

連続的 Overman/Claisen 転位の開発と  
ステモナルカロイド類の合成

2015 年度

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2015 年度

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# 目次

|                                       |     |
|---------------------------------------|-----|
| はじめに .....                            | iii |
| 略語表 .....                             | iv  |
| 緒論                                    |     |
| 第一章 カスケード型転位反応                        |     |
| 第一節 転位を含むカスケード型反応を利用した全合成例 .....      | 2   |
| 第二節 アリル-1,2-ジオールに対する Overman 転位 ..... | 4   |
| 2.1 Overman/Overman 転位 .....          | 6   |
| 2.2 オルトアミド型 Overman 転位 .....          | 7   |
| 第二章 ステモナルカロイド                         |     |
| 第一節 ステモアミド                            |     |
| 1.1 単離・構造および生物活性 .....                | 8   |
| 1.2 過去の全合成例 .....                     | 8   |
| 第二節 ネオステニン                            |     |
| 2.1 単離・構造および生物活性 .....                | 11  |
| 2.2 過去の全合成例 .....                     | 13  |
| 第三節 ステニン                              |     |
| 3.1 単離・構造および生物活性 .....                | 16  |
| 3.2 過去の全合成例 .....                     | 16  |
| 本論                                    |     |
| 第一章 連続的 Overman/Claisen 転位の開発         |     |
| 第一節 研究背景および概略 .....                   | 22  |
| 第二節 アリル-1,2-ジオールの調製 .....             | 24  |
| 第三節 オルトアミド型 Overman 転位                |     |
| 3.1 環状オルトアミドの合成 .....                 | 28  |
| 3.2 オルトアミド型 Overman 転位 .....          | 31  |
| 第四節 連続的 Overman/Claisen 転位 .....      | 35  |
| 第五節 第一章のまとめ .....                     | 37  |

|           |                                      |     |
|-----------|--------------------------------------|-----|
| 第二章       | (-)-ステモアミドの全合成                       |     |
| 第一節       | 合成計画.....                            | 38  |
| 第二節       | アリル-1,2-ジオールの合成.....                 | 39  |
| 第三節       | 連続的 Overman/Claisen 転位.....          | 40  |
| 第四節       | (-)-ステモアミドの全合成.....                  | 41  |
| 第五節       | 第二章のまとめ.....                         | 44  |
| 第三章       | (+)-ネオステニンの全合成                       |     |
| 第一節       | 合成計画.....                            | 46  |
| 第二節       | Z-アリルアルコールの合成.....                   | 48  |
| 第三節       | Claisen 転位による二連続不斉中心の導入              |     |
| 3.1       | Ireland–Claisen 転位.....              | 50  |
| 3.2       | Johnson–Claisen 転位.....              | 52  |
| 第四節       | 連続的 Overman/Claisen 転位.....          | 55  |
| 第五節       | (+)-ネオステニンの不斉全合成                     |     |
| 5.1       | ネオステニン A 環部の構築.....                  | 57  |
| 5.2       | ネオステニン B 環部の構築.....                  | 60  |
| 5.3       | SmI <sub>2</sub> 環化による C・D 環の構築..... | 62  |
| 5.4       | (+)-ネオステニンの全合成.....                  | 66  |
| 第六節       | 第三章のまとめ.....                         | 69  |
| 総括.....   |                                      | 71  |
| 実験編.....  |                                      | 75  |
| 参考文献..... |                                      | 237 |
| 謝辞.....   |                                      | 239 |

## はじめに

医薬品に代表される様々な有用物質の多くが、その構造中に窒素原子を含んでいる。特に近年、有機合成により供給が望まれるキラル化合物は複雑化しており、窒素原子を含む連続した不斉中心の効率的な合成法の開発が求められている。

一方、[3,3]シグマトロピー転位は、水酸基の立体化学を新たな炭素-窒素、炭素-炭素結合へと不斉転写できるため、キラル化合物を合成する信頼できる方法の一つとして用いられている。糖や酒石酸などのバイオマス由来の水酸基に本法を適用すれば、高い光学純度で目的化合物を供給できる。しかし、バイオマス中の複数の水酸基は区別化が難しく、遊離の水酸基存在下で選択的な変換を施すことは困難であった。その区別化のため、長年にわたり保護基が用いられてきたが、保護・脱保護に伴う総工程数の増加、ならびに総収率の低下が問題となっていた。

そこで、本研究では保護基の着脱を経由しない連続的 Overman/Claisen 転位を開発した。本反応は、バイオマス由来の2つの水酸基を加熱条件下の平衡反応により区別化し、ワンポットにて2種類の異なる転位反応を実現できた。さらに、開発した反応を用いて完全な立体選択性で含窒素2連続不斉中心を構築し、ステモナルカロイド類（ステモアミド、ネオステニン）の不斉全合成を達成したので、以下にその内容について詳述する。

## 略語表

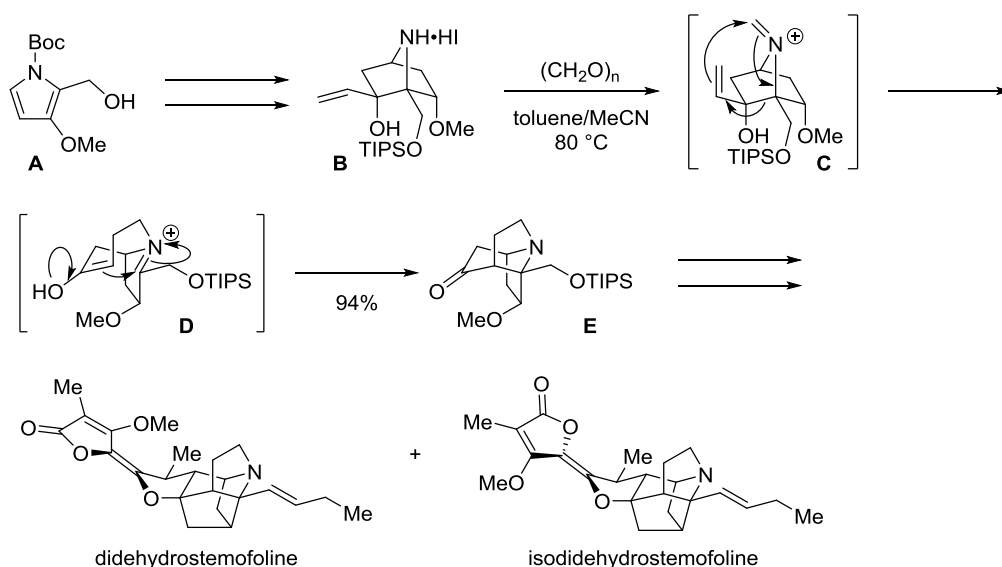
|          |   |
|----------|---|
| Ac       | acetyl  |
| BHT      | 2,6-di- <i>tert</i> -butyl-4-hydroxytoluene               |
| Bn       | benzyl  |
| Boc      | <i>t</i> -butoxycarbonyl                                  |
| Bu       | butyl   |
| CAN      | cerium (IV) ammonium nitrate                              |
| Cbz      | benzyloxycarbonyl   |
| CSA      | camphorsulfonic acid                                      |
| DBU      | 1,8-diazabicyclo[5.4.0]undec-7-ene                        |
| DDQ      | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone                 |
| DEAD     | diethyl azodicarboxylate                                  |
| DIBAL    | diisobutylaluminium hydride                               |
| DMAP     | 4-(dimethylamino)pyridine                                 |
| DMF      | <i>N,N</i> -dimethylformamide                             |
| DMPU     | 1,3-dimethyl-3,4,5,6-tetrahydro-2(1 <i>H</i> )-pyrimidone |
| DMSO     | dimethylsulfoxide   |
| EDCI     | 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide             |
| Et       | ethyl   |
| HMPA     | hexamethylphosphoramide                                   |
| <i>i</i> | iso   |
| Me       | methyl  |
| MOM      | methoxymethyl   |
| MPM      | <i>p</i> -methoxybenzyl                                   |
| Ms       | methanesulfonyl   |
| MS       | molecular sieves  |
| <i>n</i> | normal  |
| NMO      | <i>N</i> -methylmorpholine oxide                          |
| Ph       | phenyl  |
| Pr       | propyl  |
| <i>t</i> | tertiary  |
| TBAI     | tetrabutylammonium iodide                                 |
| TBDPS    | <i>tert</i> -butyldiphenylsilyl                           |
| TBS      | <i>tert</i> -butyldimethylsilyl                           |
| THF      | tetrahydrofuran   |
| TIPS     | triisopropylsilyl   |
| TMS      | trimethylsilyl  |
| TPAP     | tetra- <i>n</i> -propylammonium perruthenate              |

# 緒論

# 第一章 カスケード型転位反応

## 第一節 転位を含むカスケード型反応を利用した全合成例<sup>1</sup>

2003年、Overmanらは連続的 aza-Cope 転位/Mannich 反応を鍵工程とした、(±)-ジデヒドロステモフォリンおよび(±)-イソジデヒドロステモフォリンの全合成を報告している<sup>2</sup> (スキーム 1)。ピロロール **A** より合成した **B** を、パラホルムアルデヒド存在下加熱すると、**C** を経由して aza-Cope 転位が進行し、**D** を生じた。さらに、**D** の Mannich 反応により、三環性骨格 **E** を与えた。その後、数工程の誘導により 2 種類の天然物の全合成を達成した。

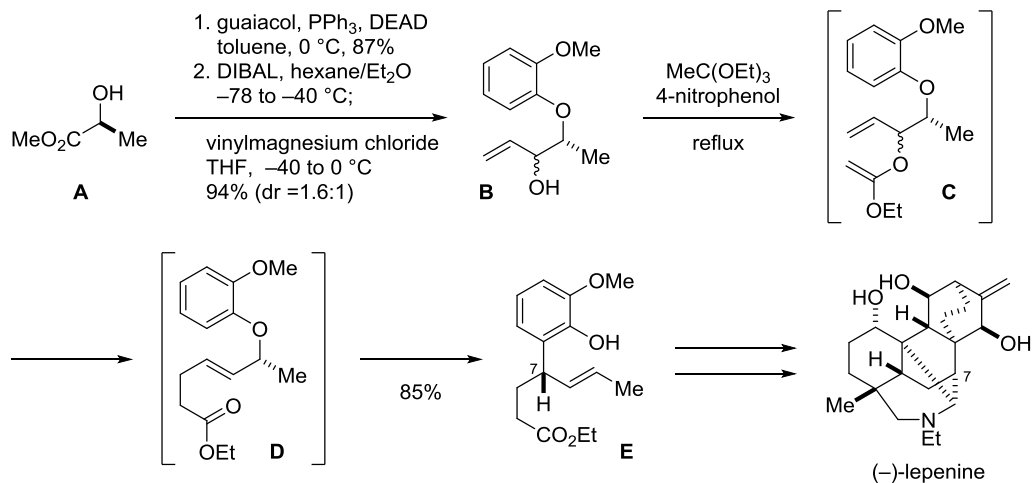


**Scheme 1.** Overman らによるジデヒドロステモフォリンの全合成

特に、目的の天然物は不斉点の密集したかご型の中心骨格を有しており、これをいかに合成するかが重要である。本合成では鍵反応の連続転位により、天然物に対応する 2 つの炭素-炭素結合と、合成困難な含窒素四置換炭素を一挙に、高収率にて構築している。

2014年、福山らは分子内 Diels-Alder 反応、Mannich 反応を鍵反応とした(-)-レペニンの全合成を報告している<sup>3</sup>。その際、7 位の立体化学の構築に連続的 Johnson-Claisen/Claisen 転位を利用している (スキーム 2)。L-乳酸メチル **A** を出発原料とし、光延反応、DIBAL 還元続くビニル化によりアリルアルコール **B** とした。**B** を  $\text{MeC}(\text{OEt})_3$ 、4-ニトロフェノール存在下加熱すると Johnson-Claisen が進行した。生じたアリルビニルエーテル **D** を経由した Claisen 転位により、レペニンの 7 位立体化学を有する転位体 **E** を得た。その後、種々官能基変換を経て、(-)-レペニンの全合成を達成した。





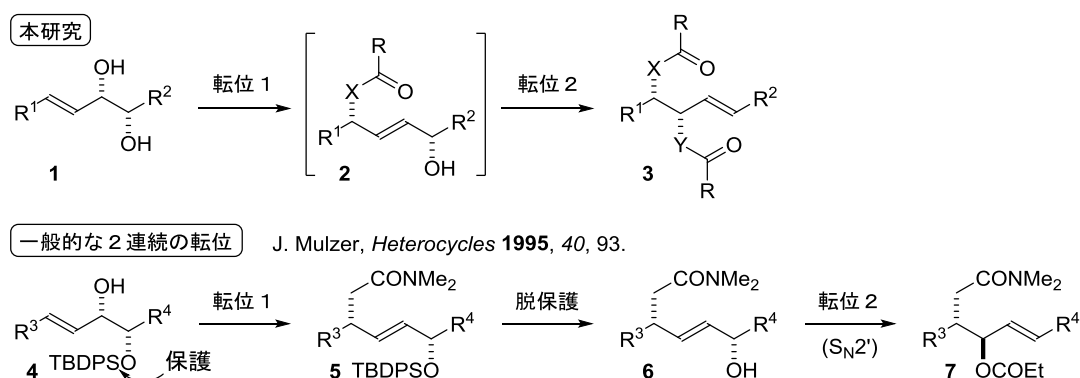
**Scheme 2.** 福山らによる(-)-レペニンの全合成

本天然物も、連続した多数の不斉点を有するかご型の構造をしており、有機合成的に非常に挑戦的な化合物である。合成序盤のワンポット連続転位反応により、ジアステレオ混合物のアリルアルコールを単一の幾何異性のオレフィンに収束させるとともに、2級水酸基の立体化学を新たな炭素-炭素結合へと不斉転写し、完全な立体選択性で7位の立体化学を構築した。

以上のように、転位を含むカスケード型反応はワンポットにて複数の新たな結合、不斉中心を一挙に導入できるため、天然物合成において非常に有用である。また、入念に基質を設計すれば、鎖状・環状化合物ともに高い立体選択性が期待できる。さらに、基質の構造が飛躍的に複雑化するため、客観的にも大変興味深い反応だと言える。

## 第二節 アリル-1,2-ジオールに対する Overman 転位

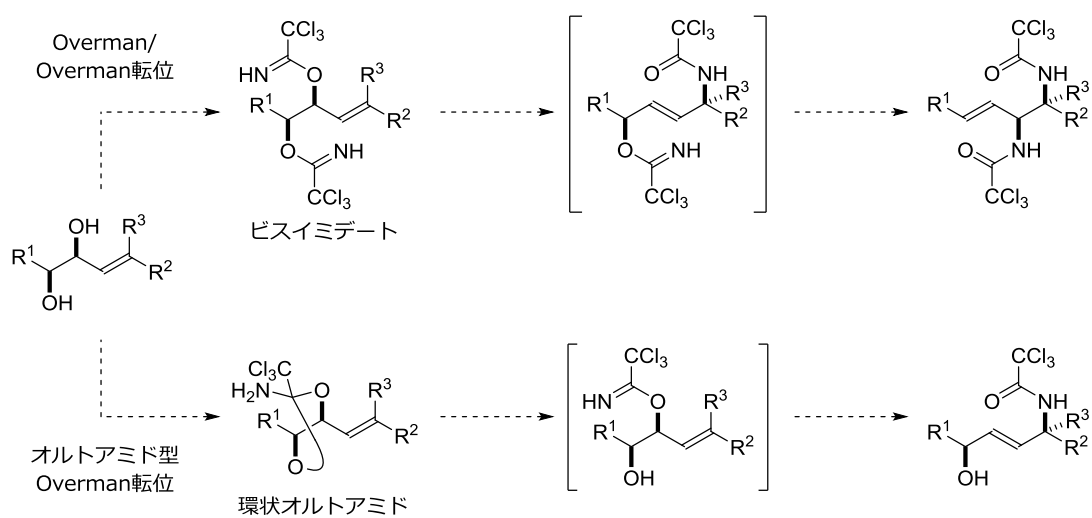
光学活性なアリルアルコールに対する [3,3] シグマトロピー転位反応は、水酸基の立体化学を新たな C-C 結合や C-N 結合へと不斉転写できるため、キラル化合物を合成する最も信頼できる方法の一つとして利用されている。本反応を最大限利用する新たな手法として、アリル-1,2-ジオールに対する連続的なシグマトロピー転位に着目した (スキーム 3)。アリル-1,2-ジオール **1** はオレフィンの隣にジオールを有する基質である。ジオール **1** は 1 回目のシグマトロピー転位で新たな結合の形成と同時にオレフィンが移動し、再びアリルアルコール **2** を生成する。生じた **2** に対し、即座に 2 回目の転位を適用すれば、2 つの置換基を一挙に導入できる。高い有用性にも関わらず、本法の全合成への応用はほとんど見られなかった。これは次のような問題点があるためである。一般的に **1** に対して 2 回のシグマトロピー転位を用いるためには、1 回目の転位におけるホモアリルアルコールの保護 (TBDPS 基) が不可欠となる<sup>4</sup>。続いて 1 回目の転位の後、2 回目の転位の前にこれを脱保護しなければならない (**5**→**6**)。そこで当研究室では、保護・脱保護を経由せずに、2 つの転位を連続して適用できる反応の開発に精力的に取り組んできた。



Scheme 3. アリル-1,2-ジオールの連続的な転位

当研究室では、光学活性なアリル-1,2-ジオールに対する Overman 転位を鍵反応とした 2 種類の連続的なシグマトロピー転位反応の開発に成功している (スキーム 4)<sup>5</sup>。1 つ目はビスイミデートを経由した Overman/Overman 転位 (上段)、2 つ目は環状オルトアミドを経由したオルトアミド型 Overman 転位 (下段) である。Overman/Overman 転位ではビスイミデートを加熱すると 2 回の Overman 転位が一挙に進行する。一方、オルトアミド型 Overman 転位では、平衡反応により  $\alpha$ -ヒドロキシイミデートが生じるため、転位回数を 1 回に制御できる。一般的に、アリル-1,2-ジオールに対して 2 回のシグマトロピー転位を用いるためには、1 回目の転位におけるホモアリルアルコールの保護が不可欠であり、2 回目の転位の前にこれを脱保護しなければならない。しかし、本手法では水酸基の保護・脱保護を経由せずに Overman 転位の回数を自在に制御できる。また、

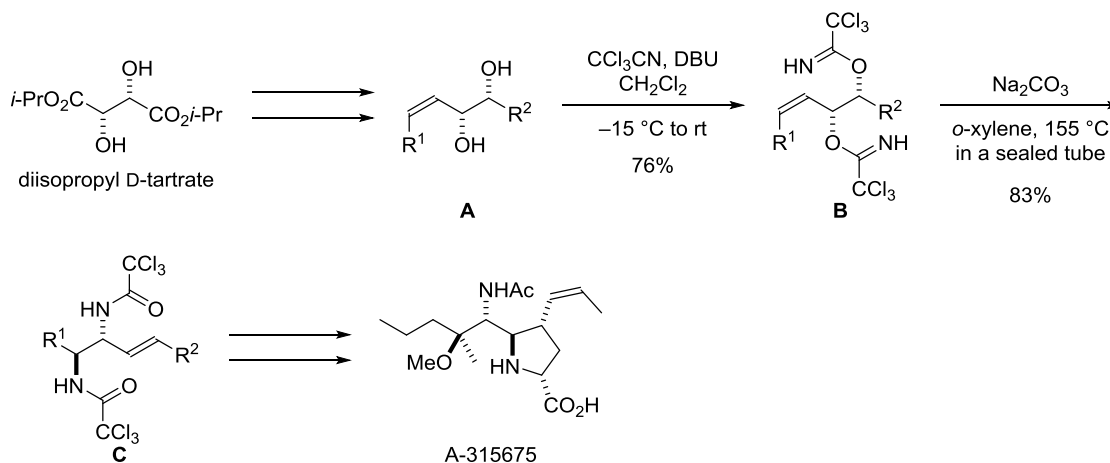
いずれの反応もいす型遷移状態を経由した高い立体選択性が期待できる。



**Scheme 4.** Overman/Overman 転位とオルトアミド型 Overman 転位

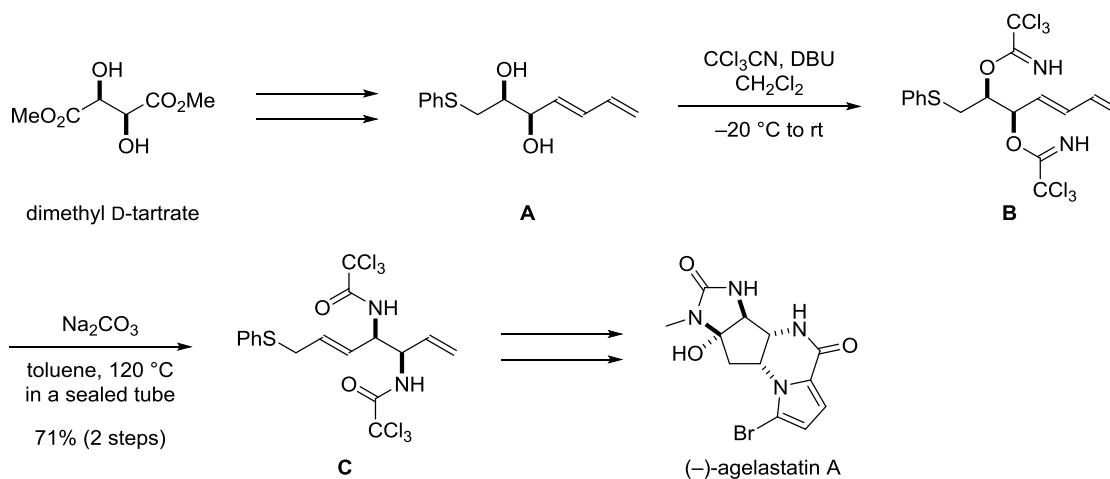
## 2.1 Overman/Overman 転位

2008年、当研究室では Overman/Overman 転位を鍵反応とした、A-315675 の全合成を報告した (スキーム 5)<sup>6</sup>。酒石酸ジイソプロピルより誘導したアリル-1,2-ジオール **A** を、ビスイミデート **B** に変換した。**B** を Na<sub>2</sub>CO<sub>3</sub> 存在下封管中 155 °C に加熱すると、対応する 2 回転位体 **C** を単一の立体異性体で与えた。得られた **C** を種々変換し、A-315675 の全合成を達成した。



Scheme 5. A-315675 の全合成

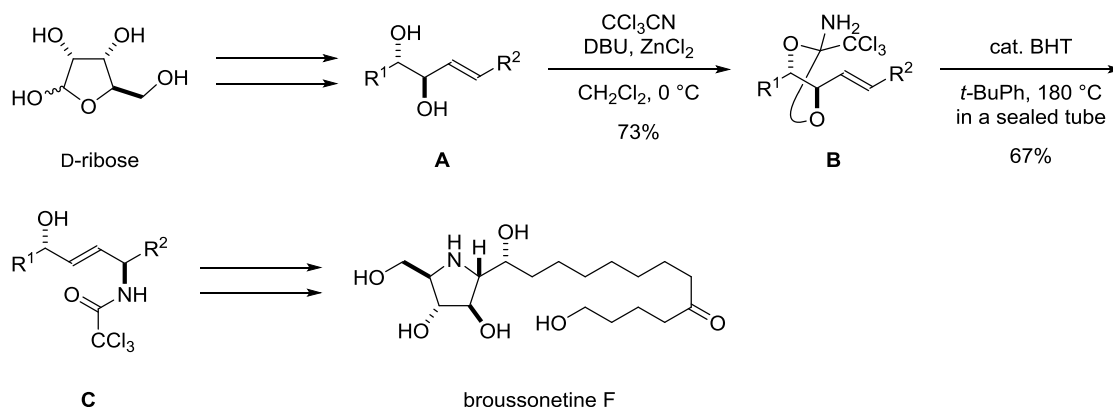
さらに 2009 年、当研究室では Overman/Overman 転位を鍵反応として、(-)-アゲラスタチン **A** の全合成を達成した (スキーム 6)<sup>7</sup>。酒石酸ジメチルを出発原料としてアリル-1,2-ジオール **A** に誘導し、ビスイミデート **B** に変換した。**B** を Na<sub>2</sub>CO<sub>3</sub> 存在下、加熱すると対応する転位体 **C** が得られた。**C** より (-)-アゲラスタチン **A** へと導いた。



Scheme 6. (-)-アゲラスタチン A の全合成

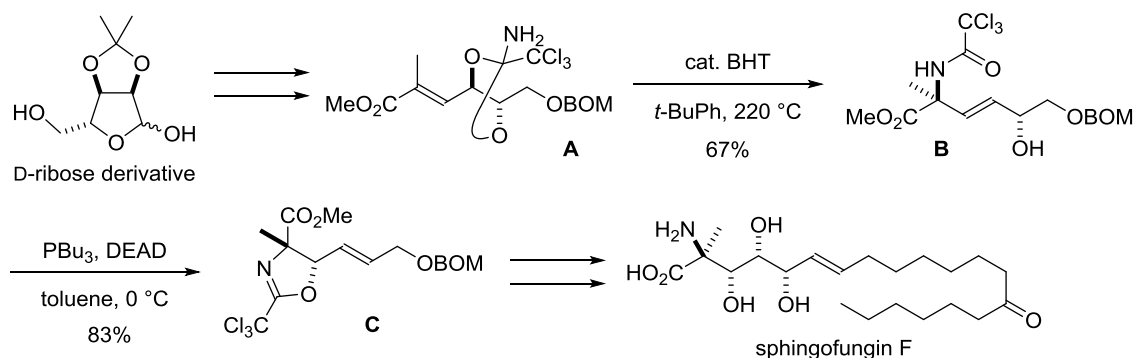
## 2.2 オルトアミド型 Overman 転位

2011 年、当研究室ではオルトアミド型 Overman 転位を鍵反応としたブロッソネチン F の全合成を達成した (スキーム 7) <sup>5a</sup>。D-リボースから誘導したアリル-1,2-ジオール **A** を環状オルトアミド **B** へ変換した。**B** を触媒量の BHT 存在下、封管中 180 °C に加熱すると、開環に続く Overman 転位が完全な立体選択性で進行し、アリルアルコール **C** を単一の立体異性体として与えた。**C** を種々変換しブロッソネチン F へと導いた。



**Scheme 7.** ブロッソネチン F の全合成

2015 年、当研究室ではオルトアミド型 Overman 転位を鍵反応としたスフィンゴファンジン F の全合成を報告している (スキーム 8) <sup>8</sup>。D-リボース誘導体より合成した環状オルトアミド **A** を封管中 220 °C に加熱すると、不飽和エステルに対するオルトアミド型 Overman 転位が進行し、転位体 **B** を収率 67% で与えた。本反応により、 $\alpha,\alpha$ -二置換アミノ酸構造が一挙に構築できた。続いて、分子内  $S_N2'$  反応により高立体選択的に酸素官能基を導入した。その後、数工程を経てスフィンゴファンジン F へと誘導している。



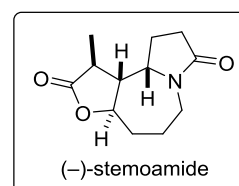
**Scheme 8.** スフィンゴファンジン F の全合成

## 第二章 ステモナルカロイド

### 第一節 ステモアミド

#### 1.1 単離・構造および生物活性

(-)-ステモアミドは 1992 年に Xu らによって、中国広東省で採取された *Stemona tuberosa* の根の抽出物より単離・構造決定されたステモナルカロイドである<sup>9</sup>。*Stemona tuberosa* をはじめ Stemonaceae (和名: ビヤクブ科) の植物は、古来より抗咳活性ならびに駆虫作用を有する薬として東洋で用

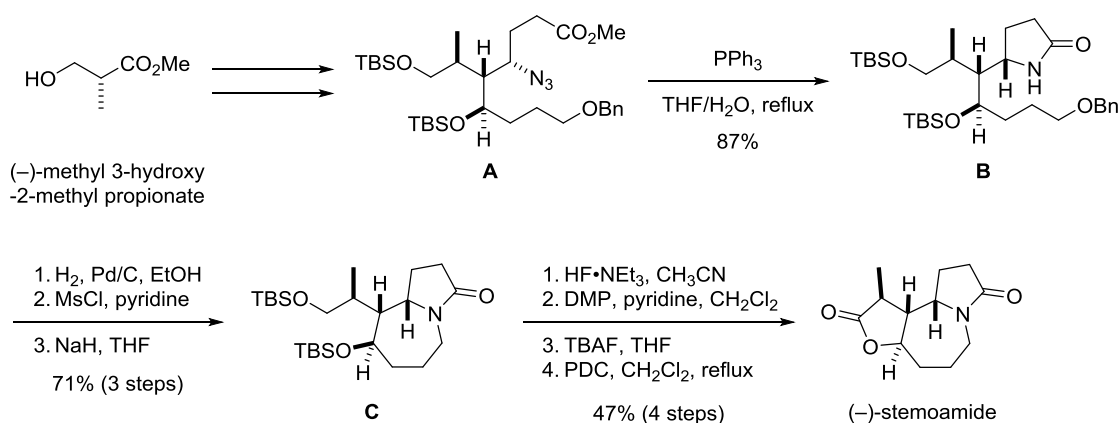


いられてきた。構造的には、ピロロ[1,2-*a*]アゼピン骨格に、 $\alpha$ -メチル- $\gamma$ -ラクトンが縮環した 3 環性骨格から成り、4 つの連続した不斉中心を有している。現在のところ、(-)-ステモアミドの生物活性は報告されていない。1994 年に Williams らにより(-)-ステモアミドの初の全合成が達成<sup>9a</sup>されており、現在も合成研究は盛んに行われている。

#### 1.2 過去の全合成例

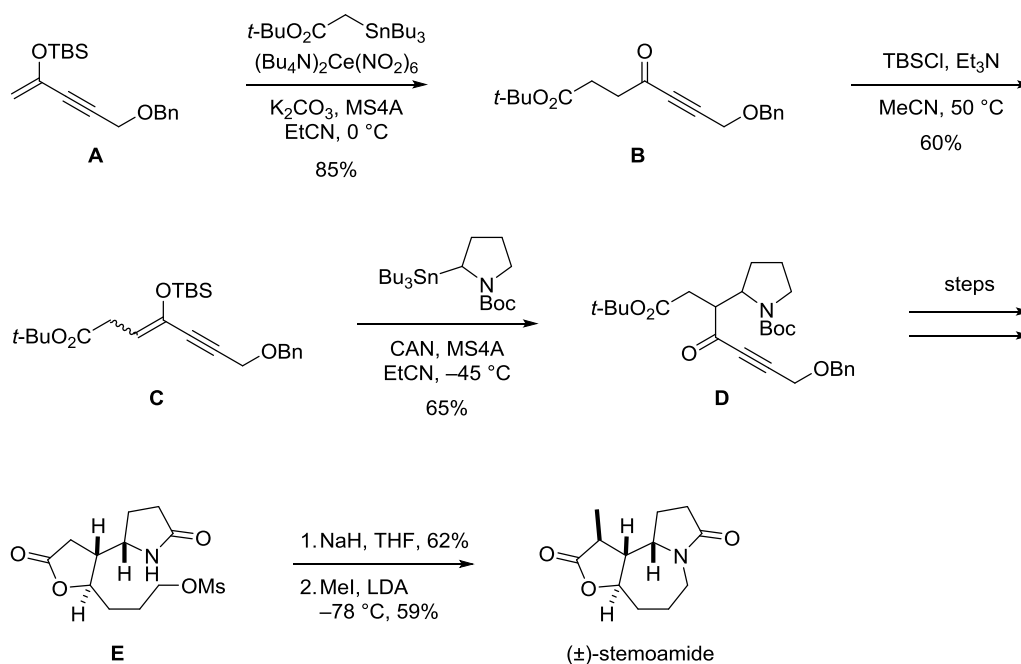
現在までに 14 例の全合成<sup>10</sup>と、5 例の形式合成<sup>11</sup>が報告されている。

1994 年、Williams らは、(-)-ステモアミドの初の全合成を報告している (スキーム 9)<sup>10a</sup>。出発原料であるメチル-3-ヒドロキシ-2-メチルプロピオネートより、Evans アルドール反応を含む数工程で誘導したアジド **A** を、 $\text{PPh}_3$  で処理して生じたアミンはワンポットにて分子内のエステルと縮合し $\gamma$ -ラクタム **B** を与えた。**B** よりベンジル基の除去、メシル化、分子内環化の 3 工程で七員環骨格を構築した。得られた **C** の一級選択的な TBS 基の除去、Dess–Martin 酸化、残る TBS 基の除去を経てラクツールへと誘導し、最後に PDC 酸化により(-)-ステモアミドの全合成を達成した。



**Scheme 9.** Williams らによる(-)-ステモアミドの全合成

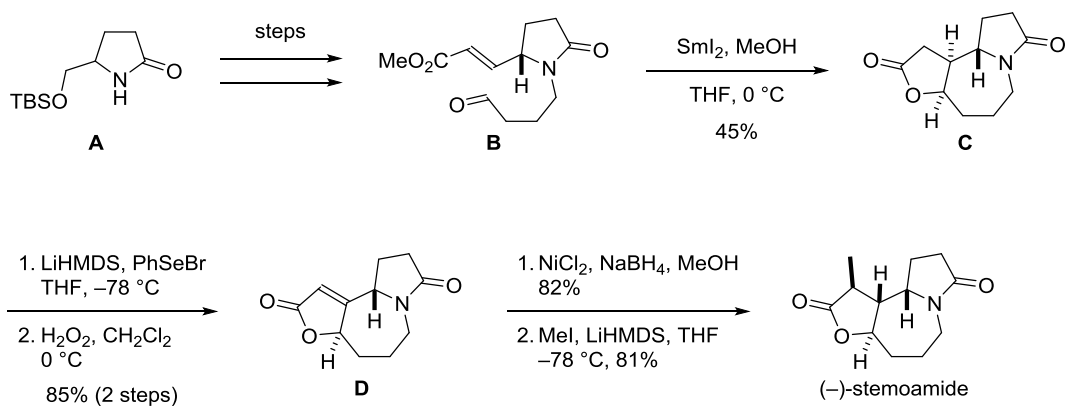
1996年、奈良坂らによる(±)-ステモアミドの全合成が報告された(スキーム10)<sup>10b</sup>。開発したスズ化合物とシリルエノールエーテルとの酸化的カップリング反応を、**A**→**B**ならびに、**C**→**D**の2回に渡り用いて、ステモアミドのすべての炭素原子を導入している。その後、種々官能基変換により合成したメシラート**E**の分子内環化の後、立体選択的なメチル基の導入を経て、(±)-ステモアミドへ誘導している。



**Scheme 10.** 奈良坂らによる(±)-ステモアミドの全合成

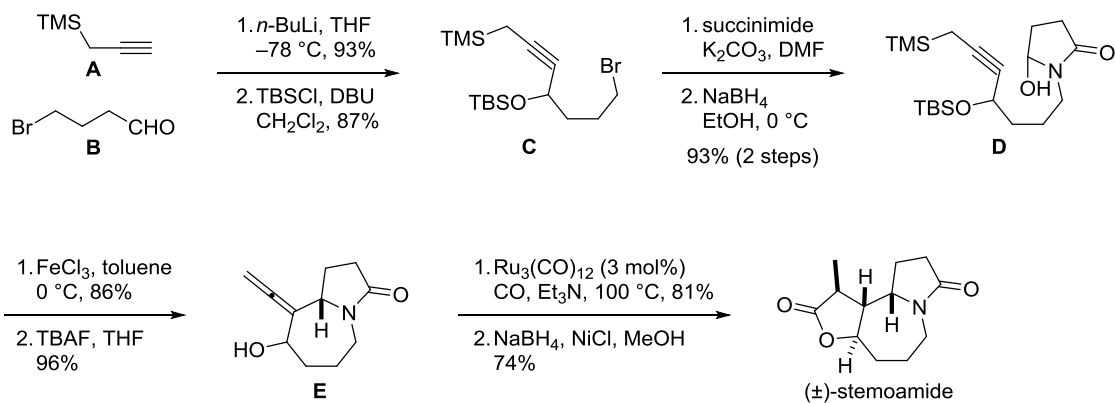
2011年、本多らは(-)-ステモアミドの全合成を報告している(スキーム11)<sup>10k</sup>。**B**をSmI<sub>2</sub>で処理すると、アルデヒドならびに不飽和エステルにサマリウムが付加してビラジカルとなり、C-C結合が形成、続いてラクトンが構築された**C**を得た。得られた**C**をブテノリドに変換し、還元して望みの立体化学へ反転した後、最後にメチル基を導入し(-)-ステモアミドへと誘導してい

る。



**Scheme 11.** 本多らによる(-)-ステモアミドの全合成

2011年、Hongらは(±)-ステモアミドの全合成を報告している(スキーム12)<sup>101</sup>。プロパルギルシラン**A**とアルデヒド**B**のカップリングで生じた水酸基をTBS基で保護して**C**とし、スクシンイミドの付加と、続く還元によりヘミアミナール**D**へと誘導した。**D**をFeCl<sub>3</sub>で処理して生じたアシルイミニウムイオンと、アセチレンとの分子内環化により7員環骨格を構築し、TBSを除去して**E**を得た。**E**のルテニウム触媒を用いた一酸化炭素挿入反応によりγ-ラク톤を構築、続く還元により(±)-ステモアミドの全合成を達成した。総工程数8、総収率37%であった。



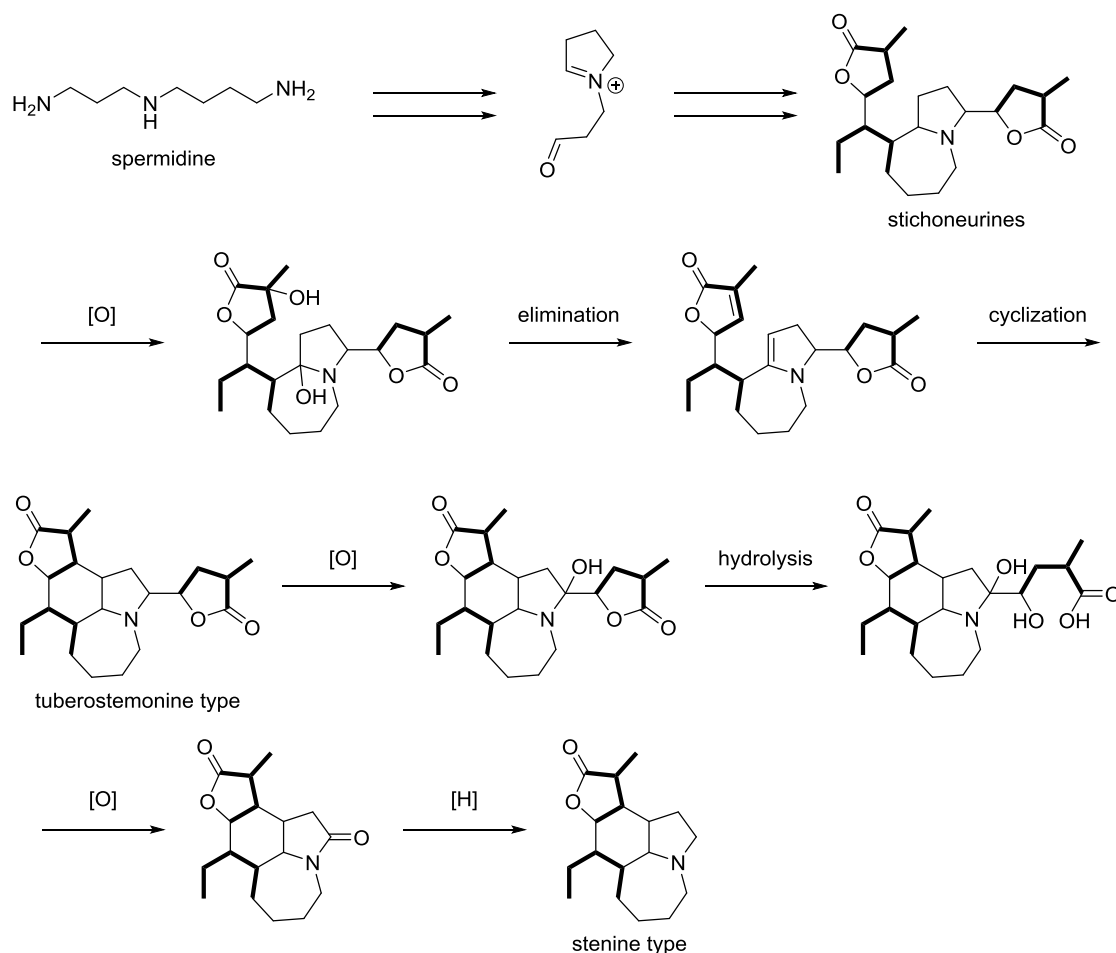
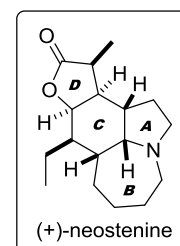
**Scheme 12.** Hongらによる(±)-ステモアミドの全合成



## 第二節 ネオステニン

### 2.1 単離・構造および生物活性

(+)-ネオステニンは、2003年 Lin らによりビャクブ科の植物 *Stemona tuberosa* の根より単離されたステモナルカロイドである<sup>12</sup>。構造的には、ピロリジン、 $\gamma$ -ラクタムを含む四環性骨格から成り、特にC環部は6つの炭素原子すべてが不斉炭素となっている。その絶対立体配置は、2010年に Jiang らにより X線結晶構造解析<sup>13</sup>により決定された。生物活性としては、0.5 M クエン酸溶液のエアロゾルに曝して作成した咳モデルマウスに対する、鎮咳活性が報告されている。



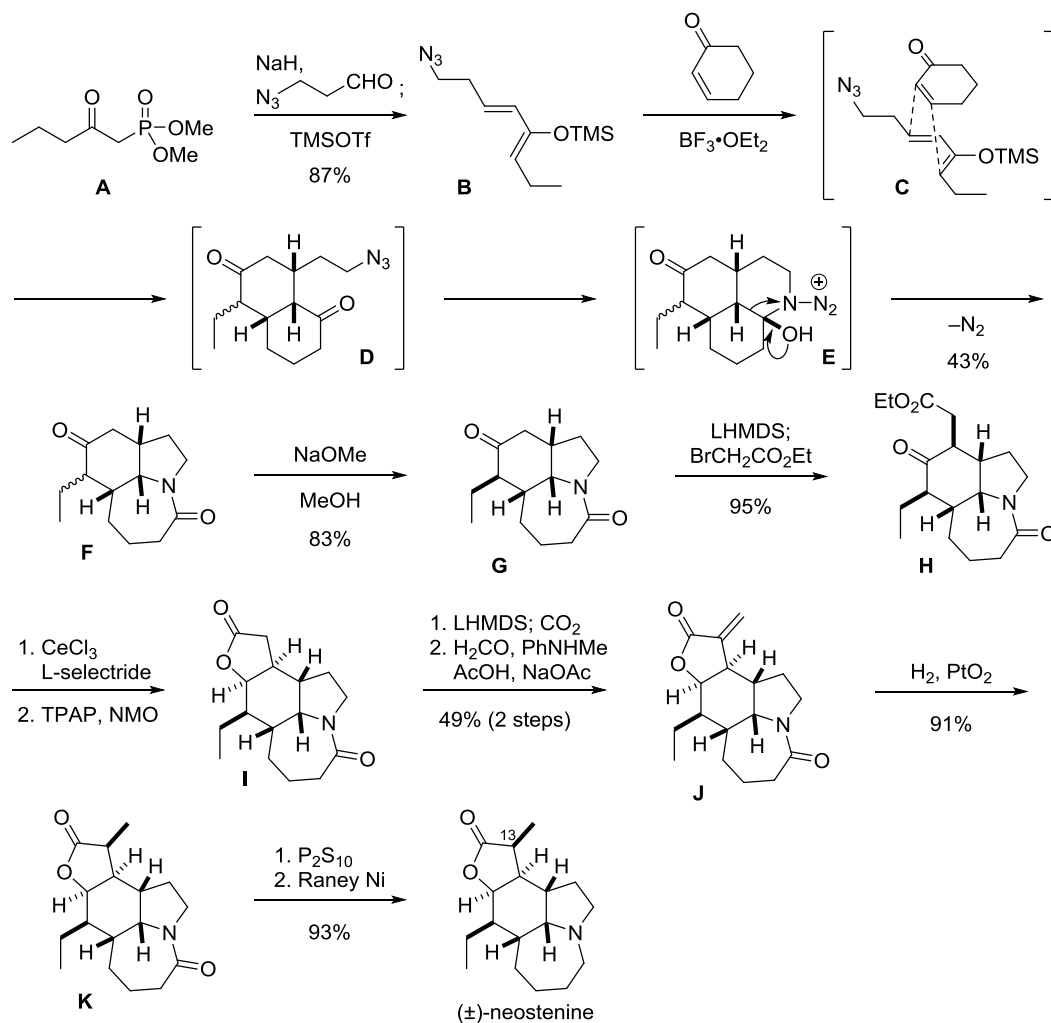
Scheme 13. ステニン型アルカロイド生合成仮説

現在提唱されている生合成仮説を示した (スキーム 13) <sup>14</sup>。スペルミジンから生じたイミニウムイオンに対する、増炭により *stichoneurine* が合成される。その後、酸化・脱離で生じたオレフィン間で環化反応が進行し、ツベロステモニン型の骨格が形成される。これがさらに酸化を受け、ジオールの酸化開裂により、ラクトン部位が除去された後、生じたラクタムが還元されると、ステニン型の骨格となる。

## 2.2 過去の全合成例

ネオステニンの全合成例は、これまでに 2008 年の Aubé らのグループと、Booker–Milburn らのグループによるラセミ体の合成のみが報告されている<sup>15</sup>。

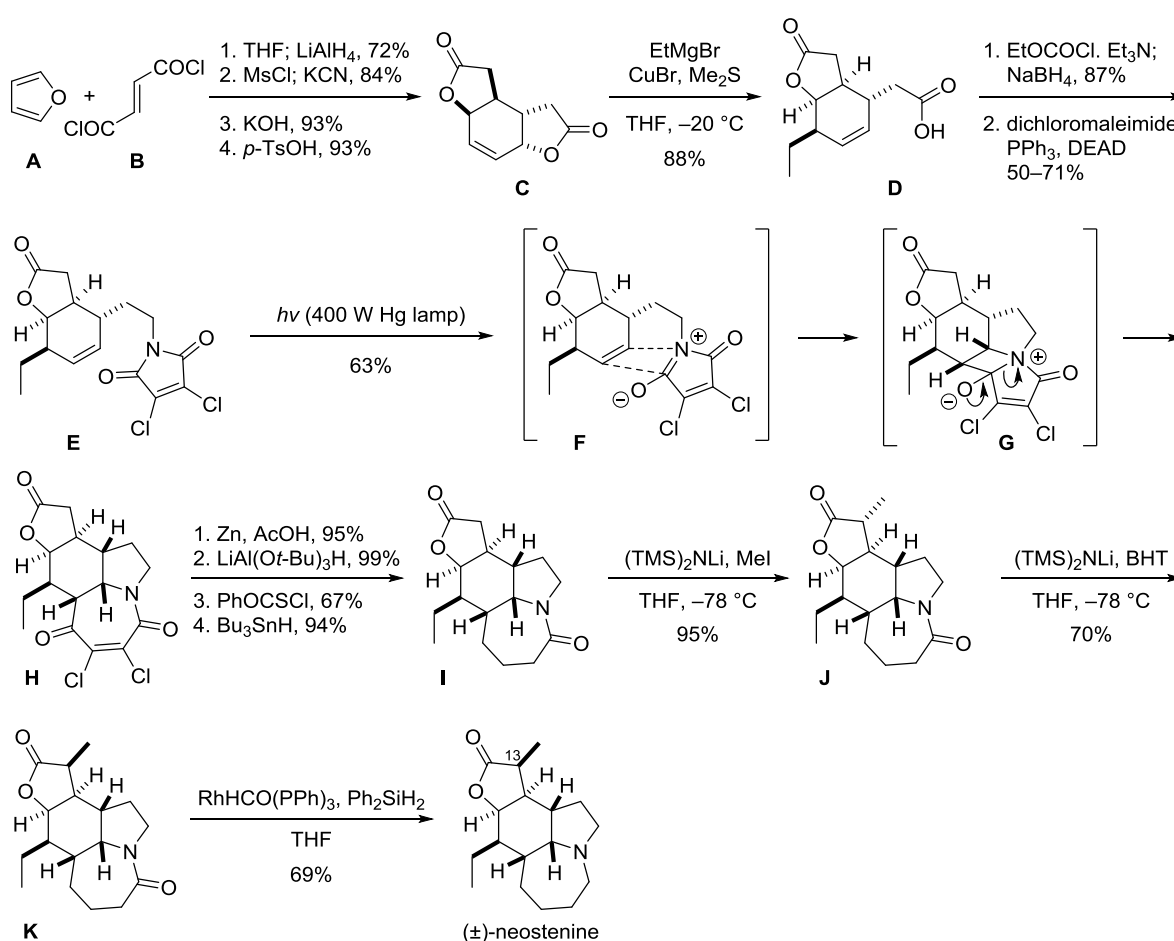
2008 年 Aubé らは、連続的 Diels–Alder/Schmidt 反応を鍵工程とした(±)-ネオステニンの全合成を報告している (スキーム 14)<sup>15a</sup>。A より合成したジエン B に対し、鍵反応である連続的 Diels–Alder/Schmidt 反応を適用した。ルイス酸として  $\text{BF}_3 \cdot \text{OEt}_2$  を用いると、C に示すように *endo* 選択的に Diels–Alder 反応が進行し、D が生じた。続いて、アジドがケトンに付加して E となり、Schmidt 転位により三環性化合物 F を与えた。塩基で処理し、エチル基を望む立体化学に異性化した後、増炭・還元により四環性化合物 I を合成した。その後、メチル基の導入 (I→J→K)、ラクタムの還元を経て(±)-ネオステニンの全合成を達成した。



Scheme 14. Aubé らによる(±)-ネオステニンの全合成

本報告は出発原料からわずか2工程目の鍵反応にて、ネオステニンに対応する三環性化合物 **F** を得ており、総工程数も13と優れた全合成である。鍵工程のカスケード反応も、収率は中程度であるが興味深い。しかし、13位メチル基の立体選択的な導入に3工程を要している。また、最後のラクタムの還元も、チオアミドを経由した2工程で達成されており、合成終盤に改善の余地があると考えられる。さらに、ラセミでは素晴らしい鍵反応であるが、高い光学純度での不斉合成への展開にはさらなる検討が必要と思われる。

同じく2008年 Aubé らに続き、Booker-Milburn らによる[5+2]光環化付加を鍵工程とした(±)-ネオステニンの全合成が報告された(スキーム15)<sup>15b</sup>。フランとフマル酸塩化物より、ビスラクトン **C** とした。**C** に対し、S<sub>N</sub>2'反応による非対称化反応により、カルボン酸 **D** に誘導した。**D** の還元で生じたアルコールに光延反応を適用し、ジクロロマレイミドを導入し **E** とした。**E** の[5+2]光付加環化反応は、**F** のような遷移状態を経由してまず[2+2]付加環化反応が進行し **G** となり、続くシクロブタン環の開裂により7員環 **H** を収率63%で与えた。その後、塩素と酸素官能基の除去、メチル基の導入を経て、(±)-ネオステニンの全合成を達成した。



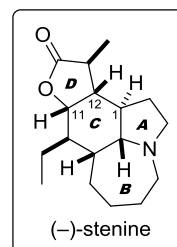
**Scheme 15.** Booker-Milburn らによる(±)-ネオステニンの全合成

本報告は天然物の対称性に着目し、 $C_2$ 対称なビスラクトン **C** を調製、続く鍵反応で残る 2 つの環を一挙に構築する効率的な全合成である。鍵工程もオリジナリティーが高く、ステモナルカロイドの共通骨格の合成に有用である。しかし、本反応で導入されるハロゲン、酸素官能基の除去に 5 工程を要している。また、合成終盤での 13 位メチル基の導入は、望む立体化学を得るために異性化の工程が必須であった。

### 第三節 ステニン

#### 3.1 単離・構造および生物活性

(-)-ステニンは 1967 年に上尾らにより、ビャクブ科の植物 *Stemona tuberosa* の根より単離されたステモナルカロイドである<sup>16</sup>。構造的にはネオステニンと同様の四環性骨格を持ち、1・11・12 位の 3 か所の立体化学のみが異なる。現在までに、ステニンの生物活性は報告されていない。

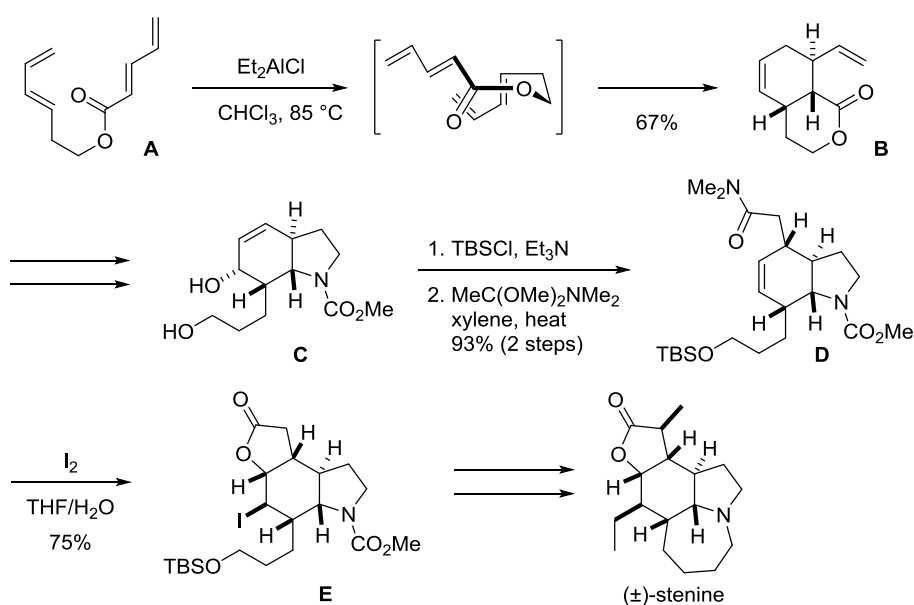


#### 3.2 過去の全合成例

ステニンの合成研究は盛んに行われており、1990 年に Hart らがラセミ体での初の全合成を報告している。また、1995 年に Wipf らが光学活性体での初の全合成を達成し、現在までにラセミ合成: 3 グループ<sup>17</sup>、不斉合成: 4 グループ<sup>18</sup>による全合成が報告されている。

##### 3.2.1 ステニンのラセミ体での全合成例

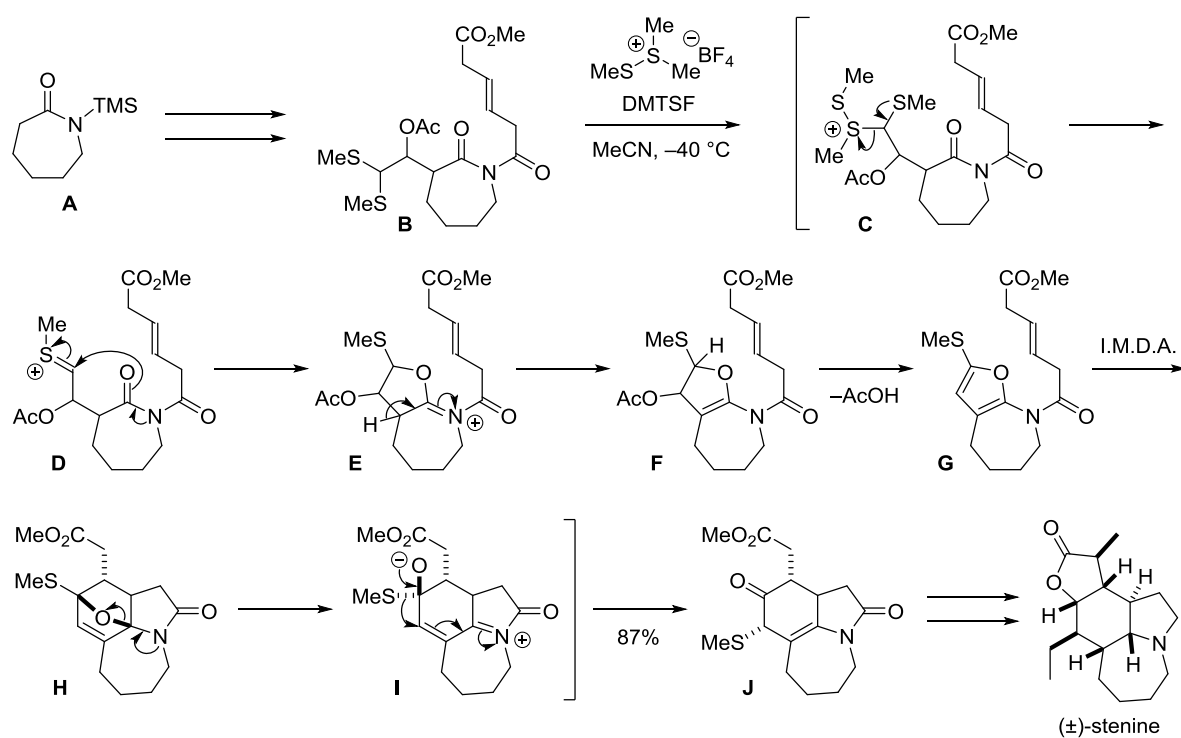
1990 年、Hart らは分子内 Diels–Alder 反応と Eschenmoser–Claisen 転位を鍵反応とした、(±)-ステニンの全合成を報告している (スキーム 16)<sup>17a</sup>。A を Et<sub>2</sub>AlCl 存在下加熱すると、分子内 Diels–Alder 反応が進行し、3 連続不斉中心を備えた B を与えた。官能基変換により C とし、一級水酸



Scheme 16. Hart らによる(±)-ステニンの全合成

基を TBS 化の後、Eschenmoser–Claisen 転位を適用し **D** とした。**D** をヨウ素で処理するとヨードラクトン化が進行し、**E** を得た。その後数工程を経て、(±)-ステニンの全合成を達成した。

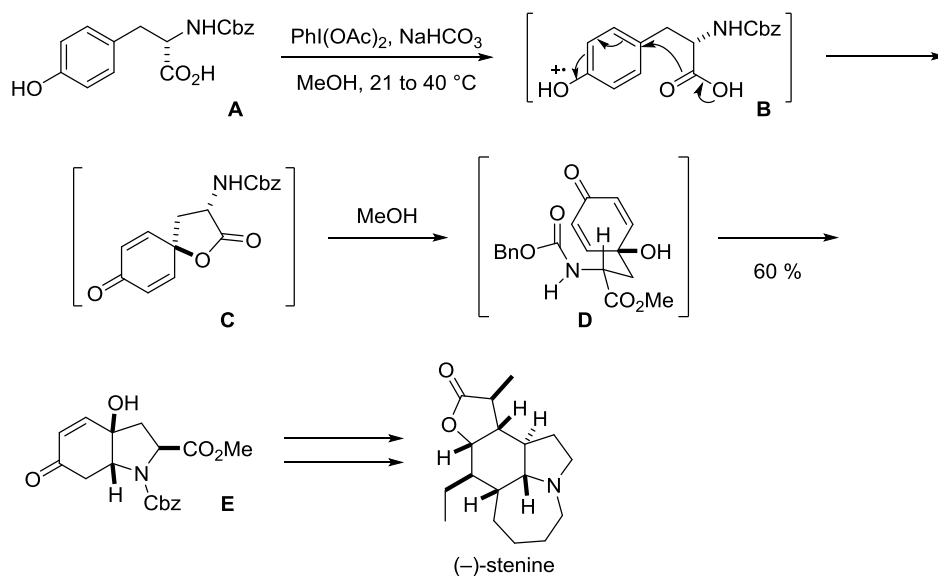
2002 年、Padwa らはフランの分子内 Diels–Alder 反応を鍵反応とした(±)-ステニンの全合成を報告している (スキーム 17) <sup>17b</sup>。ε-ラクタム **A** より誘導した **B** を DMTSF で処理すると系内でジヒドロフランが形成し (**C**→**F**)、酢酸の脱離によりフラン **G** を与える。**G** の分子内 Diels–Alder 反応は速やかに **H** を与え、続く N–O 結合の開裂、メチルチオ基の 1,2-シフトによりステニンに対応する三環性骨格 **J** が収率 87% で得られた。その後、諸工程を経て(±)-ステニンの全合成を達成した。



**Scheme 17.** Padwa らによる(±)-ステニンの全合成

### 3.2.1 ステニンの不斉全合成例

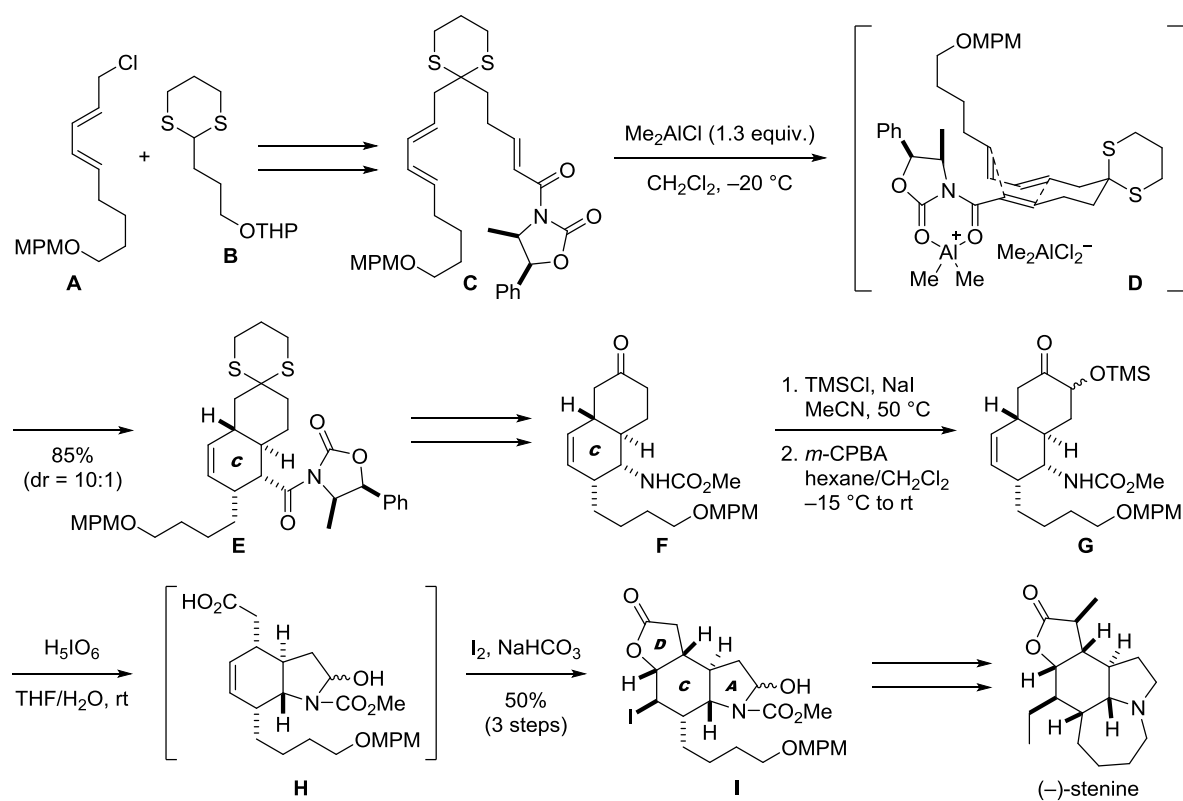
1995年、WipfらはL-チロシンの酸化に続く位置選択的な aza-Michael 反応を鍵工程とした(-)-ステニンの全合成を報告している (スキーム 18)<sup>18a</sup>。L-チロシン誘導体 **A** を  $\text{PhI}(\text{OAc})_2$  で処理すると、1電子酸化により **B** が生じ、即座にラクトン化が進行し **C** となる。**C** のメタノリシスで生じたエステルの、**D** のような立体障害の最も小さい遷移状態を経由した aza-Michael 反応により、所望の二環性化合物 **E** を得た。その後、種々官能基変換により(-)-ステニンの全合成を達成した。



Scheme 18. Wipf らによる(-)-ステニンの全合成



1996年、森本らは分子内不斉 Diels–Alder 反応を鍵反応とした(-)-ステニンの全合成を報告している (スキーム 19)<sup>18b</sup>。A と B のカップリングを経て合成した C の Diels–Alder 反応は、D のような遷移状態を経由して進行し、ステニンの C 環部に相当する 6 員環を有する E を与えた。Curtius 転位を含む数工程で誘導した F のシリルエノールエーテル化、続く Rubottom 酸化により G とした。G の酸化開裂で生じた二環性中間体 H に対し、ワンポットにてヨードラクトン化を適用し、三環性中間体 I とした。その後種々官能基変換を経て(-)-ステニンの全合成を達成した。



Scheme 19. 森本らによる(-)-ステニンの全合成

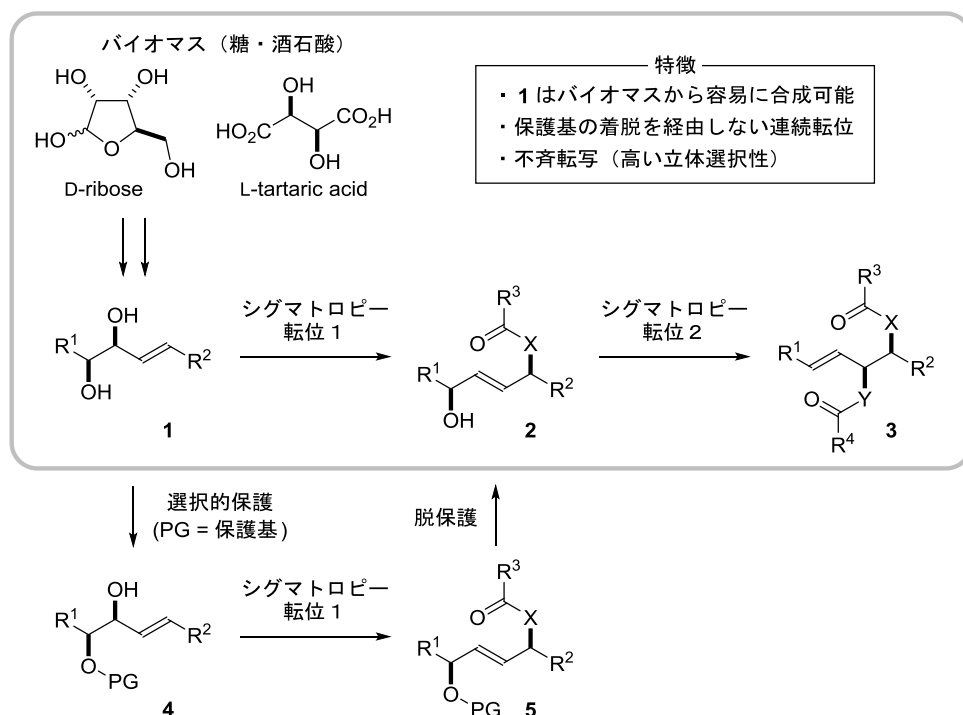


# 本論

# 第一章 連続的 Overman/Claisen 転位の開発

## 第一節 研究背景および概略

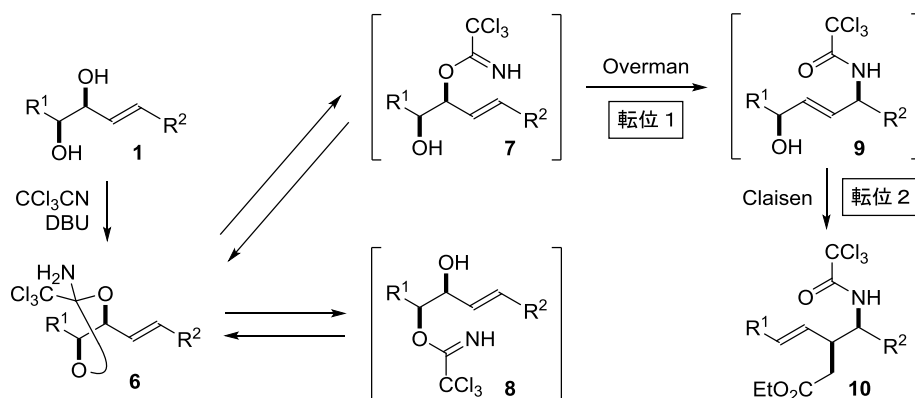
当研究室では、糖や酒石酸などの入手容易なバイオマスを用いたキラルプール法とシグマトロピー転位を組み合わせた生物活性天然物の実用的な不斉合成法の開発に取り組んでいる。バイオマス由来のアリル-1,2-ジオール **1** に対しシグマトロピー転位を用いると、新たな結合の形成と同時にアリルアルコール構造を有する **2** が生成する。生じた **2** に対し、即座に2回目のシグマトロピー転位を適用すれば、連続的転位体 **3** が得られる。本法は、バイオマスより容易に合成できるジオール **1** から、不斉転写反応により一挙に複雑な光学活性化合物が合成できる。しかし、一般的にバイオマスに由来する複数の水酸基の区別化は困難であり、選択的保護 (**1**→**4**)・脱保護 (**5**→**2**) に伴う工程数の増加が問題であった。本章では、保護基の着脱を経由しないジオール **1** の連続的 Overman/Claisen 転位の開発について述べる。



**Scheme 20.** アリル-1,2-ジオールの連続的シグマトロピー転位とその特徴

アリル-1,2-ジオール **1** からの2連続シグマトロピー転位として、1段階目に Overman 転位 (**6**→**7**→**9**)、2段階目に Claisen 転位 (**9**→**10**) を用いることにした (スキーム 21)。ジオール **1** より2つのシグマトロピー転位を連続的に達成するためには、1段階目の Overman 転位において

アリルアルコールとホモアリルアルコールの区別化が重要となる。そこで、平衡反応を利用したオルトアミド型 Overman 転位を計画した。1 を  $\text{CCl}_3\text{CN}$ 、DBU で処理すると、環状オルトアミド 6 が得られる。6 を加熱すると、開環によりアリルイミデート 7 とホモアリルイミデート 8 が生じる。8 は閉環により 6 に戻るのに対し、7 は Overman 転位が進行してアリルアルコール 9 を与えると考えた。すなわち、平衡反応により保護基の着脱を経由せずに 2 つの水酸基が区別化可能となる。さらに、生じる 9 に対しワンポットにて Claisen 転位を適用すれば、連続転位体 10 が得られると考えた。また、2 つの転位はともに 6 員環遷移状態を経由するため、高い立体選択性が期待できる。



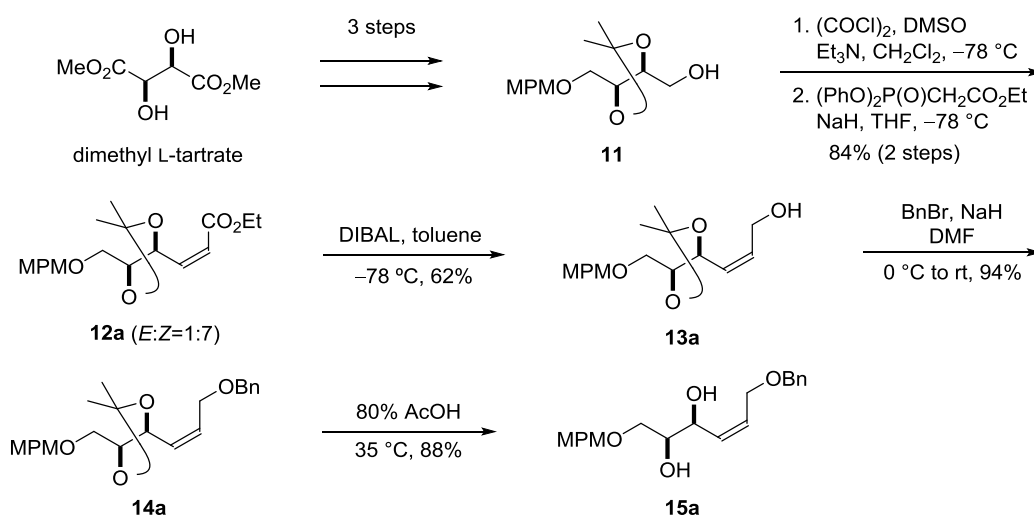
Scheme 21. 連続的 Overman/Claisen 転位

## 第二節 アリル 1,2-ジオールの調製

連続的 Overman/Claisen 転位に用いるアリル-1,2-ジオールを調製した。水酸基の立体化学が *syn* 体, *anti* 体の 2 種類、オレフィンの幾何異性が *E*, *Z*, 三置換の 3 種類、合計 6 種類のジオールを合成した<sup>19</sup>。

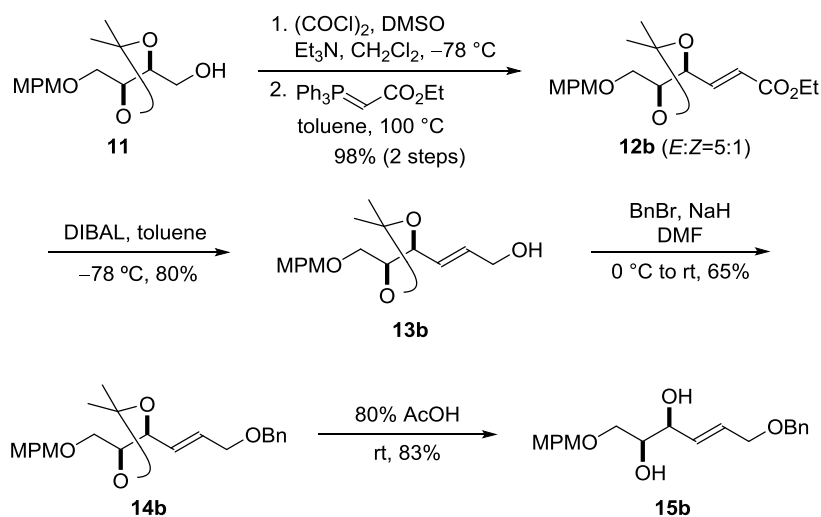
### 2.1 アリル-*syn*-ジオールの調製

まず始めに、*Z*-アリル-*syn*-ジオール **15a** を合成した (スキーム 22)。L-酒石酸ジメチルより既知の 3 工程で導いたアルコール **11** を Swern 酸化、安藤オレフィン化により *Z*-不飽和エステル **12a** とした。DIBAL 還元によりアリルアルコール **13a** とし、生じた水酸基をベンジル化し **14a** へと導いた。80% 酢酸で処理してアセタールを除去し、望む *Z*-アリル-*syn*-ジオール **15a** を合成した。



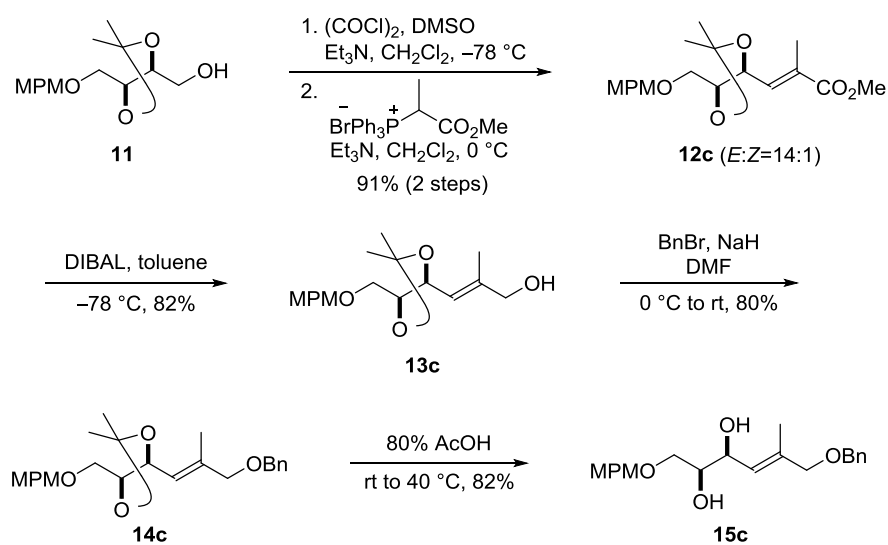
Scheme 22. *Z*-アリル-*syn*-ジオール **15a** の合成

次に、*E*-アリル-*syn*-ジオール **15b** を合成した (スキーム 23)。11 の Swern 酸化で生じたアルデヒドに Wittig 反応を適用し、*E*-不飽和エステル **12b** とした。その後、15a と同様の工程にて *E*-アリル-*syn*-ジオール **15b** を得た。



**Scheme 23.** *E*-アリル-*syn*-ジオール **15b** の合成

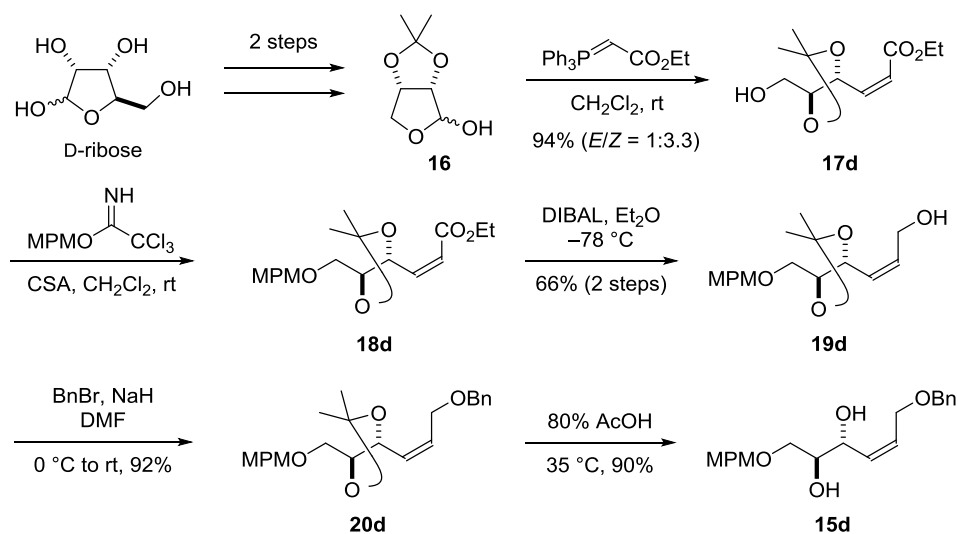
続いて、三置換アリル-*syn*-ジオール **15c** を合成した (スキーム 24)。**11** の Swern 酸化の後、対応する Wittig 試薬を添加し、不飽和エステル **12c** とした。その後、**15a** と同様の工程にて三置換アリル-*syn*-ジオール **15c** を得た。



**Scheme 24.** 三置換アリル-*syn*-ジオール **15c** の合成

## 2.2 アリル-*anti*-ジオールの調製

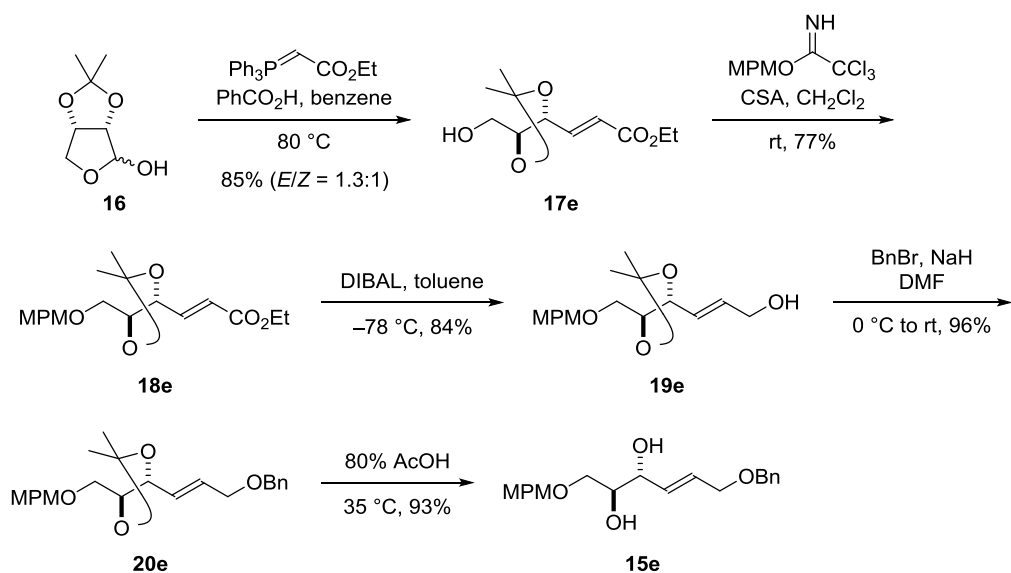
始めに、*Z*-アリル-*anti*-ジオール **15d** を合成した (スキーム 25)。D-リボースを出発原料として既知の2工程で誘導したラクツール **16** に対し、CH<sub>2</sub>Cl<sub>2</sub> 溶媒中室温にて Wittig 反応を適用すると、*Z* 選択的に不飽和エステル **17d** が得られた。**17d** の水酸基を酸性条件下 MPM で保護した。エステルの還元で生じた水酸基をベンジル化、アセタールを除去して所望の *Z*-アリル-*anti*-ジオール **15d** へと導いた。



Scheme 25. *Z*-アリル-*anti*-ジオール **15d** の合成

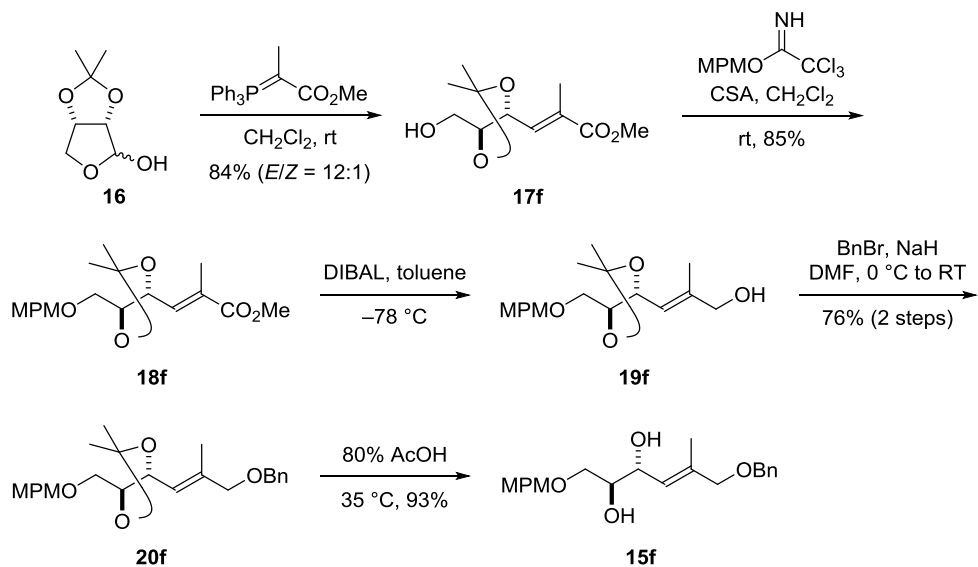
続いて、*E*-アリル-*anti*-ジオール **15e** を合成した (スキーム 26)。ラクツール **16** に加熱条件下 Wittig 反応を用いると、*E*-不飽和エステル **17e** が優先して得られた。その後、**15d** と同様の変換により *E*-アリル-*anti*-ジオール **15e** へ誘導した。





**Scheme 26.** *E*-アリル-*anti*-ジオール **15e** の合成

次に、三置換アリル-*anti*-ジオール **15f** を合成した (スキーム 27)。**16** に対する Wittig 反応は *E*-選択的に進行し、**17f** を与えた。その後、4 工程を経て三置換オレフィンに有する三置換アリル-*anti*-ジオール **15f** を得た。

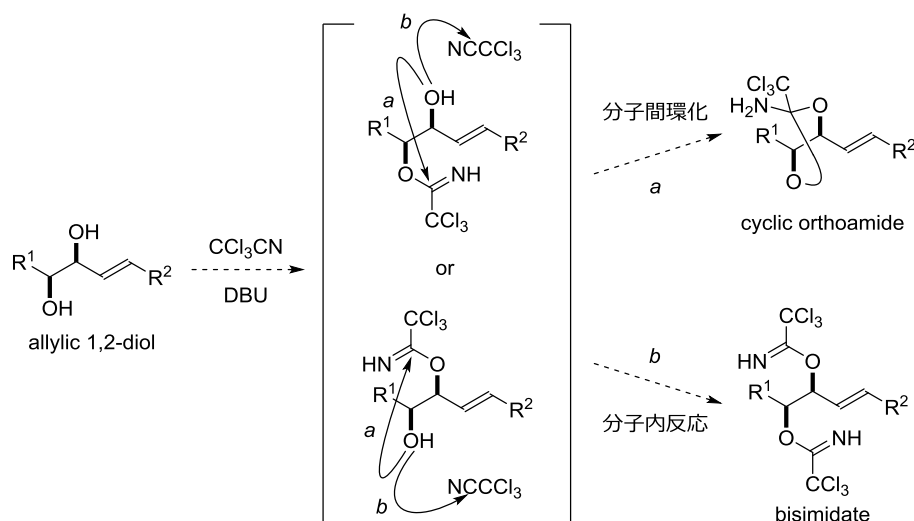


**Scheme 27.** 三置換アリル-*anti*-ジオール **15f** の合成

### 第三節 オルトアミド型 Overman 転位

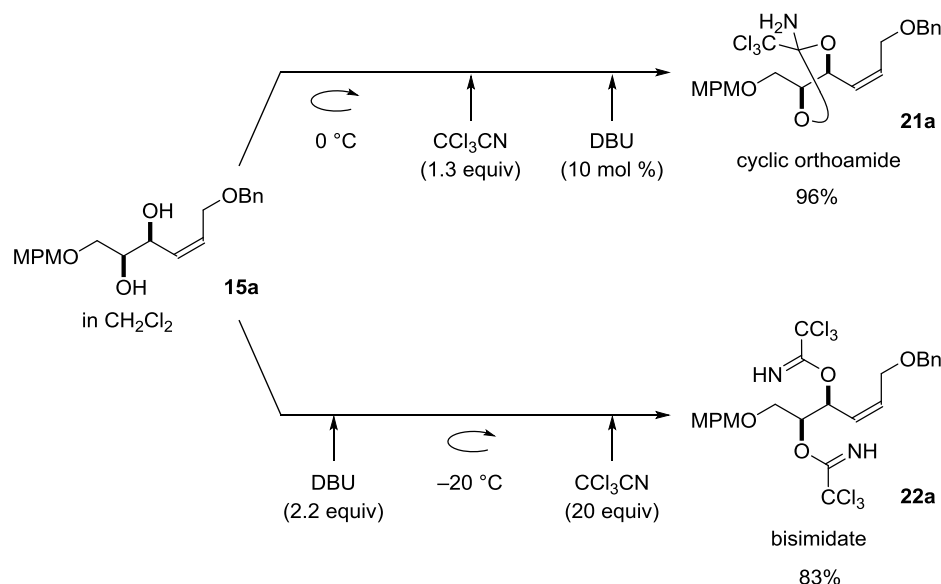
#### 3.1 環状オルトアミドの合成

アリル-1,2-ジオールより、Overman 転位を 1 回に制御するには、環状オルトアミドの選択的な合成が不可欠となる (スキーム 28)。アリル-1,2-ジオールを  $\text{CCl}_3\text{CN}$ 、DBU で処理するといずれかの水酸基が反応し 2 種類の  $\alpha$ -ヒドロキシイミデートが生じると考えられる。それぞれのイミデートにおいて、a で示した残る水酸基の分子内環化が優先すれば環状オルトアミドが得られる。一方、b で示したトリクロロアセトニトリルとの分子間反応が優先すれば、ビスイミデートが得られる。



**Scheme 28.** 環状オルトアミドの選択的合成 (作業仮説)

合成した *Z*-アリル-*syn*-ジオール **15a** に対しビスイミデートと環状オルトアミドの作り分けを検討した (スキーム 29)。その結果、用いる試薬の等量が特に重要なことが分かった。0 °C にてジオールの  $\text{CH}_2\text{Cl}_2$  溶液に、1.3 等量の  $\text{CCl}_3\text{CN}$  を加えた後、触媒量の DBU で処理すると収率 96% で環状オルトアミド **21a** が得られた。一方、ジオールを -20 °C にて 2.2 等量の DBU、過剰量の  $\text{CCl}_3\text{CN}$  で処理すると、ビスイミデート **22a** が収率 83% で得られた。

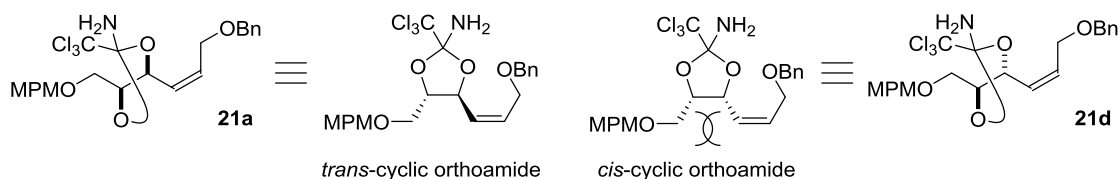


**Scheme 29.** 環状オルトアミドの選択的合成 (検討結果)

最適条件を種々のジオールに適用した (表 1)。*E-syn*-ジオール **15b**、三置換-*syn*-ジオール **15c** はそれぞれ収率 89%、91%で環状オルトアミド **21b**、**21c** を与えた。一方 *anti*-ジオールで収率よく環状オルトアミドを得るには、触媒量の  $\text{ZnCl}_2$  の添加が必須であった。*Anti*-ジオール **15d-f** を  $\text{ZnCl}_2$  存在下、 $\text{CCl}_3\text{CN}$ 、DBU で処理すると、対応する環状オルトアミド **21d**、**21e**、**21f** をそれぞれ 83%、84%、81% で与えた。

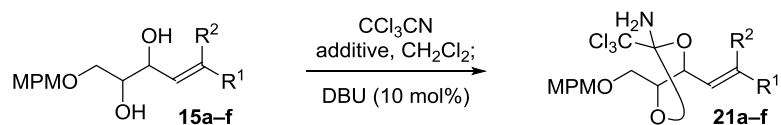
ここで、ジオールの立体化学による反応性の違いについて考える (スキーム 30)。生成物の環状オルトアミドの 5 員環構造に着目すると、*syn*-ジオール由来の環状オルトアミドは置換基が *trans* の関係に、*anti*-ジオール由来の環状オルトアミドは置換基が *cis* の関係となっていることが分かる。すなわち、立体障害の大きな *cis* 体を与える *anti*-ジオールでは分子内環化が進行しにくいため、*syn*-ジオールに比べ 10%程度環状オルトアミドの収率が低下したと考えている。 $\text{ZnCl}_2$  の効果については、その Lewis 酸性により DBU の塩基性を弱め、ビスイミデートの副生を抑制していると考えている。

なお、 $\text{ZnCl}_2$  に代わり、Brønsted 酸として酢酸の添加を試みたが、添加物を加えない場合と同様、ビスイミデートの副生は抑えられなかった。



**Scheme 30.** 5 員環環状オルトアミド側鎖の立体反発

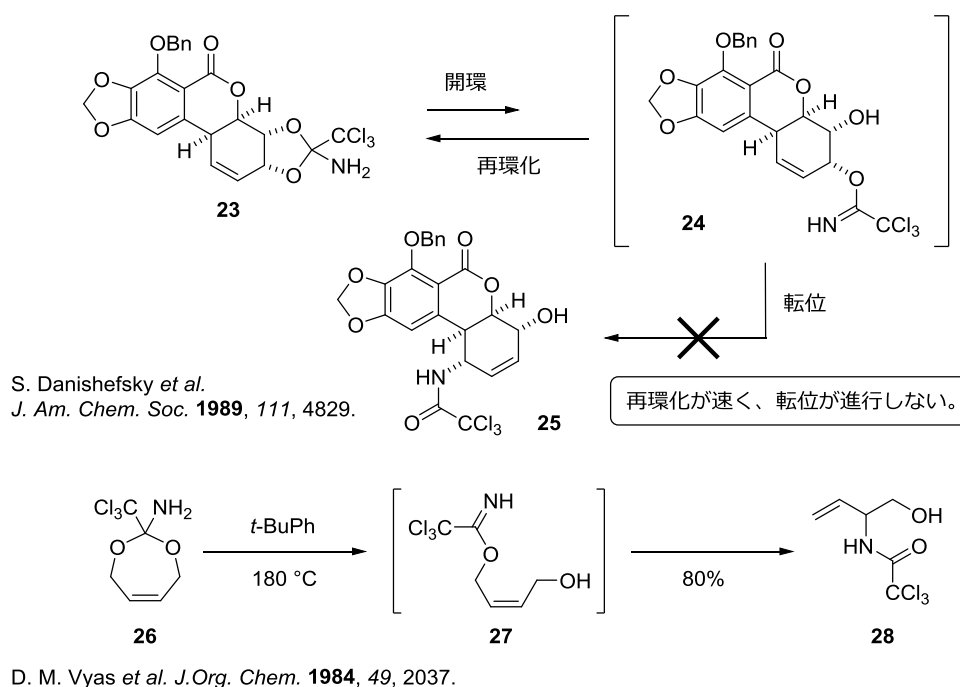
**Table 1.** 環状オルトアミドの合成



| entry | additive                     | substrate | product | yield |
|-------|------------------------------|-----------|---------|-------|
| 1     | -                            |           |         | 96%   |
| 2     | -                            |           |         | 89%   |
| 3     | -                            |           |         | 91%   |
| 4     | $\text{ZnCl}_2$<br>(10 mol%) |           |         | 83%   |
| 5     | $\text{ZnCl}_2$<br>(10 mol%) |           |         | 84%   |
| 6     | $\text{ZnCl}_2$<br>(10 mol%) |           |         | 81%   |

### 3.2 オルトアミド型 Overman 転位

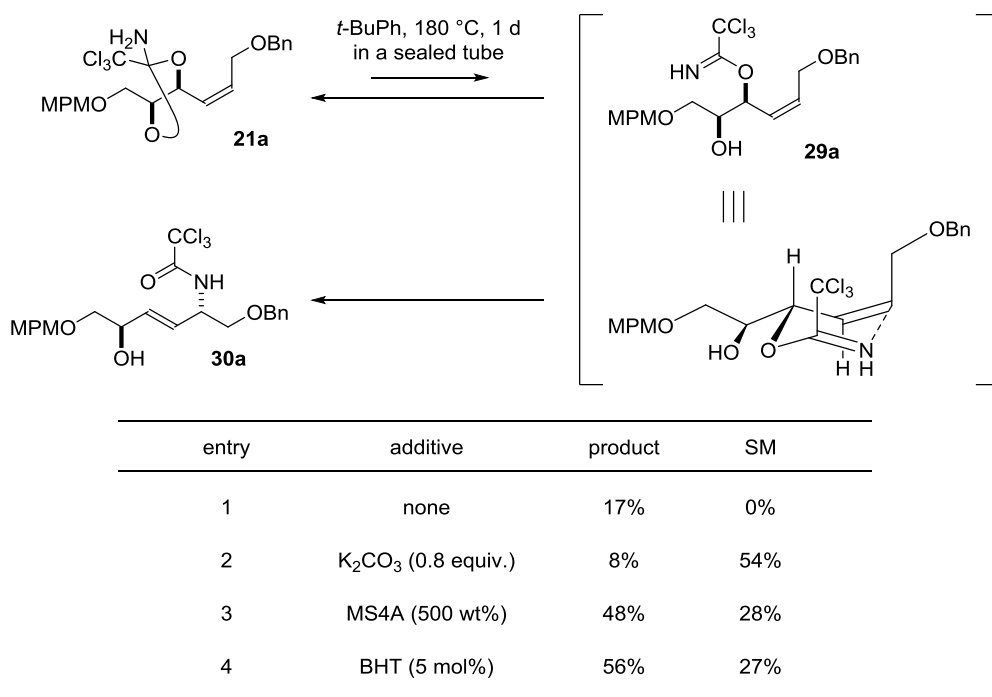
まず始めに、環状オルトアミドを経由した Overman 転位（オルトアミド型 Overman 転位）の先行例を紹介する（スキーム 31）。オルトアミド型 Overman 転位について、これまで2つの論文が報告されている。Danishefsky らは、環状オルトアミド **23** を加熱し、オルトアミドの開環、続く Overman 転位によって、窒素を一つ導入しようとした（**23**→**24**→**25**）<sup>20</sup>。しかし、実際は、転位より再環化が早かったため、転位は進行しなかったと報告している。一方、Vyas らは7員環の環状オルトアミドにおいて転位に成功している（**26**→**27**→**28**）<sup>21</sup>。以上のように、問題となる再環化を抑制し、いかに転位反応を進行させるかが鍵となる。



**Scheme 31.** オルトアミド型 Overman 転位の先行例

このように、環状オルトアミドへの再環化が競争する中、いかに転位を進行させるかが重要である。その解決策として、通常 130 °C 前後で進行する Overman 転位より高い反応温度を用いて、転位の促進を試みた（スキーム 32）。実際の実験について述べる。環状オルトアミド **21a** を封管中 180 °C で1日加熱すると、かさ高い置換基がエクアトリアル配座をとる六員環いす型遷移状態を経由して転位が進行し、収率 17% で転位体 **30a** を与えた（エントリー1）。しかし、高温下長時間の反応による化合物の分解が見られた。そこで、収率の向上を目指し化合物の分解を抑制する添加物を検討した。通常 Overman 転位で用いられる炭酸カリウムを試したところ、マスバランスは改善したが低収率となった（エントリー2）<sup>22</sup>。一方、弱い塩基性を示すモレキュラーシーブを加えると、分解が抑制され収率が向上した（エントリー3）。さらに、触媒量の BHT を添加し

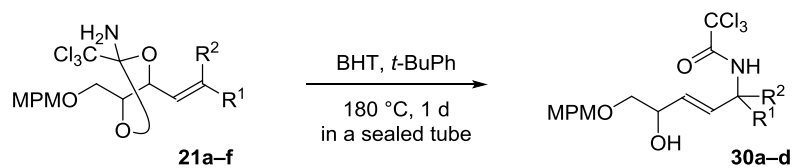
たところ、収率 56%と最も良い収率で望む転位体を得られた（エントリー4）<sup>23</sup>。



**Scheme 32.** オルトアミド型 Overman 転位の検討

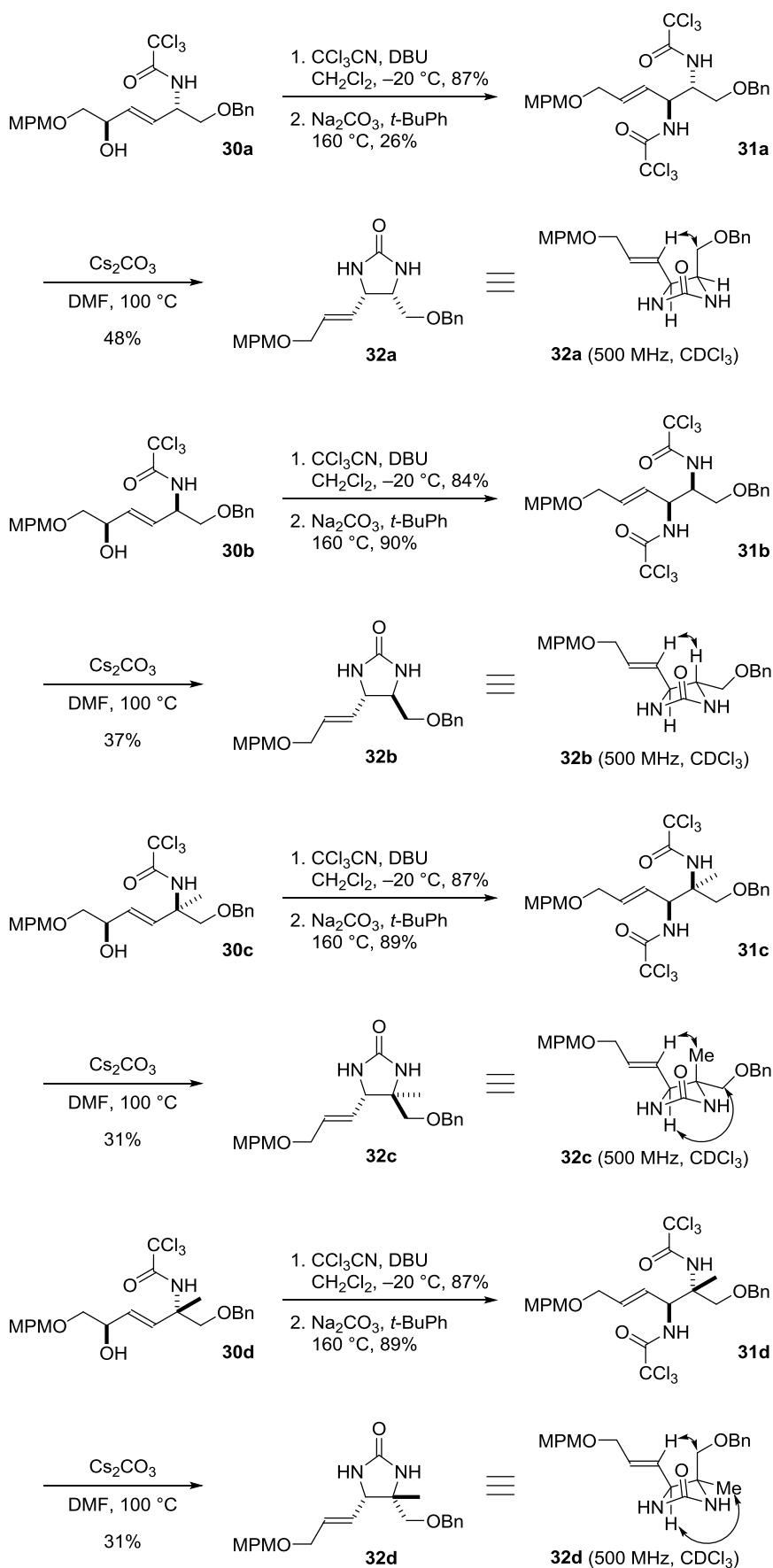
最適条件を種々のオレフィンに適用した（表 2）。*E*-オレフィン **21b** は収率 67%で対応する転位体 **30b** を与えた。一方、*anti* ジオールより誘導した *Z*-オレフィン **21d**、*E*-オレフィン **21e** はそれぞれ転位体 **30b**、**30a** を与えた。D-酒石酸、L-リボース由来のビスイミデートを用いれば、これらの転位体のエナンチオマーが合成できる。すなわち、オレフィンの幾何異性と水酸基の立体化学により、生成物の立体化学が単一に決定する。また、*syn*-、*anti*-ジオールから導いた三置換オレフィン **21c**、**21f** より、低収率ではあるが含窒素四置換炭素を有する転位体 **30c**、**30d** が合成できた。詳細については分かっていないが、二置換オレフィンに比べ、三置換オレフィンを有する基質の方が加熱による分解が激しく、TLC 上で原料と転位体の濃さが同程度になった時点で反応を止めている。

**Table 2.** オルトアミド型 Overman 転位



| entry | substrate | product | yield |
|-------|-----------|---------|-------|
| 1     |           |         | 56%   |
| 2     |           |         | 67%   |
| 3     |           |         | 34%   |
| 4     |           |         | 63%   |
| 5     |           |         | 72%   |
| 6     |           |         | 27%   |

得られた転位体 **30a-d** の立体化学を決めた (スキーム 33)。**30a** の水酸基をイミデート化、続く Overman 転位により、ビスアミド **31a** を得た。**31a** を  $\text{Cs}_2\text{CO}_3$  存在下、DMSO 溶媒中で加熱すると、イソシアネートを経由してウレア **32a** を与えた。**32a** の NOESY 実験により、転位体が予想した立体化学であることを確認した。転位体 **30b-d** も同様のルートでウレア **32b-d** に導き、立体化学を確認した。



**Scheme 33.** オルトアミド型 Overman 転位体 **30a–d** の立体化学の決定



## 第四節 連続的 Overman/Claisen 転位

オルトアミド型 Overman 転位により、転位回数を 1 度に制御できた。次に、生じたアリルアルコールに対する Claisen 転位を検討した (表 3)。Overman 転位後のワンポット化が可能な Claisen 転位として、加熱平衡で反応が進行する Eschenmoser–Claisen を試みた。しかし、望む **33a** は得られたものの、中程度の収率であった (エントリー 1)。次に酸性条件下加熱平衡で進行する Johnson–Claisen 転位を適用した。酸として、2-ニトロフェノール、プロピオン酸、ピバリン酸を試したところ、ピバリン酸が収率 71% で望む転位体 **34a** を与えた (エントリー 2–4)。さらに条件を詳細に精査した結果、ピバリン酸と触媒量の BHT を併用したとき、収率 77% と最も良い結果を与えることが分かった。

Table 3. Claisen 転位の検討

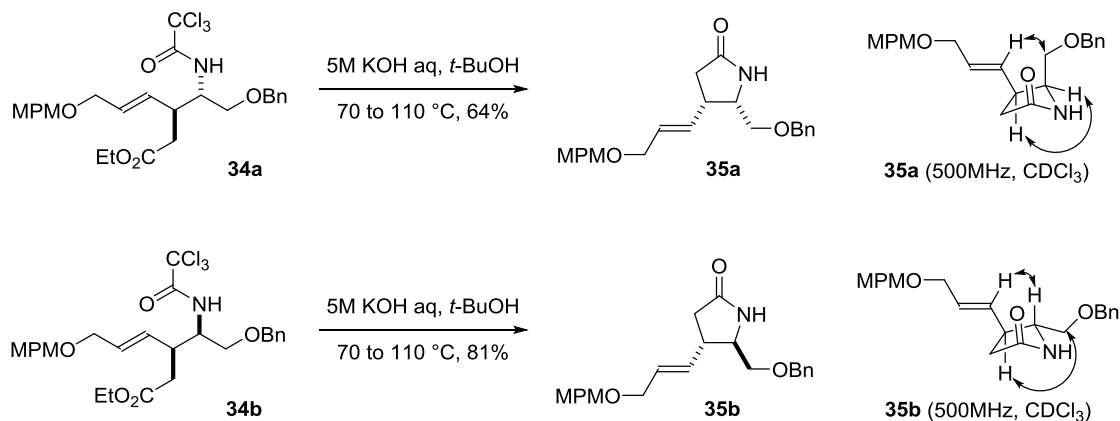
| entry | reagent                                | acid  | yield            |
|-------|--|---|------------------|
| 1     | MeC(OMe) <sub>2</sub> NMe <sub>2</sub> | -   | <b>33a</b> : 44% |
| 2     | MeC(OEt) <sub>3</sub>                  | 2-nitrophenol                                 | <b>34a</b> : 69% |
| 3     | MeC(OEt) <sub>3</sub>                  | EtCO <sub>2</sub> H                           | <b>34a</b> : 53% |
| 4     | MeC(OEt) <sub>3</sub>                  | <i>t</i> -BuCO <sub>2</sub> H                 | <b>34a</b> : 71% |
| 5     | MeC(OEt) <sub>3</sub>                  | <i>t</i> -BuCO <sub>2</sub> H, BHT (10 mol %) | <b>34a</b> : 77% |

最適化した Claisen 転位をオルトアミド型 Overman 転位とのワンポット反応へと展開した (表 4)。環状オルトアミド **21a** を触媒量の BHT 存在下加熱すると、オルトアミド型 Overman 転位が進行し、アリルアルコールを生じた。そこにワンポットにてオルト酢酸トリエチル、ピバリン酸、BHT を添加すると Johnson–Claisen 転位が進行し、対応する転位体 **34a** が収率 45% で単一立体異性体として得られた。一方、*E* 体についてもワンポット反応が収率 54% で、高立体選択的に進行した。*Anti*-ジオール由来の **21d**、**21e** もそれぞれ 54%、55% の収率で連続転位反応が進行した。

**Table 4.** ワンボット Overman/Claisen 転位

| entry  | substrate           | product              | yield |
|--|---------------------|----------------------|-------|
|  | <p><b>21a-d</b></p> | <p><b>34a, b</b></p> |       |
| <p>BHT (5 mol%), <i>t</i>-BuPh<br/>180 °C in a sealed tube;<br/>MeC(OEt)<sub>3</sub>, <i>t</i>-BuCO<sub>2</sub>H<br/>BHT (10 mol%), 140 °C</p> |                     |                      |       |
| 1  | <p><b>21a</b></p>   | <p><b>34a</b></p>    | 45%   |
| 2  | <p><b>21b</b></p>   | <p><b>34b</b></p>    | 54%   |
| 3  | <p><b>21d</b></p>   | <p><b>34b</b></p>    | 54%   |
| 4  | <p><b>21e</b></p>   | <p><b>34a</b></p>    | 55%   |

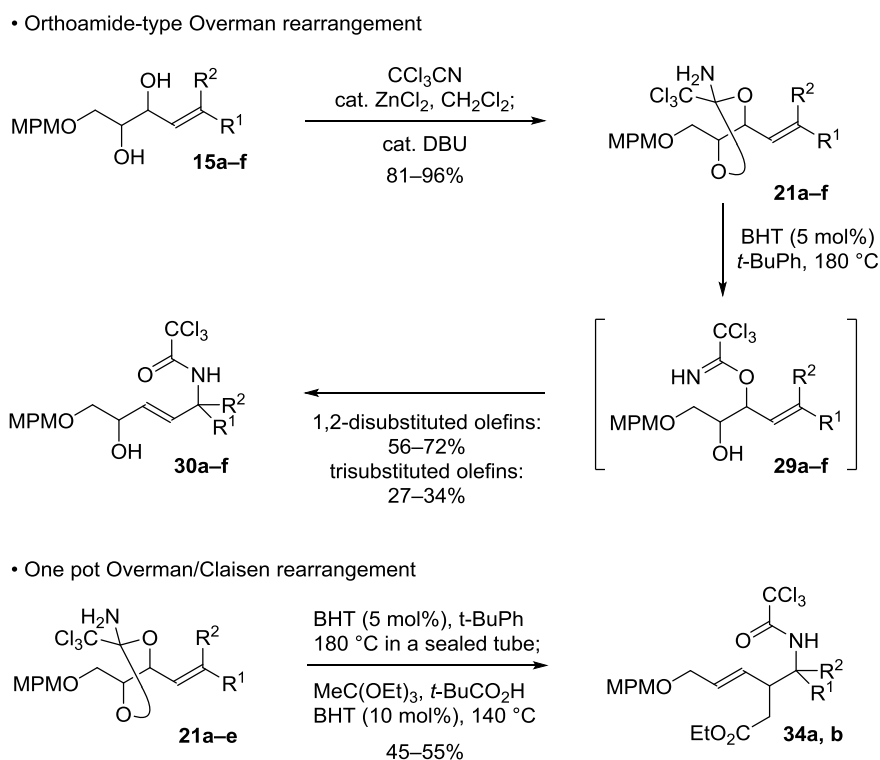
得られた Overman/Claisen 転位体の立体化学を決めた (スキーム 34)。転位体 **34a** を塩基性条件下加熱すると、ラクタム **35a** を収率 64% で与えた。**35a** の NOESY 実験により、転位体は予想した立体化学であることを確認した。**34b** についても同様の条件でラクタム **35b** へと導き、立体化学を決定した。



**Scheme 34.** 連続的 Overman/Claisen 転位体 **34a**、**34b** の立体化学の決定

## 第五節 第一章のまとめ

第一章では、光学活性なアリル-1,2-ジオールの合成とオルトアミド型 Overman 転位の基質一般性、ならびにワンポット Overman/Claisen 転位への展開について述べた。L-酒石酸ジメチル、D-リボースを出発原料とし、水酸基の立体化学、オレフィンの幾何異性の異なる 6 種類のジオール **15a-f** を調製した。**15a-f** を  $\text{CCl}_3\text{CN}$ 、触媒量の  $\text{ZnCl}_2$ 、DBU で処理すると良好な収率で環状オルトアミド **21a-f** に選択的に変換できた。得られた **21a-f** を *t*-BuPh 溶媒中、触媒量の BHT 存在下  $180\text{ }^\circ\text{C}$  に加熱すると、オルトアミドの開環により生じるアリルイミデート **29a-f** を経由して Overman 転位が進行し、対応する **30a-f** を単一の立体異性体として与えた。続いて、オルトアミド型 Overman 転位で生じるアリルアルコールに対し、即座に Claisen 転位の適用を試みた。その結果、**21a-e** からワンポットにて、対応する Overman/Claisen 転位体 **34a, b** が単一立体異性体として得られた。このように、光学活性なアリル-1,2-ジオールに対し、保護基の着脱を経ずに 2 つの異なる転位を実現できた。また、用いるジオールの立体化学とオレフィンの幾何異性の組み合わせにより、所望の立体化学の転位体が完全な立体選択性で合成可能である。さらに、本反応は比較的簡単な構造の環状オルトアミドから、ワンポットにて複雑な転位体が合成可能であり、多数の連続した不斉点を持つアルカロイド合成への応用が期待できる。

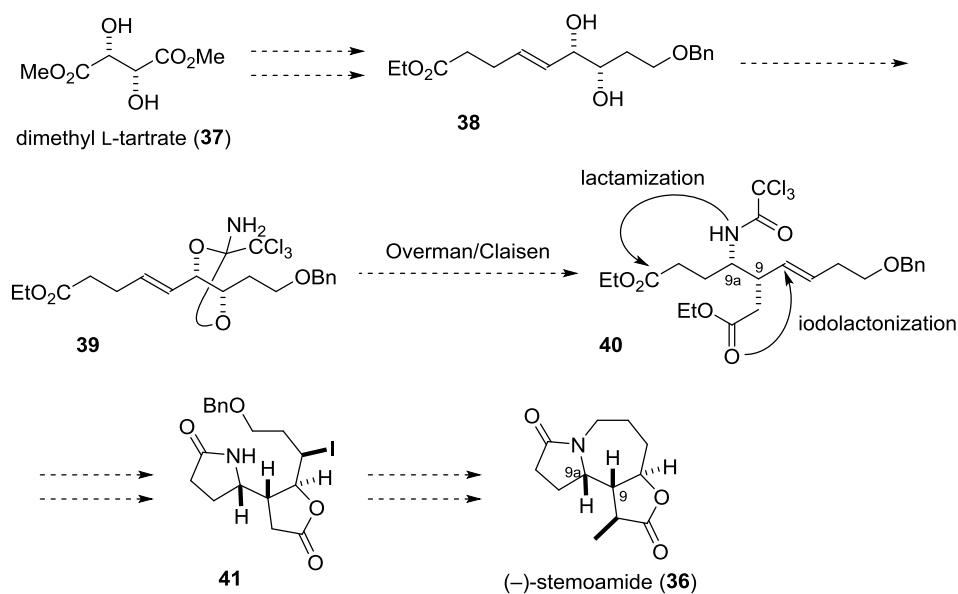


Scheme 35. アリル-1,2-ジオールの Overman/Claisen 転位

## 第二章 (-)-ステモアミドの全合成

### 第一節 合成計画

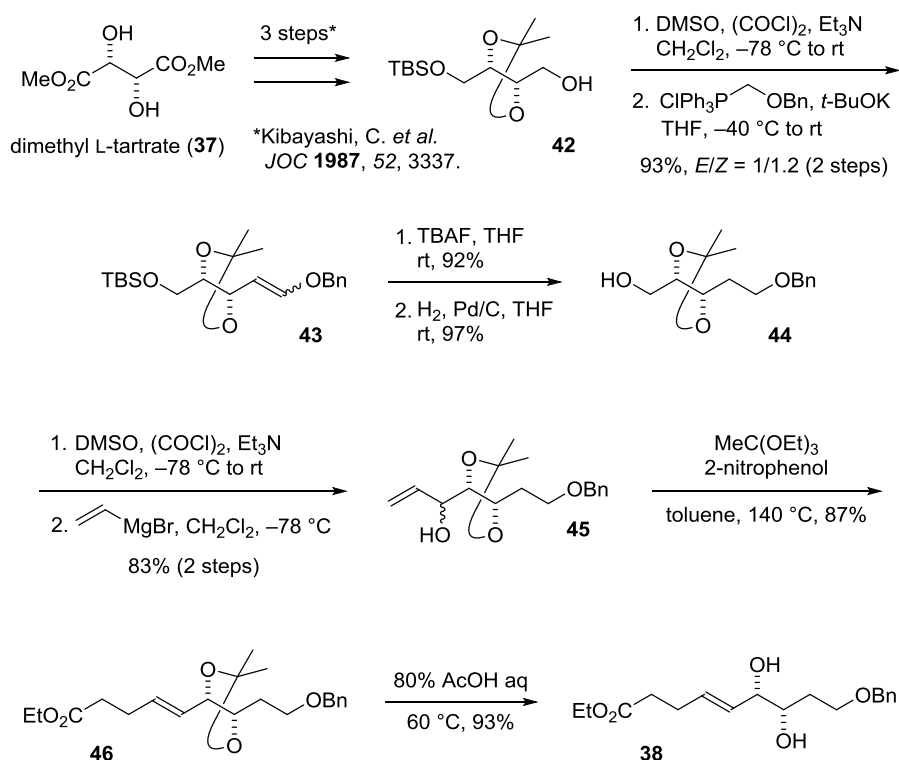
連続的 Overman/Claisen 転位は 2 つの連続した炭素-窒素、炭素-炭素結合を有する不斉炭素を一挙に構築でき、アルカロイドの有用な不斉合成法となる。そこで、本反応を鍵反応とした(-)-ステモアミド (**36**) の合成計画を立案した (スキーム 36)。L-酒石酸ジメチル (**37**) を出発原料として、アリル-1,2-ジオール **38** へと誘導した後、オルトアミド化 (**38**→**39**) と、連続的 Overman/Claisen 転位 (**39**→**40**) によりステモアミドに対応する含窒素 2 連続不斉中心 (9a・9 位) を構築する。続いて、立体選択的なヨードラクトン化と、分子内縮合によるラクタムの構築を経て、二環性中間体 **41** とする。その後、七員環の構築とメチル基の導入を経て、(-)-ステモアミド (**36**) を合成する計画である。



Scheme 36. (-)-ステモアミドの合成計画

## 第二節 アリル-1,2-ジオールの合成

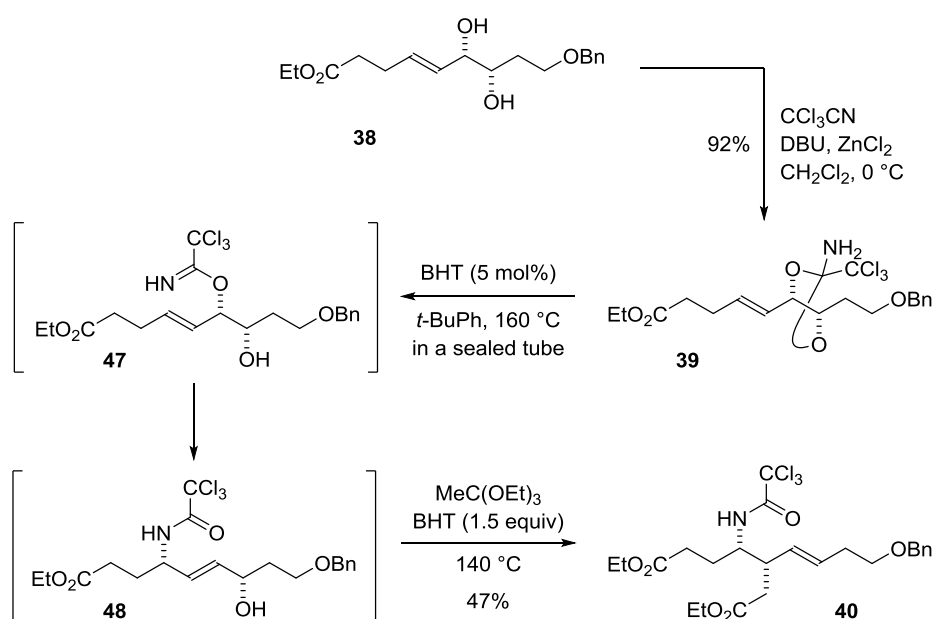
始めに、鍵反応に用いるアリル-1,2-ジオール **38** を合成した (スキーム 37)。L-酒石酸ジメチル (**37**) を出発原料とし、3 工程にて文献既知のアルコール **42**<sup>24</sup> へと導いた。**42** の Swern 酸化、Wittig 反応によりエノールエーテル **43** とした。**43** の TBS 基を除去、水素添加により **44** を得た。**44** の水酸基を酸化、生じたアルデヒドにビニル Grignard 試薬を付加すると、アリルアルコール **45** を与えた。**45** の Johnson–Claisen 転位は収率よく進行し、対応するエステル **46** を得た。**46** を 80% 酢酸で処理してアセタールを除去し、望むアリル-1,2-ジオール **38** を合成した。



Scheme 37. アリル-1,2-ジオール **38** の合成

### 第三節 連続的 Overman/Claisen 転位

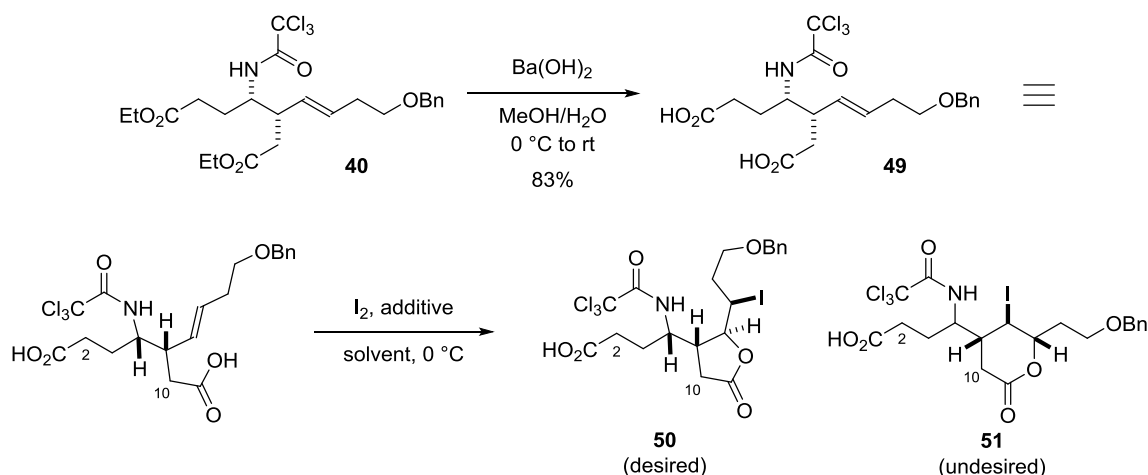
得られたアリル-1,2-ジオール **38** に対し、連続的 Overman/Claisen 転位を適用した(スキーム 38)。**38** を  $\text{CCl}_3\text{CN}$ 、DBU、 $\text{ZnCl}_2$  で処理すると、高収率で環状オルトアミド **39** に変換できた。**39** を触媒量の BHT 存在下、封管中  $160\text{ }^\circ\text{C}$  に加熱すると、環状オルトアミドの開環を経て Overman 転位が進行し、アリルアルコール **47** が生成した。そこにワンポットにて、オルト酢酸トリエチル、酸として BHT を添加し  $140\text{ }^\circ\text{C}$  で加熱すると、対応する転位体 **40** が収率 47% 単一立体異性体で得られた。このように、環状オルトアミド **39** からワンポットにてステモアミドに存在する含窒素 2 連続不斉中心の構築に成功した。



Scheme 38. 連続的 Overman/Claisen 転位

## 第四節 (-)-ステモアミドの全合成

得られた転位体 **40** から $\gamma$ -ラクトンと $\gamma$ -ラクタムを構築した (スキーム 39)。 **40** を水酸化バリウムで加水分解すると、ジカルボン酸 **49** を与えた。この時、塩基に LiOH や NaOH を用いると、トリクロロアセトアミド基の加水分解が競合し、収率が低下した。得られた **49** に対し、ヨードラクトン化を検討した<sup>25</sup>。まず、平衡反応により熱力学的に安定なトランスラクトンが優先するとされる MeCN 溶媒を用いて反応させたところ、10 位カルボン酸より環化が進行した望む $\gamma$ -ラクトン **50** が収率 53%で単一の立体異性体として得られた。この時、位置異性体である **51** も収率 18%、単一立体異性体として生じた (エントリー1)。しかし、望まない 2 位カルボン酸の副反応は全く確認されなかった。次に、速度論支配となる THF/H<sub>2</sub>O を溶媒としたが、 $\gamma$ ,  $\delta$ -ラクトンともに MeCN を用いたときと同一のジアステレオマーのみが中程度の収率で生成した (エントリー2)。収率が向上しないのは、ラクトンが生じる際に副生するヨウ化水素による基質の分解のためだと考え、NaHCO<sub>3</sub> を添加したところ、収率 75%と最も良い結果を与えた (エントリー3)。

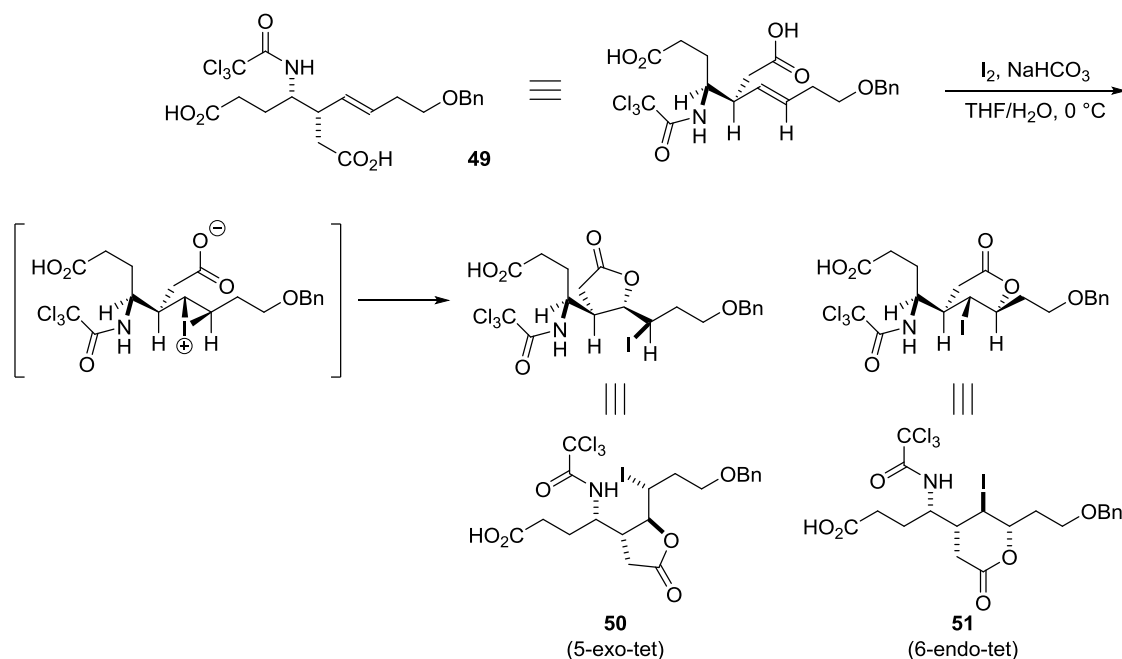


| entry | additive           | solvent              | yields    |           |
|-------|--------------------|----------------------|-----------|-----------|
|       |                    |                      | <b>50</b> | <b>51</b> |
| 1     | -                  | MeCN                 | 53%       | 18%       |
| 2     | -                  | THF/H <sub>2</sub> O | 50%       | 13%       |
| 3     | NaHCO <sub>3</sub> | THF/H <sub>2</sub> O | 75%       | 16%       |

**Scheme 39.** ヨードラクトン化の検討

ヨードラクトン化の立体ならびに位置選択性について考察する (スキーム 40)。まず、立体選択性について考える。ジカルボン酸 **49** は、アリルひずみの最も少ない立体配座が安定であると推測される。すなわち、オレフィンを紙面上に配置したとき、環化は紙面下側より進行することとなり、生成物を単一の立体異性体として与える結果となったと考えられる。次に、位置選択性

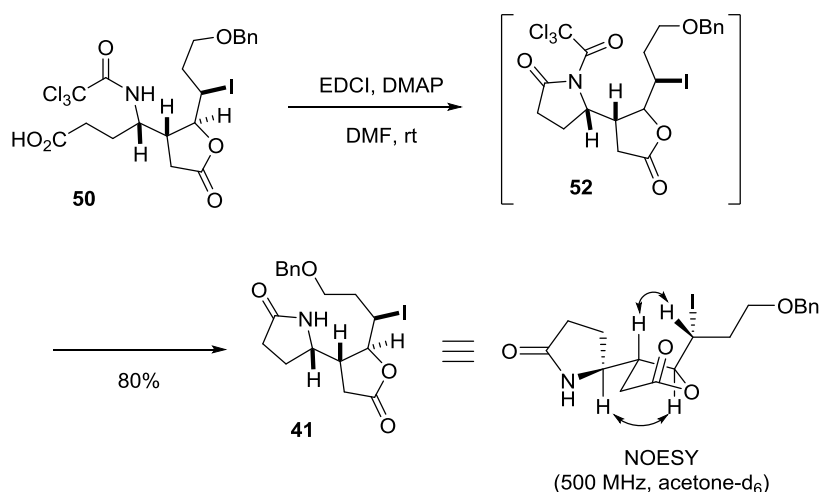
について推測する。ジカルボン酸を  $I_2/NaHCO_3$  で処理すると、ヨードニウムイオンを生じて、カルボキシレートから求核攻撃が進行する。望む $\gamma$ -ラクトン **50** および、望まない $\delta$ -ラクトン **51** はそれぞれ 5-exo-tet 型、6-endo-tet 型の環化生成物であり、前者の方が有利であると考えられる。ゆえに、本反応では望む $\gamma$ -ラクトン **50** が主生成物となったと考えられる。また、 $\delta$ -ラクトン **51** が生じたのは、分子内の窒素原子の非共有電子対がヨードニウムイオンに配位し、6-endo-tet 型の環化の安定化に寄与したため<sup>26</sup>だと推測している。



**Scheme 40.** ヨードラクトン化の立体ならびに位置選択性

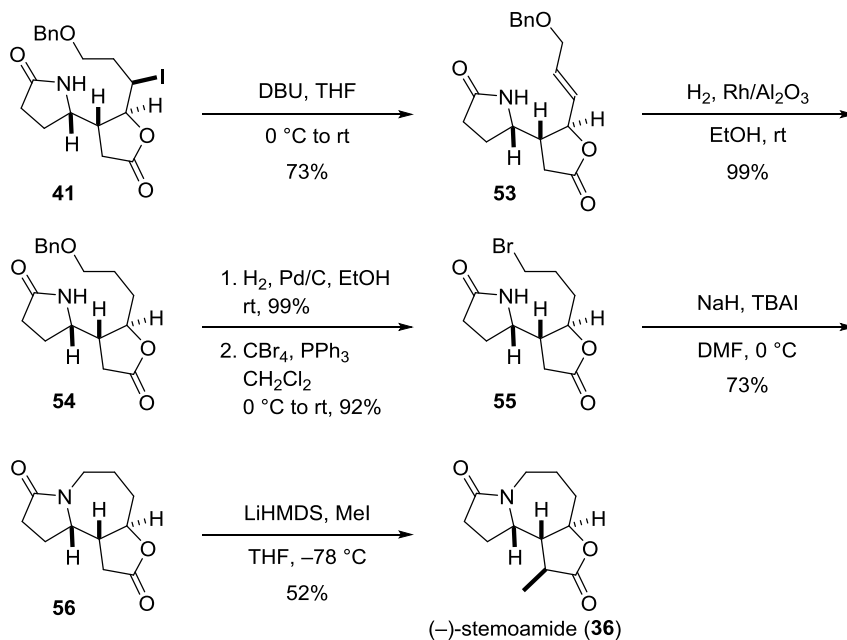
続いて、ヨードラクトン **50** を EDCI、DMAP で処理すると残るカルボキシ基とトリクロロアセトアミド基との分子内縮合、トリクロロアセチル基の除去が一挙に進行し、 $\gamma$ -ラクタム **41** を与えた (スキーム 41)。共存する 2 つのカルボキシ基の区別化を経由して、転位体から 3 工程でステモアミドに対応する $\gamma$ -ラクトン、 $\gamma$ -ラクタムを構築できた。なお、生成物の立体化学はこの時点で NOESY 実験により決定した。





**Scheme 41.**  $\gamma$ -ラクタムの構築と立体化学の決定

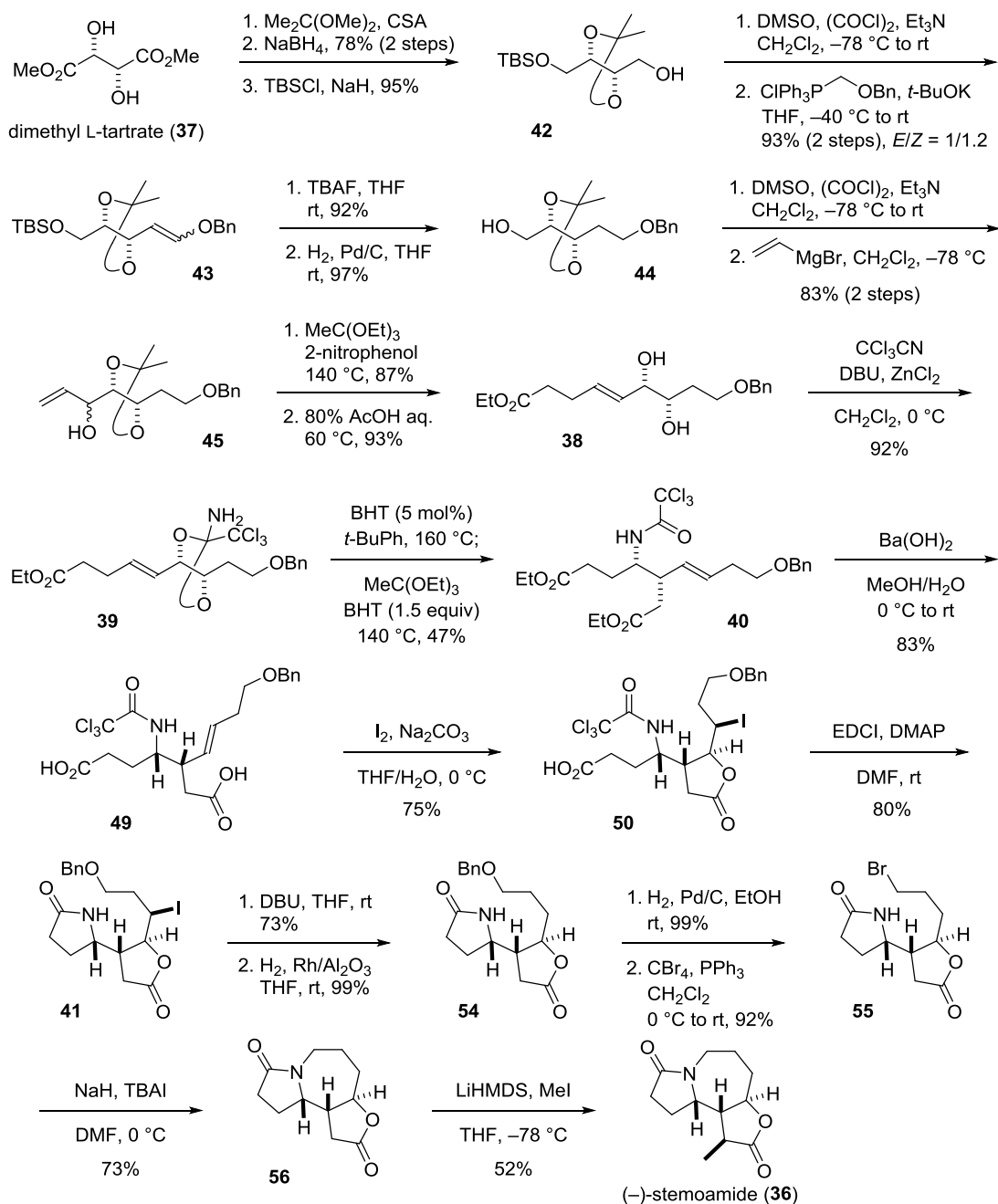
次に、ステモアミドの七員環を構築した (スキーム 42)。得られた 2 環性中間体 **41** を DBU で処理すると、ヨウ化水素が脱離し、生じたオレフィンを経由して **54** とした。続いて、ベンジル基を水素化分解で除去し、Appel 反応で臭素体 **55** へと導いた。これを TBAI 存在下、水素化ナトリウムで処理すると分子内環化が進行し、七員環を構築できた。最後に立体選択的にメチル基を導入<sup>10</sup>し、(-)-ステモアミド(**36**)の全合成を達成した。



**Scheme 42.** (-)-ステモアミドの全合成

## 第五節 第二章のまとめ

以下に第二章をまとめた。



Scheme 43. (-)-ステモアミドの全合成

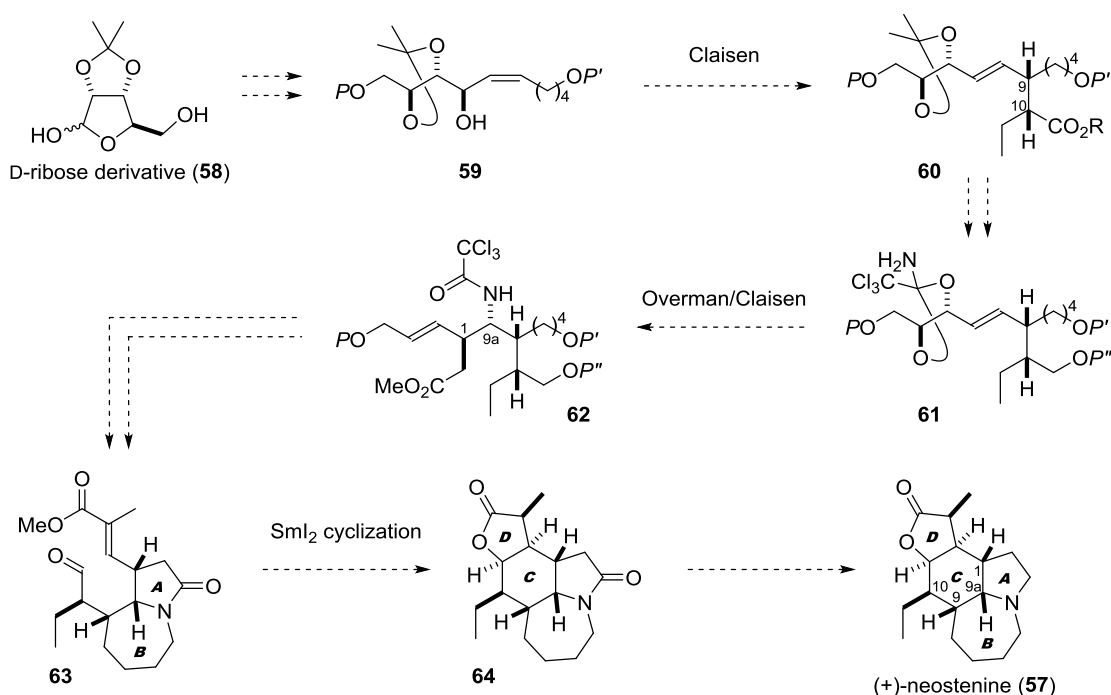
第二章では、第一章で開発した連続的 Overman/Claisen 転位を鍵反応として、(-)-ステモアミドの全合成を達成した。L-酒石酸ジメチルより誘導した環状オルトアミドに Overman/Claisen 転位を適用し、ステモアミドの 9a・9 位にあたる含窒素 2 連続不斉中心を導入した。転位体の加水分解

解で生じたジカルボン酸の、2つのカルボキシル基の区別化を経由して、転位体から3工程でステモアミドに対応する $\gamma$ -ラクトン、 $\gamma$ -ラクタムを合成できた。最後に、7員環の構築と、立体選択的なメチル基の導入を経て、(-)-ステモアミドの全合成を達成した。

### 第三章 (+)-ネオステニンの全合成

#### 第一節 合成計画

(+)-ネオステニン (**57**) は、これまでに 2 つの全合成例が報告されているが、いずれもラセミ体の合成であり、光学活性体の全合成例はない。そこで、開発した方法論のさらなる有用性を示すべく、**57** の初となる不斉全合成に取り組んだ。



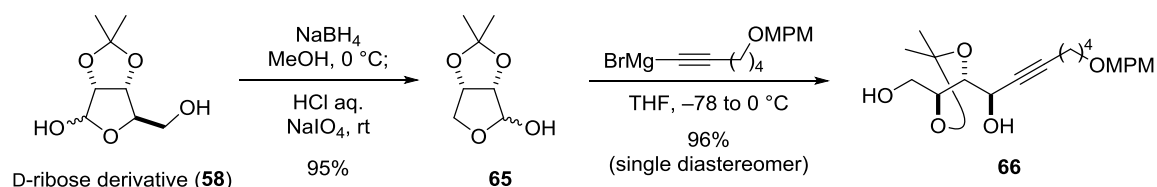
Scheme 44. (+)-ネオステニンの合成計画

本研究における合成戦略の特徴は、(+)-ネオステニン(**57**) に存在する 4 連続不斉中心を Overman/Claisen 転位を含む鎖状化合物の 3 回のシグマトロピー転位により構築する点である。一般的に環状化合物の立体制御は、分子の立体配座に大きく依存し、しばしば望まない立体化学を与える。そこで、本研究では立体配座の影響の少ない鎖状化合物の[3,3]シグマトロピー転位を用いた不斉転写により立体化学を制御し、その後環を構築する基本戦略を用いることにした。購入可能な D-リボース誘導体 (**58**) より合成したアリルアルコール **59** に対し、1 回目のシグマトロピー転位として Claisen 転位を適用し、9・10 位の 2 連続不斉炭素を導入する。続いて環状オルトアミド **61** の Overman/Claisen 転位により 9a・1 位に対応する含窒素 2 連続不斉中心を一挙に構築する。得られた転位体 **62** の窒素原子を足掛かりに、2 回の分子内環化により A・B 環を合成する。その後、数工程にて誘導したアルデヒド **63** に対し、SmI<sub>2</sub> を用いた環化反応により一挙に C・D

