Stereodivergent Synthesis of Enantioenriched Five- and Six-Membered Cyclic-1,3-diols and Applications Toward Library Synthesis

By

Gurpreet Singh

Submitted to the graduate degree program in the Department of Medicinal Chemistry and the Graduate Faculty of the University of Kansas in partial fulfillment of the requirements of the degree of Doctor of Philosophy

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Apurba Dutta, Chair

_____
Jeffrey Aubé

_____
Michael F. Rafferty

_____
Paul R. Hanson

_____
Helena C. Malinakova

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Date Defended

The Dissertation Committee for Gurpreet Singh certifies that this is the approved version of the following dissertation:

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Apurba Dutta, Chair

Date Approved

Abstract

This work describes the development of methods to access synthetically useful chiral diols in enantiomerically pure form. First chapter describes the development of a stereodivergent approach for enantioenriched synthesis of 2-cyclopentene-1,3-diol that was later converted to 4-hydroxy-2-cyclopentenones (4-HCPs), which are highly privileged synthetic building blocks with numerous applications in natural product syntheses and pharmaceuticals. The present approach enables the gram scale synthesis of 4-HCPs with chemically diverse protecting groups, in a stereodivergent manner. In chapter 2, we describe the development of a unified strategy for the stereodivergent synthesis of enantioenriched 1,3-dihydroxy substituted six-membered carbo- and heterocyclic rings. The previously known approaches for accessing these compounds involve multiple synthetic steps and one or more enzymatic steps. We developed a purely synthetic approach to synthesize enantioenriched carbo- and heterocyclic six-membered 1,3-diols from a common, highly economical commercial available starting material. In Chapter 3, we described the development of a small-molecule library of stereochemically diverse compounds by integrating enantioenriched carbo- and heterocyclic 1,3-diols, and natural α-amino acids.

Dedicated

To my father

Late S. Manjit Singh

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Abbreviations

aq	aqueous
Ac_2O	acetic anhydride
BnBr	benzyl bromide
Boc	*tert*-butyloxycarbonyl
*n*BuLi	n-butyllithium
*t*Bu	*tert*-butyl
CALB	candida antarctica lipase B
$CHCl_3$	chloroform
CH_2Cl_2	dichloromethane
CSA	camphorsulfonic acid
DEAD	diethyl azodicarboxylate
DMSO	dimethyl sulfoxide
DMAP	4-dimethylaminopyridine
DIPEA	*N*,*N*'-Diisopropylethylamine
DMF	dimethylformamide
DOS	diversity oriented synthesis
Et_2O	diethyl ether
equiv	equivalent
Et	ethyl
EtOAc	ethyl acetate
ee	enantiomeric excess
er	enantiomeric ratio
Et_3N	triethylamine
HCl	hydrochloric acid
HPLC	high performance liquid chromatography
HMPA	hexamethylphosphoramide
Hz	hertz

IR	infrared radiation
*i*Pr	isopropyl
K_2CO_3	potassium carbonate
$LiAlH_4$	lithium aluminum hydride
MeCN	acetonitrile
MeOH	methanol
MsCl	methanesulfonyl chloride
mesylation	methanesulfonation
NMR	nuclear magnetic resonance
$NaHCO_3$	sodium bicarbonate
PCC	pyridinium chlorochromate
PMB	para-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
PPh_3	triphenylphosphine
PS-C	pseudomonas cepacia lipase
PTSA	*p*-toluenesulfonic Acid
RCM	ring-closing metathesis
rt	room temperature
SM	starting material
TBAF	tetrabutylammonium fluoride
TBS	tert-butyldimethylsilyl
TBSCl	tert-butyldimethylsilyl chloride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TIPSCl	triisopropylsilyl chloride
TLC	thin layer chromatography

Chapter 1

Synthesis of Enantioenriched 4-Hydroxy-2-Cyclopentenones

1.1 Introduction to 4-hydroxy-2-cyclopentenones (4-HCPs)

Hydroxylated cyclopentanones and cyclopentenones are common motifs in a variety of natural product structures including prostaglandins (e.g. PGE_2), antibiotics pentenomycin and viridinomycin, the antitumor dienediyne natural product N1999A2, terpenes hymenolin and numerous others (Figure 1.1). In addition, the tremendous reactivity potential of the 4-HCPs that was earlier recognized in the prostaglandin chemistry, has been exploited over last several years in complex natural product syntheses.[1,2]

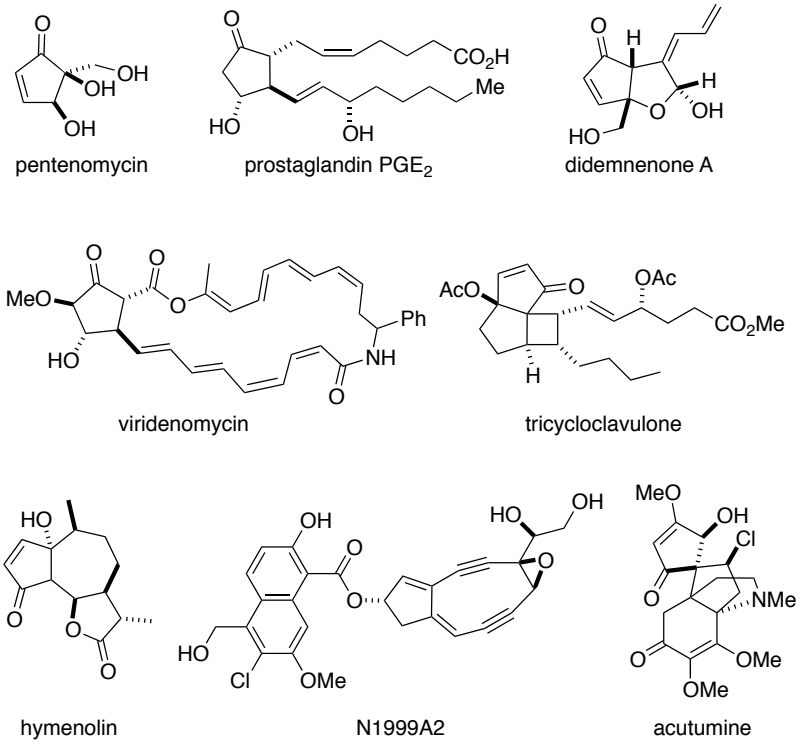
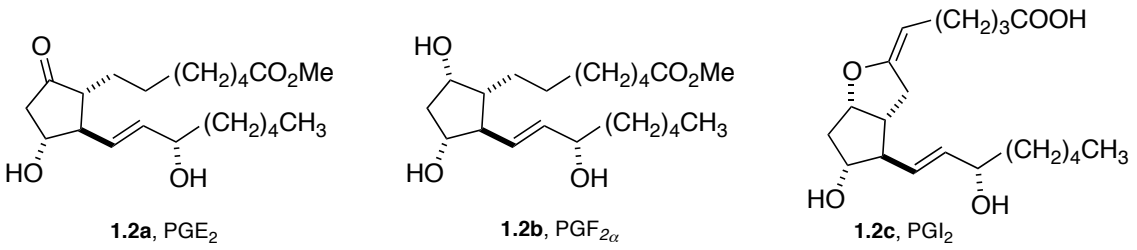


Figure 1.1. Natural products containing 4-hydroxycyclopentanone or cyclopentenone motif

1.2. 4-HCPs as important synthetic intermediates for prostaglandin synthesis

1.2.1. A brief introduction to prostaglandins

The prostaglandins (PGs) are a group of physiologically active lipid compounds derived enzymatically from fatty acids. Biosynthetically, prostaglandins are derived from arachidonic acid and are transformed by prostaglandin synthetase into a number of structurally related carbocyclic molecules. They were discovered in the early 1930s by von Euler and by the mid-1960s the structures of the first family of prostaglandins were reported by Bergstrom et al. Structurally these contain 20 carbon atoms including a 5-carbon ring and have 4 (**1.2a**, PGE_2) or 5 (**1.2b**, $PGF_{2\alpha}$ and **1.2c**, PGI_2) stereogenic centers of which 3 or 4 are the contiguous stereocenters in the cyclopentane ring (Figure 1.2). PGs have been found in almost every tissue in humans and other animals, and are responsible for the control of a number of essential biological processes including sleep, pain, fever, inflammation, menstruation, birth, and constriction of blood vessels and blood[3] clotting.



1.2a, PGE_2 **1.2b**, $PGF_{2\alpha}$ **1.2c**, PGI_2

Figure 1.2. Prostaglandin natural products

1.2.2. Emergence of 4-HCPs as potential chiral building blocks for the synthesis of prostaglandins

Because of their biological importance and structural complexity, the prostaglandins had been very important targets for synthesis both in academia and pharmaceutical industry.[2,4] Various research groups including Woodward[5], Corey[6], Stork[7], Noyori[8], Danishefsky[9] and others contributed significantly by developing innovative chemical methodologies for PG synthesis. In 1969, Corey's group reported an elegant route (Figure 1.3) for the synthesis of PGE_2 via a bicyclic lactone intermediate (**1.3a**) in which all the stereocenters were installed in the correct relative stereochemistry as in the original natural product structure.[6] The lactone (**1.3a**) was obtained via a Diels-Alder reaction of 2-substituted cyclopentadiene (**1.3b**) and 1-chloroacrylonitrile (**1.3c**) followed by Bayer-Villiger oxidation and iodolactonization.

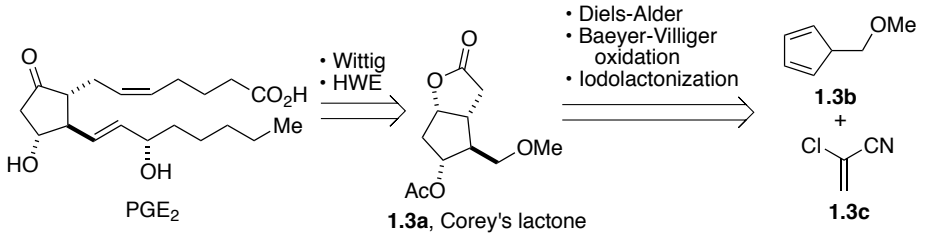
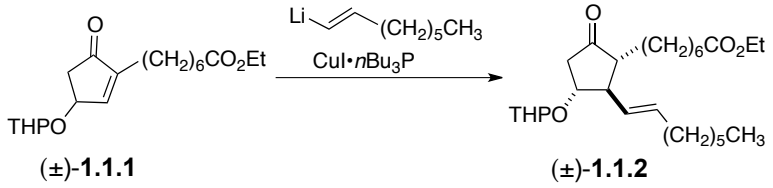


Figure 1.3. Corey's approach for the synthesis of PGE_2

Though the Corey lactone approach contained all but one stereocenter in the prostaglandin structure, its application to asymmetric synthesis of prostaglandins would require an enantioselective version of Diels-Alder reaction that was yet to be developed at that time. Contemporary to this work, several groups pursued research to develop alternative strategies for the synthesis of prostaglandin. Two publications from Sih's group brought the attention of chemists to 4-substituted cyclopentenones as the potential synthetic intermediates for prostaglandin synthesis.[10] Sih's group reported (Scheme 1.1)

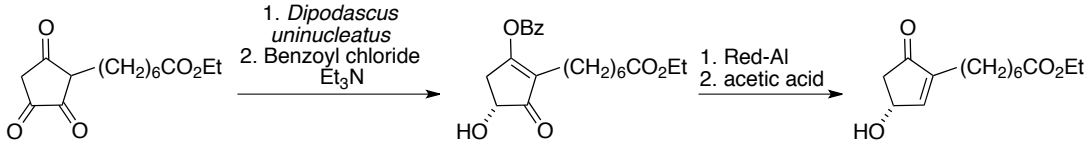
that C-4 substituent of the 4-hydroxy-2-cyclopentenone (**1.1.1**) could be used to direct the stereochemistry at both α- and β-carbons through conjugate addition of organocuprates.[10] It was an important result as it revealed that a single stereogenic center on the cyclopentenone ring could be used to install the remaining substituents in the desired stereochemistry required for the prostaglandin synthesis.



(±)-**1.1.1** (±)-**1.1.2**

Scheme 1.1. Sih's two-component approach to PGs

Sih's group also reported the synthesis of an enantiomerically pure 2-substituted-4(*R*)-hydroxycyclopent-2-en-1-one **1.2.3** through microbial reduction of 2-substituted cyclopentanetrione **1.2.1** (Scheme 1.2).[10] Reduction of the carbonyl group in **1.2.2** with Red-Al followed by exposure to acetic acid provided the enantioenriched 4-hydroxy cyclopentenone **1.2.3**.



1.2.1 **1.2.2** **1.2.3**

Scheme 1.2. Sih's approach to asymmetric synthesis of prostaglandins

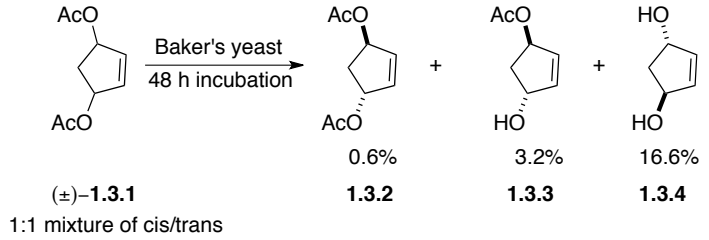
Thus interest in the total synthesis of prostaglandins by conjugate addition

alkylation prompted the researchers to develop efficient approaches for the synthesis of enantioenriched 4-hydroxycyclopent-2-en-1-one.[2,4] A number of methods to synthesize enantioenriched 4-hydroxy-cyclopentenones have been reported since then. Following section highlights the conceptually unique and/or highly utilized strategies employed for the synthesis of enantioenriched 4-HCPs.

1.3. **Synthetic approaches for the synthesis of 4-hydroxy-2-cyclopentenones**

1.3.1. **4-HCP synthesis by enzymatic hydrolysis or acylation of cyclopentenoids**

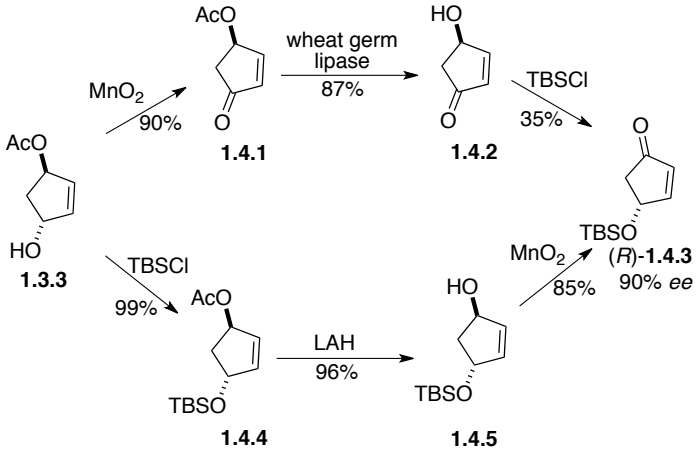
Kurozumi's group was the first one to report the synthesis of both R and S isomers of 4-*O*-silyl-protected hydroxycyclopentenone.[11] They performed the hydrolysis of a 1:1 cis/trans mixture of the racemic 2-cyclopentene-1,4-diacetate, **1.3.1**, with baker's yeast (Scheme 1.3).[11] Depending upon the difference in the rate of enzymatic hydrolysis between different isomers of **1.3.1** the reaction resulted in a net accumulation of the *trans*-monoacetate (*R,R*)-**1.3.3** and the kinetically resolved *trans*-diacetate *R,R*-**l.3.2**.



Scheme 1.3. Baker's yeast hydrolysis of 3,5-diacetoxy-1-cyclopentene

The *trans*-monoacetate (*R*)-**1.3.3** was converted into 4(*R*)-*tert*-butyldimethyl-siloxycyclopent-2-en-1-one (*R*)-**1.4.3,** by two different paths (Scheme 1.4). In the first route, the alcohol **1.3.3** was oxidized with manganese dioxide followed by hydrolysis of the acetoxy group of (*R*)-**1.4.1** with wheat germ lipase to afford the hydroxy enone **1.4.2**.

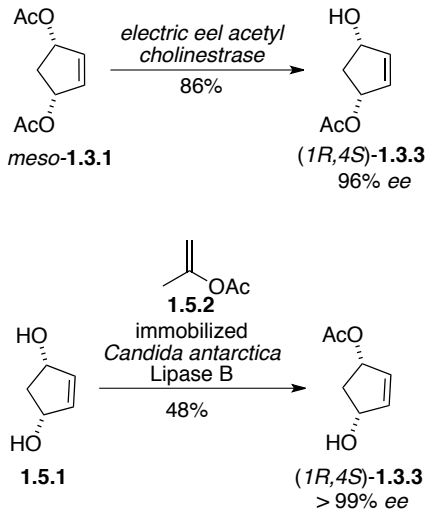
Protection of the hydroxyl group at the next step with *tert*-butyldimethylchlorosilane gave the silylether (*R*)-**1.4.3** in 90% *ee*. The alternative pathway at first involved silylation of the alcohol **1.3.3** to give silyl ether **1.4.4**. Followed by reduction of the acetate group with LAH gave the alcohol (*R*)-**1.4.5** that was oxidized with manganese dioxide to obtain the enone (*R*)-**1.4.3**. Though the latter route gave the higher overall yield of (*R*)-**1.4.3**, the enantiopurity of the product was inferior than the purity of the product obtained by using the former route.



Scheme 1.4. Kurozumi's synthesis of enantioenriched 4-HCPs

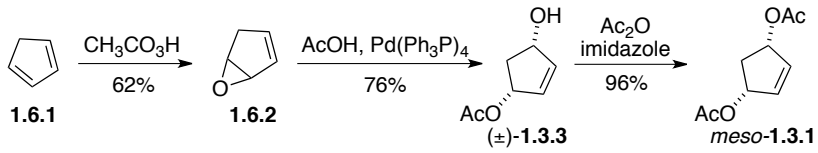
The enzymatic desymmetrization of the *meso*-cyclopentenoids has been a very effective method for the synthesis of enantioenriched 4-HCPs. The enantioselectivity of the enzymatic desymmetrization of *meso*-diacetate depends on the lipase used. Two reports have been highly cited in literature for procuring enantiopure 4-HCPs.[12,13] In 1986, Deardorff's group reported the synthesis of mono acetate (*1R*, *4S*)-**1.3.3** by using *Electric eel acetylcholinestrase* in very good yield and excellent *ee*.[12] The enantiomeric excess was further enhanced to >99% on recrystallization of the product. In 1992,

Johnson and coworkers reported Novo SP-435 mediated monoacylation of the *meso* diol **1.5.1** with isopropenyl acetate to produce (*1R*, *4S*)-**1.3.3** in 48% yield and >99% *ee*.[13]



Scheme 1.5. Enzymatic desymmetrization of *meso*-cyclopentene-1,4-diacetate

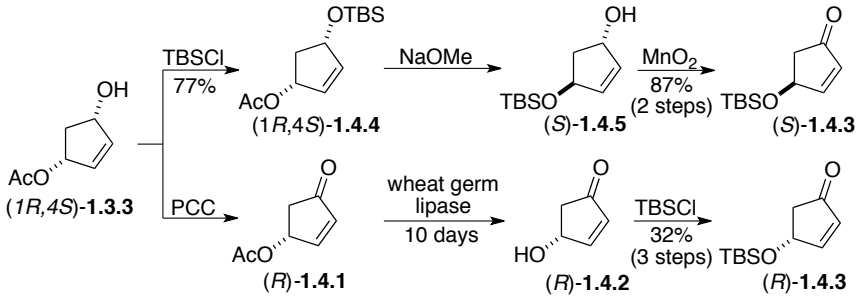
The ease of synthesis of the starting *meso*-diacetate further supports the utility of these enzymatic approaches. Furthermore, *meso*-1,4-diacetoxy-2-cyclopentene can be easily obtained from cyclopentadiene either via a tandem photooxygenation/reduction protocol, or via 3,4-epoxycyclopentene, subjected to palladium(0)-catalyzed allylic displacement (Scheme 1.6).[14]



Scheme 1.6. Synthesis of *meso*-2-cyclopentene-1,4-diacetate

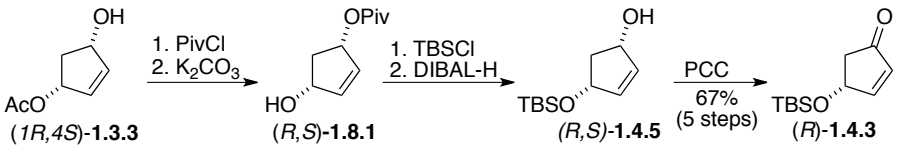
Considering the broad synthetic utility of silyl protecting group over the acetate, a

number of routes have been reported to obtain 4-*tert*-butyldimethylsilyloxy-2-cyclopentenone. Paquette et al. reported the synthesis of both *S* and *R* isomers of 4-*O*-*tert*-butyldimethylsilyloxy-cyclopentenones (Scheme 1.7).[15] TBS protection of (*1R,4S*)-**1.3.3** provided (*1R,4S*)-**1.4.4** in 77% yield. Hydrolysis of the acetate using sodium methoxide led to monosilylated diol (*S*)-**1.4.5**, which was subjected to oxidation with MnO_2 to obtain enone (*S*)-**1.4.3** in 87% over two steps. To synthesize the (*R*)-isomer, (*1R,4S*)-**1.3.3** was oxidized to obtain acylated enone (*R*)-**1.4.1**. Treatment of (*R*)-**1.4.1** with wheat germ lipase for ten days provided the hydroxy-enone (*R*)-**1.4.2** that on *O*-protection with TBSCl provided (*R*)-**1.4.3** in 32% overall yield.



Scheme 1.7. Paquette's route for the synthesis of (R)- and (S)- HCPs **1.4.3**

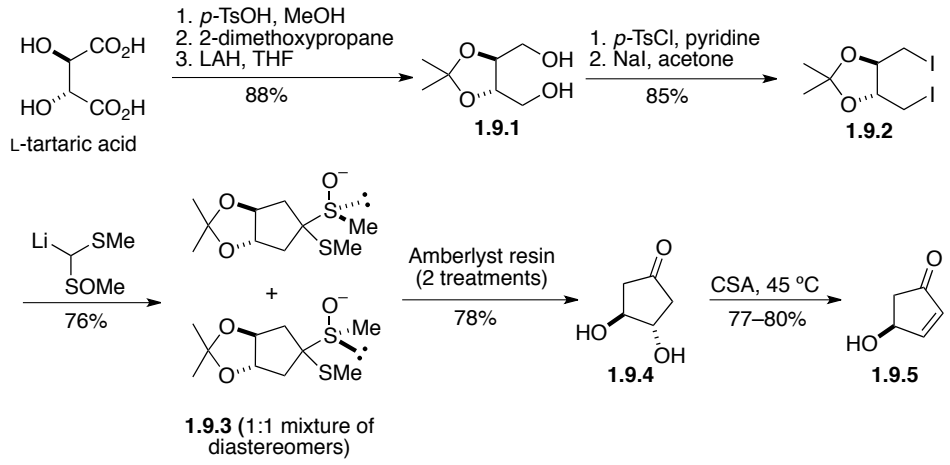
Myers's group reported an alternative to the slow enzymatic hydrolysis in the Paquette's route (Scheme 1.8).[16] They reported a route by introducing pivolyl-protected diol intermediate (*R,S*)-**1.8.1,** which was subjected to TBS protection followed by DIBAL-H mediated removal of the pivolyl protecting group to obtain monosilylated diol *(R,S)*-**1.4.5**. Finally subjecting alcohol **1.4.5** to PCC oxidation provided enone (*R*)-**1.4.3** in 67% overall yield.



Scheme 1.8. Myers's route for the synthesis of HCP (*R*)-**1.4.3**

1.3.2. Synthesis from D-tartaric acid

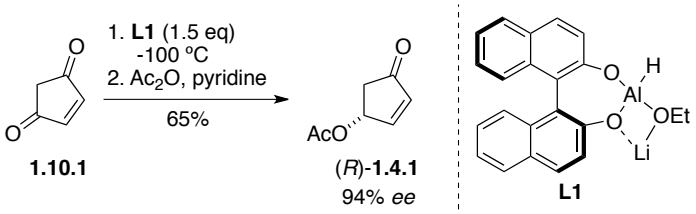
In 1976, Ogura reported the synthesis of both (*R*)- and (*S*)-4-hydroxy cyclopentenone from D- and L-tartaric acids respectively, in seven steps in 85% *ee*.[17] In 1995, Rokach and coworkers reported an improved version of this approach for large scale synthesis of (*S*)-4-hydroxy cyclopentenone by utilizing acidic Amberlyst resin at a later stage in the synthesis (Scheme 1.9).[18] Their route involved an acetonide protection of the dimethyl ester of L-tartaric acid, followed by LAH reduction to produce diol **1.9.1**, which was converted to bis iodo derivative **1.9.2** in two steps. Treatment of the iodo intermediate **1.9.2** with thiomethylmethylsulfoxide carbanion furnished **1.9.3** as a mixture of diastereomers. Cleavage of ketal and thioketal was accomplished by treatment with Amberlyst resin to produce the C_2-symmetric diol **1.9.4**. Treatment of the diol **1.9.4** with camphor sulfonic acid produced 4-hydroxycyclopentenone **1.9.5** in 99% *ee*.



Scheme 1.9. Synthesis of enantioenriched 4-HCPs from L-tartaric acid

1.3.3. Non-enzymatic desymmetrization or kinetic resolution

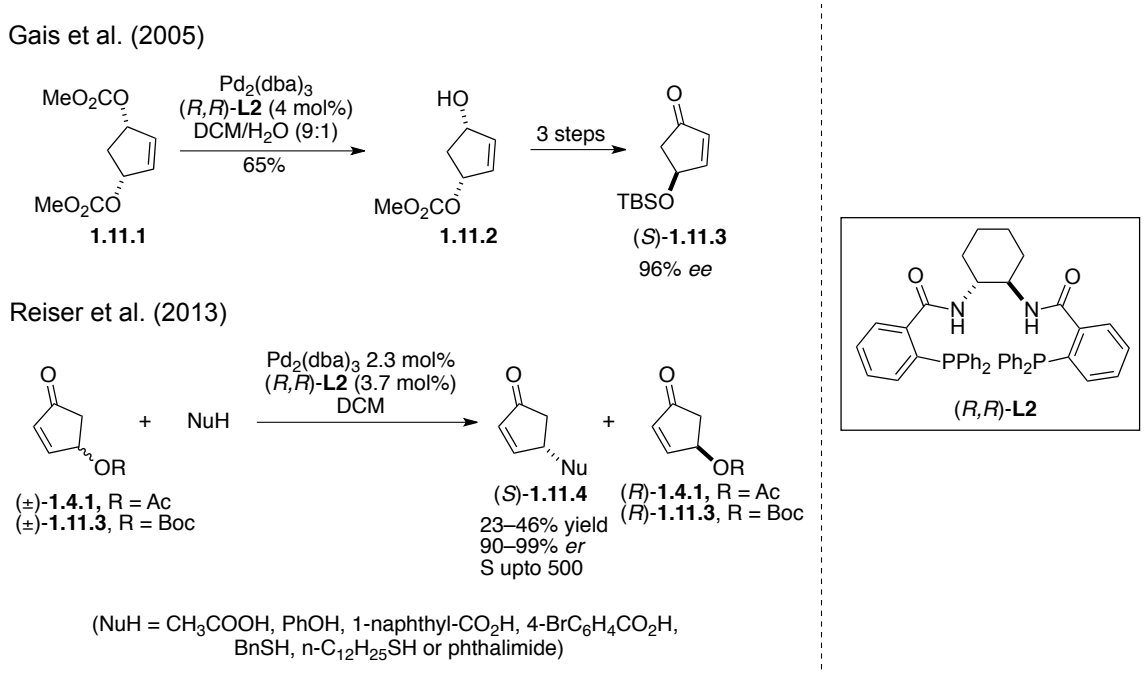
Noyori et al. reported a direct enantioselective reduction of a prochiral 1,3-diketone using a chiral hydride reducing agent, (*S*)-BINAL-H (**L1**), derived from C_2-symmetrical (*S*)-BINOL (Scheme 1.10).[8] Enantioselective reduction of 1,3-cyclopentenedione using **L1,** followed by acetylation provided 4-acetoxy-2-cyclopentenone in 65% yield and 94% *ee*.



Scheme 1.10. Noyori's BINAL-H reduction of 1,3-diketones

Transition metal catalyzed approaches have also been used to synthesize optically enriched 4-HCPs. In 2005, Gais et al. (Scheme 1.11) reported an allylic displacement reaction of the *meso* biscarbonate, **1.11.1**, with water under palladium-catalyzed

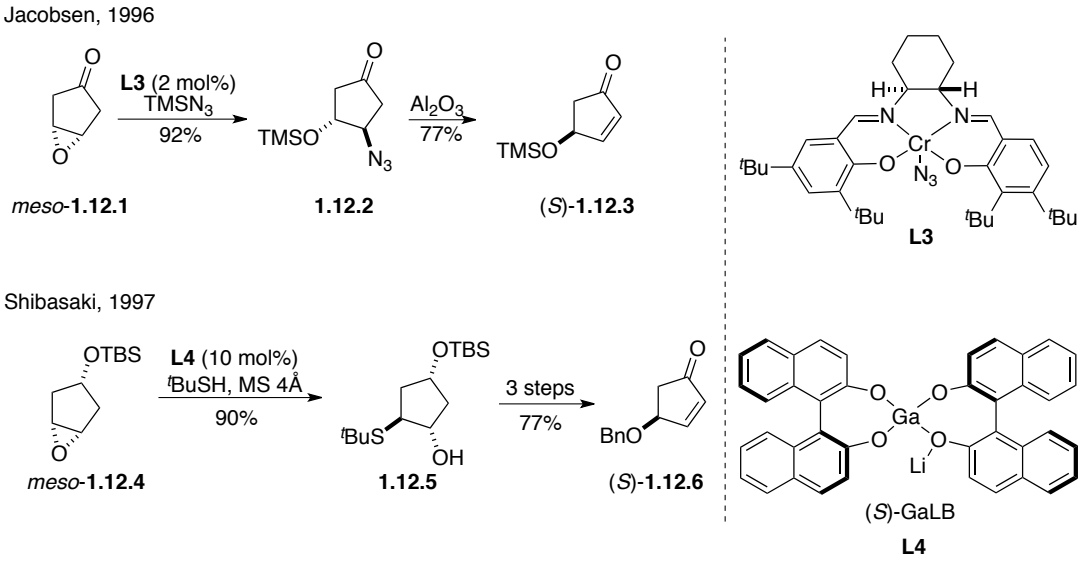
conditions using the Trost ligand (*R*,*R*)-**L2**.[19] Alcohol **1.11.2** was obtained in 87% yield and 96% *ee*, and was converted to (*S*)-4-*tert*-butyldimethylsilyloxy-2-cyclopentenone, (*S*)-**1.4.3**, in 56% yield over three steps. Recently, Reiser's group reported a palladium catalyzed kinetic resolution of racemic 4-*O*-acyl- (**1.4.1)** or *O*-boc (**1.11.3**) protected 4-hydroxy cyclopentenone by using the Trost ligand (*R,R*-**L2**).[20] They explored a number of heteroatom-based nucleophiles to obtain the 4-substituted-cyclopentenones (**1.11.4**) in excellent yields and enantiomeric ratios.



Scheme 1.11. Pd-catalyzed synthesis of 4-HCPs using Trost ligand (*R*,*R*)-**L2**

Several groups have investigated the desymmetrization of cyclopentanoid *meso* epoxides followed by β-elimination of a leaving group to achieve a short synthesis of 4-hydroxy-2-cyclopentenones (Scheme 1.12). However, only a few methods in this category provide 4-HCPs in high enantiopurity. Leighton and Jacobsen reported the asymmetric ring opening of the *meso*-epoxide **1.12.1** with sodium azide catalyzed by (*S,S*-salen)CrN_3

(**L3**), to afford the *trans*-disubstituted cyclopantanone **1.12.2**.[21] Treatment of azide **1.12.2** with alumina furnished the desired (*R*)-4-trimethylsilyloxy-2-cyclopentenone **1.12.3** in 77% overall yield and 94% *ee* (Scheme 1.12). Another catalytic approach to epoxide opening was described by Shibasaki et al., who carried out the (*S*)-GaLB catalyzed enantioselective opening of the *cis*-epoxide giving cyclopentanoid in 90% yield and 91% *ee* (Scheme 1.12).[22] In this process, catalyst plays a dual role, one as a Lewis acid at the gallium centre promoting the ring opening by coordinating to epoxide, and secondly as a Bronsted base at the lithium binaphthoxide moiety by deprotonating the incoming thiol nucleophile. The product thioether **1.12.5** was subjected to oxidation to furnish α-sulfinyl ketone, which underwent pyrrolytic β-elimination yielding the desired enantioenriched (*S*)-**1.12.6** in 77% yield over three steps.



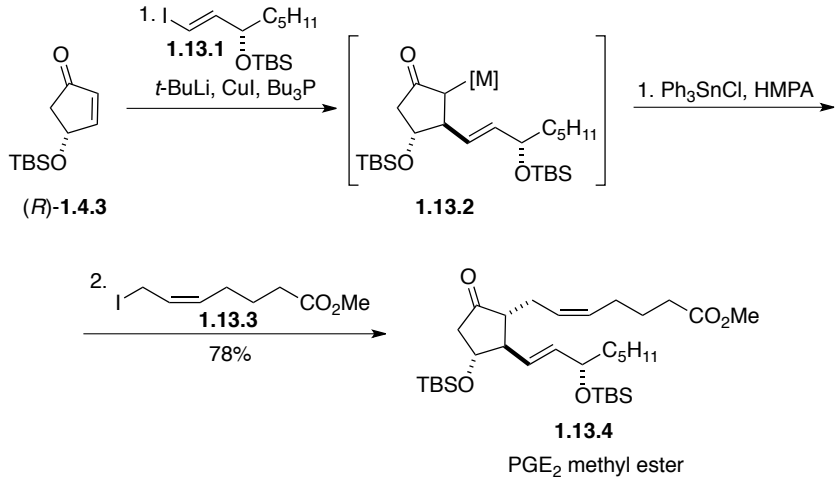
Scheme 1.12. Catalytic opening of meso-epoxides

1.4. Synthetic Applications of 4-HCPs

1.4.1. Synthetic approaches to prostaglandins from 4-HCPs

4-HCPs have been heavily employed in the synthesis of prostaglandins. This section provides a highlight of the major approaches that have targeted the synthesis of the optically enriched PGs using 4-HCPs as the chiral building block.

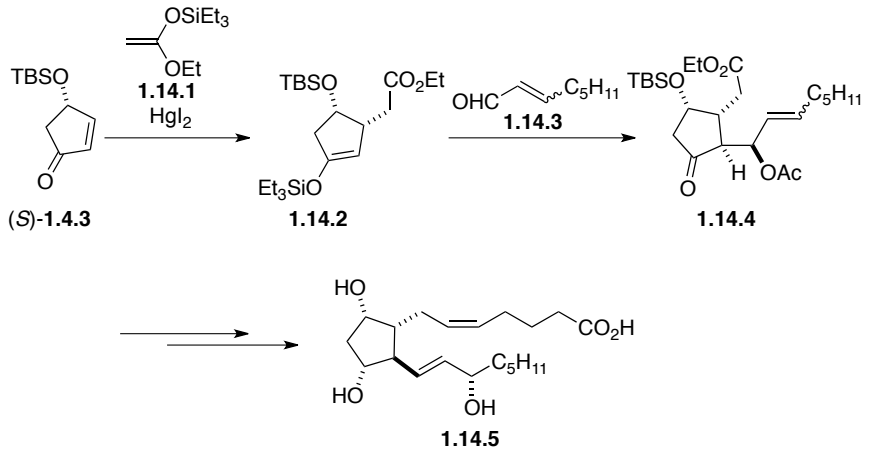
Noyori's group accomplished a three-component coupling to install both α and β chains in a one-pot sequence (Scheme 1.13).[8] The conjugate addition of the vinylcuprate **1.13.1** to the enone (*R*)-**1.4.3**, resulted in the lithium enolate that was trapped as a tin enolate **1.13.2** and was subjected to react with the allyl iodide **1.13.3** to provide methyl ester of PGE_2 **1.13.4** in 78% yield. The stereocenter in the β side chain had been preinstalled by using Noyori's BINAL-H reduction.



Scheme 1.13. Noyori's three component synthesis of PGs

Danishefsky's group reported an elegant approach using a conjugate addition of the silyl vinyl ether **1.14.1** to (*S*)-enone **1.4.3** (Scheme 1.14).[9] Unlike the previously reported

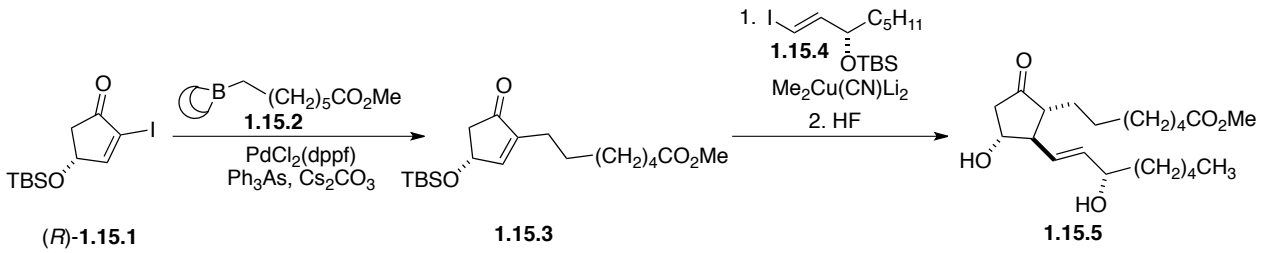
conjugated addition of cuprates, in the present case mercuric chloride mediated addition happened *syn* to the C-4 stereochemistry of the enone **1.4.3** and an *in situ* migration of silyl group led to a silyl enol ether **1.4.3** that was subjected to Lewis acid mediated aldol with an α,β unsaturated aldehyde **1.14.4**. The *trans* geometry of the olefin and the stereochemistry of the hydroxyl group in the side chain were established by palladium-mediated allylic transposition of the acetate at a later stage in the synthesis. This was the only PG synthesis that involved substrate control to set all the stereocenters (including the one in the side chain) in the natural product.



Scheme 1.14. Danishefsky's synthesis of PGs

Despite the attractiveness of the Noyori's three component coupling approach for the PG synthesis,[8] there were several synthetic limitations associated with it. The most noticeable were the problems of enolate equilibration and β-elimination of the silyloxide. Johnson and coworkers reported a synthesis of α-iodoenones that proved really useful in overcoming the problems faced in conjugate addition-alkylation approaches.[13] Suzuki coupling of the α-iodonone **1.15.1** with alkylborane **1.15.2** gave α-alkyl enone **1.15.3**.

Followed by conjugate addition of the vinyl cuprate **1.15.4** provided the desired product **1.15.5** (Scheme 1.14).[23]



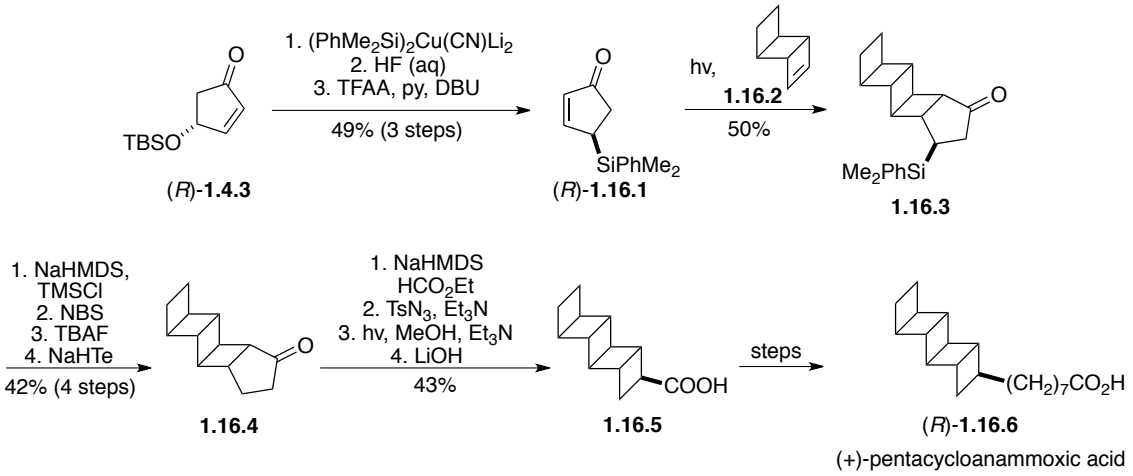
Scheme 1.15. Suzuki's route to PGs

1.4.2. Application of 4-HCPs in non-PG natural product syntheses

The developments in the prostaglandin chemistry proved the synthetic potential of this building block in undergoing multicomponent coupling reactions. In addition, stereodirecting ability of the stereogenic center present on this carbocycle, combined with the high functional group density displayed over the five-carbon cyclic skeleton attracted the attention of various research groups to utilize 4-HCP as a building block in the synthesis of complex natural products.

Corey's group reported enantioselective synthesis of pentacycloanammoxic acid, a highly strained and naturally occurring fatty acid from the anaerobic microbes *Candidatus brocadia anammoxidans*.[24] The enone (*R*)-**1.4.3** was converted to 4-silyl-substituted cyclopentenone (*R*)-**1.16.1** in three steps involving conjugate addition, desilylation followed by dehydration. The key reaction in the synthesis was a

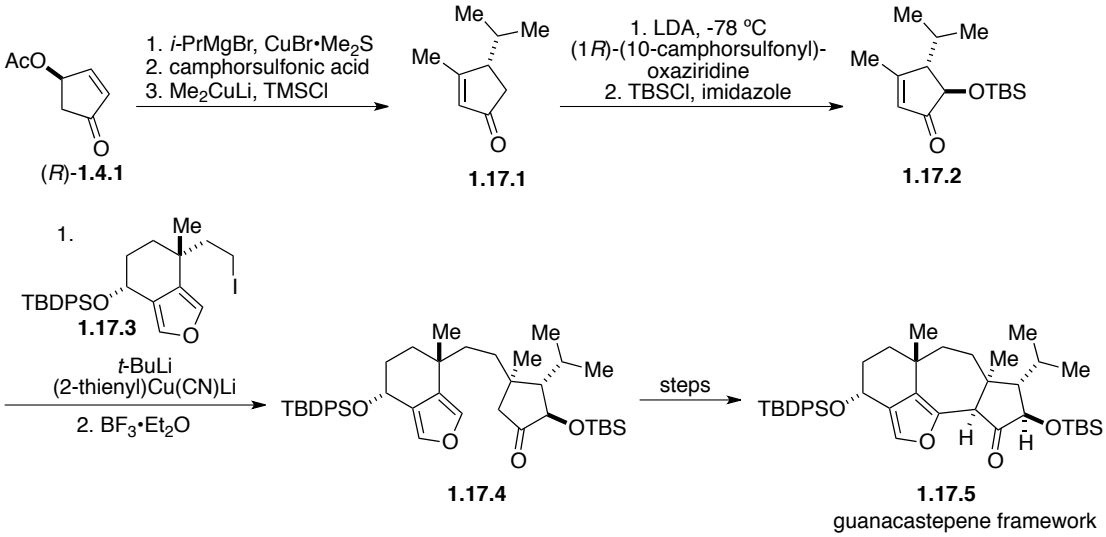
stereoselective [2+2] photochemical cycloaddition of (*R*)-**1.16.1** with the cyclobutene **1.16.2** to obtain cyclopentanone adduct **1.16.3** in high enantiopurity, which was further transformed to desilylated cyclopentanone **1.16.4** in four steps. **1.16.4** was subjected to α-diazoketone formation followed by photoinduced Wolff ring contraction and ester hydrolysis to produce carboxylic acid **1.16.5**. Further homologation using the Wittig chemistry produced (+)-pentacycloanammoxic acid (*R*)-**1.16.6**.



Scheme 1.16. Corey's synthesis of (+)-pentacycloanammoxic acid

Trauner's group reported the synthesis of the tricyclic framework found in the guanacastepene family of natural products.[25] One of the key precursors, a trisubstituted enone **1.17.2**, was generated from 4(*R*)-*O*-acetyl-2-cyclopentenone in six steps. The synthesis involved a conjugate addition of a cuprate followed by acid-promoted elimination of the acetate. A second conjugate addition of methylcuprate in the presence of TMSCl followed by Saegusa oxidation of the TMS enolate provided the intermediate

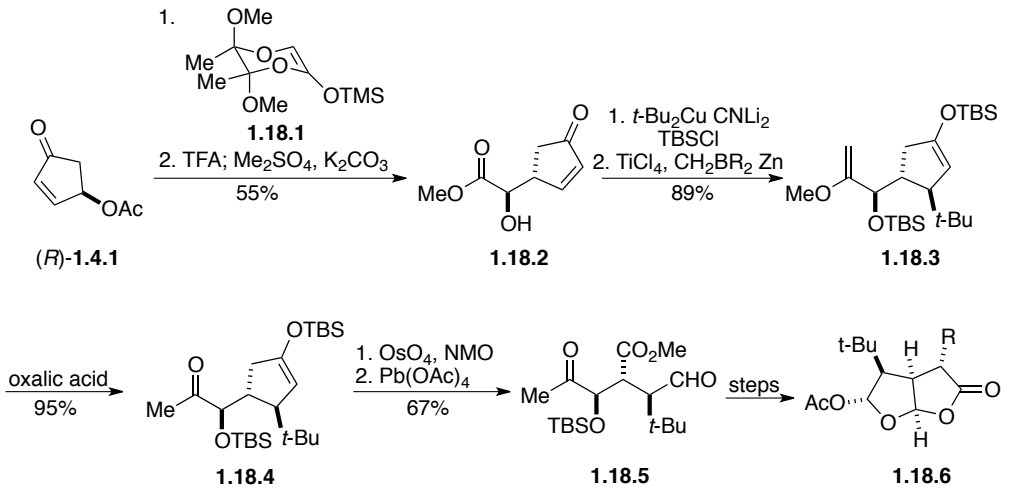
1.17.1, which was further transformed to **1.17.2** in two steps. The trisubstituted enone **1.17.2** was reacted with iodo compound through a challenging cuprate conjugate addition in the presence of a Lewis acid (Scheme 1.17).



Scheme 1.17. Trauner's synthesis of guanacastepene framework

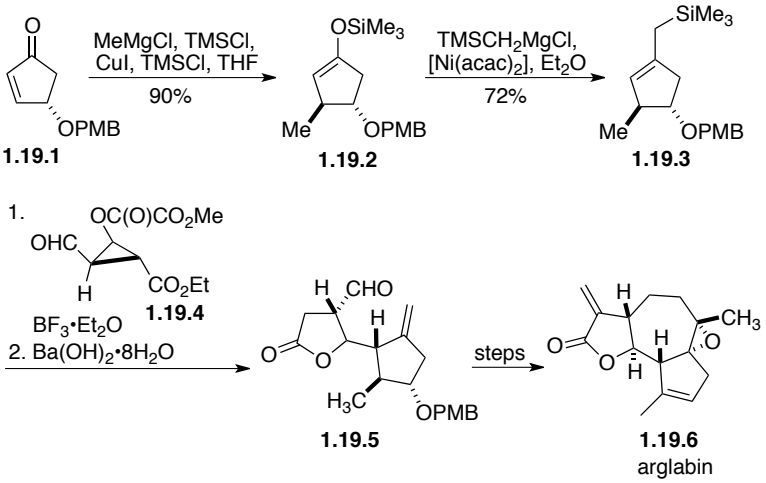
Overman's group reported the synthesis of a spongian diterpene marine natural product (Scheme 1.18).[26] They employed 4(*R*)-*O*-acetyl-hydroxy cyclopentenone (*R*)-**1.4.1** to obtain a tricarbonyl intermediate **1.18.5** in six steps. The synthesis started with combining 4(*R*)-**1.4.1** with silyl ketene acetal **1.18.1** to afford a cyclopentenone that was subjected to acidic cleavage of diacetal group. Methylation with dimethylsulfate to obtain the α-hydroxy ester **1.18.2** in 55% yield. The addition of the *tert*-butylcuprate reagent to **1.18.2** in the presence of TBSCl led to *trans*-substituted cyclopentenyl silyl ether, which was subjected to Takai methylation to produce methyl enol ether **1.18.3**. Treatment of **1.18.3** with oxalic acid led to selective cleavage of methyl enol ether to provide ketone **1.18.4**. The oxidation of silyl enol group in **1.18.4** with OsO_4 and followed by treatment

with $Pb(OAc)_4$ in methanol, formed tricarbonyl intermediate **1.18.5,** which was further transformed to spongian diterpene **1.18.6**.



Scheme 1.18. Overman's synthesis of spongian diterpenes

Recently Reiser's group reported an enantioselective synthesis of the guaianolide arglabin via a copper(I)-catalyzed asymmetric cyclopropanation (Scheme 1.19).[27] Methyl cuprate addition to OPMB protected enone **1.19.1** provided *trans* substituted silyl enol ether **1.19.2** that was subjected to Ni(II)-catalyzed cross coupling with trimethylsilylmethylenemagnesium chloride to obtain **1.19.3**. Lewis acid mediated Sakurai addition of the silane **1.19.3** to the aldehyde carbonyl group of **1.19.4** followed by exposure to basic conditions resulted in hydrolysis of oxalic ester, cyclopropane ring opening and lactonization in the same pot to give bicyclic lactone **1.19.5** as a single stereoisomer that was further transformed to arglabin.



Scheme 1.19. Total synthesis of arglabin

1.5. Results and discussion

As discussed in the previous section, several methods are known for the preparation of optically enriched *O*-protected-4-hydroxycyclopentenone. One of the most efficient routes, in terms of overall yield and enantiopurity is via enzymatic desymmetrizataion developed by Deardorffs's group that provides enone (*S*)-**1.4.3** in seven-steps (see Schemes 1.5 to Schemes 1.7).[12,15,28] To obtain the enone (*R*)-**1.4.3** it requires either seven-step synthesis[15] that include a germ lipase catalyzed acetate hydrolysis that consumes ten days (Scheme 1.7); or a nine-step route[16] that requires switching of the acetate function with pivolyl group (see Scheme 1.8). The acetate to silyl ether conversion is significant considering its applications in the synthesis. This is because a silyl group can be removed selectively under milder conditions than an acetate or other ester groups, and without the risk of undesired side reactions that may occur under the conditions required for the removal of such groups.

Also, it is worth noting that majority of the available methods to procure 4-*O*-protected hydroxy-cyclopentenones install the acetate group first that is later transformed to *O*-silyl group by additional synthetic steps. Only method which leads to a silyl protected hydroxy cyclopentenone without the intermediacy of an acetate function is the Jacobson's enantioselective chromium-salen-catalyzed opening of the *meso*-epoxide with TMS-azide (see Scheme 1.12).[21] Though Jacobson's method provides the TMS-protected enone in high yield and optical purity, it suffers from two major drawbacks: first, it requires the elimination of an equivalent amount of hydrazoic acid to form the desired enone, hence not suitable for large scale synthesis of 4-HCPs because of the hazardous by-product formation, and second, TMS protected HCPs have not found much interest from synthetic chemists because of the high acid and base sensitivity of the OTMS group.

Aube group has utilized 4-HCP in the past in context with the total synthesis projects[21] and synthesized the required HCPs by the Deardorff protocol. Considering the diverse synthetic applications of HCPs, we aimed to develop an alternative approach toward the synthesis of enantioenriched 4-HCPs with the following features:

1. A concise route involving a non-enzymatic catalytic means of introducing asymmetry, that would help to minimize the solvent waste generated in the process. The enzymatic routes in current practice generate copious amounts of the solvent waste beacause of the extensive solvet extraction required to procure the product.
2. A stereodivergent route that should provide equal access to either of the enantiomers of 4-HCP.
3. A flexible route toward the synthesis 4-HCP with different protecting groups without adding additional synthetic steps.

In considering the enzymatic route (Figure 1.4a), we noted that it involves two stereocontrolled steps: (1) the synthesis of *meso*-diacetate **1.4B** (i.e., only cis and not trans) that is generally accomplished from cyclopentadiene by $^1O_2$ chemistry or by epoxidation, followed by acetolysis of a derived π-allyl species[29] and (2) the enzyme-controlled enantioselective hydrolysis to obtain mono acetate **1.4C**.[12] In contrast, the corresponding *trans*-diol **1.4F** (Figure 1.4b) would no longer have planar symmetry but instead be a chiral, C_2-symmetric molecule. Thus, it would no longer be necessary to differentiate the two identical alcohol groups in future steps. Moreover, we felt that it would be possible to readily prepare diol **1.4F** using the known asymmetric conversion of diketone **1.4D** to diol **1.4E**,[11] followed by ring-closing metathesis. Thus, only a single stereoselective reaction would be required in the entire synthesis.

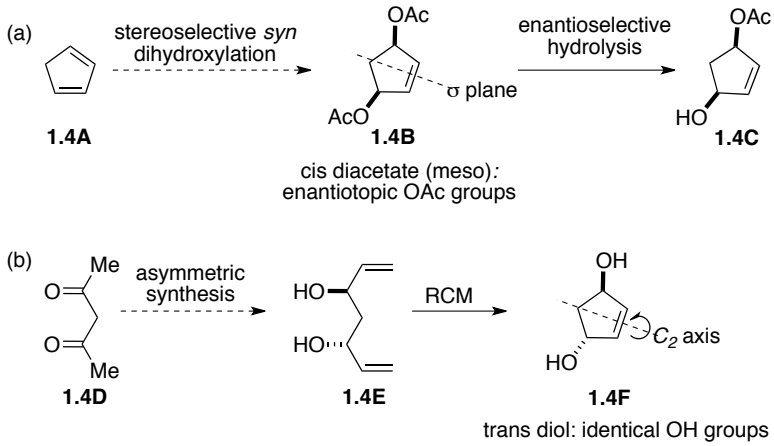
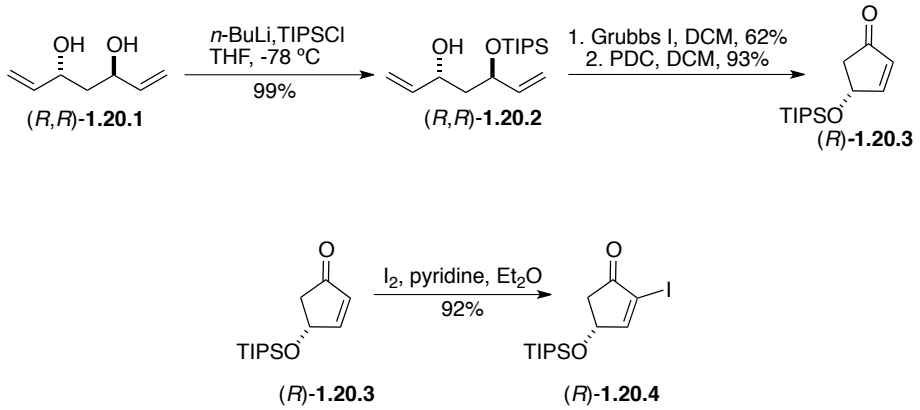


Figure 1.4. Stereochemical analysis of the enzymatic route

To realize this goal, earlier efforts by Angelica Meyer, a former graduate student in Aube group led to the development of a route towards the synthesis of TIPS-protected 4-hydroxy-2-cyclopenten-1-one (HCP).[30] She developed a route for the synthesis of

enone (*R*)-**1.20.3** via mono-TIPS protection of the C_2-symmetric diol (*R,R*)-**1.20.1** followed by ring-closing metathesis. She synthesized and employed the corresponding iodo derivative (*R*)-**1.20.4** in her efforts towards the asymmetric synthesis of cylindricine C.



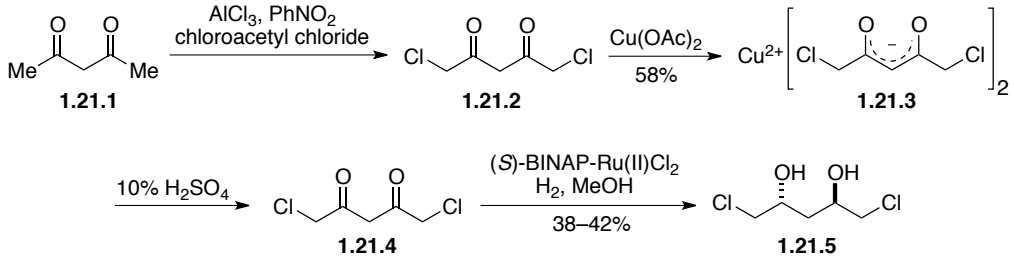
Scheme 1.20. Synthesis of (*R*)-4-hydroxy-2-cyclopentenone by Angelica Meyer

Our goal in the present work was to develop this route for the HCP synthesis with different protecting groups of wide range of chemical nature and to determine the enantiomeric ratio of the resulting enone product by using a suitable analytical technique. In the current work, we also showed the utility of this route to access either of the enantiomers of the enone. Further, a few synthetic applications of the trans diol (Figure 1.4) have been shown highlighting the utility of these intermediates in undergoing stereospecific transformations.

1.5.1. **Synthesis of (*3R, 5R*)-hepta-1,6-diene-3,5-diol**

Commercially available acetyl acetone was converted to 1,5-dichlorodione using the previously reported procedure (Scheme 1.21).[31,32] Thus, addition of acetyl acetone in a

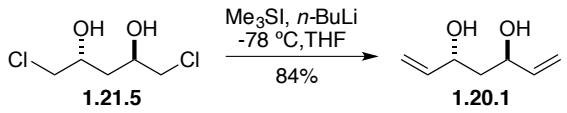
mixture of $AlCl_3$ and chloroacetyl chloride in nitrobenzene followed by distillation provided 1,5-dichlorodione **1.21.2** as a clear liquid. Dichlorodione **1.21.2** is an unstable compound that turns into a dark solid on standing at room temperature. It was converted to copper bis(dichloroacetylacetonate) **1.21.3** by treating with copper (II) acetate resulting in a light green solid that can be safely stored at room temperature for several weeks. We prepared up to 56 g of the copper salt **1.21.3** by following the method reported in the journal of *Organic Syntheses*.[31] The copper salt was converted to the corresponding dichlorodione just before performing the following hydrogenation step on treatment with aq sulfuric acid (10%). Hydrogenation of dichlorodione **1.21.2** was performed in the presence of 0.25 mol% (*S*)-BINAP-Ru(II)Cl_2 in methanol at 1200 psi at 80ºC. (*R*,*R*)-Dichlorodiol **1.21.4** was obtained in 38-40% yield by crystallization from 2:1 mixture of hexane/dichloromethane. Although we could reproduce the 40% yield of this reaction as reported by Rychnovski,[31] others have reported yield up to 68% by using modified version of the ruthenium catalyst.[33]



Scheme 1.21. Preparation of *(2R, 4R)*-1,5-dichloro-2,4-pentanediol

We used Hanson's method to convert dichlorodiol **1.21.5** to diene diol **1.20.1** (Scheme 1.22).[34] Treatment of (*R*,*R*)-dichlorodiol **1.21.5** with 10 eq of the sulphur ylide

generated by treating trimethylsulfonium iodide with *n*-butyl lithium at -30 ºC provided (3*R*,5*R*)-diene diol **1.20.1** (Scheme 1.22). It was important in this reaction to use freshly prepared trimethylsulfonium salt obtained by mixing an equimolar ratio of dimethyl sulfide and methyl iodide. The salt was recrystallized from ethanol and was dried for 24 hours under high vacuum before use.

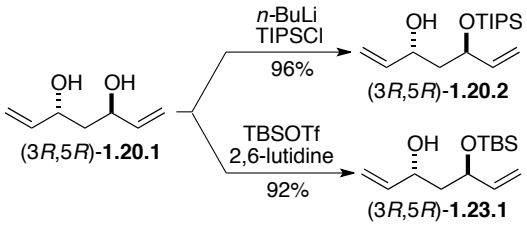


Scheme 1.22. Synthesis of *(3R,5R)*-hepta-1,6-diene-3,5-diol

Having prepared the required diene diol, our next objective was to derivatize it with suitable protecting groups. We chose TBS, 4-methoxy-benzyl, and acetate functional groups for further derivatization. We chose protecting groups according to their diverse chemical sensitivity and applications found in the literature.

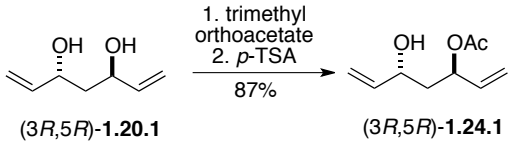
1.5.2. **Synthesis of mono-protected diols**

Mono TIPS protection of **1.20.1** was performed as previously reported by Angelica Meyer (Scheme 1.23).[30] Treatment of the diene diol with *n*-BuLi followed by the addition of TIPSCl at -78 ºC generated OTIPS protected diol **1.20.2** in 96% yield. TBS protection was tried under similar conditions (by employing TBSCl in place of TIPSCl) however only starting material was observed, presumably because of the extremely hydroscopic nature of the solid TBSCl reagent Ultimately, the OTBS product **1.23.1** was obtained in 92% yield by using TBSOTf and 2,6-lutidine at -78 ºC.



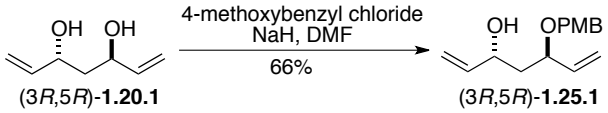
Scheme 1.23. Monosilylation of (3*R*,5*R*)-diol **1.21.1**

Acetate protection of the (3*R*,5*R*)-diol **1.20.1** using triethylamine acetyl chloride provided mono acetate compound only in 10% yield. The addition of DMAP led to a mixture of mono and diprotected products. Finally, the monoprotected acetate was obtained in 84% yield by treating diol with trimethyl orthoactetate followed by stirring in *p*-TSA in methanol (Scheme 1.24).



Scheme 1.24. Mono acylation of (3*R*,5*R*)-diol **1.20.1**

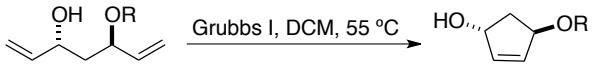
4-Methoxybenzyl protection was tried using freshly prepared 4-methoxybenzyl trichloroimidate. However, it led to a mixture of mono- and diprotected products. Finally monobenzylated product **1.25.1** was obtained in 66% yield by using NaH and PMBCl in DMF.



Scheme 1.25. 4-Methoxybenzyl protection of (3*R*,5*R*)-diol **1.21**

1.5.3. Synthesis of cyclopentene diol and enones

Ring-closing metathesis of diene diol **1.20.2** was performed with both Grubbs I[35] or Grubbs II[36] (2–3 mol%) in DCM and provided 49–53% yield in 24 h at room temperature. Increasing the catalyst loading or dilutions did not improve the reaction yields. The optimum yield was obtained by performing the reaction at 50 ºC using 3 mol% of Grubbs I catalyst. Other mono-protected dienes were subjected to RCM using Grubbs I to obtain the cyclized products in 88-92% yield (Scheme 1.26).

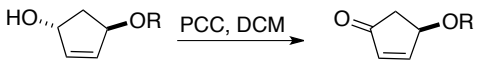


starting	R	product	yield
1.20.2	TIPS	**1.26.1**	88%
1.23.1	TBS	**1.4.5**	92%
1.24.1	Ac	**1.3.3**	87%
1.25.1	PMB	**1.26.2**	87%

Scheme 1.26. Synthesis of cyclopentenols via ring-closing methathesis (RCM)

Finally, oxidation of the cyclopentenols with pyridinium chlorochromate provided the targeted *O*-protected-4-hydroxy-2-cyclopentenones in excellent yields (Scheme 1.27). The enantiomeric ratios of the products **1.20.3**, **1.4.3** and **1.4.1** were determined by chiral gas chromatography (GC) by using Astec Chiraldex B-DM fused silica column. The OPMB protected enone **1.27.1** could not be analytically resolved after several attempts

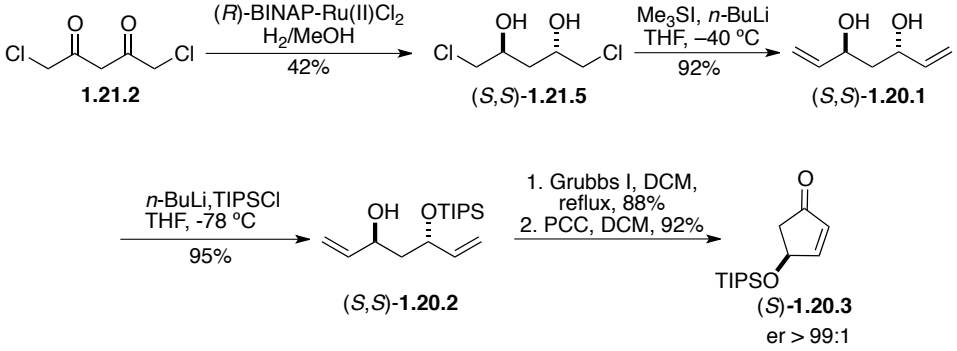
using chiral gas chromatography. Finally, the enantiomeric ratio of the OPMB enone **1.27.1** was determined by high pressure liquid chromatography (HPLC) method by developing suitable conditions on CHIRALPAK IC column.



starting	R	product	yield
1.26.1	TIPS	**1.20.3**	88%
1.4.5	TBS	**1.4.3**	92%
1.3.3	Ac	**1.4.1**	87%
1.26.2	PMB	**1.27.1**	87%

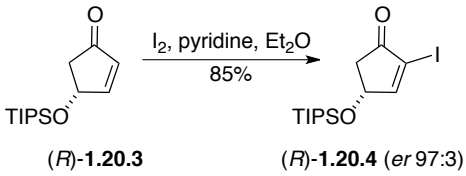
Scheme 1.27. Synthesis of 4(*R*)-*O*-protected-hydroxycyclopentenones

This route can be adopted for the synthesis of (*S*)-**1.27.1** by simply using (*R*)-BINAP in the hydrogenation step (Scheme 1.28). Besides no longer requiring different schemes for preparing the two enantiomers, the present route proceeds in acceptable overall yields from commercially available starting materials (26–32%) and compares favourably in number of steps compared to other methods (5 steps from **1.21.2** to either (*R*)- or (*S*)-**1.27.1** as opposed to 9 steps by enzymatic routes discussed above).



Scheme 1.28. Synthesis of (*S*)-4-*O*-TIPS-cyclopentenone

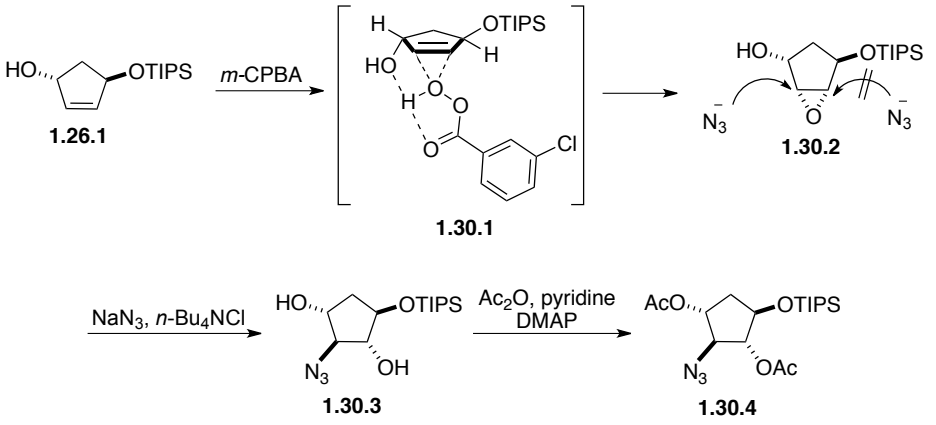
Another useful 4-HCP is the α-iodo derivative of enone **1.29.1**, which has found applications in the synthesis of prostaglandins (see Scheme 1.14).[23] Thus, we transformed both (*R*)- and (*S*)-**1.20.3** into iodides (*R*)- and (*S*)-**1.29.1** following a previously reported procedure[13] as shown in Scheme 1.27.



Scheme 1.29. Iodination of enone **1.20.4**

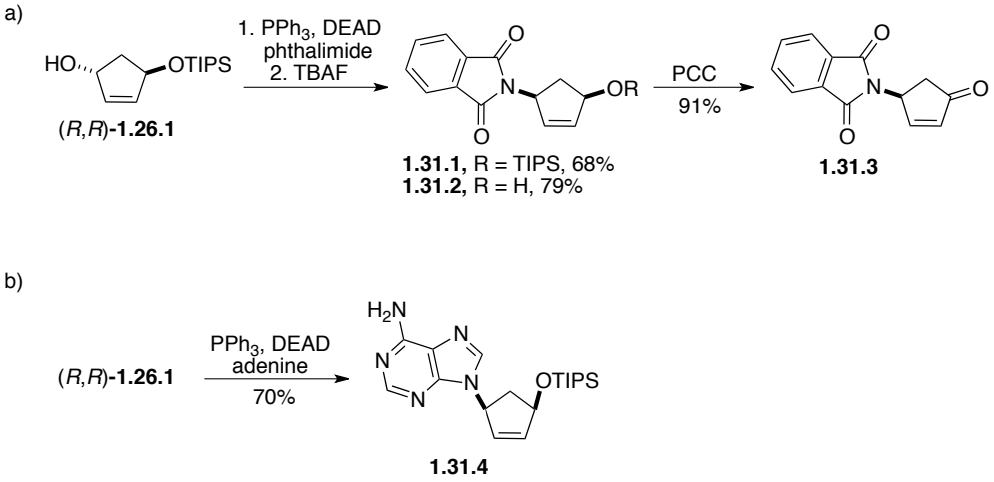
1.5.4. Derivatives of HCP

Just as 4-HCPs have been broadly employed in synthesis, the reduced alcohol precursor introduced herein should be of comparable utility. We have synthesized a few derivatives of the allylic alcohol **1.26.1**. Thus, epoxidation of allylic alcohol **1.26.1** provided **1.30.2** exclusively in 66% yield (likely due to a reinforcing combination of Henbest-like delivery of peracid and avoidance of the large OTIPS group[37]). Epoxide opening occurred regioselectively with sodium azide to provide the highly substituted cyclopentane **1.30.2** in 69% yield. The stereo- and regiochemistry of the product **1.30.3** was confirmed by 2D NMR analysis of the corresponding diacetylated compound **1.30.4**.



Scheme 1.30. Stereo and regioselective synthesis of azido derivatives of cyclopentane

In addition, amino-substituted cyclopentene derivatives were made using simple displacement chemistry (Scheme 1.31). Mitsunobu displacement of the allylic alcohol **1.26.1** with phthalimide gave **1.31.1** in 68% yield. Further subjecting to silyl deprotection with TBAF followed by PCC oxidation provided the 4-amino substituted enone **1.31.3** via the alcohol intermediate **1.31.2**. Displacement of allylic alcohol **1.26.1** with adenine under Mitsunobu conditions led to the 1,4-syn-disubstituted cyclopentene **1.31.4** in 70% yield.



Scheme 1.31. Cycopentene derivatives via Mitsunobu displacement

In summary, we have demonstrated a convenient synthesis of 4-HCPs, an important class of privileged building blocks for organic synthesis. The route is scalable to >4 g scale of the diol intermediate **1.26.1** and provides access to either enantiomeric series of 4-HCPs using the identical route. Also this method falls in the category of few known methods capable of providing silylated enones in excellent optical purities without the intermediacy of an acetate group. This approach can be used to obtain the 4-HCPs with different protecting groups in six steps from the commercially available acetylacetone using the identical route.

Chapter 2

Development of a Stereodivergent Approach Toward the Synthesis of 3,5-Dihydroxy Six-Membered Carbo- and Heterocyclic Rings

2.1. Introduction

1,3-Cyclohexanediol and 3,5-dihydroxy piperidine structural motifs are present in numerous complex natural products (Figure 2.1). Many of these natural products are biologically active. For example, 1α,25-dihydroxy D_3 (**2.1G**), a major metabolite of vitamin D_3, have wide range of biological activities including mineral homeostasis, cellular differentiation and proliferation, angiogenesis, and apoptosis.[38,39] 7-Deoxy-6-epi-castanospermine (**2.1H**), a trihydroxy indozolidine is an inhibitor of amyloglucosidase.[40] Alkaloid **2.1E** is a competitive inhibitor of α-D-glucosidase, which blocks the processing of *N*-linked glycoproteins. Polyhydroxy nortropane alkaloids calystegine B_3 (**2.1I**) and A_7 (**2.1J**) and related alkaloids of this class show potent inhibitory activity against *β*-glucosidase and galactosidase.[41]

The interesting biological properties of these natural products have inspired many to utilize polyhydroxylated diols or piperidine structural motifs for the development of new molecules of pharmaceutical or biomedical applications. Polyhydroxylated piperidines, also called iminosugars, have recently received much interest as glycosidase inhibitors with applications in the treatment of cancer and AIDS.[42] More specifically, 3,5-dihydroxy piperidines, which are deoxy analogs of imino sugars, are substructures in compounds active in the treatment of Alzheimer's disease[43] and schizophrenia.[44,45] Figure 2.2 shows examples of the compounds containing 1,3-cyclic diol moieties, which have

been reported for diverse range of biological activities. For example, salacinol-containing alditols glycosidase inhibitors (**2.2E**) as antidiabetic agents,[46] and fused tricyclic

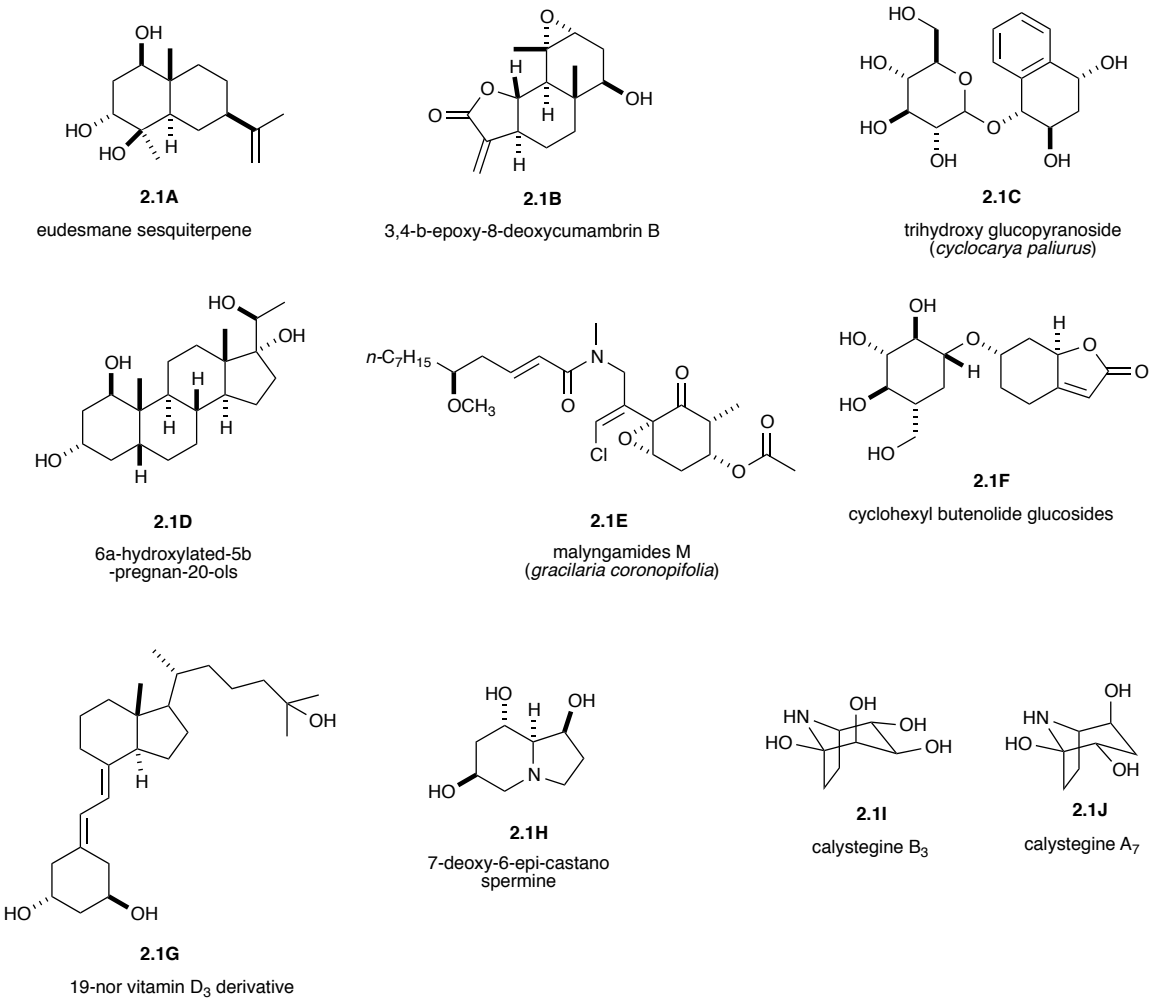


Figure 2.1. Examples of natural product structures containing a 1,3-cyclohexanediol or 3,5-dihydroxy piperidine motif

carbamates (**2.2F**) containing thienopyrimidinedione (**2.2A**) as ACC (acetyl-coA carboxylase) inhibitors[47], furopyrimidines (**2.2B**) as antihypertensive agents[48] and aryl alcohol compounds (**2.2C**) as plasminogen activator therapeutic agents for HIV patients[49] have been reported. Piperidine or tetrahydropyran based phosphatidyl inositol mimics (**2.2D)** have been reported as inhibitors of LPS-induced cytokine production and are

potent anti-inflammatory agents.[50] The presence of six-membered cyclic 1,3-diol motif in several natural and synthetic compounds of biological interest makes these attractive targets for synthesis. The following section provides a survey of the existing synthetic approaches for the synthesis of cyclohexane diols and dihydroxypiperidines.

