# ENANTIOSELECTIVE TOTAL SYNTHESIS OF (+)-MONOCERIN AND DESIGN AND SYNTHESIS OF POTENT HIV-1 PROTEASE INHIBITORS

by

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*This thesis is dedicated to my loving parents and grandmother for their love, endless support, and words of encouragement.*

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# ABSTRACT

(+)-Monocerin is a dihydroisocoumarin natural product that is consisted of a 2,3,5-trisubstituted tetrahydrofuran moiety with all-*cis* stereochemistry. (+)-Monocerin showed very potent antimalarial activity ($IC_{50}$ = 680 nM) against *Plasmodium falcifarum,* which is a multi-antimalarial drug resistant K1 strain. Our synthesis involves a Sharpless dihydroxylation as one of the key steps to efficiently provide the optically active lactone intermediate with high enantiomeric purity. Our synthesis also features a tandem Lewis acid-catalyzed diastereoselective *syn*-allylation reaction and an Oxa-Pictet-Spengler cyclization to construct an isochroman structure of (+)-monocerin (**1**) in *one-pot*. By employing several different Lewis acids and protecting groups, this allylation reaction has been thoroughly studied. The enantioselective total synthesis of (+)-monocerin and its acetate derivative was accomplished in 10 and 11 steps with 9% and 8.6% overall yield, respectively.

To further optimize the hydrogen bonding interactions as well as Van der Waals interactions within the active sites of HIV-1 protease inhibitors, we have designed and synthesized a new class of HIV-1 protease inhibitors incorporating trisubstituted-chiral-tetrahydrofuran (*tc*-THF) moieties as P2-ligands. A series of protease inhibitors were synthesized by incorporating *tc*-THF as P2-ligand in combination with the known 4-methoxybenzenesulfonamide and 4-aminobenzenesulfonamide isosteres as P2'-ligands. The effect of stereochemistry of the chiral substituents on the binding affinity was thoroughly examined. Most of these newly synthesized inhibitors displayed potent enzyme inhibitory activity.

# CHAPTER 1. ENANTIOSELECTIVE TOTAL SYNTHESIS OF (+)-MONOCERIN AND ITS ACETATE DERIVATIVE

## 1.1 Introduction

Historically, natural products (NPs) have been the most successful source of therapeutic drug candidates due to their structural diversity and biological activity.[1-6] Since thousands of years ago, NPs have been used as traditional medicines and still used today in many developing countries as the most affordable treatment for various disease.[5,7-10] These NPs can be classified into two broad categories: (i) those isolated from mammalian organisms and their metabolites; and (ii) those isolated from various biological sources, such as marine organisms, plants, non-mammalian animal species, and microorganisms including bacteria and fungi.[11] Since the beginning of early 1980s, bioactive compounds isolated from these two categories of NPs have been screened for their biological activities and many of them are made into drugs for the treatment of various disease.[11-15]

Between 1981 and 2019, around 64.9% of the FDA-approved therapeutic drugs brought to market for cancer were based on either natural products or their modified derivatives.[16] For instance, Palitaxel (Taxol®), one of the best-selling cancer drugs ever manufactured, was derived from bark of the Pacific yew, *Taxus brevifolia*, and exhibited unique microtubule stabilizing properties.[17-18] The other 35% were synthetic, but not completely random.[16] In the anti-infective area, the influence of NPs and their derivatives is remarkable as well. In 2016, Patridge *et al.* reported that 69% of all antibacterial agents were originated from NPs, with 98% isolated from microorganisms (51% from bacteria and 47% from fungi).[11] This trend of utilizing NPs and their derivatives to discover new antibacterial agents has continued until today.[11,16] Since the year 2000, approximately 77% of all FDA-approved antibiotics were either NPs or their derivatives, with 100% isolated from bacteria and pathogenic fungi.[11] Antibacterial agents derived from these microorganisms are known to target many pathways and enzymes, including topoisomerases (tetracyclines), peptidyltransferases (macrolides and ascamycins), ribosomes (aminoglycosides), and transpeptidases (beta-lactams).[11]

Macro and micro fungi have been used as food (mushrooms), traditional medicines, and ingredient to prepare alcoholic beverages (yeast) since the dawn of human history.[19] Since the discovery of penicillin from the fungus, *Penicillium notatum*, in 1929 by Fleming, there has been

a worldwide effort to discover new pharmacologically active products from these microorganisms.[19-22] Over the past decades, bioactive compounds isolated from various fungal sources have attracted considerable amount of attention from both industry and academia due to their antibacterial and antifungal potentials. Particularly, those from endophytic and marine environments have gained additional attentions as many novel bioactive NPs with cytotoxic, anticancer, antibacterial or antifungal properties have been discovered from these sources.[10,23-28] (+)-Monocerin and its analogues are the excellent examples of NPs isolated from endophytic fungal sources with a broad spectrum of biological activities.

The first portion of this chapter provides background information on the isolation, biological activities, and complete structural assignment of (+)-monocerin (**1**) and its analogues. The second portion of this chapter briefly introduces previous approaches to the asymmetric synthesis of (+)-monocerin by *Mori and Takaishi* and *Lee et al*. Lastly, a full discussion of our synthetic efforts to the enantioselective total synthesis of (+)-monocerin (**1**) and its acetate derivative, (+)-acetyl monocerin (**2**), is outlined.

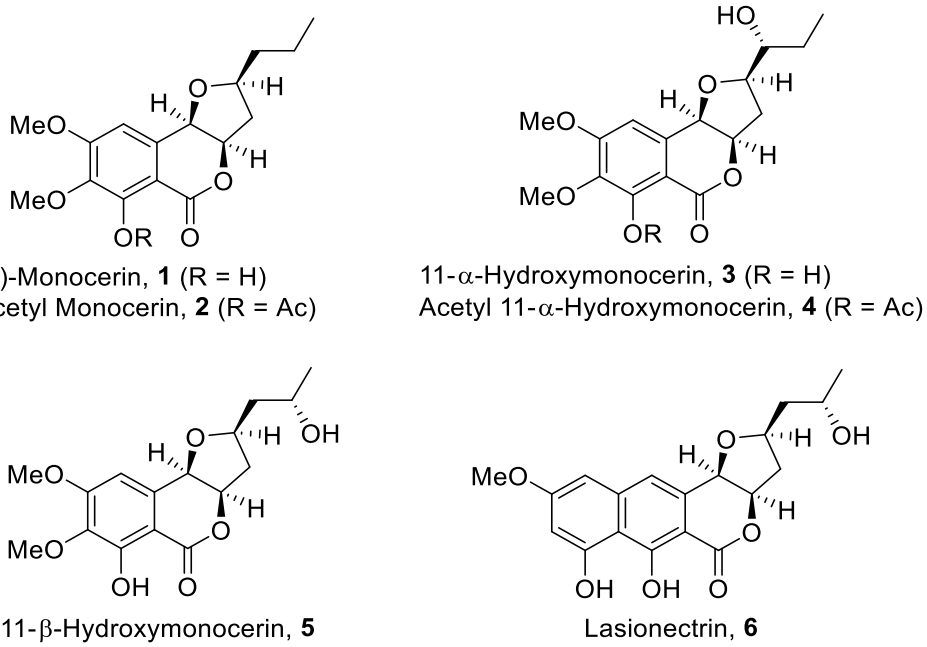



Figure 1.1 Structure of Dihydroisocoumarin Natural Products 1-6.

### 1.1.1 Isolation, Biological Activities, and Characterization of (+)-Monocerin and Its Analogues

Dihydroisocoumarin and dihydroisocoumarin derivatives are naturally occurring *cis*-fused furobenzopyranones.[29,30] These natural products are known to show a broad spectrum of biological activities, such as antifungal, insecticidal, antiparasitic, plant pathogenic, and anti-malarial properties. In 1970, Aldridge and Turner isolated (+)-monocerin (**1,** Figure 1.1) from fermentations of *Drechslera monoceras*. (+)-Monocerin (**1**) was shown to protect wheat against powdery mildew (*Erisyhe graminis*).[31] Subsequently, insecticidal properties of (+)-**1** were demonstrated by Grove and co-workers.[32]

In 2004, Axford and co-workers reported the first synthesis of the polyketide intermediate in (+)-monocerin (**1**).[33] After this total synthesis, the phytotoxic properties of (+)-monocerin (**1**) and its derivatives (**2**-**5**) have been studied.[34-38] According to the plant pathogenic study from Cuq and co-workers in 1993, (+)-**1** was able to inhibit the root growth of pregerminated seeds ($ID_{50}$ = $10^{-3}$ M).[35] Moreover, (+)-**1** successfully inhibited the viability of maize root cap cells ($ID_{50}$ = 2.5 x $10^{-4}$ M) and mesophyll protoplast suspensions ($ID_{50}$ = 8 x $10^{-5}$ M).[35]

In 2008, antimalarial properties of (+)-monocerin (**1**) against *Plasmodium falcifarum,* a multi-antimalarial drug resistant K1 strain, was first reported by Sappapan and co-workers. The $IC_{50}$ value of (+)-**1** and its acetate derivative 2 was 680 nM and 820 nM, respectively (Table 1.1).[39] None of these derivatives has shown cytotoxicity at a concentration of 20 µg/mL against the following tumor cell lines: BT474, CHAGO, Hep-G2, KATO-3, and SW-620.[39,40] Moreover, antimalarial activity of dihydroisocoumarin derivatives **3**, **4**, and **6** was studied and the results are summarized in Table 1.1.[39,40]

The absolute configuration of (+)-monocerin (**1**) was first identified by Scott and co-workers in 1984.[34] (+)-**1** is consisted of a 2,3,5-trisubstituted tetrahydrofuran moiety, which is embedded with all-*cis* stereochemistry. Considering these unique structural features coupled with a broad spectrum of biological properties, we developed a concise and enantioselective synthesis to access (+)-monocerin (**1**) and its acetate derivative (**2**).

Table 1.1 In Vitro Antimalarial Activity of Compounds 1,2,3,4, and 6 against *P. falciparum.*

| Compound | $IC_{50}$ (μM) |
|---|---|
| **1** | 0.68 |
| **2** | 0.82 |
| **3** | 7.70 |
| **4** | 9.10 |
| **6** | 11.0 ± 0.9 |
| Dihydroartemisinin | $4 \times 10^{-3}$ |

### 1.1.2 Previous Syntheses of (+)-Monocerin (1)

The intriguing structural features and broad medicinal potential of (+)-monocerin (**1**) has attracted considerable amount of synthetic attentions over the years.[41-48] The first asymmetric synthesis of (+)-monocerin (**1**) was achieved by Mori and Takaishi in the longest linear sequence of 22 steps and their retrosynthetic scheme is summarized in Figure 1.2.[41]

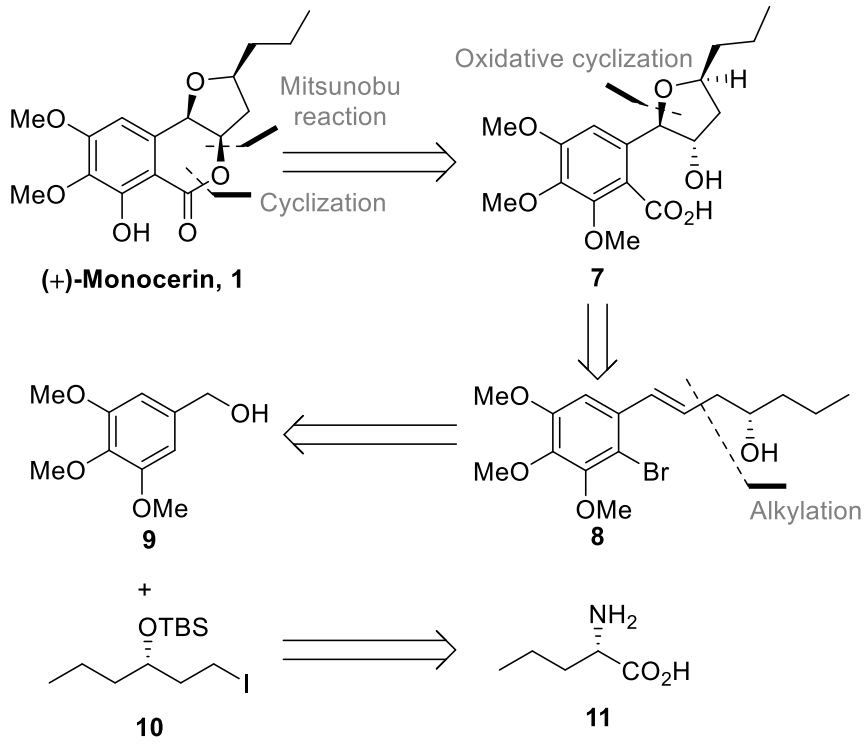



Figure 1.2 Mori and Takaishi's Retrosynthetic Analysis of (+)-Monocerin (1)

The lactone ring of (+)-monocerin (**1**) was constructed by cyclizing hydroxyl acid **7** under the Mitsunobu condition with an inversion at the C-4 position (Figure 1.2). Hydroxyl acid **7** was obtained from alcohol **8** by oxidatively cyclizing the side chain and introducing a carboxyl group to the aromatic ring (Figure 1.2). Alcohol **8** was readily synthesized by alkylation reaction between commercially available 3,4,5-trimethoxybenzyl alcohol and primary iodide **10** (Figure 1.2). Primary iodide **10** was derived from commercially available (*S*)-norvaline (**11**) following the work of Tai and co-workers (Figure 1.2).[41,49]

In 2008, Lee and co-workers reported the total synthesis of (+)-monocerin (**1**) and their strategy is shown in Figure 1.3.[43] Lee's group prepared (+)-monocerin (**1**) from MOM-protected cis-fused tetrahydrofuran **12** utilizing a Lewis acid catalyzed cyclization. Tetrahydrofuran **12** was then furnished by diastereoselective radical cyclization of vinylic ether intermediate **13.** Intermediate **13** was synthesized by a stereoselective Evans aldol reaction between commercially available 3,4,5-trimethoxybenzaldehyde **14** and chiral imide **15**. The overall yield of this route was 7.7% with 11 steps in the longest linear sequence.[43]

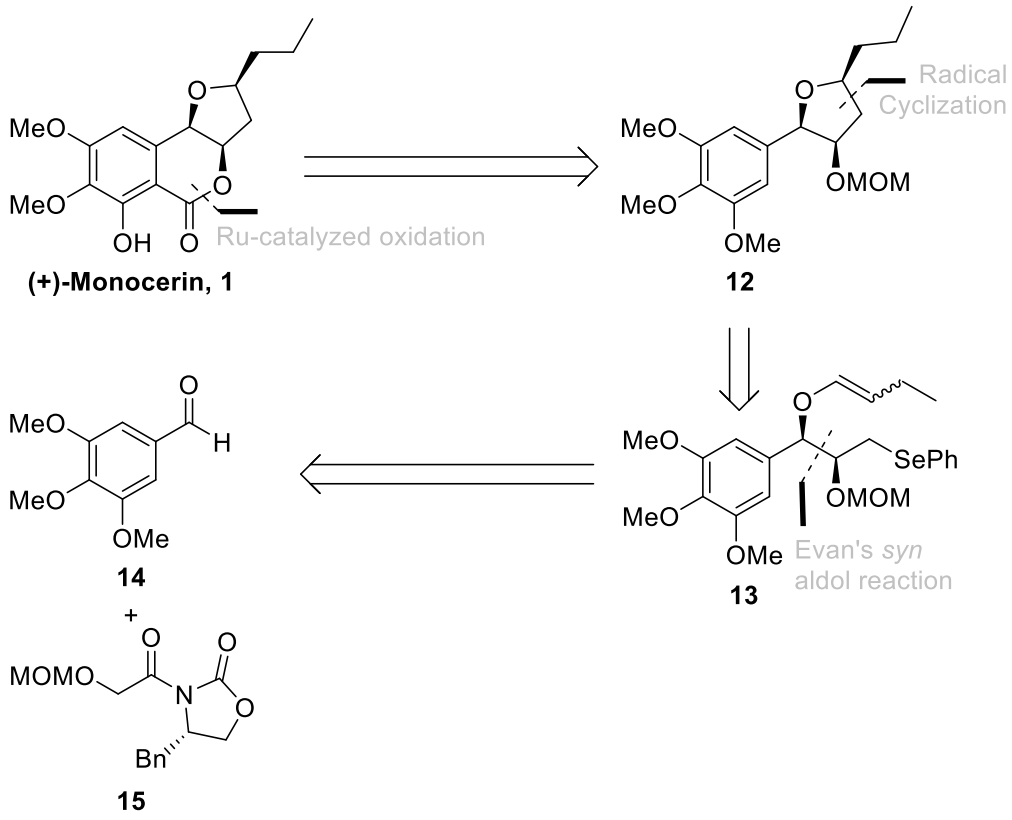



Figure 1.3 Lee's Retrosynthetic Analysis of (+)-Monocerin (1)

## 1.2 Results and Discussions

### 1.2.1 Retrosynthetic Analysis of (+)-Monocerin (1) and its acetate derivative (2)

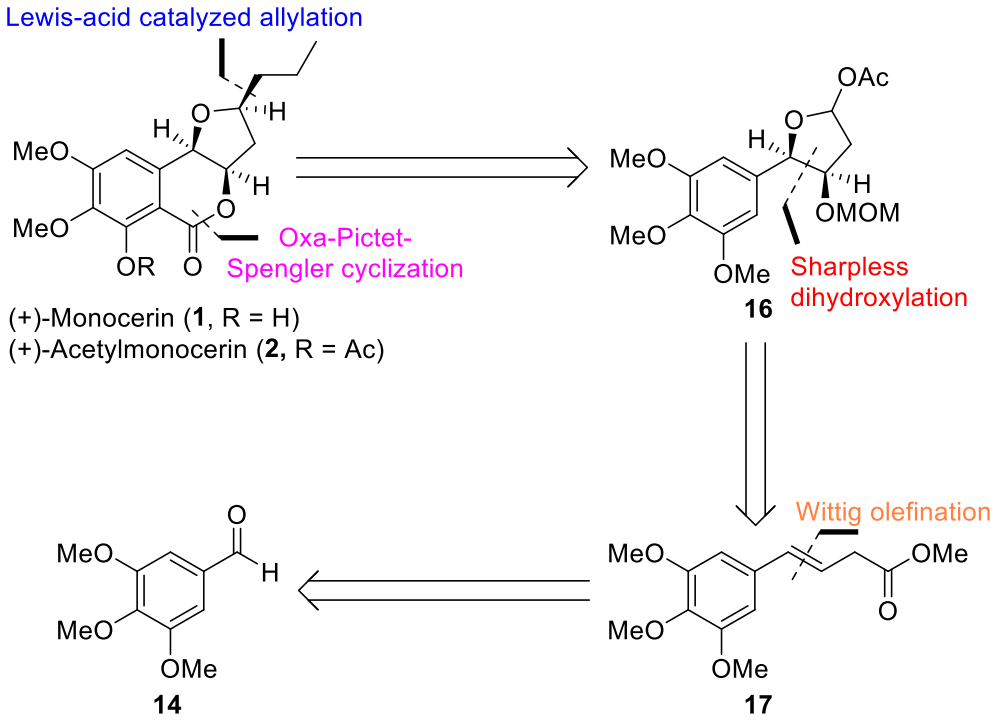


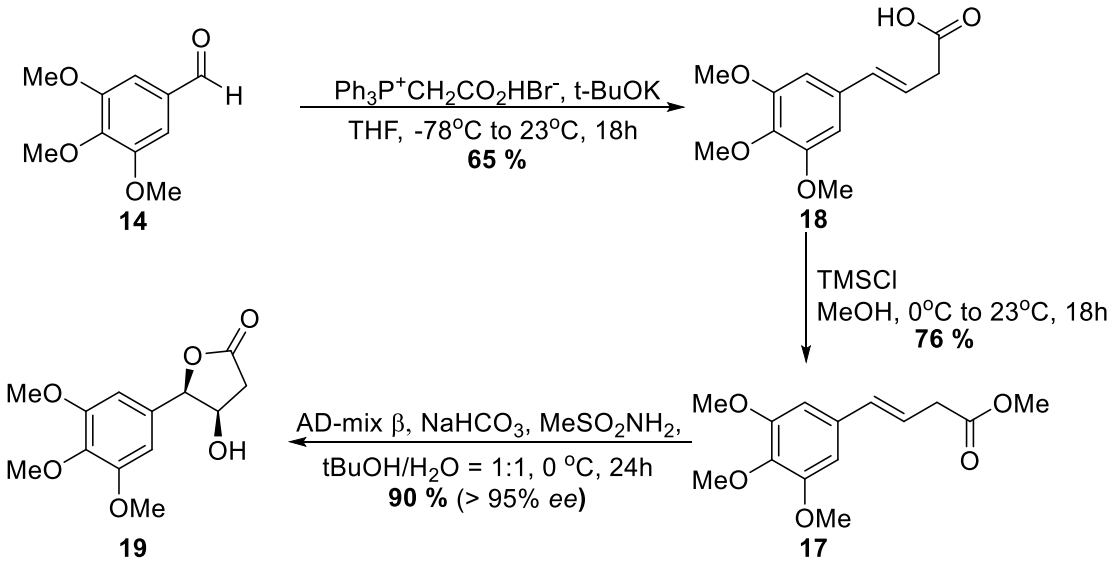

Figure 1.4 Retrosynthetic Analysis of (+)-Monocerin (1) and Its Acetate Derivative (2)

Our retrosynthetic disconnections of (+)-monocerin (**1**) is shown in Figure 1.4. Based on our strategy, we envisioned that a tandem Lewis acid catalyzed diastereoselective *syn*-allylation reaction followed by an Oxa-Pictet-Spengler cyclization would construct an isochroman structure of (+)-monocerin (**1**) in *one-pot* from MOM-protected acetate intermediate **16**.[50,51] MOM-protected acetate intermediate **16** would be installed from *E*-olefin **17** by Sharpless dihydroxylation.[52,53] *E*-olefin **17** would be readily synthesized from a commercially available 3,4,5-trimethoxybenzaldehyde **14** by Wittig olefination.[54,55]

### 1.2.2 Synthesis of Acetate Intermediates 16, 22, and 23

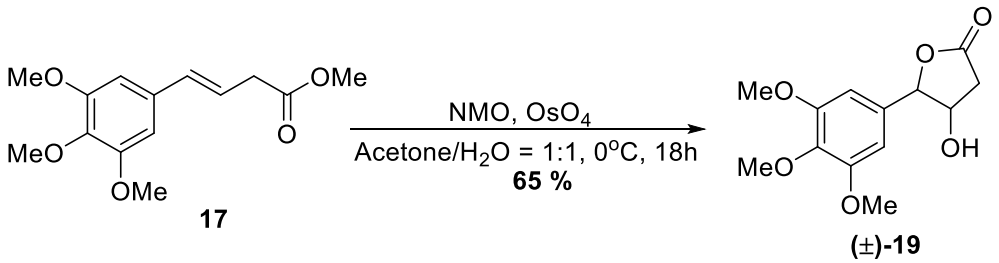
Our synthesis of multigram quantities of optically active γ-lactone **19** is shown in Scheme 1.1. Wittig olefination of commercially available 3,4,5-trimethoxybenzaldehyde **14** was carried out with ylid generated from (2-carboxyethyl)triphenyl phosphonium bromide and potassium *t*-

butoxide in THF at −78°C to 23°C for 18 h. This reaction afforded unsaturated acid **18** in 65 % yield.[54,56] Compound **18** was then converted to methyl ester **17** in 76% yield when compound 18 was treated with TMSCl in MeOH at 0°C to 23°C for 12 h. Asymmetric dihydroxylation of methyl ester **17** was conducted by using AD-mix-β, sodium bicarbonate, and methane sulfonamide in 1:1 mixture of *tert*-butoxide and water at 0°C for 22 h. The asymmetric dihydroxylation afforded β-hydroxy-γ-lactone **19** in 90% yield.[52]

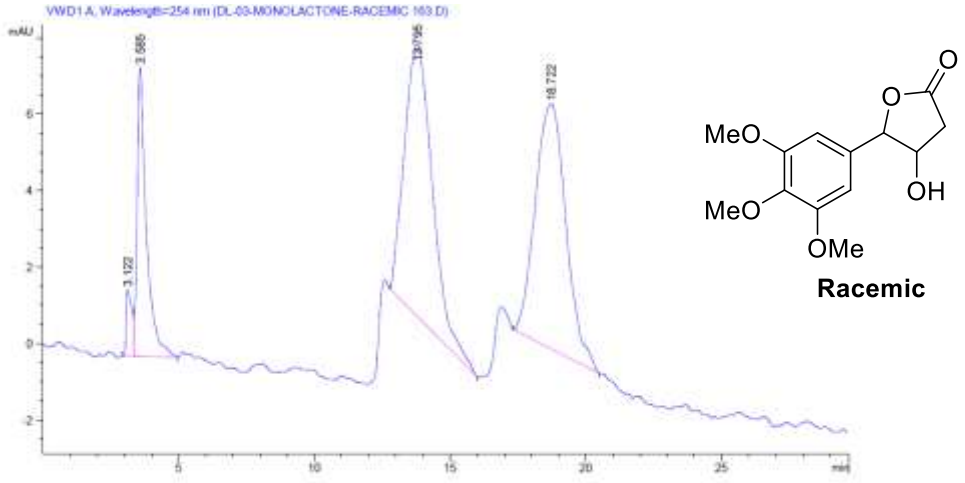



Scheme 1.1 Synthesis of Optically Active γ-Lactone 19

To determine the enantiomeric excess of optically active γ-lactone **19** from the previous reaction, racemic γ-lactone **19** was prepared from methyl ester **17** in 65 % yield by employing NMO and $OsO_4$ in 1:1 mixture of acetone and water at 0 °C for 18h. Chiral HPLC analysis (Chiralpak IC column) was utilized to determine the enantiomeric excess of the reaction; the optical purity of lactone **19** was determined to be over 95 % *ee* (Figure 1.6).

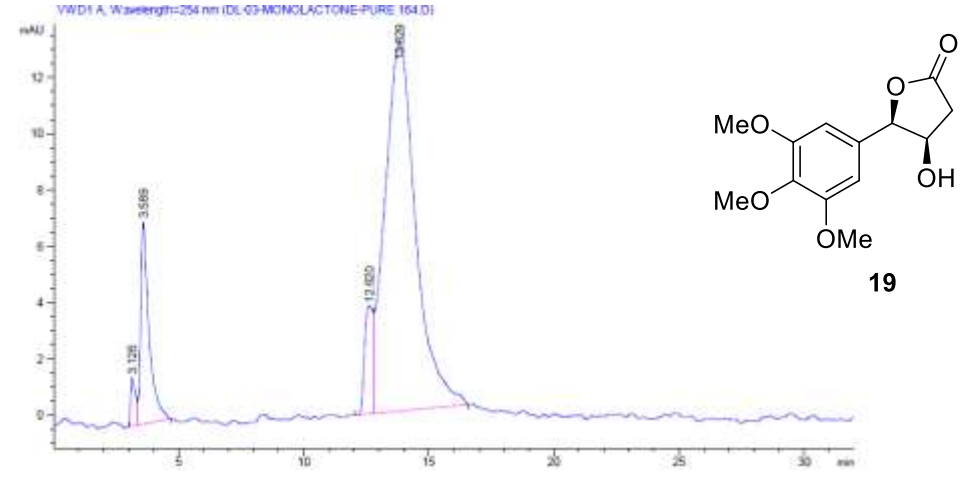



Scheme 1.2 Synthesis of Racemic γ-Lactone 19




Signal 1: VWD1 A, Wavelength=254 nm

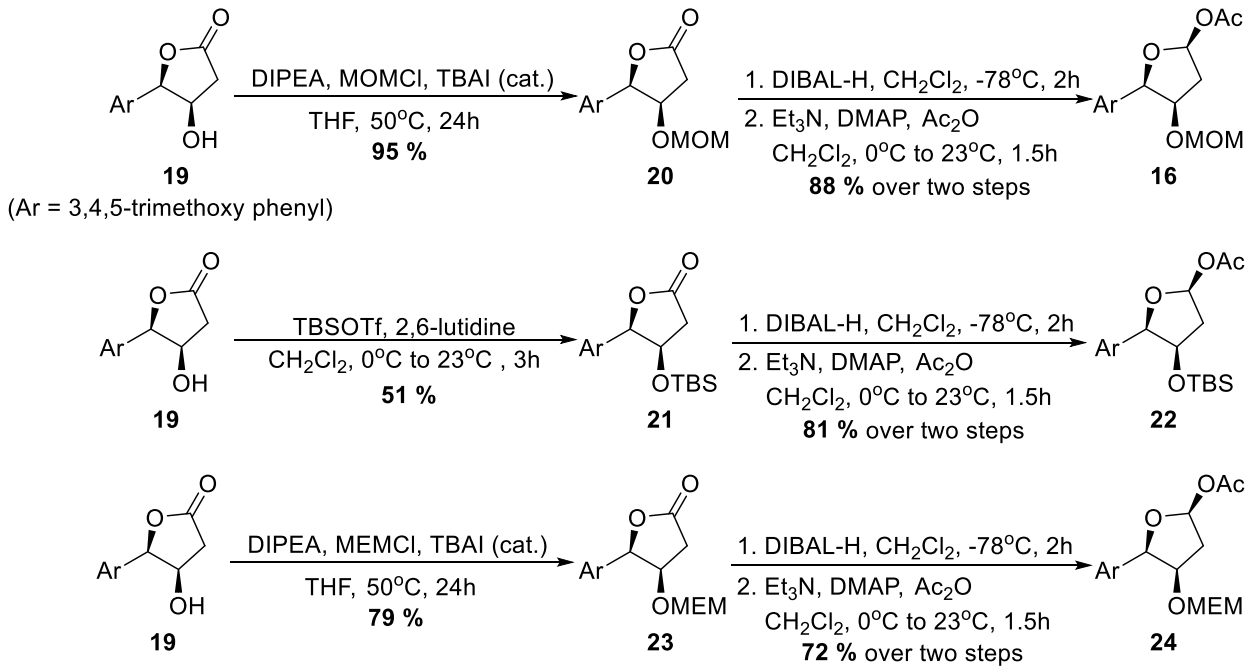
| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 3.122 | BV | 0.2052 | 25.50591 | 1.73819 | 2.0968 |
| 2 | 3.585 | VB | 0.3313 | 178.56607 | 7.56606 | 14.6793 |
| 3 | 13.795 | BB | 0.5737 | 509.21945 | 7.12620 | 41.8612 |
| 4 | 18.722 | BB | 1.0639 | 503.15558 | 6.40943 | 41.3627 |
| Totals : | | | | 1216.44701 | 22.83988 | |




Signal 1: VWD1 A, Wavelength=254 nm

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 3.126 | BV | 0.1971 | 23.82227 | 1.71505 | 1.6921 |
| 2 | 3.589 | VB | 0.3247 | 165.26210 | 7.17601 | 11.7389 |
| 3 | 12.620 | BV | 0.3677 | 89.08746 | 3.83978 | 6.3281 |
| 4 | 13.609 | VB | 1.2321 | 1129.64172 | 13.07288 | 80.2409 |
| Totals : | | | | 1407.81355 | 25.80373 | |

Figure 1.5 HPLC Analysis of γ-Lactone 19




Scheme 1.3 Synthesis of Acetate Intermediates 16, 22, and 24

As depicted in Scheme 1.3, MOM protection of the hydroxyl group of optically active lactone **19** was accomplished by using MOMCl, diisopropylethylamine (DIPEA), and tetrabutylammonium iodide (TBAI) in THF at 50 °C for 24 h. This reaction furnished MOM protected ether **20** in 95% yield. Subsequent diisobutylaluminum hydride (DIBAL-H) reduction of MOM protected ether **20** in $CH_2Cl_2$ at −78 °C for 2 h, followed by acetylation of the resulting crude lactol with acetic anhydride, triethylamine, and 4-dimethylaminopyridine (DMAP) in $CH_2Cl_2$ at 0 °C for 2 h provided **16** as a major anomer (*dr* = 14:1) in 88% combined yield over two steps (Scheme 1.3).

Likewise, TBS protection of the hydroxyl group of optically active lactone **19** was achieved by using TBSOTf and 2,6-lutidine in $CH_2Cl_2$ at 0 °C to 23 °C for 3 h. The reaction afforded TBS protected lactone **21** in **51**% yield. DIBAL-H reduction and acetylation reaction were sequentially conducted as described above to give acetate derivative **22** in 81 % yield over two steps. Similarly, MEM protected acetate derivative **24** was prepared in 57% over three steps from lactone **19** by following the procedure described above. The stereochemical identity of acetate **16**, **22**, and **24** was confirmed by using both $^1$H NMR and nuclear Overhauser enhancement spectroscopy (NOESY) experiments.

### 1.2.3 Allylation of Acetate Intermediates with Various Lewis Acids

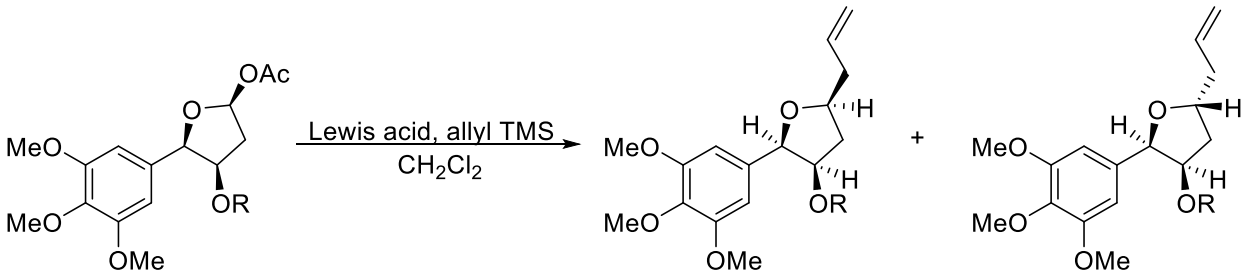
With the preparation of the three different acetate intermediates, the allylation reaction promoted by various Lewis acids was thoroughly studied. All these reactions were carried out at -78$^{o}$C and 4 equivalents of allyl trimethylsilane (allyl TMS) in $CH_2Cl_2$ were used except for Entry 10 (Table 1.2). The diastereomeric ratio of the mixtures was determined by $^{1}$H NMR analysis.

We first carried out allylation of MOM protected acetate **16** with 1.1 equivalent of $SnBr_4$ at the set reaction condition for 3h. This reaction gave a 62 to 38 mixture of compounds **25A** and **26A** in 84% combined yield (Entry 1, Table 1.2).[57] Adding 2 equivalents of $SnBr_4$ actually reduced the yield to 75% combined yield with similar diastereoselectivity (Entry 2, Table 1.2). The use of $TiCl_4$, either in 1.1 equivalent or 2 equivalents, reduced the yield to 69% and 38%, respectively (Entry 3 & 4, Table 1.2). The use of $BF_3OEt_2$ and TMSOTf as the Lewis acids also reduced the yield to 52% and 57% combined yield, respectively (Entry 5 & 6, Table 1.2). The diastereoselectivity of the allylation reaction was only slightly influenced by Lewis acid.

The allylation reaction of TBS-protected acetate **22** was then investigated. The allylation reaction of compound **22** with 1.1 equivalent of $SnBr_4$ at the set reaction gave a 70:30 mixture of allyl derivatives **25B** and **26B** in 81% combined yield (Entry 7, Table 1.2). Subsequently, allyl derivatives **25B** and **26B** were chromatographed by silica gel column chromatography and their respective stereochemical identity was confirmed by 2D-NOSEY spectrum analysis.[57] Switching the Lewis acid to $TiCl_4$ slightly improved the diastereoselectivity to 72:28, yet the reduction yield was reduced to 76% combined yield (Entry 8, Table 1.2).

The allylation reaction of MEM-protected acetate **24** with 1.1 equivalent of SnBr4 at the set reaction condition afforded approximately 1:1 mixture of allyl derivatives **25C** and **26C** in 33% combined yield (Entry 9, Table 1.2). The allylation reaction of MEM-protected acetate **24** with 1.1 equivalent of $BF_3OEt_2$ and 1.5 equivalent of allyl TMS provided **25C**and **26C** in an improved 63 to 37 *dr* with 36% yield (Entry 10, Table 1.2).[57]

Table 1.2 Allylation of Acetate Derivatives with Various Lewis Acids




**16**, R = MOM
**22**, R = TBS
**24**, R = MEM

**25A**, R = MOM
**25B**, R = TBS
**25C**, R = MEM

**26A**, R = MOM
**26B**, R = TBS
**26C**, R = MEM

| Entry | R | Lewis Acid [equiv] | Time (h) | Yield (%) | *dr* (25:26 ratio) |
|---|---|---|---|---|---|
| **1** | MOM | $SnBr_4$ [1.1] | 3 | 84 | 62 : 38 |
| **2** | MOM | $SnBr_4$ [2.0] | 3 | 75 | 63 : 37 |
| **3** | MOM | $TiCl_4$ [1.1] | 3 | 69 | 60 : 40 |
| **4** | MOM | $TiCl_4$ [2.0] | 4 | 38 | 58 : 42 |
| **5** | MOM | $BF_3{\cdot}OEt_2$ [1.1] | 3 | 52 | 63 : 37 |
| **6** | MOM | TMSOTf [1.0] | 3 | 57 | 58 : 42 |
| **7** | TBS | $SnBr_4$ [1.1] | 3 | 81 | 70 : 30 |
| **8** | TBS | $TiCl_4$ [1.1] | 3 | 76 | 72 : 28 |
| **9** | MEM | $SnBr_4$ [1.1] | 3 | 33 | 51 : 49 |
| **10**[b] | MEM | $BF_3{\cdot}OEt_2$ [1.1] | 3 | 36 | 63 : 37 |

While the observed diastereoselectivity of the Lewis acid-promoted allylation reactions was moderate at best (Table 1.2), *cis*-diastereoselectivity was consistently observed throughout the experiments. This result was in agreement with the work of Woerpel and co-workers, who have examined various Lewis acid-promoted allylation reactions with several C3-alkoxy-substituted tetrahydrofuranyl substrates.[50,51] The extent of *cis*-diastereoselectivity that we observed (Table 1.2), however, was significantly lower than that what was reported by Woerpel and co-workers (up to 20:1 *dr*).[50,51]

The diastereoselective *cis*-allylation of acetate intermediates **16**, **22**, and **24** can be rationalized using stereochemical models as depicted in Figure 1.6. As shown in Figure 1.6, allylation of acetate intermediates **16**, **22**, and **24** can proceed through oxocarbenium ion

intermediates **27** and **28** Intermediate **27** is preferred to intermediate **28** mainly due to the pseudoequatorial orientation of the bulky aromatic group at the C4 position.[51,58,89] In addition to that, intermediate **28** suffers from unfavorable 1,3-interactions between the C2-axial hydrogen and bulky aromatic group at the C4 position. Both intermediate **27** and **28**, however, show a gauche interaction between the alkoxy substituent and the bulky aromatic group (Figure 1.6). The stereoelectronically favored inside attack on the oxocarbenium ion intermediate **27**, therefore, leads to the major *cis*-diastereomer **25**.

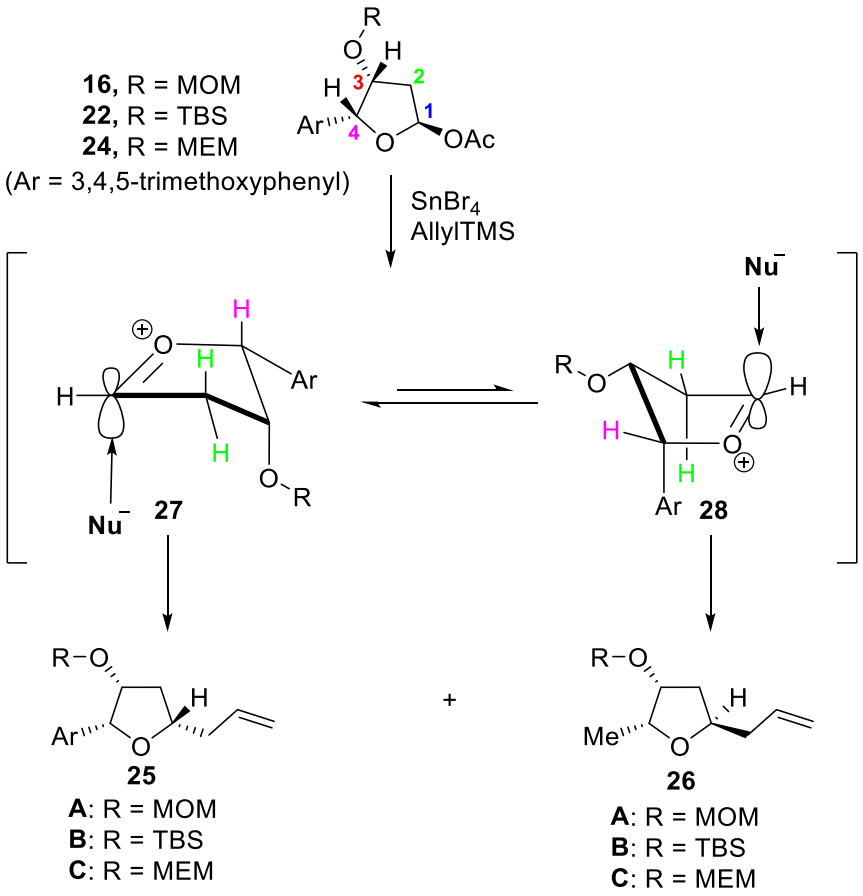



Figure 1.6 Stereochemical Analysis for *cis*-Allylation

Throughout the experiments, the hydroxyl protecting groups have remained unaffected under various reaction conditions. Changing of Lewis acids has not made much difference in diastereoselectivity (Table 1.2). The size and nature of protecting groups have only marginally influenced diastereoselectivity (Table 1.2). The moderate diastereoselectivity observed from the

allylation reactions was a consequence of competing stereoelectronic effects between C3-alkoxy substituent and bulky electron-rich aromatic group at the C4 position (Figure 1.6).

### 1.2.4 Tandem Lewis Acid-Catalyzed Diastereoselective *syn*-Allylation and Oxa-Pictet-Spengler Cyclization of Acetate Intermediates 16 and 24

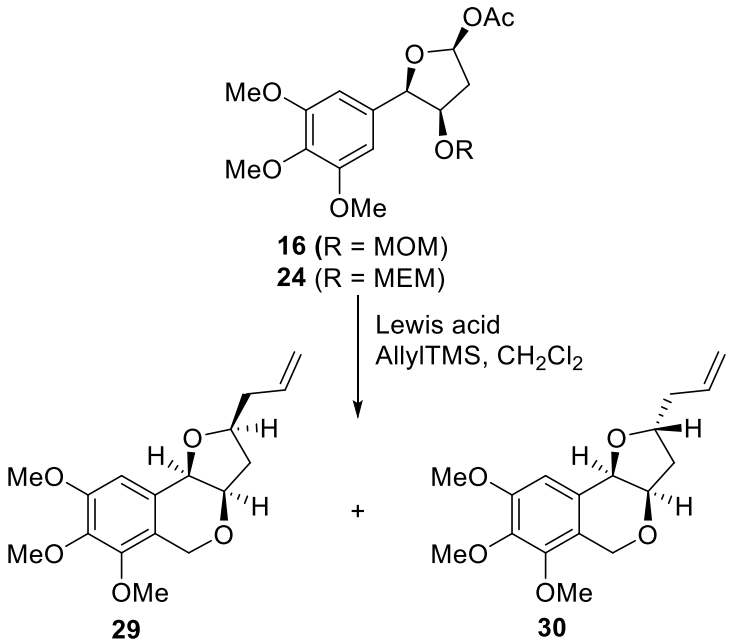
We have then investigated how temperature would affect the allylation reaction. The allylation reaction was a spot-to-spot reaction at -78 $^{o}$C when it was monitored by TLC. Very surprisingly, when allylation reaction was carried out with MOM protected acetate intermediate **16** in the presence of 1.6 equivalents of $SnBr_4$ under elevated temperature (−78 $^{o}$C to 23 °C) and extended period (4h), both a distereomeric mixture of allyl derivatives **24** and **25** and isochroman derivatives **29** and **30** were obtained in 54 % and 22 % yield, respectively.[60,61] The diastereomeric ratio between isochroman derivatives **29** and **30** was 75 to 25 according to the $^{1}$H NMR analysis (Entry 1, Table 1.3). This result has shown that the isochroman derivative **29** can be readily synthesized in "one-pot" from acetate intermediate **16**. The results of these reactions are summarized in Table 1.3.

To further optimize the reaction condition, tandem Lewis acid-catalyzed allylation/Oxa-Pictet-Spengler cyclization reaction was conducted with additional equivalents of Lewis acid and prolonged reaction time. MOM protected acetate **16** was added with 1.1 equivalent of $SnBr_4$ at −78 °C for 3 h, ensuring a complete conversion of the starting material **16** to allyl derivatives **25A** and **26A** . After this period of time, two additional equivalents of the Lewis acid was added at −78 °C, and the resulting mixture was slowly warmed to 23$^{o}$C over 12 h. This reaction afforded a complete formation of isochroman derivatives **29** and **30** as a 76:24 mixture in 35% combined yield (Entry 2, Table 1.3).

When two additional equivalents of $SnBr_4$ was added at 0°C instead of -78$^{o}$C, the reaction yield increased to 42 % combined yield with similar diastereoselectivity (Entry 3, Table 1.3). Duplicating the first reaction condition by adding 1.6 equivalents of $SnBr_4$ at -78 $^{o}$C to 23 $^{o}$C for 4h and adding two additional equivalents of $SnBr_4$ at 0$^{o}$C to 23$^{o}$C for 12 h, isochroman derivatives **29** and **30** were obtained in 52 % combined yield with 80:20 *dr* (Entry 4, Table 1.3). When $TiCl_4$ was used instead of $SnBr_4$ as a Lewis acid following the Entry 4 reaction condition, only a trace amount of the products was obtained (Entry 5, Table 1.3). Interestingly, when MEM protected

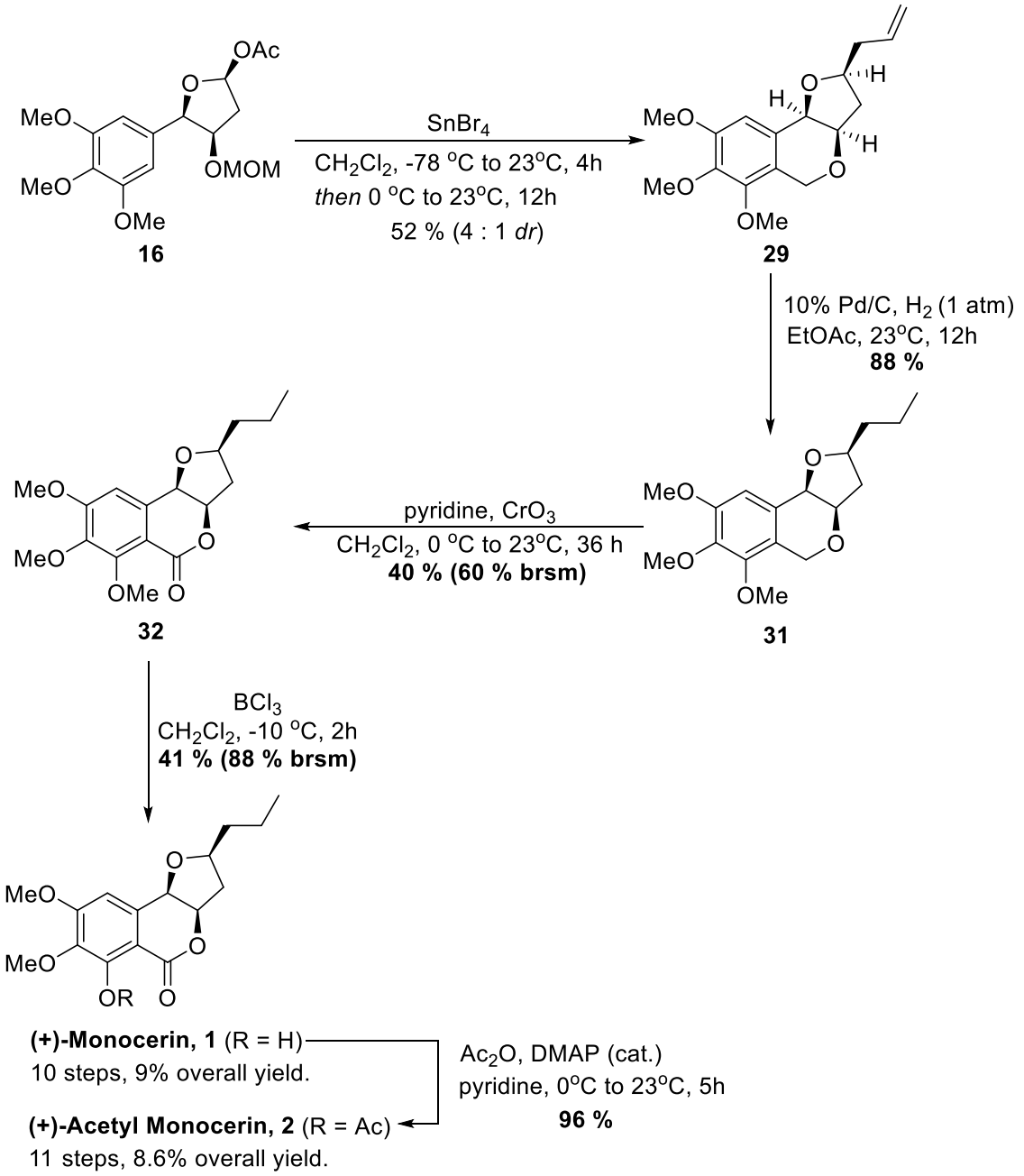
acetate **24** was subjected to the Entry 4 reaction condition, a 63 to 37 mixture of isochroman derivatives **29** and **30** was obtained in 21% combined yield (Entry 6, Table 1.3).

Table 1.3 Lewis Acid-Catalyzed Tandem Allylation and Oxa-Pictet−Spengler Cyclization of Acetate Derivative 16 and 24




| Entry | R | Lewis Acid [equiv., time] | Temperature | Yield % (25/26) | Yield % (29/30 and ratio) |
|---|---|---|---|---|---|
| **1** | **MOM** | $SnBr_4$ [1.6, 4 h] | -78 °C to 23 °C | **54** | **23** (75:25) |
| **2** | **MOM** | $SnBr_4$ [1.1, 3h], *then* [2, 12h] | -78 °C, *then* -78 °C to 23 °C | --- | **35** (76:24) |
| **3** | **MOM** | $SnBr_4$ [1.1, 3h], *then* [2, 12h] | -78 °C, *then* 0 °C to 23 °C | --- | **42** (75:25) |
| **4** | **MOM** | $SnBr_4$ [1.6, 4h], *then* [2, 12 h] | -78 °C to 23 °C, *then* 0°C to 23°C | --- | **52** (80:20) |
| **5** | **MOM** | $TiCl_4$ [1.1, 4h], *then* [1.5, 12h] | -78 °C to 23 °C, *then* 0 °C to 23 °C | *trace* | *trace* |
| **6** | **MEM** | $SnBr_4$ [1.6, 3h], *then* [2, 12h] | -78 °C to 23 °C, *then* 0 °C to 23 °C | --- | **21** (63:37) |

### 1.2.5 Synthesis of (+)-Monocerin (1) and Its Acetate Derivative (2)




Scheme 1.4 Synthesis of (+)-Monocerin (1) and Its Acetate Derivative (2)

The synthesis of (+)-monocerin (**1**) is shown in Scheme 1.4. MOM protected acetate intermediate **16** was converted to allyl isochroman derivatives **29** and **30** in 52 % combined yield with 4:1 diastereomeric ratio following the procedure described above. The stereochemical identity of isochroman derivative **29** was confirmed by the 2D-NOSEY experiment. The

diastereomers **29** and **30** were separated by silica gel chromatography, and the major diastereomer **29** was hydrogenated under 1 atmospheric pressure of $H_2$ with 10% palladium on carbon (Pd-C) as a catalyst in ethyl acetate at 23°C for 12h. This reaction afforded compound **31** in 88% yield. The $^{1}H$ and $^{13}C$ NMR spectrum of compound **31** were compared with the reported ones to validate its identity.[43]

Oxidation of bicyclic ether **31** was accomplished by using $CrO_3$ and pyridine in $CH_2Cl_2$ at 0°C to 23°C for 36 h. This reaction furnished lactone **32** in 40% yield (60% based on recovered starting material). The selective demethylation of compound **32** was achieved by treating lactone **32** with boron trichloride ($BCl_3$) in $CH_2Cl_2$ at −10 °C for 2 h. This reaction selectively provided (+)-monocerin (**1**) in 41% yield (88% based on recovered starting material). Finally, treatment of (+)-**1** with acetic anhydride and 4-DMAP in neat pyridine at 0°C to 23°C for 5h gave (+)-acetyl monocerin (**2**) in 96% yield. The optical rotation value of **2** was $[\alpha]_D^{23}$ +3.6 (c 0.29, $CHCl_3$).

The $^{1}H$ and $^{13}C$ NMR spectrum of our synthetic (+)-monocerin (**1**) matches with the previously reported ones.[41,43] The optical rotation value of our synthetic (+)-**1** {$[\alpha]_D^{23}$ +57.8 (c 0.29, $CHCl_3$)} is also in agreement with the reported value of $[\alpha]_D^{24}$ +53.0 (c 0.85, $CHCl_3$). (+)-monocerin (**1**) was, therefore, synthesized in 10 steps (9% overall yield) and its acetate derivative **2** in 11 steps (8.6% overall yield).

## 1.3 Conclusion

In summary, enantioselective total synthesis of (+)-monocerin (**1**) and (+)-acetyl monocerin (**2**) was achieved in 10 and 11 steps, respectively. The overall yield of (+)-**1** was 9% and that of **2** was 8.6% yield. The optically active γ-lactone was efficiently synthesized by using a Sharpless asymmetric dihydroxylation reaction. One of the key reactions in the (+)-**1** synthesis is a tandem Lewis acid-catalyzed diastereoselective *syn*-allylation allylation reaction followed by Oxa-Pictet-Spengler reaction to furnish the isochroman intermediate in *one-pot* (up to 4:1 *dr*). The *syn*-allylation reaction was also investigated by varying Lewis acids, yet their influence on the stereochemical outcome was determined to be very limited. Among the three different acetate intermediates, the allylation reaction of TBS protected acetate **22** with 1.1 equivalent of $SnBr_4$ gave the best combined yield and diastereoselectivity. While the diastereoselectivity of the allylation reactions was moderate (up to 2.6:1 *dr*), the *cis* selectivity was observed throughout the experiments. Since (+)-**1** and **2** show potent anti-malarial activity, the current synthesis will contribute to the synthesis of next generation anti-malarial drug with dihydroisocoumarin structure.

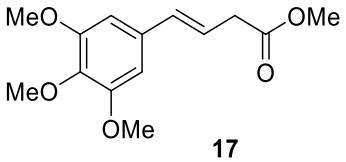
## 1.4 Supporting Information

### 1.4.1 General Information

All chemical and reagents were purchased from commercial suppliers and used without further purification unless otherwise noted. The following reaction solvents were distilled prior to use: $CH_2Cl_2$ from $CaH_2$, $Et_2O$ and THF from Na/Benzophenone, MeOH from activated Mg under Ar. All reactions were carried out under an argon atmosphere in either flame or oven-dried (120 $^oC$) glassware unless otherwise noted. TLC analysis was performed by using glass-backed Thin-Layer Silica Gel Chromatography Plates (60 Å, 250 μm thickness, F-254 indicator). Column chromatography was performed using 230-400 mesh, 60 Å pore diameter silica gel. $^1H$ and $^{13}C$ NMR spectrum was obtained at room temperature on a Bruker AV-III-HD-400, DRX500, and AV-III-800. Chemical shifts (δ values) are reported in parts per million and are referenced to the deuterated residual solvent peak. NMR data is reported as: δ value (chemical shift, *J*-value (Hz), integration, where s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sep = septet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, dq = doublet of quartets, brs = broad singlet, app = apparent). Optical rotations were recorded on

a Perkin Elmer 341 polarimeter. LRMS-ESI and HRMS spectra were recorded at the Purdue University Department of Chemistry Mass Spectrometry Center.

### 1.4.2 Experimental Procedures

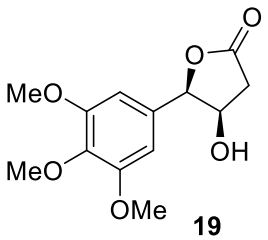



**17**

**Methyl (E)-4-(3,4,5-trimethoxyphenyl) but-3-enoate (17)**

To a cooled (-78 °C) suspension of (2-carboxyethyl) triphenylphosphonium bromide (2.99 g, 7.2 mmol, 1.2 equiv) and 3,4,5-trimethoxybenzaldehyde (1.18 g, 6 mmol, 1.0 equiv) in THF (45 mL) was slowly added 1.0 M THF solution of t-BuOK (15 mL, 15 mmol, 2.5 equiv). After addition, the mixture was stirred at -78 °C for 1 h and was then warmed to room temperature overnight. The resulting suspension was concentrated under reduced pressure, $H_2O$ (100 mL) was added, and the mixture was washed with $CH_2Cl_2$. The aqueous phase was acidified to pH = 1 with a 1 M solution of HCl and extracted with $Et_2O$ (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

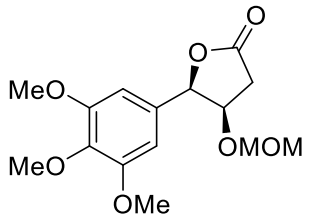
A crude β,γ-unsaturated carboxylic acid was dissolved in distilled MeOH (20 mL) and 0.97 mL of TMSCl (7.6 mmol, 1.26 equiv) was dropwise added at 0 $^oC$ under argon atmosphere. The mixture was stirred at room temperature overnight then concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (10% EtOAc in hexane) to yield **17** (746 mg, 47 % over two steps) as a yellow oil. $^1H$ NMR (400 MHz, $CDCl_3$) δ 6.58 (s, 2H), 6.41 (d, *J* = 15.8, 1H), 6.20 (dt, *J* = 15.8, 7.1 Hz, 1H), 3.86 (s, 6H), 3.83 (s, 3H), 3.71 (s, 3H), 3.24 (dd, *J* = 7.1, 1.5 Hz, 2H); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ: 171.93, 153.20, 137.73, 133.30, 132.45, 121.04, 103.27, 77.25, 76.93, 76.62, 60.82, 55.99, 51.86, 37.99, 29.59; LRMS-ESI (m/z): 267.0 $[M+H]^+$; HRMS-ESI (m/z): $C_{14}H_{18}O_5$; calc'd for $[M+Na]^+$: 289.1046, found 289.1049.




**19**

**(4R,5R)-4-hydroxy-5-(3,4,5-trimethoxyphenyl)dihydrofuran-2(3H)-one (19)**

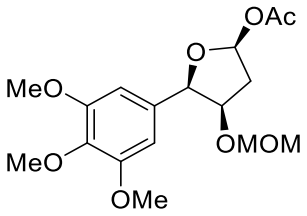
AD-mix-α (3.926 g), $NaHCO_3$ (0.706 g, 8.4 mmol), and methanesulfonamide (0.267 g, 2.8 mmol) were dissolved in t-BuOH (7 mL) and water (14 mL). After the mixture was cooled to 0 °C, methyl ester **17** (746 mg, 2.8 mmol) in t-BuOH (7 mL) was added. The mixture was stirred for 22 h at 0 °C, at which point sodium sulfite (5.0 g) was added. The mixture was stirred for 1 h at room temperature and extracted with EtOAc (3 x 100 mL). The combined organic layer was dried with $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was then purified by column chromatography on silica gel (EtOAc:Hexane, 1:1 to 4:1) to afford lactone **19** (700 mg, 90 %) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ: 6.54 (s, 1H), 5.38 (d, *J* = 3.3 Hz, 1H), 4.62 – 4.56 (m, 1H), 3.82 (s, 3H), 3.78 (s, 1H), 2.85 (ddd, *J* = 17.5, 5.0, 1.5 Hz, 1H), 2.71 (d, *J* = 17.5 Hz, 1H), 2.06 (m, 1H; O*H*); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 175.40, 153.56, 137.90, 128.46, 103.02, 85.08, 70.12, 60.72, 56.10, 38.37; LRMS-ESI (m/z): 269.0 $[M+H]^+$; HRMS-ESI (m/z): $C_{13}H_{16}O_6$; calc'd for $[M+H]^+$: 269.1020, found 269.1024; $[\alpha]_D^{20}$ – 23.9 (*c* 0.41, $CHCl_3$).




**20**

**(4R,5R)-4-(methoxymethoxy)-5-(3,4,5-trimethoxyphenyl)dihydrofuran-2(3H)-one (20)**

To a stirred solution of lactone **7** (272 mg, 1.02 mmol) in distilled THF (4 mL) were consecutively added DIPEA (1.77 mL, 10.2 mmol), TBAI (75 mg, 0.20 mmol), and MOM-Cl (0.44 mL, 5.80 mmol) were at 0 $^o$C under argon atmosphere. The reaction mixture was then stirred at 50 $^o$C for 24h. After dilution with DCM, the mixture was washed with water, dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (60% EtOAc in hexane) to give MOM protected lactone **20** (300 mg, 95%) as a yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ: 6.58 (d, *J* = 0.6 Hz, 1H), 5.43 (d, *J* = 3.8 Hz, 1H), 4.56 (ddd, *J* = 5.1, 3.8, 0.9 Hz, 1H), 4.32 (d, *J* = 7.1 Hz, 1H), 4.14 (d, *J* = 7.1 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 2H), 3.06 (s, 1H), 2.88 (dd, *J* = 17.5, 5.3 Hz, 1H), 2.73 (dd, *J* = 17.5, 0.9 Hz, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 174.95, 153.16, 137.92, 129.34, 103.57, 95.09, 84.62, 77.26, 76.94, 76.62, 74.11, 60.80, 56.14, 55.43, 37.46; LRMS-ESI (m/z): 647.2 $[2M+Na]^+$ ; HRMS-ESI (m/z): $C_{15}H_{20}O_7$; calc'd for $[M+Na]^+$: 335.1101, found 335.1103; $[\alpha]_D^{20}$ – 46.1 (*c* 0.79, $CHCl_3$).

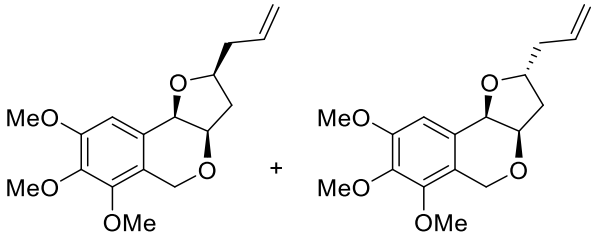



**16**

**(4R,5R)-4-(methoxymethoxy)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran-2-ol (16)**

To a stirred solution of lactone **20** (240 mg, 0.77 mmol) in dichloromethane (6 mL) at -78 $^{o}$C was added DIBAL-H (0.92 mL, 0.92 mmol) under argon atmosphere and stirred at the same temperature for 2h. After this period, the reaction mixture was quenched by the addition of MeOH (3 mL) and warmed to 23 $^{o}$C. Then, Saturated aqueous solution of sodium potassium tartarate was added and stirred vigorously at 23 $^{o}$C for 2h until it forms white suspension. The suspension was filtered through a plug of Celite and solvents were removed under reduced pressure.

To a crude lactol, DMAP (17 mg, 0.14 mmol), $Et_3N$ (0.50 mL, 3.59 mmol) and $Ac_2O$ (0.17 mL, 1.80 mmol) were added at 0 $^{o}$C under argon atmosphere and the resulting mixture was stirred for 2h. Upon completion, solvents were removed under reduced pressure and the crude product was purified by silica gel column chromatography (50 % EtOAc in hexane) to give acetate **16** (256 mg, 88 % over two steps) as a colorless oil.$^{1}$H NMR (400 MHz, $CDCl_3$) δ: δ 6.61 (s, 1H), 6.59 (dd, *J* = 6.1, 3.3 Hz, 1H), 5.09 (d, *J* = 3.8 Hz, 1H), 4.45 (ddd, *J* = 5.8, 3.8, 1.9 Hz, 1H), 4.30 (d, *J* = 7.0 Hz, 1H), 4.12 (d, *J* = 6.9 Hz, 1H), 3.84 (s, 6H), 3.81 (s, 3H), 3.06 (s, 3H), 2.53 (ddd, *J* = 14.7, 6.1, 1.9 Hz, 1H), 2.37 (ddd, *J* = 14.7, 6.1, 3.3 Hz, 1H), 2.06 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 170.17, 152.87, 137.47, 131.06, 104.21, 97.44, 95.08, 83.72, 77.26, 76.94, 76.62, 60.77, 56.05, 55.21, 40.37, 21.19; LRMS-ESI (m/z): 735.2 $[2M+Na]^+$; HRMS-ESI (m/z): $C_{17}H_{24}O_8$; calc'd for $[M+Na]^+$: 379.1363, found 379.1360.




**29** **30**

**(2S,3aR,9bR)-2-allyl-6,7,8-trimethoxy-3,3a,5,9b-tetrahydro-2H-furo[3,2-c]isochromene** (**29**) and **(2R,3aR,9bR)-2-allyl-6,7,8-trimethoxy-3,3a,5,9b-tetrahydro-2H-furo[3,2-c]isochromene (30)**

To a stirred solution of acetate **16** (13.2 mg, 0.037 mmol) in dichloromethane (2.4 mL) were added allyl trimethylsilane (24 µL, 0.148 mmol) and $SnBr_4$ (26 mg, 0.059 mmol, 1.6 equiv) at -78 $^oC$ under argon atmosphere. The reaction mixture was warmed to room temperature over 4h and the reaction progress was monitored by TLC. Additional portion of $SnBr_4$ (33 mg, 0.075 mmol, 2.0 equiv) was added at 0 $^oC$ and the resulting mixture was warmed to 23 $^oC$ overnight. After this period, the reaction mixture was quenched by the addition of saturated aqueous $Na_2HPO_4$ (0.4 mL) and extracted with dichloromethane (2 x 10 mL). The extracts were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. NMR analysis of the unpurified crude product showed a pair of diastereomers in a 4:1 ratio of 1,3-cis:trans diastereomers. The crude product was purified by silica gel column chromatography (10% EtOAc in hexane) to give **29** and **30** (5.9 mg, 52%) as a colorless oil.

1,3-*cis* **29** (major)**:** $^1$H NMR (400 MHz, $CDCl_3$) δ: 6.79 (s, 1H), 5.96 – 5.64 (m, 1H), 5.21 – 4.97 (m, 2H), 4.90 (d, *J* = 15.1 Hz, 1H), 4.42 (d, *J* = 15.1 Hz, 1H), 4.30 (d, *J* = 3.3 Hz, 1H), 4.16 (ddd, *J* = 6.8, 3.3, 1.7 Hz, 1H), 4.02 (qd, *J* = 7.4, 5.8 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 2.65 – 2.44 (m, 2H), 2.43 – 2.29 (m, 1H), 1.81 (ddd, *J* = 14.0, 7.2, 1.7 Hz, 1H).

$^{13}$C NMR (101 MHz, $CDCl_3$) δ: 152.87, 148.99, 141.69, 134.70, 126.49, 121.76, 117.10, 108.68, 78.05, 75.40, 63.27, 60.85, 60.72, 56.09, 40.34, 38.97, 29.71 (grease).

LRMS-ESI (m/z): 307.1 $[M+H]^+$

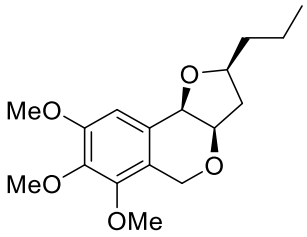
HRMS-ESI (m/z): $C_{17}H_{22}O_5$; calc'd for $[M+Na]^+$: 329.1359, found 329.1357.

$[\alpha]_D^{20}$ + 25.6 (*c* 0.67, $CHCl_3$)

1,3-*trans* **30** (minor)**:** $^1$H NMR (400 MHz, $CDCl_3$) δ: 6.79 (s, 1H), 5.92 – 5.76 (m, 1H), 5.18 – 5.04 (m, 2H), 4.91 (d, J = 15.0 Hz, 1H), 4.61 (d, J = 3.0 Hz, 1H), 4.45 – 4.32 (m, 2H), 4.26 – 4.18 (m, 1H), 3.88 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 2.48 (dt, J = 12.6, 6.2 Hz, 1H), 2.34 (dt, J = 14.0, 7.0 Hz, 1H), 2.26 (dd, J = 13.5, 5.7 Hz, 1H), 1.94 (ddd, J = 13.6, 9.8, 4.8 Hz, 1H).

$^{13}$C NMR (101 MHz, $CDCl_3$) δ: 152.81, 148.75, 141.37, 134.15, 127.18, 120.96, 117.25, 108.36, 77.60, 77.44, 74.46, 62.77, 60.74, 60.63, 55.98, 39.92, 39.37, 29.60.

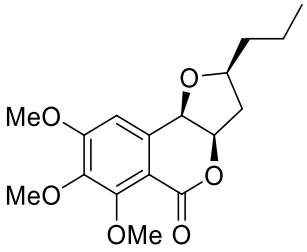
LRMS-ESI (m/z): 307.1 $[M+H]^+$




**31**

**(2S,3aR,9bR)-6,7,8-trimethoxy-2-propyl-3,3a,5,9b-tetrahydro-2H-furo[3,2-c]isochromene (31):**

To a stirred of isochromene **29** (47.4 mg, 0.156 mmol) in EtOAc (2 mL) was added 10 % Pd/C (10 mg). The resulting solution was stirred at 23 $^{o}$C under 1 atm $H_2$ gas over 12 h. Upon completion, the mixture was filtered through a plug of Celite and solvents were removed under reduced pressure. The crude product was purified by silica gel column chromatography (20 % EtOAc in hexane) to give dioxatricycle **31** (42.2 mg, 88 %); $^{1}$H NMR (400 MHz, $CDCl_3$) δ: 6.80 (s, 1H), 4.89 (d, *J* = 15.0 Hz, 1H), 4.41 (d, *J* = 15.1 Hz, 1H), 4.26 (d, *J* = 3.3 Hz, 1H), 4.20 – 4.09 (m, 1H), 3.93 (q, *J* = 7.1 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 2.52 (dt, *J* = 14.3, 7.3 Hz, 1H), 1.87 – 1.67 (m, 2H), 1.50 – 1.30 (m, 1H), 0.92 (t, *J* = 7.3 Hz, 3H);$^{13}$C NMR (101 MHz, $CDCl_3$) δ: 152.84, 148.97, 141.64, 126.63, 121.83, 108.71, 78.59, 75.20, 63.26, 60.85, 60.71, 56.09, 39.63, 38.13, 29.72 (grease), 19.61, 14.13; LRMS-ESI (m/z): 309.1 $[M+H]^+$; $[\alpha]_D^{20}$ +15.3 (*c* 0.40, $CHCl_3$); reported $[\alpha]_D^{26}$ +16.5 (*c* 1.02, $CHCl_3$) (Kwon, H.K.; Lee, Y.E.; Lee, E. *Org. Lett*. **2008**, *10*, 2995-2996.).

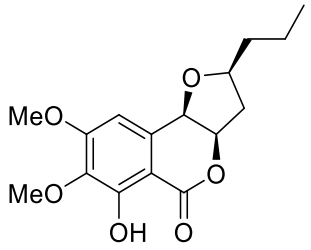



**32**

**(2S,3aR,9bR)-6,7,8-trimethoxy-2-propyl-2,3,3a,9b-tetrahydro-5H-furo[3,2-c]isochromen-5-one (32)**

To a solution of dioxatricycle **31** (41.2 mg, 0.135 mmol) in dichloromethane (4 mL), pyridine (54 µL, 0.67 mmol) and $CrO_3$ (40 mg, 0.40 mmol) were added and stirred for 36 h at 23 $^{o}$C. Thereafter, dichloromethane was pulled off under reduced pressure and ethyl acetate (10 ml) was added and filtered. The filtrate was washed with aq. $CuSO_4$ solution (3x5 ml) followed by

water (2x5 ml). The organic phase was dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (30% EtOAc in hexane) provided δ-valerolactone **32** (17.2 mg, 40%; 60% brsm) as a pale-yellow oil with the recovered starting material **31** (13.7 mg). $^1$H NMR (400 MHz, $CDCl_3$) δ: 6.78 (s, 1H), 4.94 (ddd, *J* = 5.8, 2.9, 1.0 Hz, 1H), 4.51 (d, *J* = 2.9 Hz, 1H), 4.25 – 4.06 (m, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.88 (s, 3H), 2.51 (ddd, *J* = 14.4, 8.8, 5.8 Hz, 1H), 2.16 (ddd, *J* = 14.3, 5.5, 1.1 Hz, 1H), 1.76 – 1.69 (m, 1H), 1.66 – 1.58 (m, 1H), 1.45 – 1.31 (m, 1H), 0.91 (t, *J* = 7.4 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 157.85, 144.19, 132.46, 111.16, 108.00, 79.42, 78.91, 75.00, 61.74, 61.04, 56.12, 38.96, 38.00, 13.87; LRMS-ESI (m/z): 323.0 $[M+H]^+$; HRMS-ESI (m/z): $C_{17}H_{22}O_6$; calc'd for $[M+Na]^+$: 345.1309, found 345.1306.; $[\alpha]_D^{20}$ +20.4 (*c* 0.31, $CHCl_3$); reported $[\alpha]_D^{26}$ + 21.5 (*c* 0.50, $CHCl_3$) (Kwon, H.K.; Lee, Y.E.; Lee, E. *Org. Lett*. **2008**, *10*, 2995-2996.).

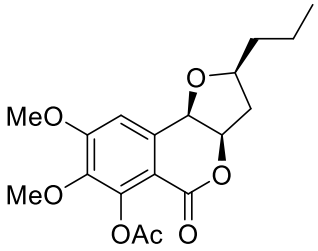



**(+)-Monocerin (1)**

**(+)-Monocerin (1)**

To a solution of δ-valerolactone **31** (13.4 mg, 0.042 mmol) in dry dichloromethane (1 mL) was added $BCl_3$ (1.0 M in DCM, 50 µL, 0.11 mmol) at -10 °C under argon atmosphere. The mixture was stirred at -10 °C for 2 h and quenched by the addition of saturated aqueous $NaHCO_3$ (1 mL). The mixture was extracted with ethyl acetate (15 mL) and the organic layer was washed with brine, dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography (20% EtOAc in hexane) gave **(+)-monocerin (1)** (4.9 mg, 41% yield; 88% yield brsm) as a colorless oil with the recovered starting material **32** (7.6 mg). $^1$H NMR (400 MHz, $CDCl_3$) δ: 11.28 (s, 1H), 6.59 (s, 1H), 5.05 (ddd, *J* = 6.3, 3.2, 1.2 Hz, 1H), 4.12 (dq, *J* = 8.6, 6.3 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 2.59 (ddd, *J* = 14.6, 8.6, 6.2 Hz, 1H), 2.16 (ddd, *J* = 14.5, 5.9, 1.2 Hz, 1H), 1.74-1.65 (m, 1H), 1.62 – 1.52 (m, 1H), 1.49 – 1.29 (m, 1H), 0.91 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 167.94, 158.84, 156.43, 137.48, 131.31, 104.50, 102.20, 81.38, 78.89, 74.64, 60.88, 56.40, 39.16, 38.19, 29.85, 14.12; LRMS-ESI (m/z): 309.1 $[M+H]^+$; HRMS-ESI (m/z): $C_{16}H_{21}O_6$; calc'd for $[M+H]^+$: 309.1333, found 309.1335; $[\alpha]_D^{20}$ +57.8 (*c* 0.29, $CHCl_3$);

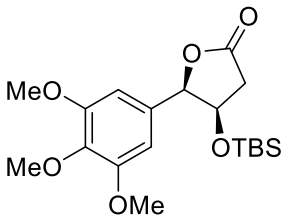
reported $[\alpha]_D^{24}$ + 53.0 (*c* 0.85, MeOH) (Aldridge, D. C.; Turner, W. B. *J. Chem. Soc. C*, **1970**, 2598–2600.).




**(+)-Acetylmonocerin (2)**

**(+)-Acetylmonocerin (2)**

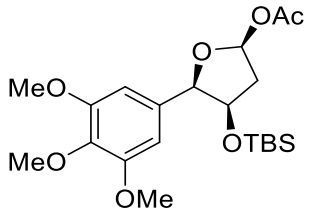
Acetic anhydride (75 µL, 0.8 mmol) and DMAP (catalytic amount) were added to a solution of **(+)-monocerin (1)** (2.2 mg, 0.007 mmol) in 0.2 mL of distilled pyridine at 0 °C under argon atmosphere, and the mixture was left stirring at room temperature for 5 h. After removing the solvent under reduced pressure, the crude product was purified by flash column chromatography on silica gel (33% EtOAc in hexane) to give 2.4 mg (96% yield) of the expected product as a white amorphous solid. $^1$H NMR (800 MHz, $CDCl_3$) δ: 6.90 (s, 1H), 4.99 (m, 1H), 4.55 (d, J = 3.1 Hz, 1H), 4.14 (m, 1H), 3.97 (s, 3H), 3.85 (s, 3H), 2.53 (ddd, J = 14.5, 8.7, 5.9 Hz, 1H), 2.42 (s, 3H), 2.13 (dd, J = 14.3, 5.5 Hz, 1H), 1.71 – 1.64 (m, 1H), 1.58 – 1.54 (m, 1H), 1.44 – 1.39 (m, 1H), 1.35 – 1.32 (m, 1H), 0.90 (t, J = 7.3 Hz, 3H); $^{13}$C NMR (201 MHz, $CDCl_3$) δ: 169.27, 159.89, 158.00, 146.10, 143.25, 132.68, 110.40, 109.93, 79.90, 78.99, 74.55, 61.24, 56.29, 39.05, 38.15, 20.99, 19.13, 13.97; LRMS-ESI (m/z): 373.1 $[M+Na]^+$; $[\alpha]_D^{25}$ +3.6 (*c* 0.29, $CHCl_3$); reported $[\alpha]_D^{24}$ – 3.0 (*c* 0.1, EtOH) for antipodal enantiomer of compound **2** (Sappapan, R.; Sommit, D.; Ngamrojanavanich, N.; Pengpreecha, S.; Wiyakrutta, S.; Sriubolmas, N.; Pudhom, K. *J. Nat. Prod.* **2008**, *71*, 1657–1659).




**21**

**(4R,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(3,4,5-trimethoxyphenyl)dihydrofuran-2(3H)-one (21)**

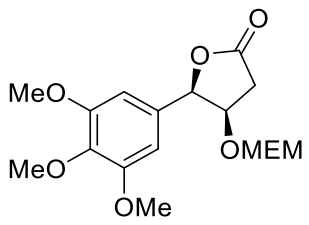
To a stirred solution of lactone **19** (95 mg, 0.354 mmol) in dichloromethane (3 mL) were added 2,6-lutidine (0.12 mL, 1.06 mmol) and TBSOTf (0.12 mL, 0.53 mmol) at 0 °C under Ar atmosphere. The reaction mixture was warmed to 23 °C and stirred for 3h. When the reaction was finished, the mixture was quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with dichloromethane. The extracts were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (40 % EtOAc in hexane) to give **21** (69 mg, 51 %) as an orange solid. $^1$H NMR (400 MHz, $CDCl_3$) δ: 6.54 (s, 2H), 5.37 (d, J = 3.5 Hz, 1H), 4.55 (ddd, J = 4.8, 3.5, 0.7 Hz, 1H), 3.85 (s, 6H), 3.82 (s, 3H), 2.87 (dd, J = 17.1, 4.8 Hz, 1H), 2.59 (dd, J = 17.1, 0.7 Hz, 1H), 0.67 (s, 8H), -0.13 (s, 3H), -0.34 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 175.54, 153.08, 137.96, 129.88, 103.79, 85.97, 71.46, 60.76, 56.12, 40.22, 25.30, 17.74, -5.36, -5.56; LRMS-ESI (m/z): $C_{19}H_{30}O_6SiNa$; calc'd for $[M+Na]^+$ : 405.17, found 405.17; $[\alpha]_D^{20}$ – 34.7 (*c* 0.29, $CHCl_3$).




**22**

**(4R,5R)-4-(methoxymethoxy)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran-2-yl acetate (22)**

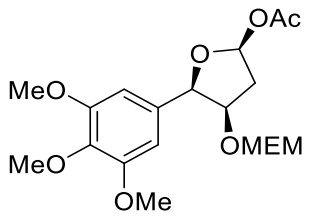
The title compound was prepared from lactone **21** (55 mg) following the procedure described for the preparation of **16**. The compound was purified by flash column chromatography (20% EtOAc in hexane) to give acetate **22** (81 % over two steps, 50 mg) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) δ: 6.60 (dd, J = 5.9, 3.8 Hz, 1H), 6.56 (d, J = 0.5 Hz, 2H), 5.03 (d, J = 3.6 Hz, 1H), 4.43 (ddd, J = 5.4, 3.6, 1.9 Hz, 1H), 3.83 (s, 6H), 3.78 (s, 3H), 2.44 – 2.27 (m, 2H), 2.05 (s, 3H), 0.67 (s, 9H), -0.17 (s, 3H), -0.35 (s, 3H); $^{13}$C NMR (Major isomer, 101 MHz, $CDCl_3$) δ: 170.30, 152.68, 137.49, 131.68, 104.59, 97.85, 85.19, 73.74, 60.72, 56.02, 43.11, 25.41, 21.21, 17.78, -5.38, -5.48; LRMS-ESI (m/z): 449.2 $[M+Na]^+$; $[\alpha]_D^{20}$ – 13.6 (*c* 0.5, $CHCl_3$).




**23**

**(4R,5R)-4-((2-methoxyethoxy)methoxy)-5-(3,4,5-trimethoxyphenyl)dihydrofuran-2(3H)-one (23)**

To a stirred solution of lactone **19** (125 mg, 0.47 mmol) in distilled THF (2 mL) were consecutively added DIPEA (0.81 mL, 4.7 mmol), TBAI (43 mg, 0.12 mmol), and MEM-Cl (0.27 mL, 2.33 mmol) were at 0 $^{o}$C under argon atmosphere. The reaction mixture was then stirred at 55 $^{o}$C for 72h. Upon completion, the mixture was diluted with EtOAc and washed with water. The organic phase was dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (80% EtOAc in hexane) to give MEM protected lactone **23** (131 mg, 79%) as a yellow solid.$^{1}$H NMR (400 MHz, $CDCl_3$) δ: 6.57 (s, 2H), 5.43 (d, J = 3.8 Hz, 1H), 4.62 (ddd, J = 5.0, 3.8, 1.0 Hz, 1H), 4.42 (d, J = 7.3 Hz, 1H), 4.23 (d, J = 7.3 Hz, 1H), 3.85 (s, 6H), 3.83 (s, 3H), 3.45 (ddd, J = 10.6, 5.6, 3.3 Hz, 1H), 3.41 – 3.36 (m, 2H), 3.32 (s, 3H), 3.22 (ddd, J = 10.6, 5.3, 3.4 Hz, 1H), 2.87 (dd, J = 17.6, 5.2 Hz, 1H), 2.74 (dd, J = 17.5, 1.0 Hz, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 174.98, 153.15, 137.88, 129.34, 103.52, 93.91, 84.61, 74.02, 71.36, 66.95, 60.80, 58.87, 56.10, 37.35; LRMS-ESI (m/z): 379.4 $[M+Na]^+$; $[\alpha]_D^{20}$ – 25.5 (*c* 0.29, $CHCl_3$).




**24**

**(4R,5R)-4-((2-methoxyethoxy)methoxy)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran-2-yl acetate (24)**

The title compound was prepared from lactone **23** (111 mg) following the procedure described for the preparation of **16**. The compound was purified by flash column chromatography (20% EtOAc in hexane) to give acetate **24** (72 % over two steps, 50 mg) as a white solid. $^{1}$H NMR (400 MHz, CDCl3) δ: 6.58 (s, 2H), 6.55 (dd, J = 6.1, 3.3 Hz, 1H), 5.07 (d, J = 3.8 Hz, 1H), 4.48 (ddd, J = 5.8, 3.8, 1.7 Hz, 1H), 4.37 (d, J = 7.2 Hz, 1H), 4.19 (d, J = 7.1 Hz, 1H), 3.81 (s, 6H), 3.78 (s, 3H), 3.41 (ddd, J = 10.4, 5.8, 3.3 Hz, 1H), 3.37 – 3.32 (m, 2H), 3.29 (s, 2H), 3.17 (ddd, J = 10.4, 5.2, 3.3 Hz, 1H), 2.50 (ddd, J = 14.7, 6.1, 1.8 Hz, 1H), 2.34 (ddd, J = 14.7, 6.0, 3.3 Hz, 1H), 2.03 (s, 3H); $^{13}$C NMR (101 MHz, CDCl3) δ: 170.19, 152.81, 137.34, 131.05, 104.07, 97.40, 93.87,

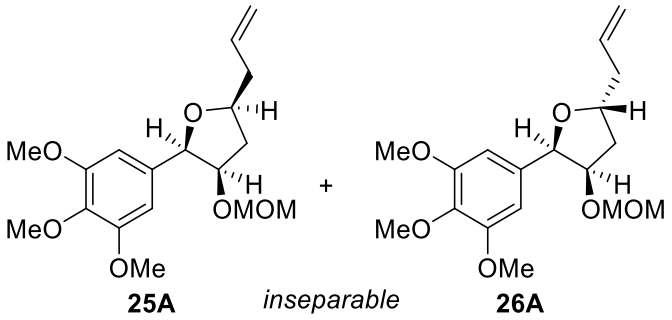
83.70, 76.54, 71.40, 66.66, 60.75, 58.83, 55.97, 40.25, 21.18; LRMS-ESI (m/z): 423.4 $[M+Na]^+$; $[\alpha]_D^{20}$ + 4.1 (*c* 0.69, $CHCl_3$).

**General Procedure for the Allylation Reaction of Tetrahydrofuran Acetates**

A solution of tetrahydrofuran acetate in $CH_2Cl_2$ were treated with allyltrimethylsilane (4.0 equiv) and Lewis acid at –78 °C under argon atmosphere. After addition of Lewis acid, the reaction mixture was stirred at –78 °C for 3h. When the reaction was finished, the reaction mixture was treated with saturated aqueous $Na_2HPO_4$ (1 mL per mmol of acetate). The aqueous layer was then extracted three times with $CH_2Cl_2$, and the collected organic phases were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure.

**General Procedure for a Oxa-Pictet-Spengler Cyclization of Tetrahydrofuran Acetates**

A solution of tetrahydrofuran acetate in $CH_2Cl_2$ (0.015 M) were treated with allyltrimethylsilane (4.0 equiv) and Lewis acid at – 78 °C under argon atmosphere. After addition of Lewis acid, the reaction mixture was slowly warmed to 23 °C. When the starting material was completely consumed, additional portion of Lewis acid was added at given temperature and the mixture was slowly warmed to 23°C overnight. Upon completion, the reaction mixture was treated with saturated aqueous $Na_2HPO_4$ (1 mL per mmol of acetate), which was extracted with $CH_2Cl_2$. The collected organic phases were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure.

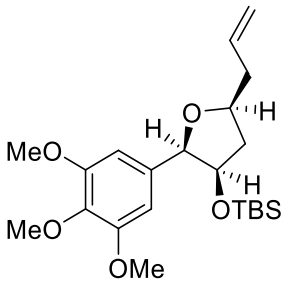



**25A** *inseparable* **26A**

**(2R,3R,5S)-5-allyl-3-(methoxymethoxy)-2-(3,4,5-trimethoxyphenyl) tetrahydrofuran (25A)** and **(2R,3R,5R)-5-allyl-3-(methoxymethoxy)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran (26A)** mixture:

Following the general procedure described above and starting from MOM protected acetate intermediate **16** (18 mg, 0.05 mmol) in $CH_2Cl_2$ (1 mL), allyl derivatives **25A** and **26A** (14.4 mg, 84% yield) were obtained as a colorless oil after the crude residue was purified by column chromatography over silica gel (5−20% EtOAc in hexanes). The results are summarized in Table

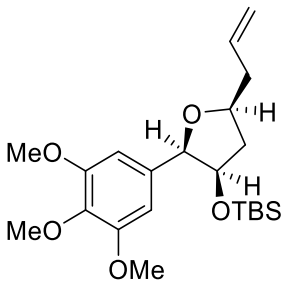
1.2 $^{1}$H NMR (mixture, 400 MHz, $CDCl_3$) δ: 6.64 (s, 3.2H), 6.61 (s, 2H), 6.00 – 5.74 (m, 2.6H), 5.18 – 5.04 (m, 5.2H), 4.93 (d, J = 3.3 Hz, 1H), 4.73 (d, J = 4.1 Hz, 1.6H), 4.58 – 4.44 (m, 1H), 4.41 – 4.25 (m, 5.3H), 4.18 – 4.01 (m, 4.8H), 3.85 (s, 15.2H), 3.81 (s, 4.6H), 3.81 (s, 3H), 3.07 (s, 4.8H), 3.04 (s, 3H), 2.70 – 2.57 (m, 1.7H), 2.52 – 2.29 (m, 5.8H), 2.19 (ddd, 1H), 1.91 (ddd, J = 13.2 Hz, 1H), 1.85 (ddd, J = 11.4, 6.0 Hz, 1.7H); $^{13}$C NMR (mixture, 101 MHz, $CDCl_3$) δ: 152.75, 134.83, 134.09, 133.62, 133.08, 117.38, 116.90, 104.23, 103.98, 95.02, 84.30, 83.68, 78.70, 77.79, 77.64, 77.10, 60.76, 55.98, 55.09, 40.42, 40.15, 38.77, 38.25; LRMS-ESI (m/z): 361.2 $[M+Na]^+$




**25B**

**(((2R,3R,5S)-5-allyl-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)oxy)(tert-butyl)dimethylsilane** (**25B)**

Following the general procedure described above and starting from TBS protected acetate derivative **22** (21.7 mg, 0.05 mmol) in $CH_2Cl_2$ (1 mL), the title compound **25B** (16.8 mg, 81% yield) was prepared as a colorless oil after the crude residue was purified by column chromatography over silica gel (5− 20% EtOAc in hexanes). The results are summarized in Table 1.2.$^{1}$H NMR (400 MHz, $CDCl_3$) δ 6.59 (s, 2H), 5.99 – 5.85 (m, 1H), 5.18 – 5.04 (m, 2H), 4.73 (d, J = 3.7 Hz, 1H), 4.30 (td, J = 3.7, 1.8 Hz, 1H), 4.22 – 4.13 (m, 1H), 3.84 (s, 6H), 3.79 (s, 3H), 2.67 (dt, J = 13.6, 6.7 Hz, 1H), 2.48 (dt, J = 13.8, 6.9 Hz, 1H), 2.35 (ddd, J = 13.6, 8.5, 5.4 Hz, 1H), 1.80 (ddd, J = 13.2, 4.4, 1.7 Hz, 1H), 0.68 (s, 9H), -0.13 (s, 3H), -0.37 (s, 3H);$^{13}$C NMR (101 MHz, $CDCl_3$) δ: 152.62, 134.40, 117.15, 104.34, 85.25, 77.73, 75.46, 60.71, 55.96, 41.74, 40.06, 25.47, 17.79, -5.35, -5.49; LRMS-ESI (m/z): 431.2 $[M+Na]^+$; $[\alpha]_D^{20}$ – 62.0 (*c* 0.79, $CHCl_3$).




**25C**

**(((2R,3R,5S)-5-allyl-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)oxy)(tert-butyl)dimethylsilane** (**25C)**

Following the general procedure described above and starting from MEM protected acetate intermediate **24** (20 mg, 0.05 mmol) in $CH_2Cl_2$ (1 mL), the title compound **25C** (6.3 mg, 33% yield) was prepared as a colorless oil after the crude residue was purified by column chromatography over silica gel (40% EtOAc in hexanes). The results are summarized in Table 1.2. $^1$H NMR (800 MHz, $CDCl_3$) δ 6.63 (s, 2H), 5.91 – 5.86 (m, 1H), 5.15 (dd, J = 35.1, 13.7 Hz, 2H), 4.96 (d, J = 3.2 Hz, 1H), 4.53 (dq, J = 12.2, 6.1 Hz, 1H), 4.49 (d, J = 7.2 Hz, 1H), 4.43 (t, J = 3.7 Hz, 1H), 4.28 (d, J = 7.2 Hz, 1H), 3.88 (s, 6H), 3.84 (s, 3H), 3.44 (ddd, J = 10.7, 6.2, 3.2 Hz, 1H), 3.41 – 3.36 (m, 2H), 3.35 (s, 3H), 3.19 (ddd, J = 10.7, 5.5, 3.2 Hz, 1H), 2.51 (dt, J = 13.2, 6.3 Hz, 1H), 2.41 (dt, J = 14.0, 6.9 Hz, 1H), 2.25 (dd, J = 13.3, 5.9 Hz, 1H), 1.93 (ddd, J = 13.6, 9.6, 4.5 Hz, 1H);$^{13}$C NMR (101 MHz, $CDCl_3$) δ: 152.91, 137.18, 134.20, 133.75, 117.51, 104.07, 93.95, 83.83, 78.72, 77.77, 71.59, 66.63, 60.88, 58.96, 56.09, 40.27, 38.77; LRMS-ESI (m/z): 405.1 $[M+Na]^+$; $[\alpha]_D^{20}$ -85.0 (*c* 0.12, $CHCl_3$).

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# CHAPTER 2. DESIGN AND SYNTHESIS OF POTENT HIV-1 PROTEASE INHIBITORS CONTAINING NOVEL CHIRAL TRISUBSTITUTED TETRAHYDROFURAN P2-LIGAND

## 2.1 Introduction

Human immunodeficiency virus (HIV) is a retrovirus that is responsible for causing acquired immunodeficiency syndrome (AIDS) to the individual who has acquired the infection.[1,2] Since the discovery of HIV in the early 1980s, more than 78 million people have been infected with this virus and approximately 32.7 million people have died from AIDS-related disease according to UNAIDS data.[3,4] An estimated 38 million people worldwide are currently living with HIV/AIDS and nearly 70% of the global cases of HIV infection has come from sub-Saharan Africa and developing countries.[3,4] Due to limited equipment and lack of education about the virus in those areas, a large population of HIV-infected patients remains undiagnosed and fails to get proper treatment until very late stage of the disease.[4,5] Currently, around 1.2 to 2.2 million people became newly infected with the virus each year and only 81% of all people living with the virus knew their HIV status.[3-6]

Up to date, there is no vaccine or treatment to eradicate the virus from an infected individual. The advent of highly active antiretroviral therapy (HAART) in the mid-1990s, however, has dramatically decreased morbidity and mortality rate among HIV-infected patients especially in developed countries.[4-10] HAART is currently the most effective AIDS treatment, and protease inhibitors (PIs) play a crucial role in HAART.[11] Currently, 26 anti-HIV compounds have been approved by the US Food and Drug Administration (FDA). Among these compounds, ten are HIV protease inhibitors and the rest are integrase inhibitors, viral attachment inhibitors, and membrane fusion inhibitors.[6,11-14] Today, various treatment regimens are available for the treatment of HIV infection and they aim to show high oral bioavailability, reduced drug-related side effects, and high potency that can decrease the concentration of HIV in blood to undetectable levels within a few weeks of treatment.[4-6]

Despite of these major advances in HIV/AIDS therapies, there are significant problems to current treatment regimens. HIV antiretroviral treatment is a lifelong commitment and may cause several side effects including: drug–drug interactions, drug toxicity, systematic complications involving major organs such as heart and kidney, neurocognitive disorders, and, most importantly,

drug resistance.[15-18] HIV is well-known for its very high rate of mutations due to the combined activity of its error-prone reverse transcriptase (RT), recombination, and short generation times. The high levels of genetic diversity of HIV generated by these mutations allows the virus to circumvent the human immune system and rapidly evolve drug resistance.[19-22]

The rapid emergence of drug resistance is the major concern for all the current HIV therapies. A new therapeutic drug, which is very successful at the beginning, can rapidly lose its potency even within few months in some cases.[23,24] It has been reported that 40-50% of the patients who achieve initial suppression eventually experience treatment failure.[25] Moreover, new individuals can be infected with these drug-resistant HIV mutant strains.[26] Therefore, novel and potent HIV inhibitors with fewer drug-related side effects and toxicity are essential for successful long-term HIV care.

### 2.1.1 HIV-1 Protease: Structure, Function, and Mechanism

HIV-1 protease (PR) is a crucial component of the HIV life cycle and it is responsible for the processing and production of all viral enzymes and proteins necessary for the generation of mature virions.[27-29] As shown in Figure 2.1, the HIV-1 PR is a homodimeric aspartyl protease containing 99 amino acids in a $C_2$-symmetric fashion with a catalytic Asp at position 25. The catalytic active site of the HIV-1 PR is consisted of Asp25-Thr26-Gly27 and Asp25'-Thr26'-Gly27' residues from each subunit of the enzymatically active dimer and located at the stable dimer interface region (Figure 2.1). Structurally, the catalytic active site is not fully exposed, being covered by a flap region formed by two flexible glycine dense β-sheets from each subsite (Figure 2.1). This flap region exists in an open conformation in the absence of a substrate and folds down to cover the active site in the presence of a substrate.[30]

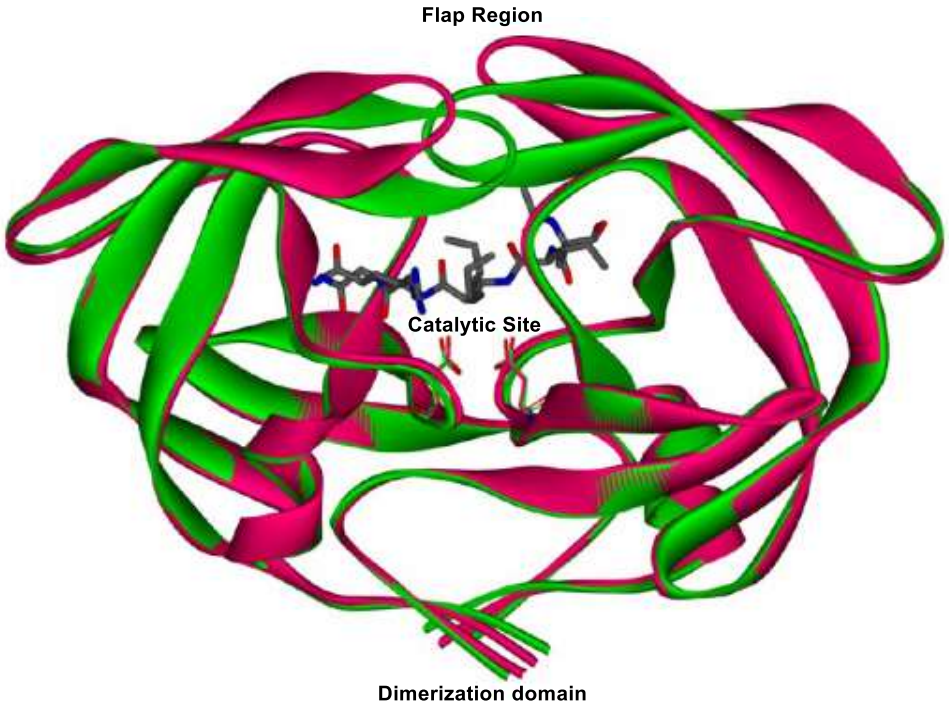



Figure 2.1 HIV-1 Protease Complexed with Substrate in Both the Flap-open Conformation (magenta, PDB entry 2PCO) and the Flap-closed Conformation (green, PDB entry 2AOD). Adopted from the literature.[6]

Earlier X-ray crystallographic studies have also shown that the HIV-1 PR strongly prefers to bind with substrates consisted of at least seven residues in an extended conformation that can form strong hydrogen bonding interactions with the enzyme active sites, denoted as $S_3$ to $S_1$ and $S_1$' to $S_3$' by standard nomenclature (Figure 2.2).[27-30] The $P_3$ to $P_1$ and $P_1$' to $P_3$' represent the corresponding amino acid residues of the native peptide substrate from the scissile bond. Structurally, the subsites $S_1$ and $S_1$', $S_2$ and $S_2$', and $S_3$ and $S_3$' are, respectively, similar due to $C_2$-symmetry of the enzyme. Moreover, the subsites $S_1$, $S_1$', $S_3$, and $S_3$' are known to favor hydrophobic residues, while the $S_2$ and $S_2$' subsites can accommodate both hydrophobic and hydrophilic residues.[27-30]

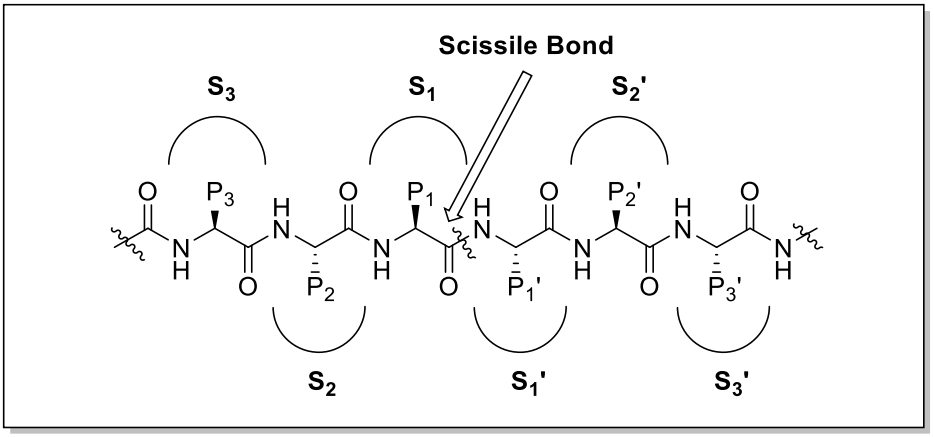
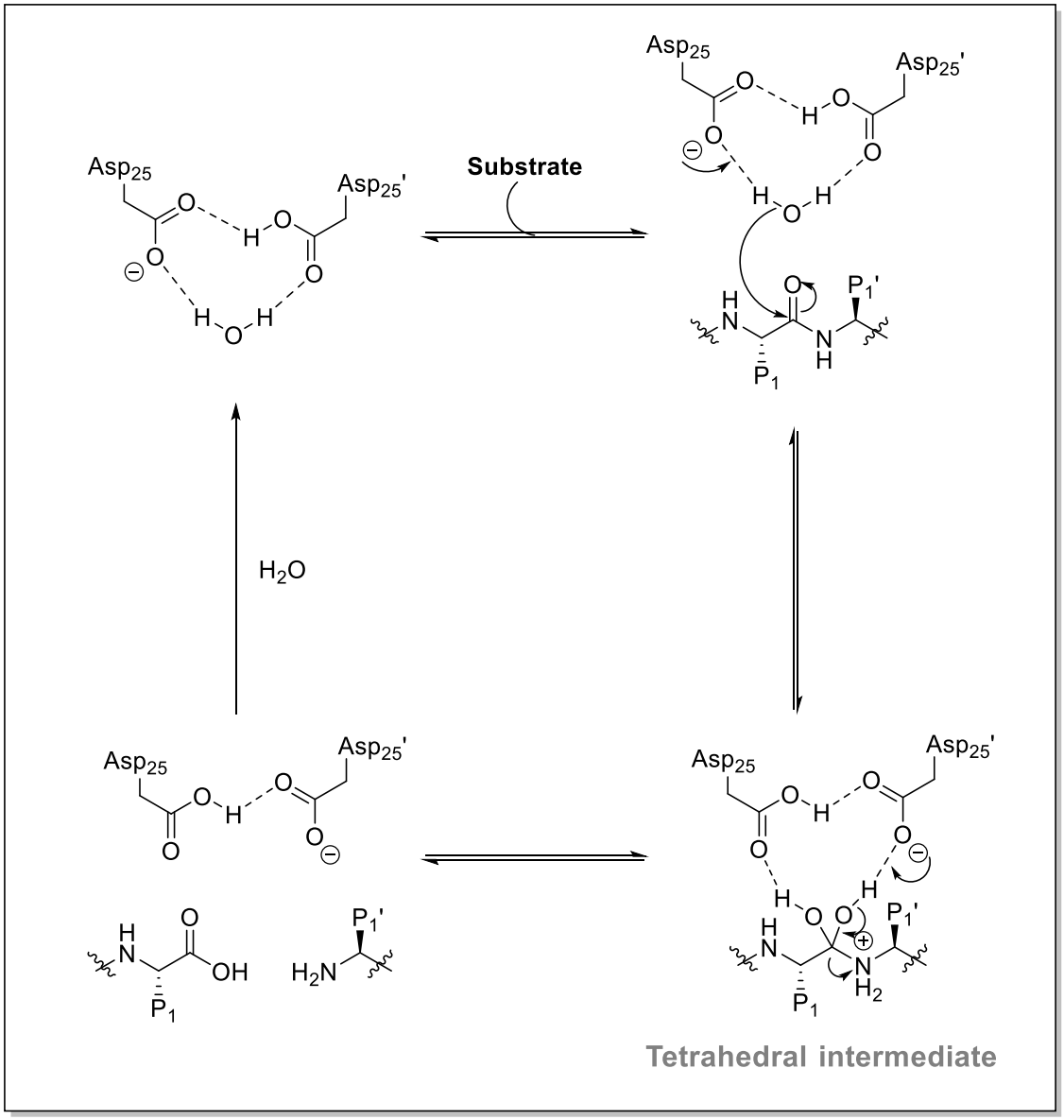



Figure 2.2 Native Substrate Bound to HIV-1 Protease

The HIV PR catalyzes the hydrolysis of the *Gag* and *Gag-Pol* polyproteins to construct various enzymes including RT, integrase (IN), and new PR and other structural proteins, such as viral envelope glycoproteins.[6] This process is completed with high selectivity and catalytic proficiency. The hydrolysis reaction of the amide bond is mediated by the catalytic aspartic acid residues Asp 25 and Asp25' and occurs between the $P_1$ and $P_1$' residues (scissile bond).[29] The first step of the hydrolysis reaction is the formation of nucleophilic water molecule by the negative aspartic side chain (Scheme 2.1).[29] When the substrate is introduced, the nucleophilic water molecule then undergoes nucleophilic addition to the carbonyl group in the scissile bond, resulting an oxyanion tetrahedral intermediate.[29] Protonation of the scissile amide N atom followed by the hydrolysis step result in the cleavage of the scissile bond to afford two new products as shown in Scheme 2.1.[29]




Scheme 2.1 Catalytic Mechanism of HIV-1 Protease

### 2.1.2 First Generation HIV-1 Protease Inhibitors

The dimerization of HIV-1 PR monomers is a crucial process for enzyme maturation and proteolytic activity.[31] Inhibition of the dimerization, therefore, is an attractive therapeutic target to fend off HIV replication. To understand more about this mechanism, the interactions between HIV-1 PR and its bound inhibitors have been investigated to determine general binding patterns of inhibitor and substrate to HIV-1 PR (Figure 2.3).[32]

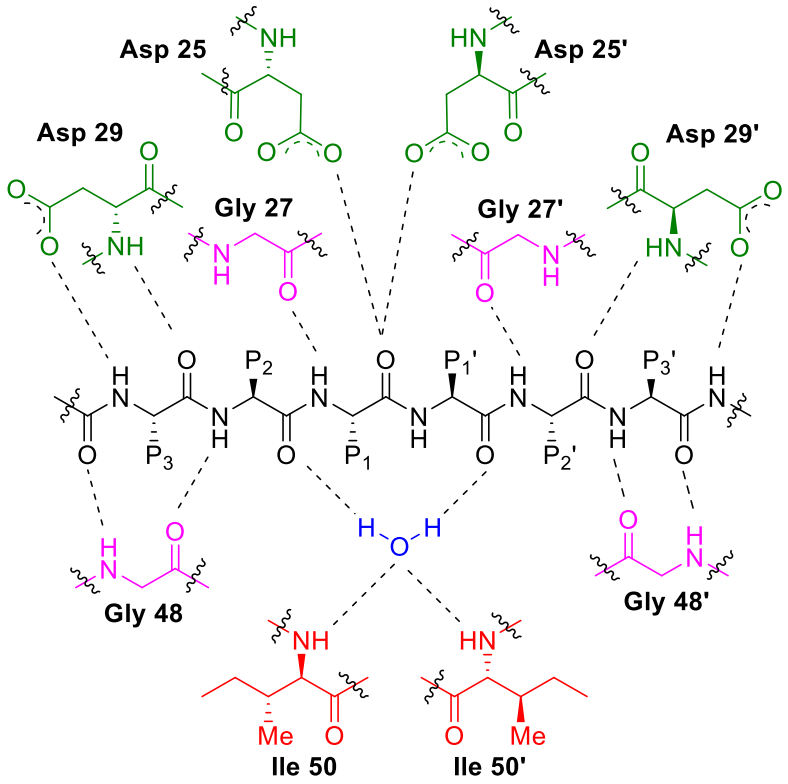



Figure 2.3 Conserved Hydrogen Bond Interactions of HIV-1 PR with Substrate in the Active Site

Extensive studies of the catalytic mechanism of HIV-1 PR have allowed the development of first-generation HIV PIs.[29] First-generation HIV PIs, developed between 1995 and 2006, are peptidic PIs used to treat patients with HIV/AIDS. For instance, saquinavir (SQV), developed in 1995, was the first FDA-approved HIV PI that showed an excellent enzyme inhibitory activity ($K_i$) of 0.12 nM.[33,34] The FDA approval of SQV has marked the beginning of HAART therapy and significantly increased the success rate of HIV treatment. Structurally, SQV contains a non-cleavable hydroxyethylamine isostere and hydroxyl group at the center of the structure that mimics the transition state of the hydrolysis step by forming hydrogen bonds with the catalytic Asp 25 and Asp 25' residues (Figure 2.4). Moreover, the P1' decahydroisoquinoline moiety and P1 phenyl moiety nicely fill in the hydrophobic volume of the S1' and S2' pocket, respectively. At the same time, the P2 carboxamide forms strong hydrogen bonds with the backbone amide groups of Asp29 and Asp30. Furthermore, SQV binds with HIV PR in an extended conformation (Figure 2.4).[34]

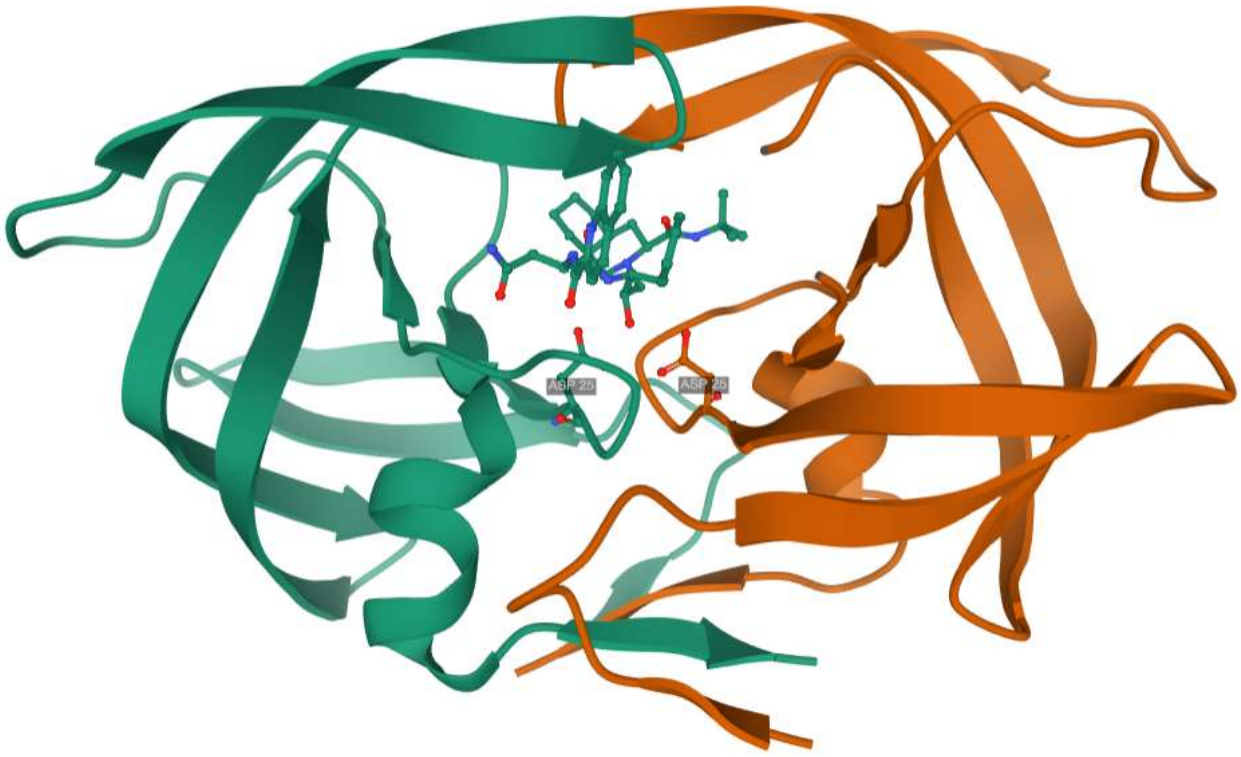



Figure 2.4 Structure of SQV Complexed with the HIV-1 PR (PDB code 3EL4).