環を構築する。最後に、ラクトン共存下、ラクタム選択的な還元により、(+)-ネオステニン(57)の全合成を達成する計画である。

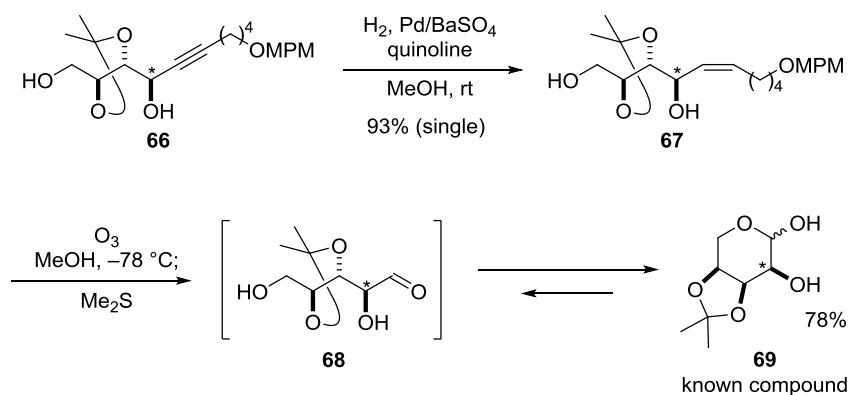
## 第二節 Z-アリルアルコールの合成

初めに、Claisen 転位に用いる Z-アリルアルコールを合成した。出発原料である D-リボース誘導体 **58** を既知のラクトール **65** へと変換した (スキーム 45)。**65** に対する Grignard 反応は望むプロパルギルアルコール **66** を単一立体異性体として与えた。



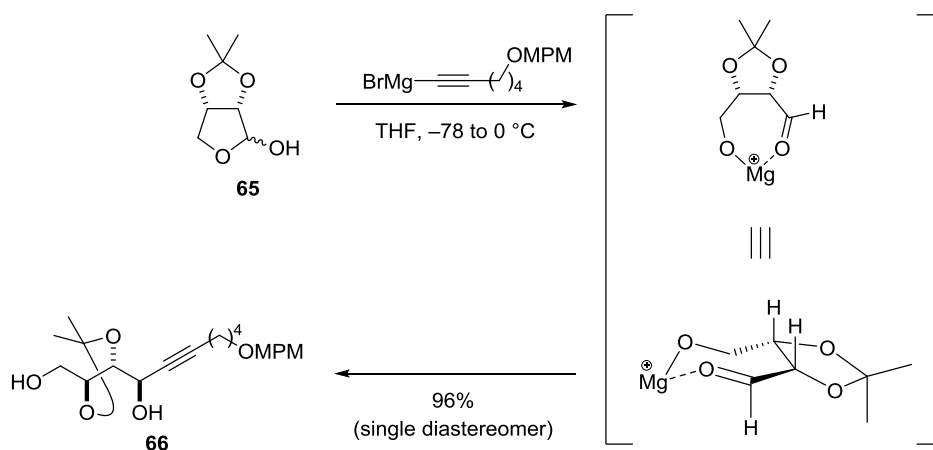
Scheme 45. プロパルギルアルコールの合成

ここで、プロパルギルアルコール **66** の立体化学の決定を試みた (スキーム 46)。アルキンの部分還元により **67** とした。生じたアルケンのオゾン分解により、アルデヒド **68** を経由しラクトール **69** が得られた。**69** は既知化合物であり<sup>27</sup>、<sup>1</sup>H NMR が一致したため、Grignard 反応で新たに生じた水酸基の立体化学は *R* であると決定した。



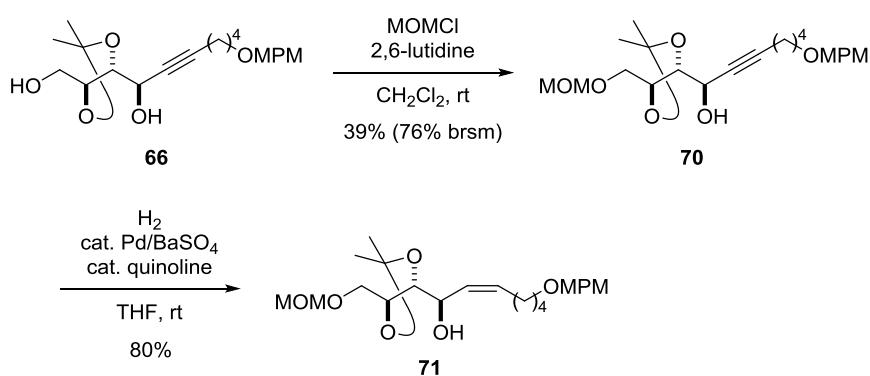
Scheme 46. プロパルギルアルコールの立体化学の決定

続いて、Grignard 反応の立体選択性について考える (スキーム 47)。本反応はキレート制御により高立体選択的に進行したと考えられる。しかし、一般的な  $\alpha$ -キレーションモデルでは、生成物の立体化学は *S* となる。ラクトール **65** に対する求核付加の選択性について、Singh らは  $\gamma$ -キレーションモデルを提唱している<sup>28</sup>。7員環キレート中間体に対し、紙面手前側から求核剤が付加すれば、生じるアルコールの立体化学は *R* となり実験結果と合致する。



**Scheme 47.** Grignard 反応の立体選択性

Grignard 反応で得られたジオール **66** の一級水酸基選択的な保護、続く部分還元により *Z*-アリルアルコール **71** へと誘導した。

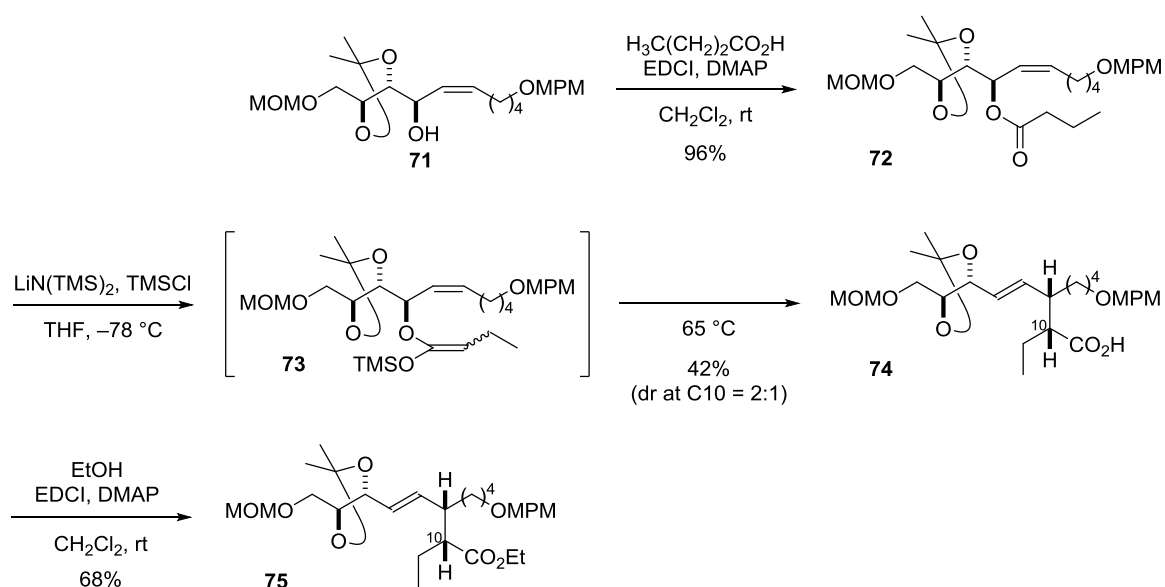


**Scheme 48.** *Z*-アリルアルコール **71** の合成

### 第三節 Claisen 転位による二連続不斉中心の導入

#### 3.1 Ireland–Claisen 転位

9・10位の2連続不斉中心を制御するため、Ireland–Claisen 転位を試みた (スキーム 49)。アリルアルコール **71** の水酸基をアシル化し、アリルエステル **72** を得た。**72** を  $-78\text{ }^{\circ}\text{C}$  にて  $\text{LiN}(\text{TMS})_2$ 、 $\text{TMSCl}$  で処理して *E*-シリルケテンアセタール **73** とした後、 $65\text{ }^{\circ}\text{C}$  に昇温すると Claisen 転位が進行し、対応するカルボン酸 **74** が収率 42% で得られた。しかし、C10 位の立体選択性は 2:1 にとどまった。得られた **74** はエタノールと縮合し、エチルエステル **75** とした。

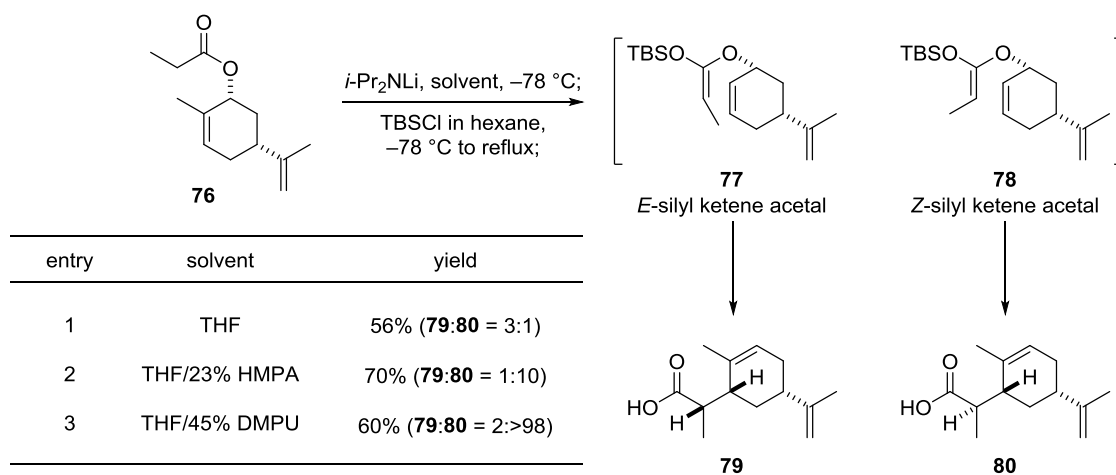


Scheme 49. *Z*-アリルアルコール **71** の Ireland–Claisen 転位

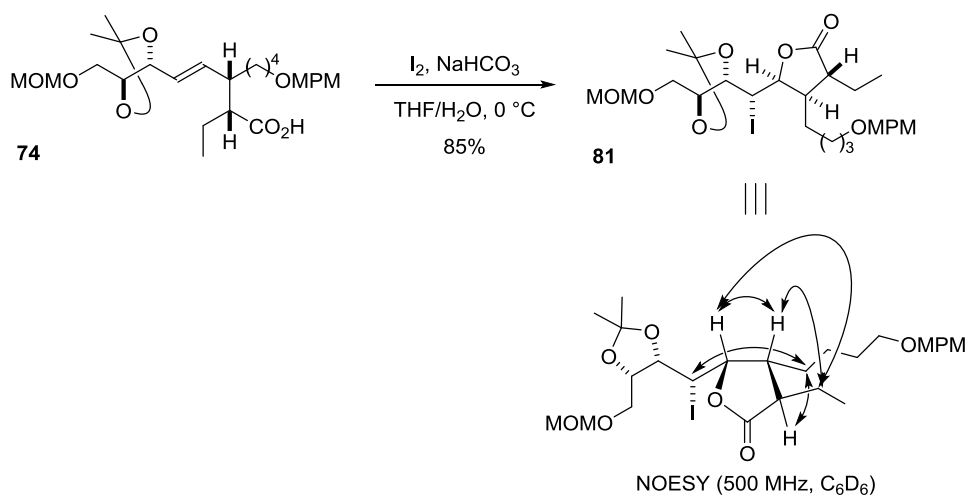
ここで、Ireland–Claisen 転位が低い選択性となった理由について考える。Ireland らは、シリルエノールエーテルを調製する際の溶媒効果についての検討を報告している (表 5)<sup>29</sup>。*E*-シリルケテンアセタールが優先する THF 溶媒では収率 56% (dr = 3:1) と低い選択性である。一方、*Z*-シリルケテンアセタールが優先する極性溶媒を添加した条件では、収率 70% (dr = 1:10)、収率 60% (dr = 2:>98) と良好な選択性で転位体が得られている (エントリー 2,3)。以上のように、*Z*-シリルケテンアセタールは極性溶媒を添加して調製できる一方、*E*-シリルケテンアセタールの選択性は基質の構造に大きく依存する。ゆえに、今回転位に用いた *Z*-アリルエステル **72** は、*E*-選択的なシリルケテンアセタールの調製が困難な基質であったと考えている。



**Table 5.** Ireland らによる溶媒効果の検討



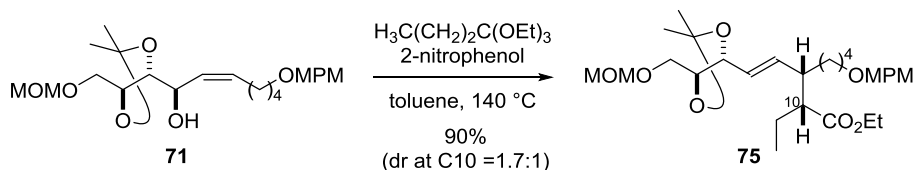
なお、転位体 **74** の立体化学は、ジアステレオマーを分離後ヨードラクトンに誘導し、NOESY 実験により決定した。



**Scheme 50.** Ireland–Claisen 転位体 **74** の立体化学の決定

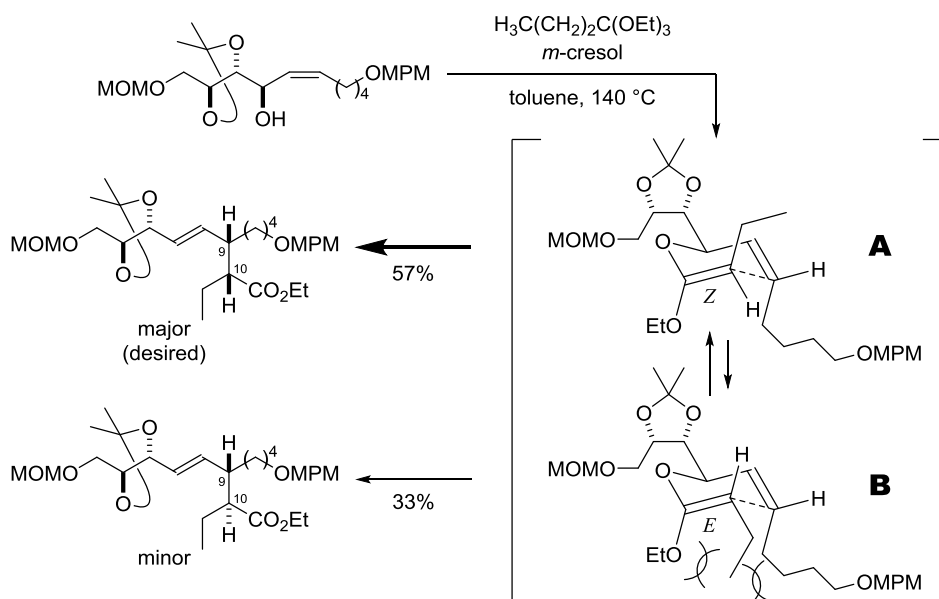
### 3.2 Johnson–Claisen 転位

次に、*Z*-アリルアルコール **71** に Johnson–Claisen 転位を適用した (スキーム 51)。**71** を、オルト酪酸トリエチル、2-ニトロフェノール存在下、封管中 140 °C に加熱すると転位が進行し、対応するエステル **75** が収率 90%、ジアステレオマー比 1.7:1 で得られた。Johnson–Claisen 転位の適用により、2 工程の短縮と、大幅な収率改善に成功した。



Scheme 51. *Z*-アリルアルコール **71** の Johnson–Claisen 転位

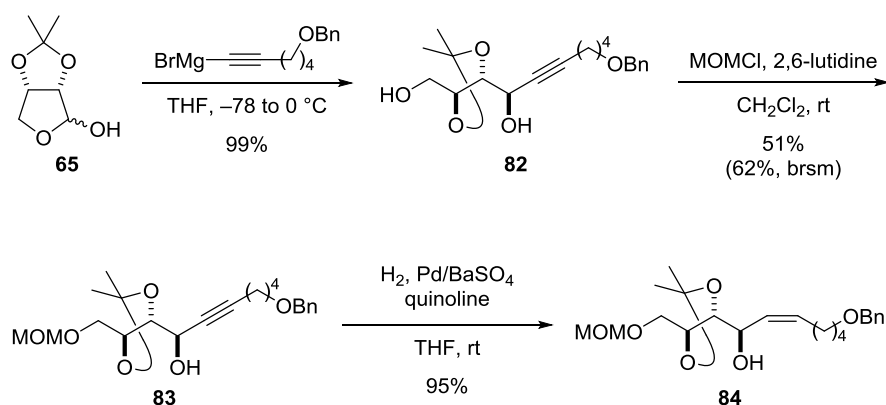
続いて、本反応の立体選択性について考察する (スキーム 52)。アリルアルコールを酸触媒存在下オルト酪酸トリエチルと加熱すると、速い平衡で存在する 2 種類のケテンアセタールを経由して転位が進行すると Daub らにより報告されている<sup>30</sup>。本反応で新たに生じる 2 つの不斉点のうち、9 位は出発原料の水酸基の立体化学ならびにオレフィンの幾何異性により完全に制御できた。一方、10 位の立体化学は転位直前のケテンアセタールの幾何異性に依存する。ケテンアセタールが *E* 体となる遷移状態 **B** では、エチル基、ベンジルオキシ基を含む置換基、エトキシ基との間に大きなゴーシュ反発が生じる。一方、ケテンアセタールが *Z* 体の遷移状態 **A** では、エチル基がアキシシャル位を占めるが、酸素原子との 1,3-ジアキシシャル反発が小さく、この遷移状態 **A** から優先して転位が進行したと考えている。なお、添加する酸の違いによる立体選択性への影響について、詳細は分かっていないが、実験結果より酸性度の小さい酸の方が望む立体化学の転位体を多く与える傾向を示すことが分かっている。以上のように Johnson–Claisen 転位の適用により、2 工程の短縮と大幅な収率改善が実現できた。



Scheme 52. Johnson–Claisen 転位の立体選択性

このように、望む立体化学が主生成物として得られたため、2種類のジアステレオマーを混合物のまま先に進めることとしたが、後の工程でも分離は困難であった。種々検討した結果、MPM基に代わりベンジル基を用いたとき、分離できることが分かった。

次に、ベンジル保護体の原料合成を示す (スキーム 53)。ラクトールに対する Grignard 反応は高収率で進行し、対応するプロパルギルアルコール **82** を与えた。**82** の一級選択的保護、続く部分還元により *Z*-アリルアルコール **84** へと導いた。

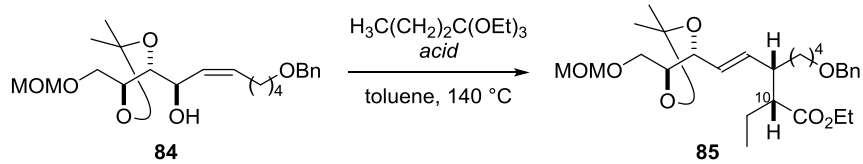


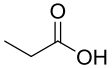
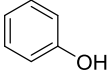
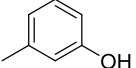
Scheme 53. *Z*-アリルアルコール **84** の合成

得られた *Z*-アリルアルコール **84** に対し、Johnson–Claisen 転位を検討した (表 6)。**84** をオルト酪酸トリエチル存在下、プロピオン酸を添加し加熱すると、転位反応が進行しエステル **85** が収率 88% (dr = 1.1:1 at C10) で得られた (エントリー1)。酸をフェノールに変更すると、ジアステレオマー比が向上した (エントリー2)。条件を詳細に精査した結果、*m*-クレゾールを用いたとき、

収率 92% (dr = 2.0:1 at C10)と最も良い結果を与えた (エントリー3)。

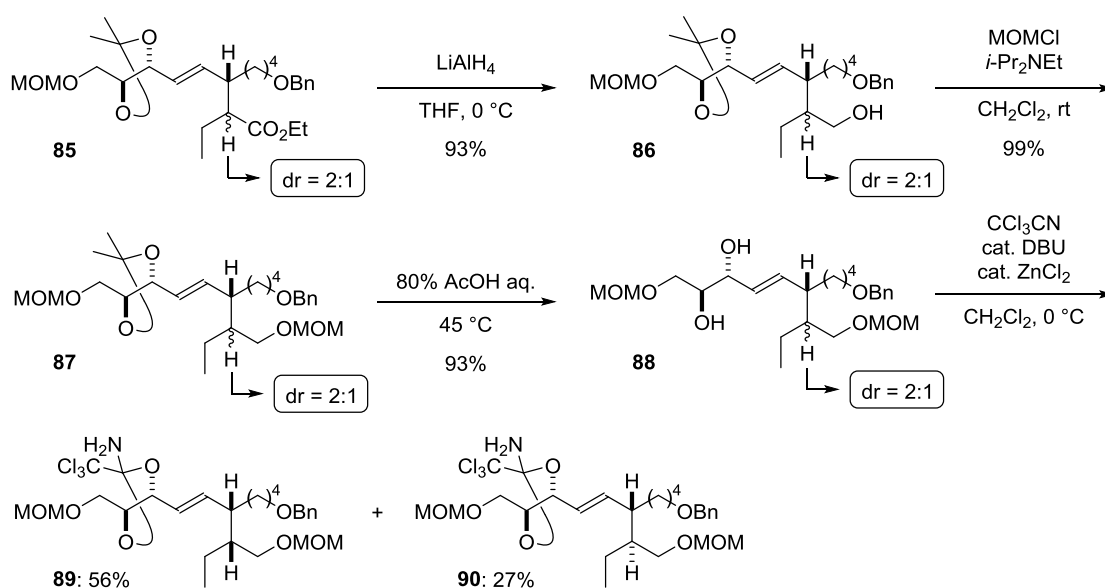
**Table 6.** Johnson–Claisen 転位の検討



| entry | acid   | yield | dr at C10 |
|-------|--|-------|-----------|
| 1     |  propionic acid | 88%   | 1.1:1     |
| 2     |  phenol         | 85%   | 1.8:1     |
| 3     |  m-cresol       | 92%   | 2.0:1     |

## 第四節 連続的 Overman/Claisen 転位

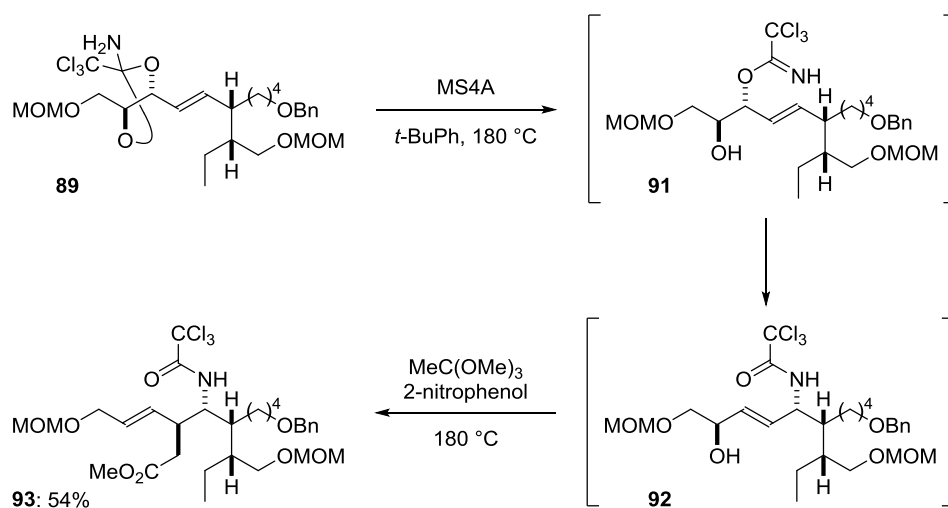
Johnson–Claisen 転位体から、環状オルトアミドを合成した (スキーム 54)。Johnson–Claisen 転位体の 2 種類のジアステレオマーは分離困難であったため、混合物のまま先へ進めた。転位体 **85** のエステルを還元し、生じた水酸基を MOM 基で保護し **87** とした。続いて、80% 酢酸でアセタールを除去してアリル-1,2-ジオール **88** を得た。**88** をトリクロロアセトニトリル、触媒量の DBU、ZnCl<sub>2</sub> で処理して環状オルトアミド **89** に変換した。この段階で Johnson–Claisen 転位由来のジアステレオマー **90** を分離できた。



Scheme 54. 環状オルトアミドの合成

得られた環状オルトアミド **89** に対し、連続的 Overman/Claisen 転位を適用した (スキーム 55)。**89** を MS4A 存在下、封管中 180 °C に加熱すると、環状オルトアミドの開環を経て Overman 転位が進行し、アリルアルコール **92** が生成した。そこにワンポットにて、オルト酢酸トリメチル、2-ニトロフェノールを添加し加熱すると、対応する転位体 **93** が収率 54% 単一立体異性体で得られた。このように、環状オルトアミド **89** からワンポットにてネオステニンに対応する含窒素 2 連続不斉中心を構築できた。

なお、本基質ではオルトアミド型 Overman 転位の添加物に MS4A を用いる方が、BHT に比べ再現性、収率ともに良い結果を与えた。

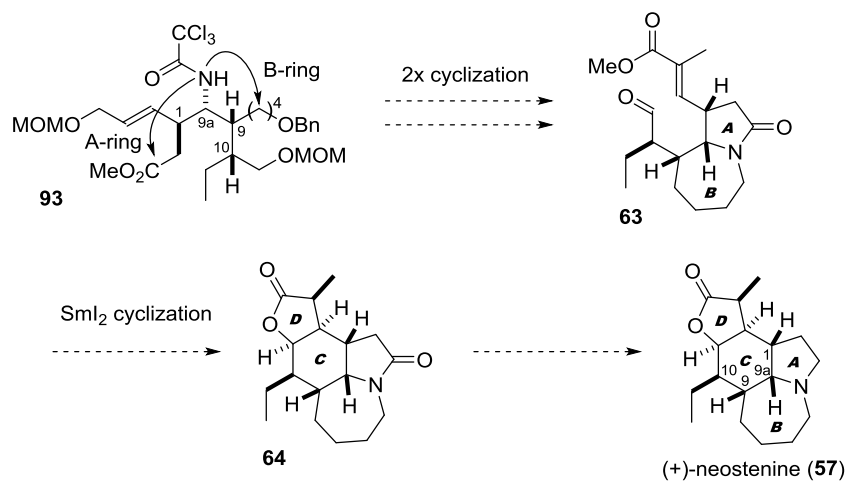


**Scheme 55.** 連続的 Overman/Claisen 転位

以上のように、連続的 Overman/Claisen 転位を含む 3 回のシグマトロピー転位により、天然物に対応する含窒素四連続不斉中心を有する鎖状中間体を合成できた。

## 第五節 (+)-ネオステニンの不斉全合成

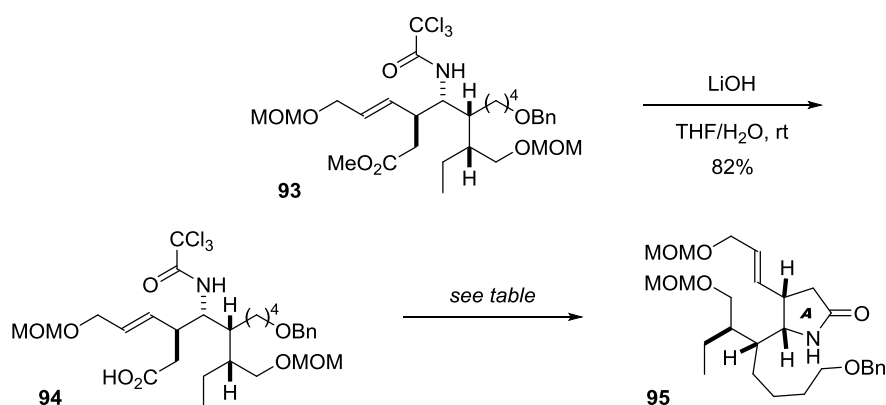
3回のシグマトロピー転位により、天然物に対応する含窒素4連続不斉中心を有する鎖状中間体を合成できた。ネオステニンの全合成に向けて、3つの環化反応による四環性骨格の構築に取り組んだ。



Scheme 56. ネオステニン全合成に向けた3つの環化反応

### 5.1 ネオステニン A 環部の構築

まず初めに、A環の合成に着手した(スキーム 57)。転位体 **93** のメチルエステルを加水分解し、カルボン酸 **94** とした。**94** を EDCI、DMAP で処理すると、トリクロロアセトアミド基との分子内縮合が進行し、ネオステニンの A 環に対応するγ-ラクタムを有する **95** が収率 80% で得られた(エントリー1)。しかし、本条件はスケールアップにより収率が低下することが分かった(エントリー2、32.5 mg、収率 61%)。詳細な理由は分かっていないが、TLC による反応追跡から活性エステルは速やかに生成するものの、その後の環化段階の速度が低下することが分かった。クロロギ酸エチルを用いた混合酸無水物法も試みたが、収率の改善は見られなかった(エントリー3)。



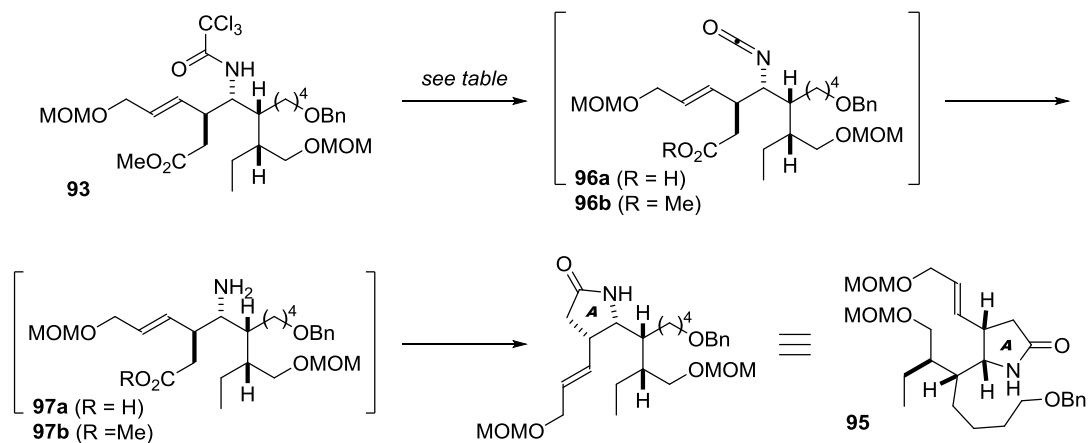
| entry | conditions  | scale   | yield |
|-------|---|---------|-------|
| 1     | EDCI, DMAP, DMF, 45 °C  | 9.8 mg  | 80%   |
| 2     |   | 32.5 mg | 61%   |
| ----- |   |         |       |
| 3     | CICO <sub>2</sub> Et, Et <sub>3</sub> N, THF, 0 °C<br>DMAP, 60 °C | 57.0 mg | 70%   |

**Scheme 57. A** 環部構築の検討

収率が上がらない原因は、トリクロロアセトアミド基の求核性の低さにあると考えた。そこで解決策として、磯部らの報告<sup>31</sup>を参考にトリクロロアセトアミド **93** をイソシアネート **96** に変換し、水の付加に続く脱炭酸によりアミンとすれば環化が円滑に進行すると期待した (表 7)。転位体 **93** を Cs<sub>2</sub>CO<sub>3</sub> 存在下、含水 DMSO 中 90 °C に加熱すると、イソシアネートの生成と脱炭酸ならびにメチルエステルの加水分解が一挙に進行し、**97a** が生じた。これを 180 °C に昇温すると、分子内環化が進行し、望むγ-ラクタム **95** を与えた (エントリー1, 2)。しかし、本条件でもスケールアップにより収率が低下した。また、メチルエステルが加水分解によりカルボン酸 **97a** になるため、環化に高温条件が必要となった。そこで、無水条件でイソシアネートとした後、室温にて重曹水で処理すればエステルを保持したままアミンを生じさせられると考えた (エントリー3,4)。無水条件で 90 °C に加熱し、室温まで放冷してから重曹水に反応溶液を滴下すると、脱炭酸が進行しアミノエステル **97b** が生じた。**97b** の分子内環化は、穏和な室温条件下で進行し、**95** を収率よく与えた。また、本条件ではスケールを上げて高い再現性を示した。



**Table 7.** イソシアネートを経由した A 環部の合成

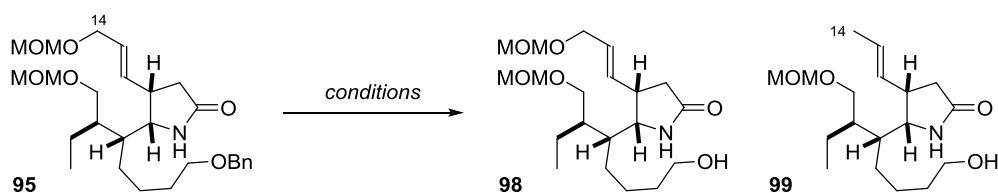


| entry | conditions   | scale   | yield |
|-------|--|---------|-------|
| 1     | Cs <sub>2</sub> CO <sub>3</sub> (2.5 eq), H <sub>2</sub> O (50 eq)<br>DMSO, 90 to 180 °C | 6.3 mg  | 76%   |
| 2     |  | 40.0 mg | 63%   |
| 3     | Cs <sub>2</sub> CO <sub>3</sub> (2.5 eq), DMSO, 90 °C<br>then NaHCO <sub>3</sub> aq., rt | 6.1 mg  | 84%   |
| 4     |  | 126 mg  | 90%   |

## 5.2 ネオステニン B 環部の構築

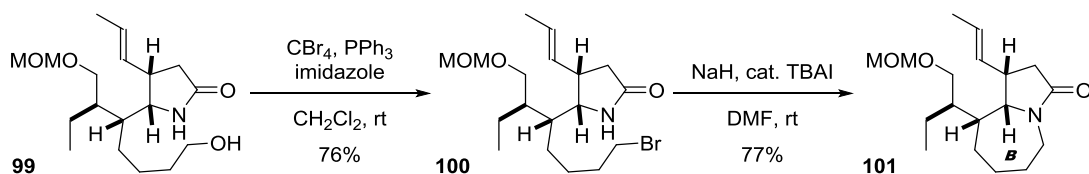
A 環部が合成できたので、続いて B 環部の構築を目指し、ベンジル基の除去を検討した(表 8)。 $\gamma$ -ラクタム **95** を MeCN/H<sub>2</sub>O 溶媒中、CAN で処理すると基質が分解するのみであった(エントリー1)。次に、DDQ を用いると、収率 76% で望むアルコール **98** が得られ、13% の原料が回収された(エントリー2)。DDQ を用いる条件では、試薬の等量、反応時間を変えても、これ以上の収率は得られなかった。次に、-78 °C にて Birch 還元を適用すると、ベンジル基のみが除去された **98** が収率 9%、ベンジル基に加え 14 位のアリルエーテル部位も除去された **99** が収率 85% で得られた(エントリー3)。14 位の MOM エーテル部位は、後のオレフィンの酸化的開裂で失われるため、**99** が単一生成物として得られる条件を探索した。温度検討の結果、-63 °C としたとき **99** のみを収率 90% で与えた。なお、-50 °C では **98** は得られないものの、少量の構造不明物の生成を <sup>1</sup>H NMR にて確認している。

Table 8. ベンジル基除去の検討



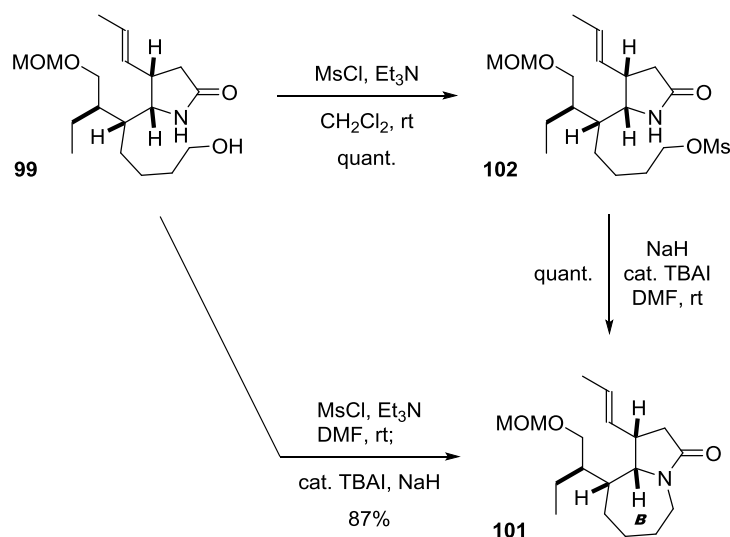
| entry | conditions   | result                           |
|-------|--|----------------------------------|
| 1     | CAN, MeCN/H <sub>2</sub> O, rt                             | decomp.                          |
| 2     | DDQ, CH <sub>2</sub> Cl <sub>2</sub> /H <sub>2</sub> O, rt | <b>98</b> : 76%, <b>95</b> : 13% |
| 3     | Li, <i>t</i> -BuOH, THF/NH <sub>3</sub> , -78 °C           | <b>98</b> : 9%, <b>99</b> : 85%  |
| 4     | Li, <i>t</i> -BuOH, THF/NH <sub>3</sub> , -63 °C           | <b>99</b> : 90%                  |

得られた **99** より、B 環部構築を検討した(スキーム 58)。**99** を Appel 反応により臭素体 **100** へと導いた。**100** を DMF 溶媒中室温にて触媒量の TBAI 存在下 NaH で処理すると、分子内環化が進行し、ネオステニンの B 環に対応する 7 員環骨格を含む二環性化合物 **101** が合成できた。



Scheme 58. 臭素体を経由した B 環部の構築

次に収率向上を目指し、脱離基をメシラートに変更した（スキーム 59、**99**→**102**→**101**）。その結果、メシル化、環化ともに定量的に反応が進行することを見出した。また、先述の Appel 反応では、副生するトリフェニルホスフィンオキシドの分離が困難であったのに対し、本条件では精製も容易になった。続いて、短工程化を目指しメシル化と環化のワンポット化を試みた（**99**→**101**）。アルコール **99** を DMF 溶媒中でメシル化し、原料の消失を確認した後に TBAI、NaH で処理すると望む **101** がワンポット反応にて、収率 87% で合成できた。



**Scheme 59.** メシラートを経由した B 環の構築

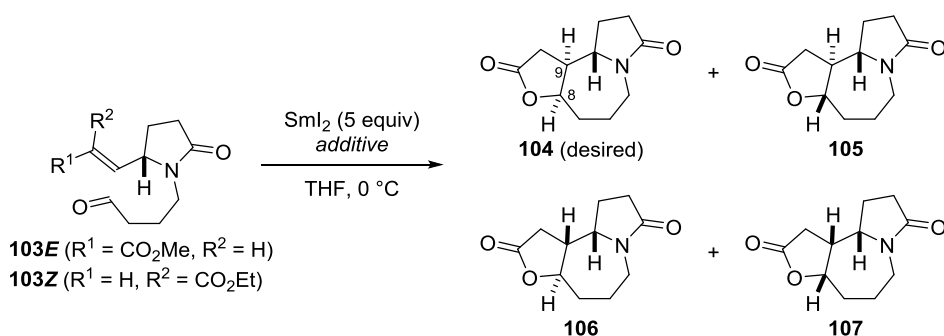
### 5.3 SmI<sub>2</sub> 環化による C・D 環の構築

複雑天然物の全合成において、SmI<sub>2</sub> のカスケード型反応や分子内環化反応への応用例が、これまでに数多く報告されている<sup>32</sup>。SmI<sub>2</sub> を用いた反応は、一般的な手法では困難な中員環の構築や、添加物による反応性や選択性の制御が可能であり、有機合成化学において非常に有用である。

特に分子内環化において、アルデヒドと不飽和カルボニルを有する基質を用いれば、 $\gamma$ -ラクタムを含む二環性骨格が合成できる。以下に、2 つの全合成への応用例を示す。

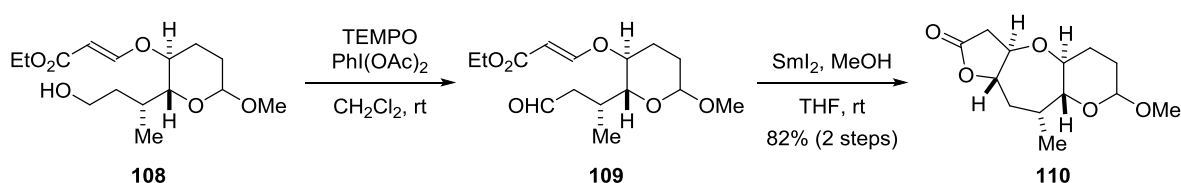
本多らは(-)-ステモアミドの全合成において、SmI<sub>2</sub> 環化を検討している (表 9)<sup>10k</sup>。その結果、MeOH のみを添加したとき、中程度の収率、dr at C8 = 1:0.9 ではあるが望む環化体 **104** を得ている (エントリー1)。なお、HMPA を添加すると基質のオレフィンの幾何異性によらず、9 位が望まない立体化学の環化体のみを与えた (エントリー2、3)。

Table 9. SmI<sub>2</sub> 環化の検討 (本多ら)



| entry | substrate   | additive                        | result                             |
|-------|-------------|---------------------------------|------------------------------------|
| 1     | <b>102E</b> | MeOH (5 equiv)                  | <b>104</b> : 32%, <b>105</b> : 28% |
| 2     | <b>102E</b> | HMPA (20 equiv), MeOH (5 equiv) | <b>106</b> : 55%, <b>107</b> : <5% |
| 3     | <b>102Z</b> | HMPA (20 equiv), EtOH (5 equiv) | <b>106</b> : 39%, <b>107</b> : 11% |

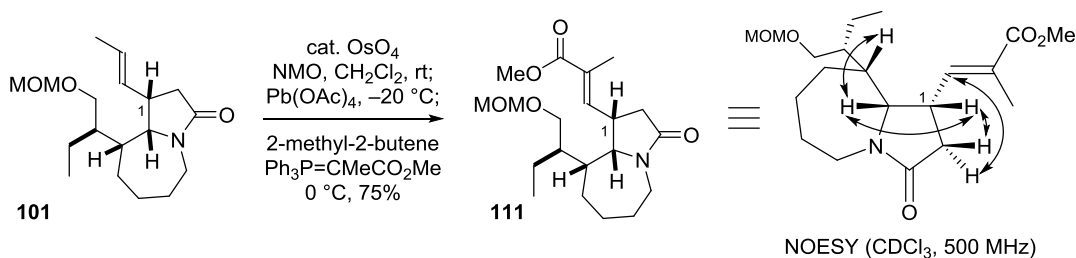
中田らはブレベトキシニン-B の全合成において、SmI<sub>2</sub> を用いた分子内環化により D 環と  $\gamma$ -ラクタムを構築している (スキーム 60)<sup>33</sup>。アルコール **108** より導いたアルデヒド **109** を、MeOH 存在下 SmI<sub>2</sub> で処理すると、新たに 2 つの環が構築された **110** を 2 工程収率 82% で与えた。環化反応は完全な立体選択性で進行し、望む **110** のみが単一の立体異性体として得られた。



**Scheme 60.** SmI<sub>2</sub>を用いた二環性骨格構築の例（中田ら）

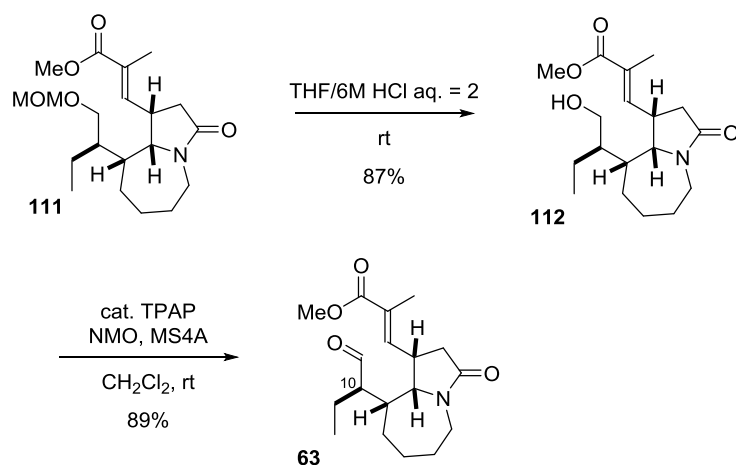
以上のように、反応の立体選択性は基質の構造に大きく依存するが、添加物等の反応条件を詳細に精査すれば、SmI<sub>2</sub>環化によりネオステニンの残るCD環部を効率的に構築できると期待した。

SmI<sub>2</sub>環化の基質合成に向けて、オレフィン部の増炭を検討した（スキーム 61）。アルデヒドが生じた際 1 位の異性化が懸念されたため、ワンポットにてジヒドロキシ化、ジオール開裂、Wittig 反応を適用した。101 より生じたジオールを、-20 °C でアルデヒドに変換した。そこに、ワンポットにて 2-メチル-2-ブテン、イリドを添加し 0 °C に昇温した。2-メチル-2-ブテンは余剰の NMO を消費し、Wittig 反応で新たに生じるオレフィンのジヒドロキシ化を防ぐ目的で添加した。このようにして、101 から 1 工程にて、望む不飽和エステル 111 が収率 75% で得られた。得られた 111 の NOESY 実験により、1 位の立体化学の保持を確認した。



**Scheme 61.** 不飽和エステル 111 の合成と立体化学の決定

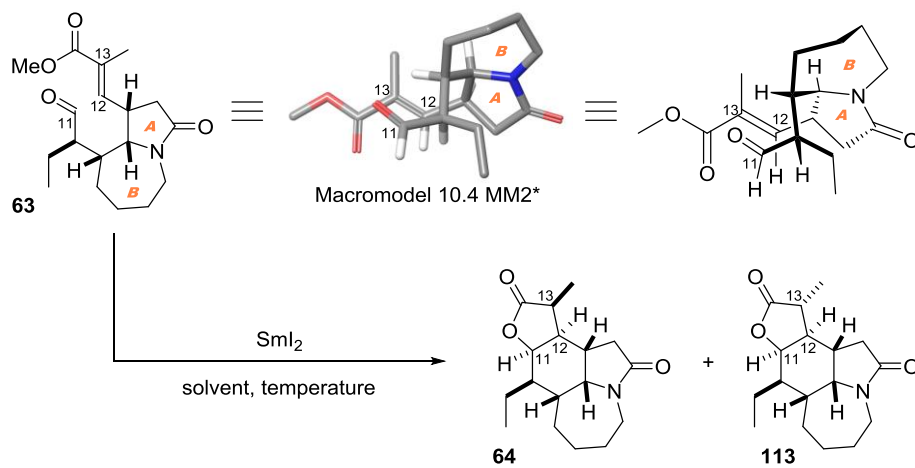
111 を塩酸で処理して、MOM 基を除去した 112 とし、生じた水酸基の酸化によりアルデヒド 63 に導いた。なお、アルデヒド 63 は安定であり、シリカゲルカラムによる精製の後も 10 位の異性化は全く観測されなかった。



Scheme 62. アルデヒド **63** の合成

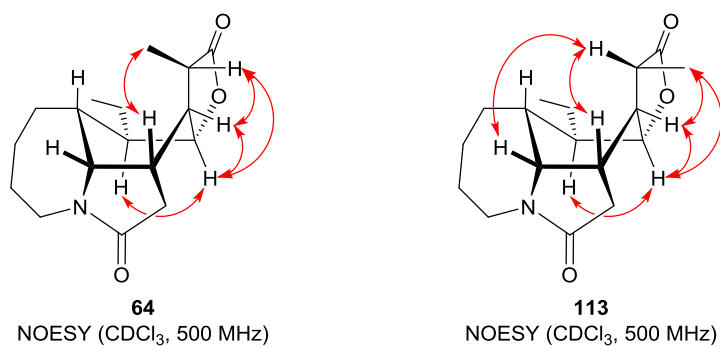
C・D環部の構築を目指し、得られたアルデヒド **63** に対し  $\text{SmI}_2$  を用いた分子内環化反応を検討した (表 10)。**63** を THF 溶媒中  $-78^\circ\text{C}$  にて  $\text{SmI}_2$  で処理すると、速やかに環化反応が進行し、収率 67%、 $\text{dr} = 1:6.8$  at C13 で環化体を与えた (エントリー1)。得られた生成物の 11 位・12 位の立体化学は完全に制御できたものの、メチル基は望まない立体配置の **113** が優先して生じた。反応温度を種々検討した結果、室温で反応した場合、望む生成物 **64** が選択的に合成できることが分かった (エントリー2, 3)。さらに、共溶媒として HMPA を用いたとき、収率 87%、 $\text{dr}$  at C13 = 5.0:1 と最も良い結果を与えた (エントリー4)。詳細な立体発現機構については現在のところ分かっていない。しかし、原料 **63** の最安定配座を分子力場計算 (MM2\*力場、マクロモデル) にて計算したところ、図に示すような配座をとっていることが分かり、これを維持して環化が進行すれば生成物のような立体構造を与える。アルデヒドとエステル $\beta$ 位の水素は下を向いているので、これが生成物の 11・12 位の $\alpha$ 体水素に対応している。このように、本反応により C・D 環ならびに 3 連続不斉中心を一挙に構築できた。

Table 10. SmI<sub>2</sub> 環化反応の検討



| entry | solvent         | temperature | yield | dr at C13 |
|-------|-----------------|-------------|-------|-----------|
| 1     | THF             | -78 °C      | 67%   | 1:6.8     |
| 2     | THF             | -40 °C      | 81%   | 1.9:1     |
| 3     | THF             | rt          | 75%   | 4.6:1     |
| 4     | THF/HMPA = 24:1 | rt          | 87%   | 5.0:1     |

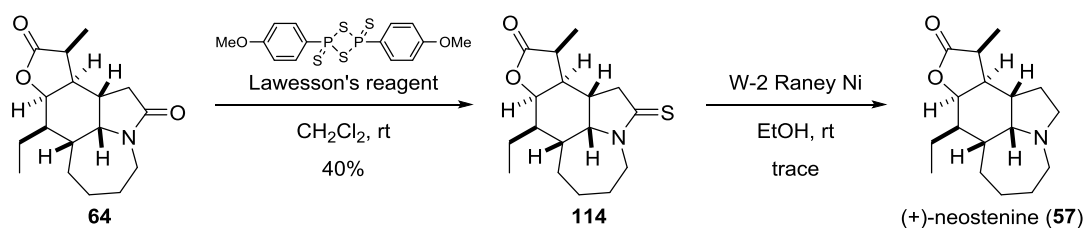
なお、得られた2種類の環化体 **64**・**113** の立体化学は、NOESY 実験により決定している。



Scheme 63. SmI<sub>2</sub> 環化体の立体化学の決定

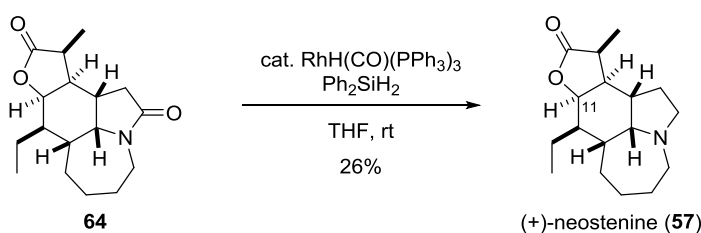
## 5.4 (+)-ネオステニンの不斉全合成

ネオステニン全合成に向けた最後の課題は、より求電子性の高い $\gamma$ -ラクトン存在下、 $\gamma$ -ラクタム選択的な還元である。まず初めに、ステニンの全合成において複数の報告のある、チオアミドを経由した還元に取り組んだ (スキーム 64) <sup>17a,b, 18a,c</sup>。SmI<sub>2</sub> 環化で得られた **64** を Lawesson 試薬で処理すると、チオアミド **114** を収率 40% で与えた。**114** を過剰の W-2 Raney Ni で処理すると、痕跡量ながら (+)-ネオステニン (**57**) が得られた。しかし、チオアミド化、還元ともに低収率であったため、最終体の各種スペクトルデータの測定は困難であった。



Scheme 64. チオアミドを経由したラクタムの還元

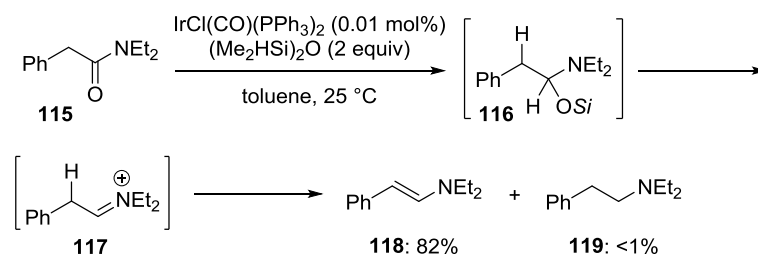
次に遷移金属触媒を用いたラクタム選択的な還元として、伊藤らの報告しているロジウム錯体を用いた (スキーム 65) <sup>34</sup>。本ロジウム錯体は、Booker-Milburn らのネオステニン全合成の最終工程にも応用されている <sup>15b</sup>。**64** を触媒量の RhH(CO)(PPh<sub>3</sub>)<sub>2</sub> 存在下、THF 溶媒中室温にて Ph<sub>2</sub>SiH<sub>2</sub> で処理すると、(+)-ネオステニン (**57**) が収率 26% で得られた。反応終了後の crude NMR にて 11 位のピークの減少を確認しており、ラクトンの還元との競合により低収率になったと考えている。



Scheme 65. Rh 錯体を用いたラクタムの還元

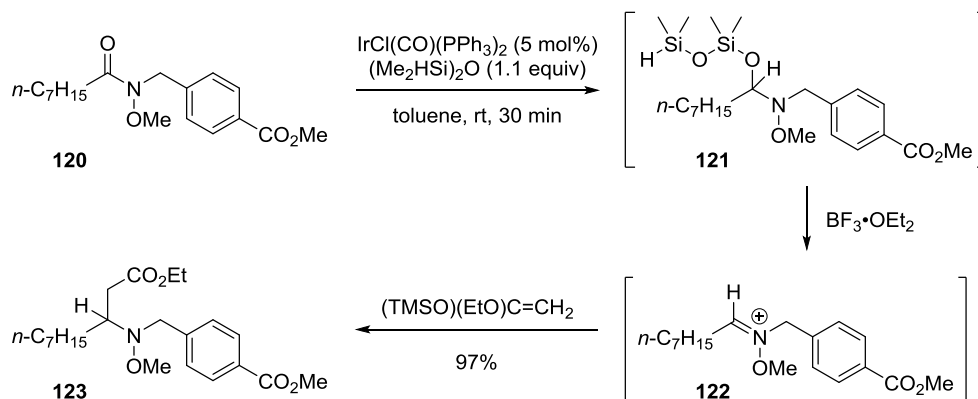
続いて、Vaska 錯体を用いたラクタム選択的な還元を試みた。Vaska 錯体を用いた官能基変換として、永島らはアミドを原料としたエナミン合成を報告している (スキーム 66) <sup>35</sup>。アミド **115** を 2 等量の (Me<sub>2</sub>HSi)<sub>2</sub>O、触媒量の Vaska 錯体で処理すると、*N,O*-アセタール **116**、イミニウムイオン **117** を経由して、対応するエナミン **118** が収率 82%、過剰に還元されたアミン **119** が <1% で得られた。





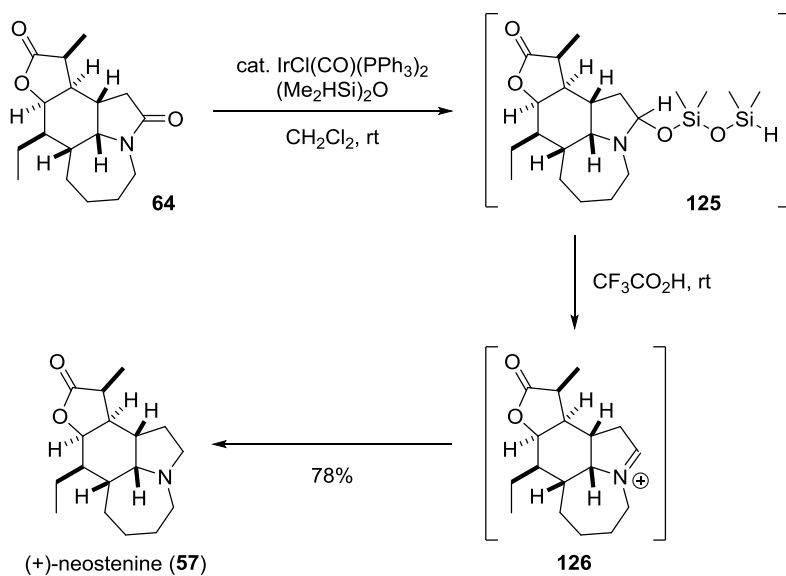
**Scheme 66.** 永島らによる Vaska 錯体を用いたエナミン合成

三級アミド由来の *N,O*-アセタールでは、窒素原子の押し込みにより自発的にイミニウムイオンを生じる。一方、*N*-メトキシアミド由来の *N,O*-アセタールならば、メトキシ基の寄与により比較的押し込みが弱くなるため、*N,O*-アセタールが安定に存在できると考え、当研究室では *N*-メトキシアミドに対する Vaska 錯体を用いた官能基選択的な還元的求核付加反応を開発している（スキーム 67）<sup>36</sup>。分子内により求電子性の高い芳香族エステルが共存する *N*-メトキシアミド **120** を、Vaska 錯体、 $(\text{Me}_2\text{HSi})_2\text{O}$  で処理すると *N,O*-アセタール **121** を与えた。**121** の存在は NMR 実験により確認している。生じた **121** に対し、炭素求核剤存在下  $\text{BF}_3 \cdot \text{OEt}_2$  で処理すると、イミニウムイオン **122** を経由して求核付加が進行し、対応するメトキシアミン **123** を収率 97% で与えた。以上のように、本反応を用いればより求電子性の高いエステル基を全く損なわずに、アミド基選択的に求核付加が可能である。



**Scheme 67.** 官能基選択的な還元的求核付加反応

そこで、官能基選択的な還元的求核付加反応の条件において、生じた *N,O*-アセタールを過剰量の  $(\text{Me}_2\text{HSi})_2\text{O}$  存在下、酸で処理すれば再びヒドリドが付加すると考え、合成したラクタム **64** へと応用した（スキーム 68）。**64** を室温にて  $(\text{Me}_2\text{HSi})_2\text{O}$ 、Vaska 錯体で処理し *N,O*-アセタール **125** とした後、ワンポットにて TFA を添加すると、イミニウムイオン **126** を経由して還元が進行し、(+)-ネオステニン (**57**) が収率 78% で合成できた。

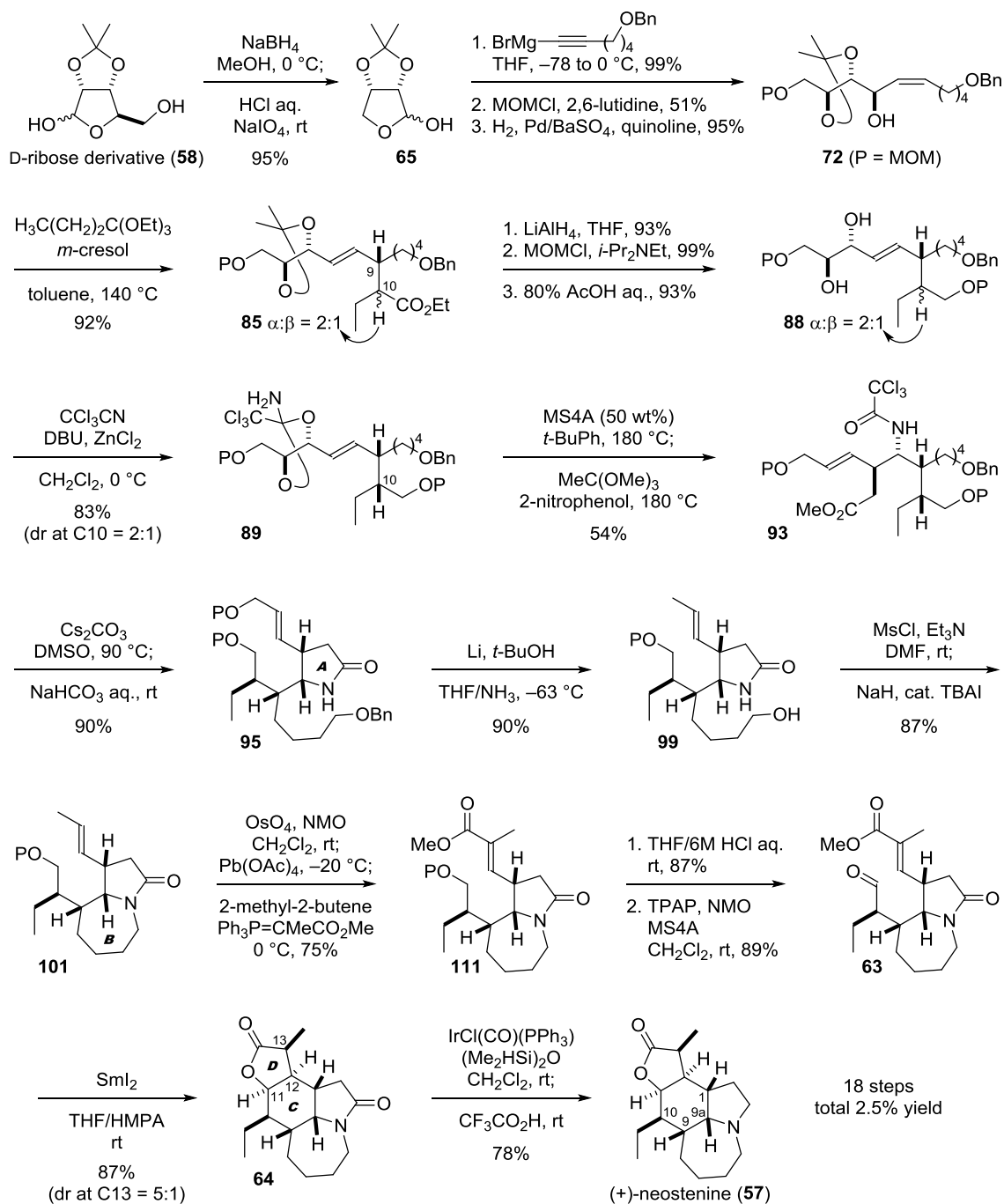


**Scheme 68.** Vaska 錯体を用いたラクタムの還元

合成した(+)-ネオステニン(57)の各種スペクトルデータは、報告されている値<sup>12,15</sup>とよい一致を示し、初となる 57 の不斉全合成を達成した。

## 第七節 第三章のまとめ

以下に第三章をまとめた。



Scheme 69. (+)-ネオステニンの全合成

第三章では、第一章で開発した連続的 Overman/Claisen 転位の有用性を示すべく、本反応を鍵反応として(+)-ネオステニンの全合成を達成した。D-リボース誘導体を出発原料とし、Overman/Claisen 転位を含む 3 回のシグマトロピー転位により、天然物に対応する含窒素 4 連続

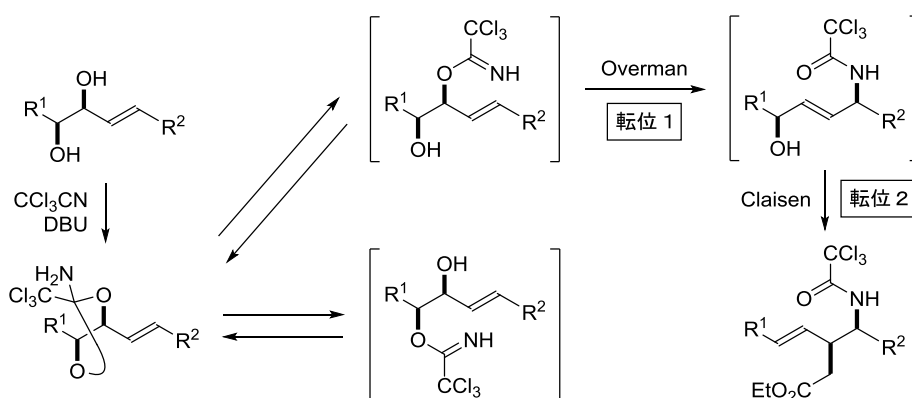
不斉中心を導入した。A・B環を合成後、SmI<sub>2</sub>環化反応により残る3連続不斉中心とC・D環を一挙に構築し、(+)-ネオステニンを全合成した。このように、連続的 Overman/Claisen 転位は、複雑な光学活性天然物の全合成にも適用可能であり、その高い実用性が明らかとなった。

# 総括

本研究では、アリル-1,2-ジオールの連続的 Overman/Claisen 転位の開発に成功した。さらに、開発した反応を利用してワンポットにて含窒素 2 連続不斉中心を構築し、(-)-ステモアミドおよび(+)-ネオステニンの全合成を達成した。

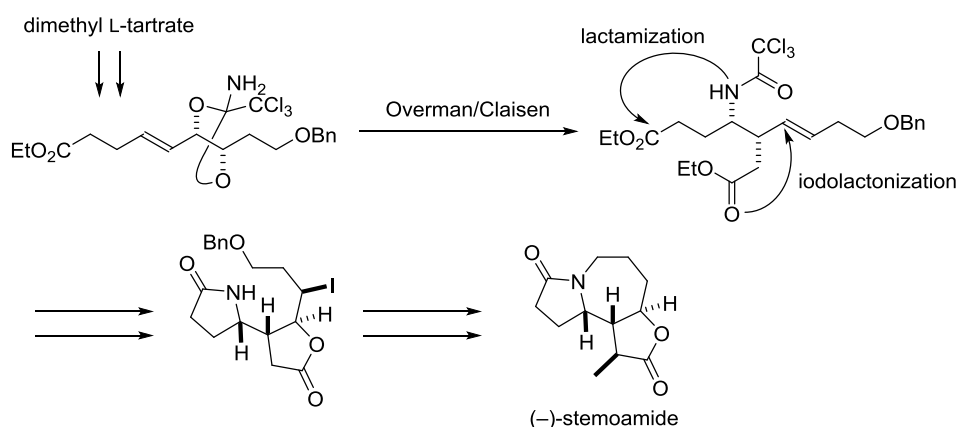
## 連続的 Overman/Claisen 転位の開発

酒石酸、リボースより合成したアリル-1,2-ジオールに対し、保護・脱保護を経由しない連続的な転位反応の開発に取り組んだ。ジオールより誘導した環状オルトアミドの平衡反応を利用し、Overman 転位を 1 回に制御できた。生じたアリルアルコールに対し Johnson–Claisen 転位を適用すると、環状オルトアミドからワンポットで連続的転位体が単一異性体として得られた。



## (-)-ステモアミドの全合成

開発した Overman/Claisen 転位を鍵反応として、(-)-ステモアミドの全合成を達成した。

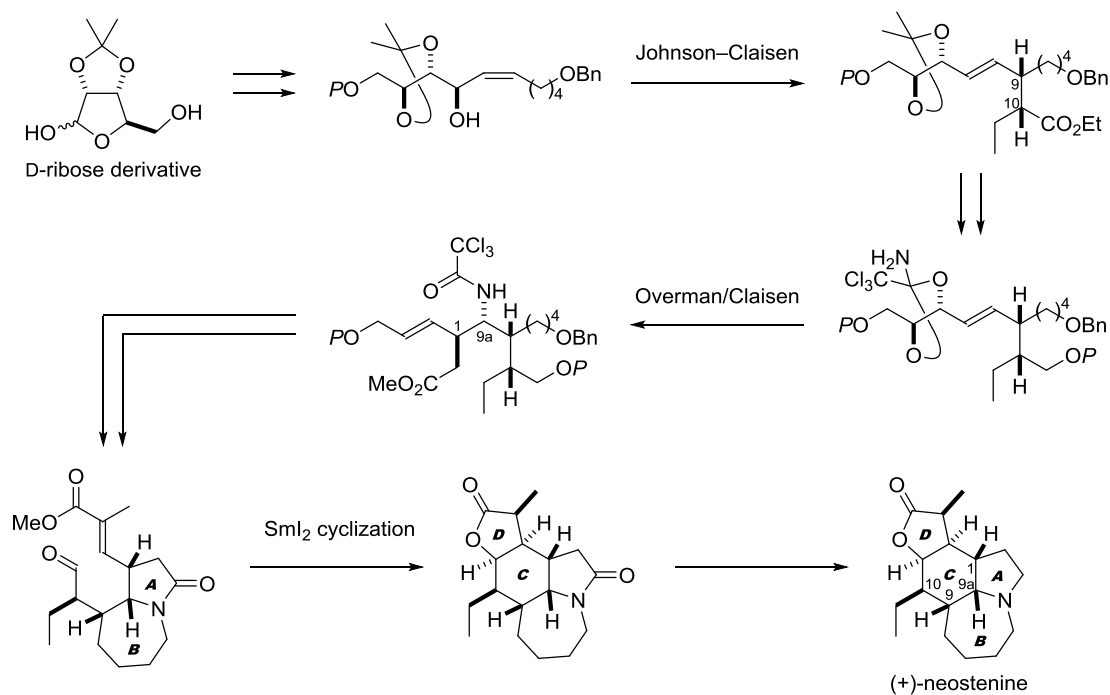


酒石酸ジメチルより導いた環状オルトアミドにワンポット Overman/Claisen 転位を適用し、含窒素 2 連続不斉中心を構築した。得られた転位体の加水分解で生じた 2 つのカルボキシル基をヨー

ドラクトン化で区別化し、続くラクタム化により 2 環性骨格を構築した。その後、7 員環の構築、メチル基の導入を経て(-)-ステモアミドを全合成した。

## (+)-ネオステニンの全合成

次に、Overman/Claisen 転位を鍵反応として、より複雑な構造の(+)-ネオステニンの全合成を達成した。D-リボース誘導体より合成した、Z-アリアルアルコールに Johnson–Claisen 転位を適用し 2 連続不斉中心を導入した。数工程で導いた環状オルトアミドの Overman/Claisen 転位により含窒素 2 連続不斉中心を構築した。A・B 環の合成を経て誘導したアルデヒドの SmI<sub>2</sub> 環化反応により、C・D 環ならびに 3 連続不斉中心を一挙に構築した。最後にラクトン共存下、ラクタム選択的な還元により(+)-ネオステニン全合成した。







# 実験編

## Table of Contents

### A. Experimental Procedures: 75-138

### B. Copies of $^1\text{H}$ and $^{13}\text{C}$ -NMR spectra of new compounds: 139-236

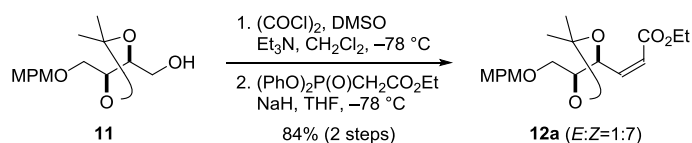
#### A. Experimental Procedures

##### General Details.

Reactions were performed in oven-dried glassware fitted with rubber septa under an argon atmosphere. Toluene, DMSO and *t*-BuPh were distilled from  $\text{CaH}_2$ . DMF was distilled from  $\text{CaSO}_4$ . HMPA was distilled from  $\text{CaO}$ . MeOH was distilled from  $\text{CaSO}_4$ . All distilled solvents,  $\text{CH}_2\text{Cl}_2$ , EtOH were dried over activated 3Å molecular sieves. THF (dehydrated, stabilizer free) was purchased from KANTO CHEMICAL CO., INC. Commercial reagents were used without further purification. Thin-layer chromatography was performed on Merck 60 F254 precoated silica gel plates, which were visualized by exposure to UV (254 nm) or stained by submersion in ethanolic ninhydrin or ethanolic phosphomolybdic acid solution followed by heating on a hot plate. Flash column chromatography was performed on silica gel (Silica Gel 60 N; 63–210 or 40–50 mesh, KANTO CHEMICAL CO., INC.). Preparative thin-layer chromatography was performed on Merck 60 F254 0.5 mm precoated silica gel plates.  $^1\text{H}$  NMR spectra were recorded at 500 MHz with JEOL ECA-500 spectrometers.  $^{13}\text{C}$  NMR spectra were recorded at 125 MHz with JEOL ECA-500 spectrometers. Chemical shifts are reported in ppm with reference to solvent signals [ $^1\text{H}$  NMR:  $\text{CDCl}_3$  (7.26),  $\text{C}_6\text{D}_6$  (7.16),  $\text{CD}_3\text{OD}$  (3.31);  $^{13}\text{C}$  NMR:  $\text{CDCl}_3$  (77.16),  $\text{C}_6\text{D}_6$  (128.06),  $\text{CD}_3\text{OD}$  (49.00)]. Signal patterns are indicated as br, broad peak; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Infrared spectra were recorded using a BRUKER ALPHA FT-IR spectrometer. Mass spectra (ESI-TOF) were measured with a Waters, LCT Premier XE. Melting points were measured with a Mitamura-Riken microhot stage. Optical rotations were measured with a JASCO P-2100 polarimeter.

## Chapter 1: Development of sequential Overman/Claisen rearrangement

### Z-Enoate **12a** (*E:Z* = 1:7)



Oxalyl chloride (26 mL, 290 mmol) was added dropwise to a solution of DMSO (26 mL, 370 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (300 mL) at -78 °C. The resulting solution was maintained for 30 min at -78 °C. A solution of alcohol **11**<sup>[1]</sup> (33.7 g, 119 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was then added dropwise via cannula at -78 °C. After the solution was maintained for 45 min at -78 °C, Et<sub>3</sub>N (55 mL, 390 mmol) was added dropwise to the solution. The resulting mixture was stirred for 15 min at -78 °C, and allowed to warm to room temperature, quenched with H<sub>2</sub>O (800 mL), and extracted with CH<sub>2</sub>Cl<sub>2</sub> (200 mL) and EtOAc (500 mL). The combined organic extracts were washed with brine (800 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to give the corresponding aldehyde as a yellow oil, which was immediately used in the next reaction without further purification.

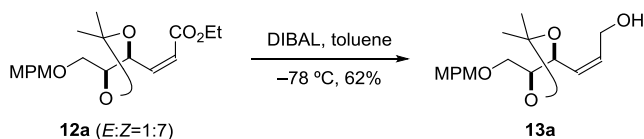
A flask was charged with the crude aldehyde and THF (200 mL), and cooled to -78 °C. Meanwhile, sodium hydride (5.0 g, 130 mmol, washed with hexane three times) was added to a solution of ethyl diphenylphosphonoacetate<sup>[2]</sup> (38.1 g, 119 mmol) and THF (150 mL) at 0 °C. The solution was stirred for 15 min at 0 °C, and cooled to -78 °C. The resulting solution was directly poured into the solution of the aldehyde through a funnel at -78 °C. The solution was stirred for 20 min at -78 °C, quenched with H<sub>2</sub>O (500 mL), and extracted with EtOAc (2x 400 mL). The combined organic extracts were washed with brine (500 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:4 to 1:2) to give 35.0 g of Z-enoate **12a** (84% for 2 steps, two isomers, *E:Z* = 1:7). For analytical samples, the isomers were purified by HPLC (PEGASIL Silica 120-5, 250×20 mm, UV 254 nm, EtOAc/hexane 1:5, 10 mL/min, Z-enoate **12a**: T<sub>R</sub> = 14.0 min, E-enoate **12b**: T<sub>R</sub> = 14.5 min) to afford pure Z-enoate **12a** and E-enoate **12b**. Z-Enoate **12a**: colorless oil; [α]<sub>D</sub><sup>26</sup> +57.6 (*c* 0.84, CHCl<sub>3</sub>); IR (film) 2980, 2940, 2870, 1720, 1710, 1610, 1510, 1250 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.17 (dd, *J* = 11.7, 8.3 Hz, 1H), 5.92 (dd, *J* = 11.7, 1.1 Hz, 1H), 5.37 (ddd, *J* = 8.3, 8.3, 1.1 Hz, 1H), 4.56 (d, *J* = 11.7 Hz, 1H), 4.47 (d, *J* = 11.7 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.95 (ddd, *J* = 8.3, 6.9, 3.2 Hz, 1H), 3.79 (s, 3H), 3.66 (dd, *J* = 10.6, 3.2 Hz, 1H), 3.62 (dd, *J* = 10.6, 6.9 Hz, 1H), 1.44 (s, 6H), 1.25 (t, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 165.5 (C), 159.3 (C), 145.6 (CH), 130.3 (C), 129.5 (CH), 123.1 (CH), 113.8 (CH), 110.4 (C), 80.6 (CH), 73.8 (CH), 73.3 (CH<sub>2</sub>), 70.4 (CH<sub>2</sub>), 60.6 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>), 27.3 (CH<sub>3</sub>), 27.2 (CH<sub>3</sub>), 14.3 (CH<sub>3</sub>); LRMS (EI) *m/z* 350 (M<sup>+</sup>, 5.1%), 292 (16), 274 (11), 263 (13), 229 (5), 170 (18), 156 (21), 141 (44), 121 (100); HRMS (EI),

<sup>[1]</sup> Carpita, A.; Braconi, S.; Rossi, R. *Tetrahedron: Asymmetry* **2005**, *16*, 2501–2508.

<sup>[2]</sup> Ando, K. *Tetrahedron Lett.* **1995**, *36*, 4105–4108.

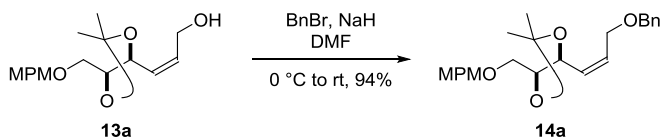
calcd for  $C_{19}H_{26}O_6 M^+$  350.1729, found 350.1745.

### Z-Allylic alcohol 13a



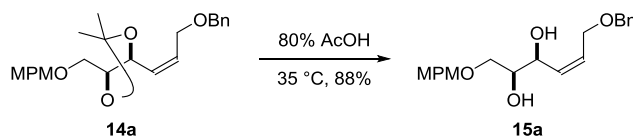
Diisobutylaluminium hydride (0.95 M in hexane, 300 mL, 290 mmol) was added dropwise to a solution of *Z*-enoate **12a** (35.0 g, 99.9 mmol, two isomers, *E:Z*=1:7) and toluene (200 mL) at  $-78\text{ }^{\circ}\text{C}$ . The solution was maintained for 1 h, quenched with 1M aqueous HCl (500 mL), allowed to warm to room temperature, and extracted with EtOAc (2x 500 mL). The combined organic extracts were washed with saturated aqueous  $\text{NaHCO}_3$  (500 mL) and brine (500 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated. The residue was purified by silica gel column chromatography (EtOAc/toluene 1:4) to give 19.2 g of *Z*-allylic alcohol **13a** (62%) and 6.40 g of *E*-allylic alcohol **13b** (21%). *Z*-Allylic alcohol **13a**: colorless oil;  $[\alpha]_D^{26} +0.2$  (*c* 0.78,  $\text{CHCl}_3$ ); IR (film) 3440, 2990, 2940, 2860, 1605,  $1510\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.87 (dtd, *J* = 11.2, 6.9, 1.1 Hz, 1H), 5.56 (ddt, *J* = 11.2, 8.3, 1.1 Hz, 1H), 4.70 (ddd, *J* = 8.3, 8.3, 1.1 Hz, 1H), 4.52 (d, *J* = 11.7 Hz, 1H), 4.49 (d, *J* = 11.7 Hz, 1H), 4.16–4.14 (m, 2H), 3.86 (dt, *J* = 8.3, 4.9 Hz, 1H), 3.80 (s, 3H), 3.59 (d, *J* = 4.9 Hz, 2H), 2.05 (brs, 1H), 1.43 (s, 3H), 1.42 (s, 3H);  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  159.5 (C), 133.8 (CH), 129.7 (C), 129.7 (CH), 129.3 (CH), 114.0 (CH), 109.6 (C), 79.7 (CH), 74.5 (CH), 73.5 ( $\text{CH}_2$ ), 69.3 ( $\text{CH}_2$ ), 58.6 ( $\text{CH}_2$ ), 55.4 ( $\text{CH}_3$ ), 27.2 ( $\text{CH}_3$ ), 27.1 ( $\text{CH}_3$ ); LRMS (EI) *m/z* 308 ( $M^+$ , 0.6%), 293 (3), 250 (9), 232 (6), 204 (6), 173 (10), 137 (74), 121(100), 99 (17); HRMS (EI), calcd for  $C_{17}H_{24}O_5 M^+$  308.1624, found 308. 1618. *E*-Allylic alcohol **13b**: colorless oil;  $[\alpha]_D^{26} -12.9$  (*c* 0.69,  $\text{CHCl}_3$ ); IR (film) 3443, 2990, 2934, 2865, 1613, 1514, 1371, 1247, 1088,  $1032\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.26 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.92 (dtd, *J* = 15.5, 5.2, 0.6 Hz, 1H), 5.72 (ddt, *J* = 15.5, 7.5, 1.7 Hz, 1H), 4.52 (s, 2H), 4.24 (ddd, *J* = 7.5, 7.5, 0.6 Hz, 1H), 4.16–4.14 (m, 2H), 3.90 (ddd, *J* = 7.5, 5.4, 3.7 Hz, 1H), 3.80 (s, 3H), 3.57 (dd, *J* = 10.6, 3.7 Hz, 1H), 3.54 (dd, *J* = 10.6, 5.4 Hz, 1H), 1.45 (brs, 1H), 1.433 (s, 3H), 1.432 (s, 3H);  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  159.4 (C), 134.2 (CH), 130.2 (C), 129.5 (CH), 128.0 (CH), 113.9 (CH), 109.5 (C), 80.2 (CH), 78.7 (CH), 73.4 ( $\text{CH}_2$ ), 69.2 ( $\text{CH}_2$ ), 62.9 ( $\text{CH}_2$ ), 55.4 ( $\text{CH}_3$ ), 27.1 ( $\text{CH}_3$ ), 27.1 ( $\text{CH}_3$ ); LRMS (EI) *m/z* 308 ( $M^+$ , 0.2%), 293 (4), 250 (8), 232 (6), 204 (6), 186 (10), 173 (10), 137 (75), 121(100); HRMS (EI), calcd for  $C_{17}H_{24}O_5 M^+$  308.1624, found 308. 1633.

### Z-Benzyl alcohol 14a



A solution of *Z*-allylic alcohol **13a** (922 mg, 2.99 mmol) and DMF (5 mL) was added to a mixture of NaH (340 mg, 9.0 mmol, washed with hexane three times) and DMF (8 mL) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C. Benzyl bromide (530  $\mu$ L, 4.5 mmol) was then added to this mixture at 0 °C. The mixture was allowed to warm to room temperature, and stirred for 2.5 h at this temperature, quenched with saturated aqueous NH<sub>4</sub>Cl (20 mL), and extracted with EtOAc (3x 20 mL). The combined organic extracts were washed with water (3x 20 mL) and brine (3x 20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:7) to give 1.12 g of *Z*-benzyl alcohol **14a** (94%): colorless oil;  $[\alpha]_D^{21}$  -0.4 (*c* 1.30, CHCl<sub>3</sub>); IR (film) 2990, 2860, 1610, 1510, 1460, 1370, 1250, 1080 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.35–7.27 (m, 5H), 7.22 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.84 (dddd, *J* = 11.2, 6.9, 6.0, 0.9 Hz, 1H), 5.59 (dddd, *J* = 11.2, 8.6, 1.4, 1.4 Hz, 1H), 4.57 (ddd, *J* = 8.6, 8.6, 0.9 Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.47 (s, 2H), 4.44 (d, *J* = 11.7 Hz, 1H), 4.11 (ddd, *J* = 12.9, 6.9, 1.4 Hz, 1H), 4.03 (ddd, *J* = 12.9, 6.0, 1.4 Hz, 1H), 3.86 (ddd, *J* = 8.6, 5.4, 3.4 Hz, 1H), 3.79 (s, 3H), 3.54 (dd, *J* = 10.6, 3.4 Hz, 1H), 3.48 (dd, *J* = 10.6, 5.4 Hz, 1H), 1.43 (s, 3H), 1.42 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  159.3 (C), 138.1 (C), 131.9 (CH), 130.1 (C), 129.7 (CH), 129.4 (CH), 128.5 (CH), 128.0 (CH), 127.9 (CH), 113.9 (CH), 109.6 (C), 80.3 (CH), 73.9 (CH), 73.4 (CH<sub>2</sub>), 72.4 (CH<sub>2</sub>), 69.0 (CH<sub>2</sub>), 65.8 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>), 27.2 (CH<sub>3</sub>), 27.1 (CH<sub>3</sub>); LRMS (EI) *m/z* 398 (M<sup>+</sup>, 0.3%), 383 (1), 261 (1), 249 (4), 232 (43), 211 (4), 188 (9), 137 (39), 121 (100), 91 (91); HRMS (EI), calcd for C<sub>24</sub>H<sub>30</sub>O<sub>5</sub> M<sup>+</sup> 398.2093, found 398.2107.

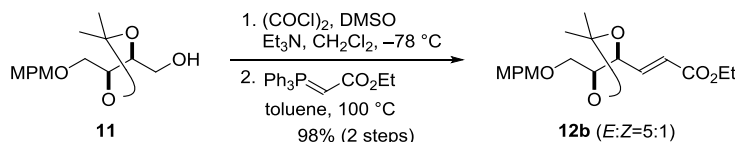
### *Z*-Allylic *syn*-diol **15a**



*Z*-Benzyl alcohol **14a** (1.05 g, 2.93 mmol) was dissolved in AcOH/H<sub>2</sub>O (4:1, 10 mL) at room temperature. This solution was warmed to 35 °C, and stirred for 10 h at 35 °C. The solution was cooled to room temperature, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:1 to 3:1) to give 837 mg of *Z*-allylic *syn*-diol **15a** (88%): colorless oil;  $[\alpha]_D^{21}$  +5.6 (*c* 1.16, CHCl<sub>3</sub>); IR (film) 3450, 3360, 2900, 1520, 1240, 1130, 1040 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.36–7.27 (m, 5H), 7.22 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.81 (dddd, *J* = 11.2, 6.6, 6.0, 0.9 Hz, 1H), 5.76 (dddd, *J* = 11.2, 8.4, 1.4, 1.4 Hz, 1H), 4.52 (d, *J* = 11.7 Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 4.43 (d, *J* = 11.7 Hz, 1H), 4.42–4.39 (m, 1H), 4.14 (ddd, *J* = 12.4, 6.6, 1.4 Hz, 1H), 4.06 (ddd, *J* = 12.4, 6.0, 1.4 Hz, 1H), 3.80 (s, 3H), 3.66–3.63 (m, 1H), 3.54 (dd, *J* = 9.7, 3.7 Hz, 1H), 3.44 (dd, *J* = 9.7, 5.7 Hz, 1H), 2.87 (brs, 1H), 2.75 (brs, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  159.5 (C), 138.0 (C), 131.8 (CH), 130.4 (CH), 129.8 (C), 129.6 (CH), 128.6 (CH), 128.0 (CH), 127.9 (CH), 114.0 (CH), 73.4 (CH<sub>2</sub>), 73.3 (CH), 72.7 (CH<sub>2</sub>), 71.1 (CH<sub>2</sub>), 68.9 (CH), 66.1 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>); LRMS (EI) *m/z*

358 ( $M^+$ , 0.1%), 250 (2), 232 (10), 149 (3), 137 (33), 121 (100), 91 (95); HRMS (EI), calcd for  $C_{21}H_{26}O_5$   $M^+$  358.1780, found 358.1786.

### *E*-Enoate **12b** (*E*:*Z* = 5:1)

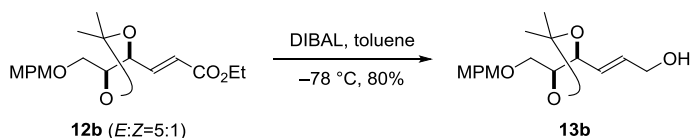


Oxalyl chloride (1.9 mL, 22 mmol) was added dropwise to a solution of DMSO (2.1 mL, 30 mmol) and  $CH_2Cl_2$  (40 mL) at  $-78\text{ }^\circ C$ . The resulting solution was maintained for 30 min at  $-78\text{ }^\circ C$ . A solution of alcohol **11** (2.09 g, 7.40 mmol) and  $CH_2Cl_2$  (19 mL) was then added dropwise via cannula at  $-78\text{ }^\circ C$ . After the solution was maintained for 45 min at  $-78\text{ }^\circ C$ ,  $Et_3N$  (8.3 mL, 59 mmol) was added dropwise to the solution. The resulting mixture was stirred for 15 min at  $-78\text{ }^\circ C$ , allowed to warm to room temperature, quenched with  $H_2O$  (80 mL), and extracted with  $CH_2Cl_2$  (40 mL) and EtOAc (80 mL). The combined organic extracts were washed with brine (80 mL), dried over  $Na_2SO_4$ , and concentrated to give the corresponding aldehyde as a yellow oil, which was immediately used in the next reaction without further purification.

A solution of the crude aldehyde and toluene (10 mL) was added to a solution of (Ethoxycarbonylmethylene)triphenylphosphorane (3.87 g, 11.1 mmol) and toluene (30 mL) at  $100\text{ }^\circ C$ . This solution was maintained for 30 min at  $100\text{ }^\circ C$ , cooled to room temperature, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:2 to 1:1) to give 2.54 g of *E*-enoate **12b**<sup>[3]</sup> (98% for 2 steps, two isomers, *E*:*Z* = 5:1). For analytical samples, the isomers were purified by HPLC (PEGASIL Silica 120–5, 250×20 mm, UV 254 nm, EtOAc/hexane 1:5, 10 mL/min, *Z*-enoate **12a**:  $T_R$  = 14.0 min, *E*-enoate **12b**:  $T_R$  = 14.5 min) to afford pure *E*-enoate **12b** and *Z*-enoate **12a**. *E*-Enoate **12b**: colorless oil;  $[\alpha]_D^{26}$   $-28.7$  ( $c$  1.22,  $CHCl_3$ ); IR (film) 2986, 1721, 1613, 1514, 1249, 1174  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.25 (d,  $J$  = 8.6 Hz, 2H), 6.88 (d,  $J$  = 8.6 Hz, 2H), 6.88 (dd,  $J$  = 15.5, 5.4 Hz, 1H), 6.08 (dd,  $J$  = 15.5, 1.4 Hz, 1H), 4.53 (d,  $J$  = 12.0 Hz, 1H), 4.51 (d,  $J$  = 12.0 Hz, 1H), 4.40 (ddd,  $J$  = 8.6, 5.4, 1.4 Hz, 1H), 4.20 (q,  $J$  = 7.2 Hz, 2H), 3.94 (ddd,  $J$  = 8.6, 4.6, 4.6 Hz, 1H), 3.81 (s, 3H), 3.60 (dd,  $J$  = 10.6, 4.6 Hz, 1H), 3.58 (dd,  $J$  = 10.6, 4.6 Hz, 1H), 1.45 (s, 3H), 1.43 (s, 3H), 1.29 (t,  $J$  = 7.2 Hz, 3H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  166.1 (C), 159.5 (C), 144.2 (CH), 129.9 (C), 129.5 (CH), 122.7 (CH), 114.0 (CH), 110.3 (C), 79.7 (CH), 77.6 (CH), 73.4 ( $CH_2$ ), 69.1 ( $CH_2$ ), 60.7 ( $CH_2$ ), 55.4 ( $CH_3$ ), 27.1 ( $CH_3$ ), 26.8 ( $CH_3$ ), 14.3 ( $CH_3$ ); LRMS (EI)  $m/z$  350 ( $M^+$ , 1.8%), 263 (13), 245 (8), 170 (14), 156 (21), 137 (71), 121 (100), 112 (40); HRMS (EI), calcd for  $C_{19}H_{26}O_6$   $M^+$  350.1729, found 350.1725.

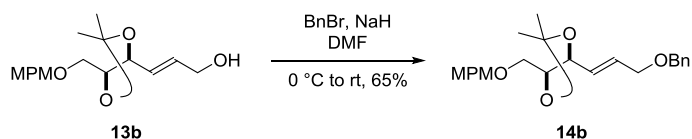
<sup>[3]</sup> Somfai, P.; Marchand, P.; Torsell, S.; Lindström, U. M. *Tetrahedron* **2003**, 59, 1293–1299.

### *E*-Allylic alcohol **13b**



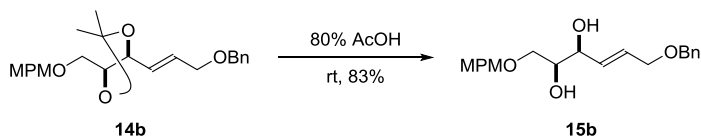
Diisobutylaluminium hydride (1.01 M in toluene, 5.4 mL, 5.5 mmol) was added dropwise to a solution of *E*-enoate **12b** (740 mg, 2.11 mmol, two isomers, *E*:*Z* = 5:1) and toluene (20 mL) at -78 °C. The solution was maintained for 1 h, quenched with 1M aqueous HCl (10 mL), allowed to warm to room temperature, and extracted with EtOAc (2x 30 mL). The combined organic extracts were washed with saturated aqueous NaHCO<sub>3</sub> (10 mL) and brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/toluene 1:4 to 1:2) to give 523 mg of *E*-allylic alcohol **13b**<sup>[3]</sup> (80%) and 41.4 mg of *Z*-allylic alcohol **13a** (6%).

### *E*-Benzyl alcohol **14b**



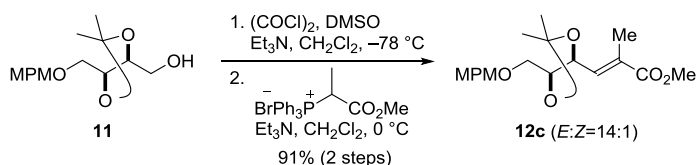
A solution of *E*-allylic alcohol **13b** (1.03 g, 3.34 mmol) and DMF (5 mL) was added to a mixture of NaH (250 mg, 6.7 mmol, washed with hexane three times) and DMF (10 mL) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C, and then benzyl bromide (600 μL, 5.0 mmol) was added to the mixture at 0 °C. The mixture was stirred for 2 h at 0 °C, allowed to warm to room temperature, and stirred for 1 h at room temperature. The reaction mixture was then quenched with saturated aqueous NH<sub>4</sub>Cl (20 mL), and extracted with EtOAc (2x 20 mL). The combined organic extracts were washed with brine (3x 20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:7) to give 701 mg of *E*-benzyl alcohol **14b** (65%): colorless oil;  $[\alpha]_D^{25}$  -16.1 (*c* 0.37, CHCl<sub>3</sub>); IR (film) 2987, 2935, 2860, 1515, 1369, 1240, 1090, 1030 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.37–7.28 (m, 5H), 7.26 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.89 (dtd, *J* = 15.5, 5.4, 0.9 Hz, 1H), 5.75 (ddt, *J* = 15.5, 7.5, 1.4 Hz, 1H), 4.53 (s, 2H), 4.50 (s, 2H), 4.25 (ddd, *J* = 7.5, 7.5, 0.9 Hz, 1H), 4.03 (dd, *J* = 5.4, 1.4 Hz, 2H), 3.91 (ddd, *J* = 7.5, 5.7, 3.4 Hz, 1H), 3.79 (s, 3H), 3.59 (dd, *J* = 10.6, 3.4 Hz, 1H), 3.54 (dd, *J* = 10.6, 5.7 Hz, 1H), 1.44 (s, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 159.3 (C), 138.2 (C), 131.5 (CH), 130.2 (C), 129.5 (CH), 129.5 (CH), 128.5 (CH), 127.83 (CH), 127.77 (CH), 113.9 (CH), 109.5 (C), 80.2 (CH), 78.7 (CH), 73.3 (CH<sub>2</sub>), 72.4 (CH<sub>2</sub>), 69.8 (CH<sub>2</sub>), 69.2 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>), 27.1 (CH<sub>3</sub>), 27.1 (CH<sub>3</sub>); LRMS (EI) *m/z* 398 (M<sup>+</sup>, 3.1%), 383 (5), 340 (3), 277 (4), 249 (6), 232 (82), 188 (16), 137 (81), 121(100); HRMS (EI), calcd for C<sub>24</sub>H<sub>30</sub>O<sub>5</sub> M<sup>+</sup> 398.2093, found 398.2093.

### *E*-Allylic *syn*-diol **15b**



*E*-Benzyl alcohol **14b** (646 mg, 1.62 mmol) was dissolved in AcOH/H<sub>2</sub>O (4:1, 6.5 mL) at room temperature. This solution was maintained for 8 h at room temperature, and then concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:1 to 2:1) to give 520 mg of *E*-allylic *syn*-diol **15b** (90%): colorless crystals, mp 41–43 °C;  $[\alpha]_D^{25} -17.4$  (*c* 0.90, CHCl<sub>3</sub>); IR (film) 3417, 2909, 2861, 1612, 1513, 1240, 1099, 1032 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.36–7.27 (m, 5H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.90 (dtd, *J* = 15.8, 5.6, 1.0 Hz, 1H), 5.76 (dd, *J* = 15.8, 6.3 Hz, 1H), 4.51 (s, 2H), 4.50 (d, *J* = 11.3 Hz, 1H), 4.45 (d, *J* = 11.3 Hz, 1H), 4.20–4.17 (m, 1H), 4.03 (d, *J* = 5.6 Hz, 2H), 3.79 (s, 3H), 3.69–3.65 (m, 1H), 3.59 (dd, *J* = 9.8, 3.5 Hz, 1H), 3.51 (dd, *J* = 9.8, 5.7 Hz, 1H), 2.73 (brs, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 159.5 (C), 138.3 (C), 131.6 (CH), 129.8 (C), 129.7 (CH), 129.6 (CH), 128.5 (CH), 127.9 (CH), 127.8 (CH), 114.0 (CH), 73.4 (CH<sub>2</sub>), 73.0 (CH), 72.9 (CH), 72.4 (CH<sub>2</sub>), 71.3 (CH<sub>2</sub>), 70.1 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>); LRMS (EI) *m/z* 358 (M<sup>+</sup>, 1.7%), 331 (2), 267 (8), 250 (14), 232 (7), 181 (6), 149 (10), 138 (67), 121 (100), 109 (20); HRMS (EI), calcd for C<sub>21</sub>H<sub>26</sub>O<sub>5</sub> M<sup>+</sup> 358.1780, found 358.1780.

### *E*-Trisubstituted enoate **12c** (*E*:*Z*=14:1)



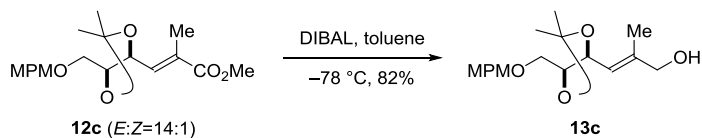
Oxalyl chloride (2.5 mL, 28 mmol) was added dropwise to a solution of DMSO (4.0 mL, 57 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (16 mL) at –78 °C. The resulting solution was maintained for 30 min at –78 °C. A solution of alcohol **11** (2.00 g, 7.08 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was then added dropwise via cannula at –78 °C. After the solution was maintained for 45 min at –78 °C, Et<sub>3</sub>N (9.9 mL, 71 mmol) was added dropwise to the solution. The resulting mixture was stirred for 15 min at –78 °C, allowed to warm to room temperature, quenched with H<sub>2</sub>O (100 mL), and extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and EtOAc (100 mL). The combined organic extracts were washed with brine (200 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to give the corresponding aldehyde as a yellow oil, which was immediately used in the next reaction without further purification.

Triethylamine (3.0 mL, 21 mmol) was added to a solution of carbomethoxy ethyl triphenyl phosphonium bromide (5.15 g, 12.0 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (40 mL) at room temperature. This solution was maintained at room temperature for 20 min. A solution of the crude aldehyde and CH<sub>2</sub>Cl<sub>2</sub> (12 mL) was



then added to the solution. The solution was stirred for 2 h at room temperature, quenched with saturated aqueous NH<sub>4</sub>Cl (50 mL), and extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and EtOAc (100 mL). The combined organic extracts were washed with brine (200 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:10 to 1:8) to give 2.26 g of *E*-trisubstituted enoate **12c** (*E*:*Z* = 14:1) (91%). For analytical samples, the isomers were purified by HPLC (PEGASIL Silica 120–5, 250×20 mm, UV 254 nm, EtOAc/hexane 1:7, 10 mL/min, *Z*-trisubstituted enoate **12g**: T<sub>R</sub> = 32.0 min, *E*-trisubstituted enoate **12c**: T<sub>R</sub> = 33.0 min) to afford pure *E*-trisubstituted enoate **12c** and *Z*-trisubstituted enoate **12g**. *E*-Trisubstituted enoate **12c**: colorless oil; [α]<sub>D</sub><sup>25</sup> –41.1 (*c* 0.96, CHCl<sub>3</sub>); IR (film) 2988, 2936, 1719, 1613, 1514, 1249, 1034 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.24 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.65 (dq, *J* = 8.4, 1.4 Hz, 1H), 4.68 (dd, *J* = 8.4, 8.4 Hz, 1H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 3.95 (ddd, *J* = 8.4, 4.9, 3.5 Hz, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.58 (dd, *J* = 10.6, 3.5 Hz, 1H), 3.52 (dd, *J* = 10.6, 4.9 Hz, 1H), 1.85 (d, *J* = 1.4 Hz, 3H), 1.45 (s, 3H), 1.45 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 168.0 (C), 159.4 (C), 137.4 (CH), 132.0 (C), 130.0 (C), 129.5 (CH), 113.9 (CH), 110.2 (C), 80.1 (CH), 74.4 (CH), 73.5 (CH<sub>2</sub>), 68.7 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>), 52.2 (CH<sub>3</sub>), 27.12 (CH<sub>3</sub>), 27.09 (CH<sub>3</sub>), 13.2 (CH<sub>3</sub>); HRMS (FAB) *m/z* calcd for C<sub>19</sub>H<sub>27</sub>O<sub>6</sub> (M+H)<sup>+</sup> 351.1808, found 351.1814. *Z*-Trisubstituted enoate **12g**: colorless oil; [α]<sub>D</sub><sup>25</sup> +22.6 (*c* 0.14, CHCl<sub>3</sub>); IR (film) 2931, 2852, 1717, 1515, 1369, 1248, 1032 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.88 (dq, *J* = 8.6, 1.4 Hz, 1H), 5.05 (dd, *J* = 8.6, 8.6 Hz, 1H), 4.56 (d, *J* = 11.7 Hz, 1H), 4.49 (d, *J* = 11.7 Hz, 1H), 3.93 (ddd, *J* = 8.6, 6.9, 2.9 Hz, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.66 (dd, *J* = 10.6, 2.9 Hz, 1H), 3.60 (dd, *J* = 10.6, 6.9 Hz, 1H), 1.95 (d, *J* = 1.4 Hz, 3H), 1.44 (s, 3H), 1.43 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 167.6 (C), 159.3 (C), 138.5 (CH), 132.0 (C), 130.4 (C), 129.5 (CH), 113.8 (CH), 110.0 (C), 80.6 (CH), 74.6 (CH), 73.3 (CH<sub>2</sub>), 70.2 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>), 51.8 (CH<sub>3</sub>), 27.29 (CH<sub>3</sub>), 27.27 (CH<sub>3</sub>), 20.8 (CH<sub>3</sub>); HRMS (FAB) *m/z* calcd for C<sub>19</sub>H<sub>27</sub>O<sub>6</sub> (M+H)<sup>+</sup> 351.1808, found 351.1797.

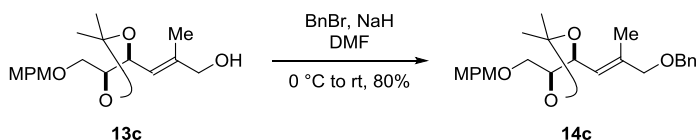
### *E*-Trisubstituted allylic alcohol **13c**



Diisobutylaluminium hydride (0.99 M in toluene, 14 mL, 14 mmol) was added dropwise to a solution of *E*-trisubstituted enoate **12c** (2.00 g, 5.71 mmol, two isomers, *E*:*Z*=14:1) and toluene (26 mL) at –78 °C. The solution was maintained for 30 min at –78 °C, quenched with 1M aqueous HCl (40 mL), and extracted with EtOAc (2x 50 mL). The combined organic extracts were washed with saturated aqueous NaHCO<sub>3</sub> (2x 50 mL) and brine (2x 50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and then concentrated. The residue was purified by silica gel column chromatography to give 1.52 g of *E*-trisubstituted allylic alcohol **13c** (82%) and *Z*-trisubstituted allylic alcohol **13g** (6%). *E*-Trisubstituted allylic alcohol **13c**: colorless oil; [α]<sub>D</sub><sup>25</sup> –4.8

(*c* 1.32, CHCl<sub>3</sub>); IR (film) 3451, 2985, 2936, 2868, 2361, 1613, 1514, 1240, 1032 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.33 (dd, *J* = 8.6, 1.4 Hz, 1H), 4.70 (dd, *J* = 8.6, 8.6 Hz, 1H), 4.52 (d, *J* = 11.7 Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.16 (dd, *J* = 12.3, 3.4 Hz, 1H), 3.98 (dd, *J* = 12.3, 5.8 Hz, 1H), 3.83 (ddd, *J* = 8.6, 4.9, 4.9 Hz, 1H), 3.80 (s, 3H), 3.62 (dd, *J* = 10.6, 4.9 Hz, 1H), 3.59 (dd, *J* = 10.6, 4.9 Hz, 1H), 2.13 (brs, 1H), 1.84 (d, *J* = 1.4 Hz, 3H), 1.43 (s, 3H), 1.41 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 159.5 (C), 142.2 (C), 129.73 (CH), 129.66 (C), 124.8 (CH), 114.0 (CH), 109.2 (C), 80.0 (CH), 75.0 (CH), 73.6 (CH<sub>2</sub>), 69.5 (CH<sub>2</sub>), 62.1 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>), 27.3 (CH<sub>3</sub>), 27.1 (CH<sub>3</sub>), 22.3 (CH<sub>3</sub>); LRMS (EI) *m/z* 322 (M<sup>+</sup>, 1.1%), 307 (4), 264 (25), 246 (9), 218 (14), 200 (23), 187 (16), 143 (35), 137 (100), 121 (100), 110 (36); HRMS (EI), calcd for C<sub>18</sub>H<sub>26</sub>O<sub>5</sub> M<sup>+</sup> 322.1780, found 322.1779. *Z*-Trisubstituted allylic alcohol **13g**: colorless oil; [α]<sub>D</sub><sup>26</sup> -5.1 (*c* 1.03, CHCl<sub>3</sub>); IR (film) 3446, 2986, 2935, 2867, 1587, 1514, 1240, 1033 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.24 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 5.33 (d, *J* = 8.7 Hz, 1H), 4.69 (dd, *J* = 8.7, 8.7 Hz, 1H), 4.52 (d, *J* = 11.7 Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.16 (d, *J* = 12.3 Hz, 1H), 3.98 (d, *J* = 12.3 Hz, 1H), 3.83 (ddd, *J* = 8.7, 4.9, 4.9 Hz, 1H), 3.80 (s, 3H), 3.61 (dd, *J* = 10.6, 4.9 Hz, 1H), 3.59 (dd, *J* = 10.6, 4.9 Hz, 1H), 2.16 (brs, 1H), 1.84 (s, 3H), 1.42 (s, 3H), 1.41 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 159.5 (C), 142.2 (C), 129.7 (CH), 129.6 (C), 124.7 (CH), 113.9 (CH), 109.2 (C), 79.5 (CH), 75.0 (CH), 73.5 (CH<sub>2</sub>), 69.5 (CH<sub>2</sub>), 62.1 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>), 27.2 (CH<sub>3</sub>), 27.1 (CH<sub>3</sub>), 22.3 (CH<sub>3</sub>); HRMS (FAB) *m/z* calcd for C<sub>18</sub>H<sub>27</sub>O<sub>5</sub> (M+H)<sup>+</sup> 323.1858, found 323.1854.

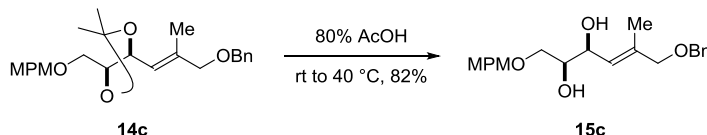
#### *E*-Trisubstituted benzyl alcohol **14c**



A solution of *E*-trisubstituted allylic alcohol **13c** (1.52 g, 4.71 mmol) and DMF (5 mL) was added to a mixture of NaH (540 mg, 14 mmol, washed with hexane three times) and DMF (8 mL) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C. Benzyl bromide (730 μL, 6.1 mmol) was then added to this mixture at 0 °C. The mixture was stirred for 30 min at 0 °C, allowed to warm to room temperature, and stirred for 2 h at room temperature. The reaction mixture was quenched with saturated aqueous NH<sub>4</sub>Cl (20 mL), and extracted with EtOAc (3x 20 mL). The combined organic extracts were washed with water (3x 20 mL), brine (3x 20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:8) to give 1.55 g of *E*-trisubstituted benzyl alcohol **14c** (80%): colorless oil; [α]<sub>D</sub><sup>25</sup> -18.1 (*c* 0.63, CHCl<sub>3</sub>); IR (film) 2986, 2859, 1613, 1514, 1369, 1248, 1074, 1031 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.36–7.28 (m, 5H), 7.25 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.49 (dq, *J* = 8.9, 1.2 Hz, 1H), 4.63 (dd, *J* = 8.9, 8.9 Hz, 1H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.50 (d, *J* = 11.7 Hz, 1H), 4.45 (s, 2H), 3.92 (s, 2H), 3.88 (ddd, *J* = 8.9, 5.4, 3.4 Hz, 1H), 3.78 (s, 3H), 3.57 (dd, *J* = 10.6,

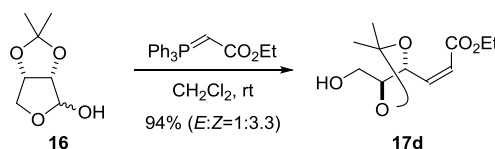
3.4 Hz, 1H), 3.52 (dd,  $J = 10.6, 5.4$  Hz, 1H), 1.71 (d,  $J = 1.2$  Hz, 3H), 1.45 (s, 3H), 1.44 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  159.3 (C), 139.2 (C), 138.4 (C), 130.2 (C), 129.5 (CH), 128.5 (CH), 127.84 (CH), 127.75 (CH), 123.7 (CH), 113.9 (CH), 109.3 (C), 80.5 (CH), 75.2 ( $\text{CH}_2$ ), 74.3 (CH), 73.4 ( $\text{CH}_2$ ), 72.0 ( $\text{CH}_2$ ), 69.1 ( $\text{CH}_2$ ), 55.4 ( $\text{CH}_3$ ), 27.3 ( $\text{CH}_3$ ), 27.1 ( $\text{CH}_3$ ), 14.5 ( $\text{CH}_3$ ); LRMS (EI)  $m/z$  412 ( $\text{M}^+$ , 11.7%), 397 (5), 354 (12), 305 (16), 246 (57), 215 (32), 200 (17), 149 (22), 137 (90), 121 (100), 111 (65); HRMS (EI), calcd for  $\text{C}_{25}\text{H}_{32}\text{O}_5$   $\text{M}^+$  412.2250, found 412.2253.

### *E*-Trisubstituted allylic *syn*-diol **15c**



*E*-Trisubstituted benzyl alcohol **14c** (1.50 g, 4.03 mmol) was dissolved in AcOH/ $\text{H}_2\text{O}$  (4:1, 30 mL) at room temperature. After this solution was maintained for 19.5 h at room temperature, the solution was heated to 40 °C, and stirred for 3 h at this temperature. The solution was cooled to room temperature, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:2 to 3:1) to give 1.12 g of *E*-trisubstituted allylic *syn*-diol **15c** (82%): colorless oil;  $[\alpha]_{\text{D}}^{25} -17.3$  ( $c$  0.70,  $\text{CHCl}_3$ ); IR (film) 3425, 2913, 2858, 1612, 1514, 1248, 1099, 1031  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36–7.28 (m, 5H), 7.24 (d,  $J = 8.9$  Hz, 2H), 6.87 (d,  $J = 8.9$  Hz, 2H), 5.52 (dq,  $J = 8.9, 1.4$  Hz, 1H), 4.48 (d,  $J = 11.5$  Hz, 1H), 4.45 (s, 2H), 4.45 (d,  $J = 11.5$  Hz, 1H), 4.46–4.42 (m, 1H), 3.93 (d,  $J = 12.6$  Hz, 1H), 3.90 (d,  $J = 12.6$  Hz, 1H), 3.79 (s, 3H), 3.64 (dddd,  $J = 7.7, 5.7, 5.7, 3.4$  Hz, 1H), 3.56 (dd,  $J = 9.7, 3.4$  Hz, 1H), 3.46 (dd,  $J = 9.7, 5.7$  Hz, 1H), 2.67–2.65 (m, 1H), 2.53–2.52 (m, 1H), 1.73 (d,  $J = 1.4$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  159.5 (C), 138.4 (C), 137.8 (C), 129.8 (C), 129.6 (CH), 128.5 (CH), 127.84 (CH), 127.76 (CH), 125.7 (CH), 114.0 (CH), 75.4 ( $\text{CH}_2$ ), 73.7 (CH), 73.5 ( $\text{CH}_2$ ), 72.1 ( $\text{CH}_2$ ), 71.1 ( $\text{CH}_2$ ), 69.1 (CH), 55.4 ( $\text{CH}_3$ ), 14.7 ( $\text{CH}_3$ ); HRMS (FAB)  $m/z$  calcd for  $\text{C}_{22}\text{H}_{29}\text{O}_5$  ( $\text{M}+\text{H}$ ) $^+$  373.2015, found 373.2016.

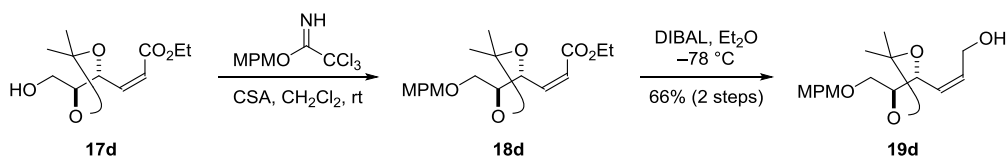
### *Z*-Enoate **17d**



(Ethoxycarbonylmethylene)triphenylphosphorane (5.77 g, 16.5 mmol) was added to a solution of lactol **16** (1.77 g, 11.0 mmol) and  $\text{CH}_2\text{Cl}_2$  (55 mL) at room temperature. The solution was maintained for 2.5 d at room temperature, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:4 to 1:2) to give 1.84 g of *Z*-enoate **17d** (72%) and 564 mg of *E*-enoate **17e** (22%). *Z*-enoate **17d**: colorless oil;  $[\alpha]_{\text{D}}^{18} -149.5$  ( $c$  0.92,  $\text{CHCl}_3$ ); IR (film) 3491, 2985, 2936, 1715, 1381, 1194,

1053  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.38 (dd,  $J = 11.7, 7.2$  Hz, 1H), 5.93 (dd,  $J = 11.7, 1.7$  Hz, 1H), 5.59 (ddd,  $J = 7.5, 7.2, 1.7$  Hz, 1H), 4.57 (ddd,  $J = 7.5, 4.9, 3.7$  Hz, 1H), 4.18 (q,  $J = 7.2$  Hz, 2H), 3.61 (dd,  $J = 11.7, 3.7$  Hz, 1H), 3.46 (dd,  $J = 11.7, 4.9$  Hz, 1H), 2.02 (brs, 1H), 1.53 (s, 3H), 1.40 (s, 3H), 1.29 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  166.2 (C), 147.4 (CH), 121.2 (CH), 109.0 (C), 78.9 (CH), 75.0 (CH), 61.6 ( $\text{CH}_2$ ), 60.8 ( $\text{CH}_2$ ), 27.5 ( $\text{CH}_3$ ), 24.8 ( $\text{CH}_3$ ), 14.3 ( $\text{CH}_3$ ); HRMS (ESI), calcd for  $\text{C}_{11}\text{H}_{18}\text{O}_5\text{Na}^+$  ( $\text{M}+\text{Na}$ ) $^+$  253.1052, found 253.1059.

### Z-Allylic alcohol **19d**

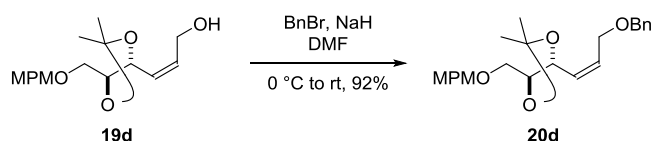


Camphorsulfonic acid (91.8 mg, 395  $\mu\text{mol}$ ) was added to a solution of *Z*-enoate **17d** (913 mg, 3.95 mmol), 4-methoxybenzyl 2,2,2-trichloroacetimidate (3.54 g, 11.8 mmol) and  $\text{CH}_2\text{Cl}_2$  (40 mL) at room temperature. The solution was maintained for 2 d at room temperature, quenched with  $\text{Et}_3\text{N}$  (110  $\mu\text{L}$ ), and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:10 to 1:3) to give 1.30 g of *Z*-methoxybenzyl ether, containing impurities derived from the reagent. For analytical sample, the mixture of **18d** was purified by HPLC (PEGASIL Silica 120–5 250 $\times$ 20 mm, UV 254 nm, EtOAc/hexane 1:6, 10 mL/min, *Z*-methoxybenzyl ether **18d**:  $T_{\text{R}} = 21.1$  min) to afford pure *Z*-methoxybenzyl ether **18d**: colorless oil;  $[\alpha]_{\text{D}}^{20} -146.2$  ( $c$  0.44,  $\text{CHCl}_3$ ); IR (film) 2986, 2935, 2904, 1716, 1514, 1248, 1221, 1193, 1076, 1037, 821  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.23 (d,  $J = 8.6$  Hz, 2H), 6.86 (d,  $J = 8.6$  Hz, 2H), 6.26 (dd,  $J = 11.7, 7.5$  Hz, 1H), 5.84 (dd,  $J = 11.7, 1.7$  Hz, 1H), 5.65 (ddd,  $J = 7.5, 7.5, 1.7$  Hz, 1H), 4.62 (ddd,  $J = 7.5, 6.6, 3.4$  Hz, 1H), 4.47 (d,  $J = 11.7$  Hz, 1H), 4.44 (d,  $J = 11.7$  Hz, 1H), 4.14 (q,  $J = 7.2$  Hz, 2H), 3.80 (s, 3H), 3.42 (dd,  $J = 10.3, 3.4$  Hz, 1H), 3.31 (dd,  $J = 10.3, 6.6$  Hz, 1H), 1.52 (s, 3H), 1.39 (s, 3H), 1.27 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  165.7 (C), 159.3 (C), 146.4 (CH), 130.3 (C), 129.4 (CH), 121.4 (CH), 113.8 (CH), 109.4 (C), 77.6 (CH), 74.3 (CH), 73.1 ( $\text{CH}_2$ ), 69.1 ( $\text{CH}_2$ ), 60.6 ( $\text{CH}_2$ ), 55.4 ( $\text{CH}_3$ ), 27.7 ( $\text{CH}_3$ ), 25.2 ( $\text{CH}_3$ ), 14.3 ( $\text{CH}_3$ ); HRMS (ESI), calcd for  $\text{C}_{19}\text{H}_{26}\text{O}_6\text{Na}^+$  ( $\text{M}+\text{Na}$ ) $^+$  373.1627, found 373.1624.

Diisobutylaluminium hydride (1.03 M in hexane, 11 mL, 11 mmol) was added dropwise to a solution of above *Z*-methoxybenzyl ether and  $\text{Et}_2\text{O}$  (38 mL) at  $-78$   $^{\circ}\text{C}$ . The solution was maintained for 1 h, quenched with saturated aqueous Rochelle salt (50 mL), allowed to warm to room temperature, stirred for 1 h, and extracted with EtOAc (3x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:5 to 1:2) to give 801 mg of *Z*-allylic alcohol **19d** (66% for 2 steps): yellow oil;  $[\alpha]_{\text{D}}^{21} -19.3$  ( $c$  1.03,  $\text{CHCl}_3$ ); IR (film) 3418, 2987, 2935, 2867, 1612, 1514, 1248, 1079, 1034  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR

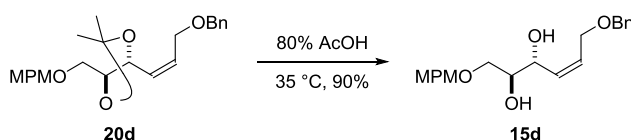
(500 MHz, CDCl<sub>3</sub>)  $\delta$  7.23 (d,  $J$  = 8.6 Hz, 2H), 6.86 (d,  $J$  = 8.6 Hz, 2H), 5.83 (dtd,  $J$  = 11.2, 6.6, 1.2 Hz, 1H), 5.54 (ddt,  $J$  = 11.2, 8.6, 1.4 Hz, 1H), 5.05 (ddd,  $J$  = 8.6, 6.6, 1.2 Hz, 1H), 4.47 (d,  $J$  = 11.5 Hz, 1H), 4.44 (d,  $J$  = 11.5 Hz, 1H), 4.34 (ddd,  $J$  = 6.9, 6.6, 5.7 Hz, 1H), 4.12 (dd,  $J$  = 6.6, 1.4 Hz, 2H), 3.79 (s, 3H), 3.47 (dd,  $J$  = 9.7, 5.7 Hz, 1H), 3.43 (dd,  $J$  = 9.7, 6.9 Hz, 1H), 2.39 (brs, 1H), 1.46 (s, 3H), 1.36 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  159.5 (C), 132.6 (CH), 129.7 (CH), 129.5 (C), 128.2 (CH), 113.9 (CH), 108.9 (C), 76.7 (CH), 73.5 (CH), 73.3 (CH<sub>2</sub>), 68.7 (CH<sub>2</sub>), 58.6 (CH<sub>2</sub>), 55.3 (CH<sub>3</sub>), 27.9 (CH<sub>3</sub>), 25.3 (CH<sub>3</sub>); HRMS (ESI), calcd for C<sub>17</sub>H<sub>24</sub>O<sub>5</sub>Na<sup>+</sup> (M+Na)<sup>+</sup> 331.1521, found 331.1525.

### Z-Benzyl ether **20d**



Sodium hydride (63% in oil, 170 mg, 4.5 mmol) was added to a solution of *Z*-allylic alcohol **19d** (693 mg, 2.25 mmol) and DMF (15 mL) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C. Benzyl bromide (540  $\mu$ L, 4.5 mmol) was then added to this mixture at 0 °C. The mixture was allowed to warm to room temperature, and stirred for 4 h at this temperature, quenched with saturated aqueous NH<sub>4</sub>Cl (16 mL), and extracted with Et<sub>2</sub>O (5x 30 mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:15 to 1:8) to give 822 mg of *Z*-benzyl ether **20d** (92%): colorless oil; [ $\alpha$ ]<sub>D</sub><sup>23</sup> -35.2 (*c* 1.17, CHCl<sub>3</sub>); IR (film) 2988, 2934, 2860, 1612, 1514, 1248, 1077 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.36–7.27 (m, 5H), 7.24 (d,  $J$  = 8.6 Hz, 2H), 6.85 (d,  $J$  = 8.6 Hz, 2H), 5.80 (dddd,  $J$  = 11.2, 6.9, 5.7, 1.2 Hz, 1H), 5.59 (dddd,  $J$  = 11.2, 8.9, 1.7, 1.4 Hz, 1H), 4.89 (ddd,  $J$  = 8.9, 6.6, 1.2 Hz, 1H), 4.49 (d,  $J$  = 12.0 Hz, 1H), 4.49 (d,  $J$  = 11.7 Hz, 1H), 4.45 (d,  $J$  = 12.0 Hz, 1H), 4.42 (d,  $J$  = 11.7 Hz, 1H), 4.31 (ddd,  $J$  = 6.6, 6.6, 5.2 Hz, 1H), 4.10 (ddd,  $J$  = 12.6, 6.9, 1.4 Hz, 1H), 4.12 (ddd,  $J$  = 12.6, 5.7, 1.7 Hz, 1H), 3.79 (s, 3H), 3.43 (dd,  $J$  = 10.0, 6.6 Hz, 1H), 3.41 (dd,  $J$  = 10.0, 5.2 Hz, 1H), 1.48 (s, 3H), 1.35 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  159.3 (C), 138.1 (C), 130.7 (CH), 130.1 (C), 129.6 (CH), 128.6 (CH), 128.5 (CH), 127.93 (CH), 127.87 (CH), 113.8 (CH), 109.1 (C), 77.2 (CH), 73.3 (CH), 73.2 (CH<sub>2</sub>), 72.4 (CH<sub>2</sub>), 69.1 (CH<sub>2</sub>), 65.7 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>), 28.0 (CH<sub>3</sub>), 25.5 (CH<sub>3</sub>); HRMS (ESI), calcd for C<sub>24</sub>H<sub>30</sub>O<sub>5</sub>Na<sup>+</sup> (M+Na)<sup>+</sup> 421.1991, found 421.1996.

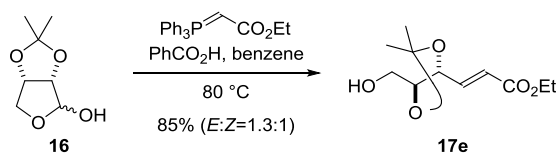
### Z-Allylic anti-diol **15d**



*Z*-Benzyl ether **20d** (748 mg, 1.88 mmol) was dissolved in AcOH/H<sub>2</sub>O (4:1, 7.5 mL) at room temperature.

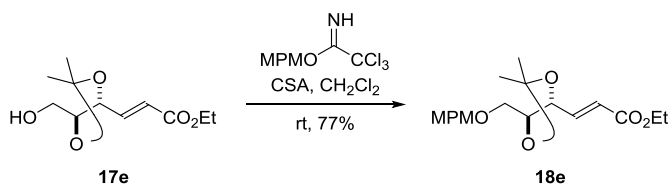
This solution was warmed to 40 °C, and stirred for 14 h at 40 °C. The solution was cooled to room temperature, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:3 to 1:1) to give 609 mg of *Z*-allylic *anti*-diol **15d** (90%): colorless oil;  $[\alpha]_D^{23} -9.1$  (*c* 1.43, CHCl<sub>3</sub>); IR (film) 3396, 2911, 2862, 1612, 1514, 1248, 1089, 1033 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.37–7.27 (m, 5H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.83 (dddd, *J* = 11.2, 6.6, 6.0, 0.9 Hz, 1H), 5.63–5.69 (m, 1H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.49 (d, *J* = 11.7 Hz, 1H), 4.49–4.47 (m, 1H), 4.48 (d, *J* = 12.3 Hz, 1H), 4.45 (d, *J* = 12.3 Hz, 1H), 4.12 (ddd, *J* = 12.3, 6.6, 0.9 Hz, 1H), 4.05 (ddd, *J* = 12.3, 6.0, 1.2 Hz, 1H), 3.79 (s, 3H), 3.75–3.70 (m, 1H), 3.61 (dd, *J* = 9.7, 6.0 Hz, 1H), 3.55 (dd, *J* = 9.7, 4.0 Hz, 1H), 2.78 (brs, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 159.5 (C), 137.8 (C), 132.2 (CH), 129.9 (CH), 129.8 (C), 129.6 (CH), 128.6 (CH), 128.03 (CH), 127.98 (CH), 114.0 (CH), 73.5 (CH<sub>2</sub>), 72.8 (CH<sub>2</sub>), 72.3 (CH), 71.1 (CH<sub>2</sub>), 69.9 (CH), 66.0 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>); HRMS (ESI), calcd for C<sub>21</sub>H<sub>26</sub>O<sub>5</sub>Na<sup>+</sup> (*M*+Na)<sup>+</sup> 381.1678, found 381.1678.

### *E*-Enoate **17e**



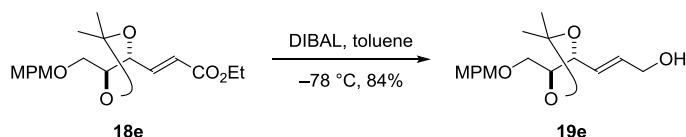
(Ethoxycarbonylmethylene)triphenylphosphorane (12.5 g, 36.0 mmol) was added to a solution of lactol **16** (3.85 g, 24.0 mmol), benzoic acid (176 mg, 1.44 mmol) and benzene (240 mL) at room temperature. The solution was heated to 80 °C, stirred for 3.5 h at 80 °C. The solution was cooled to room temperature, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:4 to 1:3) to give 2.67 g of *E*-enoate **17e** (48%) and 2.02 g of *Z*-enoate **17d** (37%). *E*-enoate **17e**: colorless oil;  $[\alpha]_D^{21} -28.9$  (*c* 1.07, CHCl<sub>3</sub>); IR (film) 3485, 2987, 2938, 1721, 1372, 1260, 1164, 1047 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.88 (dd, *J* = 15.8, 5.7 Hz, 1H), 6.13 (dd, *J* = 15.8, 1.7 Hz, 1H), 4.80 (ddd, *J* = 6.9, 5.7, 1.7 Hz, 1H), 4.37 (ddd, *J* = 6.9, 6.3, 5.4 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.61–3.53 (m, 2H), 1.83 (brs, 1H), 1.53 (s, 3H), 1.40 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 166.0 (C), 142.1 (CH), 123.3 (CH), 109.7 (C), 78.4 (CH), 76.1 (CH), 62.0 (CH<sub>2</sub>), 60.8 (CH<sub>2</sub>), 27.8 (CH<sub>3</sub>), 25.4 (CH<sub>3</sub>), 14.4 (CH<sub>3</sub>); HRMS (ESI), calcd for C<sub>11</sub>H<sub>18</sub>O<sub>5</sub>Na<sup>+</sup> (*M*+Na)<sup>+</sup> 253.1052, found 253.1051.

### *E*-Methoxybenzyl ether **18e**



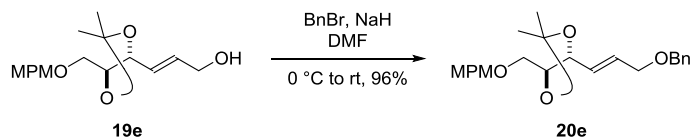
Camphorsulfonic acid (258 mg, 1.11 mmol) was added to a solution of *E*-enoate **17e** (2.57 g, 11.1 mmol), 4-methoxybenzyl 2,2,2-trichloroacetimidate (9.96 g, 33.3 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (110 mL) at room temperature. The solution was maintained for 1.5 d at room temperature, quenched with Et<sub>3</sub>N (310 μL), and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:10 to 1:3) to give 3.01 g of *E*-methoxybenzyl ether **18e** (77%): yellow oil;  $[\alpha]_D^{23} +31.0$  (*c* 0.79, CHCl<sub>3</sub>); IR (film) 2986, 1719, 1514, 1260, 1176, 1094, 1035 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.91 (dd, *J* = 15.5, 5.4 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.12 (dd, *J* = 15.5, 1.7 Hz, 1H), 4.78 (ddd, *J* = 6.6, 5.4, 1.7 Hz, 1H), 4.43 (ddd, *J* = 6.6, 6.0, 6.0 Hz, 1H), 4.39 (d, *J* = 11.2 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 3.80 (s, 3H), 3.45 (dd, *J* = 9.5, 6.0 Hz, 1H), 3.35 (dd, *J* = 9.5, 6.6 Hz, 1H), 1.50 (s, 3H), 1.38 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 166.1 (C), 159.4 (C), 142.9 (CH), 129.9 (C), 129.7 (CH), 122.7 (CH), 113.9 (CH), 109.6 (C), 76.8 (CH), 76.4 (CH), 73.3 (CH<sub>2</sub>), 68.8 (CH<sub>2</sub>), 60.6 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>), 27.8 (CH<sub>3</sub>), 25.3 (CH<sub>3</sub>), 14.4 (CH<sub>3</sub>); LRMS (EI) *m/z* 350 (M<sup>+</sup>, 8.2%), 220 (13), 137 (39), 121 (100), 112 (24), 84 (26); HRMS (EI), calcd for C<sub>19</sub>H<sub>26</sub>O<sub>6</sub> M<sup>+</sup> 350.1729, found 350.1738.

#### *E*-Allylic alcohol **19e**



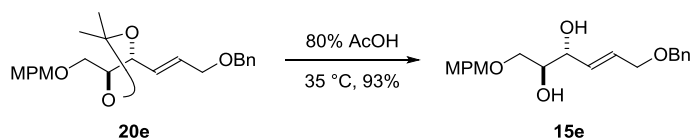
Diisobutylaluminium hydride (1.00 M in toluene, 17 mL, 17 mmol) was added dropwise to a solution of *E*-methoxybenzyl ether **18e** (1.93 g, 5.49 mmol) and toluene (55 mL) at -78 °C. The solution was maintained for 1 h, quenched with saturated aqueous Rochelle salt (50 mL), allowed to warm to room temperature, stirred for 1 h, and extracted with EtOAc (3x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/toluene 1:3 to 1:1) to give 1.46 g of *E*-allylic alcohol **19e** (84%): yellow oil;  $[\alpha]_D^{24} +9.6$  (*c* 0.95, CHCl<sub>3</sub>); IR (film) 3453, 2987, 2867, 1613, 1514, 1248, 1080, 1033 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.94 (dtd, *J* = 15.5, 5.2, 0.9 Hz, 1H), 5.73 (ddt, *J* = 15.5, 7.7, 1.7 Hz, 1H), 4.64 (ddd, *J* = 7.7, 6.6, 0.9 Hz, 1H), 4.52 (d, *J* = 11.7 Hz, 1H), 4.41 (d, *J* = 11.7 Hz, 1H), 4.35 (ddd, *J* = 6.6, 6.3, 5.7 Hz, 1H), 4.14 (dd, *J* = 5.2, 1.7 Hz, 2H), 3.80 (s, 3H), 3.44 (dd, *J* = 9.7, 6.3 Hz, 1H), 3.42 (dd, *J* = 9.7, 5.7 Hz, 1H), 1.48 (s, 3H), 1.37 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 159.4 (C), 133.6 (CH), 130.1 (C), 129.6 (CH), 126.3 (CH), 113.9 (CH), 108.9 (C), 77.7 (CH), 77.0 (CH), 73.2 (CH<sub>2</sub>), 69.1 (CH<sub>2</sub>), 62.9 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>), 28.0 (CH<sub>3</sub>), 25.4 (CH<sub>3</sub>); LRMS (EI) *m/z* 308 (M<sup>+</sup>, 1.3%), 153 (35), 136 (49), 121 (100), 89 (46) 77 (87), 59 (95); HRMS (EI), calcd for C<sub>17</sub>H<sub>24</sub>O<sub>5</sub> M<sup>+</sup> 308.1624, found 308.1615.

### *E*-Benzyl ether **20e**



Sodium hydride (63% in oil, 550 mg, 15 mmol) was added to a solution of *E*-allylic alcohol **19e** (1.49 g, 4.83 mmol) and DMF (32 mL) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C. Benzyl bromide (1.7 mL, 15 mmol) was then added to this mixture at 0 °C. The mixture was allowed to warm to room temperature, and stirred for 2 h at this temperature, quenched with saturated aqueous NH<sub>4</sub>Cl (35 mL), and extracted with Et<sub>2</sub>O (3x 40 mL). The combined organic extracts were washed with water (35 mL) and brine (35 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:10 to 1:6) to give 1.84 g of *E*-benzyl ether **20e** (96%): yellow oil;  $[\alpha]_D^{24} +7.4$  (*c* 1.23, CHCl<sub>3</sub>); IR (film) 2986, 2862, 1613, 1513, 1248, 1085, 1033 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.36–7.26 (m, 5H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 5.90 (dtd, *J* = 15.5, 5.4, 0.9 Hz, 1H), 5.72 (dtd, *J* = 15.5, 7.5, 1.4 Hz, 1H), 4.65 (ddd, *J* = 7.5, 6.6, 0.9 Hz, 1H), 4.50 (d, *J* = 11.5 Hz, 1H), 4.49 (s, 2H), 4.42 (d, *J* = 11.5 Hz, 1H), 4.36 (d, *J* = 6.6, 6.3, 5.4 Hz, 1H), 4.03 (dd, *J* = 5.4, 1.4 Hz, 2H), 3.78 (s, 3H), 3.44 (dd, *J* = 10.0, 6.3 Hz, 1H), 3.42 (dd, *J* = 10.0, 5.4 Hz, 1H), 1.49 (s, 3H), 1.38 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  159.3 (C), 138.3 (C), 130.8 (CH), 130.1 (C), 129.5 (CH), 128.5 (CH), 127.89 (CH), 127.80 (CH), 127.76 (CH), 113.9 (CH), 109.0 (C), 77.7 (CH), 77.1 (CH), 73.2 (CH<sub>2</sub>), 72.2 (CH<sub>2</sub>), 69.9 (CH<sub>2</sub>), 69.2 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>), 28.0 (CH<sub>3</sub>), 25.5 (CH<sub>3</sub>); LRMS (EI) *m/z* 398 (M<sup>+</sup>, 0.6%), 232 (11), 137 (29), 121 (100), 91 (96); HRMS (EI), calcd for C<sub>24</sub>H<sub>30</sub>O<sub>5</sub> M<sup>+</sup> 398.2093, found 398.2094.

### *E*-Allylic *anti*-diol **15e**

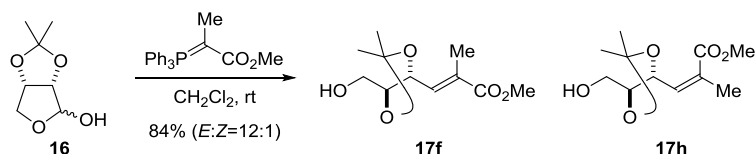


*E*-Benzyl ether **20e** (2.49 g, 6.25 mmol) was dissolved in AcOH/H<sub>2</sub>O (4:1, 13 mL) at room temperature. This solution was warmed to 35 °C, and stirred for 1.5 d at 35 °C. The solution was cooled to room temperature, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:2 to 1:1) to give 2.08 g of *E*-allylic *anti*-diol **15e** (93%): yellow oil;  $[\alpha]_D^{24} -3.3$  (*c* 0.99, CHCl<sub>3</sub>); IR (film) 3417, 2862, 1612, 1513, 1248, 1098 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.37–7.27 (m, 5H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.90 (dtd, *J* = 15.5, 5.4, 1.2 Hz, 1H), 5.78 (dtd, *J* = 15.5, 6.0, 1.4 Hz, 1H), 4.51 (s, 2H), 4.48 (d, *J* = 11.5 Hz, 1H), 4.45 (d, *J* = 11.5 Hz, 1H), 4.30–4.26 (m, 1H), 4.04 (ddd, *J* = 5.4, 1.4, 1.4 Hz, 2H), 3.81–3.76 (m, 1H), 3.79 (s, 3H), 3.60 (dd, *J* = 9.7, 5.7 Hz, 1H), 3.57 (dd, *J* = 9.7, 4.0 Hz, 1H), 2.66 (brs, 1H), 2.55 (brs, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  159.5 (C),



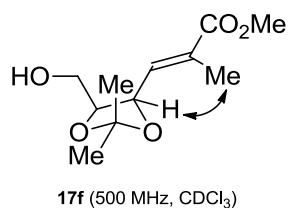
138.3 (C), 131.1 (CH), 129.8 (C), 129.6 (CH), 129.3 (CH), 128.5 (CH), 127.9 (CH), 127.8 (CH), 114.0 (CH), 73.7 (CH), 73.5 (CH<sub>2</sub>), 72.5 (CH), 72.4 (CH<sub>2</sub>), 70.9 (CH<sub>2</sub>), 70.1 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>); LRMS (EI) *m/z* 358 (M<sup>+</sup>, 0.4%), 121 (29), 88 (28), 73 (45), 70 (86), 61 (100), 58 (44); HRMS (EI), calcd for C<sub>21</sub>H<sub>26</sub>O<sub>5</sub> M<sup>+</sup> 358.1780, found 358.1768.

### *E*-Trisubstituted enoate **17f**

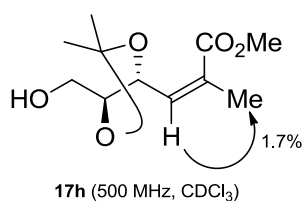


(1-methoxycarbonyl)ethylenetriphenylphosphorane (14.1 g, 40.6 mmol) was added to a solution of lactol **16** (5.00 g, 31.2 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (60 mL) at room temperature. The solution was maintained for 2 d at room temperature, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:3) to give 5.55 g of *E*-trisubstituted enoate **17f** (77%) and 475 mg of *Z*-trisubstituted enoate **17h** (7%). *E*-trisubstituted enoate **17f**: colorless oil; [α]<sub>D</sub><sup>23</sup> -27.3 (*c* 1.50, CHCl<sub>3</sub>); IR (film) 3491, 2990, 2953, 2938, 1717, 1250, 1045 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.71 (dq, *J* = 8.3, 1.4 Hz, 1H), 4.99 (dd, *J* = 8.3, 7.2 Hz, 1H), 4.34 (ddd, *J* = 7.2, 6.6, 4.3 Hz, 1H), 3.74 (s, 3H), 3.54 (dd, *J* = 11.5, 6.6 Hz, 1H), 3.51 (dd, *J* = 11.5, 4.3 Hz, 1H), 1.99 (brs, 1H), 1.88 (d, *J* = 1.4 Hz, 3H), 1.52 (s, 3H), 1.39 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 167.7 (C), 136.4 (CH), 130.9 (C), 109.5 (C), 78.6 (CH), 74.0 (CH), 62.0 (CH<sub>2</sub>), 52.2 (CH<sub>3</sub>), 27.9 (CH<sub>3</sub>), 25.3 (CH<sub>3</sub>), 13.3 (CH<sub>3</sub>); HRMS (ESI), calcd for C<sub>11</sub>H<sub>18</sub>O<sub>5</sub>Na<sup>+</sup> (M+Na)<sup>+</sup> 253.1052, found 253.1052. *Z*-Trisubstituted enoate **17h**: colorless oil; [α]<sub>D</sub><sup>21</sup> -87.2 (*c* 1.11, CHCl<sub>3</sub>); IR (film) 3493, 2989, 2933, 1716, 1380, 1228, 1127, 1045 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.08 (dq, *J* = 7.5, 1.4 Hz, 1H), 5.35 (ddq, *J* = 7.5, 6.9, 1.2 Hz, 1H), 4.50 (ddd, *J* = 6.9, 5.7, 4.0 Hz, 1H), 3.74 (s, 3H), 3.57 (dd, *J* = 11.5, 4.0 Hz, 1H), 3.47 (dd, *J* = 11.5, 5.7 Hz, 1H), 1.95 (dd, *J* = 1.4, 1.2 Hz, 3H), 1.51 (s, 3H), 1.38 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 167.8 (C), 140.8 (CH), 129.6 (C), 108.8 (C), 79.0 (CH), 75.4 (CH), 61.9 (CH<sub>2</sub>), 52.0 (CH<sub>3</sub>), 27.6 (CH<sub>3</sub>), 24.9 (CH<sub>3</sub>), 20.0 (CH<sub>3</sub>); HRMS (ESI), calcd for C<sub>11</sub>H<sub>18</sub>O<sub>5</sub>Na<sup>+</sup> (M+Na)<sup>+</sup> 253.1052, found 253.1051.

