts (**E**, **T** and **A**) were evaluated in the BAYLIS–HILLMAN reaction between methyl vinyl ketone (**10**) and aldehyde **11** (Scheme 6a). The secondary amine catalysts (**G1–G3**, **A** series) exhibited the best reaction rates, and, the use of **G3(A)** permitted to reduce the catalyst loading for this transformation from 10 to 1 mol%. This significant multivalent effect likely derived from the assistance of neighboring imidazole moieties during the reaction rate-determining step (Scheme 6b). After addition of enone **10** to aldehyde **11** catalyzed by **13a**, a second imidazole **13b** deprotonated the intermediate **14** at C-3. A final proton transfer from **13c** to **15** formed the desired product **12**. The improved efficiency of the higher generation could be ascribed to enhanced active catalysts crowding at the periphery of the multivalent system.



Scheme 6. Multivalent *N*-alkylimidazole based organocatalysts. a) Application in the BAYLIS–HILLMAN reaction. b) Proposed cooperative effect in catalysis.

A beneficial water effect was also reported. The authors commented that water played a role only as cosolvent favoring penetration of the reagents into the hydrophobic polymer. Finally, the advantage of the resin was showed in the recycling and reuse of the heterogeneous catalysts by simple filtration. The reuse of the polymer led to a 10% deterioration in catalyst activity upon each catalytic cycle. These results strongly evidenced the beneficial effects of multivalent interaction in organocatalysis. However, the use of these dendronized polymers showed drawbacks such as the resulting heterogeneous reaction conditions and the restricted effect of water as cosolvent. Therefore, additional investigation on hydrophilic supports soluble in organic media would be of interest for this developing field. Moreover, high local concentrations of water near the catalytic sites could lead to the appearance of additional cooperative effects.

2 Implementation of the Work

2.1 Aim of the Work

Dendritic architectures possess a globular structure which can be exploited for catalysts immobilization at the polymer surface. The use of such multivalent systems in catalysis could lead to cooperativity between the active species present in high concentration at their periphery. This effect could promote novel mechanisms of action which are not possible in monovalent systems. As previously described, the groups of MILLER and PORTNOY demonstrated the significance of multivalency in organocatalytic transformations by using dendronized catalysts.[17e] In their studies, also a positive influence of water on reaction rates was observed. However, the heterogeneous reaction conditions and the poor swelling property of the polystyrene core led the author to consider a sole cosolvent effect of water. Given the recognized importance of water in organocatalytic reactions with regard to reaction rates and selectivity,[18] the use of hydrophilic dendritic supports could promote positive effects due to the water assistance in the catalytic cycle.

The present work aims at investigating the effect of hydrophilic hyperbranched polyglycerol as multivalent support for organocatalyst immobilization. To carry out this study, the FRIEDEL–CRAFTS alkylations of *N*-methylpyrrole catalyzed by imidazolidin-4-one was chosen as test reaction. Initially, the solubility of the multivalent system in suitable organic solvents would be assessed through the preparation of catalysts possessing different degree of peripheral functionalization. Subsequently, the influence of water on the performance of the catalytic systems would be evaluated. Finally, the multivalent catalysts would be compared with a monovalent dendritic analog and the original organocatalyst to evaluate the appearance of cooperative effects.

2.2 List of Publications

2.2.1 Multivalent Polyglycerol Supported Imidazolidin-4-one Organocatalysts for Enantioselective Friedel–Crafts Alkylations

TOMMASO PECCHIOLI, MANOJ KUMAR MUTHYALA, RAINER HAAG* and MATHIAS CHRISTMANN*

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https://dx.doi.org/10.3762/bjoc.11.83.

Abstract

The first immobilization of a MACMILLAN'S first generation organocatalyst onto dendritic support is described. A modified tyrosine-based imidazolidin-4-one was grafted to a soluble high-loading hyperbranched polyglycerol via a copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) reaction and readily purified by dialysis. The efficiency of differently functionalized multivalent organocatalysts PG-30, PG-57 and PG-90 was tested in the asymmetric FRIEDEL–CRAFTS alkylation of *N*-methylpyrrole with *α,β*-unsaturated aldehydes. A variety of substituted enals was investigated to explore the activity of the catalytic system which was also compared with monovalent analogues. The catalyst PG-57 showed excellent turnover rates and no loss of activity due to immobilization, albeit moderate enantioselectivities were observed. Moreover, easy recovery by selective precipitation allowed the reuse of the catalyst for three cycles.

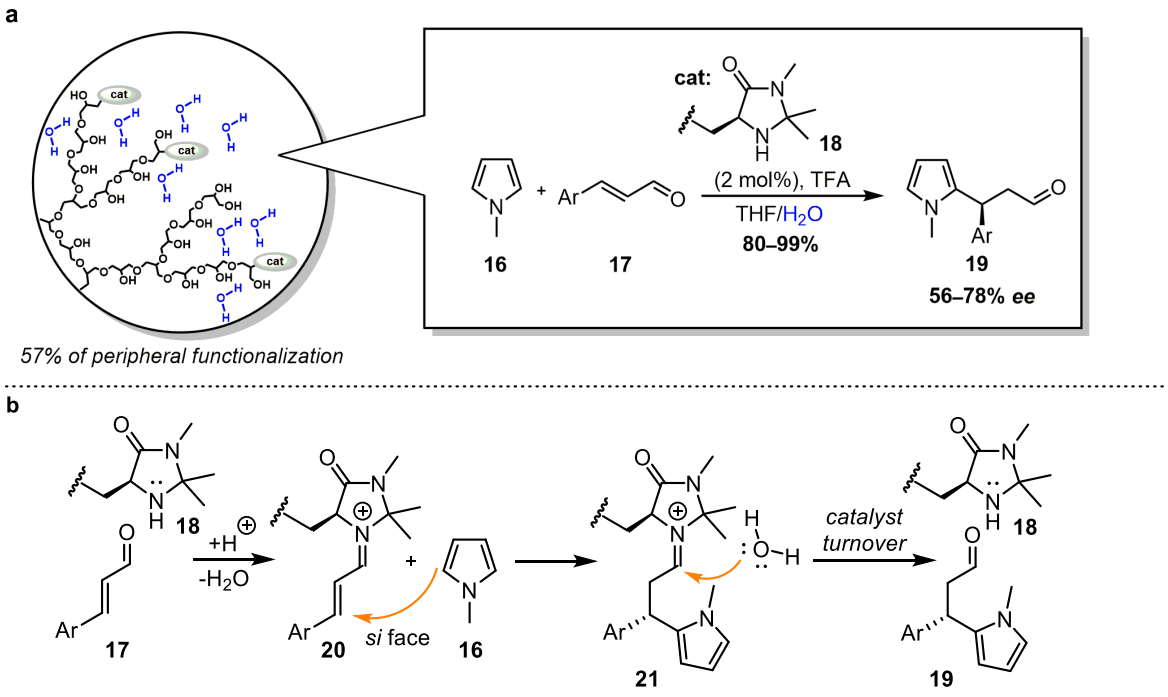
Keywords: FRIEDEL–CRAFTS; homogeneous catalysis; hyperbranched polyglycerol; imidazolidin-4-one; multivalency.

Author Contributions

The present work was carried out in the laboratories of Prof. Dr. M. CHRISTMANN and Prof. Dr. R. HAAG. The synthesis of the modified imidazolidine-4-one organocatalyst (compound **5** in the manuscript), screenings, reaction scope, and final recycling of the catalysts were carried out by T. PECCHIOLI. The co-author carried out immobilization of the organocatalyst onto three different hyperbranched polymers and onto a hydrophilic dendron.

2.3 Summary

The first project of this doctoral work presents the use of hyperbranched polyglycerol as multivalent support for organocatalysts. A MACMILLAN's first catalyst generation was grafted onto the polymeric support via CuAAC. Three different multivalent organocatalysts possessing a high (95%; PG-95), intermediate (57%; PG-57), and low (30%; PG-30) degree of functionalization at the periphery of the dendritic architecture and a monovalent analog were prepared. The catalysts were tested in the asymmetric FRIEDEL–CRAFTS alkylations of *N*-methylpyrrole (**16**) with *α,β*-unsaturated aldehydes **17** to give the enantioenriched aldehydes **19** (Scheme 7a). The reaction likely proceeded through initial acid catalyzed formation of iminium ion **20** accompanied by water elimination (Scheme 7b). Subsequently, the 1,4-addition of pyrrole **16** occurred from the less sterically hindered *si* face of **20** to give intermediate **21**. At this point, hydrolysis of iminium ion **21** released the desired product **19** and catalyst **18**.



Scheme 7. Multivalent hyperbranched polyglycerol based organocatalysts. a) Application of PG-57 in the FRIEDEL–CRAFTS alkylations of **16**. b) Reaction mechanism.

An initial screening of the reaction conditions showed that PG-30 was barely soluble in tetrahydrofuran and revealed a moderate influence of water on the reaction yields. Dilution experiments indicated that the multivalent catalysts were more efficient at lower concentrations (0.30 M) and that PG-57 was the more active system of the series. The

performance of the dendritic multi- and monovalent catalysts was compared with that of the original imidazolidin-4-one. This indicated that the presence of hydrophilic branches had a beneficial effect on the reaction yields. The positive effects could be ascribed to the high local concentrations of water which could facilitate the active organocatalyst turnover (Scheme 7b), thus excluding presence of additional cooperative effects between the active catalysts. Finally, the multivalent PG-57 was recovered at the end of the reaction by selective precipitation and reused for three cycles. A 10% deterioration in catalyst activity was observed upon each catalytic cycle. Although the use of the multivalent imidazolidine-4-ones in the FRIEDEL–CRAFTS alkylation exhibited poor multivalent effects, it has been demonstrated that hydrophilic hyperbranched polyglycerol is an efficient and convenient support for organocatalysts.

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Part II

Polycyclic Hydrocarbon Scaffolds

4 Introduction

4.1 Polycyclic Hydrocarbon Scaffolds

In the past century, organic chemists have extensively investigated the synthesis of bridged polycyclic aliphatic compounds.[1] These synthetic efforts were inspired by the aesthetic structures of these complex chemical entities. Nowadays, these molecules are approached from a new perspective by taking advantage of their physical and geometrical properties. Their rigidity and three-dimensional shapes have found application in the development of nanostructures for materials chemistry and ligands for asymmetric catalysis.[b, 2] In addition, the lipophilicity and stability of their carbon skeletons could bring positive effects on the pharmacokinetics of drug candidates. These features are significant at a time when drug discovery is turning its attention from flat-type, sp^2-based to complex sp^3-rich three-dimensional shaped molecules.[3]

Herein, the bridged polycyclic hydrocarbon scaffolds are classified through a structural analysis based on the topology and/or unsaturation of C–C bonds.

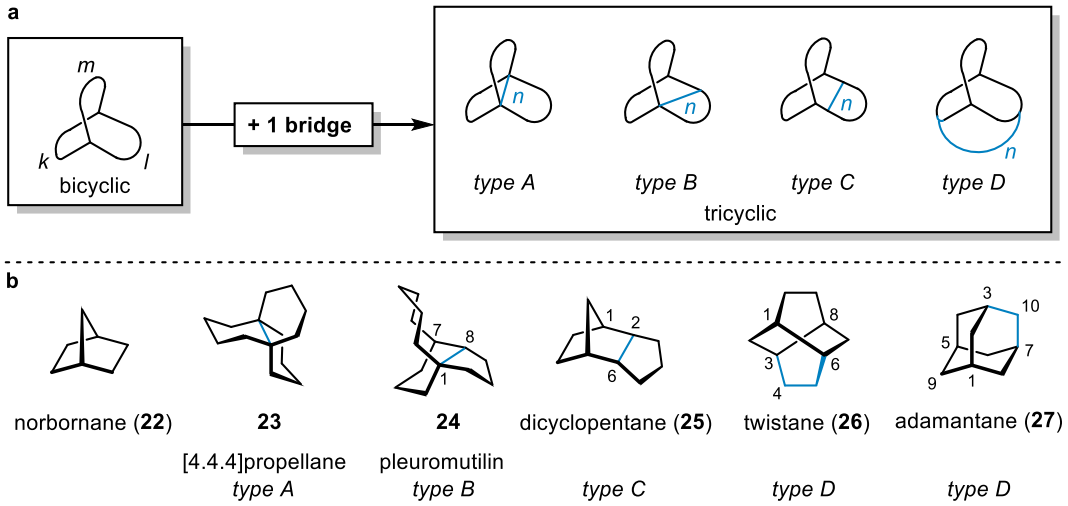
4.1.1 Saturated Bridged Polycyclic Scaffolds

The bicyclic framework is the simplest type of bridged hydrocarbon scaffold (Scheme 8a). Norbornane (**22**) is a prototypic example of bicyclic hydrocarbon (Scheme 8b). From basic bicyclic [k, l, m] structures, tricyclic [k, l, m, n] molecules with different bond connectivity are obtained by formal addition of a “n” bridge (Scheme 8a). Connection of the bridgehead atoms gives tricyclic molecules of *type A*, for instance, propellane **23** features a “zero bridge” between two quaternary carbons. If one bond is constructed from the bridgehead position toward one of the rings, a *type B* scaffold is obtained. The carbocyclic tricyclo[5.4.3.$0^{1,8}$]tetradecane core **24** of pleuromutilin antibiotics is a prominent example for this class of polycyclic compounds. A new connection within the same bridge gives *type C* skeletons, as shown in dicyclopentane (tricyclo[5.2.1.$0^{2,6}$]decane, **25**). Bond formation between different bridges leads to *type D* caged polycyclic scaffolds.[c] For instance, twistane (tricyclo[4.4.0.$0^{3,8}$]decane, **26**) and adamantane (tricyclo[3.3.1.$1^{3,7}$]decane, **27**) are

[b] Applications in materials chemistry are not discussed here.

[c] According to SCHLEYER, cage hydrocarbons can be defined as having three or more rings arranged topologically so as to enclose space in the center of the molecular structure. See ref 1.

symmetric caged hydrocarbons possessing an ellipsoid and a sphere-like shape, respectively. Higher polycyclic derivatives can be constructed following the same concept.[d]

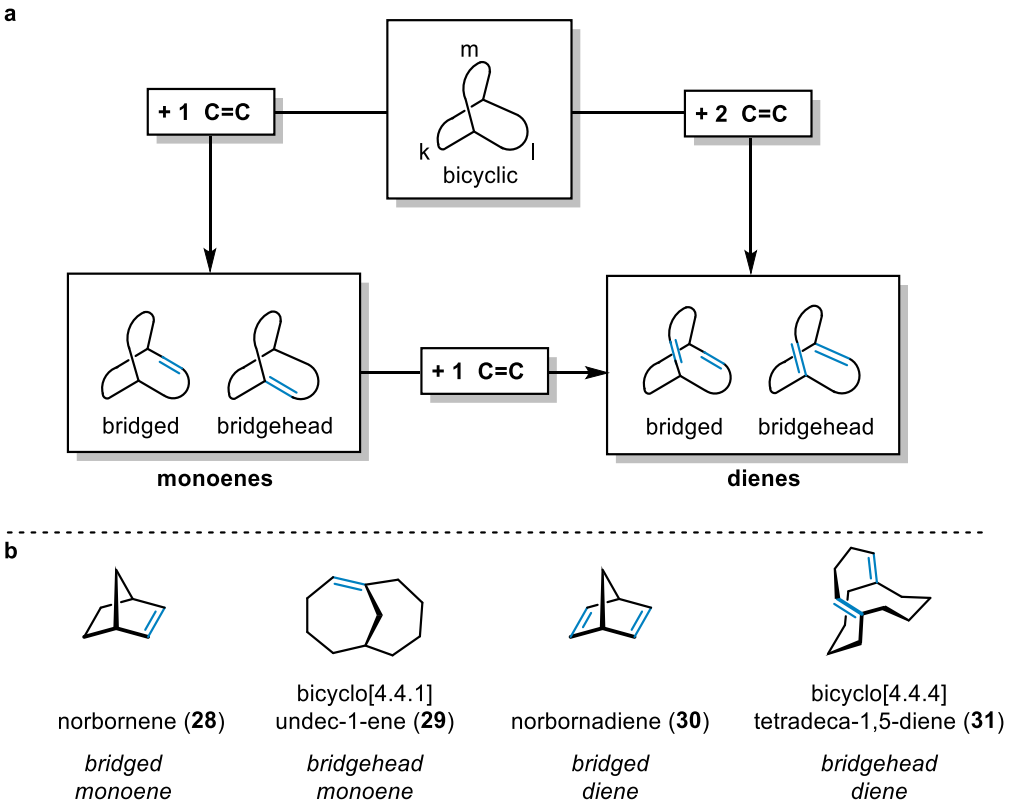


Scheme 8. Bicyclic and tricyclic bridged hydrocarbon scaffolds. a) Structural analysis. b) Representative examples.

4.1.2 Unsaturated Bridged Bicyclic Scaffolds

Alternative modifications on the basic bicyclic scaffold can be considered to access other subclasses of polycyclic molecules. Since olefins hold a central role in organic chemistry, formal additions of C–C double bonds can be operated to classify unsaturated bridged polycyclic frameworks. In general, the alkene moiety can be introduced on the bridges or on the bridgehead positions of basic bicyclic [k, l, m] structures (Scheme 9a). Addition of a double bond on one of the bridges gives *bridged monoenes*, as shown in norbornene (Scheme 9b, **28**). *Bridgehead monoenes* are characterized by the presence of a double bond at the ring junction. For instance, bicyclo[4.4.1]undec-1-ene (**29**) is a common structural motif of several biologically active sesterterpenoids isolated from a volcano ash-derived fungus *Penicillium citrinum*.[4] Starting from *bridged monoenes*, the corresponding dienes are obtained by introduction of an additional double bond.[e] *Bridged dienes* are used as ligands for transition metals: norbornadiene (**30**) is found in numerous commercially available complexes. Instead, *bridgehead dienes* are scarcely reported in the literature, probably in virtue of the synthetically challenging double bonds at the ring junctions. For instance, the 1,5-diene moiety of **31** has been targeted by several synthetic campaigns which failed in its preparation.[5]

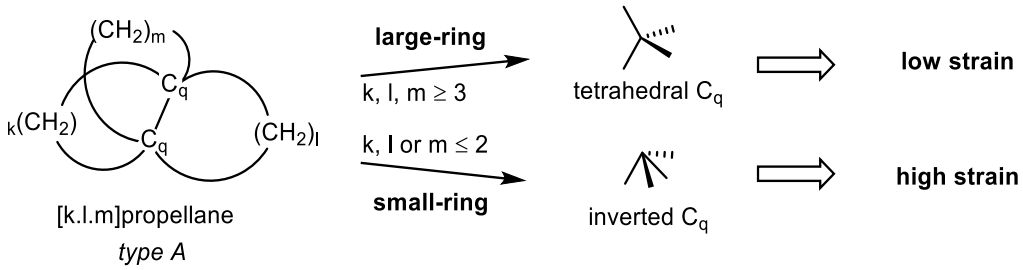
[d] Higher polycyclic molecules are not discussed here.
[e] For the construction of bicyclic dienes additional mixed topologies are not covered here.



Scheme 9. Unsaturated bicyclic hydrocarbon scaffolds. a) Structural analysis. b) Representative examples.

4.2 Propellanes

Propellanes are polycyclic molecules of *type A*. In these structures, the three rings share a common C_q–C_q bond.[6] Their trivial name was coined by GINSBURG in 1966 due to the propeller-like shape of these compounds.[7] These tricyclic molecules are divided into two subclasses characterized by the size of the three k, l and m bridges (Scheme 10). Large-ring propellanes (k, l and m $\geq$ 3) possess two tetrahedral quaternary carbons and are low strain polycyclic hydrocarbons.[8] On the other hand, small-ring propellanes (m $\leq$ 2) exhibit a certain degree of inversion from the classical tetrahedral geometry for the bridgehead carbons and show high and unusual chemical reactivity due to molecular strain.[9]

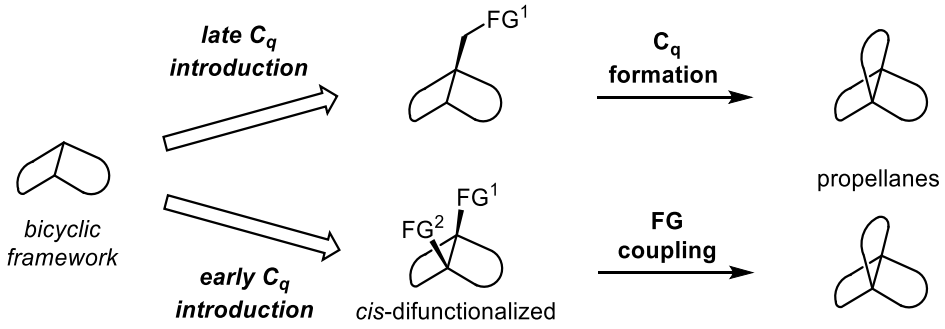


Scheme 10. General structure and classification of propellanes.

The cleavage of the central C–C bond in these strained propellanes generates the corresponding less strained bicyclic cages and causes relaxation of the bridgehead carbons to a tetrahedral geometry. For this reason, [1.1.1]propellane can be subjected to strain-release functionalization for preparing bicyclo[1.1.1]pentane derivatives as nonclassical bioisosteres of benzene for drug discovery.[9-10]

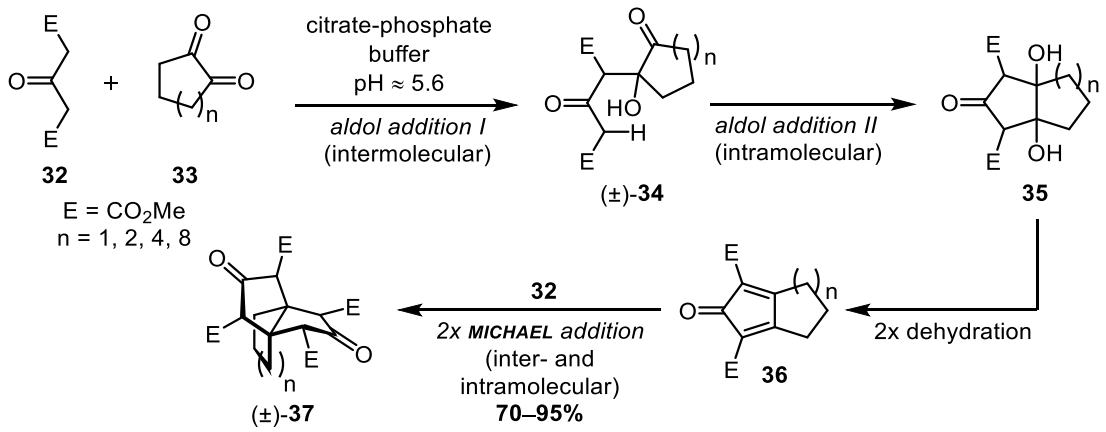
4.2.1 Synthesis of Large-Ring Propellanes

The synthesis of large-ring propellanes could be performed using two strategies distinguished by the stage in which the quaternary carbons are introduced into the molecular scaffold. The installation of both quaternary centers can occur prior to the final cyclization (*early C_q introduction,* Scheme 11) or be completed during the formation of the third ring (*late C_q introduction*).



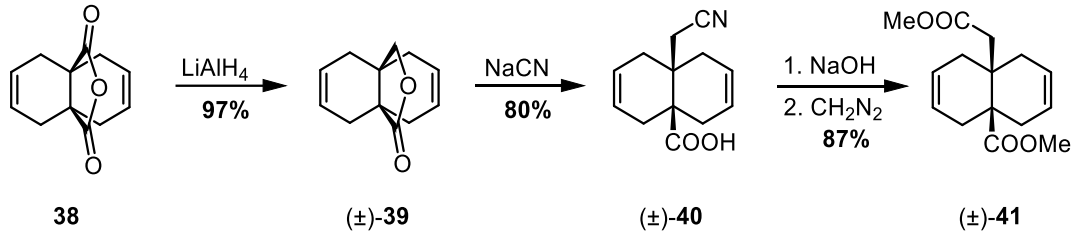
Scheme 11. Strategies for the synthesis of large-ring propellanes.

In 1978, the group of COOK[11] reported an entry to [k.3.3]propellanes (k = 3, 4, 6 and 10) using a *late C_q introduction* strategy (Scheme 12). A WEISS reaction of 1,2-diketones **33** with dimethyl 3-oxo-glutarate (**32**) was used to construct these tricyclic molecules of *type A*.[12] The reaction proceeded *via* tandem inter-/intramolecular aldol additions to form **35** which underwent double dehydration to cyclopentadienones **36**. At this point, a tandem inter-/intramolecular MICHAEL addition of glutarate **32** to acceptors **36** gave propellanes **37**.



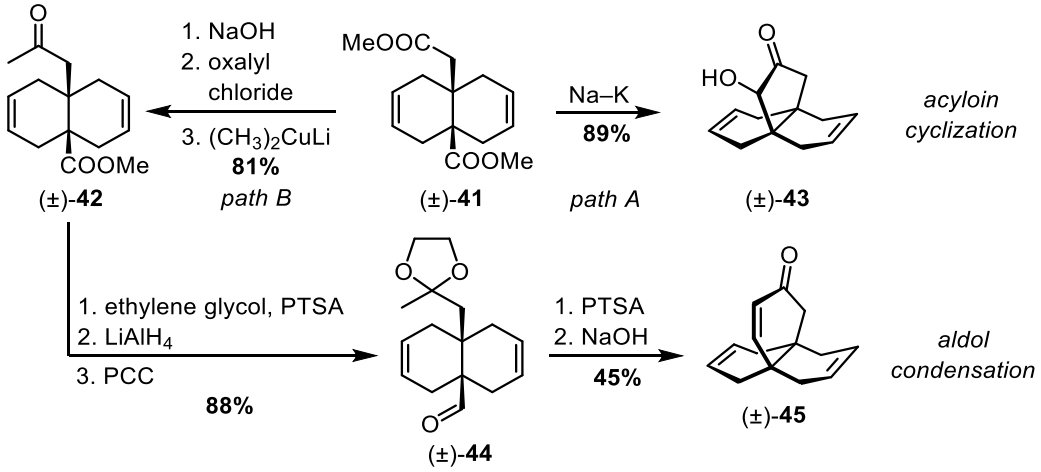
Scheme 12. One-pot synthesis of [k.3.3]propellanes **37** *via* WEISS–COOK cyclization (k = 3, 4, 6 and 10).

The group of PAQUETTE developed a synthesis of [4.4.m]propellanes (m = 3 and 4) using an *early C_q introduction* strategy (Schemes 13 and 14).[13] The synthesis of the *cis*-difunctionalized bicyclic precursor **41** required by this strategy started with the desymmetrization of anhydride **38** using lithium aluminum hydride to give lactone (±)-**39** (Scheme 13). Subsequently, the heterocyclic ring of (±)-**39** was opened using sodium cyanide. Hydrolysis of the nitrile group of (±)-**40** followed by double esterification led to bicyclic diester (±) **41**.



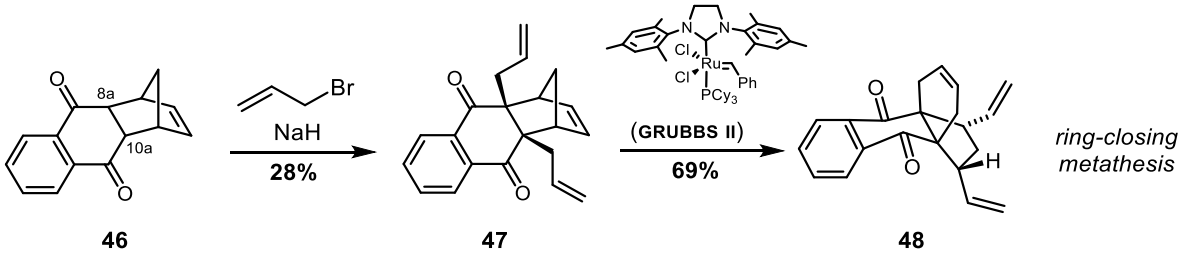
Scheme 13. Synthesis of bicyclic ester (±)-**41** by the group of PAQUETTE.

At this point, the route diverged to access the two [4.4.m]propellane scaffolds (Scheme 14). Ring closure of (±)-**41** by means of acyloin cyclization formed [4.4.3]propellane (±)-**43** (*path A*).[13a] Alternatively, diester (±)-**41** was transformed into aldehyde (±)-**44** in six steps (*path B*). The third ring of the [4.4.4]propellane (±)-**45** was formed *via* intramolecular aldol reaction of the keto aldehyde derived from the cleavage of the dioxolane functionality in (±)-**44**.[13b]



Scheme 14. PAQUETTE's synthesis of large-ring propellanes.

More recently, the group of KOTHA demonstrated that propellanes could be synthesized using an *early C_q introduction* implemented through a ring-closing metathesis (Scheme 15).[14] Diketone **46** was allylated at C-8a and C-10a to give **47** in 28% yield. Ring-closing metathesis of **47** in presence of GRUBBS II catalyst yielded [4.4.3]propellane **48**. During the reaction, the exocyclic allyl groups underwent olefin metathesis to form a new cyclohexene ring while the norbornene moiety was subjected to ring-opening.



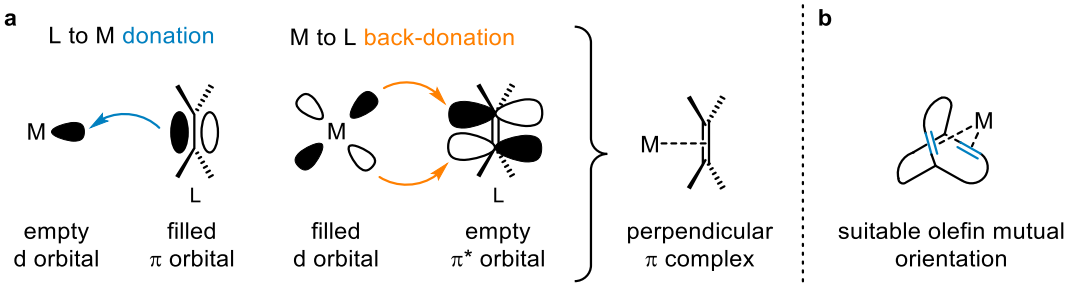
Scheme 15. KOTHA's ring-closing metathesis approach to large-ring propellanes.

The three described methodologies were used to prepare propellanes in achiral or racemic form. A general asymmetric entry to this class of molecules was still missing in the literature at the time when this doctoral work began.

4.3 Bridged Dienes

Bridged dienes possess a rigid three-dimensional structure in which the two endocyclic double bonds can adopt a mutual orientation suitable for chelating a metal center. The binding of an alkene to a metal center is described using the DEWAR–CHATT–

DUNCANSON model (Scheme 16a).[2b] The π orbital of the alkene interacts with an empty d orbital of the metal, while a back-donation occurs from a filled d orbital of the metal to the empty π* orbital of the olefin. This leads to a π complex in which the metal–alkene bond is perpendicular to the plane of the alkene, thus making bridged dienes optimal chelating ligands (Scheme 16b).



Scheme 16. Alkene bonding to a metal center. a) DEWAR–CHATT–DUNCANSON model. b) Geometry of metal/bridged diene complex.

Metal–diene complexes are commercially available. For instance, norbornadiene (**30**) is found in 38 different complexes (containing nine different metals) of which approximately 71% are based on rhodium (Figure 3).

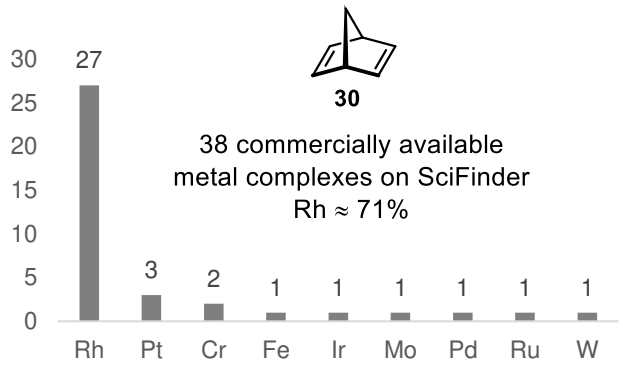


Figure 3. Commercially available metal complexes of norbornadiene (**30**) at year 2018.

In 2003, the group of HAYASHI introduced the first use of a chiral bridged diene ligand by employing the substituted norbornadiene **49** in the rhodium-catalyzed asymmetric 1,4-arylation of enones (Figure 4).[15] Since then, this transformation has been extensively used to assess the performance of new bridged diene ligands. The structural diversity of these chiral dienes has been limited to bicyclo[2.2.m] (**49**, **51**–**53**) and [3.3.m]alkane (**50**, **54**) scaffolds having one or two carbons "m" bridges and to a *type C* tricyclic framework (**55**, Figure 4).

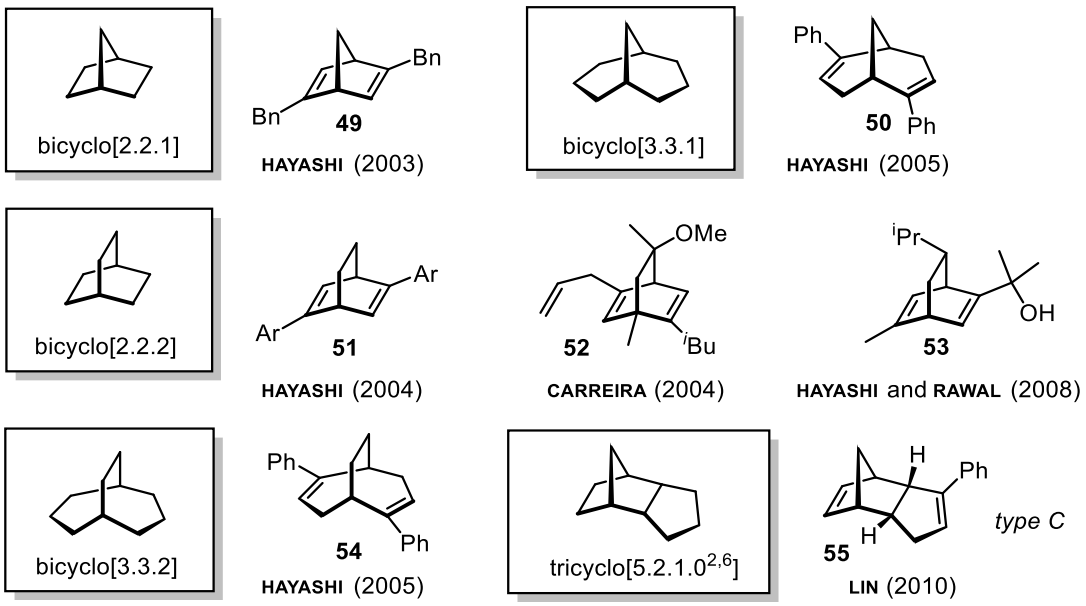
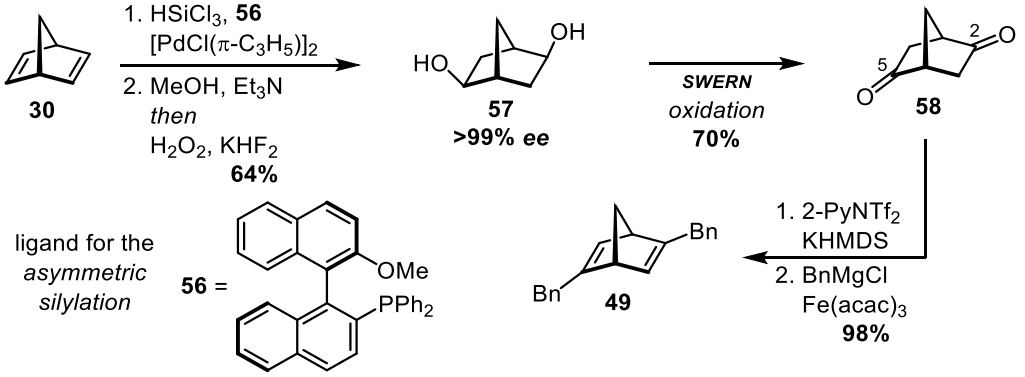


Figure 4. Selected examples of structurally diverse chiral bridged diene ligands.

The chiral bicyclo[2.2.1]heptadiene **49** was prepared from norbornadiene (**30**, Scheme 17).[15-16] Its synthesis commenced with the catalytic asymmetric hydrosilylation of **30** followed by oxidation to give diol **57** with excellent enantiomeric excess (>99% *ee*). SWERN oxidation of diol **57**, subsequent alkenyl triflate formation and iron catalyzed KUMADA cross-coupling at C-2 and C-5 of **58** delivered diene **49** in overall five steps and 44% yield starting from commercially available **30**.

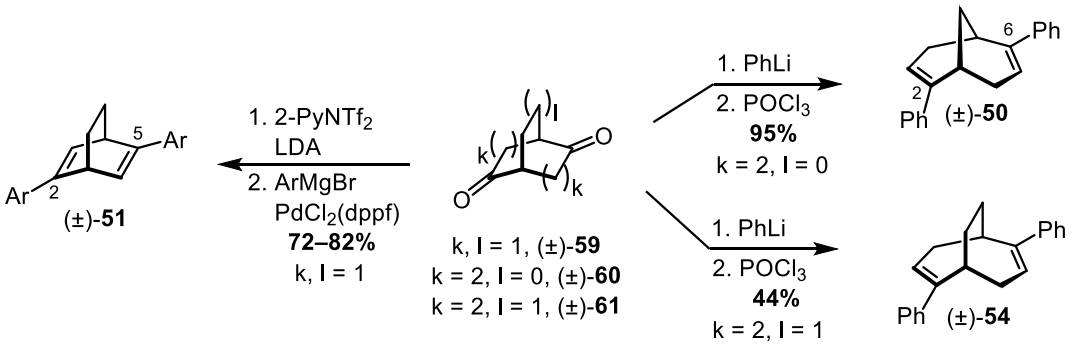


Scheme 17. Synthesis of bicyclo[2.2.1]hepta-2,5-diene ligand **49**.

The bridged diene ligands constructed on the bicyclo[2.2.2] (**51**) and [3.3.m]alkane (m = 1 or 2, **50**, **54**) scaffolds were obtained by the group of HAYASHI in two steps from diketones (±)-**59**–**61** (Scheme 18).[f, 17] An enol triflation/cross-coupling sequence from ketone (±)-**59**

[f] Racemic ketones **59** and **60** are made in two steps in 51% and 56% yields, whereas ketone (±)-**61** is obtained in three steps from (±)-**59** in 24% yield (12% over five steps). See refs 17.

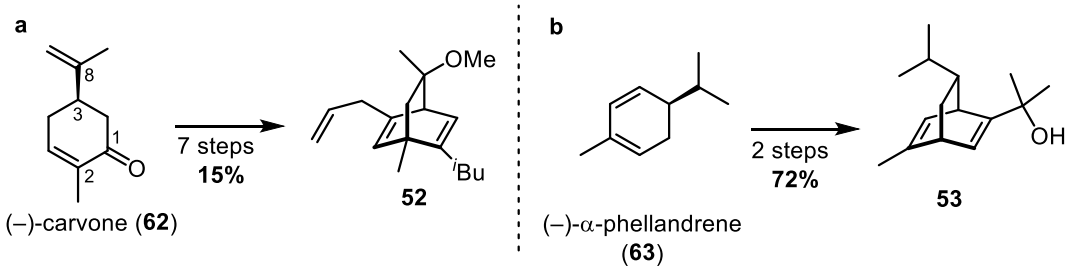
installed the 1,4-diene moiety on the bicyclo[2.2.2]octane scaffold of (±)-**51**.[18] In the case of the bicyclo[3.3.m] frameworks, the 1,5-diene moiety of (±)-**50** and (±)-**54** was generated by 1,2-addition of phenyl lithium to ketones (±)-**60** and (±)-**61** and dehydration using $POCl_3$.[19]



Scheme 18. Syntheses of bicyclo[2.2.2], [3.3.1] and [3.3.2] type diene ligands **51**, **50** and **54**.

In these preparations, the enantiomerically enriched ligands **50**, **51** and **54** (>99% *ee*) were obtained after separation of the racemic mixtures of dienes on chiral HPLC. This fact constituted a major drawback in the synthesis of these bicyclic dienes, since the yield for the desired ligand dropped of approximatively 50% in the final purification.

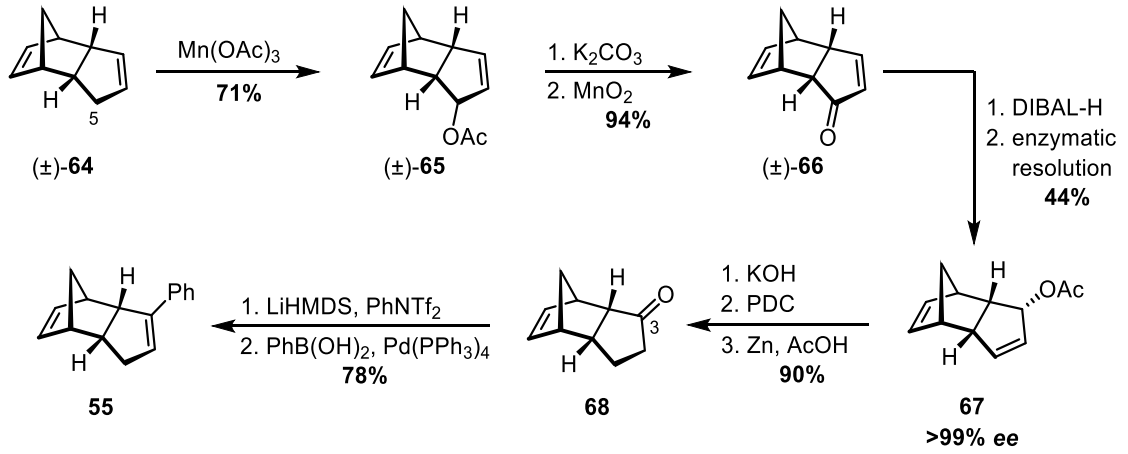
To overcome this inconvenience, bicyclo[2.2.2]octane ligands **52** and **53** were synthesized starting from inexpensive chiral pool (Scheme 19). The group of CARREIRA obtained diene **52** in seven steps from (–)-carvone (**62**, Scheme 19a),[20] whereas the groups of HAYASHI and RAWAL prepared ligand **53** in two steps using (–)-α-phellandrene (**63**) as building block (Scheme 19b).[21]



Scheme 19. Bicyclo[2.2.2]octa-2,5-dienes **52** and **53** obtained from the chiral pool. a) Ether **52** from (–)-carvone (**62**). b) Alcohol **53** from (–)-α-phellandrene (**63**).

Although the syntheses of **52** and **53** are remarkably convenient, access to both enantiomeric forms could be uneven due to the accessibility of the "non-natural" building block. For example, *ent*-**63** could be prepared in two steps from 8,9-dihydrocarvone (three steps from **62**).[22]

Chiral dienes based on higher polycyclic scaffolds are rare in the literature. The synthesis of tricyclic ligands of *type C* **55** was reported by the group of LIN (Scheme 20).[23] Starting from a racemic mixture of dicyclopentadiene (**64**), ketone (±)-**66** was obtained in three steps *via* oxidation at C-5 of (±)-**64**.[24] After the reduction of ketone (±)-**66** with DIBAL-H, the resulting racemic alcohol was separated into its enantiomers by resolution using Amano Lipase PS to give **67** (>99% *ee*).[g] The acetate functionality of **67** was cleaved using potassium hydroxide. Afterwards, the obtained allylic alcohol was oxidized with PDC and the derived enone was selectively reduced to ketone **68** using zinc and acetic acid.[25] Finally, alkenyl triflate formation followed by SUZUKI cross-coupling at C-3 of **68** yielded bridged diene **55**.



Scheme 20. Synthesis of tricyclic nona-1,5-diene type ligand **55** by the group of LIN.

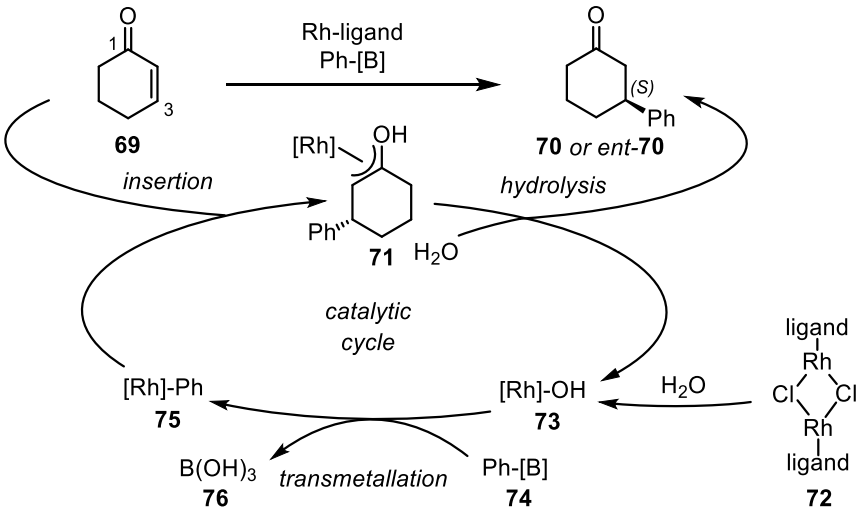
Ligand **55** was prepared in ten steps in 21% overall yield from (±)-**64**. This long approach highlighted the challenge in obtaining polycyclic hydrocarbon scaffolds in highly enantioenriched form.

4.3.1 Rhodium-Catalyzed Arylation of Cyclic Enones

Rhodium-catalyzed asymmetric arylations are powerful and selective C–C bond forming transformations.[26] Chiral dienes have been applied in a variety of arylations, including 1,2- and 1,4-additions.[2b, 27] As previously mentioned, the rhodium-catalyzed 1,4-arylation of cyclic enones is used as model reaction to compare the catalytic activity of newly disclosed ligands (Scheme 21).[26] In this reaction, a new stereogenic center is formed at the C-3 position of cyclic enone **69**. The mechanism of the 1,4-addition has been investigated by HAYASHI and coworkers.[28] Hydroxorhodium complex **73** was proposed to be the active

[g] *ent*-**67** was obtained in 48% yield with 98% *ee*. The enantiomeric excess was increased to >99% after recrystallization.

catalyst. These species could be formed *in situ* starting from chloride dimer **72**. Subsequently, transmetallation with boronic species **74** gives phenyl–rhodium complex **75** which reacts with unsaturated ketone **69** (insertion step) to generate oxa-π-allylrhodium **71**. Final hydrolysis of **71** yields 1,4-adduct **70** and regenerate hydroxorhodium **73**.



Scheme 21. Mechanism of the rhodium-catalyzed arylation of cyclohex-2-enone (**69**).

Numerous types of ligands have been tested in this reaction. Chiral diphosphines were the most studied ones, which were followed by olefins, sulfoxides and their hybrid structures.[26] Among them, chiral dienes exhibited the highest catalytic activities which allowed this transformation to be carried out at lower temperatures.[h, 29]

Bridged bicyclic dienes are further divided into two subclasses characterized by different types of diene moieties (Figure 5). Ligands **77** and **52**, based on the bicyclo[2.2.m]alkane system, possess a hexa-2,5-diene unit in which the double bonds are parallel to the plane intersecting the bridgehead atoms, thus leading to the formation of active complex **78** (Figure 5a). During the enantiodetermining insertion step, enone **69** approaches the metal from the *si* face to minimize the steric repulsion with the substituents and gives adduct **70** with excellent enantiomeric excess (96% *ee*).[30] On the other hand, bicyclo[3.3.m]alkane ligands **54** and **50** feature an octa-2,6-diene moiety (Figure 5b). The twisted geometry for the double bonds leads to the formation of complex **79**. In this coordination mode, the 2,6-disubstitution is responsible for residual steric hindrance between enone **69** and the C-3

[h] In the case of heteroatom-based ligands, the reactions are usually carried out above 40 °C. Reaction using bicyclic dienes are performed at 30 °C or room temperature.

position of ligands **54** and **50**, thus leading to lower enantiomeric excesses (83–90% *ee*) for the formation of *ent*-**70**.[31]

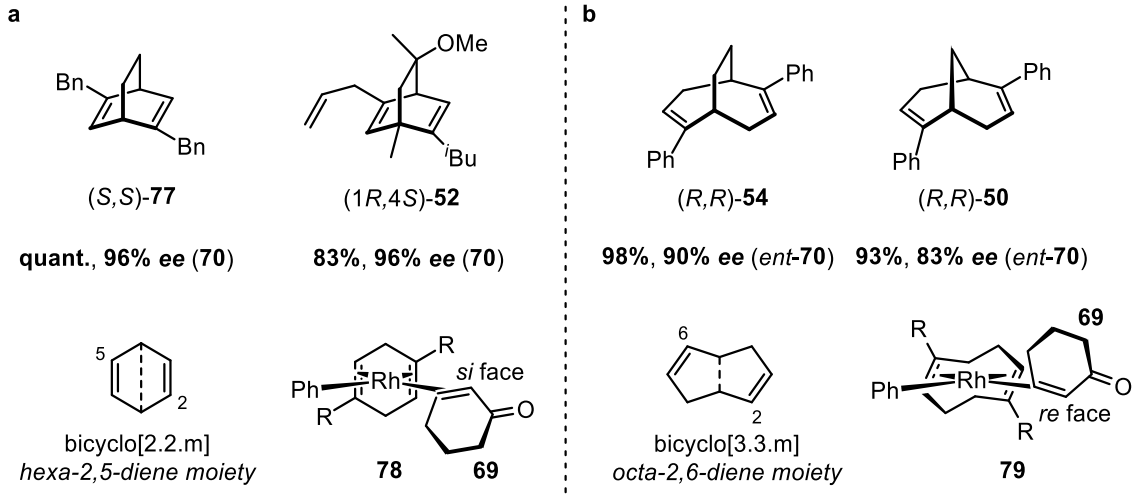


Figure 5. Bridged diene ligands based on bicyclic scaffolds: performance and coordination modes. a) Bicyclo[2.2.m] and b) bicyclo[3.3.m]alkane systems.

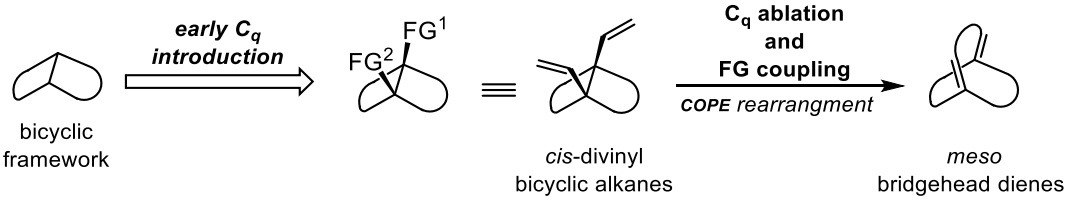
To further enhance the activity of the catalytic systems based on chiral dienes, a continuous optimization of ligand geometries and substitution patterns have been investigated during the last decades.[31] These efforts brought to the experimentation of 3,7-disubstitutions on the bicyclo[3.3.0]alkane framework to induce the best cooperation between crossed coordination to the metal center and steric repulsion of the substituents.[32] However, studies on the influence of more complex tricyclic structures in catalysis are still limited, probably due to their challenging preparation.[i]

4.4 Bridgehead Dienes

Bridgehead dienes are bicyclic molecules which possess two bridgehead double bonds in a proximate relationship. These strained molecules are rare in the literature since their preparation is not trivial and usually requires a strong driving force to place the two distorted alkenes at the ring junctions.[33] The group of SHEA developed an *early C_q introduction* approach for the synthesis of *meso* bridgehead dienes (Scheme 22).[5b] In this work, *cis*-divinyl bicyclic alkanes were subjected to COPE rearrangement to form the desired

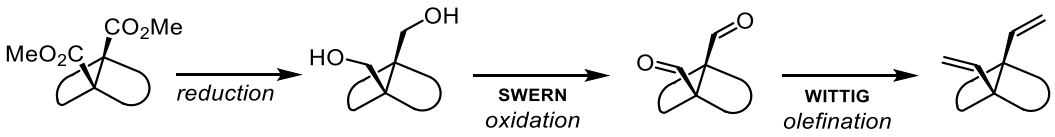
[i] Ligands **55** have been applied in the 1,2-arylation of *N*-tosylarylamines. However, their 1,6-diene moiety precluded from comparison to the bicyclic analogues based on 1,4- and 1,5-dienes.

dienes. The final functional groups coupling was accompanied by ablation of the quaternary centers to install the double bonds at the bridgehead positions.



Scheme 22. SHEA's COPE rearrangement strategy to access *meso* bridgehead dienes.

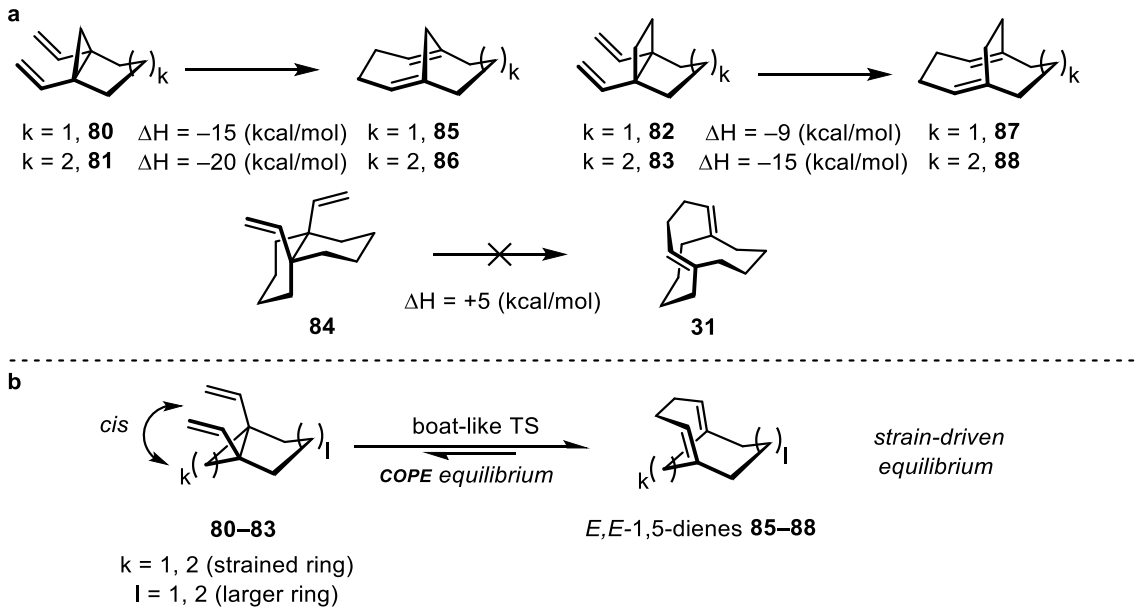
The *cis*-functionalized bicyclic alkanes were obtained in three steps from the parent esters through a reduction/oxidation sequence followed by WITTIG olefination (Scheme 23).



Scheme 23. General preparation of the *cis*-divinyl bicyclo alkanes.[j]

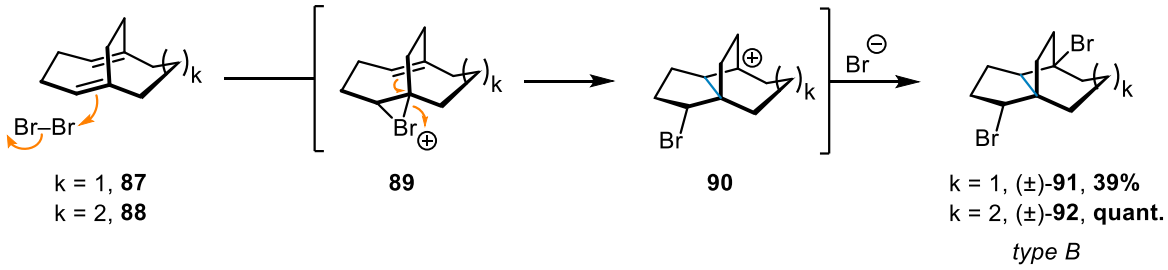
The [3,3] sigmatropic rearrangement of alkenes **80**–**83** occurred smoothly to yield the corresponding bridgehead dienes **85**–**88** (Scheme 24a). However, the ring-expansion of the larger decalin **84** failed. Negative reaction enthalpies were calculated for the formation of dienes **85**–**88** from strained cyclopropane and -butane derivatives **80**, **81** and **82**, **83**, whereas *cis*-divinyl alkane **84** was found energetically favored with respect to **31** by five kcal/mol. The outcome showed that the examined COPE equilibria lied toward the less strained products. In the ring-expansion of **80**–**83**, the reaction proceeded through a boat-like transition state in which the two vinyl groups were *cis* in respect to the strained small ring, as confirmed by the *E,E*-1,5-diene configuration of products **85**–**88** (Scheme 24b).[k] According to WISEMAN, the strain of bridgehead double bonds is closely related to the one of the corresponding *trans*-cycloalkene.[34] Being *trans*-cyclooctene the smallest isolable alkene of this class, the *Z,Z*-isomer of **85** and **86** having a *trans*-cycloheptene moiety would not be isolable. Moreover, the authors concluded that the *Z,Z*-isomer of dienes **87** and **88** would be highly energetic and reactive.[l] Therefore, the COPE reaction led to dienes **85**–**88** having a *trans,trans*-1,5-diene moiety in the largest ring.

[j] Reduction of the esters was carried out with $LiAlH_4$ in 83–90% yields. The bicyclic aldehydes and olefins were not isolated.
[k] A chair transition state would result in the formation of highly energetic *E*/*Z* isomers: except in large cycloalkadienes, *E*/*E* and *Z*/*Z* isomers are energetically favored.
[l] Diene **87** was recovered unchanged after heating at 160 °C for 24 h.



Scheme 24. COPE rearrangement of *cis*-divinyl bicyclic alkanes **80**–**83** to *meso* bridgehead dienes **85**–**88**. a) Reaction scope and b) COPE equilibrium.[m]

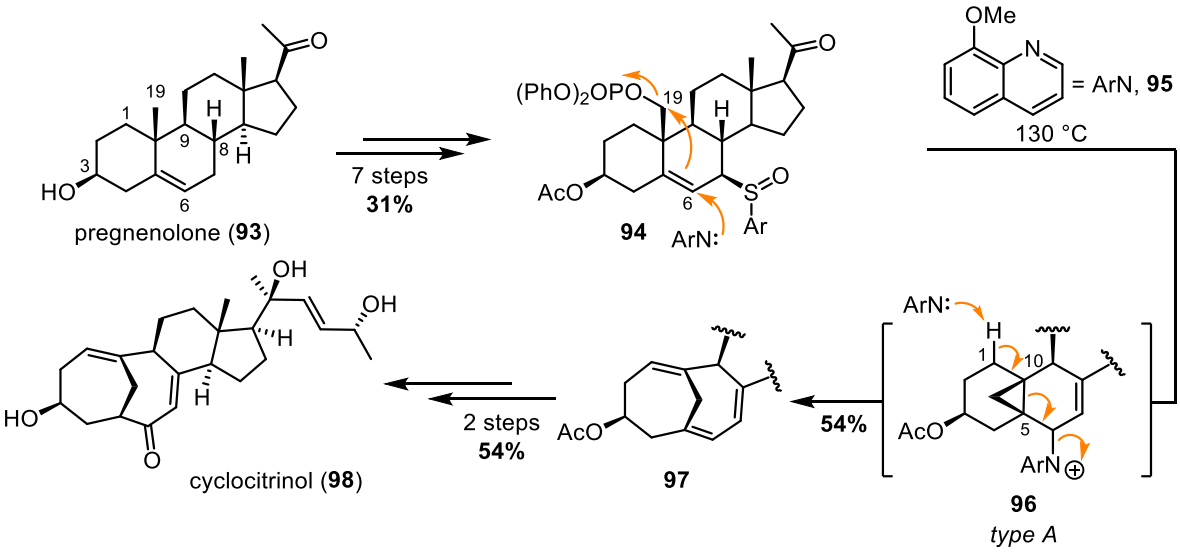
SHEA and coworkers demonstrated that the proximity of the double bonds could be exploited for the formation of a new intramolecular bond (Scheme 25).[5b] Upon treatment of bridgehead olefins **87** and **88** with bromine, a transannular C–C bond formation led to the new *type B* tricyclic hydrocarbon scaffolds of (±)-**91** and (±)-**92**, respectively. The reaction likely proceeded *via* attack of the nucleophilic alkene to bromine to form the bromonium intermediates **89**. The intramolecular C–C bond formation generated carbocations **90** which were then intercepted by the nucleophilic attack of bromide to yield (±)-**91** or (±)-**92**. However, the authors could not unambiguously establish the ionic or free radical mechanism of the reactions.[35]



Scheme 25. Intramolecular reaction of bridgehead dienes **87** and **88**.

[m] The bridgehead dienes were isolated by preparative vapor-phase chromatography using a Varian Aerograph Model 920 gas chromatograph equipped with a thermal conductivity detector. In the publication the isolated yields were not given.

Recently, the group of GUI reported a ten steps synthesis of cyclocitrinol (**98**) using pregnenolone (**93**) as C21 chiral pool (Scheme 26).[36] In this study, the bicyclo[4.4.1]undecene core of **98** was obtained through formation of bridgehead diene **97**. In the cascade reaction sequence, the nucleophilic attack of the heterocyclic nitrogen of quinine **95** at C-6 of **94** yielded cyclopropane **96** after substitution of the leaving group at C-19. Deprotonation at C-1 of **96** enabled a GROB-type fragmentation to form bridgehead diene **97**. Thus, the diene moiety of **97** was constructed by reaction of two vicinal quaternary carbons. In this case, the ablation of C-10 and C-5 occurred *via* cleavage of the central C–C bridge of small-ring propellane **96**.



Scheme 26. GUI's preparation of bridgehead diene intermediate **97** in the synthesis of cyclocitrinol (**98**).

Although bridgehead dienes are not occurring in nature, these examples showcased the relevance of this reactive intermediates in the synthesis of complex polycyclic hydrocarbon scaffolds.

4.5 Relevance in Drug Discovery

Small molecules rich in sp^2 centers characterize the majority of the compound libraries screened in drug discovery campaigns.[n] These types of molecules often show poor developability during clinal progression due to their low solubility in physiological

[n] Small molecules are defined as organic compounds of low (typically under ~ 1.000 Da) molecular weight.

conditions.[37] For these reasons, the efficiency of the pharma industry in creating new drug candidates is currently facing an increasing decline.[38] In the last decade, it has been proposed that the complexity of a molecule could positively correlate with improved compound solubility in aqueous environment and target selectivity.[39] In addition, the higher natural product-likeness of drug candidates would facilitate exploration of a broad chemical space which might result in the modulation of novel biological targets.[o, 40] To corroborate this hypothesis, the group of LOVERING defined the fraction of saturated carbons (Fsp^3) present in a given molecule (Eq. 1):[3a]

$$Fsp^3 = sp^3 \text{ hybridized carbons/total carbon count} \qquad \text{(Eq. 1)}$$

In fact, the replacement of sp^2 centers with tetrahedral carbons increases the complexity, and natural product-likeness, of a molecule without affecting its molecular weight significantly. By screening a selected database of compounds applied in drug discovery programs, the trend that complexity (measured as Fsp^3) had on clinical progression (from discovery, through phase 1–3, to drugs) was analyzed (Figure 6).[p] The average Fsp^3 showed a 31% increase from discovery to drug.

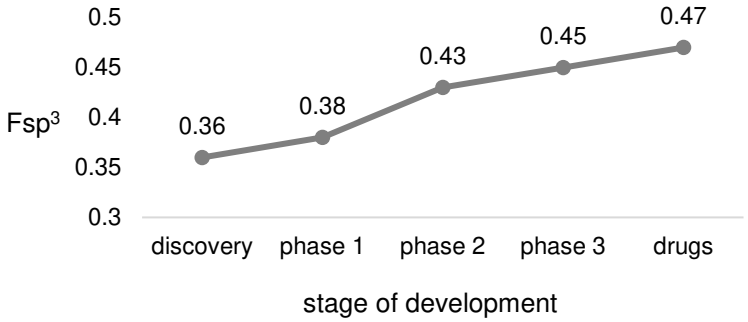


Figure 6. Mean Fsp^3 for compounds screened during drug development campaigns.

This result indicated that small molecules rich in saturated carbons have more probability to be developed into new drugs. The group also demonstrated that a higher Fsp^3 leads to enhanced solubility in water, and, in a following study, to decreased off-target bindings.[q, 3b]

[o] For small molecules, the chemical space is generally defined as the total descriptor space that encompasses all carbon-based molecules that could, in principle, be created. Descriptors are including physiochemical properties (e.g. lipophilicity) and topological features (e.g. degree of branching). For more information see Galloway, W. R.; Wilcke, D.; Nie, F.; Hadje-Georgiou, K.; Laraia, L.; Spring, D. R., Diversity-Oriented Synthesis: Developing New Chemical Tools to Probe and Modulate Biological Systems. In *Concepts and Case Studies in Chemical Biology*, Waldmann, H.; Janning, P., Eds., Wiley-VCH Verlag GmbH & Co. KGaA: 2014.

[p] The compounds were retrieved from the GVK biomarker database, web site http://www.gvkbio.com/Informatics. html/. The examined compounds were reported from 1980 and onward, had at least four carbon atoms and molecular weight under 1.000 Da.

[q] Water solubility database: http://modem.ucsd.edu/adme/databases/databases_logS.htm.