Subsequently, Ritonavir, Indinavir, Nelfinavir, and Amprenavir were developed by various pharmaceutical companies between 1996 and 1999 and they were used in the combination therapy.[6,11] As highlighted in Figure 2.5, the first-generation inhibitors featured a similar hydroxyethylamine isostere and enzyme inhibitory activity. The first-generation HIV PIs, however, showed many adverse effects. Due to their highly peptidic chemical structures, they had very poor bioavailabillty, low half-life, high metabolic clearance, and numerous side effects including nausea, diarrhea, and abdominal pain. The most concerning problem was the rapid emergence of drug-resistant HIV strains, causing most of the first-generation HIV PIs to lose their biological activity over time.[6,35]

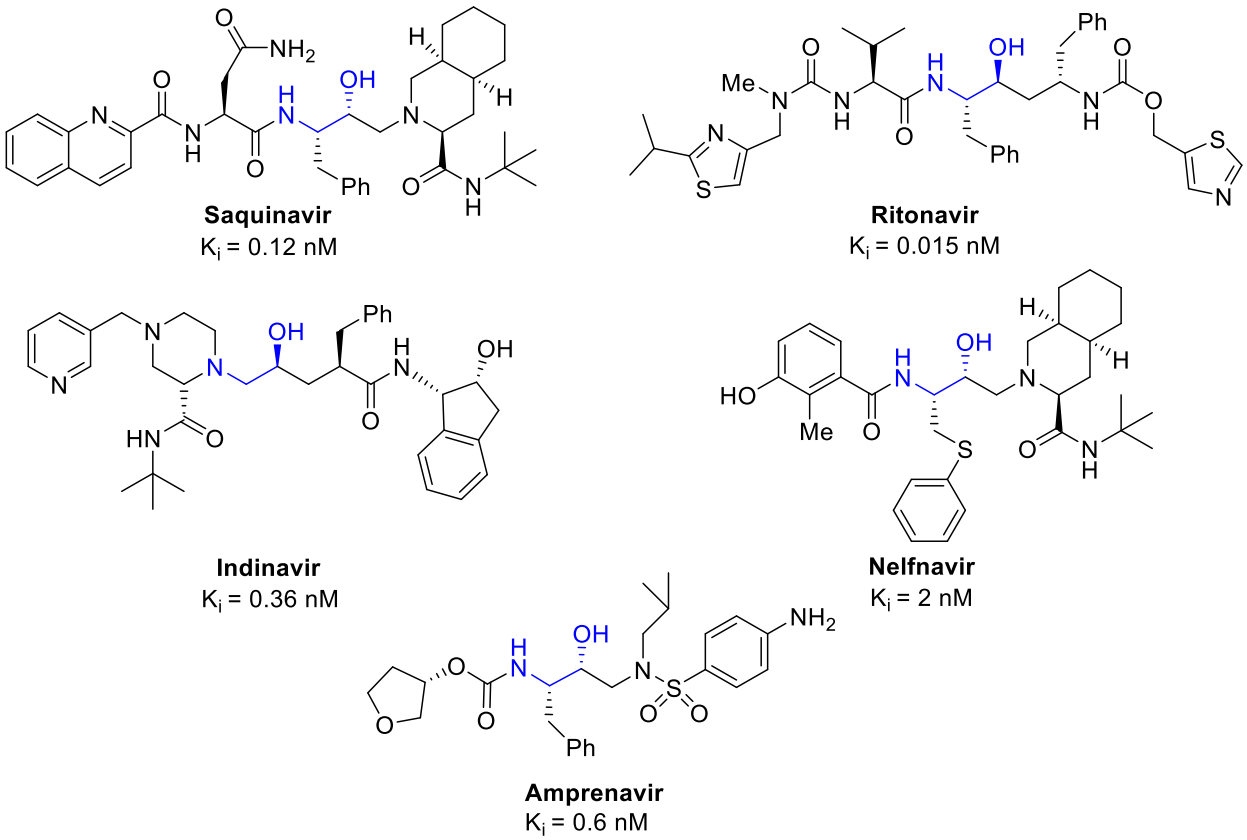



Figure 2.5 First-Generation HIV PIs.

### 2.1.3 Second Generation HIV-1 Protease Inhibitors

To overcome the limitations of the first-generation HIV PIs, second-generation HIV PIs were developed. As shown in Figure 2.6, Lopinavir, Atazanavir, Tipranavir, and Darunavir were approved by FDA as second-generation HIV PIs.[6,36] Lopinavir was approved in 2000 and significantly improved the biological properties of ritonavir; it showed an increased $K_i$ value of 1.3 pM compared to the 15 pM of ritronavir.[37] Atazanavir was approved in 2003 with a moderate $K_i$ value of 2.66 nM, but it was the first PI that can be dosed only once per day.[38] Tipranavir, which was approved in 2005, was the first non-peptidic PI with a $K_i$ value of 8 pM. Today, Tipranavir is used as a drug of last resort due to its severe side effects toward HIV-infected patients.[39] Just like Tipranavir, Darunavir (Prezista®), approved by FDA in 2006, is the non-peptidic, sulfonamide containing second-generation PIs. Darunavir is the best second-generation HIV PI in the market so far as it not only shows excellent antiviral activity profile (Ki = 16 pM and $IC_{50}$ = 4.1 nM)

against multidrug resistant HIV-1 variants with minimal cytotoxicity, but also displays high genetic barrier against drug resistance.[40]

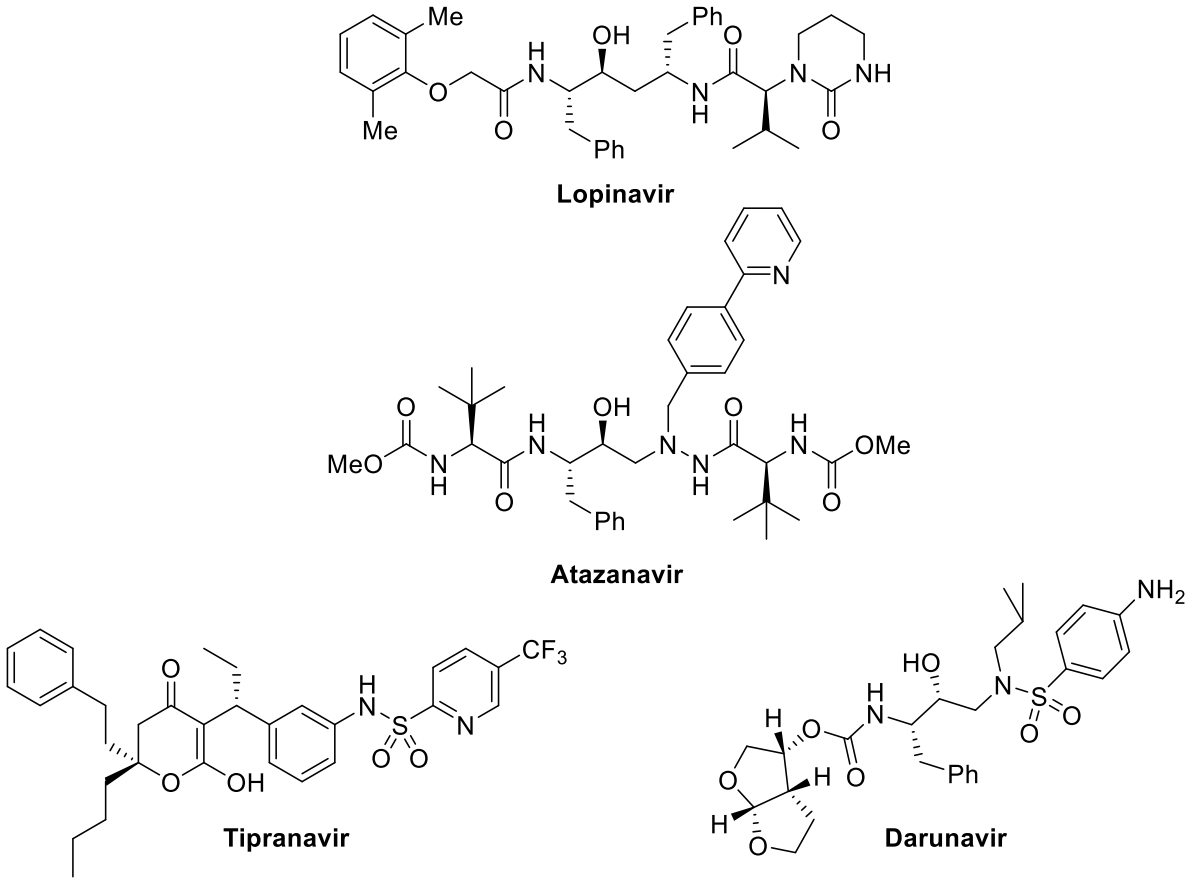



Figure 2.6 Second-Generation HIV PIs.

### 2.1.4 Backbone Binding Concept and Darunavir

Most of HIV PIs, including DRV, in the market today has at least one known mutation that reduces their overall binding affinity.[41-44] The rapid development of drug resistance is mainly due to the extremely error-prone replication process of HIV. During the replication process, RT creates the viral DNA from the viral RNA through reverse transcription at a very high rate and the created viral DNA is integrated into the host's DNA with the help of IN. Unlike eukaryotic DNA synthesis, the viral replication process is very susceptible to errors as it lacks any proofreading mechanism and, therefore, leads to multiple polymorphic mutations. Some of these mutations severely limit

the binding ability of inhibitors to the catalytic active sites of the enzyme, resulting in a loss of efficacy.[45,46]

Up to date, two classes of HIV-1 mutations have been reported: primary and secondary.[47,48] Primary mutation directly alters residues involved in substrate binding, but rarely involves ones that participate in active catalysis. Secondary mutations are changes in residues outside of the active site.[49] They are known to serve a crucial role in retaining the enzyme's native substrate binding ability after the detrimental primary mutations. Until now, it has been reported that 45 residues out of the 99 residues that compose a monomer of HIV PR are known to mutate without losing its enzymatic function. Of these 45 residues, only 11 have been identified as active site or primary mutations and the remaining ones take place either in the flap region or dimer interface of the enzyme.[50]

In our continuous efforts to combat drug resistance, our lab has developed and employed a "backbone binding" concept for designing HIV PIs.[6,30] This concept was derived from the earlier X-ray structural studies of inhibitors bound to wild-type HIV-1 PR and various mutant proteases. From these studies, our lab was able to obtain a strong evidence that the active-site backbone conformation of mutant proteases is minimally distorted compared to that of wild-type HIV-1 PR.[6,30] This phenomenon is very interesting as it indicates that the active-site backbone conformation of the HIV mutant PRs will continue to stay intact to maintain their enzymatic functions even after they undergo several mutations that cause drug resistance.[6,30]

Based upon this evidence, our lab has designed HIV PIs that can form maximum interactions, particularly hydrogen bond interactions, with the active sites of the wild type enzyme. As depicted inf Figure 2.7, our HIV PI design strategy involves P2 and P2′ ligands simultaneously forming strong hydrogen bond interactions with backbone atoms in S2 and S2′ subsites, while filling hydrophobic S1 and S1′ subsites with the hydrophobic P1 and P1′ ligands. The transition state hydroxyl group is designed to bind both to the catalytic aspartic acid residues Asp25 and Asp25' (Figure 2.7).[51]

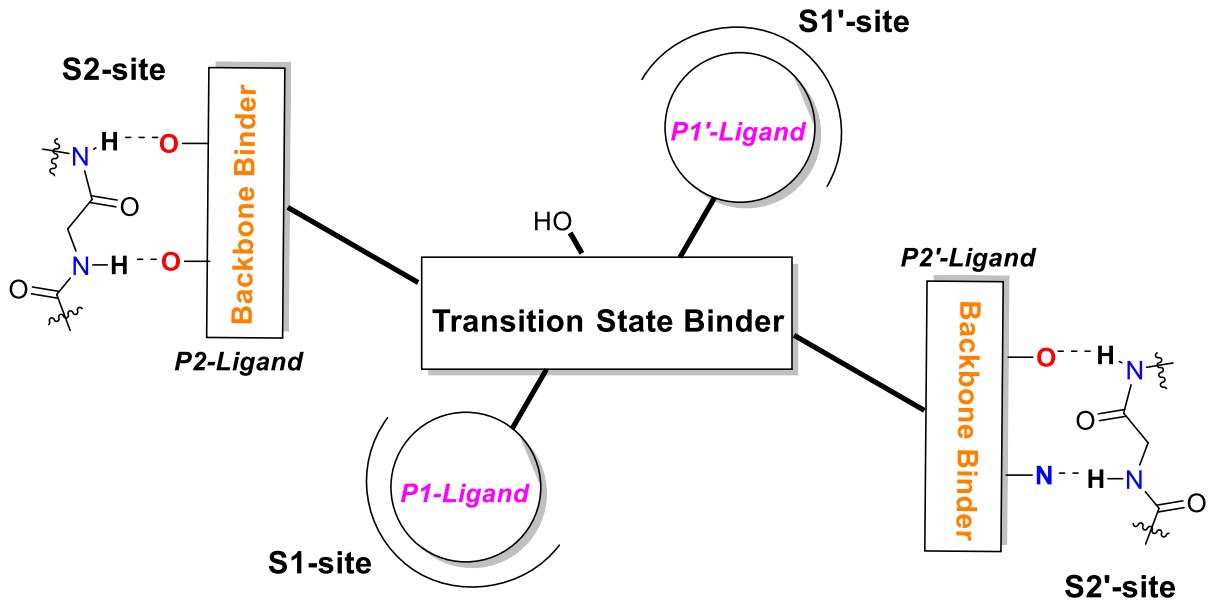



Figure 2.7 Proposed Model for the Design of HIV PIs to Combat Drug Resistance.

DRV is an excellent example of this strategy. DRV incorporates a fused *bis*-tetrahydrofuran (*bis*-THF) as the P2 ligand and (*R*)-(hydroxyethylamino)sulfonamide isostere as the P2' ligand (Figure 2.6). Numerous X-ray crystallographic studies revealed that both oxygen atoms on the *bis*-THF ligand form very strong hydrogen bonding interactions with the backbone residues Asp29 and Asp30 in the S2 active stie of the enzyme (Figure 2.8).[6,30] The distance between the top oxygen atom and the backbone amide NHs of Asp29 and Asp30 was measured to be approximately 3.1 – 3.3Å, and the distance between the bottom oxygen and the amide NH of Asp29 was determined to be 2.9 Å.[51] Both the carbamate carbonyl oxygen atom of the P2 ligand and one of the sulfonamide oxygen atoms of the P2' ligand form water-mediated hydrogen bonding with Ile50' and Ile50 residues in the flap region (Figure 2.8). Moreover, the *bis*-THF ligand nicely fills in the hydrophobic pocket in the S2 active site, thereby enhancing the Van deer Waals interactions with the enzyme.[6,30] The X-ray crystal structure of DRV bound HIV-1 PR also revealed extensive hydrogen bonding interactions between the backbone atoms of the wild-type HIV PR and DRV throughout the S2 and S2' subsites (Figure 2.9). All these interactions are responsible for DRV's excellent antiviral profile against numerous multidrug-resistant HIV-1 strains.[6,30]

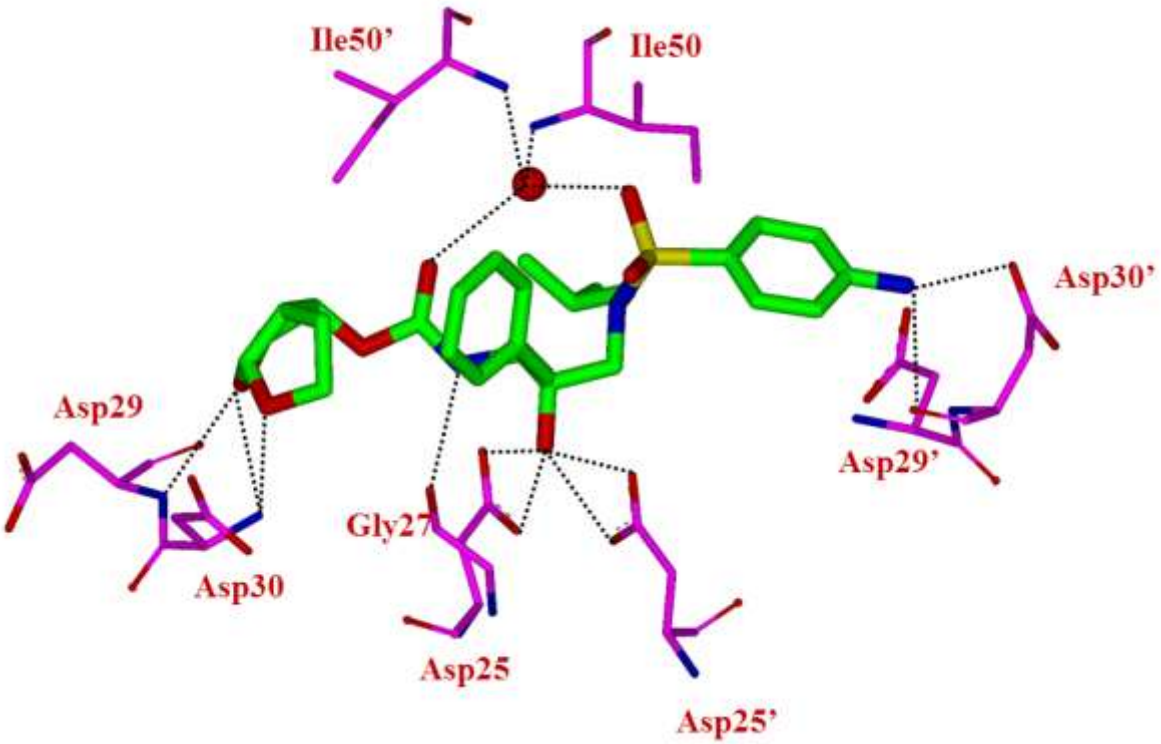



Figure 2.8 X-ray Crystal Structure of DRV-bound HIV-1 PR (PDB 2IEN). Dotted Lines Represent Strong Hydrogen Bonding Interactions.

## 2.2 Results and Discussion

### 2.2.1 Previous Synthesis of Novel HIV-1 PIs from Ghosh Lab

Despite of DRV's high genetic barrier to the development of drug resistance due to its superb active site backbone binding ability, DRV resistant HIV-1 viruses are arising and, thus, threatening a successful long-term HIV treatment.[41,43] As part of our continuous effort to develop novel PIs to combat drug resistance, our lab has designed and synthesized a variety of HIV PIs that maintains excellent potency against multidrug-resistant HIV-1 variants that show resistance against currently approved PIs. One of the most successful examples of recently synthesized novel HIV PIs is *endo* crown-like tetrahydrofuran (crn-THF) containing inhibitor **35**, which has an unprecedented 6-5-5 ring-fused structure as the P2 ligand and 4-methoxybenzenesulfonamide as the P2' ligand.[51] This inhibitor showed improved enzyme inhibitory constant ($K_i$) of 14 pM and antiviral $IC_{50}$ value of 2.7 nM compared to DRV ($K_i$ = 16 pM, $IC_{50}$ = 3.2nM). The observed improvement in potency is largely due to enhanced hydrogen bonding and van der Waal interactions in the S2 subsite resulted by the novel crown-like scaffold of the P2 ligand.[51]

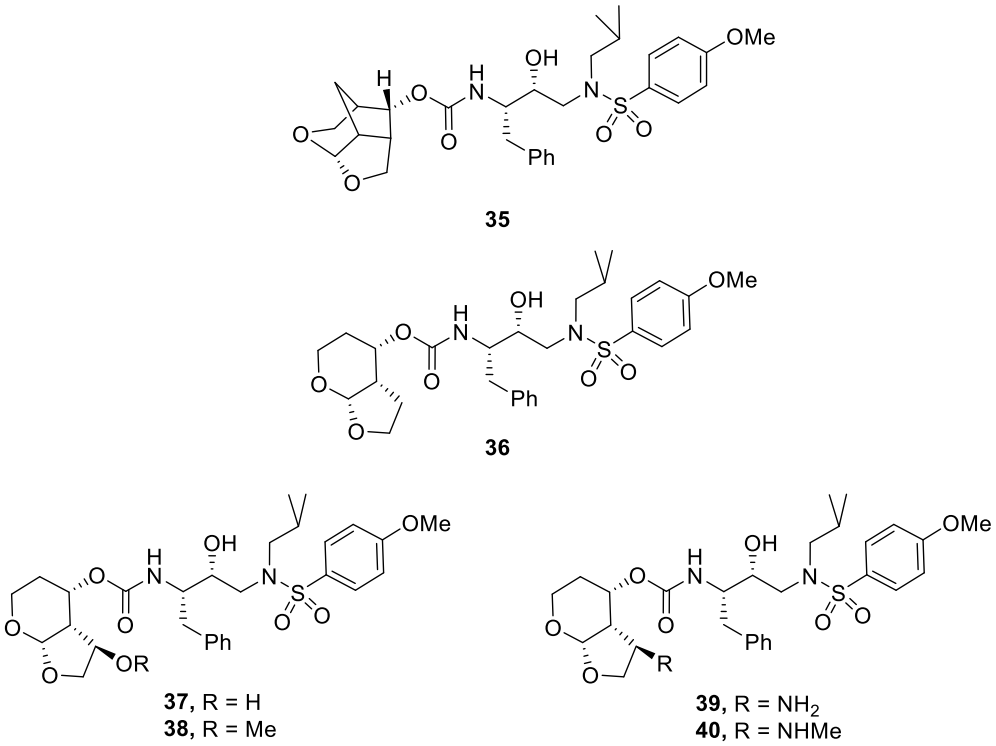



Figure 2.9 Structures of Previously Synthesized HIV PIs 35 – 40

Inhibitor **36**, which incorporates the tetrahydropyranyl-tetrahydrofuran (Tp-THF) ligand as the P2 ligand, showed even more improved $K_i$ value of 2.7 pM and $ID_{50}$ value of 0.5 nM.[52] Inhibitor **36** exhibited very high enzyme affinity and antiviral activity because its Tp-THF ring system has effectively increased the dihedral angle of the oxygen atoms of the P2 ligand and, therefore, resulted in stronger hydrogen bonding and van der Waal interactions with the active site backbone NHs atoms in the S2 subsite when compared to DRV.[52]

To investigate the effect of substituents at the C5 position of the Tp-THF ligand, inhibitors **37**-**40** were developed in 2015.[53] Inhibitor **37** with the C5 hydroxyl substituent in the Tp-THF ligand showed enzymatic Ki value of 60 pM and antiviral $IC_{50}$ value of 3.15 nM.[53] Inhibitor **38** with the C5 methoxy group, on the other hand, displayed excellent enzyme inhibitory and antiviral activities ($K_i$ = 4.5 pM, $IC_{50}$ = 0.2 nM).[53] A robust hydrogen bonding interaction between the C5 methoxy oxygen atom and the amide NH of Gly48 in the flap region was observed by X-ray crystallographic study (Figure 2.10) and this molecular interaction was the main reason for the excellent potency.[53] Inhibitor **39**, which contains the amine-substituted derivative as the P2 ligand, showed mediocre Ki value of 21.4 nM and $IC_{50}$ value of 520 nM.[53] Inhibitor **40** with the C5 alkylamine substituent demonstrated excellent biological activities (Ki = 8 pM, $IC_{50}$ = 2.7 nM), but was less potent than inhibitor **38** with the C5 alkoxy substituent.[53]

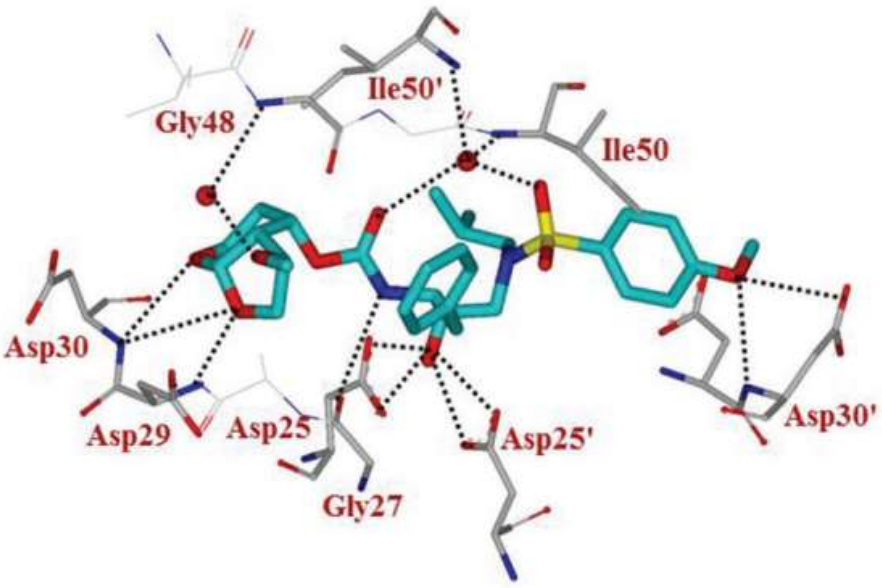



Figure 2.10 X-Ray Structure of Inhibitor 38-Bound to Wild-Type HIV-1 PR (PDB 5DGU). Dotted Lines Represent Strong Hydrogen Bonding Interactions. Adopted from the literature.[55]

### 2.2.2 Design of HIV-1 Protease Inhibitors Incorporating a Trisubstituted Chiral Tetrahydrofuran as P2 Ligand.

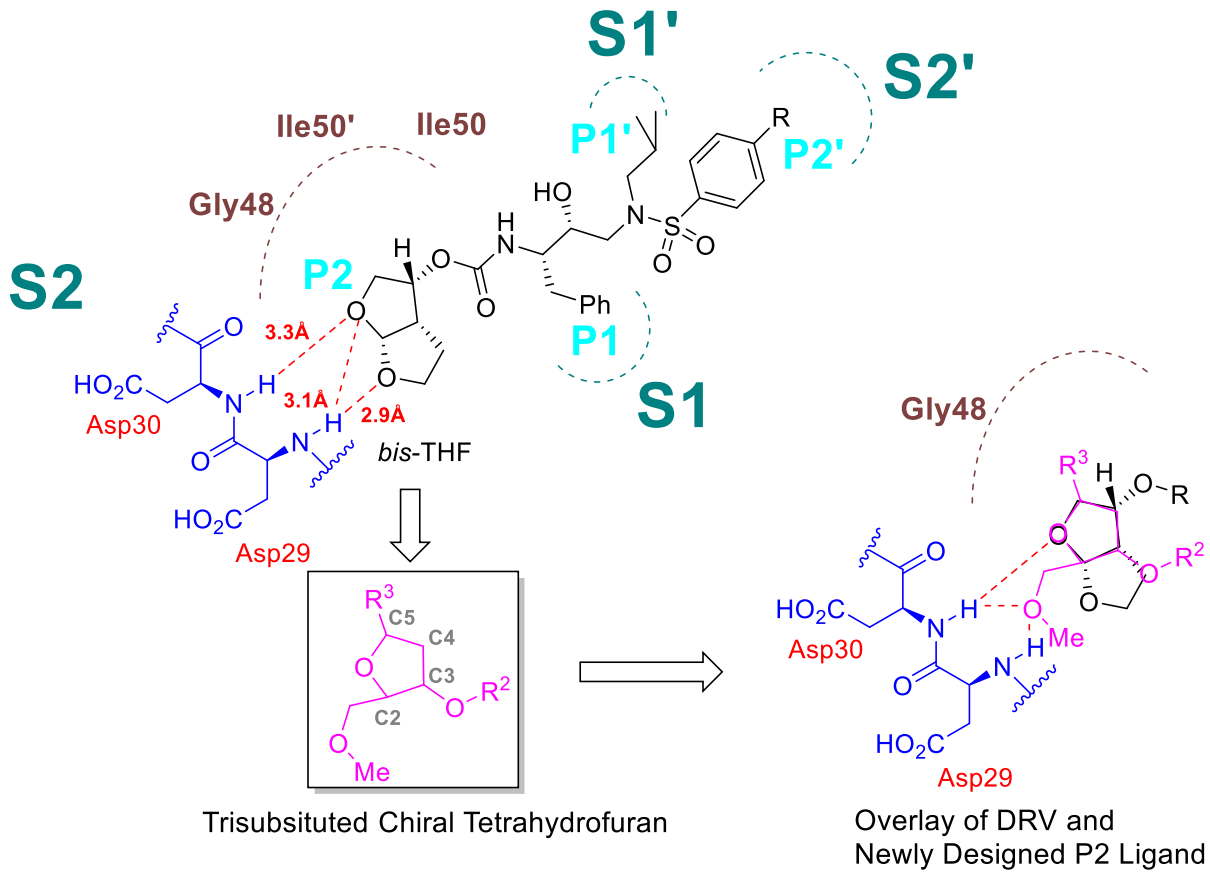



Figure 2.11 Hydrogen Bonding Interactions of DRV with S2 Region of Wild-type HIV-PR and Newly Designed Trisubstituted Chiral Tetrahydrofuran (*tc*-THF) as P2-ligand. Estimated Overlay of DRV (Black) and *tc*-THF P2 Ligand (Pink) is also shown.

The important molecular interactions between DRV and wild-type HIV PR is well depicted in Figure 2.11. Furthermore, the X-ray crystal structure of inhibitor **38**-bound HIV-PR (Figure 2.10) revealed that the strong hydrogen bonding interaction between the C5 methoxy atom of the Tp-THF P2 ligand and the amide NH of Gly48 residue in the flap region is responsible for the impressive biological results.[53] Based on the design of DRV and previously synthesized HIV PIs, we decided to develop a novel class of HIV PIs with highly stereospecific and much simpler P2 ligand structure.

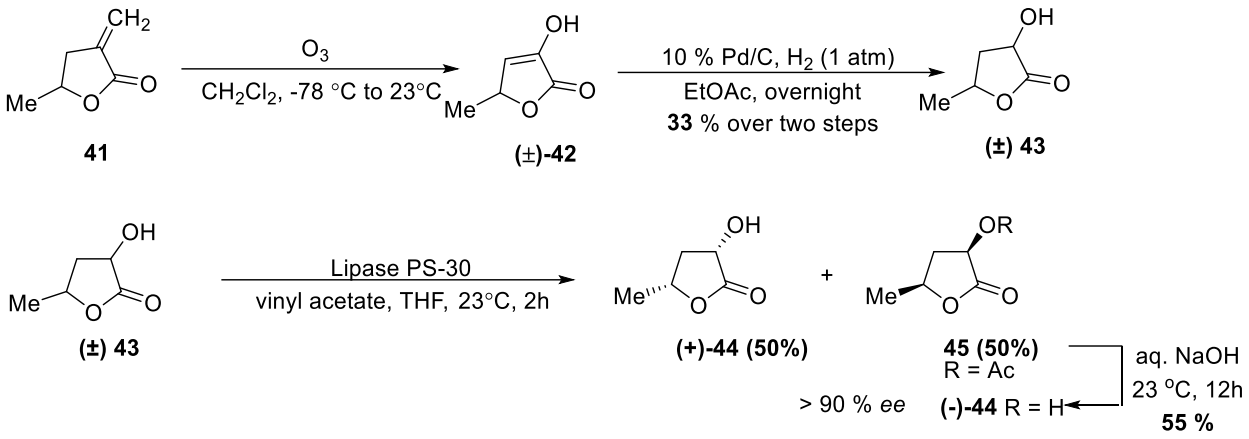
We hypothesized that incorporating trisubstituted-chiral-tetrahydrofuran (*tc*-THF) moiety as P2 ligand would significantly improve the polar interactions with both Asp29 and Asp30 active

site backbone atoms as shown on the bottom right corner of Figure 2.11. We also envisioned that installing the $R^3$ alkyl substituent at the C5 position would demonstrate enhanced hydrophobic contact with the S2 region of the active site. This additional lipophilicity would allow this novel class of inhibitors to exhibit good central nervous system (CNS) penetration properties. Moreover, we wanted to investigate whether installing the methoxy substituent on the C2 position of *tc*-THF P2-ligand would form any molecular interaction with the residues in flap region, particularly Gly48, like inhibitor **38**.

To further optimize the hydrogen bonding interactions as well as hydrophobic interactions within the HIV PR active site, several *tc*-THF P2 ligands with various stereochemistries at the C2, C3, and C5 positions were developed. Additionally, to study the biological profile of our newly designed P2 ligands, the synthesized P2 ligands were combined with the known isosteres as P2' ligand to furnish numerous novel HIV PIs. The novel PIs were tested under both *in vivo* and *in vitro* conditions according to the literature procedures and the results will be discussed in the following sections.

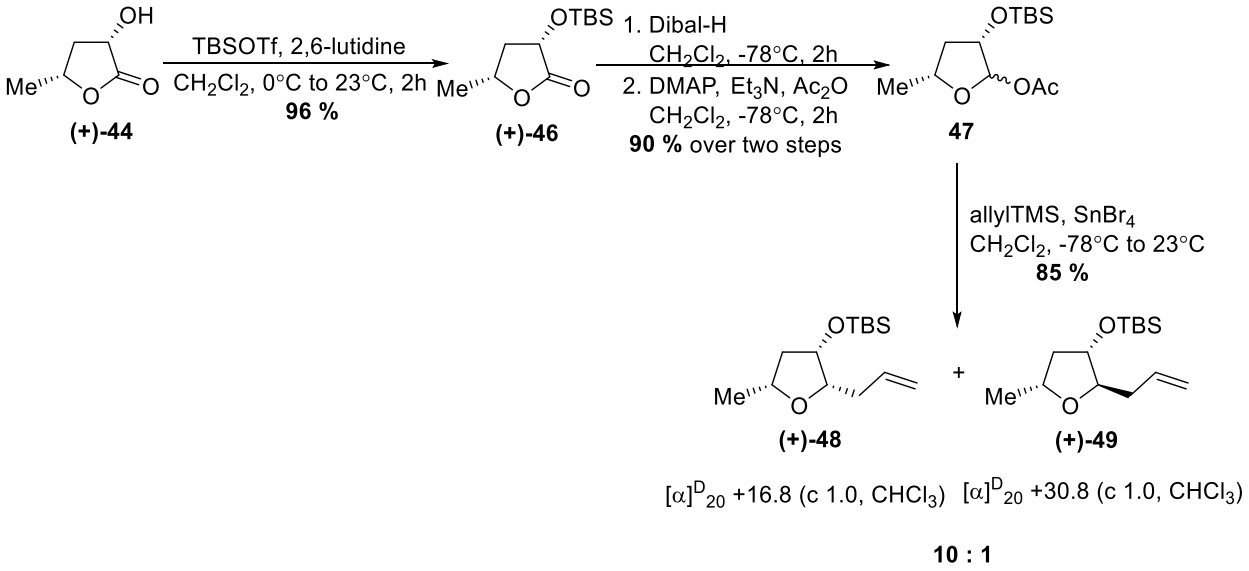
### **2.2.3** Synthesis of Novel *tc*-THF containing PIs **60**-**65**

Developing a stereospecific inhibitor is critical to understanding the inhibitor's binding ability to the enzyme. Therefore, a concise and efficient enantioselective route to prepare various trisubstituted chiral tetrahydrofuran moieties was devised. Starting from commercially available racemic α-methylene-γ-valerolactone **41,** ozonolysis followed by hydrogenation of unsaturated lactone intermediate **42** using 10% Palladium on Carbon in ethyl acetate at 1 atmospheric hydrogen pressure afforded racemic ketolactone **43** in 33% yield over two steps.[54] Enzymatic resolution of racemic ketolactone **43** with amino-lipase (PS-30) in a mixture of vinyl acetate and THF at 23$^o$C for 2h provided optically active alcohol **(+)-44** and acetate derivative **45** in 50% yield with enantiomeric excess over 90%.[55] Acetate derivative **45** was treated with aqueous sodium hydroxide at 23$^o$C for 12h to furnish optically active lactone (-)-**44** in 55% yield. Optically active alcohol **(+)-44** and **(-)-44** were prepared in multigram scale from the starting material following the described procedure above.[54,55]




Scheme 2.2 Synthesis of Optically Active Lactones (+)-44 and (-)-44

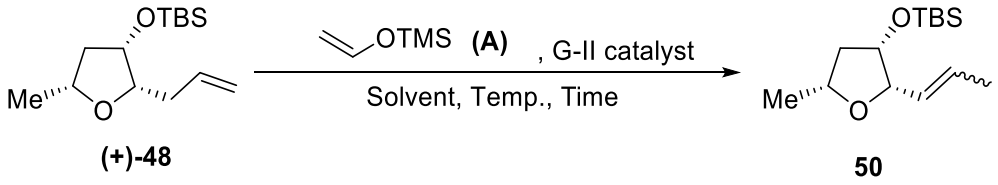
As depicted in Scheme 2.3, the hydroxyl group of optically active lactone **(+)-44** was successfully protected as a TBS-ether in 96% yield using TBSOTf and 2,6-lutidine in $CH_2Cl_2$. DIBAL-H reduction of TBS-protected lactone **(+)-46** in $CH_2Cl_2$ at -78ºC gave a mixture of intermediate lactols, which was immediately treated with acetic anhydride, triethylamine, and a catalytic amount of DMAP at -78ºC for 2h to afford acetate **47** in 90% yield over two steps. The allylation reaction of acetate **47** with allyltrimethylsilane in the presence of $SnBr_4$ provided a 10:1 mixture of allyl derivatives **(+)-48** and **(+)-49** in 85% yield.[55]




Scheme 2.3 Diastereoselective Synthesis of Allyl Derivative (+)-48

To migrate the terminal olefin of allyl derivative **(+)-48**, various conditions were tested with the second-generation Grubbs (G-II) catalyst. Following the work of Hanesian et al., terminal olefin-isomerization reaction was examined using 20 mol % of the G-II catalyst in methanol at 60°C for 4h.[56] This reaction provided olefin **50** in 67% yield (Table 1, Trial 1). Inspired by the work of Nishida and co-workers in 2002, 10 equivalents of vinyloxy-trimethylsilane (**A**) were employed in the presence of the G-II catalyst to further promote the terminal olefin-isomerization reaction (Table 2.1, Trial 2-6).[57] Among these conditions, the use of 10 equivalent of **A** with 10 mol % of the G-II catalyst in $CH_2Cl_2$ (0.0125 M) at 110°C for 24h in a sealed tube provided the best result with 95% yield (Table 2.1, Trial 3). Olefin **50** was obtained by following this optimized reaction condition.

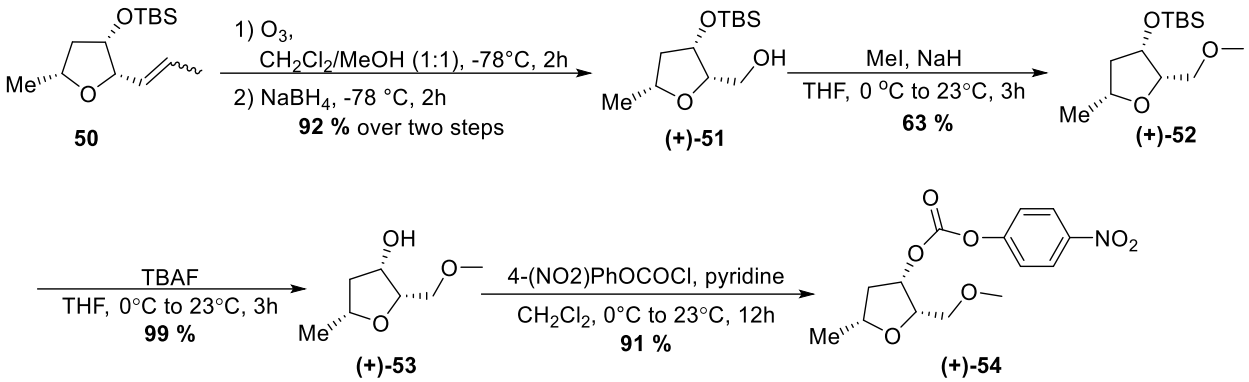
Table 2.1 Optimization of Terminal Olefin Migration Reaction




**(+)-48** **50**

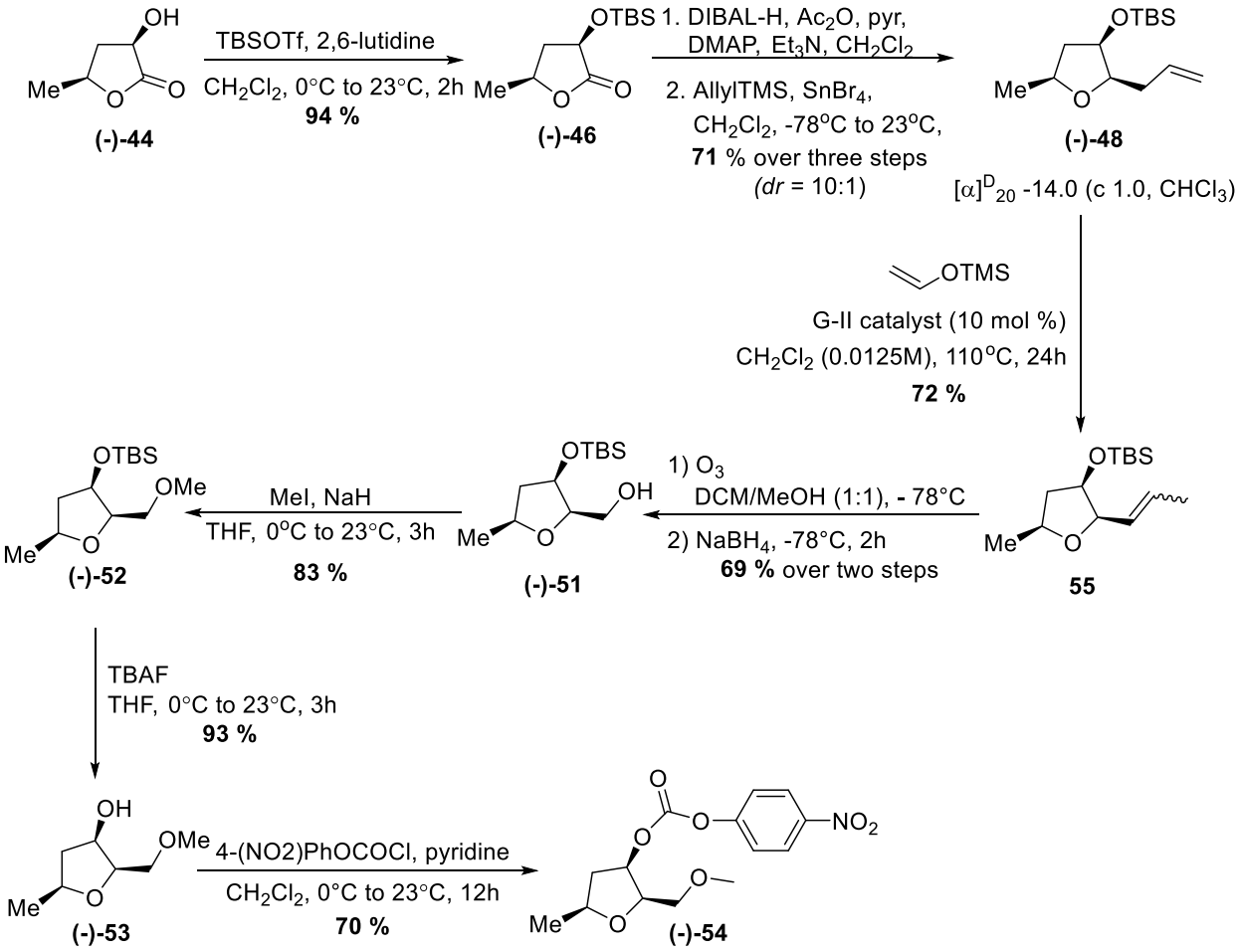
| Trial | A | G-II cat. | Solvent | [Solvent] | Temp. (°C) | Time | Yield (%) |
|---|---|---|---|---|---|---|---|
| **1** | --- | 20 mol % | MeOH | 0.075 M | 60 | 4 h | 67 |
| **2** | 10 eq. | 5 mol % | $CH_2Cl_2$ | 0.0125 M | 60 | 24 h | 61 |
| **3** | 10 eq. | 10 mol % | $CH_2Cl_2$ | 0.0125 M | 110 | 24 h | 95 |
| **4** | 10 eq. | 15 mol % | $CH_2Cl_2$ | 0.0125 M | 60 | 72 h | 54 |
| **5** | 10 eq. | 5 mol % | Toluene | 0.025 M | 110 | 24 h | 60 |
| **6** | 10 eq. | 10 mol % | Toluene | 0.0125 M | 110 | 24 h | 47 |

Olefin **50** was then subjected to ozonolysis in a 1:1 mixture of $CH_2Cl_2$ and methanol at -78°C for 2h, followed by $NaBH_4$ reduction at -78°C for additional 2h in one-pot to give alcohol **(+)-51** in 92% yield over two steps. Alcohol **(+)-51** was then treated with sodium hydride and iodomethane in THF at 0°C to 23°C for 3h to give methyl ether **(+)-52** in 63% yield. TBAF deprotection of methyl ether **(+)-52** provided alcohol **(+)-53** in almost quantitative yield. Activation of the hydroxyl group of alcohol **(+)-53** was achieved by treating it with 4-nitrophenyl chloroformate in the presence of pyridine in $CH_2Cl_2$ at 0°C to 23°C for 12h. This reaction afforded activated carbonate **(+)-54** in 91% yield.



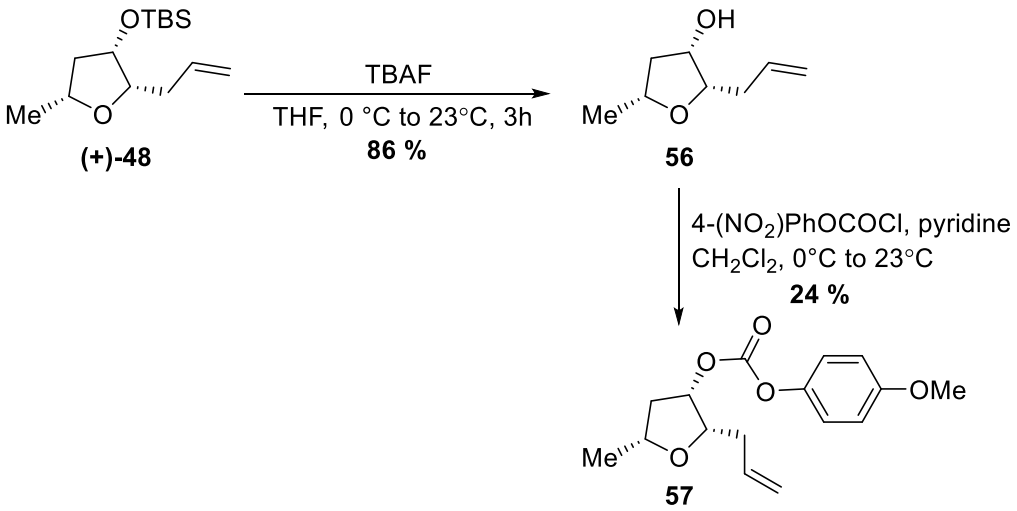

Scheme 2.4 Synthesis of Activated Carbonate **(+)**-54

Synthesis of activated carbonate **(-)-54**, which is the enantiomer of activated carbonate **(+)-54**, is shown in Scheme 2.5. Starting with optically active lactone (**-)-44,** TBS-protected lactone (**-)-46** was obtained in 94% yield using TBSOTf and 2,6-lutidine in $CH_2Cl_2$ at 0°C to 23°C for 2h. DIBAL-H reduction of TBS-protected lactone (**-)-46**, followed by the acetylation and Lewis acid-catalyzed allylation reaction afforded allyl derivative (**-)-48** in 71% yield over three steps.[55] Subsequently, allyl derivative (**-)-48** was subjected to the optimized terminal olefin-isomerization condition (Table 2.1, Trial 3) to give olefin **55** in 72% yield. Ozonolysis of olefin **55** in a 1:1 mixture of $CH_2Cl_2$ and methanol at -78°C for 2h, followed by sodium borohydride reduction in one-pot for 2h provided alcohol **(-)-51** in 69% over two steps. Methylation of the primary alcohol of compound **(-)-51** was accomplished by employing sodium hydride and iodomethane in THF at 0°C to 23°C for 2h. This reaction afforded methyl ether **(-)-52** in 83% yield. TBAF deprotection of methyl ether **(-)-52** and subsequent activation of the resulting alcohol **(-)-53** by using 4-nitrophenyl chloroformate and pyridine in $CH_2Cl_2$ at 23°C for 12h offered activated carbonate **(-)-54** in 65% yield over two steps.




Scheme 2.5 Synthesis of Activated Carbonate **(-)**-54

To study the binding affinity of C2 allyl substituent incorporating P2-ligand, activated carbonate **57** was prepared (Scheme 2.6). Treatment of allyl derivative **(+)-48** with TBAF in THF at 0°C to 23°C for 3h provided alcohol **56** in 86% yield. Activation of alcohol **56** was achieved by the coupling reaction with 4-nitrophenyl chloroformate in the presence of pyridine in $CH_2Cl_2$ at 0°C to 23°C for 12h. This reaction furnished activated carbonate **57** in 24% yield (Scheme 2.6).




Scheme 2.6 Synthesis of Activated Carbonate 57

As depicted in Scheme 2.7, inhibitors **60**, **62**, and **64** were obtained by the coupling reaction of corresponding activated carbonates **(+)-54**, **(-)-54**, and **57** with a known 4-methoxybenzenesulfonamide isostere **58** in the presence of DIPEA in $CH_3CN$ at $0^oC$ to $23^oC$. In a similar fashion, inhibitors **61**, **63**, and **65** were furnished by the coupling reaction of corresponding activated carbonates **(+)-54**, **(-)-54**, and **57** with a known 4-aminobenzenesulfonamide isostere **59**. The reaction yield for each coupling reaction is shown in Scheme 2.7.

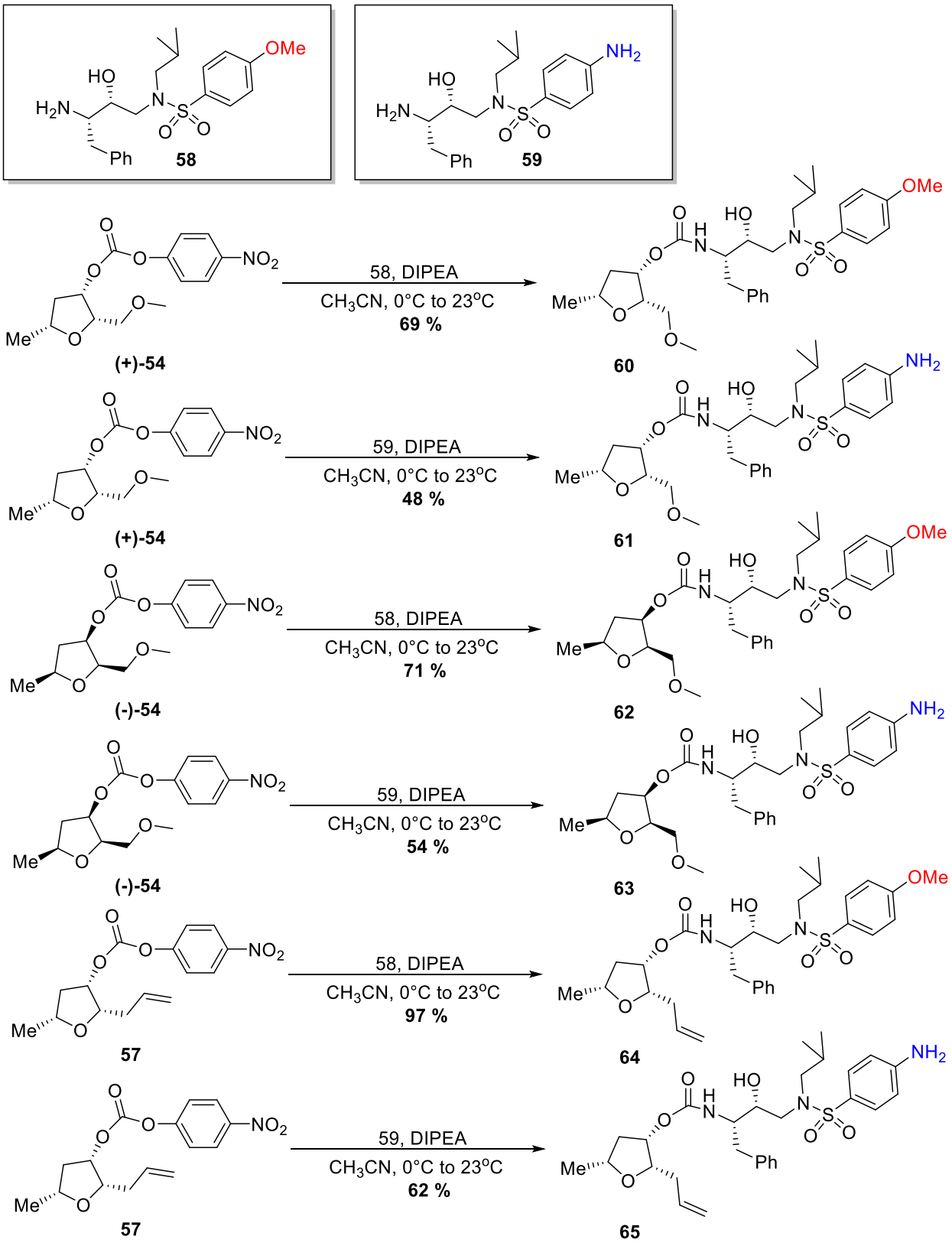
The enzymatic and cellular data of the synthesized PIs are summarized in Table 2.2. The biological results of the PIs were examined according to the literature procedure.[43] From the obtained results, two general trends were observed. Firstly, inhibitors containing 4-methoxybenzenesulfonamide as P2'-ligand (**60, 62,** and **64**) showed significantly better enzymatic inhibitory activities ($K_i$) compared to the ones incorporating 4-aminobenzenesulfonamide as P2'-ligand (**61**, **63**, and **65**) as shown in Table 2.2. Secondly, every synthesized PI exhibited very poor antiviral activity with $IC_{50}$ value > 1000 nM (Table 2.2).

Based upon the biological results collected from the synthesized HIV PIs, there are significant discrepancies between the observed enzyme inhibitory $K_i$ values and antiviral $IC_{50}$ values. To rationalize these discrepancies, a calculated partition coefficient (clogP) of the synthesized inhibitors were obtained. The calculated partition coefficient shows the intrinsic lipophilicity of a compound, with a higher clogP value indicating greater lipophilicity/lower hydrophilicity and vice versa. According to Lipinski's rule of five, most drug-like molecules with clogP values greater than 5 are likely to have poor absorption or cell membrane permeability due

to their strong hydrophobicity.[58] Therefore, the analysis of the synthesized inhibitors' clogP values would help to explain the observed large differences between the $K_i$ and $IC_{50}$ values of the inhibitors.

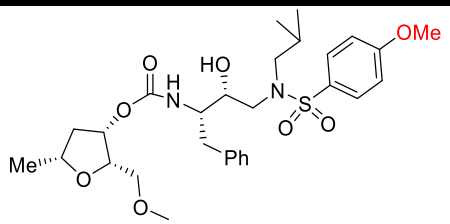
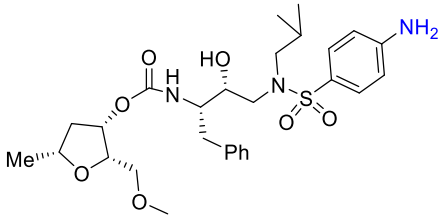
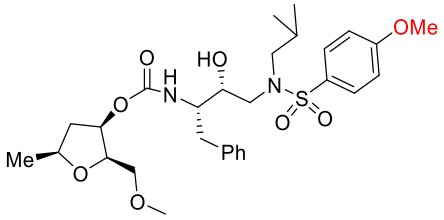
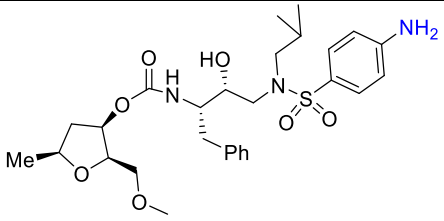
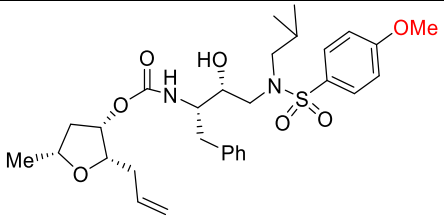
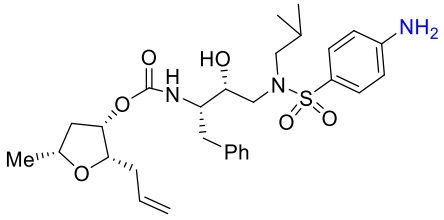
The clogP value of the six synthesized PIs was measured and the results are summarized in Table 2.2. While the clogP values never exceeded 5, most of them were very close to 5 (Table 2.2). Even the inhibitors with the lowest clogP values (**61** and **63**) were very lipophilic when compared to DRV's clogP value of 2.33.[58] Inhibitor **65** even depicted clogP value of 4.90, which is only 0.1 value away from 5 (Table 2.2). Based upon these measured clogP values, it is plausible to conclude that the six synthesized PIs are generally too lipophilic to pass through lipid cell membrane to reach the target HIV-1 enzyme, causing inappreciable antiviral $IC_{50}$ value > 1000 nM in all cases.

Among the six synthesized PIs, inhibitor **60**, which incorporates 2*S*,3*S*,5*R*-substituted-THF as P2-ligand and 4-methoxybenzenesulfonamide as P2'-ligand, showed the best *in vitro* result with enzyme inhibitory $K_i$ value of 0.28 nM (Table 2.2, Entry 1). Inhibitor **64**, which incorporates allyl substituent containing THF moiety as P2-ligand and 4-methoxybenzenesulfonamide as P2'-ligand, also displayed good enzyme inhibitory $K_i$ value of 0.4 nM (Table 2.2, Entry 5).

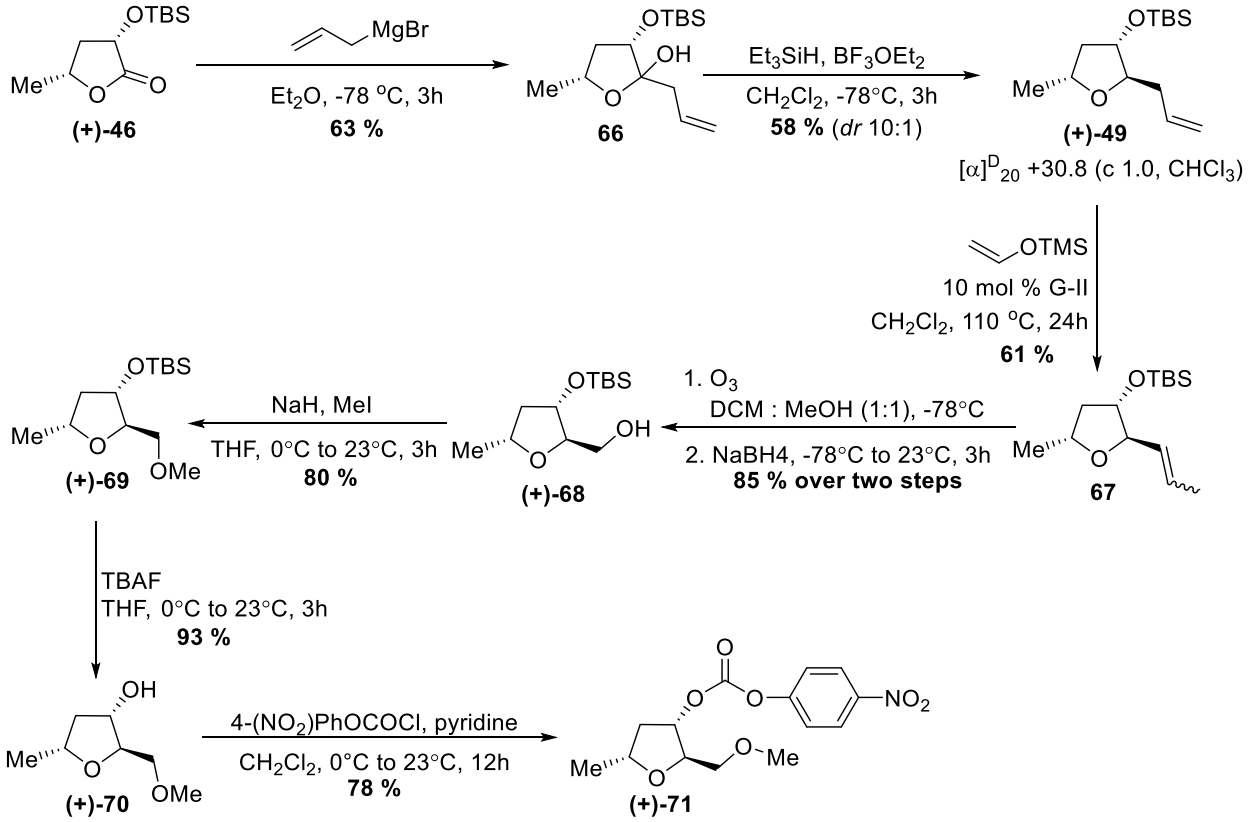



Scheme 2.7 Synthesis of Inhibitors 60-65

Table 2.2 Enzymatic and Cellular Data of Protease Inhibitors 60-65

| Entry | Inhibitor | $K_i$ (nM) | $IC_{50}$ (nM) | clogP |
|---|---|---|---|---|
| 1 |  **60** | 0.28 | >1000 | 4.79 |
| 2 |  **61** | 88 | >1000 | 3.88 |
| 3 |  **62** | 1.2 | >1000 | 4.78 |
| 4 |  **63** | 35.3 | >1000 | 3.88 |
| 5 |  **64** | 0.4 | >1000 | 4.44 |
| 6 |  **65** | 26.3 | >1000 | 4.90 |

### 2.2.4 Synthesis of Novel *tc*-THF containing PIs **76-80**

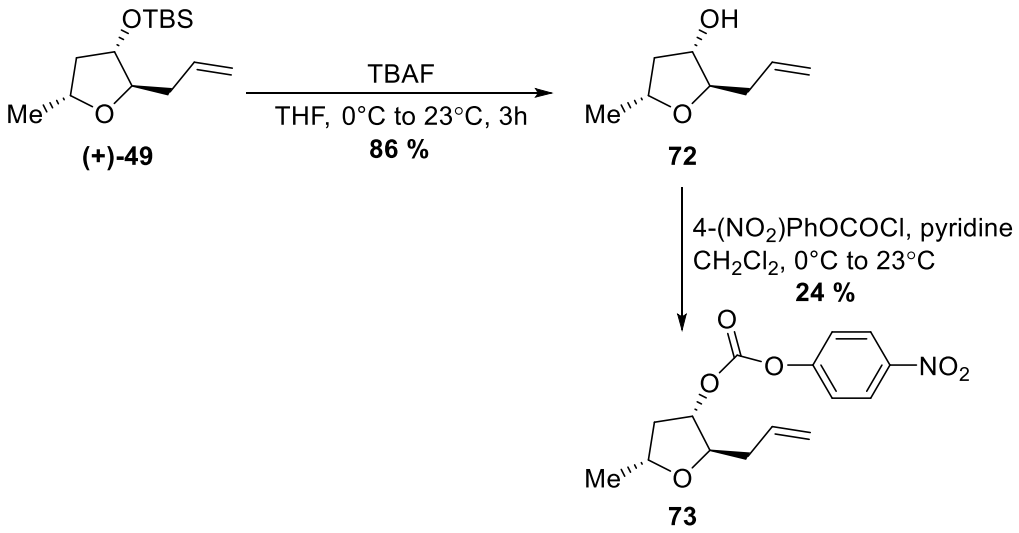



Scheme 2.8 Synthesis of Activated Carbonate **(+)**-71

To investigate the effect of changing the stereochemistry of the methoxy substituent at the C2 position on the inhibitor's binding affinity to HIV PR, a new synthetic route was devised and activated carbonate **(+)-71** was prepared from TBS-protected lactone **(+)-46** over eight steps (Scheme 2.8). Treatment of compound **(+)-46** with allylmagnesium bromide in $Et_2O$ at -78ºC for 3h afforded hemiketal intermediate **66** in 63% yield. Subsequently, hemiketal intermediate **66** was reduced to allyl derivative **(+)-49** in 58% yield (*dr* 10:1, measured by $^1H$ NMR analysis) by using triethylsilane in the presence of $BF_3OEt_2$ in $CH_2Cl_2$ at -78ºC for 3h.[54] Using the optimized terminal olefin-isomerization procedure, allyl derivative **(+)-49** was successfully converted to olefin **67** in 61% yield. Ozonolysis of olefin **67**, followed by sodium borohydride reduction of the aldehyde intermediate at -78ºC to 23ºC for 3h in one-pot gave alcohol **(+)-68** in 85% yield over two steps. Methylation of alcohol **(+)-68** with sodium hydride and iodomethane in THF at 0ºC to 23ºC for 3h afforded methyl ether **(+)-69** in 80% yield. TBAF deprotection of methyl ether **(+)-69** in THF at

0ºC to 23ºC for 3h then furnished alcohol **(+)-70** in 93% yield. Coupling reaction of alcohol **(+)-70** with 4-nitrophenyl chloroformate in the presence of pyridine in $CH_2Cl_2$ at 0ºC to 23ºC for 12h gave activated carbonate **(+)-71** in 78% yield.

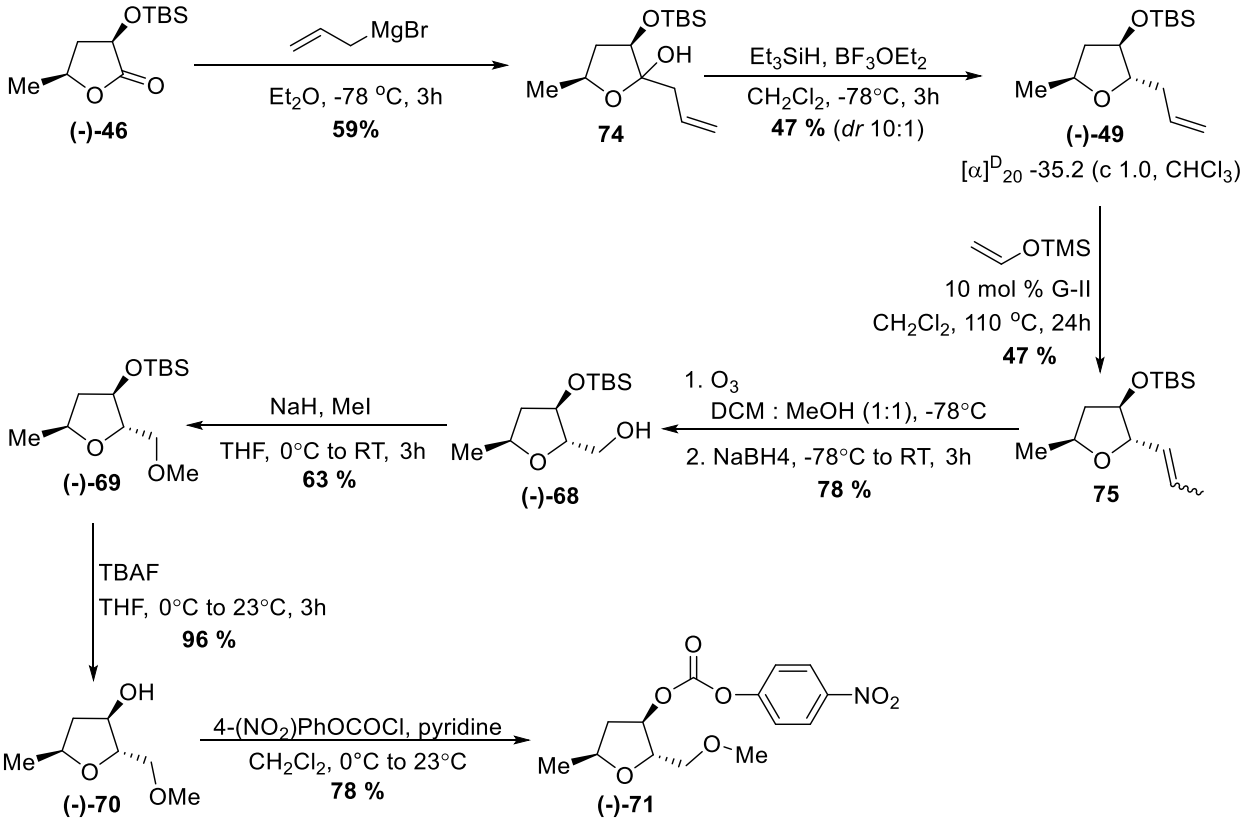
Since the enzymatic inhibitory activity of allyl substituent containing inhibitor **64** appeared promising (Table 2.2, Entry 5), we wanted to examine whether changing the stereochemistry of allyl substituent at the C2 position will improve the inhibitor's biological potency. Activated carbonate **73** was, therefore, prepared as shown in Scheme 2.9. TBAF deprotection of allyl derivative **(+)-49**, which was already prepared from Scheme 2.8, in THF at 0ºC to 23ºC for 3h provided alcohol **72** in 86% yield. Activation of alcohol **72** was achieved in 24% by treating alcohol **72** with 4-nitrophenyl chloroformate and pyridine in $CH_2Cl_2$ at 0ºC to 23ºC for 12h.




Scheme 2.9 Synthesis of Activated Carbonate 73

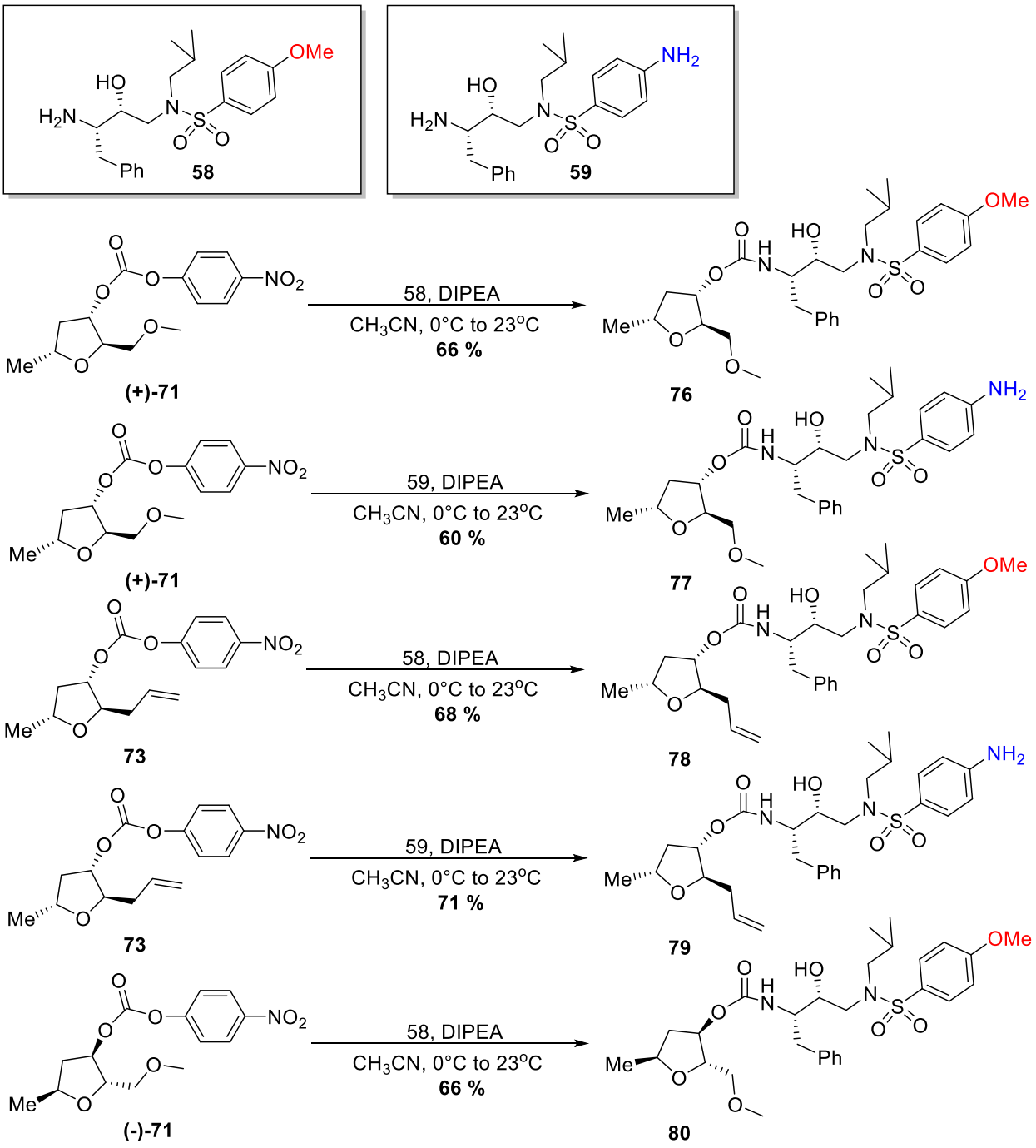
As depicted in Scheme 2.10, activated carbonate **(-)-71**, which is the enantiomer of activated carbonate **(+)-71**, was also synthesized following the procedure described above. Grignard reaction of TBS-protected lactone **(-)-46** with allylmagnesium bromide in $Et_2O$ at -78ºC for 3h, followed by triethylsilane reduction of the resulting hemiketal intermediate **74** in the presence of $BF_3OEt_2$ in $CH_2Cl_2$ at -78ºC for 3h furnished allyl derivative **(-)-49** in 28% yield over two steps (*dr* 10:1, measured by $^1H$ NMR analysis).[54] Using the optimized terminal olefin-isomerization procedure, allyl derivative **(-)-49** was successfully converted to olefin **75** in 47% yield. Ozonolysis of olefin **75**, followed by sodium borohydride reduction of the aldehyde

intermediate at -78ºC to 23ºC for 3h in one-pot gave alcohol **(-)-68** in 78% yield over two steps. Treatment of alcohol **(-)-68** with sodium hydride and iodomethane in THF at 0ºC to 23ºC for 3h yielded methyl ether **(-)-69** in 63% yield. TBAF deprotection of methyl ether **(-)-69** in THF at 0ºC to 23ºC for 3h gave alcohol **(-)-70** in 96% yield. Activation of alcohol **(-)-70** by employing 4-nitrophenyl chloroformate and pyridine in $CH_2Cl_2$ at 0ºC to 23ºC for 12h provided activated carbonate **(-)-71** in 78% yield.




Scheme 2.10 Synthesis of Activated Carbonate (-)-71

As shown in Scheme 2.11, inhibitors **76**, **78**, and **80** were prepared by the coupling reaction of corresponding activated carbonates **(+)-71**, **(-)-71**, and **73** with 4-methoxybenzenesulfonamide isostere **58** in the presence of DIPEA in $CH_3CN$ at 0ºC to 23ºC. In a similar fashion, inhibitors **77** and **79** were obtained by the coupling reaction of corresponding activated carbonates **(+)-71** and **73** with 4-aminobenzenesulfonamide isostere **59**. The reaction yield for each coupling reaction is demonstrated in Scheme 2.11.



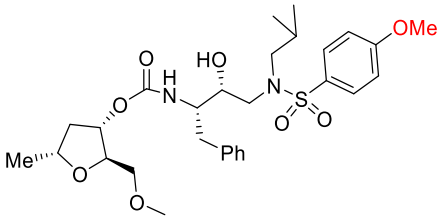
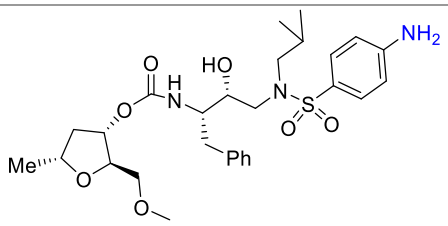
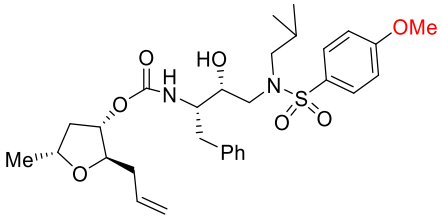
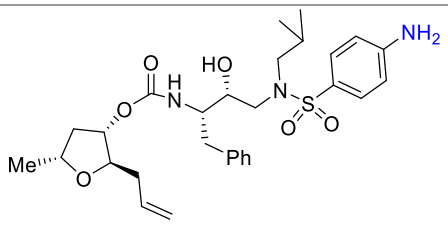
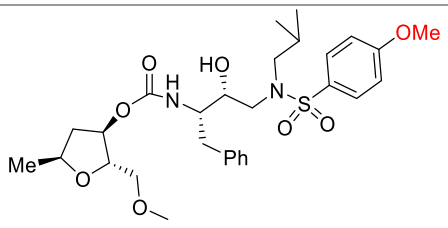

Scheme 2.11 Synthesis of Inhibitors 76-80

The biological results and clogP values of inhibitors **76** to **80** are summarized in Table 2.3. Just like the previous results, every synthesized PI exhibited inappreciable antiviral activity ($IC_{50}$ > 1000 nM), presumably, due to its lack of membrane permeability (Table 2.3). Additionally, the

inhibitors incorporating isostere **59** as P2' ligand (**76** and **78**) displayed significantly better Ki values than the ones with 4- isostere **58** as P2' ligand (**77** and **79**) as shown in Table 2.3.

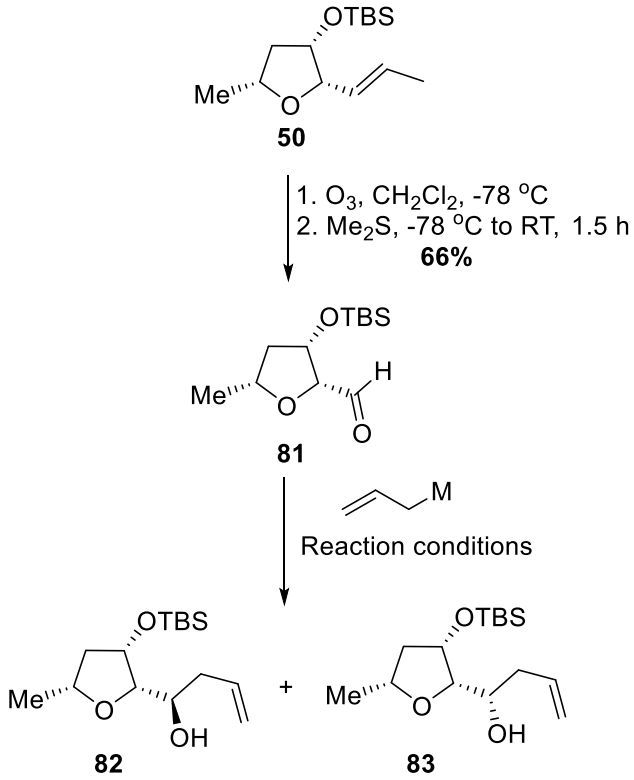
Among the newly synthesized PIs, inhibitor **76** with 2*R*,3*S*,5*R*-substituted-THF as P2 ligand and **58** as P2' ligand exhibited the best *in vitro* result with $K_i$ value of 49 pM (Table 2.3, Entry 1). In comparison to inhibitor **80** ($K_i$ = 2.6 nM)**,** inhibitor **76** exhibited approximately 50-fold greater *in vitro* potency than its enantiomer (Table 2.3, Entry 5). Moreover, when compared to inhibitor **60**, which incorporates 2*S*,3*S*,5*R*-substituted-THF as P2 ligand and isostere **58** as P2' ligand (Table 2.2, Entry 1), inhibitor **76** showed approximately 6-fold greater *in vitro* potency than its diastereomer. Based upon these results, it is plausible to conclude that 2*R* stereochemistry of the methoxy substituent is vital to the hydrogen bond interactions of the P2 ligand with the backbone amide NH in the enzyme's S2 subsite. Both inhibitor **78** and **79** (Table 2.3, Entry 3 and 4), which contain allyl substituent as P2 ligand, failed to show significantly improved enzymatic inhibitory activities when compared to their corresponding diastereomers, **64** and **65** (Table 2.2, Entry 5 and 6).

Table 2.3 Enzymatic and Cellular Data for Protease Inhibitors 76-80

| Entry | Inhibitor | $K_i$ (nM) | $IC_{50}$ (nM) | clogP |
|---|---|---|---|---|
| 1 |  **76** | 0.049 | >1000 | 4.78 |
| 2 |  **77** | 9.4 | >1000 | 3.88 |
| 3 |  **78** | 0.78 | >1000 | 5.80 |
| 4 |  **79** | 4.8 | >1000 | 4.90 |
| 5 |  **80** | 2.6 | >1000 | 4.78 |

### 2.2.5 Synthesis of Novel Bis-THF Containing PIs 92 and 93

Table 2.4 Synthesis of Optically Active Allyl Derivatives 82 and 83

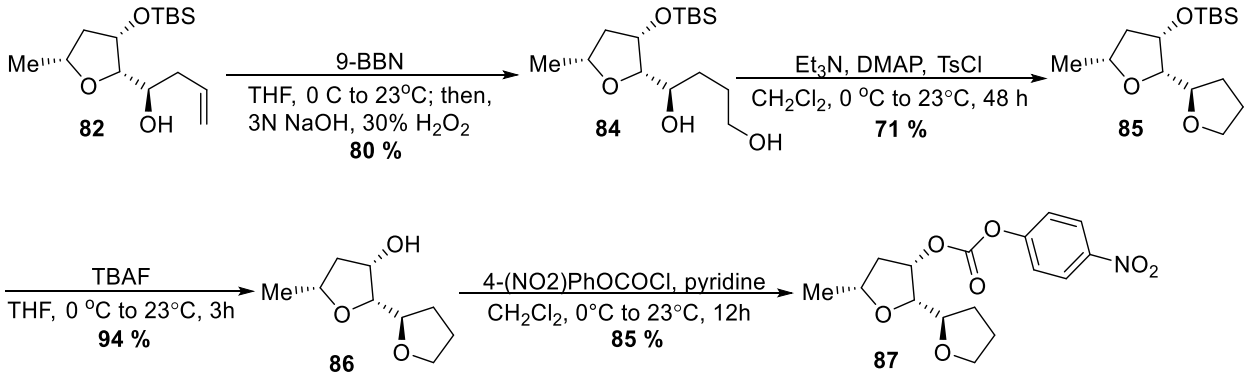



| Trial | M | Lewis Acid [equiv] | Reaction conditions | Yield (%) | *dr* (**82:83** ratio) |
|---|---|---|---|---|---|
| 1 | $SiMe_3$ | $BF_3OEt_2$ [3] | $CH_2Cl_2$, -78°C, 4h | 78 | 4.2:1 |
| 2 | $SnBu_3$ | $BF_3OEt_2$ [3] | $CH_2Cl_2$, 23°C, 4h | 98 | 4.3:1 |
| 3 | $SnBu_3$ | $MgBr_2OEt_2$ [3] | $CH_2Cl_2$, 23°C, 4h | 75 | 1:1.3 |
| 4 | MgBr | --- | $Et_2O$, -78°C, 3h | 59 | 1:1.2 |

Inspired by the design of *bis*-THF ligand in DRV and cyclic ether template in polyether antibiotic monensin A,[6,59] we developed a concise and efficient synthetic route to a new class of *bis*-THF ligand. Starting with olefin **50**, aldehyde **81** was prepared in 66% yield after ozonolysis. Aldehyde **81** was then subjected to various reaction conditions to diastereoselectively prepare

alcohol **82** (Table 2.4). Among these conditions, treatment of aldehyde **81** with 3 equivalents of $BF_3OEt_2$ and allyltributylstannane in $CH_2Cl_2$ at 23ºC for 4h gave the best result.[60] This reaction provided a 4.3:1 mixture of alcohol **82** and **83** in 98% combined yield (Table 2.4, Entry 2). The diastereomeric ratios were determined by $^1H$ NMR analysis. When $MgBr_2$ $OEt_2$ was employed as a Lewis acid instead of $BF_3$ $OEt_2$, alcohol **83** was obtained as the major product, presumably due to magnesium chelation effect, in 75% combined yield with 1.3:1 *dr* (Table 2.4, Entry 3).[61] Similar diastereoselectivity was observed when aldehyde **81** was treated only with allylmagnesium bromide in $Et_2O$ at -78ºC for 3h. This reaction offered a 1.2:1 mixture of alcohol **83** and **82** in 59% combined yield (Table 2.4, Entry 4).

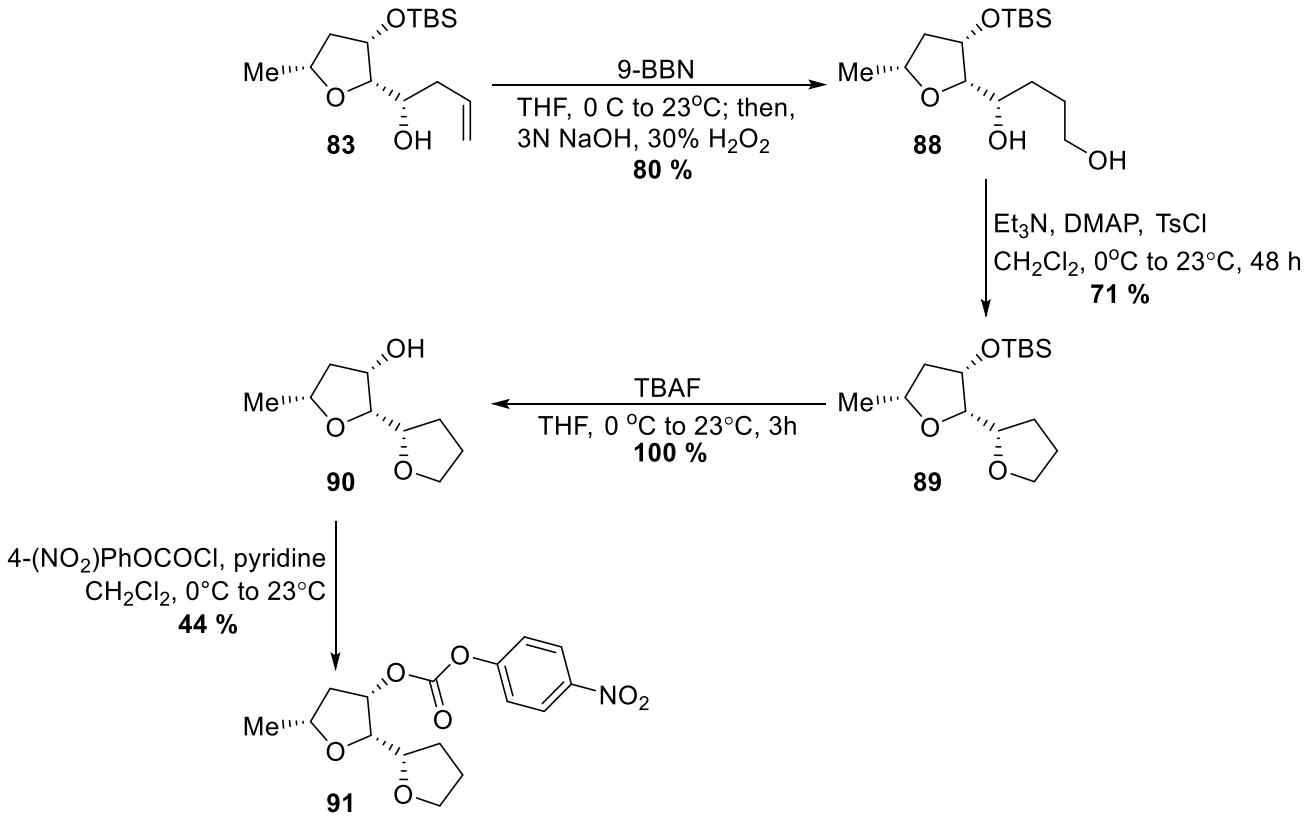
As depicted in Scheme 2.12**,** activated carbonated **87** was prepared from alcohol **82** over four steps. Hydroboration of alcohol **82** using 9-Borabicyclo[3.3.1]nonane (9-BBN) in THF at 0ºC to 23ºC for 6h followed by oxidation using 3N NaOH and 30% hydrogen peroxide at 23ºC for 3h afforded diol **84** in 80% yield.[62] Treatment of diol **84** with triethylamine, tosyl chloride, and catalytic amount of 4-DMAP successfully provided bicyclic ether **85** in 71% yield. TBAF deprotection of bicyclic ether **85** in THF at 0ºC to 23ºC for 3h gave alcohol **86** in 94% yield. Activation of alcohol **86** was achieved by employing 4-nitrophenylchloroformate and pyridine in $CH_2Cl_2$ at 0ºC to 23ºC for 12h. This reaction furnished activated carbonate **87** in 85% yield.




Scheme 2.12 Synthesis of Activated Carbonate 87

Following the same experimental procedure described above, activated carbonate **91** was prepared from alcohol **83** (Scheme 2.13). Hydroboration of alcohol **83** using 9-BBN and subsequent oxidation using 3N NaOH and 30% hydrogen peroxide provided diol **88** in 80% yield.[62] Cyclization of diol **88** using triethylamine, tosyl chloride, and catalytic amount of DMAP

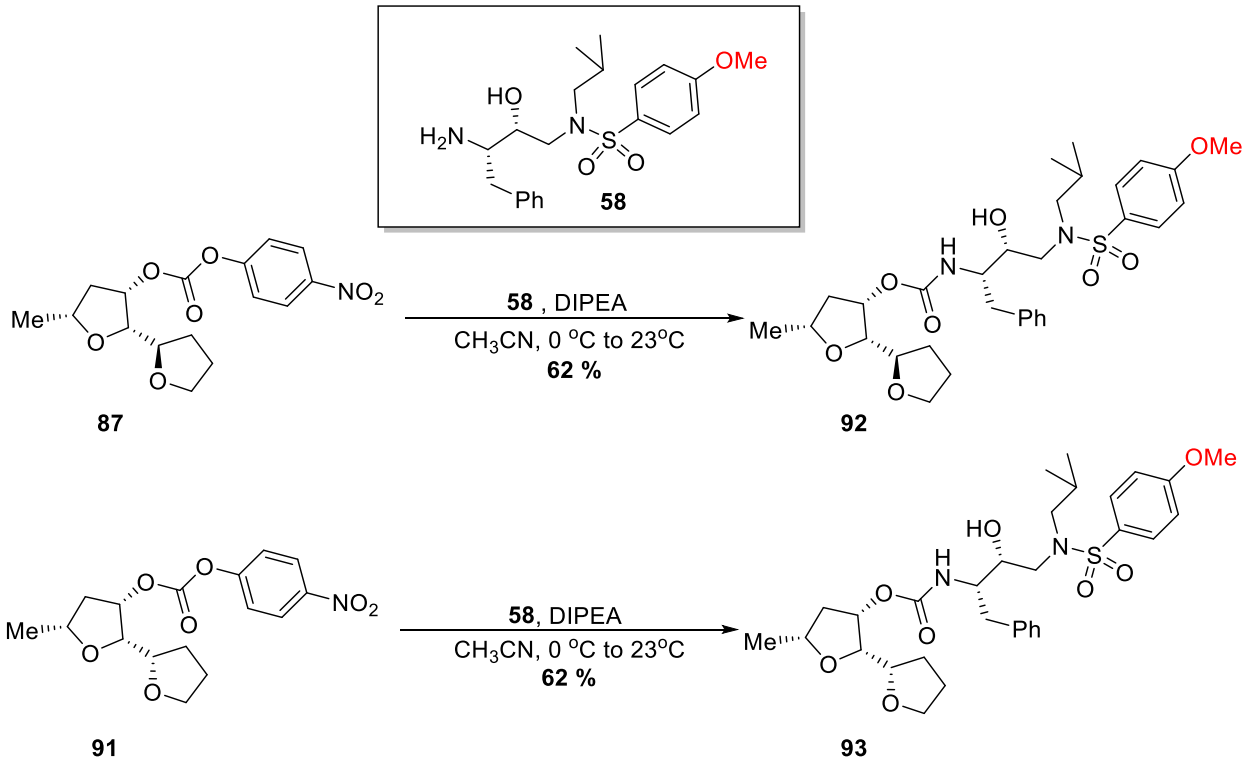
afforded bicyclic ether **89** in 71% yield. TBAF deprotection of compound **89** gave alcohol **90** in quantitative yield. Coupling reaction of alcohol **90** with 4-nitrophenylchloroformate in the presence of pyridine afforded activated carbonate **91** in 44% yield.




Scheme 2.13 Synthesis of Activated Carbonate 91

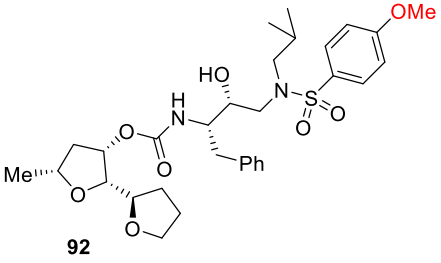
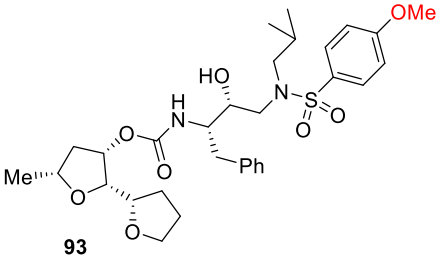
The synthesis of inhibitors **92** and **93** is shown in Scheme 2.14. Activated carbonates **87** and **88** were individually treated with 4-methoxybenzenesulfonamide isostere **58** and DIPEA in $CH_3CN$ at 0°C to 23°C to give inhibitors **92** and **93** in 62% yield, respectively.

The enzyme inhibitory Ki and antiviral $IC_{50}$ values of inhibitors **92** and **93** as well as their clogP values are summarized in Table 2.5. Unfortunately, both inhibitors **92** and **93** showed very poor antiviral activity ($IC_{50}$ > 1000nM) like the previous results, presumably due to their extremely high lipophilicity (clogP = 4.96, Table 2.5). From *in vitro* analysis, inhibitor **92** exhibited impressive $K_i$ value of 44.3 pM (Table 2.5, Entry 1), while inhibitor **93** displayed mediocre $K_i$ value of 30.8 nM (Table 2.5, Entry 2).




Scheme 2.14 Synthesis of Inhibitors 92 and 93.

Table 2.5 Enzymatic and Cellular Data for Protease Inhibitors 92 and 93

| Entry | Inhibitor | $K_i$ (nM) | $IC_{50}$ (nM) | clogP |
|---|---|---|---|---|
| 1 |  92 | 0.0443 | >1000 | 4.96 |
| 2 |  93 | 30.8 | >1000 | 4.96 |

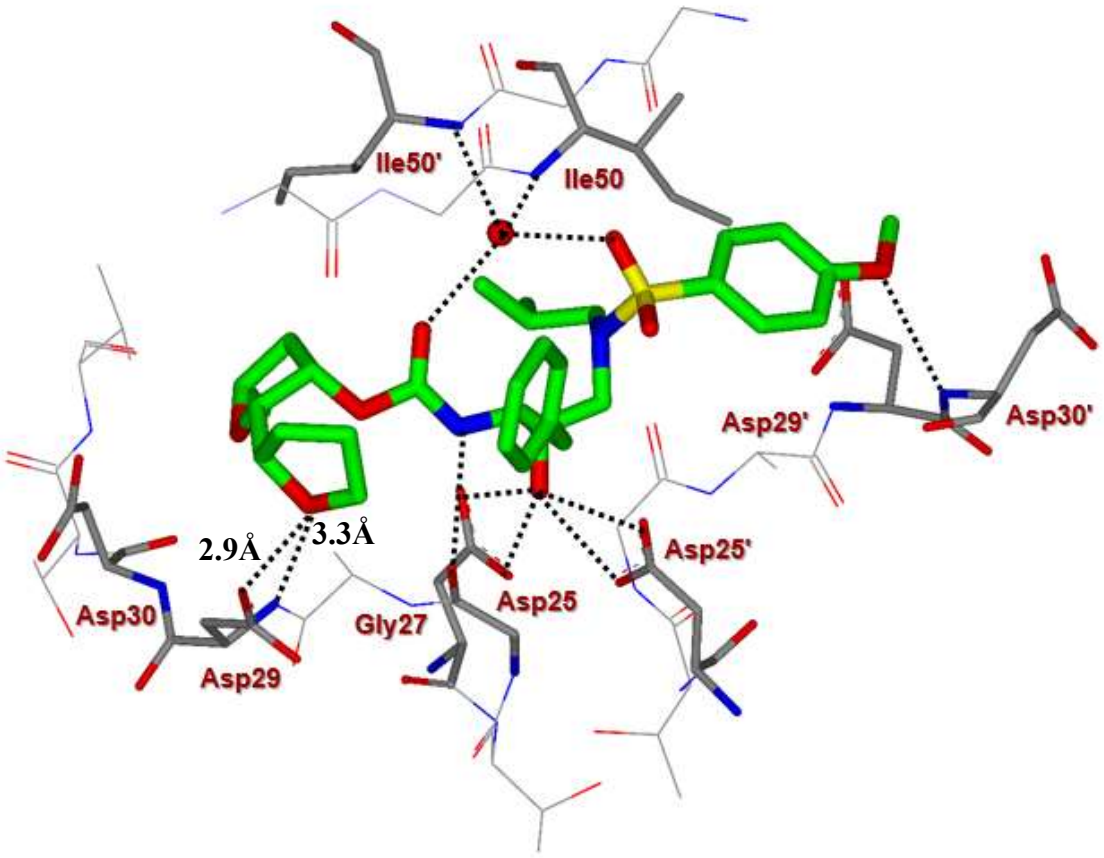


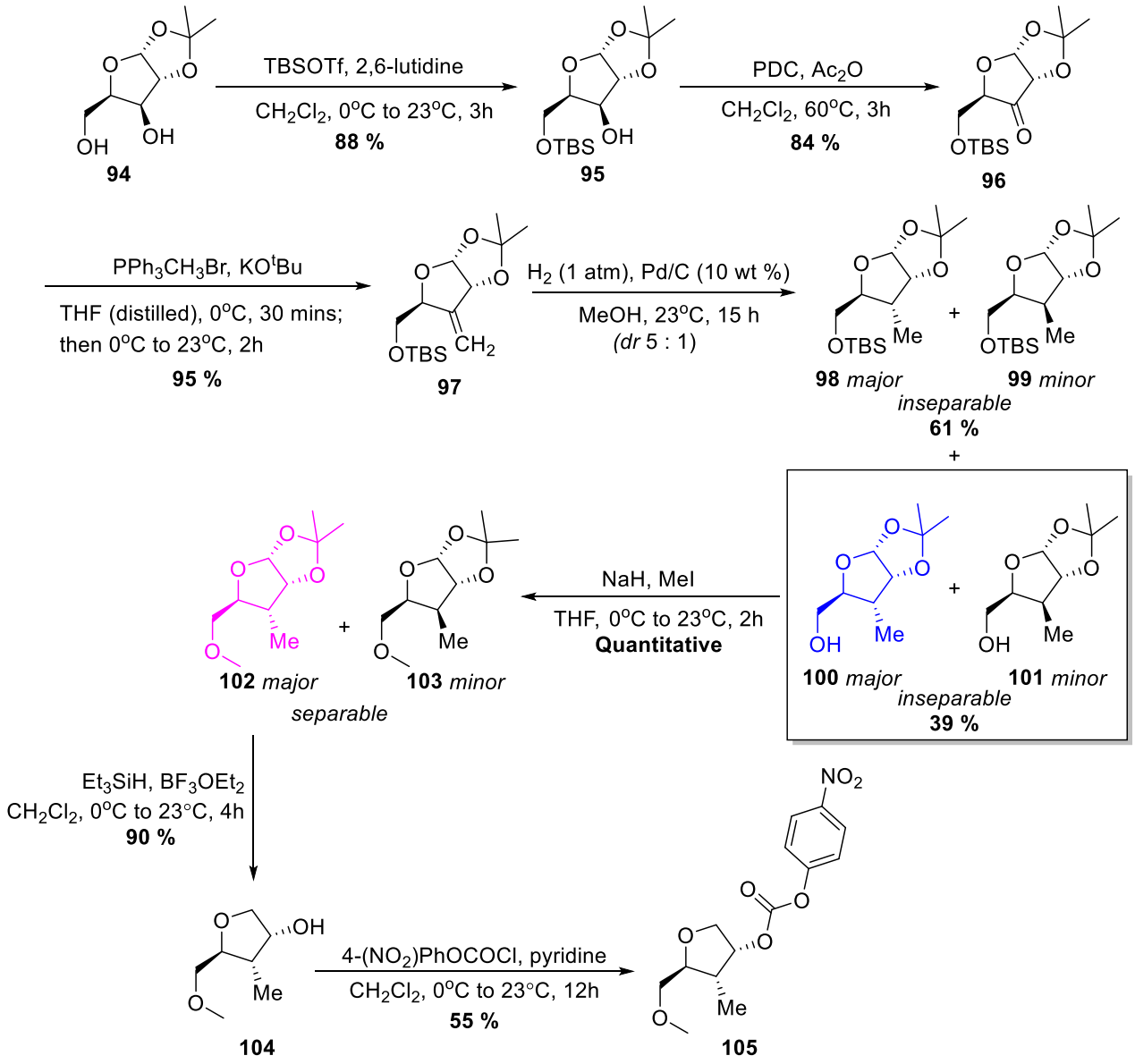

Figure 2.12 X-ray Crystal Structure of Inhibitor 93-Bound HIV-1 Protease. Hydrogen Bonds are Represented by Dotted Lines.