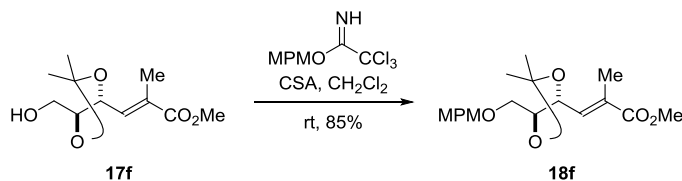
NOESY experiment for **17f**



NOE experiment for **17h**

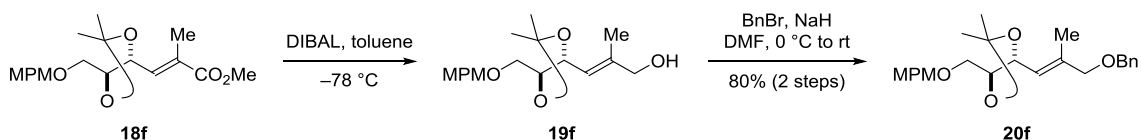


### *E*-Trisubstituted methoxybenzyl ether **18f**



Camphorsulfonic acid (197 mg, 850  $\mu$ mol) was added to a solution of *E*-trisubstituted enoate **17f** (1.96 g, 8.51 mmol), 4-methoxybenzyl 2,2,2-trichloroacetimidate (4.80 g, 17.0 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (85 mL) at room temperature. The solution was maintained for 2 d at room temperature, quenched with saturated aqueous NaHCO<sub>3</sub> (50 mL), and extracted with CHCl<sub>3</sub> (3x 50 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:19) to give 2.54 g of *E*-trisubstituted methoxybenzyl ether **18f** (85%): colorless oil;  $[\alpha]_D^{23}$  -0.87 (*c* 1.48, CHCl<sub>3</sub>); IR (film) 2989, 2937, 1718, 1514, 1248 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.21 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.67 (dq, *J* = 8.9, 1.4 Hz, 1H), 4.95 (dd, *J* = 8.9, 6.6 Hz, 1H), 4.46 (d, *J* = 11.7 Hz, 1H), 4.42 (ddd, *J* = 6.6, 6.3, 5.4 Hz, 1H), 4.39 (d, *J* = 11.7 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.46 (dd, *J* = 9.7, 6.3 Hz, 1H), 3.37 (dd, *J* = 9.7, 5.4 Hz, 1H), 1.86 (d, *J* = 1.4 Hz, 3H), 1.50 (s, 3H), 1.39 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  167.9 (C), 159.4 (C), 136.5 (CH), 130.8 (C), 130.0 (C), 129.5 (CH), 113.9 (CH), 109.5 (C), 77.2 (CH), 74.1 (CH), 73.3 (CH<sub>2</sub>), 68.8 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>), 52.1 (CH<sub>3</sub>), 28.0 (CH<sub>3</sub>), 25.5 (CH<sub>3</sub>), 13.2 (CH<sub>3</sub>); HRMS (ESI), calcd for C<sub>19</sub>H<sub>26</sub>O<sub>6</sub>Na<sup>+</sup> (*M*+Na)<sup>+</sup> 373.1627, found 373.1625.

### *E*-Trisubstituted benzyl ether **20f**

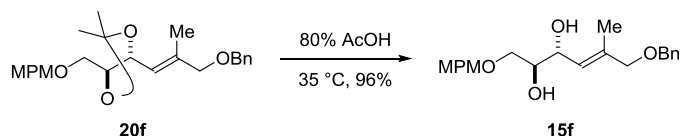


Diisobutylaluminium hydride (1.02 M in toluene, 13 mL, 13 mmol) was added dropwise to a solution of the *E*-trisubstituted *p*-methoxybenzyl ether **18f** (2.04 g, 5.38 mmol) and toluene (54 mL) at -78 °C. The solution was maintained for 1 h, quenched with saturated aqueous Rochelle salt (70 mL), allowed to warm to room temperature, stirred for 1 h, and extracted with EtOAc (3x 100 mL). The combined organic extracts were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was filtered through a pad of silica gel to give *E*-trisubstituted allylic alcohol, which was used in the next step without further purification. For analytical sample, the mixture of **19f** was purified by silica gel column chromatography (EtOAc/hexane 1:3 to 1:1) to afford pure *Z*-allylic alcohol **19f**: yellow oil;  $[\alpha]_D^{23}$  -19.6 (*c* 1.13, CHCl<sub>3</sub>); IR (film) 3446, 2933, 1613, 1514, 1248, 1077, 1038 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.24 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.47 (dq, *J* = 9.2, 1.4 Hz, 1H), 4.94 (dd, *J* = 9.2, 6.6 Hz, 1H), 4.50 (d, *J* = 11.7 Hz, 1H), 4.42 (d, *J* = 11.7 Hz, 1H), 4.34 (ddd, *J* = 6.6, 6.6, 5.2 Hz, 1H), 3.99 (s, 2H),

3.80 (s, 3H), 3.45 (dd,  $J = 10.0, 6.6$  Hz, 1H), 3.41 (dd,  $J = 10.0, 5.2$  Hz, 1H), 1.69 (d,  $J = 1.4$  Hz, 3H), 1.48 (s, 3H), 1.38 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  159.4 (C), 140.7 (C), 130.2 (C), 129.5 (CH), 120.0 (CH), 113.9 (CH), 108.7 (C), 77.1 (CH), 73.7 (CH), 73.2 ( $\text{CH}_2$ ), 69.3 ( $\text{CH}_2$ ), 68.0 ( $\text{CH}_2$ ), 55.4 ( $\text{CH}_3$ ), 28.1 ( $\text{CH}_3$ ), 25.6 ( $\text{CH}_3$ ), 14.1 ( $\text{CH}_3$ ); HRMS (ESI), calcd for  $\text{C}_{18}\text{H}_{26}\text{O}_5\text{Na}^+$  ( $\text{M}+\text{Na}$ ) $^+$  345.1678, found 345.1676.

Sodium hydride (63% in oil, 530 mg, 14 mmol) was added to a solution of above *E*-trisubstituted allylic alcohol and DMF (31 mL) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C. Benzyl bromide (1.7 mL, 14 mmol) was then added to this mixture at 0 °C. The mixture was allowed to warm to room temperature, and stirred for 2 h at this temperature, quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (10 mL), and extracted with  $\text{Et}_2\text{O}$  (2x 350 mL). The combined organic extracts were washed with water (100 mL) and brine (100 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated. The residue was purified by silica gel column chromatography ( $\text{EtOAc}$ /hexane 1:10) to give 1.83 g of *E*-trisubstituted benzyl ether **20f** (76% for 2 steps): yellow oil;  $[\alpha]_D^{23} -10.8$  ( $c$  1.37,  $\text{CHCl}_3$ ); IR (film) 2983, 2936, 2863, 1513, 1247, 1216, 1056, 1033  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35–7.27 (m, 5H), 7.23 (d,  $J = 8.6$  Hz, 2H), 6.83 (d,  $J = 8.6$  Hz, 2H), 5.51 (dqdd,  $J = 9.2, 1.4, 1.2, 1.2$  Hz, 1H), 4.96 (dd,  $J = 9.2, 6.6$  Hz, 1H), 4.50 (d,  $J = 11.7$  Hz, 1H), 4.45 (d,  $J = 12.0$  Hz, 1H), 4.43 (d,  $J = 11.7$  Hz, 1H), 4.42 (d,  $J = 12.0$  Hz, 1H), 4.36 (ddd,  $J = 6.9, 6.6, 4.9$  Hz, 1H), 3.93 (dd,  $J = 12.6, 1.2$  Hz, 1H), 3.90 (dd,  $J = 12.6, 1.2$  Hz, 1H), 3.77 (s, 3H), 3.46 (dd,  $J = 10.0, 6.9$  Hz, 1H), 3.42 (dd,  $J = 10.0, 4.9$  Hz, 1H), 1.72 (d,  $J = 1.4$  Hz, 3H), 1.49 (s, 3H), 1.39 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  159.3 (C), 138.4 (C), 137.9 (C), 130.2 (C), 129.5 (CH), 128.5 (CH), 127.8 (CH), 127.7 (CH), 122.5 (CH), 113.9 (CH), 108.8 (C), 77.1 (CH), 75.3 ( $\text{CH}_2$ ), 73.8 (CH), 73.2 ( $\text{CH}_2$ ), 71.8 ( $\text{CH}_2$ ), 69.4 ( $\text{CH}_2$ ), 55.4 ( $\text{CH}_3$ ), 28.2 ( $\text{CH}_3$ ), 25.6 ( $\text{CH}_3$ ), 14.4 ( $\text{CH}_3$ ); HRMS (ESI), calcd for  $\text{C}_{25}\text{H}_{32}\text{O}_5\text{Na}^+$  ( $\text{M}+\text{Na}$ ) $^+$  435.2147, found 435.2143.

#### *E*-Trisubstituted Allylic *anti*-diol **15f**

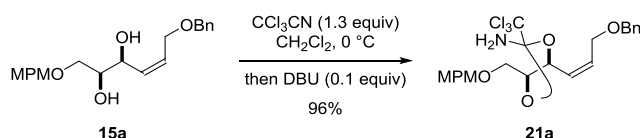


*E*-Trisubstituted benzyl ether **20f** (1.80 g, 4.21 mmol) was dissolved in  $\text{AcOH}/\text{H}_2\text{O}$  (4:1, 17 mL) at room temperature. This solution was warmed to 35 °C, and stirred for 15 h at 35 °C. The solution was cooled to room temperature, and concentrated. The residue was purified by silica gel column chromatography ( $\text{EtOAc}$ /hexane 1:2 to 1:1) to give 1.51 g of *E*-trisubstituted allylic *anti*-diol **15f** (93%): colorless oil;  $[\alpha]_D^{23} -8.4$  ( $c$  1.44,  $\text{CHCl}_3$ ); IR (film) 3421, 2912, 2859, 1612, 1513, 1248, 1071, 1029  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35–7.27 (m, 5H), 7.24 (d,  $J = 8.6$  Hz, 2H), 6.86 (d,  $J = 8.6$  Hz, 2H), 5.51 (dq,  $J = 8.9, 1.2$  Hz, 1H), 4.52 (dd,  $J = 8.9, 4.6$  Hz, 1H), 4.49 (d,  $J = 11.5$  Hz, 1H), 4.47 (d,  $J = 12.0$  Hz, 1H), 4.45 (d,  $J = 11.5$  Hz, 1H), 4.45 (d,  $J = 12.0$  Hz, 1H), 3.91 (s, 2H), 3.79 (s, 3H), 3.81–3.76 (m, 1H), 3.61 (dd,  $J =$

9.7, 6.3 Hz, 1H), 3.57 (dd,  $J = 9.7, 4.0$  Hz, 1H), 2.75 (brs, 1H), 2.52 (brs, 1H), 1.73 (d,  $J = 1.2$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  159.5 (C), 138.3 (C), 137.4 (C), 129.8 (C), 129.6 (CH), 128.5 (CH), 127.84 (CH), 127.76 (CH), 125.5 (CH), 114.0 (CH), 75.4 ( $\text{CH}_2$ ), 73.5 ( $\text{CH}_2$ ), 72.5 (CH), 72.1 ( $\text{CH}_2$ ), 71.1 ( $\text{CH}_2$ ), 70.0 (CH), 55.4 ( $\text{CH}_3$ ), 14.6 ( $\text{CH}_3$ ); HRMS (ESI), calcd for  $\text{C}_{22}\text{H}_{28}\text{O}_5\text{Na}^+$  ( $\text{M}+\text{Na}$ ) $^+$  395.1834, found 395.1836.

#### [Method A: Synthesis of cyclic orthoamides from *syn*-diols]

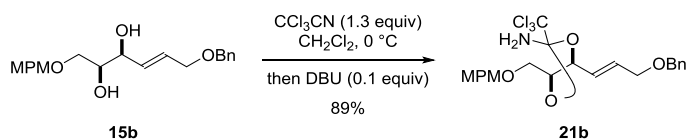
##### Cyclic orthoamide **21a**



1,8-Diazabicyclo[5.4.0]undec-7-ene (2.2  $\mu\text{L}$ , 15  $\mu\text{mol}$ ) was added dropwise to a solution of *Z*-allylic *syn*-diol **15a** (52.3 mg, 146  $\mu\text{mol}$ ),  $\text{CCl}_3\text{CN}$  (19  $\mu\text{L}$ , 190  $\mu\text{mol}$ ) and  $\text{CH}_2\text{Cl}_2$  (2.9 mL) at  $0\text{ }^\circ\text{C}$ . The solution was maintained for 4 h at  $0\text{ }^\circ\text{C}$ , allowed to warm to room temperature, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:9 to 1:3) to give cyclic orthoamide **21a** (70.3 mg, 96%, two diastereomers, dr = 1:1). For analytical samples, two diastereomers were separated by HPLC (PEGASIL Silica 120-5, 250 $\times$ 20 mm, UV 254 nm, EtOAc/hexane 1:2, 10 mL/min, **less polar diastereomer**:  $T_R = 15.0$  min, **polar diastereomer**:  $T_R = 24.0$  min). **21a** (**less polardiastereomer**): yellow oil;  $[\alpha]_D^{27} -17.6$  ( $c$  0.93,  $\text{CHCl}_3$ ); IR (film) 3420, 3340, 2940, 2860, 1610, 1520, 1460, 1250, 1080  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37–7.26 (m, 5H), 7.25–7.21 (m, 2H), 6.88–6.84 (m, 2H), 5.90 (dddd,  $J = 11.2, 6.9, 6.0, 0.9$  Hz, 1H), 5.71 (dddd,  $J = 11.2, 8.6, 1.7, 1.7$  Hz, 1H), 5.17 (ddd,  $J = 8.6, 8.6, 0.9$  Hz, 1H), 4.51 (d,  $J = 11.8$  Hz, 1H), 4.48 (d,  $J = 11.8$  Hz, 1H), 4.44 (d,  $J = 11.8$  Hz, 1H), 4.43 (d,  $J = 11.8$  Hz, 1H), 4.21 (ddd,  $J = 8.6, 4.0, 3.5$  Hz, 1H), 4.13 (ddd,  $J = 12.9, 6.9, 1.7$  Hz, 1H), 4.03 (ddd,  $J = 12.9, 5.7, 1.7$  Hz, 1H), 3.79 (s, 3H), 3.67 (dd,  $J = 11.2, 3.5$  Hz, 1H), 3.52 (dd,  $J = 11.2, 4.0$  Hz, 1H), 2.33 (brs, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  159.3 (C), 137.9 (C), 133.0 (CH), 129.6 (C), 129.4 (CH), 128.4 (CH), 127.8 (CH), 127.8 (CH), 127.0 (CH), 115.5 (C), 113.8 (CH), 103.2 (C), 83.7 (CH), 75.5 (CH), 73.3 ( $\text{CH}_2$ ), 72.5 ( $\text{CH}_2$ ), 67.8 ( $\text{CH}_2$ ), 65.8 ( $\text{CH}_2$ ), 55.2 ( $\text{CH}_3$ ); HRMS (FAB) calcd for  $\text{C}_{23}\text{H}_{27}\text{Cl}_2^{37}\text{ClNO}_5$  ( $\text{M}+\text{H}$ ) $^+$  504.0925, found 504.0926. **21a** (**polar diastereomer**): yellow oil;  $[\alpha]_D^{27} -6.1$  ( $c$  0.91,  $\text{CHCl}_3$ ); IR (film) 3420, 3340, 2940, 2860, 1610, 1520, 1460, 1250, 1080  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35–7.26 (m, 5H), 7.24–7.20 (m, 2H), 6.87–6.83 (m, 2H), 5.89 (dddd,  $J = 11.2, 6.6, 5.8, 0.9$  Hz, 1H), 5.68 (dddd,  $J = 11.2, 8.9, 1.7, 1.5$  Hz, 1H), 4.97 (ddd,  $J = 8.9, 8.9, 0.9$  Hz, 1H), 4.50 (d,  $J = 11.8$  Hz, 1H), 4.47 (d,  $J = 11.8$  Hz, 1H), 4.46 (d,  $J = 11.8$  Hz, 1H), 4.43 (d,  $J = 11.8$  Hz, 1H), 4.32 (ddd,  $J = 8.9, 5.5, 4.0$  Hz, 1H), 4.09 (ddd,  $J = 12.9, 6.6, 1.5$  Hz, 1H), 4.02 (ddd,  $J = 12.9, 5.8, 1.7$  Hz, 1H), 3.79 (s, 3H), 3.63 (dd,  $J = 11.2, 5.5$  Hz, 1H), 3.60 (dd,  $J = 11.2, 4.0$  Hz, 1H), 2.32 (brs, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  159.2 (C), 137.8 (C), 132.8 (CH), 129.8 (C), 129.3 (CH), 128.43 (CH), 128.37 (CH), 127.9

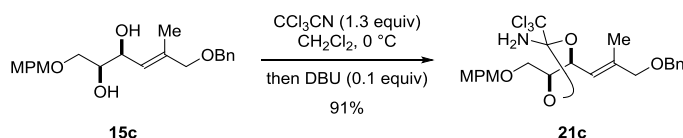
(CH), 127.8 (CH), 115.1 (C), 113.8 (CH), 103.4 (C), 82.1 (CH), 78.0 (CH), 73.1 (CH<sub>2</sub>), 72.4 (CH<sub>2</sub>), 67.5 (CH<sub>2</sub>), 65.6 (CH<sub>2</sub>), 55.2 (CH<sub>3</sub>); HRMS (FAB) calcd for C<sub>23</sub>H<sub>27</sub>Cl<sub>2</sub><sup>37</sup>ClNO<sub>5</sub> (M+H)<sup>+</sup> 504.0925, found 504.0930.

### Cyclic orthoamide 21b



Following method A, *E*-allylic *syn*-diol **15b** (53.3 mg, 149 μmol) was converted to cyclic orthoamide **21b** (67.2 mg, 89%, two diastereomers, dr = 1:1): yellow oil; [α]<sub>D</sub><sup>24</sup> -18.2 (*c* 0.84, CHCl<sub>3</sub>); IR (film) 3414, 3338, 2859, 1612, 1514, 1248, 1100, 819 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.37–7.28 (m, 5H), 7.27 (d, *J* = 8.6 Hz, 1H), 7.26 (d, *J* = 8.6 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 1H), 5.95 (dtd, *J* = 15.5, 5.2, 0.6 Hz, 1/2H), 5.93 (dtd, *J* = 15.5, 5.2, 0.6 Hz, 1/2H), 5.83 (ddt, *J* = 15.5, 7.7, 1.4 Hz, 1/2H), 5.82 (ddt, *J* = 15.5, 7.7, 1.4 Hz, 1/2H), 4.81 (dd, *J* = 8.6, 7.7, 0.6 Hz, 1/2H), 4.61 (dd, *J* = 9.2, 7.7, 0.6 Hz, 1/2H), 4.58 (d, *J* = 12.0 Hz, 1/2H), 4.56 (d, *J* = 12.0 Hz, 1/2H), 4.53 (d, *J* = 12.0 Hz, 1/2H), 4.51 (s, 1H), 4.51 (s, 1H), 4.49 (d, *J* = 12.0 Hz, 1/2H), 4.37 (ddd, *J* = 9.2, 5.7, 3.4 Hz, 1/2H), 4.25 (ddd, *J* = 8.6, 4.3, 3.4 Hz, 1/2H), 4.04 (dd, *J* = 5.2, 1.4 Hz, 1H), 4.03 (dd, *J* = 5.2, 1.4 Hz, 1H), 3.79 (s, 3/2H), 3.79 (s, 3/2H), 3.71 (dd, *J* = 11.2, 5.7 Hz, 1/2H), 3.70 (dd, *J* = 11.2, 3.4 Hz, 1/2H), 3.65 (dd, *J* = 11.2, 3.4 Hz, 1/2H), 3.58 (dd, *J* = 11.2, 4.3 Hz, 1/2H), 2.62 (brs, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 159.5 (C), 159.4 (C), 138.10 (C), 138.06 (C), 133.3 (CH), 133.3 (CH), 129.9 (C), 129.8 (C), 129.54 (CH), 129.47 (CH), 128.6 (CH), 128.6 (CH), 127.91 (CH), 127.88 (CH), 127.86 (CH), 127.86 (CH), 127.8 (CH), 126.7 (CH), 115.5 (C), 115.1 (C), 114.0 (CH), 113.9 (CH), 103.5 (C), 103.4 (C), 83.8 (CH), 82.9 (CH), 82.2 (CH), 80.3 (CH), 73.35 (CH<sub>2</sub>), 73.28 (CH<sub>2</sub>), 72.62 (CH<sub>2</sub>), 72.59 (CH<sub>2</sub>), 69.62 (CH<sub>2</sub>), 69.55 (CH<sub>2</sub>), 68.0 (CH<sub>2</sub>), 67.8 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>), 55.4 (CH<sub>3</sub>); HRMS (FAB) calcd for C<sub>23</sub>H<sub>27</sub>Cl<sub>2</sub><sup>37</sup>ClNO<sub>5</sub> (M+H)<sup>+</sup> 504.0925, found 504.0929.

### Cyclic orthoamide 21c

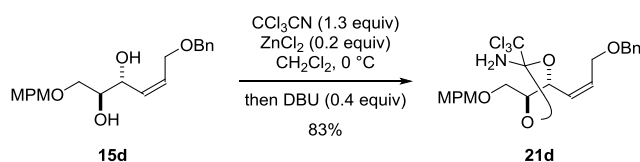


Following method A, *E*-trisubstituted allylic *syn*-diol **15c** (58.5 mg, 157 μmol) was converted to cyclic orthoamide **21c** (73.4 mg, 91%, two diastereomers, dr = 1:1): colorless oil; [α]<sub>D</sub><sup>29</sup> -26.3 (*c* 1.36, CHCl<sub>3</sub>); IR (film) 3415, 3337, 2915, 2857, 1612, 1514, 1248, 1094, 823 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.38–7.27 (m, 5H), 7.26 (d, *J* = 8.6 Hz, 1H), 7.25 (d, *J* = 8.6 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 1H), 5.61 (dq, *J* = 9.2, 1.4 Hz, 1/2H), 5.60 (dq, *J* = 9.2, 1.4 Hz, 1/2H), 5.21 (dd, *J* = 9.2, 8.9 Hz, 1/2H), 5.00 (dd, *J* = 9.2, 8.9 Hz, 1/2H), 4.59 (d, *J* = 11.7 Hz, 1/2H), 4.56 (d, *J* = 12.0 Hz, 1/2H), 4.53 (d, *J* = 11.7

Hz, 1/2H), 4.48 (d,  $J = 12.0$  Hz, 1/2H), 4.48 (d,  $J = 12.3$  Hz, 1/2H), 4.47 (d,  $J = 12.0$  Hz, 1/2H), 4.46 (d,  $J = 12.3$  Hz, 1/2H), 4.45 (d,  $J = 12.0$  Hz, 1/2H), 4.35 (ddd,  $J = 8.9, 5.7, 3.4$  Hz, 1/2H), 4.22 (ddd,  $J = 8.9, 4.0, 3.2$  Hz, 1/2H), 3.92 (s, 2H), 3.79 (s, 3/2H), 3.79 (s, 3/2H), 3.70 (dd,  $J = 11.2, 5.7$  Hz, 1/2H), 3.70 (dd,  $J = 11.2, 3.2$  Hz, 1/2H), 3.65 (dd,  $J = 11.2, 3.4$  Hz, 1/2H), 3.55 (dd,  $J = 11.2, 4.0$  Hz, 1/2H), 2.63 (brs, 2H), 1.71 (d,  $J = 1.4$  Hz, 3/2H), 1.70 (d,  $J = 1.4$  Hz, 3/2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  159.5 (C), 159.4 (C), 140.68 (C), 140.66 (C), 138.21 (C), 138.17 (C), 130.0 (C), 129.8 (C), 129.6 (CH), 129.4 (CH), 128.5 (CH), 128.5 (CH), 127.9 (CH), 127.84 (CH), 127.82 (CH), 127.81 (CH), 122.1 (CH), 121.2 (CH), 115.3 (C), 115.0 (C), 114.0 (CH), 113.9 (CH), 103.7 (C), 103.5 (C), 84.0 (CH), 82.4 (CH), 78.8 (CH), 76.1 (CH), 74.9 ( $\text{CH}_2$ ), 74.8 ( $\text{CH}_2$ ), 73.4 ( $\text{CH}_2$ ), 73.3 ( $\text{CH}_2$ ), 72.2 ( $\text{CH}_2$ ), 72.2 ( $\text{CH}_2$ ), 67.9 ( $\text{CH}_2$ ), 67.7 ( $\text{CH}_2$ ), 55.4 ( $\text{CH}_3$ ), 55.4 ( $\text{CH}_3$ ), 14.6 ( $\text{CH}_3$ ), 14.5 ( $\text{CH}_3$ ); HRMS (ESI) calcd for  $\text{C}_{24}\text{H}_{28}\text{Cl}_3\text{NO}_5\text{Na}$  ( $\text{M}+\text{Na}$ ) $^+$  538.0931, found 538.0938.

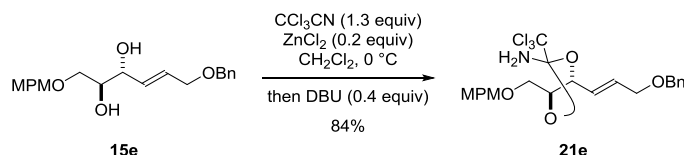
## [Method B: Synthesis of cyclic orthoamides from *anti*-diols]

### Cyclic orthoamide **21d**



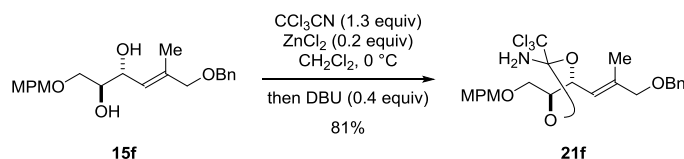
1,8-Diazabicyclo[5.4.0]undec-7-ene (8.9  $\mu\text{L}$ , 59  $\mu\text{mol}$ ) was added dropwise to a solution of *Z*-allylic *anti*-diol **15d** (106 mg, 296  $\mu\text{mol}$ ),  $\text{CCl}_3\text{CN}$  (39  $\mu\text{L}$ , 390  $\mu\text{mol}$ ),  $\text{ZnCl}_2$  (8.1 mg, 59.2  $\mu\text{mol}$ ) and  $\text{CH}_2\text{Cl}_2$  (3.0 mL) at  $0\text{ }^\circ\text{C}$ . The solution was maintained at  $0\text{ }^\circ\text{C}$  for 4 d, allowed to warm to room temperature, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:7) to give cyclic orthoamide **21d** (124 mg, 83%): colorless oil;  $[\alpha]_{\text{D}}^{28} -33.1$  ( $c$  1.28,  $\text{CHCl}_3$ ); IR (film) 3417, 3338, 2933, 2861, 1612, 1514, 1248, 1097, 823  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37–7.27 (m, 5H), 7.23 (d,  $J = 8.6$  Hz, 2H), 6.85 (d,  $J = 8.6$  Hz, 2H), 5.85 (dddd,  $J = 11.5, 6.6, 5.4, 1.2$  Hz, 1H), 5.69 (dddd,  $J = 11.5, 8.9, 1.7, 1.4$  Hz, 1H), 5.39 (ddd,  $J = 8.9, 7.7, 1.2$  Hz, 1H), 4.72 (ddd,  $J = 7.7, 7.2, 4.9$  Hz, 1H), 4.49 (d,  $J = 11.7$  Hz, 1H), 4.47 (d,  $J = 11.7$  Hz, 1H), 4.46 (d,  $J = 11.7$  Hz, 1H), 4.44 (d,  $J = 11.7$  Hz, 1H), 4.11 (ddd,  $J = 13.2, 6.6, 1.4$  Hz, 1H), 4.06 (ddd,  $J = 13.2, 5.4, 1.7$  Hz, 1H), 3.79 (s, 3H), 3.58 (dd,  $J = 10.3, 7.2$  Hz, 1H), 3.49 (dd,  $J = 10.3, 4.9$  Hz, 1H), 2.52 (brs, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  159.4 (C), 138.0 (C), 132.0 (CH), 130.0 (C), 129.5 (CH), 128.6 (CH), 127.9 (CH), 127.9 (CH), 126.2 (CH), 114.3 (C), 113.9 (CH), 102.6 (C), 79.5 (CH), 75.6 (CH), 73.1 ( $\text{CH}_2$ ), 72.7 ( $\text{CH}_2$ ), 68.2 ( $\text{CH}_2$ ), 66.0 ( $\text{CH}_2$ ), 55.4 ( $\text{CH}_3$ ); HRMS (ESI), calcd for  $\text{C}_{23}\text{H}_{26}\text{Cl}_3\text{NO}_5\text{Na}^+$  ( $\text{M}+\text{Na}$ ) $^+$  524.0774, found 524.0776.

### Cyclic orthoamide **21e**



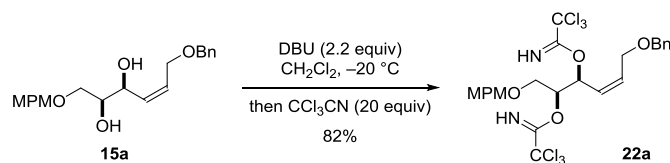
Following method B, *E*-allylic *anti*-diol **15e** (504 mg, 1.41 mmol) was converted to cyclic orthoamide **21e** (612 mg, 84%): yellow oil;  $[\alpha]_{\text{D}}^{22} -3.9$  (*c* 0.19,  $\text{CHCl}_3$ ); IR (film) 3413, 3336, 2924, 2855, 1513, 1248, 1100, 817  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36–7.27 (m, 5H), 7.23 (d,  $J = 8.6$  Hz, 2H), 6.83 (d,  $J = 8.6$  Hz, 2H), 6.00 (dtd,  $J = 15.5, 5.2, 0.6$  Hz, 1H), 5.82 (ddt,  $J = 15.5, 7.7, 1.4$  Hz, 1H), 5.10 (ddd,  $J = 7.7, 7.4, 0.6$  Hz, 1H), 4.75 (ddd,  $J = 7.4, 6.9, 5.7$  Hz, 1H), 4.50 (s, 2H), 4.48 (d,  $J = 11.8$  Hz, 1H), 4.44 (d,  $J = 11.8$  Hz, 1H), 4.05 (dd,  $J = 5.2, 1.4$  Hz, 2H), 3.78 (s, 3H), 3.59 (dd,  $J = 10.0, 6.9$  Hz, 1H), 3.50 (dd,  $J = 10.0, 5.7$  Hz, 1H), 2.53 (s, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  159.4 (C), 138.2 (C), 132.4 (CH), 130.0 (C), 129.5 (CH), 128.6 (CH), 127.8 (CH), 127.8 (CH), 125.2 (CH), 114.1 (C), 113.9 (CH), 102.6 (C), 79.8 (CH), 79.2 (CH), 73.2 ( $\text{CH}_2$ ), 72.5 ( $\text{CH}_2$ ), 69.7 ( $\text{CH}_2$ ), 68.2 ( $\text{CH}_2$ ), 55.4 ( $\text{CH}_3$ ); HRMS (FAB) calcd for  $\text{C}_{23}\text{H}_{26}\text{Cl}_3\text{NO}_5\text{Na}$  ( $\text{M}+\text{Na}$ ) $^+$  524.0775, found 524.0785.

### Cyclic orthoamide **21f**



Following method B, *E*-trisubstituted allylic *syn*-diol **15f** (97.2 mg, 261  $\mu\text{mol}$ ) was converted to cyclic orthoamide **21f** (110 mg, 81%): colorless oil;  $[\alpha]_{\text{D}}^{29} -13.3$  (*c* 1.19,  $\text{CHCl}_3$ ); IR (film) 3418, 3339, 2916, 2858, 1612, 1514, 1248, 1098, 823  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36–7.27 (m, 5H), 7.22 (d,  $J = 8.6$  Hz, 2H), 6.83 (d,  $J = 8.6$  Hz, 2H), 5.62 (dqdd,  $J = 9.2, 1.2, 0.9, 0.9$  Hz, 1H), 5.43 (dd,  $J = 9.2, 7.5$  Hz, 1H), 4.77 (ddd,  $J = 7.5, 7.5, 5.2$  Hz, 1H), 4.48 (d,  $J = 11.5$  Hz, 1H), 4.46 (d,  $J = 12.0$  Hz, 1H), 4.44 (d,  $J = 11.5$  Hz, 1H), 4.43 (d,  $J = 12.0$  Hz, 1H), 3.93 (dd,  $J = 13.2, 0.9$  Hz, 1H), 3.90 (dd,  $J = 13.2, 0.9$  Hz, 1H), 3.78 (s, 3H), 3.62 (dd,  $J = 10.3, 7.5$  Hz, 1H), 3.48 (dd,  $J = 10.3, 5.2$  Hz, 1H), 2.54 (brs, 2H), 1.72 (d,  $J = 1.2$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  159.4 (C), 139.5 (C), 138.3 (C), 130.1 (C), 129.5 (CH), 128.5 (CH), 127.8 (CH), 127.8 (CH), 120.1 (CH), 114.2 (C), 113.9 (CH), 102.7 (C), 79.4 (CH), 76.0 (CH), 74.9 ( $\text{CH}_2$ ), 73.2 ( $\text{CH}_2$ ), 72.1 ( $\text{CH}_2$ ), 68.4 ( $\text{CH}_2$ ), 55.4 ( $\text{CH}_3$ ), 14.6 ( $\text{CH}_3$ ); HRMS (ESI), calcd for  $\text{C}_{24}\text{H}_{29}\text{Cl}_3\text{NO}_5$  ( $\text{M}+\text{H}$ ) $^+$  516.1111, found 516.1109.

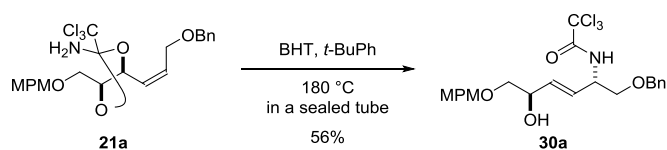
## Bisimidate **22a**



Trichloroacetonitrile (190  $\mu$ L, 1.9 mmol) was added quickly to a vigorously stirring solution of *Z*-allylic *syn*-diol **15a** (33.2 mg, 92.6  $\mu$ mol), DBU (30  $\mu$ L, 200  $\mu$ mol) and CH<sub>2</sub>Cl<sub>2</sub> (500  $\mu$ L) at -20 °C. The solution was maintained at -20 °C for 1 h, allowed to warm to room temperature, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:10 with 5.0 vol% Et<sub>3</sub>N) to give bisimidate **22a** (49.2 mg, 82%): colorless oil;  $[\alpha]_D^{24}$  -0.5 (*c* 0.93, CHCl<sub>3</sub>); IR (film) 3342, 2857, 1664, 1512, 1297, 1249, 1073, 795, 646 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.41 (s, 1H), 8.35 (s, 1H), 7.35–7.26 (m, 5H), 7.23–7.18 (m, 2H), 6.85–6.82 (m, 2H), 6.04 (dd, *J* = 9.5, 6.6 Hz, 1H), 5.97–5.92 (m, 1H), 5.56 (dddd, *J* = 11.2, 9.5, 2.0, 1.7 Hz, 1H), 5.47 (ddd, *J* = 6.6, 4.6, 4.1 Hz, 1H), 4.50 (d, *J* = 11.8 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 4.45 (s, 2H), 4.39 (ddd, *J* = 13.2, 6.9, 1.7 Hz, 1H), 4.25 (ddd, *J* = 13.2, 5.2, 2.0 Hz, 1H), 3.79 (s, 3H), 3.75 (dd, *J* = 10.9, 4.1 Hz, 1H), 3.68 (dd, *J* = 10.9, 4.6 Hz, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  162.3 (C), 161.3 (C), 159.4 (C), 138.3 (C), 135.0 (CH), 123.0 (C), 129.4 (CH), 128.5 (CH), 127.9 (CH), 127.7 (CH), 124.2 (CH), 113.9 (CH), 91.45 (C), 91.45 (C), 77.9 (CH), 73.6 (CH), 73.3 (CH<sub>2</sub>), 72.7 (CH<sub>2</sub>), 67.1 (CH<sub>2</sub>), 66.9 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>); HRMS (FAB) calcd for C<sub>25</sub>H<sub>27</sub>Cl<sub>6</sub>N<sub>2</sub>O<sub>5</sub> (M+H)<sup>+</sup> 645.0051, found 645.0031.

## [Method C: The orthoamide-type Overman rearrangement]

### Allylic amino alcohol **30a**

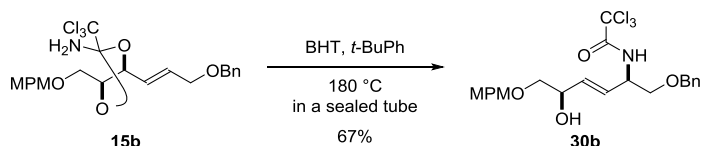


A sealed tube was charged with cyclic orthoamide **21a** (204 mg, 406  $\mu$ mol), 2,6-di-*tert*-butylhydroxytoluene (4.8 mg, 21.8  $\mu$ mol) and *t*-BuPh (15 mL). The solution was then purged with a flow of argon for 20 min, and heated to 180 °C for 27 h. After cooling to room temperature, the resulting mixture was directly purified by silica gel column chromatography (EtOAc/hexane 1:3 to 1:2) to give allylic amino alcohol **30a** (114 mg, 56%), along with recovery of **21a** (27%). **30a**: yellow oil;  $[\alpha]_D^{27}$  -0.68 (*c* 0.91, CHCl<sub>3</sub>); IR (film) 3420, 2960, 1720, 1510, 1360, 1250, 1100, 820 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.36–7.28 (m, 5H), 7.27–7.23 (m, 2H), 7.09 (d, *J* = 8.0 Hz, 1H), 6.90–6.86 (m, 2H), 5.87 (ddd, *J* = 15.5, 6.0, 1.4 Hz, 1H), 5.73 (ddd, *J* = 15.5, 5.4, 1.4 Hz, 1H), 4.58 (m, 1H), 4.54 (s, 2H), 4.49 (s, 2H), 4.36 (m, 1H), 3.80 (s, 3H), 3.63 (dd, *J* = 9.8, 4.0 Hz, 1H), 3.58 (dd, *J* = 9.8, 4.0 Hz, 1H), 3.49 (dd, *J* = 9.5,



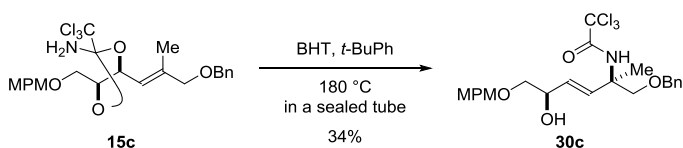
3.2 Hz, 1H), 3.31 (dd,  $J = 9.5, 8.0$  Hz, 1H), 2.49 (brs, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  161.3 (C), 159.5 (C), 137.5 (C), 131.8 (CH), 129.9 (C), 129.6 (CH), 128.7 (CH), 128.1 (CH), 127.92 (CH), 127.89 (CH), 114.0 (CH), 92.8 (C), 73.7 ( $\text{CH}_2$ ), 73.4 ( $\text{CH}_2$ ), 73.2 ( $\text{CH}_2$ ), 70.9 ( $\text{CH}_2$ ), 70.6 (CH), 55.4 ( $\text{CH}_3$ ), 52.6 (CH); HRMS (FAB) calcd for  $\text{C}_{23}\text{H}_{27}\text{Cl}_2^{37}\text{ClNO}_5$  ( $\text{M}+\text{H}$ ) $^+$  504.0925, found 504.0923.

### Allylic amino alcohol 30b



Following method C, cyclic orthoamide **15b** (205 mg, 407  $\mu\text{mol}$ ) was converted to allylic amino alcohol **30b** (138 mg, 67%): yellow oil;  $[\alpha]_{\text{D}}^{24} -0.44$  (*c* 1.11,  $\text{CHCl}_3$ ); IR (film) 3416, 3335, 2906, 2862, 1712, 1513, 1248, 1101, 821  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37–7.28 (m, 5H), 7.25 (d,  $J = 8.6$  Hz, 2H), 7.10 (d,  $J = 8.0$  Hz, 1H), 6.88 (d,  $J = 8.6$  Hz, 2H), 5.87 (ddd,  $J = 15.8, 6.3, 1.4$  Hz, 1H), 5.73 (ddd,  $J = 15.8, 5.4, 1.1$  Hz, 1H), 4.61–4.55 (m, 1H), 4.56 (d,  $J = 12.3$  Hz, 1H), 4.53 (d,  $J = 12.3$  Hz, 1H), 4.50 (d,  $J = 11.7$  Hz, 1H), 4.48 (d,  $J = 11.7$  Hz, 1H), 4.38–4.33 (m, 1H), 3.81 (s, 3H), 3.63 (dd,  $J = 9.8, 4.0$  Hz, 1H), 3.58 (dd,  $J = 9.8, 4.0$  Hz, 1H), 3.50 (dd,  $J = 9.7, 3.4$  Hz, 1H), 3.31 (dd,  $J = 9.7, 8.0$  Hz, 1H), 2.52 (brs, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  161.3 (C), 159.5 (C), 137.5 (C), 131.8 (CH), 129.9 (C), 129.6 (CH), 128.7 (CH), 128.1 (CH), 127.91 (CH), 127.88 (CH), 114.0 (CH), 92.8 (C), 73.7 ( $\text{CH}_2$ ), 73.4 ( $\text{CH}_2$ ), 73.2 ( $\text{CH}_2$ ), 70.8 ( $\text{CH}_2$ ), 70.6 (CH), 55.4 ( $\text{CH}_3$ ), 52.5 (CH); HRMS (FAB) calcd for  $\text{C}_{23}\text{H}_{26}\text{Cl}_3\text{NO}_5\text{Na}$  ( $\text{M}+\text{Na}$ ) $^+$  524.0775, found 524.0759.

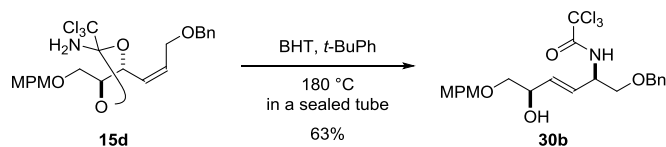
### Allylic amino alcohol 30c



Following method C, cyclic orthoamide **15c** (28.9 mg, 55.9  $\mu\text{mol}$ ) was converted to allylic amino alcohol **30c** (10.0 mg, 34%): colorless oil;  $[\alpha]_{\text{D}}^{27} -3.3$  (*c* 1.05,  $\text{CHCl}_3$ ); IR (film) 3398, 2906, 2862, 1722, 1613, 1513, 1248, 1099, 821  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37–7.28 (m, 5H), 7.25 (d,  $J = 8.6$  Hz, 2H), 7.20 (s, 1H), 6.88 (d,  $J = 8.6$  Hz, 2H), 5.90 (dd,  $J = 16.0, 1.4$  Hz, 1H), 5.64 (dd,  $J = 16.0, 5.7$  Hz, 1H), 4.58 (d,  $J = 12.6$  Hz, 1H), 4.55 (d,  $J = 12.6$  Hz, 1H), 4.50 (d,  $J = 12.0$  Hz, 1H), 4.47 (d,  $J = 12.0$  Hz, 1H), 4.35 (dddd,  $J = 8.0, 5.7, 3.4, 1.4$  Hz, 1H), 3.80 (s, 3H), 3.51 (d,  $J = 9.2$  Hz, 1H), 3.50 (dd,  $J = 9.7, 3.4$  Hz, 1H), 3.43 (d,  $J = 9.2$  Hz, 1H), 3.33 (dd,  $J = 9.7, 8.0$  Hz, 1H), 2.53 (brs, 1H), 1.53 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  160.5 (C), 159.5 (C), 137.6 (C), 132.3 (CH), 130.1 (C), 129.6 (CH), 129.4 (CH), 128.7 (CH),

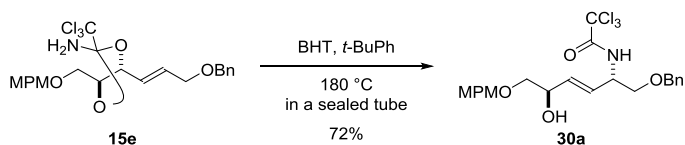
128.1 (CH), 127.8 (CH), 114.0 (CH), 93.3 (C), 75.1 (CH<sub>2</sub>), 73.9 (CH<sub>2</sub>), 73.5 (CH<sub>2</sub>), 73.2 (CH<sub>2</sub>), 70.8 (CH), 58.0 (C), 55.4 (CH<sub>3</sub>), 21.3 (CH<sub>3</sub>); HRMS (ESI), calcd for C<sub>24</sub>H<sub>28</sub>Cl<sub>3</sub>NO<sub>5</sub>Na<sup>+</sup> (M+Na)<sup>+</sup> 538.0931, found 538.0933.

### Allylic amino alcohol 30b



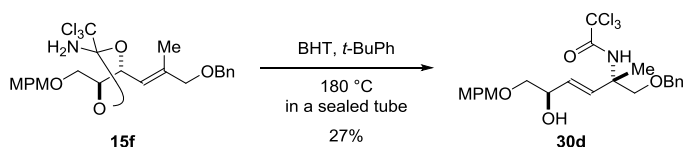
Following method C, cyclic orthoamide **15d** (28.7 mg, 57.1 μmol) was converted to allylic amino alcohol **30b** (18.1 mg, 63%).

### Allylic amino alcohol 30a



Following method C, cyclic orthoamide **15e** (200 mg, 399 μmol) was converted to allylic amino alcohol **30a** (144 mg, 72%).

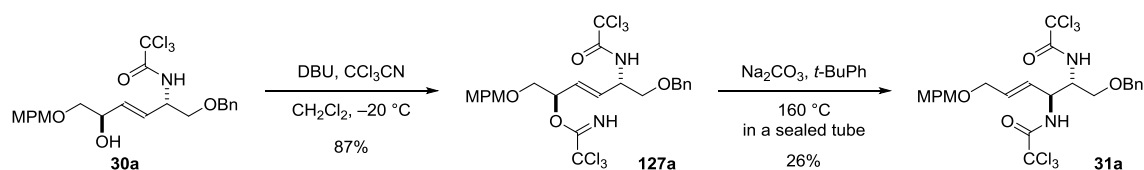
### Allylic amino alcohol 30d



Following method C, cyclic orthoamide **15f** (28.8 mg, 55.7 μmol) was converted to allylic amino alcohol **30d** (7.7 mg, 27%): colorless oil;  $[\alpha]_D^{27} -1.0$  (*c* 0.84, CHCl<sub>3</sub>); IR (film) 3398, 2907, 2862, 1722, 1613, 1513, 1248, 1099, 821 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.37–7.28 (m, 5H), 7.25 (d, *J* = 8.6 Hz, 2H), 7.22 (s, 1H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.90 (dd, *J* = 16.0, 1.4 Hz, 1H), 5.64 (dd, *J* = 16.0, 6.0 Hz, 1H), 4.58 (d, *J* = 12.3 Hz, 1H), 4.55 (d, *J* = 12.3 Hz, 1H), 4.49 (s, 2H), 4.35 (dddd, *J* = 8.3, 6.0, 3.4, 1.4 Hz, 1H), 3.81 (s, 3H), 3.51 (dd, *J* = 9.5, 3.4 Hz, 1H), 3.51 (d, *J* = 9.2 Hz, 1H), 3.43 (d, *J* = 9.2 Hz, 1H), 3.34 (dd, *J* = 9.5, 8.3 Hz, 1H), 2.53 (brs, 1H), 1.53 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 160.5 (C), 159.5 (C), 137.6 (C), 132.6 (CH), 130.0 (C), 129.6 (CH), 129.4 (CH), 128.7 (CH), 128.1 (CH), 127.8 (CH), 114.0 (CH), 93.3 (C), 75.2 (CH<sub>2</sub>), 73.9 (CH<sub>2</sub>), 73.5 (CH<sub>2</sub>), 73.2 (CH<sub>2</sub>), 71.0 (CH), 58.0 (C), 55.4 (CH<sub>3</sub>), 21.1 (CH<sub>3</sub>); HRMS (ESI), calcd for C<sub>24</sub>H<sub>28</sub>Cl<sub>3</sub>NO<sub>5</sub>Na<sup>+</sup> (M+Na)<sup>+</sup> 538.0931, found 538.0939.

## [Method D: Overman rearrangement]

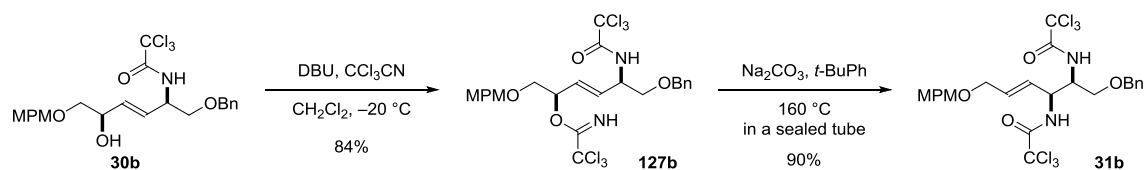
### Bisamide 31a



Trichloroacetonitrile (16  $\mu\text{L}$ , 160  $\mu\text{mol}$ ) was added quickly to a vigorously stirring solution of allylic amino alcohol **30a** (4.1 mg, 8.15  $\mu\text{mol}$ ), DBU (3.9  $\mu\text{L}$ , 26  $\mu\text{mol}$ ) and CH<sub>2</sub>Cl<sub>2</sub> (500  $\mu\text{L}$ ) at -20 °C. The solution was maintained for 1 h at -20 °C, allowed to warm to room temperature, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:3 to 1:1 with 5.0 vol% Et<sub>3</sub>N) to give imidate **127a** (4.6 mg, 87%): colorless oil;  $[\alpha]_{\text{D}}^{20}$  -4.0 (*c* 0.86, CHCl<sub>3</sub>); IR (film) 3418, 3340, 2933, 2863, 1716, 1663, 1513, 1248, 1083, 820, 795 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.38 (s, 1H), 7.36–7.27 (m, 5H), 7.24 (d, *J* = 8.6 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.96 (ddd, *J* = 15.8, 5.8, 1.2 Hz, 1H), 5.81 (ddd, *J* = 15.8, 5.7, 1.5 Hz, 1H), 5.65 (dddd, *J* = 6.6, 5.7, 3.7, 1.2 Hz, 1H), 4.62 (dddd, *J* = 8.1, 5.8, 4.0, 3.7, 1.5 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 11.8 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.51 (d, *J* = 11.8 Hz, 1H), 3.80 (s, 3H), 3.68 (dd, *J* = 10.9, 6.6 Hz, 1H), 3.63 (dd, *J* = 10.9, 3.7 Hz, 1H), 3.62 (dd, *J* = 9.7, 3.7 Hz, 1H), 3.58 (dd, *J* = 9.7, 4.0 Hz, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  161.8 (C), 161.4 (C), 159.4 (C), 137.5 (C), 130.1 (C), 129.9 (CH), 129.4 (CH), 128.7 (CH), 128.1 (CH), 127.8 (CH), 127.6 (CH), 113.9 (CH), 92.7 (C), 91.6 (C), 77.1 (CH), 73.4 (CH<sub>2</sub>), 73.1 (CH<sub>2</sub>), 70.74 (CH<sub>2</sub>), 70.69 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>), 52.3 (CH); HRMS (ESI), calcd for C<sub>25</sub>H<sub>26</sub>Cl<sub>6</sub>N<sub>2</sub>O<sub>5</sub>Na<sup>+</sup> (M+Na)<sup>+</sup> 666.9871, found 666.9873.

A sealed tube was charged with bisimidate **127a** (4.6 mg, 4.48  $\mu\text{mol}$ ), Na<sub>2</sub>CO<sub>3</sub> (0.2 mg, 1.79  $\mu\text{mol}$ ) and *t*-BuPh (0.6 mL), and the solution was purged for 5 min with a flow of argon. The solution was heated to 160 °C for 30 min. After cooling to room temperature, the resulting mixture was directly purified by silica gel column chromatography (EtOAc/hexane 1:9 to 1:2) to give bisamide **31a** (1.2 mg, 26%): colorless crystals; mp 81.0–83.0 °C;  $[\alpha]_{\text{D}}^{24}$  +4.4 (*c* 0.66, CHCl<sub>3</sub>); IR (film) 3418, 3333, 2927, 2856, 1718, 1514, 1249, 821 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.01 (d, *J* = 8.6 Hz, 1H), 7.38–7.25 (m, 6H), 7.25 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.83 (dtd, *J* = 15.5, 4.9, 1.4 Hz, 1H), 5.69 (ddt, *J* = 15.5, 5.2, 1.4 Hz, 1H), 4.86–4.81 (m, 1H), 4.54 (d, *J* = 11.2 Hz, 1H), 4.51 (d, *J* = 11.2 Hz, 1H), 4.44 (s, 2H), 4.20–4.15 (m, 1H), 4.00 (ddd, *J* = 4.9, 1.4, 1.4 Hz, 2H), 3.96 (dd, *J* = 10.0, 2.3 Hz, 1H), 3.81 (s, 3H), 3.66 (dd, *J* = 10.0, 3.2 Hz, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  162.0 (C), 161.8 (C), 159.4 (C), 136.3 (C), 130.8 (CH), 130.1 (C), 129.5 (CH), 128.9 (CH), 128.8 (CH), 128.6 (CH), 126.0 (CH), 114.0 (CH), 92.6 (C), 92.3 (C), 74.5 (CH<sub>2</sub>), 72.3 (CH<sub>2</sub>), 69.2 (CH<sub>2</sub>), 68.8 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>), 54.8 (CH), 52.4 (CH); HRMS (FAB) calcd for C<sub>25</sub>H<sub>27</sub>Cl<sub>5</sub><sup>37</sup>Cl N<sub>2</sub>O<sub>5</sub> (M+H)<sup>+</sup> 647.0022, found 647.0053.

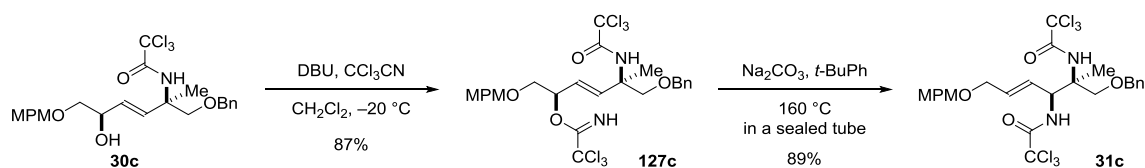
## Bisamide 31b



Following method D, allylic amino alcohol **30b** (5.0 mg, 9.94  $\mu\text{mol}$ ) was converted to imidate **127b** (5.4 mg, 84%): colorless oil;  $[\alpha]_{\text{D}}^{20} -13.0$  (*c* 0.74, CHCl<sub>3</sub>); IR (film) 3418, 3339, 2934, 2863, 1716, 1663, 1513, 1248, 1081, 820, 796  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.37 (s, 1H), 7.36–7.26 (m, 5H), 7.24 (d, *J* = 8.6 Hz, 2H), 7.08 (d, *J* = 8.3 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.97 (ddd, *J* = 15.8, 6.0, 1.2 Hz, 1H), 5.83 (ddd, *J* = 15.8, 5.7, 1.5 Hz, 1H), 5.65 (dddd, *J* = 6.6, 5.7, 4.3, 1.2 Hz, 1H), 4.61 (dddd, *J* = 8.3, 6.0, 4.0, 4.0, 1.5 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 11.7 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.51 (d, *J* = 11.7 Hz, 1H), 3.80 (s, 3H), 3.67 (dd, *J* = 10.9, 6.6 Hz, 1H), 3.64 (dd, *J* = 10.9, 4.3 Hz, 1H), 3.64 (dd, *J* = 9.7, 4.0 Hz, 1H), 3.58 (dd, *J* = 9.7, 4.0 Hz, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  161.8 (C), 161.4 (C), 159.4 (C), 137.5 (C), 130.1 (C), 129.9 (CH), 129.4 (CH), 128.7 (CH), 128.1 (CH), 127.8 (CH), 127.7 (CH), 113.9 (CH), 92.7 (C), 91.6 (C), 77.2 (CH), 73.4 (CH<sub>2</sub>), 73.1 (CH<sub>2</sub>), 70.73 (CH<sub>2</sub>), 70.67 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>), 52.4 (CH); HRMS (ESI), calcd for C<sub>25</sub>H<sub>26</sub>Cl<sub>6</sub>N<sub>2</sub>O<sub>5</sub>Na<sup>+</sup> (M+Na)<sup>+</sup> 666.9871, found 666.9870.

Following the method D, imidate **127b** (2.9 mg, 4.48  $\mu\text{mol}$ ) was converted to bisamide **31b** (2.6 mg, 90%): colorless crystals; mp 40.0–41.0 °C;  $[\alpha]_{\text{D}}^{21} +20.2$  (*c* 0.53, CHCl<sub>3</sub>); IR (film) 3325, 2931, 2856, 1691, 1514, 1249, 820  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.38 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.6 Hz, 1H), 7.37–7.29 (m, 5H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.88 (ddd, *J* = 15.5, 4.9, 4.9 Hz, 1H), 5.60 (dddd, *J* = 15.5, 7.7, 1.4, 1.4 Hz, 1H), 4.75 (ddd, *J* = 10.0, 8.0, 7.7 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.42 (s, 2H), 4.11 (dddd, *J* = 10.0, 8.6, 4.0, 2.3 Hz, 1H), 3.97 (ddd, *J* = 13.8, 4.9, 1.4 Hz, 1H), 3.93 (ddd, *J* = 13.8, 4.9, 1.4 Hz, 1H), 3.81 (s, 3H), 3.68 (dd, *J* = 9.7, 2.3 Hz, 1H), 3.55 (dd, *J* = 9.7, 4.0 Hz, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  163.2 (C), 162.1 (C), 159.5 (C), 136.9 (C), 133.4 (CH), 130.1 (C), 129.5 (CH), 128.8 (CH), 128.5 (CH), 128.3 (CH), 125.7 (CH), 114.0 (CH), 92.4 (C), 92.2 (C), 73.8 (CH<sub>2</sub>), 72.3 (CH<sub>2</sub>), 69.0 (CH<sub>2</sub>), 67.3 (CH<sub>2</sub>), 55.43 (CH<sub>3</sub>), 55.37 (CH), 53.9 (CH); HRMS (FAB) calcd for C<sub>25</sub>H<sub>27</sub>Cl<sub>6</sub>N<sub>2</sub>O<sub>5</sub> (M+H)<sup>+</sup> 645.0051, found 645.0022.

## Bisamide 31c

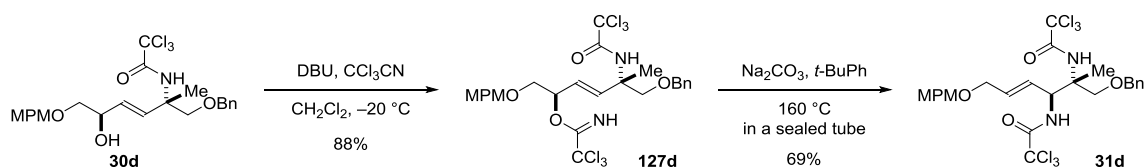


Following method D, allylic amino alcohol **30c** (2.4 mg, 4.64  $\mu\text{mol}$ ) was converted to imidate **127b** (2.7 mg, 87%): colorless oil;  $[\alpha]_{\text{D}}^{20} -20.8$  (*c* 0.75, CHCl<sub>3</sub>); IR (film) 3396, 3341, 2935, 2862, 1724, 1663, 1512,

1248, 1086, 820, 796  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.36 (s, 1H), 7.37–7.27 (m, 5H), 7.25 (d,  $J = 8.6$  Hz, 2H), 7.19 (s, 1H), 6.86 (d,  $J = 8.6$  Hz, 2H), 6.02 (dd,  $J = 15.8, 1.2$  Hz, 1H), 5.73 (dd,  $J = 15.8, 6.0$  Hz, 1H), 5.64 (dddd,  $J = 6.6, 6.0, 4.3, 1.2$  Hz, 1H), 4.57 (d,  $J = 12.3$  Hz, 1H), 4.54 (d,  $J = 12.3$  Hz, 1H), 4.54 (d,  $J = 11.8$  Hz, 1H), 4.51 (d,  $J = 11.8$  Hz, 1H), 3.80 (s, 3H), 3.68 (dd,  $J = 10.9, 6.6$  Hz, 1H), 3.65 (dd,  $J = 10.9, 4.3$  Hz, 1H), 3.50 (d,  $J = 9.2$  Hz, 1H), 3.45 (d,  $J = 9.2$  Hz, 1H), 1.53 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  161.8 (C), 160.5 (C), 159.3 (C), 137.6 (C), 134.4 (CH), 130.2 (C), 129.3 (CH), 128.7 (CH), 128.1 (CH), 127.7 (CH), 125.2 (CH), 113.9 (CH), 93.2 (C), 91.7 (C), 77.4 (CH), 75.0 ( $\text{CH}_2$ ), 73.5 ( $\text{CH}_2$ ), 73.1 ( $\text{CH}_2$ ), 71.0 ( $\text{CH}_2$ ), 57.9 (C), 55.4 ( $\text{CH}_3$ ), 21.3 ( $\text{CH}_3$ ); HRMS (ESI), calcd for  $\text{C}_{26}\text{H}_{28}\text{Cl}_6\text{N}_2\text{O}_5\text{Na}^+$  ( $\text{M}+\text{Na}$ ) $^+$  681.0027, found 681.0029.

Following the method D, imidate **127c** (2.7 mg, 4.08  $\mu\text{mol}$ ) was converted to bisamide **31c** (2.4 mg, 89%): colorless oil;  $[\alpha]_{\text{D}}^{15} -1.4$  ( $c$  1.02,  $\text{CHCl}_3$ ); IR (film) 3321, 2936, 2855, 1713, 1612, 1513, 1248, 1098, 821  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.40 (d,  $J = 8.6$  Hz, 1H), 7.36–7.28 (m, 5H), 7.23 (d,  $J = 8.6$  Hz, 2H), 6.93 (s, 1H), 6.87 (d,  $J = 8.6$  Hz, 2H), 5.90 (dtd,  $J = 15.5, 4.9, 1.2$  Hz, 1H), 5.68 (ddt,  $J = 15.5, 7.5, 1.7$  Hz, 1H), 4.74 (ddd,  $J = 8.6, 7.5, 1.2, 0.9$  Hz, 1H), 4.56 (d,  $J = 11.7$  Hz, 1H), 4.50 (d,  $J = 11.7$  Hz, 1H), 4.43 (s, 2H), 3.99 (ddd,  $J = 4.9, 1.7, 0.9$  Hz, 2H), 3.81 (s, 3H), 3.73 (d,  $J = 9.5$  Hz, 1H), 3.59 (d,  $J = 9.5$  Hz, 1H), 1.52 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  162.4 (C), 161.9 (C), 159.4 (C), 137.2 (C), 133.1 (CH), 130.1 (C), 129.5 (CH), 128.7 (CH), 128.3 (CH), 128.2 (CH), 124.5 (CH), 114.0 (CH), 92.75 (C), 92.72 (C), 74.0 ( $\text{CH}_2$ ), 72.2 ( $\text{CH}_2$ ), 71.1 ( $\text{CH}_2$ ), 69.2 ( $\text{CH}_2$ ), 60.5 (C), 58.4 (CH), 55.4 ( $\text{CH}_3$ ), 20.8 ( $\text{CH}_3$ ); HRMS (ESI), calcd for  $\text{C}_{26}\text{H}_{28}\text{Cl}_6\text{N}_2\text{O}_5\text{Na}^+$  ( $\text{M}+\text{Na}$ ) $^+$  681.0027, found 681.0035.

### Bisamide 31d

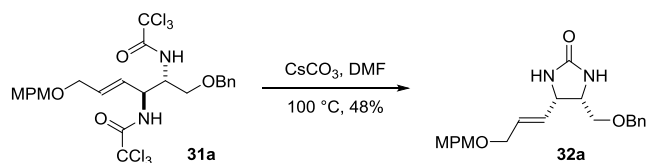


Following method D, allylic amino alcohol **30d** (2.0 mg, 3.87  $\mu\text{mol}$ ) was converted to imidate **127d** (2.3 mg, 88%): colorless oil;  $[\alpha]_{\text{D}}^{22} -5.4$  ( $c$  1.03,  $\text{CHCl}_3$ ); IR (film) 3397, 3342, 2935, 2863, 1724, 1662, 1512, 1248, 1080, 820, 795  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.36 (s, 1H), 7.37–7.28 (m, 5H), 7.25 (d,  $J = 8.6$  Hz, 2H), 7.21 (s, 1H), 6.86 (d,  $J = 8.6$  Hz, 2H), 6.02 (d,  $J = 15.8$  Hz, 1H), 5.73 (dd,  $J = 15.8, 6.0$  Hz, 1H), 5.65 (ddd,  $J = 6.9, 6.0, 4.0$  Hz, 1H), 4.56 (s, 2H), 4.54 (d,  $J = 11.8$  Hz, 1H), 4.51 (d,  $J = 11.8$  Hz, 1H), 3.80 (s, 3H), 3.69 (dd,  $J = 10.9, 6.9$  Hz, 1H), 3.65 (dd,  $J = 10.9, 4.0$  Hz, 1H), 3.49 (d,  $J = 9.2$  Hz, 1H), 3.43 (d,  $J = 9.2$  Hz, 1H), 1.53 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  161.7 (C), 160.5 (C), 159.3 (C), 137.6 (C), 134.5 (CH), 130.2 (C), 129.3 (CH), 128.7 (CH), 128.1 (CH), 127.7 (CH), 125.3 (CH), 113.9 (CH), 93.2 (C), 91.7 (C), 77.5 (CH), 75.1 ( $\text{CH}_2$ ), 73.5 ( $\text{CH}_2$ ), 73.1 ( $\text{CH}_2$ ), 71.0 ( $\text{CH}_2$ ), 58.0 (C), 55.4 ( $\text{CH}_3$ ), 21.1 ( $\text{CH}_3$ ); HRMS (ESI), calcd for  $\text{C}_{26}\text{H}_{28}\text{Cl}_6\text{N}_2\text{O}_5\text{Na}^+$  ( $\text{M}+\text{Na}$ ) $^+$  681.0027, found 681.0026.

Following the method D, imidate **127d** (2.8 mg, 4.24  $\mu\text{mol}$ ) was converted to bisamide **31d** (1.5 mg, 54%): colorless oil;  $[\alpha]_{\text{D}}^{15} +7.4$  (*c* 1.17,  $\text{CHCl}_3$ ); IR (film) 3360, 2934, 2859, 1724, 1612, 1513, 1248, 1077, 821  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.68 (d, *J* = 9.2 Hz, 1H), 7.38–7.29 (m, 6H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.87 (dddd, *J* = 15.5, 4.9, 4.9, 1.2 Hz, 1H), 5.65 (dddd, *J* = 15.5, 6.9, 1.7, 1.4 Hz, 1H), 4.69–4.64 (m, 1H), 4.57 (s, 2H), 4.42 (s, 2H), 4.02–3.94 (m, 2H), 3.81 (s, 3H), 3.68 (d, *J* = 13.8 Hz, 1H), 3.66 (d, *J* = 13.8 Hz, 1H), 1.45 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  161.83 (C), 161.80 (C), 159.4 (C), 136.4 (C), 132.6 (CH), 130.2 (C), 129.5 (CH), 128.9 (CH), 128.7 (CH), 128.4 (CH), 124.9 (CH), 114.0 (CH), 92.80 (C), 92.76 (C), 74.2 ( $\text{CH}_2$ ), 73.2 ( $\text{CH}_2$ ), 72.2 ( $\text{CH}_2$ ), 69.2 ( $\text{CH}_2$ ), 59.5 (C), 57.7 (CH), 55.4 ( $\text{CH}_3$ ), 19.2 ( $\text{CH}_3$ ); HRMS (ESI), calcd for  $\text{C}_{26}\text{H}_{28}\text{Cl}_6\text{N}_2\text{O}_5\text{Na}^+$  ( $\text{M}+\text{Na}$ ) $^+$  681.0027, found 681.0046.

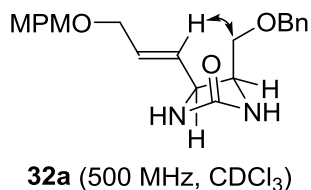
### [Method E: Stereochemical determination of the orthoamide-type Overman rearrangement]

#### Cyclic urea **32a**

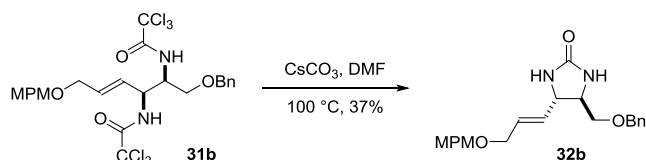


Cesium carbonate (64.9 mg, 199  $\mu\text{mol}$ ) was added to a solution of bisamide **31a** (43.0 mg, 66.4  $\mu\text{mol}$ ) and DMF (2.0 mL), and the mixture was heated to at 100  $^{\circ}\text{C}$  for 45 min. After cooling to room temperature, the resulting mixture was quenched with saturated aqueous  $\text{NaHCO}_3$  (10 mL), and extracted with EtOAc (3x 30 mL). The combined organic extracts were washed with water (20 mL) and brine (30 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:1 to 1:0) to give cyclic urea **32a** (12.3 mg, 48%): yellow oil;  $[\alpha]_{\text{D}}^{20} +9.1$  (*c* 0.62,  $\text{CHCl}_3$ ); IR (film) 3269, 2857, 1709, 1513, 1247, 1107  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36–7.27 (m, 5H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.84 (dt, *J* = 15.5, 5.4 Hz, 1H), 5.70 (ddt, *J* = 15.5, 7.5, 1.4 Hz, 1H), 4.86 (brs, 1H), 4.60 (brs, 1H), 4.51 (d, *J* = 11.8 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 4.43 (s, 2H), 4.37 (dd, *J* = 8.6, 7.5 Hz, 1H), 3.99 (ddd, *J* = 8.6, 8.6, 4.9 Hz, 1H), 3.97 (dd, *J* = 5.4, 1.4 Hz, 2H), 3.81 (s, 3H), 3.45 (dd, *J* = 9.2, 4.9 Hz, 1H), 3.42 (dd, *J* = 9.2, 8.6 Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  162.6 (C), 159.4 (C), 137.7 (C), 131.2 (CH), 130.1 (C), 129.5 (CH), 128.7 (CH), 128.1 (CH), 127.8 (CH), 127.4 (CH), 114.0 (CH), 73.7 ( $\text{CH}_2$ ), 72.4 ( $\text{CH}_2$ ), 70.1 ( $\text{CH}_2$ ), 69.4 ( $\text{CH}_2$ ), 56.2 (CH), 55.6 (CH), 55.4 ( $\text{CH}_3$ ); LRMS (EI) *m/z* 382 ( $\text{M}^+$ , 0.4%), 246 (10), 121 (100), 91 (51), 77 (19), 72 (15); HRMS (EI), calcd for  $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_4$   $\text{M}^+$  382.1893, found 382.1892.

NOESY experiment for **32a**

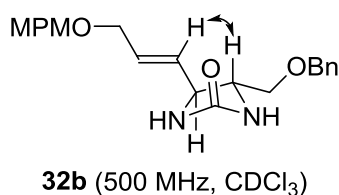


Cyclic urea **32b**

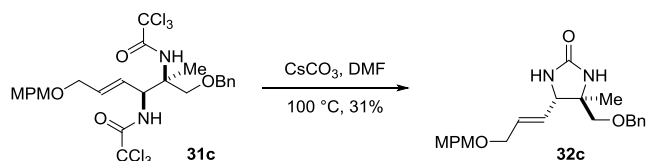


Following method E, bisamide **31b** (33.3 mg, 51.5  $\mu\text{mol}$ ) was converted to cyclic urea **32b** (7.3 mg, 54%): yellow oil;  $[\alpha]_{\text{D}}^{20}$   $-34.7$  ( $c$  0.37, CHCl<sub>3</sub>); IR (film) 3230, 2857, 1708, 1513, 1248, 1112  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.37–7.28 (m, 5H), 7.25 (d,  $J$  = 8.6 Hz, 2H), 6.88 (d,  $J$  = 8.6 Hz, 2H), 5.80–5.72 (m, 2H), 4.94 (d,  $J$  = 11.8 Hz, 1H), 4.77 (d,  $J$  = 16.6 Hz, 1H), 4.53 (s, 2H), 4.44 (s, 2H), 3.97 (d,  $J$  = 3.7 Hz, 2H), 3.93–3.89 (m, 1H), 3.80 (s, 3H), 3.67–3.62 (m, 1H), 3.50 (dd,  $J$  = 9.2, 4.3 Hz, 1H), 3.45 (dd,  $J$  = 9.2, 7.8 Hz, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  162.2 (C), 159.4 (C), 137.7 (C), 131.4 (CH), 130.1 (C), 130.0 (CH), 129.6 (CH), 128.7 (CH), 128.1 (CH), 127.9 (CH), 114.0 (CH), 73.6 (CH<sub>2</sub>), 72.4 (CH<sub>2</sub>), 71.9 (CH<sub>2</sub>), 69.4 (CH<sub>2</sub>), 58.5 (CH), 57.1 (CH), 55.4 (CH<sub>3</sub>); LRMS (EI)  $m/z$  382 ( $\text{M}^+$ , 0.7%), 246 (16), 121 (100), 91 (45), 77 (17), 56 (18); HRMS (EI), calcd for C<sub>22</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>  $\text{M}^+$  382.1893, found 382.1878.

NOESY experiment for **32b**



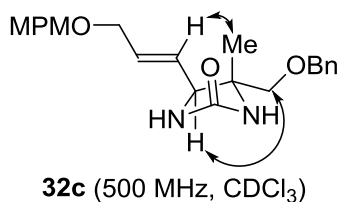
Cyclic urea **32c**



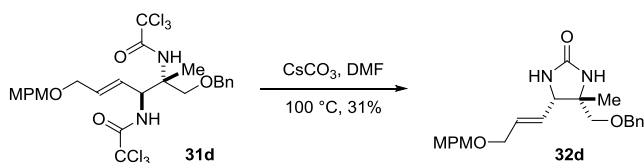
Following method E, bisamide **31c** (67.2 mg, 102  $\mu\text{mol}$ ) was converted to cyclic urea **32c** (12.6 mg, 31%): colorless crystals; mp 116–117 °C;  $[\alpha]_{\text{D}}^{15}$   $-43.4$  ( $c$  1.17, CHCl<sub>3</sub>); IR (film) 3222, 2932, 2855, 1707, 1613, 1514, 1249, 1104  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.37–7.27 (m, 5H), 7.25 (d,  $J$  = 8.6 Hz, 2H), 6.88

(d,  $J = 8.6$  Hz, 2H), 5.77 (dt,  $J = 15.5, 4.9$  Hz, 1H), 5.71 (ddt,  $J = 15.5, 6.9, 0.9$  Hz, 1H), 5.00 (brs, 1H), 4.88 (brs, 1H), 4.55 (s, 2H), 4.43 (s, 2H), 3.99 (d,  $J = 6.9$  Hz, 1H), 3.99 (dd,  $J = 4.9, 0.9$  Hz, 2H), 3.80 (s, 3H), 3.38 (s, 2H), 1.17 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  161.9 (C), 159.4 (C), 138.0 (C), 130.7 (CH), 130.2 (C), 129.5 (CH), 129.0 (CH), 128.6 (CH), 127.9 (CH), 127.7 (CH), 114.0 (CH), 76.2 ( $\text{CH}_2$ ), 73.6 ( $\text{CH}_2$ ), 72.2 ( $\text{CH}_2$ ), 69.5 ( $\text{CH}_2$ ), 60.9 (C), 60.3 (CH), 55.4 ( $\text{CH}_3$ ), 20.2 ( $\text{CH}_3$ ); HRMS (ESI), calcd for  $\text{C}_{23}\text{H}_{29}\text{N}_2\text{O}_4^+$  ( $\text{M}+\text{H}$ ) $^+$  397.2127, found 397.2126.

NOESY experiment for **32c**

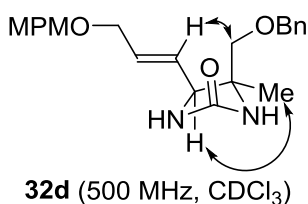


### Cyclic urea **32d**



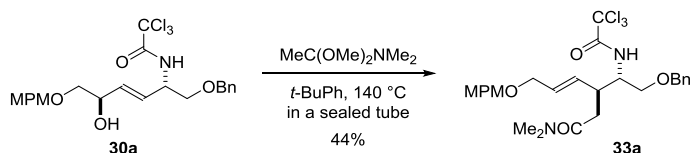
Following method E, bisamide **31d** (94.6 mg, 143  $\mu\text{mol}$ ) was converted to cyclic urea **32d** (17.8 mg, 31%): colorless oil;  $[\alpha]_{\text{D}}^{15} +21.8$  ( $c$  1.04,  $\text{CHCl}_3$ ); IR (film) 3220, 2931, 2855, 1709, 1613, 1514, 1249, 1108  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35–7.26 (m, 5H), 7.23 (d,  $J = 8.6$  Hz, 2H), 6.87 (d,  $J = 8.6$  Hz, 2H), 5.84 (dtd,  $J = 15.5, 5.4, 0.9$  Hz, 1H), 5.67 (ddt,  $J = 15.5, 7.5, 1.4$  Hz, 1H), 4.94 (brs, 1H), 4.78 (brs, 1H), 4.51 (d,  $J = 11.7$  Hz, 1H), 4.46 (d,  $J = 11.7$  Hz, 1H), 4.42 (s, 2H), 3.99 (dd,  $J = 7.5, 0.9$  Hz, 1H), 3.97 (dd,  $J = 5.4, 1.4$  Hz, 2H), 3.80 (s, 3H), 3.43 (d,  $J = 8.9$  Hz, 1H), 3.23 (d,  $J = 8.9$  Hz, 1H), 1.36 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  162.2 (C), 159.4 (C), 138.0 (C), 131.1 (CH), 130.2 (C), 129.5 (CH), 128.5 (CH), 127.8 (CH), 127.6 (CH), 127.2 (CH), 113.9 (CH), 73.6 ( $\text{CH}_2$ ), 73.4 ( $\text{CH}_2$ ), 72.2 ( $\text{CH}_2$ ), 69.4 ( $\text{CH}_2$ ), 63.7 (CH), 60.7 (C), 55.4 ( $\text{CH}_3$ ), 23.8 ( $\text{CH}_3$ ); HRMS (ESI), calcd for  $\text{C}_{23}\text{H}_{29}\text{N}_2\text{O}_4^+$  ( $\text{M}+\text{H}$ ) $^+$  397.2127, found 397.2127.

NOESY experiment for **32d**



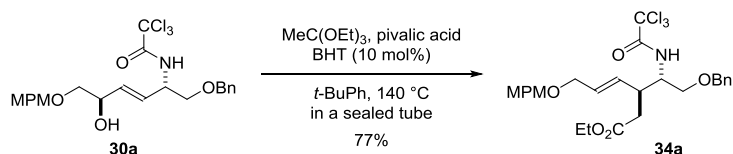


### Dimethylamide 33a



A sealed tube was charged with allylic amino alcohol **30a** (16.3 mg, 32.4  $\mu\text{mol}$ ),  $\text{MeC(OMe)}_2\text{NMe}_2$  (47.4  $\mu\text{L}$ , 324  $\mu\text{mol}$ ) and  $t\text{-BuPh}$  (1.2 mL). The solution was heated to  $170\text{ }^\circ\text{C}$ , and stirred at  $170\text{ }^\circ\text{C}$  for 30 min. After cooling to room temperature, the resulting mixture was directly purified by silica gel column chromatography (EtOAc/hexane 1:2 to 1:1) to give dimethyl amide **33a** (8.1 mg, 44%): colorless oil;  $[\alpha]_{\text{D}}^{22} -2.5$  ( $c$  0.74,  $\text{CHCl}_3$ ); IR (film) 3256, 2934, 2859, 1710, 1635, 1513, 1248, 1108, 821  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.87 (d,  $J = 8.3$  Hz, 1H), 7.34–7.27 (m, 5H), 7.24 (d,  $J = 8.6$  Hz, 2H), 6.87 (d,  $J = 8.6$  Hz, 2H), 5.77 (dddd,  $J = 15.5, 8.0, 1.2, 1.2$  Hz, 1H), 5.68 (ddd,  $J = 15.5, 5.8, 5.5$  Hz, 1H), 4.51 (d,  $J = 12.3$  Hz, 1H), 4.49 (d,  $J = 12.3$  Hz, 1H), 4.41 (d,  $J = 12.0$  Hz, 1H), 4.39 (d,  $J = 12.0$  Hz, 1H), 4.20 (dddd,  $J = 8.3, 5.2, 4.3, 4.3$  Hz, 1H), 3.99–3.91 (m 2H), 3.80 (s, 3H), 3.66 (dd,  $J = 10.0, 4.3$  Hz, 1H), 3.62 (dd,  $J = 10.0, 5.2$  Hz, 1H), 3.11 (dddd,  $J = 8.6, 8.0, 5.2, 4.3$  Hz, 1H), 2.88 (s, 3H), 2.87 (s, 3H), 2.64 (dd,  $J = 16.1, 8.6$  Hz, 1H), 2.37 (dd,  $J = 16.1, 5.2$  Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  171.4 (C), 161.9 (C), 159.3 (C), 137.9 (C), 132.3 (CH), 130.4 (C), 129.5 (CH), 129.4 (CH), 128.5 (CH), 127.9 (CH), 127.8 (CH), 113.9 (CH), 93.0 (C), 73.4 ( $\text{CH}_2$ ), 72.0 ( $\text{CH}_2$ ), 70.2 ( $\text{CH}_2$ ), 69.2 ( $\text{CH}_2$ ), 55.4 ( $\text{CH}_3$ ), 53.5 (CH), 40.6 (CH), 37.4 ( $\text{CH}_3$ ), 35.7 ( $\text{CH}_3$ ), 35.3 ( $\text{CH}_2$ ); HRMS (ESI), calcd for  $\text{C}_{27}\text{H}_{34}\text{Cl}_3\text{N}_2\text{O}_5^+$  ( $\text{M}+\text{H}$ ) $^+$  571.1533, found 571.1534.

### Ethyl ester 34a

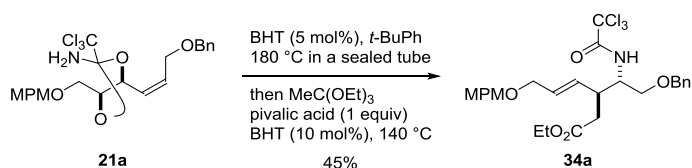


A sealed tube was charged with allylic amino alcohol **30a** (15.5 mg, 30.8  $\mu\text{mol}$ ),  $\text{MeC(OEt)}_3$  (90  $\mu\text{L}$ , 490  $\mu\text{mol}$ ), pivalic acid (3.2 mg, 30.8  $\mu\text{mol}$ ), BHT (0.7 mg, 3.08  $\mu\text{mol}$ ) and  $t\text{-BuPh}$  (1.1 mL). The solution was heated to  $140\text{ }^\circ\text{C}$ , and stirred at  $140\text{ }^\circ\text{C}$  for 1 h. After cooling to room temperature, the resulting mixture was directly purified by silica gel column chromatography (EtOAc/hexane 1:8 to 1:4) to give ethyl ester **34a** (17.6 mg, 77%): colorless oil;  $[\alpha]_{\text{D}}^{27} -8.7$  ( $c$  1.26,  $\text{CHCl}_3$ ); IR (film) 3419, 3341, 2936, 2860, 1715, 1613, 1513, 1248, 1110, 820  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36–7.27 (m, 5H), 7.22 (d,  $J = 8.6$  Hz, 2H), 7.02 (d,  $J = 9.2$  Hz, 1H), 6.87 (d,  $J = 8.6$  Hz, 2H), 5.70 (ddd,  $J = 15.8, 5.7, 5.2$  Hz, 1H), 5.63 (dddd,  $J = 15.8, 8.3, 1.2, 0.9$  Hz, 1H), 4.53 (s, 2H), 4.39 (d,  $J = 11.5$  Hz, 1H), 4.36 (d,  $J = 11.5$  Hz, 1H), 4.15 (dddd,  $J = 9.2, 6.0, 4.9, 4.0$  Hz, 1H), 4.11 (q,  $J = 7.2$  Hz, 2H), 3.95 (ddd,  $J = 12.6, 5.2, 1.2$  Hz, 1H), 3.91 (ddd,  $J =$

12.6, 5.7, 0.9 Hz, 1H), 3.80 (s, 3H), 3.61 (dd,  $J = 10.0, 4.0$  Hz, 1H), 3.55 (dd,  $J = 10.0, 4.9$  Hz, 1H), 3.05 (dddd,  $J = 8.3, 8.3, 6.0, 6.0$  Hz, 1H), 2.53 (dd,  $J = 15.8, 6.0$  Hz, 1H), 2.40 (dd,  $J = 15.8, 8.3$  Hz, 1H), 1.22 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  171.8 (C), 161.8 (C), 159.3 (C), 137.6 (C), 130.8 (CH), 130.6 (CH), 130.4 (C), 129.4 (CH), 128.7 (CH), 128.1 (CH), 127.9 (CH), 113.9 (CH), 92.9 (C), 73.4 (CH<sub>2</sub>), 71.8 (CH<sub>2</sub>), 69.9 (CH<sub>2</sub>), 68.9 (CH<sub>2</sub>), 60.8 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>), 53.3 (CH), 40.6 (CH), 36.7 (CH<sub>2</sub>), 14.4 (CH<sub>3</sub>); HRMS (ESI), calcd for  $\text{C}_{27}\text{H}_{32}\text{Cl}_3\text{NO}_6\text{Na}^+$  ( $\text{M}+\text{Na}$ )<sup>+</sup> 594.1193, found 594.1196.

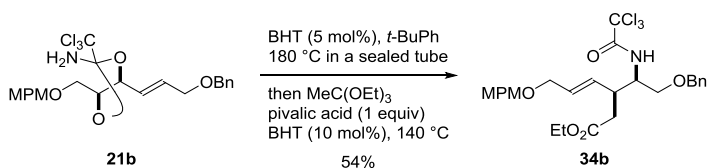
## [Method F: The sequential Overman/Claisen rearrangement in one pot]

### Ethyl ester **34a**



A sealed tube was charged with cyclic orthoamide **21a** (28.4 mg, 56.5  $\mu\text{mol}$ ), BHT (0.6 mg, 2.83  $\mu\text{mol}$ ) and *t*-BuPh (2.1 mL). The solution was purged with a flow of argon for 5 min, and heated to 180 °C for 51 h. After cooling to room temperature,  $\text{MeC}(\text{OEt})_3$  (82.9  $\mu\text{L}$ , 452  $\mu\text{mol}$ ), pivalic acid (5.8 mg, 56.5  $\mu\text{mol}$ ) and BHT (1.2 mg, 5.65  $\mu\text{mol}$ ) were added to the solution of the generated allylic amino alcohol. The resulting solution was then heated to 140 °C for 30 min. After cooling to room temperature, the resulting mixture was directly purified by silica gel column chromatography (EtOAc/hexane 1:3 to 1:2) to give ethyl ester **34a** (14.5 mg, 45%).

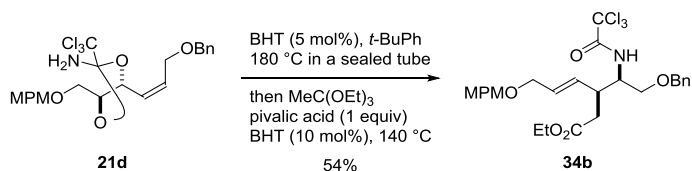
### Ethyl ester **34b**



Following method F, cyclic orthoamide **21b** (28.8 mg, 57.3  $\mu\text{mol}$ ) was converted to ethyl ester **34b** (17.6 mg, 54%): colorless oil;  $[\alpha]_{\text{D}}^{19} +12.7$  ( $c$  0.89,  $\text{CHCl}_3$ ); IR (film) 3413, 3340, 2935, 2858, 1715, 1613, 1514, 1248, 1113, 821  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35–7.26 (m, 6H), 7.23 (d,  $J = 8.6$  Hz, 2H), 6.88 (d,  $J = 8.6$  Hz, 2H), 5.69 (ddd,  $J = 15.5, 5.7, 5.4$  Hz, 1H), 5.57 (dddd,  $J = 15.5, 9.2, 1.4, 1.2$  Hz, 1H), 4.52 (d,  $J = 12.0$  Hz, 1H), 4.48 (d,  $J = 12.0$  Hz, 1H), 4.39 (s, 2H), 4.11 (dq,  $J = 12.9, 7.2$  Hz, 1H), 4.09 (dq,  $J = 12.9, 7.2$  Hz, 1H), 3.99 (dddd,  $J = 9.2, 9.2, 3.7, 2.9$  Hz, 1H), 3.94–3.87 (m, 2H), 3.81 (s, 3H), 3.63 (dd,  $J = 9.7, 2.9$  Hz, 1H), 3.49 (dd,  $J = 9.7, 3.7$  Hz, 1H), 3.07 (dddd,  $J = 9.2, 9.2, 8.0, 5.4$  Hz, 1H), 2.52 (dd,  $J = 15.8, 5.4$  Hz, 1H), 2.41 (dd,  $J = 15.8, 8.0$  Hz, 1H), 1.21 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  172.4 (C), 161.9 (C), 159.4 (C), 137.6 (C), 131.3 (CH), 130.9 (CH), 130.4 (C), 129.4 (CH), 128.6 (CH),

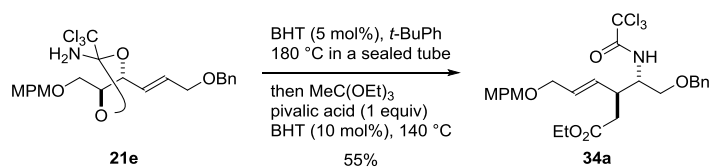
128.1 (CH), 127.9 (CH), 113.9 (CH), 92.8 (C), 73.5 (CH<sub>2</sub>), 71.8 (CH<sub>2</sub>), 69.8 (CH<sub>2</sub>), 68.8 (CH<sub>2</sub>), 60.8 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>), 54.0 (CH), 40.7 (CH), 36.9 (CH<sub>2</sub>), 14.3 (CH<sub>3</sub>); HRMS (ESI), calcd for C<sub>27</sub>H<sub>32</sub>Cl<sub>3</sub>NO<sub>6</sub>Na<sup>+</sup> (M+Na)<sup>+</sup> 594.1193, found 594.1191.

### Ethyl ester **34b**



Following method F, cyclic orthoamide **21d** (26.9 mg, 53.5 μmol) was converted to ethyl ester **34b** (16.6 mg, 54%).

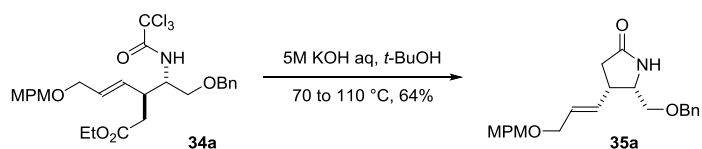
### Ethyl ester **34a**



Following method F, cyclic orthoamide **21e** (27.9 mg, 55.5 μmol) was converted to ethyl ester **34a** (17.5 mg, 55%).

### [Method G: Stereochemical determination of the sequential Overman/Claisen rearrangement]

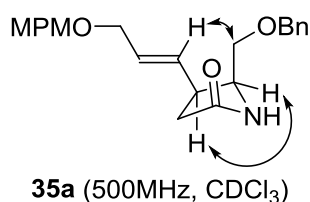
#### Lactam **35a**



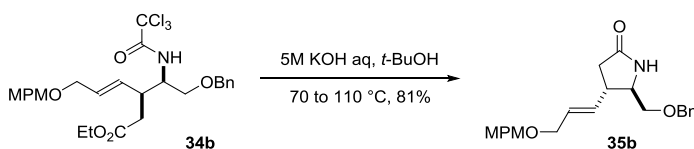
Aqueous KOH (5M, 1.3 mL, 6.5 mmol) was added to a solution of unsaturated ester **34a** (62.2 mg, 109 μmol) and *t*-BuOH (1.3 mL) at room temperature, and then heated to 70 °C. After stirring for 8 d at 70 °C, this solution was heated to 110 °C, maintained for 21 d at 110 °C, cooled to room temperature, quenched with 1M aqueous HCl (5.2 mL) and H<sub>2</sub>O (5.2 mL), and extracted with EtOAc (2x 10 mL). The combined organic extracts were washed with brine (5.0 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography (EtOAc) to give lactam **35a** (9.2 mg, 64%): colorless oil; [α]<sub>D</sub><sup>18</sup> +47.2 (*c* 1.08, CHCl<sub>3</sub>); IR (film) 3221, 2934, 2859, 1696, 1513, 1248, 1109, 1073 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.35–7.26 (m, 5H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.14 (brs, 1H), 5.71 (ddd, *J* = 15.5, 5.2, 4.0 Hz, 1H), 5.67 (dd, *J* = 15.5, 6.6 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.42 (s, 2H), 3.95–3.92 (m, 2H), 3.80 (ddd, *J* = 7.5, 7.5, 3.4 Hz, 1H), 3.80 (s, 3H), 3.46

(dd,  $J = 9.5, 3.4$  Hz, 1H), 3.39 (dd,  $J = 9.5, 7.5$  Hz, 1H), 3.23 (dddd,  $J = 9.2, 8.9, 7.5, 6.6$  Hz, 1H), 2.42 (dd,  $J = 16.6, 8.9$  Hz, 1H), 2.33 (dd,  $J = 16.6, 9.2$  Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  177.2 (C), 159.4 (C), 137.8 (C), 130.3 (C), 130.2 (CH), 129.9 (CH), 129.5 (CH), 128.6 (CH), 127.9 (CH), 127.8 (CH), 113.9 (CH), 73.6 ( $\text{CH}_2$ ), 72.1 ( $\text{CH}_2$ ), 70.9 ( $\text{CH}_2$ ), 69.9 ( $\text{CH}_2$ ), 57.0 (CH), 55.4 ( $\text{CH}_3$ ), 40.2 (CH), 36.1 ( $\text{CH}_2$ ); HRMS (ESI), calcd for  $\text{C}_{23}\text{H}_{28}\text{NO}_4^+$  ( $\text{M}+\text{H}$ ) $^+$  382.2018, found 382.2018.

NOESY experiment for **35a**

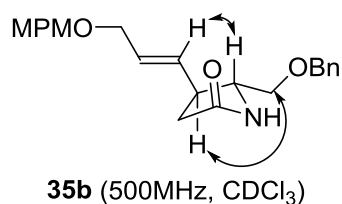


### Lactam **35b**

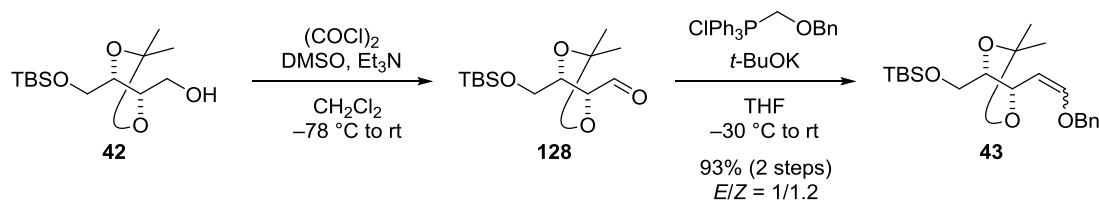


Following method G, unsaturated ester **34b** (51.8 mg, 90.4  $\mu\text{mol}$ ) was converted to lactam **35b** (28.0 mg, 81%): colorless oil;  $[\alpha]_{\text{D}}^{19} -49.9$  ( $c$  1.04,  $\text{CHCl}_3$ ); IR (film) 3217, 2901, 2856, 1698, 1612, 1513, 1248, 1110  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37–7.27 (m, 5H), 7.25 (d,  $J = 8.6$  Hz, 2H), 6.88 (d,  $J = 8.6$  Hz, 2H), 6.05 (brs, 1H), 5.69 (dd,  $J = 15.5, 7.5$  Hz, 1H), 5.63 (dt,  $J = 15.5, 5.2$  Hz, 1H), 4.54 (d,  $J = 11.8$  Hz, 1H), 4.49 (d,  $J = 11.8$  Hz, 1H), 4.43 (s, 2H), 3.95 (d,  $J = 5.2$  Hz, 2H), 3.80 (s, 3H), 3.62–3.56 (m, 2H), 3.35–3.29 (m, 1H), 2.70 (dddd,  $J = 8.9, 8.9, 7.5, 7.5$  Hz, 1H), 2.51 (dd,  $J = 16.6, 8.9$  Hz, 1H), 2.25 (dd,  $J = 16.9, 8.9$  Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  176.3 (C), 159.4 (C), 137.7 (C), 132.5 (CH), 130.2 (C), 129.5 (CH), 129.0 (CH), 128.6 (CH), 128.1 (CH), 127.8 (CH), 113.9 (CH), 73.6 ( $\text{CH}_2$ ), 72.6 ( $\text{CH}_2$ ), 72.2 ( $\text{CH}_2$ ), 69.9 ( $\text{CH}_2$ ), 59.3 (CH), 55.4 ( $\text{CH}_3$ ), 40.6 (CH), 36.9 ( $\text{CH}_2$ ); HRMS (ESI), calcd for  $\text{C}_{23}\text{H}_{28}\text{NO}_4^+$  ( $\text{M}+\text{H}$ ) $^+$  382.2018, found 382.2018.

NOESY experiment for **35b**



## Chapter 2: Total synthesis of (–)-stemoamide



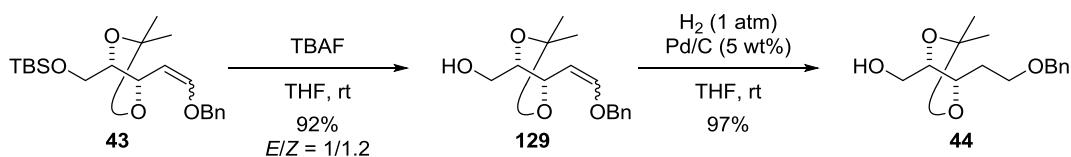
### (((4*S*,5*S*)-5-(2-(Benzyloxy)vinyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)(*tert*-butyl)dimethylsilane (43)

Oxalyl chloride (6.3 mL, 72 mmol) was added dropwise to a solution of DMSO (7.7 mL, 110 mmol) and  $\text{CH}_2\text{Cl}_2$  (340 mL) at  $-78^\circ\text{C}$ . The solution was stirred for 30 min at  $-78^\circ\text{C}$ . A solution of alcohol **42**<sup>[4]</sup> (9.99 g, 36.1 mmol) and  $\text{CH}_2\text{Cl}_2$  (18 mL) was then added dropwise via cannula at  $-78^\circ\text{C}$ . After stirring for 40 min at  $-78^\circ\text{C}$ ,  $\text{Et}_3\text{N}$  (20 mL, 150 mmol) was added dropwise to the solution. The resulting mixture was stirred for 15 min at  $-78^\circ\text{C}$ , allowed to warm to room temperature, quenched with saturated aqueous  $\text{NaHCO}_3$  (90 mL) and  $\text{H}_2\text{O}$  (90 mL), and extracted with hexane (2x 90 mL). The combined organic extracts were washed with  $\text{H}_2\text{O}$  (2x 30 mL) and brine (30 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated to give the corresponding aldehyde **128**<sup>[4]</sup>, which was immediately used in the next reaction without further purification.

Potassium *tert*-butoxide (16.2 g, 144 mmol) was added to a mixture of (benzyloxymethyl)triphenylphosphonium chloride (60.6 g, 144 mmol) and THF (340 mL) at  $-78^\circ\text{C}$ . The resulting mixture was allowed to warm to  $-30^\circ\text{C}$ . After stirring for 1.5 h at  $-30^\circ\text{C}$ , a solution of the crude aldehyde **128** and THF (18 mL) was added dropwise to the ylide via cannula at  $-30^\circ\text{C}$ . This mixture was stirred for 30 min at  $-30^\circ\text{C}$ , allowed to warm to room temperature, quenched with saturated aqueous  $\text{NaHCO}_3$  (90 mL) and  $\text{H}_2\text{O}$  (90 mL), and extracted with hexane (2x 90 mL). The combined organic extracts were washed with brine (30 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc 75:1 to 10:1) to give 12.8 g of a mixture of two enol ethers **43** (93% for 2 steps, *E/Z* = 1:1.2). For analytical samples, two isomers were separated by HPLC (PEGASIL Silica 120-5, 250x20 mm, UV 254 nm, hexane/EtOAc 9:1, 10 mL/min, **E isomer**:  $T_R = 8.7$  min, **Z isomer**:  $T_R = 10.2$  min). **43 (E isomer)**: a colorless oil;  $R_f = 0.67$  (hexane/EtOAc = 3:1);  $[\alpha]_D^{28} - 14.4$  ( $c$  1.05,  $\text{CHCl}_3$ ); IR (film): 2930, 2858, 1655, 1252, 1171, 1021, 838  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  7.39–7.30 (m, 5H), 6.65 (d,  $J = 12.6$  Hz, 1H), 4.89 (dd,  $J = 12.6, 8.9$  Hz, 1H), 4.80 (d,  $J = 11.5$  Hz, 1H), 4.75 (d,  $J = 11.5$  Hz, 1H), 4.30 (dd,  $J = 8.9, 8.9$  Hz, 1H), 3.80–3.67 (m, 3H), 1.43 (s, 3H), 1.41 (s, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  151.1 (CH), 136.5 (C), 128.7 (CH), 128.3 (CH), 127.8 (CH), 108.5 (C), 101.6 (CH), 81.9 (CH), 76.7 (CH), 71.5 ( $\text{CH}_2$ ), 62.2 ( $\text{CH}_2$ ), 27.4 ( $\text{CH}_3$ ), 27.0 ( $\text{CH}_3$ ), 26.0 ( $\text{CH}_3$ ), 18.5 (C),  $-5.2$  ( $\text{CH}_3$ ),  $-5.3$  ( $\text{CH}_3$ ); HRMS (ESI): calcd for  $\text{C}_{21}\text{H}_{34}\text{O}_4\text{SiNa}$ :

<sup>[4]</sup> Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1987**, *52*, 3337.

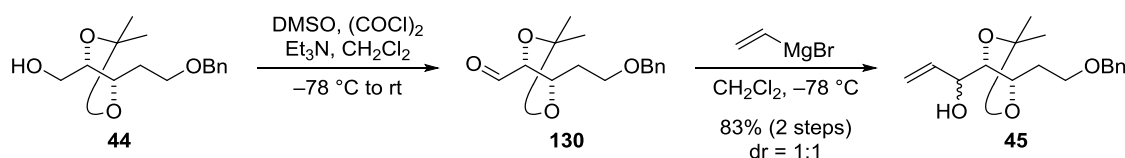
401.2124; found: 401.2114. **43 (Z isomer)**: a colorless oil;  $R_f = 0.64$  (hexane/EtOAc = 3:1);  $[\alpha]_D^{26} +1.5$  ( $c$  1.25,  $\text{CHCl}_3$ ); IR (film): 2930, 2858, 1668, 1370, 1253, 1217, 1075, 837  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  7.37–7.29 (m, 5H), 6.24 (dd,  $J = 6.3, 0.9$  Hz, 1H), 4.91 (ddd,  $J = 8.9, 8.3, 0.9$  Hz, 1H), 4.85 (d,  $J = 12.6$  Hz, 1H), 4.79 (d,  $J = 12.6$  Hz, 1H), 4.49 (dd,  $J = 8.9, 6.3$  Hz, 1H), 3.80–3.66 (m, 3H), 1.42 (s, 6H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  149.0 (CH), 137.1 (C), 128.7 (CH), 128.2 (CH), 127.6 (CH), 108.8 (C), 104.4 (CH), 82.5 (CH), 74.4 ( $\text{CH}_2$ ), 71.4 (CH), 62.8 ( $\text{CH}_2$ ), 27.4 ( $\text{CH}_3$ ), 27.1 ( $\text{CH}_3$ ), 26.1 ( $\text{CH}_3$ ), 18.6 (C), -5.2 ( $\text{CH}_3$ ), -5.3 ( $\text{CH}_3$ ); HRMS (ESI): calcd for  $\text{C}_{21}\text{H}_{34}\text{O}_4\text{SiNa}$ : 401.2124; found: 401.2114.



#### ((4*S*,5*S*)-5-(2-(Benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (**44**)

Tetrabutylammonium fluoride (1.0 M in THF, 44 mL, 44 mmol) was added to a solution of enol ethers **43** ( $E/Z = 1:1.2$ , 12.8 g, 33.7 mmol) and THF (340 mL) at 0 °C. This solution was allowed to warm to room temperature, maintained for 1 h at room temperature, and quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (85 mL) and  $\text{H}_2\text{O}$  (85 mL). The mixture was extracted with EtOAc (2x 85 mL). The combined organic extracts were washed with brine (25 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc 1:1) to give 8.19 g of a mixture of two alcohols **129** (92%,  $E/Z = 1:1.2$ ). For analytical samples, two isomers were separated by HPLC (PEGASIL Silica 120-5, 250×20 mm, UV 254 nm, hexane/EtOAc 2:3, 10 mL/min, **129 (Z isomer)**:  $T_R = 9.0$  min, **129 (E isomer)**:  $T_R = 10.5$  min). **129 (E isomer)**: a colorless oil;  $R_f = 0.56$  (hexane/EtOAc = 1:1);  $[\alpha]_D^{24} -63.2$  ( $c$  0.99, EtOAc); IR (film): 3455, 2986, 2873, 1655, 1380, 1169, 1051  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{C}_6\text{D}_6$ , 500 MHz)  $\delta$  7.14–7.03 (m, 5H), 6.42 (d,  $J = 12.6$  Hz, 1H), 4.82 (dd,  $J = 12.6, 8.9$  Hz, 1H), 4.37 (d,  $J = 12.0$  Hz, 1H), 4.34 (d,  $J = 12.0$  Hz, 1H), 4.30 (dd,  $J = 8.9, 8.9$  Hz, 1H), 3.64–3.58 (m, 2H), 3.43–3.36 (m, 1H), 1.68 (s, 1H), 1.43 (s, 3H), 1.39 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{C}_6\text{D}_6$ , 125 MHz)  $\delta$  151.1 (CH), 137.1 (C), 128.7 (CH), 128.4 (CH), 127.7 (CH), 108.5 (C), 102.3 (CH), 82.2 (CH), 76.3 (CH), 71.4 ( $\text{CH}_2$ ), 60.8 ( $\text{CH}_2$ ), 27.6 ( $\text{CH}_3$ ), 27.2 ( $\text{CH}_3$ ); HRMS (ESI): calcd for  $\text{C}_{15}\text{H}_{20}\text{O}_4\text{Na}$ : 287.1259; found: 287.1265. **129 (Z isomer)**: a colorless oil;  $R_f = 0.62$  (hexane/EtOAc = 1:1);  $[\alpha]_D^{23} -39.5$  ( $c$  1.11, EtOAc); IR (film): 3460, 2986, 2934, 2876, 1667, 1372, 1217, 1062  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{C}_6\text{D}_6$ , 500 MHz)  $\delta$  7.11–7.01 (m, 5H), 5.79–5.76 (m, 1H), 5.18 (dd,  $J = 8.3, 8.0$  Hz, 1H), 4.53 (dd,  $J = 8.3, 6.3$  Hz, 1H), 4.31–4.21 (m, 2H), 3.81–3.74 (m, 2H), 3.70–3.63 (m, 1H), 2.30–1.90 (m, 1H), 1.43 (s, 3H), 1.37 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{C}_6\text{D}_6$ , 125 MHz)  $\delta$  148.1 (CH), 137.3 (C), 128.8 (CH), 128.4 (CH), 127.6 (CH), 108.9 (C), 105.4 (CH), 82.6 (CH), 74.1 ( $\text{CH}_2$ ), 72.2 (CH), 62.0 ( $\text{CH}_2$ ), 27.5 ( $\text{CH}_3$ ), 27.2 ( $\text{CH}_3$ ); HRMS (ESI): calcd for  $\text{C}_{15}\text{H}_{20}\text{O}_4\text{Na}$ : 287.1259; found: 287.1265.

Palladium on carbon (10%, 410 mg, 5.0 wt%) was added to a solution of alcohols **129** (*E/Z* = 1:1.2, 8.19 g, 31.0 mmol) and THF (160 mL) at room temperature. The mixture was stirred under hydrogen atmosphere (1 atm) at room temperature for 14 h, filtrated through a pad of Celite, washed with EtOAc (160 mL), and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc 7:1 to 1:1) to give 8.01 g of alcohol **44** (97%): a colorless oil;  $R_f$  = 0.52 (hexane/EtOAc = 1:1);  $[\alpha]_D^{21}$  -23.6 (*c* 1.08, CHCl<sub>3</sub>); IR (film): 3451, 2987, 2933, 2869, 1371, 1215, 1093 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.37–7.27 (m, 5H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.02 (dt, *J* = 8.3, 6.0 Hz, 1H), 3.82 (ddd, *J* = 8.3, 4.3, 3.7 Hz, 1H), 3.78 (ddd, *J* = 11.7, 5.2, 3.7 Hz, 1H), 3.65 (dt, *J* = 9.5, 6.0 Hz, 1H), 3.66–3.60 (m, 1H), 3.60 (dt, *J* = 9.5, 6.6 Hz, 1H), 2.05 (dd, *J* = 7.5, 5.2 Hz, 1H), 1.92 (ddd, *J* = 6.6, 6.0, 6.0 Hz, 2H), 1.41 (s, 3H), 1.40 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  138.3 (C), 128.6 (CH), 127.85 (CH), 127.82 (CH), 108.7 (C), 81.5 (CH), 74.9 (CH), 73.3 (CH<sub>2</sub>), 67.2 (CH<sub>2</sub>), 62.1 (CH<sub>2</sub>), 33.4 (CH<sub>2</sub>), 27.4 (CH<sub>3</sub>), 27.1 (CH<sub>3</sub>); HRMS (ESI): calcd for C<sub>15</sub>H<sub>23</sub>O<sub>4</sub>: 267.1596; found: 267.1602.

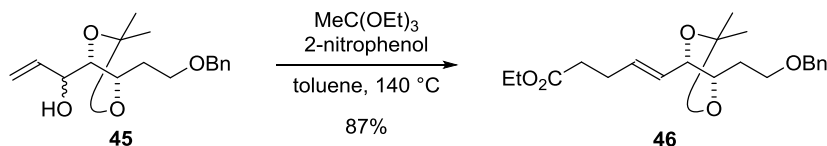


#### 1-((4*S*,5*S*)-5-(2-(Benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (**45**)

Oxalyl chloride (4.1 mL, 47 mmol) was added dropwise to a solution of DMSO (5.0 mL, 71 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (150 mL) at -78 °C. The resulting solution was stirred for 40 min at -78 °C. A solution of alcohol **44** (4.21 g, 15.8 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (8.0 mL) was then added dropwise via cannula at -78 °C. After stirring for 1 h at -78 °C, Et<sub>3</sub>N (13 mL, 95 mmol) was added dropwise to the solution. The resulting mixture was stirred for 10 min at -78 °C, allowed to warm to room temperature, quenched with saturated aqueous NaHCO<sub>3</sub> (40 mL) and H<sub>2</sub>O (40 mL), and extracted with hexane (2x 50 mL). The combined organic extracts were washed with H<sub>2</sub>O (2x 12 mL) and brine (12 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to give the corresponding aldehyde **130**, which was immediately used in the next reaction without further purification.

Vinylmagnesium bromide (1.0 M in THF, 32 mL, 32 mmol) was added to a solution of the crude aldehyde **130** and CH<sub>2</sub>Cl<sub>2</sub> (160 mL) at 0 °C. This solution was stirred for 1.5 h at 0 °C, quenched with saturated aqueous NH<sub>4</sub>Cl (40 mL) and H<sub>2</sub>O (40 mL), and extracted with hexane (2x 40 mL). The combined organic extracts were washed with brine (12 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc 10:1 to 6:1) to give 3.82 g of a mixture of allylic alcohols **45** (83% for 2 steps, dr = 1:1). For analytical samples, two isomers were separated by HPLC (PEGASIL Silica 120-5, 250×20 mm, UV 254 nm, hexane/EtOAc 3:2, 10 mL/min, **less polar diastereomer**:  $T_R$  = 9.1 min, **polar diastereomer**:  $T_R$  = 9.7 min). **45 (less polar diastereomer)**:

a colorless oil;  $R_f = 0.76$  (hexane/EtOAc = 1:1);  $[\alpha]_D^{21} -38.5$  ( $c$  1.10,  $\text{CHCl}_3$ ); IR (film): 3455, 2986, 2867, 1371, 1215, 1091  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  7.36–7.26 (m, 5H), 5.90 (ddd,  $J = 17.2, 10.6, 5.7$  Hz, 1H), 5.36 (ddd,  $J = 17.2, 1.4, 1.4$  Hz, 1H), 5.24 (ddd,  $J = 10.6, 1.4, 1.4$  Hz, 1H), 4.51 (s, 2H), 4.30–4.26 (m, 1H), 4.10 (ddd,  $J = 8.0, 8.0, 3.4$  Hz, 1H), 3.76 (dd,  $J = 8.0, 4.9$  Hz, 1H), 3.66 (ddd,  $J = 9.5, 6.9, 5.7$  Hz, 1H), 3.61 (ddd,  $J = 9.5, 7.5, 6.3$  Hz, 1H), 2.40 (brs, 1H), 2.00 (dddd,  $J = 14.0, 7.5, 6.9, 3.4$  Hz, 1H), 1.87 (dddd,  $J = 14.0, 8.0, 6.3, 5.7$  Hz, 1H), 1.40 (s, 6H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  138.3 (C), 136.2 (CH), 128.5 (CH), 127.83 (CH), 127.77 (CH), 116.9 ( $\text{CH}_2$ ), 108.8 (C), 83.0 (CH), 74.9 (CH), 73.2 ( $\text{CH}_2$ ), 72.4 (CH), 67.4 ( $\text{CH}_2$ ), 34.3 ( $\text{CH}_2$ ), 27.4 ( $\text{CH}_3$ ), 27.1 ( $\text{CH}_3$ ); HRMS (ESI): calcd for  $\text{C}_{17}\text{H}_{25}\text{O}_4$ : 293.1753; found: 293.1755. **45 (polar diastereomer)**: a colorless oil;  $R_f = 0.71$  (hexane/EtOAc = 1:1);  $[\alpha]_D^{22} -16.3$  ( $c$  1.01,  $\text{CHCl}_3$ ); IR (film): 3448, 2986, 2870, 1371, 1215, 1089  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  7.36–7.26 (m, 5H), 5.86 (ddd,  $J = 17.2, 10.6, 5.7$  Hz, 1H), 5.35 (ddd,  $J = 17.2, 1.4, 1.4$  Hz, 1H), 5.23 (ddd,  $J = 10.6, 1.4, 1.4$  Hz, 1H), 4.51 (s, 2H), 4.14–4.10 (m, 1H), 4.09 (ddd,  $J = 8.0, 8.0, 4.0$  Hz, 1H), 3.73 (dd,  $J = 8.0, 4.3$  Hz, 1H), 3.65 (ddd,  $J = 9.5, 6.6, 5.4$  Hz, 1H), 3.59 (ddd,  $J = 9.5, 7.7, 6.0$  Hz, 1H), 2.34 (d,  $J = 6.6$  Hz, 1H), 1.96 (dddd,  $J = 14.0, 7.7, 6.6, 4.0$  Hz, 1H), 1.87 (dddd,  $J = 14.0, 8.0, 6.0, 5.4$  Hz, 1H), 1.410 (s, 3H), 1.405 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  138.4 (C), 137.2 (CH), 128.5 (CH), 127.79 (CH), 127.76 (CH), 117.0 ( $\text{CH}_2$ ), 109.1 (C), 83.5 (CH), 75.1 (CH), 73.2 ( $\text{CH}_2$ ), 72.3 (CH), 67.2 ( $\text{CH}_2$ ), 33.8 ( $\text{CH}_2$ ), 27.6 ( $\text{CH}_3$ ), 27.2 ( $\text{CH}_3$ ); HRMS (ESI): calcd for  $\text{C}_{17}\text{H}_{25}\text{O}_4$ : 293.1753; found: 293.1742.

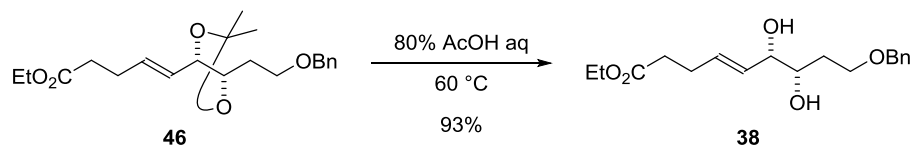


#### Ethyl (E)-5-((4S,5S)-5-(2-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-enoate (**46**)

A sealed tube was charged with allylic alcohols **45** ( $dr = 1:1$ , 3.82 g, 13.1 mmol),  $\text{MeC}(\text{OEt})_3$  (48 mL, 260 mmol), 2-nitrophenol (5.45 g, 39.2 mmol) and toluene (130 mL). The solution was heated to  $140^\circ\text{C}$ , and stirred for 6 h at  $140^\circ\text{C}$ . The resulting solution was cooled to room temperature, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc 20:1 to 9:1) to give 4.09 g of ethyl ester **46** (87%): a yellow oil;  $R_f = 0.57$  (hexane/EtOAc = 3:1);  $[\alpha]_D^{22} +20.5$  ( $c$  0.98,  $\text{CHCl}_3$ ); IR (film): 2985, 2935, 2864, 1735, 1370, 1241, 1168, 1095, 1041  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  7.36–7.26 (m, 5H), 5.84–5.75 (m, 1H), 5.46 (dd,  $J = 15.5, 8.0$  Hz, 1H), 4.50 (s, 2H), 4.12 (q,  $J = 7.2$  Hz, 2H), 4.00 (dd,  $J = 8.0, 8.0$  Hz, 1H), 3.78 (ddd,  $J = 8.0, 8.0, 4.0$  Hz, 1H), 3.62 (ddd,  $J = 9.2, 6.9, 5.7$  Hz, 1H), 3.57 (ddd,  $J = 9.2, 6.9, 6.9$  Hz, 1H), 2.41–2.34 (m, 4H), 1.87 (dddd,  $J = 14.3, 6.9, 6.9, 4.0$  Hz, 1H), 1.85–1.77 (m, 1H), 1.394 (s, 3H), 1.390 (s, 3H), 1.24 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  172.9 (C), 138.5 (C), 134.3 (CH), 128.5 (CH), 128.0 (CH), 127.74 (CH), 127.68 (CH), 108.5 (C), 82.4 (CH), 77.8 (CH), 73.1 ( $\text{CH}_2$ ), 67.1 ( $\text{CH}_2$ ), 60.5 ( $\text{CH}_2$ ), 33.7 ( $\text{CH}_2$ ), 32.1 ( $\text{CH}_2$ ), 27.7 ( $\text{CH}_2$ ), 27.4 ( $\text{CH}_3$ ), 27.1

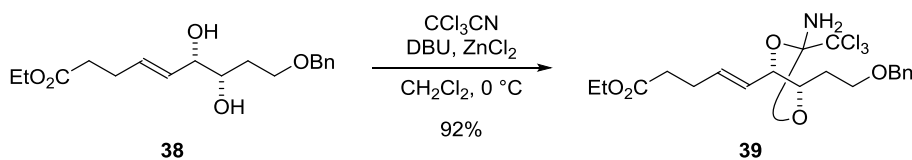


(CH<sub>3</sub>), 14.3 (CH<sub>3</sub>); HRMS (ESI): calcd for C<sub>21</sub>H<sub>30</sub>O<sub>5</sub>Na: 385.1991; found: 385.1992.



### Ethyl (6*S*,7*S*,*E*)-9-(benzyloxy)-6,7-dihydroxynon-4-enoate (**38**)

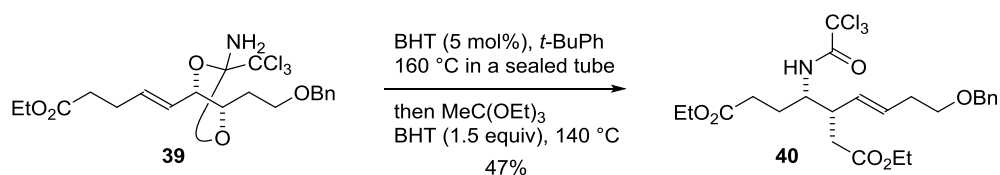
A solution of ethyl ester **46** (4.09 g, 11.3 mmol) and AcOH/H<sub>2</sub>O (4:1, 28 mL) was heated to 60 °C, and maintained at 60 °C for 5.5 h. The resulting solution was cooled to room temperature, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc 2:1 to 1:2) to give 3.40 g of allylic 1,2-diol **38** (93%): a yellow oil;  $R_f = 0.30$  (hexane/EtOAc = 1:1);  $[\alpha]_D^{24} +1.7$  ( $c$  1.44, CHCl<sub>3</sub>); IR (film): 3435, 2921, 2865, 1732, 1097 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.37–7.27 (m, 5H), 5.79–5.72 (m, 1H), 5.51 (dd,  $J = 15.5, 6.9$  Hz, 1H), 4.52 (s, 2H), 4.11 (q,  $J = 7.2$  Hz, 2H), 3.90 (dd,  $J = 6.9, 6.3, 1.2$  Hz, 1H), 3.70 (ddd,  $J = 9.2, 6.0, 4.9$  Hz, 1H), 3.68–3.63 (m, 2H), 2.42–2.34 (m, 4H), 1.80 (dddd,  $J = 14.6, 6.0, 4.6, 3.7$  Hz, 1H), 1.79–1.72 (m, 1H), 1.24 (t,  $J = 7.2$  Hz, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  173.1 (C), 137.9 (C), 132.3 (CH), 130.4 (CH), 128.6 (CH), 127.9 (CH), 127.8 (CH), 75.7 (CH), 73.8 (CH), 73.5 (CH<sub>2</sub>), 68.5 (CH<sub>2</sub>), 60.5 (CH<sub>2</sub>), 33.8 (CH<sub>2</sub>), 32.6 (CH<sub>2</sub>), 27.7 (CH<sub>2</sub>), 14.3 (CH<sub>3</sub>); HRMS (ESI): calcd for C<sub>18</sub>H<sub>26</sub>O<sub>5</sub>Na: 345.1678; found: 345.1678.



### Ethyl (*E*)-5-((4*S*,5*S*)-2-amino-5-(2-(benzyloxy)ethyl)-2-(trichloromethyl)-1,3-dioxolan-4-yl)pent-4-enoate (**39**)

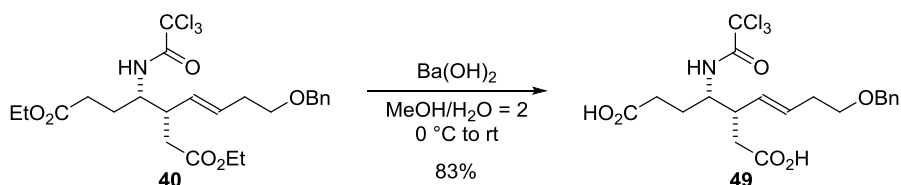
1,8-Diazabicyclo[5.4.0]undec-7-ene (470  $\mu$ L, 3.2 mmol) was added dropwise to a solution of allylic 1,2-diol **38** (3.40 g, 10.5 mmol), CCl<sub>3</sub>CN (1.4 mL, 14 mmol), ZnCl<sub>2</sub> (144 mg, 1.05 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (110 mL) at 0 °C. The solution was maintained at 0 °C for 19 h, allowed to warm to room temperature, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc 7:1 to 4:1) to give 4.52 g of a diastereomeric mixture of two orthoamides **39** (92%, dr = 1:1). For analytical samples, two diastereomers were separated by HPLC (PEGASIL Silica 120-5, 250 $\times$ 20 mm, UV 254 nm, hexane/EtOAc 2:1, 10 mL/min, **less polar diastereomer**:  $T_R = 13.5$  min, **polar diastereomer**:  $T_R = 21.1$  min). **39** (**less polar diastereomer**): a colorless oil;  $R_f = 0.72$  (hexane/EtOAc = 1:1);  $[\alpha]_D^{25} -6.9$  ( $c$  1.33, CHCl<sub>3</sub>); IR (film): 3418, 3341, 2922, 2867, 1733, 1207, 1095, 824 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.36–7.26 (m, 5H), 5.87–5.80 (m, 1H), 5.52 (dd,  $J = 15.5, 8.3$  Hz, 1H), 4.51 (d,  $J = 12.0$  Hz, 1H), 4.48 (d,

$J = 12.0$  Hz, 1H), 4.45 (dd,  $J = 8.9, 8.3$  Hz, 1H), 4.28 (ddd,  $J = 8.9, 7.7, 4.3$  Hz, 1H), 4.12 (q,  $J = 7.2$  Hz, 2H), 3.66 (ddd,  $J = 9.5, 6.0, 6.0$  Hz, 1H), 3.61 (ddd,  $J = 9.5, 7.5, 6.0$  Hz, 1H), 2.57 (brs, 2H), 2.42–2.35 (m, 4H), 2.02–1.90 (m, 2H), 1.24 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  172.8 (C), 138.3 (C), 136.1 (CH), 128.5 (CH), 127.80 (CH), 127.76 (CH), 126.8 (CH), 114.5 (C), 103.8 (C), 86.3 (CH), 80.0 (CH), 73.2 ( $\text{CH}_2$ ), 66.5 ( $\text{CH}_2$ ), 60.6 ( $\text{CH}_2$ ), 33.5 ( $\text{CH}_2$ ), 30.9 ( $\text{CH}_2$ ), 27.6 ( $\text{CH}_2$ ), 14.4 ( $\text{CH}_3$ ); HRMS (ESI): calcd for  $\text{C}_{20}\text{H}_{26}\text{NO}_5\text{Cl}_3\text{Na}$ : 488.0774; found: 488.0779. **39** (polar diastereomer); a colorless oil;  $R_f = 0.65$  (hexane/EtOAc = 1:1);  $[\alpha]_D^{25} -14.6$  ( $c$  0.85,  $\text{CHCl}_3$ ); IR (film): 3415, 3336, 2922, 2869, 1733, 1206, 1095, 824  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  7.37–7.26 (m, 5H), 5.94–5.86 (m, 1H), 5.56 (dd,  $J = 15.5, 8.3$  Hz, 1H), 4.54 (dd,  $J = 8.9, 8.3$  Hz, 1H), 4.53 (d,  $J = 12.0$  Hz, 1H), 4.50 (d,  $J = 12.0$  Hz, 1H), 4.26 (ddd,  $J = 8.9, 6.9, 5.2$  Hz, 1H), 4.12 (q,  $J = 7.2$  Hz, 2H), 3.64 (dt,  $J = 9.2, 6.0$  Hz, 1H), 3.60 (dt,  $J = 9.2, 6.6$  Hz, 1H), 2.51 (brs, 2H), 2.42–2.35 (m, 4H), 1.98–1.88 (m, 2H), 1.24 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta = 172.8$  (C), 138.4 (C), 136.3 (CH), 128.6 (CH), 127.76 (CH), 127.72 (CH), 125.4 (CH), 114.6 (C), 103.9 (C), 84.2 (CH), 82.2 (CH), 73.2 ( $\text{CH}_2$ ), 66.4 ( $\text{CH}_2$ ), 60.6 ( $\text{CH}_2$ ), 33.5 ( $\text{CH}_2$ ), 32.4 ( $\text{CH}_2$ ), 27.7 ( $\text{CH}_2$ ), 14.4 ( $\text{CH}_3$ ); HRMS (ESI): calcd for  $\text{C}_{20}\text{H}_{26}\text{NO}_5\text{Cl}_3\text{Na}$ : 488.0774; found: 488.0765.



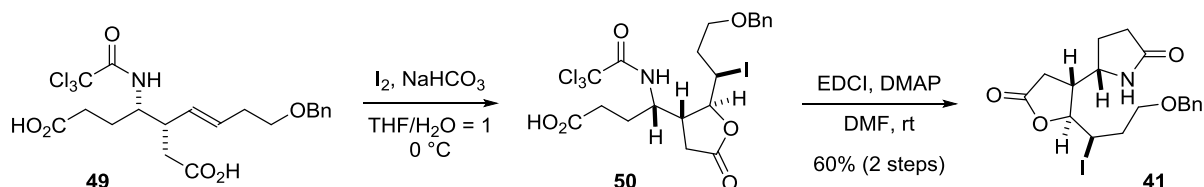
#### Diethyl (3*S*,4*S*)-3-((*E*)-4-(benzyloxy)but-1-en-1-yl)-4-(2,2,2-trichloroacetamido)heptanedioate (**40**)

A sealed tube was charged with orthoamide **39** (604 mg, 1.29 mmol), BHT (14.3 mg, 64.7  $\mu\text{mol}$ ) and *t*-BuPh (43 mL). The solution was heated to 160 °C for 15 d. After cooling to room temperature,  $\text{MeC}(\text{OEt})_3$  (1.2 mL, 6.5 mmol) and BHT (428 mg, 1.94 mmol) were added to the solution of the generated allylic amino alcohol. The solution was then heated to 140 °C for 75 min. After cooling to room temperature, the solution was directly purified by silica gel column chromatography (hexane/EtOAc 9:1) to give 328 mg of trichloroacetamide **40** (47%): a colorless oil;  $R_f = 0.83$  (hexane/EtOAc = 1:1);  $[\alpha]_D^{25} -15.3$  ( $c$  1.09,  $\text{CHCl}_3$ ); IR (film): 3334, 2981, 2929, 2856, 1732, 1714, 1518, 1176, 821  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  7.35–7.24 (m, 5H), 6.98 (d,  $J = 9.5$  Hz, 1H), 5.63 (dd,  $J = 15.2, 6.9$  Hz, 1H), 5.36 (ddt,  $J = 15.2, 9.5, 1.2$  Hz, 1H), 4.48 (s, 2H), 4.15–4.06 (m, 4H), 3.94–3.86 (m, 1H), 3.48 (t,  $J = 6.6$  Hz, 2H), 2.78–2.70 (m, 1H), 2.47 (dd,  $J = 15.8, 5.7$  Hz, 1H), 2.39 (dd,  $J = 15.8, 7.7$  Hz, 1H), 2.39–2.25 (m, 4H), 2.01 (dddd,  $J = 14.6, 7.5, 7.5, 3.2$  Hz, 1H), 1.68 (dddd,  $J = 14.6, 10.9, 7.5, 6.6$  Hz, 1H), 1.24 (t,  $J = 7.2$  Hz, 3H), 1.22 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  173.4 (C), 172.3 (C), 162.1 (C), 138.4 (C), 131.8 (CH), 129.8 (CH), 128.5 (CH), 127.7 (CH), 127.7 (CH), 92.9 (C), 73.0 ( $\text{CH}_2$ ), 69.6 ( $\text{CH}_2$ ), 60.9 ( $\text{CH}_2$ ), 60.9 ( $\text{CH}_2$ ), 54.2 (CH), 44.0 (CH), 37.2 ( $\text{CH}_2$ ), 33.1 ( $\text{CH}_2$ ), 30.7 ( $\text{CH}_2$ ), 26.5 ( $\text{CH}_2$ ), 14.31 ( $\text{CH}_3$ ), 14.29 ( $\text{CH}_3$ ); HRMS (ESI): calcd for  $\text{C}_{24}\text{H}_{33}\text{NO}_6\text{Cl}_3$ : 536.1373; found: 536.1373.



**(3*S*,4*S*)-3-((*E*)-4-(Benzyloxy)but-1-en-1-yl)-4-(2,2,2-trichloroacetamido)heptanedioic acid (49)**

Barium hydroxide octahydrate (3.28 g, 10.4 mmol) was added to a solution of trichloroacetamide **40** (558 mg, 1.04 mmol) and MeOH/H<sub>2</sub>O (2:1, 52 mL) at 0 °C. The solution was allowed to warm to room temperature, maintained for 1.5 h at room temperature, quenched with 4M aqueous HCl (5.2 mL), and extracted with CHCl<sub>3</sub> (6x 10 mL). The combined organic extracts were washed with brine (7 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc 3:2 to 2:3) to give 417 mg of bis(acid) **49** (83%): colorless crystals, mp = 102.0–103.5 °C;  $R_f = 0.19$  (EtOAc);  $[\alpha]_D^{26} -16.0$  ( $c$  1.62, CHCl<sub>3</sub>); IR (film): 3298, 2931, 1707, 1521, 821 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.35–7.25 (m, 5H), 6.93 (d,  $J = 9.5$  Hz, 1H), 5.66 (dd,  $J = 15.5, 6.9$  Hz, 1H), 5.35 (dd,  $J = 15.5, 9.5$  Hz, 1H), 4.49 (s, 2H), 4.05–3.96 (m, 1H), 3.51 (dt,  $J = 9.5, 6.3$  Hz, 1H), 3.49 (dt,  $J = 9.5, 6.6$  Hz, 1H), 2.80–2.72 (m, 1H), 2.54 (dd,  $J = 16.0, 6.6$  Hz, 1H), 2.44 (dd,  $J = 16.0, 7.2$  Hz, 1H), 2.42–2.30 (m, 4H), 2.01 (dddd,  $J = 14.6, 7.5, 7.2, 2.9$  Hz, 1H), 1.61 (ddt,  $J = 14.6, 11.2, 6.6$  Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  178.9 (C), 177.8 (C), 162.2 (C), 138.2 (C), 132.4 (CH), 129.4 (CH), 128.6 (CH), 127.9 (CH), 127.8 (CH), 92.8 (C), 73.0 (CH<sub>2</sub>), 69.4 (CH<sub>2</sub>), 53.6 (CH), 43.6 (CH), 36.9 (CH<sub>2</sub>), 33.1 (CH<sub>2</sub>), 30.3 (CH<sub>2</sub>), 26.0 (CH<sub>2</sub>); HRMS (ESI): calcd for C<sub>20</sub>H<sub>24</sub>NO<sub>6</sub>Cl<sub>3</sub>Na: 502.0567; found: 502.0558.

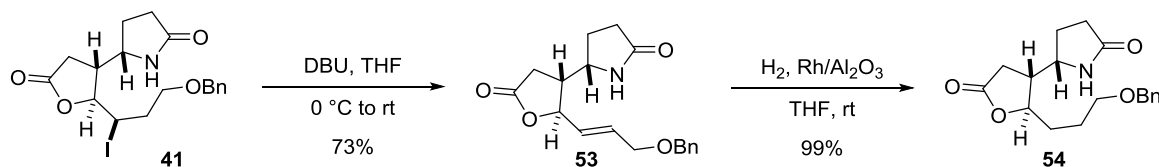


**(*S*)-5-((2*S*,3*R*)-2-((*R*)-3-(Benzyloxy)-1-iodopropyl)-5-oxotetrahydrofuran-3-yl)pyrrolidin-2-one (41)**

Iodine (1.25 g, 4.91 mmol) was added to a mixture of bis(acid) **49** (787 mg, 1.64 mmol), NaHCO<sub>3</sub> (619 mg, 7.37 mmol) and THF/H<sub>2</sub>O (1:1, 55 mL) at 0 °C. The mixture was stirred for 3 h at 0 °C, quenched with 20% aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (5.5 mL) and 1M aqueous HCl (5.5 mL), and extracted with CHCl<sub>3</sub> (6x 15 mL). The combined organic extracts were washed with brine (8 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was filtrated through a pad of silica gel, washed with hexane/EtOAc (1:1, 400 mL), and concentrated to give iodolactone **50**, which was immediately used in the next reaction without further purification.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (859 mg, 4.48 mmol) was added to the solution of iodolactone **50**, DMAP (547 mg, 4.48 mmol) and THF (150 mL) at room temperature. The solution was maintained for 16.5 h at room temperature, and concentrated. The residue was purified by

silica gel column chromatography (EtOAc) to give 436 mg of  $\gamma$ -lactam **41** (60% for 2 steps): colorless crystals, mp = 124.0–125.0 °C;  $R_f$  = 0.22 (EtOAc);  $[\alpha]_D^{25}$  +5.1 (*c* 0.91, CHCl<sub>3</sub>); IR (film): 3223, 2925, 2865, 1781, 1694, 1176, 1098, 748 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.72–7.40 (m, 1H), 7.37–7.27 (m, 5H), 4.50 (s, 2H), 4.42 (ddd, *J* = 10.3, 6.3, 4.0 Hz, 1H), 4.27 (dd, *J* = 6.0, 2.9 Hz, 1H), 3.85–3.79 (m, 1H), 3.69 (ddd, *J* = 9.5, 5.2, 4.0 Hz, 1H), 3.60 (ddd, *J* = 9.5, 9.2, 4.0 Hz, 1H), 2.82 (dd, *J* = 18.6, 10.0 Hz, 1H), 2.69–2.62 (m, 1H), 2.38 (dd, *J* = 18.6, 3.4 Hz, 1H), 2.40–2.25 (m, 2H), 2.24–2.13 (m, 2H), 1.84 (dddd, *J* = 14.6, 10.3, 4.0, 4.0 Hz, 1H), 1.78–1.68 (m, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  179.4 (C), 175.0 (C), 137.9 (C), 128.6 (CH), 128.1 (CH), 128.0 (CH), 83.8 (CH), 73.5 (CH<sub>2</sub>), 69.1 (CH<sub>2</sub>), 56.4 (CH), 43.7 (CH), 35.6 (CH), 35.3 (CH<sub>2</sub>), 30.3 (CH<sub>2</sub>), 30.3 (CH<sub>2</sub>), 24.3 (CH<sub>2</sub>); HRMS (ESI): calcd for C<sub>18</sub>H<sub>23</sub>NO<sub>4</sub>I: 444.0672; found: 444.0674.

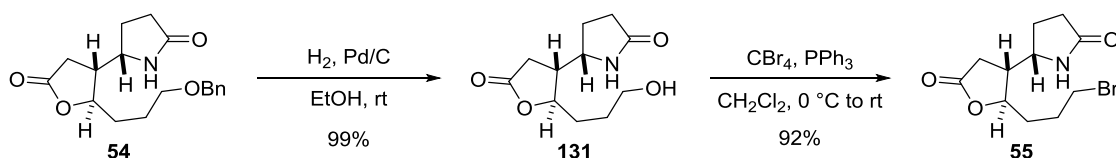


**(S)-5-((2R,3R)-2-(3-(Benzyloxy)propyl)-5-oxotetrahydrofuran-3-yl)pyrrolidin-2-one (16)**

1,8-Diazabicyclo[5.4.0]undec-7-ene (32  $\mu$ L, 210  $\mu$ mol) was added dropwise to a solution of  $\gamma$ -lactam **41** (62.7 mg, 141  $\mu$ mol) and THF (4.8 mL) at 0 °C. This solution was allowed to warm to room temperature, and maintained for 12.5 h at room temperature, and concentrated. The residue was purified by silica gel column chromatography (EtOAc) to give 32.7 mg of alkene **53** (73%): a colorless oil;  $R_f$  = 0.56 (EtOAc/MeOH = 9:1);  $[\alpha]_D^{25}$  +41.8 (*c* 1.43, CHCl<sub>3</sub>); IR (film): 3225, 2921, 2857, 1778, 1694, 1204, 1173, 1113, 974 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.85 (brs, 1H), 7.37–7.27 (m, 5H), 5.98 (dt, *J* = 15.5, 4.9 Hz, 1H), 5.77 (ddtd, *J* = 15.5, 7.2, 1.4, 1.4 Hz, 1H), 4.70 (dd, *J* = 7.2, 7.2 Hz, 1H), 4.53 (s, 2H), 4.06 (dd, *J* = 4.9, 1.4 Hz, 2H), 3.80–3.74 (m, 1H), 2.64 (dd, *J* = 17.5, 8.6 Hz, 1H), 2.47 (dd, *J* = 17.5, 8.6 Hz, 1H), 2.42–2.35 (m, 1H), 2.34 (dd, *J* = 8.6, 7.5 Hz, 2H), 2.25 (dtd, *J* = 12.6, 7.5, 7.5 Hz, 1H), 1.77–1.68 (m, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  179.3 (C), 175.1 (C), 138.0 (C), 132.4 (CH), 128.6 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 81.9 (CH), 72.8 (CH<sub>2</sub>), 69.3 (CH<sub>2</sub>), 54.6 (CH), 47.0 (CH), 30.3 (CH<sub>2</sub>), 30.2 (CH<sub>2</sub>), 25.5 (CH<sub>2</sub>); HRMS (ESI): calcd for C<sub>18</sub>H<sub>22</sub>NO<sub>4</sub>: 316.1549; found: 316.1548.

Rhodium on alumina (5%, 103 mg, 50 wt%) was added to a solution of alkene **53** (206 mg, 653  $\mu$ mol) and THF (22 mL) at room temperature. The mixture was stirred under hydrogen atmosphere (1 atm) at room temperature for 1 d, filtrated through a pad of Celite, washed with EtOAc (20 mL), and concentrated. The residue was purified by silica gel column chromatography (EtOAc/MeOH 1:0 to 9:1) to give 204 mg of benzyl ether **54** (99%): a colorless oil;  $R_f$  = 0.56 (EtOAc/MeOH = 9:1);  $[\alpha]_D^{23}$  +20.1 (*c* 1.17, CHCl<sub>3</sub>); IR (film): 3236, 2928, 2859, 1771, 1694, 1206, 1175, 1101 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.37–7.26 (m, 6H), 4.49 (s, 2H), 4.29 (ddd, *J* = 7.7, 5.4, 3.7 Hz, 1H), 3.76–3.71 (m, 1H), 3.54

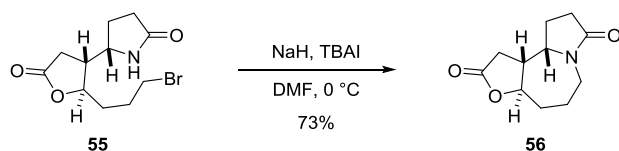
(ddd,  $J = 10.3, 9.2, 4.9$  Hz, 1H), 3.49 (ddd,  $J = 9.2, 6.3, 4.6$  Hz, 1H), 2.66 (dd,  $J = 17.8, 9.2$  Hz, 1H), 2.42 (dd,  $J = 17.8, 6.9$  Hz, 1H), 2.33 (dd,  $J = 9.2, 6.9$  Hz, 2H), 2.34–2.27 (m, 1H), 2.23 (ddt,  $J = 12.9, 7.7, 6.9$  Hz, 1H), 1.88–1.65 (m, 5H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  179.1 (C), 175.5 (C), 138.4 (C), 128.5 (CH), 127.84 (CH), 127.80 (CH), 81.9 (CH), 73.1 ( $\text{CH}_2$ ), 69.5 ( $\text{CH}_2$ ), 55.4 (CH), 45.7 (CH), 32.2 ( $\text{CH}_2$ ), 30.6 ( $\text{CH}_2$ ), 30.2 ( $\text{CH}_2$ ), 25.7 ( $\text{CH}_2$ ), 25.3 ( $\text{CH}_2$ ); HRMS (ESI): calcd for  $\text{C}_{18}\text{H}_{24}\text{NO}_4$ : 318.1705; found: 318.1706.