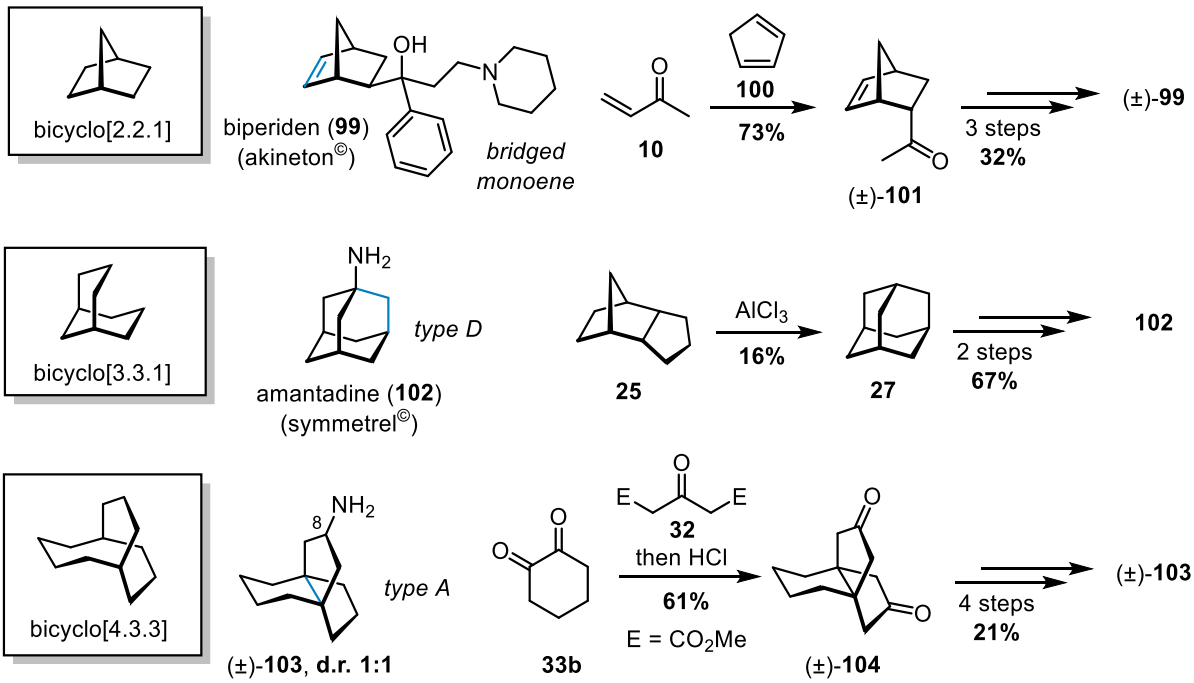
Therefore, the complexity of a molecule might reduce toxicity of drug candidates and thus their attrition during clinical trials. Since the skeletal core is the key element of molecular complexity, the development of new methods to access complex hydrocarbons scaffolds would be essential for future drug discovery campaigns.

4.5.1 Scaffold Diversity

Biologically active small molecules include a broad variety of synthetic or natural occurring Fsp^3-rich polycyclic scaffolds. Selected examples of biologically relevant bridged carbocycles are reported in Schemes 27–29.[r] The pharmaceutical industry already recognized the relevance of polycyclic hydrocarbon scaffolds. Compounds **99**, **102**, and **110** have been approved as pharmaceuticals: these and additional 17 examples are detailed in an excellent review recently disclosed by the group of WILLIAMS.[41] As previously discussed, their scaffold diversity can be analyzed by reducing the examined structures to the central bicyclic cores and then evaluating possible additional bridging connections and/or double bonds.[s]

Among the purely synthetic molecules, biperiden (**99**) is a bridged monoene derived from the bicyclo[2.2.1]heptane core (Scheme 27).[t] This norbornene derivative is obtained as racemate *via* cycloadduct (±)-**101** which is formed by DIELS–ALDER reaction of methyl vinyl ketone (**10**) with cyclopentadiene (**100**). The *type D* tricyclic amantadine (**102**) is prepared from adamantane (**27**) which is synthesized through $AlCl_3$ catalyzed rearrangement of dicyclopentane (**25**).[u] Propellamine (±)-**103**, diastereomeric at C-8, possesses a tricyclic scaffold of *type A* based on the bicyclo[4.3.3]dodecane skeleton.[v] The previously described WEISS–COOK cyclization was employed to construct the tricyclic core of (±)-**104** starting from diketone **33b**.[w, 42]

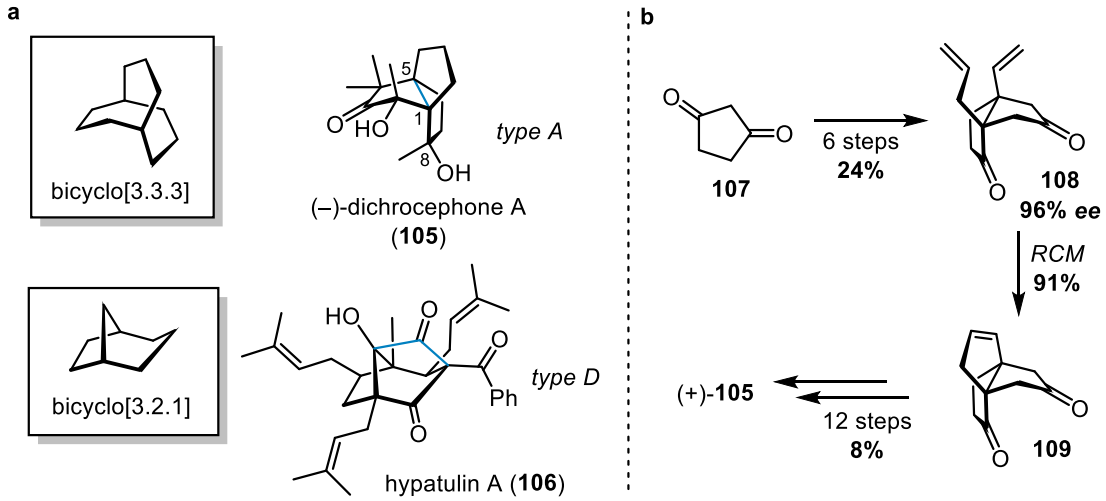
[r] Freely available biological data for the screened compounds are given in the chEMBL database link.
[s] Detailed in chapter 4.1.
[t] chEMBL database for **99**: https://www.ebi.ac.uk/chembl/compound/inspect/CHEMBL1101.
[u] chEMBL database for **102**: https://www.ebi.ac.uk/chembl/compound/inspect/CHEMBL660.
[v] chEMBL database for **103**: https://www.ebi.ac.uk/chembl/compound/inspect/CHEMBL3597327.
[w] Detailed in chapter 4.2.



Scheme 27. Selected examples of synthetic carbocycles.

Natural products and their derivatives are another source of biologically active polycyclic scaffolds. Recently, our group undertook two different synthetic projects aiming at natural occurring bridged carbocycles. Dichrocephone A (**105**) was isolated from the annual herb *Dichrocephala benthamii*, which is only distributed in China and India (Scheme 28a).[x, 43] The structure initially proposed for this tricyclic molecule of *type A*, 8-*epi*-**105**, was reassigned by SCHMIEDEL using a synergy between total synthesis and biosynthetic reasoning.[43-44] The non-natural enantiomer (+)-**105** was obtained in twelve steps from propellane **109** which was constructed by ring-closing metathesis of **108** (Scheme 28b). The synthesis of the precursor **108** was performed in six steps starting from 1,3-cyclopentadione (**107**), following an *early* C_q *introduction* strategy developed during this doctoral study by a collaboration with SCHNEIDER. In an ongoing study, LEISERING and PONATH are pursuing the first synthesis of hypatulin A (**106**, Scheme 28a).[y] This caged carbocycle was found in the dried leaves of *Hypericum patulum* and its purported structure, featuring a tricyclic scaffold of *type D* obtained from the bicyclo[3.2.1]octane core, was proposed in 2016 by KASHIWADA and coworkers.[45]

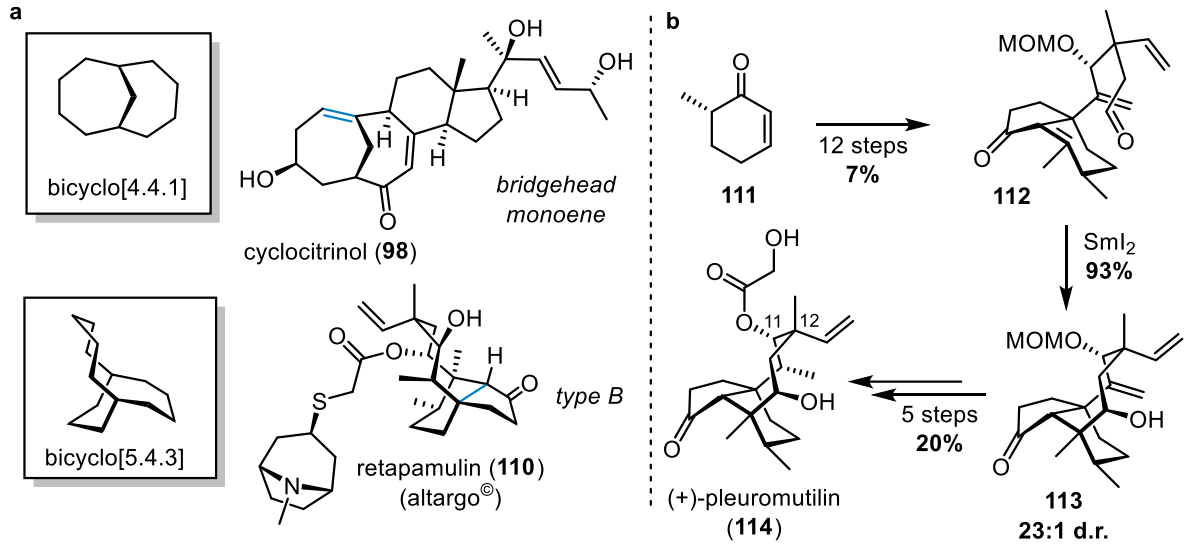
[x] For compound **105** no biological data are reported in the database. In our group, only 2.5 mg of *ent*-**105** were synthesized.
[y] For compound **106** no biological data are reported in the database. The compound has not been synthesized yet.



Scheme 28. Natural occurring bridged carbocycles targeted by our group. a) Structures of propellane **105** and caged **106**. b) Synthesis of the tricyclic core of **109** by RCM.

Two additional examples of biologically active carbocycles are shown in Scheme 29a. Cyclocitrinol (**98**) was isolated from the fungus *Penicillium citrinum*.[z, 4] Its structure was confirmed in 2018 by a total synthesis carried out in the LI group.[46] In the same year, an elegant synthesis performed by the group of GUI constructed the bicyclo[4.4.1]undecene core of **98** through an intermediate bridgehead diene, as previously detailed.[36] The *type B* retapamulin (**110**) is an antibiotic derived from the natural occurring pleorumutilin (**114**) by introducing a caged amine on the exocyclic α-hydroxy ester present at the C-11 position of the tricyclic core (Scheme 29b).[aa, 47] Recently, it has been reported that 12-*epi*-**114** provides improved biological activity.[48] This finding has promoted the total synthesis of **114** in order to access new derivatives of the tricyclic core.[49] For instance, the group of REISMAN prepared (+)-**114** in 18 steps starting from **111**, which in turn was obtained from the chiral pool (Scheme 29b).[bb, 50] The tricyclic core of *type B* typical of this class of molecules was formed by a samarium diiodide mediated intramolecular 1,4-addition in **112** to give **113**. In this study, the group gained access also to the C-11 and C-12 epimers of **114**.

[z] chEMBL database for **98**: https://www.ebi.ac.uk/chembl/compound/inspect/CHEMBL523073.
[aa] chEMBL database for **110**: https://www.ebi.ac.uk/chembl/compound/inspect/CHEMBL1658.
[bb] Compound **111** was obtained from commercially available (+)-*trans*-dihydrocarvone in one step in 57% yield. The isopropenyl exocyclic group of carvone was removed by copper and iron mediated fragmentation of hydroperoxides: for more insights see Cekovic, Z.; Dimitrijevic, L.; Djokic, G.; Srnic, T. *Tetrahedron* **1979**, *35*, 2021–2026.



Scheme 29. Selected examples of natural occurring bridged carbocycles. a) Structures of cyclocitrinol (**98**) and retapamulin (**110**). b) Synthesis of the tricyclic core of **113**.

This concise overview showcased the variety and structural complexity of biologically active polycyclic hydrocarbon scaffolds. Synthetic cores are smaller (six to nine atoms for the larger cycloalkane unit) than natural ones (seven to eleven atoms). These bicyclic and topologically diverse tricyclic skeletons were accessed using various complexity generating reactions, including DIELS–ALDER reactions, ring-closing metathesis, MICHAEL additions, cationic and radical cyclization, in a target-oriented fashion.

5 Implementation of the Work

5.1 Aim of the Work

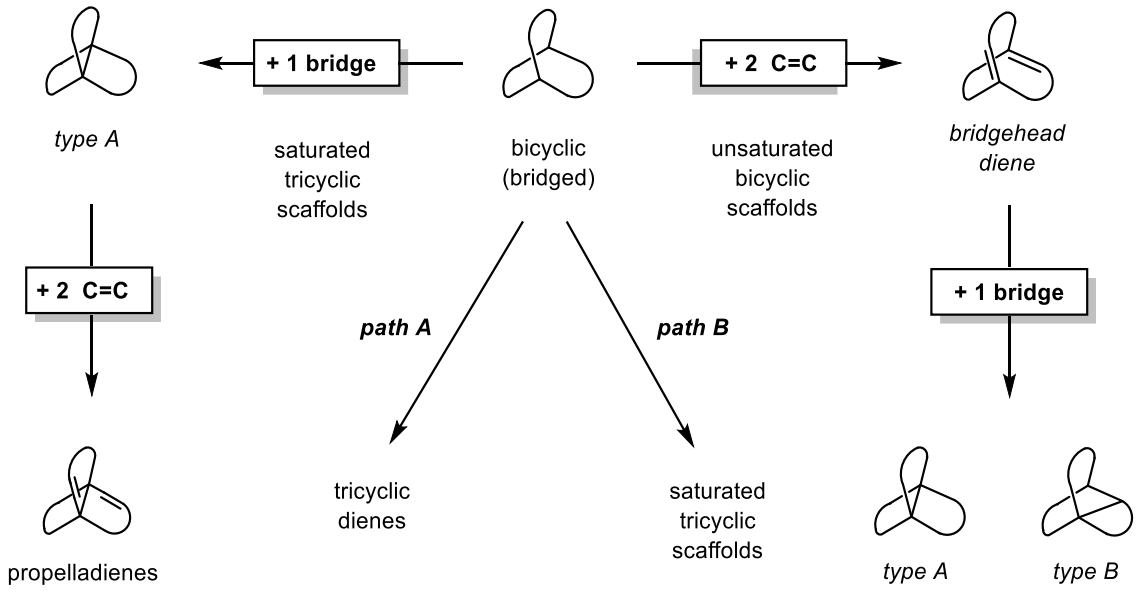
Polycyclic hydrocarbons encompass diverse rigid structures and three-dimensional shapes. The strategies applied for the synthesis of these complex motifs were mainly oriented to a single type of bicyclic or tricyclic scaffold. For the targeted scaffold type, variations on bridge sizes and appendages were carried out with the aim to expand the molecular diversity. The size of the bridges could be controlled by changing the carbon chain lengths on the cyclization precursors, as demonstrated in COOK's synthesis of propellanes, or using different ring-closing reactions, as showed by PAQUETTE.[13b] The appendage diversity could be expanded through the derivatization of proper functional groups, as achieved in the preparation of bridged dienes.[cc]

On the other hand, the modification of the C–C bond connections would give topologically different polycyclic skeletons. This task constitutes a major challenge since could require the intermediacy of strained, reactive small-ring (three and four atoms ring) carbocycles, as showed in SHEA's and GUI's works.[5b, 36]

Herein, the synthesis of topologically different polycyclic hydrocarbon scaffolds and their derivatives will be pursued in a diversity-oriented fashion. Novel tricyclic molecules will be tested in asymmetric catalysis. Furthermore, three-dimensional reactive intermediates will be employed in the exploration of Fsp^3-rich, and natural product-like, chemical space.

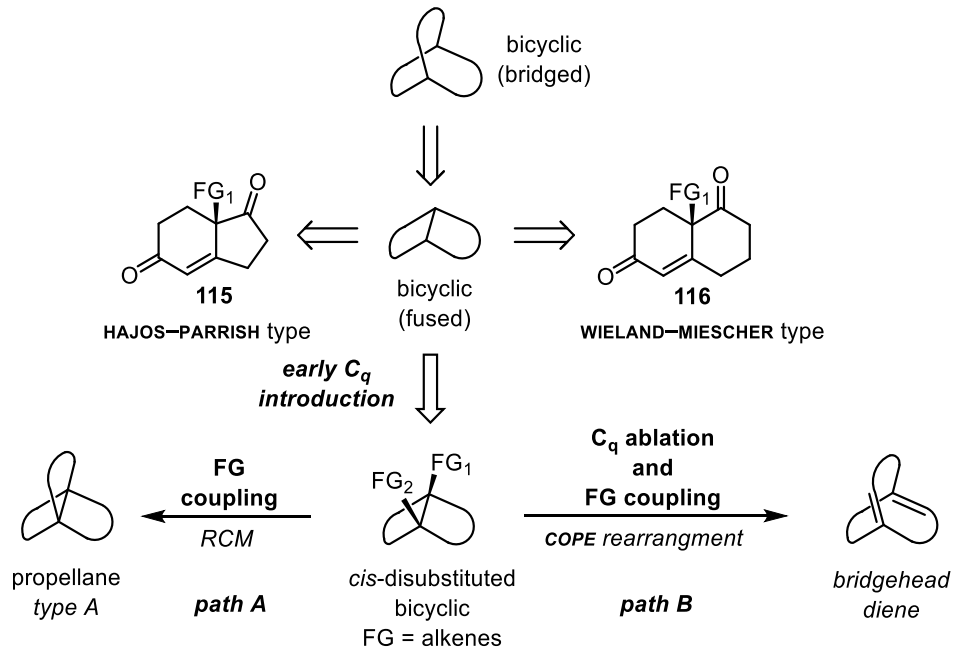
The structural analysis given in the introduction can be used to devise a synthetic plan to access diverse polycyclic scaffolds (Scheme 30). Following such method, bicyclic frameworks can undergo two different formal operations: bridge or double bonds additions. Addition of a "zero bridge" connecting the ring junctions would give tricyclic molecules of *type A* (*path A,* Scheme 30). The further introduction of two double bonds would give propelladienes. By reversing the sequence of the formal operations, an intermediate bridgehead bicyclic diene would be prepared (*path B,* Scheme 30). A further bridge addition would generate tricyclic molecules of *type A* or *B*.

[cc] Detailed in chapter 4.3.



Scheme 30. Synthetic plan for the synthesis of different polycyclic molecules.

The works of PAQUETTE and KOTHA on propellanes and the one of SHEA on bridgehead dienes showed that different polycyclic molecules could be obtained from fused bicyclic scaffolds using *early C_q introductions* strategies.[5b, 14, 13b] Taking inspiration from these investigations, the planned synthetic strategy could be implemented using *cis*-disubstituted bicyclic frameworks bearing two alkene units as exocyclic functional groups (Scheme 31). The use of RCM would form propellanes (*path A*), whereas COPE rearrangements would give bridgehead dienes (*path B*).



Scheme 31. The planned *early C_q introduction* strategy.

Variations on the bridge sizes and the use of different ring-closing reactions would be investigated to broad the diversity of propellanes. Furthermore, the introduction of a diene moiety will be pursued to prepare new tricyclic ligands whose catalytic activity would be tested using the Rh-catalyzed 1,4-arylation of cyclic enones.

Starting from the reactive bridgehead diene, topological modifications of the caged carbocyclic framework will be investigated using intramolecular reactions, as performed by SHEA and coworkers.[5b] Moreover, the synthesis of GUI showed that bridgehead dienes and tricyclic motifs of *type A* can be closely related, thus formation of propellanes from the reactive diene would also be investigated.[36] To implement these tactics, the synthesis of enantioenriched HAJOS–PARRISH and WIELAND–MIESCHER ketones derivatives **115** and **116** will be initially pursued. The two vicinal quaternary carbons required by the planned strategies would be introduced by performing 1,4-additions to the bicyclic scaffolds of **115** and **116**.

5.2 List of Publications

5.2.1 Asymmetric Synthesis of Carbocyclic Propellanes

LISA M. SCHNEIDER, VOLKER M. SCHMIEDEL, TOMMASO PECCHIOLI, DIETER LENTZ, CHRISTIAN MERTEN and MATHIAS CHRISTMANN*

This chapter was published in *Org. Lett.* **2017**, *19,* 2310–2313.

https://dx.doi.org/10.1021/acs.orglett.7b00836.

Abstract

Tricyclic *type A* hydrocarbon scaffolds (propellanes) were obtained by ring-closing metathesis of *cis*-difunctionalized fused bicyclic molecules. The first quaternary center required by the *early* C_q *introduction* strategy was formed by desymmetrization of prostereogenic 1,3-diketones using HAJOS–PARRISH–EDER–SAUER–WIECHERT type processes. The obtained bicyclic enones were subjected to conjugate additions to install the second quaternary center. The chemical diversity of propellanes was expanded using alternative cyclization reactions and achieving functionalization of all the bridges. This novel enantioselective approach renders those compounds useful as central units in fragment-based drug discovery or as ligand scaffolds.

Author Contributions

The chemical synthesis reported in this work was carried out in the laboratories of Prof. Dr. M. CHRISTMANN. The co-authors carried out all the chemical synthesis, unless otherwise stated. T. PECCHIOLI carried out the synthesis of propellanes bearing an exocyclic double bond (**40** and **41** in the manuscript) and performed the functionalization of the [4.3.3]propellane core. X-Ray diffraction analysis of the crystalline compounds and vibrational circular dichroism analyses were carried out by the co-authors.

5.2.2 Synthesis of Highly Enantioenriched Propelladienes and their Application as Ligands in Asymmetric Rh-Catalyzed 1,4-Additions

TOMMASO PECCHIOLI and MATHIAS CHRISTMANN*

This chapter was published in *Org. Lett.* **2018**, *20*, 5256–5259.

https://dx.doi.org/10.1021/acs.orglett.8b02204.

Abstract

Application of the novel methodology for the synthesis of propellanes enabled the first synthesis of highly enantioenriched [4.3.3]propelladienes. A set of five bridged bicyclo[3.3.0] dienes were obtained by enol triflation/reduction sequences and then applied as steering ligands in the rhodium-catalyzed asymmetric arylation of cyclic enones. The novel catalytic system exhibited high catalytic activity, and the 1,4-adducts were obtained in moderate to excellent yields (46–99%) with enantioselectivities up to 96% ee.

5.2.3 Strain-Release Approach to Polycyclic Hydrocarbon Scaffolds

TOMMASO PECCHIOLI, AHED ALMALLA, SIMON STEINHAUER, DIETER LENTZ and MATHIAS CHRISTMANN*

Manuscript in submission

Abstract

The first synthesis of a double bridgehead bicyclo[4.4.4]tetradeca-1,6-diene was accomplished starting from a Wieland–Miescher ketone derivative. A key tandem sigmatropic rearrangement was employed to construct the medium-ring carbocyclic cage. The relief of strain energy, which was accumulated into the two reactive bridgehead double bonds, allowed structural relaxation of the sphere-like intermediate through formation of new intramolecular C–C bonds. This methodology permitted the synthesis of topologically different carbocycles in a diversity-oriented fashion and proved to be particularly relevant in the exploration of sp^3-rich three-dimensional molecular architectures with unusual exit vectors.

Author Contributions

The chemical synthesis reported in this work was carried out in the laboratories of Prof. Dr. M. CHRISTMANN. T. PECCHIOLI carried out all the chemical synthesis, unless otherwise stated. The co-authors assisted in the preparation of carboxylic acid **14** and carried out X-ray analysis of the reported compounds.

Strain-Release Approach to Polycyclic Hydrocarbon Scaffolds

Tommaso Pecchioli, Ahed Almalla, Simon Steinhauer, Dieter Lentz and Mathias Christmann*

Abstract

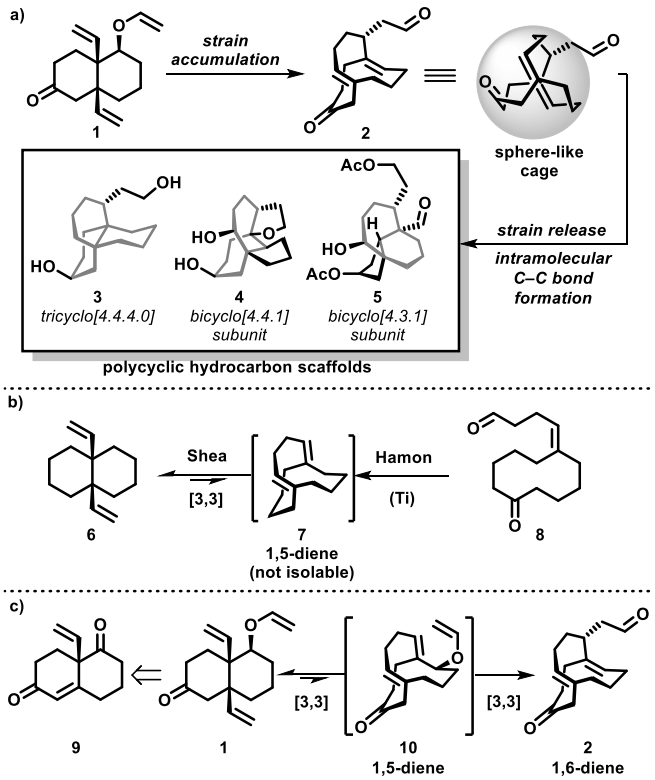
In the present work the asymmetric synthesis of medium-sized polycyclic hydrocarbon scaffolds is described. An unprecedented double bridgehead bicyclo[4.4.4]tetradeca-1,6-diene derivative was prepared by two consecutive [3,3]-sigmatropic rearrangements of a Wieland–Miescher ketone derivative. The release of strain energy was used to transform the sphere-like cage into other topologically distinct polycyclic scaffolds.

Introduction

In order to counter the decline in the creation of new chemical entities,[1] modern medicinal chemistry is turning its attention from flat, sp^2-rich to three-dimensional molecular structures.[2] In this regard, the pharmaceutical industry has recognized the relevance of polycyclic hydrocarbons, as recently reviewed by the group of Williams.[3] The release of strain energy in small-rings (three and four atoms) demonstrated to be a versatile strategy for accessing functionalized carbocycles.[4] As proposed by Alder,[5] this tactic could be exploited for preparing polycyclic molecules from highly strained medium-ring (eight to eleven atoms) carbocyclic cages. Stimulated by this prospect, we evaluated the introduction of two spatially close bridgehead olefins on the bicyclo[4.4.4]tetradecane scaffold for converting its strain energy into effective chemical reactivity. In this manuscript, we describe the release of strain from a double bridgehead medium-ring cage (**2**) to generate new C–C bonds of polycyclic hydrocarbon scaffolds of **3**–**5** (Scheme 1a).

The bicyclo[4.4.4]tetradecane architecture is among the highest strained members within the class of saturated medium-sized bicyclo[k.l.m]alkanes.[6] In 1981, Schleyer[7] predicted that the introduction of a bridgehead double bond can lower the molecular strain compared to the saturated system despite the creation of two torsionally distorted olefins. This concept was later extended to double bridgehead dienes.[8] In 1983, Alder tried to access a double bridgehead 1,6-diene.[9] Later, the synthesis of the corresponding double bridgehead 1,5-diene **7**[10] was attempted by Shea[11] (1986) and Hamon[12] (1992). The accumulation of strain in 1,5-dienes is problematic as it may be directly released via Cope rearrangement to give the thermodynamically more stable diene **6** (Scheme 1b). Herein, we report an approach to a double bridgehead 1,6-diene (**2**) that utilizes a reversible Cope rearrangement (**1**→**10**)

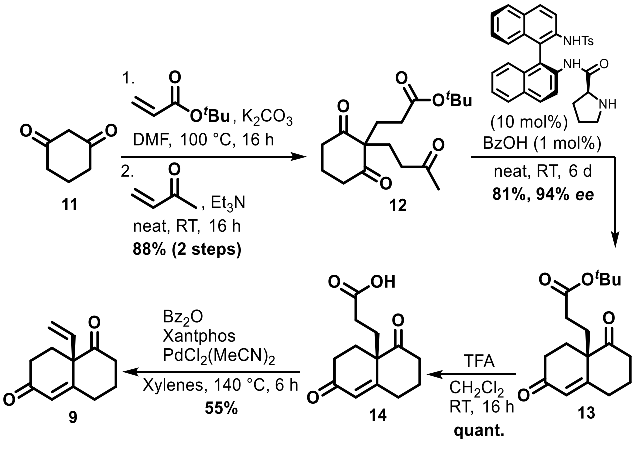
which is intercepted by a Claisen rearrangement[13] (**10**→**2**) to form the desired double bridgehead 1,6-diene (Scheme 1c). To investigate this tandem reaction, we envisioned **1** to be accessible from Wieland–Miescher ketone derivative **9** via cuprate addition.



Scheme 1. a) Overview of this work. b) Attempted synthesis of bridgehead bicyclo[4.4.4]tetradeca-1,5-diene (**7**). c) Our working proposal and retrosynthetic analysis.

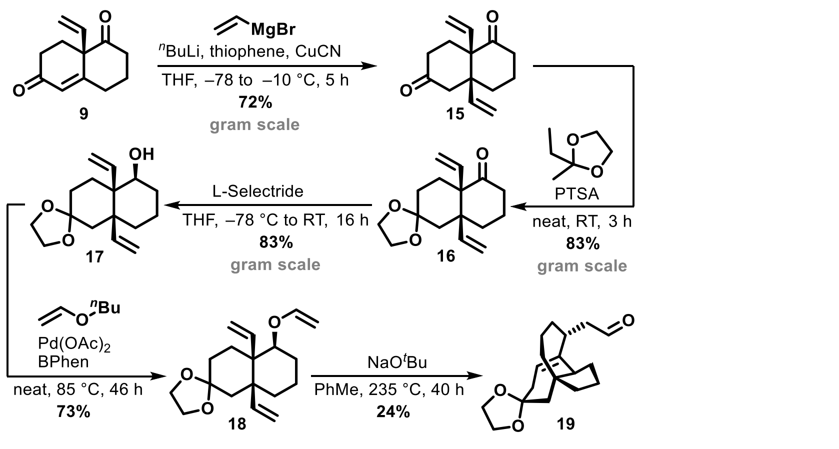
Discussion

Our route towards the sphere-like cage **2** commenced with the preparation of Wieland–Miescher ketone derivative **9** (Scheme 2). Starting from commercially available cyclohexane-1,3-dione (**11**), triketone **12** was obtained by two sequential Michael additions. Desymmetrization[14] catalyzed by a binam-*L*-prolinamide catalyst[15] enabled the synthesis of **13** in 81% yield and the installation of a quaternary center[16] in 94% *ee*. Treatment of **13** with trifluoroacetic acid generated carboxylic acid **14** in quantitative yield. Finally, the vinyl group was introduced using a modification of Stoltz's decarbonylative dehydration.[17] Accordingly, the desired Wieland–Miescher ketone derivative **9** could be isolated in 55% yield on gram scale.



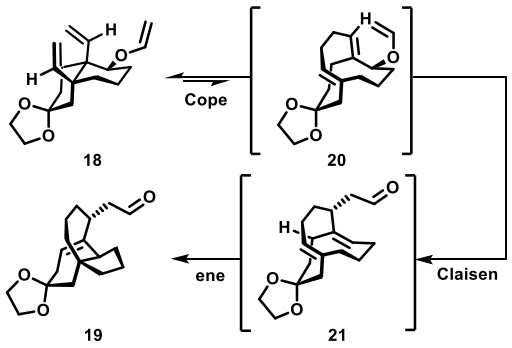
Scheme 2. Gram scale preparation of Wieland–Miescher derivative **9**.

Conjugate addition of a high-order cyano cuprate to enone from the convex face of **9**[18] gave *cis*-decalin **15** (Scheme 3). Selective acetalization of the less sterically hindered ketone furnished dioxolane **16** in 83% yield. Stereoselective reduction of the remaining carbonyl group was accomplished using L-Selectride to give alcohol **17**.[19] This material was subjected to transfer reaction[20] to yield vinyl ether **18**.[21] When the tandem process was attempted at elevated temperatures, we encountered problems with the decomposition of the starting material, probably due to the presence of residual acid. Reaction of triene **18** in the presence of alkoxides at 235 °C, as suggested by McMurry,[22] gave bridgehead alkene **19**.[23]



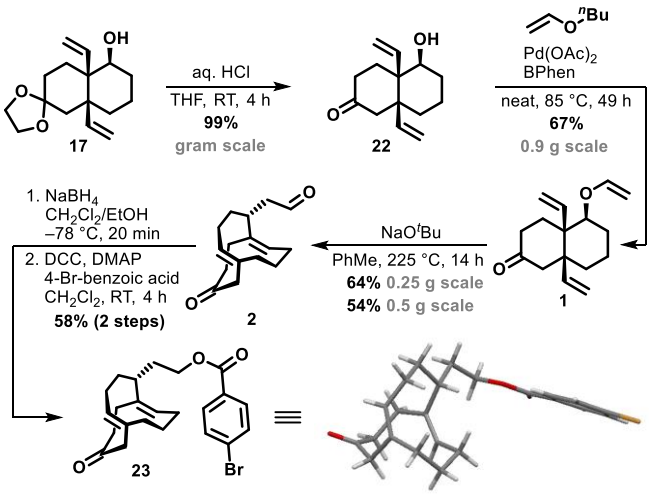
Scheme 3. Synthesis of advanced intermediate **17** and strain-releasing formation of bridgehead alkene **19**.

While the desired tandem Cope/Claisen rearrangement took place under these conditions, a subsequent strain-releasing transannular ene reaction led to the formation of **19** (Scheme 4).[24]



Scheme 4. Proposed mechanism of the Cope/Claisen/ene rearrangement.

At this point, we speculated that subtle modifications of the molecular scaffold of **18** could play a pivotal role in suppressing the undesired ene reaction (Scheme 5).

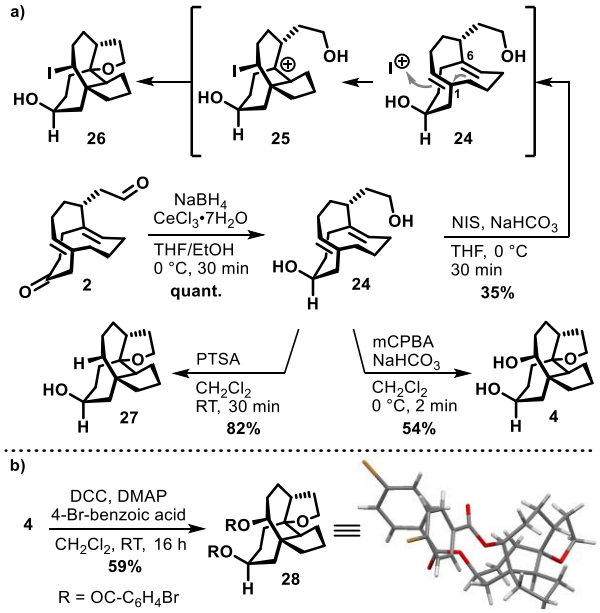


Scheme 5. Successful preparation of the double bridgehead 1,6-diene **2**.

Therefore, the acetal **17** was converted to ketone **22** in nearly quantitative yield. This material was subjected to vinyl exchange reaction to yield vinyl ether **1**. Application of the previously established conditions led to the double bridgehead 1,6-diene **2** in 64% yield, whose structure was confirmed by single crystal analysis of the bromobenzoate ester derivative **23**.[25]

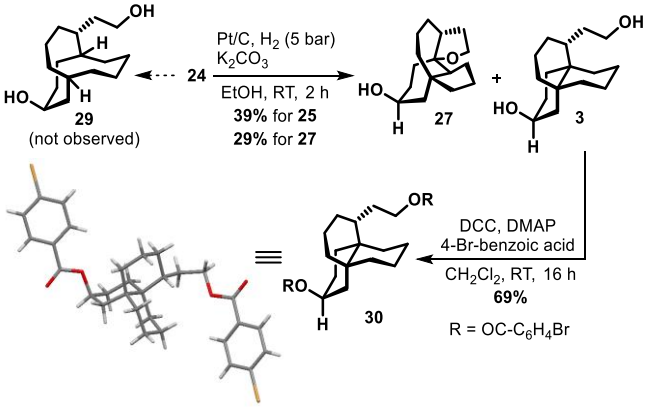
Next, we aimed to study the reactivity of the two spatially close double bonds in **2** in transannular reactions[5] (Schemes 6–8). First, the two carbonyl groups of **2** were reduced using Luche's conditions[26] to obtain diol **24** (Scheme 6a). With this substrate, cationic cascades could be performed to generate a new tetracyclic scaffold with three different substitution patterns (**4**, **26** and **27**). Thus, *N*-iodosuccinimide is attacked by the $\Delta^{1,2}$-bridgehead alkene of **24**. Within this reaction, two additional bonds, a C–C and a C–O bond,

were formed resulting in the tetracyclic iodoalcohol **26**. In an analogous fashion, protonation of **24** resulted in alcohol **27**. Treatment with m-CPBA afforded tetracyclic diol **4**. This material was converted to crystalline diester **28** which was used to confirm the tetracyclic architecture by X-ray analysis (Scheme 6b).



Scheme 6. a) Cationic cascade reactions of **24**. b) X-ray structure of **28**.

We then investigated hydrogenation of the two trisubstituted alkenes. Although Adams' catalyst was reported to promote the reduction of bridgehead double bonds,[27] in our studies diol **21** was chemically inert to those conditions. The use of platinum on charcoal under 5 bar of hydrogen pressure led to semi-hydrogenation of **24** to form ether **27** and [4.4.4]propellane **3**, likely derived from a HAT process (Scheme 7). The propellane framework was confirmed by single crystal analysis of bromobenzoate derivative **30**.

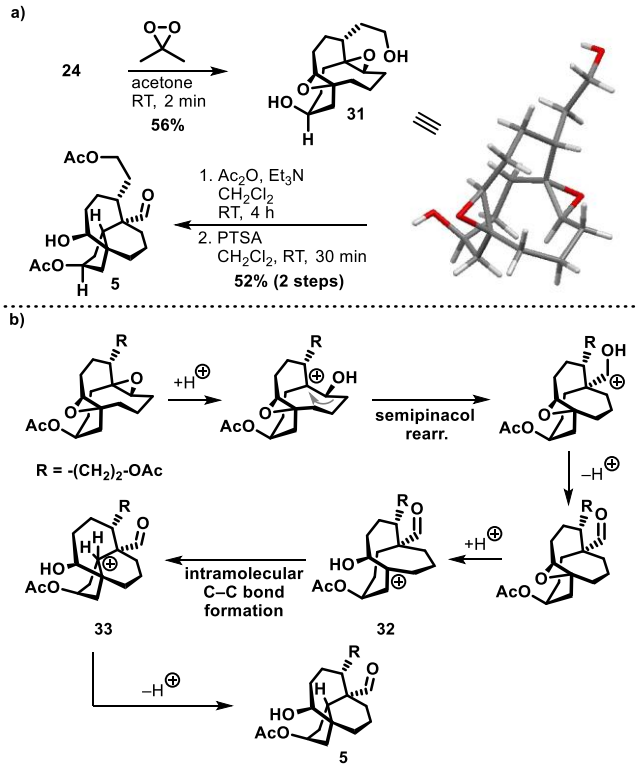


Scheme 7. Hydrogenation of bicyclo[4.4.4] diene **24**.

Our failure to find the saturated *out*/*out*-bicyclo[4.4.4]tetradecane[28] derivate **29** is in accordance with the results presented by Alder and Schleyer. Both groups predicted, that this scaffold is higher in energy compared to the [4.4.4]propellane and the corresponding bridgehead dienes, respectively. Interestingly, McMurry has been able to access *in*/*out*-bicyclo[4.4.4]tetradecane by hydrogenation of *in*-bicyclo[4.4.4]-1-tetradecene.[27b]

Epoxidation of **24** using dimethyldioxirane (DMDO) permitted further accumulation of strain in exocyclic groups (Scheme 8). The obtained *out*/*out* bisepoxide **31** represents the first example isomer of the highly strained *out*/*out* bicyclo[4.4.4]tetradecane cage which was again confirmed by X-ray.

Diacetylation of **31** was followed by treatment with Brønstedt acids to activate the spring-loaded epoxides. Semipinacol rearrangement[29] of the more sterically hindered epoxide and concomitant opening of the opposite oxirane led to **5** (Scheme 8b). The intramolecular C–C bond formation likely proceeded through a 1,5-transannular interaction in cyclodecyl cation **32** to give non-classical carbocation **33**, as described by Sorensen.[30] Finally, deprotonation assisted by the proximal acetate group gave **5**. In this sequence a different type of polycycle possessing a bicyclo[4.3.1] subunit was created.[31]



Scheme 8. a) Epoxidation of the bicyclo[4.4.4] cage of **24** and following epoxide opening. b) Proposed reaction mechanism for the strain-release intramolecular reaction.

Conclusions

In summary, the enantioselective synthesis of medium-sized cage **2** was accomplished using a ring-enlargement of a Wieland–Miescher ketone derivative. We demonstrated that the bridgehead bicyclo[4.4.4] diene system is isolable when the olefins are positioned in a 1,6-relationship. Subsequently, we showed that the release of molecular strain in medium-ring carbocyclic cages is effective in generating skeletal complexity. The use of different of C–C bond forming reactions allowed relaxation of the sphere-like core of diene **24**. A variety of topologically different carbocycles, including bicyclic and tetracyclic structures, were accessed in a diversity-oriented fashion.[2d, 2e] This approach could be applied in the exploration of sp^3-rich[2a,2c] three-dimensional molecular architectures particularly relevant for developing polycyclic frameworks with unusual exit vectors.

Acknowledgements

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31. For the structural analysis see Supporting Information.

5.3 Unpublished Results

In the present section additional studies carried out during the syntheses of propellanes and of a bridgehead bicyclo[4.4.4]tetradecadiene are described.

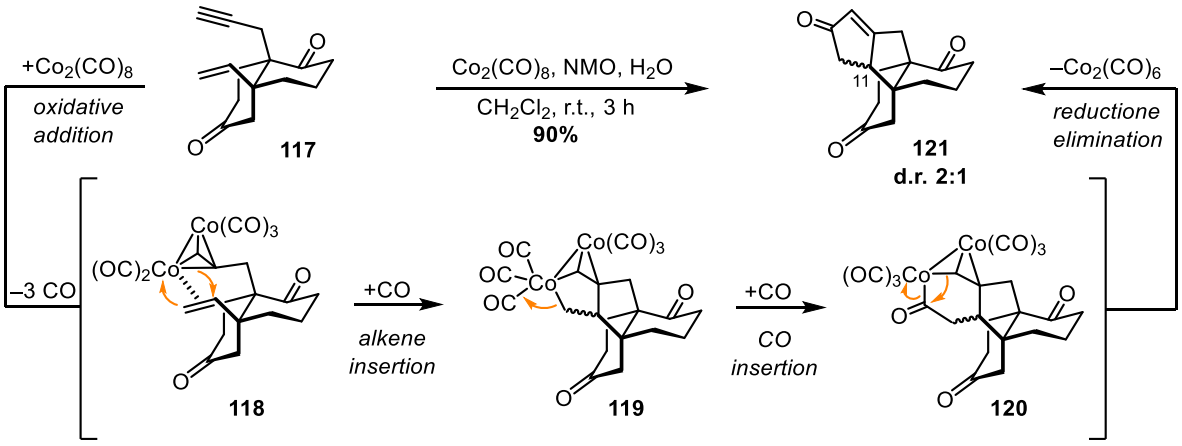
To expand the chemical diversity of propellanes, an alternative functional group pairing reaction was performed to form tetracyclic compounds. Moreover, a diastereoselective introduction of a nitrogen containing moiety on the [4.3.3]propellane scaffold was accomplished.

During the synthetic efforts toward the bridgehead diene, the formation of a tricyclic molecule of *type D* was observed.

5.3.1 Synthesis of Propellanes

Ring Closure

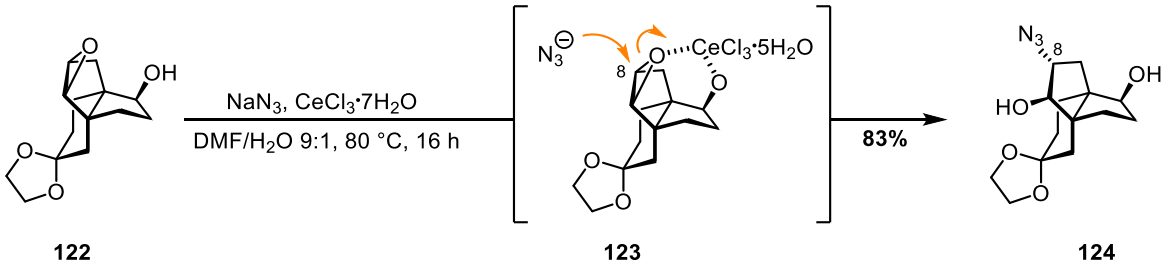
In the synthetic studies toward the carbocyclic propellanes a PAUSON–KHAND reaction was employed to form the third ring of **121** (Scheme 32). Treatment of alkyne **117** (reported in "Asymmetric Synthesis of Carbocyclic Propellanes") with stoichiometric amounts of dicobalt octacarbonyl gave the intermediate complex **118**. [51] Subsequent alkene and CO insertion formed the carbonyl functionality in **120**. Final reductive elimination of cobalt delivered tetracyclic cyclopentenone **121** as a diastereomeric (d.r. 2:1) mixture of products at C-11.



Scheme 32. Application of the PAUSON–KHAND reaction in the synthesis of propellane **121**.

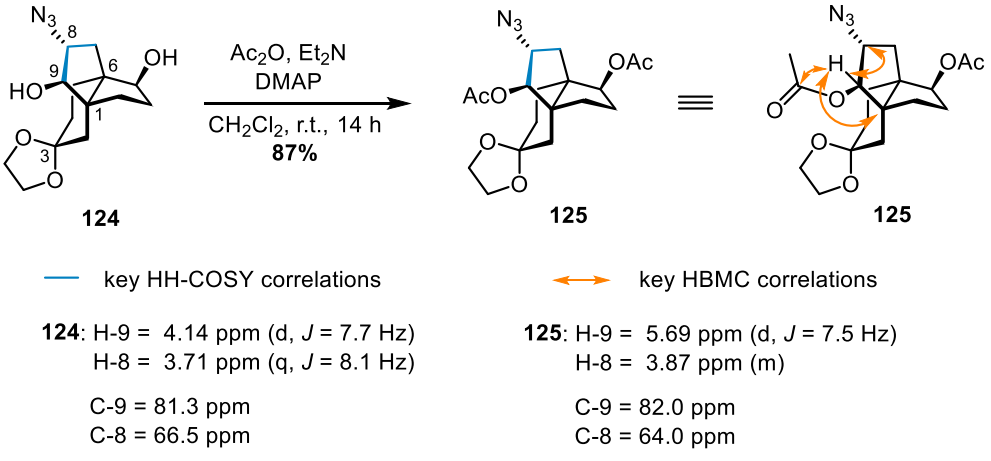
[4.3.3]Propellane Functionalization

The utility of the new synthetic entry to propellanes was demonstrated by the chemo- and diastereoselective functionalization of the *type A* polycyclic core, as detailed in the manuscript “Asymmetric Synthesis of Carbocyclic Propellanes”. During these studies, a diastereoselective introduction of an amine precursors was investigated (Scheme 33). Starting from epoxide **122**, a cerium promote epoxide opening allowed the diastereoselective installation of an azide group at C-8 of **124** likely *via* intermediate **123**.



Scheme 33. Synthesis of azido [4.3.3]propellane **124**.

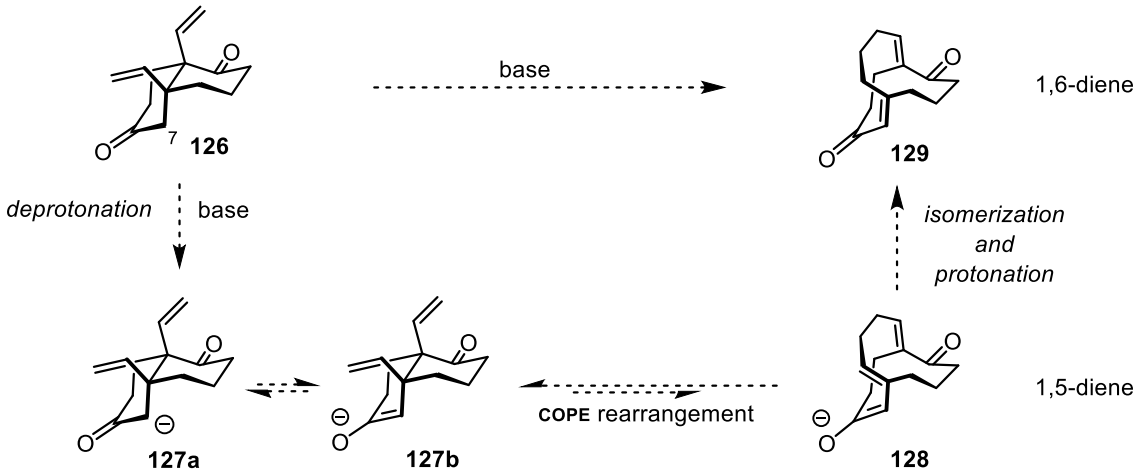
The relative configuration of the stereogenic centers was determined by analysis of the homo- and heteronuclear NMR correlations in propellane **125** obtained by acetylation of **124** (Scheme 34). HH-COSY analyses of **124** and **125** revealed the AMX_2 spin system, which was further defined by HMBC analysis of **125**. The correlations between H-9 and both C-1 and C-8 confirmed the neopentyl alcohol moiety.



Scheme 34. Structural determination of azido [4.3.3]propellanes **124** and **125**.

5.3.2 Twistane Formation

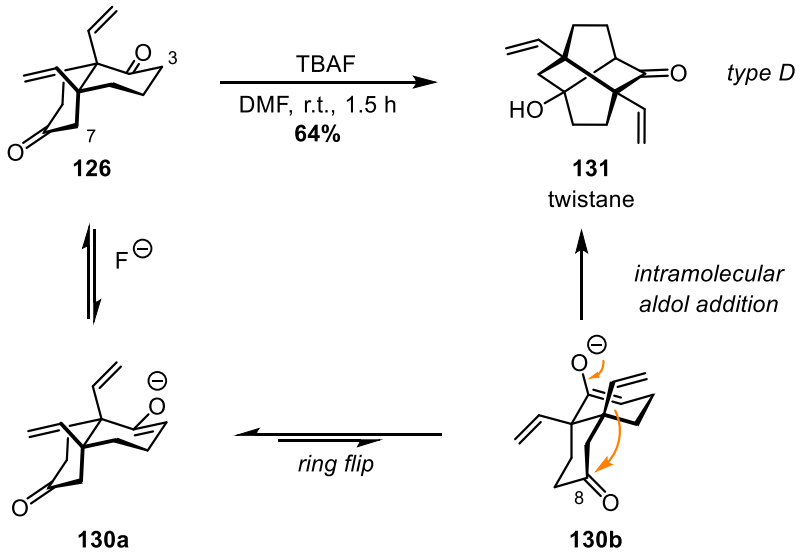
The synthetic studies carried out by the group of SHEA revealed that the COPE rearrangement of *cis*-divinyl decalin to *meso* bridgehead bicyclo[4.4.4]tetracadeca-1,5-diene is thermodynamically unfavored.[5b] To promote the installation of the bridgehead double bonds in a stable 1,6-relationship, a cascade enolate formation/COPE rearrangement/isomerization process was investigated (Scheme 35). Deprotonation at C-7 of diketone **126** would generate enolate **127**. The presence of an anionic charge or high electron density vicinal to the 1,5-diene unit in **127** would facilitate the [3,3]-sigmatropic rearrangement to 1,5-diene **128**.[dd, 52] Finally, the isomerization of dienolate **128** would shift the equilibrium toward 1,6-diene **129**.



Scheme 35. Attempted enolate promoted COPE rearrangement.

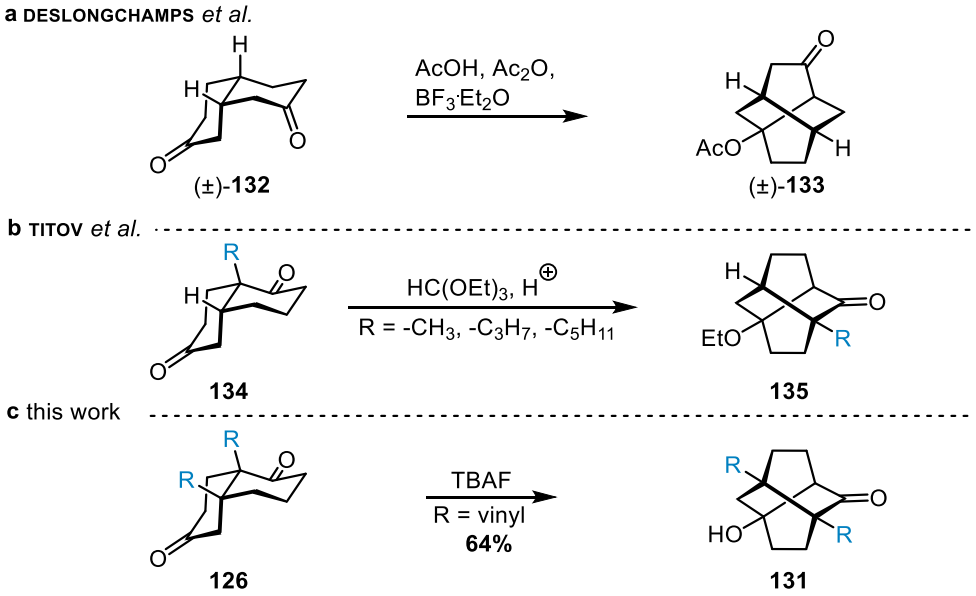
Following a procedure reported by the group of MAJETICH, diketone **126** was treated with TBAF (Scheme 36).[53] A competitive deprotonation at C-3 of **126** led to enolate **130a** which likely underwent decalin ring flipping to form **130b**. At this point, an intramolecular aldol addition at C-8 of **130b** yielded a new six membered ring. The overall process formed an additional connection between two different bridges, thus giving the twistane core (*type D*) of **131**. This serendipitous outcome expanded the variety of tricyclic scaffold (*types A*, *B* and *D*) accessed from the bicyclic WIELAND–MIESCHER ketone scaffold.

[dd] Anion formation provides an electron push that assist breaking of the vicinal C–C bond.



Scheme 36. Formation of *type D* tricyclic compound **131** from diketone **126**.

In 1968, the group of DESLONGCHAMPS prepared a racemic mixture of twistane **133** *via* intramolecular aldol addition of **132** (Scheme 37a).[54] A similar approach was also used by TITOV *et al.* to synthesize monoalkyl substituted **135** starting from enantioenriched WIELAND–MIESCHER derivatives **134** (Scheme 37b).[55] The strategy employed in this doctoral work allowed the preparation of *cis*-divinyl substituted twistane **131** which could attract further synthetic interests as caged polycyclic compound (Scheme 37c).

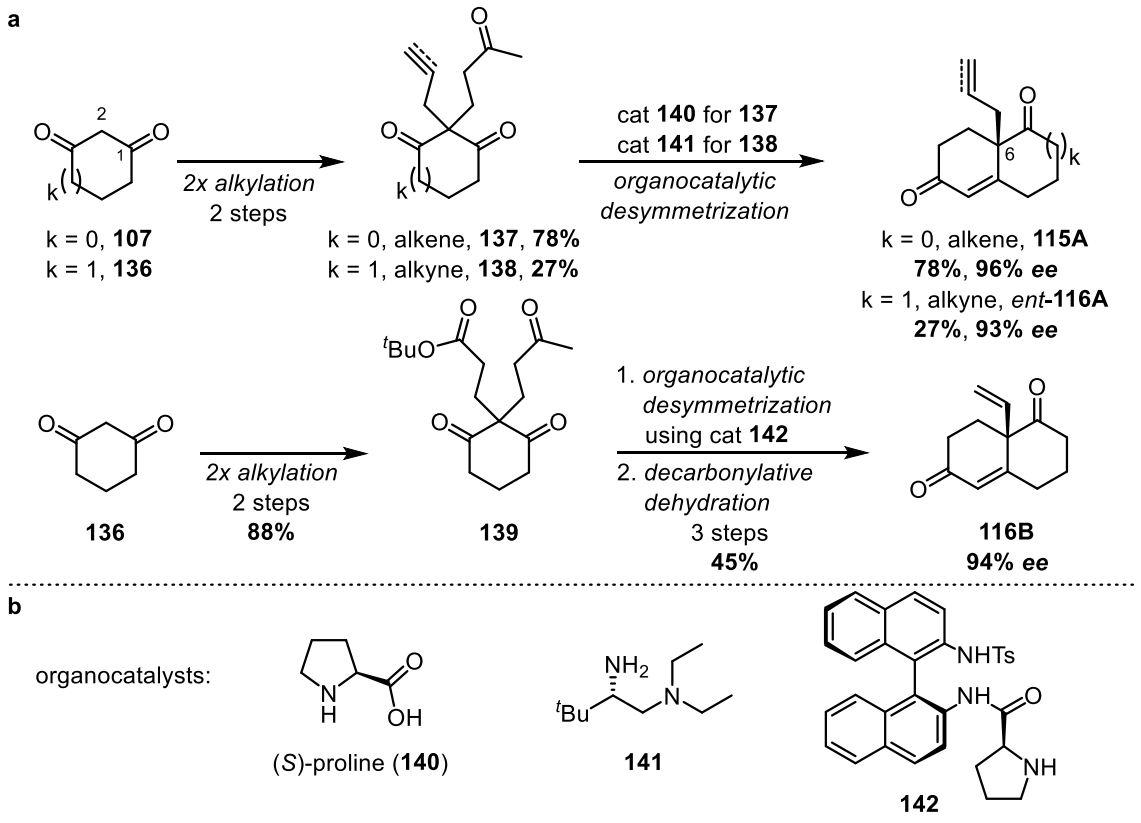


Scheme 37. Syntheses of twistane derivatives from decalindiones.[ee]

[ee] Yields for the reactions in Scheme 37a and b were not given.

5.4 Summary

The synthesis of polycyclic molecules was accomplished using the *early C_q introduction* strategy inspired by previous works of PAQUETTE, KOTHA and SHEA.[ff, 13b, 5b, 14] The study commenced with the preparation of HAJOS–PARRISH and WIELAND–MIESCHER ketones **115** and **116**, respectively (Scheme 38a). Triketones **137–139** were obtained *via* subsequent alkylations at C-2 of 1,3-cycloalkadiones **107** or **136**, thus installing a prochiral carbon at C-2 of triketones **137–139** by simple *C*-alkylations. The first quaternary carbon required by the applied strategy was introduced at the C-6 position of bicyclic enones **115** and **116** with high enantiomeric excess (93–96% *ee*) by using enantioselective versions of the ROBINSON annulation (Scheme 38).[51] The HAJOS–PARRISH derivative **115A** was obtained using (*S*)-proline (**140**, Scheme 38b), whereas formation of WIELAND–MIESCHER enone **116A** was catalyzed by primary amine **141**.[56]

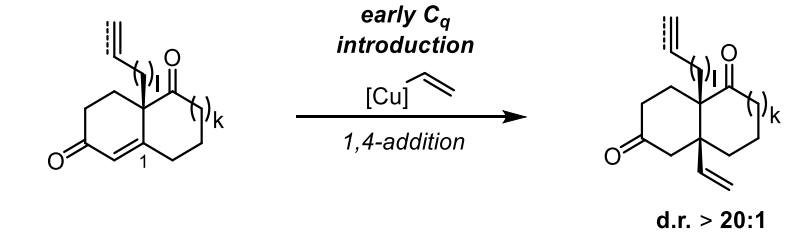


Scheme 38. Synthesis of bicyclic enones **115** and **116**. a) Reaction sequences. b) Organocatalysts employed in the desymmetrization reactions.

[ff] The strategy is reported and discussed in chapter 5.1.

A longer five steps sequence delivered enone **116B** after annulation of triketone **139** catalyzed by prolinamide **142** and subsequent vinyl group introduction at C-6 by decarbonylative dehydration.[57]

Following the planned strategy, the second quaternary carbon was installed at the C-1 position of bicyclic enones **115** and **116** by conjugate additions of vinyl cuprates (Scheme 39). This reaction led to the *cis*-disubstituted bicyclic frameworks of **117**, **126** and **143** with excellent diastereoselectivity.

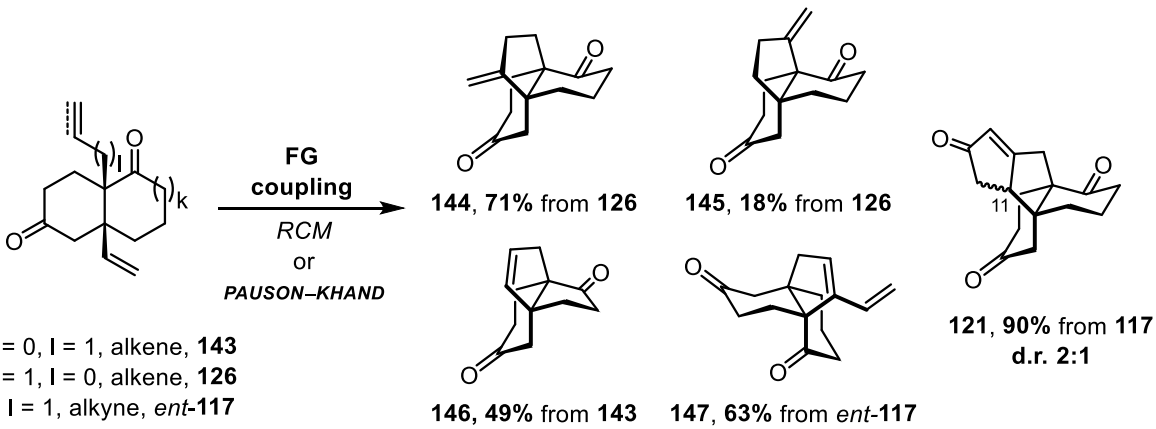


k = 0, l = 1, alkene, **115A**
k = 1, l = 0, alkene, **116B**
k, l = 1, alkyne, *ent*-**116A**

k = 0, l = 1, alkene, **143**, **49%**
k = 1, l = 0, alkene, **126**, **72%**
k, l = 1, alkyne, *ent*-**117**, **72%**

Scheme 39. Conjugate addition of vinyl cuprates to enones **115** and **116**.

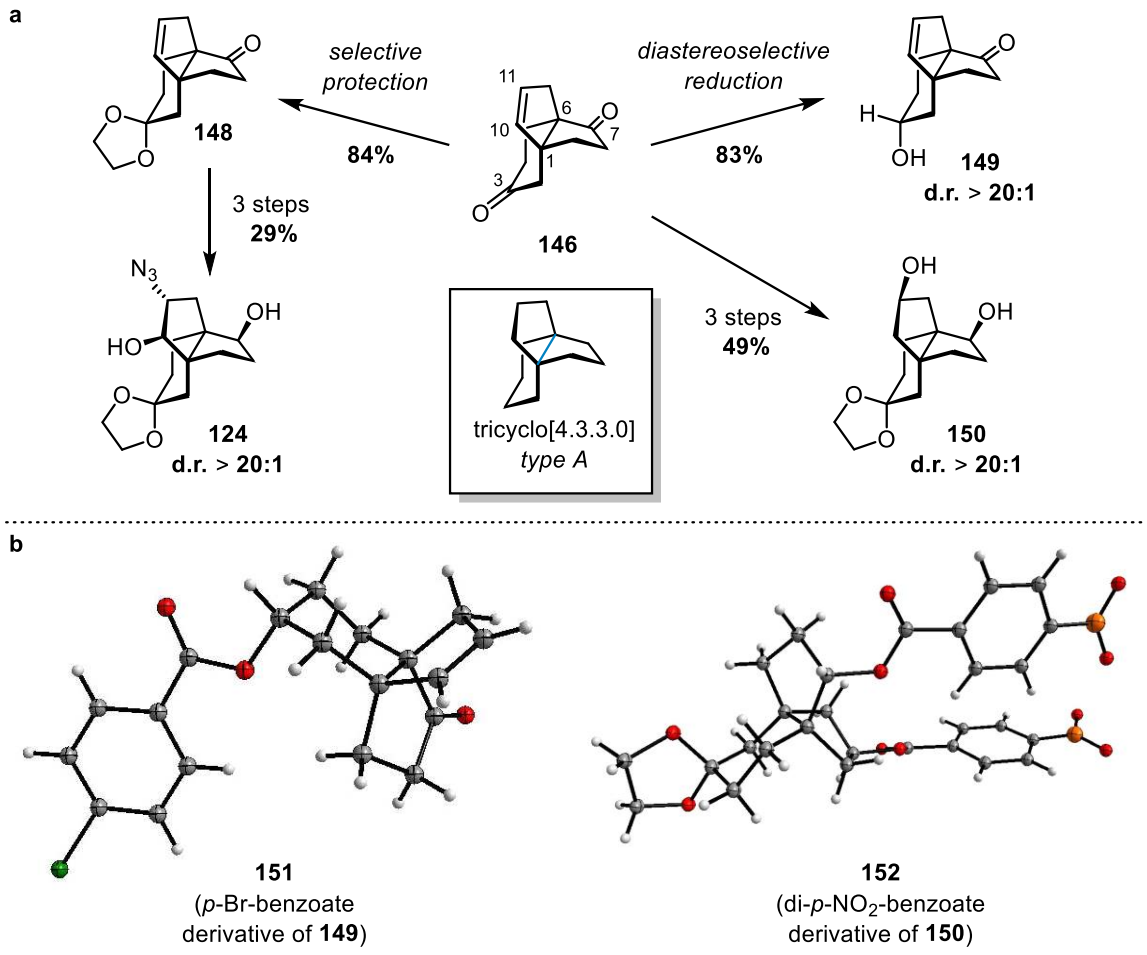
Inspired by the work of KOTHA, RCM of ketone **143** gave propellane **146** (Scheme 40).[14] When decalin **126** was subjected to RCM, a separable mixture of regioisomeric propelladiones **144** and **145** was formed through a formal intramolecular hydrovinylation.[58] As shown by PAQUETTE, alternative cyclization reactions could be employed to expand the structural diversity of propellanes.[13b] Therefore, diene **147** and cyclopentanone **121** were obtained from alkyne **117** using an enyne metathesis and a PAUSON–KHAND reaction, respectively.



k = 0, l = 1, alkene, **143**
k = 1, l = 0, alkene, **126**
k, l = 1, alkyne, *ent*-**117**

Scheme 40. Synthesis of propellanes *via* ring-closing reactions.