To explain this extreme difference in the enzyme inhibitory activity shown between inhibitor **92** and **93** (Table 2.5), X-ray crystal structure of inhibitor **93**-bound HIV-1 PR was obtained (Figure 2.12). As shown in Figure 2.12, the oxygen atom of the second THF ring forms strong hydrogen bonding interactions with the backbone amide NH and carboxylate group of Asp29 in 3.3Å and 2.9Å distance, respectively. The oxygen atom of the first, trisubstituted THF ring, however, fails to form strong hydrogen bonding interactions with the backbone atoms in the enzyme due to the orientation of the second THF ring (Figure 2.12). Moreover, the methyl substituent at the C5 position only marginally fills the hydrophobic pocket in the $S_2$ active site of the enzyme in contrast to our anticipation (Figure 2.12).

One of the most interesting discoveries from Figure 2.12 is the conformation of the first, trisubstituted THF structure when its C3 carbamate substituent is in the α-orientation. The first, trisubstituted THF moiety tends to adopt an envelope conformation that is facing inwards and its

C3 carbamate substituent contributes to maintaining such the conformation. With this finding, we decided to prepare novel *tc*-THF P2 ligands with α-methyl substituent at the C3 position to sustain the favorable inward envelope conformation and carbamate substituent at the C4 position to mimic the structure of DRV. Moreover, the effect of stereochemistry of the C2 methoxy group will be examined as well.

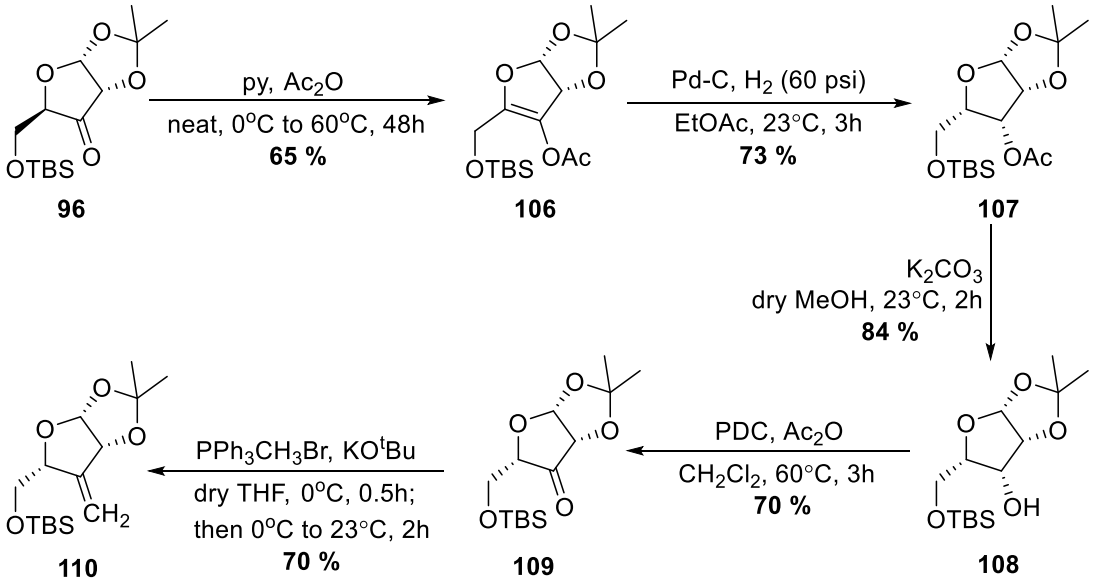
### 2.2.6 Synthesis of Highly Potent *tc*-THF Containing PIs 116 and 117




Scheme 2.15 Synthesis of Activated Carbonate 105

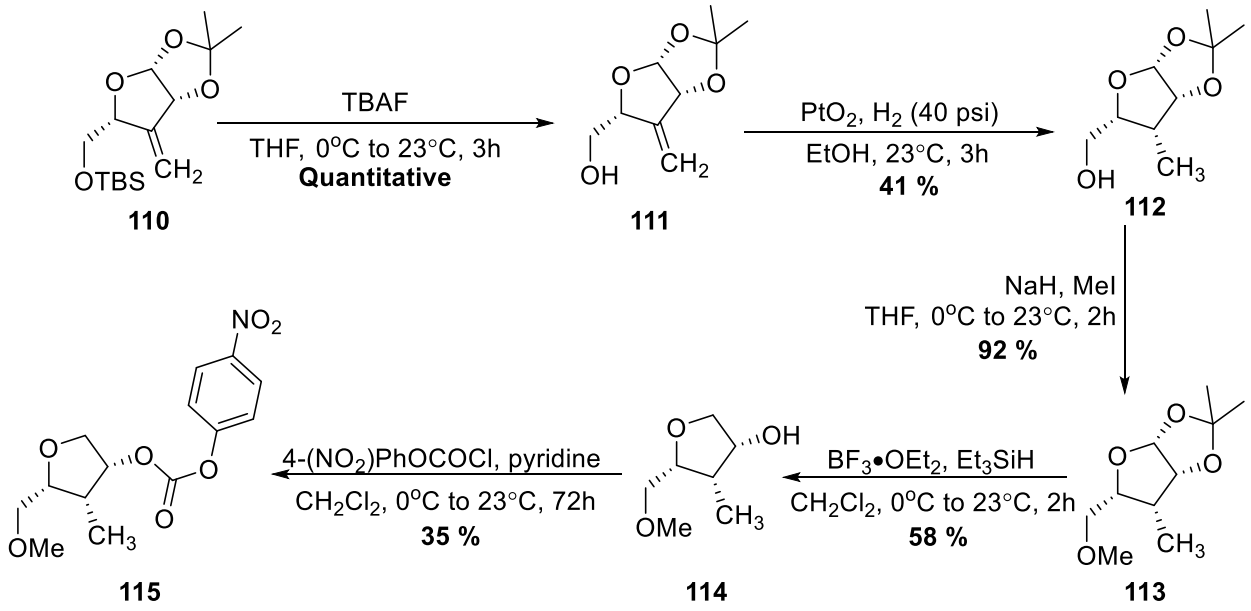
For the enantioselective synthesis of activated carbonate **105**, we first converted commercially available xylofuranose **94** to TBS-protected alcohol **95** by using one equivalent of TBSOTf and 2,6-lutidine in $CH_2Cl_2$ at 0°C to 23°C for 3h (Scheme 2.15). This reaction successfully yielded alcohol **95** in 88% yield. PDC oxidation of alcohol **95** in the presence of acetic anhydride in $CH_2Cl_2$ under reflux for 3h afforded ketone **96** in 84% yield. Wittig olefination of ketone **96** with methyltriphenylphosphonium bromide and potassium tert-butoxide in distilled THF at 0°C to 23°C for 2.5h gave olefin **97** in 95% yield.[63,64] Interestingly, when olefin **97** was hydrogenated under 1 atmospheric pressure of hydrogen gas in the presence of Palladium on Carbon in *undistilled* methanol at 23°C for 15h, both an inseparable mixture of compounds **98** and **99** and an inseparable mixture of compound **100** and **101** were obtained in 61% and 39% yield, respectively. The diastereomeric ratio, which was examined by $^1$H NMR analysis, was 5:1 for both mixtures. Subsequent treatment of inseparable mixture of compound **100** and **101** with sodium hydride and iodomethane in THF at 0°C to 23°C for 2h provided a separable mixture of methyl ether **102** and **103** in quantitative yield. Methyl ether **102** was then treated with two equivalents of $BF_3OEt_2$ and four equivalents of triethylsilane in $CH_2Cl_2$ at 0°C to 23°C for 4h to give alcohol **104** in 90% yield in one step. Coupling reaction of alcohol **104** with 4-nitrophenyl chloroformate in the presence of pyridine in 0°C to 23°C for 12h furnished activated carbonate **105** in 55% yield (Scheme 2.15).

To install alpha methoxy group at the C2 position, ketone **96** was first treated with acetic anhydride in neat pyridine at 0°C to 60°C for 48h to afford olefin **106** in 65% yield (Scheme 2.16).[65] Hydrogenation of olefin **106** in EtOAc and Palladium on Carbon at the initial pressure of 60 psi of hydrogen gas at 23°C for 3h furnished acetate **107** in 73% yield as a single isomer.[66] Deacetylation of acetate **107** was accomplished by using potassium carbonate in dry methanol at 23°C for 2h. This reaction provided alcohol **108** in 84% yield. PDC oxidation of alcohol **108** in the presence of acetic anhydride in $CH_2Cl_2$ at 60°C for 3h offered ketone **109** in 70% yield.[67] Wittig olefination of ketone **109** with methyltriphenylphosphonium bromide and potassium tert-butoxide in distilled THF at 0°C to 23°C for 2.5h yielded olefin **110** in 70% yield (Scheme 2.16).[63,64]




Scheme 2.16 Synthesis of Olefin 110

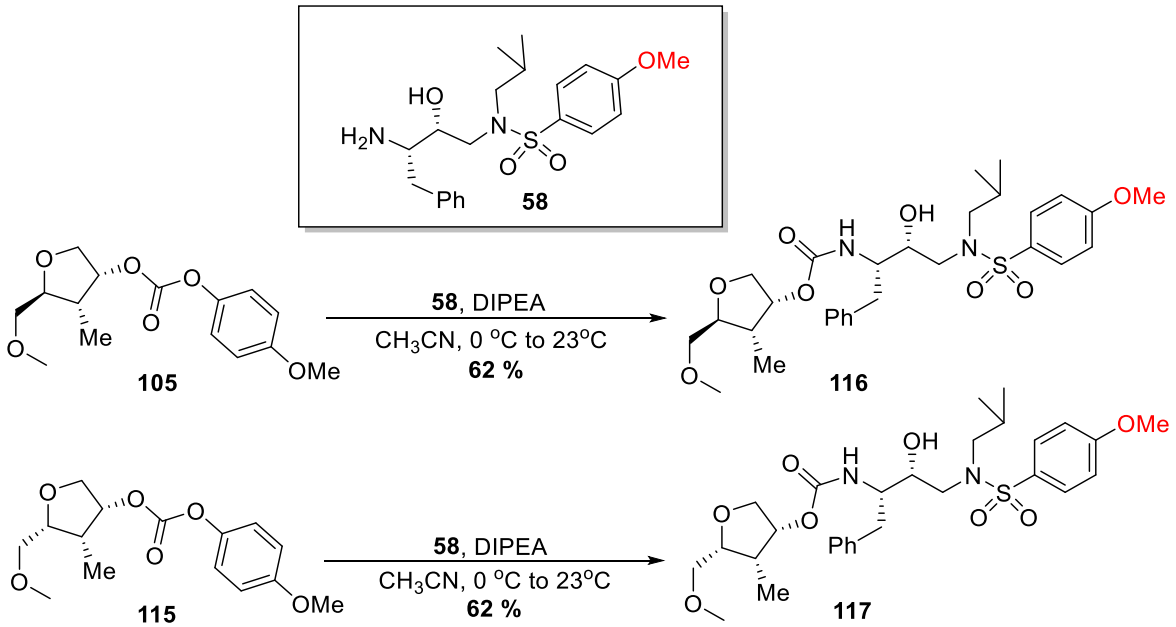
Olefin **110** was converted to activated carbonate **116** in five steps as shown in Scheme 2.17. TBAF deprotection of olefin **110** in THF at 0ºC to 23ºC for 3h gave alcohol **111** in quantitative yield. Hydrogenation of compound **111** over Adam's catalyst at the initial pressure of 40 psi of hydrogen gas in absolute ethanol at 23ºC for 3h afforded alcohol **112** in 41% yield.[66] Treatment of alcohol **112** with sodium hydride and iodomethane in THF at 0ºC to 23ºC for 2h provided methyl ether **113** in 92% yield. Alcohol **114** was obtained from methyl ether **113** in 58% yield by using triethylsilane and $BF_3$ $OEt_2$ in $CH_2Cl_2$ at 0ºC to 23ºC for 2h. Coupling reaction of alcohol **114** with 4-nitrophenylchloroformate and pyridine in $CH_2Cl_2$ at 0ºC to 23ºC for 72h furnished activated carbonate **115** in 35% yield.




Scheme 2.17 Synthesis of Activated Carbonate 115

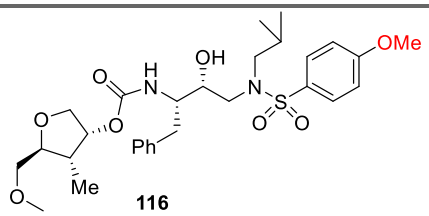
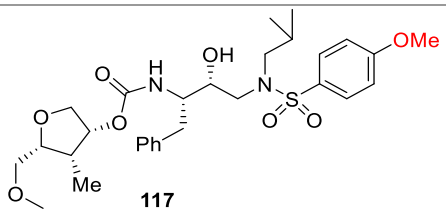
As shown in Scheme 2.18, the coupling reaction of activated carbonate **105** with isostere **58** in the presence of DIPEA in $CH_3CN$ at 23°C afforded inhibitor **116** in 62% yield. Similarly, the coupling reaction of activated carbonates **115** with isostere **58** in the presence of DIPEA in $CH_3CN$ at 23°C furnished inhibitor **117** in 62% yield (Scheme 2.18).

The biological results and clogP values of inhibitors **116** and **117** are summarized in Table 2.6. The $K_i$ and $IC_{50}$ values of these inhibitors were obtained by following the literature procedure.[43] Inhibitor **116**, which incorporates 2*S*,3*R*,4*R*-substituted-THF as P2 ligand and isostere **58** as P2' ligand showed excellent enzyme inhibitory value of 7.35 pM, which is approximately two-fold more potent *in vitro* than DRV ($K_i$ = 16 pM, $IC_{50}$ = 3.2 nM). While inhibitor **116** demonstrated clogP value of 4.78, inhibitor **116** exhibited meaningful $IC_{50}$ value of 835±68 nM unlike the previous results. Installing the beta methoxy group at the C3 position and alpha carbamate at the C4 position has clearly increased the inhibitor's membrane permeability *in vivo* analysis. Inhibitor **117**, which contains 2*R*,3*R*,4R-substituted-THF as P2 ligand and isostere **58** as P2' ligand, displayed disappointing Ki value of 0.74 nM and $IC_{50}$ > 1000 nM. This result has once again proved that the β-orientation of the C2 methoxy substituent is very important in both increasing the inhibitor's cell membrane permeability and improving the binding affinity of *tc*-THF P2 ligand to the active site backbone atoms of the enzyme.




Scheme 2.18 Synthesis of Inhibitors 116 and 117

Table 2.6 Enzymatic and Cellular Data for Protease Inhibitors 116 and 117

| Entry | Inhibitor | $K_i$ (nM) | $IC_{50}$ (nM) | | clogP |
|---|---|---|---|---|---|
| 1 |  | 0.00735 | 835±68 | | 4.78 |
| 2 |  | 0.74 | >1000 | | 4.78 |

## 2.3 Conclusion

In summary, we have designed and synthesized a new class of HIV PIs with trisubstituted chiral tetrahydrofuran (*tc*-THF) derivatives as P2 ligands and isosteres, **58** and **59**, as P2' ligands. The newly designed *tc*-THFs were obtained in optically pure forms by first employing the enzymatic resolution of racemic lactone **43** followed by Lewis acid-mediated diastereoselective *cis*-allylation reaction of the resulting optically active lactones. Using this sequence of reactions, various *tc*-THFs were prepared for SAR studies. The stereochemistry of the C2 methoxy group has been determined to be the key factor affecting the binding affinity of *tc*-THF containing P2 ligands; beta C2 methoxy group containing P2 ligands showed much more enhanced *in vitro* results when compared to alpha C2 methoxy group containing P2 ligands. Moreover, using 4-aminobenzenesulfonamide as P2' ligand has greatly reduced the inhibitors' potency by ten to several hundred folds. Among the newly synthesized PIs, inhibitor **116**, which incorporates 2*S*,3*R*,4*R*-substituted-THF as P2 ligand and 4-methoxybenzenesulfonamide isostere **58** as P2' ligand, showed the best biological results ($K_i$ = 7.35 pM, $IC_{50}$ = 835±68 nM). Rest of the synthesized PIs showed a range of mediocre to good enzyme inhibitory activities and very poor antiviral activities with $IC_{50}$ value higher than 1000 nM. The observed insignificant $IC_{50}$ values from the synthesized PIs are, presumably, due to their high lipophilicity and, thus, lack of membrane permeability. Moreover, positioning the carbamate substituent at the C3 position may have negatively influenced the binding ability of the synthesized P2 ligands.

## 2.4 Supporting Information

### 2.4.1 General Information

Please see Chapter 1.4.1.

### 2.4.2 Experimental Procedures

**General Procedure A: Preparation of Activated Alcohol**

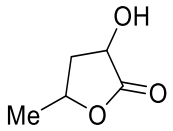
To a solution of alcohol in $CH_2Cl_2$ (10 mL per mmol of alcohol) was added pyridine (5 equiv) at 23 °C under argon atmosphere, and the reaction mixture was cooled to 0 °C followed by addition of 4-nitrophenyl chloroformate (2.2 equiv). The reaction mixture was warmed to 23 °C and stirred for 12 h. Upon completion, solvents were removed under reduced pressure and crude product was purified by silica gel column chromatography.

**General Procedure B: Preparation of Inhibitor with Isostere A**

To a stirred solution of activated alcohol and isostere A in acetonitrile (2 mL) was added DIPEA (8 equiv.) at 0 $^oC$ under argon atmosphere. The reaction mixture was stirred at room temperature until completion. Upon completion, solvents were removed under reduced pressure and crude residue was purified by silica gel column chromatography.

**General Procedure C: Preparation of Inhibitor with Isostere B**

To a stirred solution of activated alcohol and isostere B in acetonitrile (2 mL) was added DIPEA (8 equiv.) at 0 $^oC$ under argon atmosphere. The reaction mixture was stirred at room temperature until completion. Upon completion, solvents were removed under reduced pressure and crude residue was purified by silica gel column chromatography.



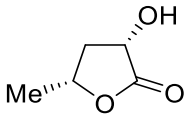

**(±)-43**

3-Hydroxy-5-methyldihydrofuran-2(3*H*)-one ((±)-**43**)

To a stirred solution of α-methylene-γ-butyrolactone (**41**) (6.12g, 54.58 mmol) in $CH_2Cl_2$ (20 mL) at -78$^oC$ was bubbled a stream of ozone until a blue color persisted. The ozone stream was then stopped and purged with a stream of oxygen to remove the excess ozone. After adding dimethyl sulfide (12 mL, 163.74 mmol), the reaction mixture was warmed to 23$^oC$ and stirred for

4h. The reaction mixture was concentrated under reduced pressure and the crude product **42** (4.9 g, 79 % yield) was used for the next step with any further purification.

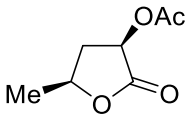
To a stirred solution of unsaturated lactone intermediate **42** (3.5 g, 31 mmol) in EtOAc (20 mL) was added Pd-C (150 mg, 10 wt %), The resulting solution was stirred at 23 $^{o}$C under 1 atm $H_2$ gas over 24 h. Upon completion, the mixture was filtered through a plug of Celite and solvents were removed under reduced pressure. The crude product was purified by silica gel column chromatography (50 % EtOAc in hexanes) to give racemic lactone **43** (2.87 g, 79 %). $^{1}$H NMR (400 MHz, $CDCl_3$) δ: 4.57 (dd, *J* = 11.3, 8.4 Hz, 1H), 4.54 – 4.45 (m, 1H), 4.03 (brs,1H), 2.70 (ddd, *J* = 12.6, 8.4, 5.1 Hz, 1H), 1.90 – 1.80 (m, 1H), 1.43 (d, *J* = 6.2 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 178.2, 73.9, 69.1, 38.8, 20.9.




**(+)-44**

(3*S*,5*R*)-3-hydroxy-5-methyldihydrofuran-2(3*H*)-one **(+)-44**

To a solution of racemic lactone **43** (960 mg, 8.23 mmol) in THF (15 mL) were added vinyl acetate (13.3 mL, 144.9 mmol) and Lipase PS-30 (0.9 g) at 23$^{o}$C under argon atmosphere. The reaction mixture was stirred for 2h (50:50 by $^{1}$H NMR). After this period, the reaction mixture was filtered through a plug of Celite and solvents were removed under reduced pressure. The crude product was purified by silica gel column chromatography (20% to 50% EtOAc in hexanes) to give alcohol **(+)-44** (485 mg, 50 % yield) as a colorless oil and acetate **45** (650 mg, 50 % yield);$^{1}$H NMR (400 MHz, CDCl3) δ: 4.58 (dd, *J* = 11.2, 8.4 Hz, 1H), 4.52 – 4.44 (m, 1H), 4.18 (brs, 1H), 2.69 (ddd, *J* = 12.9, 8.3, 5.1 Hz, 1H), 1.89 – 1.79 (m, 1H), 1.42 (d, *J* = 6.3 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl3) δ: 178.3, 73.9, 69.0, 38.8, 20.9; LRMS-ESI (m/z): 139.2 $(M+Na)^{+}$;$[\alpha]_D^{20}$ +2.8 (c 1.0, $CHCl_3$); reported (Ahrens, H.; Paetow, M.; Hoppe, D. *Tetrahedron Lett*. **1992**, *33*, 5327-5330) $[\alpha]_D^{20}$ +3.6 (c 0.8, $CH_3OH$).

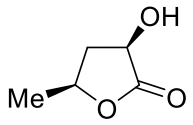



**45**

(3*R*,5*S*)-5-methyl-2-oxotetrahydrofuran-3-yl acetate **45**:

$^{1}$H NMR (400 MHz, $CDCl_3$) δ: 5.45 (dd, *J* = 10.9, 8.6 Hz, 1H), 4.59 – 4.47 (m, 1H), 2.76 (ddd, *J* = 12.7, 8.5, 5.3 Hz, 1H), 2.10 (s, 3H), 1.83 (dt, *J* = 12.5, 10.6 Hz, 1H), 1.43 (d, *J* = 6.3 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 172.5, 169.8, 73.6, 69.0, 36.7, 21.0, 20.6; LRMS-ESI (m/z): 181.2 $(M+Na)^+$ ;$[\alpha]_D^{20}$ -18.45 (c 1.0, $CHCl_3$)

Both alcohol **(+)-44** and acetate **45** gave NMR spectroscopic data and optical rotation that agree with the reported ones.[55]

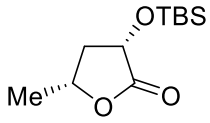



**(-)-44**

(*3R,5S*)-3-hydroxy-5-methyldihydrofuran-2(3H)-one (**(-)-44**)

To a stirred solution of acetate **45** (320 mg, 2.02 mmol) in MeOH (5 mL) was added aqueous NaOH (10 % solution, 5 mL) and the mixture was stirred at 23 $^{o}$C for 12 h. After this period, the reaction mixture was acidified with 1N HCl solution and solvents were concentrated under reduced pressure. The aqueous layer was extracted multiple times with EtOAc. The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (60 % EtOAc in hexane) to give alcohol **(-)-44** (144 mg, 61 %) as a colorless oil.

For NMR data, please see lactone **(+)-44**; LRMS-ESI (m/z): 139.2 $(M+Na)^+$;$[\alpha]_D^{20}$ – 2.3 (c 1.0, $CH_3OH$); reported (Ghosh, A.K. and Nyalapatla, P.R. *Org. Lett.* **2016**, *18*, 2296-2299) $[\alpha]_D^{20}$ – 2.3 (c 1.0, $CH_3OH$).

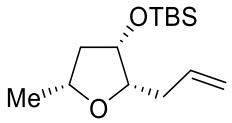



**(+)-46**

(*3S,5R*)-3-((*tert*-butyldimethylsilyl)oxy)-5-methyldihydrofuran-2(3H)-one (**(+)-46**)

To a stirred solution of alcohol **(+)-44** (485 mg, 4.18 mmol) in $CH_2Cl_2$ (10 mL) were added 2,6-lutidine (1.45 ml, 12.54 mmol) and TBSOTf (1.45 mL, 6.27 mmol) at 0 $^{o}$C under argon atmosphere. The reaction mixture was warmed to 23 $^{o}$C and stirred for 1 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with $CH_2Cl_2$. The extracts were washed with saturated aqueous NaCl, dried ($Na_2SO_4$), and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (10 % EtOAc in

hexanes) to lactone **(+)-46** (923 mg, 96 %) as a white amorphous solid;[1]H NMR (400 MHz, $CDCl_3$) δ: 4.46 – 4.34 (m, 2H), 2.56 (ddd, *J* = 12.6, 8.1, 5.3 Hz, 1H), 1.77 (dt, *J* = 12.4, 10.3 Hz, 1H), 1.37 (d, *J* = 6.3 Hz, 3H), 0.85 (d, *J* = 3.8 Hz, 9H), 0.10 (d, *J* = 17.0 Hz, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 175.8, 72.6, 69.8, 40.0, 25.7, 21.1, 18.2, -4.7, -5.3; LRMS-ESI (m/z): 253.2 $(M+Na)^+$; $[\alpha]_D^{20}$ -16.0 (c 1.0, $CHCl_3$); reported (Ghosh, A.K. and Nyalapatla, P.R. *Tetrahedron.* **2017**, *73*, 1820-1830) $[\alpha]_D^{20}$ – 16.4 (c 0.96, $CHCl_3$).



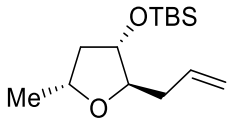

**(+)-48**

(((*2S,3S,5R*)-2-allyl-5-methyltetrahydrofuran-3-yl)oxy)(*tert*-butyl)dimethylsilane (**(+)-48**)

To a stirred solution of lactone **(+)-44** (415 mg, 1.80 mmol) in $CH_2Cl_2$ (16 mL) at -78 °C was added DIBAL-H (1 M in Hexanes, 2.70 ml, 2.70 mmol) under argon atmosphere and stirred at the same temperature for 2h. The reaction was quenched by the addition of MeOH (3 mL) and warmed to 23 °C. Then, saturated aqueous solution of sodium potassium tartarate was added and stirred vigorously at 23 °C for 2h until it forms white suspension. The white suspension was filtered through a plug of Celite and the filtrate were concentrated under reduced pressure. To a crude lactol (417 mg) was added DMAP (44 mg, 0.36 mmol), $Et_3N$ (1 mL, 7.19 mmol) and $Ac_2O$ (0.42 mL, 4.50 mmol) at 0 °C under argon atmosphere and stirred for 2h. Upon, completion, solvents were concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (15 % EtOAc in hexane) to give acetate intermediate **47** (445 mg, 90 % yield over two steps).

To a solution of acetate intermediate **47** (344 mg, 1.26 mmol) in $CH_2Cl_2$ (12 .60 mL, 0.1 M) was added allyltrimethylsilane (0.80 mL, 5.02 mmol) at 23 °C under argon atmosphere and then cooled to - 78 °C. After addition of $SnBr_4$ (660 mg, 1.50 mmol), the mixture was warmed to 23 °C over 2h. Upon completion, the reaction was quenched by the addition of saturated aqueous $Na_2HPO_4$ and extracted with $CH_2Cl_2$. The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. $^1$H NMR analysis of the unpurified crude product showed a pair of diastereomers in a 10:1 ratio. The crude product was purified by silica gel column chromatography (70% $CH_2Cl_2$ in hexanes) to give *major* olefin **(+)-48** (256 mg, 80 %) as a colorless oil and *minor* olefin **(+)-49** (25 mg, 8%) as a colorless oil;[1]H NMR (400 MHz, $CDCl_3$) δ: 5.85 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.09 (d, *J* = 17.2 Hz, 1H), 5.02 (d, *J* = 10.2 Hz, 1H), 4.22

(dt, *J* = 6.4, 3.7 Hz, 1H), 3.96-3.89 (m, 1H), 3.63 (q, *J* = 6.2 Hz, 1H), 2.42-2.32 (m, 2H), 2.26 (dt, *J* = 13.4, 6.9 Hz, 1H), 1.47 (ddd, *J* = 13.0, 6.6, 2.9 Hz, 1H), 1.29 (d, *J* = 6.2 Hz, 3H), 0.89 (s, 9H), 0.04 (d, *J* = 4.3 Hz, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 135.9, 116.4, 83.2, 73.7, 73.5, 43.5, 34.4, 25.9, 22.2, 18.2, -4.4, - 4.9; LRMS-ESI (m/z): 279.3 $(M+Na)^+$; $[\alpha]_D^{20}$ +16.8 (c 1.0, $CHCl_3$); reported (Ghosh, A.K. and Nyalapatla, P.R. *Org. Lett.* **2016**, *18*, 2296-2299) $[\alpha]_D^{20}$ – 16.4 (c 1.0, $CHCl_3$) for its enantiomer.

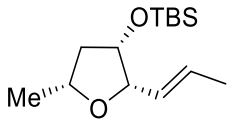



**(+)-49**

(((2*R*,3*S*,5*R*)-2-allyl-5-methyltetrahydrofuran-3-yl)oxy)(*tert*-butyl)dimethylsilane (**(+)-49)**

To a stirred solution of lactone **(+)-46** (317 mg, 1.38 mmol) in $CH_2Cl_2$ (14 mL) was added allylmagnesium bromide solution (1.0 M in $Et_2O$, 1.65 mL, 1.65 mmol) at -78$^o$C under argon atmosphere. After stirring for 3h at the same temperature, the reaction was quenched by the addition of saturated aqueous $NH_4Cl$ and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The crude product was passed through a flash silica gel column to afford hemiketal **66** (282 mg, 61%).

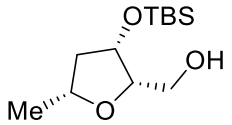
To hemiketal **66** (282 mg, 1.04 mmol) in $CH_2Cl_2$ (8.5 mL) were consecutively added $Et_3SiH$ (1.03 mL, 6.47 mmol) and $BF_3$ $OEt_2$ (0.38 mL, 3.11 mmol) at -78 $^o$C under argon atmosphere. After stirring for 2 h at the same temperature, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were washed with brine, dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (5% EtOAc in hexanes) to afford **(+)-49** (154 mg, 58%) as a yellow oil.; $^1$H NMR (400 MHz, $CDCl_3$) δ: 5.84 (ddt, *J* = 17.0, 9.8, 6.8 Hz, 1H), 5.14 – 5.01 (m, 2H), 4.20 – 4.11 (m, 1H), 4.04 – 3.97 (m, 1H), 3.85 – 3.79 (m, 1H), 2.35 – 2.27 (m, 1H), 2.28 – 2.16 (m, 2H), 1.57 – 1.50 (m, 1H), 1.28 (d, *J* = 6.2 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 134.8, 116.8, 83.5, 76.1, 73.6, 42.4, 37.6, 25.7, 22.1, 17.8, -4.6, -4.9; LRMS-ESI (m/z): 279.3 $(M+Na)^+$; $[\alpha]_D^{20}$ +30.8 (c 1.0, $CHCl_3$).




**50**

*tert*-butyldimethyl(((*2S,3S,5R*)-5-methyl-2-(prop-1-en-1-yl)tetrahydrofuran-3-yl)oxy)silane (**50**)

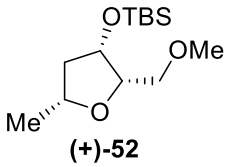
To a stirred mixture of olefin **(+)-48** (144 mg, 0.56 mmol) and vinyloxy-trimethylsilane (0.84 mL, 5.60 mmol) in $CH_2Cl_2$ (45 mL) was added Grubb's second generation catalyst (48 mg, 0.056 mmol) at 23 $^oC$ under argon atmosphere. The reaction mixture was refluxed at 110 $^oC$ for 24 h in a sealed tube. The mixture was cooled to 23 $^oC$ and concentrated under reduced pressure to remove solvents. The crude residue was purified by silica gel column chromatography (2 % diethyl ether in hexanes) to give olefin **50** (136 mg, 95%) as a colorless oil; $^1H$ NMR (400 MHz, $CDCl_3$) δ: 5.73 – 5.62 (m, 2H), 4.24 – 4.23 (m, 1H), 4.04 – 3.97 (m, 2H), 2.31 – 2.28 (m, 1H), 1.71 (d, *J* = 5.2 Hz, 3H), 1.60 – 1.50 (m, 1H), 1.33 (d, *J* = 5.2 Hz, 3H), 0.88 (s, 9H), 0.02 (s, 6H); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ: 129.4, 128.4, 84.5, 74.9, 73.6, 43.4, 25.7. 22.0, 18.1, 17.8, -4.4, -4.7; LRMS-ESI (m/z): 279.3 $(M+Na)^+$; $[\alpha]_D^{20}$ +28.0 (c 1.0, $CHCl_3$)




**(+)-51**

(((*2S,3S,5R*)-3-((*tert*-butyldimethylsilyl)oxy)-5-methyltetrahydrofuran-2-yl)methanol (**(+)-51**)

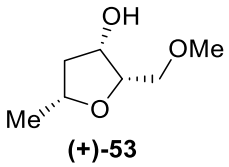
A solution of olefin **50** (36 mg, 0.14 mmol) in a 1:1 mixture of $CH_2Cl_2$ and MeOH (3.6 mL) was cooled down to -78 $^oC$. Ozone was passed into the solution until the color of the solution turned to pale blue. The reaction mixture was then purged with oxygen for 5 min and $NaBH_4$ (16 mg, 0.43 mmol) was added. After stirring for 2 h at -78 $^oC$, the reaction mixture was diluted with EtOAc and quenched with saturated aqueous $NH_4Cl$. The aqueous layer was extracted with EtOAc. The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (10% EtOAc in hexanes to 30% EtOAc in hexanes) to give alcohol **(+)-51** (32 mg, 92% yield over two steps) as a white amorphous solid; $^1H$ NMR (400 MHz, $CDCl_3$) δ:4.54 – 4.46 (m, 1H), 3.98 – 3.92 (m, 1H), 3.83 – 3.77 (m, 3H), 2.32 – 2.27 (m, 1H), 1.36 – 1.27 (m, 1H), 1.24 (d, *J* = 6.2 Hz, 1H), 0.90 (s, 9H), 0.04 (s, 6H); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ: 81.2, 74.5, 73.5, 62.7, 43.4, 25.6, 21.3, 17.8, -4.7, -5.3; LRMS-ESI (m/z): 269.2 $(M+Na)^+$; $[\alpha]_D^{20}$ +13.9 (c 1.0, $CHCl_3$).




**(+)-52**

*tert*-butyl(((*2S,3S,5R*)-2-(methoxymethyl)-5-methyltetrahydrofuran-3-yl)oxy)dimethylsilane (**(+)-52**)

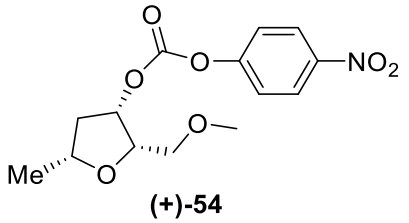
To a stirred solution of alcohol **(+)-51** (32 mg, 0.13 mmol) in THF (2.6 mL) was added NaH (60% dispersion in mineral oil, 31 mg, 0.77 mmol) at 0 $^{o}$C under argon atmosphere. After stirring for 10 min at 0 $^{o}$C, MeI (88 µL, 1.42 mmol) was added and the reaction mixture was slowly warmed to 23 $^{o}$C over 3h. Upon completion, the reaction was quenched with saturated aqueous $NH_4Cl$ and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated reduced pressure. Purification by silica gel column chromatography gave **(+)-52** (21 mg, 0.08 mmol) as a colorless oil. $^{1}$H NMR (400 MHz, $CDCl_3$) δ: 4.35 – 4.29 (m, 1H), 3.98 (q, *J* = 6.8 Hz, 1H), 3.81 (q, *J* = 6.4 Hz, 1H), 3.58 – 3.52 (m, 2H), 3.38 (s, 3H), 2.32 – 2.25 (m, 1H), 1.54 – 1.44 (m, 1H), 1.32 (d, *J* = 6.4 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 81.8, 74.1, 73.1, 72.1, 59.1, 43.4, 25.6, 21.8, 17.9, -4.8, -5.3; LRMS-ESI (m/z): 283.2 $(M+Na)^+$; $[\alpha]_D^{20}$ +18.7 (c 1.0, $CHCl_3$).




**(+)-53**

(*2S,3S,5R*)-2-(methoxymethyl)-5-methyltetrahydrofuran-3-ol (**(+)-53**)

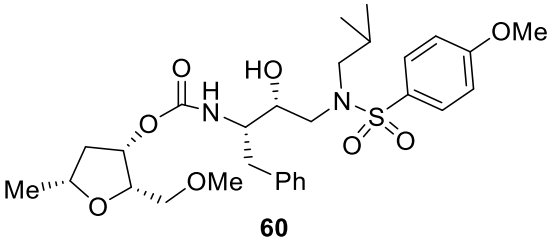
To a mixture of compound **(+)-52** (16 mg, 0.06 mmol) in THF (2 mL) was added TBAF solution (1M in THF, 0.15 mL, 0.15 mmol) at 0$^{o}$C under argon atmosphere. The reaction mixture was warmed to room temperature and stirred for 3h. The reaction was quenched with water and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography (40 % EtOAc in hexanes) to give alcohol **(+)-53** (8 mg, quantitative) as a white amorphous solid.$^{1}$H NMR (400 MHz, $CDCl_3$) δ: 4.44 – 4.39 (m, 1H), 3.99 – 3.89 (m, 1H), 3.85 – 3.60 (m, 3H), 3.41 (s, 3H), 2.75 (brs, 1H), 2.44 – 2.32 (m, 1H), 1.56 – 1.45 (m, 1H), 1.33 (d, *J* = 6.0 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 80.2, 73.9, 73.8, 71.6, 59.4, 43.2, 21.4; LRMS-ESI (m/z): 169.1 $(M+Na)^+$;$[\alpha]_D^{20}$ +3.8 (c 0.33, $CHCl_3$)



**(+)-54**

*(2S,3S,5R)*-2-(methoxymethyl)-5-methyltetrahydrofuran-3-yl (4-nitrophenyl) carbonate (**(+)-54**)

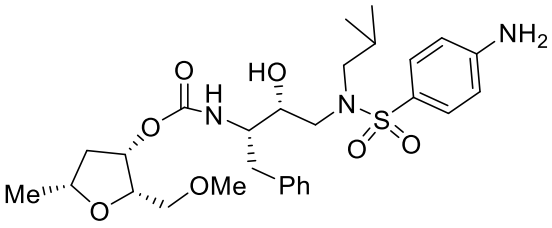
Following **General Procedure A**, activated alcohol **(+)-54** (17 mg, 91 % yield) was prepared as a white amorphous solid from alcohol **(+)-53** (8 mg, 0.06 mmol).$^{1}$H NMR (400 MHz, $CDCl_3$) δ: 8.28 (d, *J* = 9.0 Hz, 2H), 7.38 (d, *J* = 9.0 Hz, 2H), 5.34 (p, *J* = 3.8 Hz, 1H), 4.10 – 3.95 (m, 2H), 3.67 (d, *J* = 5.7Hz, 2H), 3.41 (s, 3H), 2.66 – 2.53 (m, 1H), 1.76 – 1.70 (m, 1H), 1.37 (d, *J* = 6.1 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 155.4, 152.0, 145.3, 125.2, 121.6, 80.2, 79.7, 74.1, 70.6, 59.3, 40.3, 21.1; LRMS-ESI (m/z): 344.2 $(M+Na)^+$;$[\alpha]_D^{20}$ +5.8 (c 0.33, $CHCl_3$)



**60**

(*2S,3S,5R*)-2-(methoxymethyl)-5-methyltetrahydrofuran-3-yl ((*2S,3R*)-3-hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate (**60**)

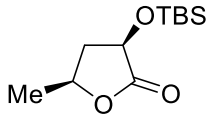
Following **General Procedure B**, inhibitor **60** (8 mg, 58 % yield) was prepared as a white amorphous solid from activated alcohol **(+)-54** (7 mg, 0.02 mmol). $^{1}$H NMR (400 MHz, $CDCl_3$) δ: 7.71 (d, *J* = 8.9 Hz, 2H), 7.34 – 7.17 (m, 7H), 6.98 (d, *J* = 8.9 Hz, 2H), 5.18 – 5.11 (m, 1H), 4.84 (d, *J* = 8.3 Hz, 1H), 3.93 (q, *J* = 6.6 Hz, 1H), 3.87 (s, 3H), 3.86 – 3.77 (m, 4H), 3.38 – 3.31 (m, 2H), 3.30 (s, 3H), 3.14 (dd, *J* = 15.2, 8.3 Hz, 1H), 3.07 – 2.91 (m, 3H), 2.86 (dd, *J* = 14.1, 8.4 Hz, 1H), 2.79 (dd, *J* = 13.4, 6.7 Hz, 1H), 2.47 – 2.36 (m, 1H), 1.87 – 1.76 (m, 1H), 1.46 (dd, *J* = 14.0, 7.7 Hz, 1H), 1.29 (d, *J* = 6.1 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 163.0, 148.4, 137.5, 129.7, 129.4, 128.5, 126.5, 114.26, 80.4, 75.5, 74.0, 72.6, 70.8, 59.2, 58.7, 55.5, 54.9, 55.6, 40.6, 35.2, 27.2, 21.2, 20.1, 19.8; LRMS-ESI (m/z): 578.0 $(M+H)^+$; HRMS-ESI (m/z): $C_{29}H_{42}N_2O_8S$; calc'd for $[M+H]^+$: 579.2735, found 579.2740; $[\alpha]_D^{20}$ +13.3 (c 0.33, $CHCl_3$).




**61**

(*2S,3S,5R*)-2-(methoxymethyl)-5-methyltetrahydrofuran-3-yl((*2S,3R*)-4-((4-amino-*N*-isobutylphenyl)sulfonamido)-3-hydroxy-1-phenylbutan-2-yl)carbamate (**61**)

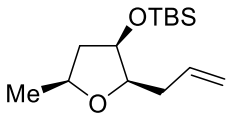
Following **General Procedure C**, inhibitor **61** (7 mg, 69 % yield) was prepared as a yellow amorphous solid from activated alcohol **(+)-54** (6 mg, 0.02 mmol).$^{1}$H NMR (400 MHz, $CDCl_3$) δ: 7.55 (d, *J* = 8.7 Hz, 2H), 7.32 – 7.20 (m, 7H), 6.68 (d, *J* = 8.7 Hz, 2H), 5.18 – 5.12 (m, 1H), 4.85 (d, *J* = 8.4 Hz, 1H), 3.98 – 3.89 (m, 1H), 3.86 – 3.81 (m, 3H), 3.40 – 3.32 (m, 2H), 3.31 (s, 3H), 3.14 (dd, *J* = 15.1, 8.3 Hz, 1H), 3.08 – 2.81 (m, 5H), 2.76 (dd, *J* = 13.4, 6.6 Hz, 1H), 2.41 (dt, *J* = 14.1, 7.2 Hz, 1H), 1.88 – 1.74 (m, 2H), 1.52 – 1.42 (m, 2H), 1.30 (d, *J* = 6.1 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 4H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 155.7, 150.6, 137.6, 129.4, 129.3, 128.4, 128.3, 126.5, 114.0, 80.4, 77.1, 75.5, 74.0, 72.7, 70.9, 59.2, 58.8, 54.9, 53.7, 40.6, 35.3, 27.2, 21.2, 20.1, 19.8; LRMS-ESI (m/z): 564.0 $(M+H)^+$; HRMS-ESI (m/z): $C_{28}H_{41}N_3O_7S$; calc'd for $[M+H]^+$: 564.2738, found 564.2733; $[\alpha]_D^{20}$ +18.6 (c 0.33, $CHCl_3$).




**(-)-46**

(*3R,5S*)-3-((*tert*-butyldimethylsilyl)oxy)-5-methyldihydrofuran-2(3H)-one (**(-)-46**)

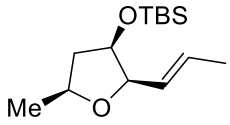
Lactone **(-)-46** (268 mg, 94 % yield) was obtained as a white amorphous solid from alcohol **(-)-44** (144 mg, 1.24 mmol) by following the procedure described above for its enantiomer **(+)-44**. For NMR data, please see lactone **(+)-46**; LRMS-ESI (m/z): 253.2 $(M+Na)^+$; $[\alpha]_D^{20}$ + 15.5 (c 1.0, $CHCl_3$); reported (Ghosh, A.K. and Nyalapatla, P.R. *Org. Lett.* **2016**, *18*, 2296-2299) $[\alpha]_D^{20}$ + 16.95 (c 1.15, $CHCl_3$).




**(-)-48**

(*3R,5S*)-3-hydroxy-5-methyldihydrofuran-2(3H)-one (**(-)-48**)

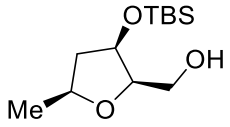
By following the procedure outlined for the preparation of its enantiomer **(+)-48**, olefin **(-)-48** (115 mg, 59 % yield) was obtained as a colorless oil from lactone **(-)-46** (210 mg, 0.77 mmol) with *dr* 10:1 after the diastereoselective allylation reaction. For NMR data, please see **(+)-48**; LRMS-ESI (m/z): 253.2 $(M+Na)^+$; $[\alpha]_D^{20}$ -14.0 (c 1.0, $CHCl_3$); reported (Ghosh, A.K. and Nyalapatla, P.R. *Org. Lett.* **2016**, *18*, 2296-2299) $[\alpha]_D^{20}$ -16.8 (c 1.0, $CHCl_3$).




**55**

*tert*-butyldimethyl(((*2R,3R,5S*)-5-methyl-2-(prop-1-en-1-yl)tetrahydrofuran-3-yl)oxy)silane **(55**)

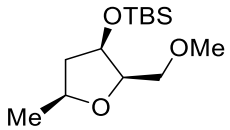
Olefin **55** (43 mg, 72 % yield) was obtained as a colorless oil from olefin **(-)-48** (60 mg, 0.24 mmol) by following the procedure described above for its enantiomer **50**. For NMR data, please see compound **50**; LRMS-ESI (m/z): 279.3 $(M+Na)^+$; $[\alpha]_D^{20}$ -26.2 (c 1.0, $CHCl_3$).




**(-)-51**

((*2R,3R,5S*)-3-((*tert*-butyldimethylsilyl)oxy)-5-methyltetrahydrofuran-2-yl)methanol (**(-)-51**)

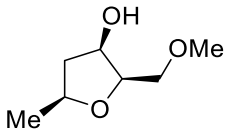
Alcohol **(-)-51** (23 mg, 65 % yield) was obtained as a white amorphous solid from olefin **55** (36 mg, 0.14 mmol) by following the procedure described above for its enantiomer **(+)-51**. For NMR data, please see compound **(+)-51;** LRMS-ESI (m/z): 269.2 $(M+Na)^+$; $[\alpha]_D^{20}$ -15.0 (c 1.0, $CHCl_3$).




**(-)-52**

*tert*-butyl(((*2R,3R,5S*)-2-(methoxymethyl)-5-methyltetrahydrofuran-3-yl)oxy)dimethylsilane (**(-)-52**)

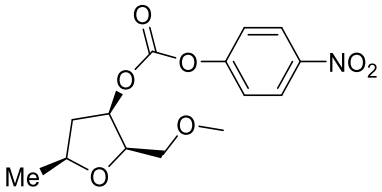
Compound **(-)-52** (21 mg, 83 % yield) was obtained as a colorless oil from alcohol **(-)-51** (23 mg, 0.09 mmol) by following the procedure described above for its enantiomer **(+)-52**. For NMR, please see compound **(+)-52;** LRMS-ESI (m/z): 283.2 $(M+Na)^+$; $[\alpha]_D^{20}$ -18.6 (c 1.0, $CHCl_3$).




**(-)-53**

(*2R,3R,5S*)-2-(methoxymethyl)-5-methyltetrahydrofuran-3-ol (**(-)-53**)

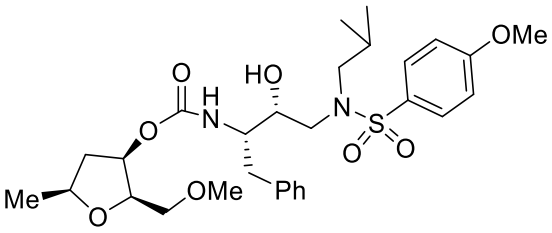
Alcohol **(-)-53** (9 mg, 93 % yield) was prepared as a white amorphous solid from compound **(-)-52** (19 mg, 0.07 mmol) by following the procedure described above for its enantiomer **(+)-53**. For NMR data, please see compound **(+)-53**; LRMS-ESI (m/z): 169.1 $(M+Na)^+$; $[\alpha]_D^{20}$ -4.2 (c 1.0, $CHCl_3$).




**(-)-54**

(*2R,3R,5S*)-2-(methoxymethyl)-5-methyltetrahydrofuran-3-yl (4-nitrophenyl) carbonate (**(-)-54**)

Following **General Procedure A**, activated alcohol **(-)-54** (16 mg, 70 % yield) was prepared as a white amorphous solid from alcohol **(-)-53** (9 mg, 0.07 mmol) by following the procedure described above for its enantiomer **(+)-54**. For NMR data, please see compound **(+)-54**; LRMS-ESI (m/z): 344.2 $(M+Na)^+$; $[\alpha]_D^{20}$ -6.2 (c 0.33, $CHCl_3$).

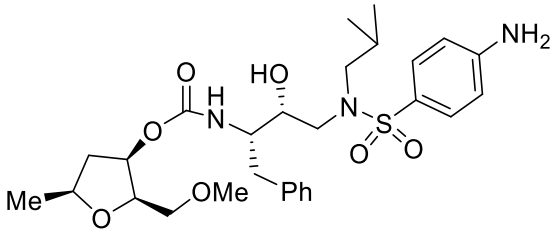



**62**

(*2R,3R,5S*)-2-(methoxymethyl)-5-methyltetrahydrofuran-3-yl.((*2S,3R*)-3-hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate (**62**)

Following **General Procedure B**, inhibitor **62** (7 mg, 71 % yield) was prepared as a white amorphous solid from activated alcohol **(-)-54** (5 mg, 0.02 mmol). $^1H$ NMR (400 MHz, $CDCl_3$) δ: 7.71 (d, *J* = 8.8 Hz, 2H), 7.33 – 7.17 (m, 5H), 6.99 (d, *J* = 8.8 Hz, 2H), 5.11 – 5.05 (m, 1H), 4.84 (d, *J* = 8.6 Hz, 1H), 3.94 (h, *J* = 6.4 Hz, 1H), 3.88 (s, 3H), 3.86 – 3.77 (m, 4H), 3.52 – 3.49 (m, 2H), 3.34 (s, 3H), 3.14 (dd, *J* = 15.1, 8.4 Hz, 1H), 3.05 – 2.94 (m, 3H), 2.89 – 2.76 (m, 3H), 2.38 – 2.30 (m, 1H), 1.90 – 1.77 (m, 1H), 1.60 (brs, 1H), 1.33 – 1.28 (m, 2H), 0.93 (d, *J* = 6.6 Hz, 3H),

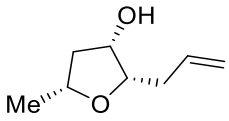
0.88 (d, *J* = 6.6 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 163.0, 155.7, 137.5, 129.7, 129.4, 128.4, 126.5, 114.3, 80.1, 75.8, 74.0, 72.5, 71.1, 59.2, 58.7, 55.5, 54.9, 53.6, 40.6, 35.3, 27.2, 21.3, 20.1, 19.8; LRMS-ESI (m/z): 578.0 $(M+Na)^+$; HRMS-ESI (m/z): $C_{29}H_{42}N_2O_8S$; calc'd for $[M+Na]^+$: 601.2554, found 601.2557; $[\alpha]_D^{20}$ +10.2 (c 0.13, $CHCl_3$).




**63**

(*2R,3R,5S*)-2-(methoxymethyl)-5-methyltetrahydrofuran-3-yl.((*2S,3R*)-4-((4-amino-*N*-isobutylphenyl)sulfonamido)-3-hydroxy-1-phenylbutan-2-yl)carbamate (**63**)

Following **General Procedure C**, inhibitor **63** (16 mg, 54 % yield) was prepared from activated alcohol **(-)-54** (16 mg, 0.05 mmol). $^1$H NMR (500 MHz, $CDCl_3$) δ: 7.54 (d, *J* = 8.7 Hz, 2H), 7.33 – 7.16 (m, 5H), 6.67 (d, *J* = 8.7 Hz, 2H), 5.06 (ddd, *J* = 6.8, 4.3, 2.5 Hz, 1H), 4.87 (d, *J* = 8.6 Hz, 1H), 4.18 (brs, 1H), 3.94 (ddt, *J* = 13.6, 7.4, 6.2 Hz, 1H), 3.89 – 3.81 (m, 4H), 3.50 (d, *J* = 4.7 Hz, 2H), 3.33 (s, 3H), 3.13 (dd, *J* = 15.1, 8.2 Hz, 1H), 3.05 – 2.91 (m, 3H), 2.83 (dd, *J* = 14.0, 8.6 Hz, 1H), 2.76 (dd, *J* = 13.3, 6.6 Hz, 1H), 2.33 (dt, *J* = 14.2, 7.1 Hz, 1H), 1.88 – 1.75 (m, 1H), 1.27 (d, *J* = 15.5 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ: 155.6, 150.7, 137.6, 129.4, 128.4, 126.4, 126.0, 114.0, 80.1, 75.7, 74.1, 72.6, 71.1, 59.2, 58.8, 54.9, 53.7, 40.6, 35.3, 27.2, 21.3, 20.1, 19.8; LRMS-ESI (m/z): 564.0 $(M+Na)^+$; HRMS-ESI (m/z): $C_{28}H_{41}N_3O_7S$; calc'd for $[M+Na]^+$: 586.2557, found 586.2562; $[\alpha]_D^{20}$ +1.6 (c 0.13, $CHCl_3$).

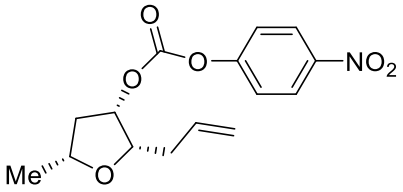



**56**

(*2S,3S,5R*)-2-allyl-5-methyltetrahydrofuran-3-ol (**56**)

To a stirred solution of olefin **(+)-48** (21 mg, 0.08 mmol) in THF (2 mL) was added TBAF solution (1M in THF, 0.20 mL, 0.20 mmol) at 0°C under argon atmosphere. The reaction mixture was warmed to 23 °C and stirred for 3 h. After this period, the reaction was quenched with water

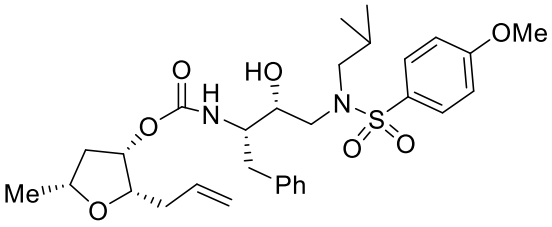
and the aqueous layer was extracted with EtOAc. The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (20 % EtOAc in hexane) to give alcohol **56** (10 mg, 86 %) as a white amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$) δ: 5.94 – 5.82 (m, 1H), 5.20 – 5.05 (m, 2H), 4.27 – 4.17 (m, 1H), 3.98 – 3.88 (m, 1H), 3.66 – 3.55 (m, 1H), 2.50 – 2.35 (m, 3H), 1.70 (brs, 1H), 1.54 – 1.44 (m, 1H), 1.33 (d, *J* = 6.2 Hz, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 134.7, 117.0, 82.3, 73.5, 73.1, 43.1, 33.4, 21.9; LRMS-ESI (m/z): 165.1 $(M+Na)^+$; $[\alpha]_D^{20}$ +8.6 (c 0.33, $CHCl_3$).




**57**

(*2S,3S,5R*)-2-allyl-5-methyltetrahydrofuran-3-yl (4-nitrophenyl) carbonate (**57**)

Following **General Procedure A**, activated alcohol **57** (5 mg, 24 % yield) was prepared as a white amorphous solid from alcohol **56** (10 mg, 0.07 mmol).$^1$H NMR (400 MHz, $CDCl_3$) δ: 8.28 (d, *J* = 9.2 Hz, 2H), 7.38 (d, *J* = 9.2 Hz, 2H), 5.91 – 5.80 (m, 1H), 5.26 (ddd, *J* = 6.6, 3.9, 2.3 Hz, 1H), 5.22 – 5.07 (m, 2H), 4.02 (ddt, *J* = 13.5, 7.3, 6.2 Hz, 1H), 3.83 (ddd, *J* = 7.3, 6.5, 3.9 Hz, 1H), 2.64 – 2.55 (m, 1H), 2.55 – 2.46 (m, 2H), 1.77 – 1.69 (m, 1H), 1.37 (d, *J* = 6.1 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 155.4, 152.1, 145.3, 133.9, 125.2, 121.6, 117.4, 80.9, 80.7, 73.7, 40.5, 33.4, 21.3; LRMS-ESI (m/z): 330.1 $(M+Na)^+$; $[\alpha]_D^{20}$ +8.0 (c 0.33, $CHCl_3$).

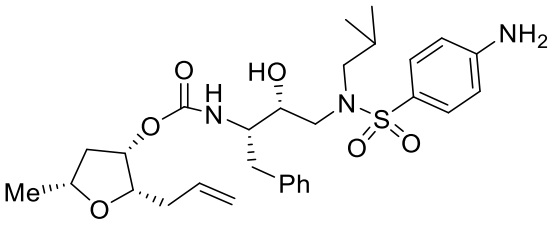



**64**

(*2S,3S,5R*)-2-allyl-5-methyltetrahydrofuran-3-yl.((*2S,3R*)-3-hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate (**64**)

Following **General Procedure B**, inhibitor **64** (7 mg, 97 % yield) was prepared as a white amorphous solid from activated alcohol **57** (5 mg, 0.02 mmol). $^1$H NMR (500 MHz, $CDCl_3$) δ: 7.72 (d, *J* = 8.9 Hz, 2H), 7.30 – 7.19 (m, 5H), 6.98 (d, *J* = 8.9 Hz, 2H), 5.70 (ddt, *J* = 18.8, 9.1, 6.9 Hz, 1H), 5.08 – 4.97 (m, 3H), 4.85 (d, *J* = 8.2 Hz, 1H), 3.88 (s, 3H), 3.86 – 3.81 (m, 3H), 3.62

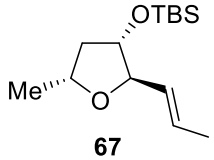
(ddd, *J* = 7.8, 5.9, 4.0 Hz, 1H), 3.15 (dd, *J* = 15.1, 7.7 Hz, 1H), 3.07 – 2.93 (m, 3H), 2.90 – 2.75 (m, 2H), 2.41 (dt, *J* = 14.3, 7.2 Hz, 1H), 2.19 (dt, *J* = 14.5, 7.4 Hz, 1H), 2.14 – 2.06 (m, 1H), 1.89 – 1.77 (m, 1H), 1.45 (ddd, *J* = 14.0, 7.3, 2.4 Hz, 1H), 1.28 (d, *J* = 6.2 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.5 Hz, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ: 163.0, 155.8, 137.4, 134.4, 129.4, 129.3, 128.5, 126.5, 116.9, 114.3, 81.3, 75.6, 73.5, 72.7, 58.7, 55.6, 54.9, 53.7, 53.4, 40.7, 35.3, 33.2, 27.2, 21.3, 20.1, 19.8; LRMS-ESI (m/z): 575.0 $(M+H)^+$; HRMS-ESI (m/z): $C_{30}H_{42}N_2O_7S$; calc'd for $[M+Na]^+$: 597.2605, found 597.2611; $[\alpha]_D^{20}$ +12.1 (c 0.13, $CHCl_3$).




**65**

(*2S,3S,5R*)-2-allyl-5-methyltetrahydrofuran-3-yl.((*2S,3R*)-4-((4-amino-*N*-isobutylphenyl)sulfonamido)-3-hydroxy-1-phenylbutan-2-yl)carbamate (**65**)

Following **General Procedure C**, inhibitor **65** (7 mg, 62 % yield) was prepared as a yellow amorphous solid from activated alcohol **57** (7 mg, 0.02 mmol).$^1$H NMR (400 MHz, $CDCl_3$) δ: 7.55 (d, *J* = 8.2 Hz, 2H), 7.34 – 7.14 (m, 5H), 6.69 (d, *J* = 8.2 Hz, 2H), 5.72 – 5.62 (m, 1H), 5.07 – 5.03 (m, 1H), 5.02 – 4.96 (m, 2H), 4.85 (d, *J* = 7.8 Hz, 1H), 3.92 – 3.85 (m, 1H), 3.84 (s, 3H), 3.62 – 3.60 (m, 1H), 3.18 – 2.72 (m, 6H), 2.44 – 2.30 (m, 1H), 2.25 – 2.05 (m, 2H), 1.88 – 1.78 (m, 1H), 1.49 – 1.41 (m, 1H), 1.27 (d, *J* = 6.2 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 155.9, 137.6, 134.5, 129.5, 129.4, 128.5, 126.6, 117.0, 114.2, 81.42, 75.7, 73.6, 72.8, 58.8, 55.0, 53.8, 40.8, 35.4, 33.3, 27.3, 21.4, 20.2, 19.9; LRMS-ESI (m/z): 560.0 $(M+H)^+$; HRMS-ESI (m/z): $C_{29}H_{41}N_3O_6S$; calc'd for $[M+Na]^+$: 582.2608, found 582.2615; $[\alpha]_D^{20}$ +14.3 (c 0.33, $CHCl_3$).

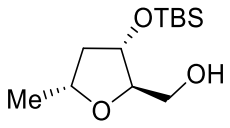



**67**

*tert*-butyldimethyl(((*2R,3S,5R*)-5-methyl-2-(prop-1-en-1-yl)tetrahydrofuran-3-yl)oxy)silane (**67**)

By following the procedure outlined for the preparation of olefin **50**, olefin **67** (40 mg, 34 %; 61% brsm) was obtained as a colorless oil from compound **(+)-49** (115 mg, 0.45 mmol)

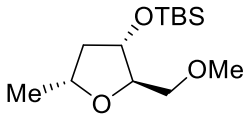
after terminal olefin migration; 51 mg of the starting material, **(+)-49**, was recovered.[1]H NMR (400 MHz, $CDCl_3$) δ: 5.78 – 5.65 (m, 1H), 5.44 – 5.31 (m, 1H), 4.23 – 4.15 (m, 1H), 4.12 – 3.95 (m, 2H), 2.30 – 2.21 (m, 1H), 1.69 (d, *J* = 4.1 Hz, 3H), 1.68 – 1.55 (m, 1H), 1.28 (d, *J* = 4.1 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 130.2, 128.6, 85.2, 76.6, 73.4, 42.4, 25.6, 22.2, 18.0, 17.6, -4.7, -5.3. LRMS-ESI (m/z): 279.3 $(M+Na)^+$




**(+)-68**

((*2R,3S,5R*)-3-((*tert*-butyldimethylsilyl)oxy)-5-methyltetrahydrofuran-2-yl)methanol (**(+)-68**)

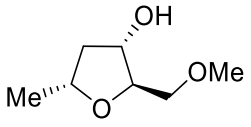
By following the procedure outlined for the preparation of alcohol **(+)-51**, alcohol **(+)-68** (16 mg, 85 % yield over two steps) was obtained as a yellowish oil from olefin **67** (19 mg, 0.08 mmol) after ozonolysis and $NaBH_4$ reduction. $^1$H NMR (400 MHz, $CDCl_3$) δ: 4.28 – 4.14 (m, 2H), 3.86 – 3.79 (m, 1H), 3.80 – 3.50 (m, 2H), 2.31 – 2.20 (m, 1H), 2.01 (brs, 1H), 1.65 – 1.58 (m, 1H), 1.30 (d, *J* = 5.2 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 84.6, 74.4, 72.8, 62.2, 42.9, 26.6, 21.8, 17.8, -4.7, -5.3. LRMS-ESI (m/z): 269.2 $(M+Na)^+$; $[\alpha]_D^{20}$ +33.0 (c 1.0, $CHCl_3$).




**(+)-69**

*tert*-butyl(((*2R,3S,5R*)-2-(methoxymethyl)-5-methyltetrahydrofuran-3-yl)oxy)dimethylsilane (**(+)-69**)

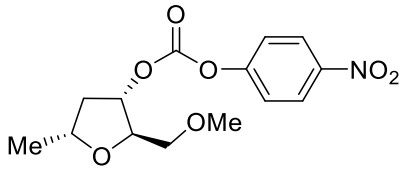
By following the procedure outlined for the preparation of methyl ether **(+)-52**, methyl ether **(+)-69** (14 mg, 90% yield) was obtained as a yellow oil from alcohol **(+)-68** (15 mg, 0.06 mmol) after methylation. $^1$H NMR (400 MHz, $CDCl_3$) δ: 4.44 – 4.15 (m, 2H), 3.90 – 3.85 (m, 1H), 3.51 – 3.47 (m, 1H), 3.40 – 3.38 (m, 1H), 3.38 (s, 3H), 2.28 – 2.20 (m, 1H), 1.60 – 1.52 (m, 1H), 1.29 (d, *J* = 6.2 Hz, 3H), 0.88 (s, 9H), 0.01 (s, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 83.3, 74.1, 73.3, 72.8, 59.2, 42.7, 25.6, 21.8, 17.9, -4.6, -5.3; LRMS-ESI (m/z): 283.2 $(M+Na)^+$; $[\alpha]_D^{20}$ +37.0 (c 0.67, $CHCl_3$).




**(+)-70**

(*2R,3S,5R*)-2-(methoxymethyl)-5-methyltetrahydrofuran-3-ol (**(+)-70**)

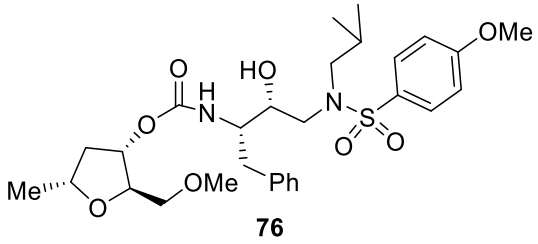
By following the procedure outlined for the preparation of alcohol **(+)-53**, alcohol **(+)-70** (7 mg, 93 % yield) was obtained as a colorless oil from methyl ether **(+)-69** (14 mg, 0.05 mmol) after TBAF deprotection.$^{1}$H NMR (400 MHz, $CDCl_3$) δ: 4.30 – 4.14 (m, 2H), 3.96 – 3.88 (m, 1H), 3.54 – 3.47 (m, 1H), 3.46 - 3.40 (m, 1H), 3.38 (s, 3H), 2.43 – 2.35 (m, 1H), 2.12 (brs, 1H), 1.63 – 1.57 (m, 1H), 1.30 (d, *J* = 6.2 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 82.6, 74.4, 74.2, 73.4, 59.3, 42.2, 21.8; LRMS-ESI (m/z): 169.1 $(M+Na)^+$; $[\alpha]_D^{20}$ +17.3 (c 0.33, $CHCl_3$).




**(+)-71**

(*2R,3S,5R*)-2-(methoxymethyl)-5-methyltetrahydrofuran-3-yl (4-nitrophenyl) carbonate (**(+)-71**)

Following **General Procedure A**, activated alcohol **(+)-71** (13 mg, 78 % yield) was prepared as a white amorphous solid from alcohol **(+)-70** (7 mg, 0.05 mmol). $^{1}$H NMR (400 MHz, $CDCl_3$) δ: 8.28 (d, *J* = 9.2 Hz, 2H), 7.38 (d, *J* = 9.2 Hz, 2H), 5.22 (ddd, *J* = 7.2, 4.1, 3.1 Hz, 1H), 4.40 – 4.32 (m, 1H), 4.29 (td, *J* = 4.5, 3.1 Hz, 1H), 3.57 – 3.48 (m, 2H), 3.39 (s, 3H), 2.57 (dt, *J* = 13.9, 7.1 Hz, 1H), 1.82 (ddd, *J* = 13.6, 6.2, 4.0 Hz, 1H), 1.34 (d, *J* = 6.3 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 155.4, 152.2, 145.5, 125.3, 121.7, 81.9, 81.7, 75.2, 73.1, 59.5, 39.2, 21.5; LRMS-ESI (m/z): 344.2 $(M+Na)^+$; $[\alpha]_D^{20}$ +18.9 (c 0.13, $CHCl_3$).

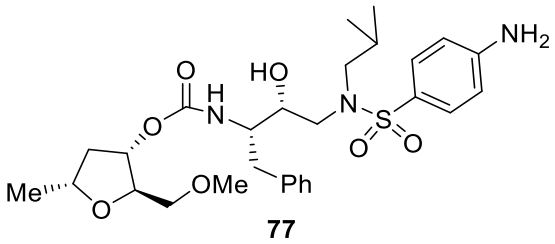



**76**

(*2R,3S,5R*)-2-(methoxymethyl)-5-methyltetrahydrofuran-3-yl ((*2S,3R*)-3-hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate (**76**)

Following **General Procedure B**, inhibitor **76** (10 mg, 76 % yield) was prepared as a white amorphous solid from activated alcohol **(+)-71** (7 mg, 0.02 mmol). $^{1}$H NMR (400 MHz, $CDCl_3$)

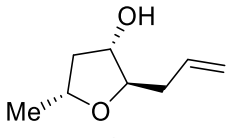
δ: 7.70 (d, *J* = 8.9 Hz, 2H), 7.31 – 7.20 (m, 5H), 6.97 (d, *J* = 8.8 Hz, 2H), 4.96 – 4.91 (m, 1H), 4.88 (d, *J* = 8.4 Hz, 1H), 4.28 – 4.19 (m, 1H), 3.87 (s, 3H), 3.85 – 3.79 (m, 1H), 3.43 – 3.35 (m, 2H), 3.33 (s, 3H), 3.16 – 3.07 (m, 1H), 3.03 – 2.85 (m, 5H), 2.79 (dd, *J* = 13.3, 6.6 Hz, 1H), 2.41 – 2.29 (m, 1H), 1.87 – 1.75 (m, 1H), 1.63 – 1.51 (m, 2H), 1.29 – 1.26 (m, 3H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 163.0, 156.0, 137.5, 129.7, 129.4, 128.4, 126.5, 114.3, 108.6, 82.1, 76.8, 74.6, 73.1, 72.5, 59.2, 58.7, 55.5, 55.1, 53.6, 39.3, 35.3, 27.2, 21.4, 20.1, 19.8. LRMS-ESI (m/z): 579.0 $(M+H)^+$; HRMS-ESI (m/z): $C_{29}H_{42}N_2O_8S$; calc'd for $[M+Na]^+$: 601.2554, found 601.2558; $[\alpha]_D^{20}$ +24.1 (c 0.13, $CHCl_3$).




**77**

(*2R,3S,5R*)-2-(methoxymethyl)-5-methyltetrahydrofuran-3-yl ((*2S,3R*)-4-((4-amino-*N*-isobutylphenyl)sulfonamido)-3-hydroxy-1-phenylbutan-2-yl)carbamate (**77**)

Following **General Procedure C**, inhibitor **77** (6.5 mg, 60 % yield) was prepared as a yellow amorphous solid from activated alcohol **(+)-71** (6 mg, 0.02 mmol).$^1$H NMR (500 MHz, $CDCl_3$) δ: 7.54 (d, *J* = 8.7 Hz, 2H), 7.33 – 7.16 (m, 5H), 6.68 (d, *J* = 8.5 Hz, 2H), 4.95 – 4.90 (m, 1H), 4.88 (d, *J* = 8.8 Hz, 1H), 4.29 – 4.18 (m, 2H), 3.94 – 3.87 (m, 2H), 3.87 – 3.75 (m, 2H), 3.41 – 3.36 (m, 2H), 3.34 (s, 3H), 3.11 (dd, *J* = 15.1, 8.3 Hz, 1H), 3.03 – 2.84 (m, 5H), 2.76 (dd, *J* = 13.3, 6.7 Hz, 1H), 2.42 – 2.31 (m, 1H), 1.88 – 1.74 (m, 1H), 1.60 – 1.49 (m, 1H), 1.24 (d, *J* = 4.1 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ: 155.9, 150.6, 137.5, 129.4, 129.4, 128.4, 126.5, 114.0, 82.1, 74.6, 73.1, 72.5, 59.2, 58.8, 55.0, 53.7, 39.3, 35.3, 27.2, 21.4, 20.1, 19.8; LRMS-ESI (m/z): 564.0 $(M+H)^+$; HRMS-ESI (m/z): $C_{28}H_{41}N_3O_7S$; calc'd for $[M+Na]^+$: 586.2557, found 586.2564; $[\alpha]_D^{20}$ +17.7 (c 0.20, $CHCl_3$).

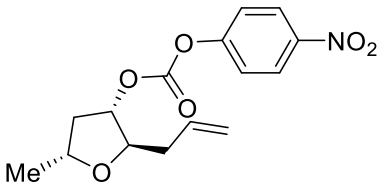



**72**

(*2R,3S,5R*)-2-allyl-5-methyltetrahydrofuran-3-ol (**72**)

By following the procedure outlined for the preparation of alcohol **57**, alcohol **72** (16 mg, 98 % yield) was obtained from **(+)-49** (29 mg, 0.11 mmol) as a yellow oil after TBAF deprotection.

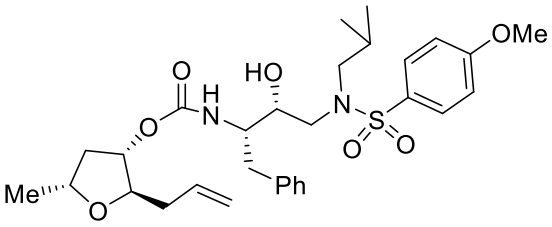
$^1$H NMR (400 MHz, $CDCl_3$) δ: 5.92 – 5.78 (m, 1H), 5.19 – 5.06 (m, 2H), 4.23 – 4.09 (m, 2H), 3.87 (td, *J* = 6.6, 4.6 Hz, 1H), 2.42 – 2.21 (m, 4H), 1.71 (s, 1H), 1.58 (ddd, *J* = 13.0, 7.4, 5.9 Hz, 1H), 1.31 (d, *J* = 6.2 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 134.2, 117.4, 83.7, 76.3, 73.3, 42.1, 37.6, 22.1; LRMS-ESI (m/z): 165.1 $(M+Na)^+$; $[\alpha]_D^{72}$ +37.1 (c 1.0, $CHCl_3$).




**73**

(*2R,3S,5R*)-2-allyl-5-methyltetrahydrofuran-3-yl (4-nitrophenyl) carbonate (**73**)

Following **General Procedure A**, activated alcohol **73** (10 mg, 30 % yield) was prepared as a yellow oil from alcohol **72** (16 mg, 0.11 mmol).$^1$H NMR (500 MHz, $CDCl_3$) δ: 8.28 (d, *J* = 9.2 Hz, 2H), 7.39 (d, *J* = 9.2 Hz, 2H), 5.89 – 5.78 (m, 1H), 5.20 – 5.11 (m, 2H), 5.03 (ddd, *J* = 7.1, 3.4, 2.7 Hz, 1H), 4.36 – 4.28 (m, 1H), 4.26 (td, *J* = 6.7, 2.7 Hz, 1H), 2.60 – 2.51 (m, 1H), 2.34 (tt, *J* = 6.8, 1.3 Hz, 2H), 1.82 (ddd, *J* = 13.9, 5.8, 3.5 Hz, 1H), 1.34 (d, *J* = 6.3 Hz, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ: 155.4, 152.1, 145.4. 133.4, 125.3, 121.8, 118.0, 83.3, 82.1, 73.9, 53.4, 38.6, 37.3, 21.7; LRMS-ESI (m/z): 330.1 $(M+Na)^+$; $[\alpha]_D^{20}$ +15.1 (c 0.64, $CHCl_3$).

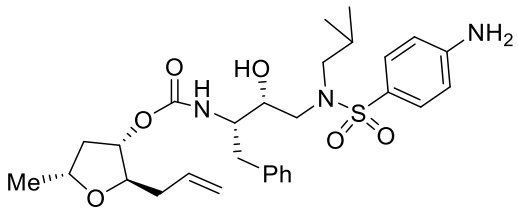



**78**

(*2R,3S,5R*)-2-allyl-5-methyltetrahydrofuran-3-yl ((*2S,3R*)-3-hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate (**78**)

Following **General Procedure B**, inhibitor **78** (8.5 mg, 68 % yield) was prepared as a white amorphous solid from activated alcohol **73** (6.5 mg, 0.02 mmol). $^1$H NMR (800 MHz, $CDCl_3$) δ: 7.71 (d, *J* = 8.8 Hz, 2H), 7.33 – 7.20 (m, 5H), 6.98 (d, *J* = 8.5 Hz, 2H), 5.81 – 5.70 (m, 1H), 5.12 – 5.03 (m, 2H), 4.83 (d, *J* = 9.0 Hz, 1H), 4.81 – 4.78 (m, 1H), 4.22 – 4.15 (m, 1H), 3.88 (s, 3H), 3.87 – 3.77 (m, 3H), 3.12 (dd, *J* = 15.0, 8.5 Hz, 1H), 3.04 – 2.98 (m, 2H), 2.96 (dd, *J* = 13.2, 8.4 Hz, 1H), 2.89 (dd, *J* = 14.0, 8.8 Hz, 1H), 2.79 (dd, *J* = 13.5, 6.7 Hz, 1H), 2.40 – 2.33 (m, 1H), 2.25 – 2.16 (m, 2H), 1.86 – 1.78 (m, 1H), 1.65 – 1.53 (m, 2H), 1.24 (d, *J* = 6.4 Hz, 3H), 0.91 (d, *J*

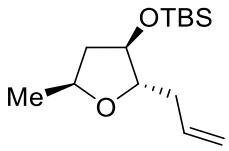
= 6.2 Hz, 3H), 0.87 (d, *J* = 6.5 Hz, 3H); $^{13}$C NMR (201 MHz, $CDCl_3$) δ: 137.6, 134.0, 129.5, 129.5, 128.5, 126.6, 117.4, 114.4, 82.3, 78.9, 73.7, 72.6, 58.8, 55.6, 55.1, 53.7, 39.0, 37.3, 35.4, 27.3, 21.7, 20.1, 19.9; LRMS-ESI (m/z): 575.0 $(M+H)^+$; HRMS-ESI (m/z): $C_{30}H_{42}N_2O_7S$; calc'd for $[M+Na]^+$: 597.2605, found 597.2613;$[\alpha]_D^{20}$ +23.3 (c 0.13, $CHCl_3$).




**79**

(*2R,3S,5R*)-2-allyl-5-methyltetrahydrofuran-3-yl ((*2S,3R*)-4-((4-amino-*N*-isobutylphenyl)sulfonamido)-3-hydroxy-1-phenylbutan-2-yl)carbamate (**79**)

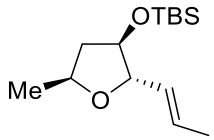
Following **General Procedure C**, inhibitor **79** (5.5 mg, 71 % yield) was prepared as a white amorphous solid from activated alcohol **73** (4 mg, 0.01 mmol). $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.54 (d, *J* = 8.4 Hz, 2H), 7.34 – 7.17 (m, 5H), 6.69 (d, *J* = 8.4 Hz, 2H), 5.79 – 5.69 (m, 1H), 5.13 – 5.01 (m, 2H), 4.88 – 4.76 (m, 2H), 4.23 – 4.12 (m, 1H), 3.84 (s, 3H), 3.17 – 3.08 (m, 1H), 3.05 – 2.83 (m, 5H), 2.81 – 2.72 (m, 1H), 2.40 – 2.30 (m, 1H), , 2.24 – 2.14 (m, 2H), 1.85 – 1.75 (m, 1H), 1.60 – 1.51 (m, 1H), 1.22 (d, *J* = 6.4 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.5Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 156.0, 150.5, 137.6, 134.0, 129.5, 128.5, 126.6, 117.4, 114.2, 82.2, 78.8, 73.7, 72.6, 58.8, 55.1, 53.8, 39.0, 37.3, 35.4, 27.3, 21.7, 20.2, 19.9. LRMS-ESI (m/z): 560.0 $(M+H)^+$; HRMS-ESI (m/z): $C_{29}H_{41}N_3O_6S$; calc'd for $[M+H]^+$: 560.2789, found 560.2794; $[\alpha]_D^{20}$ +29.8 (c 0.13, $CHCl_3$).




**(-)-49**

(((*2S,3R,5S*)-2-allyl-5-methyltetrahydrofuran-3-yl)oxy)(*tert*-butyl)dimethylsilane (**(-)-49**)

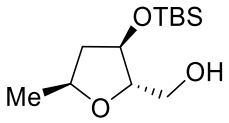
Allyl derivative **(-)-49** (43 mg, 28 % over two steps) was obtained as a single isomer from lactone **(-)-2** (144 mg, 0.63 mmol) over two steps as a colorless oil by following the procedure described above for its enantiomer **(+)-49.** For NMR data, please see compound **(+)-49**. LRMS-ESI (m/z): 279.3 $(M+Na)^+$; $[\alpha]_D^{20}$ -35.2 (c 1.0, $CHCl_3$).




**75**

*tert*-butyldimethyl(((*2S,3R,5S*)-5-methyl-2-(prop-1-en-1-yl)tetrahydrofuran-3-yl)oxy)silane (**75**)

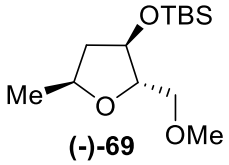
To a stirred mixture of olefin **(-)-49** (43 mg, 0.17 mmol) and vinyloxy-trimethylsilane (0.25 mL, 1.68 mmol) in toluene (8.2 mL) was added the second-generation Grubb's catalyst (7 mg, 0.008 mmol) at 23 $^{o}$C under argon atmosphere. The reaction mixture was heated to 110 $^{o}$C and vigorously stirred for 24 h. After this period, the mixture was cooled to 23 $^{o}$C and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (2 % Diethyl ether in hexanes) to give olefin **75** (20 mg, 47 %) as a colorless oil. For NMR data, please see compound **67**. LRMS-ESI (m/z): 279.3 $(M+Na)^{+}$.




**(-)-68**

((*2S,3R,5S*)-3-((*tert*-butyldimethylsilyl)oxy)-5-methyltetrahydrofuran-2-yl)methanol (**(-)-68**)

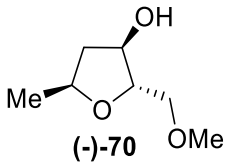
Alcohol **(-)-68** (15 mg, 78 %) was obtained as a yellow oil from olefin **75** (20 mg, 0.08 mmol) by following the procedure described above for its enantiomer **(+)-68.** For NMR data, please see compound **(+)-68**. LRMS-ESI (m/z): 269.2 $(M+Na)^{+}$; $[\alpha]_D^{20}$ -32.2 (c 0.50, $CHCl_3$).




**(-)-69**

*tert*-butyl(((*2S,3R,5S*)-2-(methoxymethyl)-5-methyltetrahydrofuran-3-yl)oxy)dimethylsilane (**(-)-69**)

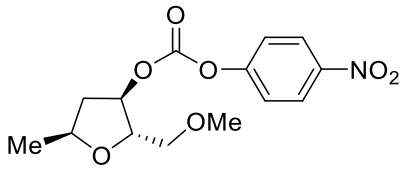
Compound **(-)-69** (9.5 mg, 63 %) was obtained as a yellow oil from alcohol **(-)-68** (14.5 mg, 0.06 mmol) by following the procedure described above for its enantiomer **(+)-69.** For NMR data, please see compound **(+)-69**. LRMS-ESI (m/z): 283.2 $(M+Na)^{+}$; $[\alpha]_D^{20}$ -36.6 (c 0.30, $CHCl_3$).




**(-)-70**

(*2S,3R,5S*)-2-(methoxymethyl)-5-methyltetrahydrofuran-3-ol (**(-)-70**)

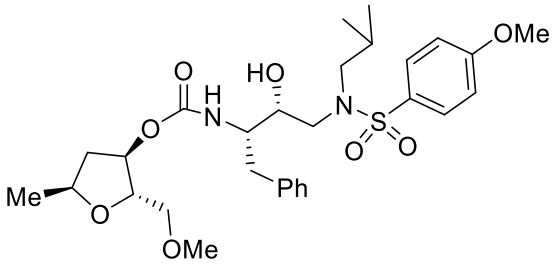
Compound **(-)-70** (4.6 mg, 96 %) was obtained as a colorless oil from alcohol **(-)-69** (8 mg, 0.03 mmol) by following the procedure described above for its enantiomer **(+)-70.** For NMR data, please see compound **(+)-70**. LRMS-ESI (m/z): 169.1 $(M+Na)^+$; $[\alpha]_D^{20}$ -16.7 (c 0.13, $CHCl_3$).




**(-)-71**

(*2S,3R,5S*)-2-(methoxymethyl)-5-methyltetrahydrofuran-3-yl (4-nitrophenyl) carbonate (**(-)-71**)

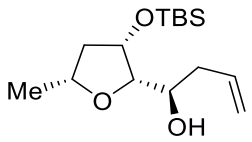
By following **General Procedure A**, activated alcohol **(-)-71** (4 mg, 40 % yield) was prepared as a white amorphous solid from alcohol **(-)-70** (4.6 mg, 0.03 mmol). For NMR data, please see compound **(+)-71**. LRMS-ESI (m/z): 344.2 $(M+Na)^+$; $[\alpha]_D^{20}$ -19.1 (c 0.13, $CHCl_3$).




**80**

(*2S,3R,5S*)-2-(methoxymethyl)-5-methyltetrahydrofuran-3-yl ((*2S,3R*)-3-hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate (**80**)

By following **General Procedure B**, inhibitor **80** (4.3 mg, 66 % yield) was prepared as a white amorphous solid from activated alcohol **(-)-71** (3.5 mg, 0.01 mmol). $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.70 (d, *J* = 8.7 Hz, 2H), 7.34 – 7.17 (m, 5H), 6.98 (d, *J* = 8.7 Hz, 2H), 4.93 – 4.88 (m, 1H), 4.85 – 4.80 (m, 1H), 4.26 – 4.20 (m, 1H), 4.07 – 4.04 (m, 1H), 3.88 (s, 3H), 3.87 – 3.82 (m, 2H), 3.41 (d, *J* = 4.3 Hz, 2H), 3.34 (s, 3H), 3.20 – 3.10 (m, 1H), 3.05 – 2.89 (m, 5H), 2.84 – 2.75 (m, 1H), 2.38 – 2.26 (m, 1H), 1.68 – 1.61 (m, 1H), 1.51 – 1.44 (m, 1H), 1.22 (d, *J* = 6.2 Hz, 3H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.87 (d, *J* = 6.4 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 163.1, 156.0, 137.6, 129.8, 129.5, 129.3, 128.5, 126.6, 114.4, 82.0, 77.2, 74.8, 73.2, 72.6, 59.3, 58.8, 55.6, 55.0, 53.8, 39.4, 35.6, 27.3, 21.6, 20.1, 19.9; LRMS-ESI (m/z): 579.0 $(M+H)^+$; HRMS-ESI (m/z): $C_{29}H_{42}N_2O_8S$; calc'd for $[M+Na]^+$: 601.2554, found 601.2560; $[\alpha]_D^{20}$ + 0.94 (c 0.10, $CHCl_3$).

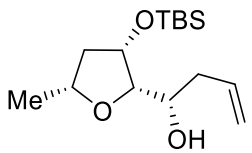



**82**

(*R*)-1-((*2S,3S,5R*)-3-((*tert*-butyldimethylsilyl)oxy)-5-methyltetrahydrofuran-2-yl)but-3-en-1-ol (**82**)

Ozone gas was bubbled into a solution of olefin **50** (78 mg, 0.30 mmol) in $CH_2Cl_2$ (5 mL) at -78 °C for 10 min. After the solution turned to pale blue, oxygen was bubbled into the solution for 10 min and triphenylphosphine (96 mg, 0.36 mmol) was added. The reaction mixture was stirred for 15 min at -78 °C and warmed to rt for 1h. After this period, solvent was concentrated under reduced pressure and the crude residue was passed through a flash silica gel column to afford aldehyde **81** (56 mg, 76 % yield) as a colorless oil. This sensitive aldehyde was used immediately after the quick purification step with 50% EtOAc in hexanes.

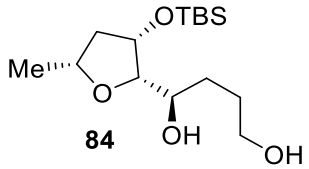
To a stirred solution of aldehyde **81** (56 mg, 0.23 mmol) in distilled $CH_2Cl_2$ (5 mL) were consecutively added allyltributylstannane (0.29 mL, 0.91 mmol) and $BF_3$ $OEt_2$ (85 µL, 0.69 mmol) at -78 $^oC$ under argon atmosphere. The reaction mixture was slowly warmed to room temperature over 6h and stirred at room temperature for 12h. After this period, the reaction was quenched with saturated aqueous $NH_4Cl$ and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (5% EtOAc in hexanes to 10% EtOAc in hexanes) to give olefin **82** (52 mg, 79 %) as a colorless oil with *dr* of 4.2:1; $^1$H NMR (400 MHz, $CDCl_3$) δ: 5.98 – 5.86 (m, 1H), 5.21 – 5.05 (m, 2H), 4.56 (dt, J = 6.6, 5.5 Hz, 1H), 4.02 – 3.84 (m, 2H), 3.56 (dd, J = 7.5, 5.4 Hz, 1H), 3.00 (brs, 1H), 2.57 – 2.48 (m, 1H), 2.35 – 2.23 (m, 2H), 1.54 (ddd, J = 12.6, 8.1, 5.5 Hz, 1H), 1.29 (d, J = 6.1 Hz, 3H), 0.91 (s, 9H), 0.11 (d, J = 2.3 Hz, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 135.2, 117.1, 82.6, 74.3, 73.4, 70.2, 42.7, 38.3, 25.7, 21.7, 17.8, -4.4, -5.3; LRMS-ESI (m/z): 309.2 $(M+Na)^+$; $[\alpha]_D^{20}$ +24.8 (*c* 1.0, $CHCl_3$).




**83**

(*S*)-1-((*2S,3S,5R*)-3-((*tert*-butyldimethylsilyl)oxy)-5-methyltetrahydrofuran-2-yl)but-3-en-1-ol (**83**)

Aldehyde **81** (43 mg, 65 % yield) was obtained from olefin **50** (57 mg, 0.22 mmol) as described above**.** To a stirred solution of aldehyde **80** (43 mg, 0.18 mmol) in distilled $CH_2Cl_2$ (5 mL) were consecutively added $MgBr_2$ $OEt_2$ (137 mg, 0.53 mmol) and allyltributylstannane (0.27 mL, 0.88 mmol) at 23 $^oC$ under argon atmosphere. After stirring for 4 h at 23 $^oC$, the reaction was quenched with saturated aqueous $NH_4Cl$ and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (5% EtOAc in hexanes to 10% EtOAc in hexanes) to afford colorless oil olefin **83** (22 mg, 42 %) as a major product with *dr* of 1.3:1; $^1H$ NMR (400 MHz, $CDCl_3$) δ: 5.90 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.18 – 5.04 (m, 2H), 4.42 (dt, *J* = 6.5, 4.7 Hz, 1H), 4.01 – 3.88 (m, 2H), 3.57 (t, *J* = 4.6 Hz, 1H), 3.14 (brs, 1H), 2.33 (dt, *J* = 19.5, 6.4 Hz, 3H), 1.54 (td, *J* = 7.8, 3.8 Hz, 1H), 1.34 (d, *J* = 6.1 Hz, 3H), 0.90 (s, 9H), 0.09 (s, 6H); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ: 135.1, 116.9, 83.2, 74.6, 73.4, 70.1, 43.7, 37.7, 25.6, 21.4, 17.8, -4.5, -5.3; LRMS-ESI (m/z): 309.2 $(M+Na)^+$; $[\alpha]_D^{20}$ + 16.7 (*c* 0.67, $CHCl_3$).

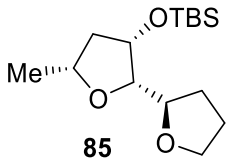



**84**

(*R*)-1-((*2S,3S,5R*)-3-((*tert*-butyldimethylsilyl)oxy)-5-methyltetrahydrofuran-2-yl)butane-1,4-diol (**84**)

To a stirred solution of olefin **82** (45 mg, 0.16 mmol) in distilled THF (1.6 mL) was added dropwise a solution of 9-BBN (0.5 M in THF, 0.80 mL, 0.40 mmol) at 0$^oC$ under argon atmosphere. The mixture was warmed to room temperature and stirred for 6 h. Upon completion, aqueous 3N NaOH solution (0.5 mL) and 30% $H_2O_2$ (1 mL) were added and the resulting mixture was stirred for 3 h at room temperature. Water (2 mL) was added and the aqueous layer was extracted with $Et_2O$ (3 x 20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (60 % EtOAc in hexanes to 80% EtOAc in hexanes) to provide diol **84** (38 mg, 80 %) as a colorless oil;$^1H$ NMR (400 MHz, $CDCl_3$) δ: 4.57 (q, *J* = 6.1 Hz, 1H), 3.99 – 3.89 (m, 1H), 3.84 (ddd, *J* = 10.2, 8.1, 2.6 Hz, 1H), 3.66 (dtd, *J* = 15.8, 11.0, 5.4 Hz, 2H), 3.55 (dd, *J* = 7.7, 5.7 Hz, 1H), 2.27 (dt, *J* = 12.8, 6.4 Hz, 1H), 1.90 (dtd, *J* = 13.9, 6.7, 2.6 Hz, 1H), 1.76 (dq, *J* = 9.1, 6.9, 6.4 Hz, 2H), 1.53 (ddd, *J* = 12.9, 8.5, 6.0 Hz, 2H), 1.27 (d, *J* = 6.1 Hz, 3H), 0.90 (s, 9H), 0.11

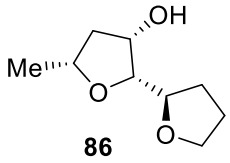
(s, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 82.5, 74.6, 73.3, 71.2, 63.0, 42.5, 30.8, 29.3, 25.6, 21.6, 17.8, -4.4, -5.3; LRMS-ESI (m/z): 327.2 $(M+Na)^+$; $[\alpha]_D^{20}$ +18.7 (*c* 1.0, $CHCl_3$).




**85**

*tert*-butyldimethyl(((*2S,2'R,3S,5R*)-5-methyloctahydro-[2,2'-bifuran]-3-yl)oxy)silane (**85**)

To a stirred solution of diol **84** (35 mg, 0.11 mmol) in $CH_2Cl_2$ (1.8 mL) were added triethylamine (0.10 mL, 0.71 mmol) and DMAP (2.6 mg, 0.02 mmol) at 0 $^oC$ under argon atmosphere. After stirring for 10 mins, 4-toluenesulfonyl chloride (27.2 mg, 0.14 mmol) was added and the resulting mixture was stirred for 24 h at room temperature. The reaction was quenched with saturated aqueous $NH_4Cl$ and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (20% EtOAc in hexanes) to give bicyclic ether **85** (23 mg, 71%) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ: 4.35 (ddd, *J* = 6.6, 4.3, 2.7 Hz, 1H), 4.06 – 3.97 (m, 2H), 3.85 (td, *J* = 7.8, 7.3, 3.7 Hz, 1H), 3.71 – 3.60 (m, 2H), 2.26 (ddd, *J* = 13.4, 7.7, 6.0 Hz, 1H), 2.05 – 1.96 (m, 1H), 1.94 – 1.82 (m, 3H), 1.49 (ddd, *J* = 13.1, 6.1, 2.8 Hz, 1H), 1.30 (d, *J* = 6.2 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 80.1, 77.0, 73.9, 73.0, 67.7, 43.2, 28.1, 25.9, 25.7, 22.0, 18.0, -5.0, -5.2; LRMS-ESI (m/z): 309.2 $(M+Na)^+$; $[\alpha]_D^{20}$ +4.3 (*c* 1.0, $CHCl_3$).

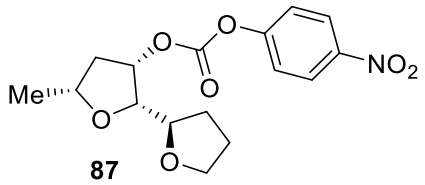



**86**

(*2R,2'R,3S,5R*)-5-methyloctahydro-[2,2'-bifuran]-3-ol (**86**)

To a stirred solution of bicyclic ether **85** (18 mg, 0.06 mmol) was added TBAF solution (1M in THF, 0.10 mL, 0.10 mmol) at 0$^o$C under argon atmosphere. The mixture was stirred for 3h at room temperature. The reaction was quenched with saturated aqueous $NH_4Cl$ and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (80% EtOAc in hexanes) to give alcohol **86** (10 mg, quantitative) as a colorless oil.$^1$H NMR (400 MHz, $CDCl_3$) δ: 4.46 (dt, *J* = 7.4, 3.8 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 1H), 4.02 –

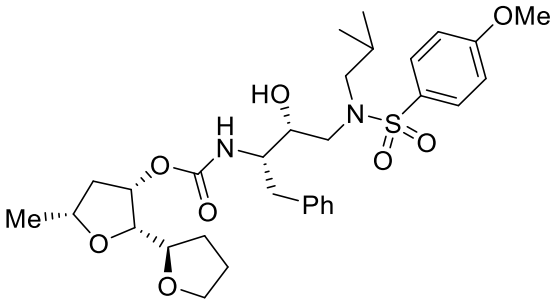
3.92 (m, 1H), 3.89 (dt, *J* = 8.2, 6.4 Hz, 1H), 3.75 (dt, *J* = 8.2, 6.9 Hz, 1H), 3.49 (dd, *J* = 7.8, 4.4 Hz, 1H), 2.93 (s, 1H), 2.36 (dt, *J* = 13.8, 7.0 Hz, 1H), 2.19 – 2.10 (m, 1H), 1.98 – 1.88 (m, 2H), 1.87 – 1.75 (m, 1H), 1.60 – 1.51 (m, 1H), 1.33 (d, *J* = 6.2 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 84.5, 77.8, 77.2, 76.9, 76.6, 74.6, 73.3, 68.2, 42.1, 25.4, 21.6. LRMS-ESI (m/z): 195.1 $(M+Na)^+$; $[\alpha]_D^{20}$ +10.0 (*c* 0.34, $CHCl_3$).




**87**

(*2S,2'R,3S,5R*)-5-methyloctahydro-[2,2'-bifuran]-3-yl (4-nitrophenyl) carbonate (**87**)

By following **General Procedure A**, activated carbonate **87** (17 mg, 82 %) was prepared from alcohol **86** (10 mg, 0.06 mmol).$^1$H NMR (400 MHz, $CDCl_3$) δ: 8.27 (d, *J* = 9.2 Hz, 2H), 7.39 (d, *J* = 9.2 Hz, 2H), 5.40 (ddd, *J* = 7.0, 4.3, 2.9 Hz, 1H), 4.18 – 4.10 (m, 1H), 4.07 (td, *J* = 7.3, 6.1 Hz, 1H), 3.91 – 3.84 (m, 1H), 3.76 (dt, *J* = 8.3, 6.8 Hz, 1H), 3.68 (dd, *J* = 7.9, 4.3 Hz, 1H), 2.58 (dt, *J* = 14.2, 7.1 Hz, 1H), 2.19 – 2.05 (m, 1H), 2.01 – 1.84 (m, 3H), 1.75 (ddd, *J* = 14.2, 7.1, 2.9 Hz, 1H), 1.35 (d, *J* = 6.2 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 125.2, 121.7, 83.2, 80.0, 76.2, 74.2, 68.3 40.2, 29.2, 25.6, 21.3; LRMS-ESI (m/z): 360.2 $(M+Na)^+$; $[\alpha]_D^{20}$ +21.9 (*c* 0.30, $CHCl_3$).

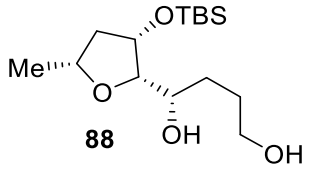



**92**

(*2S,2'S,3S,5R*)-5-methyloctahydro-[2,2'-bifuran]-3-yl ((*2S,3R*)-3-hydroxy-4-((N-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate (**92**)

By following **General Procedure B**, inhibitor **92** (16 mg, 83 % yield) was prepared from activated alcohol **34** (11 mg, 0.03 mmol) as a white amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.71 (d, *J* = 8.7 Hz, 2H), 7.36 – 7.17 (m, 5H), 6.98 (d, *J* = 8.9 Hz, 2H), 5.25 - 5.20 (m, 1H), 4.82 (d, *J* = 7.9 Hz, 1H), 3.98 (q, *J* = 6.6 Hz, 1H), 3.90 (s, 1H), 3.88 (s, 3H), 3.86 - 3.80 (m, 3H), 3.67 - 3.63 (m, 2H), 3.16 – 2.91 (m, 6H), 2.81 (dd, *J* = 13.4, 6.8 Hz, 1H), 2.43 (dt, *J* = 14.2, 7.1 Hz, 1H), 1.89 -1.78 (m, *J* = 6.5 Hz, 5H), 1.58 – 1.40 (m, 2H), 1.27 (d, *J* = 6.1 Hz, 3H), 0.91 (d, *J* = 6.6

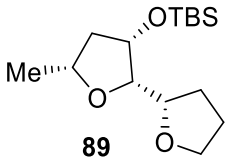
Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 162.9, 155.9, 137.5, 129.8, 129.4, 129.4, 128.4, 126.4, 114.2, 83.3, 77.2, 76.9, 76.6, 76.3, 75.3, 73.9, 72.4, 68.0, 58.6, 55.5, 54.9, 53.5, 40.6, 35.0, 28.1, 27.1, 25.9, 21.4, 20.1, 19.8; LRMS-ESI (m/z): 605.03 $(M+H)^+$; HRMS-ESI (m/z): $C_{31}H_{44}N_2O_8S$; calc'd for $[M+Na]^+$: 627.2716, found 627.2716; $[\alpha]_D^{20}$ +27.3 (*c* 0.67, $CHCl_3$).



**88**

(*S*)-1-((*2S,3S,5R*)-3-((*tert*-butyldimethylsilyl)oxy)-5-methyltetrahydrofuran-2-yl)butane-1,4-diol (**88**)

To a stirred solution of olefin **83** (33 mg, 0.12 mmol) in distilled THF (1.6 mL) was added dropwise a solution of 9-BBN (0.5 M in THF, 0.80 mL, 0.40 mmol) at 0°C under argon atmosphere. The mixture was warmed to room temperature and stirred for 6 h. Upon completion, aqueous 3N NaOH solution (0.5 mL) and 30% $H_2O_2$ (1 mL) were added and the resulting mixture was stirred for 3 h at room temperature. Water (2 mL) was added and the aqueous layer was extracted with $Et_2O$ (3 x 20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (60 % EtOAc in hexanes to 80% EtOAc in hexanes) to provide diol **88** (22 mg, 64 %) as a colorless oil.$^1$H NMR (400 MHz, $CDCl_3$) δ: 4.47 – 4.38 (m, 1H), 3.94 (dt, *J* = 7.6, 6.3 Hz, 1H), 3.87 (dt, *J* = 8.0, 4.0 Hz, 1H), 3.66 (dt, *J* = 7.5, 5.6 Hz, 2H), 3.60 – 3.51 (m, 1H), 2.30 (dt, *J* = 13.1, 6.7 Hz, 1H), 1.79 – 1.70 (m, 2H), 1.67 (ddd, *J* = 11.9, 5.7, 2.8 Hz, 2H), 1.52 (ddd, *J* = 13.0, 7.7, 4.3 Hz, 1H), 1.32 (d, *J* = 6.2 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 6H; $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 84.1, 74.6, 73.4, 70.8, 62.8, 43.7, 30.6, 29.8, 25.6, 21.4, 17.8, -4.5, -5.3; LRMS-ESI (m/z): 327.2 $(M+Na)^+$; $[\alpha]_D^{20}$ +20.4 (*c* 1.0, $CHCl_3$).

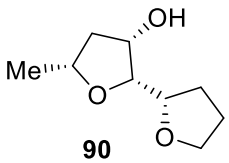


**89**

*tert*-butyldimethyl(((*2S,2'S,3S,5R*)-5-methyloctahydro-[2,2'-bifuran]-3-yl)oxy)silane (**89**)

To a stirred solution of diol **88** (22 mg, 0.07 mmol) in $CH_2Cl_2$ (1.8 mL) were added triethylamine (0.10 mL, 0.71 mmol) and DMAP (2.6 mg, 0.02 mmol) at 0 °C under argon

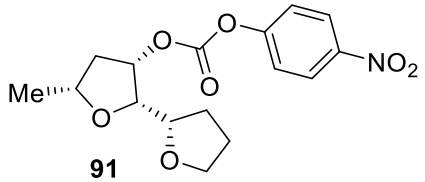
atmosphere. After stirring for 10 mins, 4-toluenesulfonyl chloride (27.2 mg, 0.14 mmol) was added and the resulting mixture was stirred for 24 h at room temperature. The reaction was quenched with saturated aqueous $NH_4Cl$ and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (20% EtOAc in hexanes) to give compound **89** (18 mg, 88%).$^1$H NMR (400 MHz, $CDCl_3$) δ: 4.29 (ddd, *J* = 6.5, 4.1, 2.7 Hz, 1H), 4.18 – 4.08 (m, 1H), 4.06 – 3.98 (m, 1H), 3.93 – 3.83 (m, 1H), 3.80 – 3.72 (m, 1H), 3.48 (dd, *J* = 8.4, 4.2 Hz, 1H), 2.33 – 2.24 (m, 1H), 2.10 – 1.98 (m, 1H), 1.90 – 1.83 (m, 2H), 1.55 – 1.44 (m, 2H), 1.34 (d, *J* = 6.1 Hz, 3H), 0.88 (s, 9H), 0.05 (d, *J* = 4.7 Hz, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 86.2, 78.1, 74.4, 73.4, 67.9, 43.5, 28.0, 25.8, 25.6, 22.0, 17.8, -4.2, -5.3; LRMS-ESI (m/z): 309.2 $(M+Na)^+$; $[\alpha]_D^{20}$ +30.9 (*c* 0.50, $CHCl_3$).