**(S)-5-((2R,3R)-2-(3-Bromopropyl)-5-oxotetrahydrofuran-3-yl)pyrrolidin-2-one (55)**

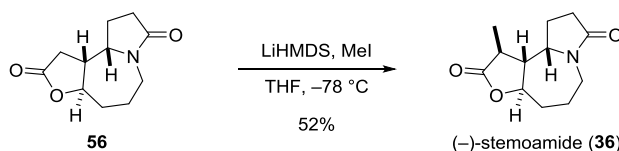
Palladium on carbon (10%, 112 mg, 100 wt%) was added to a solution of benzyl ether **54** (112 mg, 353  $\mu\text{mol}$ ) and EtOH (12 mL) at room temperature. The mixture was stirred under hydrogen atmosphere (1 atm) at room temperature for 18.5 h, filtrated through a pad of Celite, washed with EtOH (15 mL), and concentrated. The residue was purified by silica gel column chromatography ( $\text{CHCl}_3$  to EtOH) to give 79.7 mg of alcohol **131** (99%): colorless crystals, mp = 107.0–108.0  $^\circ\text{C}$ ;  $R_f = 0.14$  (EtOAc/MeOH = 4:1);  $[\alpha]_D^{26} +53.6$  ( $c$  1.16, MeOH); IR (film): 3307, 2932, 2877, 1767, 1683, 1205  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 500 MHz)  $\delta$  4.39 (ddd,  $J = 8.3, 5.7, 3.7$  Hz, 1H), 3.86–3.81 (m, 1H), 3.62 (dt,  $J = 10.9, 6.0$  Hz, 1H), 3.60 (dt,  $J = 10.9, 6.0$  Hz, 1H), 2.73 (dd,  $J = 17.2, 8.6$  Hz, 1H), 2.47 (dd,  $J = 17.2, 7.2$  Hz, 1H), 2.43 (dddd,  $J = 12.9, 8.6, 7.2, 5.7$  Hz, 1H), 2.37–2.27 (m, 3H), 1.88–1.59 (m, 5H);  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 125 MHz)  $\delta$  181.3 (C), 178.3 (C), 83.9 (CH), 62.3 ( $\text{CH}_2$ ), 56.7 (CH), 46.7 (CH), 32.6 ( $\text{CH}_2$ ), 31.2 ( $\text{CH}_2$ ), 31.0 ( $\text{CH}_2$ ), 29.6 ( $\text{CH}_2$ ), 26.0 ( $\text{CH}_2$ ); HRMS (ESI): calcd for  $\text{C}_{11}\text{H}_{17}\text{NO}_4\text{Na}$ : 250.1055; found: 250.1059.

Triphenylphosphine (112 mg, 426  $\mu\text{mol}$ ) was added to a solution of alcohol **131** (64.5 mg, 284  $\mu\text{mol}$ ),  $\text{CBr}_4$  (282 mg, 851  $\mu\text{mol}$ ) and  $\text{CH}_2\text{Cl}_2$  (9.5 mL) at 0  $^\circ\text{C}$ . The solution was allowed to warm to room temperature, maintained for 10 h at room temperature, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/MeOH 19:1) to give 75.6 mg of bromide **55** (92%): a colorless oil;  $R_f = 0.41$  (EtOAc/MeOH = 9:1);  $[\alpha]_D^{26} +24.5$  ( $c$  1.19,  $\text{CHCl}_3$ ); IR (film): 3225, 2928, 1771, 1694, 1259, 1201, 1181  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  6.69 (brs, 1H), 4.28 (ddd,  $J = 9.2, 6.0, 3.4$  Hz, 1H), 3.84–3.79 (m, 1H), 3.50 (ddd,  $J = 10.0, 7.5, 5.2$  Hz, 1H), 3.46 (ddd,  $J = 10.0, 6.9, 5.4$  Hz, 1H), 2.70 (dd,  $J = 17.8, 9.2$  Hz, 1H), 2.44 (dd,  $J = 17.8, 7.5$  Hz, 1H), 2.41–2.29 (m, 4H), 2.16–2.07 (m, 1H), 2.04–1.91 (m, 2H), 1.81–1.73 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  179.3 (C), 175.3 (C), 81.1 (CH), 55.3 (CH), 45.9 (CH), 33.7 ( $\text{CH}_2$ ), 33.3 ( $\text{CH}_2$ ), 30.5 ( $\text{CH}_2$ ), 30.4 ( $\text{CH}_2$ ), 28.5 ( $\text{CH}_2$ ), 25.3 ( $\text{CH}_2$ ); HRMS (ESI): calcd for  $\text{C}_{11}\text{H}_{16}\text{NO}_3\text{BrNa}$ : 312.0211; found: 312.0215.



**(3a*R*,10a*S*,10b*R*)-octahydro-2*H*-furo[3,2-*c*]pyrrolo[1,2-*a*]azepine-2,8(1*H*)-dione (**56**)**

Sodium hydride (63% in oil, 14 mg, 360  $\mu\text{mol}$ ) was added to a solution of bromide **55** (35.1 mg, 121  $\mu\text{mol}$ ), TBAI (4.5 mg, 12.1  $\mu\text{mol}$ ) and DMF (12 mL) at 0  $^\circ\text{C}$ . The resulting mixture was stirred for 2 h at 0  $^\circ\text{C}$ , quenched with 1M aqueous HCl (1.5 mL), and stirred for 14 h. The reaction mixture was extracted with EtOAc (6x 2 mL). The combined organic extracts were washed with brine (2x 2 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated. The residue was purified by silica gel column chromatography (EtOAc/MeOH 1:0 to 19:1) to give 18.5 mg of azepane **56** (73%): a colorless oil;  $R_f = 0.42$  (EtOAc/MeOH = 4:1);  $[\alpha]_D^{24} -143.2$  ( $c$  1.07,  $\text{CHCl}_3$ ); IR (film): 2935, 1775, 1676, 1420, 1185, 1015  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  4.29 (ddd,  $J = 10.3, 10.3, 2.9$  Hz, 1H), 4.15 (ddd,  $J = 13.8, 2.3, 2.3$  Hz, 1H), 3.99 (ddd,  $J = 10.6, 6.9, 6.3$  Hz, 1H), 2.85 (dddd,  $J = 12.6, 10.3, 8.9, 6.9$  Hz, 1H), 2.71–2.64 (m, 1H), 2.65 (dd,  $J = 17.5, 8.9$  Hz, 1H), 2.61 (dd,  $J = 17.5, 12.6$  Hz, 1H), 2.45–2.36 (m, 3H), 2.07 (dddd,  $J = 12.3, 6.3, 5.7, 3.4$  Hz, 1H), 1.91–1.82 (m, 1H), 1.71 (dddd,  $J = 12.3, 10.6, 10.6, 10.6$  Hz, 1H), 1.62–1.51 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  174.8 (C), 174.2 (C), 79.9 (CH), 56.2 (CH), 45.0 (CH), 40.3 ( $\text{CH}_2$ ), 34.8 ( $\text{CH}_2$ ), 31.1 ( $\text{CH}_2$ ), 30.7 ( $\text{CH}_2$ ), 25.6 ( $\text{CH}_2$ ), 22.8 ( $\text{CH}_2$ ); HRMS (ESI): calcd for  $\text{C}_{11}\text{H}_{16}\text{NO}_3$ : 210.1130; found: 210.1131.

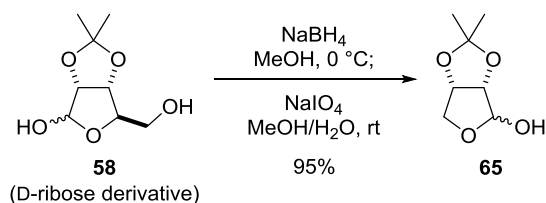


**(-)-Stemoamide (**36**)**

*n*-Butyllithium (1.4 M in hexane, 190  $\mu\text{L}$ , 270  $\mu\text{mol}$ ) was added to a solution of  $(\text{TMS})_2\text{NH}$  (65  $\mu\text{L}$ , 270  $\mu\text{mol}$ ) and THF (1.0 mL) at  $-78\text{ }^\circ\text{C}$ . The solution was maintained for 15 min at  $-78\text{ }^\circ\text{C}$ . A solution of azepane **56** (16.0 mg, 76.5  $\mu\text{mol}$ ) and THF (500  $\mu\text{L}$ ) was then added dropwise to the solution of  $\text{LiN}(\text{TMS})_2$  via cannula at  $-78\text{ }^\circ\text{C}$ . The resulting solution was allowed to warm to  $-40\text{ }^\circ\text{C}$ , stirred for 1 h at  $-40\text{ }^\circ\text{C}$ , cooled to  $-78\text{ }^\circ\text{C}$ , and stirred for 1 h. Methyl iodide (5.9  $\mu\text{L}$ , 120  $\mu\text{mol}$ ) was then added dropwise to the solution at  $-78\text{ }^\circ\text{C}$ . After stirring for 15 min at  $-78\text{ }^\circ\text{C}$ , the solution was allowed to warm to room temperature, and maintained for 13.5 h at room temperature. The solution was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (1.0 mL) and 20% aqueous  $\text{Na}_2\text{S}_2\text{O}_3$  (1.0 mL), and extracted with EtOAc (4x 2 mL). The combined organic extracts were washed with brine (2 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated. The residue was purified by silica gel column chromatography (EtOAc/MeOH 1:0 to 9:1) to give 8.9 mg of (-)-stemoamide **36** (52%): colorless crystals, mp = 184.0–185.0  $^\circ\text{C}$  [lit.<sup>3k</sup> mp = 184–185  $^\circ\text{C}$ ];  $R_f = 0.52$

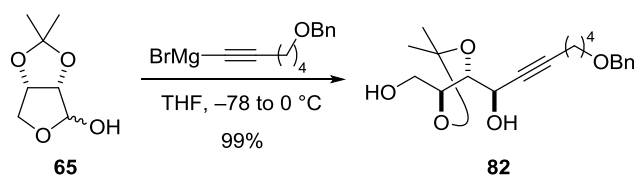
(EtOAc/MeOH = 4:1);  $[\alpha]_D^{21} -180.7$  (*c* 0.89, MeOH) [lit.<sup>3a</sup>  $[\alpha]_D^{26} -181$  (*c* 0.89, MeOH)]; IR (film): 2938, 1765, 1685, 1422, 1192, 1009  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  4.20 (ddd, *J* = 10.3, 10.3, 3.2 Hz, 1H), 4.19–4.13 (m, 1H), 3.99 (ddd, *J* = 10.9, 6.4, 6.4 Hz, 1H), 2.69–2.62 (m, 1H), 2.60 (dq, *J* = 12.3, 6.9 Hz, 1H), 2.45–2.36 (m, 4H), 2.08–2.02 (m, 1H), 1.91–1.81 (m, 1H), 1.71 (dddd, *J* = 11.7, 10.9, 10.9, 10.9 Hz, 1H), 1.59–1.47 (m, 2H), 1.31 (d, *J* = 6.9 Hz, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  177.5 (C), 174.2 (C), 77.8 (CH), 56.0 (CH), 52.8 (CH), 40.4 ( $\text{CH}_2$ ), 37.5 (CH), 34.9 ( $\text{CH}_2$ ), 30.8 ( $\text{CH}_2$ ), 25.8 ( $\text{CH}_2$ ), 22.7 ( $\text{CH}_2$ ), 14.3 ( $\text{CH}_3$ ); HRMS (ESI): calcd for  $\text{C}_{12}\text{H}_{18}\text{NO}_3$ : 224.1287; found: 224.1291.

### Chapter 3: Total synthesis of (+)-neostenine



#### (3a*S*,6a*S*)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol (**65**)

Sodium borohydride (3.18 g, 84.0 mmol) was divided into four portions, and added to a solution of **58** and MeOH (21 mL) at 0 °C every 15 min. The resulting mixture was stirred for more 15 min, quenched with H<sub>2</sub>O (21 mL) and 1M HCl aq. (80 mL), and allowed to warm to room temperature. Sodium periodate (4.49 g, 21.0 mmol) was added to the mixture at room temperature. After stirring for 10 min at room temperature, the reaction mixture was quenched with saturated aqueous NaHCO<sub>3</sub> (30 mL). The resulting mixture was filtrated to remove white solid, which was washed with EtOAc (50 mL). The combined filtrate was extracted with EtOAc (12x 50 mL). The combined organic extracts were washed with brine (200 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane 1:3) to give 1.60 g of lactol **65** (95%), which was identical to reported data.<sup>[5]</sup>



#### (*R*)-7-(benzyloxy)-1-((4*R*,5*S*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)hept-2-yn-1-ol (**82**)

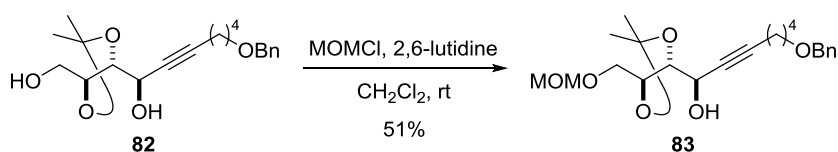
*i*-Propyl bromide (13 mL, 140 mmol) was added dropwise to a stirring mixture of Mg (3.72 g, 110 mmol), (CH<sub>2</sub>Br)<sub>2</sub> (130 μL, 1.5 mmol) and THF (230 mL) at room temperature. After stirring for 4 h at room temperature, this reaction mixture was added dropwise to the alkyne<sup>[6]</sup> (28.8 g, 153 mmol) via cannula at room temperature. The resulting mixture was heated to 50 °C, was maintained at 50 °C for 1 h, and cooled to -78 °C. A solution of lactol **65** (4.91 g, 30.6 mmol) and THF (76 mL) was added to the mixture of the magnesium acetylide via cannula at -78 °C. The resulting mixture was stirred for 1 h at -78 °C, and warmed to 0 °C. After stirring for 18 h at 0 °C, the reaction mixture was quenched with saturated aqueous NH<sub>4</sub>Cl (300 mL) and H<sub>2</sub>O (300 mL), and extracted with EtOAc (3x 100 mL). The combined organic extracts were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was purified

<sup>[5]</sup> R. H. Shah, *Carbohydr. Res.* **1986**, *155*, 212–216.

<sup>[6]</sup> a) A. W. Burgstahler, L. O. Weigel, M. E. Sanders, C. G. Shaefer, *J. Org. Chem.* **1977**, *42*, 566–568; b) K. C. Nicolaou, C. A. Veale, S. E. Webber, H. Katerinopoulos, *J. Am. Chem. Soc.* **1985**, *107*, 7515–7518.

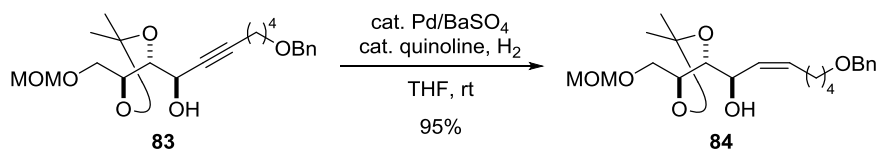


by silica gel column chromatography (hexane /EtOAc 1:3) to give 10.6 g of diol **82** (99%): a colorless oil;  $[\alpha]_D^{23} +11.5$  (*c* 1.05, CHCl<sub>3</sub>); IR (film) 3383, 2937, 2866, 1372, 1218, 1077, 1046 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.36–7.25 (m, 5H), 4.59–4.54 (m, 1H), 4.50 (s, 2H), 4.30 (ddd, *J* = 6.3, 5.7, 4.6 Hz, 1H), 4.18 (dd, *J* = 6.3, 6.3 Hz, 1H), 3.95 (dd, *J* = 11.7, 5.7 Hz, 1H), 3.88 (dd, *J* = 11.7, 4.6 Hz, 1H), 3.52–3.45 (m, 1H), 3.49 (t, *J* = 6.3 Hz, 2H), 2.89 (brs, 1H), 2.26 (td, *J* = 6.9, 2.0 Hz, 2H), 1.75–1.69 (m, 2H), 1.65–1.58 (m, 2H), 1.48 (s, 3H), 1.37 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 138.4 (C), 128.5 (CH), 127.8 (CH), 127.7 (CH), 108.7 (C), 86.9 (C), 79.3 (CH), 78.7 (C), 77.3 (CH), 73.0 (CH<sub>2</sub>), 69.9 (CH<sub>2</sub>), 61.6 (CH), 60.5 (CH<sub>2</sub>), 28.9 (CH<sub>2</sub>), 27.5 (CH<sub>3</sub>), 25.31 (CH<sub>2</sub>), 25.26 (CH<sub>3</sub>), 18.7 (CH<sub>2</sub>); HRMS (ESI), calcd for C<sub>20</sub>H<sub>28</sub>O<sub>5</sub>Na<sup>+</sup> (*M*+Na)<sup>+</sup> 371.1834, found 371.1833.



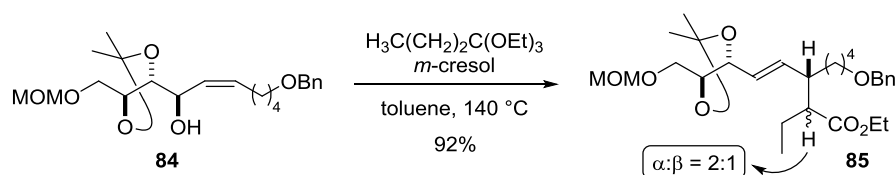
**(*R*)-7-(benzyloxy)-1-((4*R*,5*S*)-5-((methoxymethoxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)hept-2-yn-1-ol (**83**)**

Chloromethyl methyl ether (3.2 mL, 42 mmol) was added to a solution of diol **82** (7.40 g, 21.2 mmol), 2,6-lutidine (7.4 mL, 64 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (210 mL) at 0 °C. This solution was maintained for 5 min at 0 °C, and then allowed to warm to room temperature. The solution was maintained for 9 h at room temperature, quenched with 0.2M aqueous HCl (100 mL), and extracted with EtOAc (3x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc 3:1) to give 4.24 g of MOM ether **83** (51%), along with recovery of 1.34 g of diol **82** (18%). MOM ether **83**: a colorless oil;  $[\alpha]_D^{23} +6.9$  (*c* 1.00, CHCl<sub>3</sub>); IR (film) 3441, 2937, 2884, 1372, 1216, 1109, 1042 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.36–7.25 (m, 5H), 4.67 (s, 2H), 4.52–4.48 (m, 1H), 4.49 (s, 2H), 4.39 (ddd, *J* = 6.0, 6.0, 6.0 Hz, 1H), 4.20 (dd, *J* = 6.0, 6.0 Hz, 1H), 3.91 (dd, *J* = 10.6, 6.0 Hz, 1H), 3.76 (dd, *J* = 10.6, 6.0 Hz, 1H), 3.48 (t, *J* = 6.0 Hz, 2H), 3.38 (s, 3H), 3.07 (d, *J* = 5.4 Hz, 1H), 2.26 (td, *J* = 7.2, 2.0 Hz, 2H), 1.75–1.69 (m, 2H), 1.67–1.59 (m, 2H), 1.48 (s, 3H), 1.38 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 138.7 (C), 128.5 (CH), 127.7 (CH), 127.6 (CH), 109.1 (C), 97.0 (CH<sub>2</sub>), 86.9 (C), 79.6 (CH), 78.6 (C), 75.9 (CH), 73.0 (CH<sub>2</sub>), 69.9 (CH<sub>2</sub>), 66.0 (CH<sub>2</sub>), 61.8 (CH), 55.8 (CH<sub>3</sub>), 29.0 (CH<sub>2</sub>), 27.6 (CH<sub>3</sub>), 25.4 (CH<sub>3</sub>), 25.3 (CH<sub>2</sub>), 18.8 (CH<sub>2</sub>); HRMS (ESI), calcd for C<sub>22</sub>H<sub>32</sub>O<sub>6</sub>Na<sup>+</sup> (*M*+Na)<sup>+</sup> 415.2097, found 415.2103.



**(*R,Z*)-7-(benzyloxy)-1-((4*R*,5*S*)-5-((methoxymethoxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)hept-2-en-1-ol (**84**)**

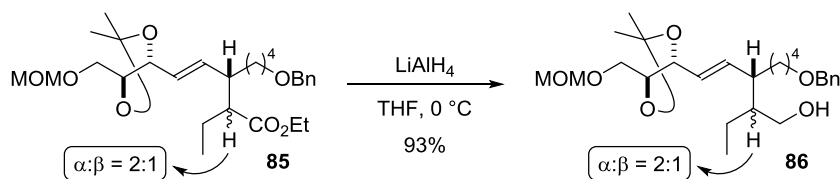
Palladium on BaSO<sub>4</sub> (5%, 212 mg, 5.0 wt%) was added to a solution of MOM ether **83** (4.24 g, 10.8 mmol), quinoline (49 μL, 410 μmol) and THF (110 mL) at room temperature. After stirring for 30 min, the flask was purged with hydrogen. The mixture was stirred under hydrogen atmosphere (1 atm) at room temperature for 1 d, filtrated through a pad of Celite, washed with EtOAc (100 mL), and concentrated. The residue was diluted with EtOAc (50 mL) and 0.1M aqueous HCl (5.0 mL), and extracted with EtOAc (2x 10 mL). The combined organic extracts were washed with brine (5.0 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc 3:1 to 2:1) to give 4.03 g of alkene **84** (95%): a colorless oil;  $[\alpha]_D^{27} -15.0$  (*c* 0.96, CHCl<sub>3</sub>); IR (film) 3470, 2934, 2861, 1217, 1106, 1080, 1040 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.36–7.25 (m, 5H), 5.66 (dtd, *J* = 10.9, 7.5, 0.9 Hz, 1H), 5.49 (ddt, *J* = 10.9, 8.6, 1.4 Hz, 1H), 4.69 (s, 2H), 4.54 (dddd, *J* = 8.6, 8.6, 3.4, 0.9 Hz, 1H), 4.49 (s, 2H), 4.39 (ddd, *J* = 6.9, 5.7, 5.7 Hz, 1H), 4.07 (dd, *J* = 8.6, 5.7 Hz, 1H), 3.87 (dd, *J* = 10.3, 6.9 Hz, 1H), 3.63 (dd, *J* = 10.3, 5.7 Hz, 1H), 3.47 (t, *J* = 6.3 Hz, 2H), 3.40 (s, 3H), 2.90 (d, *J* = 3.4 Hz, 1H), 2.25–2.11 (m, 2H), 1.68–1.61 (m, 2H), 1.53–1.46 (m, 2H), 1.40 (s, 3H), 1.34 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 138.7 (C), 134.7 (CH), 129.1 (CH), 128.5 (CH), 127.7 (CH), 127.6 (CH), 108.8 (C), 97.0 (CH<sub>2</sub>), 79.9 (CH), 76.0 (CH), 73.0 (CH<sub>2</sub>), 70.3 (CH<sub>2</sub>), 66.5 (CH<sub>2</sub>), 65.6 (CH), 55.8 (CH<sub>3</sub>), 29.5 (CH<sub>2</sub>), 27.98 (CH<sub>2</sub>), 27.97 (CH<sub>3</sub>), 26.3 (CH<sub>2</sub>), 25.4 (CH<sub>3</sub>); HRMS (ESI), calcd for C<sub>22</sub>H<sub>34</sub>O<sub>6</sub>Na<sup>+</sup> (*M*+Na)<sup>+</sup> 417.2253, found 417.2253.



**Ethyl (2*R*,3*S*)-7-(benzyloxy)-2-ethyl-3-((*E*)-2-((4*R*,5*S*)-5-((methoxymethoxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)vinyl)heptanoate (**85**)**

A sealed tube was charged with alkene **84** (2.00 g, 5.07 mmol), H<sub>3</sub>C(CH<sub>2</sub>)<sub>2</sub>C(OEt)<sub>3</sub> (11 mL, 51 mmol), *m*-cresol (1.6 mL, 15 mmol) and toluene (72 mL). The solution was heated to 140 °C, and stirred at 140 °C for 6.5 d. The resulting solution was cooled to room temperature, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc 9:1 to 7:1) to give 2.30 g of ethyl ester **85** (92%, 2:1 inseparable mixture of diastereomers): a colorless oil;  $[\alpha]_D^{26} +2.5$  (*c* 1.04, CHCl<sub>3</sub>, 2:1

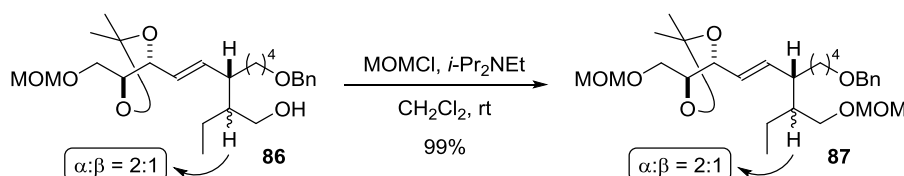
mixture of diastereomers); IR (film) 2935, 2876, 1730, 1455, 1370, 1215, 1153, 1112, 1045  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 2.0:1 mixture of diastereomers)  $\delta$  7.36–7.25 (m, 5H), 5.64 (dd,  $J = 15.5, 9.5, 0.9$  Hz, 2/3H), 5.45 (dd,  $J = 15.5, 6.9$  Hz, 1/3H), 5.40 (dd,  $J = 15.5, 8.0$  Hz, 1/3H), 5.38 (dd,  $J = 15.5, 7.7$  Hz, 2/3H), 4.64–4.57 (m, 1/3H), 4.62 (s, 4/3H), 4.61 (s, 2/3H), 4.59 (ddd,  $J = 7.7, 6.9, 0.9$  Hz, 2/3H), 4.48 (s, 4/3H), 4.47 (s, 2/3H), 4.35–4.29 (m, 1H), 4.14 (q,  $J = 7.2$  Hz, 2/3H), 4.11 (q,  $J = 7.2$  Hz, 4/3H), 3.52–3.46 (m, 4/3H), 3.50 (dd,  $J = 6.3, 4.3$  Hz, 2/3H), 3.43 (t,  $J = 6.6$  Hz, 4/3H), 3.42 (t,  $J = 6.6$  Hz, 2/3H), 3.34 (s, 2H), 3.34 (s, 1H), 2.30–2.19 (m, 5/3H), 2.15 (ddd,  $J = 10.6, 9.5, 4.0$  Hz, 1/3H), 1.69–1.43 (m, 5H), 1.50 (s, 1H), 1.45 (s, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , 2.0:1 mixture of diastereomers)  $\delta$  175.4 (C), 174.8 (C), 138.73 (C), 138.71 (C), 136.3 (CH), 135.9 (CH), 128.5 (CH), 128.5 (CH), 127.74 (CH), 127.72 (CH), 127.68 (CH), 127.63 (CH), 127.61 (CH), 127.2 (CH), 109.1 (C), 109.0 (C), 96.8 ( $\text{CH}_2$ ), 96.8 ( $\text{CH}_2$ ), 78.00 (CH), 77.99 (CH), 77.20 (CH), 77.17 (CH), 73.01 ( $\text{CH}_2$ ), 72.99 ( $\text{CH}_2$ ), 70.3 ( $\text{CH}_2$ ), 70.3 ( $\text{CH}_2$ ), 67.5 ( $\text{CH}_2$ ), 67.4 ( $\text{CH}_2$ ), 60.2 ( $\text{CH}_2$ ), 60.1 ( $\text{CH}_2$ ), 55.40 ( $\text{CH}_3$ ), 55.39 ( $\text{CH}_3$ ), 52.2 (CH), 51.8 (CH), 45.4 (CH), 45.0 (CH), 32.7 ( $\text{CH}_2$ ), 32.0 ( $\text{CH}_2$ ), 29.8 ( $\text{CH}_2$ ), 29.7 ( $\text{CH}_2$ ), 28.0 ( $\text{CH}_3$ ), 28.0 ( $\text{CH}_3$ ), 25.50 ( $\text{CH}_3$ ), 25.48 ( $\text{CH}_3$ ), 24.1 ( $\text{CH}_2$ ), 24.0 ( $\text{CH}_2$ ), 23.4 ( $\text{CH}_2$ ), 23.4 ( $\text{CH}_2$ ), 14.51 ( $\text{CH}_3$ ), 14.49 ( $\text{CH}_3$ ), 12.2 ( $\text{CH}_3$ ), 12.0 ( $\text{CH}_3$ ); HRMS (ESI), calcd for  $\text{C}_{28}\text{H}_{44}\text{O}_7\text{K}^+$  ( $\text{M}+\text{K}$ ) $^+$  531.2724, found 531.2725.



**(2R,3S)-7-(benzyloxy)-2-ethyl-3-((E)-2-((4R,5S)-5-((methoxymethoxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)vinyl)heptan-1-ol (86)**

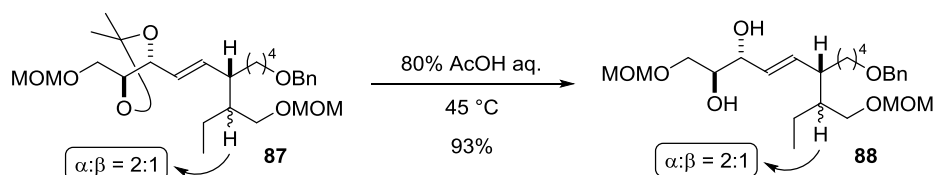
Lithium aluminium hydride (1.11 g, 29.7 mmol) was added to a solution of ethyl ester **85** (4.87 g, 4.73 mmol) and THF (100 mL) at 0 °C. The resulting mixture was stirred for 2.5 h at 0 °C, quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (25 mL) and  $\text{H}_2\text{O}$  (25 mL), and extracted with EtOAc (8x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc 2:1 to 1:1) to give 4.15 g of alcohol **86** (93%, 2:1 inseparable mixture of diastereomers): a colorless oil;  $[\alpha]_D^{26} -9.8$  ( $c$  1.01,  $\text{CHCl}_3$ , 2:1 mixture of diastereomers); IR (film) 3476, 2933, 2875, 1455, 1370, 1215, 1111, 1044  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ , 2:1 mixture of diastereomers)  $\delta$  7.36–7.25 (m, 5H), 5.61 (dd,  $J = 15.5, 9.5$  Hz, 2/3H), 5.59 (dd,  $J = 15.5, 9.5$  Hz, 1/3H), 5.43 (dd,  $J = 15.5, 7.7$  Hz, 1/3H), 5.42 (dd,  $J = 15.5, 7.7$  Hz, 2/3H), 4.65–4.58 (m, 1H), 4.62 (s, 2H), 4.49 (s, 2H), 4.32 (ddd,  $J = 7.5, 7.5, 4.6$  Hz, 1H), 3.62 (dd,  $J = 10.9, 4.3$  Hz, 1H), 3.57–3.50 (m, 2H), 3.49 (dd,  $J = 10.6, 7.5$  Hz, 1H), 3.44 (t,  $J = 6.6$  Hz, 2H), 3.35 (s, 3H), 2.33–2.25 (m, 1/3H), 2.18–2.08 (m, 2/3H), 1.73 (brs, 2/3H), 1.67–1.12 (m, 28/3H), 1.45 (s, 3H), 1.38 (s, 3H), 0.91 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , 2:1 mixture of diastereomers)  $\delta$  138.7 (C), 138.7

(C), 137.8 (CH), 137.3 (CH), 128.5 (CH), 128.5 (CH), 127.8 (CH), 127.6 (CH), 126.6 (CH), 126.1 (CH), 108.9 (C), 108.9 (C), 96.8 (CH<sub>2</sub>), 96.8 (CH<sub>2</sub>), 78.21 (CH), 78.16 (CH), 77.12 (CH), 77.09 (CH), 70.3 (CH<sub>2</sub>), 70.3 (CH<sub>2</sub>), 70.4 (CH<sub>2</sub>), 70.4 (CH<sub>2</sub>), 67.5 (CH<sub>2</sub>), 67.4 (CH<sub>2</sub>), 63.5 (CH<sub>2</sub>), 63.1 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>), 55.4 (CH<sub>3</sub>), 46.8 (CH), 46.4 (CH), 43.7 (CH), 43.5 (CH), 31.8 (CH<sub>2</sub>), 31.8 (CH<sub>2</sub>), 29.8 (CH<sub>2</sub>), 29.8 (CH<sub>2</sub>), 28.1 (CH<sub>3</sub>), 28.1 (CH<sub>3</sub>), 25.5 (CH<sub>3</sub>), 25.5 (CH<sub>3</sub>), 24.6 (CH<sub>2</sub>), 24.5 (CH<sub>2</sub>), 21.6 (CH<sub>2</sub>), 20.1 (CH<sub>2</sub>), 12.6 (CH<sub>3</sub>), 11.9 (CH<sub>3</sub>); HRMS (ESI), calcd for C<sub>26</sub>H<sub>42</sub>O<sub>6</sub>K<sup>+</sup> (M+K)<sup>+</sup> 489.2618, found 489.2617.



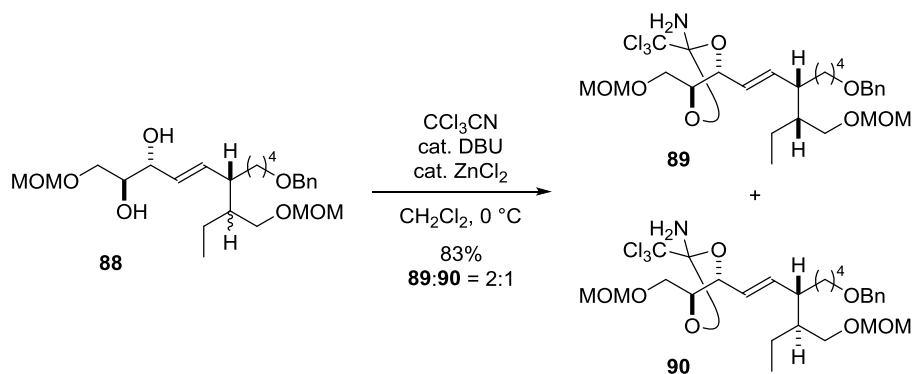
**(4*R*,5*S*)-4-((*S*,*E*)-7-(benzyloxy)-3-((*R*)-1-(methoxymethoxy)butan-2-yl)hept-1-en-1-yl)-5-((methoxymethoxy)methyl)-2,2-dimethyl-1,3-dioxolane (87)**

Chloromethyl methyl ether (2.1 mL, 28 mmol) was added to a solution of alcohol **86** (4.15 g, 9.21 mmol), *i*-Pr<sub>2</sub>NEt (9.4 mL, 55 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (46 mL) at 0 °C. This solution was maintained for 5 min at 0 °C, and then allowed to warm to room temperature. The solution was maintained for 8 h at room temperature, quenched with H<sub>2</sub>O (10 mL) and 4M aqueous HCl (6.9 mL), and extracted with CHCl<sub>3</sub> (6x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc 4:1) to give 4.53 g of MOM ether **87** (99%, 2:1 inseparable mixture of diastereomers): a colorless oil; [α]<sub>D</sub><sup>26</sup> -3.2 (*c* 0.98, CHCl<sub>3</sub>); IR (film) 2933, 2878, 1455, 1215, 1110, 1048 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 2:1 mixture of diastereomers) δ 7.36–7.25 (m, 5H), 5.55 (dd, *J* = 15.5, 9.2 Hz, 2/3H), 5.54 (dd, *J* = 15.2, 9.2 Hz, 1/3H), 5.39 (dd, *J* = 15.2, 8.0 Hz, 1/3H), 5.38 (dd, *J* = 15.5, 8.0 Hz, 2/3H), 4.65–4.57 (m, 1H), 4.62 (s, 2H), 4.59 (s, 2/3H), 4.58 (s, 4/3H), 4.48 (s, 2H), 4.36–4.30 (m, 1H), 3.54–3.42 (m, 3H), 3.44 (t, *J* = 6.6 Hz, 2H), 3.41–3.35 (m, 1H), 3.36 (s, 1H), 3.35 (s, 2H), 3.34 (s, 3H), 2.31–2.22 (m, 1/3H), 2.22–2.14 (m, 2/3H), 1.67–1.10 (m, 9H), 1.50 (s, 3H), 1.38 (s, 3H), 0.90 (t, *J* = 7.5 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, 2:1 mixture of diastereomers) δ 138.7 (C), 138.7 (C), 137.4 (CH), 137.2 (CH), 128.5 (CH), 128.5 (CH), 127.8 (CH), 127.6 (CH), 126.8 (CH), 126.5 (CH), 109.0 (C), 109.0 (C), 96.78 (CH<sub>2</sub>), 96.78 (CH<sub>2</sub>), 96.76 (CH<sub>2</sub>), 96.76 (CH<sub>2</sub>), 78.34 (CH), 78.30 (CH), 77.3 (CH), 77.2 (CH<sub>2</sub>), 73.0 (CH<sub>2</sub>), 70.46 (CH<sub>2</sub>), 70.45 (CH<sub>2</sub>), 68.5 (CH<sub>2</sub>), 68.3 (CH<sub>2</sub>), 67.5 (CH<sub>2</sub>), 67.5 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>), 55.4 (CH<sub>3</sub>), 55.3 (CH<sub>3</sub>), 55.3 (CH<sub>3</sub>), 44.5 (CH), 44.2 (CH), 43.5 (CH), 43.4 (CH), 31.8 (CH<sub>2</sub>), 31.8 (CH<sub>2</sub>), 29.95 (CH<sub>2</sub>), 29.91 (CH<sub>2</sub>), 28.1 (CH<sub>3</sub>), 28.1 (CH<sub>3</sub>), 25.5 (CH<sub>3</sub>), 25.5 (CH<sub>3</sub>), 24.6 (CH<sub>2</sub>), 24.5 (CH<sub>2</sub>), 22.1 (CH<sub>2</sub>), 20.8 (CH<sub>2</sub>), 12.5 (CH<sub>3</sub>), 11.9 (CH<sub>3</sub>); HRMS (ESI), calcd for C<sub>28</sub>H<sub>46</sub>O<sub>7</sub>K<sup>+</sup> (M+K)<sup>+</sup> 533.2881, found 533.2880.



**(6*S*,7*R*,10*S*,11*R*,*E*)-10-(4-(benzyloxy)butyl)-11-ethyl-2,4,13,15-tetraoxahexadec-8-ene-6,7-diol (**88**)**

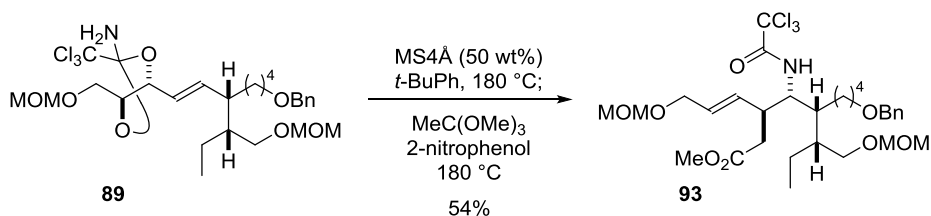
A flask was charged with MOM ether **87** (4.53 g, 9.16 mmol) and AcOH/H<sub>2</sub>O (4:1, 23 mL). The solution was then heated to 45 °C, and maintained at 45 °C for 9 h. The resulting solution was cooled to room temperature, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc 1:2 to 1:9) to give 3.88 g of allylic 1,2-diol **88** (93%, 2:1 inseparable mixture of diastereomers): a colorless oil;  $[\alpha]_D^{26} -0.2$  (*c* 1.04, CHCl<sub>3</sub>); IR (film) 3449, 2932, 2878, 1454, 1151, 1109, 1044 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 2:1 mixture of diastereomers)  $\delta$  7.36–7.25 (m, 5H), 5.55 (dd, *J* = 15.5, 8.9 Hz, 2/3H), 5.55 (dd, *J* = 15.5, 8.6 Hz, 1/3H), 5.49 (dd, *J* = 15.5, 5.7 Hz, 1/3H), 5.48 (dd, *J* = 15.5, 6.3 Hz, 2/3H), 4.64 (s, 2/3H), 4.63 (s, 4/3H), 4.59 (s, 2/3H), 4.57 (s, 4/3H), 4.48 (s, 2H), 4.22–4.16 (m, 1H), 3.77–3.71 (m, 1H), 3.69 (dd, *J* = 10.6, 3.2 Hz, 1/3H), 3.68 (dd, *J* = 10.6, 3.2 Hz, 2/3H), 3.60 (dd, *J* = 10.6, 6.6 Hz, 2/3H), 3.60 (dd, *J* = 10.6, 6.9 Hz, 1/3H), 3.51 (dd, *J* = 9.7, 5.2 Hz, 2/3H), 3.50–3.30 (m, 10/3H), 3.37 (s, 3H), 3.35 (s, 1H), 3.34 (s, 2H), 2.92 (brs, 1H), 2.46 (brs, 2/3H), 2.31–2.24 (m, 1/3H), 2.20–2.12 (m, 2/3H), 1.76 (brs, 1/3H), 1.67–1.23 (m, 26/3H), 1.21–1.12 (m, 1/3H), 0.90 (t, *J* = 7.2 Hz, 1H), 0.90 (t, *J* = 7.2 Hz, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, 2:1 mixture of diastereomers)  $\delta$  138.7 (C), 138.7 (C), 136.2 (CH), 135.8 (CH), 129.7 (CH), 129.4 (CH), 128.5 (CH), 128.5 (CH), 127.8 (CH), 127.8 (CH), 127.6 (CH), 127.6 (CH), 97.21 (CH<sub>2</sub>), 97.20 (CH<sub>2</sub>), 96.79 (CH<sub>2</sub>), 96.76 (CH<sub>2</sub>), 73.93 (CH), 73.87 (CH), 73.01 (CH<sub>3</sub>), 73.01 (CH<sub>3</sub>), 72.95 (CH), 72.95 (CH), 70.4 (CH<sub>2</sub>), 70.4 (CH<sub>2</sub>), 69.71 (CH<sub>2</sub>), 69.69 (CH<sub>2</sub>), 68.6 (CH<sub>2</sub>), 68.4 (CH<sub>2</sub>), 55.6 (CH<sub>3</sub>), 55.6 (CH<sub>3</sub>), 55.42 (CH<sub>3</sub>), 55.38 (CH<sub>3</sub>), 44.6 (CH), 44.3 (CH), 43.6 (CH), 43.5 (CH), 31.8 (CH<sub>2</sub>), 31.7 (CH<sub>2</sub>), 29.83 (CH<sub>2</sub>), 29.80 (CH<sub>2</sub>), 24.54 (CH<sub>2</sub>), 24.48 (CH<sub>2</sub>), 22.2 (CH<sub>2</sub>), 20.8 (CH<sub>2</sub>), 12.5 (CH<sub>3</sub>), 11.8 (CH<sub>3</sub>); HRMS (ESI), calcd for C<sub>25</sub>H<sub>42</sub>O<sub>7</sub>Na<sup>+</sup> (*M*+Na)<sup>+</sup> 477.2828, found 477.2828.



**(4*R*,5*S*)-4-((*S*,*E*)-7-(benzyloxy)-3-((*R*)-1-(methoxymethoxy)butan-2-yl)hept-1-en-1-yl)-5-((methoxymethoxy)methyl)-2-(trichloromethyl)-1,3-dioxolan-2-amine (**89**)**

1,8-Diazabicyclo[5.4.0]undec-7-ene (240  $\mu$ L, 1.6 mmol) was added dropwise to a solution of allylic

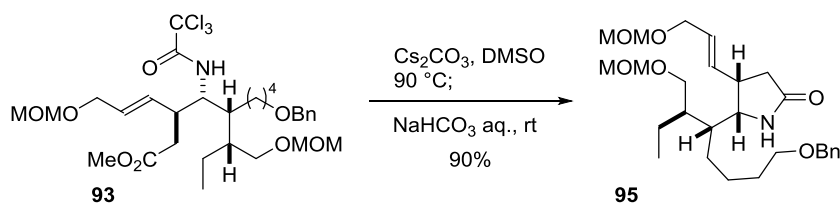
1,2-diol **88** (1.86 g, 4.09 mmol), CCl<sub>3</sub>CN (530 μL, 5.3 mmol), ZnCl<sub>2</sub> (55.8 mg, 409 μmol) and CH<sub>2</sub>Cl<sub>2</sub> (140 mL) at 0 °C. The solution was maintained at 0 °C for 20 h, allowed to warm to room temperature, and concentrated. The residue was purified by silica gel column chromatography (toluene/EtOAc 2:1) to give 1.37 g of orthoamide **89** (56%) and 653 mg of orthoamide **90** (27%). Orthoamide **89**: a colorless oil; [α]<sub>D</sub><sup>25</sup> -6.7 (c 1.04, CHCl<sub>3</sub>); IR (film) 3419, 3334, 2932, 2878, 1200, 1108, 1046 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.36–7.25 (m, 5H), 5.66 (dd, *J* = 15.2, 9.5 Hz, 1H), 5.48 (dd, *J* = 15.2, 8.3 Hz, 1H), 5.04 (dd, *J* = 8.3, 7.7 Hz, 1H), 4.74 (ddd, *J* = 8.6, 7.7, 3.7 Hz, 1H), 4.61 (s, 2H), 4.57 (s, 2H), 4.48 (s, 2H), 3.72 (dd, *J* = 10.6, 8.6 Hz, 1H), 3.50 (dd, *J* = 10.6, 3.7 Hz, 1H), 3.49 (dd, *J* = 9.7, 5.2 Hz, 1H), 3.44 (t, *J* = 6.6 Hz, 2H), 3.39 (dd, *J* = 9.7, 5.7 Hz, 1H), 3.34 (s, 6H), 2.53 (brs, 2H), 2.23–2.16 (m, 1H), 1.67–1.53 (m, 2H), 1.52–1.44 (m, 2H), 1.40–1.20 (m, 3H), 1.38 (dq, *J* = 7.2, 7.2 Hz, 2H), 0.90 (t, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 139.5 (CH), 138.7 (C), 128.5 (CH), 127.7 (CH), 127.6 (CH), 124.1 (CH), 114.2 (C), 102.7 (C), 96.8 (CH<sub>2</sub>), 96.6 (CH<sub>2</sub>), 80.4 (CH), 79.4 (CH), 73.0 (CH<sub>2</sub>), 70.4 (CH<sub>2</sub>), 68.1 (CH<sub>2</sub>), 66.3 (CH<sub>2</sub>), 55.38 (CH<sub>3</sub>), 55.36 (CH<sub>3</sub>), 44.1 (CH), 43.7 (CH), 31.6 (CH<sub>2</sub>), 29.9 (CH<sub>2</sub>), 24.5 (CH<sub>2</sub>), 22.0 (CH<sub>2</sub>), 11.9 (CH<sub>3</sub>); HRMS (ESI), calcd for C<sub>27</sub>H<sub>42</sub>NO<sub>7</sub>Cl<sub>3</sub>Na<sup>+</sup> (M+Na)<sup>+</sup> 620.1925, found 620.1924. Orthoamide **90**: a colorless oil; [α]<sub>D</sub><sup>27</sup> -12.7 (c 1.00, CHCl<sub>3</sub>); IR (film) 3418, 3333, 2933, 2879, 1201, 1151, 1109, 1047 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.36–7.25 (m, 5H), 5.65 (dd, *J* = 15.5, 9.5 Hz, 1H), 5.49 (dd, *J* = 15.5, 8.3 Hz, 1H), 5.04 (dd, *J* = 8.3, 7.7 Hz, 1H), 4.74 (ddd, *J* = 8.6, 7.7, 3.7 Hz, 1H), 4.61 (s, 2H), 4.59 (d, *J* = 6.6 Hz, 1H), 4.57 (d, *J* = 6.6 Hz, 1H), 4.48 (s, 2H), 3.72 (dd, *J* = 10.6, 8.6 Hz, 1H), 3.50 (dd, *J* = 10.6, 3.7 Hz, 1H), 3.46 (dd, *J* = 9.7, 4.9 Hz, 1H), 3.44 (t, *J* = 6.6 Hz, 2H), 3.37 (dd, *J* = 9.7, 7.5 Hz, 1H), 3.35 (s, 3H), 3.34 (s, 3H), 2.54 (brs, 2H), 2.36–2.28 (m, 1H), 1.67–1.50 (m, 3H), 1.49–1.20 (m, 5H), 1.14 (ddq, *J* = 13.8, 9.2, 7.2 Hz, 1H), 0.90 (t, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 139.1 (CH), 138.7 (C), 128.5 (CH), 127.8 (CH), 127.7 (CH), 124.5 (CH), 114.2 (C), 102.7 (C), 96.8 (CH<sub>2</sub>), 96.6 (CH<sub>2</sub>), 80.5 (CH), 79.4 (CH), 73.0 (CH<sub>2</sub>), 70.4 (CH<sub>2</sub>), 68.5 (CH<sub>2</sub>), 66.4 (CH<sub>2</sub>), 55.45 (CH<sub>3</sub>), 55.41 (CH<sub>3</sub>), 44.4 (CH), 43.4 (CH), 31.7 (CH<sub>2</sub>), 29.9 (CH<sub>2</sub>), 24.6 (CH<sub>2</sub>), 20.6 (CH<sub>2</sub>), 12.6 (CH<sub>3</sub>); HRMS (ESI), calcd for C<sub>27</sub>H<sub>42</sub>NO<sub>7</sub>Cl<sub>3</sub>Na<sup>+</sup> (M+Na)<sup>+</sup> 620.1925, found 620.1926.



**Methyl (3*S*,4*S*,5*R*)-9-(benzyloxy)-5-((*R*)-1-(methoxymethoxy)butan-2-yl)-3-((*E*)-3-(methoxymethoxy) prop-1-en-1-yl)-4-(2,2,2-trichloroacetamido)nonanoate (**93**)**

A sealed tube was charged with orthoamide **89** (182 mg, 304 μmol), MS4Å (91.0 mg, 50 wt%) and *t*-BuPh (12 mL). The mixture was heated to 180 °C for 5 d. After cooling to room temperature, MeC(OMe)<sub>3</sub> (380

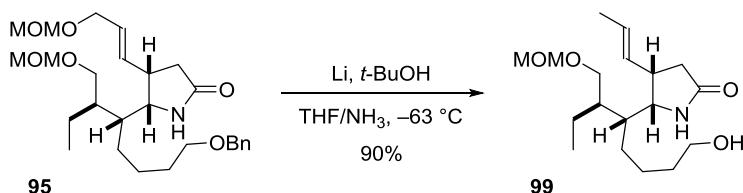
$\mu\text{L}$ , 3.0 mmol) and 2-nitrophenol (127 mg, 912  $\mu\text{mol}$ ) were added to the mixture of the generated allylic amino alcohol. The mixture was then heated to 180  $^{\circ}\text{C}$  for 3 h. After cooling to room temperature, the mixture was directly purified by silica gel column chromatography (hexane/EtOAc 2:1) to give 107 mg of trichloroacetamide **93** (54%): a yellow oil;  $[\alpha]_{\text{D}}^{24} +37.1$  ( $c$  1.03,  $\text{CHCl}_3$ ); IR (film) 3324, 2935, 2879, 1737, 1715, 1513, 1149, 1105, 1044, 821  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36–7.25 (m, 5H), 6.96 (d,  $J = 10.3$  Hz, 1H), 5.69–5.60 (m, 2H), 4.61 (d,  $J = 6.6$  Hz, 1H), 4.59 (d,  $J = 6.6$  Hz, 1H), 4.58 (s, 2H), 4.51 (d,  $J = 12.0$  Hz, 1H), 4.48 (d,  $J = 12.0$  Hz, 1H), 4.04 (ddd,  $J = 10.3, 7.2, 5.7$  Hz, 1H), 4.00 (d,  $J = 4.6$  Hz, 2H), 3.66 (s, 3H), 3.58 (dd,  $J = 10.0, 3.7$  Hz, 1H), 3.52–3.45 (m, 2H), 3.39 (dd,  $J = 10.0, 9.5$  Hz, 1H), 3.35 (s, 3H), 3.34 (s, 3H), 3.03 (dddd,  $J = 8.3, 6.6, 6.0, 5.7$  Hz, 1H), 2.57 (dd,  $J = 15.8, 6.0$  Hz, 1H), 2.37 (dd,  $J = 15.8, 8.3$  Hz, 1H), 1.86–1.79 (m, 1H), 1.66–1.48 (m, 4H), 1.48–1.31 (m, 4H), 1.13 (ddq,  $J = 14.0, 10.0, 7.2$  Hz, 1H), 0.90 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  172.3 (C), 161.9 (C), 138.7 (C), 130.7 (CH), 130.6 (CH), 128.5 (CH), 127.8 (CH), 127.6 (CH), 96.7 ( $\text{CH}_2$ ), 95.6 ( $\text{CH}_2$ ), 93.3 (C), 73.1 ( $\text{CH}_2$ ), 70.2 ( $\text{CH}_2$ ), 69.0 ( $\text{CH}_2$ ), 67.4 ( $\text{CH}_2$ ), 55.7 ( $\text{CH}_3$ ), 55.5 (CH), 55.4 ( $\text{CH}_3$ ), 51.8 ( $\text{CH}_3$ ), 41.4 (CH), 41.0 (CH), 40.5 (CH), 36.9 ( $\text{CH}_2$ ), 30.3 ( $\text{CH}_2$ ), 28.4 ( $\text{CH}_2$ ), 25.7 ( $\text{CH}_2$ ), 21.0 ( $\text{CH}_2$ ), 13.0 ( $\text{CH}_3$ ); HRMS (ESI), calcd for  $\text{C}_{30}\text{H}_{46}\text{NO}_8\text{Cl}_3\text{Na}^+$  ( $\text{M}+\text{Na}$ ) $^+$  676.2187, found 676.2166.



**(4*S*,5*S*)-5-((3*R*,4*R*)-8-(benzyloxy)-3-((methoxymethoxy)methyl)octan-4-yl)-4-(*E*)-3-(methoxymethoxy)prop-1-en-1-yl)pyrrolidin-2-one (**95**)**

Cesium carbonate (157 mg, 481  $\mu\text{mol}$ ) was added to a solution of trichloroacetamide **93** (126 mg, 192  $\mu\text{mol}$ ) and DMSO (19 mL). The resulting mixture was heated to 90  $^{\circ}\text{C}$  for 1.5 h. After cooling to room temperature, the resulting mixture was poured into ice-cold saturated aqueous  $\text{NaHCO}_3/\text{H}_2\text{O}$  (1:1, 38 mL). This solution was maintained for 30 min at 0  $^{\circ}\text{C}$ , and then allowed to warm to room temperature. The solution was maintained for 21 h at room temperature, and extracted with EtOAc (4x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc 1:2 to EtOAc/MeOH 19:1) to give 82.6 mg of lactam **95** (90%): a colorless oil;  $[\alpha]_{\text{D}}^{26} -15.6$  ( $c$  1.08,  $\text{CHCl}_3$ ); IR (film) 3211, 2933, 2877, 1695, 1149, 1106, 1046  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36–7.26 (m, 5H), 6.19 (brs, 1H), 5.78 (ddt,  $J = 15.5, 9.7, 1.2$  Hz, 1H), 5.63 (dt,  $J = 15.5, 5.7$  Hz, 1H), 4.61 (d,  $J = 6.6$  Hz, 1H), 4.59 (s, 2H), 4.57 (d,  $J = 6.6$  Hz, 1H), 4.48 (s, 2H), 4.01 (dd,  $J = 5.7, 1.2$  Hz, 2H), 3.61 (dd,  $J = 10.0, 2.6$  Hz, 1H), 3.55 (dd,  $J = 10.3, 6.0$  Hz, 1H), 3.50 (dd,  $J = 10.0, 5.4$  Hz, 1H), 3.45–3.40 (m, 2H), 3.34 (s, 3H), 3.33 (s, 3H), 3.10

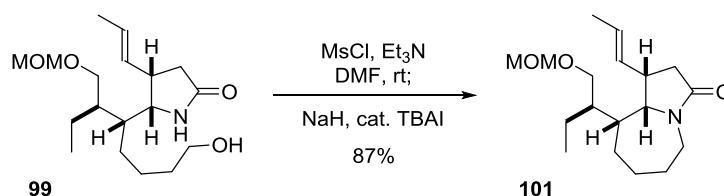
(dddd,  $J = 9.7, 8.0, 6.0, 3.2$  Hz, 1H), 2.52 (dd,  $J = 16.9, 8.0$  Hz, 1H), 2.15 (dd,  $J = 16.9, 3.2$  Hz, 1H), 1.65–1.46 (m, 5H), 1.45–1.34 (m, 2H), 1.31–1.19 (m, 2H), 1.17–1.09 (m, 1H), 0.93 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  177.2 (C), 138.6 (C), 131.3 (CH), 128.7 (CH), 128.5 (CH), 127.74 (CH), 127.69 (CH), 96.9 ( $\text{CH}_2$ ), 95.7 ( $\text{CH}_2$ ), 73.1 ( $\text{CH}_2$ ), 70.2 ( $\text{CH}_2$ ), 67.4 ( $\text{CH}_2$ ), 66.9 ( $\text{CH}_2$ ), 60.1 (CH), 55.7 ( $\text{CH}_3$ ), 55.3 ( $\text{CH}_3$ ), 41.76 (CH), 41.73 (CH), 40.6 (CH), 37.8 ( $\text{CH}_2$ ), 30.2 ( $\text{CH}_2$ ), 28.9 ( $\text{CH}_2$ ), 24.5 ( $\text{CH}_2$ ), 24.2 ( $\text{CH}_2$ ), 13.1 ( $\text{CH}_3$ ); HRMS (ESI), calcd for  $\text{C}_{27}\text{H}_{43}\text{NO}_6\text{Na}^+$  ( $\text{M}+\text{Na}$ ) $^+$  500.2988, found 500.2980.



**(4*S*,5*S*)-5-((3*R*,4*R*)-8-hydroxy-3-((methoxymethoxy)methyl)octan-4-yl)-4-((*E*)-prop-1-en-1-yl)pyrrolidin-2-one (99)**

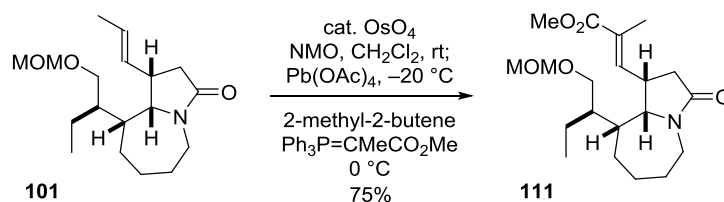
Lithium (75.8 mg, 11.8 mmol) was added to a solution of lactam **95** (281 mg, 588  $\mu\text{mol}$ ),  $t$ -BuOH (5.6 mL, 59 mmol) and THF/ $\text{NH}_3$  (2:1, 29 mL) at  $-63$   $^\circ\text{C}$ , which was prepared using  $\text{CHCl}_3$ /dry ice bath. The resulting mixture was stirred for 1 h at  $-63$   $^\circ\text{C}$ , quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (15 mL), and extracted with EtOAc (2x 10 mL). The combined organic extracts were washed with brine (5 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated. The residue was purified by silica gel column chromatography (EtOAc/MeOH 1:0 to 19:1) to give 173 mg of alcohol **99** (90%): a colorless oil;  $[\alpha]_D^{26} -10.5$  ( $c$  1.01,  $\text{CHCl}_3$ ); IR (film) 3368, 3241, 2932, 2877, 1691, 1108, 1047  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.26 (brs, 1H), 5.55–5.46 (m, 2H), 4.61 (d,  $J = 6.6$  Hz, 1H), 4.58 (d,  $J = 6.6$  Hz, 1H), 3.64–3.59 (m, 2H), 3.61 (dd,  $J = 10.0, 2.9$  Hz, 1H), 3.53 (dd,  $J = 10.0, 5.7$  Hz, 1H), 3.52 (dd,  $J = 10.0, 5.7$  Hz, 1H), 3.34 (s, 3H), 3.04 (dddd,  $J = 9.2, 8.0, 5.7, 3.4$  Hz, 1H), 2.49 (dd,  $J = 16.6, 8.0$  Hz, 1H), 2.12 (dd,  $J = 16.6, 3.4$  Hz, 1H), 1.72 (d,  $J = 4.0$  Hz, 1H), 1.69 (d,  $J = 4.9$  Hz, 3H), 1.70–1.63 (m, 1H), 1.61–1.45 (m, 4H), 1.45–1.35 (m, 2H), 1.34–1.19 (m, 2H), 1.17–1.09 (m, 1H), 0.94 (t,  $J = 7.5$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  177.7 (C), 129.2 (CH), 127.6 (CH), 96.9 ( $\text{CH}_2$ ), 67.2 ( $\text{CH}_2$ ), 62.7 ( $\text{CH}_2$ ), 60.2 (CH), 55.7 ( $\text{CH}_3$ ), 42.0 (CH), 41.8 (CH), 40.5 (CH), 38.0 ( $\text{CH}_2$ ), 33.1 ( $\text{CH}_2$ ), 28.7 ( $\text{CH}_2$ ), 24.0 ( $\text{CH}_2$ ), 18.1 ( $\text{CH}_3$ ), 13.1 ( $\text{CH}_3$ ); HRMS (ESI), calcd for  $\text{C}_{18}\text{H}_{34}\text{NO}_4^+$  ( $\text{M}+\text{H}$ ) $^+$  328.2488, found 328.2484.





**(1*S*,9*R*,9*aS*)-9-((*R*)-1-(methoxymethoxy)butan-2-yl)-1-((*E*)-prop-1-en-1-yl)octahydro-3*H*-pyrrolo[1,2-*a*]azepin-3-one (101)**

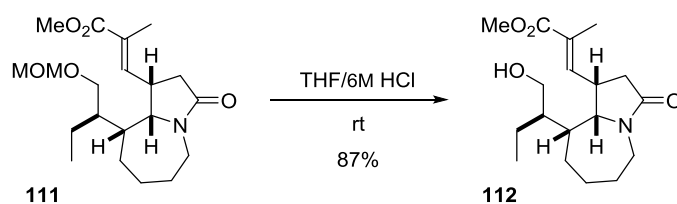
Methanesulfonyl chloride (61  $\mu\text{L}$ , 790  $\mu\text{mol}$ ) was added dropwise to a solution of alcohol **99** (173 mg, 528  $\mu\text{mol}$ ),  $\text{Et}_3\text{N}$  (220  $\mu\text{L}$ , 1.6 mmol) and DMF (26 mL) at room temperature. After stirring for 1 h at room temperature, TBAI (19.5 mg, 52.8  $\mu\text{mol}$ ) and NaH (63% in oil, 201 mg, 5.28 mmol) were added to the solution at room temperature. The resulting mixture was stirred for 12 h at room temperature, and quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (15 mL) and 20% aqueous  $\text{Na}_2\text{S}_2\text{O}_3$  (1.5 mL). The mixture was extracted with EtOAc (2x 10 mL). The combined organic extracts were washed with brine (5 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated. The residue was purified by silica gel column chromatography (EtOAc/MeOH 1:0 to 9:1) to give 141 mg of azepane **101** (87%): a colorless oil;  $[\alpha]_{\text{D}}^{27} -85.6$  ( $c$  1.05,  $\text{CHCl}_3$ ); IR (film) 2929, 1688, 1422, 1151, 1107, 1047  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.55 (ddq,  $J = 15.2, 9.5, 1.4$  Hz, 1H), 5.45 (dq,  $J = 15.2, 6.3$  Hz, 1H), 4.62 (d,  $J = 6.6$  Hz, 1H), 4.60 (d,  $J = 6.6$  Hz, 1H), 4.09–4.03 (m, 1H), 3.89 (dd,  $J = 5.7, 5.7$  Hz, 1H), 3.58 (dd,  $J = 10.0, 4.3$  Hz, 1H), 3.55 (dd,  $J = 10.0, 4.6$  Hz, 1H), 3.36 (s, 3H), 3.02 (dddd,  $J = 9.5, 7.7, 5.7, 1.7$  Hz, 1H), 2.67 (ddd,  $J = 13.8, 11.7, 1.2$  Hz, 1H), 2.58 (dd,  $J = 16.3, 7.7$  Hz, 1H), 2.17 (dd,  $J = 16.3, 1.7$  Hz, 1H), 1.96–1.89 (m, 1H), 1.86–1.67 (m, 3H), 1.65 (dd,  $J = 6.3, 1.4$  Hz, 3H), 1.63–1.52 (m, 3H), 1.49–1.33 (m, 3H), 1.25–1.15 (m, 1H), 0.89 (t,  $J = 7.5$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  174.1 (C), 130.9 (CH), 126.6 (CH), 96.9 ( $\text{CH}_2$ ), 67.9 ( $\text{CH}_2$ ), 63.8 (CH), 55.6 ( $\text{CH}_3$ ), 42.9 (CH), 41.1 ( $\text{CH}_2$ ), 40.7 (CH), 40.5 (CH), 38.9 ( $\text{CH}_2$ ), 30.3 ( $\text{CH}_2$ ), 29.8 ( $\text{CH}_2$ ), 26.9 ( $\text{CH}_2$ ), 22.1 ( $\text{CH}_2$ ), 18.0 ( $\text{CH}_3$ ), 11.6 ( $\text{CH}_3$ ); HRMS (ESI), calcd for  $\text{C}_{18}\text{H}_{32}\text{NO}_3^+$  ( $\text{M}+\text{H}$ ) $^+$  310.2382, found 310.2380.



**Methyl (*E*)-3-((1*S*,9*R*,9*aS*)-9-((*R*)-1-(methoxymethoxy)butan-2-yl)-3-oxooctahydro-1*H*-pyrrolo[1,2-*a*]azepin-1-yl)-2-methylacrylate (111)**

Osmium tetroxide (0.1M in  $\text{CH}_2\text{Cl}_2$ , 230  $\mu\text{L}$ , 23  $\mu\text{mol}$ ) was added to the solution of azepane **101** (173 mg, 528  $\mu\text{mol}$ ), NMO (107 mg, 911  $\mu\text{mol}$ ) and  $\text{CH}_2\text{Cl}_2$  (15 mL) at room temperature. The solution was maintained for 11 h at room temperature. After cooling to  $-20$   $^\circ\text{C}$ ,  $\text{Pb}(\text{OAc})_4$  (222 mg, 501  $\mu\text{mol}$ ) was added to the solution of the generated diol. The solution was stirred for 15 min at  $-20$   $^\circ\text{C}$ ,

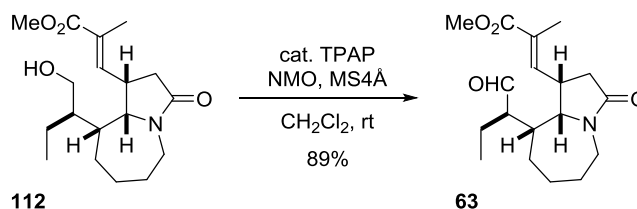
2-methyl-2-butene (620  $\mu$ L, 4.6 mmol) and  $\text{Ph}_3\text{P}=\text{CMeCO}_2\text{Me}$  (1.96 g, 4.56 mmol) were added to the solution of the generated aldehyde. The resulting solution was allowed to warm to 0  $^\circ\text{C}$ , stirred for 7 h at 0  $^\circ\text{C}$ , and quenched with brine (8 mL),  $\text{H}_2\text{O}$  (2 mL) and  $\text{Na}_2\text{SO}_3$  (28.2 mg, 20 wt%). The mixture was extracted with EtOAc (2x 5 mL). The combined organic extracts were washed with brine (5 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated. The residue was purified by silica gel column chromatography ( $\text{CHCl}_3/\text{EtOAc}$  9:1) to give 124 mg of methyl enoate **111** (75%): a colorless oil;  $[\alpha]_D^{25} -139.6$  (*c* 1.02,  $\text{CHCl}_3$ ); IR (film) 2929, 2882, 1715, 1691, 1436, 1251, 1236, 1152, 1110, 1046  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.95 (dq, *J* = 11.5, 1.4 Hz, 1H), 4.63 (d, *J* = 6.6 Hz, 1H), 4.61 (d, *J* = 6.6 Hz, 1H), 4.14 (ddd, *J* = 14.0, 3.4, 3.4 Hz, 1H), 4.03 (dd, *J* = 5.7, 5.7 Hz, 1H), 3.75 (s, 3H), 3.57 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.55 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.38 (dddd, *J* = 11.5, 7.5, 5.7, 1.2 Hz, 1H), 3.37 (s, 3H), 2.74–2.67 (m, 1H), 2.70 (dd, *J* = 16.3, 7.5 Hz, 1H), 2.12 (dd, *J* = 16.3, 1.2 Hz, 1H), 1.98–1.92 (m, 1H), 1.92–1.78 (m, 2H), 1.84 (d, *J* = 1.4 Hz, 3H), 1.62–1.45 (m, 3H), 1.45–1.31 (m, 3H), 1.27–1.19 (m, 1H), 0.88 (t, *J* = 7.2 Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  173.2 (C), 168.3 (C), 140.8 (CH), 127.1 (C), 96.9 ( $\text{CH}_2$ ), 67.9 ( $\text{CH}_2$ ), 64.3 (CH), 55.7 ( $\text{CH}_3$ ), 52.2 ( $\text{CH}_3$ ), 42.7 (CH), 41.3 ( $\text{CH}_2$ ), 40.8 (CH), 38.3 ( $\text{CH}_2$ ), 36.1 (CH), 30.2 ( $\text{CH}_2$ ), 29.8 ( $\text{CH}_2$ ), 27.1 ( $\text{CH}_2$ ), 22.1 ( $\text{CH}_2$ ), 12.8 ( $\text{CH}_3$ ), 11.5 ( $\text{CH}_3$ ); HRMS (ESI), calcd for  $\text{C}_{20}\text{H}_{34}\text{NO}_5^+$  ( $\text{M}+\text{H}$ ) $^+$  368.2437, found 368.2437.



**Methyl (*E*)-3-((1*S*,9*R*,9*aS*)-9-((*R*)-1-hydroxybutan-2-yl)-3-oxooctahydro-1*H*-pyrrolo[1,2-*a*]azepin-1-yl)-2-methylacrylate (**S3**)**

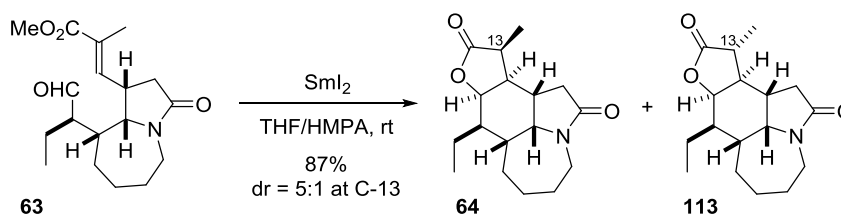
Aqueous HCl (6M, 3.6 mL, 22 mmol) was added dropwise to a solution of methyl enoate **111** (126 mg, 343  $\mu$ mol) and THF (7.3 mL) at room temperature. The solution was maintained for 18.5 h at room temperature, diluted with brine (3 mL), and extracted with EtOAc (8x 3 mL). The combined organic extracts were washed with brine (2 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated. The residue was purified by silica gel column chromatography (EtOAc/MeOH 1:0 to 19:1) to give 96.6 mg of alcohol **112** (87%): colorless crystals; mp 147.0–148.0  $^\circ\text{C}$ ;  $[\alpha]_D^{26} -134.8$  (*c* 0.98,  $\text{CHCl}_3$ ); IR (film) 3403, 2951, 2930, 1716, 1671, 1435, 1316, 1238, 1120  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.95 (dq, *J* = 11.5, 1.4 Hz, 1H), 4.10 (dd, *J* = 6.0, 5.4 Hz, 1H), 4.11–4.06 (m, 1H), 3.75 (s, 3H), 3.75–3.66 (m, 2H), 3.39 (dddd, *J* = 11.5, 7.7, 6.0, 2.0 Hz, 1H), 2.76 (ddd, *J* = 14.0, 11.5, 1.2 Hz, 1H), 2.69 (dd, *J* = 16.3, 7.7 Hz, 1H), 2.14 (dd, *J* = 16.3, 2.0 Hz, 1H), 2.01–1.96 (m, 1H), 1.90–1.77 (m, 2H), 1.84 (d, *J* = 1.4 Hz, 3H), 1.60–1.40 (m, 5H), 1.36–1.21 (m, 3H), 0.89 (t, *J* = 7.2 Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  173.2 (C), 168.4 (C), 140.9 (CH),

127.4 (C), 64.3 (CH), 62.5 (CH<sub>2</sub>), 52.2 (CH<sub>3</sub>), 42.8 (CH), 42.0 (CH), 41.5 (CH<sub>2</sub>), 38.3 (CH<sub>2</sub>), 36.2 (CH), 30.1 (CH<sub>2</sub>), 29.6 (CH<sub>2</sub>), 27.2 (CH<sub>2</sub>), 21.6 (CH<sub>2</sub>), 12.8 (CH<sub>3</sub>), 11.9 (CH<sub>3</sub>); HRMS (ESI), calcd for C<sub>18</sub>H<sub>30</sub>NO<sub>4</sub><sup>+</sup> (M+H)<sup>+</sup> 324.2175, found 324.2175.



**Methyl (*E*)-2-methyl-3-((1*S*,9*R*,9*aS*)-3-oxo-9-((*R*)-1-oxobutan-2-yl)octahydro-1*H*-pyrrolo[1,2-*a*]azepin-1-yl)acrylate (**13**)**

Tetrapropylammonium perruthenate (0.8 mg, 2.26 μmol) was added to a mixture of alcohol **29** (14.6 mg, 45.1 μmol), NMO (10.6 mg, 90.3 μmol) and MS4Å (73.0 mg, 500 wt%) and CH<sub>2</sub>Cl<sub>2</sub> (26 mL) at room temperature. After stirring at room temperature for 1 h, the reaction mixture was directly purified by silica gel column chromatography (EtOAc to EtOAc/MeOH 19:1) to give 12.9 mg of aldehyde **13** (89%): colorless crystals; mp 112.5–113.5 °C; [α]<sub>D</sub><sup>25</sup> −148.9 (*c* 1.00, CHCl<sub>3</sub>); IR (film) 2930, 2857, 1716, 1691, 1238, 1120 cm<sup>−1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.53 (d, *J* = 4.9 Hz, 1H), 6.84 (dq, *J* = 11.7, 1.4 Hz, 1H), 4.22–4.16 (m, 1H), 3.81 (dd, *J* = 6.3, 5.4 Hz, 1H), 3.74 (s, 3H), 3.20 (ddd, *J* = 11.7, 7.5, 5.4 Hz, 1H), 2.68–2.60 (m, 1H), 2.61 (dd, *J* = 16.3, 7.5 Hz, 1H), 2.14 (ddd, *J* = 11.2, 9.2, 6.3 Hz, 1H), 2.05 (d, *J* = 16.3 Hz, 1H), 2.02 (dddd, *J* = 11.2, 9.7, 4.9, 2.9 Hz, 1H), 1.95 (d, *J* = 1.4 Hz, 3H), 1.98–1.91 (m, 1H), 1.88–1.81 (m, 1H), 1.76 (dq, *J* = 14.3, 7.5, 2.9 Hz, 1H), 1.64–1.57 (m, 1H), 1.55 (ddq, *J* = 14.3, 9.7, 7.5 Hz, 1H), 1.52–1.35 (m, 2H), 1.26–1.16 (m, 1H), 0.84 (t, *J* = 7.5 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 204.0 (CH), 173.3 (C), 168.3 (C), 139.9 (CH), 127.7 (C), 63.7 (CH), 54.4 (CH), 52.2 (CH<sub>3</sub>), 41.7 (CH), 41.3 (CH<sub>2</sub>), 38.0 (CH<sub>2</sub>), 35.2 (CH), 30.3 (CH<sub>2</sub>), 30.0 (CH<sub>2</sub>), 26.7 (CH<sub>2</sub>), 20.7 (CH<sub>2</sub>), 12.8 (CH<sub>3</sub>), 11.2 (CH<sub>3</sub>); HRMS (ESI), calcd for C<sub>18</sub>H<sub>28</sub>NO<sub>4</sub><sup>+</sup> (M+H)<sup>+</sup> 322.2018, found 322.2016.



**(3*1R*,7*aR*,8*R*,8*aR*,11*S*,11*aR*,11*bS*)-8-ethyl-11-methyldodecahydroazepino[3,2,1-*hi*]furo[3,2-*e*]indole-2,10-dione (**64**)**

**Preparation of a solution of SmI<sub>2</sub> in THF<sup>[7]</sup>**

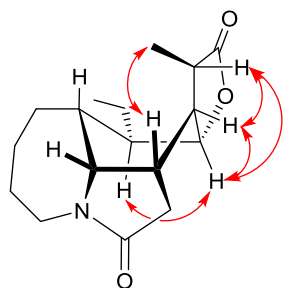
<sup>[7]</sup> P. Girard, J. L. Namy, H. B. Kagan, *J. Am. Chem. Soc.* **1980**, *102*, 2693–2698.

A solution of 1,2-diiodoethane (ca. 1 g) and Et<sub>2</sub>O (10 mL) was washed with 20% aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 mL), H<sub>2</sub>O (3x 10 mL), and dried over Na<sub>2</sub>SO<sub>4</sub>. The solution was concentrated under reduced pressure for 2 h to give 1,2-diiodoethane (478 mg, 1.7 mmol). In a glove box, freshly purified 1,2-diiodoethane was dissolved in THF (17 mL, WAKO, deoxygenated, stabilizer free). This solution was added to Sm (510 mg, 3.39 mmol) at room temperature. The blue suspension was stirred for 1 d at room temperature. The concentration of the SmI<sub>2</sub> solution was determined as 58 mM by titration with 2-heptanone.<sup>[8]</sup>

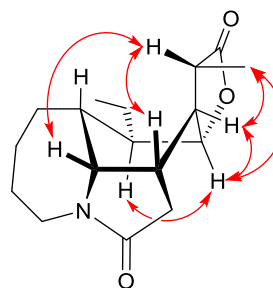
A solution of SmI<sub>2</sub> (58 mM in THF, 2.1 mL, 120 μmol) was added dropwise to a solution of aldehyde **63** (12.9 mg, 40.1 μmol), HMPA (160 μL) and THF (1.8 mL) at room temperature. The resulting mixture was stirred for 4 h, quenched with saturated aqueous Rochelle salt/H<sub>2</sub>O (1:1, 2.0 mL), and extracted with EtOAc (4x 2.0 mL). The combined organic extracts were washed with brine (1.0 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/MeOH 19:1) to give 8.4 mg of lactone **64** (72%) and 1.7 mg of lactone **113** (15%). Lactone **64**: colorless crystals; mp 159.5–160.5 °C;  $[\alpha]_D^{26} +129.2$  (c 1.00, CHCl<sub>3</sub>); IR (film) 2930, 1771, 1685, 1415, 1165, 967 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 4.51 (dd, *J* = 3.7, 2.6 Hz, 1H), 4.15–4.08 (m, 1H), 3.79 (dd, *J* = 4.3, 2.3 Hz, 1H), 2.95–2.87 (m, 1H), 2.90 (qd, *J* = 7.2, 6.9 Hz, 1H), 2.59 (dd, *J* = 15.8, 6.0 Hz, 1H), 2.18–2.08 (m, 2H), 2.05 (d, *J* = 15.8 Hz, 1H), 2.01 (ddd, *J* = 9.2, 6.0, 4.3 Hz, 1H), 1.98–1.92 (m, 1H), 1.91–1.83 (m, 2H), 1.66 (dq, *J* = 13.5, 7.5, 4.3 Hz, 1H), 1.54 (dddd, *J* = 12.0, 11.2, 4.3, 2.6 Hz, 1H), 1.47–1.36 (m, 4H), 1.21 (d, *J* = 7.2 Hz, 3H), 1.00 (t, *J* = 7.5 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 178.8 (C), 174.6 (C), 78.0 (CH), 64.0 (CH), 44.3 (CH<sub>2</sub>), 41.85 (CH), 41.81 (CH), 40.2 (CH<sub>2</sub>), 36.0 (CH), 35.0 (CH), 32.6 (CH), 30.9 (CH<sub>2</sub>), 26.8 (CH<sub>2</sub>), 25.9 (CH<sub>2</sub>), 20.8 (CH<sub>2</sub>), 11.3 (CH<sub>3</sub>), 9.6 (CH<sub>3</sub>); HRMS (ESI), calcd for C<sub>17</sub>H<sub>26</sub>NO<sub>3</sub><sup>+</sup> (M+H)<sup>+</sup> 292.1913, found 292.1912. Lactone **113**: a colorless oil;  $[\alpha]_D^{22} +71.6$  (c 0.32, CHCl<sub>3</sub>); IR (film) 2930, 1770, 1685, 1456, 1163, 968 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 4.81 (dd, *J* = 6.3, 4.0 Hz, 1H), 3.81 (dd, *J* = 5.7, 4.0 Hz, 1H), 3.62 (ddd, *J* = 14.0, 7.7, 1.7 Hz, 1H), 3.34 (ddd, *J* = 14.0, 8.3, 2.6 Hz, 1H), 2.57 (dd, *J* = 16.0, 7.5 Hz, 1H), 2.41 (qd, *J* = 7.5, 2.9 Hz, 1H), 2.18 (dddd, *J* = 8.0, 7.5, 5.7, 2.9 Hz, 1H), 2.11 (dd, *J* = 16.0, 2.9 Hz, 1H), 2.01–1.94 (m, 1H), 2.00 (ddd, *J* = 8.0, 6.3, 2.9 Hz, 1H), 1.93–1.86 (m, 1H), 1.84–1.77 (m, 1H), 1.75–1.68 (m, 1H), 1.66–1.42 (m, 6H), 1.34 (d, *J* = 7.5 Hz, 3H), 1.02 (t, *J* = 7.5 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 179.3 (C), 174.2 (C), 77.0 (CH), 62.5 (CH), 44.1 (CH), 44.0 (CH<sub>2</sub>), 43.2 (CH), 38.6 (CH<sub>2</sub>), 37.5 (CH), 36.1 (CH), 35.7 (CH), 30.4 (CH<sub>2</sub>), 27.1 (CH<sub>2</sub>), 25.5 (CH<sub>2</sub>), 20.9 (CH<sub>2</sub>), 15.8 (CH<sub>3</sub>), 11.7 (CH<sub>3</sub>); HRMS (ESI), calcd for C<sub>17</sub>H<sub>26</sub>NO<sub>3</sub><sup>+</sup> (M+H)<sup>+</sup> 292.1913, found 292.1909.

<sup>[8]</sup> A. Dahlén, G. Hilmersson, *Eur. J. Inorg. Chem.* **2004**, 3020–3024.

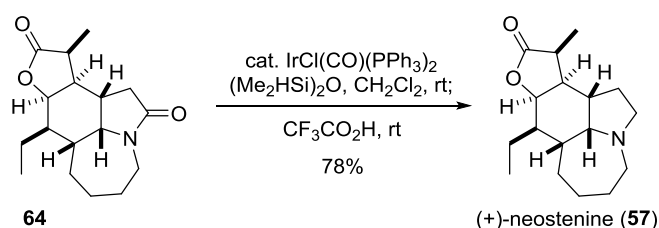
NOESY experiments for **64** and **113**



**64** (500 MHz, CDCl<sub>3</sub>)



**113** (500 MHz, CDCl<sub>3</sub>)

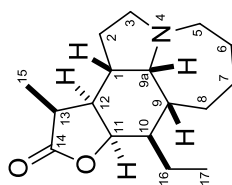


**(+)-Neostenine (57)**

1,1,3,3-Tetramethyldisiloxane (47  $\mu$ L, 260  $\mu$ mol) was added to a solution of lactone **64** (7.7 mg, 26  $\mu$ mol), IrCl(CO)(PPh<sub>3</sub>)<sub>2</sub> (2.1 mg, 2.6  $\mu$ mol) and CH<sub>2</sub>Cl<sub>2</sub> (2.6 mL) at room temperature. After stirring for 1.5 h at room temperature, CF<sub>3</sub>CO<sub>2</sub>H (6.1  $\mu$ L, 79  $\mu$ mol) was added to the solution at room temperature. The resulting solution was maintained for 2 h at room temperature, quenched with saturated aqueous NaHCO<sub>3</sub> (1.3 mL), and extracted with EtOAc (4x 2.0 mL). The combined organic extracts were washed with brine (1.0 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was purified by preparative thin-layer chromatography (EtOAc/MeOH 1:1), and subsequent basic alumina column chromatography (hexane) to give 5.7 mg of (+)-neostenine (**57**) (78%): colorless crystals; mp 93.0–94.0 °C [lit.<sup>[9]</sup> mp 90–92 °C]; [ $\alpha$ ]<sub>D</sub><sup>25</sup> +73.9 (*c* 0.10, MeOH) [lit.<sup>[9]</sup> [ $\alpha$ ]<sub>D</sub><sup>20</sup> +73.6 (*c* 0.10, MeOH)]; IR (film) 2932, 2877, 1770, 1458, 1379, 1165, 984 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  4.51 (dd, *J* = 4.0, 2.9 Hz, 1H), 3.19 (ddd, *J* = 10.0, 8.0, 6.3 Hz, 1H), 2.87 (ddd, *J* = 12.6, 4.0, 4.0 Hz, 1H), 2.84 (qd, *J* = 7.2, 6.6 Hz, 1H), 2.44 (ddd, *J* = 10.0, 10.0, 5.2 Hz, 1H), 2.40 (dd, *J* = 5.4, 3.2 Hz, 1H), 2.32 (ddd, *J* = 12.6, 11.2, 2.9 Hz, 1H), 2.25 (ddd, *J* = 9.5, 6.6, 4.0 Hz, 1H), 1.99 (dddd, *J* = 12.6, 10.0, 7.7, 6.3 Hz, 1H), 1.88 (dddd, *J* = 9.5, 7.7, 5.4, 1.2 Hz, 1H), 1.85–1.52 (m, 9H), 1.46–1.36 (m, 2H), 1.21 (d, *J* = 7.2 Hz, 3H), 0.98 (t, *J* = 7.5 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  179.9 (C), 79.5 (CH), 71.0 (CH), 56.0 (CH<sub>2</sub>), 55.8 (CH<sub>2</sub>), 43.1 (CH), 42.6 (CH), 37.6 (CH), 37.4 (CH), 34.4 (CH), 30.3 (CH<sub>2</sub>), 28.6 (CH<sub>2</sub>), 28.2 (CH<sub>2</sub>), 21.3 (CH<sub>2</sub>), 21.2 (CH<sub>2</sub>), 11.4 (CH<sub>3</sub>), 10.2 (CH<sub>3</sub>); HRMS (ESI), calcd for C<sub>17</sub>H<sub>28</sub>NO<sub>2</sub><sup>+</sup> (M+H)<sup>+</sup> 278.2120, found 278.2118.

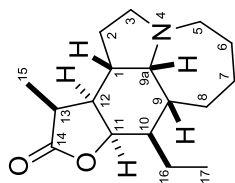
<sup>[9]</sup> H.-S. Chung, P.-M. Hon, G. Lin, P. P.-H. But, H. Dong, *Planta Med.* **2003**, *69*, 914.

Comparison of <sup>1</sup>H NMR of neostenine (**1**)



|                 | our synthetic sample                             | Booker-Milburn                                   | Aubé   | natural sample                                   |
|-----------------|--|--|--|--|
|                 | <sup>1</sup> H NMR (500 MHz, CDCl <sub>3</sub> ) | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) | <sup>1</sup> H NMR (300 MHz, CDCl <sub>3</sub> ) |
| H-11            | 4.51 (dd, J = 4.0, 2.9 Hz, 1H)                   | 4.51 (dd, J = 4.0, 2.5 Hz, 1H)                   | 4.51 (m, 1H)                                     | 4.50 (m, 1H)                                     |
| H-3             | 3.19 (ddd, J = 10.0, 8.0, 6.3 Hz, 1H)            | 3.25-3.17 (m, 1H)                                | 3.19 (m, 1H)                                     | 3.22 (m, 1H)                                     |
| H-5             | 2.87 (ddd, J = 12.6, 4.0, 4.0 Hz, 1H)            | 2.90-2.81 (m, 2H)                                | 2.86 (m, 1H)                                     | 2.89 (m, 1H)                                     |
| H-13            | 2.84 (qd, J = 7.2, 6.6 Hz, 1H)                   |  |  | 2.81 (m, 1H)                                     |
| H-3             | 2.44 (ddd, J = 10.0, 10.0, 5.2 Hz, 1H)           | 2.48-2.23 (m, 4H)                                | 2.48-2.39 (m, 2H)                                | 2.45 (m, 2H)                                     |
| H-9a            | 2.40 (dd, J = 5.4, 3.2 Hz, 1H)                   |  |  |  |
| H-5             | 2.32 (ddd, J = 12.6, 11.2, 2.9 Hz, 1H)           |  | 2.33 (m, 1H)                                     | 2.27 (m, 1H)                                     |
| H-12            | 2.25 (ddd, J = 9.5, 6.6, 4.0 Hz, 1H)             |  | 2.26 (m, 1H)                                     | 1.3-2.0 (m, 14H)                                 |
| H-2             | 1.99 (dddd, J = 12.6, 10.0, 7.7, 6.3 Hz, 1H)     | 2.04-1.92 (m, 1H)                                | 1.98 (m, 1H)                                     |  |
| H-1             | 1.88 (dddd, J = 9.5, 7.7, 5.4, 1.2 Hz, 1H)       | 1.91-1.57 (m, 10H)                               | 1.91-1.56 (m, 10H)                               |  |
| H-6,7,8,9,10,16 | 1.85-1.52 (m, 9H)                                |  |  |  |
| H-2,16          | 1.46-1.36 (m, 2H)                                | 1.48-1.36 (m, 2H)                                | 1.41 (m, 1H)                                     |  |
| H-15            | 1.21 (d, J = 7.2 Hz, 3H)                         | 1.21 (d, J = 7.5 Hz, 3H)                         | 1.22 (d, J = 7.2 Hz, 3H)                         | 1.20 (d, J = 7.2 Hz, 3H)                         |
| H-17            | 0.98 (t, J = 7.5 Hz, 3H)                         | 0.99 (t, J = 7.5 Hz, 3H)                         | 0.99 (t, J = 7.3 Hz, 3H)                         | 0.97 (t, J = 7.5 Hz, 3H)                         |

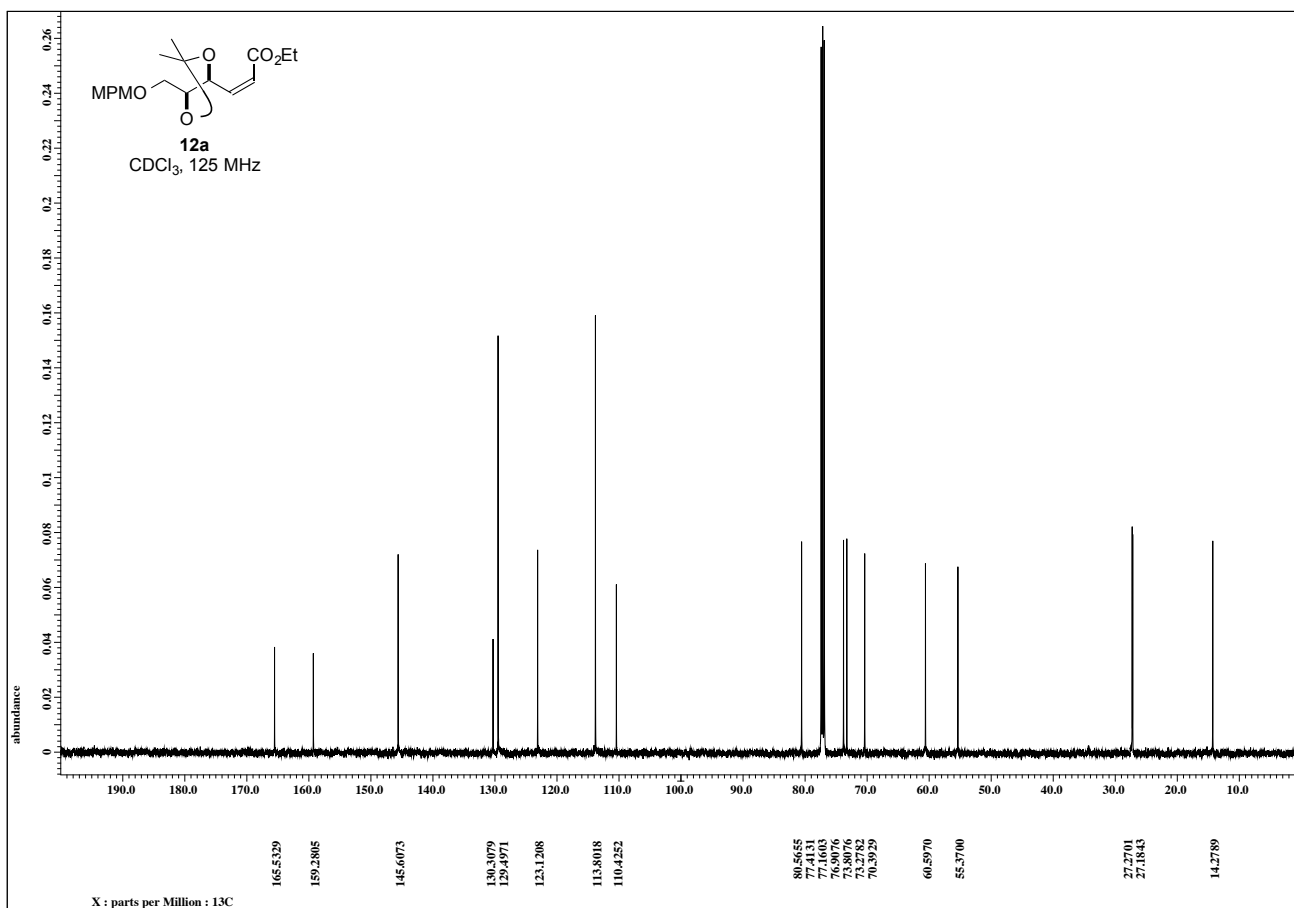
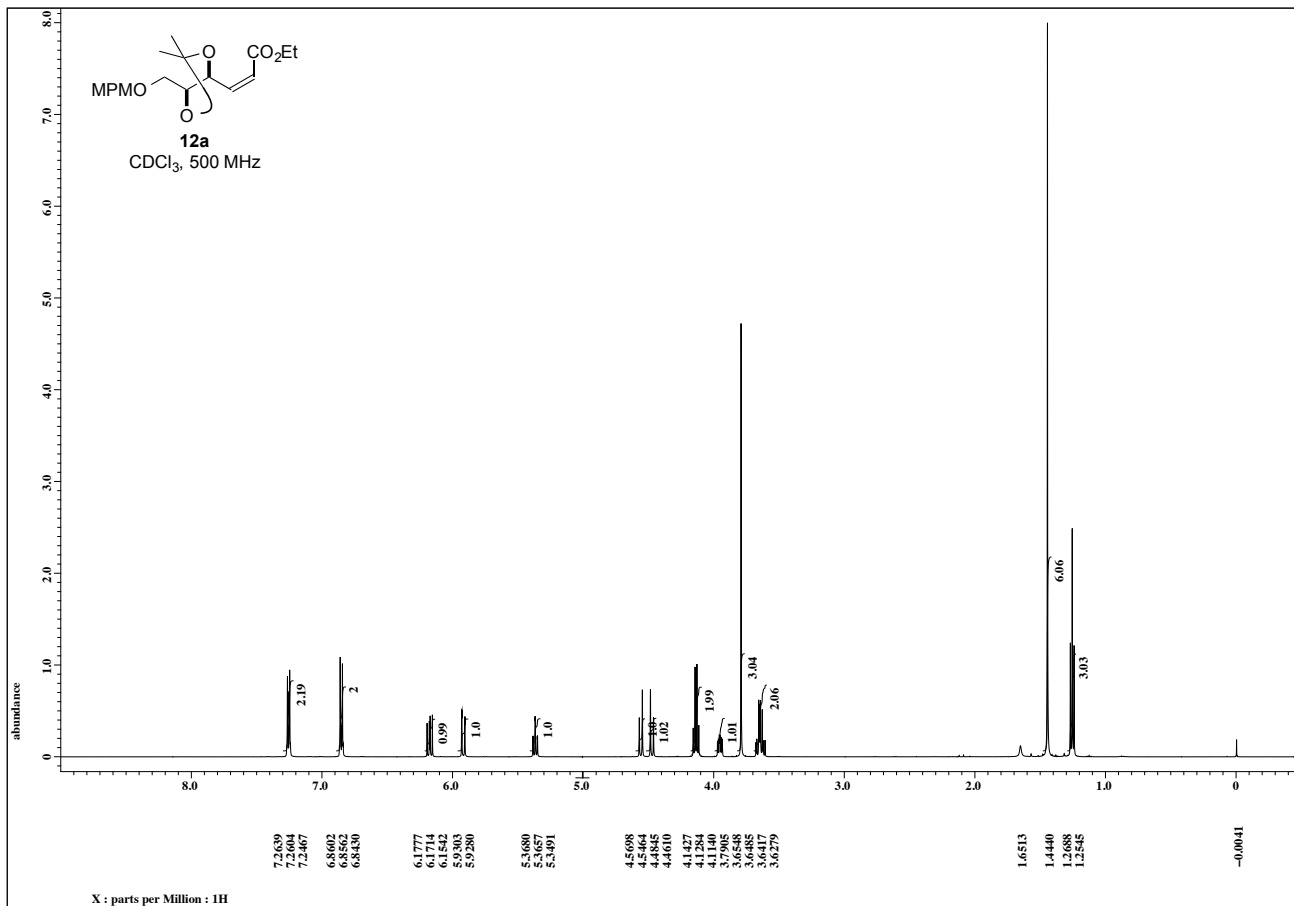
Comparison of  $^{13}\text{C}$  NMR of neostenine (**1**)

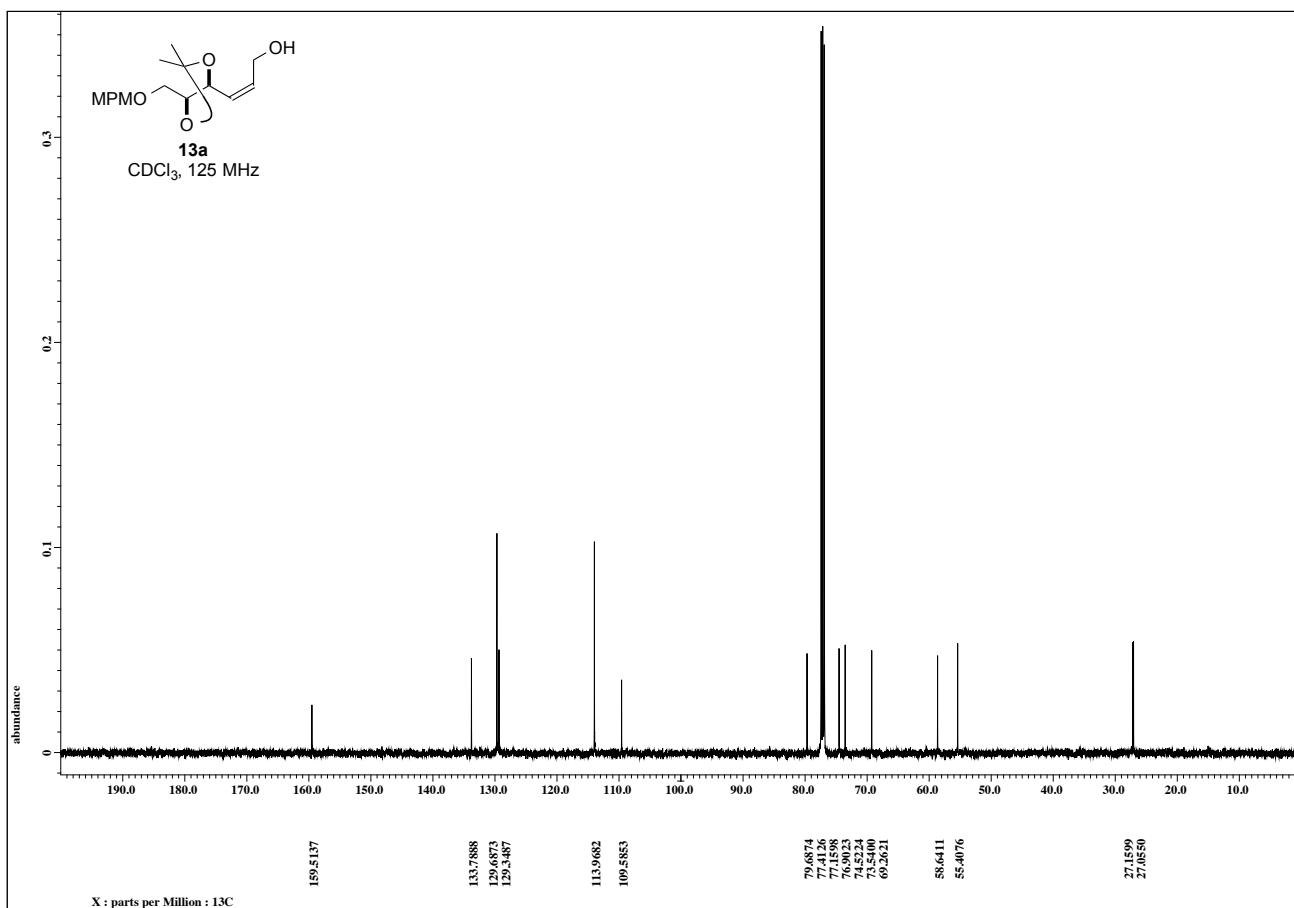
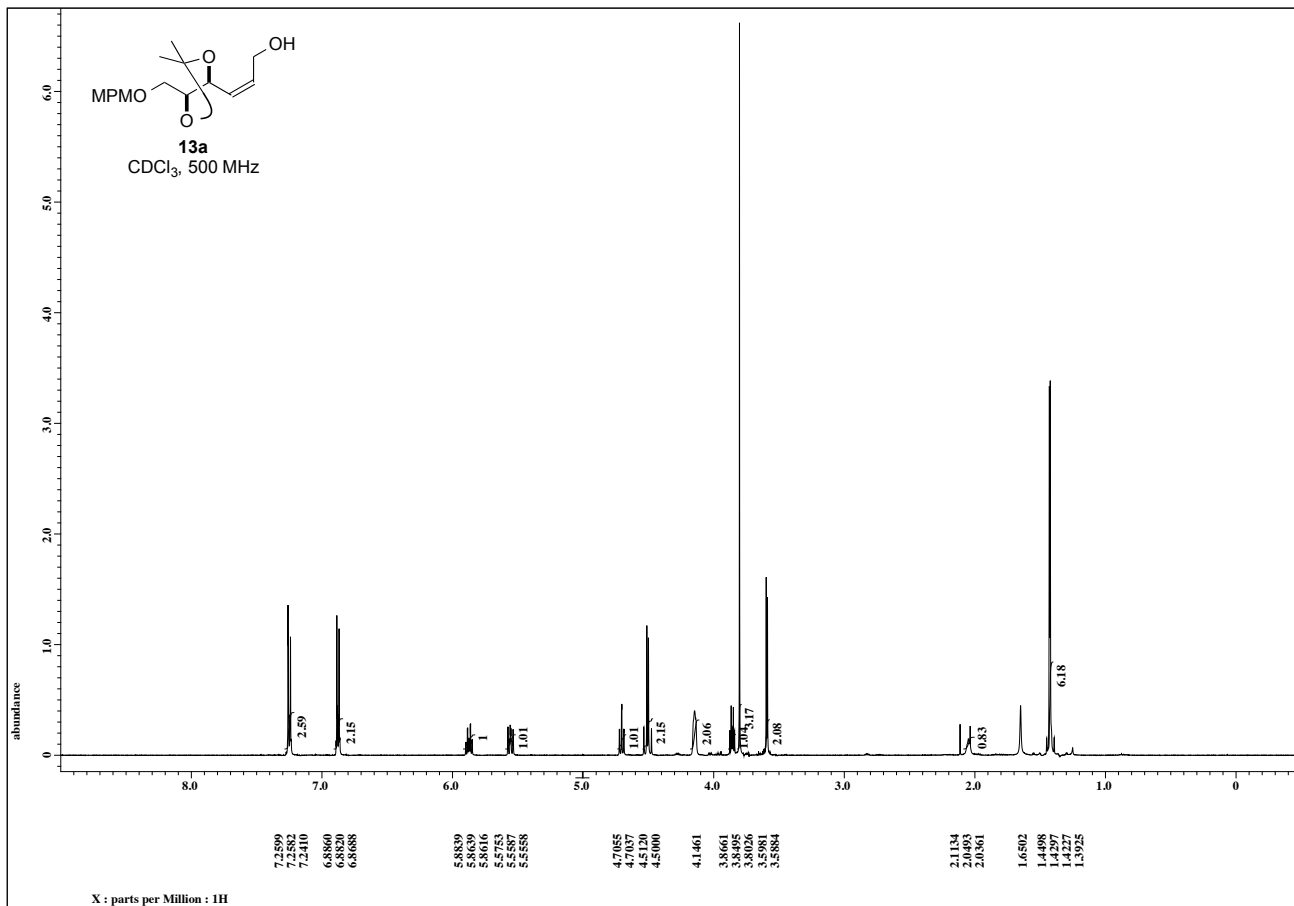


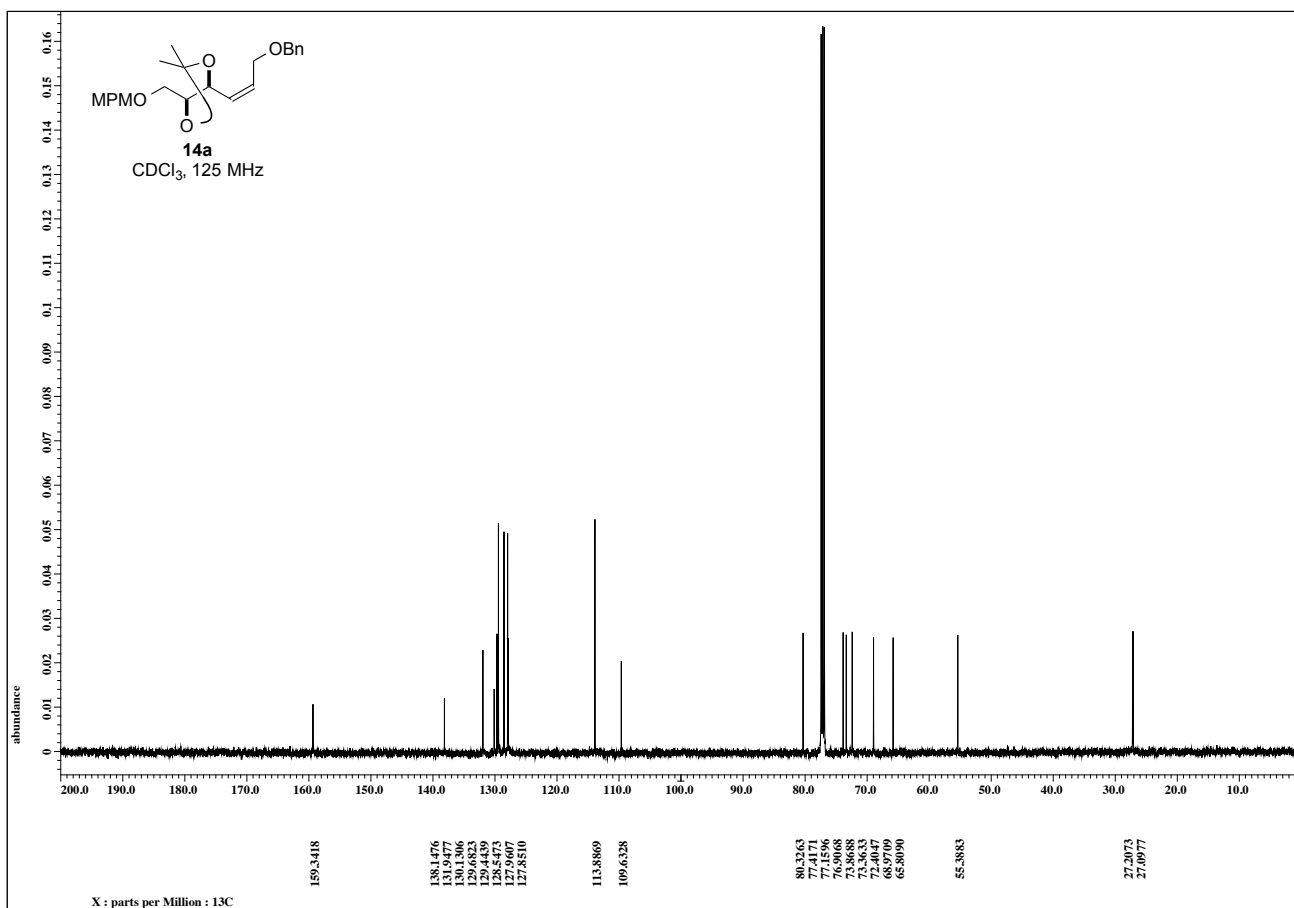
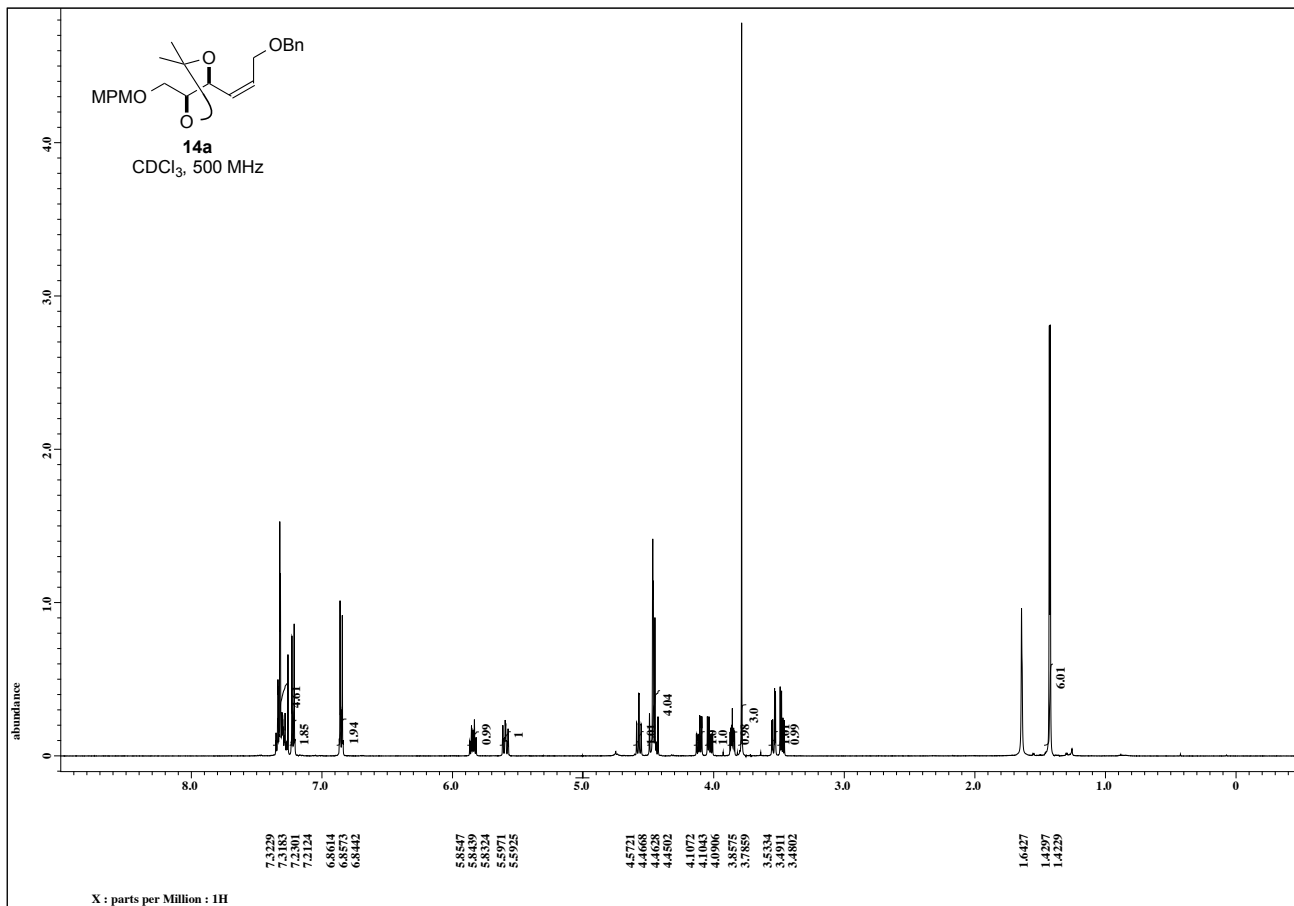
|               | our synthetic sample                                   | Booker-Milburn   | Aubé   | natural sample  |
|---------------|--|--|--|---|
|               | $^{13}\text{C}$ NMR (125 MHz, $\text{CD}_3\text{Cl}$ ) | $^{13}\text{C}$ NMR (101 MHz, $\text{CD}_3\text{Cl}$ ) | $^{13}\text{C}$ NMR (100 MHz, $\text{CD}_3\text{Cl}$ ) | $^{13}\text{C}$ NMR (75 MHz, $\text{CD}_3\text{Cl}$ ) |
| C-14          | 179.9 (C)  | 179.6 (C)  | 180.2  | 180.24  |
| C-11          | 79.5 (CH)  | 79.3 (CH)  | 79.9   | 79.87   |
| C-9a          | 71.0 (CH)  | 70.9 (CH)  | 71.4   | 71.52   |
| C-3           | 56.0 ( $\text{CH}_2$ )                                 | 55.9 ( $\text{CH}_2$ )                                 | 56.4   | 56.44   |
| C-5           | 55.8 ( $\text{CH}_2$ )                                 | 55.6 ( $\text{CH}_2$ )                                 | 56.1   | 56.28   |
| C-12          | 43.1 (CH)  | 42.9 (CH)  | 43.5   | 43.38   |
| C-13          | 42.6 (CH)  | 42.5 (CH)  | 43.0   | 43.04   |
| C-1 or 10     | 37.6 (CH)  | 37.4 (CH)  | 38.0   | 39.79   |
| C-1 or 10     | 37.4 (CH)  | 37.3 (CH)  | 37.8   | 37.81   |
| C-9           | 34.4 (CH)  | 34.3 (CH)  | 34.8   | 34.79   |
| C-2           | 30.3 ( $\text{CH}_2$ )                                 | 30.2 ( $\text{CH}_2$ )                                 | 30.7   | 30.65   |
| C-6,7,8 or 16 | 28.6 ( $\text{CH}_2$ )                                 | 28.4 ( $\text{CH}_2$ )                                 | 28.9   | 28.86   |
| C-6,7,8 or 16 | 28.2 ( $\text{CH}_2$ )                                 | 28.1 ( $\text{CH}_2$ )                                 | 28.6   | 28.67   |
| C-6,7,8 or 16 | 21.3 ( $\text{CH}_2$ )                                 | 21.2 ( $\text{CH}_2$ )                                 | 21.7   | 21.70   |
| C-6,7,8 or 16 | 21.2 ( $\text{CH}_2$ )                                 | 21.1 ( $\text{CH}_2$ )                                 | 21.6   | 21.63   |
| C-17          | 11.4 ( $\text{CH}_3$ )                                 | 11.3 ( $\text{CH}_3$ )                                 | 11.8   | 11.84   |
| C-15          | 10.2 ( $\text{CH}_3$ )                                 | 10.1 ( $\text{CH}_3$ )                                 | 10.6   | 10.67   |

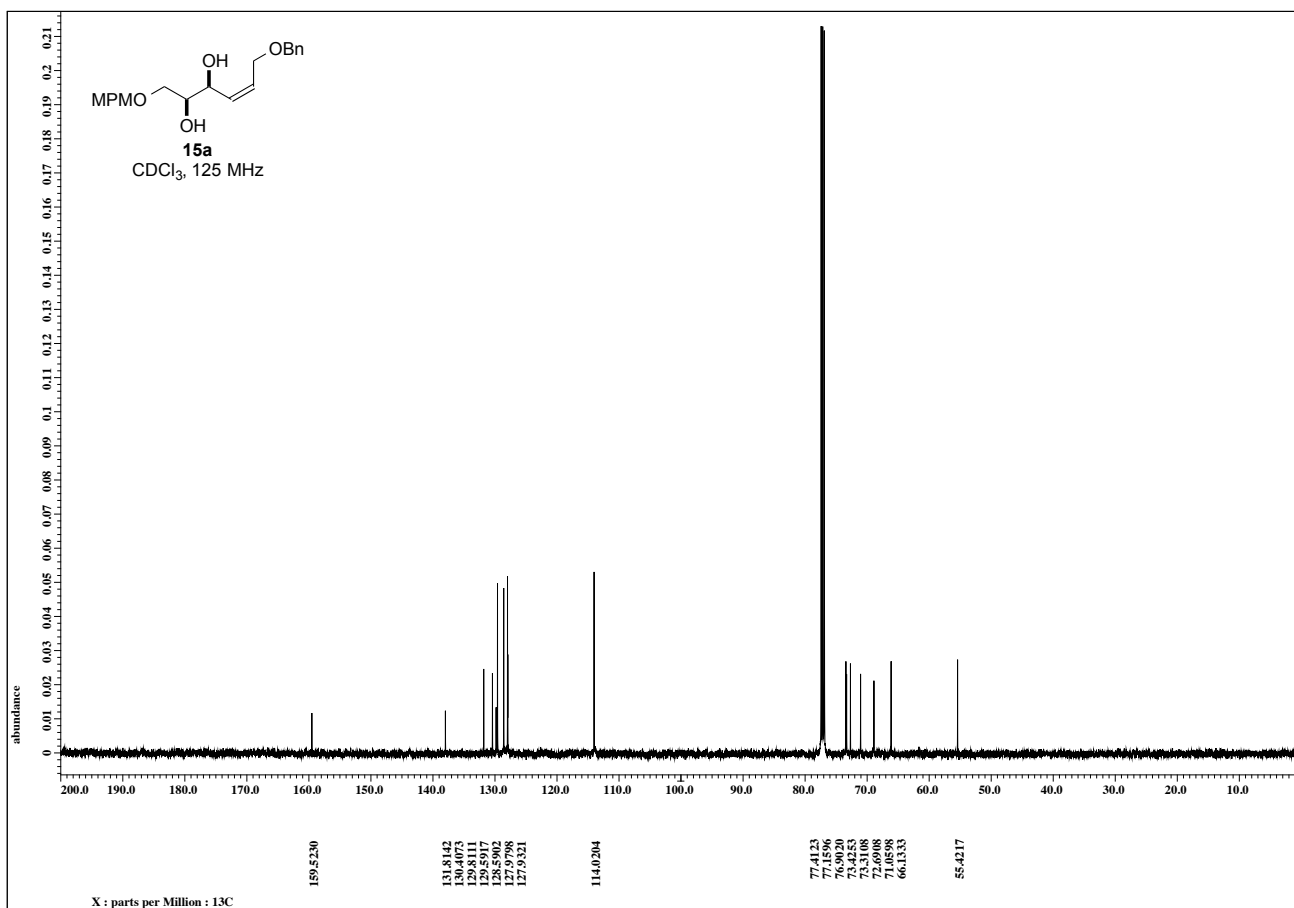
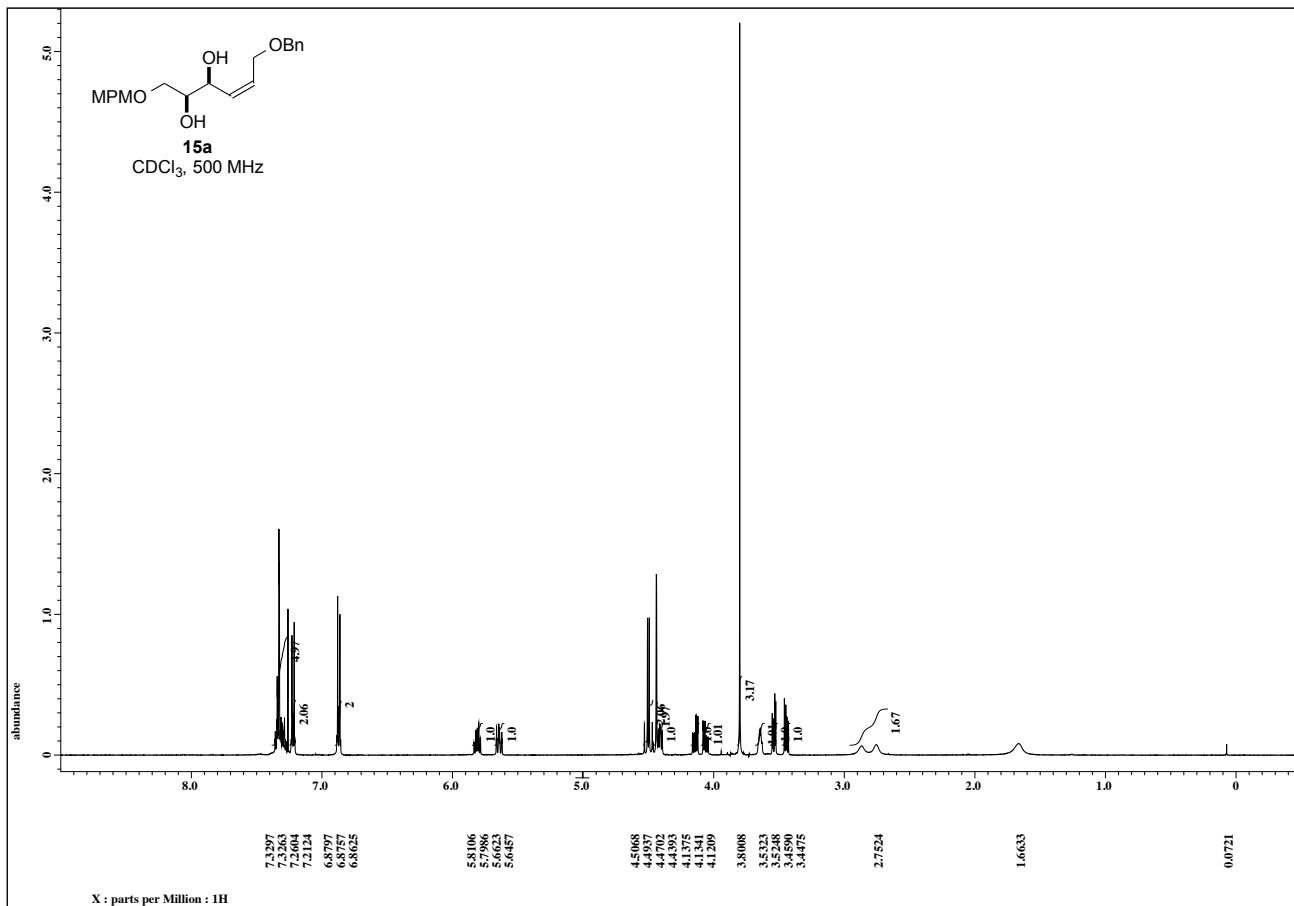


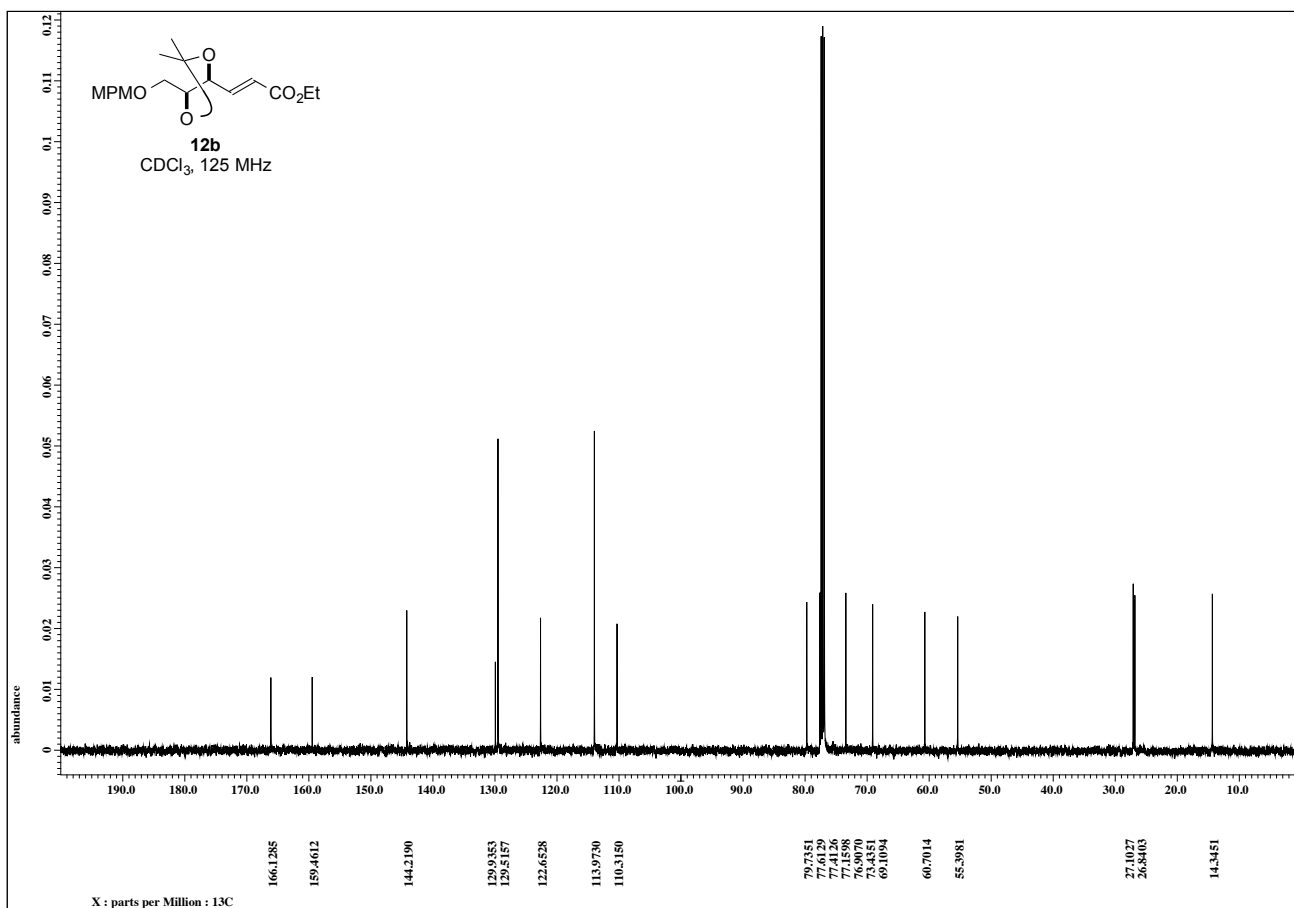
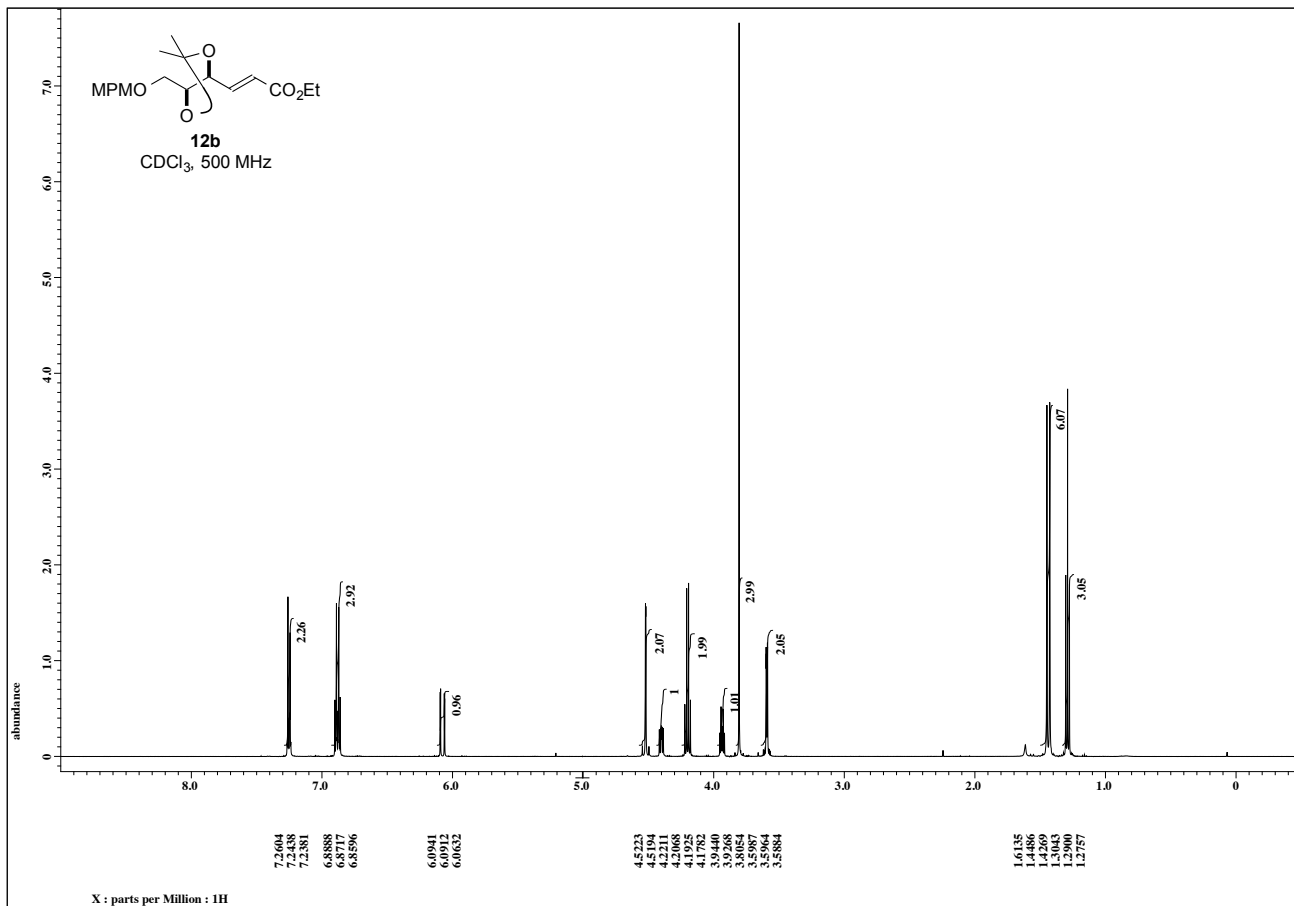


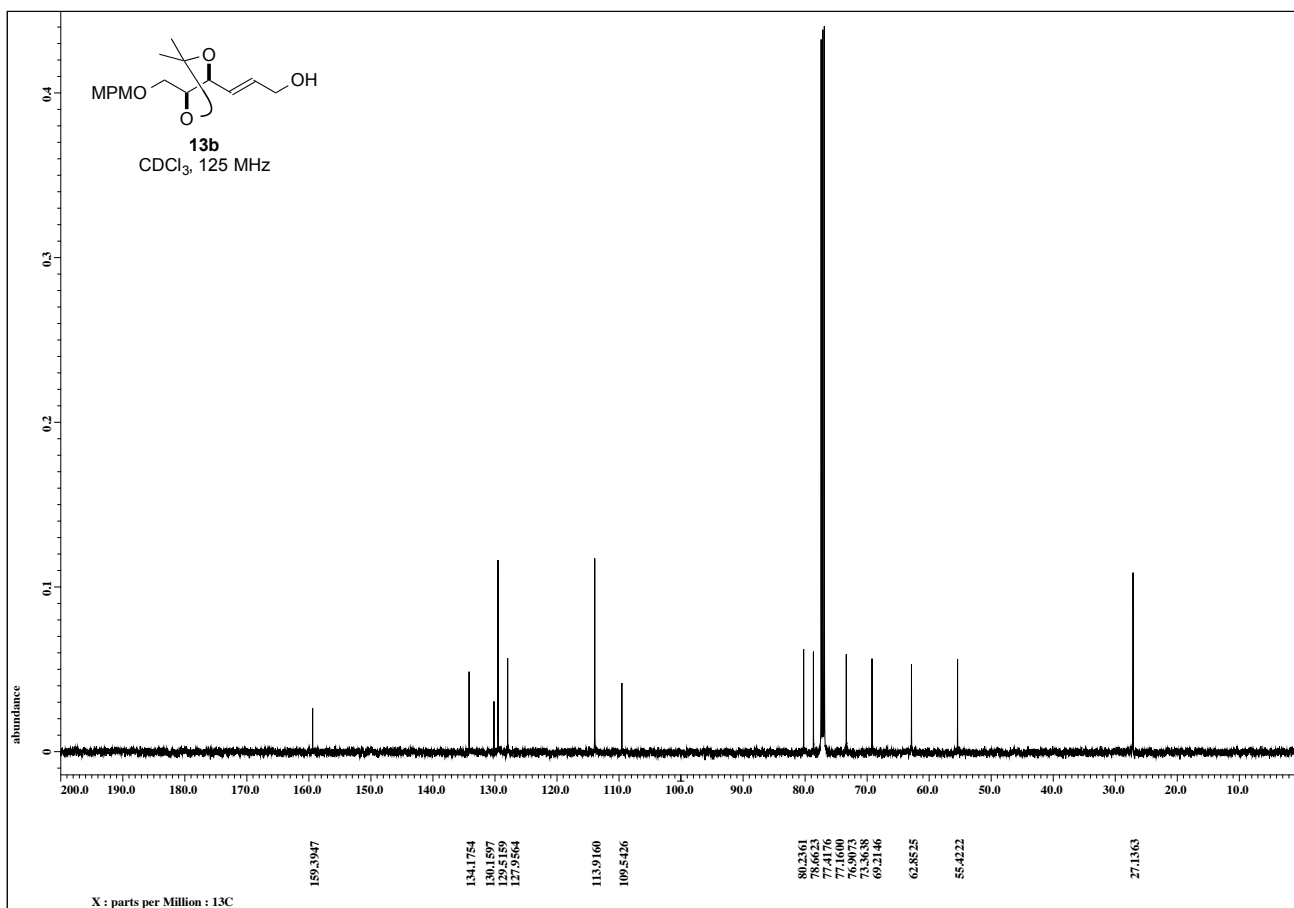
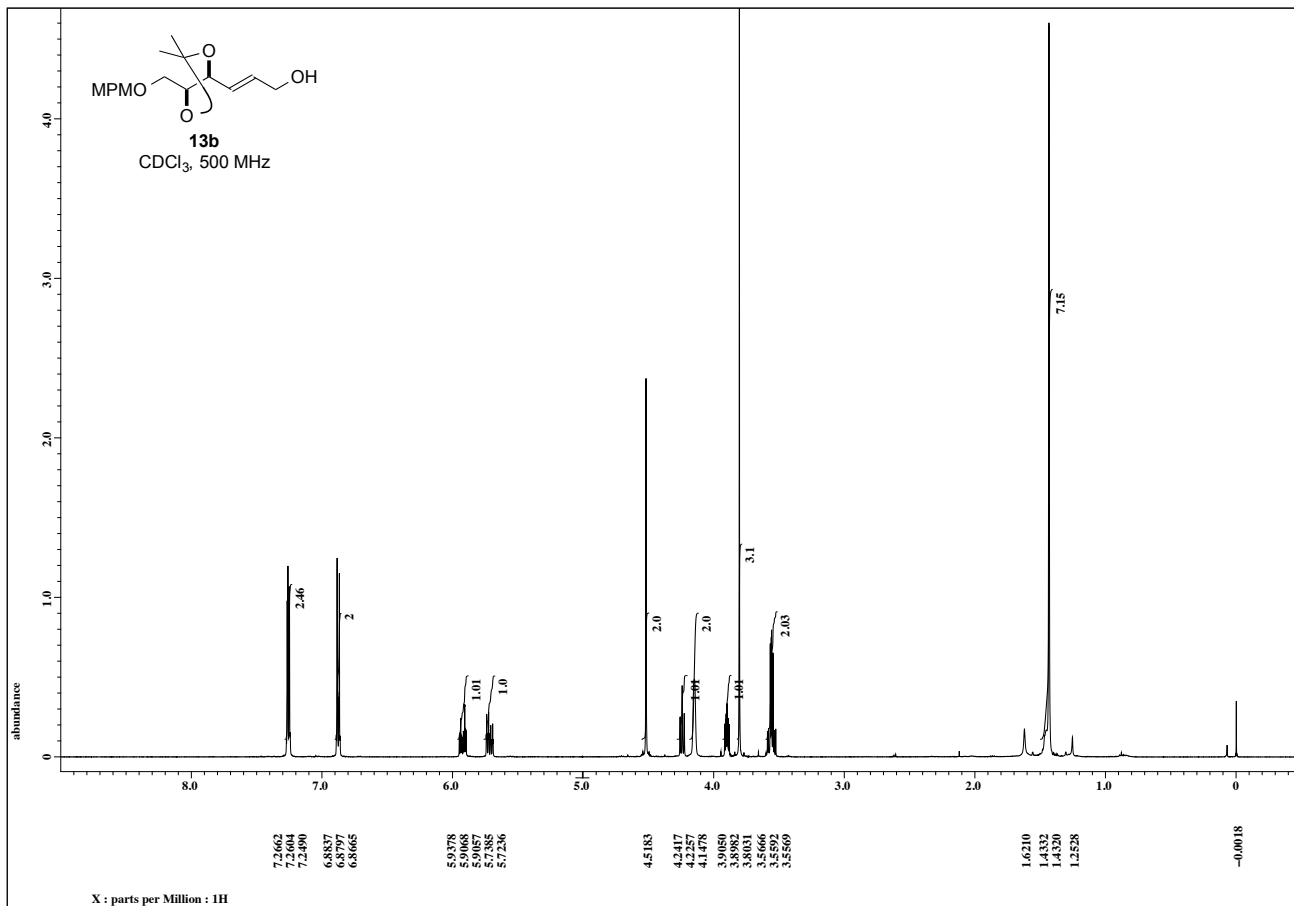


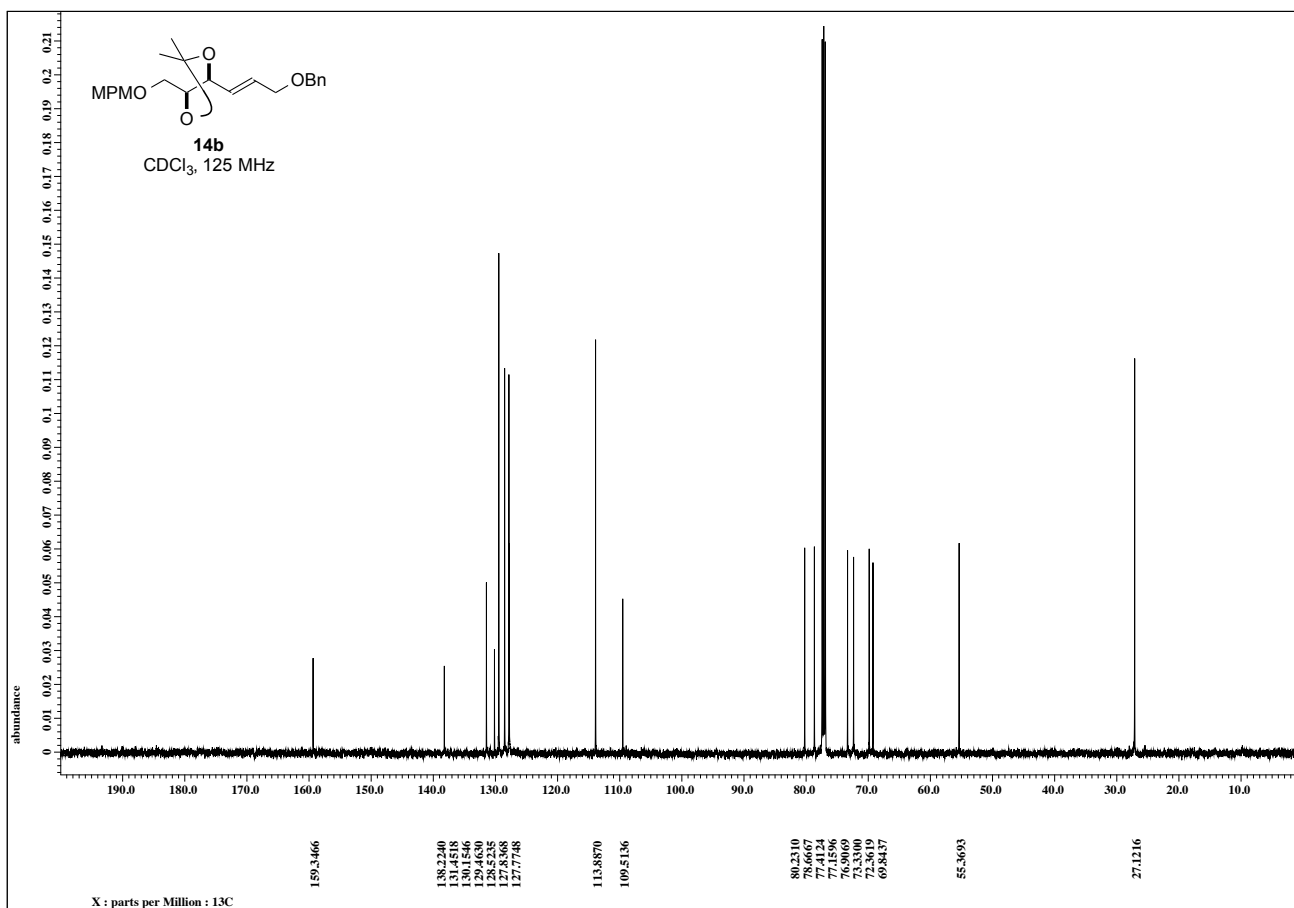
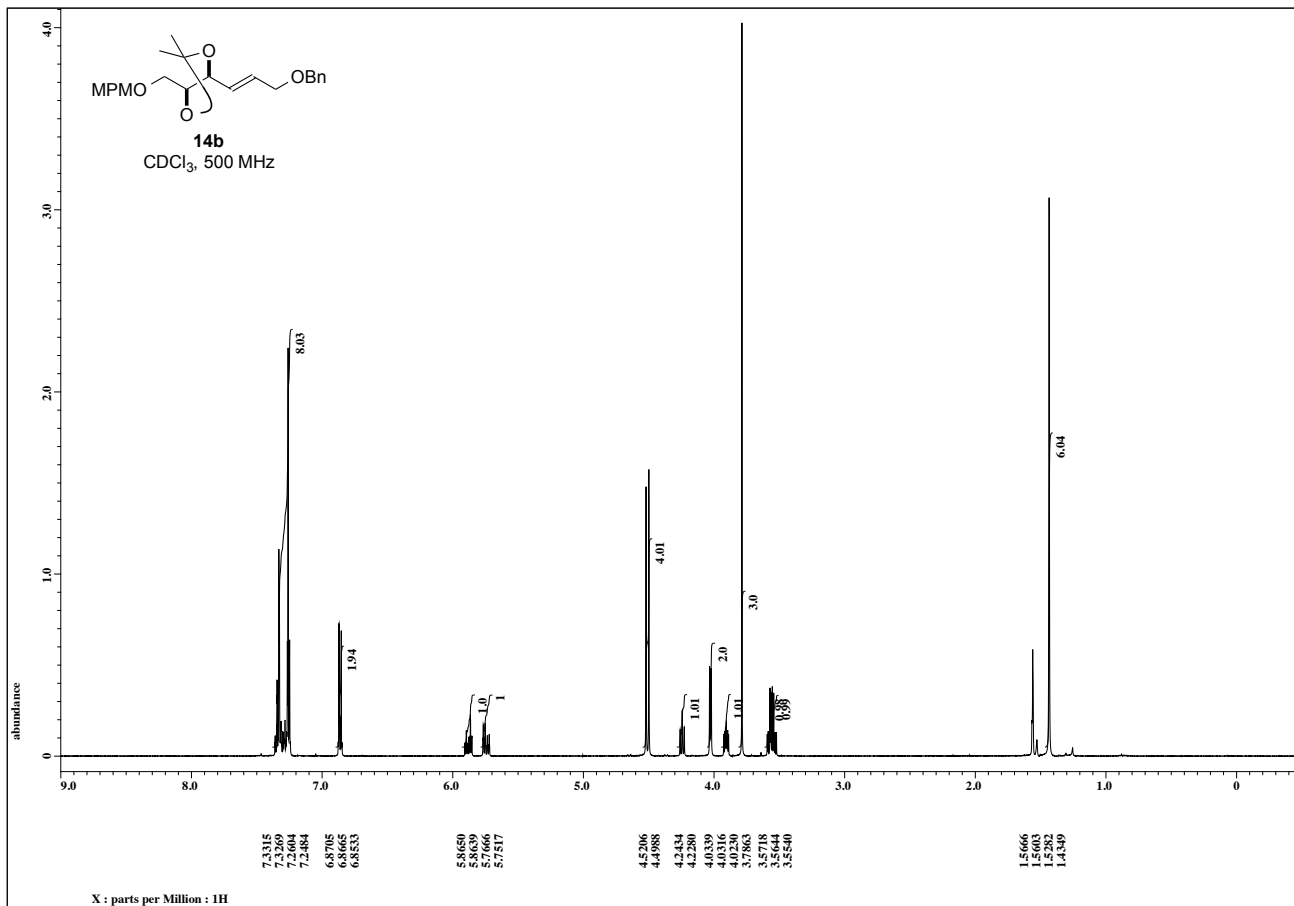