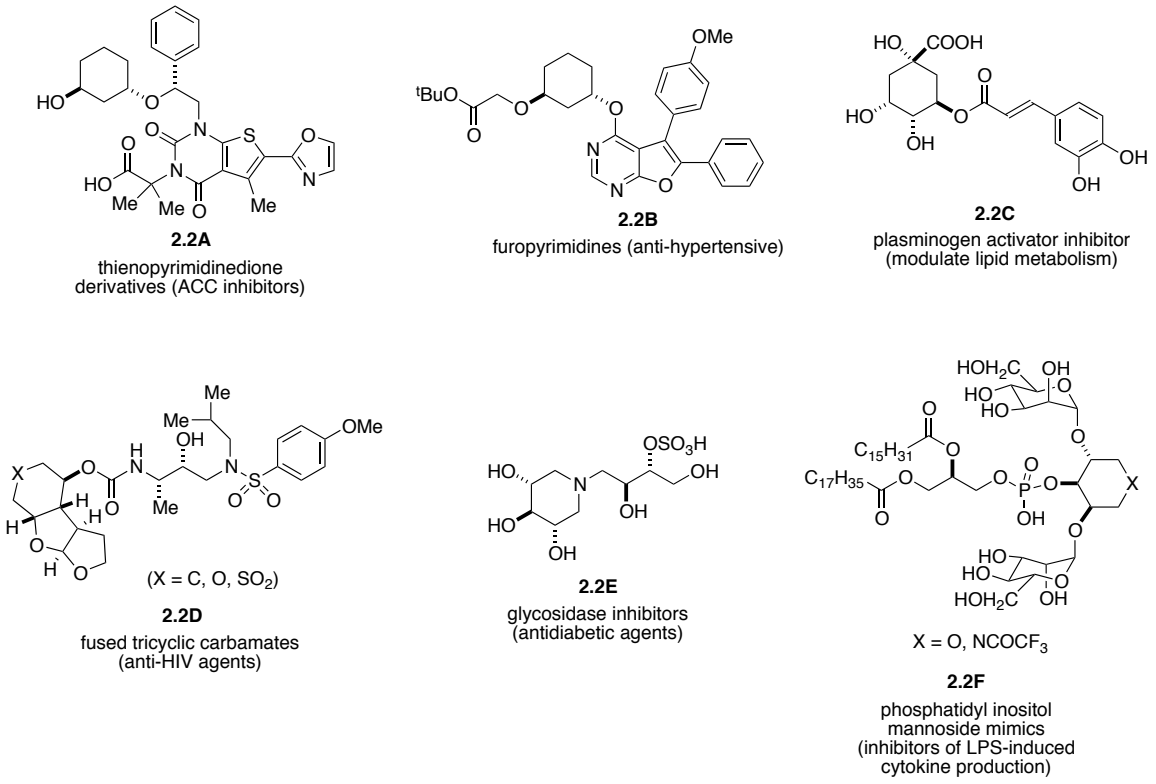


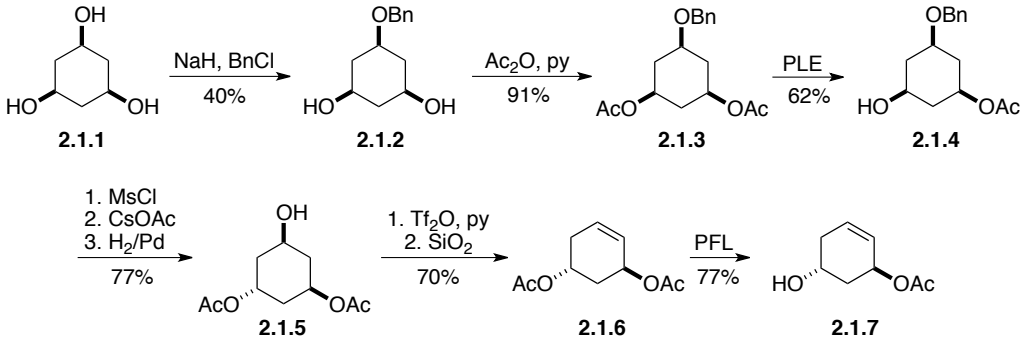
Figure 2.2. Synthetic compounds of therapeutic importance containing six-membered carbo- or heterocyclic-1,3-diol motif

2.2. Synthesis and applications of cyclohexane-1,3-diols

1,3-Cyclohexanediols are attractive targets for synthesis because of their presence in important natural product structures and biologically important molecules. Different approaches for diastereo- and enantioselective synthesis of 1,3-cyclohexanediols and their derivatives have been developed; however, they suffer from moderate yields and

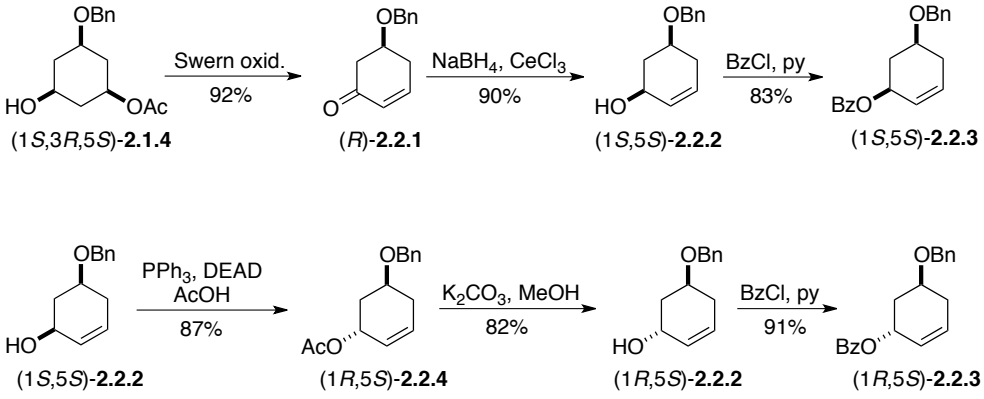
low selectivity.[51–54] A few examples of desymmetrization of cis-1,3-cyclohexanediol using enzymatic resolution have previously been reported.[55–59]

In 1990, Suemune group reported a nine-step synthesis of *trans*-(*R*,*R*)-cyclohexene diol **2.1.7** via enzymatic desymmetrization (Scheme 2.1).[58] They performed the benzylation of commercially available *cis*-phloroglucitol **2.1.1** ($73 for 1 g from Sigma) with sodium hydride and benzyl chloride to obtain **2.1.2** as a monobenzylated product in 40% yield. Subsequent diacetylation of **2.1.2** provided the *meso* diacetate product **2.1.3** in 91% yield. Porcine liver esterase (PLE)-catalyzed hydrolysis of diacetate **2.1.3** produced desymmetrized monoacetate **2.1.4** in 62% yield and 87% *ee*. The inversion of the alcohol stereocenter in **2.1.4** via mesylation and elimination, followed by hydrogenation produced **2.1.5** in 77% yield over three steps. Triflate formation followed by silica gel mediated elimination resulted in diacetate **2.1.6** in 70% yield. Finally, *Pseudomonas fluorescens* lipase (PFL)-catalyzed hydrolysis of the diacetate **2.1.6** produced mono acetate **2.1.7** in 77% yield.



Scheme 2.1. Suemune's approach toward the synthesis of cyclohexane-1,3-diol

Later, in 1992, Suemune group reported the synthesis of both *cis*-(1*S*,5*S*)-**2.2.3** and *trans*-1*R*,5*S*)-**2.2.3** cyclohexane-1,3-diols by utilizing enantioenriched triol (1*S*,3*R*,5*S*)-**2.1.4** (Scheme 2.2).[59] The trihydroxy compound **2.1.4** was subjected to Swern oxidation. Oxidation of the hydroxyl function as well as acetate elimination under the Swern oxidation conditions produced the enone **2.2.1** in 92% yield. Reduction of the ketone function in **2.2.1** with sodium borohydride produced the syn dihydroxy compound **2.2.2** in 90% yield. Treatment of **2.2.2** with benzoyl chloride in pyridine provided the (1*S*,5*S*)-diol derivative **2.2.3** in 83% yield. Mitsunobu inversion of the alcohol stereocenter in (1*S*,5*S*)-**2.2.2** with acetic acid as nucleophile formed the acetylated product (1*R*,5*S*)-**2.2.4** that was hydrolyzed to produce mono-benzylated *trans*-diol (1*R*,5*S*)-**2.2.2**. Subsequent benzoylation resulted in enantioenriched (1*R*,5*S*)-**2.2.3** in 91% yield.

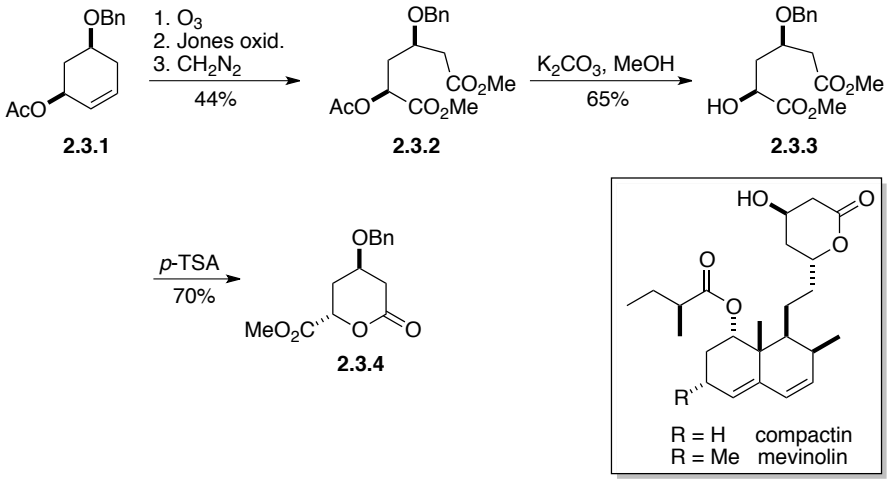


Scheme 2.2. Suemune's synthesis of enantioenriched *cis* and *trans*-cyclohexene-1,3-diols

They further applied these newly developed cyclohexanediol building blocks for the synthesis of lactone moiety of compactin (Scheme 2.3a) and toward a formal synthesis of quinic acid (Scheme 2.3b).[59] Compactin and mevinolin are potent competitive inhibitors

of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase, the rate-limiting enzyme in cholesterol biosynthesis. The Suemune group prepared the compactin lactone in five steps from **2.3.1** that was obtained by the above-described route. Ozonolysis of the cyclohexene diol **2.3.1**, Jones oxidation and esterification with diazomethane produced diester **2.3.2** in 44% yield over three steps. Diester **2.3.2** was hydrolyzed using potassium carbonate in methanol and was subjected to acid-catalyzed lactonization to afford the desired lactone product **2.3.4**. For the synthesis of quinic acid they utilized a trans diol (1*R*,5*S*)-**2.3.1**.[59] The synthesis started with the diastereoselective epoxidation of the diol **2.3.1** with *m*-CPBA to produce epoxide **2.3.5** as a single diastereomer. Epoxide opening of **2.3.5** with acetic acid followed by acetylation produced the triacetate **2.3.6**. Palladium-catalyzed hydrogenation followed by ruthenium-mediated oxidation afforded the trihydroxy ketone **2.3.8**, an advanced intermediate for quinic acid synthesis.

a)



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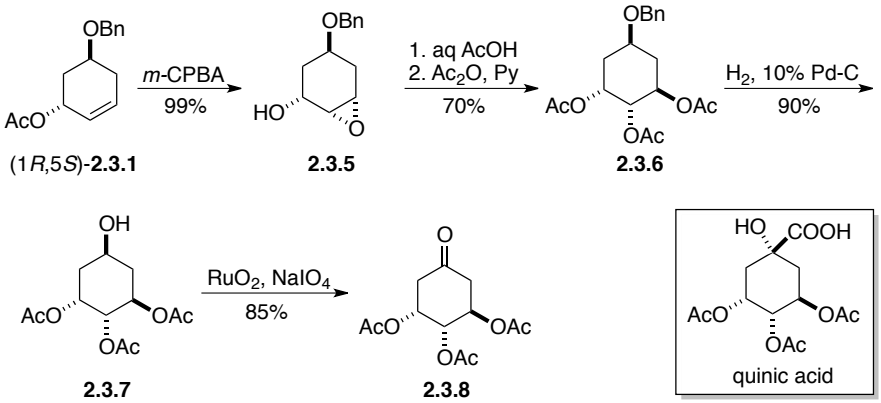
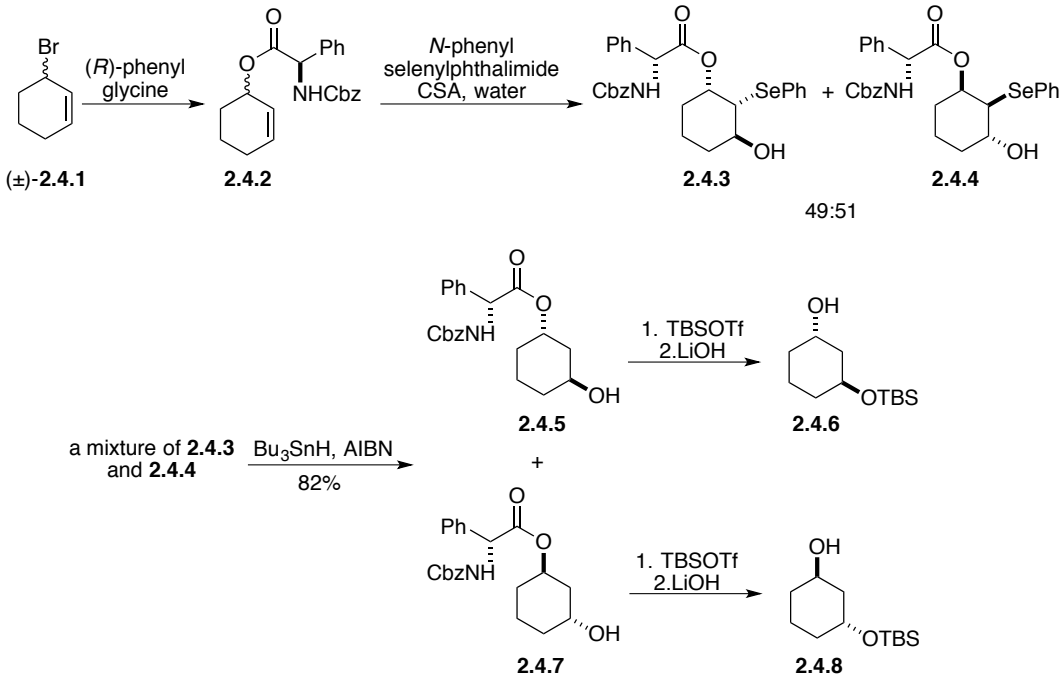


Scheme 2.3. Applications of cyclohexanediols toward, a) the synthesis of compactin lactone b) formal synthesis of quinic acid

In 2007, Sweeney's group reported a chiral pool approach toward the synthesis of enantioenriched 1,3-cyclohexanediols. They prepared both (*R*,*R*)- and (*S*,*S*)-cyclohexanediols via regio- and diastereospecific hydroxyselenation of cyclohex-2-enyl phenylglycinates.[60] Racemic allylic bromide **2.4.1** was treated with DBU and (*R*)-phenylglycinate to produce 1:1 diastereometric mixture of the ester **2.4.2**. The key step in

this approach was the regioselective hydroxyselenylation of **2.4.2** with N-phenylselenylphthalimide and camphorsulfonic acid (CSA) to produce inseparable diastereomeric mixture of **2.4.3** and **2.4.4**. They proposed that a hydrogen bonding interaction of the selenylphthalimide electrophile with the glycinate moiety directed the incoming electrophile to the syn face of the olefin **2.3A** (Fig 2.3) resulting in selenium ion **2.3B**, which is opened by the hydroxyl nucleophile regioselectively by an axial attack. Subjecting **2.4.3** and **2.4.4** mixture to deselenylating conditions produced the trans diols **2.4.5** and **2.4.7,** which were separated by column chromatography. The isolated diastereomers **2.4.5** and **2.4.7** were converted to monosilylated products (*S*,*S*)-**2.4.6** and (*R*,*R*)-**2.4.8**, respectively.



Scheme 2.4. Sweeney's approach toward the synthesis of 1,3-cyclohexanediol

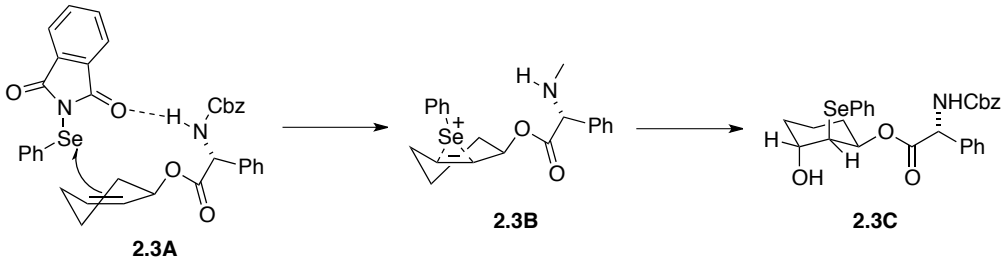
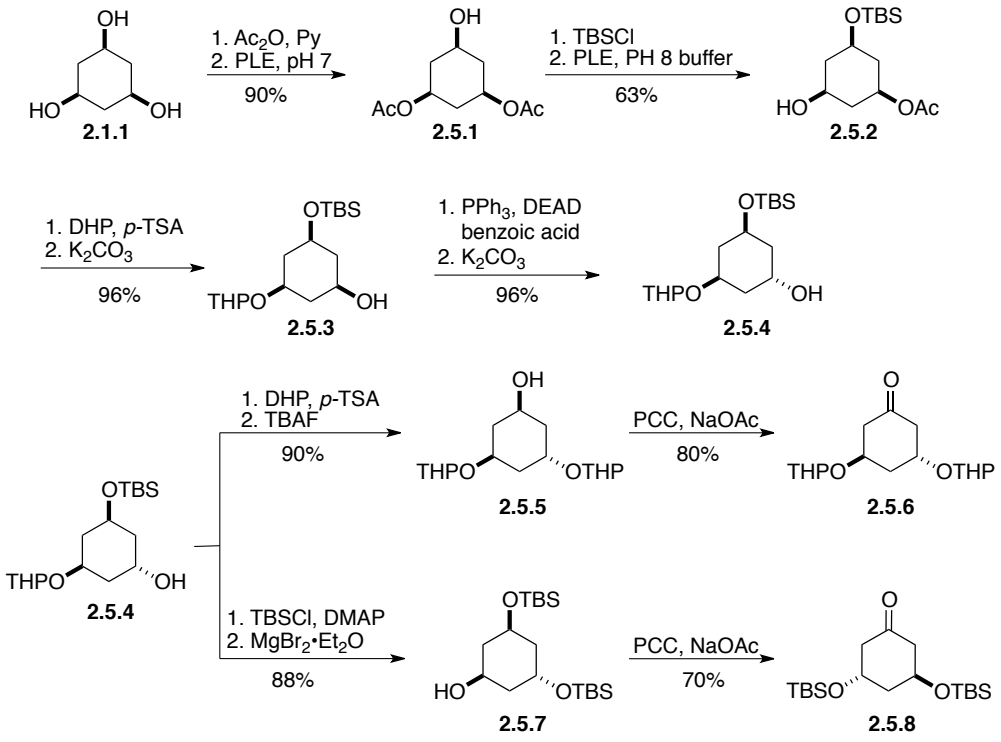


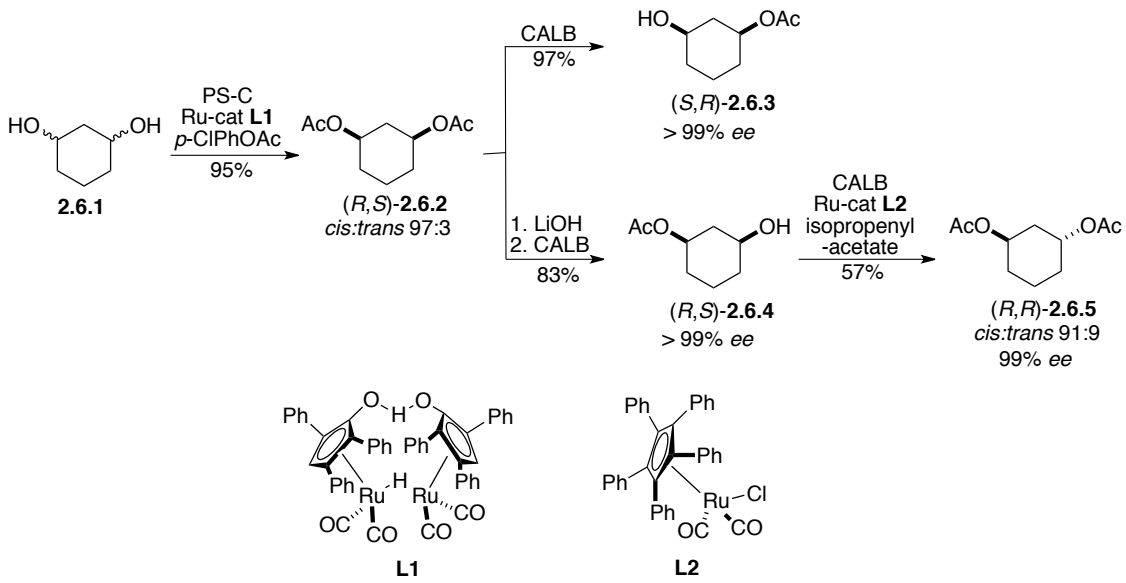
Figure 2.3. Mechanistic rationale for diastereo- and regioselective hydroxyselenylation

In 2001, Kalkote group reported an enzymatic synthesis of both enantiomers of diprotected *trans*-3,5-dihydroxy-1-cyclohexanone starting from phloroglucitol **2.1.1**.[61] Triacetylation of **2.1.1** followed by enzyme-mediated hydrolysis afforded the diacetate compound **2.5.1**. Silylation of **2.5.1** using TBSCl followed by PLE catalyzed desymmetrization provided the enantioenriched monoacetate product **2.5.2**. THP protection of the **2.5.2** and subsequent basic hydrolysis formed the alcohol **2.5.3**. The alcohol stereocenter in **2.5.3** was inverted via a Mitsunobu displacement with benzoic acid followed by hydrolysis to obtain **2.5.4**. Compound **2.5.4** bearing two orthogonal protecting groups was used as a common precursor to access both the enantiomers of the diol *trans*-3,5-dihydroxy-1-cyclohexanone. THP protection followed by TBS deprotection produced the pseudo C_2-symmetric cyclohexanol **2.5.5.** Oxidation of the alcohol function provided THP protected *trans*-3*R*,5*R*-dihydroxy-1-cyclohexanone *R*,*R*-**2.5.6**. Alternatively, silyl protection of the hydroxyl group followed by THP deprotection under mildly Lewis acidic conditions formed bis-silylated triol **2.5.7**. Subsequent oxidation with pyridinium chlorochromate (PCC) provided the (*S*,*S*)-**2.5.6**



Scheme 2.5. Kalkote's approach toward the synthesis of enantioenriched 3,5-dihydroxy cyclohexanone

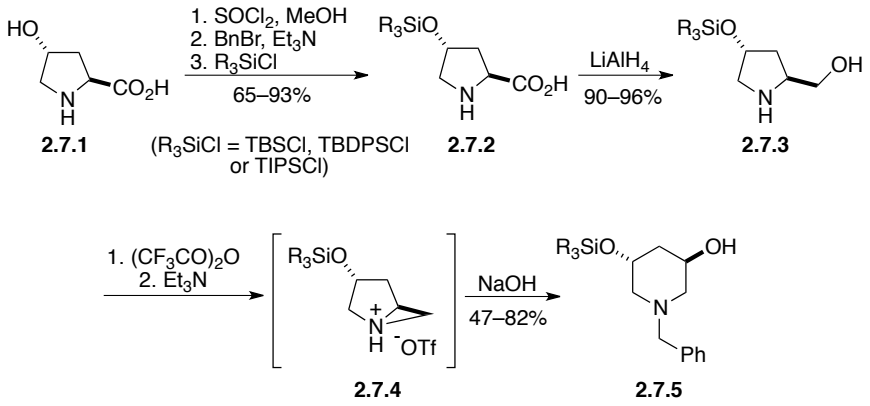
In 2006, Bäckvall's group reported an elegant chemoenzymatic approach for the synthesis of enantioenriched 1,3-cyclohexanediols by enzymatic desymmetrization of an equilibrating mixture of cis and trans cyclohexane-1,3-diols (Scheme 2.6).[62] A cis/trans mixture of 1,3-cyclohexanediol **2.6.1** was converted to *meso* diacetate **2.6.2** by combining ruthenium-catalyzed epimerization with *Pseudomonas cepacia* lipase (PS-C)-mediated acylation. Hydrolysis of the *meso* diacetate **2.6.2** with *Candida antarctica* Lipase B (CALB) produced the enantioenriched *cis* monoacetate (*S*,*R*)-**2.6.3** in 97% yield and >99% *ee*. Hydrolysis of the *cis* diacetate **2.6.2** with lithium hydroxide followed by CALB-catalyzed monoacylation produced the enantiomeric (*R*,*S*)-**2.6.4**. Combining Ru-catalyzed epimerization with CALB-catalyzed transesterification, **2.6.4** was converted to *trans*-diacetate (*R*,*R*)-**2.6.5** in 99% *ee*.



Scheme 2.6. Bäckvall's chemoenzymatic approach toward the synthesis of enantioenriched 1,3-cyclohexanediols

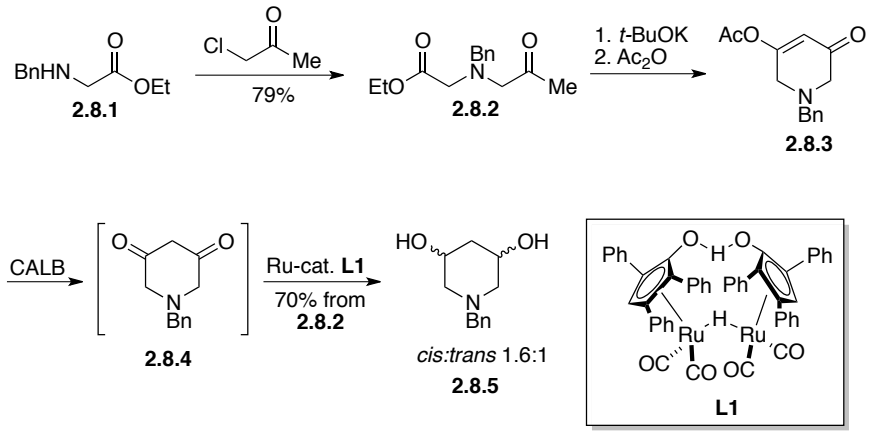
2.2. Synthesis and applications of 3,5-dihydroxy piperidines

In 2006, Cossy's group reported the synthesis of enantioenriched 3,5-dihydroxy piperidine via a ring-expansion approach from 4-hydroxyproline.[63] They developed a seven-step route to obtain *N*-benzyl-3,5-dihydroxy piperidine from 4-hydroxyproline. Hydroxyproline **2.7.1** was converted to silyl-protected hydroxyl proline **2.7.2** in three steps. Subsequent reduction of the carboxylic acid group with LAH produced alcohol **2.7.3** in excellent yield. Activation of the alcohol as triflate followed by treatment with triethylamine produced a [5,3]-bicyclic intermediate **2.7.4** that underwent ring expansion on treatment with sodium hydroxide to produce *N*-benzyl-3,5-dihydroxy-piperdine **2.7.5**.



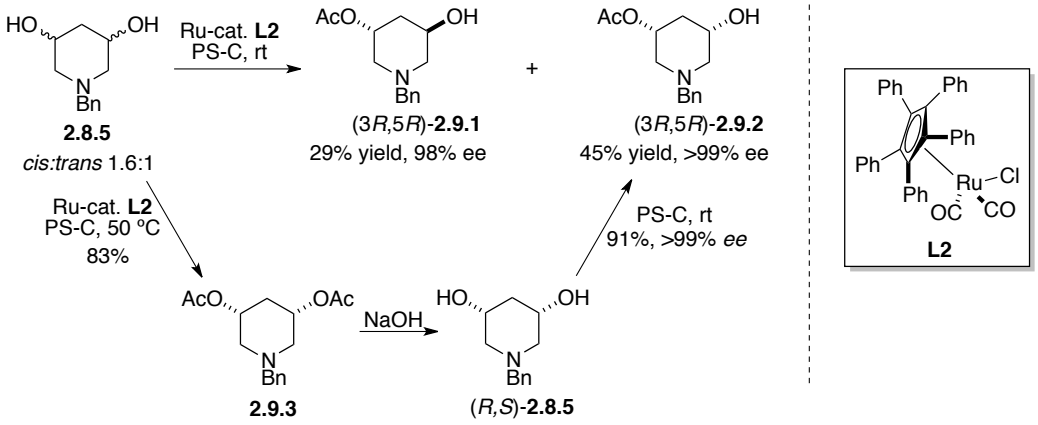
Scheme 2.7. Cossy's ring-expansion approach towards enantioenriched 3,5-dihydroxy piperidines

In 2006, Bäckvall group reported synthesis of both racemic and asymmetric synthesis of 3,5-disubstituted piperidines.[64] They synthesized a cis/trans mixture of 3,5-dihydroxy piperidine from the commercially available *N*-benzylglycinate (Scheme 2.8). The glycinate **2.8.1** was *N*-alkylated with chloroacetone to obtain **2.8.2**. Intramolecular Claisen condensation of **2.8.2** followed by trapping of the enolate with acetic anhydride resulted in *β*-acetoxyenone **2.8.3**. The deacetylation of **2.8.3** with CALB resulted in diketone **2.8.4** that was subjected to ruthenium-catalyzed transfer hydrogenation conditions to obtain cis/trans mixture of **2.8.5** in 70% yield.



Scheme 2.8. Bäckvall's synthesis of racemic 3,5-dihydroxy piperidines

Bäckvall's approach for the synthesis of enantioenriched 3,5-dihydroxypiperidines involved chemoenzymatic dynamic kinetic asymmetric transformation of a racemic cis/trans mixture of 3,5-dihydroxy-piperidines (Scheme 2.9). PS-C-catalyzed monoacylation of cis/trans mixture of **2.8.5** resulted in 2:3 mixture of (3*R*,5*R*)-**2.9.1** and (3*R*,5*S*)-**2.9.2**. The trans product (3*R*,5*R*)-**2.9.1** and the cis product (3*R*,5*S*)-**2.9.2** were isolated in 29% yield and 45% yield respectively with *ee* > 98% by chromatographic separation. Alternatively, PS-C mediated acylation at 50 ºC resulted exclusively in *meso*-diacylated compound **2.9.3** that was hydrolyzed with sodium hydroxide in methanol to produce *meso*-diol (*R,S*)-**2.8.5**. A second PS-C-catalyzed acylation gave the product (3*R*,5*S*)-**2.9.2** in 91% yield and >99% *ee*.



Scheme 2.9. Bäckvall's chemoenzymatic approach toward the synthesis of enantioenriched 3,5-dihydroxy piperidines

2.3. **Results and discussion**

As discussed in the previous section, 3,5-dihydroxy six-membered carbo- and heterocyclic rings are of considerable interest for both the synthetic and pharmaceutical community because of their presence in natural product structures as well as emerging applications in the synthesis of noval biologically important molecules. The available

routes for the synthesis of enantioenriched 1,3-cyclohexanediol and 3,5-dihydroxypiperdines involve multiple steps, extensive use of protecting group chemistry, multiple enzymes, and transition metal catalysts. We believe that a shorter route that can provide these important building blocks in significant quantities and high enantiopurities would be of general use to fulfill existing needs and may encourage researchers to further explore the synthetic and pharmaceutical applications of these versatile building blocks.

Having developed a concise route for the synthesis of enantioenriched cyclopentenones (Chapter 1), we aimed to utilize the Rychnovski's dichlorodiol[31] for the synthesis of six-membered rings (Figure 2.4). The proposed approach was most plausibly extendable for the synthesis of six-membered heterocyclic 1,3-diols. In this work, we describe the development of a unified strategy for the stereodivergent synthesis of enantioenriched 1,3-dihydroxy substituted six-membered carbocyclic and heterocyclic rings.

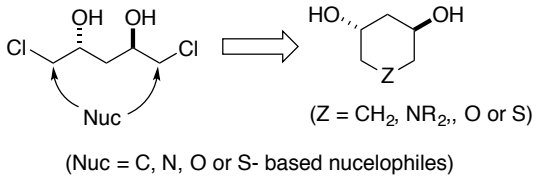
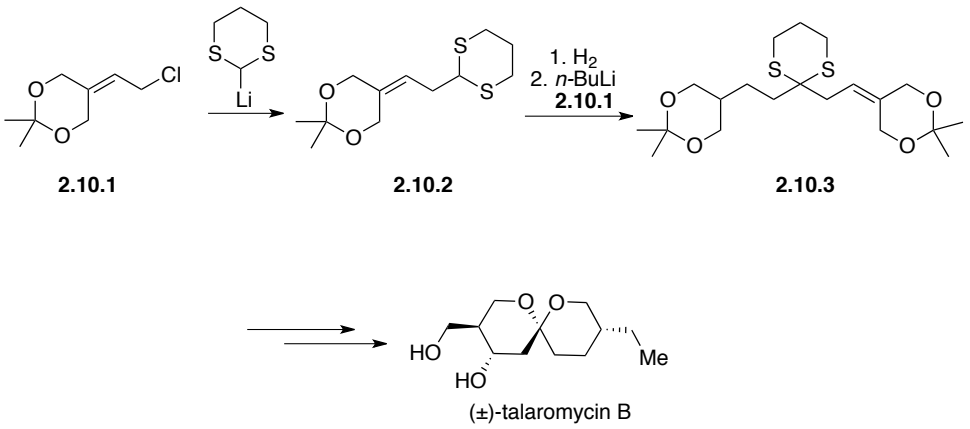


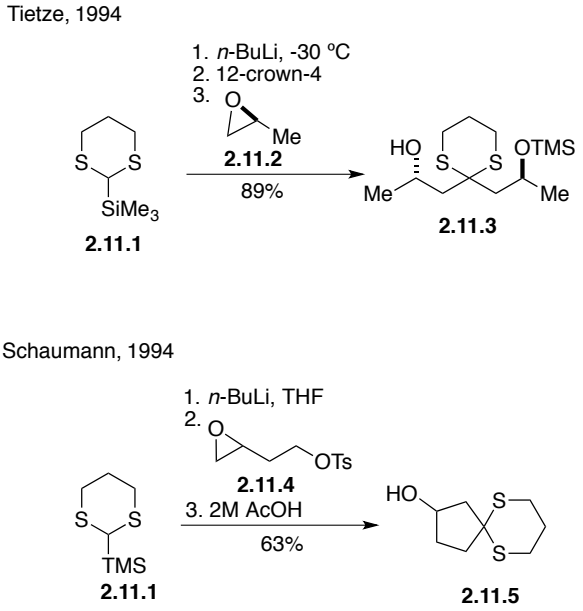
Figure 2.4. A novel approach toward six-membered cyclic-1,3-diols

To begin with the synthesis of carbocyclic diols, we initially considered using dithiane based carbanion nucleophile. 1,3-Dithianes were introduced in 1965 by Corey and Seebach as reagents for C–C bond formation by nucleophilic displacement and carbonyl addition.[65] Schreiber group reported the application of this chemistry in the total synthesis of the avian toxin talaromycin B (Scheme 2.10).[66]



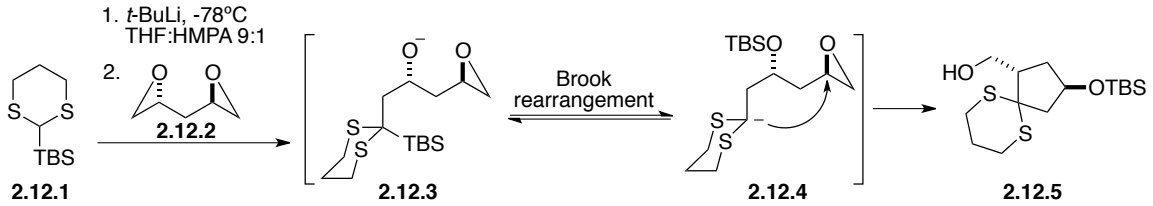
Scheme 2.10. Schreiber's synthesis of talaromycin B

In 1994, Tietze group reported the application of silyl-dithiane based carbanion for the synthesis of homocoupled diol **2.11.3**.[67] They performed the opening of epoxide **2.11.2** with TMS dithiane **2.11.1** followed by crown ether promoted 1,4-Brook rearrangement to reveal the second carbanion that reacted with another equivalent of epoxide **2.11.2** to furnish a homocoupled diol **2.11.3** (Scheme 2.11). Further advancement of this chemistry for multi-component reactions to access complex polyols has been well studied by Smith and coworkers.[68,69] However, to our surprise, there are very few examples in literature of the use of silylated dithianes for intramolecular C–C bond formation. In 1994, Schaumann reported the reaction of TMS-dithiane (**2.11.1**) with a dual electrophilic substrate **2.11.4** bearing an epoxide and tosylate functional groups.[70] Nucleophilic addition of the dithiane carbanion, silyl migration followed by intramolecular displacement of the tosylate resulted in ring closure to provide cyclopentanol product **2.11.5**.



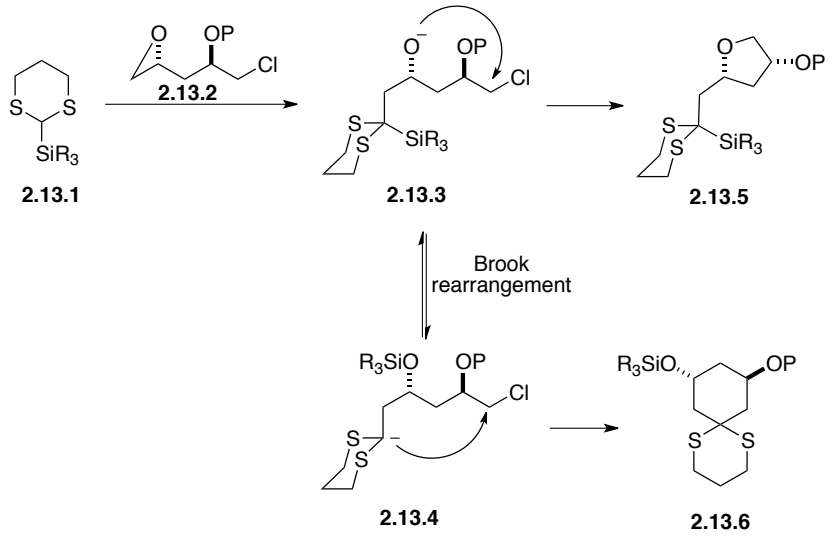
Scheme 2.11. Earlier examples of TMS-dithiane as carbanion nucleophile

A recent example involving dithiane mediated cyclization of a bis epoxide to obtain carbanucleosides was reported by Linclau's group (Scheme 2.11).[71,72,71] They proposed that opening of the epoxide **2.12.2** with the lithiated 2-silyl-1,3-dithiane followed by 1,4-Brook rearrangement generated the carbanion **2.12.4**. Newly generated carbanion **2.12.4** attacked the second epoxide regioselectively at the internal carbon leading to the formation of a five-membered ring **2.12.5**. To direct this route for the synthesis of six-membered ring, it would require intramolecular attack of the *in situ* generated nucleophile to happen at the terminal carbon and not the internal carbon.



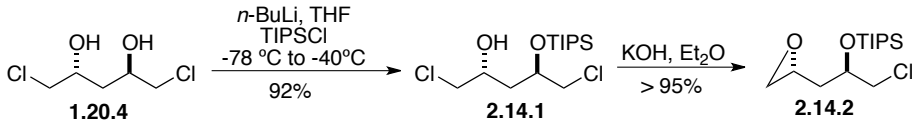
Scheme 2.12. Linclau's approach to carabanucleosides

We designed a modified substrate **2.13.2** similar to the one used by Schaumann (see scheme 2.11), bearing two differentially electrophilic carbons, an epoxide and a primary halide, which would undergo sequential C–C bond formation conceivably leading to a six-membered carbocycle (Scheme 2.12). The success of this approach would require control of the order and timing of three important chemical events taking place in this reaction. First, lithiated-1,3-dithiane **2.13.1** mediated chemoselective opening of the epoxide **2.13.2** in the presence of a primary halide to form an alkoxide **2.13.3**, which could in principle displace the halogen leading to an undesired furan product **2.13.5**. However, a timely Brook rearrangement prompted by a polar solvent would mask the alkoxide by *C*- to *O*-transfer of the silyl group resulting in a reactive carbanion intermediate **2.13.4**, hence ruling out the possibility of furan ring formation. Finally, intramolecular displacement of the chloride would provide the desired cyclized six-membered product **2.13.6**.



Scheme 2.13. Our design rationale for the synthesis of cyclohexane-1,3-diols

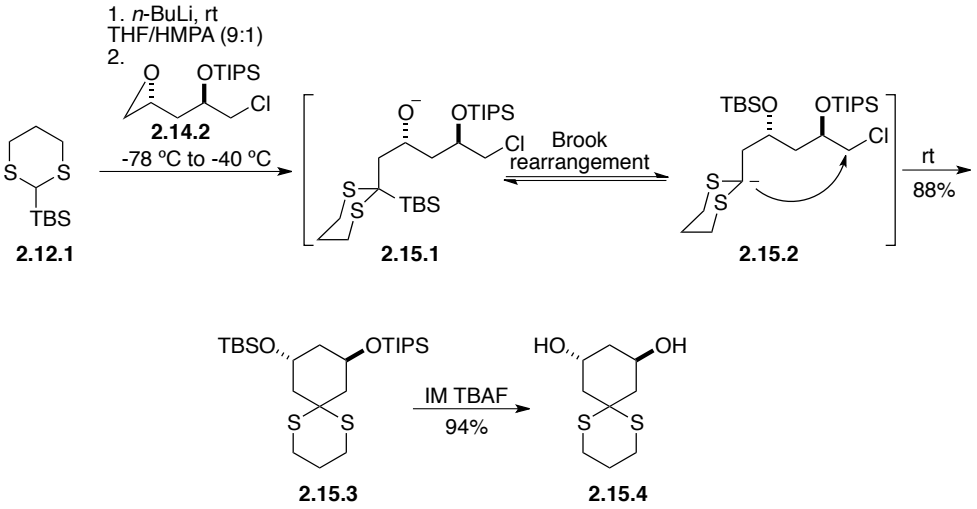
Considering the robustness of the silyl protecting groups in synthesis and our own experience with the TIPS as a protecting group, we planned to explore the dithiane chemistry using a TIPS-protected substrate. Considering the possibility of the epoxide formation under strong basic conditions, we attempted the mono silylation under low temperature conditions (Scheme 2.14). Addition of 1 eq of *n*-BuLi to the precooled solution of dichlorodiol **1.20.4** in THF at -78 ºC was followed by the addition of 1 equiv of TIPSCl at the same temperature. Allowing the solution to warm to rt for 16h yielded the mono silylated product **2.14.1** in 68% yield. Next we monitored the progress of reaction while maintaining low temperature conditions. It was observed that the desired mono-silylated product formation occurred at -78 ºC; however, the progress of the reaction was very slow. Slowly allowing the reaction to warm to -40 ºC and maintaining the temperature at -40 ºC for 6 h led to complete consumption of the starting material. The reaction was quenched with saturated ammonium chloride at -40 ºC. The monosilylated product **2.14.1** was isolated in 92% yield, which was converted to epoxide **2.14.2** in quantitative yield using powdered potassium hydroxide in anhydrous diethyl ether as solvent.



Scheme 2.14. Synthesis of the epoxide substrate

Having prepared the required epoxide substrate **2.14.2**, we reacted it with dithiane-based nucleophile (Scheme 2.15). Our objective was to promote the selective epoxide opening before the halogen displacement could take place. It is known in

literature that terminal epoxides can be opened at low temperature with dithiane-based carbanion nucleophiles; however the S_N2 displacement of chloride is slow at sub-zero temperature.[73] On the basis of this, we thought it would be possible to control the order of epoxide opening and halogen displacement by temperature control. The lithiation of TBS dithiane was carried out at room temperature with *n*-BuLi in a 9:1 mixture of THF/HMPA using *n*-BuLi as base. The resulting yellow solution was added to a pre-cooled solution of the epoxide **2.14.2** in THF/HMPA (9:1) at -78 ºC. The reaction mixture was maintained at -78 ºC for 0.5 h and then raised to -40 ºC for 2 h. Consumption of the starting material was observed by TLC at -40 ºC, indicating opening of the epoxide. Further allowing the reaction to stir at rt for 18 h formed the cyclized product **2.15.3** in 88% yield. The disilyl cyclohexanediol **2.15.3** was treated with 1 M TBAF in THF to produce C_2-symmetric 1,3-cyclohexanediol **2.15.4** in 94% yield.

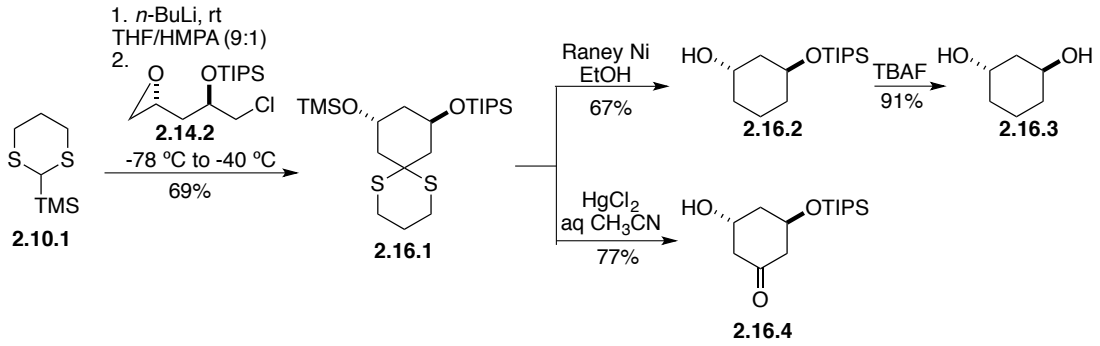


Scheme 2.15. Synthesis of 1,3-cyclohexanediol

Having succeeded in executing the proposed reaction, we were interested in obtaining the monoprotected version of the diol **2.15.4** as it would be synthetically more

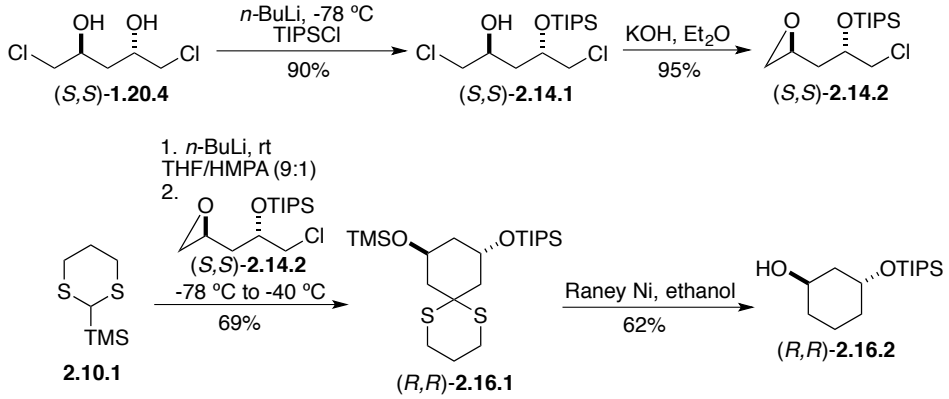
useful substrate. Mono deprotection of the product **2.15.3** may not be feasible and we were unaware of any methods for the chemoselective deprotection of either TBS or TIPS in the presence of the other. So we decided to use the silyl groups of significantly different strength in the above reaction, which can be differentiated easily at a later stage. We performed the above reaction exactly following the conditions described above except by using TMS dithiane instead of TBS dithiane to obtain the cyclohexane **2.16.1** in 69% yield (Scheme 2.16).

Raney nickel-mediated reduction of **2.16.1** in refluxing ethanol led to the loss of the TMS group as well as removal of the dithiane resulting in cyclohexane-1,3-diol **2.16.2** in 67% yield. Deprotection of the dithiane in **2.16.1** by using mercuric chloride in aqueous acetonitrile resulted in the keto product **2.16.4** in 77% yield.



Scheme 2.16. Deprotection of dithiane

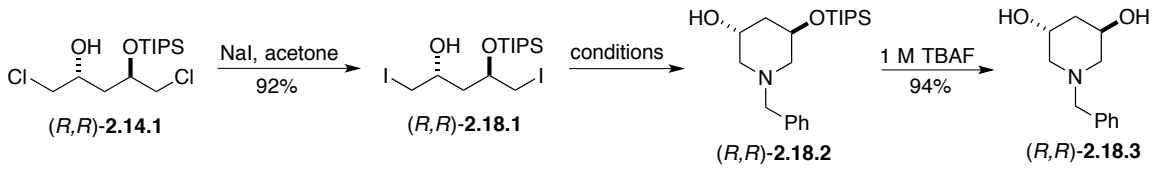
Following the same route as described above for (*S*,*S*)-**2.16.2**, (*R*,*R*)-**2.16.2** was prepared in 4 steps from (*S*,*S*)-**1.20.4** (Scheme 2.17).



Scheme 2.17. Synthesis of (*1S*,*3S*)-cyclohexane-1,3-diol

Synthesis of 3,5-dihydroxypiperidine

Synthesis of 3,5-dihydroxypiperidine using the addition of a primary amine to dichlorodiol **2.14.1** was attempted under different conditions (Table 2.1). However, the reaction was very slow and took 48 h to undergo completion with the best yield of 41% (Table 2.1, entry 1–4). To facilitate this reaction we converted the dichloro diol (*R*,*R*)-**2.14.1** to diiodo derivative (*R*,*R*)-**2.18.1** in 92% yield by treatment with sodium iodide in acetone. Treatment of the diiodo compound (*R*,*R*)-**2.18.1** with benzyl amine in acetonitrile at 80 ºC produced the desired piperidine (*R*,*R*)-**2.18.2** in 66% yield. Switching the solvent to ethanol improved the yields significantly, resulting in 85% yield of the piperidine product. Under microwave heating conditions and using ethanol as solvent the reaction was completed in 2 h, providing the piperidine product (*R*,*R*)-**2.18.2** in 88% yield. Treatment of (*R*,*R*)-**2.18.2** with 1M TBAF in THF provided the dihydroxy piperidine (*R*,*R*)-**2.18.3** in 94% yield and *er* > 99:1 (determined by chiral HPLC).

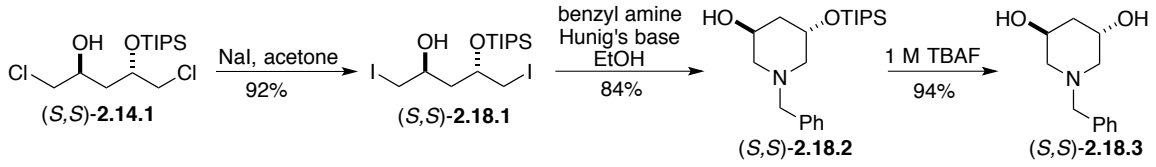


Scheme 2.18. Synthesis of (3*R*,5*R*)-1-benzylpiperidine-3,5-diol

Table 2.1. Optimization of conditions for the synthesis of 3,5-dihydroxy piperidines

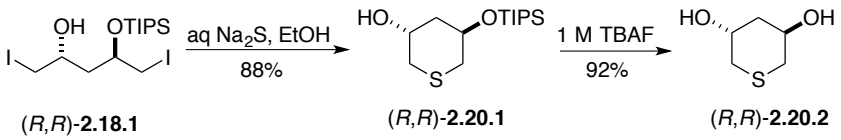
entry	X	conditions	yield
1	Cl	2 eq Hunig's base, THF, reflux, 48 h	17%
2	Cl	2 eq Hunig's base, ACN, 80 ºC, 48 h	41%
3	Cl	2 eq Hunig's base, ACN, *n*-Bu_4NI, 50 ºC, 48 h	10%
4	Cl	2 eq Hunig's base, DMF, *n*-Bu_4NI, 80 ºC, 48 h	39%
5	I	2 eq Hunig's base, ACN, 80 ºC, 24 h	66%
6	I	2 eq Hunig's base, EtOH, 100 ºC, 24 h	85%
7	I	Hunig's base, 2 eq EtOH, 100 ºC, μW, 2 h	88%

By using the diiodo diol (*S*,*S*)-**2.18.1** as starting material, *N*-benzylated-3,5 dihydroxylated piperidine (*S*,*S*)-**2.18.2** was obtained in four steps (Scheme 2.19). The TIPS cleavage using TBAF provided (*S*,*S*)-**2.18.3** in 94% yield and er > 99:1.



Scheme 2.19. Synthesis of (3*S*,5*S*)-1-benzylpiperidine-3,5-diol

3,5-Dihydroxy tetrahydrothiopyran **2.20.1** was synthesized using sodium sulfide as the source of sulfur nucleophile (Scheme 2.20). After optimization (Table 2.2) we obtained 3,5-disubstituted tetrahydrothiopyran (*R*,*R*)-**2.20.1** in 88% yield (*er* = 97:3, determined by chiral GC) by using 10 eq of aq sodium sulfide and diiodo diol (*R*,*R*)-**2.18.1**, under refluxing conditions in ethanol in 24 h (Table 2.2). Under microwave conditions the reaction was completed in 2 h providing similar yields as obtained under the standard heating conditions. Subsequent deprotection of the silyl group provided (*R*,*R*)-**2.20.2** in 92% yield.



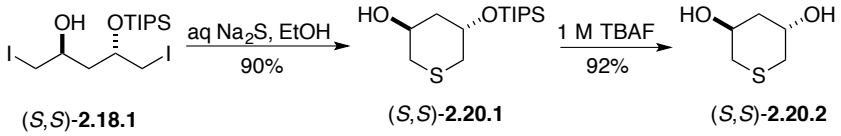
Scheme 2.20. Synthesis of (*R*,*R*)-3,5-dihydroxy tetrahydrothiopyran

Table 2.2. Optimization of the thiopyran ring formation

entry	conditions	yield
1	1 eq Na_2S, CH_3CN, 24 h	23%
2	2 eq Na_2S, CH_3CN, 24 h	41%
3	10 eq Na_2S, EtOH, reflux, 16 h	88%
4	10 eq Na_2S, EtOH, μW, 100 ºC, 2 h	90%

Starting with diiododiol (*S*,*S*)-**2.18.1**, using identical route as described for the synthesis of (*R*,*R*)-**2.20.2**, 3,5-disubstituted tetrahydrothiopyran (*S*,*S*)-**2.20.1** was obtained in 90%

yield and *er* 97:3 (Scheme 2.21). Treatment of (*S*,*S*)-**2.20.1** with TBAF provided diol (*S*,*S*)-**2.20.2** in 92% yield.



(*S*,*S*)-**2.18.1** (*S*,*S*)-**2.20.1** (*S*,*S*)-**2.20.2**

Scheme 2.21. Synthesis of (*S*,*S*)-3,5-dihydroxy tetrahydrothiopyran

In summary, we have developed a concise stereodivergent approach for the synthesis of enantioenriched six-membered 3,5-disubstituted carbo- and heterocycles. As compared to the previously reported routes to access these compounds, the present approach is much shorter and can provide trans-cyclohexane-1,3-diols in four steps and the piperidine diols in three steps from the previously reported dichlorodiol. We also extended our approach toward the synthesis of enantioenriched dihydroxy tetrahydrothiopyran ring, which are being increasingly represented in newly discovered molecules of biological importance.

Chapter 3

Development of Libraries Based on 5- and 6-Membered Cyclic 1,3-Diols

3.1. Introduction

The development of small-molecule libraries for biological screening remains an important area of interest for drug and probe discovery.[74] Although target-oriented synthesis[75] of small molecules plays an important role to identify hits, it remains short of probing novel and complex targets. Many disorders, such as cancer and neurodegenerative diseases, are often associated with complex interactions involving transcription factors, protein-protein interactions and DNA–protein interactions.[76] Such targets have been considered "undruggable" due to the challenges they pose to a typical drug discovery program.[77] In this context, screening of small-molecule collections to identify hits that can perturb the function of gene products, has proved an effective way of understanding complex biological processes, and allows for discovering new targets and compounds with potential therapeutic applications.[78,] However, to ensure the success of these efforts, it is essential that such molecule collections are diverse and contain compounds of suitable structural complexity.[79] Diversity is important, as in phenotypic screens (cell-based or organism-based) there is no single particular target, any one of the cell's or organism's entire pool of macromolecules could be an eventual target.[80,81] Complexity is another important component as many biological processes, particularly those based on protein–protein interactions are known to be disrupted by structurally complex natural products.

3.2. Diversity-oriented synthesis based on natural products

Natural products have long inspired drug discovery and chemical biology. For example, natural products such as camptothecins, taxoids and vinca alkaloids have been used in clinic.[82] Also, natural products such as actinonin,[83] geldanamycin,[84] trapoxin[85] and rapamycin[86] have been important tools to study and discover new therapeutic targets (Figure 3.1). Natural product isolation is an important means of providing access to novel natural product structures. Engineered biosynthesis has been emerging as an important technological means to access new natural products for testing purposes. In the similar context, diversity-oriented synthesis of natural product-inspired libraries has emerged as a very successful strategy to access skeletally diverse, structurally complex, stereochemically rich, and densely functionalized molecules. Such libraries have resulted in the discovery of new biologically active molecules.

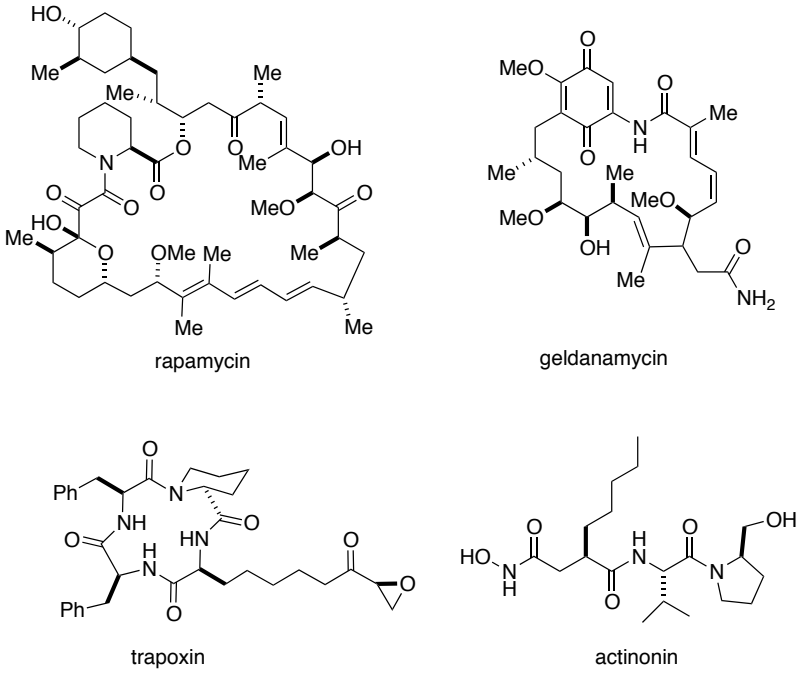


Figure 3.1. Examples of natural products having applications in chemical biology

3.3. **Design strategies for DOS of natural product-like libraries**

Shang and Tan have reviewed the design strategies of natural product-like libraries, separating them into three broad categories: (1) libraries based upon the individual natural products; (2) libraries based upon a common substructure found across a class of natural products; and (3) libraries that mimic the structural features of natural products in a more general sense.[87]

3.3.1. *Libraries based on core scaffolds of individual natural products*

Such libraries have been initially targeted to optimize the parent activity of the natural product.[88] Natural product cores can also be used as biologically validated frameworks that can be decorated with diverse functional groups. Such libraries may have the potential to address biological targets different than the one targeted by the parent natural product.[82] For example, Waldman and coworkers developed a 147 compound butenolide library based on the natural product dysidiolide [a cell division cycle 25 homolog A (Cdc25A) inhibitor]. From this collection they identified several sub-micromolar inhibitors of acetylcholine esterase (AChE), 11-β-hydroxysteroid dehydrogenase 1 and 2 (11βHSD1 and 11βHSD2).[89,90]

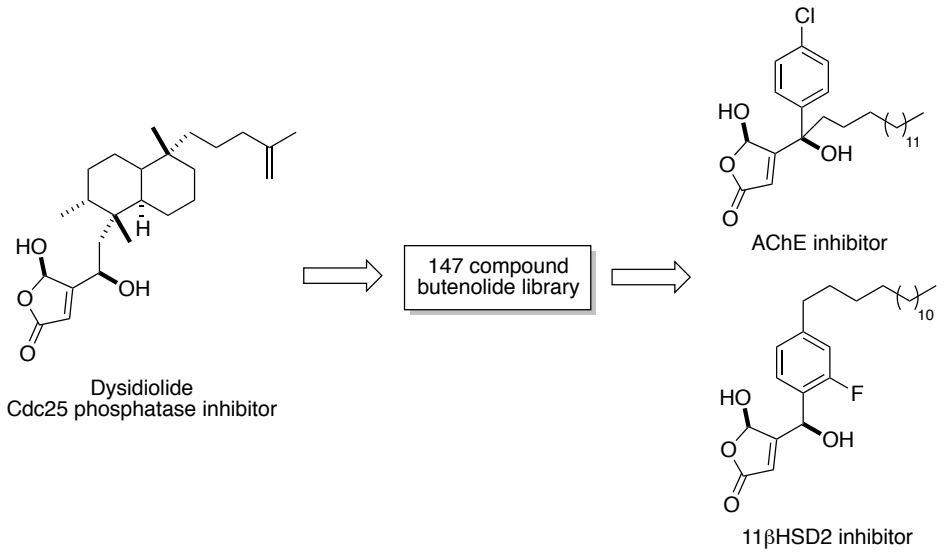


Figure 3.2. Dysidiolide inspired library of butenolide derivatives[89]

Another example such an approach was reported by the Schreiber group.[91] They constructed a library of spirooxindoles based on spirotryprostatin B, a mammalian cell-cycle inhibitor. Several enhancers of latrunculin B (an actin polymerization inhibitor) have been identified from this collection (Figure 3.3).

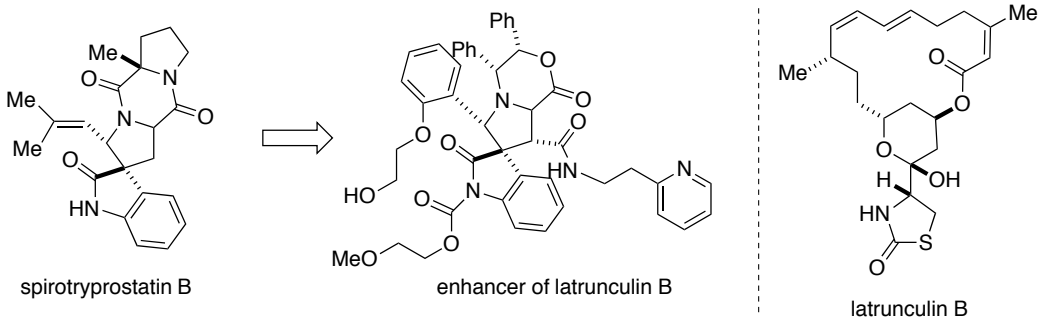


Figure 3.3. Library of spirooxindoles based on spirotryprostatin B[91]

3.3.2. *Libraries based on common substructures from classes of natural products*

Libraries based on the specific substructures, generally found within a class of natural products have increased potential to generate structural diversity that may address a wide range of biological targets. An early example of such an effort was reported by the Nicolaou group. They constructed a 10,000 compound library based on 2,2-dimethylbenzopyrans, a structural motif found in numerous natural products with diverse activities.[92–94] Screening of this library in different assays led to the discovery of compounds showing wide range of activities (Figure 3.4). An inhibitor of NADH ubiquinone oxidoreductase was identified.[95] Also, they have identified a compound active against six different MRSA strains, which is equipotent to vancomycin.[95] Screening against a reporter gene assay led to the identification of novel non-steroidal agonists of the farnesoid X reporter.[96]

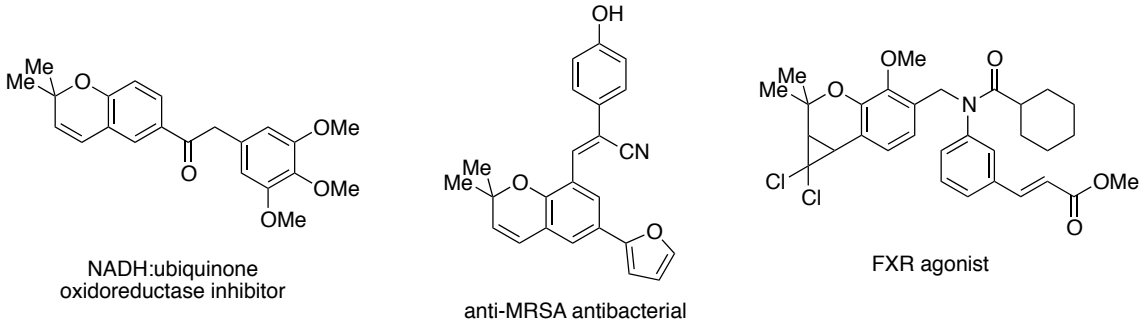


Figure 3.4. Library comprising 2,2-dimethylbenzopyrans as structural motif[93,94,

3.2.3. *Libraries with general structural characteristics of natural products*

This approach utilizes the structural features of the natural products in a general sense and has no direct connection to specific structures from natural products. However success of the libraries developed by this approach demonstrates the possibility to

identify truly novel pharmacophores that are considered undruggable. For example Schreiber and coworkers developed 1,3-dioxane-based libraries in this category.[97,98] They have identified uretupamine B, a functional-selective inhibitor of the yeast nutrient signaling protein Ure2p. Diversifying 1,3-dioxane core with the metalloprotein binding side chains led to the discovery of the inhibitors of the histone deacetylase family (HDAC). They have identified two selective histone deacetylase, tubacin, a selective inhibitor of HDAC6, which is a α-tubulin deacetylase, and histacin, that have true histone deacetylase activity and does not inhibit HDAC6 (Figure 3.5). These studies led to the identification of HDAC6 as a novel potential antimetastatic and antiangiogenic therapeutic target.

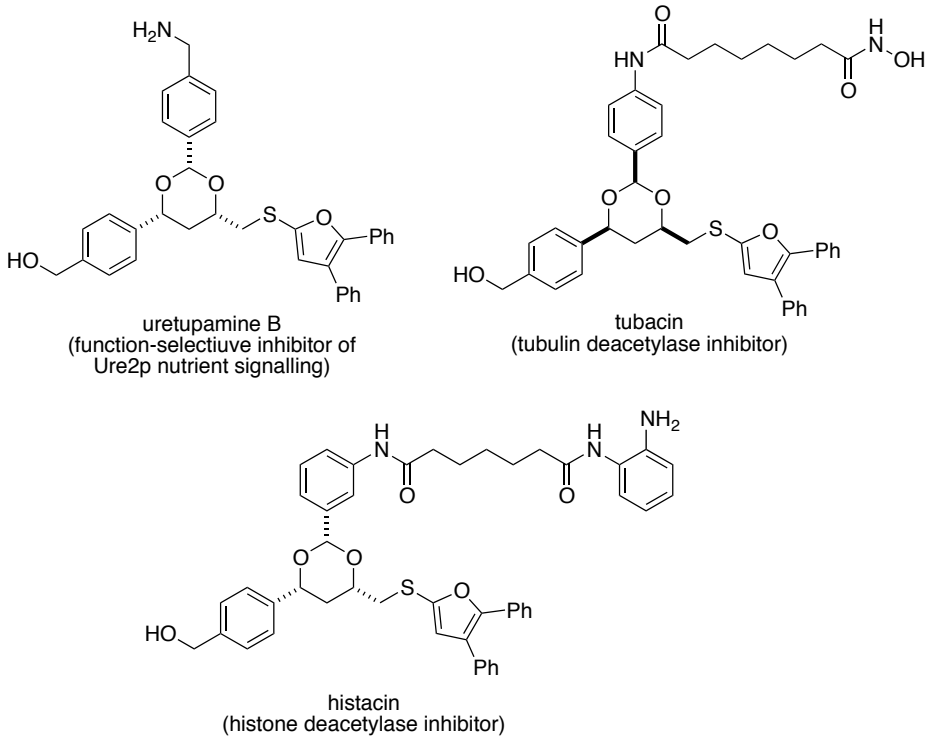


Figure 3.5. Inhibitors identified from Schreiber's dioxane based library[97,]

Boger and coworkers developed structurally diverse libraries using amide-bond-forming reactions, resulting in peptide like collection of compounds.[99] Several protein-protein interaction inhibitors have been identified from these libraries including antagonists of the MMP2-avb3,[100] Epo-EpoR,[101] Lef-1–β-catenin,[102] and Myc-Max[103,104] protein–protein interactions (Figure 3.6).

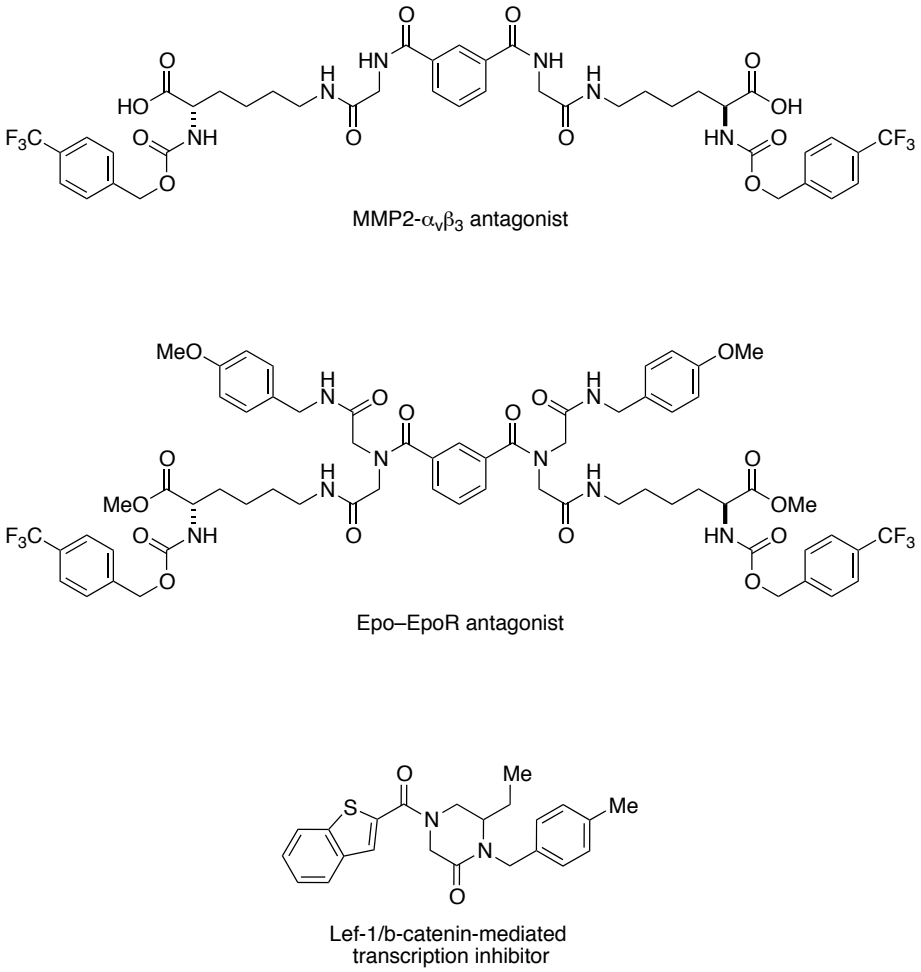


Figure 3.6. Protein–protein interaction inhibitors identified from a peptide-like library[99]

3.3. Small-molecule libraries of stereochemically diverse compounds

Generally, the focus of the above-cited approaches has been to achieve diversity through functional group variation among the members of the library. An alternative approach of varying functional group presentation is through extensive stereochemical diversification. Though constitutionally identical, the stereoisomeric compounds have topographical differences, resulting in distinct interactions with the macromolecular targets. The molecules generated by such approach are designed to explore the conformational space through geometric variation of the ligand scaffold. Though natural product-inspired libraries are often skeletally and stereochemically diverse however there are few examples in literature where an exhaustive stereochemical diversification has been used around a scaffold to produce a collection of small-molecules of diverse topology. An early example was reported by Paterson and co-workers in 1992.[105] They generated a library of 32 polyketide stereopentads by exhaustive stereochemical diversification. In 1999, Schreiber group reported conformationally diverse macrocyclic lactones by using stereoisomeric building blocks (Figure 3.7).[106]

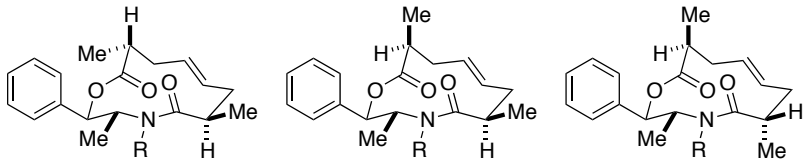


Figure 3.7. Conformationally diverse lactones[105]

An excellent example of a library of spatially separated compounds was described by the Ellman group in 1998. They developed a library of 204 spatially separate compounds to

target diverse aspartyl proteases. The screening of this library resulted in the identification of potent cathepsin D inhibitors (Figure 3.8).[107]

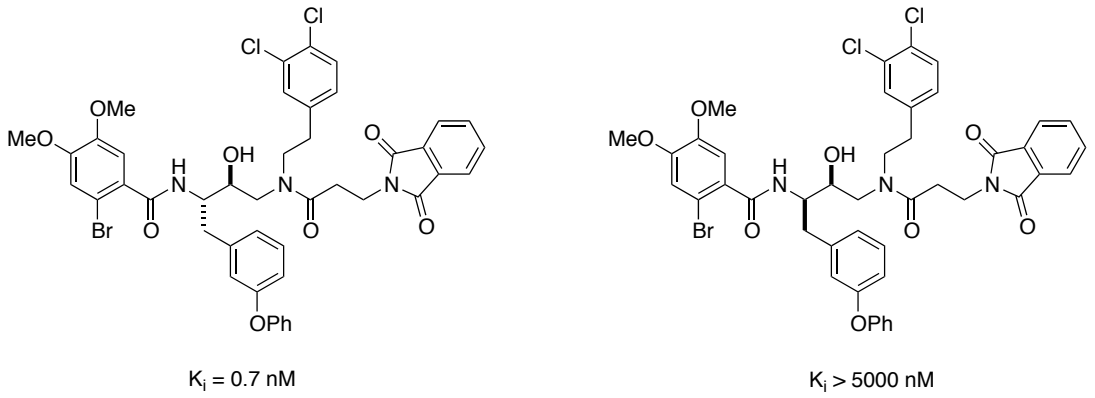


Figure 3.8. Examples from Ellman's library of spatially separated compounds determining cathepsin D inhibitory activity[107]

In 2000, the Verdine group reported a modular approach towards the synthesis of stereodiversified natural product-like libraries.[108,109] They generated the libraries of all the possible stereoisomers of the cis-1,4-enediol and cis-1,5-enediols via silyl-tethered ring-closing metathesis (Figure 3.9).