**90**

(*2R,2'S,3S,5R*)-5-methyloctahydro-[2,2'-bifuran]-3-ol (**90**)

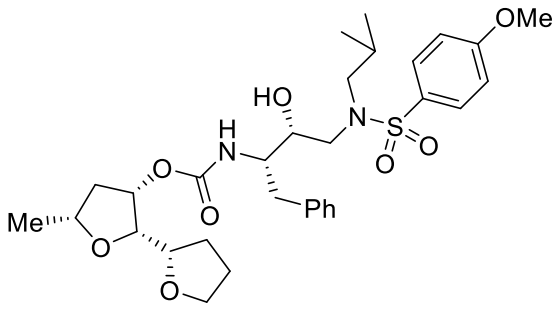
To a stirred solution of compound **89** (17 mg, 0.06 mmol) was added TBAF solution (1M in THF, 0.10 mL, 0.10 mmol) at 0ºC under argon atmosphere. The mixture was stirred for 3h at room temperature. The reaction was quenched with with saturated aqueous $NH_4Cl$ and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (80% EtOAc in hexanes) to give alcohol **90** (11 mg, quantitative).$^1$H NMR (400 MHz, $CDCl_3$) δ: 4.36 (dt, *J* = 6.5, 4.5 Hz, 1H), 4.16 (dt, *J* = 7.0, 3.5 Hz, 1H), 4.02 – 3.88 (m, 2H), 3.86 – 3.78 (m, 1H), 3.65 (dd, *J* = 5.0, 3.9 Hz, 1H), 2.40 – 2.29 (m, 1H), 2.10 – 1.80 (m, 5H), 1.58 – 1.52 (m, 1H), 1.32 (d, *J* = 6.1 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 83.2, 78.1, 74.2, 73.4, 68.9, 43.7, 28.0, 25.6, 21.7. LRMS-ESI (m/z): 195.1 $(M+Na)^+$; $[\alpha]_D^{20}$ +24.6 (*c* 0.33, $CHCl_3$).




**91**

(*2S,2'S,3S,5R*)-5-methyloctahydro-[2,2'-bifuran]-3-yl (4-nitrophenyl) carbonate (**91**)

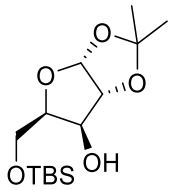
By following **General Procedure A**, activated carbonate **91** (8 mg, 44 %) was prepared from alcohol **90** (9 mg, 0.05 mmol).$^{1}$H NMR (400 MHz, $CDCl_3$) δ: 8.28 (d, *J* = 9.1 Hz, 2H), 7.38 (d, *J* = 9.1 Hz, 2H), 5.29 (p, *J* = 3.3 Hz, 1H), 4.15 (q, *J* = 7.4 Hz, 1H), 4.12 - 4.04 (m, 1H), 3.97 – 3.88 (m, 1H), 3.88 – 3.78 (m, 1H), 3.72 (dd, *J* = 7.2, 4.3 Hz, 1H), 2.61 (dt, *J* = 14.2, 7.1 Hz, 1H), 2.09 – 2.01 (m, 1H), 1.95 – 1.91 (m, 1H), 1.76 (ddd, *J* = 14.2, 7.4, 2.9 Hz, 1H), 1.65 (dq, *J* = 11.8, 8.1 Hz, 2H), 1.39 (d, *J* = 6.1 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 155.3, 152.1, 145.4, 125.2, 121.6, 83.8, 80.6, 74.2, 68.4, 60.3, 40.6, 28.1, 25.7, 21.1. LRMS-ESI (m/z): 360.1 $(M+Na)^+$; $[\alpha]_D^{20}$ +9.6 (*c* 0.27, $CHCl_3$).




**93**

(*2S,2'R,3S,5R*)-5-methyloctahydro-[2,2'-bifuran]-3-yl ((*2S,3R*)-3-hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate (**93**)

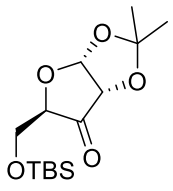
By following **General Procedure B**, inhibitor **93** (4.8 mg, 62 % yield) was prepared from activated alcohol **30** (4 mg, 0.01 mmol). $^{1}$H NMR (400 MHz, $CDCl_3$) δ: 7.72 (d, *J* = 8.8 Hz, 2H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.21 (d, *J* = 7.6 Hz, 3H), 6.99 (d, *J* = 8.4 Hz, 2H), 5.14 – 5.05 (m, 1H), 4.84 (d, *J* = 8.4 Hz, 1H), 3.99 – 3.95 (m, 1H), 3.88 (s, 3H), 3.86 – 3.80 (m, 2H), 3.79 – 3.71 (m, 2H), 3.51 (dd, *J* = 7.8, 4.4 Hz, 1H), 3.35 (s, 1H), 3.16 (dd, *J* = 15.2, 8.1 Hz, 1H), 3.08 (dd, *J* = 14.3, 4.0 Hz, 1H), 3.03 – 2.93 (m, 2H), 2.82 – 2.78 (m, 2H), 2.42 – 2.34 (m, 1H), 1.85 – 1.78 (m, 2H), 1.77 – 1.72 (m, 1H), 1.51 – 1.46 (m, 1H), 1.35 – 1.31(m, 1H), 1.30 (d, *J* = 6.1 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 2.5 Hz, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 163.1, 155.6, 137.6, 129.8, 129.5, 129.4, 128.5, 126.5, 114.4, 84.3, 77.5, 75.6, 74.3, 73.0, 68.2, 58.8, 55.6, 55.0, 53.7, 41.0, 35.6, 27.2, 25.9, 21.4, 20.2, 19.9. LRMS-ESI (m/z): 605.0 $(M+H)^+$; HRMS-ESI (m/z): $C_{31}H_{44}N_2O_8S$; calc'd for $[M+Na]^+$: 627.2716, found 627.2716; $[\alpha]_D^{20}$ +4.4 (*c* 0.13, $CHCl_3$).




**95**

(*3aR,5R,6S,6aR*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol (**95**)

To a stirred solution of commercially available xylofuranose **94** (2.32g, 12.20 mmol) in $CH_2Cl_2$ were added 2,6-lutidine (2.83 mL, 24.40 mmol) and TBSOTf (2.94 mL, 12.81 mmol) at 0 $^oC$ under Ar atmosphere. The mixture was stirred at room temperature for 3h and quenched with water and extracted with $CH_2Cl_2$. The combined organic layer was dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography (20 % EtOAc in hexanes) to give alcohol **95** as a colorless oil (3.26 g, 88 %). $^1H$ NMR (400 MHz, $CDCl_3$) δ: 7.26 (s, 1H), 5.96 (d, *J* = 3.7 Hz, 1H), 4.50 (d, *J* = 3.7 Hz, 1H), 4.42 (d, *J* = 2.7 Hz, 1H), 4.33 (t, *J* = 2.7 Hz, 1H), 4.16 – 4.06 (m, 3H), 1.48 (s, 3H), 1.32 (s, 3H), 0.89 (s, 9H), 0.11 (d, *J* = 2.0 Hz, 6H); $^{13}C$ NMR (101 MHz, $CDCl_3$) δ: 111.4, 104.9, 85.5, 78.0, 77.1, 62.3, 26.7, 26.1, 25.6, 18.0, -5.6, -5.7; LRMS-ESI (m/z): 327.2 $(M+Na)^+$; $[\alpha]_D^{20}$ – 11.0 (*c* 1.0, $CHCl_3$); reported (Parr, I. B. and Horenstein, B. A. *J. Org. Chem.***1997**,*62*, 7489.) $[\alpha]_D^{20}$ – 9.3.

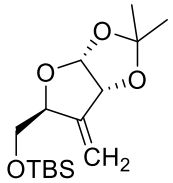



**96**

(*3aR,5R,6aS*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyldihydrofuro[2,3-d][1,3]dioxol-6(5H)-one (**96**)

To a stirred solution of compound **95** (2.60 g, 8.47 mmol) in $CH_2Cl_2$ (34 mL) were added PDC (2.23 g, 5.93 mmol) and acetic anhydride (1.85 mL, 19.58 mmol) under Ar atmosphere. The resulting mixture was refluxed for 4h. After TLC showed complete disappearance of the starting material, the mixture was cooled to room temperature and solvents were concentrated reduced pressure. The residue was dissolved in 50 mL of EtOAc and filtered through a pad of silica gel. Solids were thoroughly washed with EtOAc and the filtrate was concentrated reduced pressure. The crude product was then purified by flash silica gel column chromatography (20 % EtOAc in

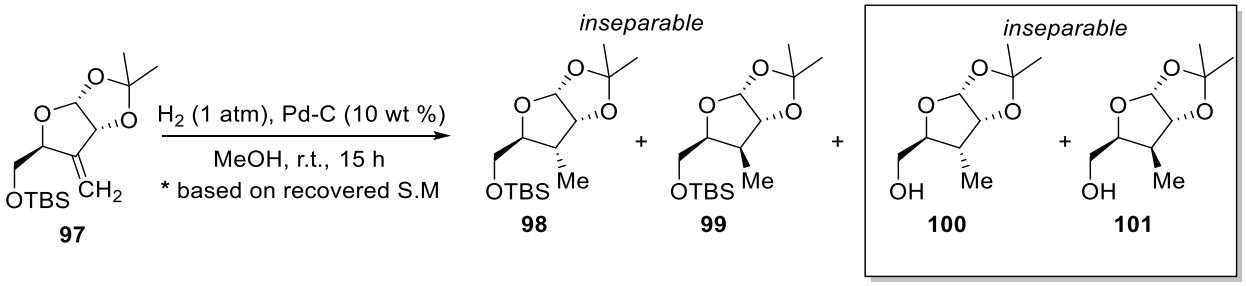
hexanes) to obtain compound **96** as a yellow amorphous solid (2.15 g, 84 %). $^1$H NMR (400 MHz, $CDCl_3$) δ: 6.13 (d, *J* = 4.5 Hz, 1H), 4.36 (td, *J* = 2.0, 1.1 Hz, 1H), 4.27 (dd, *J* = 4.6, 1.1 Hz, 1H), 3.91 – 3.77 (m, 2H), 1.44 (d, *J* = 3.1 Hz, 6H), 0.85 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 211.0, 114.0, 103.7, 81.7 6, 77.0, 63.9, 27.6, 27.1, 25.7, 18.0, -5.6, -5.8; LRMS-ESI (m/z): 325.2 $(M+Na)^+$; $[\alpha]_D^{20}$ + 122 (*c* 1.0, $CHCl_3$); reported (Parr, I. B. and Horenstein, B. A. *J. Org. Chem.***1997**,*62*, 7489.) $[\alpha]_D^{20}$ + 114.




**97**

*Tert*-butyl(((*3aR,5S,6aR*)-2,2-dimethyl-6-methylenetetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methoxy)dimethylsilane (**97**)

To a stirred solution of triphenylphosphonium bromide (5.35 g, 14.97 mmol) in dry THF (90 mL) at 0 $^o$C was added potassium tert-butoxide (1 M in THF, 12.50 mL, 12.50 mmol) under Ar atmosphere. The mixture was stirred at the same temperature for 30 mins. The starting material **96** (1.51 g, 5 mmol) in 25 mL of THF was added dropwise into the yellow solution. The mixture was gradually warmed to room temperature over 2h. After addition of water (100 mL), the reaction mixture was extracted with EtOAc (100 mL x 2). The combined organic extracts were dried ($Na_2SO_4$), filtered, and concentrated reduced pressure. The crude residue was purified by flash silica gel chromatography (5% EtOAc in hexanes) to give olefin **97** as a yellow oil (1.42g, 95 %). $^1$H NMR (400 MHz, $CDCl_3$) δ: 5.84 (d, *J* = 4.1 Hz, 1H), 5.41 (dd, *J* = 2.3, 1.2 Hz, 1H), 5.25 (t, *J* = 1.7 Hz, 1H), 4.87 (dq, *J* = 4.1, 1.3 Hz, 1H), 4.74 (dddt, *J* = 4.1, 3.5, 2.1, 1.1 Hz, 1H), 3.80 – 3.63 (m, 2H), 1.48 (d, *J* = 0.8 Hz, 3H), 1.37 (d, *J* = 0.8 Hz, 3H), 0.87 (s, 9H), 0.04 (d, *J* = 1.7 Hz, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 147.5, 112.4, 111.4, 104.9, 81.9, 80.7, 65.6, 27.5, 27.2, 25.8, 18.1, -5.5, -5.6. LRMS-ESI (m/z): 323.2 $(M+Na)^+$

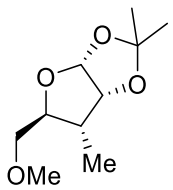


((*3aR,5S,6R,6aR*)-2,2,6-trimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methanol (**40**)

To a solution of olefin **97** (570 mg, 1.89 mmol) in undistilled methanol (13.50 mL) was added Pd-C (60 mg, 10 wt %) under argon atmosphere. Argon atmosphere was then removed by reduced pressure and hydrogenation was performed under one atmospheric pressure of hydrogen gas. After 15 h of stirring at 23$^{o}$C, TLC showed the presence of a major mixture of **98** and **99** (*Rf* = 0.75 in 20 % EtOAc in hexane) and a minor mixture of **100** and **101** (*Rf* = 0.12 in 20 % EtOAc in hexane). The mixture was passed through a plug of Celite and the solvent was concentrated reduced pressure. The crude residue was purified by silica gel column chromatography (10% EtOAc in hexanes to 60% EtOAc in hexanes) to furnish both a mixture of compounds **98** and **99** (347 mg, 61 % yield) and a mixture of compounds **100** and **101** (135 mg, 96 % yield). Both mixtures showed *dr* of 5:1, which was determined by $^{1}$H NMR spectroscopic analysis.

**98** and **99**: $^{1}$H NMR (mixture, 400 MHz, $CDCl_3$) δ: 5.79 (m, 0.2H), 5.77 (dd, *J* = 3.8, 1.5 Hz, 1H), 4.54 (t, *J* = 4.1 Hz, 1H), 4.34 (d, *J* = 3.6 Hz, 0.2H), 3.84 – 3.76 (m, 2H), 3.69 (dd, *J* = 11.9, 2.5 Hz, 1H), 3.63 – 3.58 (m, 0.2H), 2.36 (m, *J* = 7.5 Hz, 0.2H), 2.10 – 1.99 (m, 1H), 1.52 (d, *J* = 6.2 Hz, 4H), 1.32 (d, *J* = 9.3 Hz, 4H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 12H), 0.06 (d, *J* = 2.0 Hz, 6H); $^{13}$C NMR (mixture, 101 MHz, $CDCl_3$) δ: 111.2, 104.5, 83.1, 83.0, 79.6, 62.5, 40.3, 39.0, 26.7, 26.3, 26.1, 25.8, 25.8, 18.3, 10.4, 9.3, -5.4, -5.5.

**100** and **101**: $^{1}$H NMR (mixture, 400 MHz, $CDCl_3$) δ: 5.77 (d, J = 3.3 Hz, 0.2H), 5.76 – 5.70 (m, 1H), 4.52 (q, J = 4.3, 3.0 Hz, 1H), 3.86 – 3.75 (m, 2H), 3.73 – 3.66 (m, 0.2H), 3.61 (dd, J = 11.6, 4.3 Hz, 0.2H), 3.50 (ddd, J = 12.1, 3.7, 1.6 Hz, 1H), 2.44 (s, 1H), 2.33 – 2.19 (m, 0.2H), 2.01 (ddt, J = 8.2, 6.7, 3.2 Hz, 1H), 1.45 (s, 3H), 1.28 (s, 3H), 1.25 (d, J = 1.6 Hz, 0.6H), 1.01 (dd, J = 6.9, 1.7 Hz, 3H), 0.80 (dd, J = 7.4, 1.7 Hz, 0.6H); $^{13}$C NMR (mixture, 101 MHz, $CDCl_3$) δ: 111.4, 104.7, 104.3, 86.6, 83.0, 82.9, 80.1, 61.8, 61.2, 40.3, 38.0, 26.6, 26.5, 26.2, 26.0, 10.7, 9.0.

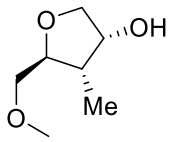



**102**

(*3aR,5S,6R,6aR*)-5-(methoxymethyl)-2,2,6-trimethyltetrahydrofuro[2,3-d][1,3]dioxole (**41**)

To a solution of alcohol **100** and **101** (135 mg, 0.72 mmol) in THF (3.5 mL) was added NaH (60% dispersion in mineral oil, 57 mg, 1.43 mmol) at 0 $^{o}$C under argon atmosphere. After stirring for 10 mins at 0 $^{o}$C, MeI (90 µL, 1.43 mmol) was added and the reaction mixture was

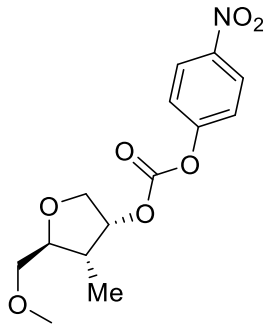
slowly warmed to 23 °C over 2h. Upon completion, the reaction was quenched with saturated aqueous $NH_4Cl$ and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated reduced pressure. Purification by silica gel column chromatography (5 % EtOAc in hexanes to 15% EtOAc in hexanes) gave 120 mg of **102** (83% yield) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ: 5.80 (d, *J* = 3.7 Hz, 1H), 4.53 (t, *J* = 4.2 Hz, 1H), 3.91 – 3.79 (m, 1H), 3.61 (dd, *J* = 10.9, 2.5 Hz, 1H), 3.42 (dd, *J* = 10.9, 4.7 Hz, 1H), 3.38 (s, 3H), 2.06 – 1.88 (m, 1H), 1.49 (s, 3H), 1.31 (s, 3H), 1.06 (d, *J* = 6.8 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 111.2, 104.8, 82.6, 81.6, 71.7, 59.4, 39.2, 26.6, 26.2, 9.2; LRMS-ESI (m/z): 225.2 $(M+Na)^+$; $[\alpha]_D^{20}$ + 84.3 (*c* 1.0, $CHCl_3$).




**104**

(*3R,4S,5S*)-5-(methoxymethyl)-4-methyltetrahydrofuran-3-ol (**104**)

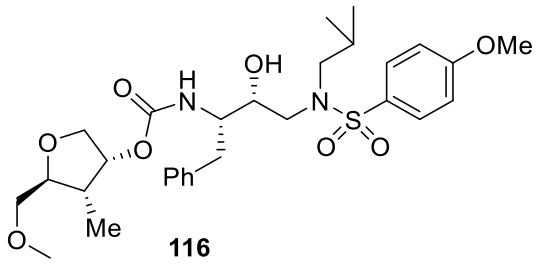
To a stirred mixture of **102** (60 mg, 0.27 mmol) in distilled $CH_2Cl_2$ (2.8 mL) was added $Et_3SiH$ (340 µL, 1.07 mmol) at 0 °C under argon atmosphere. After stirring for 10 min, $BF_3OEt_2$ (160 µL, 0.53 mmol) was added at the same temperature. The resulting mixture was stirred at 0 °C for additional 15 min and stirred for 4 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were combined, dried ($Na_2SO_4$), filtered, and concentrated reduced pressure. The crude residue was purified by silica gel column chromatography (70% EtOAc in hexanes) to give alcohol **104** (35 mg, 90% yield) as a while amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$) δ: 4.21 (t, *J* = 4.4 Hz, 1H), 3.99 (dd, *J* = 9.9, 3.9 Hz, 1H), 3.76 (d, *J* = 9.9 Hz, 2H), 3.52 (dd, *J* = 10.6, 2.8 Hz, 1H), 3.37 (m, 4H), 2.19 (s, 1H), 1.97 (brs, 1H), 1.05 (d, *J* = 6.9 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 82.1, 75.2, 74.4, 73.6, 59.2, 40.2, 10.0; LRMS-ESI (m/z): 169.1 $(M+Na)^+$; $[\alpha]_D^{20}$ +69.8 (*c* 0.53, $CHCl_3$).



**105**

(*3R,4R,5S*)-5-(methoxymethyl)-4-methyltetrahydrofuran-3-yl (4-nitrophenyl) carbonate (**105**)

Following **General Procedure A**, activated carbonate **105** (49 mg, 86% yield) was prepared from alcohol **104** (27 mg, 0.18 mmol). $^{1}$H NMR (400 MHz, $CDCl_3$) δ: 8.27 (d, *J* = 9.2 Hz, 2H), 7.37 (d, *J* = 9.2 Hz, 2H), 5.26 (ddd, *J* = 5.3, 4.0, 1.3 Hz, 1H), 4.19 (dd, *J* = 11.1, 4.1 Hz, 1H), 3.99 (dd, *J* = 11.1, 1.3 Hz, 1H), 3.84 (ddd, *J* = 10.1, 4.9, 2.7 Hz, 1H), 3.60 (dd, *J* = 10.7, 2.7 Hz, 1H), 3.45 (dd, *J* = 10.7, 5.0 Hz, 1H), 3.40 (s, 3H), 2.31 (dqd, *J* = 10.0, 6.9, 5.1 Hz, 1H), 1.13 (d, *J* = 6.9 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 155.3, 152.2, 145.4, 125.2, 121.7, 82.7, 82.4, 72.7, 72.5, 59.4, 38.9, 9.8; LRMS-ESI (m/z): 334.1 $(M+Na)^+$; $[\alpha]_D^{20}$ +41.4 (*c* 0.63, $CHCl_3$).

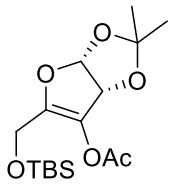


**116**

(*3R,4R,5S*)-5-(methoxymethyl)-4-methyltetrahydrofuran-3-yl ((2S,3R)-3-hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate (**116**)

By following **General Procedure B,** inhibitor **116** (12 mg, 57% yield)was prepared from activated carbonate **105** (11 mg, 0.04 mmol). $^{1}$H NMR (400 MHz, $CDCl_3$) δ: 7.70 (d, *J* = 8.9 Hz, 2H), 7.31 – 7.17 (m, 5H), 6.98 (d, *J* = 8.9 Hz, 2H), 5.09 (t, *J* = 4.8 Hz, 1H), 4.88 (d, *J* = 8.6 Hz, 1H), 4.03 (dd, *J* = 10.6, 4.3 Hz, 1H), 3.87 (s, 3H), 3.85 – 3.80 (m, 2H), 3.73 (d, *J* = 10.5 Hz, 2H), 3.67 – 3.60 (m, 1H), 3.52 (dd, *J* = 10.5, 2.7 Hz, 1H), 3.41 - 3.33 (m, 4H), 3.14 (d, *J* = 15.2 Hz, 1H), 3.07 (d, *J* = 13.9 Hz, 1H), 3.02 – 2.91 (m, 2H), 2.82 (dd, *J* = 32.8, 13.7 Hz, 2H), 2.09 – 2.02 (m, 1H), 1.82 (dt, *J* = 13.7, 6.8 Hz, 1H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.77 (d, *J* = 6.9 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 163.0, 137.5, 129.4, 129.4, 128.4, 126.5, 114.3, 82.7, 77.1, 73.2, 73.0, 72.6, 59.3, 58.8, 55.6, 54.9, 53.8, 39.0, 35.6, 27.2, 20.1, 19.8, 9.7; LRMS-

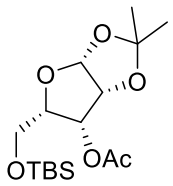
ESI (m/z): 579.0 $(M+H)^+$; HRMS-ESI (m/z): $C_{29}H_{42}N_2O_8S$; calc'd for $[M+Na]^+$: 601.2554, found 601.2560; $[\alpha]_D^{20}$ +123.2 (*c* 1.0, $CHCl_3$).




**106**

(*3aR,6aR*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-*3a,6a*-dihydrofuro[2,3-d][1,3]dioxol-6-yl acetate (**106**)

Lactone **96** (2.04g, 6.75 mmol) was dissolved in pyridine 4 mL, 47.26 mmol) at 0 °C under argon atmosphere, and acetic anhydride (2 mL, 2.02 mmol) was added dropwise to the mixture. The resulting mixture was heated to 60 °C and stirred for 48 h. The mixture was then poured into cold water. The aqueous layer was extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography (5% EtOAc in hexanes to 20% EtOAc in hexanes) to give olefin **106** (1.17g, 51%) as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ: 6.00 (d, *J* = 5.4 Hz, 1H), 5.40 (dt, *J* = 5.5, 1.0 Hz, 1H), 4.20 – 4.11 (m, 2H), 2.18 (s, 3H), 1.50 (s, 3H), 1.44 (s, 3H), 0.87 (s, 9H), 0.06 (d, *J* = 2.0 Hz, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 168.6, 146.9, 127.3, 113.0, 103.8, 80.8, 55.7, 27.8, 27.7, 25.7, 20.4, 18.3, -5.5, -5.6; LRMS-ESI (m/z): 367.2 $(M+Na)^+$; $[\alpha]_D^{20}$ -1.3 (*c* 1.53, $CHCl_3$).

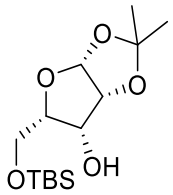



**107**

(*3aR,5S,6R,6aR*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl acetate (**45**)

To a solution of olefin **106** (1.47g, 4.27 mmol) in EtOAc (50 mL) was added Pd-C (150 mg, 10 wt %) under argon atmosphere. The resulting mixture was hydrogenated at the initial pressure of 60 psi in a Parr apparatus for 3h. Filtration through a pad of Celite, concentration under reduced pressure, and flash silica gel column chromatography (3% EtOAc in hexanes) gave acetate **107** (1.45 g, 98 %) as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ: 5.75 (d, *J* = 4.2 Hz, 1H), 5.13

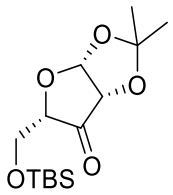
(t, *J* = 6.0 Hz, 1H), 4.77 (dd, *J* = 5.7, 4.2 Hz, 1H), 4.15 (q, *J* = 6.2 Hz, 1H), 3.98 (dd, *J* = 10.4, 6.6 Hz, 1H), 3.85 (dd, *J* = 10.4, 5.8 Hz, 1H), 2.13 (s, 3H), 1.56 (s, 3H), 1.36 (d, *J* = 0.7 Hz, 3H), 0.88 (s, 9H), 0.07 (d, *J* = 1.8 Hz, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 170.0, 114.3, 104.6, 80.0, 79.0, 71.3, 61.8, 26.7, 26.7, 25.7, 20.6, 18.2, -5.4, -5.5; LRMS-ESI (m/z): 369.2 $(M+Na)^+$; $[\alpha]_D^{20}$ +46.3 (*c* 1.0, $CHCl_3$)




**108**

(*3aR,5S,6R,6aR*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol (**108**)

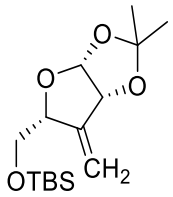
To a mixture of acetate **107** (1.08 g, 3.11 mmol) in dry MeOH (15.60 mL) was added $K_2CO_3$ (644 mg, 4.66 mmol) at room temperature under argon atmosphere. The mixture was stirred for 2 h and quenched with water (20 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography (20 % EtOAc in hexanes) to give alcohol **108** (793 mg, 84 %) as a colorless oil.$^1$H NMR (400 MHz, $CDCl_3$) δ: 5.70 (d, *J* = 4.1 Hz, 1H), 4.61 (dd, *J* = 5.8, 4.1 Hz, 1H), 4.30 (q, *J* = 5.8 Hz, 1H), 4.15 – 4.07 (m, 1H), 4.01 (dt, *J* = 6.7, 5.9 Hz, 1H), 3.83 (dd, *J* = 10.2, 5.8 Hz, 1H), 3.19 (d, *J* = 5.8 Hz, 1H), 1.58 (s, 3H), 1.37 – 1.35 (m, 3H), 0.88 (s, 9H), 0.07 (s, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 114.1, 104.8, 81.1, 79.9, 70.8, 62.5, 26.9, 26.4, 25.8, 18.2, -5.4, -5.5; LRMS-ESI (m/z): 327.2 $(M+Na)^+$; $[\alpha]_D^{20}$ +1.32 (*c* 0.50, $CHCl_3$).




**109**

(*3aR,5S,6aS*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyldihydrofuro[2,3-d][1,3]dioxol-6(5H)-one (**109**)

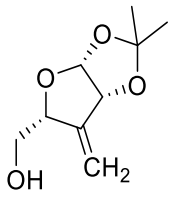
By following the procedure outlined for compound **96**, lactone **109** (690 mg, 70% yield) was obtained as a colorless oil from alcohol **108** (983 mg, 3.23 mmol) by PDC oxidation.[1]H NMR (400 MHz, $CDCl_3$) δ: 6.01 (d, *J* = 4.3 Hz, 1H), 4.39 (dd, *J* = 4.4, 0.8 Hz, 1H), 4.21 – 4.17 (m, 1H), 3.97 – 3.86 (m, 2H), 1.52 (s, 3H), 1.39 (s, 3H), 0.88 (s, 9H), 0.07 (s, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 207.3, 114.7, 102.5, 82.5, 76.7, 63.7, 27.4, 26.8, 25.8, 18.3, -5.4, -5.5; LRMS-ESI (m/z): 325.2 $(M+Na)^+$; $[\alpha]_D^{20}$ -28.7 (*c* 2.0, $CHCl_3$).




**110**

*Tert*-butyl(((*3aR,5R,6aR*)-2,2-dimethyl-6-methylenetetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)methoxy)dimethylsilane (**110**)

By following the procedure outlined for the preparation of olefin **97**, olefin **110** (440 mg, 70 %) was obtained as a colorless oil from lactone **109** (634 mg, 2.10 mmol) by Wittig olefination. [1]H NMR (400 MHz, $CDCl_3$) δ: 5.80 (d, *J* = 3.9 Hz, 1H), 5.43 (dd, *J* = 2.1, 1.0 Hz, 1H), 5.29 (t, *J* = 1.5 Hz, 1H), 4.85 (d, *J* = 3.9 Hz, 1H), 4.49 (tt, *J* = 6.6, 1.9 Hz, 1H), 3.87 (dd, *J* = 10.0, 6.4 Hz, 1H), 3.71 (dd, *J* = 10.0, 6.9 Hz, 1H), 1.53 (s, 3H), 1.34 (s, 3H), 0.89 (s, 9H), 0.07 (d, *J* = 3.4 Hz, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 145.6, 113. 7, 113.0, 105.3, 83.1, 81.4, 66.7, 27.3, 26.3, 25.8, 18.3, -5.3, -5.4; LRMS-ESI (m/z): 323.2 $(M+Na)^+$; $[\alpha]_D^{20}$ +19.1 (*c* 2.25, $CHCl_3$).

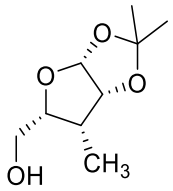



**111**

((*3aR,5R,6aR*)-2,2-dimethyl-6-methylenetetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)methanol (**111**)

To a stirred solution of olefin **110** (408 mg, 1.36 mmol) in THF (6.8 mL) at 0°C was added TBAF solution (1M in THF, 2 mL, 2 mmol) under argon atmosphere. The mixture was warmed to room temperature and stirred for 3h. The reaction was quenched with water and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash silica gel column

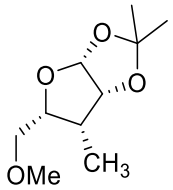
chromatography (60 % EtOAc in hexanes) to give alcohol **111** (253 mg, quantitative) as a colorless oil.$^{1}$H NMR (400 MHz, $CDCl_3$) δ: 5.84 (d, *J* = 3.9 Hz, 1H), 5.50 (dd, *J* = 2.2, 1.0 Hz, 1H), 5.27 (dd, *J* = 1.9, 1.3 Hz, 1H), 4.90 (dt, *J* = 3.9, 1.2 Hz, 1H), 4.66 (ddt, *J* = 6.4, 4.0, 2.0 Hz, 1H), 3.77 (dddd, *J* = 37.7, 11.6, 7.1, 4.1 Hz, 3H), 2.23 (t, *J* = 6.5 Hz, 1H), 1.56 (s, 3H), 1.36 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 144.8, 113.7, 113.3, 105.2, 83.5, 81.1, 65.7, 27.2, 26.4; LRMS-ESI (m/z): 209.1 $(M+Na)^+$; $[\alpha]_D^{20}$ + 26.0 (*c* 1.0, $CHCl_3$); reported (Doboszewski, B. and Herdewijin, P. *Tetrahedron*, **2008**, *64*, 5551-5562) $[\alpha]_D^{24}$ +28.8 (c 0.77, $CHCl_3$).



**112**

((*3aR,5R,6R,6aR*)-2,2,6-trimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)methanol (**112**)

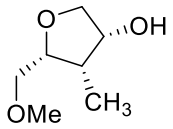
To a solution of alcohol **111** (240 mg, 1.29 mmol) in absolute EtOH (2 mL) was added $PtO_2$ (20 mg) under Ar atmosphere. The reaction mixture was hydrogenated in a Parr apparatus at the initial pressure of 40 psi for 12h. Filtration through a plug of Celite, concentration at reduced pressure, and purification by silica gel column chromatography (50% EtOAc in hexanes) gave alcohol **112** (99 mg, 41% yield) as a colorless oil.$^{1}$H NMR (400 MHz, $CDCl_3$) δ: 5.77 (d, *J* = 3.9 Hz, 1H), 4.51 (dd, *J* = 5.4, 3.9 Hz, 1H), 4.15 (ddd, *J* = 9.7, 8.3, 4.0 Hz, 1H), 3.86 (dd, *J* = 11.6, 9.7 Hz, 1H), 3.46 (dd, *J* = 11.6, 4.1 Hz, 1H), 2.59 (s, 1H), 2.45 – 2.35 (m, 1H), 1.49 (s, 3H), 1.24 (s, 3H), 1.04 (d, *J* = 7.3 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 111. 9, 105.7, 84.2, 82.2, 62.4, 38.6, 26.4, 25.3, 7.62; LRMS-ESI (m/z): 211.1 $(M+Na)^+$; $[\alpha]_D^{20}$ -40.8 (*c* 0.31, $CHCl_3$); reported (Doboszewski, B. and Herdewijin, P. *Tetrahedron*, **2008**, *64*, 5551-5562) $[\alpha]_D^{24}$ -44.4(c 2.5, $CHCl_3$).



**113**

(*3aR,5R,6R,6aR*)-5-(methoxymethyl)-2,2,6-trimethyltetrahydrofuro[2,3-*d*][1,3]dioxole (**113**)

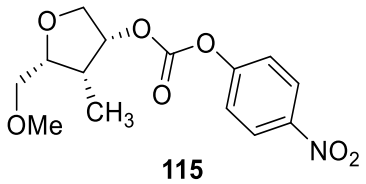
Compound **113** (38 mg, 92 %) was obtained as a colorless oil from alcohol **112** (39 mg, 0.21 mmol) by following the procedure outlined for the preparation of compound **102**. $^{1}$H NMR (400 MHz, $CDCl_3$) δ: 5.79 (d, *J* = 3.8 Hz, 1H), 4.52 (dd, *J* = 5.2, 3.9 Hz, 1H), 4.23 (td, *J* = 8.0, 5.1 Hz, 1H), 3.65 (dd, *J* = 10.1, 7.8 Hz, 1H), 3.53 (dd, *J* = 10.1, 5.0 Hz, 1H), 3.38 (s, 3H), 2.49 – 2.36 (m, 1H), 1.58 – 1.54 (m, 3H), 1.30 (d, *J* = 0.8 Hz, 3H), 1.11 (d, *J* = 7.3 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 111.8, 105.9, 82.3, 82.2, 73.0, 58.9, 39.0, 26.6, 25.5, 8.2; LRMS-ESI (m/z): 225.1 $(M+Na)^+$;$[\alpha]_D^{20}$ -42.4 (*c* 0.48, $CHCl_3$)




**114**

(*3R,4S,5R*)-5-(methoxymethyl)-4-methyltetrahydrofuran-3-ol (**114**)

Alcohol **114** (12 mg, 58 %) was obtained as a colorless oil from compound **113** (29 mg, 0.14 mmol) by following the procedure outlined for the preparation of alcohol **104**, $^{1}$H NMR (400 MHz, $CDCl_3$) δ: 4.24 (d, *J* = 11.7 Hz, 1H), 4.10 (ddd, *J* = 9.6, 2.7, 1.4 Hz, 1H), 4.03 (dt, *J* = 9.7, 3.8 Hz, 1H), 3.88 (d, *J* = 9.5 Hz, 1H), 3.86 – 3.78 (m, 1H), 3.56 (ddd, *J* = 10.7, 2.7, 1.0 Hz, 1H), 3.42 (s, 3H), 3.34 (dt, *J* = 10.7, 1.2 Hz, 1H), 2.53 – 2.42 (m, 1H), 1.08 (d, *J* = 7.2 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 79.5, 76.3, 73.3, 72.1, 59.1, 40.1, 8.8; LRMS-ESI (m/z): 169.1 $(M+Na)^+$; $[\alpha]_D^{20}$ -9.9 (*c* 0.16, $CHCl_3$).

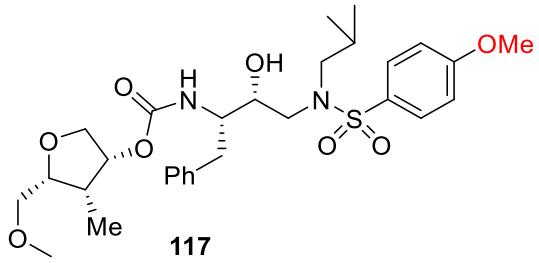



**115**

(*3R,4R,5R*)-5-(methoxymethyl)-4-methyltetrahydrofuran-3-yl (4-nitrophenyl) carbonate (**115**)

By following **General Procedure A**, activated carbonate **115** (5.2 mg, 35 %) was prepared from alcohol **114** (6.4 mg, 0.04 mmol) as a white amorphous solid. $^{1}$H NMR (400 MHz, $CDCl_3$) δ: $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 8.29 (d, *J* = 9.2 Hz, 2H), 7.39 (d, *J* = 9.2 Hz, 2H), 5.26 (ddd, *J* = 5.9, 4.2, 2.2 Hz, 1H), 4.23 (dt, *J* = 8.1, 4.1 Hz, 1H), 4.13 – 4.03 (m, 2H), 3.52 (dd, *J* =

10.0, 8.0 Hz, 1H), 3.44 (dd, *J* = 10.0, 4.3 Hz, 1H), 3.41 (s, 3H), 2.73 – 2.62 (m, 1H), 1.11 (d, *J* = 7.3 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 155.3, 152.2, 125.3, 121.7, 81.6, 79.3, 72.6, 71.7, 59.2, 38.7, 29.6, 7.9; LRMS-ESI (m/z): 334.1 $(M+Na)^+$; $[\alpha]_D^{20}$ +7.3 (*c* 0.15, $CHCl_3$).




**117**

(*3R,4R,5R*)-5-(methoxymethyl)-4-methyltetrahydrofuran-3-yl ((*2S,3R*)-3-hydroxy-4-((*N*-isobutyl-4-methoxyphenyl)sulfonamido)-1-phenylbutan-2-yl)carbamate (**117**)

By following **General Procedure B**, inhibitor **117** (7.5 mg, 87%) was prepared from activated carbonate **115** (4.6 mg, 0.01 mmol) as a white amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.73 (d, *J* = 8.9 Hz, 2H), 7.32 – 7.22 (m, 5H), 7.01 (d, *J* = 8.9 Hz, 2H), 5.11 – 5.06 (m, 1H), 4.90 (d, *J* = 8.4 Hz, 1H), 4.12 (td, *J* = 8.0, 3.6 Hz, 1H), 3.92 (dd, *J* = 10.4, 4.6 Hz, 1H), 3.90 (d, *J* = 1.8 Hz, 3H), 3.87 (d, *J* = 8.1 Hz, 2H), 3.84 (dd, *J* = 10.3, 2.1 Hz, 1H), 3.75 (s, 1H), 3.42 – 3.36 (m, 4H), 3.34 (dd, *J* = 10.1, 3.8 Hz, 1H), 3.16 (dd, *J* = 15.2, 8.5 Hz, 1H), 3.09 (dd, *J* = 14.3, 4.4 Hz, 1H), 3.02 (dd, *J* = 15.1, 2.4 Hz, 1H), 2.98 (dd, *J* = 13.5, 8.4 Hz, 1H), 2.87 (dd, *J* = 14.1, 8.4 Hz, 1H), 2.82 (dd, *J* = 13.3, 6.7 Hz, 1H), 2.47 (td, *J* = 7.5, 5.7 Hz, 1H), 1.88 – 1.84 (m, 1H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.75 (d, *J* = 7.3 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 163.1, 156.0, 137.6, 129.7, 129.5, 129.4, 128.6, 126.6, 114.4, 79.4, 72.9, 72.8, 72.0, 59.2, 58.9, 55.7, 55.1, 53.8, 38.8, 35.7, 27.3, 20.2, 19.9, 7.8. LRMS-ESI (m/z): 579.0 $(M+H)^+$; HRMS-ESI (m/z): $C_{29}H_{42}N_2O_8S$; calc'd for $[M+H]^+$: 579.2735, found 579.2742; $[\alpha]_D^{20}$ +7.7 (*c* 0.45, $CHCl_3$).

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# CHAPTER 3. PROGRESS TOWARD THE ASYMMETRIC SYNTHESIS OF (-)-RASFONIN

(-)-Rasfonin (**118**) contains five chiral stereogenic centers and is consisted of a main α,β-unsaturated pyranone structure with a tetramethylated alkyl side chain (segment **A**) and a bottom ester appendage (segment **B**) tethered to the main structure on carbon 4 (Figure 3.1). In addition to this natural product's synthetically interesting moiety, **118** has gained a significant amount of attentions as it exhibited highly potent anticancer activities by actively inducing apoptosis in *ras*-mutated cancer cells. We were interested in synthesizing this natural product by using the Negishi's zirconium-catalyzed asymmetric carboalumination (ZACA) reaction to readily access the main core with the tetramethylated alkyl side chain in the natural product synthesis.

The first portion of this chapter provides background information about cancer and role of apoptosis in cancer. The second portion of the chapter details the isolation and biological activity of (-)-rasfonin **(118)**. Previous synthetic efforts by *Huang et al.* and *Boeckman et al.* will be outlined. Lastly, our synthetic attempts to the asymmetric synthesis of the segment A of (-)-rasfonin (**118**) will be discussed.

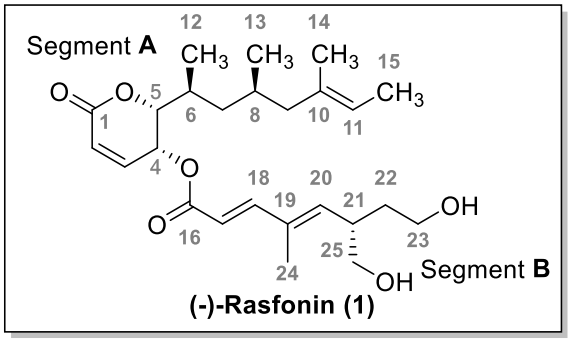



Figure 3.1 Structure of (-)-Rasfonin

## 3.1 Introduction

Cancer is one of the major leading causes of death worldwide, and it is the second leading cause of death in the United States with heart disease being the first.[1]According to the NIH data, around 1.8 million new cases of cancer will be diagnosed and approximately 0.6 million people will die from this disease in the United States in 2020.[2] The overall cancer death rate, however, has steadily declined over 25 years between 1991 and 2016 by a total of 27%, equating to an estimated 2.6 million fewer cancer deaths than the projected casualty if mortality rates had remained at their height.[3] The decline in cancer death rate over the past 25 years is largely due to the advancement of cancer treatment strategies, early detection of cancer, and increased awareness about cancer among population.[3]

To comprehend the mechanism of cancer progression, the role of apoptosis in cancer must be understood.[4] In a multicellular organism, tight regulation of the number of cells is very critical for its survival. When cells are damaged or no longer needed from a variety of tissues, cells in a healthy multicellular organism commit suicide by activating an intracellular death program.[5-9] This program is called apoptosis and it is well-known to play a crucial role in various regulating processes. For instance, apoptosis is responsible for maintaining constant cell numbers in tissues undergoing cell turnover by controlling the rate of cell death.[5] In addition, apoptosis is involved in the formation of fingers and toes of the developing embryo.[10] Moreover, apoptosis is accountable for proper development and functioning of the immune system by eliminating virus-infected cells and cells carrying potentially harmful mutations including the ones that might cause cancer development.[11]

Cancer results from an unregulated proliferation of cells/tissues that arises from mutations at the molecular level. In other words, cancer can be described as a state of lack of apoptosis and surplus activation of cell survival pathway.[4] In normal cells, apoptosis is carried out by a class of cysteine protein called caspases (cysteine aspartyl-specific proteases) which cleaves target proteins upon receiving either extracellular signals, such as ones produced by cytotoxic T cells in response to damaged or infected cells, or intracellular signals including DNA damage, growth factor deprivation, and cytokine deprivation.[9,11-13] Both apoptotic pathways are highly regulated, ensuring that apoptosis occurs only when it is properly signaled (Figure 3.2).[9] In cancer cells, however, mutations and silencing of key apoptotic genes often nullify these apoptotic

mechanisms.[14] For instance, the downregulation of p53, a tumor suppressor gene, is the most common mutation found in cancer cells, amounting approximately 50%.[15-17]

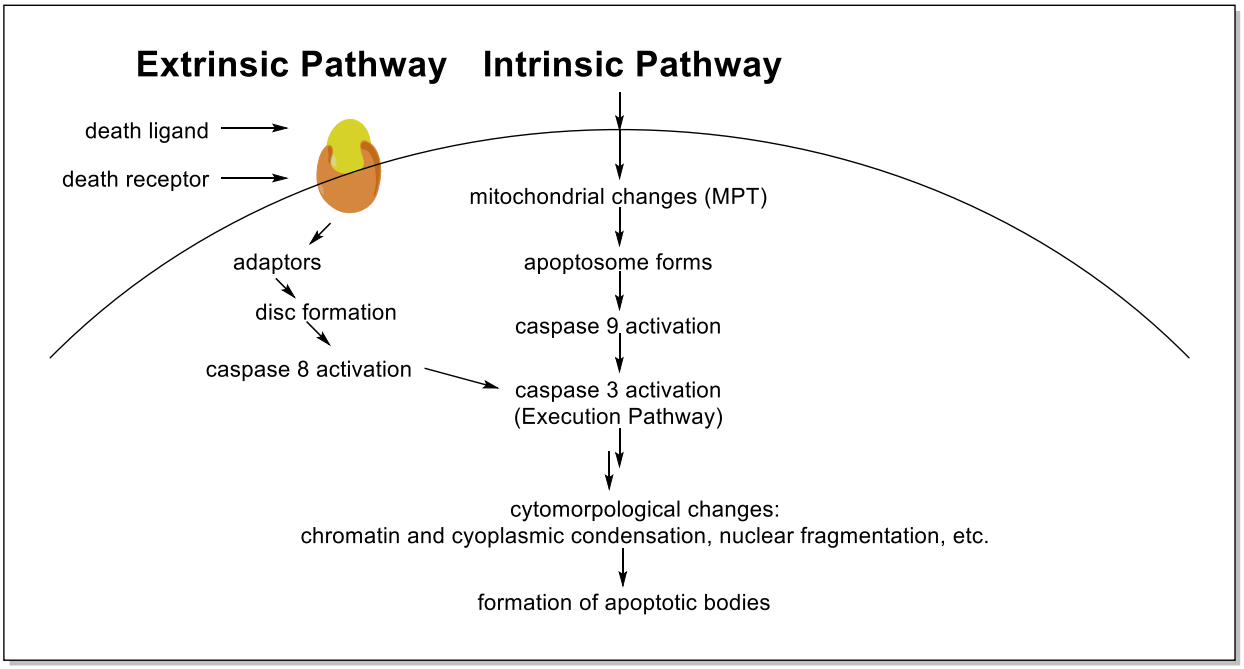



Figure 3.2 Schematic representation of apoptotic events with two main pathways of apoptosis indicated: *extrinsic* and *intrinsic*.

Overactivation of *Ras* proto-oncogene is another common mutation found in human cancer cells.[18] The *ras* protein is a molecular switch for signal transduction pathways that regulate cell proliferation, differentiation, and apoptosis.[19] There are at least three *Ras* genes the human genome, including *H-ras*, *K-ras*, and *N-ras*.[17,19,] It has been reported that approximately 30% of human cancer cells possess *Ras* mutations and *K-ras* mutations occur in almost 90% of pancreatic cancer.[20,21] In normal cells, *Ras* protein is tightly regulated, and its activation is dependent on its binding to GDP, which shifts it to the non-active state by the GTPase activating protein (RasGAP), or GTP, which shifts it to the active state by the guanine nucleotide exchange factor (RasGEF) enzyme family (Figure 3.3).[17,22] When mutated, regulation by RasGAP is often inactivated, causing *Ras* protein to remain continuously active and inhibit apoptosis correspondingly. Overactivation of *Ras*, therefore, leads to uncontrolled proliferation of cells and tumor aggressiveness by regulating the downstream c-Raf/MEK/ERK signaling pathway in proteins.[23]

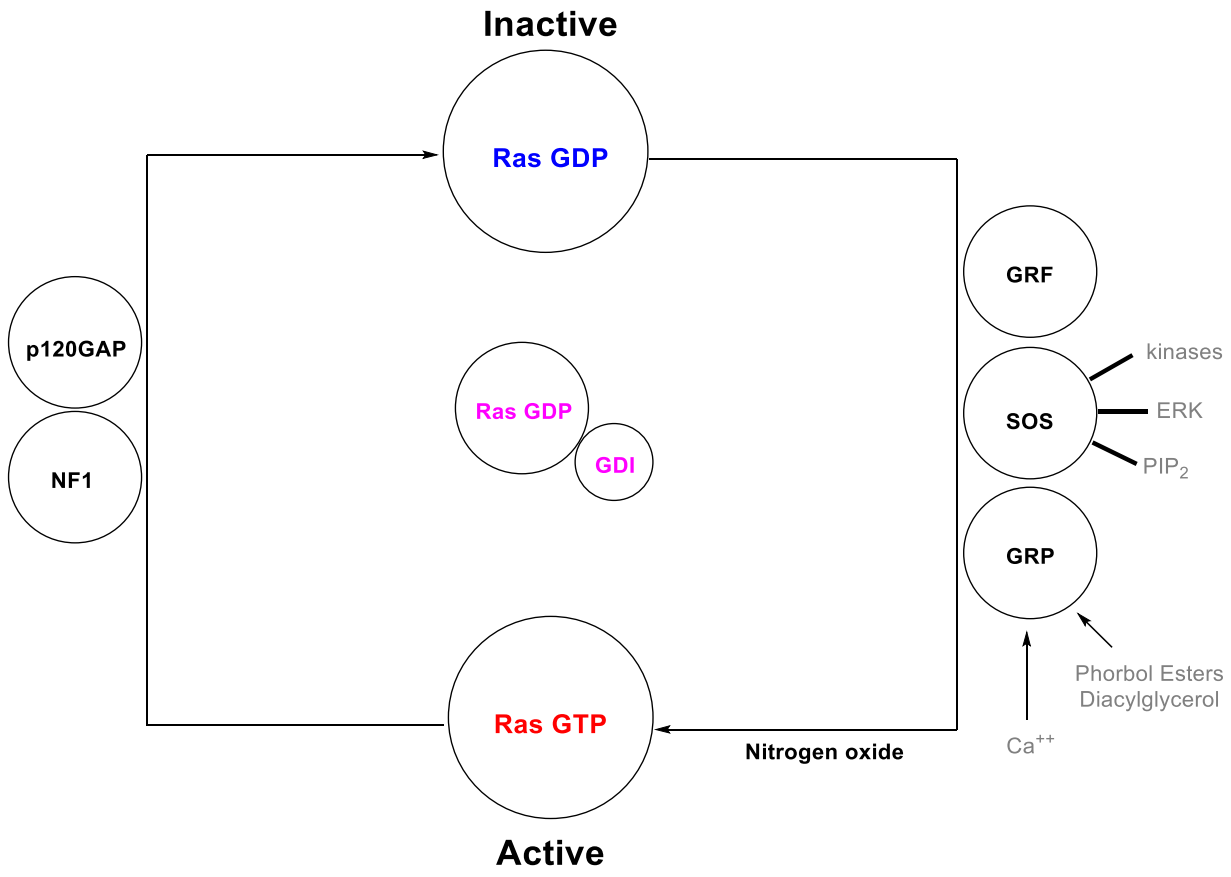



Figure 3.3 Schematic view of *Ras* proteins cycle between the inactive GDP-bound and the active GTP-bound states with *Ras* regulatory and exchange factors.

Given the prevalence of *Ras* mutations in cancer, *Ras* has long been viewed as a central target for therapeutic inhibition.[24] Despite of continuous efforts to develop pharmacological inhibitors of *Ras* over several decades, FDA-approved anti-*Ras* drug is nonexistent. The major difficulty of developing the *Ras* inhibitor is attributed to the protein's lack of deep pocket, which hinders binding of small molecule inhibitors to the protein's active sites.[25] Recently, several successes in the development of direct *Ras* inhibitors have been reported, revitalizing *Ras* inhibitor research for cancer chemotherapy.[24,26,27] (-)-Rasfonin (**118**), which is known to selectively induce apoptosis in *ras*-dependent cancer cells, has gained a significant amount of attention for this reason.

### 3.1.1 Isolation and Characterization of (-)-Rasfonin

(-)-Rasfonin (**118**), the α,β-unsaturated pyranone containing natural product, was isolated by Hayakawa and co-workers in 2000 from the fermentation broth of *Taleromyces sp.* 3656-A1.[28]

In the same year, Ishibashi and co-workers isolated **118** from the ethyl acetate extract of fungi imperfecti *Trichurus terrophilus* culture.[29] The compound is named after the G-protein *ras* as it is widely known to selectively destroy *ras*-dependent cells. Through chemical and spectroscopic studies,[28,29] **118** was found to have absolute chemistry of five chiral centers as 5*R*,6*R*,7*S*,9*R*, and 6′*S* as shown in Figure 3.1.

### 3.1.2 Biological Activities of (-)-Rasfonin

Since the isolation of (-)-rasfonin (**118**) in 2000, biological activities of **118** have been examined by several researchers. In 2000, Hayakawa and co-workers first revealed that **118** can selectively destroy *ras*-dependent Ba/F3-V12 cells with an $IC_{50}$ value of 0.16 μg/mL.[28] It was also reported that **118** showed no cytotoxicity against non-*ras*-dependent cell lines when they were treated with **118** at concentrations less than 1.25 μg/mL.[28] Moreover, 1 μg/mL of **118** was sufficient to induce apoptosis in significant numbers of *ras*-dependent Ba/F3-V12 cells, showing condensed chromatin and fragmented DNA in those cells.[28] In 2003, Ishibashi and co-workers also reported that proliferation of mouse splenic lymphocytes stimulated with concanavalin A and lipopolysaccharide can be suppressed by **118** with $IC_{50}$ values of 0.7 and 0.5 μg/mL, respectively.[29]

In 2014, Xiao and co-workers demonstrated the effects of **118** on K-*ras*-mutated pancreatic cancer cells both *in vitro* and *in vivo*.[21] *In vitro* studies, **118** successfully reduced proliferation of two human pancreatic cancer cell lines, Panc-1 (mutated K-*ras*) and BxPC-3 (wild-type K-*ras*), with $IC_{50}$ values of 5.5μM and 10μM, respectively.[21] Further experiments also revealed that Son of sevenless 1 (Sos1) expression (Figure 3.3) was inhibited by **118**, though activities of RasGEF and RasGAP were unchanged.[21] *In vivo* experiments, the growth of xenograft tumors, originated from Panc-1 cells, was successfully delayed by 30 mg/kg of **118**. Tumor mass was reported to eventually decrease after 20 days of treatment of **118**.[21]

## 3.2 Boeckman's Total Synthesis of (-)-Rasfonin

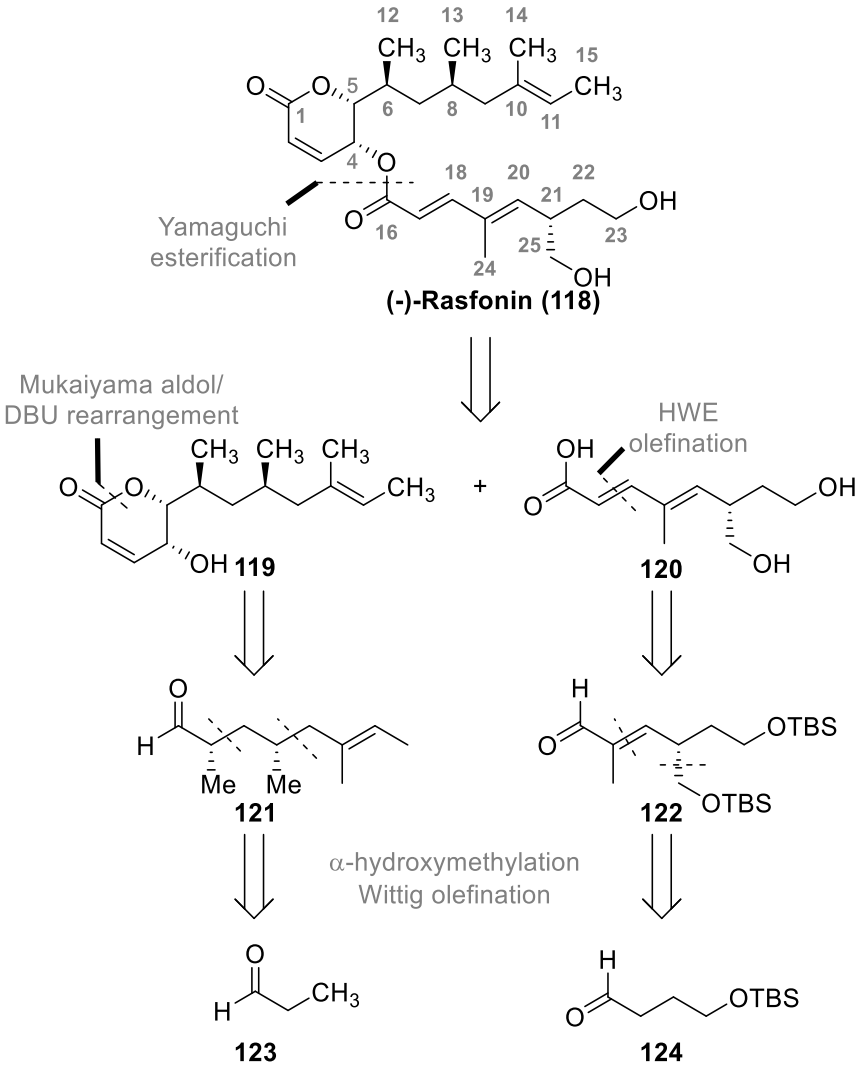
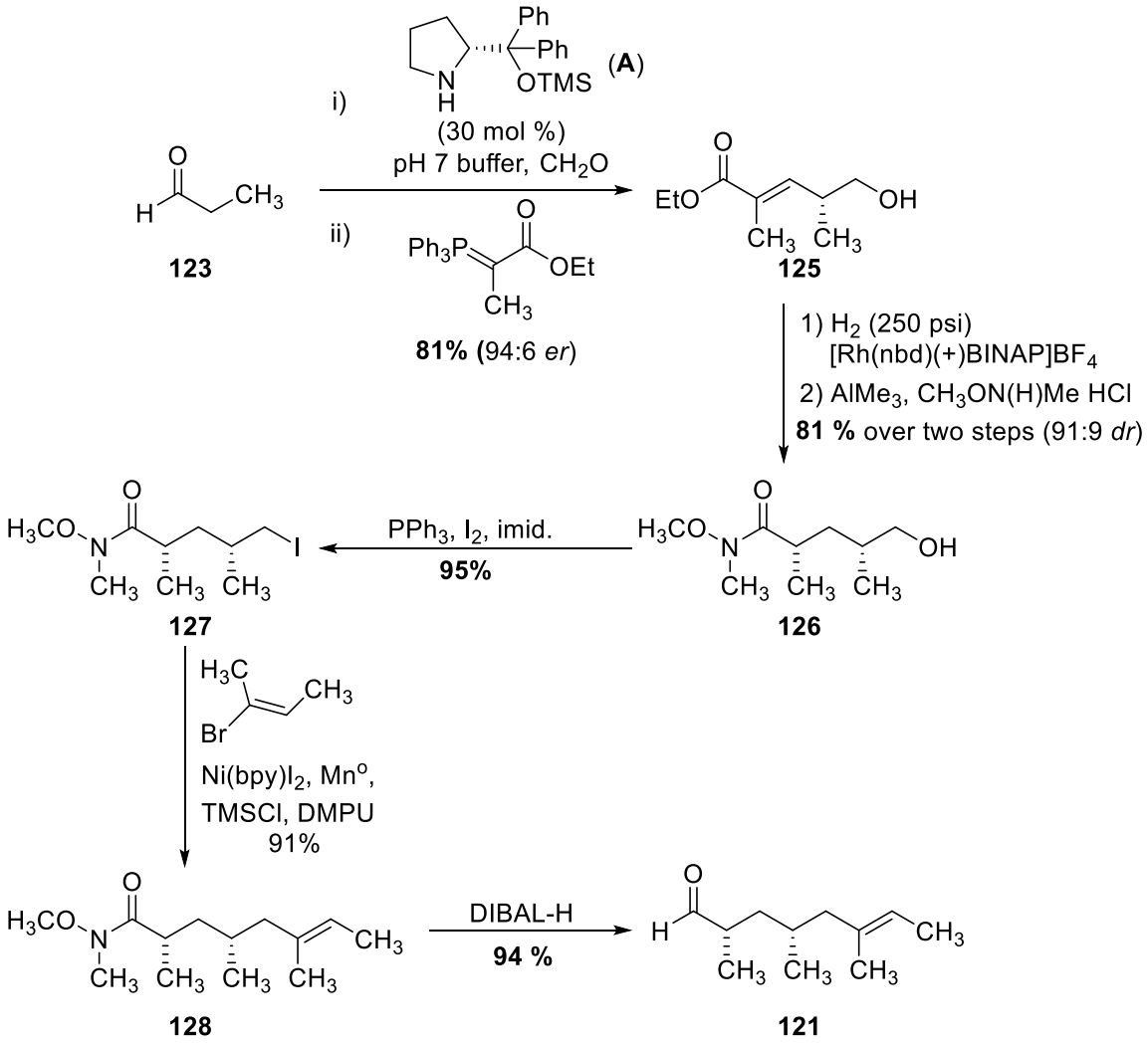



Figure 3.4 Boeckman's Retrosynthetic Analysis of (-)-Rasfonin (118)

In 2018, Boeckman and co-workers reported the total synthesis of (-)-rasfonin (**118**) with 13 longest linear steps in 10% overall yield.[30] Their total analysis is the shortest synthetic route reported up to date and their retrosynthetic analysis is depicted in Figure 3.4. Boeckman's group was able to construct (-)-rasfonin (**118**) from pyranone **119** and (*E*,*E*)-acid **120** by a Yamaguchi esterification. Pyranone **119** was successfully obtained from aldehyde **121** by a CBS-catalyzed vinylogous Mukaiyama aldol reaction, followed by a DBU-catalyzed furanone-to-pyranone rearrangement reaction. Aldehyde **121** was furnished from propionaldehyde **123** through a tandem catalytic α-hydroxymethylation and Wittig olefination sequence. (*E*,*E*)-acid **120** was synthesized

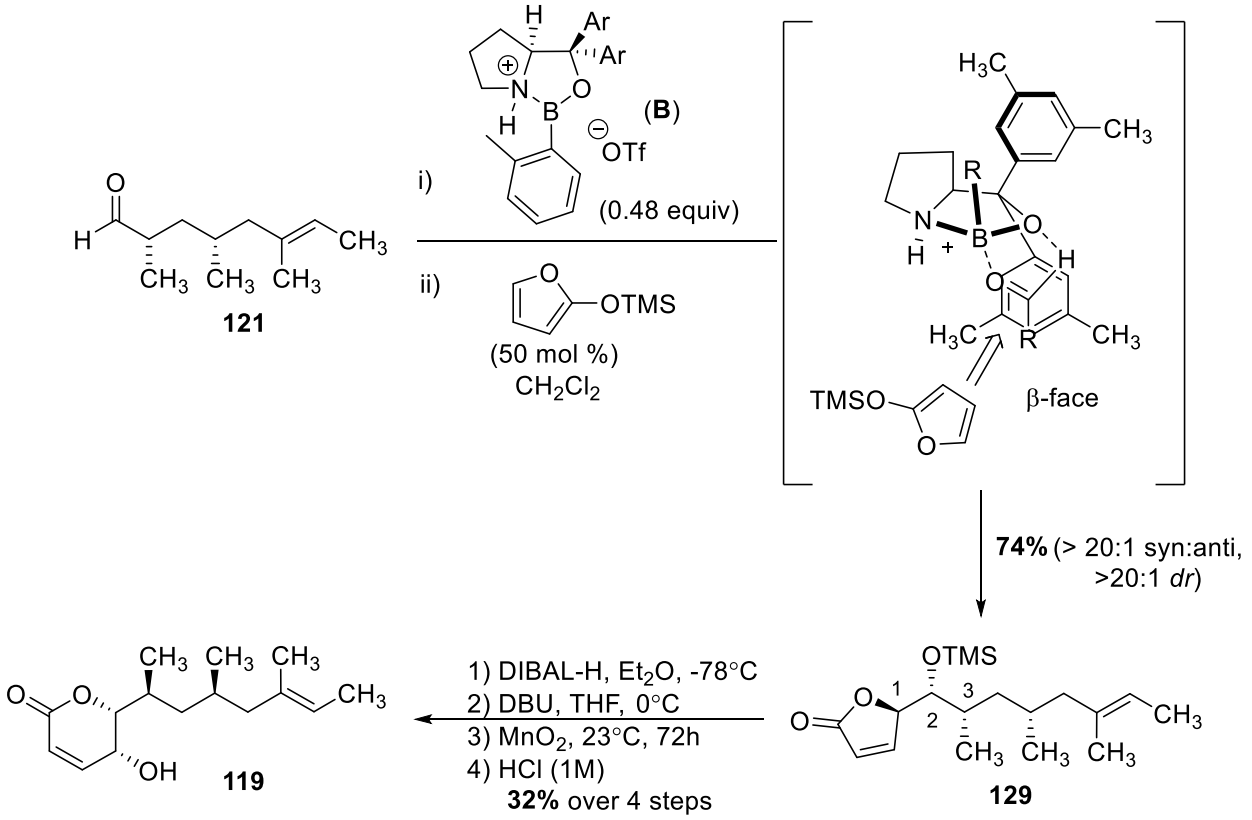
from aldehyde **122** via a Horner-Wadsworth-Emmons procedure. Aldehyde **122** was furnished from aliphatic aldehyde **124** following the same sequence of tandem catalytic α-hydroxymethylation and Wittig olefination reaction.




Scheme 3.1 Syntehsis of Aldehyde 121

Starting with propionaldehyde **123**, treatment of **123** with formalin and (*S*)-Jorgensen-Hayashi prolinol catalyst (**A**) in buffered media (pH = 7), followed by a treatment of ethyl 2-(triphenylphosphaneylidene)propanoate offered unsaturated ester **125** in 81% yield with 94:6 enantiomeric ratio (Scheme 3.1).[31] The resulting unsaturated ester **125** was subjected to Evan's asymmetric hydrogenation conditions that using [Rh(nbd)(+)BINAP]$BF_4$ catalyst under 250 psi of hydrogen gas (nbd = norboradiene).[32] This reaction gave intermediate saturated ester, which

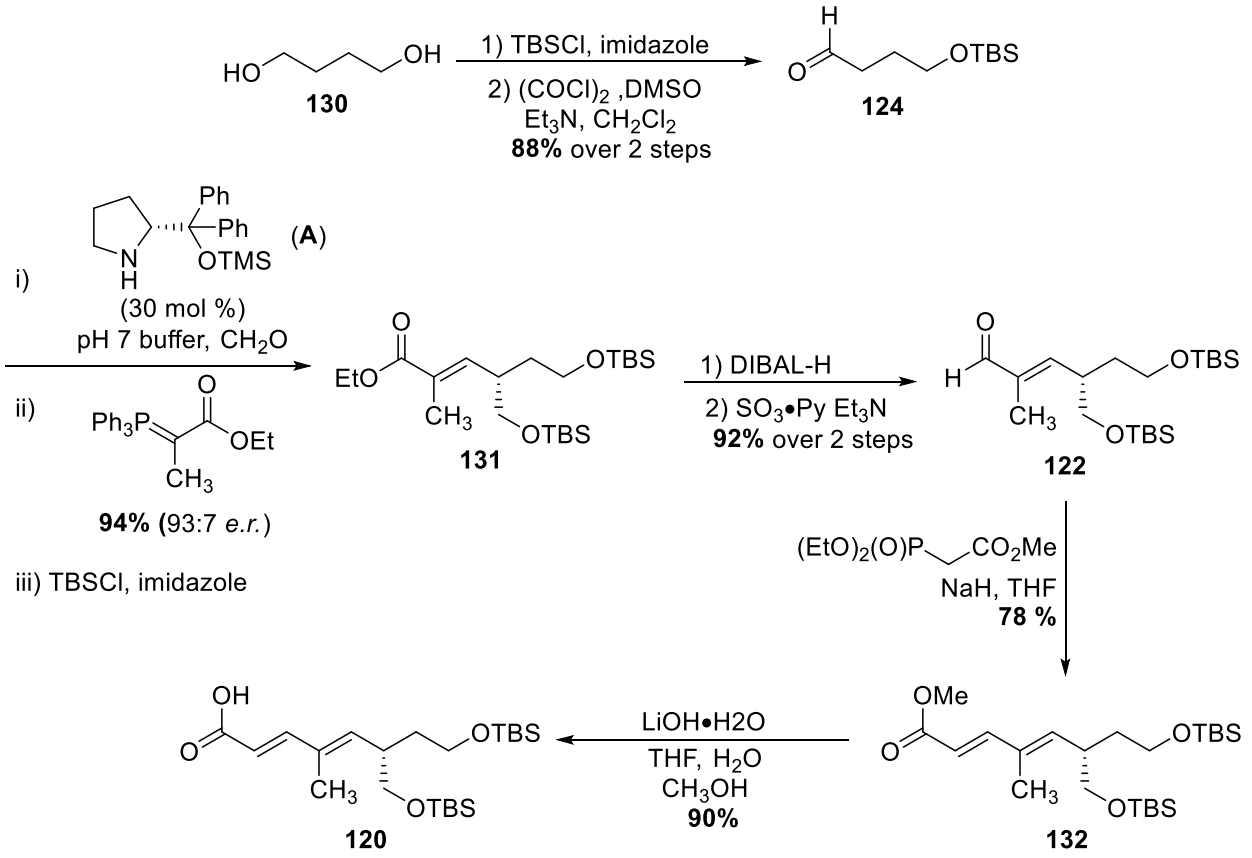
was subsequently converted to chiral Weinreb amide **126** in 81% yield over two steps by following the standard conditions.[33] Appel reaction of Weinreb amide **126** afforded iodide **127** in 95% yield.[34] Ni-catalyzed coupling reaction of iodide **127** in the presence of (bpy)$NiI_2$ (bpy=bipyridyl), $Mn^{o}$, and commercially available (*E*)-2-bromo-2-butene provided amide **128** in excellent yield.[35] DIBAL reduction of amide **128** furnished aldehyde intermediate **121** in 94% yield.




Scheme 3.2 Synthesis of Pyranone 119

Completion of the pyranone segment of (-)-rasfonin (**118**) is shown in Scheme 3.2. CBS-catalyzed Mukaiyama aldol reaction with (furan-2-yloxy)trimethylsilane and the Corey's oxazaborolidine catalyst **B**, which is generated *in situ* from the oxazaborolidine and triflic acid at -78°C, provided furanone **129** in good yield and high diastereoselectivity.[36] The observed high diastereoselectivity can be rationalized through a transition state shown in Scheme 3.2. According to this transition state model, that the alkyl group orientation of the aldehyde is dictated by the bulky aryl substituent of the catalyst **B** ($C_2$-$C_3$ diastereoselectivity), and the orientation of the incoming siloxyfuran is controlled by the stereochemistry of boron substituent ($C_1$-$C_2$

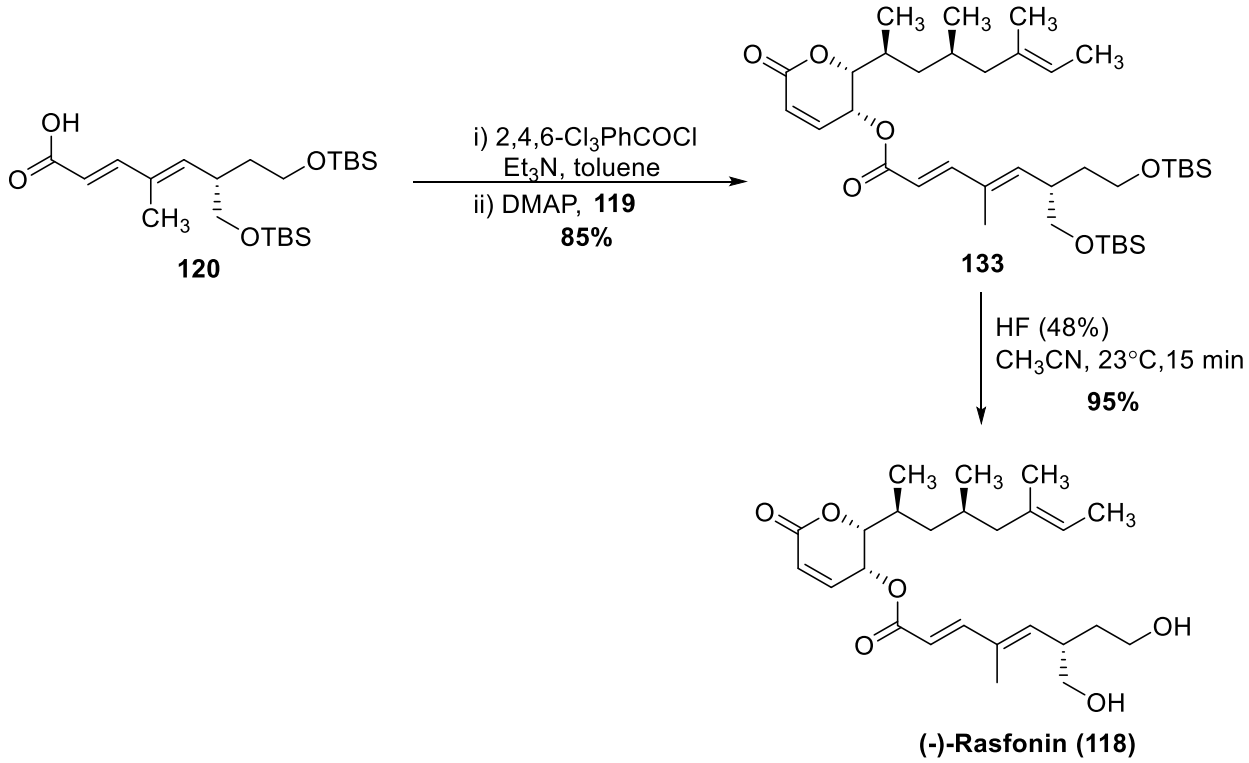
diastereoselectivity).[36] Successive reduction of furanone **129** with DIBAL-H, treatment of DBU, oxidation with $MnO_2$, and deprotection of the TMS group with 1M HCl provided the desired unsaturated pyranone **119** in 32% yield over 4 steps.[30]




Scheme 3.3 Synthesis of (*E*,*E*)-Carboxylic Acid 120

Construction of (*E*,*E*)-acid **120** was accomplished in 7 steps from 1,4-butenediol **130** (Scheme 3.3). Mono-TBS protection of compound **130,** followed by Swern oxidation provided aldehyde **124** in 88% over two steps.[37] Treatment of aldehyde **124** with formalin and the catalyst **A** in buffered media (pH = 7), followed by a successive treatment of ethyl 2-(triphenylphosphaneylidene)propanoate and TBS protection conditions offered unsaturated ester **131** in excellent yield and enantioselectivity. DIBAL reduction of unsaturated ester **131** followed by Parikh-Doering oxidation afforded unsaturated aldehyde **122** in 92% yield over two steps with α-olefin intact.[38] Horner-Wadsworth-Emmons olefination of aldehyde **122** in the presence of sodium hydride gave methyl ester **132** in 78% yield.[39] Hydrolysis of methyl ester **132** by using

excess amount of $LiOH \cdot H_2O$ in a 2:1:2 mixture of $THF:H_2O:CH_3OH$ furnished the carboxylic acid **120** in 90% yield.




Scheme 3.4 Synthesis of (-)-Rasfonin

To finish up the synthesis, Yamaguchi esterification of pyranone **119** and carboxylic acid **120** afforded compound **133** in 85% yield (Scheme 3.4).[40] Final treatment of compound **133** with HF (48%) in acetonitrile at 23ºC for 15 min furnished (-)-rasfonin (**118)** in 95% yield.

## 3.3 Results and Discussion

### 3.3.1 First Retrosynthetic Analysis of Segment A of (-)-Rasfonin

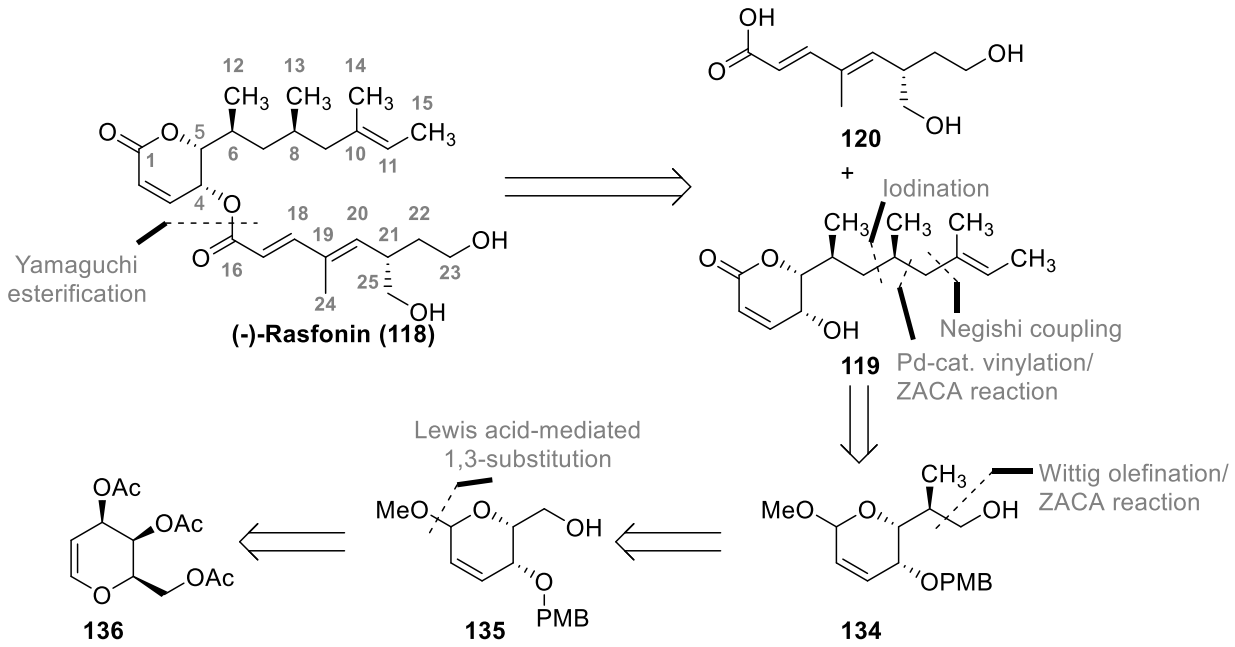


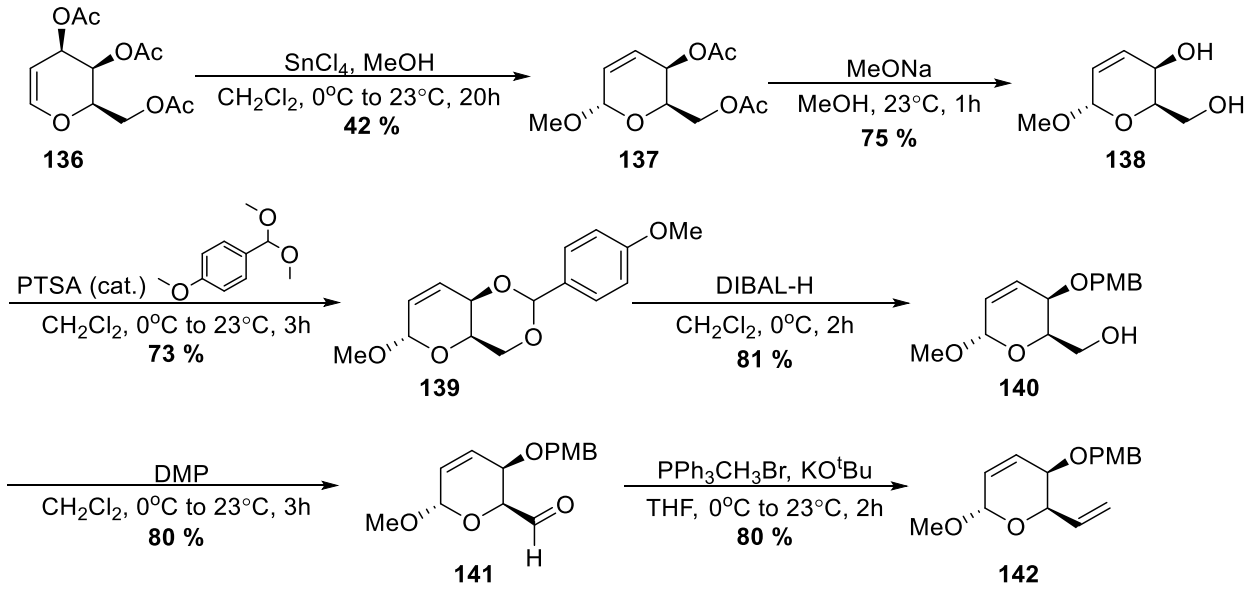

Figure 3.5 Retrosynthetic analysis of Segment A of (-)-Rasfonin (118)

Our retrosynthetic analysis of (-)-rasfonin (**118**) is shown in Figure 3.5. Based on our strategy, we envisioned that **118** would be prepared from carboxylic acid **120** and pyranone **119** by a Yamaguchi esterification. Pyranone **119** would be installed from alcohol **134** through a four-step process: i) iodination, ii) zincation followed by Pd-catalyzed vinylation, iii) ZACA reaction, and iv) Negishi coupling with vinyl bromide.[41,42] Alcohol **134** would be obtained from compound **135** by sequential Wittig olefination and ZACA reaction. Compound **135** would be readily synthesized from commercially available 3,4,6-Tri-*O*-acetyl-D-glactal **136** after Lewis acid-mediated methanol addition.

### 3.3.2 Attempted Synthesis of Segment A of (-)-Rasfonin

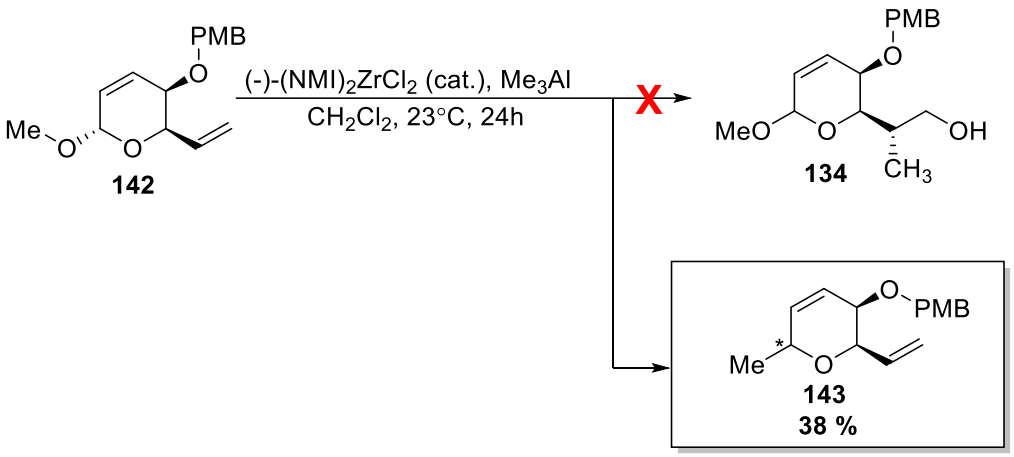
Our synthesis of segment **A** of (-)-rasfonin (**118)** begins with $SnCl_4$-catalyzed $SN_2$' addition of methanol to commercially available 3,4,6-Tri-*O*-acetyl-D-glactal **136** in $CH_2Cl_2$ at 0$^o$C to 23$^o$C for 20h (Scheme 3.5). This reaction exclusively afforded 1,3-substitution product, diacetate **137**,

in 42% yield as a single isomer. Deacetylation of diacetate **137** with sodium methoxide in methanol at 23°C for 1h provided diol **138** in 75% yield. Subsequent treatment of diol **138** with *p*-anisaldehyde dimethyl acetal and a catalytic amount of *para*-toluenesulfonic acid in $CH_2Cl_2$ at 0°C to 23°C for 3h offered compound **139** in 73% yield. DIBAL reduction of compound **139** in $CH_2Cl_2$ at 0°C for 3h regioselectively furnished primary alcohol **140** in 81% yield.[xx] Dess-Martin oxidation of primary alcohol **140** in $CH_2Cl_2$ at 0°C to 23°C for 3h gave aldehyde **141** in 80% yield.[43] Wittig olefination of aldehyde **141** using methyltriphenylphosphonium bromide and potassium *tert*-butoxide in THF at 0°C to 23°C for 2h yielded olefin **142** in 80% yield (Scheme 3.5).[44,45]




Scheme 3.5 Synthesis of Olefin 142

As shown in Scheme 3.6, olefin **142** was subjected to Negishi's ZACA reaction condition by employing trimethylaluminum and a catalytic amount of (-)-$(NMI)_2ZrCl_2$ (NMI = 1-neomenthylindenyl) in $CH_2Cl_2$ at 23°C for 24h.[46-50] Unfortunately, the ZACA oxidation reaction failed to furnish the expected product **134**, but instead afforded methylated product **143** in 38% yield with approximately 20:1 diastereomeric ratio. The stereochemistry of the C6 methyl substituent is currently under investigation.




Scheme 3.6 Attempted ZACA-Reaction of Olefin 142

### 3.3.3 Modified Synthesis of Segment A of (-)-Rasfonin

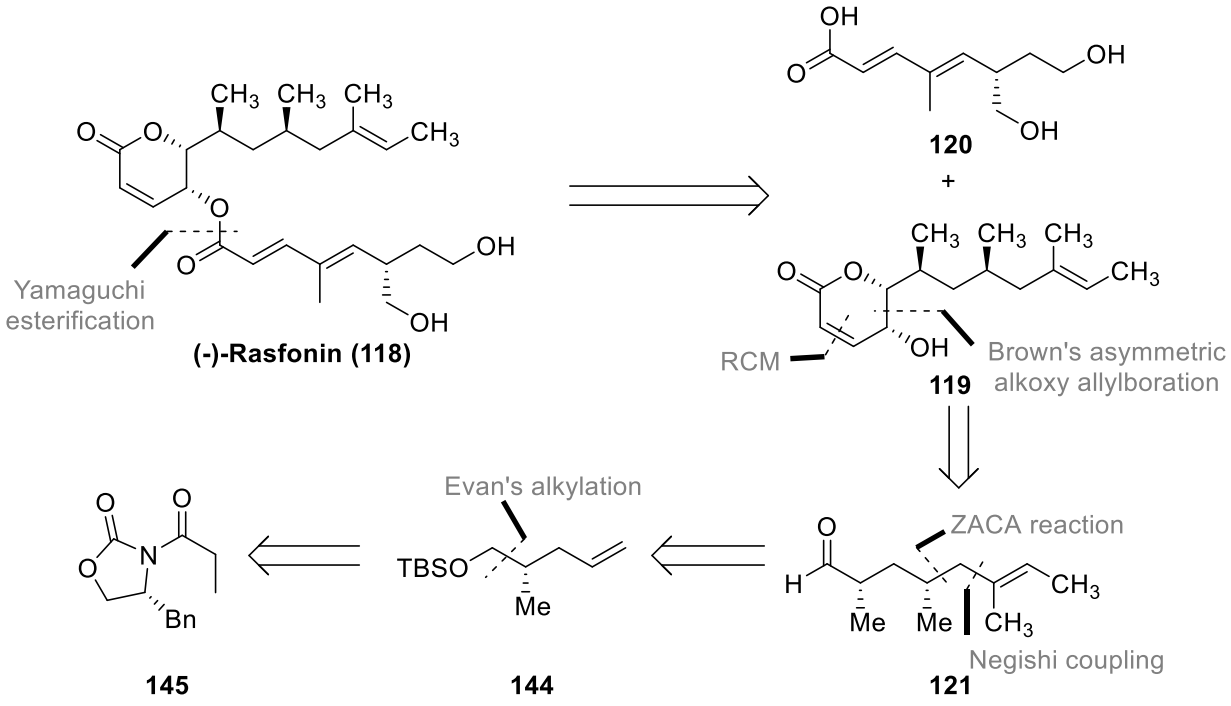
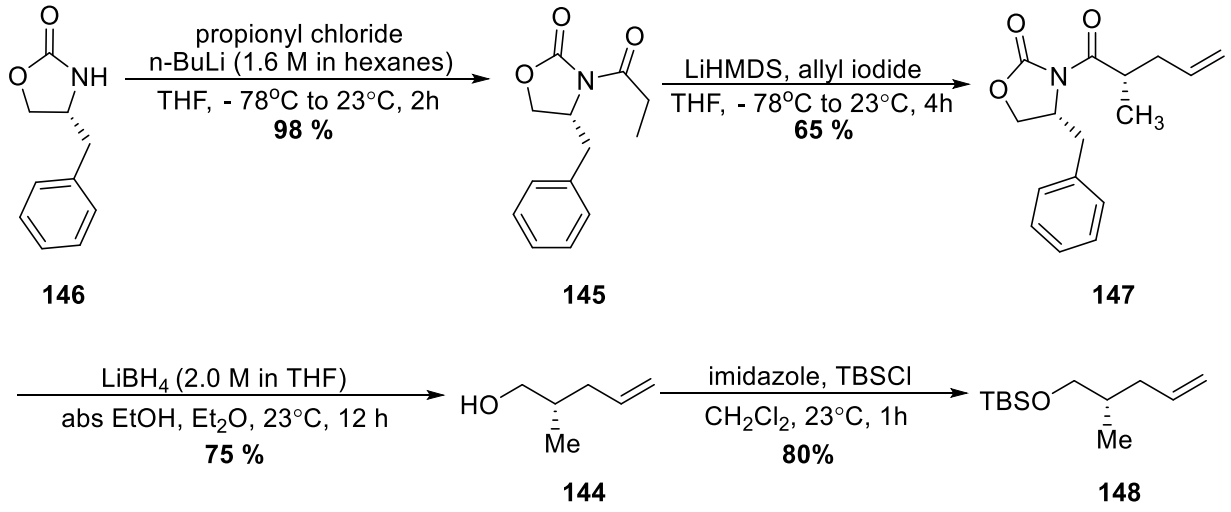



Figure 3.6 2nd Retrosynthetic Analysis of Segment A of (-)-Rasfonin (118)

Difficulties of installing the chiral methyl substituent on the olefin group in compound **142** due to its Lewis acid prone nature prompted a new synthetic strategy. The new retrosynthetic analysis is outlined in Figure 3.6. We envisioned that (-)-rasfonin (**118**) would be obtained from carboxylic acid **120** and pyranone **119** through a Yamaguchi esterification. Pyranone **119** would

be prepared from aldehyde **121** by a Brown's asymmetric alkoxy allylboration[51] and ring closing metastasis by using the second-generation Grubb's catalyst. We also envisioned that aldehyde **121** would be synthesized from TBS-protected alcohol **144** through a tandem ZACA reaction and Negishi coupling.[41,42] Finally, TBS-protected alcohol **144** would be readily furnished from Evan's chiral auxiliary **145** by an Evan's alkylation reaction.[52]

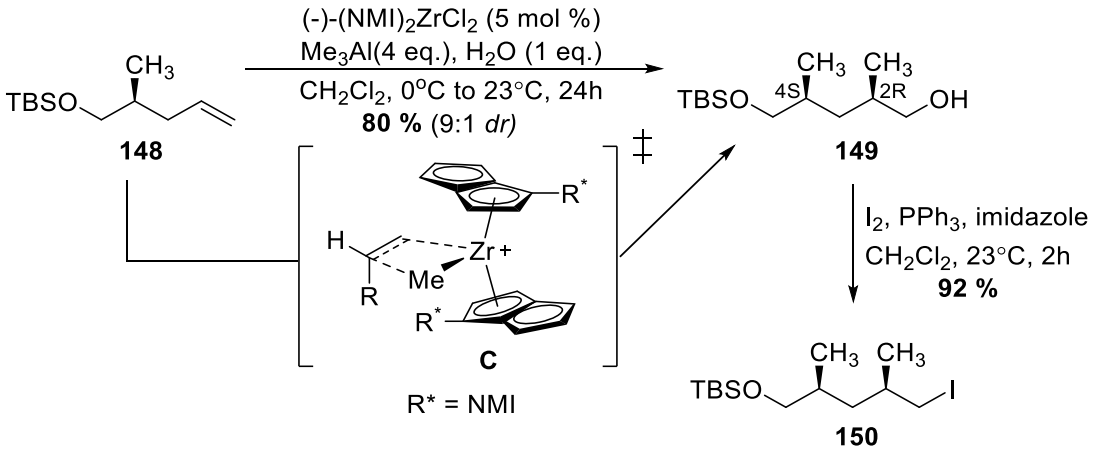
The synthesis of TBS-protected alcohol **148** is depicted in Scheme 3.7. Evan's chiral oxazolidinone **145** was prepared in 98% yield when *n*-butyllithium and propionyl chloride were added to compound **146** in THF at -78ºC to 23ºC for 2h.[52] Subsequent treatment of compound **145** with LiHMDS and allyl iodide in THF -78ºC to 23ºC for 2h offered allyl derivative **147** in 65% yield with a high level of diastereoselectivity (>20:1 *dr*). Reduction of compound **147** was achieved with lithium borohydride and absolute ethanol in diethyl ether in 23ºC for 12h, affording primary alcohol **144** in 75% yield.[53] TBS protection of primary alcohol **144** by using TBSCl and imidazole in $CH_2Cl_2$ at 23ºC for 1h furnished TBS-protected alcohol **148** in 80% yield.




Scheme 3.7 Synthesis of TBS-protected Alcohol 148

Now with compound **148** in our hands, Negishi's ZACA reaction was tested again to diastereoselectively install methyl substituent and hydroxyl group. The use of 5 mol % of (-)-$(NMI)_2ZrCl_2$, 4 equivalents of trimethylaluminum solution (2.0M in hexanes), and 1 equivalent of water additive in $CH_2Cl_2$ at 0ºC to 23ºC for 24h successfully converted compound **148** to alcohol **149** in 80% yield with a 9:1 *dr* (Scheme 3.8).[54] The diastereoselectivity of the ZACA reaction can

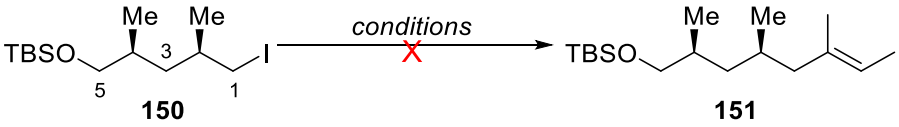
be rationalized by the proposed transition state in Scheme 3.8, in which the $C_2$-symmetric zirconium cation intermediate interacts with the *re*-face of the terminal olefin of compound **148** for a four-centered *syn* addition of Me-Zr that eventually leads to the formation of 2*R* methyl substituent on carbon 2.[46] The stereochemical identity of the major product **149** was confirmed by comparing the obtained spectroscopic and optical rotation data with the reported ones.[55] Appel reaction of primary alcohol **149** by using iodine, triphenylphosphine, and imidazole in $CH_2Cl_2$ at 23°C for 2h afforded iodide **150** in 92% yield.[34]



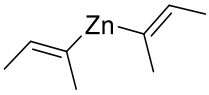

Scheme 3.8 Synthesis of Iodide 150

To prepare aldehyde **121** (Figure 3.6), primary iodide **150** was subjected to various conditions, which are detailed in Table 3.1. Several attempts were made to couple primary iodide **150** with (*E*)-2-bromo-2-butene, including: i) an iron-catalyzed cross-coupling between alkenyl Grignard reagents and primary iodide **150** (Table 3.1, Entry 1,2)[56,57]; ii) Cu mediated-coupling reaction using and *t*-BuLi (Table 3.1, Entry 3) [58,59] or *n*-BuLi (Table 3.1, Entry 4); iii) direct lithiation of the primary iodide with (*E*)-2-bromo-2-butene (Table 3.1, Entry 5); iv) Negishi's coupling reaction (Table 3.1, Entry 6)[59]; v) Zn-Cu mediated coupling reaction (Table 3.1, Entry 7) [60]; vi) the use of lithium metal for the lithiation of the primary iodide (Table 3.1, Entry 8); vii) and the Weix's Ni-catalyzed coupling reaction protocol[35] (Table 3.1, Entry 9). All these attempts, however, were fruitless, either forming a side product or recovering the starting material **150**.

Table 3.1 Failed Attempts to Chain Elongation




**150** **151**

| **Entry** | Conditions | Results |
|---|---|---|
| 1 | 1. Mg, (*E*)-2-bromo-2-butene, $I_2$, dry THF, reflux, 0.5h; then,<br>2. **150**, anhydrous $FeCl_3$, TMEDA, 0°C to 23°C, 0.5h | No reaction |
| 2 | 1. *t*-BuLi, (*E*)-2-bromo-2-butene, dry $Et_2O$, -78°C, 2h; 0°C, 45 min;<br>2. MgBr $OEt_2$, THF, -78°C, 2h; then,<br>3. **150**, anhydrous $FeCl_3$, TMEDA, 0°C to 23°C, 0.5h | No reaction |
| 3 | 1. *t*-BuLi, (*E*)-2-bromo-2-butene, dry THF, -78°C, 2h;<br>2. CuCN, dry THF, -78°C; -50°C, 1h; then,<br>3. **150**, dry THF, -50°C, 2h; 0°C, 2h; 23°C, 0.5 h | No reaction |
| 4 | 1. *n*-BuLi, (*E*)-2-bromo-2-butene, dry THF, -78°C, 0.5h;<br>2. CuCN, dry THF, -78°C to 23°C, 2h; then<br>3. **150**, dry THF, -78°C, 2h. | No reaction |
| 5 | 1. *t*-BuLi, (*E*)-2-bromo-2-butene, $Et_2O$, -78°C, 2h; then<br>2. **150**, dry $Et_2O$, 0°C to 23°C, 1h | $CH_3$ formation on C1 carbon |
| 6 | 1. **150**, *t*-BuLi, $ZnCl_2$, dry THF, -78°C, 10 min; 0°C, 0.5h; then,<br>2. $Pd(PPh_3)_4$, (*E*)-2-bromo-2-butene, dry THF, 0°C to 23°C, 12h | No reaction |
| 7 |  , CuI (20 mol %)<br>THF, 0°C to 23°C, 12h | No reaction |
| 8 | 1. Li, (*E*)-2-bromo-2-butene, $Et_2O$, 23°C, 2h; then<br>2. **150**, dry THF, 0°C to 23°C, 2h | No Reaction |
| 9 | (*E*)-2-bromo-2-butene, $bpyNiI_2$, Mn°, old TMSCl, distilled DMPU, 23°C, 12h | No Reaction |

Although the coupling reaction of primary iodide **150** and (*E*)-2-bromo-2-butene is unfeasible at this stage, the coupling reaction at the very last step of the synthesis has been reported by Bhuniya and co-workers employing Zn/Cu.[60] Treatment of primary alcohol **149** with sodium hydride, 4-methoxy benzylchoride, and a catalytic amount of tetrabutylammonium iodide in DMF at 0°C to 23°C for 12h provided compound **152** in 62% yield (Figure 3.7). The synthesis of pyranone **119** will be attempted following the proposed synthetic route depicted in Figure 3.7.

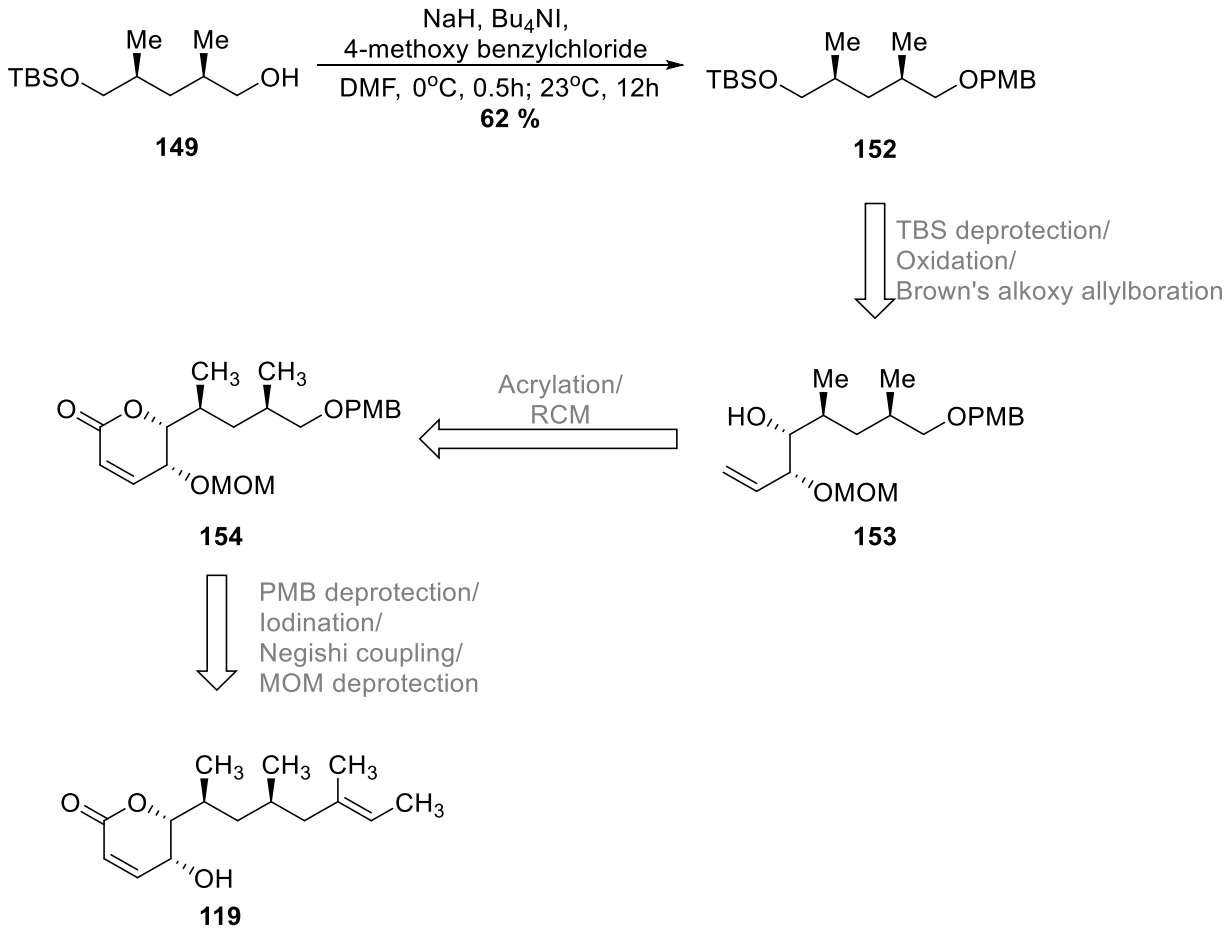



Figure 3.7 Proposed Synthetic Route to Obtain Pyranone 119

## 3.4 Conclusion

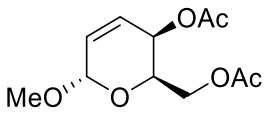
In conclusion, we have attempted to synthesize segment **A** of (-)-rasfonin (**118**) by employing a ZACA reaction to diastereoselectively install the methyl substituents. In our first attempt, we used a commercially available 3,4,6-Tri-*O*-acetyl-D-glactal as the starting material and constructed the α,β-unsaturated pyranone core in the early steps (Scheme 3.5). Surprisingly, ZACA reaction of olefin **142** provided methylated pyranone **143,** instead of the expected product **134**, as a major product (Scheme 3.6). A new synthetic route, therefore, had to be devised. In our second attempt, we used Evan's chiral oxazolidinone **146** as the starting material and used Evan's alkylation protocol (Scheme 3.7) to diastereoselectively install one of the methyl substituents (>20:1 *dr*). A subsequent ZACA reaction of olefin **148** (Scheme 3.8) was also successful, affording the desired alcohol **149** in a good yield with high diastereoselectivity (9:1 *dr*). The coupling reaction of iodide **150** and (*E*)-2-bromo-2-butene, however, was very troublesome (Table 3.1). We believe that this synthetic route is viable if the coupling reaction is taken at the very last step of the segment **A** synthesis (Figure 3.7).

## 3.5 Supporting Information

### 3.5.1 General Information

Please see Chapter 1.4.1.