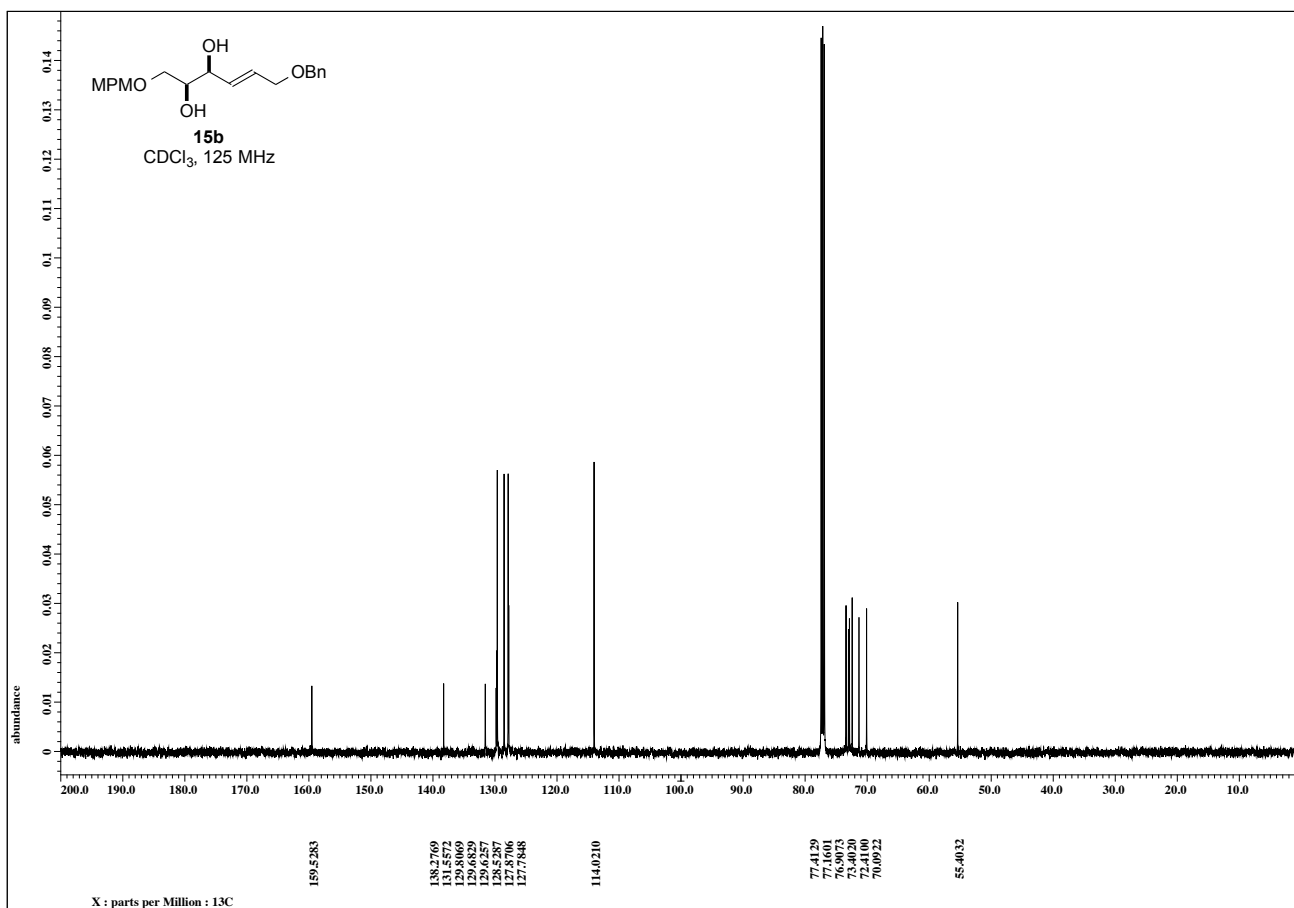
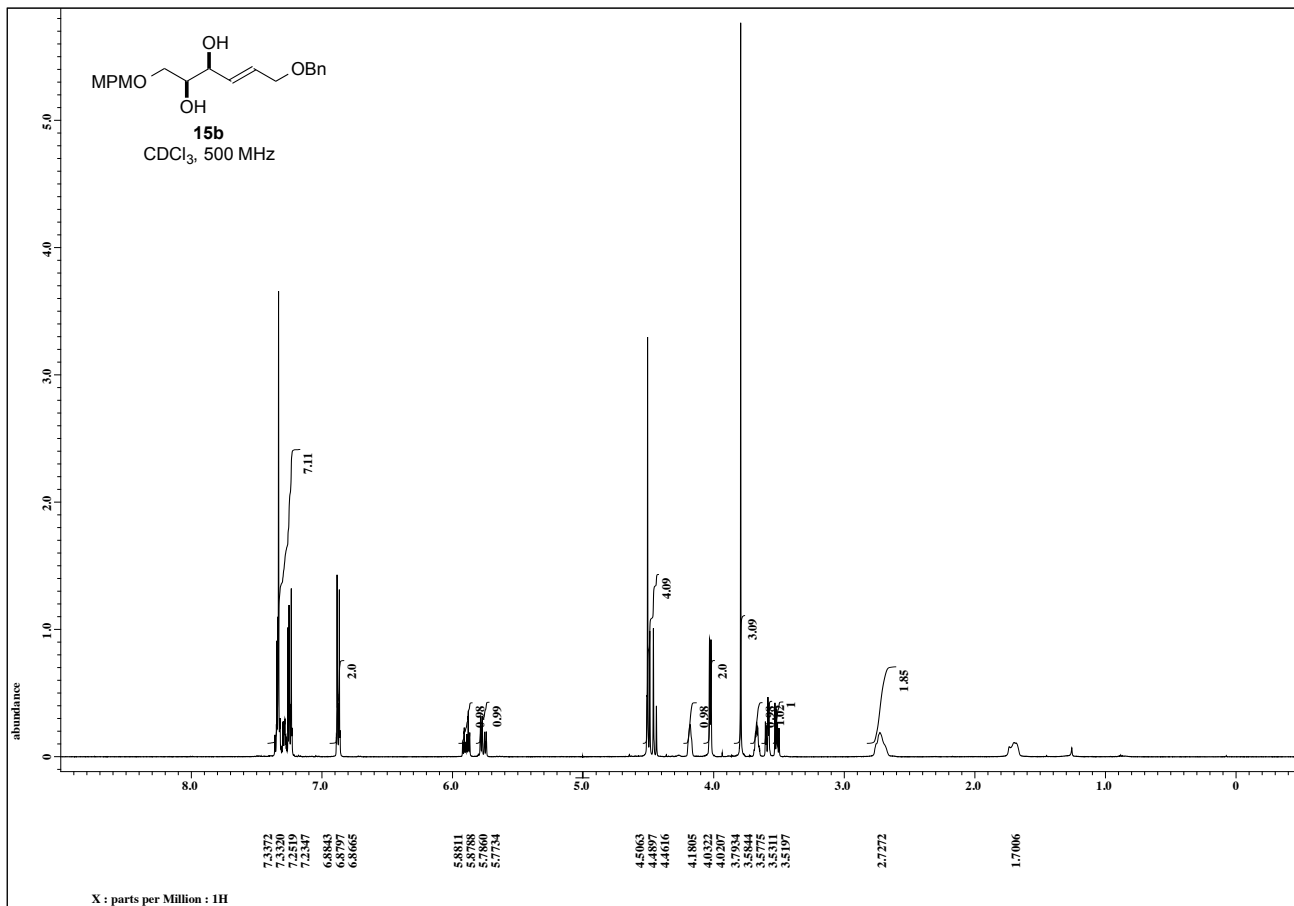




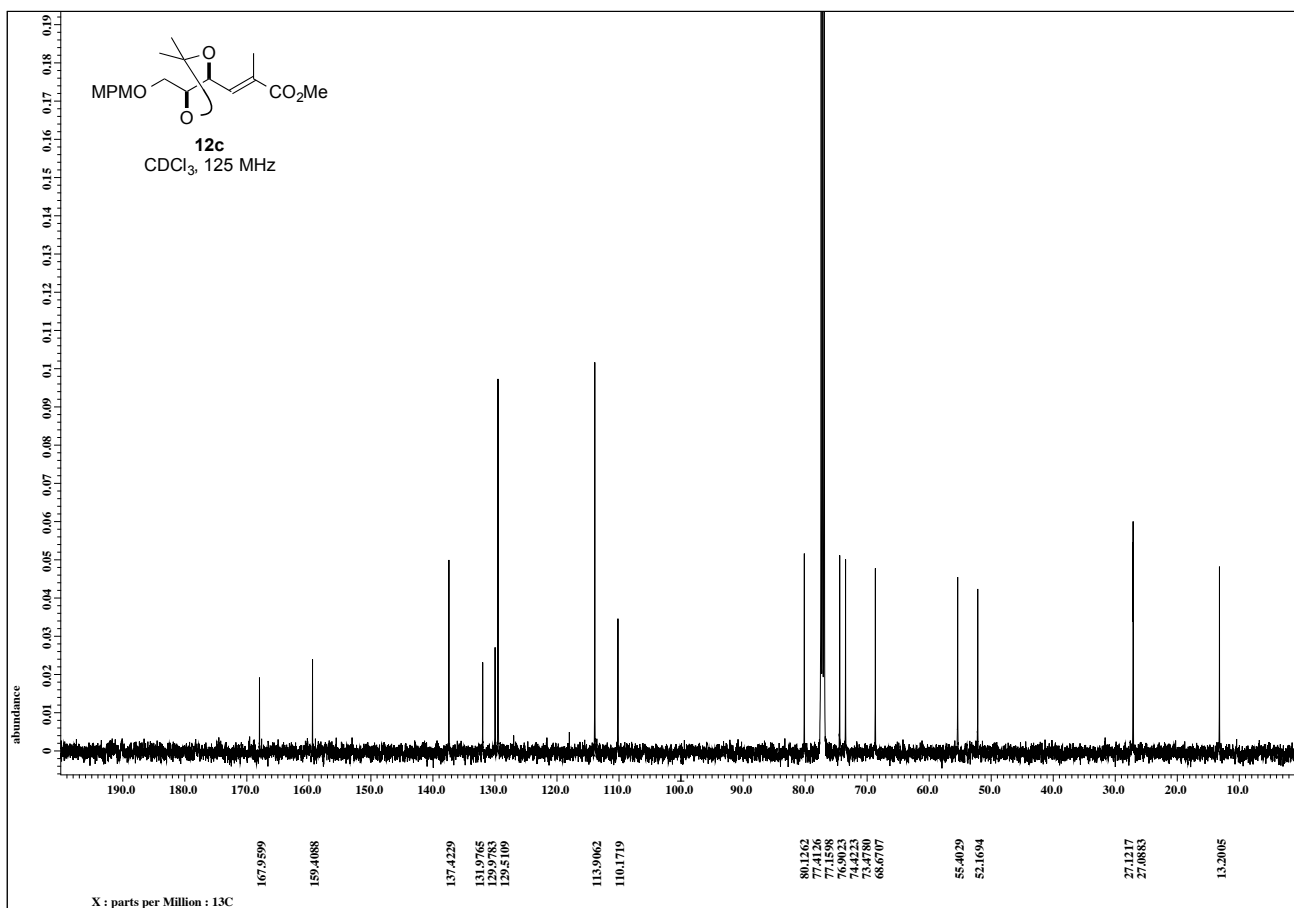
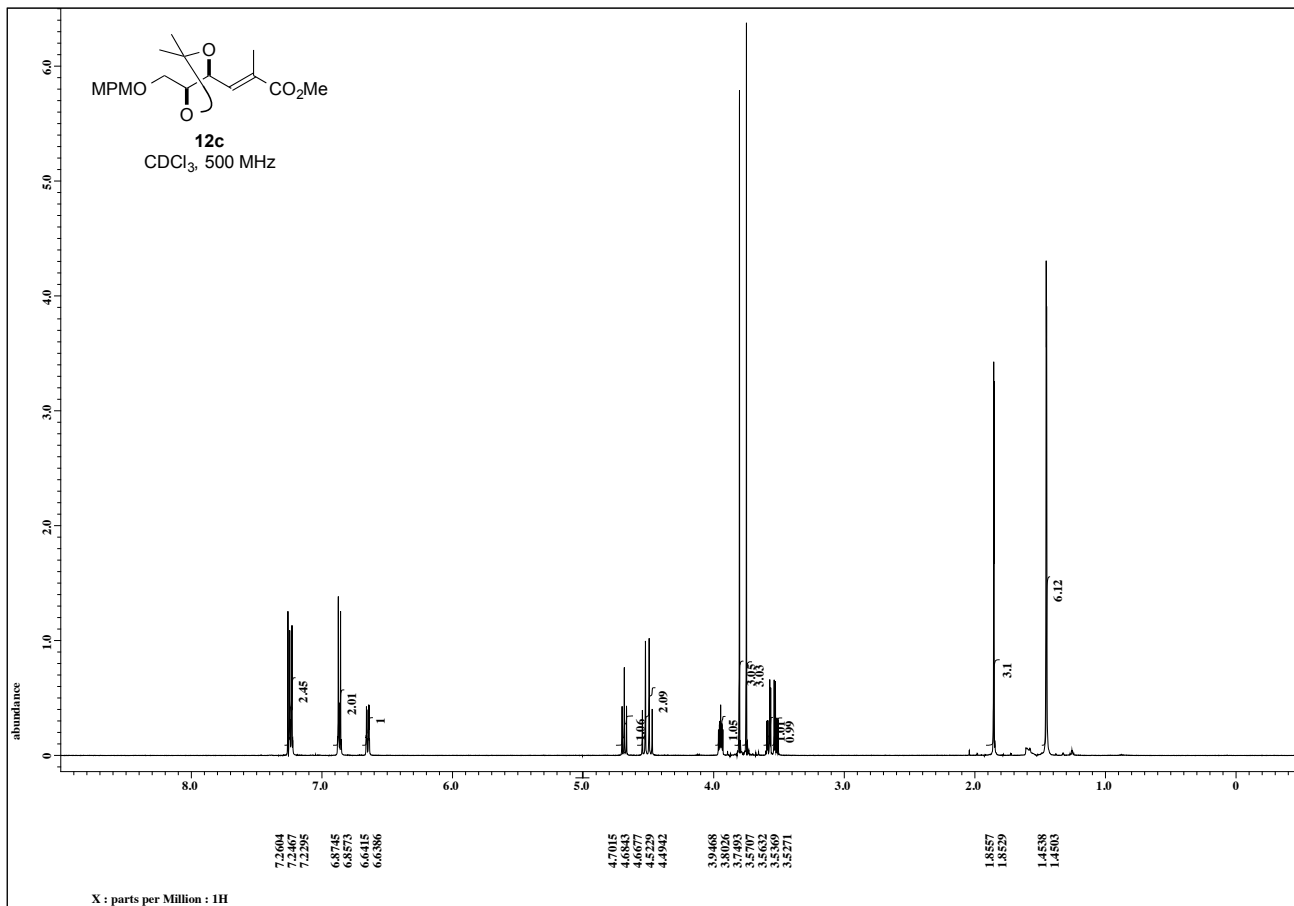


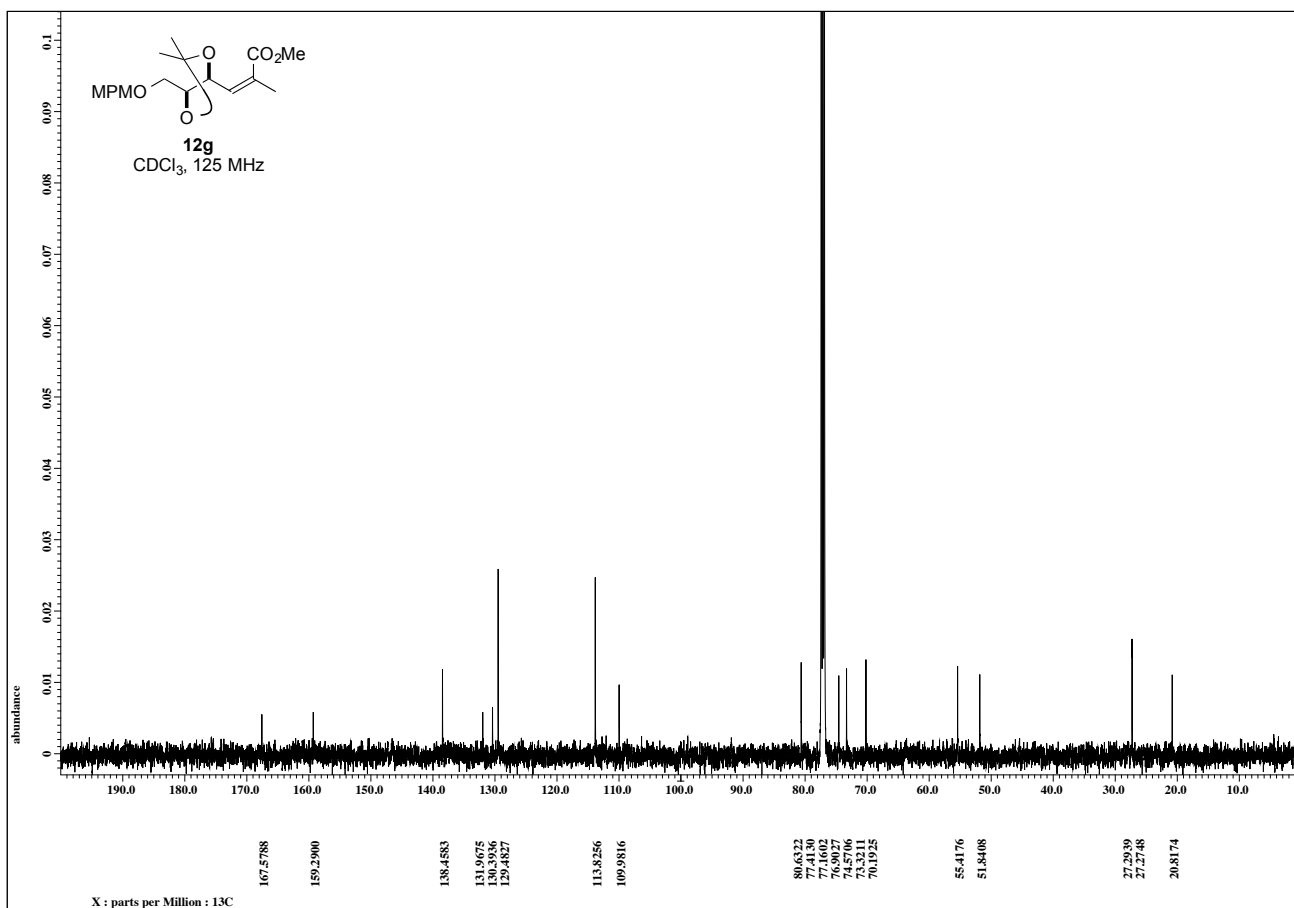
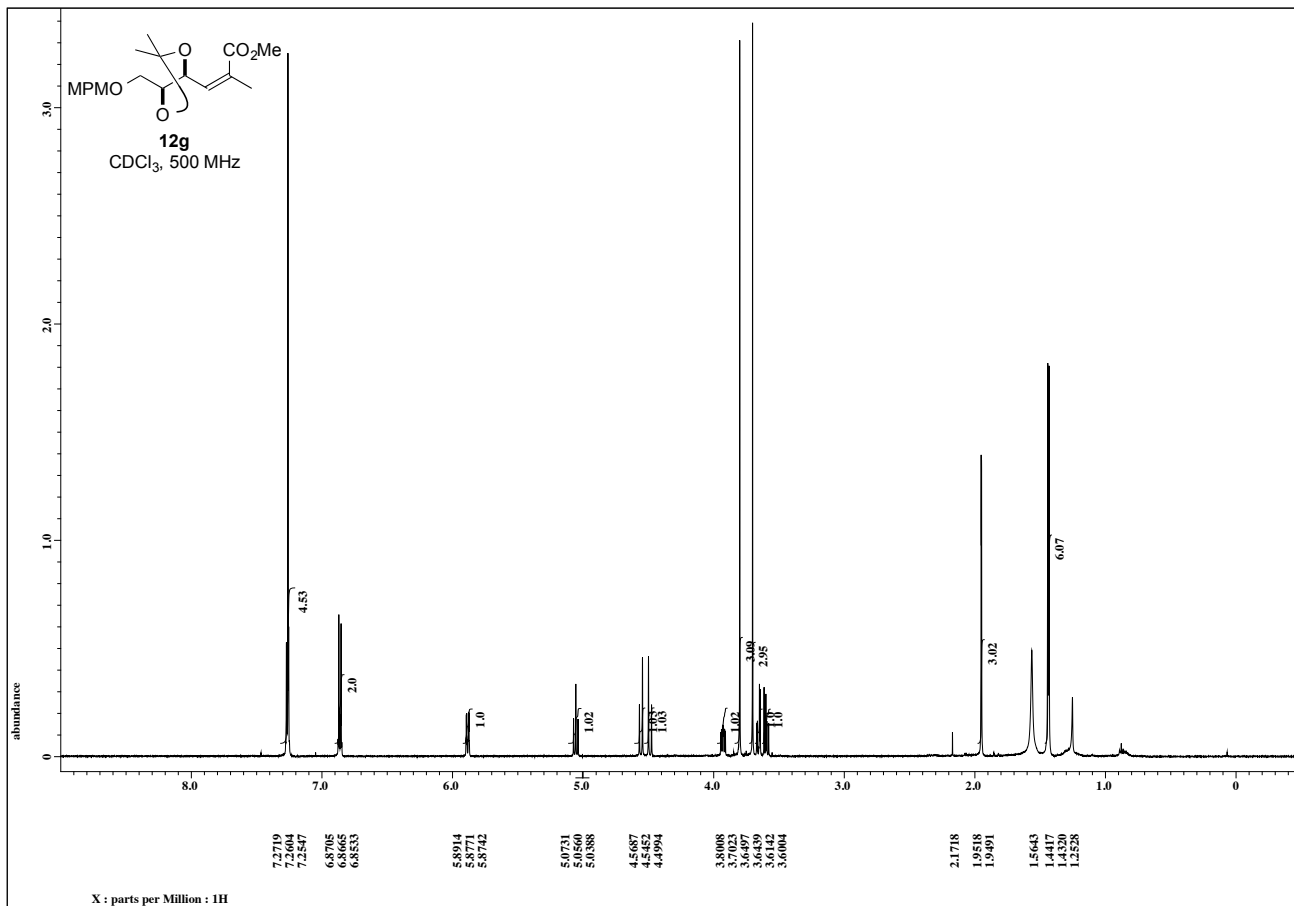


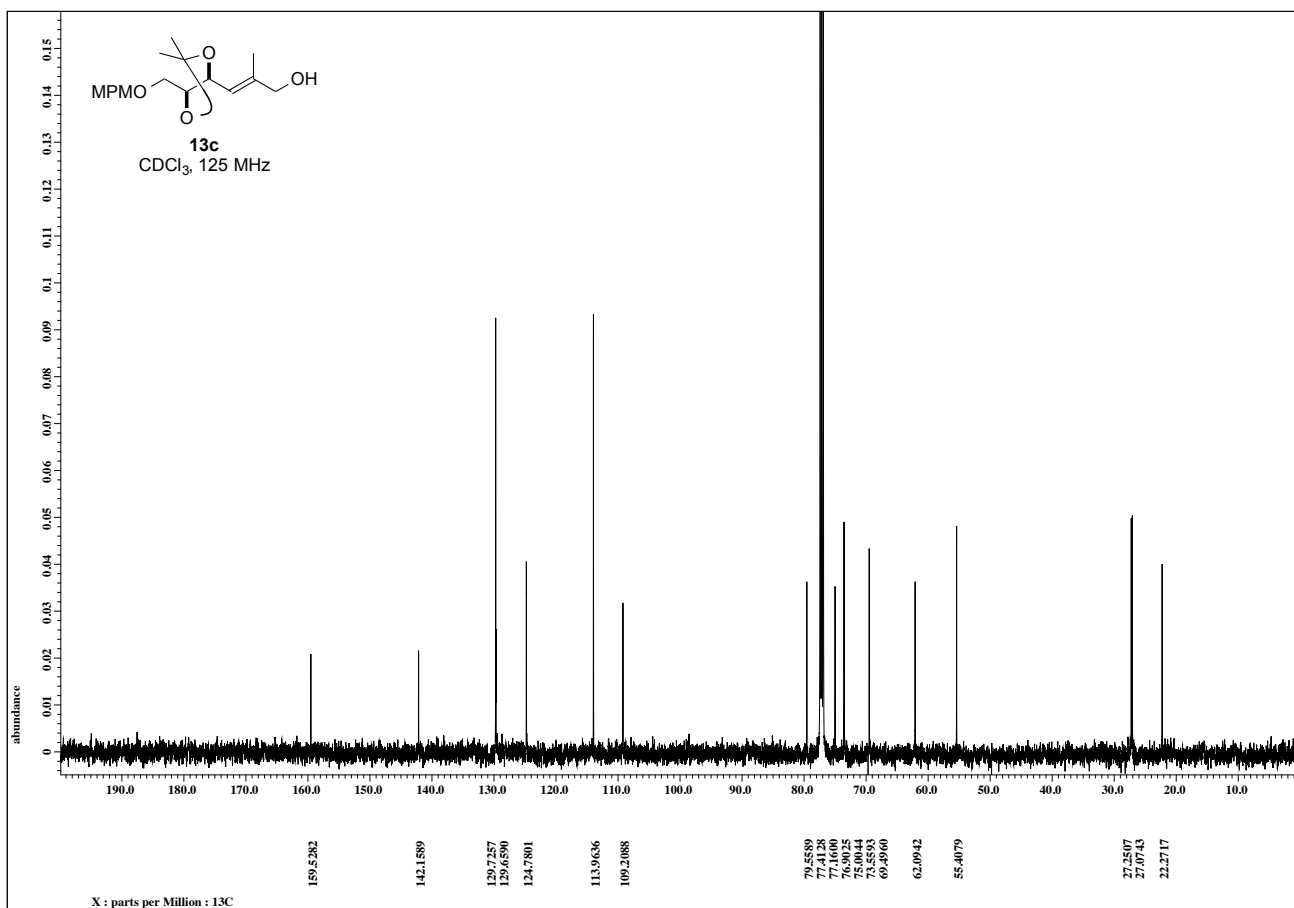
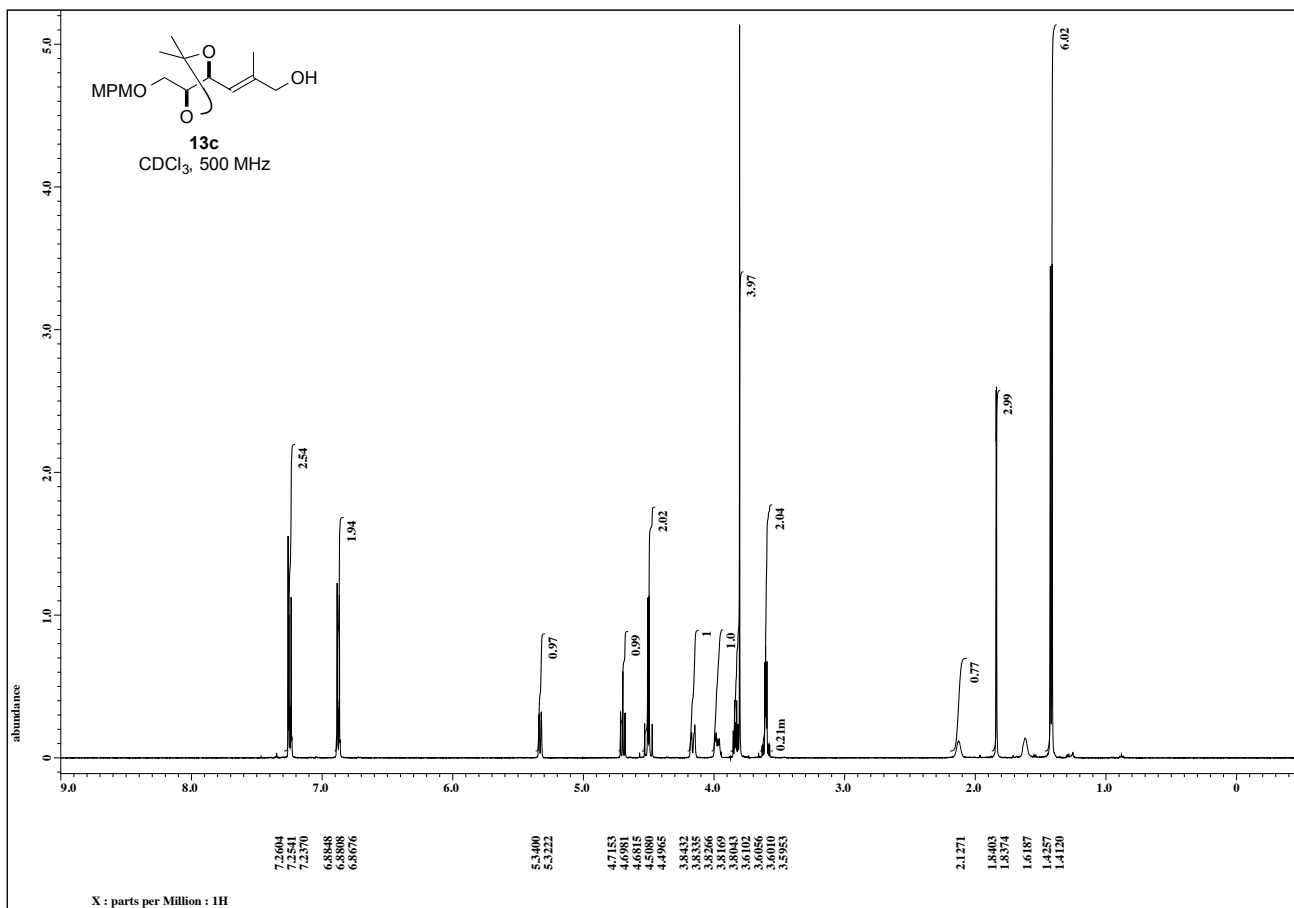


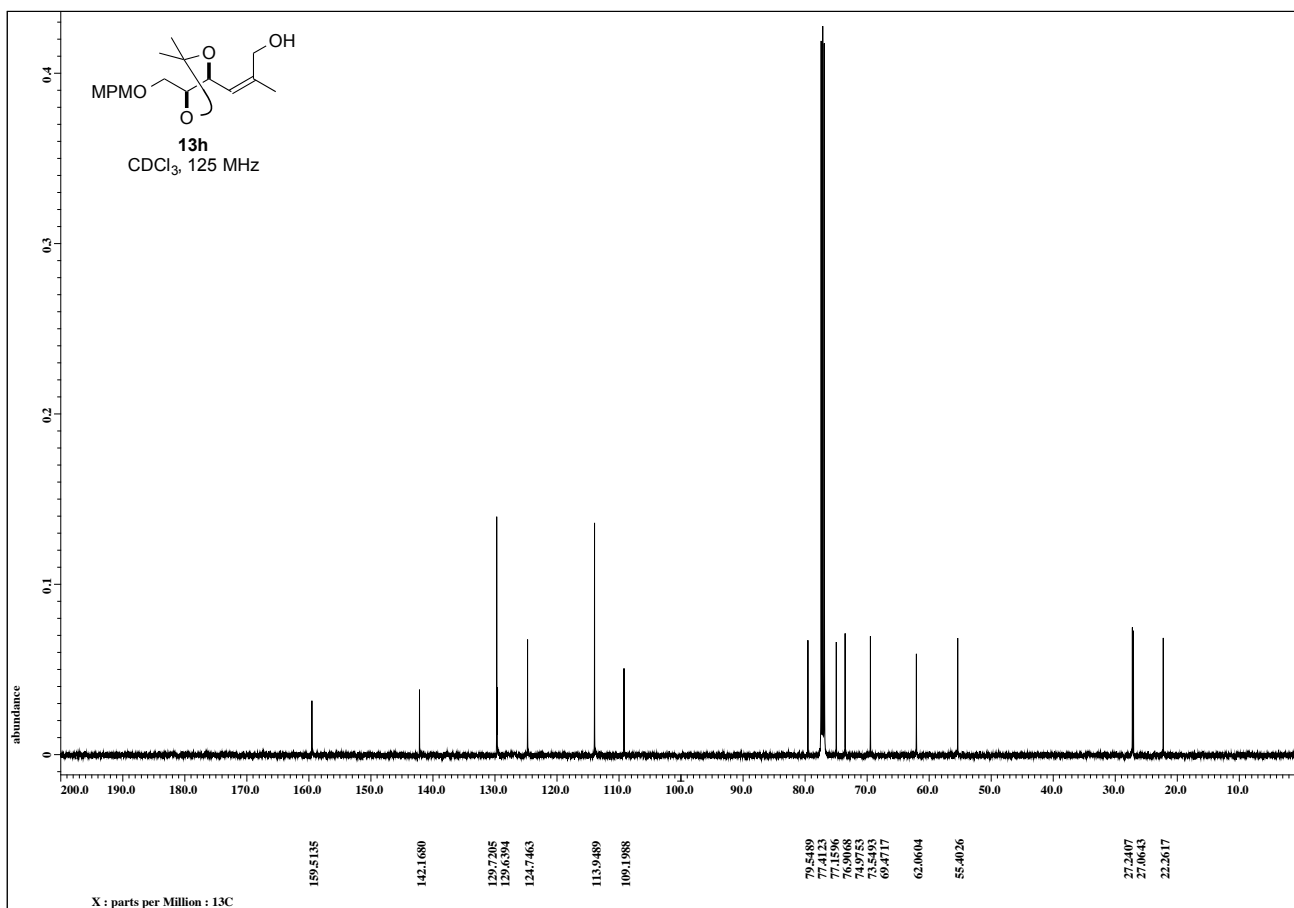
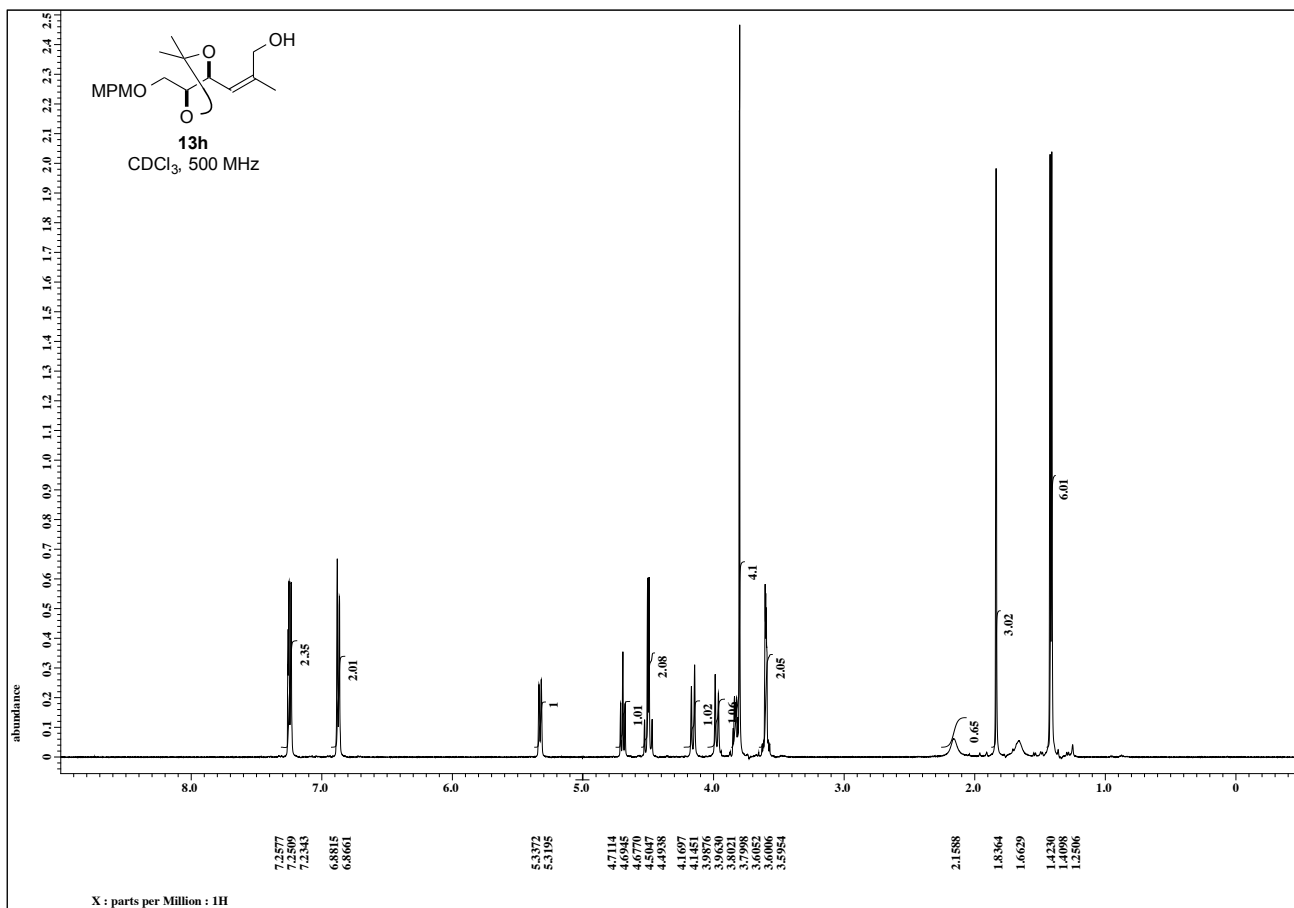


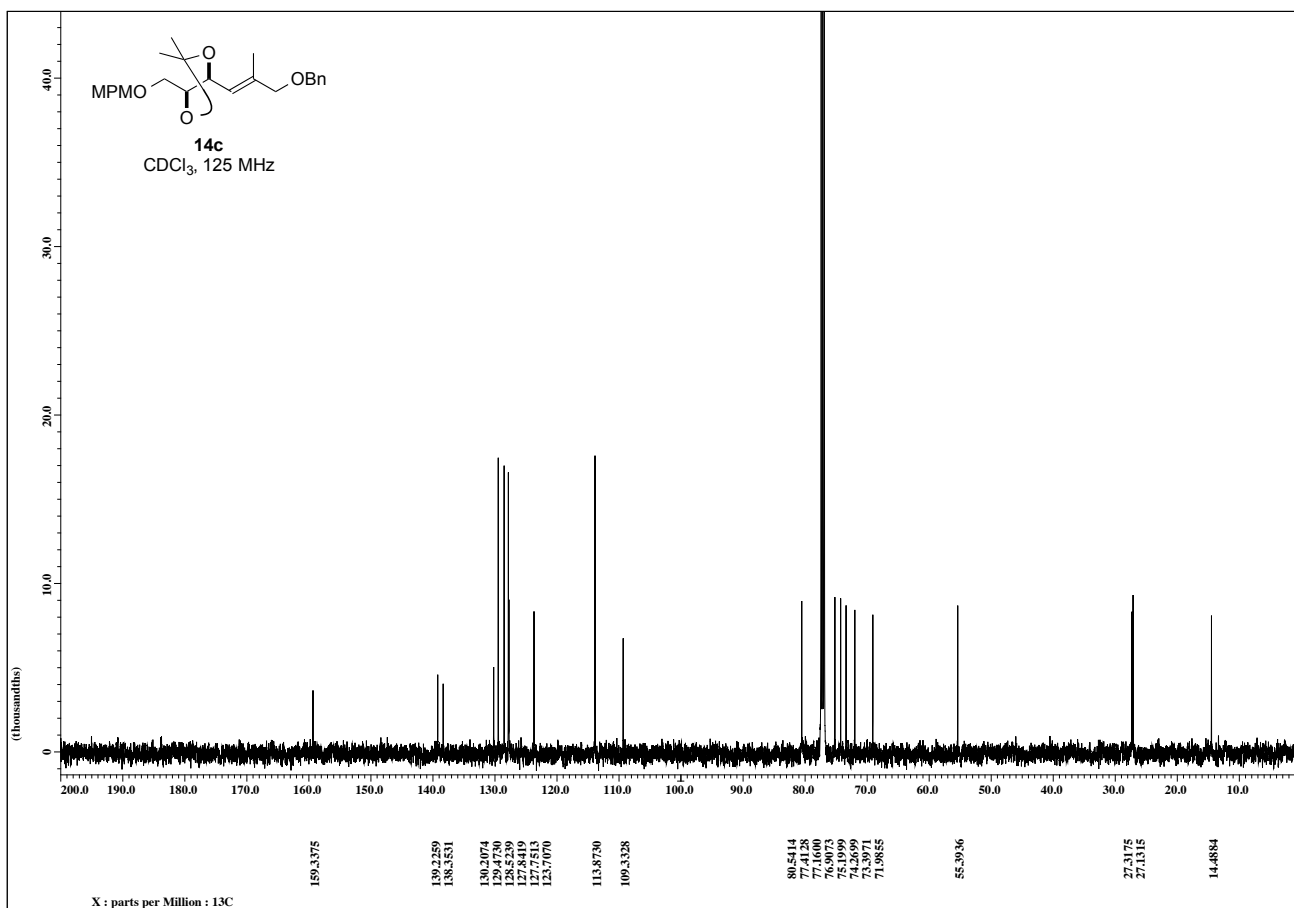
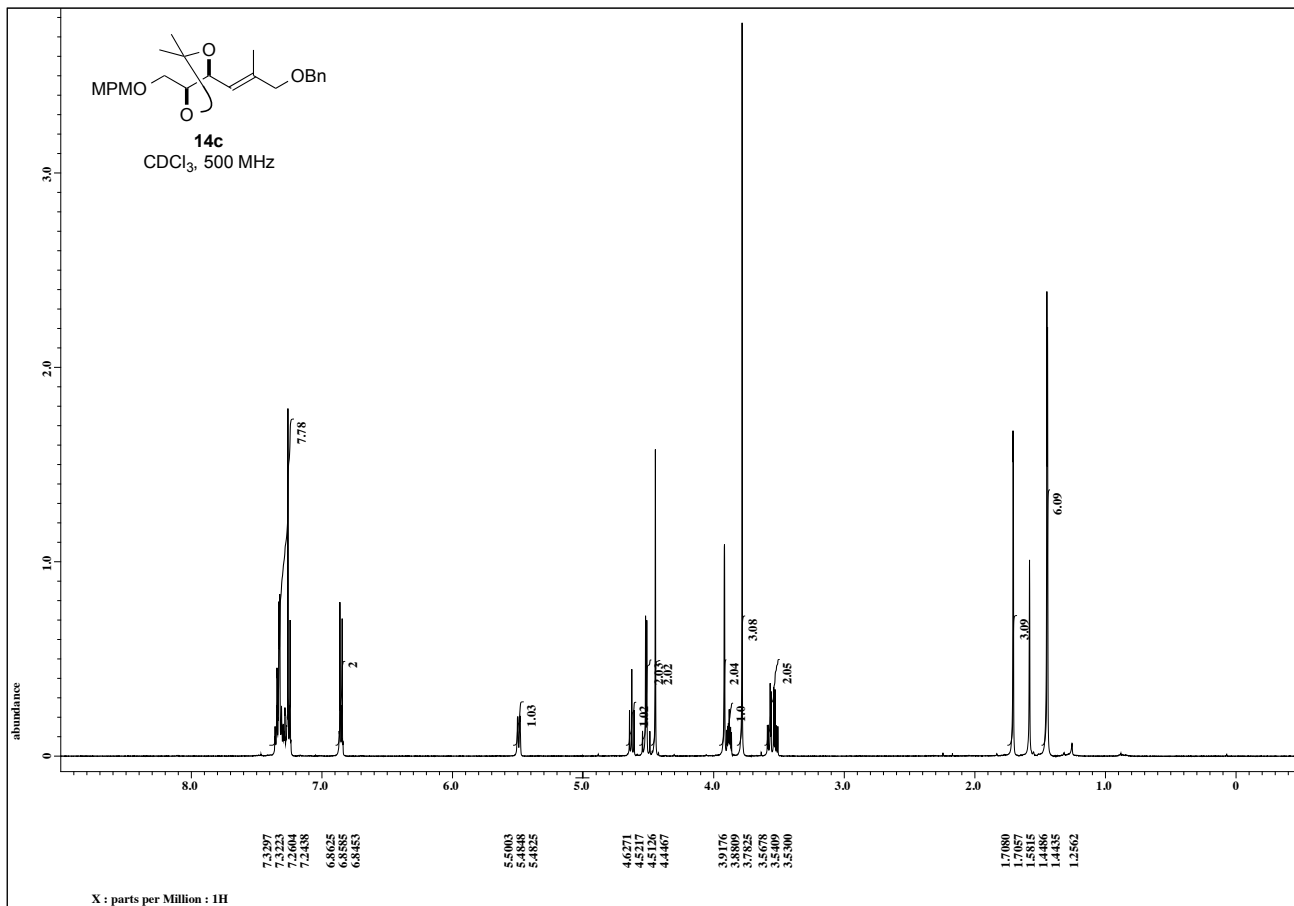


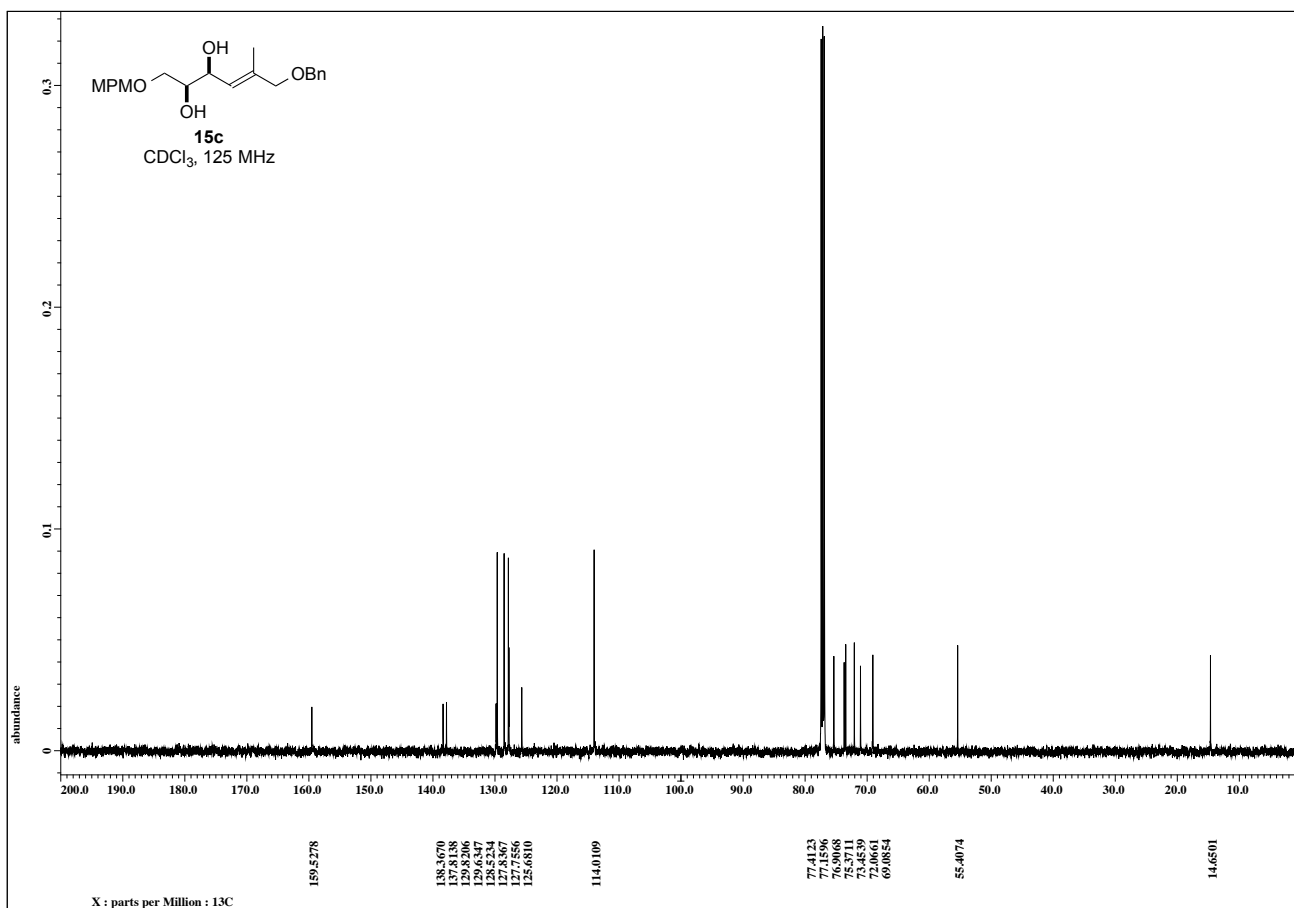
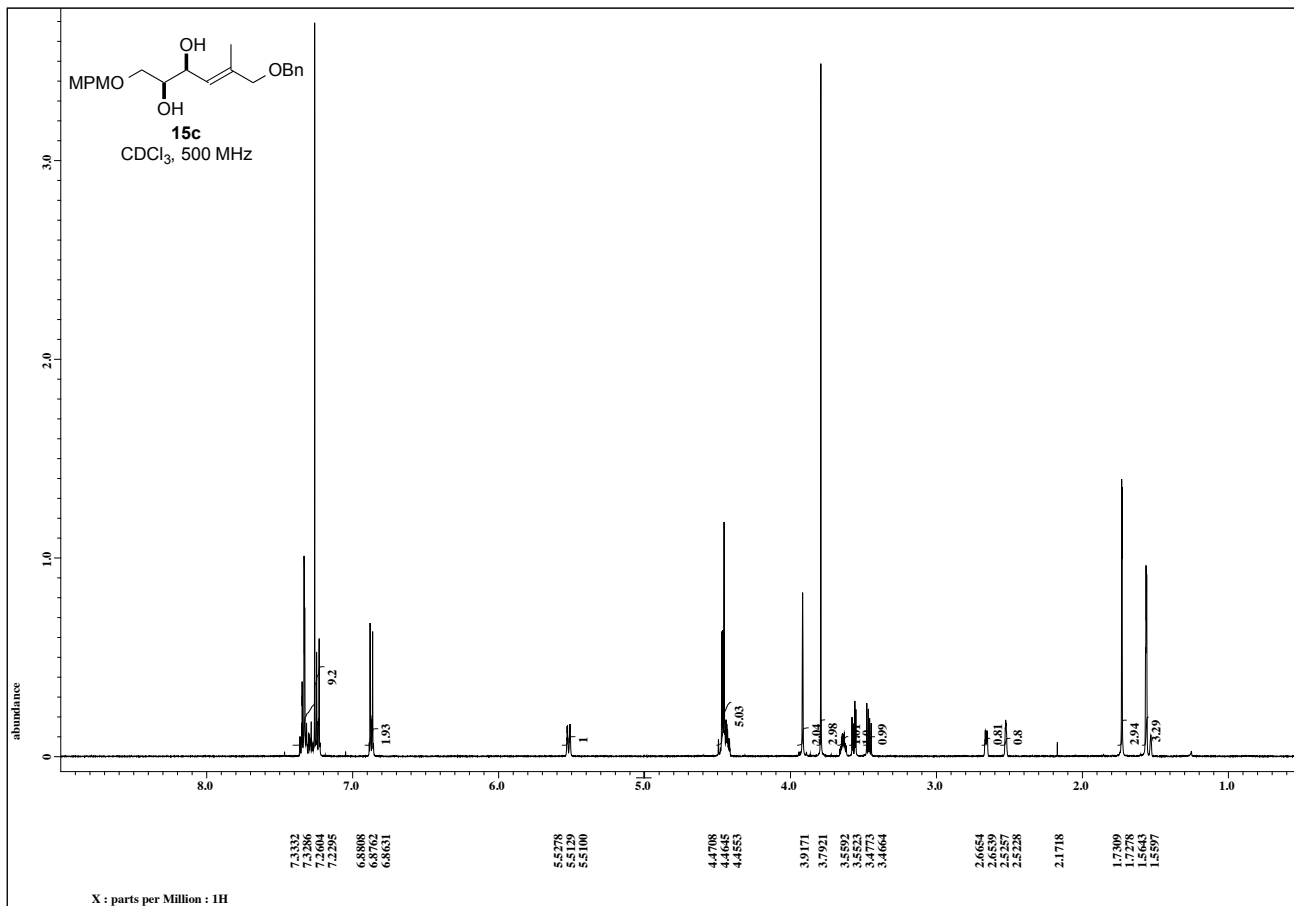


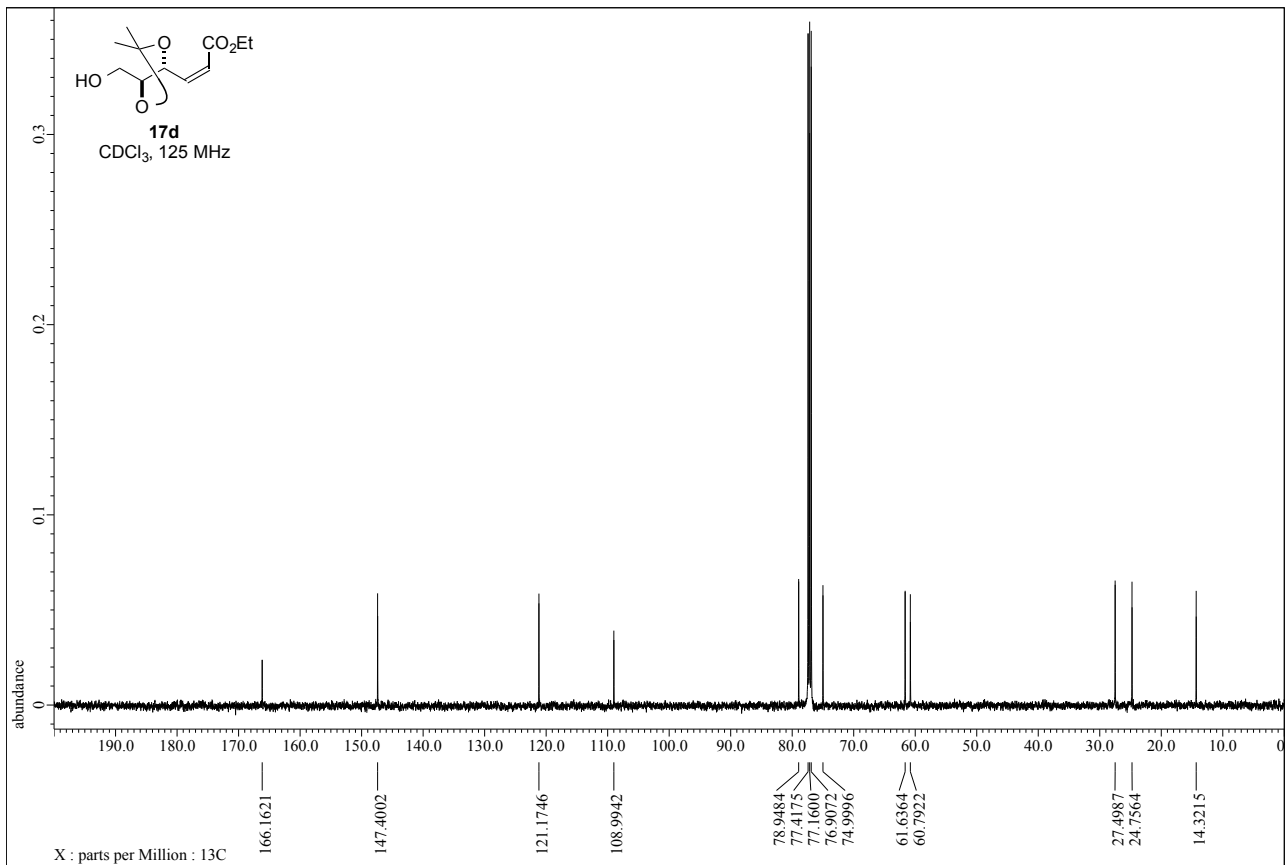
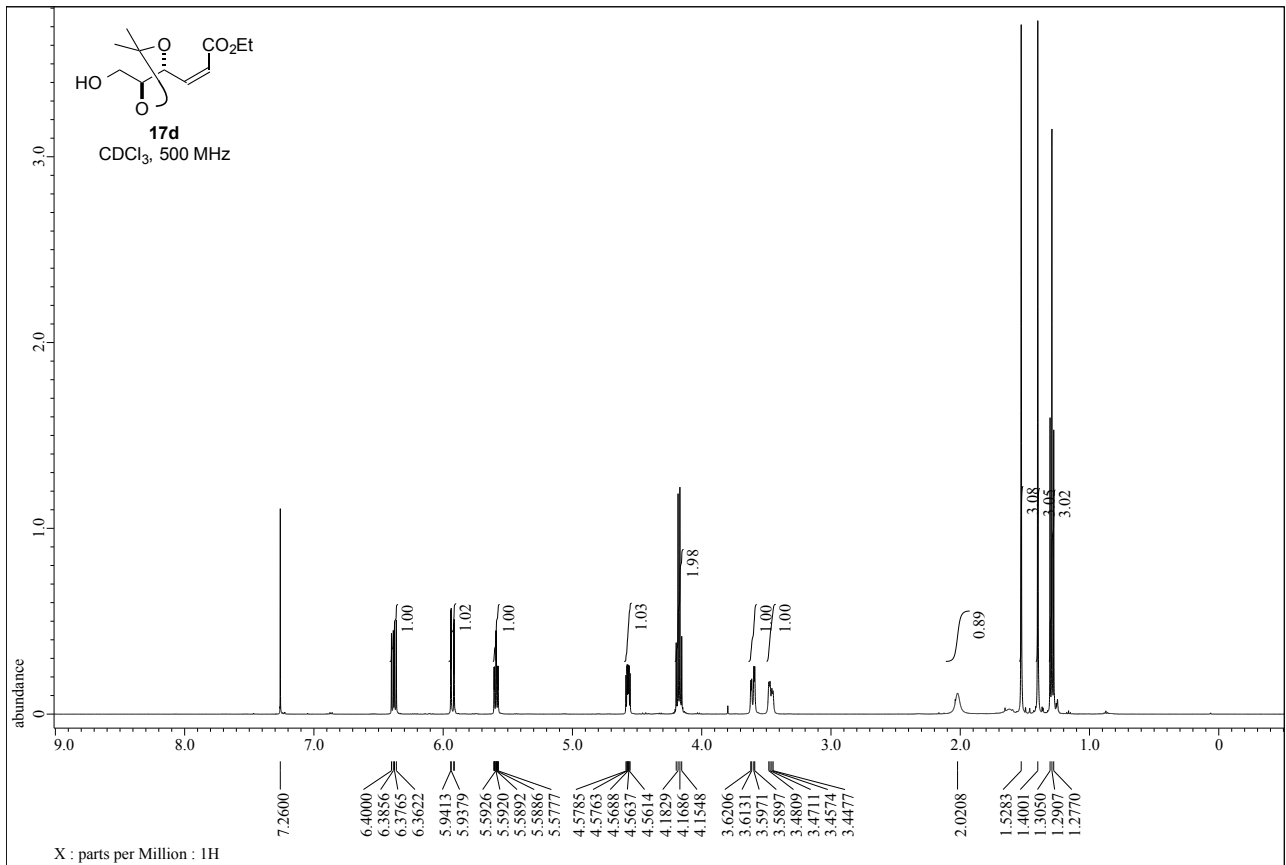


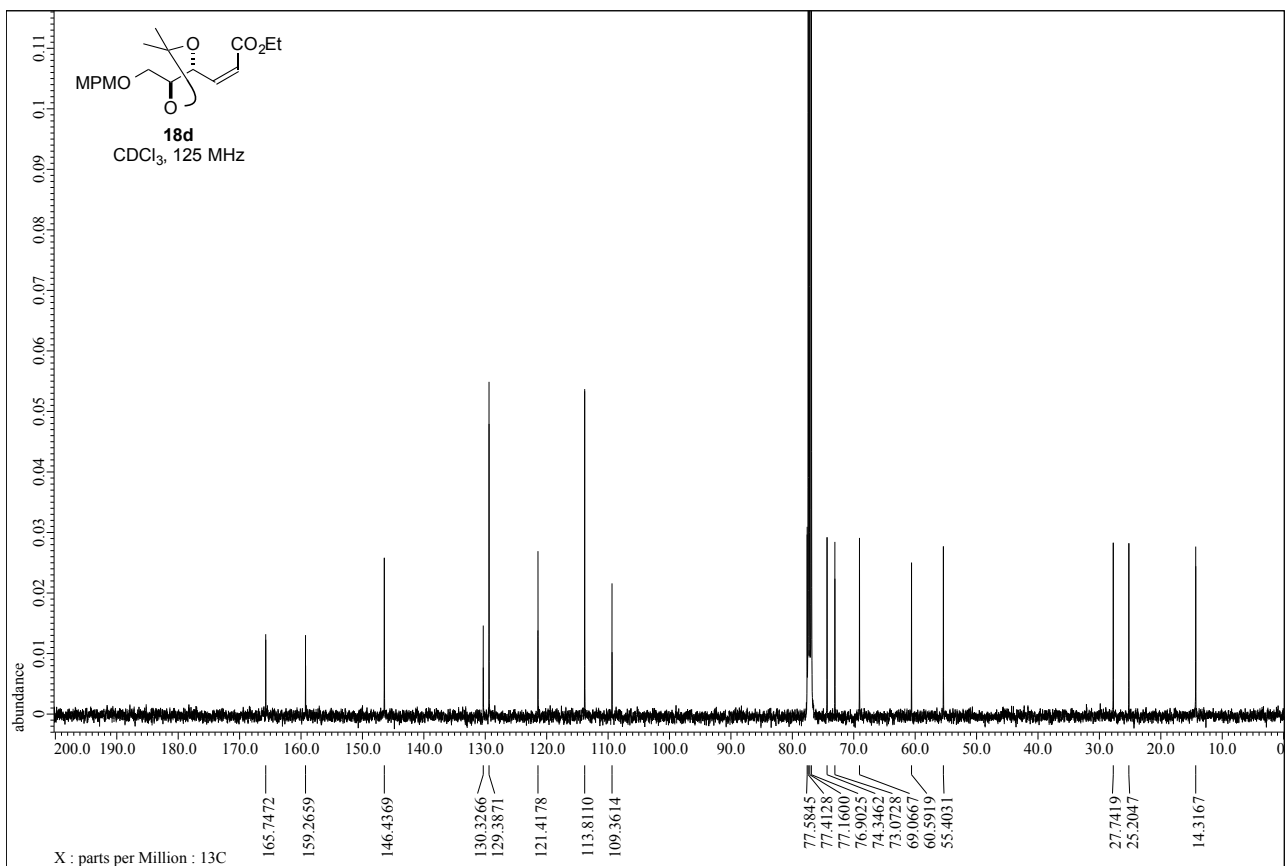
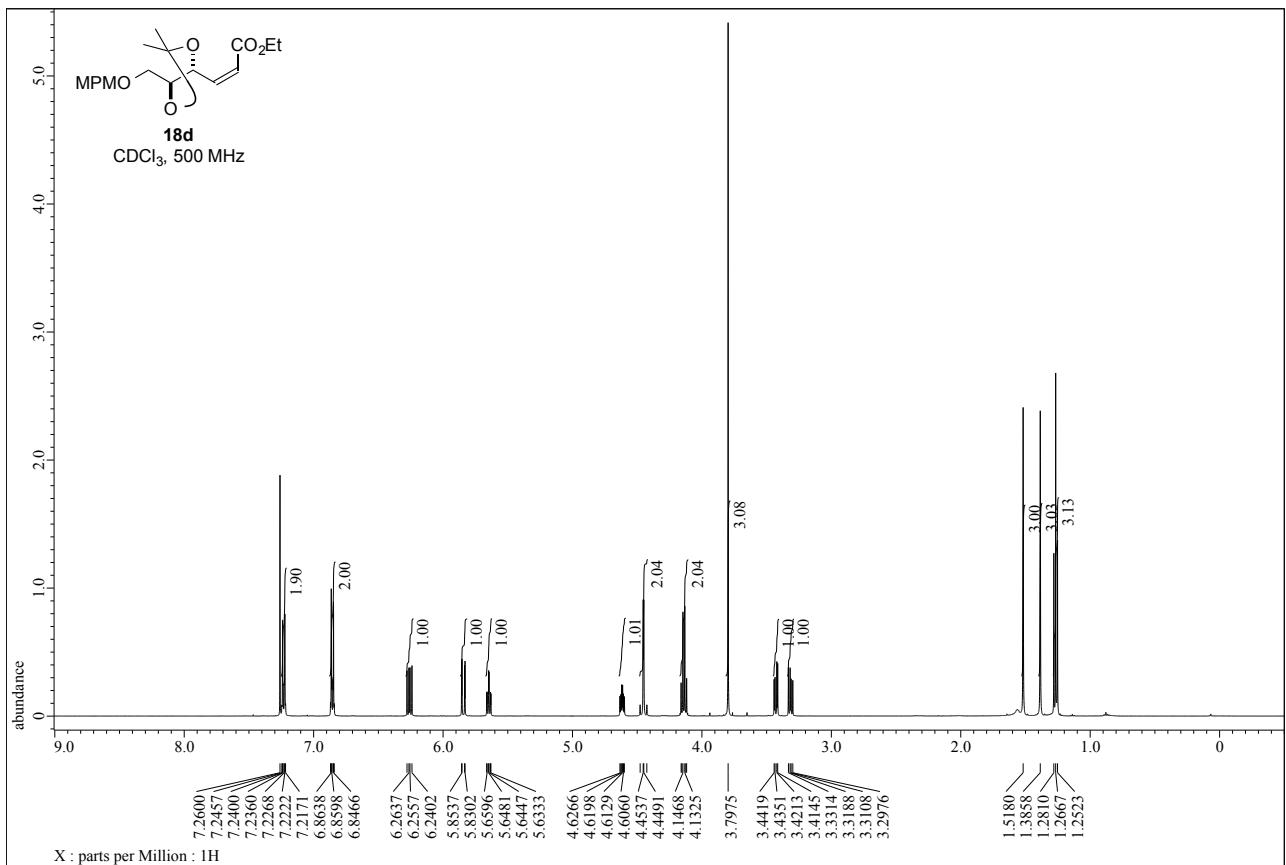




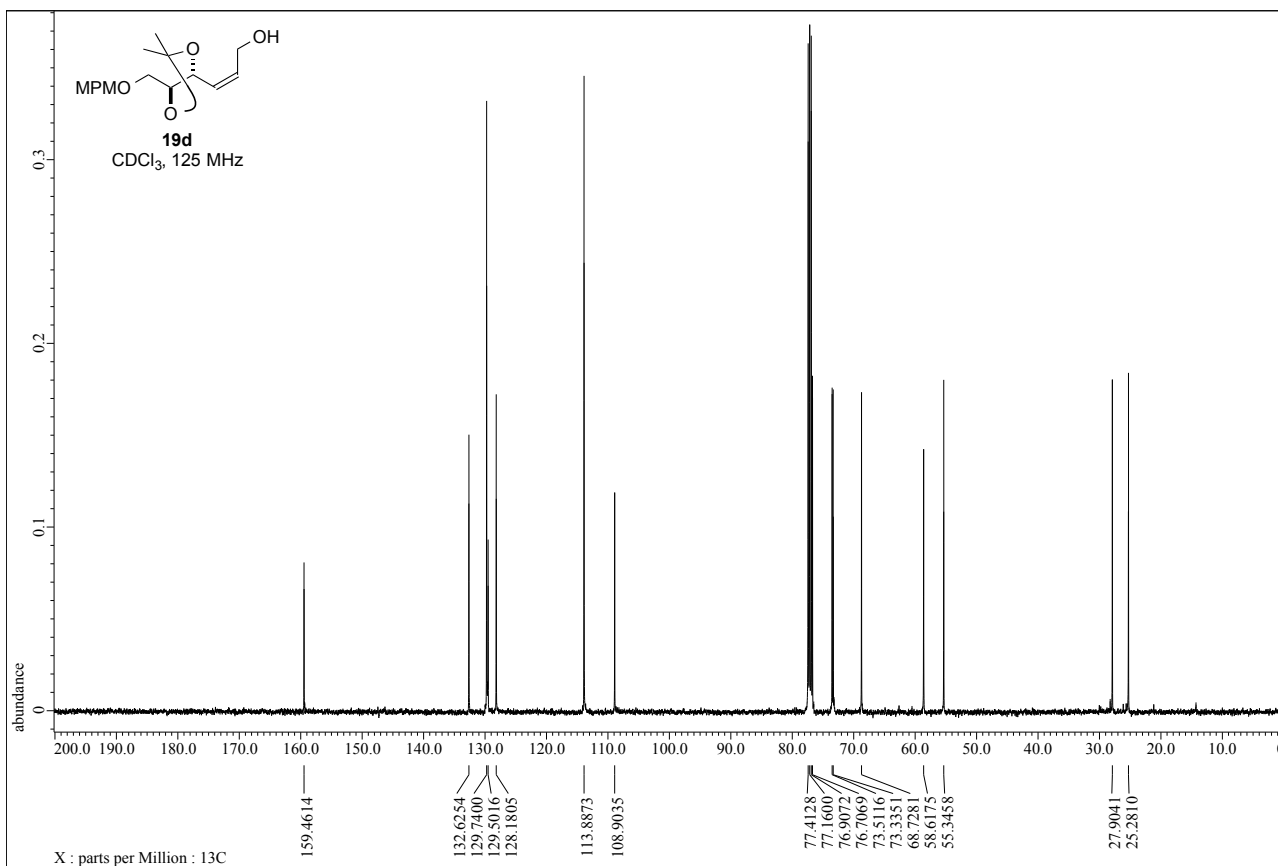
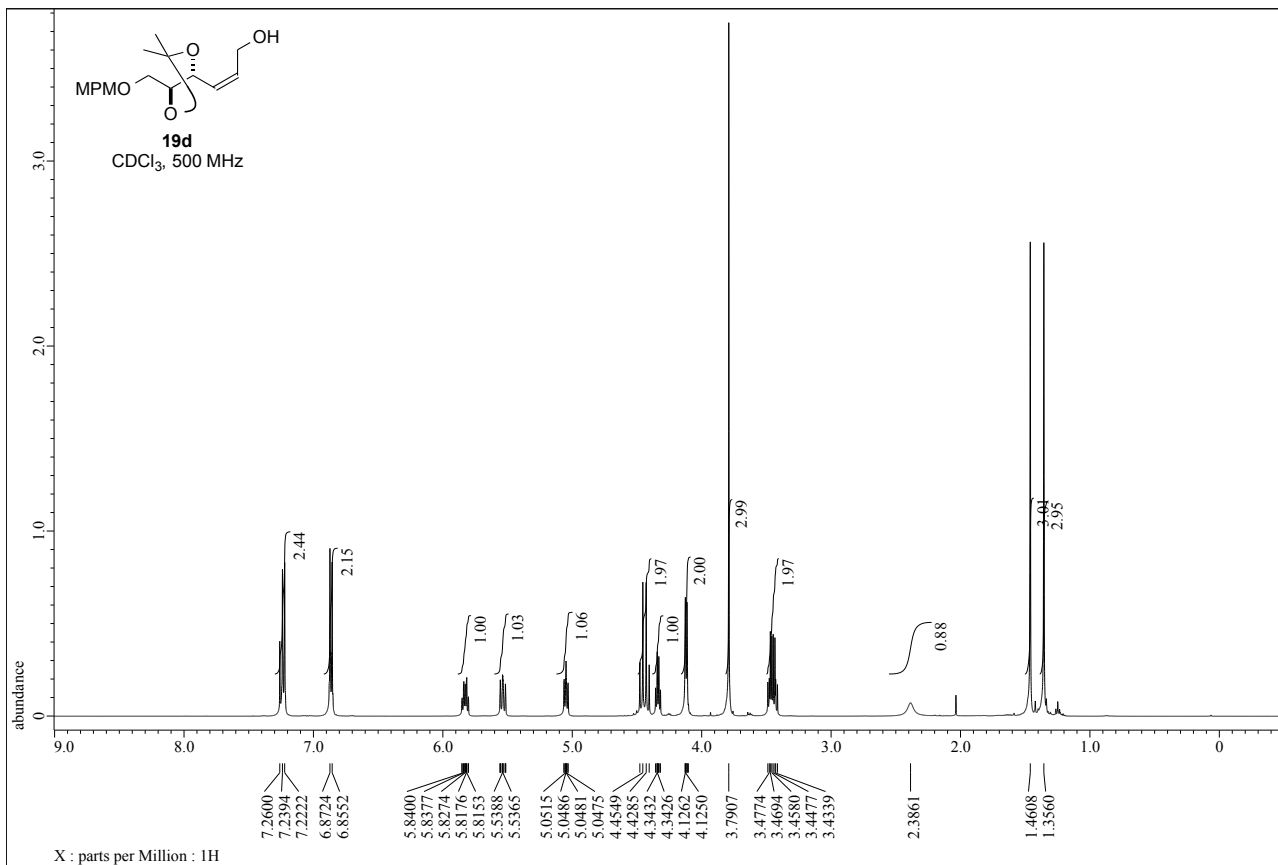


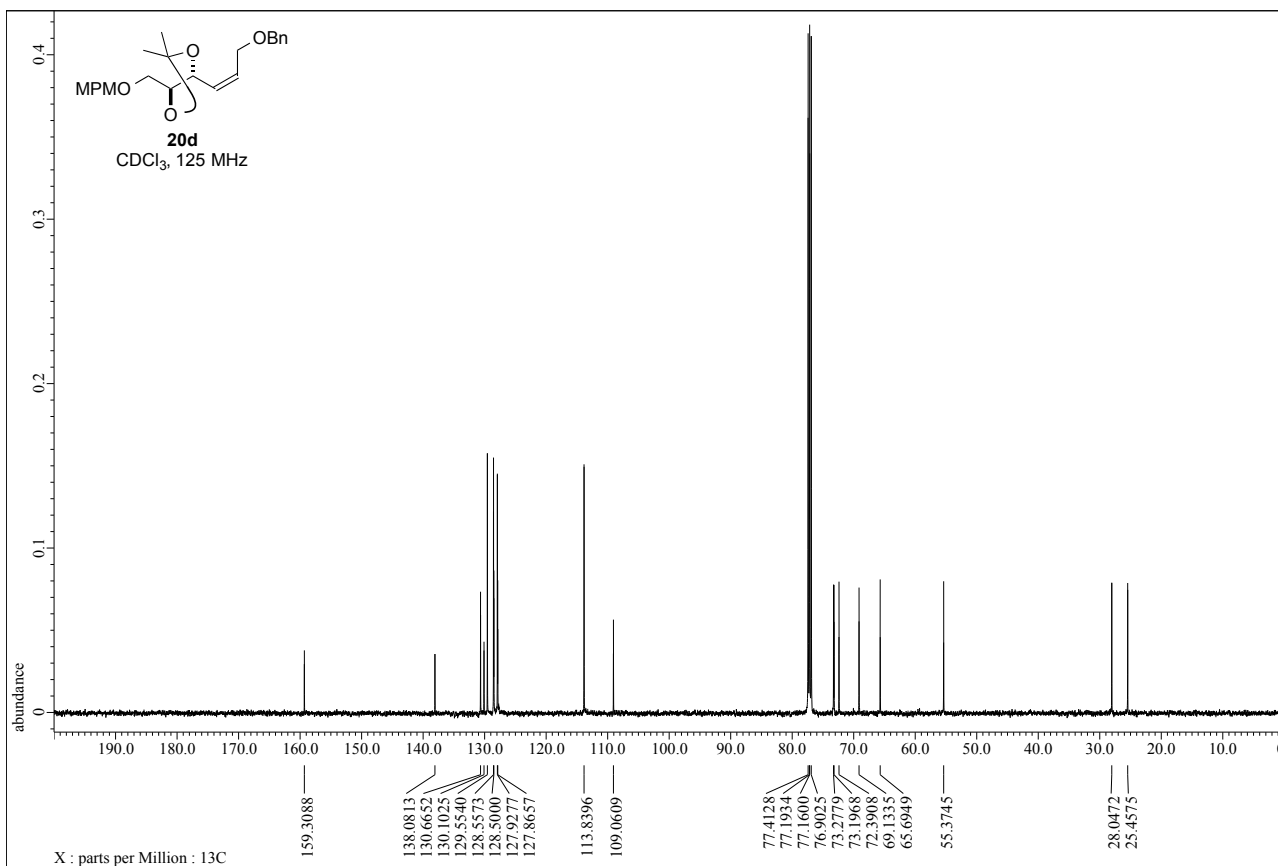
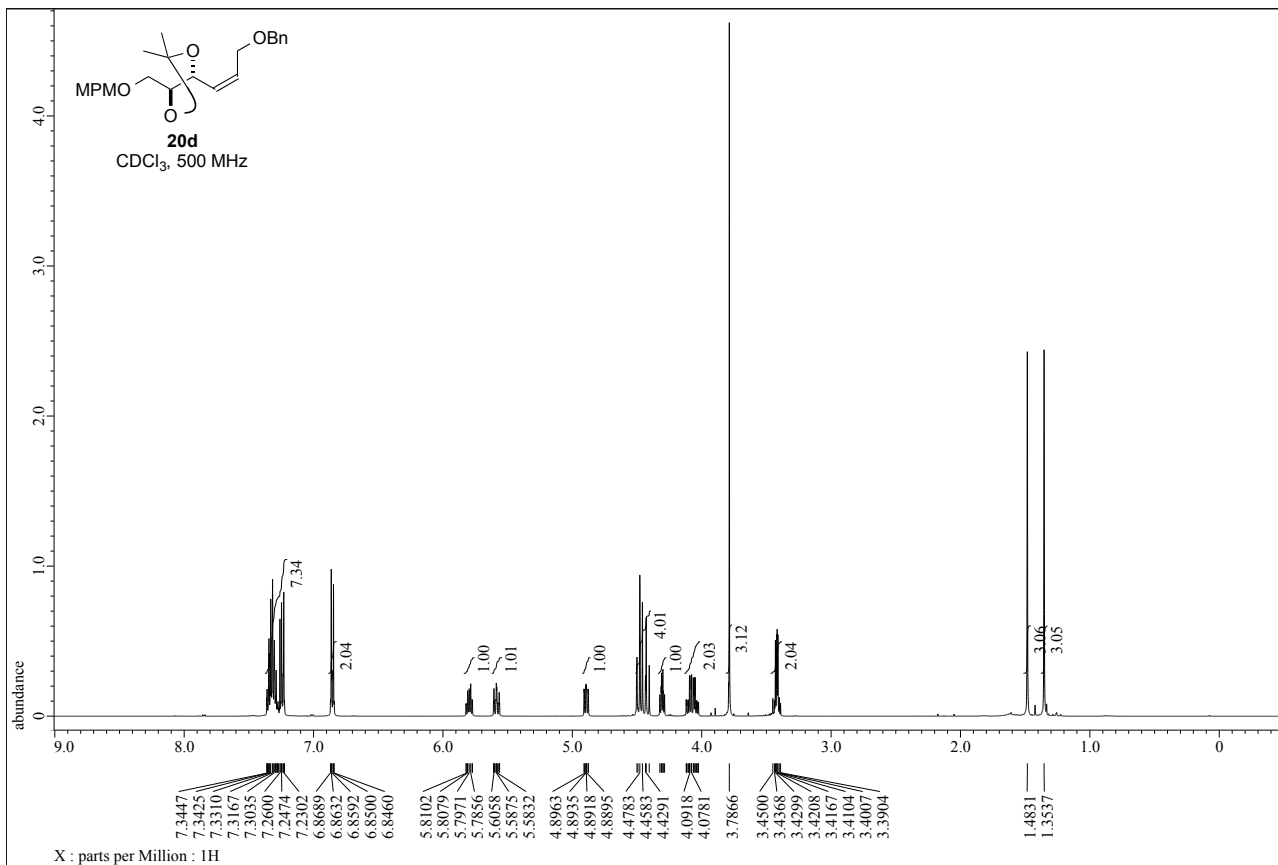


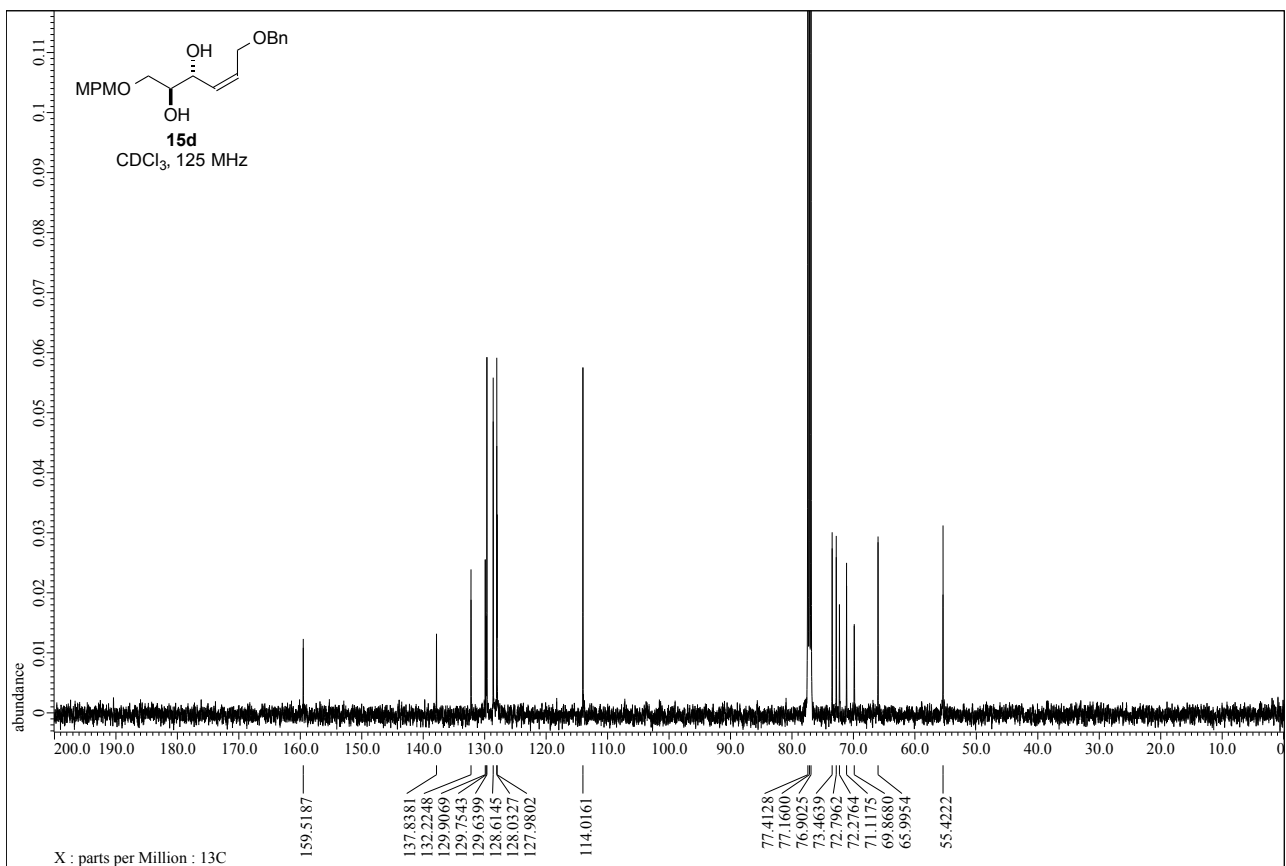
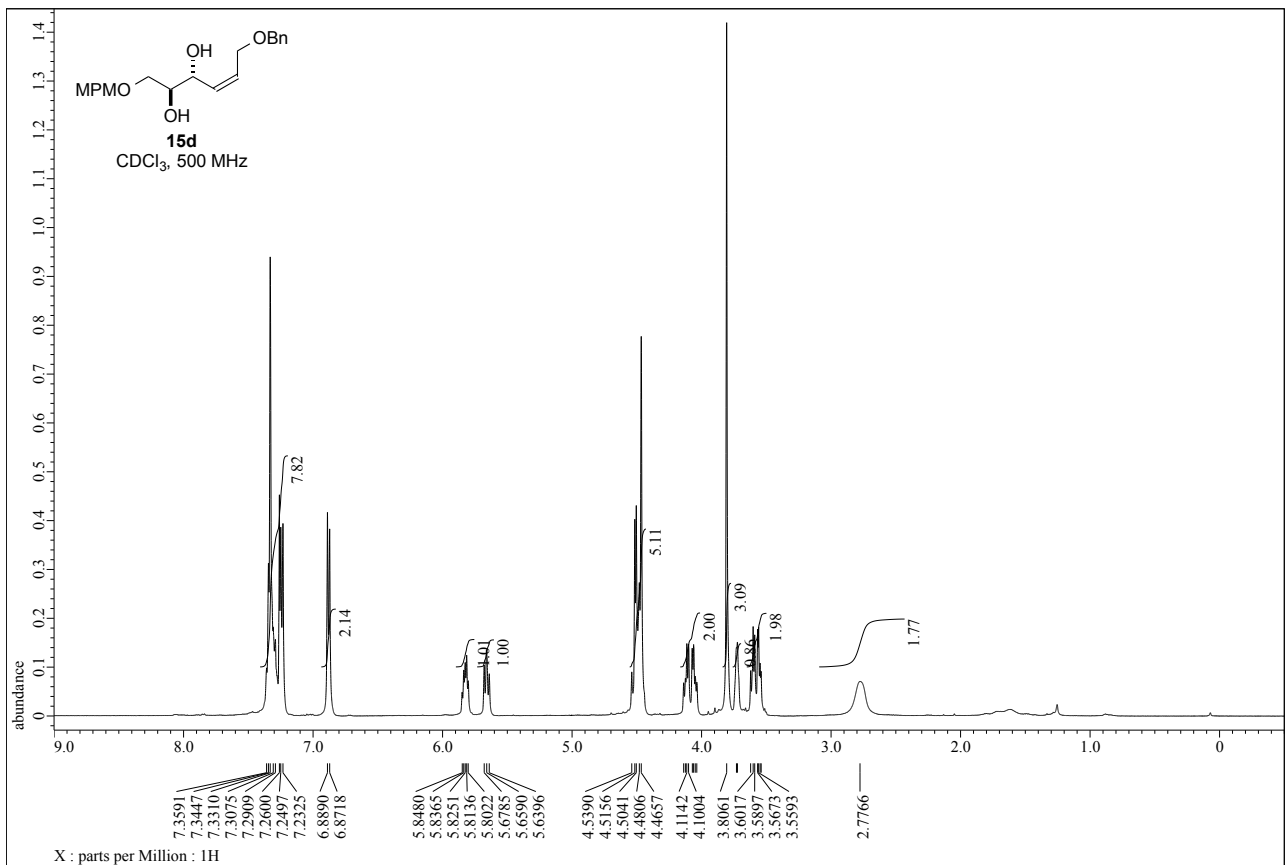


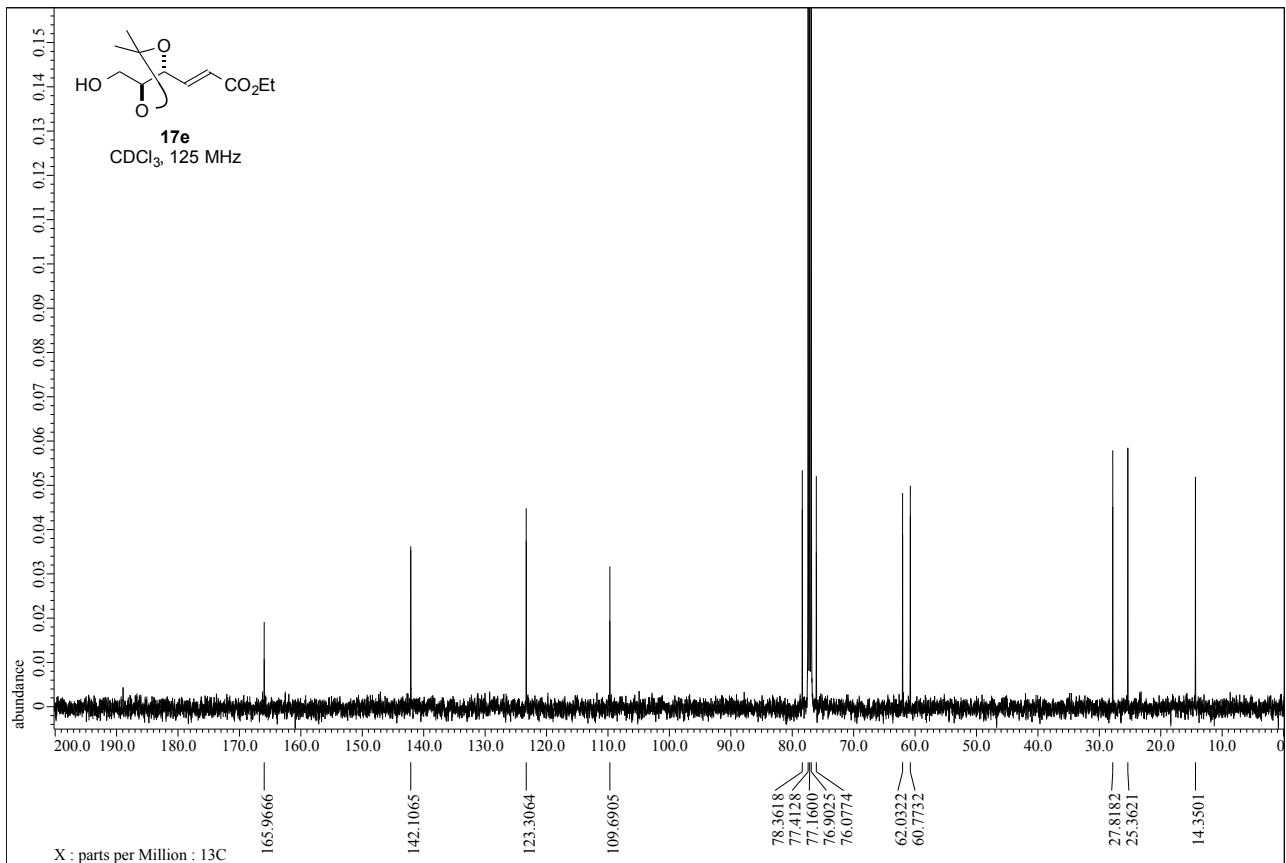
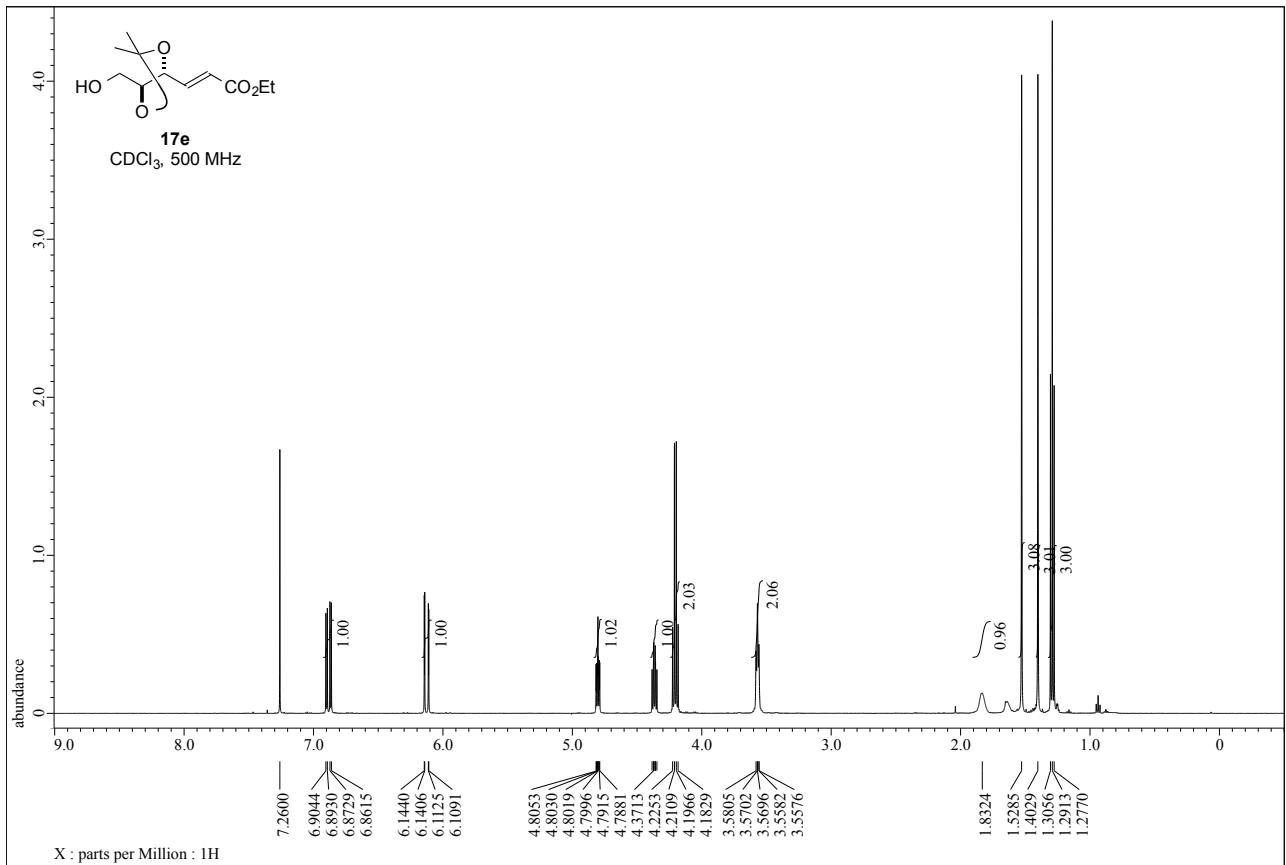


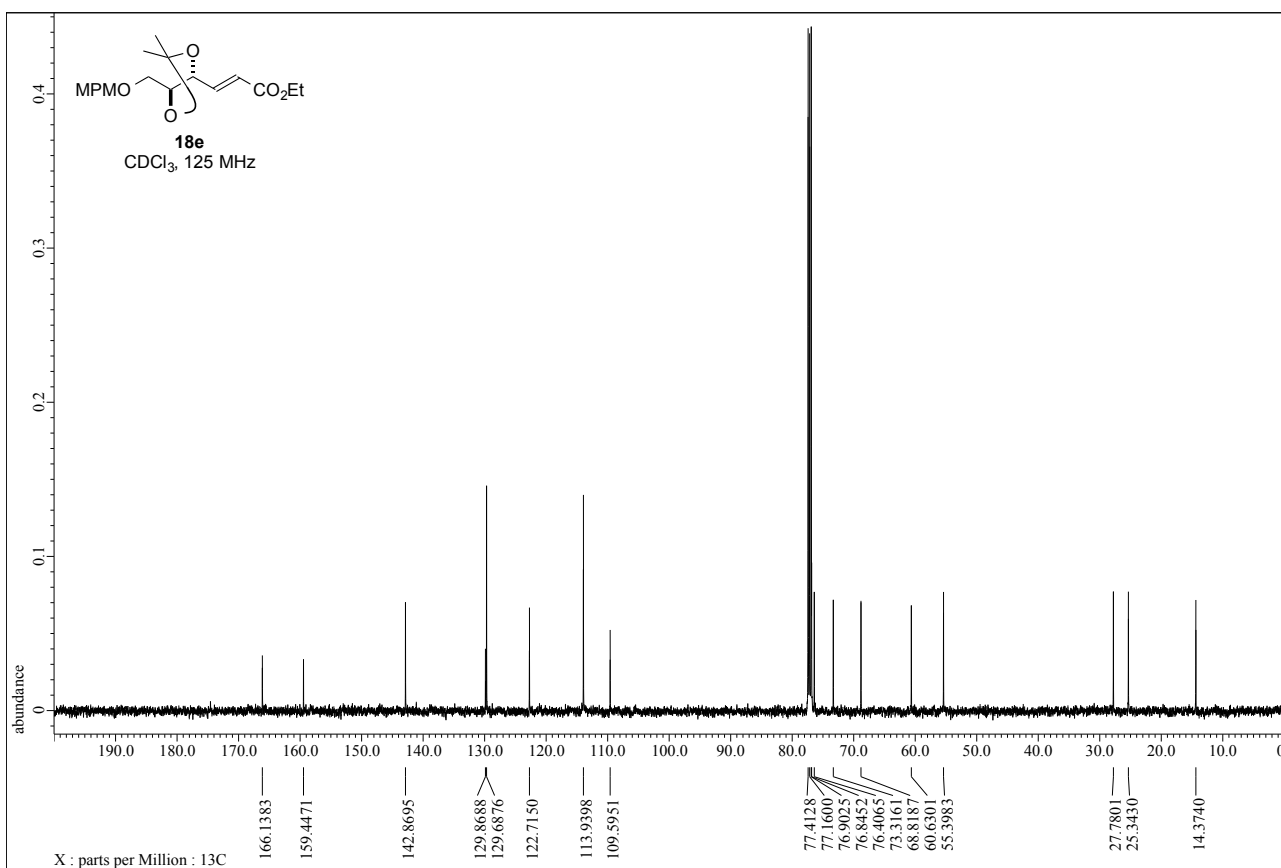
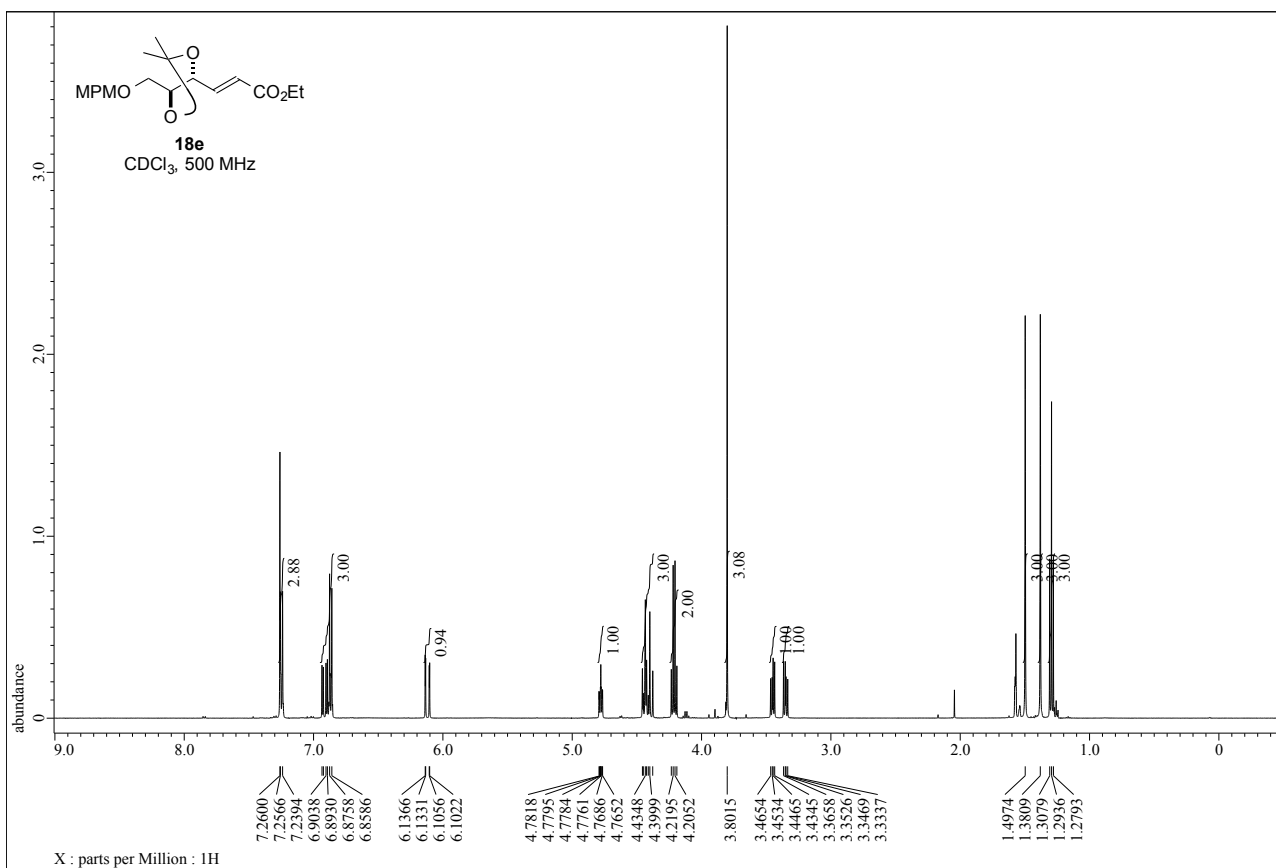


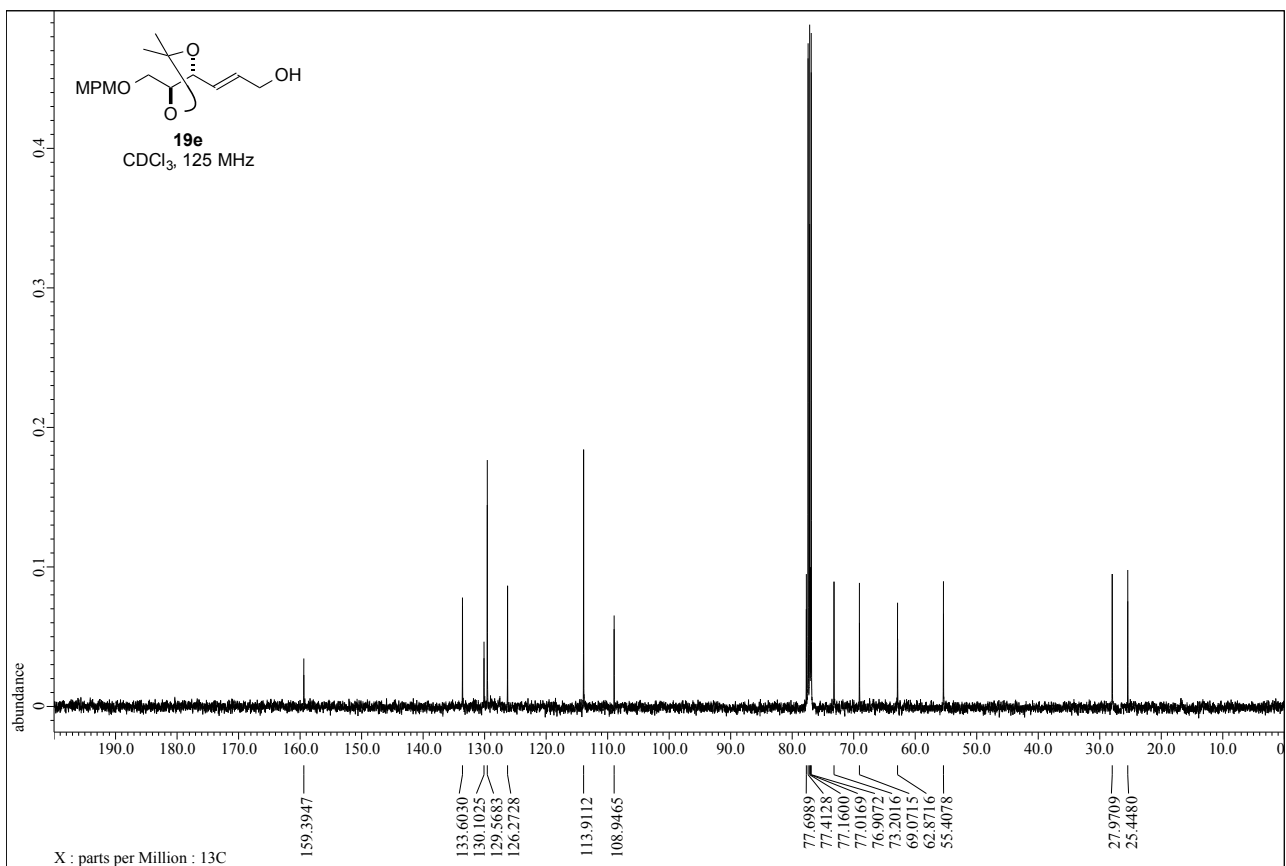
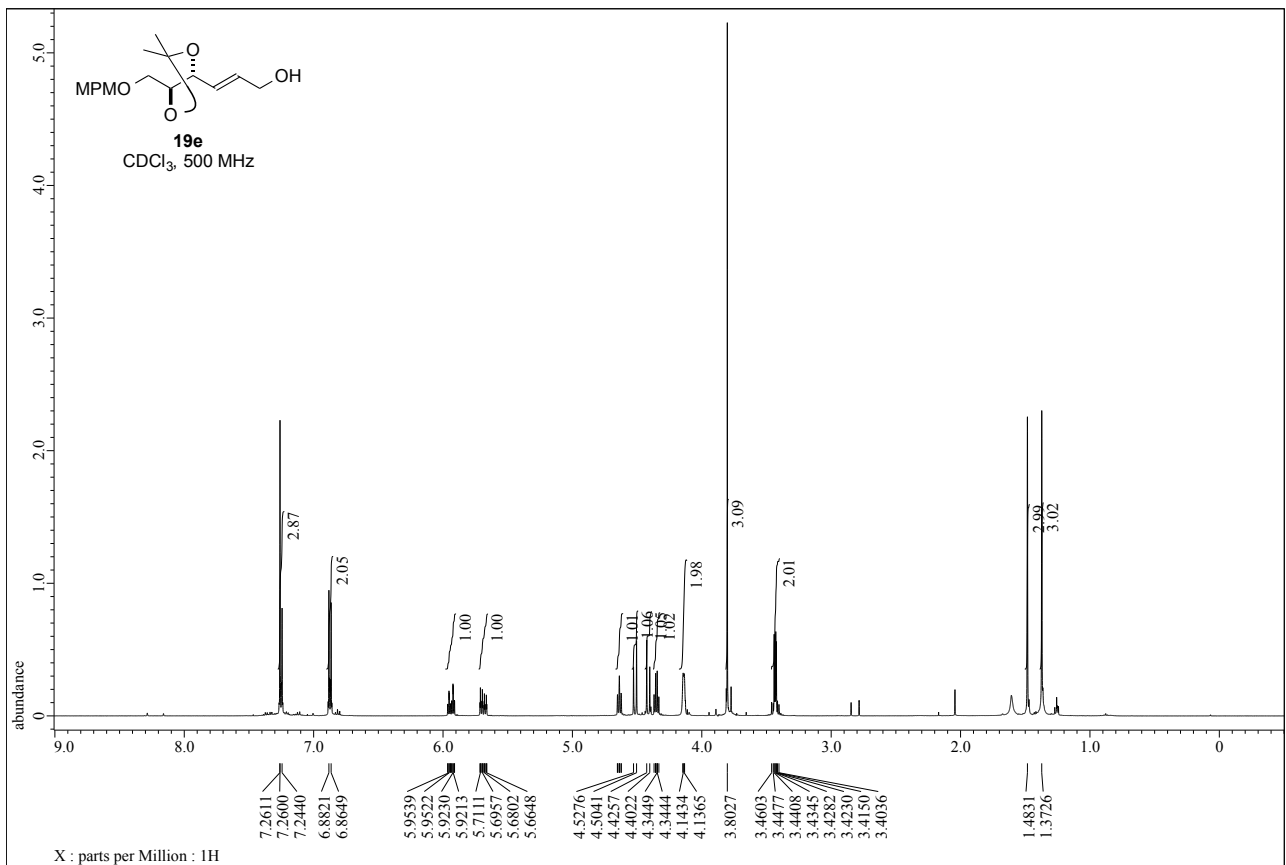


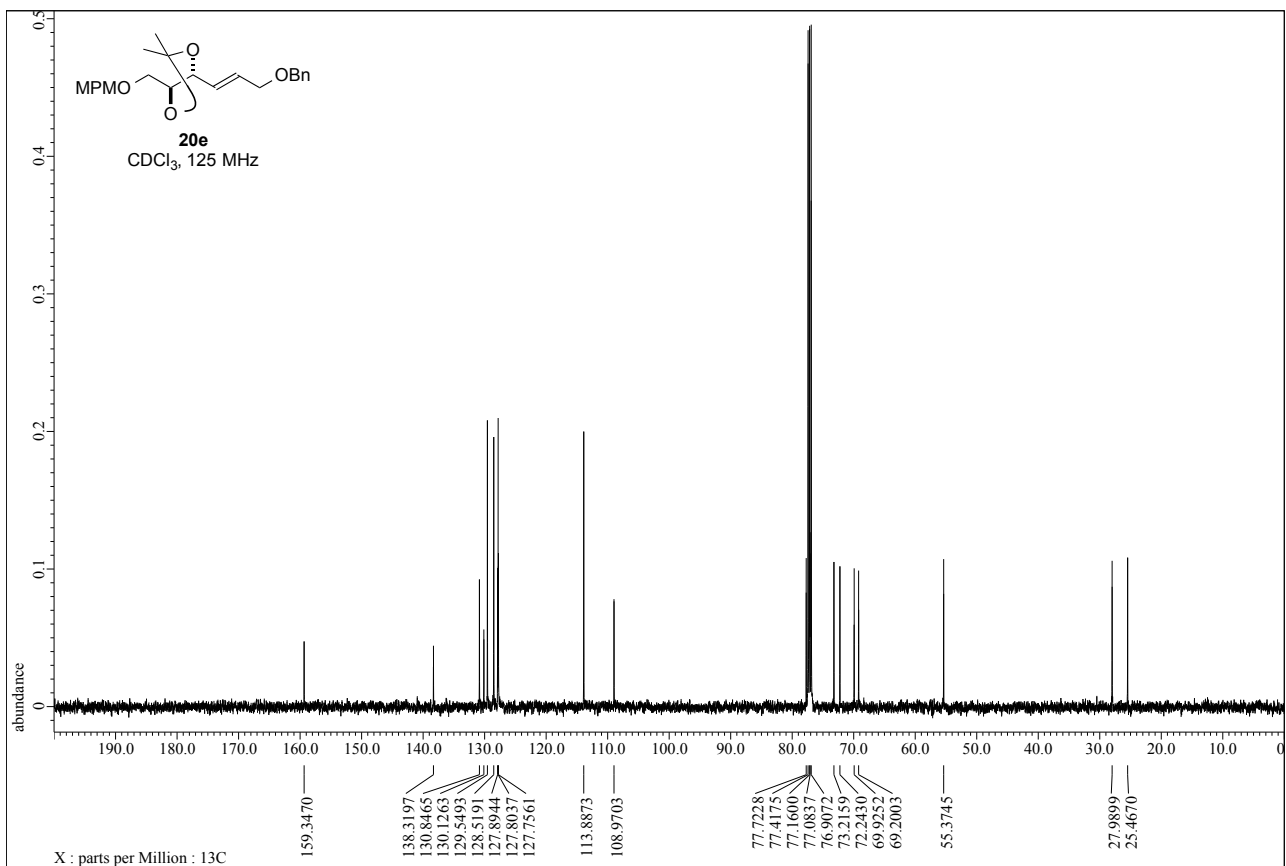
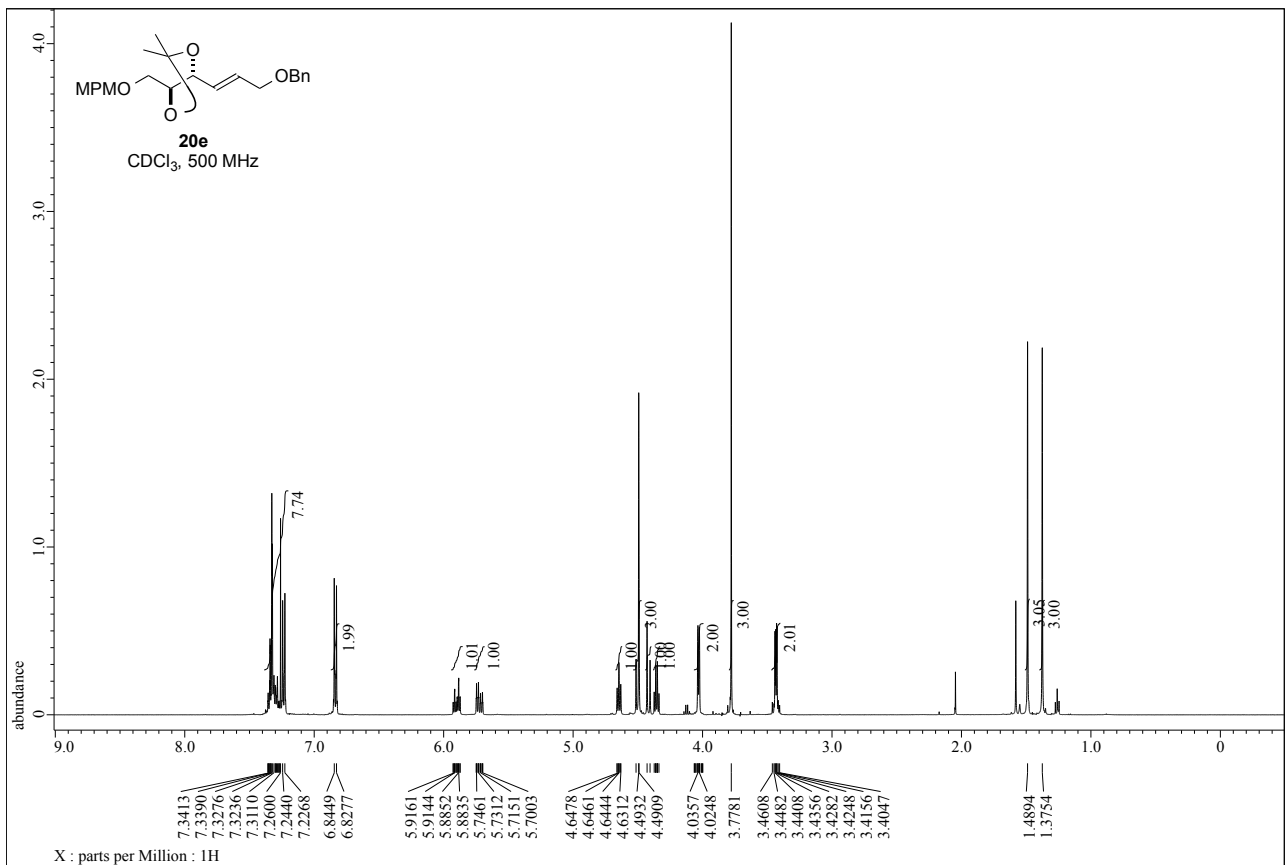


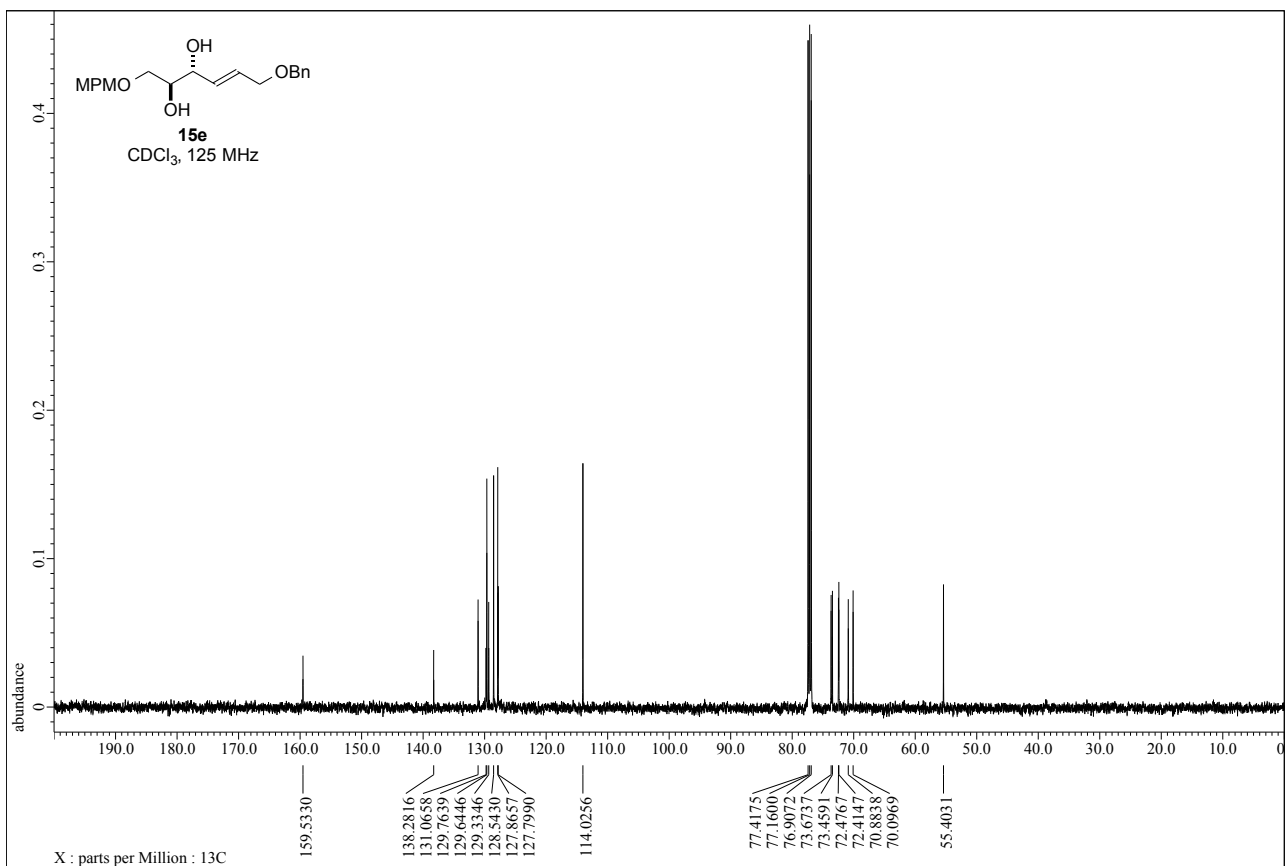
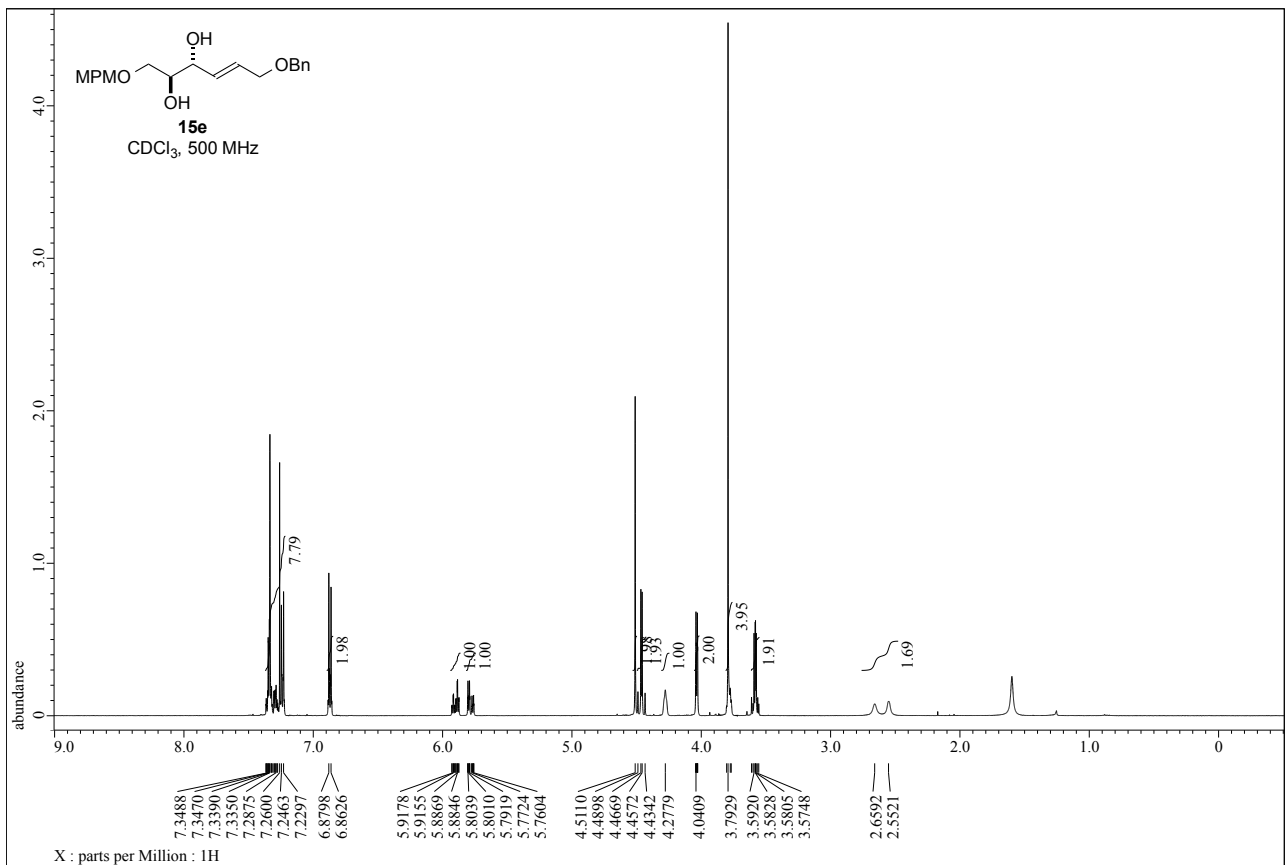




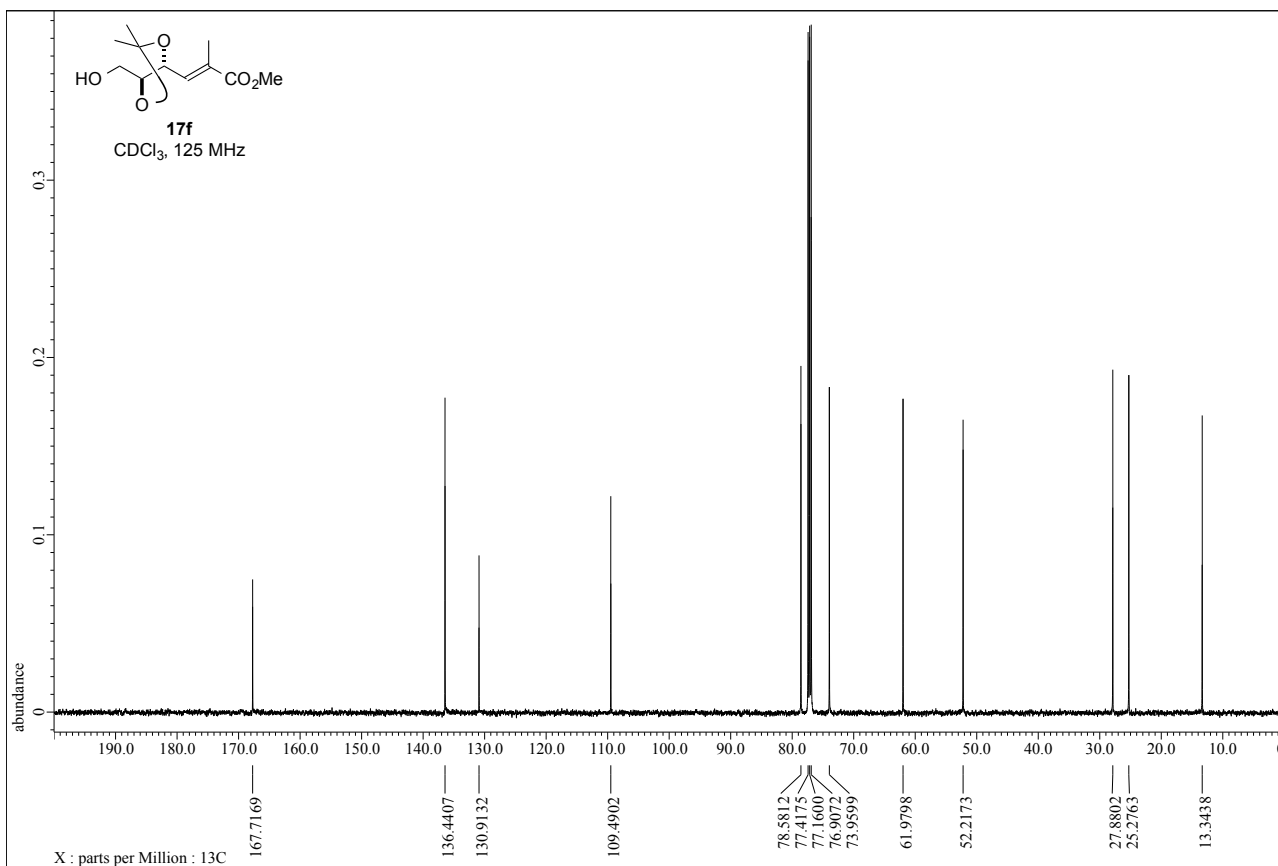
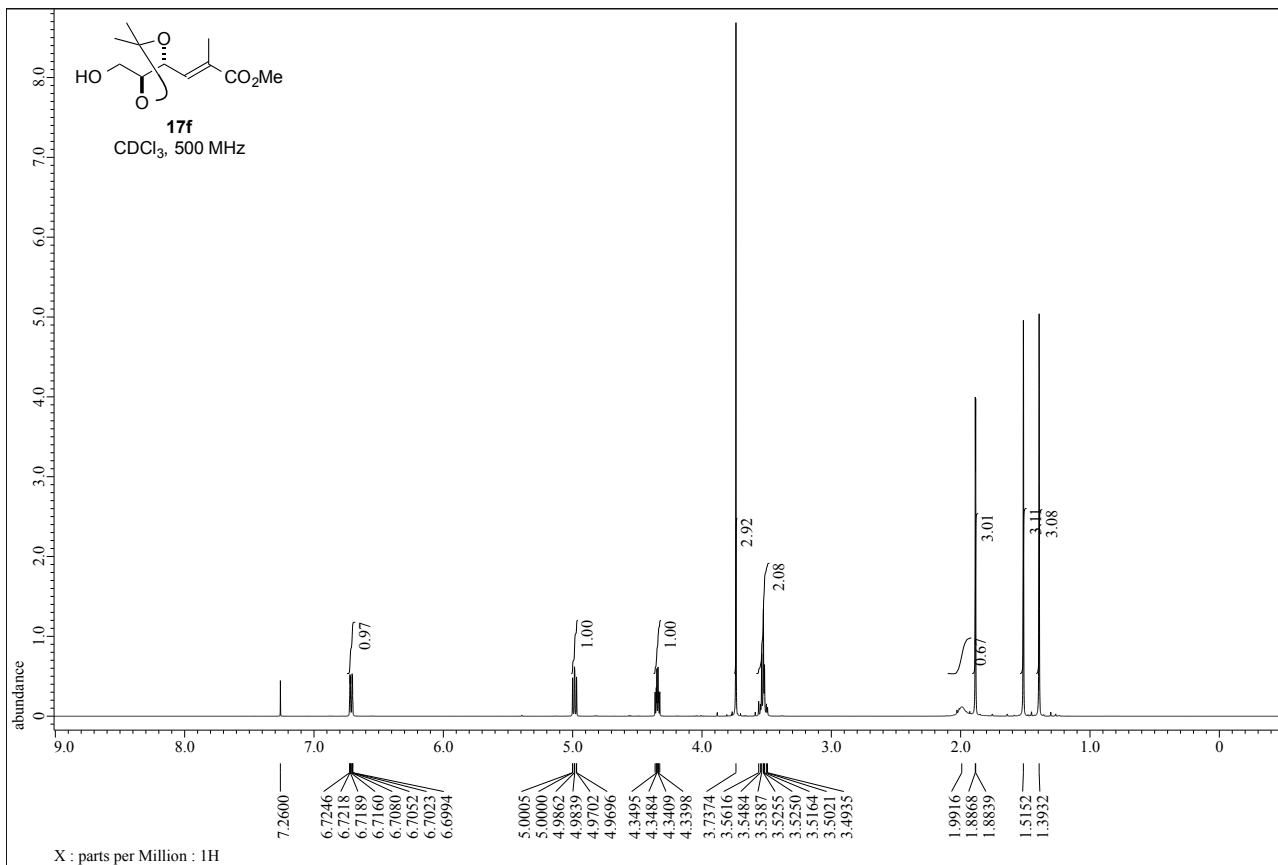


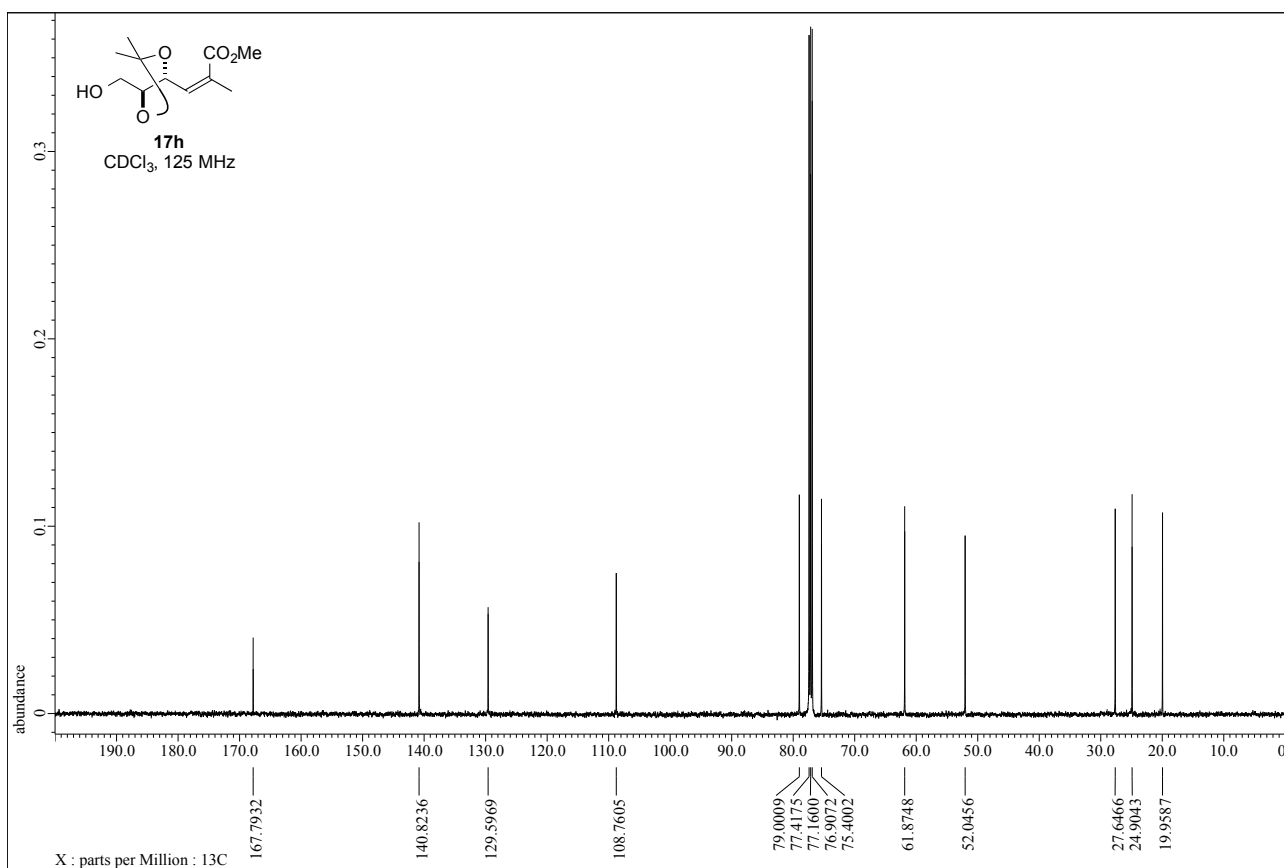
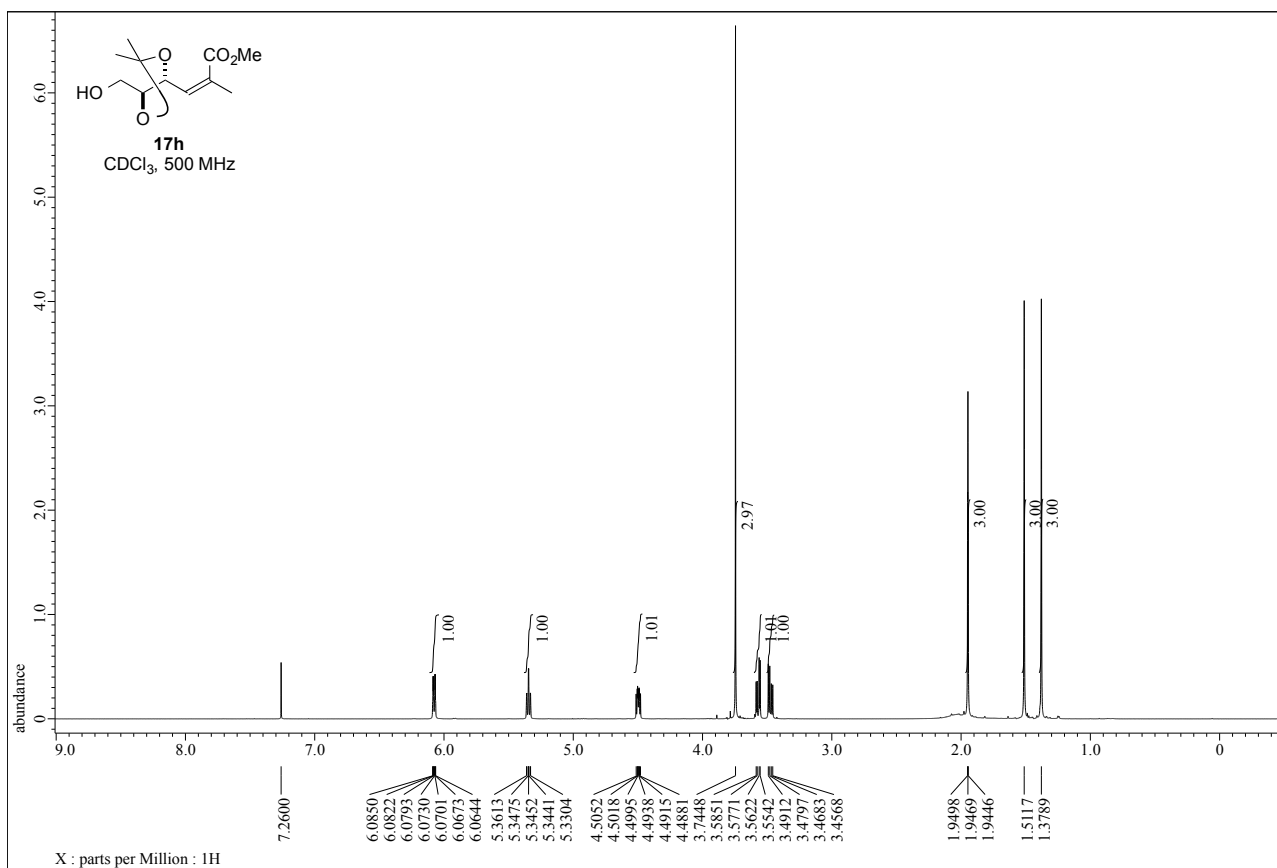


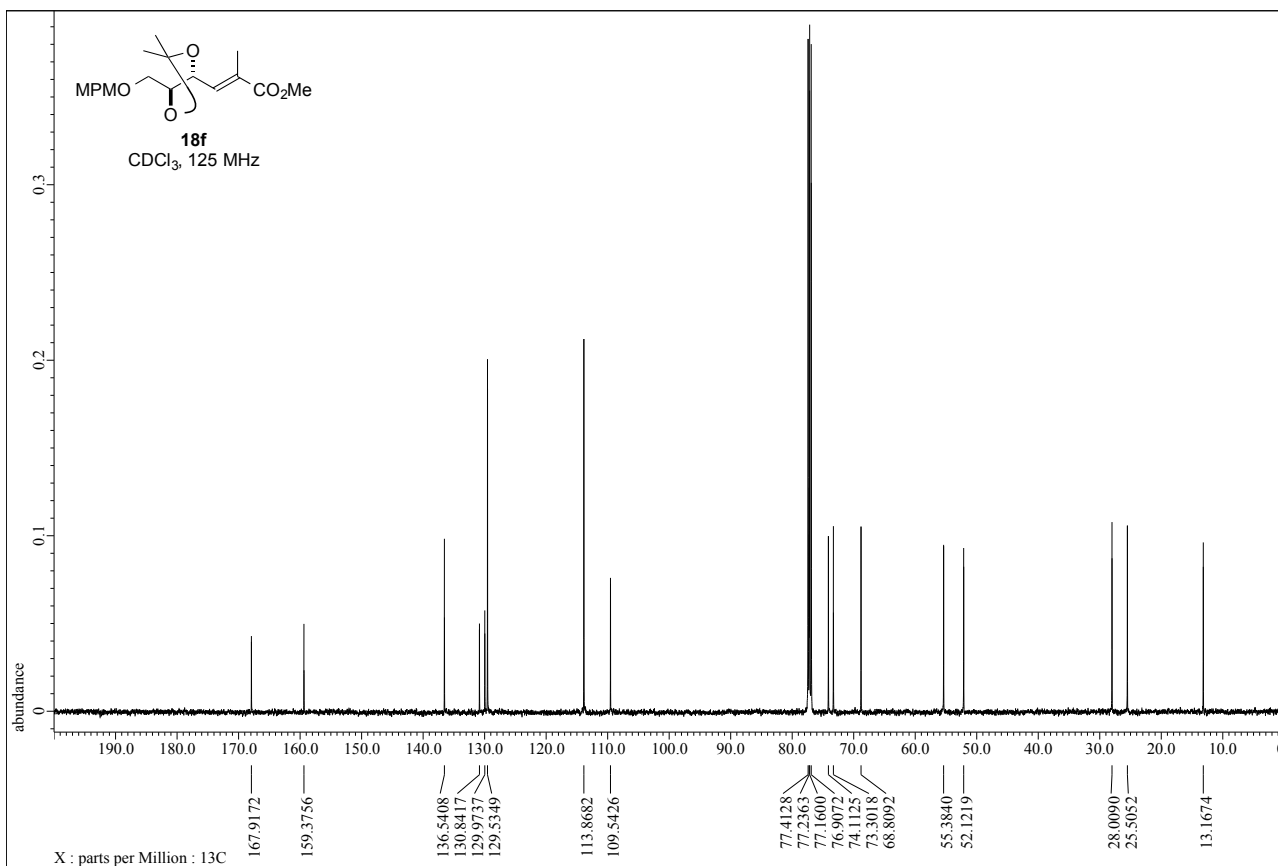
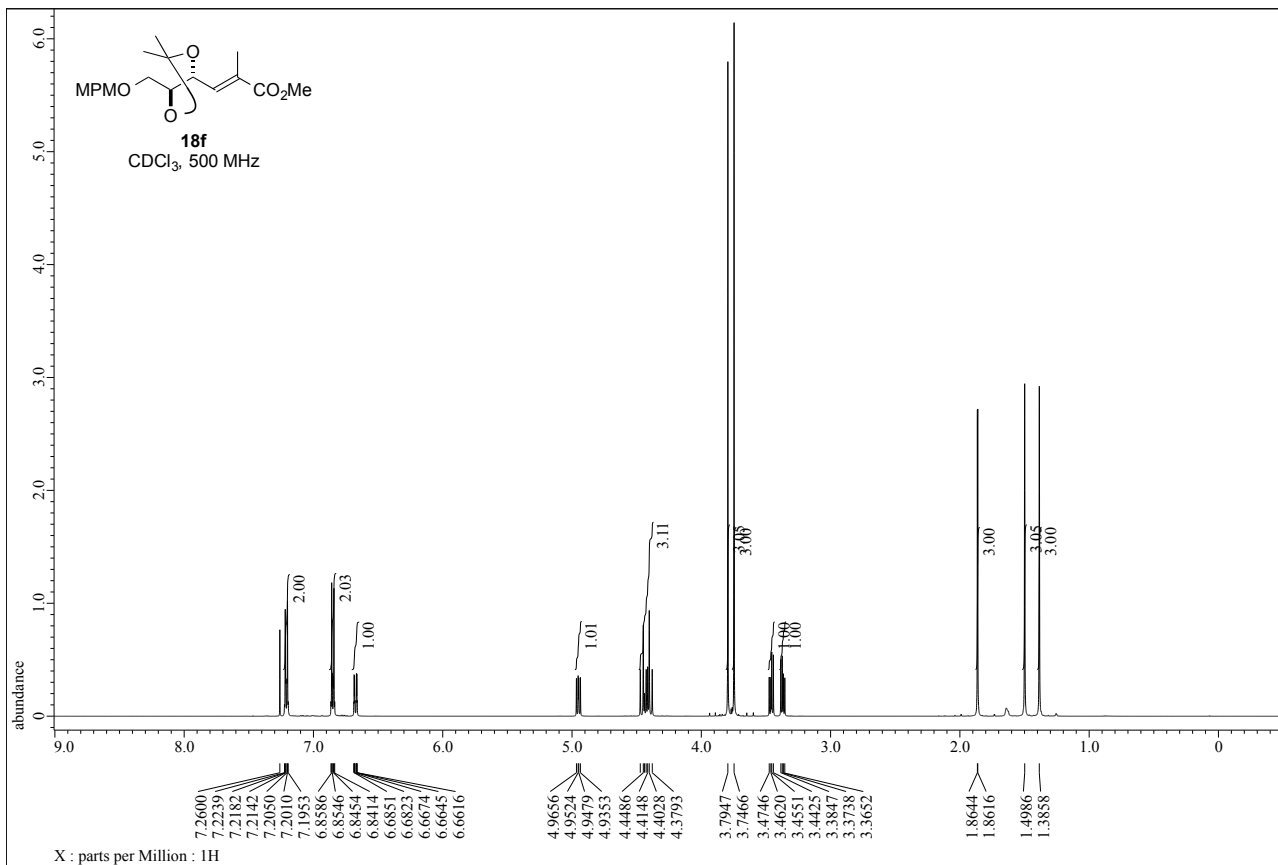


