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Part I: An Approach To The Synthesis Of Plakortethers A-E Part II: Rhodium-Catalyzed Intramolecular C-H Insertion On Diazosulfonates And Its Synthetic Applications

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PART I: AN APPROACH TO THE SYNTHESIS OF PLAKORTETHERS A–E
PART II: RHODIUM-CATALYZED INTRAMOLECULAR C–H INSERTION ON DIAZOSULFONATES AND ITS SYNTHETIC APPLICATIONS

by

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This dissertation, submitted by Duminda S Liyanage in partial fulfillment of the requirements for the Degree of Doctor of Philosophy from the University of North Dakota, has been read by the Faculty Advisory Committee under whom the work has been done and is hereby approved.

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This dissertation meets the standards for the appearance, conforms to the style and format requirements of the Graduate School of the University of North Dakota, and is hereby approved.

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Title	Part I: An Approach to the Synthesis of Plakortethers A–E Part II: Rhodium-Catalyzed Intramolecular C–H Insertion on Diazosulfonates and its Synthetic Applications
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Date December 11th, 2014

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF SCHEMES

LIST OF TABLES

COMPOUND NUMBERING SYSTEM

The following method is used for numbering of the chemical compounds in Schemes, Figures, and Tables. The first letter (**S**, **F** or **T**) that appears in the number of the compound denotes a Scheme, Figure or a Table, respectively. The number that appears before the decimal point denotes the Scheme, Figure or Table number. The digits after the decimal point indicate the compound's number within that particular Scheme, Figure or Table. For example, compound "**F4.1**" indicates compound number **1** in Figure 4, compound "**S53.5**" indicates compound number **5** in Scheme 53, whereas compound "**T2.3**" indicates compound number **3** in Table 2.

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“This dissertation is dedicated to two individuals to whom I am in debt: my ever loving late mother (AMMA), the most important positive influence in my life, and my father (THATHTHA). I owe everything in my life to their love, guidance, persistent effort in nurturing and educating me to be the best human being that I can be”

ABSTRACT

This research work consists of two independent studies. The first study is the development of a synthetic route to plakortethers A–E along with possible derivatives. The second study focuses on the synthetic applications of rhodium-catalyzed intramolecular C–H insertion on diazosulfonates.

Plakortethers (A–G) represent a set of marine natural products, which contain of a characteristic tetrasubstituted tetrahydrofuran fragment. This group of compounds was isolated from the Caribbean sponge *Plakortis simplex*. Their selective cytotoxic activity against the RAW 264–7 cell lines (murine macrophage) makes them promising candidates for biological studies and, along with their unusual structure, warrants the synthesis of these natural products. In the approach to plakortethers A–E, the key efforts were directed at the assembly of the important structural element: the tetrasubstituted tetrahydrofuran ring with three stereocenters. To achieve this goal, initially, it was intended to use trans-annular iodocyclization to obtain the embedded tetrasubstituted tetrahydrofuran backbone in plakortethers. Due to the synthetic difficulties encountered in preparation of the necessary intermediates, the construction of the tetrahydrofuran ring was proposed to be achieved *via* an acyclic intermediate using cyclization of an episulfonium ion onto an alcohol to control stereochemistry. Construction of the key precursor to the episulfonium ion with desired stereochemistry was envisioned from a

six-membered lactone (valerolactone) intermediate. The requisite lactones were prepared *via* enolate alkylation for the future studies of the episulfonium ion cyclization step.

The second study focuses on the use of rhodium-catalyzed intramolecular C–H insertion on diazosulfonates as a tool for the synthesis of organic molecules. Dirhodium-induced intramolecular C–H insertion on diazo carbonyl compounds is a relatively well-studied reaction. In a wide variety of cases it lead to the preferential formation of five-membered cycles. In the earlier work in our lab, it was found that sulfone and sulfonate diazocompounds undergo intramolecular C–H insertion to form predominantly six-membered cyclic sulfones and sulfonates (δ-sultones) over their five-membered counterparts. δ-Sultones can serve as viable synthetic intermediates. Preliminary work on the transformations of these compounds done in our research group has identified that, upon treatment with THBP and *t*-BuOK, δ-sultones undergo oxidative desulfonation to form five-membered lactones (γ-butyrolactones). Butyrolactones are a common fragment in natural compounds and are valuable as synthetic intermediates. In the current study, the conditions for this oxidative desulfonation of δ-sultones to γ-butyrolactones were optimized, along with testing of the scope of this transformation. Optimization studies resulted in satisfactory yields of γ-butyrolactones from δ-sultones with 5 eq of THBP and 6 eq of *t*-BuOK in THF or DME as a solvent at room temperature. These conditions have been utilized to synthesize a γ-butyrolactone key intermediate that was used in the previously reported total synthesis of natural product (–)-eburnamonine.

CHAPTER I

POLYKETIDES FROM SPONGES OF GENUS PLAKORTIS

1.1 Introduction and background of the chemistry in oceans

Nature provides us with a considerable number of highly functionalized natural products with great structural divergence. Oceans, which cover almost 75% of the Earth's surface, contain a variety of fauna and flora species, which have no terrestrial counterparts.[1] These marine species, unexploited prior to 1980,[1] are an endless source of compounds with interesting pharmacological activity.[2] Marine organisms have attracted enormous interest from scientists in recent decades. The large numbers of structurally diverse compounds that were obtained from marine organisms have been populating the ever-expanding library of natural products.[3, 4]

Among marine organisms, the chance of finding bioactive compounds is remarkably higher in slow moving or sessile invertebrates such as sponges, coelenterates (e.g., soft corals), ascidians (e.g., sea squirts), mollusks (e.g., sea hares) and bryozoans.[3, 5] Many of the organisms in these phyla are brightly colored, lacking a spine or protective shell and often lacking any physical defense from predators. Therefore, many of the bioactive compounds are involved in their defensive mechanisms as a chemical weapon.[1]

About one third of all marine natural products have been isolated from sponges.[1] Sponges are among the most studied marine organisms,[3, 4] making them currently the most popular source of novel compounds. Among the different classes of

bioactive natural products isolated from sponges, a group of compounds known as polyketides plays an essential role in terms of structural diversity and biological activity.

1.2 Polyketides from oceans

Polyketides have been isolated from bacteria, fungi, sponges, plants, and animals. These isolates are usually biosynthesized through the decarboxylation condensation of acetyl-CoA-derived starter units and malonyl-CoA-derived extender units.[6, 7] Although they are also known to be produced by bacteria and fungi, marine sponges are the major source of polyketides. This group of compounds exhibits a bewildering structural diversity and a broad array of biological activities, including antibiotic (e.g., erythromycin), antitumor (e.g., bryostatins) and immunosuppressant (e.g., rapamycin) actions.[8] These numerous polyketides isolated from marine sponges can occur as simple small molecules and also as complex large molecules.[9] Some examples of polyketides are shown in Figure 1, ranging from such simple compounds like 6-methylsalicylic acid (**F1.1**)[9] and butenolide **F1.2**[10] to elaborate amphothericin B (**F1.4**)[11] and brevetoxin A (**F1.6**).[12] The biological activity of these compounds also ranges widely as antibiotics (**F1.1**), insecticides (**F1.2**), potential drugs towards polio and hepatitis (**F1.3**),[13] fungicides (**F1.4**), and antimalarial drugs (**F1.5**)[14] and neurotoxins (**F1.6**).

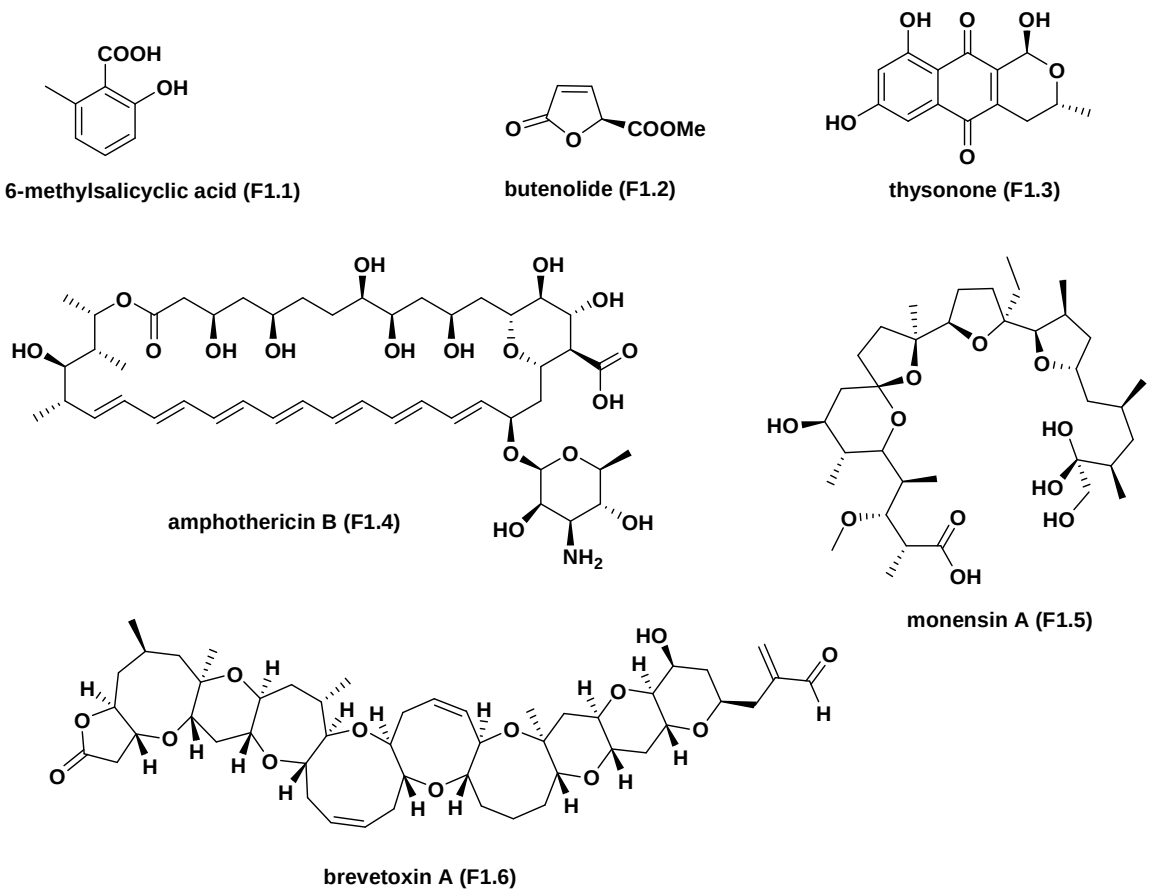
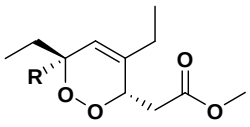


Figure 1. Examples of polyketides isolated from various marine sources.[9–14]

1.3 Polyketides isolated from genus *Plakortis*

Marine sponges of the genus *Plakortis* (family Plakinidae, class Demospongiae, order Homosclerophorida) are known to be rich sources of structurally unique and biologically active isolates.[15] They are well known for their prolific production of bioactive polyketides, such as a large number of cyclic peroxides (**F2.1–F2.7**),[16] α-,γ-pyrones (**F2.8**–**F2.12**), butenolides (**F2.13**–**F2.15**), cyclic furan esters (**F2.16**–**F2.18**), and bicyclic lactones (**F2.19–F2.21**).[17–19] Thousands of compounds isolated from this vastly diverse group (genus *Plakortis*) have been found to exhibit a range of biological activities. Examples encompass anti-tumor (**F2.2–F2.5**, **F2.8–F2.21**)[15, 20–30] anti-fungal

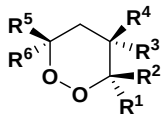
(**F2.20**),[20] anti-malarial (**F2.1**, **F2.6**),[28, 31] anti-bacterial (**F2.14**, **F2.15**),[17, 21, 32] anti-leishmanial (**F2.15**, **F2.18**, **F2.19**)[33] and other important pharmacological activities, including promotion of Ca^{2+} uptake in the cardiac sarcoplasmic reticulum (**F2.7, F2.19**).[33–35]



F2.1: R = $CH_2CH(Et)(CH)_2CH_2CH_3$

F2.2: R = $CH_2CH(Et)(CH_2)_2CH_3$

F2.3: R = $CH_2CH(Me)CH_2CH(Et)(CH_2)_3CH_3$

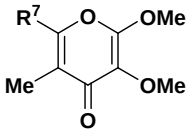


F2.4: R^1 = H; R^2 = CH_2COOMe; R^3 = H; R^4 = H; R^5 = $C_{13}H_{26}CH=CHCH=CHCH_3$; R^6 = OMe

F2.5: R^1 = CH_2COOH; R^2 = H; R^3 = Me; R^4 = H; R^5 = OMe; R^6 = $(CH_2)_7(CH)_2CH_3$

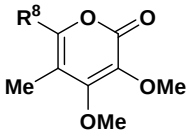
F2.6: R^1 = CH_2COOMe; R2 = H; R^3 = Me; R^4 = H; R^5 = OMe; R^6 = $(CH_2)_3(CH)_2=(CH)_2CH_2CH_3$

F2.7: R^1 = CH_2COOMe; R^2 = H; R^3 = Et; R^4 = H; R^5 = $(CH_2)_3CH(Et)(CH)_2CH_2CH_3$; R^6 =Et



F2.8: R^7 = $CH_2CH=C(Me)(CH_2)_2CH=C(Me)CH_2C(Me)=CHCH_2Ph$

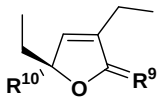
F2.9: R^7 = $CH_2CH=C(Me)(CH_2)_9SC(=O)H$



F2.10: R^8 = $CH_2CH=C(Me)(CH_2)_6Ph$

F2.11: R^8 = $CH_2CH=C(Me)(CH_2)_8Ph$

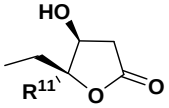
F2.12: R^8 =$(CH_2)_{10}SCH_3$



F2.13: R^9 = O; R^{10} = $(CH_2)_3CH(Et)CH_2(CH)_2CH_3$

F2.14: R^9 = CHCOOMe; R^{10} = $CH_2CH(Et)(CH_2)_3CH_3$

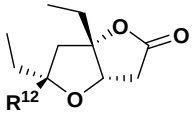
F2.15 R^9 = CHCOOMe; R^{10} = $CH_2C(Et)=CHCH(OH)CH_2CH_3$



F2.16: R^{11} = $CH=C(Et)CH_2CH(Et)(CH_2)_3CH_3$

F2.17: R^{11} = $CH_2CH(Et)CH_2CH(Me)(CH_2)_3CH_3$

F2.18: R^{11} = $CH_2CH(Et)CH_2CH(Et)(CH_2)_3CH_3$



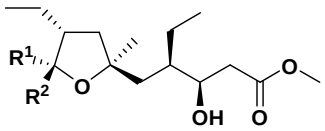
F2.19: R^{12} = $(CH_2)_3CH(Et)(CH)_2CH_2CH_3$

F2.20: R^{12} = $CH=C(Me)CH_2CH(Et)CH_2CH(Et)(CH)_2CH_2CH_3$

F2.21: R^{12} = $CH_2CH(Et)(CH)_2CH_2CH_3$

Figure 2. Selected bioactive polyketides isolated from genus *Plakortis*.

In addition to the aforementioned polyketides, plakortethers A–G isolated from the Caribbean sponge *Plakortis simplex*, exhibit unusual structure bearing a polysubstituted tetrahydrofuran ring. Biological studies on plakortethers A–G have concluded that the plakortethers A, B, D, and E are cytotoxic against the RAW 264–7 cell line with IC_{50} values of 7.9, 10.0, 8.4 and 11.6 μg/mL, respectively.[2]



F3.1 A R^1 = H, R^2 = CH=CHCH$_3$ (trans)
F3.2 B R^1 = H, R^2 = $CH_2CH_2CH_3$
F3.3 C R^1 = H, R^2 = $CHClCH_2CH_3$(*R*)
F3.4 D R^1 = H, R^2 = $C(=O)CH_2CH_3$
F3.5 E R^1 = H, R^2 = $CHOHCH_2CH_3$ (*S*)
F3.6 F R^1 = OMe, R^2 = H
F3.7 G R^1 = H, R^2 = OMe

Figure 3. Plakortethers A–G from *Plakortis simplex*.[2]

1.4 Synthetic progress towards the construction of polysubstituted tetrahydrofuran rings of polyketides from genus *Plakortis*

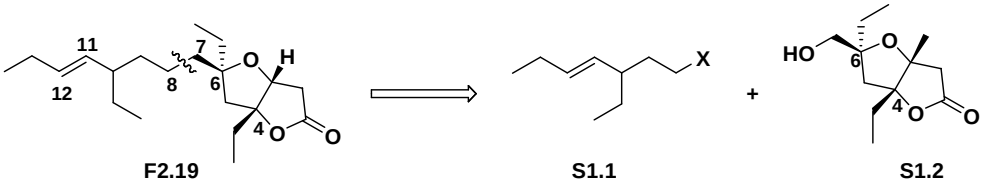
Even when showing promising and potent pharmacological activities, natural compounds isolated from marine organisms rarely raise the interest of pharmaceutical companies, because they are difficult to acquire in sufficient amounts for clinical use. Obtaining such compounds from natural resources means excessive harvesting of the marine organisms and destruction of the nature balance. The problem is to conciliate expansion requirements for human beings and protection of the marine environment and biodiversity. Oceans are showing increasing signs of overexploitation and degradation, ensuing in loss of both productivity and biodiversity. In this circumstance, an enormous collection of marine organisms producing compounds of industrial concern appears impractical, and total synthesis is one of the best possible ways to address this problem.

This chapter presents a review of reported synthetic advances made towards the total synthesis of selected polyketides, which bear a polysubstituted tetrahydrofuran ring,

along with the reported syntheses of plakortethers F and G (**F9.1–F9.7**). Further elaboration of different approaches towards the construction of polysubstituted tetrahydrofuran ring will be highlighted.

1.4.1 Total synthesis of plakortone D

Hayes *et al*.[36] were the first to report the total synthesis of plakortone D (**F2.19**). The authors clarified the uncertain structural and stereochemical features of this compound and also enabled the acquisition of other plakortones and analogues of the correct stereochemical series. The key disconnection is at C7-C8 thus providing lactone **S1.2** along with the side chain unit **S1.1**, which require control at C10 and eventually an *E*-double bond (C11-C12). The main focus of the total synthesis of plakortone D is to incorporate quaternary centers at C-4 and C-6 in the 2,6-dioxabicyclo[3.3.0]octan-3-one moiety of the plakortone core **S1.2** (Scheme 1).

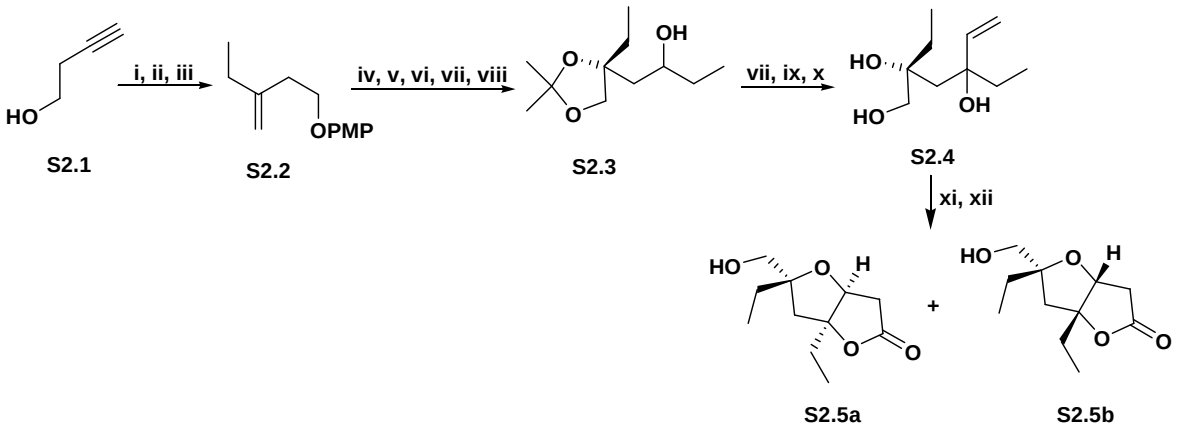


F2.19 **S1.1** **S1.2**

Scheme 1. Retrosynthetic analysis of plakortone D.[36]

The total synthesis is initiated by protection of 3-butyn-1-ol **S2.1** and conversion of the resulted alkyne to alkene **S2.2** (Scheme 2). Asymmetric dihydroxylation of compound **S2.2** by AD mix-β followed by deprotection, oxidation, and addition steps provided the sensitive triol **S2.4** as a mixture of diastereomers. The isomers is subjected to the Pd(II)-mediated lactone forming reaction cascade (hydroxycyclization,

carbonylation and lactonization), which resulted in the desired key intermediate **S2.5a** along with **S2.5b** in a separable mixture.[36–38]

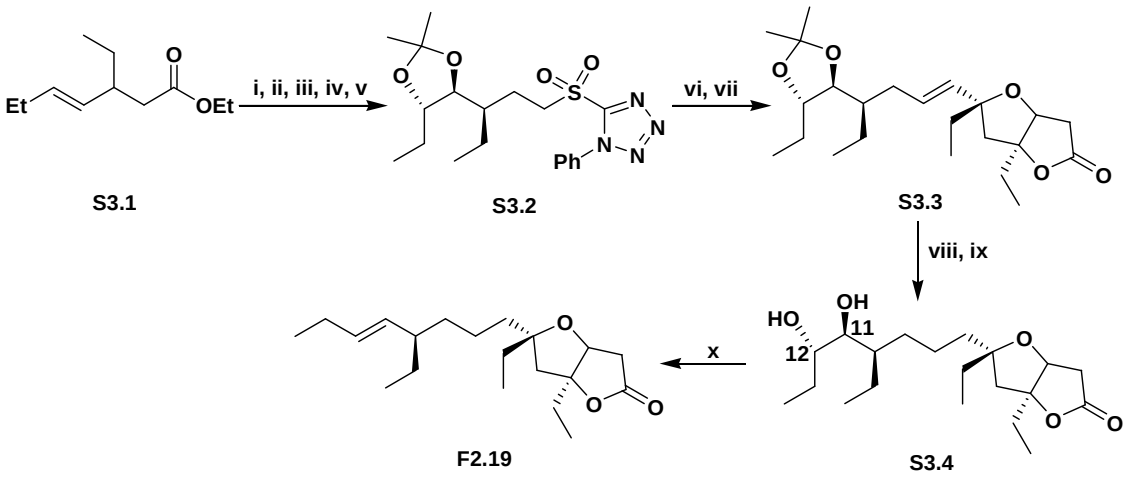


S2.1 S2.2 S2.3 S2.4 S2.5a S2.5b

i) DEAD, PPh_3, PMP; ii) 9-BBN; iii) EtMgBr, $Fe(acac)_3$; iv) AD Mix-b; v)$Me_2C(OMe)_2$, PTSA; vi) CAN; vii) TPAP/NMO; viii) EtMgBr; ix) CH_2=$CHMgBr$; x) Dowex 50; xi) $PdCl_2$, $CuCl_2$, NaOAc, AcOH, CO; xii) K_2CO_3

Scheme 2. Synthesis of the bicyclic lactones **S2.5a** and **S2.5b**.[36]

Sulfone **S3.2** is constructed *via* five steps starting from the *γ,δ*-unsaturated ester **S3.1** (Scheme 3). The previously prepared hydroxymethyl lactone **S2.5a** (Scheme 3) is oxidized to the corresponding aldehyde, which is immediately coupled with the anion of sulfone **S3.2** affording lactone **S3.3**. The key diol **S3.4** is obtained by removal of acetonide, followed by hydrogenation. Generation of the C11-C12 *E*-double bond is achieved by the stereospecific *syn* removal of the 1,2-diol using triethyl orthoformate. This afforded an orthoester, which provided plakortone D **F2.19**, after heating at 180 ^{o}C for 1 h.[36]



i) AD mix-β, $MsNH_2$; ii)LAH; iii) $Me_2C(OMe)_2$,PTSA; iv) 1phenyl-1*H*-tetrazole-5-thiol, DEAD, PPh_3; v) $(NH_4)_6Mo_7O_{24}.4H_2O$, H_2O_2; vi) KHMDS; vii) aldehyde of S2.5a; viii) MeOH, PTSA; ix) H_2/Pd-C; x) $HC(OEt)_3$

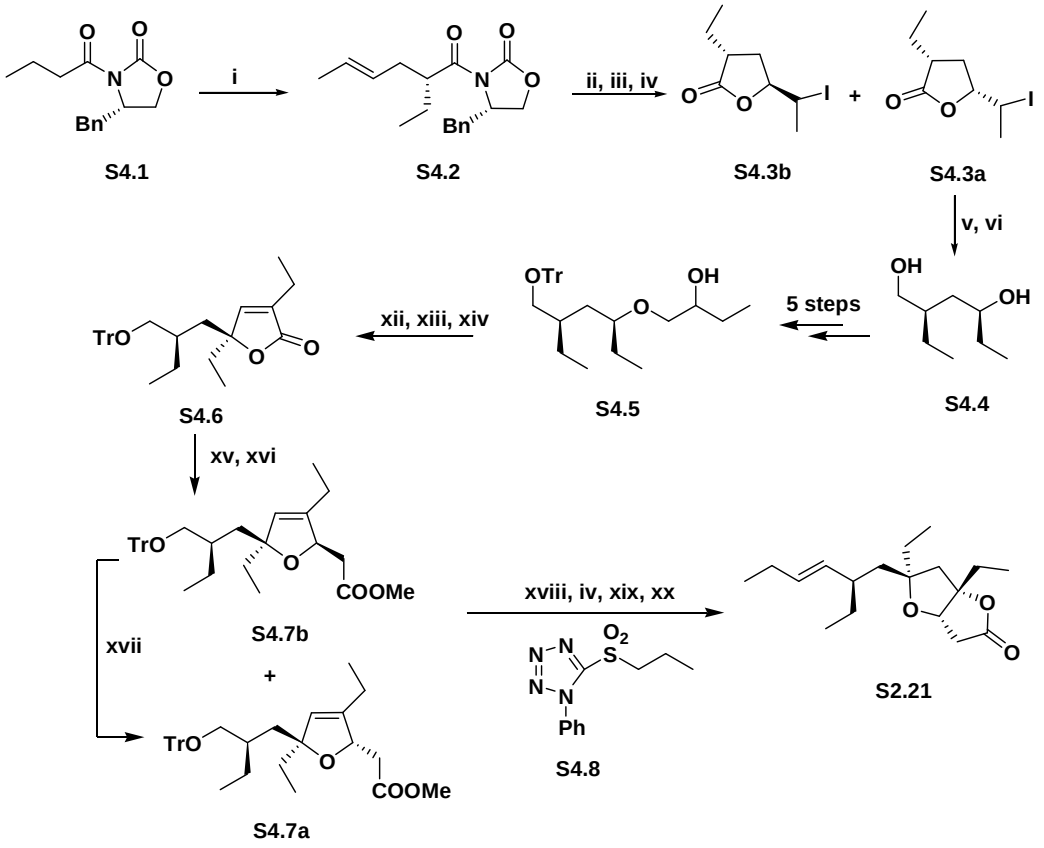
Scheme 3. Synthesis and structural confirmation of plakortone D.[36]

1.4.2 Total synthesis of Plakortone E

Although plakortone E (**S2.21**) has a bicyclic lactone moiety similar to plakortone D (**F2.19**), Akiyama *et al*. followed a different approach to construct the lactone rings for total synthesis of plakortone E.[27] The authors initiated the synthesis with Evans asymmetric alkylation of the chiral imide **S4.1** with crotyl bromide to get compound **S4.2** (Scheme 4). The chiral auxiliary in alkene **S4.2** is removed by hydrolytic cleavage with lithium hydroperoxide followed by iodolactonization of the resultant carboxylic acid to produce iodolactones **S4.3a** and **S4.3b** in a 2:1 ratio. Iodolactone **S4.3a** is separated from the mixture and reduced to the corresponding lactone, which is then treated with $LiAlH_4$ to furnish the diol **S4.4**. The resulted diol **S4.4** is transferred to alcohol **S4.5** *via* five steps.

Compound **S4.5** is then oxidized with IBX to the corresponding ketone, which on reaction with lithiotrimethylsilyldiazomethane in THF afforded dihydrofuran *via* C–H insertion reaction of the alkylidene carbene. Allylic oxidation of the dihydrofuran with

CrO_3 and 3, 5-dimethylpyrazole constructed lactone **S4.6** with proper stereochemistry. Reduction of **S4.6** with DIBAL-H followed by treatment of the resultant hemiacetal with methyl (triphenylphosphoranylidene)acetate is produced diastereomeric methyl esters **S4.7a** and **S4.7b** as a 1:1 mixture. The undesired ester **S4.7b** is converted into **S4.7a** through epimerization process. Finally, ester **S4.7a** is converted to the target plakortone E **F2.21** through four steps as shown in Scheme 4.

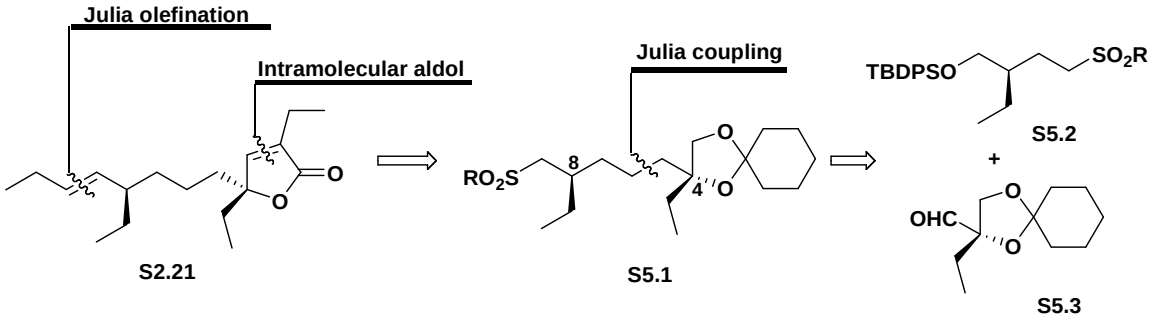


i) LDA, crotyl bromide; ii) H_2O_2, LiOH, THF-H_2O; iii) PivCl, Et_3N and then Me_2NH-HCl, Et_3N; iv) I_2, $NaHCO_3$; v) Bu_3SnH, AIBN; vi) LiAlH; vii) TrCl, Et_3N; viii) allyl bromide, NaH; ix) OsO_4, NMO; x) $NaIO_4$; xi) EtMgBr; xii) IBX, Py, DMSO; xiii) $TMSCHN_2$, BuLi; xiv) CrO_3, 3,5-dimethyl pyrazole; xv) DIBALH; xvi) $Ph_3PCHCO_2CH_3$; xvii) DBU; xviii) LiOH, EtOH-H_2O; xix) Bu_3SnH, AIBN; xx) S4.8, KHMDS

Scheme 4. Asymmetric synthesis of plakortone E.[27]

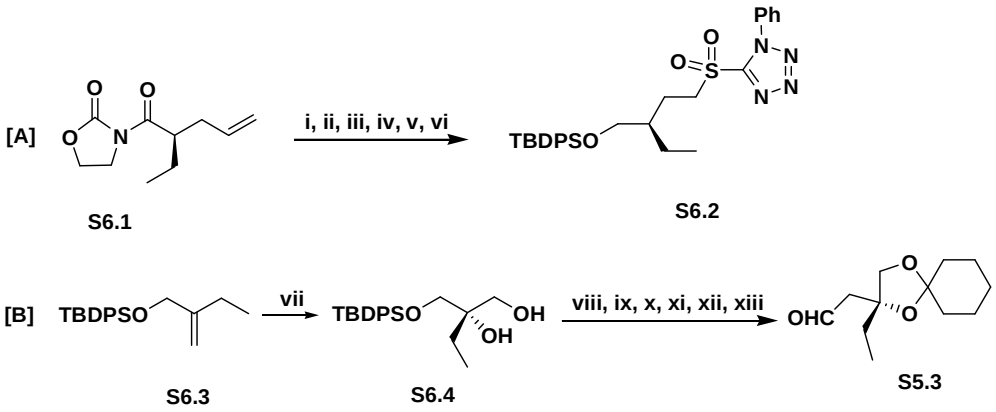
1.4.3 Total synthesis of Plakortone G

Kowashi *et al.* have reported the successful total synthesis of plakortone G (**F2.13**).[29] The authors used intramolecular aldol reaction to construct an α,β-unsaturated-γ-lactone moiety as indicated in Scheme 5. Selective *E*-olefination is approached *via* a Julia olefination. Introduction of the C-4 and C-8 chiral centers is performed before construction of **S5.1** by the Julia coupling reaction between the sulfone unit **S5.2** and the aldehyde unit **S5.3** (Scheme 5).



Scheme 5. Retrosynthetic analysis of plakortone G.[29]

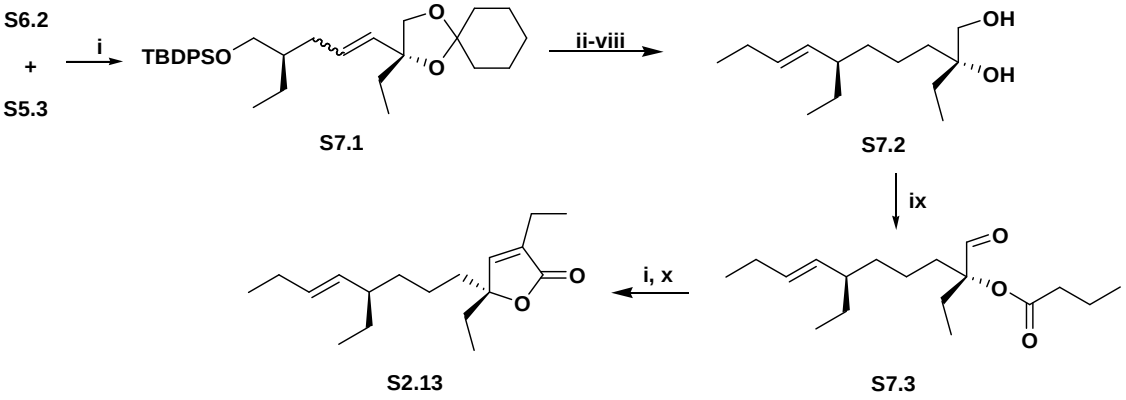
The synthesis of pakortone G required two major precursors, sulfone **S6.2** and aldehyde **S5.3** (Scheme 6). The authors prepared sulfone **S6.2** in six steps, starting with the acyl oxazolidinone derivative **S6.1**. Interlocution of the first chiral center (**S6.4**) is performed by exposing alkene **S6.3** to the asymmetric dihydroxylation conditions. The resulted diol **S6.4** is converted to the target aldehyde **S5.3** in five steps.



i) $LiBH_4$; ii) TBDSCl, ImH, MS 4Å ; iii) OsO_4, NMO, $NaIO_4$; iv) $NaBH_4$;
v) 1-phenyl-1*H*-tetrazole-5-thiol, DIAD, *n*-Bu_3P; vi) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, H_2O_2; vii) AD mix-α;
viii) cyclohexanone dimethylacetal, CSA; ix) TBAF; x) PNBCl, Py; xi) recrystallization;
xii) K_2CO_3; xiii) SO_3•Py, DMSO, Et_3N

Scheme 6. [A] Preparation of precursor **S6.2**; [B] Preparation of precursor **S5.3**.[29]

The modified Julia coupling reaction of sulfone **S6.2** with the aldehyde unit **S5.3** produced alkene **S7.1** as a mixture of the geometric isomers (Scheme 7). Diol **S7.2** is prepared in seven steps from compound **S7.1**. Oxidation of the primary alcohol in **S7.2**, and successive acylation afforded **S7.3**, a precursor of the intramolecular aldol reaction. Cyclization of compound **S7.3** with LiHMDS followed by dehydration with MsCl/Et_3N gave desired plakortone G (**F2.13**).[29]

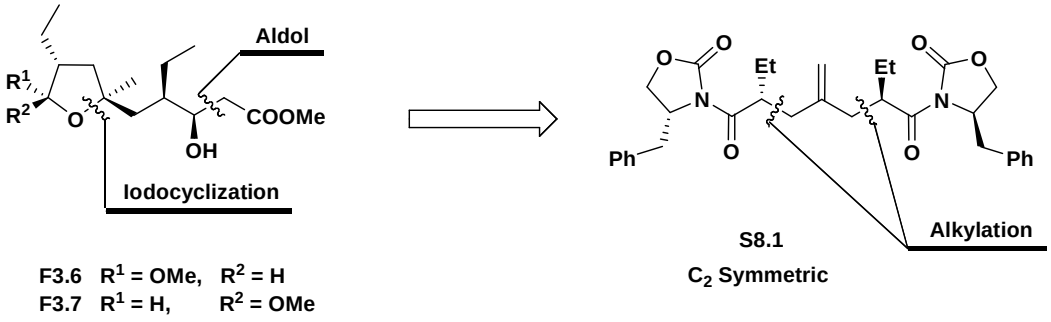


i) LiHMDS; ii) H_2, $Pd(OH)_2$-C; iii) TBAF; iv) TsCl, Et_3N; v) 1-phenyl-1*H*-tetrazole-5-thiol, *t*-BuOK;
vi) LiHMDS, propanal, DME; vii) 2M HCl; viii) SO_3.Py, DMSO, Et_3N; ix) *n*-PrCOCl, DMAP; x) MsCl, Et_3N

Scheme 7. Total synthesis of plakortone G.[29]

1.4.4 Total synthesis of plakortethers F and G

A retrosynthetic plan for the syntheses of plakortethers F (**F3.6**) and G (**F3.6**) is designed in Dr. Novikov's group by recognizing the symmetry of intermediate **S8.1**.[18] The disconnection of the 3-hydroxyester *via* acetate aldol condensation and the tetrahydrofuran ring *via* iodocyclization lead to the C_2-symmetric intermediate **S8.1**. This intermediate is assembled *via* a bis-alkylation of allylic dihalide by a chiral auxiliary-modified butyrate (Scheme 8).

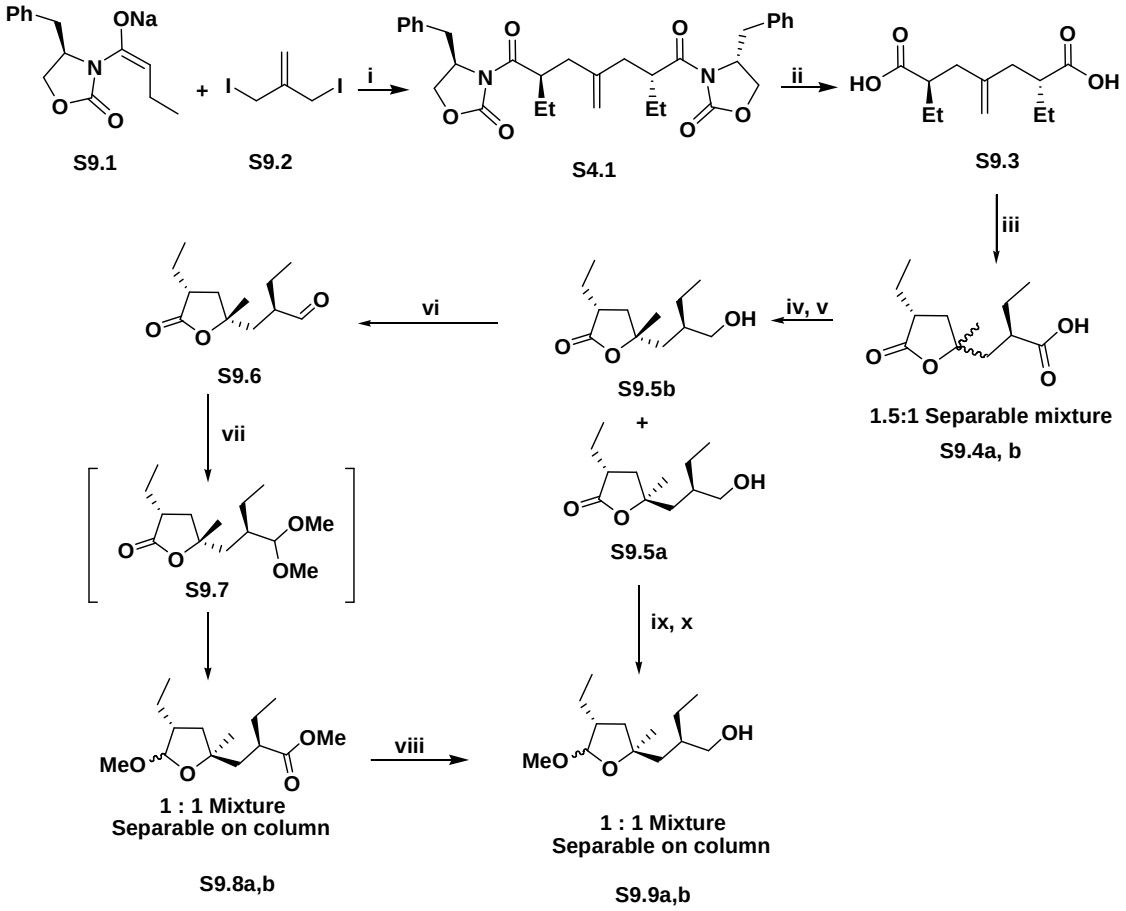


Scheme 8. Retrosynthetic analysis of plakortethers F and G.[18]

The total synthesis is initiated with bis-alkylation of 3-iodo-2-(iodomethyl)prop-1-ene **S9.2** with the enolate of oxazolidinone **S9.1** (Scheme 9). Peroxide-assisted hydrolysis followed by cyclization with trifluoroacetic acid at room temperature resulted in diastereomeric lactonic acids **S9.4a** and **S9.4b** as a separable mixture in a ratio of 1.5:1. The conversion of the lactone acids **S9.4a** and **S9.4b** to the corresponding alcohols **S9.5a** (minor) and **S9.5b** (major) is accomplished in two steps.

As shown in Scheme 9, the major diastereomer **S9.5b** is converted to the desired key intermediates **S9.9a** and **S9.9b**. Oxidation of **S9.5b** followed by the treatment with *para*-toluenesulfonic acid in methanol afforded a 1:1 separable mixture of diastereomers **S9.8a** and **S9.8b**. The resulted acetals **S9.8a** and **S9.8b** are then reduced to their

corresponding alcohols **S9.9a** and **S9.9b**. Reduction of the minor diastereomer **S9.5a** followed by treatment with *para*-toluenesulfonic acid in methanol yielded in alcohols **S9.9a** and **S9.9b** as a 1:1 mixture. Diastereomers **S9.9a** and **S9.9b** are isolated as pure compounds after separation.[18]

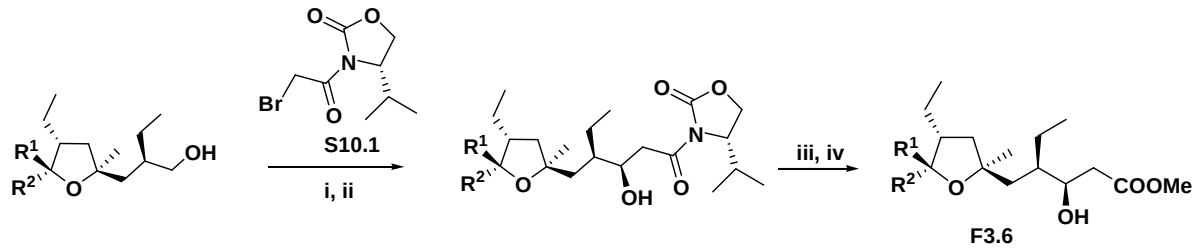


i) -55 °C, 24 h; ii) LiOH-H_2O_2, THF-H_2O; iii) TFA, 8 h; iv) BuOCOCl, Et_3N; v) $NaBH_4$; vi) Swern oxidation; vii) MeOH, TsOH, 24 h; viii) LAH; ix) DIBAL; x) Py•TsOH, MeOH

Scheme 9. Preparation of the key intermediates **S9.9a** and **S9.9b**.[18]

The separated diastereomers **S9.9a** and **S9.9b** are independently converted to plakortether F (**F3.6**) and plakortether G (**F3.7**). Alcohols **S9.9a** and **S9.9b** are independently subjected to the Swern oxidation followed by SmI_2-iodide mediated Reformatsky reaction, hydrolysis, and esterification. This reaction sequence is provided

methyl esters **S3.6** and **S3.7** (Scheme 10). Successful synthesis of plakortether F is confirmed by matching the synthesized plakortether F with reported physical data of the compound.[18]



S9.9a $R^1 = H; R^2 = OMe$
S9.9b $R^1 = OMe; R^2 = H$

S10.2a $R^1 = H; R^2 = OMe$
S10.2b $R^1 = OMe; R^2 = H$

S3.6 $R^1 = H; R^2 = OMe$
S3.7 $R^1 = OMe; R^2 = H$

i) Swern oxidation; ii) compound S10.1, SmI_2, THF, -78 ^oC; iii) $LiOH-H_2O_2$; iv) $TMSCHN_2$

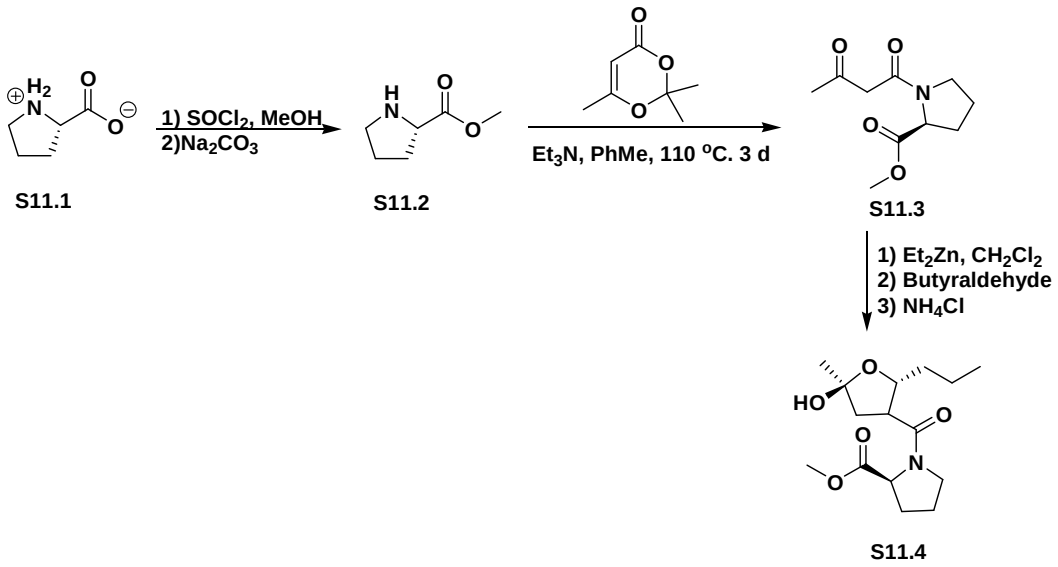
Scheme 10. Completion of the synthesis of plakortether F (**S3.6**) and plakortether G (**S3.7**).[18]

1.4.5 Progress towards the synthesis of plakortether B through a zinc-mediated homologation

In the synthesis of plakortethers F (**S3.6**) and G (**S3.7**) by John *et al.*, the resulted cyclized key product **S9.4** from acid-mediated cyclization step is poorly diastereoselective.[18] Zercher and co-workers intended to address this issue by utilizing the tandem homologation-aldol reaction as the key step to construct the plakortether core during the approach towards plakortether B (**S3.2**). Although the synthetic trials performed to establish proper stereocenters at the tetrahydrofuran ring using such homologation method were not successful, the method starting with L-proline is synthetically interesting and hence, it is worth to discuss.[39]

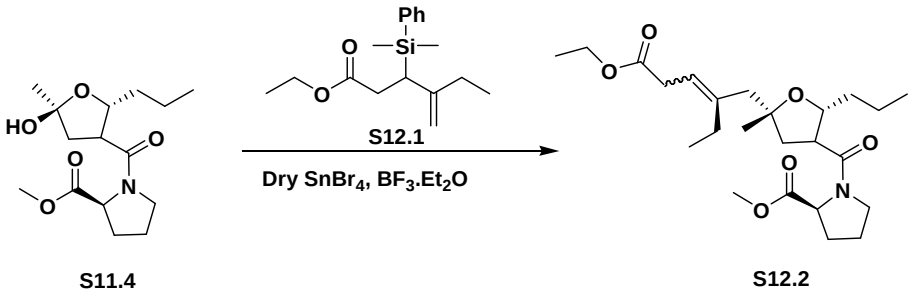
As shown in Scheme 11, the methyl ester of commercially available L-proline (**S11.2**) is obtained *via* an acid-catalyzed esterification of the amino acid **S11.1** in methanol. The resulting cyclic amine **S11.2** is added to the diketene acetone adduct and

refluxed in toluene for three days. The expected product *β*-keto amide **S11.3** is isolated only in low yields after purification. The *β*-keto amide is subjected to tandem homologation-aldol reaction conditions. The resulting crystal structure of the major isomer **S11.4** revealed that the homologation-aldol reaction of *β*-keto amides is *syn*-selective. Even though L-proline-induced stereocontrol provided the incorrect absolute configuration for the formation of naturally occurring plakortether B, the authors decided to perform subsequent model studies using the synthesized intermediate.



Scheme 11. Synthesis of chiral *β*-keto amide **S11.4**.[39]

As shown in Scheme 12, the advanced intermediate **S12.2** is synthesized by reductive allylation of the previously prepared enantiopure hemiketal **S11.4** exploiting the substituted allylsilane (**S12.1**) and $BF_3 \cdot Et_2O$.