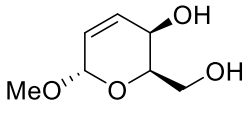
### 3.5.2 Experimental Procedures




**137**

((2*R*,3*R*,6*S*)-3-acetoxy-6-methoxy-3,6-dihydro-2H-pyran-2-yl)methyl acetate (**137**)

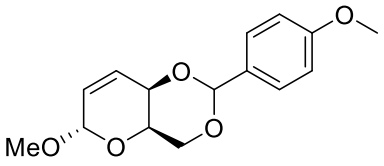
To a stirred solution of commercially available **136** (3 g, 11.02 mmol) in distilled MeOH (0.9 mL, 22.04 mmol), $SnCl_4$ (1 M in $CH_2Cl_2$, 3.31 mL, 3.31 mmol) was slowly added at 0$^o$C under argon atmosphere. The reaction mixture was stirred for 2h and additional $SnCl_4$ (1 M in $CH_2Cl_2$, 2 mL, 2 mmol) and distilled MeOH (1.8 mL, 44.08 mmol) were added at 0$^o$C. The resulting mixture was warmed to room temperature and vigorously stirred for 18 h.; the reaction has not gone to completion. Sat. aq. $NaHCO_3$ was added to quench the reaction and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic layers were washed with brine, dried ($Na_2SO_4$), and concentrated under reduced pressure. Purification of the residue by column chromatography (20% EtOAc in hexane) gave 1.126 g of compound **137** as a yellow amorphous solid (42 % yield).$^1$H NMR (400 MHz, Chloroform-*d*) δ 6.11 (ddd, *J* = 10.1, 5.4, 1.1 Hz, 1H), 6.05 – 6.00 (m, 1H), 5.03 – 4.99 (m, 1H), 4.96 (dd, *J* = 2.9, 1.2 Hz, 1H), 4.35 – 4.29 (m, 1H), 4.23 (d, *J* = 6.0 Hz, 2H), 3.44 (s, 3H), 2.08 (d, *J* = 1.7 Hz, 6H); $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 170.53, 170.26, 130.37, 125.16, 94.80, 66.62, 62.74, 62.66, 55.49, 20.73, 20.68. LRMS-ESI (m/z): 245.1 $(M+H)^+$




**138**

(2*R*,3*R*,6*S*)-2-(hydroxymethyl)-6-methoxy-3,6-dihydro-2H-pyran-3-ol (**138**)

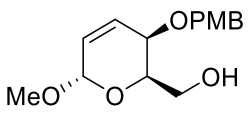
To a stirred solution of diacetate **137** (1.126g, 4.61 mmol) in distilled MeOH (23 mL) was treated with NaOMe (50 mg, 0.92 mmol) at 23ºC under Ar atmosphere. After stirring for 1 h, the reaction mixture was concentrated under reduced pressure. The crude residue was purified by flash column chromatography (90% EtOAc in hexane) to give diol **138** (550 mg, 75% yield) as a white amorphous solid. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 6.12 (ddd, *J* = 10.0, 5.5, 1.1 Hz, 1H), 5.96 – 5.83 (m, 1H), 4.92 (dd, *J* = 3.1, 1.1 Hz, 1H), 4.02 (td, *J* = 5.5, 2.3 Hz, 1H), 3.96 – 3.86 (m, 3H), 3.42 (s, 3H), 2.81 – 2.62 (m, 2H); $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 129.27, 128.28, 95.19, 70.03, 62.63, 62.39, 55.51. LRMS-ESI (m/z): 161.1 $(M+H)^+$




**139**

(4*aR*,6*S*,8*aR*)-6-methoxy-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-*d*][1,3]dioxine (**139**)

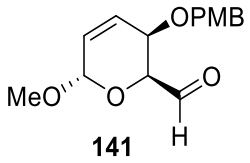
To a stirred solution of diol **138** in distilled $CH_2Cl_2$, *p*-anisaldehyde dimethyl acetal and pTSA $H_2O$ were added at 0ºC under Ar atmosphere. The resulting mixture was warmed to room temperature and vigorously stirred for 3h. Upon completion, a few drops of $Et_3N$ was added to neutralize the mixture, which was then concentrated under reduced pressure. The crude residue was purified via silica gel column chromatography (15 % to 30 % EtOAc in hexane) to give 690 mg of compound **140** as a white amorphous solid (73 % yield). $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 7.43 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 6.11 (dd, J = 10.0, 5.4 Hz, 1H), 6.03 (dd, J = 10.0, 3.1 Hz, 1H), 5.52 (s, 1H), 5.08 (d, J = 3.0 Hz, 1H), 4.40 – 4.30 (m, 1H), 4.23 (dd, J = 2.5, 0.8 Hz, 1H), 4.12 (dd, J = 5.5, 2.0 Hz, 1H), 3.81 (s, 1H), 3.77 (s, 3H), 3.45 (s, 3H); $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 159.96, 130.31, 130.04, 127.48, 126.09, 113.46, 100.62, 95.69, 69.90, 67.24, 61.65, 55.63, 55.18. LRMS-ESI (m/z): 279.1 $(M+H)^+$




**140**

((2*R*,3*R*,6*S*)-6-methoxy-3-((4-methoxybenzyl)oxy)-3,6-dihydro-2H-pyran-2-yl)methanol (**140**)

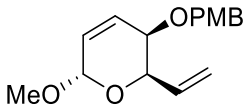
To a stirred solution of compound **140** (550 mg, 1.98 mmol) in distilled $CH_2Cl_2$, DIBAL-H (1 M in hexane, 4.0 mL, 4.00 mmol) was added dropwise at 0°C under Ar atmosphere. After 2h, methanol (4 mL) and aq. Sodium potassium tartrate solution (4 mL) were successively added at room temperature and the resulting mixture was vigorously stirred for 0.5 h. Thereafter, suspensions were filtered out via a pad of Celite and the filtrate was concentrated under reduced pressure. The crude residue was purified via silica gel column chromatography (40 % EtOAc in hexane) to give primary alcohol **150** (450 mg, 81 % yield) as a white amorphous solid. $^1$H NMR (400 MHz, Chloroform-*d*) δ 7.25 (d, *J* = 8.9 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.15 (ddd, *J* = 10.1, 5.2, 1.1 Hz, 1H), 6.01 (dd, *J* = 10.1, 3.0 Hz, 1H), 5.03 – 4.95 (m, 1H), 4.61 (d, *J* = 11.5 Hz, 1H), 4.45 (d, *J* = 11.5 Hz, 1H), 4.05 (ddd, *J* = 6.3, 4.6, 2.8 Hz, 1H), 3.96 (dd, *J* = 11.7, 6.2 Hz, 1H), 3.80 (s, 4H), 3.71 (dd, *J* = 5.2, 2.8 Hz, 1H), 3.43 (s, 3H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 159.34, 129.86, 129.60, 129.40, 126.38, 113.85, 95.08, 70.37, 70.05, 67.63, 62.81, 55.51, 55.18. LRMS-ESI (m/z): 303.2 $(M+Na)^+$




**141**

(2*S*,3*R*,6*S*)-6-methoxy-3-((4-methoxybenzyl)oxy)-3,6-dihydro-2H-pyran-2-carbaldehyde (**141**)

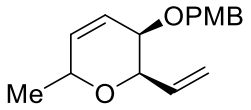
To a stirred solution of primary alcohol **150** (530 mg, 1.89 mmol) in dry $CH_2Cl_2$ (20 mL), Dess-Martin reagent (962 mg, 2.27 mmol) was added at 0°C under Ar atmosphere. The reaction mixture was stirred for 2h at room temperature. Upon completion, 20 mL of $NaHCO_3$ and $Na_2S_2O_3$ (1:1, v:v) was added and the resulting mixture was stirred for 0.5 hour. The reaction mixture was extracted with EtOAc and the collected organic layers were dried with $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified via silica gel column chromatography (20 % to 40% EtOAc in hexane) to give aldehyde **141** (421mg, 80 % yield) as a white amorphous solid. $^1$H NMR (400 MHz, Chloroform-*d*) δ 9.73 (s, 1H), 7.20 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.11 – 5.95 (m, 2H), 5.09 (dt, *J* = 2.9, 0.7 Hz, 1H), 4.48 (d, *J* = 6.3 Hz, 2H), 4.45 – 4.35 (m, 1H), 4.09 (dd, *J* = 4.9, 3.2 Hz, 1H), 3.80 (s, 3H), 3.46 (s, 3H); $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 200.22, 159.33, 129.59, 129.51, 129.39, 125.84, 113.74, 95.12, 75.45, 70.93, 67.10, 55.94, 55.17. LRMS-ESI (m/z): 279.1 $(M+H)^+$




**142**

(2*R*,3*R*,6*S*)-6-methoxy-3-((4-methoxybenzyl)oxy)-2-vinyl-3,6-dihydro-2*H*-pyran (**142**)

To a solution of $PPh_3CH_3Br$ (782 mg, 2.19 mmol) in THF (2 mL) was added $KO^tBu$ (1 M in THF, 2 mL, 2.00 mmol) at room temperature under Ar atmosphere. The resulting mixture was stirred for 30 mins and then a solution of aldehyde **141** (277 mg, 1.00 mmol) in THF (3 mL) was added to the mixture at 0°C. The mixture was then allowed to warm to room temperature and stirred for 2 hours. Upon completion, the reaction mixture was quenched with a satd. solution of NH4Cl and extracted with EtOAc. The collected organic layer was dried over $Na_2SO_4$, filtered, and concentrated at reduced pressure. The crude residue was purified by silica gel column chromatography (10 % EtOAc in hexane) to give olefin **142** (220 mg, 80 %) as a colorless oil. $^1$H NMR (400 MHz, Chloroform-*d*) δ 7.28 – 7.19 (m, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.16 – 6.02 (m, 2H), 5.98 (dd, *J* = 10.1, 3.0 Hz, 1H), 5.46 (dt, *J* = 17.3, 1.7 Hz, 1H), 5.30 (dt, *J* = 10.6, 1.7 Hz, 1H), 5.01 – 4.97 (m, 1H), 4.52 (d, *J* = 4.5 Hz, 2H), 4.50 – 4.42 (m, 1H), 3.79 (s, 3H), 3.65 (dd, *J* = 5.1, 2.8 Hz, 1H), 3.43 (d, *J* = 0.5 Hz, 3H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 159.10, 134.87, 130.49, 129.29, 129.11, 127.43, 116.71, 113.62, 95.15, 71.42, 70.48, 68.81, 55.46, 55.17. LRMS-ESI (m/z): 277.2 $(M+H)^+$

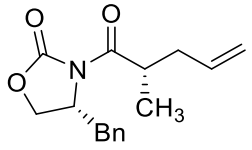



**143**

(2*R*,3*R*)-3-((4-methoxybenzyl)oxy)-6-methyl-2-vinyl-3,6-dihydro-2*H*-pyran (**143**)

To a solution of trimethylaluminum (0.05 mL, 0.105 mmol) and (-)-ZACA catalyst (2.5mg, 0.035 mmol) in distilled $CH_2Cl_2$ (0.2 mL) was added a solution of olefin **142** (19 mg, 0.07 mmol) in $CH_2Cl_2$ (0.4 mL) via a cannula at 23°C after 5 mins of stirring. The resulting mixture was vigorously stirred at the same temperature for 24h. After this period, the mixture was treated with a vigorous stream of oxygen bubbled through it for 1 h at 0 °C and then stirred for 5 h further under an atmosphere of oxygen at 23°C. The reaction mixture was quenched with 1N HCl, extracted with DCM, washed with brine, dried over MgSO4 and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (5% EtOAc in hexanes) to give 6.9 mg of compound **143** (38% yield) as a colorless oil. The diastereomeric ratio of the mixtures,

determined by $^{1}$H NMR analysis, was 20:1. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 7.29 – 7.22 (m, 2H), 6.86 (d, J = 8.7 Hz, 2H), 6.13 (ddd, J = 17.3, 10.6, 6.6 Hz, 1H), 5.83 (s, 2H), 5.45 (ddd, J = 17.3, 1.8, 1.3 Hz, 1H), 5.33 (ddd, J = 10.5, 1.8, 1.2 Hz, 1H), 4.51 (s, 2H), 4.39 (tt, J = 5.6, 1.4 Hz, 2H), 3.94 (dt, J = 4.1, 2.0 Hz, 1H), 3.79 (s, 3H), 1.22 (d, J = 6.8 Hz, 3H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 159.09, 134.47, 133.65, 130.50, 129.29, 124.14, 118.38, 113.64, 73.20, 70.28, 70.16, 67.08, 55.18, 29.60, 19.35. LRMS-ESI (m/z): 283.1 $(M+Na)^{+}$



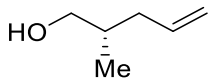

**147**

(*R*)-4-benzyl-3-((*S*)-2-methylpent-4-enoyl)oxazolidin-2-one (**147**)

To a stirred solution of (*R*)-4-benzyloxazolidin-2-one **146** (3.01 g, 17 mmol) in THF (60 mL) was dropwise added a solution of *n*-BuLi (1.6M in hexanes, 11.70 mL, 18.7 mmol) at -78$^{o}$C under argon atmosphere over 10 minutes. After this period, propionyl chloride (1.63 mL, 18.7 mmol) was added ) at -78$^{o}$C. The resulting mixture was stirred for 30 min at -78$^{o}$C and then warmed to 23$^{o}$C and stirred for 2h. Upon completion, sat. aq. $NH_4Cl$ was added to quench the reaction. The layers were separated and $CH_2Cl_2$ was used to extract organic layers. The combined organic layers were washed with water, dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (20% EtOAc in hexanes) to afford compound **145** (3.85g, 97% yield) as a white amorphous solid.

To a stirred solution of LiHMDS (1.0M in THF, 19.8 mL, 19.8 mmol) was dropwise added a solution of compound **145** (3.85g, 16.5 mmol) in THF (25 mL) over 30 minutes at -78$^{o}$C under argon atmosphere. After stirring for 30 mins, allyl bromide (4.4 mL, 49.5 mmol) was added dropwise at the same temperature and the resulting mixture was slowly warmed to 23$^{o}$C over 4h. After this period, the reaction was quenched by the addition of sat. aq. $NH_4Cl$. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (15% EtOAc in hexanes) to give 2.69g of compound **147** (65% yield) as a yellow oil. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.16 (m, 5H), 5.83 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1H), 5.14 – 5.00 (m, 2H), 4.68 (ddt, *J* = 9.8, 7.3, 3.3 Hz, 1H), 4.24 – 4.08 (m, 2H), 3.87 (h, *J* = 6.8 Hz, 1H), 3.29 (dd, *J* = 13.3, 3.4 Hz, 1H), 2.70 (dd, *J* = 13.3, 9.8 Hz, 1H), 2.53 (dddd, *J* = 13.7, 6.8,

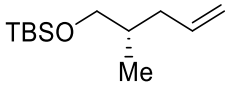
5.5, 1.3 Hz, 1H), 2.24 (dtt, *J* = 14.0, 7.0, 1.2 Hz, 1H), 1.19 (d, *J* = 6.8 Hz, 3H); $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 176.43, 153.02, 135.28, 135.17, 129.32, 128.85, 127.23, 117.13, 65.92, 55.31, 38.02, 37.89, 37.06, 16.34. LRMS-ESI (m/z): 296.2 $(M+Na)^+$




**144**

(*S*)-2-methylpent-4-en-1-ol (**144**)

To a stirred solution of compound **147** (938 mg, 3.43 mmol) in $Et_2O$ (27.5 mL) was consecutively added absolute EtOH (0.30 mL, 5.15mmol) and $LiBH_4$ solution (2.0M in THF, 2.6 mL, 5.15 mmol) at 0ºC under argon atmosphere. The reaction mixture was warmed to room temperature overnight, then was quenched by the addition of aqueous solution of NaOH (1M, 20mL, 20 mmol). The mixture was stirred for 1h until both layers became clear. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (20% EtOAc in hexanes) to give 260 mg of compound **144** (75% yield) as a colorless oil. $^1$H NMR (400 MHz, Chloroform-*d*) δ 6.06 – 5.96 (m, 2H), 5.85 (ddd, *J* = 10.2, 3.0, 0.7 Hz, 1H), 5.44 – 5.29 (m, 2H), 4.45 (dt, *J* = 6.9, 2.7 Hz, 1H), 4.28 (ddt, *J* = 5.6, 2.7, 1.4 Hz, 1H), 3.88 – 3.82 (m, 1H), 1.27 (d, *J* = 6.9 Hz, 3H); $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 134.85, 134.03, 125.79, 117.69, 72.51, 68.87, 63.98, 18.21. LRMS-ESI (m/z): 123.1 $(M+Na)^+$

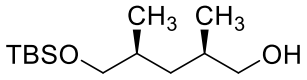



**148**

(*S*)-*tert*-butyldimethyl((2-methylpent-4-en-1-yl)oxy)silane (**148**)

To a stirred solution of **144** (240 mg, 2.4 mmol) in $CH_2Cl_2$ (12 mL) was consecutively added imidazole (327 mg, 4.8 mmol) and TBSCl (433 mg, 2.88 mmol) at 23ºC under Ar atmosphere. The reaction mixture was stirred for 1h and quenched with water. The aqueous layer was extracted with $CH_2Cl_2$, and the combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (5% EtOAc in hexanes) to give 411 mg of compound **144** (80% yield) as a colorless oil. $^1$H NMR (400 MHz, Chloroform-*d*) δ 5.79 (dddd, *J* = 17.0, 10.2, 7.5, 6.8 Hz, 1H), 5.07 – 4.89 (m, 2H), 3.51 – 3.29 (m, 2H), 2.26 – 2.12 (m, 1H), 1.85 (dtt, *J* = 13.8, 7.6, 1.2 Hz, 1H), 1.78 – 1.61 (m, 1H), 0.92

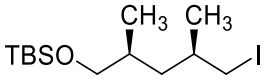
– 0.86 (m, 12H), 0.04 (s, 6H); $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 137.23, 115.52, 67.64, 37.53, 35.57, 25.83, 18.22, 16.23, -5.49. LRMS-ESI (m/z): 237.2 $(M+Na)^+$




**149**

(2*R*,4*S*)-5-((*tert*-butyldimethylsilyl)oxy)-2,4-dimethylpentan-1-ol (**149**)

A solution of $Me_3Al$ (2.0 M in hexanes, 1 mL, 2 mmol)) and (-)-$(NMI)_2ZrCl_2$ catalyst (16.7 mg, 0.025 mmol) in distilled $CH_2Cl_2$ (6 mL) was treated with $H_2O$ (9 µL, 0.5 mmol) at -78 ºC under Ar atmosphere. The cooling bath was immediately removed, and the mixture was warmed to room temperature. The resulting brown solution was cooled to 0ºC prior to the addition of a solution of compound **148** (107 mg, 0.50 mmol) in distilled $CH_2Cl_2$ (5 mL) via a cannula. After the addition, the resulting mixture was warmed to room temperature and was vigorously stirred for 24 h. After this period, the reaction mixture was quenched by bubbling $O_2$ through the solution until all volatiles were evaporated. The resulting slurry was diluted with $CH_2Cl_2$ and 2N NaOH was added (pH < 3). The aqueous layer was extracted with $CH_2Cl_2$ (50 mL x 2). The combined organic layers were dried ($Na_2SO_4$) filtered and concentrated under reduced pressure. The crude residue was purified via silica gel column chromatography (10 % to 50 % ethyl acetate in hexane) to give 98 mg of the expected product as a colorless oil (80 % yield). The $^1$H NMR analysis showed that the diastereomeric ratio of the reaction was approximately 9:1. $^1$H NMR (400 MHz, Chloroform-*d*) δ 3.49 (dd, *J* = 10.6, 5.2 Hz, 1H), 3.45 – 3.33 (m, 3H), 1.85 (s, 1H), 1.69 (dtd, *J* = 14.6, 7.9, 7.3, 5.7 Hz, 2H), 1.43 (dt, *J* = 13.6, 6.7 Hz, 1H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.91 – 0.86 (m, 12H), 0.03 (s, 6H); $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 68.17, 68.05, 37.17, 33.15, 33.12, 25.83, 18.23, 17.70, 17.60, -5.50. LRMS-ESI (m/z): 269.2 $(M+Na)^+$

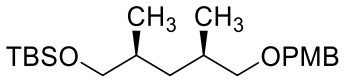



**150**

*tert*-butyl(((2*S*,4*R*)-5-iodo-2,4-dimethylpentyl)oxy)dimethylsilane (**150**)

A solution of $I_2$ (47 mg, 0.18 mmol), $PPh_3$ (48 mg, 0.18 mmol), and imidazole (14mg, 0.2 mmol) in $CH_2Cl_2$ (0.5 mL) was stirred for 15 mins prior to the addition of a solution of compound **149** (38 mg, 0.15 mmol) in $CH_2Cl_2$ (1 mL) at room temperature under argon atmosphere. After the addition of compound **149**, the resulting mixture was stirred for 2h. Then, the solvent was removed *in vacuo* and the resulting solid residue was suspended in a minimal amount of $CH_2Cl_2$ and loaded

on to a column of silica gel. Eluting with hexane afforded a red solution that was washed with saturated sodium bisulfite and brine, dried over MgSO4, filtered, and concentrated to give 90 mg (92%) of the title compound as a colorless oil. $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 3.44 (dd, *J* = 9.8, 5.5 Hz, 1H), 3.36 (dd, *J* = 9.8, 6.3 Hz, 1H), 3.26 (dd, *J* = 9.6, 4.0 Hz, 1H), 3.11 (dd, *J* = 9.6, 6.1 Hz, 1H), 1.64 (dq, *J* = 8.0, 6.4 Hz, 1H), 1.58 – 1.49 (m, 1H), 1.41 (ddd, *J* = 13.5, 7.3, 6.0 Hz, 1H), 0.99 (dd, *J* = 6.3, 2.3 Hz, 4H), 0.89 (d, *J* = 6.3 Hz, 12H), 0.04 (s, 6H); $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 68.08, 40.29, 33.07, 31.83, 25.86, 21.40, 18.23, 17.95, 17.06, -5.47. LRMS-ESI (m/z): 379.1 $(M+Na)^{+}$




**152**

*Tert*-butyl(((2*S*,4*R*)-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentyl)oxy)dimethylsilane (**152**)

To a solution of primary alcohol **149** (175mg, 0.71 mmol) in dry DMF (1.4 mL) at 0$^{o}$C was added NaH (60% dispersion in oil, 43 mg, 1.07 mmol). After stirring for 30 min at 0$^{o}$C, $Bu_4NI$ (13 mg, 0.036 mmol) and 4-methoxy benzylchloride (144 µL, 1.07 mmol) were successively added under argon atmosphere. The resulting mixture was warmed to room temperature and vigorously stirred overnight. The reaction was quenched by the addition of water, and the aqueous layer was extracted with hexanes (20 mL x 5). The collected organic layers were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography to give **152** as a colorless oil (160 mg, 60% yield). $^{1}$H NMR (400 MHz, Chloroform-*d*) δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.43 (d, *J* = 2.5 Hz, 2H), 3.80 (s, 3H), 3.47 (dd, *J* = 9.7, 5.3 Hz, 1H), 3.33 (ddd, *J* = 9.7, 6.0, 3.4 Hz, 2H), 3.17 (dd, *J* = 9.1, 7.2 Hz, 1H), 1.85 (ddd, *J* = 13.8, 6.9, 5.2 Hz, 1H), 1.70 (pd, *J* = 6.9, 5.3 Hz, 1H), 1.42 (dt, *J* = 13.6, 6.7 Hz, 1H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.92 – 0.89 (m, 12H), 0.04 (s, 6H). $^{13}$C NMR (101 MHz, Chloroform-*d*) δ 158.94, 130.84, 128.95, 113.60, 75.64, 72.52, 68.14, 55.13, 37.68, 33.10, 30.88, 25.88, 18.25, 18.11, 17.64, -5.44. LRMS-ESI (m/z): 389.3 $(M+Na)^{+}$

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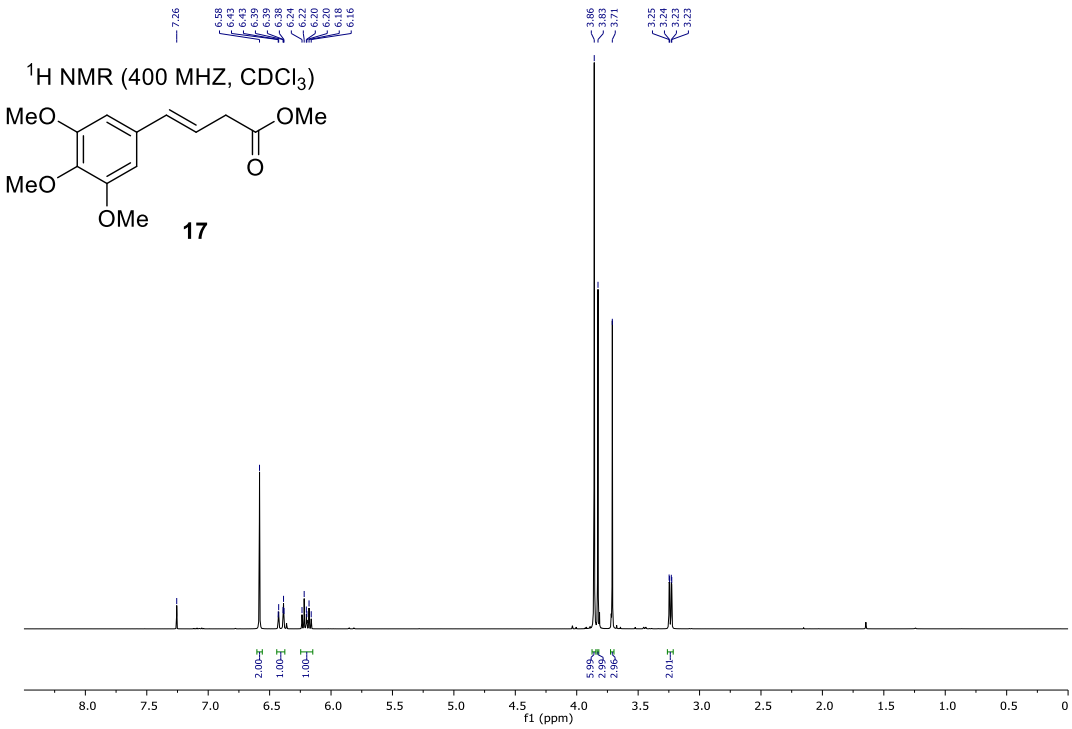
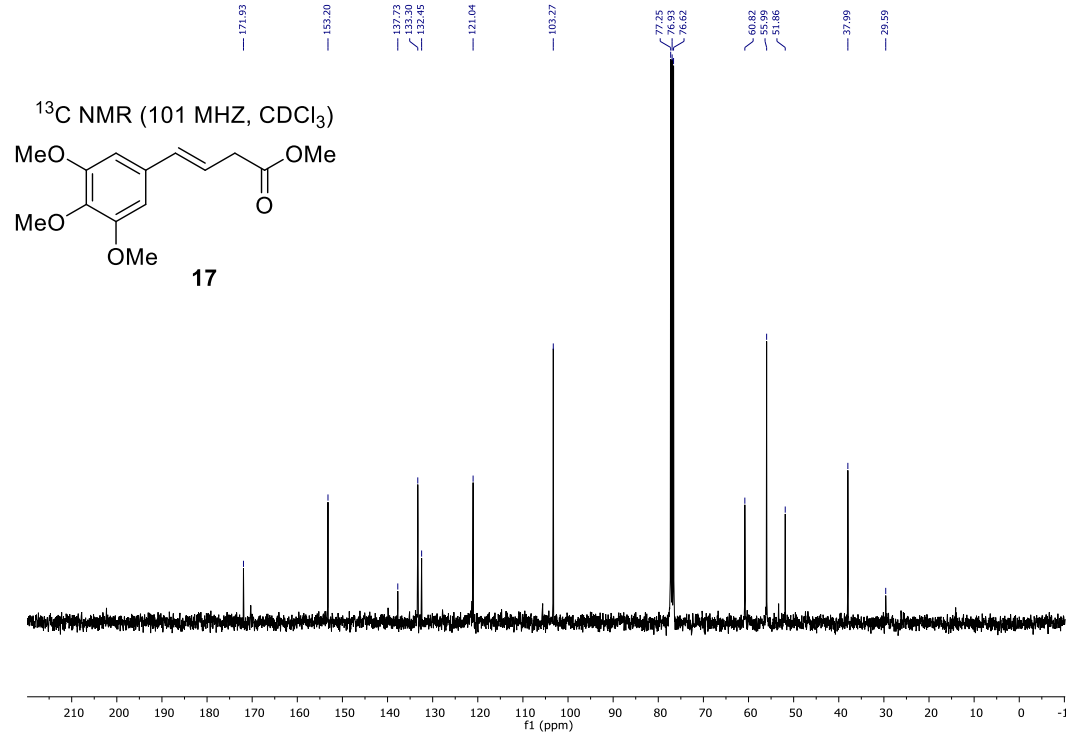
# APPENDIX: NMR SPECTRA



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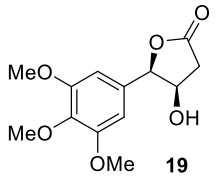
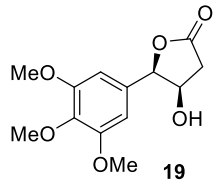



**19**




$^{13}$C NMR (101 MHZ, $CDCl_3$)

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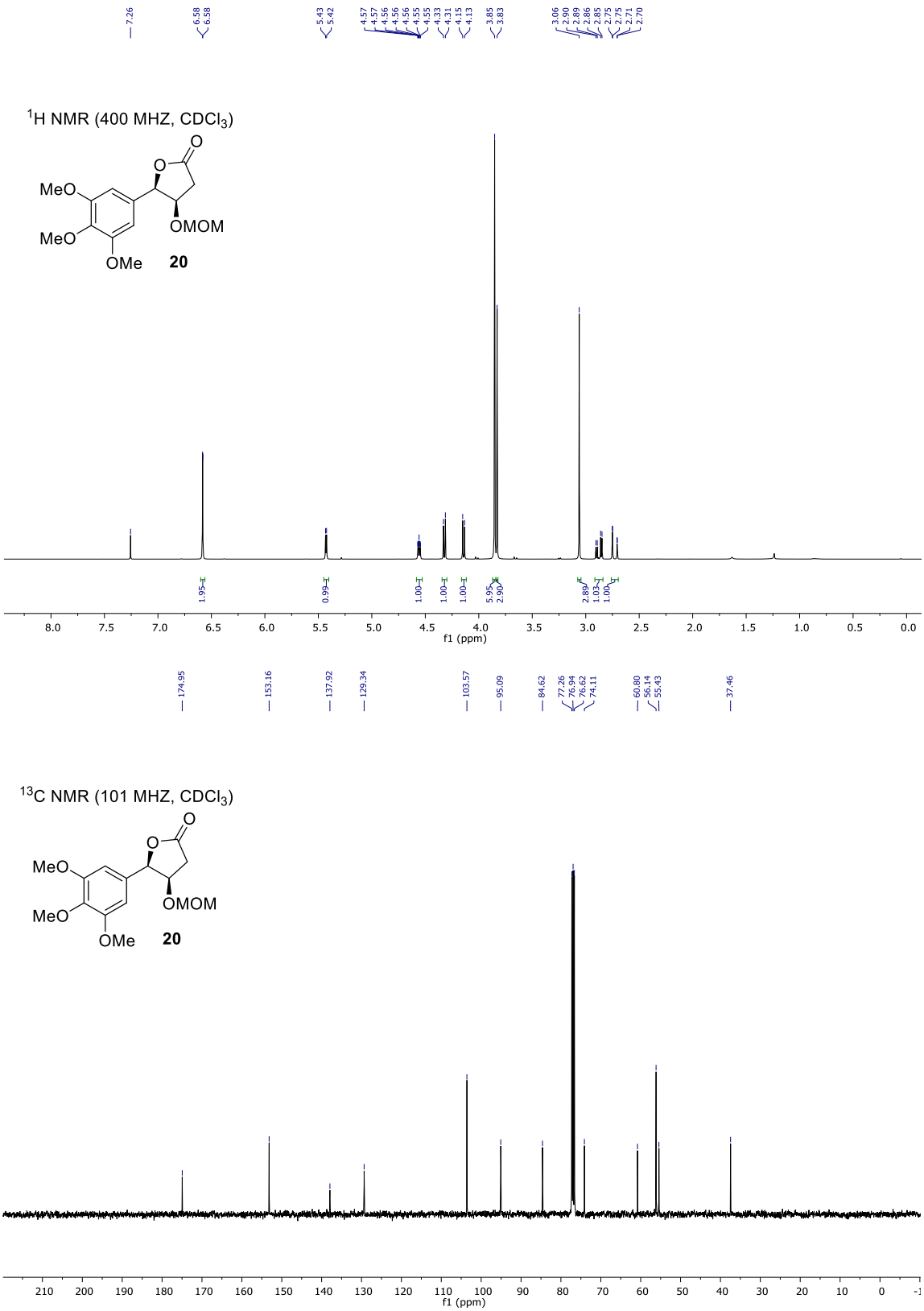
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4.56
4.56
4.56
4.55
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4.33
4.31
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2.75
2.71
2.70
1H NMR (400 MHZ, CDCl3)
MeO
MeO
OMe
O
O
OMOM
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0.99
1.00
1.00
1.00
5.95
2.90
2.89
1.03
1.00
8.0
7.5
7.0
6.5
6.0
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5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
174.95
153.16
137.92
129.34
103.57
95.09
84.62
77.26
76.94
76.62
74.11
60.80
56.14
55.43
37.46
13C NMR (101 MHZ, CDCl3)
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OMe
O
O
OMOM
20
210
200
190
180
170
160
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130
120
110
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90
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50
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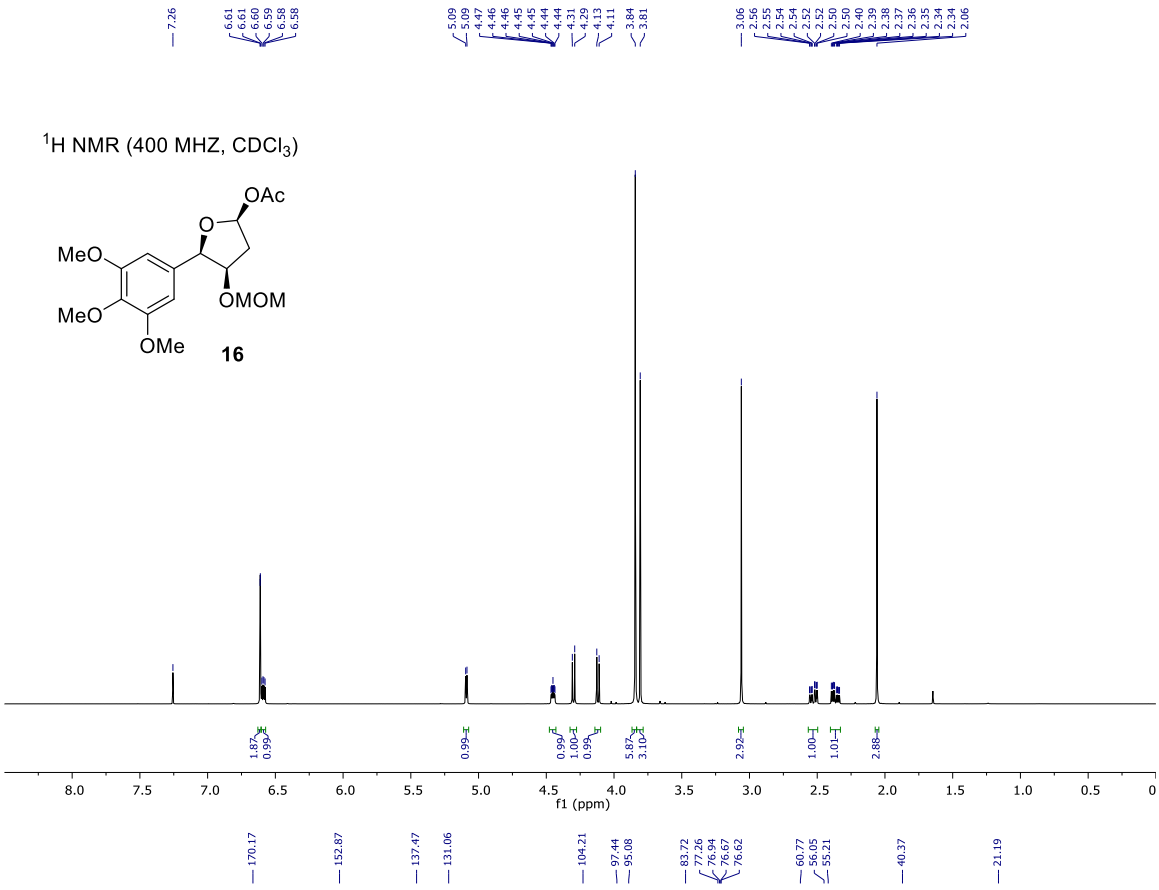
f1 (ppm)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4.31
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2.34
2.34
2.06
1H NMR (400 MHZ, CDCl3)
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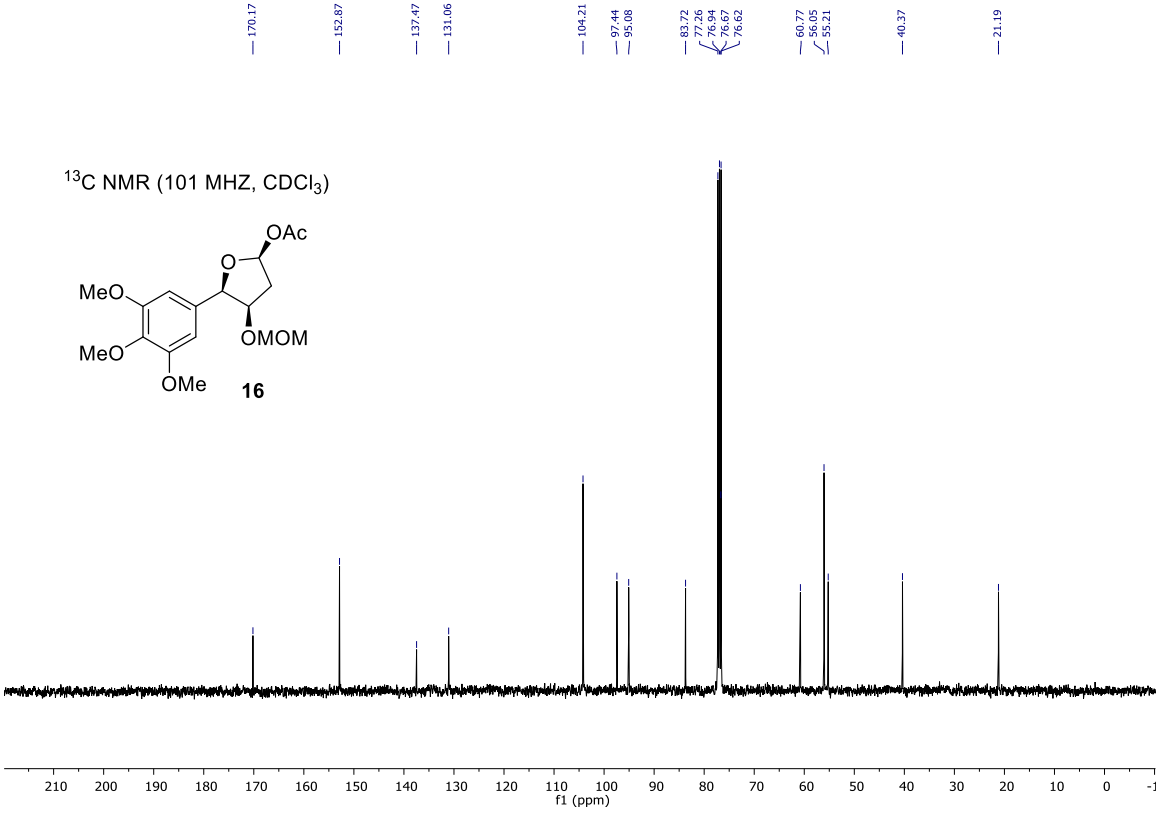
MeO
OMOM
MeO
OMe
16
1.87
0.99
0.99
0.99
1.00
0.99
5.87
3.10
2.92
1.00
1.01
2.88
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)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104.21
97.44
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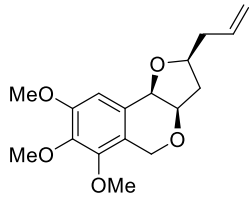
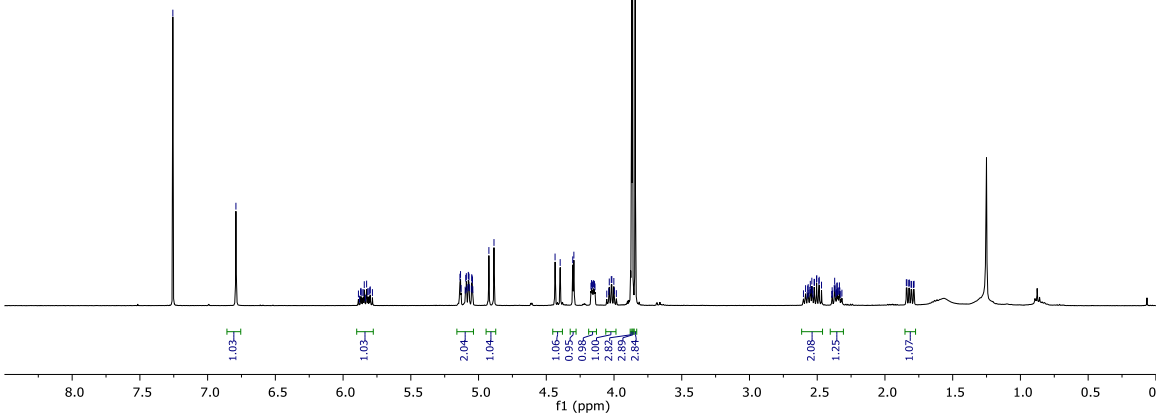
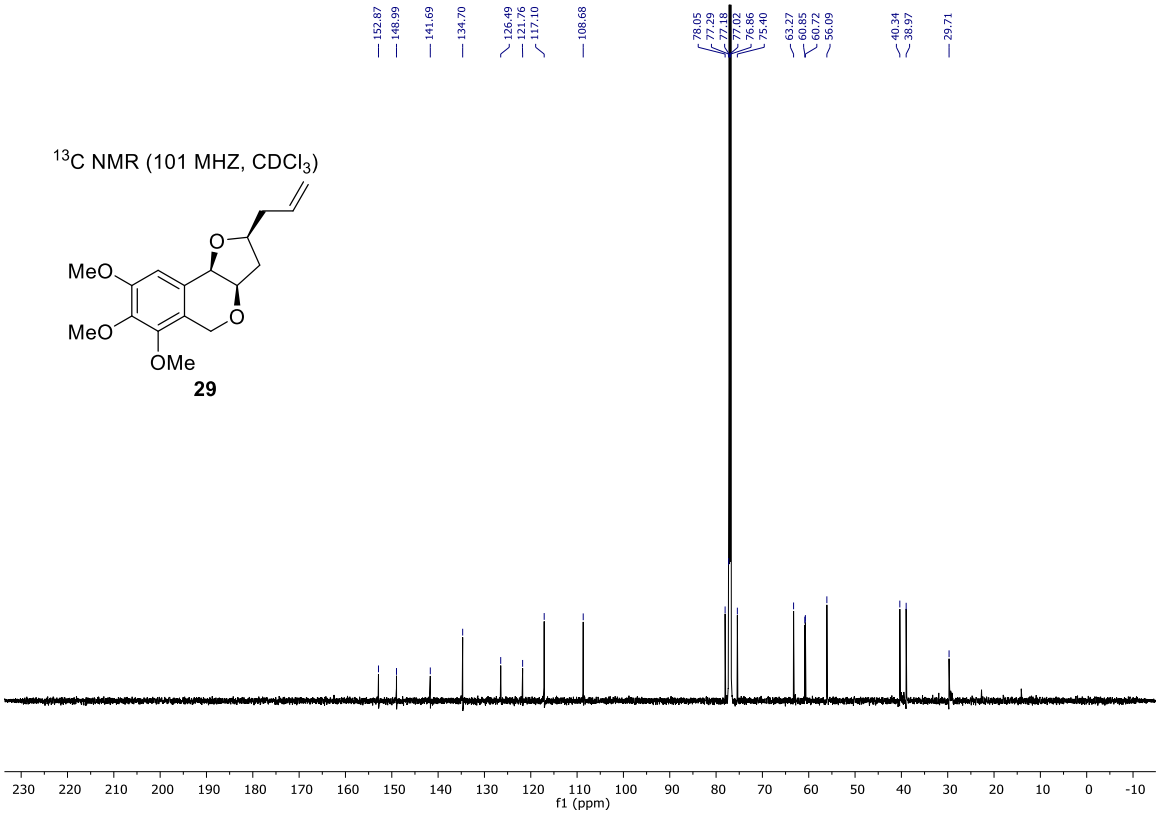
83.72
77.26
76.94
76.67
76.62
60.77
56.05
55.21
40.37
21.19
13C NMR (101 MHZ, CDCl3)
OAc
O
MeO
OMOM
MeO
OMe
16
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

$^{1}$H NMR (400 MHZ, $CDCl_3$)




**29**



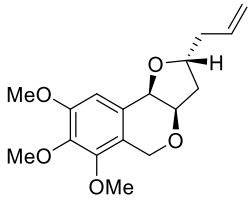




$^{13}$C NMR (101 MHZ, $CDCl_3$)

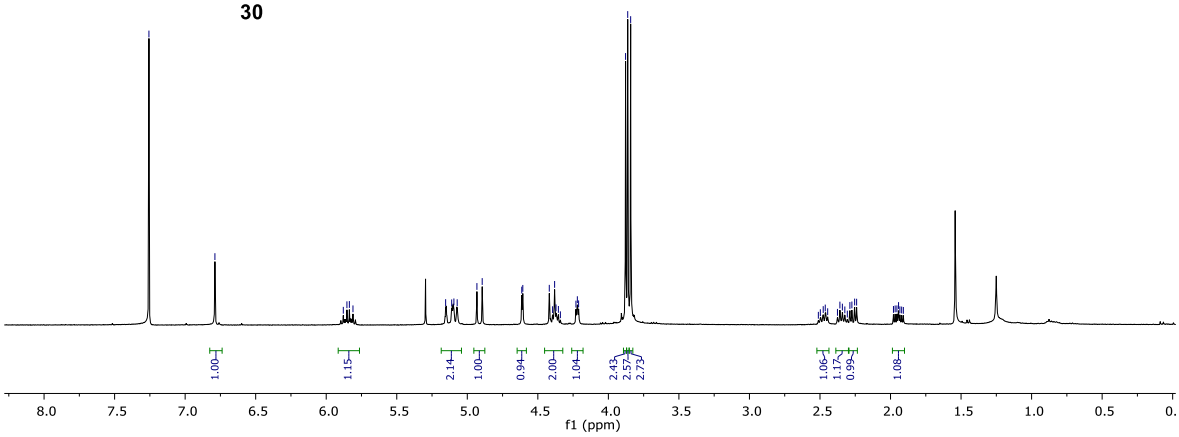


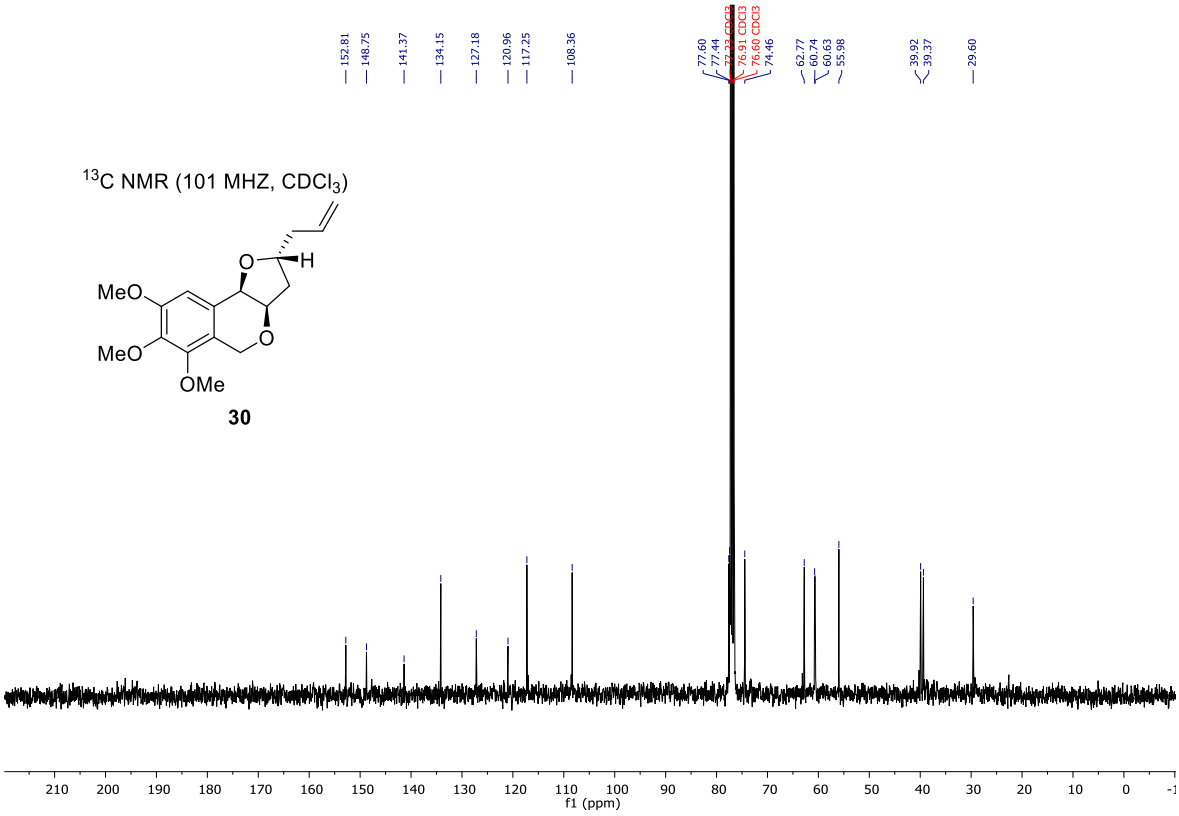

**29**


$^{1}$H NMR (400 MHZ, $CDCl_3$)




**30**



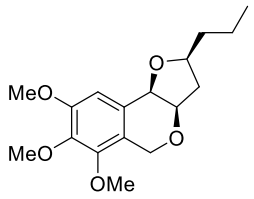




$^{13}$C NMR (101 MHZ, $CDCl_3$)

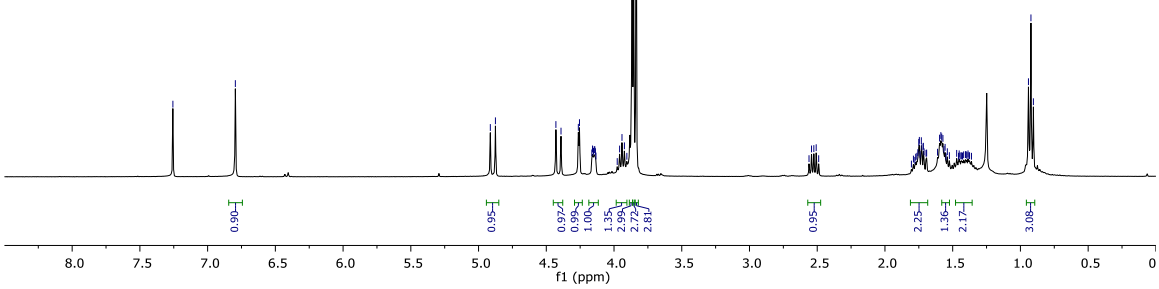


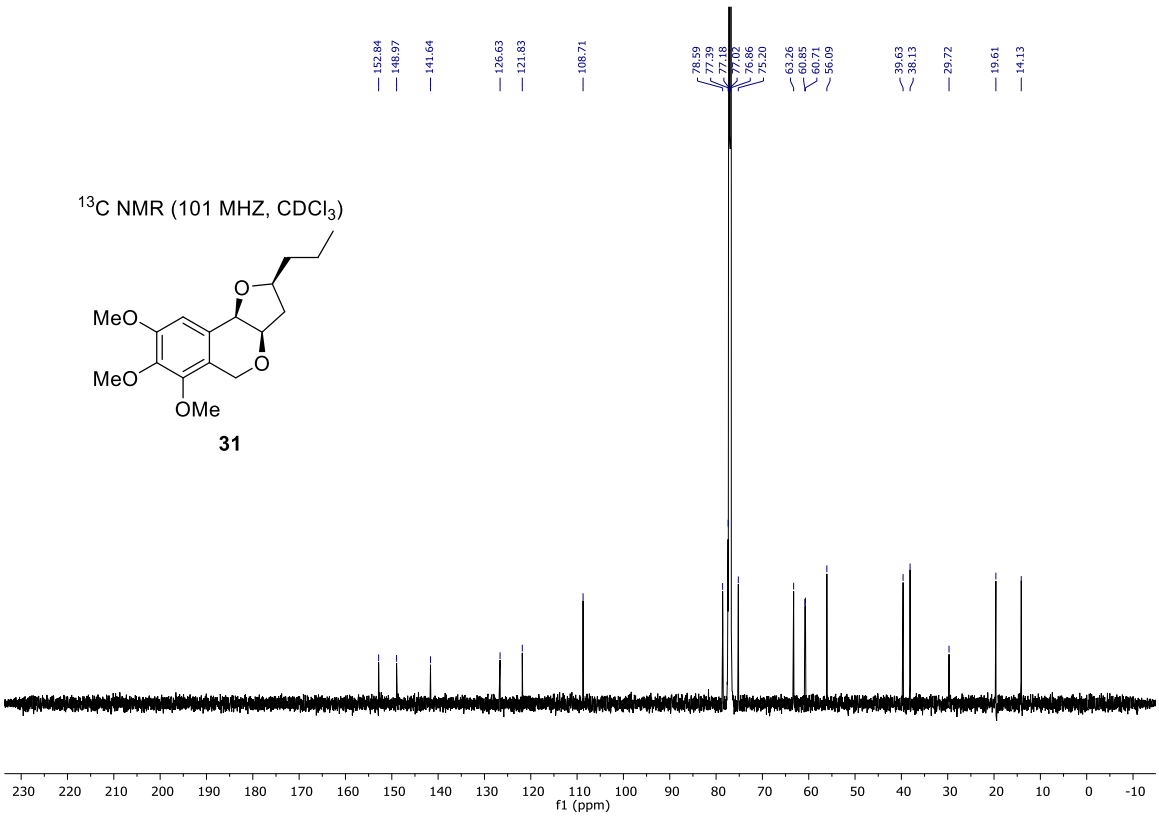

**30**

$^{1}$H NMR (400 MHZ, $CDCl_3$)




**31**

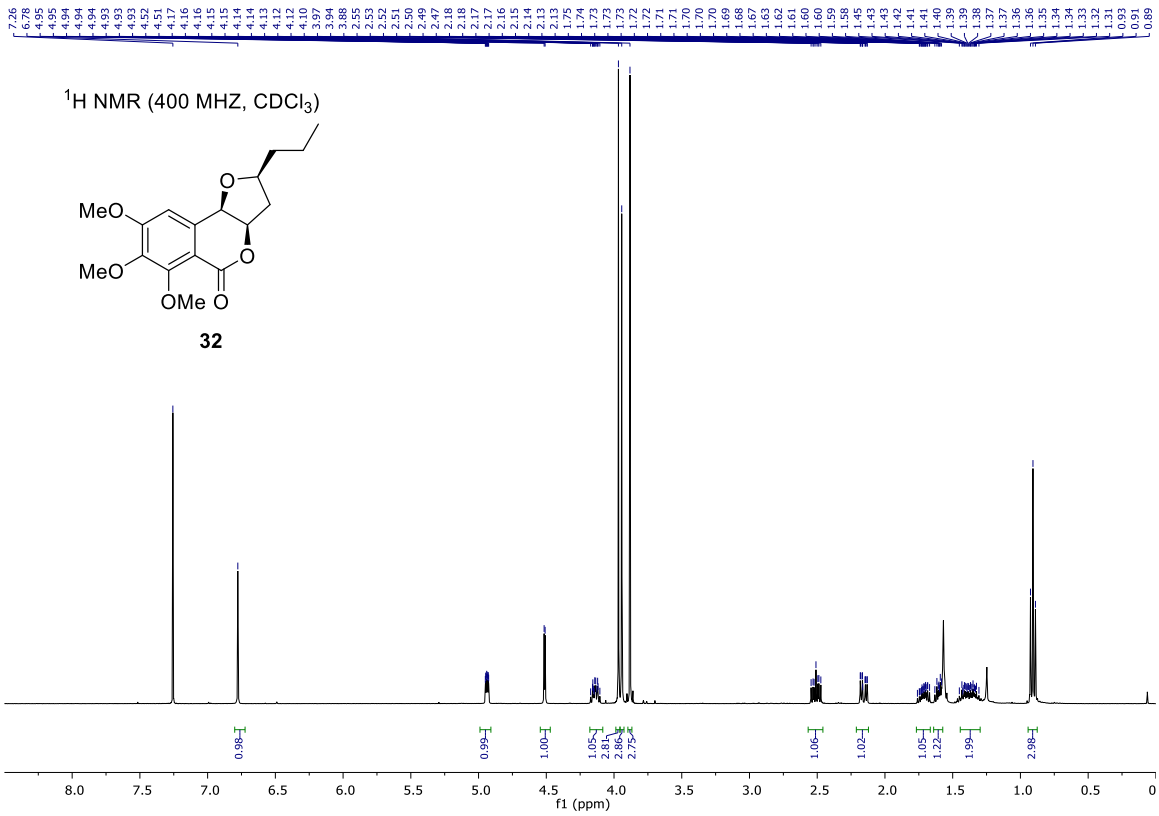


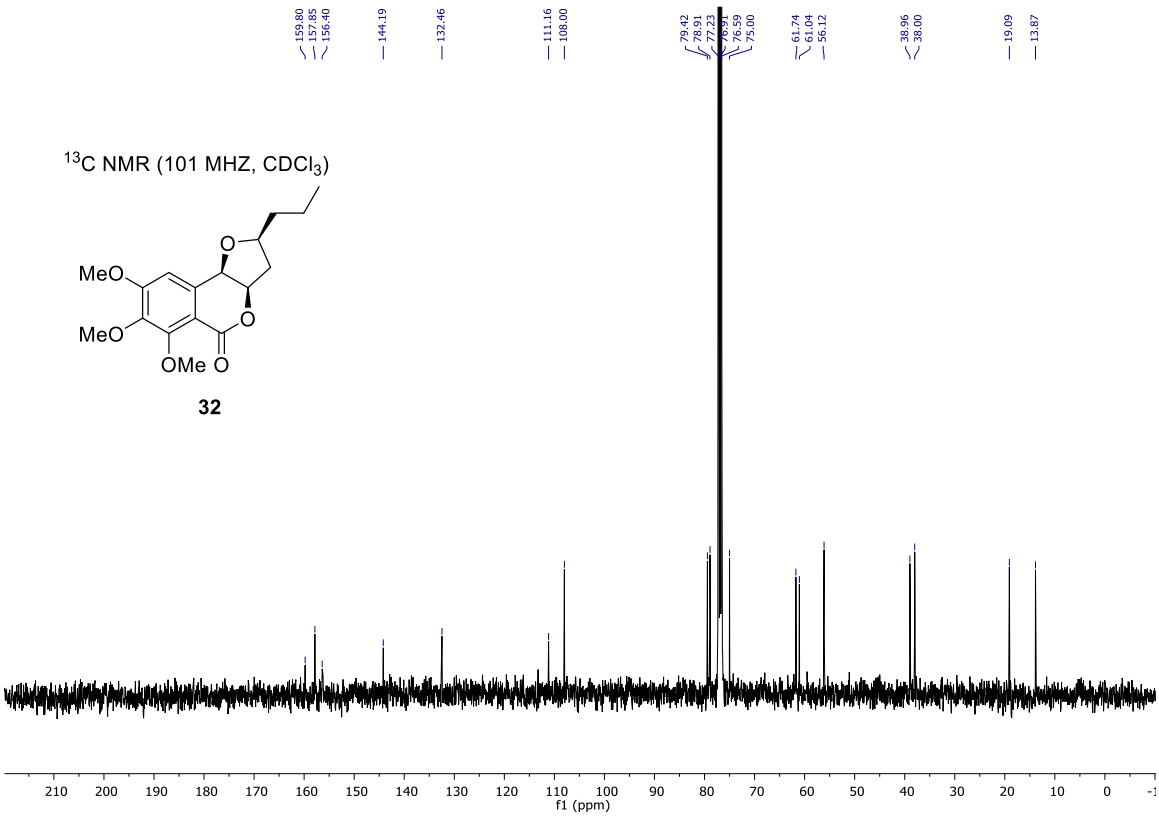




$^{13}$C NMR (101 MHZ, $CDCl_3$)

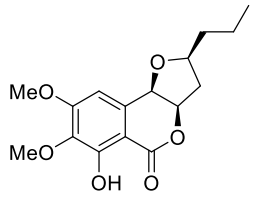



**31**

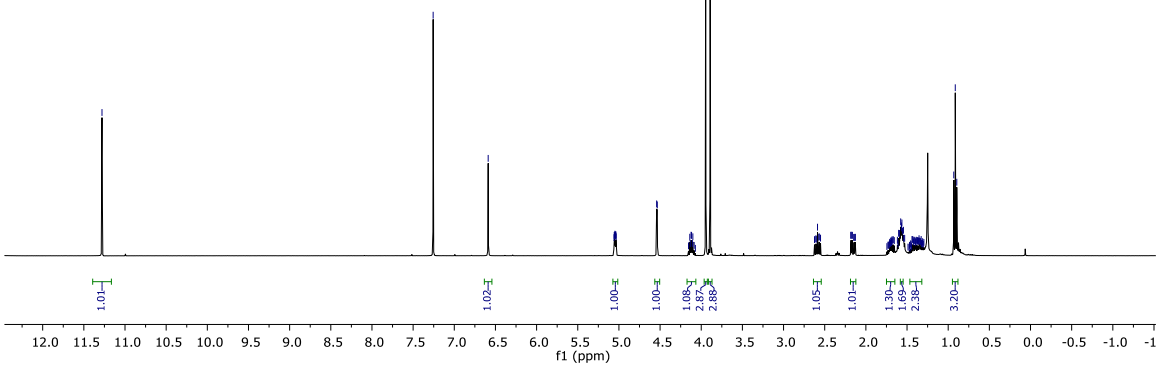

$^1$H NMR (400 MHZ, CDCl$_3$)
MeO
MeO
OMe
O
O
O
32
f1 (ppm)


$^{13}$C NMR (101 MHZ, CDCl$_3$)
MeO
MeO
OMe
O
O
O
32
f1 (ppm)

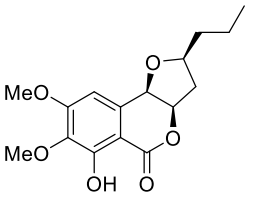
$^{1}$H NMR (400 MHZ, $CDCl_3$)



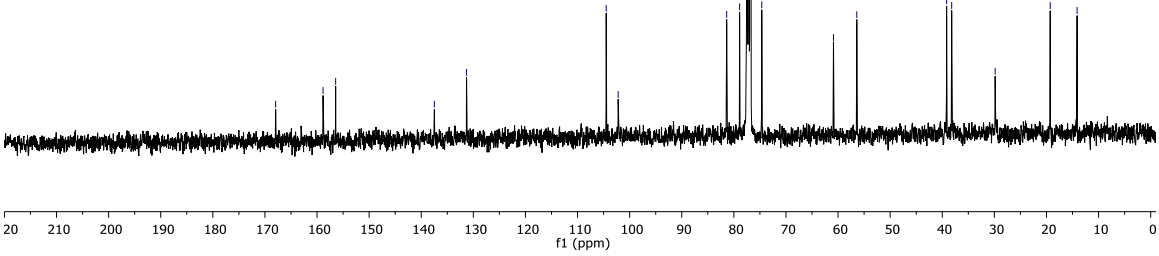

**(+)-Monocerin (1)**

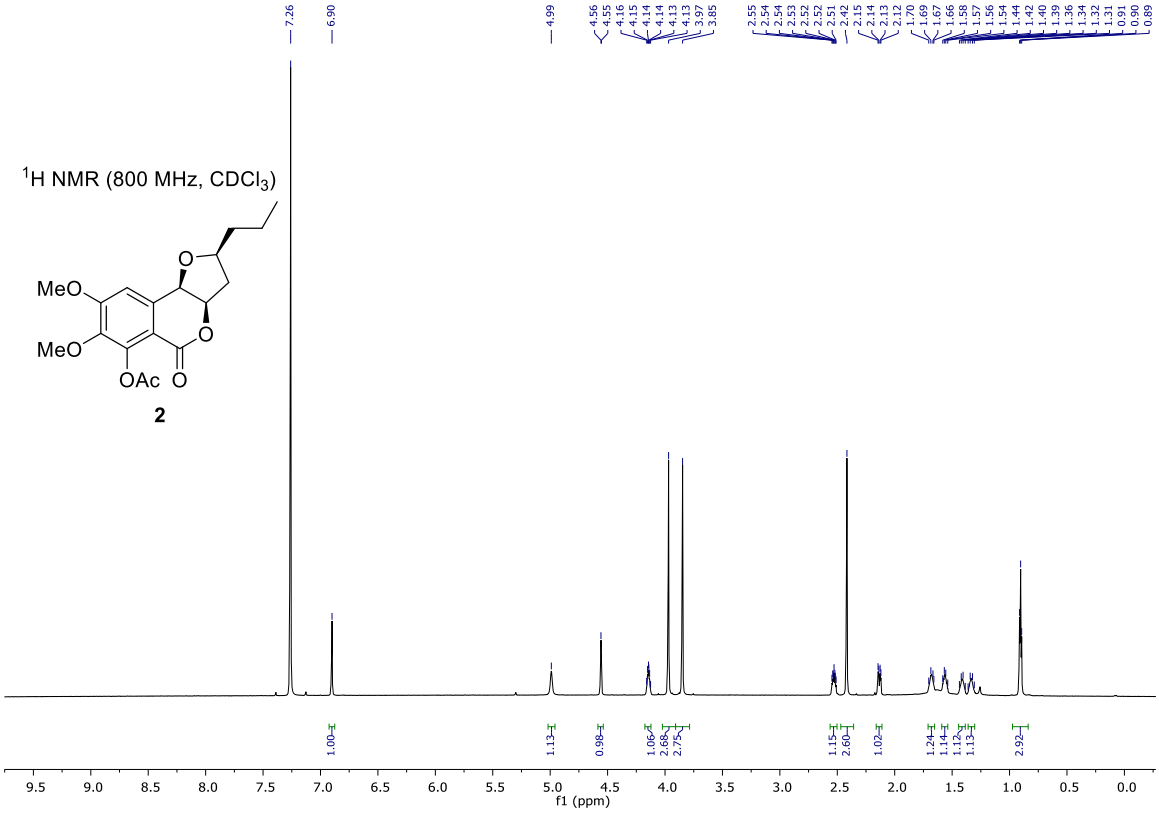


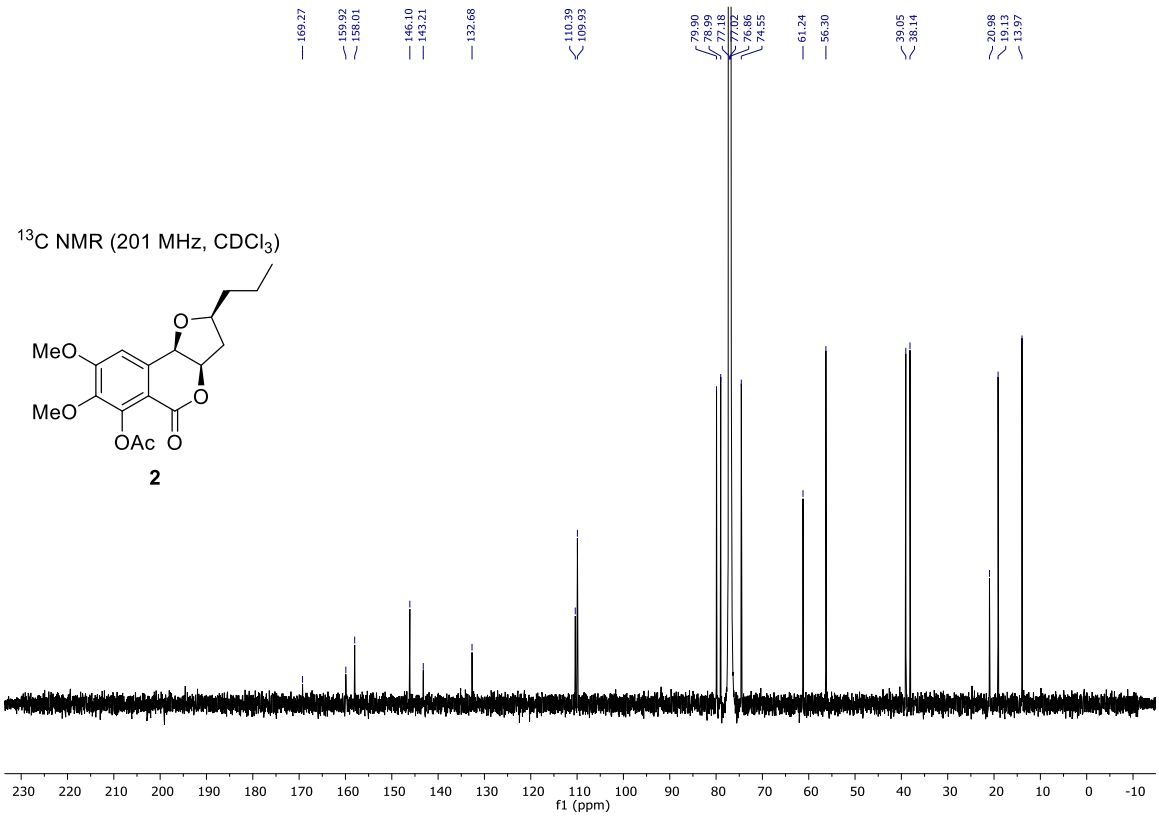

$^{13}$C NMR (100 MHZ, $CDCl_3$)

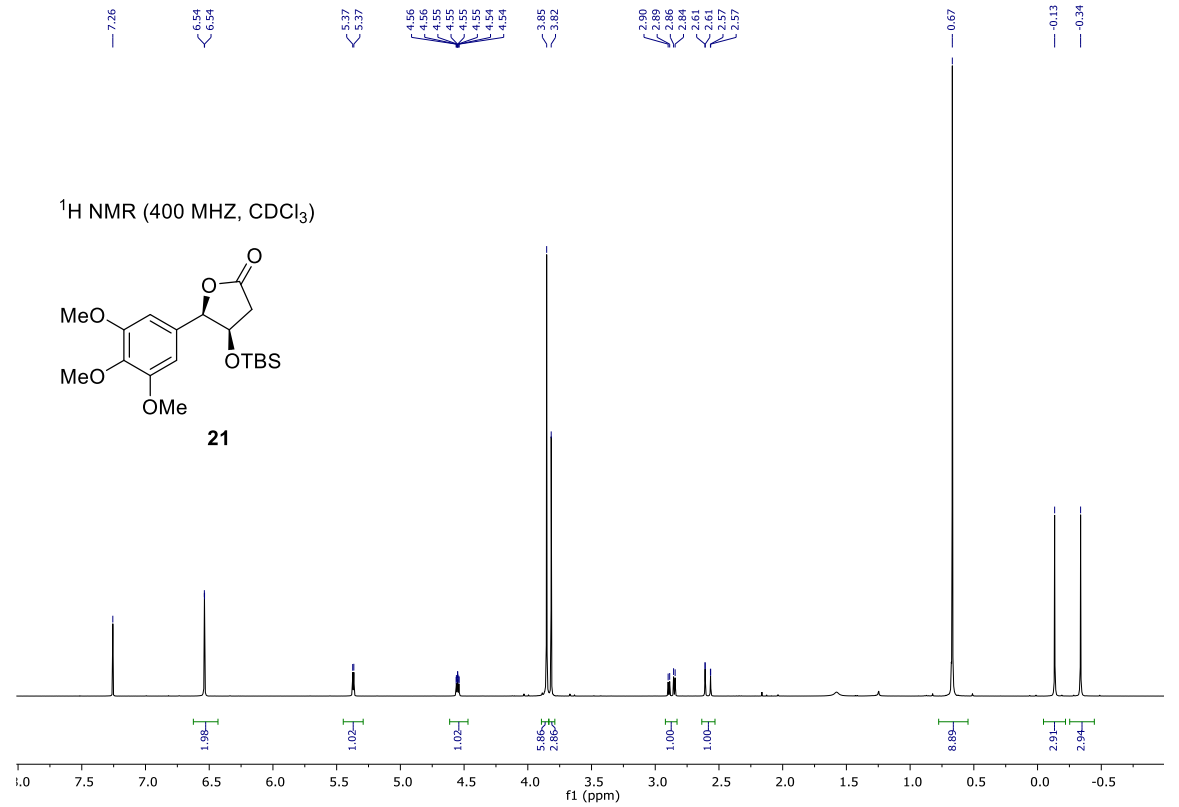



**(+)-Monocerin (1)**




$^1$H NMR (800 MHz, $CDCl_3$)
MeO
MeO
OAc O
O
O
O
2
7.26
6.90
4.99
4.56
4.55
4.16
4.15
4.14
4.14
4.14
4.13
4.13
3.97
3.85
2.55
2.54
2.54
2.53
2.52
2.52
2.51
2.42
2.15
2.14
2.13
2.12
1.70
1.69
1.67
1.66
1.58
1.57
1.56
1.54
1.44
1.42
1.40
1.39
1.36
1.34
1.32
1.31
1.01
0.90
0.89
1.00
1.13
0.98
1.06
2.68
2.75
1.15
2.60
1.02
1.24
1.14
1.12
1.13
2.92
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

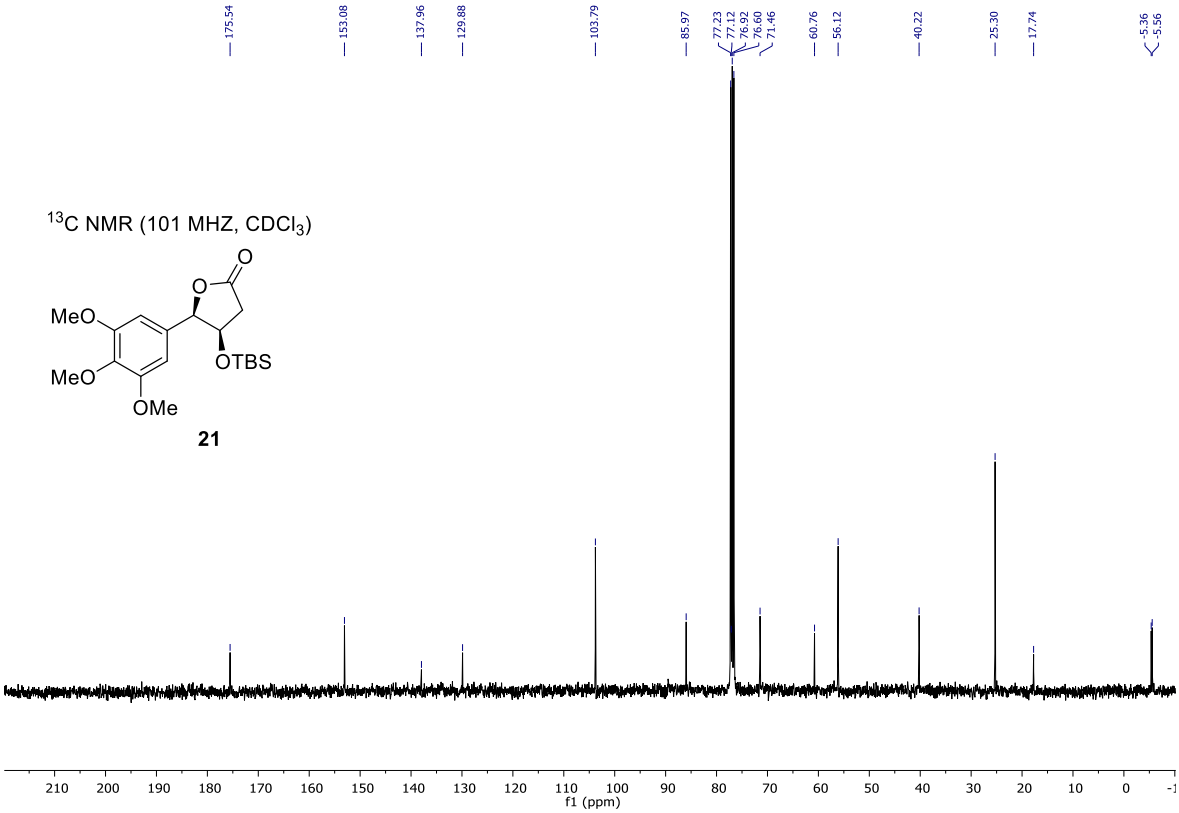

$^{13}$C NMR (201 MHz, $CDCl_3$)
MeO
MeO
OAc O
O
O
O
2
169.27
159.92
158.01
146.10
143.21
132.68
110.39
109.93
79.90
78.99
77.18
77.02
76.86
74.55
61.24
56.30
39.05
38.14
20.98
19.13
13.97
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)




$^{1}$H NMR (400 MHZ, $CDCl_3$)



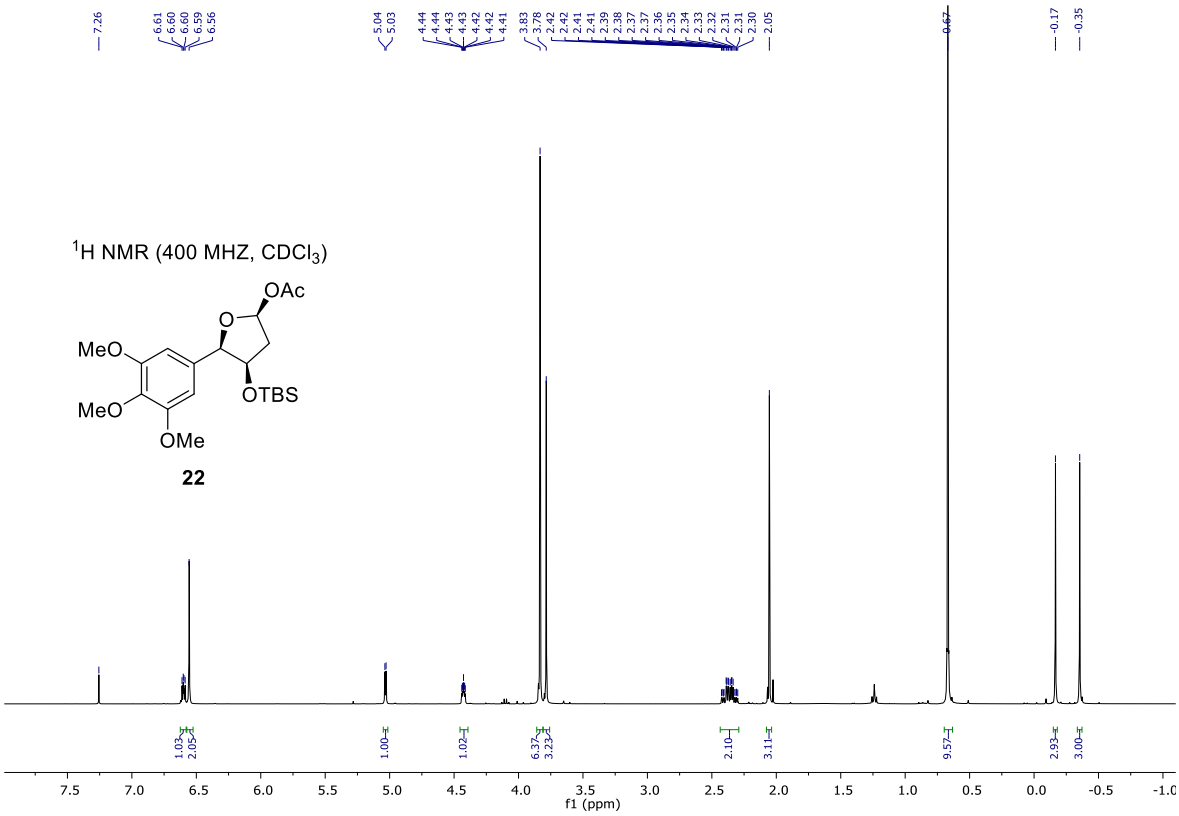

**21**

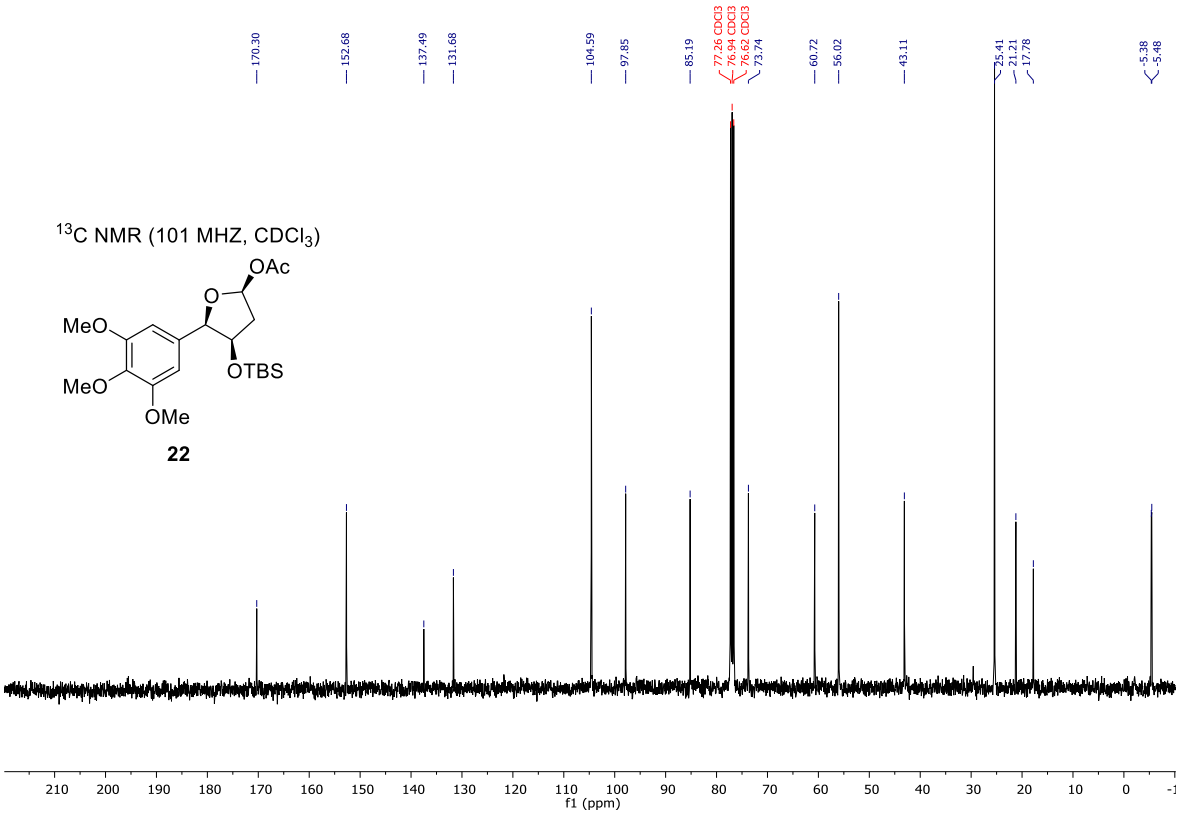


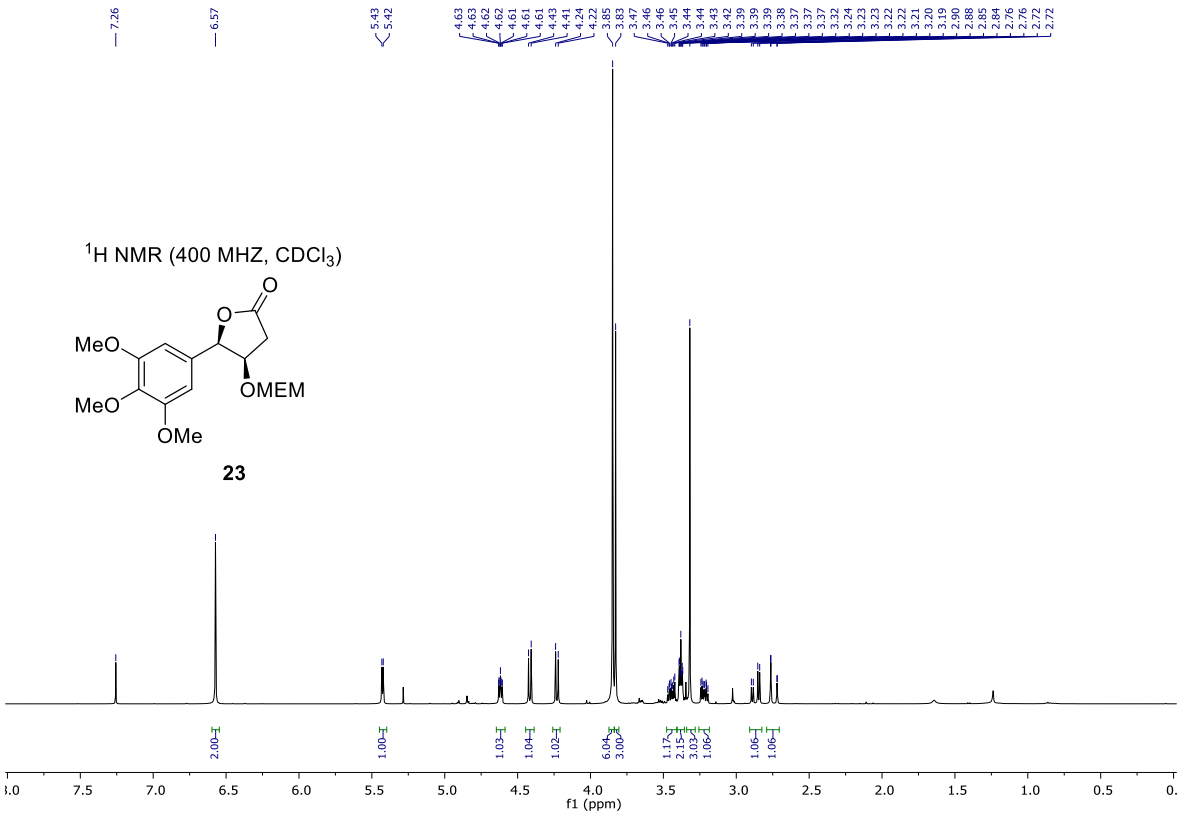

$^{13}$C NMR (101 MHZ, $CDCl_3$)

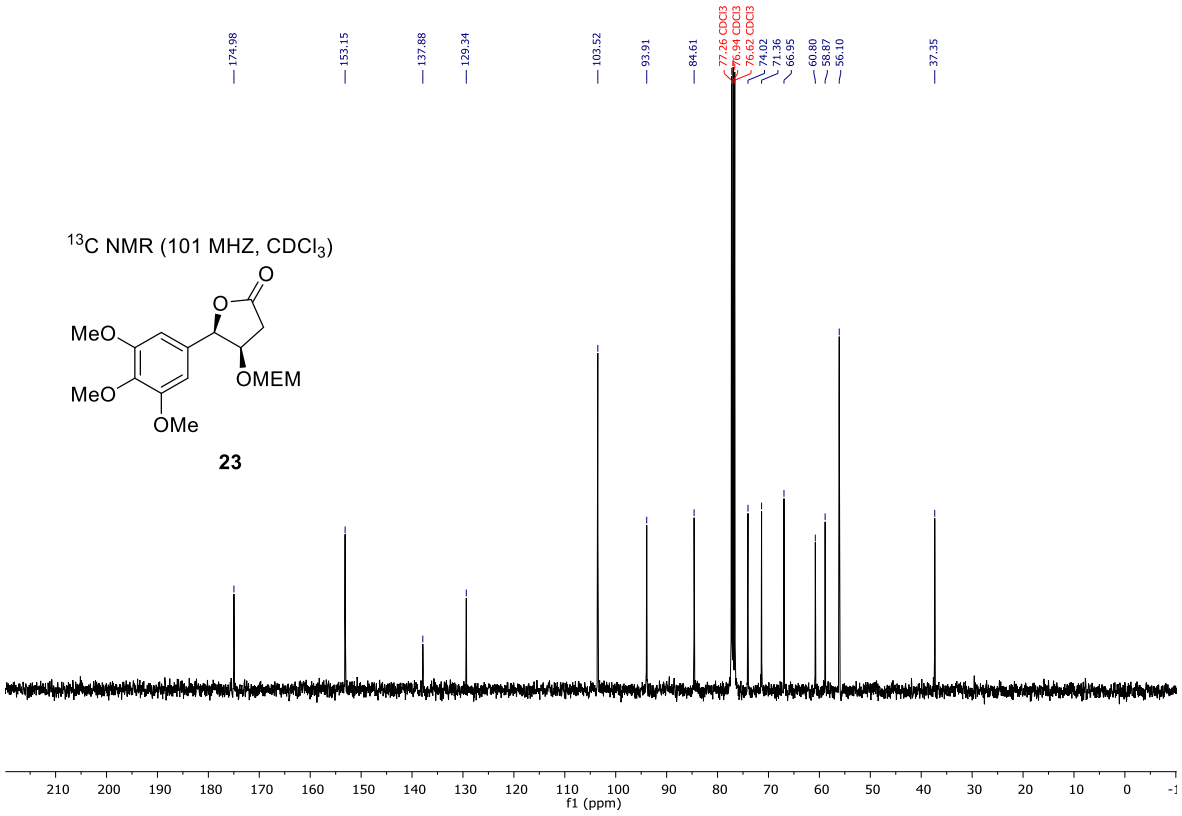



**21**

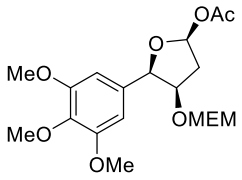

$^1$H NMR (400 MHZ, $CDCl_3$)
OAc
O
MeO
MeO
OTBS
OMe
22
f1 (ppm)


$^{13}$C NMR (101 MHZ, $CDCl_3$)
OAc
O
MeO
MeO
OTBS
OMe
22
f1 (ppm)

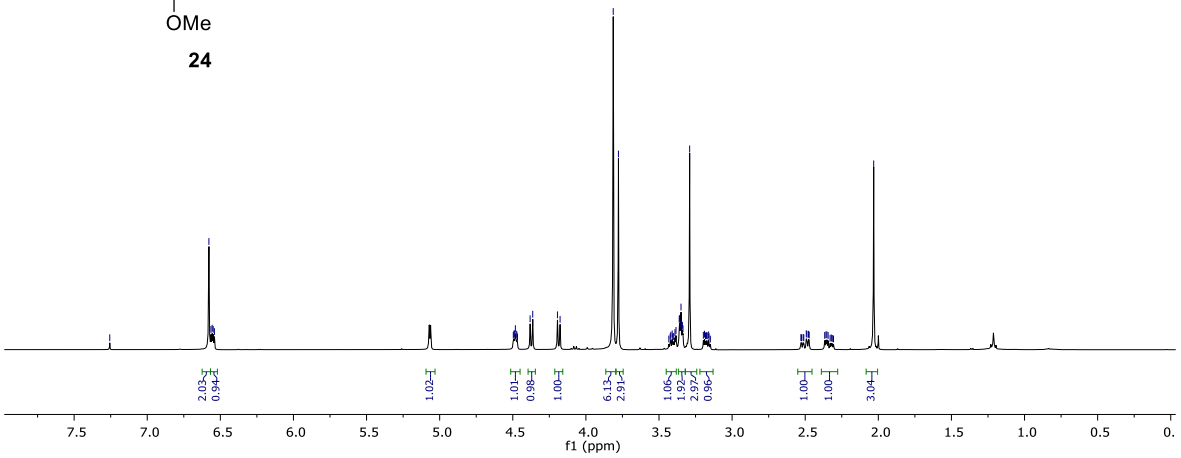

$^1$H NMR (400 MHZ, $CDCl_3$)
MeO
MeO
OMe
O
O
OMEM
23
f1 (ppm)


$^{13}$C NMR (101 MHZ, $CDCl_3$)
MeO
MeO
OMe
O
O
OMEM
23
f1 (ppm)

$^{1}$H NMR (400 MHZ, $CDCl_3$)

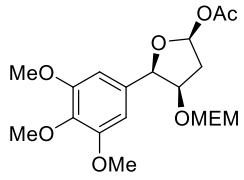



**24**

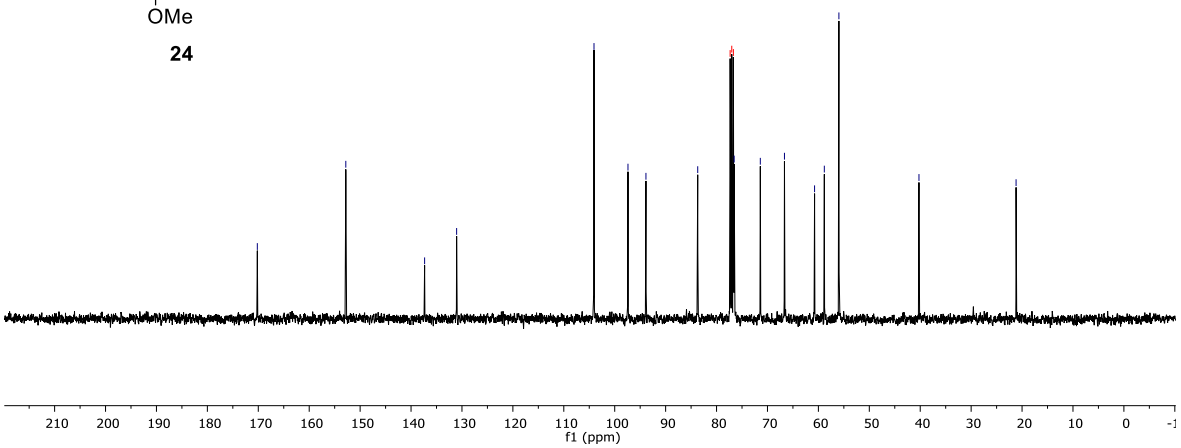


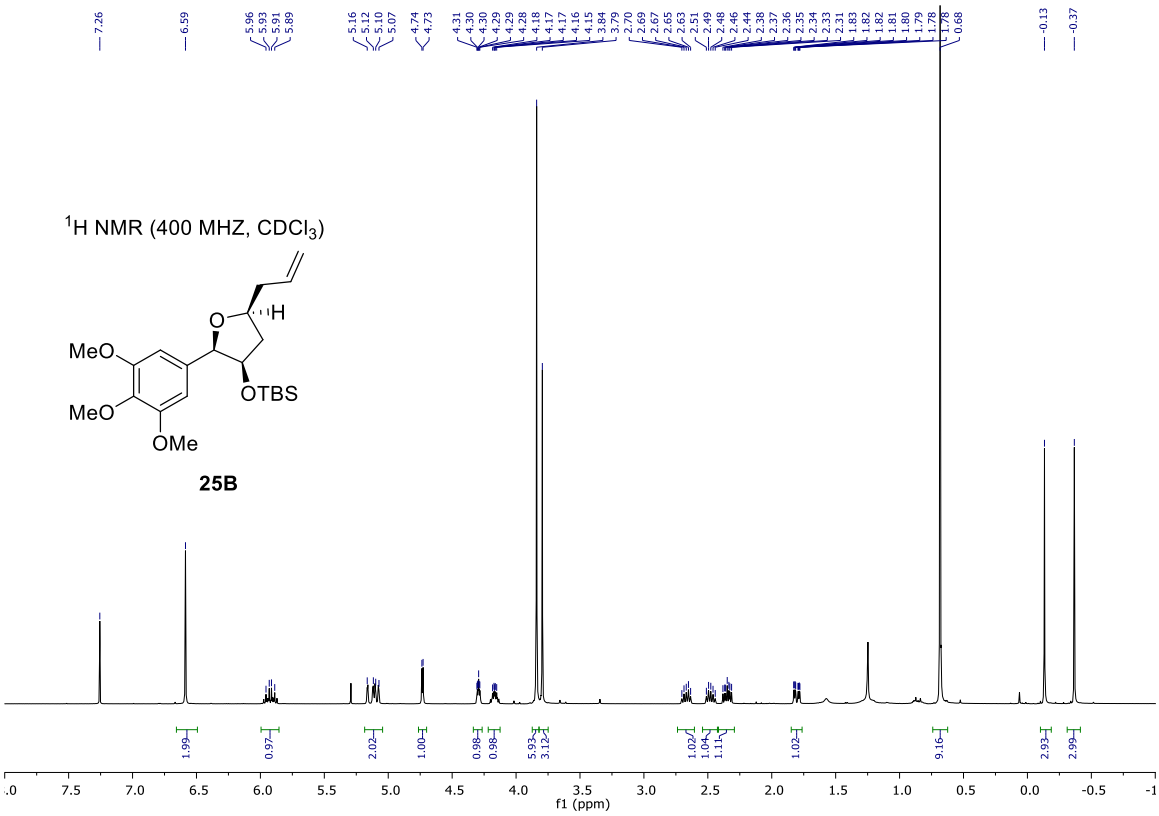


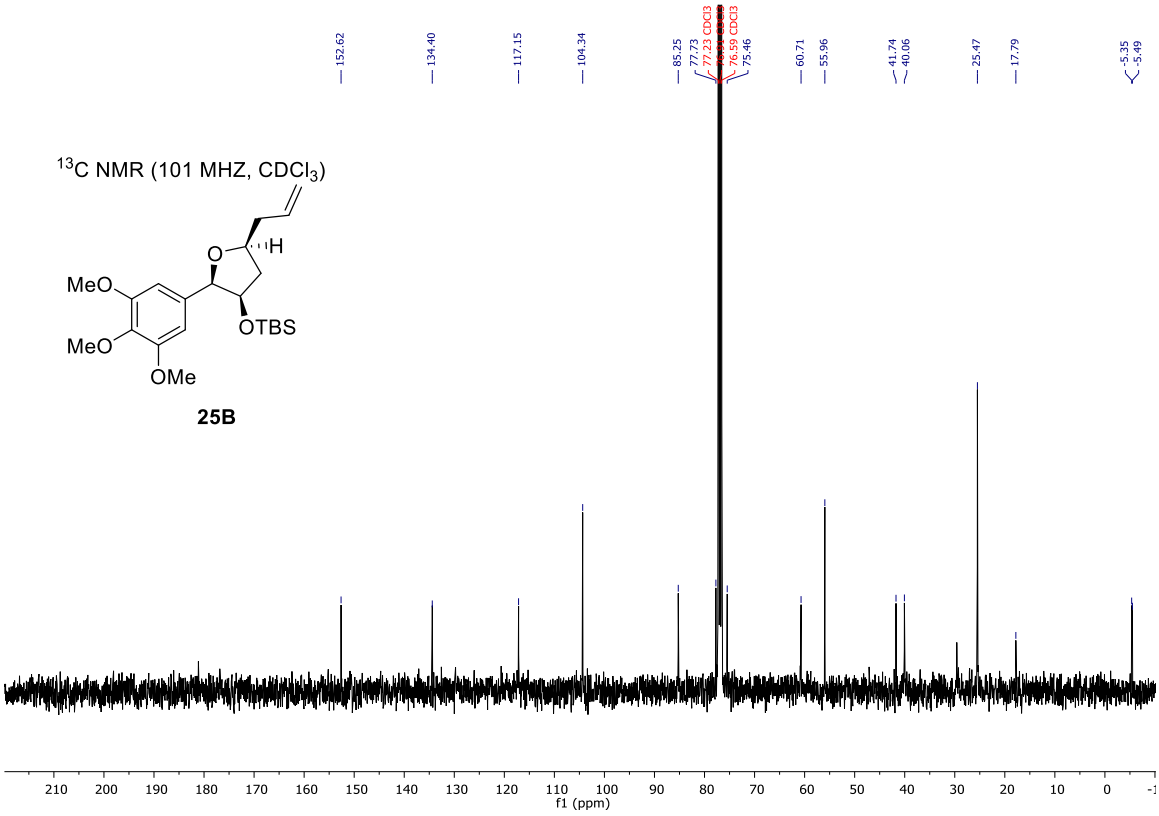
$^{13}$C NMR (101 MHZ, $CDCl_3$)

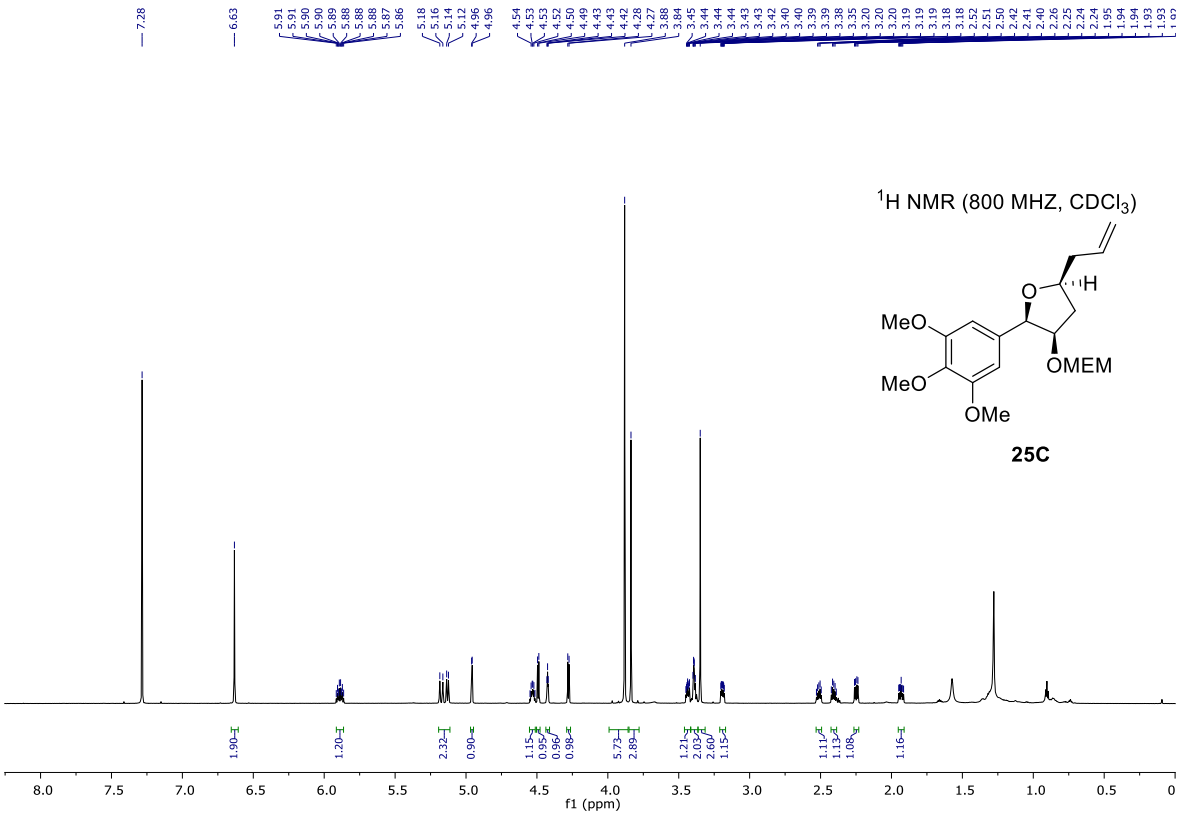


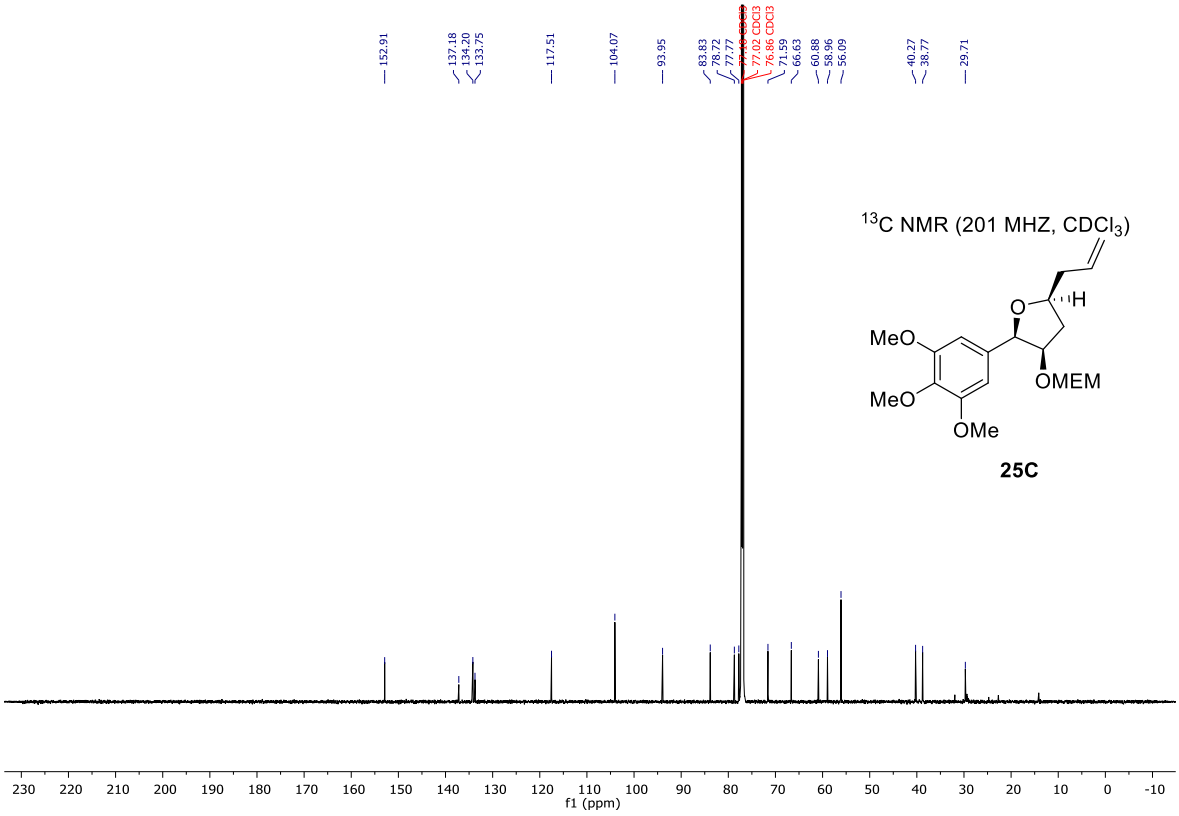

**24**

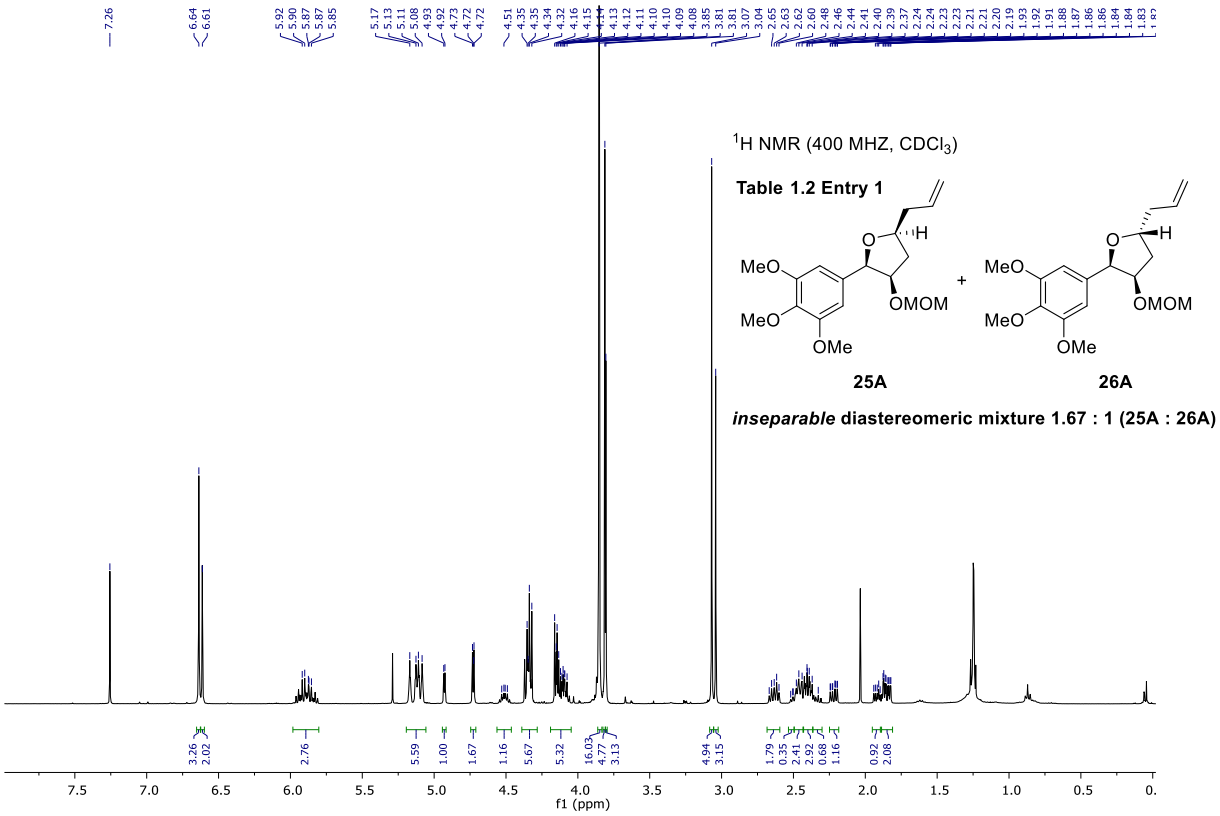


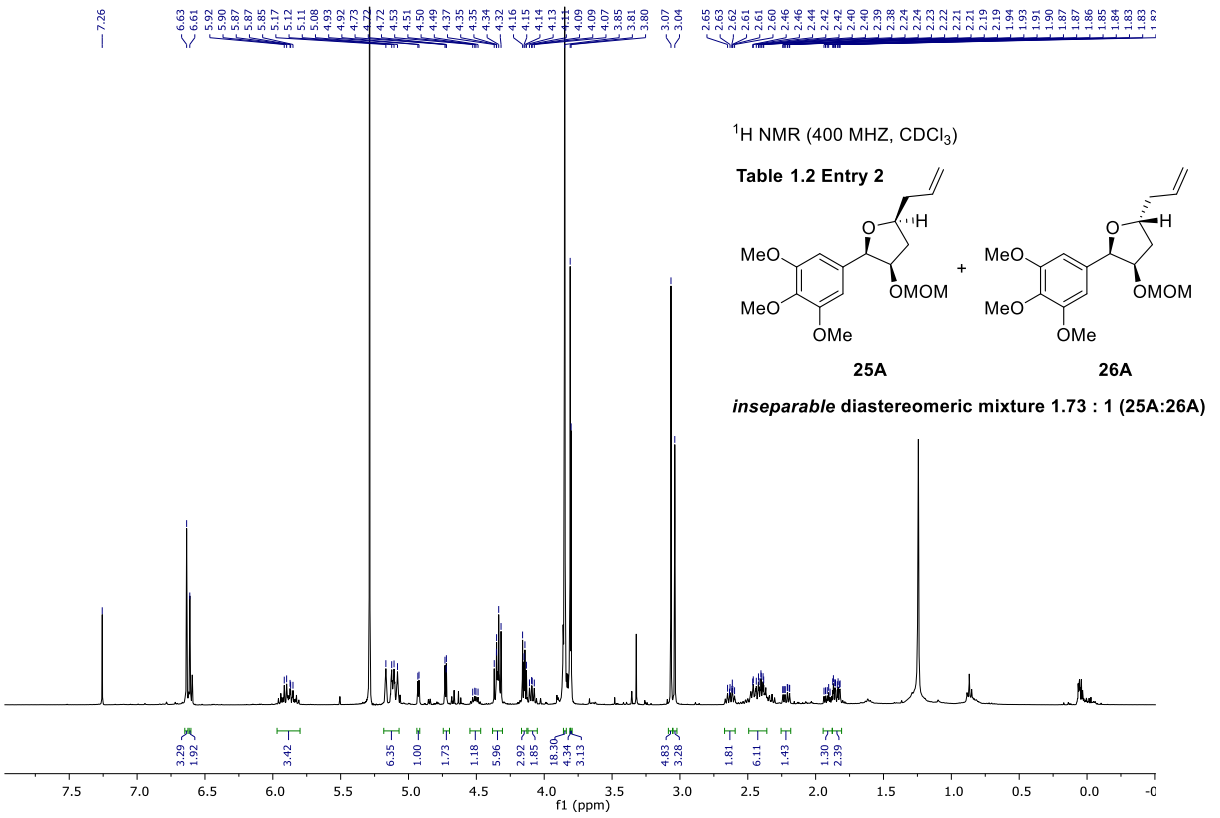

$^1$H NMR (400 MHZ, $CDCl_3$)
MeO
MeO
OMe
O
H
OTBS
25B
f1 (ppm)