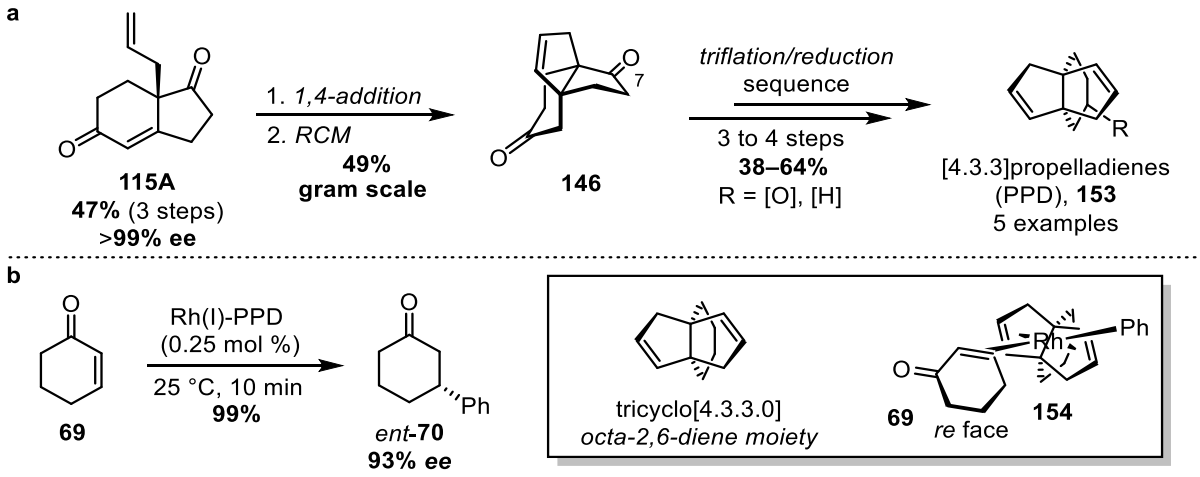
The versatility of this synthetic approach permitted variations of ring sizes and appendages of the final tricyclic scaffolds. A further validation of the new methodology was accomplished by selective functionalization of propellenedione **146** (Scheme 41a). The two keto groups of **146** were differentiated by selective reactions at the less sterically hindered C-3 position: protection gave dioxolane **148**, whereas reduction yielded alcohol **149** with excellent diastereomeric ratio. Heteroatoms were introduced at the C-10 and/or C-11 positions of the cyclopentene ring of **146** to give diols **124** and **150**. The formation of these substituted carbocycles showed that all the three bridges of the [4.3.3]propellane scaffold can be functionalized in a diastereoselective fashion. Structure and absolute configuration of propellanes **149** and **150** were confirmed by single crystal analysis of the corresponding esters **151** and **152** (Scheme 41b).



Scheme 41. Chemo- and diastereoselective functionalization of [4.3.3]propellane **146**. a) Overview of the synthesis. b) X-Ray crystal structure of **151** and **152**.

This study showed that enantioenriched propellanes (93–96% *ee*) can be prepared in five to six steps starting from 1,3-cycloalkadiones (**107** or **136**) and stereoselectively functionalized with different heteroatoms at the three bridges.

With an asymmetric entry to the propellanes in hand, the impact of this polycyclic scaffold in catalysis was evaluated through the synthesis of novel chiral diene ligands. Initially, enone **115A** was obtained in high enantioenriched form (>99% *ee*) after recrystallization (Scheme 42a), thus avoiding resolution of the racemic mixtures usually encountered in the synthesis of chiral diene ligands. Subsequently, conjugate addition and following ring-closing metathesis gave propellane **146** performing the reactions on gram scale. A bicyclo[3.3.0]octa-2,6-diene moiety was installed on the propellane scaffold of **146** *via* enol triflation at C-7 followed by reduction, a protocol which was used for synthesis of several bridged dienes. Propelladiene (PPD) ligands **153** were obtained in overall eight to nine steps (9–15% overall yields) starting from 1,3-cyclopentadione (**107**).[gg] Their performance was then tested in the Rh-catalyzed 1,4-arylation of cyclic enones (Scheme 42b). Adduct *ent*-**70** was formed in excellent yield and enantiomeric excess (99%, 93% *ee*). The stereochemical outcome of the reaction was rationalized by the formation of complex **154** in which cyclohex-2-enone (**69**) coordinated to rhodium from the *re* face.

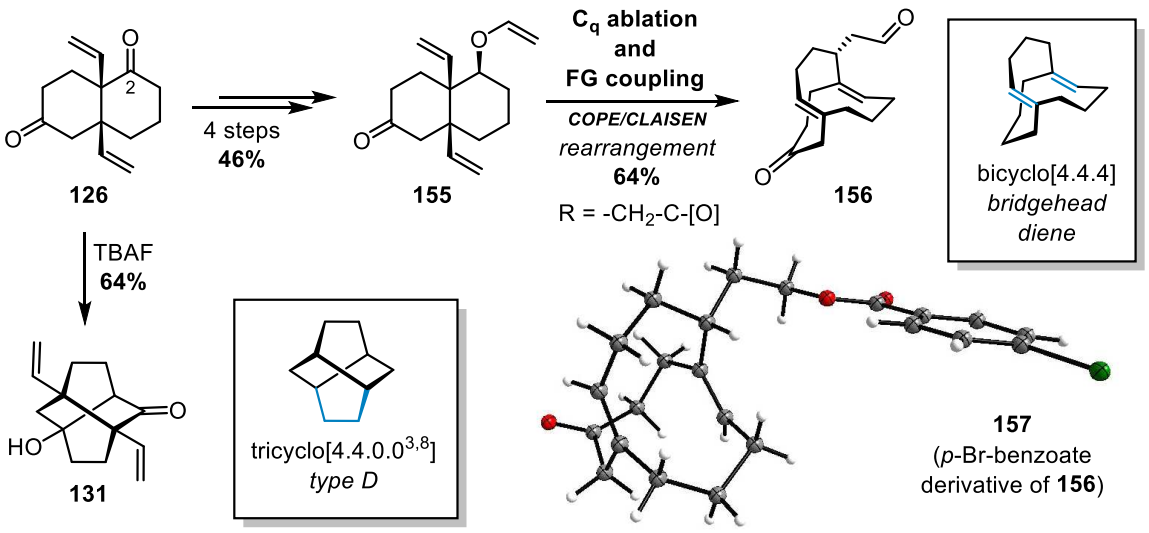


Scheme 42. Highly enantioenriched PPD ligands. a) Synthesis of PPDs. b) Application in the Rh-catalyzed arylation of cyclic enones.

When compared to the reported bicyclo[3.3.m] type ligands (m = 0–2), the use of tricyclic PPDs led to higher turnover frequency.[59, 32]

[gg] LIN's tricyclic diene **55** was obtained in ten steps (21% overall yields) *via* enzymatic resolution of the intermediate racemic alcohols.

In the last project, the C–C bond network typical of bicyclic WIELAND–MIESCHER type ketones was modified to generate topologically different bridged polycyclic scaffolds. The works of SHEA and GUI showed that bicyclic bridgehead dienes are closely related to tricyclic scaffolds of *type A* and *B*. Their studies indicated that the installation of double bonds at the bridgehead positions requires release of strain in small-ring carbocycles, thus hampering synthesis of these dienes from low strain precursors. In this work, the formation of a medium-sized bridgehead diene was achieved using a tandem process (Scheme 43). Ketone **126**, previously obtained using the *early C_q introduction* strategy, was elaborated at C-2 to deliver triene **155** in four steps. The fused bicyclic skeleton of **155** was then transformed into the bridged bicyclic framework of **156** through a COPE/CLAISEN rearrangement. Single crystal analysis of *p*-bromo-benzoate derivative **157** confirmed the structure and absolute configuration of caged **156**. The isolation of this compound, demonstrated that the bridgehead bicyclo[4.4.4]tetradecadiene system is stable when the double bonds are placed in a 1,6-relantionship.[hh] During this study, *cis*-disubstituted twistane **131** was serendipitously obtained by treatment of dione **126** with TBAF. This outcome further expanded the skeletal diversity available from bicyclic **126** to the tricyclic compound of *type D* **131**.

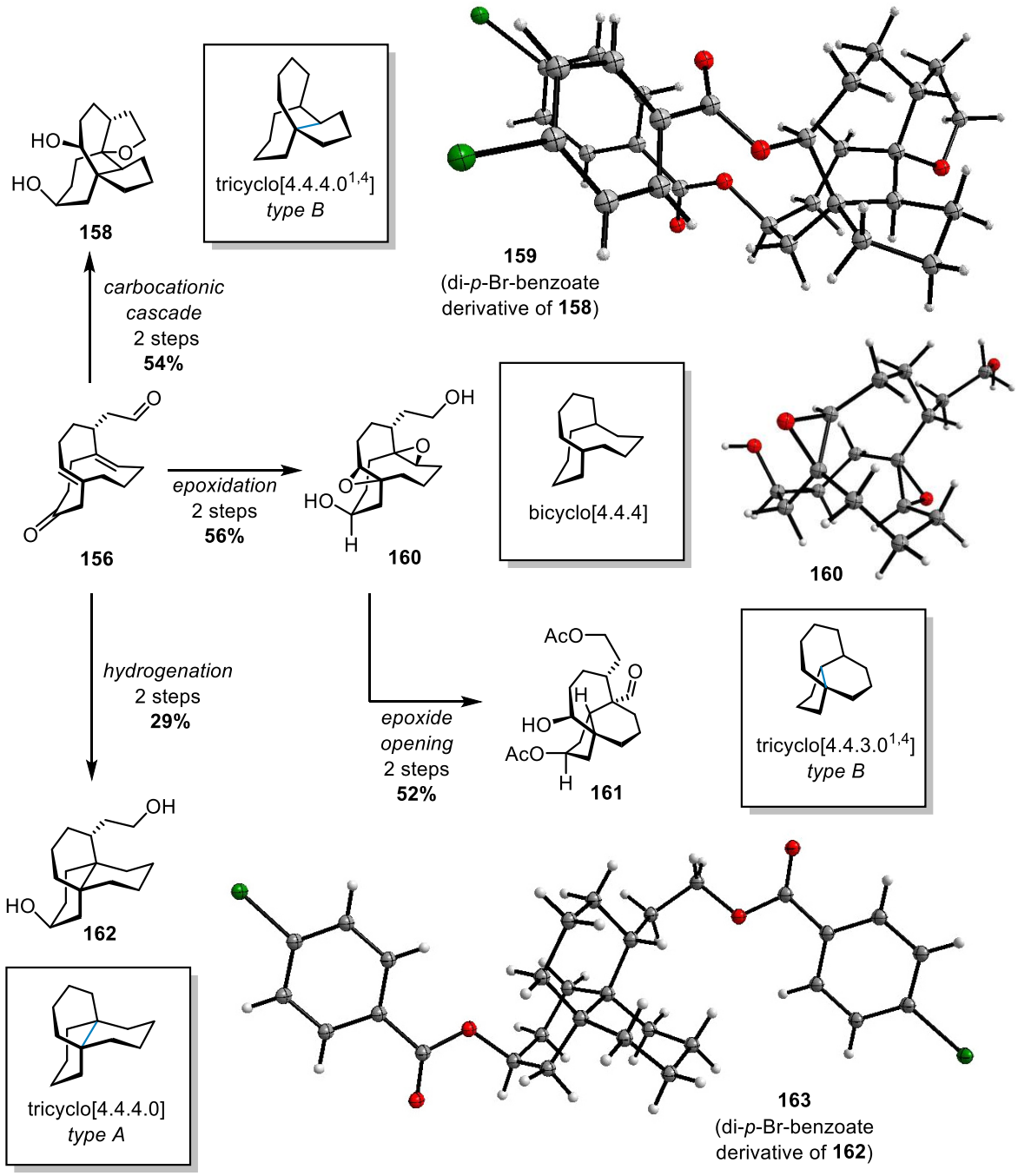


Scheme 43. Synthesis of bridgehead diene **156** and twistanol **131**.

Different polycyclic scaffolds were accessed from the strained diene **156** by intramolecular C–C bond formations (Scheme 44). Thus, a carbocationic cascade gave the tricyclic *type B*

[hh] The groups of SHEA and HAMOND attempted the synthesis of bicyclo[4.4.4]tetradeca-1,5-diene (**31**). However, the bridgehead diene directly converted into the less strained *cis*-divinyl decalin **84**. See chapter 4.4 and refs 5.

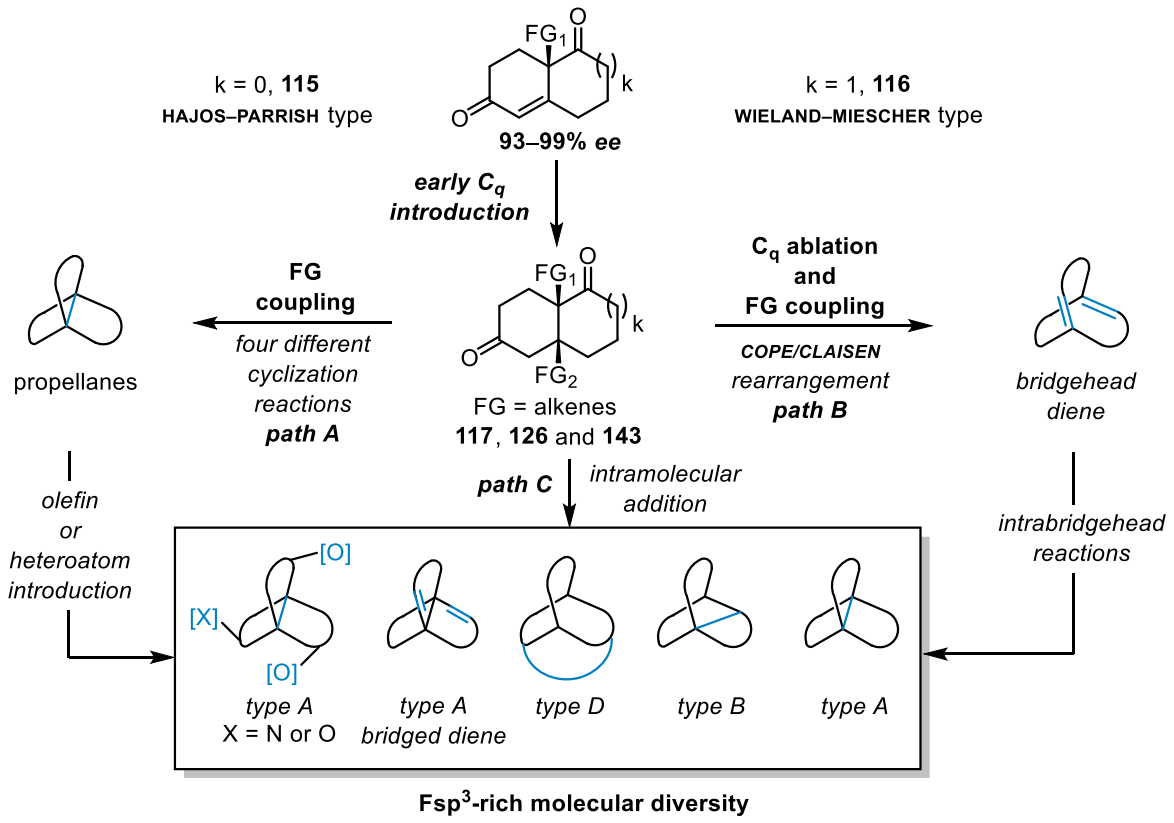
scaffold of **158**, epoxide rearrangement of **160** formed the *type B* skeleton of **161**, whereas hydrogenation of diene **156** led to [4.4.4]propellane **162** (*type A* scaffold) in two steps.



Scheme 44. Synthesis of polycyclic hydrocarbon scaffolds from **156** *via* intramolecular C–C bond formations.

The structure and absolute configuration of epoxide **160** was confirmed by X-ray analysis. In the case of diol **158** and propellane **162** *p*-bromobenzoate derivatives **159** and **163** were prepared and obtained as single crystals.

In summary, it has been demonstrated that the bicyclic frameworks of WIELAND–MIESCHER and HAJOS–PARRISH **115** and **116** can be modified through an *early* C_q *introduction* strategy. Polycyclic hydrocarbon scaffolds of different three-dimensional shapes and topologies were obtained with high enantiomeric excess (93 to >99% *ee*, Scheme 45). Large-ring propellanes (*type A* scaffold, *path A* and *B*), bridged cyclodecanes (*type B* scaffold, *path B*), and a symmetric twistane (*type D* scaffold, *path C*) were successfully prepared. Variation on ring sizes and substituents of the building blocks, the use of alternative cyclization reactions, olefinations, selective functionalization and intramolecular reactions were employed to access diverse carbocyclic molecules in a diversity-oriented fashion.



Scheme 45. Diversity-oriented approach to polycyclic hydrocarbon scaffolds.

The introduction of exocyclic molecular fragments and additional hydrogen bond donor and acceptors on the polycyclic scaffolds would further broad their diversity and eventually furnish sp^3-rich, three-dimensional molecular entities suitable for drug discovery campaigns.

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Appendix

Appendix 1 — Supporting Information

i. Multivalent Polyglycerol Supported Imidazolidin-4-one Organocatalysts for Enantioselective Friedel–Crafts Alkylations

The supporting information is given under the following link:
https://dx.doi.org/10.3762/bjoc.11.83.

ii. Asymmetric Synthesis of Carbocyclic Propellanes

The supporting information is given under the following link:
https://dx.doi.org/10.1021/acs.orglett.7b00836

iii. Synthesis of Highly Enantioenriched Propelladienes and their Application as Ligands in Asymmetric Rh-Catalyzed 1,4-Additions

The supporting information is given under the following link:
https://dx.doi.org/10.1021/acs.orglett.8b02204

iv. Strain-Release Approach to Polycyclic Hydrocarbon Scaffold

Strain-Release Approach to Polycyclic Hydrocarbon Scaffolds

Tommaso Pecchioli, Ahed Almalla, Simon Steinhauer, Dieter Lentz and Mathias Christmann*

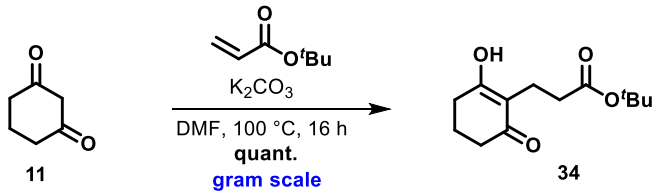
Table of Contents

General information

Commercial reagents and solvents were used as received unless otherwise stated. Anhydrous dichloromethane, diethyl ether and toluene were purified with a MB-SPS-800 (Braun) solvent purification system unless otherwise stated. Anhydrous DMF was purchased from Acros Organics in sealed bottles under an argon atmosphere in presence of molecular sieves (4 Å). Tetrahydrofuran has been distilled over Na/benzophenone. Xylenes have been dried over 3 Å MS. Solvents have been deoxygenated through argon bubbling when stated. *N*-Tosyl-(S_a)-binam-*L*-prolinamide was prepared according to the literature.[1] Benzoic anhydride (Bz_2O) has been purified following known protocols.[2] Thiophene has been distilled and stored over 3 Å MS. CuCN has been purified following known protocols.[2] Dimethyldioxirane has been prepared following known procedure and titrated prior use.[3] All reactions have been carried out under magnetic stirring and were monitored by TLC analysis on 0.25 mm silica gel plates. Column chromatography has been carried out on silica gel (32–63 μm or 230–400 mesh) or Al_2O_3 (neutral, 6% water, activity grade III). Yields refer to spectroscopically and analytically pure compounds unless otherwise stated. When stated, purity was calculated by ^{1}H-NMR. ^{1}H-NMR and ^{13}C-NMR spectra have been recorded on 400, 500, and 700 MHz instruments. Chemical shifts are reported relative to $CDCl_3$ (^{1}H: δ = 7.26 ppm; ^{13}C: δ = 77.0 ppm), CD_3OD (^{1}H: δ = 3.31 ppm; ^{13}C: δ = 49.0 ppm), and C_6H_6 (^{1}H: δ = 7.16 ppm). For detailed peak assignments 2D spectra have been measured (COSY, DEPT, HMQC, HMBC, and NOESY as necessary). IR spectra have been recorded with an FT-IR spectrometer. Mass spectra have been recorded on a quadrupole mass spectrometer by direct inlet. HRMS analyses have been performed with an FTICR mass spectrometer (ESI-TOF, 4 μL/min, 1.0 bar, 4 kV). Optical rotation measurements have been performed using a 1 dm optical-path length cell with the frequency of the Na_D line measured at the indicated temperature and concentration reported in g/100 mL. HPLC analyses have been performed on an Agilent Technologies 1200 Series equipped with a Chiralpak IC column.

Experimental Procedures

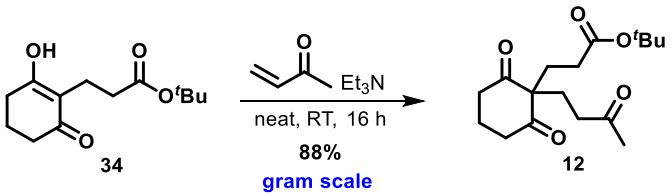
***tert*-Butyl 3´-(2-hydroxy-6-oxocyclohex-1-en-1-yl)propanoate (34)[4]**



To a solution of 1,3-cyclohexadione (**11**) (1.50 g, 13.4 mmol, 1.0 equiv.) in anhydr. dimethylformamide (14 mL) was added potassium carbonate (2.22 g, 16.1 mmol, 1.2 equiv.) at room temperature. The mixture was stirred 10 minutes and then *tert*-butyl acrylate (2.39 mL, 16.1 mmol, 1.2 equiv.) was added. Afterward, the reaction mixture was stirred at 100 °C for 16 h. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was dissolved in water (30 mL) and washed with dichloromethane (2x10 mL). The aqueous phase was acidified with aq. HCl (1 M) till pH 1-3 and extracted with dichloromethane (4x150 mL). The combined organic phases were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residual dimethylformamide was removed in vacuo to give crude ester **34** as a brown oil (3.33 g, quant.), which was used in the next step without purification. A spectroscopically pure sample was obtained as a yellow oil after purification by column chromatography (ethyl acetate/pentane 2:1).

R_f = 0.69 (ethyl acetate/pentane 2:1, anisaldehyde; UV active at 254 nm); **^{1}H-NMR** ($CDCl_3$, 500 MHz): δ = 9.80 (br. s, 1H), 2.47–2.44 (m, 6H), 2.32 (dd, J = 7.3, 6.0 Hz, 2H), 1.91 (p, J = 6.5 Hz, 2H), 1.44 ppm (s, 9H); **^{13}C-NMR** ($CDCl_3$, 126 MHz): δ = 198.9, 178.1, 173.7, 115.0, 82.6, 36.8, 34.5, 29.4, 28.2 (3C), 20.7, 16.8 ppm; **IR** ($CDCl_3$): $\tilde{\nu}$ = 3132, 2978, 2937, 1717, 1589, 1379, 1369, 1282, 1257, 1153, 1076 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{13}H_{20}O_4Na$ $[M+Na]^+$ 263.1254, found: 263.1255.

***tert*-Butyl-3´-(2,6-dioxo-1-(3-oxobutyl)cyclohexyl)propanoate (12)[5]**

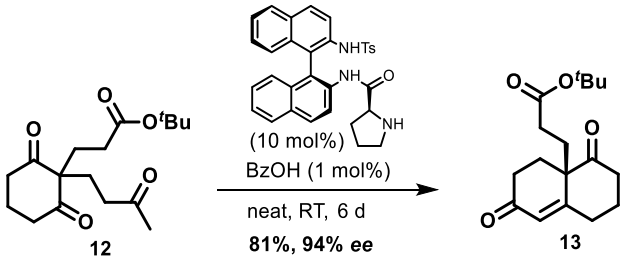


To the crude ester **34** (2.94 g, 12.3 mmol, 1.0 equiv.), were added freshly distilled methyl vinyl ketone (1.23 mL, 14.7 mmol, 1.2 equiv.) and triethylamine (17 µL, 0.122 mmol, 1 mol%). The reaction mixture was stirred at room temperature for 16 h to give an orange oil. Purification of the residue by column chromatography (silica gel, pentane/ethyl acetate = 6:1) yielded triketone **12** (3.34 g, 88%) as an orange oil.

R_f = 0.37 (pentane/ethyl acetate 3:1, anisaldehyde); **^{1}H-NMR** ($CDCl_3$, 500 MHz): δ = 2.66–2.57 (m, 4H), 2.30 (t, J = 7.4 Hz, 2H), 2.06–2.02 (m, 5H), 1.99–1.92 (m, 6H), 1.37 ppm (s, 9H); **^{13}C-NMR** ($CDCl_3$, 126 MHz): δ = 209.6 (2C), 207.4, 172.0, 80.8, 67.0, 38.4 (2C), 38.2, 30.3, 30.0, 29.1, 28.1 (3C), 28.0, 17.2 ppm; **IR** ($CDCl_3$): $\tilde{\nu}$ = 2975,

2934, 1717, 1689, 1365, 1149, 1027, 846 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{17}H_{26}O_5Na$ $[M+Na]^+$ 333.1672, found: 333.1662.

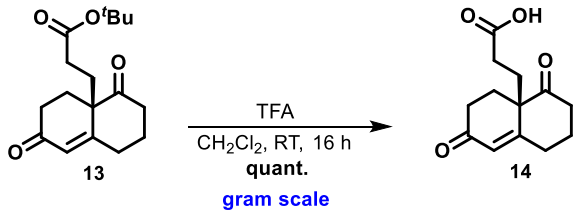
(8a*R*)-*tert*-Butyl-3´-(3,4,8,8a-Tetrahydronaphthalene-1,6(2H,7H)-dione-8a-yl)propanoate (13)[5]



A mixture of triketone **12** (1.86 g, 5.98 mmol, 1.0 equiv.), *N*-tosyl-(S_a)-binam-*L*-prolinamide (320 mg, 0.598 mmol, 10 mol%), and benzoic acid (7.3 mg, 0.0598 mmol, 1 mol%) was stirred in a standard glass vial at room temperature for 6 d. The reaction mixture was directly absorbed onto silica and purified by column chromatography (silica gel, pentane/ethyl acetate = 6:1) to give the enone **13** (1.42 g, 81%, 94% *ee*) as a colorless oil. The enantiomeric excess was determined by chiral HPLC on a Chiralpak IC column (^{n}hexane/isopropanol 65:35, 0.8 mL/min, λ = 254 nm, 20 °C): *S* isomer t_r = 22.4 min and *R* isomer t_r = 27.9 min.

R_f = 0.32 (pentane/ethyl acetate 6:1, anisaldehyde; UV active at 254 nm); **[α]$_D^{22}$** = +56.9 (c = 1.00, chloroform); **^{1}H-NMR** ($CDCl_3$, 500 MHz): δ = 5.87 (d, *J* = 1.8 Hz, 1H), 2.81 (dddd, *J* = 15.4, 13.6, 5.3, 2.0 Hz, 1H), 2.73 (ddd, *J* = 15.3, 13.8, 6.1 Hz, 1H), 2.51–2.43 (m, 2H), 2.40–2.36 (m, 2H), 2.29–2.20 (m, 2H), 2.18–2.12 (m, 2H), 2.09–1.97 (m, 3H), 1.68 (qt, *J* = 13.6, 4.3 Hz, 1H), 1.41 (s, 9H); **^{13}C-NMR** ($CDCl_3$, 126 MHz): δ = 210.1, 198.1, 171.8, 165.4, 126.7, 81.2, 54.0, 38.5, 33.5, 31.9, 30.3, 29.7, 28.1 (3C), 25.7, 23.4 ppm; **IR** ($CDCl_3$): $\tilde{\nu}$ = 2926, 1717, 1686, 1369, 1223, 1153 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{17}H_{25}O_4$ $[M+H]^+$ 293.1748, found: 293.1756.

(8a*R*)-(3,4,8,8a-Tetrahydronaphthalene-1,6(2H,7H)-dione-8a-yl)propanoic acid (14)

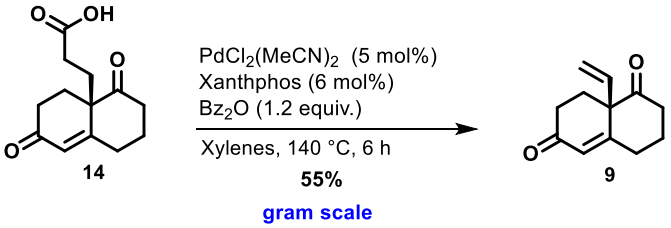


To a solution of ester **13** (1.42 g, 4.86 mmol, 1.0 equiv.) in dichloromethane (10 mL), trifluoroacetic acid (3.72 mL, 48.6 mmol, 10.0 equiv.) was added at 0 °C. The solution was stirred at 0 °C for 5 minutes and then at room temperature for 16 h. The solvent was removed under reduced pressure, and the residual TFA azeotropically removed using toluene, to give the spectroscopically pure acid **14** (1.15 g, quant.) as a brown oil, which solidified during storage at 4 °C.

m.p.= 106–108 °C; **R_f** = 0.26 (pentane/ethyl acetate 1:1 + 1% AcOH, anisaldehyde; UV active at 254 nm); **[α]$_D^{22}$** = +56.9 (c = 1.00, chloroform); **^{1}H-NMR** ($CDCl_3$, 700 MHz): δ = 5.91 (d, *J* = 1.8 Hz, 1H), 2.81 (dddd, *J* = 15.4, 13.5, 5.2, 2.0 Hz, 1H), 2.71 (ddd, *J* = 15.4, 13.7, 6.2 Hz, 1H), 2.54–2.49 (m, 2H), 2.47–2.43 (m, 1H), 2.41–2.35 (m, 2H),

2.34–2.29 (m, 1H), 2.23 (ddd, *J* = 16.3, 9.9, 5.3 Hz, 1H), 2.19–2.15 (m, 2H), 2.10 (ddd, *J* = 14.4, 9.9, 5.5 Hz, 1H), 2.04 (dddd, *J* = 14.8, 13.6, 5.1, 1.2 Hz, 1H), 1.71 ppm (qt, *J* = 13.6, 4.2 Hz, 1H);**^{13}C-NMR** ($CDCl_3$, 176 MHz): δ = 210.1, 198.2, 177.2, 165.3, 126.8, 53.8, 38.5, 33.4, 31.9, 29.3, 28.8, 25.6, 23.3 ppm; **IR** ($CDCl_3$): $\tilde{\nu}$ = 3187, 2952, 2871, 1708, 1651, 1415, 1220, 1142 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{13}H_{17}O_4$ $[M+H]^+$ 237.1122, found 237.1127.

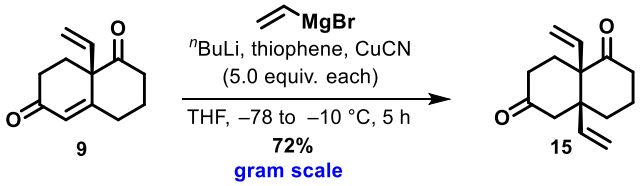
(8a*R*)-8a-Vinyl-3,4,8,8a-tetrahydronaphthalene-1,6(2*H*,7*H*)-dione (9)[6]



Carboxylic acid **14** (2.46 g, 10.4 mmol, 1.0 equiv.), $PdCl_2(MeCN)_2$ (135 mg, 0.521 mmol, 5 mol%), Xanthphos (361 mg, 0.625 mmol, 6 mol%) and benzoic anhydride (2.83 g, 12.5 mmol, 1.2 equiv.) were a placed in a flame dried 250 mL Schlenk flask, and the system was evacuated and backfilled with argon 3 times. Xylenes (52 mL) were added and the mixture heated 140 °C and refluxed till completion of the reaction as indicated by TLC. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (30 mL), washed with sat. aq. $NaHCO_3$ (30 mL), aq. HCl (1 M; 3x30 mL), then again with sat. aq. $NaHCO_3$ (2x30 mL), and brine (30 mL). The combined organic phases were dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, pentane/ethyl acetate = 8:1) yielded enone **9** (1.10 g, 55%) as a yellow oil. Addition of solid carboxylic acid and careful temperature control are necessary to achieve reproducibility on gram scale.

R_f = 0.14 (pentane/ethyl acetate 10:1, anisaldehyde UV active at 254 nm); **$[\alpha]_D^{22}$** = –69.9 (c = 0.91, chloroform); **^{1}H-NMR** ($CDCl_3$, 700 MHz): δ = 6.04 (d, *J* = 2.0 Hz, 1H), 5.67 (dd, *J* = 17.4, 10.3 Hz, 1H), 5.41 (d, *J* = 10.4 Hz, 1H), 5.17 (d. *J* = 17.3 Hz, 1H), 2.72 (dddd, *J* = 14.9, 12.7, 5.2, 2.0 Hz, 1H), 2.63 (ddd, *J* = 15.2, 12.9, 5.8 Hz, 1H), 2.54 (dtd, *J* = 15.2, 3.8, 1.8 Hz, 1H), 2.48 (dtd, *J* = 15.2, 4.1, 1.8 Hz, 1H), 2.39–2.30 (m, 2H), 2.23 (ddd, *J* = 14.0, 4.7, 3.1 Hz, 1H), 2.15–2.09 (m, 2H), 1.72 ppm (qt, *J* = 12.9, 4.2 Hz, 1H); **^{13}C-NMR** ($CDCl_3$, 176 MHz): δ = 208.5, 198.7, 162.4, 136.5, 128.4, 119.3, 58.9, 38.9, 33.5, 32.5, 29.5, 22.8 ppm; **IR** ($CDCl_3$): $\tilde{\nu}$ = 2956, 2893, 2871, 1712, 1665, 1619, 1417, 1220, 1146, 923, 873 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{12}H_{14}O_2Na$ $[M+Na]^+$ 191.1067, found: 191.1067.

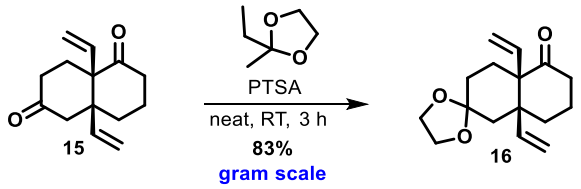
(4a*R*,8a*R*)-4a,8a-Divinyl-2,5-dioxo-octahydro-1*H*-naphthalene (15)[6c]



To a solution of thiophene (2.92 mL, 36.5 mmol, 5.0 equiv.) in anhydr. tetrahydrofuran (121 mL), *n*-butyllithium (2.5 M in hexane; 14.6 mL, 36.5 mmol, 5.0 equiv.) was added dropwise at –30 °C and the resulting yellow solution stirred for additional 30 minutes. At the same time, flame dried copper(I) cyanide (3.27 g, 36.5 mmol, 5.0 equiv.) was suspended in anhydr. tetrahydrofuran (183 mL) and cooled to –78 °C. The 2-thienyllithium solution was then added at –78 °C to the CuCN suspension via cannula, followed by the addition of vinylmagnesium bromide (0.7 M in THF; 52.1 mL, 36.5 mmol, 5.0 equiv.). The resulting grey solution was warmed to room temperature and then cooled to –78 °C. At this point, a solution of enone **9** (1.39 g, 7.30 mmol, 1.0 equiv.) in anhydr. tetrahydrofuran (73 mL) was added at the same temperature. The mixture was stirred for 15 minutes at –78 °C, then immediately warmed to –35 °C, and finally to –10 °C during 4 h. The reaction mixture was quenched with aq. NH_4Cl/NH_3 (9:1; 200 mL), stirred at 0 °C until the color turned dark blue, and then extracted with ethyl acetate (3x250 mL). The combined organic phases were washed with brine (300 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, pentane/ethyl acetate = 10:1) yielded diene **15** (1.15 g, 72%, d.r.>20:1) as a white solid.

m.p.= 47–48 °C; $\mathbf{R_f}$ = 0.26 (pentane/ethyl acetate 10:1, anisaldehyde); $[\alpha]_D^{21}$ = –43.8 (c = 0.81, chloroform); **^{1}H-NMR** ($CDCl_3$, 700 MHz): δ = 6.24 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.85 (dd, *J* = 17.5, 11.1 Hz, 1H), 5.26 (d, *J* = 10.9 Hz, 1H), 5.19 (dd, *J* = 11.1, 0.6 Hz, 1H), 5.14 (dd, *J* = 17.5, 0.5 Hz, 1H), 5.04 (d, *J* = 17.6 Hz, 1H), 2.71 (ddd, *J* = 14.9, 13.5, 7.6 Hz, 1H), 2.63 (dddd, *J* = 15.3, 13.1, 7.1, 1.0 Hz, 1H), 2.48 (d, *J* = 14.4 Hz, 1H), 2.47 (ddd, *J* = 13.3, 7.7, 2.1 Hz, 1H), 2.37 (ddt, *J* = 14.8, 5.2, 1.7 Hz, 1H), 2.29 (ddt, *J* = 15.3, 4.9, 2.2 Hz, 1H), 2.21 (td, *J* = 13.9, 4.8 Hz, 1H), 2.16 (dd, *J* = 14.3, 2.4 Hz, 1H), 2.04 (dddt, *J* = 14.6, 7.4, 4.9, 2.4 Hz, 1H), 1.90 (qt, *J* = 13.7, 4.7 Hz, 1H), 1.70 (td, *J* = 13.5, 5.4 Hz, 1H), 1.43 ppm (ddt, *J* = 14.3, 4.1, 2.1 Hz, 1H); **^{13}C-NMR** ($CDCl_3$, 176 MHz): δ = 210.9, 210.4, 140.2, 138.3, 118.3, 116.5, 57.6, 50.0, 47.1, 38.5, 37.8, 31.5, 28.9, 21.7 ppm; **IR** ($CDCl_3$): $\tilde{\nu}$ = 2950, 2880, 1705, 1630, 1420, 1295, 1210, 995, 925 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{14}H_{18}O_2Na$ $[M+Na]^+$ 241.1199, found: 241.1209.

(4a*R*,8a*R*)-4a,8a-Divinyl-5-oxo-octahydro-1*H*-spiro[naphthalene-2,2´-1´,3´-dioxolane] (16)

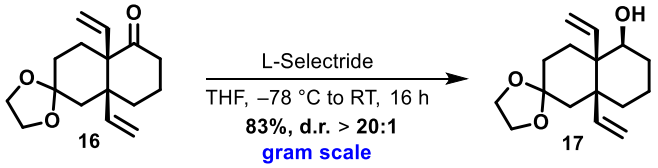


To a solution of diketone **15** (1.24 g, 5.69 mmol, 1.0 equiv.) in 2-ethyl-2-methyl-1,3-dioxolane (3.52 mL, 28.5 mmol, 5.0 equiv.), *p*-toluensulfonic acid monohydrate (PTSA) (54.2 mg, 0.280 mmol, 5 mol%) was added at room temperature and the mixture stirred for 3 h. After addition of sat. aq. $NaHCO_3$ (5 mL), the mixture was extracted with ethyl acetate (3x20 mL). The combined organic phases were washed with brine (20 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, pentane/ethyl acetate = 20:1 then 4:1) yielded dioxolane **16** (1.24 g, 83%, 95% brsm) as a white solid, followed by unreacted diketone **15** (160 mg).

m.p. = 66–68 °C; $\mathbf{R_f}$ = 0.21 (pentane/ethyl acetate 20:1, anisaldehyde); $[\alpha]_D^{21}$= +1.29 (c = 0.76, chloroform); **^{1}H-NMR** ($CDCl_3$, 700 MHz): δ = 6.44 (dd, *J* = 17.7, 11.2 Hz, 1H), 6.04 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.13 (d, *J* = 10.8

Hz, 1H), 5.12 (dd, *J* = 11.2, 1.2 Hz, 1H), 5.06 (dd, *J* = 17.6, 1.3 Hz, 1H), 4.95 (d, *J* = 17.6 Hz, 1H), 3.94–3.82 (m, 4H), 2.51 (ddd, *J* = 14.8, 13.3, 7.2 Hz, 1H), 2.30–2.25 (m, 2H), 2.03 (td, *J* = 13.6, 4.2 Hz, 1H), 1.96–1.92 (m, 1H), 1.87 (qt, *J* = 13.4, 4.0 Hz, 1H), 1.80 (d, *J* = 13.8 Hz, 1H), 1.70–1.66 (m, 3H), 1.41 ppm (dd, *J* = 13.9, 2.6 Hz, 1H); **^{13}C-NMR** ($CDCl_3$, 176 MHz): δ = 210.9, 144.0, 140.0, 117.1, 112.7, 109.2, 64.5, 63.8, 57.5, 46.5, 42.1, 38.4, 31.9, 30.8, 27.0, 21.1 ppm; **IR** ($CDCl_3$): $\tilde{\nu}$ = 3080, 2935, 2880, 1705, 1625, 1425, 1360, 1135, 1075, 950, 910 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{16}H_{22}O_3Na$ $[M+Na]^+$ 285.1461, found: 285.1454.

(4a*R*,5*S*,8a*R*)-4a,8a-Divinyl-5-hydroxy-octahydro-1*H*-spiro[naphthalene-2,2´-1´,3´-dioxolane] (17)



To a solution of ketone **16** (1.24 g, 4.72 mmol, 1.0 equiv.) in anhydr. tetrahydrofuran (24 mL), L-Selectride (1.0 M in THF; 14.2 mL, 14.2 mmol, 3.0 equiv.) was added dropwise at –78 °C, the mixture stirred 30 minutes at –78 °C and allowed to warm to room temperature overnight. At this point, the reaction mixture carefully treated with aq. NaOH (2.0 M; 71 mL, 30 equiv.) and aq. H_2O_2 (35% w/w; 12 mL, 30 equiv.) at 0 °C, and stirred for additional 30 min. The mixture was quenched with sat. aq. $Na_2S_2O_3$ (50 mL) and extracted with diethyl ether (3x80 mL). The combined organic phases were washed with sat. aq. NH_4Cl (80 mL), brine (80 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, pentane/ethyl acetate = 6:1 then 2:1) yielded unreacted **16** (132 mg), followed by the desired alcohol **17** (1.03 g, 83%, 93% brsm, d.r.>20:1) as a colorless oil. For the structural analysis GOESY experiments are reported.

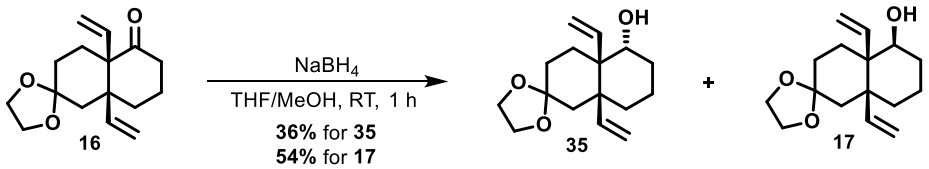
R$_f$ = 0.27 (pentane/ethyl acetate 6:1, anisaldehyde); **[α]$_D^{22}$** = +6.05 (c = 0.78, chloroform);

^{1}H-NMR ($CDCl_3$, 500 MHz): δ = 6.33 (dd, *J* = 17.6, 11.2 Hz, 1H), 5.99 (dd, *J* = 17.7, 11.2 Hz, 1H), 5.27 (d, *J* = 11.3 Hz, 1H), 5.07 (d, *J* = 18.3 Hz, 1H), 4.91 (d, *J* = 11.1 Hz, 1H), 4.86 (d, *J* = 17.7 Hz, 1H), 3.93–3.83 (m, 5H), 2.16–2.09 (m, 2H), 1.86–1.75 (m, 3H), 1.74–1.65 (m, 3H), 1.60 (qt, *J* = 14.0, 3.5 Hz, 1H), 1.38–1.23 (m, 3H), 1.28 ppm (dd, *J* = 13.7, 2.8 Hz, 1H); **^{13}C-NMR** ($CDCl_3$, 126 MHz): δ = 145.7, 139.5, 117.3, 110.6, 109.2, 67.4, 64.3, 63.8, 46.3, 43.4, 40.9, 31.8, 31.2, 30.1, 23.7, 20.4 ppm;

^{1}H-NMR (C_6D_6, 500 MHz): δ = 6.65 (dd, *J* = 17.7, 11.1 Hz, 1H), 5.84 (dd, *J* = 17.7, 11.2 Hz, 1H), 5.05 (dd, *J* = 11.2, 1.7 Hz, 1H), 4.98 (dd, *J* = 11.4, 1.7 Hz, 1H), 4.95 (d, *J* = 17.7, 1.8 Hz, 1H), 4.84 (d, *J* = 17.5, 1.5 Hz, 1H), 3.77 (dd, *J* = 12.1, 4.4 Hz, 1H) 3.51–3.48 (m, 4H), 2.24 (dt, *J* = 13.9, 3.6 Hz, 1H), 2.13 (d, *J* = 13.9 Hz, 1H), 1.98 (td, *J* = 13.9, 4.2 Hz, 1H), 1.83 (td, *J* = 13.9, 4.0 Hz, 1H), 1.74 (dt, J = 13.4, 3.3 Hz, 1H), 1.63–1.58 (m, 1H), 1.55 (dd, *J* = 13.9, 4.7 Hz, 1H), 1.39–1.33 (m, 1H), 1.30 (dd, J = 14.1, 2.6 Hz, 1H), 1.31–1.22 (m, 2H), 1.17–1.11 (m, 1H), 1.07 ppm (dd, *J* = 12.8, 4.4 Hz, 1H); **^{13}C-NMR** (C_6D_6, 126 MHz): δ = 146.5, 140.1, 116.7, 110.2, 109.4, 67.2, 64.3, 63.8, 46.5, 43.7, 41.4, 32.0, 31.3, 30.6, 24.2, 20.6 ppm;

IR ($CDCl_3$): $\tilde{\nu}$ = 3475, 3080, 2935, 2870, 1455, 1365, 1140, 1085, 1060, 995, 910 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{16}H_{24}O_3Na$ $[M+Na]^+$ 287.1617, found: 287.1625.

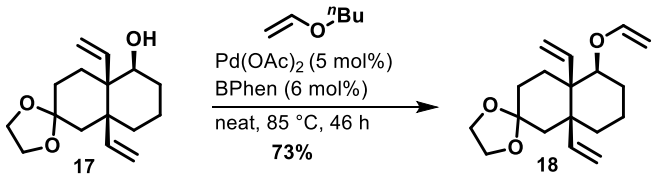
(4a*R*,5*R*,8a*R*)-4a,8a-Divinyl-5-hydroxy-octahydro-1*H*-spiro[naphthalene-2,2´-1´,3´-dioxolane] (35)



To a solution of ketone **16** (117 mg, 0.446 mmol, 1.0 equiv.) in tetrahydrofuran/methanol (10:1; 2.2 mL), sodium borohydride (11.8 mg, 0.312 mmol, 0.7 equiv.) was added at room temperature and the mixture stirred for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (2 mL) and extracted with ethyl acetate (3x3 mL). The combined organic phases were washed with brine (3 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, pentane/ethyl acetate = 12:1) yielded alcohol **35** (41.9 mg, 36%) as a colorless oil, followed by alcohol **17** (63.2 mg, 54%). For the structural analysis GOESY experiments are reported.

Data for **35:** R_f = 0.28 (pentane/ethyl acetate 12:1, anisaldehyde); $[\alpha]_D^{22}$ = –40.1 (c = 1.47, chloroform); **^{1}H-NMR** ($CDCl_3$, 500 MHz): δ = 6.36 (dd, *J* = 17.5, 11.2 Hz, 1H), 5.90 (ddd, *J* = 17.9, 11.3, 1.4 Hz, 1H), 5.36 (dd, *J* = 11.3, 1.4 Hz, 1H), 5.17 (dd, *J* = 17.9, 1.4 Hz, 1H), 5.10 (dd, *J* = 11.2, 1.1 Hz, 1H), 4.99 (dd, *J* = 17.5, 1.1 Hz, 1H), 4.00–3.94 (m, 2H), 3.89–3.83 (m, 2H), 3.69 (dd, *J* = 11.1, 4.7 Hz, 1H), 2.56–2.50 (m, 1H), 1.99 (tdd, *J* = 14.5, 4.1, 1.3 Hz, 1H), 1.85 (dt, *J* = 14.7, 3.7 Hz, 1H), 1.84–1.79 (m, 1H), 1.77–1.69 (m, 3H), 1.67–1.52 (m, 5H), 1.14–1.10 ppm (m, 1H); **^{13}C-NMR** ($CDCl_3$, 126 MHz): δ = 142.9, 140.1, 117.5, 113.5, 109.5, 69.7, 64.7, 63.4, 47.7, 44.4, 41.4, 31.9, 30.6, 27.5, 20.1, 18.8.ppm; **IR** ($CDCl_3$): $\tilde{\nu}$ = 3490, 2935, 2870, 1360, 1195, 1110, 1075, 1045, 1005 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{16}H_{25}O_3$ $[M+H]^+$ 265.1798, found: 265.1806.

(4a*R*,5*S*,8a*R*)-4a,8a-Divinyl-5-(vinyloxy)octahydro-1*H*-spiro[naphthalene-2,2´-1´,3´-dioxolane] (18) [7]

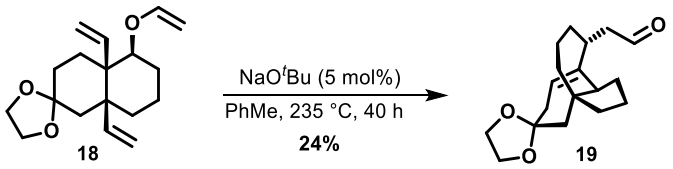


To a solution of alcohol **17** (60.4 mg, 0.228 mmol, 1.0 equiv.) in freshly distilled butyl vinyl ether (2.3 mL), bathophenanthroline (BPhen) (4.5 mg, 0.0137 mmol, 6 mol%) and $Pd(OAc)_2$ (2.6 mg, 0.0114 mmol, 5 mol%) were added. The reaction mixture was vigorously stirred for 10 minutes at room temperature and then heated under air at 85 °C for 46 h. The mixture was cooled to room temperature, filtered over a pad of activated carbon, rinsed with dichloromethane and concentrated under reduced pressure. Purification of the residue by column chromatography (alumina, neutral activity III; pentane/ethyl acetate = 80:1 to 3:1) yielded vinyl ether **18** (48.2 mg, 73%, 96% brsm) as a colorless oil, followed by the unreacted alcohol **17** (14.9 mg).

R_f = 0.15 (pentane/ethyl acetate 80:1, anisaldehyde); $[\alpha]_D^{21}$ = +5.63 (c = 0.87, chloroform); **^{1}H-NMR** ($CDCl_3$, 500 MHz): δ = 6.39–6.30 (m, 2H), 6.03 (dd, *J* = 17.5, 11.2 Hz, 1H), 5.19 (d, *J* = 11.2 Hz, 1H), 5.08 (d, *J* = 17.5 Hz, 1H), 4.93 (d, *J* = 11.2 Hz, 1H), 4.86 (d, *J* = 17.6 Hz, 1H), 4.26 (d, *J* = 14.2 Hz, 1H), 4.19–4.14 (m, 1H), 3.96–3.85 (m, 5H), 2.14 (d, *J* = 14.1 Hz, 1H), 2.05–2.00 (m, 1H), 1.91–1.68 (m, 5H), 1.63–1.53 (m, 3H), 1.41–1.28 ppm (m, 2H);

^{13}C-NMR ($CDCl_3$, 126 MHz): δ = 151.6, 145.6, 138.9, 116.2, 110.6, 109.1, 87.9, 76.4, 64.3, 63.9, 44.9, 43.7, 41.0, 31.4, 30.3, 26.9, 24.0, 20.2 ppm; **IR** ($CDCl_3$): $\tilde{\nu}$ = 2935, 2875, 1635, 1150, 1365, 1195, 1165, 1140, 1090, 1065, 985, 945, 910 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{18}H_{27}O_3$ $[M+H]^+$ 291.1955, found: 291.1953.

(1*Z*,6*S*,10*S*,11*S*)-(Spiro[tricyclo[4.4.4.0^{6,11}]tetradec-1-ene-4,2´-1´,3´-dioxolane]-10-yl)acetaldehyde (19)

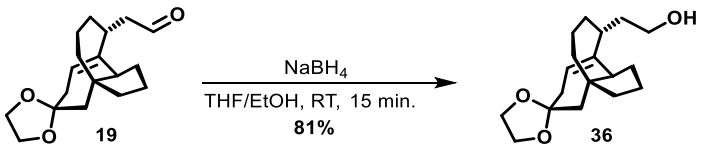


General procedure for the tandem sigmatropic rearrangement

Sodium *tert*-butoxide (NaO^{t}Bu) (0.6 mg, 6.40 µmol, 5 mol%) was dissolved in anhydr. and deoxygenated toluene (2.6 mL). The freshly prepared solution was transferred via syringe in an oven dried ACE pressure tube sealed with a septum and charged with vinyl ether **18** (37.1 mg, 0.128 mmol, 1.0 equiv.) under an argon atmosphere. The mixture was saturated with argon a second time, the septum was removed, and the tube sealed. Afterward, the solution was heated to 235 °C for 40 h in absence of light. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, pentane/ethyl acetate = 15:1) yielded alkene **19** (8.9 mg, 24%) as a colorless oil. For the structural analysis GOESY experiments for the derivative **38** are reported.

R$_f$ = 0.33 (pentane/ethyl acetate 15:1, anisaldehyde); **[α]$_D^{20}$** = –2.77 (c = 0.65, chloroform); **^{1}H-NMR** ($CDCl_3$, 700 MHz): δ = 9.66 (dd, *J* = 2.5, 1.8 Hz, 1H), 5.31 (dd, *J* = 8.2, 5.4 Hz, 1H), 3.99 (ddd, *J* = 7.8, 6.6, 5.1 Hz, 1H), 3.93–3.90 (m, 1H), 3.88–3.85 (m, 1H), 3.84–3.81 (m, 1H), 3.04 (dd, *J* = 13.0, 6.7 Hz, 1H), 2.92 (dq, *J* = 12.4, 6.5 Hz, 1H), 2.78 (dd, *J* = 14.6, 5.3 Hz, 1H), 2.64 (ddd, *J* = 16.7, 8.1, 2.5 Hz, 1H), 2.47 (ddd, *J* = 16.7, 6.9, 1.9 Hz, 1H), 2.26 (ddd, *J* = 14.6, 8.2, 1.9 Hz, 1H), 2.21 (ddd, *J* = 14.5, 11.7, 1.2 Hz, 1H), 1.99–1.91 (m, 2H), 1.90 (dd, *J* = 13.8, 1.8 Hz, 1H), 1.86 (d, *J* = 13.8 Hz, 1H), 1.84–1.80 (m, 1H), 1.70–1.48 (m, 6H), 1.18 (dd, *J* = 14.4, 8.1 Hz, 1H), 0.97 ppm (qd, *J* = 12.9, 3.7 Hz, 1H); **^{13}C-NMR** ($CDCl_3$, 176 MHz): δ = 202.7, 147.6, 115.4, 107.4, 65.0, 63.3, 53.7, 51.9, 47.8, 43.2, 41.6, 39.4, 37.8, 35.9, 34.4, 31.6, 25.5, 22.5 ppm; **IR** ($CDCl_3$): $\tilde{\nu}$ = 2920, 2865, 1725, 1455, 1220, 1100, 1075, 1030, 970 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{18}H_{26}O_3Na$ $[M+Na]^+$ 313.1774, found: 313.1789.

(1*Z*,6*S*,10*S*,11*S*)-(Spiro[tricyclo[4.4.4.0^{6,11}]tetradec-1-ene-4,2´-1´,3´-dioxolane]-10-yl)ethanol (36)

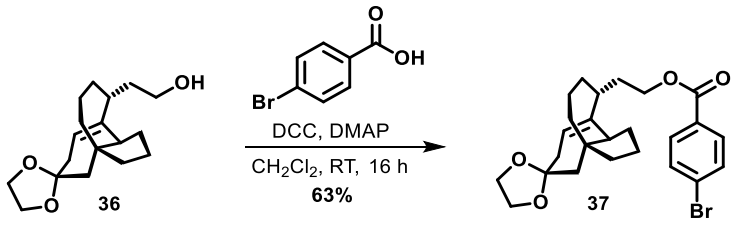


To a solution of aldehyde **19** (8.2 mg, 0.0282 mmol, 1.0 equiv.) in tetrahydrofuran/ethanol (3:1; 0.3 mL), sodium borohydride (0.6 mg, 0.157 mmol, 0.6 equiv.) was added at room temperature and the mixture stirred for 15 minutes. The reaction was quenched with sat. aq. $NaHCO_3$ (2 mL) and extracted with ethyl acetate (3x3 mL). The combined organic phases were washed with brine (3 mL), dried with Na_2SO_4, filtered and concentrated under reduced

pressure. Purification of the residue by column chromatography (silica gel, pentane/ethyl acetate = 3:1) yielded alcohol **36** (6.7 mg, 81%) as a colorless oil.

R_f = 0.36 (pentane/ethyl acetate 3:1, anisaldehyde); **$[\alpha]_D^{21}$** = –19.4 (c = 0.62, chloroform); **^{1}H-NMR** ($CDCl_3$, 700 MHz): δ = 5.37 (dd, *J* = 8.2, 5.4 Hz, 1H), 4.02–3.99 (m, 1H), 3.94–3.90 (m, 1H), 3.88–3.81 (m, 2H), 3.65 (td, *J* = 6.7, 1.9 Hz, 2H), 3.03 (dd, *J* = 13.0, 6.5 Hz, 1H), 2.80 (dd, *J* = 14.5, 5.4 Hz, 1H), 2.43 (ddd, *J* = 13.3, 11.7, 5.7 Hz, 1H), 2.27 (ddd, *J* = 14.5, 8.2, 1.9 Hz, 1H), 2.21 (dd, *J* = 13.3, 12.0 Hz, 1H), 1.95–1.78 (m, 6H), 1.67 (dt, *J* = 12.9, 6.7 Hz, 1H), 1.63–1.48 (m, 7H), 1.16 (dd, *J* = 14.4, 8.0 Hz, 1H), 0.94 ppm (qd, *J* = 12.8, 3.8 Hz, 1H); **^{13}C-NMR** ($CDCl_3$, 176 MHz): δ = 148.5, 114.3, 107.6, 65.0, 63.3, 61.8, 53.8, 52.1, 43.1, 41.6, 40.0, 37.9, 36.4, 36.4, 35.9, 31.7, 25.6, 22.6 ppm; **IR** ($CDCl_3$): $\tilde{\nu}$ = 3370, 2925, 2865, 1450, 1220, 1100, 1075, 1050, 1030, 980, 945 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{18}H_{28}O_3Na$ $[M+Na]^+$ 315.1930, found: 315.1936.

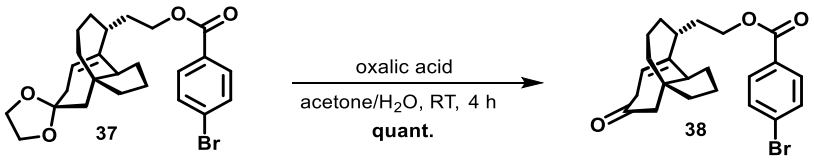
(1*Z*,6*S*,10*S*,11*S*)-(Spiro[tricyclo[4.4.4.0^{6,11}]tetradec-1-ene-4,2′-1′,3′-dioxolane]-10-yl)ethyl *p*-bromobenzoate (37)



To a solution of alcohol **36** (6.7 mg, 0.0228 mmol, 1.0 equiv.) in dichloromethane (0.25 mL), were added 4-dimethylaminopyridine (DMAP) (4.6 mg, 0.0380 mmol, 1.7 equiv.), *N,N'*-dicyclohexylcarbodiimide (DCC) (7.8 mg, 0.0380 mmol, 1.7 equiv.), and 4-bromobenzoic acid (7.6 mg, 0.0380 mmol, 1.7 equiv.). The reaction mixture was stirred at room temperature for 16 h, then diluted with diethyl ether (5 mL) and filtered. The resulting filtrate was washed with sat. aq. $NaHCO_3$ (3 mL), water (3 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, pentane/ethyl acetate = 20:1) yielded ester **37** (7.5 mg, 69%) as a colorless oil.

R_f = 0.18 (pentane/ethyl acetate 20:1, anisaldehyde; UV active at 254 nm); **$[\alpha]_D^{21}$** = –38.4 (c = 0.63, chloroform);**^{1}H-NMR** ($CDCl_3$, 700 MHz): δ = 7.88–7.86 (m, 2H), 7.58–7.57 (m, 2H), 5.39 (dd, *J* = 8.2, 5.4 Hz, 1H), 4.36–4.27 (m, 2H), 4.02–3.99 (m, 1H), 3.94–3.90 (m, 1H), 3.89–3.82 (m, 2H), 3.02 (dd, *J* = 13.0, 6.1 Hz, 1H), 2.80 (dd, *J* = 14.5, 5.3 Hz, 1H), 2.49 (dq, *J* = 14.6, 5.5 Hz, 1H), 2.28 (ddd, *J* = 14.5, 8.2, 1.8 Hz, 1H), 2.23 (dd, *J* = 14.0, 11.5 Hz, 1H), 2.01–1.95 (m, 2H), 1.91–1.85 (m, 4H), 1.81–1.77 (m, 1H), 1.61–1.48 (m, 6H), 1.17 (dd, *J* = 14.4, 7.9 Hz, 1H), 0.99 ppm (qd, *J* = 12.7, 3.8 Hz, 1H); **^{13}C-NMR** ($CDCl_3$, 176 MHz): δ = 166.0, 147.5, 131.8 (2C), 131.2 (2C), 129.6, 128.0, 114.3, 107.5, 65.0, 64.1, 63.3, 53.8, 52.0, 43.2, 41.6, 39.9, 37.9, 36.5, 35.9, 32.2, 31.6, 25.6, 22.6 ppm; **IR** ($CDCl_3$): $\tilde{\nu}$ = 2930, 2865, 1720, 1585, 1395, 1265, 1105, 1065, 1010, 755 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{25}H_{32}BrO_4$ $[M+H]^+$ 475.1479, found: 475.1492.

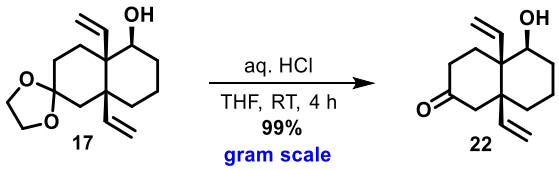
(1*Z*,6*S*,10*S*,11*S*)-(-4-Oxo-tricyclo[4.4.4.0^{6,11}]tetradec-1-en-10-yl)ethyl *p*-bromobenzoate (38)



To a solution of dioxolane **37** (7.5 mg, 0.0158 mmol, 1.0 equiv.) in acetone/water (5:1; 0.6 mL), was added oxalic acid (14.2 mg, 0.158 mmol, 10.0 equiv.) and the mixture stirred at room temperature for 4 h. The mixture was neutralized by the addition of sat. aq. $NaHCO_3$ and extracted with ethyl acetate (3x3 mL). The combined organic phases were washed with brine (3 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by preparative TLC (silica gel, pentane/ethyl acetate = 35:1) yielded ketone **38** (6.8 mg, quant.) as a colorless vitreous oil. For the structural analysis GOESY experiments are reported.

R_f = 0.33 (pentane/ethyl acetate 10:1, anisaldehyde; UV active at 254 nm); **$[\alpha]_D^{20}$** = +13.9 (c = 0.57, chloroform);**^{1}H-NMR** ($CDCl_3$, 700 MHz): δ = 7.89–7.87 (m, 2H), 7.59–7.57 (m, 2H), 5.45 (dd, *J* = 8.6, 4.8 Hz, 1H), 4.36–4.28 (m, 2H), 3.65 (dd, *J* = 12.5, 5.9 Hz, 1H), 3.35 (dd, *J* = 12.5, 5.9 Hz, 1H), 2.86 (ddd, *J* = 13.2, 8.6, 1.7 Hz, 1H), 2.63 (d, *J* = 12.4 Hz, 1H), 2.55–2.50 (m, 1H), 2.52 (dd, *J* = 12.5, 1.7 Hz, 1H), 2.00–1.95 (m, 2H), 1.92–1.85 (m, 3H), 1.72–1.63 (m, 3H), 1.61–1.56 (m, 3H), 1.46–1.42 (m, 1H), 1.37–1.33 (m, 1H), 0.93–0.87 ppm (m, 1H); **^{13}C-NMR** ($CDCl_3$, 176 MHz): δ = 205.6, 166.0, 147.6, 131.9 (2C), 131.2 (2C), 129.5, 128.1, 113.0, 63.7, 61.3, 52.6, 47.8, 43.6, 39.9, 39.5, 38.9, 36.6, 32.1, 31.1, 25.5, 22.2 ppm; **IR** ($CDCl_3$): $\tilde{\nu}$ = 2920, 2855, 1720, 1695, 1585, 1445, 1270, 1220, 775 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{23}H_{28}BrO_3$ $[M+H]^+$ 453.1036, found: 453.1048.