Scheme 12. Reductive allylation of compound **S11.4**.[39]

The authors concluded the synthesis by providing several important suggestions as follows. The amide moiety of **S12.2** can be reduced chemoselectively using Wittig reaction followed by a selective reduction of the terminal alkene, which would afford the ethyl moiety embedded in plakortether B. The authors have also suggested that it would be possible to obtain the enantiomer of plakortether B by performing a diastereoselective hydroboration-oxidation of the trisubstituted alkene. Finally, the authors pointed out the importance and possibility of utilizing D-proline instead of L-proline, to obtain the plakortether core with correct stereochemistry during the tandem homologation-aldol reaction.[39]

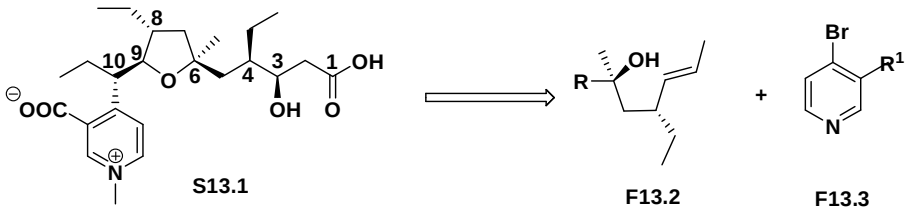
1.4.6 Diastereoselective Pd-catalyzed carboetherification reaction to establish polysubstituted tetrahydrofuran in simplakidine A

Even though there are developed synthetic methodologies to construct polysubstituted tetrahydrofuran rings, this research area is still challenging, due to low efficiency of the available methods. Ward *et al.*[40] were trying to discourse this issue by consuming a Pd-catalyzed carboetherification reaction developed in their research group to establish polysubstituted tetrahydrofuran rings. The authors demonstrated high

efficiency of the developed method in constructing polysubstituted tetrahydrofuran ring of Simplakidine A (**S13.1**).[40]

Simplakidine A (**S13.1**) is a unique 4-alkyl substituted pyridinium alkaloid isolated from the Caribbean sponge *Plakortis simplex* and also an unique example of a trigonelline nucleus substituted at position C-4 with a complex polyketide-derived moiety. Although Simplakidine A exhibits weak cytotoxicity due to its high polarity, this molecule is synthetically important since it shares its basic backbone and the polysubstituted tetrahydrofuran ring with that of plakortethers A–G.[41, 42]

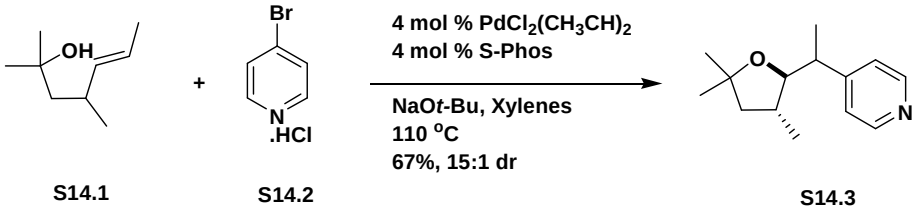
As shown in Scheme 13, the authors envisioned the retrosynthetic analysis by generating tetrahydrofuran core through a Pd-catalyzed carboetherification between a tertiary alcohol bearing a pendant *E*-alkene **S13.2** and a suitably substituted 4-bromopyridine derivative (**S13.3**). The construction of the desired stereocenters at C9 and C10 is intended to be accomplished *via* a ring-closing reaction.[40]



Scheme 13. Strategy for the synthesis of Simplakidine A (**S13.1**).[40]

Ward *et al*. assumed that the two substituents on C6 of Simplakidine A (Scheme 13) are approximately close in size (e.g., Me *vs i*-Bu).[40] Due to this reason, it is suggested that the diastereotopic face selectivity of the alkene carboetherification reaction could likely be controlled by the stereochemical configuration at C8 of substrate **S13.2** rather than C6. Hence, the simple tertiary alcohol **S14.1** is chosen to be a reasonable

approximation to **S13.2** for the model study. The Pd/S-Phos-catalyzed coupling of alcohol **S14.1** with 4-bromopyridine hydrochloride resulted in the desired moiety **S14.3** with 15:1 *dr* in 67% yield (Scheme 14).



Scheme 14. Model scheme to study the developed transformation towards polysubstituted tetrahydrofuran ring in Simplakidine A.

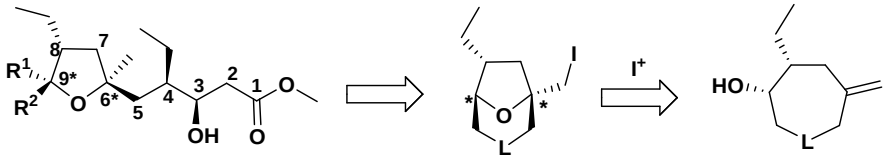
CHAPTER II

AN APPROACH TO THE TOTAL SYNTHESIS OF PLAKORTETHERS A–E

Successful syntheses of plakortethers F (**F3.6)** and G (**F3.7)** were carried out in our research group by taking advantage of the C_2 symmetry in the structure (discussed in Chapter I, Section 1.4.4).[18] However, there are no reports on the synthesis of plakortethers A–E (**F3.1**–**F3.5**). Because of the above reason and their biological activity (Section 1.3, Scheme 3), our research was extended to develop a synthetic route to plakortethers A–E along with possible derivatives.

2.1 Synthetic approach towards plakortethers A–E *via* trans-annular iodocyclization

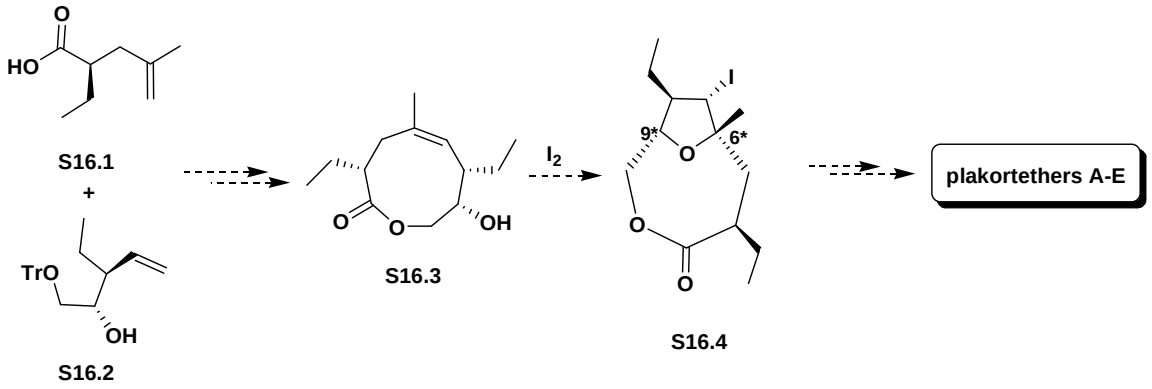
Synthesis of plakortethers A–E is more challenging than that of the F and G counterparts, and it requires construction of a tetrasubstituted tetrahydrofuran ring with the correct stereochemistry of the chiral centers at both C-6 and C-9 positions. To address this challenge, initially it was envisioned to use trans-annular iodocyclization to obtain the embedded tetrasubstituted tetrahydrofuran ring in plakortethers (Scheme 15).[43]



F3.0 **S15.1** **S15.2**

Scheme 15. Retrosynthetic analysis of plakortethers A–E.

Bicyclic lactone **S16.4** was proposed as the key intermediate of the synthesis of the targeted plakortether core *via* trans-annular iodocyclization. As shown in Scheme 16, the key intermediate **S16.4** was intended to be obtained by coupling acid **S16.1** with alcohol **S16.2** followed by ring-closure metathesis (RCM). Iodocyclization of macrolactone **S16.3** would produce bicyclic lactone **S16.4**, which could be converted to plakortethers A–E. The synthesis of starting acid **S16.4** was successful, while preparation of the desired alcohol **S16.2** demonstrated synthetic difficulties. Therefore, the synthetic route towards plakortether core through such key intermediate was closed.[43]



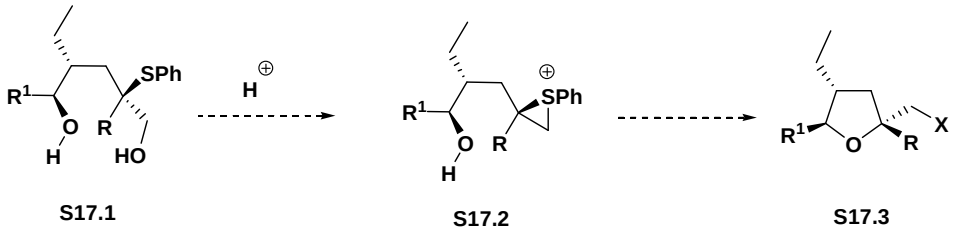
Scheme 16. Synthetic plan towards plakortethers A–E *via* trans-annular iodocyclization.

2.2 Synthetic approach towards plakortethers A–E based on episulfonium ion

2.2.1 Key step of the reactions: assembly of the tetrasubstituted tetrahydrofuran ring

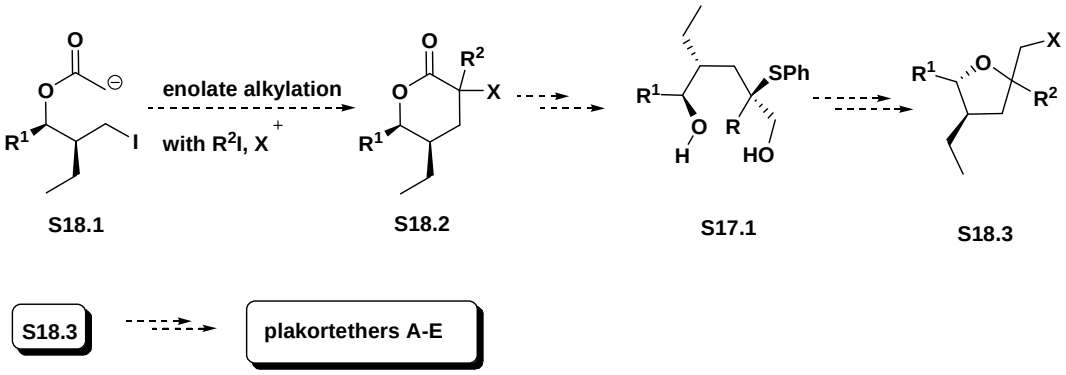
The aforementioned situation prompted us to explore an alternate synthetic pathway to construct the tetrasubstituted tetrahydrofuran ring, which does not rely on trans-annular iodocyclization. As a result, assembly of the tetrasubstituted tetrahydrofuran ring was proposed to be achieved through stereoselective cyclization

promoted by reacting episulfonium ion **S17.2** with hydroxyl group in the same molecule (Scheme 17).



Scheme 17. Synthetic plan to assemble the tetrasubstituted tetrahydrofuran ring **S17.3**.

The episulfonium ion can be generated from diol **S17.1**, which is readily available from six-membered lactone **S18.2** (valerolactone). Therefore, our initial goal was to synthesize valerolactones. The sequence outlined in Scheme 18 was used for an approach towards lactones.

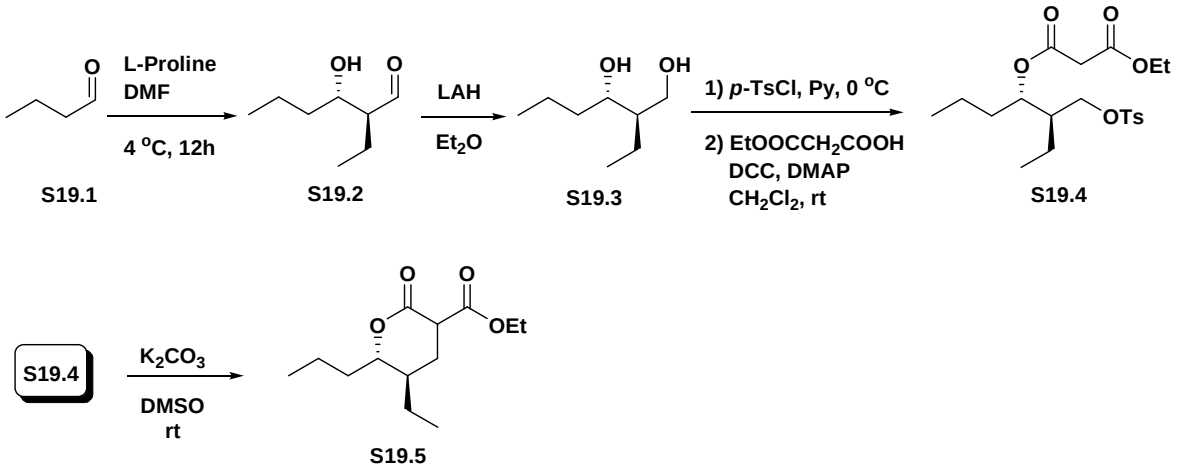


Scheme 18. Assembly of the tetrasubstituted tetrahydrofuran ring in compound **S18.3**.

2.2.2 Attempt to synthesize the valerolactone

The approach was initiated by establishing chiral centers in **S19.2** through direct asymmetric aldol self-condensation of propanaldehyde using L-proline as a catalyst in dimethylformamide (Scheme 19).[44] Resulting aldehyde **S19.2** was reduced to diol **S19.3**

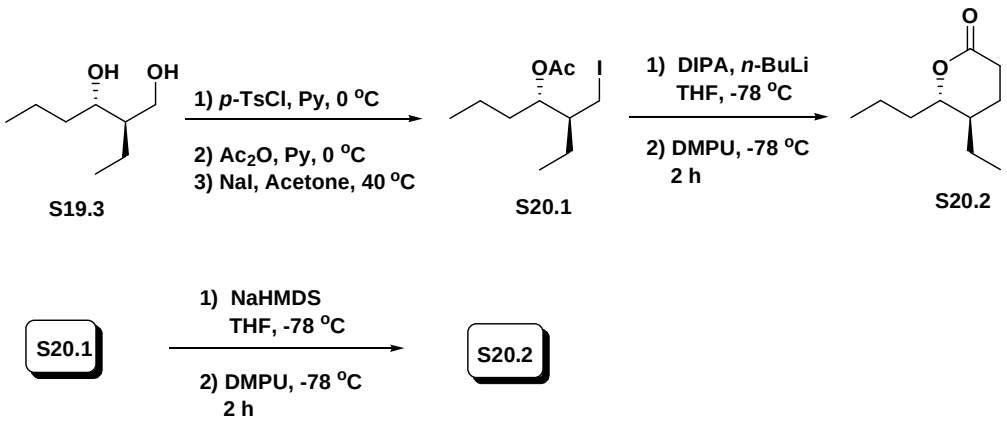
with $LiAlH_4$. Subsequently, the primary hydroxyl group of diol **S19.3** was tosylated followed by Steglich esterification of the secondary alcohol with 2-(ethoxycarbonyl)acetic acid, DCC and DMAP, which gave ester **S19.4**. Lactonization was carried out by exposing the obtained ester **S19.4** to potassium carbonate and dimethylsufoxide. The ^{1}H NMR data of the crude product did not prove the formation of lactone **S19.5**. This provoked us to modify the synthetic scheme mainly by changing the conditions for the cyclization step.



Scheme 19. Attempt to prepare valerolactone **S19.5**.

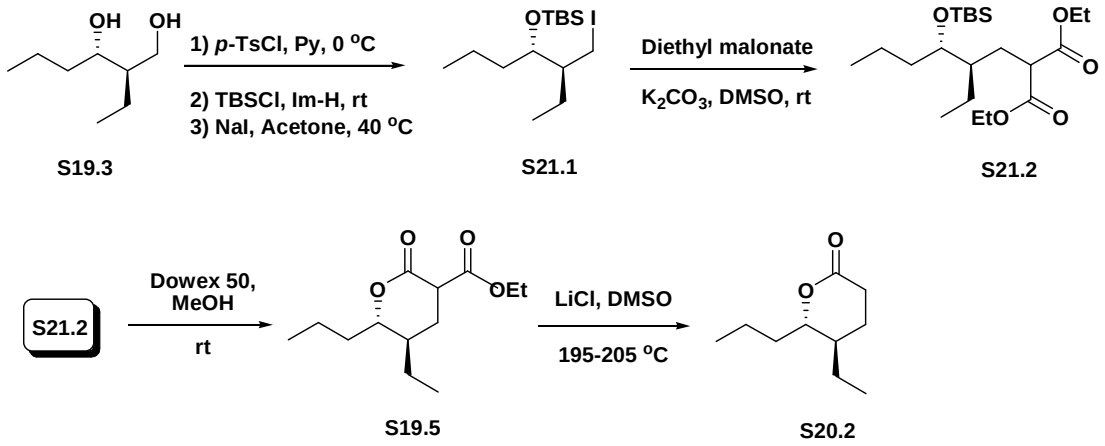
Preparation of valerolactone **S20.2** (Scheme 20), in turn, would require diol **S19.3**, which was previously prepared (Scheme 19). Monotosylation of the primary alcohol in diol **S19.3**, then acetylation of the secondary alcohol followed by detosylation with iodine resulted in compound **S20.1** (Scheme 20). Cyclization of **S20.1** was tried in the presence of NaHMDS and freshly prepared LDA with and without DMPU.[45] The trials without DMPU ended up giving the starting material or unidentified products. When reactions were carried out under the same conditions (with NaHMDS or freshly prepared LDA) in the presence of DMPU, ^{1}H NMR of the resulting compound was

compatible with that of valerolactone **S20.2** shown in Scheme 20. This shows that the polar aprotic solvent significantly assists the reaction. A satisfactory purification method has yet to be developed due to the volatility of the valerolactone.



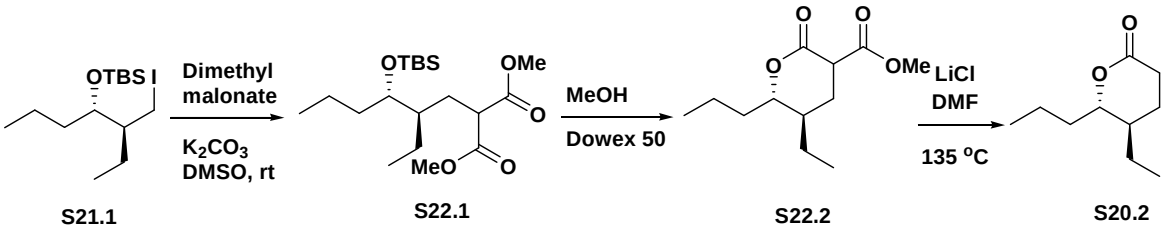
Scheme 20. Attempt to prepare valerolactone **S20.2** *via* different cyclization conditions.

Meanwhile different approaches were carried out to obtain valerolactone **S20.2** as shown in Schemes 21 and 22. The primary hydroxyl group of diol **S19.3** was tosylated and the secondary OH moiety was protected by TBS followed by substitution with iodide resulting in compound **S21.1**. The TBS-protected iodide **S21.1** was exposed to diethyl malonate in the presence of potassium carbonate and dimethyl sulfoxide to produce **S21.2**. Valerolactone **S19.5** was obtained from **S21.2** with Dowex 50 and methanol and then subjected to the Krapcho decarboxylation[46, 47] conditions (lithium chloride in dimethyl sulfoxide at 195–205°C). ^{1}H NMR spectrum showed some significant peaks to prove the formation of the desired valerolactone **S20.2**. Once again the purification method has to be improved due to the volatility of valerolactone.



Scheme 21. A synthesis of valerolactone **S20.2**.

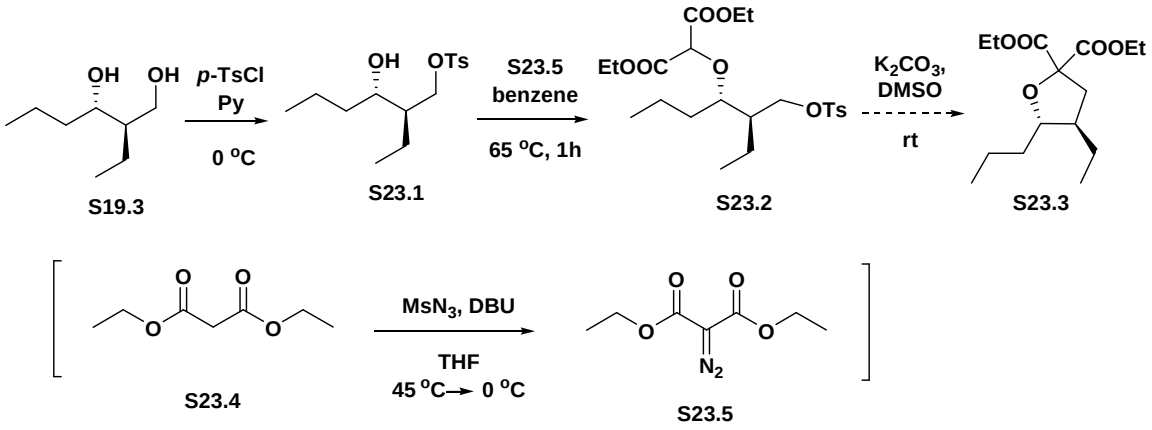
Diethyl malonate used in Scheme 21 was replaced with the dimethyl malonate analogue in Scheme 22 due to the possibility of decarboxylation of methyl ester at lower temperatures (135 °C rather than 195 °C) in the presence of dimethylformamide and lithium chloride. These conditions also resulted in a crude product with trace amounts of valerolactone **S20.2**. This could be mainly due to the high temperatures applied during decarboxylation.



Scheme 22. Modified reaction pathway by replacing diethyl malonate with dimethyl malonate.

Parallel to the reaction sequence shown in Scheme 22, preparation of the cyclic compound **S23.3** as a part of the assembly of the tetrasubstituted tetrahydrofuran ring in compound **S17.3** was investigated (Scheme 23). The monotosylated derivative **S23.1** was synthesized from diol **S19.3** with *p*-TsCl and pyridine at 0 °C and was exposed to diethyl

diazomalonate (preparation was carried out with MsN_3 and DBU on diethyl malonate) to obtain compound **S23.2**.[48] Cyclization of crude **S23.2** was attempted in the presence of potassium carbonate and dimethyl sulfoxide. Unexpectedly, the signals of tetrahydrofuran ring **S23.3** were not detected in the ^{1}H NMR spectrum of the reaction mixture.

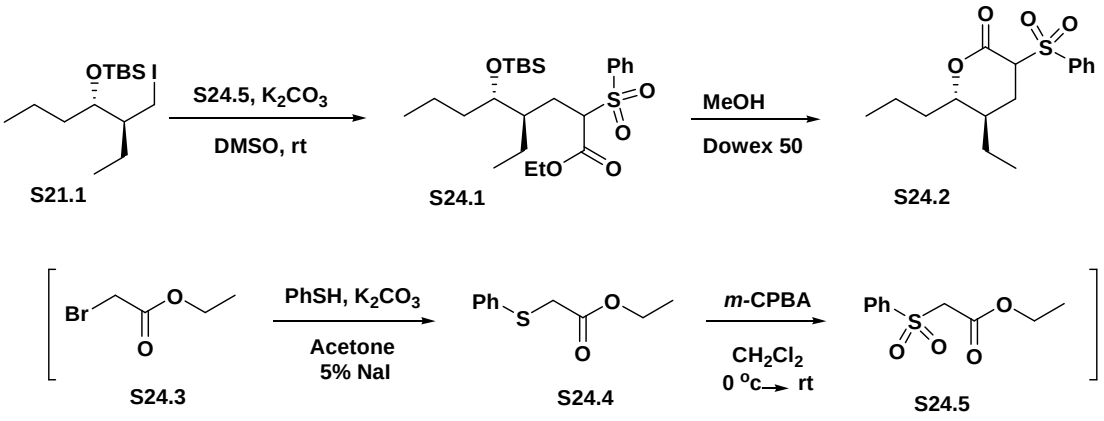


Scheme 23. Attempt to obtain cyclize compound **S23.5** using diethyl diazomalonate.

Due to the complications encountered during the preparation of valerolactone, diethyl and dimethyl malonates were replaced with phenylsulfonylacetate **S24.5** (Scheme 24) to ensure easier handling during the synthesis, by elevating the boiling point of the resulting valerolactone **S24.2**. To prepare sulfone **S24.5**, halide **S24.3** was subjected to nucleophilic substitution by thiophenol in the presence of potassium carbonate and catalytic amounts of sodium iodide in refluxing acetone. The resulting ethyl 2-(phenylthio)acetate **S24.4** was oxidized to phenylsulfonylacetate **S24.5** by using excess *m*-CPBA in dichloromethane.[49]

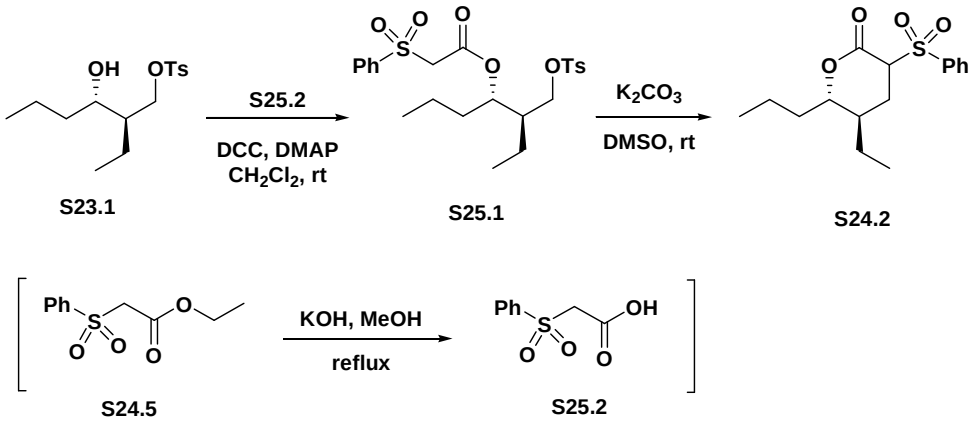
The TBS-protected **S21.1** was exposed to phenylsulfonylacetate **S24.5** in the presence of potassium carbonate and dimethyl sulfoxide to obtain **S24.1** (Scheme 24). The starting material was recovered from this reaction upon treatment with Dowex 50

and methanol. Cyclization also attempted on compound **S24.1** using *p*-TsOH and ethanol in dichloromethane; however, this transformation provided only unidentified products. From the observations it is clear that the main challenge of the proposed synthetic scheme comes from the cyclization step. This could be due to improper orientation of the reaction sites. This hypothesis was achieved by changing the positions of the substitute sites (Scheme 25).



Scheme 24. Attempt to prepare valerolactone **S24.2** using phenylsulfonylacetate **S24.5**.

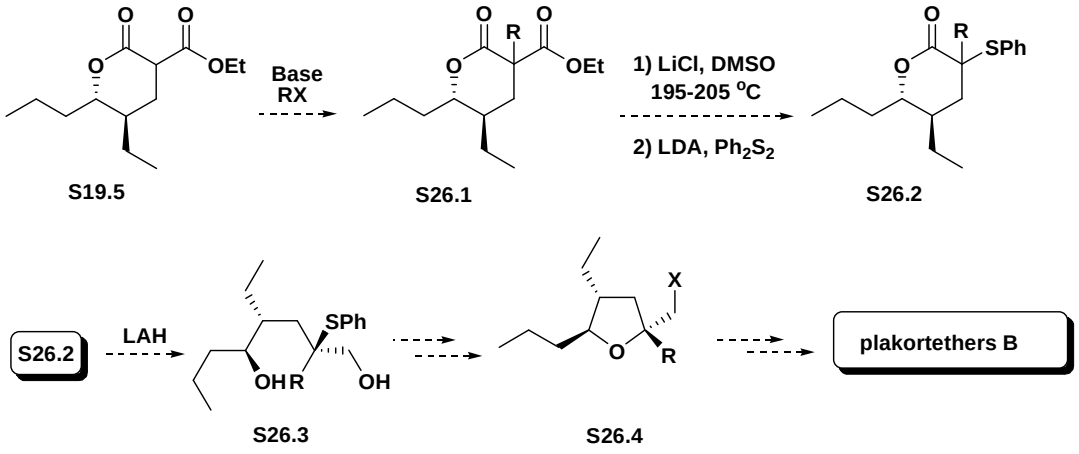
The cyclization was attempted using an alternative synthetic route as shown in Scheme 25. The previously prepared alcohol **S23.1** was esterified using DCC, DMAP and carboxylic acid **S25.2** (prepared by hydrolysis of ester **S24.5** as shown in Scheme 25).[50] Sulfone **S25.1** was exposed to potassium carbonate and dimethyl sulfoxide, which yielded a mixture of unidentified products and no trace of the desired compound was found in the ^{1}H NMR spectrum of the crude product. Similar results were obtained in the preparation of valerolactone **S24.2** from compound **S25.1**, sodium hydride in tetrahydrofuran.



Scheme 25. Attempt to prepare valerolactone **S24.2** following an alternative synthetic route.

2.2.3 A plan for further use of the prepared lactone

As explained in the previous sections, decarboxylation of **S19.5** was problematic due to the formation of the highly volatile valerolactone **S20.2**. Bearing a substituent on valerolactone **S26.1** would help reduce volatility during the decarboxylation step. Therefore, Scheme 26 was suggested, a modification of Scheme 19 to obtain a valerolactone with a substituent R at 4th position, which would ensure easier handling of the substrate.



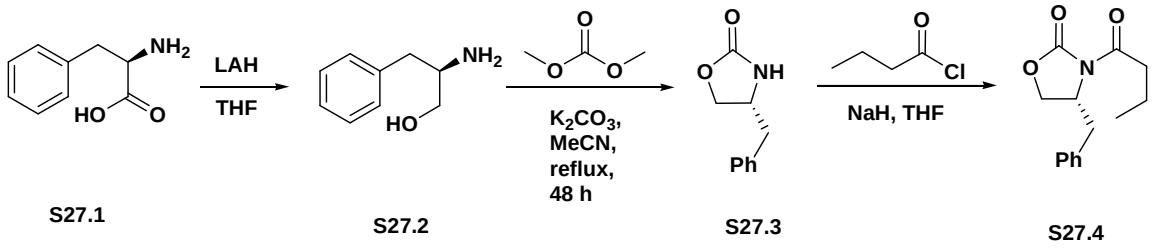
Scheme 26. A proposed synthetic pathway to obtain a substituted tetrahydrofuran ring.

Valerolactone **S19.5** could be alkylated to obtain its derivative **S26.1**. Decarboxylation with lithium chloride in DMSO at 195–205 °C followed by the PhS group substitution in the presence of Ph_2S_2 and LDA should result in the formation of PhS-substituted valerolactone **S26.2**. LAH reduction of valerolactone **S26.2** should form **S26.3**, which is expected to be converted to the five-membered key intermediate **S26.4**.

2.3 Preparation of the unified substrate for synthesis of plakortethers A–E

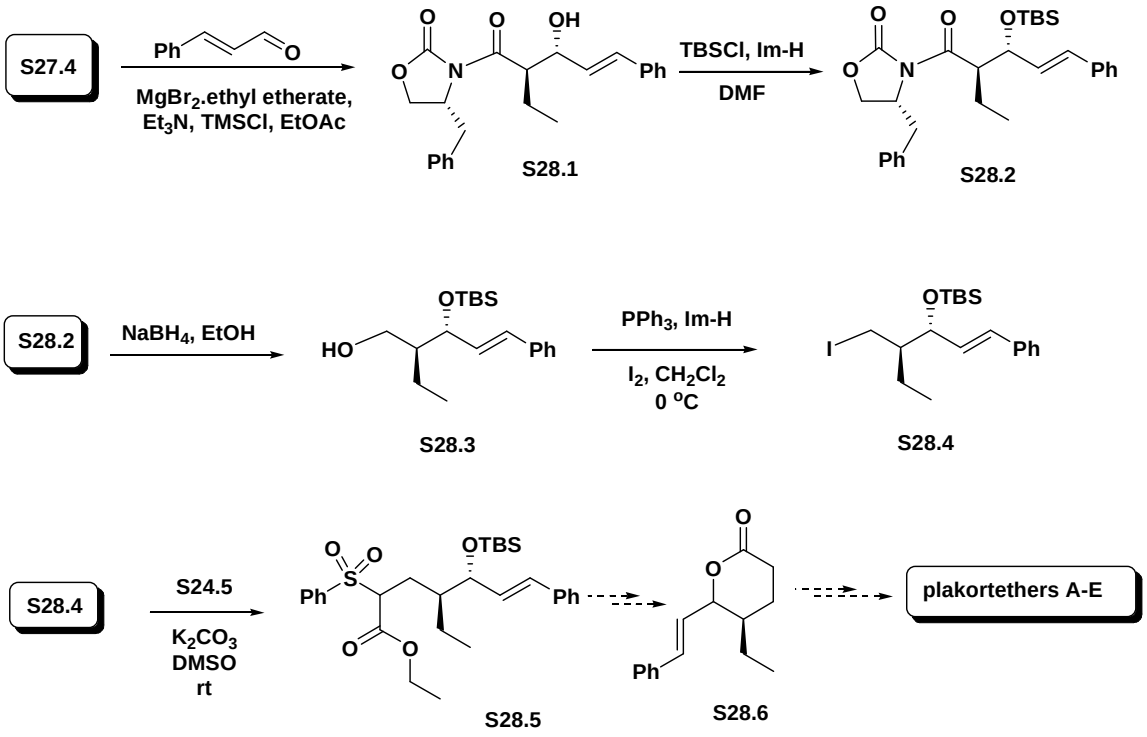
Although the above discussed synthetic routes were planned only to proceed towards plakortether B, the proposed valerolactone **S28.6** (Scheme 28) would be a potential intermediate in the synthesis of plakortethers A–E. Its preparation, in turn, requires enantiopure alcohol **S28.3**, which can be prepared using a chiral auxiliary.

The auxiliary **S27.3**, developed in Evans' group, was selected for this purpose.[51, 52] It was prepared from commercially available phenylalanine **S27.1**. Alcohol **S27.2** was obtained by reducing carboxylic acid **S27.1** with LAH. The Evans oxazolidinone **S27.3** was successfully synthesized by refluxing alcohol **S27.2** for 48 h with dimethyl carbonate in the presence of potassium carbonate as a base.[53] Oxazolidinone **S27.3** was then acylated with butyryl chloride using sodium hydride to result in the acylated chiral auxiliary **S27.4**.[43]



Scheme 27. Synthesis of acylated chiral auxiliary **S27.4**.

The oxazolidinone derivative **S28.1** was obtained by aldol condensation of **S27.4** with cinnamaldehyde in the presence of $MgBr_2$·ethyl etherate, triethylamine, TMSCl and ethyl acetate.[54] TBS-protection of the alcohol by TBSCl and imidazole in dimethylformamide followed by reductive cleavage of the chiral auxiliary resulted in alcohol **S28.3**. This compound was converted to the iodinated derivative **S28.4** using PPh_3, imidazole and iodine in dichloromethane.[55] Since it is difficult to remove PPh_3 from the reaction mixture during the purification process, an alternative method was followed to prepare iodinated compound **S28.4**. Alcohol **S28.3** was first tosylated in the presence of *p*-TsCl and pyridine followed by detosylation with iodine (acetone, sodium iodide at 40 ^{o}C), which also resulted in **S28.4** with a compatible yield. Iodide **S28.4** was exposed to ester **S24.5** to produce sulfone **S28.5**. Initial purification using column chromatography on silica gel gave a mixture of products. Therefore, the optimization of the purification method is necessary for this step.



Scheme 28. Attempt to prepare the unified substrate **S28.6** for the synthesis of plakortethers A–E.

2.4 Conclusion

In summary, during the approach to plakortethers A–E, the key efforts were directed at assembling the tetrahydrofuran ring containing two stereocenters at positions C-6 and C-9. This was proposed to be achieved through stereoselective cyclization of the episulfonium ion into an alcohol. In the initial synthetic plan, preparation of δ-varerolatones were studied, as they are important intermediates in the synthesis of plakortethers A–E. An approach to the preparing δ-varerolatones by enolate alkylation was evaluated and several reaction conditions were examined. Due to the problems encountered during the purification process and volatility of the lactone, low yields were obtained. This issue can be overcome by modifying the substrate with a suitable substituent as proposed in Scheme 26. Even though the plakortether core could not

achieved during the study, the target δ-varerolatone was constructed. Future endeavors should be focused on optimizing the yields of this and other low-yielding synthetic steps, which would provide building blocks for the construction of the plakortether core.

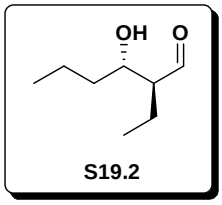
CHAPTER III

EXPERIMENTAL SECTION FOR APPROACH TO THE TOTAL SYNTHESIS OF PLAKORTETHERS A–E

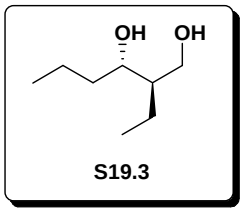
3.1 General information and instrumentation

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 500 NMR spectrometer. All spectra were obtained in deuterochloroform ($CDCl_3$). Chemical shifts are reported in ppm relative to tetramethylsilane (TMS). Spin-spin coupling constants, *J*, are reported in hertz (Hz). Infrared (IR) spectra were acquired on a Perkin Elmer Spectrum 400 FT-IR/FT-FIR spectrometer. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F254 (E. Merck no. 5715–7) pre-coated plates. Purification by column chromatography was performed using 40–63 μm silica gel (Merck, Geduran, no.11567-1) as the stationary phase. THF was distilled over sodium-benzophenone under nitrogen before use. CH_2Cl_2 was distilled over calcium hydride under nitrogen atmosphere. All other chemicals were used as purchased without further purification, unless mentioned.

3.2 Procedures and physical data for compounds from Scheme 19

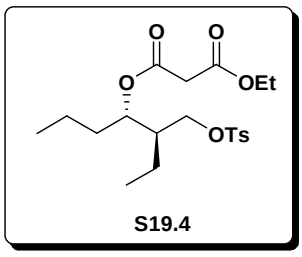


(2*S*,3*S*)-2-Ethyl-3-hydroxyhexanal (S19.2). A solution of freshly distilled propanaldehyde (1.00 g, 17.0 mmol) and L-proline (157 mg, 1.40 mmol) in DMF was stirred at 4 °C for 10 h. The resulting solution was diluted with diethyl ether (10 mL) and washed successively with water and brine. The combined aqueous layers were extracted with diethyl ether (3 × 10 mL), dried over anhydrous magnesium sulfate, filtered and the crude product was concentrated under vacuum. Purification by column chromatography on silica gel (5:2, pentane-DEE) yielded aldehyde **S19.2** (1.60 g, 65%) as a clear liquid. R_f = 0.55 (5:1, pentane-DEE): The physical data of **S19.2** match with its previously reported data of the compound.[56]



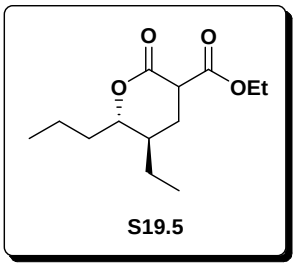
(2*R*,3*S*)-2-Ethylhexane-1,3-diol (S19.3). Aldehyde **S19.2** (50.0 mg, 0.294 mmol) and 50 mL of diethyl ether was added to a round bottom flask under nitrogen and the mixture was cooled to 0 °C. LAH (27.0 mg, 0.734 mmol) was then added to the reaction mixture, and stirred for 16 h at rt. The reaction mixture was cooled to 0 °C and quenched with water (0.1 mL) followed by 0.1 mL of 15% aqueous solution of KOH and additional 30 μL of water. The resulting mixture was stirred for 1 h at rt and then with anhydrous magnesium sulfate for another 1 h, followed by filtration through a short Celite plug. The solid on the Celite plug was washed several times with diethyl ether. Volatiles were removed under vacuum and the resulting residue was purified by column chromatography on silica gel (1:3, EtOAc-hexane) affording 254 mg (81%) of diol **S19.3** as a colorless viscous liquid.

R_f = 0.45 (1:1, EtOAc-hexane). The physical data of **S19.3** match with its previously reported data of the compound.[57]



S19.4

(2*R*,3*S*)-3-[2-(Ethoxycarbonyl)acetoyloxy]-2-ethylhexyl 4-methylbenzenesulfonate (S19.4). A solution of 2-(phenylsulfonyl)acetic acid (15.9 mg, 0.120 mmol) and DCC (49.5 mg, 0.240 mmol) in dichloromethane (2.5 mL) was stirred for 30 min under nitrogen at rt. Then DMAP (9.8 mg, 0.080 mmol) and alcohol **S19.3** (20.0 mg, 0.0800 mmol) was added to the reaction mixture and stirred for 16 h at rt. The reaction mixture was diluted with 1:1 mixture of ethyl acetate and hexane (10 mL). The organic layer was washed with a 1 N aqueous solution of HCl (10 mL), saturated aqueous solution of sodium bicarbonate (10 mL), and brine. Purification by column chromatography on silica gel (1:7, EtOAc-hexane) provided 20.0 mg (67%) of compound **S19.4** as a pale yellow oil. R_f = 0.30 (1:5, EtOAc-hexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.80 (t, J = 7.0 Hz, 6H), 1.20 (t, J = 7.6 Hz, 3H), 1.20–1.50 (m, 6H), 1.70 (m, 1H), 3.90–4.10 (m, 4H), 3.20 (s, 3H), 4.95 (m, 1H), 7.30 (d, J = 6.4 Hz, 2H), 7.70 (d, J = 7.1 Hz, 2H).

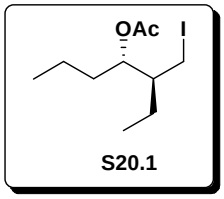


S19.5

Ethyl (5*R*,6*S*)-5-ethyl-2-oxo-6-propyltetrahydro-2H-pyran-3-carboxylate (S19.5). A flame-dried round bottom flask was charged with compound **S19.4** (25.0 mg, 0.0700 mmol), potassium carbonate (27.9 mg, 0.200 mmol)

and with 2 mL of anhydrous DMSO under nitrogen. The reaction mixture was stirred for 18 h at rt. Upon completion, the reaction was quenched with water and the product was extracted with 1:1 mixture of ethyl acetate and hexane (10 mL). The organic layer was further washed with water (2 × 10 mL) and the resulting organic layer was dried with anhydrous magnesium sulfate, filtered and concentrated under vacuum. Purification by chromatography on silica gel (1:7, EtOAc-hexane) provided 15.2 mg (62%) of the valerolactone **S19.5** as a colorless viscous liquid. R_f = 0.35 (1:5, EtOAc-hexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.85 (t, J = 6.9 Hz, 3H), 0.90 (t, J = 7.0 Hz, 3H), 1.28 (t, J = 6.8 Hz, 3H), 1.30 (m, 2H), 1.33 (m, 2H), 1.53 (m, 2H), 1.70 (m, 1H), 2.09 (dd, J = 14.0, 7.7 Hz, 1H), 2.15 (dd, J = 14.0, 7.4 Hz, 1H), 3.30 (dd, J = 13.9, 7.0 Hz, 1H), 3.40 (t, J = 14.0 Hz, 1H), 4.20 (q, J = 7.0 Hz, 2H).

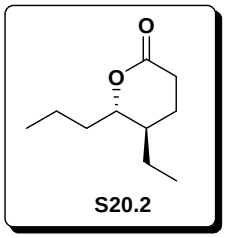
3.3 Procedures and physical data for compounds from Scheme 20



(3*S*,4*S*)-3-(Iodomethyl)heptan-4-yl acetate (S20.1). A round bottom flask was charged with diol **S19.3** (360 mg, 2.47 mmol) in 25 mL of pyridine. The resulting solution was cooled to 0 ^{o}C followed by addition of *p*-tosyl chloride (470 mg, 2.47 mmol) and the reaction mixture was stirred at 0 ^{o}C for 15 h. Upon completion, acetic anhydride (503 mg, 4.93 mmol) was added to the reaction mixture at 0 ^{o}C. The reaction mixture was stirred for 24 h and diluted with 25 mL of ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium bicarbonate (15 mL), water (15 mL) and brine. The resulting organic layer was dried with anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The obtained mixture was added to a round bottom flask along

with sodium iodide (1.17 g, 7.83 mmol) followed by 20 mL of acetone. Then the reaction mixture was refluxed at 40–50 °C for 24 h. Upon completion, volatiles of the reaction mixture were removed under reduced pressure and the resulting residue was dissolved in 1:1 mixture of ethyl acetate and hexane (20 mL). The organic layer was then washed with water (20 mL) and brine, then dried over anhydrous magnesium sulfate and filtered. The volatiles were removed under reduced pressure. Purification by column chromatography on silica gel (0.5:9.5, EtOAc-hexane) yielded 650 mg (89% over two steps) of compound **S20.1** as a pale yellow oil. R_f = 0.55 (1:9, EtOAc-hexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.80 (t, J = 6.5 Hz, 3H), 0.90 (t, J = 7.0 Hz, 3H), 1.30–1.35 (m, 4H), 1.45 (m, 2H), 1.95 (s, 3H), 2.00 (m, 1H), 3.10 (dd, J = 12.5, 6.5 Hz, 1H), 3.20 (dd, J = 13.0, 6.8 Hz, 1H), 4.8 (m, 1H).

Preparation of S20.2 following method 1



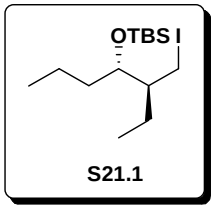
(5*R*,6*S*)-5-Ethyl-6-propyltetrahydro-2H-pyran-2-one (S20.2). A solution of diispropylamine (41.1 mg, 0.410 mmol) in 1 mL of anhydrous THF was cooled to −78 °C. To this solution, *n*-butyllithium (0.16 mL, 0.40 mmol of a 2.5 M solution in hexane) was added. After stirring the mixture for 15 min at −78 °C, a solution of compound **S20.1** (100 mg, 0.340 mmol) and DMPU (50 μL, 0.40 mmol) in 2 mL of THF was added dropwise over 2 h period. Upon completion of the reaction, 5 mL of saturated aqueous solution of ammonium chloride was added and the reaction mixture was brought to rt. The resulting reaction mixture was diluted with 20 mL of diethyl ether. The organic layer was then washed with water (2 × 10mL) and brine. The organic layer was dried over anhydrous

magnesium sulfate and filtered. Volatiles were removed under reduced pressure. Purification of the resulting residue by column chromatography on silica gel (1:5, DEE-petroleum ether) afforded 5.0 mg (9%) of crude valerolactone **S20.2** as a colorless liquid. Due to the low yield and volatility of valerolactone **S20.2**, the crude product was not subjected to purification. The ^{1}H NMR spectrum of the crude product of the compound **S20.2** exhibited some significant peaks relevant to **S20.2**.

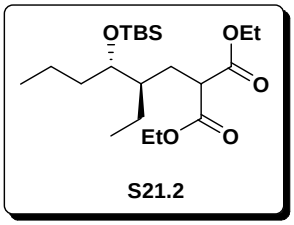
Preparation of S20.2 following method 2

(5*R*,6*S*)-5-Ethyl-6-propyltetrahydro-2H-pyran-2-one (S20.2). A solution of compound **S20.1** (100 mg, 0.340 mmol) and DMPU (40 μL, 0.34 mmol) in 2 mL of THF was cooled to −78 °C under nitrogen. Then a solution of NaHMDS (1.06 mL, 0.740 mmol) was added dropwise to the reaction. The mixture was stirred for 7 h. Upon completion, the reaction mixture was quenched with 5 mL of saturated aqueous solution of ammonium chloride and brought to rt. The resulting mixture was diluted with 20 mL of diethyl ether and washed with water (2 × 10mL) and brine. Then the organic layer was dried over anhydrous magnesium sulfate and filtered. Volatiles were removed under reduced pressure. Purification of the resulting residue by column chromatography on silica gel (1:5, DEE-petroleum ether) afforded 3.0 mg (5%) of compound **S20.2** as a colorless liquid. The ^{1}HNMR spectrum of the crude product of **S20.2** exhibited some significant peaks compatible with previously prepared **S20.2**.

3.4 Procedures and physical data for compounds from Scheme 21

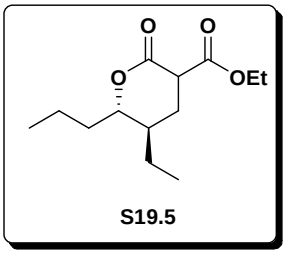


***tert*-Butyl[(3*S*,4*S*)-3-(iodomethyl)heptan-4-yloxy]dimethylsilane (S21.1)**. A flame-dried round bottom flask was charged with compound **S21.1** (20.0 mg, 0.800 mmol) in 2 mL of anhydrous dichloromethane, followed by addition of imidazole (13.5 mg, 0.200 mmol) and TBSCl (15.1 mg, 0.100 mmol). After a white precipitate formed, the reaction mixture was stirred for 2 h at rt under nitrogen atmosphere. The reaction mixture was then quenched with saturated aqueous solution of sodium bicarbonate and the crude product was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product of the TBS-protected compound was added to a round bottom flask along with sodium iodide (84.7 mg, 0.565 mmol) followed by 10 mL of acetone. The reaction mixture was refluxed at 40–50 °C for 24 h. Upon completion of the reaction, volatiles were removed under reduced pressure and the crude product was dissolved in a 1:1 mixture of ethyl acetate and hexane (10 mL). The organic layer was subsequently washed with water (10 mL) and brine. The resulting organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel (1:9, EtOAc-hexane) provided 27 mg (90% over two steps) of compound **S21.1** as a pale yellow oil. R_f = 0.50 (1:9, EtOAc-hexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.00 (s, 6H), 0.80 (s, 9H), 0.85 (t, J = 6.9, 6.5 Hz, 3H), 0.90 (t, J = 7.0 Hz, 3H), 1.20 (m, 2H), 1.30 (m, 2H), 1.45 (m, 2H), 1.50 (m, 1H), 3.30 (m, 1H), 3.06 (dd, J = 11.5, 6.7 Hz, 1H), 3.25 (dd, J = 12.0, 7.0 Hz, 1H).