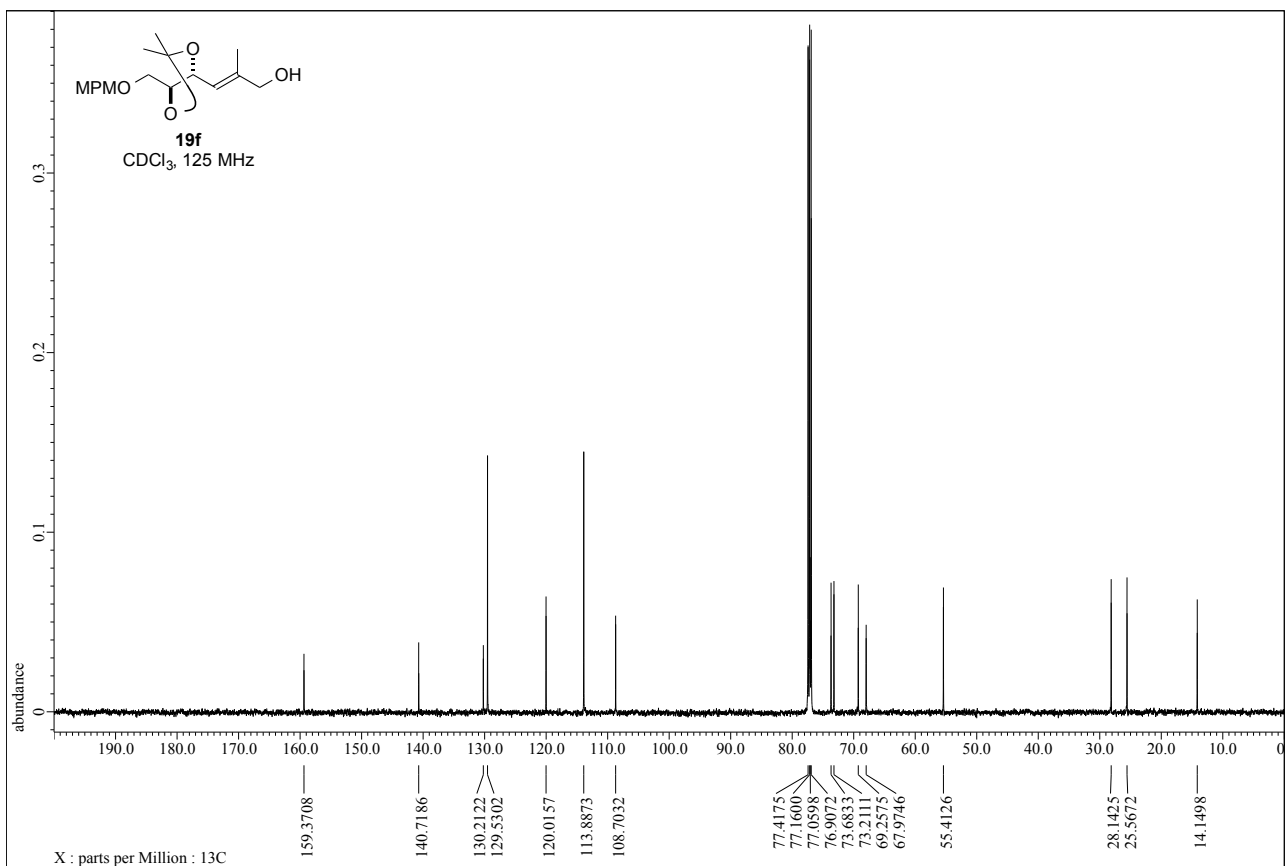
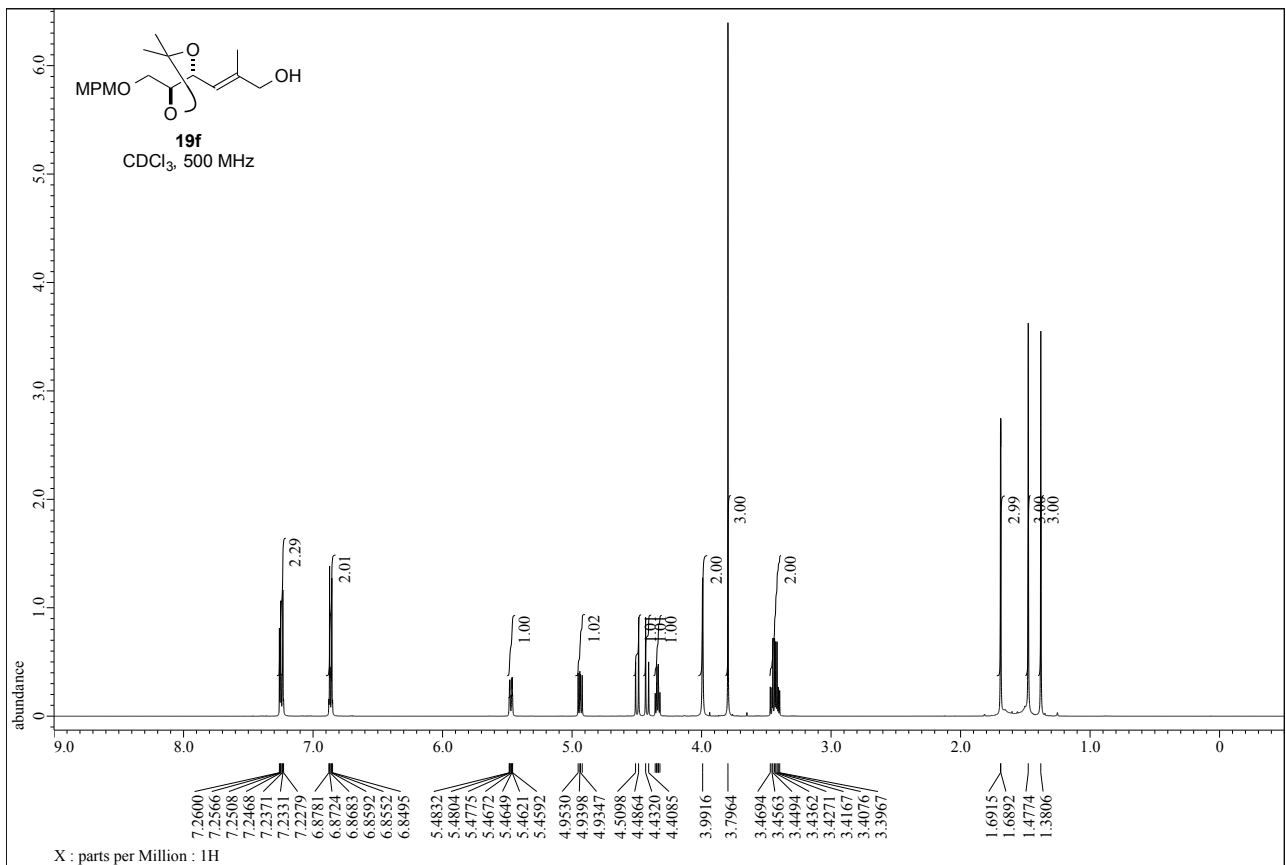


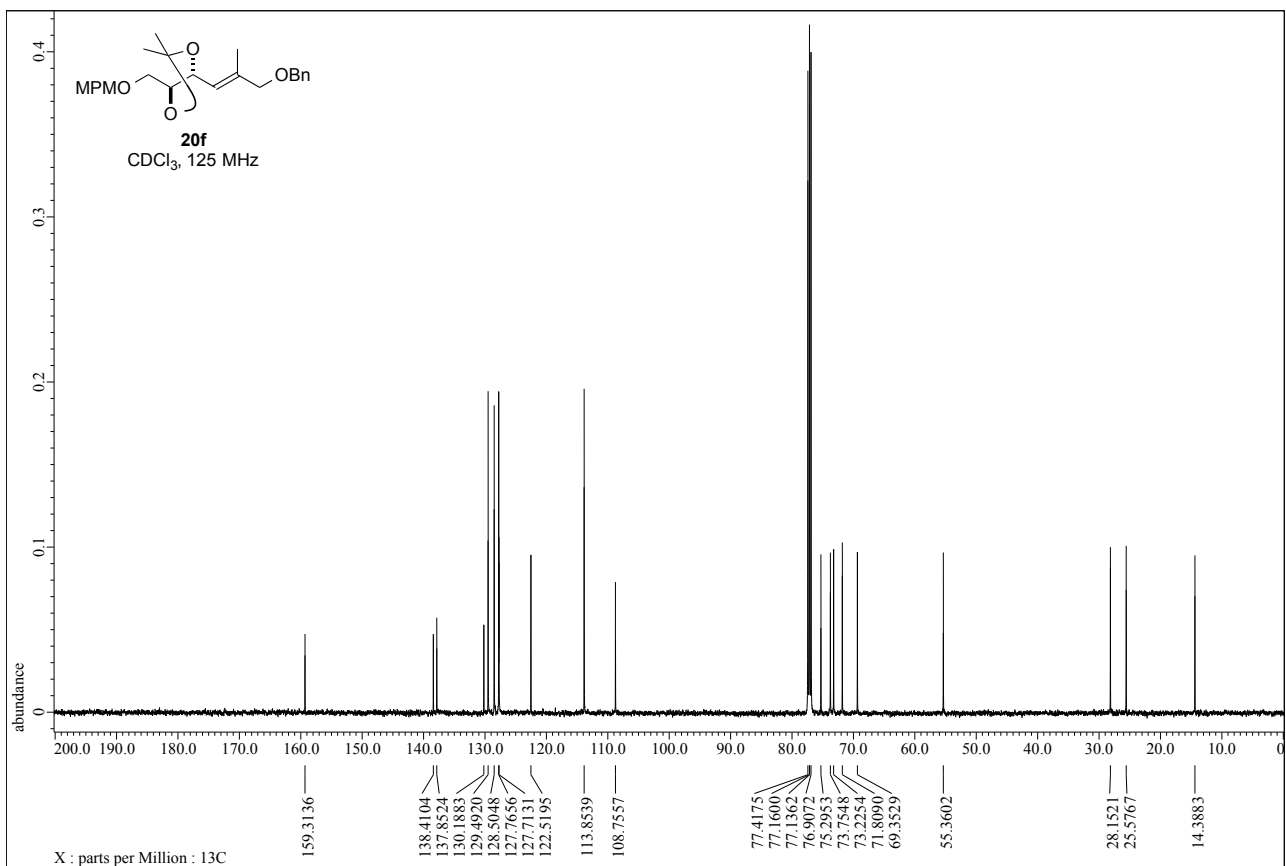
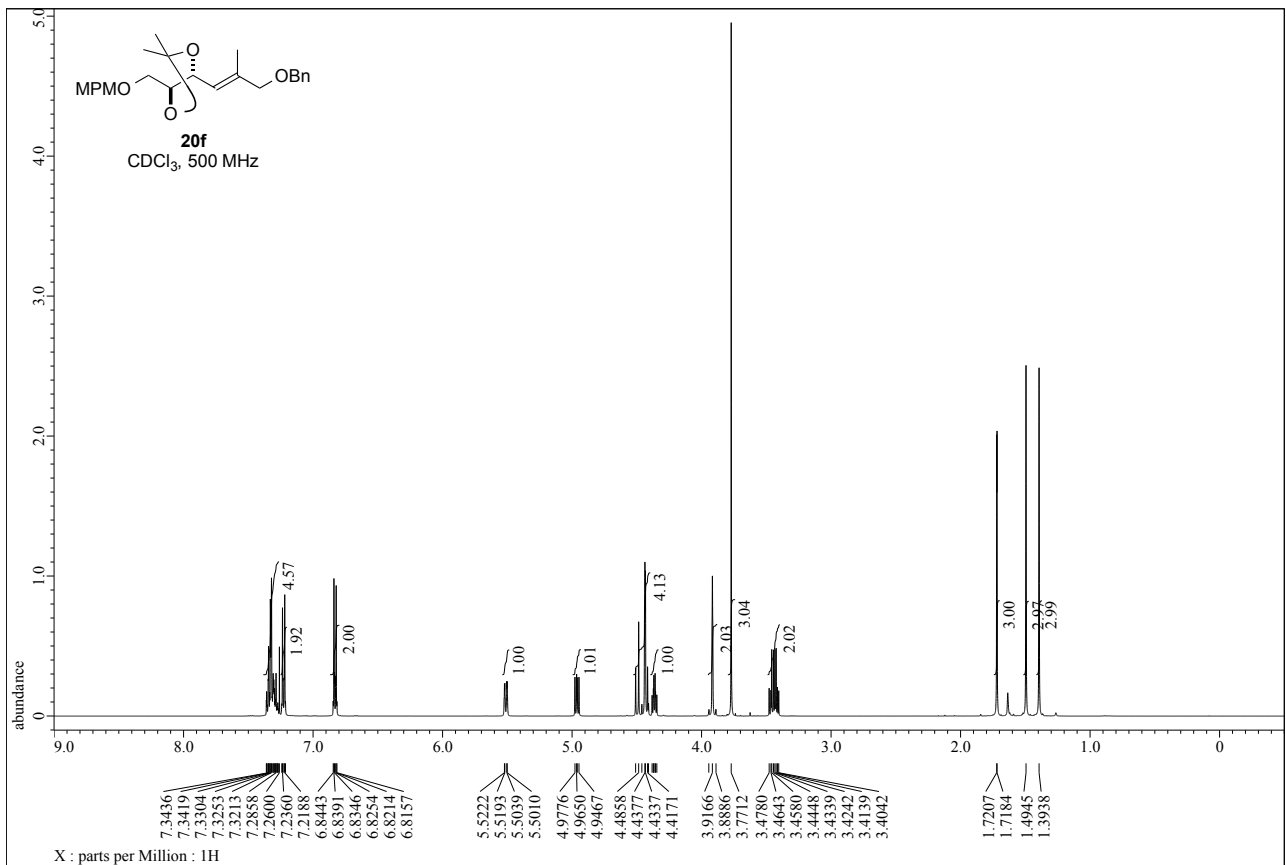


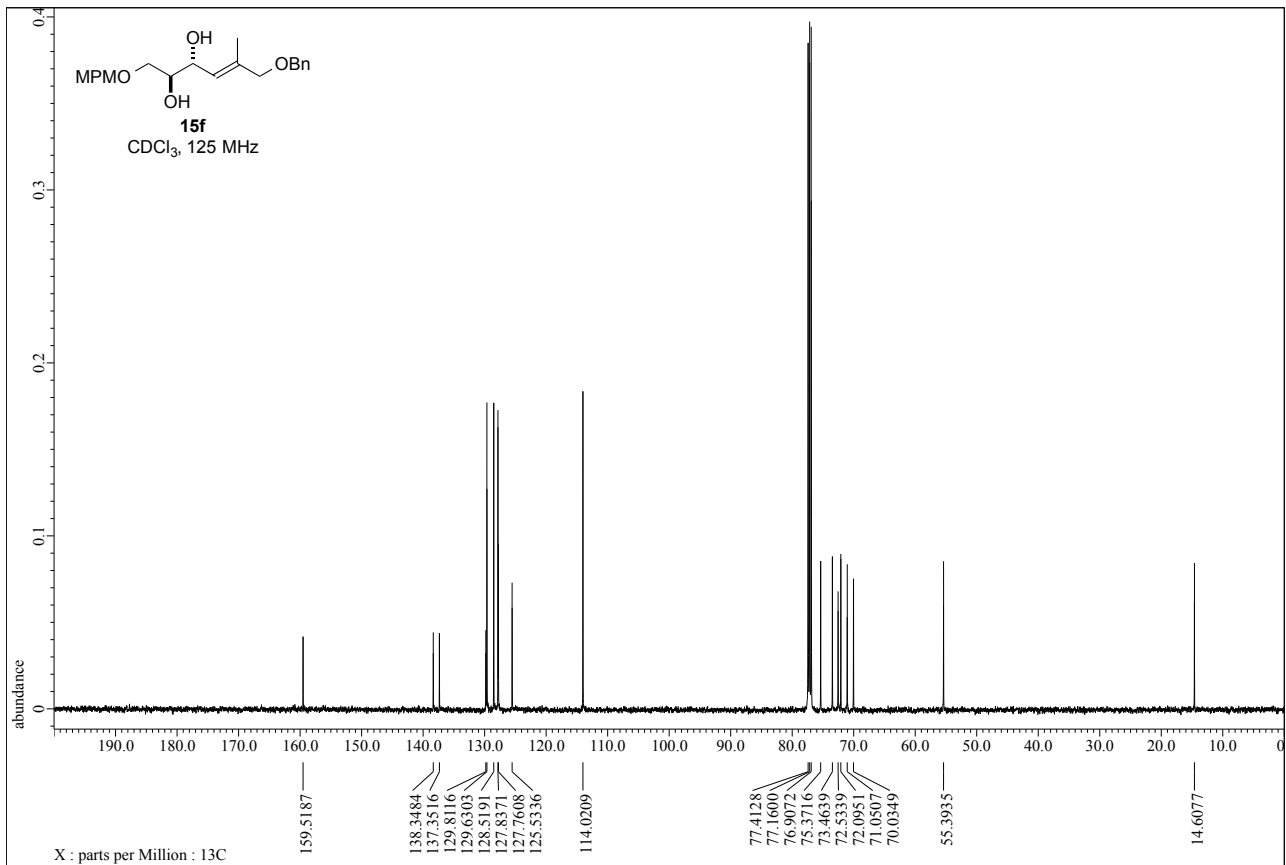
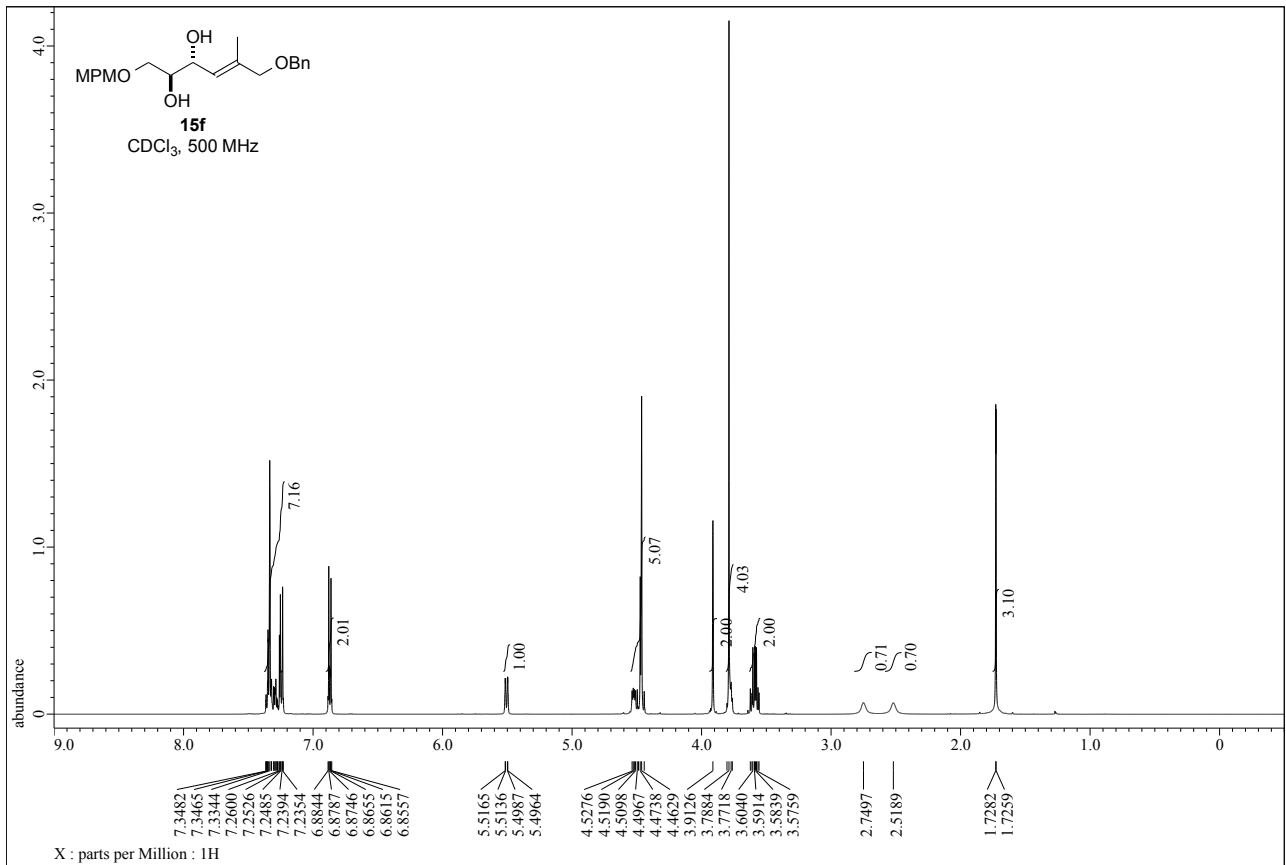


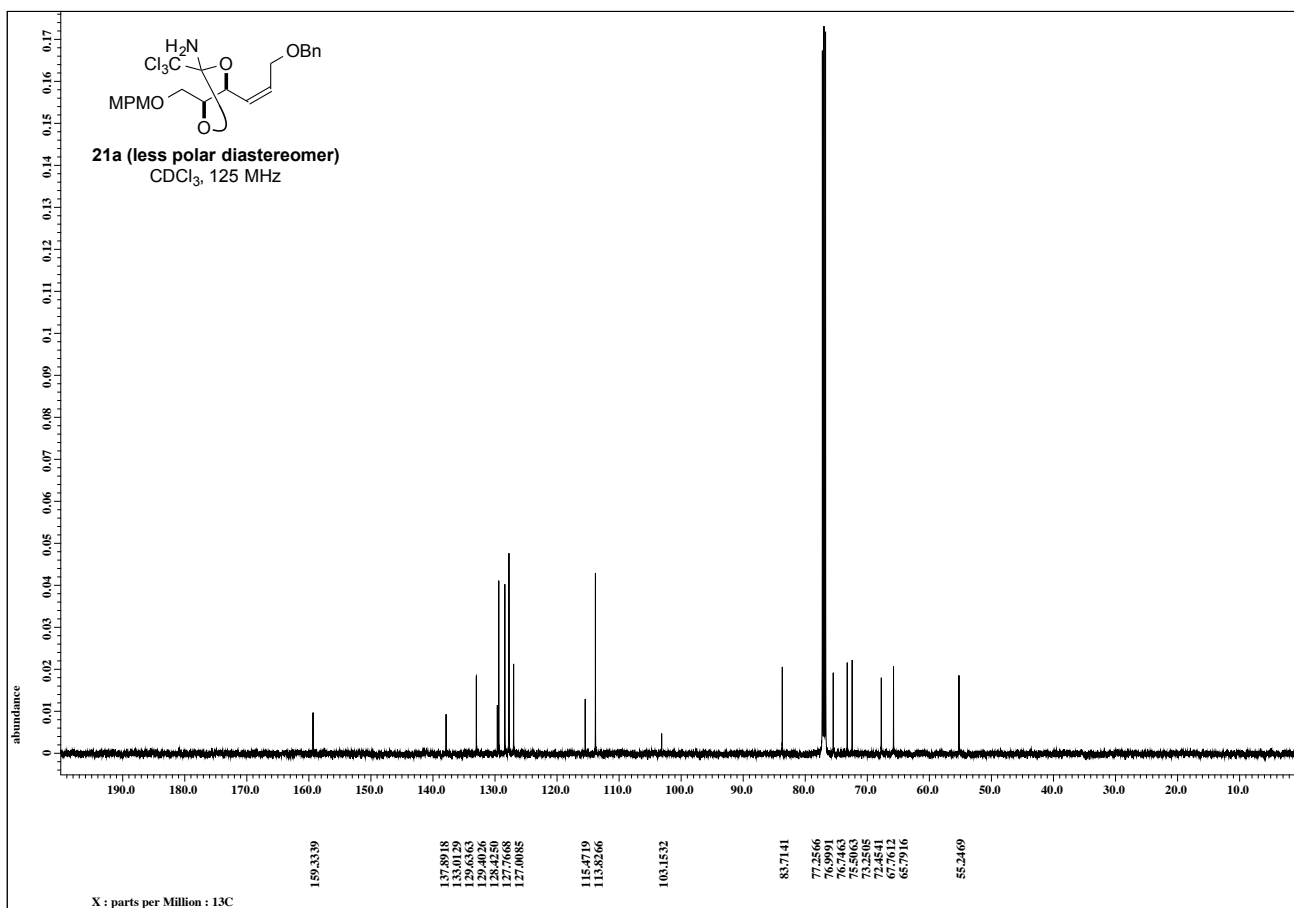
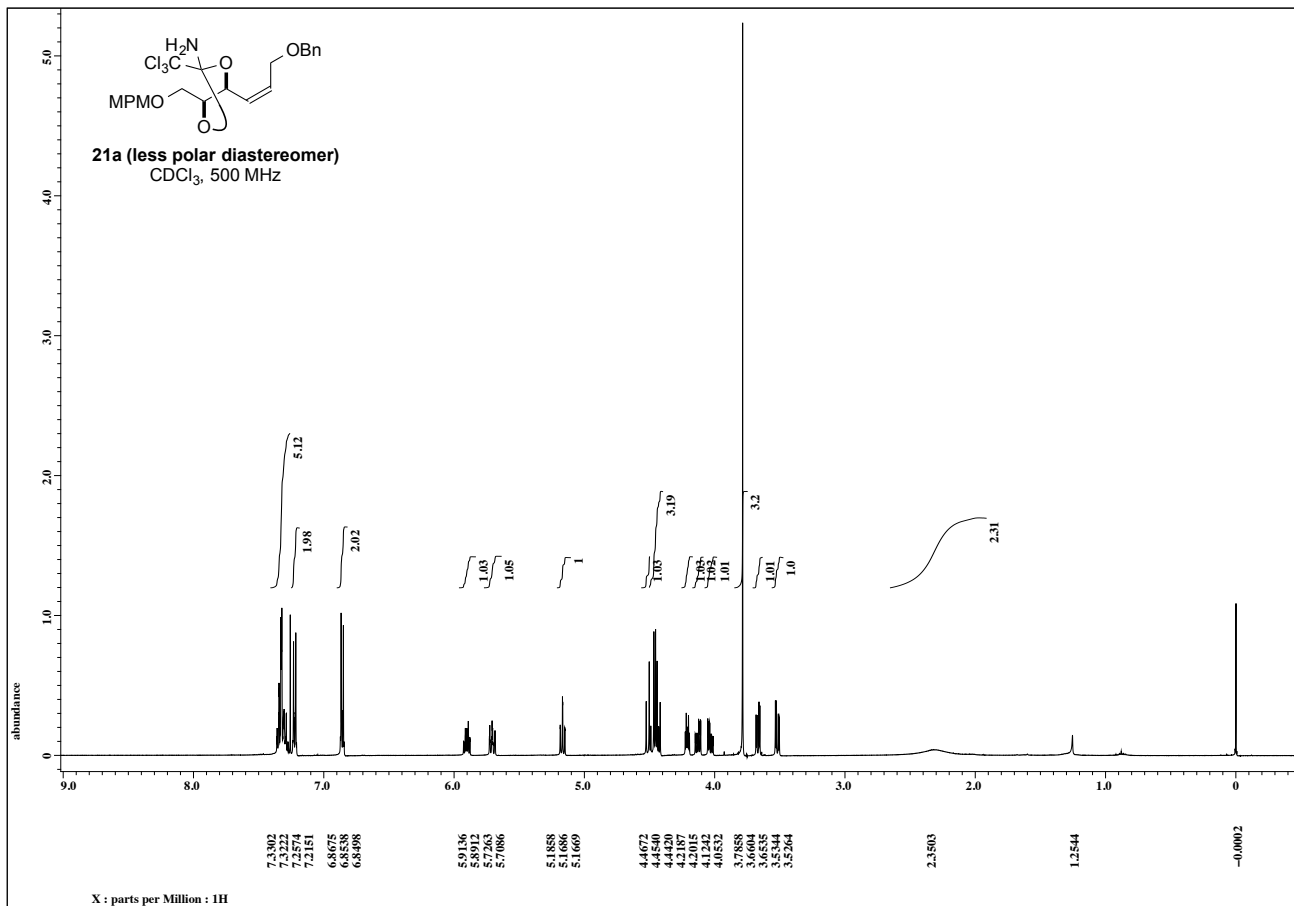


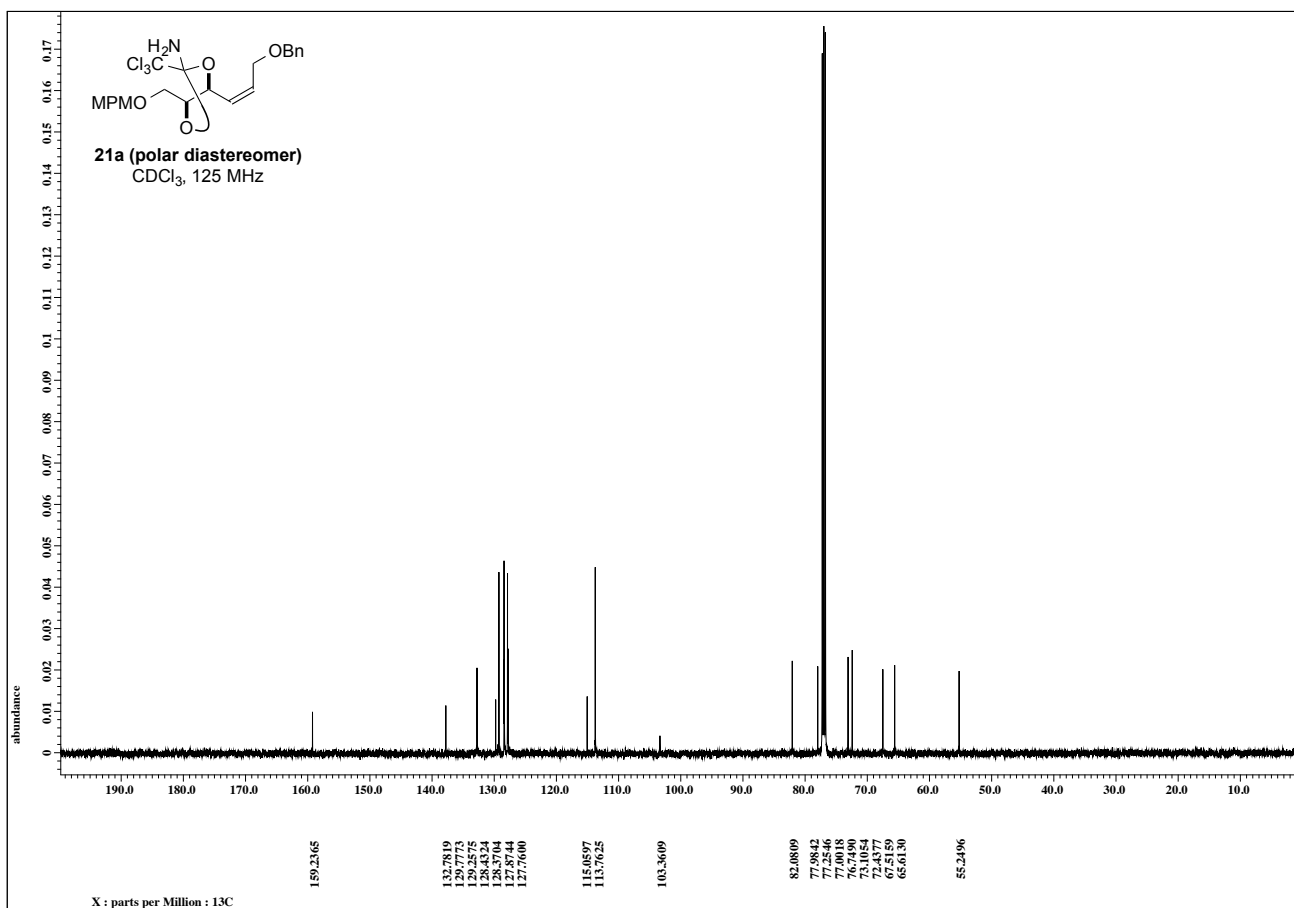
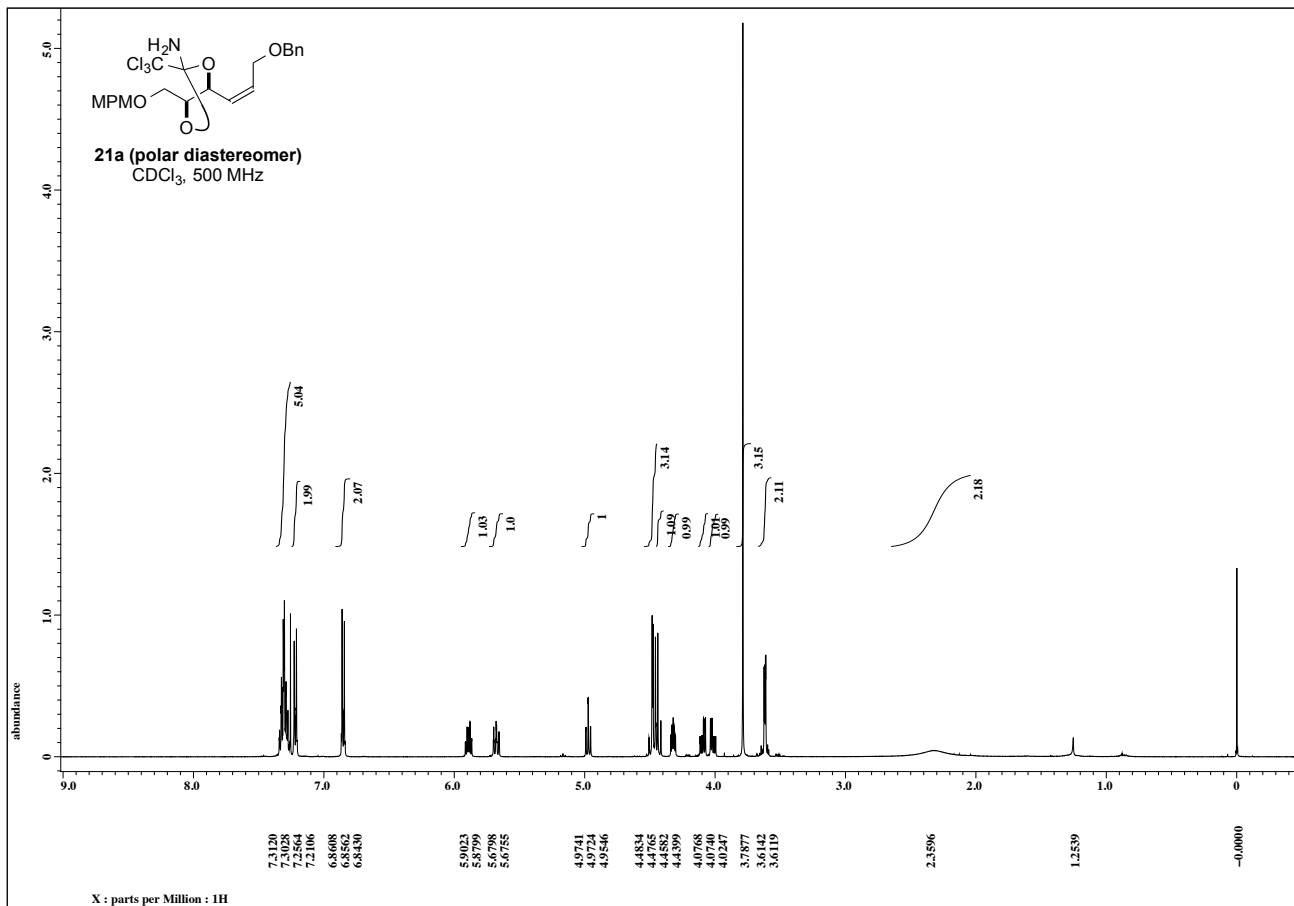




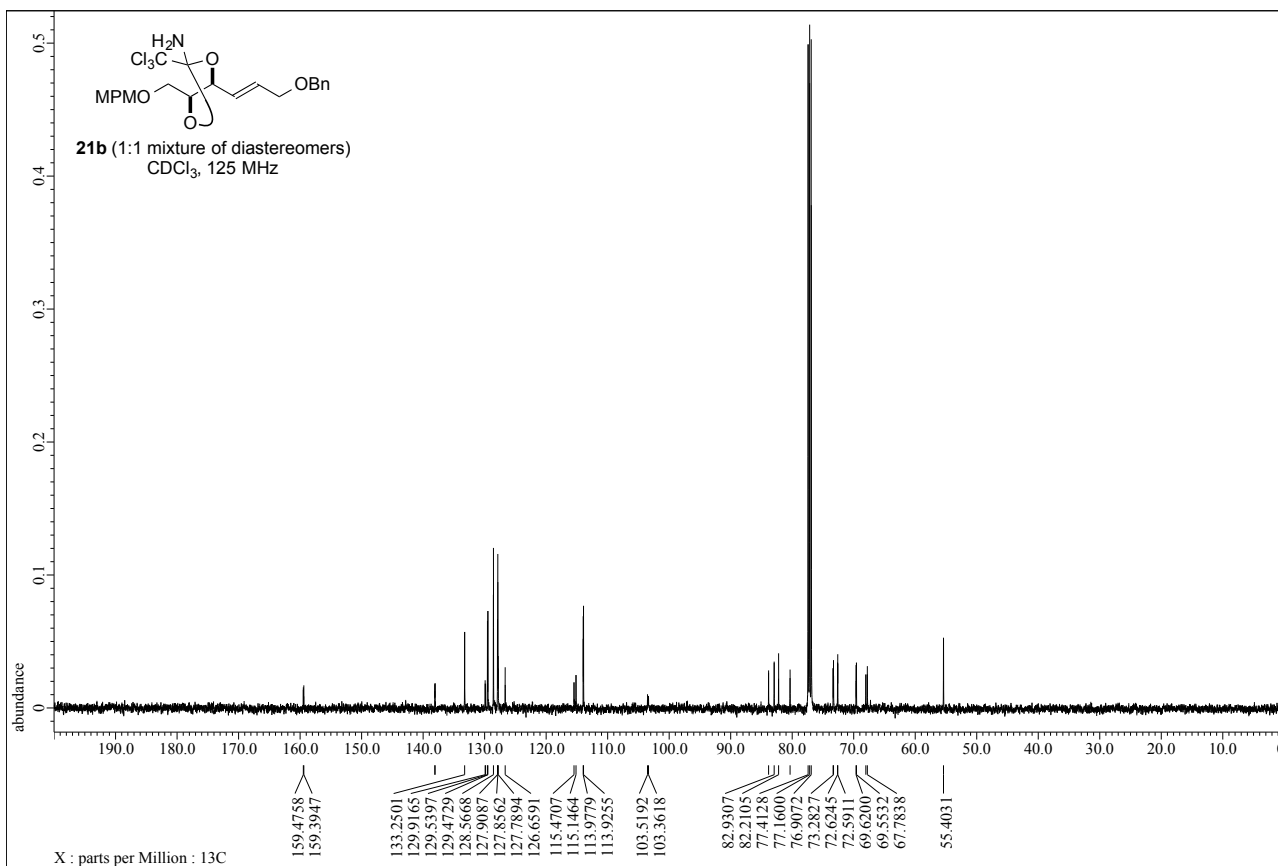
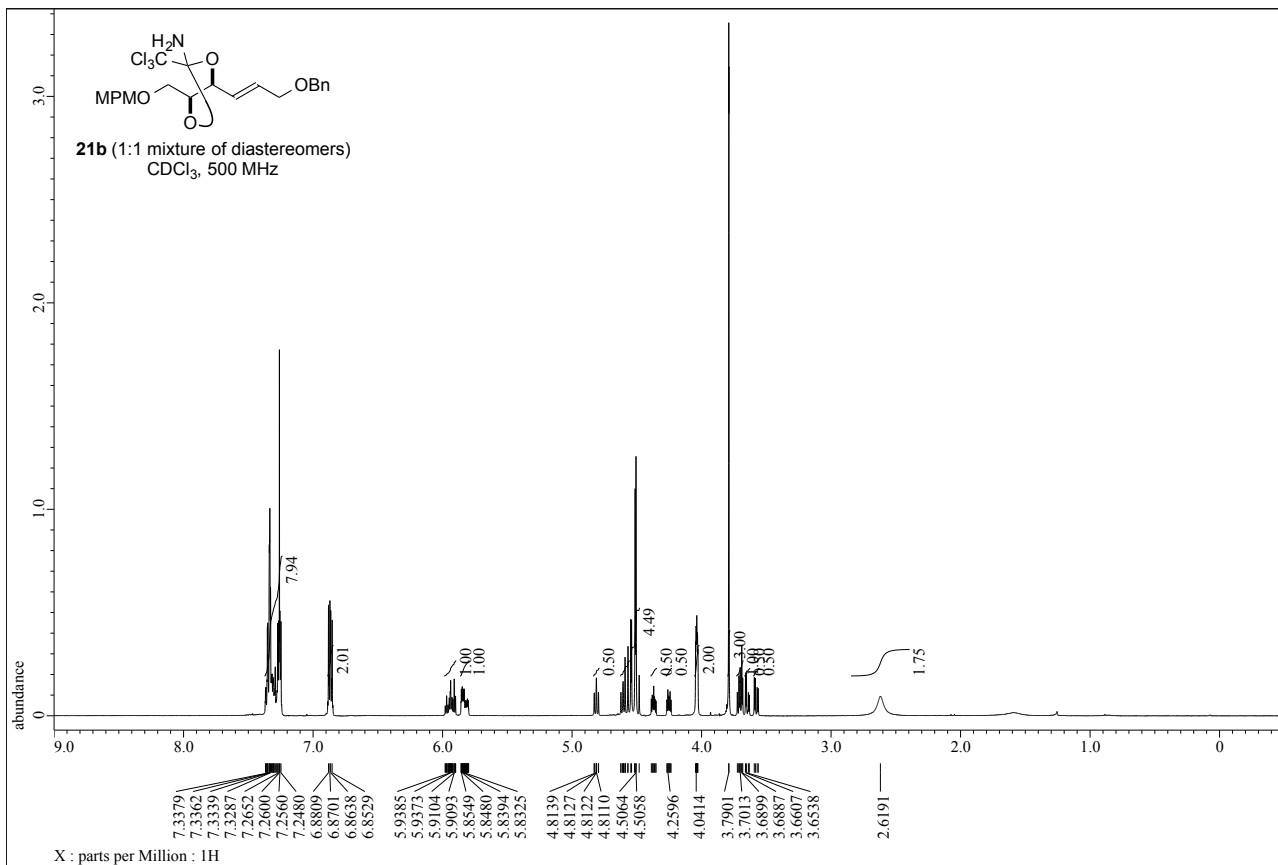


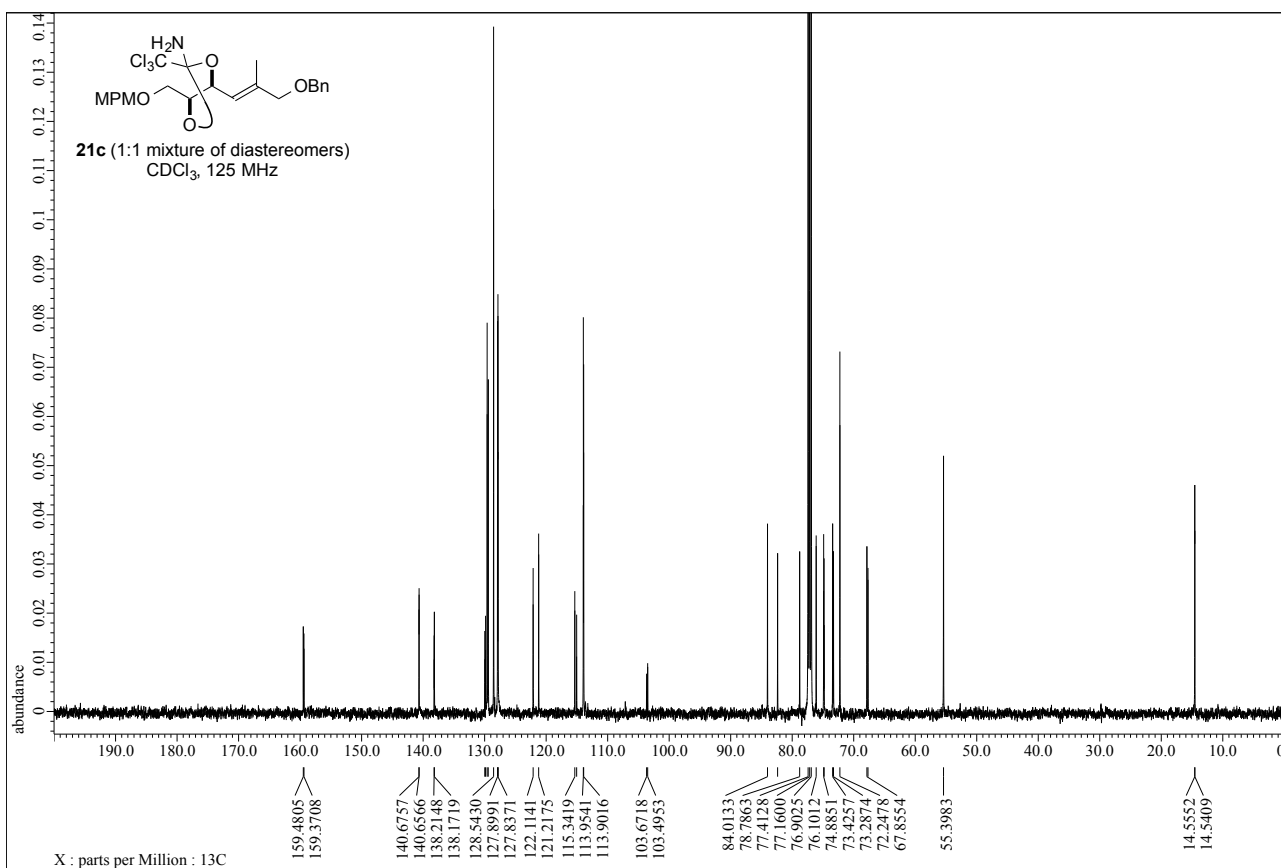
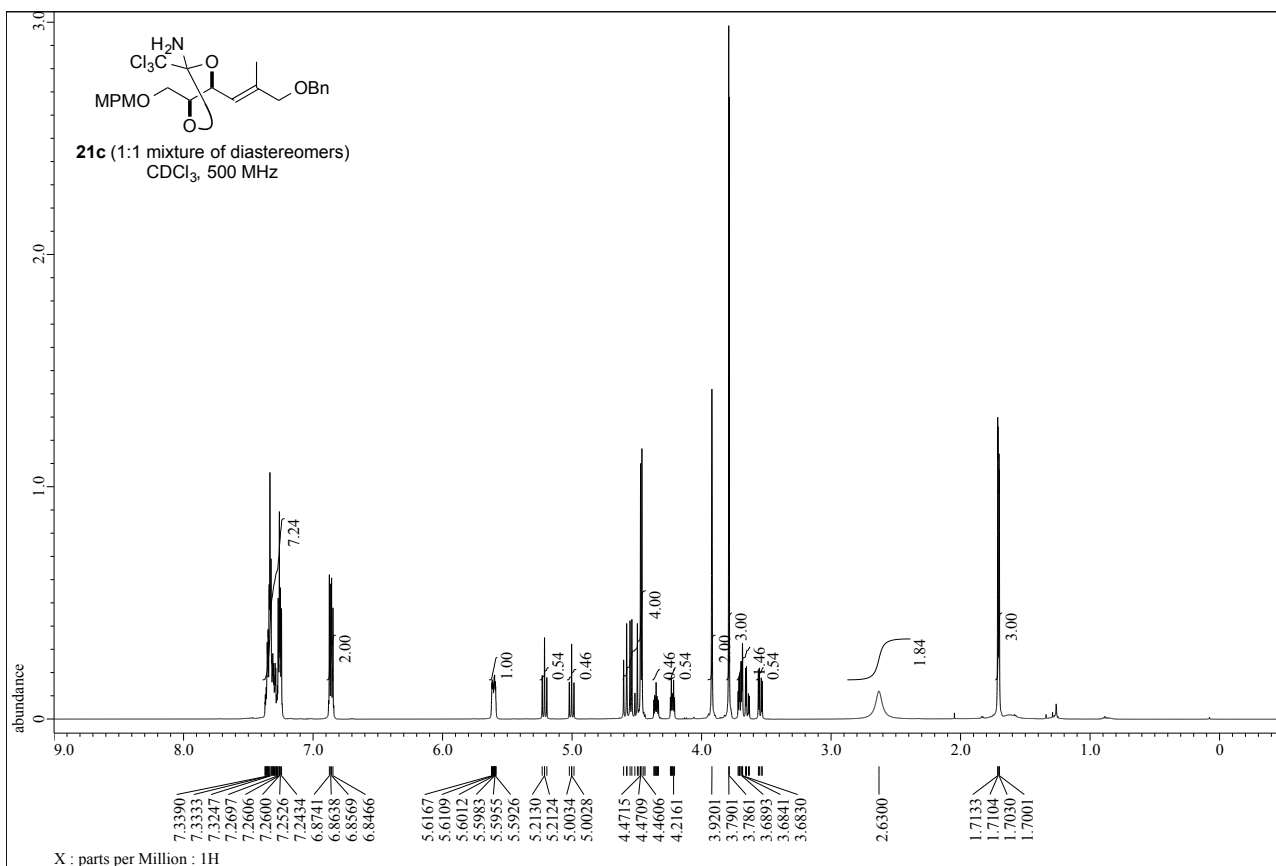


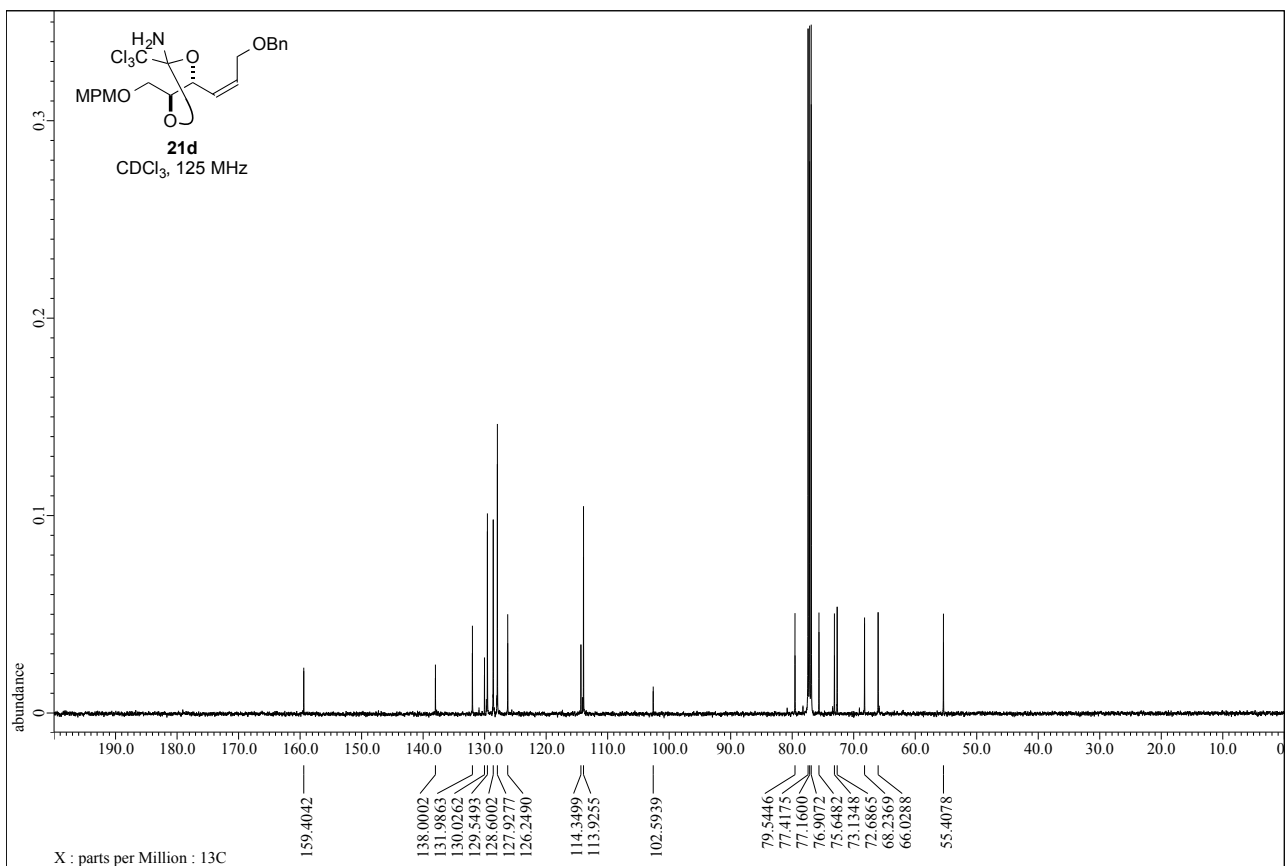
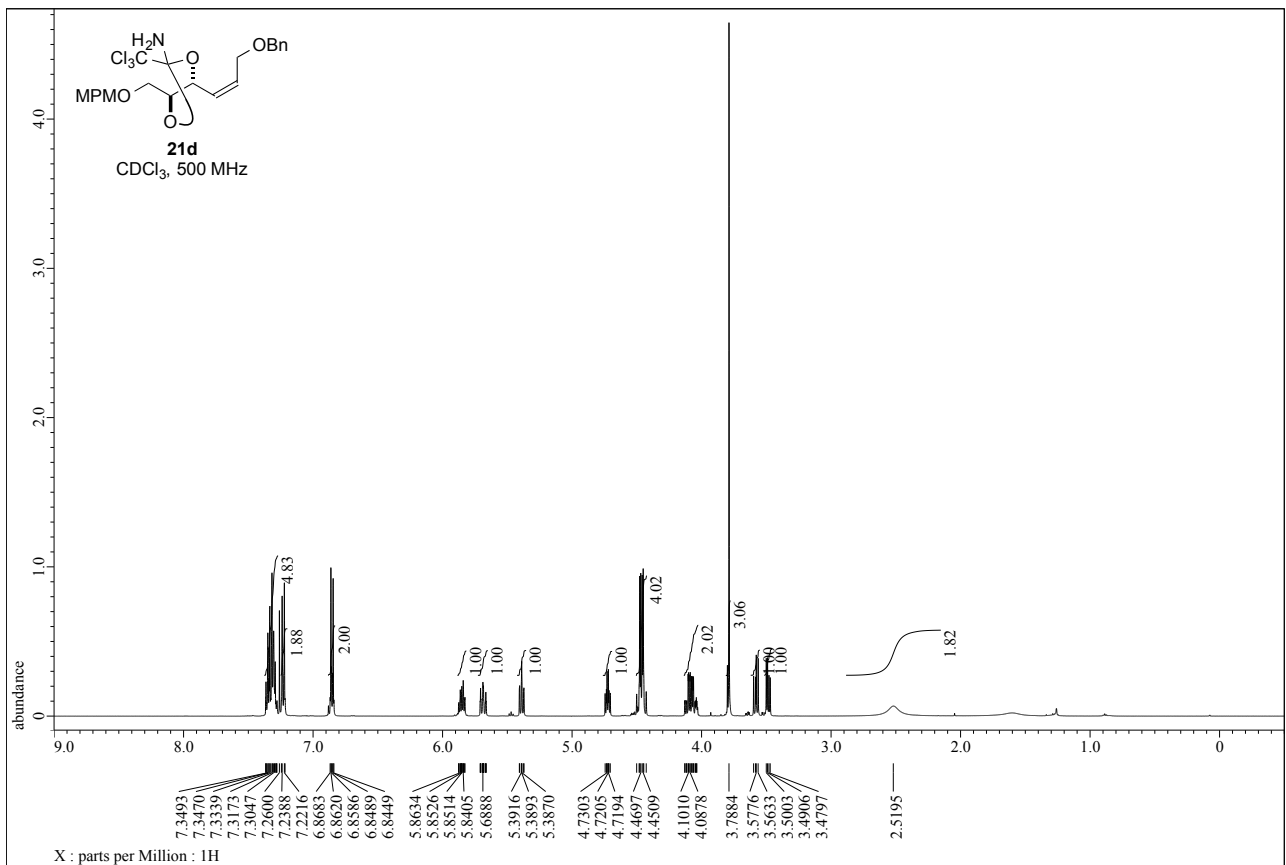


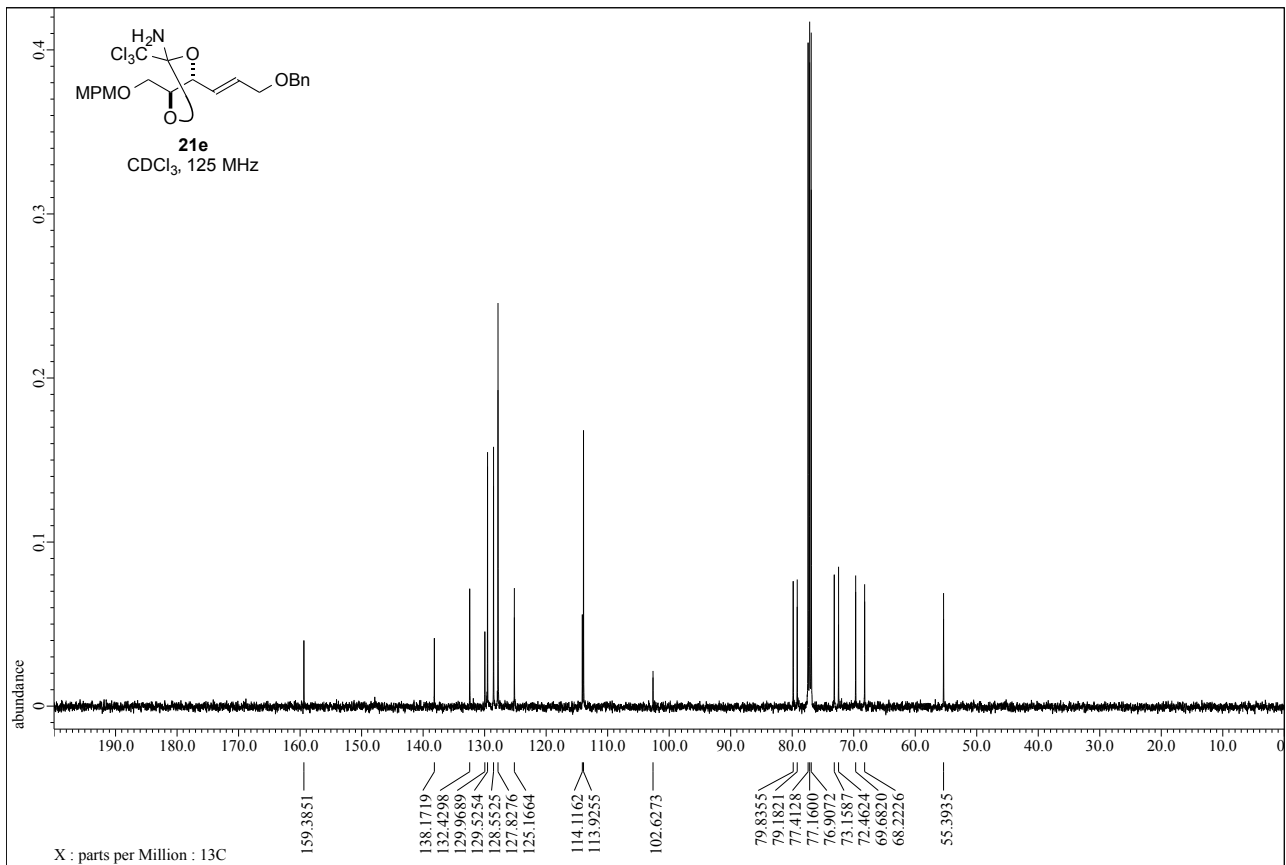
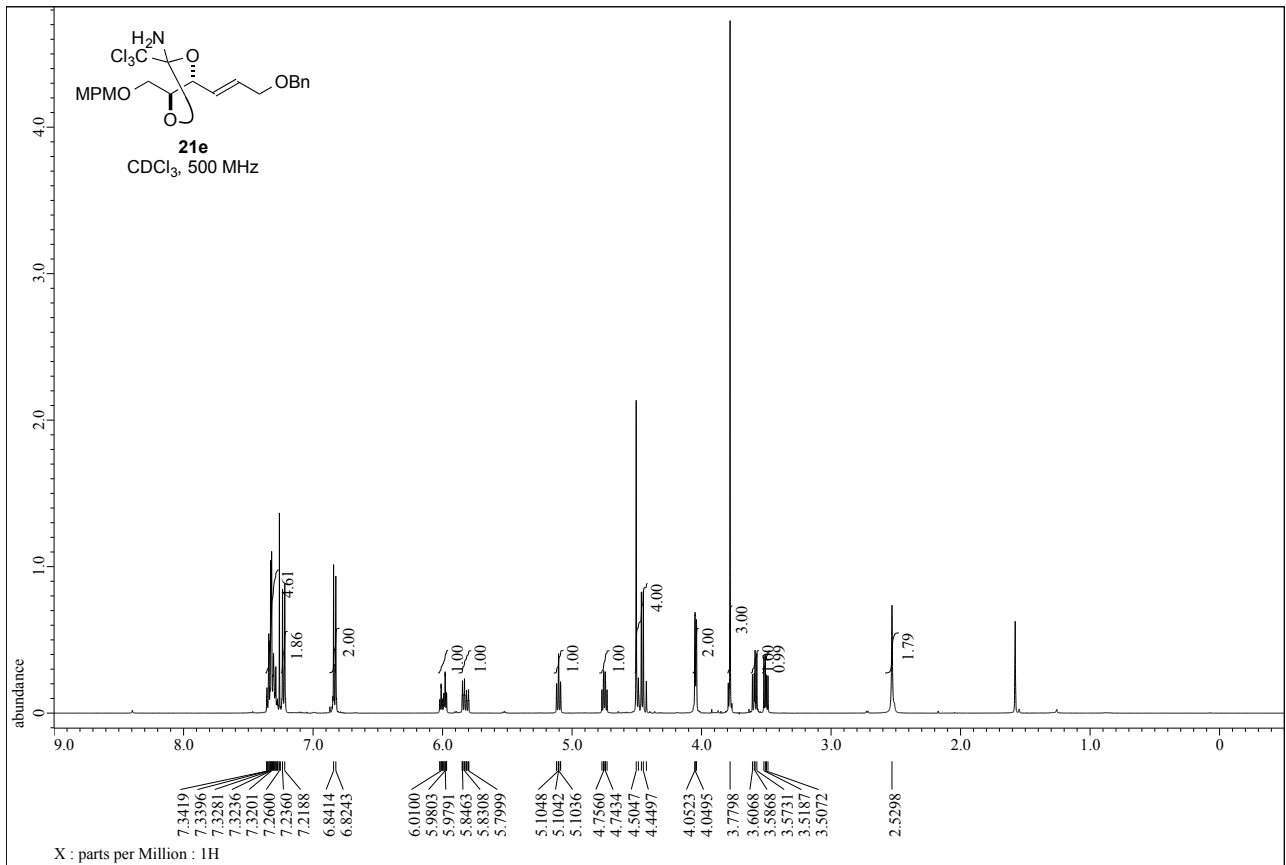


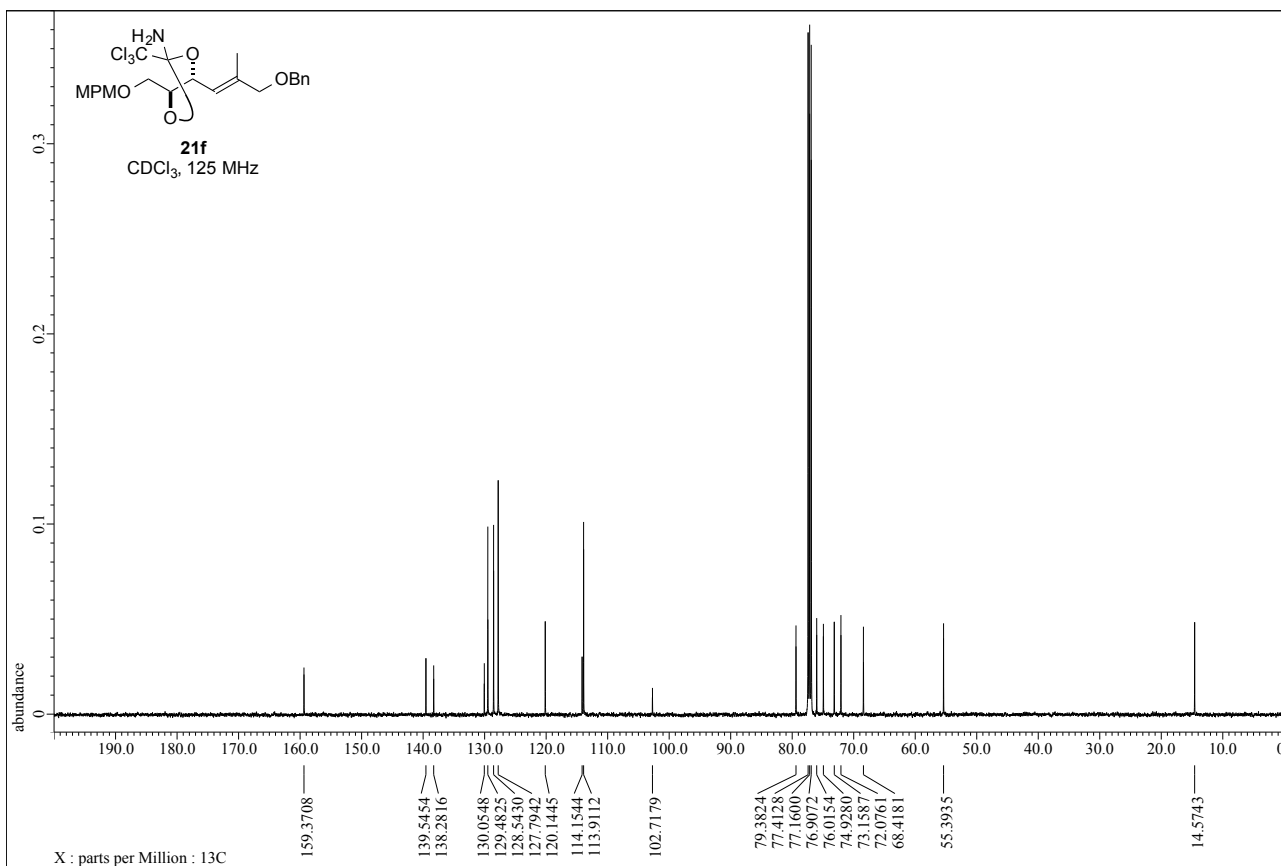
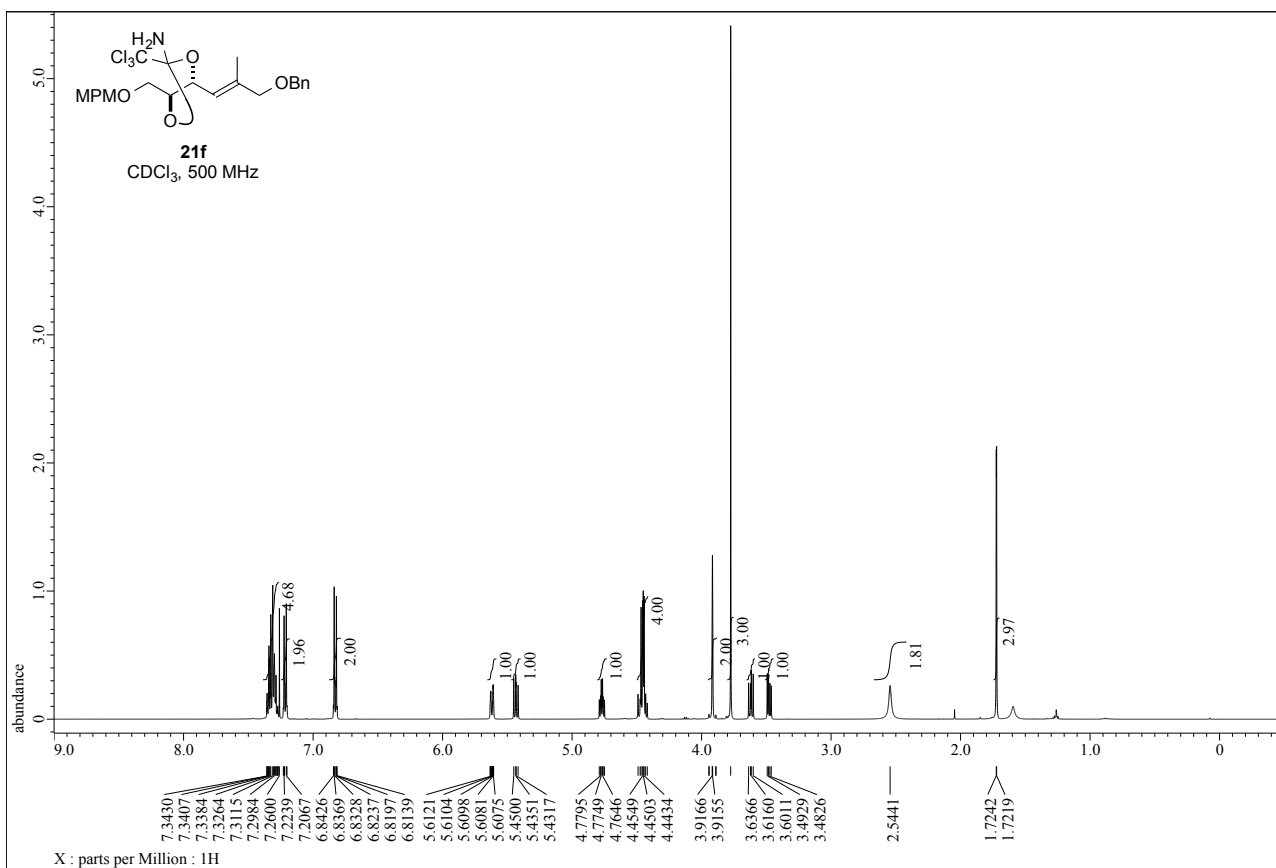


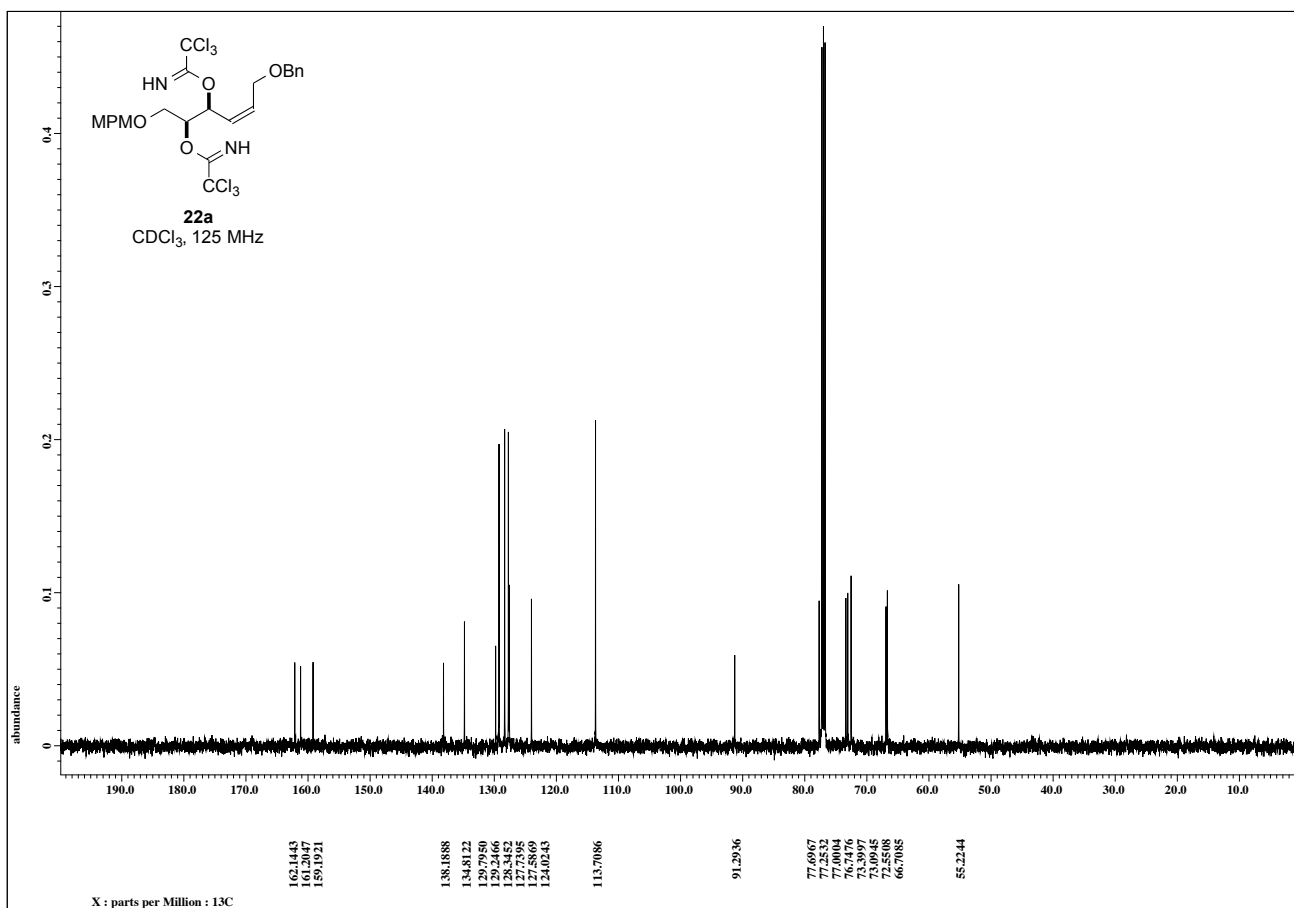
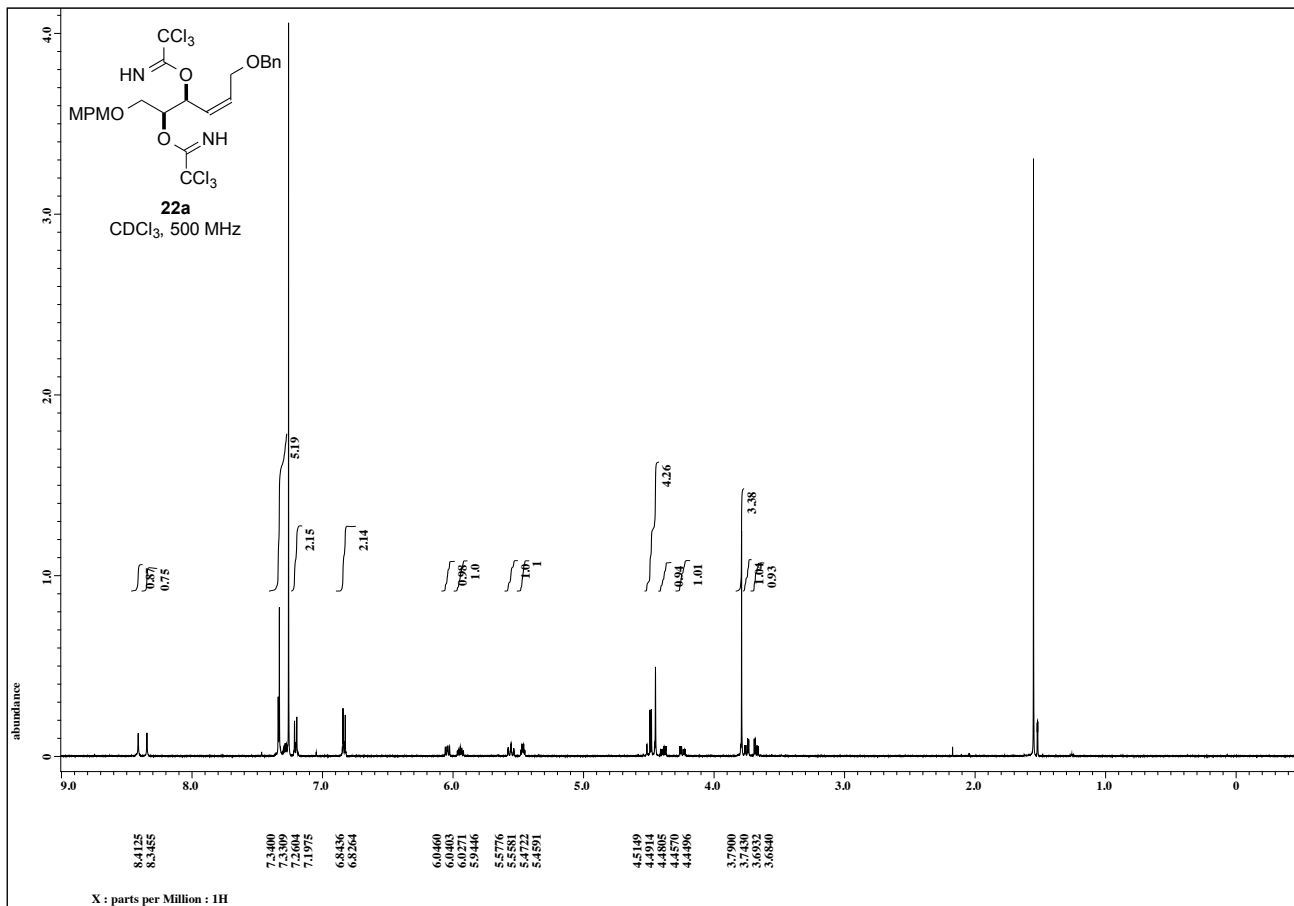


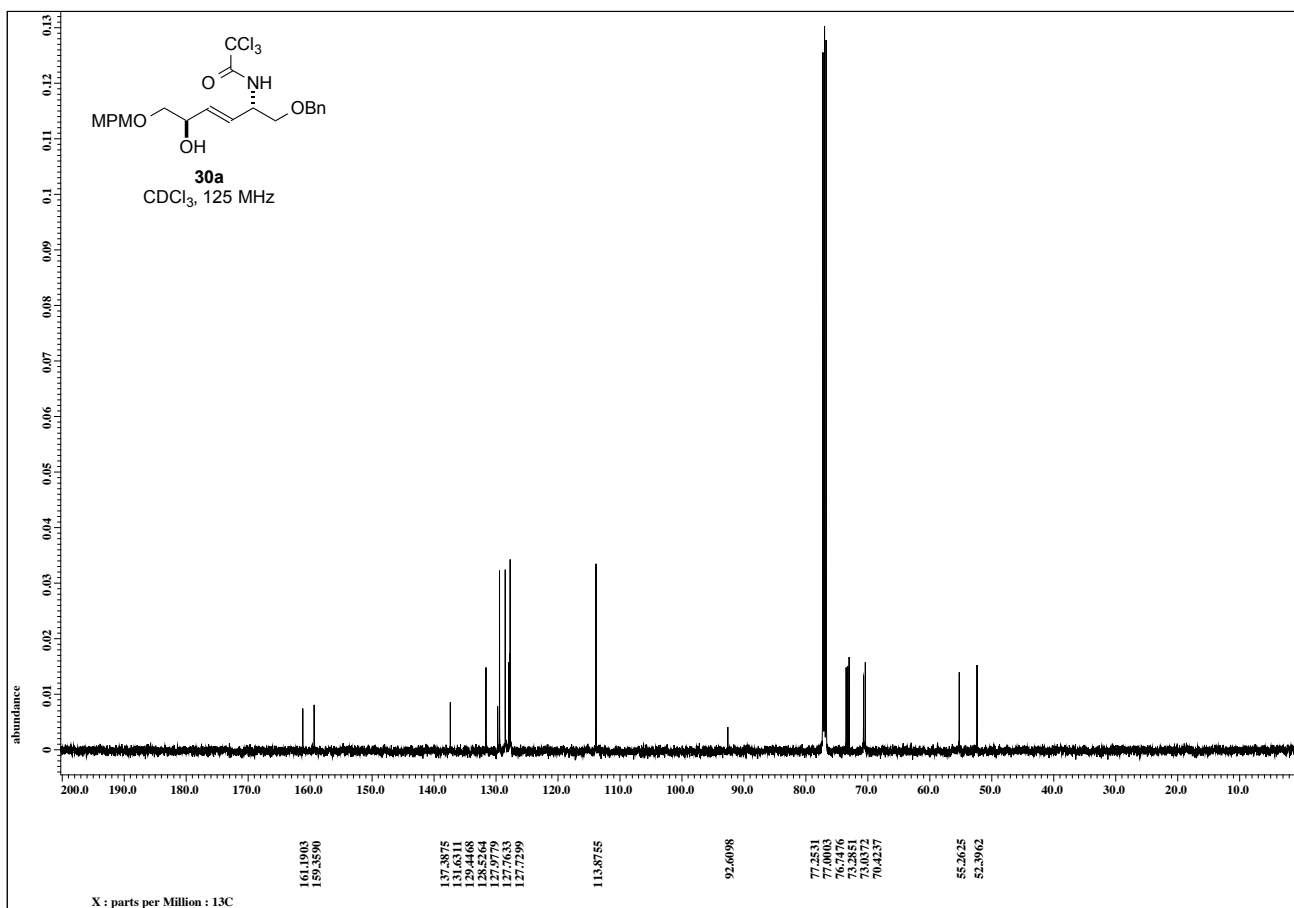
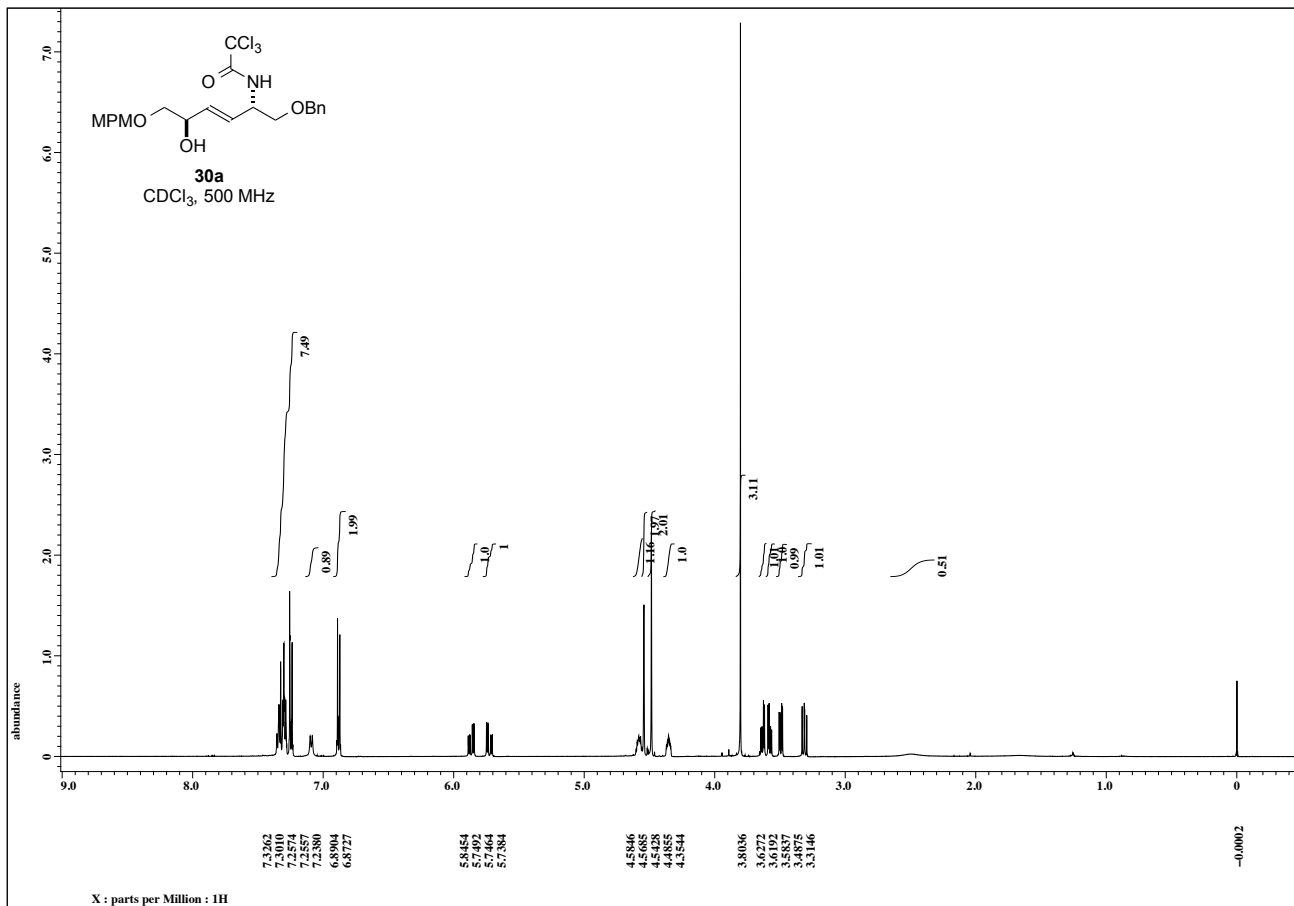


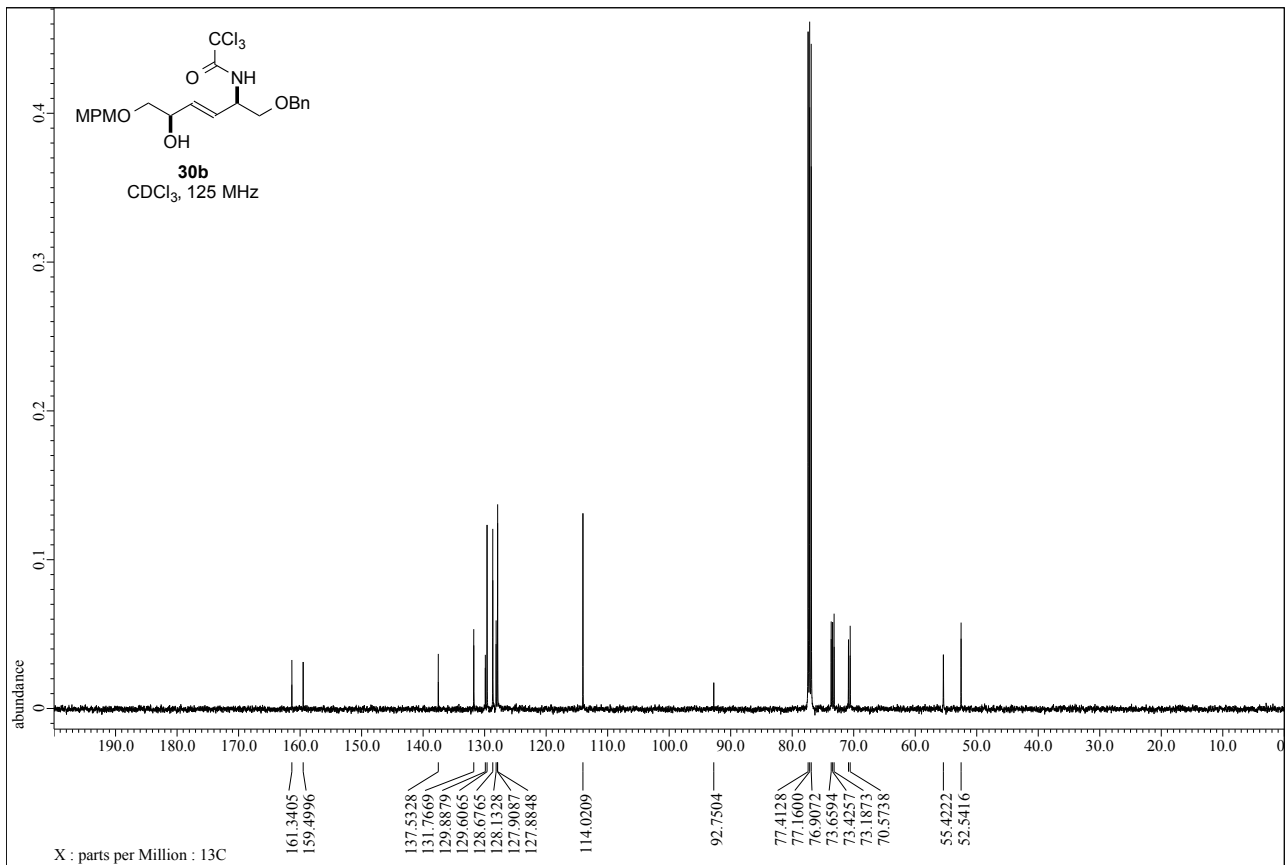
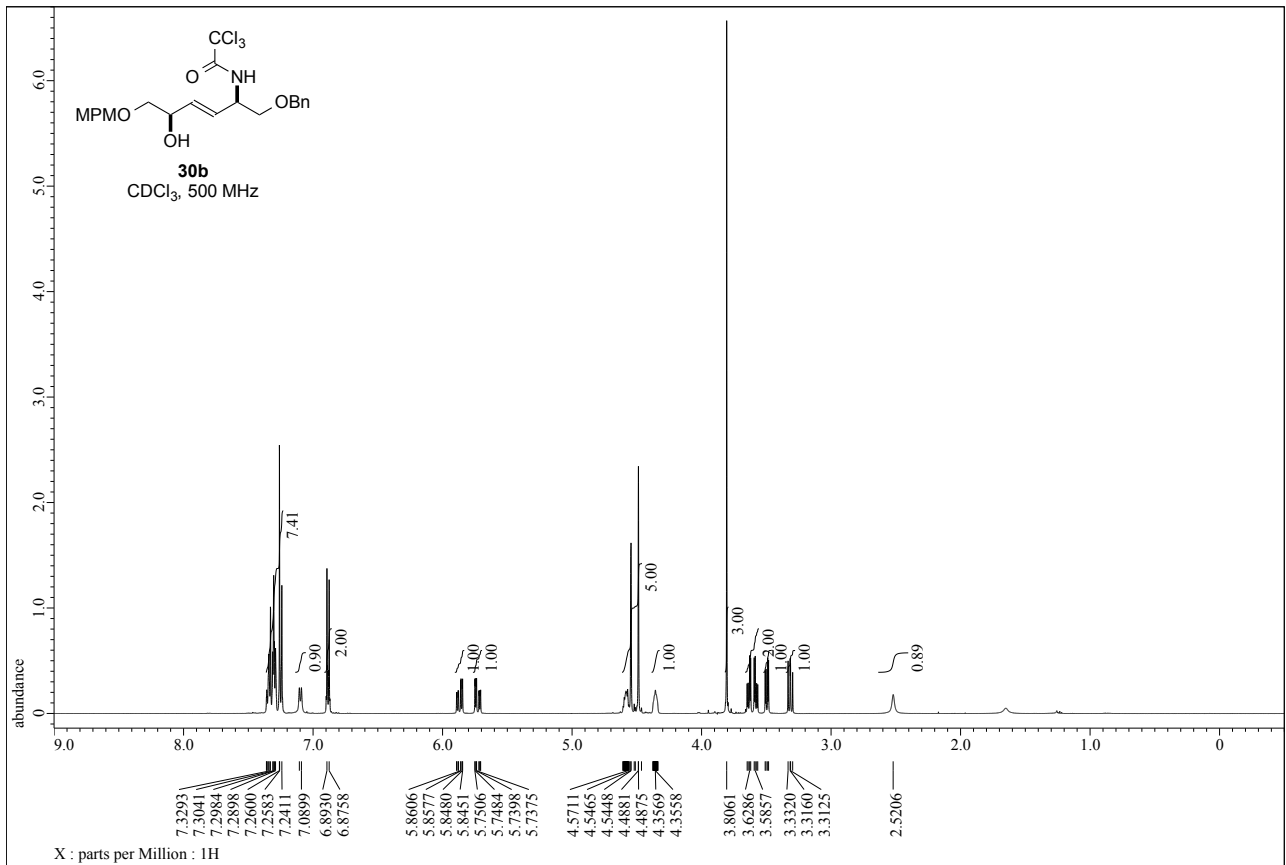




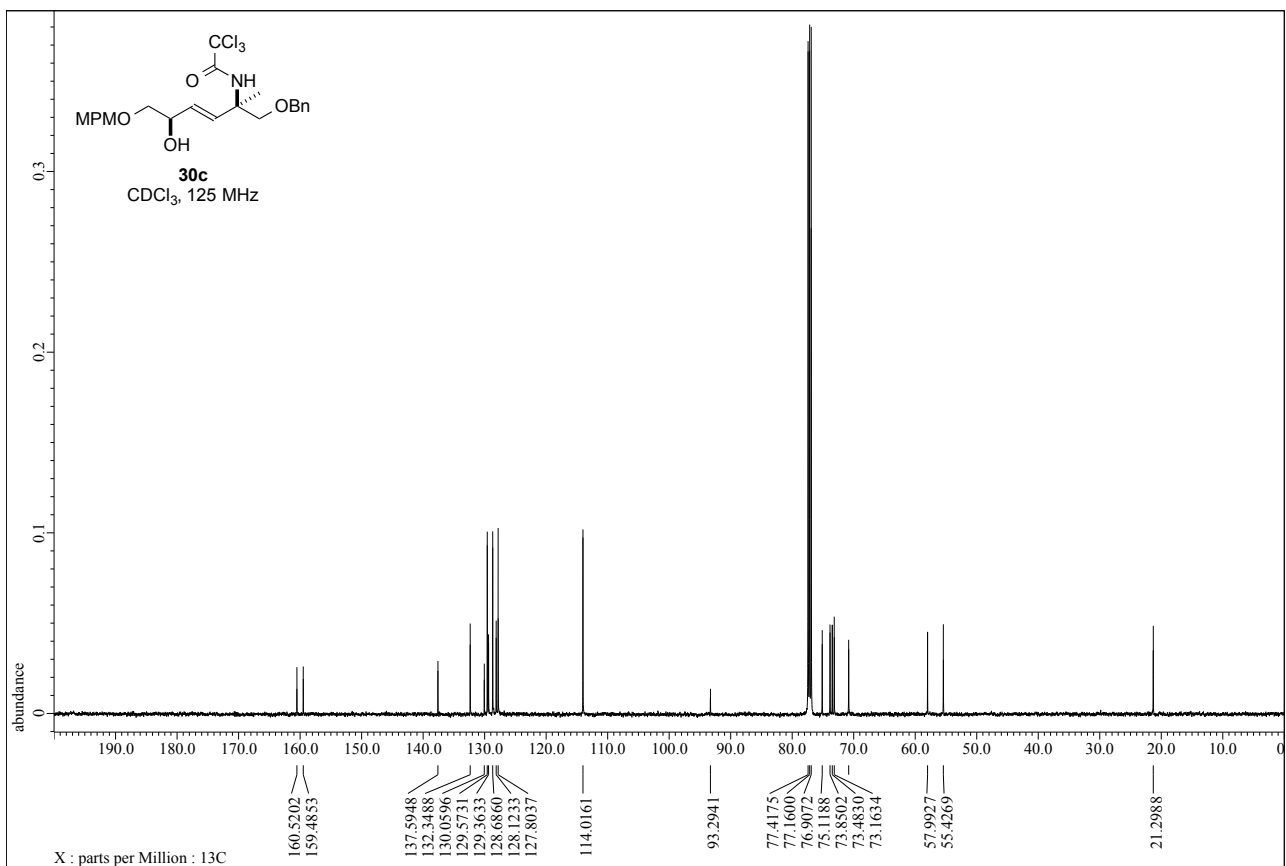
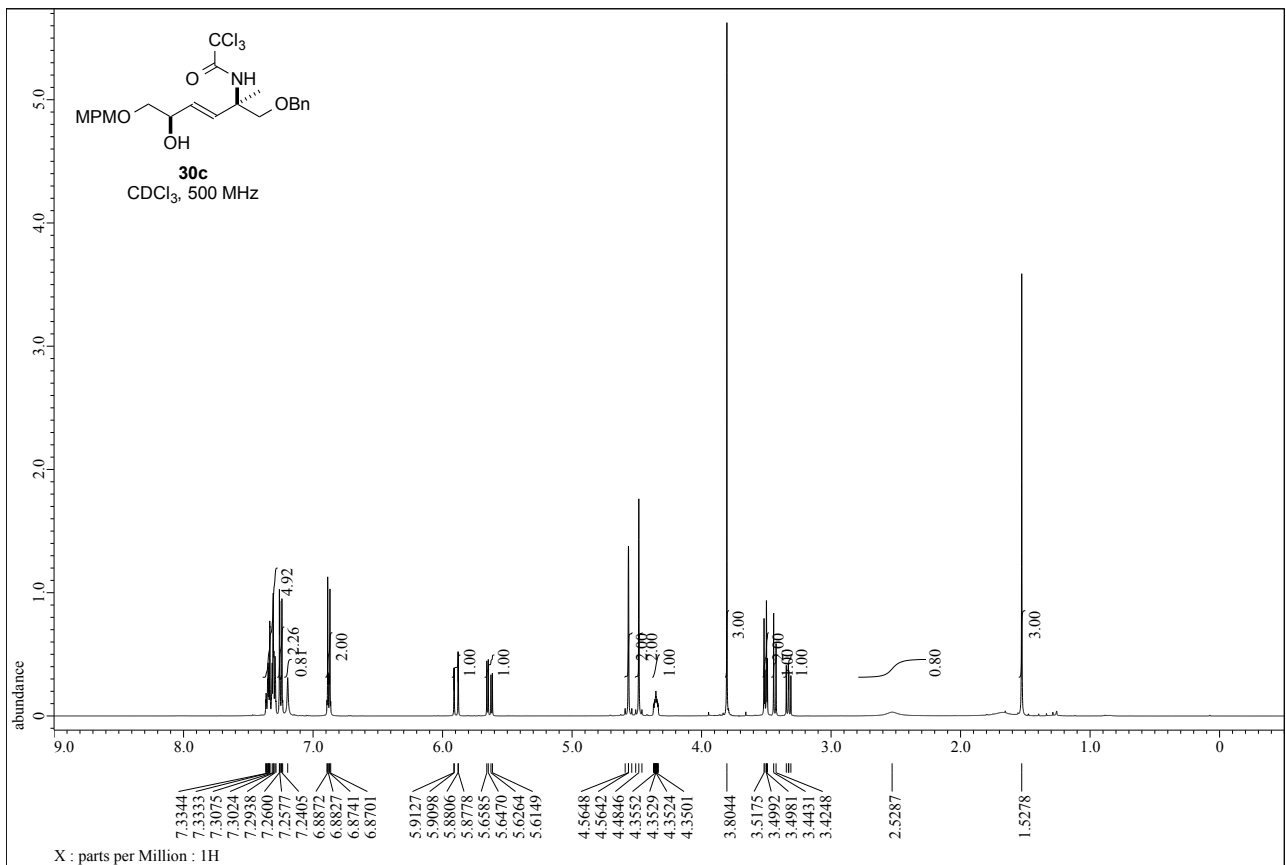


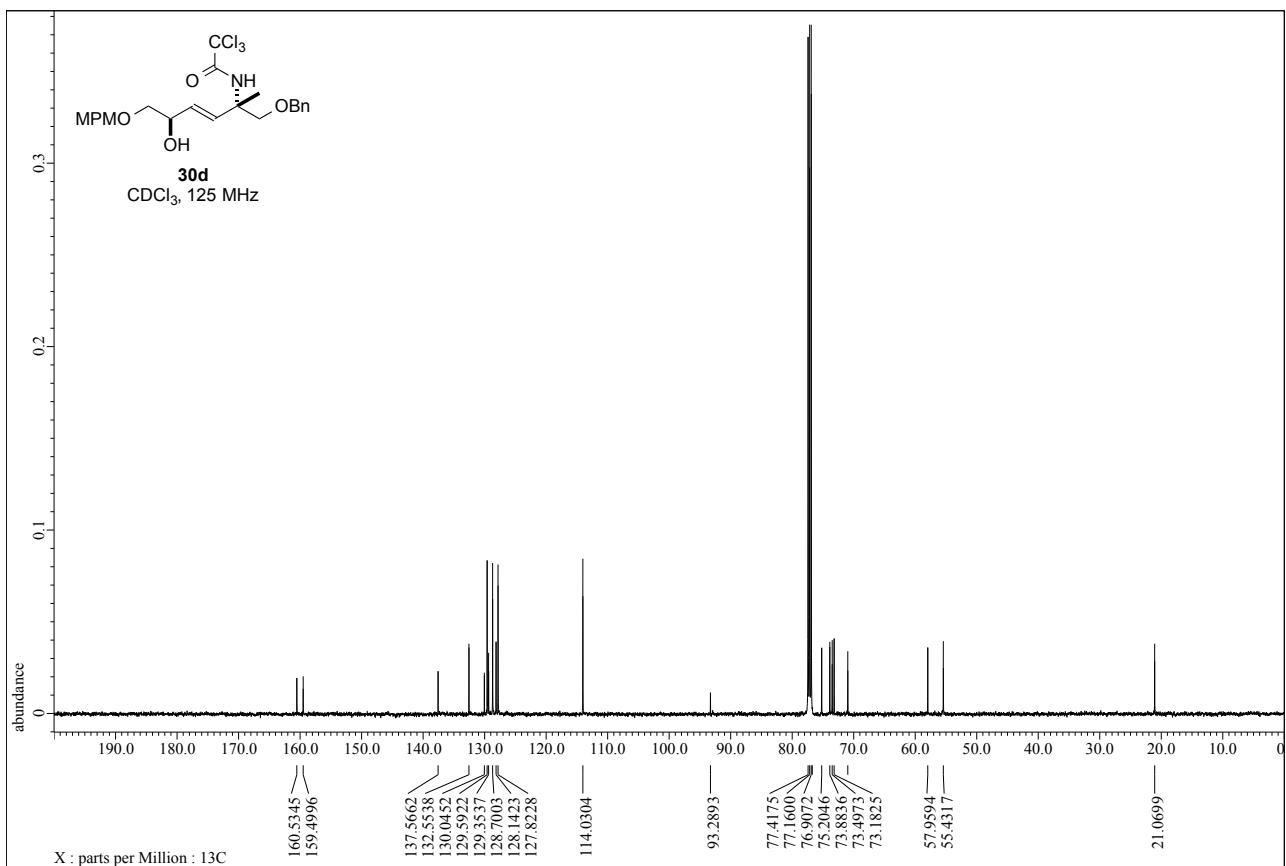
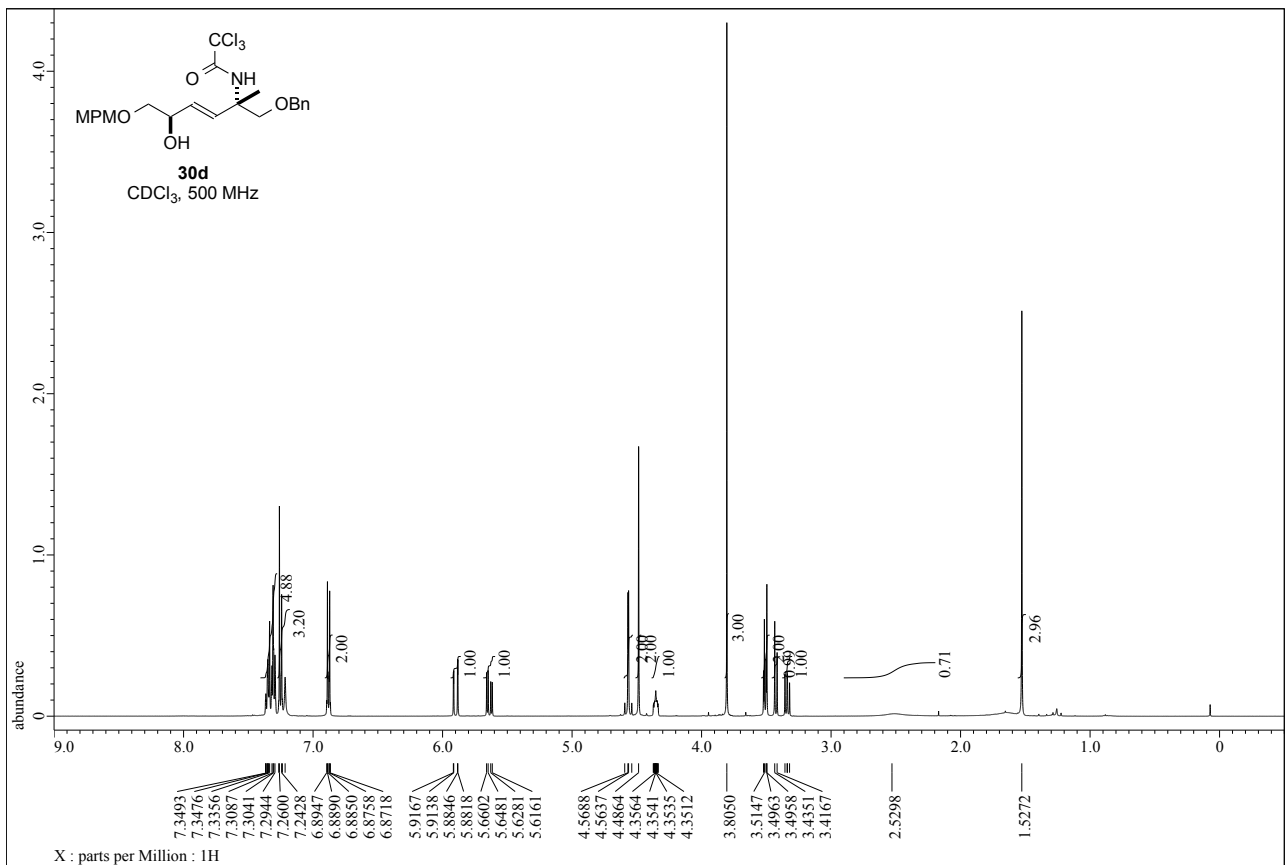


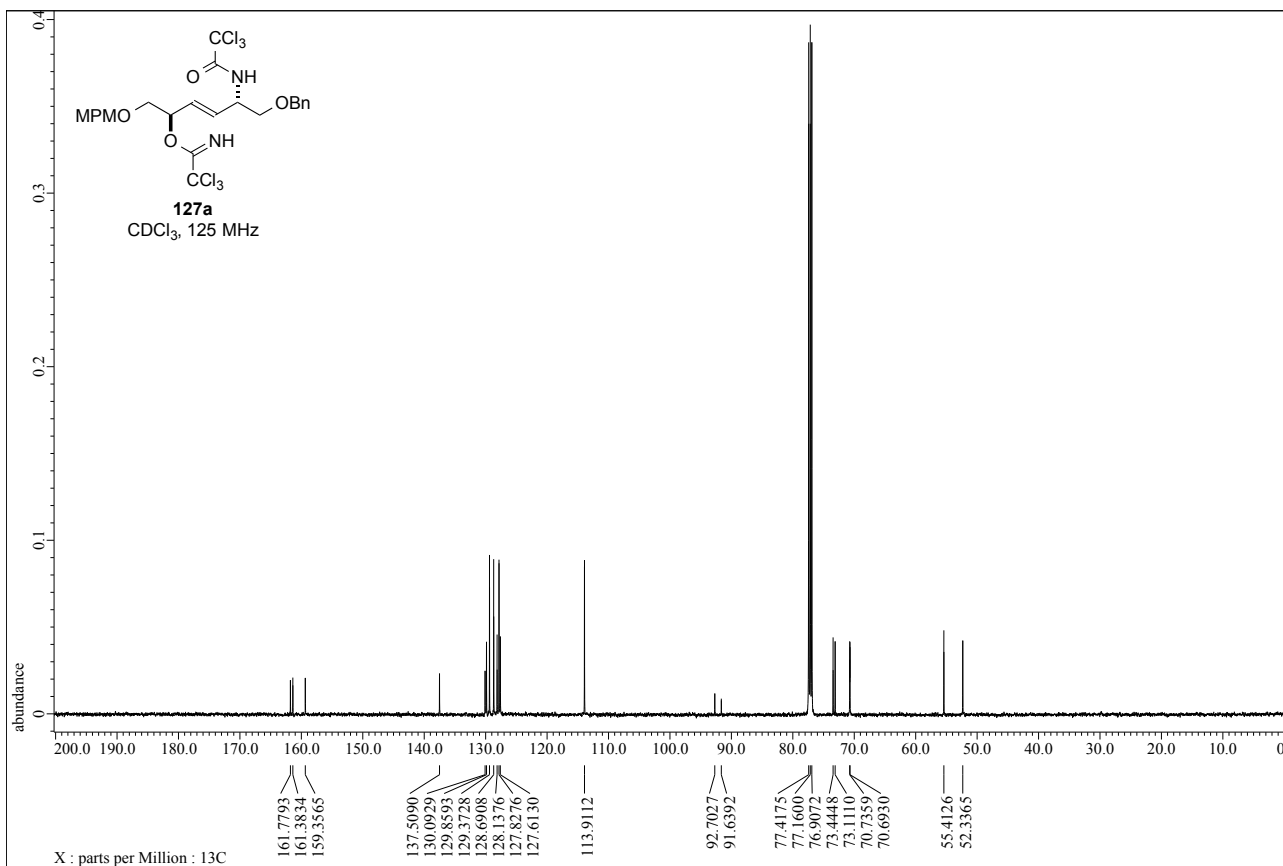
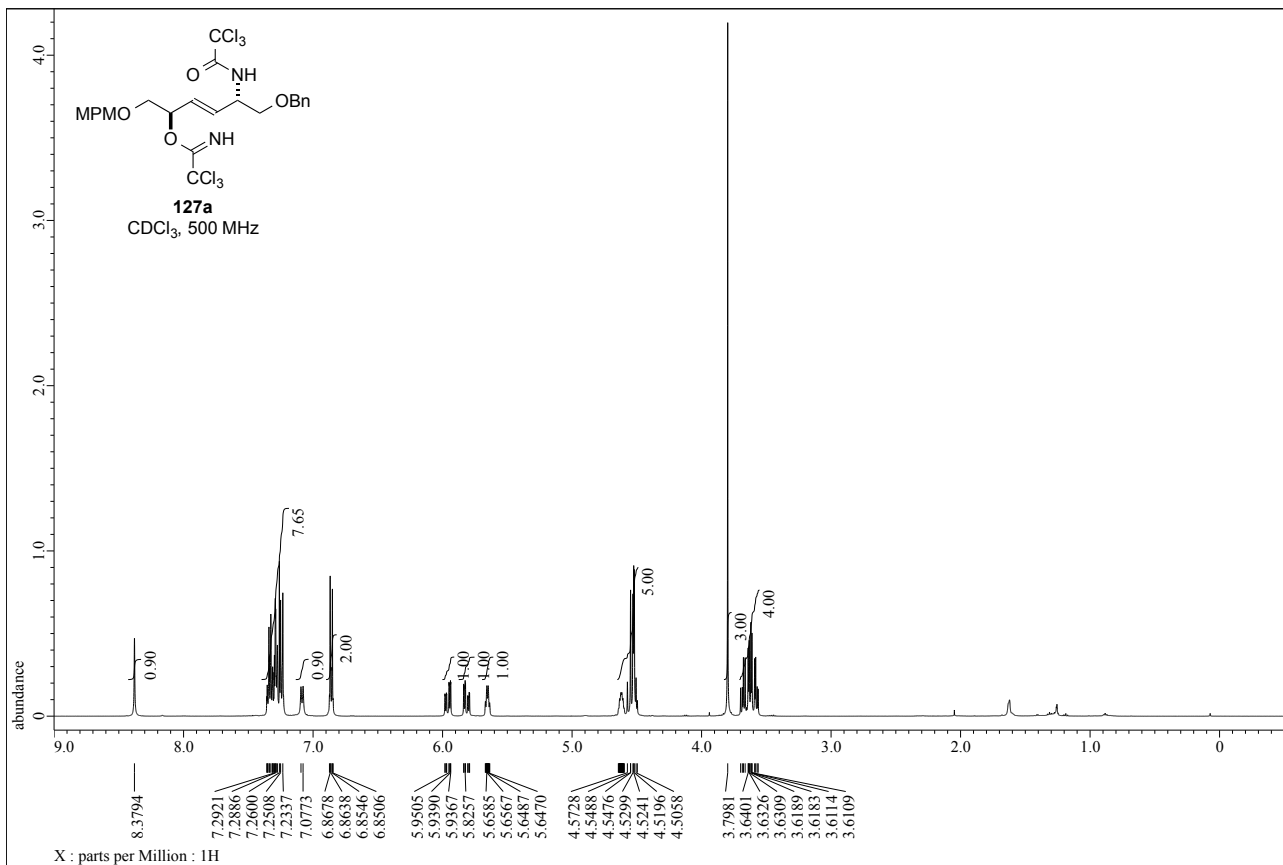


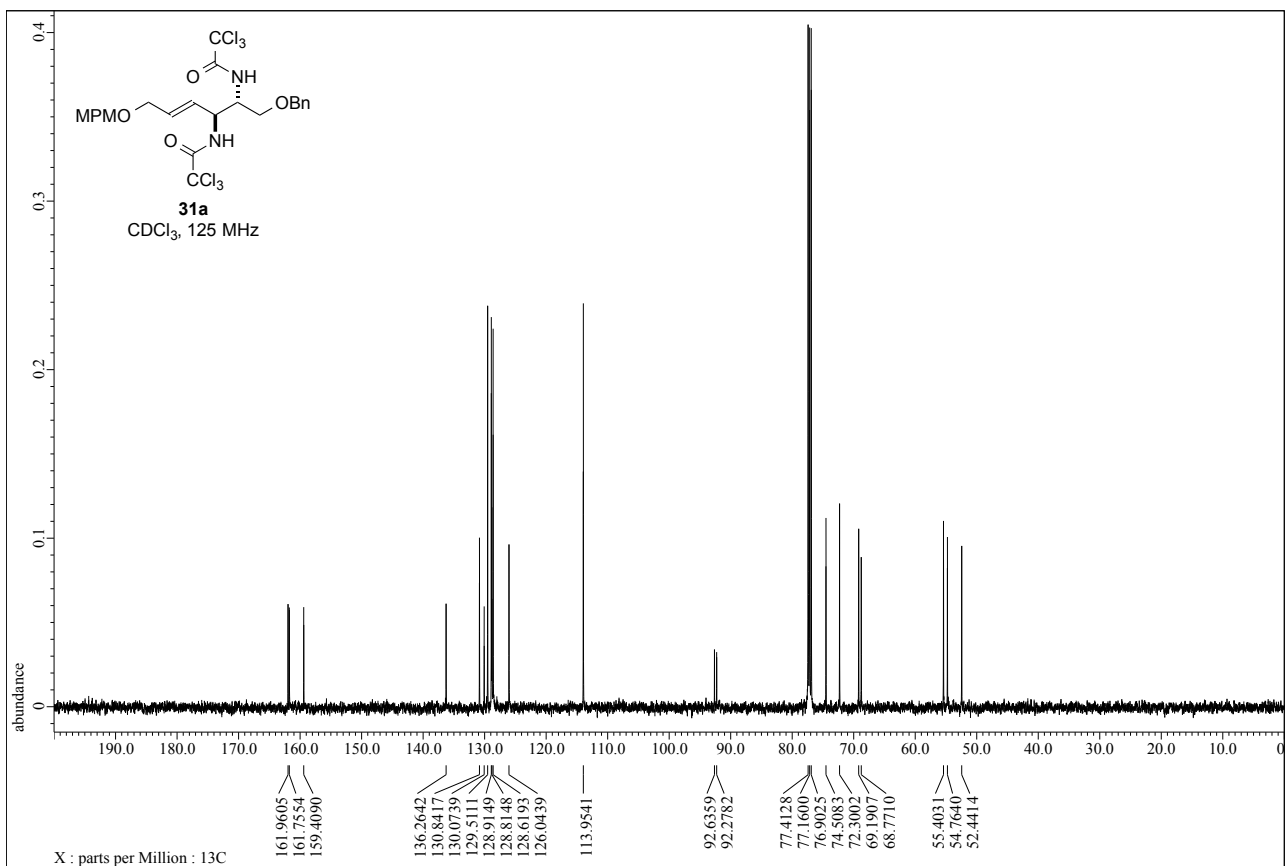
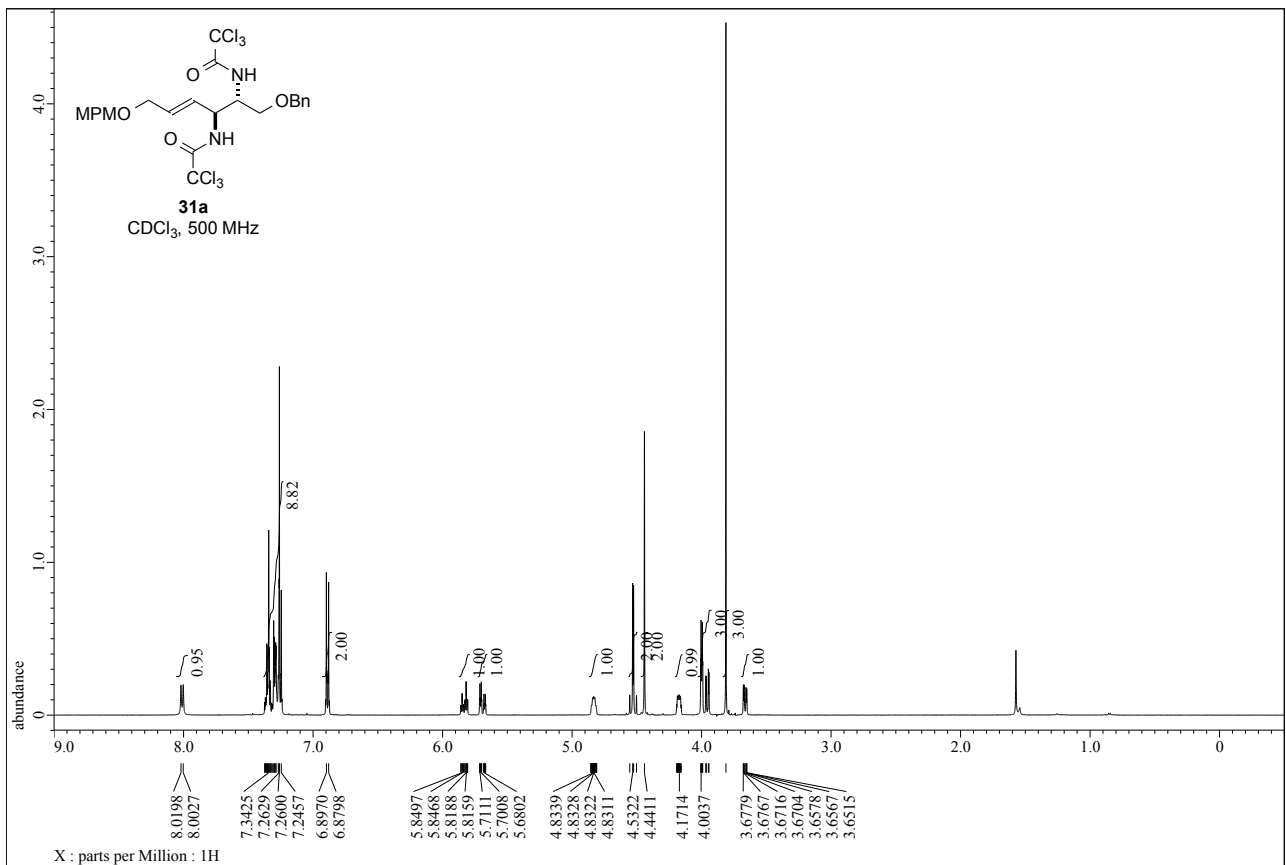


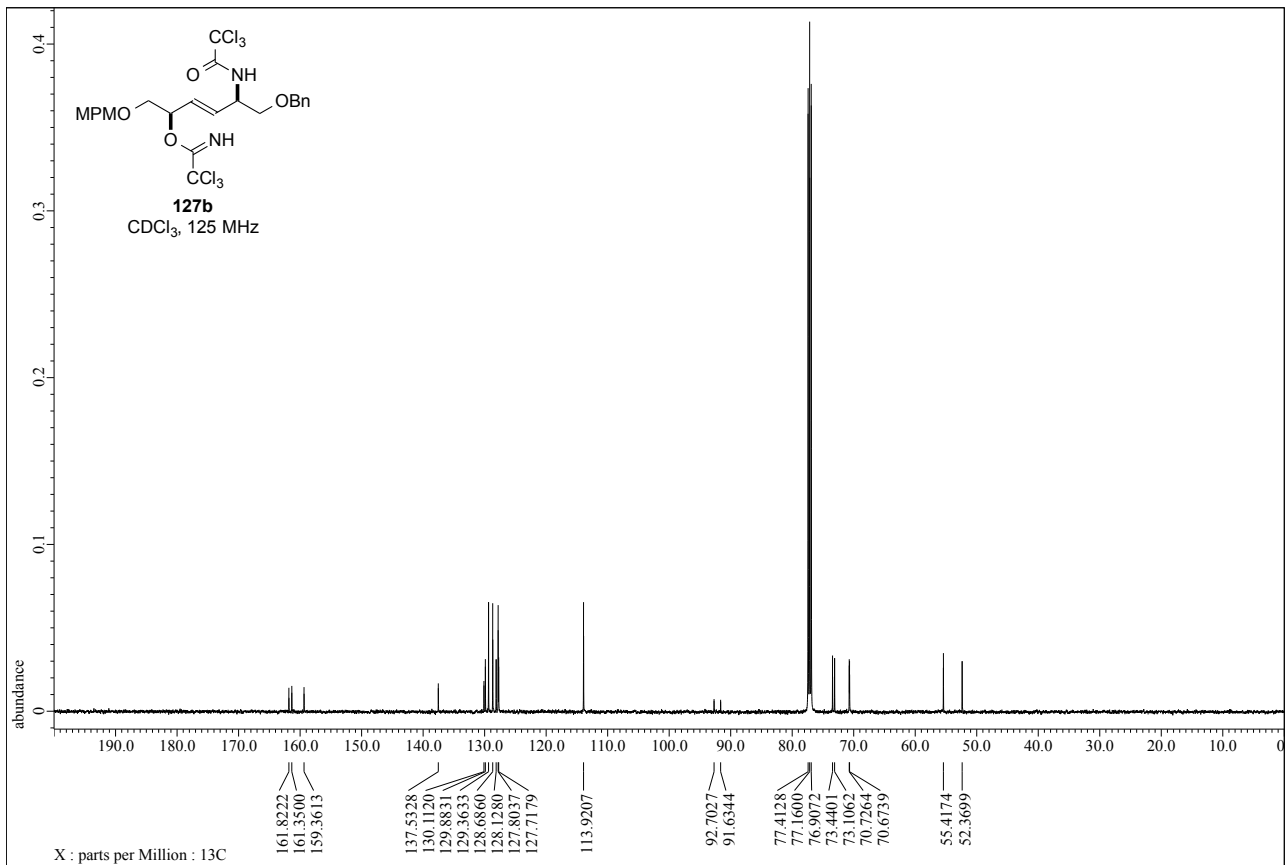
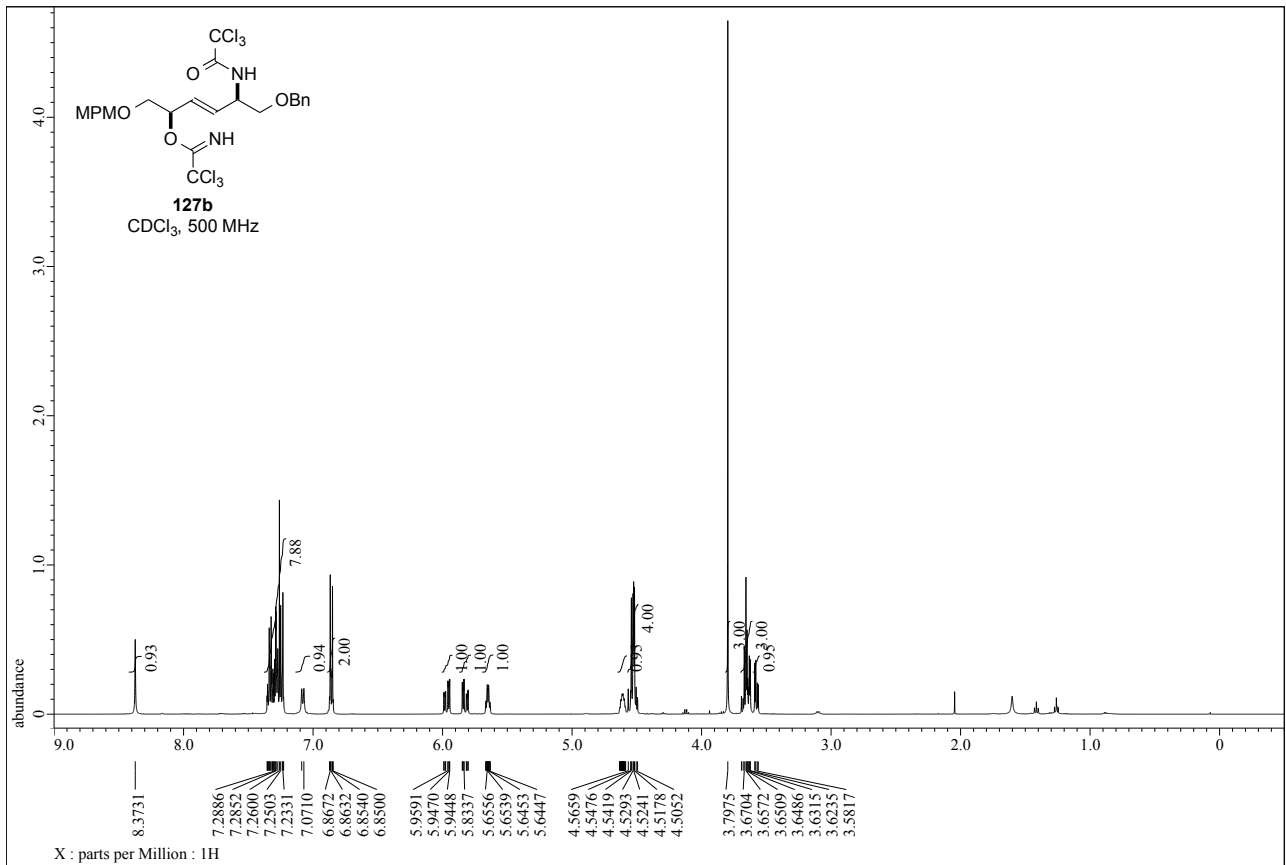


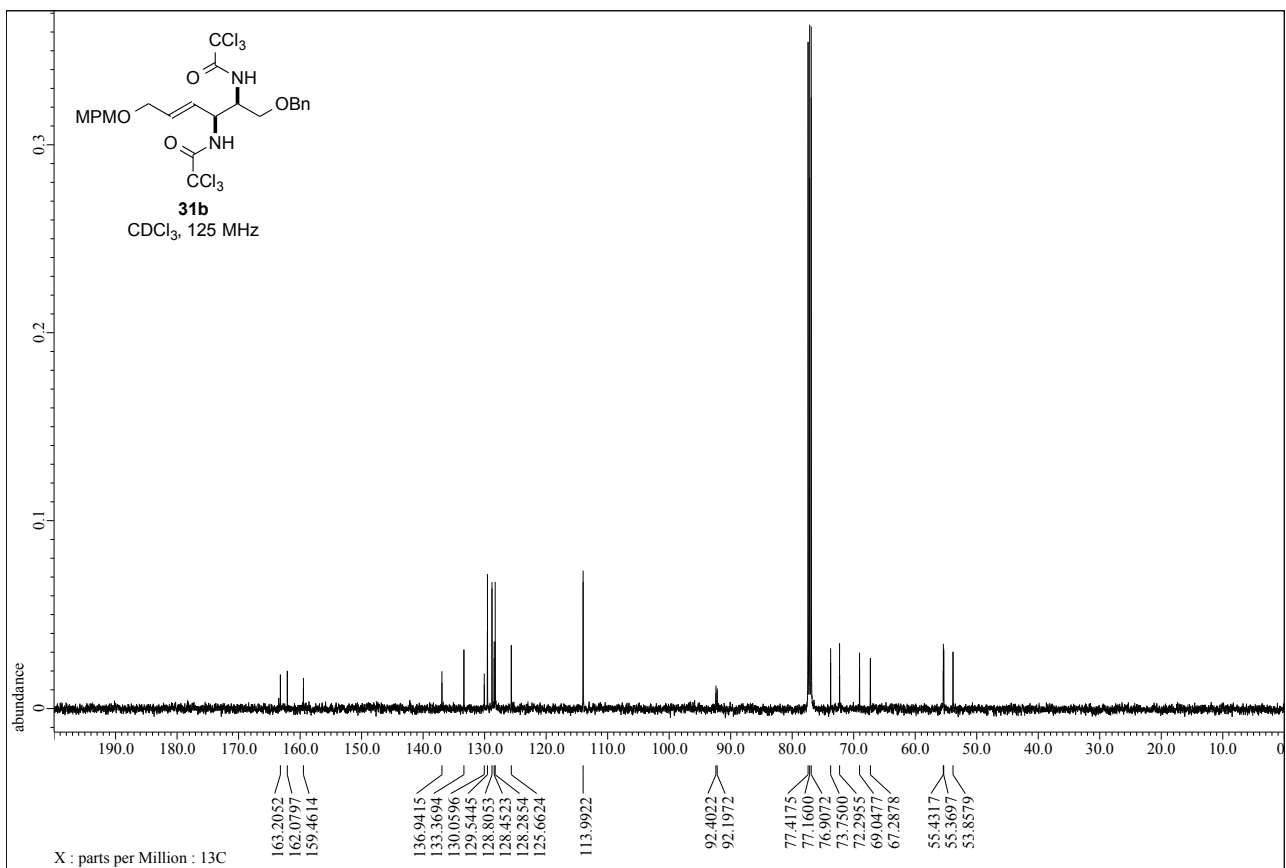
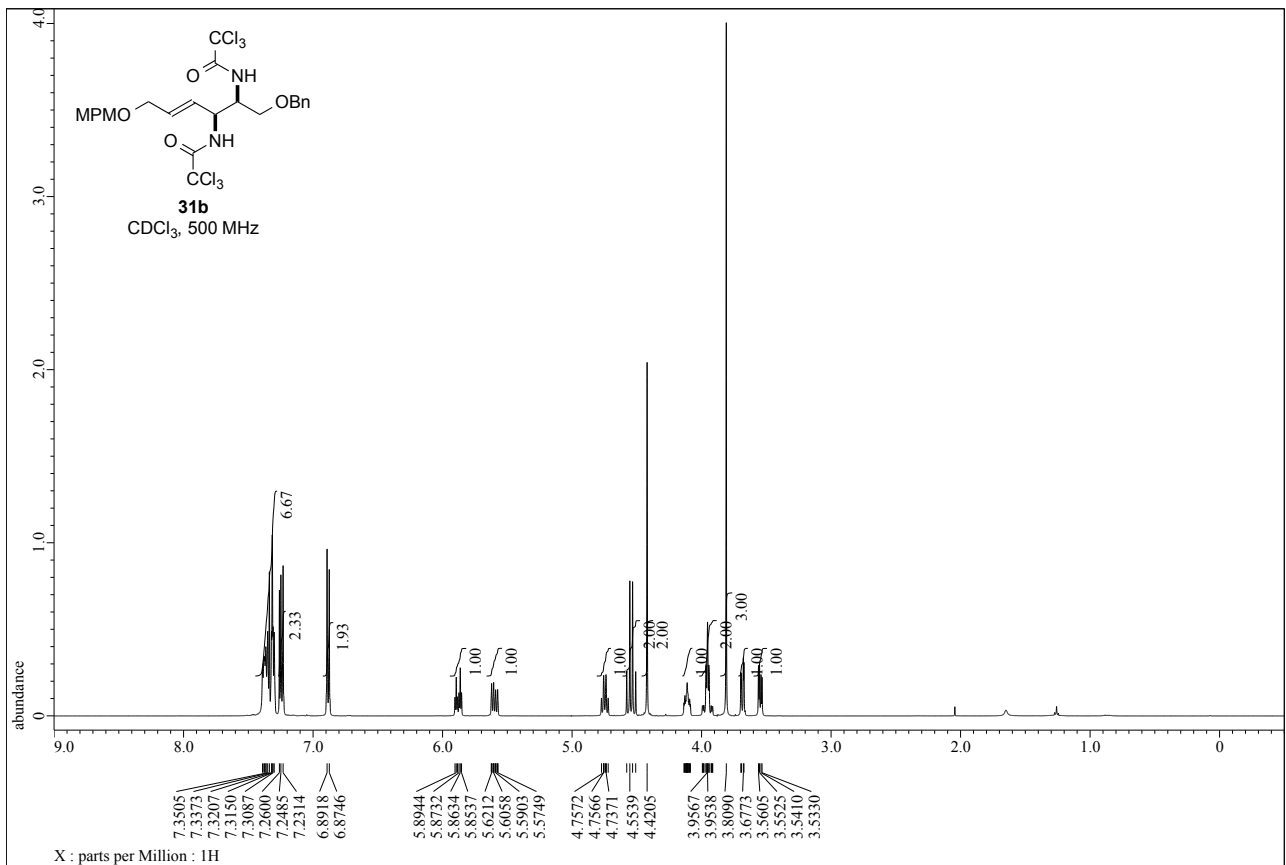


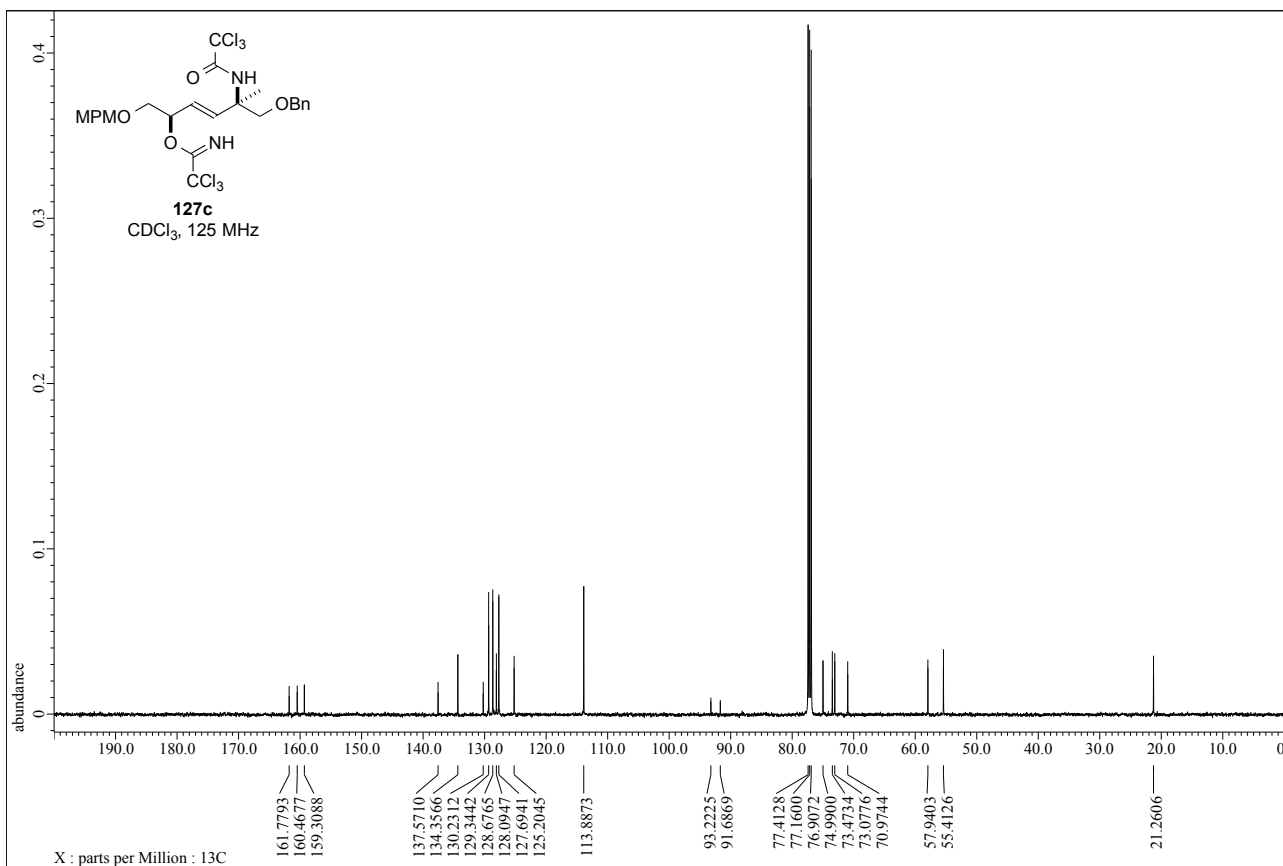
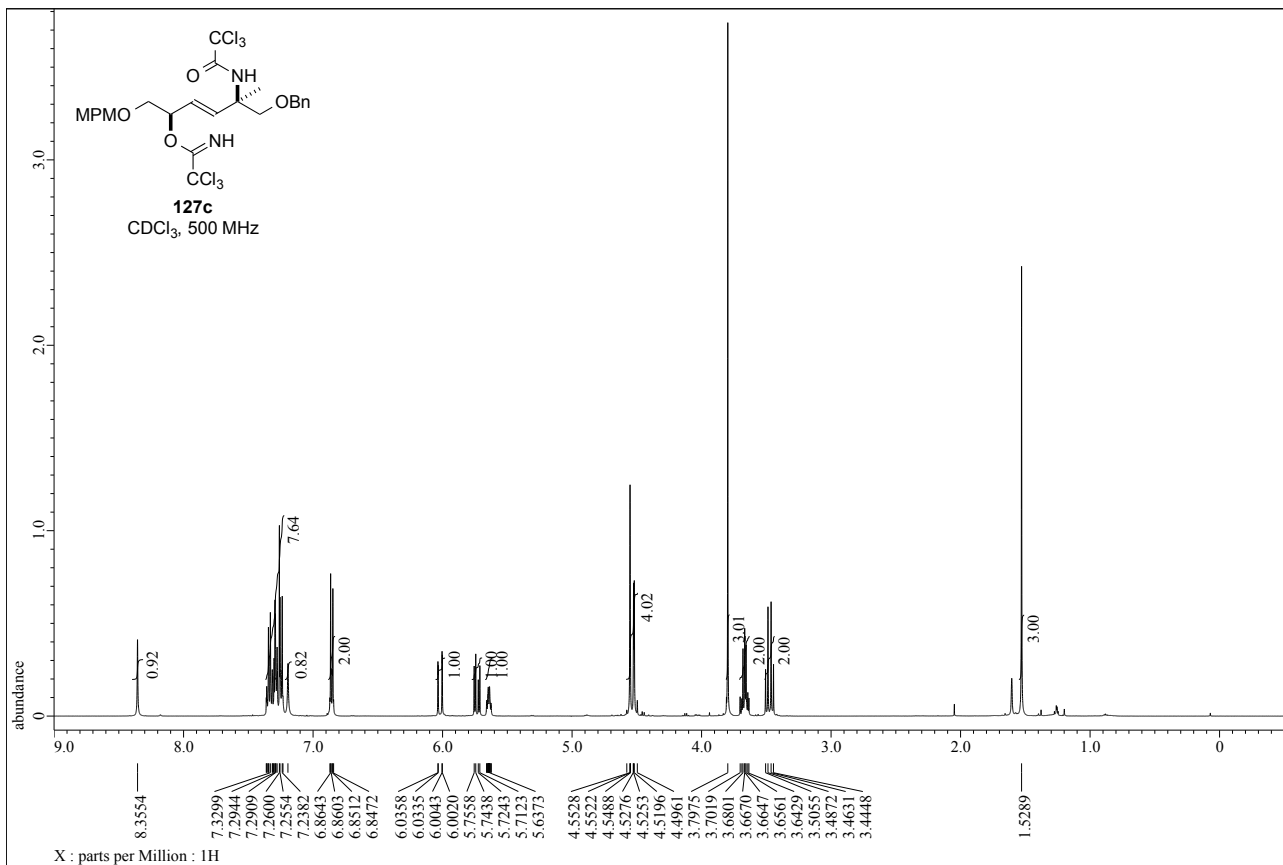