(4a*R*,1*S*,8a*R*)-1-Hydroxy-6(7*H*)-naphthalenone-octahydro-4a,8a-divinyl (22)

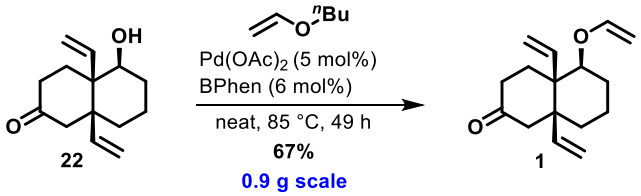


To a solution of alcohol **17** (1.09 g, 4.13 mmol, 1.0 equiv.) in tetrahydrofuran (41 mL), aq. HCl (2 M; 8.3 mL, 4.0 equiv.) was added and the mixture stirred at room temperature for 5 h. At this point, sat. aq. $NaHCO_3$ was added until neutralization and the mixture extracted with ethyl acetate (3x60 mL). The combined organic phases were washed with brine (50 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure to yield the spectroscopically pure diene **22** (909 mg, 99%) as a white solid.

m.p. = 71–73 °C; **R_f** = 0.18 (pentane/ethyl acetate 3:1, anisaldehyde); **$[\alpha]_D^{22}$** = +17.6 (c = 0.94, chloroform); **^{1}H-NMR** ($CDCl_3$, 700 MHz): δ = 6.28 (dd, *J* = 17.7, 11.3 Hz, 1H), 5.82–5.70 (br m, 1H), 5.43 (dd, *J* = 11.3, 1.3 Hz, 1H), 5.17 (br d, *J* = 17.7 Hz, 1H), 5.03 (d, *J* = 11.2 Hz, 1H), 4.99 (d, *J* = 17.6, 1H), 4.11–4.07 (m, 1H), 2.89–2.79 (m, 1H), 2.51–2.44 (m, 1H), 2.39–2.31 (m, 2H), 2.21 (br d, *J* = 15.3 Hz, 1H), 1.95–1.83 (m, 2H), 1.82–1.76 (m, 1H), 1.72 (td, *J* = 13.7, 5.0 Hz, 1H), 1.71–1.63 (m, 1H), 1.54–1.39 (m, 2H), 1.19–1.11 ppm (m, 1H); **^{13}C-NMR** ($CDCl_3$, 176 MHz): δ = 211.5, 143.0, 138.0, 118.9, 115.0, 67.5, 47.6, 46.5, 45.4, 37.1, 32.3, 31.4, 26.4, 20.5 ppm; **IR**

($CDCl_3$): $\tilde{\nu}$ = 3450, 2940, 2870, 1705, 1220, 1060, 915 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{14}H_{20}O_2Na$ $[M+Na]^+$ 243.1355, found: 243.1364.

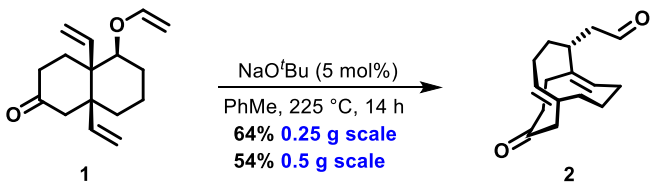
(4a*R*,1*S*,8a*R*)-1-Vinyloxy-6(7*H*)-naphthalenone-octahydro-4a,8a-divinyl (1) [7]



To a solution of alcohol **22** (909 mg, 4.13 mmol, 1.0 equiv.) in freshly distilled butyl vinyl ether (42 mL), bathophenanthroline (BPhen) (82.3 mg, 0.248 mmol, 6 mol%) and $Pd(OAc)_2$ (46.3 mg, 0.206 mmol, 5 mol%) were added. The reaction mixture was vigorously stirred at room temperature for 10 minutes, and then heated under air at 85 °C for 42 h and at 100 °C for additional 7 h. The mixture was then cooled to room temperature, filtered over a pad of activated carbon, rinsed with dichloromethane and concentrated under reduced pressure. Purification of the residue by column chromatography (alumina, neutral activity III; pentane/ethyl acetate = 30:1 then 3:1) yielded vinyl ether **1** (679 mg, 67%, 79% brsm) as a white solid, followed by unreacted alcohol **22** (137 mg).

m.p. = 51–53 °C; $\mathbf{R_f}$ = 0.18 (pentane/ethyl acetate 30:1, anisaldehyde); $[\alpha]_D^{22}$ = +16.0 (c = 0.85, chloroform); **^{1}H-NMR** ($CDCl_3$, 700 MHz): δ = 6.38–6.30 (m, 1H), 6.27 (dd, *J* = 17.6, 11.3 Hz, 1H), 5.82 (br s, 1H), 5.32 (d, *J* = 11.3 Hz, 1H), 5.12 (d, *J* = 17.5 Hz, 1H), 5.04 (d, *J* = 11.1 Hz, 1H), 4.97 (d, *J* = 17.6 Hz, 1H), 4.39–4.27 (m, 1H), 4.29 (d, *J* = 14.1 Hz, 1H), 3.99 (d, *J* = 6.5 Hz, 1H), 2.81 (br s, 1H), 2.42–2.30 (m, 2H), 2.29–2.22 (m, 1H), 2.24 (dt, *J* = 13.9, 5.0 Hz, 1H), 2.05–1.96 (m, 1H), 1.88–1.82 (m, 3H), 1.78–1.73 (m, 1H), 1.68–1.58 (m, 1H), 1.25–1.10 ppm (m, 1H); **^{13}C-NMR** ($CDCl_3$, 176 MHz): δ = 211.2, 151.3, 143.0, 137.5, 118.0, 114.9, 88.4, 47.5, 45.5, 45.1, 37.2, 32.5, 26.8, 26.4, 20.1 ppm (C1 was not detected); **IR** ($CDCl_3$): $\tilde{\nu}$ = 3085, 3015, 2950, 2870, 1710, 1630, 1615, 1185, 1160, 1070, 915 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{16}H_{22}O_2Na$ $[M+Na]^+$ 269.1512, found: 269.1513.

(1*E*,5*R*,6*Z*)-(12-Oxobicyclo[4.4.4]tetradeca-1,6-dien-5-yl)acetaldehyde (2)



257 mg scale

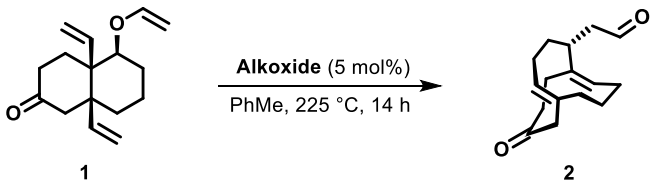
Diene **2** was prepared following the general procedure (page S9) using NaO^tBu (5.0 mg), toluene (21 mL), and vinyl ether **1** (257 mg, 1.04 mmol) at 225 °C for 14 h. Purification of the residue by column chromatography (silica gel, pentane/ethyl acetate = 10:1) yielded unreacted vinyl ether **1** (54.4 mg) followed by diene **2** (165 mg, 64%, 82% brsm) as a colorless oil. The product is prone to decomposition and it must be stored at –24 °C in absence of light.

558 mg scale

Diene **2** was prepared following the general procedure (page S9) using NaO^{t}Bu (10.8 mg), toluene (45 mL), and vinyl ether **1** (558 mg, 2.27 mmol) at 225 °C for 14 h. Purification of the residue by column chromatography (silica gel, pentane/ethyl acetate = 10:1) yielded diene **2** (302 mg, 54%) as a colorless oil. The product is prone to decomposition and it must be stored at –24 °C in absence of light.

$\mathbf{R}_f$ = 0.29 (pentane/ethyl acetate 10:1, anisaldehyde; UV active at 254 nm); $[\alpha]_D^{21}$ = –108 (c = 0.74, chloroform); **^{1}H-NMR** ($CDCl_3$, 500 MHz): δ = 9.55 (dd, J = 2.9, 2.0 Hz, 1H), 5.23 (ddd, J = 12.0, 4.3, 1.9 Hz, 1H), 5.14 (dt, J = 11.9, 2.2 Hz, 1H), 3.47–3.41 (m, 1H), 3.09 (ddd, J = 11.9, 9.7, 4.8 Hz, 1H), 3.00 (s, 2H), 2.71 (ddd, J = 14.7, 13.3, 3.5 Hz, 1H), 2.60 (qd, J = 12.5, 2.2 Hz, 1H), 2.51–2.46 (m, 2H), 2.37 (dddt, J = 13.4, 9.5, 5.6, 1.8 Hz, 1H), 2.31 (ddd, J = 16.0, 6.7, 2.0 Hz, 1H), 2.26–2.22 (m, 1H), 2.21 (ddd, J = 16.0, 8.1, 2.9 Hz, 1H), 2.11–2.06 (m, 2H), 1.89 (br d, J = 14.7 Hz, 1H), 1.63–1.57 (m, 1H), 1.53 (ddt, J = 14.0, 5.2, 2.6 Hz, 1H), 1.47–1.38 (m, 1H), 1.31 ppm (dtd, J = 14.3, 12.3, 2.2 Hz, 1H); **^{13}C-NMR** ($CDCl_3$, 126 MHz): δ = 211.8, 202.0, 137.2, 132.6, 127.8, 127.6, 51.4, 49.4, 39.5, 36.3, 32.2, 28.3, 28.1, 28.0, 26.9, 21.9 ppm; **IR** ($CDCl_3$): $\tilde{\nu}$ = 2920, 2855, 1720, 1690, 1455, 1220, 1110, 935, 860 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{16}H_{22}O_2Na$ $[M+Na]^+$ 269.1512, found: 269.1517.

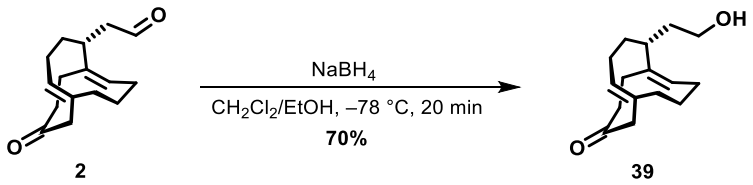
Alkoxide screening in the tandem sigmatropic rearrangement[8]



1 **2**

Entry	Alkoxide	Yield (%)
1	$NaOC(CH_3)_2CH_2CH_3$	44
2	Li^{t}BuO	48
3	Na^{t}BuO	64
4	K^{t}BuO	complex mixture

(1*E*, 5*R*,6*Z*)-(12-Oxobicyclo[4.4.4]tetradeca-1,6-dien-5-yl)ethanol (39)[9]



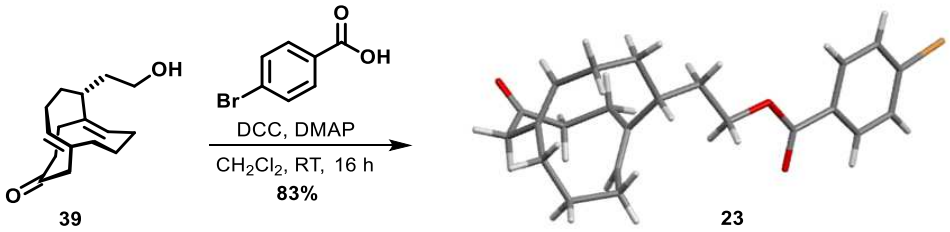
2 **39**

Sodium borohydride (10.5 mg, 0.278 mmol, 4.6 equiv.) was dissolved in anhydr. ethanol (0.8 mL) at room temperature and followed by the addition of anhydr. dichloromethane (1.8 mL). The mixture was cooled to –78 °C, then a solution of aldehyde **2** (14.9 mg, 0.0604 mmol, 1.0 equiv.) in anhydr. dichloromethane/ethanol (7:3; 0.9 mL) was added dropwise, and the reaction mixture stirred for 20 min. The excess of $NaBH_4$ was quenched at –78 °C

with propanal (249 µL, 3.47 mmol, 57.5 equiv.). After 5 min of additional stirring, sat. aq. $NaHCO_3$ (3 mL) was added and the reaction mixture extracted with ethyl acetate (3x5 mL). The combined organic phases were washed with brine (5 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, pentane/ethyl acetate = 3:1) yielded alcohol **39** (10.5 mg, 70%) as a colorless oil.

R_f = 0.27 (pentane/ethyl acetate 3:1, anisaldehyde; UV active at 254 nm); **$[\alpha]_D^{22}$** = –27.6 (c = 0.65, chloroform); **^{1}H-NMR** ($CDCl_3$, 700 MHz): δ = 5.26 (ddd, *J* = 11.9, 4.1, 1.6 Hz, 1H), 5.17 (dt, *J* = 11.9, 1.4 Hz, 1H), 3.50 (ddd, *J* = 11.3, 6.2, 5.2 Hz, 1H), 3.45 (ddd, *J* = 10.9, 8.1, 5.6 Hz, 1H), 3.14 (ddd, *J* = 11.9, 10.0, 4.9 Hz, 1H), 3.00 (s, 2H), 2.98–2.94 (m, 1H), 2.70 (ddd, *J* = 14.7, 13.4, 3.5 Hz, 1H), 2.56 (qd, *J* = 12.5, 2.2 Hz, 1H), 2.49–2.45 (m, 2H), 2.40–2.35 (m, 1H), 2.24–2.20 (m, 1H), 2.12 (ddd, *J* = 15.1, 7.0, 4.9 Hz, 1H), 2.10–2.06 (m, 1H), 1.90–1.86 (m, 1H), 1.60–1.48 (m, 3H), 1.46–1.40 (m, 3H), 1.32 ppm (qd, *J* = 12.2, 2.2 Hz, 1H); **^{13}C-NMR** ($CDCl_3$, 176 MHz): δ = 212.4, 138.7, 132.2, 128.7, 127.5, 60.8, 51.8, 39.6, 38.3, 38.0, 32.3, 29.2, 28.3, 27.9, 27.0, 22.1 ppm; **IR** ($CDCl_3$): $\tilde{\nu}$ = 3410, 2925, 2855, 1685, 1455, 1055, 1020 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{16}H_{25}O_2$ $[M+H]^+$ 249.1849, found: 249.1845.

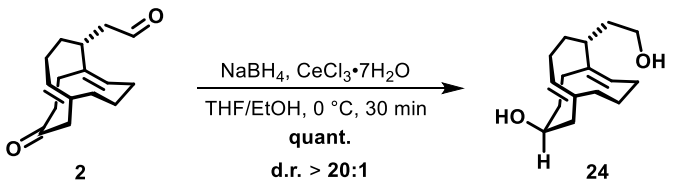
(1*E*,5*R*,6*Z*)-(12-Oxobicyclo[4.4.4]tetradeca-1,6-dien-5-yl)ethyl *p*-bromobenzoate (23)



To a solution of alcohol **39** (5.1 mg, 0.0204 mmol, 1.0 equiv.) in dichloromethane (0.2 mL), were added 4-dimethylaminopyridine (DMAP) (4.3 mg, 0.0350 mmol, 1.7 equiv.), *N,N'*-dicyclohexylcarbodiimide (DCC) (7.2 mg, 0.0350 mmol, 1.7 equiv.), and 4-bromobenzoic acid (7.0 mg, 0.0350 mmol, 1.7 equiv.). The reaction mixture was stirred at room temperature for 4 h, then diluted with diethyl ether (5 mL) and filtered. The resulting filtrate was washed with sat. aq. $NaHCO_3$ (3 mL), water (3 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, pentane/ethyl acetate = 15:1) yielded ester **23** (7.3 mg, 83%) as a white solid. The single crystals for X-ray analysis were obtained by vapor diffusion using degassed pentane/ethyl acetate at –26 °C.

m.p. = 82–85 °C; **R_f** = 0.18 (pentane/ethyl acetate 15:1, anisaldehyde; UV active at 254 nm); **$[\alpha]_D^{23}$** = –97.4 (c = 0.61, chloroform); **^{1}H-NMR** ($CDCl_3$, 700 MHz): δ = 7.88–7.86 (m, 2H), 7.59–7.57 (m, 2H), 5.29 (ddd, *J* = 11.9, 4.2, 1.8 Hz, 1H), 5.17–5.14 (m, 1H), 4.17 (ddd, *J* = 11.5, 6.9, 4.8 Hz, 1H), 4.09 (ddd, *J* = 11.0, 8.6, 6.2 Hz, 1H), 3.11 (ddd, *J* = 11.7, 9.8, 4.7 Hz, 1H), 3.02–2.96 (m, 3H), 2.68 (ddd, *J* = 14.6, 13.4, 3.5 Hz, 1H), 2.57 (qd, *J* = 12.5, 2.2 Hz, 1H), 2.51 (ddd, *J* = 11.9, 7.3, 5.5 Hz, 1H), 2.42–2.35 (m, 2H), 2.26–2.22 (m, 1H), 2.13 (ddd, *J* = 15.1, 7.4, 4.8 Hz, 1H), 2.01–1.97 (m, 1H), 1.89–1.85 (m, 1H), 1.74 (dddd, *J* = 13.5, 8.6, 6.9, 4.7 Hz, 1H), 1.62–1.52 (m, 3H), 1.43–1.32 ppm (m, 2H); **^{13}C-NMR** ($CDCl_3$, 176 MHz): δ = 212.1, 165.9, 137.0, 132.4, 131.9 (2C), 131.2 (2C), 129.5, 128.3, 128.2, 128.1, 63.1, 51.5, 39.7, 38.2, 33.9, 32.2, 29.0, 28.3, 28.1, 26.7, 22.0 ppm; **IR** ($CDCl_3$): $\tilde{\nu}$ = 2925, 2850, 1715, 1695, 1590, 1450, 1270, 1220, 1115, 1100, 1010, 845 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{23}H_{27}BrO_3Na$ $[M+Na]^+$ 453.1036, found: 453.1057.

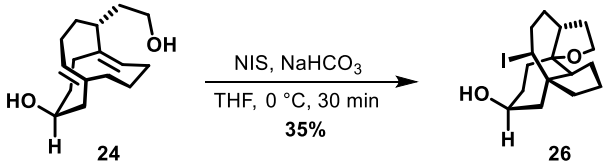
(1*E*,5*R*,6*Z*,12*S*)-(12-Hydroxybicyclo[4.4.4]tetradeca-1,6-dien-5-yl)ethanol (24)



To a mixture of diene **2** (136 mg, 0.551 mmol, 1.0 equiv.) and $CeCl_3$•$7H_2O$ (243 mg, 0.652 mmol, 1.2 equiv.) in tetrahydrofuran/ethanol (1:1; 6 mL), was added sodium borohydride (89.7 mg, 2.37 mmol, 4.3 equiv.) at 0 °C and the mixture stirred for 30 minutes. The mixture was treated with sat. aq. Na_2CO_3 (6 mL) and water (10 mL), and then extracted with ethyl acetate (3x10 mL). The combined organic phases were washed with brine (20 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure to yield crude diol **24** (138 mg, quant., d.r.> 20:1) as a white solid. The product is prone to decomposition and it must be stored at –24 °C in absence of light.

m.p. = 108–112 °C; $\mathbf{R}_f$ = 0.25 (pentane/ethyl acetate 1:1, anisaldehyde; UV active at 254 nm); $[\alpha]_D^{20}$ = –282 (c = 0.68, CH_3OH); **^{1}H-NMR** (CD_3OD, 700 MHz): δ = 5.50–5.42 (m, 1H), 5.18 (ddd, J = 11.9, 4.3, 1.5 Hz, 1H), 4.47–4.44 (m, 1H), 3.43–3.35 (m, 2H), 2.92–2.88 (m, 1H), 2.71 (td, J = 14.1, 3.4 Hz, 1H), 2.56–2.48 (m, 2H), 2.38–2.31 (m, 1H), 2.30 (dd, J = 14.0, 4.7 Hz, 1H), 2.20–2.08 (m, 4H), 2.05–2.00 (m, 1H), 1.88–1.80 (m, 2H), 1.62–1.58 (m, 1H), 1.50–1.43 (m, 4H), 1.33–1.25 ppm (m, 1H); **^{13}C-NMR** (CD_3OD, 176 MHz) δ = 140.6, 136.7, 128.5, 117.3, 71.0, 60.8, 39.6, 39.5, 34.8, 33.8, 30.1, 29.3, 29.2 (2C), 24.1 ppm (C-11 was not detected); **IR** ($CDCl_3$): $\tilde{\nu}$ = 3355, 2920, 2855, 1455, 1260, 1220, 1055, 1020, 860 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{16}H_{27}O_2$ $[M+H]^+$ 251.2006, found: 251.2004.

(1*R*,5*R*,8*S*,9*S*,11*S*,14*S*)-8-Iodo-11-hydroxy-2-oxatetracyclo[7.4.4.0^{1,5}.0^{9,14}]heptadecane (26)

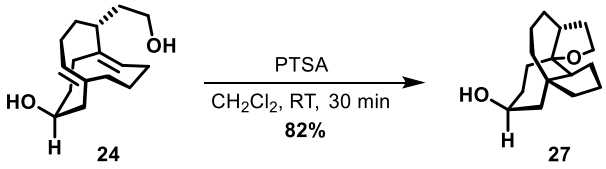


To a mixture of diene **24** (5.0 mg, 0.0200 mmol, 1.0 equiv.) and sodium hydrogen carbonate (3.4 mg, 0.0400 mmol, 2.0 equiv.) in tetrahydrofuran (0.2 mL), was added *N*-iodosuccinimide (NIS) (6.7 mg, 0.0300 mmol, 1.5 equiv.) at 0 °C. The reaction mixture was stirred at room temperature for 30 minutes and quenched with sat. aq. $Na_2S_2O_3$ (1 mL). The mixture was extracted with dichloromethane (3x2 mL), washed with sat. aq. $NaHCO_3$ (3 mL), water (3 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, pentane/ethyl acetate = 3:1) yielded iodoalcohol **26** (2.6 mg, 35%) as a colorless oil.

$\mathbf{R}_f$ = 0.33 (pentane/ethyl acetate 3:1; anisaldehyde); $[\alpha]_D^{20}$ = –52.8 (c = 0.62, chloroform); **^{1}H-NMR** ($CDCl_3$, 700 MHz): δ = 5.71 (d, J = 11.7 Hz, 1H), 4.27–4.24 (m, 1H), 3.84 (ddd, J = 9.8, 8.6, 2.4 Hz, 1H), 3.78 (q, J = 8.6 Hz, 1H), 2.57 (br d, J = 14.7 Hz, 1H), 2.51 (dd, J = 13.0, 5.4 Hz, 1H), 2.35–2.29 (m, 2H), 2.18 (dd, J = 15.6, 12.5 Hz, 1H), 2.16–2.11 (m, 1H), 2.05 (dd, J = 15.2, 12.7 Hz, 1H), 1.96–1.86 (m, 4H), 1.76–1.66 (m, 4H), 1.61 (dd, J = 15.1, 4.4 Hz, 1H), 1.58–1.48 (m, 4H), 1.42–1.35 ppm (m, 1H); **^{13}C-NMR** ($CDCl_3$, 176 MHz) δ = 85.2, 69.9, 64.3, 53.6,

51.9, 51.7, 49.8, 45.9, 42.4, 37.3, 31.9, 30.8, 30.3, 28.1, 24.4, 23.2 ppm; **IR** ($CDCl_3$): $\tilde{\nu}$ = 3420, 2940, 2870, 1450, 1220, 1010, 980 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{16}H_{25}IO_2Na$ $[M+Na]^+$ 399.0791, found: 399.0792.

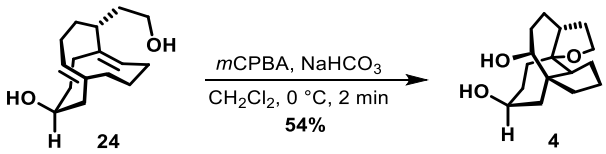
(1*R*,5*R*,9*S*,11*S*,14*S*)-11-Hydroxy-2-oxatetracyclo[7.4.4.0^{1,5}.0^{9,14}]heptadecane (27)



To a solution of diene **24** (3.8 mg, 0.0152 mmol, 1.0 equiv.) in dichloromethane (1.5 mL), was added *p*-toluensulfonic acid monohydrate (PTSA) (0.3 mg, 1.52 µmol, 10 mol%) at room temperature. The reaction mixture was stirred for 30 minutes and quenched with sat. aq. $NaHCO_3$ (1 mL). The mixture was extracted with dichloromethane (3x2 mL), washed with water (3 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, pentane/ethyl acetate = 3:1) yielded alcohol **27** (3.1 mg, 82%) as a colorless oil.

R*f* = 0.30 (pentane/ethyl acetate 3:1; anisaldehyde); **[α]*D*^{20}** = +55.0 (c = 0.40, chloroform); **^{1}H-NMR** ($CDCl_3$, 700 MHz): δ = 4.22 (tt, *J* = 4.8, 2.0 Hz, 1H), 3.84–3.77 (m, 2H), 2.39 (ddd, *J* = 15.0, 12.1, 1.5 Hz, 1H), 2.28 (dd, *J* = 15.2, 12.3 Hz, 1H), 2.22–2.16 (m, 2H), 2.13–2.10 (m, 1H), 1.96–1.92 (m, 1H), 1.85 (dtt, *J* = 12.6, 3.7, 1.9 Hz, 1H), 1.81–1.73 (m, 4H), 1.70–1.63 (m, 3H), 1.60–1.55 (m, 2H), 1.52–1.46 (m, 2H), 1.45–1.34 ppm (m, 4H) (the alcohol proton was not detected); **^{13}C-NMR** ($CDCl_3$, 176 MHz) δ = 85.4, 70.6, 64.4, 53.5, 52.0, 44.1, 43.6, 43.4, 40.1, 32.6, 30.7, 29.8, 28.9, 24.6, 23.0, 23.0 ppm; **IR** ($CDCl_3$): $\tilde{\nu}$ = 3415, 2920, 2860, 1065, 1020, 985 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{16}H_{27}O_2$ $[M+H]^+$ 251.2006, found: 251.2012.

(1*R*,5*R*,8*S*,9*S*,11*S*,14*S*)-8,11-Dihydroxy-2-oxatetracyclo[7.4.4.0^{1,5}.0^{9,14}]heptadecane (4)

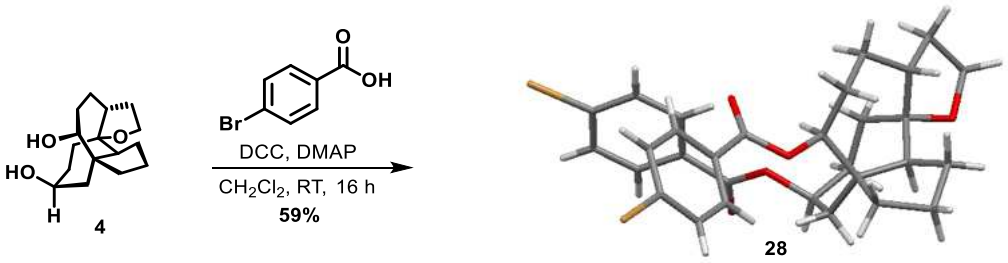


To a mixture of diol **24** (11.7 mg, 0.0467 mmol, 1.0 equiv.) and sodium hydrogen carbonate ($NaHCO_3$) (11.8 mg, 0.140 mmol, 3.0 equiv.) in dichloromethane (0.5 mL), was added *m*-chloroperoxybenzoic acid (*m*CPBA) (70% purity; 17.6 mg, 0.0701 mmol, 1.5 equiv.) at 0 °C. The reaction mixture was stirred at room temperature for 2 minutes and then quenched with sat. aq. $Na_2S_2O_3$ (1 mL). The mixture was extracted with dichloromethane (3x2 mL), washed with sat. aq. $NaHCO_3$ (3 mL), water (3 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, pentane/ethyl acetate = 3:1) yielded diol **4** (6.7 mg, 54%) as a colorless oil.

R*f* = 0.29 (ethyl acetate/pentane 3:1; anisaldehyde); **[α]*D*^{20}** = +13.3 (c = 0.56, chloroform); **^{1}H-NMR** ($CDCl_3$, 700 MHz): δ = 4.57 (d, *J* = 11.1 Hz, 1H), 4.26–4.24 (m, 1H), 3.81–3.74 (m, 2H), 2.25–2.22 (m, 2H), 2.12–2.07 (m, 3H), 1.96–1.92 (m, 1H), 1.88–1.80 (m, 5H), 1.78–1.71 (m, 4H), 1.61–1.56 (m, 2H), 1.52 (dd, *J* = 15.0, 4.9 Hz, 1H), 1.48–

1.36 (m, 3H), 1.31 ppm (ddd, *J* = 13.3, 7.1, 2.0 Hz, 1H); **^{13}C-NMR** ($CDCl_3$, 176 MHz) δ = 85.3, 75.8, 70.3, 64.0, 53.6, 48.9, 48.1, 42.4, 36.1, 33.2, 31.9, 30.4, 28.5, 27.1, 24.4, 23.6 ppm; **IR** ($CDCl_3$): $\tilde{\nu}$ = 3390, 2930, 2865, 1220, 1020, 980, 955 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{16}H_{26}O_3Na$ $[M+Na]^+$ 289.1774, found: 289.1788.

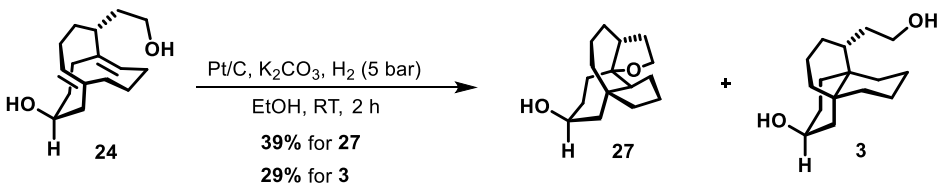
(1*R*,5*R*,8*S*,9*S*,11*S*,14*S*)-2-Oxatetracyclo[7.4.4.0^{1,5}.0^{9,14}]heptadecan-8,11-diyl di(*p*-bromobenzoate) (28)



To a solution of diol **4** (6.7 mg, 0.0252 mmol, 1.0 equiv.) in dichloromethane (1.5 mL), were added 4-dimethylaminopyridine (DMAP) (30.8 mg, 0.252 mmol, 10.0 equiv.), *N,N'*-dicyclohexylcarbodiimide (DCC) (52.0 mg, 0.252 mmol, 10.0 equiv.), and 4-bromobenzoic acid (50.7 mg, 0.252 mmol, 10.0 equiv.). The reaction mixture was stirred at room temperature for 16 h, then diluted with diethyl ether (5 mL) and filtered. The resulting filtrate was washed with sat. aq. $NaHCO_3$ (3 mL), water (3 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, pentane/ethyl acetate = 10:1) yielded ester **28** (9.4 mg, 59%) as a white solid. The single crystals for X-ray analysis were obtained by vapor diffusion using pentane/chloroform at 4 °C.

m.p. = 78–80 °C; **R_f** = 0.35 (pentane/ethyl acetate 10:1, anisaldehyde; UV active at 254 nm); **$[\alpha]_D^{21}$** = +155 (*c* = 0.43, chloroform); **^{1}H-NMR** ($CDCl_3$, 700 MHz): δ = 7.90–7.88 (m, 2H), 7.63–7.61 (m, 2H), 7.59–7.57 (m, 2H), 7.50–7.48 (m, 2H), 5.59 (dd, *J* = 10.5, 1.6 Hz, 1H), 5.49–5.47 (m, 1H), 3.86–3.81 (m, 2H), 2.44 (dd, *J* = 13.0, 5.7 Hz, 1H), 2.29 (d, *J* = 15.7 Hz, 1H), 2.24–2.18 (m, 3H), 2.13 (dd, *J* = 15.4, 12.7 Hz, 1H), 2.08–1.96 (m, 3H), 1.94–1.84 (m, 4H), 1.82–1.75 (m, 2H), 1.74–1.68 (m, 2H), 1.66–1.61 (m, 2H), 1.57–1.52 ppm (m, 1H); **^{13}C-NMR** ($CDCl_3$, 176 MHz) δ = 165.4, 165.2, 131.8 (2C), 131.7 (2C), 131.6 (2C), 130.9 (2C), 129.7, 129.3, 128.0, 128.0, 84.9, 81.7, 73.9, 64.2, 53.6, 47.4, 45.5, 42.6, 37.6, 31.7, 30.6, 29.9, 26.5, 25.8, 24.6, 24.5.ppm; **IR** ($CDCl_3$) $\tilde{\nu}$ =2935, 2865, 1710, 1585, 1390, 1265, 1105, 1010, 770 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{30}H_{32}Br_2O_5K$ $[M+K]^+$ 669.0248, found: 669.0276.

(1*S*,3*S*,6*S*,7*R*)-(3-Hydroxy[4.4.4]propellan-7-yl)ethanol (3)



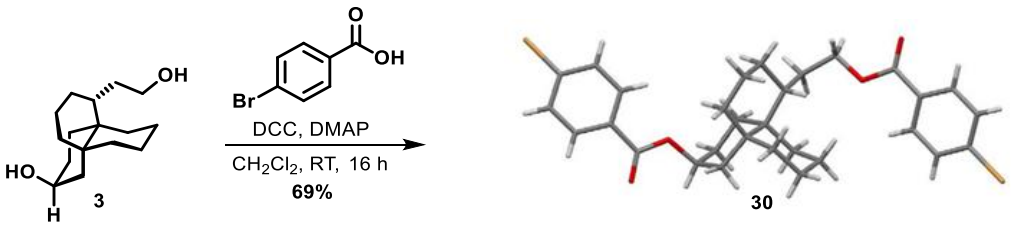
To a solution of diene **24** (17.5 mg, 0.0698 mmol, 1.0 equiv.) in ethanol (1.5 mL), were added potassium carbonate (K_2CO_3) (96.5 mg, 0.698 mmol, 10.0 equiv.) and Pt/C (10 wt. %; 9.8 mg) at room temperature. The reaction mixture was stirred in an autoclave under a hydrogen pressure (5 bar) for 2 h. The suspension was filtered over celite and

concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, pentane/ethyl acetate = 4:1) yielded [4.4.4]propellane **3** (5.1 mg, 29%) as a vitreous oil, followed by ether **27** (6.9 mg, 39%) as a colorless oil.

Data for **3**: $\mathbf{R_f}$ = 0.20 (pentane/ethyl acetate 4:1; anisaldehyde); $\mathbf{[\alpha]_D^{21}}$ = +56.6 (*c* = 0.38, chloroform); **^{1}H-NMR** ($CDCl_3$, 700 MHz): δ = 4.17–4.15 (m, 1H), 3.74–3.71 (m, 1H), 3.61–3.57 (m, 1H), 2.62 (td, *J* = 13.7, 4.6 Hz, 1H), 2.20 (dd, *J* = 15.2, 4.1 Hz, 1H), 2.13–2.07 (m, 2H), 2.03 (br t, *J* = 11.6 Hz, 1H), 1.85 (tt, *J* = 14.4, 4.4 Hz, 1H), 1.71–1.64 (m, 2H), 1.64–1.55 (m, 4H), 1.52–1.47 (m, 2H), 1.46–1.40 (m, 2H), 1.36–1.28 (m, 2H), 1.20 (s br, 2H), 1.10–1.05 (m, 1H), 1.00 (dt, *J* = 15.2, 2.4 Hz, 1H), 0.92–0.88 (m, 1H), 0.86–0.83 (m, 1H), 0.71–0.67 ppm (m, 1H); **^{13}C-NMR** ($CDCl_3$, 176 MHz) δ = 67.9, 62.6, 39.6, 38.0, 36.0, 35.7, 33.0, 32.8, 31.8, 28.2, 27.6, 26.3, 22.0, 21.5, 20.8, 20.8 ppm; **IR** ($CDCl_3$): $\tilde{\nu}$ = 3340, 2940, 2920, 2860, 1465, 1220, 1050, 1020, 970 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{16}H_{28}O_2Na$ $[M+Na]^+$ 275.1981, found: 275.1971.

Data for **27**: **^{1}H-NMR** ($CDCl_3$, 700 MHz): δ = 4.23–4.20 (m, 1H), 3.84–3.76 (m, 2H), 2.39 (dd, *J* = 15.1, 12.1 Hz, 1H), 2.28 (dd, *J* = 15.3, 12.4 Hz, 1H), 2.21–2.16 (m, 2H), 2.13–2.09 (m, 1H), 1.96–1.92 (m, 1H), 1.86–1.83 (m, 1H), 1.81–1.72 (m, 4H), 1.70–1.63 (m, 3H), 1.60–1.55 (m, 2H), 1.51–1.47 (m, 2H), 1.45–1.35 ppm (m, 4H); **^{13}C-NMR** ($CDCl_3$, 176 MHz) δ = 85.4, 70.6, 64.4, 53.5, 52.0, 44.1, 43.5, 43.4, 40.1, 32.6, 30.6, 29.8, 28.8, 24.6, 23.0, 23.0 ppm. Spectroscopic data are in agreement with the ones obtained for ether **27**.

(1*S*,3*S*,6*S*,7*R*)-(3-*p*-bromobenzoyloxy-[4.4.4]propellan-7-yl)ethyl *p*-bromobenzoate (30)

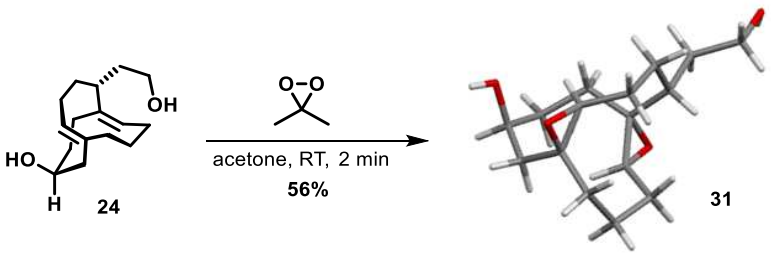


To a solution of diol **3** (3.6 mg, 0.0143 mmol, 1.0 equiv.) in dichloromethane (0.5 mL), were added 4-dimethylaminopyridine (DMAP) (17.3 mg, 0.143 mmol, 10.0 equiv.), *N,N'*-dicyclohexylcarbodiimide (DCC) (29.3 mg, 0.143 mmol, 10.0 equiv.), and 4-bromobenzoic acid (28.6 mg, 0.143 mmol, 10.0 equiv.). The reaction mixture was stirred at room temperature for 4 h, then diluted with diethyl ether (5 mL), and filtered. The resulting filtrate was washed with sat. aq. $NaHCO_3$ (3 mL), water (3 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, pentane/ethyl acetate = 60:1) yielded ester **30** (6.1 mg, 69%) as a white solid. The single crystals for X-ray analysis were obtained by vapor diffusion using pentane/chloroform at 4 °C.

m.p. = 159–160 °C; $\mathbf{R_f}$ = 0.37 (pentane/ethyl acetate 60:1; anisaldehyde; UV active at 254 nm); $\mathbf{[\alpha]_D^{21}}$ = +40.7 (*c* = 0.44, chloroform); **^{1}H-NMR** ($CDCl_3$, 700 MHz): δ = 7.91–7.89 (m, 4H), 7.60–7.58 (m, 4H), 5.35–5.32 (m, 1H), 4.40–4.37 (m, 1H), 4.31–4.27 (m, 1H), 2.49 (td, *J* = 13.8, 4.4 Hz, 1H), 2.33 (dd, *J* = 15.7, 4.3 Hz, 1H), 2.16–2.08 (m, 3H), 1.96–1.92 (m, 2H), 1.87–1.83 (m, 1H), 1.77–1.61 (m, 2H), 1.66–1.60 (m, 1H), 1.55–1.44 (m, 4H), 1.43–1.36 (m, 2H), 1.31–1.22 (m, 3H), 0.98 (d, *J* = 12.7 Hz, 1H), 0.93–0.87 (m, 1H), 0.74 ppm (d, *J* = 13.9 Hz, 1H); **^{13}C-NMR** ($CDCl_3$, 176 MHz) δ = 166.1, 165.5, 131.9 (2C), 131.9 (2C), 131.2 (2C), 131.2 (2C), 130.1, 129.5, 128.1, 128.0,

71.9, 65.1, 37.8, 36.4, 35.5, 35.2, 33.4, 31.5, 29.9, 29.0, 27.7, 25.2, 21.9, 21.5, 21.4, 20.8 ppm; **IR** ($CDCl_3$): $\tilde{\nu}$ = 2925, 2865, 1715, 1590, 1460, 1395, 1265, 1220, 1115, 1100, 1010, 770 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{30}H_{34}Br_2O_4Na$ $[M+Na]^+$ 639.0716, found: 639.0700.

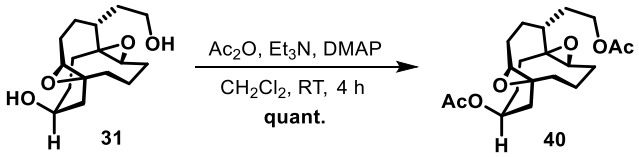
(1*S,3S,6R,7S,9R,14S*)-(14-hydroxy-2,8-dioxatetracyclo[5.5.4.0^{1,3}.0^{7,9}]hexadecane-6-yl)ethanol (31)



To a solution of diene **24** (119 mg, 0.474 mmol, 1.0 equiv.) in acetone (7 mL), was added dimethyldioxirane (0.074 M; 0.948 mmol, 12.8 mL, 2.0 equiv.) and the mixture was stirred at room temperature for 2 minutes. The solution was concentrated under reduced pressure and the residue purified by column chromatography (silica gel, dichloromethane/methanol = 30:1) to yield *out*/*out* bisepoxide **31** (74.7 mg, 56%) as a white solid. The single crystals for X-ray analysis were obtained by recrystallization in ethyl acetate.

m.p. = 148–150 °C; $\mathbf{R_f}$ = 0.31 (dichloromethane/methanol 30:1, anisaldehyde); $[\alpha]_D^{20}$ = –2.03 (c = 1.06, chloroform); **^{1}H-NMR** ($CDCl_3$, 500 MHz): δ = 4.18–4.13 (m, 2H), 3.74 (ddd, *J* = 11.2, 7.3, 5.3 Hz, 1H), 3.61 (dt, *J* = 11.5, 5.7 Hz, 1H), 3.10 (d, *J* = 9.6 Hz, 1H), 2.46 (br s, 2H), 2.37 (dd, *J* = 16.6, 13.0 Hz, 1H), 2.25 (dd, *J* = 17.1, 5.4 Hz, 1H), 2.13 (dd, *J* = 17.1, 2.0 Hz, 1H), 2.02–1.83 (m, 6H), 1.82–1.71 (m, 3H), 1.70–1.55 (m, 5H), 1.49 (ddt, *J* = 15.3, 13.0, 2.1 Hz, 1H), 1.26 ppm (td, *J* = 14.1, 4.9 Hz, 1H); **^{13}C-NMR** ($CDCl_3$, 126 MHz): δ = 69.0, 66.5, 65.4, 65.3, 64.1, 60.8, 39.1, 36.8, 36.2, 33.4, 31.4, 29.0, 25.3, 24.6, 24.4, 22.3 ppm; **IR** ($CDCl_3$): $\tilde{\nu}$ = 3405, 2920, 2860, 1450, 1220, 1060, 985, 915, 870, 815 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{16}H_{26}O_4Na$ $[M+Na]^+$ 305.1723, found: 305.1729.

(1*S,3S,6R,7S,9R,14S*)-(14-Acetoxy-2,8-dioxatetracyclo[5.5.4.0^{1,3}.0^{7,9}]hexadecan-6-yl)ethyl acetate (40)

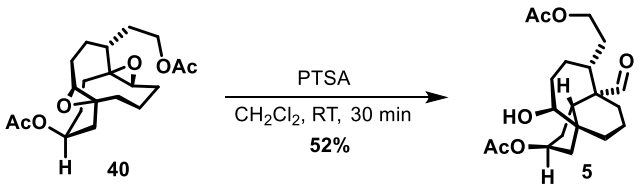


To a solution of epoxide **31** (14.7 mg, 0.0520 mmol, 1.0 equiv.) in dichloromethane (0.5 mL), was added 4-dimethylaminopyridine (DMAP) (1.3 mg, 0.0104 mmol, 20 mol%), triethylamine (36 µL, 0.260 mmol, 5.0 equiv.), and acetic anhydride (24.6 µL, 0.260 mmol, 5.0 equiv.), and the mixture was stirred at room temperature for 3 h. At this point, additional triethylamine (36 µL, 0.260 mmol, 5.0 equiv.) and acetic anhydride (24.6 µL, 0.260 mmol, 5.0 equiv.) were added, and the mixture stirred for 1 h. The reaction was quenched by with water (2 mL), stirred for 10 minutes, and extracted with dichloromethane (2x4 mL). The combined organic phases were washed with brine (5 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure to yield crude acetate **40** (19.1

mg, quant.) as a colorless oil. A spectroscopically pure sample was obtained as a white solid after purification by column chromatography (silica gel, pentane/ethyl acetate = 2:1).

m.p. = 130–132 °C; $\mathbf{R_f}$ = 0.17 (pentane/ethyl acetate 4:1, anisaldehyde); $[\alpha]_D^{21}$ = +13.0 (c = 1.34, chloroform); **^{1}H-NMR** ($CDCl_3$, 500 MHz): δ = 5.17–5.14 (m, 1H), 4.19–4.13 (m, 2H), 3.77 (d, *J* = 9.2 Hz, 1H), 3.09 (d, *J* = 9.9 Hz, 1H), 2.46 (dd, *J* = 17.2, 5.3 Hz, 1H), 2.26 (dd, *J* = 16.0, 13.5 Hz, 1H), 2.09 (dd, *J* = 17.2, 2.1 Hz, 1H), 2.06–1.99 (m, 3H), 2.04 (s, 3H), 2.04 (s, 3H), 1.97–1.93 (m, 3H), 1.87 (dt, *J* = 16.1, 5.4 Hz, 1H), 1.81 (dd, *J* = 16.4, 6.2 Hz, 1H), 1.77–1.71 (m, 1H), 1.66–1.55 (m, 5H), 1.51–1.46 (m, 1H), 1.27 ppm (td, *J* = 14.5, 4.4 Hz, 1H); **^{13}C-NMR** ($CDCl_3$, 176 MHz): δ = 171.2, 169.9, 70.7, 66.6, 65.5, 64.6, 63.2, 63.0, 39.9, 33.8, 33.5, 32.0, 30.4, 27.1, 25.4, 24.8, 24.3, 23.2, 21.5, 21.2 ppm ; **IR** ($CDCl_3$): $\tilde{\nu}$ = 2925, 2855, 1735, 1455, 1370, 1235, 1040, 990 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{20}H_{30}O_6Na$ $[M+Na]^+$ 389.1934, found: 389.1944.

(1*S*,2*S*,5*S*,6*S*,8*S*,10*S*)-(1-Formyl-5-hydroxy-8-acetoxytricyclo[4.4.3.0^{6,10}]tridecan-2-yl)ethyl acetate (5)



To a solution of epoxide **40** (16.0 mg, 0.0437 mmol, 1.0 equiv.) in dichloromethane (0.45 mL), was added *p*-toluensulfonic acid monohydrate (PTSA) (0.4 mg, 2.18 µmol, 5 mol%) at room temperature. The reaction mixture was stirred at room temperature for 30 minutes and quenched with sat. aq. $NaHCO_3$ (1 mL). The mixture was extracted with dichloromethane (3x2 mL), washed with water (3 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, pentane/ethyl acetate = 1:1) yielded aldehyde **5** (8.3 mg, 52%) as a colorless oil. For the structural analysis GOESY experiments are reported.

$\mathbf{R_f}$ = 0.22 (pentane/ethyl acetate 1:1, anisaldehyde); $[\alpha]_D^{21}$ = –14.2 (*c* = 0.59, chloroform); **^{1}H-NMR** ($CDCl_3$, 700 MHz): δ = 9.48 (s, 1H), 5.17–5.15 (m, 1H), 4.09 (ddd, *J* = 11.1, 7.5, 4.8 Hz, 1H), 3.99 (ddd, *J* = 11.1, 7.9, 6.7 Hz, 1H), 3.58 (dd, *J* = 11.2, 5.7 Hz, 1H), 2.42 (dd, *J* = 12.2, 7.6 Hz, 1H), 2.15–2.11 (m, 1H), 2.03 (s, 3H), 2.02 (s, 3H), 2.02–2.01 (m, 1H), 1.98 (dd, *J* = 3.1, 1.6 Hz, 1H), 1.97–1.91 (m, 2H), 1.75–1.65 (m, 3H), 1.64–1.56 (m, 6H), 1.51–1.46 (m, 1H), 1.33 (dt, *J* = 13.8, 6.6 Hz, 1H), 1.10 ppm (ddd, *J* = 14.1, 8.6, 4.9 Hz, 1H); **^{13}C-NMR** ($CDCl_3$, 176 MHz): δ = 204.5, 171.1, 170.7, 80.3, 74.9, 63.3, 51.1, 48.5, 48.0, 43.6, 39.3, 36.6, 35.4, 31.8, 26.6, 26.3, 24.2, 21.5, 21.1, 17.4; **IR** ($CDCl_3$): $\tilde{\nu}$ = 3525, 2935, 2865, 2360, 2315, 1730, 1715, 1515, 1460, 1370, 1240, 1030 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{20}H_{30}O_6Na$ $[M+Na]^+$ 389.1934, found: 389.1941.

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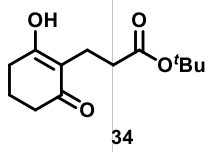
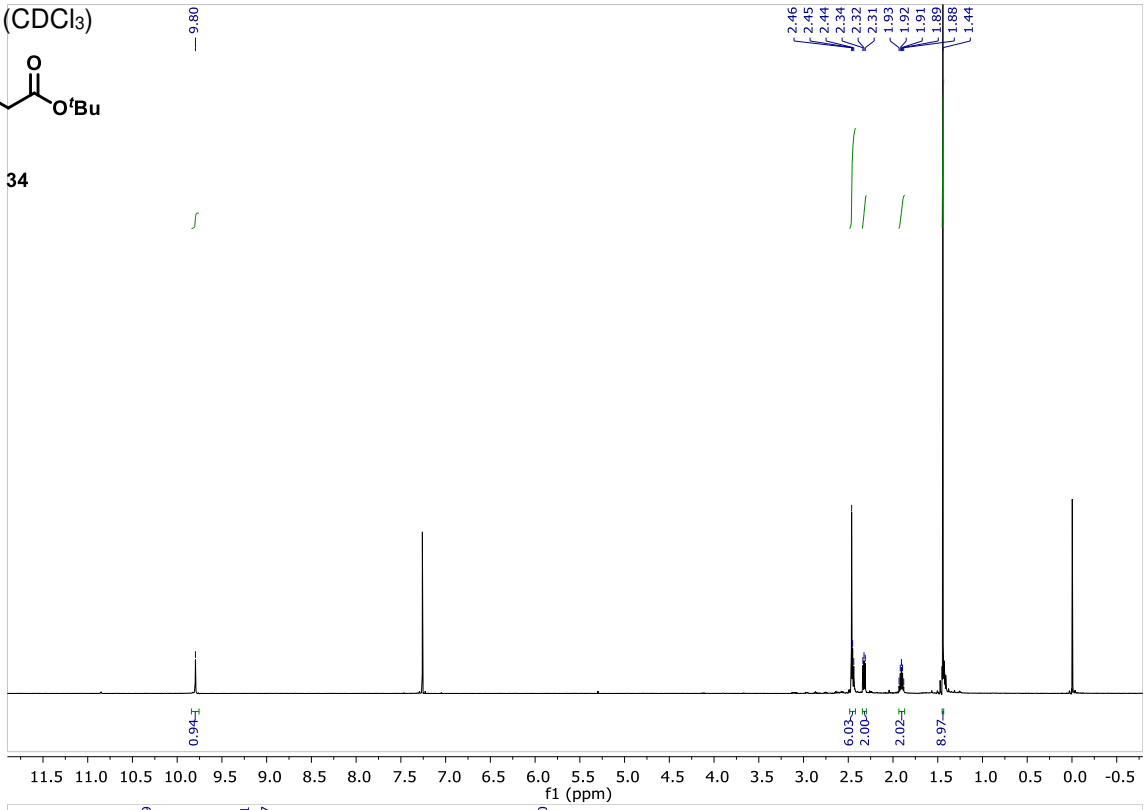
NMR Spectra

^{1}H-NMR ($CDCl_3$)



34



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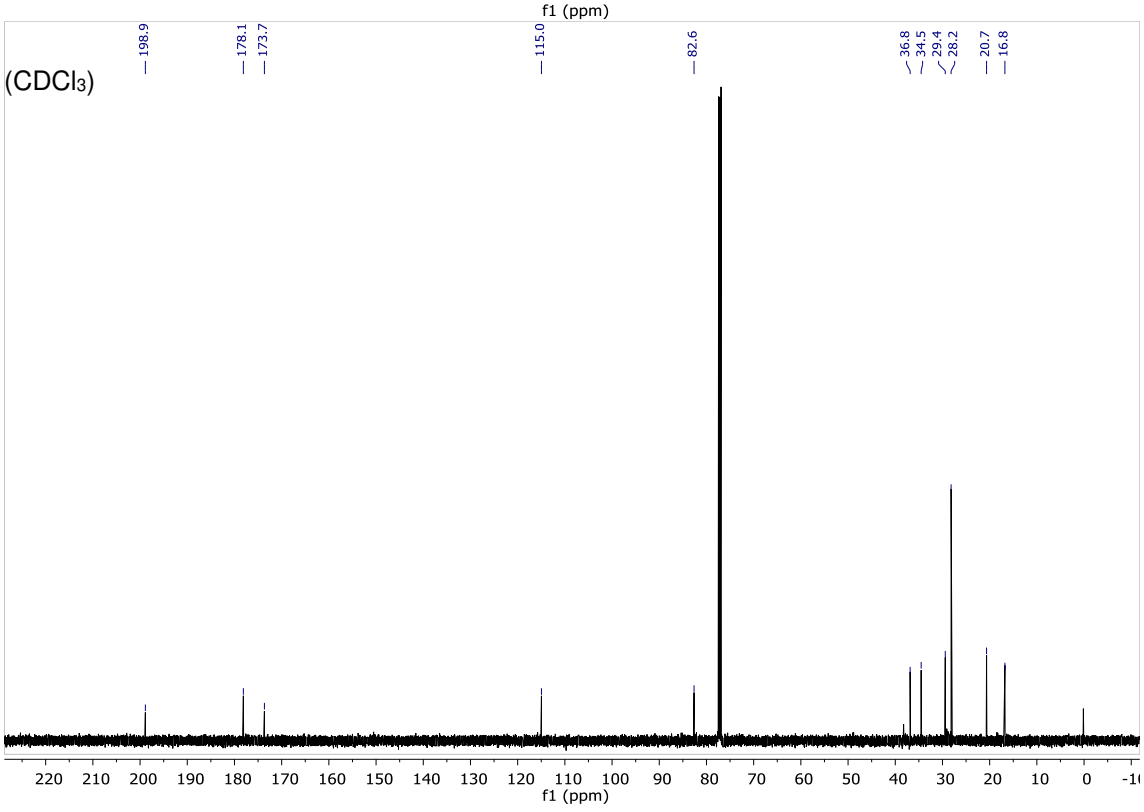

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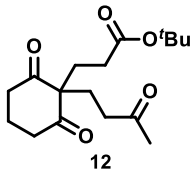

12

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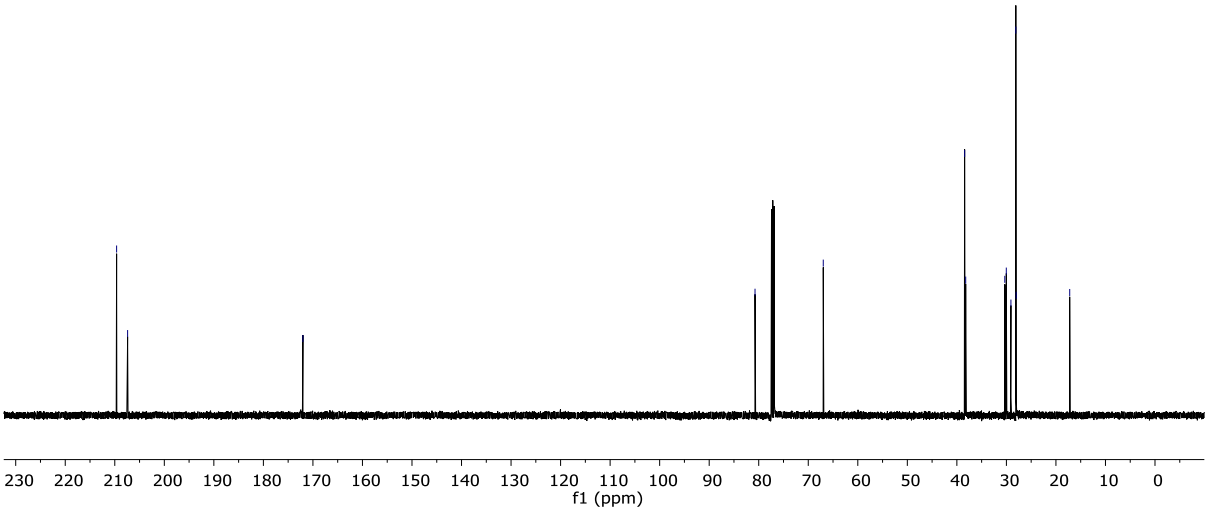

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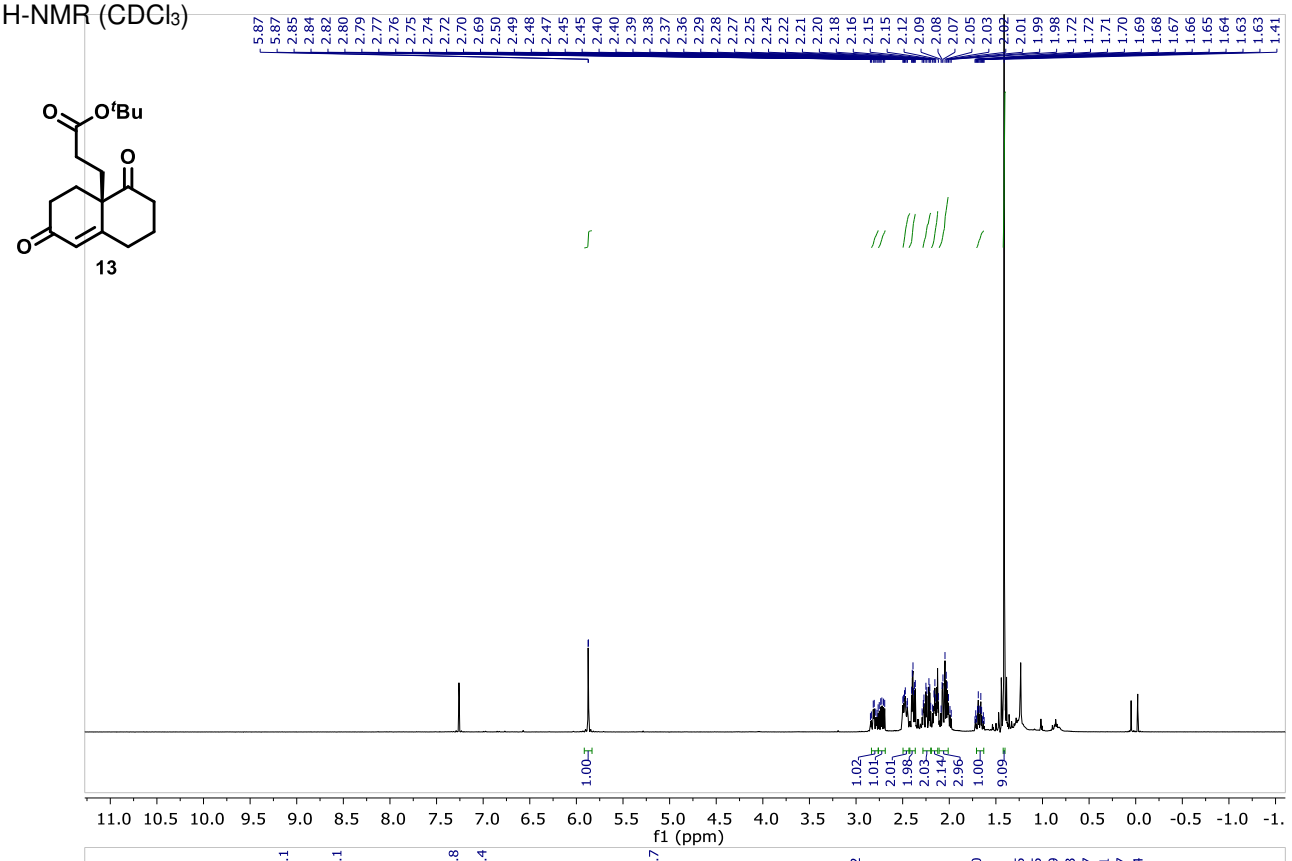

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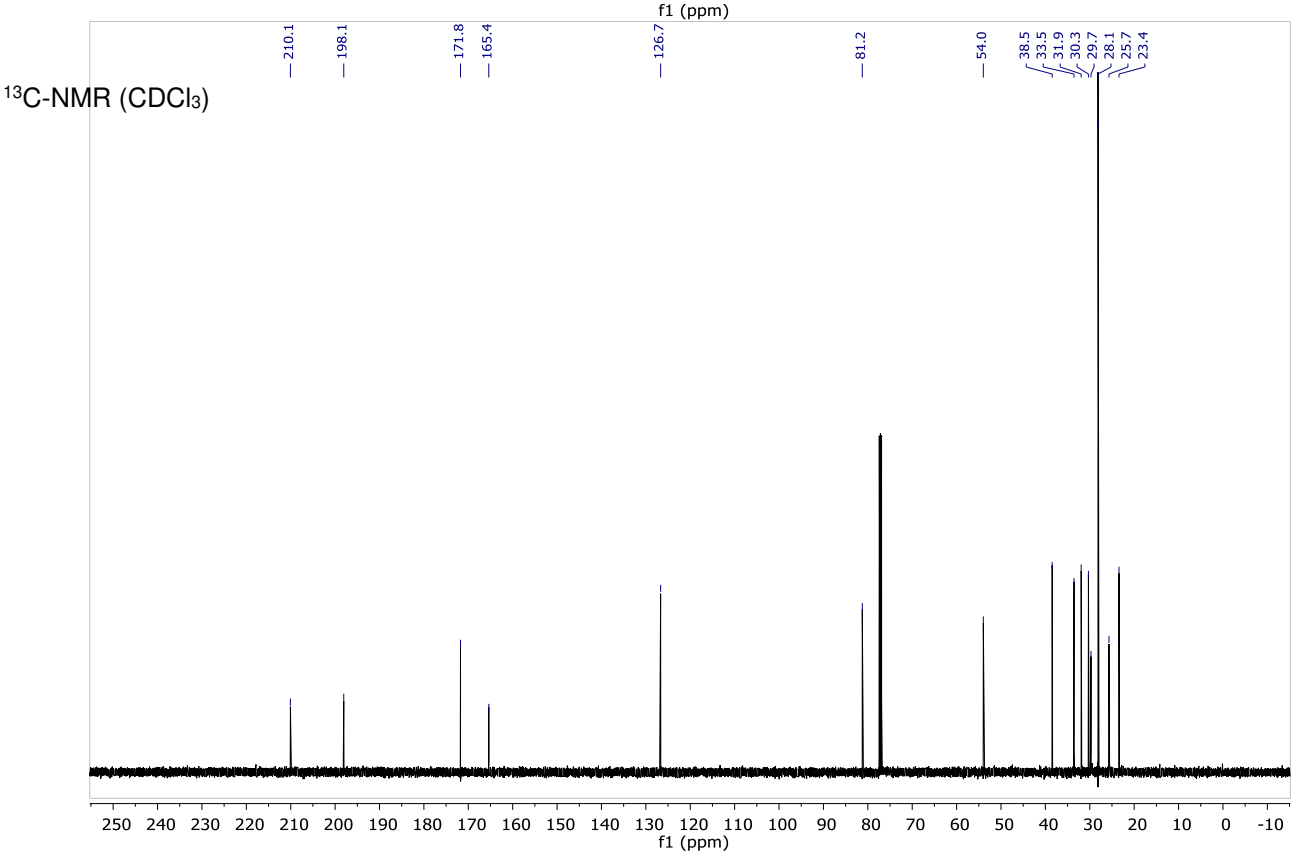

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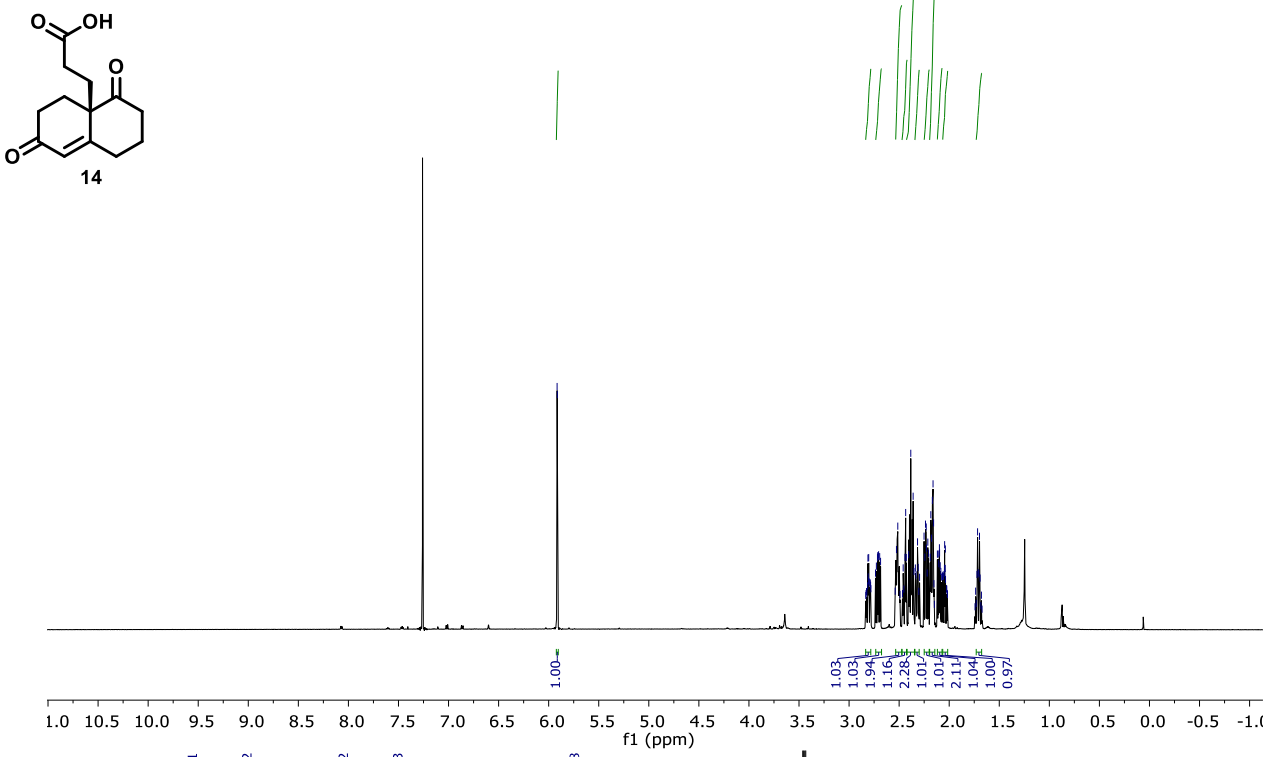