S21.2

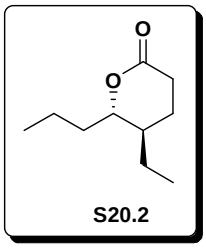
Diethyl 2-[(2*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-2-ethylhexyl]malonate (S21.2). A flame dried round bottom flask was charged with compound **S21.1** (25.0 mg, 0.0700 mmol) and with potassium carbonate (27.9 mg, 0.200 mmol) under nitrogen. 2 mL of anhydrous DMSO was added to the solid mixture followed by diethyl malonate (16.1 mg, 0.100 mmol). The reaction mixture was then stirred for 18 h at rt. Upon completion, the reaction was quenched with water and the product was extracted with a 1:1 mixture of ethyl acetate and hexane (10 mL). The organic layer was further washed with water (2 × 10 mL) and the resulting organic layer was dried with anhydrous magnesium sulfate, filtered and concentrated under vacuum. Purification by chromatography on silica gel (1:7, EtOAc-hexane) provided 15.2 mg (62%) of compound **S21.2** as a colorless viscous liquid. R_f = 0.50 (1:5, EtOAc-hexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.00 (s, 6H), 0.80 (s, 9H), 0.85 (t, J = 6.9, 6.5 Hz, 6H), 0.90 (t, J = 7.0 Hz, 3H), 1.25 (t, J = 6.8 Hz, 6H), 1.40 (m, 2H), 1.30 (m, 2H), 1.40 (m, 1H), 1.50 (m, 2H), 1.95(m, 2H), 3.40 (t, J = 7.0 Hz, 3H), 3.55 (m, 2H), 4.18 (q, J = 7.0 Hz, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ –5.0 (CH_3), 13.0 (CH_3), 13.2 (CH_3), 14.5 (CH_3), 20.0 (CH_2), 26.0 (CH_3), 28.8 (CH_2), 37.0 (CH_2), 36.0 (CH_2), 43.0 (CH), 50.5(CH), 61.5 (CH_2), 62(CH_2), 74(CH), 170.0 (C).



S19.5

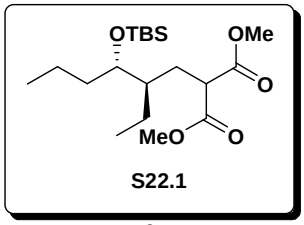
Ethyl (5*R*,6*S*)-5-ethyl-2-oxo-6-propyltetrahydro-2H-pyran-3-carboxylate (S19.5). Compound **S21.2** (25.0 mg, 0.0700 mmol) was dissolved in 1 mL of anhydrous methanol and catalytic amount of Dowex 50 was added to

the reaction mixture. The reaction mixture was stirred for 24 h at rt. Upon completion, the mixture was filtered through a thin Celite plug and the volatiles were removed under reduced pressure. Purification of the crude product by column chromatography on silica gel (1:7, EtOAc-hexane) afforded 7.5 mg (44%) of compound **S19.5** as a colorless liquid. R_f = 0.35 (1:5, EtOAc-hexane). The physical data of **S19.5** match with its previously reported data of the compound.



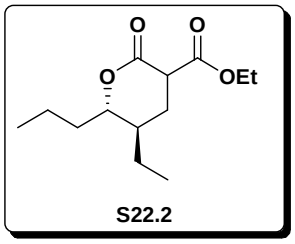
Diethyl 2-[(2*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-2-ethylhexyl]malonate (S20.2). A round bottom flask was charged with compound **S19.5** (15.0 mg, 0.0600 mmol), lithium chloride (7.9 mg, 0.19 mmol) and 2 mL of DMSO. After addition of 2–3 drops of water, the reaction was refluxed for 7 h at 195–205 °C under nitrogen. Then the mixture was cooled to rt and the product was extracted with diethyl ether (10 mL). The organic layer was washed with water (2 × 10mL) and brine. The resulting organic extract was dried with anhydrous magnesium sulfate, filtered and volatiles were removed under reduced pressure. Purification of the resulting residue by column chromatography on silica gel (1:5, DEE-petroleum ether) afforded 2 mg (3.5%) of compound **S20.2** as a colorless liquid. R_f = 0.30 (1:5, DEE-petroleum ether). ^{1}H NMR spectrum of the crude product of **S20.2** exhibited some significant peaks match with its previously reported data of the compound **S20.2**.

3.5 Procedures and physical data for compounds from Scheme 22



S22.1

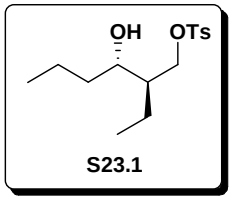
Dimethyl 2-[(2*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-2-ethylhexyl]malonate (S22.1). The compound **S22.1** was obtained using the procedure described for compound **S21.2**. Purification by column chromatography on silica gel (1:7, EtOAc-hexane) yielded 19.5 mg (68%) of compound **S22.1** as a colorless viscous liquid. R_f = 0.52 (1:5, EtOAc-hexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.00 (s, 6H), 0.85 (s, 12H), 1.15 (t, J = 7.3 Hz, 3H), 1.20–1.50 (m, 6H), 1.55 (m, 1H), 1.99 (m, 2H), 3.15 (dd, J = 13.8, 6.8 Hz, 1H), 3.20 (m, 1H), 3.57 (s, 6H).



S22.2

Methyl (5*R*,6*S*)-5-ethyl-2-oxo-6-propyltetrahydro-2H-pyran-3-carboxylate (S22.2). The compound **S22.2** was obtained using the same procedure described for compound **S19.5**. Purification by column chromatography on silica gel (1:7, EtOAc-hexane) yielded 19.5 mg (68%) of the compound **S22.2** as a colorless viscous liquid. R_f = 0.35 (1:5, EtOAc-hexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.85 (t, J = 6.5 Hz, 3H), 0.90 (m, 2H), 1.15 (t, J = 7.3 Hz, 3H), 1.40 (m, 4H), 1.50 (m, 2H), 1.85 (m, 1H), 2.20–2.40 (m, 2H), 3.40 (dd, J = 14, 5.9 Hz, 1H), 3.90 (s, 3H).

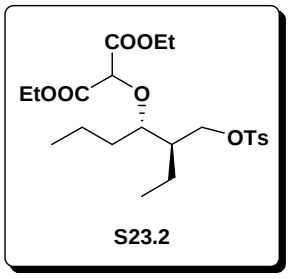
3.6 Procedures and physical data for compounds from Scheme 23



S23.1

(2*R*,3*S*)-2-Ethyl-3-hydroxyhexyl 4-methylbenzenesulfonate (S23.1). A solution of diol **S19.3** (100 mg, 0.690 mmol) in pyridine (5 mL) was cooled to 0 °C. Tosyl chloride (131 mg, 0.690 mmol)

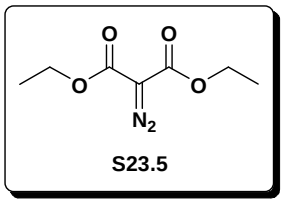
was then added to the reaction mixture and stirred overnight at 0 °C. Upon completion of the reaction, it was diluted with 10 mL of ethyl acetate. The reaction mixture was then washed with water (10 mL), 1 N aqueous solution of HCl (10 mL) and again with water (10 mL). The organic layer was dried with anhydrous magnesium sulfate, filtered and volatiles were removed under reduced pressure. Purification of the crude product by column chromatography on silica gel (1:9, DEE-petroleum ether) yielded 150 mg (88%) of compound **S23.1** as a viscous liquid. R_f = 0.3 (1:9 DEE-petroleum ether). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.85 (t, J = 7.5 Hz, 3H), 0.9 (t, J = 6.7 Hz, 3H), 1.20–1.50 (m, 5H), 1.90 (broad s, 1H), 2.45 (s, 3H), 3.50 (m, 1H), 4.22 (dd, J = 11.0, 5.5 Hz, 1H), 4.10 (dd, J = 11.5, 6.0 Hz, 1H), 7.40 (d, J = 7.6 Hz, 2H), 8.20 (d, J = 7.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 11.7 (CH_3), 14.2 (CH_3), 19.4 (CH_2), 19.8 (CH_3), 21.2 (CH_2), 37.2 (CH_2), 45.0 (CH), 70.2 (CH_2), 71.3(CH), 128.3 (CH), 130.3 (CH), 133.2 (C), 145.2 (C).



S23.2

(2*S*,3*S*)-3-(Di(ethoxycarbonyl)methyl)-2-ethylhexyl 4-methylbenzenesulfonate (S23.2) A solution of alcohol **S23.1** (50.0 mg, 0.200 mmol) and diethyl diazomalonate (**S23.5**) (36.9 mg, 0.200 mmol) in 2.5 mL of anhydrous Benzene was heated at 65 °C for 1 h, with catalytic amounts of rhodium acetate (0.01 mol %) under nitrogen. The solvent was evaporated under reduced pressure and the resulting residue was dissolved in 10 mL of ethyl acetate. The insoluble material was filtered through a Celite plug and the resulting organic layer was washed with saturated aqueous solution of sodium bicarbonate (10 mL) and then with water (2 × 10 mL). The organic layer was dried with anhydrous magnesium sulfate and filtered. Volatiles were

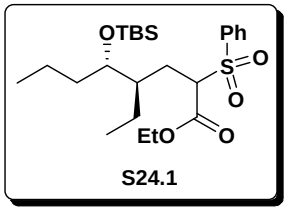
evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel (1:7, EtOAc-hexane) afforded 60 mg (68%) of compound **S23.2** as a pale yellow oil with a yield of. R_f = 0.35 (1:7, EtOAc-hexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.7 (t, J = 7.5 Hz, 3H), 0.80 (t, J = 7.2 Hz, 3H), 1.20 (t, J = 6.9 Hz, 3H), 1.20–1.50 (m, 6H), 1.70 (m, 1H), 2.38 (s, 3H), 3.44 (m, 1H), 3.95 (dd, J = 11.5, 6.0 Hz, 1H), 4.12 (dd, J = 12.0, 6.7 Hz, 1H), 4.15 (q, J = 13.8 Hz, 2H), 4.30 (s, 1H), 7.3 (d, J = 7.5 Hz, 2H), 7.7 (d, J = 7.0 Hz, 2H).



S23.5

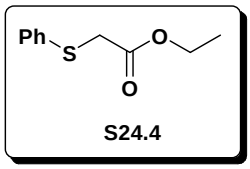
Diethyl diazopropanedioate (S23.5) A solution of diethyl malonate ester (1.00 g, 6.00 mmol) in 10 mL of THF was cooled to –45 °C and charged with mesyl azide (2.18 g, 18.0 mmol). DBU (1.4 mL, 9.0 mmol) was then added dropwise over 2–3 min period to the reaction mixture. After stirring at –45 °C for 1 h, the reaction mixture was brought to rt over 15–20 min period and diluted with 10 mL of half saturated aqueous solution of ammonium sulfate. The product was extracted with dichloromethane (3 × 10 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and volatiles were removed under reduced pressure. Purification of the resulting residue by column chromatography on silica gel (1:7, EtOAc-hexane) afforded 850 mg (73%) of compound **S23.5** as a colorless liquid. R_f = 0.40 (1:5, EtOAc-hexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.15 (t, J = 12.5 Hz, 6H), 4.15 (q, J = 11.5 Hz, 4H). IR (CH_2Cl_2, cm^{-1}, ν): 2175.80, 1725.54.

3.7 Procedures and physical data for compounds from Scheme 24



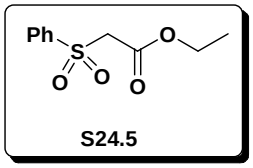
S24.1

(4*R*,5*S*)-Ethyl 5-(*tert*-butyldimethylsilyloxy)-4-ethyl-2-(phenylsulfonyl)octanoate (S24.1). Compound **S24.1** was obtained using the procedure described for compound **S19.5**, replacing diethyl malonate with ethyl 2-(phenylsulfonyl)acetate (**S24.5**). Purification by column chromatography on silica gel (1:7, EtOAc-hexane) provided 16 mg (86%) of compound **S24.1** as a colorless viscous liquid. R_f = 0.50 (1:5, EtOAc-hexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.00 (s, 6H), 0.85 (s, 9H), 09. (t, J = 15.4 Hz, 3H), 1.10 (t, J = 12.7 Hz, 3H), 1.15 (t, J = 11.9 Hz, 3H), 1.20–1.50 (m, 6H), 1.90 (m, 1H), 2.20 (m, 2H), 3.20 (m, 2H), 3.50 (m, 1H), 4.10 (q, J = 13.6 Hz, 2H).



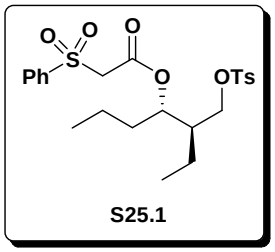
S24.4

Ethyl 2-(phenylthio)acetate (S24.4). Ethyl bromoacetate (2.00 g, 12.0 mmol) was added to a round bottom flask along with 10 mL of acetone under nitrogen environment. Sodium iodide (0.09 g, 5 mol %) and potassium carbonate (2.49 g, 18.0 mmol) were then added. After stirring the reaction mixture for 10 min, thiophenol (1.2 mL, 12 mmol) was added. The reaction mixture was refluxed overnight, the acetone was evaporated and the residue was diluted with 50 mL of ethyl acetate. The organic layer was washed with water (2 × 10mL) and brine followed by drying with anhydrous magnesium sulfate and filtering. Volatiles were removed under reduced pressure and 2.35 g (100%) of crude product was obtained as a pale yellow oil. R_f = 0.50 (1:7, EtOAc-hexane). The physical data of compound **S24.4** match with its previously reported data of the compound.[58]



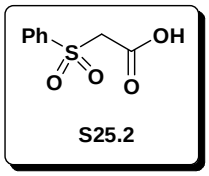
Ethyl 2-(phenylsulfonyl)acetate (S24.5). A round bottom flask was charged with crude compound **S24.4** (2.35 g, 12.0 mmol) and 20 mL of anhydrous dichlormethane. The resulting reaction mixture was cooled to 0 °C, *m*-CPBA (5.18 g, 30.0 mmol) was added and was stirred for 12 h at rt under nitrogen. Once the reaction was completed, the reaction mixture was taken up in 50 mL of dichloromethane and washed successively with saturated aqueous solution of sodium sulfite (10 mL), saturated aqueous solution of sodium bicarbonate (10 mL) and brine. The organic layer was then dried with anhydrous magnesium sulfate, filtered and volatiles were evaporated under reduced pressure. Purification of the crude product by column chromatography on silica gel (1:5, EtOAc-hexane) yielded 2.46 g (90%) of compound **S24.5** as a pale yellow liquid. R_f = 0.20 (1:3, EtOAc-hexane): The physical data of **S24.5** match with its previously reported data of the compound.[58]

3.8 Procedures and physical data for compounds from Scheme 25



(2*R*,3*S*)-3-[2-(Phenylsulfonyl)acetoyloxy]-2-ethylhexyl 4-methylbenzenesulfonate (S25.1). A solution of 2-(phenylsulfonyl)acetic acid (**S25.2**) (52.9 mg, 0.260 mmol) and DCC (163 mg, 0.790 mmol) in dichloromethane (2.5 ml) was stirred for 30 min under nitrogen environment at rt. DMAP (35.3 mg, 0.260 mmol) and alcohol **S19.3** (66.0 mg, 0.260 mmol) were then added and stirred for 16 h at rt. The reaction mixture was diluted with a 1:1 mixture of ethyl acetate and hexane (10 mL). The organic layer was washed with a 1 N aqueous solution of HCl (10 mL), saturated aqueous solution of sodium bicarbonate (10 mL), and brine. Volatiles were removed under

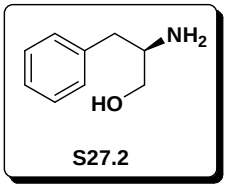
reduced pressure. Purification of the resulting crude product by column chromatography on silica gel (1:7, EtOAc-hexane) provided 50 mg (40%) of compound **S25.1** as a colorless viscous liquid. R_f = 0.40 (1:5, EtOAc-hexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.75 (t, J = 6.4 Hz, 6H), 1.20–1.50 (m, 6H), 2.38 (s, 3H), 2.40 (m, 1H), 3.50 (s, 2H), 3.80 (dd, J = 10.2, 5.1 Hz, 1H), 4.00 (dd, J = 11.0, 6.3 Hz, 1H), 4.90 (m, 1H), 7.00–7.50 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 11.6 (CH_3), 11.8 (CH_3), 18.6 (CH_2), 19.8 (CH_3), 22.2 (CH_2), 32.7 (CH), 34.1 (CH), 43.1 (CH_2), 69.4 (CH_2), 69.8 (CH), 128.4 (CH), 129.5 (CH), 129.9 (CH), 130.3 (CH), 133.1 (C), 135.4 (C), 138.8 (C), 145.2 (C), 169.5 (C).



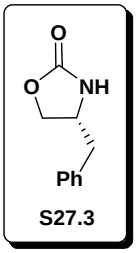
S25.2

2-(Phenylsulfonyl)acetic acid (S25.2). A round bottom flask was charged with ester **S24.5** (100 mg, 0.440 mmol), potassium hydroxide (123 mg, 2.19 mmol) and methanol (5 mL). The reaction mixture was refluxed overnight at 70–80 °C. Upon completion of the reaction, the volatiles were removed under reduced pressure. The remaining residue was dissolved in 10 mL of water and organic impurities were extracted with a 1:1 mixture of ethyl acetate and hexane (15 mL). The aqueous layer was acidified with an aqueous solution of 1N hydrochloric acid, and the resulting carboxylic acid was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were then dried with anhydrous magnesium sulfate and filtered. Evaporation of volatiles under reduced pressure resulted in 84 mg (97%) of pure compound **S25.2** as a colorless liquid. R_f = 0.10 (1:5, EtOAc-hexane). The physical data of **S25.2** match with its previously reported data of the compound.[58]

3.9 Procedures and physical data for compounds from Scheme 27

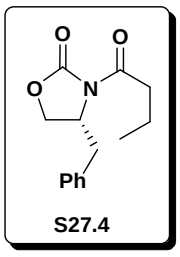


(*R*)-2-Amino-3-phenylpropan-1-ol (S27.2). L-Phenylalanine (4.00 g, 24.4 mmol) and LAH (2.77 g, 73.2 mmol) were added to a round bottomed flask under nitrogen environment. 60 mL of THF was added and the reaction mixture was refluxed for 24 h under nitrogen. The reaction mixture was slowly cooled to 0 °C and quenched with deionized water (9 mL) followed by addition of 9 mL of a 15% aqueous solution of KOH and additional 3 mL of deionized water. The resulting mixture was stirred for 1 h, filtered and dried with anhydrous magnesium sulfate, then filtered through a Celite plug and washed the Celite with excess dichloromethane. Volatiles were removed under vacuum yielding alcohol **S27.2** (3.50 g, 95%) as a white solid. R_f = 0.25 (1:1, EtOAc-hexane). The physical data of **S27.2** match with its previously reported data of the compound.[53]



(*R*)-4-Benzyloxazolidin-2-one (S27.3). A mixture of acetonitrile (50.0 mL) and dimethyl carbonate (8.3 mL, 99 mmol) was added to a round bottomed flask containing a mixture of amine **S27.2** (3.00 g, 19.8 mmol) and potassium carbonate (16.44 g, 119.0 mmol). The reaction mixture was refluxed for 48 h under nitrogen environment and then cooled to room temperature. The reaction mixture was filtered through a Celite plug and was washed with a 1:1 mixture of ethyl acetate and hexane (25 mL). The organic layer was concentrated under vacuum and resulting residue was purified by column chromatography on silica gel (1:2–1:9, EtOAc-hexane) to afford 2.62 g (73 %) of

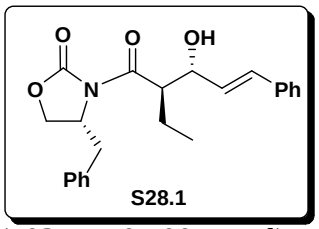
compound **S27.3** as a white solid. R_f = 0.35 (1:1, EtOAc-hexane). The physical data of **S27.3** match with its previously reported data of the compound.[53]



S27.4

(*R*)-4-Benzyl-3-butyryloxazolidin-2-one (S27.4). (*R*)-4-benzyloxazolidin-2-one (**S27.3**) (2.00 g, 12.1 mmol) and sodium hydride (0.43 g, 18 mmol) were added to a round bottomed flask. The mixture was dissolved in THF (40 mL) and butyryl chloride (1.30 g, 12.1 mmol) was then added to the mixture, followed by stirring for 1 h under nitrogen atmosphere. Upon completion, the reaction mixture was quenched with a solution of saturated ammonium chloride and the compound was extracted with ethyl acetate. The organic extract was then washed with a solution of saturated ammonium chloride (10 mL), deionized water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the resulting residue by column chromatography on silica gel (1:5, EtOAc-hexane) provided 2.15 g (72%) of compound **S27.4** as a pale yellow oil. R_f = 0.50 (1:3, EtOAc-hexane): The physical data of **S27.4** match with its previously reported data of the compound.[53]

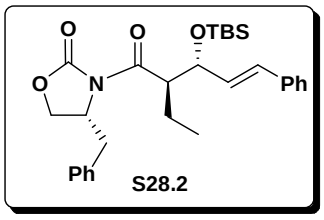
3.10 Procedures and physical data for compounds from Scheme 28



S28.1

(*R*)-4-Benzyl-3-[(2*R*,3*R*,*E*)-2-ethyl-3-hydroxy-5-phenylpent-4-enoyl]oxazolidin-2-one (S28.1). Compound **S27.4** (1.00 g, 4.00 mmol) was added to $MgBr_2 \cdot Et_2O$ (103 mg, 0.400 mmol) in a round bottom flask and flushed with nitrogen. 10 mL of ethyl acetate was added to the mixture followed by a subsequent addition of triethylamine (1.1

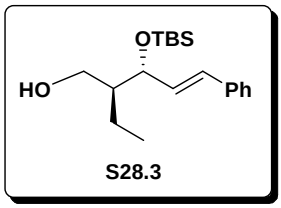
mL, 8.0 mmol), cinnamaldehyde (0.6 mL, 5 mmol) and TMSCl (0.8 mL, 6 mmol). The reaction mixture was stirred at 23 °C for 24 h. Upon completion, the resulting yellow slurry was pushed through a plug of silica with diethyl ether. Volatiles were removed under vacuum, and to the remaining residue, 15 mL of methanol was added along with 4–5 drops of trifluoroacetic acid. The mixture was stirred at rt for 30 min and volatiles were removed under reduced pressure. Purification of the resulting crude product by column chromatography on silica gel (1:7, EtOAc-hexane) afforded 1.53 g (87%) of compound **S28.1** as a pale yellow oil. R_f = 0.40 (1:5, EtOAc-hexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.9 (t, J = 11.5 Hz, 3H), 1.75 (m, 2H), 2.6 (dd, J = 11.7, 6.8 Hz, 1H), 2.6 (dd, J = 11.9, 7.0 Hz, 1H), 3.00 (dd, J = 12.1, 6.9 Hz, 1H), 3.30 (dd, J = 12.0, 6.8 Hz, 1H), 4.12 (t, J = 12.8 Hz, 1H), 4.15 (dd, J = 14.5, 7.3 Hz, 1H), 4.35 (dd, J = 14.6, 6.8 Hz, 1H), 4.75 (m, 1H), 6.35 (dd, J = 15.5, 3.6 Hz 1 H), 6.70 (d, J = 16.0 Hz, 1H), 7.15–7.35 (m, 10H).



S28.2

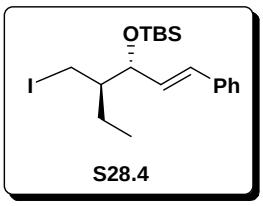
(*R*)-4-Benzyl-3-[(2*R*,3*R*,*E*)-3-(*tert*-butyldimethylsilyloxy)-2-ethyl-5-phenylpent-4-enoyl]oxazolidin-2-one (S28.2). A flame-dried round bottom flask was charged with compound **S28.1** (1.50 g, 3.04 mmol) and anhydrous DMF (10 mL). Imidazole (518 mg, 7.60 mmol) and TBSCl (572 mg, 3.80 mmol) were successively added to the solution. After a white precipitate formed, the reaction mixture was stirred overnight at rt. The reaction mixture was quenched with saturated aqueous solution of sodium bicarbonate (25 mL) and the compound was extracted with ethyl acetate (3 × 20 ml). The combined organic extracts were dried over anhydrous

magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the resulted crude product by column chromatography on silica gel (1:7, EtOAc-hexane) afforded 1.70 g (87%) of compound **S28.2** as a pale yellow oil. R_f = 0. 32 (1:5, EtOAc-hexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.00 (s, 6H), 0.70 (s, 9H), 0.75 (t, J = 12.7 Hz, 3H), 1.59 (m, 2H), 2.50 (m, 1H), 3.35 (dd, J = 10.6, 4.1 Hz, 1H), 4.12 (m, 1H), 4.18 (dd, J = 14.0, 6.9 Hz, 1H), 4.43 (dd, J = 13.50, 7.4 Hz, 1H), 4.60 (m, 1H), 6.25 (dd, J = 16.2, 7.3 Hz, 1H), 6.62 (d, J = 16.6 Hz, 1H), 7.10–7.40 (m, 10H).



(2*S*,3*R*,*E*)-3-(*tert*-Butyldimethylsilyloxy)-2-ethyl-5-phenylpent-4-en-1-ol (S28.3). Compound **S28.2** (175 mg, 0.350 mmol) was dissolved in 3 mL of abs. ethanol and the solution was cooled to 0 °C. Sodium borohydride (67.0 mg, 1.77 mmol) was then added to the solution at 0 °C followed by stirring for 24 h at rt. The reaction mixture was quenched with saturated aqueous solution of sodium bicarbonate (10 mL) at 0 °C and was warmed up to rt. The product was extracted with 20 mL of dichloromethane and the organic layer was successively washed with water (2 × 10 mL) and brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the resulted crude by column chromatography on silica gel (1:7, EtOAc-hexane) afforded 85 mg (75%) of compound **S28.3** as a colorless oil. R_f = 0.35 (1:5, EtOAc-hexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.00 (s, 6H), 0.75 (t, J = 6.9 Hz, 3H), 0.9 (s, 9H), 2.00 (m, 1H), 1.40 (m, 1H), 2.90 (s, 1H), 3.50 (dd, J = 10.8, 4.8 Hz, 1H), 3.80 (dd, J = 9.5, 4.5 Hz, 1H), 4.30 (t, J = 4.0 Hz, 1H), 6.10 (dd, J = 16.1, 3.6 Hz, 1H), 6.40 (dd, J = 15.7, 6.8 Hz, 1H), 7.10– 7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ

5.0 (CH_3), 13.35 (CH_3), 19.0 (CH_2), 26.41 (CH_3), 48.27 (CH), 63.2 (CH_2), 78.4 (CH), 126.9 (CH), 128.1 (CH), 129.0 (C), 131.0 (CH), 132. 2 (CH), 137.1 (C).



[(*E*,3*R*,4*R*)-4-(Iodomethyl)-1-phenylhex-1-en-3-yloxy](*tert*-Butyl)dimethylsilane (S28.4). A round bottom flask was charged with compound **S28.3** (35.0 mg, 0.109 mmol) and dichloromethane (1 mL) at 0 °C followed by successive addition of imidazole (14.9 mg, 0.218 mmol), triphenylphosphine (57.2 mg, 0.220 mmol) and iodine (55.3 mg, 0.220 mmol). After stirring for 20 min, the reaction mixture was diluted with hexane, filtered through a celite plug followed by rinsing thoroughly with hexane. The filtrate was concentrated under reduced pressure and the resulting residue was purified using column chromatography on silica gel (1:7, EtOAc-hexane) yielding 39 mg (83%) of compound **S28.4** as a pale yellow oil. R_f = 0.50 (1:5, EtOAc-hexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.00 (s, 6H), 0.75 (t, J = 6.9 Hz, 3H), 0.85 (s, 9H), 1.30 (m, 2H), 1.50 (m, 1H), 3.30 (dd, J = 10.7, 4.6 Hz, 1H), 3.50 (dd, J = 9.7, 4.5 Hz, 1H), 4.10 (t, J = 4.0 Hz, 1H), 6.10 (dd, J = 16.0, 7.6 Hz, 1H), 6.10 (d, J = 16.7, 1H), 7.20–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 4.0 (CH_3), 11.89 (CH_2), 18.5 (CH_3), 23.43 (CH_2), 47.79 (CH), 76.5 (CH), 126.9 (CH), 128.1 (CH), 129.0 (C), 131.5 (CH), 132. 1 (CH), 137.1 (C).

CHAPTER IV

BACKGROUND OF THE RHODIUM CATALYZED INTRAMOLECULAR C–H INSERTION ON DIAZOSULFONATES AND ITS SYNTHETIC APPLICATIONS

4.1 Introduction and background on C–C bond formation through activation of C–H bonds

Controlling product selectivity in carbon−hydrogen (C−H) bond functionalization reactions represents one of the great challenges in modern synthetic chemistry.[59] Over the years, conventional approaches towards the synthesis of organic molecules have neglected sp^3 C–H bonds, which are highly abundant in organic molecules and are usually the most ubiquitous "functional group".[60–61] The sp^3 C–H bond has a bond length of 1.09 Å, bond energy of 413 kJ/mol, and a small difference in electronegativity between carbon and hydrogen, making this C–H bond nonpolar.[59, 62, 63] In general, C–H bonds are considered inert due to the absence of empty orbitals of low energy or filled orbitals of high energy that can readily facilitate chemical reactions.[64, 65] The inertness and ubiquitous nature of sp^3 C–H bonds make the development of synthetically useful reactions challenging. Efficient and selective C–H bond functionalization strategies could lead to more effective carbon–carbon (C–C) bond formation reactions and address important unsolved synthetic challenges.[66–68] Towards this end, unique reagents are needed that are reactive enough to cleave the relatively stable C–H bonds but, at the same time, selectively discriminate the different types of C–H bonds in organic molecules.[69–74]

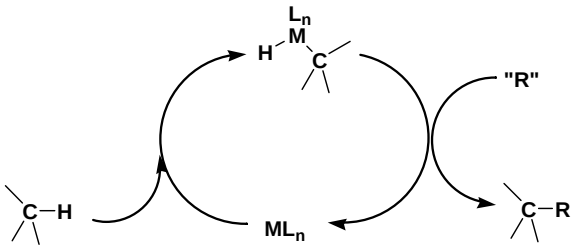
The sp^3 C–H bonds adjacent to heteroatoms or functional groups are considered to be activated sp^3 C–H bonds. Since such C–H bonds are weaker and thus more reactive

than their unactivated counterparts, these bonds can be selectively functionalized. At the same time, the selective activation of sp^3 hybridized C–H bonds is known to be both kinetically and thermodynamically unfavorable. Nevertheless, much progress has been made in recent years to selectively activate these bonds as shown by the work of many researchers.[65, 75–84]

Traditionally, C–C bond formation *via* activation of C–H bond was entirely dependent on radical reactions.[85–86] The high abundance of C–H bonds in organic substrates and the complications associated with controlling radical reactions limited the applications of these type of reactions. However, over the past two decades there has been an explosive growth in the development of methodologies for C–H functionalization and the application of these technologies for the synthesis of complex targets such as natural products and pharmaceutical agents. As a result, a variety of regio- and stereoselective C–H functionalization methods became available for the assembly of complex molecules. These tools can streamline multi-step chemical routes by eliminating unnecessary functional group transformations. Thanks to many contributors in the field, C–H functionalization has reached an era in which certain C–H bond can now be considered a synthon for both C–C and C–heteroatom moieties.[87]

Out of the reactions available, two significant transition metal-based methodologies have emerged for C–H bond functionalization, specifically with respect to new C–C bond formation.[65, 67, 78, 88] The first of these conversions is direct C–H activation, requiring a reactive transition metal complex (Ru, Ir, Rh or Pd) to transform a relatively strong C–H bond (90–105 kcal/mol) to a weaker carbon–metal bond (50–80 kcal/mol), followed by subsequent C–C bond formation (Scheme 29).[75, 89–91] Shilov,[92]

Bercaw,[65] Bergman,[82] Crabtree,[93, 94] Murai[77] and Goldman[95] are the pioneers of this direct C–H insertion methodologies, which date back to the 1970s and 1980s.



Scheme 29. Direct C–H activation mechanism, "R" represents a nucleophile and ML_n represents a reactive transition metal complex.[88]

Direct activation of C–H bonds generally involves harsh reaction conditions. Such conditions may not be tolerated by other functional groups in the substrate. In addition, the reactive transition metal complex may bind too tightly to the C–H bond by limiting the use of this transformation for synthetic purposes.[65, 91, 96] Unlike the above method of transition-metal-based transformations for functionalizing C–H bonds, metal carbenoid C–H insertion proceeds under relatively mild conditions and tolerates many functional groups.

4.2 Rhodium(II) complexes in carbenoid C–H insertion

During the initial efforts of functionalizing C–H bonds using metal carbenoids, copper complexes were employed with different levels of success. However, due to the high electrophilicity of copper, copper carbenoids tend to be too reactive to undergo selective C–H activation reactions.[88]

Introduction of dirhodium complexes has greatly enlarged the spectrum of metal carbenoid-mediated C–H insertion reactions. Rh(II) complexes are among the most effective and versatile catalysts and have been used in a variety of synthetically useful transformations.[97–105] The major factor behind the superiority of Rh(II) complexes is thought to be the formation of a dirhodium bridge caged within a 'lantern' structure.[106–107] It is believed that only one of the two Rh atoms actually binds to the carbene; the other unbound atom assists as an electron pool to increase the electrophilicity of the carbenoid moiety and facilitates the cleavage of Rh–C bond upon completion of the reaction.[69, 108]

More recently, dirhodium carboxylates and dirhodium carboxamides have emerged as the most effective and most widely used catalysts for C–H insertion reactions.[88, 109, 110] Some of the commonly used catalysts are $Rh_2(OAc)_4$ (**F4.1**, rhodium acetate), $Rh_2(tfa)_4$ (**F4.2**, rhodium trifluoroacetate), $Rh_2(esp)_2$ {**F4.3**, [bis(rhodium(*α*,*α*,*α′*,*α′*-tetramethyl-1,3-benzenedipropionic acid)]}, and $Rh_2(acam)_4$ (**F4.4**, rhodium acetamide) (Figure 4) among others. Electron-withdrawing ligands tend to increase the reactivity of the catalyst towards diazo decomposition, while electron-donating ligands tend to decrease the reactivity of the catalyst towards diazo decomposition. Out of the catalysts listed, rhodium acetamide, **F4.4**, is considered to be the least reactive and most selective.

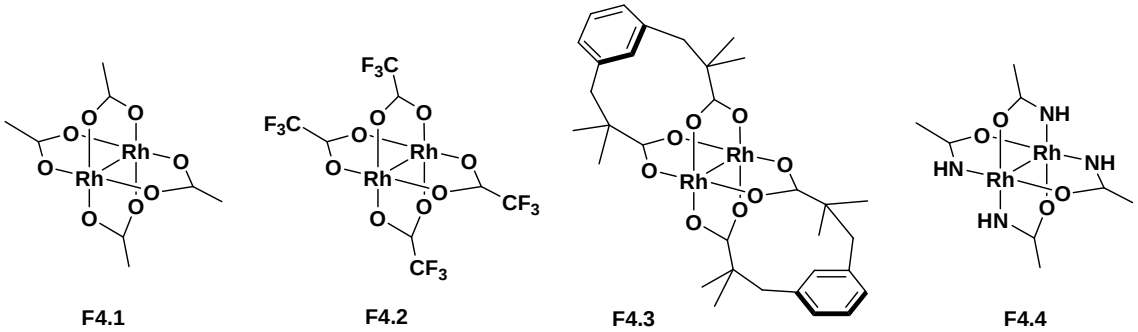
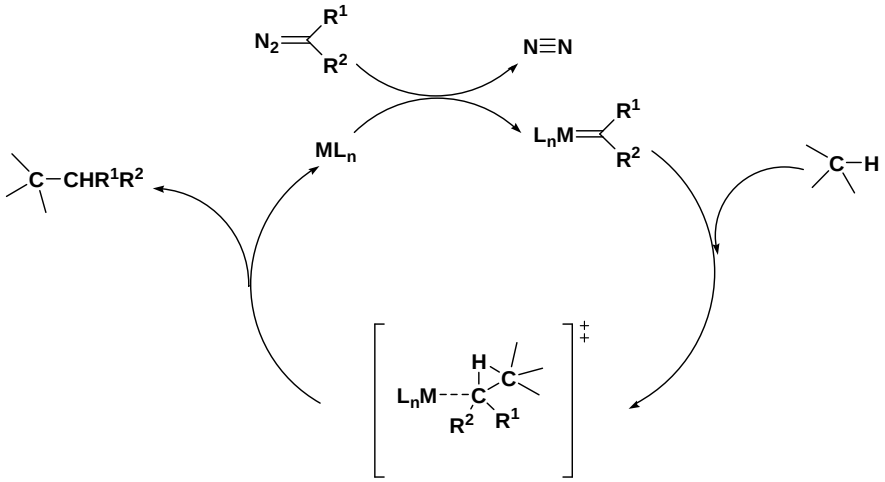


Figure 4. Common Rh-catalysts used for the C–H insertion reaction of diazo compounds.[88, 109, 110]

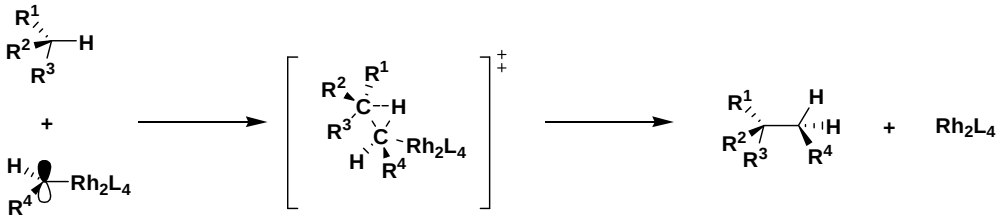
4.2.1 Rhodium-catalyzed C–H insertion mechanism

In the 80s, Doyle was the first to propose a widely accepted mechanism for Rh(II)-catalyzed transformations of diazo compounds.[69] According to his mechanism, the catalytic cycle of Rh-catalyzed C–H insertion reactions proceeds through three main steps: Rh-assisted nitrogen extrusion from the diazo compound, activation of the C–H bond and C–C bond formation.[108, 111, 112] In this method, the reactive transition metal complex inserts into a C–H bond to create a three-membered cyclic transition state, which directly provides the functionalized products (Scheme 30).[88] If the metal carbenoid is highly electrophilic, competing side reactions become an issue. On the other hand, if the electrophilicity is insufficient, the metal carbenoid lacks reactivity to insert into an unactivated C–H bond.[66, 88]



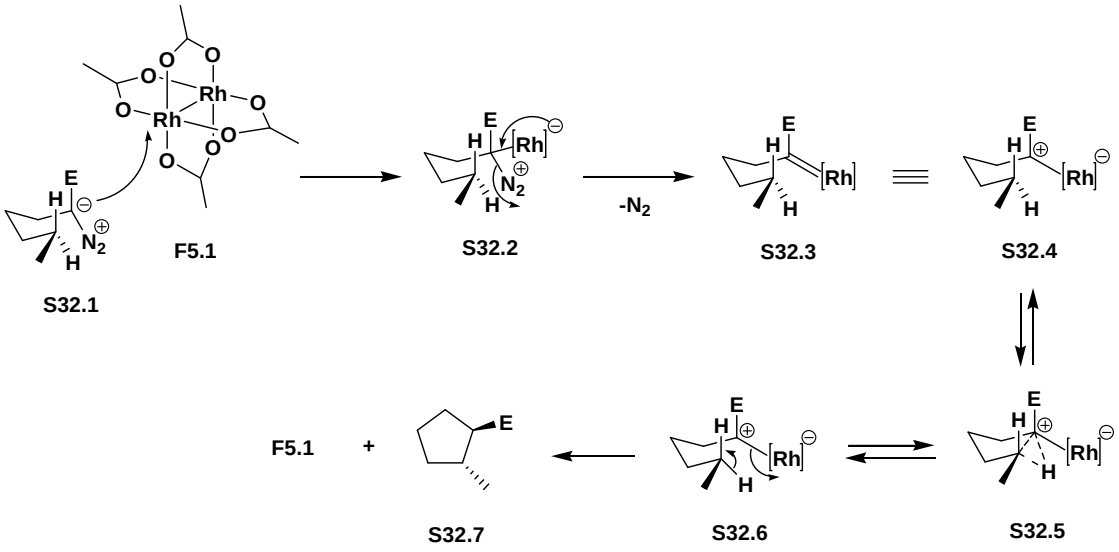
Scheme 30. Catalytic cycle for C–H functionalization by metal carbenoid insertion from diazo compounds.[88]

The author of this work suggested a transition state for the C–H bond activation based on the literature preferences and their own experimental data.[69] They suggested that after nitrogen extrusion, there is an overlap of the carbenoids *p*-orbital with the *σ*-orbital of the reacting C–H bond to form a three-membered concerted transition state (Scheme 31).[112] The author also have proposed that the C–C bond formation with the carbenoid carbon proceeds at the same time as the ligated metal dissociates, but not to the same extent. Although Doyle's catalytic cycle is generally accepted, the sequence of C–H activation and C–C bond formation steps has been a subject of considerable speculation.



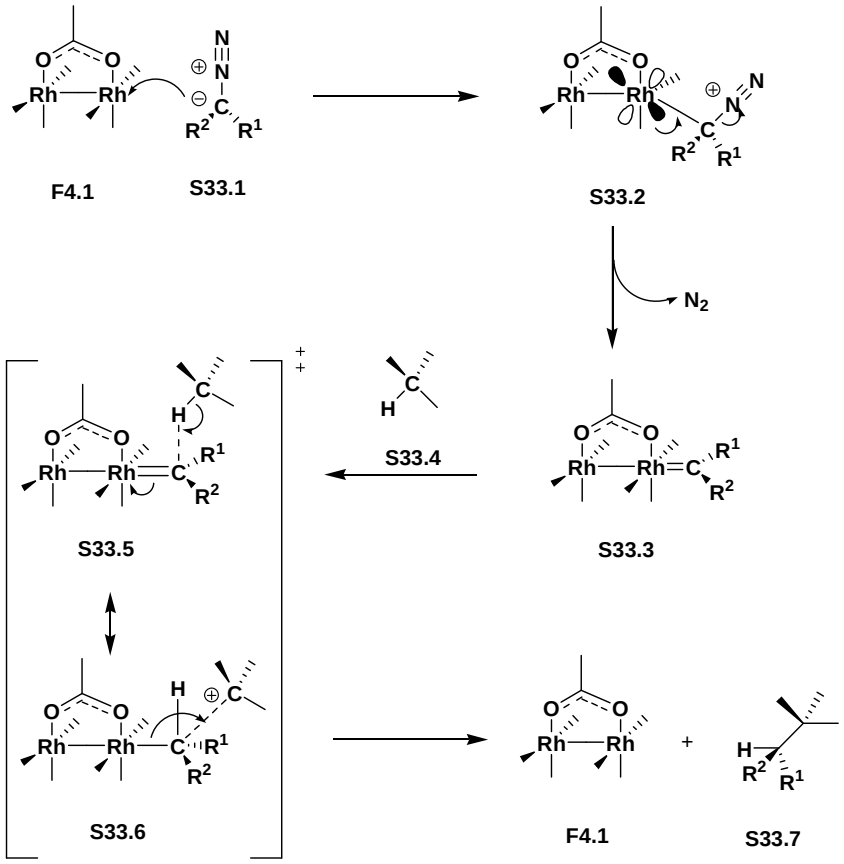
Scheme 31. Proposed transition state by Doyle for Rh-catalyzed C–H insertion from diazo precursors.[112]

As an extension for the study by Doyle, a mechanism for the intramolecular C–H insertion reaction of α-diazoesters with $Rh_2(OAc)_4$ has been proposed by Taber *et al.*[73] (Scheme 32). During the initial studies, the authors were able to use a computational approach to reliably predict the major diastereomers formed in Rh-mediated cyclization of α-diazoesters to acylcyclopentanes. According to this model, coordination of α-diazoester **S32.1** to the open axial position of $Rh_2(OAc)_4$, **F4.1**, affords complex **S32.2**. Back donation of electron density from Rh to the adjacent carbon with simultaneous extrusion of nitrogen give carbenoid **S32.3**, which may also be depicted as an inverted ylide **S32.4**. The reversible formation of a three-center two-electron bond affords complex **S32.5**. For bond formation to proceed, a four-membered transition state (TS) **S32.6** is needed, in which the Rh–C bond is aligned with the target C–H bond. Provided sufficient overlap exists, the electron pair of the C–H bond moves to form a new C–C bond, and synchronously, the electron pair of the Rh–C bond moves to form a new C–H bond. This results in formation of product **S32.7** and regeneration of catalyst **F4.1**.[73, 113]



Scheme 32. Proposed mechanism by Taber *et al.* for Rh-catalyzed C–H insertion from diazo precursors.[73]

In 2002, Nakamura *et al*.[108] proposed a transition state model of Rh(II)-catalyzed C–H activation, which confirmed the TS model proposed by Doyle.[69] Using B3LYP density functional theory on dirhodium tetracarboxylate-catalyzed C–H bond activation, the authors discovered the energetics, geometry of important intermediates and TS in the catalytic cycle, thereby providing a more accurate TS model. Based on the analysis, the authors proposed that the reaction is initiated by formation of a complex between the Rh catalyst **F4.1** and the diazo compound **S33.1** (Scheme 33). Back donation of electrons from Rh(II) 4*dxz* orbital to the C–N σ*-orbital provides the driving force for nitrogen extrusion to form the Rh carbenoid **S33.3**. The Rh carbenoid is highly electrophilic because of its empty 2*p* orbital. As such, C–H activation and formation of the C–C bond proceed in a single step *via* a three-membered hydride transfer-like TS (**S33.5** and **S33.6**) with small activation energy.



Scheme 33. Proposed mechanism by Nakamura *et al.* for Rh-catalyzed C–H insertion from diazo precursors.[108]

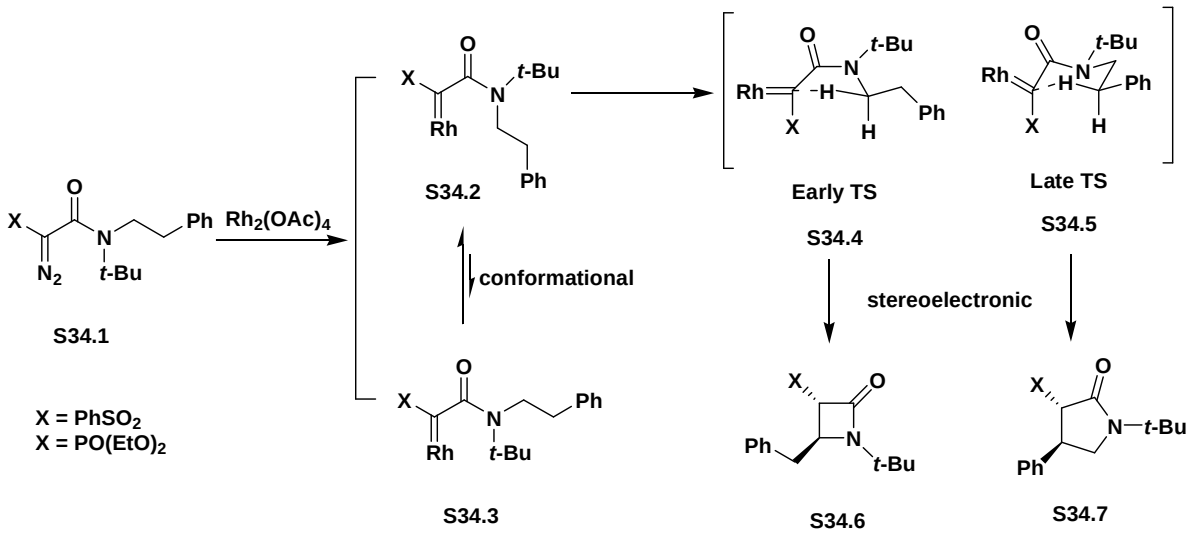
4.2.2 Synthetic utility of rhodium-induced intramolecular C–H insertion

In the last three decades, a significant increase in the utilization of diazocarbonyl compounds as precursors in C–C bond formation reactions has been witnessed. Rh-induced carbene insertion into C–H bonds has emerged as a powerful and valuable synthetic method, thanks to the pioneering works of Davis,[114–118] Doyle,[112, 119] Du Bois,[120] Taber[121, 122] and other. These Rh-induced insertion reactions can either be intermolecular or intramolecular.[123–127] Intermolecular versions have certain limitations. Obtaining desired regioselectivity and high yields in intermolecular C–H insertion reactions has proven challenging mainly due to competing side reactions (e.g., carbene

dimerization). With the exception of a few selected substrates, only intramolecular C–H insertion is deemed synthetically useful.[72, 124, 125, 128–135]

In general, Rh(II) carboxamidates are considered to be one of the best classes of catalyst for Rh-induced intramolecular C–H insertions.[136] The intramolecular C–H insertion reaction has demonstrated an overwhelming preference for the formation of five-membered rings and a reactivity order of tertiary > secondary >> primary in regards to the insertion into the pertinent C–H bond.[137, 138] This inherent preference can be occasionally overridden by conformational and steric effects in the substrate. The nature of the ligands on Rh-catalyst also influences the size of the ring (e.g., four- and six-membered rings may be formed) and on the regio- and stereochemical outcome of the product.[106, 139, 140]

Competing influences may give rise to a mixture of insertion products, as illustrated in the case of β- (**S34.6**) and γ-lactam (**S34.7**) formation from the C–H insertion reaction of α-diazoacetamides (**S34.1**, Scheme 34).[139, 141] The formation of a β-lactam is favored by the influence of the amide nitrogen and a strong electron-withdrawing substituent (e.g., X = COMe) attached to the carbene carbon. Presence of a strong electron-withdrawing substituent presumably disallows an early transition state (**S34.4**), leading directly to the β-lactam product **S34.7**. In the absence of a strong electron-withdrawing substituent (when X = $PhSO_2$ or $PO(EtO)_2$), later transition state **S34.5** is reached and γ-lactam **S34.7** is formed.