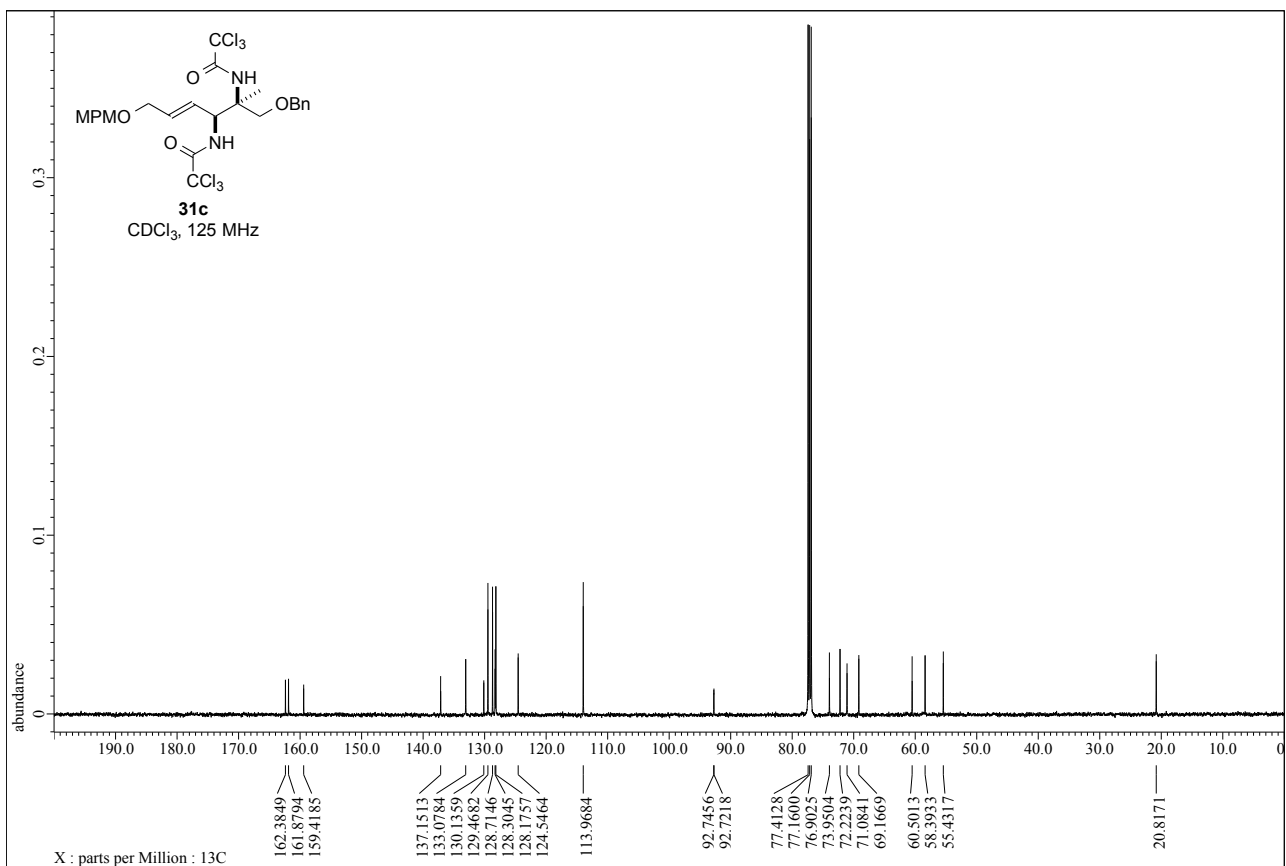
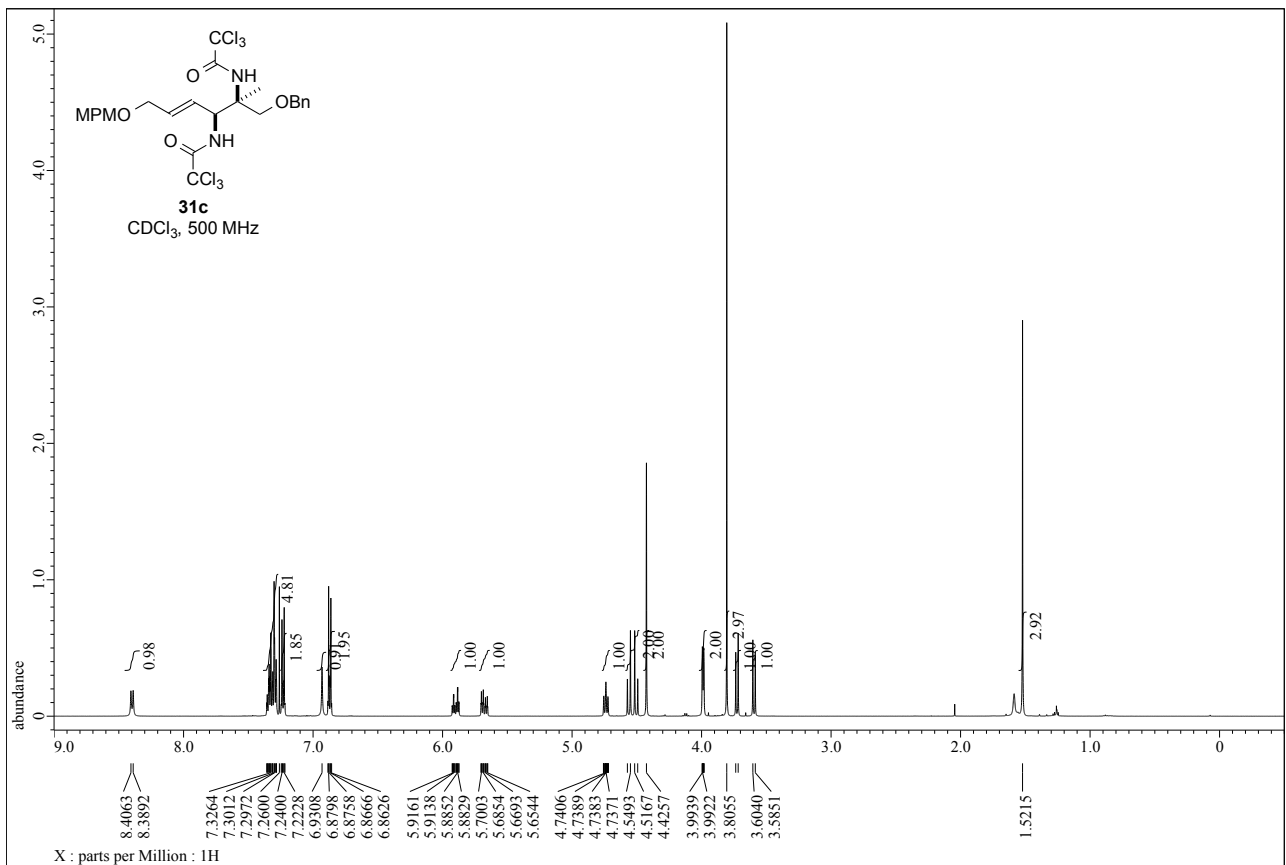




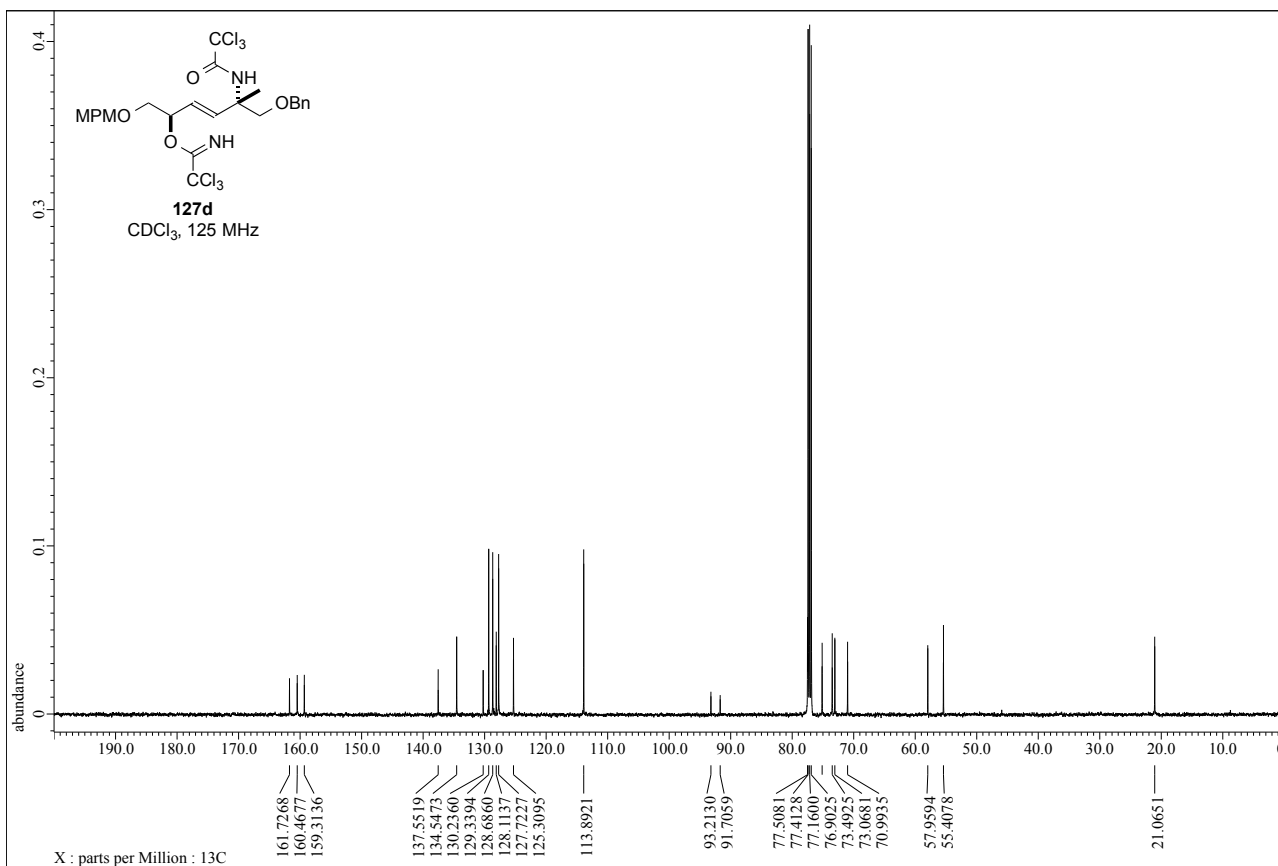
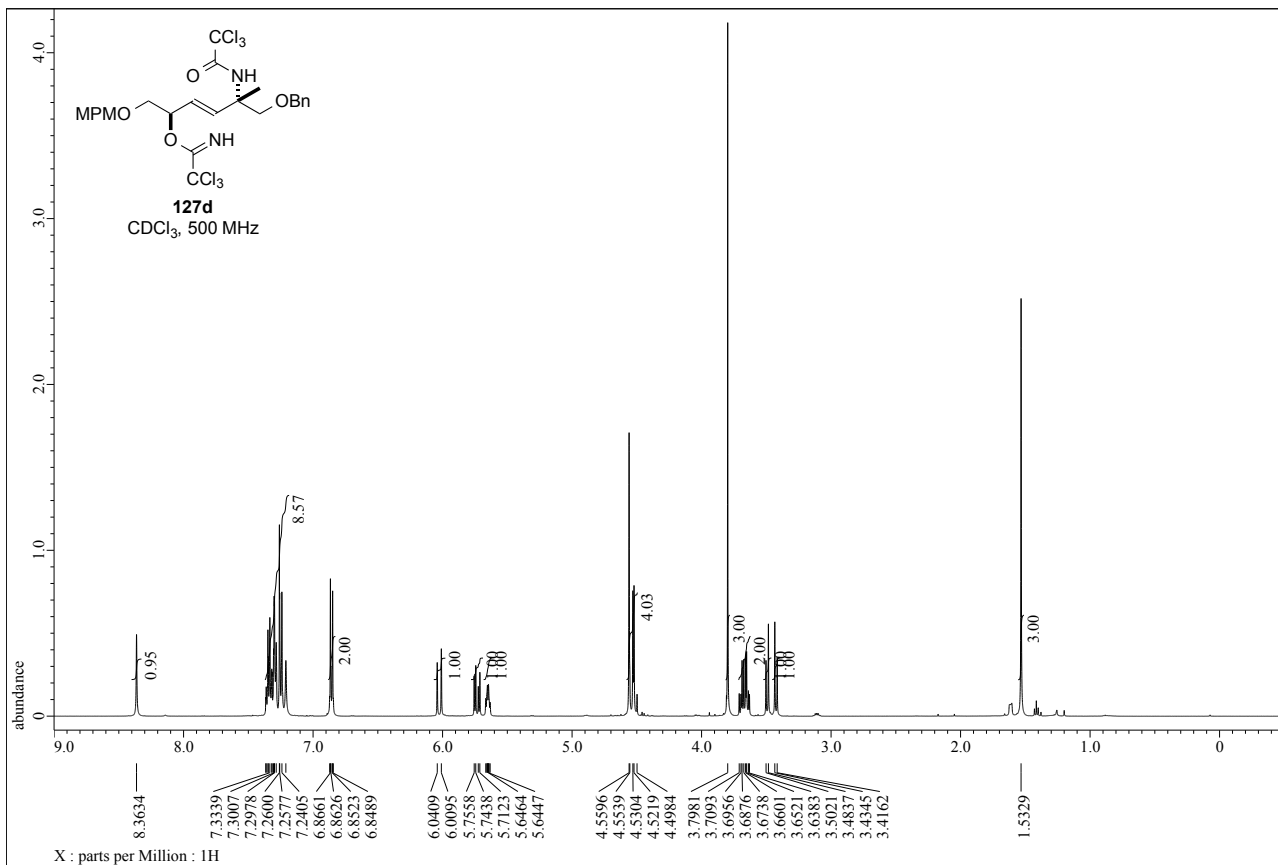


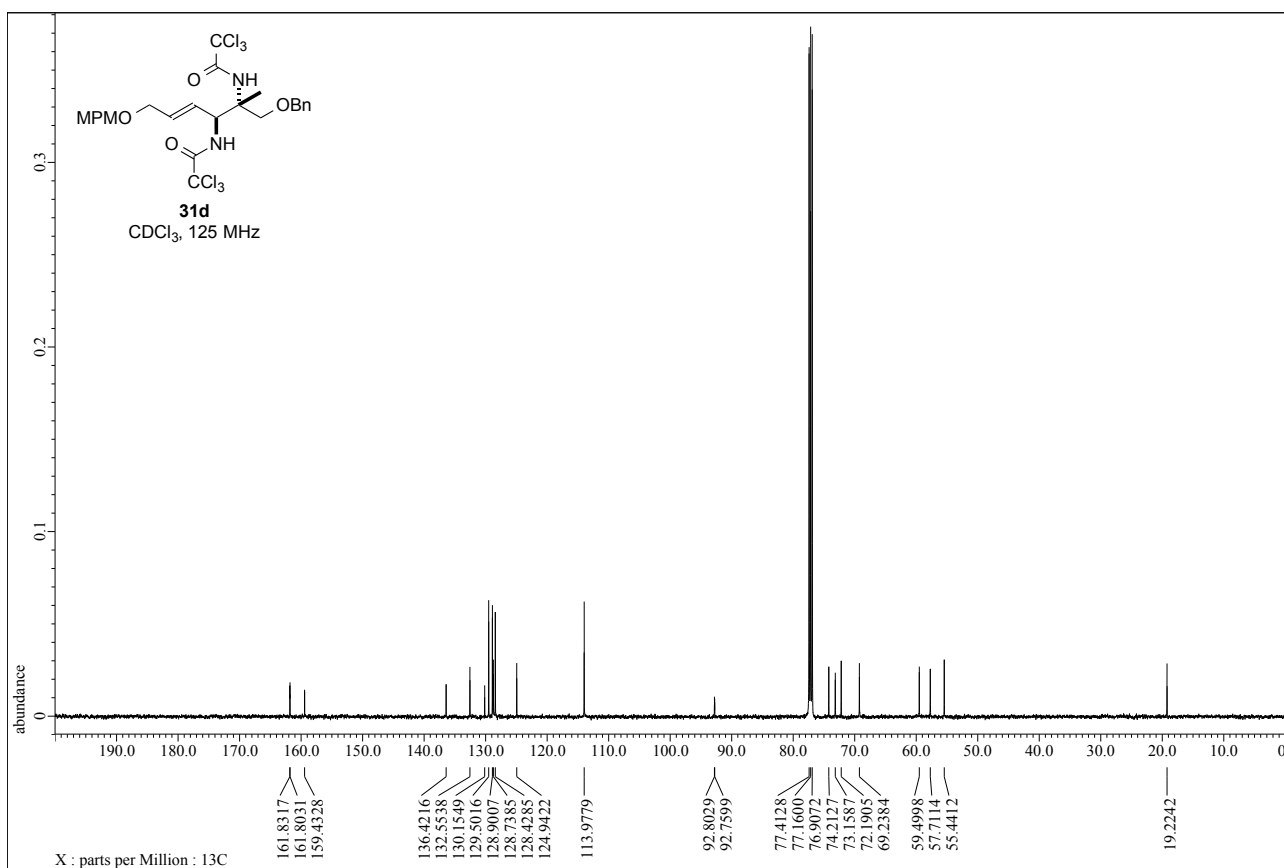
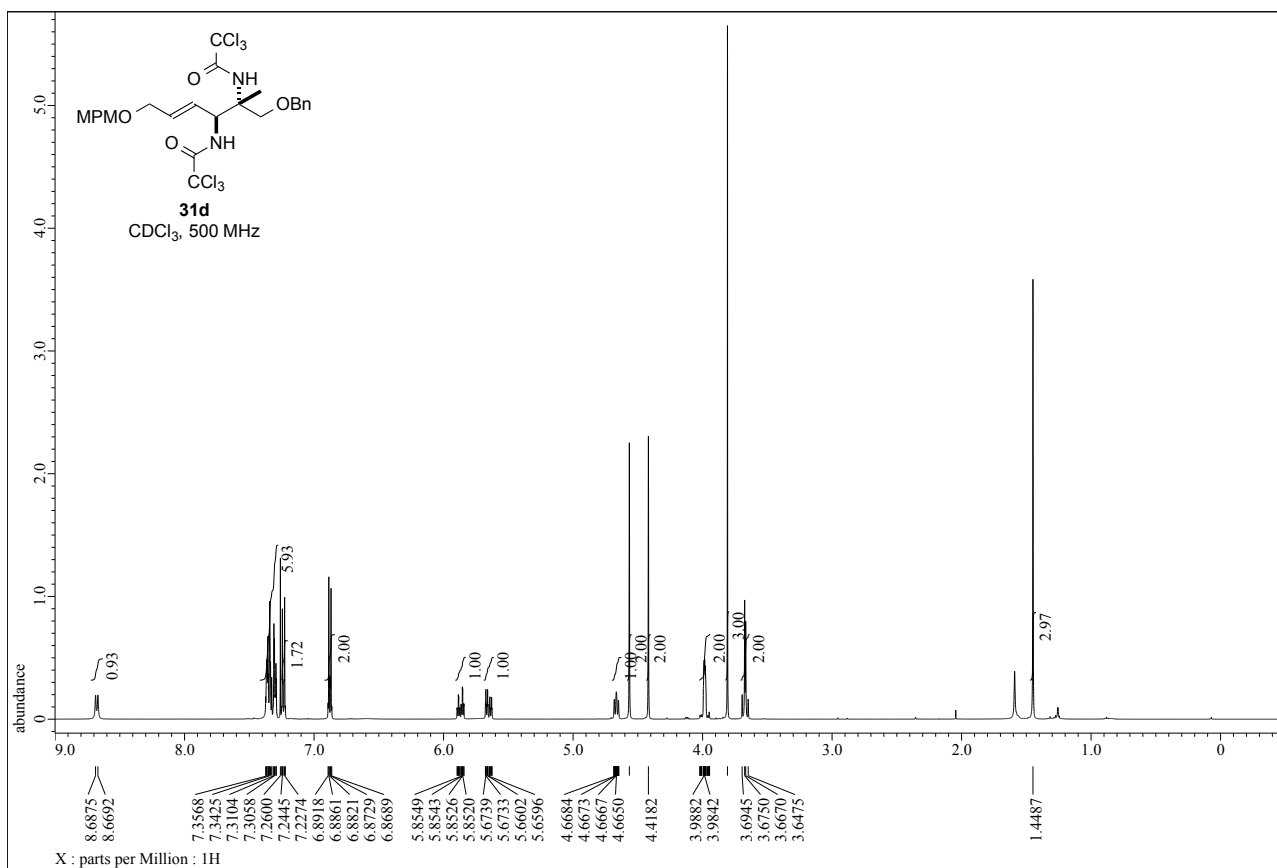


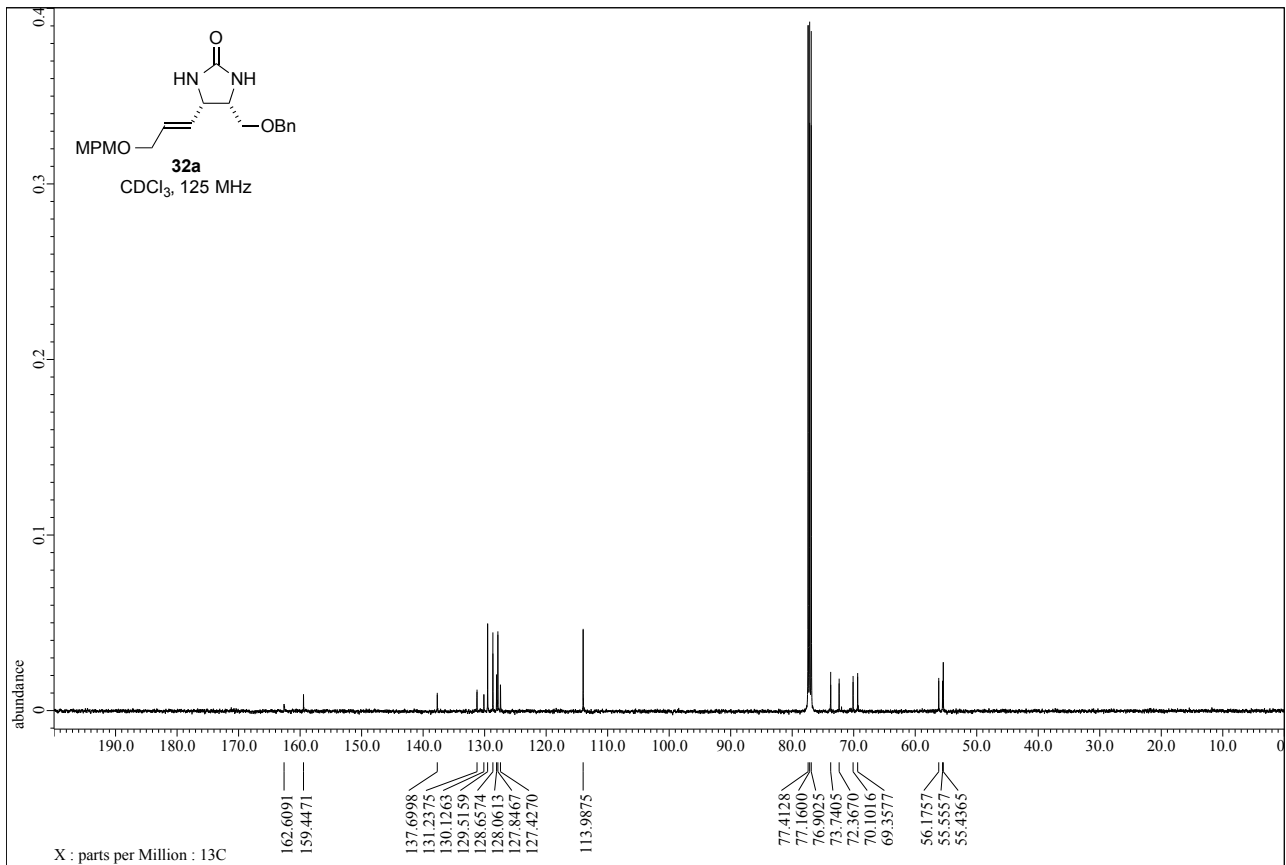
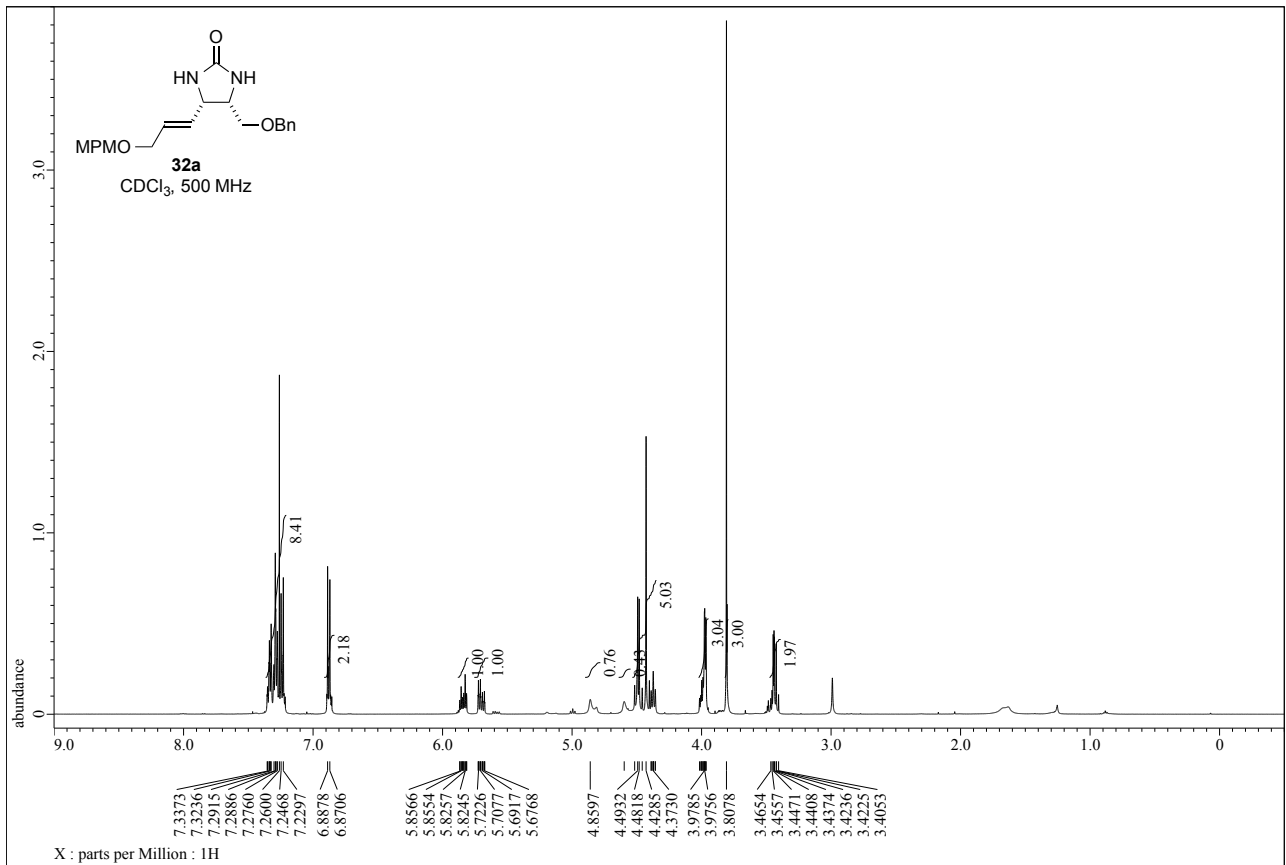


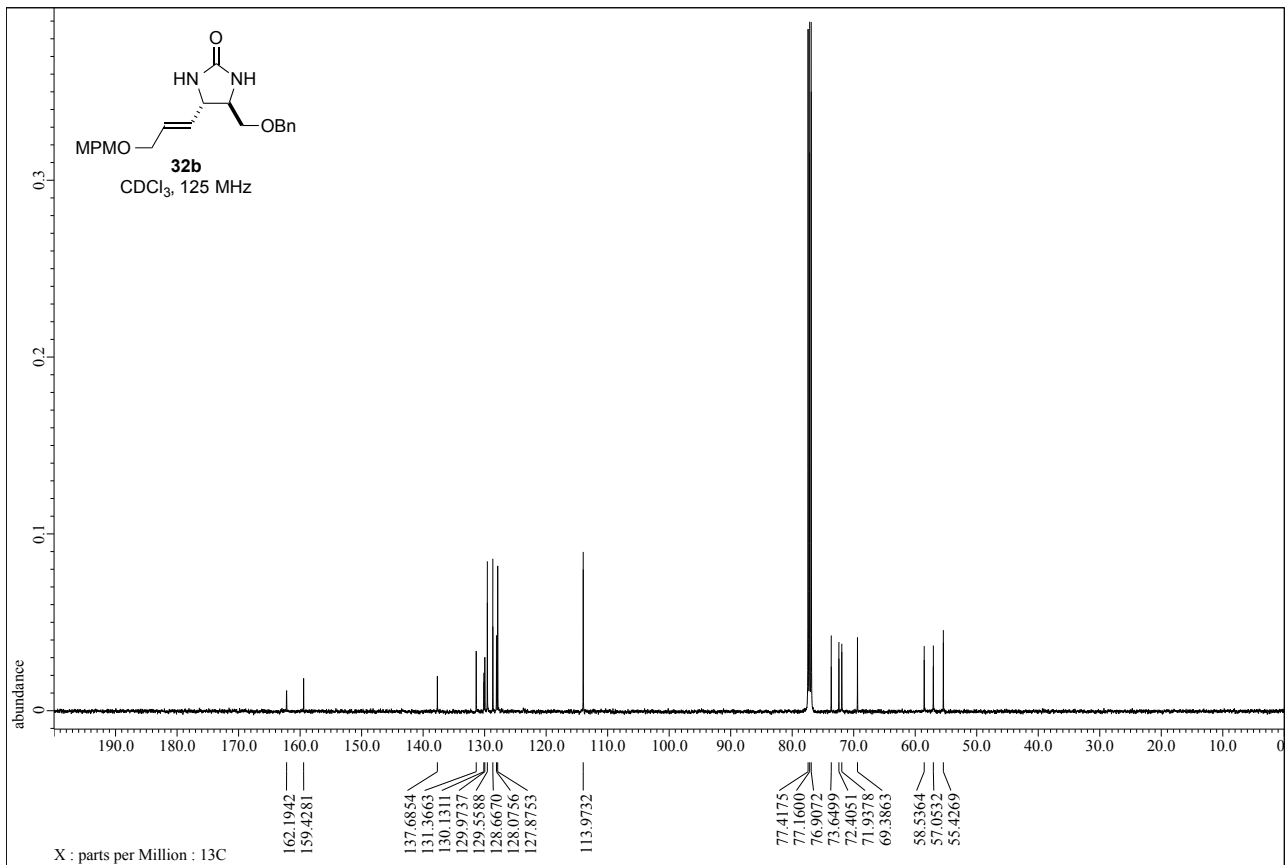
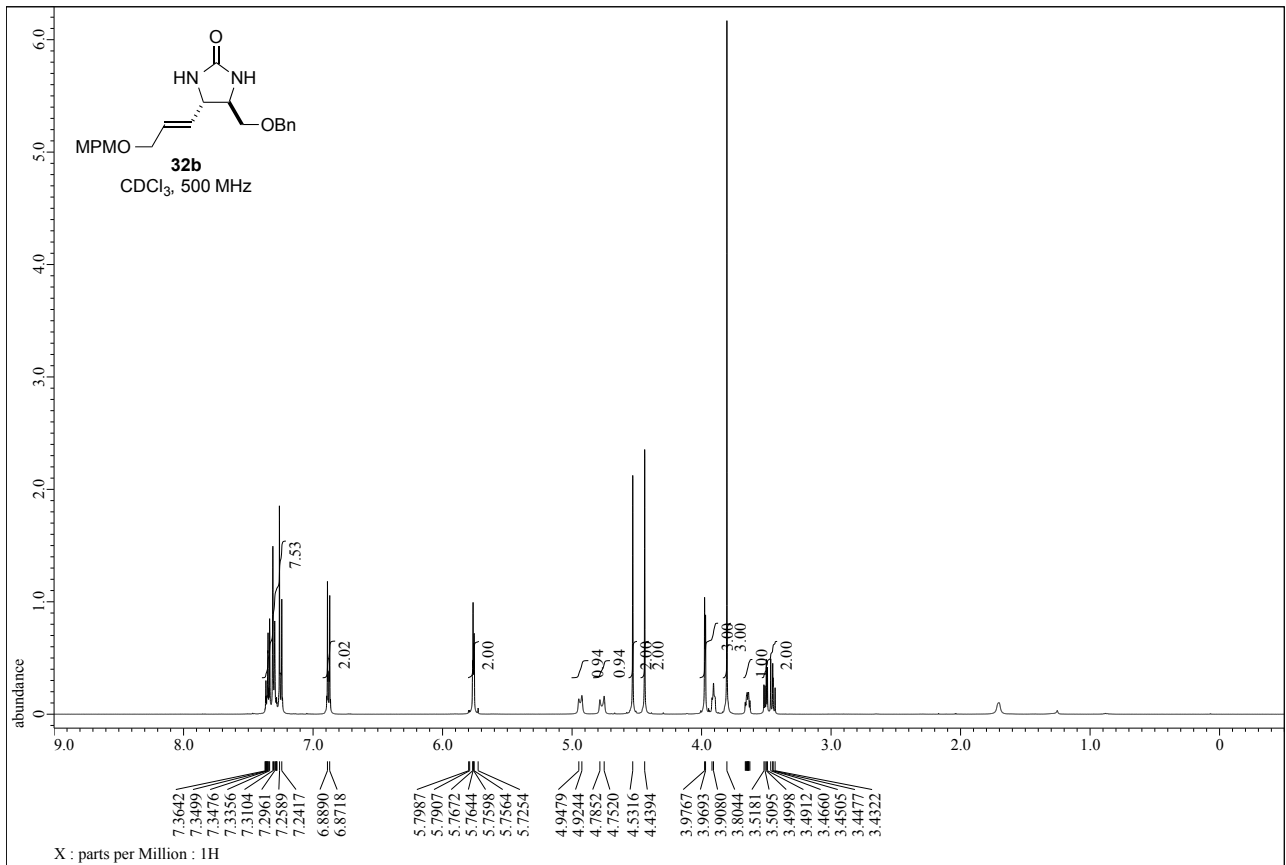


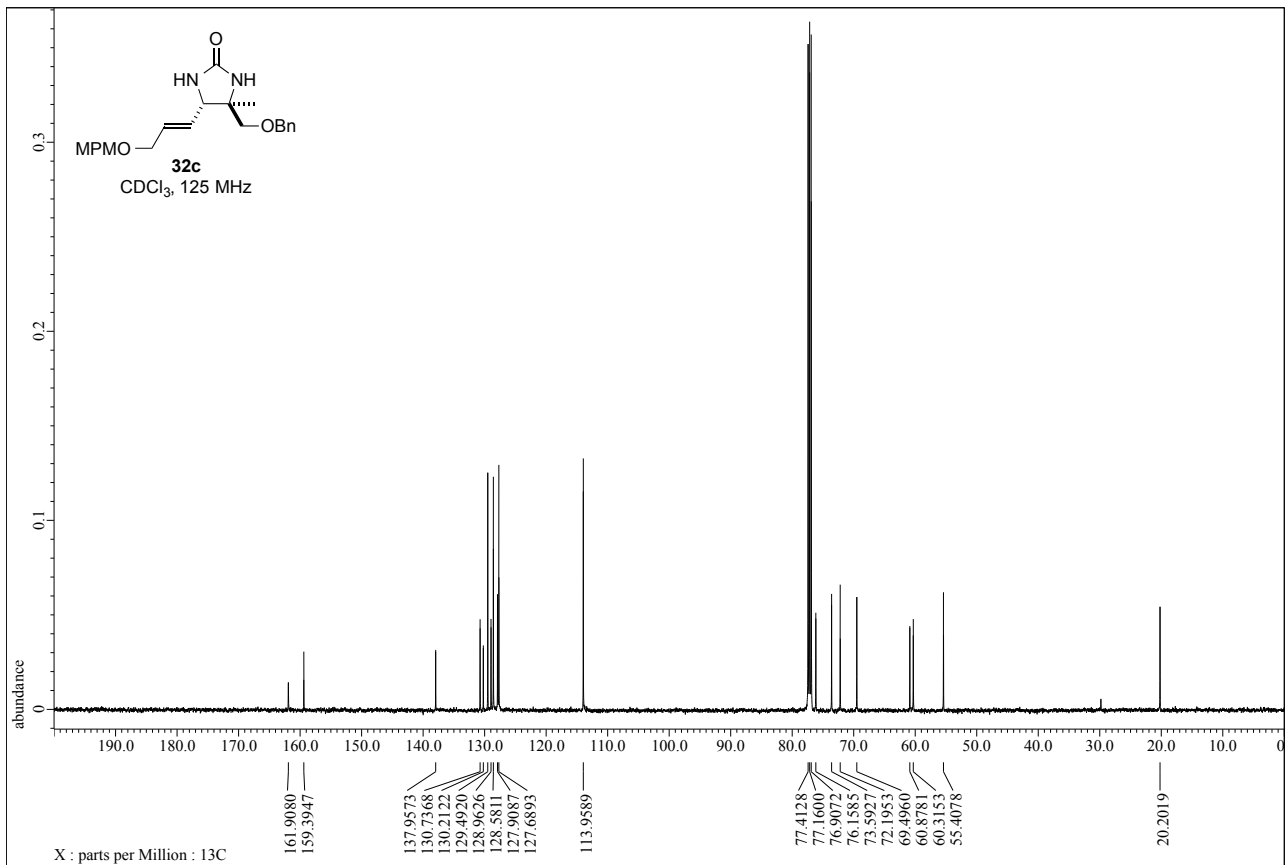
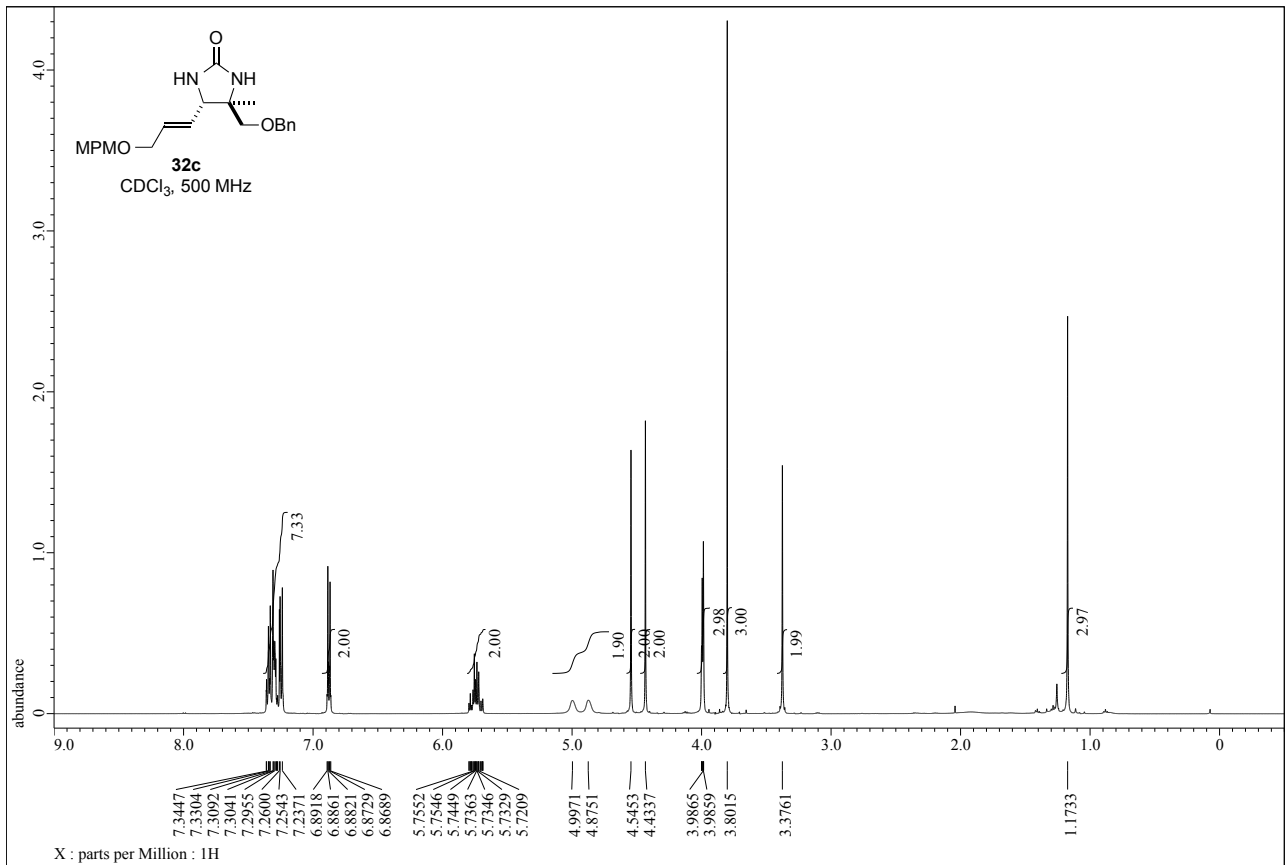


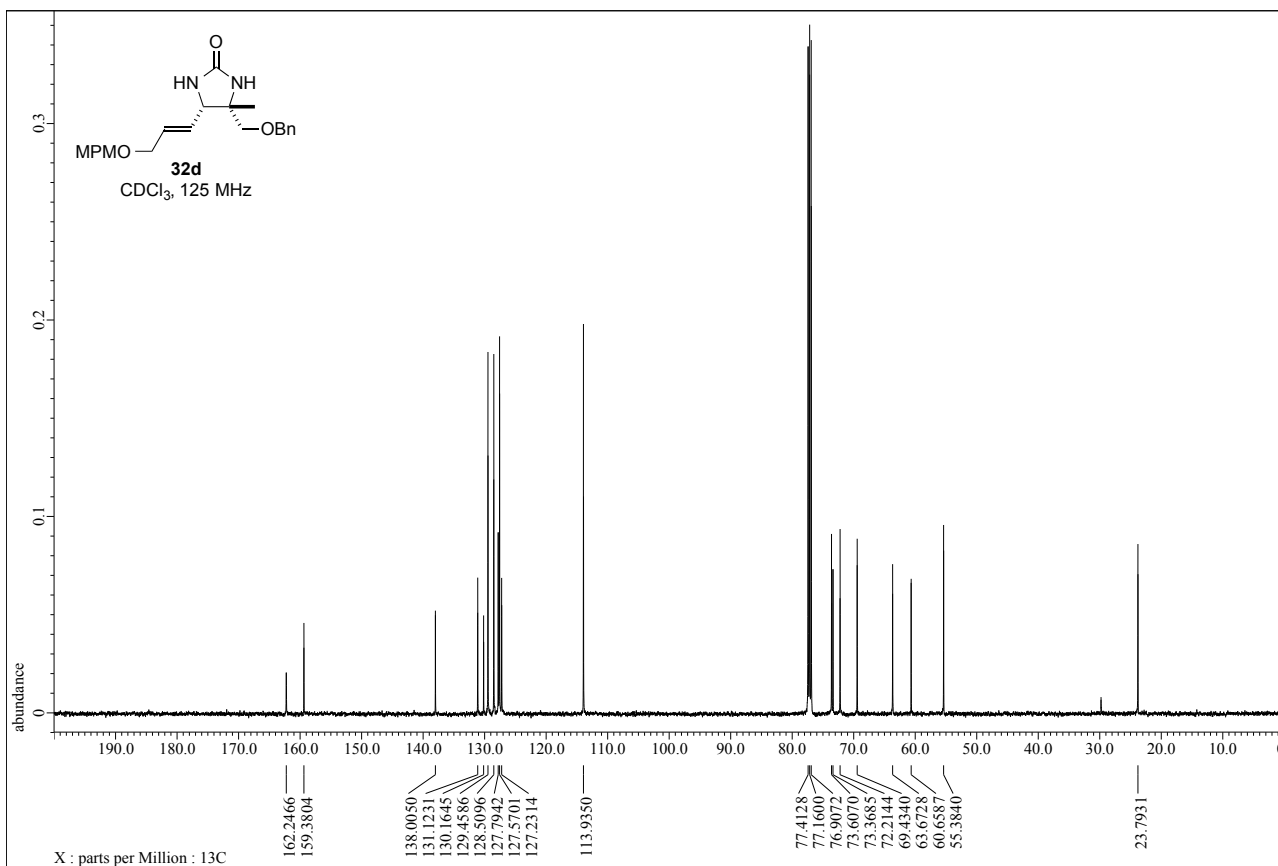
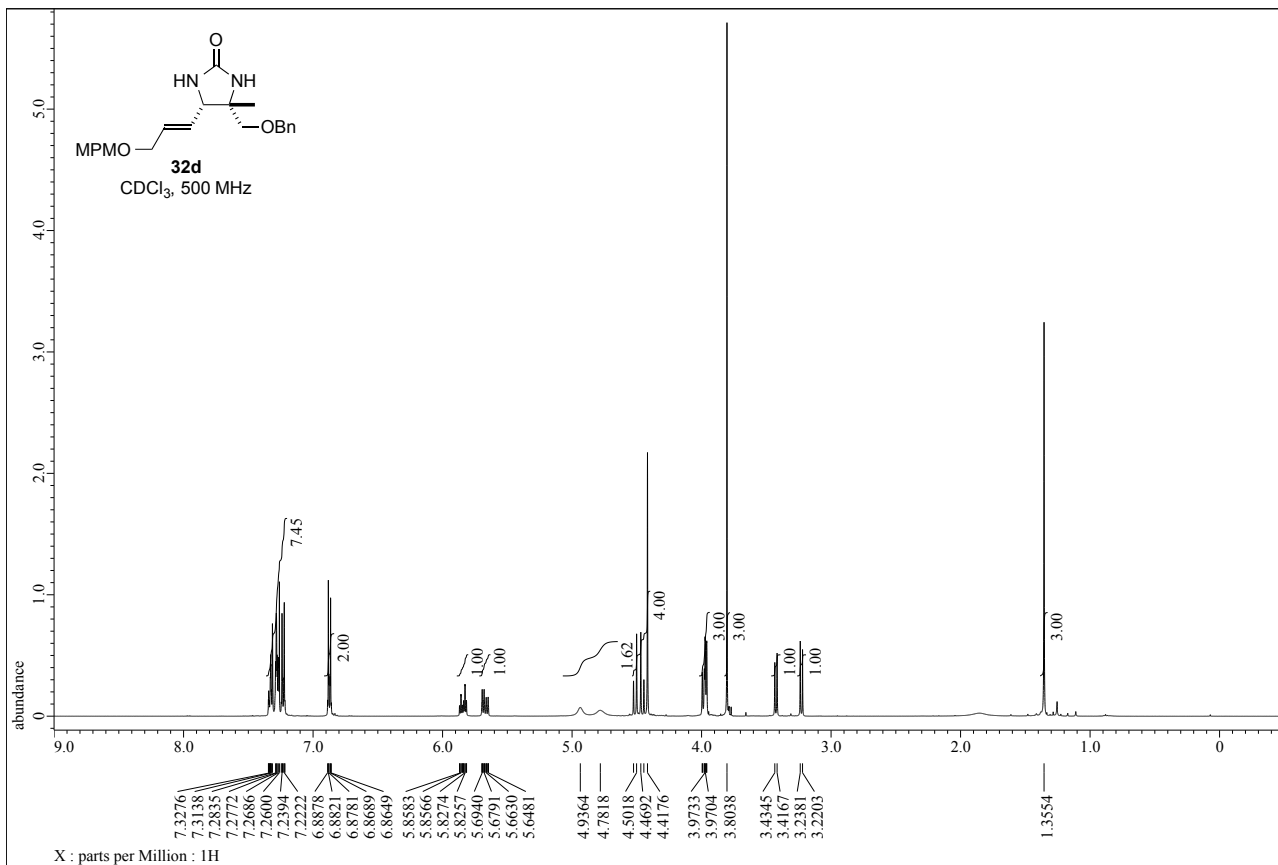


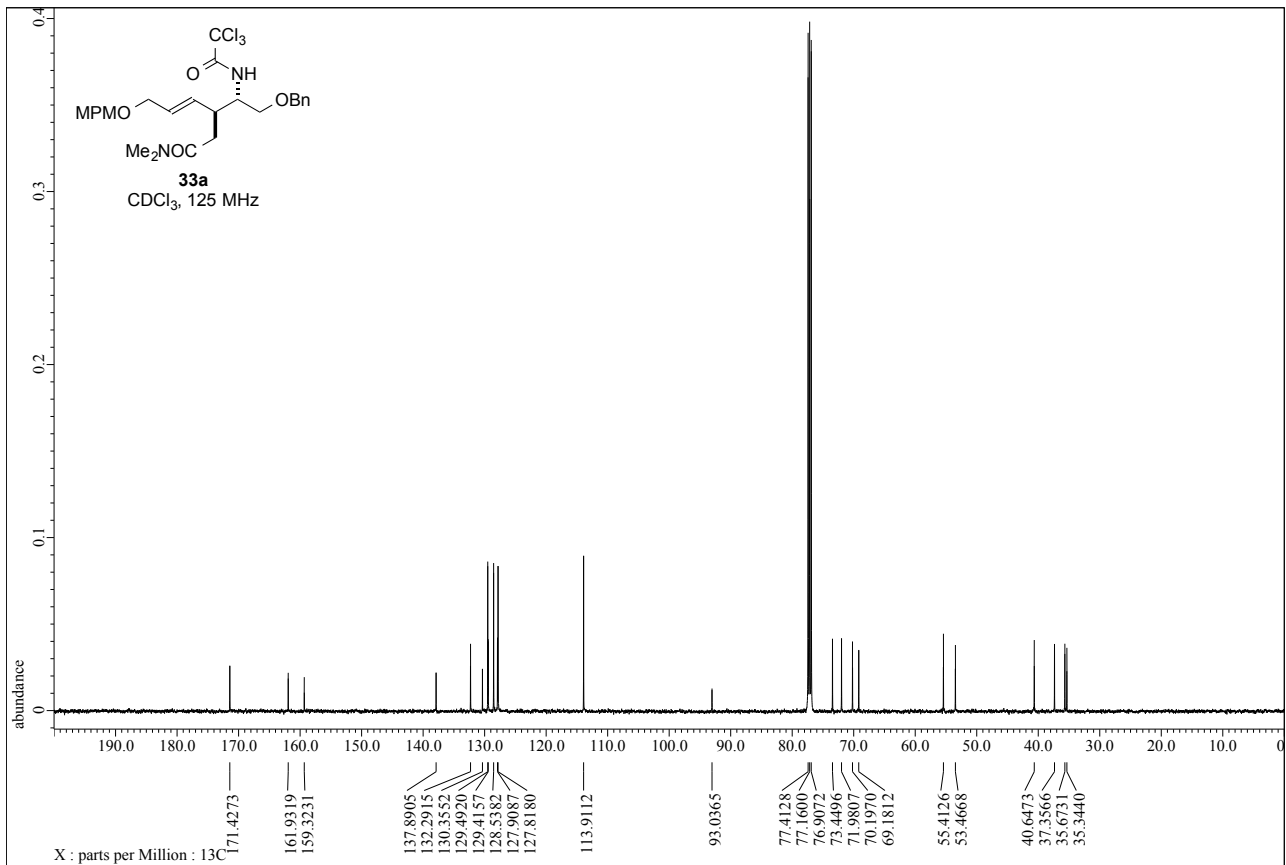
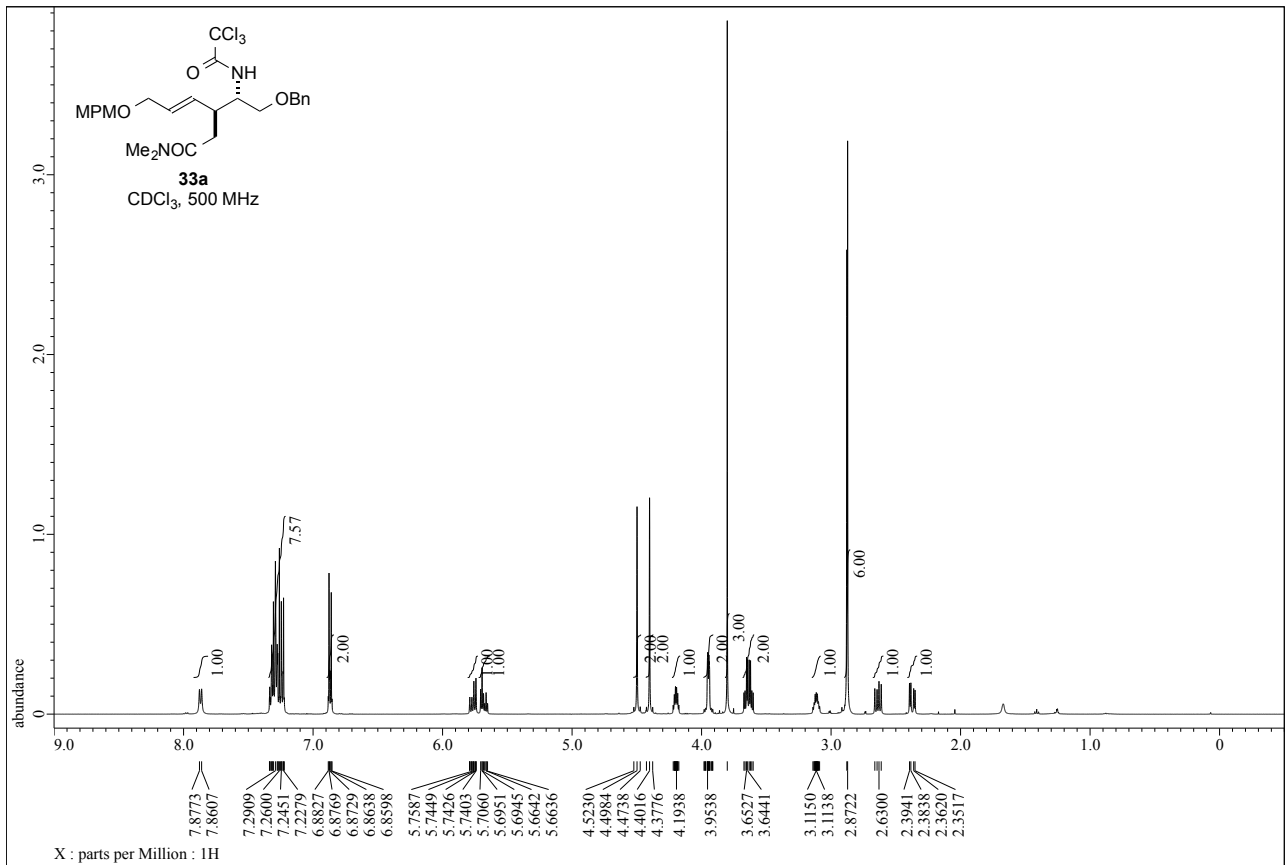


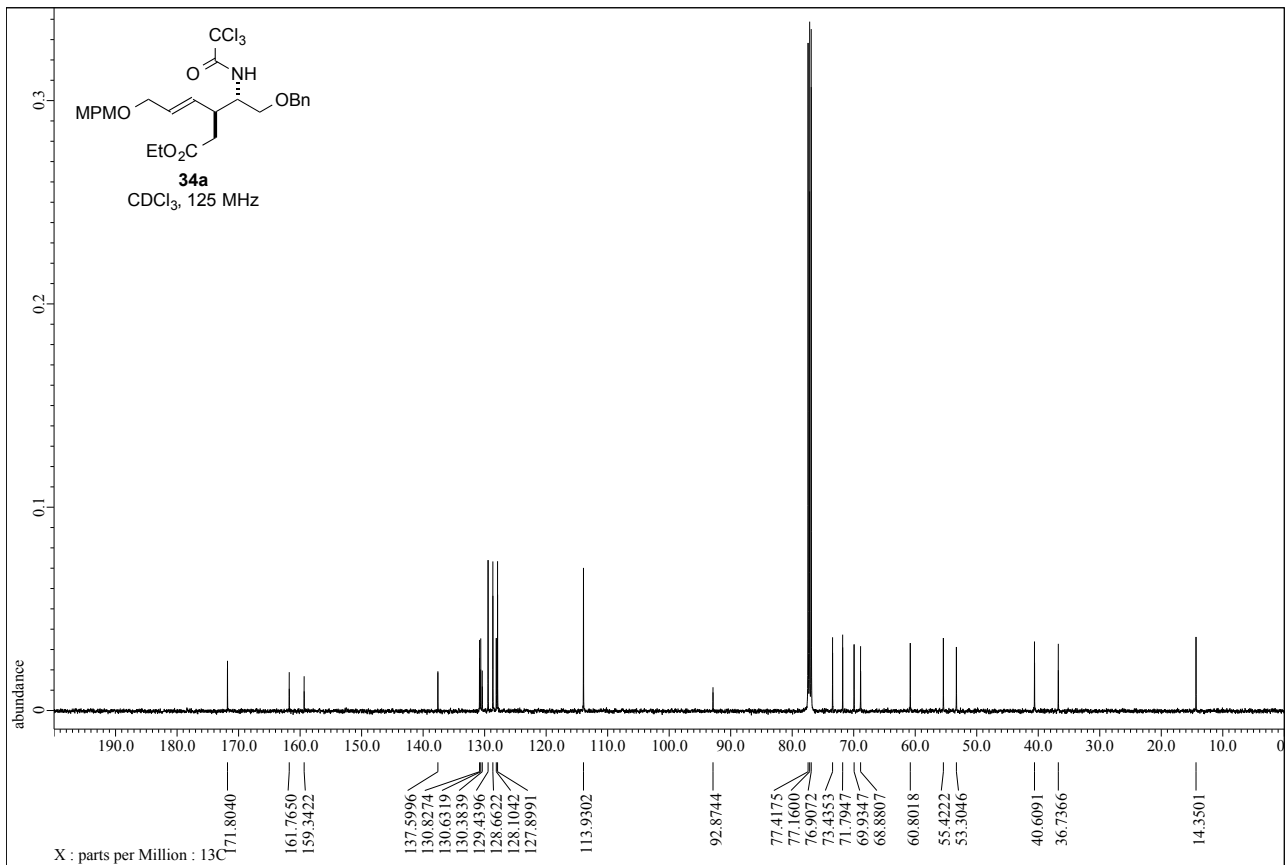
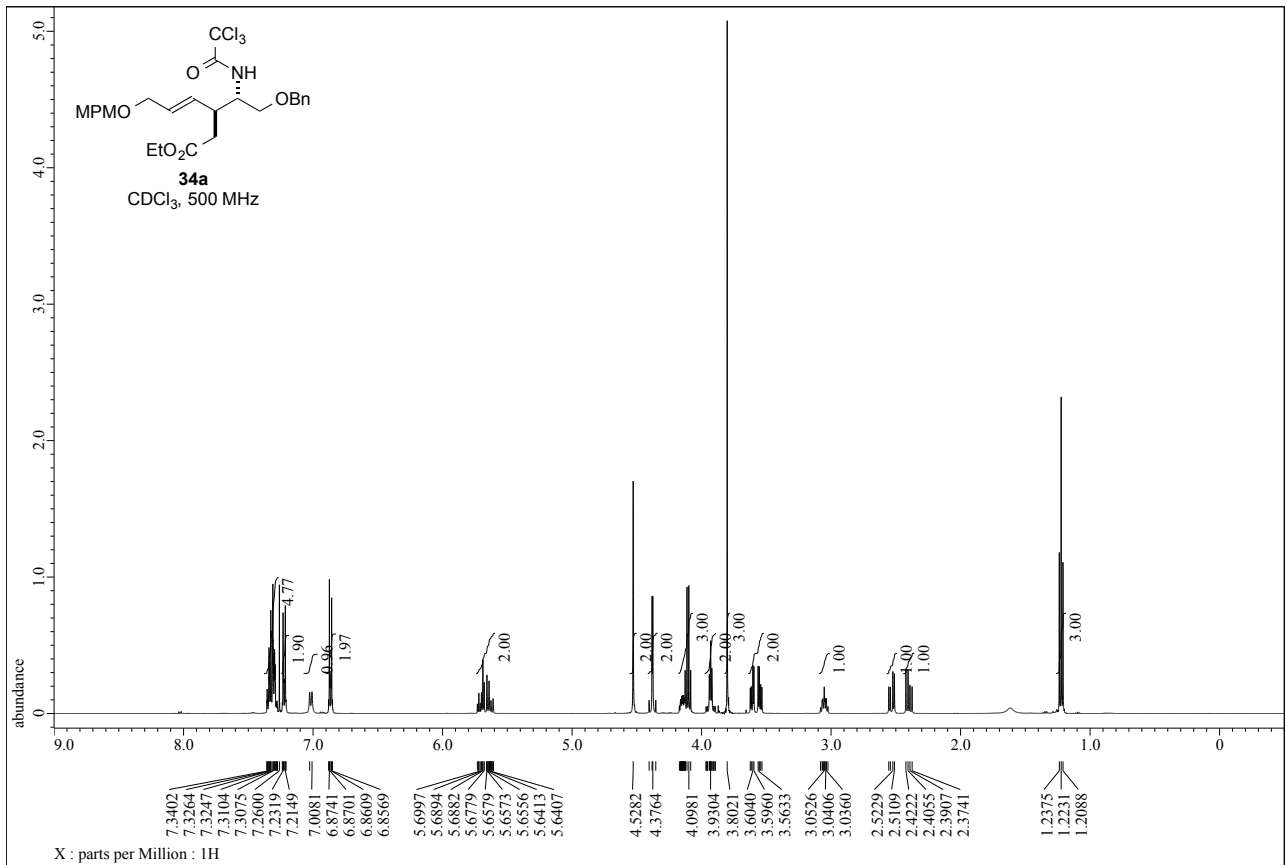




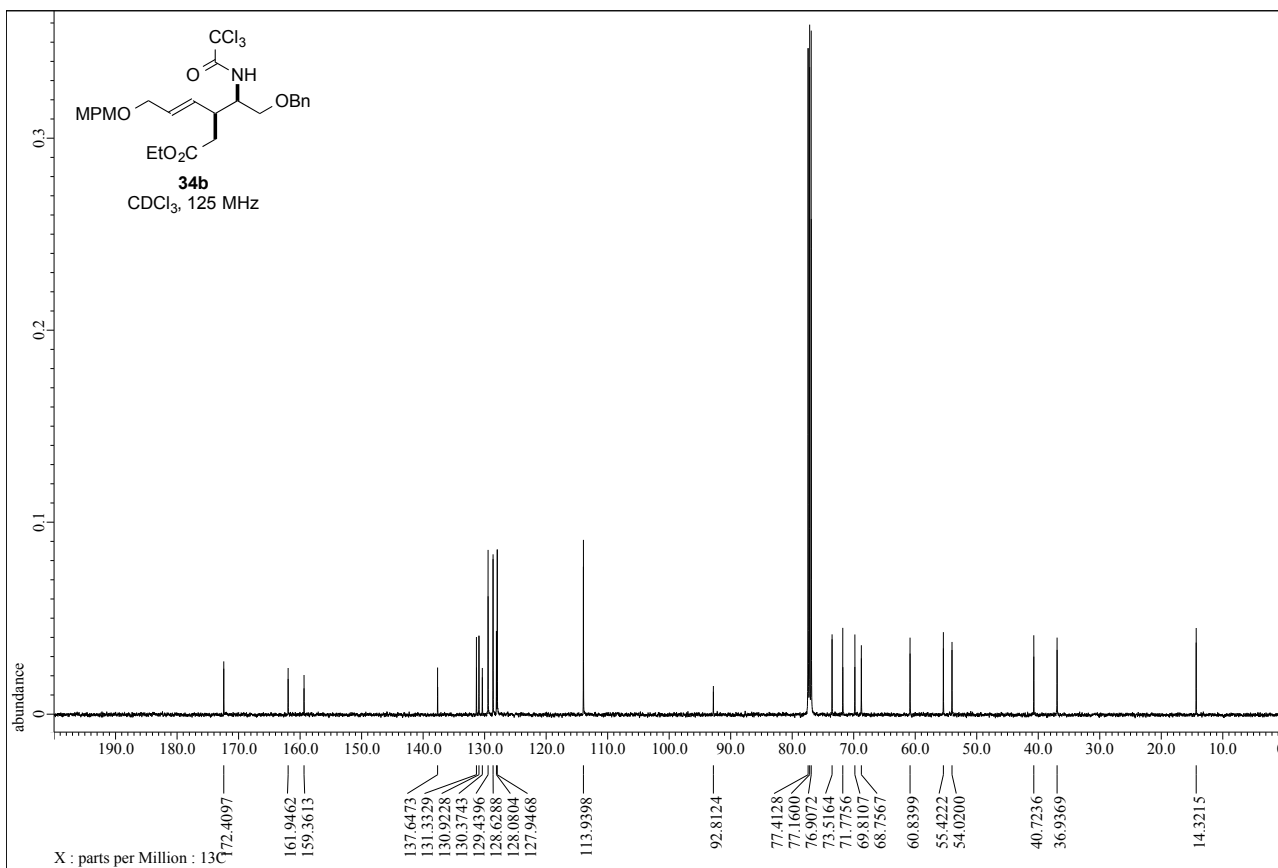
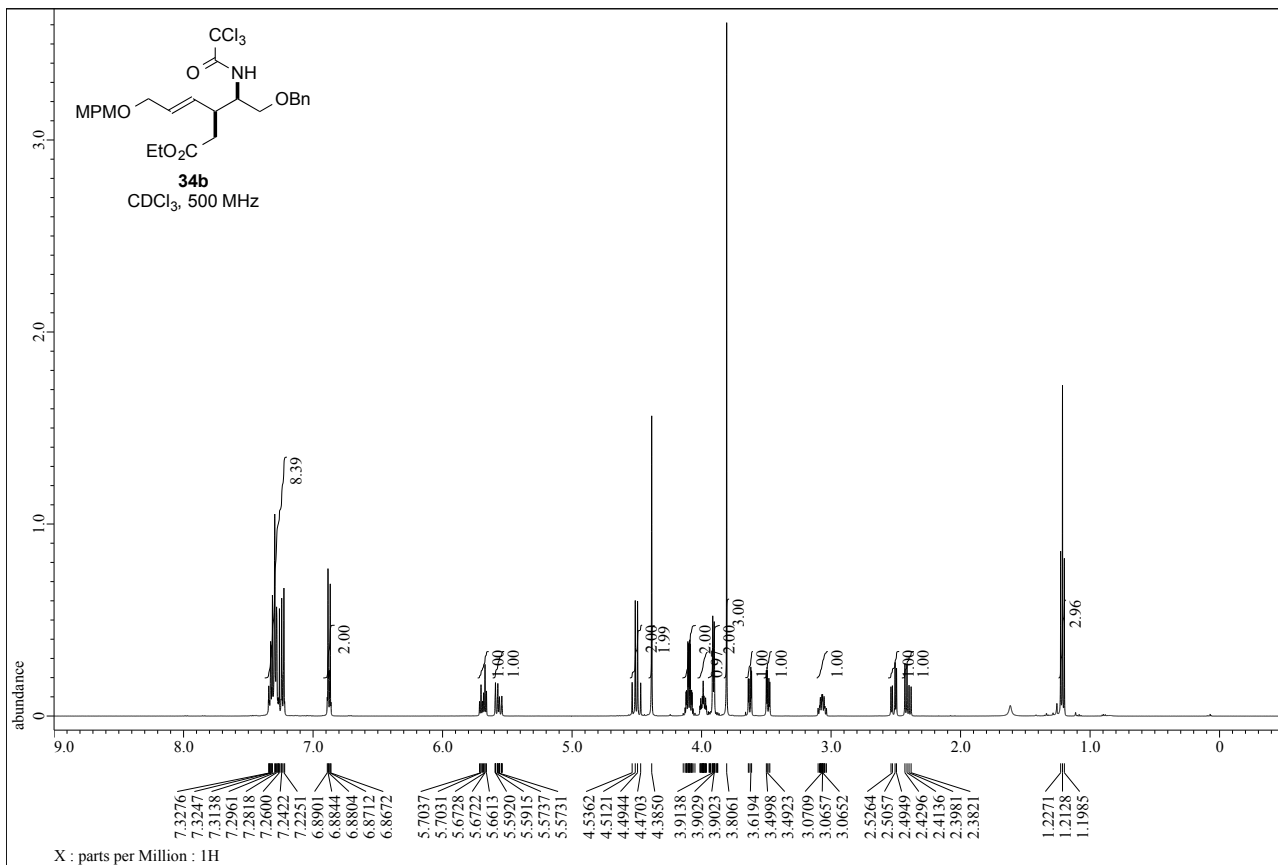


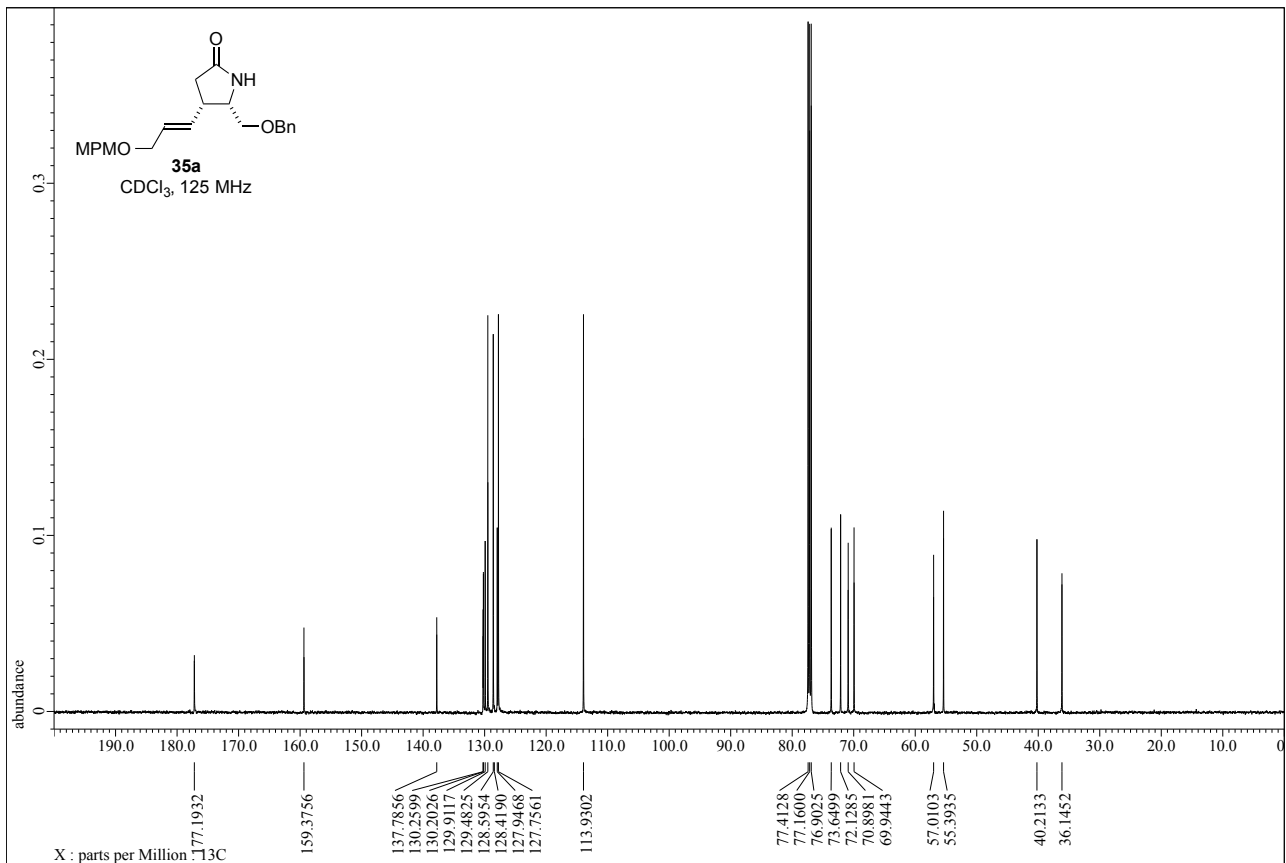
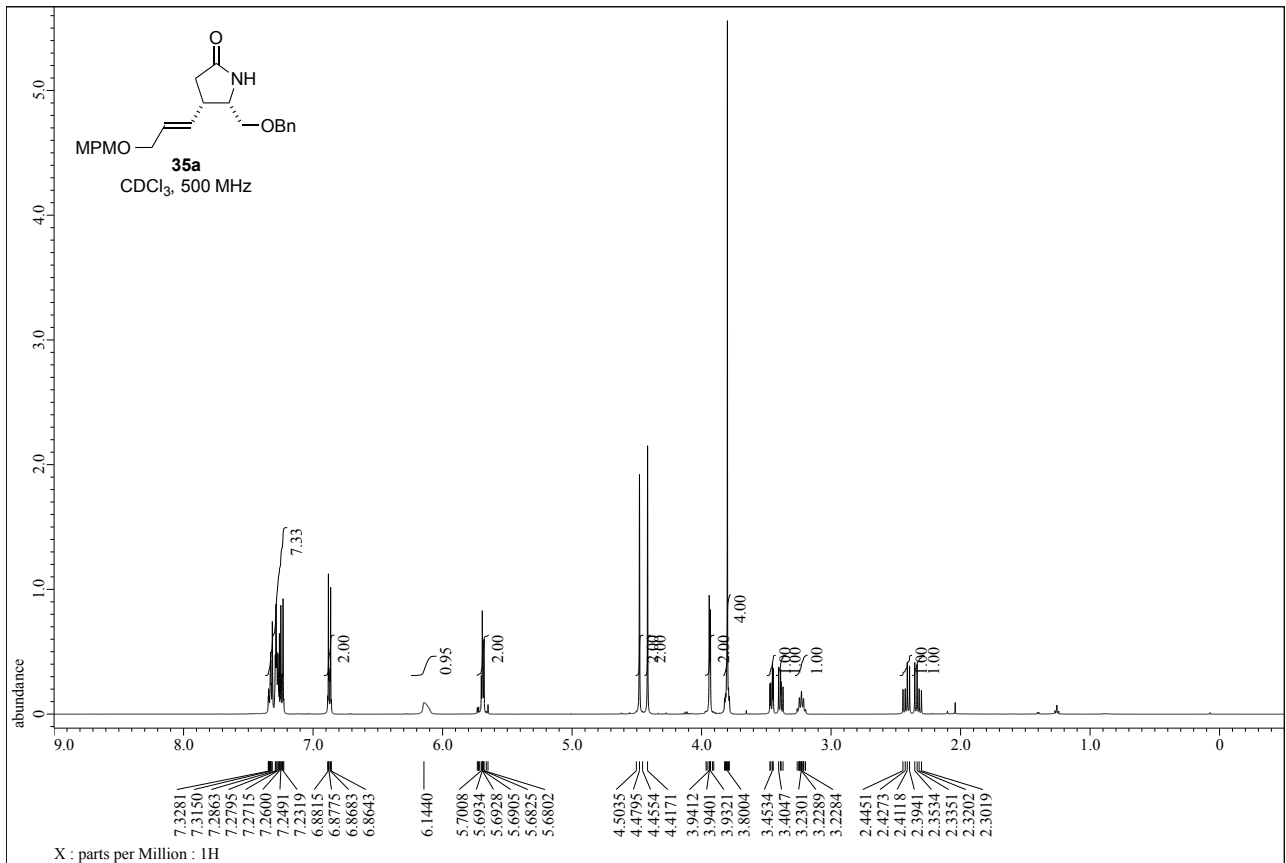


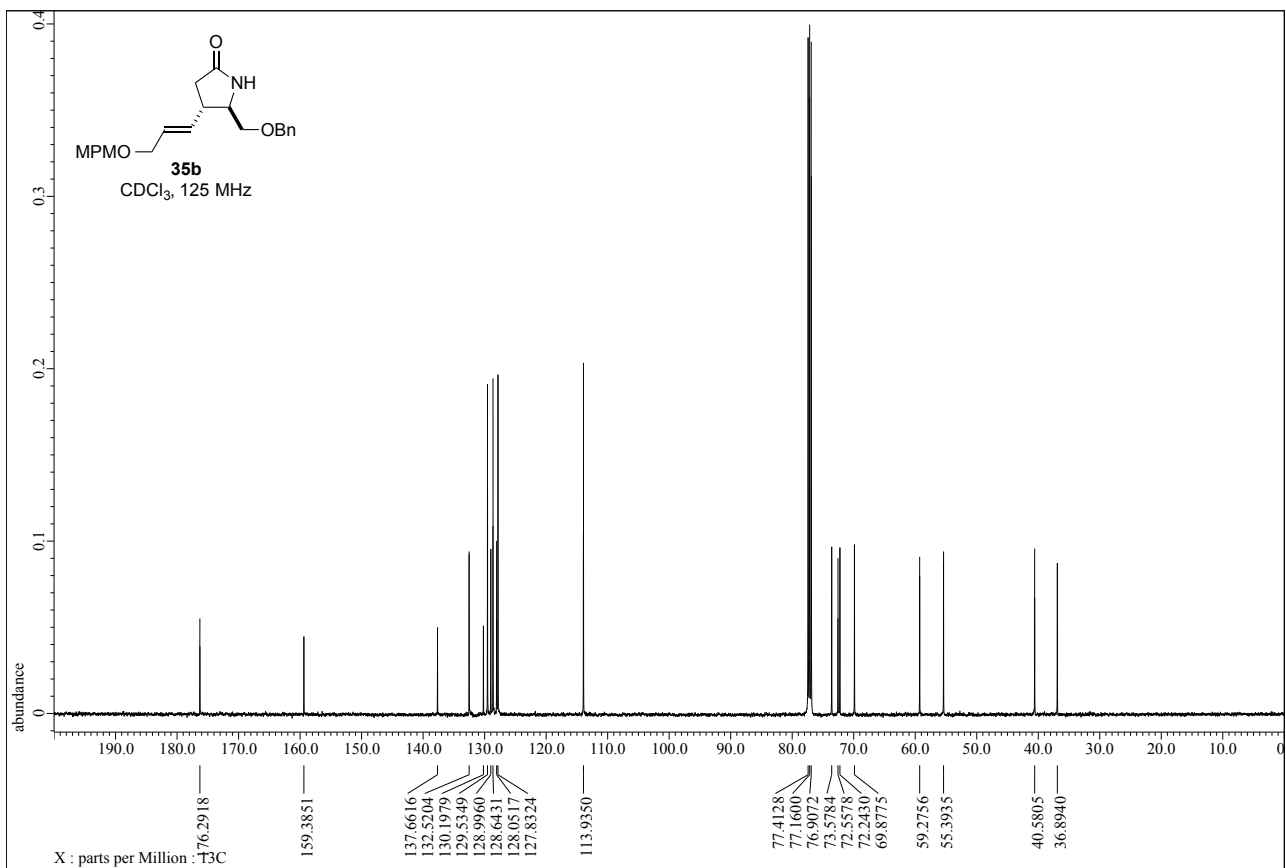
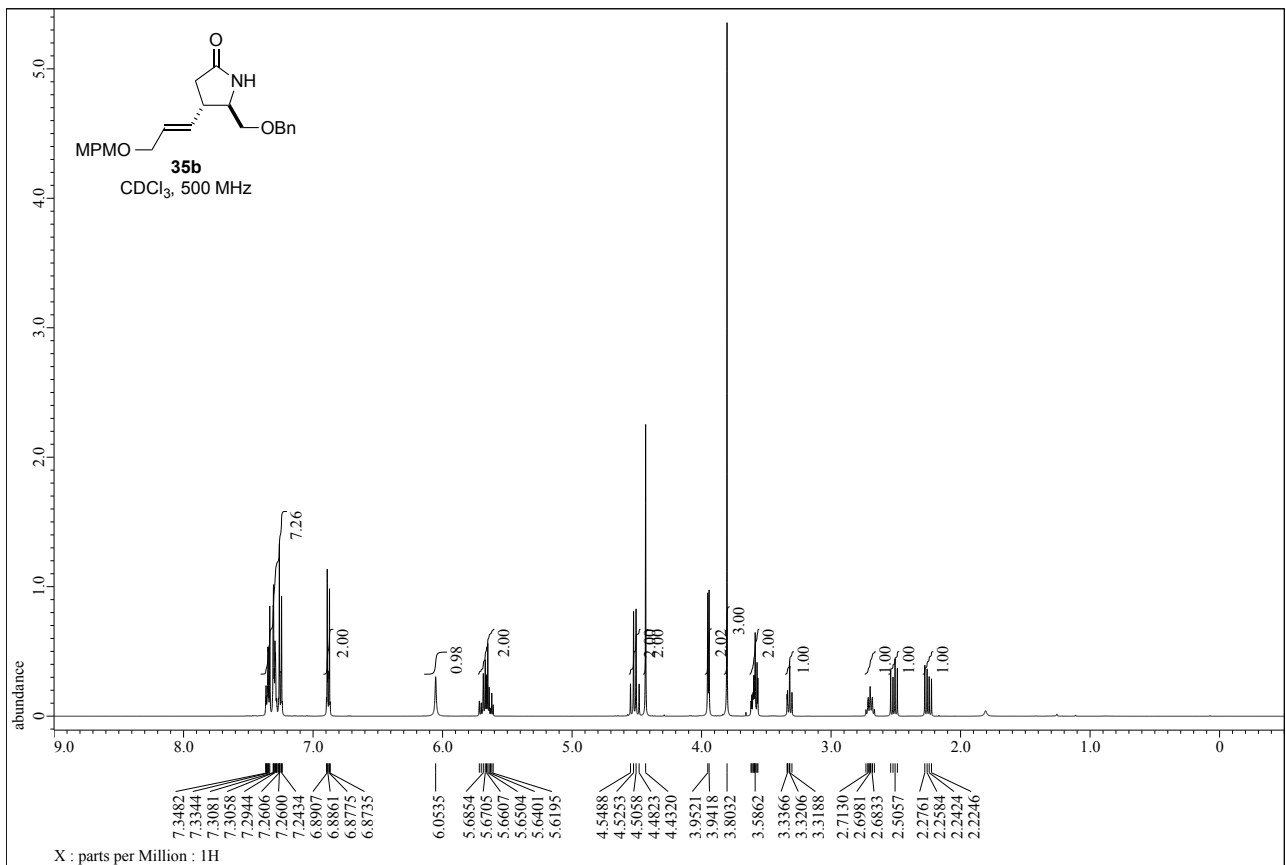






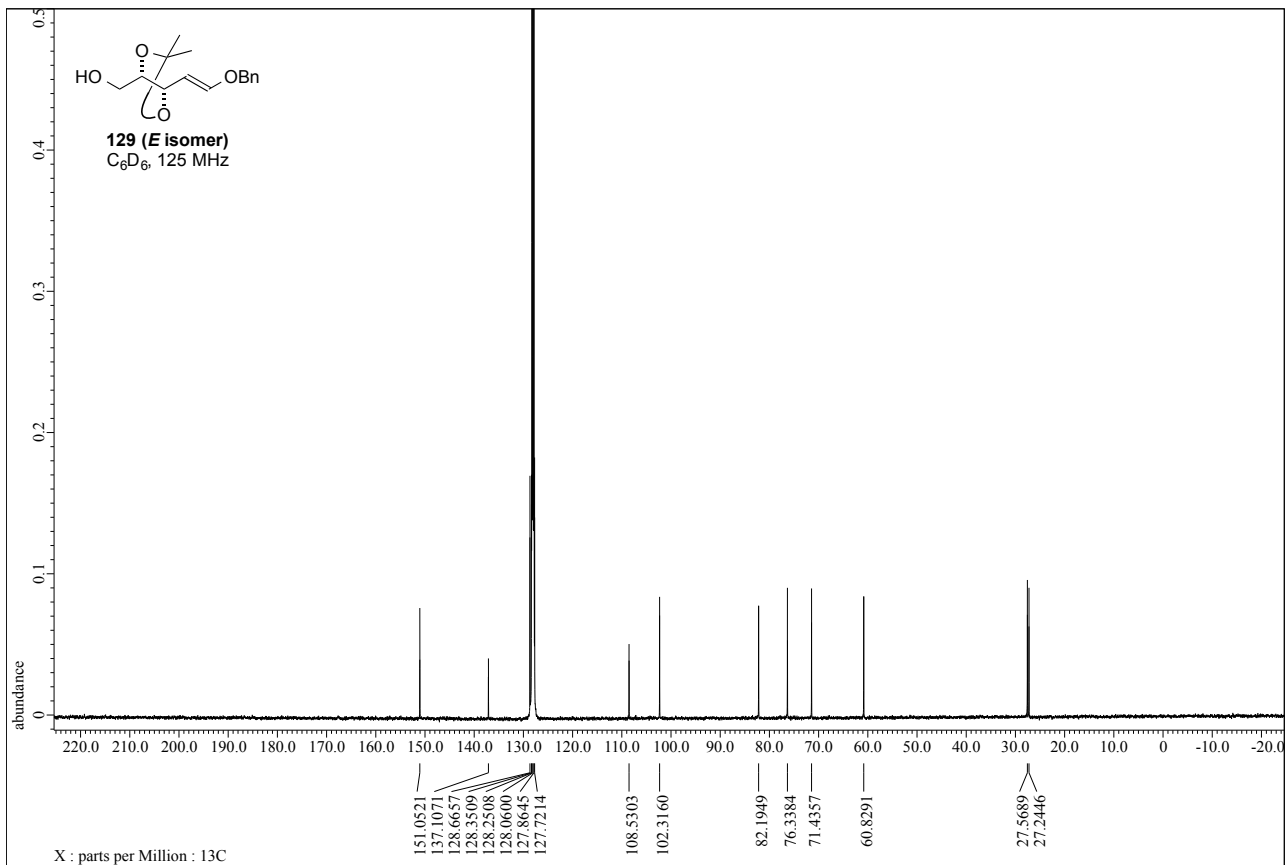
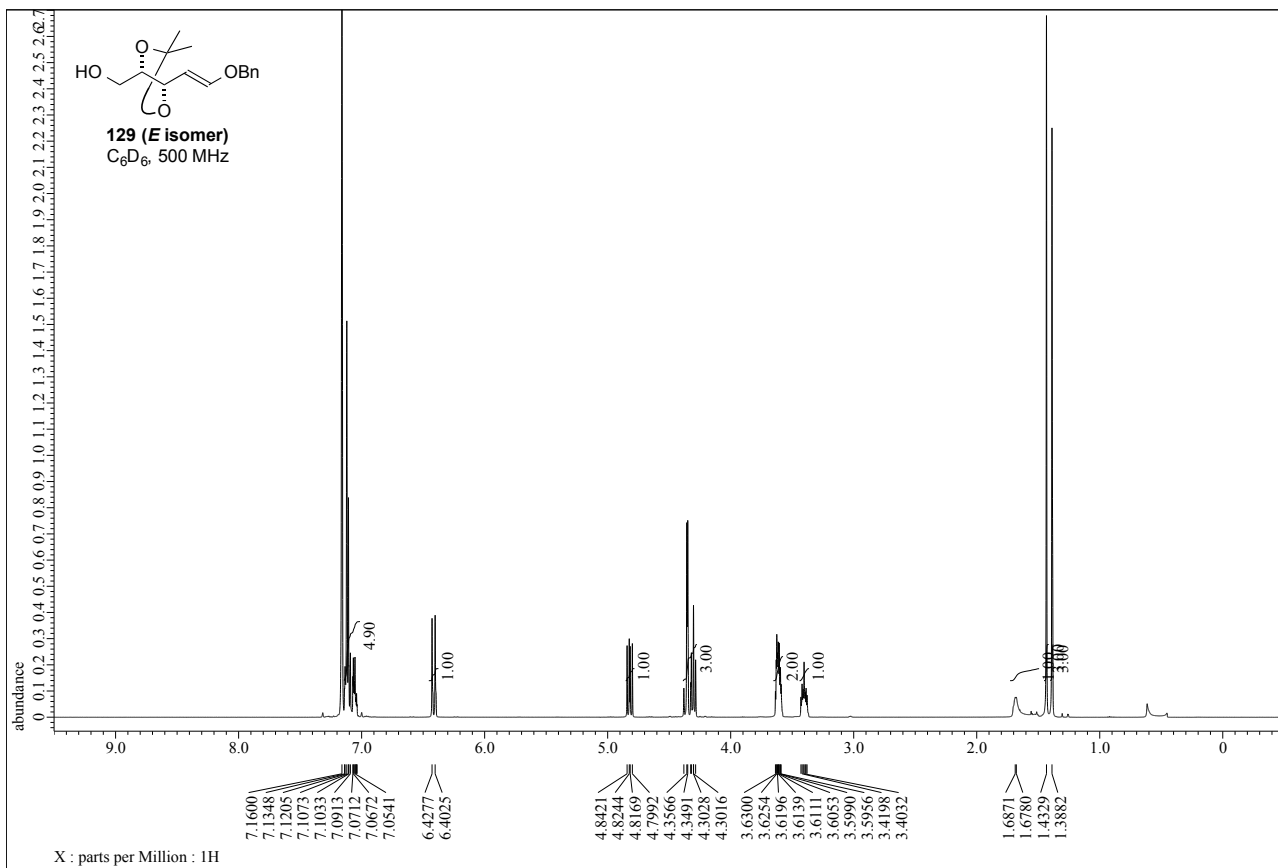


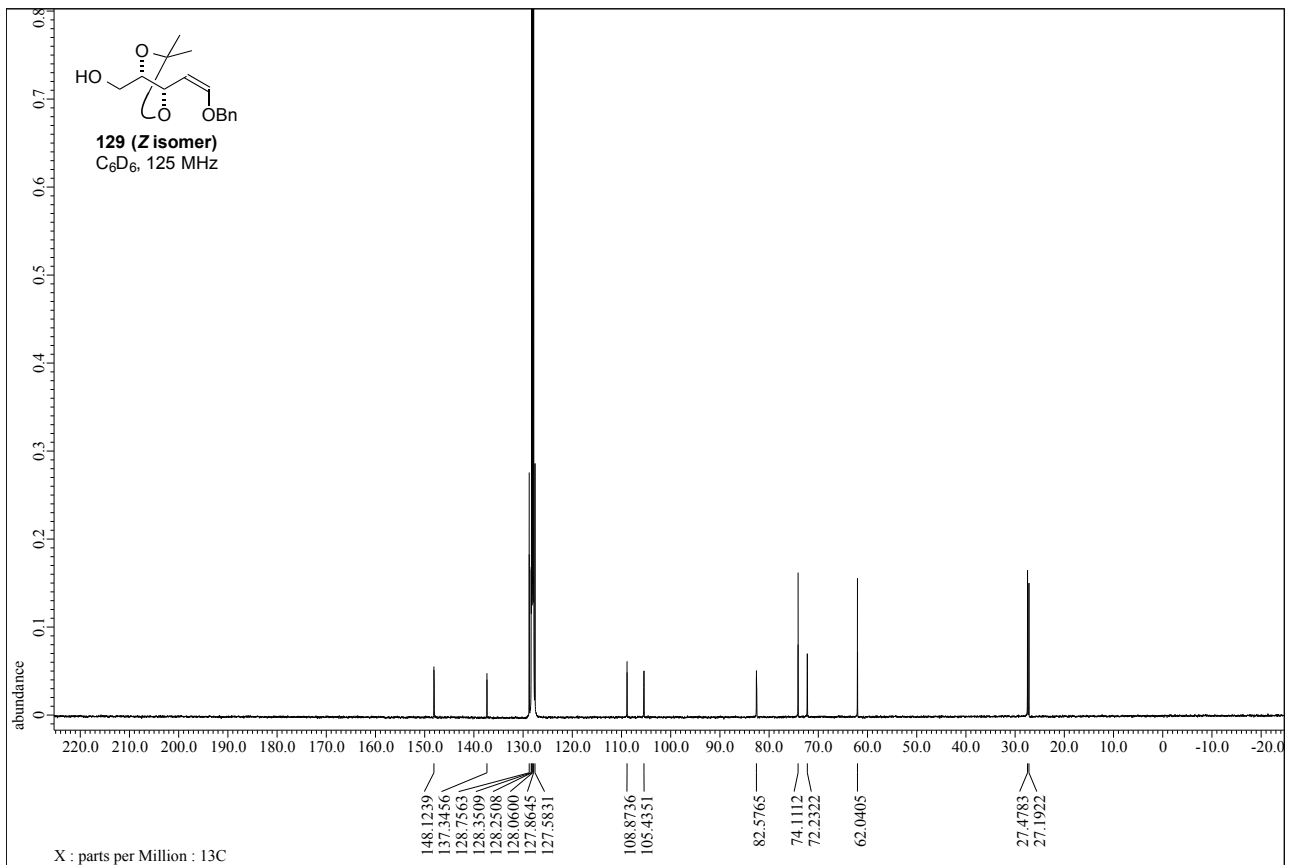
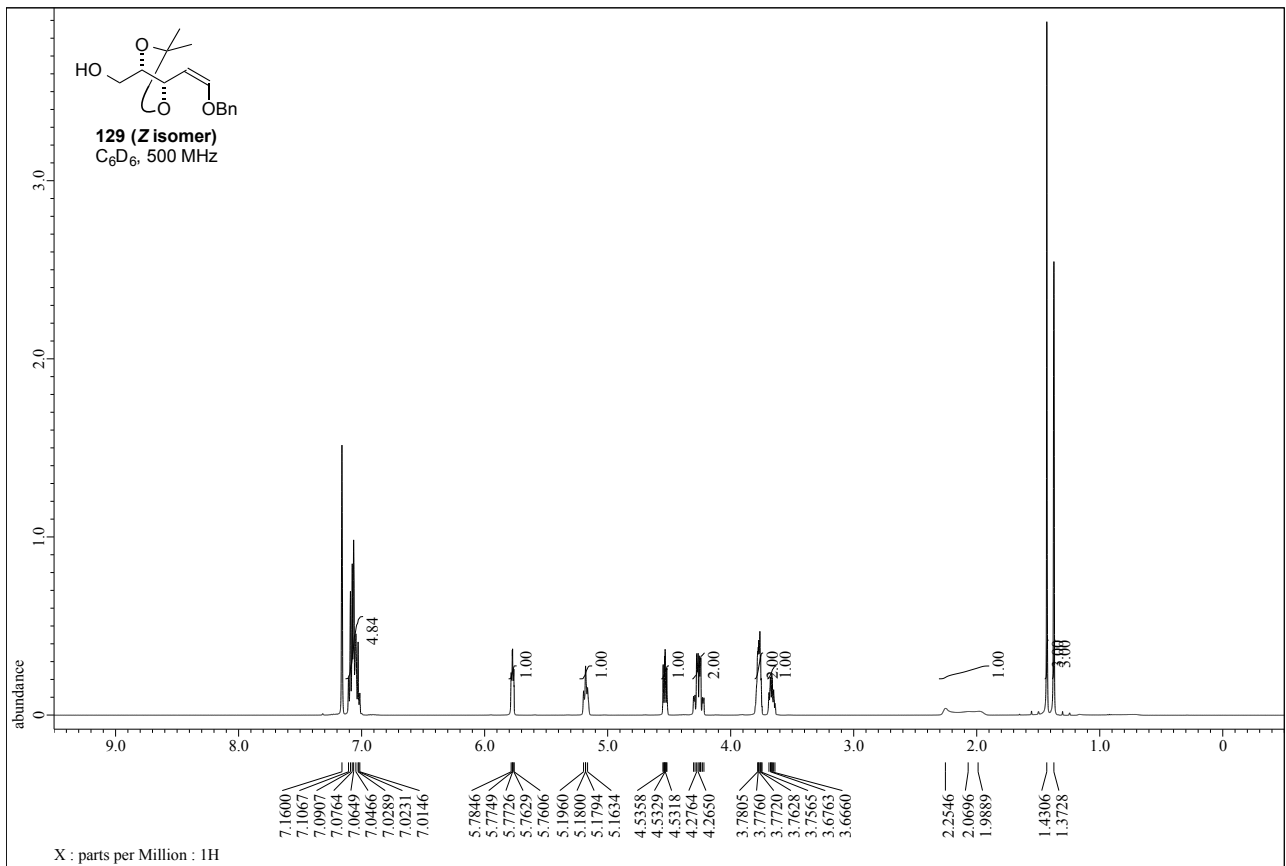


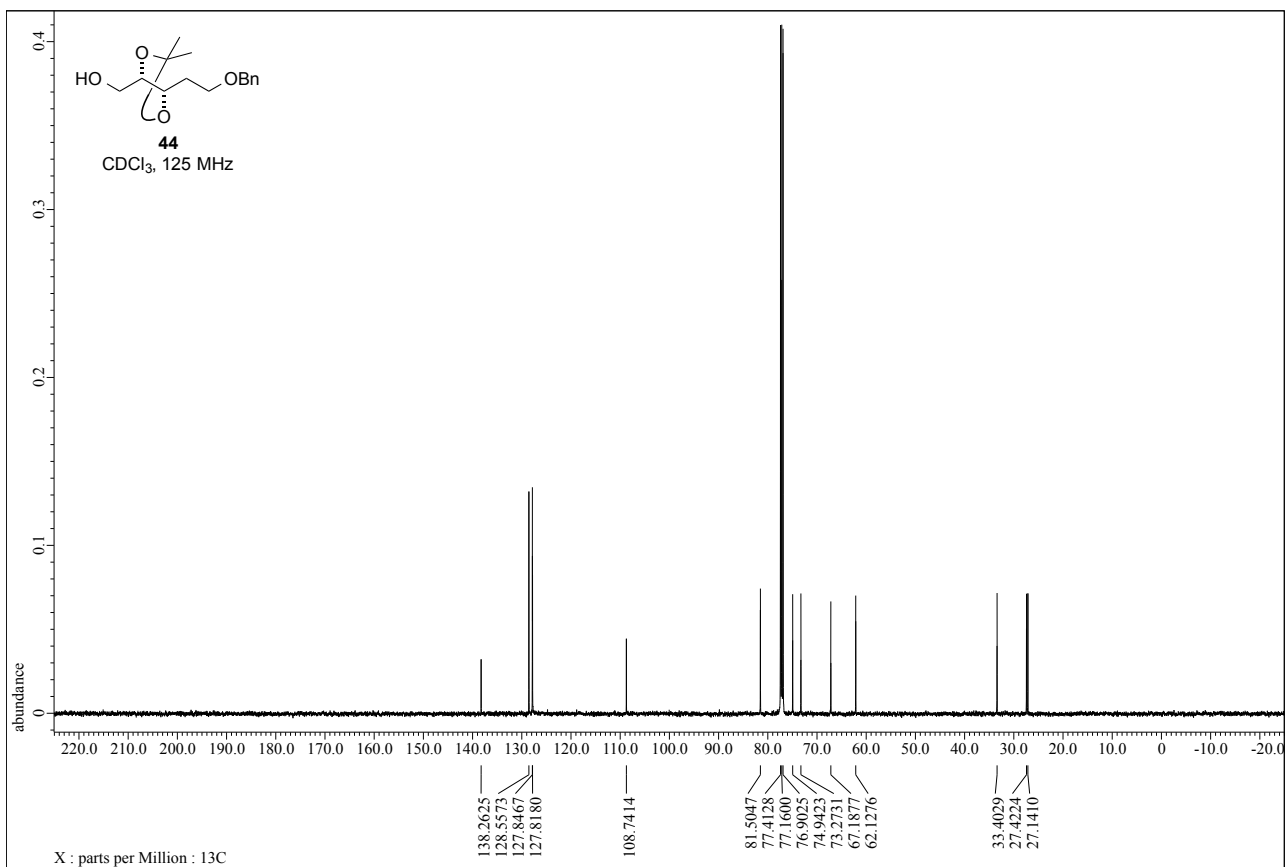
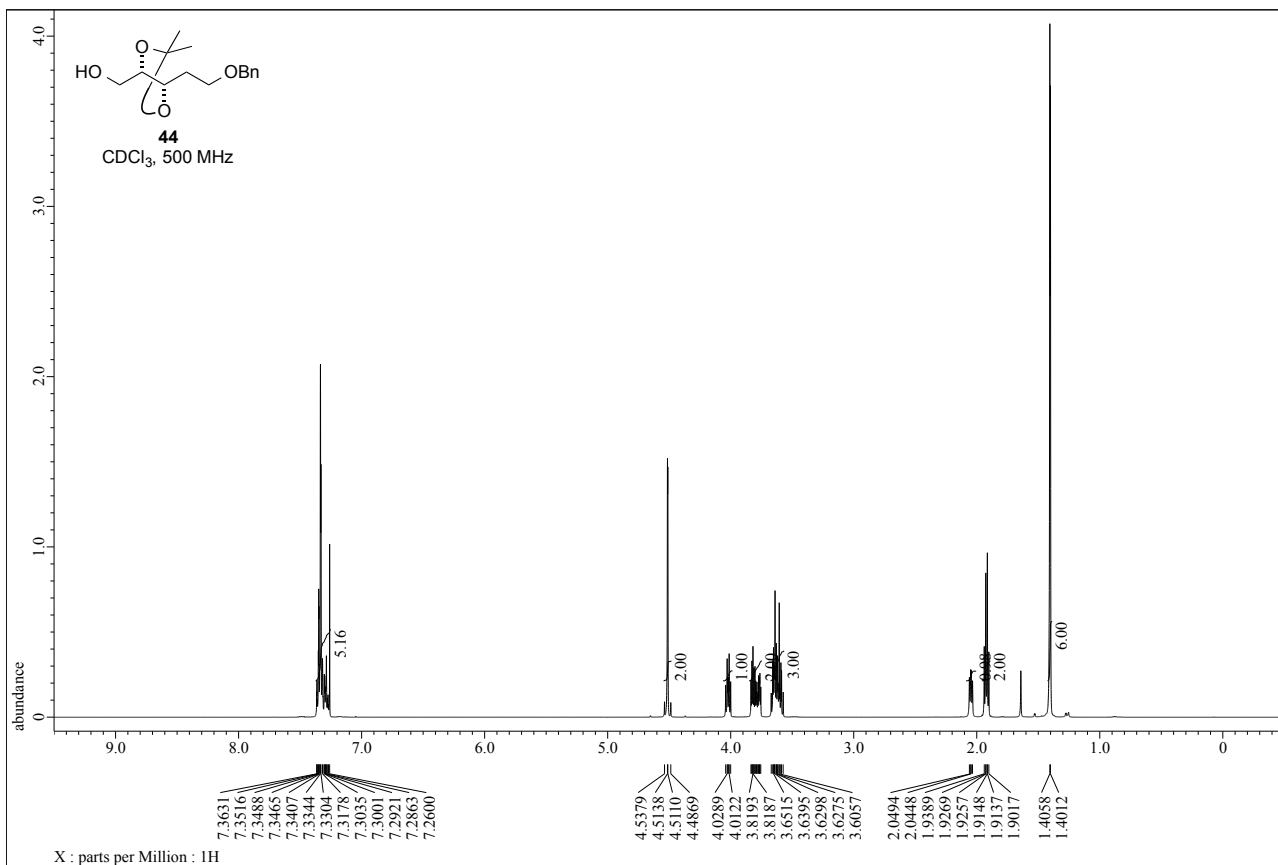




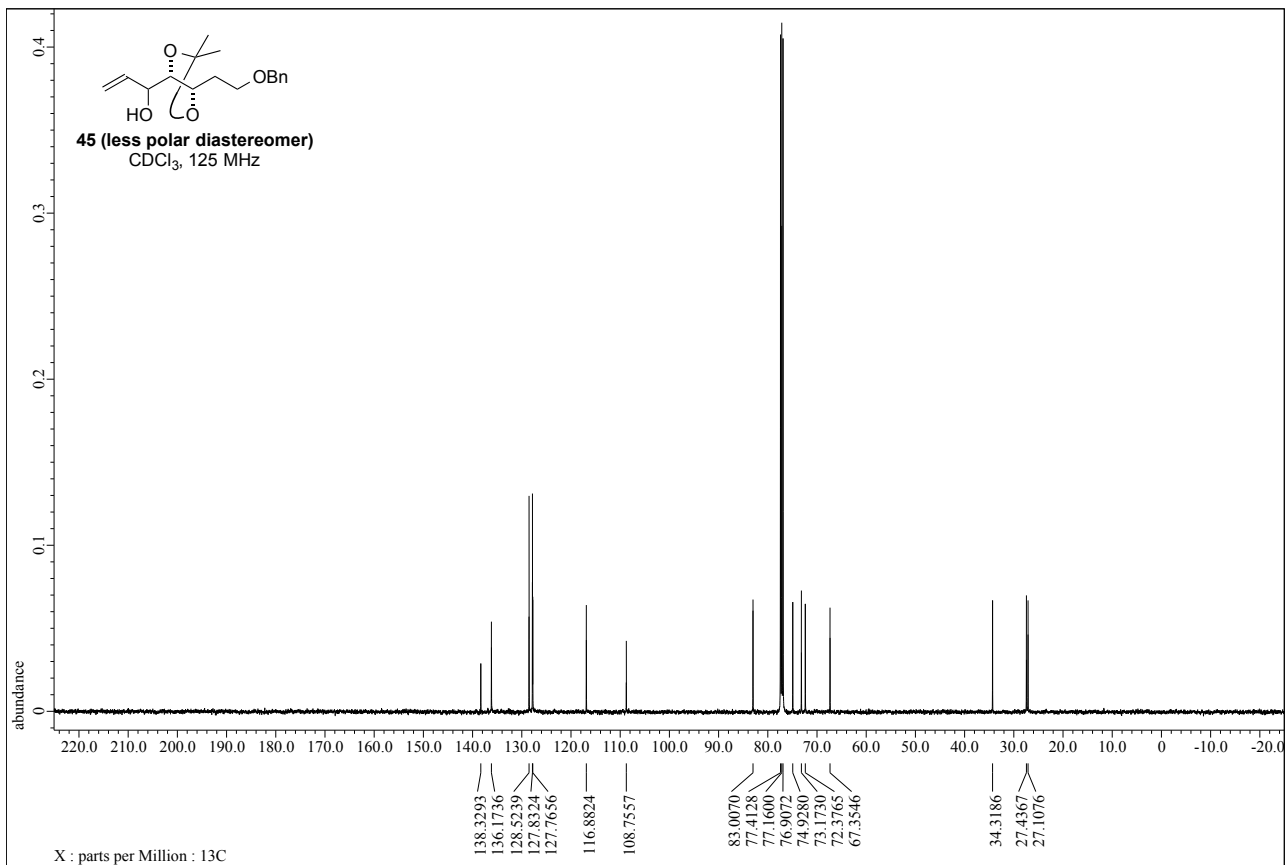
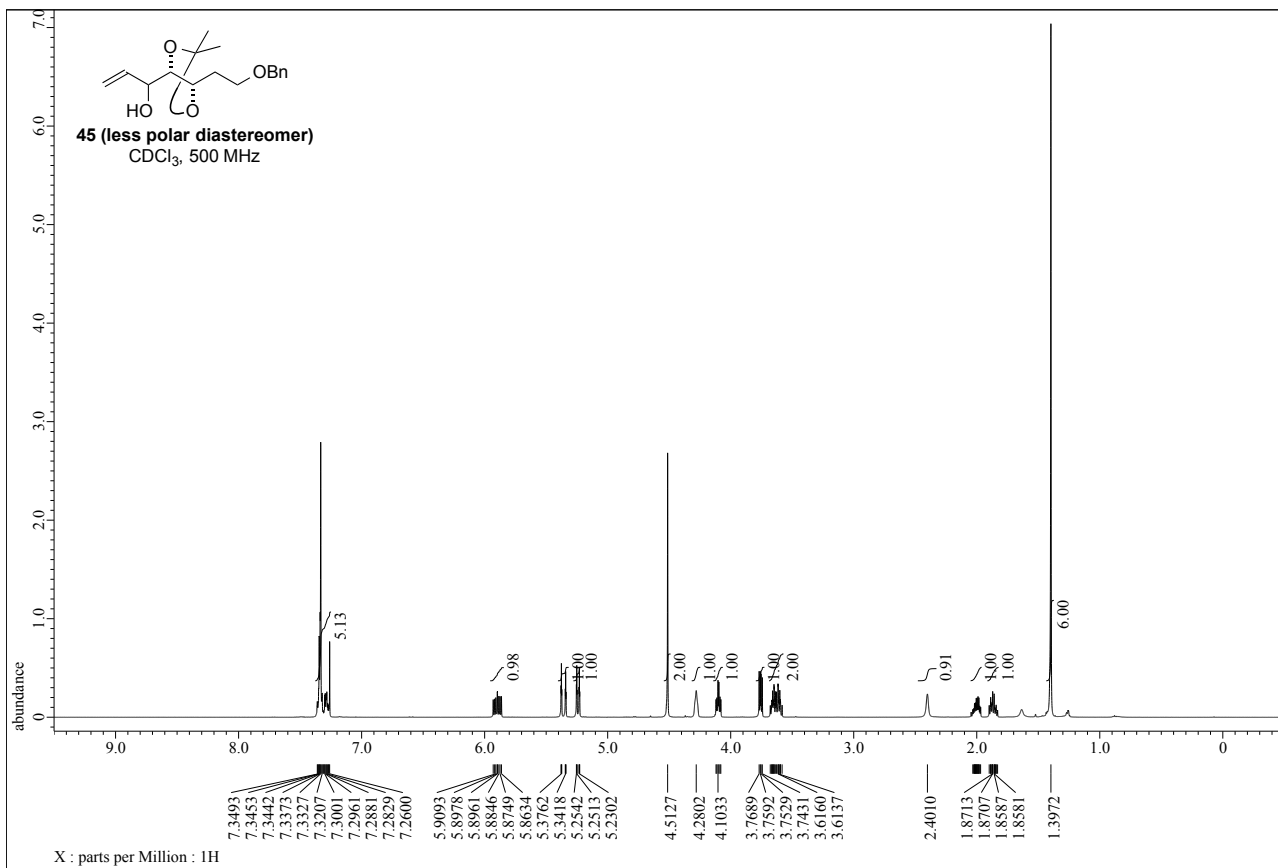


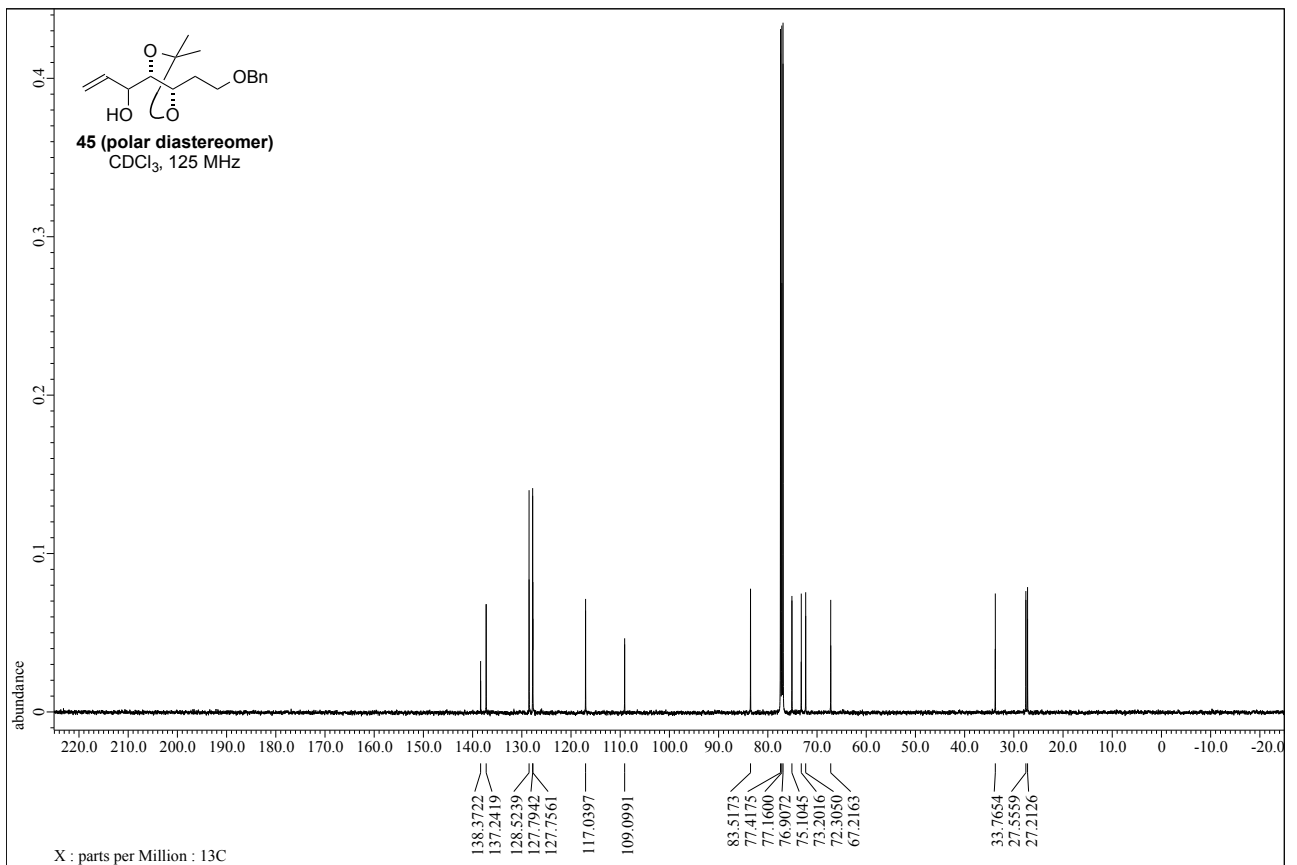
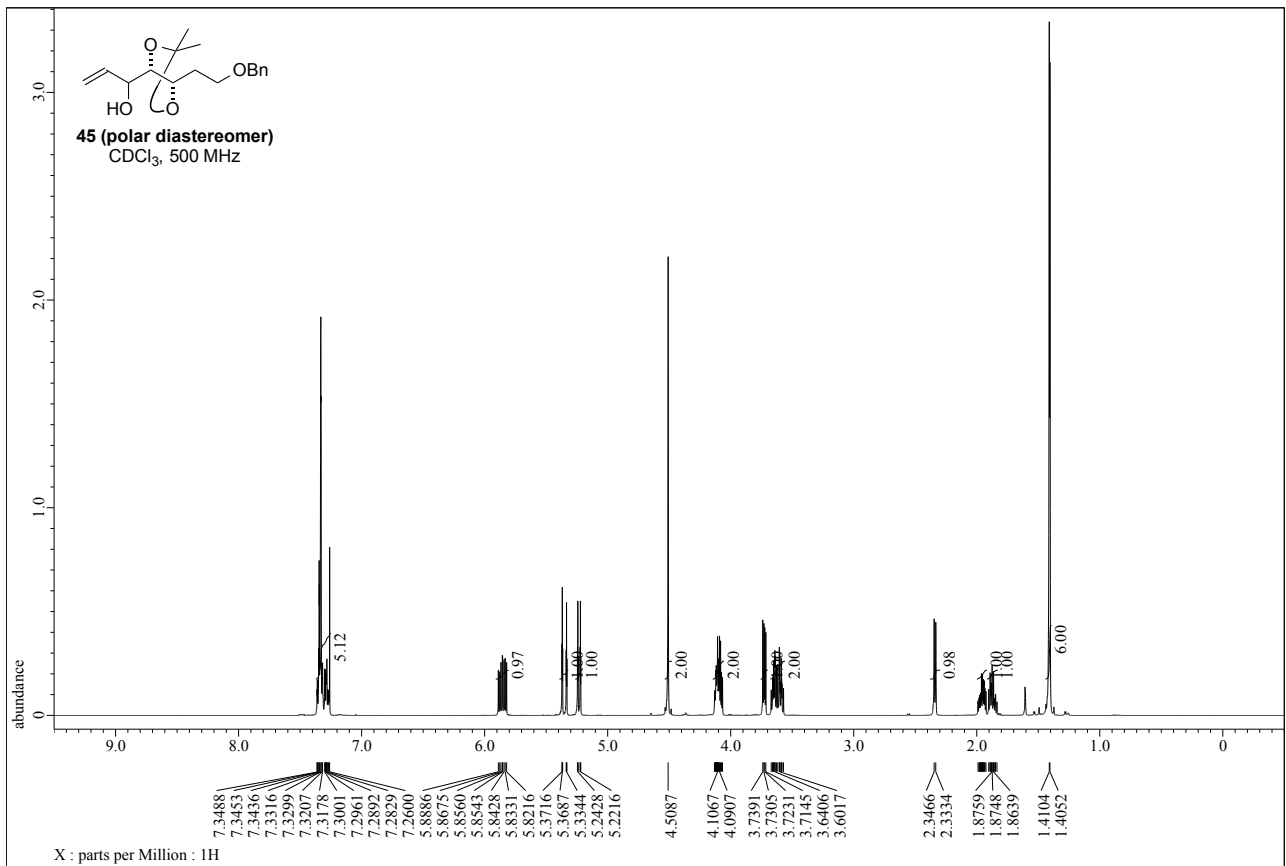


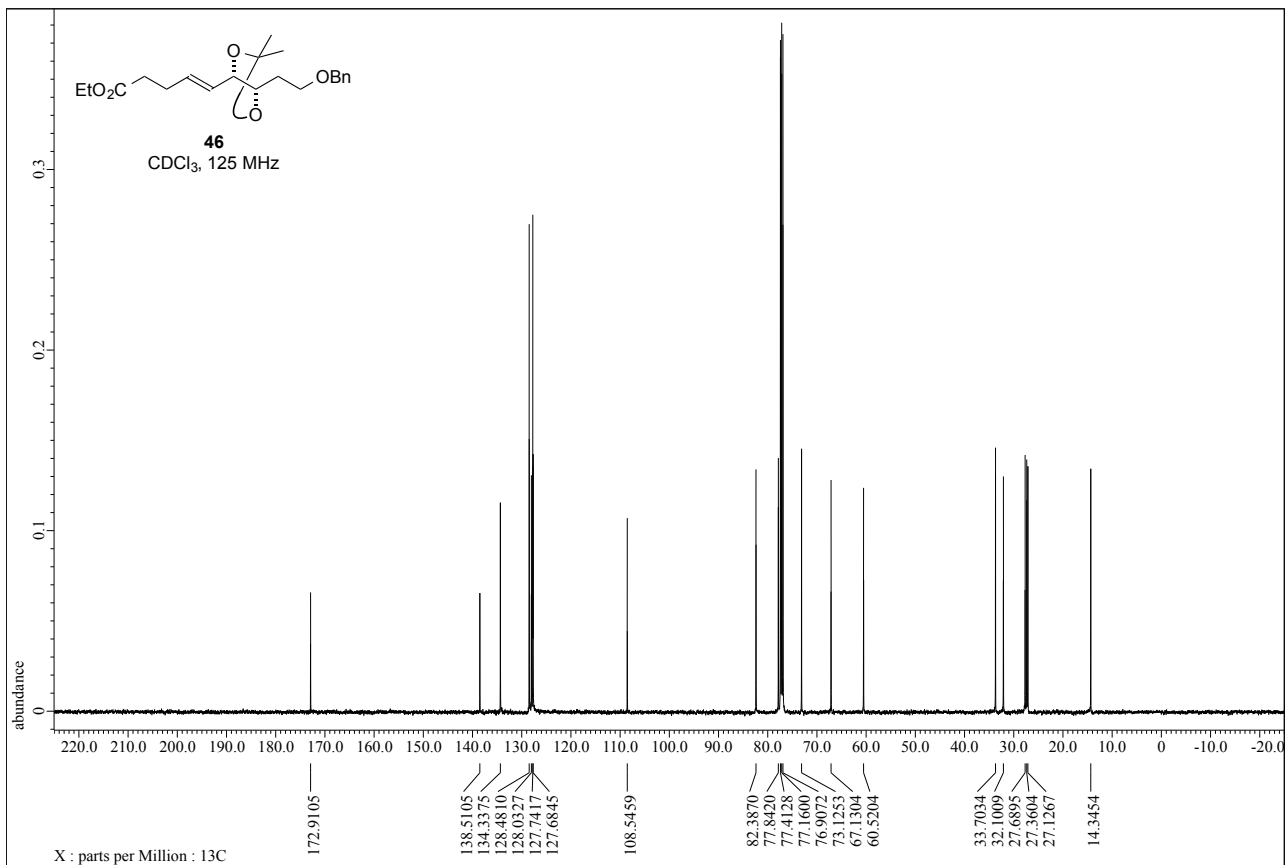
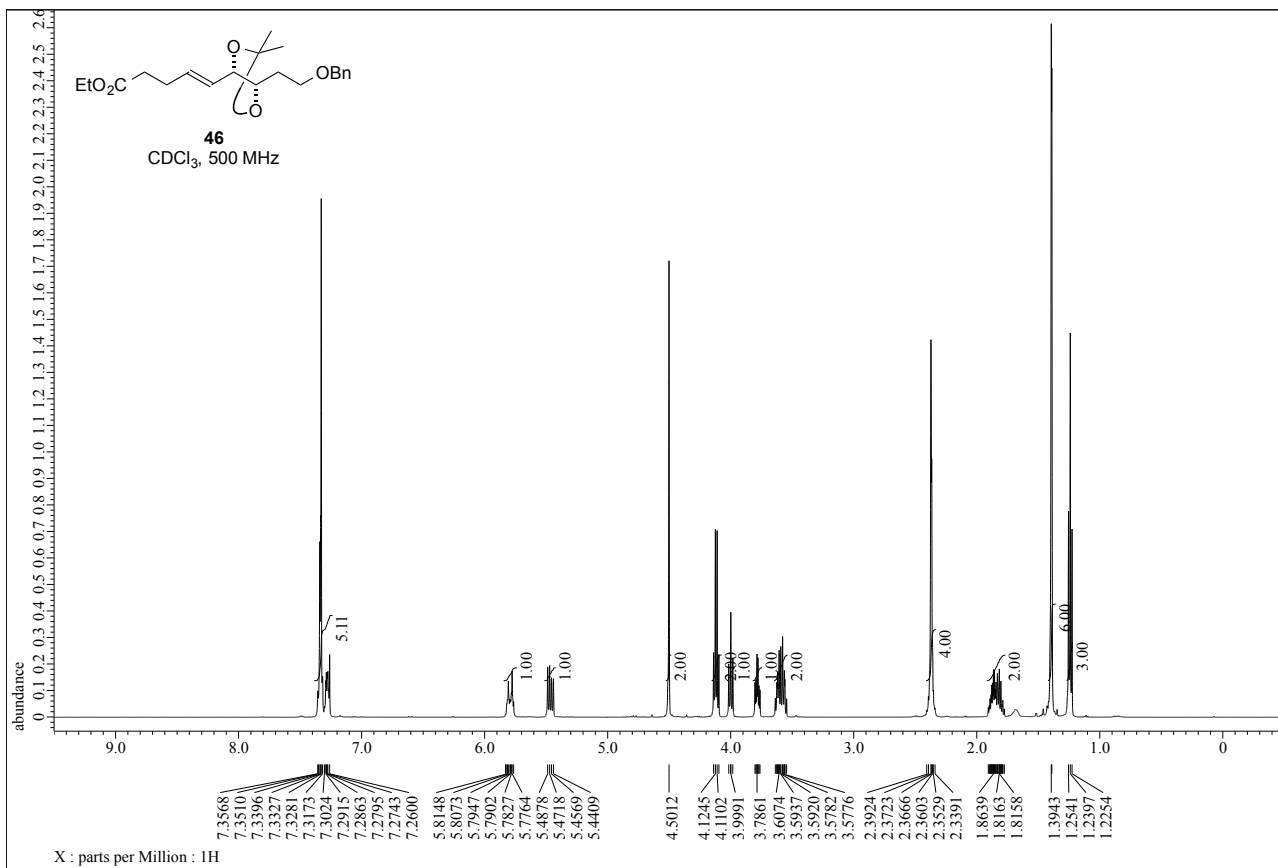


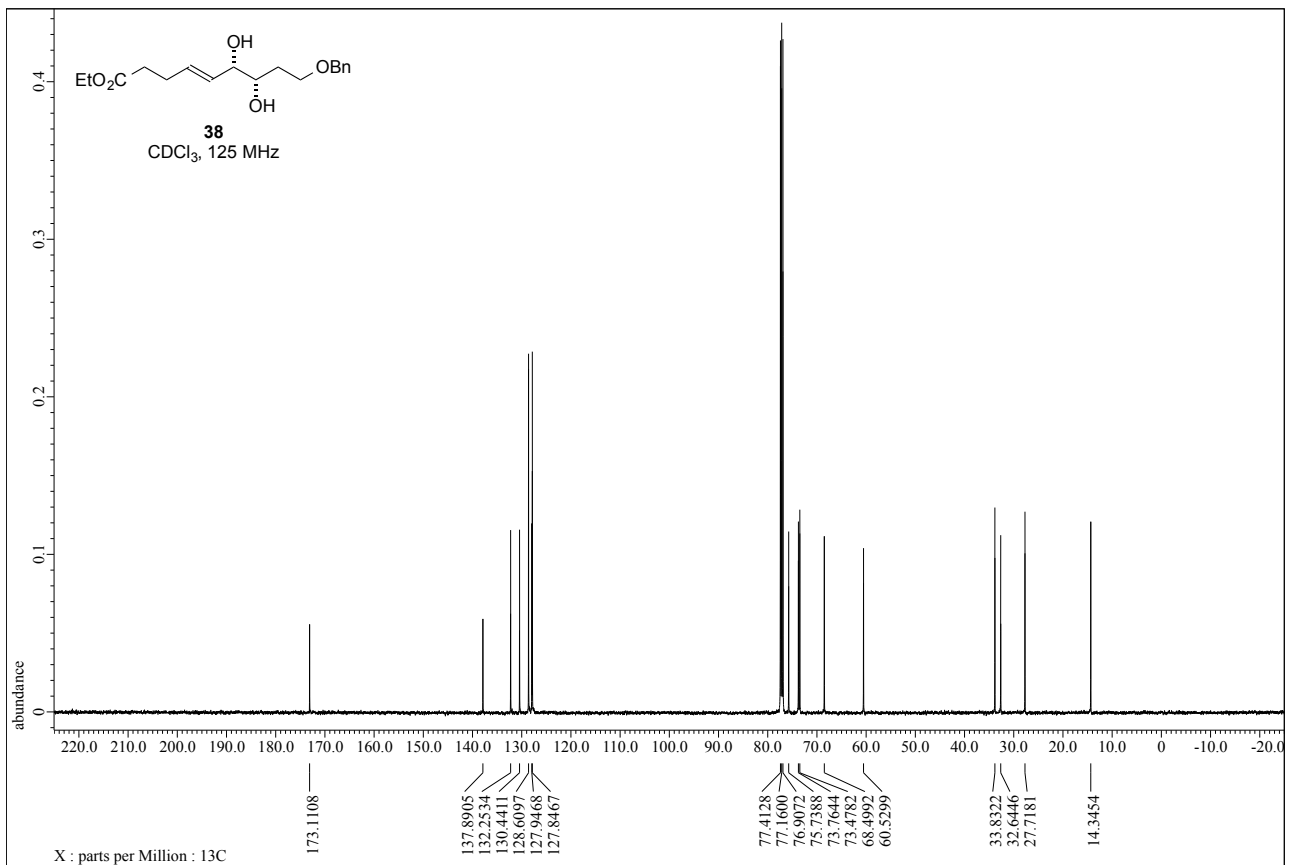
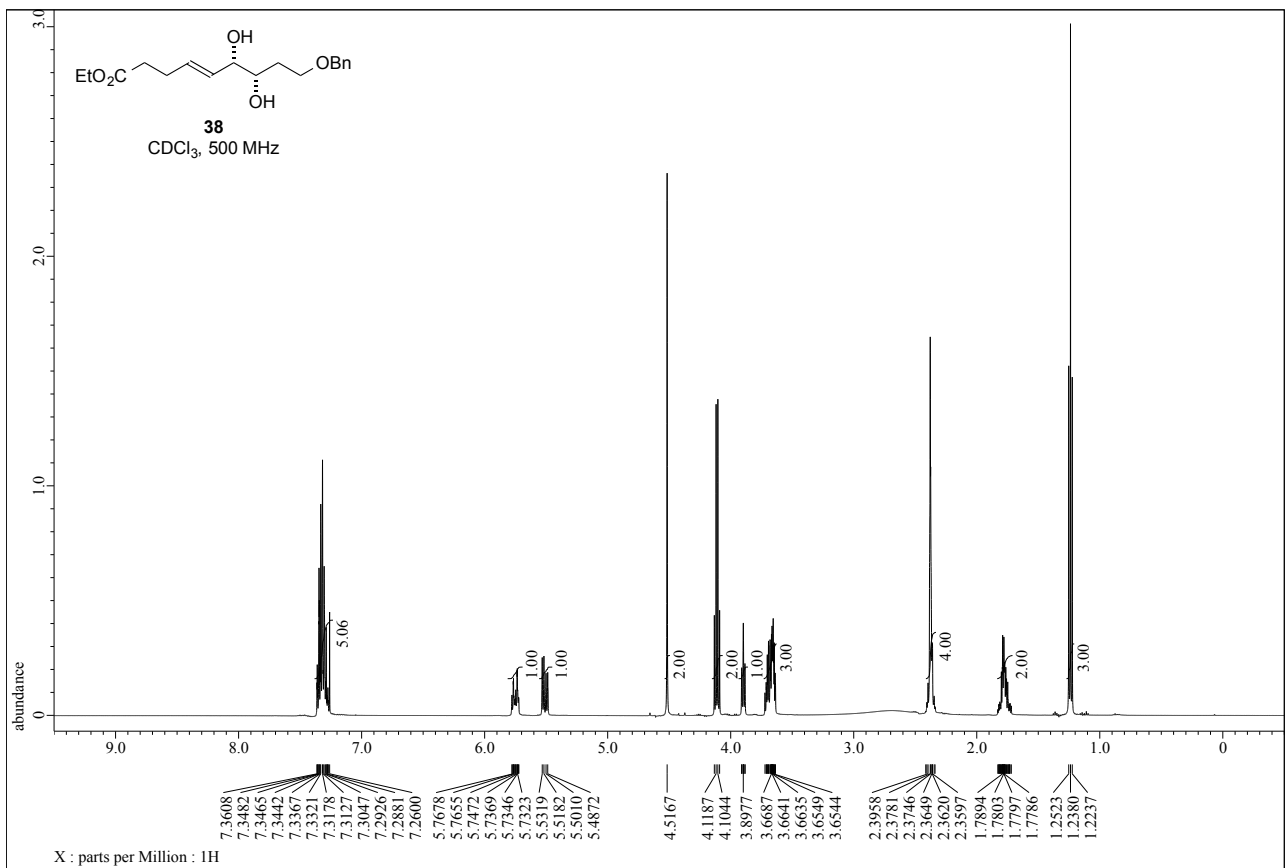


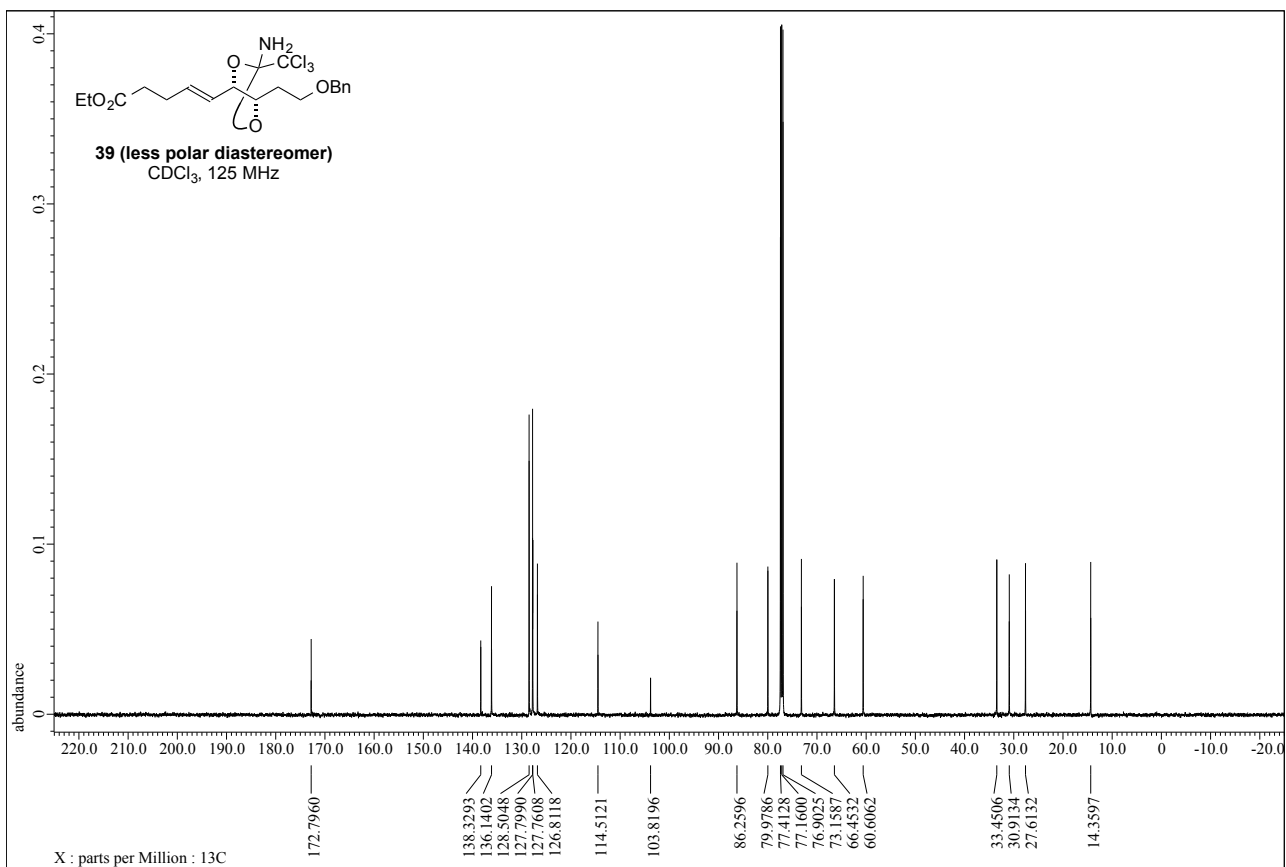
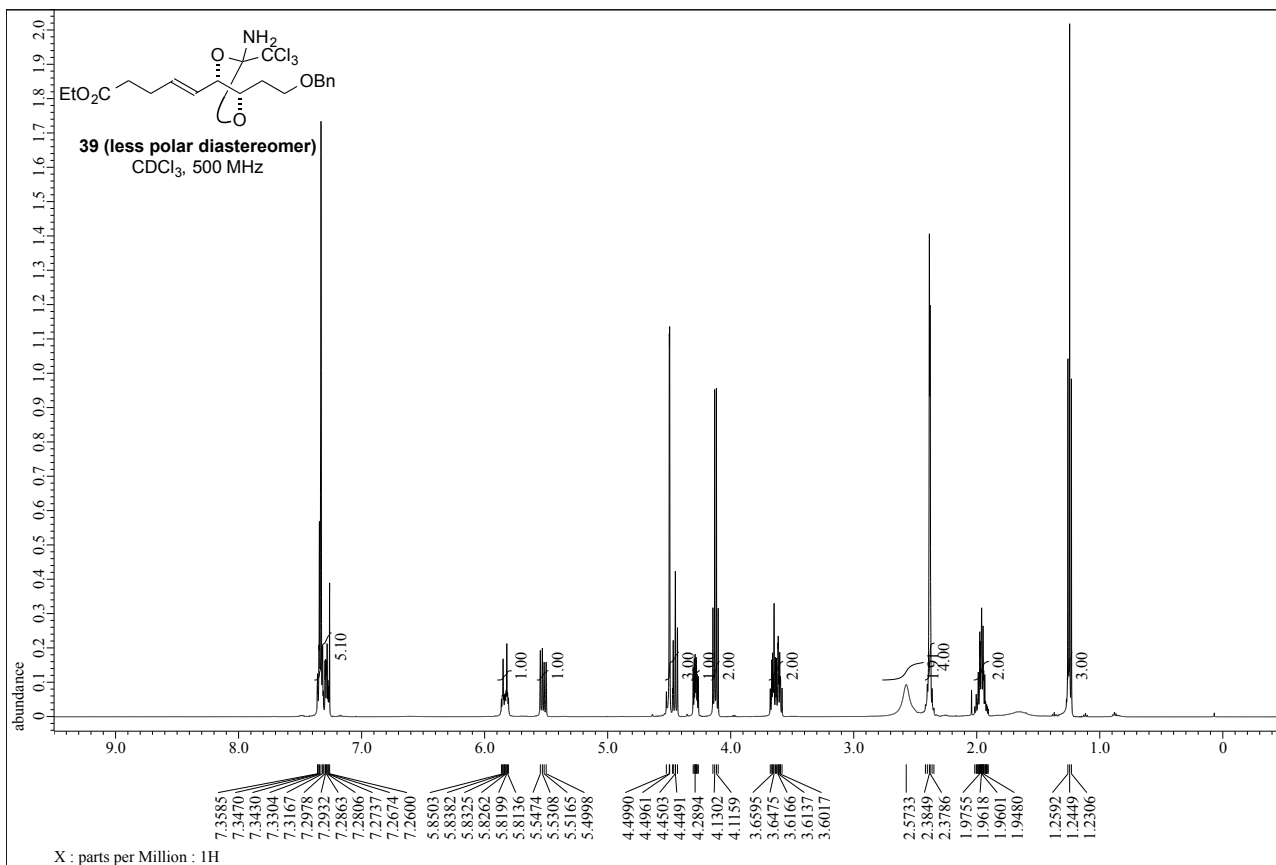


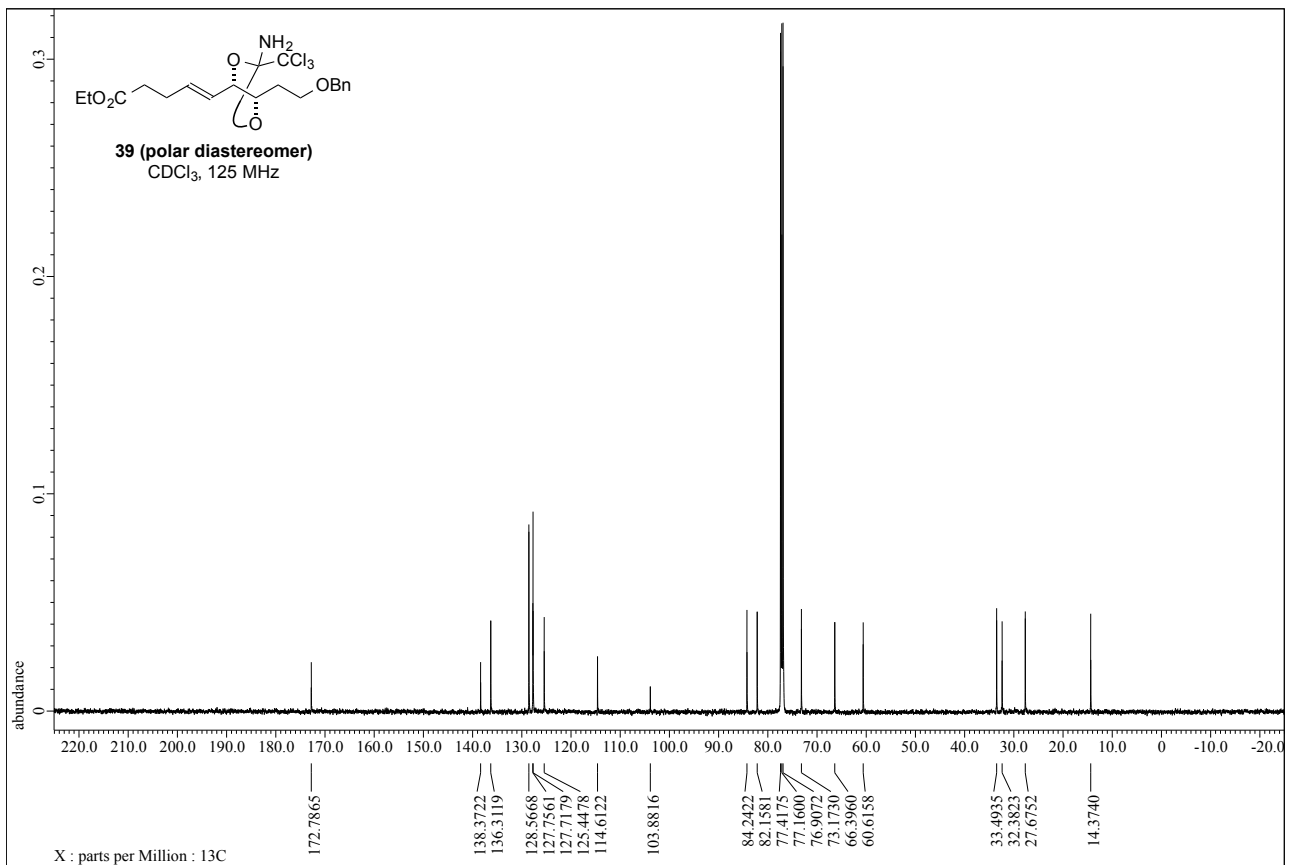
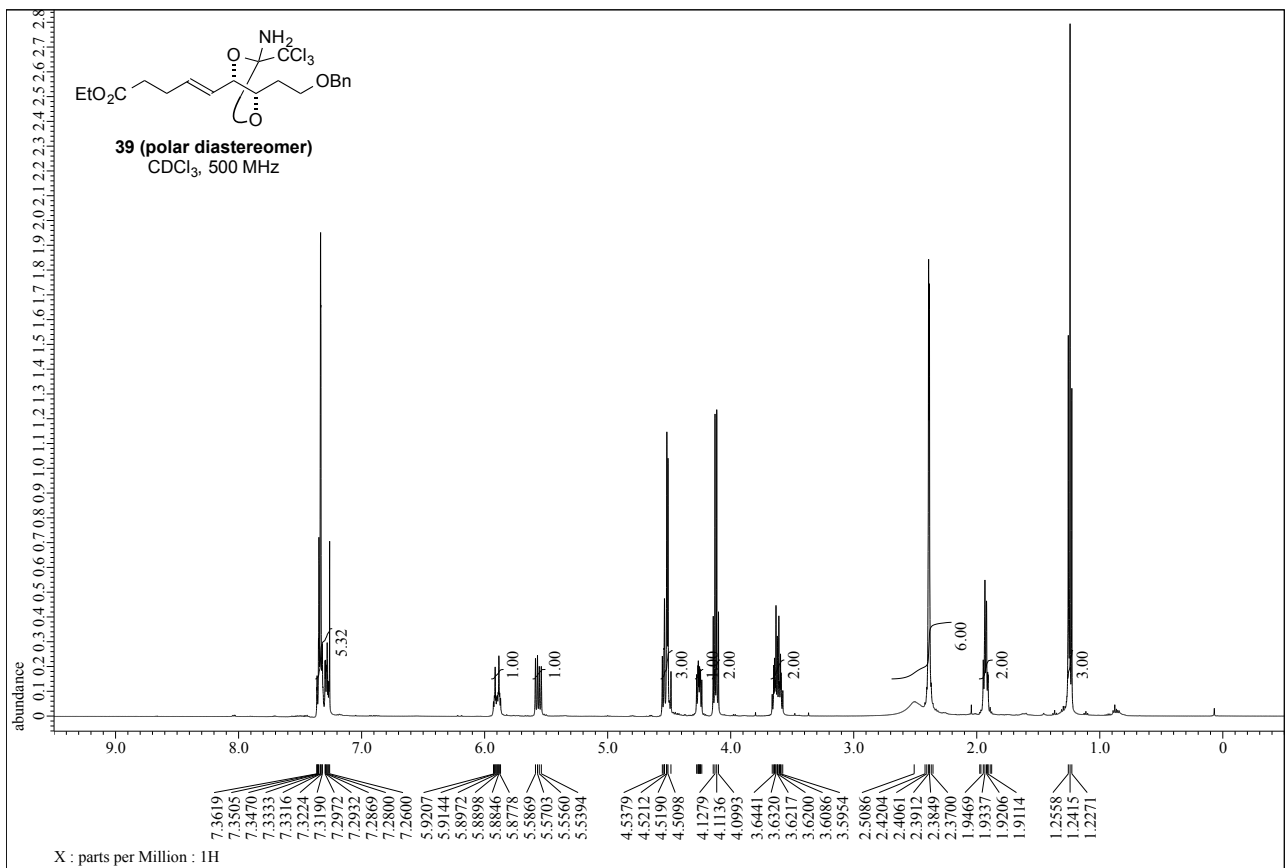