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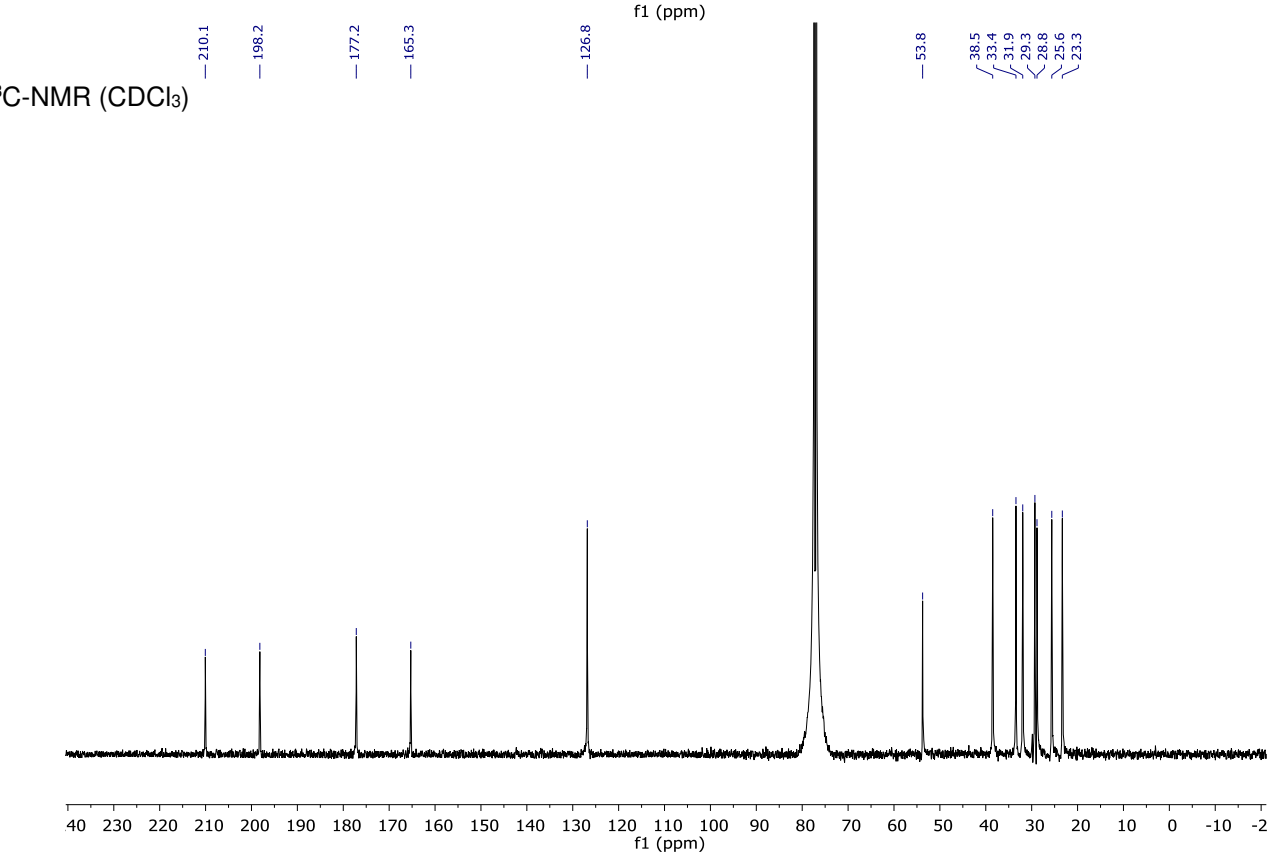

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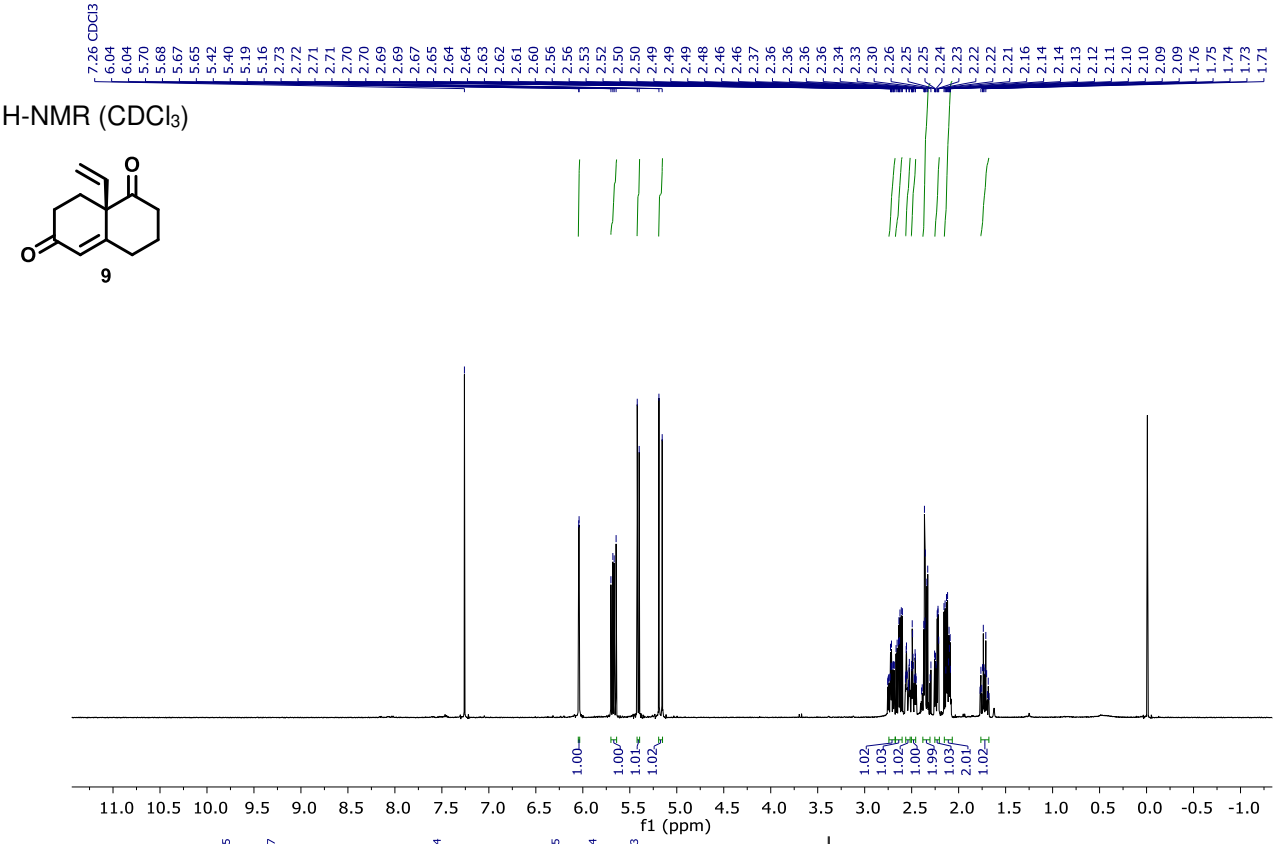

9

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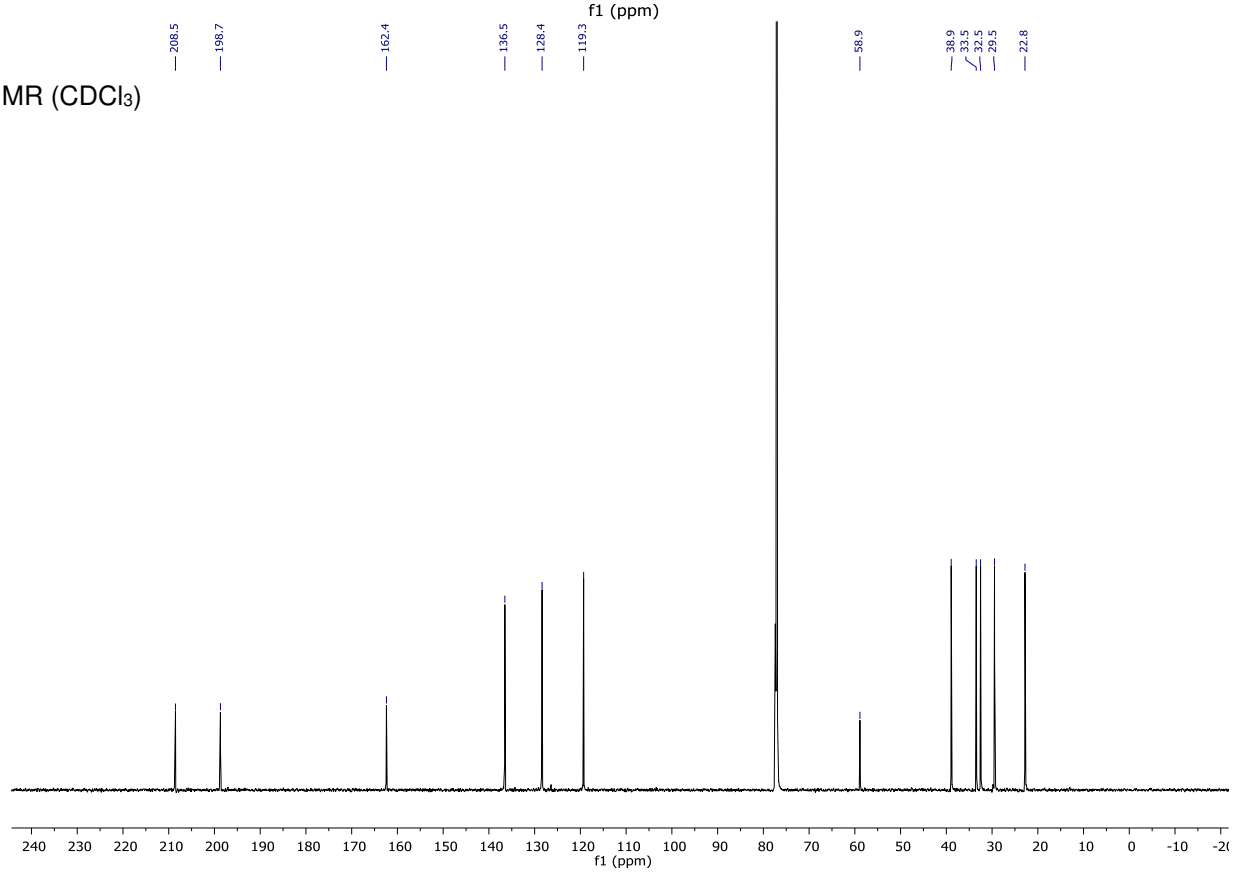

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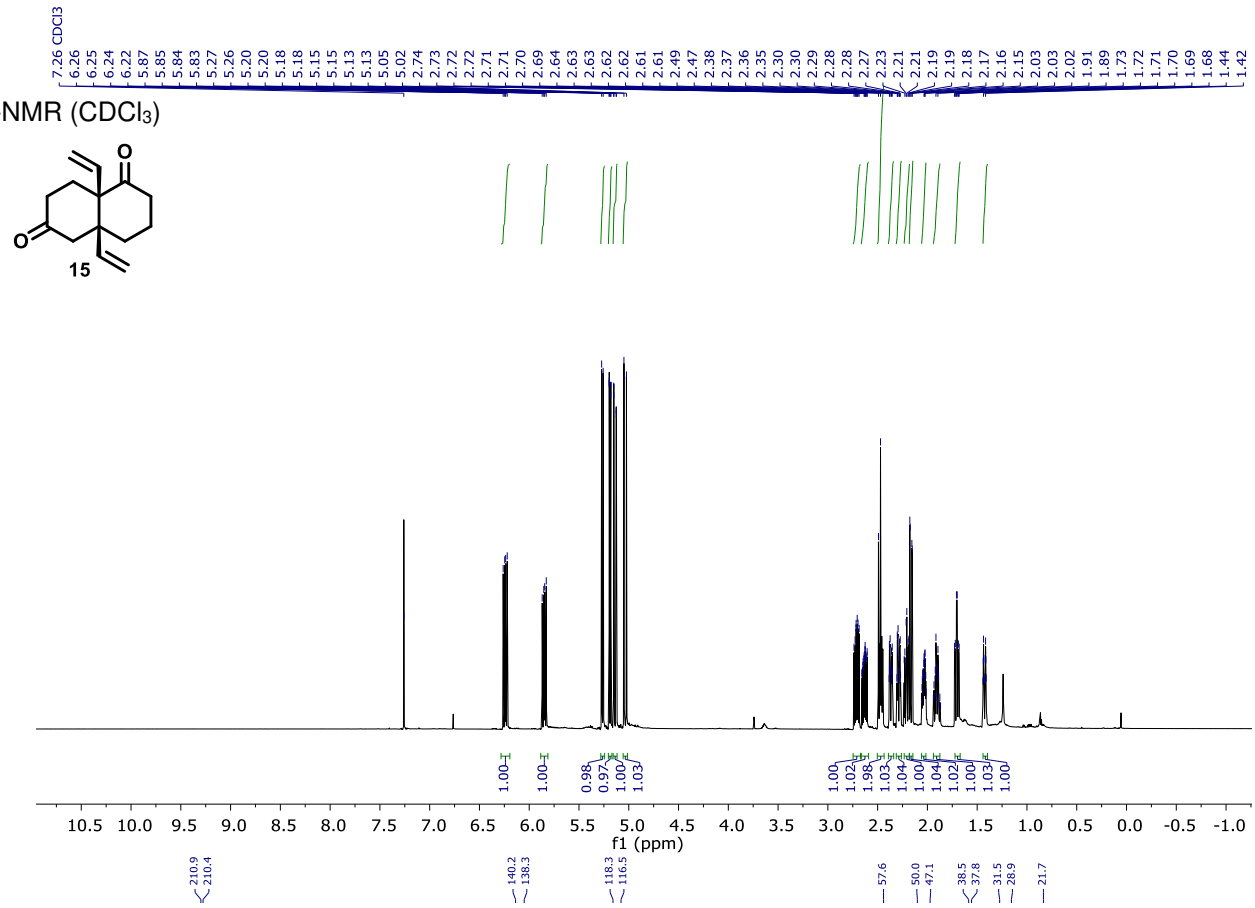

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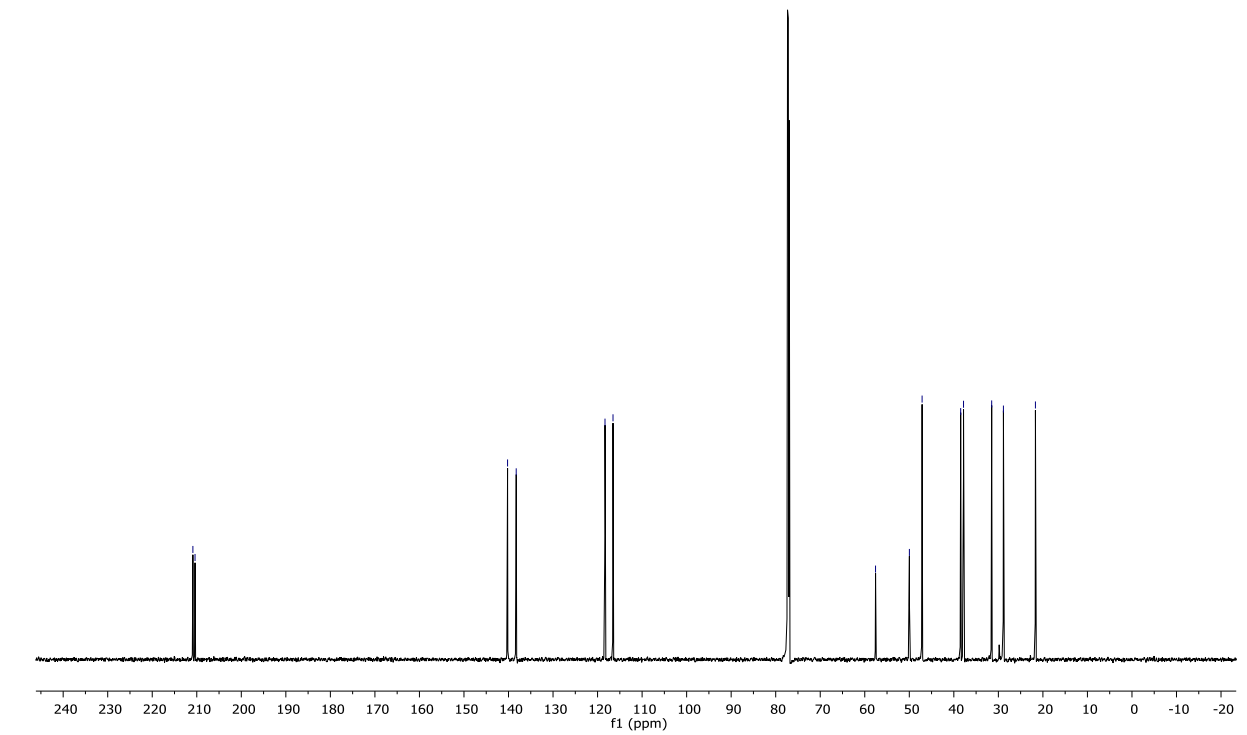

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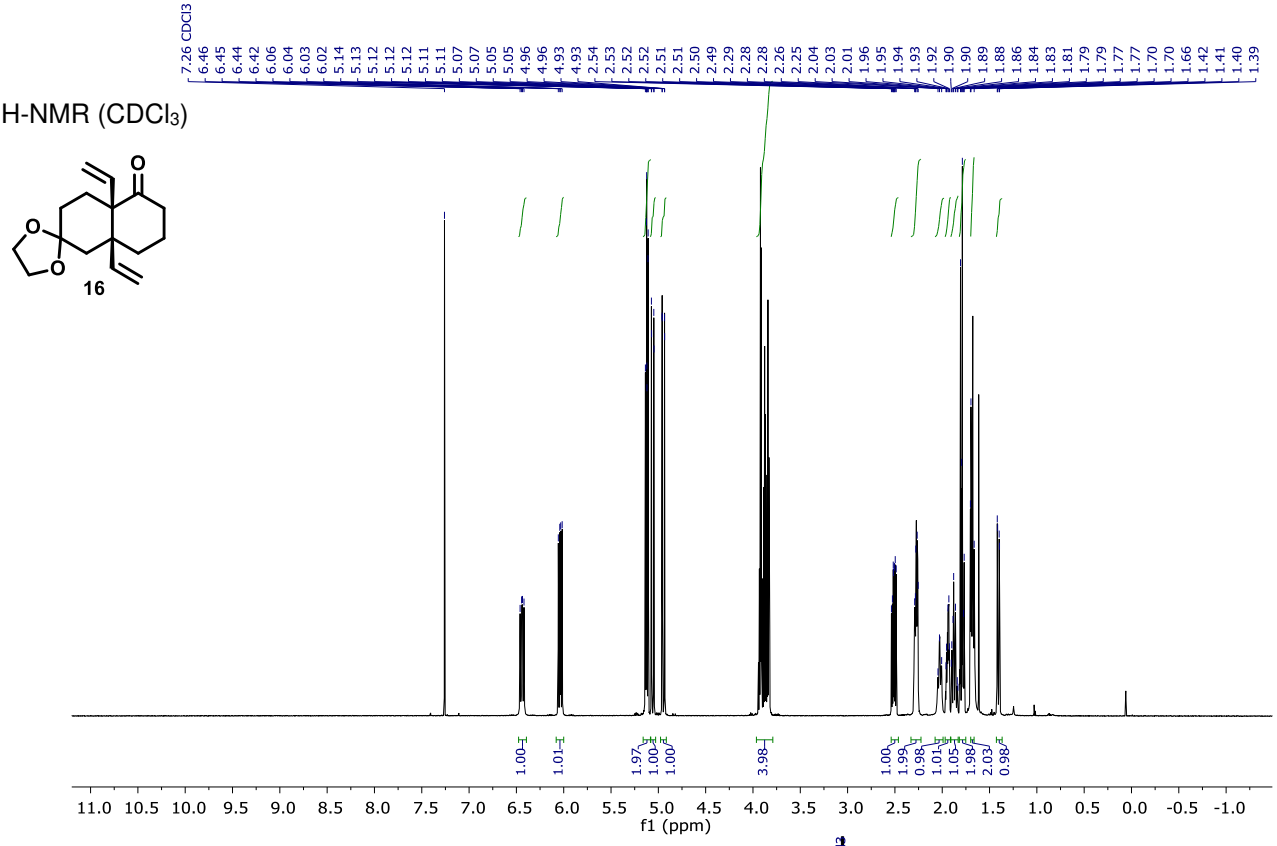

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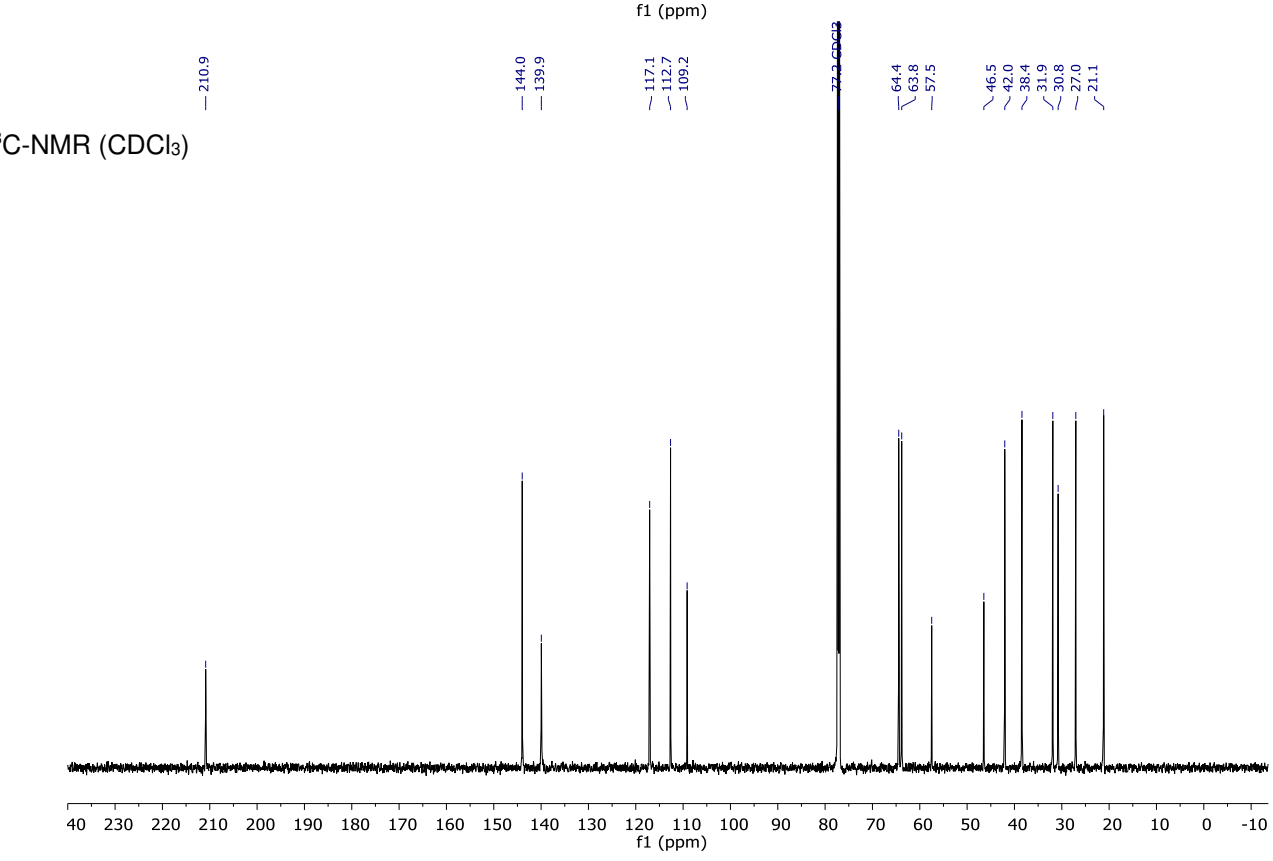

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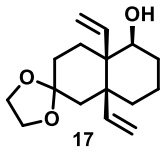

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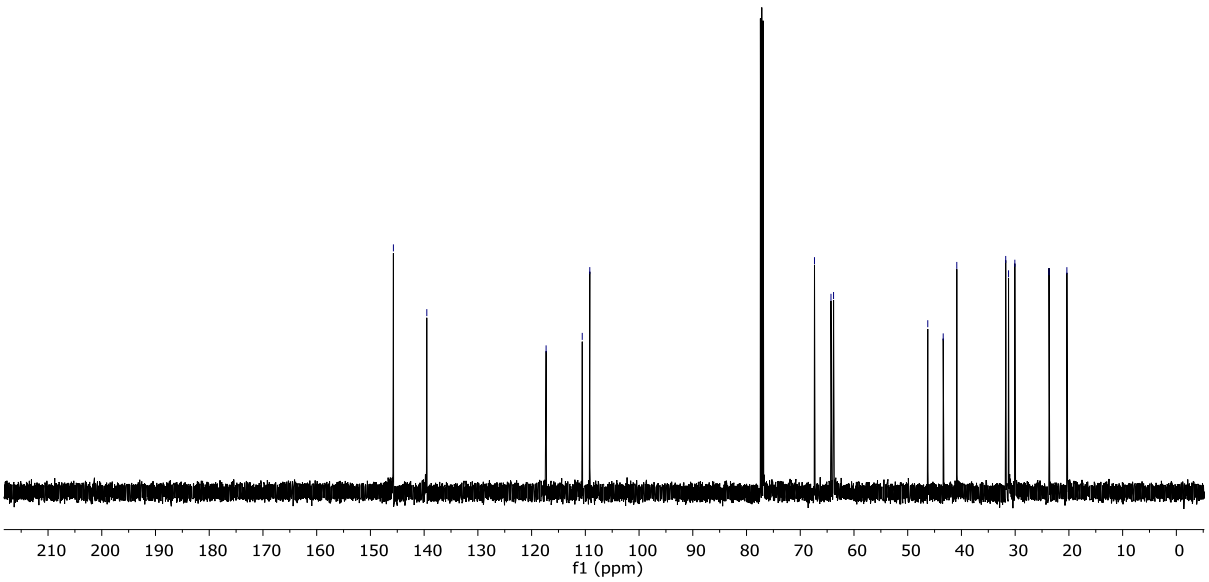
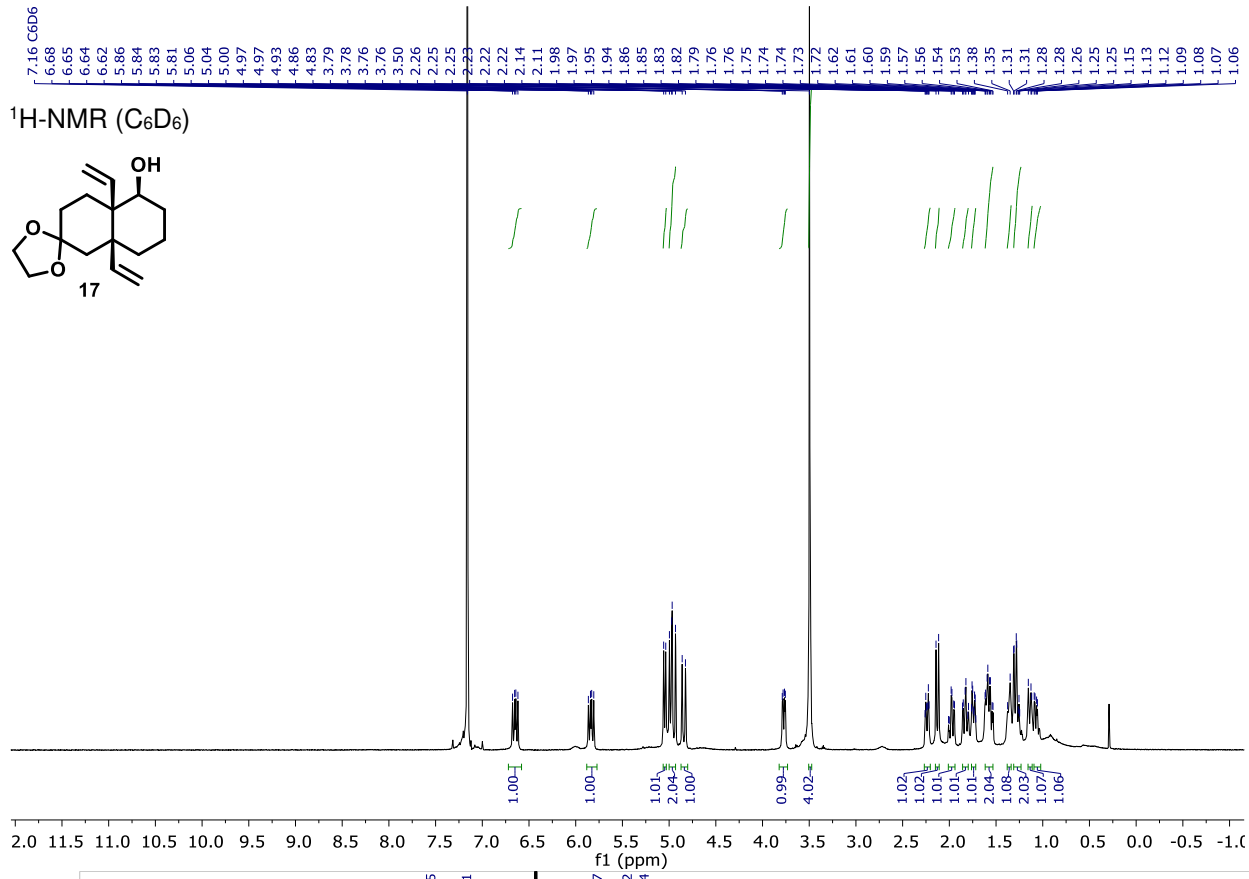
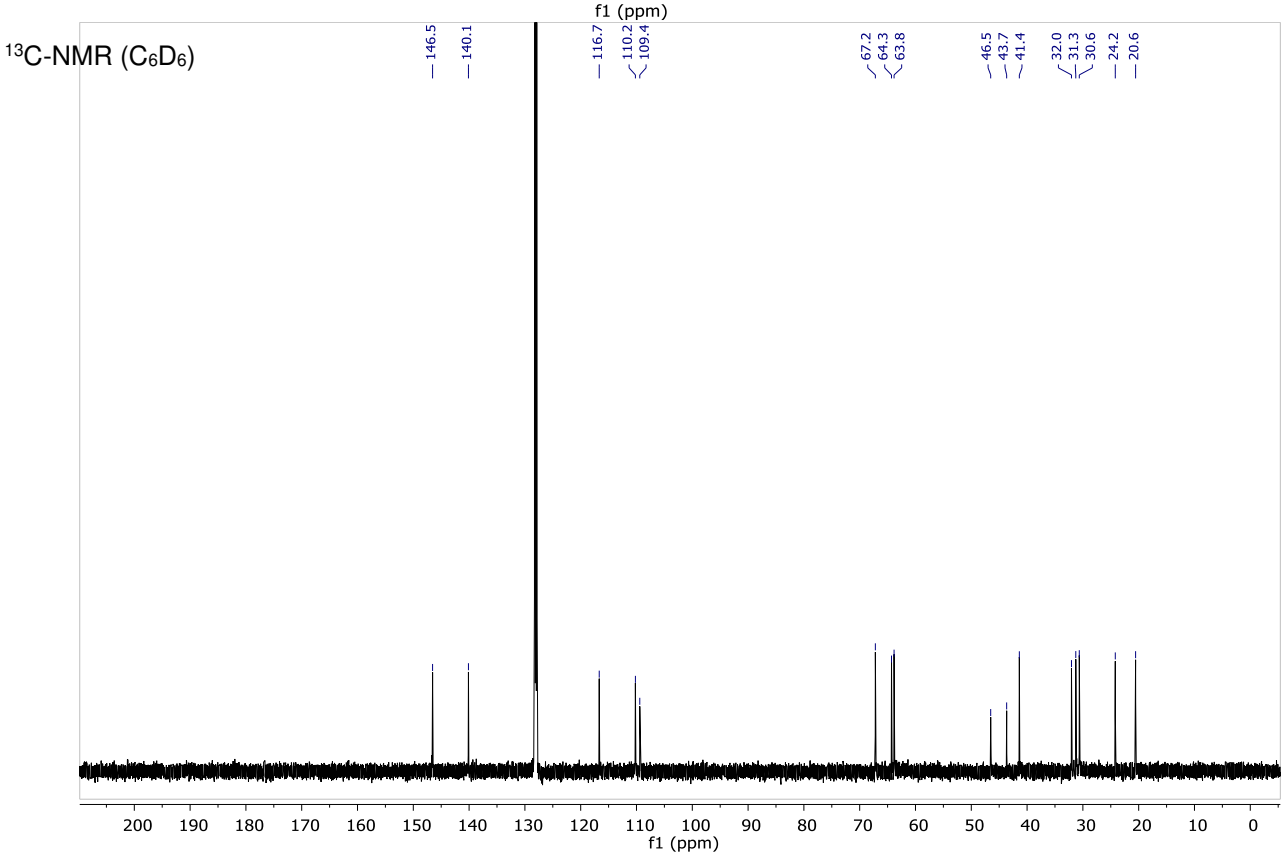
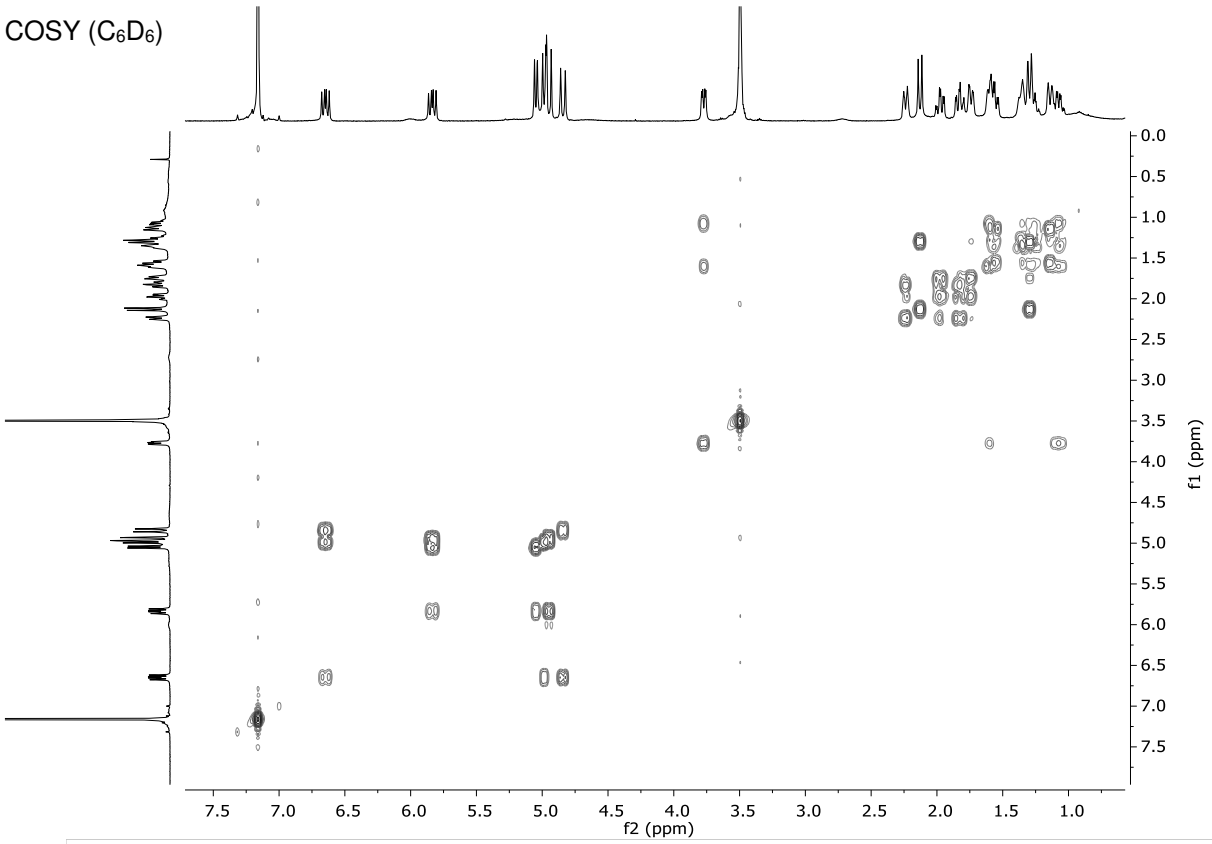


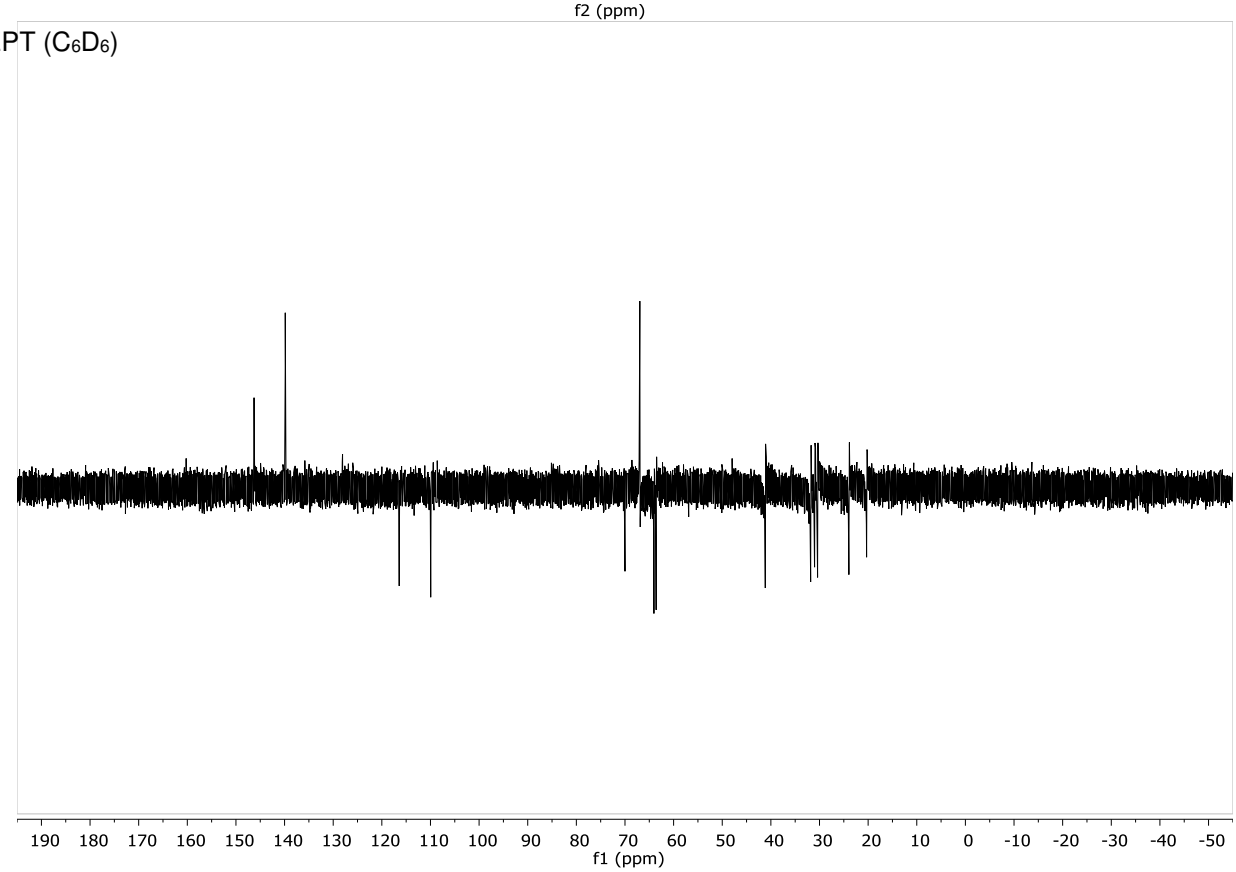

7.16 C6D6
6.68 6.65 6.64 6.62 5.86 5.84 5.83 5.81 5.06 5.04 5.00 4.97 4.97 4.93 4.86 4.83 3.79 3.78 3.76 3.76 3.50 2.26 2.25 2.25 2.23 2.22 2.22 2.14 2.11 1.98 1.97 1.95 1.94 1.86 1.85 1.83 1.82 1.79 1.76 1.76 1.75 1.74 1.74 1.73 1.72 1.62 1.61 1.60 1.59 1.57 1.56 1.54 1.53 1.38 1.35 1.31 1.31 1.28 1.28 1.26 1.25 1.25 1.15 1.13 1.12 1.09 1.08 1.07 1.06
1H-NMR (C6D6)
OH
O
O
17
1.00 1.00 1.01 2.04 1.00 0.99 4.02 1.02 1.02 1.01 1.01 1.01 2.04 1.08 2.03 1.07 1.06
2.0 11.5 11.0 10.5 10.0 9.5 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
f1 (ppm)


13C-NMR (C6D6)
146.5 140.1 116.7 110.2 109.4 67.2 64.3 63.8 46.5 43.7 41.4 32.0 31.3 30.6 24.2 20.6
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

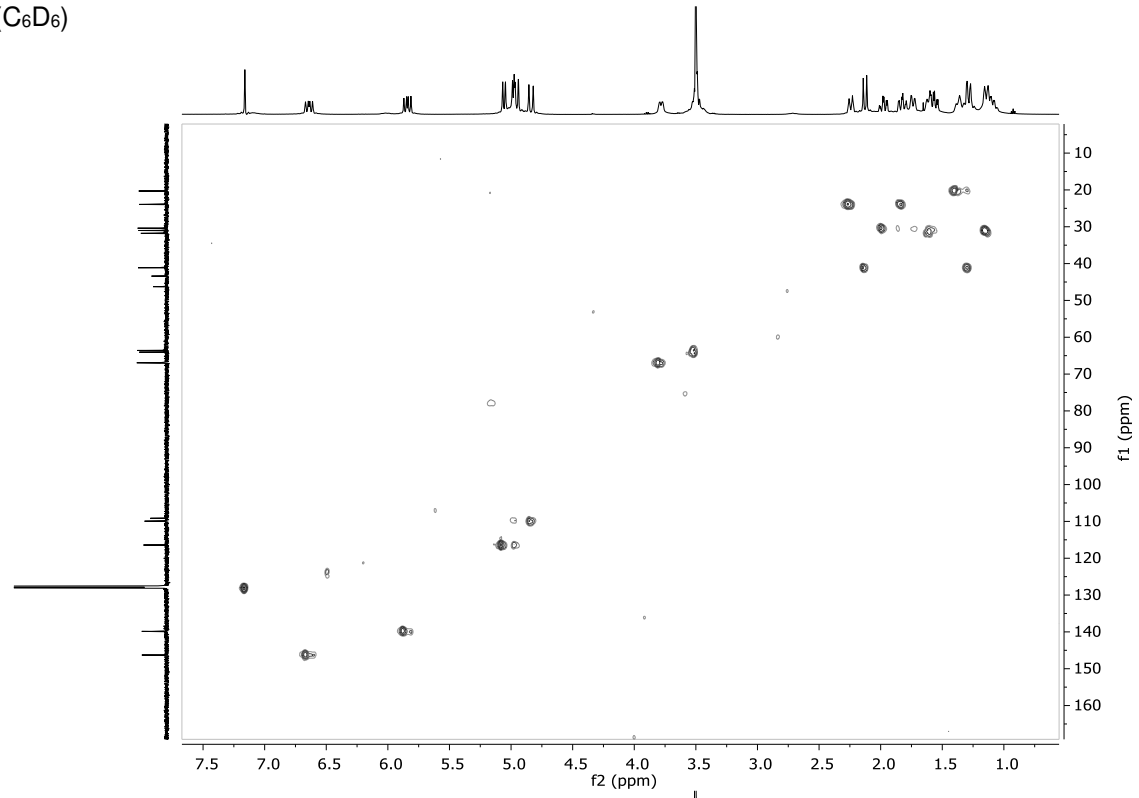
COSY (C_6D_6)



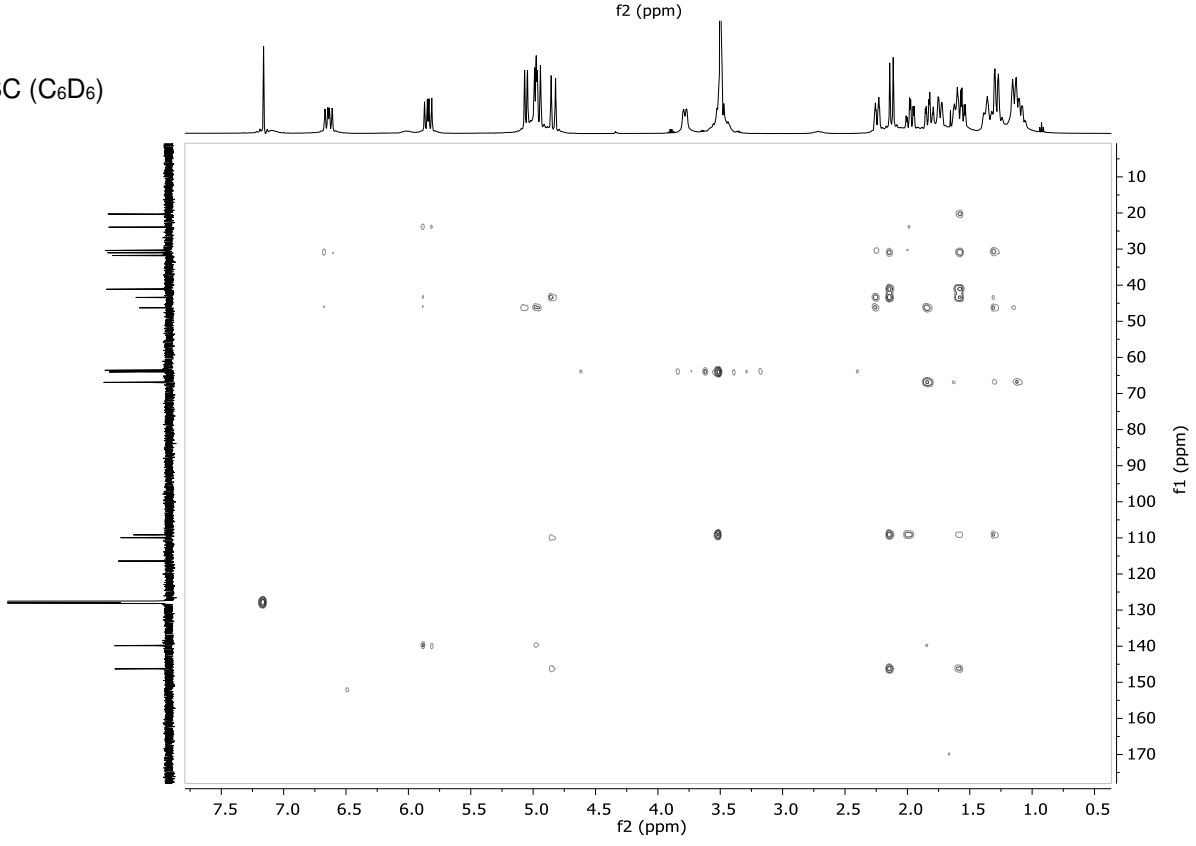
DEPT (C_6D_6)



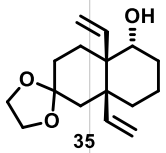
HMQC (C_6D_6)

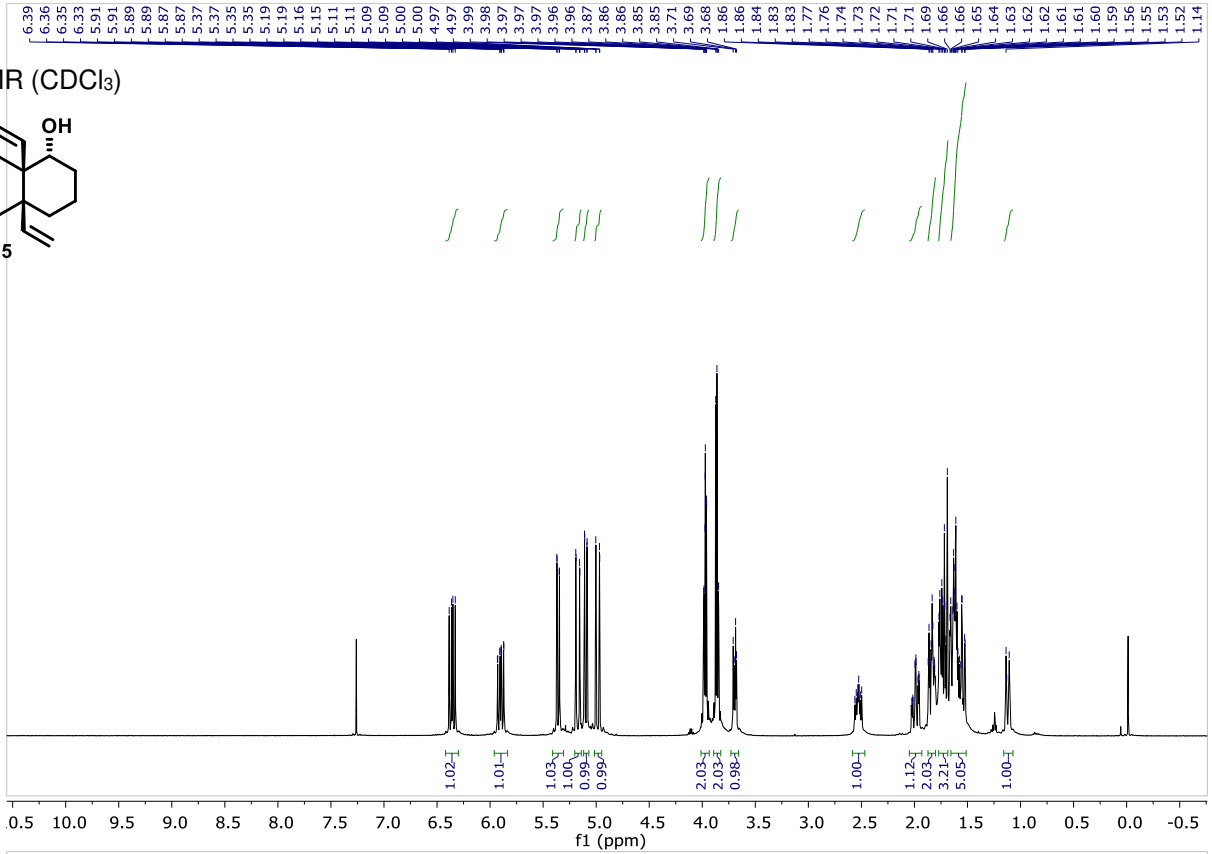


HMBC (C_6D_6)

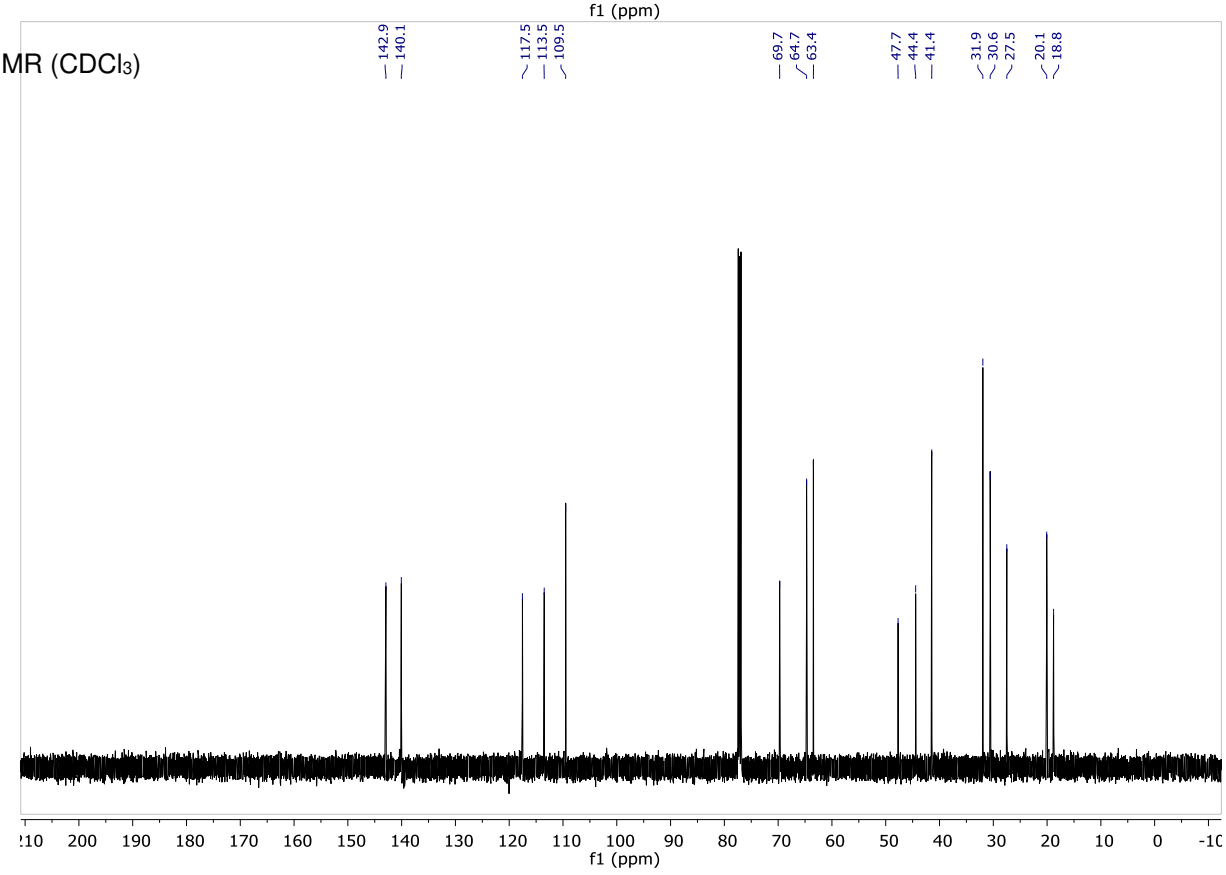


^{1}H-NMR ($CDCl_3$)

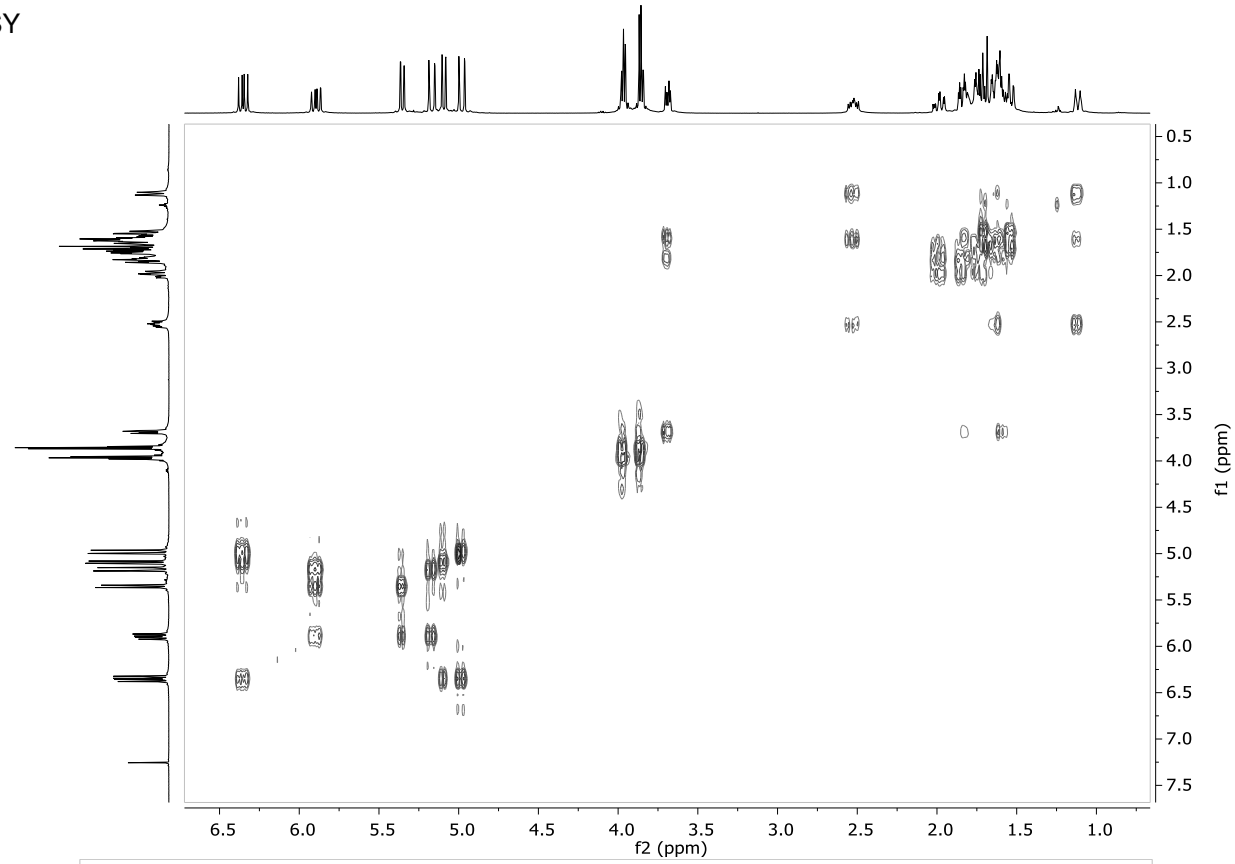




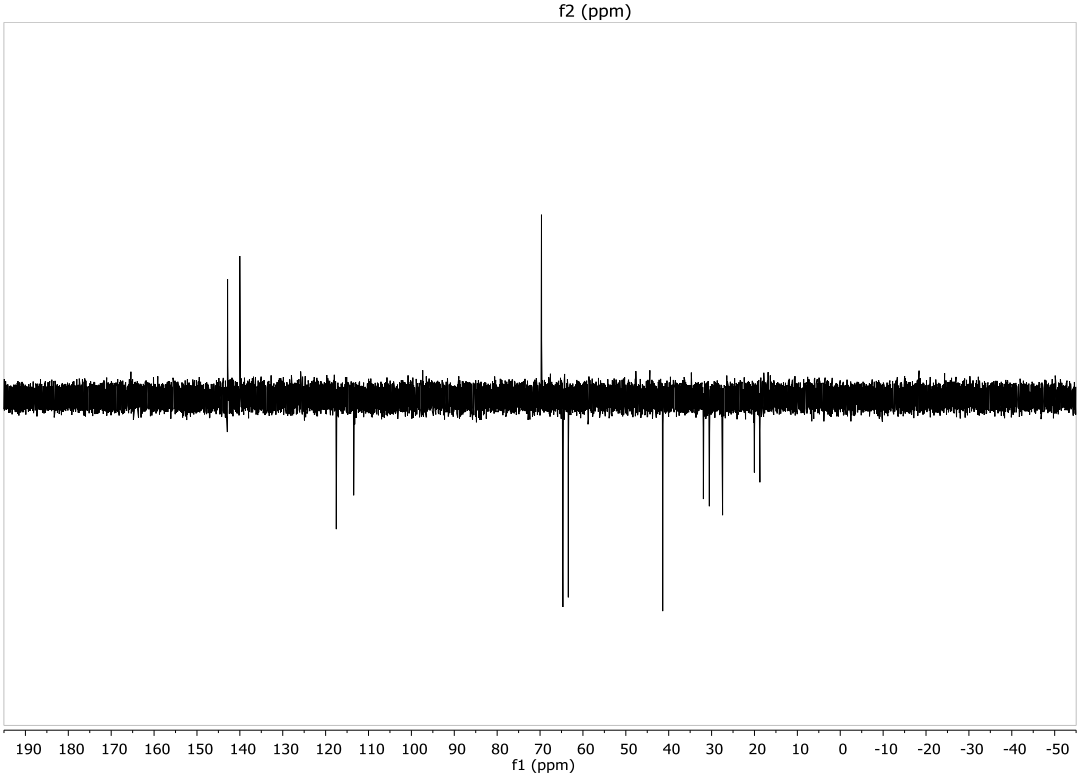
^{13}C-NMR ($CDCl_3$)



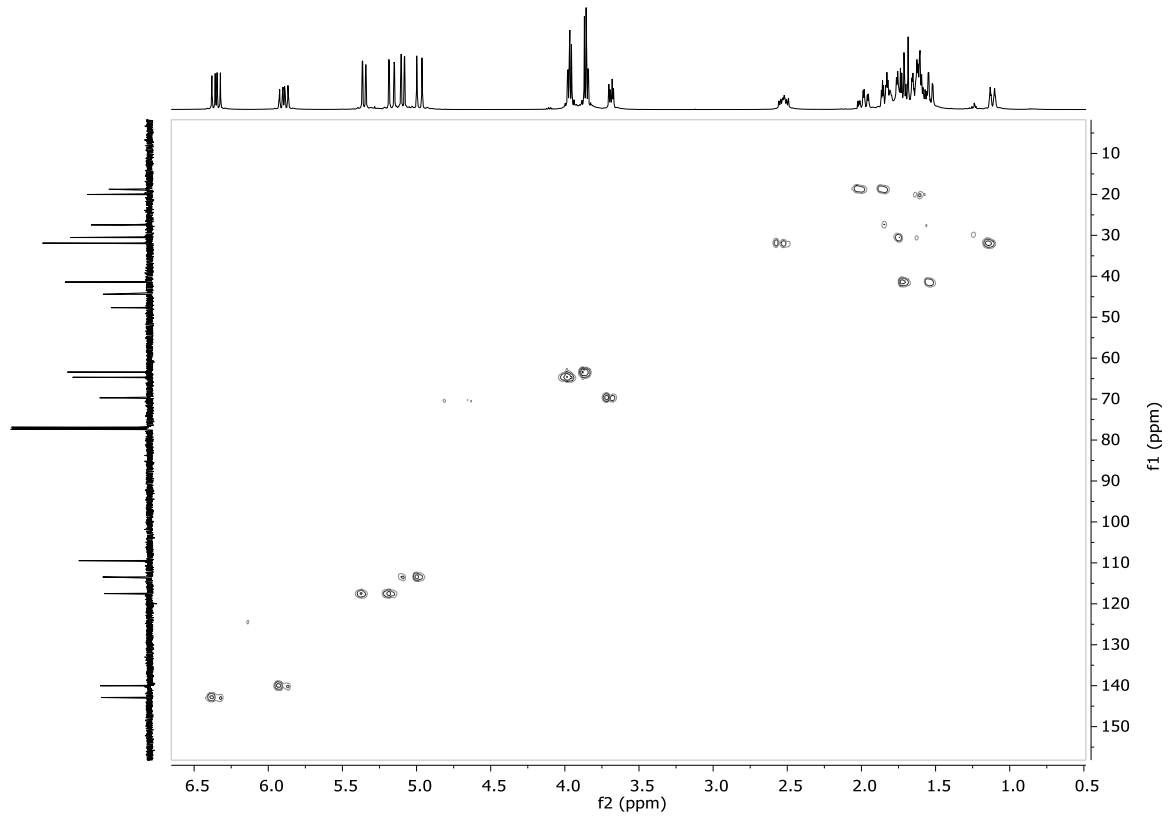
COSY


0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
f1 (ppm)
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)

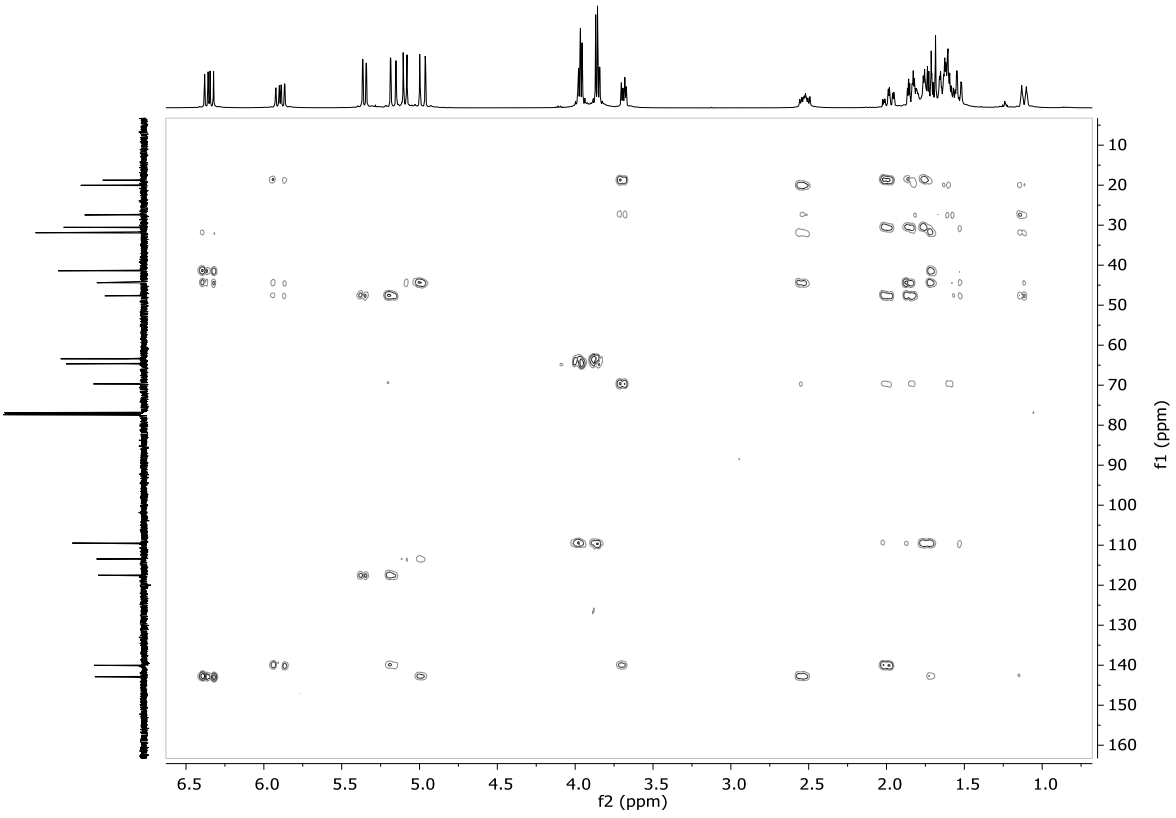
DEPT


190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50
f1 (ppm)