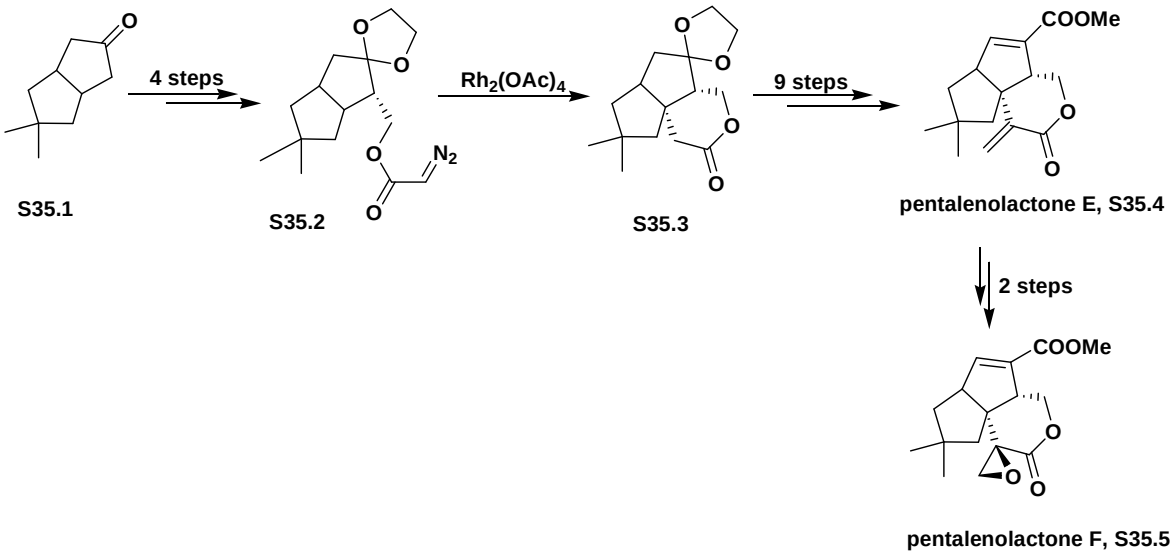


Scheme 34. Formation of β- and γ-lactams by intramolecular Rh-catalyzed insertion.[139]

4.2.3 Application of rhodium-induced intramolecular C–H insertion towards natural product synthesis

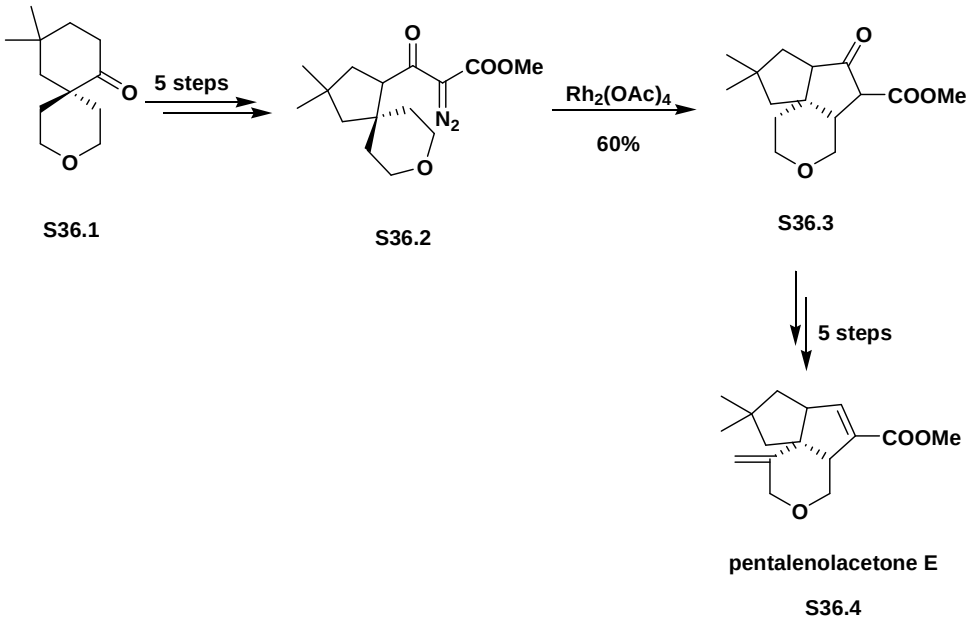
Synthetic methodologies are the main essential force of total synthesis. Impressive simplification of total synthesis of complex natural product using Rh-catalyzed intramolecular C–H insertion as a powerful synthetic methodology will be discussed under this section.

As mentioned, the majority of studies involving Rh-mediated intramolecular C–H insertion have observed the preferential five-membered ring formation. Nevertheless, the first application of C–H insertion to natural product synthesis reported by Cane and Thomas, involved a six-membered ring formation (Scheme 35).[142] The authors were able to synthesize methyl esters of pentalenolactone E **S35.4** and F **S35.5**. The synthesis was carried out *via* a route based on the intramolecular C–H insertion of α-acyldiazo **S35.2** yielding the key intermediate, γ-lactone **S35.3**.



Scheme 35. Synthesis of pentalenolactone E and F.[142]

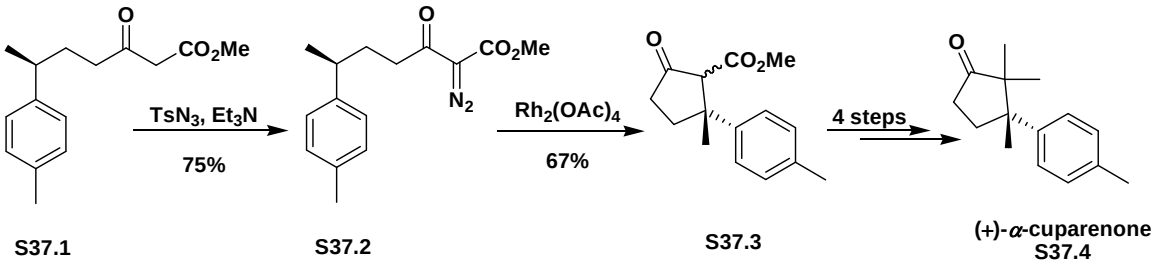
Taber and Schuchardt[143] synthesized the previously discussed pentalenolactone E **S35.4**, using an alternative route in which a five-membered ring is constructed (Scheme 36).[143] In the key step, tricyclic ketone **S36.3** is furnished by $Rh_2(OAc)_4$-catalyzed intramolecular C–H insertion of α-diazo-β-ketoester **S36.2**, which contains two chiral center. The ester is converted to tricyclic ketone **S36.3** with high asymmetric induction resulting in two additional chiral centers. The total synthesis of pentalenolactone E **S36.4** is then completed with five more steps.



S36.1 S36.2 S36.3 S36.4

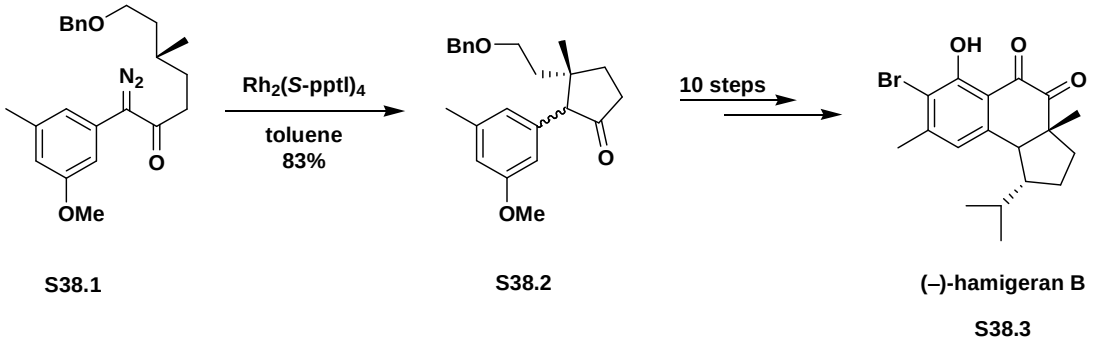
Scheme 36. Use of intramolecular Rh-catalyzed C–H insertion in the synthesis of pentalenolactone E by Taber and co-workers.[143]

Another notable feature of intramolecular C–H insertion is its inherent ability to convert an acyclic tertiary chiral center into a quaternary chiral center with retention of absolute configuration.[103, 113, 144] This phenomenon has been exploited by Taber and co-workers in the synthesis of (+)-α-cuparenone **S37.4** (Scheme 37)[103] and (–)-hamigeran B **S38.3** (Scheme 38).[144] The synthesis of (+)-α-cuparenone is initiated with diazo transfer of β-ketoester **S37.1** to afford α-diazo-β-ketoester **S37.2** in 75% yield (Scheme 37). Rh-catalyzed decomposition of α-diazo-β-ketoester **S37.2** affords the key intermediate cyclopentanone **S37.3** in 67% yield with retention of configuration at the newly constructed quaternary center. Additional four steps resulted in the target product.



Scheme 37. Intramolecular C–H insertion in the synthesis of (+)-α-cuparenone **S37.4** reported by Taber and co-workers.[103]

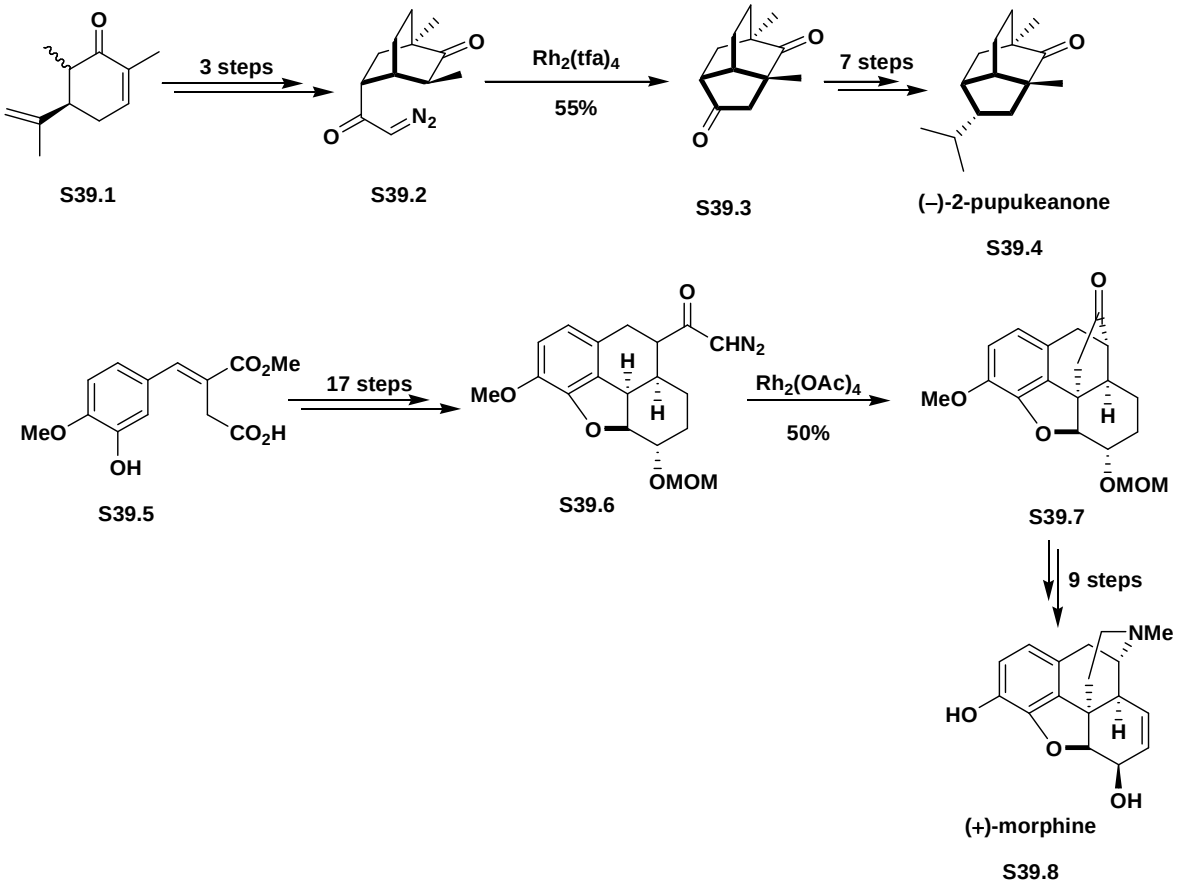
In 2008, the same authors reported the synthesis of (–)-hamigeran B **S38.3**, using a similar approach. In this case, a mixture of diastereomers is obtained because of the stereogenic center adjacent to the carbonyl moiety. The compound with the desired configuration is conveniently obtained by equilibrating the mixture in the presence of acid catalyst. Subsequent steps furnished the product (–)-hamigeran B **S38.3** as shown in Scheme 38.[144]



Scheme 38. Intramolecular Rh-catalyzed insertion applied to the synthesis of (–)-hamigeran B.[144]

Preparation of the key chiral cyclopentanone intermediates (**S39.3** and **S39.7**) of (−)-2-pupukeanone **S39.4**[145] and (+)-morphine **S39.8**[146] demonstrate the effectiveness of the C–H insertion reaction during the construction of C–C bonds in strained fused-ring systems. The synthesis of (–)-2-pupukeanone **S39.4** was initiated with 6-methyl carvone

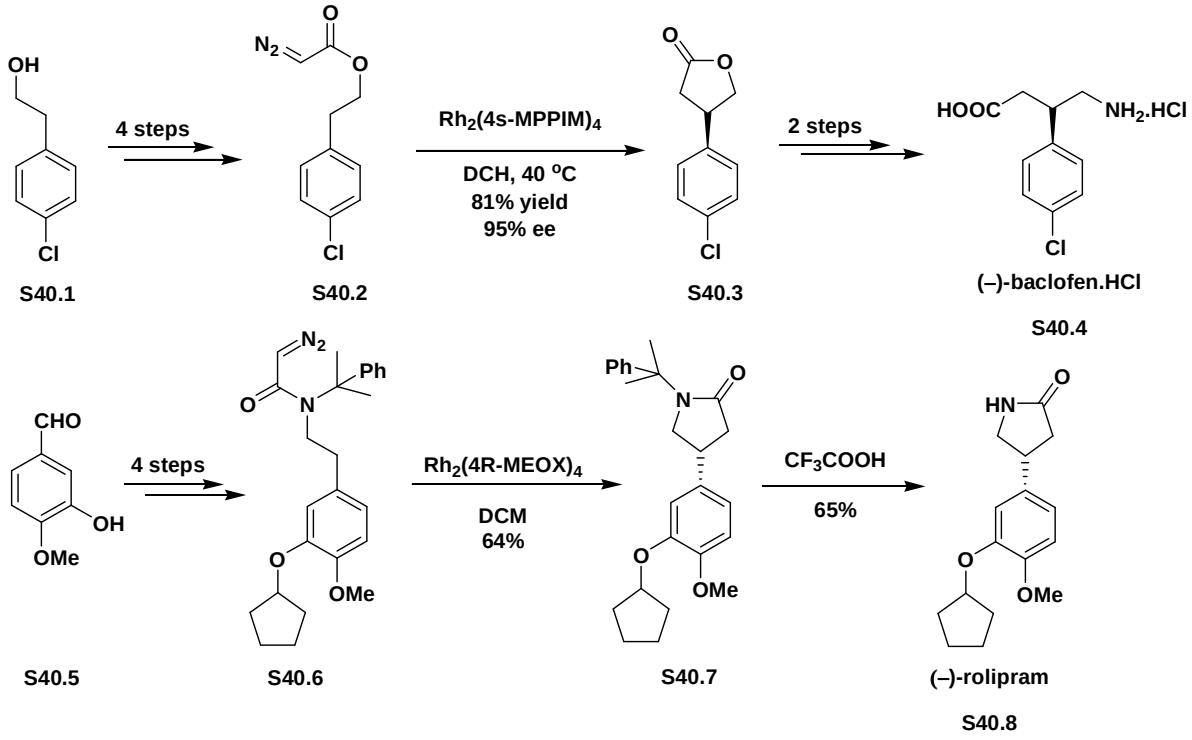
S39.1. In the presence of $Rh_2(tfa)_4$, diazoketone **S39.2** affords fused cyclopentanone **S39.3** (55%), and the synthesis of (−)-2-pupukeanone is completed with additional seven more steps. The synthesis of (+)-morphine **S39.8** is initiated with an acid derivative of isovanillin **S39.5**. Treatment of **d**iazoketone **S39.6** with $Rh_2(OAc)_4$ affords 50% yield of the strained fused cyclopentanone **S39.7**, which is converted in nine steps to (+)-morphine.



Scheme 39. Intramolecular C–H insertion in the synthesis of (−)-2-pupukeanone **S39.4** and (+)-morphine **S39.8**.[145, 146]

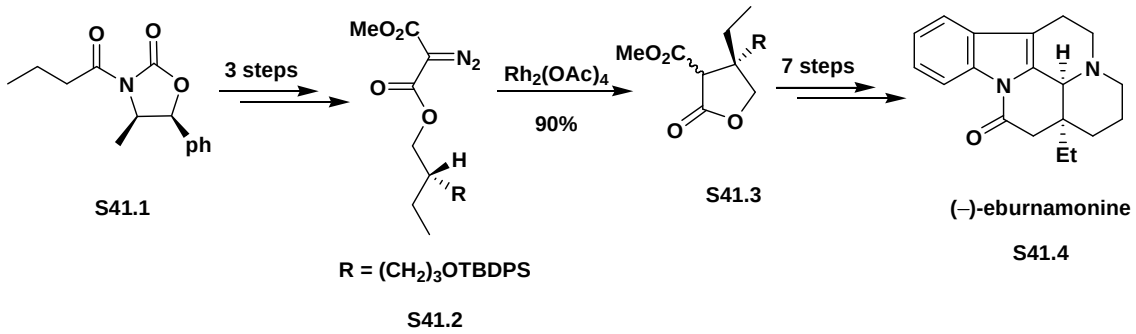
Intramolecular C–H insertion has been broadly used in the synthesis of γ-butyrolactones and γ-lactams. The synthesis of (*R*)-baclofen·HCl **S40.4** and (*R*)-rolipram

S40.8 can be considered as notable examples (Scheme 40).[147, 148] The synthesis of (*R*)-baclofen.HCl is initiated with *p*-chlorophenethyl alcohol **S40.1**. The Rh_2(*S*-MPPIM)$_4$-catalyzed intramolecular C–H insertion reaction of diazoacetate **S40.2** affords the γ-butyrolactone **S40.3** in 81% yield and 99% *ee*, and the desired product **S40.4** is obtained in 60% overall yield.[149] Hu and co-workers have described the synthesis of (–)-rlipram, **S40.8** starting from isovanillin **S40.5**.[150] Utilizing cumyl (2,2-dimethylbenzyl) as an *N*-protecting group, the Rh_2(MEOX)$_4$-catalyzed intramolecular C–H insertion reaction of α-diazoacetamide **S34.6** affords the γ-lactum **S40.7** in 64% yield and 46% *ee*. Removal of the cumyl protecting group furnished the final target compound **S40.8** in 15% overall yield.



Scheme 40. Synthesis of γ-butyrolactones and γ-lactams by intramolecular Rh-catalyzed insertion.[147, 148]

The C–H insertion reaction has also been used in the formation of a chiral γ-lactone precursor for naturally occurring indole alkaloid (–)-eburnamonine **S41.4** (Scheme 41).[99] Starting with *N*-butanoyloxazolidinone **S41.1**, diazoester **S41.2** is prepared in three steps, which upon treatment with $Rh_2(OAc)_4$, affords chiral γ-lactone intermediate **S41.3** in 90% yield.



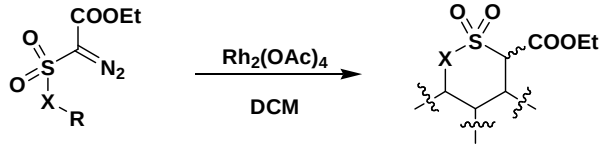
Scheme 41. Intramolecular C–H insertion to form a quaternary chiral center in the synthesis of (−)-eburnamonine **S41.4**.[99]

4.3 Rhodium-catalyzed intramolecular C–H insertion on disulfones and disulfonates

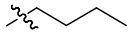
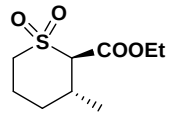
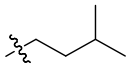
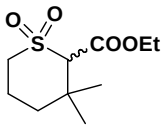
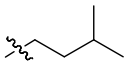
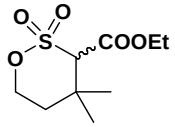
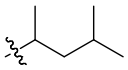
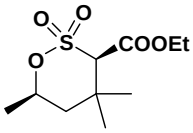
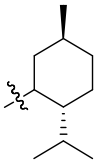
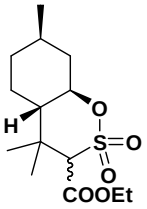
Rh-catalyzed intramolecular C–H insertion of α-diazosulfones is a relatively well-studied reaction. In a wide variety of cases it leads to the preferential formation of five-membered cyclic sulfones.[151, 152] However, Espino *et al*.[120] have reported the formation of six-membered cyclic sulfamates *via* Rh-catalyzed intramolecular N–H insertion of Rh-nitrenoids generated from the corresponding sulfamate esters. The authors have suggested that the difference in bond lengths and bond angles around the sulfur atom is responsible for this preference towards six-membered ring formation.[153–156] In 2007, branching off the Du Bois's work, John and Novikov[49] demonstrated that the preferential formation of cyclic six-membered sulfones and sulfonates can also be achieved through Rh-catalyzed intramolecular carbene C–H insertion reactions of aliphatic α-diazosulfones

and α-diazosulfonates (Table 2). Using this method, available chiral starting materials (**T2.1**–**T2.5**) can be easily converted into useful synthetic intermediates. Bequette *et al*.[157] have demonstrated the potential of this approach by converting the δ-sultone from (–)-citronellol to (+)-bakuchiol, a natural product with various biological activities.

Table 1. Formation of six-membered rings from α-diazosulfones and α-diazosulfonates reported by John and Novikov.[49]



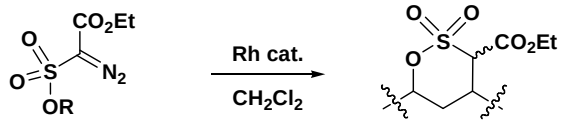
S P

S	X	R	P	Yield (%)
T2.1	CH_2			55[a]
T2.2	CH_2			56
T2.3	O			53
T2.4	O			55[a]
T2.5	O			80[b]

a: Isolated as a single isomer.
b: Diastereomeric ratio varied from experiment to experiment, ranging from complete to 2:1 in favor of the same diastereomer.

A complimentary report by Wolckenhauer *et al*. has also confirmed the preferential formation of δ-sultones (**T3.1**–**T3.8**) from α-diazosulfonate substrates (Table 3).[158] Notably, the preference for a six-membered ring is maintained even when formation of a strained system is required, as evidenced by the reactions of substrates **T3.5–T3.8**.

Table 2. Formation of δ-sultones from the C–H insertion reaction of α-diazosulfonates reported by Wolckenhauer *et al.*[158]



S P

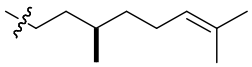
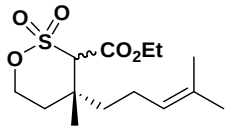
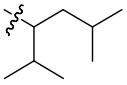
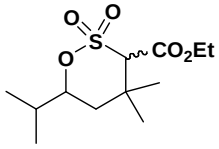
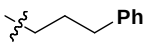
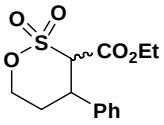
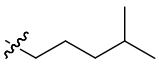
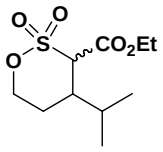
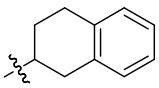
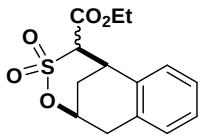
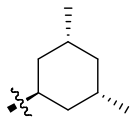
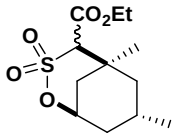
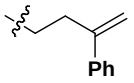
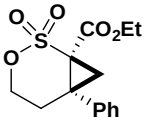
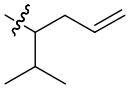
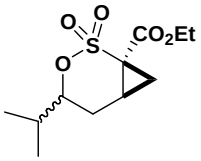
S	R	P	Yield (%)
T3.1			84[a]
T3.2			94[a]
T3.3			85[a]
T3.4			64[a]
T3.5			57[c]

Table 2. Cont.

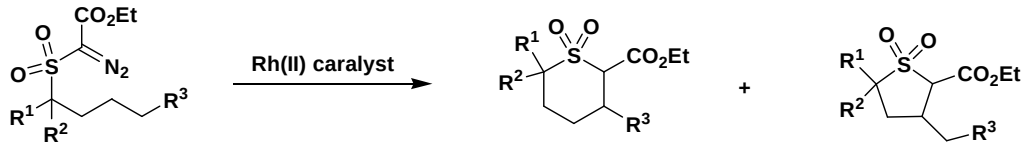
S	R	P	Yield (%)
T3.6			60[d]
T3.7			68[a]
T3.8			77[a]

Rh catalyst: a = $Rh_2(OAc)_4$, b = $Rh_2(esp)_2$, c = $Rh_2(O_2CCPh_3)_4$, d = $Rh_2(tfa)_4$

Although the formation of δ-sultones as the major products from intramolecular Rh-catalyzed C–H insertion on alkylsulfonyl diazoacetate substrates was observed by John *et al*. in their first report,[49] a later, more detailed analysis by Jungong *et al*.[159] has revealed this preference is sensitive to the substrate structure and the catalyst used (Table 4). As discussed in previous sections, intramolecular C–H insertion is favored at sites that stabilize positive charges. For example, substrate **T4.4** (R^3 = Me) favored primarily the six-membered product **P.1**, whereas substrate **T4.1** (R^3 = H) afforded primarily the five-membered product **P.2.** Presumably, this is due to the lesser substitution at the C–H insertion site. Trimethyl-substituted substrate **T4.8** (R^1, R^2, R^3 = Me) also afforded primarily the five-membered product **P.2**, as compared to substrate **T4.4** (R^1, R^2 = H, R^3 = Me). In this case, the steric compression of the angle at the sulfonyl group likely favors

the formation of a five-membered ring. The catalyst also influences the outcome of the reaction as evidenced by the effect of a strongly electron-withdrawing ligand, (pfb). Reactions catalyzed by a Rh(II) complex with this ligand tend to favor the formation of five-membered rings, while those with electron-donating ligands tend to favor six-membered rings. This suggests that the electronic environment on the metal center is another critical factor in determining selectivity.

Table 3. Formation of five-membered versus six-membered rings from C–H insertion reaction of diazosulfones reported by Jungong *et al*.[159]



S P 1 P 2

S	R^1	R^2	R^3	catalyst	Yield of **P.1**[a] (%)	Yield of **P.2**[a] (%)
T4.1	H	H	H	$Rh_2(OAc)_4$	2	25
T4.2	H	H	H	$Rh_2(esp)_2$	4	45
T4.3	H	H	H	$Rh_2(pfb)_2$	Not detected	80
T4.4	H	H	Me	$Rh_2(OAc)_4$	65	9
T4.5	Me	H	Me	$Rh_2(OAc)_4$	40	24
T4.6	Me	H	Me	$Rh_2(esp)_2$	26	34
T4.7	Me	H	Me	$Rh_2(pfb)_2$	8	60

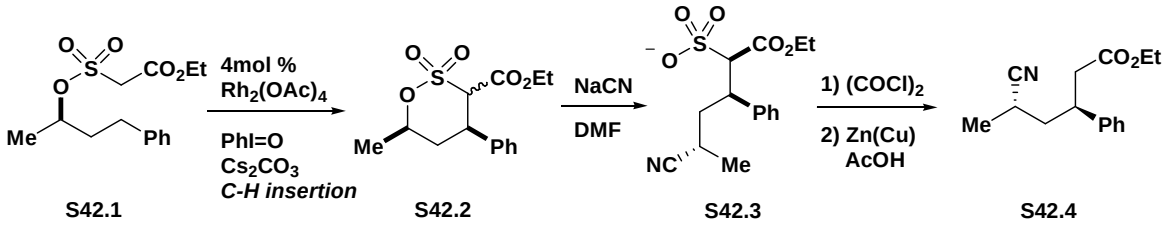
Table 3. Cont.

S	R_1	R_2	R_3	catalyst	Yield of **P.1**[a] (%)	Yield of **P.2**[a] (%)
T4.8	Me	Me	Me	$Rh_2(OAc)_4$	5	75
T4.9	Me	Me	Me	$Rh_2(pfb)_2$	Not detected	64

a: Isolated yields, combined for both diastereomers.

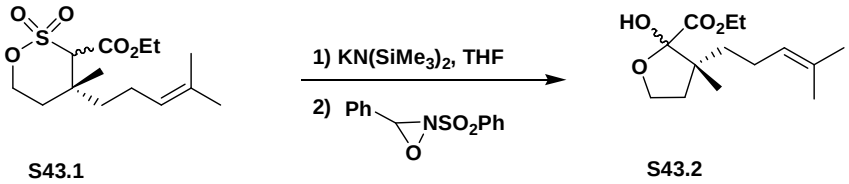
4.4 Synthetically useful intermediates from cyclic six-membered sulfones and sulfonates

The chemistry of the novel cyclic six-membered sulfones and sulfonates as synthetic intermediates remains largely unexplored.[160] Only a few cases have been reported in the literature where cyclic six-membered sulfones and sulfonates have been converted into synthetically viable intermediates. Particularly, it has been shown by Du Bois's research group[158] that the carbon–oxygen bond of δ-sultones **S42.2** can be displaced with nucleophiles such as NaCN, NaN_3, NaOAc, and thiolates to form analogues of the sulfonate salt **S42.3**. Direct extrusion of SO_3 from the subsequent salts under a variety of conditions proved ineffective, but the salts could be effectively converted to acyclic esters by a two-step sequence (Scheme 42).



Scheme 42. Nucleophilic substitution reactions of δ-sultones reported by Wolckenhauer *et al*.[158]

Wolckenhauer *et al.*[158] have also observed the desulfonation of δ-sultones under oxidative conditions to furnish five-membered lactol **S43.2**. The conversion is reported to involve an oxygen transfer followed by a C–S bond cleavage to afford α-keto ester, which is trapped internally by the awaiting hydroxyl group (Scheme 43).

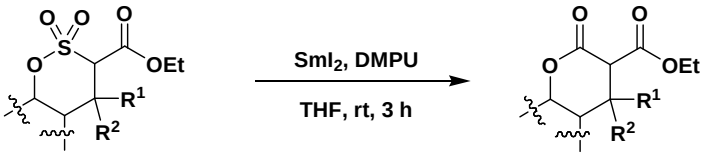


S43.1 **S43.2**

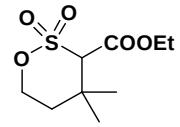
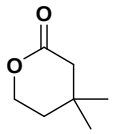
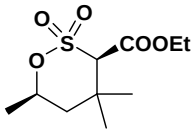
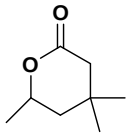
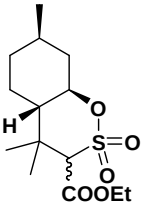
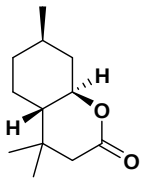
Scheme 43. Desulfonation of δ-sultones to form substituted lactones reported by Wolckenhauer *et al.*[158]

There are many examples of reductive desulfonation of α-arylsulfonyl esters.[161–163] However, the aryl group on the sulfur atom is essential for this transformation. δ-Sultones did not react in the presence of known reducing agents such as Al/Hg,[164] Na/Hg,[165] Mg-MeOH,[162] and SmI_2-MeOH,[161] which are routinely used for desulfonation of aryl sulfonyl compounds. Duffy *et al.*[163] reported desulfonation of fluoroalkylsulfonyl oxindoles by using SmI_2 with prolonged reaction times. However, there are no such examples for α-alkoxysulfonyl substituted esters. Jungong *et al.*[164] have successfully used the modified reaction conditions used by Duffy *et al.*[163] by combining DMPU along with SmI_2, which slowly react with δ-sultones to afford γ-valerolactones (Table 4).[164]

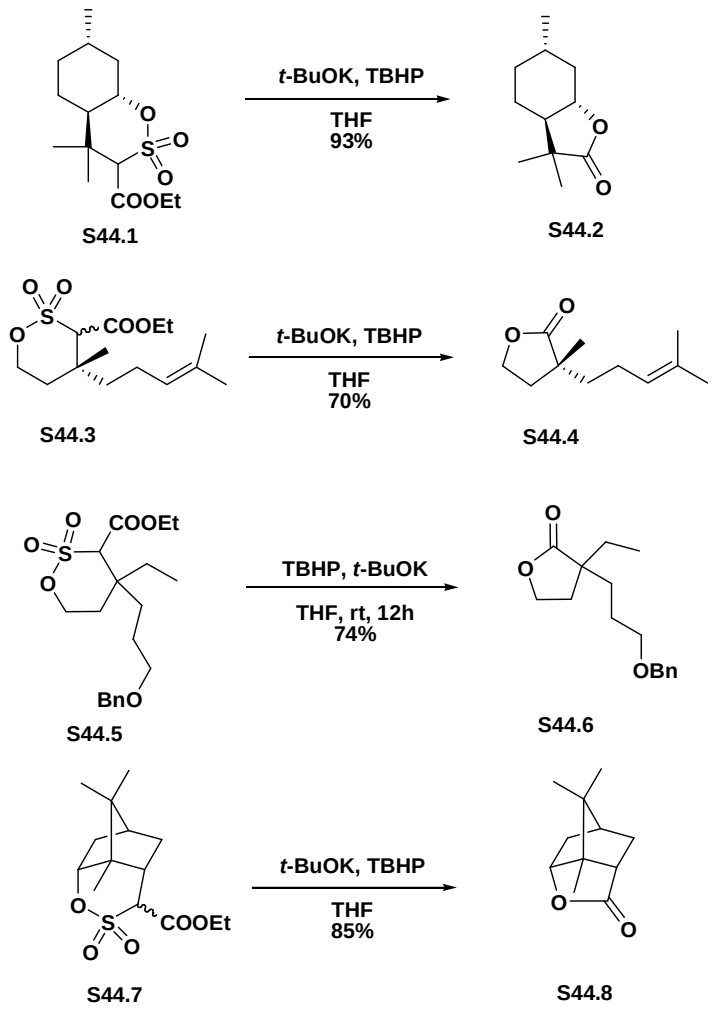
Table 4. SmI_2 reduction of δ-sultones to form γ-valerolactone reported by Jungong *et al.*[164]



S P

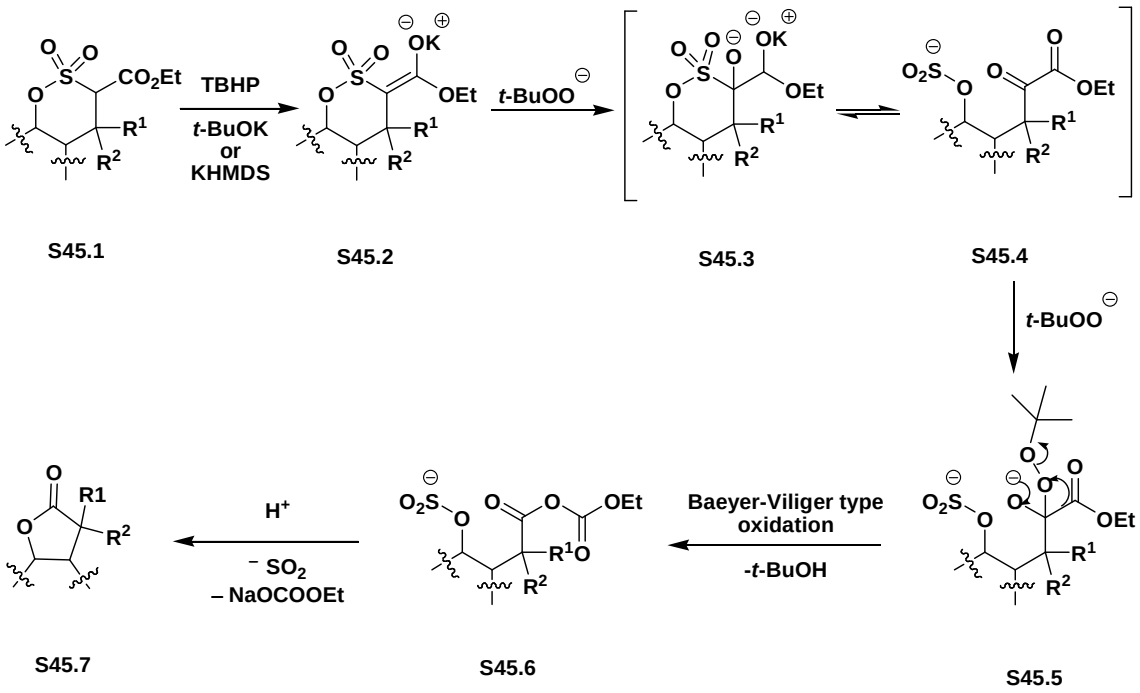
S	Time	P	Yield (%)
	45 min		47
	3 h		45
	3 h		85

Following the example of oxidative desulfonation of □-sultones reported by Wolckenhauer *et al.*,[158] studies in our lab have found that the δ-sultone exposed to *tert*-butyl hydrogen peroxide (TBHP) in the presence of a suitable base, undergoes. oxidative desulfonation along with decarboxylation leading to formation of γ-butyrolactone.[166] Common bases such as NaH, DBU, K_2CO_3, KOH, *t*-TEA, NaHMDS, and KHMDS have been surveyed in efforts to identify an appropriate base for the desulfonation process. It is found that KHMDS and *t*-BuOK are effective bases for this purpose. Several examples of oxidative desulfonation of δ-sultones with ranging yields were found (Scheme 44).



Scheme 44. TBHP oxidative desulfonation of δ-sultones to γ-butyrolactones.[166]

Presumably, the product formation would proceed through three steps: formation of the enolate, subsequent oxidation and cyclization. Formation of potassium enolate **S45.2** with *t*-BuOK followed by the deprotonation of TBHP would form a *t*-butyl hydroperoxide nucleophile, which after reaction would give a potassium alkoxide ring structure (**S45.3).** C–S bond cleavage would result in **S45.4**, and it is possible that **S45.4** would further be oxidized through Baeyer-Villiger type oxidation providing mixed anhydride **S45.6**. SO_2 extrusion of anhydride **S45.6** followed by cyclization would furnish the desired five-membered lactone **S45.7**.



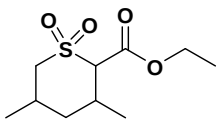
Scheme 45. Proposed mechanism of TBHP oxidative desulfonation of δ-sultones to γ-butyrolactones.[166]

CHAPTER V

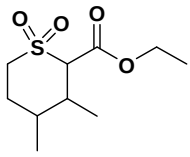
RHODIUM-CATALYZED INTRAMOLECULAR C–H INSERTION ON DIAZOSULFONATES AND THEIR SYNTHETIC APPLICATIONS

As an extension and optimization of the previous work done in our research group on C–H insertion of diazosulfones and diazosulfonates,[49, 157, 159, 160, 164] other synthetic intermediates from common precursors were explored. Such intermediates include six-membered sulfones (**F5.1** and **F5.2**), δ-sultones (**T5.1a–T5.1h**) and γ-butyrolactones (**T5.2a**–**T5.2h**).[167]

Since reactions towards diazosulfone **T4.5** provided good diastereoselectivity, as reported in early studies by Jungong *et al*., it was intended to synthesize six-membered cyclic sulfones **F5.1** and **F5.2**, which are structurally similar to the previously synthesized sulfone.[164] This way sulfone substrates with 1,3 (**F5.1**) and 1,2 (**F5.2**) chiral centers could be conveniently assembled.[167]



F5.1



F5.2

Figure 5. Six-membered sulfones as synthetic targets.

Synthesis of δ-sultones **T5.1a** and **T5.1b** was planned from easily available chiral starting materials isomethol and (–)-borneol, respectively. Preparation of δ-sultone **T5.1c** and benzyl-protected δ-sultone**T5.1d** was intended due to their potential towards the construction of γ-butyrolactones **T5.2c** and **T5.2d**, which can serve as key intermediates in the synthesis of (–)-eburnamonine **S41.4** (Scheme 54).[168] Remaking of the already reported δ-sultones **T5.1e–T5.1h**[49, 157] was planned to optimize the oxidative desulfonation of δ-sultone substrates to γ-butyrolactone. Synthesis of the above mention six-membered sulfones (**F5.1** and **F5.2)** and δ-sultones (**T5.1a–T5.1h**) requires their corresponding diazo substrates; their preparation will be discussed under Section 5.1.1 and 5.1.2.

Table 5. δ-Sultones and γ-butyrolactones as synthetic targets.

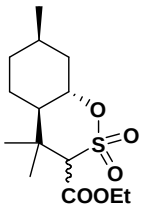
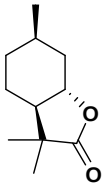
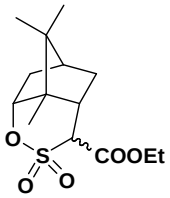
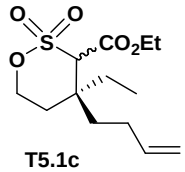
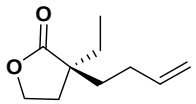
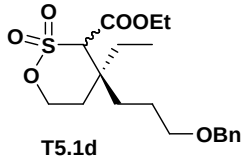
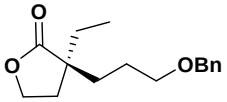
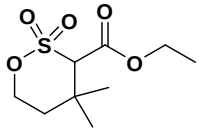
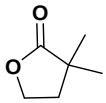
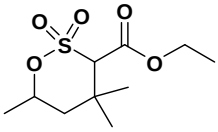
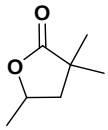
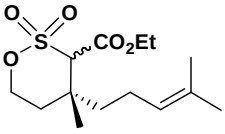
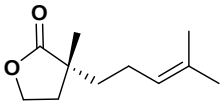
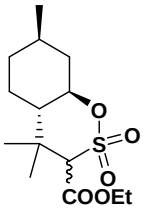
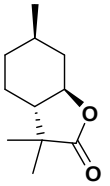
δ-Sultones	γ-Butyrolactones
 **T5.1a**	 **T5.2a**
 **T5.1b**	 **T5.2b**

Table 5. Cont.

δ-Sultones	γ-Butyrolactones
 T5.1c	 S5.2c
 T5.1d	 T5.2d
 T5.1e	 T5.2e
 T5.1f	 T5.2f
 T5.1g	 T5.2g
 T5.1h	 T5.2h

5.1 Results and discussion

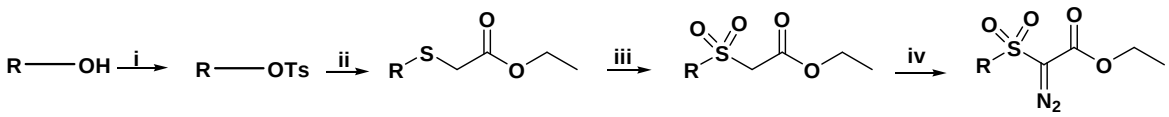
5.1.1 Preparation of diazosulfones

Synthesis of diazo sulfones **F5.1** and **F5.2** required the corresponding starting alcohols **T6.1a** and **T6.1b**.

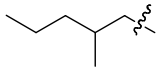
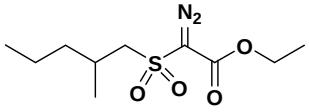
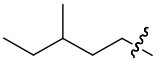
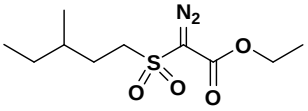
LAH reduction of 2-methyl-2-pentenal to its corresponding alcohol followed by hydrogenation with H_2/Pt successfully resulted in desired alcohol **T6.1a**. Conversion of 2-amino-3-methylpentanoic acid to 2-chloro-3-methylpentanoic acid in the presence of HCl and $NaNO_2$, followed by LAH reduction yielded alcohol **T6.1b**.

The required diazosulfones were prepared according to the method shown in Table 6, using alcohols **T6.1a** and **T6.1b** as starting materials. Alcohol **T6.1** was treated with *p*-TsCl using pyridine as a solvent at room temperature to yield tosylated compound **T6.2**, which was then converted to its corresponding sulfide **T6.3** by reacting with ethyl mercaptoacetate and K_2CO_3 in acetone at rt. Sulfone **T6.4** obtained from the Oxone oxidation of sulfide **T6.3**, was then treated with MsN_3 in the presence of DBU to yield the desired diazosulfone **T6.5** (Table 6).

Table 6. Preparation of diazosulfones.[49, 167]



i) *p*-TsCl, Pyridine at rt; ii) Ethyl mercaptoacetate, K_2CO_3 in acetone at rt; iii) Oxone in H_2O/acetone (2:1) at rt; iv) MsN_3, DBU in THF at -45 ^oC

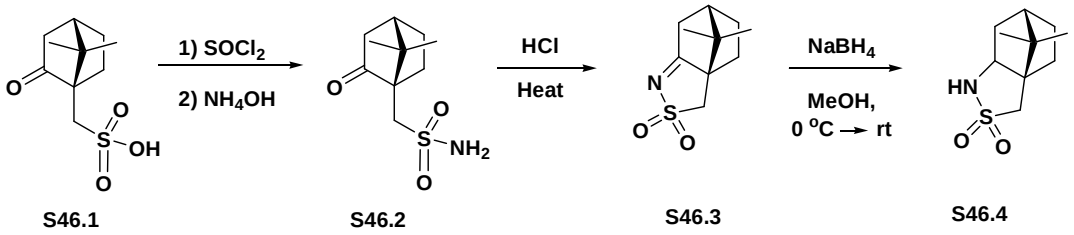
Entry	R substituent	Diazo compound, **T6.5**	Yield (%)		
			T6.2	**T6.4**	**T6.5**
T6.1a		 **T6.5a**	90	88	80
T6.1b		 **T6.5b**	92	90	82

5.1.2 Preparation of alcohol substrates for diazosulfonates

Several commercially available alcohols (**T7.1a**, **T7.1b**, **T7.1e**, **T7.1g** and **T7.1h**) and some easily prepared alcohols (**T7.1c**, **T7.1d** and **T7.1f**) were used as substrates for diazosulfonates. The synthesis of alcohols **T7.1c**, **T7.1d** and **T7.1f** will be discussed in the following section.

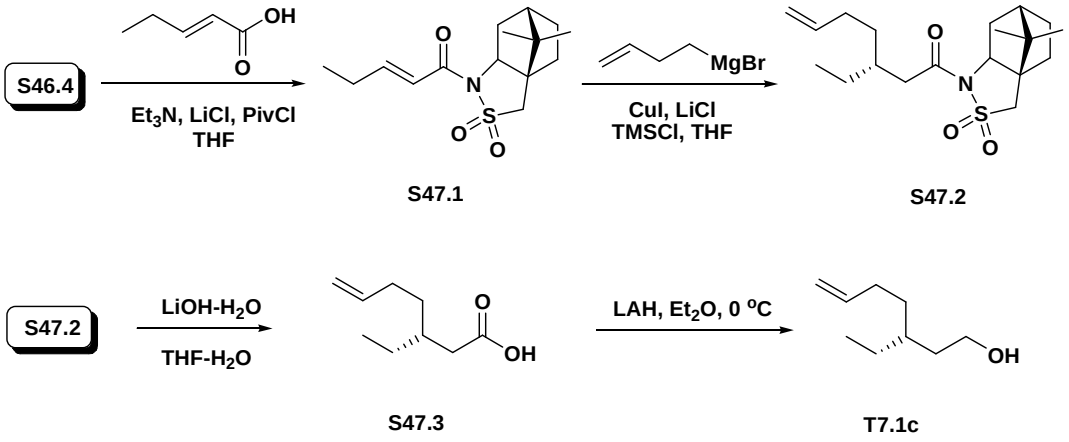
Alcohol **T7.1f** was prepared by oxidation of isopentanol *via* Swern oxidation[169] followed by exposure to methylmagnesium iodide in diethyl ether at −78 ^oC. The enantiopure alcohol **T7.1c** was prepared as a potential precursor to the natural product (−)-eburnamonine. To obtain alcohol **T7.1c** as a single enantiomer, the camphor auxiliary

S46.4 was selected. The latter was prepared from commercially available and optically pure camphorsulfonic acid **S46.1**. Compound **S46.2** yielded upon treatment with thionyl chloride followed by ammonium hydroxide (Scheme 46). The resulting camphor sulfonamide was cyclized to furnish compound **S46.3** by heating it in a 0.5 N solution of HCl. It was further reduced to the desired chiral auxiliary **S46.4** by $NaBH_4$ in MeOH.[170]



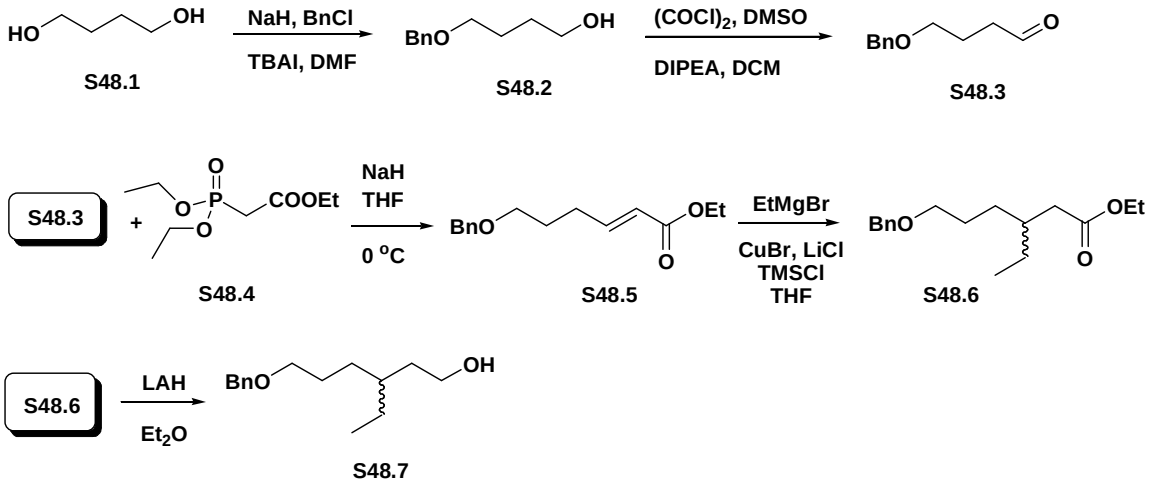
Scheme 46. Synthesis of camphor auxiliary **S46.4**.[170]

The camphor auxiliary **S46.4** upon treatment with (*E*)-pent-2-enoic acid in the presence of triethylamine, lithium chloride and pivaloyl chloride resulted in compound **S47.1**.[171] Compound **S47.1** yielded the acylated product **S47.2** upon treatment with 3-butenylmagnesium bromide. The hydrolytic cleavage of the auxiliary followed by LAH reduction resulted in alcohol **T7.1c**.[172]



Scheme 47. Synthesis of enantiopure alcohol **T7.1c** using a camphor auxiliary.