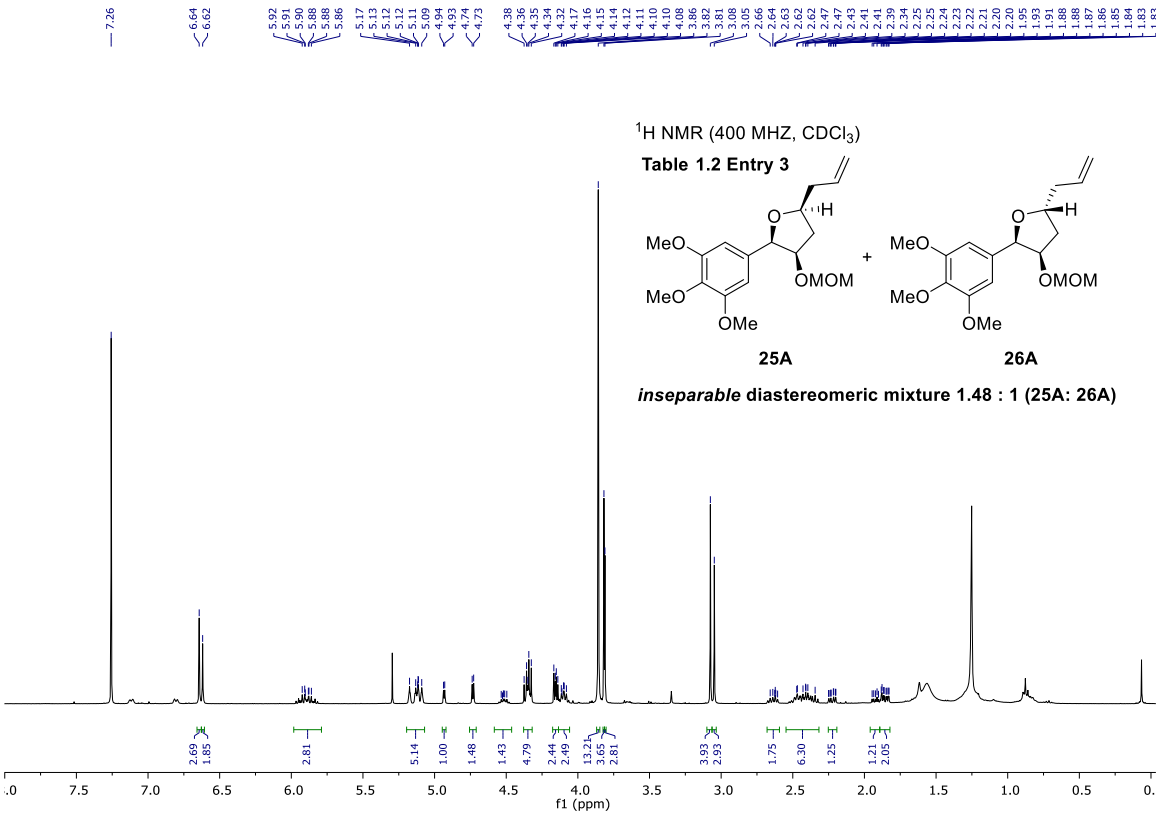

$^{13}$C NMR (101 MHZ, $CDCl_3$)
MeO
MeO
OMe
O
H
OTBS
25B
f1 (ppm)

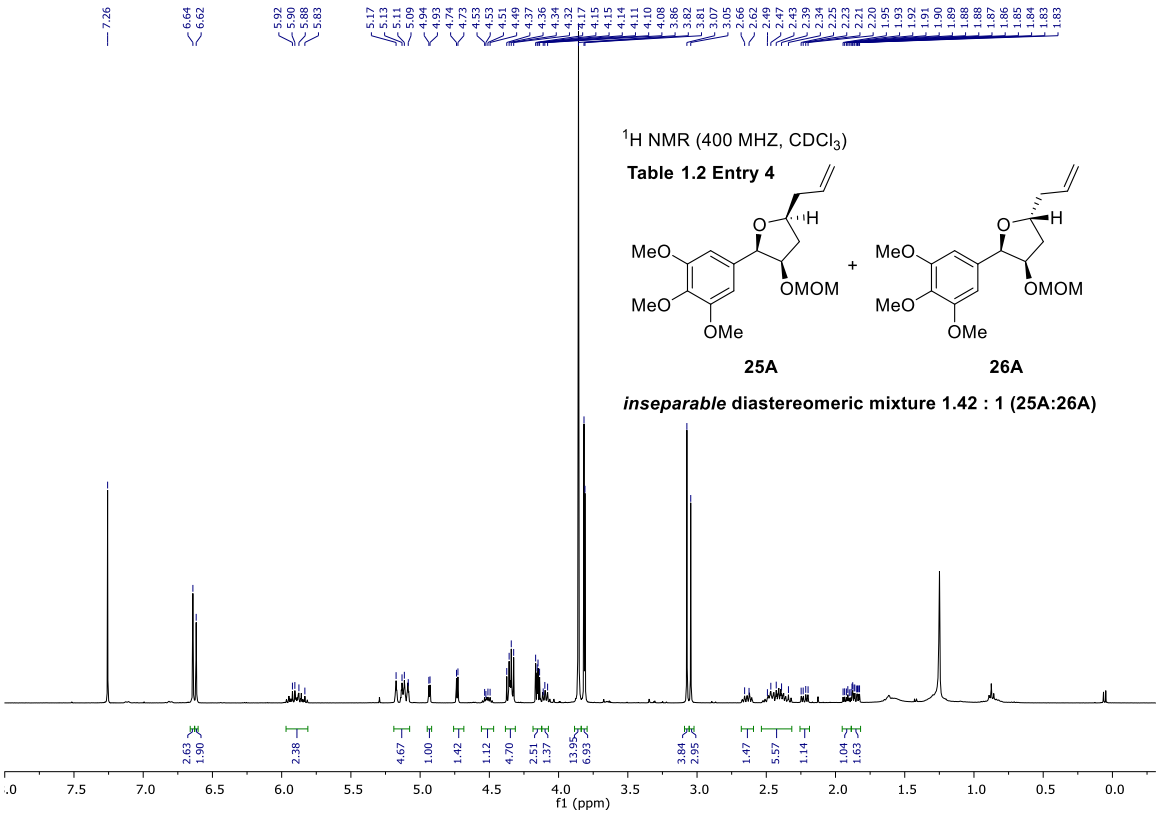

7.28
6.63
$^1$H NMR (800 MHZ, CDCl$_3$)
MeO
MeO
OMe
OMEM
O
H
25C
f1 (ppm)

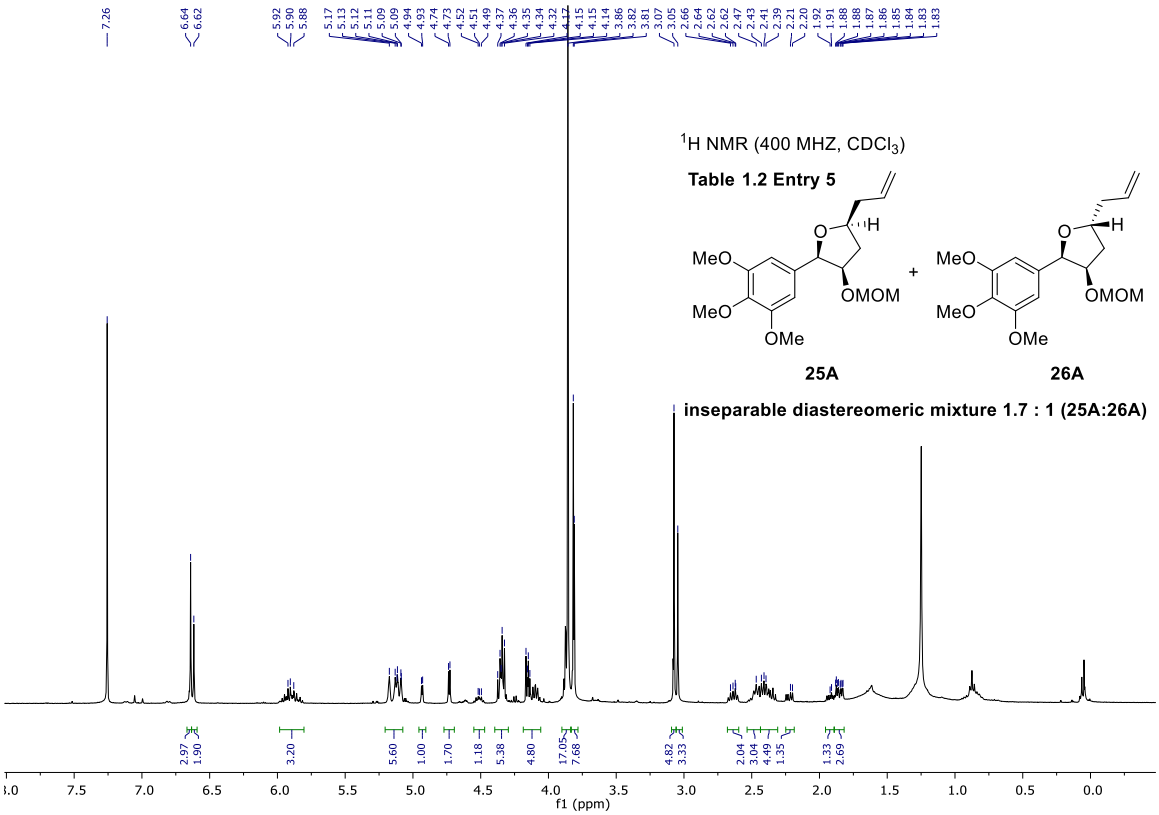

152.91
137.18
134.20
133.75
117.51
104.07
93.95
83.83
78.72
77.77
77.02 CDCl3
76.86 CDCl3
71.59
66.63
60.88
58.96
56.09
40.27
38.77
29.71
$^{13}$C NMR (201 MHZ, CDCl$_3$)
MeO
MeO
OMe
OMEM
O
H
25C
f1 (ppm)

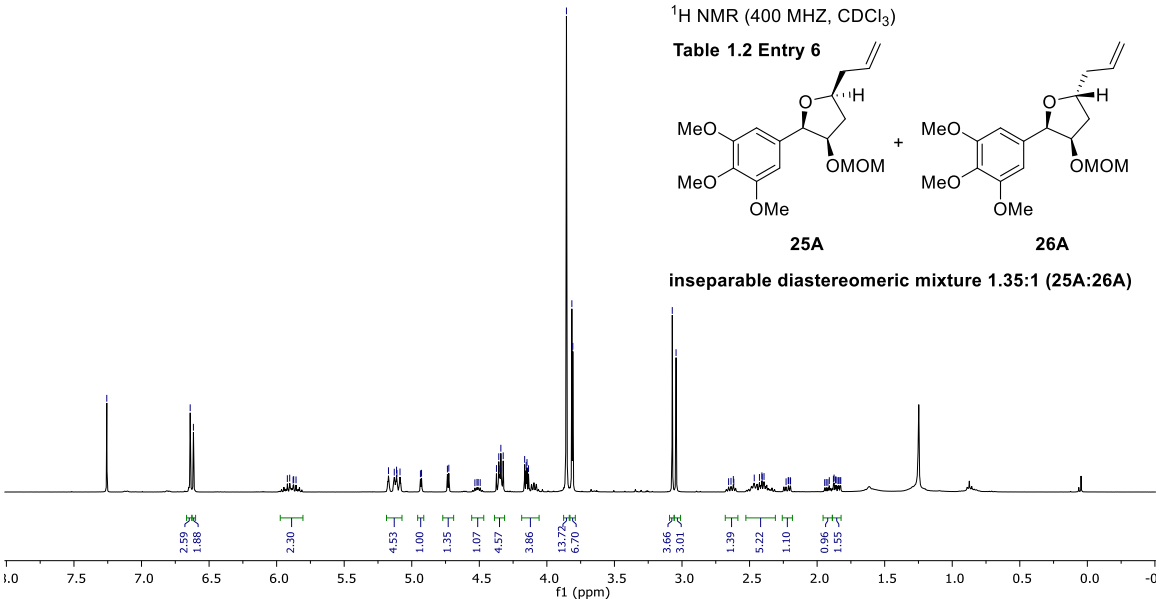

$^1$H NMR (400 MHZ, $CDCl_3$)
Table 1.2 Entry 1
MeO
MeO
OMe
OMOM
25A
26A
*inseparable* diastereomeric mixture 1.67 : 1 (25A : 26A)
f1 (ppm)


$^1$H NMR (400 MHZ, $CDCl_3$)
Table 1.2 Entry 2
MeO
MeO
OMe
OMOM
25A
26A
*inseparable* diastereomeric mixture 1.73 : 1 (25A:26A)
f1 (ppm)


$^1$H NMR (400 MHZ, $CDCl_3$)
Table 1.2 Entry 3
MeO
MeO
OMe
OMOM
25A
26A
*inseparable* diastereomeric mixture 1.48 : 1 (25A: 26A)
f1 (ppm)

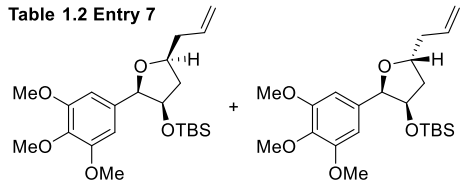

$^1$H NMR (400 MHZ, $CDCl_3$)
Table 1.2 Entry 4
MeO
MeO
OMe
OMOM
25A
26A
*inseparable* diastereomeric mixture 1.42 : 1 (25A:26A)
f1 (ppm)


$^1$H NMR (400 MHZ, $CDCl_3$)
Table 1.2 Entry 5
MeO
MeO
OMe
OMOM
H
O
+
25A
26A
inseparable diastereomeric mixture 1.7 : 1 (25A:26A)
f1 (ppm)


$^1$H NMR (400 MHZ, $CDCl_3$)
Table 1.2 Entry 6
MeO
MeO
OMe
OMOM
H
O
+
25A
26A
inseparable diastereomeric mixture 1.35:1 (25A:26A)
f1 (ppm)

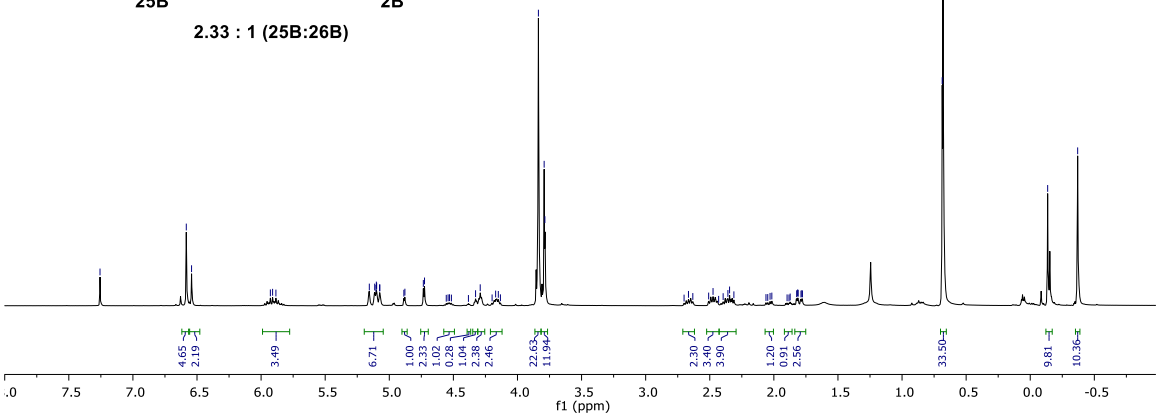
$^1$H NMR (400 MHZ, $CDCl_3$)

**Table 1.2 Entry 7**



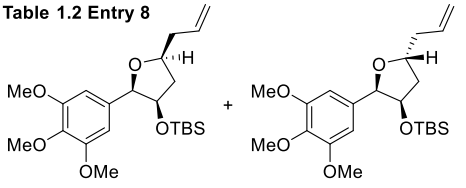

**25B** **2B**

**2.33 : 1 (25B:26B)**



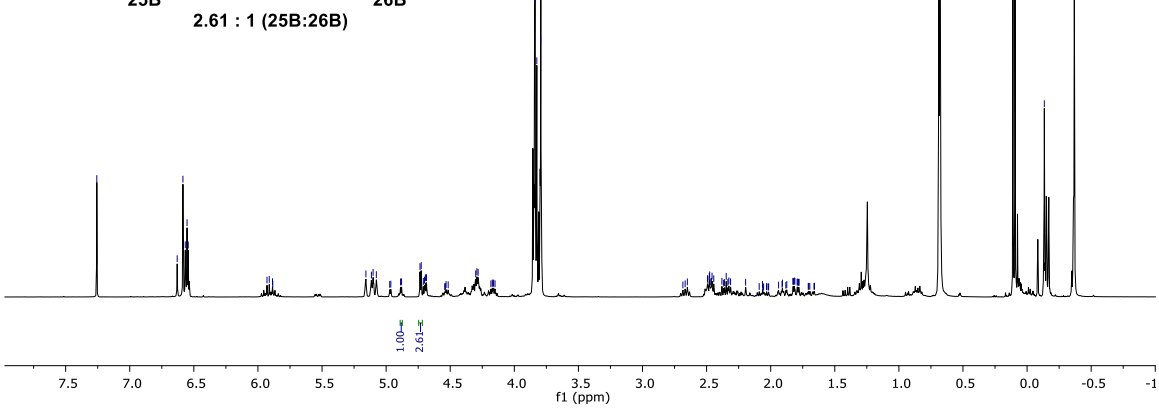

$^1$H NMR (400 MHZ, $CDCl_3$)

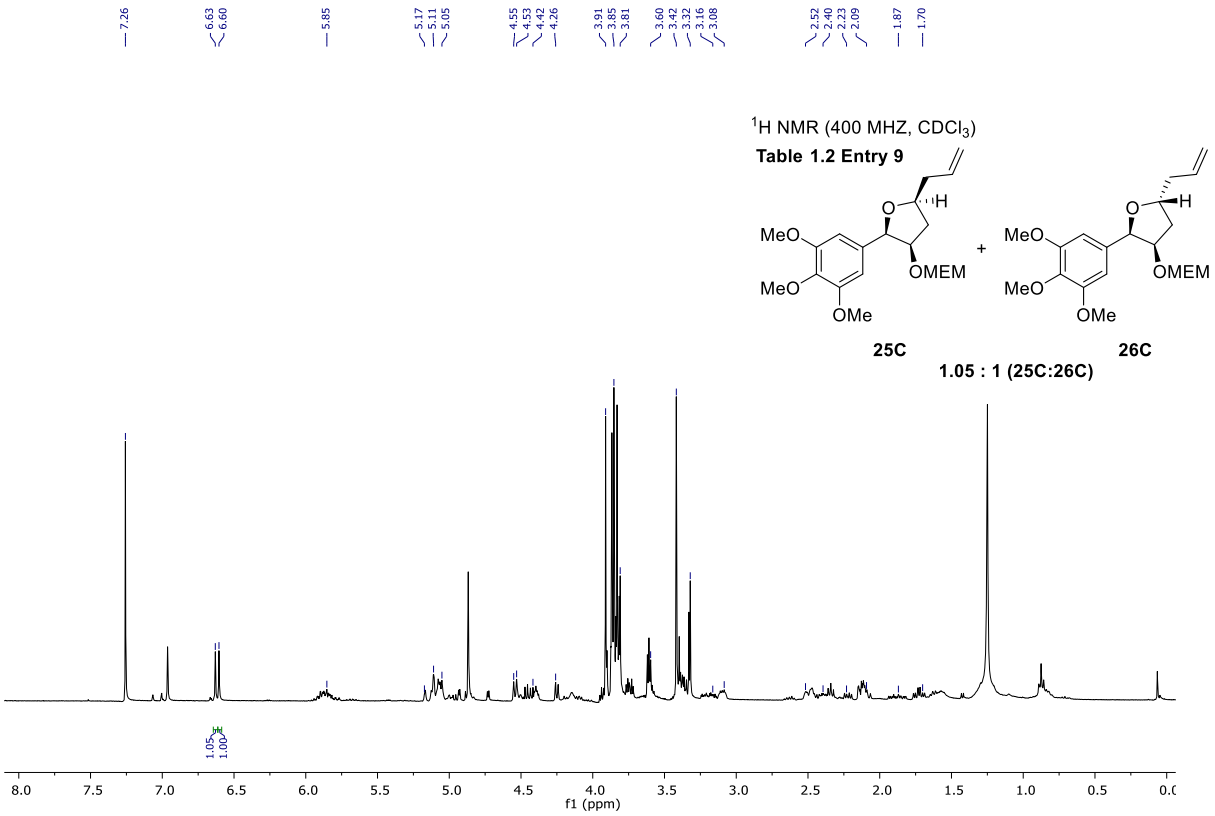
**Table 1.2 Entry 8**

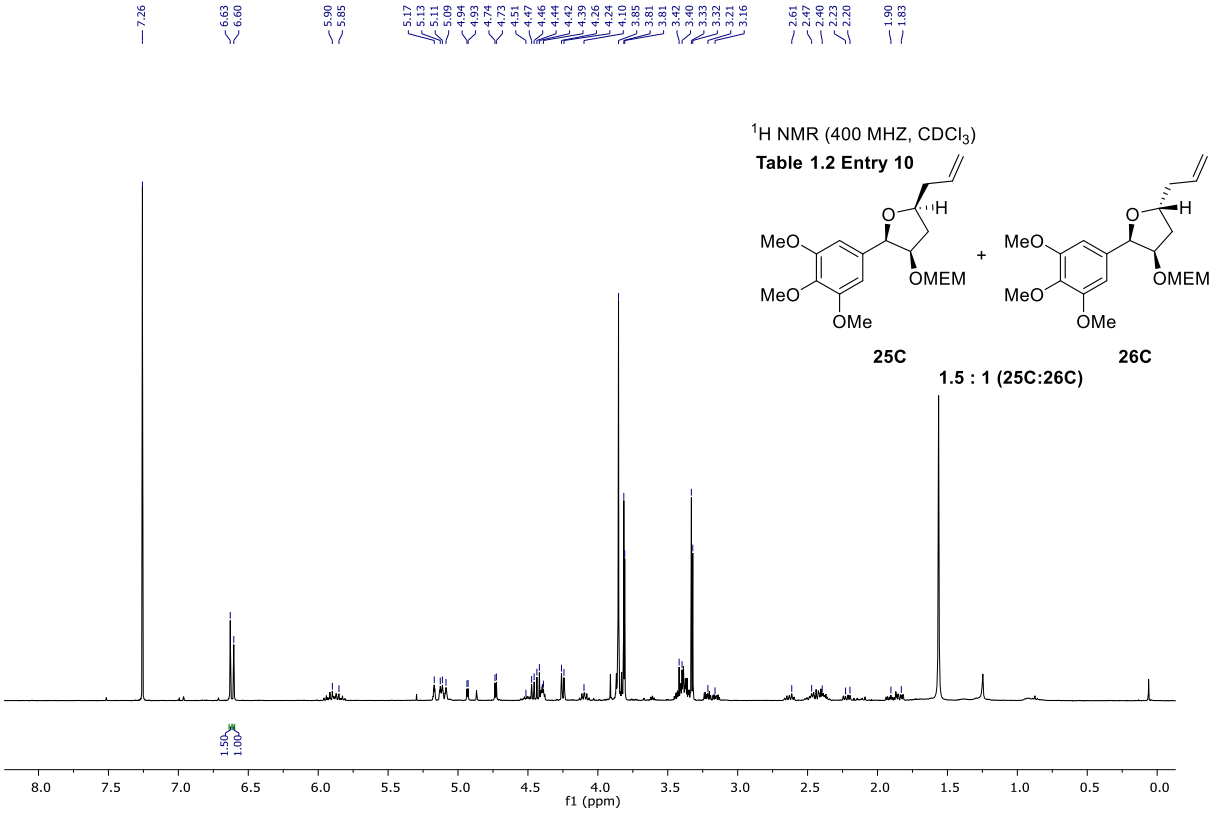


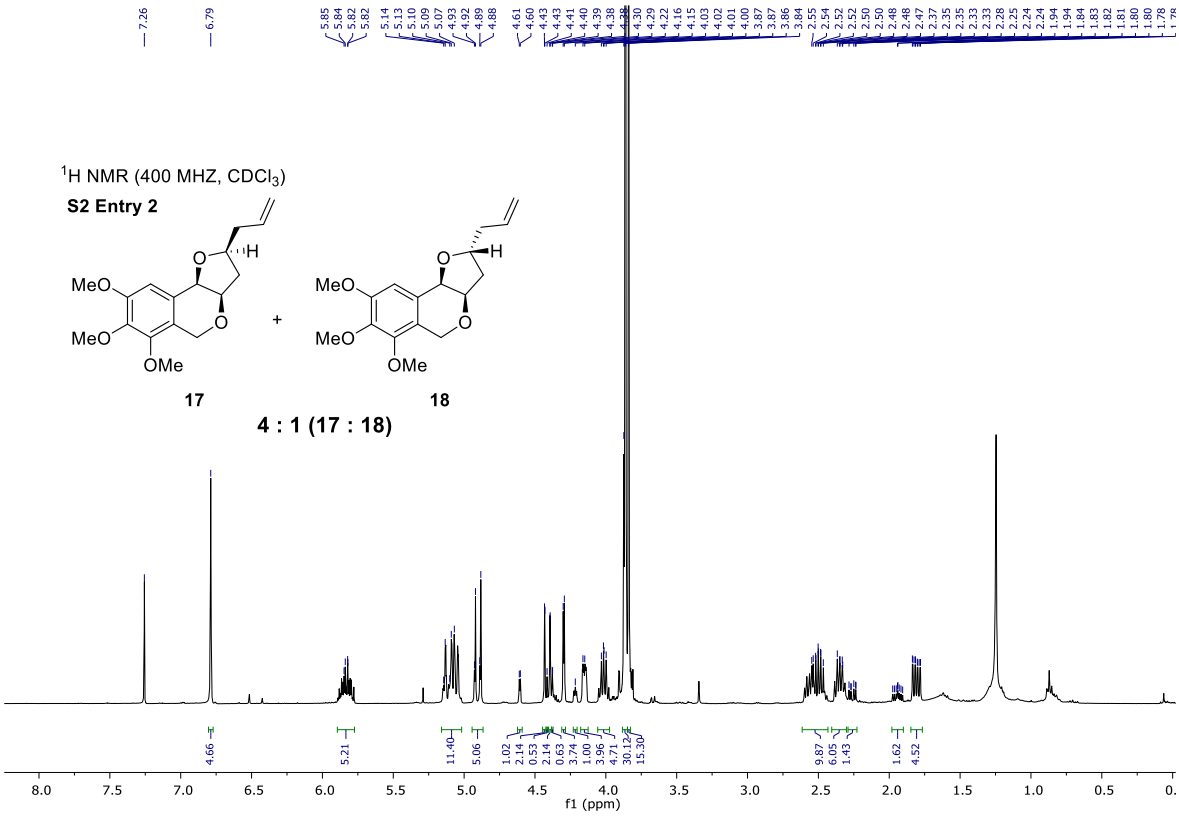

**25B** **26B**

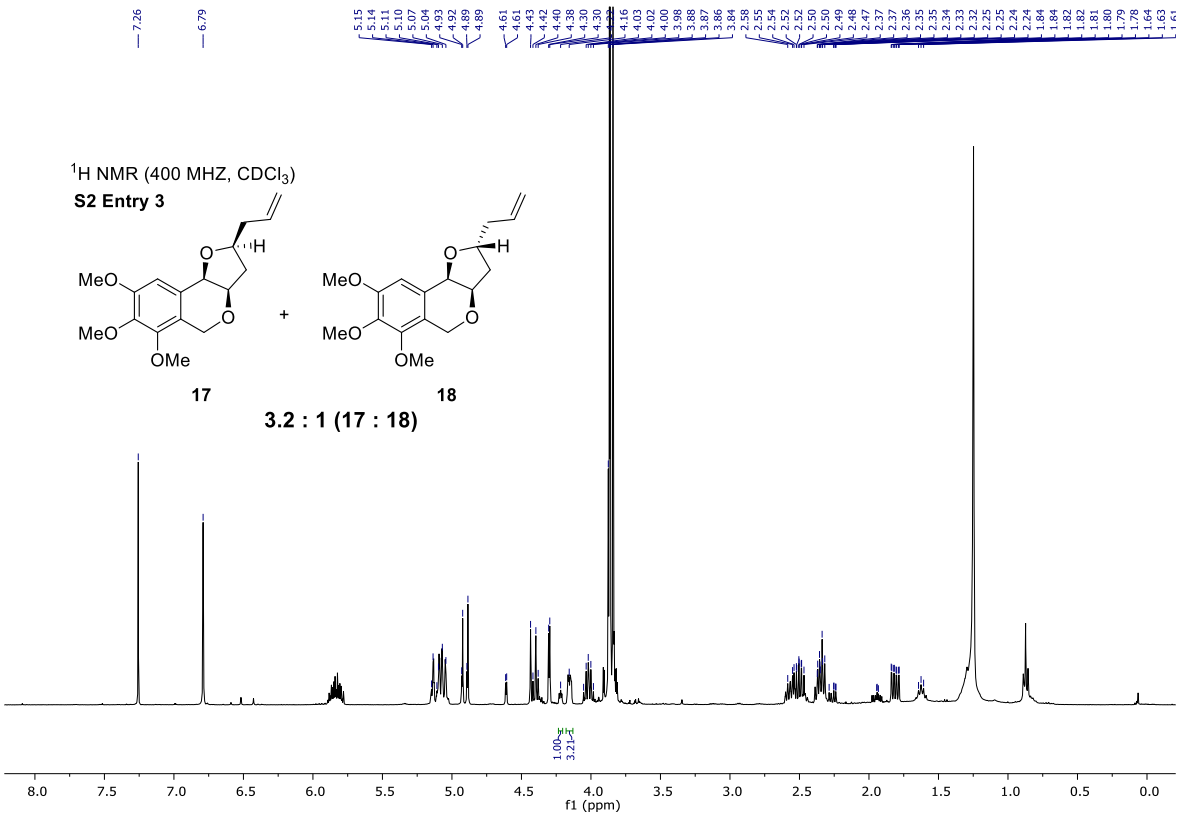
**2.61 : 1 (25B:26B)**

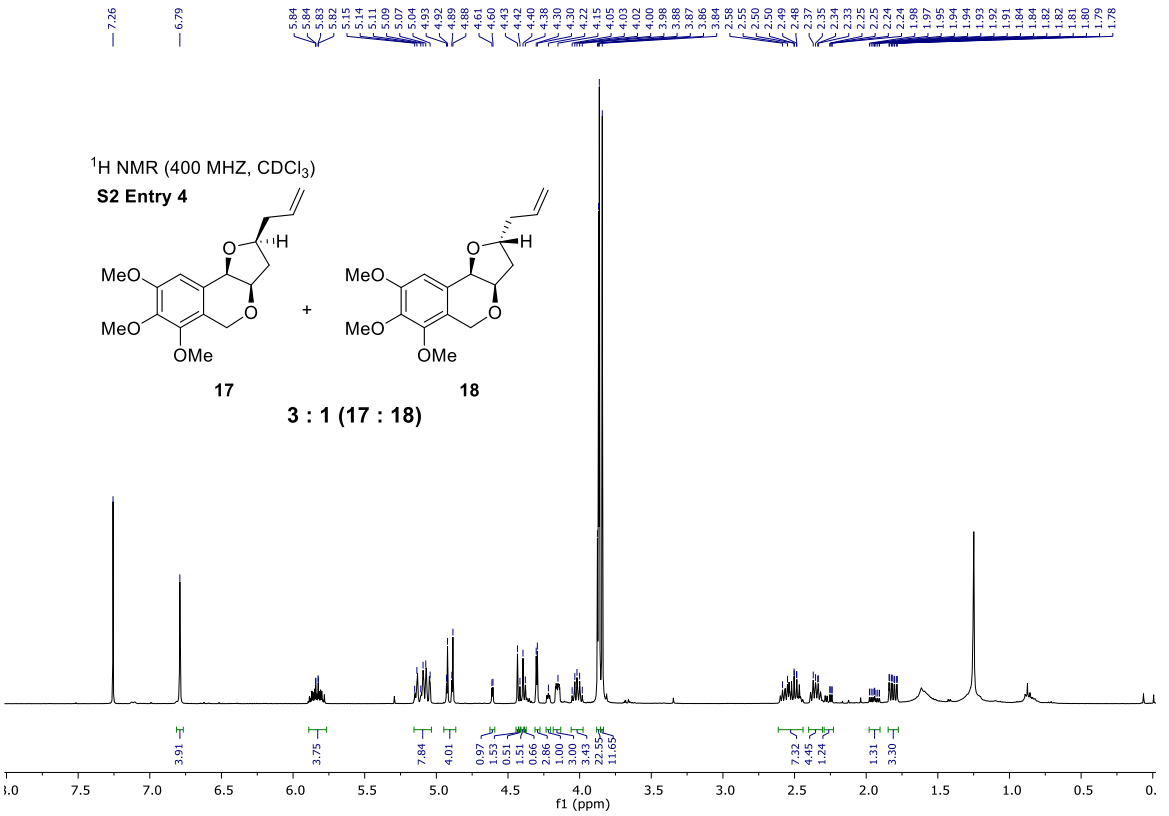


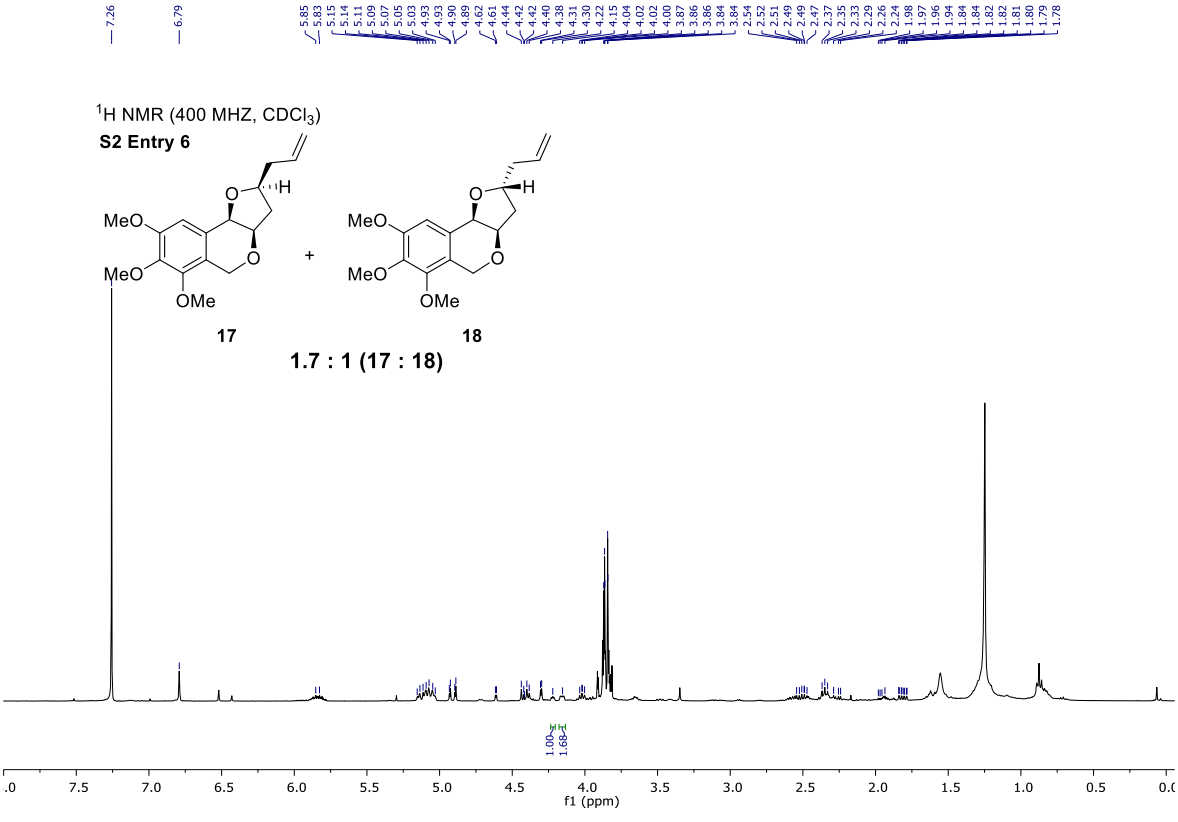

7.26
6.63
6.60
5.85
5.17
5.11
5.05
4.55
4.53
4.42
4.26
3.91
3.85
3.81
3.60
3.42
3.32
3.16
3.08
2.52
2.40
2.23
2.09
1.87
1.70
1H NMR (400 MHZ, CDCl3)
Table 1.2 Entry 9
MeO
MeO
OMe
O
H
OMEM
+
25C
26C
1.05 : 1 (25C:26C)
1.05
1.00
f1 (ppm)

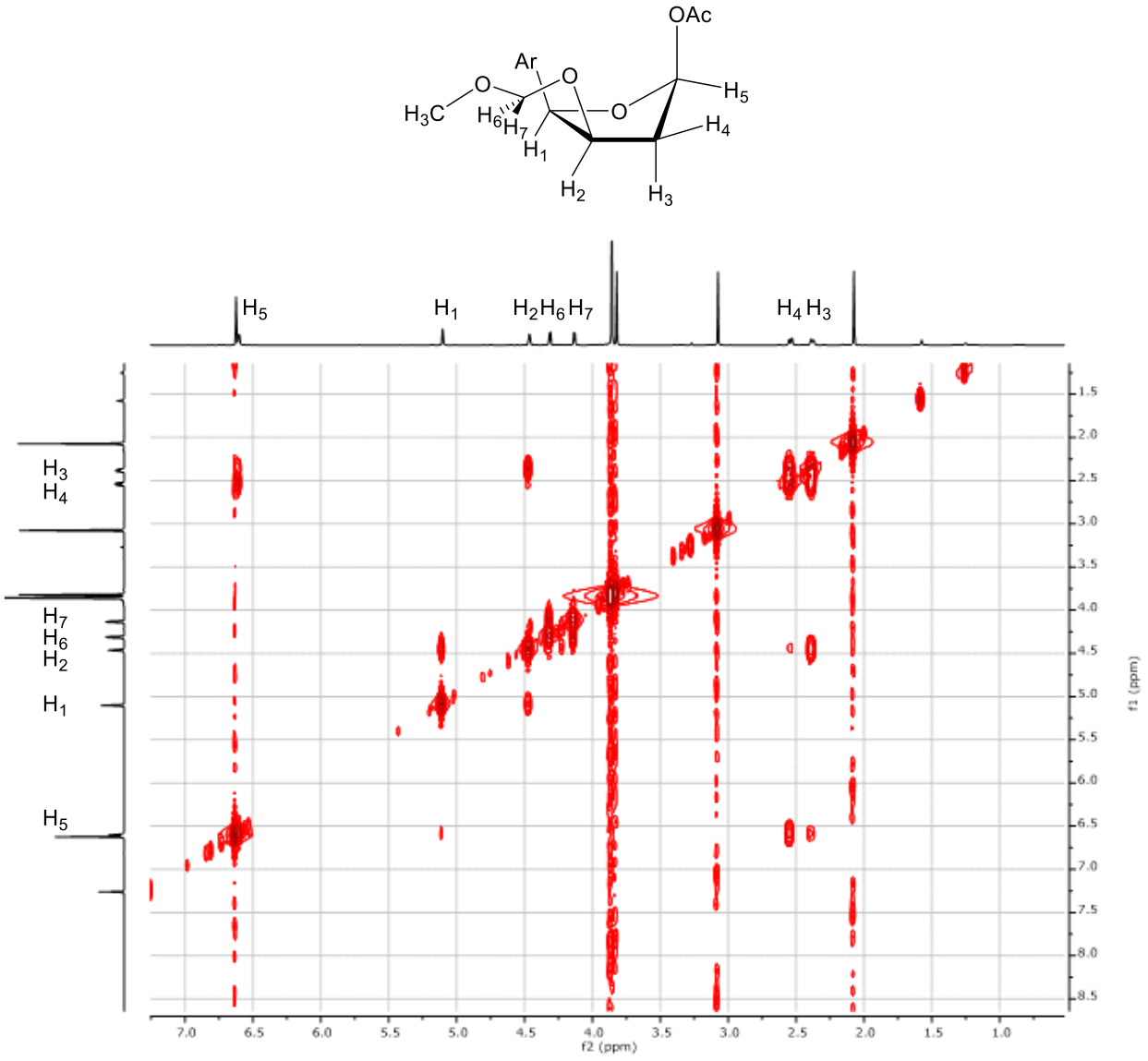

7.26
6.63
6.60
5.90
5.85
5.17
5.13
5.11
5.09
4.94
4.93
4.74
4.73
4.51
4.47
4.46
4.44
4.42
4.39
4.26
4.24
4.10
3.85
3.81
3.81
3.42
3.40
3.33
3.32
3.21
3.16
2.61
2.47
2.40
2.23
2.20
1.90
1.83
1H NMR (400 MHZ, CDCl3)
Table 1.2 Entry 10
MeO
MeO
OMe
O
H
OMEM
+
25C
26C
1.5 : 1 (25C:26C)
1.50
1.00
f1 (ppm)


$^1$H NMR (400 MHZ, $CDCl_3$)
S2 Entry 2
MeO
MeO
OMe
O
H
+
17
18
4 : 1 (17 : 18)
f1 (ppm)

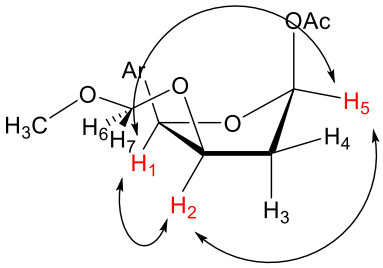

$^1$H NMR (400 MHZ, $CDCl_3$)
S2 Entry 3
MeO
MeO
OMe
O
H
+
17
18
3.2 : 1 (17 : 18)
f1 (ppm)


$^1$H NMR (400 MHZ, $CDCl_3$)
S2 Entry 4
MeO
MeO
OMe
O
H
+
17
18
3 : 1 (17 : 18)
f1 (ppm)

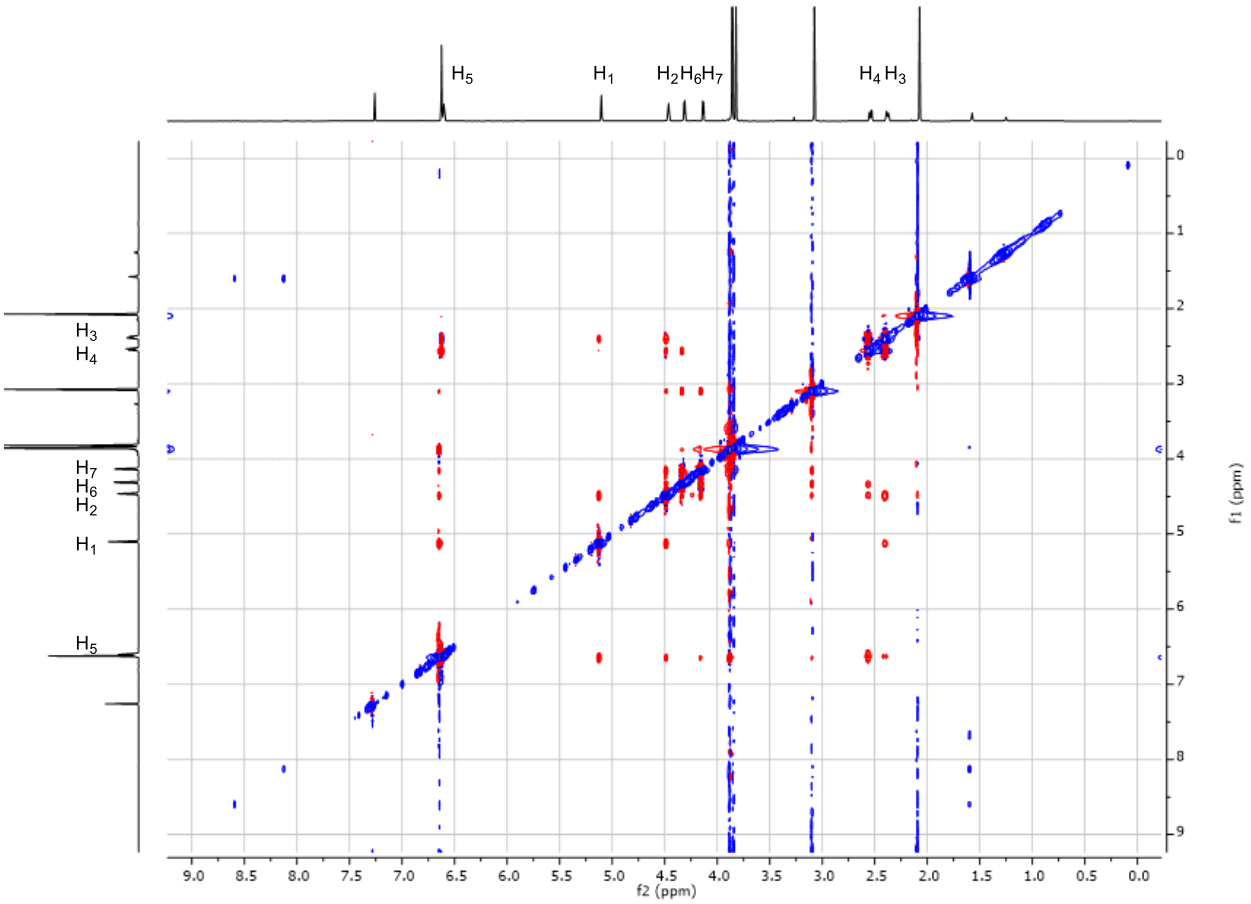

$^1$H NMR (400 MHZ, $CDCl_3$)
S2 Entry 6
MeO
MeO
OMe
O
H
+
17
18
1.7 : 1 (17 : 18)
f1 (ppm)



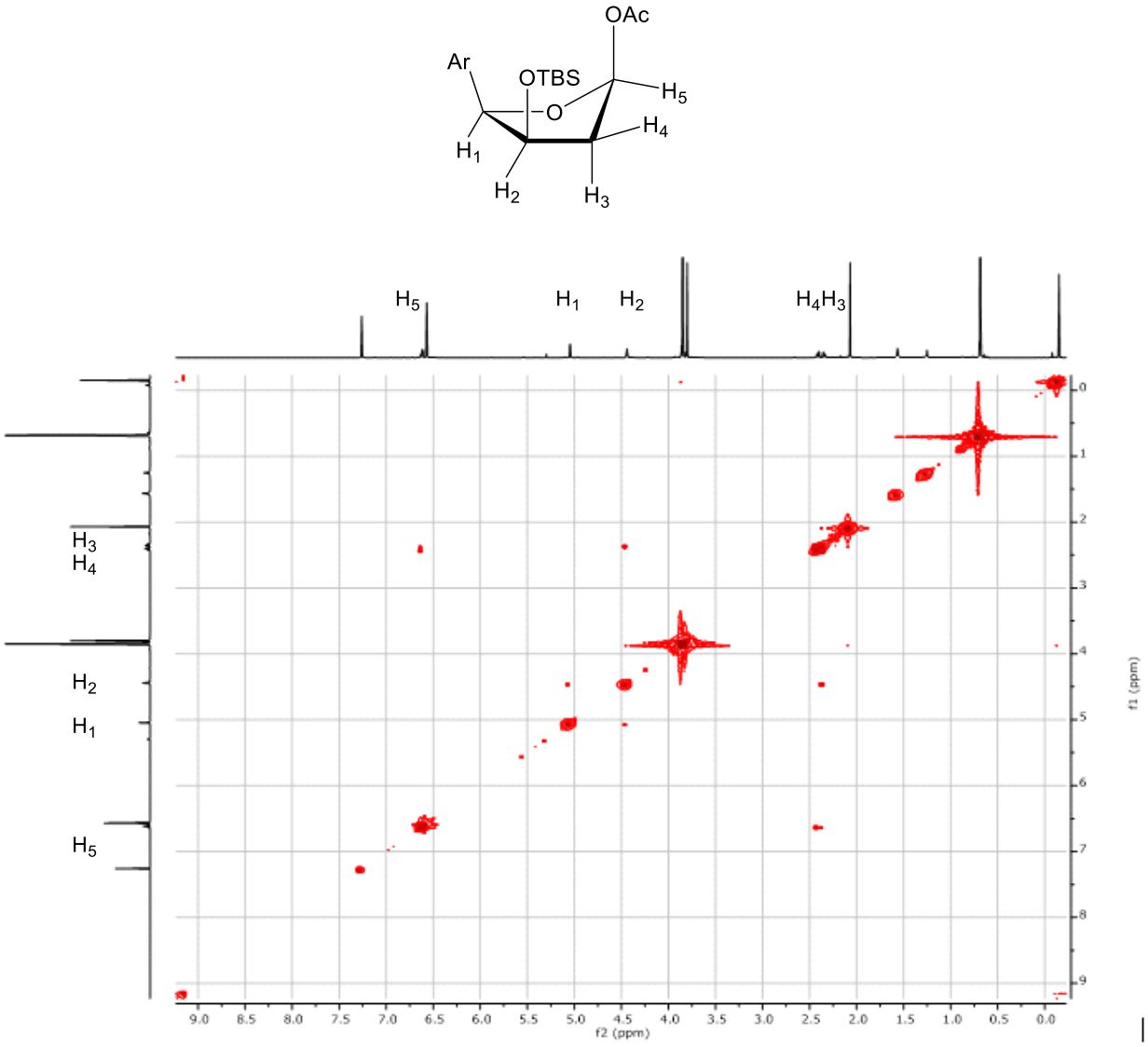

COSY NMR (800 MHz $CDCl_3$) spectrum of compound **16**



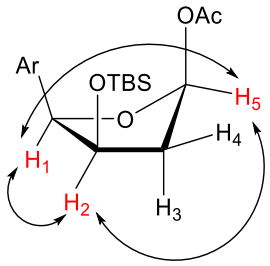

- The arrows show the key nOe interactions between $H_1$ and $H_2$, $H_2$ and $H_5$, and $H_1$ and $H_5$.



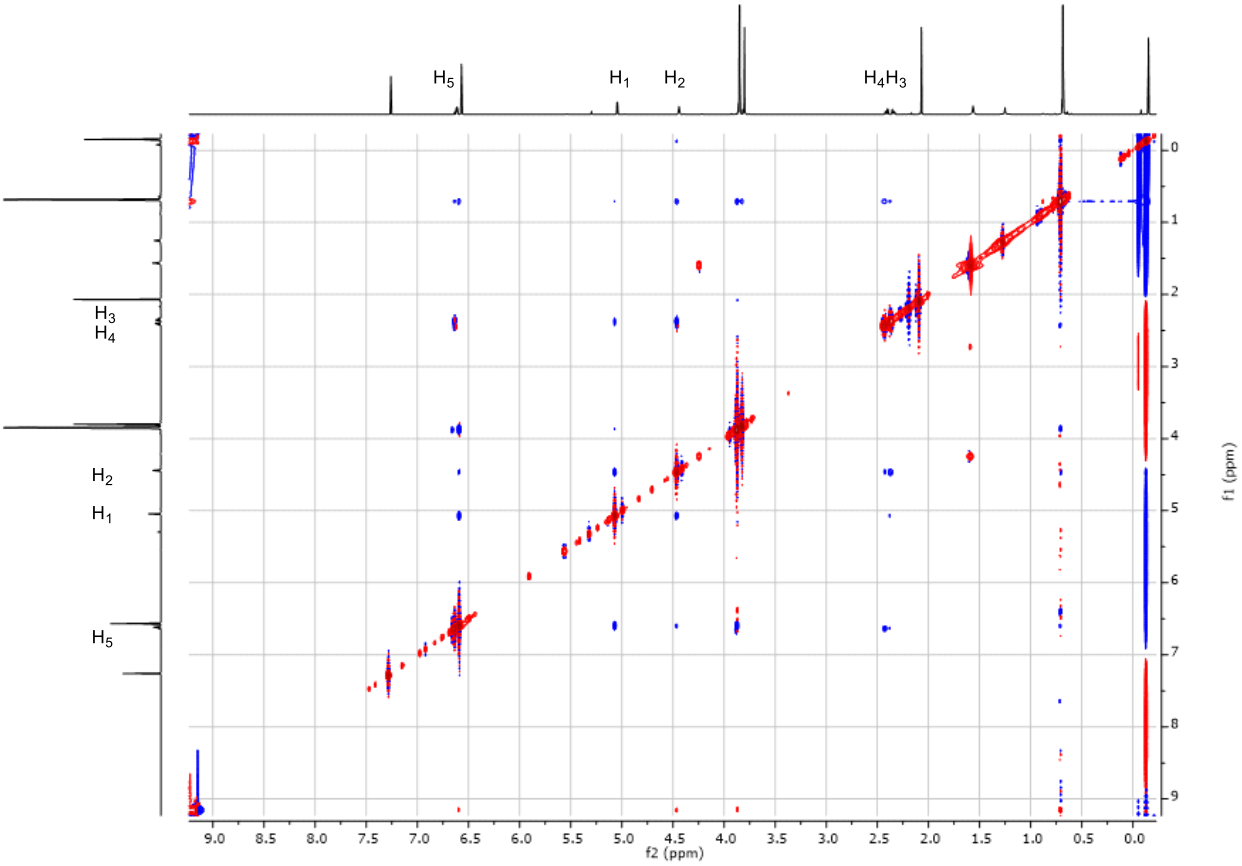

NOESY NMR (201 MHz $CDCl_3$) spectrum of compound **16**



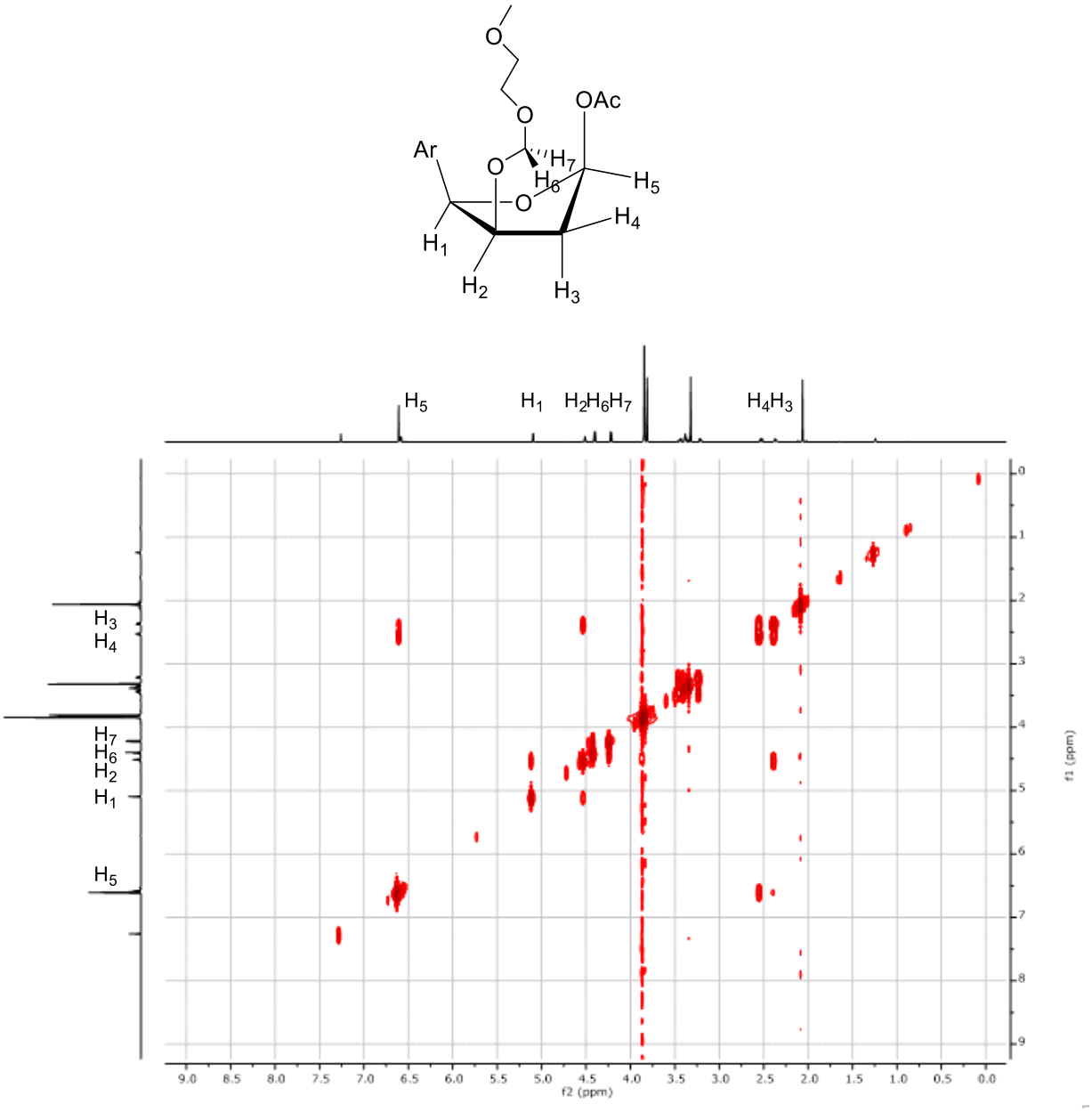

COSY NMR (800 MHz $CDCl_3$) spectrum of compound **22**



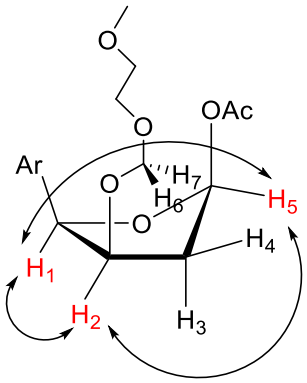

- The arrows show the key nOe interactions between $H_1$ and $H_2$, $H_2$ and $H_5$, and $H_1$ and $H_5$.



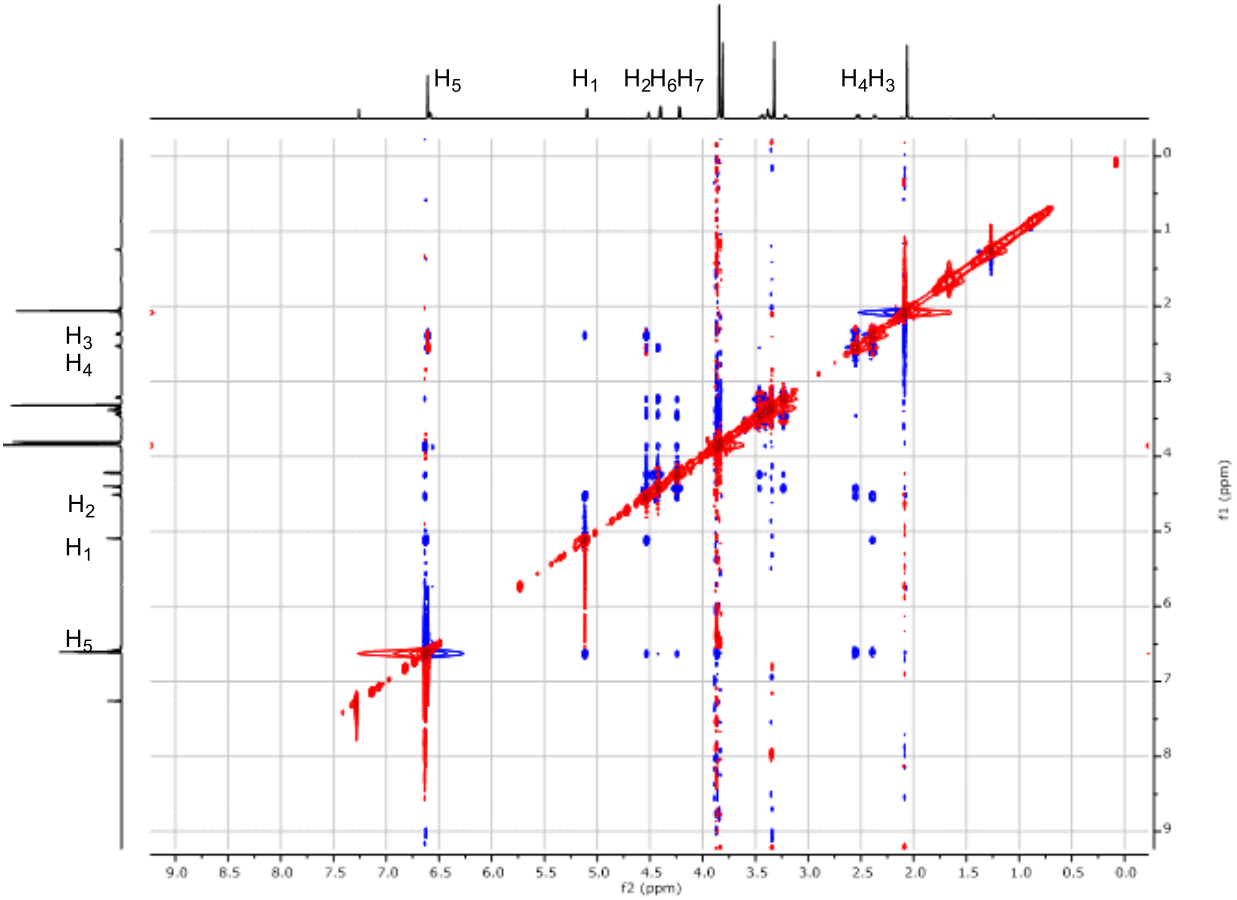

NOESY NMR (201 MHz $CDCl_3$) spectrum of compound **22**



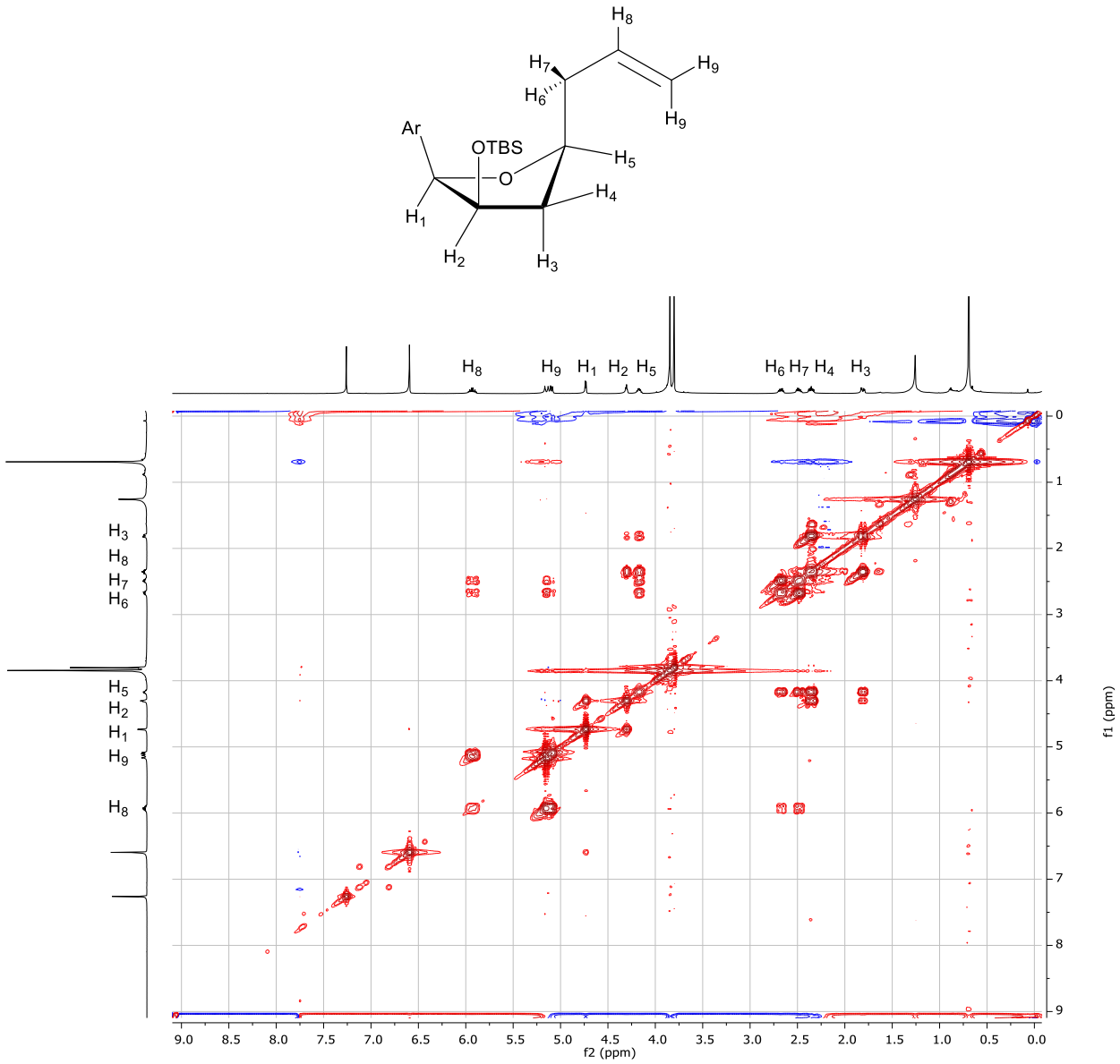

COSY NMR (800 MHz $CDCl_3$) spectrum of compound **24**



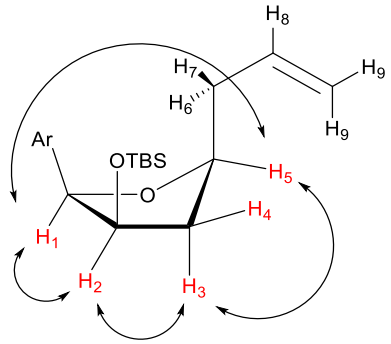

The arrows show the key nOe interactions between $H_1$ and $H_2$, $H_2$ and $H_5$, and $H_1$ and $H_5$.



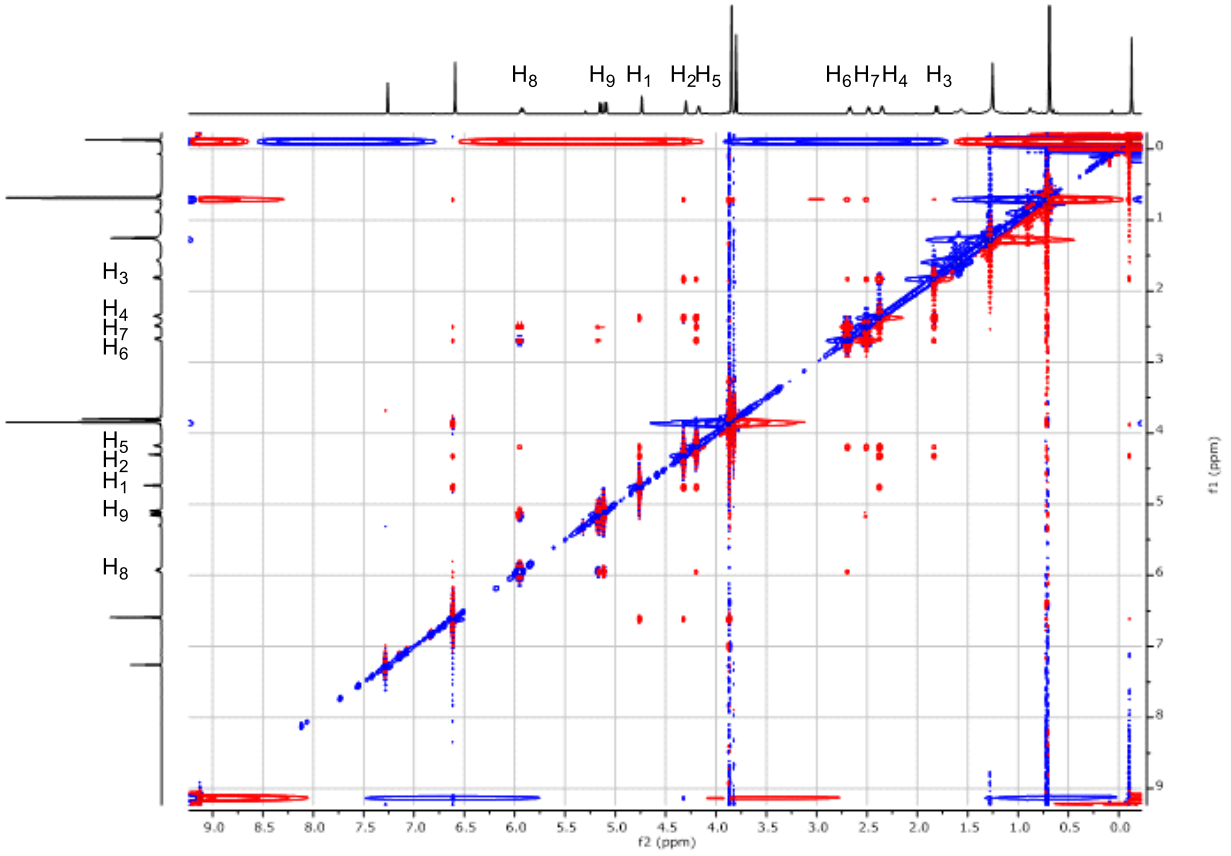

NOESY NMR (201 MHz $CDCl_3$) spectrum of compound **24**



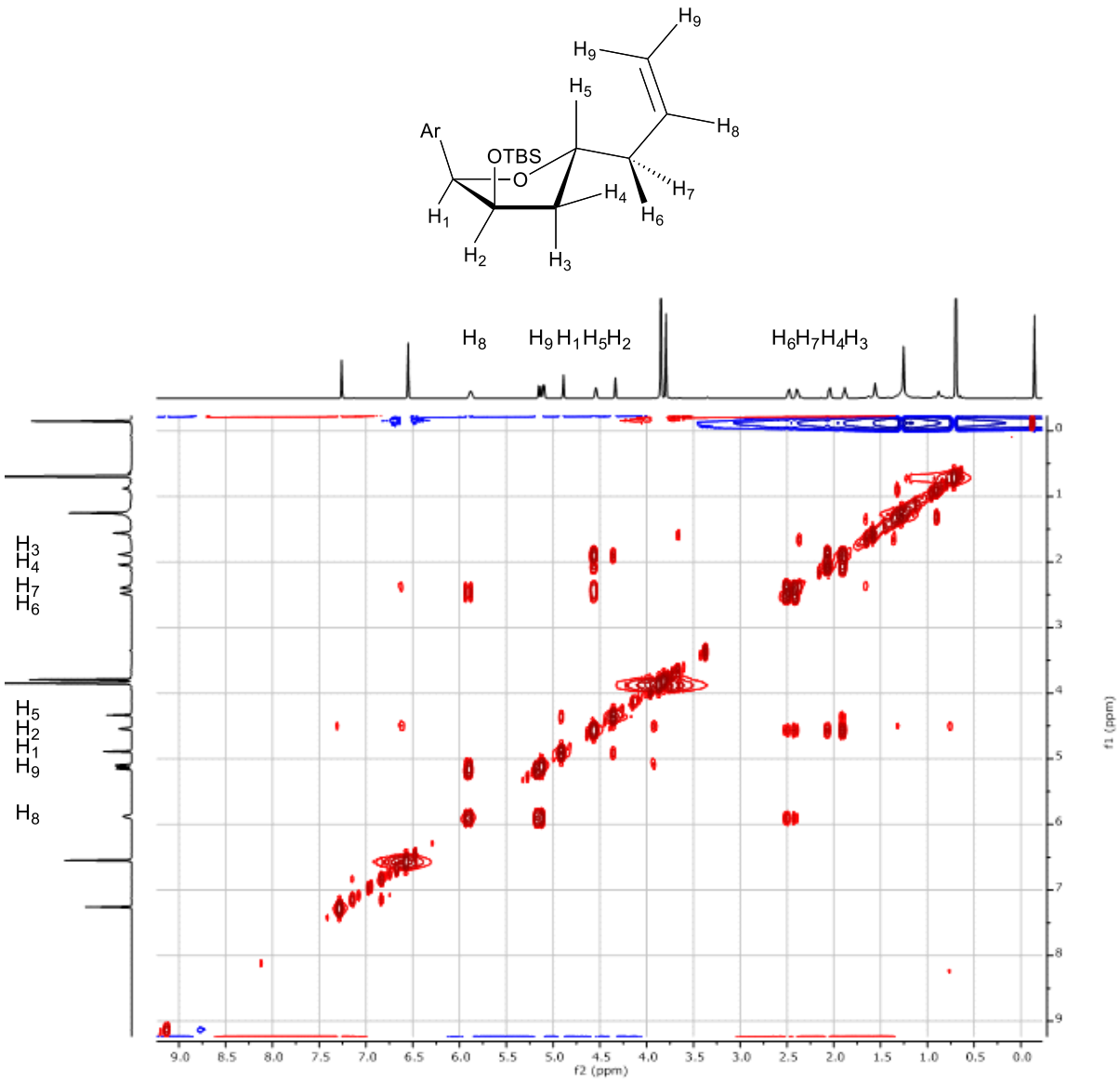

COSY NMR (800 MHz $CDCl_3$) spectrum of compound **25B**



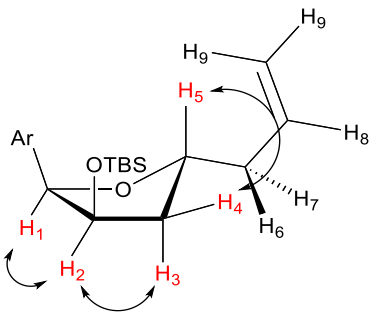

The arrows show the key nOe interactions between $H_1$ and $H_2$, $H_2$ and $H_3$, $H_3$and $H_5$, and $H_1$ and $H_5$.



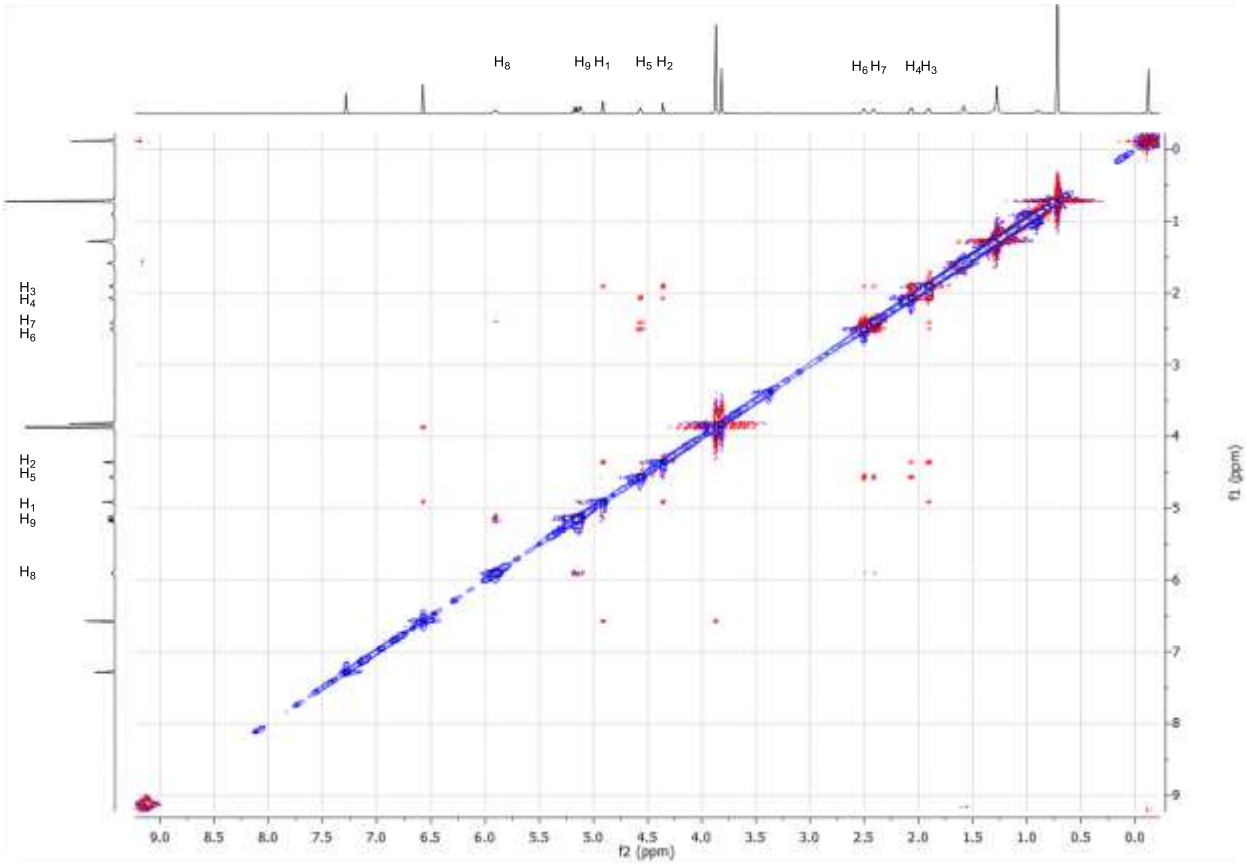

NOESY NMR (201 MHz $CDCl_3$) spectrum of compound **25B**



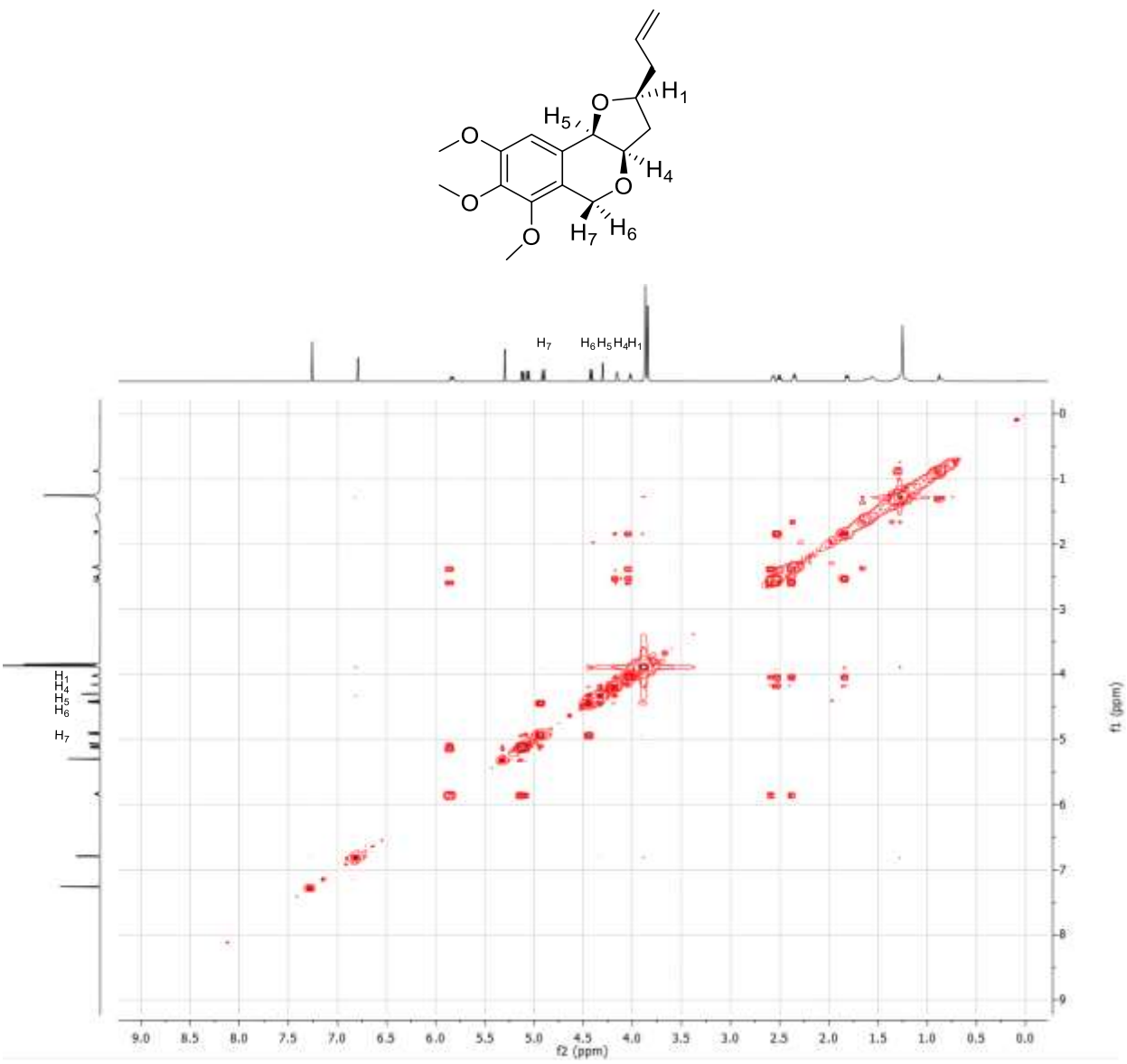

COSY NMR (800 MHz $CDCl_3$) spectrum of compound **26B**



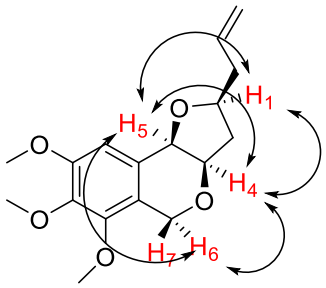

The arrows show the key nOe interactions between $H_1$ and $H_2$, $H_2$ and $H_3$, and $H_4$ and $H_5$.



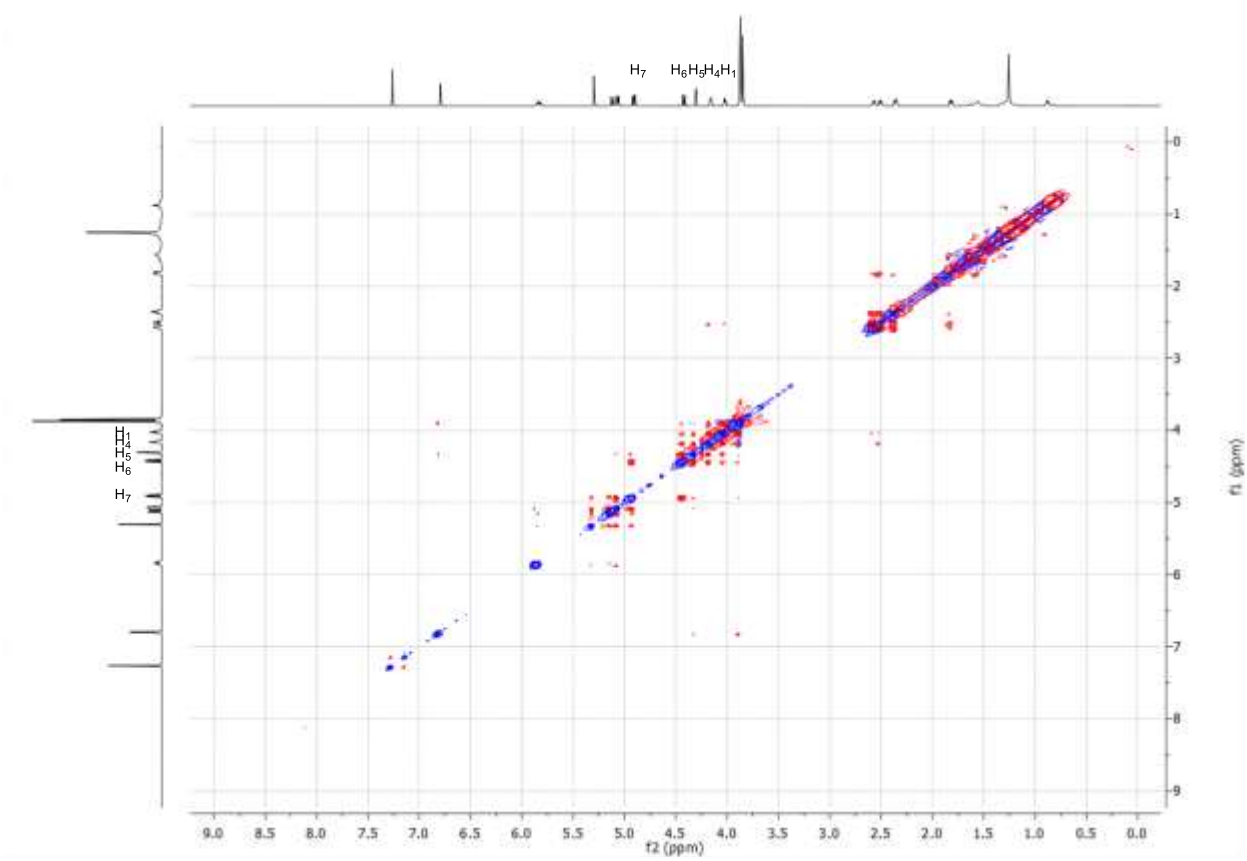

NOESY NMR (201 MHz $CDCl_3$) spectrum of compound **26B**




COSY NMR (800 MHz $CDCl_3$) spectrum of compound **29**

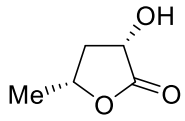



The arrows show the key nOe interactions between $H_1$ and $H_4$, $H_1$ and $H_5$, $H_4$ and $H_5$, $H_4$ and $H_6$, and $H_5$ and $H_6$.