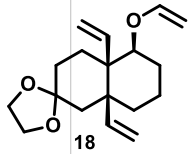
HMQC



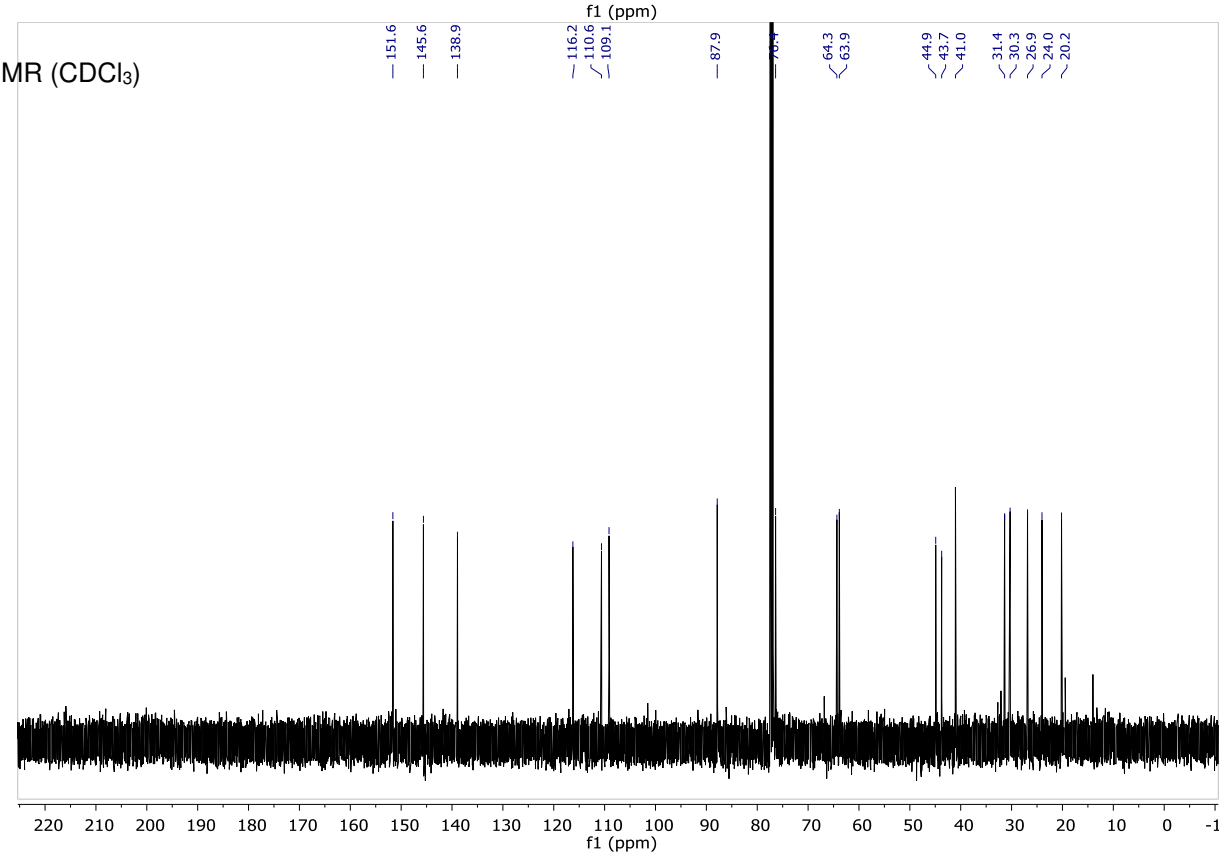
HMBC



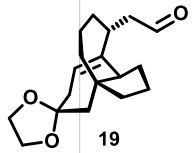
^{1}H-NMR ($CDCl_3$)



^{13}C-NMR ($CDCl_3$)

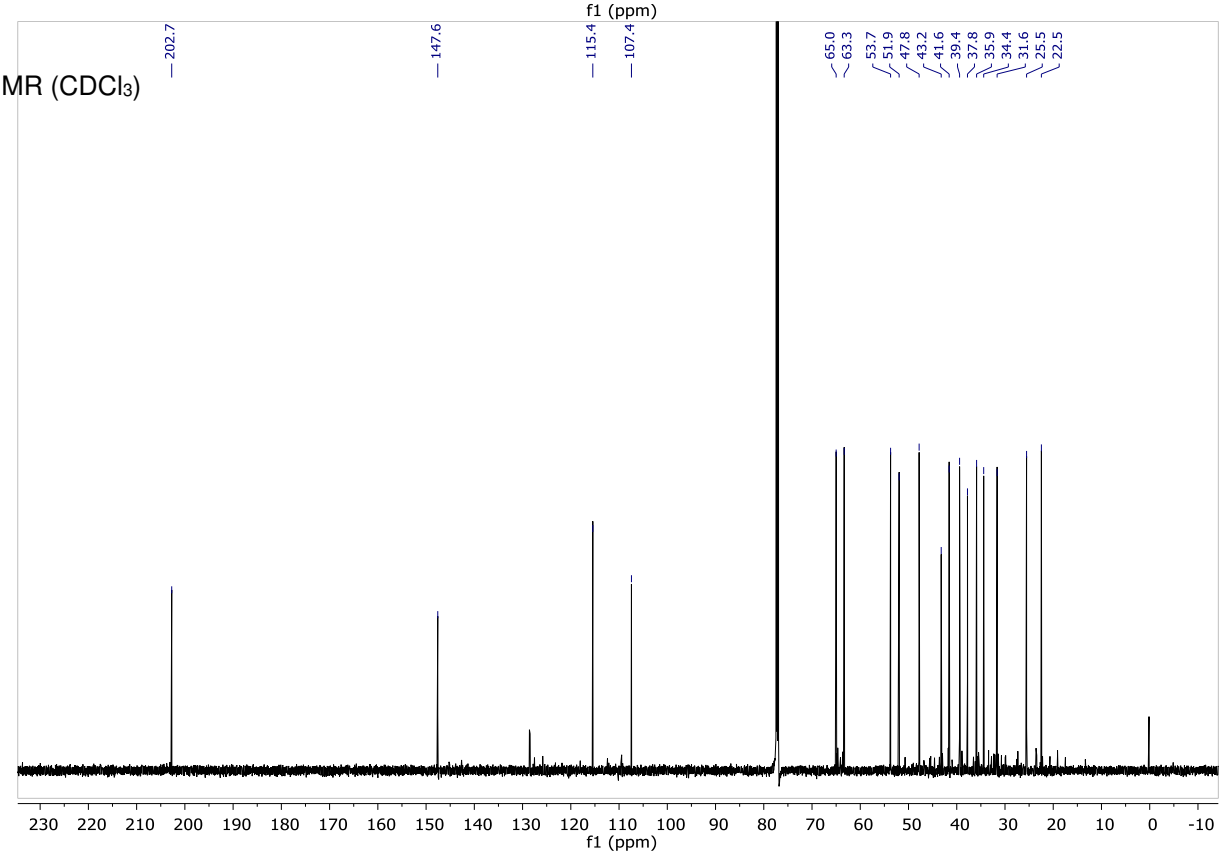


^{1}H-NMR ($CDCl_3$)

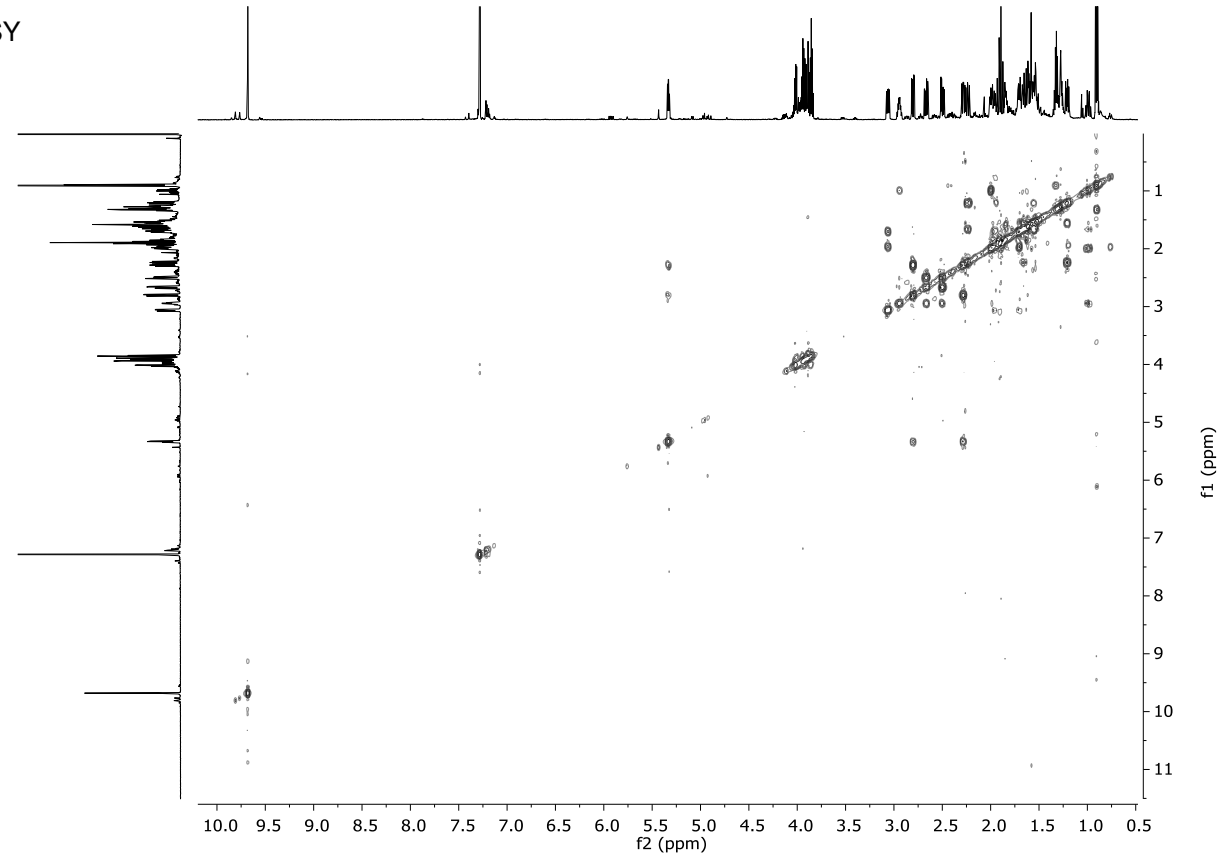


19

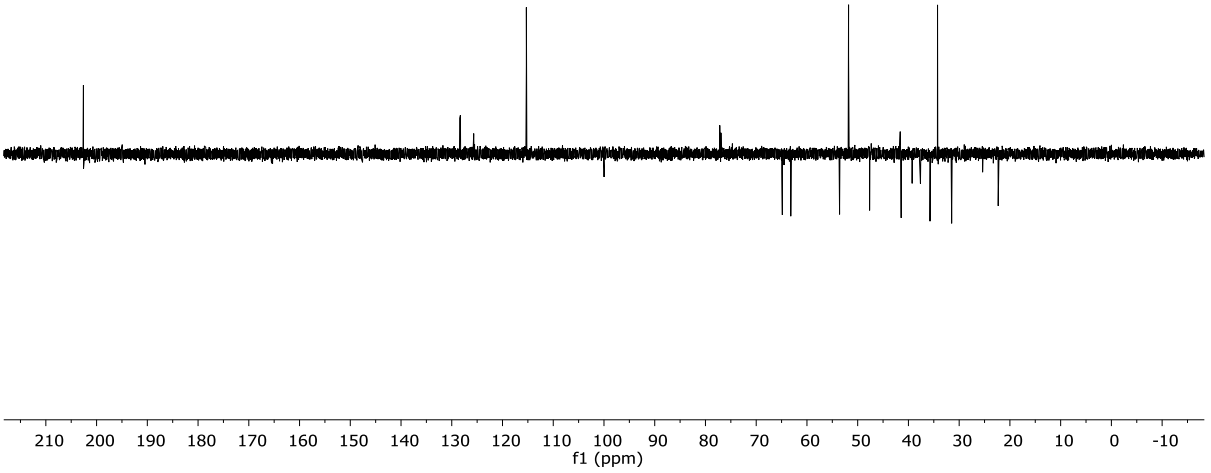
^{13}C-NMR ($CDCl_3$)



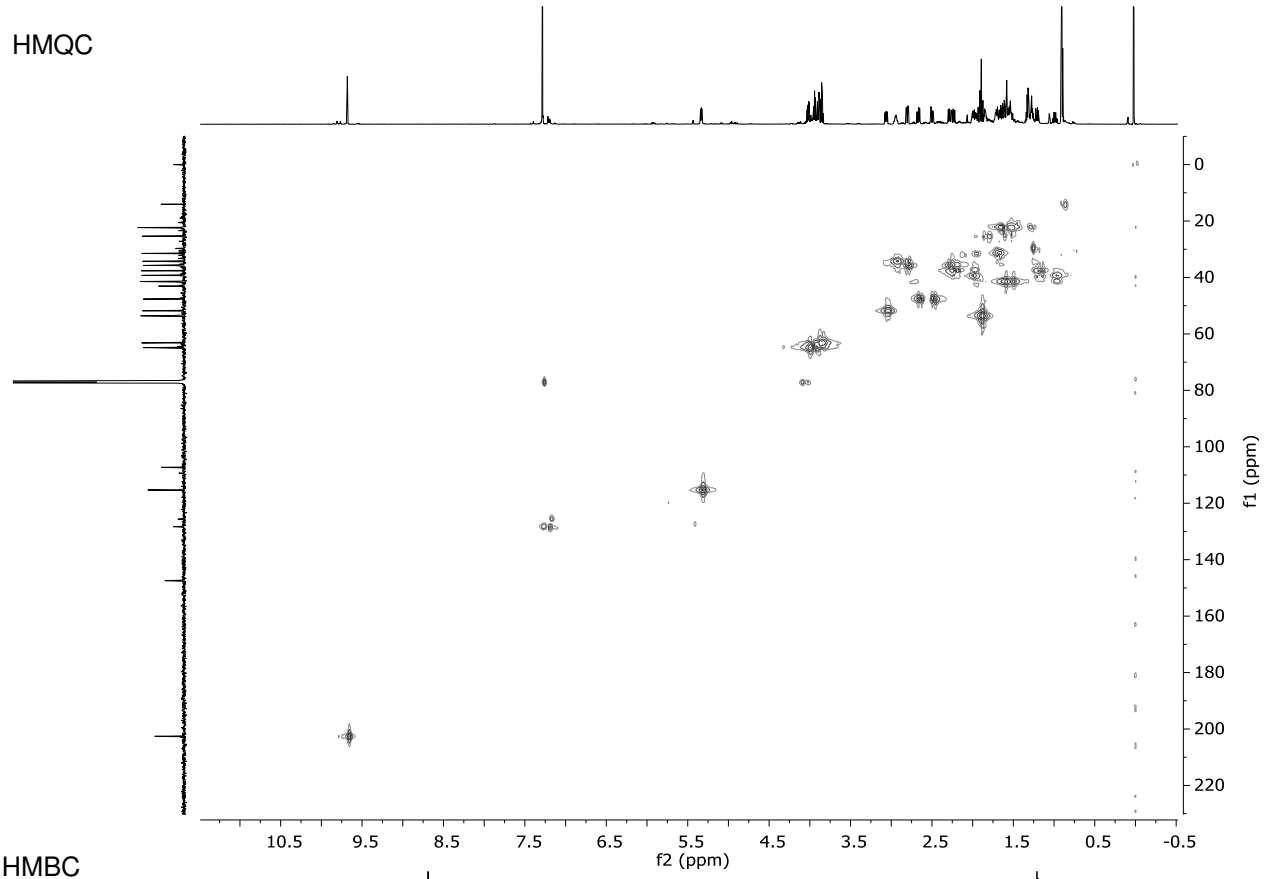
COSY


10.0 9.5 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
f2 (ppm)
1 2 3 4 5 6 7 8 9 10 11
f1 (ppm)

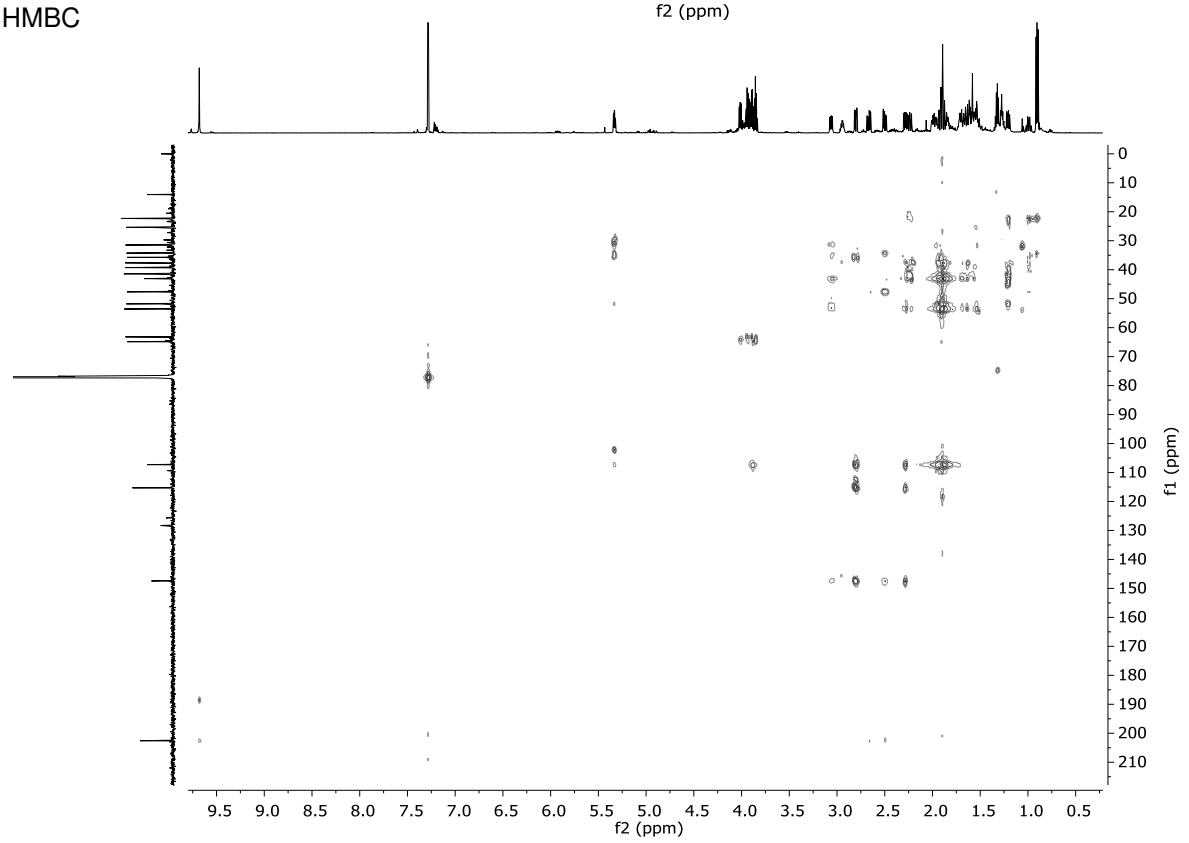
DEPT


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

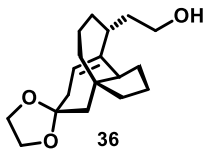
HMQC


10.5 9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5 -0.5
f2 (ppm)
0 20 40 60 80 100 120 140 160 180 200 220
f1 (ppm)

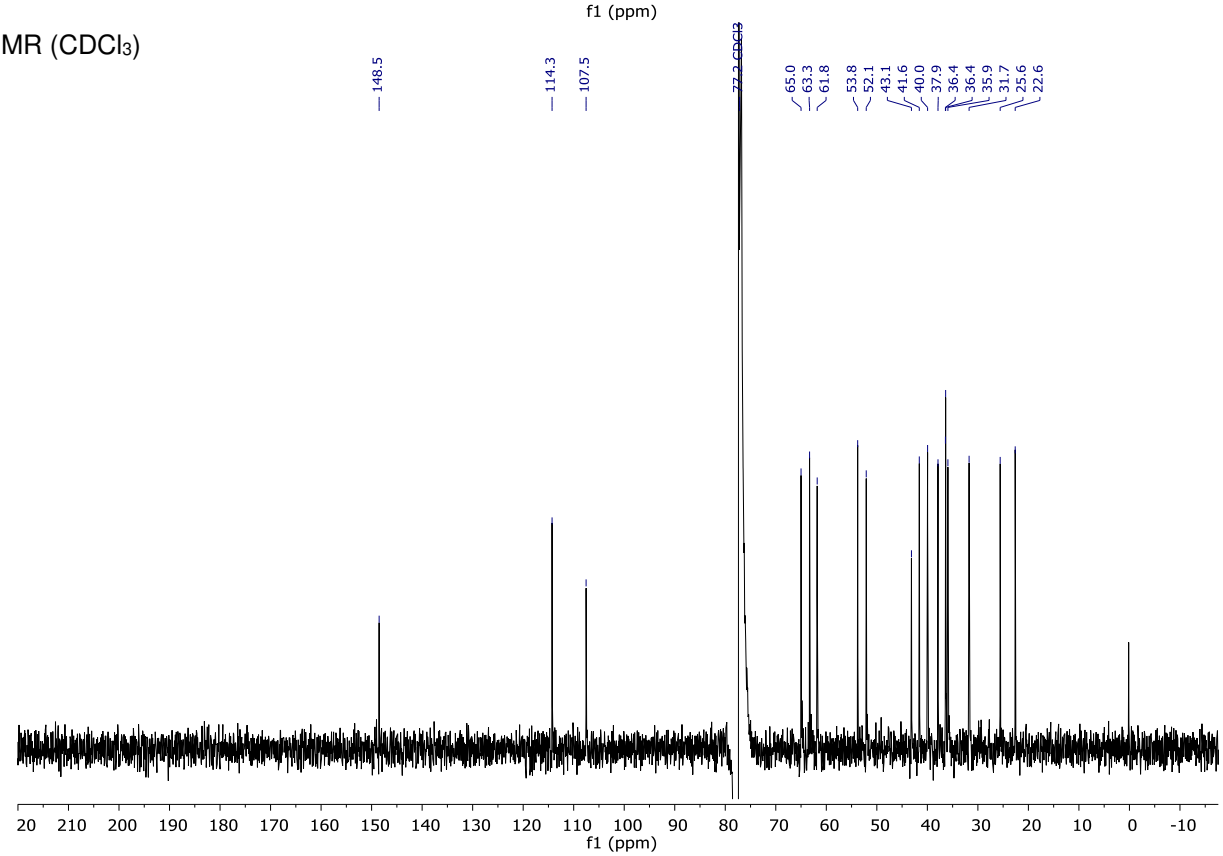
HMBC


9.5 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
f2 (ppm)
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210
f1 (ppm)

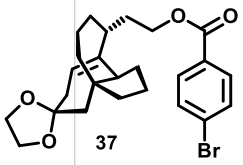
^{1}H-NMR ($CDCl_3$)



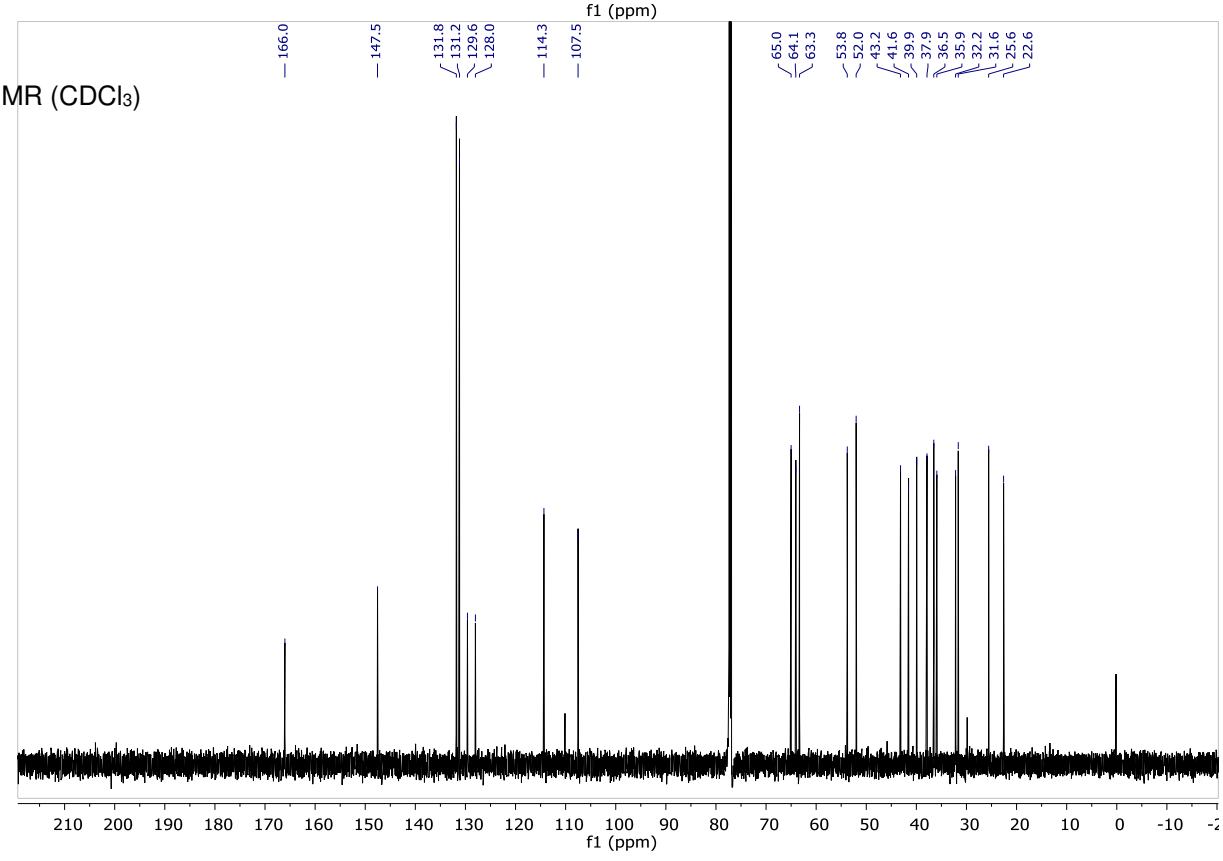
^{13}C-NMR ($CDCl_3$)



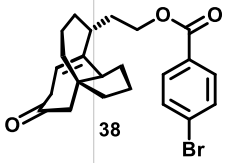
^{1}H-NMR ($CDCl_3$)



^{13}C-NMR ($CDCl_3$)

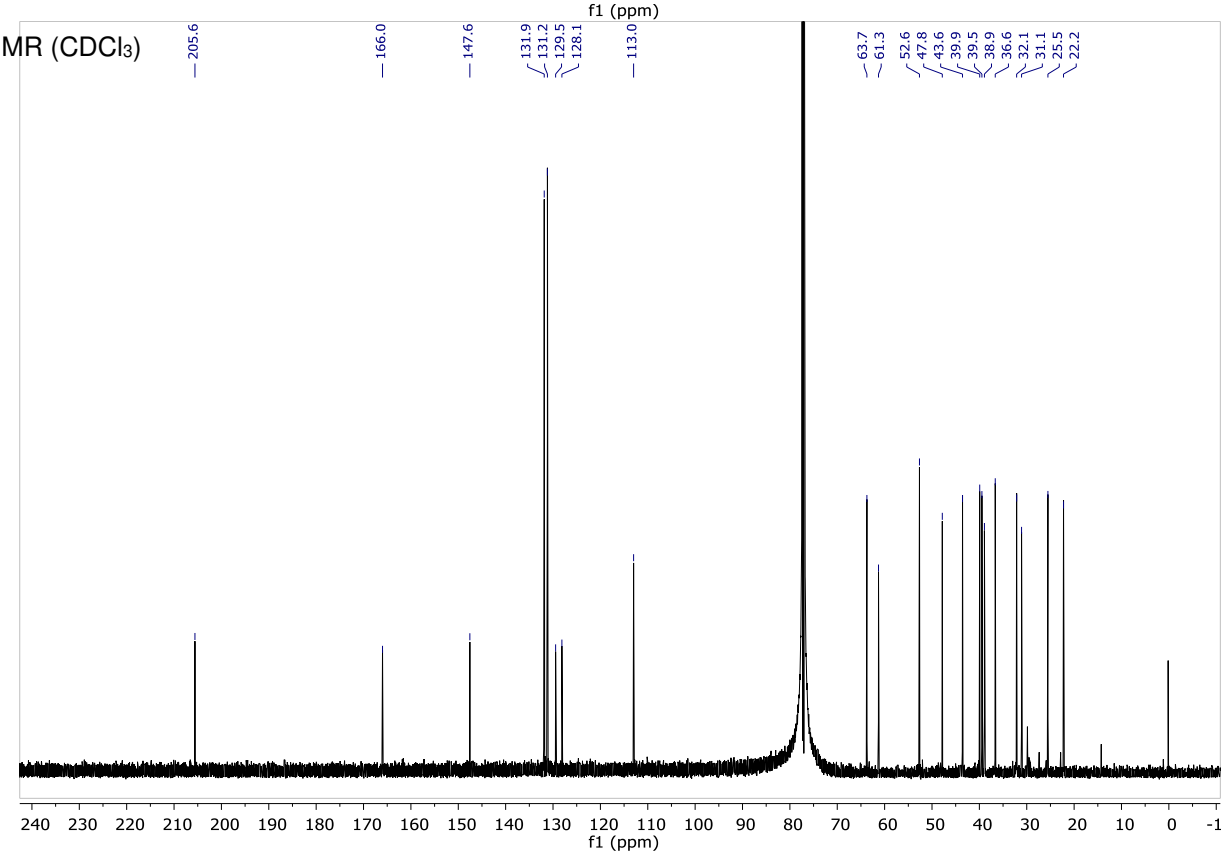


^{1}H-NMR ($CDCl_3$)

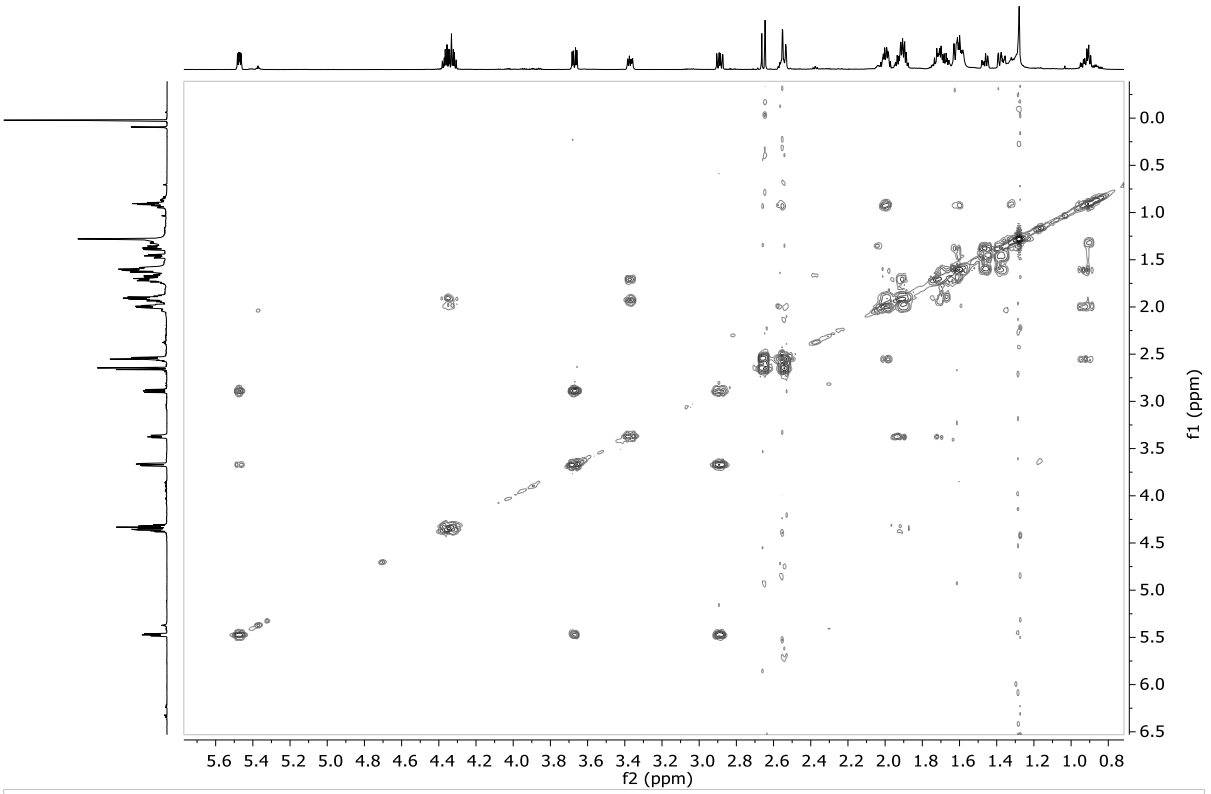


38

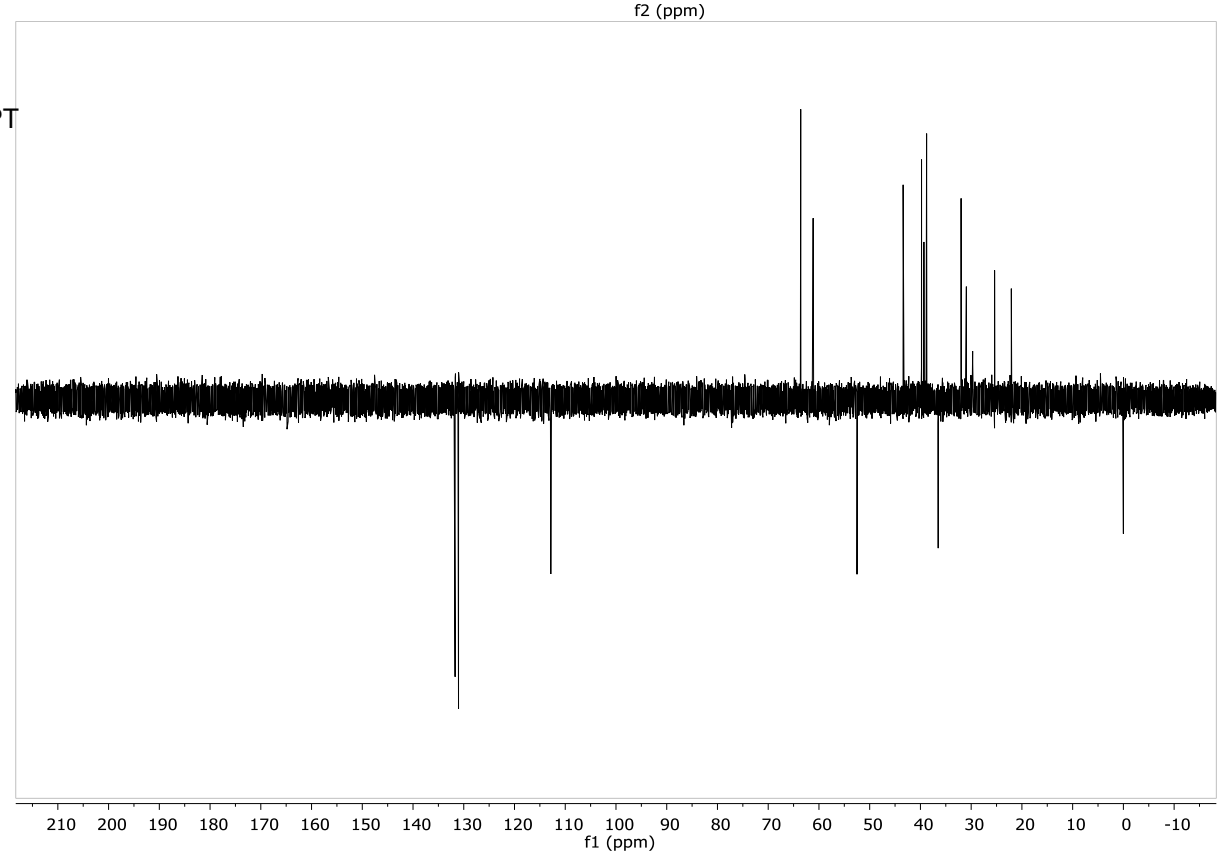
^{13}C-NMR ($CDCl_3$)



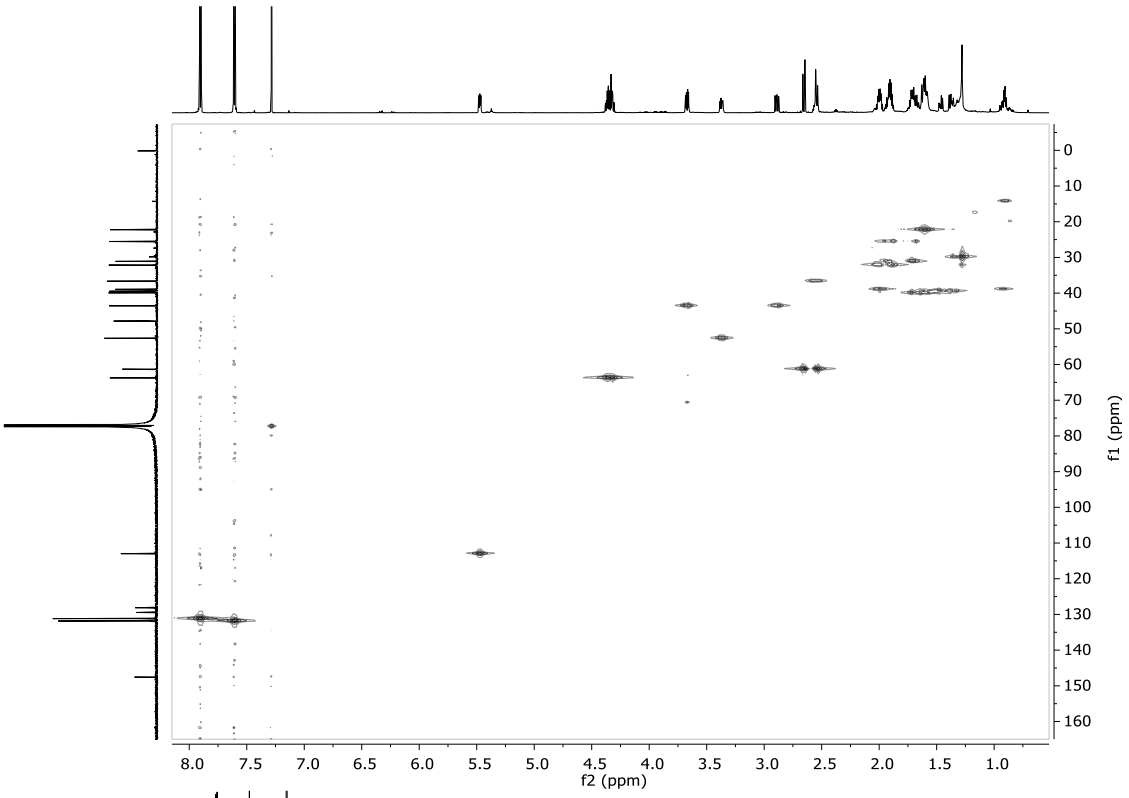
COSY


0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
f1 (ppm)
5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8
f2 (ppm)

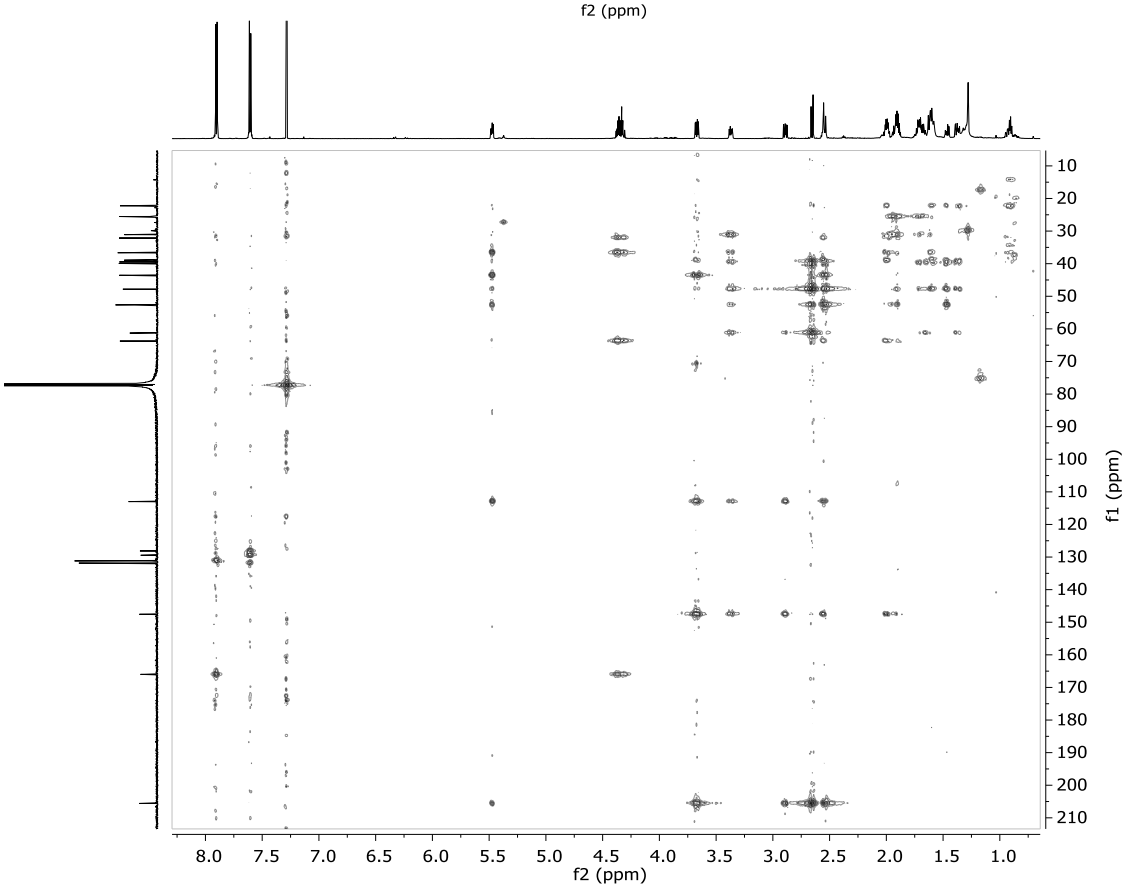
DEPT


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

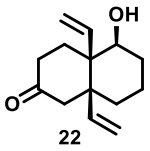
HMQC



HMBC

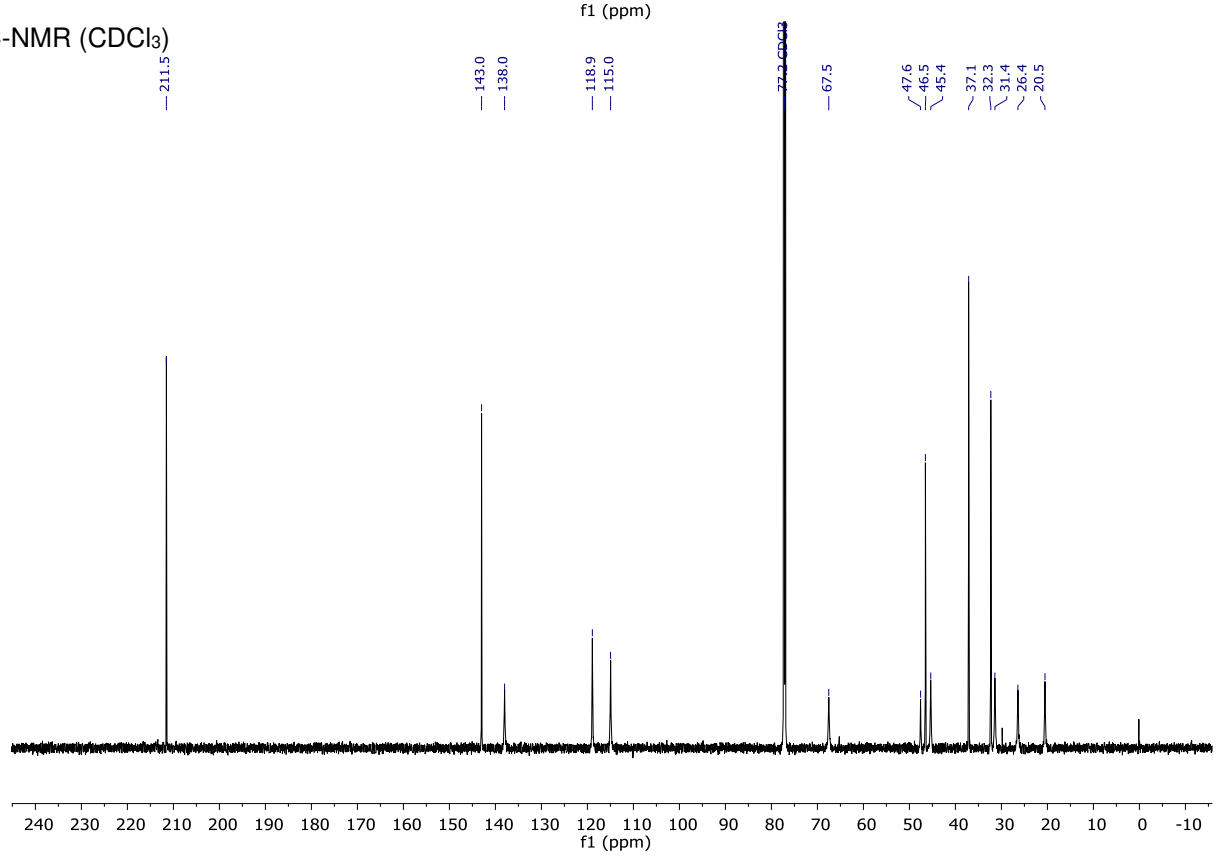


^{1}H-NMR ($CDCl_3$)

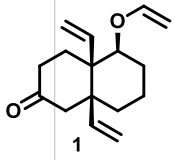


22

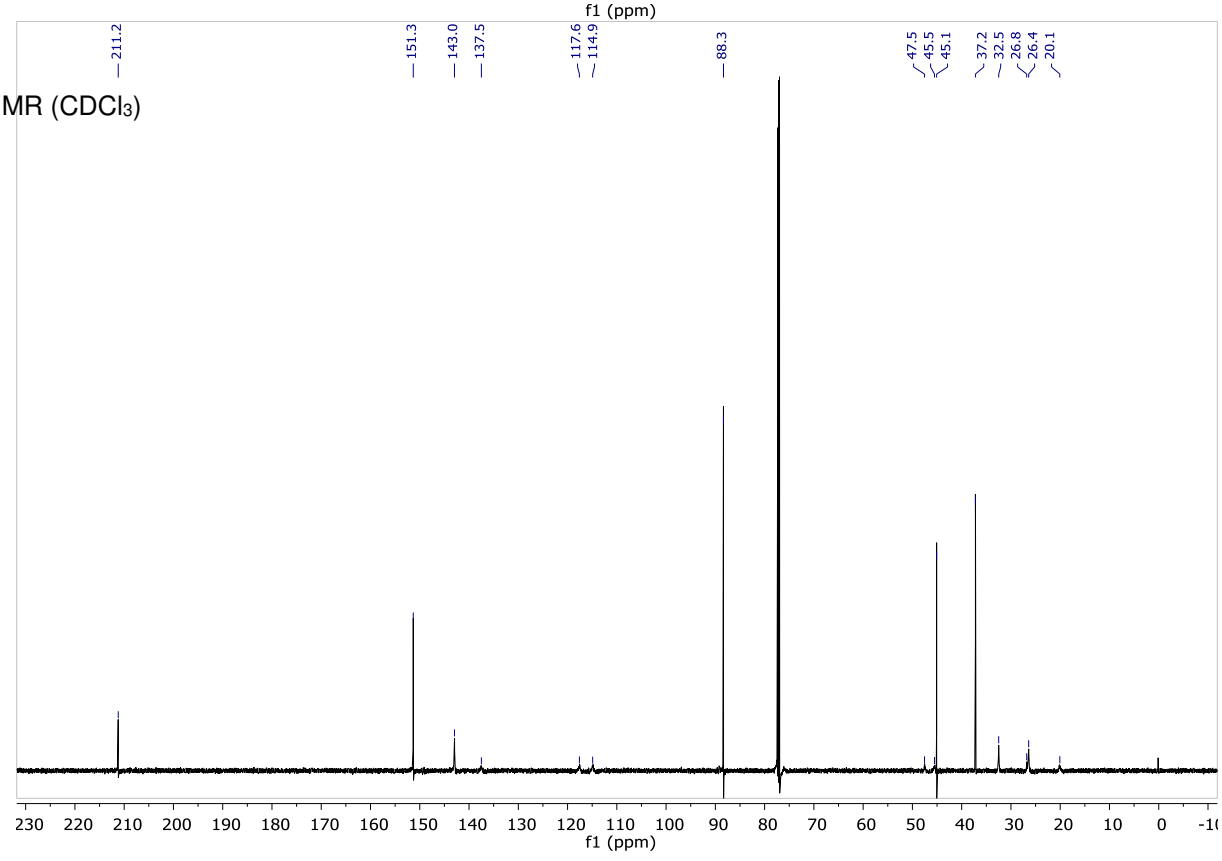
^{13}C-NMR ($CDCl_3$)



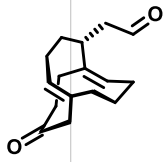
^{1}H-NMR ($CDCl_3$)



^{13}C-NMR ($CDCl_3$)

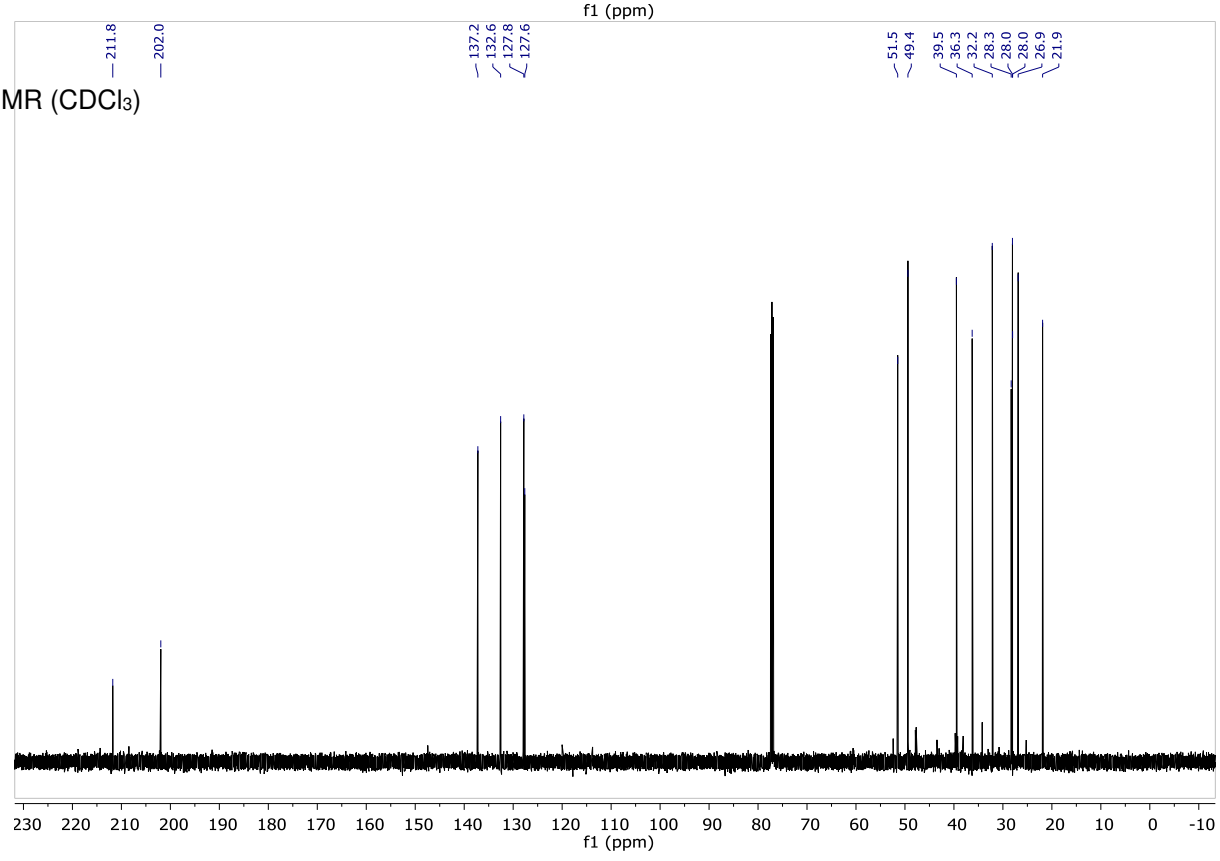


^{1}H-NMR ($CDCl_3$)

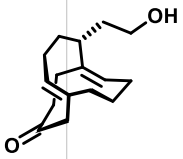


2

^{13}C-NMR ($CDCl_3$)

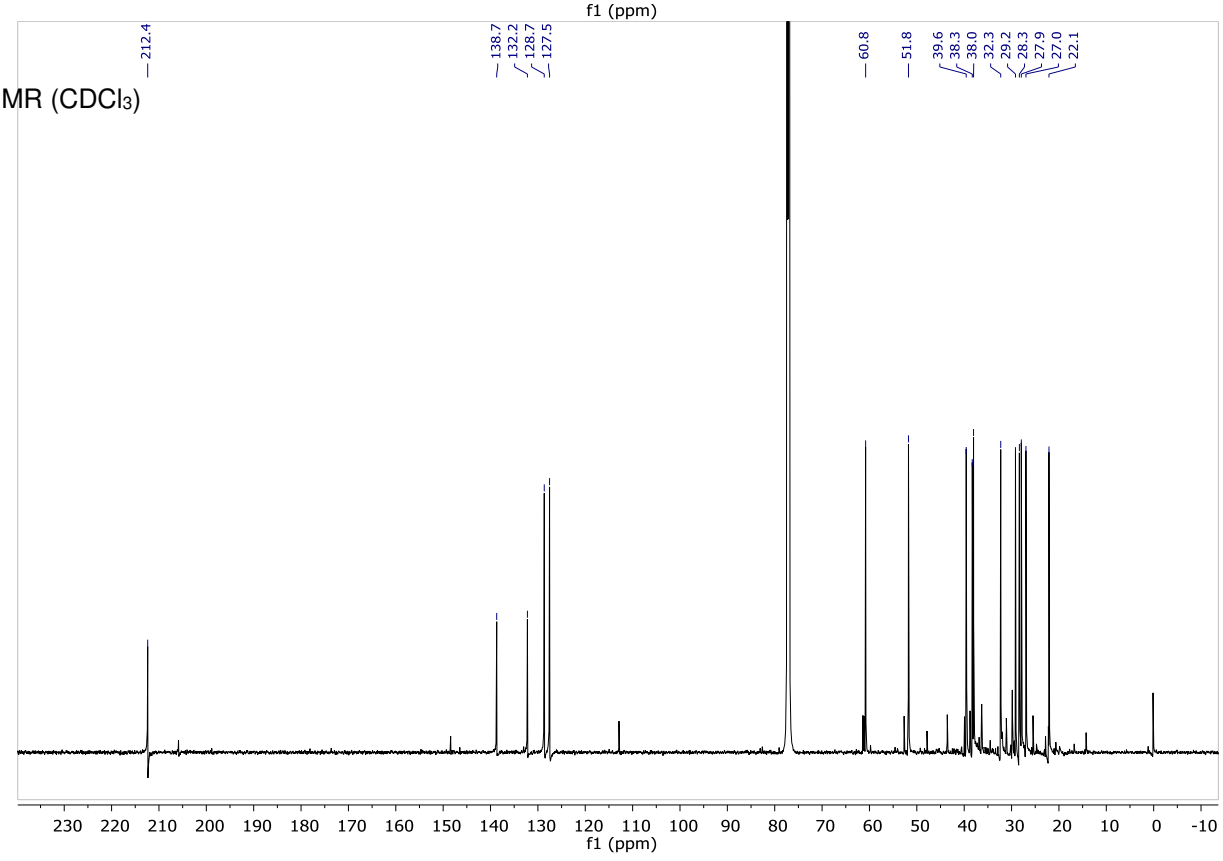


^{1}H-NMR ($CDCl_3$)

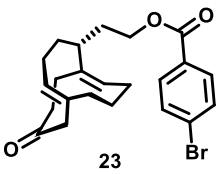


39

^{13}C-NMR ($CDCl_3$)

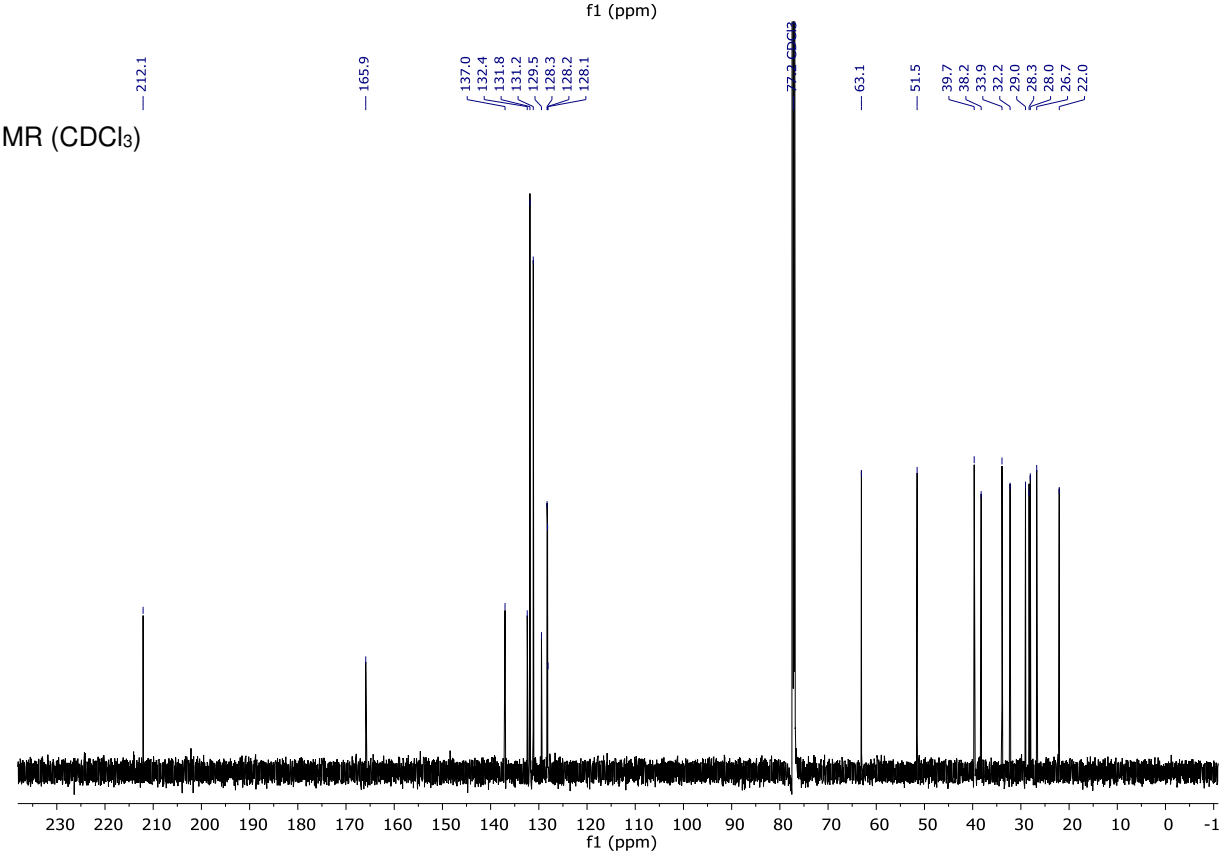


^{1}H-NMR ($CDCl_3$)

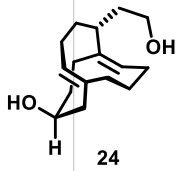


23

^{13}C-NMR ($CDCl_3$)

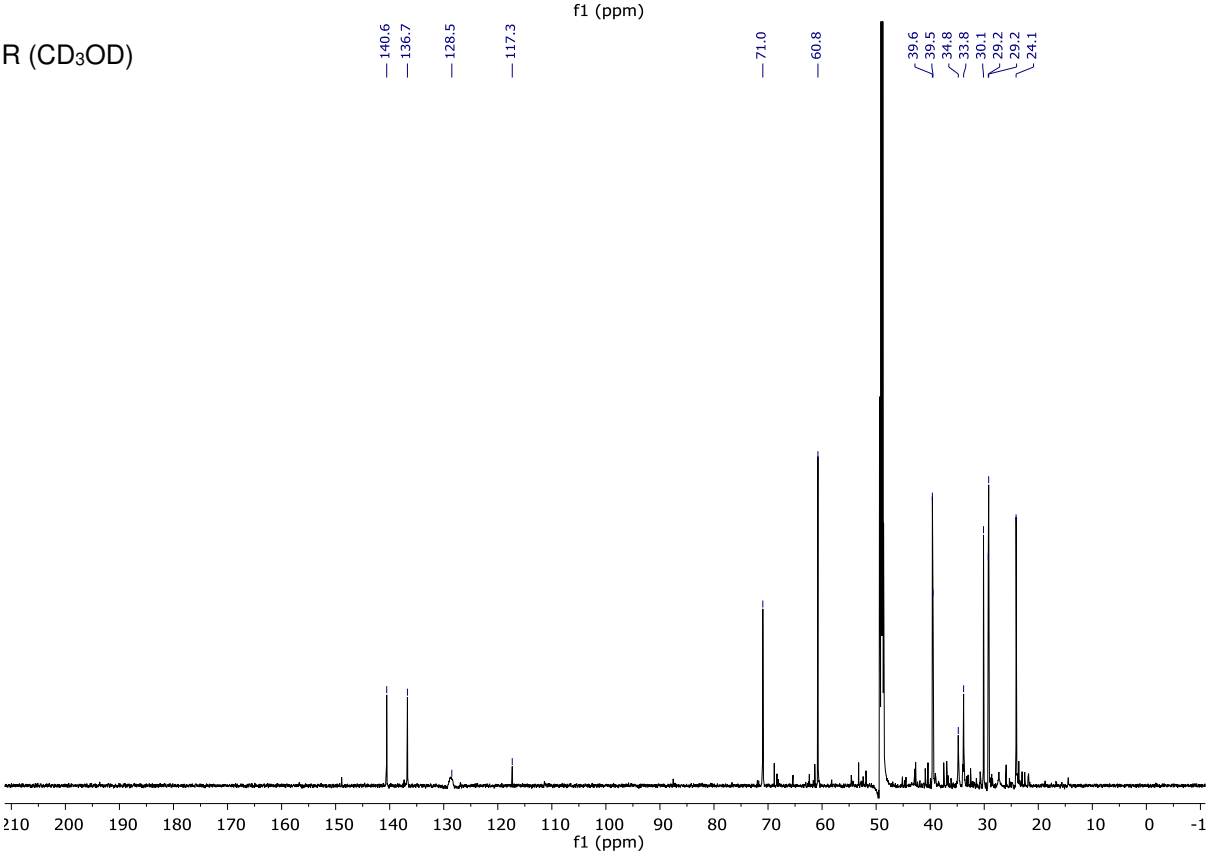


^{1}H-NMR (CD_3OD)

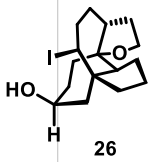


24

^{13}C-NMR (CD_3OD)