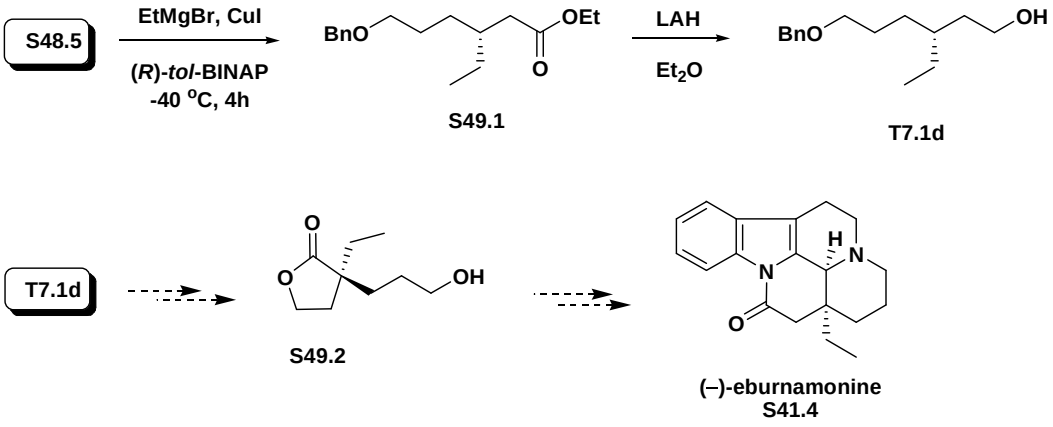
The preparation of enantiopure alcohol **T7.1d** is necessary in order to prepare a single enantiomer of key intermediate **S49.2** for the synthesis of (−)-eburnamonin **S41.4** (Scheme 49).[168] Prior to the preparation of enantiopure **T7.1d**, racemic alcohol **S48.7** was prepared to investigate the feasibility of the proposed reaction scheme (Scheme 48). Synthesis of racemic alcohol **S48.7** was initiated with diol **S48.1**. Swern oxidation of monobenzylated diol **S48.2**[169] resulted in aldehyde **S48.3**, which was subjected to the Horner–Wadsworth–Emmons reaction with triethylphosphonoacetate in the presence of sodium hydride at 0 ^{o}C to produce α,β-unsaturated ester **S48.5**.[173] Ester **S48.6** was obtained *via* Michael type 1,4 addition of ethylmagnesium bromide in the presence of copper bromide, lithium chloride and trimethylsilyl chloride. Resulted ester **S48.6** was reduced with LAH to furnish racemic alcohol **S48.7**. In order to obtain key intermediate **S49.2** in Scheme 49, it is necessary to establish a corresponding stereocenter on ester **S48.6**. Preparation of ester **S48.6** with high enantiomeric excess will be shown in Scheme 49.



Scheme 48. Synthesis of racemic alcohol **S48.7**.

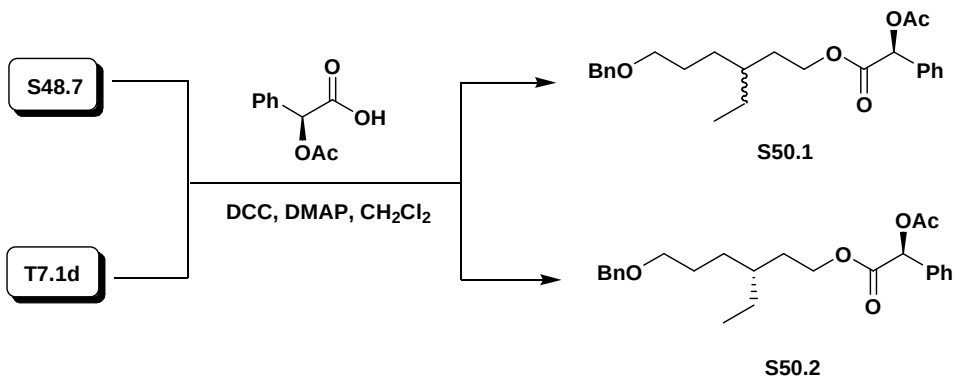
5.1.3 Coupling of the substrates with chiral molecules to study enantioselectivity

The chiral center of the ester **S49.1** was established by regio- and enantioselective addition of a Grignard reagent to α,β-unsaturated ester **S48.5**, employing commercially available chiral catalyst *tol*-BINAP. This catalyst along with copper iodide promote the regio- and enantioselective addition.[174] Therefore, the synthesis of chiral ester **S49.1** was carried out in *t*-BuOMe as a solvent at −40 ^{o}C with ethylmagnesium bromide and copper iodide in the presence of chiral catalyst (*R*)-*tol*-BINAP.[174] LAH reduction of the resulting ester **S49.1** gave corresponding alcohol **T7.1d** (Scheme 49).



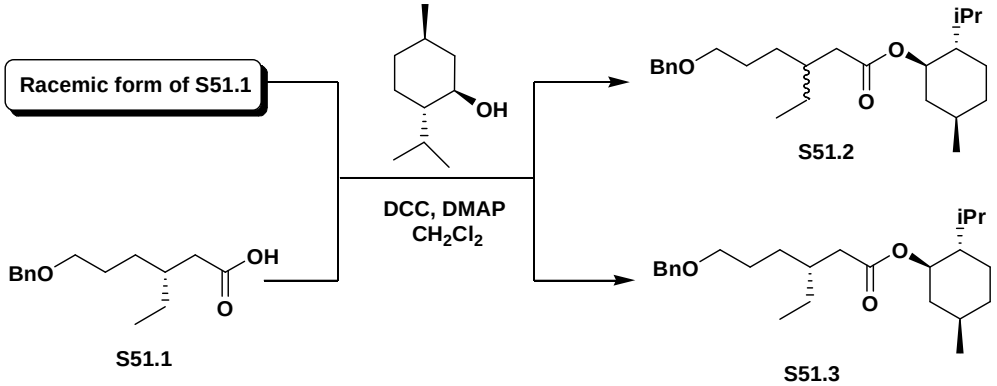
Scheme 49. Highly enantioselective synthesis of alcohol **T7.1d**.

The enatiomeric excess of the prepared alcohol **T7.1d** was determined by coupling it with selected chiral derivatizing agents.[175] Initially, chiral (*S*)-2-acetoxy-2-phenylacetic acid was used for this purpose. Diastereomeric esters **S50.1** and **S50.2** were obtained by coupling of alcohols **S48.7** and **T7.1d** with chiral (*S*)-2-acetoxy-2-phenylacetic acid, under Steglich esterification reaction conditions (DCC, DMAP in dichloromethane, Scheme 50). No distinctive signal separation could be seen in the ^{1}H NMR spectrum of **S50.2**.



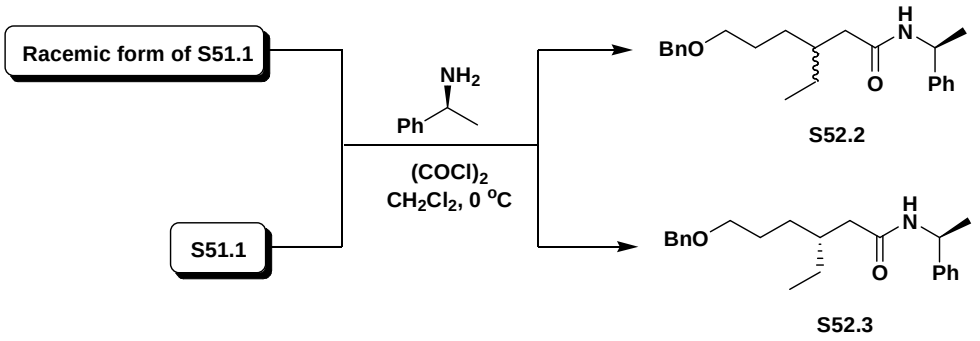
Scheme 50. Coupling of racemic and chiral alcohols with (*S*)-2-acetoxy-2-phenylacetic acid).[175]

To overcome the issue in Scheme 50, it was envisioned to introduce new chiral center of the diastereomeric ester (**S51.3**) closer to the existing chiral center. The pure enantiomer of commercially available L-menthol was chosen to serve this purpose. To couple with L-menthol, it was necessary to convert racemic ester **S48.6** and chiral ester **S49.1** to their carboxylic acid derivatives **S51.2** and **S51.3**. Hydrolysis of esters **S48.6** and **S49.1** gave their corresponding carboxylic acids, which were then reacted with L-menthol to produce esters **S51.2** and **S51.3** (Scheme 51). Similarly to the previous example (Scheme 50), the L-menthol-coupled ester showed no resolved peaks in the ^{1}H NMR spectrum.



Scheme 51. Coupling of racemic and chiral carboxylic acids with (1*R*,2*S*,5*R*)-(−)-menthol.

Since the chiral esters **S50.2** and **S51.3** could not provide NMR spectra appropriate for determination of *de*, the pure enantiomer of (*S*)-1-phenylethylamine was recognized as a suitable chiral derivatizing agent, because of its ability to form amides with carboxylic acids (Scheme 52). (*S*)-1-Phenylethylamine was coupled with racemic and chiral carboxylic acids **S51.1** to obtain the corresponding racemic (**S52.2**) and chiral (**S52.3**) amides. The ^{1}H NMRspectrum of the resulted chiral amide **S52.3** displayed several distinct peaks from which an enatiomeric ratio could be discerned. The diastereomeric excess (88%) of amide **S52.3** was found by considering the integrated area of the two peaks (at 4.46–4.46 ppm) assigned the benzyl protons (^{1}H NMR spectrum is shown in appendix III, Figure 6).



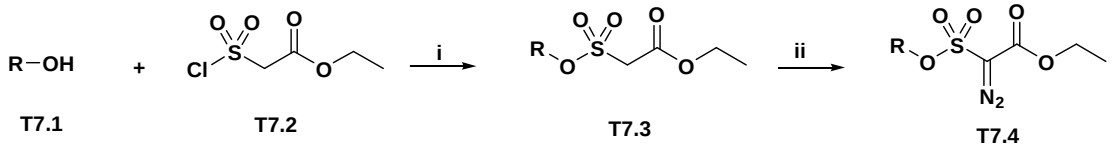
Scheme 52. Formation of amides with carboxylic acids and (*S*)-1-phenylethylamine.

5.1.4 Preparation of diazosulfonates

The commercially available alcohols [(–)-isomenthol (**T7.1a**), (–)-borneol (**T7.1c**), isopentanol (**T7.1e**), (–)-citronellol (**T7.1g**), (–)-menthol (**T7.1h**)] and prepared alcohols (**T7.1c**, **T7.1d** and **T7.1f**) were used to furnish their corresponding diazosulfonates, following a two-step sequence as shown in Table 7. The corresponding alcohols were treated with ethyl chlorosulfonylacetate, **T7.2** (prepared from ethyl

chloroacetate as described in reference[49]) to obtain sulfonates **T7.3a–h**.[48, 158] Although triethylamine had previously been used as a base[49] for the sulfonation step, imidazole has proven to be an excellent base for this reaction, and its use improved the yield of sulfonate **T7.3** significantly. The obtained sulfonates were subjected to different diazo transfer conditions: a) MsN_3, DBU, THF, −45 ^oC; b) MsN_3, DIPEA, MeCN, 0 ^oC and c) $NosN_3$, DIPEA, DMF, 0 ^oC. According to the reported work by John and Novikov,[49] $NosN_3$ is a superior diazo transfer agent for this step. Nonetheless, use of MsN_3 simplified the purification process without affecting the yield of the desired diazo compound (**T7.4**). Hence, MsN_3 was used as an efficient diazo transfer agent as shown in Table 7. In the presence of MsN_3, DIPEA in MeCN at 0 ^oC, **T7.3e** and **T7.3f** were successfully converted to their corresponding diazo compounds **T7.4e** and **T7.4f**. Due to poor yields obtained under these conditions for some of the diazosulfonates, the reactions were repeated by replacing the base and the solvent with DBU and THF respectively. Under these conditions, the yields of diazo compounds **T7.1a**, **T7.1b**, **T7.1g** and **T7.1h** improved significantly. Even though purification was easily achieved when the reaction was carried out in the presence of MsN_3, the preparation of diazo **T7.1d** was considerably more efficient with $NosN_3$ than with MsN_3. Unexpectedly, partial decomposition was observed with diazo **T7.1c**, resulting in very low yield. This step has yet to be optimized for this particular compound.

Table 7. Preparation of diazosulfonates.[49, 167]



T7.1 T7.2 T7.3 T7.4

i) Im-H in THF at rt; ii) Conditions for diazo synthesis (a) MsN_3, DBU, THF, -45 °C; (b) MsN_3, DIPEA, MeCN, 0 °C; (c) $NosN_3$, DIPEA, DMF, 0 °C

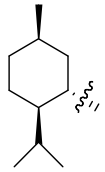
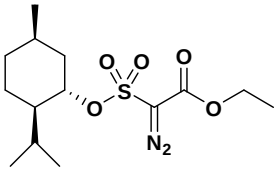
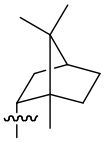
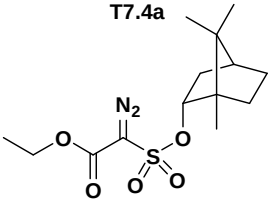
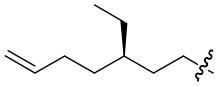
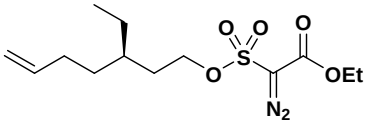
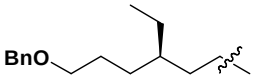
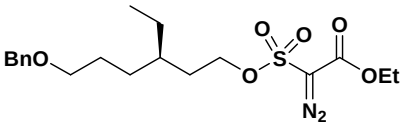
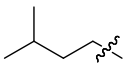
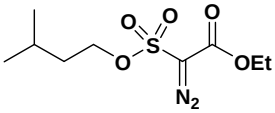
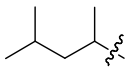
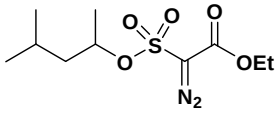
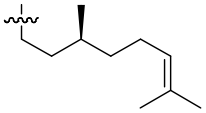
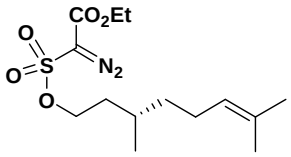
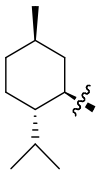
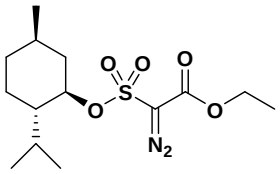
Entry	R substituent	Diazo compound, T7.4	Yield (%) T7.3	Yield (%) T7.4
T7.1a		 T7.4a	98	81[a]
T7.1b		 T7.4b	90	95[a]
T7.1c		 T7.4c	74	27[c]
T7.1d		 T7.dh	90	94[c]
T7.1e		 T7.4e	73	68[b]

Table 7. Cont.

Entry	R substituent	Diazo compound, T7.4	Yield (%)	
			T7.3	T7.4
T7.1f		 **T7.4f**	75	70[b]
T7.1g		 **T7.4g**	95	90[a]
T7.1h		 **T7.4h**	95	75[a]

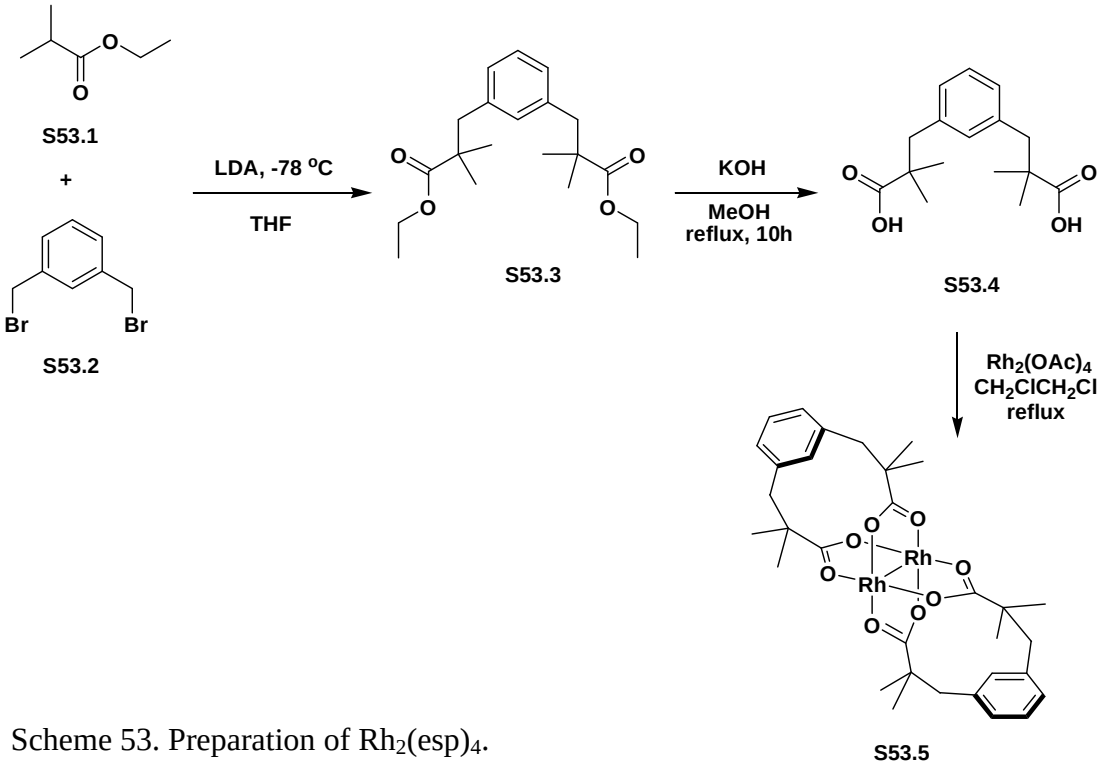
[a] Yield in the preparation of diazo compound using condition (a); [b]: Yield in the preparation of diazo compound using condition (b); [c]: Yield in the preparation of diazo compound using condition (c).

5.1.5 C–H insertion of diazosulfones and diazosulfonates

According to the work reported by John and Novikov,[49] diazosulfones and sulfonates undergo C–H insertion reactions to selectively form six-membered ring structures, despite the sterics at the tertiary carbon center.[49] In addition, the authors found that the same influence is exerted in the presence of $Rh_2(pfb)_4$, with strong electron-withdrawing ligands. This suggests that the electronic environment is another key aspect towards selectivity. Therefore, careful selection of the Rh(II) catalyst for intramolecular

C–H insertion of diazosulfones and sulfonates should allow more control over the selectivity.[166]

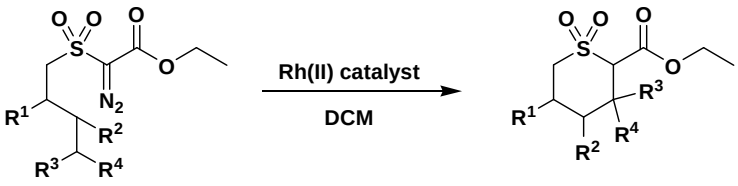
Commercially available $Rh_2(OAc)_4$ has proven to be one of the most suitable catalysts for the C–H insertion reaction of carbethoxy sulfones and sulfonates.[49, 166, 176] Du Bois has recommended $Rh_2(esp)_4$ as a superior catalyst for particular intramolecular C–H insertion reactions,[109] therefore, $Rh_2(esp)_4$ was used when appropriate. Preparation of $Rh_2(esp)_4$ was carried out in our lab utilizing readily available materials according to the synthetic procedure proposed by Du Bois,[109] with few modifications (Scheme 53). The synthesis of the catalyst was initiated by dialkylation of ethyl isobutyrate **S53.1** with freshly prepared LDA at −78 ^{o}C and with dibromo *m*-xylene **S53.2** to obtain diester **S53.3**. Hydrolysis of resulted diester **S53.3** to its corresponding dicarboxylate **S53.4** followed by metalation with $Rh_2(OAc)_4$ afforded the desired $Rh_2(esp)_2$ complex **S53.5** in 55% yield.



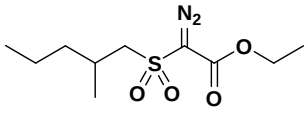
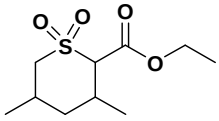
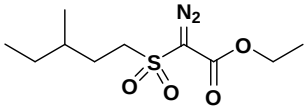
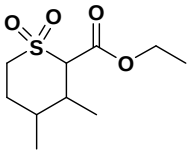
Scheme 53. Preparation of $Rh_2(esp)_4$.

The previously obtained diazosulfones (**T6.5a** and **T6.5b**) had been converted into their six-membered cyclic sulfones (**F5.1** and **F5.2**) in Dr. Novikov's lab (Table 8).[167]

Table 8. C–H insertion of carbethoxy sulfones.[49, 167]



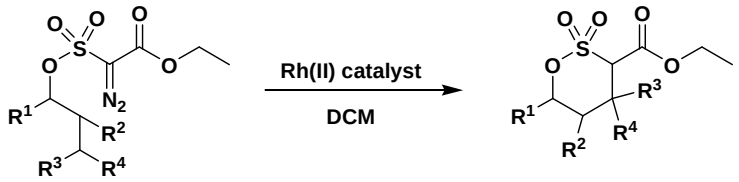
Substrate T6.5 Product F5.0

Substrate T6.5	Conditions	Product T8.1	Yield (%)
 T6.5a	$Rh_2(OAc)_4$, DCM reflux, 1h	 F5.1	60
 T6.5b	$Rh_2(OAc)_4$, DCM reflux, 1h	 F5.2	65

The previously obtained diazosulfonates (Table 7) were subjected to C–H insertion conditions with the aim of constructing δ-sultones under the influence of a suitable Rh(II) catalyst. Notably, the effective formation of new stereocenters in sultones **T5.1a**, **T5.1b**, **T5.1g** and **T5.1h** was observed. Due to this reason, these intermediates can serve as potential synthetic precursors to natural products.[167] Synthesis of (+)-bakuchiol was achieved using **T5.1g** as the key intermediate providing a quaternary center,

demonstrating the utility of the C–H insertion methodology.[157] The diazosulfonate **T7.4d** was subjected to C–H insertion conditions [2 mol% of $Rh_2(OAc)_2$] and unexpectedly it gave unidentified products. Modification of this step using $Rh_2(esp)_2$ led to the successful synthesis of the corresponding δ-sultone **T5.1d**.[158] The resulted benzyl-protected diastereomers **T5.1d**, could be used to construct the five-membered lactone **T5.2d**, which is the key intermediate of the (–)-eburnamonine (**S41.4**) synthesis (Scheme 54).[168] Additionally, preparation of **T5.1c** was planned because of its viability in the synthesis of five-membered lactone **T5.2c** (Scheme 55), which would also serve as a precursor to (–)-eburnamonine. Unexpectedly, exposure of substrate **T7.4c** to the diazo reaction conditions resulted in unidentified byproducts, with no desired cyclized products. The cyclization of (–)-menthol diazosulfonate **T7.4h** and (–)-isomenthol diazosulfonate **T7.4a** also provided useful synthetic intermediates **T5.1h** and **T5.1a** in considerably high yields. The diastereomeric ratio of δ-sultones **T5.1h** and **T5.1a** was erratically different from one experiment to the next. This behavior can be attributed to the changing nature of $Rh_2(OAc)_4$ catalyst during the reaction.[49, 109] In the case of (–)-borneol diazosulfonate **T7.4b**, two products (**T5.1b$_1$** and **T5.1b$_2$**) were formed unexpectedly. Greater amount of unexpected product **T5.1b$_1$** was formed by C–H insertion involving the methyl group, whereas the expected δ-sultone **T5.1b$_2$** was formed as the minor product by C–H insertion into the methylene bridge.

Table 9. C–H insertion of carbethoxy sulfonates.[49, 167]



Substrate T7.4 Product T5.1

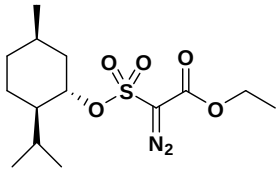
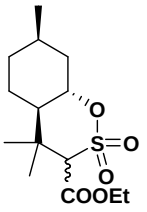
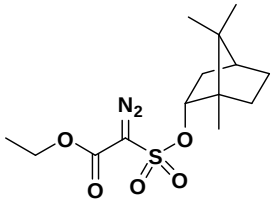
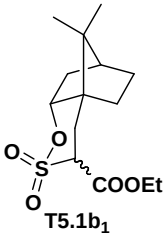
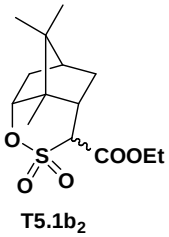
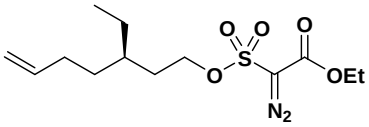
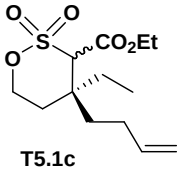
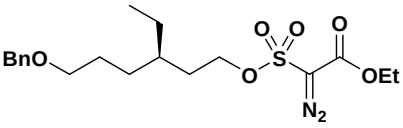
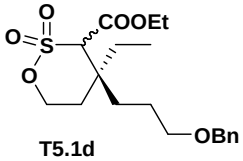
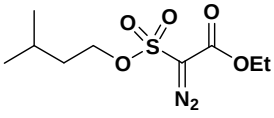
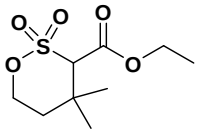
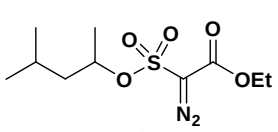
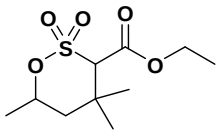
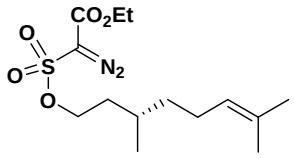
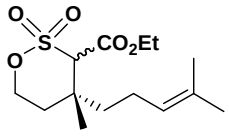
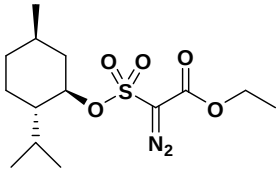
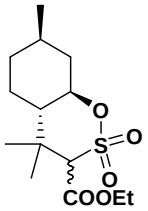
Substrate T7.4	Conditions	Product T9.1	Yield (%)
 T7.4a	$Rh_2(OAc)_4$, DCM reflux, 1h	 T5.1a	85
 T7.4b	$Rh_2(OAc)_4$, DCM reflux, 1h	 $T5.1b_1$  $T5.1b_2$	75 (~9:1)
 T7.4c	$Rh_2(OAc)_4$, DCM rt, 10h	 T5.1c	0
 T7.4d	$Rh_2(esp)_4$, DCM rt, 15h	 T5.1d	81
 T7.4e	$Rh_2(OAc)_4$, DCM reflux, 1h	 T5.1e	60

Table 9. Cont.

Substrate T7.4	Conditions	Product T9.1	Yield (%)
 T7.4f	$Rh_2(OAc)_4$, DCM reflux, 1h	 T5.1f	75
 T7.4g	$Rh_2(OAc)_4$, DCM reflux, 1h	 T5.1g	85
 T7.4h	$Rh_2(OAc)_4$, DCM reflux, 1h	 T5.1h	80

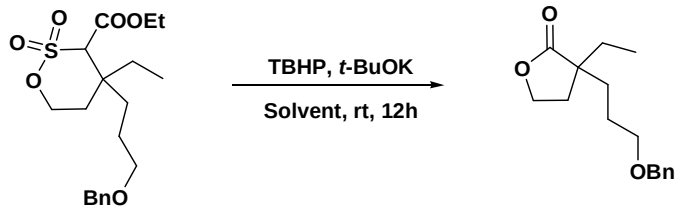
5.1.6 Oxidative conversion of δ-sultones to γ-butyrolactones

According to the previous work done in Novikov's research group,[166] *δ*-sultones when exposed to TBHP in the presence of KHMDS or *t*-BuOK are oxidatively converted to *γ*-butyrolactone. Since low yields were obtained in many cases of the reaction, optimization of the conditions for desulfonation of each substrate was necessary.

Optimization studies for the synthesis of *γ*-butyrolactone **S44.6** from desulfonation of *δ*-sultone **S44.5** are described in Table 10. The determined optimal conditions, shown in entries 7 and 8 produced *γ*-butyrolactone **S44.6** with a satisfactory

yield (75%) using 5 eq of TBHP and 6 eq of *t*-BuOK in, DME or THF as a solvent at rt. According to the data shown in Table 10, the lesser amount of base and oxidizing agent are not sufficient to drive the reaction to its completion. Meanwhile, too many equivalents of base and oxidizing agent leads to reduction in the yield of the desired *γ*-butyrolactone. Therefore, addition of 5 eq of the oxidizing agent, THBP, to the reaction mixture followed by the addition of 6 eq of the base, *t*-BuOK, in the presence of THF or DME as a solvent at room temperature were determined to be the optimized reaction conditions for oxidative desulfonation of *δ*-sultones to *γ*-butyrolactones.

Table 10. TBHP oxidative desulfonation of *δ*-sultones to *γ*-butyrolactones.



S44.5 S44.6

Entry	Conditions	Solvent	Yield (%)
1	First (3 eq)TBHP, then (4 eq) *t*-BuOK	THF	42
2	First (4 eq) *t*-BuOK , then (3 eq) TBHP	THF	20
3	Mixture of (3 eq)TBHP and (4 eq) *t*-BuOK	THF	SM
4	First (3 eq)TBHP, then (2 eq) K_2CO_3	THF	SM
5	First (3 eq)TBHP, then (4 eq) *t*-BuOK	DEE	SM
6	First (3 eq)TBHP, then (4 eq) *t*-BuOK	DME	40

Table 10. Cont.

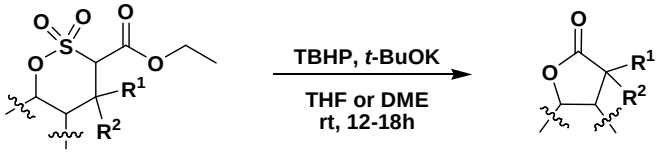
Entry	Conditions	Solvent	Yield (%)
7	First (5 eq)TBHP, then (6 eq) *t*-BuOK	DME	75
8	First (5 eq)TBHP, then (6 eq) *t*-BuOK	THF	74
9	First (10 eq)TBHP, then (12 eq) *t*-BuOK	THF	50
10	First (7 eq)TBHP, then (8 eq) *t*-BuOK	THF	65

SM=Starting material

To demonstrate the application of the oxidative conversion of δ-sultones to γ-butyrolactones using the above optimized conditions, δ-sultone substrates shown in Table 9 were selected. The conversion of simple δ-sultones **T5.1e** and **T5.1f** to γ-butyrolactones **T5.2e** and **T5.2f** was carried out resulting in 54% and 60% yields of the products, respectively. These two δ-sultones **T5.1e** and **T5.1f** exhibited the viability of the optimized oxidative desulfonation conditions on simple substrates. These relatively low yields could be due to volatility and water solubility of these low molecular weight γ-butyrolactones. To evaluate the extent of this problem, the lactones **T5.2e** and **T5.2f** were prepared using alternative routes as explained in Appendix II, Scheme 58. The volatility of **T5.2e** and **T5.2f** were assessed using a rotary evaporator. From this study, it was concluded that although lactones **T5.2e** and **T5.2f** are not extremely volatile, there is a high tendency to lose the product during the long exposure to vacuum and elevated temperatures (above 30 ^{o}C). Taking this information into account, lactones **T5.2e** and

T5.2f (Table 11) were treated carefully. In the case of δ-sultone **T5.1b$_1$**, the product **T5.2b$_1$** was isolated with 70% yield. Surprisingly, the desired product **T5.2b$_2$** could not be obtained from **T5.1b$_2$**. Instead, unidentified byproducts formed. The construction of γ-butyrolactone **T5.2d** from δ-sultone **T5.1d** in the presence of both THF and DME resulted in compatible yields, confirming that these two solvents are suitable for the oxidative desulfonation step. To demonstrate the importance of these γ-butyrolactone precursors in the synthesis of natural product, a synthetic approach towards (–)-eburnamonin,[168] consuming γ-butyrolactone **T5.2d** as a key intermediate, will be discussed in Section 5.2.

Table 11. TBHP oxidative desulfonation of δ-sultones to γ-butyrolactones.



T5.1 T5.2

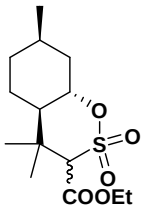
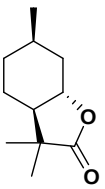
Substrate T5.1	Solvent	Product T5.2	Yield (%)
 T5.1a	DME	 T5.2a	90

Table 11. Cont.

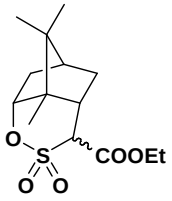
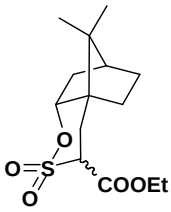
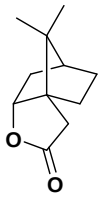
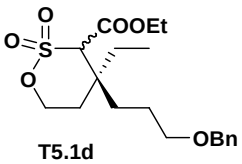
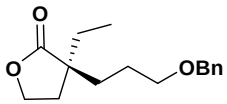
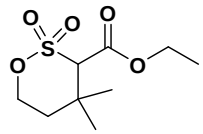
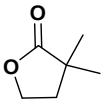
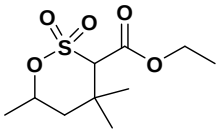
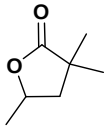
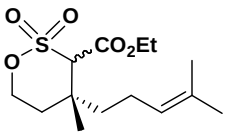
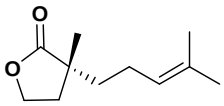
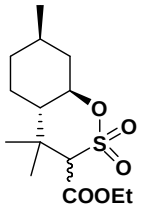
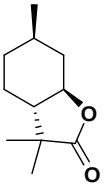
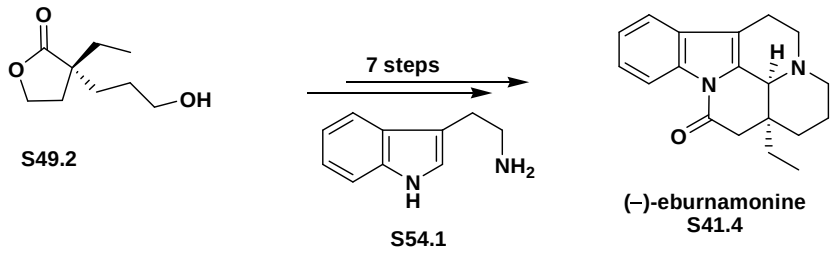
Substrate T5.1	Solvent	Product T5.2	Yield (%)
 T5.1b$_1$	DME	 T5.2b$_1$	70
 T5.1b$_2$	THF	 T5.2b$_2$	0
 T5.1d	THF DME	 T5.2d	75 74
 T5.1e	THF	 T5.2e	54
 T5.1f	THF	 T5.2f	60
 T5.1g	THF	 T5.2g	72

Table 11. Cont.

Substrate T5.1	Solvent	Product T5.2	Yield (%)
 T5.1h	THF	 T5.2h	93

5.2 Studies towards the synthesis of (–)-eburnamonine

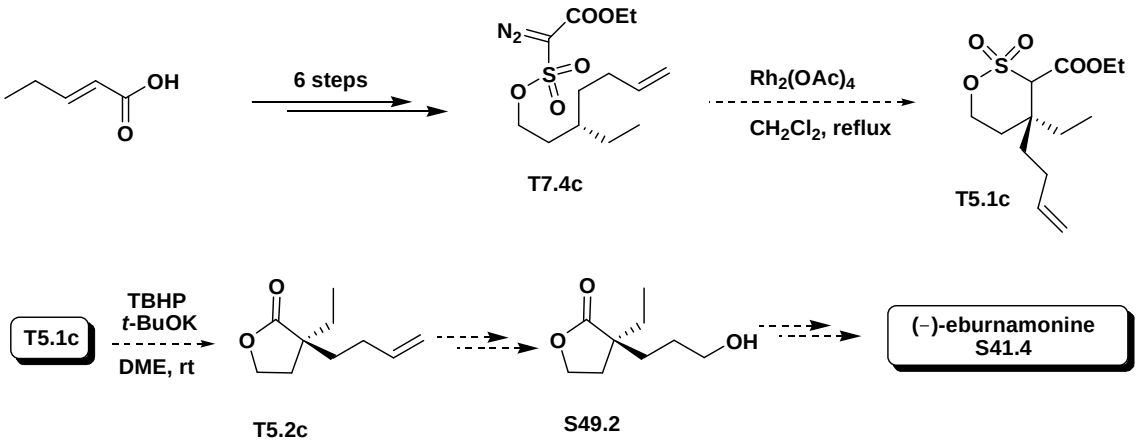
(–)-Eburnamonine is a pentacyclic indole alkaloid isolated from *Hunteria eburnea* plant. This important alkaloid is a cerebrovascular agent and has received considerable and sustained attention from chemists due to their structural complexity and biological activities.[177] Several total syntheses of (–)-eburnamonine have been carried out during the past four decades.[168, 178–180] In the total synthesis of (–)-eburnamonine by Node *et al.*,[168] the five-membered lactone **S49.2** is a key intermediate from which (–)-eburnamonine is obtained after an additional seven steps utilizing tryptamine **S54.1** (Scheme 54).[168] Using the developed methodology, γ-butyrolactone **S49.2** can be prepared from a δ-sultone **T5.1d** using oxidative desulfonation.



Scheme 54. Synthesis of (–)-eburnamonine.[168]

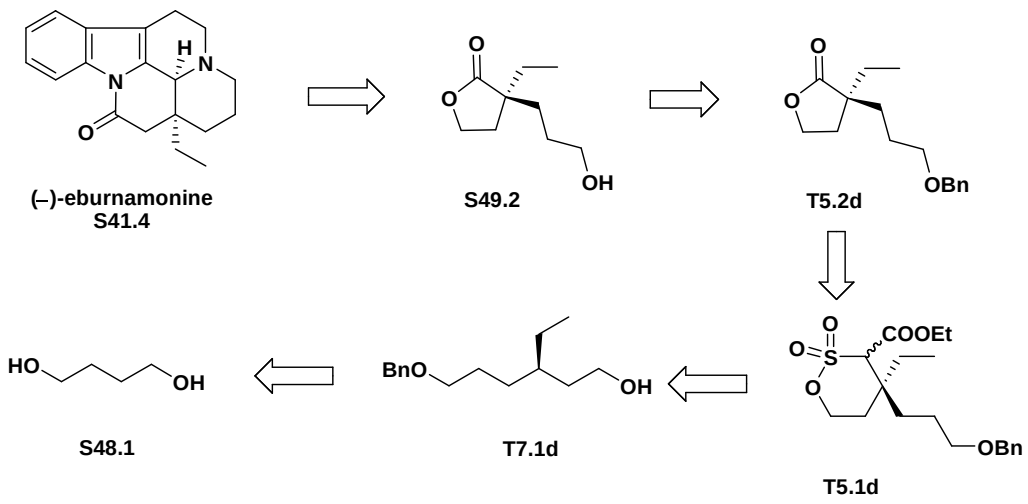
It was envisioned that the chiral lactone **T5.2c** and **T5.2d** could provide potential synthetic intermediates in the approach towards γ-butyrolactone **S49.2**. Synthesis of both γ-butyrolactones **T5.2c** and **T5.2d** were carried out in parallel.

Our approach toward the synthesis of butyrolactone **T5.2c** (Scheme 55) was initiated with previously prepared enantiopure **T7.1c** (Scheme 47), which was then converted to diazo compound **T7.4c** *via* two steps (Table 7). The diazo substrate **T7.4c** was exposed to the C–H insertion reaction conditions (Table 9). The attempt was unsuccessful and no cyclized products were isolated. However, the synthesis of the key intermediate γ-butyrolactone **S49.2** was successfully achieved *via* benzyl-protected γ-butyrolactone **T5.2d** as shown in Schemes 56 and 57.



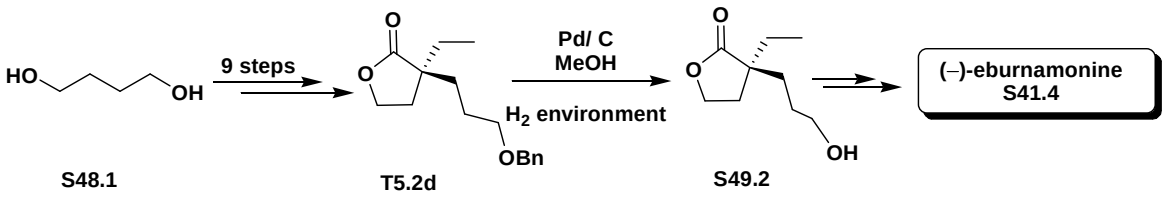
Scheme 55. Approach towards the synthesis of γ-butyrolactone **T5.2c**.

As shown in the retrosynthetic analysis (Scheme 56), total formal synthesis of (–)-eburnamonine can be achieved using commercially available 1,4-butanediol **S48.1** as a low-cost and readily available starting material.



Scheme 56. Retrosynthetic analysis of (–)-eburnamonine.

The chiral lactone **T5.2d**, which was synthesized from diol **S48.1**, was subjected to catalytic hydrogenolysis conditions to deprotect the benzyl group. The resulting lactone **S49.2** can be a potential synthetic intermediate towards the synthesis of (–)-eburnamonine (Scheme 57).[168]



Scheme 57. Preparation of chiral key intermediate **S49.2** to form (–)-eburnamonine.

5.3 Conclusion

In summary, new potentially useful synthetic intermediates were prepared by diazosulfonate and diazosulfone C–H insertion from easily available starting materials. Oxidative conversion of δ-sultones, which are the product of C–H insertion on diazosulfonates, to γ-butyrolactones by treatment with TBHP and *t*-BuOK was optimized

to provide consistently good yields of the lactone products. Using this methodology, the key intermediate in the synthesis of (−)-eburnamonine was prepared from commercially available 1,4-butane diol.

CHEPTER VI

EXPERIMENTAL SECTION FOR RHODIUM-CATALYZED INTRAMOLECULAR C–H INSERTION STUDIES ON DIAZOSULFONATES

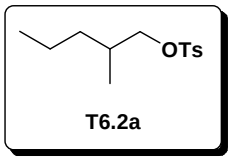
6.1 General information and instrumentation

All reactions were carried out under an inert nitrogen atmosphere unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 500 NMR spectrometer. All spectra were obtained in deuterochloroform ($CDCl_3$). Chemical shifts are reported in ppm relative to tetramethylsilane (TMS). Spin-spin coupling constants, *J*, are reported in hertz (Hz). Infrared (IR) spectra were acquired on a Perkin Elmer Spectrum 400 FT-IR/FT-FIR spectrometer. HRMS data were obtained on an Agilent 61969A TOF high resolution mass spectrometer using electrospray ionization (ESI). Melting points were determined on a MEL-TEMP melting point apparatus. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F254 (E. Merck no. 5715-7) pre-coated plates. Purification by column chromatography was performed using 40-63 μm silica gel (Merck, Geduran, no. 11567-1) as the stationary phase. THF was distilled over sodium-benzophenone under nitrogen before use. Dichloromethane was distilled over calcium hydride under nitrogen atmosphere. All other chemicals were used as purchased without further purification, unless mentioned.

6.2 Procedures and physical data for compounds from Table 6

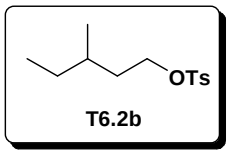
General procedure for tosylation (T6.2a–T6.2b)

A solution of alcohol **T6.1** (1 equiv) and tosyl chloride (3 equiv) in pyridine (10 mL/mmol) was stirred at rt for 24 h. Upon completion of the reaction, the reaction mixture was diluted with 10 mL of ethyl acetate, washed with water (10 mL), a 1 N solution of hydrochloric acid (10 mL) and again with water (10 mL). The organic layer was then dried with anhydrous magnesium sulfate, filtered and volatiles were removed under reduced pressure. The crude product was purified by column chromatography on silica gel using petroleum ether.



T6.2a

2-Methylpentyl 4-methylbenzenesulfonate (T6.2a). The compound was purified by column chromatography on silica gel (petroleum ether). Pale yellow oil (90%). R_f = 0.40 (petroleum ether). The physical data of **T6.2a** match with its previously reported data of the compound.[49]



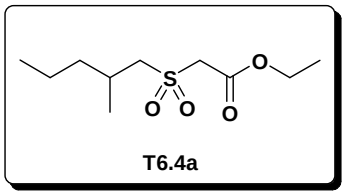
T6.2b

3-Methylpentyl 4-methylbenzenesulfonate (T6.2b). The compound was purified by column chromatography on silica gel (petroleum ether). Pale yellow oil (94%). R_f = 0.35 (petroleum ether). The physical data of **T6.2b** match with its previously reported data of the compound.[49]

General procedure for sulfones (T6.4a–T6.4b)

The corresponding tosylated compound **T6.2** (1.0 equiv, 0.5 to 5 mmol) was dissolved in acetone (20 mL/mmol) under nitrogen atmosphere. K_2CO_3 (2.0 equiv) was then added to

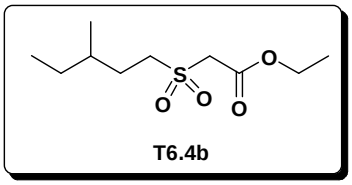
the reaction mixture followed by ethyl mercaptoacetate (1.5 mmol). The reaction mixture was then stirred for 24 h at rt. The volatiles were removed under reduced pressure, and the resulted residue was partitioned between ethyl acetate (20 mL) and water (10 mL). After separating the organic layer, the aqueous layer was further washed with ethyl acetate (2 × 20 mL). The combined organic layers were dried with anhydrous magnesium sulfate and volatiles were removed under reduced pressure. The obtained crude sulphide **T6.3** was dissolved in acetone (2 mL), then water was added (5 mL) followed by Oxone (4 mmol). The reaction mixture was stirred for 12 h at rt. Upon completion of the reaction, the product was extracted with ethyl acetate (20 mL). The separated aqueous layer was washed again with two additional portions of ethyl acetate (10 mL). The combined organic layers were dried with anhydrous magnesium sulfate, filtered and volatiles were removed under reduced pressure. The crude sulfone was purified by column chromatography on silica column (EtOAc-hexanes) to yield the pure product.



T6.4a

Ethyl 2-(2-methylpentylsulfonyl)acetate (T6.4a). The compound was purified by column chromatography on silica gel (1:5, EtOAc-hexane). Pale yellow oil (88%). R_f = 0.30 (1:5, EtOAc-hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91 (t, J = 7.0 Hz, 3H), 1.16 (d, J = 6.5 Hz, 3H), 1.33 (t, J = 7.0 Hz, 3H), 1.29–1.39 (m, 4H), 1.46–1.55 (m, 1H), 3.09 (dd, J = 14.0, 8.0 Hz, 1H), 3.32 (dd, J = 14.0, 4.5 Hz, 1H), 3.95 (s, 2H), 4.28 (q, J = 7.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1 (CH_3), 14.4 (CH_3), 19.8 (CH_2), 20.0 (CH_3), 28.0 (CH), 39.1 (CH_2), 58.9 (CH_2), 59.8 (CH_2), 62.8 (CH_2), 163.4 (C). HRMS

(ESI) calcd for $C_{10}H_{24}NO_4S$ $[M+NH_4]^+$ 254.1432, found 254.1425. Note: equivalence of the two CH_3 groups is coincidental.

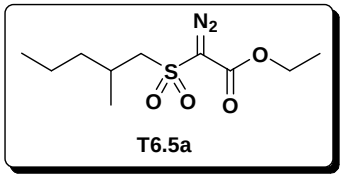


Ethyl 2-(3-methylpentylsulfonyl)acetate (6.4b). The compound was purified by column chromatography on silica gel (1:5, EtOAc-hexane). Pale yellow oil (90%). R_f = 0.30 (1:5, EtOAc-hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91 (t, J = 7.5 Hz, 3H), 0.94 (d, J = 7.0 Hz, 3H), 1.20–1.28 (m, 1H), 1.33 (t, J = 7.0 Hz, 3H), 1.34–1.43 (m, 1H), 1.49–1.56 (m, 1H), 1.64–1.73 (m, 1H), 1.85–1.94 (m, 1H), 3.19–3.33 (m, 2H), 3.92 (s, 2H), 4.28 (q, J = 7.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.3 (CH_3), 14.2 (CH_3), 18.9 (CH_3), 28.3 (CH_2), 29.1 (CH_2), 33.8 (CH), 51.9 (CH_2), 57.4 (CH_2), 62.9 (CH_2), 163.3 (C). HRMS (ESI) calcd for $C_{10}H_{24}NO_4S$ $[M+NH_4]^+$ 254.1432, found 254.1421.

General procedure for diazo compounds (T6.5a–T6.5b).

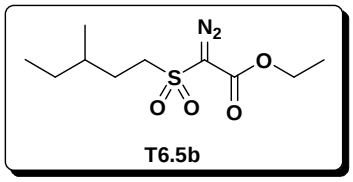
The corresponding sulfone ester **T6.4** (1 mmol) in THF (5mL/mmol) was cooled to –45 ^{o}C and to this solution mesyl azide was added (1.1 equiv). DBU (1.5 equiv) was then added dropwise over a 2–3 min period. After stirring at –45 ^{o}C for 1 h, the solution was warmed to 25 ^{o}C over a 15–20 min period, diluted with 20 mL of half-saturated aqueous solution of ammonium sulfate, and the aqueous layer was extracted with 3 × 10 mL of dichloromethane. The combine organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (1:9–1:5, EtOAc-hexanes) yielded the pure product.