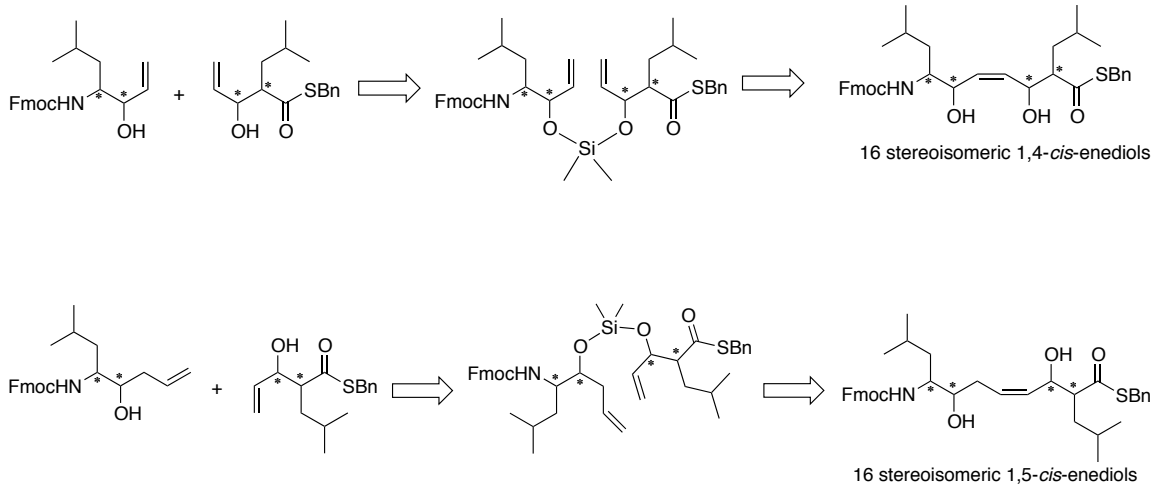


Figure 3.9. Stereodiversified library of enediols from Verdine's group[108,109]

3.4. Results and Discussion

As discussed in the introduction above that the development of small-molecule libraries is an important area of interest to reveal novel biological targets of therapeutic relevance. Natural product structures have been motivation as well inspiration to design such libraries. Various strategies have been used in this regard as discussed in the introduction. However, there are not many stereochemically diverse libraries reported in the literature.

In the present work, we describe the development of a small-molecule library of stereochemically diverse compounds by integrating structural features of prostaglandin natural products, a highly important and physiologically relevant class of natural products, and α-amino acids that are natural chiral building blocks.

3.4.1. *Library Design*

We recognized that the stereo elements on a small five-membered carbocycle, 2-cyclopentene-1,4-diol can be utilized to target stereochemically diverse compounds. This idea was enabled by easy access to either of the enantiomer of 2-cyclopentene- *trans*-1,4-diol on gram scale by the recently developed approach in our laboratory (discussed in Chapter 1). Also, it was easily conceivable that the cis isomers of the diols could be synthesized via Mitsunobu inversion of one of the alcohol stereocenter in 2-cyclopentene- *trans*-1,4-diol. The presence of alcohol functionality provides an opportunity for easy synthetic derivatization.

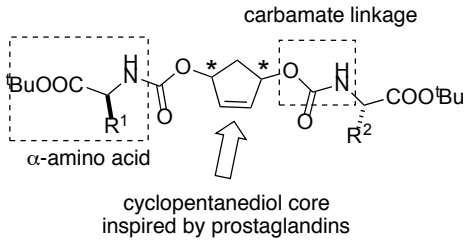


Figure 3.10. Integrating prostaglandin core with amino acids

One could readily append side chains by either an ester or a carbamate linkage; however we chose to avoid esters considering the high hydrolytic nature of this group under biological conditions. The carbamate linkage was chosen due to ease of synthesis and because carbamates have been effectively used in both drug molecules and screening libraries. Natural amino acids were chosen as the side chain derivatizing partners. Amino acids are unarguably biologically relevant, and are economical means of adding complexity because of the presence of a chiral center, and provide diversity by means of both polar and non-polar side chains. The presence of carboxylic acid in the side chain adds another feature of prostaglandins that have carboxylic acid side chains. We chose ten different amino acids having significantly different side chains for the library particularly, tryptophan having a heterocyclic indolyl side chain; amino acids with polar side chains serine, asparagine, glutamic acid, non-polar side chains alanine, leucine, methionine, phenylalanine, and the cyclic amino acid proline were employed.

3.4.1. *Library Plan (Figure 3.11)*

For the cyclopentenediol library, we decided to use all four isomers of the monoprotected 2-cyclopentene-1,4-diol. As depicted in Figure 3.11, we planned to derivatize the diol with four different amino acids, L-alanine, L-proline, L-tryptophan and

L-asparagine at the first step, leading to four scaffolds of amino acid derived alcohols. Each scaffold would then be derived with six different amino acids, leading to 24 compounds. Ultimately using all of the four isomers of 2-cyclopentene-1,4-diol, a 96 compound library was planned.

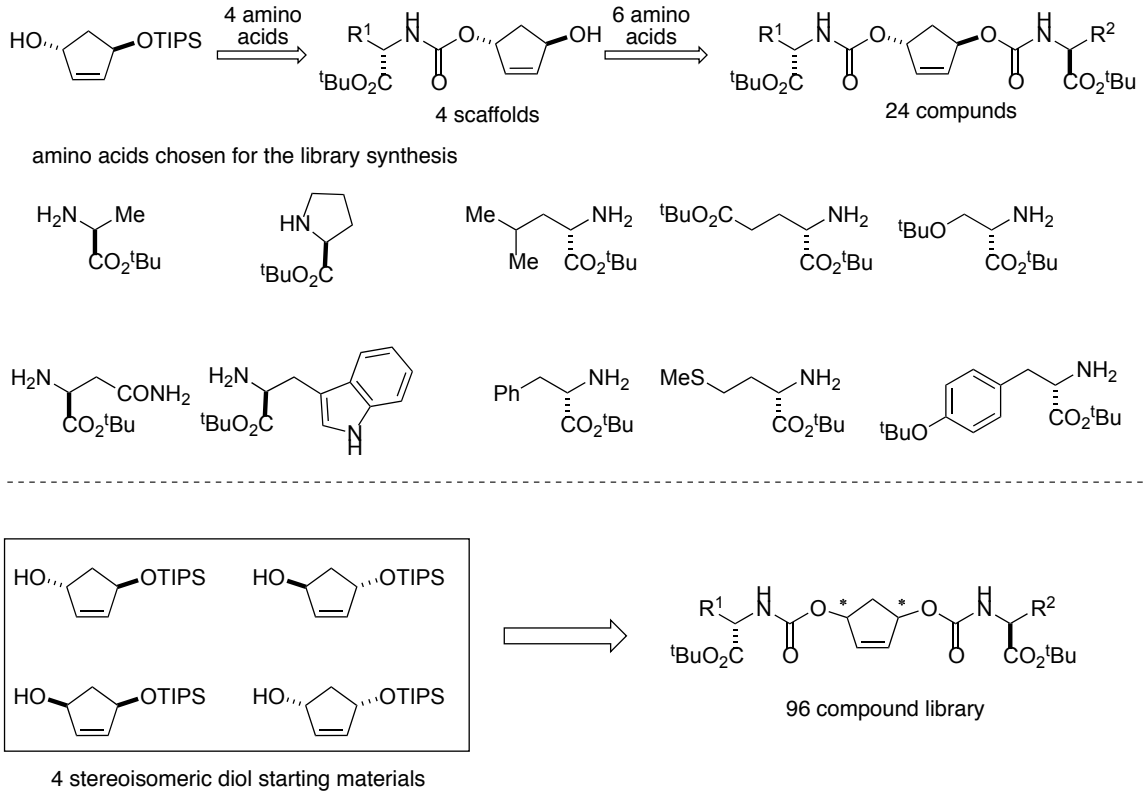
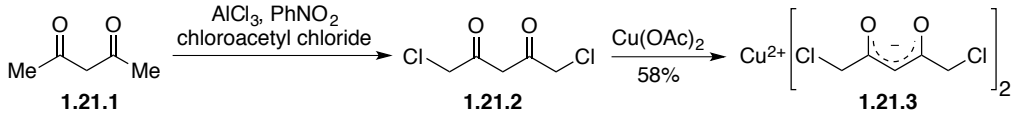


Figure 3.11. Library plan

3.4.2. *Library synthesis*

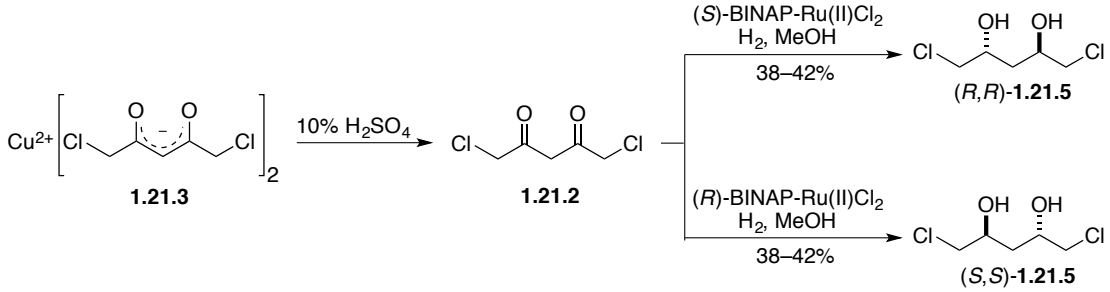
To accomplish the planned library, each of the isomeric 2-cyclopentene-1,3-diol was prepared in excess of 3–4 g quantities using the synthetic route discussed in Chapter 1. Thus, starting with the commercially available acetyl acetone, dichloro compound **1.21.2** was prepared at 65 g scale and was preserved as a copper salt **1.21.3** (Scheme 3.1).

Copper salt **1.21.3** was hydrolyzed with aqueous sulfuric acid to obtain dichlorodione **1.21.2** just prior to the Noyori hydrogenation step (Scheme 3.2).



Scheme 3.1. Synthesis of dichlorodione

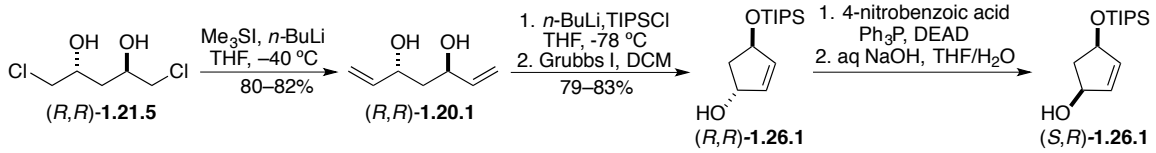
Following Rychnovski's procedure, asymmetric reduction of 22 g of **1.21.2** in a Parr hydrogenator at 1250 psi provided 8.7 g of the enantioenriched (*R,R*)-dichlorodiol **1.21.5** after recrystallization from hexane–DCM.[110] Switching the catalyst to (*R*)-BINAP-Ru(II)Cl_2 provided the (*S,S*)-**1.21.5** following the same procedure (Scheme 3.2).



Scheme 3.2. Synthesis of dichlorodiols

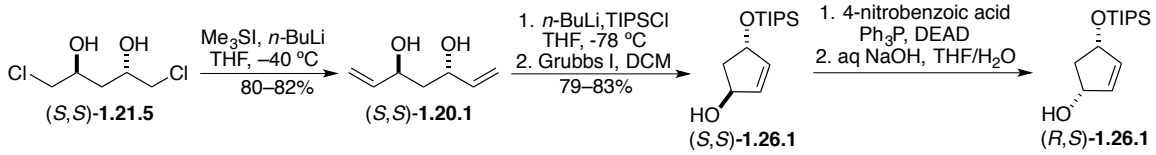
In the next step, dichlorodiol **1.21.5** was subjected to the Corey-Chaykovski homologation.[34] However, the amount of trimethylsulfonium salt and the volume of *n*-BuLi required for this step limited the scalability of this step. So Corey-Chaykovski homologation of **1.21.5** was performed in batches at 4 g scale to accumulate 10 g of diene diol (*R,R*)-**1.21.2** (Scheme 3.3). Monosilylation of dienediol (*R,R*)-**1.21.2** followed by ring-closing metathesis using the Grubbs I catalyst provided 9 g of cyclopentenol (*R,R*)-

1.26.1. Cis diol (*S,R*)-**1.26.1** was obtained in two steps via Mitsunobu reaction of (*R,R*)-**1.26.1** with 4-nitrobenzoic acid followed by basic hydrolysis of the resulting benzoate ester. Both (*R,R*)-**1.26.1** and (*S,R*)-**1.26.1** were prepared on 4 g scale.



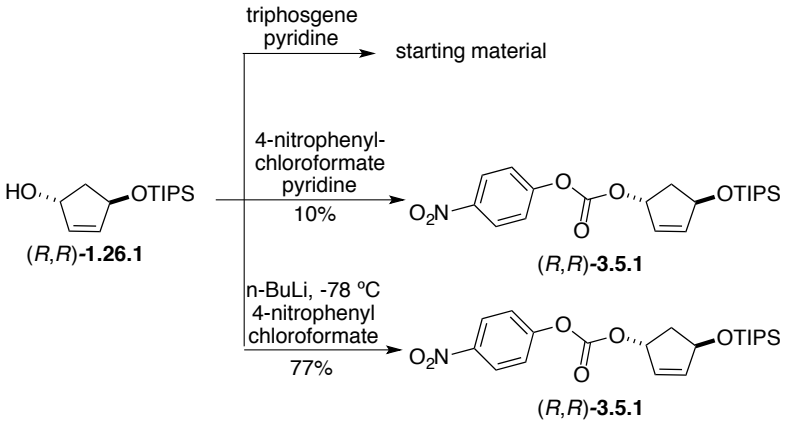
Scheme 3.3. Synthesis of diols (*R,R*)-**1.25.1** and (*S,R*)-**1.25.1**

Following the same process as described above, (*S,S*)-**1.26.1** and (*R,S*)-**1.26.1** were prepared in ca. 4 g quantities each starting from the dichlorodiol (*S,S*)-**1.20.4** (Scheme 3.4).



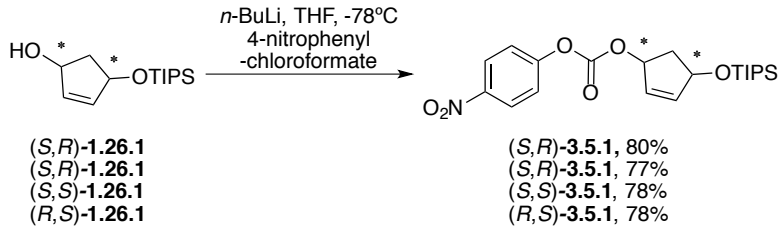
Scheme 3.4. Synthesis of diols (*S,S*)-**1.26.1** and (*R,S*)-**1.26.1**

The alcohol (*R,R*)-**1.26.1** was treated with triphosgene and pyridine in an attempt to synthesize chloroformate, however various attempts towards this goal were not successful. Switching to another carbonylating reagent, 4-nitrophenyl chloroformate provided the desired product only in 10% yield. The majority of the starting material was isolated in this case. Finally, we considered using *n*-butyl lithium under low temperature conditions to deprotonate the alcohol and quenching the anion with the excess of carbonylating reagent. Following this method, the resulting carbonate **3.5.1** was isolated in 77% yield.



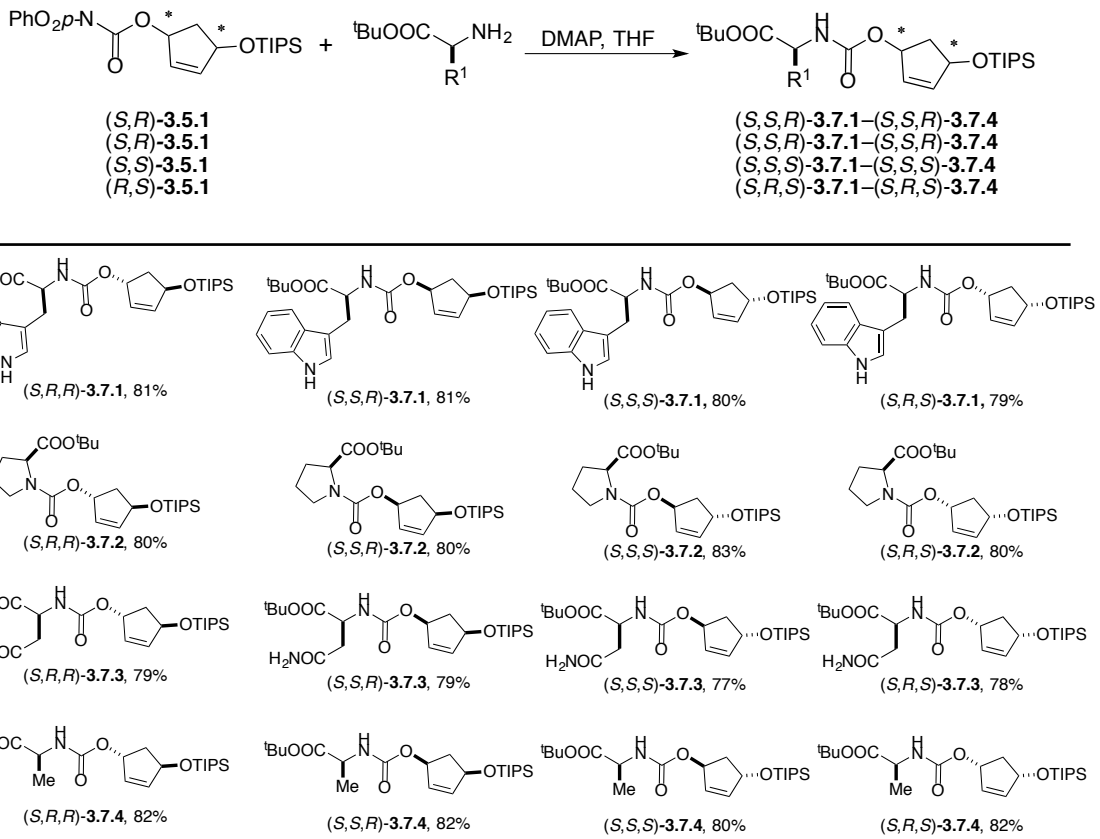
Scheme 3.5. Synthesis of alcohol carbonate

Using the conditions optimized above, the isomeric alcohols **1.26.1** were converted to carbonates on a scale of 2.5 to 3.0 g (Scheme 3.6).



Scheme 3.6. Synthesis of carbonates

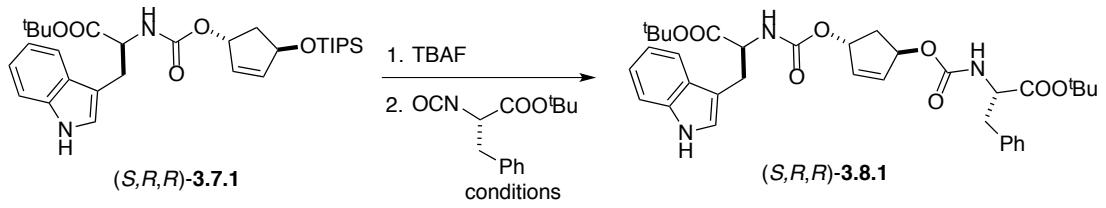
Reaction of carbonate (*R,R*)-**3.5.1** with amino acid ester in the presence of catalytic amount of DMAP in THF at 100 ºC formed the amino acid carbamates in 72–82% yield (Scheme 3.6).



Scheme 3.7. Synthesis of silyl monocarbamates

3.4.3. *Optimization of library method*

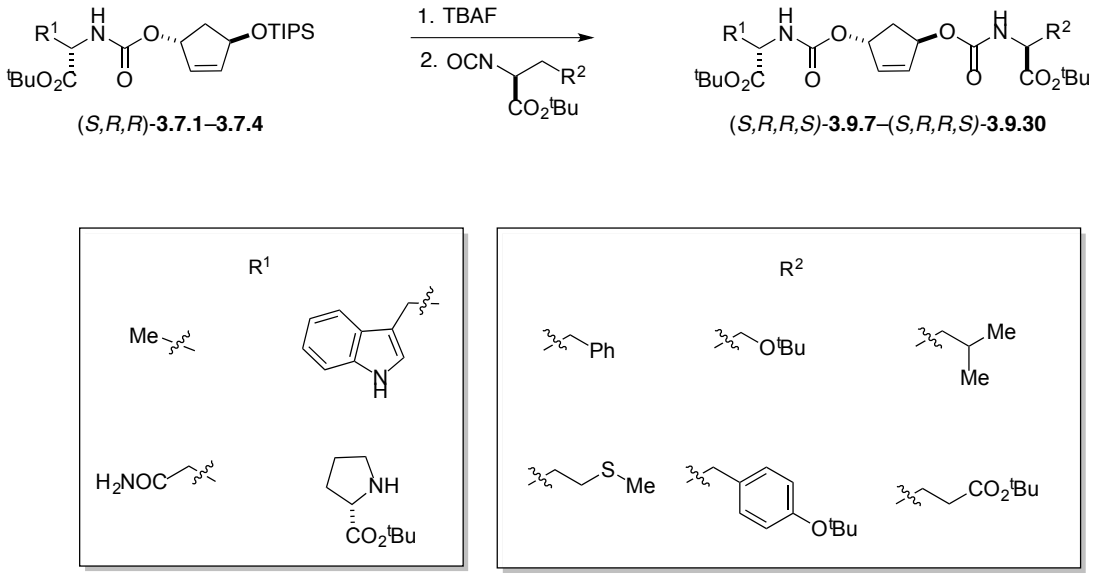
Silyl carbamate (*S,R,R*)-**3.7.1** subjected to TIPS deprotection using TBAF and the resulting crude alcohol was treated with amino acid isocyanate. However the reaction of isocyanate with alcohol was very slow in refluxing toluene for 48 h, leaving a significant amount of starting material (Scheme 3.8). Ultimately, reacting alcohols with excess of neat isocyanates (3 equiv) in the presence of catalytic amount of *N*,*N*-dimethylaminopyridine at 100 ºC led to successful completion of reaction.



conditions	yield
Et_3N, THF, 24 h, rt	< 10%
DMAP, THF, reflux, 24 h	< 10%
toluene, DMAP, reflux, 48 h	67%
DMAP, 100 ºC, no solvent, 2 h	84%

Scheme 3.8. Optimization of method for biscarbamate synthesis

The above-optimized conditions were used for the synthesis of a validation library of bis carbamates. Alcohols **3.7.1–3.7.4** were reacted with six different amino acid isocyantes in two-dram vials on a 24-well heating block (Scheme 3.9). The reaction mixture was cooled to room temperature and was dissolved in dichloromethane. Each of the reaction mixture was transferred to reaction tubes charged with tris-(2-aminoethyl)-amine, polymer bound resin) on a 24-well (4x6) Mini-Block^{TM} reaction array. The contents were filtered through the tris-(2-aminoethyl)-amine resin and the resin was washed with dichloromethane. The reaction contents were collected in collection tubes and the solvent was evaporated under by purging nitrogen gas. The crude reaction mixtures were subjected to mass-directed automated purification resulting in 18 biscarbamates in 4–62 mg quantities and purities >90%. The purification results of the 24 compounds are listed in Table 3.1.



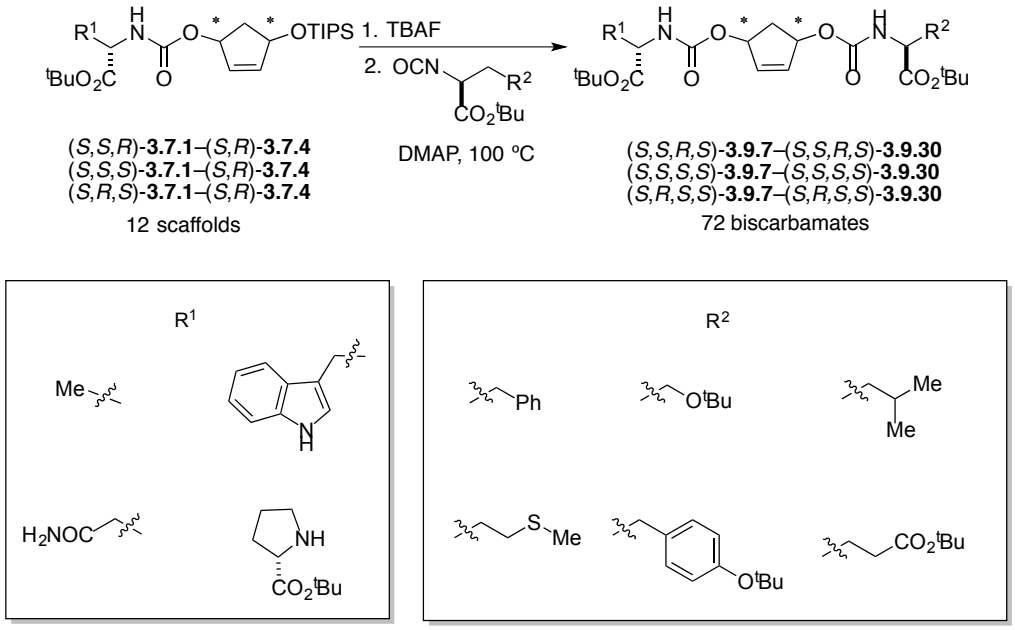
Scheme 3.9. Synthesis of (*S*,*R*,*R*,S)-biscarbamate library

Table 3.1. Biscarbamate Library[a]

entry	compound	R^1	R^2	amount (mg)	purity (%)
1	(*S*,*R*,*R*,*S*)-**3.9.7**	3-indolyl-ylmethyl	$PhCH_2$	24	100
2	(*S*,*R*,*R*,*S*)-**3.9.8**	3-indolyl-ylmethyl	$^tBuOCH_2$	62	98
3	(*S*,*R*,*R*,*S*)-**3.9.9**	3-indolyl-ylmethyl	$(CH_3)_2CHCH_2$	34	94
4	(*S*,*R*,*R*,*S*)-**3.9.10**	3-indolyl-ylmethyl	$CH_3SCH_2CH_2$	25	79
5	(*S*,*R*,*R*,*S*)-**3.9.11**	3-indolyl-ylmethyl	$^tBuO_2CCH_2CH_2$	54	99
6	(*S*,*R*,*R*,*S*)-**3.9.12**	3-indolyl-ylmethyl	*p*-$^tBuOPhCH_2$	25	92
7	(*S*,*R*,*R*,*S*)-**3.9.13**	H_2NCOCH_2	$PhCH_2$	27	100
8	(*S*,*R*,*R*,*S*)-**3.9.14**	H_2NCOCH_2	$^tBuOCH_2$	44	98
9	(*S*,*R*,*R*,*S*)-**3.9.15**	H_2NCOCH_2	$(CH_3)_2CHCH_2$	39	39
10	(*S*,*R*,*R*,*S*)-**3.9.16**	H_2NCOCH_2	$CH_3SCH_2CH_2$	26	100
11	(*S*,*R*,*R*,*S*)-**3.9.17**	H_2NCOCH_2	$^tBuO_2CCH_2CH_2$	66	98
12	(*S*,*R*,*R*,*S*)-**3.9.18**	H_2NCOCH_2	*p*-$^tBuOPhCH_2$	22	39
13	(*S*,*R*,*R*,*S*)-**3.9.19**	L-proline	$PhCH_2$	34	100
14	(*S*,*R*,*R*,*S*)-**3.9.20**	L-proline	$^tBuOCH_2$	10	98
15	(*S*,*R*,*R*,*S*)-**3.9.21**	L-proline	$(CH_3)_2CHCH_2$	18	97
16	(*S*,*R*,*R*,*S*)-**3.9.22**	L-proline	$CH_3SCH_2CH_2$	71	100
17	(*S*,*R*,*R*,*S*)-**3.9.23**	L-proline	$^tBuO_2CCH_2CH_2$	25	56
18	(*S*,*R*,*R*,*S*)-**3.9.24**	L-proline	*p*-$^tBuOPhCH_2$	34	98
19	(*S*,*R*,*R*,*S*)-**3.9.25**	CH_3	$PhCH_2$	5	78
20	(*S*,*R*,*R*,*S*)-**3.9.26**	CH_3	$^tBuOCH_2$	27	96
21	(*S*,*R*,*R*,*S*)-**3.9.27**	CH_3	$(CH_3)_2CHCH_2$	29	41
22	(*S*,*R*,*R*,*S*)-**3.9.28**	CH_3	$CH_3SCH_2CH_2$	39	98
23	(*S*,*R*,*R*,*S*)-**3.9.29**	CH_3	$^tBuO_2CCH_2CH_2$	33	92
24	(*S*,*R*,*R*,*S*)-**3.9.30**	CH_3	*p*-$^tBuOPhCH_2$	38	65

[a] Please see experimental section for the purification method details.

Following the library method optimized above, the silyl carbamates (*S,S,R*)-, (*S,S,S*)- and (*S,R,S*)-**3.7.1–3.7.4** were used for a 72 compound library synthesis (Scheme 3.10**)**.



Scheme 3.10. Synthesis of 72-membered biscarbamate library

Ten crude reaction mixtures were randomly chosen from this pool, were purified by column chromatography and the structures were confirmed by NMR and mass analysis. The rest of the compounds were submitted for mass-directed purification. However the analysis by mass did not respond well unlike the case of validation library (Note: the Agilent Purification system which was originally used for the validation library by Patrick Porubsky, was out of order and the current set of compounds was processed by Ben Nuenswander over a different system). Various attempts were made by analyzing the individual fractions by proton nmr to detect the desired compound fractions however it was a futile exercise considering the multiple fractions being produced for each

individual crude reaction mixture. The crude products could not be recovered because of the numerous fractions generated in the purification process.

3.4.4. *Library of C_2-symmetric biscarbamates*

With an objective to increase the diversity, we also targeted the six-membered bis carbamates by taking advantage of the method described in Chapter 2. In this part of the project, we targeted a library of 24 C_2-symmetric compounds based on the five and six-membered carbo- and heterocyclic diols (Figure 3.12).

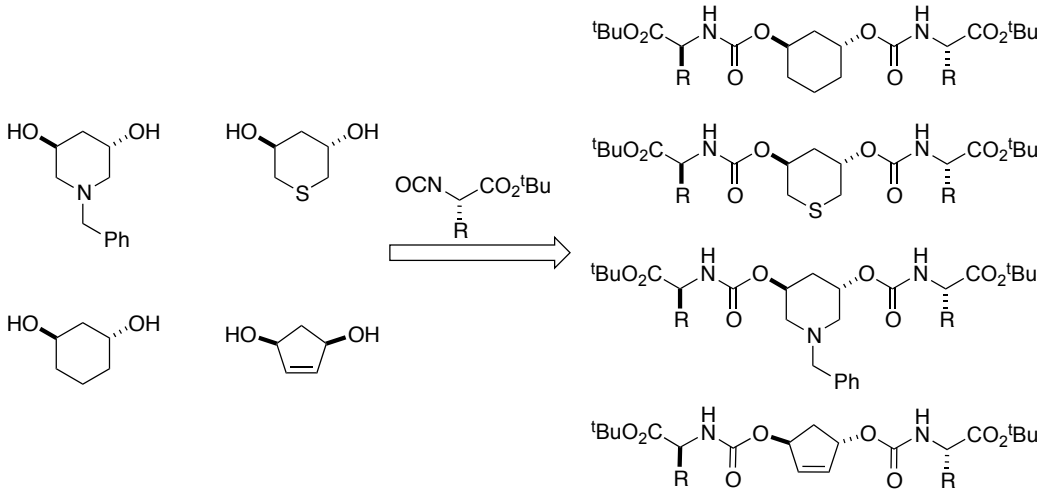
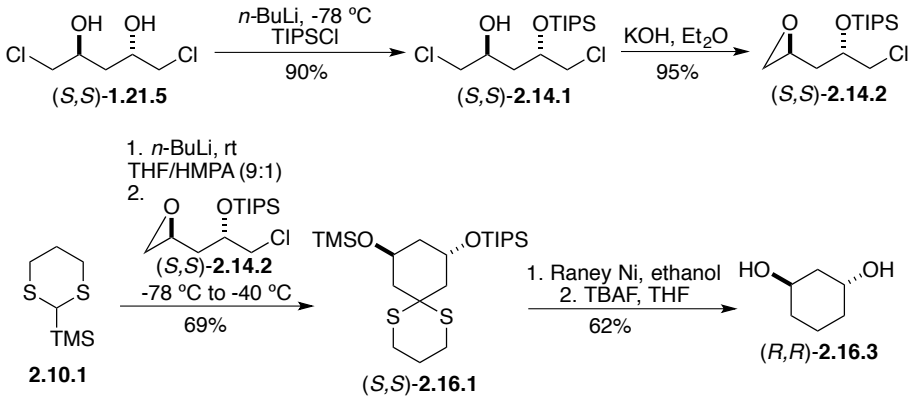


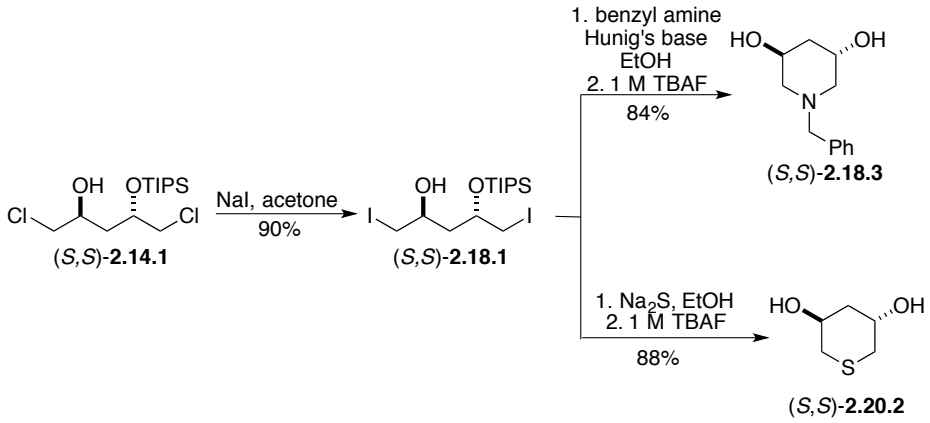
Figure 3.12. Six-membered C_2-symmetric biscarbamates

To accomplish this goal, we scaled-up each of the *trans*-diols **2.16.3**, **2.18.3**, **2.20.2** and **3.12.1** to 200 mg scale. Mono TIPS protection of dichloro diol (*S,S*)-**1.21.5** provided diol (*S,S*)-**2.14.1** that was treated with powdered potassium hydroxide to form epoxide (*S,S*)-**2.14.2**. Epoxide opening with lithiated 2-TMS-dithiane followed by intramolecular cyclization via SN2 displacement of chloro led to the production of cyclohexane product (*S,S*)-**2.16.3**. Reductive removal of dithiane using Raney Ni followed by TIPS cleavage using TBAF provided cyclohexane diol (*R,R*)-**2.16.3** in 62% yield.



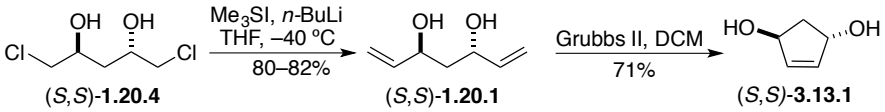
Scheme 3.11. Synthesis of (*S*,*S*)-cyclohexane-1,3-diol

Mono TIPS protected dichlorodiol was converted to diiodo diol (*S,S*)-**2.18.1** that was converted to dihydroxy piperididne (*S,S*)-**2.18.3** in two steps (Scheme 3.12). Treatment of diiododiol with sodium sulfide in ethanol followed by TIPS cleavage with TBAF provided diol (*S,S*)-**2.20.2** in 88% yield.



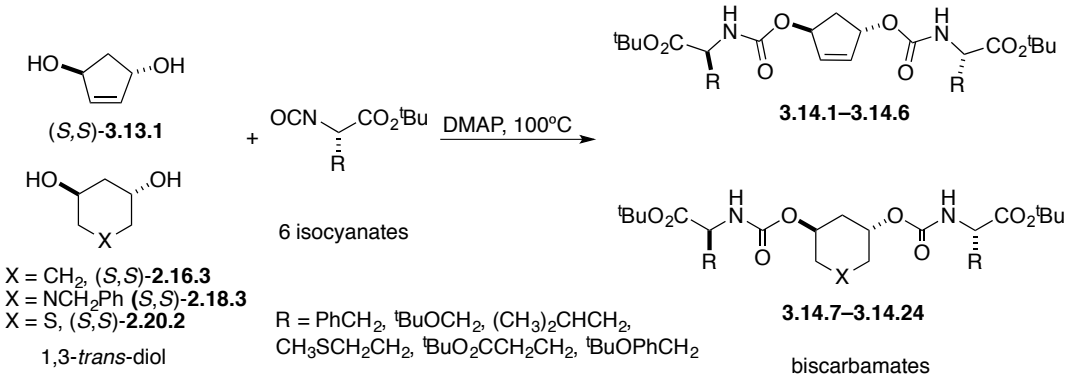
Scheme 3.12. Synthesis of heterocyclic diols

Five-membered diol (*S*,*S*)-**3.12.1** was prepared in 71% yield by subjecting diene diol (*S*,*S*)-**1.21.2** to the ring-closing metathesis conditions using the Grubbs II catalyst.



Scheme 3.13. Synthesis of (*S*,*S*)-2-cyclopentene-1,3-diol

The (*S,S*)-diols **2.16.3**, **2.18.3**, **2.20.2** and **3.13.1** were subjected to react with the six different amino acid isocyanates in 2 mL vials placed in a 24-well heating block for four hours at 100 ºC (Scheme 3.13). A random subset of five of the resulting reaction mixtures were purified by column chromatography and fully characterized to confirm structures.



Scheme 3.13. Synthesis of library of five- and six-membered C_2-symmetric biscarbamates

In summary, we targeted 120 compound library of biscarbamates using five- and six-membered cyclic 1,3-diols. Twenty stereochemically diverse scaffolds were successfully prepared on 150–300 mg scale in enantiomerically enriched form. A suitable method was optimized for the library synthesis using Mini-Block^{TM} platform and purification results showed promising results during validation, producing 18 compounds on an average of 35 mg quantity and purities >90%. This library effort was enabled by developing synthetic approaches to access enantioenriched five and six-membered carbo-

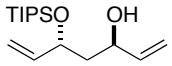
and heterocyclic diols. With an optimized method in hand and the synthetic access to the enantiopure building blocks, a larger library campaign could be enabled if supported by a suitable analytical and purification system. We believe that stereochemical diversity of such a library collection may provide varying topographical features to these molecules and the appended amino acid side chains will enable to probe the important interactions in biological targets.

Chapter 4

Experimental

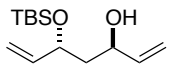
General Methods. All reactions were carried out in oven- or flame-dried glassware under argon atmosphere using standard gas-tight syringes, cannulas, and septa. Et_2O, THF and CH_2Cl_2 were purified by passage through an alumina based commercial purification system (Solv-Tek). Column chromatography was performed with Sorbent Technologies (30930M-25, Silica Gel 60A, 40-63 μm) and thin layer chromatography was performed on silica gel 60F254 plates (EM-5717, Merck). ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AV-400 spectrometer and calibrated to the solvent peak. High-resolution mass spectra (HRMS) were recorded on Waters LCT premier Micromass from MS Technologies. Observed optical rotations at 589 nm, were measured using AUTOPOL IV Model automatic polarimeter. IR spectra were recorded on Shimadzu FTIR-8400S instrument. The *er* values of the compounds (*R*)-**1.20.3**, (*S*)-**1.20.3**, (*R*)-**1.4.3**, (*R*)-**1.4.1**, (*R*)-**1.20.4**, (*S*)-**1.20.4**, (*R*,*R*)-**2.16.2**, (*S*,*S*)-**2.16.2**, (*R*,*R*)-**2.20.1** and (*S*,*S*)-**2.20.1** were determined by gas chromatography using a 5975CVL MSD triple-axis detector. The *er* value of the compounds (*R*)-**1.27.1**, (*R*)-**2.18.3** and (*S*)-**2.18.3** were determined by chiral HPLC on an IC column with a 996 UV detector. Preparative reverse-phase HPLC was performed on a Waters 2767 preparative system [UV (214 nm, 2996 PAD) and mass detection (Micromass ZQ)], using a Waters X-Bridge C18 column (19 x 150, 19 x 10 mm guard column), and water/acetonitrile as eluent with 20% increase in gradient over 4 min at a flow rate of 20 mL/min.

Known compounds: The compounds **1.20.1,** (*R,R*)-**1.20.4** (*S,S*)-**1.20.4** were prepared according to the reported procedures.[31, 34]



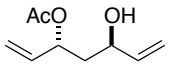
(*R,R*)-**1.20.2**

(3*R*,5*R*)-5-((Triisopropylsilyl)oxy)hepta-1,6-dien-3-ol (1.20.2). To a stirred solution of (3*R*,5*R*)-hepta-1,6-diene-3,5-diol **1.20.1** (2.7 g, 21.1 mmol) in THF (200 mL) at –78 ºC, was added *n*-BuLi (9.3 mL, 2.5 M in hexanes, 23.2 mmol) dropwise. The solution was allowed to stir for 20 min at –78 ºC followed by the slow addition of TIPSCl (4.9 mL, 23.2 mmol). After 2 h, the reaction was allowed to slowly warm to rt overnight and was quenched with saturated NH_4Cl(100 mL). The organic phase was washed with saturated NH_4Cl (3 × 100 mL), brine, dried (Na_2SO_4), filtered, and concentrated. The crude extract was purified by silica gel chromatography (10% EtOAc/hexanes) to afford the product as yellow oil (5.4 g, 96%). R_f = 0.73 (20% EtOAc/hexanes); IR (neat) 3423 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.94 (ddd, *J* = 17.1, 10.5, 5.9 Hz, 1H), 5.83 (ddd, *J* = 17.1, 10.4, 5.6 Hz, 1H), 5.26 (ddd, *J* = 12.0, 1.5, 1.5 Hz, 1H), 5.22 (ddd, *J* = 11.8, 1.4, 1.4 Hz, 1H), 5.14 (ddd, *J* = 10.5, 1.4, 1.4 Hz, 1H), 5.09 (ddd, *J* = 10.5, 1.5, 1.5 Hz, 1H), 4.62–4.56 (m, 1H), 4.47–4.37 (m, 1H), 3.59 (bs, 1H), 1.87 (ddd, *J* = 14.0, 9.6, 4.4 Hz, 1H), 1.68 (ddd, *J* = 14.4, 4.4, 2.8 Hz, 1H), 1.03–1.10 (m, 21H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 140.9, 140.0, 114.9, 114.0, 73.2, 69.6, 43.2, 18.01, 17.99, 12.2; *m/z* (ESI+) found $[M+H]^+$ 285.2253, $C_{16}H_{33}O_2Si$ requires 285.2250; $[\alpha]_D^{23.6}$ –5.4 (*c* 1.0, DCM).



(*R,R*)-**1.23.1**

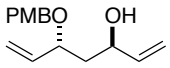
(3*R*,5*R*)-5-((*tert*-Butyldimethylsilyl)oxy)hepta-1,6-dien-3-ol (*R,R*-1.23.1). To a stirred solution of (3*R*,5*R*)-hepta-1,6-diene-3,5-diol (150 mg, 1.17 mmol) and *tert*-butyldimethylsilyltrifluoromethane sulfonate (1.17 mmol, 0.269 mL) in THF (20 mL) at –78 ºC, 2,6-lutidine (1.36 mL, 11.7 mmol) was added dropwise via syringe. The solution was allowed to stir for 2 h at –78 ºC. The reaction was quenched with aq NH_4Cl (20 mL) and extracted with ethyl acetate (3 × 30 mL). The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by silica gel chromatography (10% EtOAc in hexane) to afford the desired product as colorless oil (260 mg, 92%). R_f = 0.62 (20% EtOAc/hexanes); IR (neat) 3419 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.91–5.81 (m, 2H), 5.26 (dt, *J* = 4.0, 1.6 Hz, 1H), 5.22 (dt, *J* = 3.6 Hz, 1H), 5.09 (ddt, *J* = 20.0, 10.4, 1.6 Hz, 2H), 4.51–4.47 (m, 1H), 4.41–4.36 (m, 1H), 3.26 (d, *J* = 2.8 Hz, 1H), 1.77–1.65 (m, 2H), 0.91 (s, 9H), 0.08 (d, *J* = 12.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0, 140.3, 114.8, 114.1, 72.4, 69.7, 43.4, 25.9, 18.2, -4.3, -4.9; *m/z* (ESI+) found $[M+H]^+$ 243.1780, $C_{13}H_{27}O_2Si$ requires 243.1780; $[\alpha]_D^{23.4}$ –11 (*c* 8.9, DCM).



(*R,R*)-**1.24.1**

(3*R*,5*R*)-5-Hydroxyhepta-1,6-dien-3-yl acetate (1.24.1). To a stirred solution of (3*R*,5*R*)-hepta-1,6-diene-3,5-diol (200 mg, 1.56 mmol) in acetonitrile (15 mL), triethyl orthoacetate (0.43 mL, 2.34 mmol) and *p*-toluenesulfonic acid (20 mg) were added. The reaction mixture was stirred at rt for 1h and a mixture of hydrochloric acid in methanol (0.2 mL HCl in 1 mL MeOH) was added to it. The stirring was continued for another 3 h

at rt. The reaction was quenched with saturated $NaHCO_3$ solution (10 mL) and was extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under vacuum. Purification via column chromatography provided the desired product as colorless oil (213 mg, 82%). R_f = 0.52 (20% EtOAc/hexanes); IR (neat) 3426, 1717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.87–5.75 (m, 2H), 5.48–5.42 (m, 1H), 5.23 (d, *J* = 17.2 Hz, 2H), 5.10 (dd, *J* = 23.2, 10.4 Hz, 2H), 4.08 (bs, 1H), 2.73 (s, 1H), 2.06 (s, 3H), 1.85–1.64 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 140.2, 136.3, 116.6, 114.8, 71.8, 68.7, 42.0, 21.2; *m/z* (ESI+) found $[M+H]^+$ 171.1017, $C_9H_{15}O_3$ requires 171.1021; $[\alpha]_D^{23.6}$ +16 (*c* 12.6, DCM).

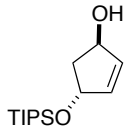


R,R-**1.25.1**

(3*R*,5*R*)-5-((4-Methoxybenzyl)oxy)hepta-1,6-dien-3-ol (1.25.1). To a 100 mL round bottom flask containing sodium hydride (83 mg of 50% dispersion, 1.72 mmol, prewashed with hexane) under argon, a solution of (3*R*,5*R*)-hepta-1,6-diene-3,5-diol (200 mg, 1.56 mmol) in THF (20 mL) was transferred via syringe at 0 ºC. The solution was stirred for 30 min. at rt and again cooled to 0 ºC. A solution of 4-methyoxybenzyl chloride (366 mg in 2 mL of THF, 2.34 mmol) was added via syringe and the reaction mixture was stirred at rt for overnight. The reaction was quenched with saturated NH_4Cl solution (10 mL) and was extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated under vacuum. Purification via column chromatography provided the desired product as colorless oil

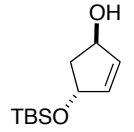
(236 mg, 66%). R_f = 0.55 (20% EtOAc/hexanes); IR (neat) 3430 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 5.93–5.79 (m, 2H), 5.32–5.26 (m, 3H), 5.12 (ddd, *J* = 10.5, 1.6, 1.6 Hz, 1H), 4.56 (d, *J* = 11.2 Hz, 1H), 4.47–4.37 (m, 1H), 4.30 (d, *J* = 11.2 Hz, 1H), 4.16–4.09 (m, 1H), 3.82 (s, 3H), 2.97 (m, 1H), 1.90 (ddd, *J* = 14.4, 8.4, 3.2 Hz, 1H), 1.73 (ddd, *J* = 14.8, 8.0, 3.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 140.8, 138.1, 130.2, 129.6, 117.3, 114.1, 113.9, 77.7, 70.2, 69.8, 55.4, 41.8; *m/z* (ESI+) found $[M+H]^+$ 249.1490, $C_{15}H_{21}O_3$ requires 249.1491; $[\alpha]_D^{23.6}$ +139 (*c* 6.4, DCM).

General procedure for the synthesis of cyclopentenols (1.26.1, 1.4.5, 1.3.3 and 1.26.2) via ring-closing metathesis. A solution of starting diene in DCM (0.02 M) was purged with argon for 5 min and Grubbs-I catalyst (3 mol%) was added to it under argon. The reaction mixture was stirred for 1 h at 50 ºC and quenched with DMSO (1 mL). The solution was stirred under air for 5 min and concentrated. The solvent was evaporated and the crude reaction mixture was purified by silica gel column chromatography to obtain the desired product.



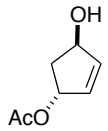
R,R-**1.26.1**

(1*R*,4*R*)-4-((Triisopropylsilyl)oxy)cyclopent-2-enol (1.26.1). Following above general procedure diene **1.20.1** (5.00 g, 17.6 mmol) provided cyclopentenol **1.26.1** (4.14 g, 92%) as a colorless oil. R_f = 0.41 (20% EtOAc/hexanes); IR (neat) 3322 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.04–5.80 (m, 2H), 5.24–5.06 (m, 1H), 4.98 (d, *J* = 1.9 Hz, 1H), 2.24–1.96 (m, 3H), 1.17–0.91 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.5, 135.5, 76.6, 76.2, 44.8, 18.1, 18.0, 12.2; *m/z* (ESI+) found $[M+H]^+$ 257.1933, $C_{14}H_{29}O_2Si$ requires 257.1937; $[\alpha]_D^{23.4}$ +108 (*c* 2.2, DCM). ***(1S,4S)*-1.26.1.** $[\alpha]_D^{23.4}$ –103.5 (*c* 3.0, DCM).



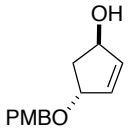
R,R-**1.4.5**

(1*R*,4*R*)-4-((*tert*-Butyldimethylsilyl)oxy)cyclopent-2-enol (1.4.5). Following above general procedure diene **1.23.1** (200 mg, 17.6 mmol) provided cyclopentenol **1.4.5** (156 mg, 88%) as a colorless oil. R_f = 0.44 (20% EtOAc/hexanes); IR (neat) 3327; ^1H NMR (400 MHz, $CDCl_3$) δ 5.95–5.90 (m, 2H), 5.08–5.05 (m, 1H), 5.03–4.97 (m, 1H), 2.08–1.97 (m, 2H), 1.74 (s, 1H), 0.88 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.5, 135.6, 76.7, 76.3, 44.6, 26.0, 18.3, –4.5; *m/z* (ESI+) found $[M+H]^+$ 215.1465, $C_{11}H_{23}O_2Si$ requires 215.1467; $[\alpha]_D^{23.6}$ +120 (*c* 5.4, DCM).



R,R-**1.3.3**

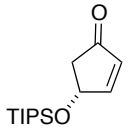
(1*R*,4*R*)-4-Hydroxycyclopent-2-en-1-yl acetate (1.3.3). Following above general procedure diene **1.24.1** (200 mg, 1.17 mmol) provided cyclopentenol **1.3.3** (147 mg, 88%) as a colorless oil. IR (neat) 3374, 1723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.12–6.06 (m, 1H), 6.01–5.95 (m, 1H), 5.81–5.74 (m, 1H), 5.04–4.97 (m, 1H), 2.49 (br s, 1H), 2.17 (ddd, *J* = 14.8, 6.8, 2.8 Hz, 1H), 2.06 (ddd, *J* = 14.8, 7.2, 3.6 Hz, 1H), 2.00 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 139.9, 132.8, 79.1, 75.8, 40.6, 21.2; *m/z* (ESI+) found $[M+H]^+$ 143.0703, $C_7H_{11}O_3$ requires 143.0708; $[\alpha]_D^{23.2}$ +227 (*c* 4.9, DCM).



(*R,R*)-**1.26.2**

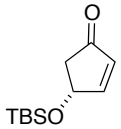
(1*R*,4*R*)-4-((4-Methoxybenzyl)oxy)cyclopent-2-enol (1.26.2). Following above general procedure diene **1.25.1** (200 mg, 0.81 mmol) provided cyclopentenol **1.26.2** (159 mg, 89%) as a colorless oil. R_f = 0.40 (30% EtOAc/hexanes); IR (neat) 3364 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.26 (m, 2H), 6.93–6.87 (m, 2H), 6.12–6.03 (m, 2H), 5.08–5.00 (m, 1H), 4.85–4.78 (m, 1H), 4.50 (d, *J* = 11.2 Hz, 1H), 4.45 (d, *J* = 11.2 Hz, 1H), 3.82 (s, 3H), 2.22 (ddd, *J* = 14.4, 6.8, 3.2 Hz, 1H), 2.00 (ddd, *J* = 14.4, 6.8, 2.8 Hz, 1H), 1.85 (bs, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 137.9, 135.1, 130.6, 129.5, 113.9, 82.9, 70.9, 55.4, 41.1; *m/z* (ESI+) found $[M+H]^+$ 221.1179, $C_{13}H_{17}O_3$ requires 221.1178; $[\alpha]_D^{23.4}$ +139 (*c* 6.4, DCM).

General procedure for the synthesis of cyclopentenones (1.20.3, **1.4.3**, **1.4.1** and **1.27.1).** To a stirred solution of starting cyclopentenol in DCM (0.1 M) was added pyridinium chlorochromate (1.5 equiv) at 0 ºC. The reaction mixture was stirred at rt for 6 h followed by filtration over Celite. The Celite bed was washed with diethyl ether. The combined filtrate was concentrated and purified by silica gel column chromatography to afford the desired enone.



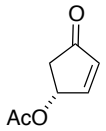
(*R*)-**1.20.3**

(*R*)-4-((Triisopropylsilyl)oxy)cyclopent-2-enone (1.20.3). Following the general procedure above, cyclopentenol **1.26.1** (2.00 g, 7.81 mmol) provided cyclopentenone **1.20.3** (1.86 g, 94%) as a colorless oil. R_f = 0.30 (10% EtOAc/hexanes); IR (neat) 1725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 5.7, 2.3 Hz, 1H), 6.16 (dd, *J* = 5.7, 1.2 Hz, 1H), 5.06 (m, 1H), 2.73 (dd, *J* = 18.1, 5.9 Hz, 1 H), 2.28 (dd, *J* = 18.1, 2.2 Hz, 1H), 1.21–0.98 (m, 3H), 1.06 (d, *J* = 5.4 Hz, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.5, 163.8, 134.3, 70.9, 45.4, 18.0, 17.9, 12.1; *m/z* (ESI+) found $[M+H]^+$ 255.1786, $C_{14}H_{27}O_2Si$ requires 255.1780; $[\alpha]_D^{23.8}$ –53 (*c* 1.05, MeOH). Chiral GC separation: Astec Chiraldex B-DM fused silica capillary column, 30m × 0.25 mm × 0.12 mm, temperature 175 ºC, t_R = 37.9 min, t_S = 38.7 min, *er* 97:3. By following the same procedure, cyclopentenol (*S*)-**1.26.1** (100 mg, 0.39 mmol) provided cyclopentenone (*S*)-**1.20.3** (93 mg, 94%) as a colorless oil. (*S*)-**1.20.3** *er* 99:1.



(*R*)-**1.4.3**

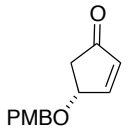
(*R*)-4-((*tert*-Butyldimethylsilyl)oxy)cyclopent-2-enone (1.4.3). Following above general procedure cyclopentenol **1.4.5** (120 mg, 0.56 mmol) provided cyclopentenone **1.4.3** (110 mg, 93%) as a colorless oil. R_f = 0.73 (20% EtOAc/hexane); IR (neat) 1722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 5.6, 2.4 Hz, 1H), 6.16 (dd, *J* = 5.6, 1.2 Hz, 1H), 5.10–4.94 (m, 1H), 2.69 (dd, *J* = 18.4, 6.0 Hz, 1H), 2.22 (dd, *J* = 18.0, 2.0 Hz, 1H), 0.88 (s, 9H), 0.11 (d, *J* = 4.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.4, 163.8, 134.4, 70.8, 44.95, 25.7, 18.1, –4.6 (2); *m/z* (ESI+) found $[M+H]^+$ 213.1315, $C_{11}H_{21}O_2Si$ requires 213.1311; $[\alpha]_D^{23.6}$ +64 (*c* 1.6, MeOH). Chiral GC separation: Astec Chiraldex B-DM fused silica capillary column, 30m × 0.25 mm × 0.12 mm, temperature 175 ºC, t_R = 14.38 min, t_S = 15.11 min, *er* 97:3.



(*R,R*)-**1.4.1**

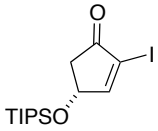
(*R*)-4-Oxocyclopent-2-en-1-yl acetate (1.4.1). Following above general procedure cyclopentenol **1.3.3** (100 mg, 0.70 mmol) provided cyclopentenone **1.4.1** (91 mg, 92%) as a colorless oil. R_f = 0.73 (20% EtOAc/hexanes); IR (neat) 1720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 5.6, 2.4 Hz, 1H), 6.31 (dd, *J* = 5.6, 1.2 Hz, 1H), 5.85–5.80 (m, 1H), 2.80 (dd, *J* = 18.7, 6.4 Hz, 1H), 2.30 (dd, *J* = 18.7, 2.0 Hz, 1H), 2.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.0, 170.5, 159.0, 137.0, 72.0, 41.0, 20.8; *m/z* (ESI+) found

$[M+H]^+$ 141.0550, $C_7H_9O_3$ requires 141.0552; $[\alpha]_D^{23.8}$ +100 (*c* 1.4, MeOH). Astec Chiraldex B-DM fused silica capillary column, 30m × 0.25 mm × 0.12 mm, temperature 105–110 ºC, t_R = 9.85 min, t_S = 10.77 min, *er* 98.2.



(*R*)-**1.27.1**

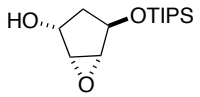
***(R)*-4-((4-Methoxybenzyl)oxy)cyclopent-2-enone (1.27.1).** Following above general procedure cyclopentenol **1.26.2** (130 mg, 0.59 mmol) provided cyclopentenone **1.27.1** (119 mg, 92%) as a colorless oil. R_f = 0.73 (20% EtOAc/hexanes); IR (neat) 1714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 5.7, 2.3 Hz, 1H), 7.29 (d, J = 8.6 Hz, 2H), 6.91 (d, J = 8.6 Hz, 2H), 6.24 (dd, *J* = 5.7, 1.2 Hz, 1H), 4.78–4.72 (m, 1H), 4.56 (dd, *J* = 21.3, 11.3 Hz, 2H), 3.81 (s, 3H), 2.67 (dd, *J* = 18.4, 6.0 Hz, 1H), 2.34 (dd, *J* = 18.0, 2.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.9, 161.3, 159.5, 135.5, 129.5, 129.5, 113.9, 76.5, 71.6, 55.2, 41.8; *m/z* (ESI+) found $[M+H]^+$ 219.1023, $C_{13}H_{15}O_3$ requires 219.1021; $[\alpha]_D^{23.3}$ +51 (*c* 3.9, DCM). HPLC (Chiralpak IC column *n*-hexane/*i*-PrOH = 90/10, flow rate = 1.0 mL/min, t_R = 38.29 min, t_S = 38.8, *er* >99:1).



(*R*)-**1.20.4**

(*R*)-2-Iodo-4-((triisopropylsilyl)oxy)cyclopent-2-enone (1.20.4). To a stirred solution of I_2 (110 mg, 0.43 mmol) in Et_2O (10 mL) was added pyiridine (0.02 mL, 0.25 mmol)

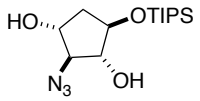
followed by dropwise addition of enone **1.20.3** (89 mg, 0.35 mmol) at rt. The reaction flask was completely covered with aluminum foil to protect from light. After 24 h, the reaction was quenched with aq $Na_2S_2O_3$ (50 mL). The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The resulting oil was purified using silica gel chromatography (10% Et_2O in hexane) to afford the product as colorless oil (11 g, 85%). R_f = 0.45 (20% EtOAc/hexanes); IR (neat) 1726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 2.5 Hz, 1H), 6.04 (ddd, *J* = 6.0, 2.3, 2.3, 1H), 2.90 (dd, *J* = 18.1, 6.0 Hz, 1H), 2.40 (dd, *J* = 18.1, 2.1 Hz, 1H), 1.30–0.87 (m, 3H), 1.07 (d, *J* = 5.3 Hz, 18H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 200.4, 169.4, 105.0, 72.4, 43.0, 18.0 (2), 12.1; *m/z* (ESI+) found $[M+H]^+$ 381.0750, $C_{14}H_{26}IO_2Si$ requires 381.0747; $[\alpha]_D^{23.7}$ +23 (*c* 4.3, DCM). Chiral GC separation: Astec Chiraldex B-DM fused silica capillary column, 30m × 0.25 mm × 0.12 mm, temperature 175 ºC, t_R = 20.99 min, t_S = 21.84 min, *er* 97:3. (*S*)-**1.20.4** $[\alpha]_D^{23.7}$ –25 (c 2.7, DCM), *er* 99:1.



1.30.2

(1*R*,2*R*,4*R*,5*R*)-4-((Triisopropylsilyl)oxy)-6-oxabicyclo[3.1.0]hexan-2-ol (1.30.2). To a solution of (1*R*,4*R*)-4-((triisopropylsilyl)oxy)cyclopent-2-enol (500 mg, 1.95 mmol) in DCM (20 mL) *m*-CPBA (657 mg, 2.93 mmol) was added at 0 ºC and the reaction mixture was stirred at rt for 28 h. The reaction mixture was quenched with saturated $Na_2S_2O_3$ (20 mL) and extracted with DCM (3 × 50 mL). The combined organic layer was washed with saturated $NaHCO_3$, brine and dried (Na_2SO_4). Evaporation of the solvent followed by column chromatography (silica gel, 10% EtOAc/hexane) gave the desired product as

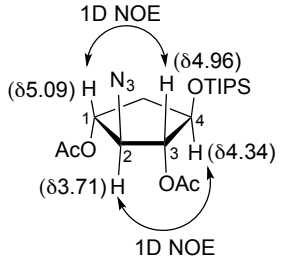
colorless oil (350 mg, 66%). R_f = 0.37 (10% EtOAc/hexanes); IR (neat) 3320 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.50 (td, *J* = 7.9, 0.9 Hz, 1H), 4.42 (d, *J* = 5.3 Hz, 1H), 3.57–3.51 (m, 1H), 3.43–3.36 (m, 1H), 2.30 (m, 1H), 1.96 (dd, *J* = 13.7, 8.0 Hz, 1H), 1.47 (ddd, *J* = 13.5, 8.0, 5.4 Hz, 1H), 1.12–0.94 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 72.3, 71.7, 58.7, 58.6, 39.1, 18.0, 12.1; *m/z* (ESI+) found $[M+H]^+$ 273.1883, $C_{14}H_{29}O_3Si$ requires 273.1886; $[\alpha]_D^{25.3}$ +26 (*c* 2.5, DCM).

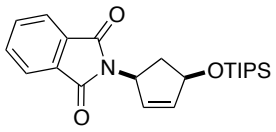


1.30.3

(1*R*,2*S*,3*R*,4*R*)-2-Azido-4-((triisopropylsilyl)oxy)cyclopentane-1,3-diol (1.30.3). To a solution of (1*R*,2*R*,4*R*,5*R*)-4-((triisopropylsilyl)oxy)-6-oxabicyclo[3.1.0]hexan-2-ol (150 mg, 0.55 mmol) in DMF (10 mL), tetrabutylammonium chloride (153 mg, 0.55 mmol) and sodium azide (358 mg, 5.5 mmol) were added. The reaction mixture was heated at 80 ºC for 24 h. The solvent was removed under reduced pressure and the residue was diluted with water. The reaction mixture was extracted with ethyl acetate and was dried (Na_2SO_4). Evaporation of the solvent followed by column chromatography (silica gel, 20% EtOAC/Hexane) provided the desired product as colorless oil. R_f = 0.30 (20% EtOAc/hexanes); IR (neat) 3320, 2102 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.24–4.12 (m, 1H), 3.84 (dt, *J* = 7.8, 4.9 Hz, 1H), 3.53 (t, *J* = 7.4 Hz, 1H), 2.28 (d, *J* = 4.6 Hz, 1H), 2.10 (m, 1H), 2.07–2.00 (m, 2H), 1.66 (m, 1H), 1.13–1.00 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 82.5, 75.1, 72.7, 72.2, 40.2, 17.9, 12.1; *m/z* (ESI+) found $[M+H]^+$ 316.2055, $C_{14}H_{30}N_3O_3Si$ requires 316.2056; $[\alpha]_D^{25.3}$ –53 (*c* 0.6, DCM).

Stereo- and regiochemistry of the compound **1.30.3** was confirmed by 2D HNMR analysis of the corresponding diacetate **1.30.4,** which was made by treating **1.30.3** with acetic anhydride and pyridine. IR (neat) 2104, 1747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 (dd, *J* = 13.2, 6.1 Hz, 1H), 4.96 (t, *J* = 5.1 Hz, 1H), 4.34 (dd, *J* = 11.3, 5.7 Hz, 1H), 3.71 (t, *J* = 5.5 Hz, 1H), 2.33 – 2.18 (m, 1H), 2.09 (s, 3H), 2.07 (s, 3H), 2.03–1.89 (m, 1H), 1.16–0.90 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 170.0, 82.4, 75.8, 73.6, 68.8, 38.0, 21.0, 20.9, 17.82, 17.78, 12.0. Both H1 and H3 show COSY correlation with H2 that confirms the regiochemistry of azide. Further existence of 1D NOE correlation of H1 with H3 and H2 with H4 confirms the stereochemistry of the compound **1.30.4**, hence establishing the structure **1.30.1**.

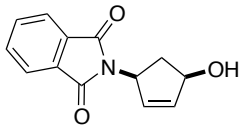




1.31.1

2-((1*S*,4*R*)-4-((Triisopropylsilyl)oxy)cyclopent-2-en-1-yl)isoindoline-1,3-dione (1.31.1). To a solution of cyclopentenol **1.26.1** (300 mg, 1.17 mmol), phthalimide (344 mg, 2.34 mmol) and triphenylphosphine (614 mg, 2.34 mmol) in benzene (10 mL) diethyldiazocarboxylate (0.36 mL, 2.34 mmol) was added dropwise at rt and the reaction

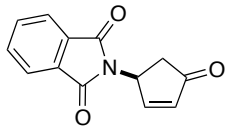
mixture stirred at rt for 24 h. The reaction mixture was quenched with water (10 mL) and was extracted with diethylether (3 × 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. Column chromatography of the crude provided the desired product as viscous oil (319 mg, 68%). R_f = 0.74 (20% EtOAc/hexanes); IR (neat) 1698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85–7.74 (m, 2H), 7.74–7.62 (m, 2H), 6.01 (ddd, *J* = 5.6, 2.5, 1.8 Hz, 1H), 5.86 (dt, *J* = 5.7, 1.7 Hz, 1H), 5.10 (tq, *J* = 8.4, 2.0 Hz 1H), 4.91 (tq, *J* = 6.9, 1.7 Hz, 1H), 2.75 (dt, *J* = 12.3, 7.4 Hz, 1H), 2.20–2.05 (ddd, *J* = 12.4, 8.4, 6.8 Hz, 1H), 1.16–0.95 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 137.1, 134.0, 132.0, 130.8, 123.2, 75.6, 53.4, 40.4, 18.1, 12.21; *m/z* (ESI+) found $[M+H]^+$ 386.2147, $C_{22}H_{32}NO_3Si$ requires 386.2151; $[\alpha]_D^{24.7}$ –97 (*c* 5.2, DCM).



1.31.2

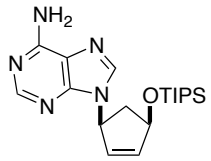
2-((1*S*,4*R*)-4-Hydroxycyclopent-2-en-1-yl)isoindoline-1,3-dione (1.31.2). To a solution of 2-((1*S*,4*R*)-4-((triisopropylsilyl)oxy)cyclopent-2-en-1-yl)isoindoline-1,3-dione (100 mg, 0.25 mmol) in THF (5 mL), tetrabutylammonium fluoride (0.5 mL of 1M solution in THF, 0.5 mmol) was added dropwise and stirred at rt for 1 h. The reaction mixture was quenched with water (5 mL) and was extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated. Column chromatography (silica gel, 30% EtOAc/Hexane) of the crude provided the desired product as viscous oil (45 mg, 79%). R_f = 0.20 (20%

EtOAc/hexanes); IR (neat) 3315, 1697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86–7.79 (m, 2H), 7.77–7.69 (m, 2H), 6.23 (dt, *J* = 5.6, 2.0 Hz 1H), 5.75 (dd, *J* = 5.5, 2.6 Hz, 1H), 5.25 (ddd, *J* = 9.6, 4.4, 2.2 Hz, 1H), 4.76 (m, 1H), 4.15–4.01 (m, 1H), 2.84 (ddd, *J* = 15.4, 9.6, 7.8 Hz, 1H), 1.99 (ddd, *J* = 15.4, 2.0, 1.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 138.6, 134.4, 131.9, 130.3, 123.5, 76.0, 53.1, 38.3; *m/z* (ESI+) found $[M+H]^+$ 230.0809, $C_{13}H_{12}NO_3$ requires 230.0817; $[\alpha]_D^{25.1}$ –120 (*c* 3.0, DCM).



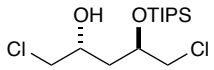
1.31.3

(*S*)-2-(4-Oxocyclopent-2-en-1-yl)isoindoline-1,3-dione (1.31.3). To a solution of 2-((1*S*,4*R*)-4-hydroxycyclopent-2-en-1-yl)isoindoline-1,3-dione (40 mg, 0.18 mmol) in dichloromethane (3 mL), pyridiniumchlorochromate (56 mg, 0.26 mmol) was added at 0 ºC. The reaction mixture was stirred at RT for 1h and was diluted with Et_2O (15 mL). The mixture was filtered through Celite. Evaporation of solvent followed by column chromatography (silica gel, 10% EtOAc/hexane) gave the desired product as colorless oil (36 mg, 91%). IR (neat) 1721, 1698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90–7.81 (m, 2H), 7.80–7.70 (m, 2H), 7.52 (dd, *J* = 5.7, 2.4 Hz, 1H), 6.44 (dd, *J* = 5.7, 2.2 Hz, 1H), 5.54 (ddt, *J* = 6.9, 3.3, 2.3 Hz, 1H), 2.80 (qd, *J* = 18.3, 5.2 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 205.3, 167.7, 159.7, 136.3, 134.6, 131.8, 123.7, 49.8, 39.7; *m/z* (ESI+) found $[M+H]^+$ 228.0661, $C_{13}H_{10}NO_3$ requires 228.0661; $[\alpha]_D^{25.3}$ –67 (*c* 2.0, DCM).



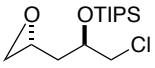
1.31.4

9-((1*S*,4*R*)-4-((Triisopropylsilyl)oxy)cyclopent-2-en-1-yl)-9*H*-purin-6-amine (1.31.4). To a solution of (1*R*,4*R*)-4-((triisopropylsilyl)oxy)cyclopent-2-enol (100 mg, 0.39 mmol), adenine (106 mg, 0.78 mmol) and triphenylphosphine (205 mg, 0.78 mmol) in THF (10 mL), diethyldiazocarboxylate (0.12 mL, 0.78 mmol) was added dropwise at rt and the reaction mixture stirred for 24 h. The reaction mixture was quenched with water (5 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. Column chromatography (silica gel, 30% EtOAc/hexane) of the crude provided the desired product as viscous oil (103 mg, 70%). R_f = 0.35 (30% EtOAc/hexanes); IR (neat) 3360 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.07 (s, 1H), 6.26 (dt, *J* = 5.6, 2.0 Hz, 1H), 6.23 (m, 2H), 6.00 (dd, *J* = 5.5, 2.2 Hz, 1H), 5.63 (m, 1H), 5.00 (dt, *J* = 6.8, 2.0 Hz, 1H), 2.96 (ddd, *J* = 14.9, 8.2, 6.9 Hz, 1H), 1.88 (dt, *J* = 14.4, 3.1 Hz, 1H), 1.20–0.99 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 153.0, 149.7, 139.8, 139.3, 131.3, 119.6, 75.6, 56.7, 42.8, 18.1, 12.1; *m/z* (ESI+) found $[M+H]^+$ 374.2370, $C_{19}H_{32}N_5OSi$ requires 374.2376; $[\alpha]_D^{25.3}$ –53 (*c* 0.6, DCM).



(*R,R*)-**2.14.1**

(2*R*,4*R*)-1,5-Dichloro-4-((triisopropylsilyl)oxy)pentan-2-ol (2.14.1). To a solution of dichloro diol **1.21.5** (1.00 g, 5.76 mmol) in THF (60 mL) at –78 ºC, *n*-BuLi (2.5 mL, 5.76 mmol, 2.5 M in hexanes) was added dropwise. The reaction mixture was stirred at –78 ºC for 30 min. Triisopropylsilyl chloride (1.11 g, 5.76 mmol) was added via syringe and the reaction mixture was brought to –40 ºC over 2 h. The reaction was allowed to stir at –40 ºC for 4 h and the progress of the reaction was monitored by TLC. The reaction was quenched with saturated aq NH_4Cl and was extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude reaction mixture was purified by column chromatography to obtain the product as colorless oil in 94% yield (1.85 g). R_f = 0.35 (10% EtOAc/hexanes); IR (neat) 3360 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.34–4.28 (m, 1H), 4.16–4.05 (m, 1H), 3.59 (dd, *J* = 10.9, 4.3 Hz, 1H), 3.57–3.51 (m, 2H), 3.49 (dd, *J* = 11.1, 6.2 Hz, 1H), 3.11 (s, 1H), 1.89–1.85 (m, 2H), 1.14–1.02 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 70.7, 68.1, 50.2, 47.2, 38.0, 18.1, 18.07, 12.6; *m/z* (ESI+) found $[M+H]^+$ 329.1470, $C_{14}H_{31}Cl_2O_2Si$ requires 329.1470; $[\alpha]_D^{24.2}$ +31.7 (*c* .86, DCM). (2*S*,4*S*)-**2.14.1** $[\alpha]_D^{23.9}$ –30.3 (*c* 1.0, DCM).

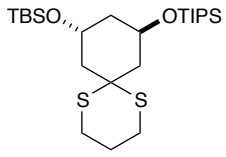


(*R,R*)-**2.14.2**

(((*R*)-1-Chloro-3-((*R*)-oxiran-2-yl)propan-2-yl)oxy)triisopropylsilane (2.14.2). To a solution of (2*R*,4*R*)-1,5-diiodo-4-((triisopropylsilyl)oxy)pentan-2-ol **2.14.1** (1.0 g, 3.0

mmol) in anhydrous Et_2O (25 mL) dry KOH powder (0.56 g, 9.9 mmol) was added at 0 ºC and the mixture was stirred at room temperature for 3 h. The reaction mixture was filtered through a bed of anhydrous $MgSO_4$, and the $MgSO_4$ was washed with diethyl ether. The filtrate was concentrated and was subjected to column chromatography to obtain the product as colorless oil in 97% yield (860 mg). R_f = 0.35 (30% EtOAc/hexanes); IR (neat) 2945, 2867, 2358, cm^{-1}; ^1H NMR (400 MHz, CDCl3) δ 4.24 (tt, *J* = 6.4, 4.6 Hz, 1H), 3.57 (dd, *J* = 4.5, 11.0 Hz, 1H), 3.53 (dd, *J* = 6.5, 11.0 Hz, 1H), 3.09 (dddd, *J* = 6.6, 5.1, 3.9, 2.7 Hz, 1H), 2.82 (dd, *J* = 5.1, 4.0 Hz, 1H), 2.55 (dd, *J* = 5.1, 2.7 Hz, 1H), 1.89 (ddd, *J* = 14.0, 6.2, 4.9 Hz, 1H), 1.86–1.79 (m, 1H), 1.12–1.03 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 70.8, 49.1, 48.4, 47.6, 38.2, 18.22, 18.20, 12.7; *m/z* (ESI+) found 293.1700 $[M+H]^+$, $C_{14}H_{30}ClO_2Si$ requires 293.1704; $[\alpha]_D^{25.3}$ +25.1 (*c* 2.3 , DCM).

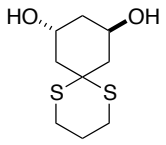
By following above procedure, (2*S*,4*S*)-**2.14.1** (600 mg, 1.82 mmol) in anhydrous Et_2O (20 mL) on treatment with dry KOH powder (306 mg, 5.5 mmol) provided (2*S*,4*S*)-**2.14.2** as a colorless oil in 95% yield (506 mg). $[\alpha]_D^{24.4}$ –24.6 (*c* 1.1, DCM).