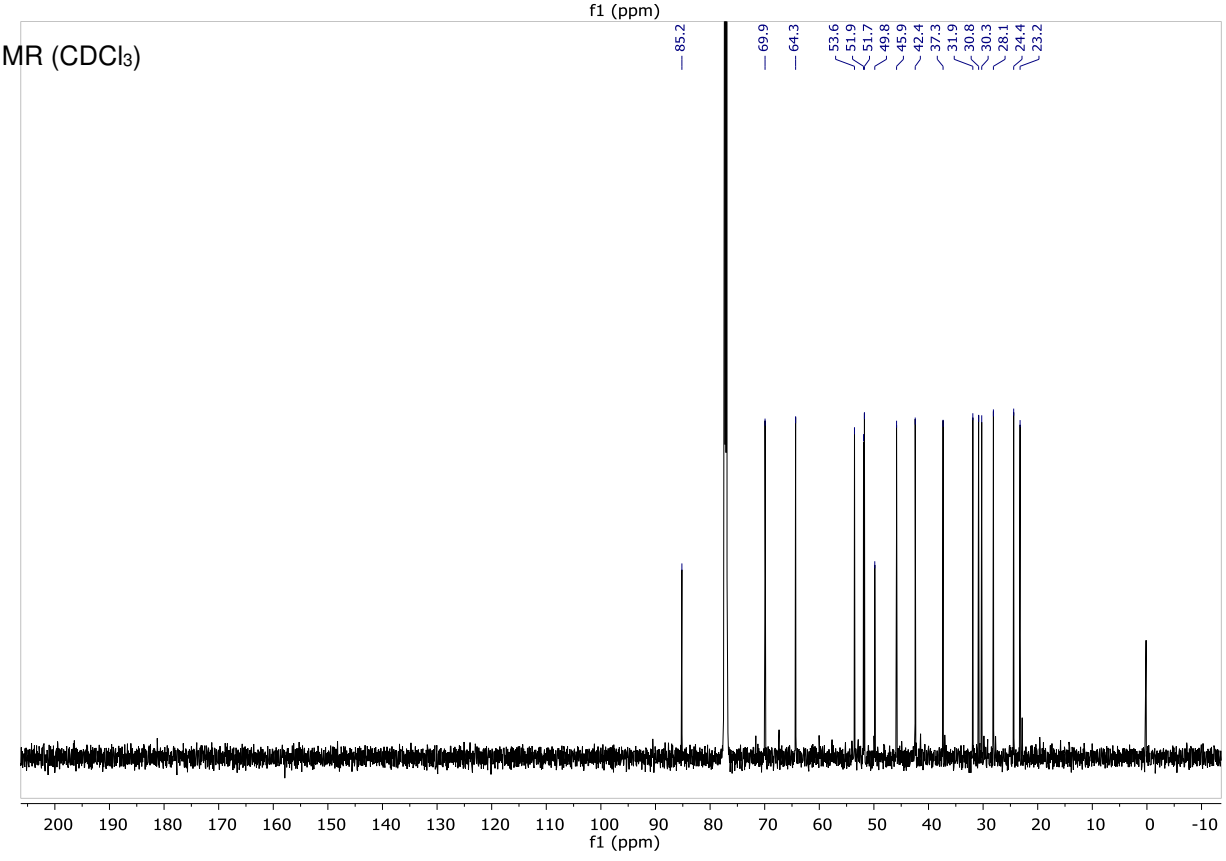


^{1}H-NMR ($CDCl_3$)

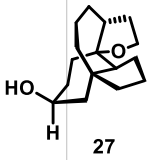


26

^{13}C-NMR ($CDCl_3$)

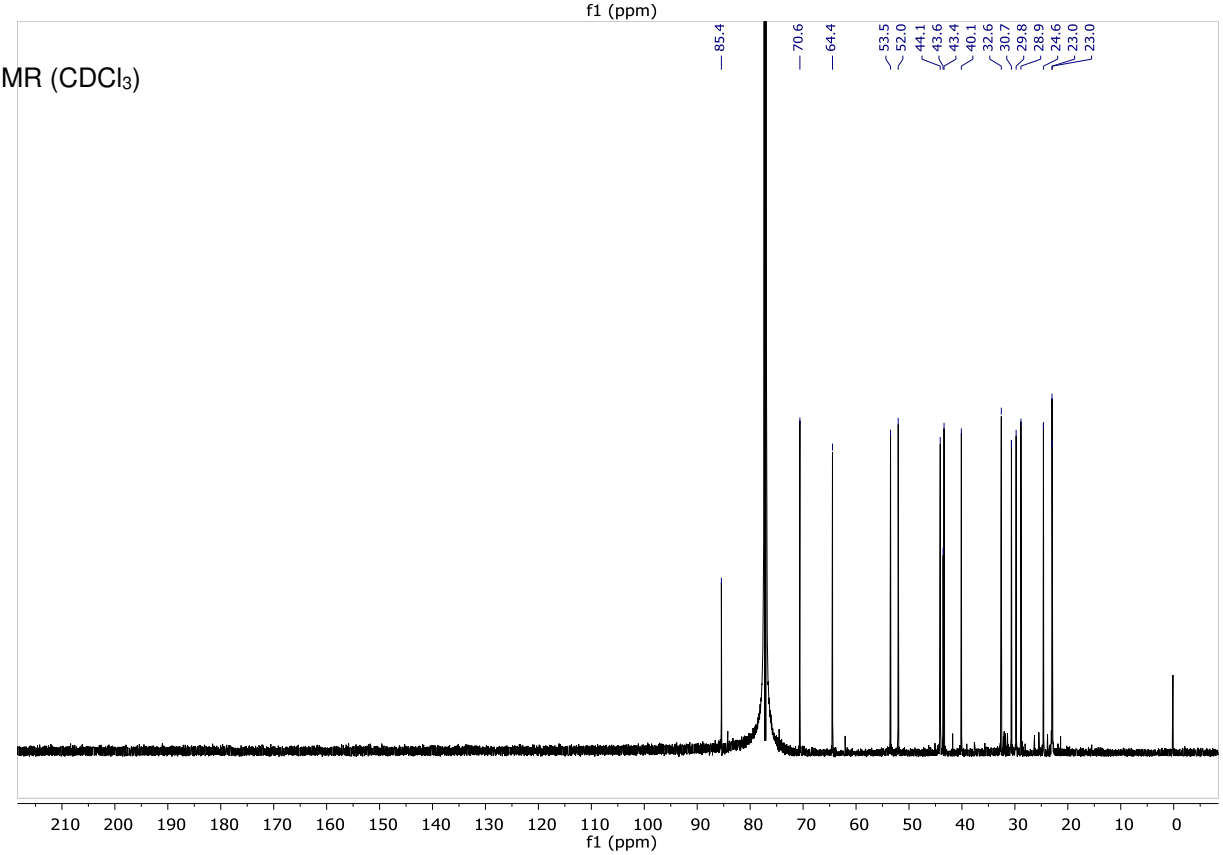


^{1}H-NMR ($CDCl_3$)

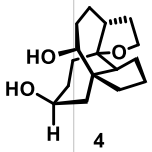


27

^{13}C-NMR ($CDCl_3$)

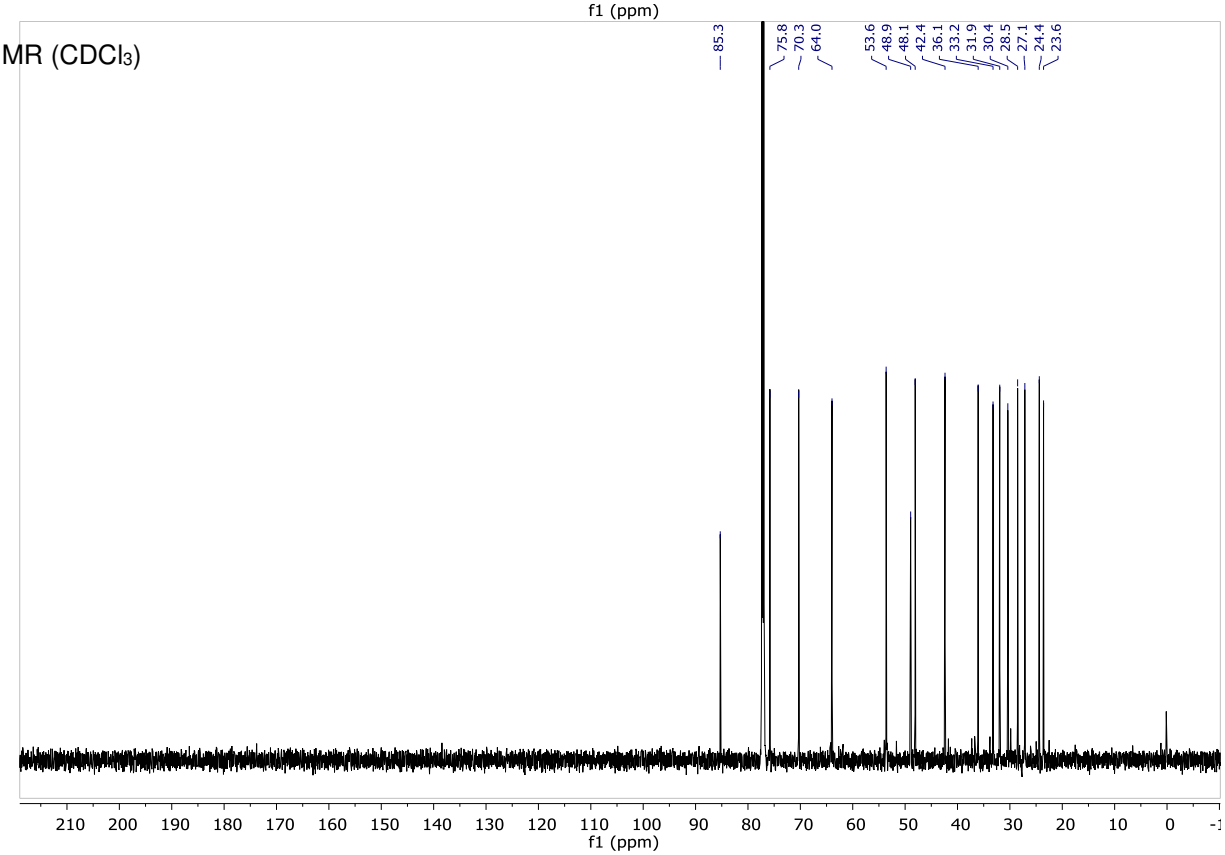


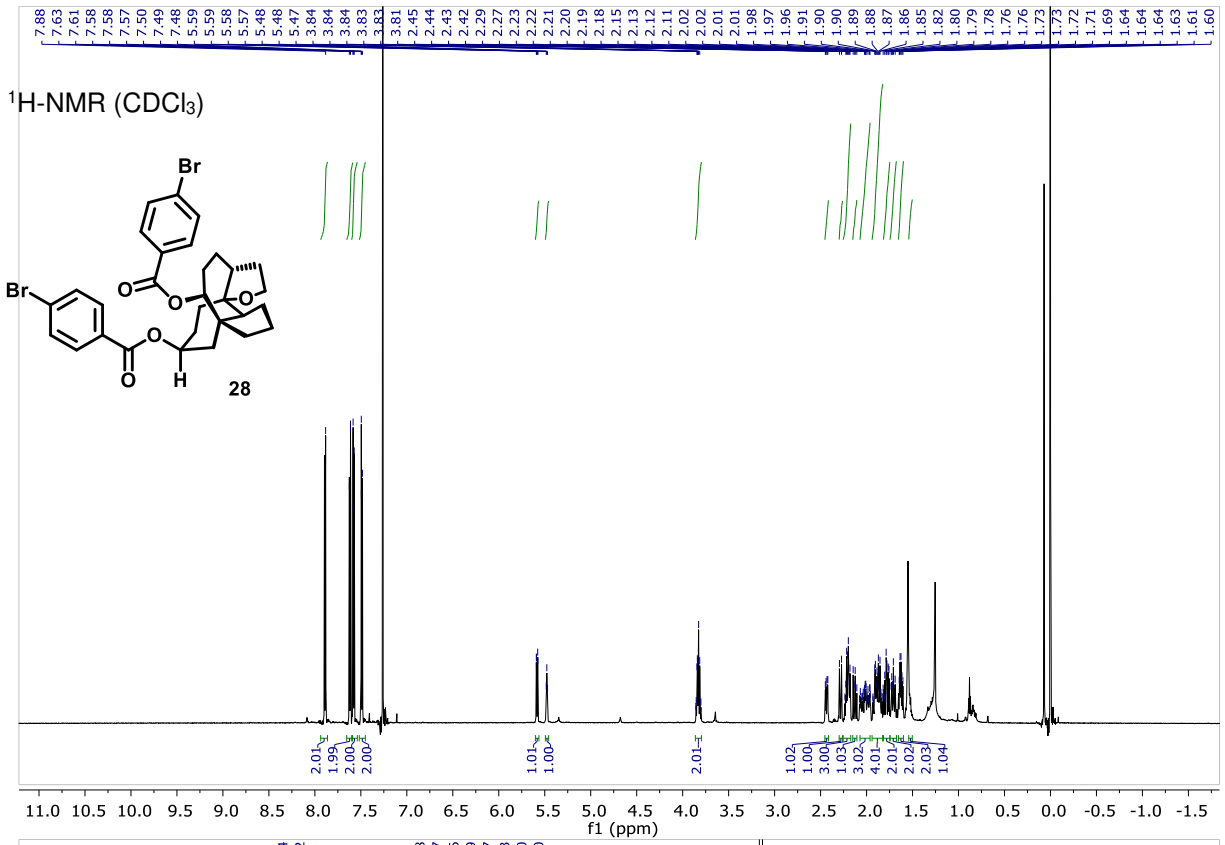
^{1}H-NMR ($CDCl_3$)

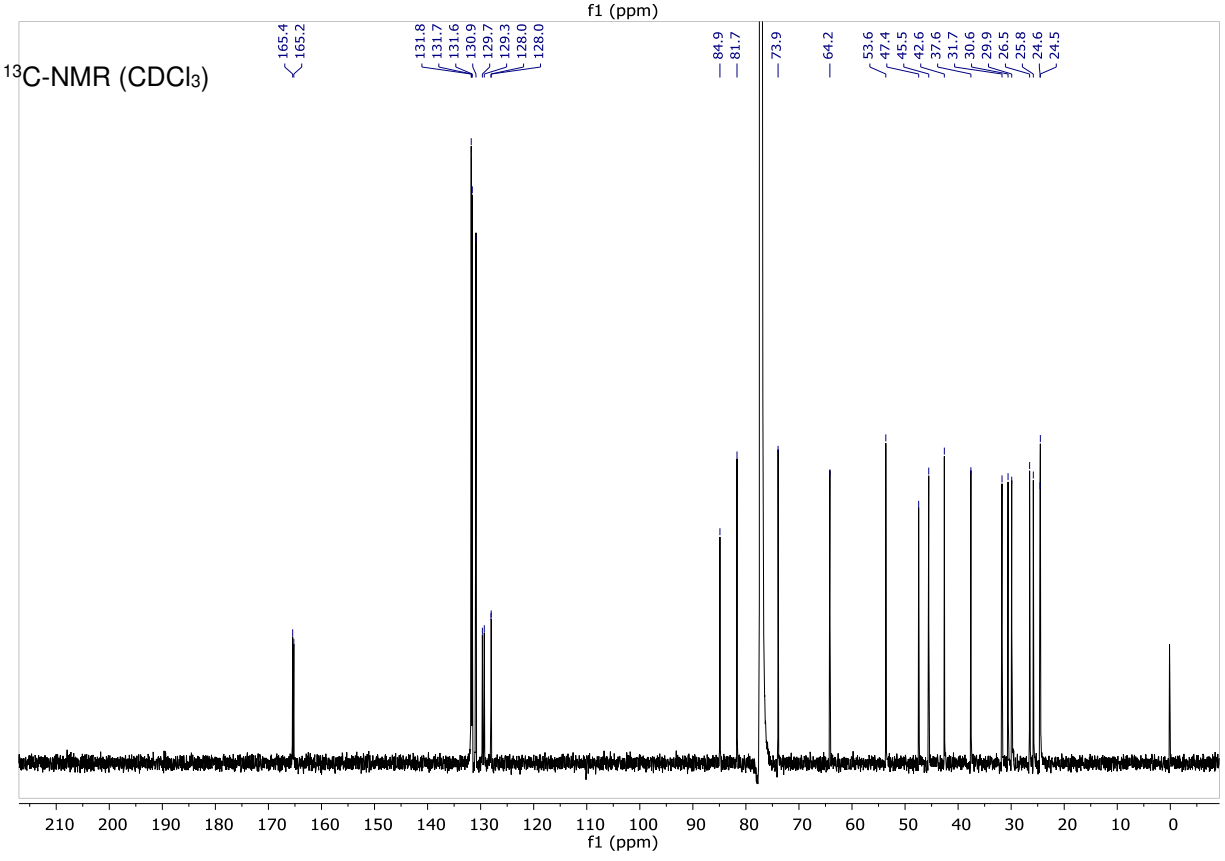


4

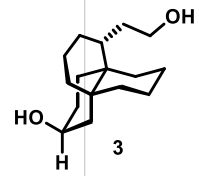
^{13}C-NMR ($CDCl_3$)




^{1}H-NMR ($CDCl_3$)
Br
Br
O
O
O
O
O
H
28
f1 (ppm)

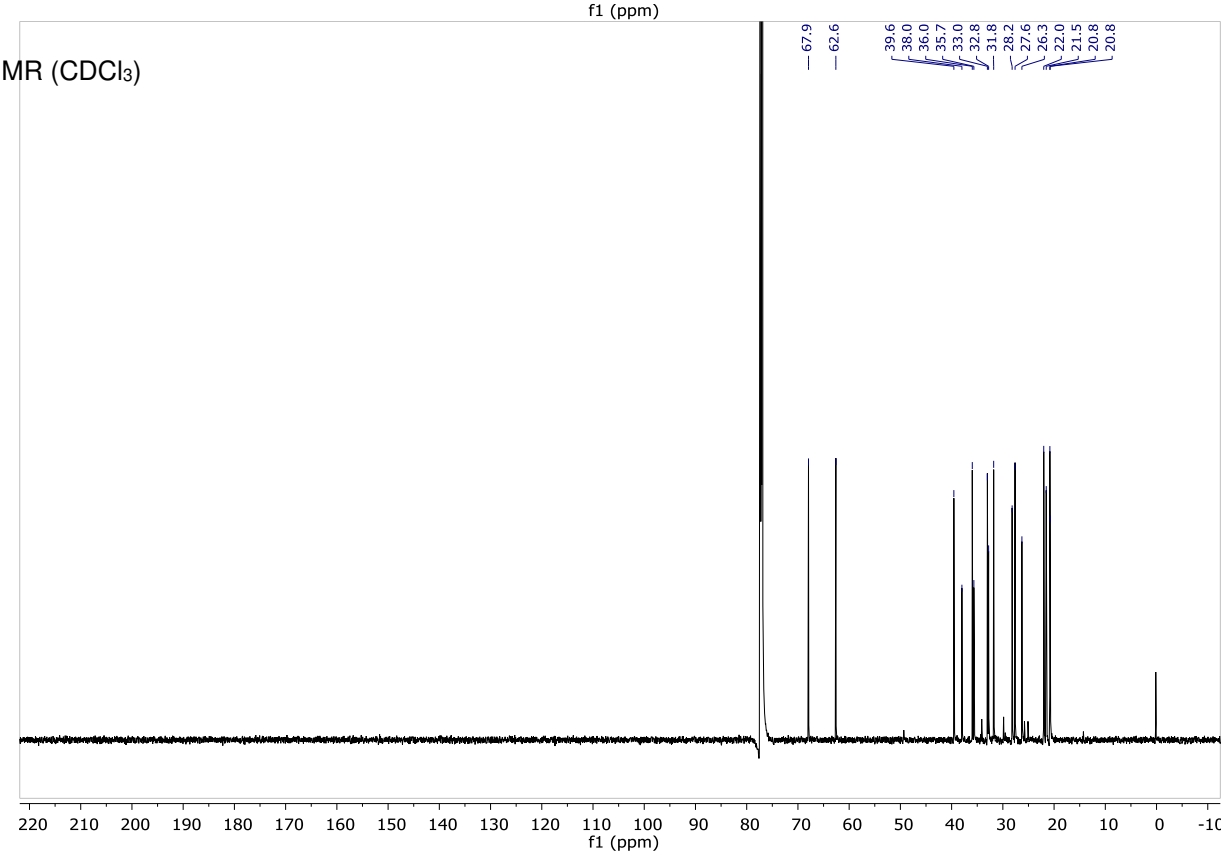

^{13}C-NMR ($CDCl_3$)
f1 (ppm)

^{1}H-NMR ($CDCl_3$)

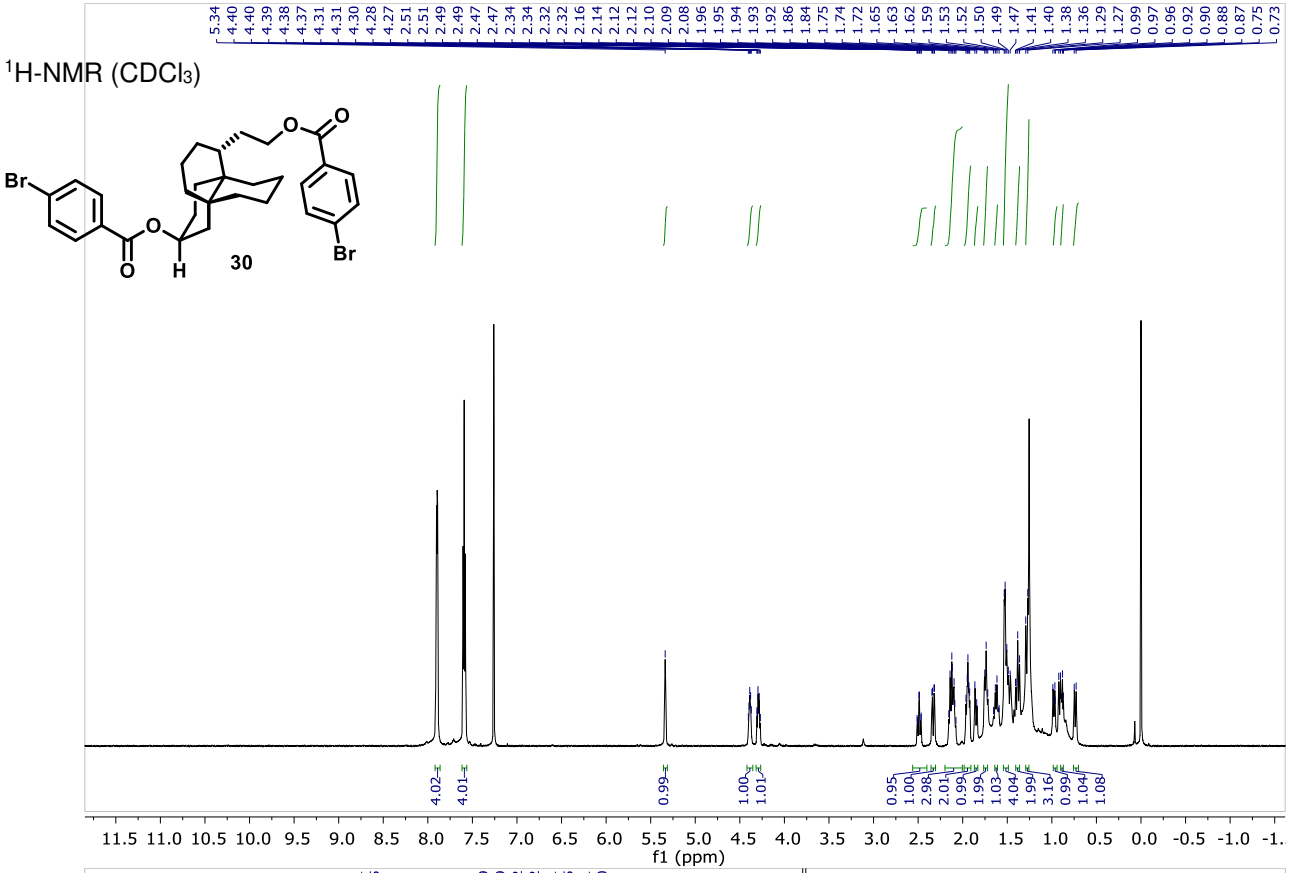


3

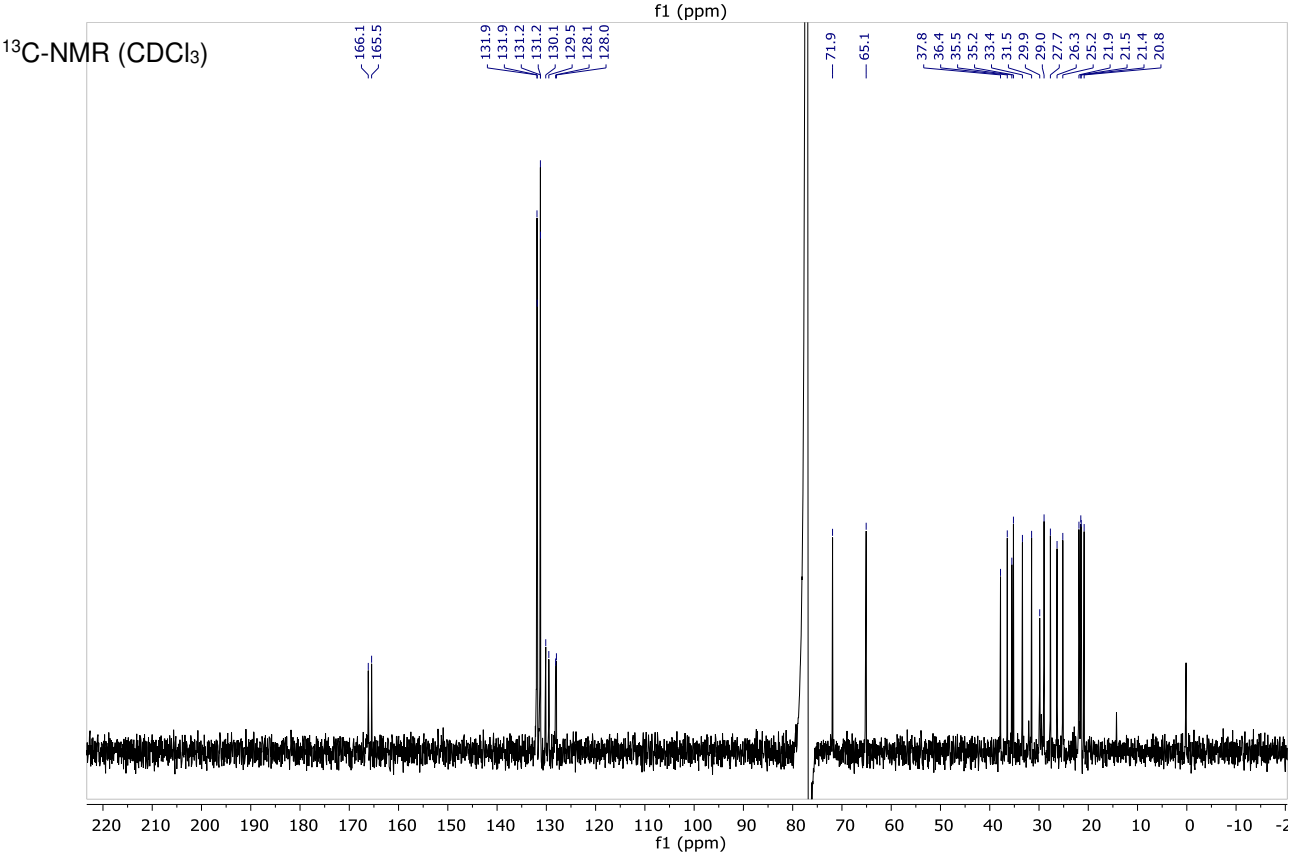
^{13}C-NMR ($CDCl_3$)



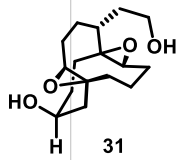
^{1}H-NMR ($CDCl_3$)



^{13}C-NMR ($CDCl_3$)

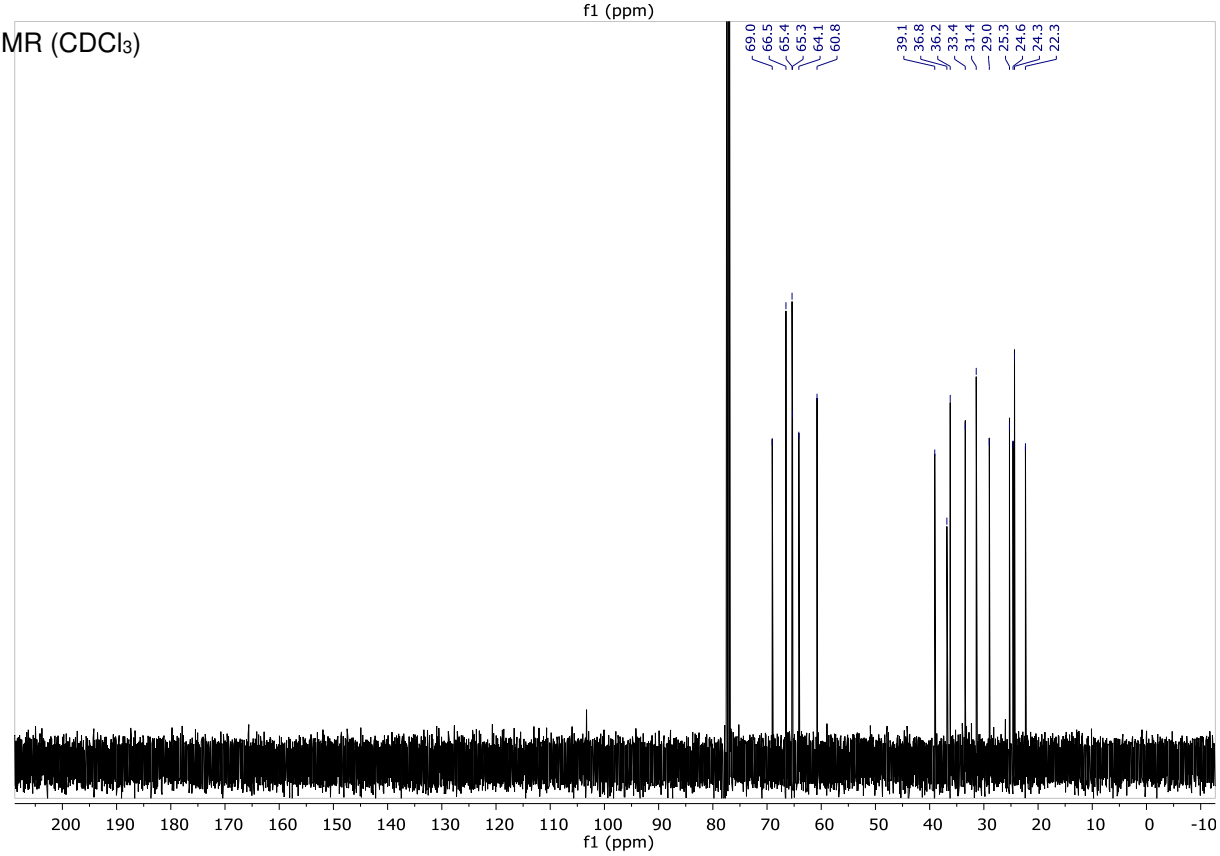


^{1}H-NMR ($CDCl_3$)

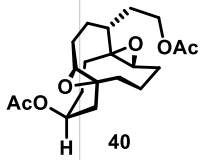


31

^{13}C-NMR ($CDCl_3$)

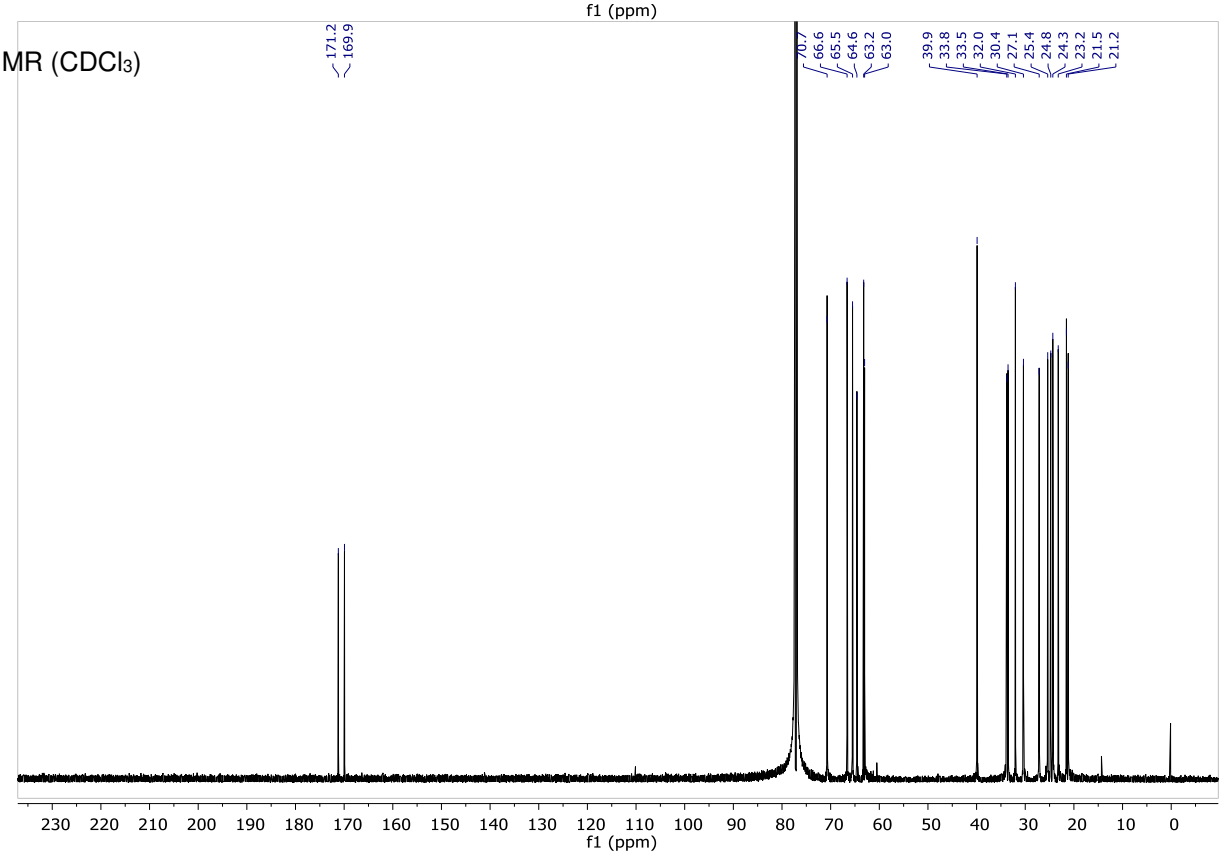


^{1}H-NMR ($CDCl_3$)

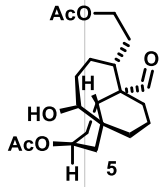


40

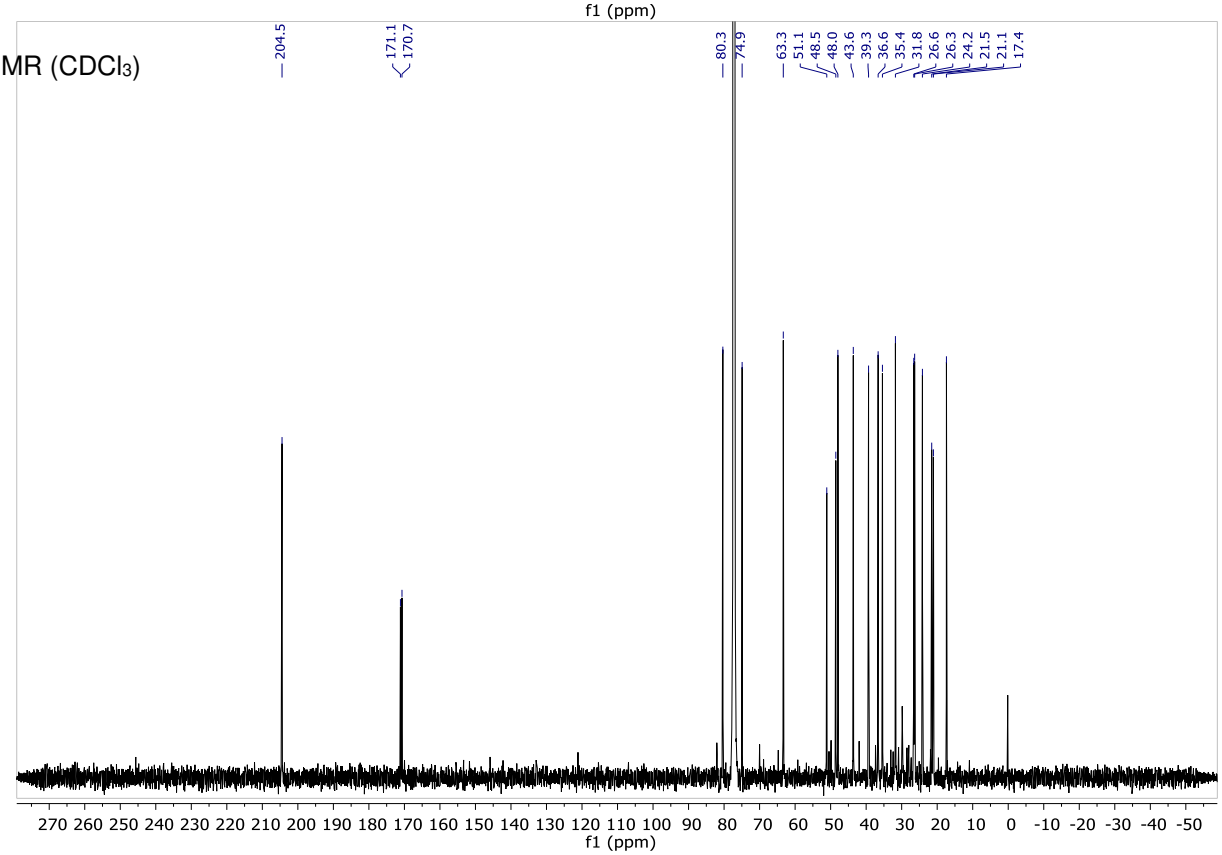
^{13}C-NMR ($CDCl_3$)



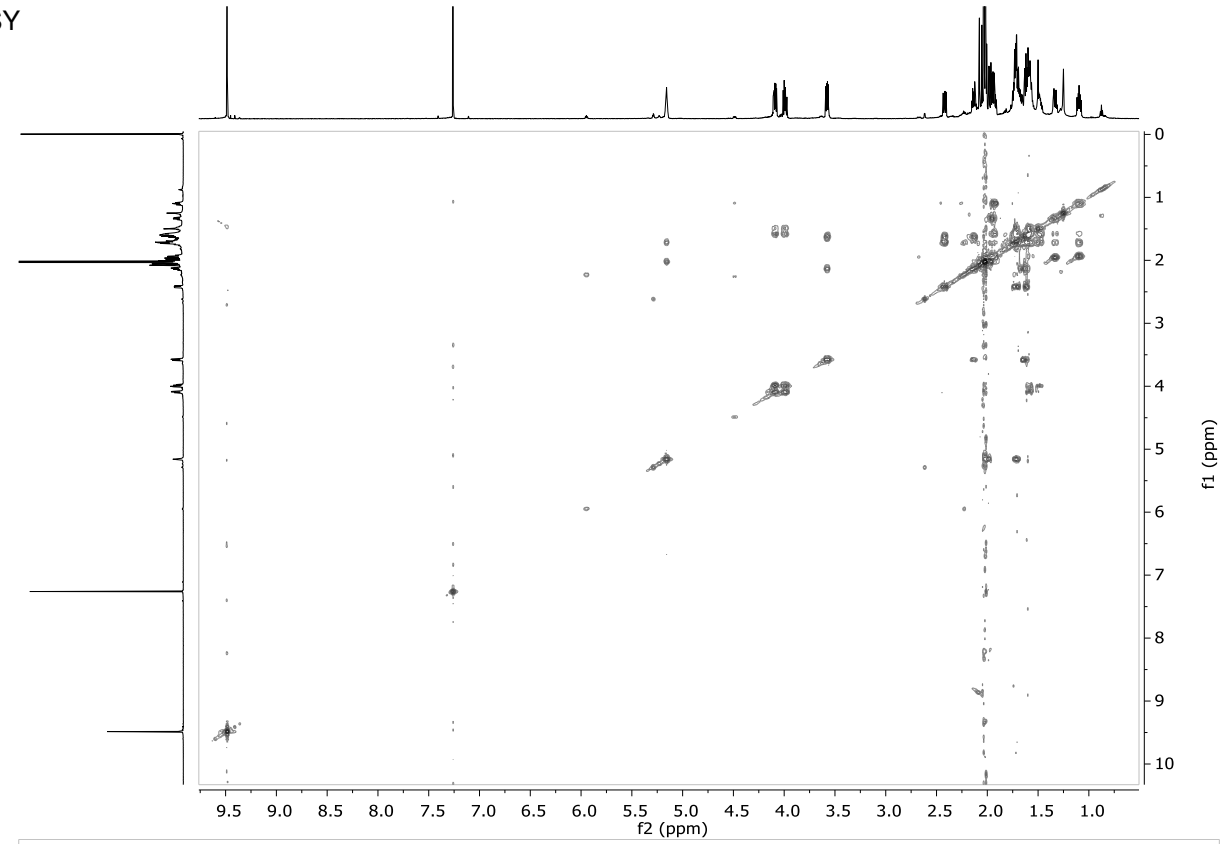
^{1}H-NMR ($CDCl_3$)



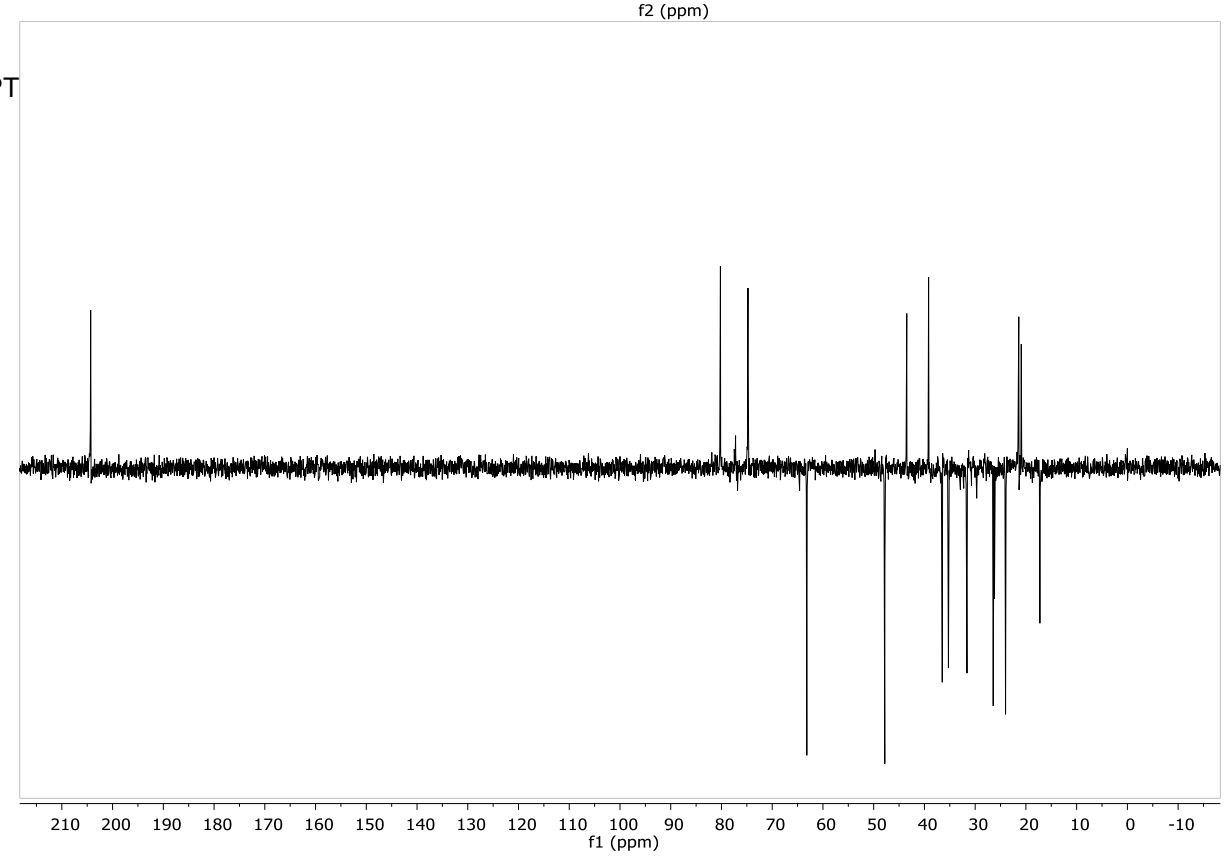
^{13}C-NMR ($CDCl_3$)



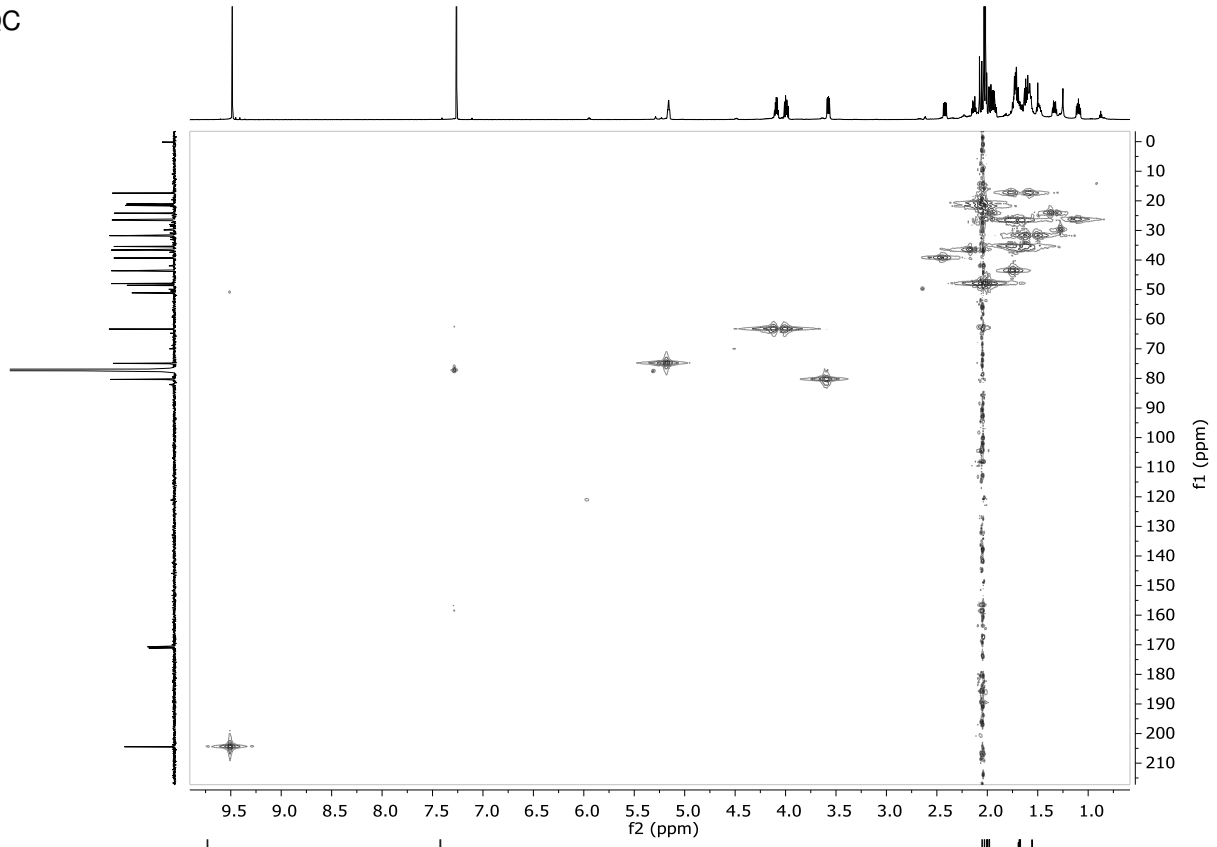
COSY



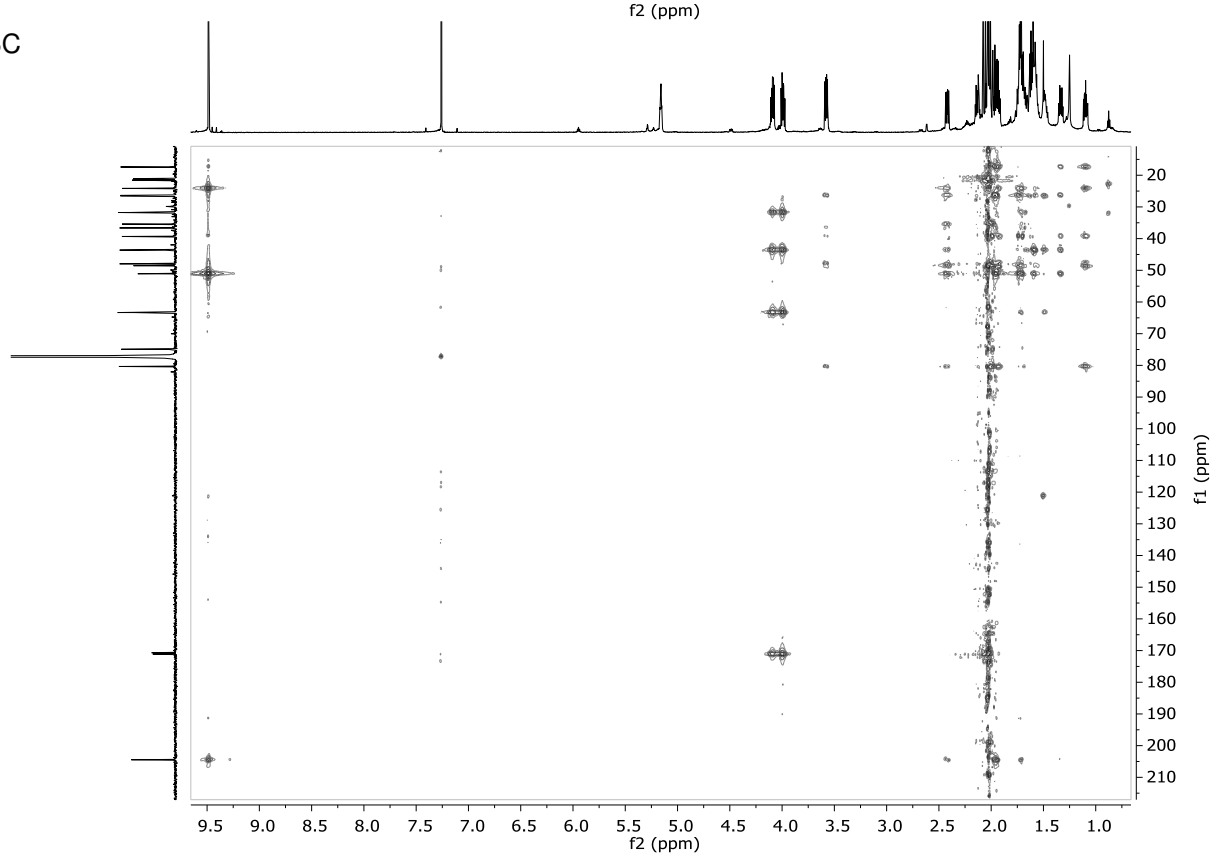
DEPT



HMQC

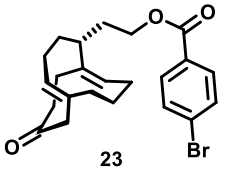


HMBC



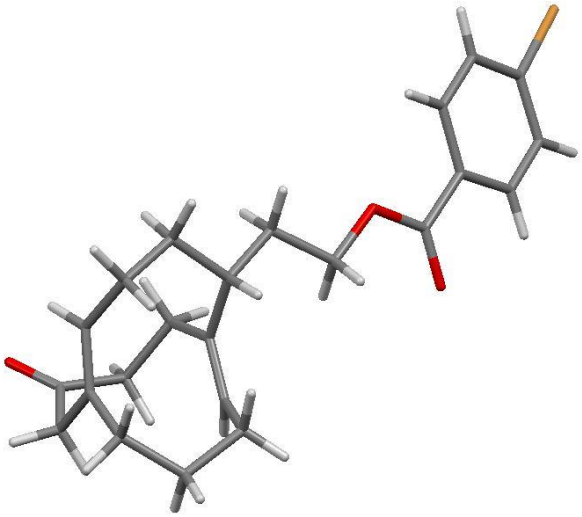
X-Ray

Bridgehead diene 23



23

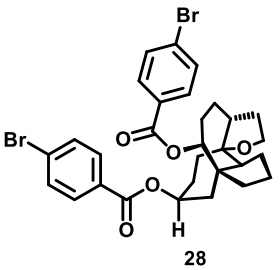
$C_{23}H_{27}BrO_3$ (MW: 431.37)



Unit cell parameters: a = 11.4866 (6), b = 7.4426 (4), c = 23.6356 (13) P21

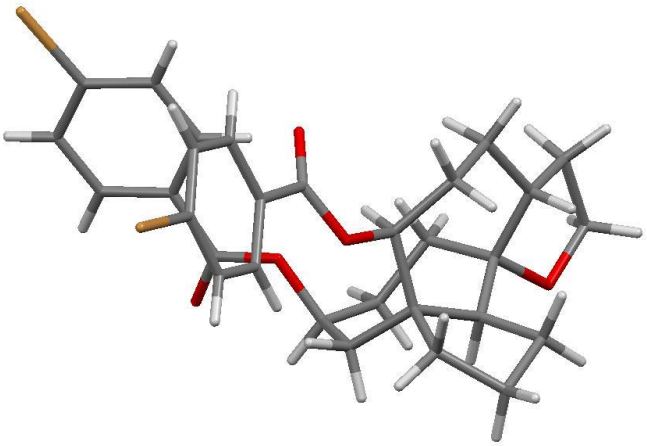
CCDC 1866516 contains the supplementary crystallographic data for this structure. These data are provided free of charge by The Cambridge Crystallographic Data Center https://www.ccdc.cam.ac.uk/.

Tetracyclic ether 28



28

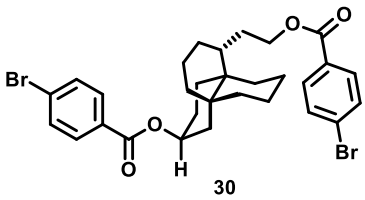
$C_{30}H_{32}Br_2O_5$ (632.39)



Unit cell parameters: a = 9.7539 (4), b = 14.7474 (7), c = 9.8702 (4) P21

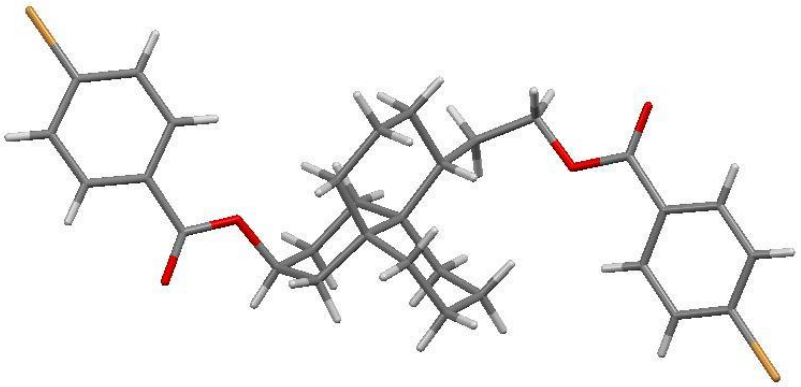
CCDC 1869020 contains the supplementary crystallographic data for this structure. These data are provided free of charge by The Cambridge Crystallographic Data Center https://www.ccdc.cam.ac.uk/.

[4.4.4]propellane 30



30

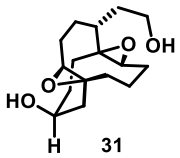
$C_{30}H_{34}Br_2O_4$ (MW: 618.41)



Unit cell parameters: a = 12.949 (11), b = 7.449 (7), c = 13.734 (10) P21

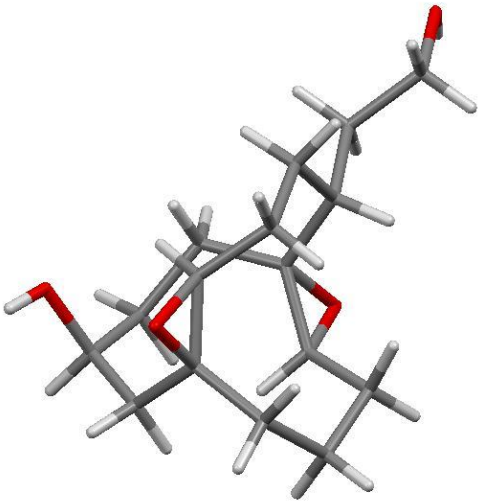
CCDC 1866518 contains the supplementary crystallographic data for this structure. These data are provided free of charge by The Cambridge Crystallographic Data Center https://www.ccdc.cam.ac.uk/.

Bisepoxide 31



31

$C_{16}H_{26}O_4$ (MW: 282.38)



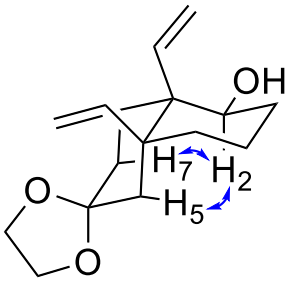
Unit cell parameters: a = 7.6719 (8), b = 7.6719 (8), c = 48.508 (8) P43

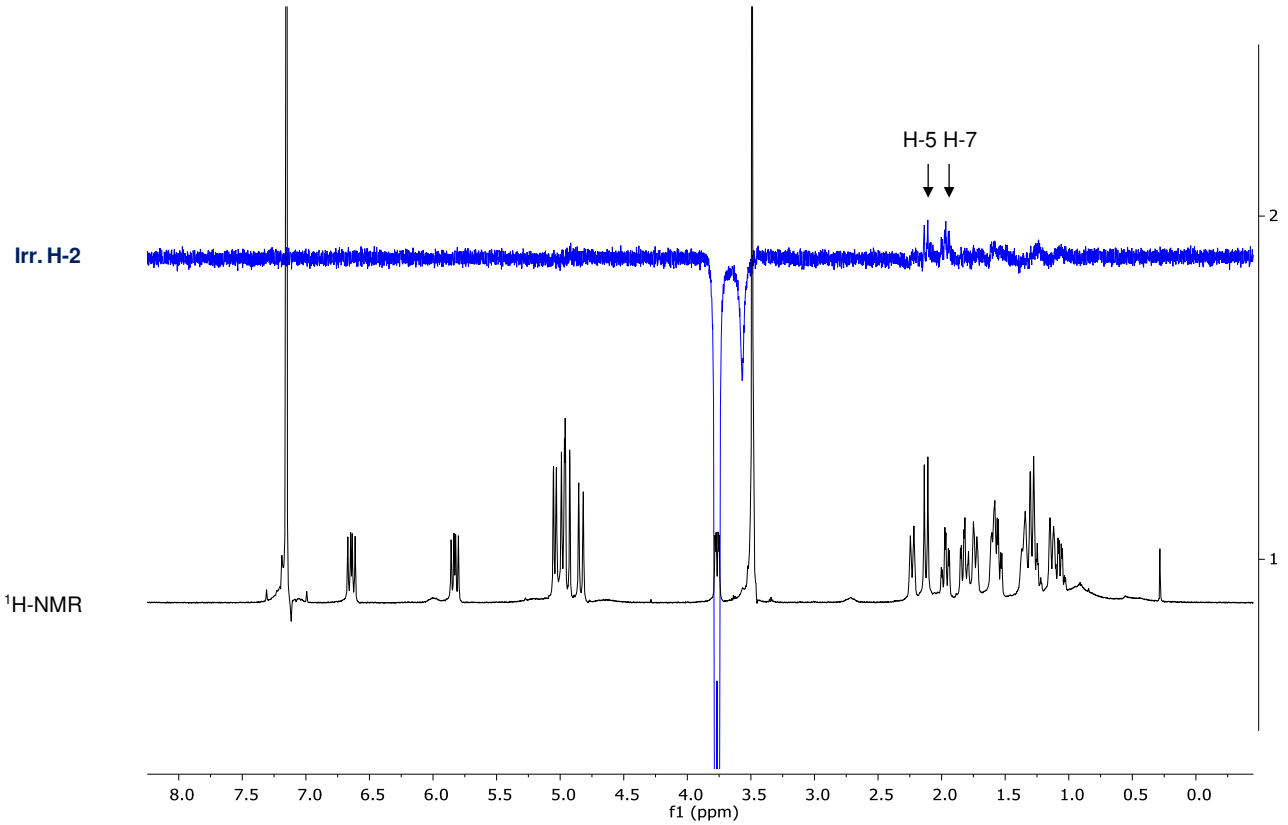
CCDC 1866517 contains the supplementary crystallographic data for this structure. These data are provided free of charge by The Cambridge Crystallographic Data Center https://www.ccdc.cam.ac.uk/.