Note: All diazo compounds do not show the diazo carbon in their ^{13}C spectra. IR (neat, cm^{-1}, ν): 2130 (N=N=C)



T6.5a

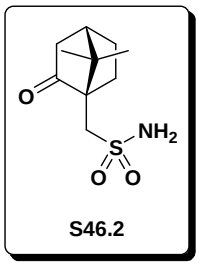
Ethyl 2-(2-methylpentylsulfonyl)diazoacetate (6.5a). The compound was purified by column chromatography on silica gel (1:5, EtOAc-hexane). Colorless oil (80%). R_f = 0.32 (1:5, EtOAc-hexane). ^1H NMR (500 MHz, $CDCl_3$): δ 0.92 (t, J = 7.0 Hz, 3H), 1.15 (d, J = 7.0 Hz, 3H), 1.30 (t, J = 6.9 Hz, 3H), 1.34–1.41 (m, 4H), 2.15–2.25 (m, 1H), 3.21 (dd, J = 14.0, 8.0 Hz, 1H), 3.45 (dd, J = 14.0, 4.5 Hz, 1H), 4.34 (q, J = 7.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1 (CH_3), 14.5 (CH_3), 19.7 (CH_2), 19.9 (CH_3), 28.9 (CH), 38.9 (CH_2), 62.7 (CH_2), 63.0 (CH_2), 160.4 (C). IR (neat, cm^{-1}, ν): 2129, 1714, 1333, 1146.



T6.5b

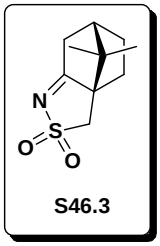
Ethyl 2-(3-methylpentylsulfonyl)diazoacetate (6.5b). The compound was purified by column chromatography on silica gel (1:5, EtOAc-hexane). Colorless oil (88%). R_f = 0.32 (1:5, EtOAc-hexane). ^1H NMR (500 MHz, $CDCl_3$): δ 0.89 (t, J = 7.0 Hz, 3H), 0.91 (d, J = 7.0 Hz, 3H), 1.18–1.26 (m, 1H), 1.34 (t, J = 7.0 Hz, 3H), 1.34–1.42 (m, 1H), 1.46–1.54 (m, 1H), 1.60–1.68 (m, 1H), 1.80–1.88 (m, 1H), 3.32–3.46 (m, 2H), 4.34 (q, J = 7.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.3 (CH_3), 14.5 (CH_3), 19.0 (CH_3), 29.0 (CH_2), 29.1 (CH_2), 33.5 (CH), 54.9 (CH_2), 62.7 (CH_2), 160.3 (C). IR (neat, cm^{-1}, ν): 2129, 1711, 1333, 1146.

6.3 Procedures and physical data for compounds from Scheme 46



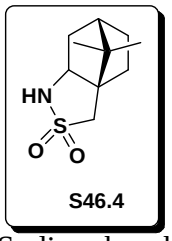
S46.2

1-[(1*R*,4*S*)-7,7-Dimethyl-2-oxobicyclo[2.2.1]hept-1-yl]methanesulfonamide (S46.2). Into a two-necked round-bottom flask, a reflux condenser was fitted with a bubbler for monitoring gas evolution. Camphorsulfonic acid **S46.1** (3.00 g, 12.9 mmol) and 50 mL of anhydrous chloroform were added to the flask. The suspension of camphorsulfonic acid was heated to reflux and freshly distilled thionyl chloride (1.5 mL, 20 mmol) was then added dropwise over a 1 h period. Heating was continued for 12–14 h until gas evolution (sulfur dioxide and hydrogen chloride) had ceased. The resultant solution of camphorsulfonyl chloride in chloroform was converted to camphorsulfonamide without further purification. A two-neck round-bottom flask was charged with 45 mL of ammonium hydroxide and the solution was cooled to 0 ^{o}C. The above-prepared crude camphorsulfonyl chloride solution was added dropwise to the ammonium hydroxide solution at 0–10°C over a period of 1 h. The reaction mixture was warmed to room temperature and stirred for 4 h. The organic layer was separated and the aqueous layer was washed with dichloromethane (3 × 25 mL). The combined organic layers were washed with brine (25 mL), dried over anhydrous magnesium sulfate and filtered. The volatiles were removed under reduced pressure yielding 2.99 g (92%) of crude camphorsulfonamide **S46.2** as a white solid. The physical data of **S46.2** match with its previously reported data of the compound.[170]



S46.3

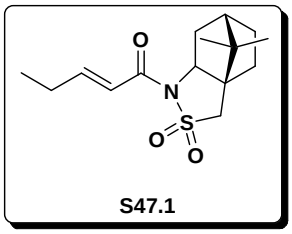
(1*R*,7*S*)-10,10-Dimethyl-3-thia-4-azatricyclo[5.2.1.01,5]dec-4-ene 3,3-dioxide (S46.3). 125 mL of a 1 N solution of HCl was added to crude camphorsulfonamide **S46.2** (2.99 g, 12.9 mmol) and the reaction mixture was refluxed overnight. Upon completion of the reaction, needle-like crystals were collected by filtering through a sintered funnel and crystals were washed with copious amounts of water. The product was dried under vacuum yielding 1.50 g (55%) of the cyclized compound **S46.3** as white crystals. The physical data of **S46.3** match with its previously reported data of the compound.[170]



S46.4

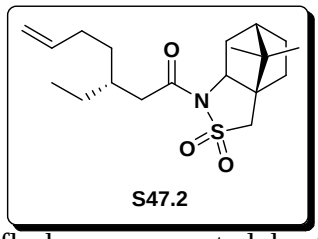
(1*R*,7*S*)-10,10-Dimethyl-3-thia-4-azatricyclo[5.2.1.01,5]decane 3,3-dioxide (S46.4). The compound **S46.3** (1.50 g, 7.00 mmol) was dissolved in 20 mL of anhydrous methanol and the mixture was cooled to 0 ^{o}C. Sodium borohydride (400 mg, 11.0 mmol) was then added to the reaction mixture and stirred for 4 h at 0 ^{o}C. Then 10 mL of a 0.1 N solution of HCl was added to the mixture and volatiles were removed under reduced pressure. The remaining aqueous layer was extracted with ethyl acetate (2 × 50 mL) followed by drying over anhydrous magnesium sulfate and filtration. Volatiles were removed under reduced pressure and 1.28 g (86%) of the crude product **S46.4** was obtained as a white solid. The physical data of **S46.4** match with its previously reported data of the compound.[170]

6.4 Procedures and physical data for compounds from Scheme 47



S47.1

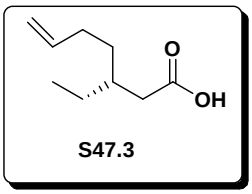
(2*E*)-1-[(1*R*,7*S*)-10,10-dimethyl-3,3-dioxido-3-thia-4-azatricyclo[5.2.1.01,5]dec-4-yl]pent-2-en-1-one (S47.1). To the solution of (*E*)-pent-2-enoic acid (100 mg, 1.00 mmol) and triethylamine (252 mg, 2.50 mmol) in 5 mL of THF, pivaloyl chloride (120 mg, 1.00 mmol) was added at –25 ^{o}C. The resulting mixture was stirred at –20 ^{o}C for 2 h. Lithium chloride (46.6 mg, 1.10 mmol) was then added, followed by camphor auxiliary **S46.4** (215 mg, 1.00 mmol). The mixture was warmed to rt and stirred for 4h. THF was removed under reduced pressure, and the resulting residue was diluted with 10 mL of ethyl acetate and 10 mL of a 5% solution of potassium hydrogen sulfate. The organic layer was further washed with a solution of potassium hydrogen sulfate (10 mL), brine (10 mL), a 1 M aqueous solution of sodium bicarbonate (2 × 10 mL) and again with brine (10 mL).The organic layer was dried over anhydrous magnesium sulfate, filtered and volatiles were removed under reduced pressure. Purification of the resulting residue by column chromatography on silica gel (1:7, EtOAc-hexane) afforded 2.60 g (64%) of compound **S47.1** as a pale yellow oil. R_f = 0.25 (1:5, EtOAc-hexane). The physical data of **S47.1** match with its previously reported data of the compound.[181]



S47.2

Allylated camphor auxiliary (S47.2). Copper(I) bromide (9.5 mg, 0.050 mmol) and lithium chloride (4.2 mg, 0.10 mmol) were added to a dried round bottom flask. The flask was evacuated, heated with a heat gun and allowed to cool to rt under vacuum after which it was filled with nitrogen. THF (1.0 mL) was then added to the above mixture and

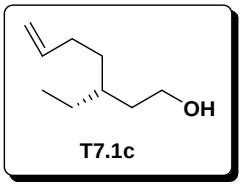
the reaction mixture was stirred for 10 min. The resulting homogeneous reaction mixture was cooled to 0 ^{o}C and ester **S47.1** (73.4 mg, 0.250 mmol) in 1.0 mL of THF was added followed by trimethylsilyl chloride (38 μL, 0.30 mmol). The solution was stirred at 0 ^{o}C for 15 min. A 2.0 M solution of ethylmagnesium bromide in THF (185 μL, 0.370 mmol) was then added dropwise. The resulting reaction mixture was stirred for 1 h at 0 ^{o}C and poured into 10 mL of saturated aqueous solution of ammonium chloride. The mixture was extracted with diethyl ether (3 × 5 mL). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and volatiles were removed under reduced pressure. Purification of the resulting residue by column chromatography on silica gel (1:7, EtOAc-hexane) yielded 54 mg (62%) of compound **S47.2** as a white solid. R_f = 0.35 (1:5, EtOAc-hexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.85 (t, J = 7.0 Hz, 3H), 0.99–1.15 (s, 6H), 1.30–1.50 (m, 11H), 1.90 (m, 1H), 2.10 (m, 3H), 2.50–2.70 (m, 1H), 3.35 (q, J = 14.1 Hz, 2H), 3.90 (t, J = 6.0 Hz, 1H), 4.90 (dd, J = 16.6, 5.0 Hz, 2H), 5.80 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 10.1 (CH_2), 19.2 (CH_3), 20.1 (CH_3), 25.7 (CH_2), 29.6 (CH_2), 30.2 (CH_2), 32.1 (CH_2), 34.9 (CH_2), 35.3 (CH_2), 37.9 (CH_2), 39.0 (CH), 43.7 (C), 47.1 (CH), 47.6 (C), 52.3 (CH_2), 64.6 (CH), 113.7 (CH_2), 138.1 (CH), 171.1 (C).



S47.3

(*S*)-3-Ethylhept-6-enoic acid (S47.3). 1:4 mixture of THF and water (3 mL) was added to compound **S47.2** (54.0 mg, 0.160 mmol) and the reaction mixture was cooled to 0 ^{o}C. Hydrogen peroxide (18 μL from a 30% aqueous solution of hydrogen peroxide, 0.63 mmol) was then added followed by lithium hydroxide (9.9 mg, 0.24 mmol) and the

reaction mixture was stirred for 5 h. Upon completion, the reaction was quenched with saturated aqueous solution of sodium sulfite (3 mL), THF was removed under reduced pressure and the auxiliary was removed by extracting the aqueous layer to dichloromethane (3 × 10 mL). The aqueous layer was cooled to 0 ^{o}C and the mixture was brought to pH=1 with a 6 N solution of HCl and phosphoric buffer. The acidified aqueous layer was then extracted with ethyl acetate (5 × 10 mL), the combined extracts were dried with anhydrous magnesium sulfate, filtered and volatiles were removed under reduced pressure yielding 24 mg (99%) of the crude carboxylic acid **S47.3** as a colorless oil. R_f = 0.20 (1:5, EtOAc-hexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.80 (t, J = 12.8 Hz, 3H), 1.25–1.40 (m, 4H), 1.80 (m, 1H), 2.0 (m, 2H), 2.20 (d, J = 11.1 Hz, 2H), 4.38 (dd, J = 12.5, 4.5 Hz, 2H), 5.75 (m, 1H), 10.21–10.55 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 11.1 (CH_3), 26.5 (CH_2), 32. 9 (CH_2), 36.0 (CH), 36.1 (CH_2), 38.8 (CH_2), 115.0 (CH_2), 139.0 (CH), 180.4 (C).

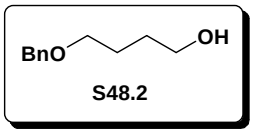


T7.1c

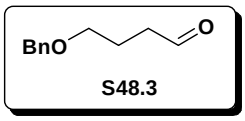
3-Ethylhept-6-en-1-ol (T7.1c). Lithium aluminum hydride (25.5 mg, 0.670 mmol) was added to a solution of carboxylic acid **S47.3** (42.0 mg, 0.270 mmol) at 0 ^{o}C. The reaction mixture was refluxed for 12 h under nitrogen at rt. Upon completion, the reaction mixture was cooled to 0 ^{o}C and quenched with deionized water, a solution of 15% potassium hydroxide followed by additional amount of deionized water. The resulting mixture was stirred for 1 h with anhydrous magnesium sulfate. The resulting reaction mixture was filtered through a celite plug and volatiles were removed under reduced pressure. Purification of the crude product by column chromatography on silica gel (1:3, EtOAc-

hexane) afforded 13.8 mg (72%) of alcohol **T7.1c** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.90 (t, J = 11.8 Hz, 3H), 1.70 (s, 1H), 3.40 (t, J = 12.5 Hz, 2H), 1.20–1.40 (m, 5H), 1.55 (m, 2H), 2.05 (m, 2H), 4.95 (dd, J = 12.1, 2.8 Hz, 2H), 5.80 (m, 1H).

6.5 Procedures and physical data for compounds from Scheme 48

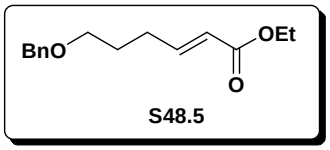


4-(Benzyloxy)butan-1-ol (S48.2). Butane-1,4-diol (5.00 g, 55.5 mmol) in DMF (5 mL) was added dropwise at 0 ^{o}C to a stirred suspension of sodium hydride (882 mg, 22.2 mmol). After stirring for 30 min, NBu_4I (21 mg, 0.055 mmol) was added. Benzyl chloride (2.88 g, 22.8 mmol) in DMF (5 mL) was then added to the reaction mixture dropwise at 0 ^{o}C. After stirring the reaction mixture at rt for 14 h, water (25 mL) was added and the product was extracted with diethyl ether (50 mL). The organic layer was washed with brine and dried with anhydrous magnesium sulfate, filtered and volatiles were evaporated under reduced pressure. Purification of the resulting residue by column chromatography on silica gel (1:7, EtOAc-hexane) yielded 2.60 g (70%) of compound **S48.2** as a pale yellow oil. R_f = 0.35 (1:5, EtOAc-hexane). The physical data of **S48.2** match with its previously reported data of the compound.[182]



4-(Benzyloxy)butanal (S48.3). To a solution of oxalyl chloride (1.3 mL, 15 mmol) in 5 mL of dichloromethane, dimethyl sulfoxide (2.4 mL, 34 mmol) was added at −78 ^{o}C and stirred for 15 min. Alcohol **S48.2** (2.43 g, 13.5 mmol) in 5 mL of dichloromethane was added dropwise to the reaction mixture and stirred for 30 min at −78 ^{o}C followed by the addition of *N*,*N*-ethyl-

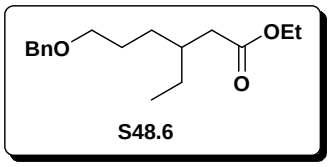
diidopropylamine (11.1 mL, 67.4 mmol). The mixture was warmed to –60 ^{o}C over 30 min and diluted with water (10 mL) at 0 ^{o}C. The reaction mixture was extracted with diethyl ether (15 mL), and the organic layer was washed with a solution of 2 N hydrochloric acid, saturated aqueous solution of sodium bicarbonate (10 mL) and brine followed by drying with anhydrous magnesium sulfate and filtration. Volatiles were removed under reduced pressure. Purification of the resulting residue by column chromatography (1:5, EtOAc-hexane) afforded 2.30 g (95%) of compound **S48.3** as a colorless oil. R_f = 0.38 (1:5, EtOAc-hexane). The physical data of **S48.3** match with its previously reported data of the compound.[183]



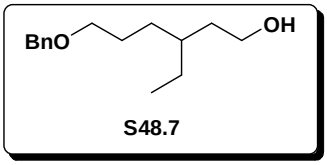
S48.5

(*E*)-Ethyl 6-(benzyloxy)hex-2-enoate (S48.5). To a solution of sodium hydride (92.5 mg, 2.32 mmol, 60% dispersion in mineral oil, washed free of oil with anhydrous THF) triethyl phosphonoacetate (380 mg, 1.70 mmol) in 2 mL of THF was added at 0 ^{o}C. The mixture was stirred for 30 min at 0 ^{o}C and a solution of aldehyde **S48.3** (275 mg, 1.54 mmol) was added dropwise under nitrogen. The resulting reaction mixture was left to stir for 30 min at 0 ^{o}C, and quenched with saturated aqueous solution of ammonium chloride (15 mL). The reaction mixture was allowed to warm up to rt and the product was extracted with ethyl acetate (2 × 15 mL) and the combined organic extracts were dried over anhydrous magnesium sulfate and filtered. Volatiles were removed under reduced pressure. Purification of the resulting residue by column chromatography on silica gel (1:9, EtOAc-hexane) afforded 268 mg (70%) of unsaturated ester **S48.5** as a colorless oil. R_f =

0.40 (1:7, EtOAc-hexane): The physical data of **S48.5** match with its previously reported data of the compound.[182]



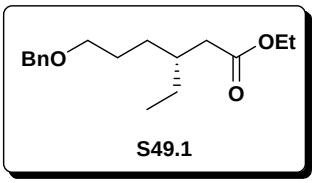
Ethyl 6-(benzyloxy)-3-ethylhexanoate (S48.6). Copper(I) bromide (14.5 mg, 0.100 mmol) and lithium chloride (8.5 mg, 0.20 mmol) were added to a round bottom flask. The flask was evacuated, heated with a heat gun, allowed to cool to rt under vacuum and then filled with nitrogen. THF (3 mL) was then added and the reaction mixture was stirred for 10 min. The mixture was cooled to 0 ^{o}C and ester **S48.5** (250 mg, 1.01 mmol) in 2 mL of THF was added followed by trimethylsilyl chloride (140 μL, 1.11 mmol). The solution was stirred at 0 ^{o}C for 15 min and 2.0 M ethylmagnesium bromide in THF (0.8 mL, 1 mmol) was added dropwise. The resulting reaction mixture was stirred for 1 h at 0 ^{o}C and poured into 10 mL of saturated aqueous solution of ammonium chloride. The mixture was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and filtered. Volatiles were removed under reduced pressure. Purification of the crude product by column chromatography on silica gel (1:5, EtOAc-hexane) provided 275 mg (90%) of pure ester **S48.6** as a pale yellow oil. R_f = 0.40 (1:3, EtOAc-hexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.75 (t, J = 7.4 Hz, 3H), 1.10 (t, J = 7.2 Hz, 3H), 1.15–1.30 (m, 4H), 1.48 (m, 2H), 1.70 (m, 1H), 2.10 (dd, J = 13.6, 6.9 Hz, 2H), 3.20 (t, J = 7.4 Hz, 2H), 3.98 (q, J = 6.9 Hz, 2H), 4.35 (s, 2H), 7.10–7.30 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 11.2 (CH_3), 14.7 (CH_3), 26.7 (CH_2), 27.2 (CH_2), 30.2 (CH_2), 36.7 (CH), 39.2 (CH_2), 60.6 (CH_2), 71.0 (CH_2), 73.3 (CH_2), 127.9 (CH), 128.04 (CH), 128.8 (C), 139.0 (C), 174.0 (C). HRMS (ESI) calcd for $C_{17}H_{26}O_3Na$ $[M+Na]^+$ 301.1774, found 301.1743.



S48.7

6-(Benzyloxy)-3-ethylhexan-1-ol (S48.7). A round bottom flask was charged with ester **S48.6** (275 mg, 0.990 mmol) and flushed with nitrogen followed by the addition of anhydrous diethyl ether (5 mL). The solution was cooled to 0 ^{o}C and lithium aluminum hydride (45.0 mg, 1.18 mmol) was added. The reaction mixture was stirred for 24 h at rt. Upon the completion of the reaction, the mixture was cooled to 0 ^{o}C and quenched with water (50 μL) followed by addition of 50 μL of a solution of 15% potassium hydroxide and 150 μL of water. The resulting mixture was stirred for 1 h and dried with anhydrous magnesium sulfate. The mixture was filtered through a Celite plug and the Celite plug was rinsed with excess diethyl ether. Volatiles were removed under vacuum yielding 216 mg (95%) of alcohol **S48.7** as a colorless oil. R_f = 0.20 (1:5, EtOAc-hexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.75 (t, J = 8.1 Hz, 3H), 1.25 (m, 2H), 1.25 (m, 2H), 1.50 (m, 2H), 1.35 (m, 1H), 2.17 (m, 2H), 3.50 (t, J = 6.7 Hz, 2H), 2.50 (s, 1H), 3.50 (t, J = 6.7 Hz, 2H), 4.40 (s, 2H), 7.20–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 11.1 (CH_3), 26.4 (CH_2), 27.2 (CH_2), 29.9 (CH_2), 35.9 (CH), 36.7 (CH_2), 61.20 (CH_2), 71.30 (CH_2), 73.35 (CH_2), 127.95 (CH), 128.11 (CH), 128.8 (CH), 139.0 (C). HRMS (ESI) calcd for $C_{17}H_{26}O_3Na$ $[M+H]^+$ 237.1849, found 237.1853.

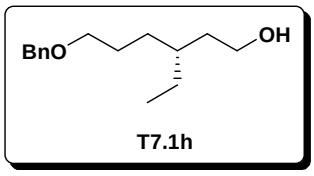
6.6 Procedures and physical data for compounds from Scheme 49



S49.1

(*R*)-Ethyl 6-(benzyloxy)-3-ethylhexanoate (S49.1). (*R*)-*tol*-BINAP (10.2 mg, 0.0150 mmol) and CuI (1.9 mg, 0.010 mmol) was dissolved in methyl *tert*-butyl ether

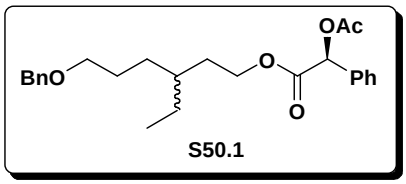
(1.0 mL) in a round bottom flask and stirred under nitrogen at rt until a yellow suspension was observed. The mixture was then cooled to −78 ^{o}C and ethylmagnesium bromide (2.0 M in diethyl ether, 0.5 mL) was added. After stirring for 10 min, a solution of unsaturated ester **S49.5** (50.0 mg, 0.200 mmol) in methyl *tert*-butyl ether (250 μL) was added dropwise over 1 h by syringe pump. After stirring at −78 ^{o}C for 3 h, methanol (0.5 mL) and a solution of saturated ammonium chloride (2 mL) were sequentially added, and the mixture was warmed to rt. After extracting with diethyl ether (3 × 5 mL), the combined organic layers were dried over anhydrous sodium sulfate and concentrated under high vacuum to obtain a crude product as a yellow oil. Purification of the resulting crude mixture by column chromatography on silica gel (1:4, EtOAc-hexane) afforded 48.0 mg (89%) of ester **S49.1** as a pale yellow oil. R_f = 0.40 (1:3, EtOAc-hexane). $[\alpha]_D^{23}$ = +10.8 (*c* 0.120, $CHCl_3$). The physical data of **S49.1** match with the data reported for racemic ester **S48.6**.



T7.1h

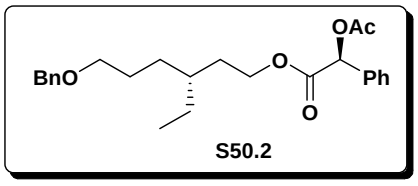
(*R*)-6-(Benzyloxy)-3-ethylhexan-1-ol (T7.1d). The compound **T7.1d** was obtained using the procedure described for compound **S48.7** in Scheme 48. 216 mg (92%) of the compound **T7.1d** was isolated as a colorless viscous oil. R_f = 0.200 (1:5, EtOAc-hexane). $[\alpha]_D^{23}$ = +10.2 (*c* 0.20, $CHCl_3$). The physical data of **T7.1d** match with the data reported for racemic alcohol **S48.7**.

6.7 Procedures and physical data for compounds from Scheme 50



S50.1

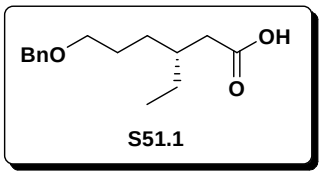
(*S*)-6-(Benzyloxy)-3-ethylhexyl 2-acetoxy-2-phenylacetate (S50.1). A round bottom flask was charged with (*S*)-2-acetoxy-2-phenylacetic acid (12.3 mg, 0.0600 mmol), *N*,*N*'-Dicyclohexylcarbodiimide (13.1 mg, 0.0640 mmol) followed by 1 mL of dichloromethane. The resulting solution was stirred for 30 min, after which alcohol **S48.7** (10.0 mg, 0.0400 mmol) dissolved in dichloromethane (0.5 mL) was added to it, followed by 4-dimethylaminopyridine (2.6 mg, 0.020 mmol). The reaction mixture was stirred overnight at rt under nitrogen. Upon completion of the reaction, the mixture was taken up in ethyl acetate (5 mL), washed with a 1 N solution of hydrochloric acid (3 × 5 mL), saturated aqueous solution of sodium bicarbonate (5 mL) and brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and volatiles were removed under reduced pressure. Purification of the resulting residue by column chromatography on silica gel (1:7, EtOAc-hexane) afforded 15 mg (86%) of compound **S50.1** as a colorless oil. R_f = 0.45 (1:5, EtOAc-hexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.70 (t, J = 7.5 Hz, 3H), 1.20 (m, 4H), 1.40–1.50 (m, 5H), 2.10 (s, 3H), 3.35 (t, J = 7.3 Hz, 2H), 4.40 (s, 2H), 4.50 (t, J = 6.5 Hz, 2H), 6.80 (s, 1H), 7.20–7.40 (m, 10H).



S50.2

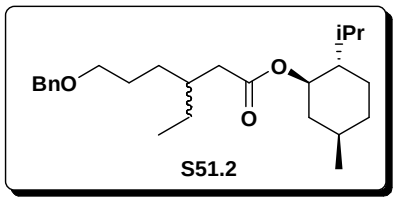
Note: The compound **S50.2** was obtained using the procedure described for compound **S50.1**. The physical data of **S50.2** match with the data reported for **S50.1**.

6.8 Procedures and physical data for compounds from Scheme 51



S51.1

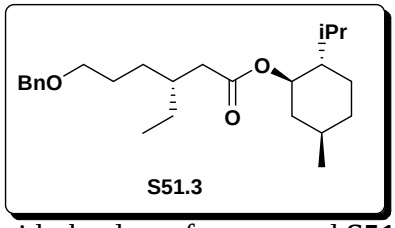
(*R*)-6-(Benzyloxy)-3-ethylhexanoic acid (S51.1). A round bottm flask was charged with ester **S49.1** (56.0 mg, 0.200 mmol), potassium hydroxide (90.4 mg, 1.60 mmol) and methanol (2.5 mL). The reaction mixture was refluxed over night at 70–80 ^{o}C. Upon completion of the reaction, the volatiles were removed under reduced prssure. The remaining residue was dissolved in 10 mL of water and organic impurities were extracted using a 1:1 mixture od etheyl acetate and hexane (15 mL). The aqeuous layer was acidified with a 1 N solution of hydrochloric acid and the carboxylic acid was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were then dried with anhydrous magnesium sulfate and filtered. Volatiles were removed under reduced pressure resulting 49.8 mg (98%) of pure product **S51.1** as a colourless liquid. R_f = 0.25 (1:5, EtOAc-hexane). $[\alpha]_D^{23}$ = +8.9 (*c* 0.025, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.80 (t, *J* = 7.5 Hz, 3H), 1.20 (m, 2H), 1.20–1.30 (m, 4H), 1.70–1.80 (m, 1H), 2.00 (dd, *J* = 14.05, 7.5 Hz, 1H), 2.20 (dd, *J* = 13.57, 6.9 Hz, 1H), 3.50 (t, *J* = 6.8 Hz, 2H), 4.40 (s, 2H), 7.20–7.30 (m, 5H), 9.87–10.20 (s, 1H).



S51.2

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 6-(benzyloxy)-3-ethylhexanoate (S51.2). The compound **S51.2** was obtained using the procedure described for compound **S50.1** in Scheme 50. Purification with column chromatography on silica gel (1:9, EtOAc-hexane) afforded 30 mg (71%) of compound **S51.2** as a colorless viscous liquid. R_f = 0.50 (1:7, EtOAc-hexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ

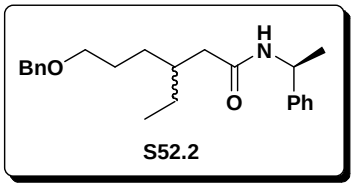
0.78–0.83 (m, 12H), 1.25–1.35 (m, 6H), 1.55–1.60 (m, 6H), 1.80 (m, 2H), 1.90 (m, 2H), 2.15 (dt, *J* = 12.5, 6.5 Hz, 1H), 3.40 (t, *J* = 13.0 Hz, 3H), 3.90 (m, 1H), 4.40 (s, 2H), 7.20–7.30 (m, 5H).



S51.3

Note: The compound **S51.3** was obtained using the procedure described for compound **S50.1** in Scheme 50. The physical data of **S51.3** match with the data of compound **S51.2**.

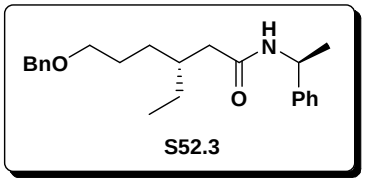
6.9 Procedures and physical data for compounds from Scheme 52



S52.2

6-(Benzyloxy)-3-ethyl-*N*-[(*S*)-1-phenylethyl]hexanamide (S52.2). A solution of carboxylic acid (5.0 mg, 0.020 mmol) in 0.5 mL dichloromethane was cooled to 0 ^{o}C and oxalyl chloride (5.1 mg, 0.040 mmol) was added dropwise. The reaction was stirred at 0 ^{o}C for 1 h and the volatiles were removed under reduced pressure. The residue was dissolved in 0.1 mL dichloromethane followed by the addition of (*S*)-1-phenylethylamine (2.9 mg, 0.024 mmol) and triethylamine (3.1 mg, 0.030 mmol). Then the reaction mixture was stirred for 2 h at 0 ^{o}C. Upon completion, the reaction was quenched with water. The product was extracted with dicholoromethane (4 × 5 mL). The combined extracts were washed with a 1 N solution of hydrochloric acid (5 mL) followed by saturated aqueous solution of sodium bicarbonate (5 mL). The resulting organic layer was dried over anhydrous magnesium sulfate and volatiles were removed under vacuum. Purification of the resulting residue by column chromatography on silica gel (1:5–3:1,

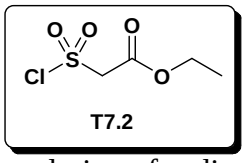
EtOAc-hexane) afforded 6 mg (85%) of amide **S52.2** as a colorless oil. R_f = 0.10 (1:5, EtOAc-hexane) $[\alpha]_D^{23}$ = –26 (*c* 0.034, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.77 (t, *J* = 7.5 Hz, 3H), 1.25–1.29 (m, 4H), 1.40 (d, *J* = 6.9 Hz, 3H), 1.50–1.60 (m, 2H), 1.80 (m, 1H), 2.20 (m, 2H), 3.35 (t, *J* = 6.9 Hz, 2H), 4.40 (s, 2H), 5.59 (q, *J* = 7.2 Hz, 2H), 7.20–7.30 (m, 10H).



S52.3

Note: The compound **S52.3** was obtained using the procedure described for compound **S52.2**. The physical data of **S52.3** match with the data reported for **S52.2**. The compound showed two significant peaks around 4.30–4.50 ppm as a proof of enatiomeric excess (Appendix III, Figure 6)

6.10 Procedures and physical data for compounds from Table 7



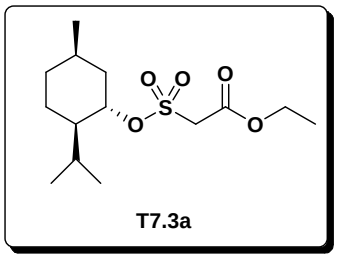
T7.2

Ethyl chlorosulfonylacetate (T7.2). A solution of ethyl chloroacetate (8.8 mL, 71 mmol) in 40 mL of ethanol was added to a solution of sodium sulfite (6.00 g, 47.6 mmol) in 40 mL of water. The mixture was reflux for 6 h and volatiles were then removed under reduced pressure. The concentrated materials were azeotropically dried with toluene (3 × 40 mL) to afford a white solid. The product was allowed to stand under vacuum at 100 ^{o}C for 12 h. The flask was then fitted with a reflux condenser and flushed with nitrogen. To the resulting white solid, succession of 50 mL toluene, DMF (348 mg, 4.76 mmol), and oxalyl chloride (12.08 g, 95.20 mmol) was added. The white suspension was heated at 100 ^{o}C for 3 h. The resulting turbid solution was cooled to 25 ^{o}C and filtered through a small pad of Celite.

The flask and filter cake were washed with an additional 200 mL of toluene. The filtrate was concentrated under reduced pressure, and the resulting yellow residue was purified by distillation under high vacuum at 170–180 ^{o}C to afford 3.25 g (50%) the sulfonyl chloride as a pale yellow oil, which was stored under nitrogen. The physical data of **T7.2** match with its previously reported data of the compound.[184]

General procedure for Sulfonates (T7.3a–T7.3h)

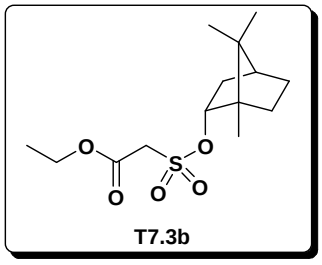
A solution of ethyl chlorosulfonylacetate **S7.2** (355 mg, 1.80 mmol) in 2.5 mL of THF was added dropwise to a mixture of corresponding alcohol **S7.1** (355 mg, 1.50 mmol) and imidazole (123 mg, 1.80 mmol) in 2.5 mL of THF. Upon completion of the reaction after 16 h, the mixture was diluted with 20 mL of water, and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined dichloromethane layers were washed with a 1 N solution of hydrochloric acid, saturated aqueous solution of sodium bicarbonate and brine. The organic layer was then dried over anhydrous sodium sulfate and volatiles were removed under reduced pressure. The resulting crude product was purified by column chromatography on silica gel (1:7, EtOAc-hexane) affording the pure sulfonate **S7.3**.



T7.3a

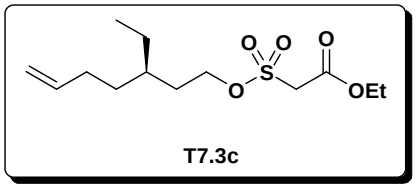
(1*S*,2*R*,5*R*)-Ethyl-2-{[5-methyl-2-(1-methylethyl)cyclohexyl]oxy}sulfonyl acetate (T7.3a). The compound was purified by column chromatography on silica gel (1:3, EtOAc-hexane). Colorless solid (98%). R_f =

0.40 (1:5, EtOAc-hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ0.91 (d, J = 6.5 Hz, 6H), 0.96 (d, J = 6.5 Hz, 3H), 1.10–1.20 (m, 1H), 1.32 (t, J = 7.0 Hz, 3H), 1.44–1.62 (m, 4H), 1.65–1.80 (m, 2H), 1.85–1.94 (m, 2H), 4.28 (q, J = 7.0 Hz, 2H), 4.05 (s, 2H), 5.05–5.09 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ14.2(CH_3), 19.8 (CH_3), 19.8 (CH_3), 21.1 (CH_2), 21.2 (CH_3), 26.3 (CH), 27.2(CH), 29.3 (CH_2), 36.3 (CH_2), 46.0 (CH), 56.1 (CH_2), 62.8 (CH_2), 84.5(CH), 162.3(C), HRMS (ESI) calcd for $C_{14}H_{30}NO_5S$ $[M+NH_4]^+$ 324.1850, found 324.1820.



T7.3b

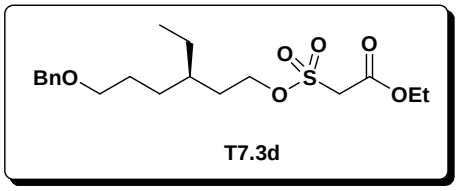
Ethyl (1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-oxysulfonylacetate (T7.3b). The compound was purified by column chromatography on silica gel (1:3, EtOAc-hexane). Colorless solid (90%). R_f = 0.40 (1:5, EtOAc-hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ0.89 (s,3H), 0.90 (s, 3H), 0.94 (s, 3H), 1.29–1.37 (m, 5 H), 1.40 (dd, J = 14.0, 3.0 Hz, 1H), 1.73–1.82 (m, 2H), 1.87–1.94 (m, 1H), 2.34–2.42 (m, 1H), 4.07 (s, 2H), 4.29 (q, J = 7.0 Hz, 2H), 4.92 (ddd, J = 10.0, 3.0, 2.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ13.3 (CH_3), 14.2 (CH_3), 19.0 (CH_3), 20.0 (CH_3), 26.8 (CH_2), 28.0 (CH_2), 36.5 (CH_2), 44.8 (CH), 48.0 (C), 50.0 (C), 55.6 (CH_2), 62.8 (CH_2), 90.2 (CH), 162.2 (C). HRMS (ESI) calcd for $C_{14}H_{28}NO_5S$ $[M+NH_4]^+$ 322.1683, found 322.1675.



T7.3c

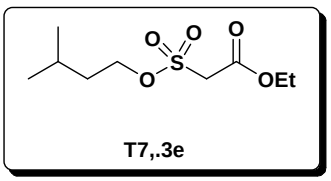
Ethyl ({[(3*R*)-3-ethylhept-6-en-1-yl]oxy}sulfonyl)acetate (T7.3c). The compound was purified by column chromatography on silica

gel (1:5, EtOAc-hexane). Colorless oil (74%). R_f = 0.35 (1:5, EtOAc-hexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.80 (t, J = 6.9 Hz, 3H), 0.85 (t, J = 6.9 Hz, 3H), 1.34 (m, 4H), 1.48 (m, 1H), 1.75 (m, 2H),2.05 (m, 2H), 4.15 (s, 2H), 4.27 (q, J = 7.3 Hz, 2H), 4.35 (t, J = 11.6 Hz, 2H), 4.99 (dd, J = 17.3, 6.5 Hz, 2H), 5.80 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 10.8 (CH_3), 14.7 (CH_3), 25. 7 (CH_2), 32. 4 (CH_2), 32. 8 (CH), 35.2 (CH_2), 54.00 (CH_2), 55.3 (CH_2), 63.1 (CH_2), 71.4 (CH_2), 115.0 (CH_2), 139.1 (CH), 162.5 (C).



T7.3d

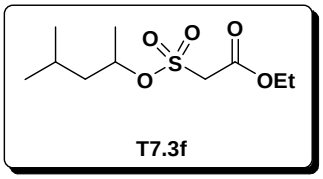
(*R*)-Ethyl 2-(6-(benzyloxy)-3-ethylhexyloxysulfonyl)acetate (T7.3d). The compound was purified by column chromatography on silica gel (1:7, EtOAc-hexane). Pale yellow oil (90%). R_f = 0.30 (1:5, EtOAc-hexane). $[\alpha]_D^{23}$ = +14.78 (*c* 0.115, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.90 (t, J = 7.4 Hz, 3H), 1.30 (t, J = 6.9 Hz, 3H), 1.35–1.40 (m, 4H), 1.50 (m, 1H), 1.62 (m, 1H), 1.75 (m, 2H), 3.50 (t, J = 6.4 Hz, 2H), 4.08 (s, 2H), 4.28 (q, J = 7.1 Hz, 2H), 4.38 (t, J = 6.9 Hz, 2H), 4.55 (s, 2H), 7.30–7.50 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 10.9 (CH_3), 14.3 (CH_3), 25.1 (CH_2), 27.02 (CH_2), 29.6 (CH_2), 32.9 (CH), 35.6 (CH_2), 52.0 (CH_2), 60.1 (CH_2), 69.0 (CH_2), 71.3 (CH_2), 73.3 (CH_2), 127.9 (CH), 128.02 (CH), 128.8 (CH), 139.0 (C), 162.5 (C). HRMS (ESI) calcd for $C_{19}H_{21}O_6S$ $[M+H]^+$ 387.1836, found 387.1792.



T7,.3e

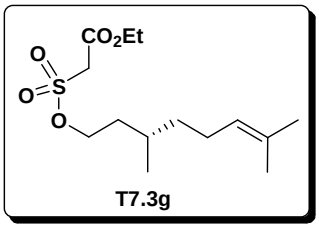
Ethyl-2-[(3-methylbutoxy)sulfonyl]acetate (T7.3e). The compound was purified by column chromatography on silica gel (1:5, EtOAc-hexane). Colorless oil (73%). R_f =

0.40 (1:5, EtOAc-hexane). The physical data of **T7.3e** match with its previously reported data of the compound.[49]



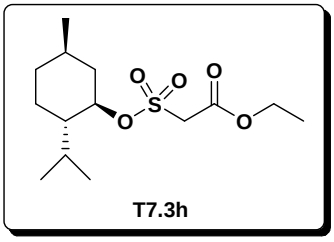
T7.3f

Ethyl-2-[(1,3-dimethylbutoxy)sulfonyl]acetate (T7.3f). The compound was purified by column chromatography on silica gel (1:5, EtOAc-hexane). Colorless oil (75%). R_f = 0.45 (1:5, EtOAc-hexane). The physical data of **T7.3f** match with its previously reported data of the compound.[49]



T7.3g

(*S*)-Ethyl 2-(3,7-dimethyloct-6-enyloxysulfonyl)acetate (T7.3g). The compound was purified by column chromatography on silica gel (1:5, EtOAc-hexane). Colorless oil (98%). R_f = 0.30 (1:3, EtOAc-hexane). The physical data of **T7.3g** match with its previously reported data of the compound.[157]



T7.3h

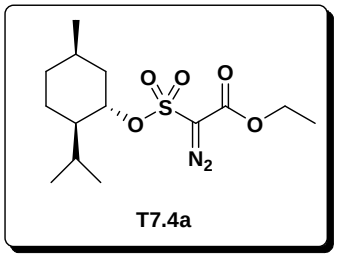
(1*R*,2*S*,5*R*)-Ethyl-2-[5-methyl-2-(1-methylethyl)cyclohexyl)oxy]sulfonyl acetate (T7.3h)). The compound was purified by column chromatography on silica gel (1:3, EtOAc-hexane). Colorless solid (95%). R_f = 0.40 (1:5, EtOAc-hexane). The physical data of **T7.3h** match with its previously reported data for the compound.[49]

General procedure for diazosulfonates (T7.4a–T7.4h).

Procedure with nosyl azide: The corresponding sulfonate (1 equiv) was dissolved in DMF (5 mL/mmol) and stirred under nitrogen at 0 ^{o}C. Nosyl azide (1.2 equiv) and *N*,*N*-diisopropylethylamine (2 equiv) were then added sequentially. The resulting reaction mixture was stirred at 0 ^{o}C for 7–8 h. Upon completion of the reaction, the reaction mixture was taken up in ethyl acetate (10 mL) and the organic layer was washed with water (2 × 10 mL) followed by the saturated brine solution (2 × 10 mL). The organic phase was then dried with anhydrous sodium sulfate. The volatiles were evaporated under reduced pressure to yield the crude product that was purified using column chromatography on silica column (1:5–1:3, EtOAc-hexanes) to yield the desired pure product.

Procedure with mesyl azide: The same procedure described for preparation of diazo sulfones **T6.5a** and **T6.5b** was followed.

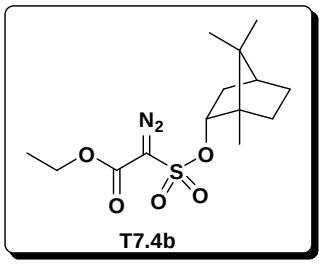
Note: all diazocompounds do not show the diazo carbon in ^{13}C spectra. IR data are provided, showing the diazo stretch at ~ 2130 cm^{-1}.



T7.4a

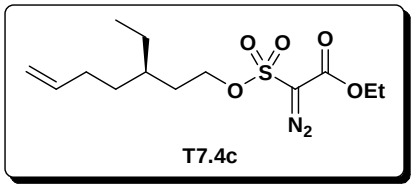
(1*S*,2*R*,5*R*)-Ethyl-2-diazo-2-{[5-methyl-2-(1-methylethyl)cyclohexyl]oxy}sulfonyl acetate (T7.3a). The compound was purified by column chromatography on silica gel (1:3, EtOAc-hexane). Colorless solid (81%). R_f = 0.50 (1:5, EtOAc-hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91 (d, J = 6.5 Hz, 3H), 0.92 (d, J = 6.5 Hz, 3H), 0.96 (d, J = 6.5 Hz, 3H), 1.10–1.18 (m, 1H), 1.33 (t, J = 7.0 Hz, 3H),

1.42–1.62 (m, 4H), 1.64–1.79 (m, 2H), 1.80–1.98 (m, 2H), 4.34 (q, J = 7.0 Hz, 2H), 5.04–5.08 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.5 (CH_3), 19.8 (CH_3), 21.0(CH_3), 21.1 (CH_2), 21.2 (CH_3), 26.2 (CH), 27.2 (CH), 29.2 (CH_2), 36.2 (CH_2), 46.0 (CH), 62.8 (CH_2), 86.0 (CH), 159.8 (C). IR (neat, cm^{-1}, ν): 2137, 1723, 1383, 1183.



T7.4b

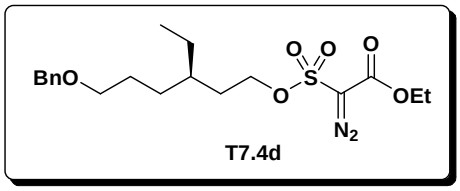
Ethyl (1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-oxysulfonyldiazoacetate (T7.4b). The compound was purified by column chromatography on silica gel (1:3, EtOAc-hexane). Colorless oil (95%). R_f = 0.40 (1:5, EtOAc-hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90 (s, 3H), 0.91 (s, 3H), 0.92 (s, 3H), 1.28–1.40 (m, 6H), 1.73–1.80 (m, 2H), 1.89–1.96 (m, 1H), 2.33–2.41 (m, 1H), 4.34 (q, J = 7.0 Hz, 2H), 4.92 (dt, J = 10.0, 2.5 Hz, 1H), ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.2 (CH_3), 14.5 (CH_3), 19.0 (CH_3), 19.9 (CH_3), 26.8 (CH_2), 28.0 (CH_2), 36.2 (CH_2), 44.8 (CH), 48.0 (C), 50.0 (C), 62.8 (CH_2), 62.8 (CH_2), 91.6 (CH), 159.8 (C). IR (neat, cm^{-1}, ν): 2138, 1723, 1381, 1182.



T7.4c

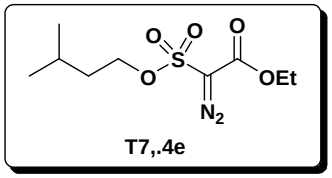
Ethyl diazo({[(3*R*)-3-ethylhept-6-en-1-yl]oxy}sulfonyl)acetate (T7.4c). The compound was purified by column chromatography on silica gel (1:3, EtOAc-hexane). Colorless oil (27%). R_f = 0.50 (1:5, EtOAc-hexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.80 (t, J = 6.9 Hz, 3H), 0.85 (t, J = 6.9 Hz, 3H), 1.30–1.40 (m, 5H), 1.5 (m, 1H), 1.70 (m, 1H), 2.05 (m, 2H), 4.30 (q, J = 7.3 Hz, 2H), 4.38 (t, J = 11.6 Hz, 2H), 4.98 (dd, J = 17.3, 2.5 Hz, 2H), 5.80 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ

10.8 (CH_3), 14.7 (CH_3), 25. 7 (CH_2), 32. 4 (CH_2), 32. 6 (CH), 35.2 (CH_2), 54.0 (CH_2), 63.1 (CH_2), 72.6 (CH_2), 115.0 (CH_2), 139.1 (CH), 159.9 (C). IR (CH_2Cl_2, cm^{-1}, ν): 2135. 3, 1724.42.



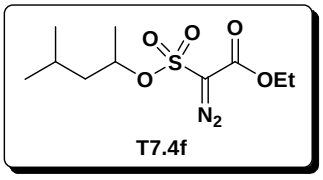
T7.4d

(*R*)-Ethyl 2-[6-(benzyloxy)-3-ethylhexyloxysulfonyl]-2-diazoacetate (T7.4d). The compound was purified by column chromatography on silica gel (1:3, EtOAc-hexane). Colorless oil (80%). R_f = 0.30 (1:3, EtOAc-hexane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.75 (t, J = 7.4 Hz, 3H), 1.25 (t, J = 6.8 Hz, 3H), 1.20–1.30 (m, 4H), 1.40 (m, 1H), 1.52 (m, 2H), 1.65 (m, 2H), 3.35 (t, J = 6.7 Hz, 2H), 4.25 (q, J = 7.0 Hz, 2H), 4.30 (t, J = 6.8 Hz, 2H), 4.43 (s, 2H), 7.20–7.40 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 8.84 (CH_3), 11.9 (CH_3), 24.85 (CH_2), 28.94 (CH_2), 31.78 (CH_2), 32.46 (CH_2), 46.31 (CH), 60.0 (CH_2), 65.33 (CH_2), 70.32 (CH_2), 73.10 (CH_2), 127.76 (CH), 127.81 (CH), 128.55 (CH), 138.52 (C), 181.40 (C). IR (CH_2Cl_2, cm^{-1}, ν): 2135.74, 1722.51.