(*R,R*)-**2.15.3**

***tert*-Butyldimethyl(((8*R*,10*R*)-10-((triisopropylsilyl)oxy)-1,5-dithiaspiro[5.5]undecan-8-yl)oxy)silane (2.15.3).** To a solution of *tert*-butyl(1,3-dithian-2-yl)dimethylsilane (46 mg, 0.19 mmol) in THF (0.9 mL), *n*-BuLi (0.086 mL, 2.5 M in hexanes), was added dropwise at room temperature. The resulting yellow solution was stirred for 15 min and

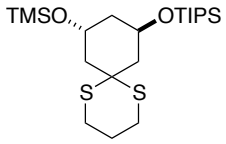
was transferred dropwise via syringe to a solution of epoxide (*R*,*R*)-**2.14.2** (56 mg, 0.19 mmol) in THF/HMPA (0.9 mL/0.1 mL) precooled to –40 ºC. The reaction mixture was stirred at –40 ºC for 30 min and then was allowed to rise to room temperature for 16 h. The reaction was diluted with water and was extracted with Et_2O. The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography to obtain the product as colorless oil in 69% yield (860 mg). R_f = 0.40 (5% EtOAc/hexanes); IR (neat) 2358, 2329 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.37 (tt, *J* = 7.6, 3.6 Hz, 1H), 4.25 (tt, *J* = 6.2, 3.4 Hz, 1H), 2.91 (ddd, *J* = 14.4, 8.4, 3.5 Hz, 1H), 2.79 (ddd, *J* = 6.0, 3.8, 1.6 Hz, 2H), 2.74 (dt, *J* = 10.9, 3.6 Hz, 1H), 2.44 (d, *J* = 13.4 Hz, 1H), 2.13 (dd, *J* = 13.9, 3.5 Hz, 1H), 2.01–1.74 (m, 5H), 1.67 (ddd, *J* = 13.0, 7.9, 3.4 Hz, 1H), 1.07 (s, 21H), 0.89 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 67.0, 66.2, 48.6, 46.0, 45.6, 43.8, 26.8, 26.0, 25.6, 18.3, 18.2, 12.5, -4.7, -4.8; *m/z* (ESI+) found $[M+Na]^+$ 513.2685, $C_{24}H_{50}O_2S_2SiNa$ requires 513.2688; $[\alpha]_D^{25.3}$ –6.0 (*c* 1, DCM).



(*R*,*R*)-**2.15.4**

(8*R*,10*R*)-1,5-Dithiaspiro[5.5]undecane-8,10-diol (2.15.4). To a solution of *tert*-butyldimethyl(((8*R*,10*R*)-10-((triisopropylsilyl)oxy)-1,5-dithiaspiro[5.5]undecan-8-yl)oxy)silane in THF (50 mg, 0.10 mmol), tetrabutylammonium fluoride (0.15 ml, 0.15 mmol, 1M solution in THF) was added and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water and was extracted with

ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude reaction mixture was purified by column chromatography to obtain the product as colorless oil in 91% yield (20 mg). R_f = 0.30 (30% EtOAc/hexanes); IR (neat) 3360 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.29–4.22 (m, 2H), 3.00–2.85 (m, 6H), 2.27 (dd, *J* = 14.0, 6.8 Hz, 2H), 2.18 (dd, *J* = 14.0, 4.1 Hz, 2H), 2.02 (p, *J* = 5.7 Hz, 2H), 1.87 (t, *J* = 5.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 65.4, 48.3, 43.9, 42.3, 26.5, 25.3; *m/z* (ESI+) found $[M+H]^+$ 221.0672, $C_9H_{17}O_2S_2$ requires 221.0670; $[\alpha]_D^{25.3}$ +39.5 (*c* .85, DCM).

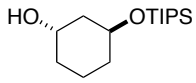


(*R,R*)-**2.16.1**

Triisopropyl(((8*R*,10*R*)-10-((trimethylsilyl)oxy)-1,5-dithiaspiro[5.5]undecan-8-yl)oxy)silane (2.16.1). To a solution of (1,3-dithian-2-yl)trimethylsilane (36 mg, 0.18 mmol) in THF (0.5 mL) *n*-BuLi (0.092 mL, 0.21 mmoL) was added dropwise at room temperature. The resulting yellow solution was stirred for 15 min and was transferred dropwise via syringe to a solution of epoxide (*R,R*)-**2.14.2** (50 mg, 0.17 mmol) in THF/HMPA (1.7 mL/0.8 mL) precooled to –40 ºC. The resulting light yellow solution was stirred at –40 ºC for 1 h and was then brought to room temperature for 16 h. The reaction mixture was diluted with water and was extracted with diethyl ether. The combined organic layer was washed with brine, dried, filtered and concentrated. The crude product was purified by column chromatography to obtain the product as colorless oil in 72% yield (55 mg). R_f = 0.35 (5% EtOAc/hexanes); IR (neat) 2358, 2329 cm^{-1}; ^1H

NMR (400 MHz, $CDCl_3$) δ 4.36 (td, *J* = 5.7, 2.9 Hz, 1H), 4.30 (dt, *J* = 8.0, 4.2 Hz, 1H), 2.93 (ddd, *J* = 14.4, 8.5, 3.6 Hz, 1H), 2.87–2.77 (m, 2H), 2.77–2.71 (m, 1H), 2.47–2.38 (m, 1H), 2.15 (dd, *J* = 14.1, 3.6 Hz, 1H), 2.05–1.87 (m, 3H), 1.81 (dt, *J* = 13.4, 8.4 Hz, 2H), 1.67 (ddd, *J* = 12.5, 8.2, 3.4 Hz, 1H), 1.08 (s, 21H), 0.13 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 67.2, 65.9, 48.7, 46.0, 45.7, 43.8, 26.8, 26.7, 25.6, 18.33, 18.29, 12.5, 0.2; *m/z* (ESI+) found $[M+Na]^+$ 471.2219, $C_{21}H_{44}O_2S_2Si_2Na$ requires 471.2219; $[\alpha]_D^{25.3}$ +103.5 (*c* 2.1, DCM).

By following above procedure, 500 mg (1.71 mmol) of the (((*S*)-1-chloro-3-((*S*)-oxiran-2-yl)propan-2-yl)oxy)triisopropylsilane was converted to (*S*,*S*)-(1.1 g, 2.4 mmol). $[\alpha]_D^{25.3}$ –104.7 (*c* 2.3, DCM).

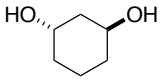


(*S,S*)-**2.16.2**

(1*S*,3*S*)-3-((Triisopropylsilyl)oxy)cyclohexanol (2.16.2). To a solution of triisopropyl(((8*R*,10*R*)-10-((trimethylsilyl)oxy)-1,5-dithiaspiro[5.5]undecan-8-yl)oxy)silane (50 mg, 0.11 mmol) in ethanol (1 mL), Raney Nickel (0.3 mL suspension in water) was added in one portion and the reaction mixture was heated to reflux for 4 h. Reaction did not go to completion in 4h [Note: In some cases, an additional 5 mL suspension of Raney Nickel (washed with ethanol) was added and the reaction was refluxed for further 16 h.] The grey suspension was filtered through a plug of silica and the filtrate was concentrated. The crude reaction mixture was purified by column chromatography to obtain the product in 77% yield (20 mg, 0.085 mmol) as colorless oil. R_f = 0.32 (10% EtOAc/hexanes); IR (neat) 3378 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$) δ

4.22 (tt, *J* = 5.8, 3.1 Hz, 1H), 4.07 (td, *J* = 8.9, 4.3 Hz, 1H), 2.00–1.66 (m, 3H), 1.66–1.42 (m, 7H), 1.41–1.19 (m, 2H), 1.13–0.92 (m, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 68.2, 67.6, 43.5, 35.3, 34.3, 19.4, 18.6, 12.8; $[\alpha]_D^{25.3}$ +39.5 (*c* 2.1, DCM); *m/z* (ESI+) found $[M+Na]^+$ 295.2066, $C_{15}H_{32}NaO_2Si$ requires 295.2069. Chiral GC separation: Astec Chiraldex B-DM fused silica capillary column, 30m × 0.25 mm × 0.12 mm, temperature 145 ºC, t_R = 10.33 min, t_S = 11.03 min, *er* 99>1.

Similarly, 1.02 g (2.28 mmol) of the triisopropyl (((8*S*,10*S*)-10-((trimethylsilyl)oxy)-1,5-dithiaspiro[5.5]undecan-8-yl)oxy)silane in ethanol (20 mL) was treated with Raney-Nickel (5 mL of 50% aq suspension washed with ethanol) to provide (1*R*,3*R*)-3-((Triisopropylsilyl)oxy)cyclohexanol as colorless oil (430 mg, 1.35 mmol). $[\alpha]_D^{25.3}$ –42.5 (*c* 2.3, DCM); *er* >99:1.

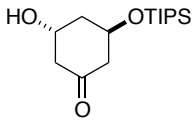


(*S,S*)-**2.16.3**

(1*S*,3*S*)-Cyclohexane-1,3-diol (2.16.3). To a solution of (1*S*,3*S*)-3-((triisopropylsilyl)oxy)cyclohexanol **2.16.2** (50 mg, 0.11 mmol) in THF (0.5 mL), tetrabutylammonium fluoride (0.15 ml, 0.15 mmol, 1M solution in THF) was added and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water and was extracted with ethyl acetate. The combined organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude reaction mixture was purified by column chromatography to obtain the product as colorless oil in 91% yield (20 mg). R_f = 0.2 (100% EtOAc); IR (neat) 3378 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15–4.06 (m, 2H), 1.83–1.55 (m, 8H), 1.52–1.35 (m, 2H); ^{13}C NMR (101 MHz,

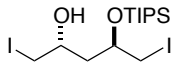
$CDCl_3$) δ67.1, 42.2, 33.9, 18.9; $[\alpha]_D^{25.3}$ +3.7 (*c* 2.0, DCM); *m/z* (ESI+) found $[M+Na]^+$ 139.0734, $C_6H_{12}NaO_2$ requires 139.0735.

By following above procedure, 410 mg (1.50 mmol) of the (1*R*,3*R*)-3-((triisopropylsilyl)oxy)cyclohexanol was converted to (1*R*,3*R*)-cyclohexane-1,3-diol **2.16.3** (218 mg, 1.35 mmol); $[\alpha]_D^{25.3}$ – 3.5 (*c* , DCM).



(*R,R*)-**2.16.4**

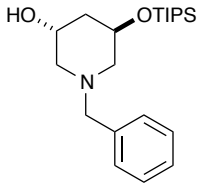
(3*S*,5*S*)-3-Hydroxy-5-((triisopropylsilyl)oxy)cyclohexanone (2.16.4). To a solution of triisopropyl(((8*S*,10*S*)-10-((trimethylsilyl)oxy)-1,5-dithiaspiro[5.5]undecan-8-yl)oxy)silane (50 mg, 0.11 mmol) in acetonitrile (0.5 mL), $HgCl_2$ (59 mg, 0.22 mmol) was added in one portion and the reaction mixture was stirred vigorously at room temperature for 16 h. The white suspension was filtered through a plug of silica and the filtrate was concentrated. The crude reaction mixture was purified by column chromatography to obtain the product in 76% yield (20 mg, 0.085 mmol) as a colorless oil. R_f = 0.33 (50% EtOAc/hexanes); IR (neat) 3380, 1719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.51 (tt, *J* = 6.3, 3.4 Hz, 1H), 4.43 (t, *J* = 4.0 Hz, 1H), 2.72 (ddt, *J* = 14.2, 4.6, 1.6 Hz, 1H), 2.56 (ddt, *J* = 14.3, 4.0, 1.2 Hz, 1H), 2.47 (ddt, *J* = 14.2, 5.6, 1.5 Hz, 1H), 2.38 (ddd, *J* = 14.2, 8.2, 1.2 Hz, 1H), 2.18 (dddt, *J* = 13.1, 6.5, 3.8, 1.4 Hz, 1H), 2.00–1.92 (m, 1H), 1.64 (s, 1H), 1.13–0.96 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.6, 67.1, 66.5, 50.4, 50.0, 41.7, 18.1, 12.3; *m/z* (ESI+) found $[M+Na]^+$ 309.1859, $C_{15}H_{30}O_2SiNa$ requires 309.1862; $[\alpha]_D^{25.3}$ +42.5 (*c* 1.1, DCM).



(*R*,*R*)-**2.18.1**

(2*R*,4*R*)-1,5-Diiodo-4-((triisopropylsilyl)oxy)pentan-2-ol (2.18.1). A mixture of dichorodiol **2.14.1** (300 mg, 0.91 mmol) and NaI in acetone was allowed to reflux for 24 h. The reaction mixture was concentrated and was subjected to column chromatography to obtain the diiodo product as colorless oil in 94% yield (439 mg). R_f = 0.35 (10% EtOAc/hexanes); IR (neat) 3360 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.29 (ddt, *J* = 8.0, 5.7, 4.1 Hz, 1H), 3.93–3.83 (m, 1H), 3.60 (dd, *J* = 11.0, 4.3 Hz, 1H), 3.54 (dd, *J* = 11.0, 8.1 Hz, 1H), 3.31 (dd, *J* = 10.1, 4.5 Hz, 1H), 3.22 (dd, *J* = 10.1, 6.1 Hz, 1H), 3.20–3.16 (m, 1H), 1.99 (ddd, *J* = 14.4, 5.7, 2.4 Hz, 1H), 1.85 (ddd, *J* = 14.1, 10.2, 3.5 Hz, 1H), 1.10–1.05 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 71.0, 67.6, 46.8, 40.0, 18.2, 18.1, 15.2, 12.5; *m/z* (ESI+) found $[M+H]^+$ 513.0180, $C_{14}H_{31}I_2O_2Si$ requires 513.0183; $[\alpha]_D^{25.3}$ –22.7 (*c* 1.2 , DCM).

By following above procedure, (2*S*,4*S*)-**2.18.1** was obtained in 90% yield using (2*S*,4*S*)-**2.14.1** (1.5 g, 4.5 mmol). $[\alpha]_D^{25.3}$ +20.7 (*c* 0.53, DCM).



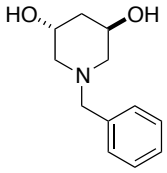
(*R*,*R*)-**2.18.2**

(3*R*,5*R*)-1-Benzyl-5-((triisopropylsilyl)oxy)piperidin-3-ol (2.18.2).

To a solution of diiodo diol (2*R*,4*R*)-**2.19.1** (50 mg, 0.097) in ethanol, benzylamine (0.013 mL, 0.12 mmol) was added and the resulting mixture was refluxed for 16 h at 100 ºC. The reaction mixture was diluted with water and was extracted with ethyl acetate. The

combined organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude reaction mixture was purified by column chromatography to obtain the product as colorless oil in 71% yield (25 mg, 0.69 mmol). R_f = 0.35 (30% EtOAc/hexanes); IR (neat) 3310 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.21 (m, 5H), 4.09 (tt, *J* = 9.7, 4.7 Hz, 1H), 3.95 (s, 1H), 3.56 (d, *J* = 3.0 Hz, 2H), 2.95 (ddt, *J* = 10.8, 3.8, 1.8 Hz, 1H), 2.76 (ddt, *J* = 11.4, 3.8, 1.8 Hz, 1H), 2.50 (d, *J* = 10.3 Hz, 1H), 2.19 (dd, *J* = 11.5, 1.9 Hz, 1H), 2.14 (td, *J* = 5.3, 4.4, 3.2 Hz, 1H), 1.93 (dd, *J* = 10.7, 9.4 Hz, 1H), 1.38 (ddd, *J* = 13.2, 10.4, 2.9 Hz, 1H), 1.08–0.91 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.0, 129.1, 128.4, 127.3, 66.3, 65.4, 62.4, 61.4, 59.0, 41.3, 18.2, 12.4; *m/z* (ESI+) found $[M+H]^+$ 364.2676, $C_{21}H_{38}NO_2Si$ requires 364.2672. $[\alpha]_D^{25.3}$ +18.3 (*c* 2.1, DCM).

Similarly, a mixture of (2*S*,4*S*)-**2.18.1** (710 mg, 1.38 mmol) on treatment with benzyl amine (1.66 mmol, 0.18 mL) in ethanol (40 mL) provided (3*S*,5*S*)-1-benzyl-5-((triisopropylsilyl)oxy)piperidin-3-ol as colorless oil in 80% yield (402 mg, 1.11 mmol); $[\alpha]_D^{24.2}$ –19.0 (*c* 1.0, DCM).

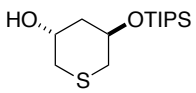


(*R*,*R*)-**2.18.3**

(3*R*,5*R*)-1-Benzylpiperidine-3,5-diol (2.18.3). To a solution of (3*R*,5*R*)-**2.19.2** (300 mg, 0.83 mmol) in THF 1M tetrabutylammonium fluoride (1.2 mL, 1.2 mmol) was added and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water and was extracted with ethyl acetate. The combined organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude reaction mixture

was purified by column chromatography to obtain the product as light brown oil (161 mg, 0.78 mmol). R_f = 0.2 (5% MeOH/DCM); IR (neat) 3360 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.23 (m, 5H), 4.06–3.98 (m, 2H), 3.64–3.54 (m, 2H), 2.80–2.48 (m, 2H), 2.45–2.27 (m, 2H), 2.13 (s, 2H), 1.82–1.71 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.5, 129.3, 128.6, 127.6, 65.3, 62.4, 59.8, 40.4; *m/z* (ESI+) found $[M+H]^+$ 208.1337, $C_{12}H_{18}NO_2$ requires 208.1338; $[\alpha]_D^{25.3}$ +16.1 (*c* 2.0, DCM). HPLC (Chiralpak IC column *n*-hexane/*i*-PrOH = 90/10, flow rate = 1.0 mL/min, $t_{R,R}$ = 22.96 min, $t_{S,S}$ = 24.67, *er* >99:1).

Similarily, a solution of (3*S*,5*S*)-**2.18.2** (395 mg, 1.08 mmol) in THF, on treatment with tetrabutylammonium fluoride (1.8 mL, 1M in THF) provided (3*R*,5*R*)-1-benzylpiperidine-3,5-diol as colorless oil in 92% yield (220 mg, 1.0 mmol); $[\alpha]_D^{23.2}$ –17.0 (*c* 1.1, DCM); *er* >99:1.

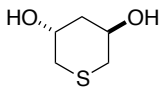


(*R,R*)-**2.20.1**

(3*R*,5*R*)-5-((Triisopropylsilyl)oxy)tetrahydro-2*H*-thiopyran-3-ol (2.20.1). To a solution of diiodo diol (2*R*,4*R*)-**2.18.1** (50 mg, 0.15 mmol) in ethanol (1 mL), aqueous sodium sulfide (120 mg, 1.5 mmol) was added and the resulting mixture was refluxed for 16 h at 100 ºC. The solvent was evaporated and the reaction mixture was extracted with ethyl acetate. The reaction mixture was diluted with water and was extracted with ethyl acetate. The combined organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude reaction mixture was purified by column chromatography to obtain the product as light yellow oil in 88% yield (38 mg, 0.13 mmol). R_f = 0.35 (20%

EtOAc/hexanes); IR (neat) 3421 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.52 (m, 1H), 4.03 (m, 1H), 3.82–3.67 (m, 2H), 2.90–2.77 (m, 1H), 2.77–2.63 (m, 1H), 2.26 (ddd, *J* = 13.4, 7.4, 6.3 Hz, 1H), 1.82 (ddd, *J* = 13.0, 5.7, 3.6 Hz, 1H), 1.25 (s, 1H), 1.08–1.01 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 78.8, 76.0, 73.0, 41.1, 37.9, 18.2, 12.2; *m/z* (ESI+) found $[M+H]^+$ 291.1814, $C_{14}H_{31}O_2SSi$ requires 291.1814; $[\alpha]_D^{25.3}$ +17.6 (*c* 0.85, DCM). Chiral GC separation: Astec Chiraldex B-DM fused silica capillary column, 30m × 0.25 mm × 0.12 mm, temperature 160 ºC, $t_{R,R}$ = 13.39 min, $t_{S,S}$ = 15.40 min, $er_{R,R}$ 97:3.

In an identical manner as described above, a solution of (2*S*,4*S*)-**2.18.1** (1.23 g, 2.41 mmol) in ethanol (40 mL), aqueous sodium sulfide (1.88 g, 24.1 mmol) on refluxing for 20 h at 100 ºC, followed by column chromatography provided (3*S*,5*S*)-5-((triisopropylsilyl)oxy)tetrahydro-2*H*-thiopyran-3-ol as light yellow oil in 87% yield (618 mg, 2.12 mmol). $[\alpha]_D^{24.2}$ –18.0 (*c* 1.0, DCM); $er_{S,S}$ 97:3.

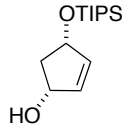


(*R*,*R*)-**2.20.2**

(3*R*,5*R*)-Tetrahydro-2*H*-thiopyran-3,5-diol (2.20.2). To a solution of (3*R*,5*R*)-**2.20.1** (312 mg, 1.21 mmol) in THF, tetrabutylammonium fluoride (1.8 mL, 1M in THF) was added and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water and was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude reaction mixture was purified by column chromatography to obtain the product as colorless viscous mass in 92% yield (149 mg, 1.1 mmol). R_f = 0.25 (100% EtOAc); IR (neat) 3306 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ^1H NMR (400 MHz, $CDCl_3$) δ 4.21–

4.02 (m, 2H), 2.65 (ddd, *J* = 13.3, 3.1, 1.0 Hz, 2H), 2.44 (ddd, *J* = 13.3, 7.4, 1.1 Hz, 2H), 2.23 (s, 2H), 1.73 (t, *J* = 5.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 65.6, 41.6, 35.3; *m/z* (ESI+) found $[M+Na]^+$ 157.0297, $C_5H_{10}NaO_2S$ requires 157.0299; $[\alpha]_D^{23.8}$ +6.3 (*c* 2.1, EtOH).

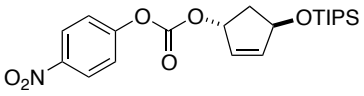
Similarly, a solution of (3*S*,5*S*)-5-((triisopropylsilyl)oxy)tetrahydro-2*H*-thiopyran-3-ol **2.20.1** (618 mg, 1.21 mmol) in THF, on treatment with tetrabutylammonium fluoride (1.8 mL, 1M in THF) provided (3*S*,5*S*)-tetrahydro-2*H*-thiopyran-3,5-diol as colorless viscous mass in 92% yield (149 mg, 1.1 mmol); $[\alpha]_D^{23.2}$ –6.9 (*c* 1.1, EtOH).



(1*R*,4*S*)-**1.26.1**

(1*R*,4*S*)-4-((triisopropylsilyl)oxy)cyclopent-2-enol (1.26.1). To a solution of (1*S*,4*S*)-4-((triisopropylsilyl)oxy)cyclopent-2-enol (3.41 g, 13.2 mmol) in THF (100 mL), triphenyl phosphine (13.8 g, 52.8 mmol) and 4-nitrophenyl benzoic acid (8.8 g, 52.8) were added. Then diethylazodicarboxylate (8.3 mL, 52.8 mmol) was added dropwise and the reaction mixture was stirred at room temperature for overnight. The reaction mixture was quenched with ammonium chloride and was extracted with diethyl ether. The combined organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was dissolved in methanol and sodium methoxide (20 mol%, 58 mg) was added and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was filtered through a plug of anhydrous magnesium sulfate and was concentrated. The product was obtained by column chromatography in 72% yield (2.4 g) as colorless oil. R_f = 0.35 (10% EtOAc/hexanes); IR (neat) 3282 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98–

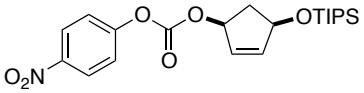
5.88 (m, 2H), 4.73 (ddt, *J* = 6.9, 4.4, 1.3 Hz, 1H), 4.57 (ddt, *J* = 7.2, 4.6, 1.4 Hz, 1H), 2.70 (dt, *J* = 13.9, 7.0 Hz, 1H), 2.15 (s, 1H), 1.56 (dt, *J* = 13.7, 4.5 Hz, 1H), 1.24–0.87 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.2, 135.7, 75.3, 75.2, 45.1, 18.1, 18.09, 12.2; *m/z* (ESI+) found $[M+H]^+$ 257.1934, $C_{14}H_{29}O_2Si$ requires 257.1937; $[\alpha]_D^{25.3}$ –19.4 (*c* 2.0, DCM). *Ent*-**1.26.1** (2.43 g) was prepared starting from (1*R*,4*R*)-4-((triisopropylsilyl)oxy)cyclopent-2-enol (3.5 g, 13.2 mmol); $[\alpha]_D^{25.3}$ +20.0 (*c* 2.3, DCM).



(*R,R*)-**3.5.1**

4-Nitrophenyl ((1*R*,4*R*)-4-((triisopropylsilyl)oxy)cyclopent-2-en-1-yl) carbonate (*R,R*-3.5.1). To a solution of (1*R*,4*R*)-4-((triisopropylsilyl)oxy)cyclopent-2-enol (3.5 g, 13.6 mmol) in THF (136 mL), at -78 ºC, *n*-BuLi (5.4 mL, 2.5 M in hexanes) was added dropwise. The solution was stirred for 30 minutes at –78 ºC and a solution of 4-nitrophenyl chloroformate (5.48 g, 27.2 mmol, in 20 mL THF) was added to it quickly. The reaction mixture was stirred at –78 ºC for 1 h and was quenched with saturated ammonium chloride while reaction still at – 78 ºC. The reaction was extracted with diethyl ether. The combined organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude reaction mixture was purified by column chromatography to obtain the product as colorless oil in 77% yield (4.4 g). R_f = 0.45 (10% EtOAc/hexanes); IR (neat) 1770 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 9.2 Hz, 2H), 7.39 (d, *J* = 9.2 Hz, 2H), 6.14 (dt, *J* = 5.6, 1.6 Hz, 1H), 5.99 (ddd, *J* = 5.6, 1.9, 1.3 Hz, 1H), 5.51 (ddt, *J* = 7.3, 5.0, 1.0 Hz, 1H), 4.84 (ddt, *J* = 6.9, 4.8, 1.0 Hz, 1H), 2.94 (dt, *J* = 14.0, 7.3 Hz, 1H), 1.85 (dt, *J* = 13.9, 4.9 Hz, 1H), 1.31 – 0.71 (m, 21H); ^{13}C

NMR (101 MHz, $CDCl_3$) δ 155.7, 152.3, 145.5, 143.4, 129.7, 125.4, 121.9, 84.6, 76.2, 41.6, 18.1, 12.2; *m/z* (ESI+) found $[M+H]^+$ 422.1999, $C_{21}H_{32}NO_6Si$ requires 422.1999; $[\alpha]_D^{25.3}$ +23.5 (*c* 0.95, DCM). 4-Nitrophenyl ((1*S*,4*S*)-4-((triisopropylsilyl)oxy)cyclopent-2-en-1-yl) carbonate *S,S*-**3.5.2** was obtained in similar manner from (1*S*,4*S*)-4-((triisopropylsilyl)oxy)cyclopent-2-enol; $[\alpha]_D^{25.3}$ –23.7 (*c* 1.2, DCM).

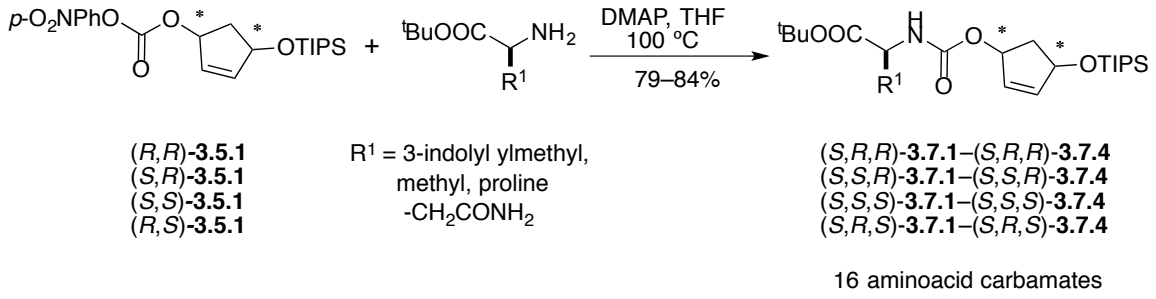


(1*S*,4*R*)-**3.5.1**

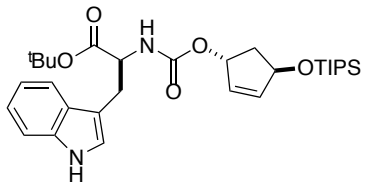
4-Nitrophenyl ((1*S*,4*R*)-4-((triisopropylsilyl)oxy)cyclopent-2-en-1-yl) carbonate (*S,R*-3.5.1). Starting with 3.5 g (13.6 mmol) of (1*S*,4*R*)-4-((triisopropylsilyl)oxy)cyclopent-2-enol, the carbonate product was obtained in 77% yield (4.4 g, 10.4 mmol) as a colorless oil. R_f = 0.42 (10% EtOAc/hexanes); IR (neat) 1769 cm^{-1}; δ ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 9.2 Hz, 2H), 7.36 (d, *J* = 9.2 Hz, 2H), 6.21 (dd, *J* = 5.8, 1.9 Hz, 1H), 6.04 (ddd, *J* = 5.6, 2.4, 1.4 Hz, 1H), 5.82 (dd, *J* = 7.0, 2.0 Hz, 1H), 5.20 (ddd, *J* = 6.3, 4.1, 1.8 Hz, 1H), 2.40 (ddd, *J* = 14.7, 6.6, 1.9 Hz, 1H), 2.16 (ddd, *J* = 14.7, 6.9, 4.2 Hz, 1H), 1.18–0.98 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3, 145.5, 140.9, 129.7, 125.4, 122.0, 82.3, 74.8, 41.2, 18.11, 18.09, 17.8, 12.2; *m/z* (ESI+) found $[M+H]^+$ 422.1992 , $C_{21}H_{31}NO_6Si$ requires 422.1999; $[\alpha]_D^{25.3}$ –27.1 (*c* 0.15, DCM).

Starting with 1.7 g (6.6 mmol) of (1*R*,4*S*)-4-((triisopropylsilyl)oxy)cyclopent-2-enol, carbonate product *S,R*-**3.5.1** was obtained in 79% yield (2.2 g, 5.2 mmol) as a colorless oil. $[\alpha]_D^{25.3}$ +29.4 (*c* 1.3, DCM).

Parallel synthesis of silyl carbamates



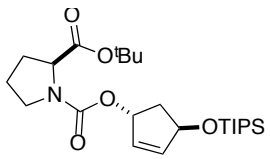
A solution of the carbonate **3.5.1** (1 eq, 1.8 mmol) in THF (10 mL) was added to a 20 mL microwave vial placed on a heating block fitted on a magnetic stirrer. *N*,*N*'-dimethyl aminopyridine (10 mol%), Hunig's base (2 eq) and amino acid hydrochloride (1.2 eq) were added and the vial was sealed with an aluminum cap. The reaction mixture was heated at 80 ºC for 18 h. The solvent was evaporated and the crude product was purified by column chromatography (silica gel, ethyl acetate/hexane as eluent) to obtain the product **3.7.1** in 79–84% yield. All of the sixteen isomers of **3.7.1** were prepared on 600–700 mg scale. Each of the isomers were individually purified using silica-gel column chromatography, and were characterized by nmr and mass analysis. The characterization data is provided below.



(*S,R,R*)-**3.7.1**

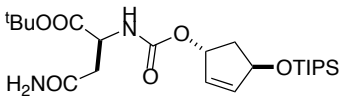
(*S*)-*tert*-Butyl 3-(1*H*-indol-3-yl)-2-(((((1*R*,4*R*)-4-((triisopropylsilyl)oxy)cyclopent-2-en-1-yl)oxy)carbonyl)amino)propanoate (*S,R,R*-**3.7.1**). Yield 84%; R_f = 0.2 (30%

EtOAc/hexanes); IR (neat) 1747, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.40–7.29 (m, 1H), 7.19 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.12 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.01 (d, *J* = 2.3 Hz, 1H), 6.04 (dd, *J* = 5.8, 1.8 Hz, 1H), 5.93 (dt, *J* = 5.9, 1.7 Hz, 1H), 5.74 (dt, *J* = 7.2, 2.3 Hz, 1H), 5.18 (d, *J* = 8.1 Hz, 1H), 5.13–5.06 (m, 1H), 4.59 (dt, *J* = 8.2, 5.8 Hz, 1H), 3.27 (qd, *J* = 14.8, 5.8 Hz, 2H), 2.16 (ddd, *J* = 14.5, 5.4, 2.6 Hz, 1H), 2.11–2.02 (m, 1H), 1.38 (s, 9H), 1.06 (d, *J* = 4.3 Hz, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 155.9, 140.9, 136.2, 131.8, 128.0, 122.8, 122.2, 119.6, 119.1, 111.2, 110.5, 82.1, 79.7, 76.4, 55.1, 41.7, 28.1, 18.1, 12.2; *m/z* (ESI+) found $[M+H]^+$ 543.3255, $C_{30}H_{47}N_2O_5Si$ requires 543.3254; $[\alpha]_D^{23.6}$ +232 (*c* 1.0, DCM).



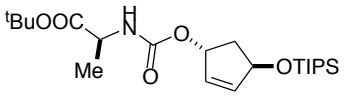
(*S,R,R*)-**3.7.2**

(*S*)-2-*tert*-Butyl 1-((1*R*,4*R*)-4-((triisopropylsilyl)oxy)cyclopent-2-en-1-yl) pyrrolidine-1,2-dicarboxylate (*S,R,R*-**3.7.2**). Yield 82%; R_f = 0.3 (30% EtOAc/hexanes); IR (neat) 1749, 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.06–5.91 (m, 4H), 5.83 (d, *J* = 8.4 Hz, 1H), 5.69 (m, 1H), 5.10 (ddd, *J* = 6.7, 4.1, 2.0 Hz, 1H), 4.39 (dt, *J* = 9.0, 4.7 Hz, 1H), 2.85 (dd, *J* = 16.0, 5.1 Hz, 1H), 2.70 (dd, *J* = 16.0, 4.4 Hz, 1H), 2.18 (ddd, *J* = 14.4, 6.7, 2.3 Hz, 1H), 2.05 (ddd, *J* = 14.4, 7.0, 4.0 Hz, 1H), 1.42 (s, 10H), 1.08–0.99 (m, 21H); ^{13}C NMR (101 MHz, CDC_3) δ 172.7, 170.2, 156.4, 141.0, 131.7, 126.2, 115.8, 82.5, 79.9, 76.4, 51.3, 41.6, 37.6, 28.0, 18.0, 12.2; *m/z* (ESI+) found $[M+H]^+$ 454.2985, $C_{24}H_{44}NO_5Si$ requires 454.2989; $[\alpha]_D^{23.6}$ +179 (*c* 1.0, DCM).



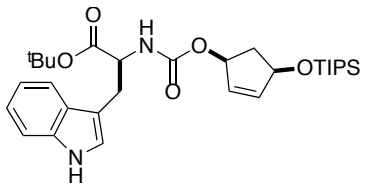
(*S,R,R*)-**3.7.3**

(*S*)-*tert*-Butyl 4-amino-4-oxo-2-(((((1*R*,4*R*)-4-((triisopropylsilyl)oxy)cyclopent-2-en-1-yl)oxy)carbonyl)amino)butanoate (*S,R,R*-**3.7.3**). Yield 79%; R_f = 0.32 (70% EtOAc/hexanes); IR (neat) 1745, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.01–5.95 (m, 1H), 5.95–5.87 (m, 1H), 5.74–5.65 (m, 1H), 5.11–4.98 (m, 1H), 4.17–4.04 (m, 1H), 3.58–3.27 (m, 2H), 2.21–1.97 (m, 3H), 1.95–1.73 (m, 2H), 1.43–1.35 (m, 9H), 1.06–0.95 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 170.3, 156.4, 141.1, 140.2, 82.5, 79.9, 76.3, 51.3, 41.6, 29.9, 28.0, 18.1, 12.1; *m/z* (ESI+) found $[M+H]^+$ 471.2990, $C_{23}H_{43}N_2O_6Si$ requires 471.2989; $[\alpha]_D^{23.6}$ +89 (*c* 1.1, MeOH).



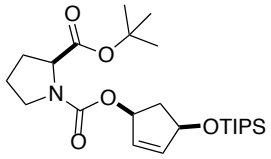
(*S,R,R*)-**3.7.4**

(*S*)-*tert*-Butyl-2-(((((1*R*,4*R*)-4-((triisopropylsilyl)oxy)cyclopent-2-en-1-yl)oxy)carbonyl)amino)propanoate (*S,R,R*-**3.7.4**). Yield 83%; R_f = 0.40 (20% EtOAc/hexanes); IR (neat) 1747, 1711 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.02–5.99 (m, 1H), 5.95–5.88 (m, 1H), 5.75–5.65 (m, 1H), 5.22 (m, 1H), 5.09 (qd, *J* = 3.8, 1.7 Hz, 1H), 4.18–4.01 (m, 1H), 2.17 (ddd, *J* = 14.4, 6.7, 2.3 Hz, 1H), 2.05 (ddd, *J* = 14.5, 7.0, 4.0 Hz, 1H), 1.42 (s, 9H), 1.32 (d, *J* = 7.2 Hz, 3H), 1.12–0.93 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 155.7, 140.8, 131.8, 81.8, 79.6, 76.4, 50.1, 41.7, 28.0, 19.0, 18.0, 12.2; *m/z* (ESI+) found $[M+H]^+$ 428.2832, $C_{22}H_{42}NO_5Si$ requires 428.2832; $[\alpha]_D^{23.6}$ –69.7 (*c* 1.2, DCM).



(*S,S,R*)-**3.7.1**

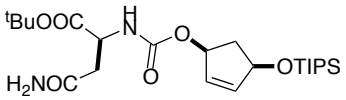
(*S*)-*tert*-Butyl 3-(1*H*-indol-3-yl)-2-(((((1*S*,4*R*)-4-((triisopropylsilyl)oxy)cyclopent-2-en-1-yl)oxy)carbonyl)amino)propanoate (*S,S,R*-**3.7.1**). Yield 81%; R_f = 0.20 (20% EtOAc/hexanes); IR (neat) 1744, 1713 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60–8.31 (m, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.19 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.15–7.07 (m, 1H), 7.00 (d, *J* = 2.3 Hz, 1H), 6.08 (dd, *J* = 5.6, 1.9 Hz, 1H), 5.93 (dt, *J* = 5.7, 1.8 Hz, 1H), 5.78–5.53 (m, 1H), 5.40–5.15 (m, 1H), 5.14–4.95 (m, 1H), 4.70–4.30 (m, 1H), 3.28 (qd, *J* = 14.9, 5.8 Hz, 2H), 2.19 (ddd, *J* = 14.5, 6.7, 2.2 Hz, 1H), 2.11–2.00 (m, 1H), 1.42 (s, 9H), 1.06 (d, *J* = 3.9 Hz, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 162.8, 156.4, 140.9, 139.1, 136.2, 131.2, 127.6, 123.0, 122.3, 119.7, 111.3, 109.8, 82.7, 78.0, 74.9, 55.2, 41.5, 28.0, 17.98, 17.95, 12.1; *m/z* (ESI+) found $[M+H]^+$ 543.3256, $C_{30}H_{47}N_2O_5Si$ requires 543.3254; $[\alpha]_D^{23.6}$ –23.7 (*c* 2.0, MeOH).



(*S,S,R*)-**3.7.2**

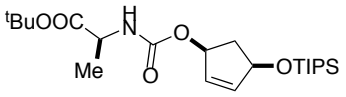
(*S*)-2-*tert*-Butyl 1-((1*S*,4*R*)-4-((triisopropylsilyl)oxy)cyclopent-2-en-1-yl) pyrrolidine-1,2-dicarboxylate (*S,S,R*-**3.7.2**). Yield 79%; R_f = 0.35 (70% EtOAc/hexanes); IR (neat) 1749, 1715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94–5.72 (m, 2H), 5.42–5.29 (m, 1H), 4.70 (m, 1H), 4.12–4.08 (m, 1H), 3.57–3.25 (m, 2H), 2.87–2.71 (m, 1H), 2.22–1.71 (m, 3H), 1.69–1.50 (m, 1H), 1.37 (m, 10H), 1.02 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ

172.0, 154.7, 138.3, 131.8, 81.1, 77.5, 74.9, 46.8, 42.0, 30.9, 28.0, 24.2, 23.5, 17.99, 17.98, 12.2; *m/z* (ESI+) found $[M+H]^+$ 454.2989, $C_{24}H_{44}NO_5Si$ requires 454.2989; $[\alpha]_D^{23.6}$ +37.7 (*c* 1.0, DCM).



(*S,S,R*)-**3.7.3**

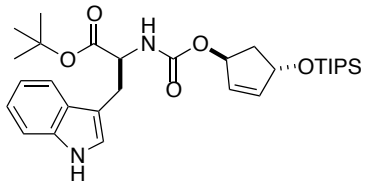
(*S*)-*tert*-Butyl 4-amino-4-oxo-2-(((((1*S*,4*R*)-4-((triisopropylsilyl)oxy)cyclopent-2-en-1-yl)oxy)carbonyl)amino)butanoate (*S,S,R*-**3.7.3**). Yield 80%; R_f = 0.40 (20% EtOAc/hexanes); IR (neat) 1745, 1700, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.17–5.82 (m, 4H), 5.38 (t, *J* = 6.5 Hz, 1H), 4.75 (dtd, *J* = 7.2, 2.8, 1.3 Hz, 1H), 4.56–3.89 (m, 1H), 2.98–2.53 (m, 3H), 1.63 (dt, *J* = 13.7, 5.1 Hz, 1H), 1.42 (s, 9H), 1.35–1.12 (m, 1H), 1.11–0.91 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 163.3, 156.3, 139.0, 126.2, 115.8, 82.5, 77.7, 74.9, 51.3, 41.8, 37.6, 28.0, 18.03, 18.01, 12.2; *m/z* (ESI+) found $[M+H]^+$ 471.2887, $C_{23}H_{43}N_2O_6Si$ requires 471.2890; $[\alpha]_D^{24.6}$ +30.4 (*c* 0.95, DCM).



(*S,S,R*)-**3.7.4**

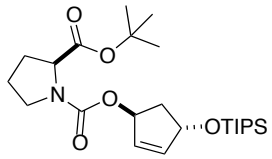
(*S*)-*tert*-Butyl-2-(((((1*S*,4*R*)-4-((triisopropylsilyl)oxy)cyclopent-2-en-1-yl)oxy)carbonyl)amino)propanoate (*S,S,R*-**3.7.4**). Yield 82%; R_f = 0.42 (20% EtOAc/hexanes); IR (neat) 1747, 1710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.94 (dt, *J* = 5.6, 1.6 Hz, 1H), 5.92–5.78 (m, 1H), 5.54–5.01 (m, 2H), 4.87–4.60 (m, 1H), 4.27–3.92 (m, 1H), 2.79 (dt, *J* = 13.7, 7.3 Hz, 1H), 1.61 (dt, *J* = 13.6, 5.2 Hz, 1H), 1.41 (s, 9H), 1.32

(d, J = 7.1 Hz, 3H), 1.03–0.99 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 155.6, 138.8, 131.5, 81.8, 77.4, 74.9, 50.2, 41.7, 28.0, 18.0, 12.1; *m/z* (ESI+) found $[M+H]^+$ 428.2830, $C_{22}H_{42}NO_5Si$ requires 428.2832; $[\alpha]_D^{23.6}$ –30.4 (*c* 1.2, DCM).



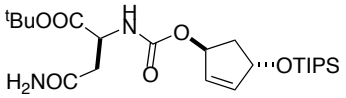
(*S,S,S*)-**3.7.1**

(*S*)-*tert*-Butyl 3-(1*H*-indol-3-yl)-2-(((((1*S*,4*S*)-4-((triisopropylsilyl)oxy)cyclopent-2-en-1-yl)oxy)carbonyl)amino)propanoate (*S,S,S*-**3.7.1**). Yield 80%; R_f = 0.22 (20% EtOAc/hexanes); IR (neat) 1744, 1712 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60–8.31 (m, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.19 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H), 7.15–7.07 (m, 1H), 7.00 (d, J = 2.3 Hz, 1H), 6.08 (dd, J = 5.6, 1.9 Hz, 1H), 5.93 (dt, J = 5.7, 1.8 Hz, 1H), 5.78–5.53 (m, 1H), 5.40–5.15 (m, 1H), 5.14–4.95 (m, 1H), 4.70–4.30 (m, 1H), 3.28 (qd, J = 14.9, 5.8 Hz, 2H), 2.19 (ddd, J = 14.5, 6.7, 2.2 Hz, 1H), 2.11–2.00 (m, 1H), 1.42 (s, 9H), 1.06 (d, J = 3.9 Hz, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 156.4, 136.2, 131.3, 127.7, 126.2, 122.9, 122.2, 119.6, 118.8, 115.7, 111.3, 82.5, 80.2, 76.3, 55.2, 41.5, 28.0, 18.0, 12.1; *m/z* (ESI+) found $[M+H]^+$ 543.3250, $C_{30}H_{47}N_2O_5Si$ requires 543.3254; $[\alpha]_D^{23.9}$ +157 (*c* 1.3, DCM).



(*S,S,S*)-**3.7.2**

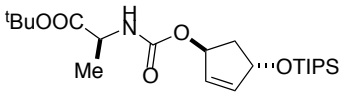
(*S*)-2-*tert*-Butyl 1-((1*S*,4*R*)-4-((triisopropylsilyl)oxy)cyclopent-2-en-1-yl) pyrrolidine-1,2-dicarboxylate (*S,S,S*-**3.7.2**). Yield 83%; R_f = 0.42 (20% EtOAc/hexanes); IR (neat) 1745, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.17–5.82 (m, 4H), 5.38 (t, *J* = 6.5 Hz, 1H), 4.75 (dtd, *J* = 7.2, 2.8, 1.3 Hz, 1H), 4.56–3.89 (m, 1H), 2.98–2.53 (m, 3H), 1.63 (dt, *J* = 13.7, 5.1 Hz, 1H), 1.42 (s, 9H), 1.35–1.12 (m, 1H), 1.11–0.91 (m, 22H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 170.3, 163.3, 156.3, 139.0, 131.4, 126.2, 115.8, 82.5, 77.7, 74.9, 51.3, 41.8, 37.6, 28.0, 18.0 (d, *J* = 1.8 Hz), 12.2; *m/z* (ESI+) found $[M+H]^+$ 454.2994, $C_{24}H_{44}NO_5Si$ requires 454.2989; $[\alpha]_D^{23.6}$ +202.3 (*c* 1.0, DCM).



(*S,S,S*)-**3.7.3**

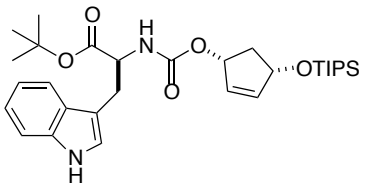
(*S*)-*tert*-Butyl 4-amino-4-oxo-2-(((((1*S*,4*S*)-4-((triisopropylsilyl)oxy)cyclopent-2-en-1-yl)oxy)carbonyl)amino)butanoate (*S,S,S*-**3.7.3**). Yield 77%; R_f = 0.34 (70% EtOAc/hexanes); IR (neat) 1746, 1699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.03–5.60 (m, 2H), 5.39 (m, 1H), 4.73 (dtd, *J* = 7.1, 5.1, 2.4 Hz, 1H), 4.11 (m, 1H), 3.46–3.80 (m, 2H), 2.94–2.67 (m, 1H), 2.25–1.74 (m, 3H), 1.62 (m, 1H), 1.40 (m, 9H), 1.02 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 154.7, 154.4, 138.4, 138.3, 132.2, 131.8, 81.1, 77.5, 74.9, 59.9, 59.5, 46.8, 46.4, 42.0, 41.8, 30.9, 30.0, 28.0, 24.3, 23.5, 18.0, 12.1; *m/z*

(ESI+) found $[M+H]^+$ 471.2889, $C_{23}H_{43}N_2O_6Si$ requires 471.2890; $[\alpha]_D^{23.6}$ +214 (*c* 1.0, MeOH).



(*S,S,S*)-**3.7.4**

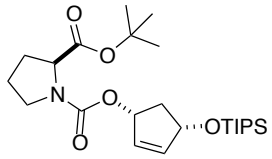
(*S*)-*tert*-Butyl-2-(((((1*S*,4*S*)-4-((triisopropylsilyl)oxy)cyclopent-2-en-1-yl)oxy)carbonyl)amino)propanoate (*S,S,S*-**3.7.4**). Yield 80%; R_f = 0.45 (20% EtOAc/hexanes); IR (neat) 1747, 1717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.04 (dd, *J* = 5.7, 1.8 Hz, 1H), 5.94 (ddd, *J* = 5.6, 2.4, 1.4 Hz, 1H), 5.79–5.58 (m, 1H), 5.25–4.88 (m, 2H), 4.35–3.83 (m, 1H), 2.19 (ddd, *J* = 14.5, 6.7, 2.2 Hz, 1H), 2.05 (ddd, *J* = 14.4, 7.0, 4.1 Hz, 1H), 1.44 (s, 9H), 1.33 (d, *J* = 7.2 Hz, 3H), 1.12–0.96 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 155.7, 141.0, 131.7, 81.9, 79.7, 76.4, 50.2, 41.7, 28.1, 19.0, 18.1.05, 18.04, 12.2; *m/z* (ESI+) found $[M+H]^+$ 428.2829, $C_{22}H_{42}NO_5Si$ requires 428.2832; $[\alpha]_D^{23.0}$ +129.7 (*c* 0.87, DCM).



(*S,R,S*)-**3.7.1**

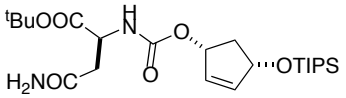
(*S*)-*tert*-Butyl 3-(1*H*-indol-3-yl)-2-(((((1*R*,4*S*)-4-((triisopropylsilyl)oxy)cyclopent-2-en-1-yl)oxy)carbonyl)amino)propanoate (*S,R,S*-**3.7.1**). Yield 79%; R_f = 0.22 (20% EtOAc/hexanes); IR (neat) 1748, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H),

7.61 (d, J = 7.8 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.18 (t, J = 7.2 Hz, 1H), 7.12 (t, J = 7.4 Hz, 1H), 6.98 (d, J = 2.4 Hz, 1H), 5.99 (d, J = 5.8 Hz, 1H), 5.86 (d, J = 5.6 Hz, 1H), 5.52–5.15 (m, 2H), 4.78 (t, J = 6.3 Hz, 1H), 4.60 (dt, J = 8.2, 5.8 Hz, 1H), 3.27 (m, 2H), 2.87 (dt, J = 14.1, 7.3 Hz, 1H), 1.65 (dt, J = 13.6, 5.3 Hz, 1H), 1.39 (s, 9H), 1.09 (d, J = 4.5 Hz, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 155.8, 138.8, 136.2, 131.6, 127.9, 122.9, 122.1, 119.6, 119.0, 111.2, 110.3, 82.0, 77.4, 75.0, 55.1, 53.5, 41.9, 28.0, 18.06, 18.05, 12.2; *m/z* (ESI+) found $[M+H]^+$ 543.3250, $C_{30}H_{47}N_2O_5Si$ requires 543.3254; $[\alpha]_D^{23.9}$ +107 (*c* 1.0, DCM).



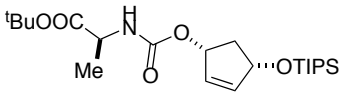
(*S,R,S*)-**3.7.2**

(*S*)-2-*tert*-Butyl 1-((1*R*,4*S*)-4-((triisopropylsilyl)oxy)cyclopent-2-en-1-yl) pyrrolidine-1,2-dicarboxylate (*S,R,S*-**3.7.2**). Yield 80%; R_f = 0.35 (20% EtOAc/hexanes); IR (neat) 1749, 1715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03–5.79 (m, 2H), 5.56–5.31 (m, 1H), 4.90–4.55 (m, 1H), 4.18 (m, 1H), 3.69–3.22 (m, 2H), 2.84 (m, 1H), 2.16 (dd, J = 6.5, 2.8 Hz, 1H), 2.03–1.75 (m, 3H), 1.72–1.51 (m, 1H), 1.42 (m, 9H), 1.03 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 154.8, 138.5, 132.1, 81.2, 77.5, 75.0, 59.9, 46.5, 30.9, 28.1, 24.3, 23.5, 18.06, 18.04, 12.1; *m/z* (ESI+) found $[M+H]^+$ 454.2985, $C_{24}H_{44}NO_5Si$ requires 454.2989; $[\alpha]_D^{23.7}$ +169 (*c* 1.1, DCM).



(*S,R,S*)-**3.7.3**

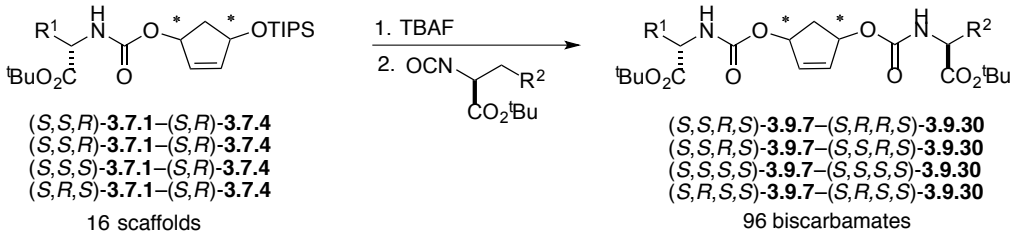
(*S*)-*tert*-Butyl 4-amino-4-oxo-2-(((((1*R*,4*S*)-4-((triisopropylsilyl)oxy)cyclopent-2-en-1-yl)oxy)carbonyl)amino)butanoate (*S,R,S*-**3.7.3**). Yield 78%; R_f = 0.35 (30% EtOAc/hexanes); IR (neat) 1744, 1704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21 (s, 2H), 6.08–5.88 (m, 2H), 5.83 (dt, *J* = 5.6, 1.6 Hz, 1H), 5.36 (t, *J* = 6.4 Hz, 1H), 4.85–4.58 (m, 1H), 4.38 (dt, *J* = 9.6, 5.0 Hz, 1H), 2.90–2.70 (m, 2H), 2.65 (dd, *J* = 16.3, 4.2 Hz, 1H), 1.59 (dt, *J* = 13.6, 5.3 Hz, 1H), 1.39 (s, 9H), 1.00 (d, *J* = 4.6 Hz, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 170.3, 156.2, 138.8, 131.5, 82.2, 77.5, 74.9, 51.3, 41.7, 37.5, 27.9, 17.92, 17.90 12.1; *m/z* (ESI+) found $[M+H]^+$ 471.2889, $C_{23}H_{43}N_2O_6Si$ requires 471.2890; $[\alpha]_D^{23.6}$ +202 (*c* 1.4, DCM).

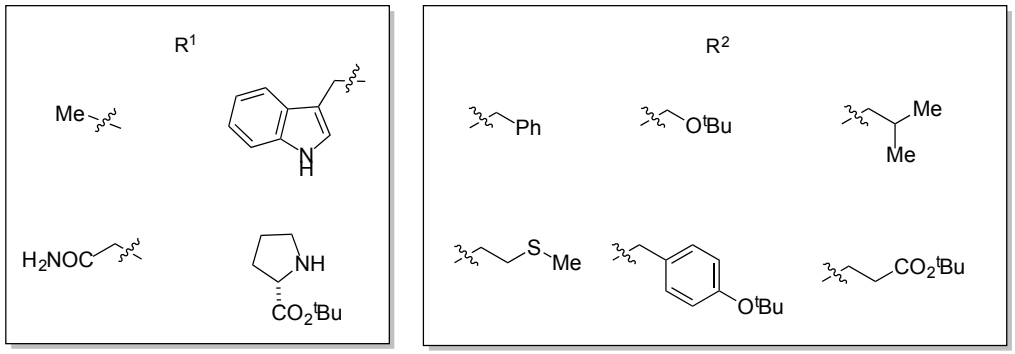


(*S,R,S*)-**3.7.4**

(*S*)-*tert*-Butyl-2-(((((1*R*,4*S*)-4-((triisopropylsilyl)oxy)cyclopent-2-en-1-yl)oxy)carbonyl)amino)propanoate (*S,R,S*-**3.7.4**). Yield 82%; R_f = 0.42 (20% EtOAc/hexanes); IR (neat) 1749, 1712 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01–5.92 (m, 1H), 5.92–5.72 (m, 1H), 5.62–5.02 (m, 2H), 4.90–4.62 (m, 1H), 4.39–3.87 (m, 1H), 2.84 (dt, *J* = 14.1, 7.3 Hz, 1H), 1.72–1.52 (m, 1H), 1.45 (s, 9H), 1.35 (d, *J* = 7.1 Hz, 3H), 1.12–0.96 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.22, 155.5, 138.7, 131.6, 81.8, 77.3, 74.9, 50.1, 41.9, 28.0, 18.9, 18.01, 17.99, 12.16; *m/z* (ESI+) found $[M+H]^+$ 428.2830, $C_{22}H_{42}NO_5Si$ requires 428.2832; $[\alpha]_D^{23.4}$ +132 (*c* 1.1, DCM).

Library Synthesis

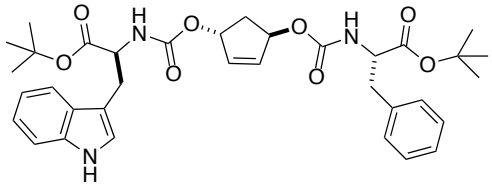




Step I. Each of the silyl monocarbamates **3.7.1**–**3.7.4** were treated with tetrabutylammonium fluoride (2 equiv) in THF for 2h. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), filtered and concentrated to obtain the corresponding unprotected alcohol that was used as starting for the next without subsequent purification.

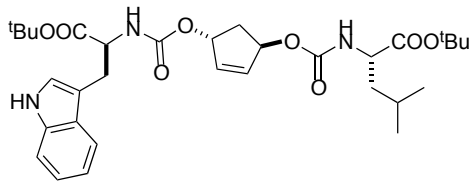
Step II. To 2 dram vials placed on a 6x4-well heating block, 50 mg of the alcohol obtained in step I, amino acid isocyanate (3 eq) and 10% *N,N'*-DMAP were added. The block was heated to 100 ºC for 2 h. After cooling, 2 mL of dichloromethane was added to each vial. The contents were transferred to collection tubes, purged with nitrogen gas in a sample evaporator. The crude reaction mixtures (*S,R,R,S*)-**3.9.7–**(*S,R,R,S*)-**3.9.30** on mass-directed purification produced 18 compounds in >90% purity and amounts in the

range of 4–62 mg. A random subset of ten compounds from the crude library of the 72 compound library [(*S,S,R,S*)-**3.9.7**–(*S,S,R,S*)-**3.9.30,** [(*S,S,S,S*)-**3.9.7**–(*S,S,S,S*)-**3.9.30** and (*S,R,S,S*)-**3.9.7**–(*S,R,S,S*)-**3.9.30**] were purified by column chromatography to obtain the 25–37 mg of the desired biscarbamate products (the spectral data are listed below). The rest of the crude library compounds were subjected to mass-directed purification and analysis.



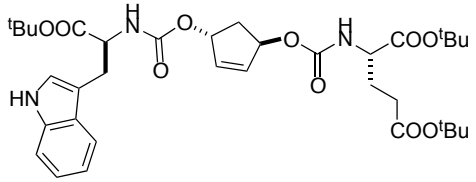
(*S,R,R,S*)-**3.9.7**

(*S*)-*tert*-Butyl-2-(((((1*R*,4*R*)-4-((((*S*)-1-(*tert*-butoxy)-1-oxo-3-phenylpropan-2-yl)carbamoyl)oxy)cyclopent-2-en-1-yl)oxy)carbonyl)amino)-3-(1*H*-indol-3-yl)propanoate (3.9.7). Yield 29%; R_f = 0.3 (30% EtOAc/hexanes); IR (neat) 1749, 1693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.50–6.82 (m, 9H), 6.06 (s, 2H), 5.73 (d, *J* = 5.9 Hz, 2H), 5.22 (dd, *J* = 20.4, 8.3 Hz, 2H), 4.77–4.49 (m, 2H), 3.37–3.18(m, 2H), 3.14–3.00 (m, 2H), 2.14 (t, *J* = 5.1 Hz, 2H), 1.43 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 171.1, 170.7, 155.7, 136.2, 135.6, 129.6, 128.5, 127.9, 127.1, 122.8, 122.2, 119.6, 118.9, 111.3, 110.4, 82.4, 82.1, 79.1, 78.9, 60.5, 55.3, 53.5, 38.6, 37.9, 28.1, 21.1, 14.3; *m/z* (ESI+) found $[M+H]^+$ 634.3130, $C_{35}H_{44}N_3O_8$ requires 634.3128; $[\alpha]_D^{22.9}$ +112 (*c* 1.0, DCM).



(*S,R,R,S*)-**3.9.9**

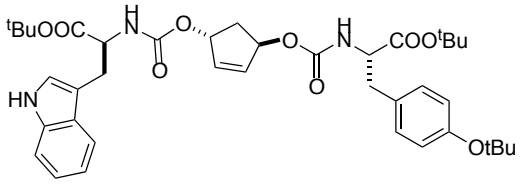
(*S*)-*tert*-Butyl 2-(((((1*R*,4*R*)-4-((((*S*)-1-(*tert*-butoxy)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamoyl)oxy)cyclopent-2-en-1-yl)oxy)carbonyl)amino)-4-methylpentanoate (3.9.9). Yield 44%; R_f = 0.2 (30% EtOAc/hexanes); IR (neat) 1749, 1703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (m, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.21 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1H), 7.14 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.04 (d, *J* = 2.3 Hz, 1H), 6.22–5.92 (m, 2H), 5.84–5.51 (m, 2H), 5.15 (m, 2H), 4.72–4.20 (m, 1H), 3.39–3.16 (m, 2H), 2.17 (m, 2H), 1.78–1.55 (m, 1H), 1.48 (s, 9H), 1.41 (s, 9H), 1.04–0.88 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 171.2, 155.7, 136.2, 135.8, 135.6, 127.9, 122.8, 122.3, 119.7, 119.0, 111.3, 110.5, 100.1, 82.1, 82.0, 79.0, 55.1, 42.2, 38.0, 29.8, 28.1, 28.07, 25.0, 23.0, 22.1, 21.2; *m/z* (ESI+) found $[M+H]^+$ 600.3285, $C_{32}H_{46}N_3O_8$ requires 600.3285; $[\alpha]_D^{23.0}$ –143.9 (*c* 1.0, DCM).



(*S,R,R,S*)-**3.9.11**

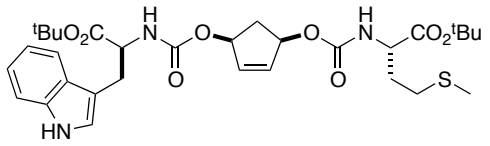
(*S*)-Di-*tert*-butyl 2-(((((1*R*,4*R*)-4-((((*S*)-1-(*tert*-butoxy)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamoyl)oxy)cyclopent-2-enyl)oxy)carbonyl)amino)pentanedioate (3.9.11). Yield 62%; R_f = 0.4 (30% EtOAc/hexanes); IR (neat) 1748, 1714, 1693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.19 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1H), 7.13 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.02 (d, *J* =

2.3 Hz, 1H), 6.07 (s, 2H), 5.87–5.48 (m, 2H), 5.43–5.17 (m, 2H), 4.74–4.20 (m, 2H), 3.37–3.16 (m, 2H), 2.50–2.12 (m, 5H), 1.99–1.81 (m, 1H), 1.48 (s, 9H), 1.47 (s, 9H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 171.2, 155.9, 155.7, 136.2, 135.7, 135.6, 127.9, 122.9, 122.2, 119.6, 118.9, 111.3, 110.7, 110.3, 82.4, 82.1, 80.8, 79.1, 78.9, 55.1, 54.0, 37.8, 31.6, 28.2, 28.1, 28.0, 21.1, 14.3; *m/z* (ESI+) found $[M+H]^+$ 672.3490, $C_{35}H_{50}N_3O_{10}$ requires 672.3496; $[\alpha]_D^{23.6}$ +249 (*c* 1.0, DCM).



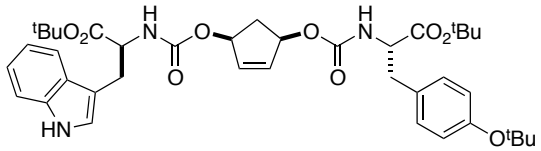
(*S,R,R,S*)-**3.9.8**

(*S*)-*tert*-Butyl 2-(((((1*R*,4*R*)-4-((((*S*)-1-(*tert*-butoxy)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamoyl)oxy)cyclopent-2-en-1-yl)oxy)carbonyl)amino)-3-(4-(*tert*-butoxy)phenyl)propanoate 3.9.8). Yield 67%; R_f = 0.3 (30% EtOAc/hexanes); IR (neat) 1748, 1728, 1715, 1693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (m, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.22–7.14 (m, 1H), 7.15–7.09 (m, 1H), 7.09–6.98 (m, 3H), 6.91 (d, *J* = 8.1 Hz, 2H), 6.05 (s, 2H), 5.87–5.47 (m, 2H), 5.25–4.87 (m, 2H), 4.72–4.21 (m, 2H), 3.34–3.14 (m, 2H), 3.02 (d, *J* = 6.1 Hz, 2H), 2.23–2.07 (m, 2H), 1.38 (s, 9H), 1.38 (s, 9H), 1.32 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 170.7, 155.7, 155.6, 154.5, 136.2, 135.7, 131.1, 130.1, 127.9, 124.2, 122.8, 122.3, 121.7, 119.7, 119.0, 111.3, 110.5, 82.4, 82.2, 79.1, 78.9, 78.6, 55.3, 55.1, 38.1, 37.9, 29.0, 28.1, 21.2, 14.2; *m/z* (ESI+) found $[M+H]^+$ 706.3703, $C_{39}H_{52}N_3O_9$ requires 706.3704; $[\alpha]_D^{23.6}$ –219 (*c* 1.6, MeOH).



(*S,R,S,R*)-**3.9.10**

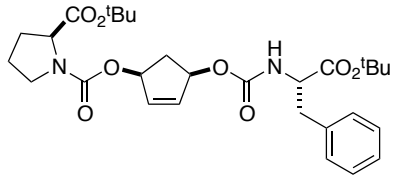
(*S*)-*tert*-Butyl 2-(((((1*R*,4*S*)-4-((((*S*)-1-(*tert*-butoxy)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamoyl)oxy)cyclopent-2-en-1-yl)oxy)carbonyl)amino)-4-(methylthio)butanoate (3.9.10). Yield 52%; R_f = 0.2 (30% EtOAc/hexanes); IR (neat) 1745, 1727, 1699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (m, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.19 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.11 (dd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.03 (m, 1H), 6.05 (m, 2H), 5.56 - 5.37 (m, 2H), 5.37 - 4.99 (m, 2H), 4.73 – 4.08 (m, 2H), 3.41 – 3.05 (m, 2H), 2.95 – 2.64 (m, 1H), 2.51 (m, 2H), 2.12 (m, 4H), 1.92 (m, 1H), 1.74 (dt, *J* = 14.9, 3.6 Hz, 1H), 1.47 (s, 9H), 1.37 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 170.6, 155.5, 155.4, 136.1, 134.8, 134.6, 127.8, 122.6, 122.2, 119.5, 118.9, 111.1, 110.4, 82.4, 82.0, 79.1, 78.9, 54.8, 53.7, 37.3, 32.4, 29.9, 28.0, 27.9, 15.5; 15.4; *m/z* (ESI+) found $[M+H]^+$ 618.2850, $C_{31}H_{44}N_3O_8S$ requires 618.2849; $[\alpha]_D^{24.1}$ +189 (*c* 1.0, MeOH).



(*S,R,S,R*)-**3.9.12**

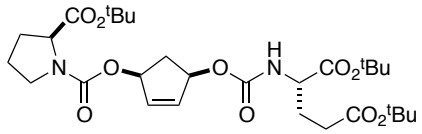
(*S*)-*tert*-Butyl 2-(((((1*R*,4*S*)-4-((((*S*)-1-(*tert*-butoxy)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamoyl)oxy)cyclopent-2-en-1-yl)oxy)carbonyl)amino)-3-(4-(*tert*-butoxy)phenyl)propanoate (3.9.12). Yield 56%; R_f = 0.4 (30% EtOAc/hexanes); IR (neat) 1748, 1714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 8.22 (m, 1H), 7.60 (d, *J* = 7.8 Hz,

1H), 7.38 - 7.31 (m, 1H), 7.18 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 7.11 - 6.90 (m, 4H), 6.90 (d, J = 8.5 Hz, 2H), 6.04 (s, 2H), 5.48 – 5.36 (m, 2H), 5.19 (dd, J = 27.1, 8.1 Hz, 2H), 4.64 - 4.41 (m, 2H), 3.41 - 2.60 (m, 5H), 1.83 – 1.43 (m, 1H), 1.37 (s, 18H), 1.32 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 170.8, 155.5, 155.3, 154.4, 136.2, 135.0, 134.7, 131.0, 130.1, 127.9, 124.3, 122.8, 122.3, 119.6, 119.1, 111.2, 110.5, 82.4, 82.2, 78.5, 77.5, 77.2, 76.8, 55.4, 54.9, 38.1, 37.5, 30.0, 28.1, 15.4; *m/z* (ESI+) found $[M+H]^+$ 706.3699, $C_{39}H_{52}N_3O_9$ requires 706.3704; $[\alpha]_D^{23.6}$ +66 (*c* 0.89, MeOH).



(*S,R,S,R*)-**3.9.19**

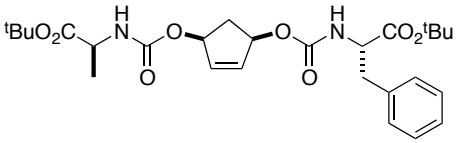
(*S*)-1-((1*S*,4*R*)-4-((((*S*)-1-(*tert*-Butoxy)-1-oxo-3-phenylpropan-2-yl)carbamoyl)oxy)cyclopent-2-en-1-yl) 2-*tert*-butyl pyrrolidine-1,2-dicarboxylate (3.9.19). Yield 62%; R_f = 0.3 (30% EtOAc/hexanes); IR (neat) 1748, 1714, 1693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 7.30 – 7.14 (m, 3H), 7.13 - 7.05 (m, 2H), 6.11 – 5.80 (m, 2H), 5.58 – 5.30 (m, 2H), 5.16 - 4.82 (m, 1H), 4.55 – 4.22 (m, 1H), 4.21–4.02 (m, 1H), 3.58 – 3.26 (m, 2H), 3.00 (m, 2H), 2.87 - 2.70 (m, 1H), 2.24 – 2.01 (m, 1H), 1.98 – 1.46 (m, 4H), 1.38 (m, 9H), 1.33 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 171.9, 170.7, 155.4, 154.7, 154.6, 136.2, 135.0, 134.3, 129.6, 82.4, 81.2, 81.3, 60.7, 55.2, 46.9, 46.4, 38.7, 37.6, 31.0, 28.1, 28.0, 23.4; *m/z* (ESI+) found $[M+H]^+$ 545.2863, $C_{29}H_{41}N_2O_8$ requires 545.2863; $[\alpha]_D^{23.6}$ +136.4 (*c* 1.0, MeOH).



(*S,R,S,R*)-**3.9.23**

(*S*)-2-*tert*-Butyl 1-((1*S*,4*R*)-4-((((*S*)-1,5-di-*tert*-butoxy-1,5-dioxopentan-2-yl)carbamoyl)oxy)cyclopent-2-en-1-yl) pyrrolidine-1,2-dicarboxylate (3.9.23)

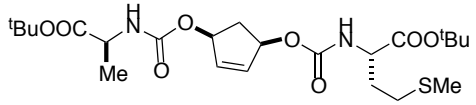
Yield 46%; R_f = 0.5 (30% EtOAc/hexanes); IR (neat) 1744, 1714, 1693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 6.24 – 5.95 (m, 2H), 5.89 – 5.63 (m, 2H), 5.22 (d, J = 8.1 Hz, 1H), 4.32 – 3.97 (m, 2H), 3.64 – 3.27 (m, 2H), 2.50 – 1.62 (m, 10H), 1.45 (s, 9H), 1.43 (s, 9H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 171.9, 171.2, 155.9, 154.8, 154.4, 136.3, 136.2, 135.4, 135.1, 82.4, 81.4, 81.2, 80.8, 79.2, 79.1, 60.0, 59.6, 54.0, 46.9, 46.5, 37.8, 31.6, 31.0, 30.0, 28.2, 28.1, 28.1, 24.3, 23.5; *m/z* (ESI+) found $[M+H]^+$ 583.3228, $C_{29}H_{47}N_2O_{10}$ requires 583.3231; $[\alpha]_D^{23.6}$ +176 (*c* 1.0, MeOH).



(*S,R,S,R*)-**3.9.25**

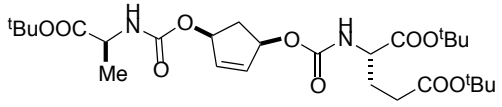
(*S*)-*tert*-Butyl 2-(((((1*R*,4*S*)-4-((((*S*)-1-(*tert*-butoxy)-1-oxopropan-2-yl)carbamoyl)oxy)cyclopent-2-en-1-yl)oxy)carbonyl)amino)-3-phenylpropanoate (3.9.25). Yield 49%; R_f = 0.3 (30% EtOAc/hexanes); IR (neat) 1744, 1690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.34 – 7.20 (m, 3H), 7.20 - 7.13 (m, 2H), 6.15 – 5.89 (m, 2H), 5.57 – 5.36 (m, 2H), 5.36 - 4.89 (m, 2H), 4.68–4.41 (m, 1H), 4.55 – 3.97 (m, 1H), 3.06 (d, J =

7.5 Hz, 2H), 2.92 – 2.74 (m, 1H), 1.74 (m, 1H), 1.46 (s, 9H), 1.39 (s, 9H), 1.36 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 170.7, 155.7, 155.4, 136.2, 134.8, 129.6, 128.5, 127.1, 119.2, 82.4, 82.1, 78.2, 55.3, 50.2, 39.2, 38.7, 37.6, 28.3, 28.1, 19.1; *m/z* (ESI+) found $[M+H]^+$ 519.2700, $C_{27}H_{39}N_2O_8$ requires 519.2706; $[\alpha]_D^{23.6}$ +173 (*c* 1.0, DCM).



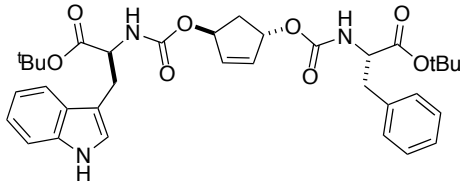
(*S,R,S,R*)-**3.9.28**

(*S*)-*tert*-Butyl 2-(((((1*R*,4*S*)-4-((((*S*)-1-(*tert*-butoxy)-1-oxopropan-2-yl)carbamoyl)oxy)cyclopent-2-en-1-yl)oxy)carbonyl)amino)-4-(methylthio)butanoate (3.9.28). Yield 60%; R_f = 0.2 (30% EtOAc/hexanes); IR (neat) 1747, 1705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.09 (d, *J* = 8.3 Hz, 2H), 5.50 (dt, *J* = 7.6, 4.0 Hz, 2H), 5.28 (dd, *J* = 23.0, 7.9 Hz, 1H), 4.57–4.16 (m, 2H), 3.93 (p, *J* = 6.9 Hz, 1H), 2.84 (dt, *J* = 15.0, 7.5 Hz, 1H), 2.52 (m, 2H), 2.20–2.05 (m, 4H), 1.95 (m, 1H), 1.76 (dt, *J* = 14.8, 3.8 Hz, 1H), 1.47 (s, 9H), 1.46 (s, 9H), 1.37 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.97, 170.95, 155.5, 155.2, 134.7, 134.6, 82.4, 81.9, 53.7, 53.5, 50.1, 46.2, 37.4, 32.5, 29.9, 28.0, 27.9, 18.9, 15.5; *m/z* (ESI+) found $[M+H]^+$ 503.2427, $C_{23}H_{39}N_2O_8$ requires 503.2427; $[\alpha]_D^{23.6}$ –66.4 (*c* 0.90, DCM).