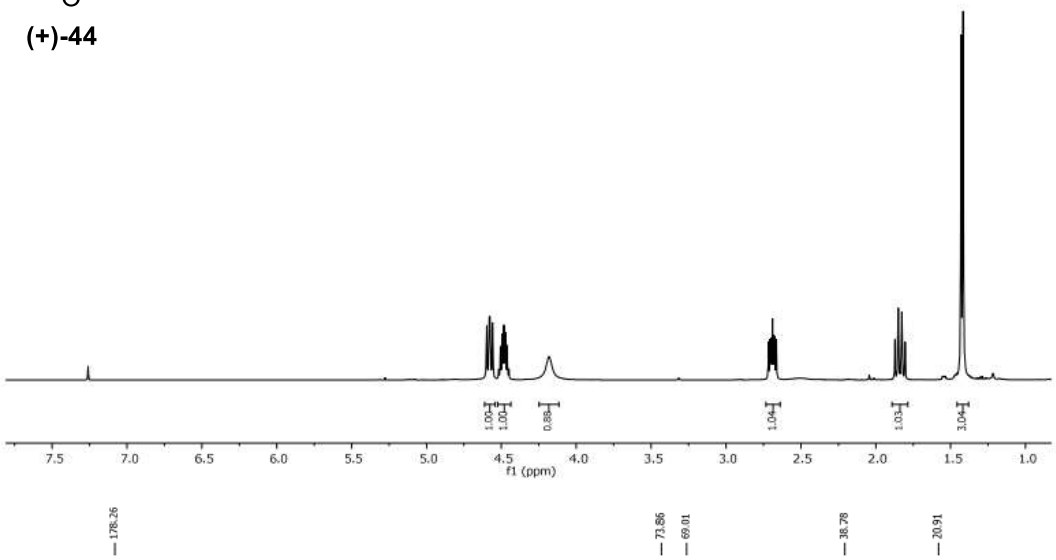



NOESY NMR (201 MHz $CDCl_3$) spectrum of compound **29**

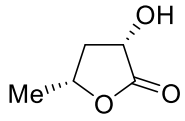
$^{1}$H NMR (500 MHz, $CDCl_3$)



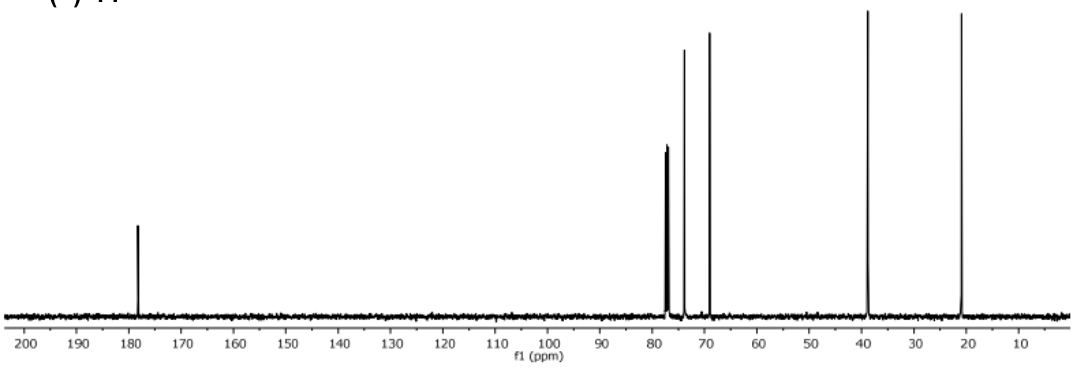

**(+)-44**



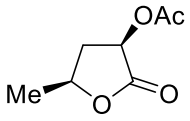

$^{13}$C NMR (125 MHz, $CDCl_3$)




**(+)-44**



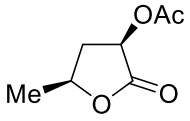
$^{1}$H NMR (500 MHz, $CDCl_3$)



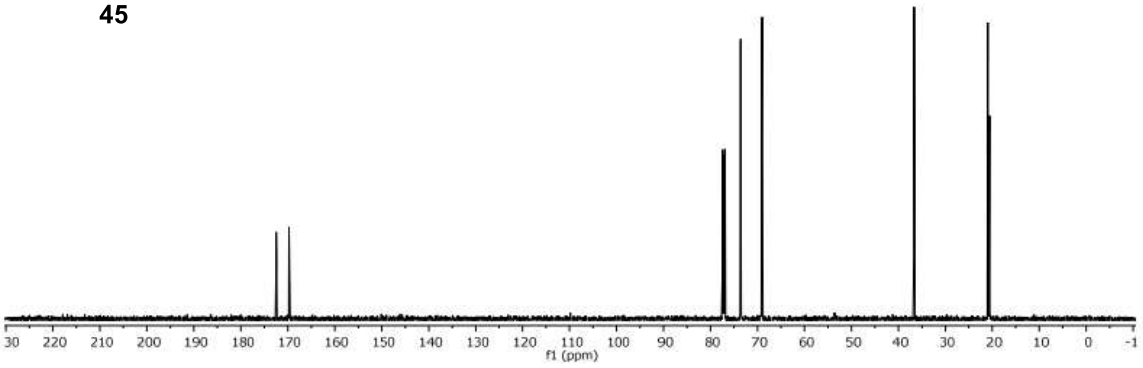

**45**



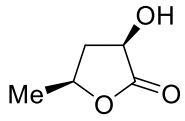

$^{13}$C NMR (125 MHz, $CDCl_3$)




**45**



$^{1}$H NMR (500 MHz, $CDCl_3$)



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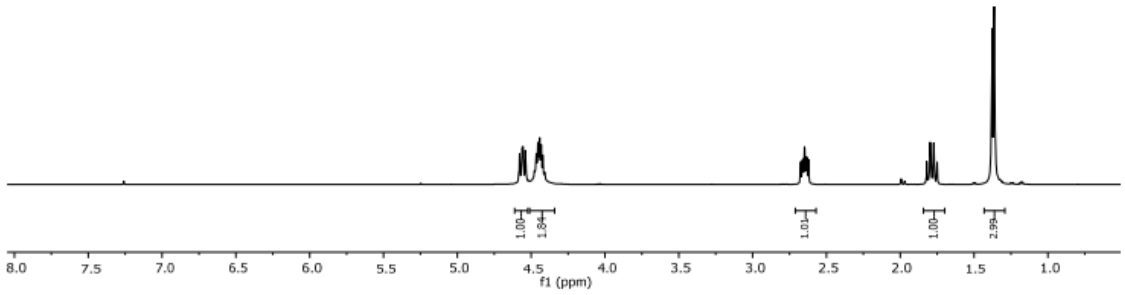
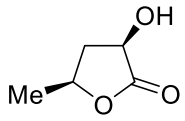
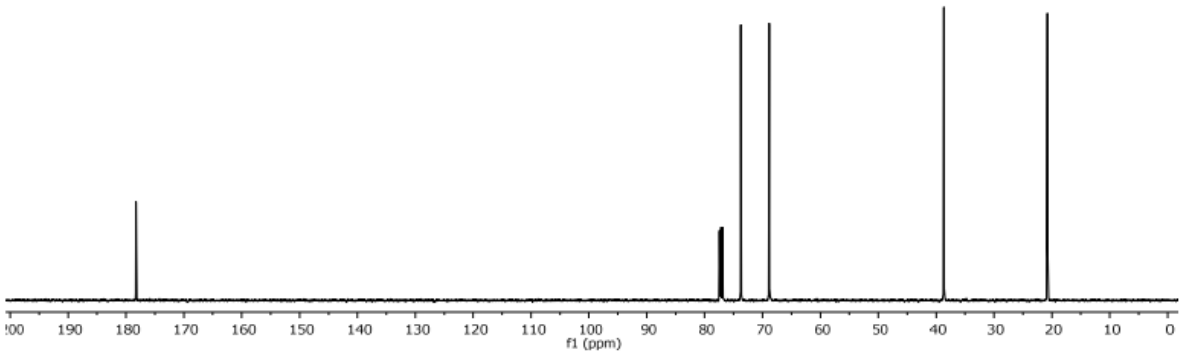


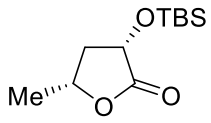
$^{13}$C NMR (125 MHz, $CDCl_3$)



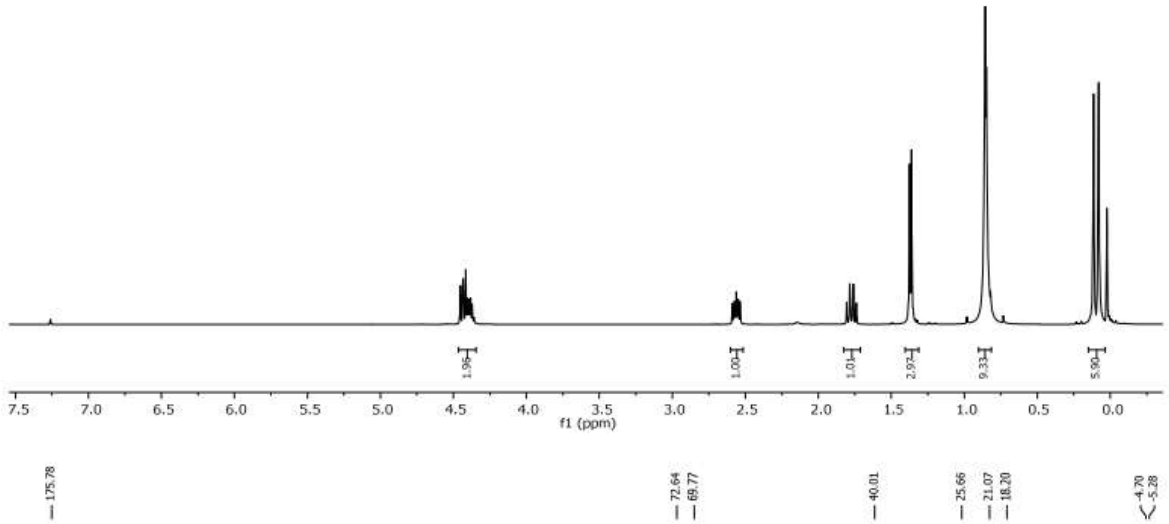
**(+)-44**



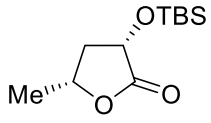
$^{1}$H NMR (500 MHz, $CDCl_3$)




**(+)-46**

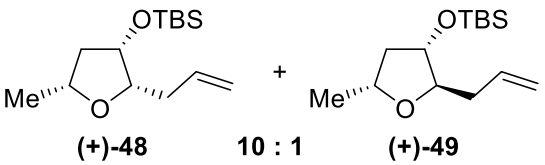



$^{13}$C NMR (125 MHz, $CDCl_3$)



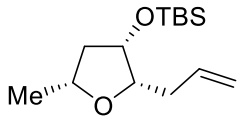

**(+)-46**

$^1$H NMR (500 MHz, $CDCl_3$)




**(+)-48** **10 : 1** **(+)-49**

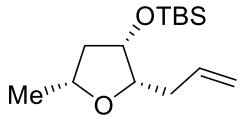
$^{1}$H NMR (500 MHz, $CDCl_3$)



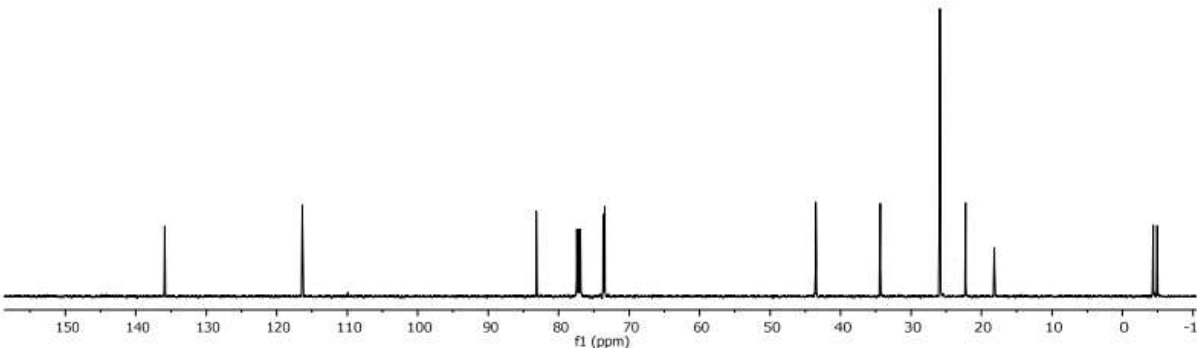

**(+)-48**



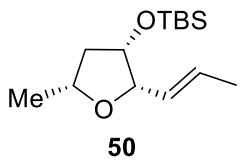

$^{13}$H NMR (125 MHz, $CDCl_3$)




**(+)-48**



$^{1}$H NMR (400 MHz, $CDCl_3$)




**50**

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Current Data Parameters
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EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
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Time                   17.16
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PULPROG                zg30
TD                    16384
SOLVENT               CDCl3
NS                        8
DS                        2
SWH                5617.978 Hz
FIDRES             0.342894 Hz
AQ                 1.4582260 sec
RG                      715
DW                   89.000 usec
DE                   127.14 usec
TE                    300.0 K
D1                 2.00000000 sec
P1                    9.50 usec
SFO1               400.1694000 MHz
NUCLEUS                  1H

F2 - Processing parameters
SI                      8192
SF                 400.1669660 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00

1D NMR plot parameters
CX                     20.00 cm
F1P                   10.100 ppm
F1                   4041.69 Hz
F2P                  -0.100 ppm
F2                   -40.02 Hz
PPMCM                0.51000 ppm/cm
HZCM                 204.06516 Hz/cm
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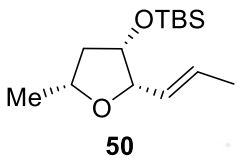
$^{13}$C NMR (101 MHz, $CDCl_3$)




**50**

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Current Data Parameters
NAME                  DL_1_151
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
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Time                   17.20
INSTRUM                spect
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PULPROG              zgpg30
TD                    32768
SOLVENT               CDCl3
NS                      161
DS                        2
SWH                23809.523 Hz
FIDRES             0.726609 Hz
AQ                 0.6881780 sec
RG                    16384
DW                   21.000 usec
DE                   30.00 usec
TE                    300.0 K
D12                0.00002000 sec
DL6                   21.00 dB
D1                 2.00000000 sec
CPDPRG               waltz16
P31                   76.00 usec
D11                0.03000000 sec
DL5                   18.00 dB
P1                     8.60 usec
SFO1               100.6330000 MHz
NUCLEUS                  13C

F2 - Processing parameters
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SF                 100.6220720 MHz
WDW                       EM
SSB                        0
LB                      3.00 Hz
GB                         0
PC                      1.00

1D NMR plot parameters
CX                     20.00 cm
F1P                   201.000 ppm
F1                   20225.04 Hz
F2P                  -1.000 ppm
F2                   -100.62 Hz
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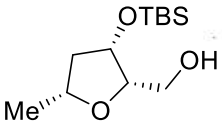
$^{1}$H NMR (400 MHz, $CDCl_3$)




**(+)-51**




Current Data Parameters
NAME DL_1_166
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20170518
Time 11.38
INSTRUM spect
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PULPROG zg30
TD 16384
SOLVENT CDCl3
NS 8
DS 2
SWH 5617.978 Hz
FIDRES 0.342894 Hz
AQ 1.4582260 sec
RG 715
DW 89.000 usec
DE 127.14 usec
TE 300.0 K
D1 2.00000000 sec
P1 9.50 usec
SFO1 400.1694000 MHz
NUCLEUS 1H

F2 - Processing parameters
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WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
F1P 13.102 ppm
F1 5242.99 Hz
F2P -0.937 ppm
F2 -374.99 Hz
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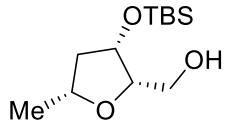
$^{13}$C NMR (101 MHz, $CDCl_3$)




**(+)-51**




Current Data Parameters
NAME DL_1_166
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
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Time 11.45
INSTRUM spect
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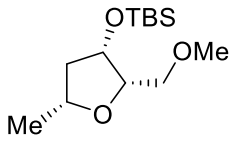
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 101
DS 2
SWH 23809.523 Hz
FIDRES 0.726609 Hz
AQ 0.6881780 sec
RG 16384
DW 21.000 usec
DE 30.00 usec
TE 300.0 K
D12 0.00002000 sec
DL5 21.00 dB
D1 2.00000000 sec
CPDPRG waltz16
P31 76.00 usec
D11 0.03000000 sec
DL5 18.00 dB
P1 8.60 usec
SFO1 100.6330000 MHz
NUCLEUS 13C

F2 - Processing parameters
SI 16384
SF 100.6220720 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
F1P 226.916 ppm
F1 22832.76 Hz
F2P -9.707 ppm
F2 -976.77 Hz
PPMCM 11.83116 ppm/cm
HZCM 1190.47520 Hz/cm

$^{1}$H NMR (400 MHz, $CDCl_3$)




**(+)-52**



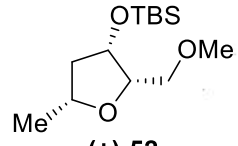

Current Data Parameters
NAME DL-1-168-M
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20170518
Time 22.26
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 16384
SOLVENT CDCl3
NS 8
DS 2
SWH 5617.978 Hz
FIDRES 0.342894 Hz
AQ 1.4582260 sec
RG 715
DW 89.000 usec
DE 127.14 usec
TE 300.0 K
D1 2.00000000 sec
P1 9.50 usec
SFO1 400.1694000 MHz
NUCLEUS 1H

F2 - Processing parameters
SI 8192
SF 400.1669660 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
F1P 10.100 ppm
F1 4041.69 Hz
F2P -0.100 ppm
F2 -40.02 Hz
PPMCM 0.51000 ppm/cm
HZCM 204.08516 Hz/cm

$^{13}$C NMR (101 MHz, $CDCl_3$)




**(+)-52**



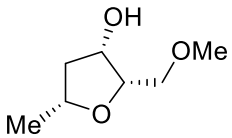

Current Data Parameters
NAME DL-1-168-M
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20170518
Time 22.32
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 101
DS 2
SWH 23809.523 Hz
FIDRES 0.726609 Hz
AQ 0.6881780 sec
RG 16384
DW 21.000 usec
DE 30.00 usec
TE 300.0 K
D12 0.00002000 sec
DL6 21.00 dB
D1 2.00000000 sec
CPDPRG waltz16
P31 75.00 usec
D11 0.03000000 sec
DL5 18.00 dB
P1 8.60 usec
SFO1 100.6330000 MHz
NUCLEUS 13C

F2 - Processing parameters
SI 16384
SF 100.6220720 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
F1P 226.916 ppm
F1 22832.76 Hz
F2P -9.707 ppm
F2 -976.77 Hz
PPMCM 11.93116 ppm/cm
HZCM 1190.47620 Hz/cm

$^{1}$H NMR (400 MHz, $CDCl_3$)

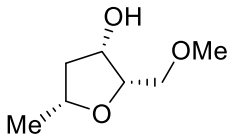



**(+)-53**




```
Current Data Parameters
NAME                  DL-1-169
EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20170522
Time                     21.09
INSTRUM                  spect
PROBHD     5 mm QNP  1H
PULPROG                  zg30
TD                      16384
SOLVENT                  CDCl3
NS                           8
DS                           2
SWH                5617.978 Hz
FIDRES             0.342894 Hz
AQ                 1.4582250 sec
RG                        1024
DW                   89.000 usec
DE                   127.14 usec
TE                    300.0 K
D1                 2.00000000 sec
P1                    9.50 usec
SFO1              400.1694000 MHz
NUCLEUS                    1H

F2 - Processing parameters
SI                        8192
SF                400.1669650 MHz
WDW                         EM
SSB                          0
LB                        0.30 Hz
GB                           0
PC                        1.00

1D NMR plot parameters
CX                       20.00 cm
F1P                     10.100 ppm
F1                    4041.69 Hz
F2P                    -0.100 ppm
F2                    -40.02 Hz
PPMCM                 0.51000 ppm/cm
HZCM                204.08516 Hz/cm
```

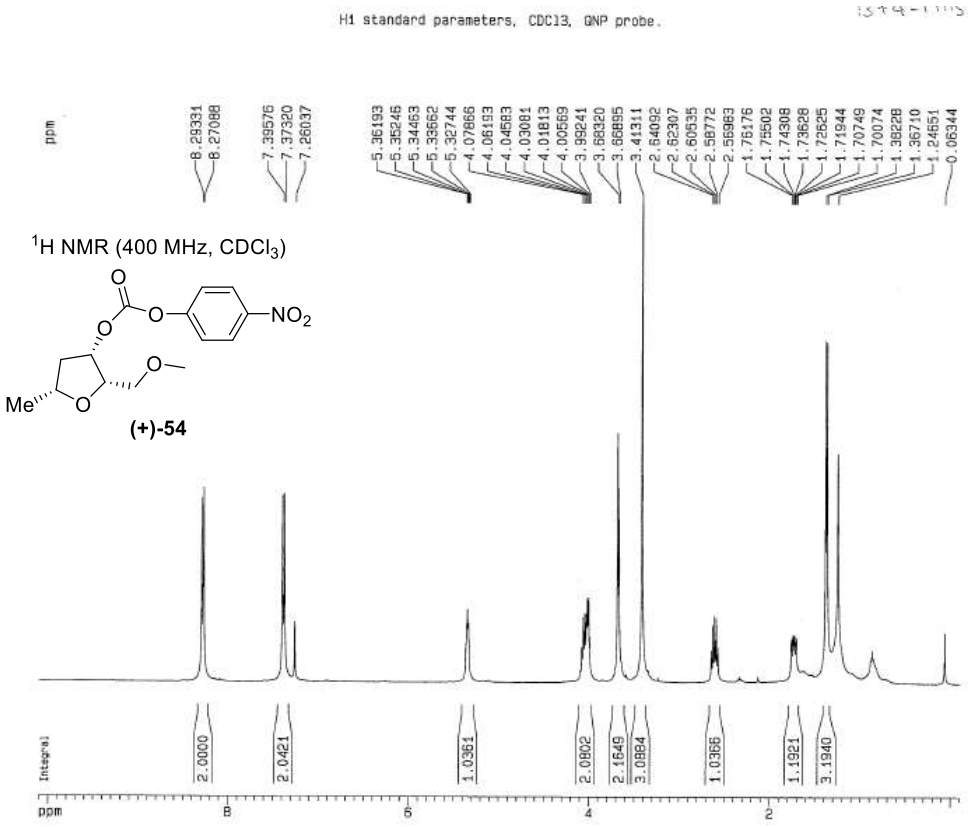
$^{13}$C NMR (101 MHz, $CDCl_3$)




**(+)-53**




```
Current Data Parameters
NAME                  DL-1-169
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20170522
Time                     21.13
INSTRUM                  spect
PROBHD     5 mm QNP  1H
PULPROG                  zgpg30
TD                      32768
SOLVENT                  CDCl3
NS                          77
DS                           2
SWH               23809.523 Hz
FIDRES             0.726509 Hz
AQ                 0.6881790 sec
RG                       16384
DW                   21.000 usec
DE                   30.00 usec
TE                    300.0 K
D12                0.00002000 sec
DL6                  21.00 dB
D1                 2.00000000 sec
CPDPRG                   waltz16
P31                   76.00 usec
D11                0.03000000 sec
DL5                  18.00 dB
P1                    8.60 usec
SFO1              100.6330000 MHz
NUCLEUS                    13C

F2 - Processing parameters
SI                       16384
SF                100.6220720 MHz
WDW                         EM
SSB                          0
LB                        3.00 Hz
GB                           0
PC                        1.00

1D NMR plot parameters
CX                       20.00 cm
F1P                    226.916 ppm
F1                   22832.75 Hz
F2P                    -9.707 ppm
F2                    -976.77 Hz
PPMCM                11.83115 ppm/cm
HZCM              1190.47620 Hz/cm
```

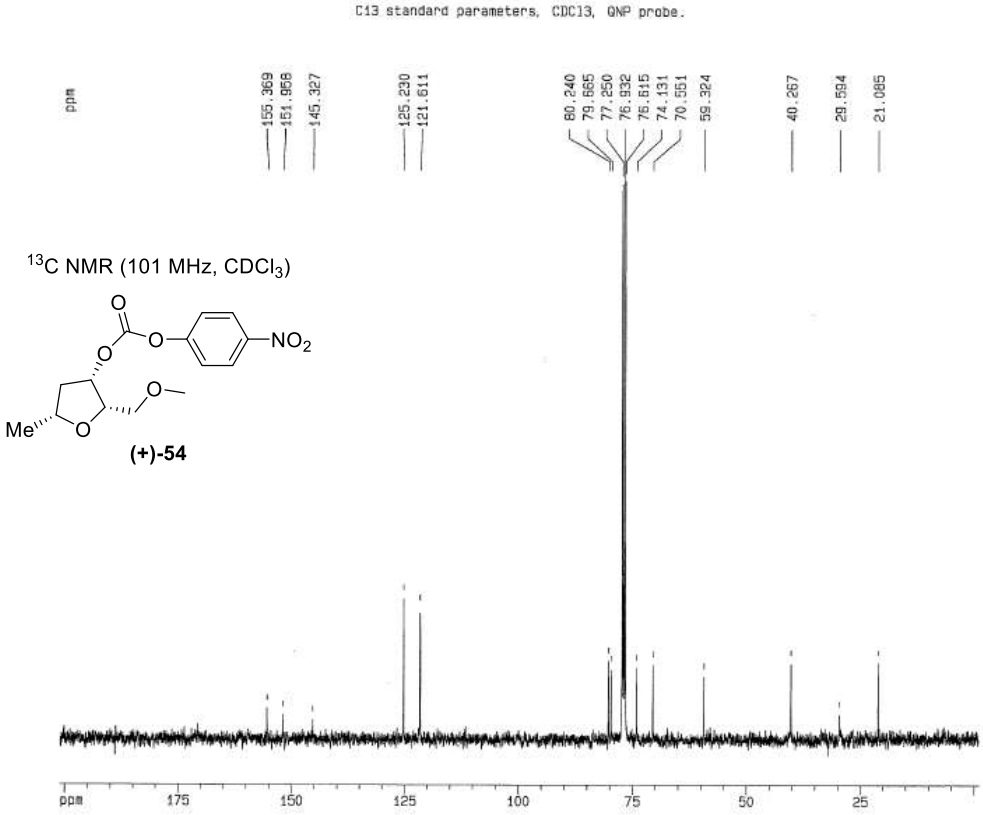



$^{1}$H NMR (400 MHz, $CDCl_3$)



**(+)-54**

```
Current Data Parameters
NAME                DL-1-170
EXPNO                      1
PROCNO                     1

F2 - Acquisition Parameters
Date_              20170523
Time                  15.33
INSTRUM               spect
PROBHD     5 mm QNP  1H
PULPROG                zg30
TD                    16384
SOLVENT               CDCl3
NS                        8
DS                        2
SWH               5617.978 Hz
FIDRES            0.342894 Hz
AQ                1.4582260 sec
RG                     2048
DW                  89.000 usec
DE                  127.14 usec
TE                   300.0 K
D1                2.00000000 sec
P1                    9.50 usec
SFO1            400.1694000 MHz
NUCLEUS                  1H

F2 - Processing parameters
SI                     8192
SF              400.1669560 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00

1D NMR plot parameters
CX                   20.00 cm
F1P                 10.100 ppm
F1                4041.69 Hz
F2P                -0.100 ppm
F2                 -40.02 Hz
PPMCM             0.51000 ppm/cm
HZCM            204.08516 Hz/cm
```

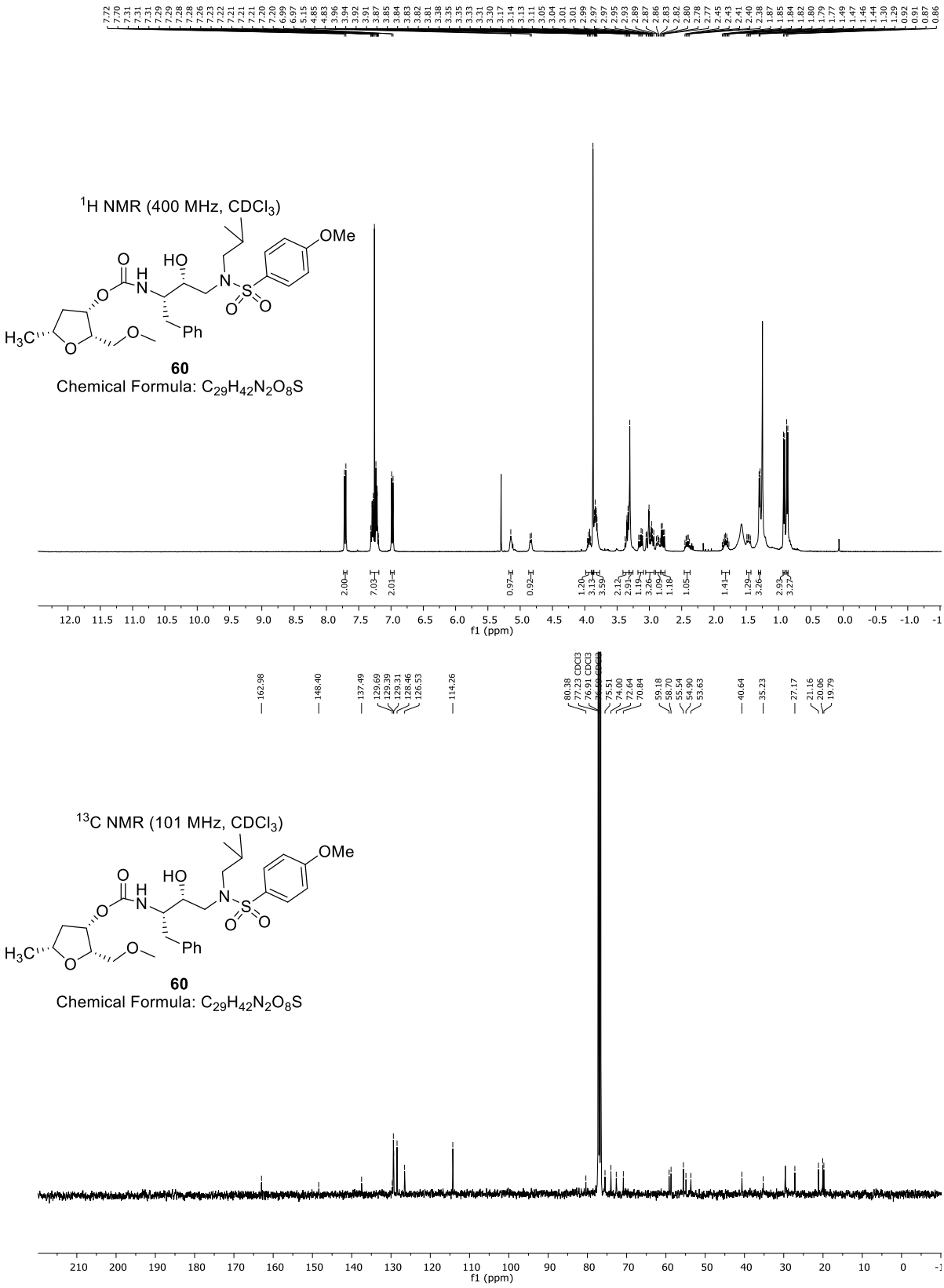


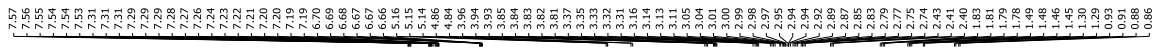

$^{13}$C NMR (101 MHz, $CDCl_3$)

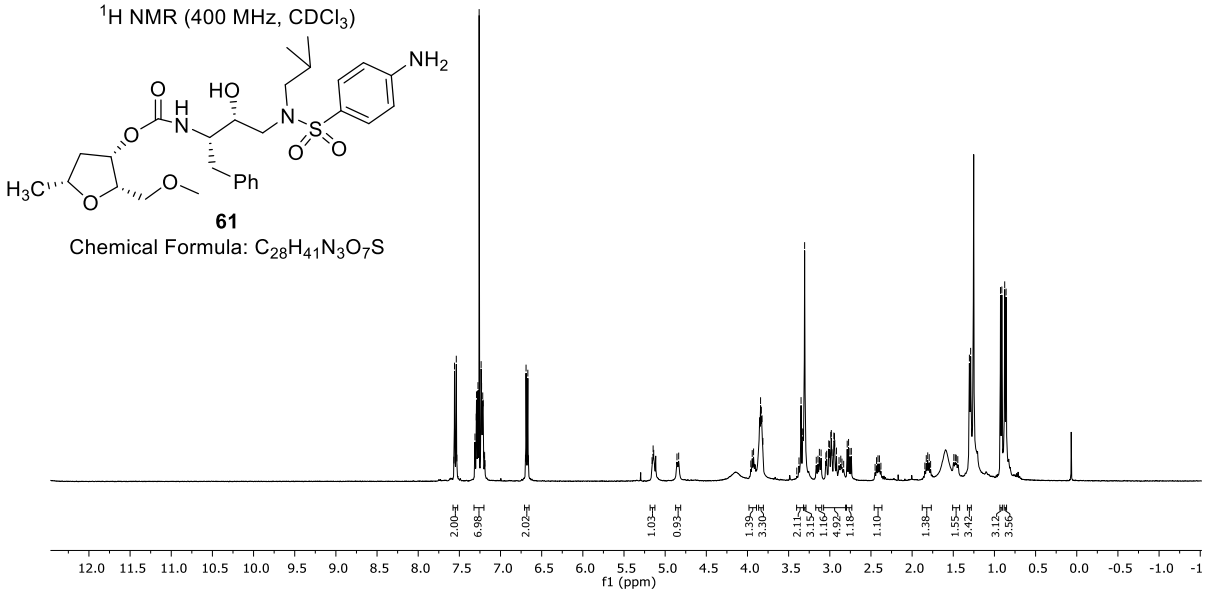


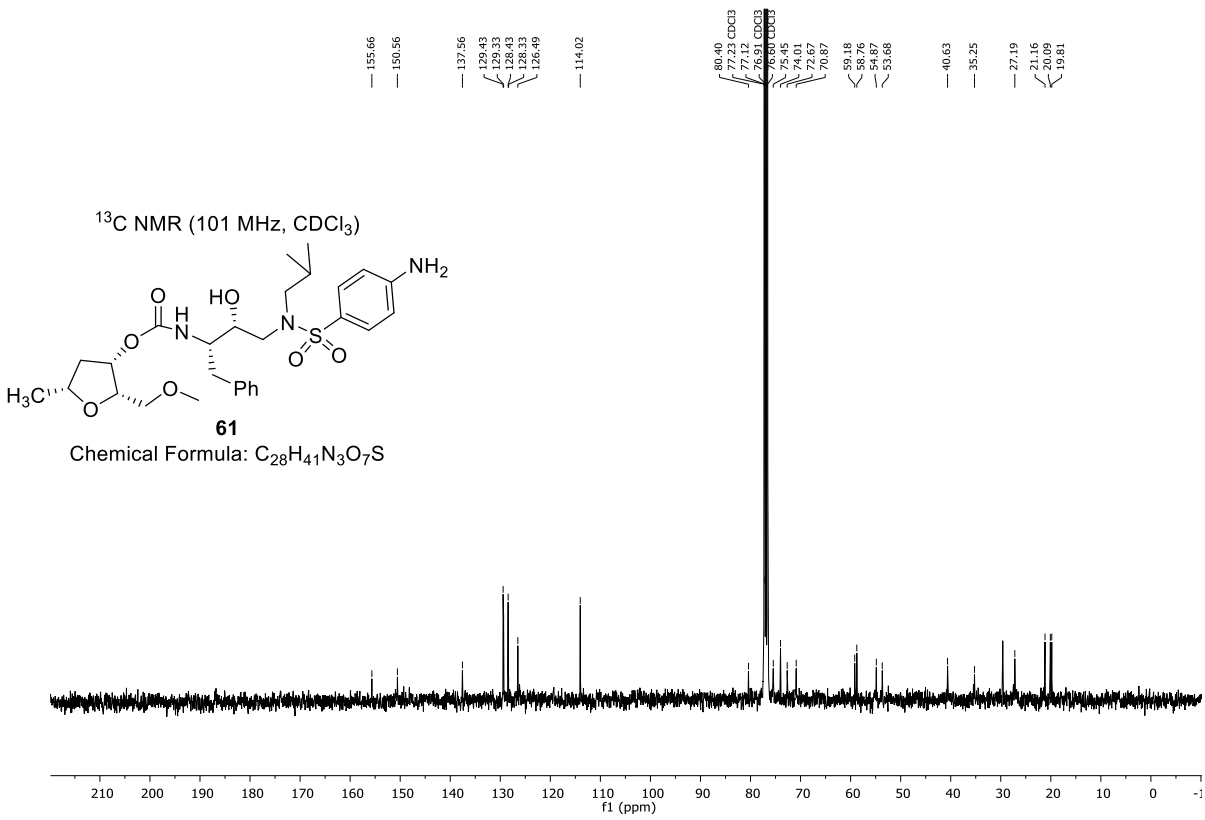
**(+)-54**

```
Current Data Parameters
NAME                DL-1-170
EXPNO                      2
PROCNO                     1

F2 - Acquisition Parameters
Date_              20170523
Time                  15.36
INSTRUM               spect
PROBHD     5 mm QNP  1H
PULPROG             zgpg30
TD                    32768
SOLVENT               CDCl3
NS                      205
DS                        2
SWH              23809.523 Hz
FIDRES            0.726609 Hz
AQ                0.6881780 sec
RG                    16384
DW                  21.000 usec
DE                  30.00 usec
TE                   300.0 K
D12               0.00002000 sec
DL6                 21.00 dB
D1                2.00000000 sec
CPDPRG              waltz16
P31                   76.00 usec
D11               0.03000000 sec
DL5                 18.00 dB
P1                    8.60 usec
SFO1            100.6330000 MHz
NUCLEUS                 13C

F2 - Processing parameters
SI                    16384
SF              100.6220720 MHz
WDW                    EM
SSB                     0
LB                   3.00 Hz
GB                      0
PC                   1.00

1D NMR plot parameters
CX                   20.00 cm
F1P                201.000 ppm
F1                20225.04 Hz
F2P                -1.000 ppm
F2                 -100.62 Hz
PPMCM            10.10000 ppm/cm
HZCM           1016.28290 Hz/cm
```

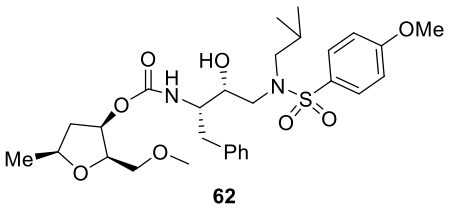

$^{1}$H NMR (400 MHz, CDCl$_3$)
OMe
HO
O
H
N
O
N
S
O
O
H$_3$C
O
O
Ph
60
Chemical Formula: C$_{29}$H$_{42}$N$_2$O$_8$S
f1 (ppm)
$^{13}$C NMR (101 MHz, CDCl$_3$)
OMe
HO
O
H
N
O
N
S
O
O
H$_3$C
O
O
Ph
60
Chemical Formula: C$_{29}$H$_{42}$N$_2$O$_8$S
f1 (ppm)




$^{1}$H NMR (400 MHz, $CDCl_3$)
61
Chemical Formula: $C_{28}H_{41}N_3O_7S$
f1 (ppm)

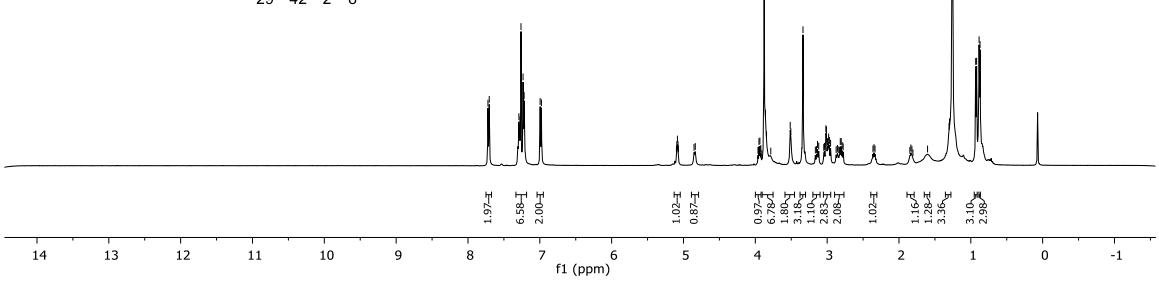

$^{13}$C NMR (101 MHz, $CDCl_3$)
61
Chemical Formula: $C_{28}H_{41}N_3O_7S$
f1 (ppm)

$^{1}$H NMR (500 MHz, $CDCl_3$)

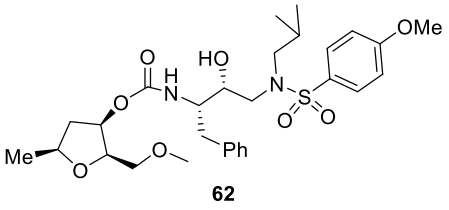


**62**

Chemical Formula: $C_{29}H_{42}N_2O_8S$



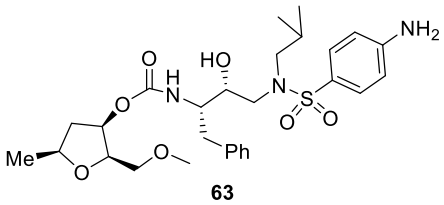
$^{13}$C NMR (126 MHz, $CDCl_3$)



**62**

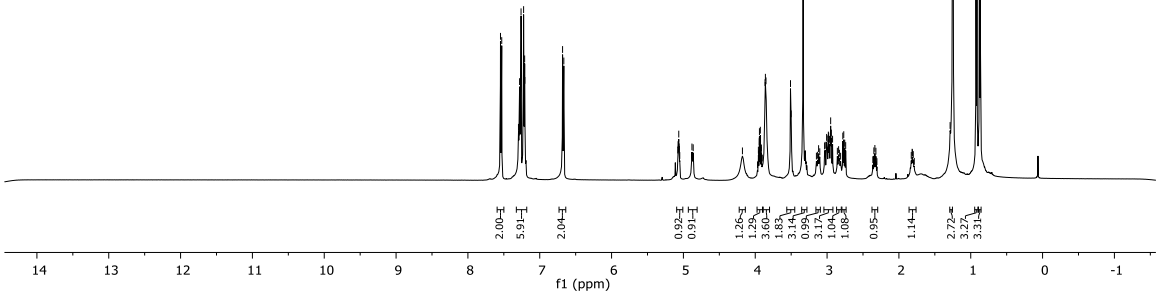
Chemical Formula: $C_{29}H_{42}N_2O_8S$

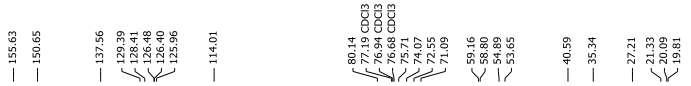
$^{1}$H NMR (500 MHz, $CDCl_3$)



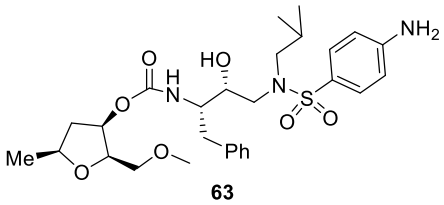
**63**

Chemical Formula: $C_{28}H_{41}N_3O_7S$



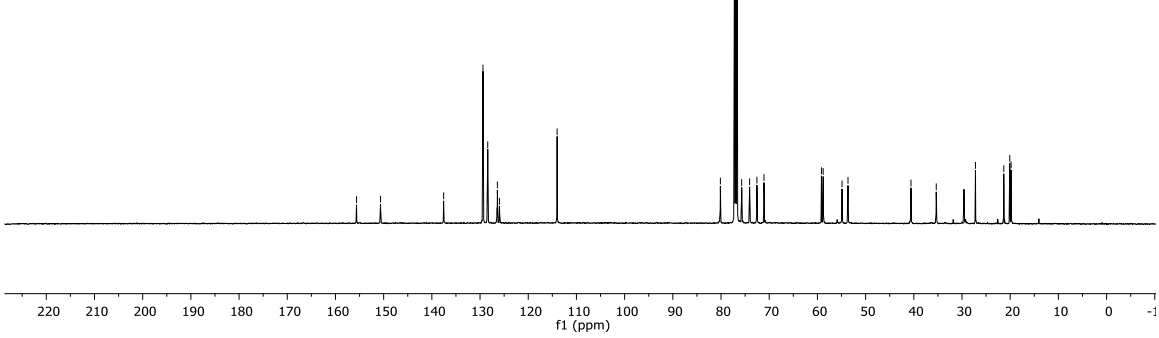


$^{13}$C NMR (126 MHz, $CDCl_3$)

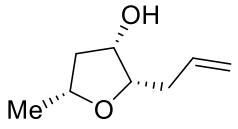


**63**

Chemical Formula: $C_{28}H_{41}N_3O_7S$



$^{1}$H NMR (400 MHz, $CDCl_3$)




**56**



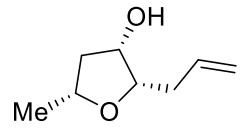

Current Data Parameters
NAME DL_1_165
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20170516
Time 21.31
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 16384
SOLVENT CDCl3
NS 8
DS 2
SWH 5617.978 Hz
FIDRES 0.342894 Hz
AQ 1.4582260 sec
RG 1024
DW 89.000 usec
DE 127.14 usec
TE 300.0 K
D1 2.00000000 sec
P1 9.50 usec
SFO1 400.1694000 MHz
NUCLEUS 1H

F2 - Processing parameters
SI 8192
SF 400.1669660 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
F1P 9.892 ppm
F1 3958.51 Hz
F2P 0.016 ppm
F2 6.41 Hz
PPMCM 0.49381 ppm/cm
HZCM 197.60478 Hz/cm

$^{13}$C NMR (101 MHz, $CDCl_3$)




**56**

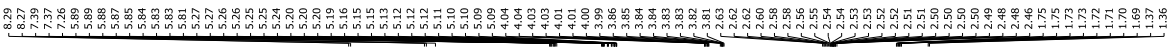



Current Data Parameters
NAME DL_1_165
EXPNO 2
PROCNO 1

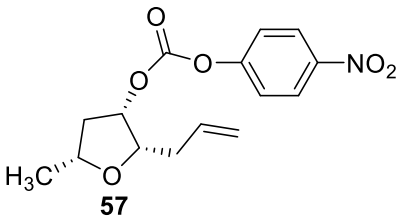
F2 - Acquisition Parameters
Date_ 20170516
Time 21.38
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 98
DS 2
SWH 23809.523 Hz
FIDRES 0.726609 Hz
AQ 0.6881780 sec
RG 16384
DW 21.000 usec
DE 30.00 usec
TE 300.0 K
D12 0.00002000 sec
DL6 21.00 dB
D1 2.00000000 sec
CPDPRG waltz16
P31 76.00 usec
D11 0.03000000 sec
DL5 18.00 dB
P1 8.60 usec
SFO1 100.6330800 MHz
NUCLEUS 13C

F2 - Processing parameters
SI 16384
SF 100.6220720 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.00

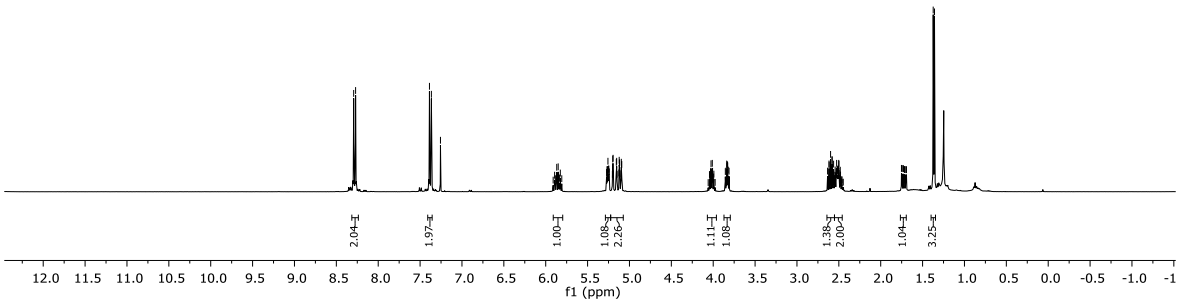
1D NMR plot parameters
CX 20.00 cm
F1P 201.000 ppm
F1 20225.04 Hz
F2P -1.000 ppm
F2 -100.62 Hz
PPMCM 10.10000 ppm/cm
HZCM 1016.28290 Hz/cm



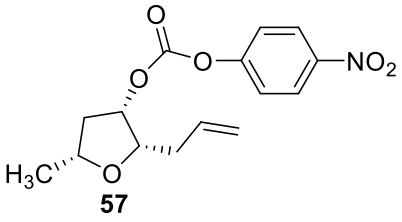
$^{1}$H NMR (400 MHz, $CDCl_3$)



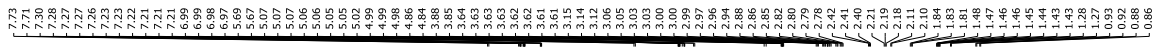
**57**



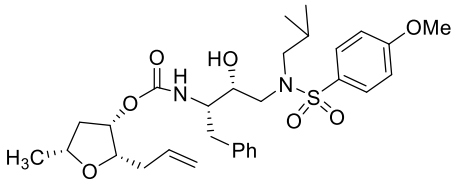
$^{13}$C NMR (101 MHz, $CDCl_3$)



**57**



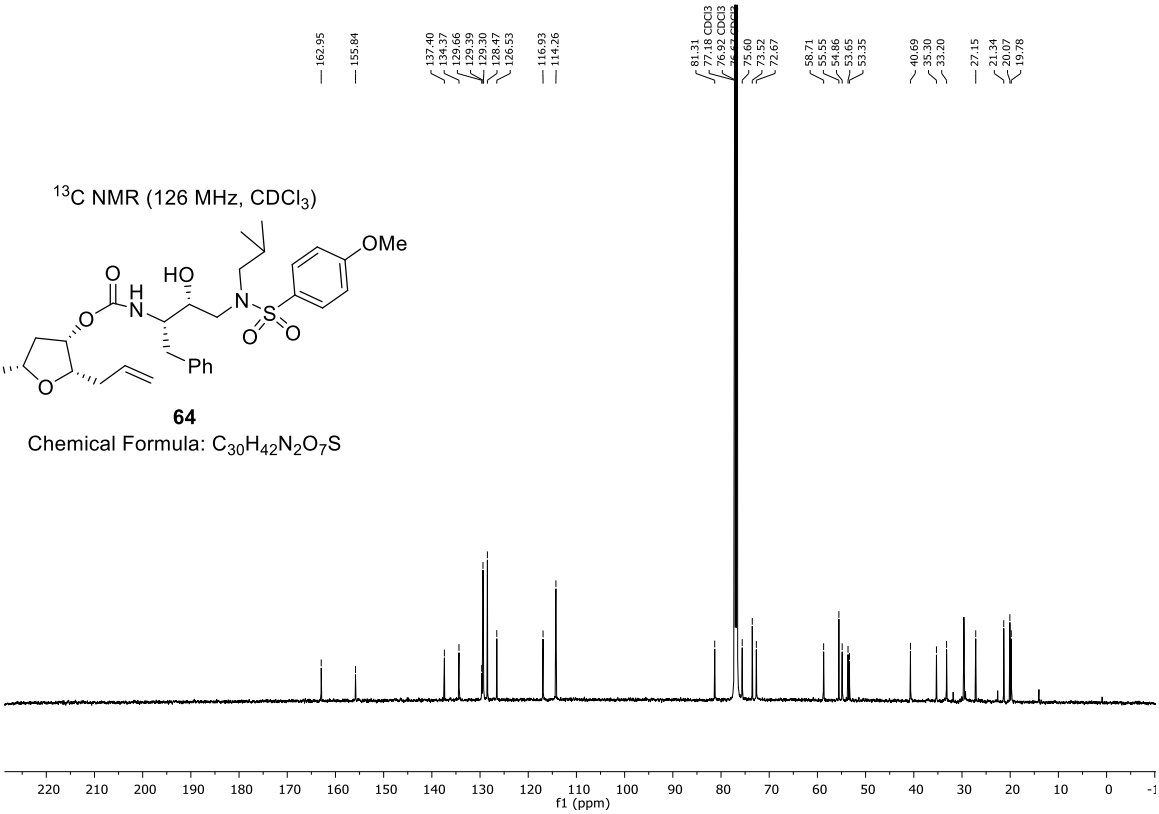
$^{1}$H NMR (500 MHz, $CDCl_3$)



**64**

Chemical Formula: $C_{30}H_{42}N_2O_7S$





$^{13}$C NMR (126 MHz, $CDCl_3$)

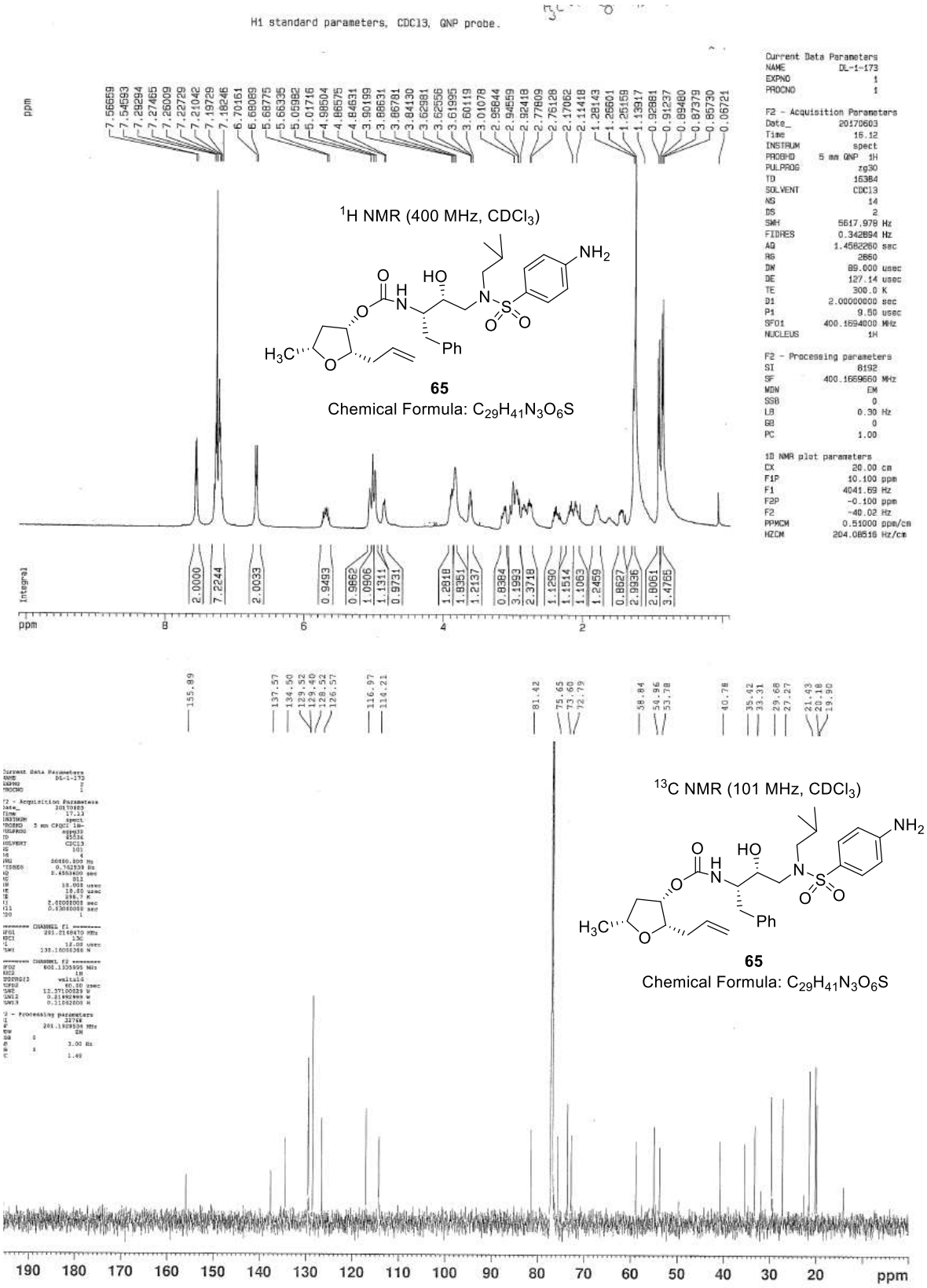


**64**

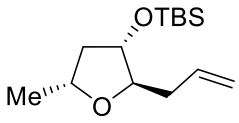
Chemical Formula: $C_{30}H_{42}N_2O_7S$



$^{1}$H NMR (500 MHz, $CDCl_3$)


H1 standard parameters, CDCl3, QNP probe.
$^1$H NMR (400 MHz, $CDCl_3$)
65
Chemical Formula: $C_{29}H_{41}N_3O_6S$
$^{13}$C NMR (101 MHz, $CDCl_3$)
65
Chemical Formula: $C_{29}H_{41}N_3O_6S$
ppm

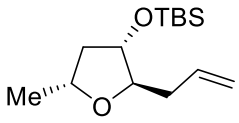
$^{1}$H NMR (400 MHz, $CDCl_3$)




**(+)-49**

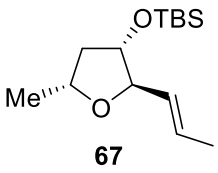



$^{13}$C NMR (101 MHz, $CDCl_3$)




**(+)-49**

$^{1}$H NMR (400 MHz, $CDCl_3$)




**67**



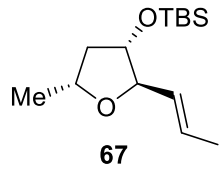

Current Data Parameters
NAME DL_1_128_c
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20170308
Time 15.31
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 15384
SOLVENT CDCl3
NS 8
DS 2
SWH 5617.978 Hz
FIDRES 0.342894 Hz
AQ 1.4582260 sec
RG 715
DW 89.000 usec
DE 127.14 usec
TE 300.0 K
D1 2.00000000 sec
P1 9.50 usec
SF01 400.1694000 MHz
NUCLEUS 1H

F2 - Processing parameters
SI 8192
SF 400.1689660 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
F1P 10.100 ppm
F1 4041.89 Hz
F2P -0.100 ppm
F2 -40.02 Hz
PPMCM 0.51000 ppm/cm
HZCM 204.08516 Hz/cm

$^{13}$C NMR (101 MHz, $CDCl_3$)




**67**



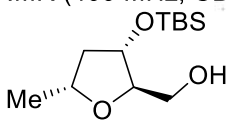

Current Data Parameters
NAME DL_1_128_c
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20170308
Time 15.35
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 209
DS 2
SWH 23809.523 Hz
FIDRES 0.726609 Hz
AQ 0.6881780 sec
RG 16384
DW 21.000 usec
DE 30.00 usec
TE 300.0 K
D12 0.00002000 sec
DL6 21.00 dB
D1 2.00000000 sec
CPDPRG waltz16
PCPD1 76.00 usec
D11 0.03000000 sec
DL5 18.00 dB
P1 8.60 usec
SF01 100.6330000 MHz
NUCLEUS 13C

F2 - Processing parameters
SI 16384
SF 100.6220720 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
F1P 201.000 ppm
F1 20225.04 Hz
F2P -1.000 ppm
F2 -100.62 Hz
PPMCM 10.10000 ppm/cm
HZCM 1016.28290 Hz/cm

$^1$H NMR (400 MHz, $CDCl_3$)




**(+)-68**



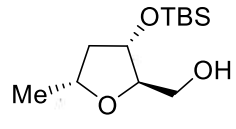

Current Data Parameters
NAME DL_1_130
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20170313
Time 15.37
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zg30
TD 16384
SOLVENT CDCl3
NS 34
DS 2
SWH 5617.978 Hz
FIDRES 0.342894 Hz
AQ 1.4582260 sec
RG 715
DW 89.000 usec
DE 127.14 usec
TE 300.0 K
D1 2.00000000 sec
P1 9.50 usec
SFO1 400.1694000 MHz
NUCLEUS 1H

F2 - Processing parameters
SI 8192
SF 400.1689660 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
F1P 10.100 ppm
F1 4041.69 Hz
F2P -0.100 ppm
F2 -40.02 Hz
PPMCM 0.51000 ppm/cm
HZCM 204.08616 Hz/cm

$^{13}$C NMR (101 MHz, $CDCl_3$)




**(+)-68**



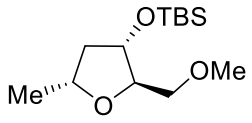

Current Data Parameters
NAME DL_1_130
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20170313
Time 16.12
INSTRUM spect
PROBHD 5 mm QNP 1H
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 177
DS 2
SWH 23809.523 Hz
FIDRES 0.726609 Hz
AQ 0.6881780 sec
RG 16384
DW 21.000 usec
DE 30.00 usec
TE 300.0 K
D12 0.00002000 sec
DL6 21.00 dB
D1 2.00000000 sec
CPDPRG waltz16
P31 76.00 usec
D11 0.03000000 sec
DL5 18.00 dB
P1 8.60 usec
SFO1 100.6330000 MHz
NUCLEUS 13C

F2 - Processing parameters
SI 16384
SF 100.6220720 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
F1P 201.000 ppm
F1 20225.04 Hz
F2P -1.000 ppm
F2 -100.62 Hz
PPMCM 10.10000 ppm/cm
HZCM 1016.28290 Hz/cm

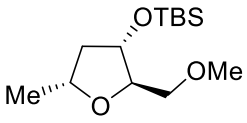
$^1$H NMR (400 MHz, $CDCl_3$)




**(+)-69**

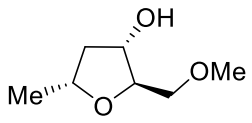



$^{13}$C NMR (101 MHz, $CDCl_3$)




**(+)-69**

$^{1}$H NMR (400 MHz, $CDCl_3$)



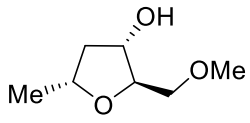

**(+)-70**



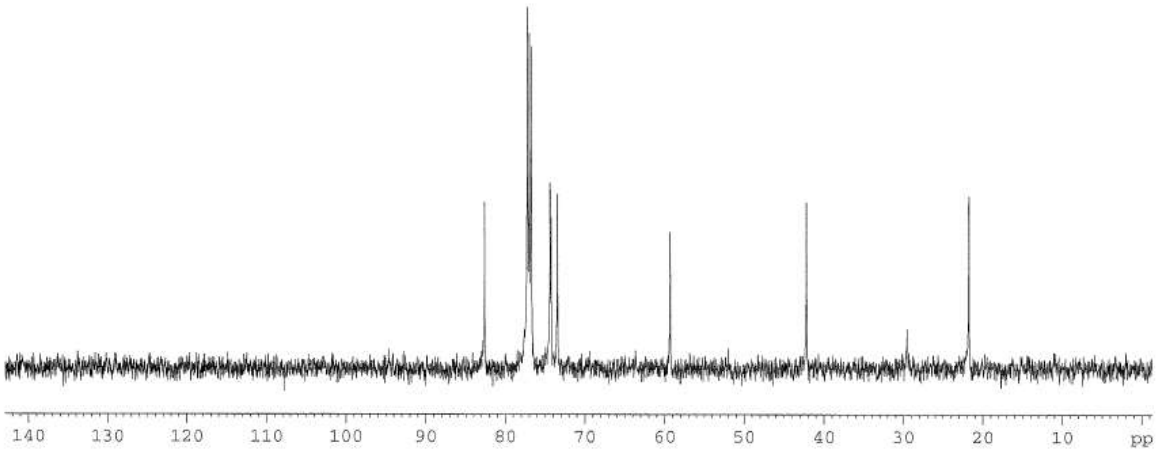




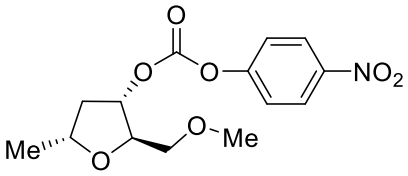
$^{13}$C NMR (101 MHz, $CDCl_3$)




**(+)-70**



$^{1}$H NMR (500 MHz, $CDCl_3$)

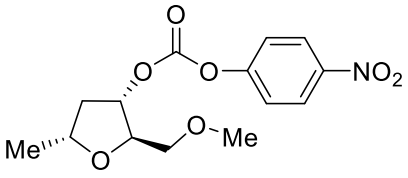


**(+)-71**

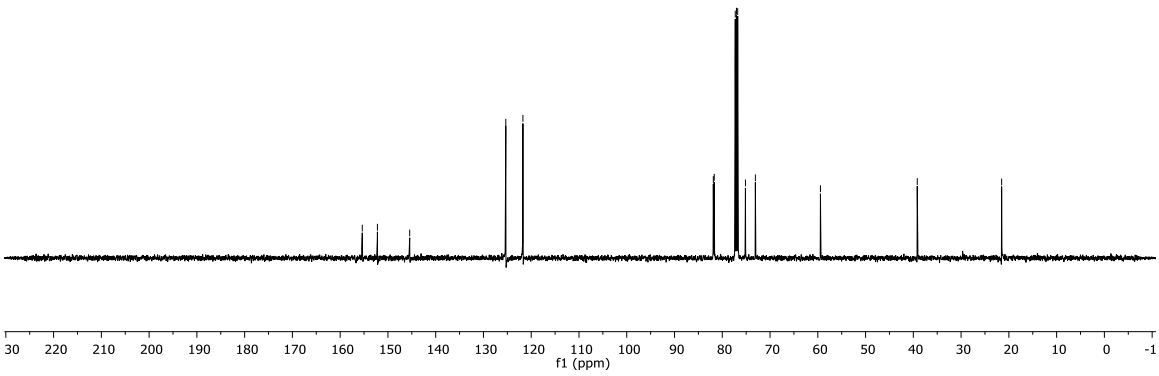


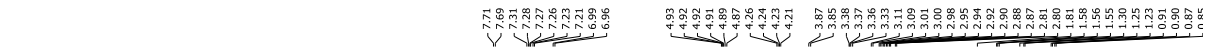


$^{13}$C NMR (126 MHz, $CDCl_3$)

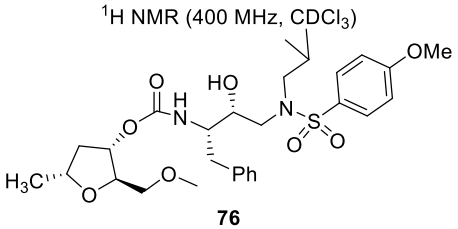


**(+)-71**



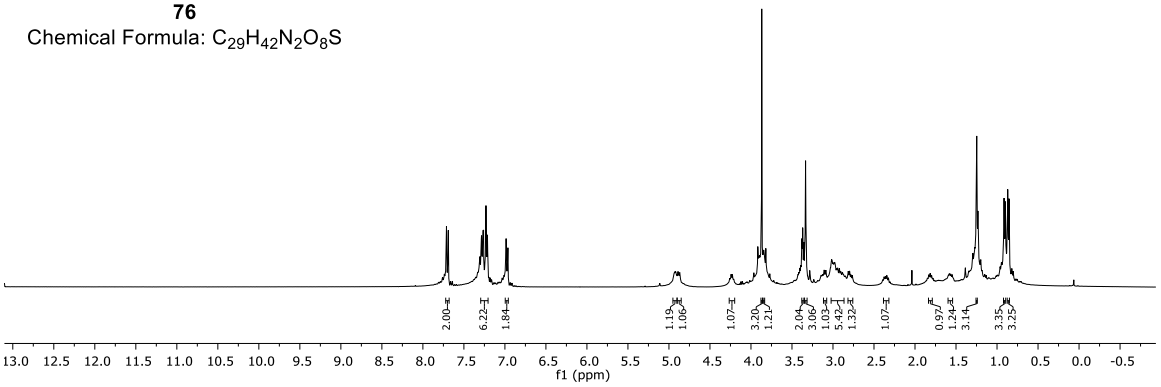


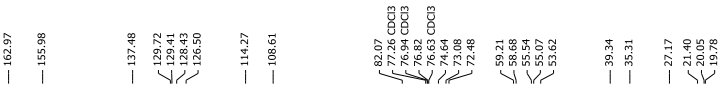
$^{1}$H NMR (400 MHz, $CDCl_3$)



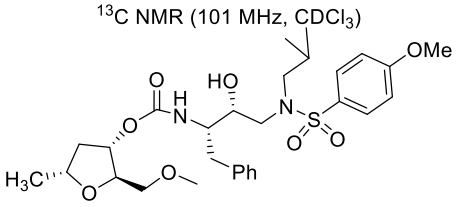
**76**

Chemical Formula: $C_{29}H_{42}N_2O_8S$



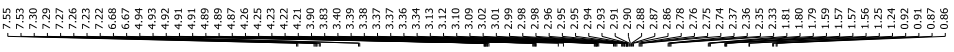


$^{13}$C NMR (101 MHz, $CDCl_3$)

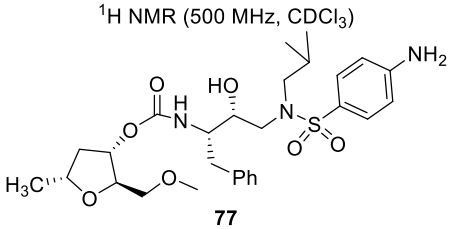


**76**

Chemical Formula: $C_{29}H_{42}N_2O_8S$

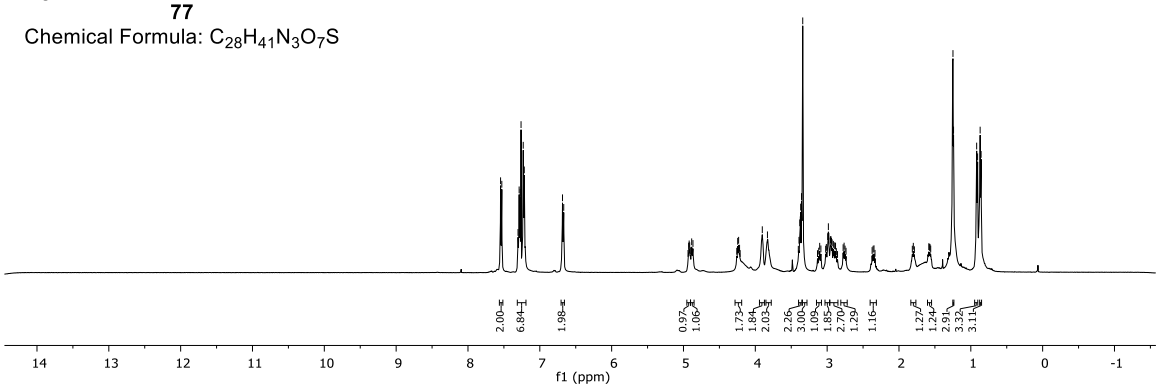


$^{1}$H NMR (500 MHz, $CDCl_3$)

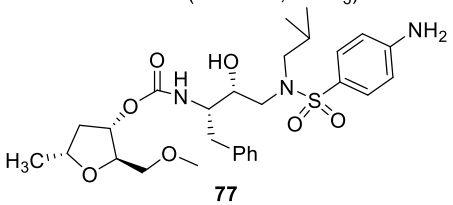


**77**

Chemical Formula: $C_{28}H_{41}N_3O_7S$

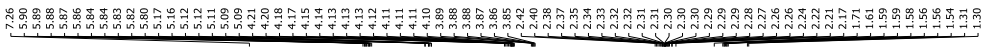


$^{13}$C NMR (126 MHz, $CDCl_3$)

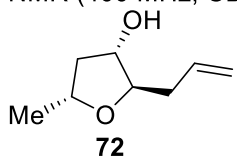


**77**

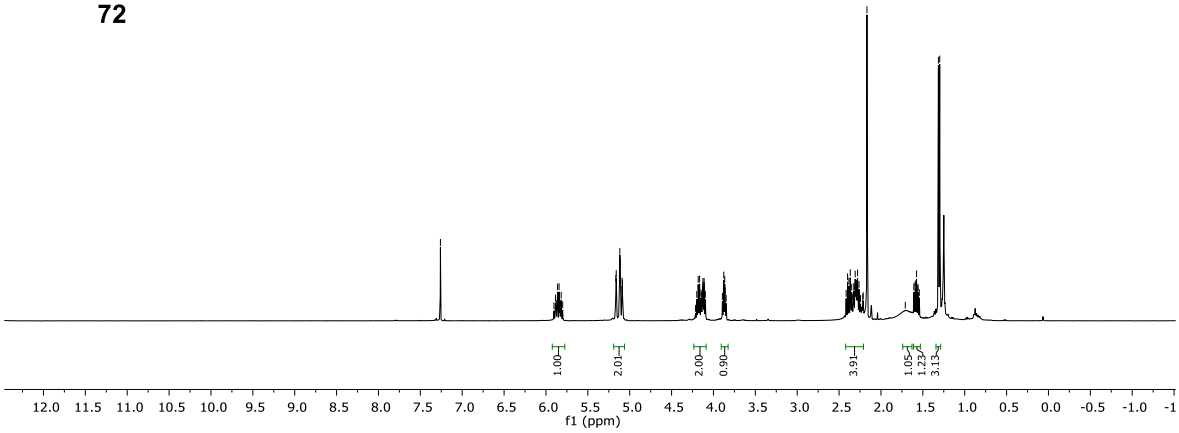
Chemical Formula: $C_{28}H_{41}N_3O_7S$

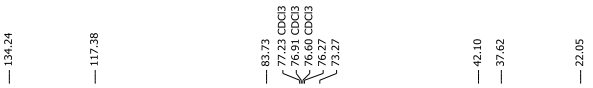


$^{1}$H NMR (400 MHz, $CDCl_3$)

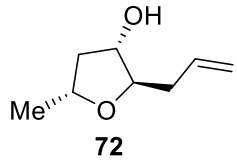



**72**

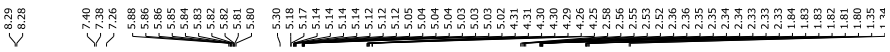


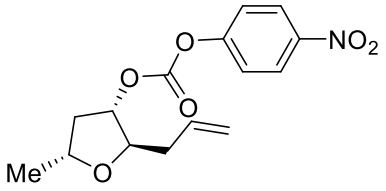

$^{13}$C NMR (101 MHz, $CDCl_3$)



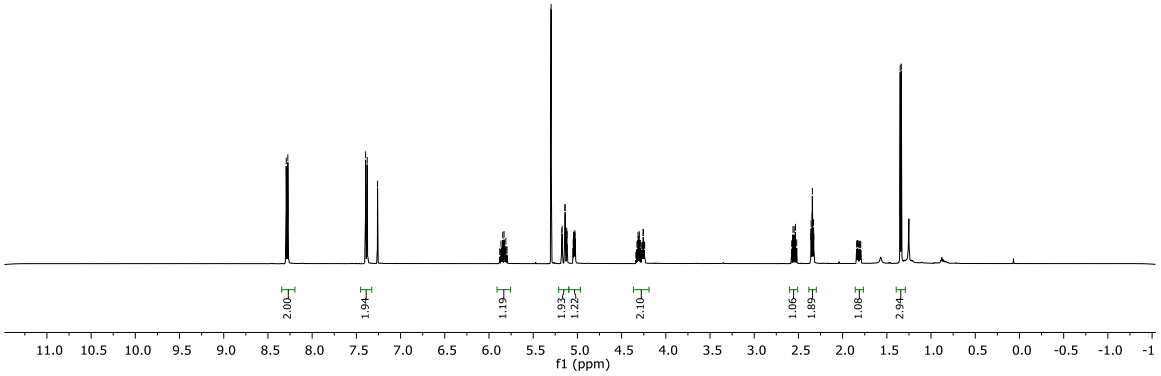

**72**



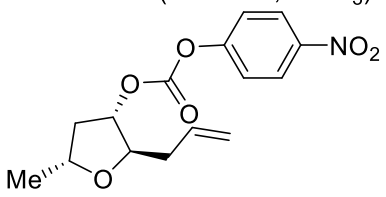
$^{1}$H NMR (500 MHz, $CDCl_3$)



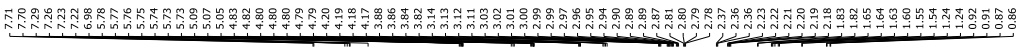
**73**



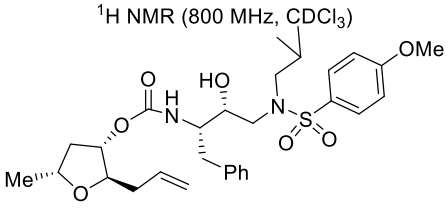
$^{13}$C NMR (126 MHz, $CDCl_3$)



**73**

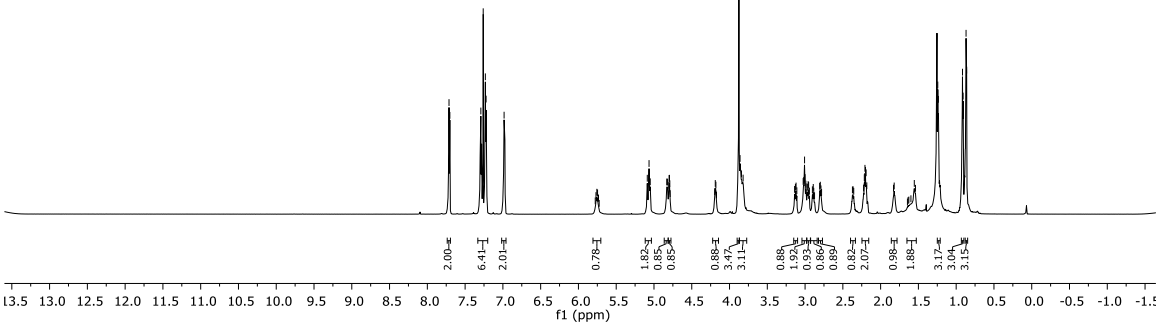


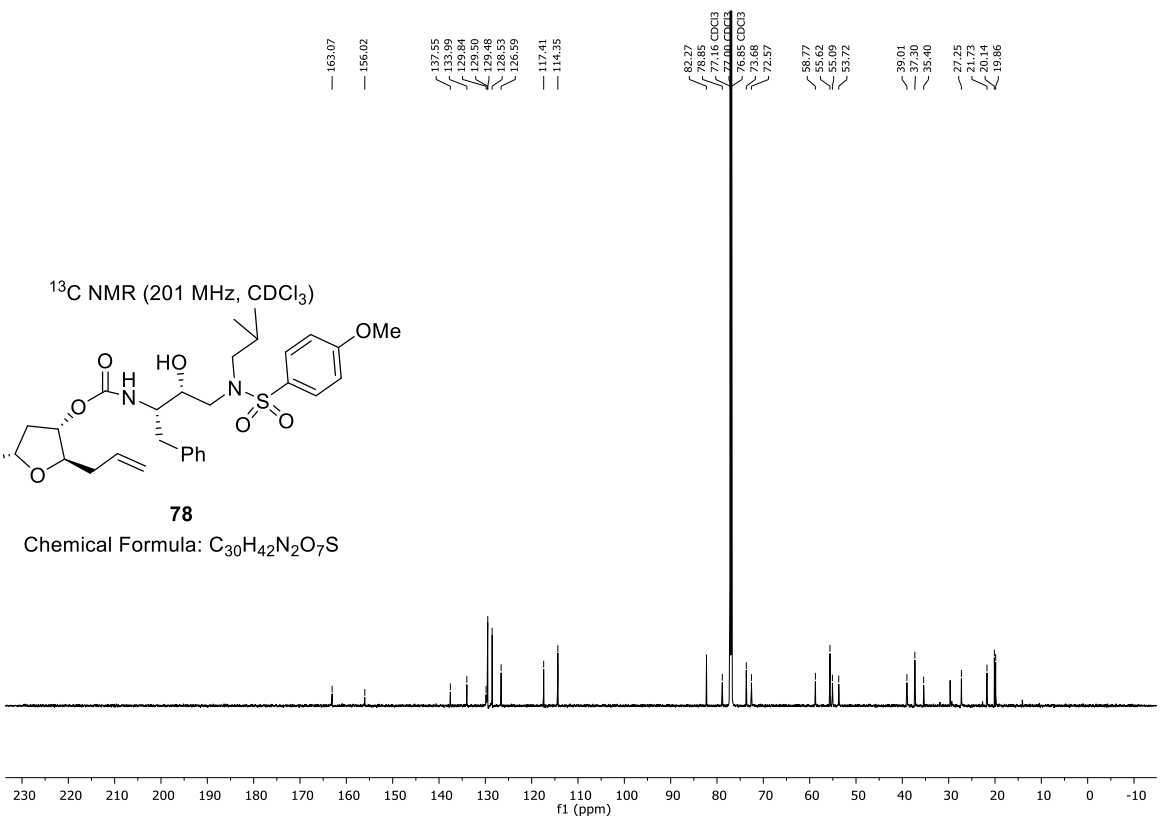
$^{1}$H NMR (800 MHz, $CDCl_3$)



**78**

Chemical Formula: $C_{30}H_{42}N_2O_7S$



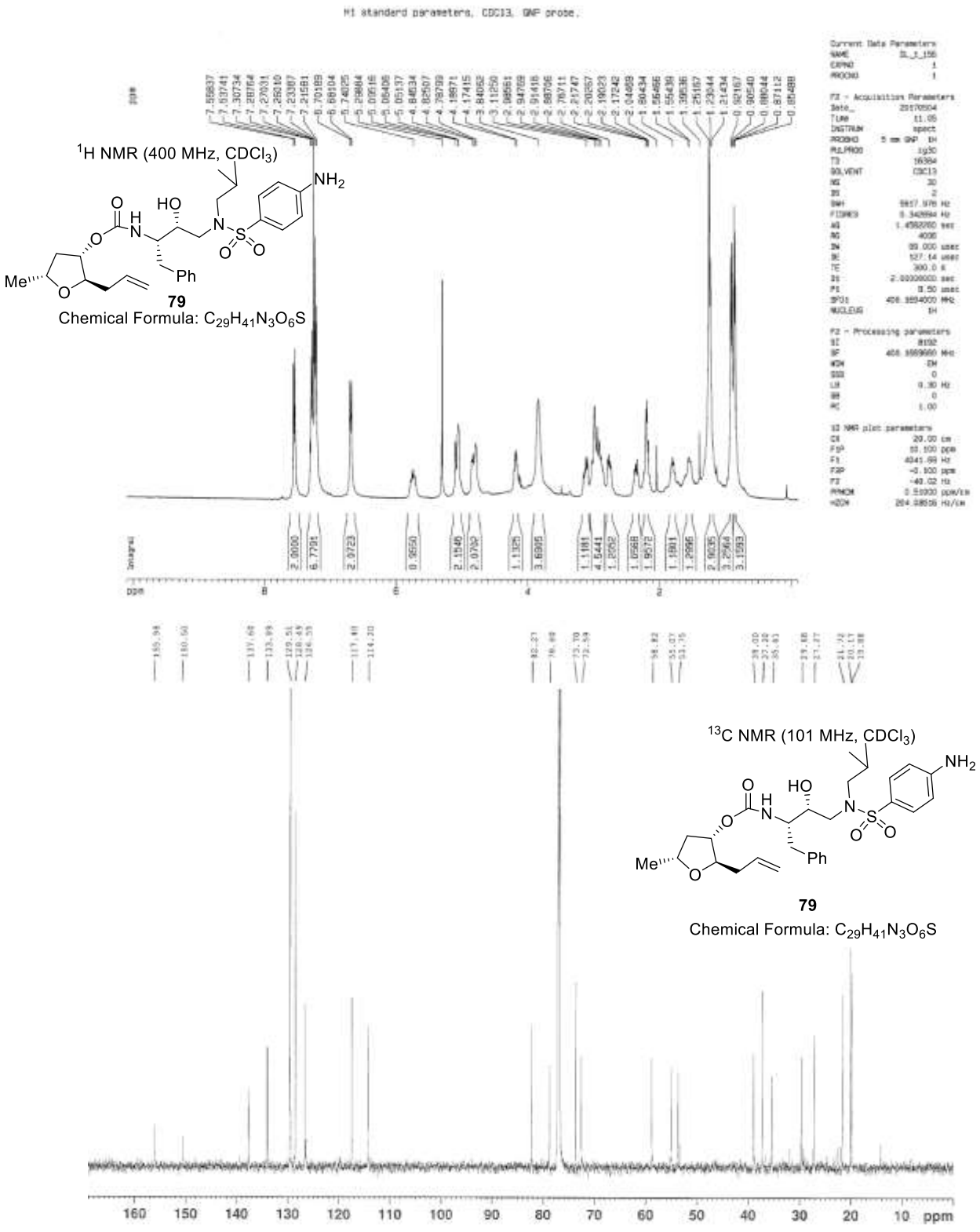


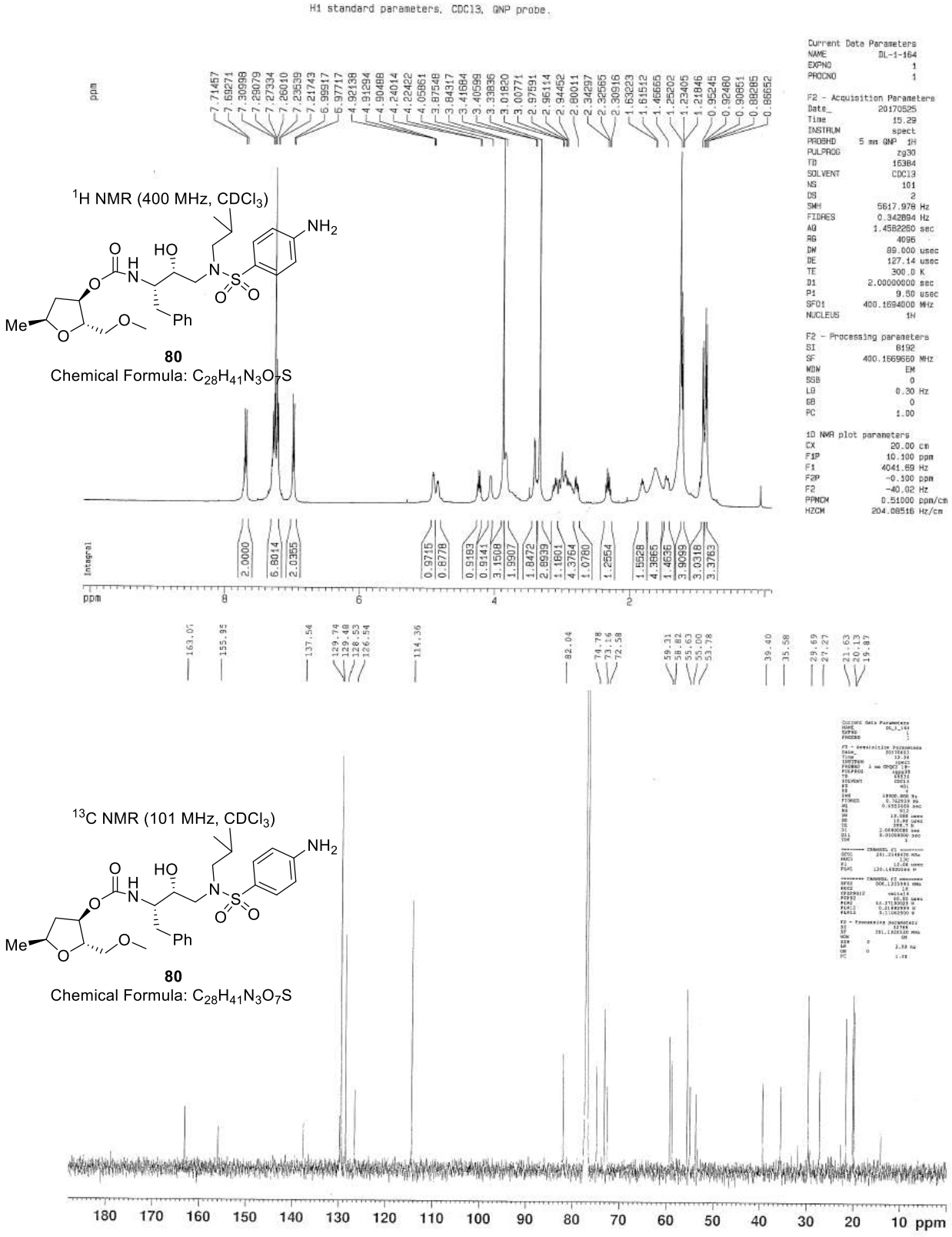
$^{13}$C NMR (201 MHz, $CDCl_3$)

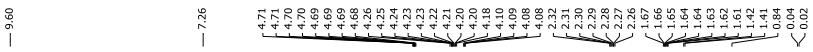


**78**

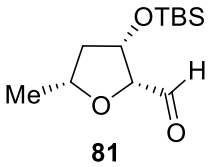
Chemical Formula: $C_{30}H_{42}N_2O_7S$


$^1$H NMR (400 MHz, $CDCl_3$)
$^{13}$C NMR (101 MHz, $CDCl_3$)
79
Chemical Formula: $C_{29}H_{41}N_3O_6S$


H1 standard parameters, CDCl3, QNP probe.
1H NMR (400 MHz, CDCl3)
80
Chemical Formula: C28H41N3O7S
13C NMR (101 MHz, CDCl3)
80
Chemical Formula: C28H41N3O7S




$^{1}$H NMR (400 MHz, $CDCl_3$)

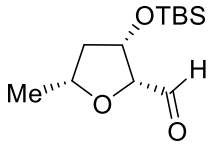



**81**

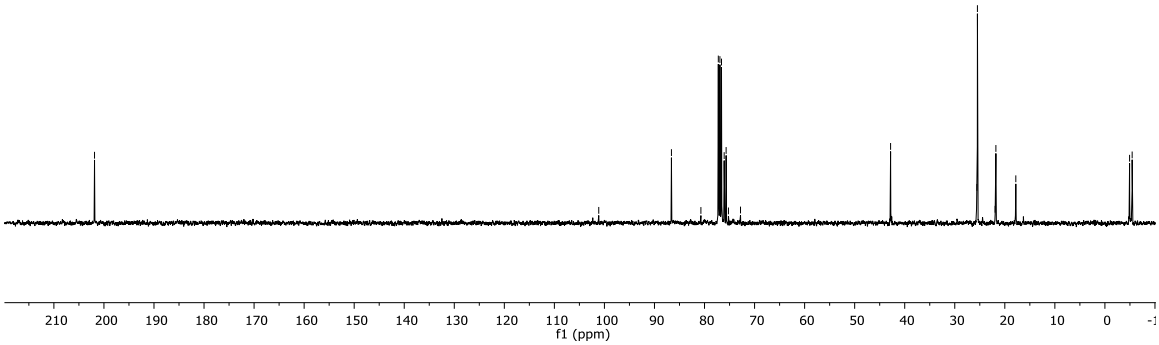




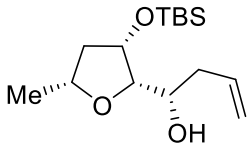
$^{13}$C NMR (101 MHz, $CDCl_3$)




**81**



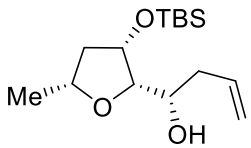
$^{1}$H NMR (400 MHz, $CDCl_3$)




**82**

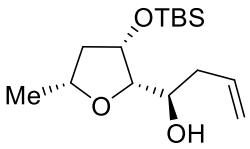



$^{13}$C NMR (101 MHz, $CDCl_3$)




**82**

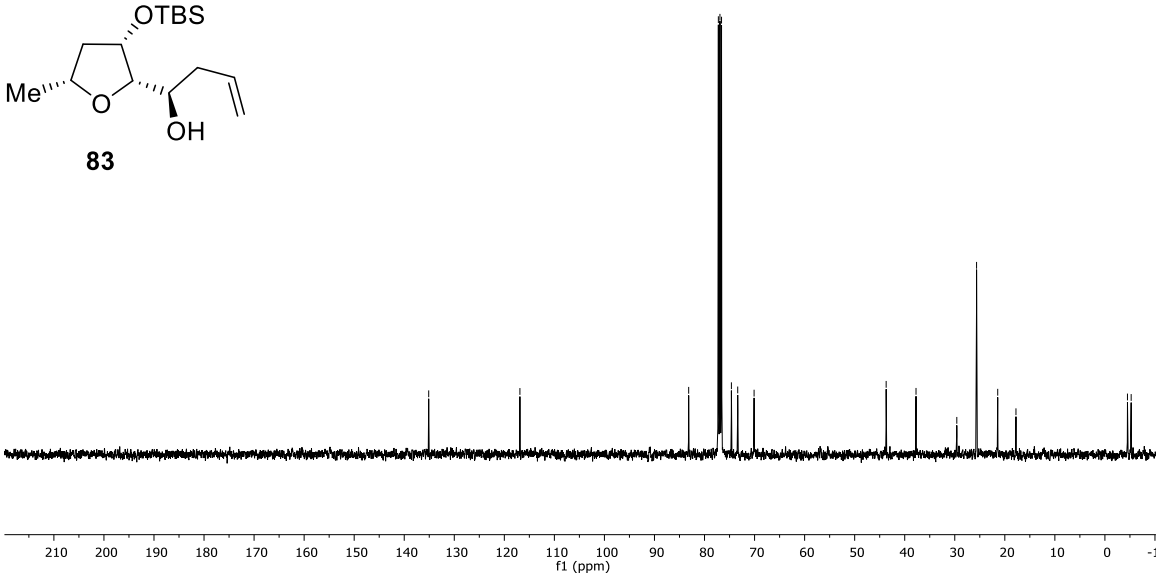
$^{1}$H NMR (400 MHz, $CDCl_3$)

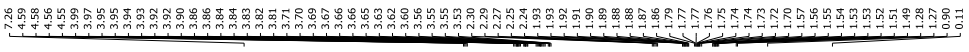



**83**

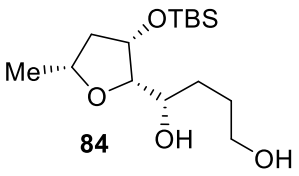



$^{13}$C NMR (101 MHz, $CDCl_3$)





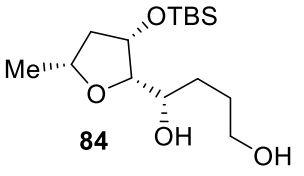
$^{1}$H NMR (400 MHz, $CDCl_3$)



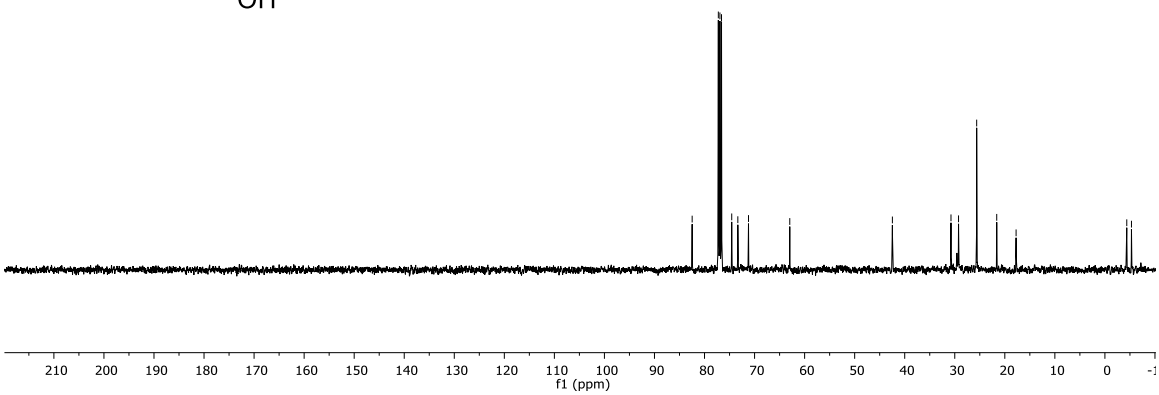

**84**

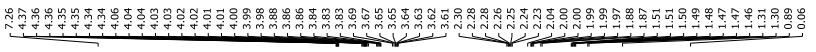



$^{13}$C NMR (101 MHz, $CDCl_3$)

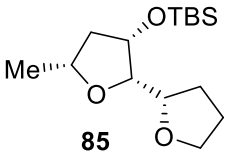



**84**





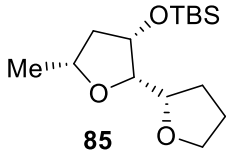
$^{1}$H NMR (400 MHz, $CDCl_3$)



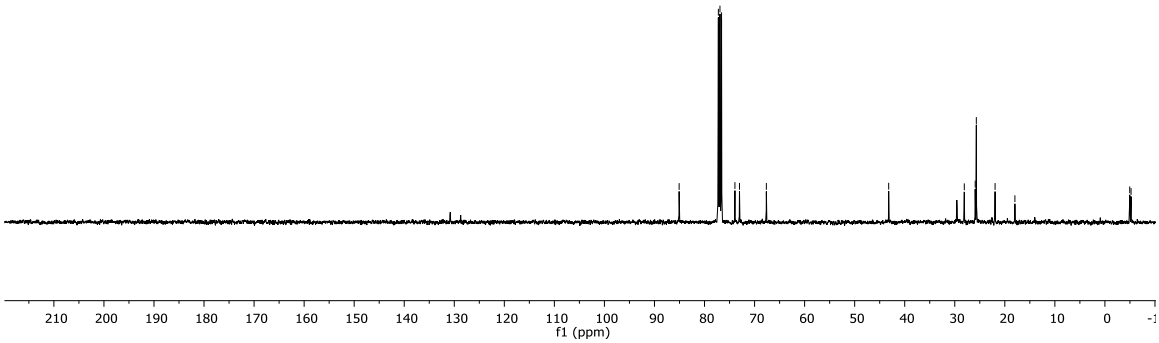

**85**

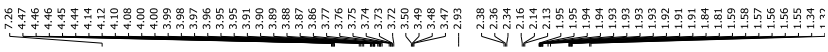



$^{13}$C NMR (101 MHz, $CDCl_3$)

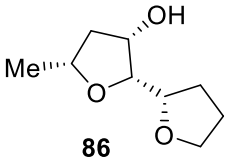



**85**

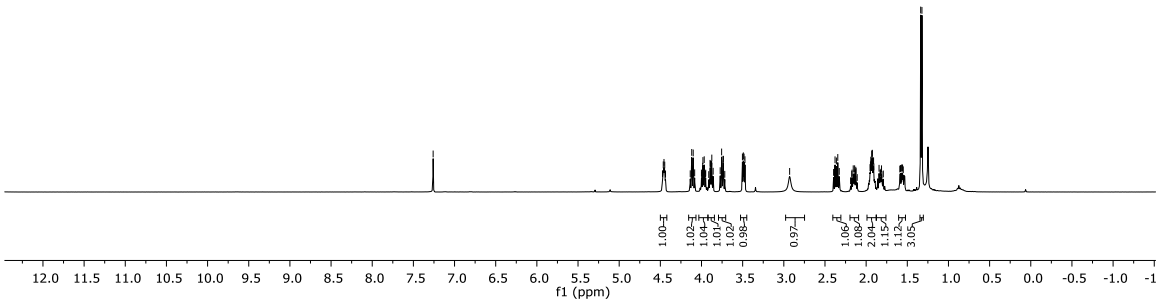




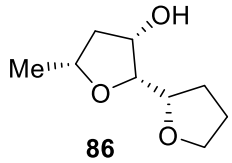
$^{1}$H NMR (400 MHz, $CDCl_3$)



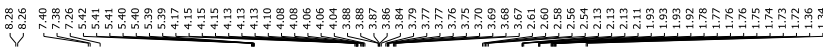
**86**



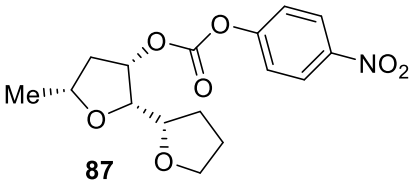
$^{13}$C NMR (101 MHz, $CDCl_3$)



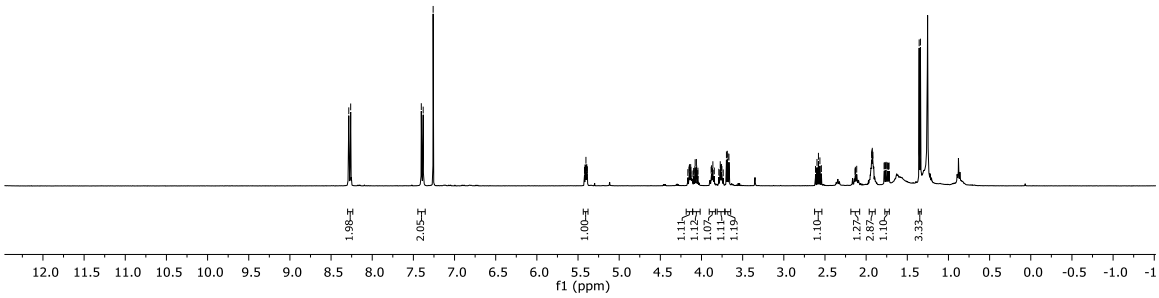
**86**



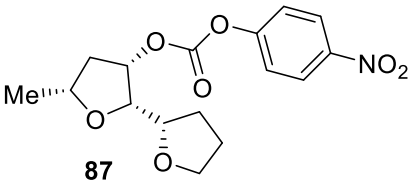
$^{1}$H NMR (400 MHz, $CDCl_3$)




**87**

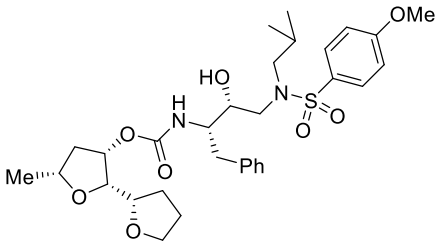



$^{13}$C NMR (101 MHz, $CDCl_3$)



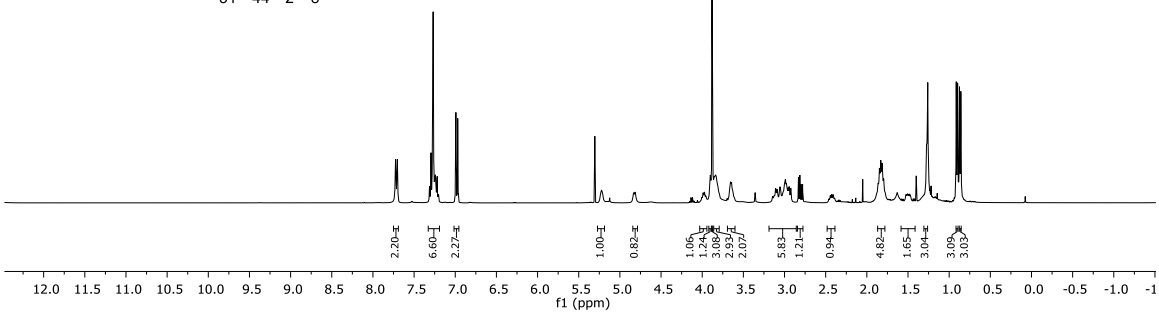

**87**

$^{1}$H NMR (400 MHz, $CDCl_3$)



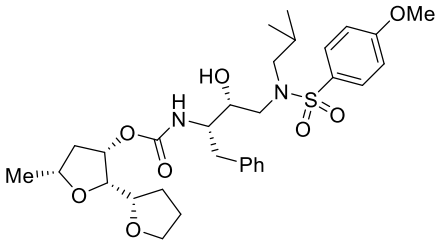

**92**

Chemical Formula: $C_{31}H_{44}N_2O_8S$



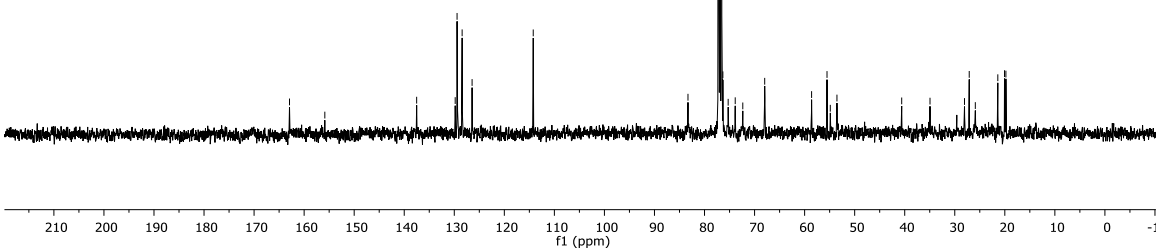


$^{13}$C NMR (101 MHz, $CDCl_3$)

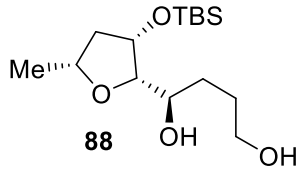



**92**

Chemical Formula: $C_{31}H_{44}N_2O_8S$



$^{1}$H NMR (400 MHz, $CDCl_3$)

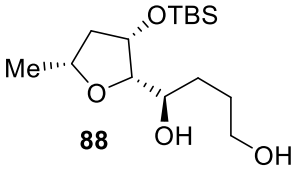




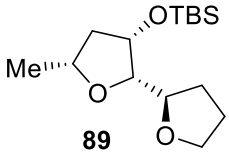





$^{13}$C NMR (101 MHz, $CDCl_3$)



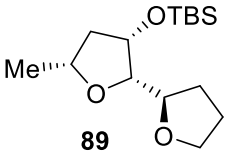
$^{1}$H NMR (400 MHz, $CDCl_3$)



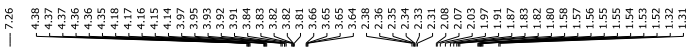

**89**



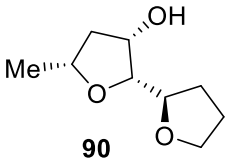

$^{13}$C NMR (101 MHz, $CDCl_3$)



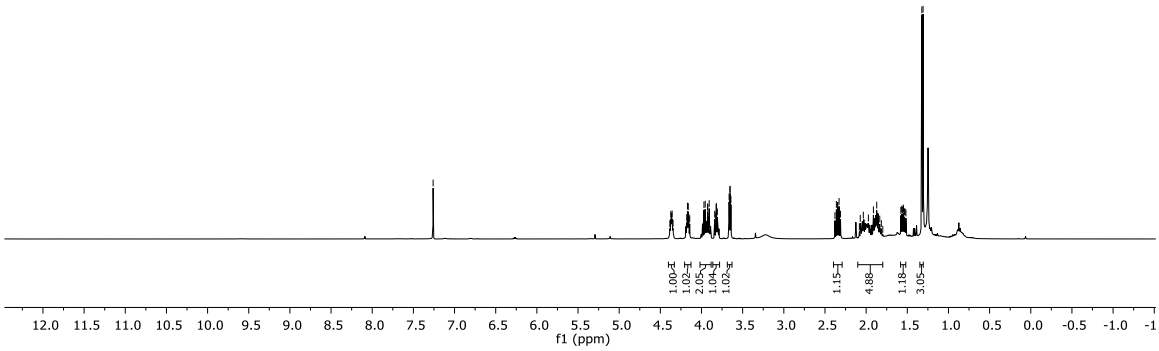

**89**



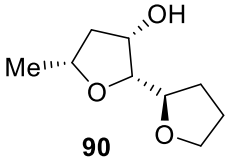

$^{1}$H NMR (400 MHz, $CDCl_3$)



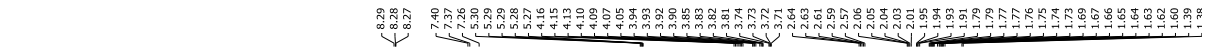

**90**



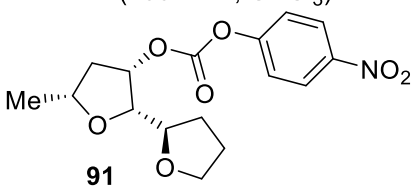

$^{13}$C NMR (101 MHz, $CDCl_3$)



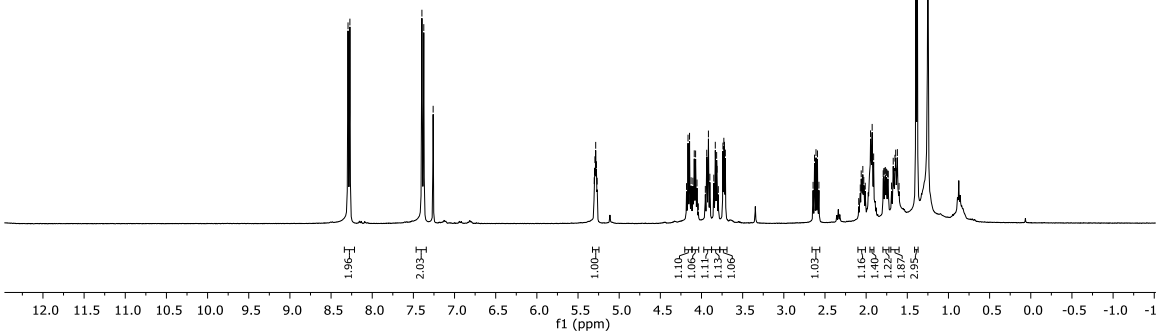

**90**

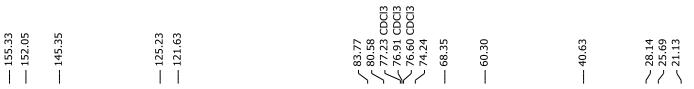


$^{1}$H NMR (400 MHz, $CDCl_3$)

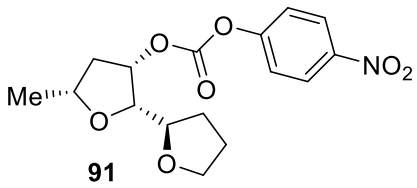



**91**

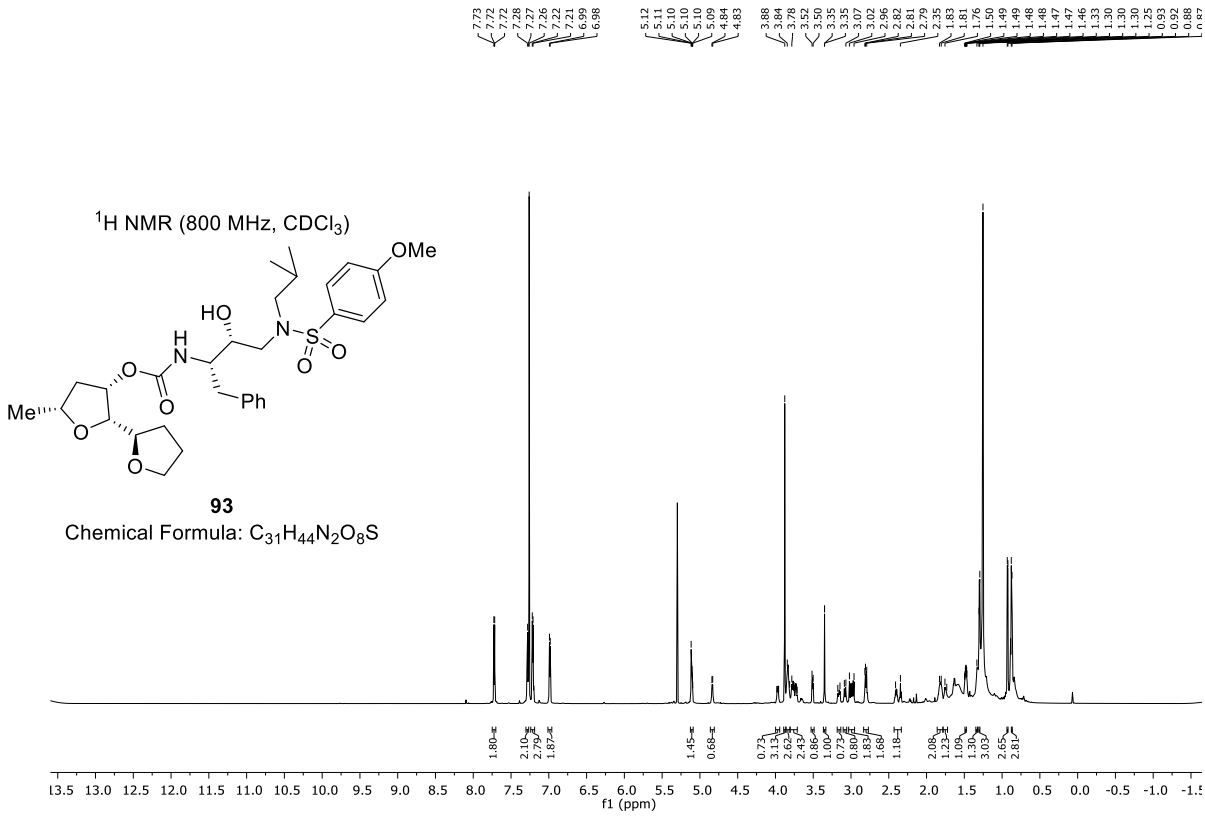


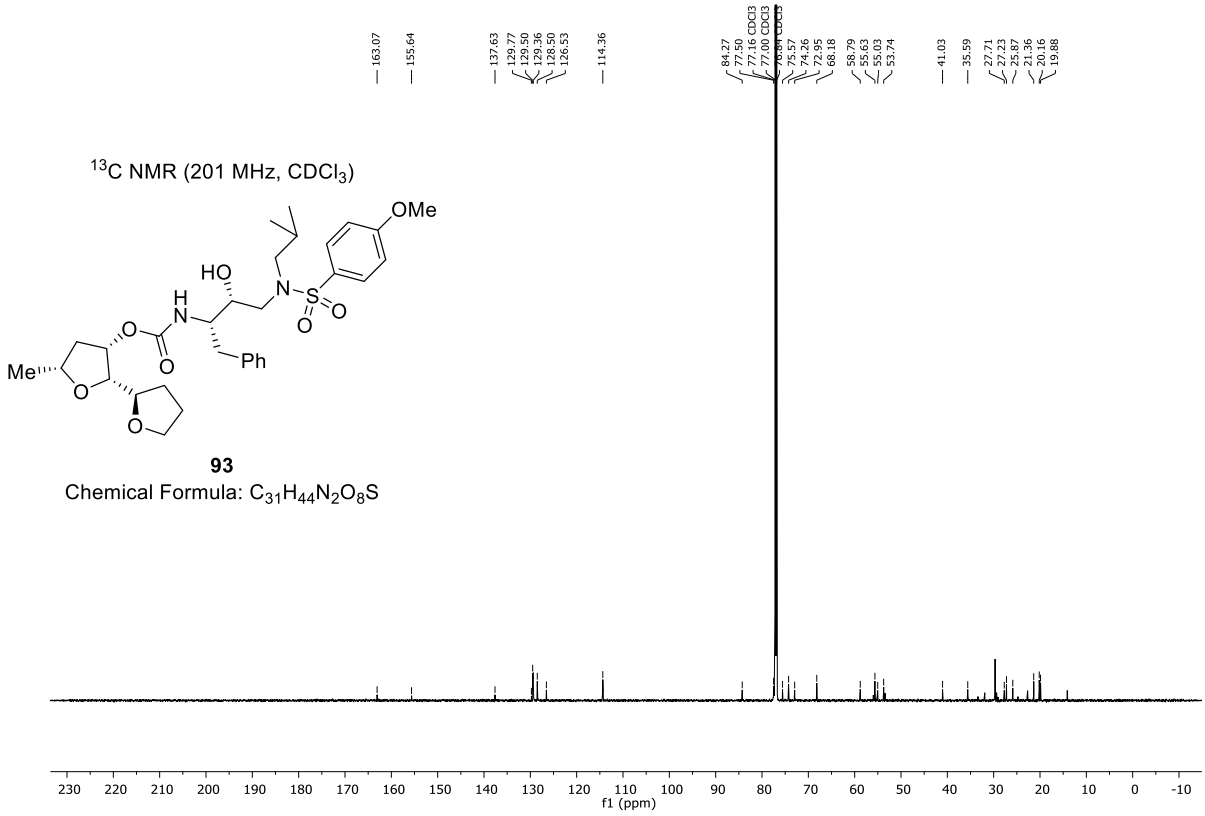




$^{13}$C NMR (101 MHz, $CDCl_3$)

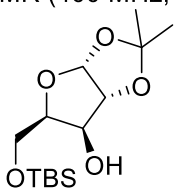



**91**


$^1$H NMR (800 MHz, $CDCl_3$)
OMe
HO
N
S
O
H
N
O
O
Ph
Me
O
O
93
Chemical Formula: $C_{31}H_{44}N_2O_8S$
f1 (ppm)


$^{13}$C NMR (201 MHz, $CDCl_3$)
OMe
HO
N
S
O
H
N
O
O
Ph
Me
O
O
93
Chemical Formula: $C_{31}H_{44}N_2O_8S$
f1 (ppm)

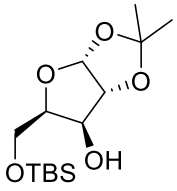
$^{1}$H NMR (400 MHz, $CDCl_3$)




**95**

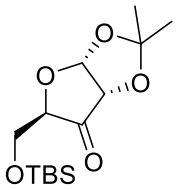



$^{13}$C NMR (101 MHz, $CDCl_3$)




**95**

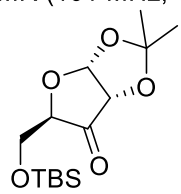
$^{1}$H NMR (400 MHz, $CDCl_3$)




**96**

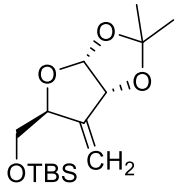



$^{13}$C NMR (101 MHz, $CDCl_3$)




**96**

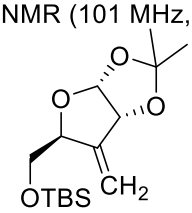
$^{1}$H NMR (400 MHz, $CDCl_3$)



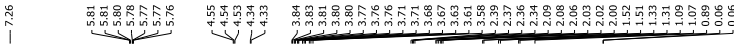

**97**



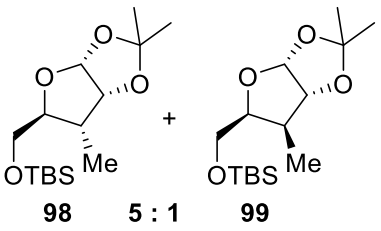

$^{13}$C NMR (101 MHz, $CDCl_3$)



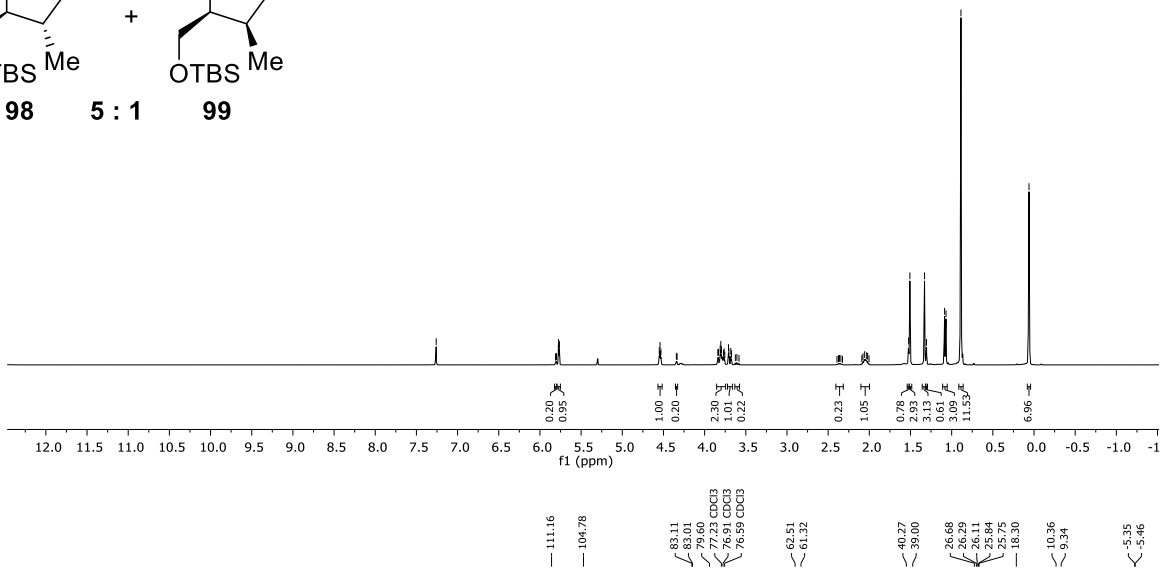

**97**



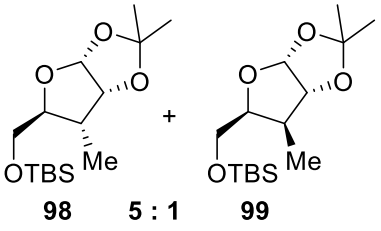
$^{1}$H NMR (400 MHz, $CDCl_3$)



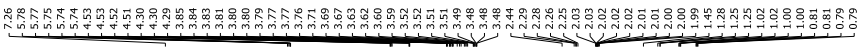

**98** **5 : 1** **99**



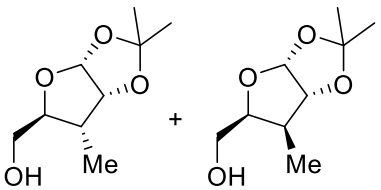

$^{13}$C NMR (101 MHz, $CDCl_3$)




**98** **5 : 1** **99**



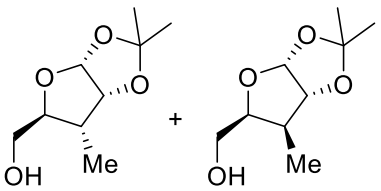
$^{1}$H NMR (400 MHz, $CDCl_3$)