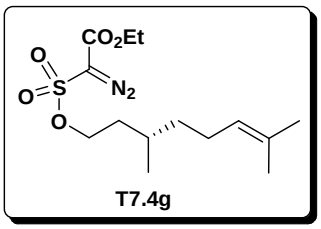
T7,.4e

Ethyl-2-diazo-2-[(3-methylbutoxy)sulfonyl]acetate (T7.4e). The compound was purified by column chromatography on silica gel (1:3, EtOAc-hexane). Colorless oil (68%). R_f = 0.40 (1:3, EtOAc-hexane). The physical data of **T7.4e** match with its previously reported data of the compound.[49]



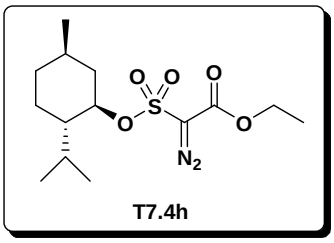
T7.4f

Ethyl-2-diazo-2-[(1,3-dimethylbutoxy)sulfonyl]acetate (T7.4f). The compound was purified by column chromatography on silica gel (1:3, EtOAc-hexane). Colorless oil (70%). R_f = 0.40 (1:3, EtOAc-hexane). The physical data of **T7.4f** matches with its previously reported data of the compound.[49]



T7.4g

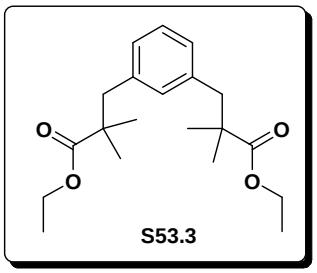
(*S*)-Ethyl 2-diazo-2-(3,7-dimethyloct-6-enyloxysulfonyl)acetate T7.4g. The compound was purified by column chromatography on silica gel (1:3, EtOAc-hexane). Colorless oil (74%). R_f = 0.30 (1:3, EtOAc-hexane). The physical data of **T7.4g** matches with its previously reported data of the compound.[157]



T7.4h

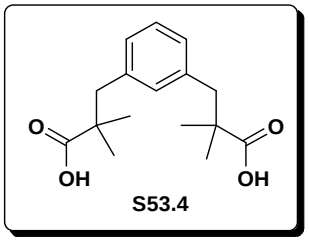
(1*R*,2*S*,5*R*)-Ethyl-2-diazo-2-{[5-methyl-2-(1-methylethyl)cyclohexyl]oxy}sulfonyl acetate (T7.4h). The compound was purified by column chromatography on silica gel (1:3, EtOAc-hexane). Colorless oil (75%). R_f = 0.50 (1:5, EtOAc-hexane). $[\alpha]_D^{23}$ = +24.05 (*c* 0.05, $CHCl_3$). The physical data of **T7.4h** match with its previously reported data of the compound.[49]

6.11 Procedures and physical data for compounds from Scheme 53



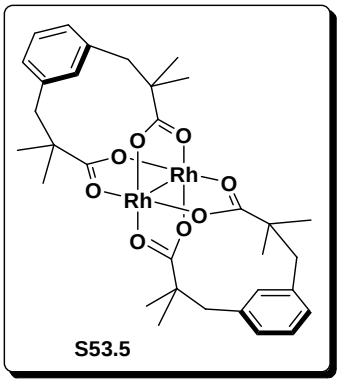
S53.3

***α,α,α',α'*-Tetramethyl-1,3-benzenediethyldipropionate (S53.3)**. *n*-Butyllithium (1.9 mL of a 2.5 M solution in hexanes, 4.7 mmol) was added slowly to a solution of diisopropylamine (0.7 mL, 5 mmol) in 1 mL of THF at –78 ^{o}C. The mixture was stirred for 30 min followed by the dropwise addition of ethylisobuterate, **S53.1** (549 mg, 4.73 mmol). The reaction was stirred at 0 ^{o}C for an additional 1.5 h. A solution of a α,α'-bromo-*m*-xylene (500 mg, 1.89 mmol) in 4 mL of THF was slowly added to the reaction flask. The resulting reaction mixture was warmed to rt and stirred for another 10 h. The reaction was quenched with 10 mL of water and the product was extracted with ethyl acetate (15 mL). The organic layer was further washed with 10 mL brine, dried over anhydrous sodium sulfate and volatiles were removed under reduced pressure. Purification of the oily residue by column chromatography on silica gel (2.5–5%, DEE-petroleum ether) yielded 215 mg (50%) of the desired diester **S53.3** as a semi-solid. R_f = 0.30 (0.5:9.5, DEE-petroleum ether). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.15 (s, 12H), 1.20 (t, J = 6.8 Hz, 6H), 2.80 (s, 4H), 4.10 (q, 4H), 6.90 (s, 1H), 6.95 (d, J = 7.9 Hz, 2H), 7.15 (t, J = 7.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ14.57 (CH_3), 25.34 (CH_3), 43.82 (C), 46.54 (CH_2), 60.74 (CH_2), 127.91 (CH), 128.65 (CH), 132.64 (CH), 137.94 (C), 177.82 (C).



S53.4

***α,α,α',α'*-Tetramethyl-1,3-benzenedipropionic acid (S53.4)**. The compound **S53.4** was obtained using the procedure described for compound **S51.1** in Scheme 51. The product was isolated (172 mg, 96%) as a colorless solid. The physical data of **S53.4** match with its previously reported data of the same diacid.[109]



S53.5

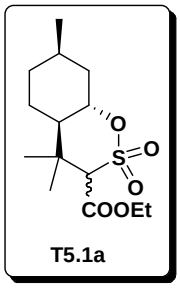
$Rh_2(esp)_2$ (S53.5). A 15 mL round bottom flask was charged with $Rh_2(OAc)_4$ (137 mg, 0.310 mmol), *α,α,α',α'*-tetramethyl-1,3-benzenedipropionic acid (17.0 mg, 0.0620 mmol), and 3.0 mL of 1,2-dichloroethane. The reaction mixture was refluxed under nitrogen. After twenty minutes, the flask was removed from the heating bath and the contents slowly cooled (5 min) to 23 °C. The vessel was charged with 17.0 mg (0.2 equiv) of the diacid, sealed, and heating at 125 °C was resumed. This process was repeated an additional three times at twenty minutes intervals, following which the reaction was stirred at 125 °C for 5 h. Within this period, the reaction mixture slowly became turbid. A second equivalent of dicarboxylic acid was then introduced in a similar fashion (5 portions of 17.0 mg at 20 minute intervals). Once again, the mixture was stirred at 125 °C for an additional 5 h, during which time the reaction became homogenous. The deep green solution was cooled to 23 °C and volatiles were removed under reduced pressure. Purification of the resulting deep green residue by column chromatography on silica gel using gradient elution

(1:15–1:10, EtOAc-hexane) furnished 122 mg (55%) of the catalyst $Rh_2(esp)_2$ as a green microcrystalline solid. R_f = 0.43 (20:1, DCM-EtOAc). The physical data of **S53.5** match with its previously reported data of the catalyst.[109]

6.12 Procedures and physical data for compounds from Table 9

General procudeure for cyclization through C–H insertion (T9.1a–T9.1h).

To the suspension of a rhodium catalyst ($Rh_2(OAc)_4$ or $Rh_2(esp)_4$) (2 mol %) in dichloromethane (4 mL/mmol) a solution of the corresponding diazo compound (1 equiv, 0.1–1 mmol) in dichloromethane (2 mL/mmol) was added at rt over a period of 1 h using a syringe pump. Upon completion of the addition, the reaction mixture was stirred at rt for an additional 15 h. The volatiles were removed under reduced pressure and the crude reaction mixture was purified using column chromatography on silica column (1:5–1:3, EtOAc-hexanes). In many cases, additional purification on a silica gel column (1:9–1:10, DEE-petroleum ether) was required to yield the pure product.

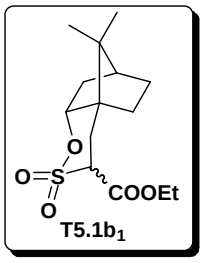


T5.1a

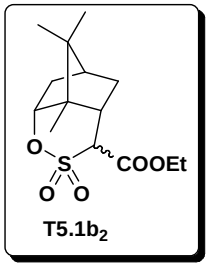
Ethyl (4*aR*,7*R*,8*aS*)-4,4,7-trimethyloctahydro-1,2-benzoxathiine-3-carboxylate 2,2-dioxide (T5.1a). Less polar isomer of T5.1a. The compound was purified by column chromatography on silica gel (1:4, DEE-petroleum ether). Colorless oil (88%). R_f = 0.30 (1:4, DEE-petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.02 (d, J = 7.5 Hz, 3H), 1.11 (s, 3H), 1.33 (t, J = 7.0 Hz, 3H), 1.35 (s, 3H), 1.55–1.65 (m, 3H), 1.88 (td, J = 12.0, 5.0 Hz, 1H), 1.97–2.03 (m, 2H), 2.22–2.29 (m, 2H), 3.78 (s, 1H), 4.27 (qd, J = 7.0, 2.0 Hz, 2H), 4.77 (td, J = 11.0, 4.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.2 (CH_3), 18.2 (CH_3), 19.0

(CH_2), 22.7 (CH_3), 26.9 (CH_3), 28.4 (CH), 30.9 (CH_2), 37.8 (CH_2), 38.9 (C), 44.2 (CH), 62.5 (CH_2), 71.7 (CH), 81.9 (CH), 165.3 (C), HRMS (ESI) calcd for $C_{14}H_{28}NO_5S$ $[M+NH_4]^+$ 322.1683, found 322.1667. **More polar isomer of T5.1a.** ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.02 (d, J = 7.5 Hz, 3H), 1.14 (s, 3H), 1.33 (s, 3H), 1.34 (t, J = 7.0 Hz, 3H), 1.51–1.64 (m, 3H), 1.67–1.79 (m, 2H), 1.96–2.01 (m, 1H), 2.21–2.29 (m, 2H), 3.87 (s, 1H), 4.32 (q, J = 7.0 Hz, 2H), 4.78 (td, J = 11.0, 4.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3 (CH_3), 16.3 (CH_3), 18.1 (CH_3), 19.2 (CH_2), 27.4 (CH_3), 28.3 (CH), 30.8 (CH_2), 37.8 (CH_2), 40.5 (C), 51.4 (CH), 62.6 (CH_2), 72.3 (CH), 81.2 (CH), 163.8 (C). HRMS (ESI) calcd for $C_{14}H_{28}NO_5S$ $[M+NH_4]^+$ 322.1683, found 322.1705.

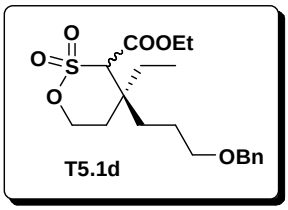
Borneol sulfonate ethylester (T5.1b)



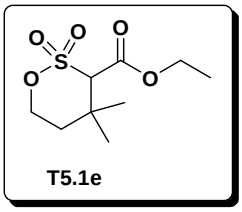
Ethyl 11,11-dimethyl-5-oxa-4-thiatricyclo[6.2.1.01,6]undecane-3-carboxylate 4,4-dioxide (T5.1b$_1$). The compound was ppurified by column chromatography on silica gel (1:5, DEE-petroleum ether). Colorless oil (88%). R_f = 0.25 (1:5, DEE-petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (s, 3H), 0.97 (s, 3H), 1.28 (dd, J = 14.0, 5.0 Hz, 1H), 1.32 (t, J = 7.0 Hz, 3H), 1.34–1.47 (m, 2H), 1.78–1.99 (m, 2H), 2.00 (dd, J = 14.0, 4.5 Hz, 1H), 2.15–2.21 (m, 1H), 2.25–2.35 (m, 2H), 3.95 (dd, J = 13.0, 5.0 Hz, 1H), 4.25–4.34 (m, 2H), 5.00 (ddd, J = 11.0, 5.0, 2.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1 (CH_3), 18.7 (CH_3), 19.8 (CH_3), 24.7 (CH_2), 28.0 (CH_2), 28.8 (CH_2), 32.5 (CH_2), 45.7 (CH), 46.7 (C), 47.5 (C), 61.0 (CH), 63.1 (CH_2), 88.5 (CH), 164.7 (C). HRMS (ESI) calcd for $C_{14}H_{23}O_5S$ $[M+H]^+$ 303.1266, found 303.1261.



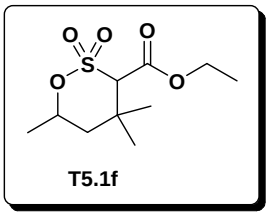
Ethyl 8,9,9-trimethyl-4-oxa-5-thiatricyclo[5.2.1.03,8]decane-6-carboxylate 5,5-dioxide (T5.1b$_2$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (s, 3H), 0.98 (s, 3H), 1.08 (s, 3H), 1.35 (t, J = 7.0 Hz, 3H), 1.88 (t, J = 4.0 Hz, 1H), 2.11 (dd, J = 13.0, 5.0 Hz, 1H), 2.14–2.23 (m, 2H), 2.45 (dd, J = 14.0, 4.0 Hz, 1H), 2.73–2.78 (m, 1H), 4.15 (d, J = 4.0 Hz, 1H), 4.30–4.38 (m, 2H), 4.80 (dt, J = 10.0, 3.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 11.9 (CH_3), 14.2 (CH_3), 18.90 (CH_3), 18.92 (CH_3), 28.4 (CH_2), 30.2 (CH_2), 42.3 (CH), 43.5 (CH), 47.9 (C), 49.7 (C), 60.8 (CH), 63.1 (CH_2), 95.3 (CH), δ 164.7 (C). HRMS (ESI) calcd for $C_{14}H_{23}O_5S$ $[M+H]^+$ 303.1266, found 303.1293.



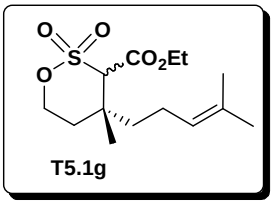
Benzyl protected sulfonate ethylester (T5.1d). The compound was purified by column chromatography on silica gel (1:5, EtOAc-hexane). Colorless oil (80%). R_f = 0.30 (1:5, EtOAc-hexane). $[\alpha]_D^{23}$ = +13 (c 0.018, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.80 (t, J = 7.5 Hz, 3H), 1.20 (m, 7H), 1.40–1.50 (m, 4H), 2.50 (dd, J = 10.9, 6.0 Hz, 1H), 3.32 (dd, J = 11.8, 5.9 Hz, 1H), 3.40 (dd, J = 10.8, 5.9 Hz, 1H), 3.60 (dd, J = 11.5, 6.9 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 4.40 (s, 1H), 4.55 (s, 2H), 7.20–7.30 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 7.84 (CH_3), 14.3 (CH_3), 23.30 (CH_2), 25.1 (CH_2), 27.4 (C), 29.7 (CH_2), 32.8 (CH_2), 41.9 (CH_2), 62.8 (CH_2), 68.4 (CH_2), 75.0 (CH_2), 75.8 (CH), 127.5 (CH), 128.7 (CH), 128.7 (CH), 138.0 (C), 165.0 (C). HRMS (ESI) calcd for $C_{19}H_{29}O_6S$ $[M+H]^+$ 385.1685, found 385.1639.



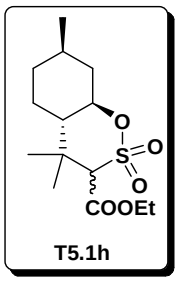
Ethyl-4,4-dimethyl-1,2-oxathiane-2,2-dioxide-3-carboxylate (T5.1e). The compound was purified by column chromatography on silica gel (1:6, EtOAc-hexane). Colorless oil (60%). R_f = 0.20 (1:5, EtOAc-hexane). The physical data of **T5.1e** matches with its previously reported data of the compound.[49]



Ethyl-4,4,6-trimethyl-1,2-oxathiane-2,2-dioxide-3-carboxylate (T5.1f). The compound was purified by column chromatography on silica gel (1:5, EtOAc-hexane). Colorless oil (75%). R_f = 0.30 (1:5, EtOAc-hexane). The physical data of **T5.1f** matches with its previously reported data of the compound.[49]



Ethyl (4*R*)-4-methyl-4-(4-methylpent-3-en-1-yl)-1,2-oxathiane-3-carboxylate 2,2-dioxide (T5.1g). The compound was purified by column chromatography on silica gel (1:5, EtOAc-hexane). Colorless oil (85%). R_f = 0.3 (1:1, EtOAc-hexane). The physical data of **T5.1g** matches with its previously reported data of the compound.[157]

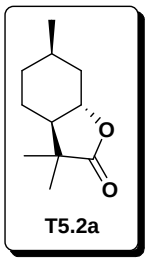


Ethyl (4*aS*,7*R*,8*aR*)-4,4,7-trimethyloctahydro-1,2-benzoxathiine-3-carboxylate 2,2-dioxide (T5.1h). The compound was purified by column chromatography on silica gel (1:4, DEE-petroleum ether). Colorless oil (80%). R_f = 0.30 (1:4, DEE-petroleum ether). The physical data of **T5.1h** match with its previously reported data of the compound.[49]

6.13 Procedures and physical data for compounds from Table 11

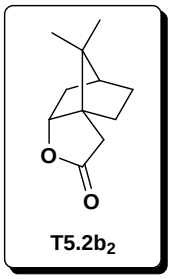
General procedure for oxidation of *δ*-sultones with TBHP/*t*-BuOK

To a solution of *δ*-sultone in THF (2.5 mL/mmol) was added potassium *tert*-butoxide (10 equiv.) or KHMDS (10 equiv.) followed by *tert*-butyl hydroperoxide (4 equiv.). After stirring at rt for 16 h, sodium sulfite was added and the resulting suspension stirred for 15 min to destroy excess *tert*-butyl hydroperoxide. This was followed by the addition of 20 mL of 1 N solution of hydrochloric acid and the resulting mixture was extracted with diethyl ether, washed with brine, dried over anhydrous magnesium sulfate and evaporated to afford a crude product, which was purified by flash chromatography.



T5.2a

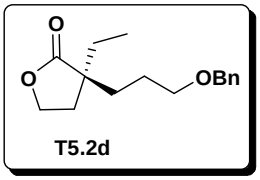
(3a*R*,6*R*,7a*S*)-Hexahydro-3,3,6-trimethylbenzofuran-2(3H)-one (T5.2a). The compound was purified by column chromatography on silica gel (1:4, DEE-petroleum ether). Colorless solid (90%). R_f = 0.30 (1:4, DEE-petroleum ether). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.04–1.08 (d, J = 7.5 Hz, 3H), 1.08 (s, 3H), 1.20 (s, 3H), 1.40–1.50 (m, 1H), 1.55–1.70 (m, 5H), 2.10 (m, 1H), 2.30 (m, 1H), 4.10 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 17.77 (CH_3), 19.59 (CH_3), 23.84 (CH_2), 28.61 (CH), 31.40 (CH_2), 36.55 (CH_2), 42.67 (C), 55.35 (CH), 77.2 (CH), 182.98 (C). HRMS (ESI) calcd for $C_{11}H_{18}O_2$ $[M+H]^+$ 183.1379, found 183.1423.



T5.2b$_2$

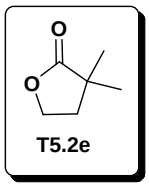
7,8,8-Trimethyl-4-oxatricyclo[4.2.1.03,7]nonan-5-one (**T5.2b$_1$**). The compound was purified by column chromatography on silica gel (1:4, DEE-petroleum ether). Colorless oil (70%). R_f = 0.30 (1:4, DEE-petroleum ether). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.86 (s, 3H), 0.88 (s,

3H), 1.05 (s, 3H), 1.39 (d, J = 14.2, 1H), 1.5 (d, J = 12.6, 1H), 1.87 (m, 1H), 2.12–2.30 (m, 3H), 4.35 (d, 1H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 11.6 (CH_3), 19.4 (CH_3), 20.5 (CH_3), 33.4 (CH_2), 36.8 (CH_2), 46.3 (CH), 46.6 (CH), 49.2 (C), 58.8 (C), 87.1 (CH), 181.5 (C).



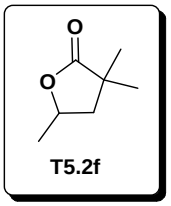
T5.2d

(*S*)-3-(3-(Benzyloxy)propyl)-3-ethyl-dihydrofuran-2(3H)-one (T5.2d). The compound was purified by column chromatography on silica gel (1:5, EtOAc-hexane). Colorless oil (75%). R_f = 0.40 (1:5, EtOAc-hexane). $[\alpha]_D^{23}$ = +11 (c 0.010, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.85 (t, J = 7.5 Hz, 3H), 1.50–1.70 (m, 6H), 2.00 (t, J = 7.0 Hz, 2H), 3.50 (m, 2H), 4.20 (t, J = 7.6 Hz, 2H), 4.55 (s, 2H), 7.20–7.30 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 8.84 (CH_3), 24.83 (CH_2), 28.94 (CH_2), 31.78 (CH_2), 32.46 (CH_2), 46.31(C), 65.6 (CH_2), 70.6 (CH_2), 73.4 (CH_2), 128.7 (CH), 128.8 (CH), 130.0 (CH), 138.8 (C), 181.0 (C). HRMS (ESI) calcd for $C_{16}H_{23}O_3$ $[M+H]^+$ 263.1647, found 263.1623

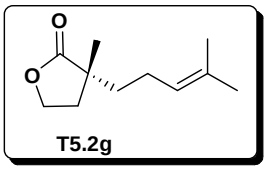


T5.2e

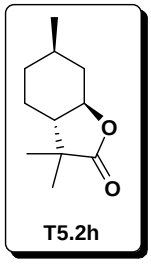
Dihydro-3,3-dimethylfuran-2(3H)-one (T5.2e). The compound was purified by column chromatography on silica gel (1:9–1:3, DEE-petroleum ether). Colorless oil (54%). The physical data of **T5.2e** match with its previously reported data of the compound.[185]



Dihydro-3,3,5-trimethylfuran-2(3H)-one (T5.2f). The compound was purified by column chromatography on silica gel (1:9–1:3, DEE-petroleum ether). Colorless oil (60%). The physical data of **T5.2f** match with its previously reported data of the compound.[185]

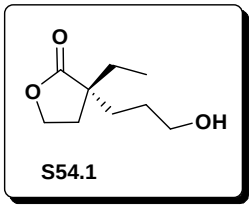


3-Methyl-3-(4-methyl-3-pentenyl)dihydrofuran-2-one (**T5.2g**). The compound was purified by column chromatography on silica gel (1:1, DCM-pentane). Pale yellow oil (72%). R_f = 0.30 (1:1, DCM-pentane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.20–1.30 (s, 3H), 1.55 1.65 (m, 5H), 1.65 (s, 3H), 1.87–2.10 (m, 3H), 2.20–2.30 (m, 1H), 4.25 (m, 2H), 5.10 (m, 1H). ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz): δ 17.87 (CH_3), 22.70 (CH_2), 23.32 (CH_3), 25.56 (CH_3), 34.69 (CH_2), 37.42 (CH_2), 42.37 (C), 65.16 (CH_2), 123.40 (CH), 132.65 (C), 182.11 (C).



(3a*S*,6*R*,7a*R*)-Hexahydro-3,3,6-trimethylbenzofuran-2(3H)-one (T5.2h). The compound was purified by column chromatography on silica gel (1:4, DEE-petroleum ether). Colorless solid (93%). R_f = 0.30 (1:4, DEE-petroleum ether). The physical data of **T5.2h** match with its previously reported data of the compound.[186]

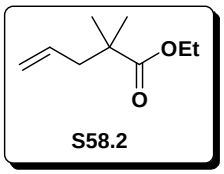
6.14 Procedures and physical data for compounds from Scheme 57



(*S*)-3-Ethyl-dihydro-3-(3-hydroxypropyl)furan-2(3H)-one (S49.2). The benzyl protected **T5.2d** (20.0 mg, 0.0760 mmol) was stirred with 2 mL of methanol, followed by the addition of

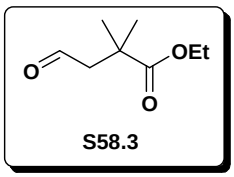
palladium on carbon (8.1 mg, 0.0076 mmol) for 12 h under a hydrogen atmosphere. Upon completion of the reaction, the resulting reaction mixture was filtered through a silica plug, and the solid was further washed with 15 mL of dichloromethane. The combined rganic layers were concentrated under reduced pressure. Purification of the resulting residue by column chromatography on silica gel (1:3, EtOAc-hexane) afforded 13.0 mg (99%) as colorless oil. R_f = 0.30 (3:1, EtOAc-hexane). $[\alpha]_D^{23}$ = +9.25 (*c* 0.005, $CHCl_3$). The physical data of **S49.2** match with its previously reported data of the compound.[168]

6.15 Procedures and physical data for compounds from Scheme 58



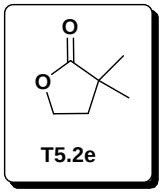
S58.2

Ethyl 2,2-dimethylpent-4-enoate (S58.2). The compound **S58.2** was prepared using the procedure described for compound **S53.3** in Scheme 53. 290 mg (86%) of the compound **S58.2** was isolated as a colorless liquid. The physical data of **S58.2** match with its previously reported data of the compound.[187]

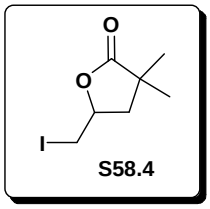


S58.3

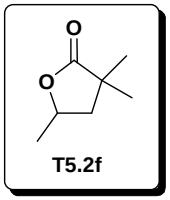
Ethyl 2-(formylmethyl)-2-methylpropanoate (S58.3). A solution of alkene **S58.2** (100 mg, 0.640 mmol) in 20 mL of dichloromethane was cooled to −78 ^oC and ozone was bubbled through the solution for 2−3 h until the reaction mixture turned to a light blue color. Then dimethyl sulfide (141 μL, 1.09 mmol) was added to the mixture at −78 ^oC and the mixture was stirred overnight at rt. Volatiles were removed under reduced pressure affording the crude aldehyde as a colorless liquid. The physical data of **S58.3** match with its previously reported data of the compound.[188]



Dihydro-3,3-dimethylfuran-2(3H)-one (T5.1e). The aldehyde **S58.3** (300 mg, 1.90 mmol) was dissolved in 5 mL of methanol and the solution was cooled to 0 ^{o}C followed by the addition of sodium borohydride (78.9 mg, 2.09 mmol). The resulting reaction mixture was stirred overnight at rt. Then the reaction was quenched with 5 mL of saturated aqueous solution of sodium bicarbonate (10 mL). The product was extracted with dichloromethane (2 × 10 mL) followed by washing the organic extracts with water (2 × 10 mL) and brine. The resulting organic layer was dried with anhydrous magnesium sulfate, filtered. Removal of volatiles under reduced pressure afforded 13.0 mg (25%) (over three steps from the staring ester **S58.1**) of lactone **ST5.2e** as a colorless oil. The physical data of **T5.2e** match with its previously reported data of the compound.[185]



Dihydro-5-(iodomethyl)-3,3-dimethylfuran-2(3H)-one (S58.4). Alkene **S58.2** (100 mg, 0.640 mmol) was stirred in THF-water (2:1) and an iodine crystal was added (243 mg, 1.92 mmol). The resulted reaction mixture was stirred 5 h at rt. Upon completion of the reaction, the product was extracted with dichloromethane and the organic layer was washed with water (2 × 10 mL) followed by 10 mL of saturated brine solution. The organic layer was then dried with anhydrus sodium sulfate and volatiles were removed under reduced pressure. Purification of the resulting crude mixture by column chromatography on silica gel (1:5, EtOAc-hexane) afforded 139 mg (85%) of the iodolactone **S58.4** as a colorless oil. The physical data of **S58.4** match with its previously reported data of the compound.



Dihydro-3,3,5-trimethylfuran-2(3H)-one (T5.2f). Iodolacone **S58.4** (70.0 mg, 0.280 mmol) was refluxed in a stirred suspension of Raney nickel (700 mg) in isopropanal (3 mL) for 15 min. Upon completion of the reaction, the mixture was cooled to rt, the organic layer was decanted from the Raney nicke, and the catalyst was washed with dichloromethane (3 × 5 mL). The combined organic layers were fileted through a Celite plug, which was washed with an additional 5 mL of dichloromethane. Removal of volatiles under reduced pressure afforded 27.0 mg (77%) of lactone **S58.4** as a colourless liquid. The physical data of **T5.2f** match with its previously reported data of the compound.[185]

APENDIX I

LIST OF ABBREVIATIONS AND ACRONYMS

abs.	absolute
Ac	acetyl
AD	asymmetric dihydroxylation
AIBN	azobis(isobutyronitrile)
acac	acetylacetone
ATP	adenosine triphosphate
9-BBN	9-borabicyclo[3.3.1]nonane
B3LYP	Becke,3-parameter, Lee-Yang-Parr
Bn	benzyl
Bu	butyl
Bz	benzoyl
CAN	cerium(IV) ammonium nitrate
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-dicyclohexylcarbodiimide
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DEE	diethyl ether
DEPT	distortionless enhancement by polarization transfer

DET	diethyltryptamine
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIPEA/DIEA	*N*,*N*-diisoropylethylamine
DMAP	dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
EDG	electron-donating group
ee	enatiomeric excess
Et	ethyl
equiv.	equivalent
EWG	electron-withdrawing group
FT-IR	fourier transform infrared spectroscopy
h	hour
HMPA	hexamethylphosphoramide
HOBT	hydroxybenzotriazole
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
IBX	iodoxy benzoic acid

Im-H	imidazole
i-Pr	isopropyl
KHMDS	potassium hexamethyldisilazane
LAH	lithium aluminum hydride
LD50	lethal dose, 50%
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazane
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeOH	methanol
MeCN	acetonitrile
MEOX	4(*S*)-methyl 2-oxooxazolidinecarboxylate
MPPIM	4(*S*)-methyl 1-(3-phenylpropanoyl)-2-oxaimidazolidinecarboxylate
MS	molecular sieves
Ms	mesyl
MTPA	α-methoxy-α-trifluoromethylphenylacetic acid
NaHMDS	sodium hexamethyldisilazane
NMO	*N*-methylmorpholine-N-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Nos	Nosyl
Pd	palladium
Pet	petroleum

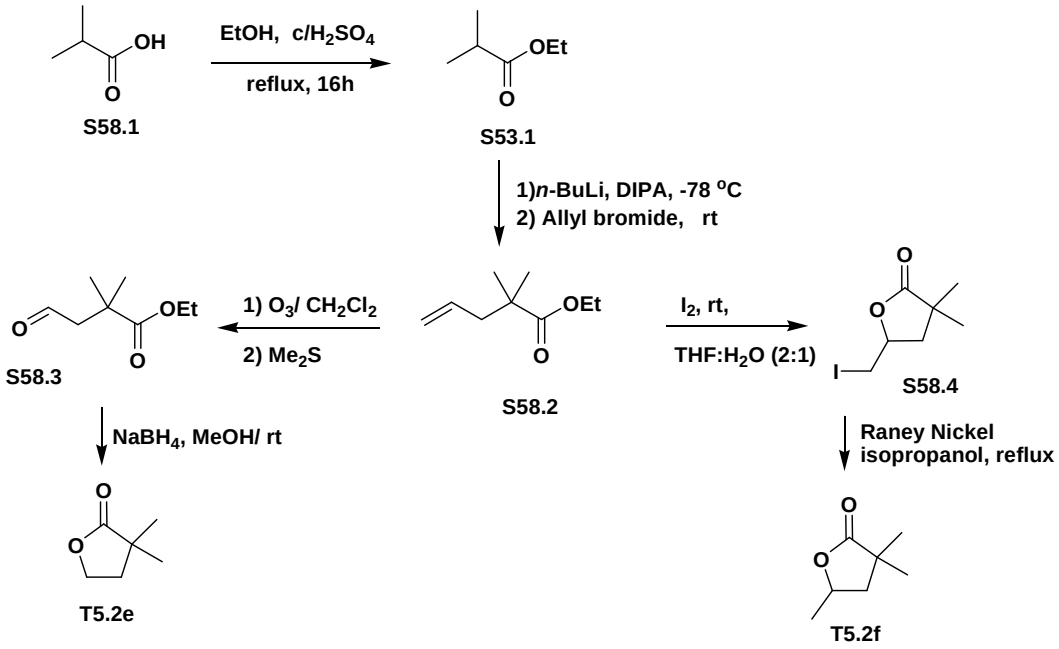
Pfb	perfluorobutyrate
PGME	phenylglycine methyl ester
Ph	phenyl
Piv	pivaloyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
PNB	propylene glycol butyl ether
Pr	propyl
PTLC	preparative thin layer chromatography
PTSA	*para*-toluenesulfonic acid
Py	pyridine
PyBOP	(benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
RCM	ring-closing metathesis
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBDS	(*S*)-2-(*tert*-butylamino)-3-hydroxypropanoic acid
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
Tf	trifluoromethanesulfyl
TFA	trifluoroacetate

THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
TOF	time of flight
tol-BINAP	2,2′-*bis*(di-*p*-tolylphosphino)-1,1′-binaphthyl
TPAP	tetrapropylammonium perruthenate
Tr	trityl
p-Ts	*para*-toluenesulfonyl
TS	transition state

APENDIX II

SCHEMES FOR THE ALTERNATIVE SYNTHESIS OF
T5.2e AND **T5.2f**

Ethyl isobutyrate **S51.1** was obtained *via* Fischer esterification of isobutyric acid **S58.1**. Ethyl isobutyrate was allylated[189] with freshly prepared LDA at –78 ^{o}C, followed by ozonolysis with reductive work-up with dimethyl sulfide to produce aldehyde **S58.3**.[55] Reduction of aldehyde **S58.3** to its corresponding alcohol and cyclization of the alcohol to five-membered lactone **T5.2e** occurred within a single pot in the presence of sodium borohydride and methanol at 0 ^{o}C. Lactone **T5.2e** was obtained in 25% yield from starting acid **S58.1,** over three steps. Iodolactonization of ester **S58.2** followed by hydrogenolysis of iodolactone **S58.4** resulted the desired lactone **T5.2f**.



Scheme 58. Alternative synthetic routes for the preparation of **T5.2e** and **T5.2f**.

APENDIX III

SELECTED SPECTRA

FIGURES **6**–**22**

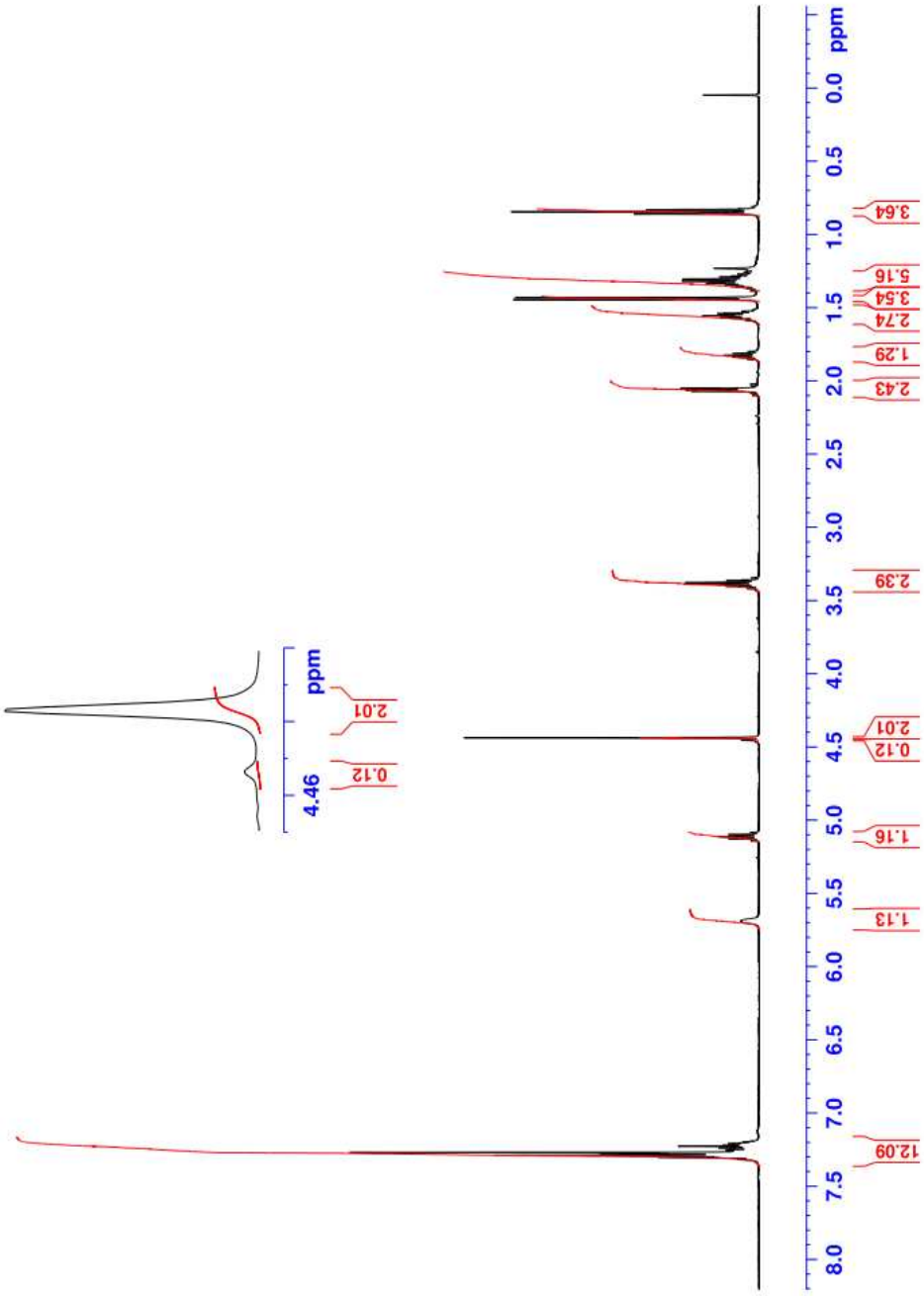


Figure 6. ^{1}H NMR (500 MHz) spectrum of 6-(benzyloxy)-3-ethyl-N-((*S*)-1-phenylethyl)hexanamide (**S52.3**) in $CDCl_3$.

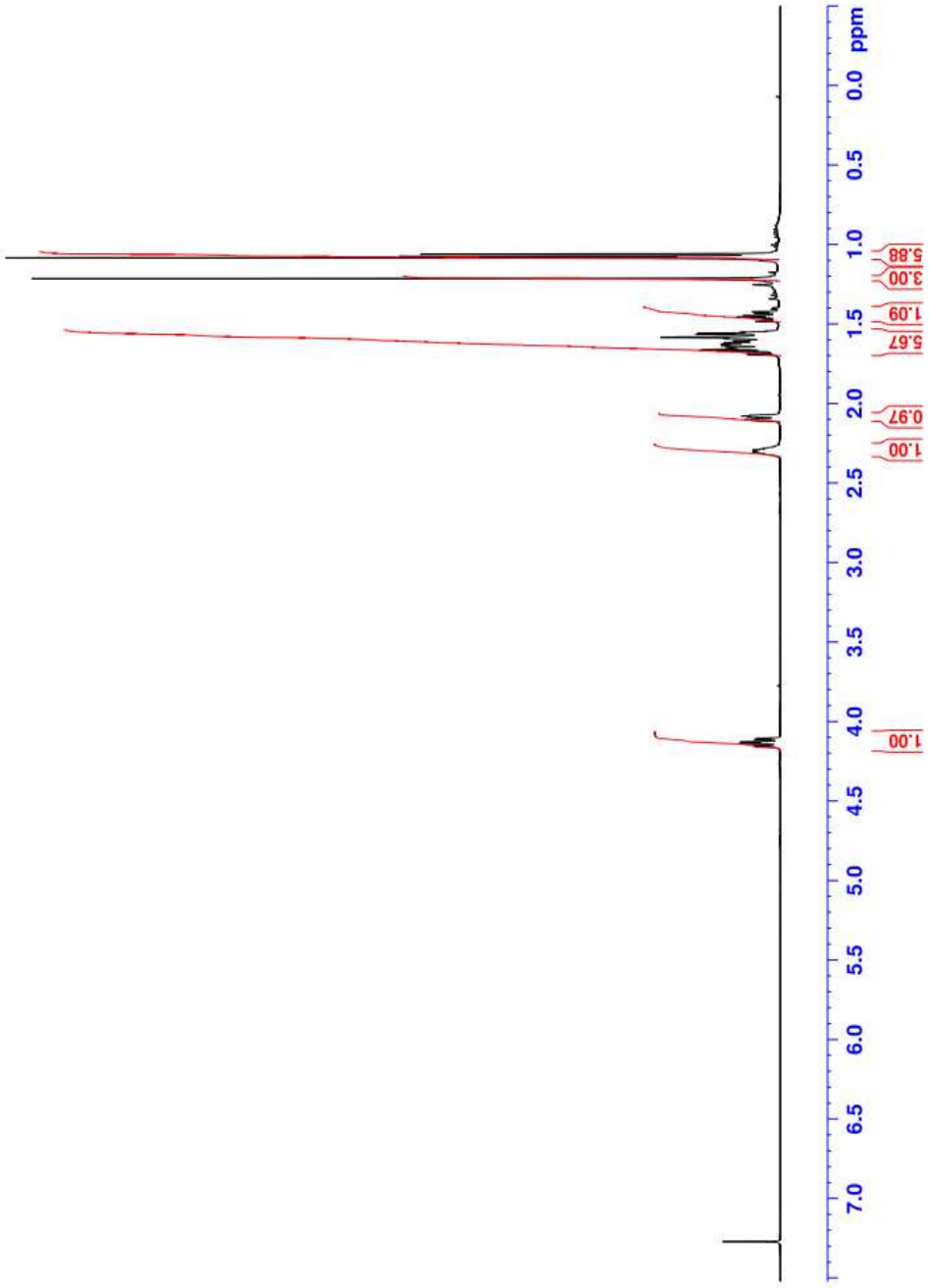


Figure 7. ^{1}H NMR (500 MHz) spectrum of (3a*R*,6*R*,7a*S*)-hexahydro-3,3,6-trimethylbenzofuran-2(3H)-one (**T5.2a**) in $CDCl_3$.

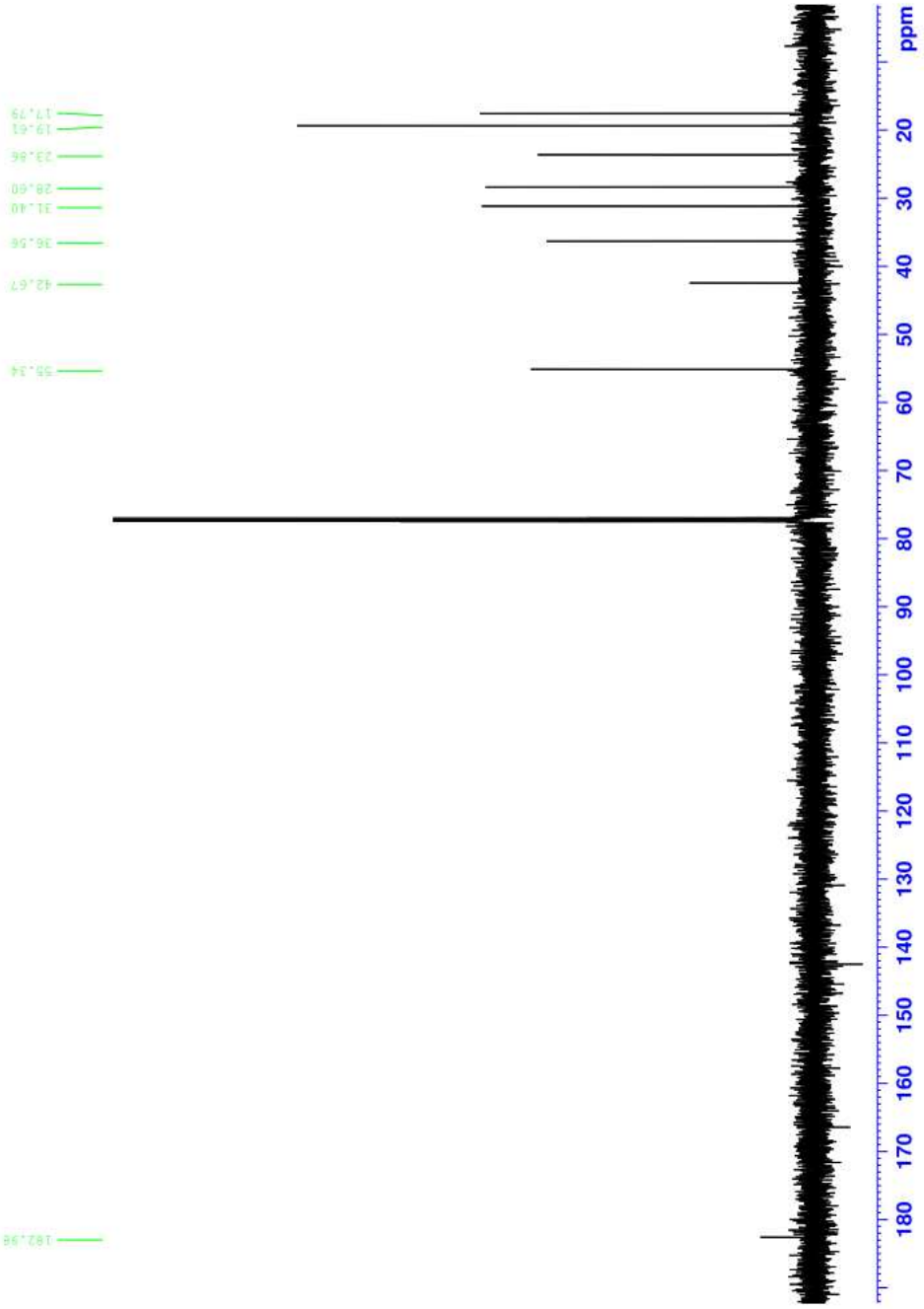


Figure 8. $^{13}C\{^{1}H\}$ NMR (125 MHz) spectrum of (3a*R*,*6R*,7a*S*)-hexahydro-3,3,6-trimethylbenzofuran-2(3H)-one (**T5.2a**) in $CDCl_3$.

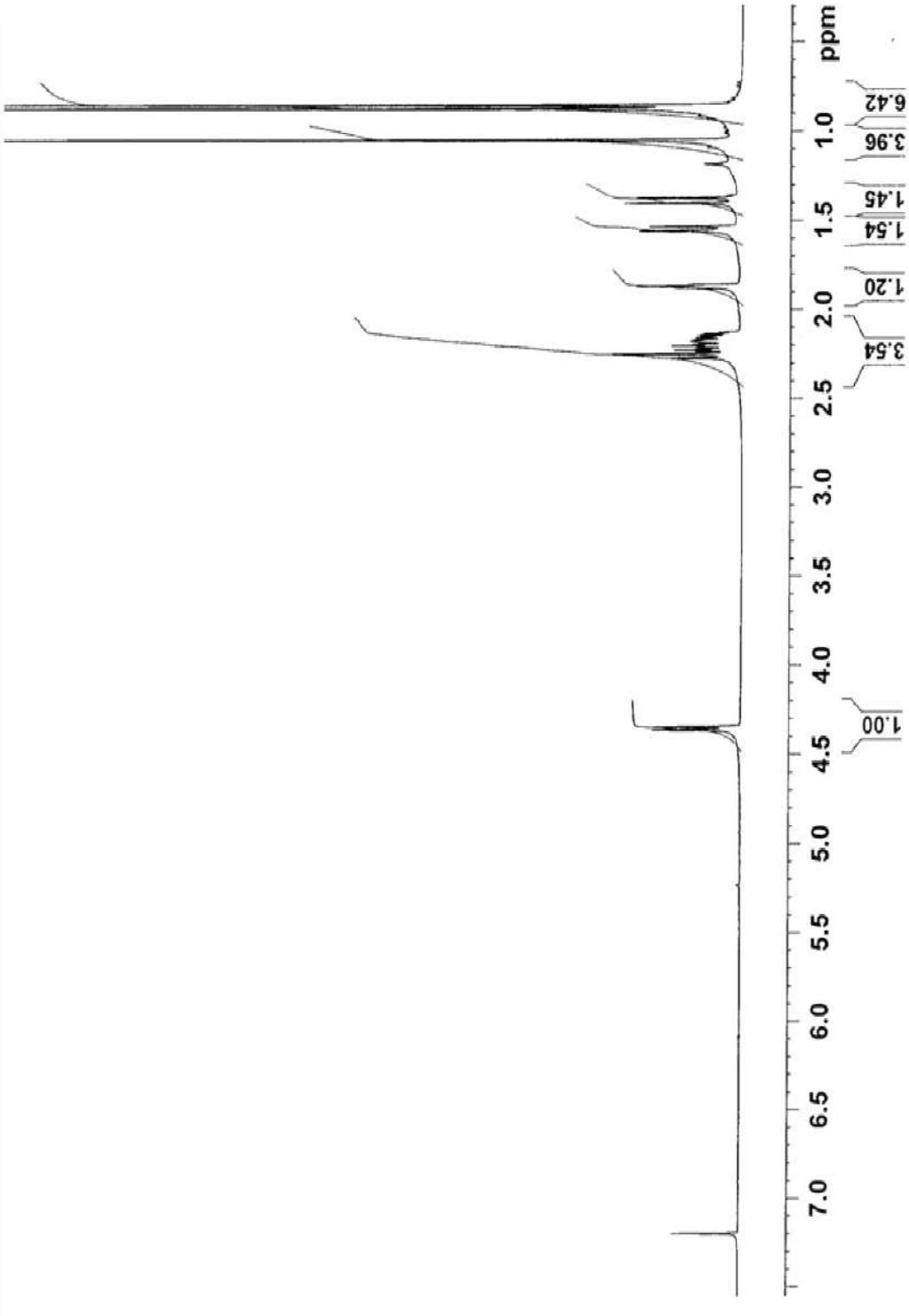


Figure 9. ^{1}H NMR (500 MHz) spectrum of 7,8,8-trimethyl-4-oxatricyclo [4.2.1.03,7]nonan-5-one (**T5.2b$_1$**)in $CDCl_3$.