(*S,R,S,R*)-**3.9.29**

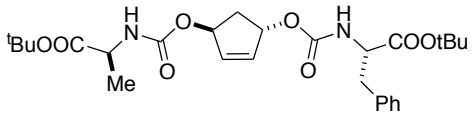
(*S*)-di-*tert*-Butyl 2-(((((1*R*,4*S*)-4-((((*S*)-1-(*tert*-butoxy)-1-oxopropan-2-yl)carbamoyl)oxy)cyclopent-2-en-1-yl)oxy)carbonyl)amino)pentanedioate (3.9.29). Yield 60%; R_f = 0.3 (30% EtOAc/hexanes); IR (neat) 1746, 1700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05 (m, 2H), 5.58–5.38 (m, 2H), 5.36–5.00 (m, 2H), 4.34–4.03 (m, 2H), 2.85 (dt, *J* = 15.0, 7.6 Hz, 1H), 2.45–2.04 (m, 3H), 2.01–1.69 (m, 2H), 1.49 (s, 9H), 1.48 (s, 9H), 1.46 (s, 9H), 1.38 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 172.0, 171.2, 155.7, 155.3, 134.9, 134.8, 82.4, 82.0, 80.8, 79.1, 54.0, 50.2, 41.1, 40.3, 37.5, 31.6, 28.2, 28.13, 28.10, 19.0; *m/z* (ESI+) found $[M+H]^+$ 557.3070, $C_{27}H_{45}N_2O_{10}$ requires 557.3074; $[\alpha]_D^{24.6}$ +77 (*c* 1.0, DCM).



(*S,S,S,S*)-**3.9.7**

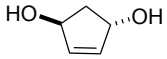
(*S*)-*tert*-Butyl 2-(((((1*S*,4*S*)-4-((((*S*)-1-(*tert*-butoxy)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)carbamoyl)oxy)cyclopent-2-en-1-yl)oxy)carbonyl)amino)-3-(4-(*tert*-butoxy)phenyl)propanoate 3.9.7). Yield 59%; R_f = 0.2 (30% EtOAc/hexanes); IR (neat) 1749, 1705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.48–6.91 (m, 9H), 6.07 (s, 2H), 5.72 (s, 2H), 5.13 (dd, *J* = 31.1, 8.2 Hz, 2H), 4.70–4.26 (m, 2H), 3.45–3.13 (m, 2H), 3.06 (d, *J* = 6.2 Hz, 2H), 2.36–1.90 (m, 2H), 1.40 (s, 9H), 1.38 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ171.1, 170.6, 136.2, 135.8, 135.6, 129.6,

128.5, 127.9, 127.0, 122.7, 122.3, 119.6, 119.1, 111.2, 110.6; 110.4, 82.4, 82.1, 79.1, 78.9, 60.5, 55.3, 53.5, 38.6, 37.9, 28.1, 21.1, 14.3; *m/z* (ESI+) found $[M+H]^+$ 634.3125, $C_{35}H_{44}N_3O_8$ requires 634.3128; $[\alpha]_D^{23.6}$ +73 (*c* 1.1, DCM).



(*S,S,S,S*)-**3.9.25**

(*S*)-*tert*-Butyl 2-(((((1*S*,4*S*)-4-((((*S*)-1-(*tert*-butoxy)-1-oxopropan-2-yl)carbamoyl)oxy)cyclopent-2-en-1-yl)oxy)carbonyl)amino)-3-phenylpropanoate (3.9.25). Yield 52%; R_f = 0.3 (30% EtOAc/hexanes); IR (neat) 1747, 1703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ7.36–7.07 (m, 5H), 6.22–6.00 (m, 2H), 5.85–5.59 (m, 2H), 5.26–4.90 (m, 2H), 4.68–4.57 (m, 1H), 4.34–3.95 (m, 1H), 3.19–2.82 (m, 2H), 2.35–1.89 (m, 2H), 1.46 (s, 9H), 1.39 (s, 9H), 1.35 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ171.5, 172.3, 170.7, 136.2, 135.7, 129.7, 129.6, 128.5, 128.4, 127.1, 126.8, 82.4, 79.1, 78.9, 55.2, 54.6, 38.9, 38.6, 37.6. 28.10, 28.08; (*m/z* (ESI+) found $[M+H]^+$ 519.2706, $C_{27}H_{39}N_2O_8$ requires 519.2706; $[\alpha]_D^{23.6}$ –155 (*c* 1.0, DCM).

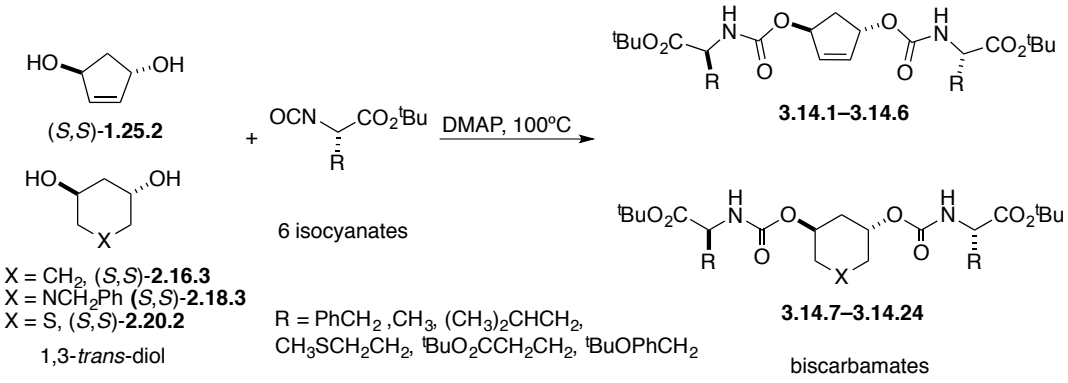


(*S,S*)-**3.13.2**

(1*S*,3*S*)-Cyclopent-4-ene-1,3-diol (*S,S*-**3.13.2**)**.** A solution of (3*S*,5*S*)-hepta-1,6-diene-3,5-diol (500 mg, 3.91 mmol) in DCM (78 mL) and methanol (78 mL) was purged with argon for 15 min and 5 mol% of Grubbs II catalyst (166 mg) was added to it. The reaction mixture was stirred at rt for 6 h and was quenched with DMSO (1 mL). The reaction mixture was stirred under air for 5 min and concentrated. The crude product was

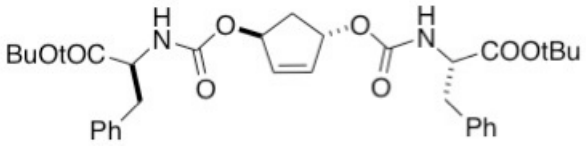
purified by silica gel chromatography (100% EtOAc) to afford the product as colorless oil (266 mg, 68%). R_f = 0.20 (100% EtOAc); IR (neat) 3420 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.05–6.01 (m, 2H), 5.07 (t, J = 4.8 Hz, 2H), 2.10 (t, J = 5.0 Hz, 2H), 1.56 (br s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.4, 76.4, 44.4; *m/z* (ESI+) found $[M+Na]^+$ 123.0421, $C_5H_8NaO_2$ requires 123.0422; $[\alpha]_D^{23.6}$ –232 (*c* 1.0, MeOH).

Parallel synthesis of C_2-symmetric biscarbamates



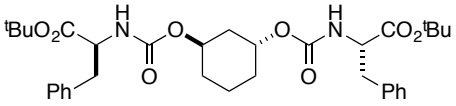
On a 6x4-well heating block, 24 two-dram vials were placed. Each of the C_2-symmetric diols (30 mg) was charged separately into 6 two-dram vials. Then amino acid isocyanate (3 eq) were charged and 10% *N,N'*-DMAP were added. To each vial 0.1 mL of THF was added to facilitate the mixing of the reagents. The vials were closed with Teflon caps and the block was heated to 100 ºC for 2 h. Following cooling 2 mL of dichloromethane was added to each vial. The contents of the vials were transferred to 24 different collection tubes. The solvent was evaporated by purging nitrogen gas to obtain the crude reaction products. A random subset of five compounds from the crude library of 24 compounds

was purified by column chromatography to obtain the products 25–35 mg of quantity (the spectral data is listed below). The rest of the crude library compounds were subjected to mass-directed purification and analysis, however due to lack of an analytical response the product peaks could not be identified.



(*S,S,S,S*)-**3.14.1**

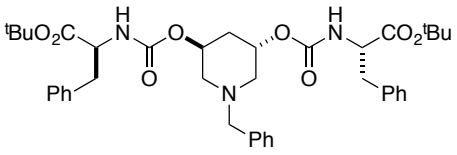
(2*S*,2'*S*)-Di-*tert*-butyl 2,2'-((((1*S*,3*S*)-cyclopent-4-ene-1,3-diylbis(oxy))bis(carbonyl))bis(azanediyl))bis(3-phenylpropanoate (3.14.1). Yield 66%; R_f = 0.3 (30% EtOAc/hexanes); IR (neat), 1744, 1693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ7.37–7.05 (m, 10H), 6.07–5.97 (m, 2H), 5.79–5.64 (m, 2H), 5.18 (m, 2H), 4.51–4.21 (m, 2H), 3.16–2.86 (m, 4H), 2.17 (t, *J* = 5.1 Hz, 2H), 1.41 (s, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ170.6, 155.5, 136.2, 135.6, 129.5, 128.5, 127.1, 82.3, 79.0, 55.2, 38.6, 37.8, 28.0; (*m/z* (ESI+) found $[M+H]^+$ 595.3018, $C_{33}H_{43}N_2O_8$ requires 595.3019; $[\alpha]_D^{24.2}$ +139 (*c* 1.0, DCM).



(*S,S,S,S*)-**3.14.7**

(2*S*,2'*S*)-Di-*tert*-butyl 2,2'-((((1*S*,3*S*)-cyclohexane-1,3-diylbis(oxy))bis(carbonyl))bis(azanediyl))bis(3-phenylpropanoate) (3.14.7). Yield 62%; R_f = 0.3 (25% EtOAc/hexanes); IR (neat) 1746, 1698 cm^{-1}; ^1H NMR (400 MHz,

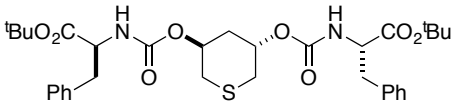
$CDCl_3$) δ7.62–6.81 (m, 10H), 5.36–4.82 (m, 2H), 4.73–4.23 (m, 4H), 3.25–2.80 (m, 4H), 2.36–2.13 (m, 2H), 2.05–1.84 (m, *J* = 5.9, 1H), 1.39 (s, 18H), 1.62–0.95 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 155.0, 136.2, 129.5, 128.4, 126.9, 82.2, 71.2, 55.0, 38.4, 31.1, 27.9, 20.0; *m/z* (ESI+) found $[M+H]^+$ 611.3330, $C_{34}H_{47}N_2O_8$ requires 611.3332; $[\alpha]_D^{23.6}$ +275 (*c* 1.0, DCM).



(*S,S,S,S*)-**3.14.13**

(2*S*,2'*S*)-Di-*tert*-butyl 2,2'-(((((3*R*,5*R*)-1-benzylpiperidine-3,5-diyl)bis(oxy))bis(carbonyl))bis(azanediyl))bis(3-phenylpropanoate) (3.14.13).

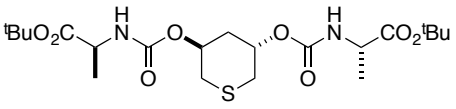
Yield 51%; R_f = 0.3 (50% EtOAc/hexanes); IR (neat) 1744, 1700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ7.36–6.90 (m, 15H), 5.22–5.02 (m, 3H), 4.54–4.20 (m, 2H), 3.62–3.37 (m, 2H), 2.97 (d, *J* = 6.1 Hz, 4H), 2.62–2.46 (m, 2H), 2.42–2.24 (m, 2H), 1.84–1.52 (m, 3H), 1.31 (m, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 155.1, 137.4, 136.3, 129.6, 129.1, 128.5, 128.4, 127.3, 127.0, 82.3, 68.5, 62.3, 56.1, 55.3, 38.7, 34.5, 28.0; *m/z* (ESI+) found $[M+H]^+$ 702.3749, $C_{40}H_{52}N_3O_8$ requires 702.3754; $[\alpha]_D^{23.6}$ +109.7 (*c* 1.0, DCM).



(*S,S,S,S*)-**3.14.19**

(2*S*,2'*S*)-Di-*tert*-butyl 2,2'-(((((3*S*,5*S*)-tetrahydro-2*H*-thiopyran-3,5-diyl)bis(oxy))bis(carbonyl))bis(azanediyl))bis(3-phenylpropanoate) (3.14.19).

Yield 57%; R_f = 0.4 (50% EtOAc/hexanes); IR (neat) 1747, 1697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.32–7.11 (m, 10H), 5.30–4.93 (m, 4H), 4.55–4.33 (m, 2H), 3.16–2.91 (m, 4H), 2.78–2.65 (m, 2H), 2.59–2.48 (m, 2H), 1.87–1.68 (m, 2H), 1.40 (s, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ170.5, 154.7, 136.2, 129.6, 128.5, 127.1, 82.4, 69.1, 55.3, 38.7, 36.0. 31.6, 28.1; (*m/z* (ESI+) found $[M+H]^+$ 629.2899, $C_{33}H_{45}N_2O_8S$ requires 629.2897; $[\alpha]_D^{23.7}$ –129 (*c* 1.7, DCM).



(*S,S,S,S*)-**3.14.20**

(2*S*,2'*S*)-Di-*tert*-butyl 2,2'-(((((3*R*,5*R*)-tetrahydro-2*H*-thiopyran-3,5-diyl)bis(oxy))bis(carbonyl))bis(azanediyl))dipropanoate (3.14.20).

Yield 59%; R_f = 0.3 (50% EtOAc/hexanes); IR (neat) 1744, 1698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 5.41–4.89 (m, 4H), 4.33– 4.20 (m, 2H), 2.77 (dd, *J* = 13.5 Hz, 2.5 Hz, 2 H), 2.68–2.53 (m, 2H), 2.19–1.76 (m, 2H), 1.46 (s, 18 H), 1.37 (d, *J* = 7.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 154.6, 81.9, 68.9, 50.1, 36.0, 31.6, 27.9, 18.8; *m/z* (ESI+) found $[M+H]^+$ 477.2270, $C_{21}H_{37}N_2O_8S$ requires 477.2271; $[\alpha]_D^{23.9}$ +181(*c* 1.0, DCM).

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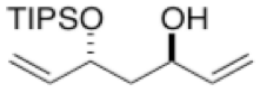
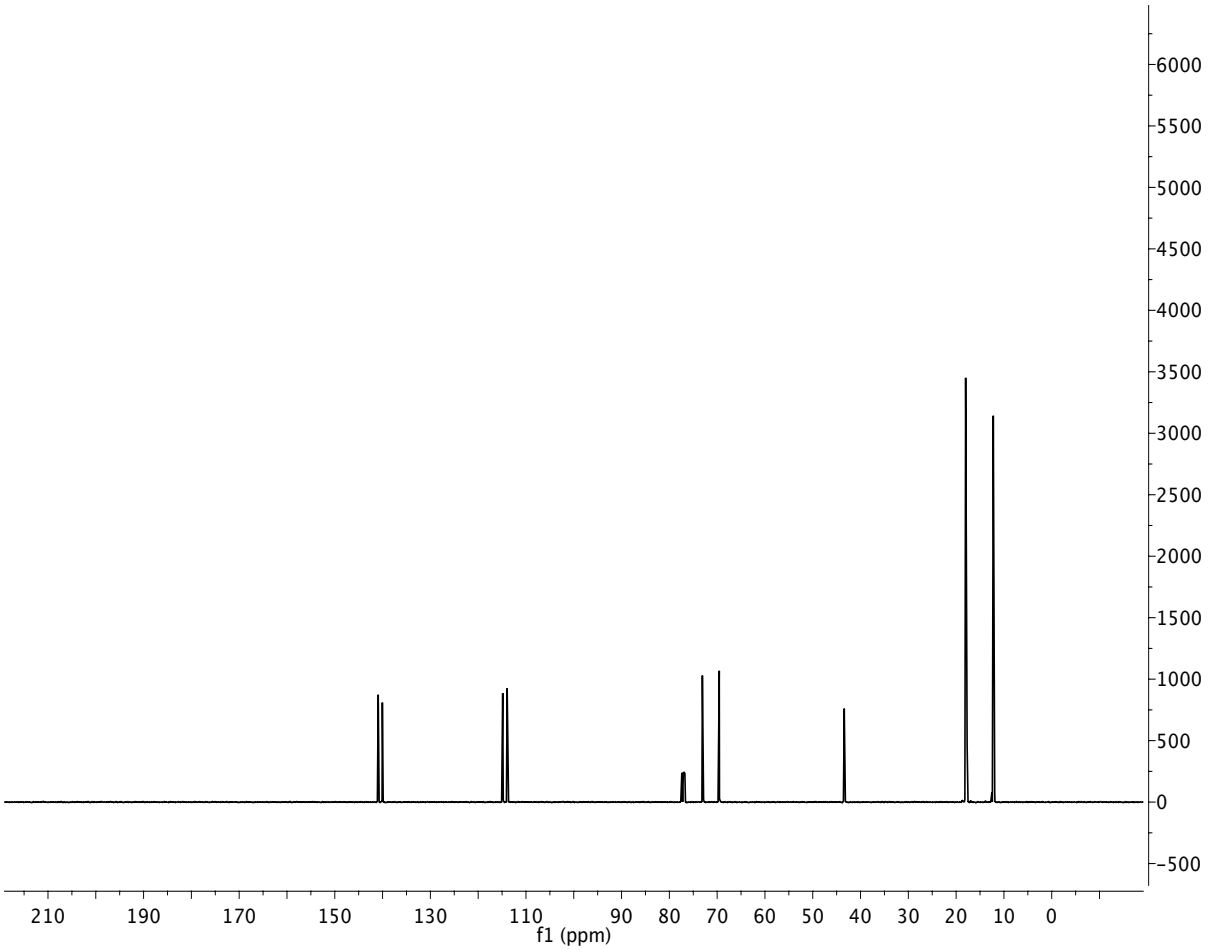
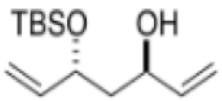


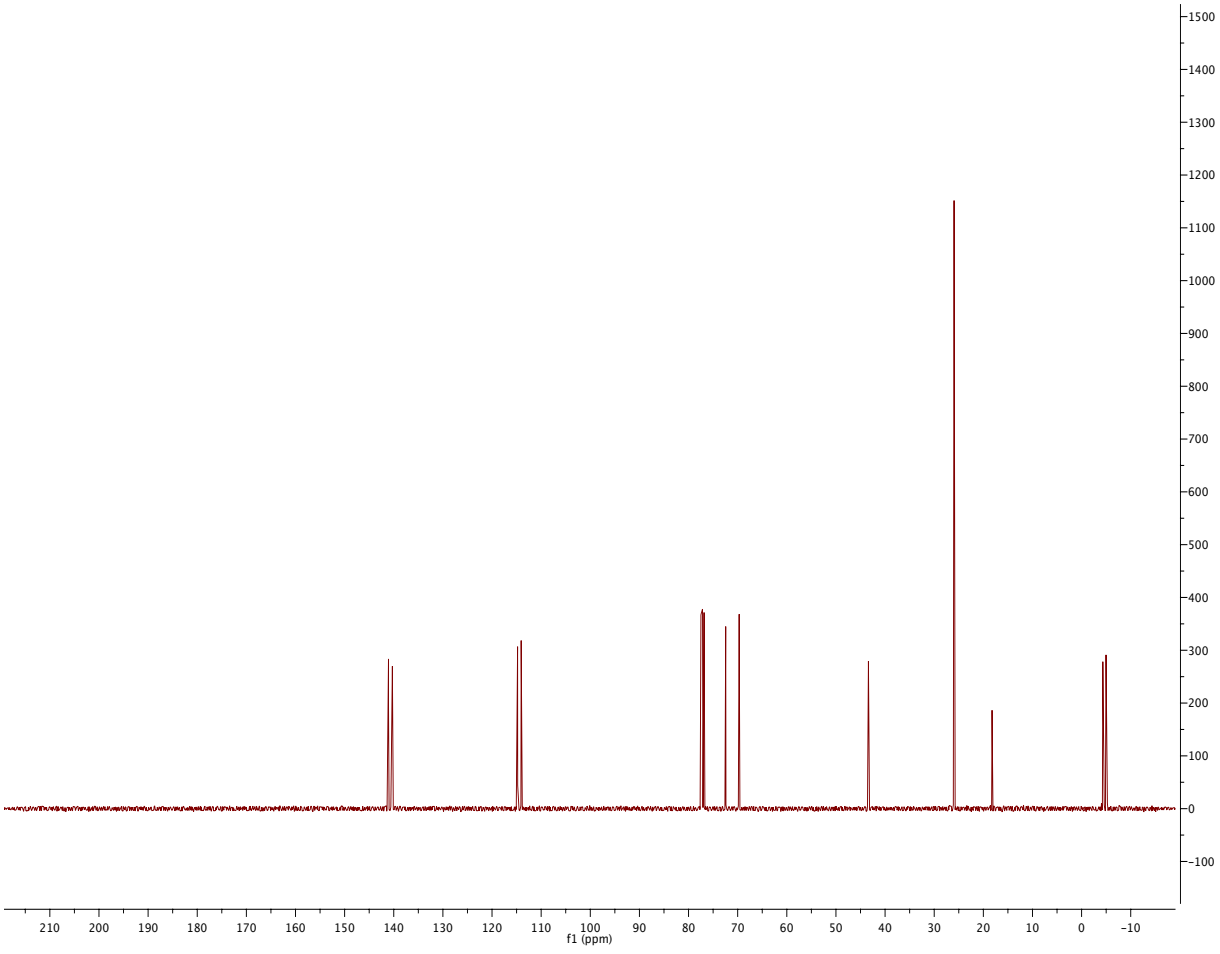
(*R*,*R*)-**1.20.1**

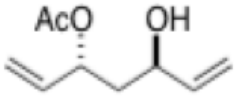



TBSO
OH

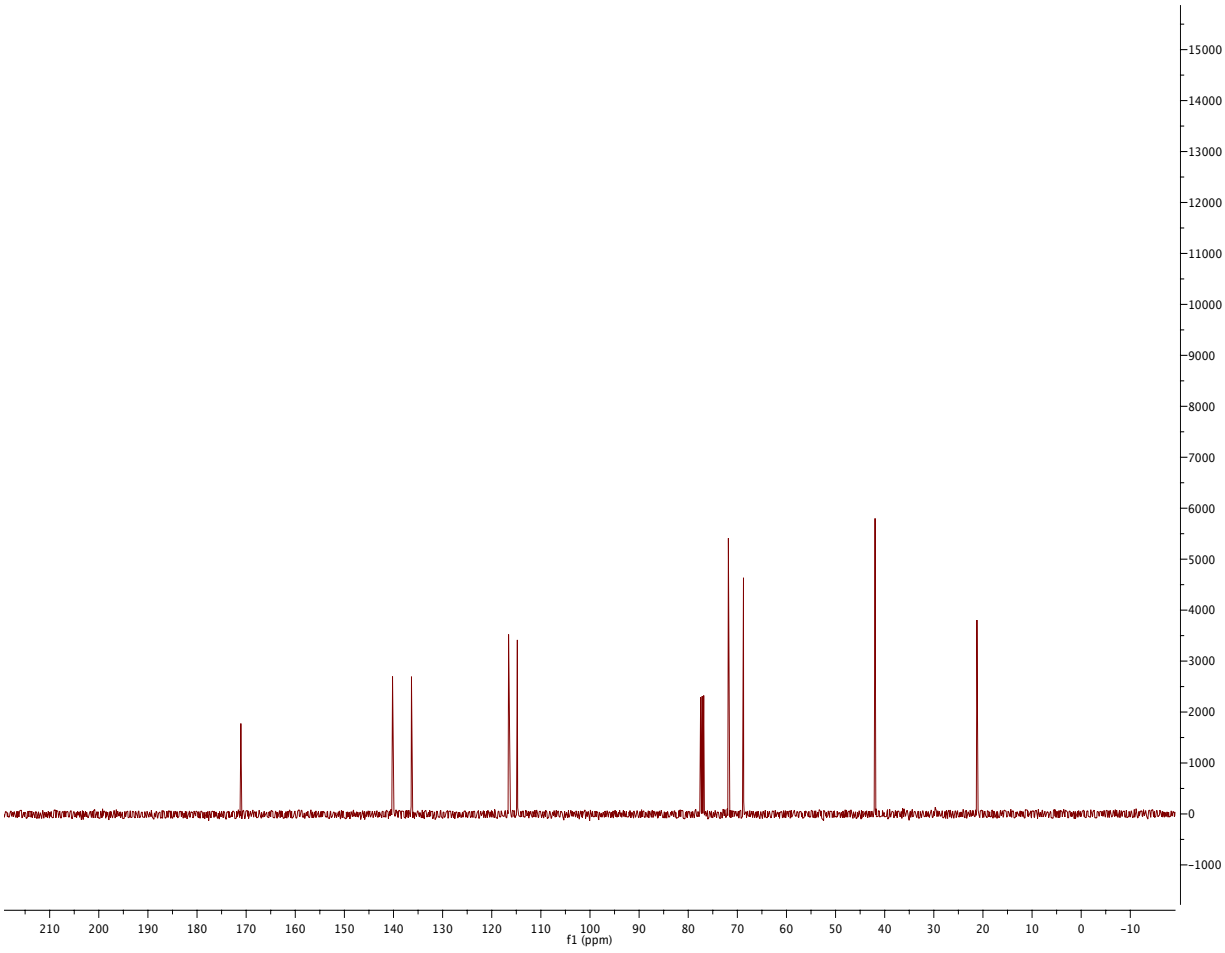
(*R*,*R*)-**1.23.1**

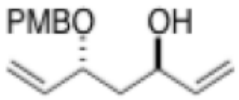
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
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)

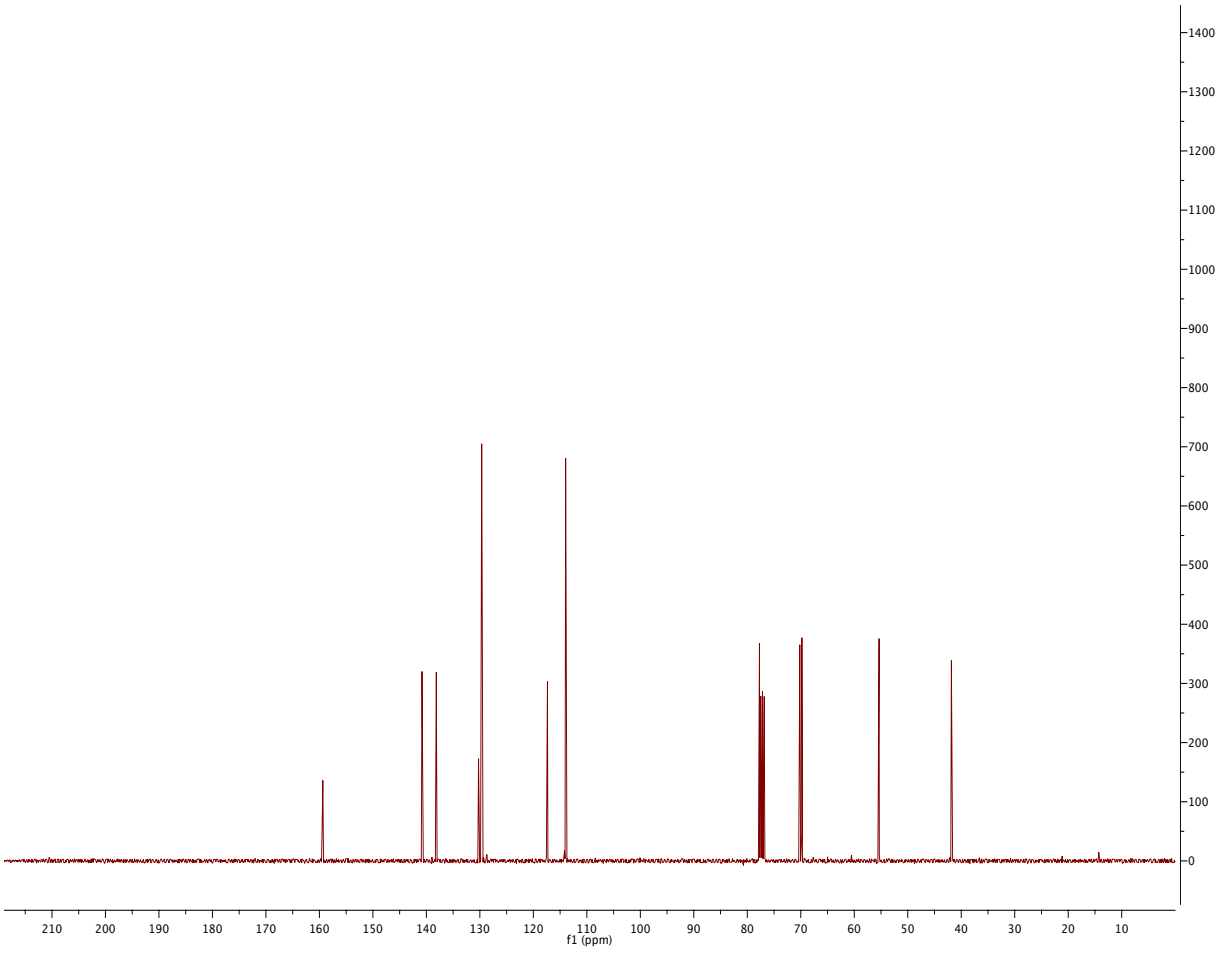


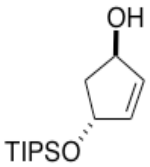
(*R*,*R*)-**1.24.1**





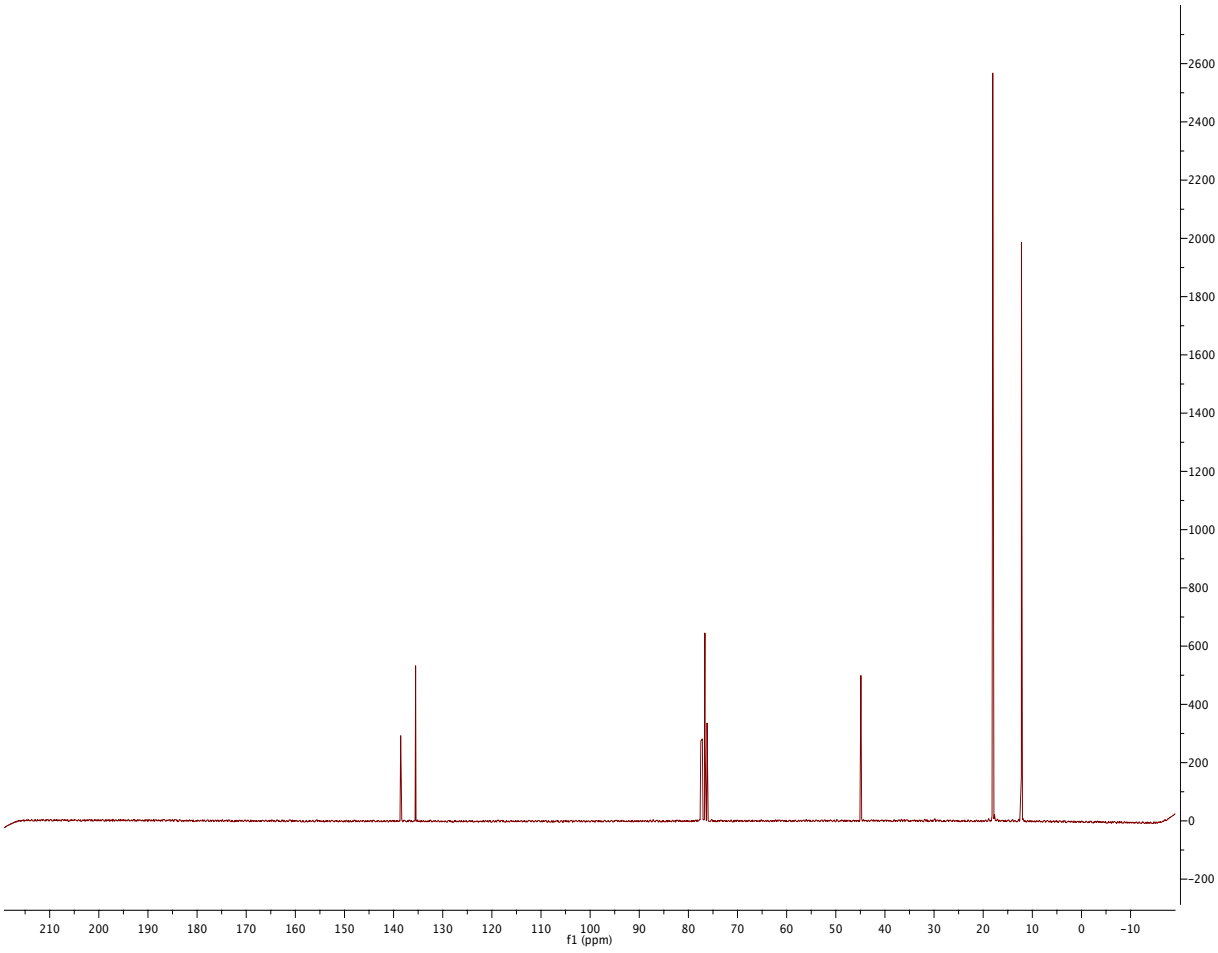
(*R*,*R*)-**1.25.1**

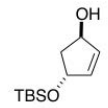



OH
TIPSO

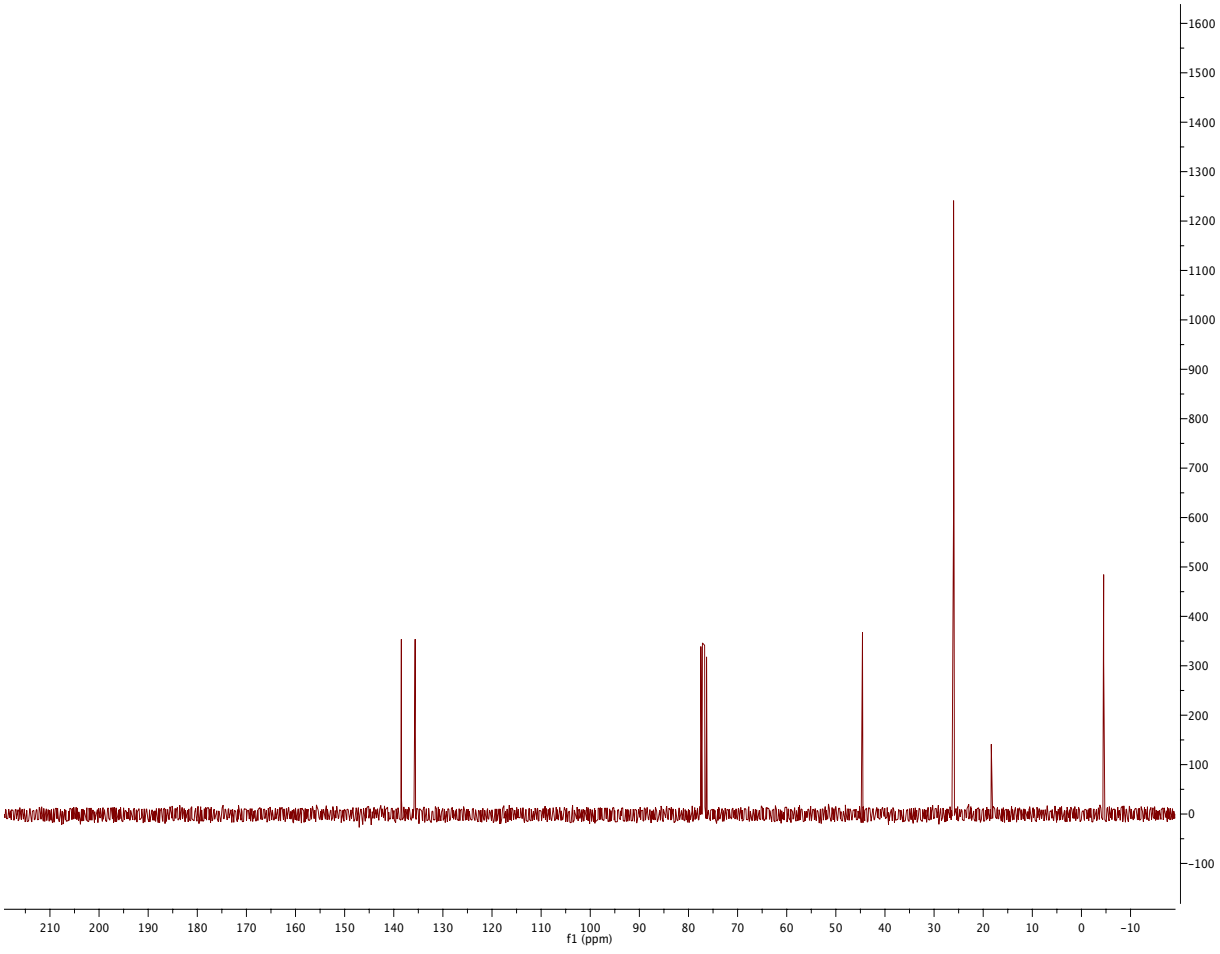
(*R*,*R*)-**1.25.1**

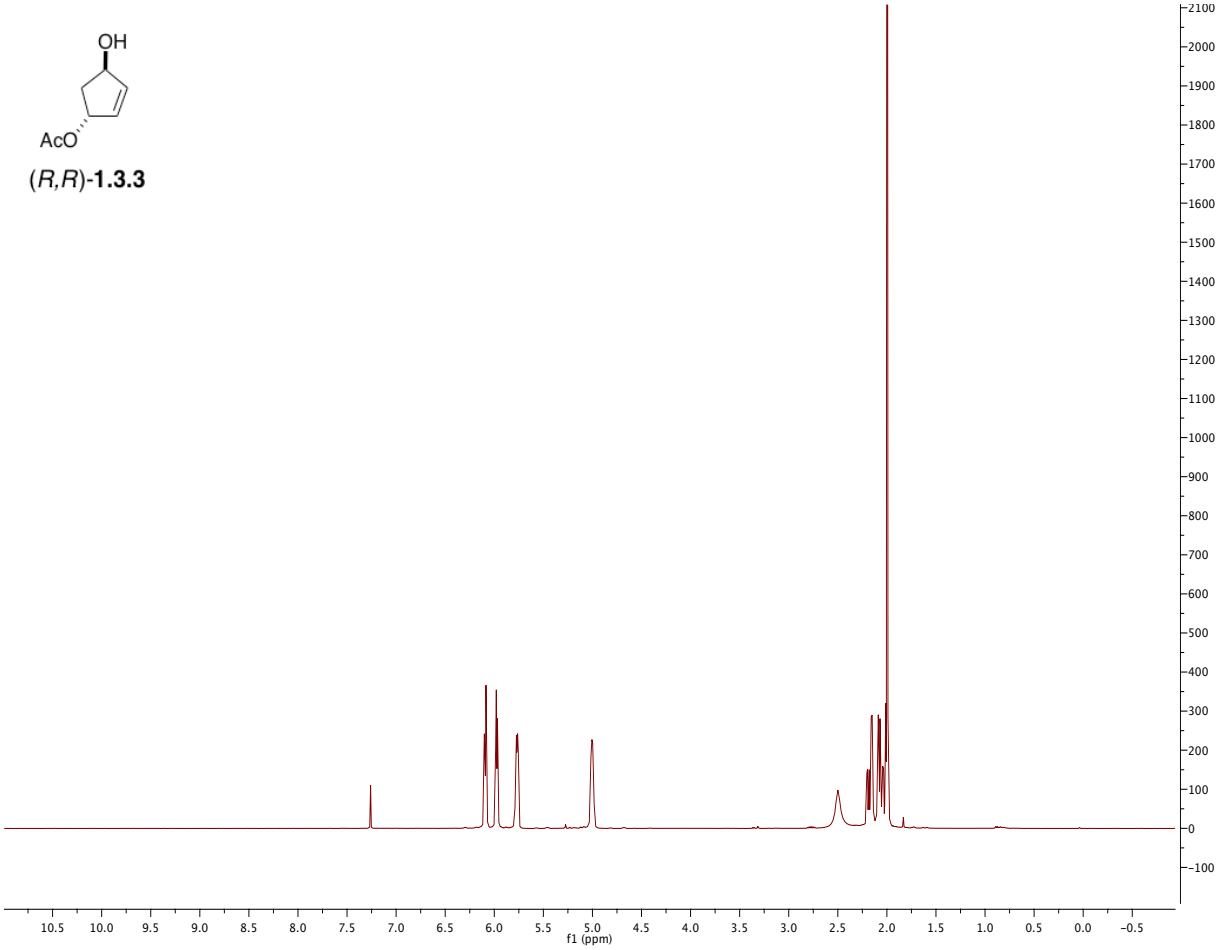
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
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)

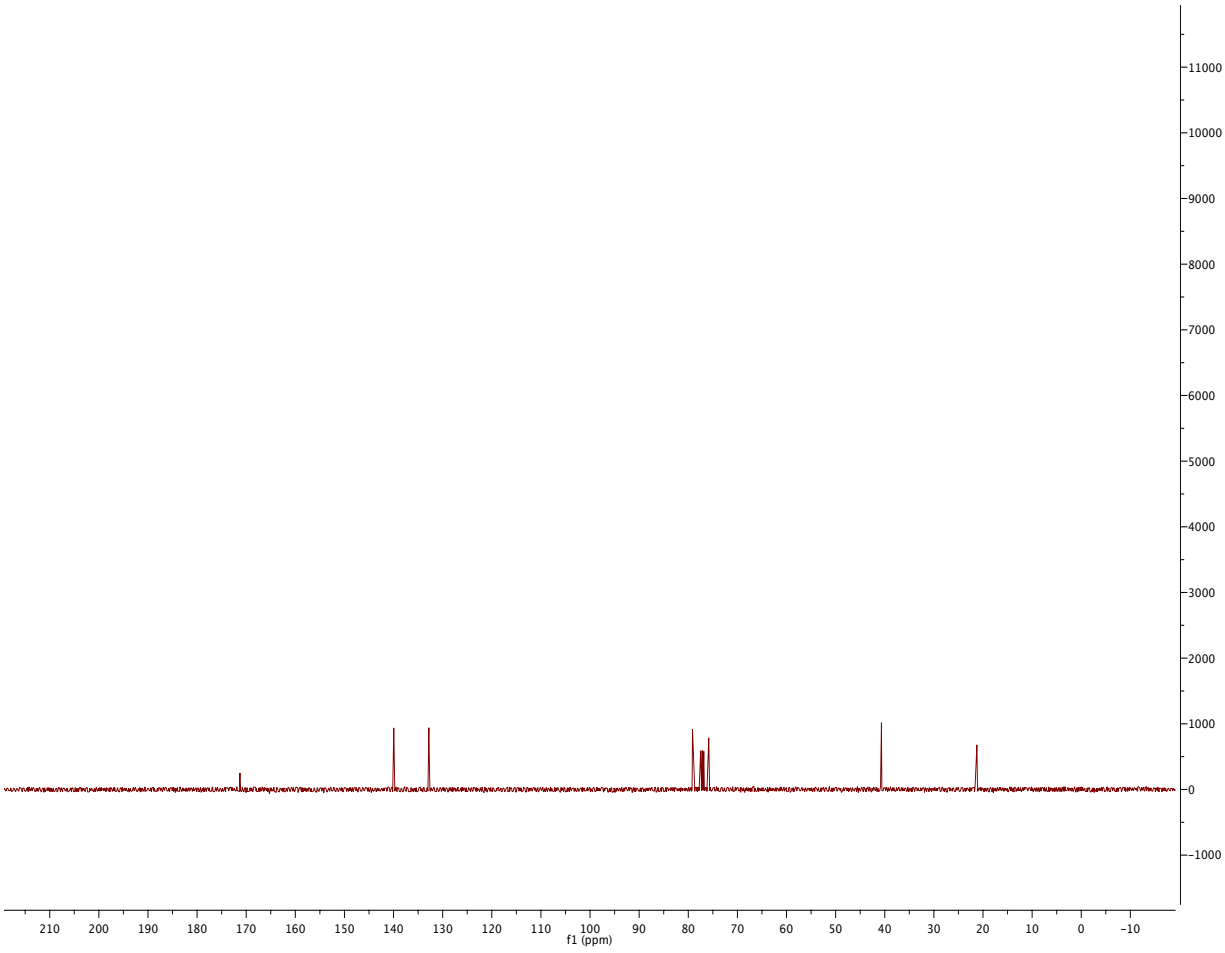


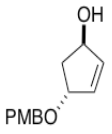
***R,R*-1.4.5**





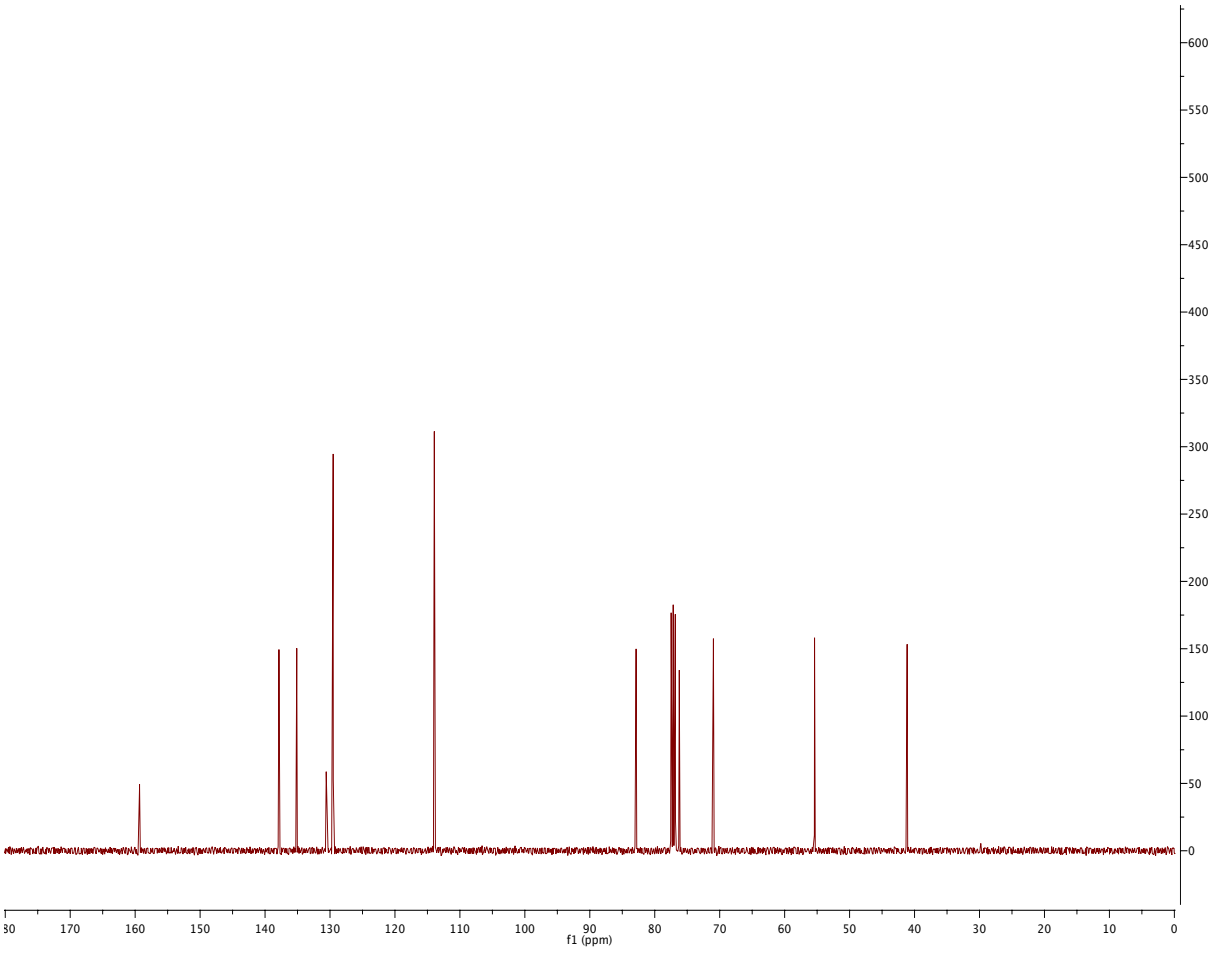
(*R*,*R*)-**1.3.3**

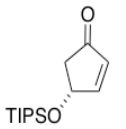



OH
PMBO

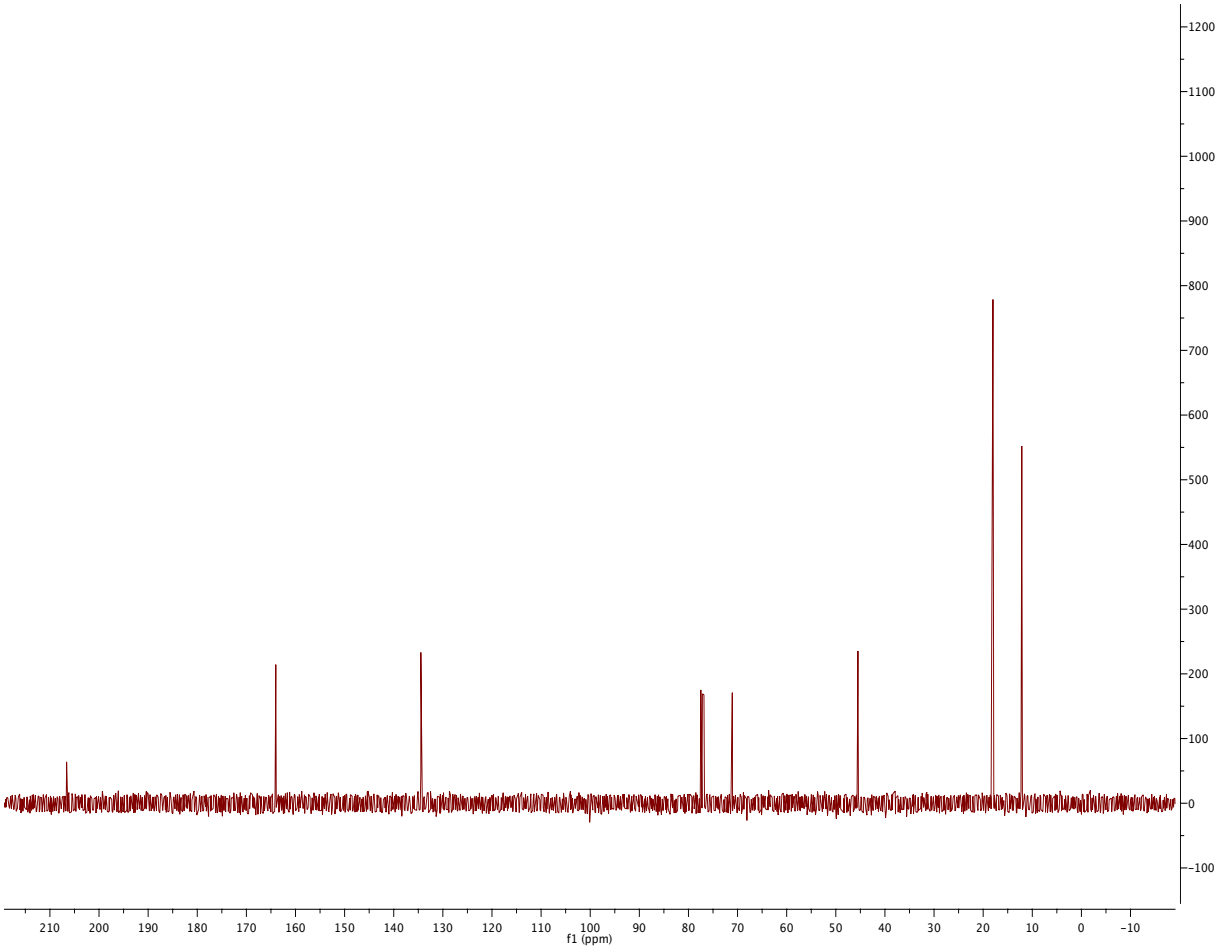
(*R*,*R*)-**1.26.1**

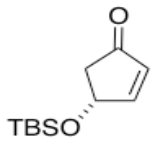
4500
4000
3500
3000
2500
2000
1500
1000
500
0
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5 −1.0
f1 (ppm)


600
550
500
450
400
350
300
250
200
150
100
50
0
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



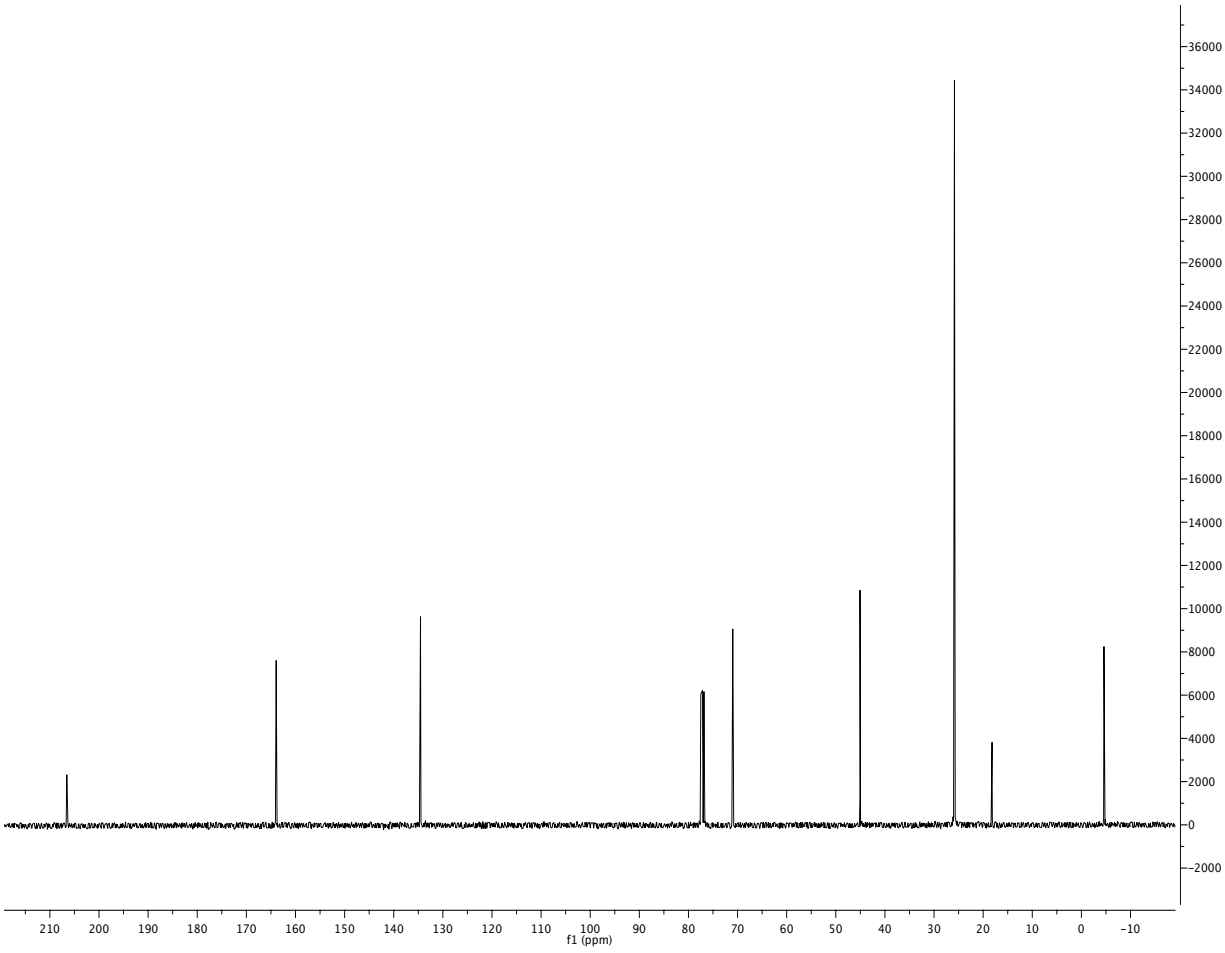
(*R*)-**1.20.3**




O
TBSO

(*R*)-**1.4.3**

4000
3500
3000
2500
2000
1500
1000
500
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)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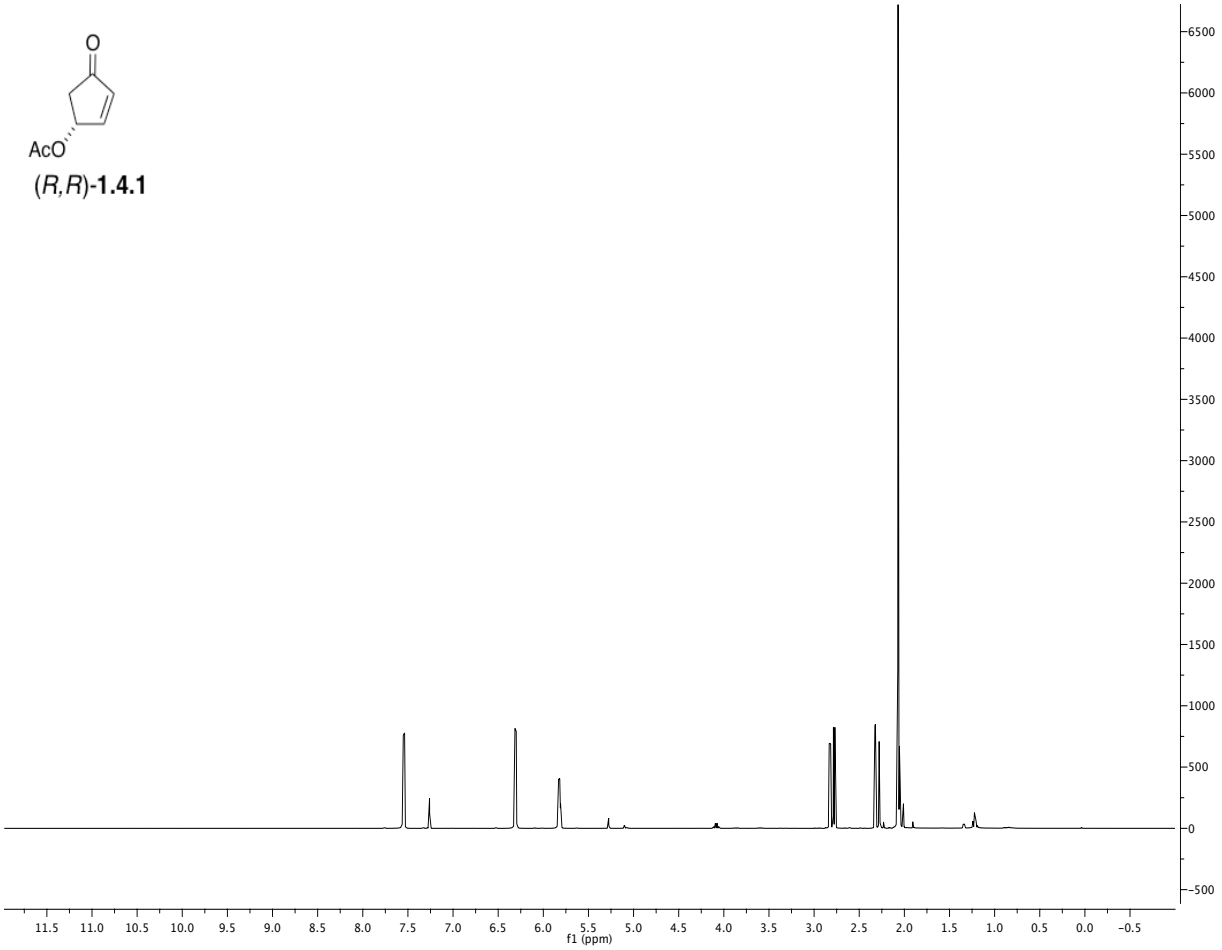
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
AcO
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6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
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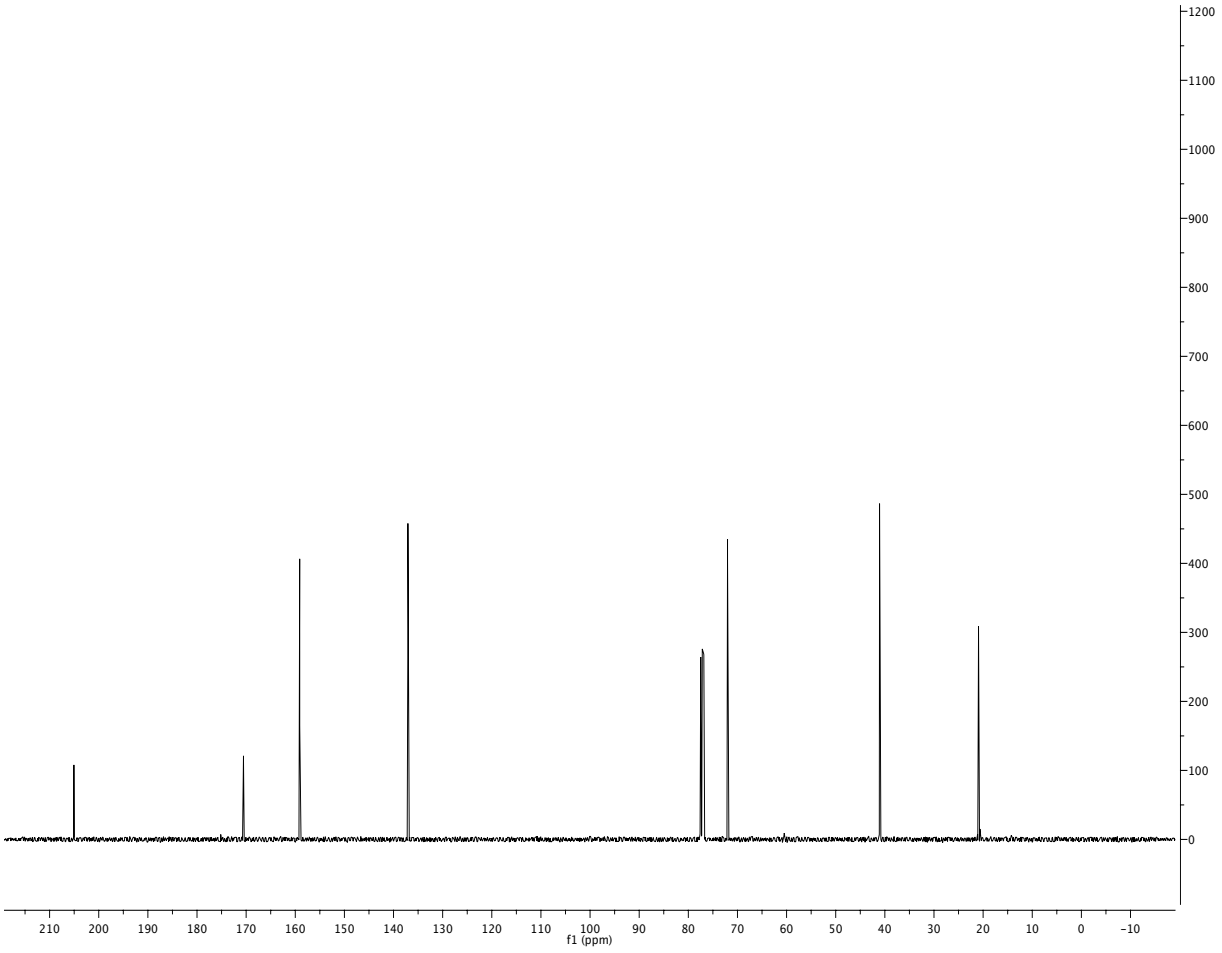
f1 (ppm)

(*R*,*R*)-**1.4.1**


1200
1100
1000
900
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700
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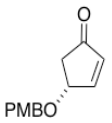
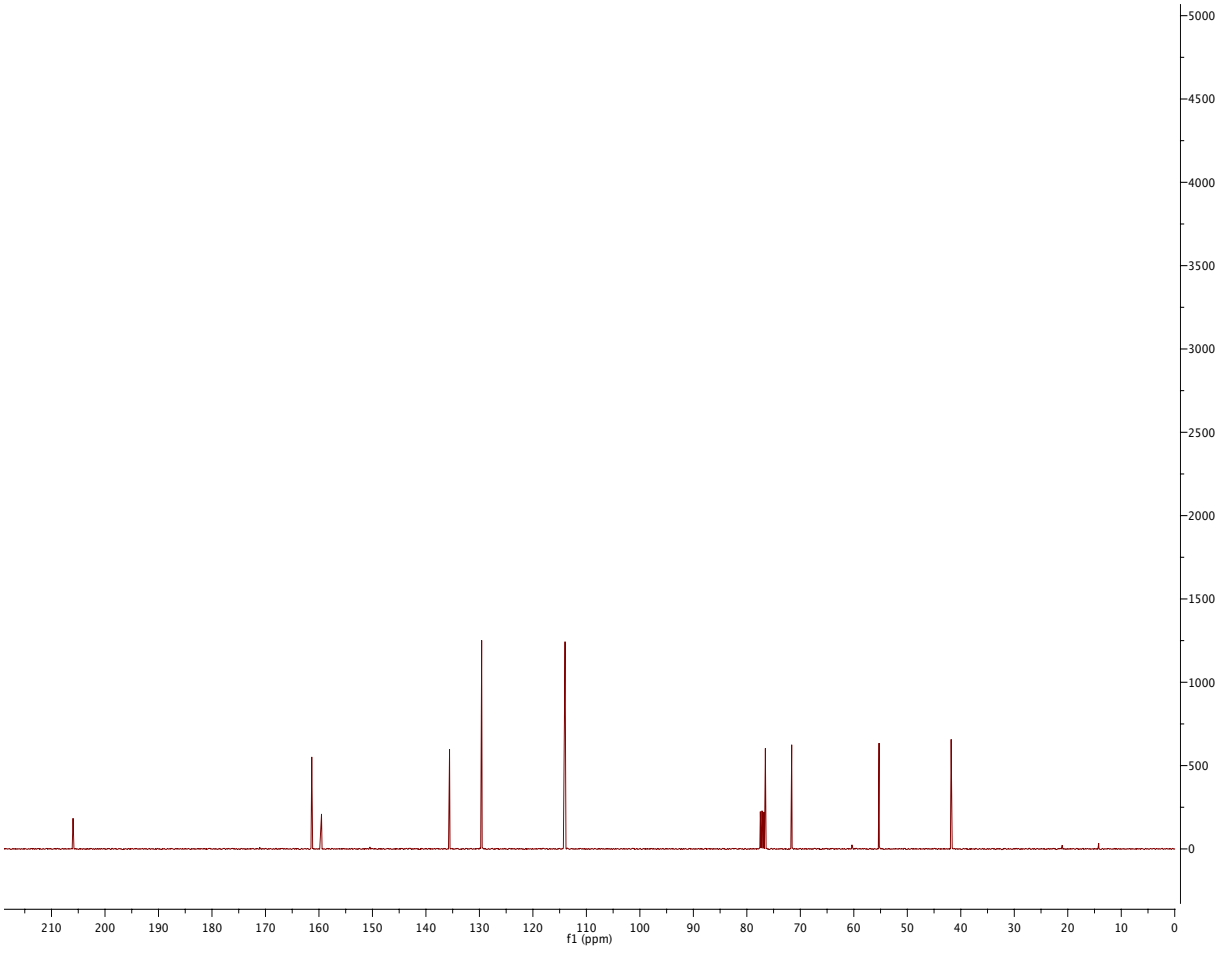
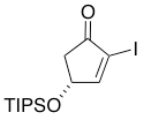
400
300
200
100
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
PMBO

(*R*)-**1.27.1**

4500
4000
3500
3000
2500
2000
1500
1000
500
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 -1.0
f1 (ppm)


5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
I
TIPSO

(*R*,*R*)-**1.20.4**

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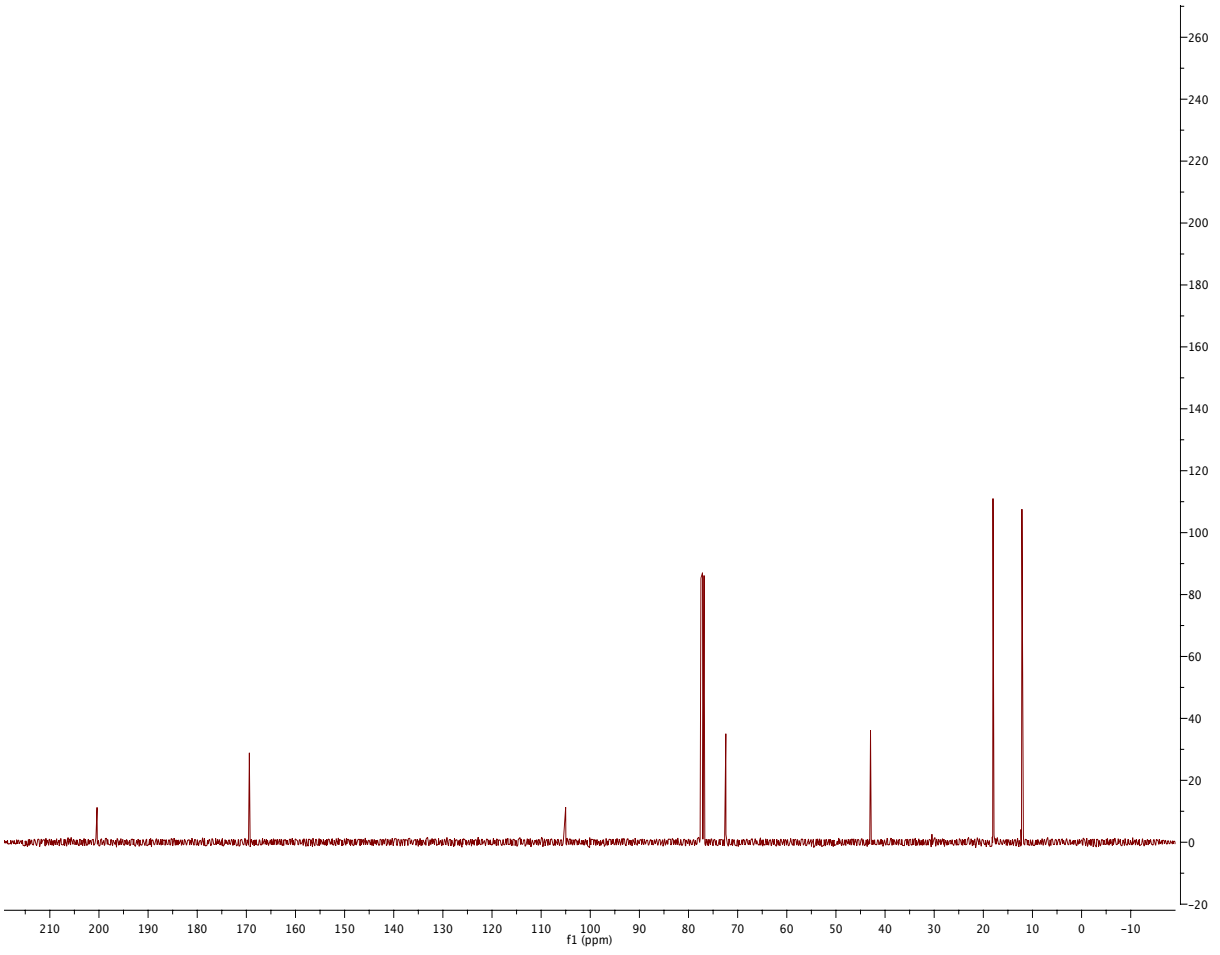
3000
2500
2000
1500
1000
500
0
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 −3 −4
f1 (ppm)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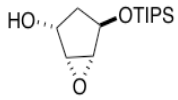
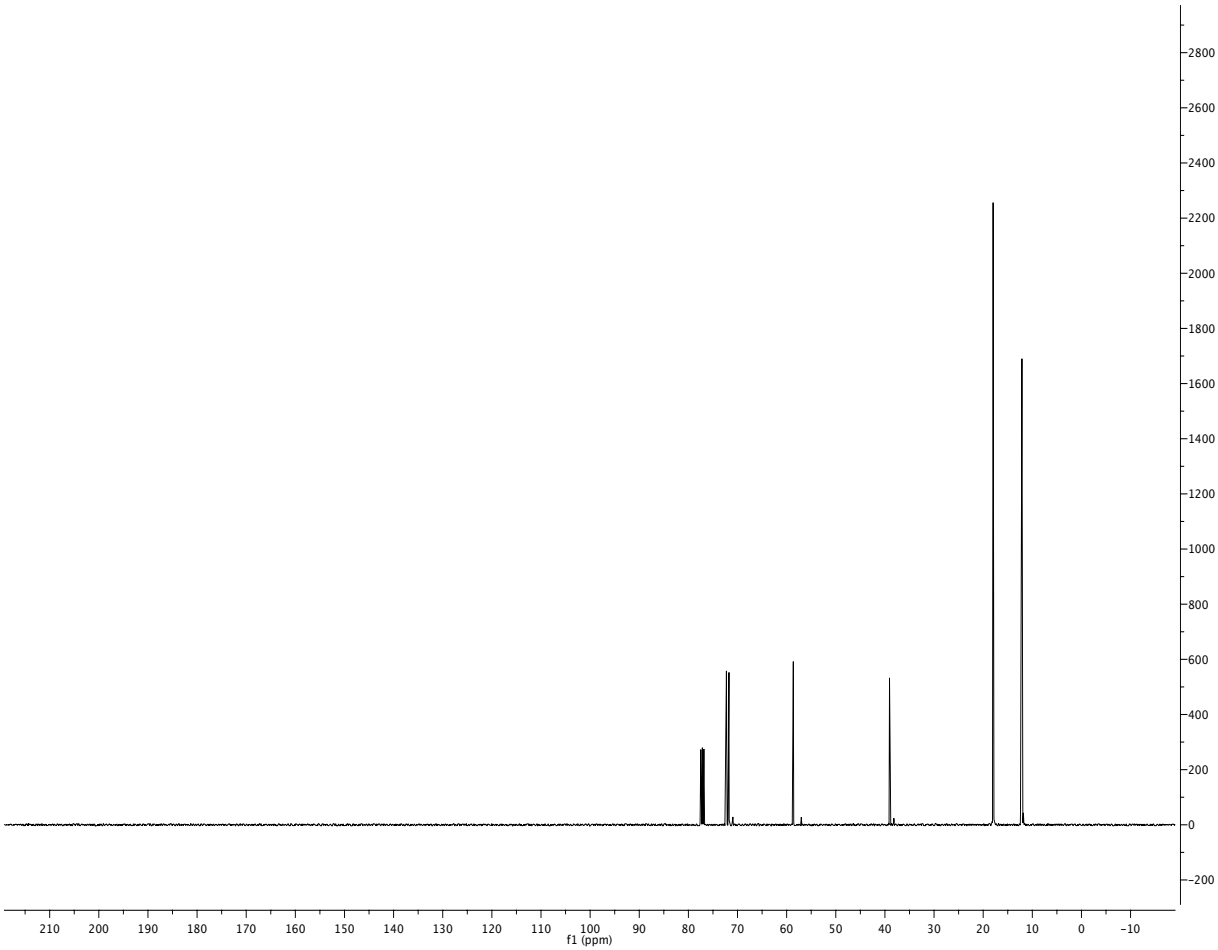
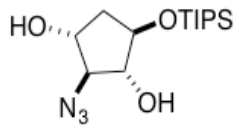
240
220
200
180
160
140
120
100
80
60
40
20
0
−20
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)