GOESY experiments

Bisvinyl decaline 14

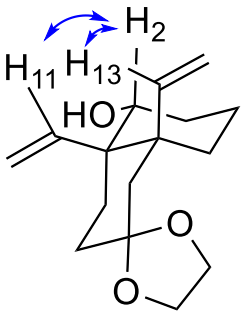
GOESY (C_6D_6)

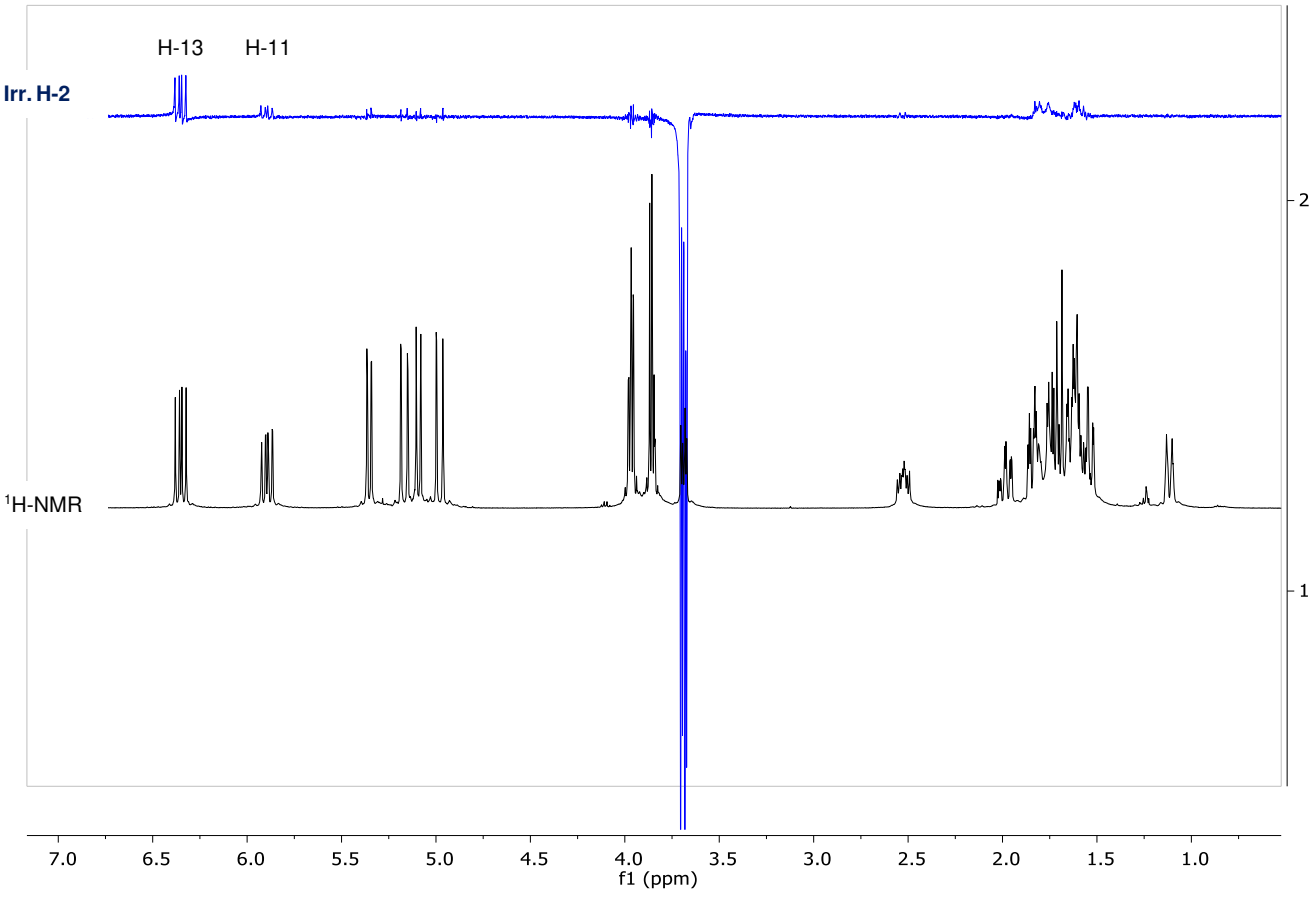




Bisvinyl decaline 35

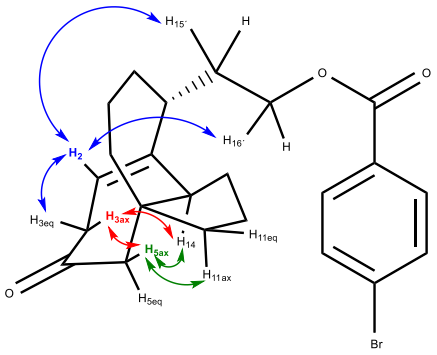
GOESY ($CDCl_3$)

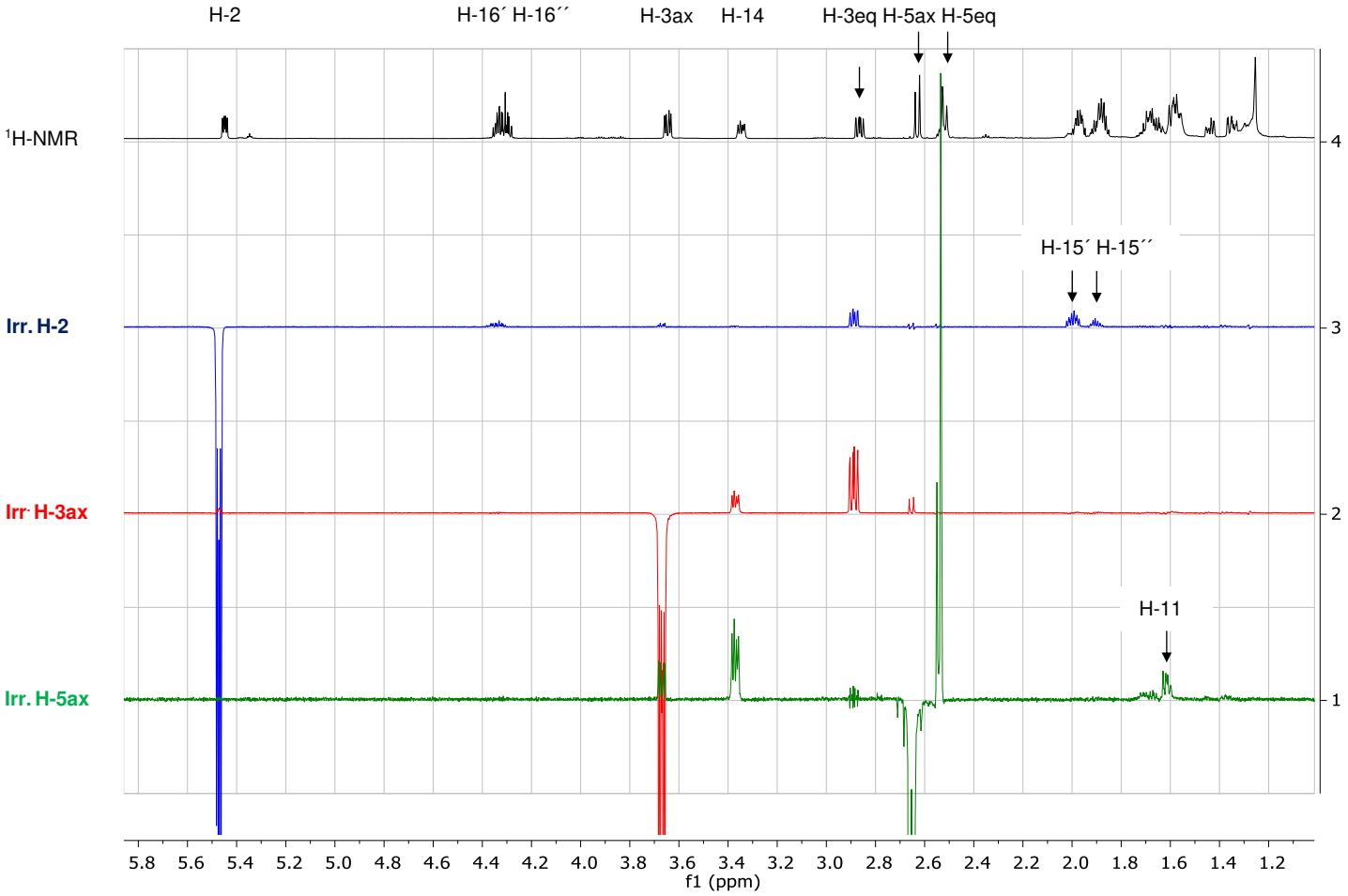




Tricyclic ketone 38

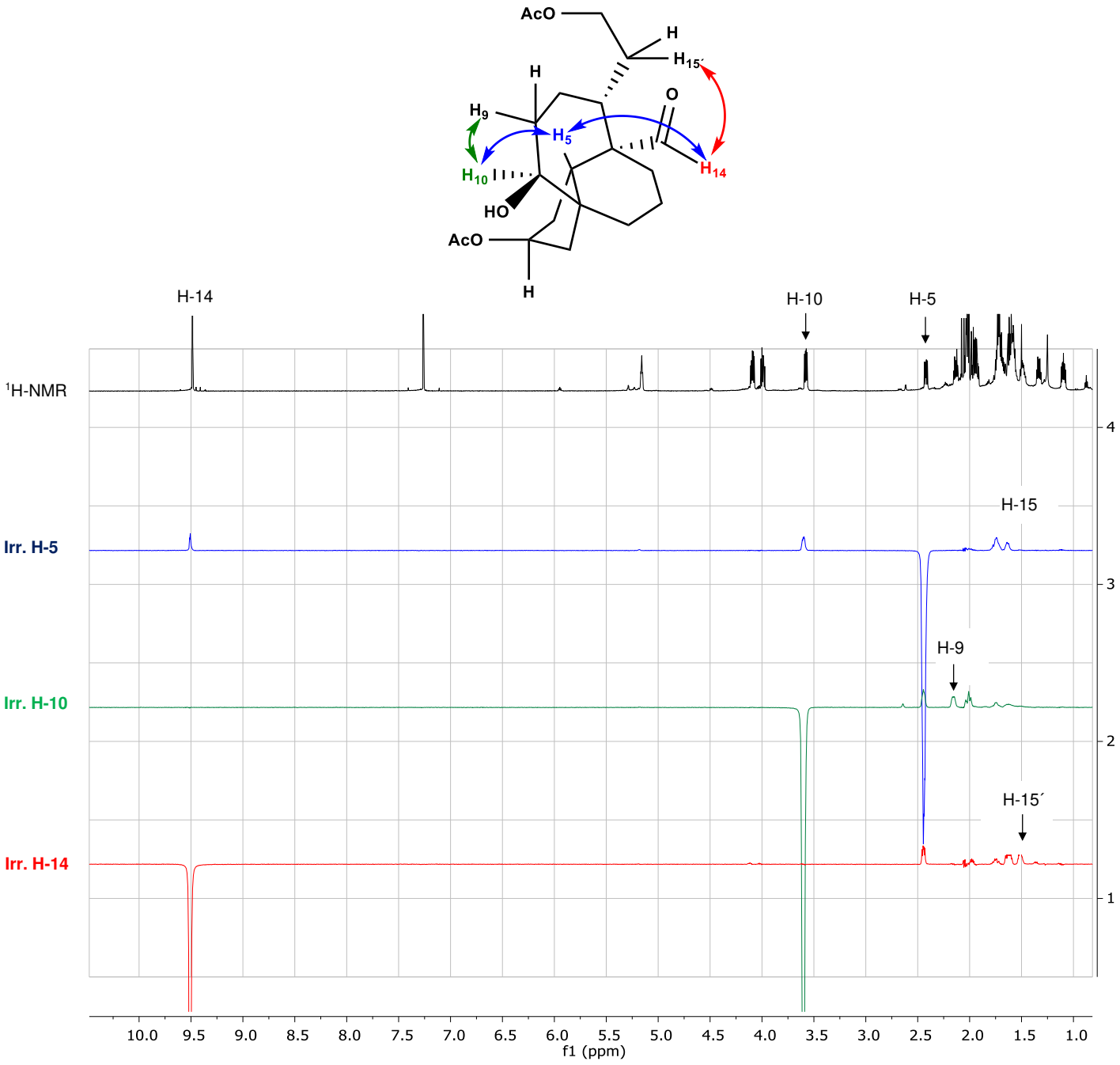
GOESY ($CDCl_3$)





Tricyclic aldehyde 5

GOESY ($CDCl_3$)

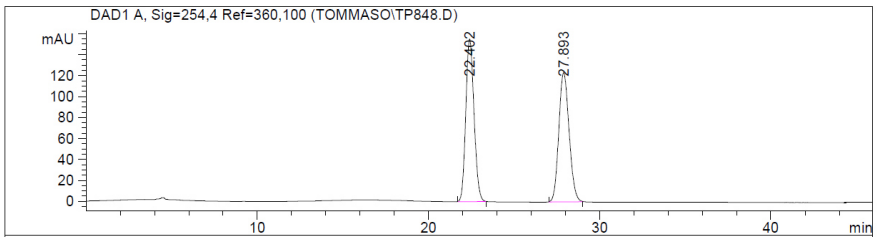


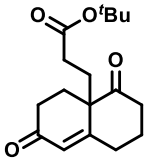
HPLC Chromatograms

Conditions

Chiral column: Chiralpak IC; eluent: *n*hexane/isopropanol 65:35 (20 °C); flow rate: 0.8 mL/min; λ = 254 nm

Racemic mixture

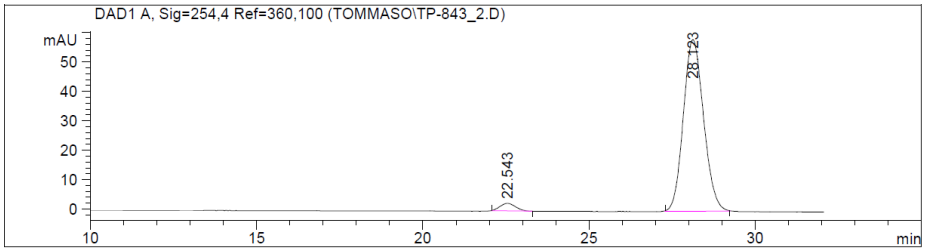


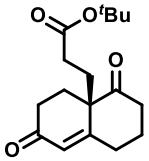


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.402	BB	0.5197	5189.05957	155.34134	50.1248
2	27.893	BB	0.6497	5163.22705	123.50129	49.8752
Totals :				1.03523e4	278.84263	

Enantioenriched





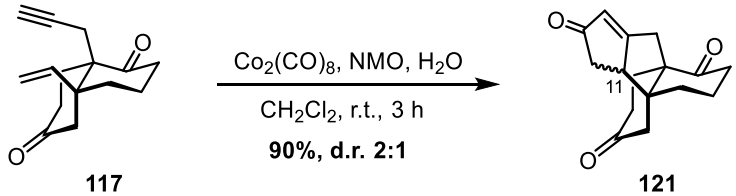
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.543	BB	0.4639	82.07320	2.53350	3.2215
2	28.123	BB	0.6596	2465.59888	58.27390	96.7785
Totals :				2547.67208	60.80740	

Appendix 2 — Unpublished Results

General information

Commercial reagents and solvents were used as received unless otherwise stated. Anhydrous dichloromethane was purified with a MB-SPS-800 (Braun) solvent purification system. Anhydrous DMF was purchased from Acros Organics in sealed bottles under an argon atmosphere in presence of molecular sieves (4 Å). All reactions have been carried out under magnetic stirring and were monitored by TLC analysis on 0.25 mm silica gel plates. Column chromatography has been carried out on silica gel (32–63 µm or 230–400 mesh). Yields refer to spectroscopically and analytically pure compounds. ^{1}H-NMR and ^{13}C-NMR spectra have been recorded on 400, 500, and 700 MHz instruments. Chemical shifts are reported relative to $CDCl_3$ (^{1}H: δ = 7.26 ppm; ^{13}C: δ = 77.0 ppm). For detailed peak assignments 2D spectra have been measured (COSY, DEPT, HMQC, HMBC, and NOESY as necessary). IR spectra have been recorded with an FT-IR spectrometer. Mass spectra have been recorded on a quadrupole mass spectrometer by direct inlet. HRMS analyses have been performed with an FTICR mass spectrometer (ESI-TOF, 4 µL/min, 1.0 bar, 4 kV). Optical rotation measurements have been performed using a 1 dm optical-path length cell with the frequency of the Na_D line measured at the indicated temperature and concentration reported in g/100 mL.

Synthesis of [4.4.3]propellane **121**

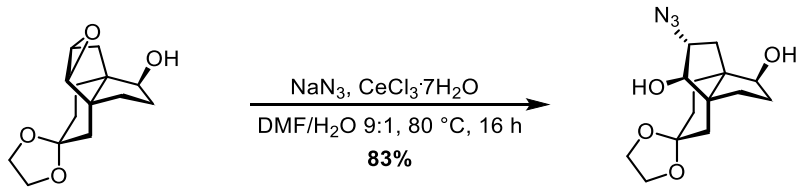


117 **121**

To a solution of alkyne **117** (8.00 mg, 0.0347 mmol, 1.00 equiv.) in anhydr. dichloromethane (1.7 mL) was added $Co_2(CO)_8$ (14.2 mg, 0.0416 mmol, 1.20 equiv.) and the mixture was stirred at room temperature for 1 h till complete complexation of the starting material as indicated by TLC. Afterwards, water (5.00 µL, 0.278 mmol, 8.00 equiv.) was added and the mixture cooled to 0 °C. NMO (32.5 mg, 0.278 mmol, 8.00 equiv.) was added, the reaction mixture was stirred at room temperature for 3 h and then concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, pentane/ethyl acetate = 3:2) yielded a diastereomeric mixture of enones **121** (8.10 mg, 90%, d.r.= 2:1 at C-11) as a white solid.

m.p. = 110–119 °C; R_f = 0.24 (pentane/ethyl acetate 3:2); **^{1}H-NMR** ($CDCl_3$, 700 MHz): *major* δ = 6.06–6.06 (m, 1H), 3.28–3.25 (m, 1H), 2.98 (d, J = 19.5 Hz, 1H), 2.88 (ddd, J = 14.2, 6.1, 2.7 Hz, 1H), 2.62–2.56 (m, 3H), 2.53–2.43 (m, 3H), 2.35–2.26 (m, 1H), 2.21–2.16 (m, 2H), 2.10–1.88 (m, 2H), 1.77 (td, J = 14.3, 4.3 Hz, 1H), 1.43 (td, J = 13.8, 3.9 Hz, 1H), 1.37–1.33 ppm (m, 1H); *minor* δ = 6.09–6.08 (m, 1H), 4.00 (d, J = 19.9 Hz, 1H), 3.11–3.08 (m, 1H), 2.71–2.64 (m, 2H), 2.53–2.43 (m, 2H), 2.35–2.26 (m, 2H), 2.10–1.88 (m, 7H), 1.72–1.68 (m, 1H), 1.26–1.24 ppm (m, 1H); **^{13}C-NMR**; ($CDCl_3$, 700 MHz): *major* δ = 210.4, 210.2, 208.7, 183.4, 128.5, 58.4, 54.3, 53.6, 45.5, 39.1, 38.8, 37.7, 37.0, 30.8, 27.8, 21.5 ppm; *minor* δ = 211.1, 210.4, 208.8, 185.4, 127.8, 60.7, 53.0, 51.6, 44.7, 36.9, 36.7, 35.8, 30.3, 30.0, 29.1, 21.7 ppm; **IR** ($CDCl_3$): $\tilde{\nu}$ = 2945, 2881, 1670, 1627, 1433, 1306, 1221, 773 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{16}H_{18}O_3Na$: 281.1148 $[M+Na]^+$; found: 281.1136.

Synthesis of [4.3.3]propellane **124**

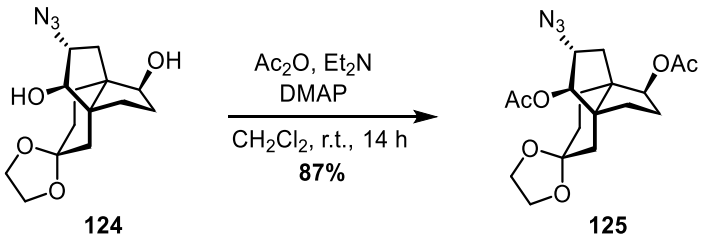


122 **124**

To a solution of epoxide **122** (57.0 mg, 0.226 mmol, 1.00 equiv.) in DMF/H_2O (9:1; 2.3 mL) $CeCl_3$•$7H_2O$ (84.2 mg, 0.226 mmol, 1.00 equiv.) and NaN_3 (58.7 mg, 0.903 mmol, 4.00 equiv.) were added and the reaction mixture was stirred at 80 °C for 16 h. After completion of the reaction as indicated by TLC, water (2 mL) was added and the mixture was extracted with ethyl acetate (3x5 mL). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, pentane/ethyl acetate = 2:1) yielded diol **124** (55.5 mg, 83%) as a colorless oil.

R_f = 0.17 (pentane/ethyl acetate 2:1); **$[\alpha]_D^{25}$** = –32.9 (c= 1.06, chloroform); **^{1}H-NMR** ($CDCl_3$, 500 MHz): δ = 4.14 (d, J = 7.7 Hz, 1H), 4.04 (t, J = 6.4 Hz, 1H), 3.95–3.84 (m, 4H), 3.71 (q, J = 8.1 Hz, 1H), 2.72 (br s, 1H), 2.37 (dd, J = 14.4, 9.3 Hz, 1H), 2.06–1.97 (m, 3H), 1.89 (d, J = 14.7 Hz, 1H), 1.71–1.52 (m, 5H), 1.47 (d, J = 14.7 Hz, 1H), 1.29–1.20 ppm (m, 2H); **^{13}C-NMR** ($CDCl_3$, 126 MHz): δ = 108.9, 81.3, 77.9, 66.5, 64.5, 63.7, 52.1, 50.7, 39.9, 33.4, 32.1, 30.4, 30.3, 30.0 ppm; **IR** ($CDCl_3$): $\tilde{\nu}$ = 3410, 2926, 2098, 1220, 1112, 1063, 908, 772, 731 cm^{-1}; **HRMS** (ESI): m/z : calculated for $C_{14}H_{21}N_3O_4Na$: 318.1424 $[M+Na]^+$; found: 318.1423.

Synthesis of [4.3.3]propellane **125**

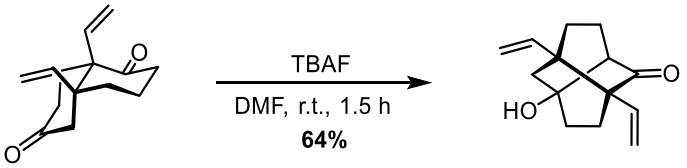


124 **125**

A solution of diol **124** (6.6 mg, 0.0223 mmol, 1.00 equiv.) in dichloromethane (0.2 mL) was treated with Et_3N (12.4 µL, 0.0892 mmol, 4.00 equiv.), 4-dimethylaminopyridine (0.8 mg, 6.69 µmol, 0.30 equiv.) and Ac_2O (8.43 µL, 0.0892 mmol, 4.00 equiv.). The reaction mixture was stirred at room temperature for 14 h, then quenched with the addition of sat. aq. NH_4Cl (0.2 mL) and extracted with dichloromethane (3x4 mL). The combined organic phases were washed with water (4 mL) and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, pentane/ethyl acetate = 10:1) yielded diester **125** (7.4 mg, 87%) as a colorless oil. The structure was confirmed by HH-COSY and HMBC analyses.

R_f = 0.22 (pentane/ethyl acetate 10:1); **$[\alpha]_D^{25}$** = +23.6 (c= 0.52, chloroform); **^{1}H-NMR** ($CDCl_3$, 500 MHz): δ = 5.70 (d, J = 7.5 Hz, 1H), 5.11 (t, J = 7.0 Hz, 1H), 3.99–3.95 (m, 2H), 3.91–3.83 (m, 3H), 2.31 (dd, J = 14.5, 9.4 Hz, 1H), 2.19–2.14 (m, 1H), 2.10 (s, 3H), 2.07 (s, 3H), 2.00 (ddd, J = 14.1, 9.9, 7.0 Hz, 1H), 1.85 (d, J = 14.6 Hz, 1H), 1.81–1.67 (m, 4H), 1.63–1.58 (m, 1H), 1.43 (dd, J = 14.5, 7.5 Hz, 1H), 1.36 (d, J = 14.6 Hz, 1H), 1.33–1.28 ppm (m, 1H); **^{13}C-NMR** ($CDCl_3$, 176 MHz): δ = 170.9, 170.3, 108.0, 82.1, 78.7, 64.5, 64.5, 64.0, 52.1, 50.3, 38.6, 35.1, 32.0, 30.7, 29.7, 28.7, 21.3, 21.2 ppm; **IR** ($CDCl_3$): $\tilde{\nu}$ = 2952, 2925, 2882, 2097, 1733, 1364, 1230, 1039, 770 cm^{-1}; **HRMS** (ESI): m/z : calculated for $C_{18}H_{25}N_3O_6Na$: 402.1635 $[M+Na]^+$; found: 402.1637.

Synthesis of twistane **131**



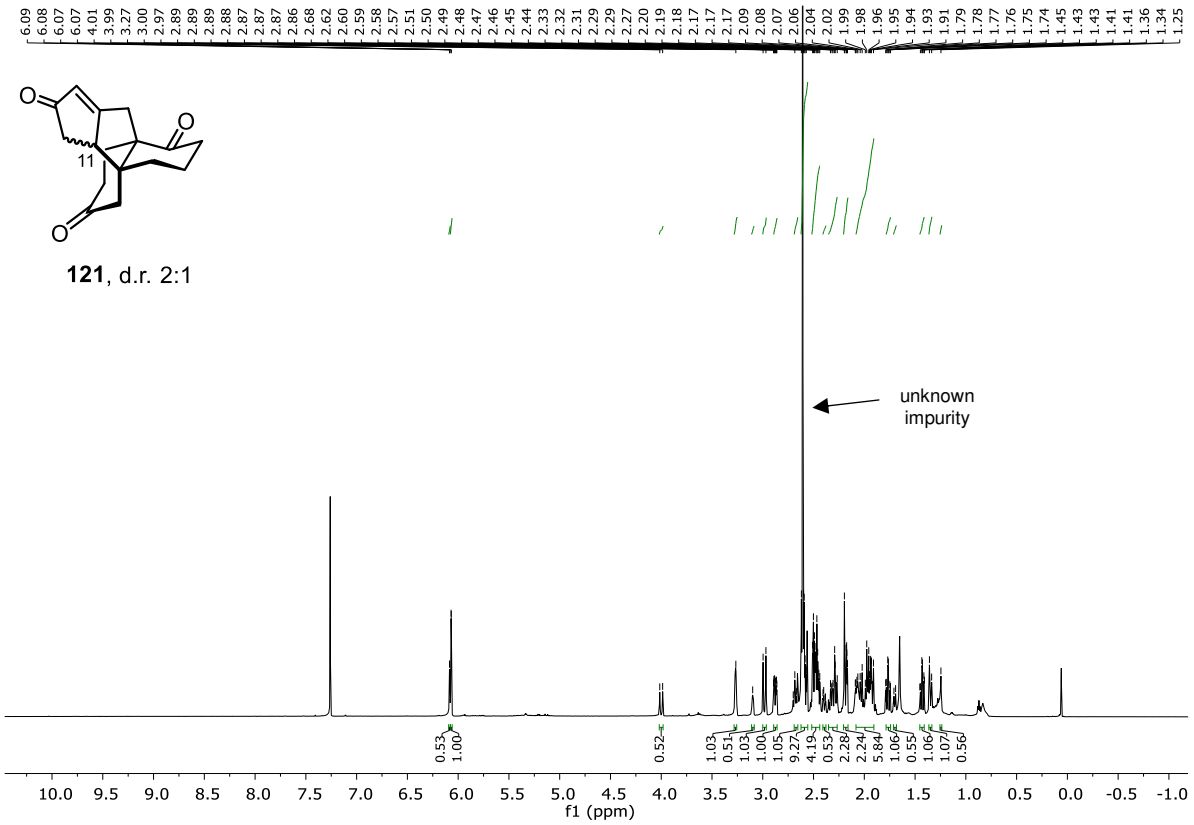
126 **131**

A solution of dione **126** (14.0 mg, 0.0641 mmol, 1.00 equiv.) in DMF (0.2 mL) was treated with TBAF (1 M in THF; 77.0 µL, 0.0769 mmol, 1.20 equiv.) and stirred at room temperature for 1.5 h. The mixture was treated with H_2O (2 mL) and extracted with ethyl acetate (3x4 mL).

The combined organic phases were washed with water (4 mL) and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, pentane/ethyl acetate = 2:1) yielded twistanol **131** (8.9 mg, 64%) as a vitreous oil.

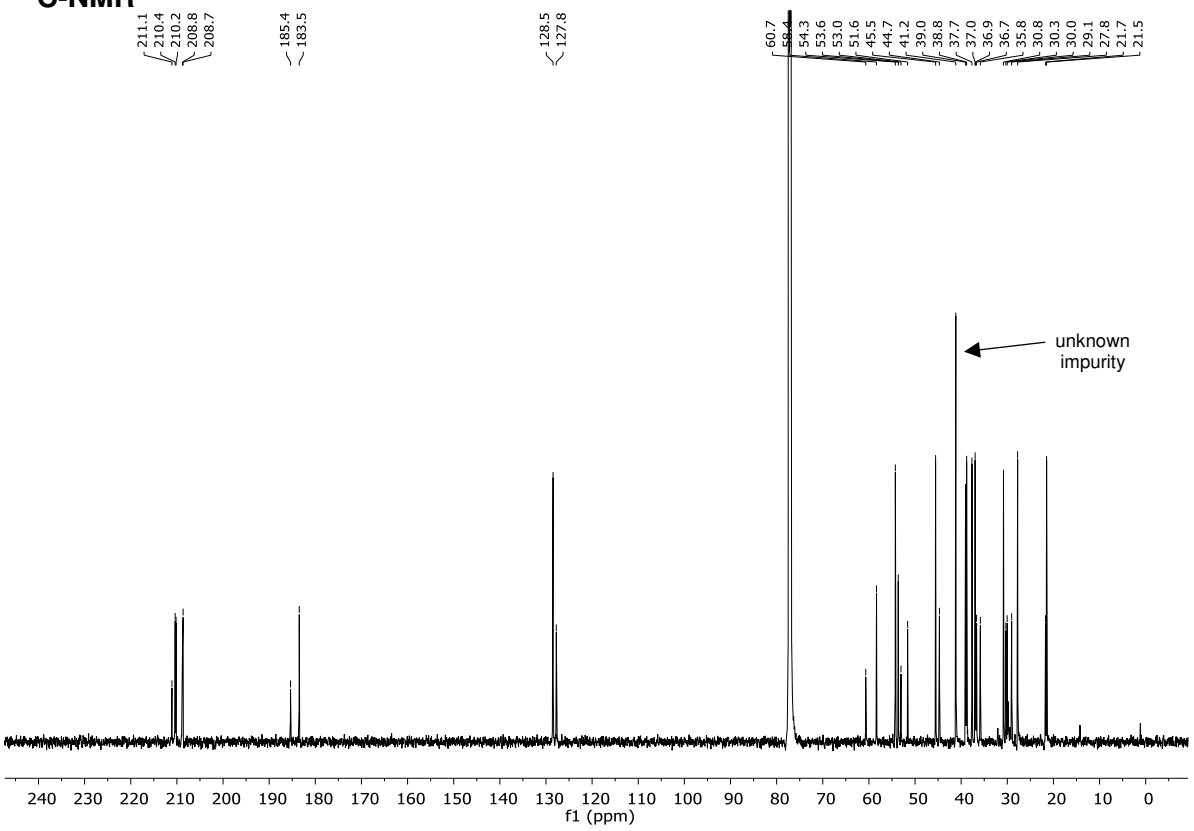
R_f = 0.30 (pentane/ethyl acetate 2:1); $[\alpha]_D^{20}$ = +307 (*c* = 0.75, chloroform); **^{1}H-NMR** ($CDCl_3$, 700 MHz): δ = 5.77 (dd, *J* = 17.6, 11.1 Hz, 1H), 5.69 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.32 (dd, *J* = 11.1, 1.3 Hz, 1H), 5.04 (dd, *J* = 11.2, 1.4 Hz, 1H), 5.04 (dd, *J* = 17.6, 1.3 Hz, 1H), 5.00 (dd, *J* = 17.4, 1.1 Hz, 1H), 2.30 (dd, *J* = 4.5, 1.1 Hz, 1H), 2.16 (dtd, *J* = 13.2, 9.9, 1.7 Hz, 1H), 1.96 (ddd, *J* = 12.2, 2.6, 1.2 Hz, 1H), 1.93–1.88 (m, 2H), 1.84 (dd, *J* = 11.8, 9.9 Hz, 1H), 1.72–1.67 (m, 2H), 1.66–1.62 (m, 2H), 1.61–1.57 ppm (m, 2H); **^{13}C-NMR** ($CDCl_3$, 176 MHz): δ = 216.9, 140.3, 133.5, 117.8, 113.3, 73.1, 57.0, 56.2, 46.5, 40.7, 35.0, 27.9, 23.8, 22.3 ppm; **IR** ($CDCl_3$): $\tilde{\nu}$ = 3418, 3084, 3006, 2952, 2871, 1721, 1417, 1335, 1153, 920 cm^{-1}; **HRMS** (ESI): m/z calculated for $C_{14}H_{18}O_2Na$ $[M+Na]^+$ 241.1199, found: 241.1204.

^{1}H-NMR

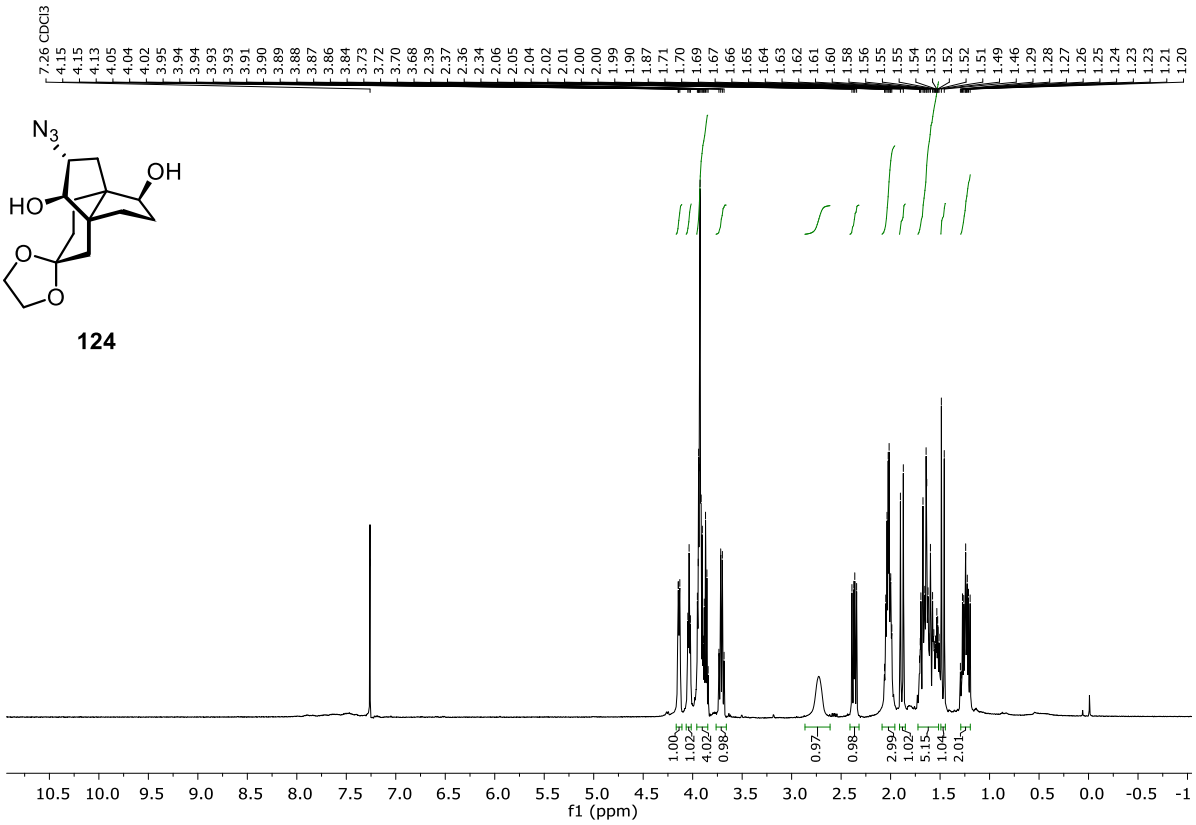


121, d.r. 2:1

^{13}C-NMR

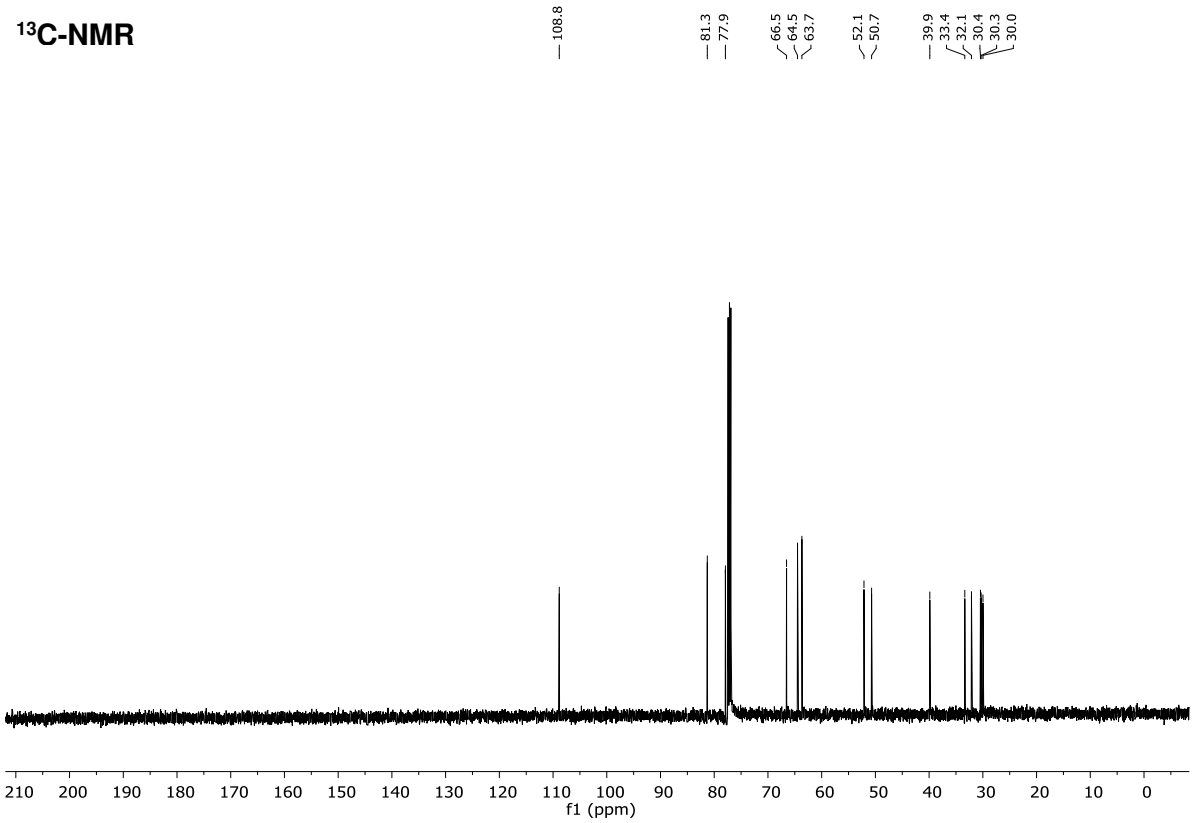


^{1}H-NMR

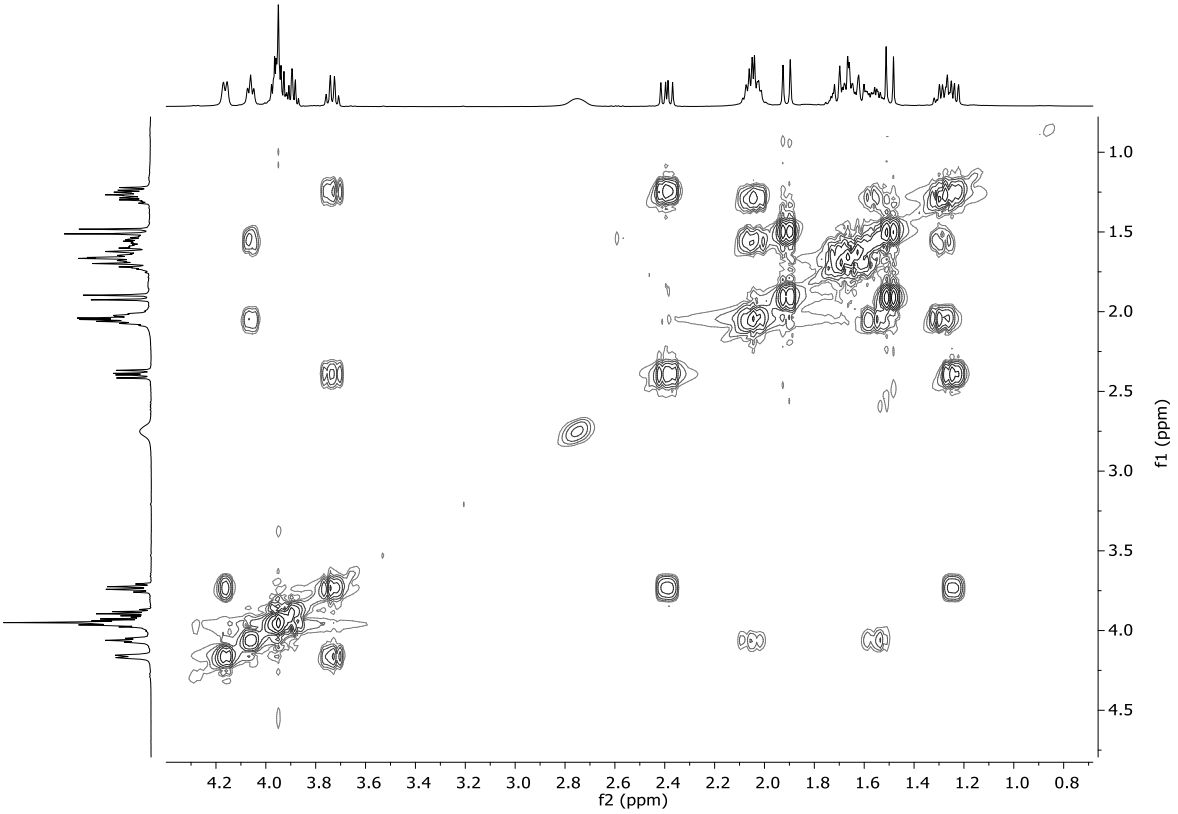


124

^{13}C-NMR



HH-COSY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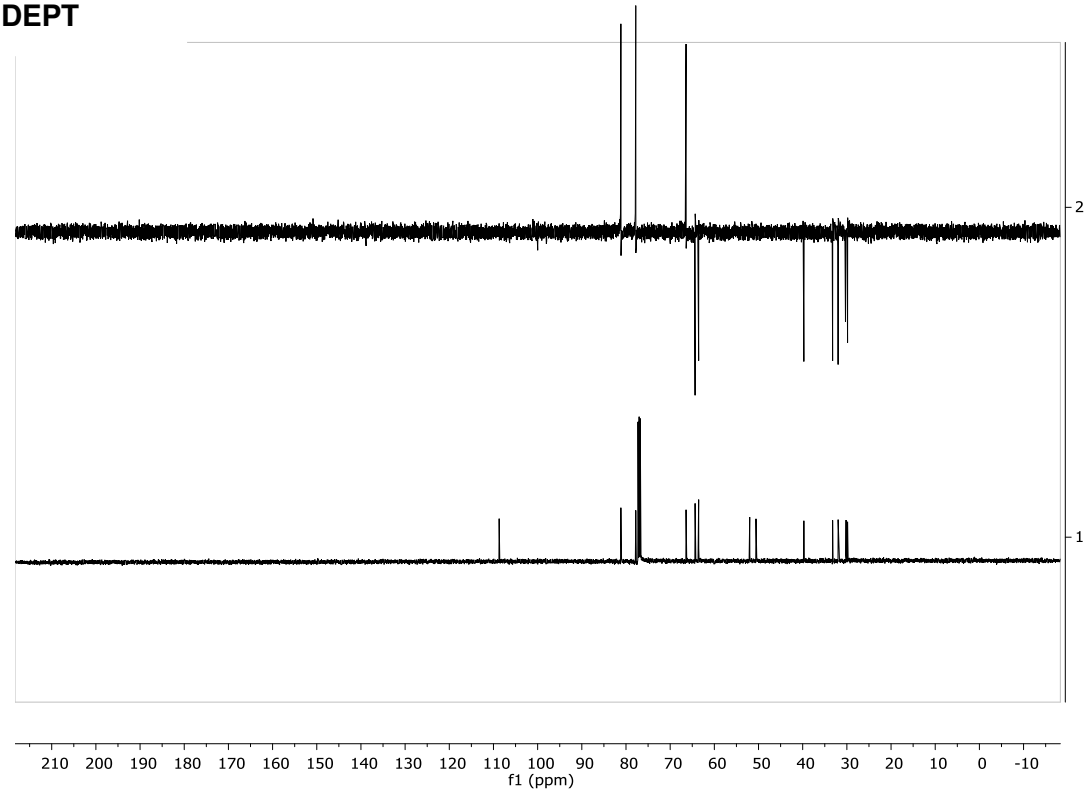
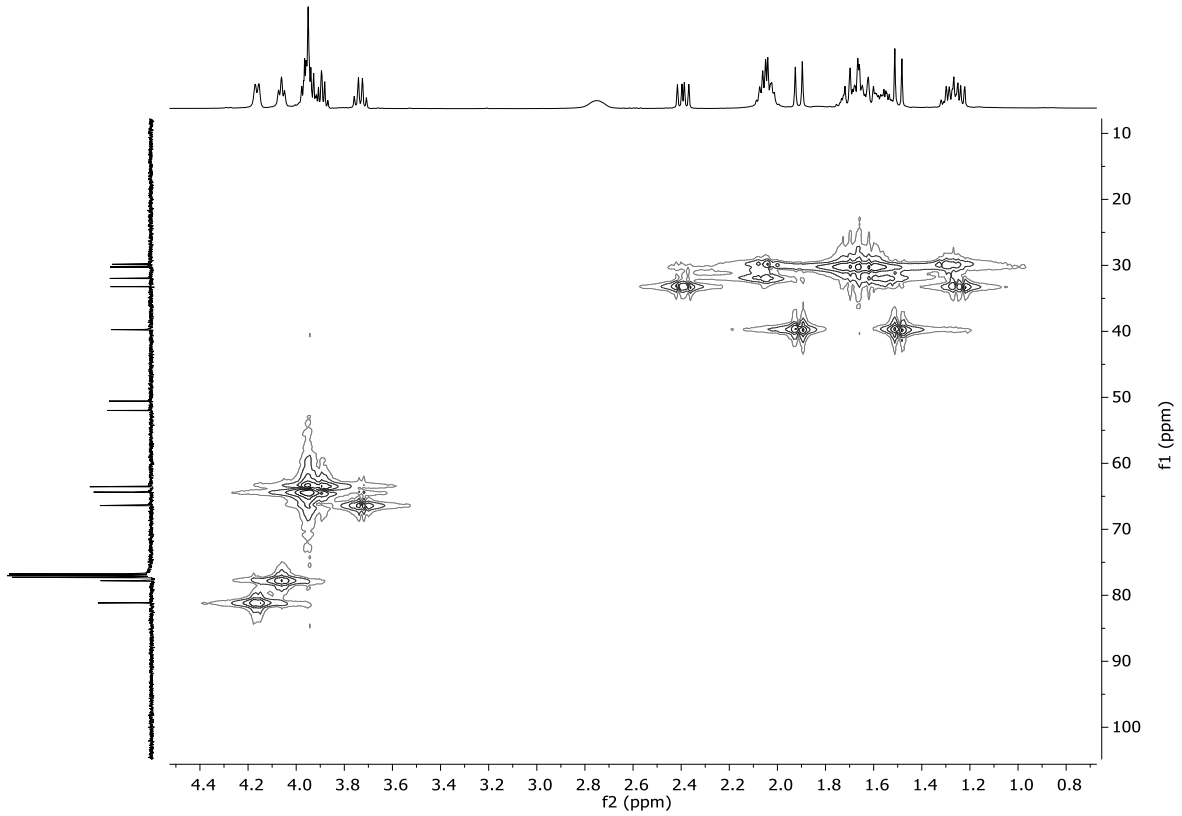
1.5
2.0
2.5
3.0
3.5
4.0
4.5
f1 (ppm)
4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8
f2 (ppm)

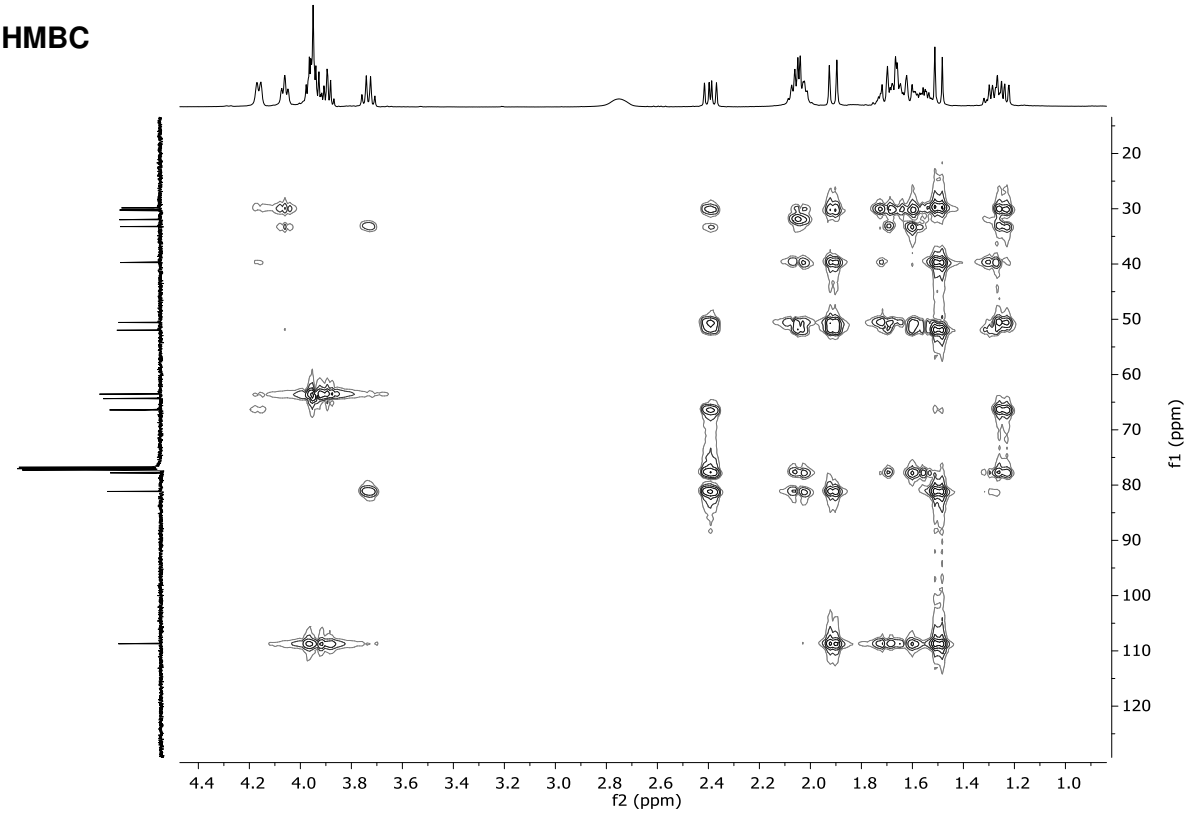
DEPT


2
1
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

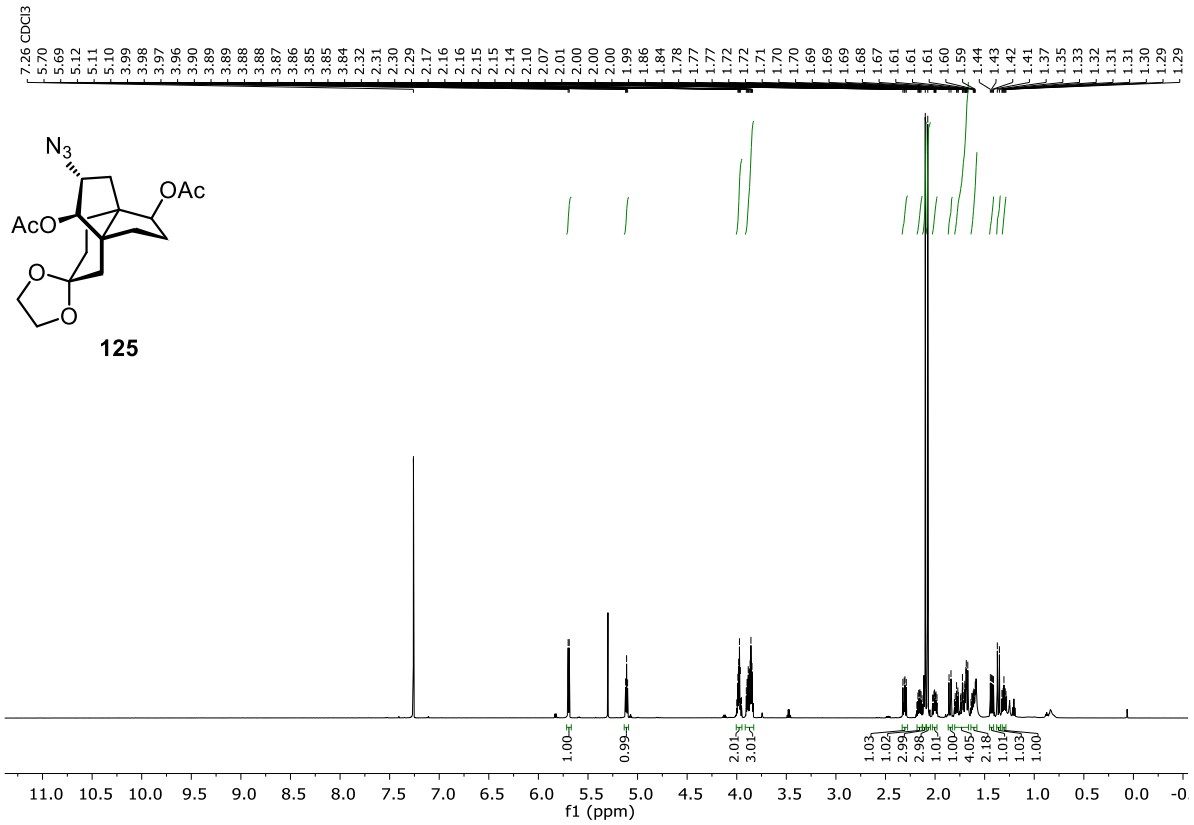
HMQC


10
20
30
40
50
60
70
80
90
100
f1 (ppm)
4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8
f2 (ppm)

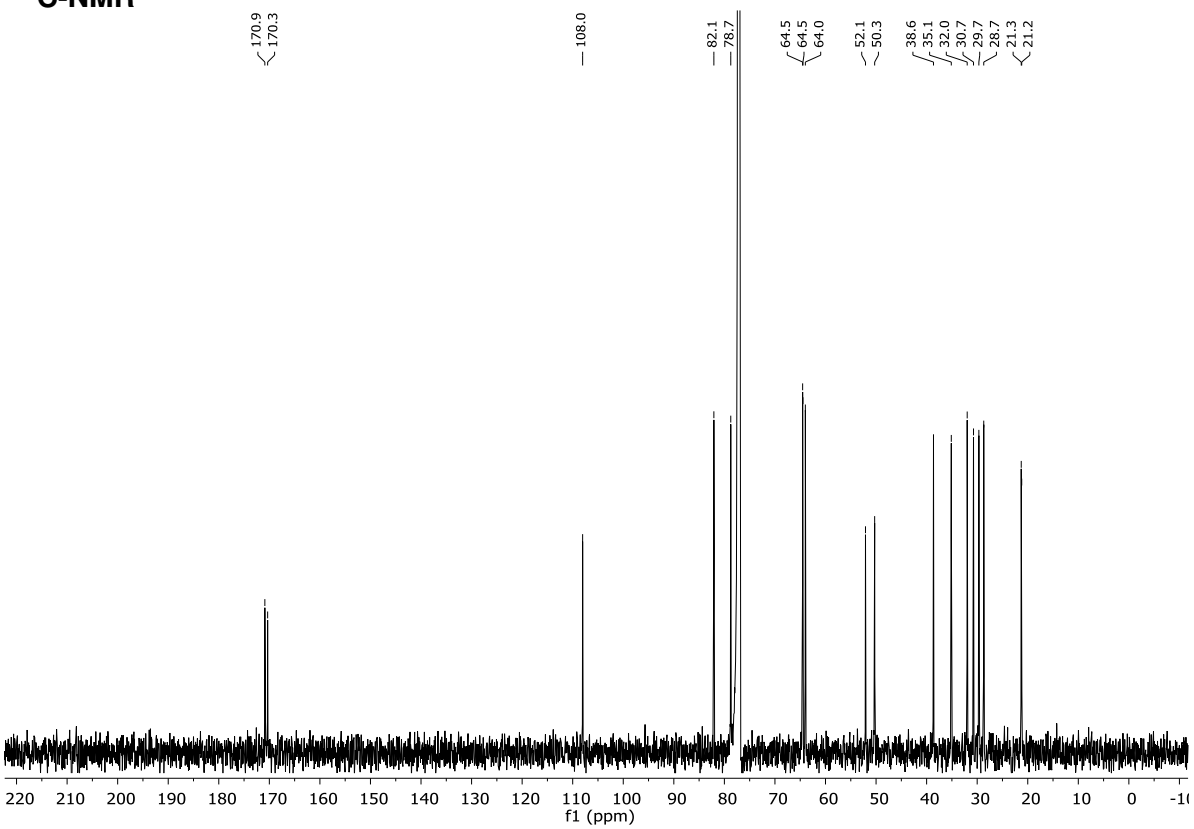
HMBC


20
30
40
50
60
70
80
90
100
110
120
f1 (ppm)
4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0
f2 (ppm)

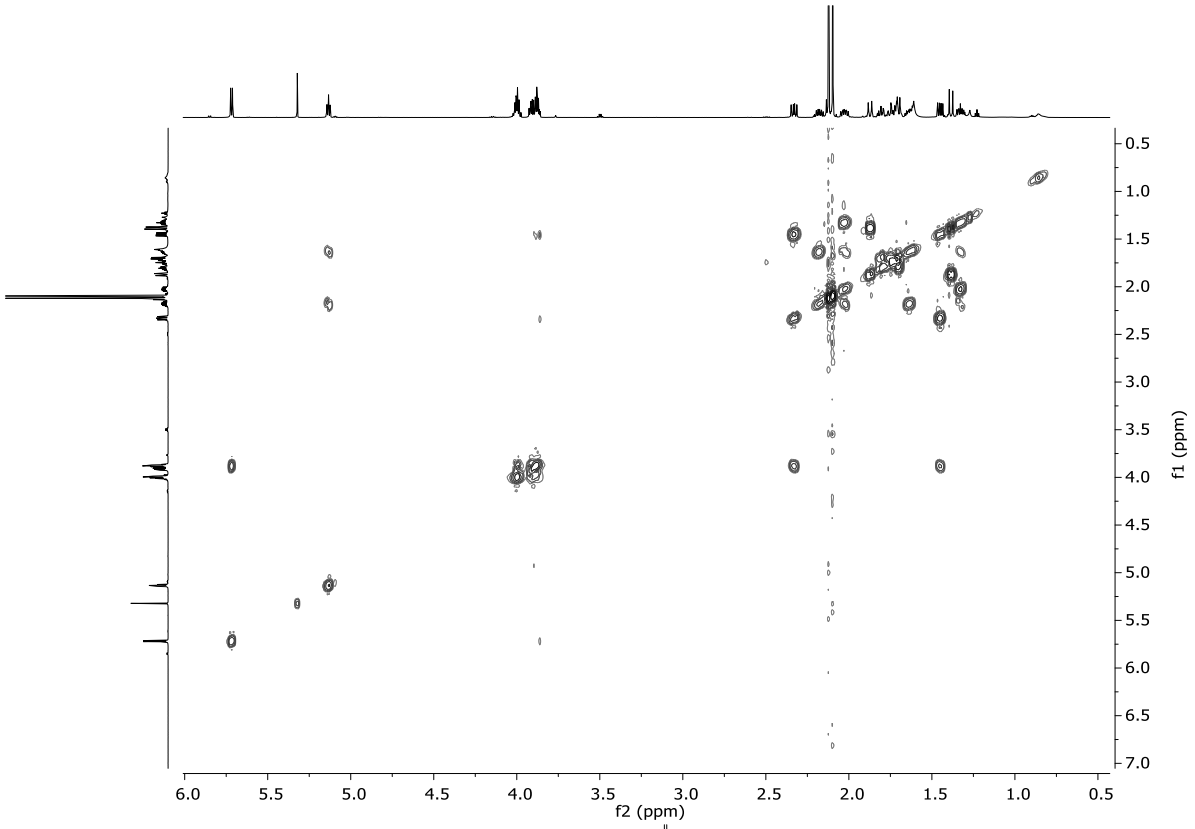
^{1}H-NMR



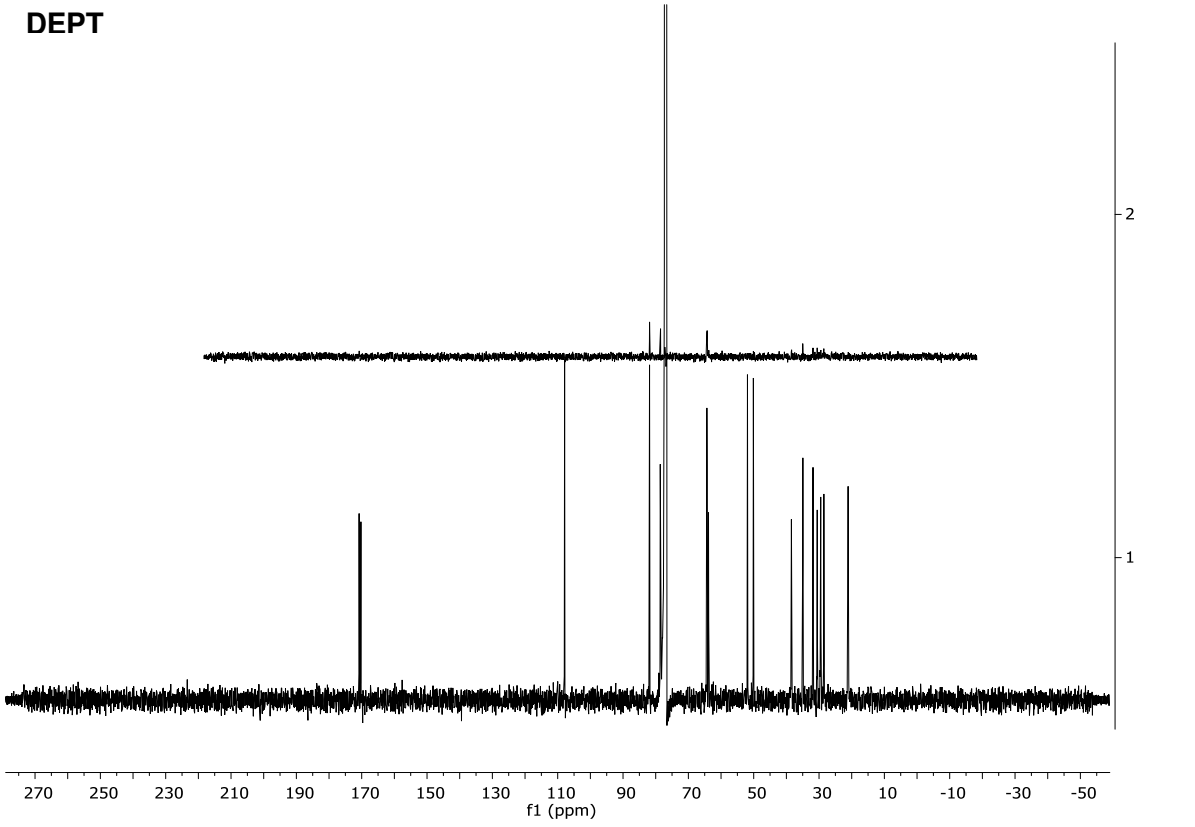
^{13}C-NMR



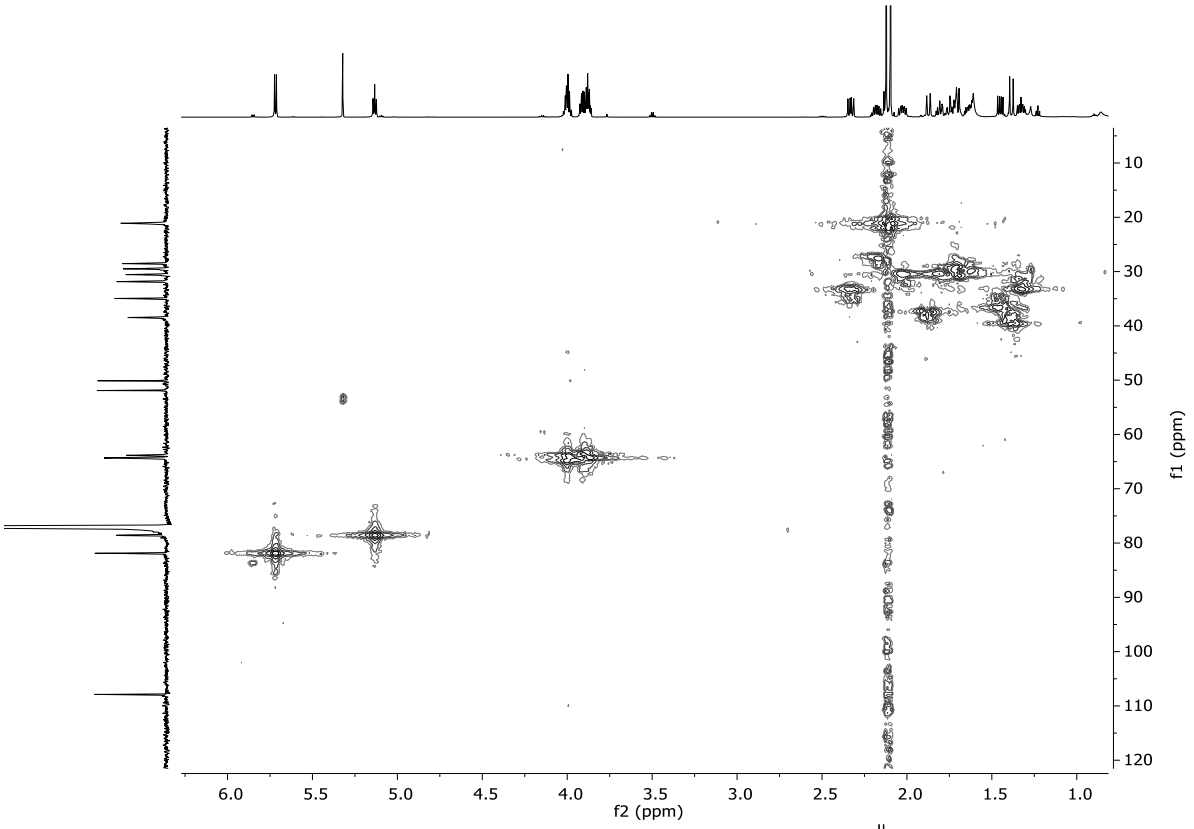
HH-COSY


0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
f1 (ppm)
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)

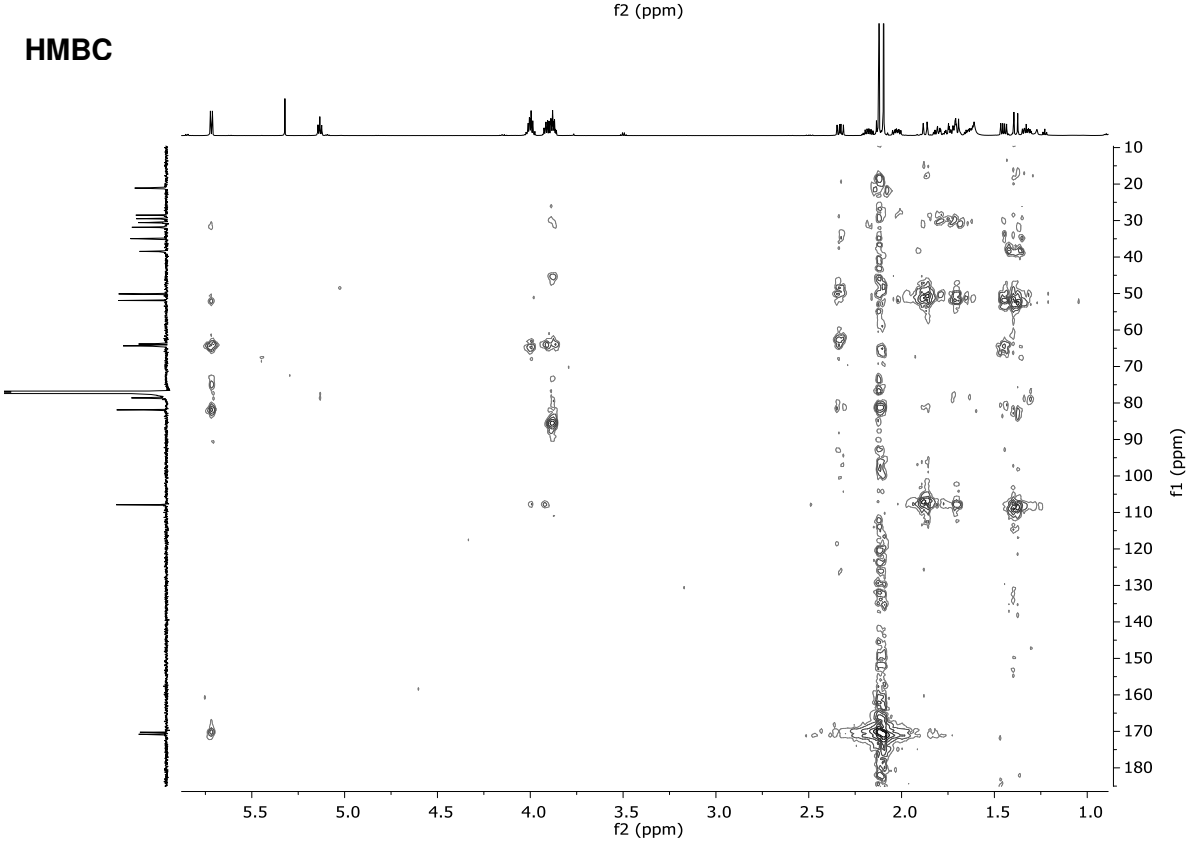
DEPT


2
1
270
250
230
210
190
170
150
130
110
90
70
50
30
10
-10
-30
-50
f1 (ppm)

HMQC



HMBC



Appendix 3 — Curriculum Vitae

The curriculum Vitae is not published in the online version for reason of data protection.