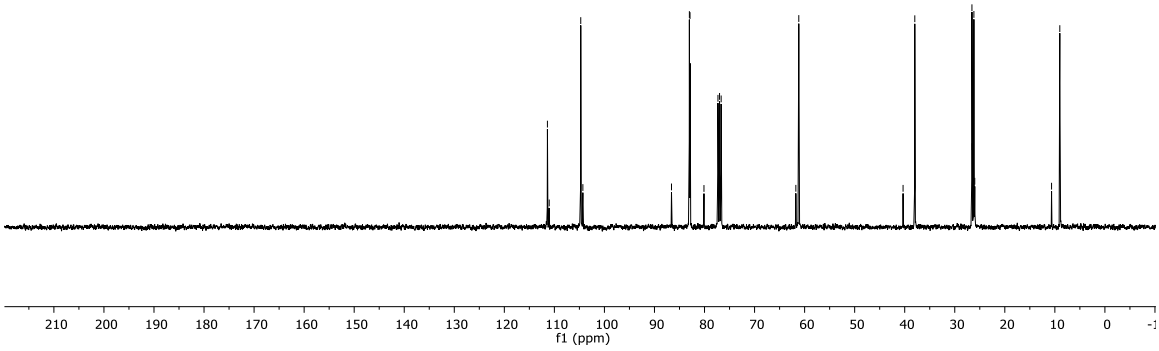
**100** **5 : 1** **101**



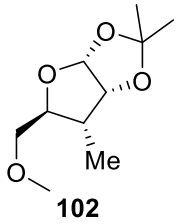
$^{13}$C NMR (101 MHz, $CDCl_3$)



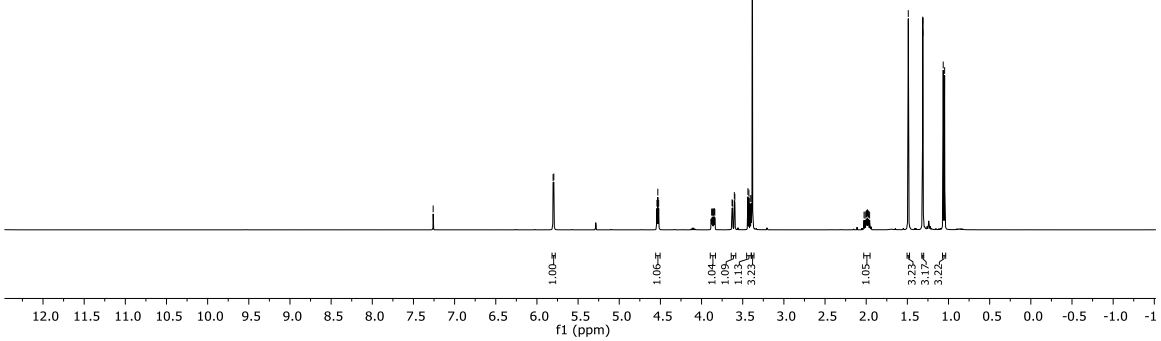
**101** **5 : 1** **101**




$^{1}$H NMR (400 MHz, $CDCl_3$)

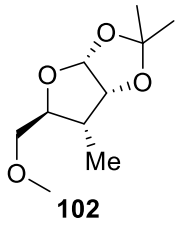



**102**

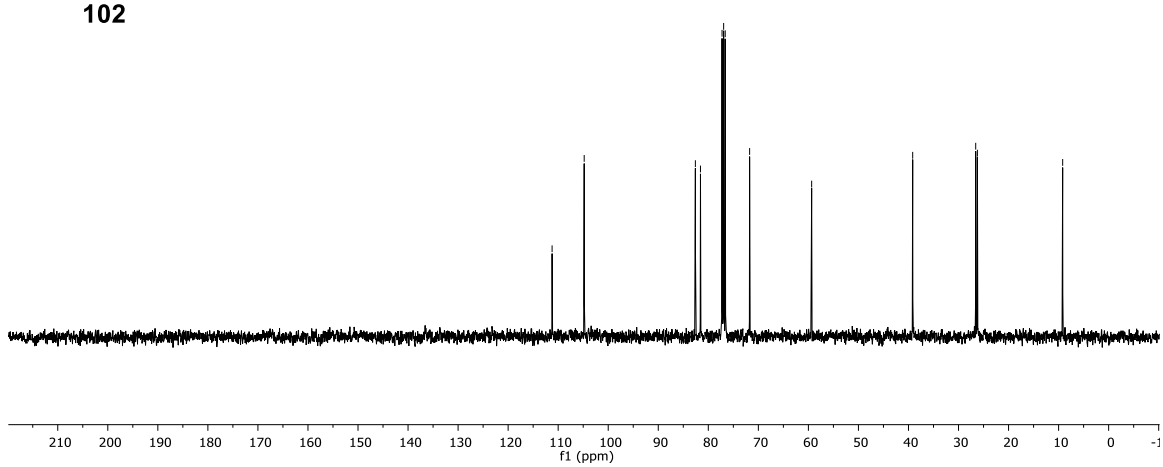


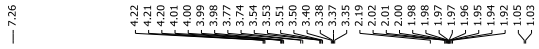


$^{13}$C NMR (101 MHz, $CDCl_3$)

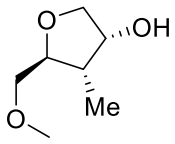



**102**

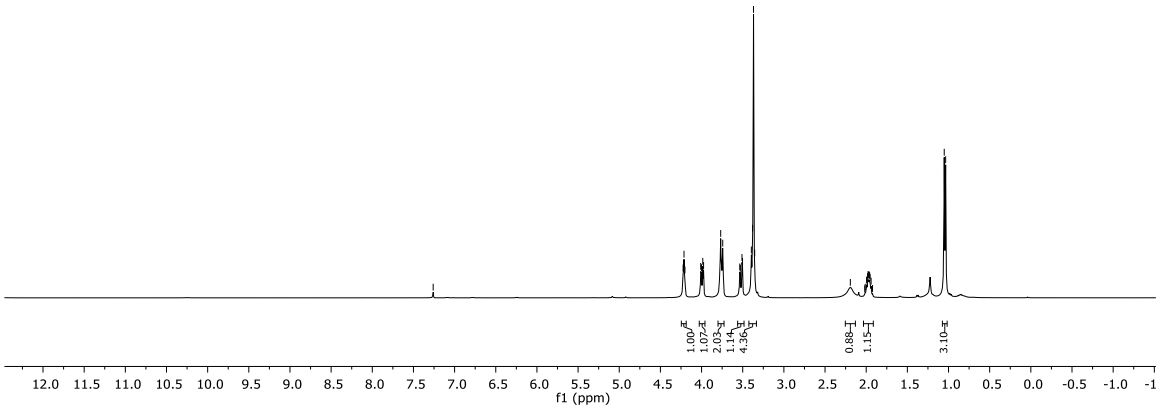





$^{1}$H NMR (400 MHz, $CDCl_3$)

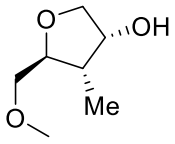



**104**

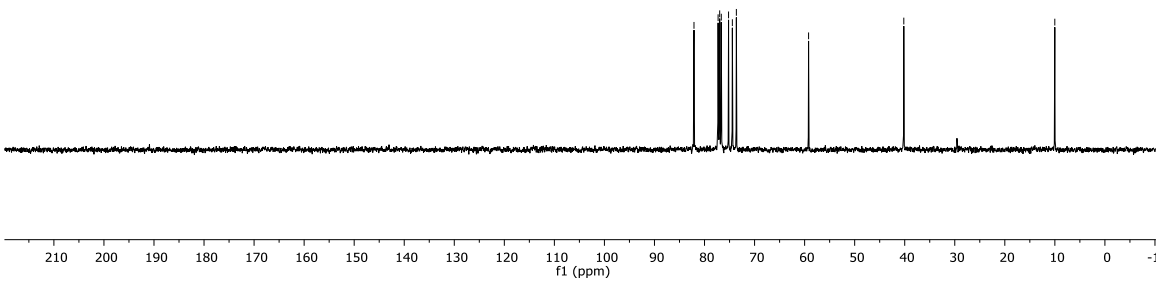




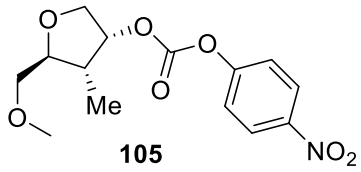
$^{13}$C NMR (101 MHz, $CDCl_3$)




**104**



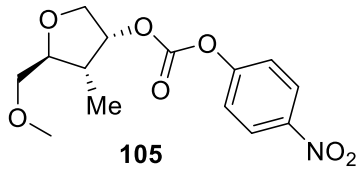
$^{1}$H NMR (400 MHz, $CDCl_3$)



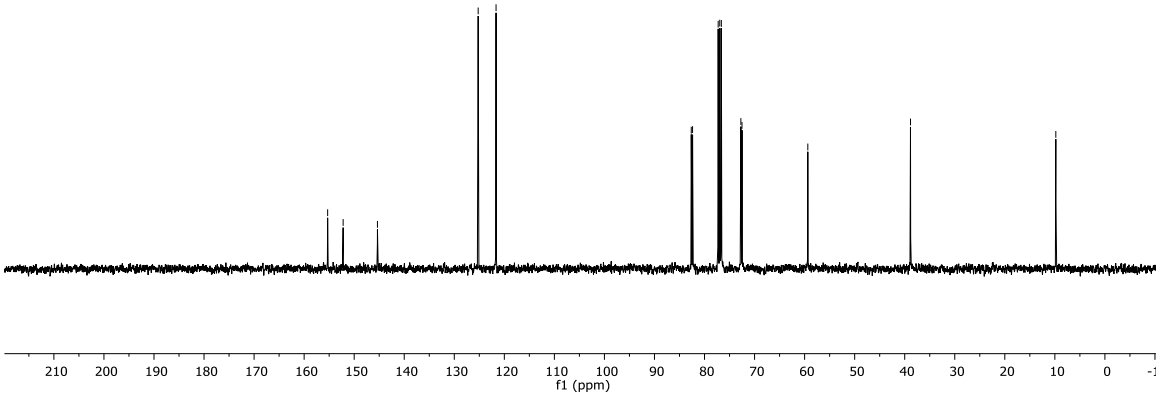
**105**

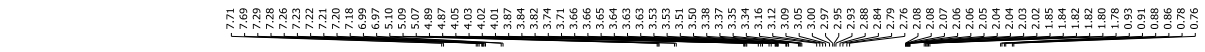


$^{13}$C NMR (101 MHz, $CDCl_3$)

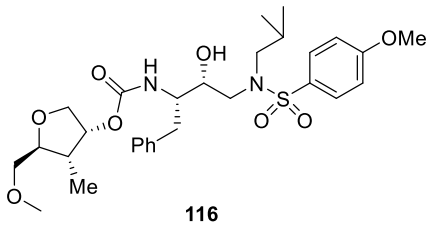


**105**



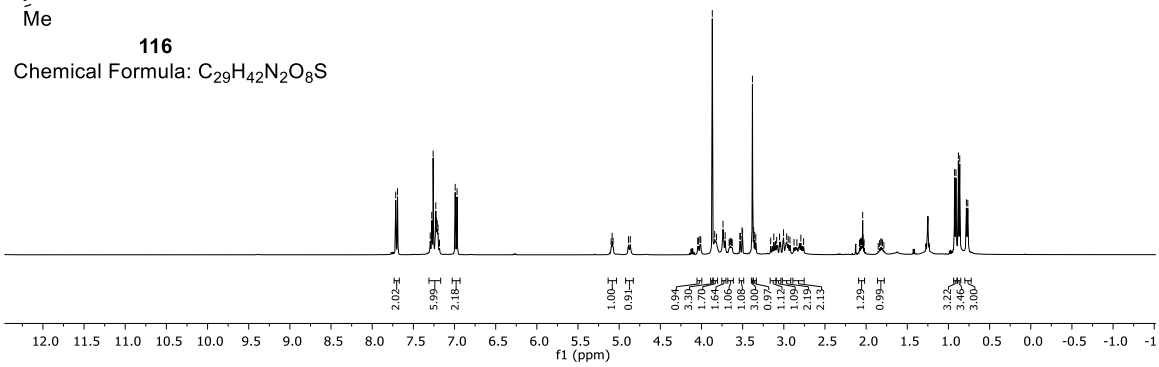


$^{1}$H NMR (400 MHz, $CDCl_3$)

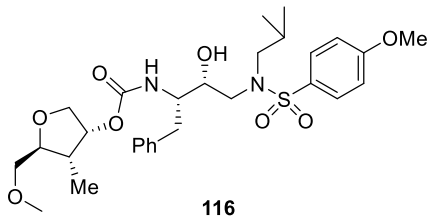


**116**

Chemical Formula: $C_{29}H_{42}N_2O_8S$



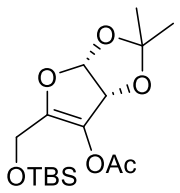
$^{13}$C NMR (101 MHz, $CDCl_3$)



**116**

Chemical Formula: $C_{29}H_{42}N_2O_8S$

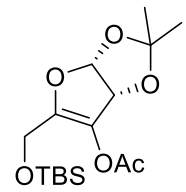
$^{1}$H NMR (400 MHz, $CDCl_3$)




**106**

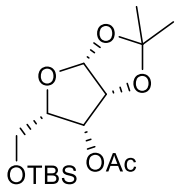



$^{13}$C NMR (101 MHz, $CDCl_3$)



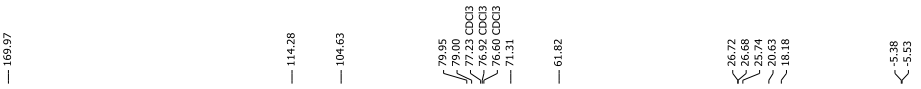

**106**


$^{1}$H NMR (400 MHz, $CDCl_3$)

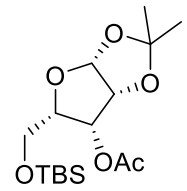



**107**



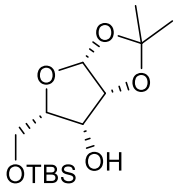




$^{13}$C NMR (101 MHz, $CDCl_3$)




**107**

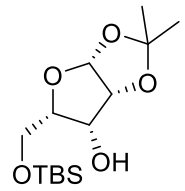
$^{1}$H NMR (400 MHz, $CDCl_3$)




**108**

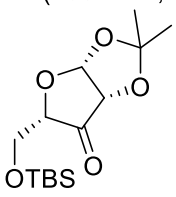



$^{13}$C NMR (101 MHz, $CDCl_3$)




**108**

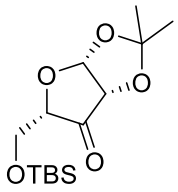
$^{1}$H NMR (400 MHz, $CDCl_3$)




**109**

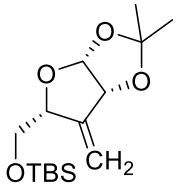



$^{13}$C NMR (101 MHz, $CDCl_3$)




**109**

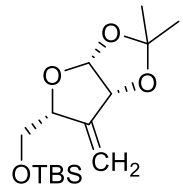
$^{1}$H NMR (400 MHz, $CDCl_3$)




**110**

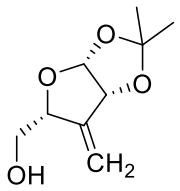



$^{13}$C NMR (101 MHz, $CDCl_3$)

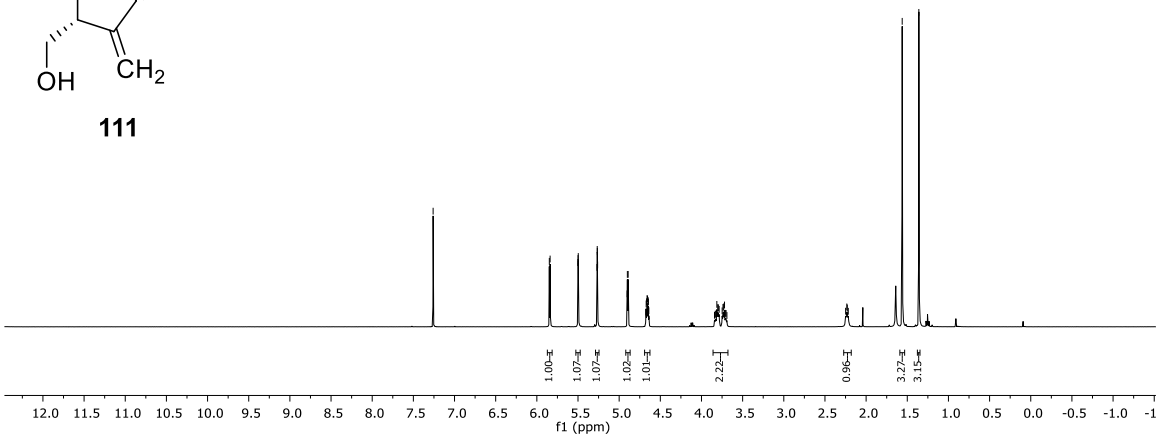



**110**

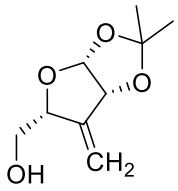

$^{1}$H NMR (400 MHz, $CDCl_3$)



**111**

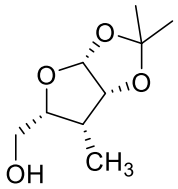



$^{13}$C NMR (101 MHz, $CDCl_3$)



**111**

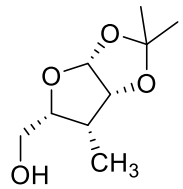
$^{1}$H NMR (400 MHz, $CDCl_3$)



**112**

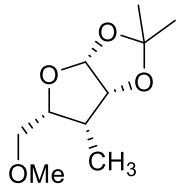



$^{13}$C NMR (101 MHz, $CDCl_3$)



**112**

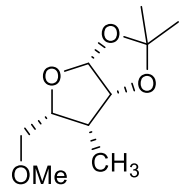
$^{1}$H NMR (400 MHz, $CDCl_3$)



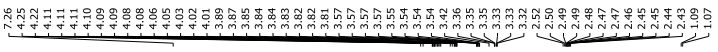

**113**



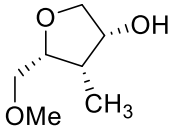

$^{13}$C NMR (101 MHz, $CDCl_3$)




**113**



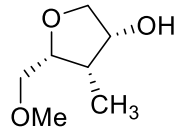
$^{1}$H NMR (400 MHz, $CDCl_3$)



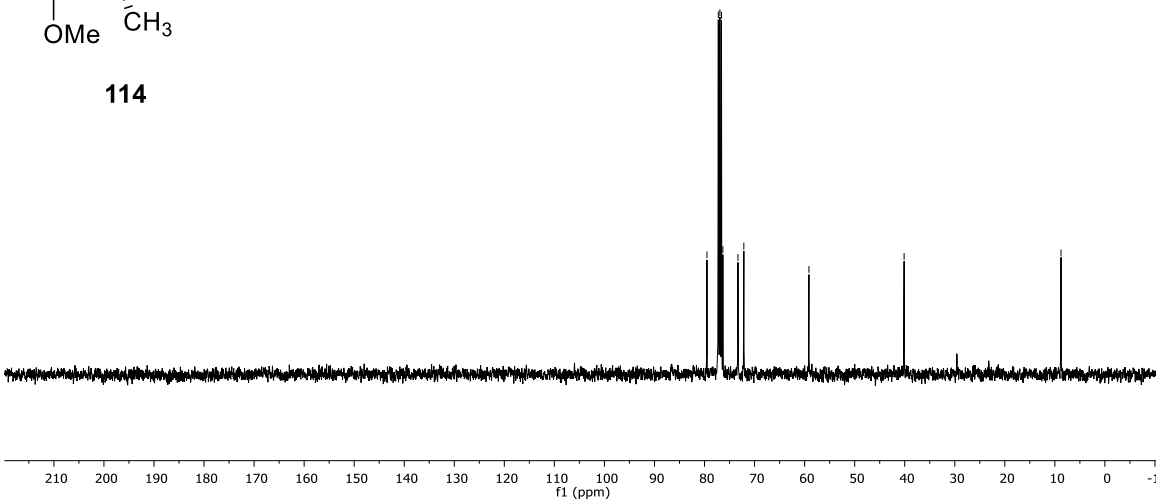
**114**



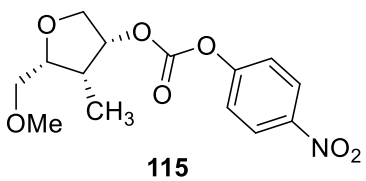
$^{13}$C NMR (101 MHz, $CDCl_3$)



**114**



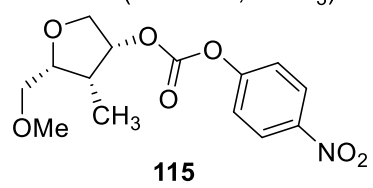
$^{1}$H NMR (400 MHz, $CDCl_3$)



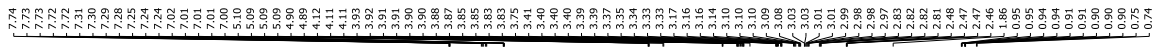
**115**



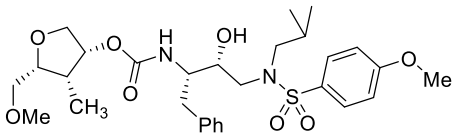

$^{13}$C NMR (101 MHz, $CDCl_3$)



**115**

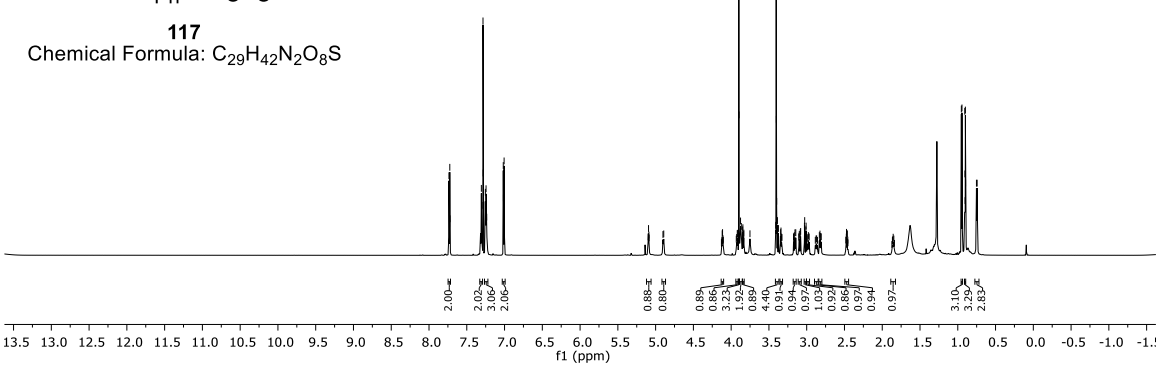


$^{1}$H NMR (800 MHz, $CDCl_3$)

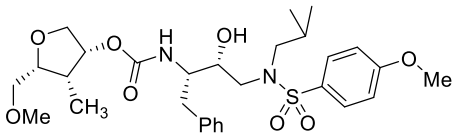


**117**

Chemical Formula: $C_{29}H_{42}N_2O_8S$

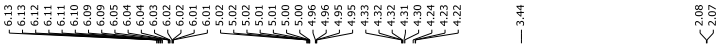


$^{13}$C NMR (201 MHz, $CDCl_3$)

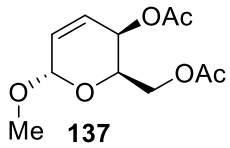


**117**

Chemical Formula: $C_{29}H_{42}N_2O_8S$

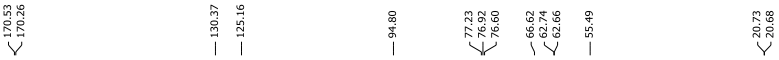



$^{1}$H NMR (400 MHz, $CDCl_3$)

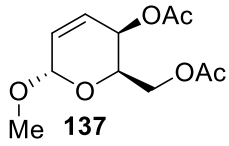



**137**



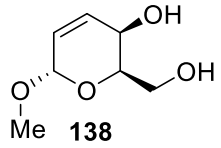

$^{13}$C NMR (101 MHz, $CDCl_3$)



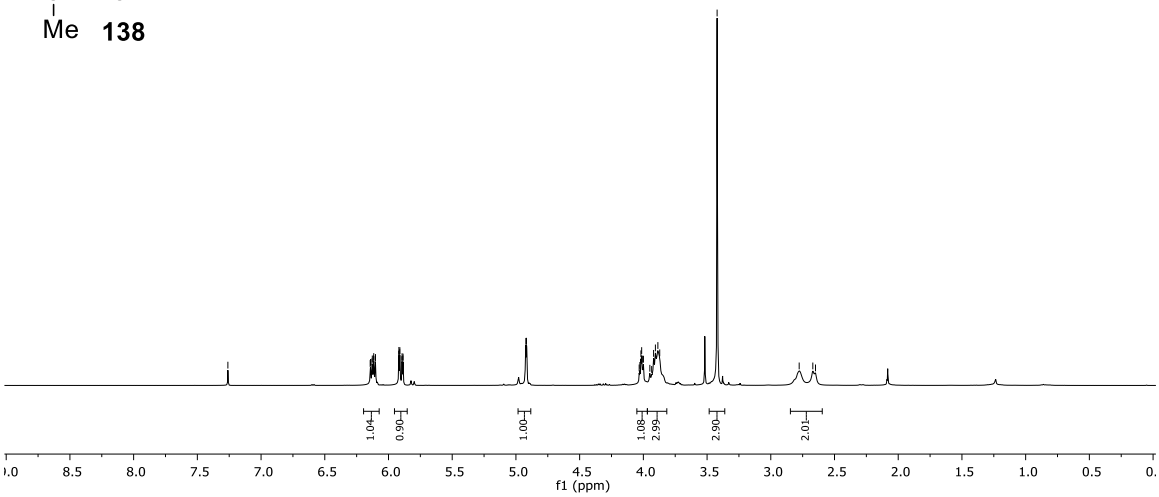

**137**

7.26
6.14 6.14 6.13 6.13 6.12 6.12 6.10 6.10 5.92 5.92 5.91 5.91 5.90 5.89 5.89 5.89
4.92 4.92
4.03 4.03 4.02 4.01 4.01 4.00 3.95 3.93 3.92 3.91 3.89 3.87 3.42
2.78 2.67 2.65

$^{1}$H NMR (400 MHz, $CDCl_3$)

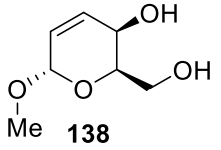



**138**

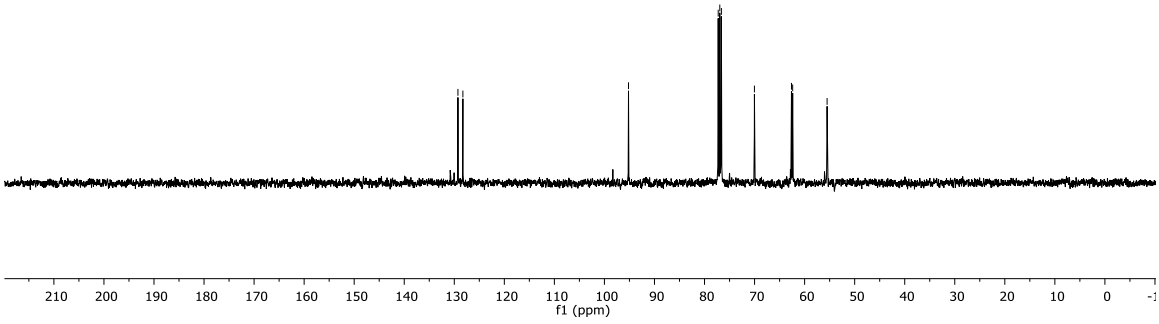



129.27
128.28
95.19
77.26
76.95
76.63
70.03
62.63
62.39
55.51

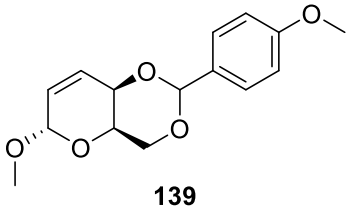
$^{13}$C NMR (101 MHz, $CDCl_3$)



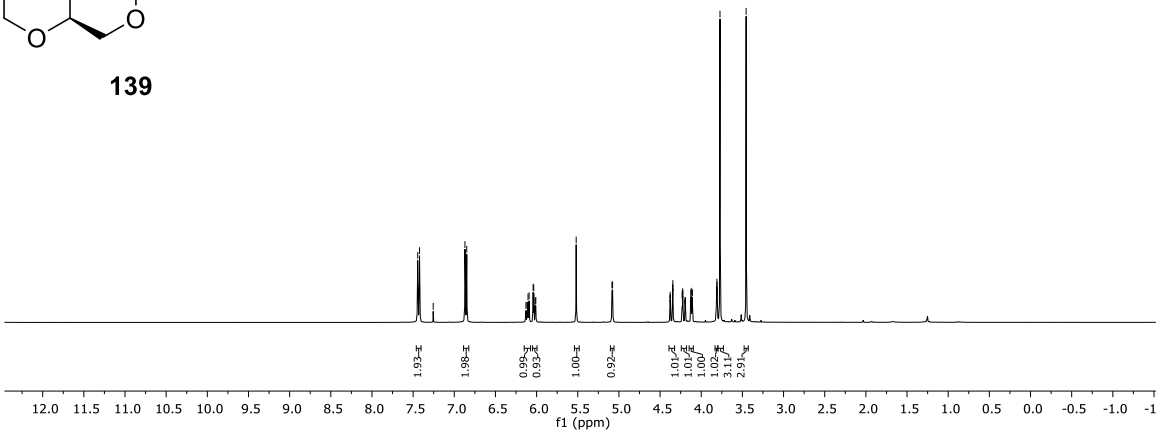

**138**

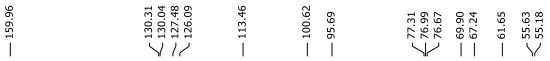



$^{1}$H NMR (400 MHz, $CDCl_3$)

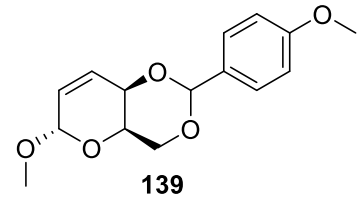


**139**

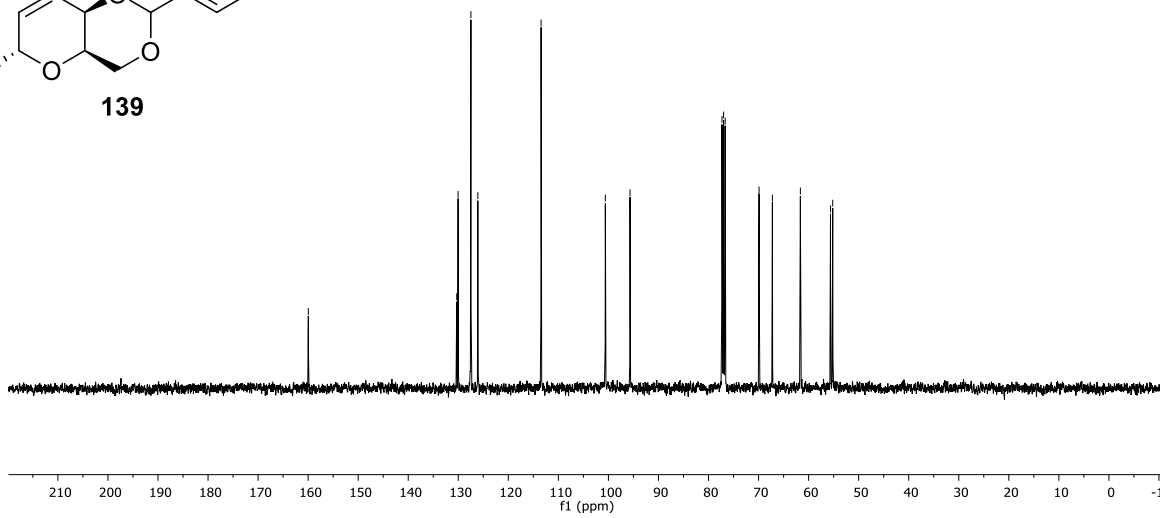


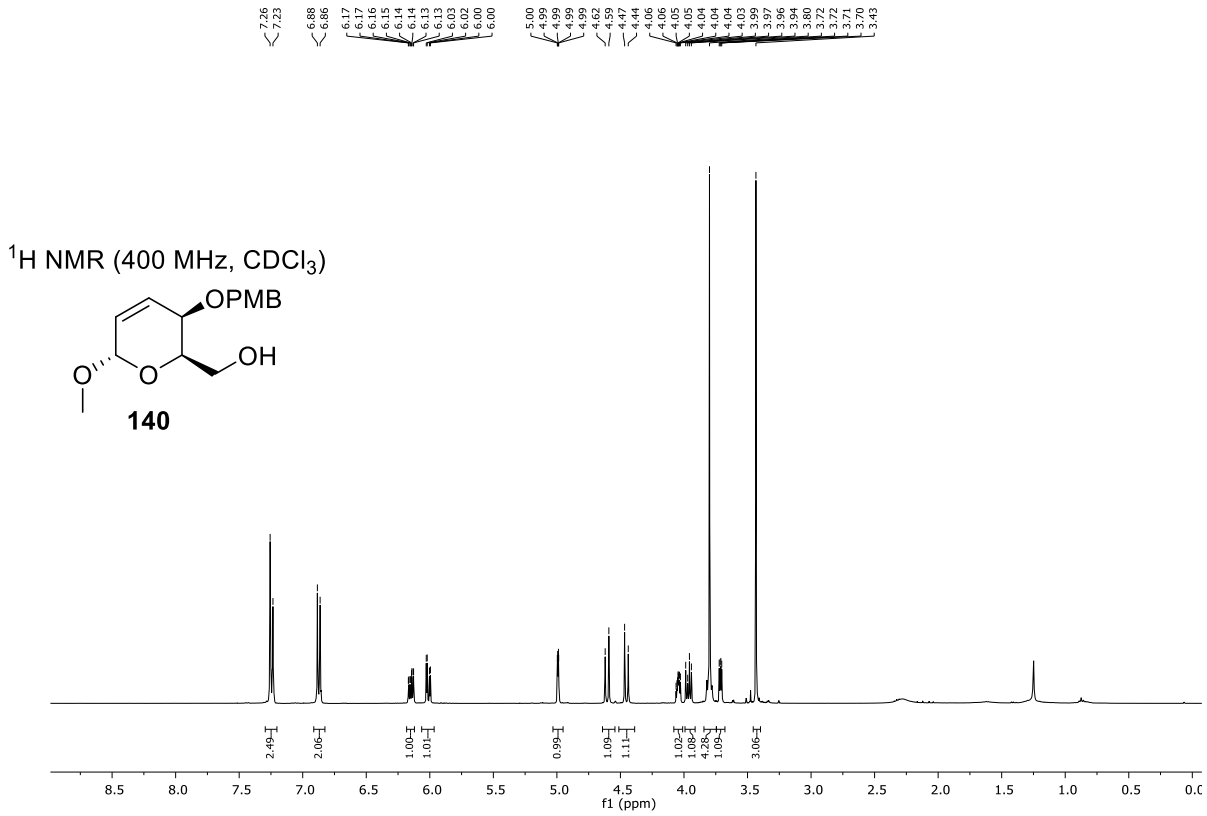




$^{13}$C NMR (101 MHz, $CDCl_3$)



**139**




7.26
7.23
6.88
6.86
6.17
6.17
6.16
6.15
6.14
6.14
6.13
6.03
6.02
6.00
6.00
5.00
4.99
4.99
4.99
4.99
4.62
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4.44
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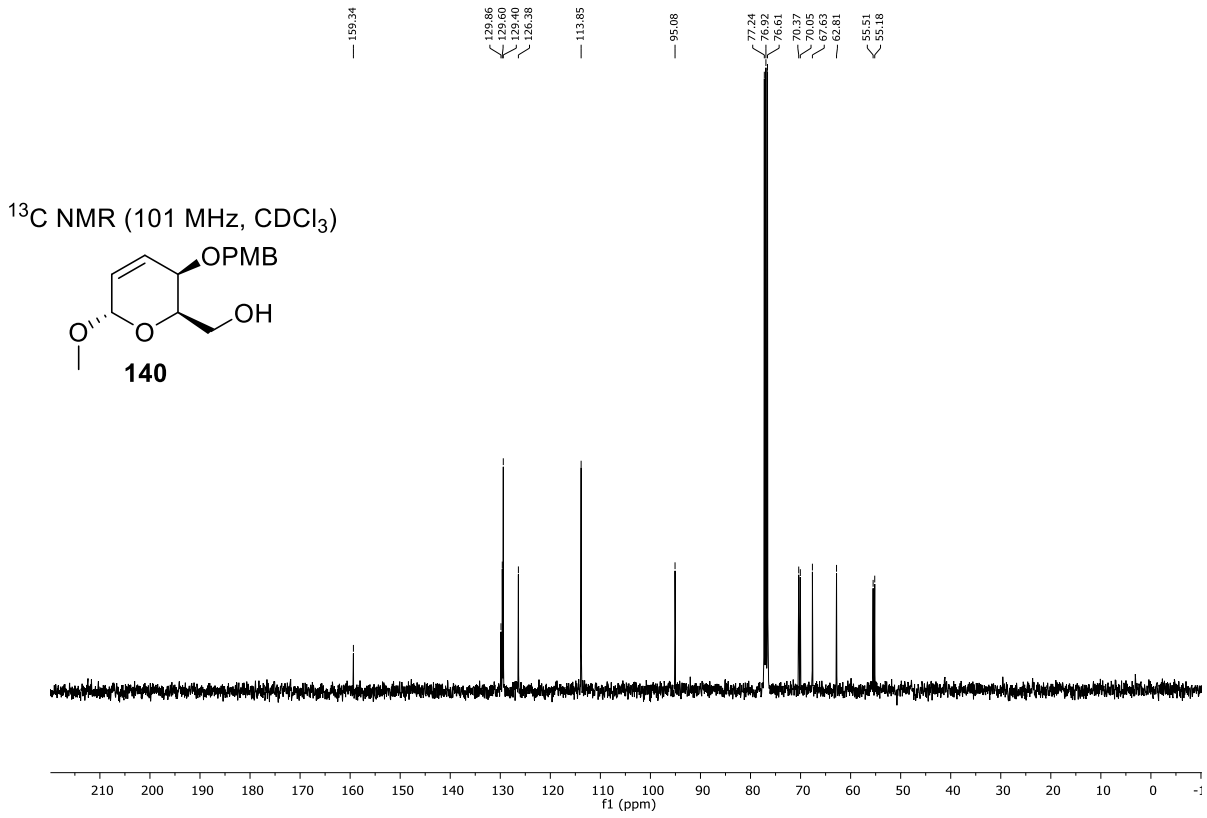
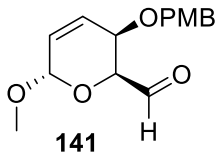
4.04
4.04
4.03
3.99
3.97
3.96
3.94
3.80
3.72
3.72
3.71
3.70
3.43
1H NMR (400 MHz, CDCl3)
OPMB
OH
O
O
140
2.49
2.06
1.00
1.01
0.99
1.09
1.11
1.02
1.08
4.28
1.09
3.06
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


159.34
129.86
129.60
129.40
126.38
113.85
95.08
77.24
76.92
76.61
70.37
70.05
67.63
62.81
55.51
55.18
13C NMR (101 MHz, CDCl3)
OPMB
OH
O
O
140
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

$^{1}$H NMR (400 MHz, $CDCl_3$)




**141**

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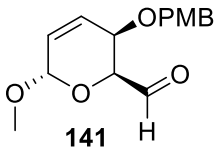


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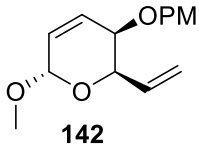


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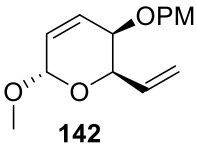


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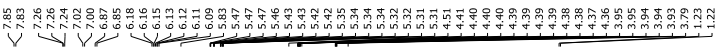

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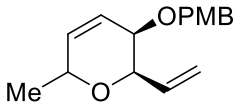
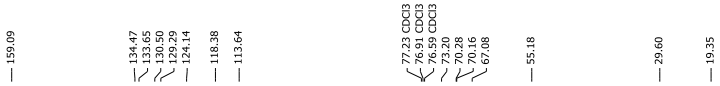



**143**

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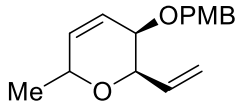


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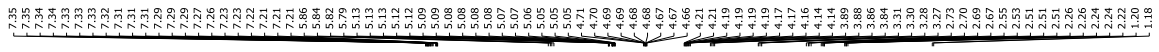

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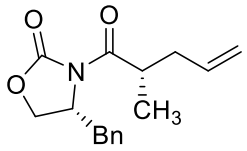

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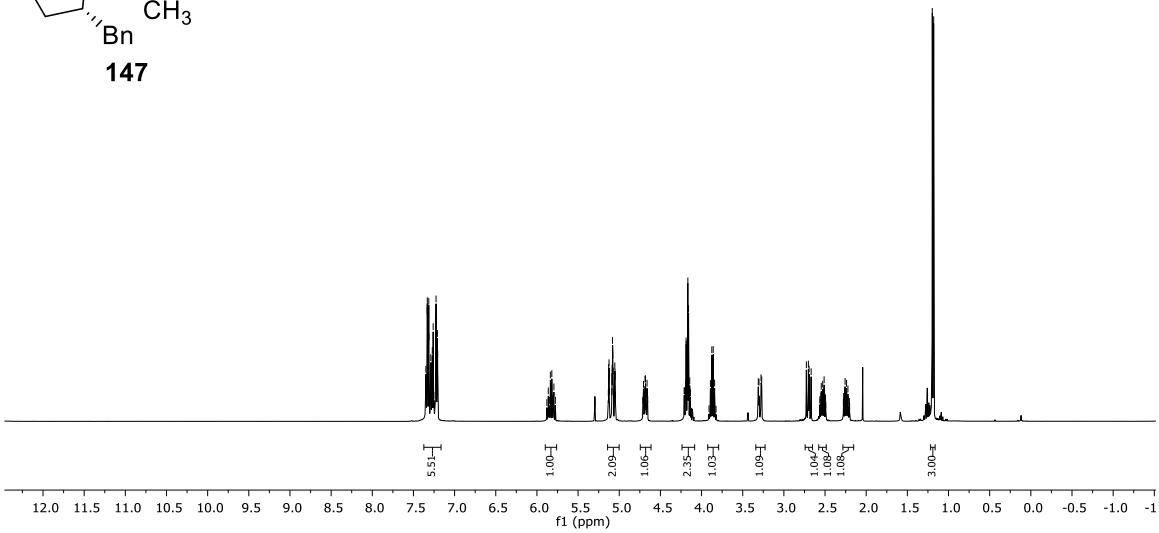

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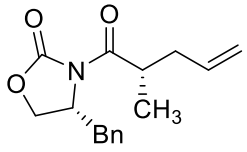

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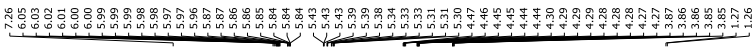
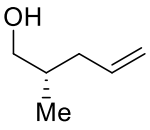


$^{1}$H NMR (400 MHz, $CDCl_3$)



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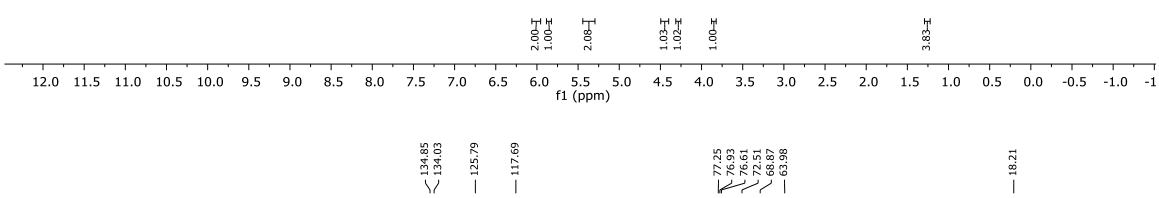
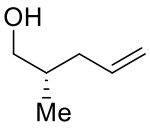




$^{13}$C NMR (101 MHz, $CDCl_3$)



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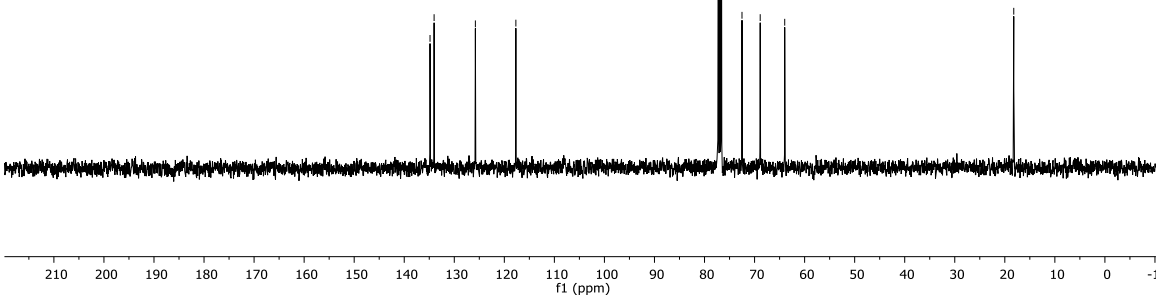
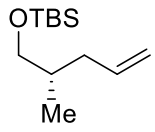


$^{1}$H NMR (400 MHz, $CDCl_3$)

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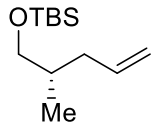


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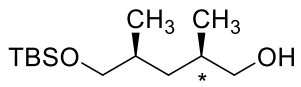
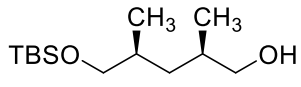



**149**

9:1 *dr*




$^{13}$C NMR (101 MHz, $CDCl_3$)




**149**

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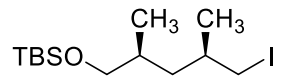


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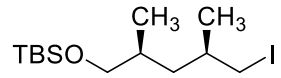
$^{13}$C NMR (101 MHz, $CDCl_3$)

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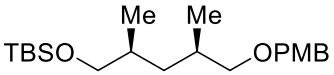


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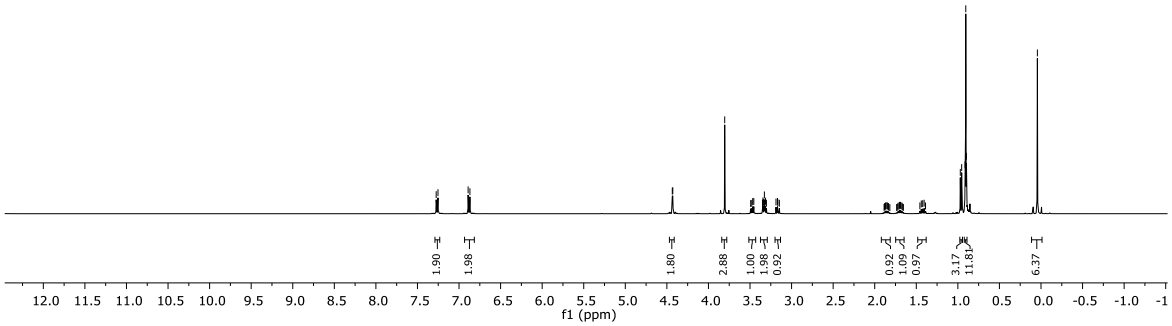


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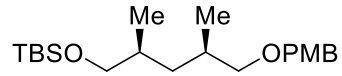


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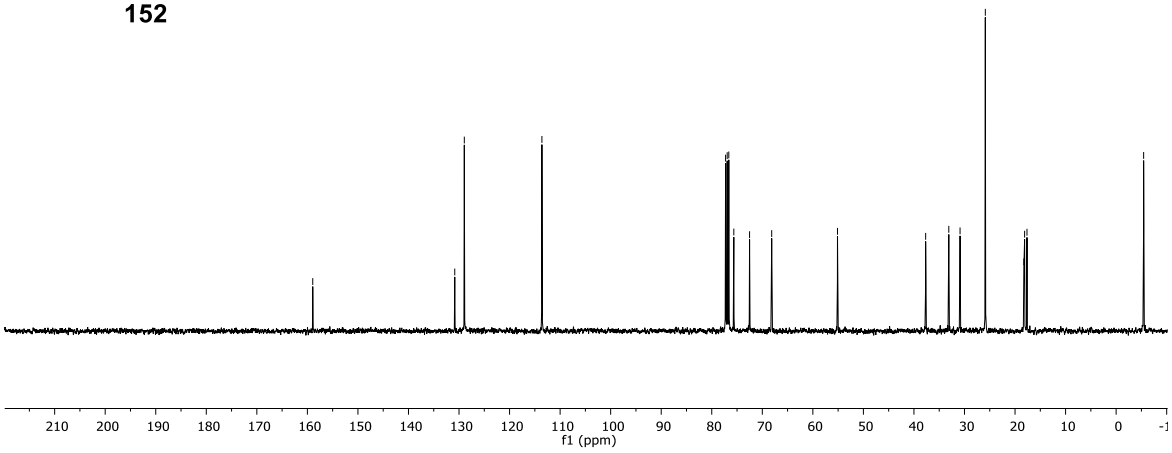

# VITA

Daniel Sung Koo Lee was born on April 1992 in Los Angeles, California. He graduated high school from Korea Kent Foreign School in Seoul, South Korea in 2011. He then attended Grinnell College in Iowa for his undergraduate education. Here, he began to further his chemi In 2015, he earned his Bachelor of Arts in Chemistry and moved to Purdue University, Indiana to start his graduate study. He joined the research group of Professor Arun K. Ghosh and focused on the enantioselective total synthesis of (+)-monocerin, which is a potent antimalarial agent. He also synthesized numerous potent HIV-1 protease inhibitors. He defended his thesis in November 2020.

# PUBLICATION

JOC The Journal of Organic Chemistry Cite This: J. Org. Chem. 2019, 84, 6191−6198 Article pubs.acs.org/joc

# Enantioselective Total Synthesis of (+)-Monocerin, a Dihydroisocoumarin Derivative with Potent Antimalarial Properties

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Supporting Information




**ABSTRACT:** We describe here the enantioselective synthesis of (+)-monocerin and its acetate derivative. The present synthesis features an efficient optically active synthesis of the β-hydroxy-γ-lactone derivative with high enantiomeric purity using Sharpless dihydroxylation as the key step. The synthesis also highlights a tandem Lewis acid-catalyzed, oxocarbenium ion-mediated diastereoselective *syn*-allylation reaction, and a methoxymethyl group promoted methylenation reaction. We investigated this reaction with a variety of Lewis acids. A selective $CrO_3$-mediated oxidation of isochroman provided the corresponding lactone derivative. The synthesis is quite efficient and may be useful for the preparation of derivatives.

## INTRODUCTION

Dihydrocoumarin and dihydroisocoumarin derivatives frequently occur in nature.[1,2] These natural products exhibit a wide range of biological properties including antifungal, insecticidal, antiparasitic, and plant pathogenic activity.[3−5] Monocerin (**1**, Figure 1), which was first isolated by Aldridge and Turner from *Exserohilum monoceras* (Drechsler), is a dihydroisocoumarin natural product that protects wheat against the powdery mildew *Erysiphe graminis*.[6] Aldridge and Turner also demonstrated monocerin's antifungal properties. Subsequently, Grove and Pople identified monocerin as a constituent of the entomogenous fungus *Fusarium larvarum* Fuckel and showed its insecticidal properties.[7] The assignment of absolute configuration of monocerin was addressed by Grove and Pople as well as by Scott and co-workers.[7,8] Subsequently, the synthesis and biosynthesis of the first polyketide synthase-free intermediate in monocerin was reported by Axford and co-workers.[9] Since then, there have been many reports concerning the phytotoxic properties of monocerin and its derivatives **2**−**4**.[6,10−13] In 2008, Sappapan and co-workers reported potent antimalarial properties of monocerin against the multidrug-resistant strain of *Plasmodium falciparum* with an $IC_{50}$ value of 680 nM.[14] Its acetate derivative **2** also showed good antimalarial activity ($IC_{50}$ = 820 nM).[14] Lasionectrin (**5**), a dihydronaphthopyrone natural product, was isolated from fermentations of the fungus *Lasionectria* (F-176,994).[15] Like monocerin, lasionectrin also exhibited antimalarial activity, although subsequently weaker than that of monocerin.[15] Monocerin features a 4-oxyisochroman-1-one structural unit and 2,3,5-trisubstituted tetrahydrofuran ring containing all-*cis* stereochemistry.

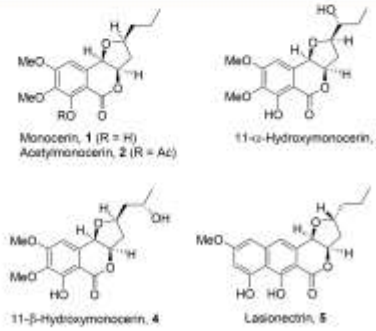


**Figure 1.** Structures of dihydroisocoumarin natural products **1**−**5**.

Structural features and broad-spectrum biological properties of monocerin led to considerable synthetic attention over the years. Mori and Takaishi reported the first synthesis of monocerin in racemic form.[16] Simpson and co-workers then reported a biomimetic synthesis of monocerin.[17] Since then, monocerin and its derivatives have attracted much synthetic interest due to their broad medicinal potential. A number of

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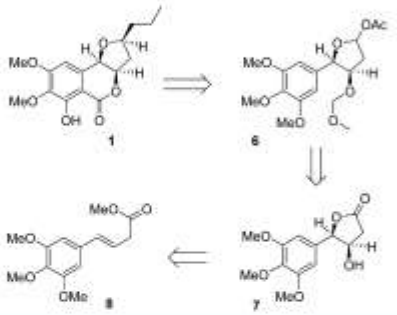
total syntheses of monocerin have been reported.[18−23] Recently, an enantioselective total synthesis of lasionectrin has also been reported.[24] Herein, we report a short and practical synthesis of monocerin and its acetate derivative in optically active form. The synthesis features Sharpless asymmetric dihydroxylation, Lewis acid-catalyzed, oxocarbenium ion-mediated stereoselective allylation, formulation reaction, and $CrO_3$-mediated oxidation of the benzopyran to a dihydroisocoumarin derivative. The synthesis is potentially amenable toward the synthesis of structural variants of monocerin for biological studies.

## RESULTS AND DISCUSSION

Our synthetic strategy for (+)-monocerin is shown in Scheme 1. We planned an oxocarbenium ion-mediated allylation of

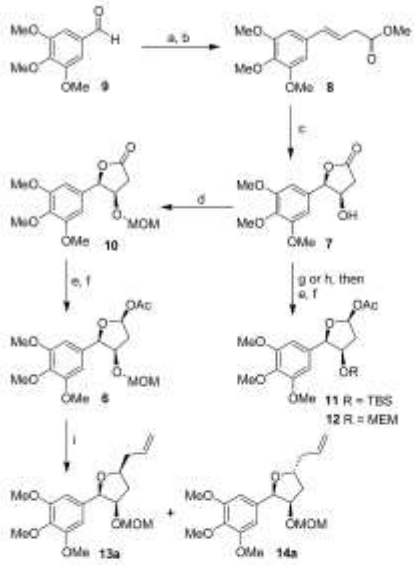
**Scheme 1. Retrosynthetic Analysis of (+)-Monocerin**



acetate derivative **6** for stereoselective installation of the propyl chain of monocerin. We also envisioned an intramolecular oxocarbenium ion-mediated formulation of the aromatic ring through the MOM group to install the isochroman structure. We planned to investigate these transformations in a "one-pot" operation. A related C3-benzyloxy-substituted five-membered ring oxocarbenium ion has been shown to promote allylation selectivity to provide the 1,3-*cis* product.[25,26] The stereochemical outcome and selectivity with a methoxymethyl group are expected to be similar. The key allylation substrate can be synthesized from 3-hydroxy-γ-lactone **7**, which can be synthesized in an optically active manner by asymmetric dihydroxylation of *E*-olefin **8**.[27,28] The requisite *E*-olefin can be synthesized by a stereoselective Wittig olefination using a γ-oxido-ylid and commercially available 3,4,5-trimethoxy benzaldehyde.[29,30]

Our synthesis of multigram quantities of γ-lactone **7** and its derivatives is shown in Scheme 2; Wittig olefination of 3,4,5-trimethoxybenzaldehyde **9** was carried out with ylid generated from (2-carboxyethyl)triphenyl phosphonium bromide and potassium *t*-butoxide in THF at −78 to 23 °C for 18 h.[29,31] The resulting β,γ-unsaturated acid was esterified by exposure to TMSCl in MeOH at 0 to 23 °C for 12 h to provide methyl ester **8** in 49% yield over two steps. Asymmetric dihydroxylation of methyl ester **8** with AD-mix-β in the presence of methanesulfonamide and sodium bicarbonate in aqueous *t*-BuOH at 0 °C for 22 h afforded β-hydroxy-γ-lactone **7** in 90% yield.[27] Optical purity of lactone **7** was over 95% ee, as determined by chiral HPLC analysis using a chiralpak IC column. Protection of the hydroxyl group as a MOM ether was

**Scheme 2. Synthesis of Allyl Derivatives 13a and 14a[a]**



[a]Reagents and conditions: (a) $Ph_3P^+CH_2CO_2H\,Br^-$, *t*-BuOK, THF, −78 to 23 °C, 18 h, (65%); (b) TMSCl, dry MeOH, 0 to 23 °C, 18 h (76%); (c) AD-mix-β, $NaHCO_3$, $MeSO_2NH_2$, *t*-BuOH/$H_2O$ = 1.1, 0 °C, 24 h (90%); (d) DIPEA, MOMCl, TBAI (cat.), THF, 50 °C, 24 h (95%); (e) DIBAL-H, toluene, −78 °C; (f) $Et_3N$, DMAP, $Ac_2O$, DCM, 0 to 23 °C, 1.5 h (88%); (g) TBSOTf, 2,6-lutidine, DCM, 0 to 23 °C, 3 h (51%); (h) MEMCl, DIPEA, TBAI, THF, 0 to 55 °C, 72 h (79%); (i) allyltrimethylsilane, $SnBr_4$, DCM, −78 °C, 3 h, (84%).

achieved by reaction of lactone **7** with MOMCl in THF in the presence of diisopropylethylamine (DIPEA) and a catalytic amount of tetrabutylammonium iodide (TBAI) at 50 °C for 24 h to provide MOM ether **10** in 95% yield. It was then converted to acetate derivative **6** in a two-step sequence: first, by DIBAL-H reduction in $CH_2Cl_2$ at −78 °C for 2 h, followed by acetylation of the resulting crude lactol with acetic anhydride and triethylamine in the presence of a catalytic amount of DMAP in $CH_2Cl_2$ at 0 °C for 2 h to provide **6** as the major anomer along with a small amount of the other anomer (ratio 14:1) in 88% combined yield over two steps. Lactone **7** was converted to TBS-protected acetate derivative **11** by protection of the hydroxyl group as TBS ether followed by DIBAL-H reduction and acetylation, as described above. Similarly, lactone **7** was also converted to MEM-derivative **12**, as described above. The stereochemistry of the chiral center bearing an acetate group for **6**, **11**, and **12** was assigned by using $^1$H NMR nuclear Overhauser enhancement spectroscopy (NOESY) experiments (see the Supporting Information).

With the synthesis of these acetates, we have investigated allylation promoted by various Lewis acids. We first carried out allylation of **6** with 1.1 equiv of $SnBr_4$ and 4 equiv of allyltrimethylsilane in $CH_2Cl_2$ at −78 °C for 3 h. This resulted in a mixture (62:38) of allyl derivatives **13a** and **14a** in 84% combined yield. The ratio was determined by $^1$H NMR analysis of diastereomeric protons. We then investigated other Lewis acids under various conditions, and the results are



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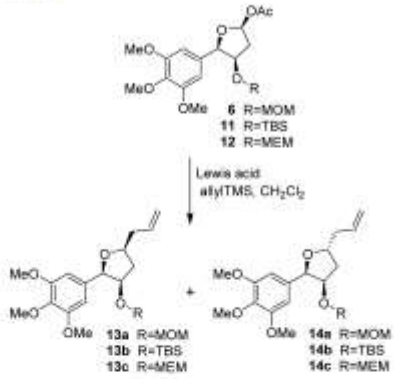
shown in Table 1. The use of 2 equiv of $SnBr_4$ did not improve diastereoselectivity, and the reaction yield was reduced (entry 2). The use of 1.1 equiv of $TiCl_4$ resulted in 69% yield of a mixture of diastereomers (60:40) similar to $SnBr_4$ reaction (entry 3). An increase of Lewis acid to 2 equiv resulted in a decrease of reaction yields as well as a slight reduction of diastereomeric ratio (entry 4). We also investigated the allylation reaction with $BF_3{\cdot}OEt_2$ and TMSOTf as the Lewis acids. In both cases, the reaction provided similar diastereomeric ratios, and the reaction yields were 52 and 57%, respectively (entries 5 and 6). We then examined allylation of TBS-protected acetate derivative **11** with 1.1 equiv of $SnBr_4$ and 4 equiv of allyltrimethylsilane in $CH_2Cl_2$ at −78 °C for 3 h. This has resulted in a slight improvement in the diastereomeric ratio (70:30) of allyl derivatives **13b** and **14b** in 81% yield (entry 7). The use of 1.1 equiv of $TiCl_4$ also provided comparable diastereoselectivity and yield (entry 8). Interestingly, allylation of MEM-protected acetate derivative **12** with 1.1 equiv of $SnBr_4$ and 4 equiv of allyltrimethylsilane in $CH_2Cl_2$ at −78 °C for 3 h resulted in allyl derivatives **13c** and **14c** in a 1:1 ratio and 33% yield (entry 9). The reaction of **12** with 1.1 equiv of $BF_3{\cdot}OEt_2$ and 1.5 equiv of allyltrimethylsilane provided allyl derivatives **13c** and **14c** in a 63:37 ratio, and the reaction yield was 36% (entry 10). While the observed diastereoselectivity of allylation was moderate, we assigned stereochemical identity of diastereomers **13b** and **14b** by using $^1H$ NMR NOESY experiments (see the Supporting Information for details).

**Table 1. Allylation of Acetate Derivatives with Various Lewis Acids**[a]




| entry | compd. | Lewis acid (equiv) | time | yield (%) | *dr* (**13**/**14** ratio) |
|---|---|---|---|---|---|
| 1 | **6** | $SnBr_4$ (1.1) | 3 h | 83.9 | 62:38 |
| 2 | **6** | $SnBr_4$ (2.0) | 3 h | 75.1 | 63:37 |
| 3 | **6** | $TiCl_4$ (1.1) | 3 h | 69.4 | 60:40 |
| 4 | **6** | $TiCl_4$ (2.0) | 4 h | 38.2 | 58:42 |
| 5 | **6** | $BF_3{\cdot}OEt_2$ (1.1) | 3 h | 52.1 | 63:37 |
| 6 | **6** | TMSOTf (1.0) | 3 h | 57.1 | 58:42 |
| 7 | **11** | $SnBr_4$ (1.1) | 3 h | 80.7 | 70:30 |
| 8 | **11** | $TiCl_4$ (1.1) | 3 h | 76 | 72:28 |
| 9 | **12** | $SnBr_4$ (1.1) | 3 h | 32.7 | 51:49 |
| 10[b] | **12** | $BF_3{\cdot}OEt_2$ (1.1) | 3 h | 36.4 | 63:37 |

[a]All reactions were carried out in $CH_2Cl_2$ at −78 °C and allyltrimethylsilane (4.0 equiv). Ratios were determined by $^1H$ NMR analysis. [b]1.5 equiv of allyl trimethylsilane was added instead of 4 equiv.

The observed *cis*-diastereoselectivity is consistent with C3-alkoxy-substituted tetrahydrofuranyl substrates examined by Woerpel and co-workers.[25,26] However, the extent of diastereoselectivity of allylation is significantly lower presumably due to competing stereoelectronic effects. As shown in Figure 2, allylation of acetates can proceed through oxocarbenium ion intermediates **15** and **16**. Intermediate **15** is preferred over **16** due to the pseudoequatorial orientation of the bulky trimethoxyphenyl group at the C4 position.[26,32,33] The axial alkoxy group forms a gauche interaction with the aromatic group. Inside attack on the oxocarbenium ion intermediate **15** leads to the major diastereomer **13**. Intermediate **16** also shows a gauche interaction as well as 1,3-interactions between the bulky aromatic group and the C2-axial hydrogen. Changing of Lewis acids did not make much difference in selectivity. The size and nature of protecting groups also did not show much influence in diastereoselectivity. Moreover, the protecting groups remained unaffected under the reaction conditions.

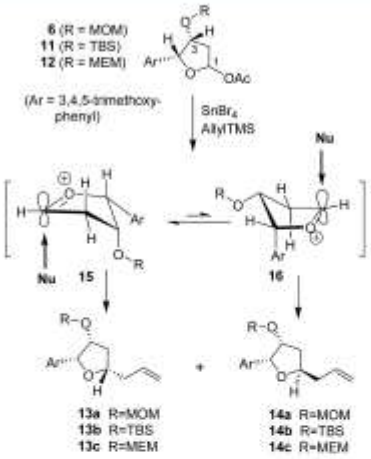



**Figure 2.** Stereochemical analysis of *cis*-allylation reaction.

We then investigated a Lewis acid-catalyzed allylation reaction at −78 to 23 °C in an effort to promote selective allylation, as well as to carry out Friedel−Crafts alkylation through the MOM or MEM groups onto the aromatic ring in a one-pot operation.[34,35] The results of these tandem allylation and Oxa-Pictet−Spengler cyclization are shown in Table 2. Initial reaction of MOM derivative **6** with 1.6 equiv of $SnBr_4$ in the presence of allyltrimethylsilane at −78 to 23 °C for 4 h provided a diastereomic mixture of allylated products **13a** and **14a** in 54% yield as well as isochroman derivatives **17** and **18** in 22% yield (entry 1, Table 2). To promote complete formation of isochroman derivatives, we examined the reaction with additional equivalents of Lewis acid, and the reaction was carried out for a longer period of time. Thus, the reaction of MOM derivative **6** was carried out with 1.6 equiv of $SnBr_4$ in the presence of allyltrimethylsilane at −78 to 23 °C for 4 h. Reaction was monitored by TLC and showed complete consumption of the starting acetate derivatives. After this



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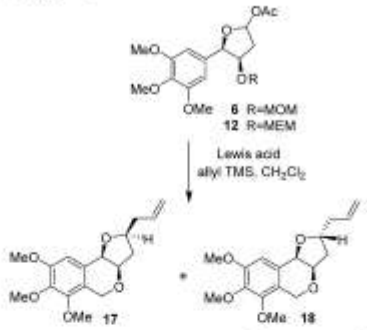
Table 2. Lewis Acid-Catalyzed Tandem Allylation and Oxa-Pictet–Spengler Cyclization of Acetate Derivative 6 and 12[a]



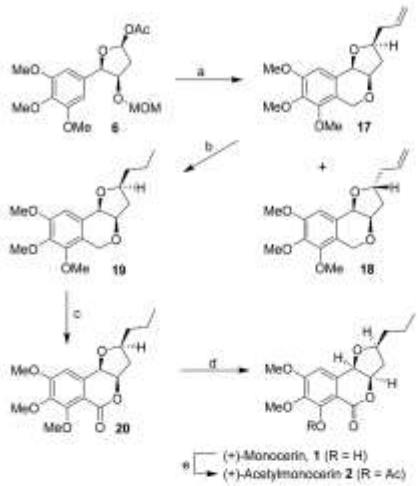

| entry | compd. | Lewis acid (equiv, time) | yield % (13/14) | yield % (17/18 and ratio) |
|---|---|---|---|---|
| 1 | 6 | $SnBr_4$ (1.6, 4 h) | 54 | 22 (3:1) |
| 2[b] | 6 | $SnBr_4$ (1.6, 4 h), then (2, 12 h) | | 52 (4:1) |
| 3[c] | 6 | $SnBr_4$ (1.1, 3 h), then (2, 12 h) | - | 35 (3.2:1) |
| 4[b,d] | 6 | $SnBr_4$ (1.1, 3 h), then (2, 12 h) | | 42 (3:1) |
| 5[c] | 6 | $TiCl_4$ (1, 4 h), then (1.5, 12 h) | trace | trace |
| 6[b] | 12 | $SnBr_4$ (1.6, 3 h), then (2, 12 h) | | 21 (1.7:1) |

[a]All reactions were carried out in $CH_2Cl_2$ with 4 equiv of allyltrimethylsilane at −78 to 23 °C. [b]Additional Lewis acid was added at 0 °C, and the reaction mixture was slowly warmed to 23 °C. [c]Additional Lewis acid was added at −78 °C, and the reaction mixture was warmed to 23 °C. [d]After adding 1.1 equiv of Lewis acid, the reaction mixture was stirred at −78 °C for 3 h.

period, the reaction was cooled to 0 °C, 2 equiv of $SnBr_4$ was added, and the resulting mixture was warmed to 23 °C for 12 h. This resulted in the formation of isochroman derivatives **17** and **18** in 52% yield. The diastereomeric ratio was determined to be 4:1 by $^1H$ NMR analysis (entry 2). Addition of additional equivalents of Lewis acid was then investigated at lower temperature. Acetate **6** was treated with 1.1 equiv of $SnBr_4$ at −78 to 23 °C for 3 h, and 2 equiv of $SnBr_4$ was added at −78 °C. The resulting mixture was allowed to warm from −78 to 23 °C for 12 h. This reaction protocol furnished products **17** and **18** as a mixture (3.2:1) of diastereomers in 35% yield (entry 3). In a further optimization effort, acetate **6** was treated with 1.1 equiv of $SnBr_4$ at −78 °C for 3 h, then 2 equiv of $SnBr_4$ was added at −78 °C, and the reaction was warmed to 23 °C for 12 h. This has resulted to products **17** and **18** as a 3:1 mixture in 42% combined yield (entry 4). Oxa-Pictet–Spengler cyclization of acetate derivative **6** with $TiCl_4$ in place of $SnBr_4$ under similar reaction conditions, however, provided only a trace amount of the products (entry 5). Interestingly, the reaction of MEM derivative **12** with $SnBr_4$ and allyltrimethylsilane using conditions described in entry 2 provided a mixture (1.7:1) of isochroman derivatives **17** and **18** in 21% combined yield (entry 6).

The synthesis of (+)-monocerin is shown in Scheme 3. MOM ether **6** was converted to allylated Oxa-Pictet–Spengler products **17** and **18**. The diastereomers were separated by silica gel chromatography, and the major isomer **17** was

Scheme 3. Synthesis of (+)-Monocerin[a]




[a]Reagents and conditions: (a) $SnBr_4$, allyltrimethylsilane, $CH_2Cl_2$, −78 to 23°C, 18 h (52%); (b) $H_2$, 10% Pd-C, EtOAc, 23 °C, 12 h (88%); (c) $CrO_3$, pyridine, $CH_2Cl_2$, 0 to 23 °C, 36 h (40%, 60% brsm); (d) $BCl_3$, $CH_2Cl_2$, −10 °C, 2 h (41%, 88% brsm); (e) $Ac_2O$, pyridine, $CH_2Cl_2$, 23 °C, 5 h (96%).

hydrogenated under a hydrogen-filled balloon in the presence of a catalytic amount of 10% Pd-C in ethyl acetate at 23 °C for 12 h to provide saturated bicyclic ether **19** in 88% yield. The $^1H$ NMR and $^{13}C$ NMR spectra of our synthetic bicyclic ether **19** showed excellent agreement with the reported derivative.[18] Furthermore, NOESY correlation of *cis*-hydrogens in compound **17** supported stereochemistry of **17** and **19** (see the Supporting Information for details). Oxidation of the isochroman ring was carried out with $CrO_3$ and pyridine in $CH_2Cl_2$ at 0 to 23 °C for 36 h to provide lactone derivative **20** in 40% yield (60% brsm). To complete the synthesis of monocerin, selective deprotection of methyl ether was carried out by exposure to $BCl_3$ in $CH_2Cl_2$ at −10 °C for 2 h to provide synthetic (+)-monocerin **1** in 41% yield (88% brsm). The $^1H$ NMR and $^{13}C$ NMR spectra of synthetic (+)-monocerin $\{[\alpha]_D^{23}$ + 57.8 (*c* 0.29, $CHCl_3$)} are in complete agreement with spectra reported for the natural (+)-monocerin $\{[\alpha]_D^{24}$ + 53 (*c* 0.85, $CHCl_3$)}.[6] We have also synthesized (+)-acetoxymonocerin **2** by treatment of **1** with acetic anhydride and pyridine in the presence of a catalytic amount of DMAP at 0 to 23 °C for 5 h to furnish acetate derivative **2** in 96% yield. $\{[\alpha]_D^{23}$ + 3.6 (*c* 0.29, $CHCl_3$)}. Thus, (+)-monocerin **1** was synthesized in 10 steps in an overall 9% yield. The acetate derivative **2** was obtained in 11 steps in an overall 8.6% yield.

## ■ CONCLUSIONS

In summary, we have accomplished an enantioselective total synthesis of (+)-monocerin and its acetate derivative. The synthesis highlights a Lewis acid-catalyzed, tandem oxocarbenium ion-mediated stereoselective allylation and Friedel–Crafts-type alkylation to provide the isochroman framework in a one-pot operation. The allylation reaction was investigated with various Lewis acids and by varying protecting groups at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the C3 position. While the stereochemical outcome for the major product has all *cis*-stereochemistry, the extent of diastereoselectivity was moderate due to competing stereoelectronic effects. The allylation substrate $\beta$-hydroxy-$\gamma$-lactone was synthesized conveniently in optically active form using Sharpless asymmetric dihydroxylation as the key step. The corresponding *E*-olefin was prepared selectivity by olefination with $\gamma$-oxido-ylid. Since monocerin and derivatives show a broad range of biological activity, the current synthesis will provide access to structural variants in optically active form.

## EXPERIMENTAL SECTION

All chemical and reagents were purchased from commercial suppliers and used without further purification, unless otherwise noted. The following reaction solvents were distilled prior to use: $CH_2Cl_2$ from calcium hydride, diethyl ether and tetrahydrofuran from Na/benzophenone, and methanol from activated magnesium under argon. All reactions were carried out under an argon atmosphere in either flame- or oven-dried (120 °C) glassware. TLC analysis was conducted using glass-backed thin-layer silica gel chromatography plates (60 Å, 250 $\mu$m in thickness, F-254 indicator). Column chromatography was performed using 230−400 mesh silica gel (pore diameter, 60 Å). $^1$H NMR spectra were recorded at room temperature on a 400 MHz spectrometer. $^{13}$C NMR spectra were recorded on 100 and 200 MHz spectrometers. Chemical shifts ($\delta$ values) were reported in parts per million and are referenced to the deuterated residual solvent peak. NMR data are reported as follows: $\delta$ value (chemical shift, *J*-value (Hz), integration, where s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sep = septet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, dq = doublet of quartets, brs = broad singlet, app = apparent). Optical rotations were recorded on a digital polarimeter. Low-resolution mass spectrometry (LRMS) and high-resolution mass spectrometry (HRMS) spectra were recorded at the Purdue University Department of Chemistry Mass Spectrometry Center. These experiments were performed under ESI+ and positive atmosphere pressure chemical ionization (APCI+) conditions using an Orbitrap XL Instrument.

**Methyl (*E*)-4-(3,4,5-Trimethoxyphenyl)but-3-enoate (8).** To a cooled suspension of (2-carboxyethyl) triphenylphosphonium bromide (2.99 g, 7.2 mmol, 1.2 equiv) and 3,4,5-trimethoxybenzaldehyde (1.18 g, 6 mmol, 1.0 equiv) in THF (45 mL) at −78 °C was slowly added a solution of *t*-BuOK (15 mL, 15 mmol, 1.0 M THF solution, 2.5 equiv). After addition, the mixture was stirred at −78 °C for 1 h and was then warmed to 23 °C overnight. The resulting suspension was concentrated under reduced pressure, $H_2O$ (100 mL) was added, and the mixture was washed with $CH_2Cl_2$. The aqueous phase was acidified to pH = 1 with a 1 M solution of HCl and extracted with $Et_2O$ (3×). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

The crude $\beta,\gamma$-unsaturated carboxylic acid above was then dissolved in distilled MeOH (20 mL), and TMSCl (0.97 mL, 1.26 equiv) was dropwise added at 0 °C under argon atmosphere. The mixture was stirred at 23 °C overnight and then concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (10% EtOAc in hexanes) to yield **8** (746 mg, 49% over two steps) as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.58 (s, 2H), 6.41 (d, *J* = 15.8, 1H), 6.20 (dt, *J* = 15.8, 7.1 Hz, 1H), 3.86 (s, 6H), 3.83 (s, 3H), 3.71 (s, 3H), 3.24 (dd, *J* = 7.1, 1.5 Hz, 2H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): $\delta$ 171.9, 153.2, 137.7, 133.3, 132.5, 121.0, 103.3, 60.8, 56.0, 51.9, 38.0. LRMS (ESI) 267.0 ([M + H]$^+$). HRMS (ESI-Orbitrap) *m/z*: [M + Na]$^+$ calcd for $C_{14}H_{18}O_5Na$, 289.1046; found, 289.1049.

**(4*R*,5*R*)-4-Hydroxy-5-(3,4,5-trimethoxyphenyl)-dihydrofuran-2(3*H*)-one (7).** AD-mix-$\beta$ (3.926 g), $NaHCO_3$ (706 mg, 8.4 mmol), and methanesulfonamide (267 mg, 2.8 mmol) were dissolved in *t*-BuOH (7 mL) and water (14 mL). After the mixture was cooled to 0 °C, methyl ester **8** (746 mg, 2.8 mmol) in *t*-BuOH (7 mL) was added. The mixture was stirred at 0 °C for 22 h. After this period, sodium sulfite (5.0 g) was added. The mixture was stirred for 1 h at 23 °C and extracted with EtOAc (3×). The combined organic layer was dried with $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was then purified by column chromatography on silica gel (50−80% EtOAc in hexanes) to afford lactone **7** (700 mg, 90%) as a white amorphous solid. $[\alpha]_D^{25}$ − 23.9 (*c* 0.41, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.54 (s, 2H), 5.38 (d, *J* = 3.3 Hz, 1H), 4.62−4.56 (m, 1H), 3.82 (s, 6H), 3.78 (s, 3H), 2.85 (ddd, *J* = 17.5, 5.0, 1.5 Hz, 1H), 2.71 (d, *J* = 17.5 Hz, 1H), 2.06 (m, 1H, OH); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): $\delta$ 175.4, 153.6, 137.9, 128.5, 103.0, 85.1, 70.1, 60.7, 56.1, 38.4. LRMS (ESI) 269.0 [M + H]$^+$. HRMS (ESI-Orbitrap) *m/z*: [M + H]$^+$ calcd for $C_{13}H_{16}O_6$ + H, 269.1020; found, 269.1024.

**(4*R*,5*R*)-4-(Methoxymethoxy)-5-(3,4,5-trimethoxyphenyl)-dihydrofuran-2(3*H*)-one (10).** To a stirred solution of lactone **7** (272 mg, 1.02 mmol) in distilled THF (4 mL) at 0 °C under argon atmosphere were consecutively added DIPEA (1.77 mL, 10.2 mmol), TBAI (75 mg, 0.20 mmol), and MOM-Cl (0.44 mL, 5.80 mmol). The reaction mixture was then stirred at 50 °C for 24 h. After dilution with $CH_2Cl_2$, the mixture was washed with water, dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (60% EtOAc in hexane) to give MOM-protected lactone **10** (300 mg, 95%) as a yellow amorphous solid. $[\alpha]_D^{20}$ − 46.1 (*c* 0.79, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.58 (d, *J* = 0.6 Hz, 2H), 5.43 (d, *J* = 3.8 Hz, 1H), 4.56 (ddd, *J* = 5.1, 3.8, 0.9 Hz, 1H), 4.32 (d, *J* = 7.1 Hz, 1H), 4.14 (d, *J* = 7.1 Hz, 1H), 3.85 (s, 6H), 3.83 (s, 3H), 3.06 (s, 3H), 2.88 (dd, *J* = 17.5, 5.3 Hz, 1H), 2.73 (dd, *J* = 17.5, 0.9 Hz, 1H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): $\delta$ 174.9, 153.2, 137.9, 129.3, 103.6, 95.1, 84.6, 74.1, 60.8, 56.1, 55.4, 37.5. LRMS (ESI) 647.2 [2M + Na]$^+$. HRMS (ESI-Orbitrap) *m/z*: [M + Na]$^+$ calcd for $C_{15}H_{20}O_7Na$, 335.1101; found, 335.1103.

**(4*R*,5*R*)-4-(Methoxymethoxy)-5-(3,4,5-trimethoxyphenyl)-tetrahydrofuran-2-ol (6).** To a stirred solution of lactone **10a** (240 mg, 0.77 mmol) in $CH_2Cl_2$ (6 mL) at −78 °C under argon atmosphere was added DIBAL-H (0.92 mL, 0.92 mmol), and the resulting mixture was stirred at the same temperature for 2 h. After this period, the reaction mixture was quenched by the addition of MeOH (3 mL) and warmed to 23 °C. Then, saturated aqueous solution of sodium potassium tartarate was added and stirred vigorously at 23 °C for 2 h until it forms into a white suspension. The suspension was filtered through a plug of Celite, and solvents were removed under reduced pressure.

To a crude lactol, DMAP (17 mg, 0.14 mmol), $Et_3N$ (0.50 mL, 3.59 mmol), and $Ac_2O$ (0.17 mL, 1.80 mmol) were added at 0 °C under argon atmosphere, and the resulting mixture was stirred for 2 h. Upon completion, solvents were removed under reduced pressure, and the crude product was purified by column chromatography over silica gel (50% EtOAc in hexanes) to give acetate **6** (240 mg) as the major isomer and the corresponding minor anomer (16 mg) as colorless oils in 88% over two steps. Acetate **6**: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.61 (s, 1H), 6.59 (dd, *J* = 6.1, 3.3 Hz, 1H), 5.09 (d, *J* = 3.8 Hz, 1H), 4.45 (ddd, *J* = 5.8, 3.8, 1.9 Hz, 1H), 4.30 (d, *J* = 7.0 Hz, 1H), 4.12 (d, *J* = 6.9 Hz, 1H), 3.84 (s, 6H), 3.81 (s, 3H), 3.06 (s, 3H), 2.53 (ddd, *J* = 14.7, 6.1, 1.9 Hz, 1H), 2.37 (ddd, *J* = 14.7, 6.1, 3.3 Hz, 1H), 2.06 (s, 3H). $^{13}$C{$^1$H} NMR (major anomer, 101 MHz, $CDCl_3$): $\delta$ 170.2, 152.9, 137.5, 131.1, 104.2, 97.4, 95.1, 83.7, 76.6, 60.8, 56.1, 55.2, 40.4, 21.2. LRMS (ESI), 735.2 ([2M + Na]$^+$). HRMS (ESI-Orbitrap) *m/z*: [M + Na]$^+$ calcd for $C_{17}H_{26}O_8Na$, 379.1363; found, 379.1360. Minor isomer: $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.63 (s, 2H), 6.42 (d, *J* = 5.8 Hz, 1H), 5.08 (d, *J* = 4.5 Hz, 1H), 4.42−4.35 (m, 2H), 4.23−4.17 (m, 1H), 3.88−3.85 (s, 6H), 3.83 (s, *J* = 0.9 Hz, 3H), 3.11 (s, 3H), 2.50−2.42 (m, 1H), 2.40−2.34 (m, 1H), 2.13 (s, 3H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): $\delta$ 170.4, 152.8, 132.14, 129.8, 104.4, 98.0, 95.2, 86.4, 75.4, 60.8, 56.0, 55.2, 39.3, 21.4. LRMS (ESI), 357.1 ([M + H]$^+$).

**(4*R*,5*R*)-4-(Methoxymethoxy)-5-(3,4,5-trimethoxyphenyl)-tetrahydrofuran-2-yl Acetate (11).** To a stirred solution of lactone **7** (95 mg, 0.354 mmol) in $CH_2Cl_2$ (3 mL) at 0 °C under argon



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atmosphere were added 2,6-lutidine (0.12 mL, 1.06 mmol) and TBSOTf (0.12 mL, 0.53 mmol). The reaction mixture was warmed to 23 °C and stirred for 3h. When the reaction was finished, the mixture was quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with dichloromethane. The extracts were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (40% EtOAc in hexanes) to give silyl ether derivative (69 mg, 51%) as an orange amorphous solid. $[\alpha]_D^{20}$ − 34.7 (*c* 0.29, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): δ 6.54 (s, 2H), 5.37 (*d*, *J* = 3.5 Hz, 1H), 4.55 (*ddd*, *J* = 4.8, 3.5, 0.7 Hz, 1H), 3.85 (s, 6H), 3.82 (s, 3H), 2.87 (*dd*, *J* = 17.1, 4.8 Hz, 1H), 2.59 (*dd*, *J* = 17.1, 0.7 Hz, 1H), 0.67 (s, 9H), −0.13 (s, 3H), −0.34 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 175.5, 153.1, 138.0, 129.9, 103.8, 86.0, 71.5, 60.8, 56.1, 40.2, 25.3, 17.7, −5.4, −5.6. LRMS (ESI), 405.2 $[M + Na]^+$.

The title compound was prepared from above lactone (55 mg), reduced, and protected as acetate derivatives following the procedure described for the preparation of acetate **6**. The compound was purified by flash column chromatography over silica gel (20% EtOAc in hexanes) to give acetate **11** (50 mg, 81% over two steps) as a white amorphous solid. $[\alpha]_D^{20}$ − 13.6 (*c* 0.5, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): δ 6.60 (*dd*, *J* = 5.9, 3.8 Hz, 1H), 6.56 (*d*, *J* = 0.5 Hz, 2H), 5.03 (d, *J* = 3.6 Hz, 1H), 4.43 (*ddd*, *J* = 5.4, 3.6, 1.9 Hz, 1H), 3.83 (s, 6H), 3.78 (s, 3H), 2.44−2.27 (m, 2H), 2.05 (s, 3H), 0.67 (s, 9H), −0.17 (s, 3H), −0.35 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.3, 152.7, 137.5, 131.7, 104.6, 97.9, 85.2, 73.7, 60.7, 56.0, 43.1, 25.4, 21.2, 17.8, −5.4, −5.5. LRMS (ESI), 449.2 $[M + Na]^+$. HRMS (ESI-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{21}H_{34}O_7SiNa$, 449.1966; found, 449.1969.

**(4*R*,5*R*)-4-((2-Methoxyethoxy)methoxy)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran-2-yl Acetate (12).** To a stirred solution of lactone **7** (125 mg, 0.47 mmol) in distilled THF (2 mL) at 0 °C under argon atmosphere were consecutively added DIPEA (0.81 mL, 4.7 mmol), TBAI (43 mg, 0.12 mmol), and MEM-Cl (0.27 mL, 2.33 mmol). The resulting reaction mixture was stirred at 55 °C for 72 h. Upon completion, the mixture was diluted with EtOAc and washed with water. The organic phase was dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (80% EtOAc in hexanes) to give MEM-protected lactone (131 mg, 79%) as a yellow amorphous solid. $[\alpha]_D^{20}$ − 25.5 (*c* 0.29, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): δ 6.57 (s, 2H), 5.43 (*d*, *J* = 3.8 Hz, 1H), 4.62 (*ddd*, *J* = 5.0, 3.8, 1.0 Hz, 1H), 4.42 (d, *J* = 7.3 Hz, 1H), 4.23 (d, *J* = 7.3 Hz, 1H), 3.85 (s, 6H), 3.83 (s, 3H), 3.45 (*ddd*, *J* = 10.6, 5.6, 3.3 Hz, 1H), 3.41−3.36 (m, 2H), 3.32 (s, 3H), 3.22 (*ddd*, *J* = 10.6, 5.3, 3.4 Hz, 1H), 2.87 (*dd*, *J* = 17.6, 5.2 Hz, 1H), 2.74 (*dd*, *J* = 17.5, 1.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 175.0, 153.2, 137.9, 129.3, 103.5, 93.9, 84.6, 74.0, 71.4, 67.0, 60.8, 58.9, 56.1, 37.4. LRMS (ESI), 379.4 $[M + Na]^+$.

The title compound was prepared from above lactone (111 mg) following the procedure described for the preparation of acetate **6**. The compound was purified by flash column chromatography (20% EtOAc in hexane) to give acetate **12** (50 mg, 72% over two steps) as a white amorphous solid. $[\alpha]_D^{20}$ + 4.1 (*c* 0.69, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): δ 6.58 (s, 2H), 6.55 (*dd*, *J* = 6.1, 3.3 Hz, 1H), 5.07 (*d*, *J* = 3.8 Hz, 1H), 4.48 (*ddd*, *J* = 5.8, 3.8, 1.7 Hz, 1H), 4.37 (d, *J* = 7.2 Hz, 1H), 4.19 (*d*, *J* = 7.1 Hz, 1H), 3.81 (s, 6H), 3.78 (s, 3H), 3.41 (*ddd*, *J* = 10.4, 5.8, 3.3 Hz, 1H), 3.37−3.32 (m, 2H), 3.29 (s, 3H), 3.17 (*ddd*, *J* = 10.4, 5.2, 3.3 Hz, 1H), 2.50 (*ddd*, *J* = 14.7, 6.1, 1.8 Hz, 1H), 2.34 (*ddd*, *J* = 14.7, 6.0, 3.3 Hz, 1H), 2.03 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.2, 152.8, 137.3, 131.1, 104.1, 97.4, 93.9, 83.7, 76.5, 71.4, 66.7, 60.8, 58.8, 56.0, 40.3, 21.2. LRMS (ESI), 423.2 $[M + Na]^+$. HRMS (ESI-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{19}H_{28}O_9Na$, 423.1626; found, 423.1623.

**General Procedure for the Allylation of Tetrahydrofuranyl Acetate.** A solution of tetrahydrofuranyl acetate in distilled $CH_2Cl_2$ at −78 °C under argon atmosphere was treated with allyltrimethylsilane (4.0 equiv) and Lewis acid. The resulting reaction mixture was stirred at −78 °C for 3 h. After this period, the reaction mixture was treated with saturated aqueous $Na_2HPO_4$ (1 mL per mmol of acetate). The aqueous layer was then extracted three times with $CH_2Cl_2$, and the collected organic phases were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure.

*Preparation of (2R,3R,5S)-5-Allyl-3-(methoxymethoxy)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran (13a) and (2R,3R,5R)-5-Allyl-3-(methoxymethoxy)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran (14a) Mixture.* Following the general procedure described above and starting from acetate **6** (18 mg, 0.05 mmol) in $CH_2Cl_2$ (1 mL), compounds **13a** and **14a** (14.4 mg, 84% yield) were obtained as a colorless oil after the crude residue was purified by column chromatography over silica gel (5−20% EtOAc in hexanes). The results are summarized in Table S1. $^1H$ NMR (mixture, 400 MHz, $CDCl_3$): δ 6.64 (s, 3.2H), 6.61 (s, 2H), 6.00−5.74 (m, 2.6H), 5.18−5.04 (m, 5.2H), 4.93 (*d*, *J* = 3.3 Hz, 1H), 4.73 (*d*, *J* = 4.1 Hz, 1.6H), 4.58−4.44 (m, 1H), 4.41−4.25 (m, 5.3H), 4.18−4.01 (m, 4.8H), 3.85 (s, 15.2H), 3.81 (s, 4.6H), 3.81 (s, 3H), 3.07 (s, 4.8H), 3.04 (s, 3H), 2.70−2.57 (m, 1.7H), 2.52−2.29 (m, 5.8H), 2.19 (*ddd*, 1H), 1.91 (*ddd*, *J* = 13.2 Hz, 1H), 1.85 (*ddd*, *J* = 11.4, 6.0 Hz, 1.7H). $^{13}C\{^1H\}$ NMR (mixture, 100 MHz, $CDCl_3$): δ 152.8, 134.8, 134.1, 133.6, 133.1, 117.4, 116.9, 104.2, 104.0, 95.0, 84.30, 83.7, 78.7, 77.8, 77.6, 77.1, 60.8, 56.0, 55.1, 40.4, 40.2, 38.8, 38.3. LRMS (ESI) *m/z*: 361.2 $[M + Na]^+$. HRMS (ESI-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{18}H_{26}O_6Na$, 361.1622; found, 361.1624.

*Preparation of (((2R,3R,5S)-5-Allyl-2-(3,4,5-trimethoxyphenyl)-tetrahydrofuran-3-yl)oxy)(tert-butyl)dimethylsilane (13b).* Following the general procedure described above and starting from acetate **11** (21.7 mg, 0.05 mmol) in $CH_2Cl_2$ (1 mL), the title compound **13b** (16.8 mg, 81% yield) was prepared as a colorless oil after the crude residue was purified by column chromatography over silica gel (5−20% EtOAc in hexanes). The results are summarized in Table S1. $[\alpha]_D^{20}$ − 62.0 (*c* 0.79, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): δ 6.59 (s, 2H), 5.99−5.85 (m, 1H), 5.18−5.04 (m, 2H), 4.73 (*d*, *J* = 3.7 Hz, 1H), 4.30 (td, *J* = 3.7, 1.8 Hz, 1H), 4.22−4.13 (m, 1H), 3.84 (s, 6H), 3.79 (s, 3H), 2.67 (dt, *J* = 13.6, 6.7 Hz, 1H), 2.48 (dt, *J* = 13.8, 6.9 Hz, 1H), 2.35 (*ddd*, *J* = 13.6, 8.5, 5.4 Hz, 1H), 1.80 (*ddd*, *J* = 13.2, 4.4, 1.7 Hz, 1H), 0.68 (s, 9H), −0.13 (s, 3H), −0.37 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.6, 135.3, 133.9, 116.6, 104.6, 85.9, 77.4, 74.6, 60.7, 55.9, 41.0, 40.6, 25.5, 17.7, −5.3, −5.6. LRMS (ESI), 431.2 $[M + Na]^+$. HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{39}O_5Si$, 409.2405; found, 409.2401.

*Preparation of (((2R,3R,5S)-5-Allyl-2-(3,4,5-trimethoxyphenyl)-tetrahydrofuran-3-yl)oxy)(tert-butyl)dimethylsilane (13c).* Following the general procedure described above and starting from acetate **12** (20 mg, 0.05 mmol) in $CH_2Cl_2$ (1 mL), the title compound **13c** (6.3 mg, 33% yield) was prepared as a colorless oil after the crude residue was purified by column chromatography over silica gel (40% EtOAc in hexanes). The results are summarized in Table S1. $[\alpha]_D^{20}$ − 85.0 (*c* 0.12, $CHCl_3$). $^1H$ NMR (800 MHz, $CDCl_3$): δ 6.63 (s, 2H), 5.91−5.86 (m, 1H), 5.15 (*dd*, *J* = 35.1, 13.7 Hz, 2H), 4.96 (*d*, *J* = 3.2 Hz, 1H), 4.53 (dq, *J* = 12.2, 6.1 Hz, 1H), 4.49 (d, *J* = 7.2 Hz, 1H), 4.43 (t, *J* = 3.7 Hz, 1H), 4.28 (d, *J* = 7.2 Hz, 1H), 3.88 (s, 6H), 3.84 (s, 3H), 3.44 (*ddd*, *J* = 10.7, 6.2, 3.2 Hz, 1H), 3.41−3.36 (m, 2H), 3.35 (s, 3H), 3.19 (*ddd*, *J* = 10.7, 5.5, 3.2 Hz, 1H), 2.51 (dt, *J* = 13.2, 6.3 Hz, 1H), 2.41 (dt, *J* = 14.0, 6.9 Hz, 1H), 2.25 (*dd*, *J* = 13.3, 5.9 Hz, 1H), 1.93 (ddd, *J* = 13.6, 9.6, 4.5 Hz, 1H). $^{13}C\{^1H\}$ NMR (200 MHz, $CDCl_3$): δ 152.9, 137.2, 134.2, 133.8, 117.5, 104.1, 94.0, 83.8, 78.7, 77.8, 71.6, 66.6, 60.9, 59.0, 56.1, 40.3, 38.8. LRMS (ESI), 405.1 $[M + Na]^+$. HRMS (ESI-Orbitrap) *m/z*: $[M + Na]^+$ calcd for $C_{20}H_{30}O_7Na$, 405.1884; found, 405.1882.

*(2S,3aR,9bR)-2-Allyl-6,7,8-trimethoxy-3,3a,5,9b-tetrahydro-2H-furo[3,2-c]isochromene (17).* To a stirred solution of acetate **6** (13.2 mg, 0.037 mmol) in $CH_2Cl_2$ (2.4 mL) at −78 °C under argon atmosphere were added allyltrimethylsilane (24 μL, 0.148 mmol) and $SnBr_4$ (26 mg, 0.059 mmol, 1.6 equiv). The reaction mixture was stirred for 3 h at the same temperature, and the reaction progress was monitored by TLC. When the starting material was completely consumed, additional portion of $SnBr_4$ (33 mg, 0.075 mmol, 2.0 equiv) was added at 0 °C, and the resulting mixture was warmed to 23 °C overnight. After this period, the reaction mixture was quenched by the addition of saturated aqueous $Na_2HPO_4$ (0.4 mL) and extracted



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with dichloromethane (2×). The extracts were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. NMR analysis of the unpurified crude product showed a pair of diastereomers in a 4:1 ratio (*cis*/*trans* diastereomers). The crude product was purified by column chromatography over silica gel (10% EtOAc in hexanes) to give **17** and **18** (5.9 mg, 52%) as a colorless oil. $[\alpha]_D^{20}$ + 25.6 (*c* 0.67, $CHCl_3$). *cis*-Isomer **17** (major): $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.79 (s, 1H), 5.96−5.64 (m, 1H), 5.21−4.97 (m, 2H), 4.90 (d, *J* = 15.1 Hz, 1H), 4.42 (d, *J* = 15.1 Hz, 1H), 4.30 (d, *J* = 3.3 Hz, 1H), 4.16 (ddd, *J* = 6.8, 3.3, 1.7 Hz, 1H), 4.02 (qd, *J* = 7.4, 5.8 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 2.65−2.44 (m, 2H), 2.43−2.29 (m, 1H), 1.81 (ddd, *J* = 14.0, 7.2, 1.7 Hz, 1H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): $\delta$ 152.9, 149.0, 141.7, 134.7, 126.5, 121.8, 117.1, 108.7, 78.1, 75.4, 63.3, 60.9, 60.7, 56.1, 40.3, 39.0. LRMS (ESI), 307.1 [M + H]$^+$. HRMS (ESI-Orbitrap) *m*/*z*: [M + Na]$^+$ calcd for $C_{17}H_{22}O_5$, 329.1359; found, 329.1357. *trans*-Isomer **18** (minor): $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.79 (s, 1H), 5.92−5.76 (m, 1H), 5.18−5.04 (m, 2H), 4.91 (d, *J* = 15.0 Hz, 1H), 4.61 (d, *J* = 3.0 Hz, 1H), 4.45−4.32 (m, 2H), 4.26−4.18 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 2.48 (dt, *J* = 12.6, 6.2 Hz, 1H), 2.34 (dt, *J* = 14.0, 7.0 Hz, 1H), 2.26 (dd, *J* = 13.5, 5.7 Hz, 1H), 1.94 (ddd, *J* = 13.6, 9.8, 4.8 Hz, 1H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): $\delta$ 152.8, 148.8, 141.4, 134.2, 127.2, 121.0, 117.3, 108.4, 77.6, 77.4, 74.5, 62.8, 60.7, 60.6, 56.0, 39.9, 39.4. LRMS (ESI), 307.1 [M + H]$^+$.

*(2S,3aR,9bR)-6,7,8-Trimethoxy-2-propyl-3,3a,5,9b-tetrahydro-2H-furo[3,2-c]isochromene (19).* To a stirred of isochromene **17** (47.4 mg, 0.156 mmol) in EtOAc (2 mL) at 23 °C was added 10% Pd/C (10 mg). The resulting solution was stirred at 23 °C under a hydrogen-filled balloon over 12 h. Upon completion, the mixture was filtered through a plug of Celite, and solvents were removed under reduced pressure. The crude product was purified by silica gel column chromatography (20% EtOAc in hexane) to give propyl derivative **19** (42.2 mg, 88%). $[\alpha]_D^{20}$ + 15.3 (*c* 0.40, $CHCl_3$); reported $[\alpha]_D^{26}$ + 16.5 (*c* 1.02, $CHCl_3$).[17] $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.80 (s, 1H), 4.89 (d, *J* = 15.0 Hz, 1H), 4.41 (d, *J* = 15.1 Hz, 1H), 4.26 (d, *J* = 3.3 Hz, 1H), 4.20−4.09 (m, 1H), 3.93 (q, *J* = 7.1 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 2.52 (dt, *J* = 14.3, 7.3 Hz, 1H), 1.80−1.69 (m, 2H), 1.61−1.52 (m, 1H),1.47−1.36 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): $\delta$ 152.8, 148.9, 141.6, 126.6, 121.8, 108.7, 78.6, 77.4, 75.2, 63.3, 60.9, 60.7, 56.1, 39.6, 38.1, 19.6, 14.1. LRMS (ESI), 309.1 [M + H]$^+$.

*(2S,3aR,9bR)-6,7,8-Trimethoxy-2-propyl-2,3,3a,9b-tetrahydro-5H-furo[3,2-c]isochromen-5-one (20).* To a solution of propyl derivative **19** (41.2 mg, 0.135 mmol) in $CH_2Cl_2$ (4 mL), pyridine (54 μL, 0.67 mmol), and $CrO_3$ (40 mg, 0.40 mmol) were added and stirred for 36 h at 23 °C. After this period, the reaction mixture was concentrated under reduced pressure, and ethyl acetate (10 mL) was added and filtered. The filtrate was washed with aqueous $CuSO_4$ solution followed by water. The organic phase was dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. Flash chromatography over silica gel (30% EtOAc in hexanes) provided δ-valerolactone **20** (17.2 mg, 40%; 60% brsm) as a pale yellow oil with the recovered starting material **19** (13.7 mg). $[\alpha]_D^{20}$ + 20.4 (*c* 0.31, $CHCl_3$); reported $[\alpha]_D^{24}$ + 21.5 (*c* 0.50, $CHCl_3$).[18] $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.78 (s, 1H), 4.94 (ddd, *J* = 5.8, 2.9, 1.0 Hz, 1H), 4.51 (d, *J* = 2.9 Hz, 1H), 4.25−4.06 (m, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.88 (s, 3H), 2.51 (ddd, *J* = 14.4, 8.8, 5.8 Hz, 1H), 2.16 (ddd, *J* = 14.3, 5.5, 1.1 Hz, 1H), 1.76−1.69 (m, 1H), 1.66−1.58 (m, 1H), 1.45−1.31 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): $\delta$ 159.8, 157.9, 156.4, 144.2, 132.5, 111.2, 108.0, 79.4, 78.9, 75.0, 61.7, 61.0, 56.1, 39.0, 38.0, 19.1, 13.9. LRMS (ESI), 323.0 [M + H]$^+$. HRMS (ESI-Orbitrap) *m*/*z*: [M + Na]$^+$ calcd for $C_{17}H_{22}O_5Na$, 345.1309; found, 345.1306.

*(+)-Monocerin (1).* To a solution of δ-valerolactone **20** (13.4 mg, 0.042 mmol) in dry $CH_2Cl_2$ (1 mL) at −10 °C under argon atmosphere was added $BCl_3$ (1.0 M in DCM, 50 μL, 0.11 mmol). The mixture was stirred at −10 °C for 2 h, and the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (1 mL). The mixture was extracted with ethyl acetate, and the organic layer was washed with brine, dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography over silica gel (20% EtOAc in hexanes) gave (+)-monocerin (**1**) (4.9 mg, 41% yield; 88% yield brsm) as a colorless oil with the recovered starting material **20** (7.6 mg). $[\alpha]_D^{20}$ + 57.8 (*c* 0.29, $CHCl_3$); reported $[\alpha]_D^{24}$ + 53.0 (*c* 0.85, MeOH).[5] $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 11.28 (s, 1H), 6.59 (s, 1H), 5.05 (ddd, *J* = 6.3, 3.2, 1.2 Hz, 1H), 4.54 (d, *J* = 3.1 Hz, 1H), 4.12 (dq, *J* = 8.6, 6.3 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 2.59 (ddd, *J* = 14.6, 8.6, 6.2 Hz, 1H), 2.16 (ddd, *J* = 14.5, 5.9, 1.2 Hz, 1H), 1.74−1.65 (m, 1H), 1.62−1.52 (m, 1H), 1.49−1.29 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): $\delta$ 167.9, 158.8, 156.4, 137.5, 131.3, 104.5, 102.2, 81.4, 78.9, 74.6, 60.9, 56.4, 39.2, 38.2, 19.3, 14.1. LRMS (ESI), 309.1 [M + H]$^+$. HRMS (ESI-Orbitrap) *m*/*z*: [M + H]$^+$ calcd for $C_{16}H_{21}O_5$, 309.1333; found, 309.1335.

*(+)-Acetylmonocerin (2).* Acetic anhydride (75 μL, 0.8 mmol) and DMAP (catalytic amount) were added to a solution of (+)-monocerin (**1**) (2.2 mg, 0.007 mmol) in 0.2 mL of distilled pyridine at 0 °C under argon atmosphere, and the mixture was stirred at 23 °C for 5 h. After removing the solvent under reduced pressure, the crude product was purified by flash column chromatography on silica gel (33% EtOAc in hexanes) to give (+)-acetylmonocerin (**2**) (2.4 mg, 96% yield) as a white amorphous solid. $[\alpha]_D^{23}$ + 3.6 (*c* 0.29, $CHCl_3$); reported $[\alpha]_D^{24}$ − 3.0 (*c* 0.1, EtOH) for enantiomer of compound **2**.[19] $^1$H NMR (800 MHz, $CDCl_3$): $\delta$ 6.90 (s, 1H), 4.99 (m, 1H), 4.55 (d, *J* = 3.1 Hz, 1H), 4.14 (m, 1H), 3.97 (s, 3H), 3.85 (s, 3H), 2.53 (ddd, *J* = 14.5, 8.7, 5.9 Hz, 1H), 2.42 (s, 3H), 2.13 (dd, *J* = 14.3, 5.5 Hz, 1H), 1.71−1.64 (m, 1H), 1.58−1.54 (m, 1H), 1.44−1.39 (m, 1H), 1.35−1.32 (m, 1H), 0.90 (t, *J* = 7.3 Hz, 3H). $^{13}$C{$^1$H} NMR (200 MHz, $CDCl_3$): $\delta$ 169.3, 159.9, 158.0, 146.1, 143.3, 132.7, 110.4, 109.9, 79.9, 79.0, 74.6, 61.2, 56.3, 39.0, 38.2, 21.0, 19.1, 14.0. LRMS (ESI), 373.1 [M + Na]$^+$.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b00414.

Full spectroscopic data for all compounds (PDF)

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### Notes

The authors declare no competing financial interest.

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