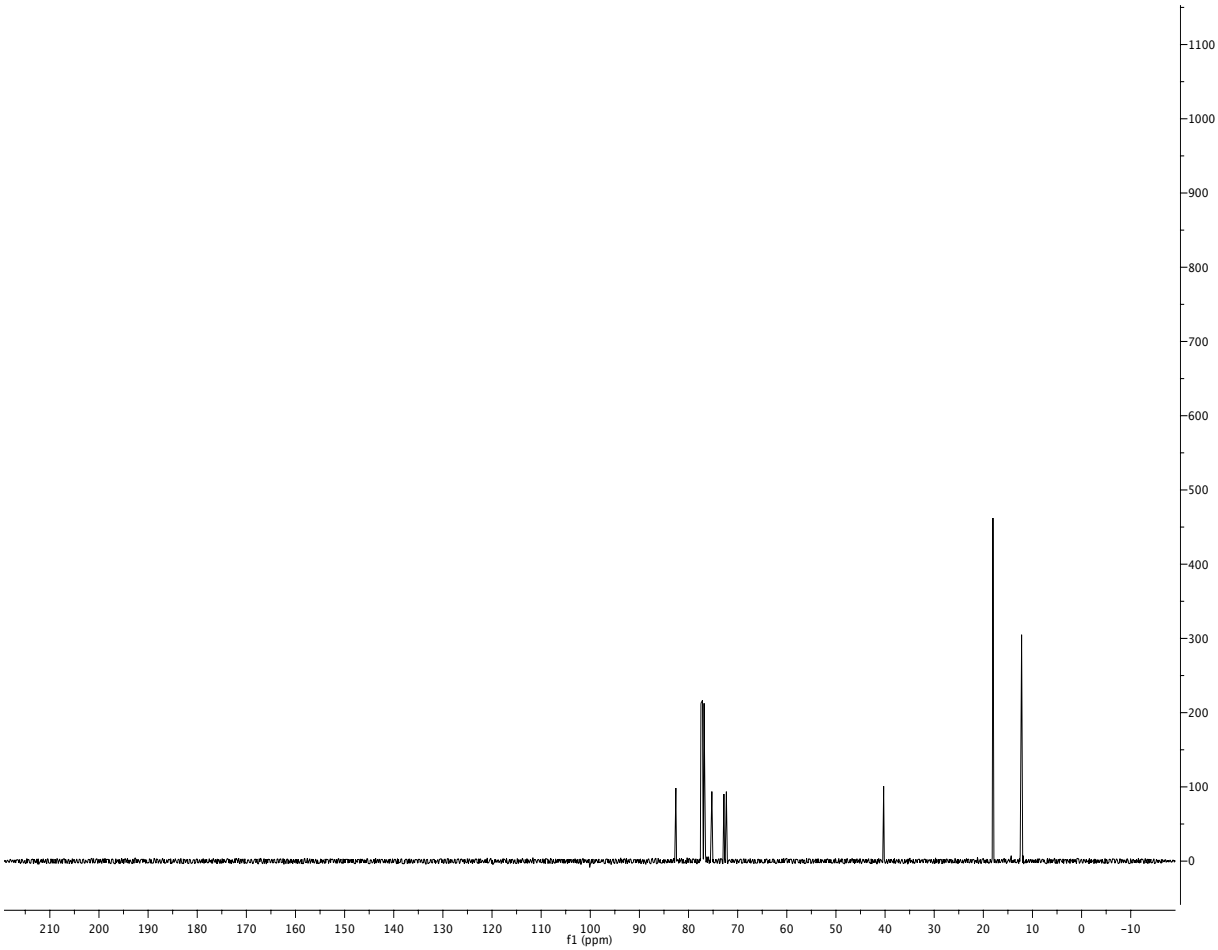


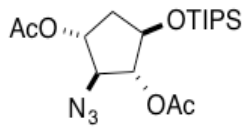
1.30.2



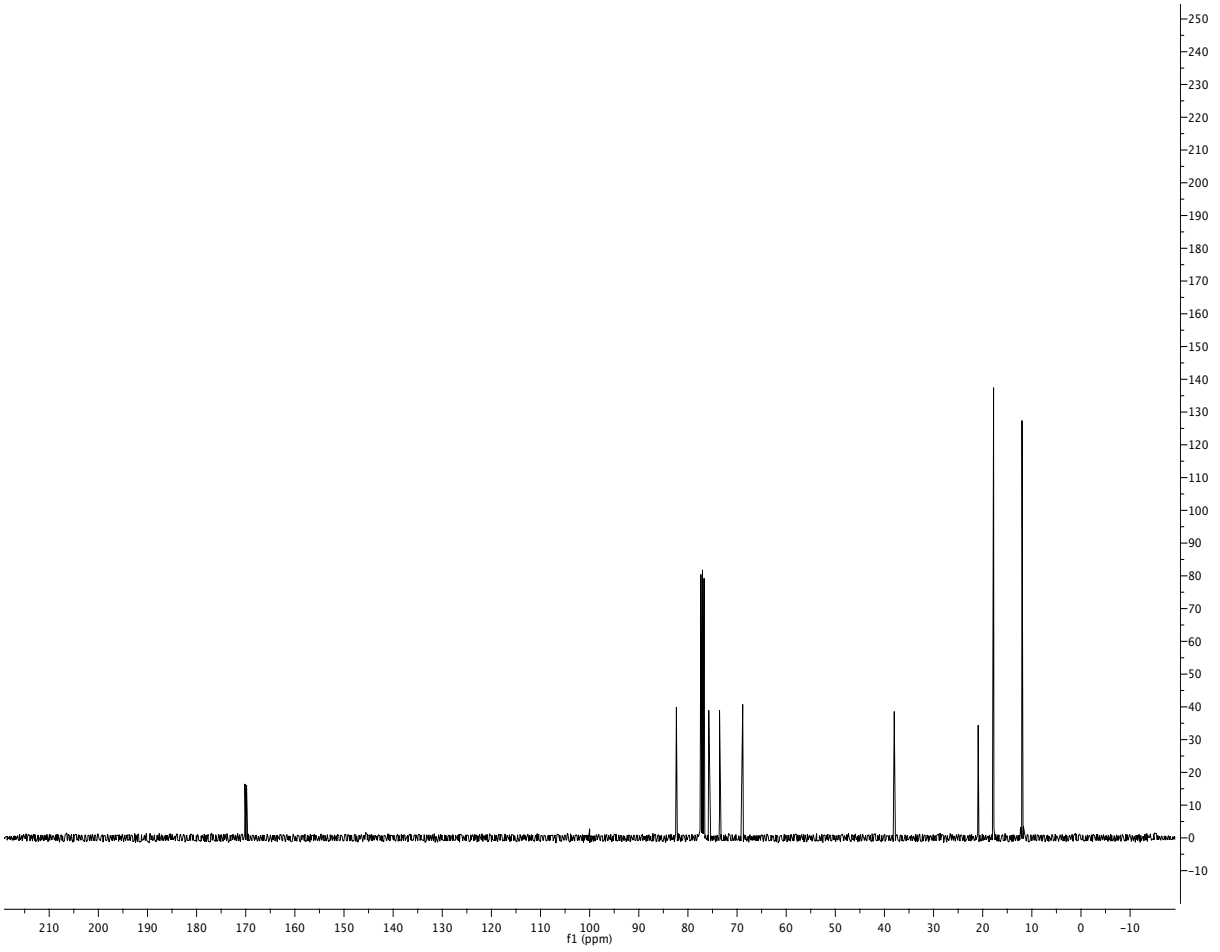


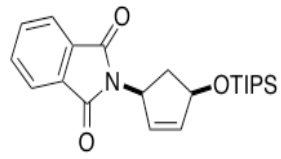
1.30.3





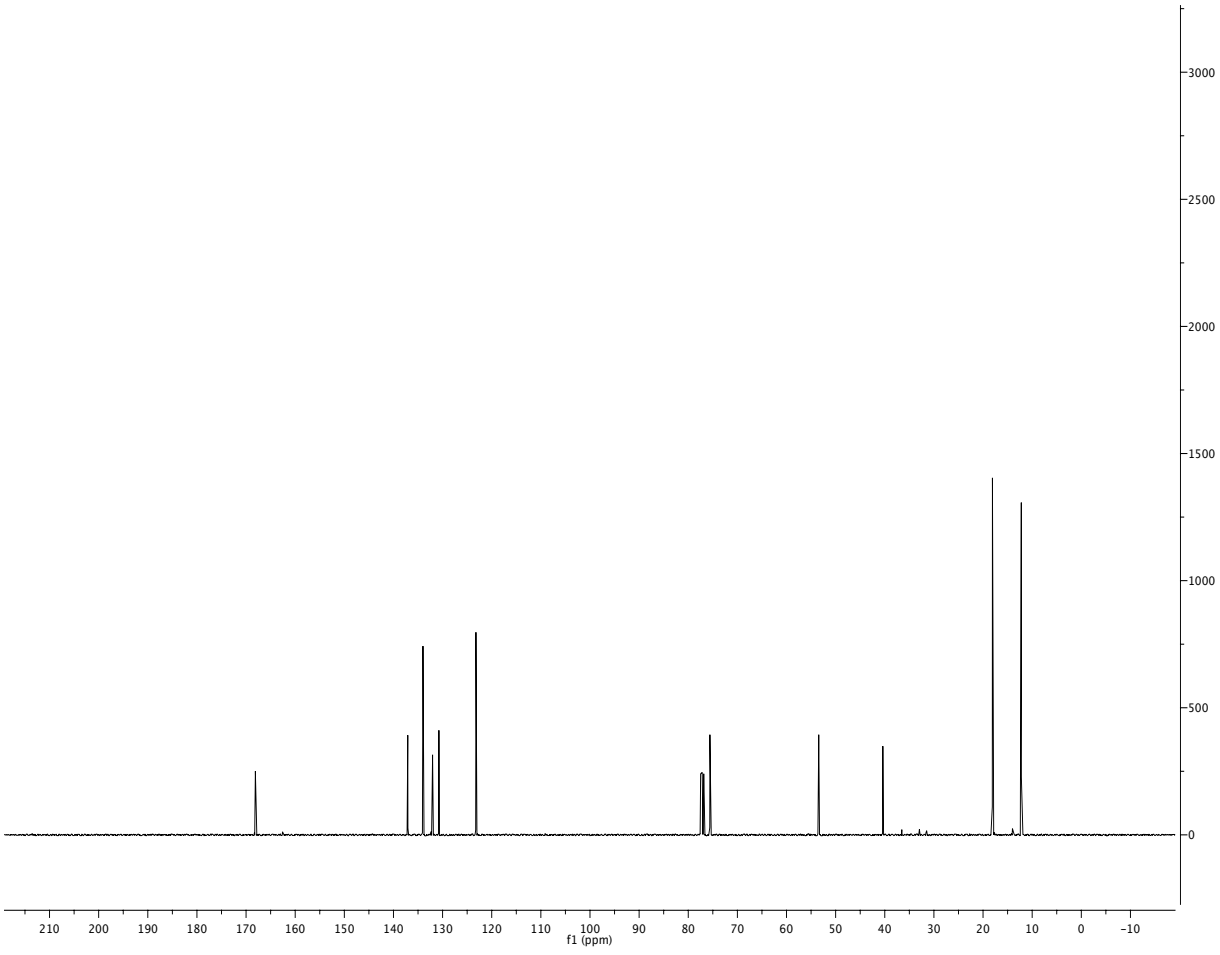
1.30.4

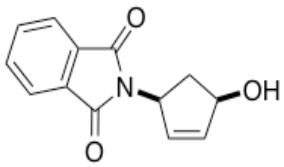



O
N
OTIPS
O

1.31.1

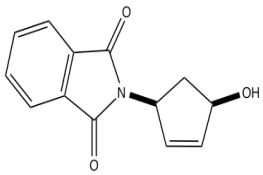
1000
900
800
700
600
500
400
300
200
100
0
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


3000
2500
2000
1500
1000
500
0
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)

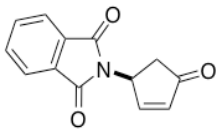

O
N
OH
O

1.31.2

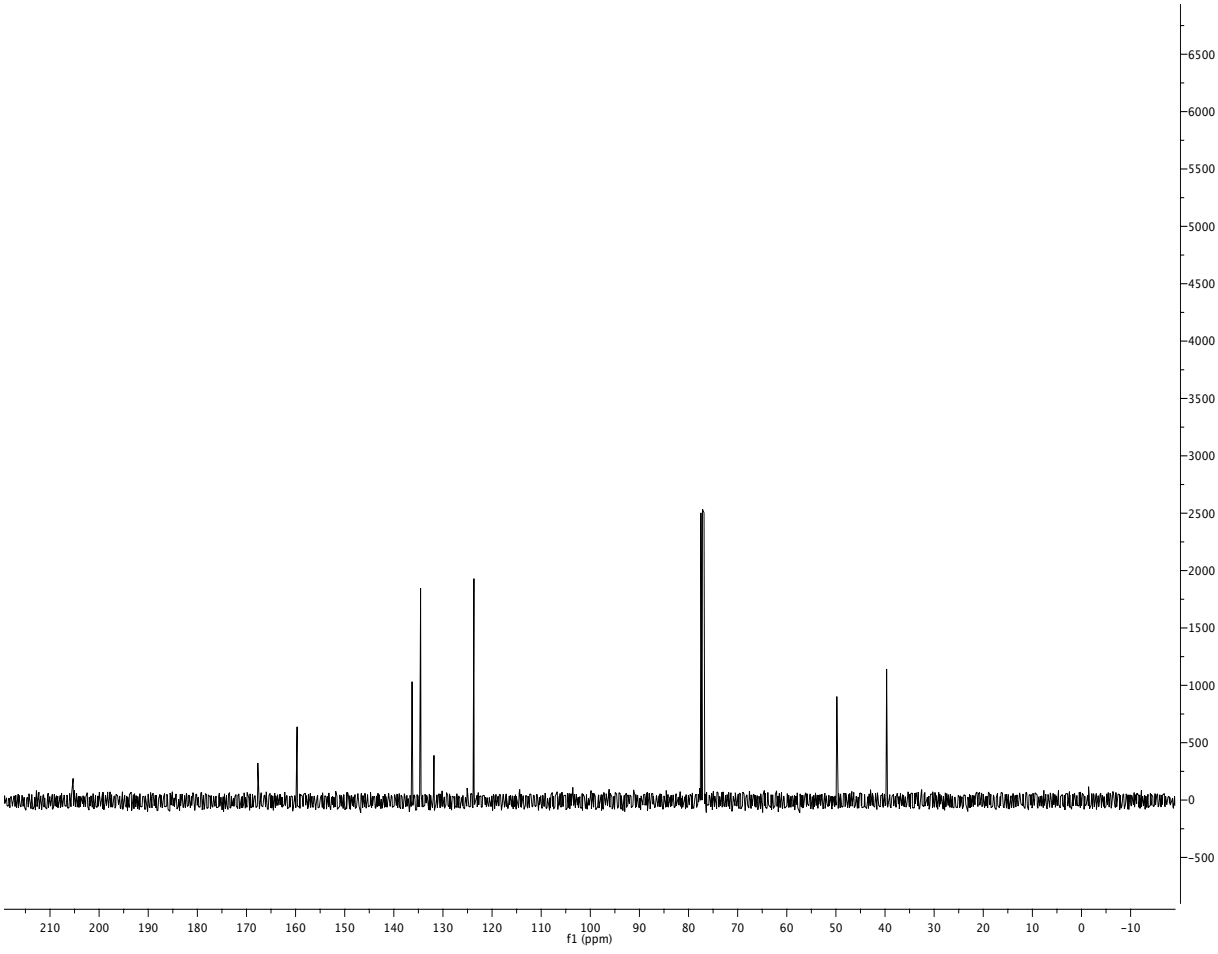
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

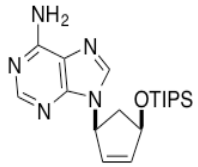

O
N
OH
O

420
400
380
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
-40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

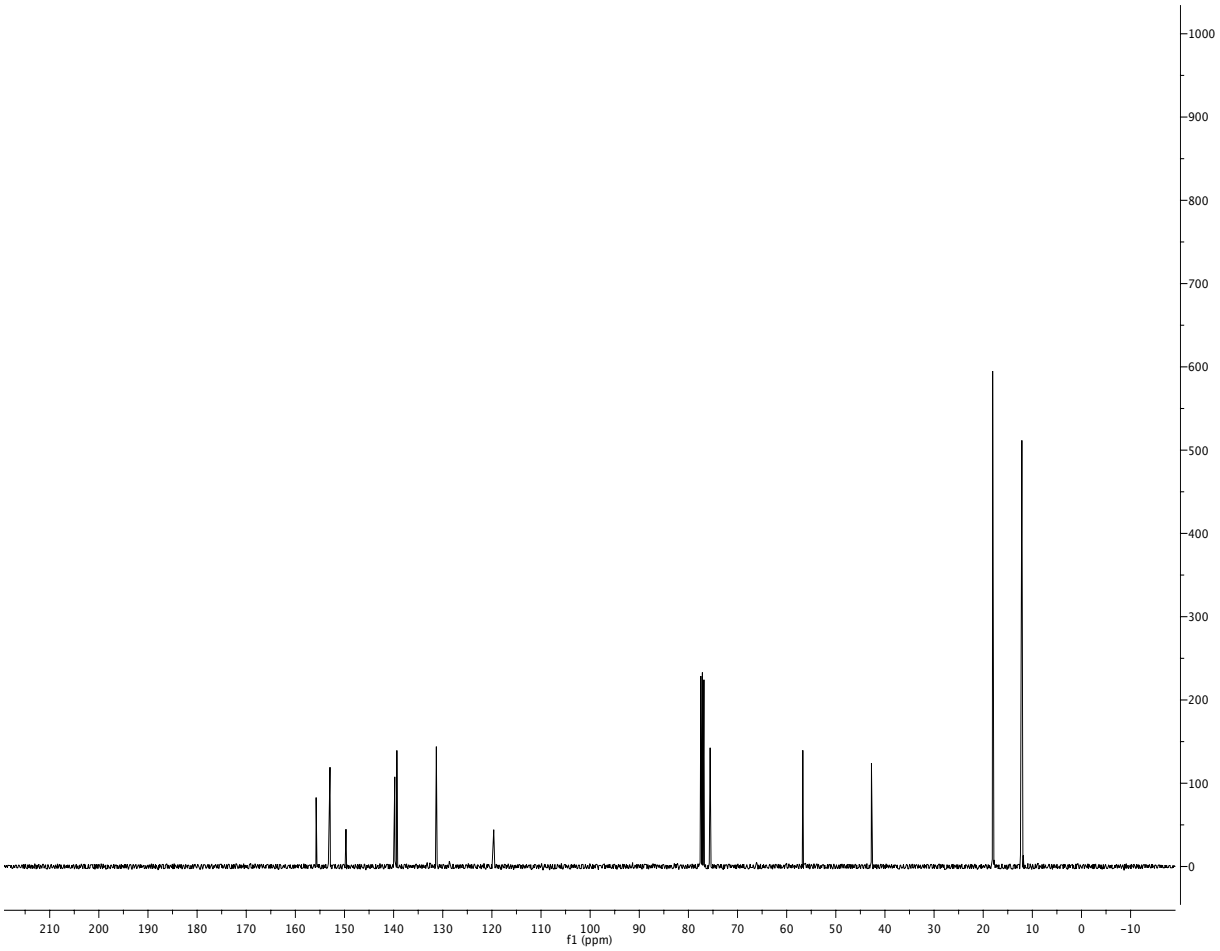


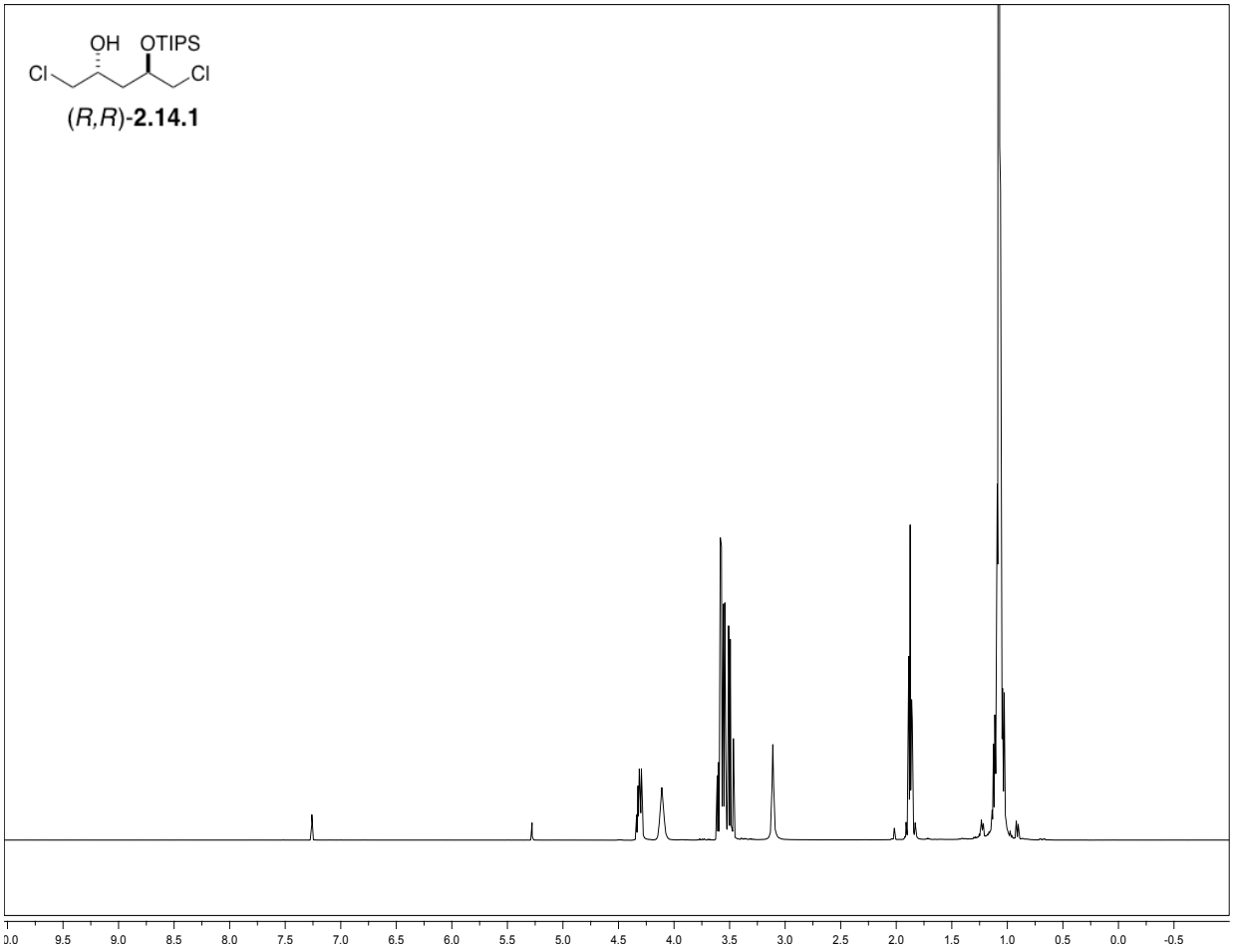
1.31.3

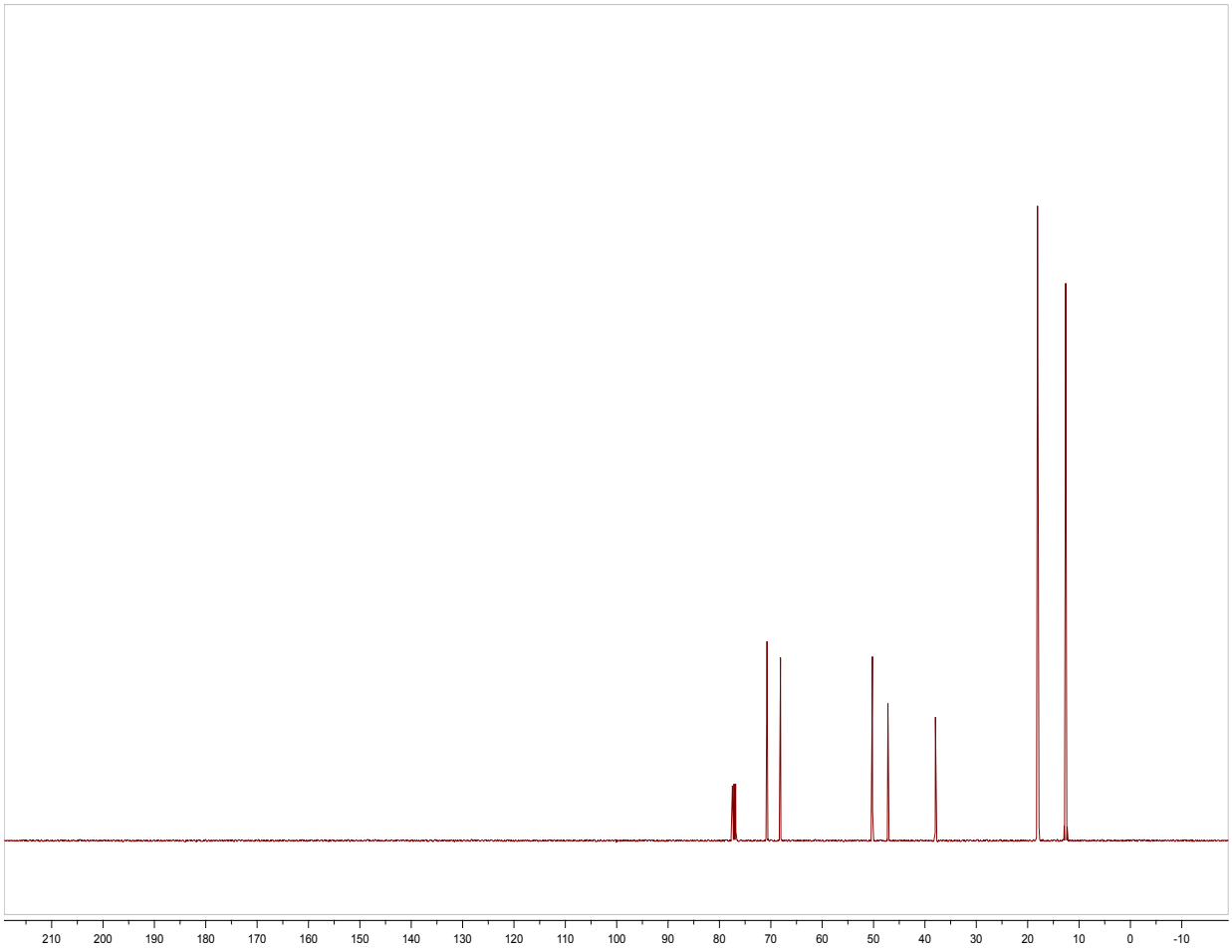


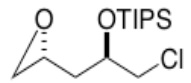


1.31.4



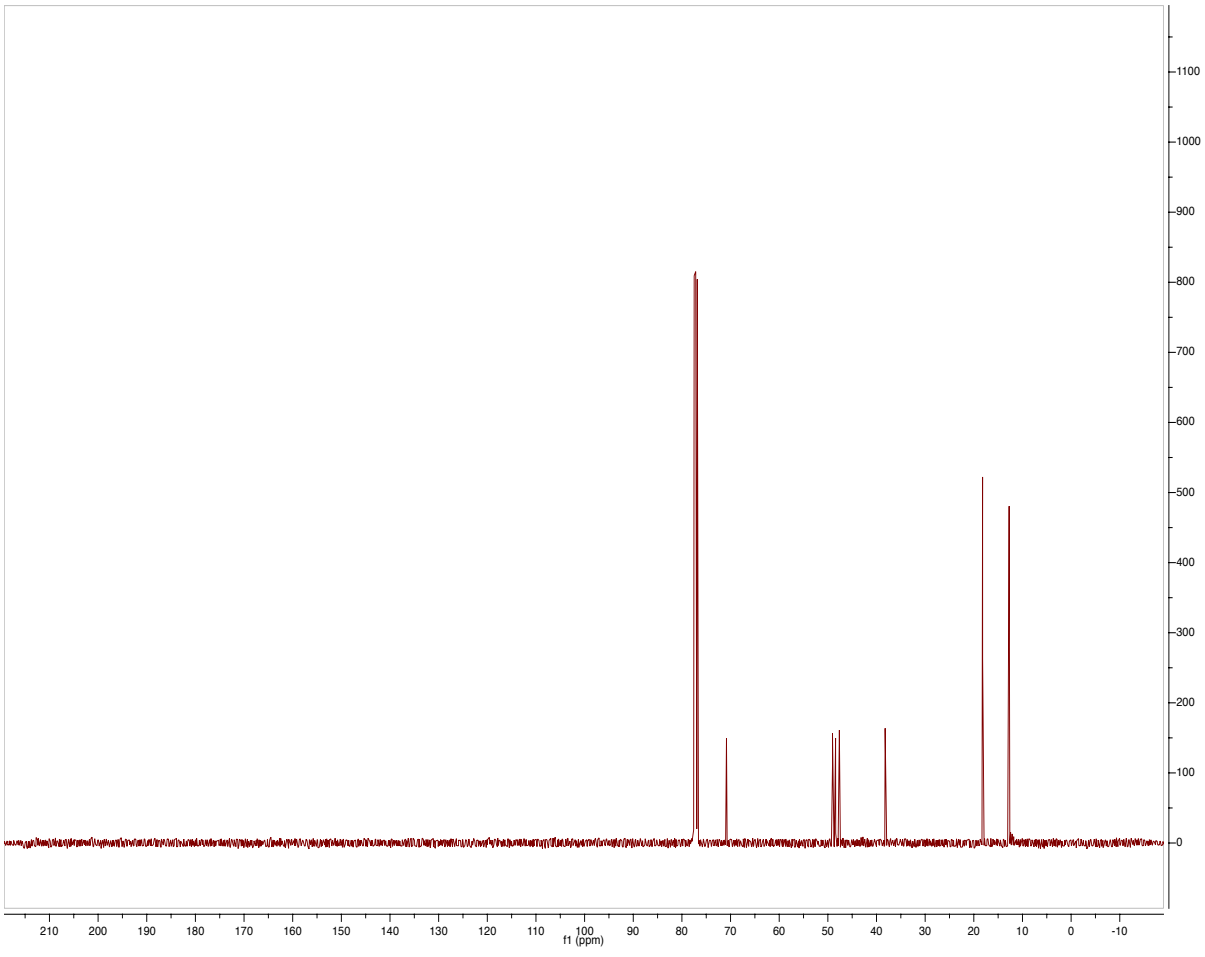

OH
OTIPS
Cl
Cl
(R,R)-2.14.1
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

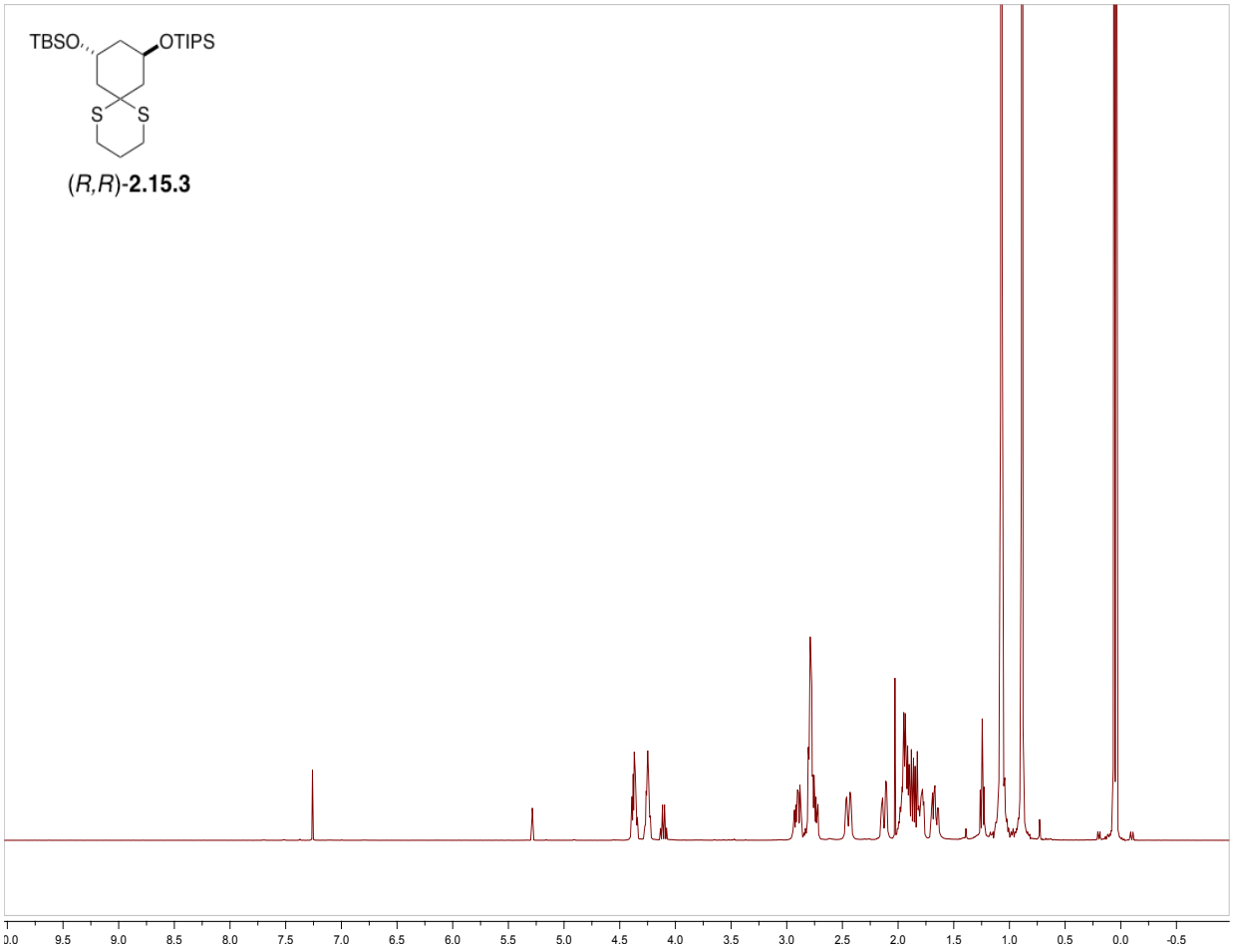

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


O
OTIPS
Cl

(*R*,*R*)-**2.14.2**

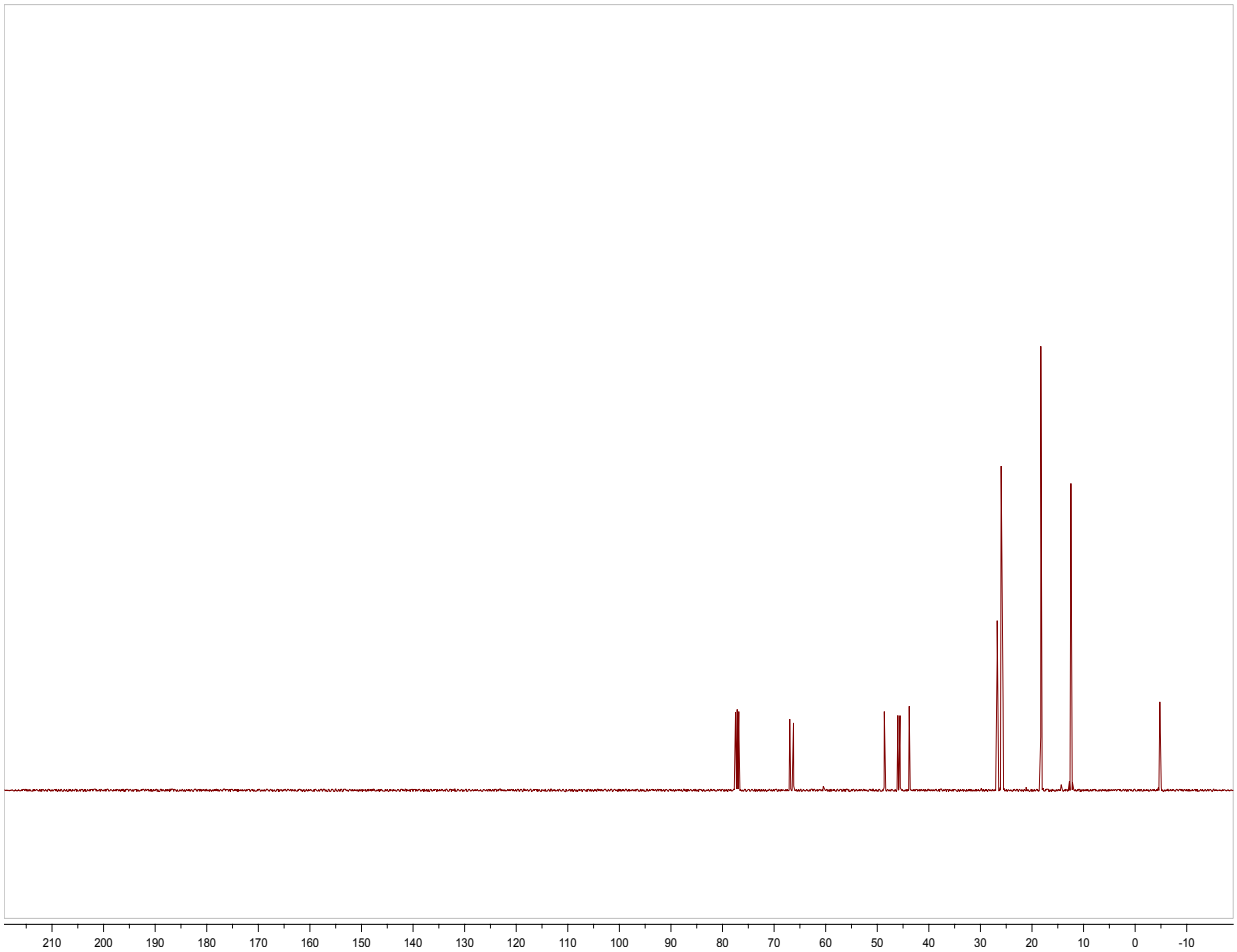
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

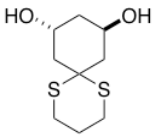

1100
1000
900
800
700
600
500
400
300
200
100
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


TBSO
OTIPS
S
S

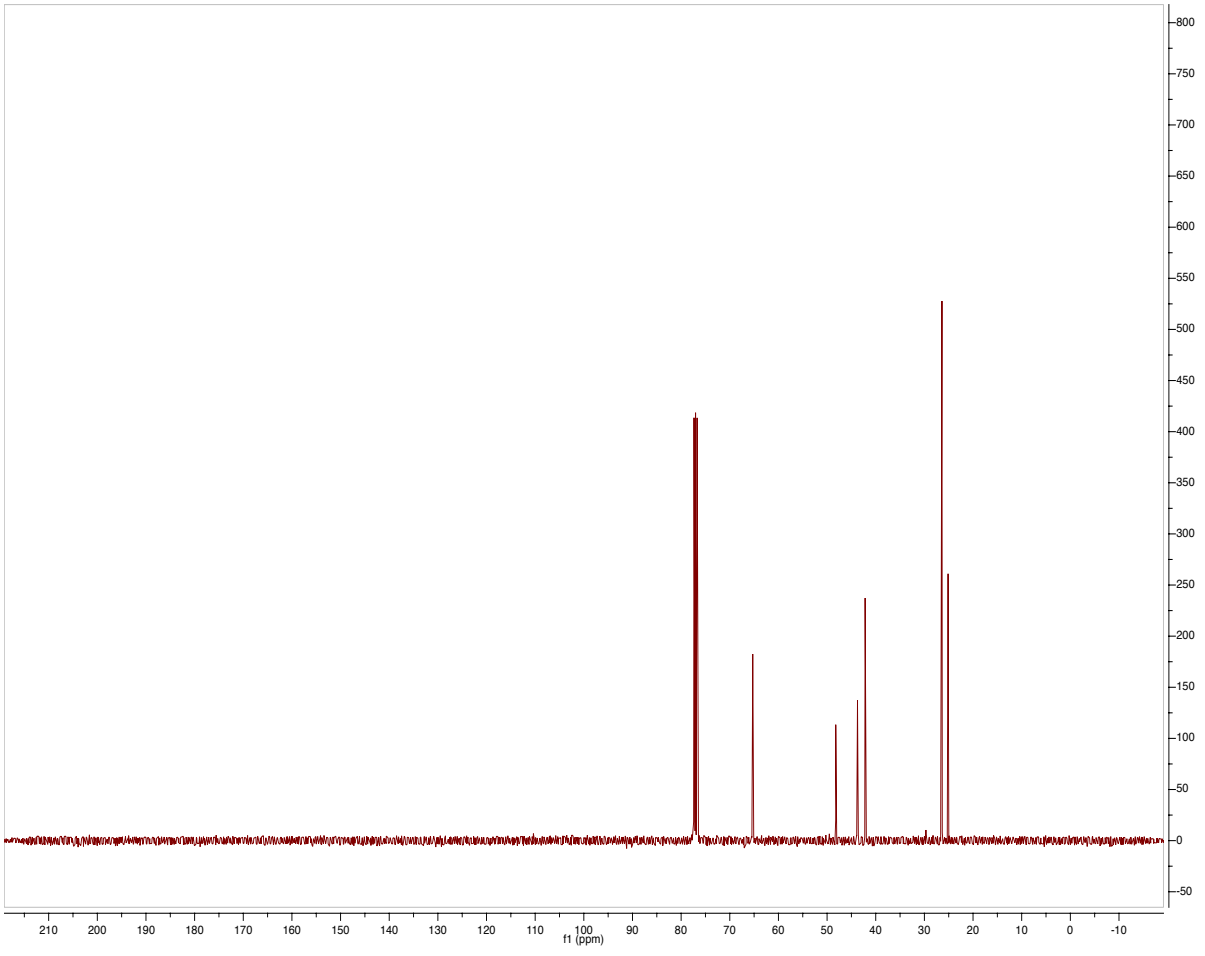
(*R*,*R*)-**2.15.3**

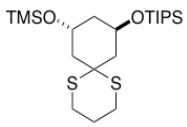
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


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



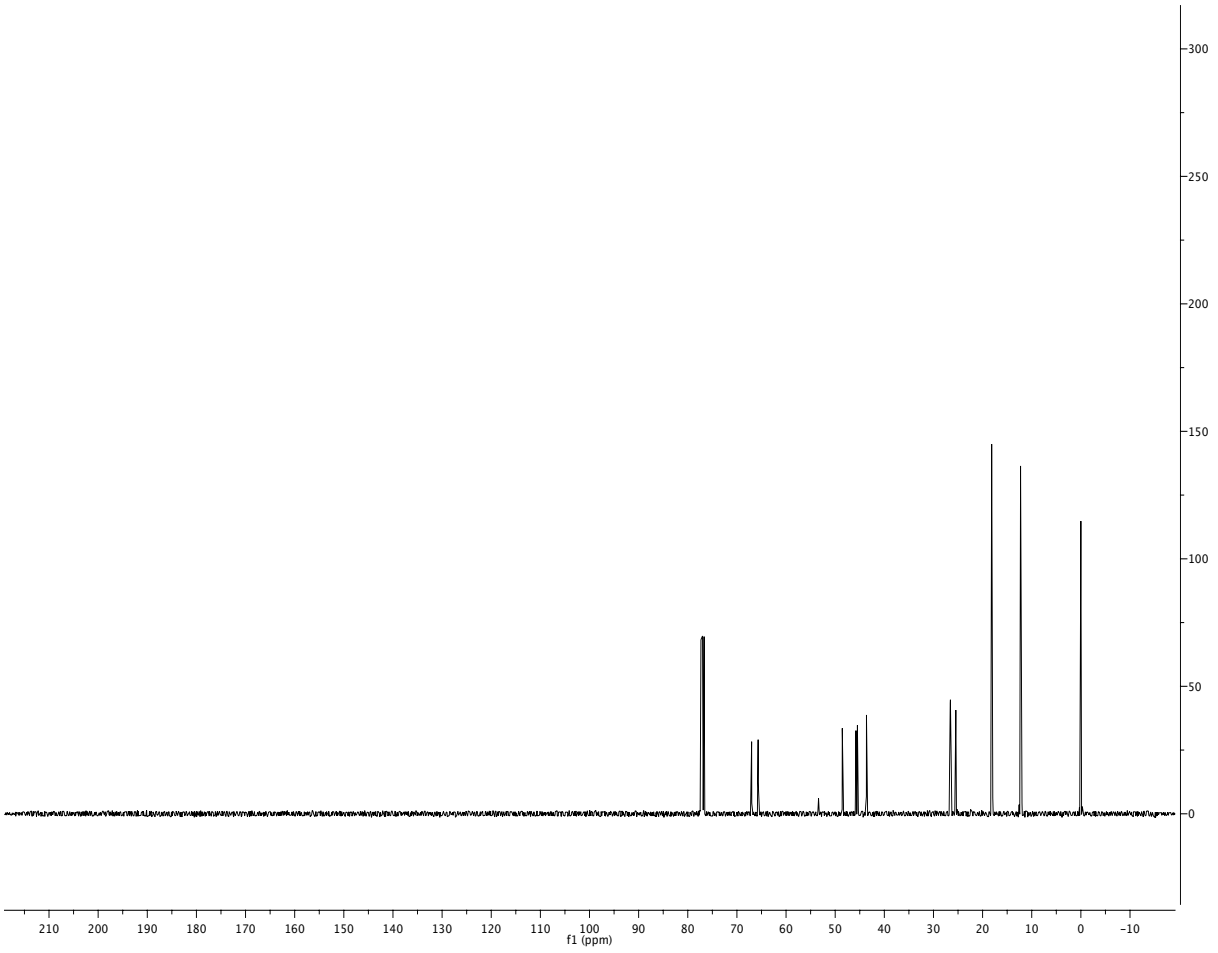
(*R*,*R*)-**2.15.4**

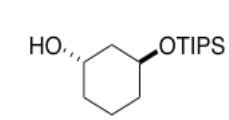



TMSO
OTIPS
S
S

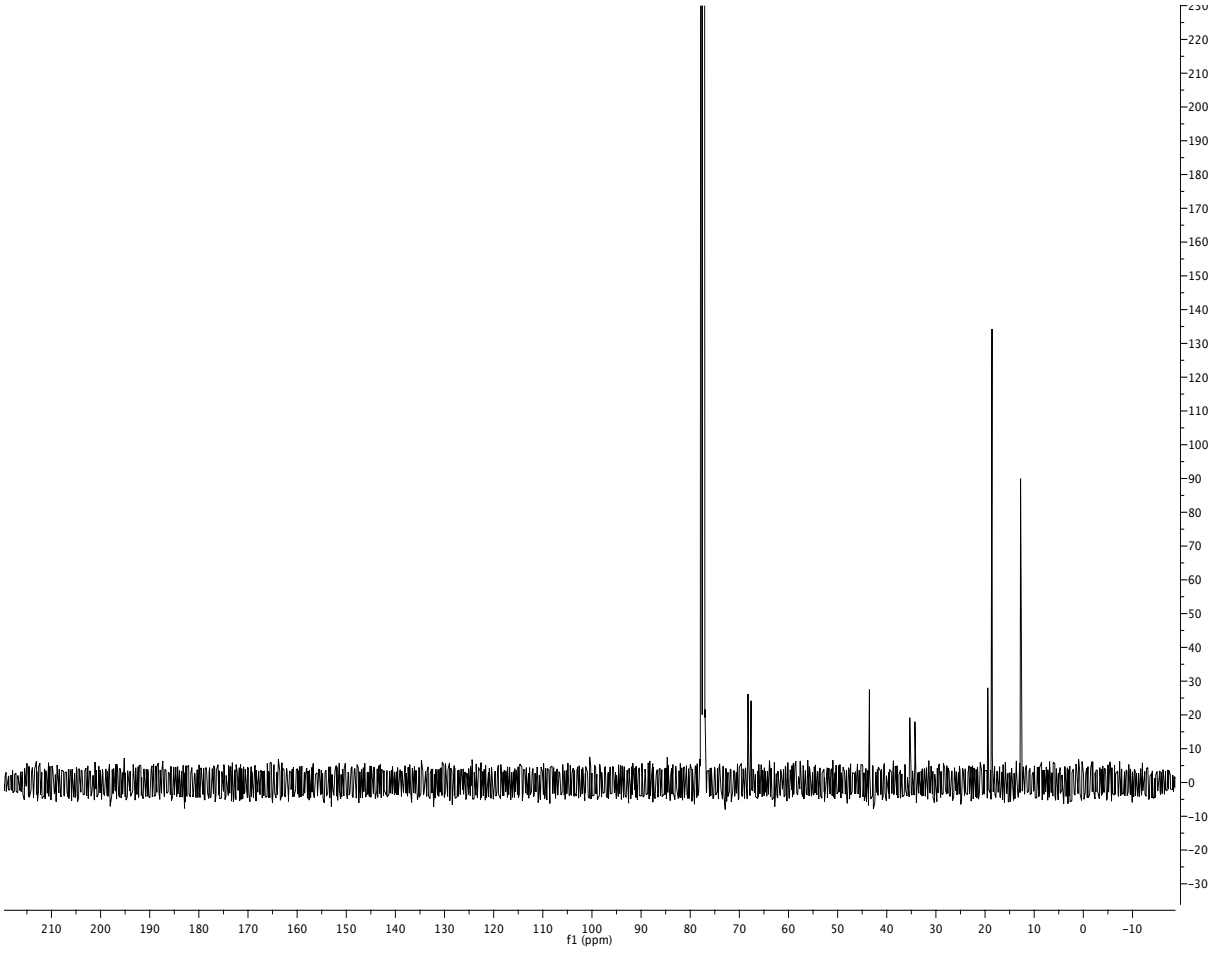
(*R*,*R*)-**2.16.1**

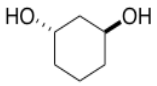
1000
900
800
700
600
500
400
300
200
100
0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


300
250
200
150
100
50
0
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)

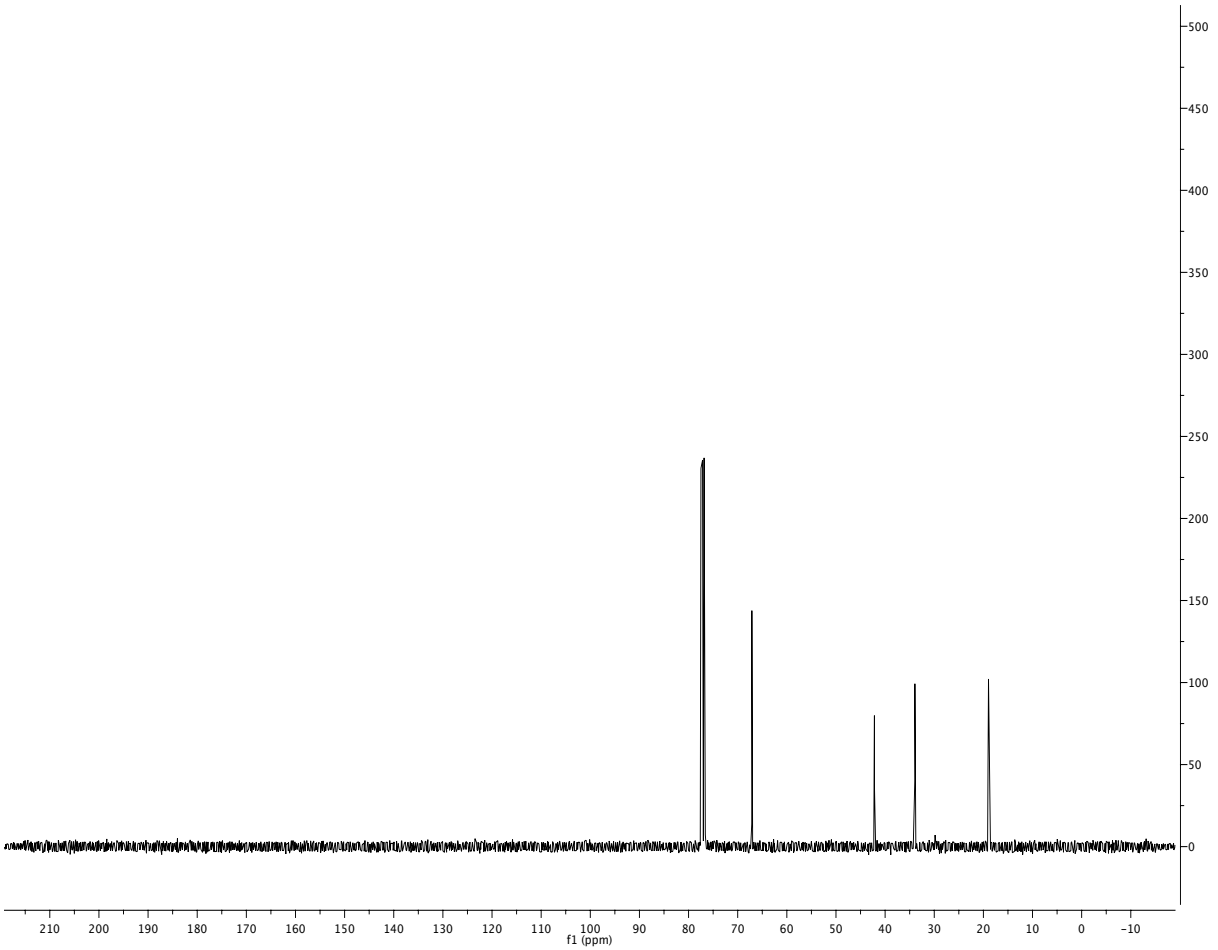


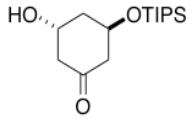
(*S*,*S*)-**2.16.2**



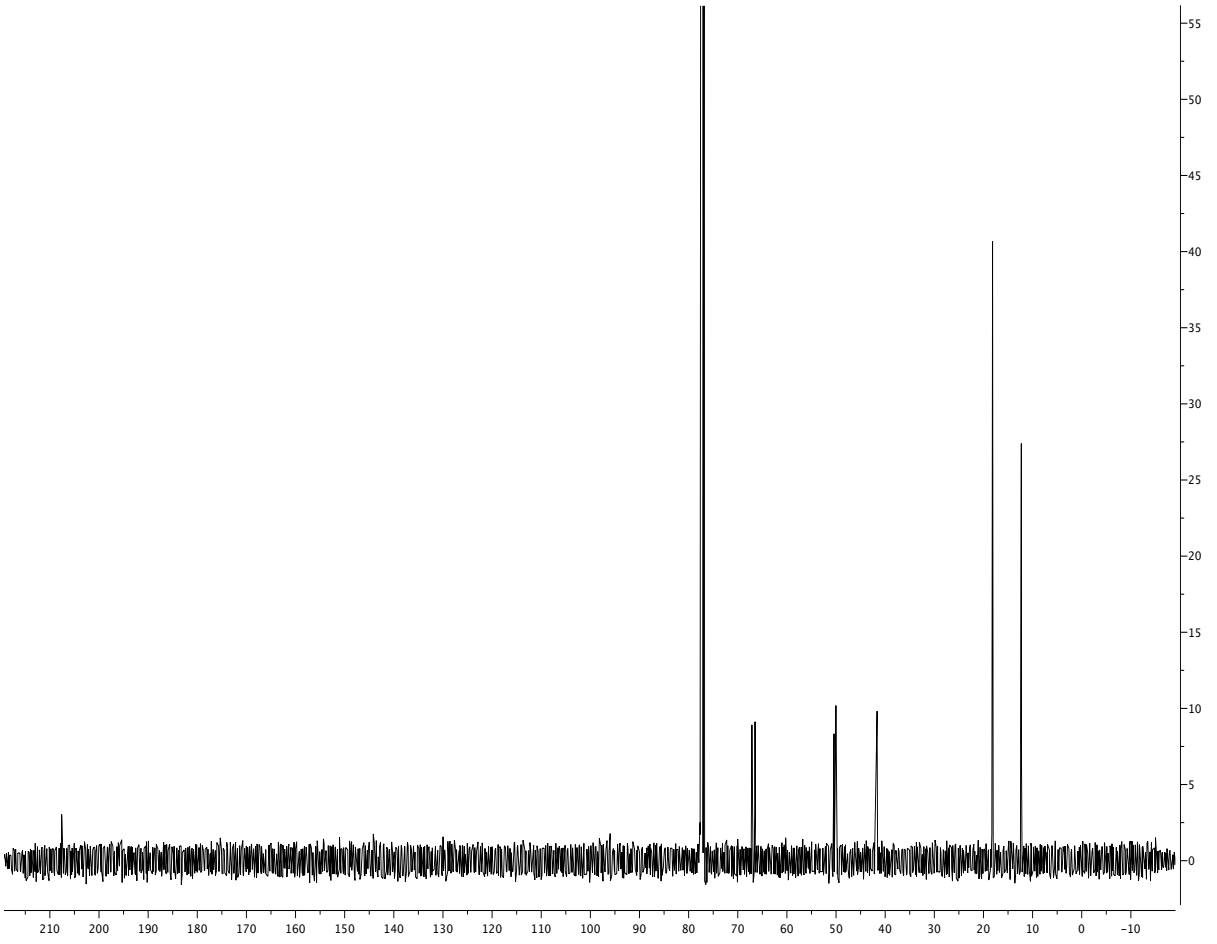


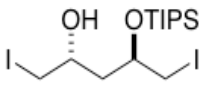
(*S*,*S*)-**2.16.3**





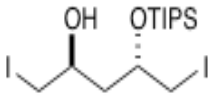
(*R*,*R*)-**2.16.4**



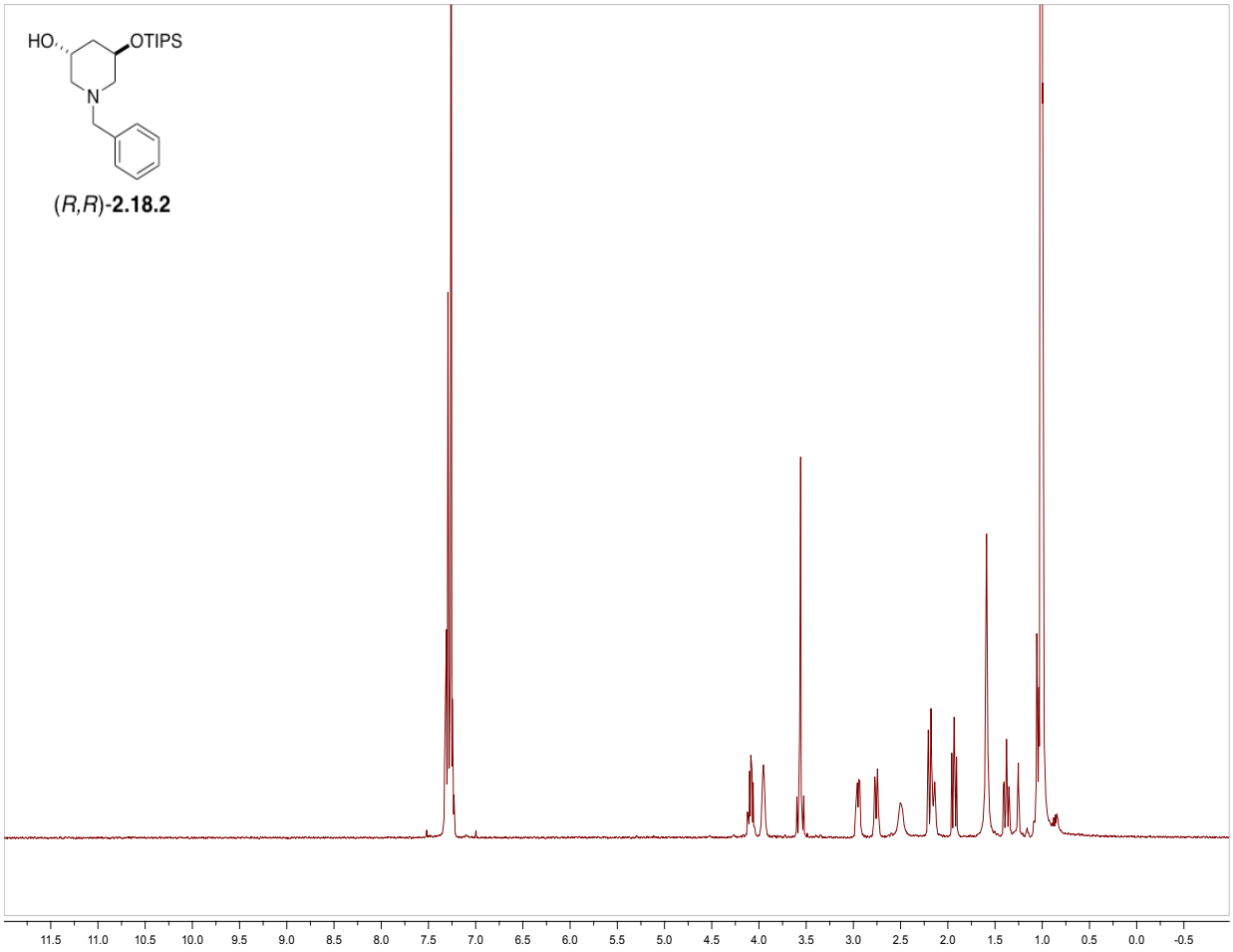

OH
OTIPS
I
I

(*R*,*R*)-**2.18.1**

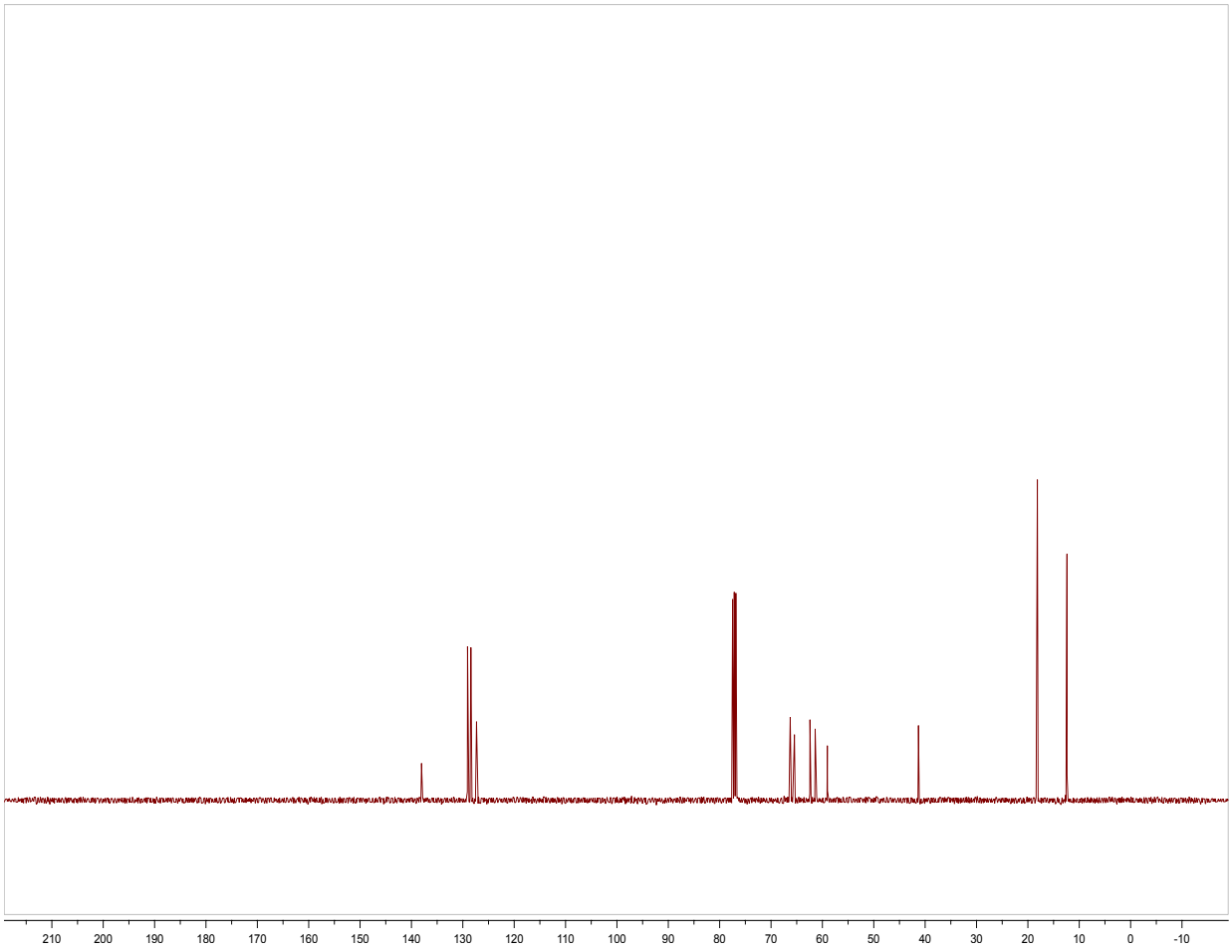
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

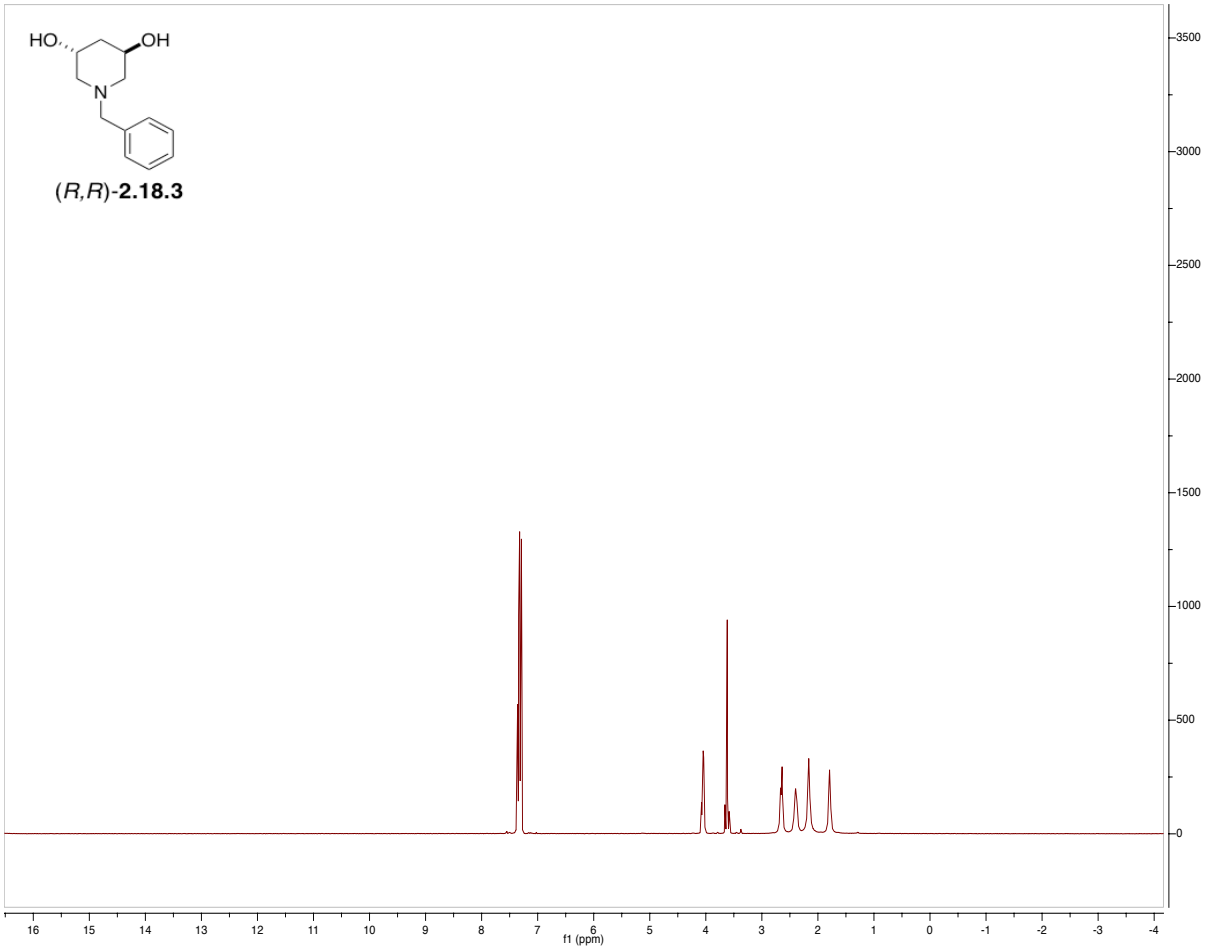

OH
OTIPS
I
I

1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
190
185
180
175
170
165
160
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
f1 (ppm)

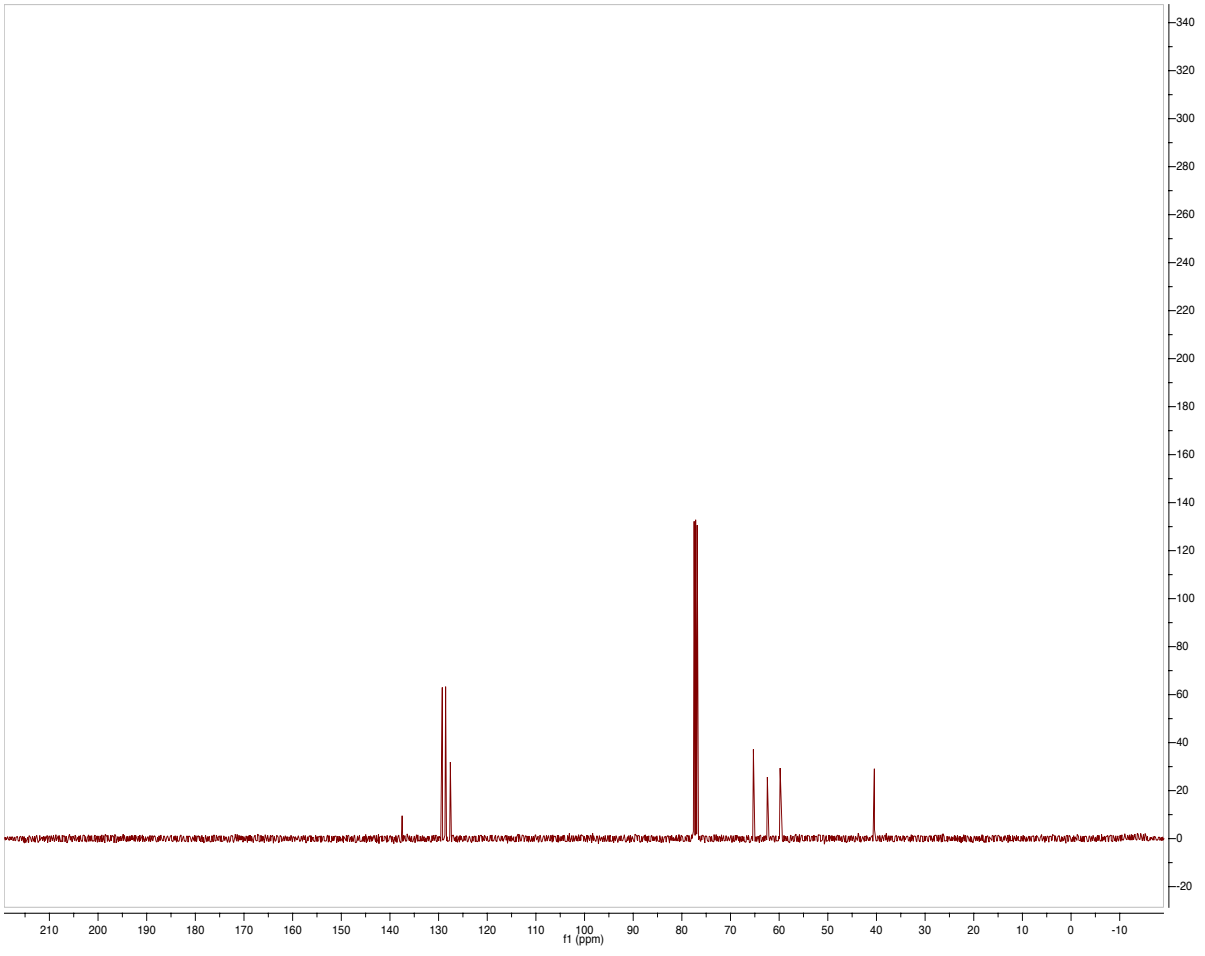

HO
OTIPS
N
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

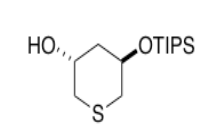
(*R*,*R*)-**2.18.2**


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


HO
OH
N
3500
3000
2500
2000
1500
1000
500
0
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4
f1 (ppm)

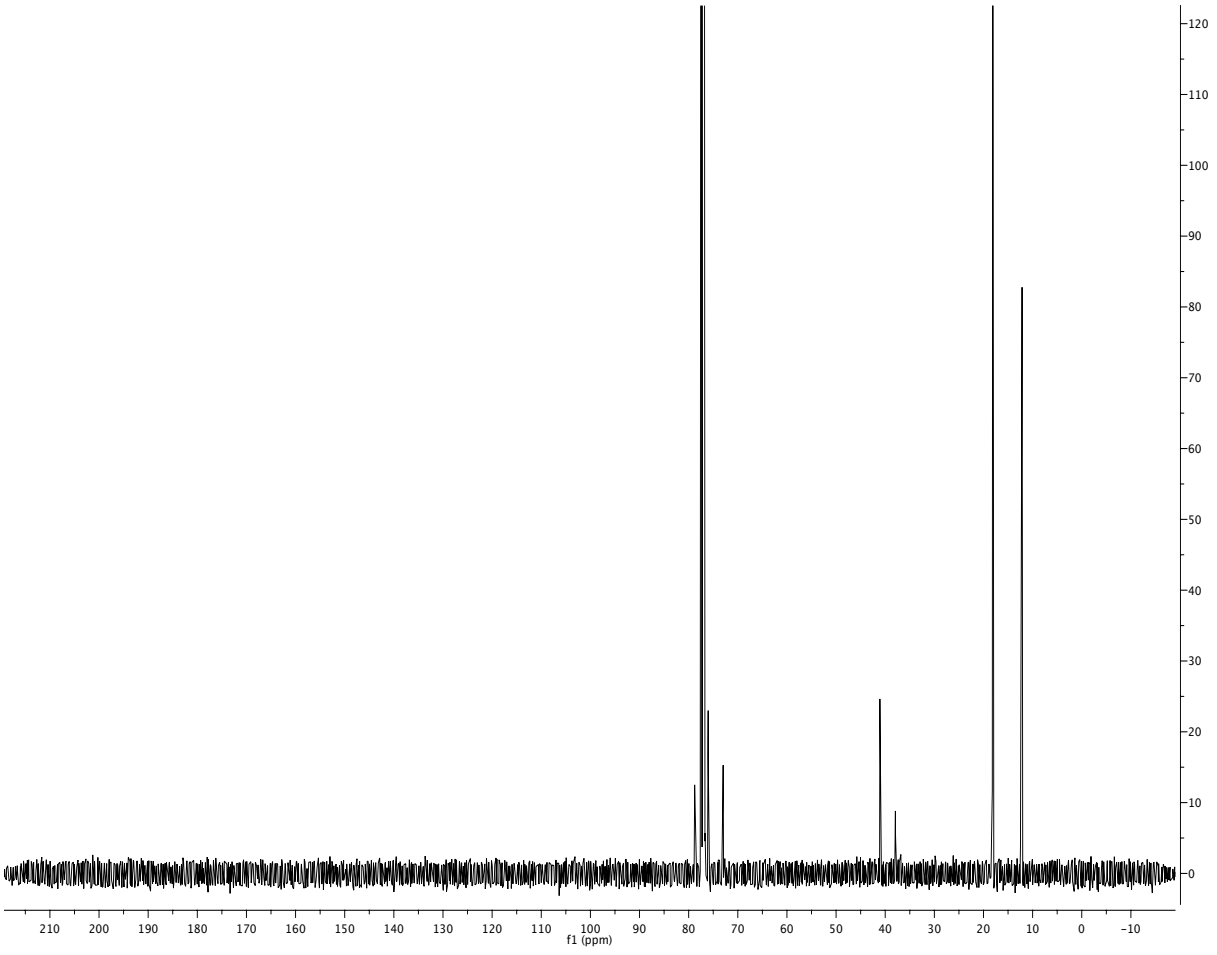
(*R*,*R*)-**2.18.3**

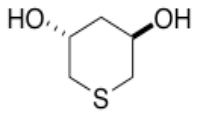

340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


HO
OTIPS
S

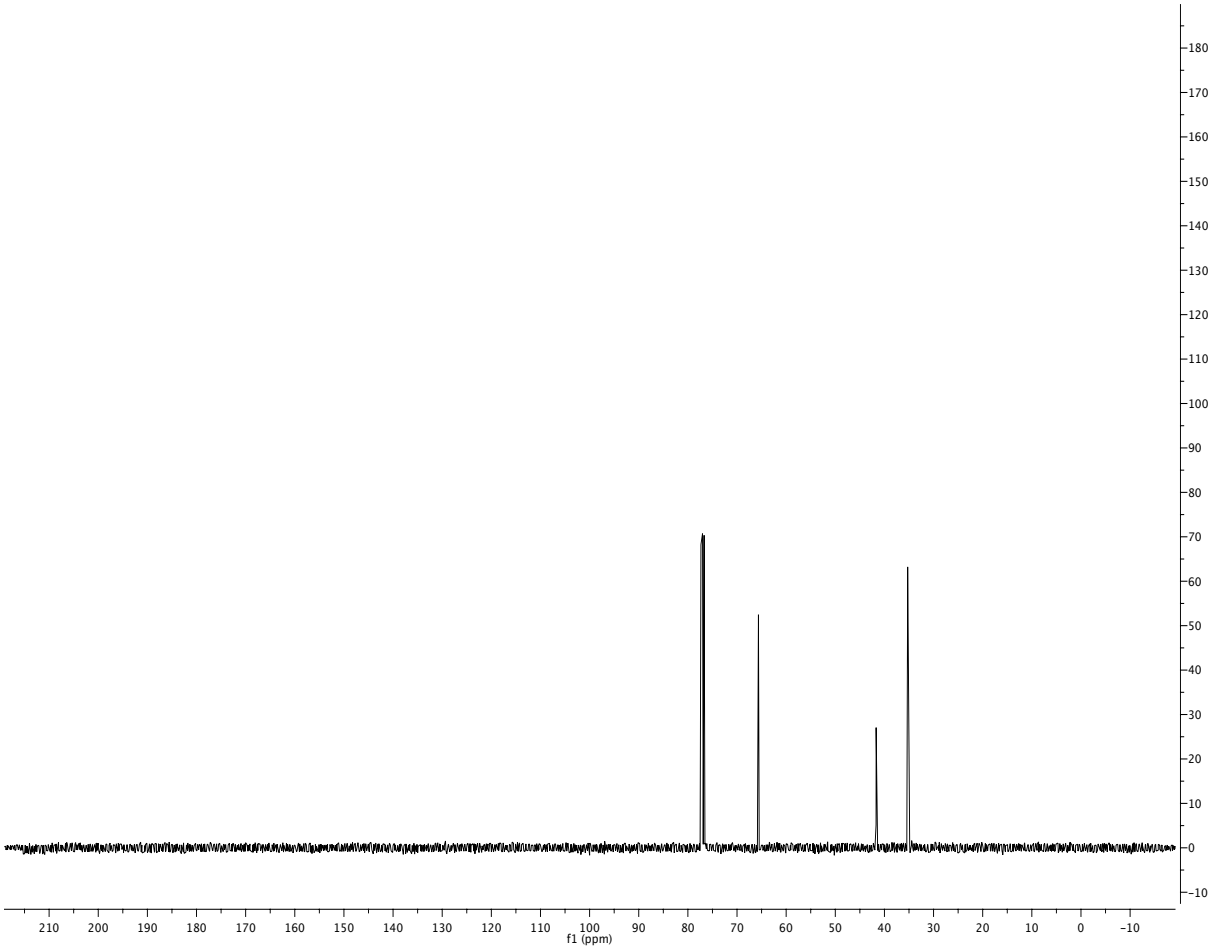
(*R*,*R*)-**2.20.1**

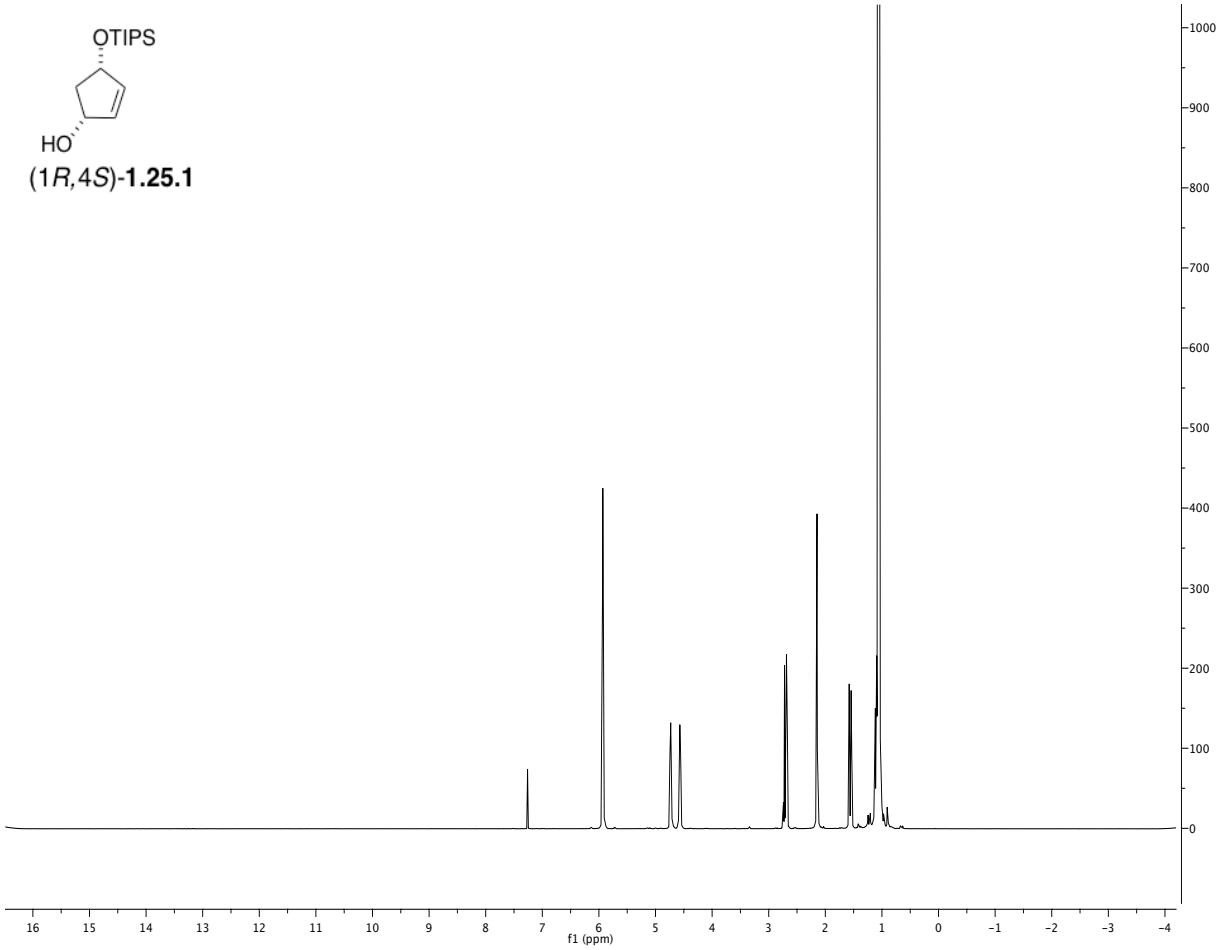
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