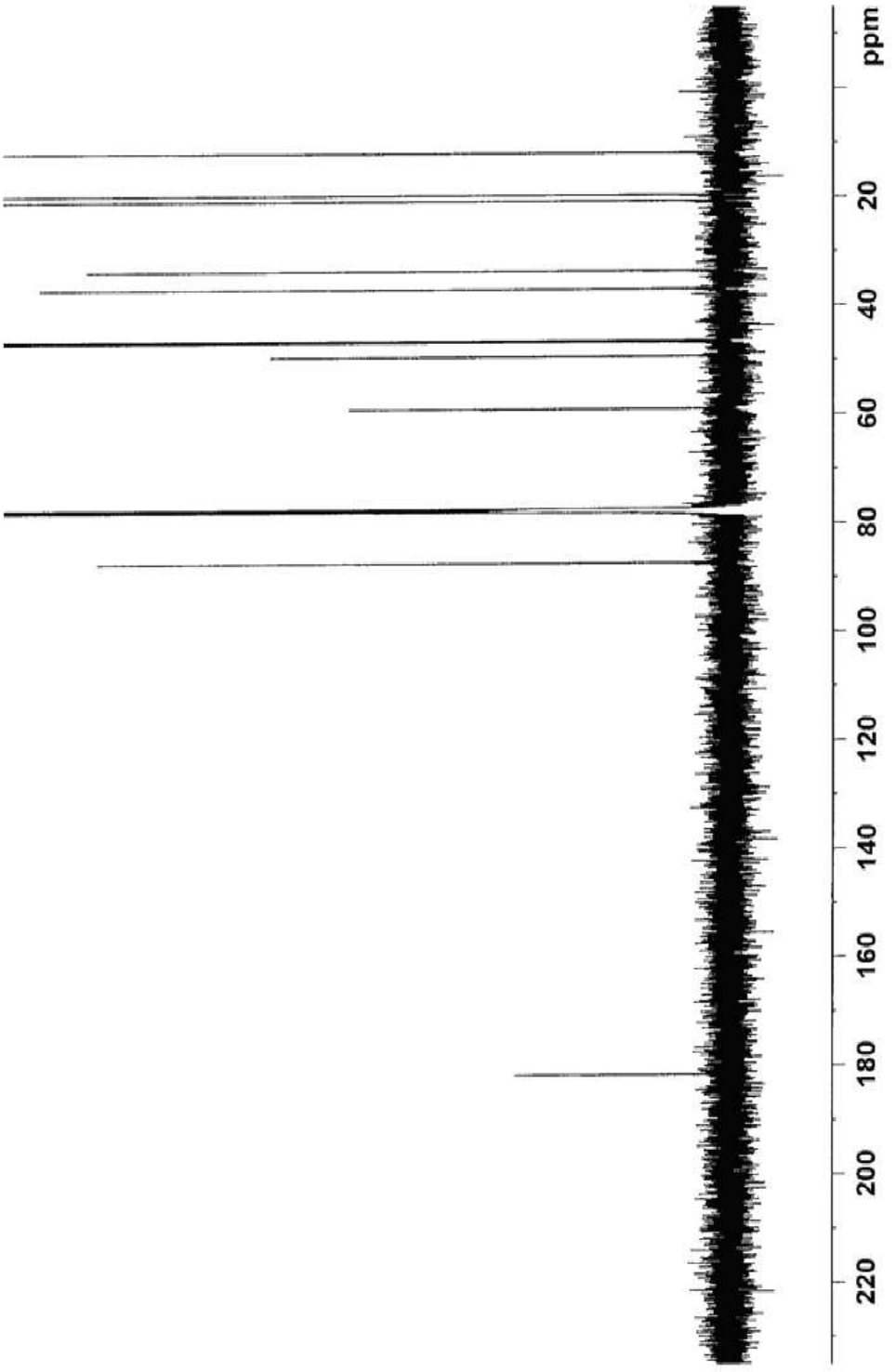


Figure 10. $^{13}C\{^{1}H\}$ NMR (125 MHz) spectrum of 7,8,8-trimethyl-4-oxatricyclo [4.2.1.03,7]nonan-5-one (**T5.2b$_1$**)in $CDCl_3$.

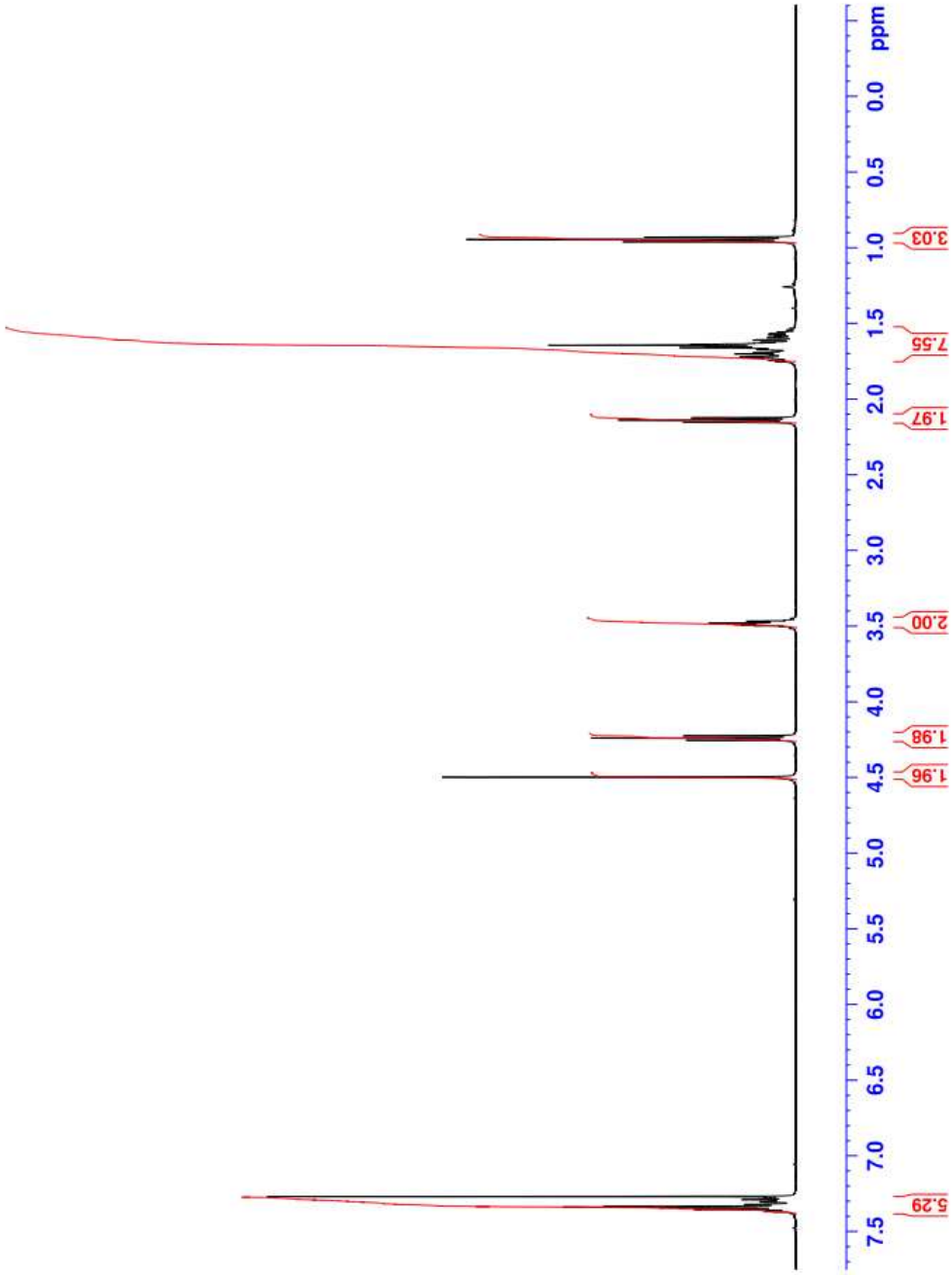


Figure 11. ^{1}H NMR (500 MHz) spectrum of (S)-3-(3-(benzyloxy)propyl) -3-ethyl-dihydrofuran-2(3H)-one (**T5.2d**) in $CDCl_3$.

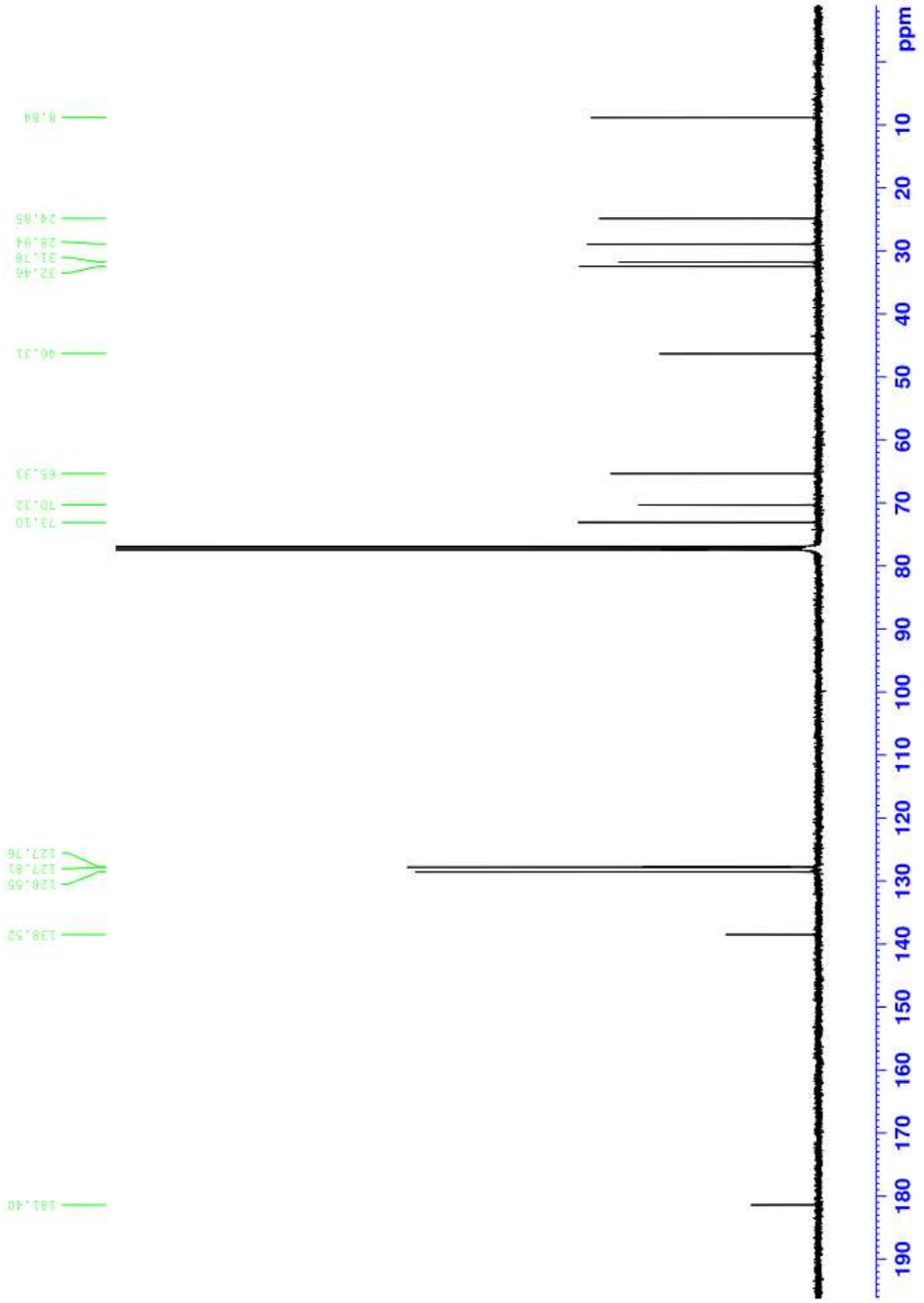


Figure 12. $^{13}C\{^{1}H\}$ NMR (125 MHz) spectrum of (S)-3-(3-(benzyloxy)propyl) -3-ethyl-dihydrofuran-2(3H)-one (**T5.2d**) in $CDCl_3$.

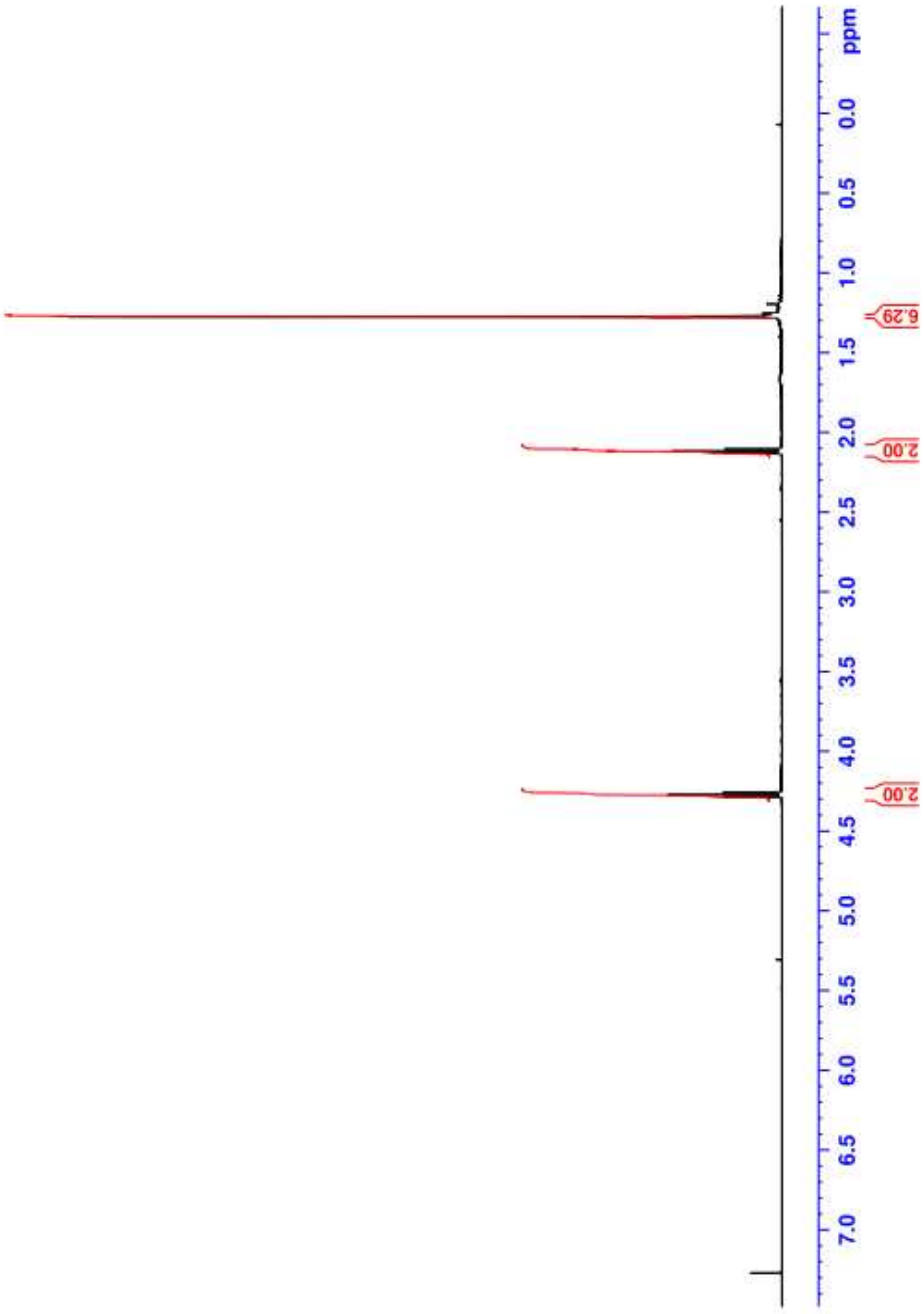


Figure 13. ^{1}H NMR (500 MHz) spectrum of dihydro-3,3-dimethylfuran-2(3H)-one (**T5.2e**) in $CDCl_3$.

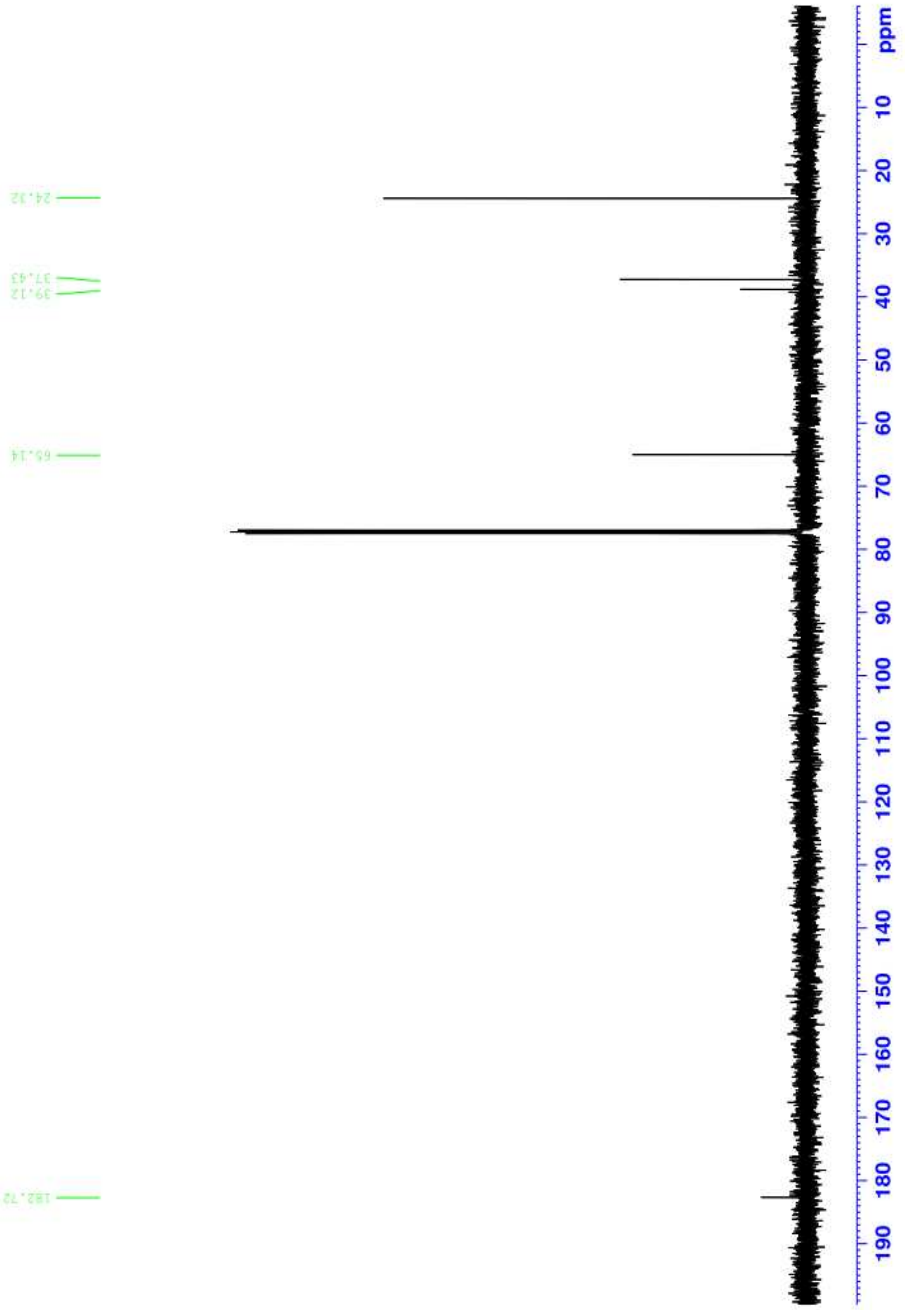


Figure 14. $^{13}C\{^{1}H\}$ NMR (125 MHz) spectrum of dihydro-3,3-dimethylfuran-2(3H)-one (**T5.2e**) in $CDCl_3$.

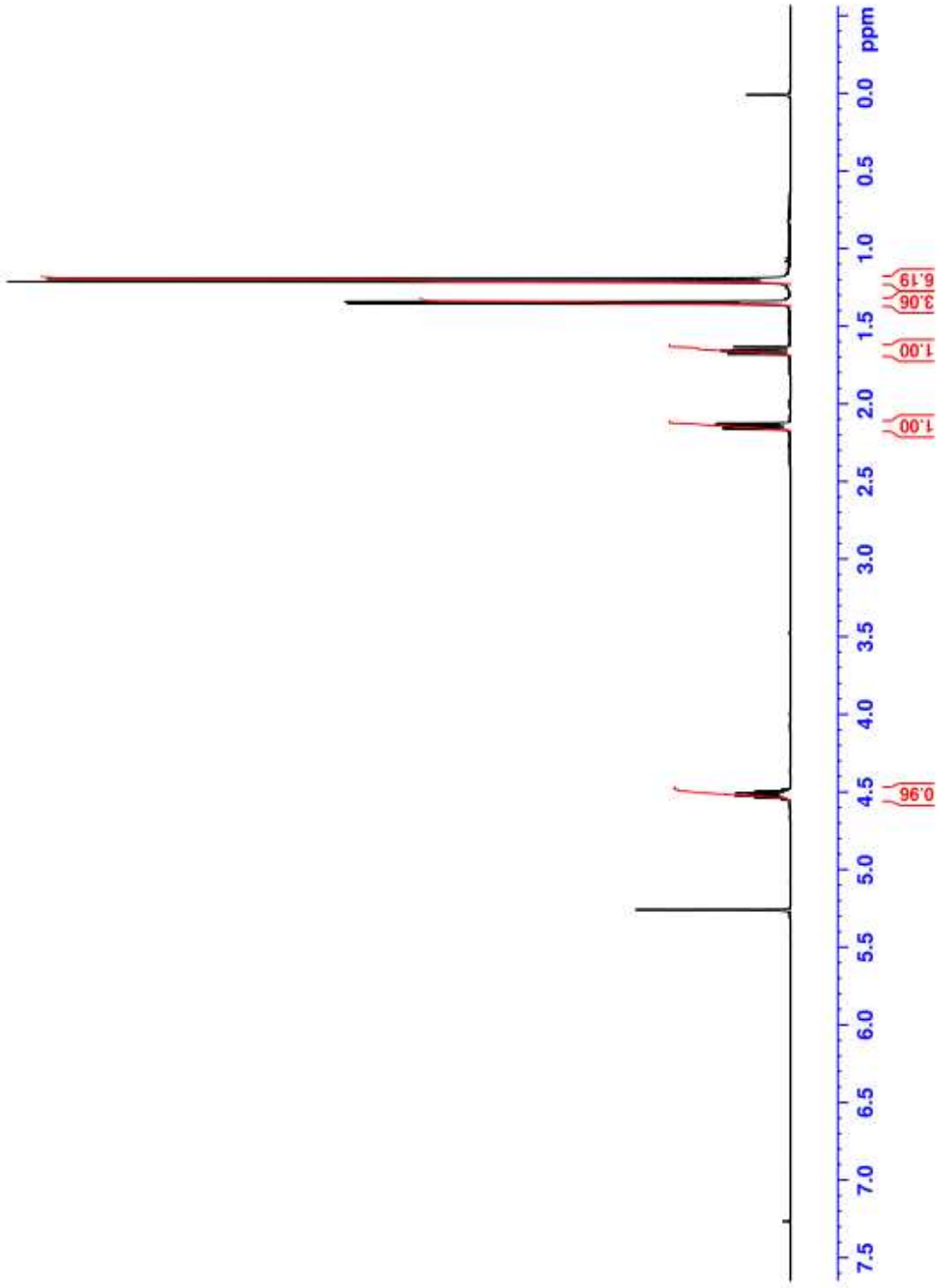


Figure 15. ^{1}H NMR (500 MHz) spectrum of dihydro-3,3,5-trimethylfuran-2(3H)-one (**T5.2f**) in $CDCl_3$.

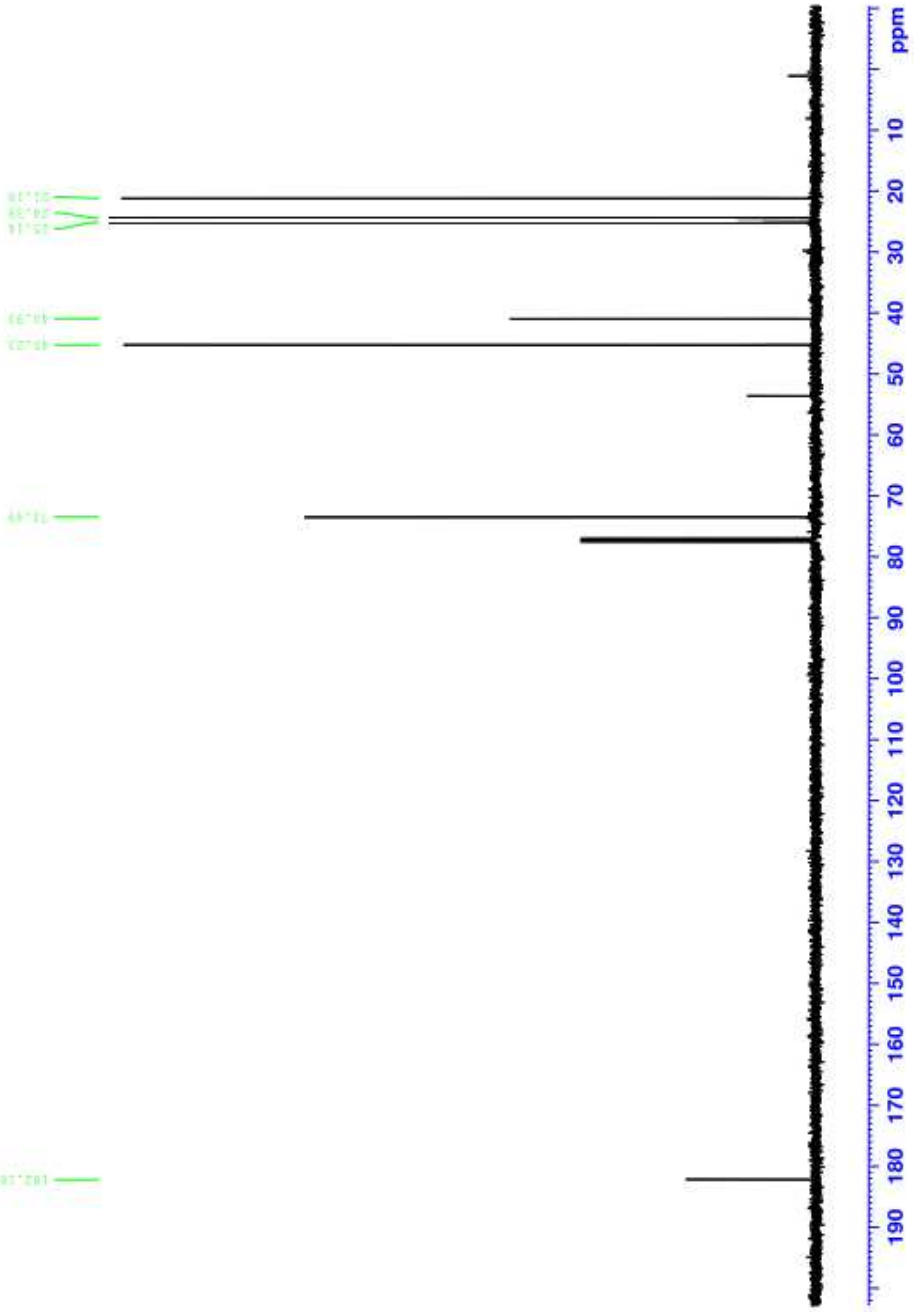


Figure 16. $^{13}C\{^{1}H\}$ NMR (125 MHz) spectrum of dihydro-3,3,5-trimethylfuran-2(3H)-one (**T5.2f**) in $CDCl_3$.

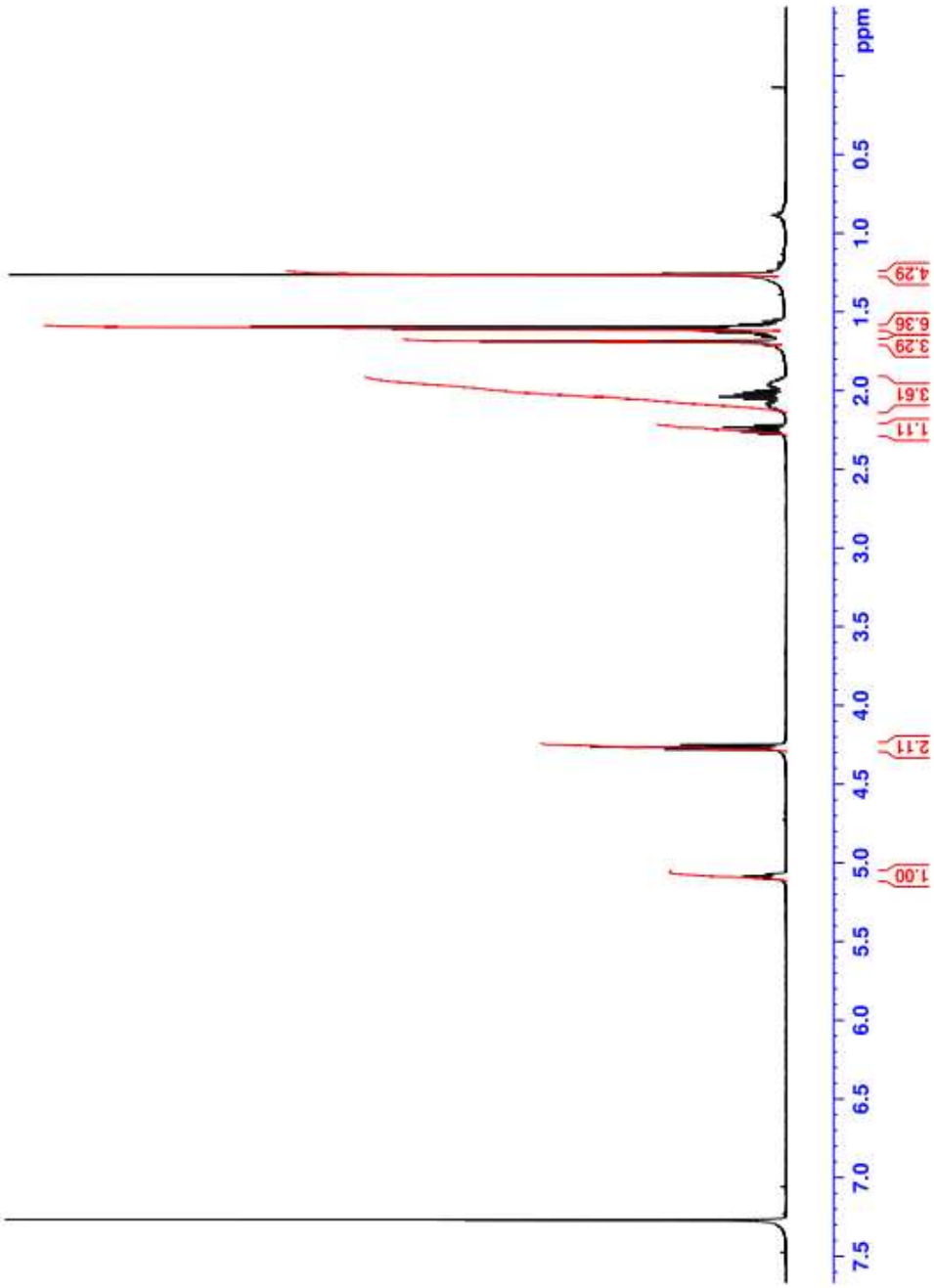


Figure 17. ^{1}H NMR (500 MHz) spectrum of 3-methyl-3-(4-methyl-3-pentenyl) dihydrofuran-2-one (**T5.2g**) in $CDCl_3$.

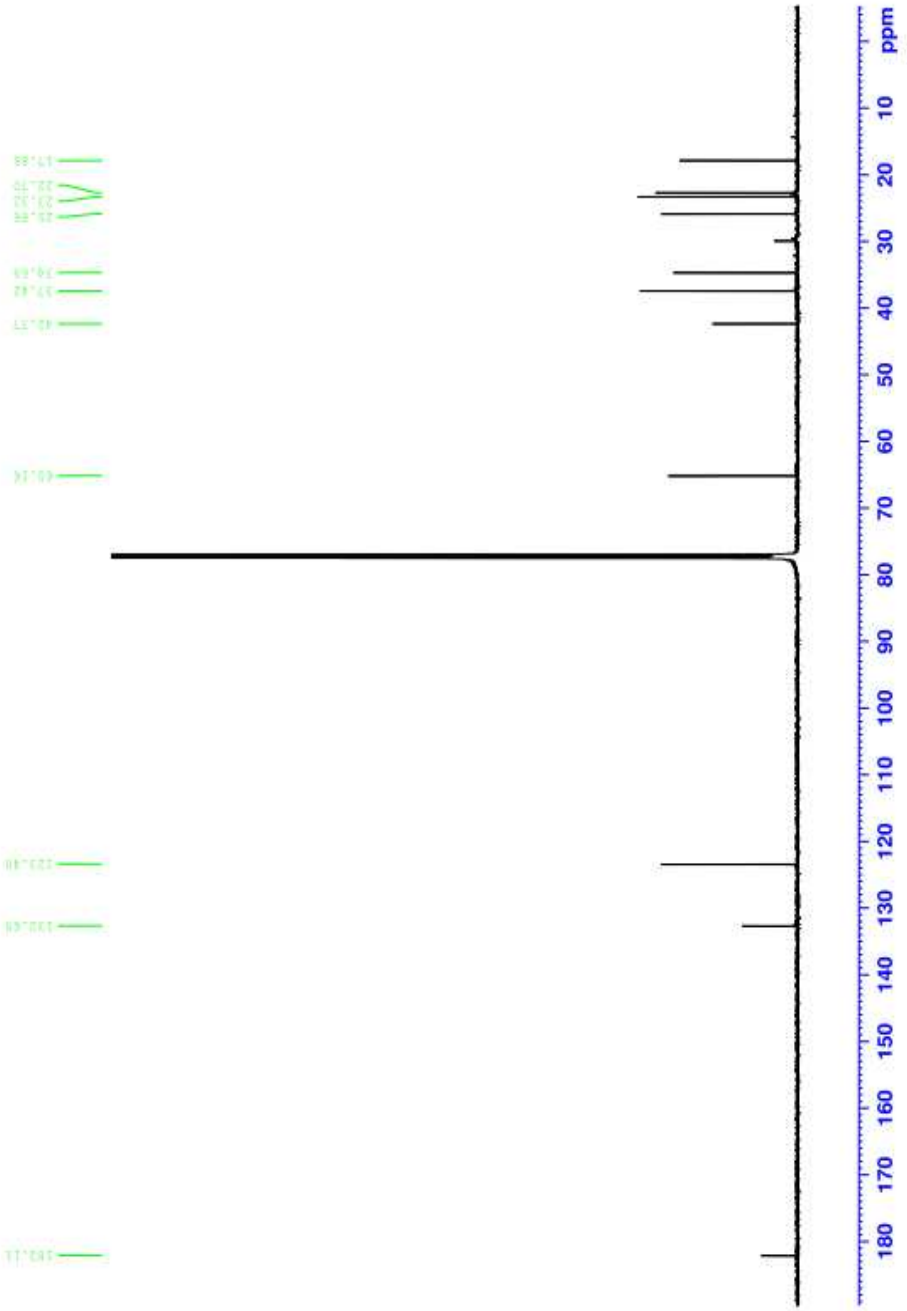


Figure 18. $^{13}C\{^{1}H\}$ NMR (125 MHz) spectrum of 3-methyl-3-(4-methyl-3-pentenyl)dihydrofuran-2-one (**T5.2g**) in $CDCl_3$.

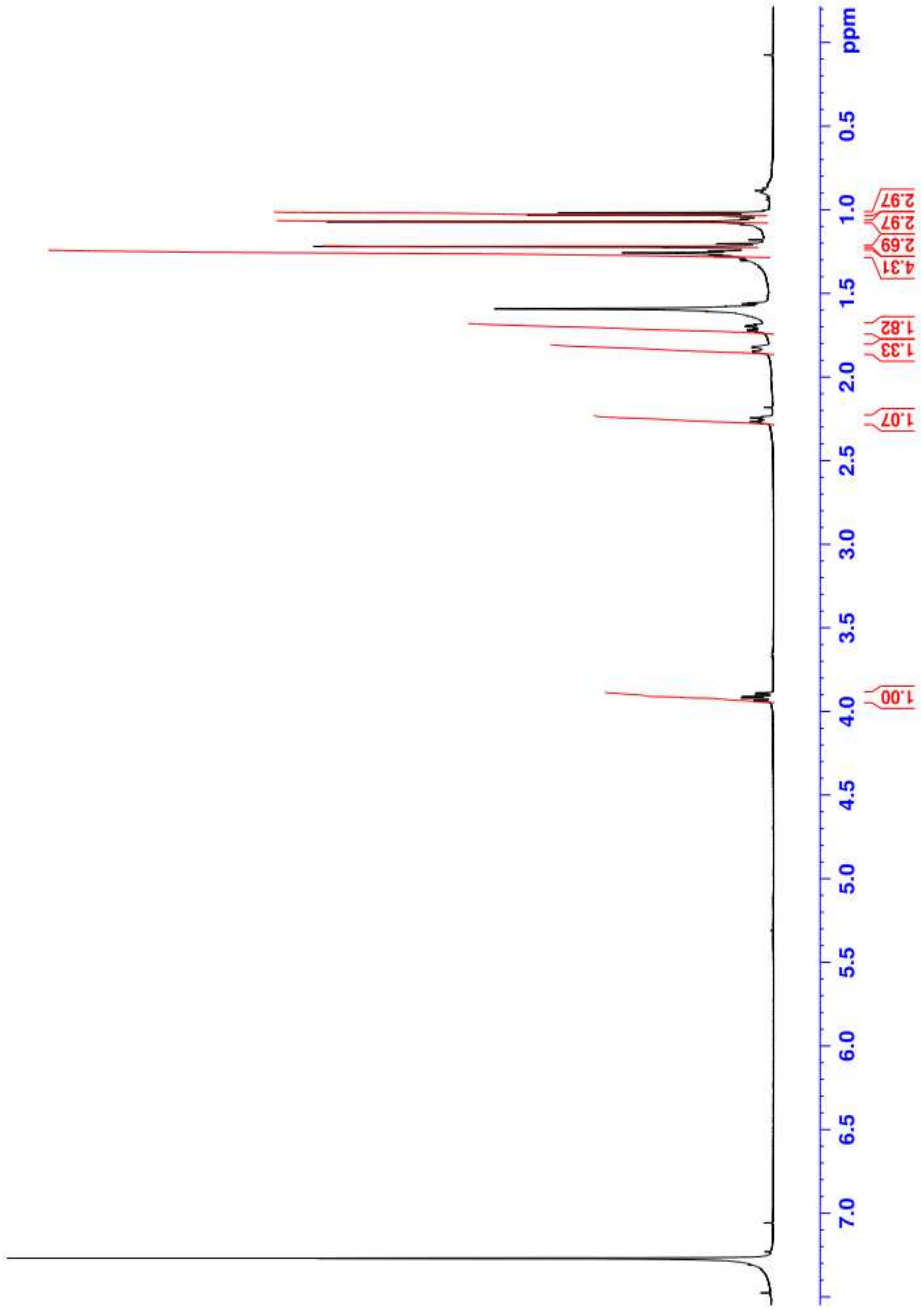


Figure 19. ^{1}H NMR (500 MHz) spectrum of (*3aS*,*6R*,7a*R*)-hexahydro-3,3,6-trimethylbenzofuran-2(3H)-one (**T5.2h**). in $CDCl_3$.

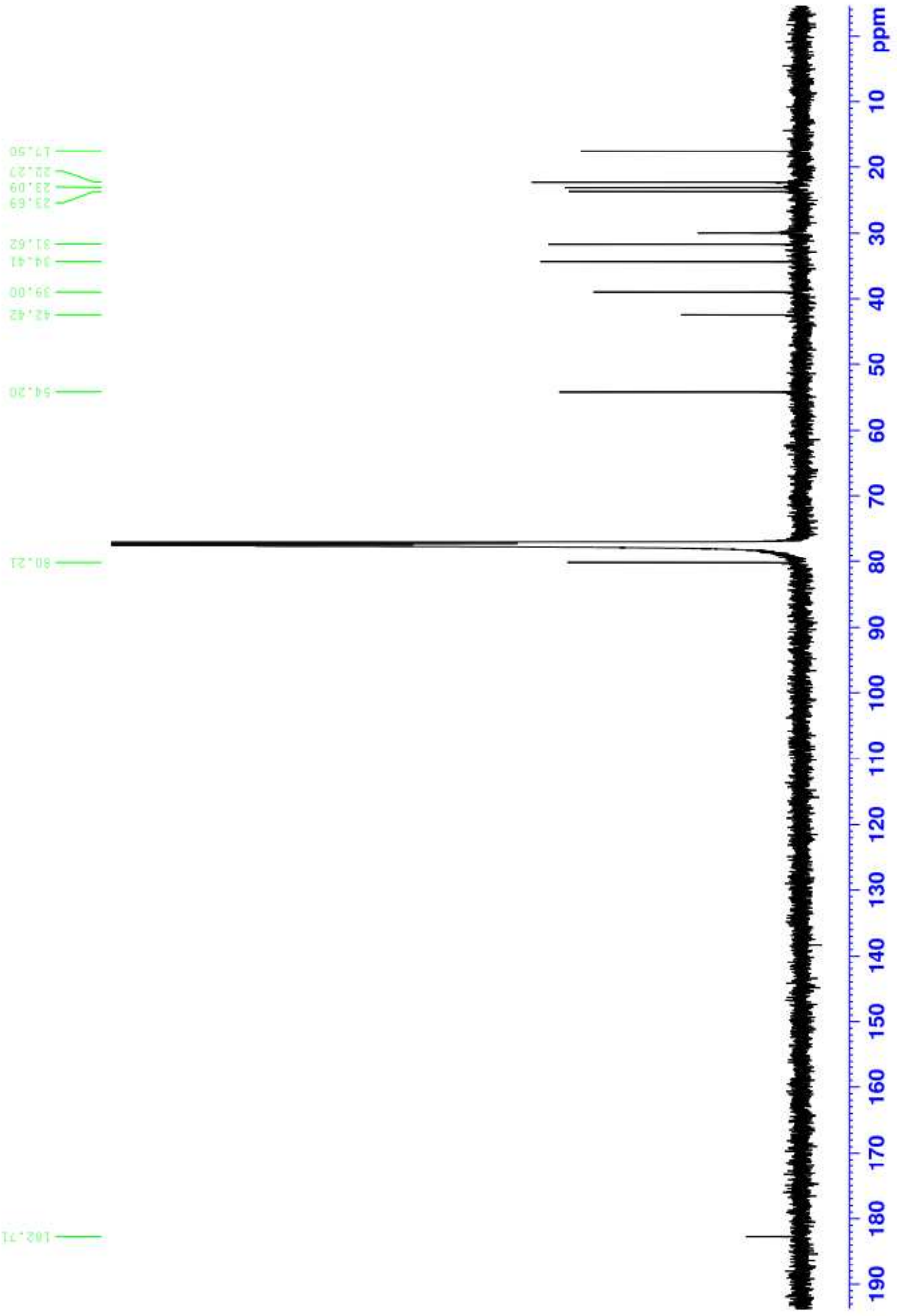


Figure 20. $^{13}C\{^{1}H\}$ NMR (125 MHz) spectrum of (3a*S*,*6R*,7a*R*)-hexahydro-3,3,6-trimethylbenzofuran-2(3H)-one (**T5.2h**). in $CDCl_3$.

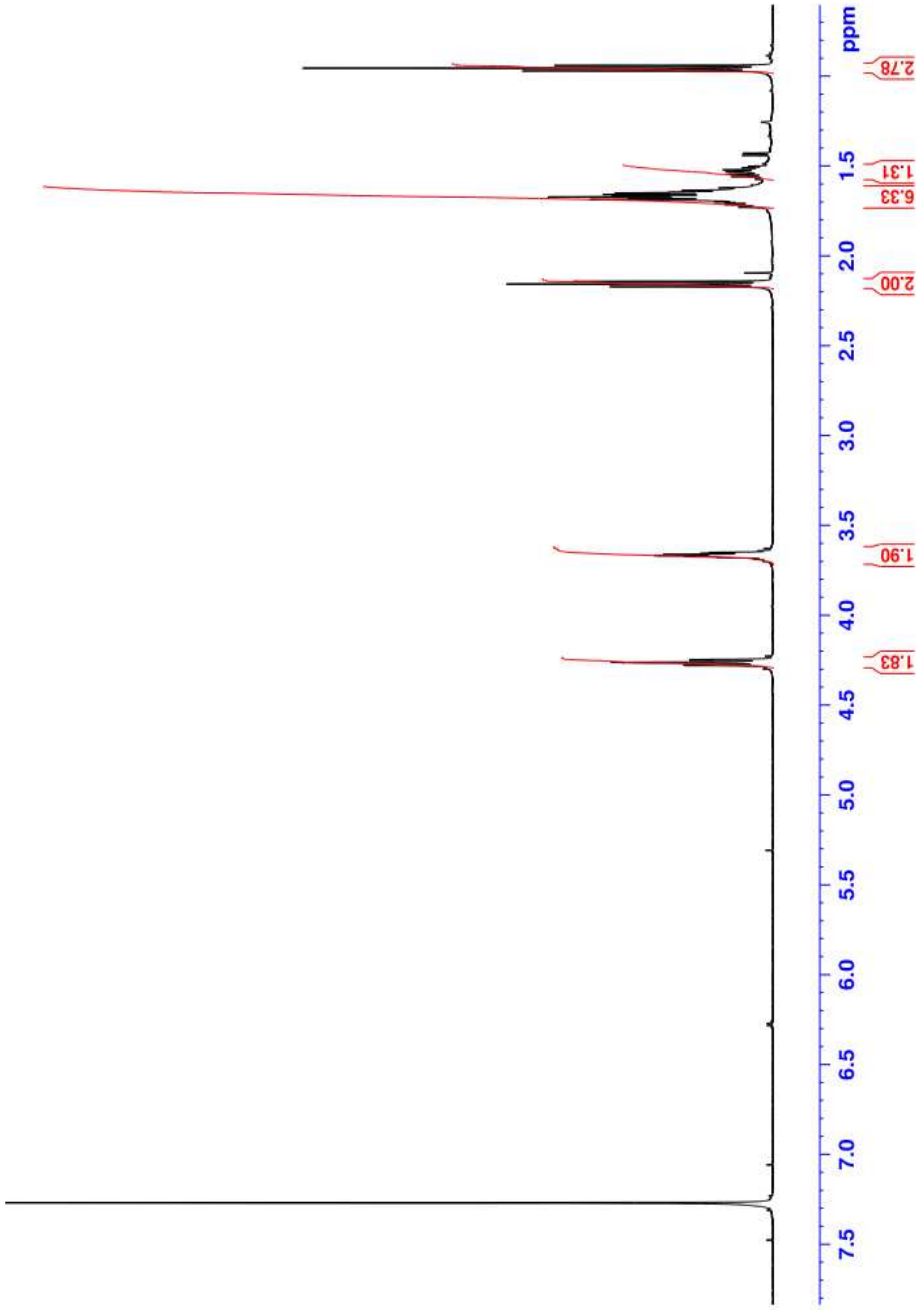


Figure 21. ^{1}H NMR (500 MHz) spectrum of (*S*)-3-ethyl-dihydro-3-(3-hydroxypropyl) furan-2(3H)-one (**S49.2**).

.

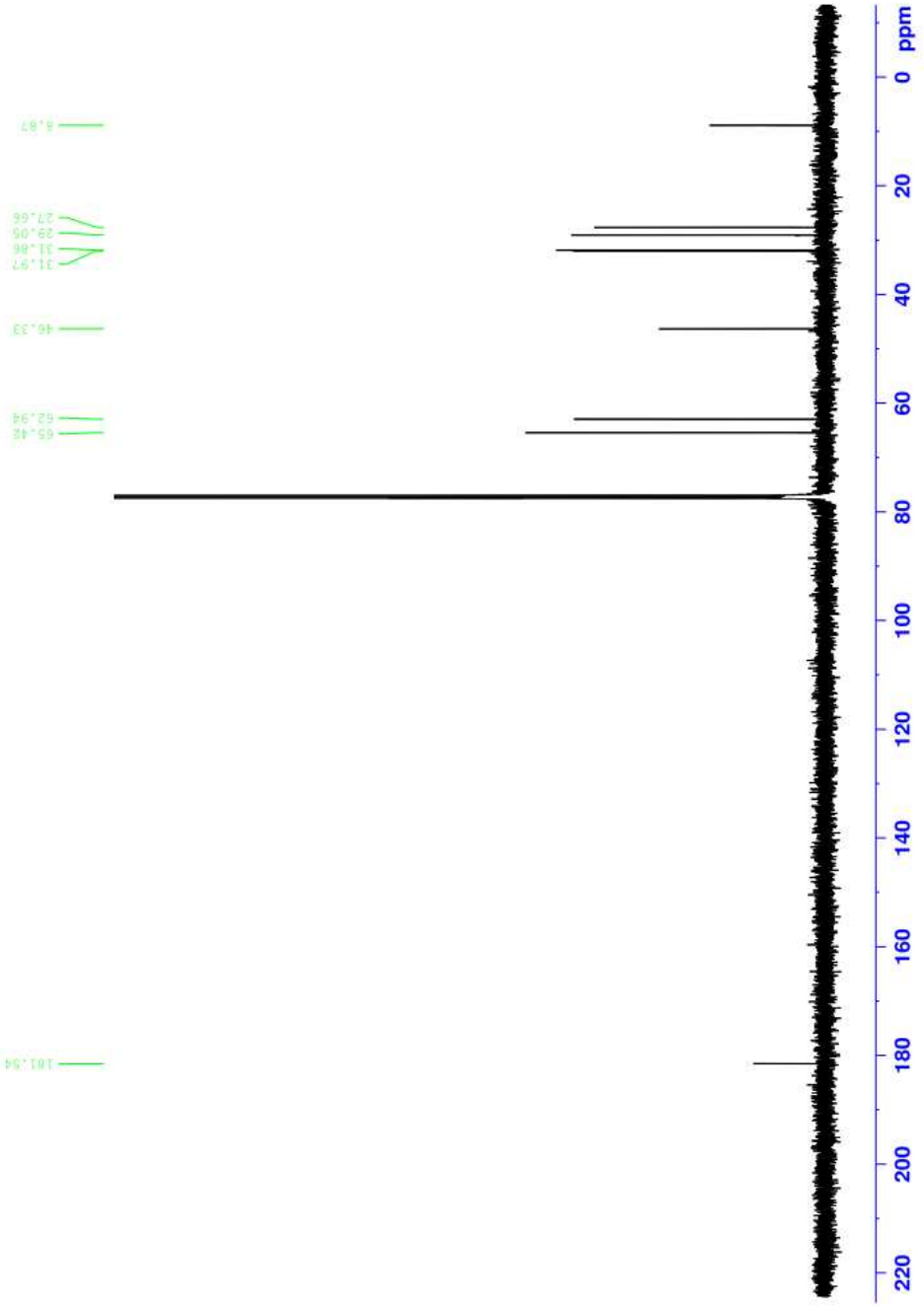


Figure 22. $^{13}C\{^{1}H\}$ NMR (125 MHz) spectrum of (*S*)-3-ethyl-dihydro-3-(3-hydroxypropyl)furan-2(3H)-one (**S49.2**)

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