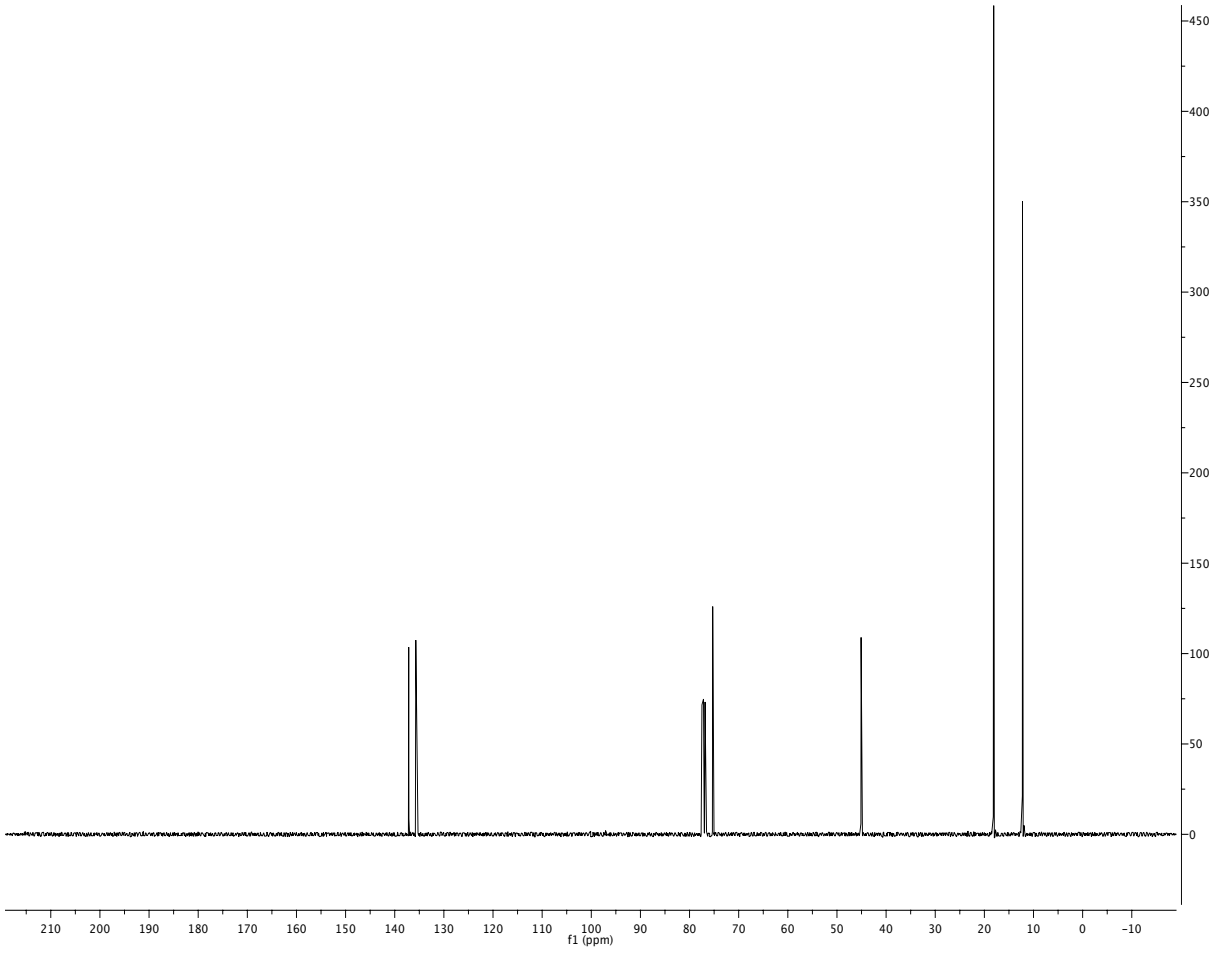

120
110
100
90
80
70
60
50
40
30
20
10
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

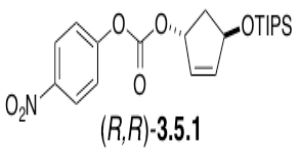


(*R*,*R*)-**2.20.2**

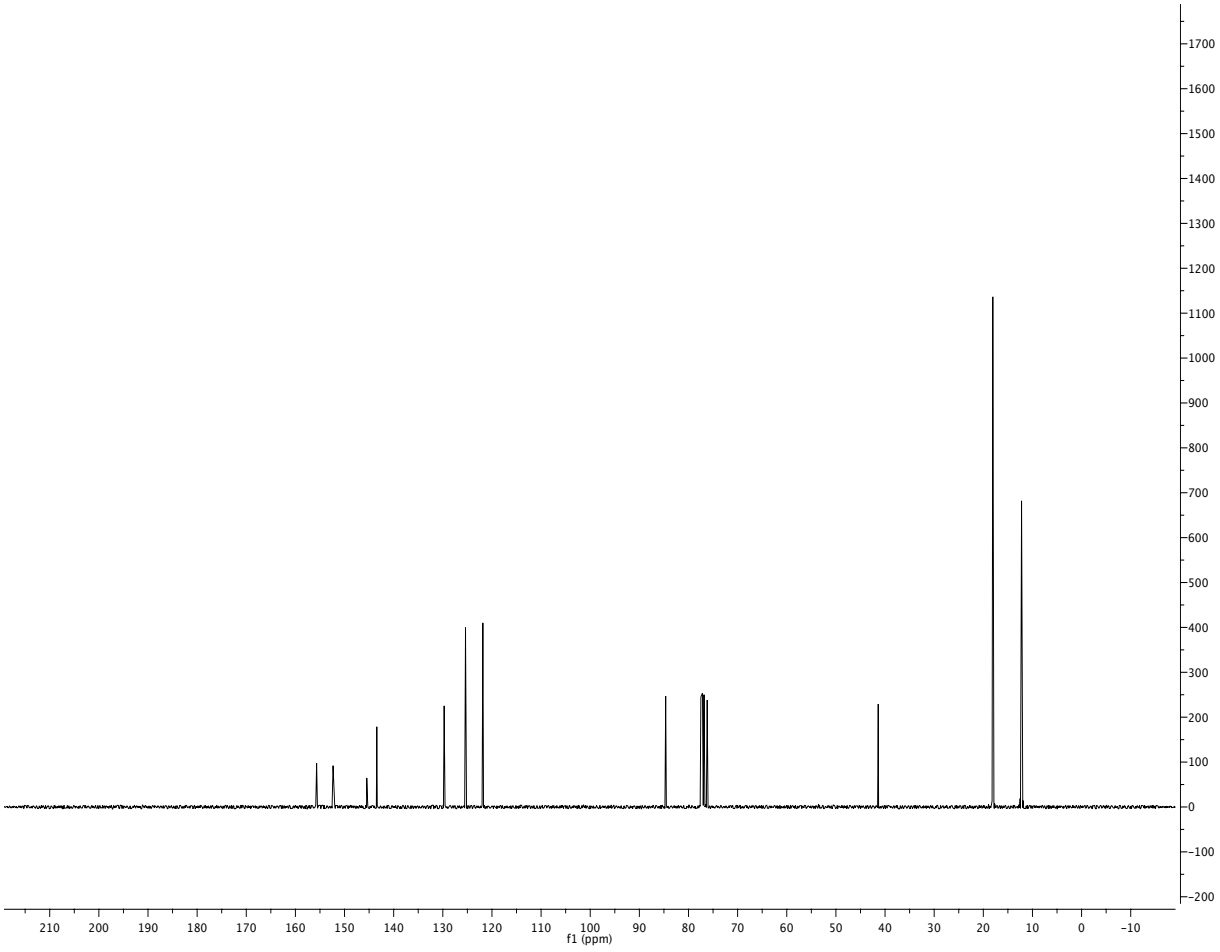


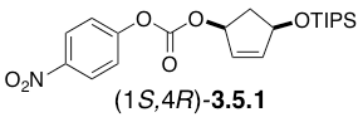

OTIPS
HO
(1R,4S)-1.25.1
f1 (ppm)


f1 (ppm)



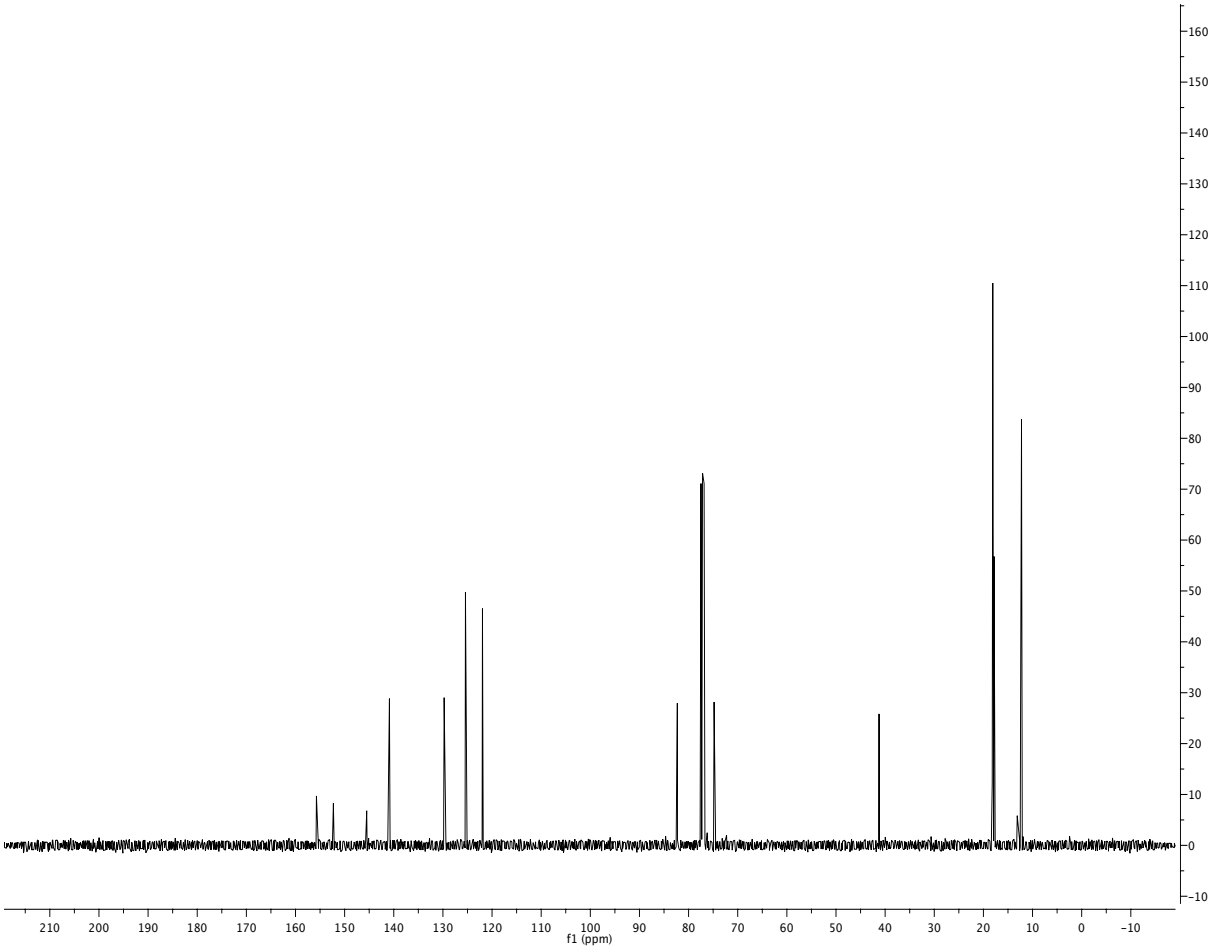
(*R*,*R*)-**3.5.1**

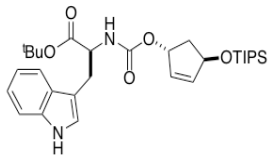



O
O
O
OTIPS
O2N

(1*S*,4*R*)-**3.5.1**

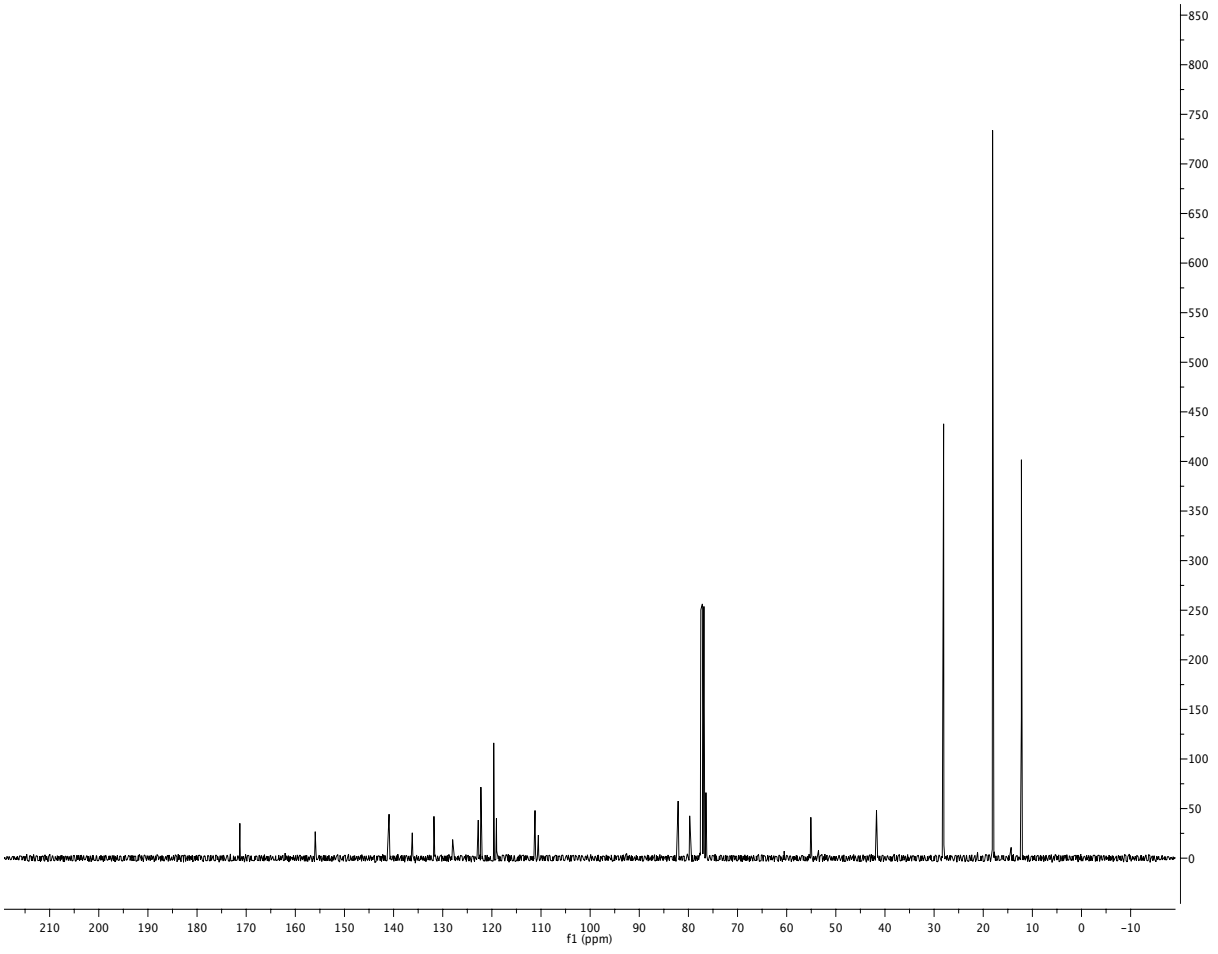
2500
2000
1500
1000
500
0
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 −3 −4
f1 (ppm)

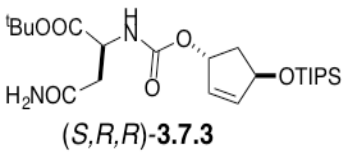

160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)


O
H
N
O
O
tBuO
OTIPS
N
H

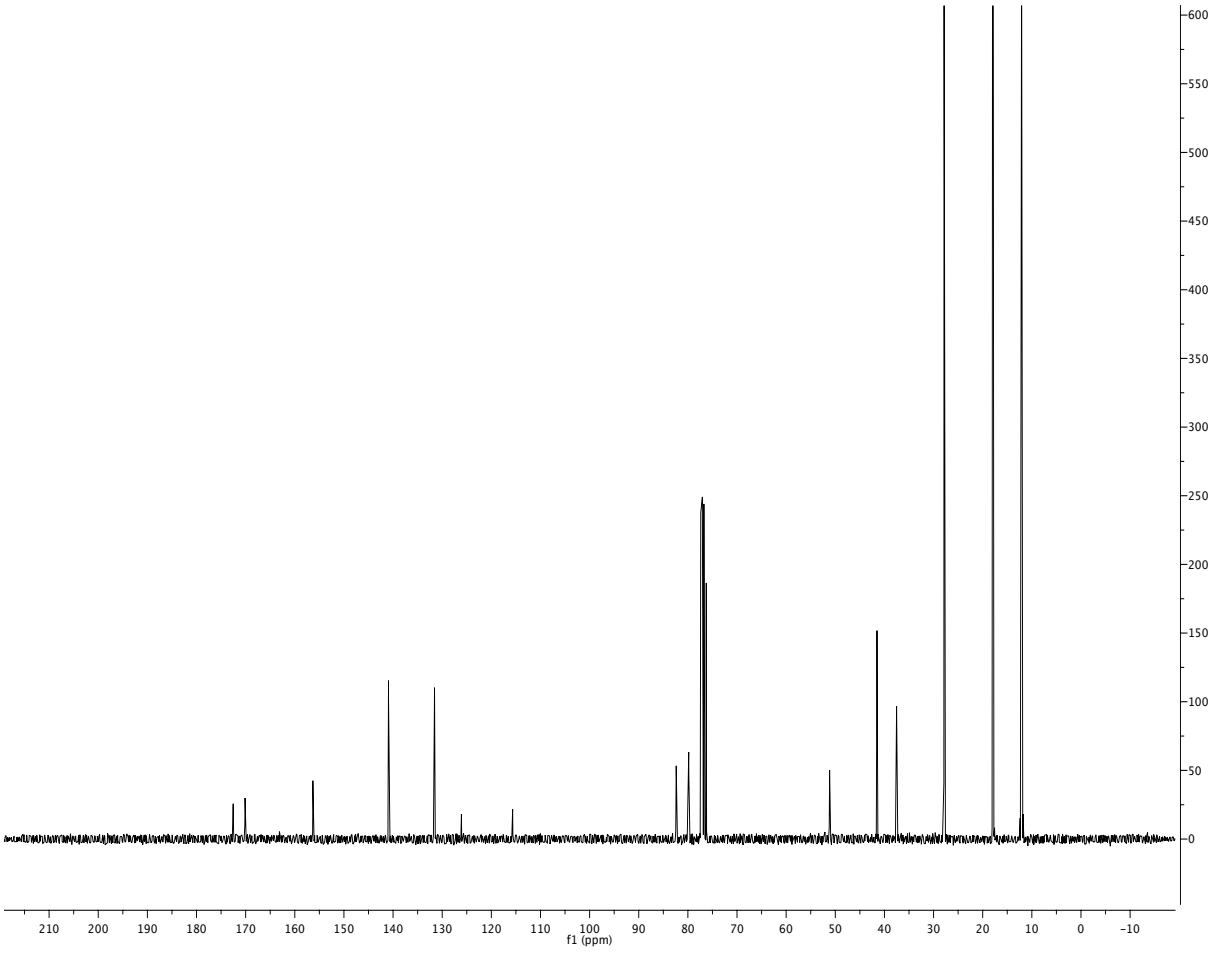
(*S*,*R*,*R*)-**3.7.1**

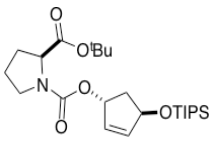
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 −3 −4
f1 (ppm)


850
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
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)

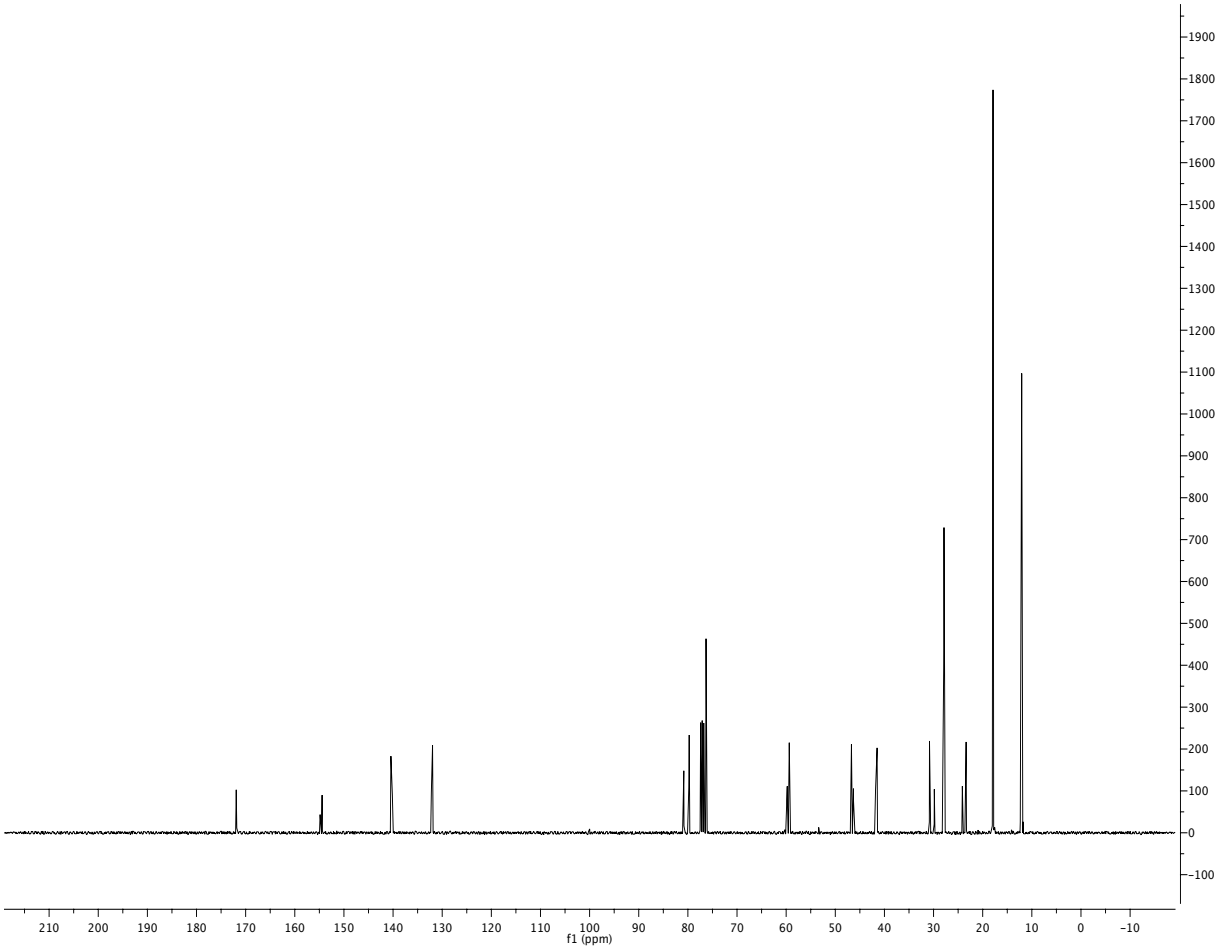


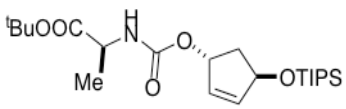
(*S*,*R*,*R*)-**3.7.3**



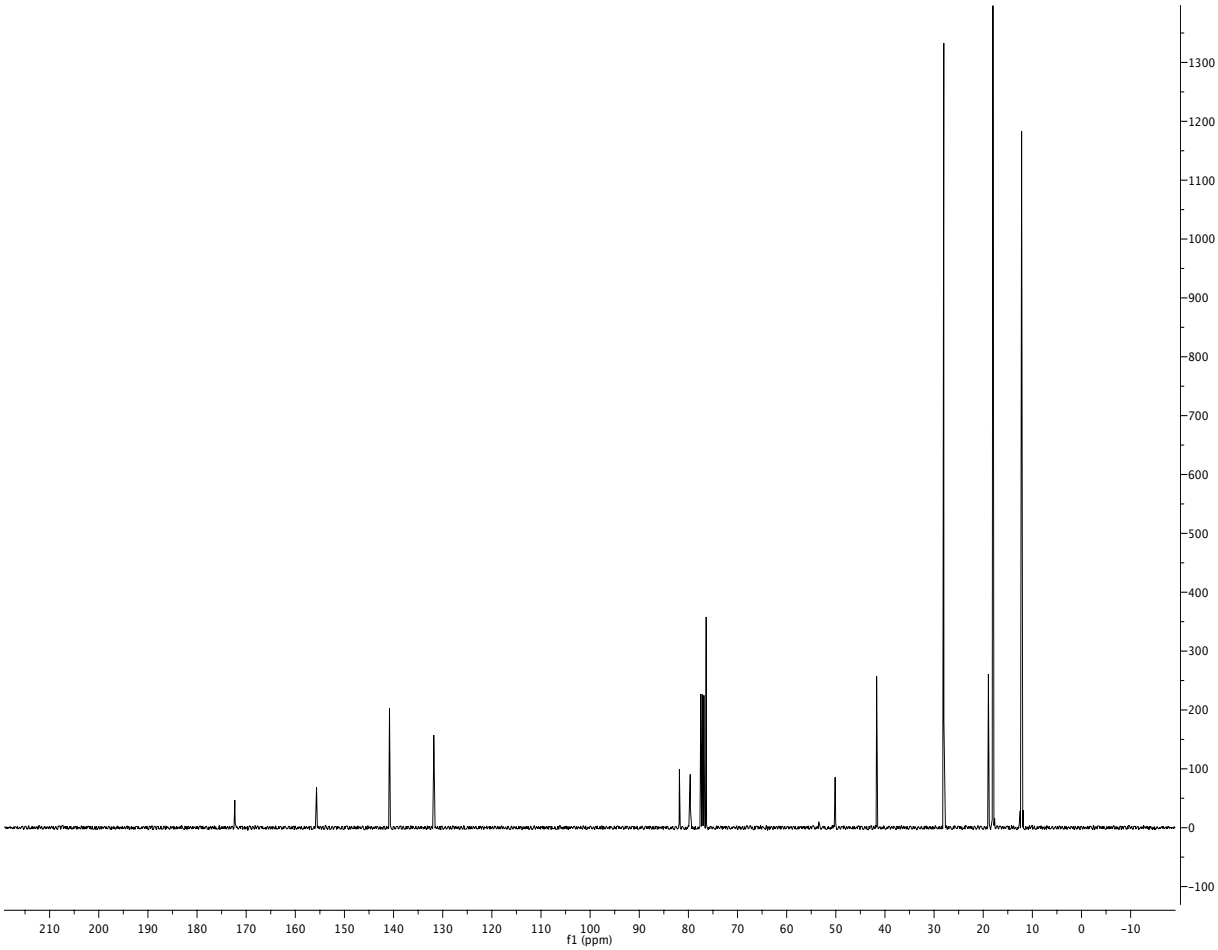


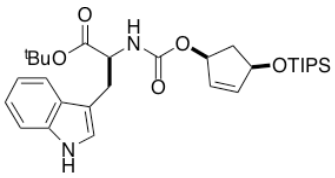
(*S,R,R*)-**3.7.2**



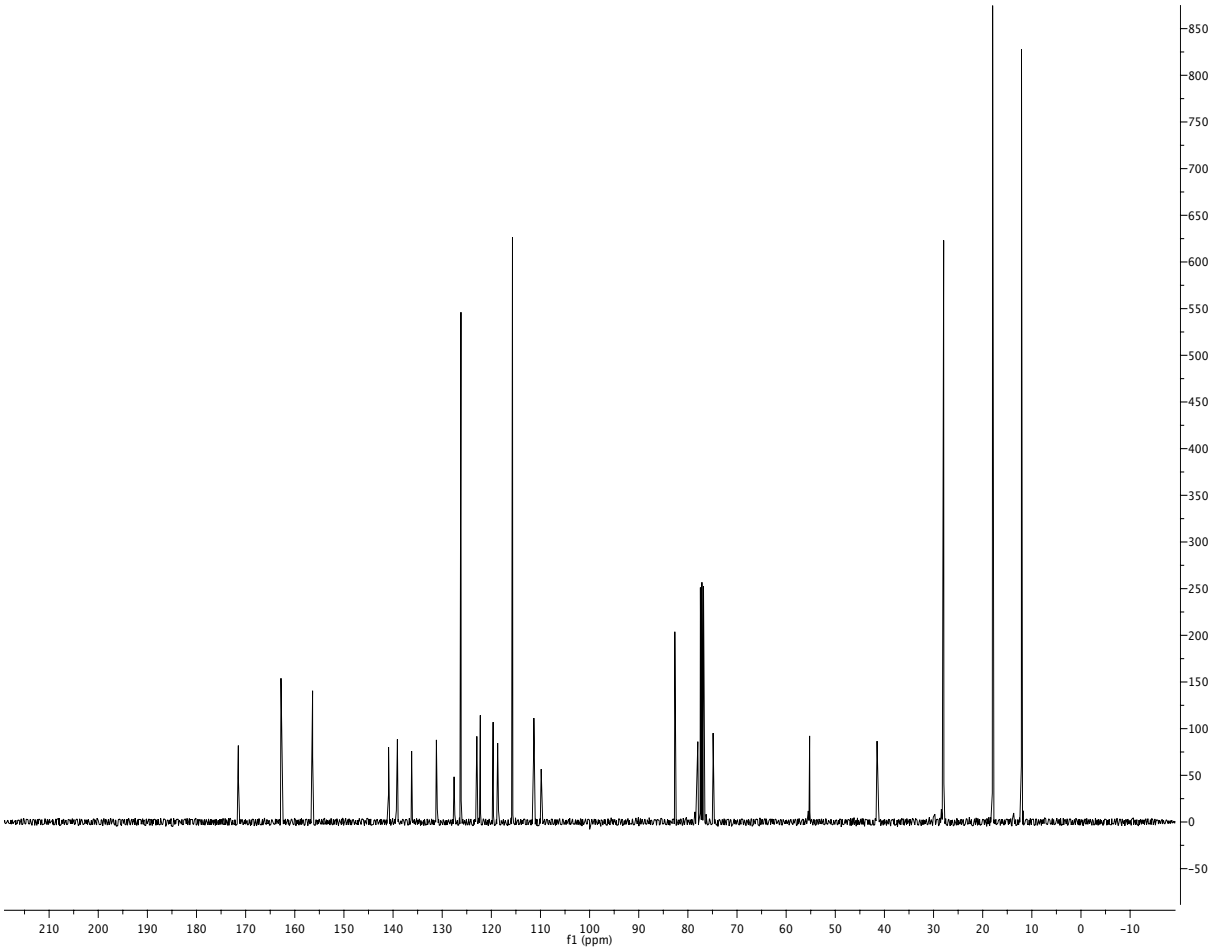


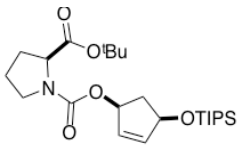
(*S*,*R*,*R*)-**3.7.4**



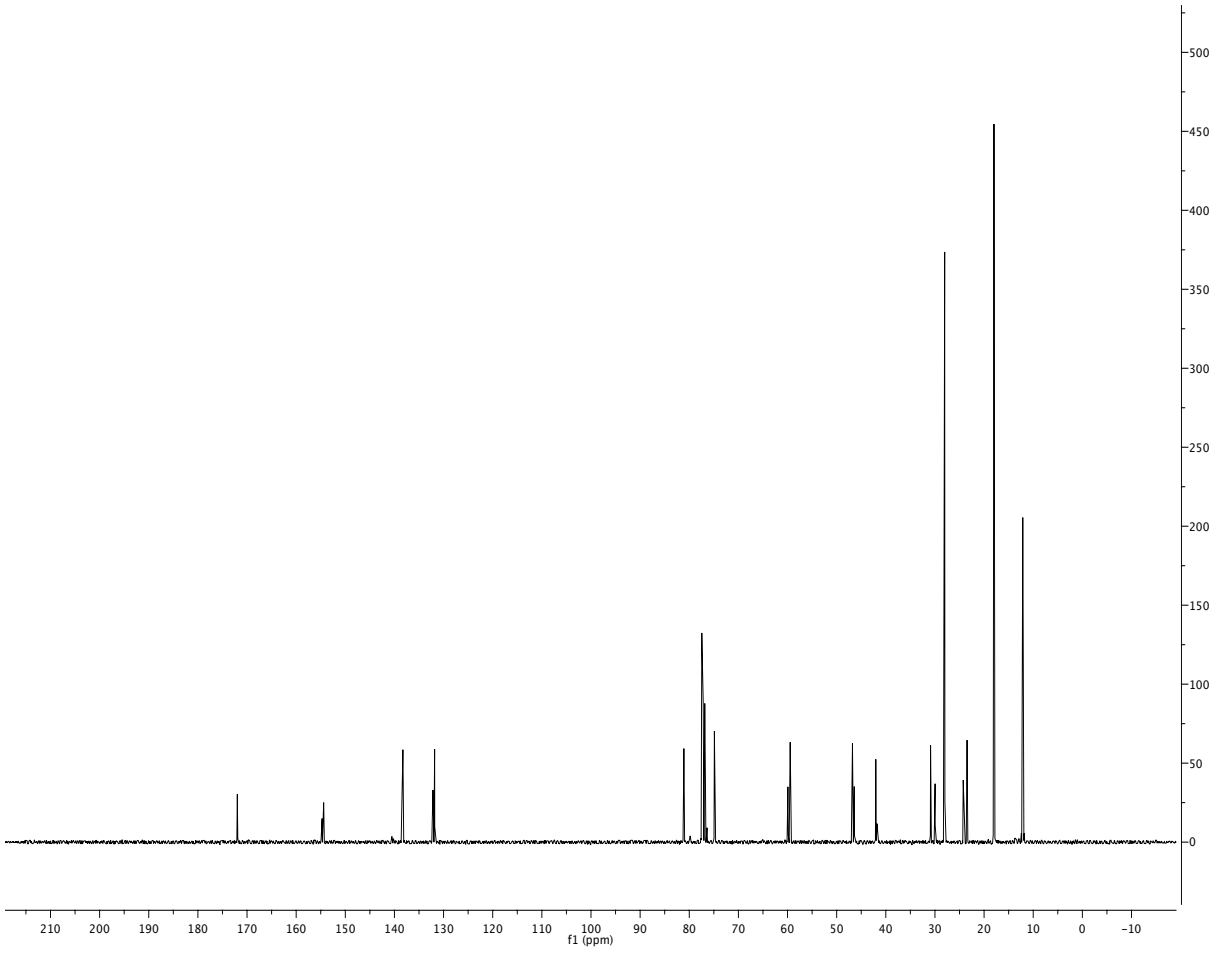


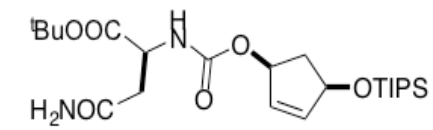
(*S,S,R*)-**3.7.1**



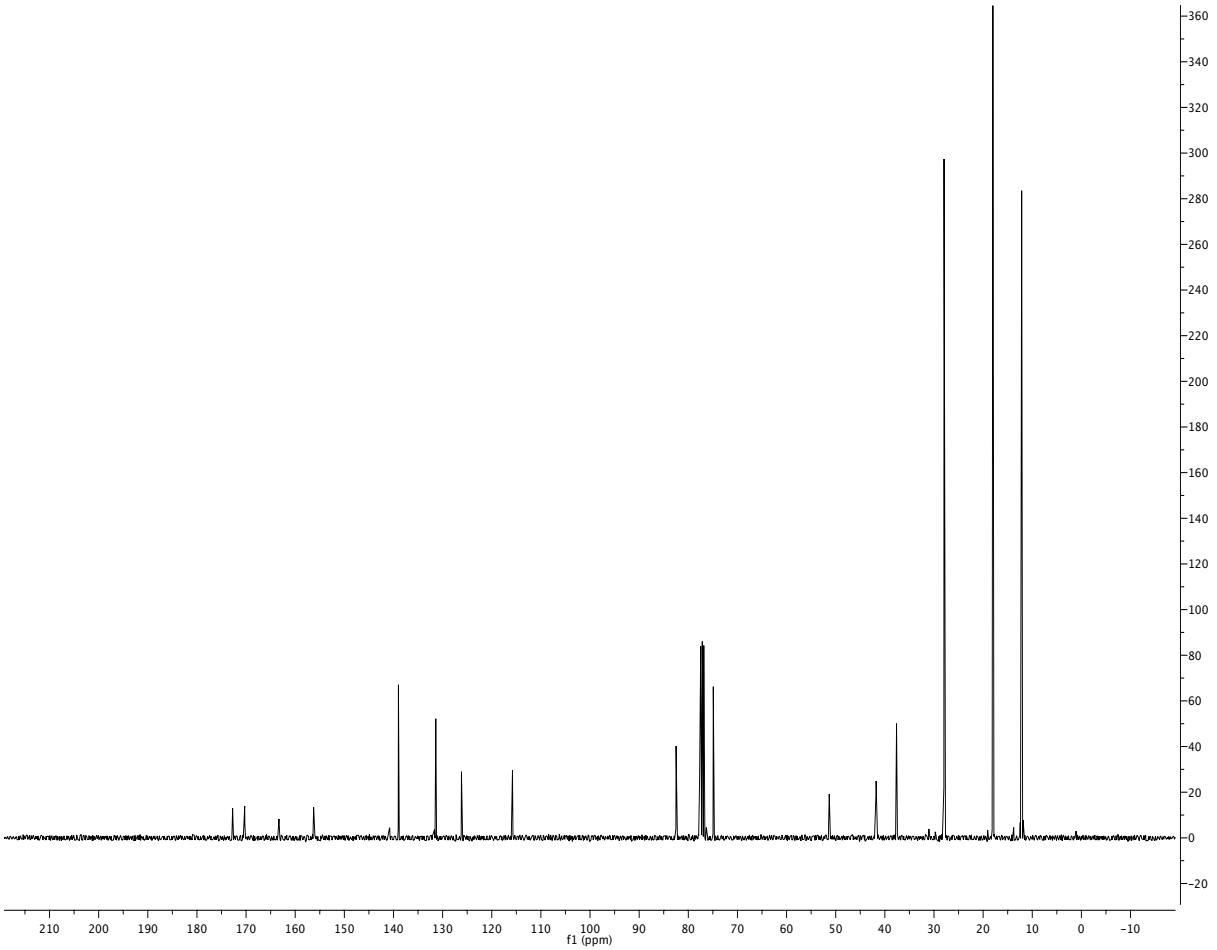


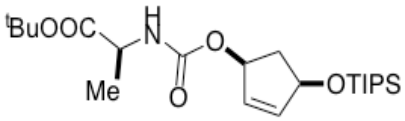
(*S*,*S*,*R*)-**3.7.2**



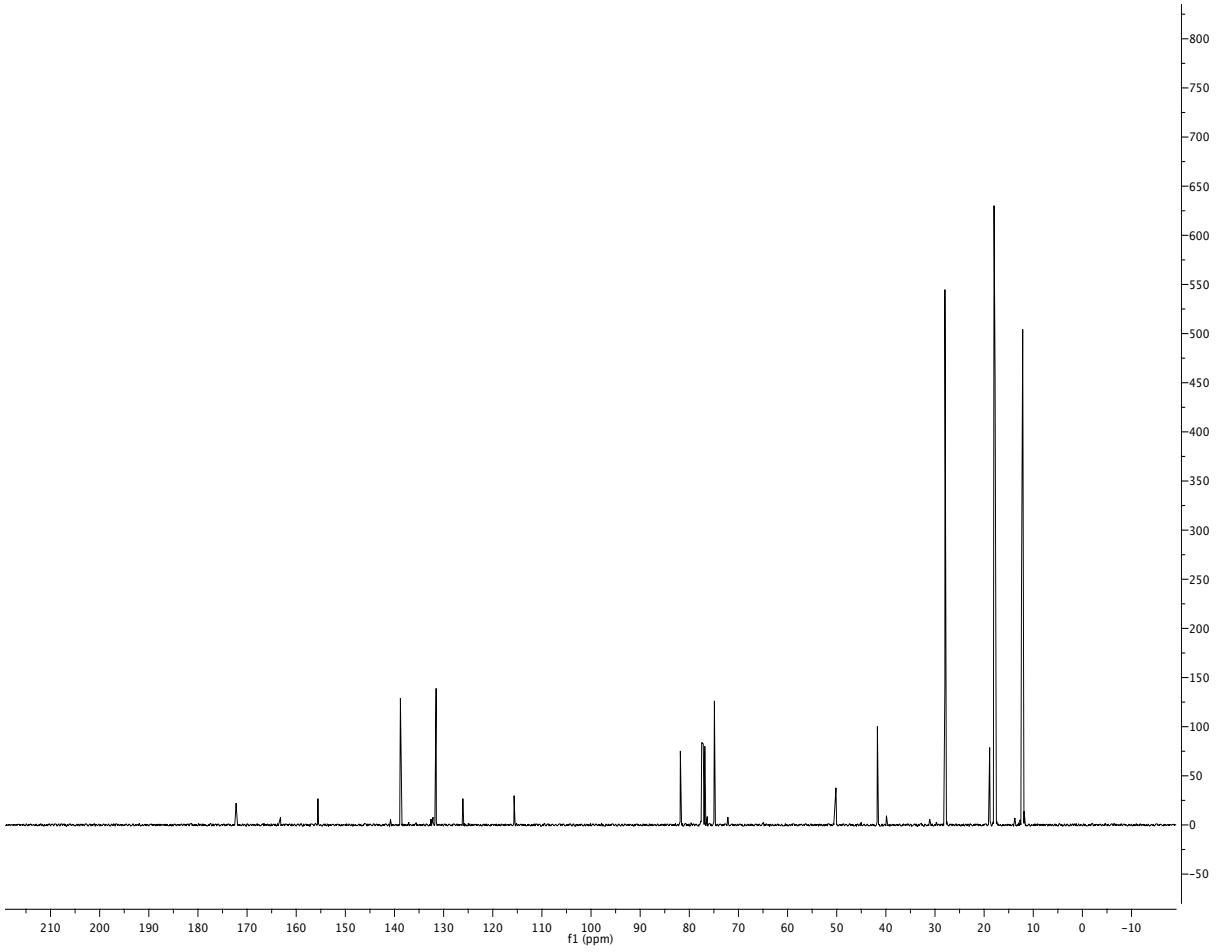


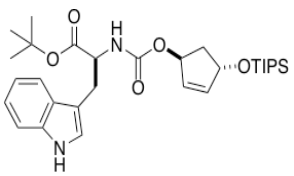
(*S*,*S*,*R*)-**3.7.3**





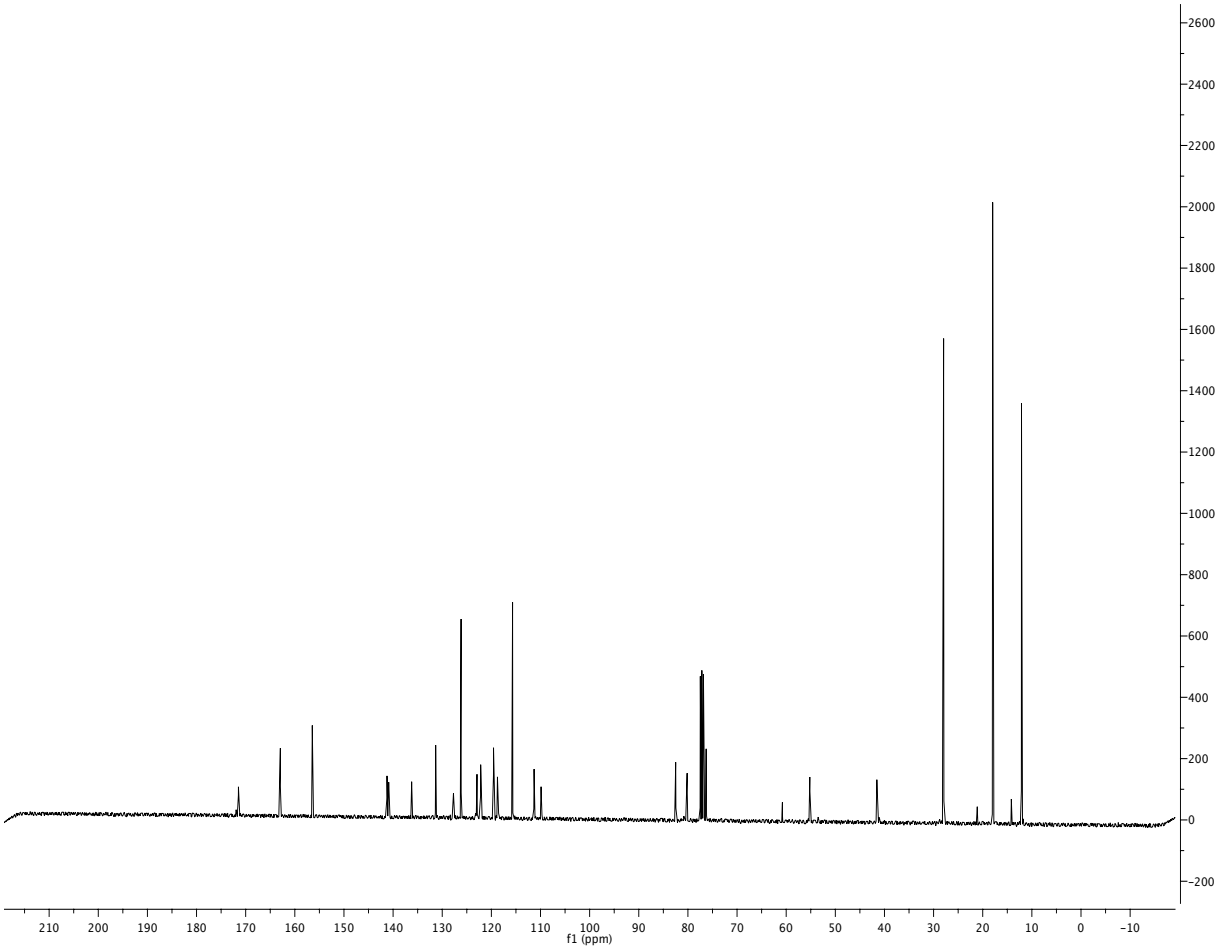
(*S,S,R*)-**3.7.4**

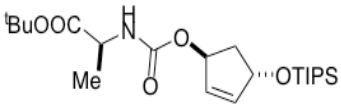



O
O
H
N
O
O
OTIPS
N
H

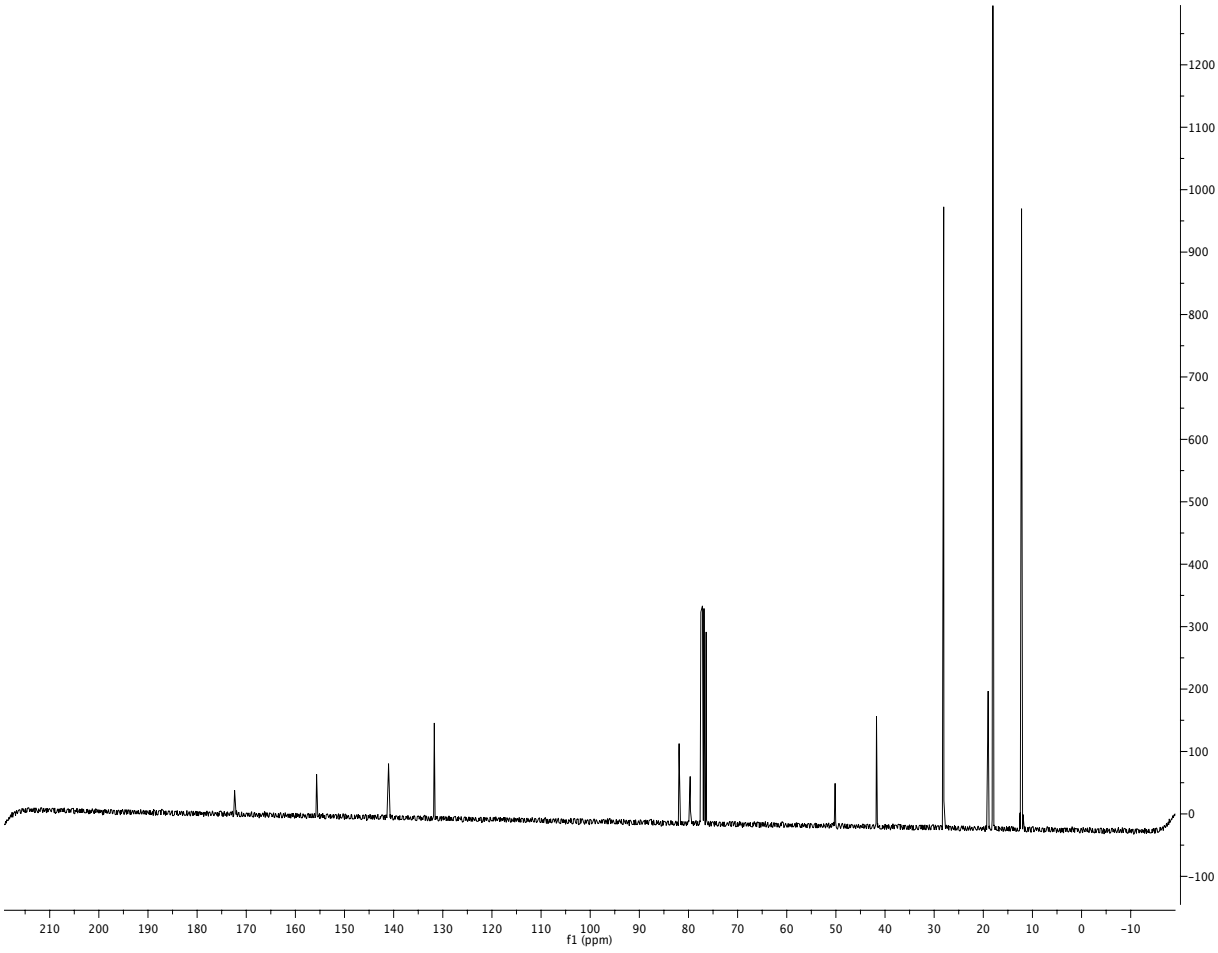
(*S*,*S*,*S*)-**3.7.1**

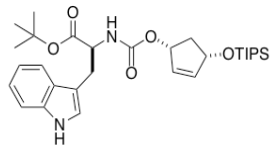
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5 −1.0
f1 (ppm)


2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
−200
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)



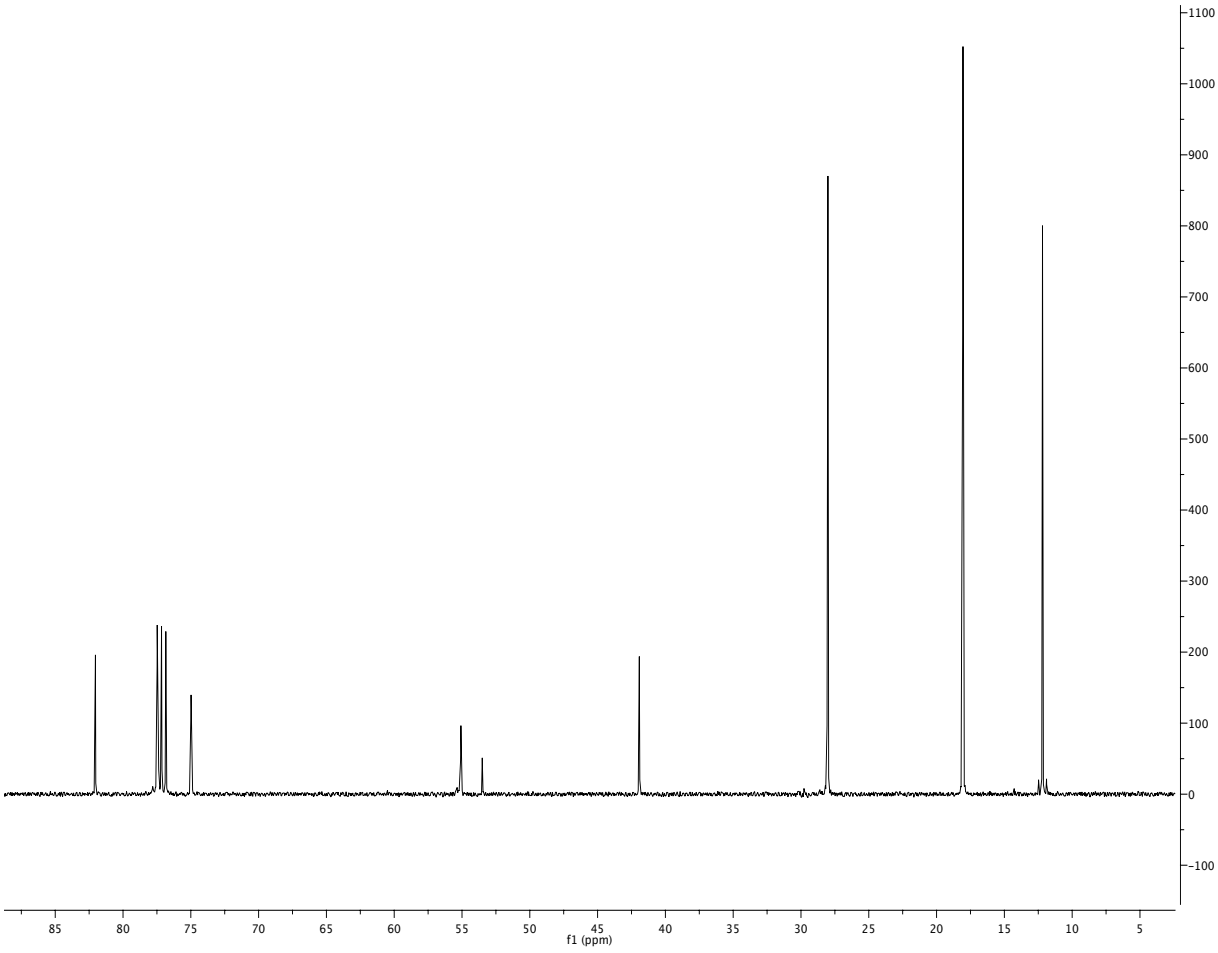
(*S,S,S*)-**3.7.4**

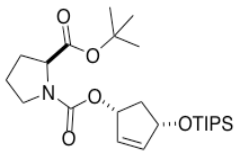



O
O
H
N
O
O
OTIPS
N
H

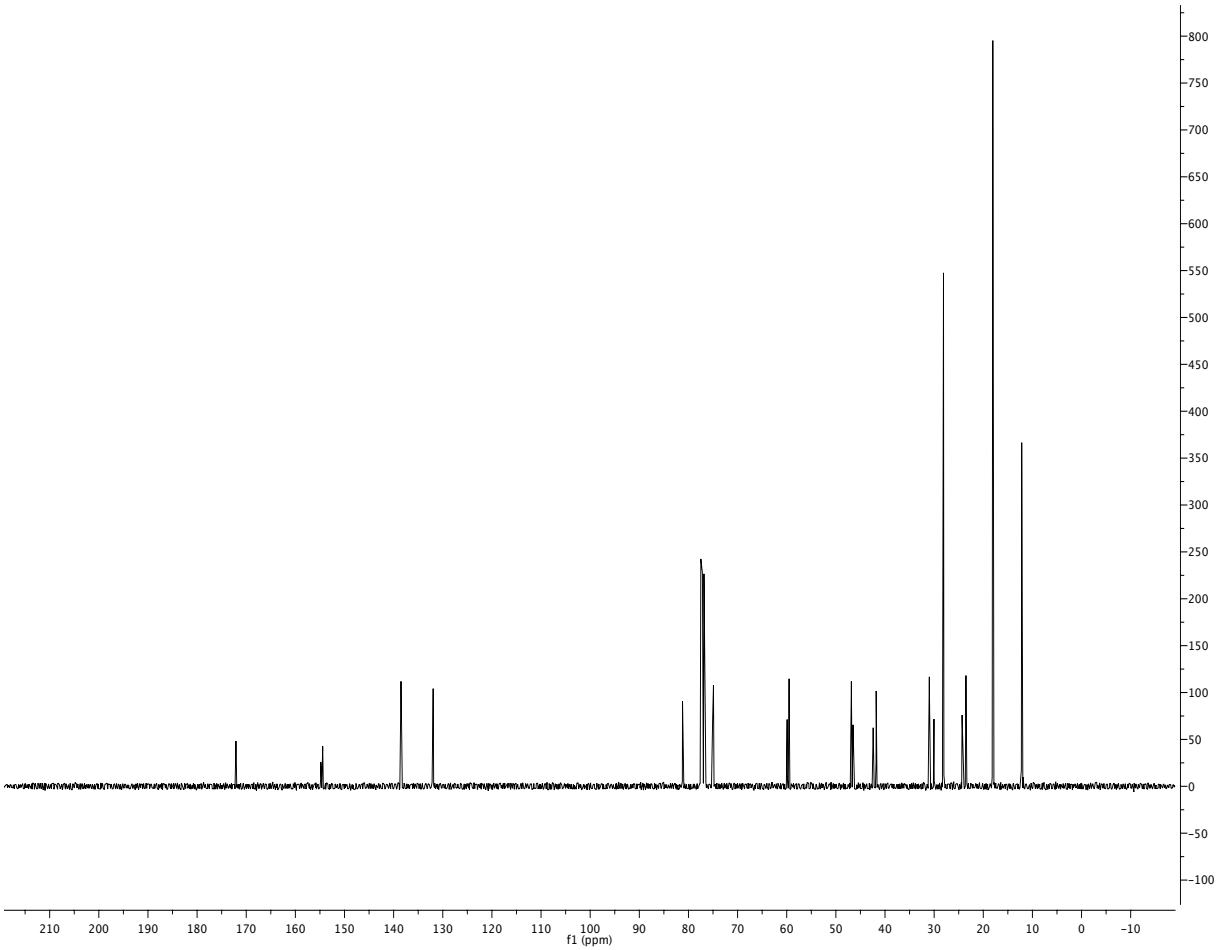
(*S*,*R*,*S*)-**3.7.1**

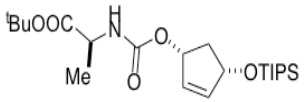
900
850
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


1100
1000
900
800
700
600
500
400
300
200
100
0
-100
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
f1 (ppm)

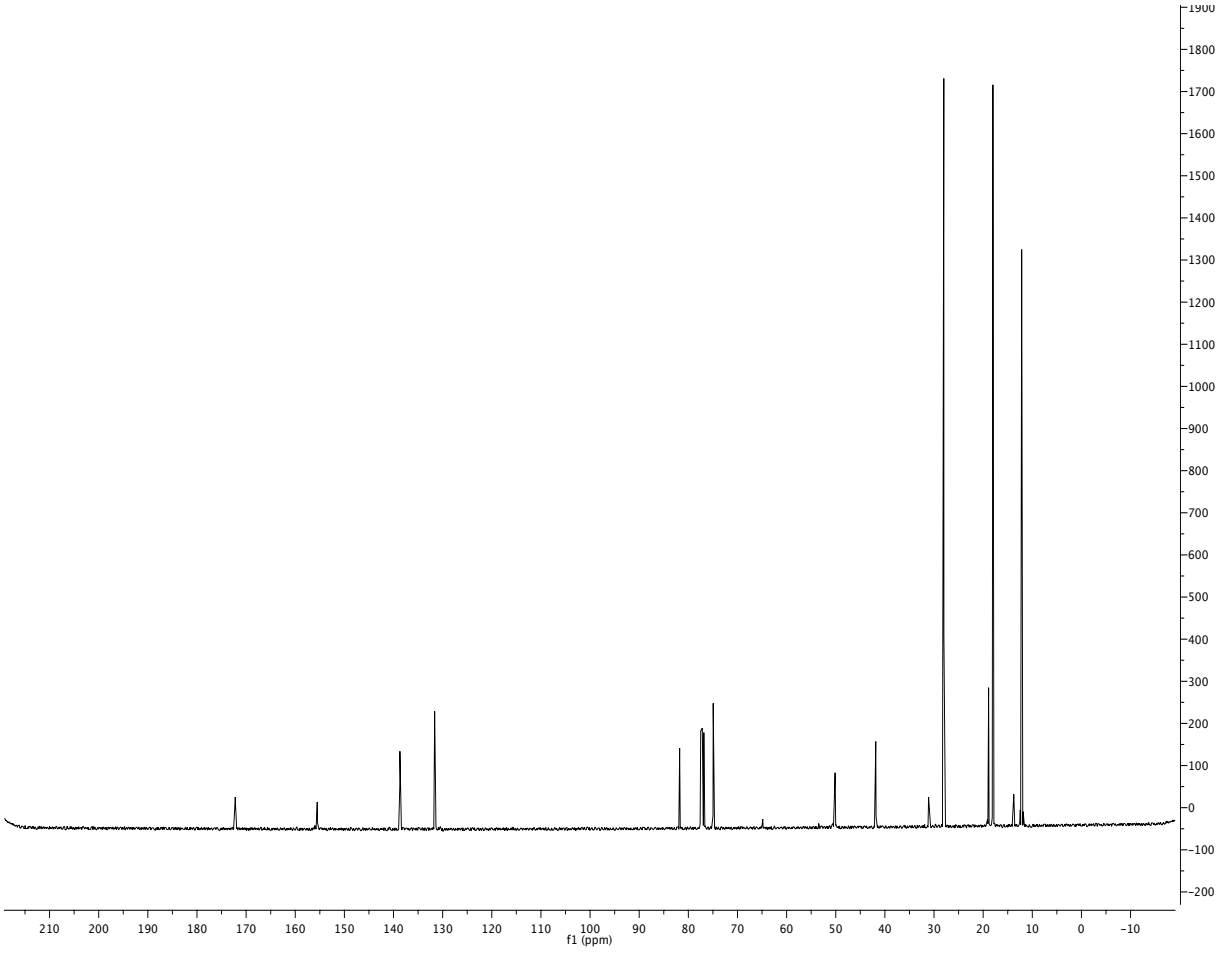


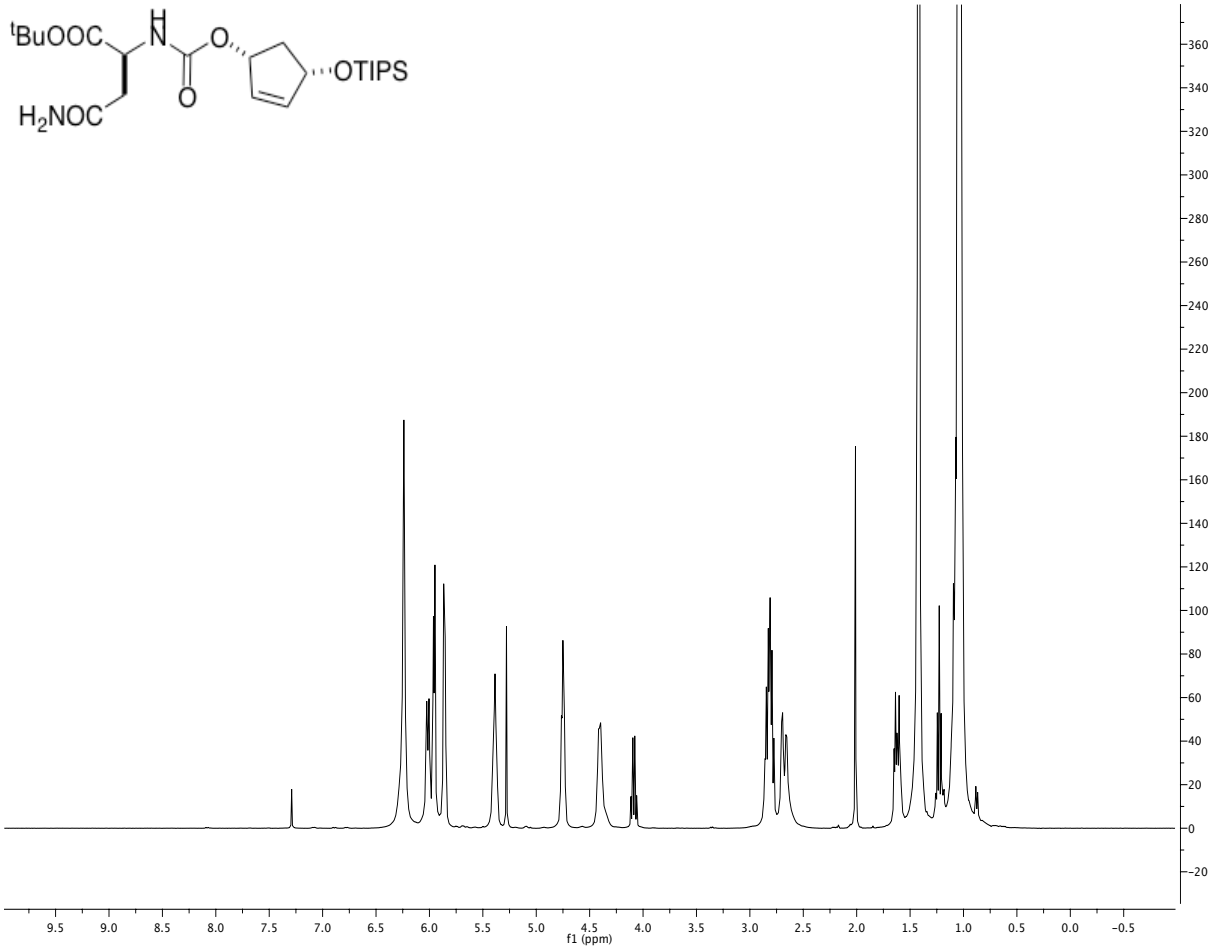
(*S*,*R*,*S*)-**3.7.2**

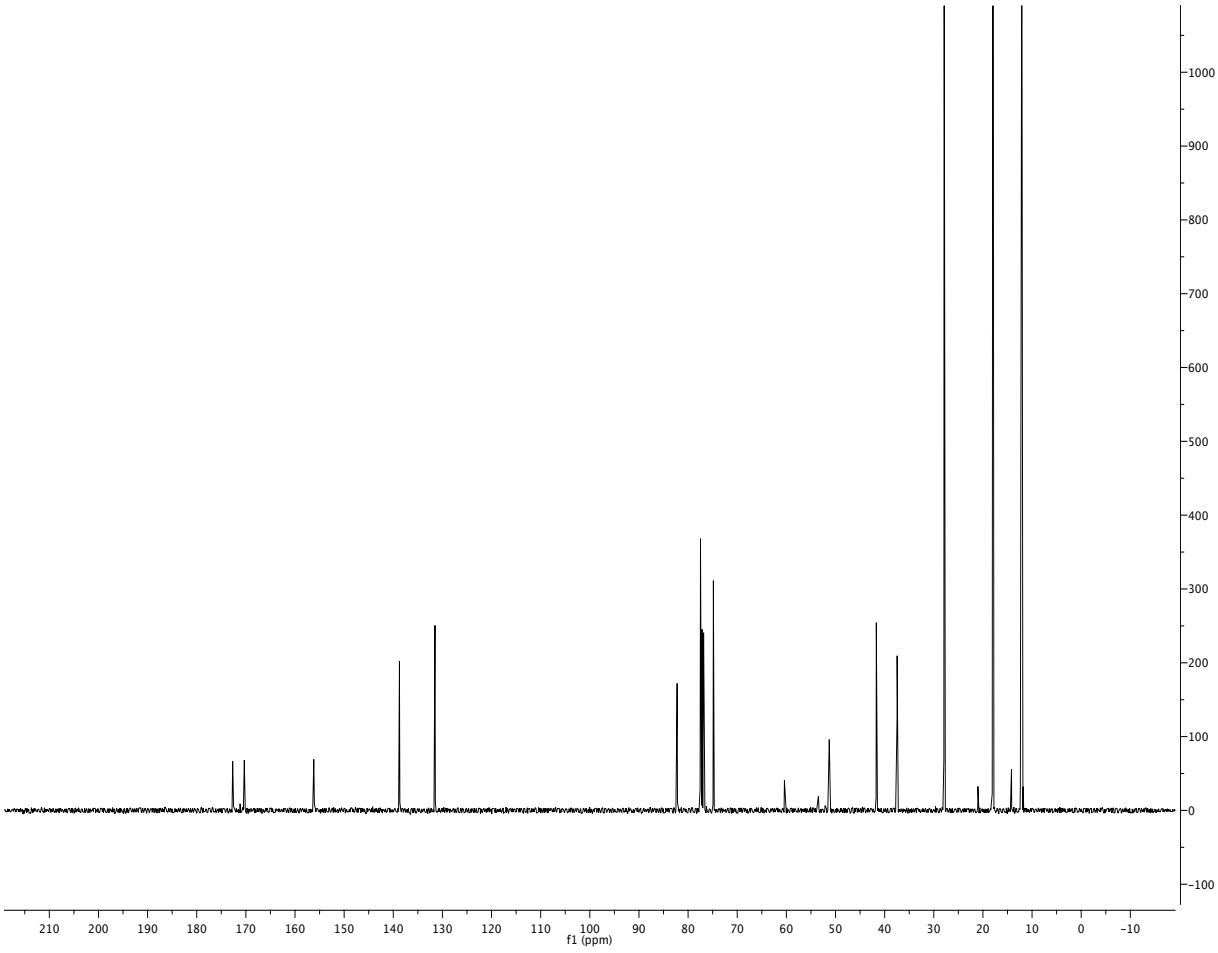


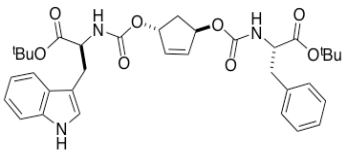


(*S*,*R*,*S*)-**3.7.4**

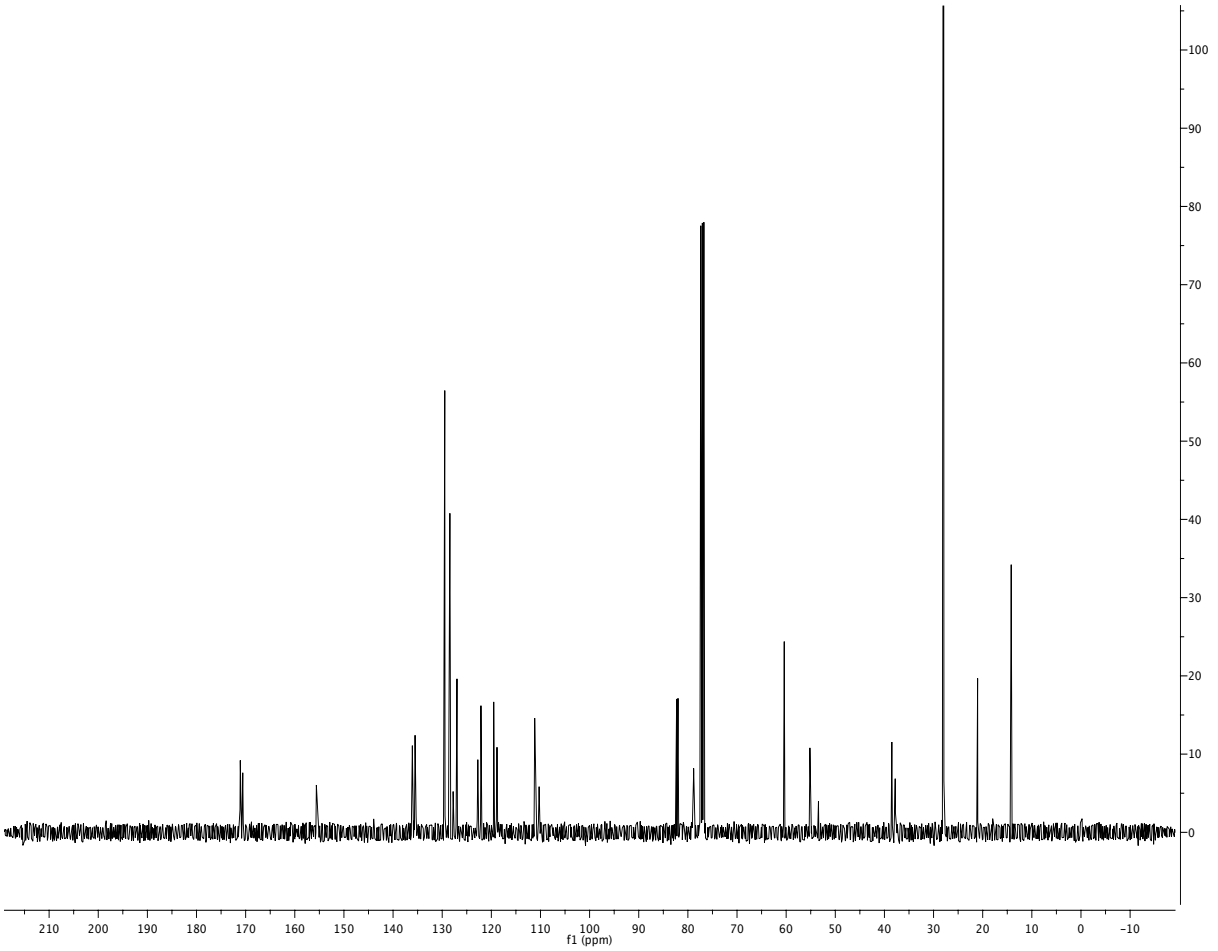


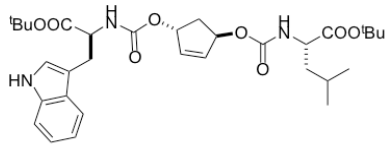

tBuOOC
H2NOC
H
N
O
O
OTIPS
f1 (ppm)


f1 (ppm)

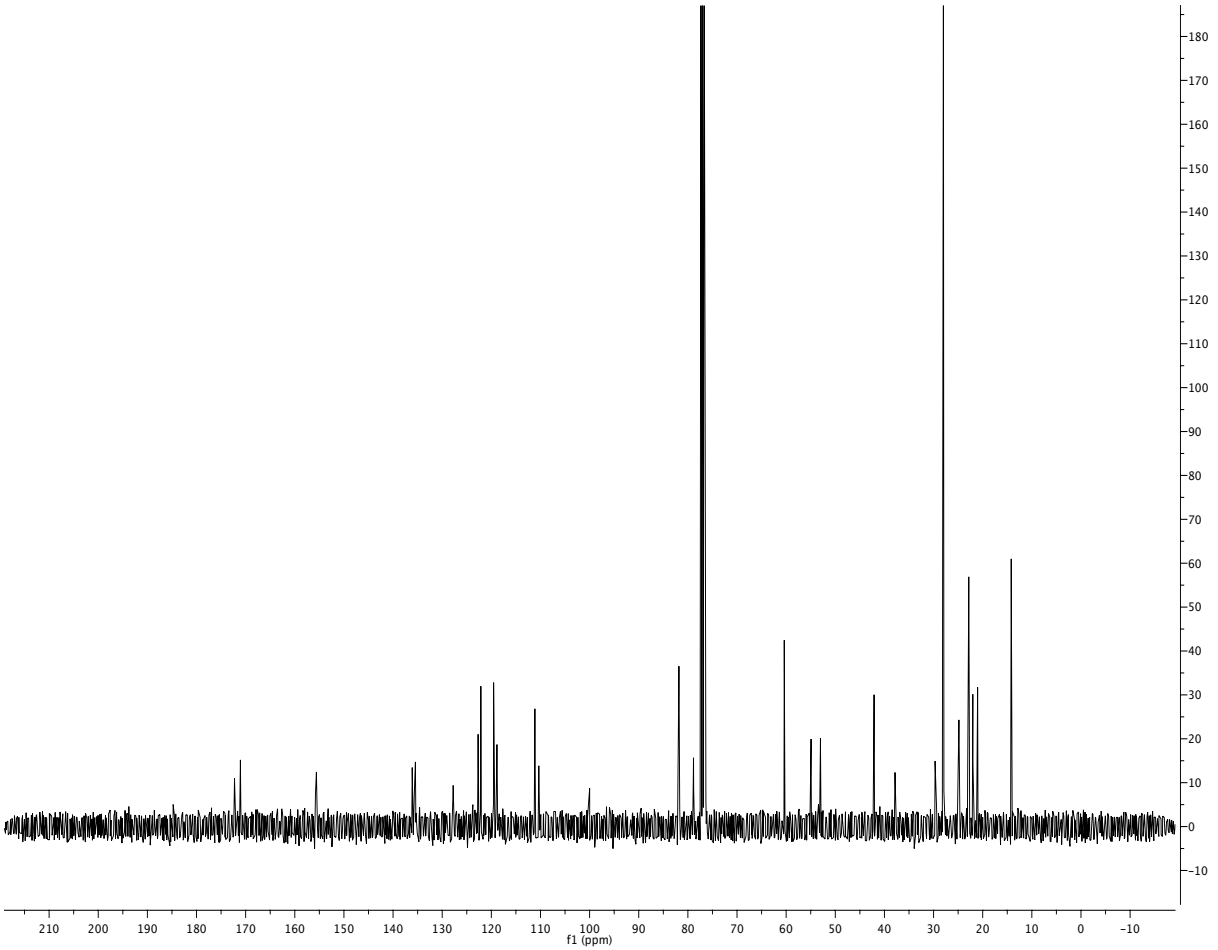


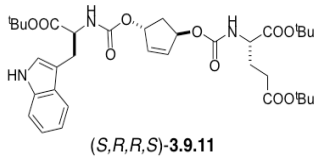
(*S*,*R*,*R*,*S*)-**3.9.7**



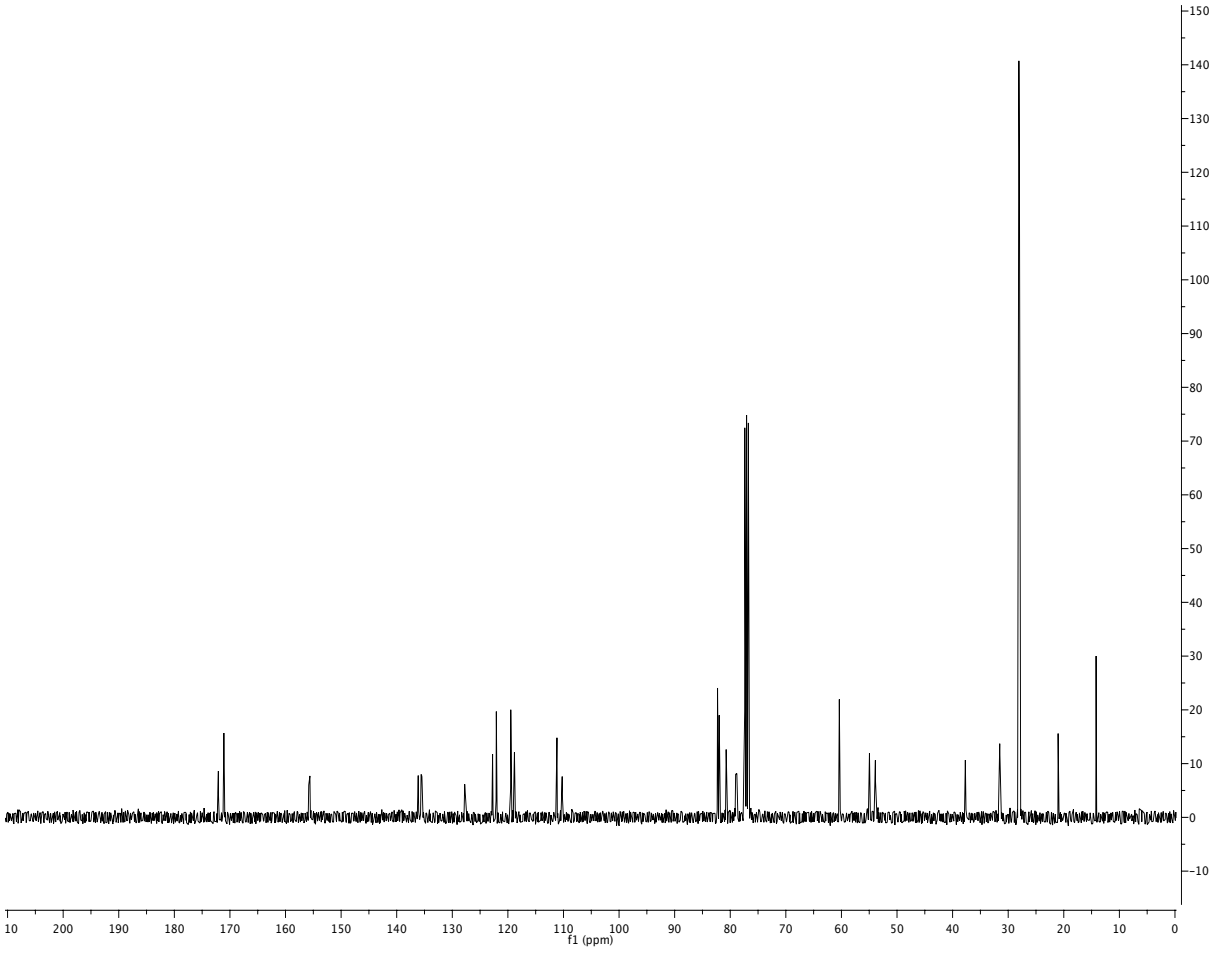


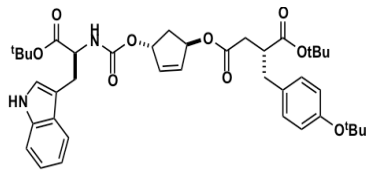
(*S*,*R*,*R*,*S*)-**3.9.7**



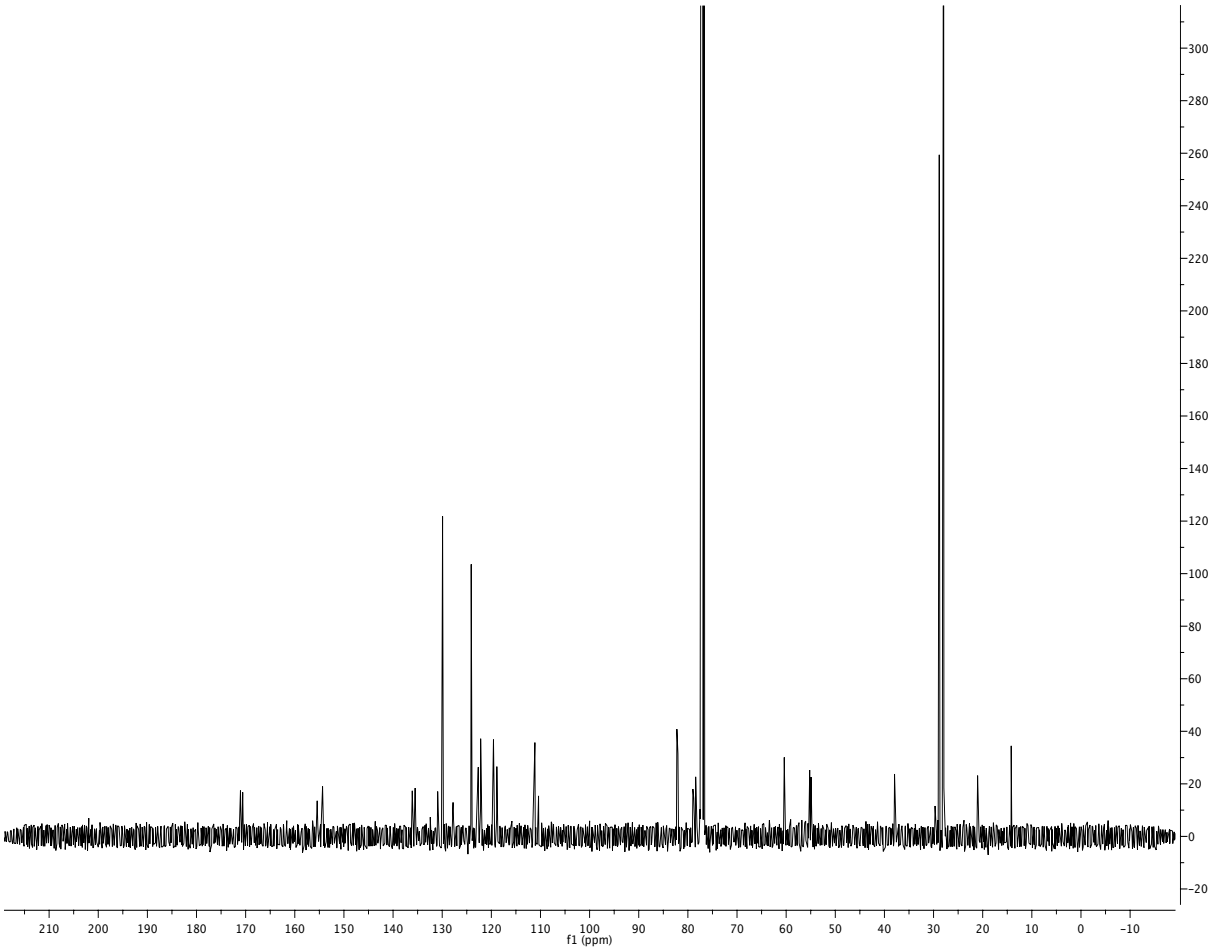


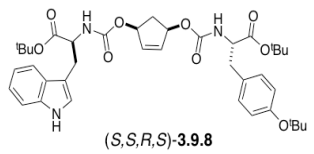
(*S*,*R*,*R*,*S*)-**3.9.11**




O
H
N
O
O
O
O
O
OtBu
tBuO
HN
O
OtBu

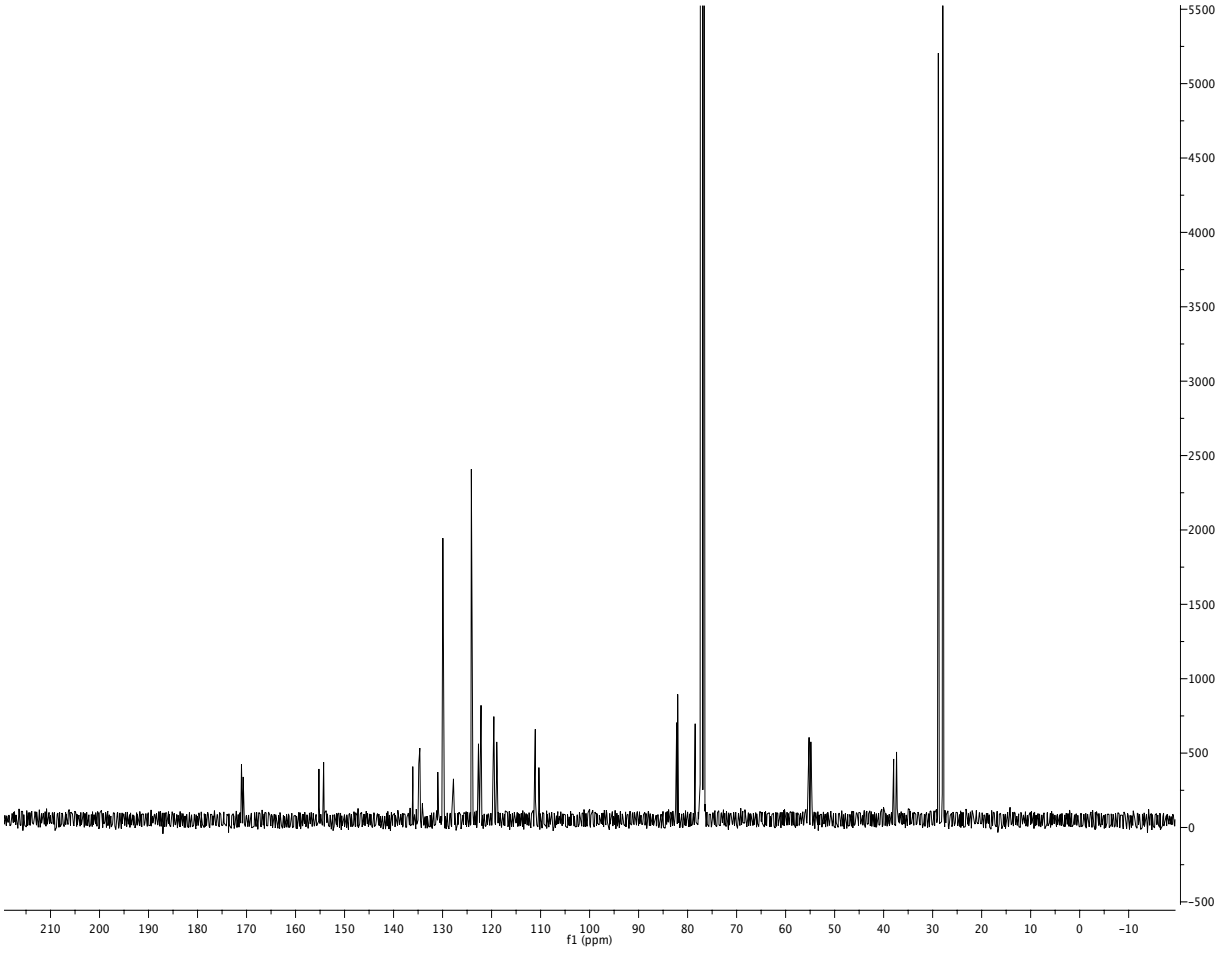
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
f1 (ppm)

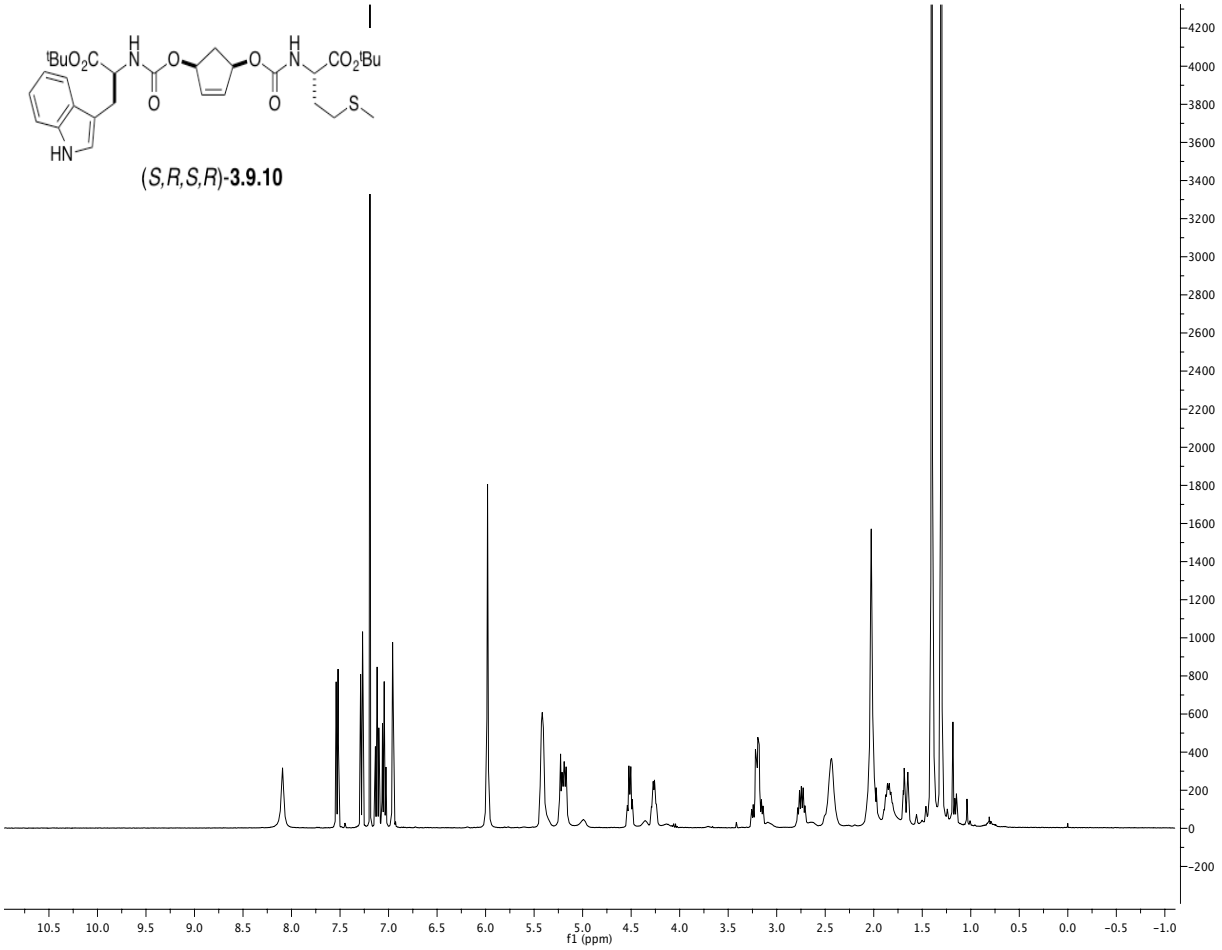

300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



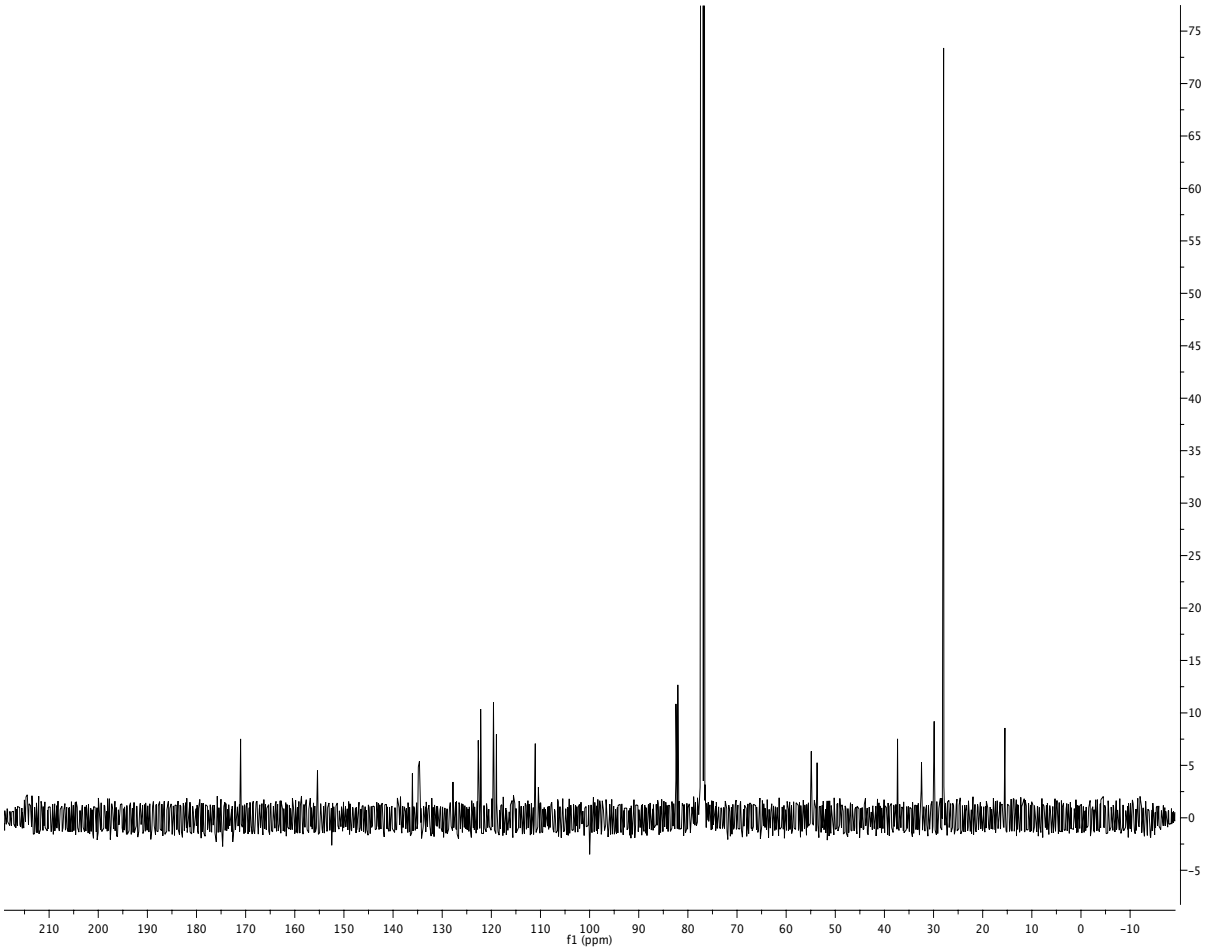
(*S*,*S*,*R*,*S*)-**3.9.8**

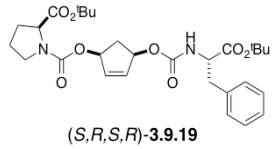
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
14.5 14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0
f1 (ppm)


5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
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)



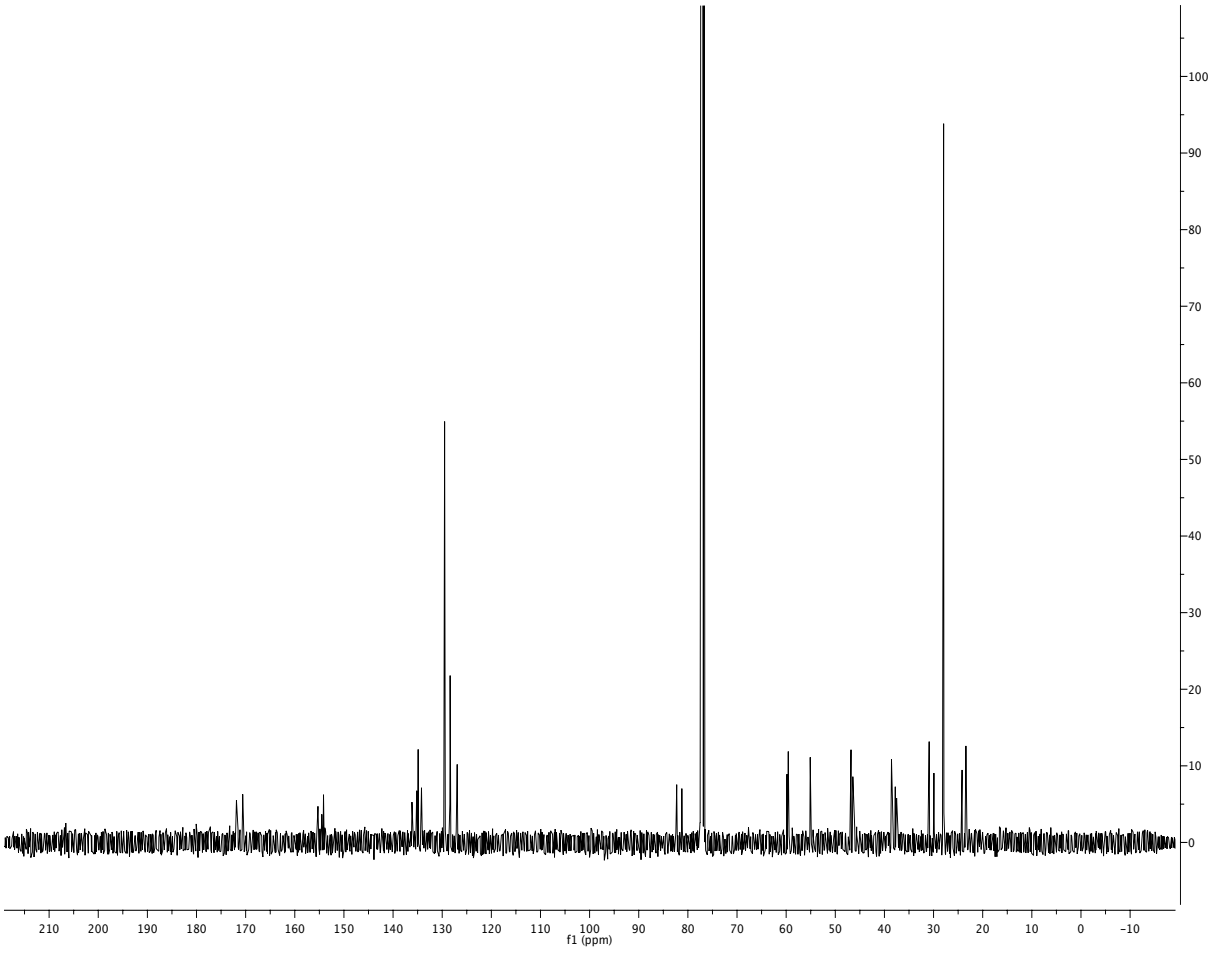
(*S,R,S,R*)-**3.9.10**

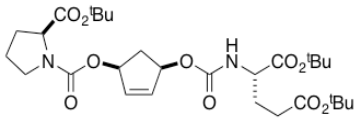



CO2tBu
N
O
O
O
H
N
O
CO2tBu

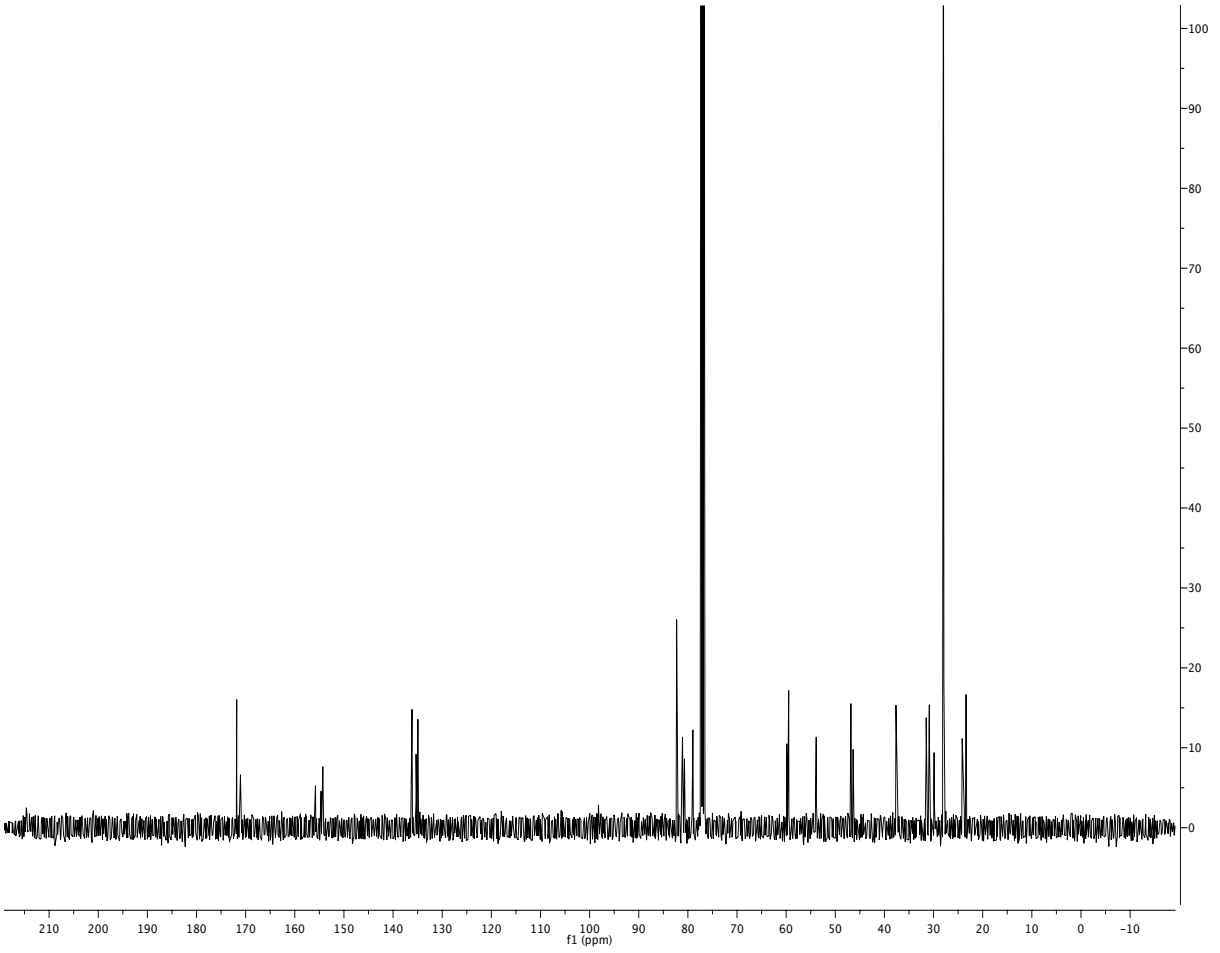
(*S*,*R*,*S*,*R*)-**3.9.19**

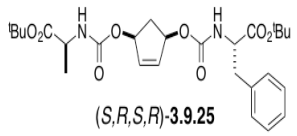
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


100
90
80
70
60
50
40
30
20
10
0
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)



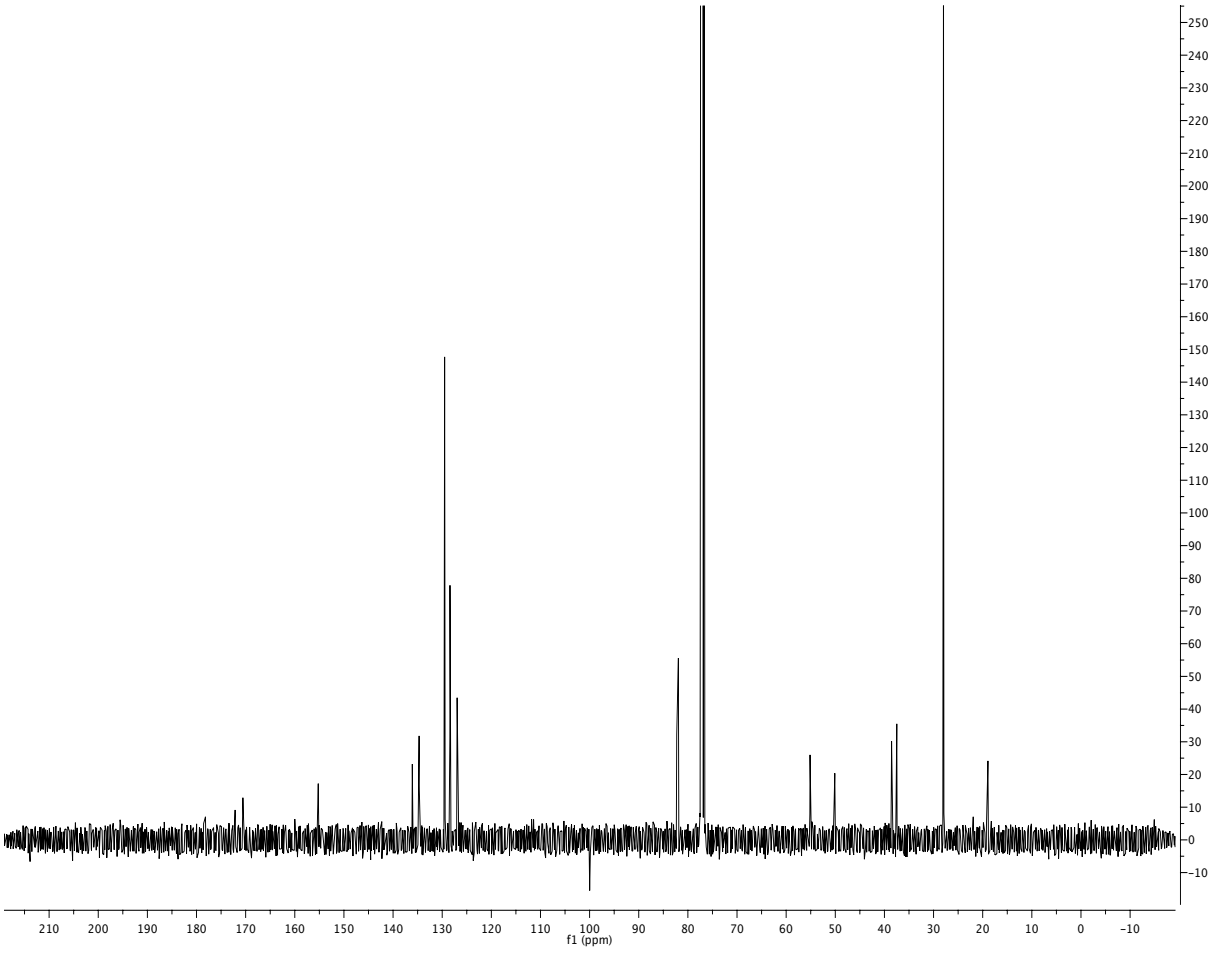
(*S*,*R*,*S*,*R*)-**3.9.23**

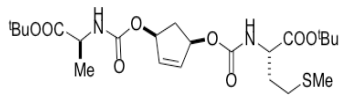




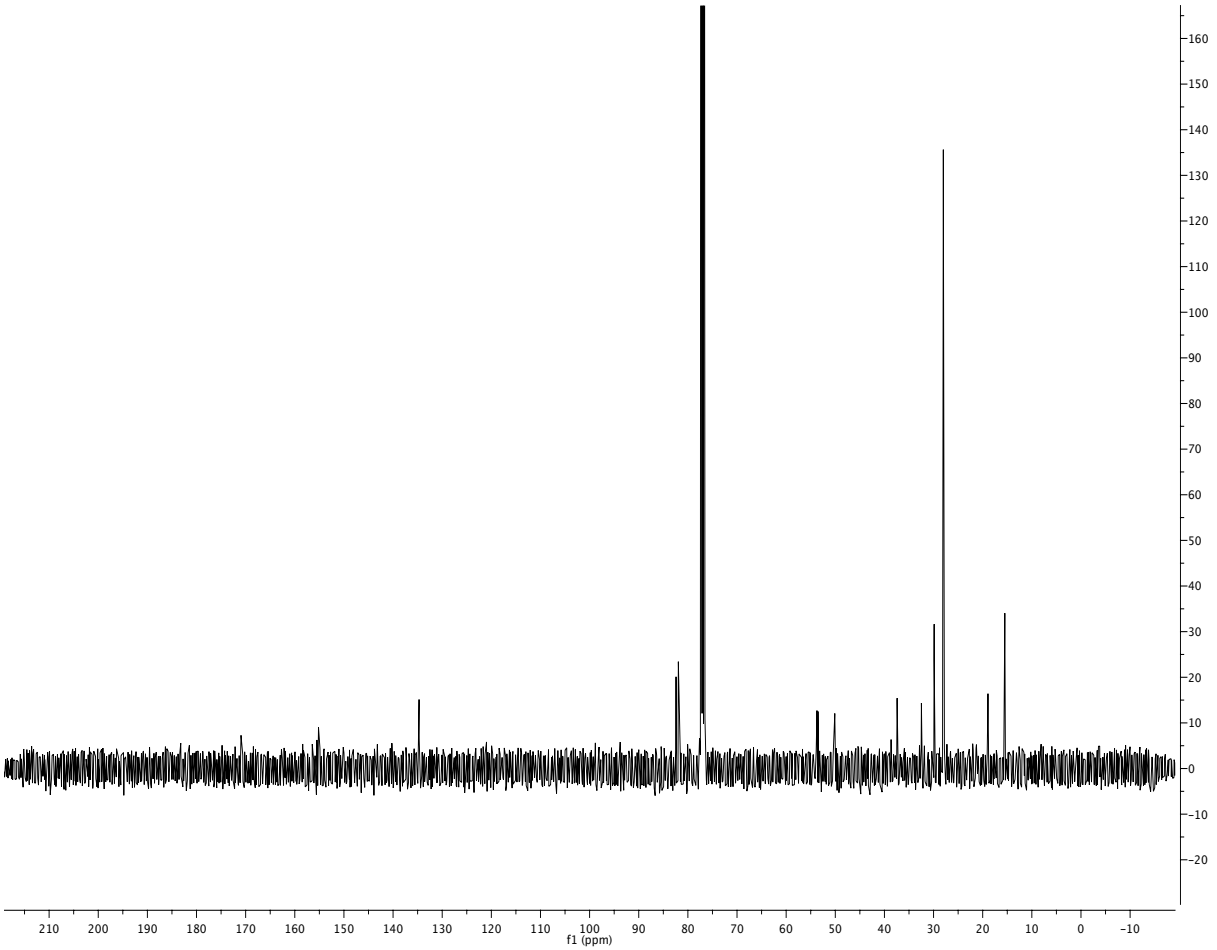
(*S,R,S,R*)-**3.9.25**

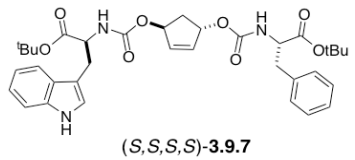
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


250
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
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)

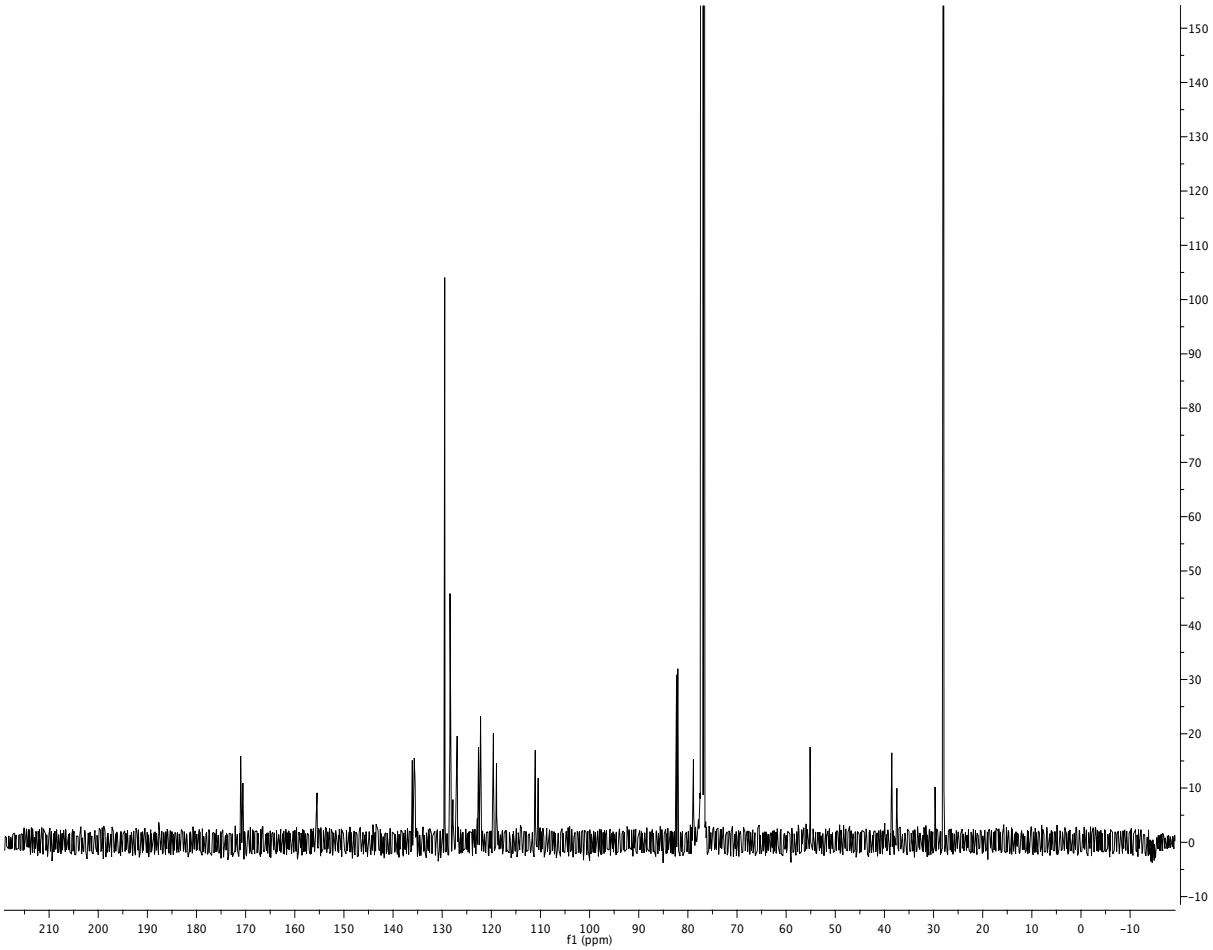


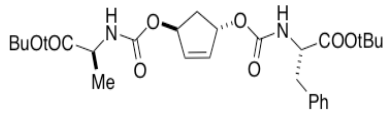
(*S*,*R*,*S*,*R*)-**3.9.28**





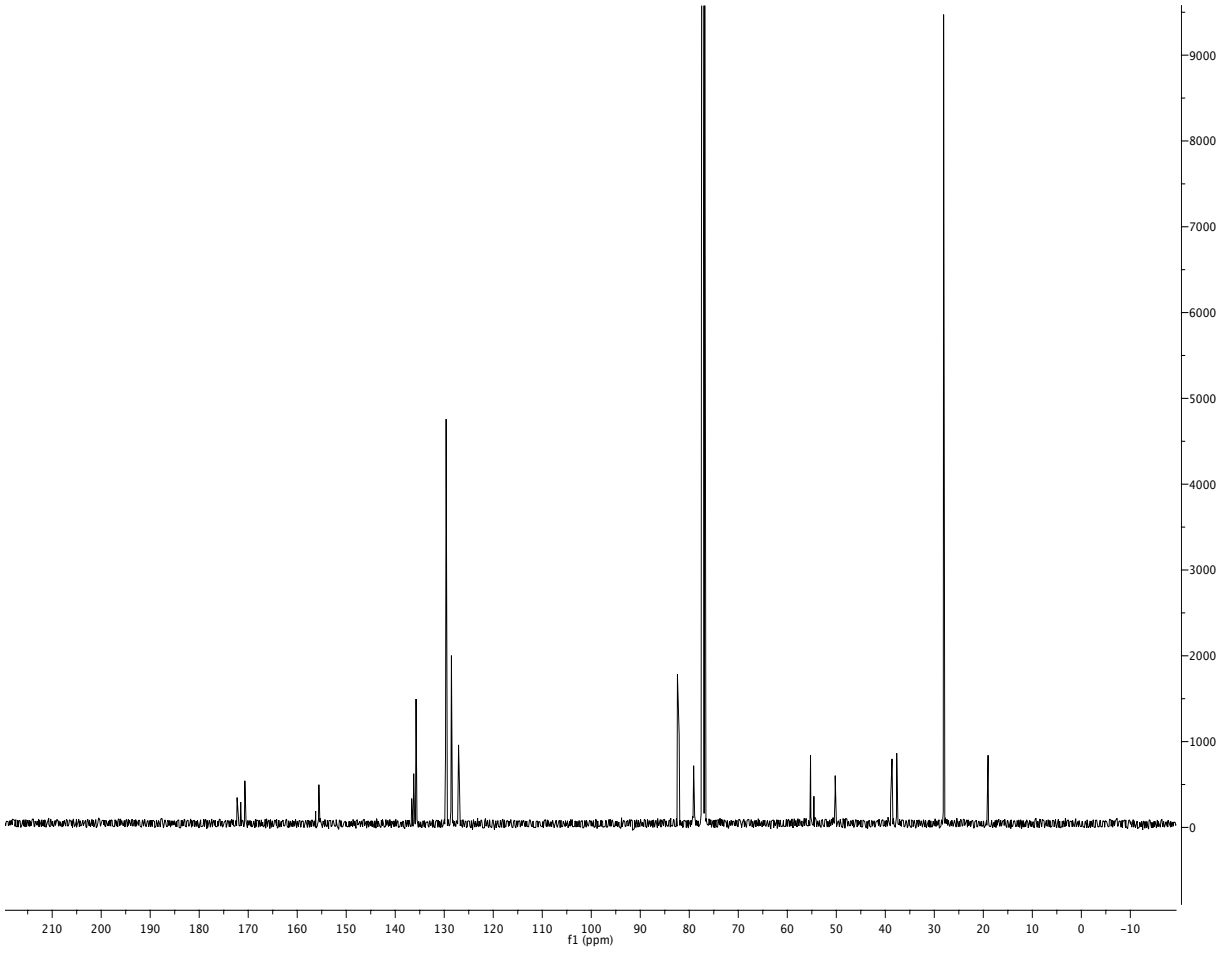
(*S*,*S*,*S*,*S*)-**3.9.7**

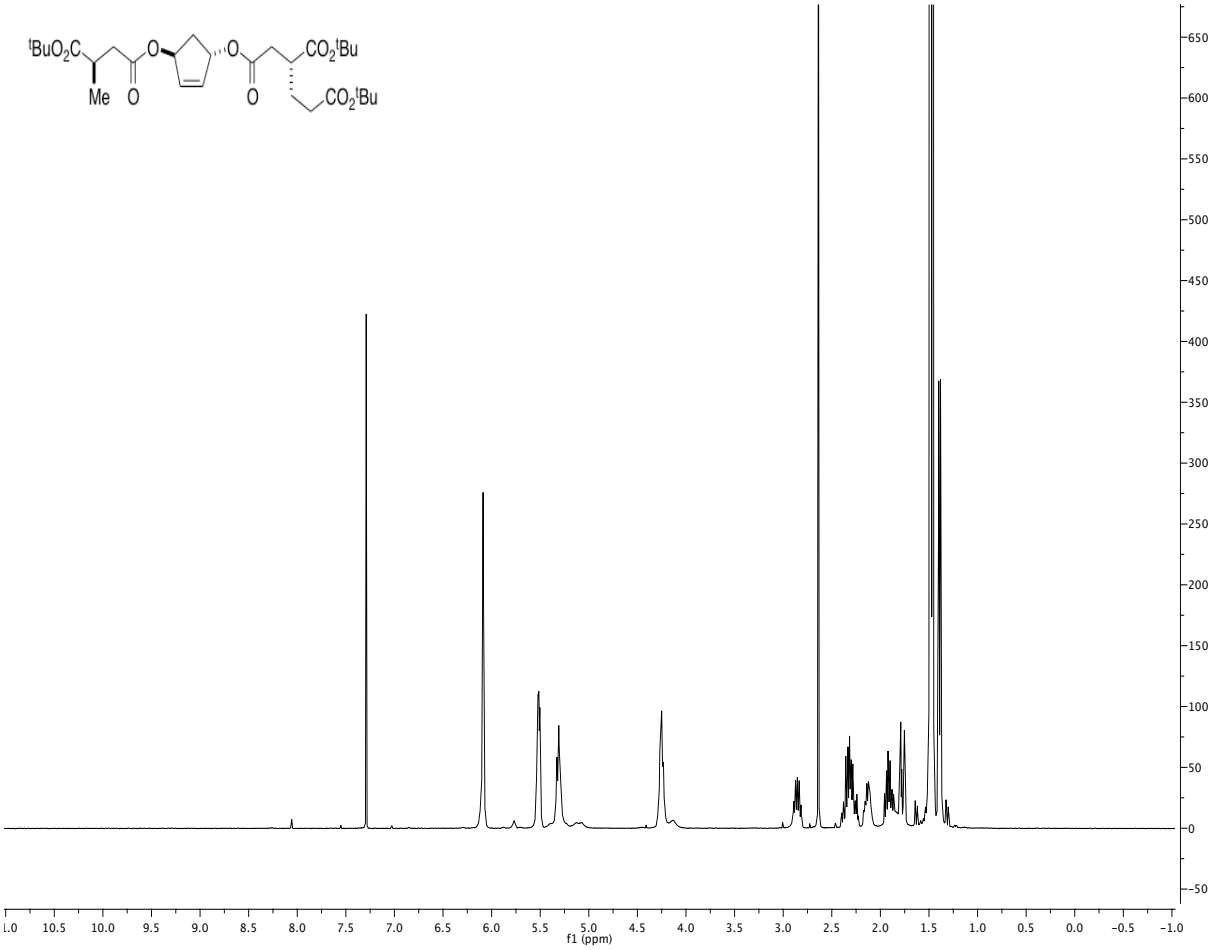


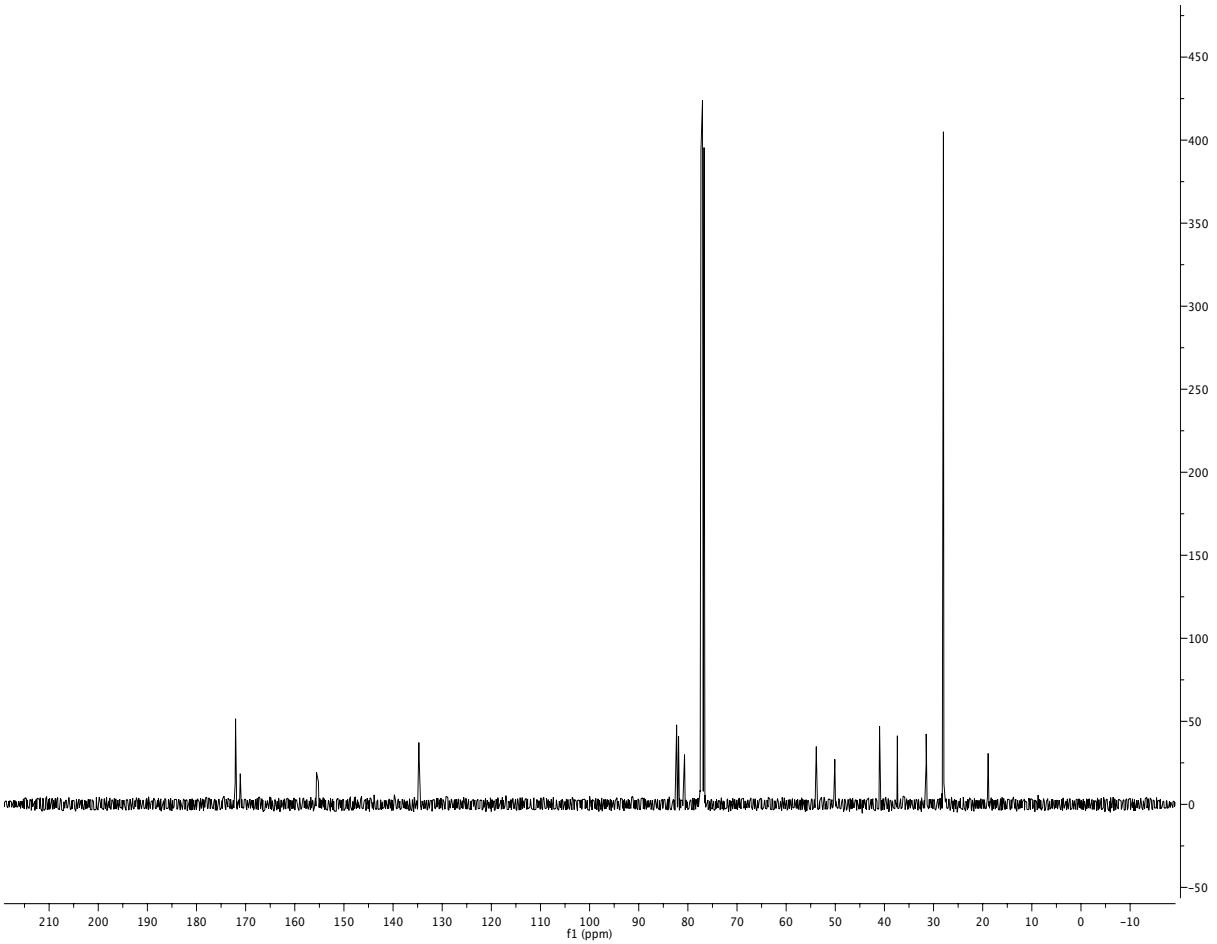

BuOtOC
H
N
O
Me
O
O
O
H
N
COOtBu
O
Ph

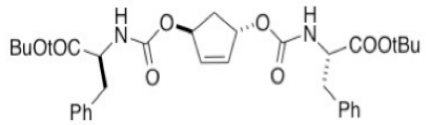
(*S*,*S*,*S*,*S*)-**3.9.25**

45000
40000
35000
30000
25000
20000
15000
10000
5000
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 −1.0
f1 (ppm)


9000
8000
7000
6000
5000
4000
3000
2000
1000
0
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)

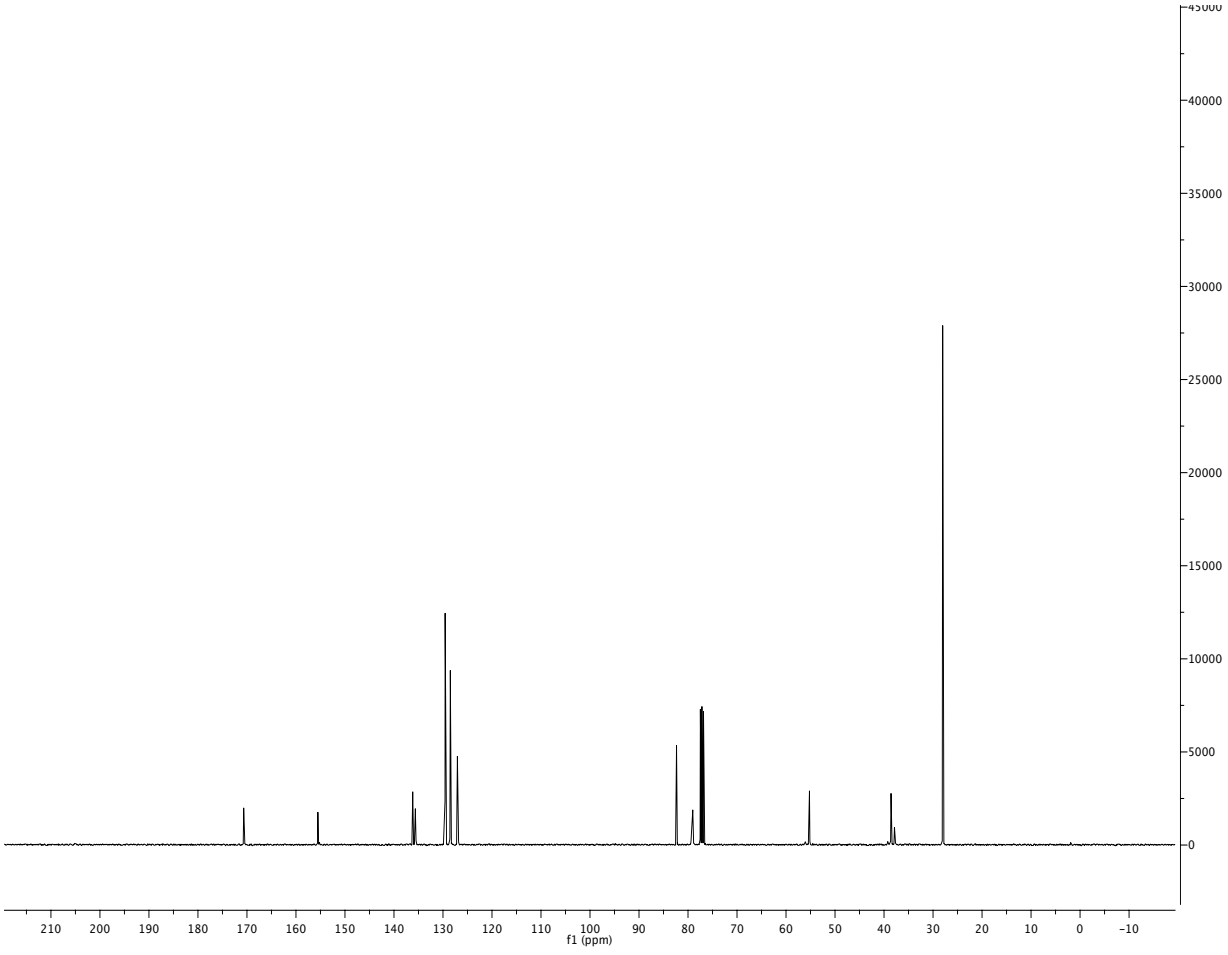

tBuO2C
Me
O
O
O
O
CO2tBu
CO2tBu
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

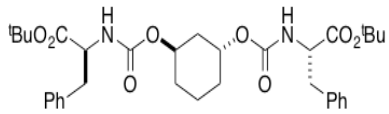

450
400
350
300
250
200
150
100
50
0
-50
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


BuOtOC
H
N
O
O
O
O
H
N
COOtBu
Ph
Ph

(*S*,*S*,*S*,*S*)-**3.14.1**

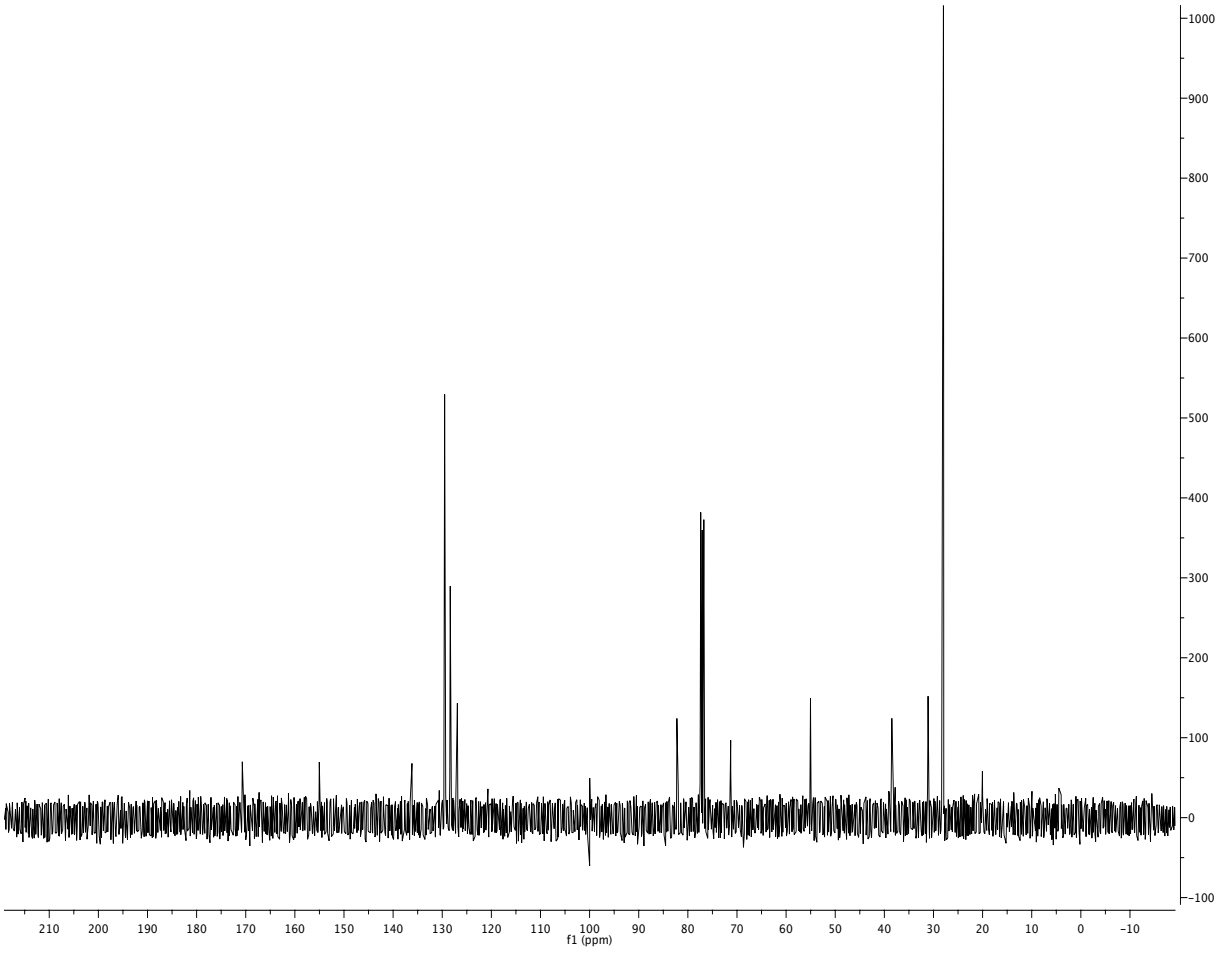
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

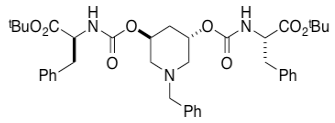

40000
35000
30000
25000
20000
15000
10000
5000
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


tBuO2C
H
N
O
O
O
O
H
N
CO2tBu
Ph
Ph

(*S,S,S,S*)-**3.14.7**

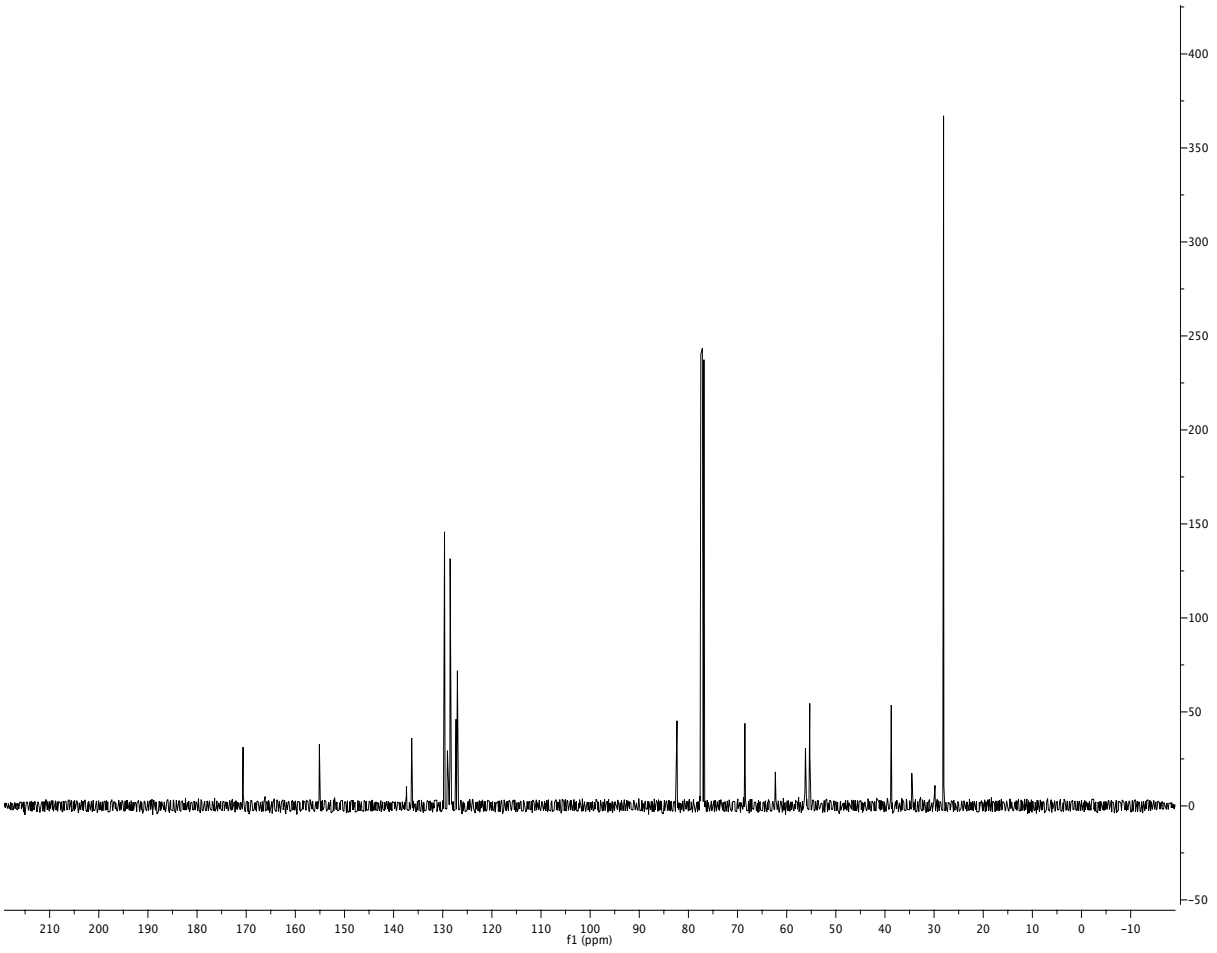
400
350
300
250
200
150
100
50
0
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 −3 −4
f1 (ppm)

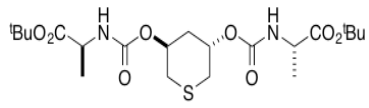

1000
900
800
700
600
500
400
300
200
100
0
−100
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)


tBuO2C
H
N
O
O
O
H
N
CO2tBu
Ph
O
O
Ph
N
Ph

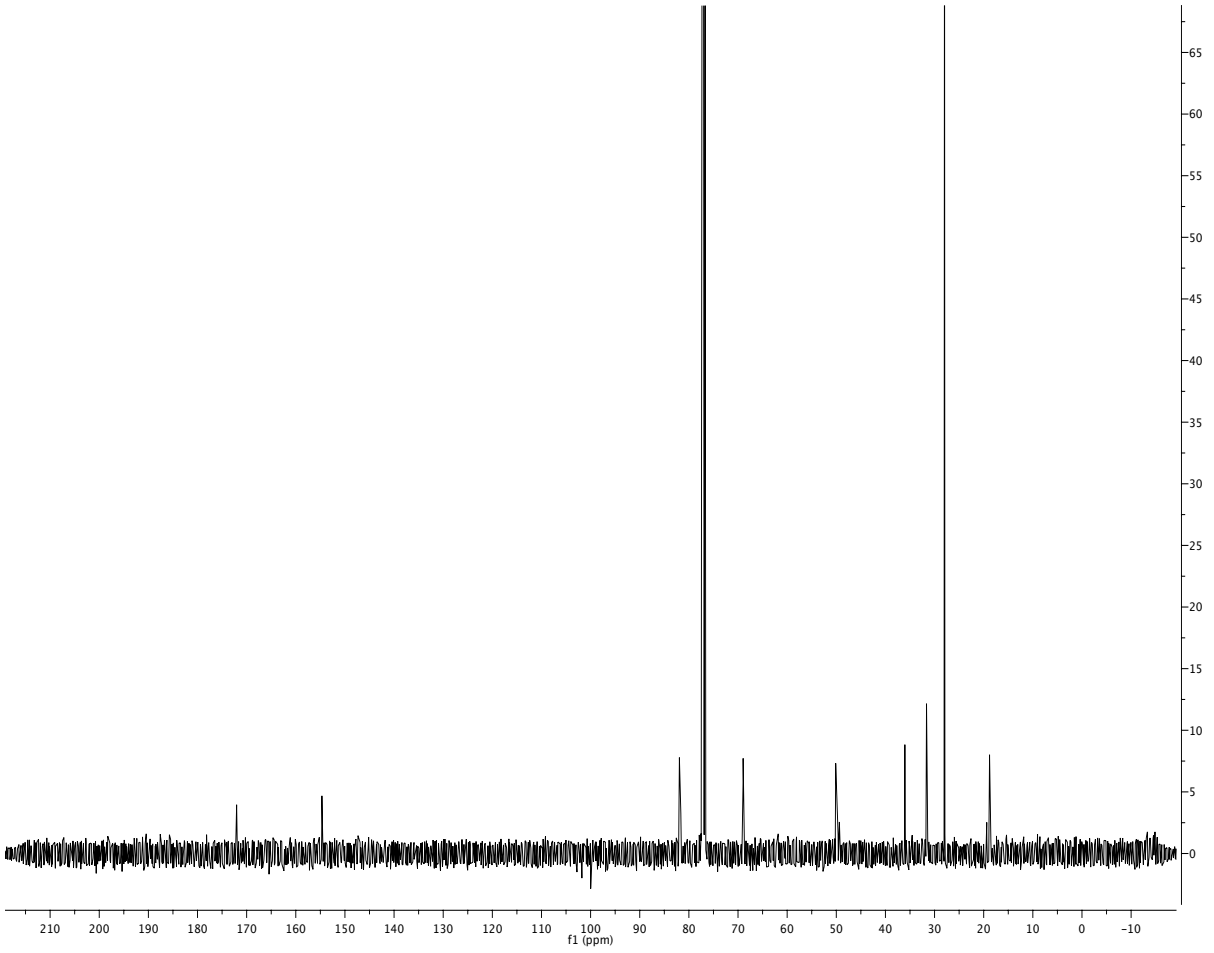
(*S,S,S,S*)-**3.14.13**

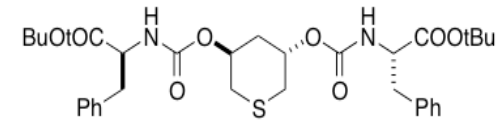
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


400
350
300
250
200
150
100
50
0
-50
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)

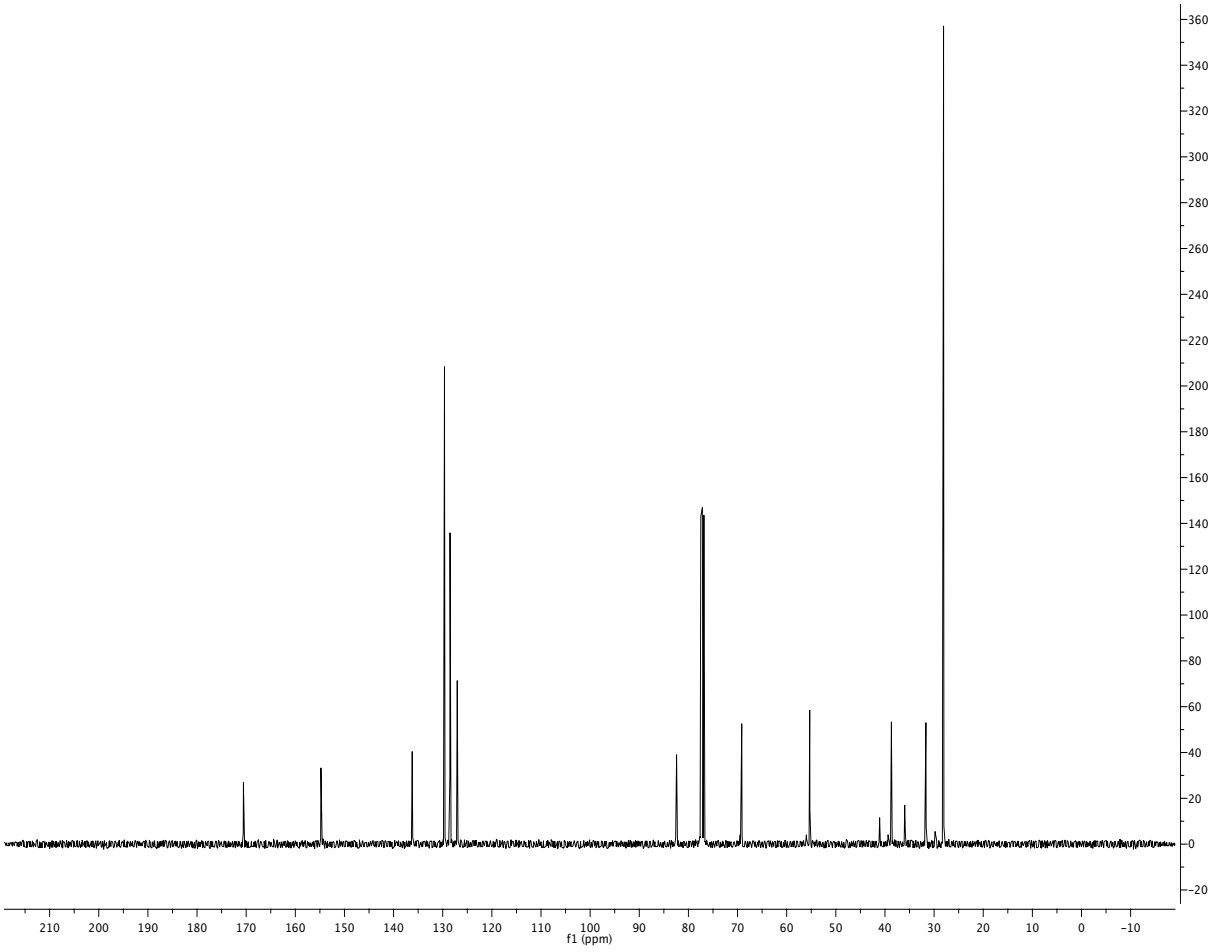


(*S*,*S*,*S*,*S*)-**3.14.20**




BuOtOC
H
N
O
O
O
S
O
H
N
COOtBu
Ph
Ph

11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
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)


360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
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)