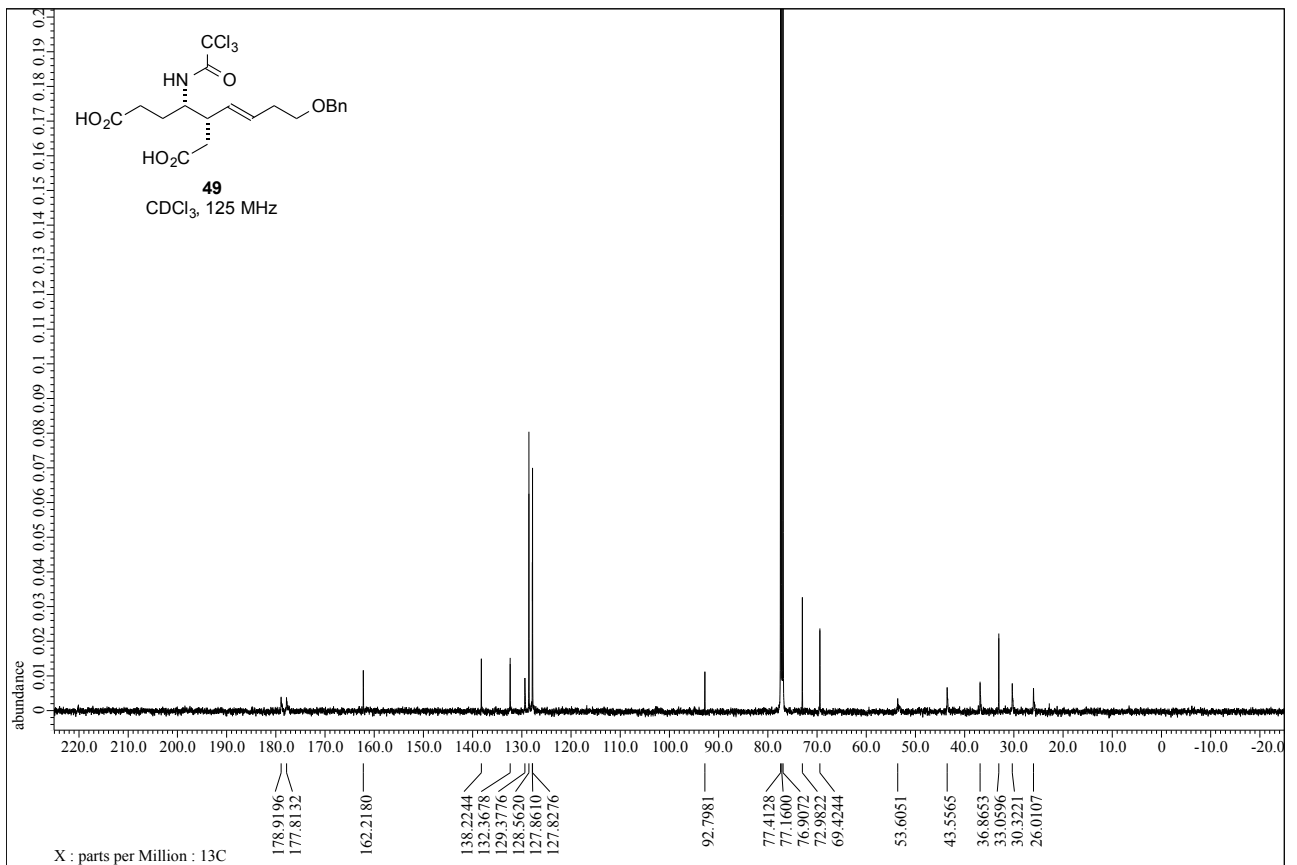
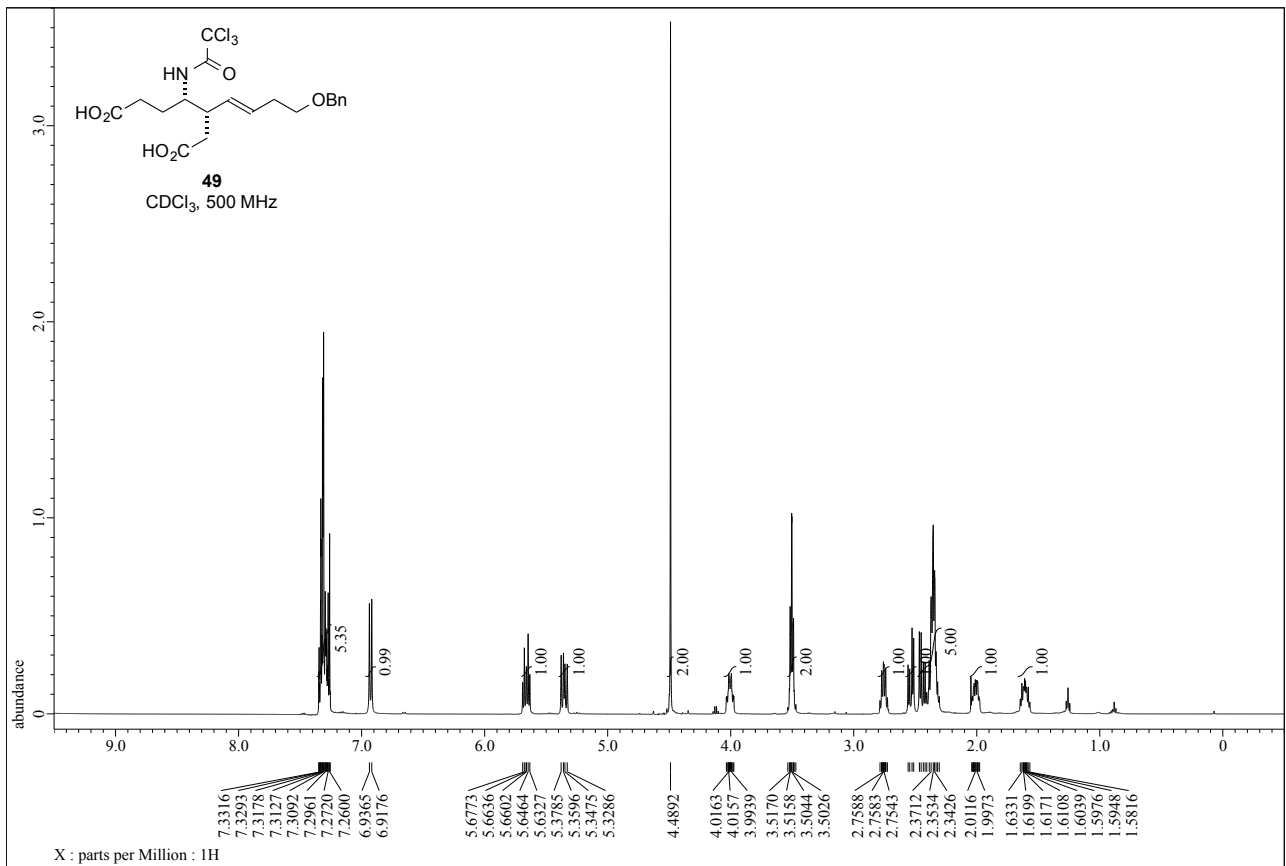




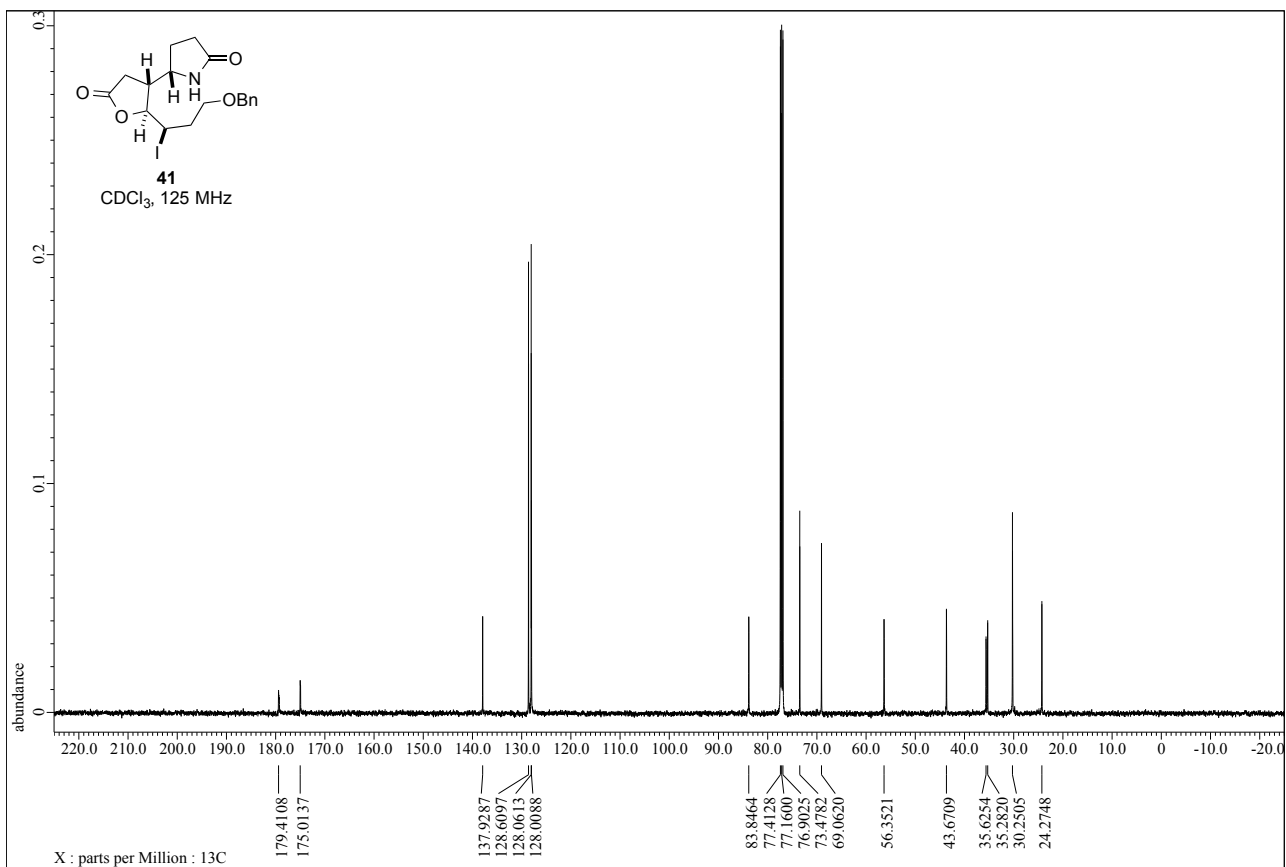
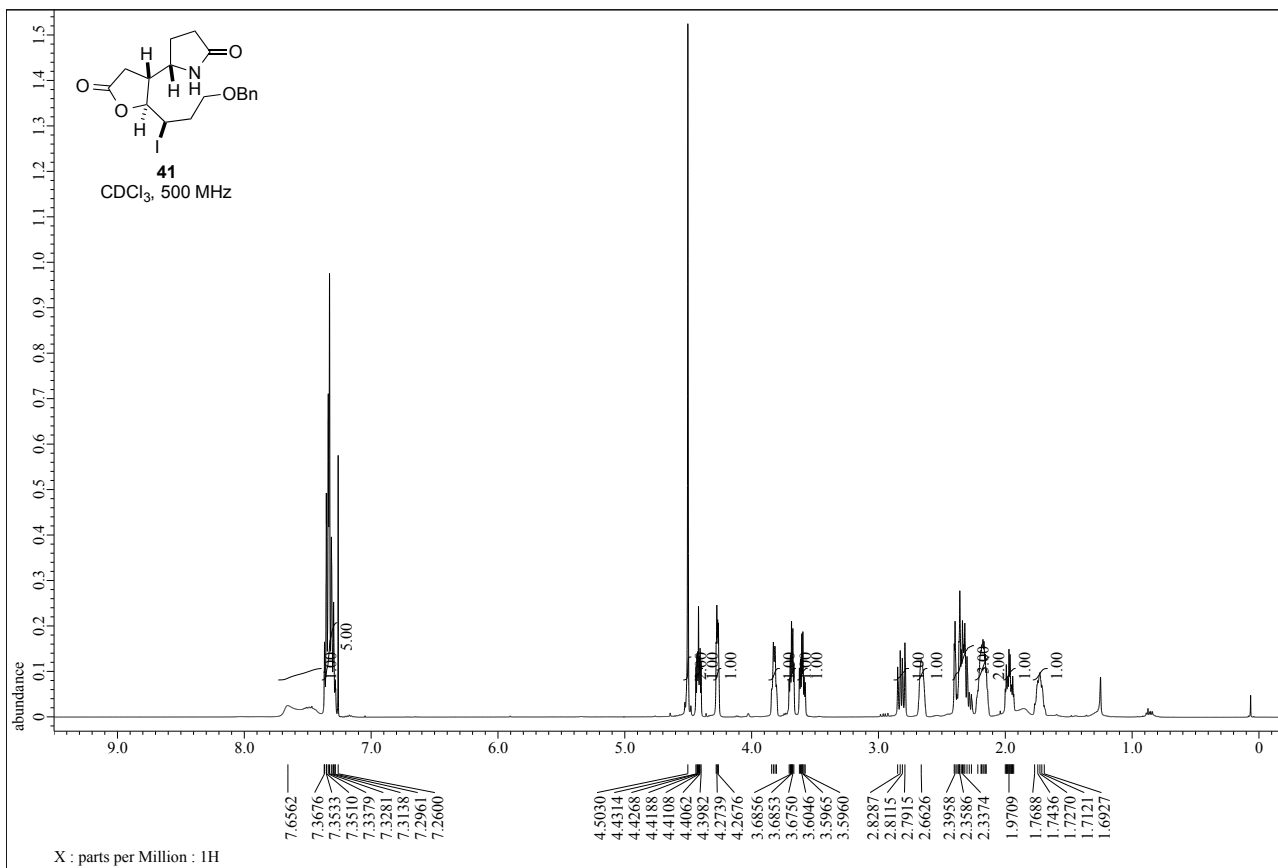


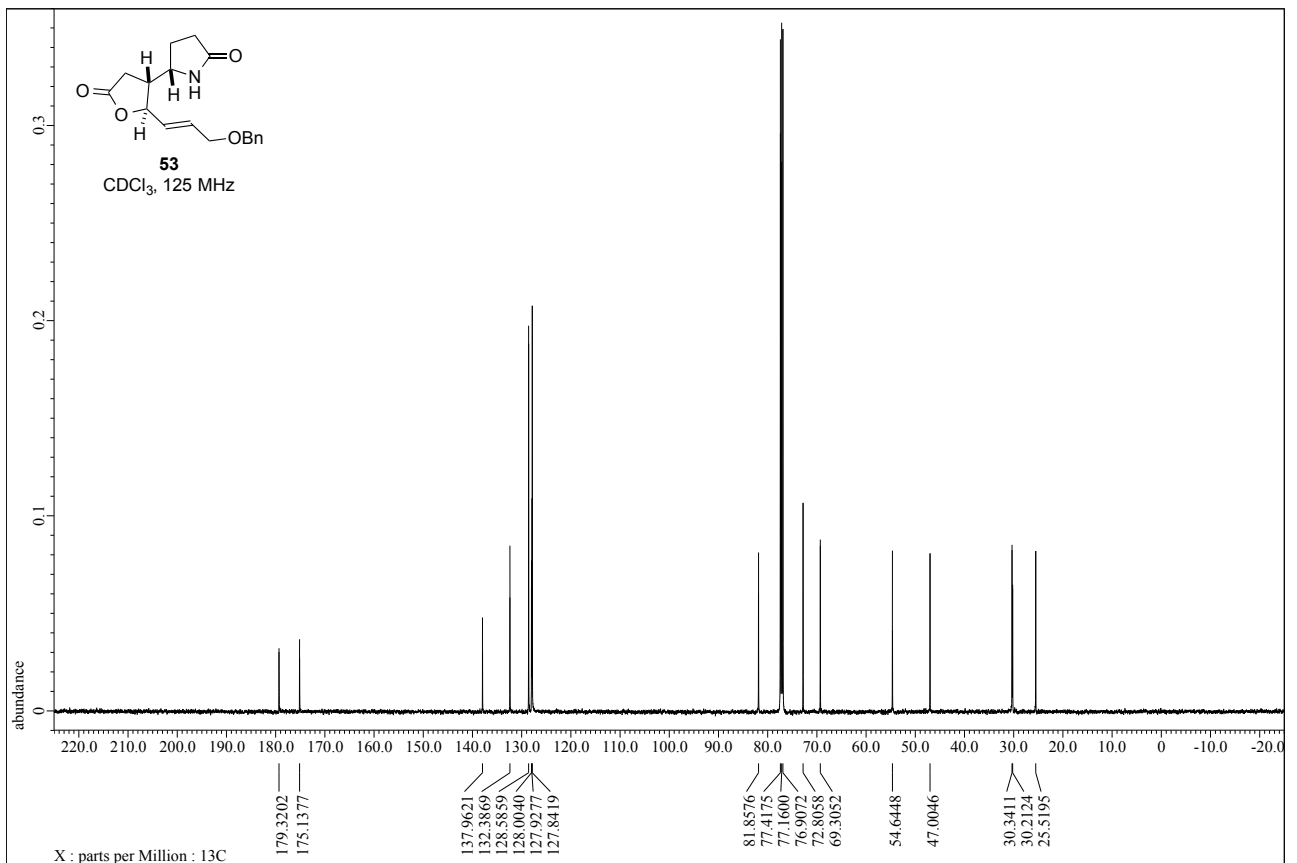
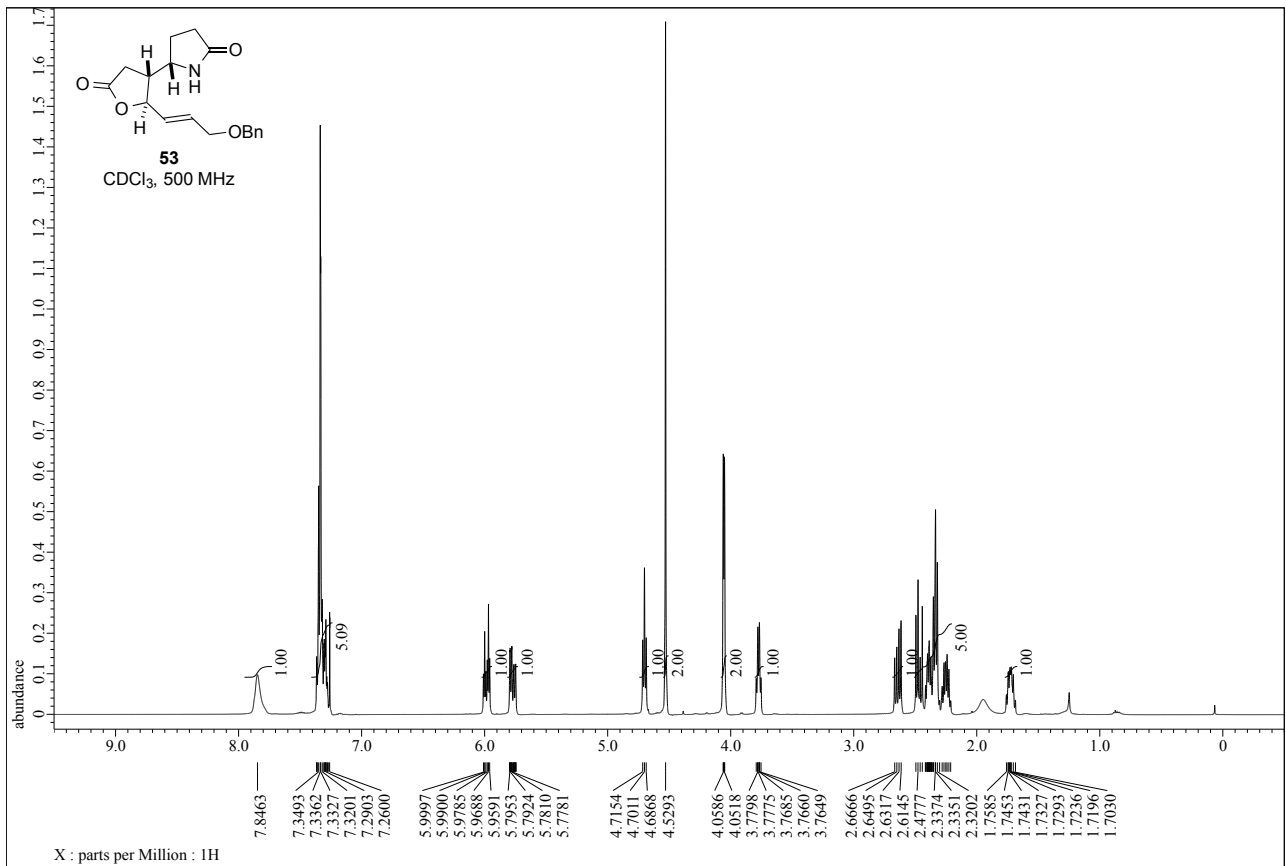


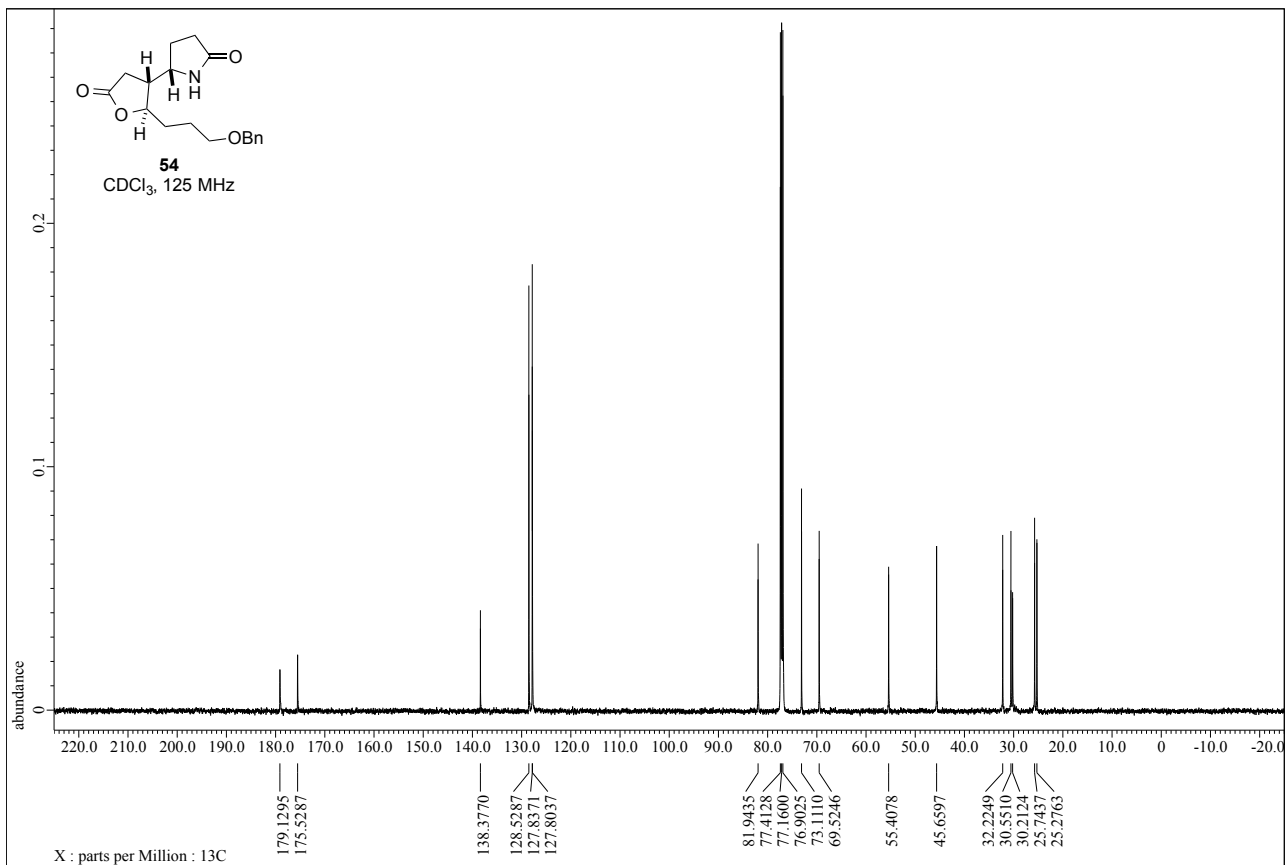
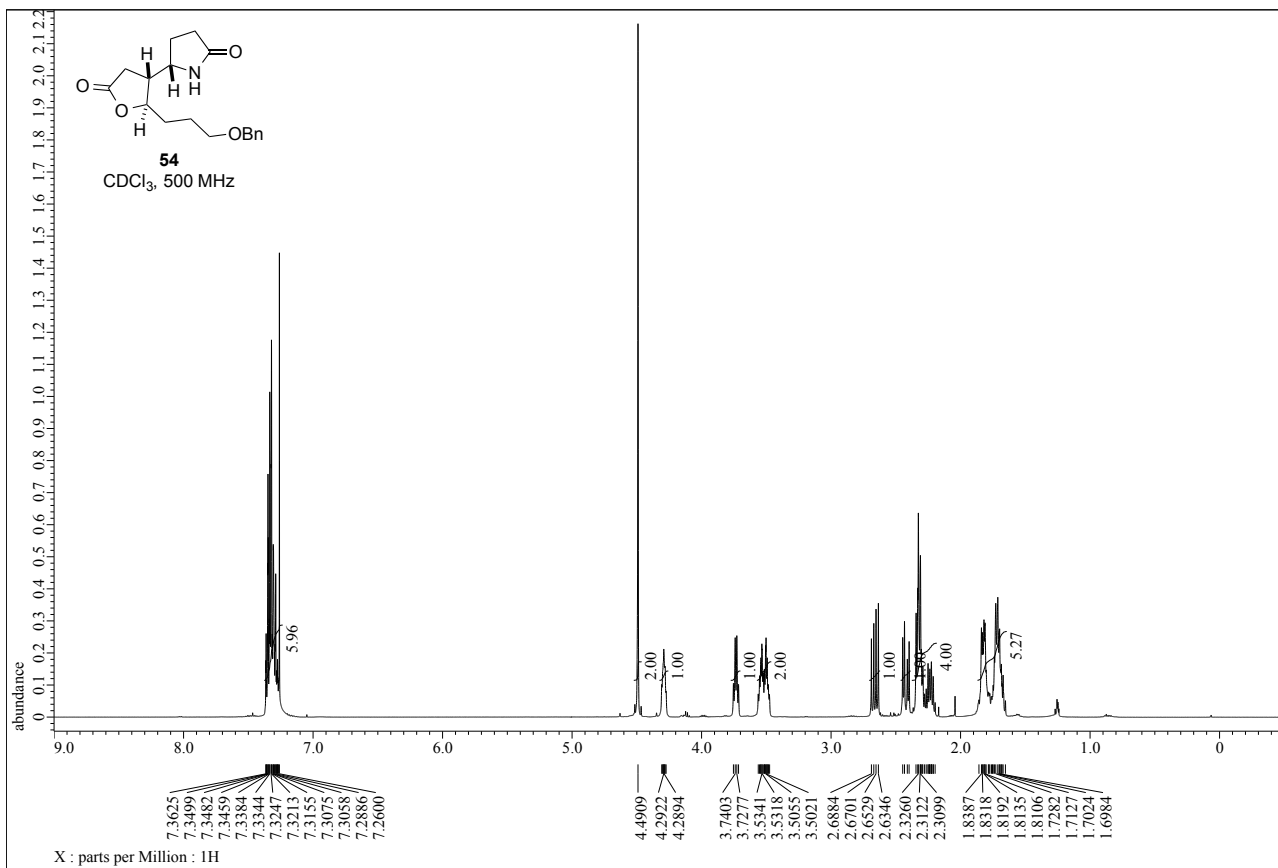


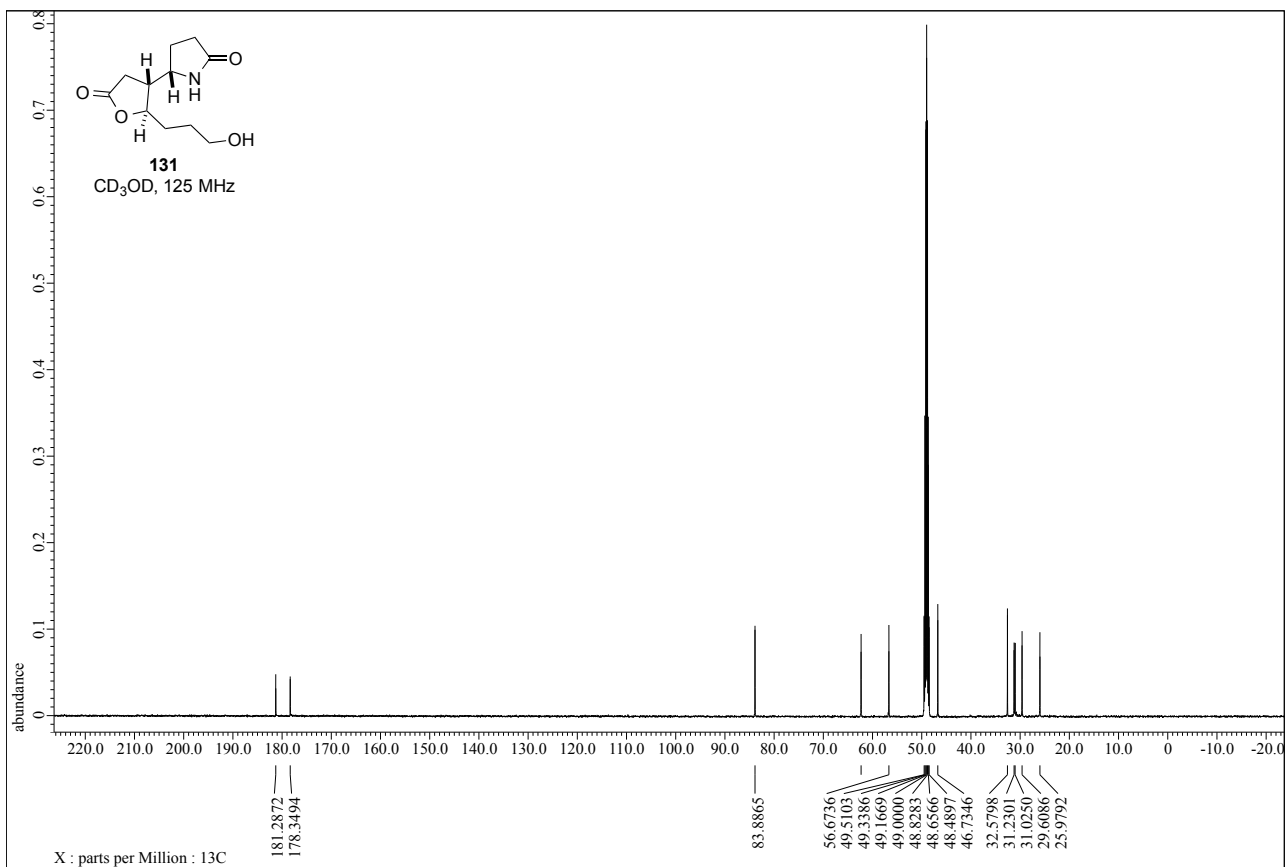
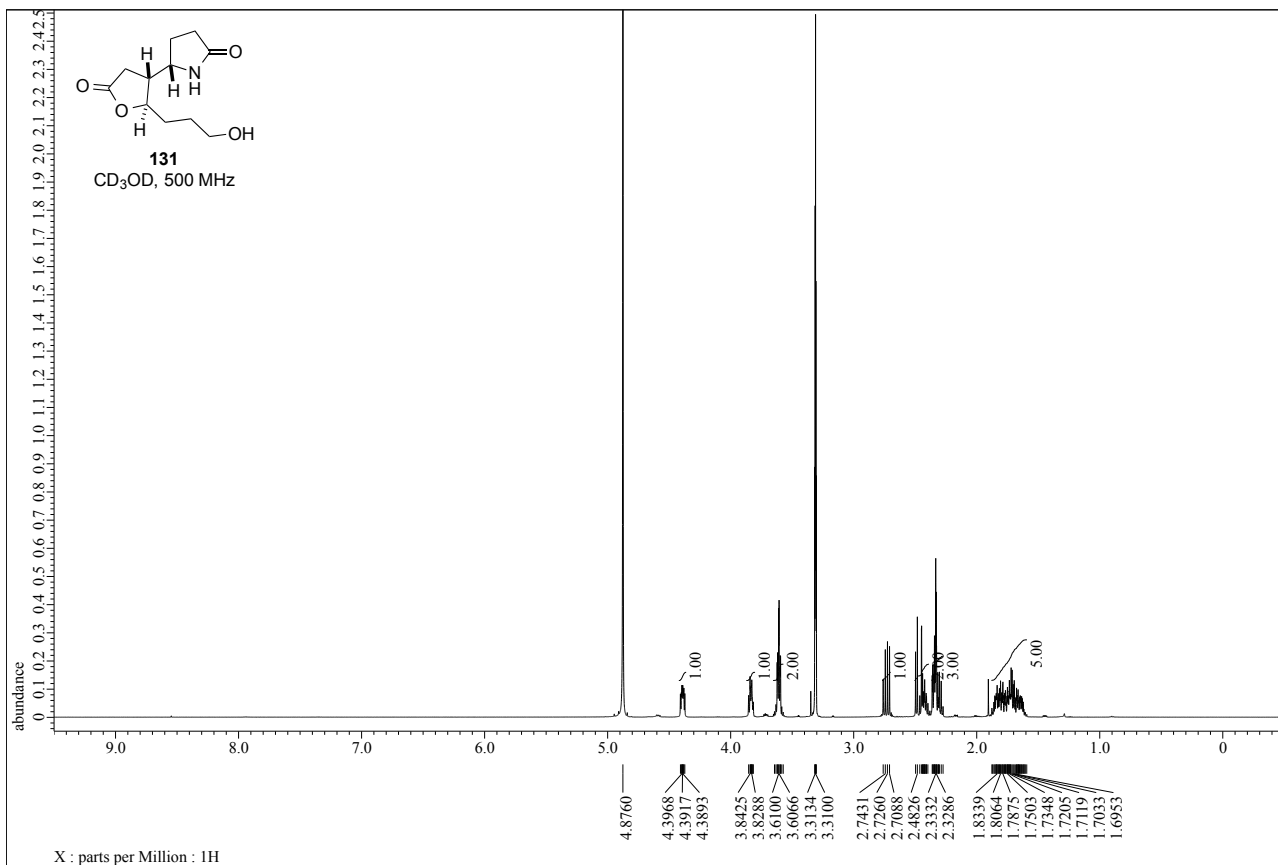


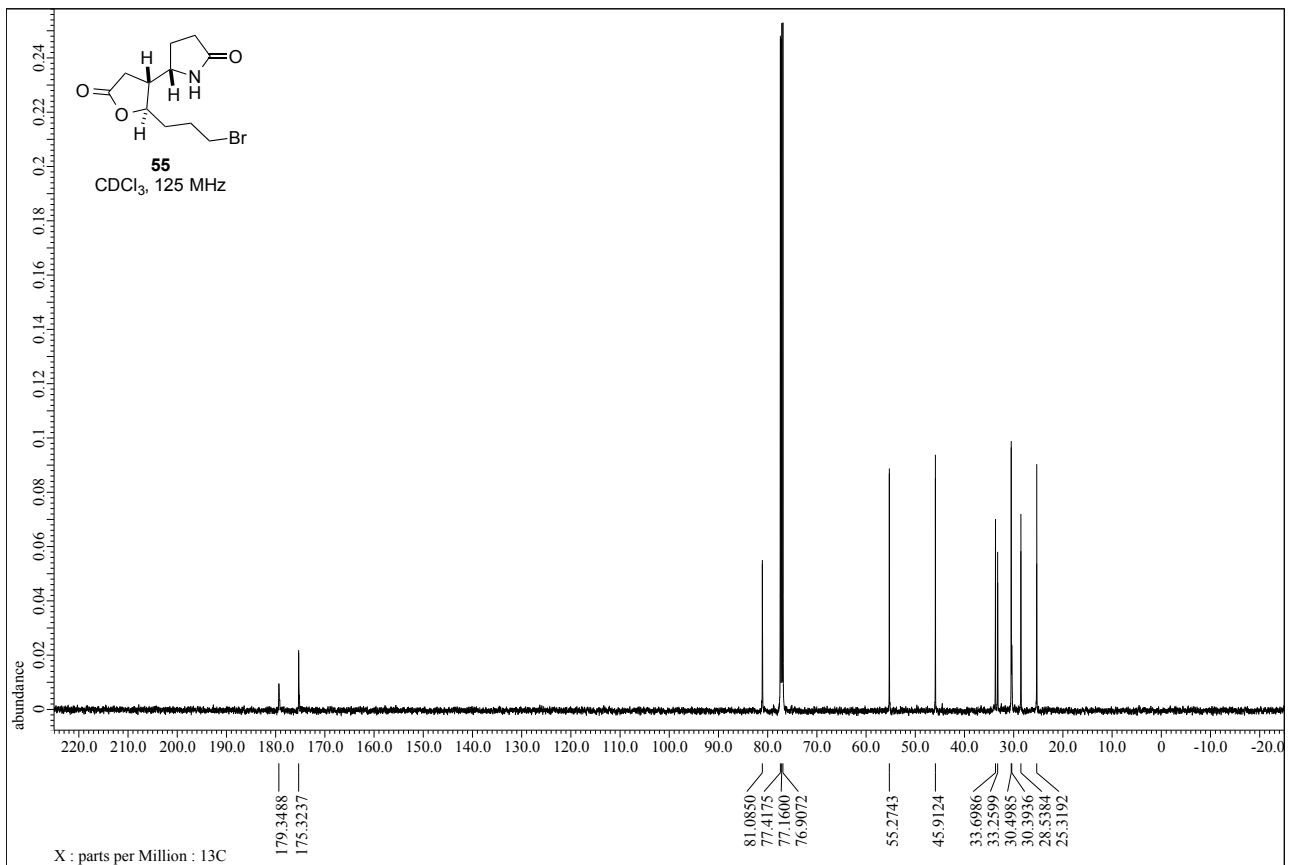
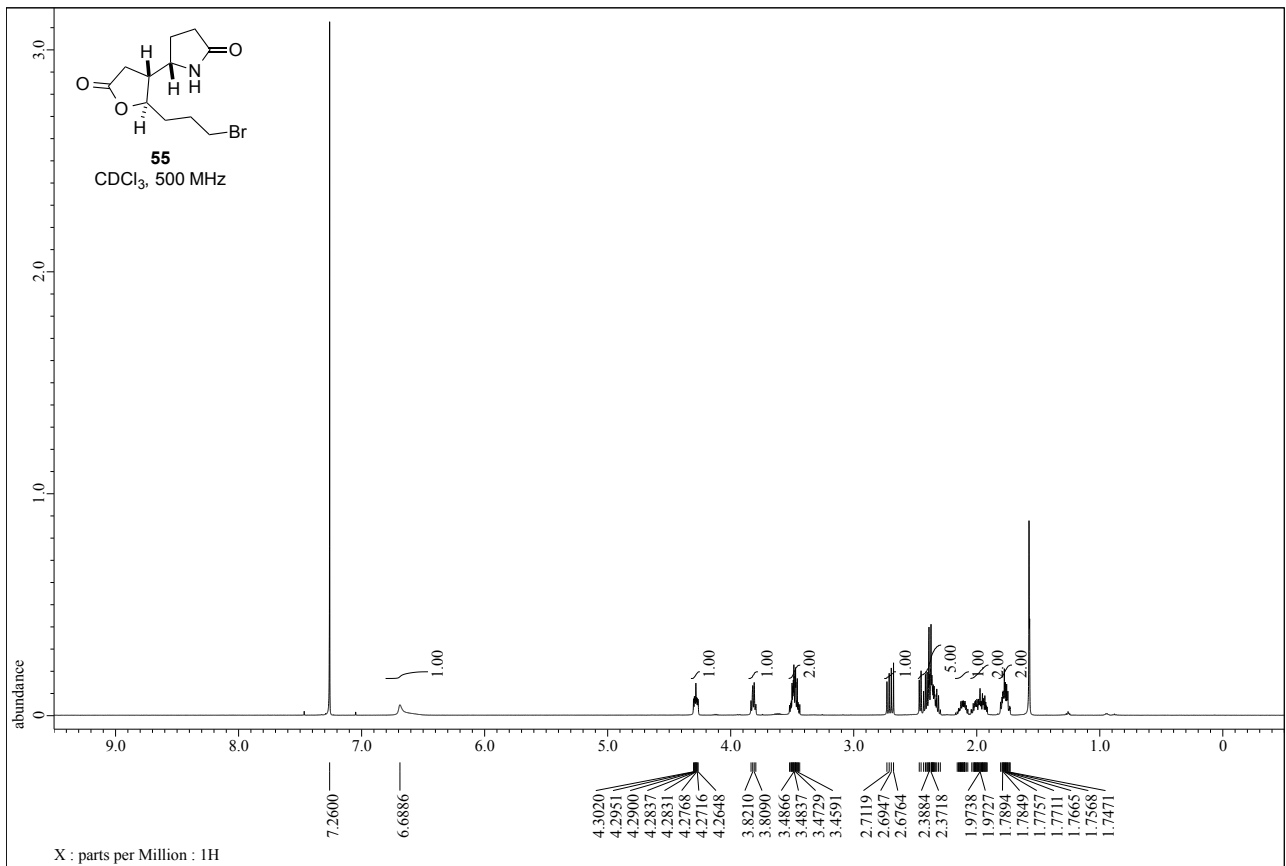


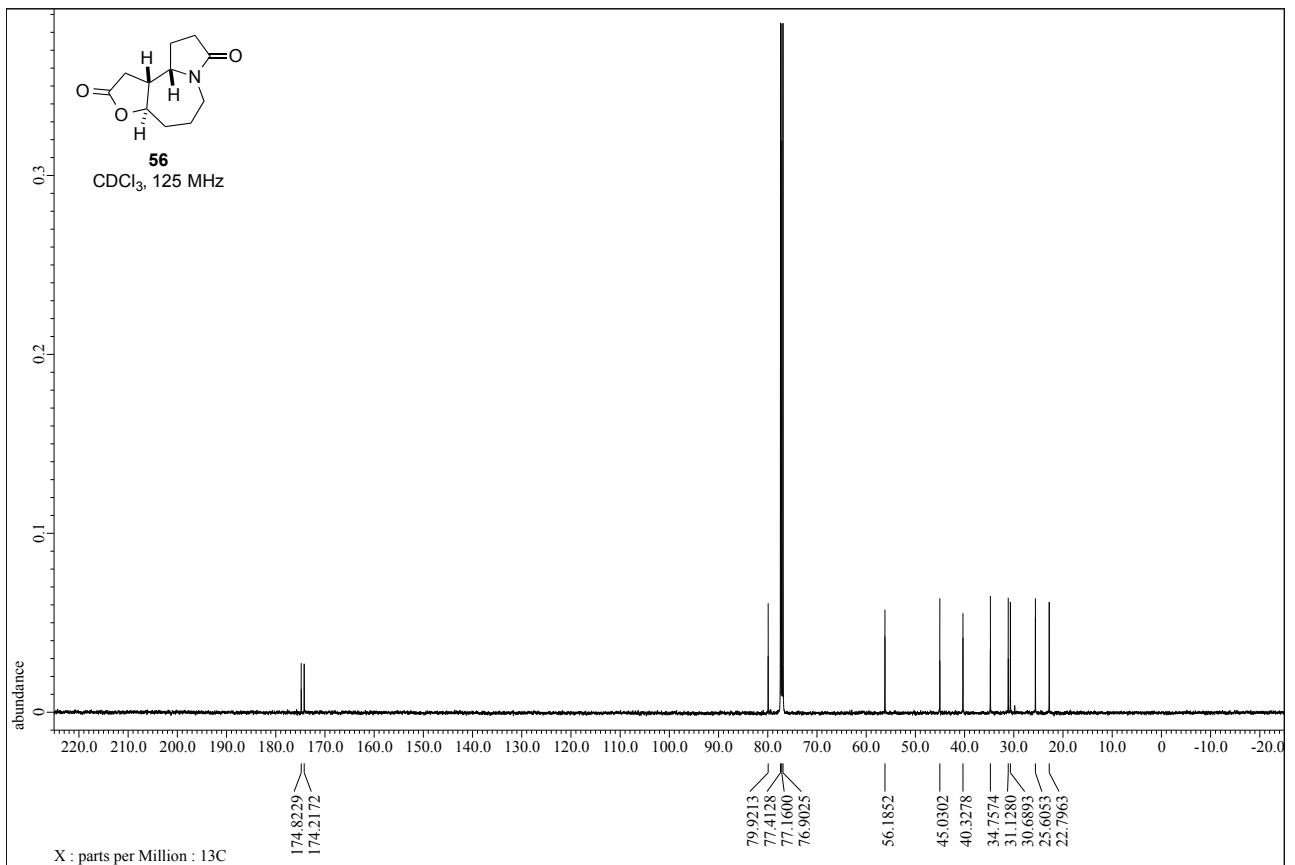
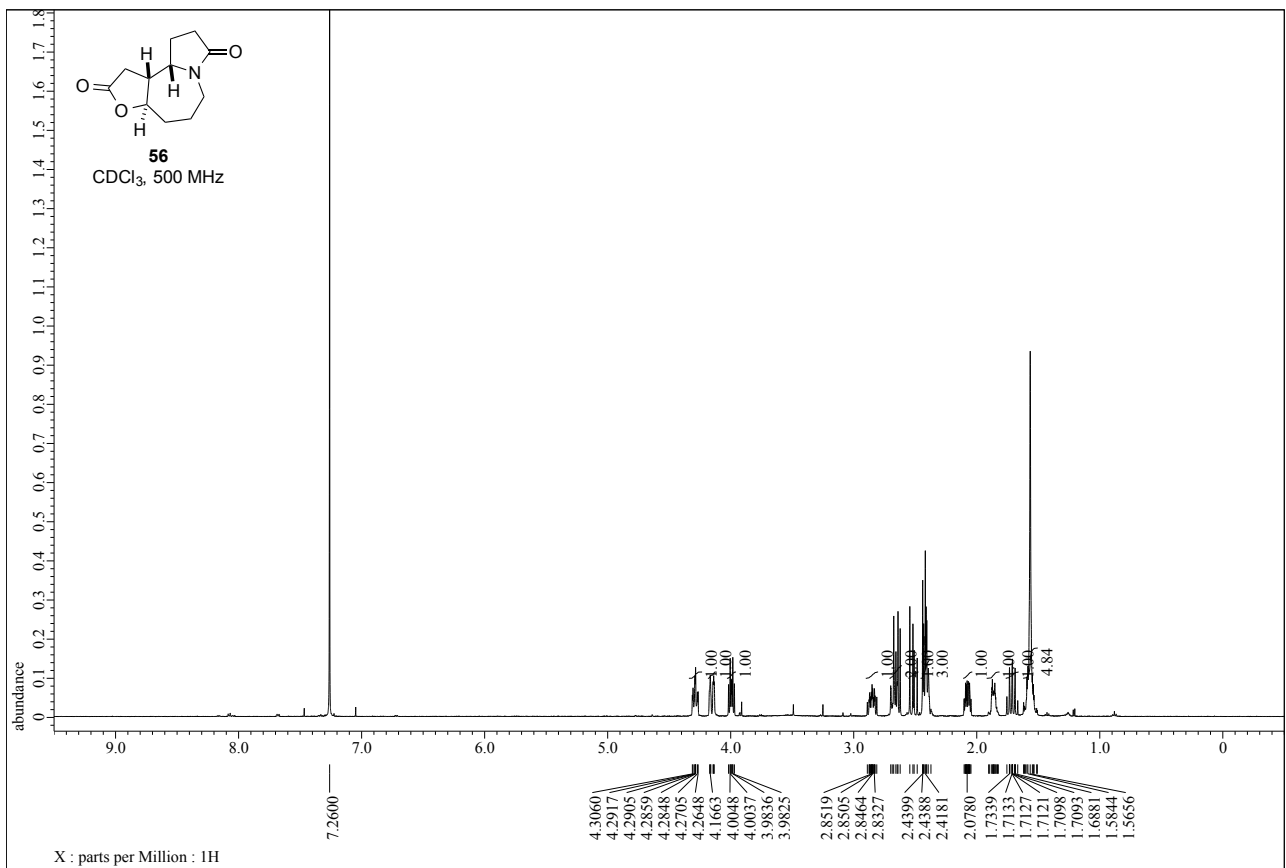


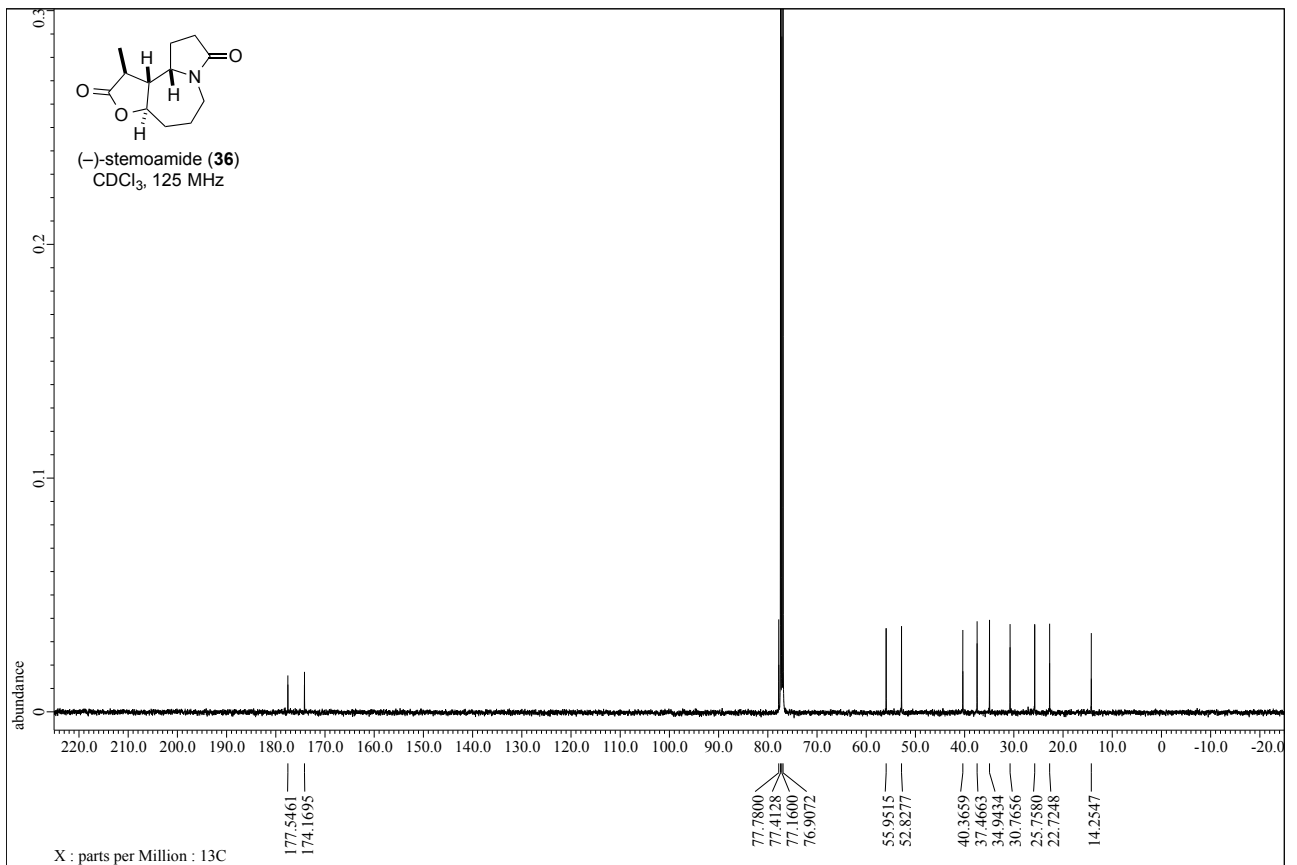
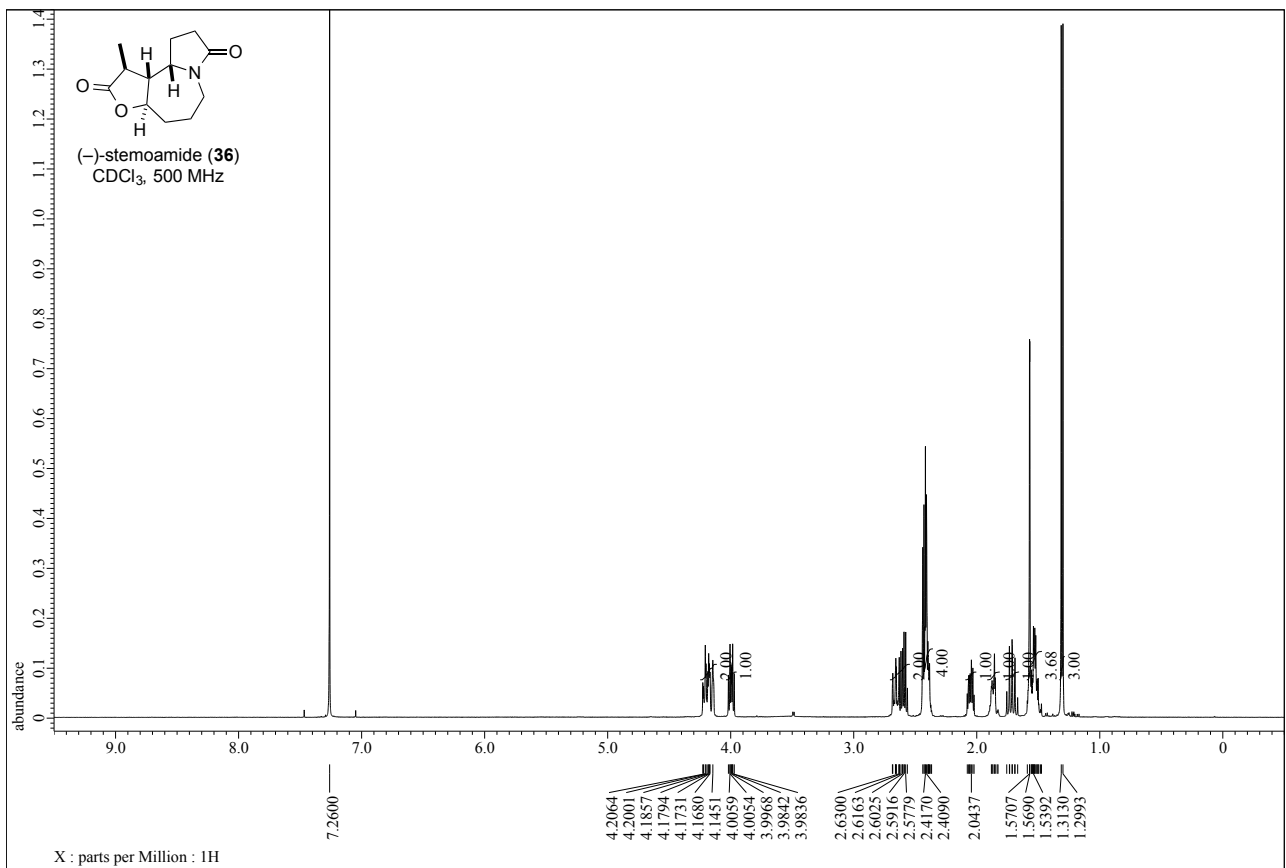


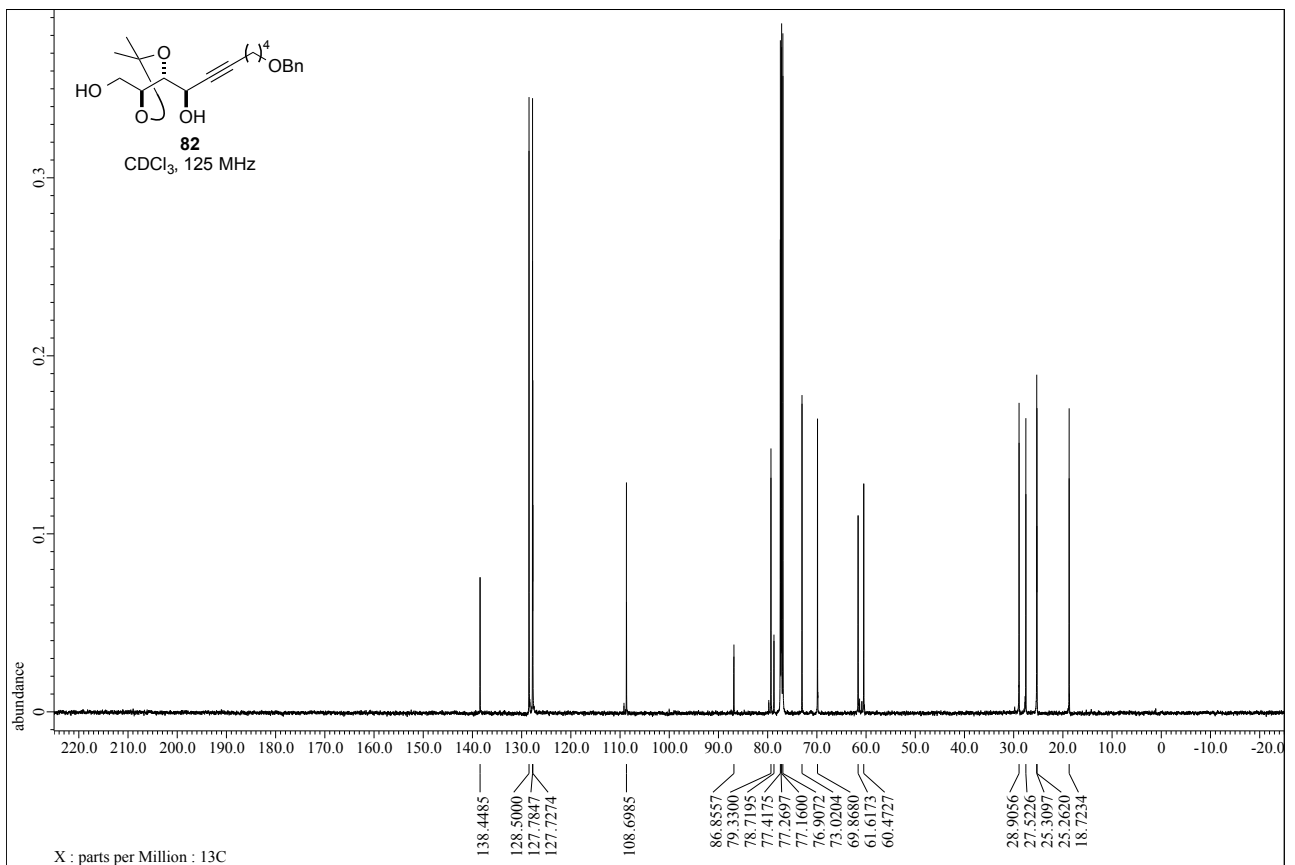
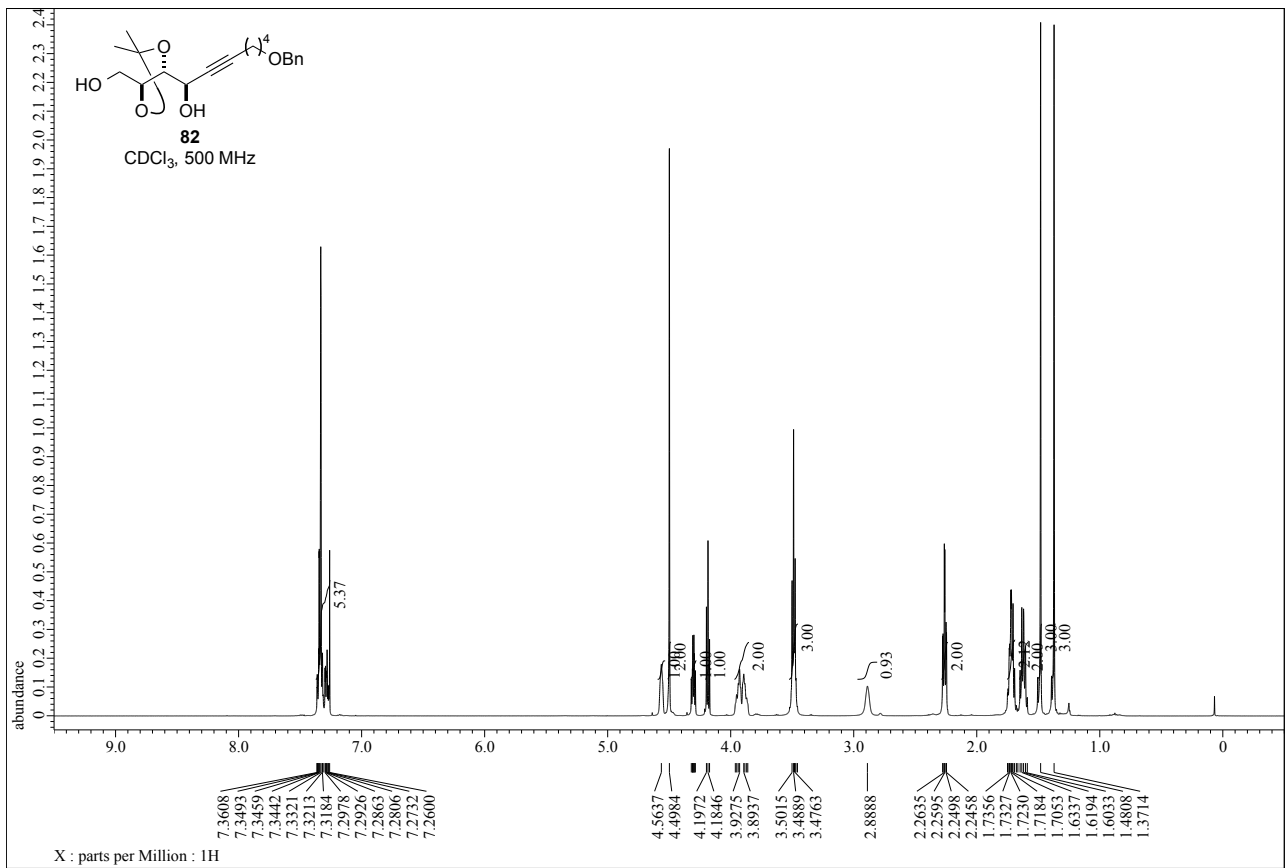




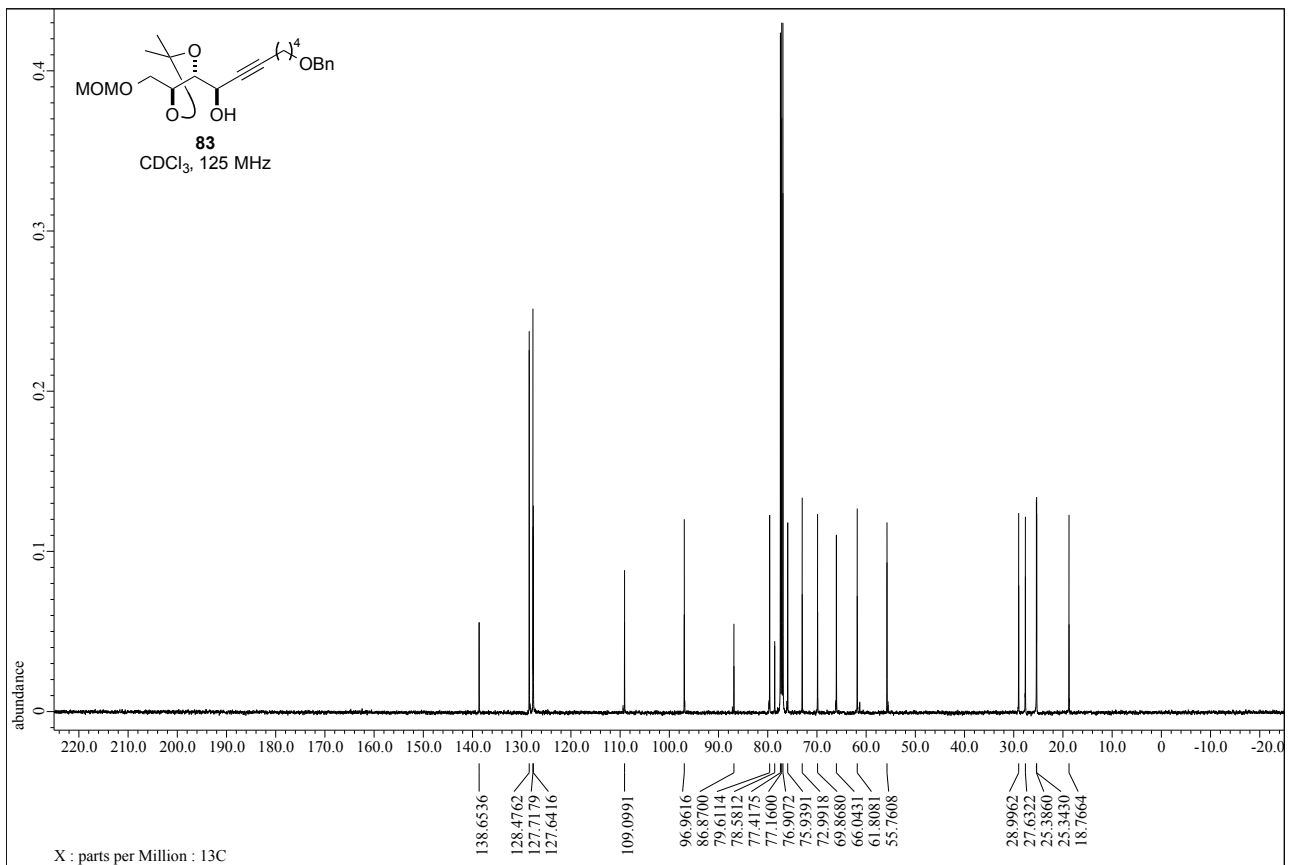
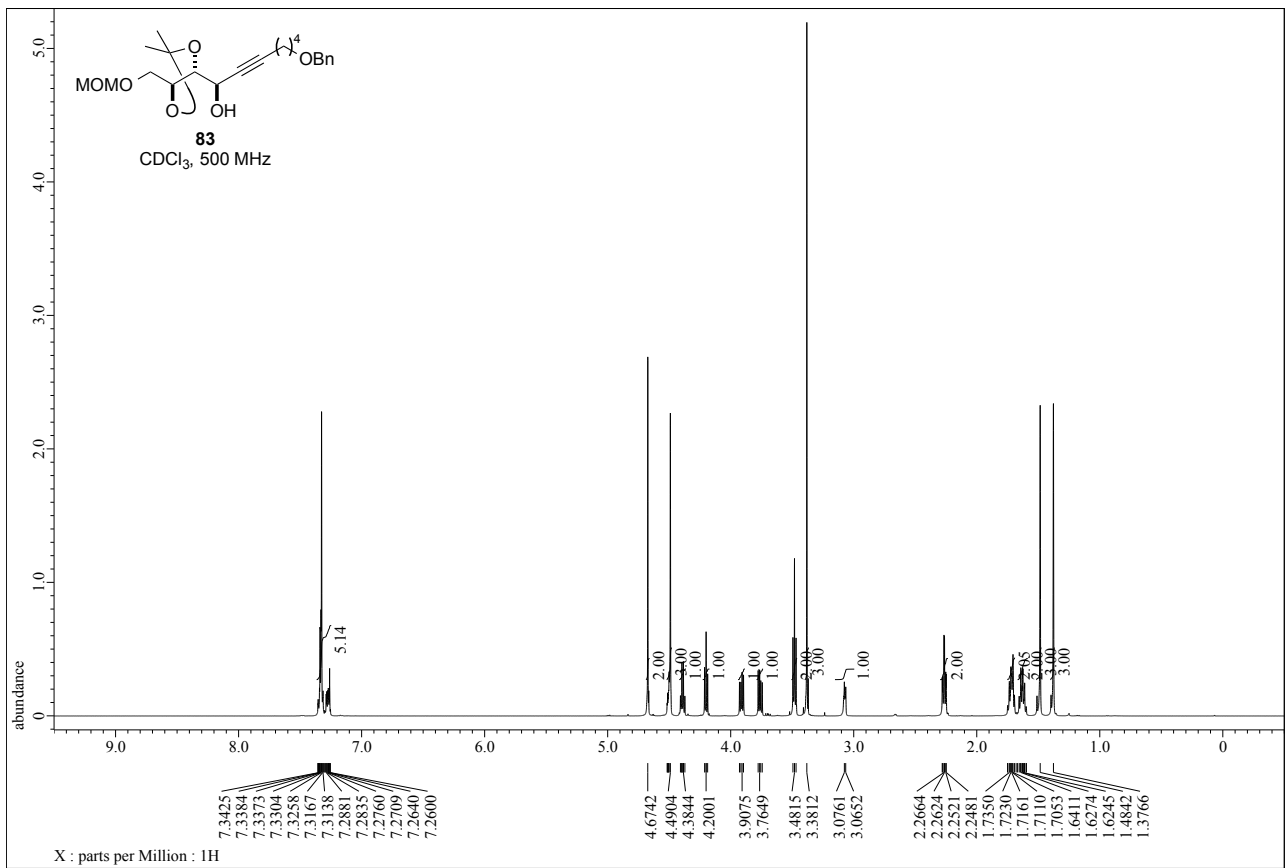


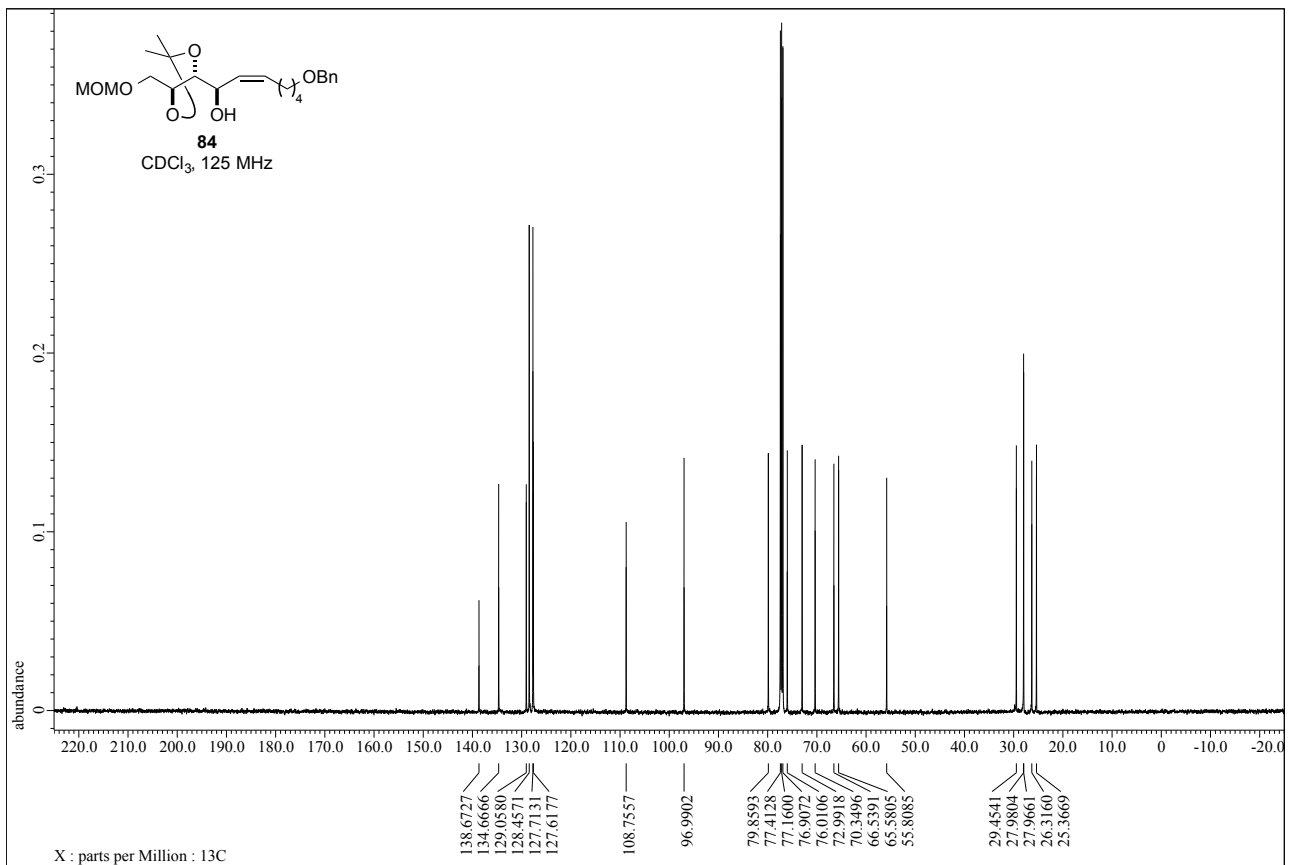
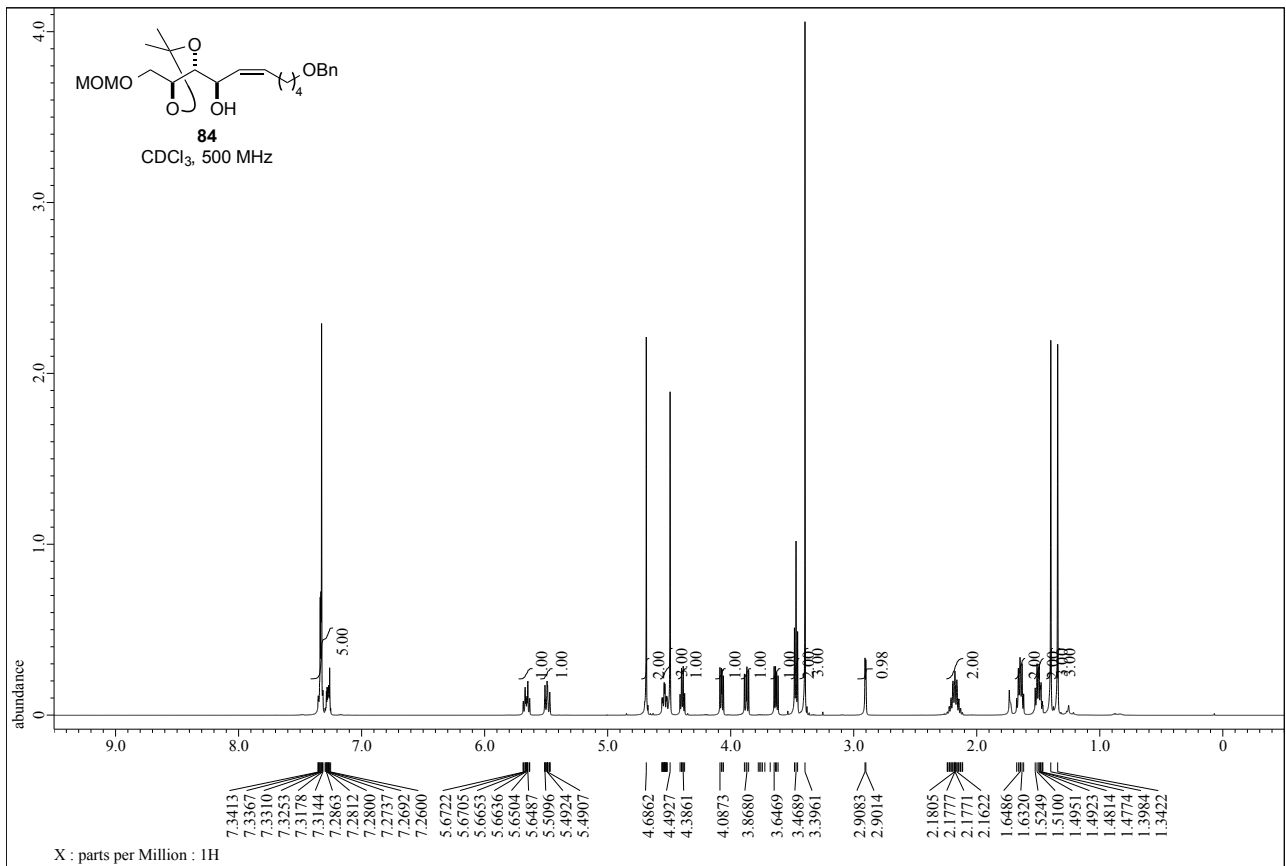


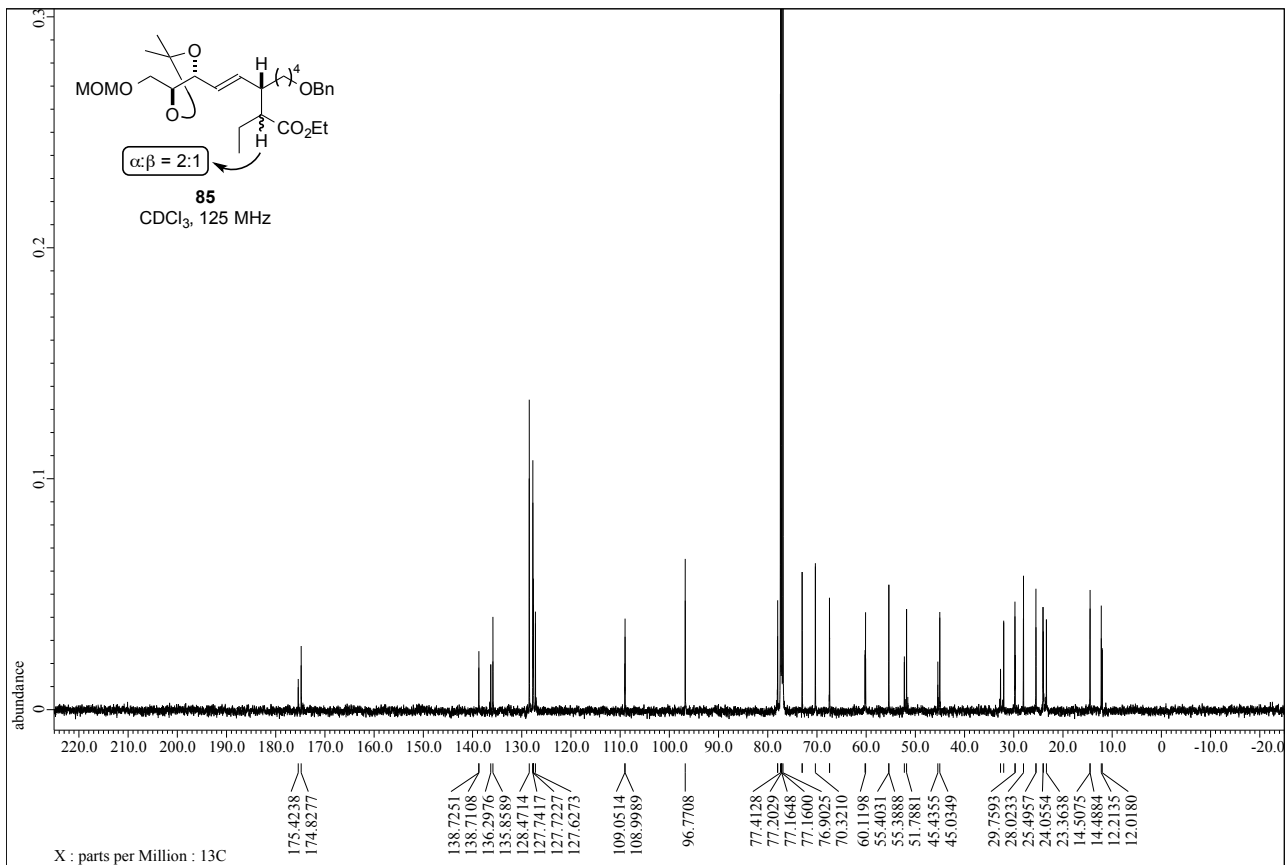
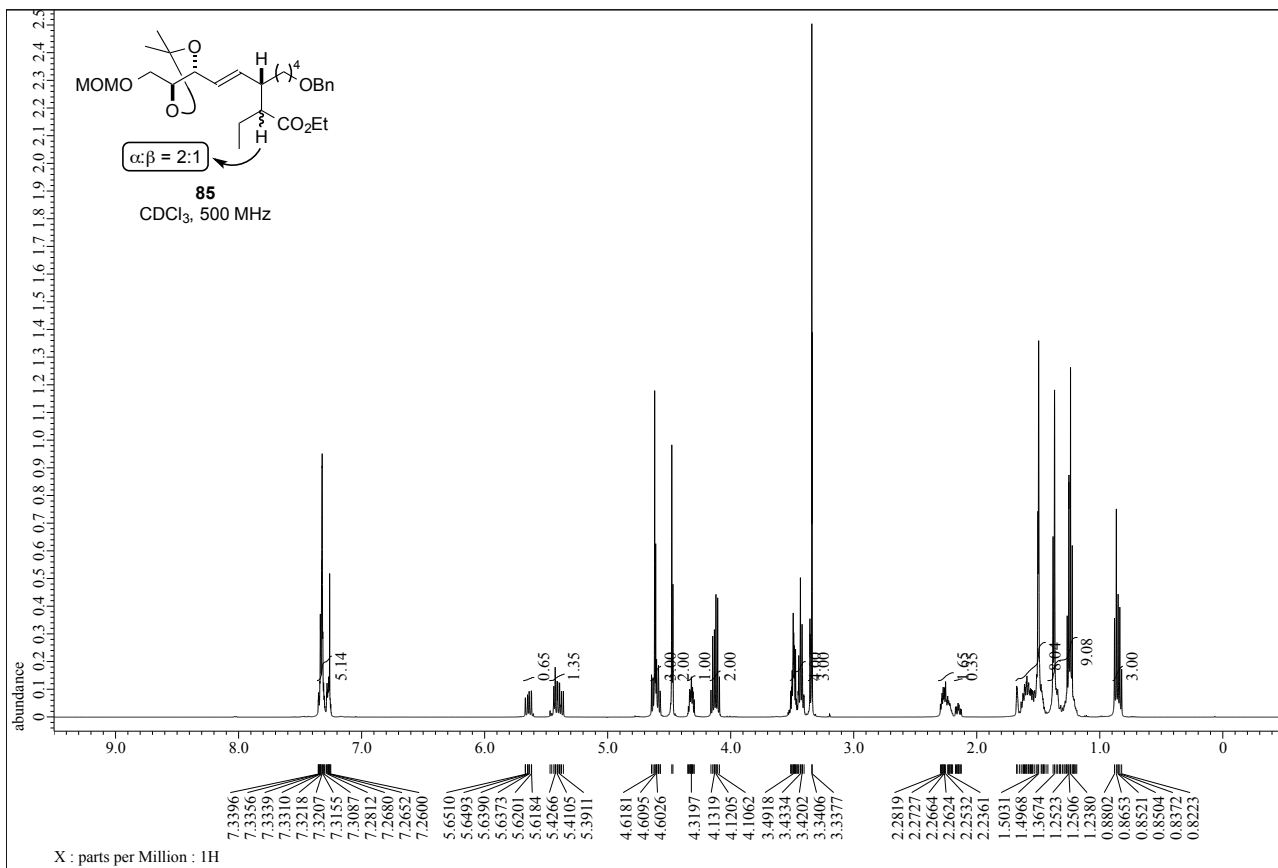


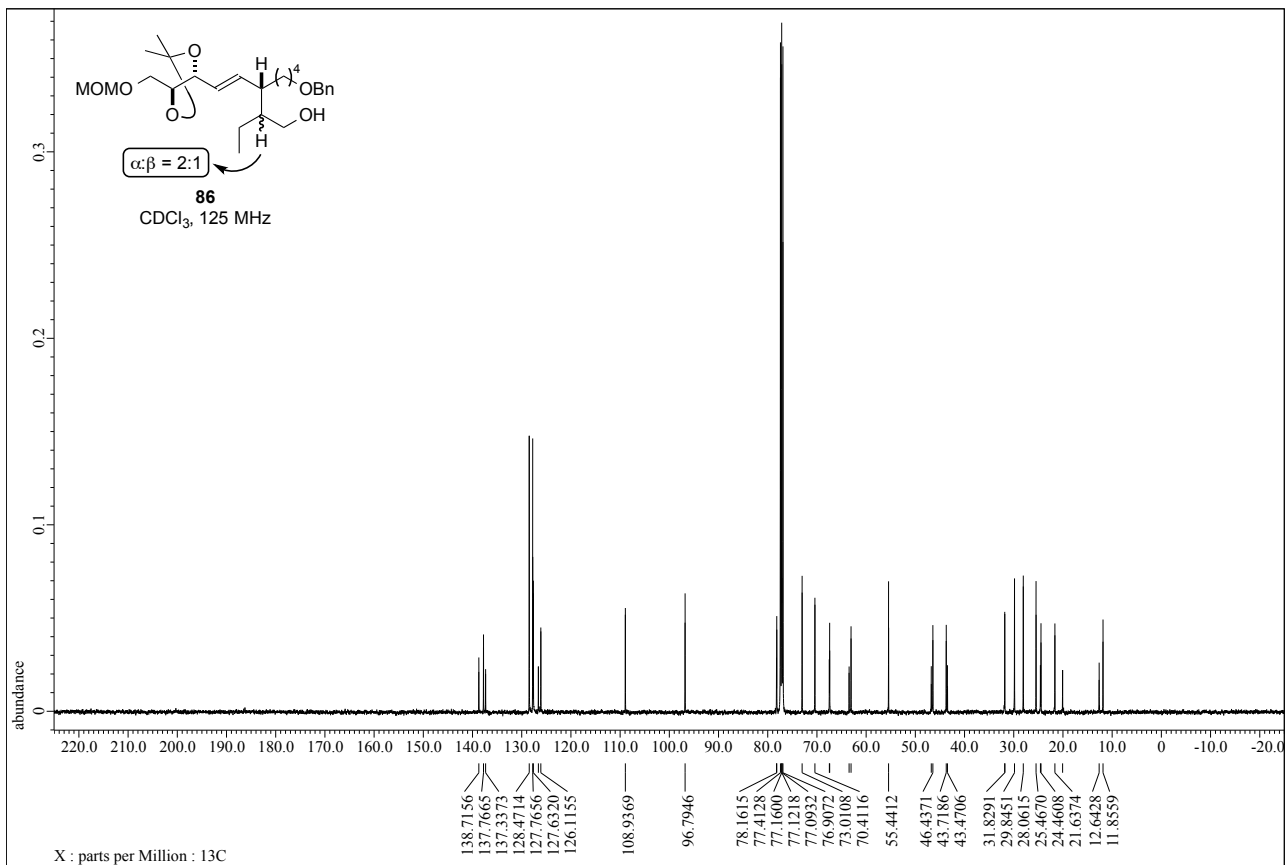
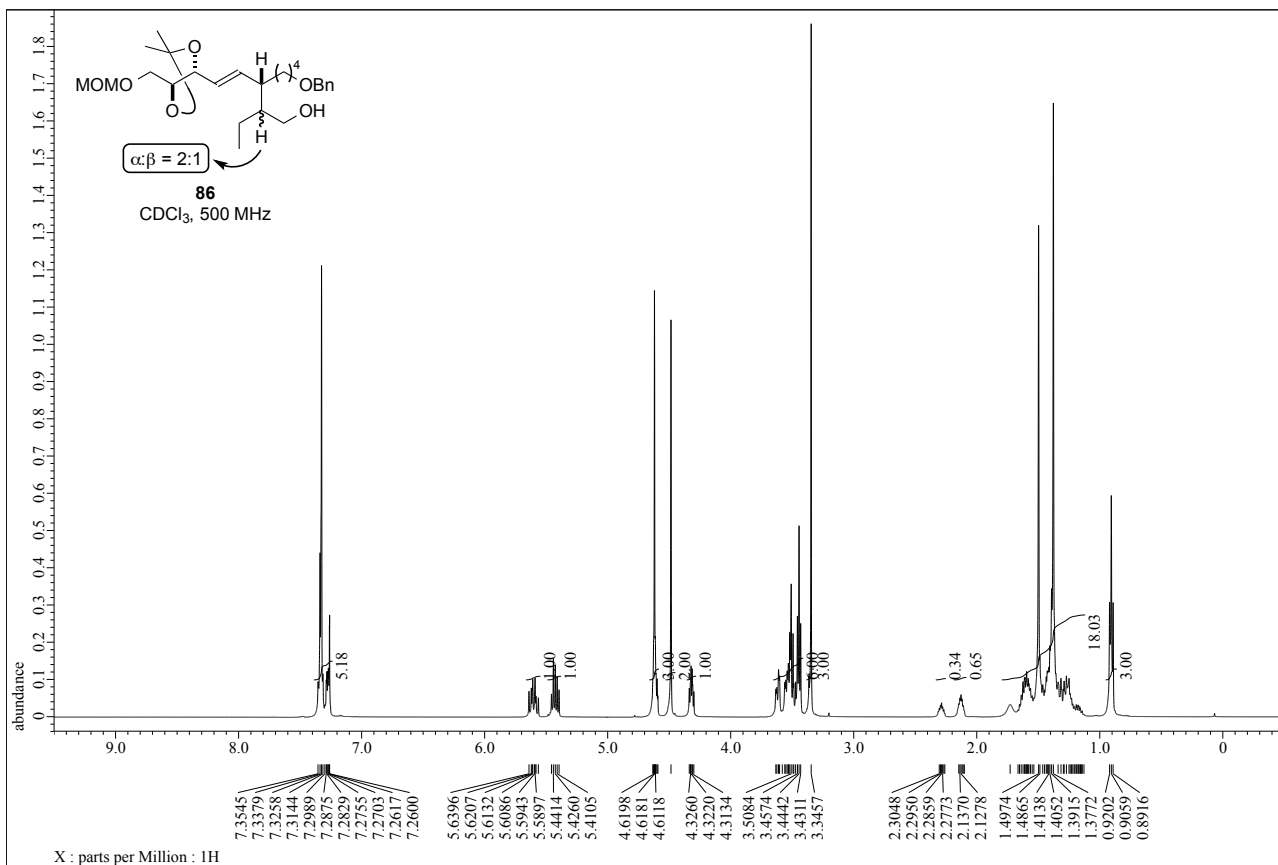


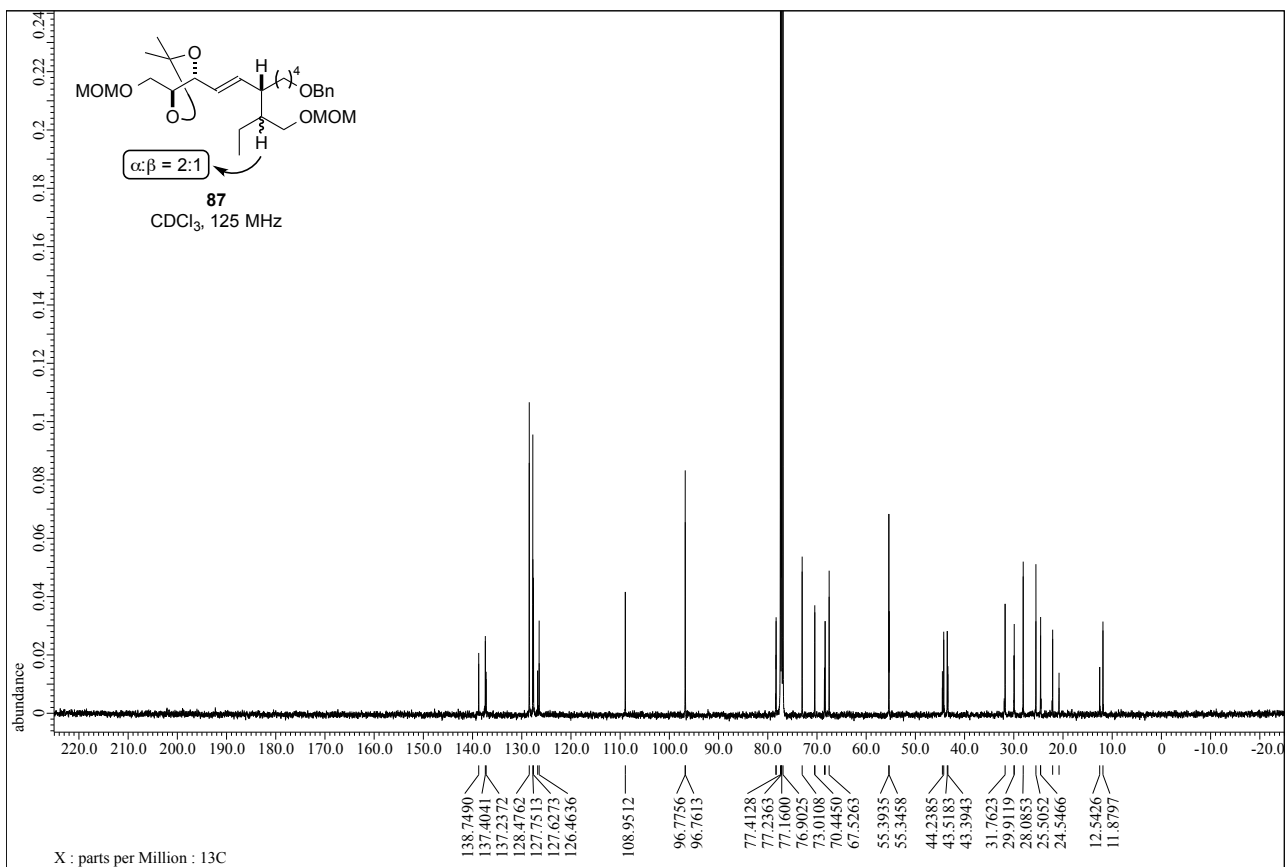
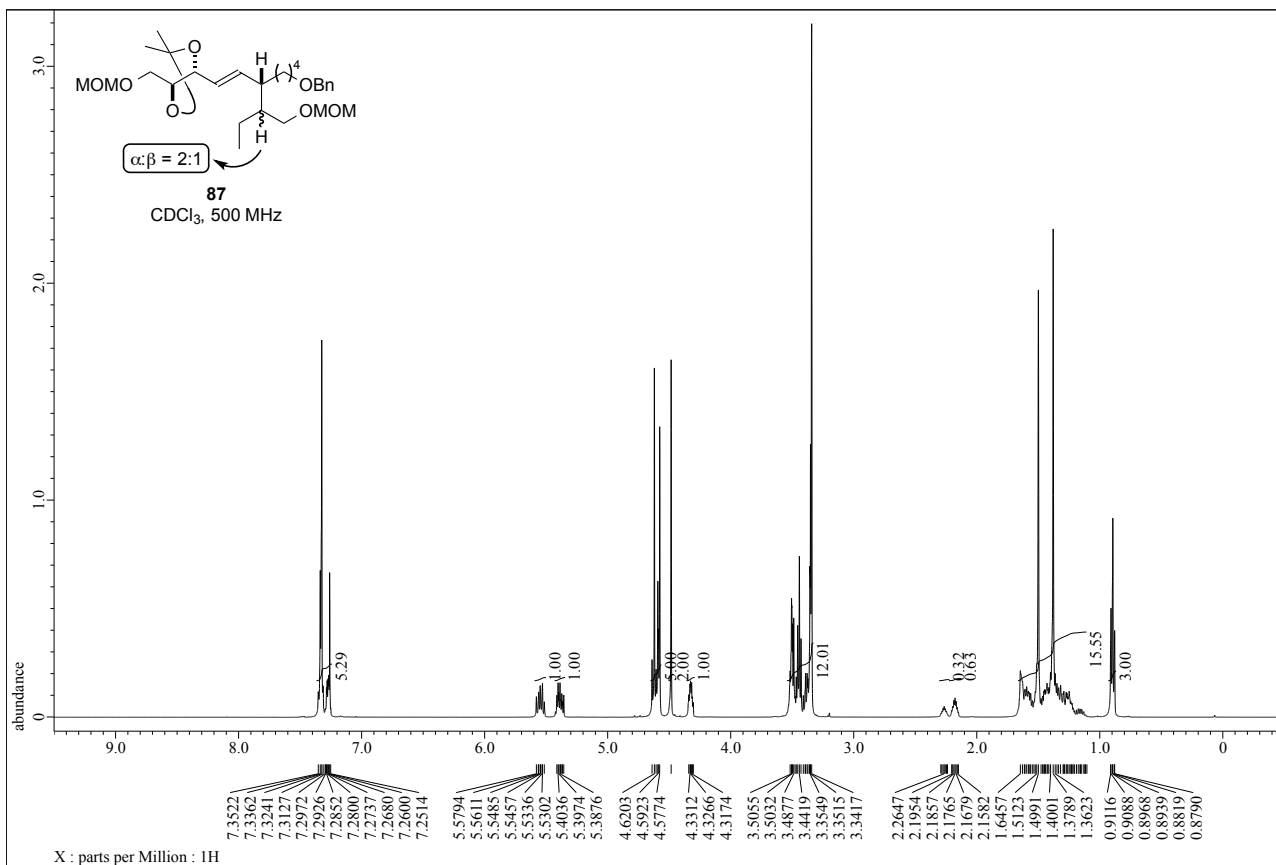


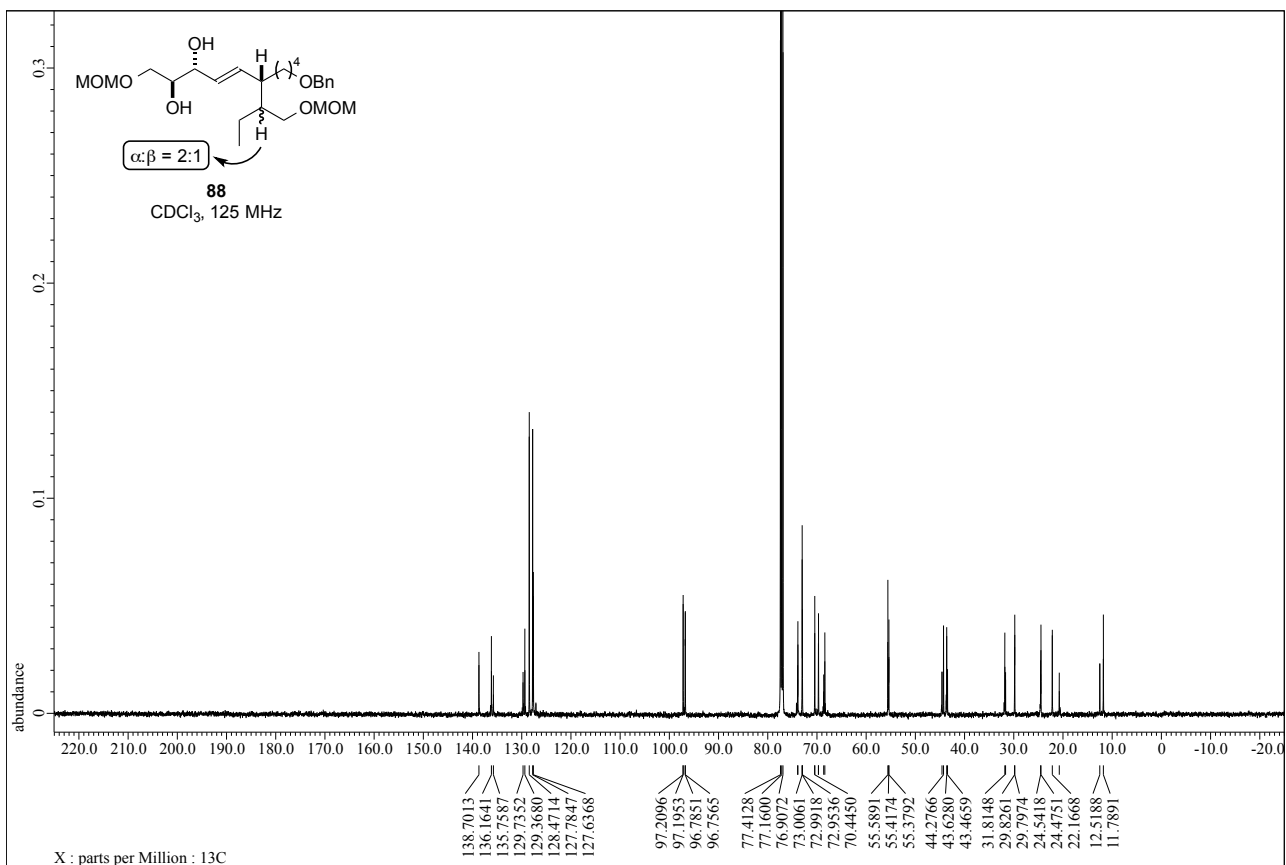
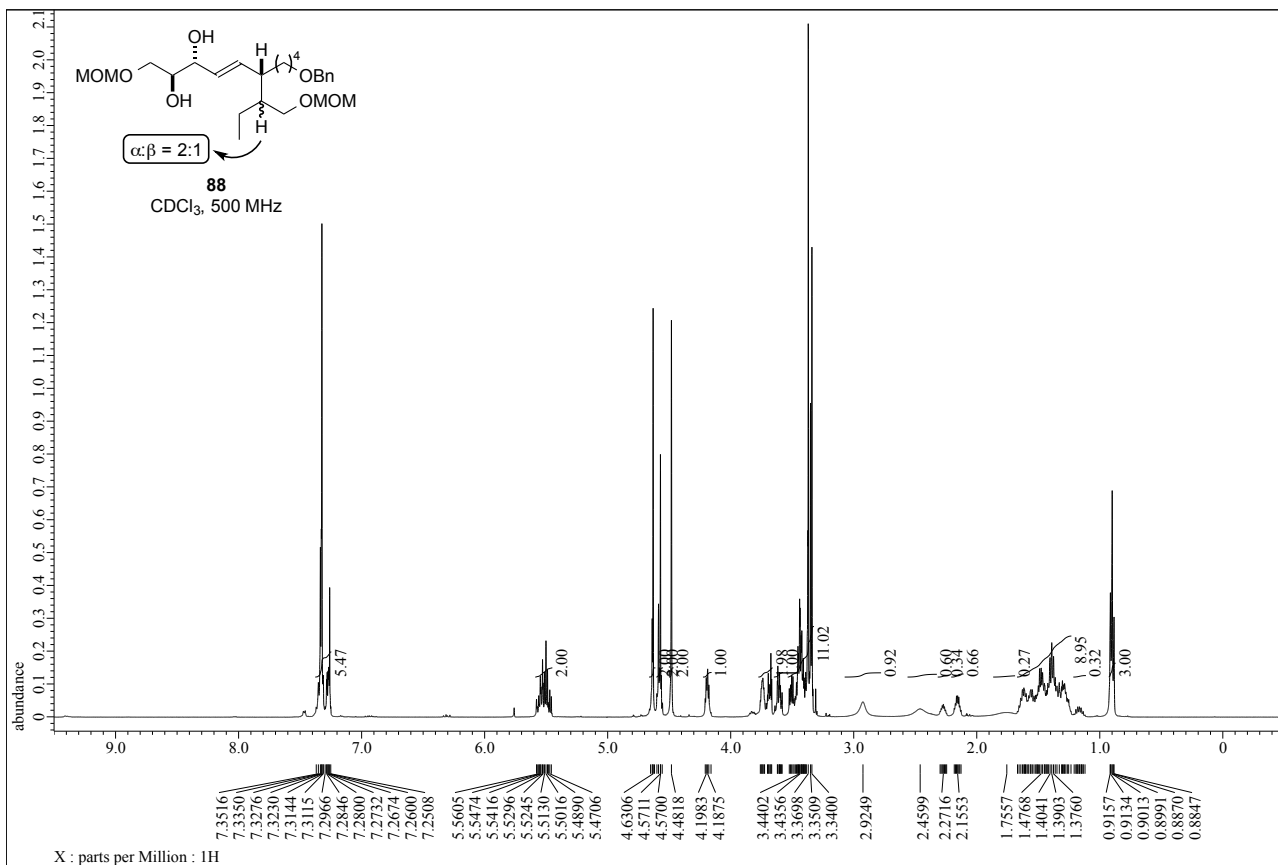


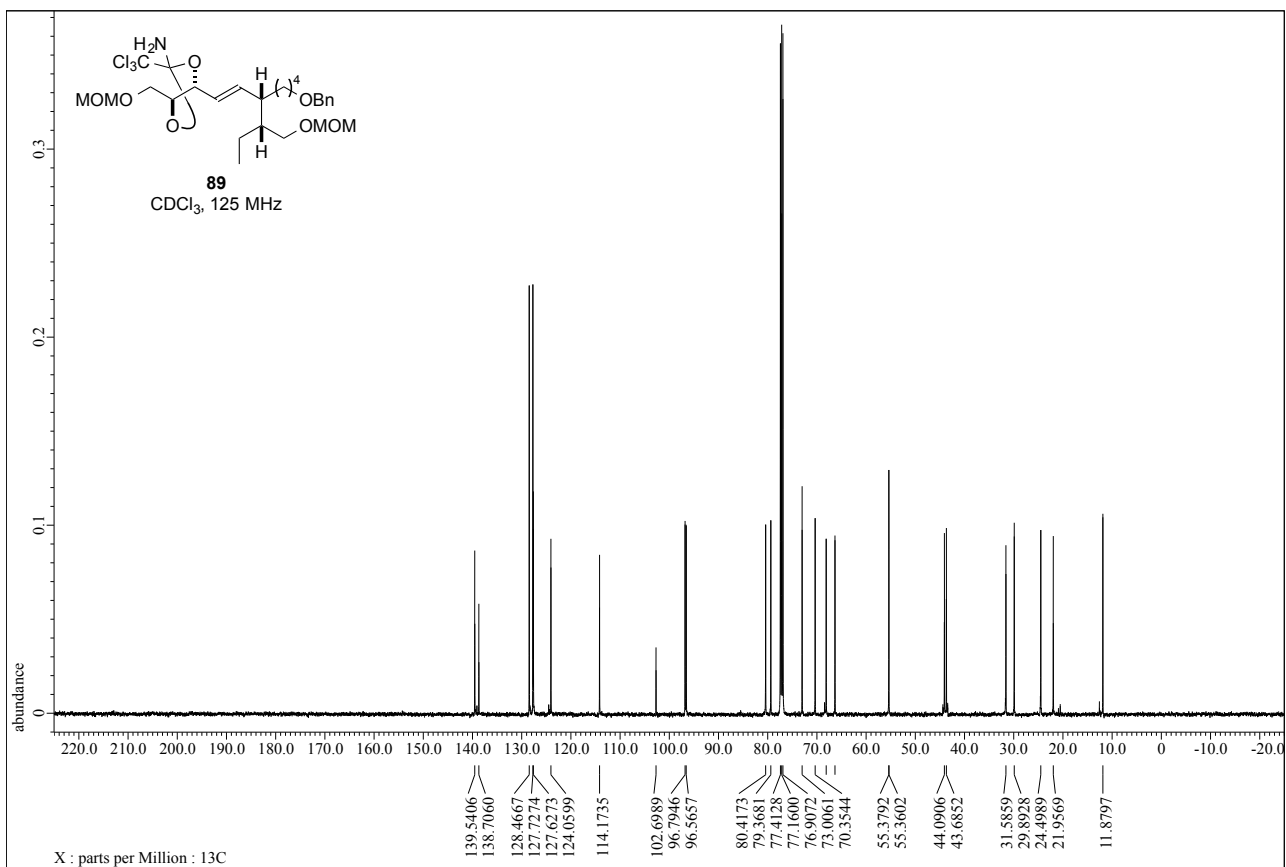
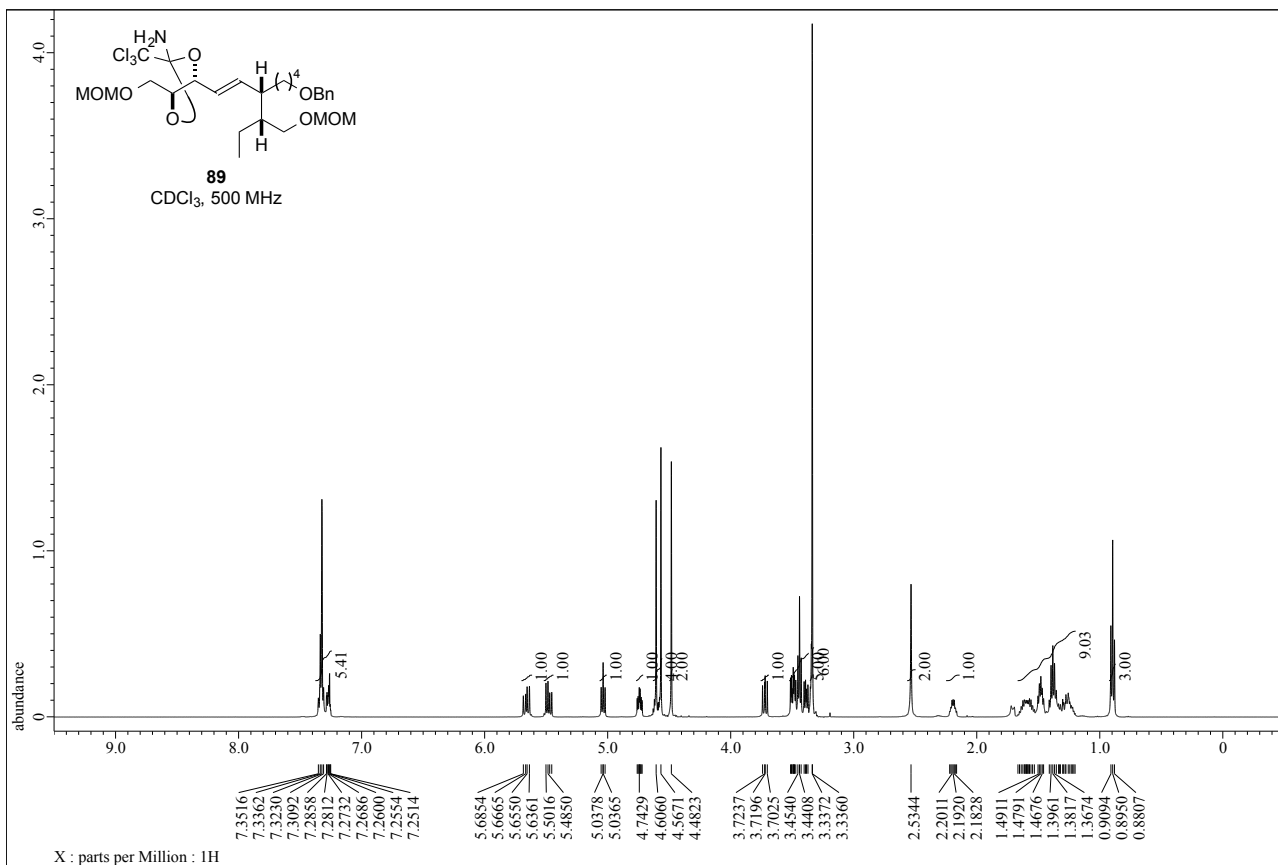






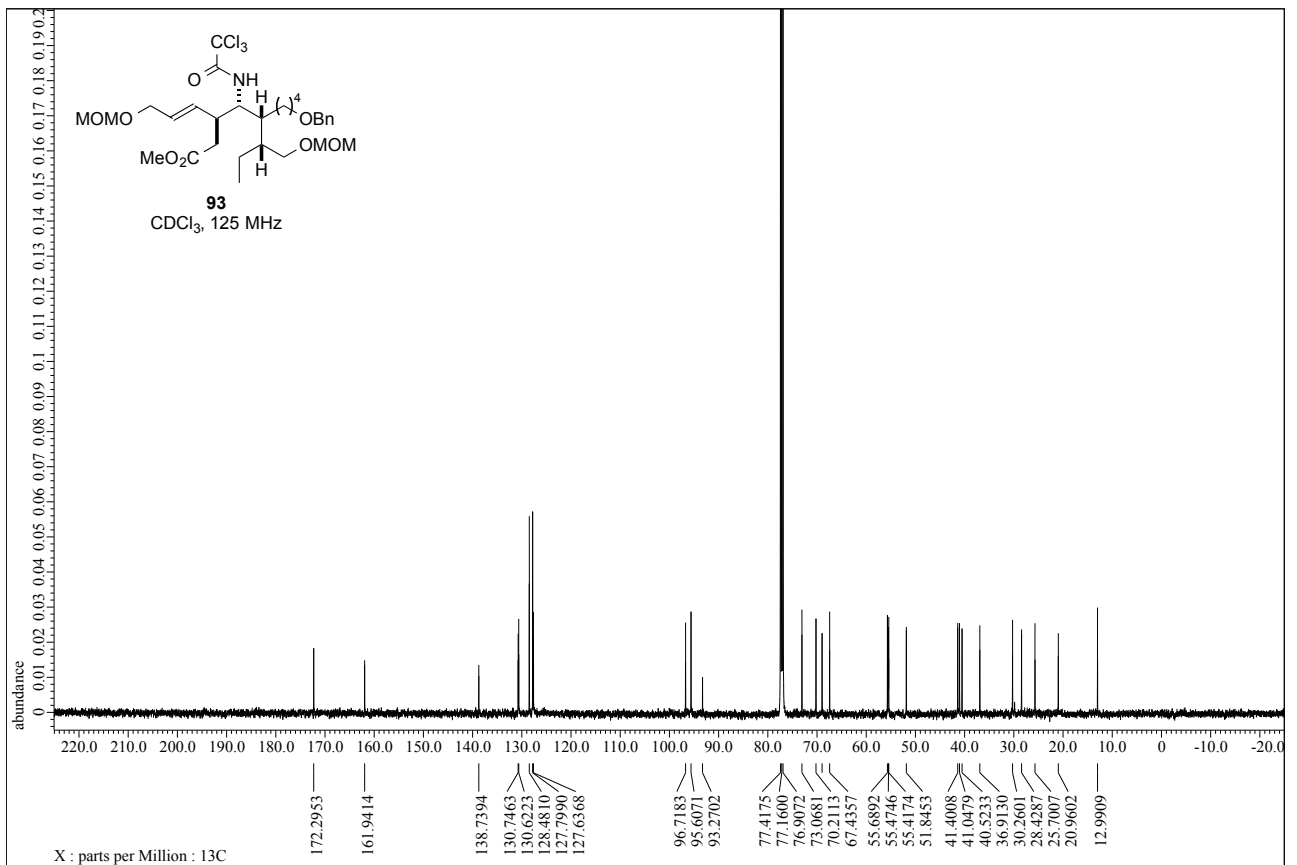
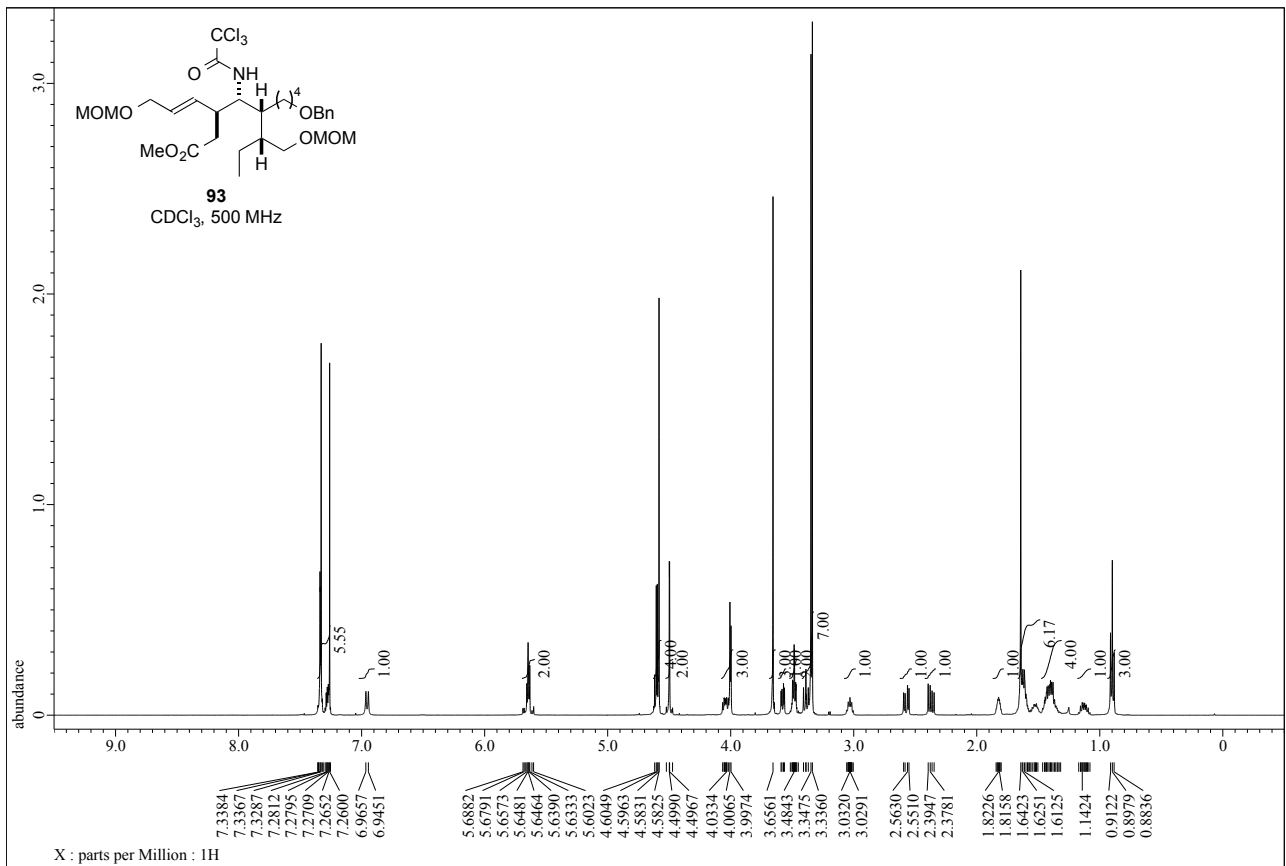


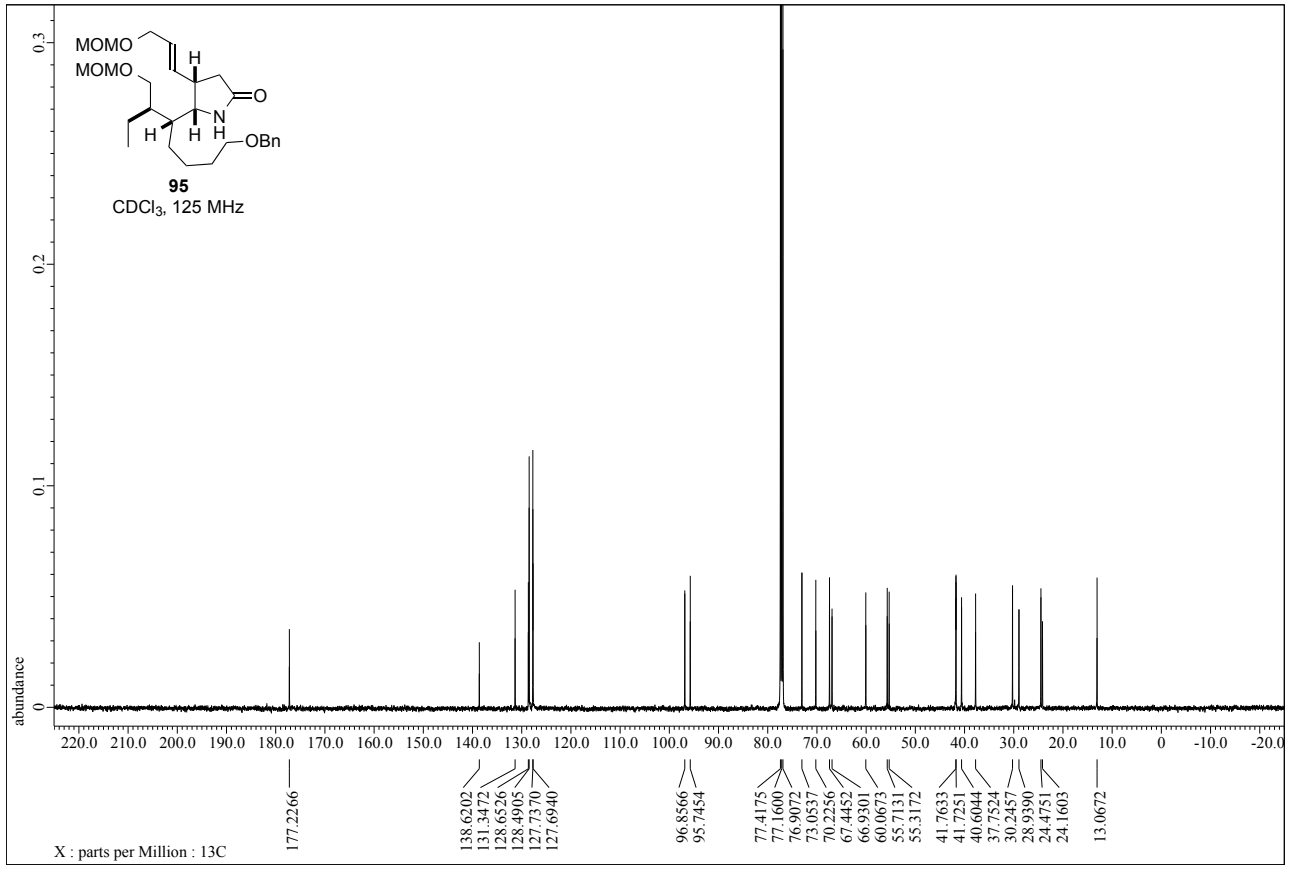
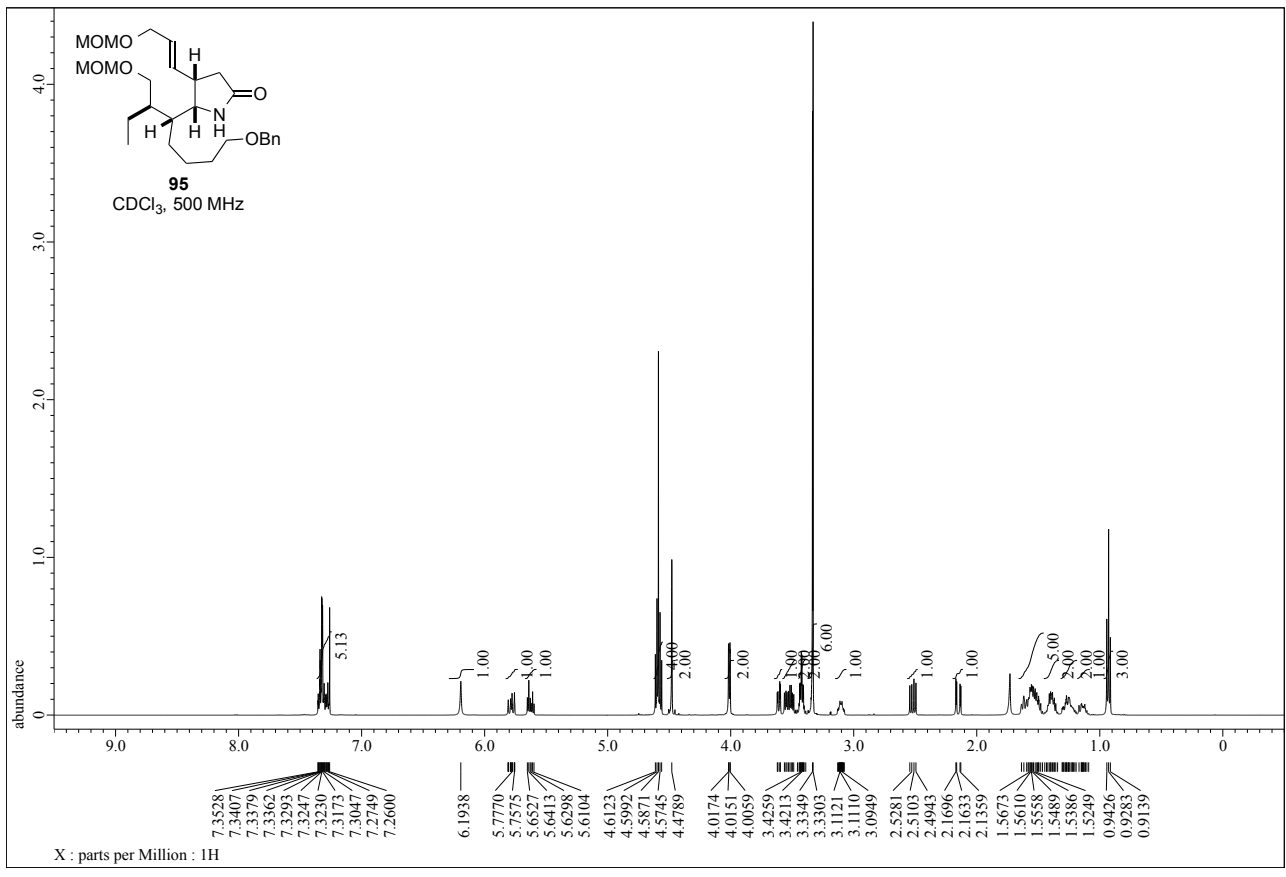


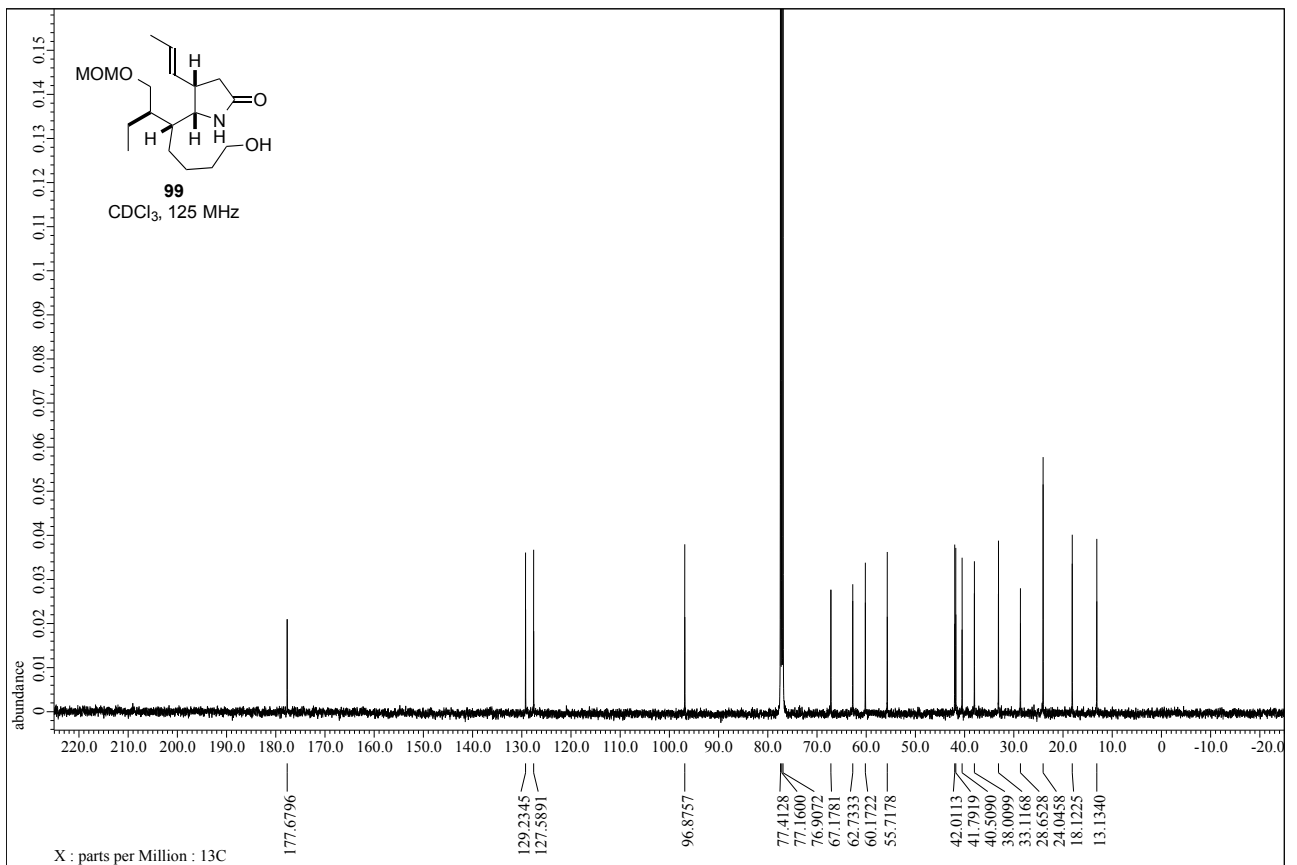
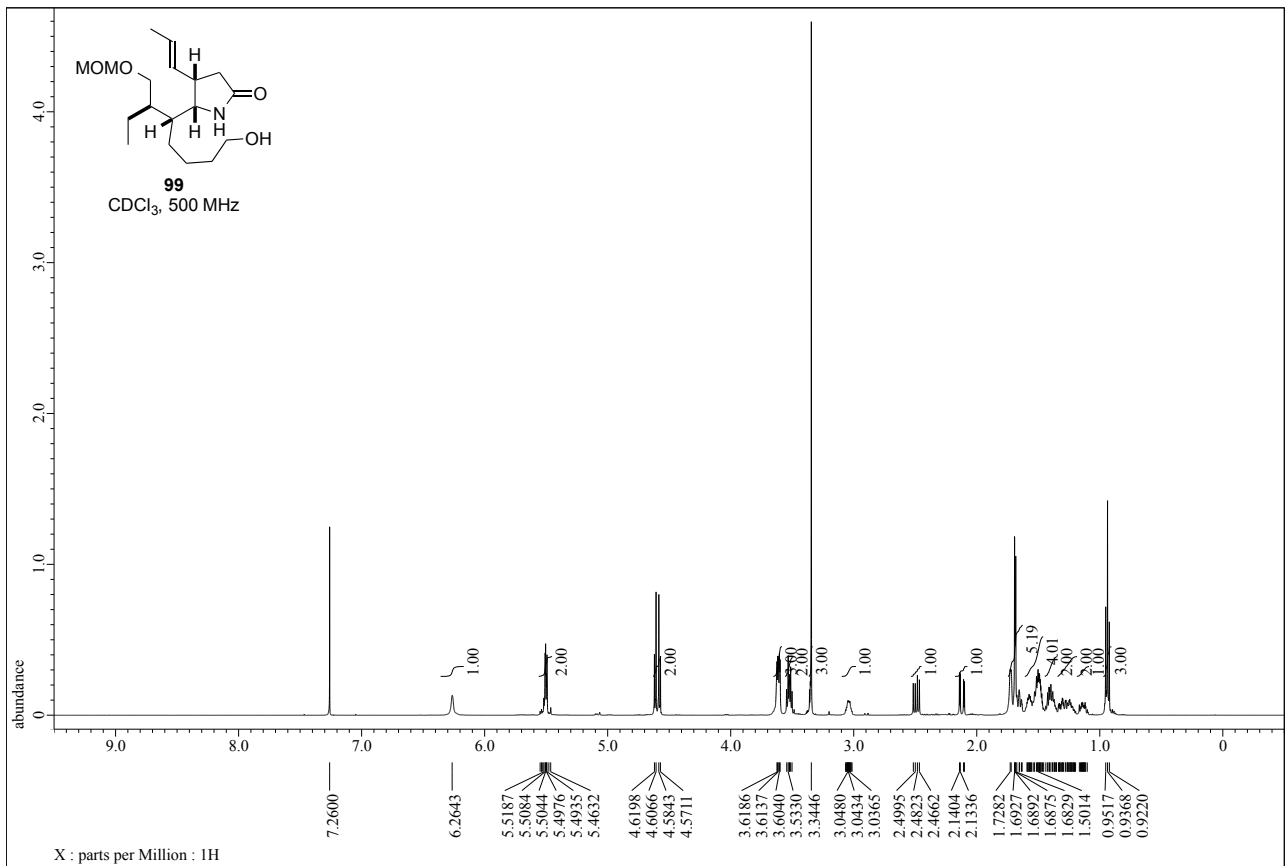


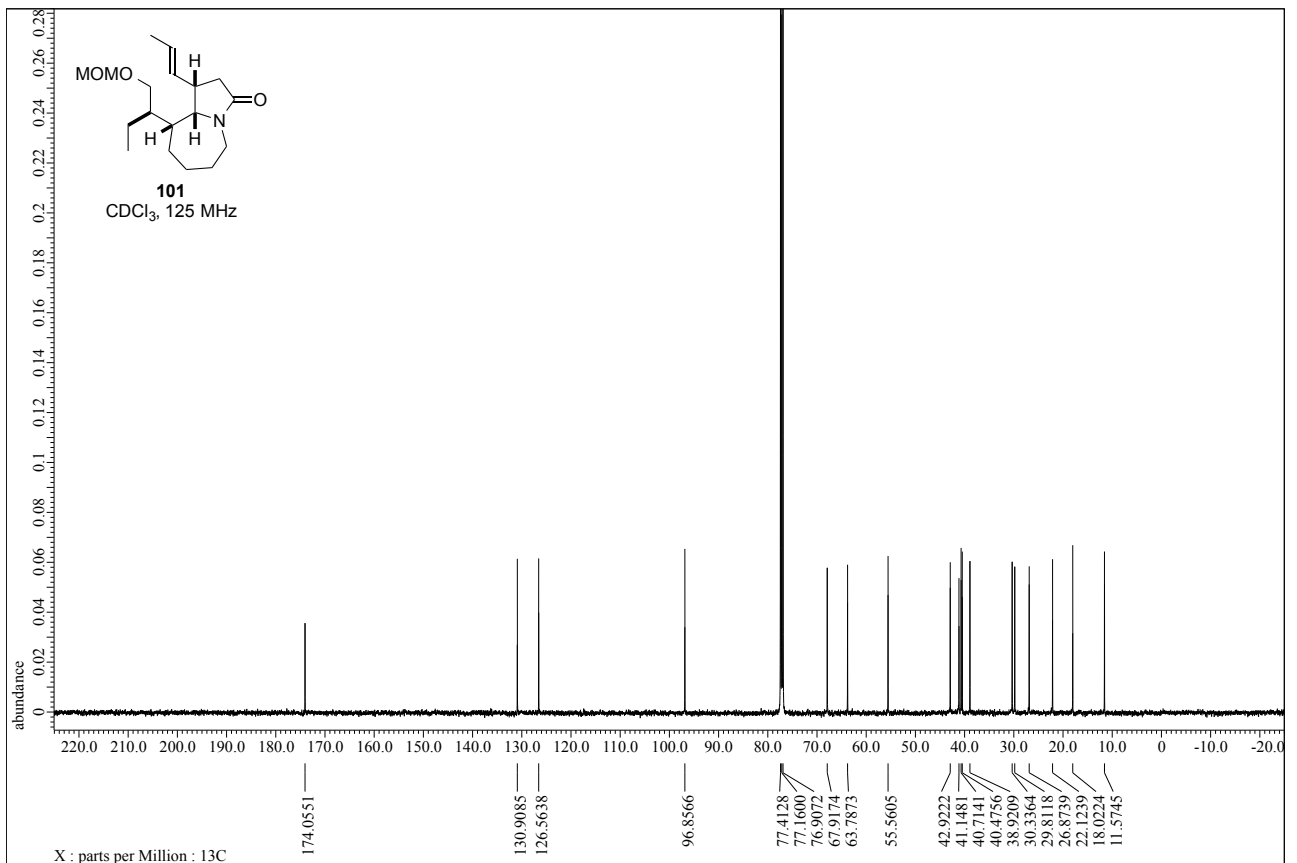
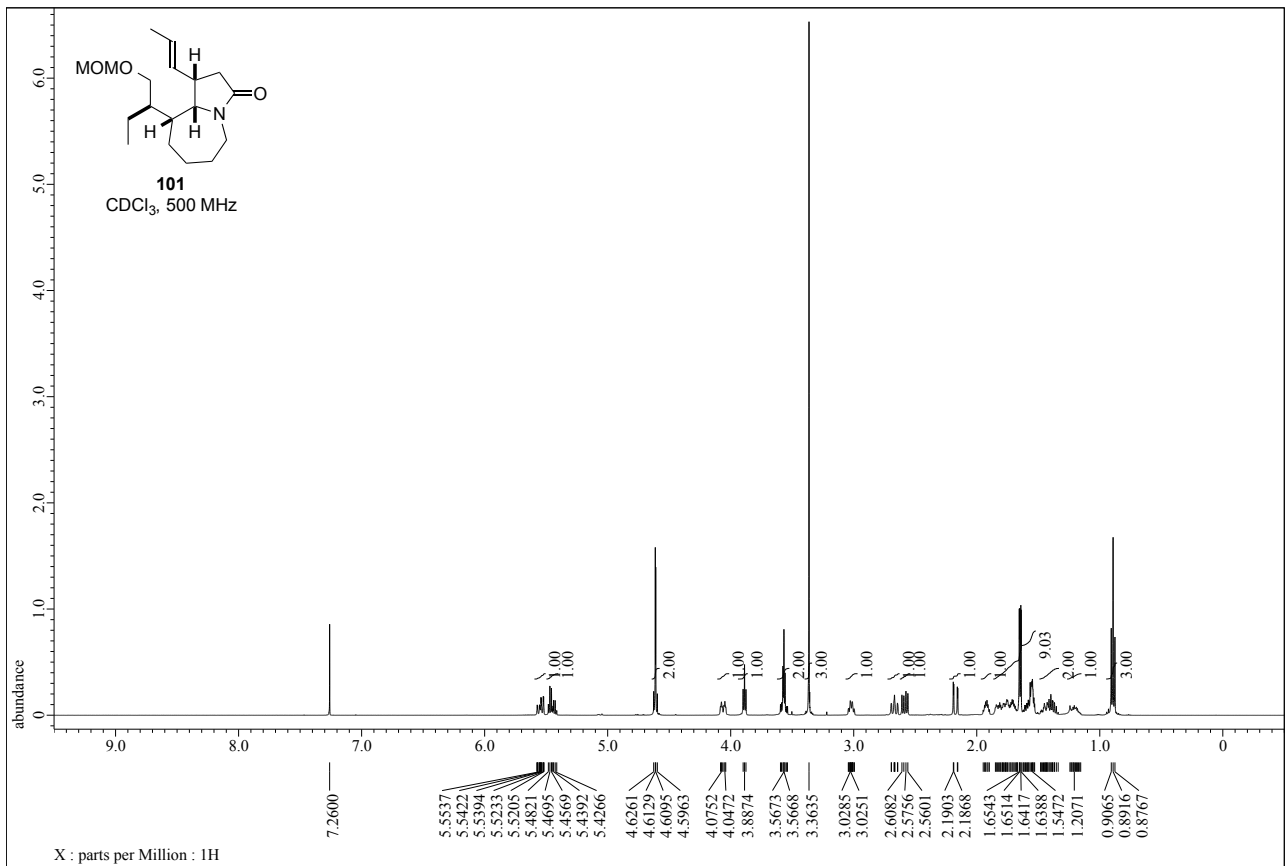


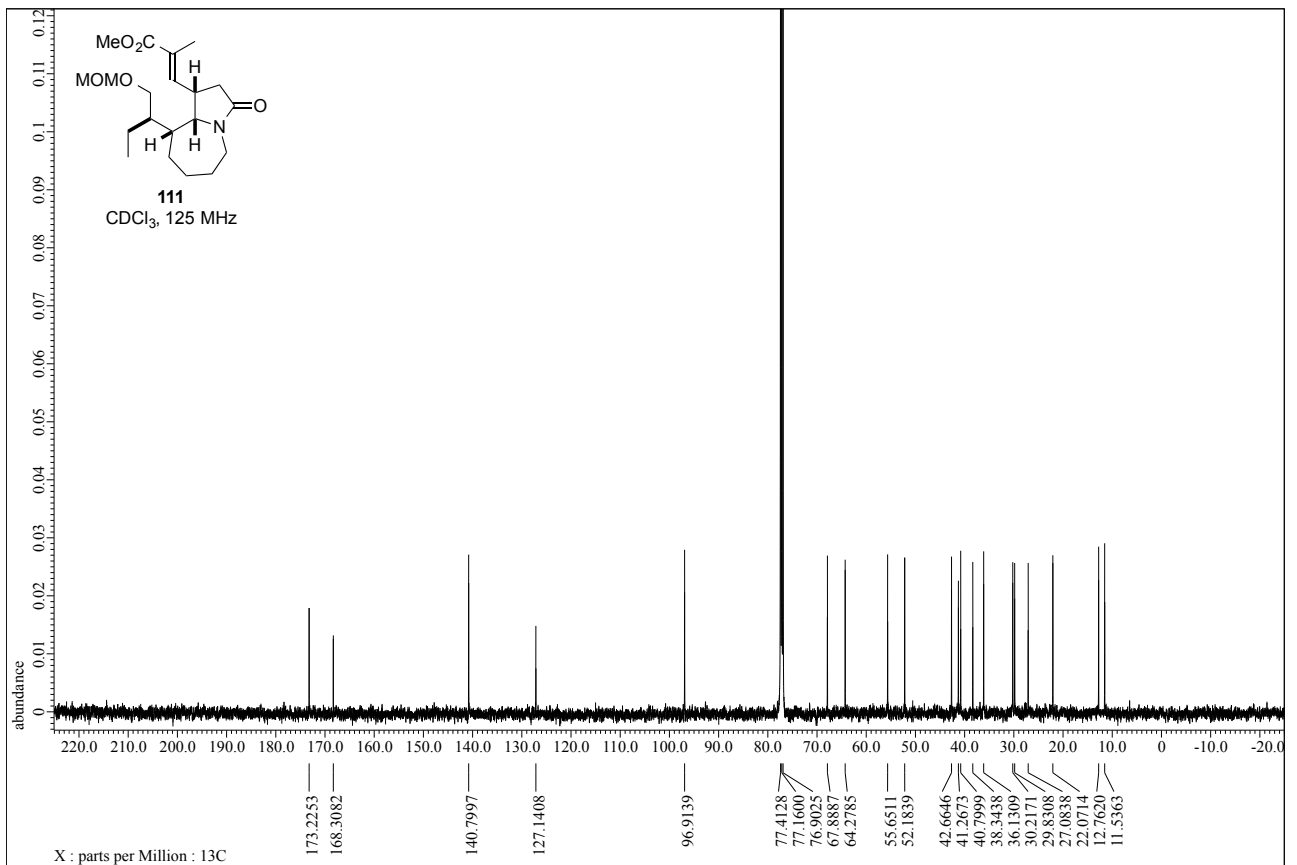
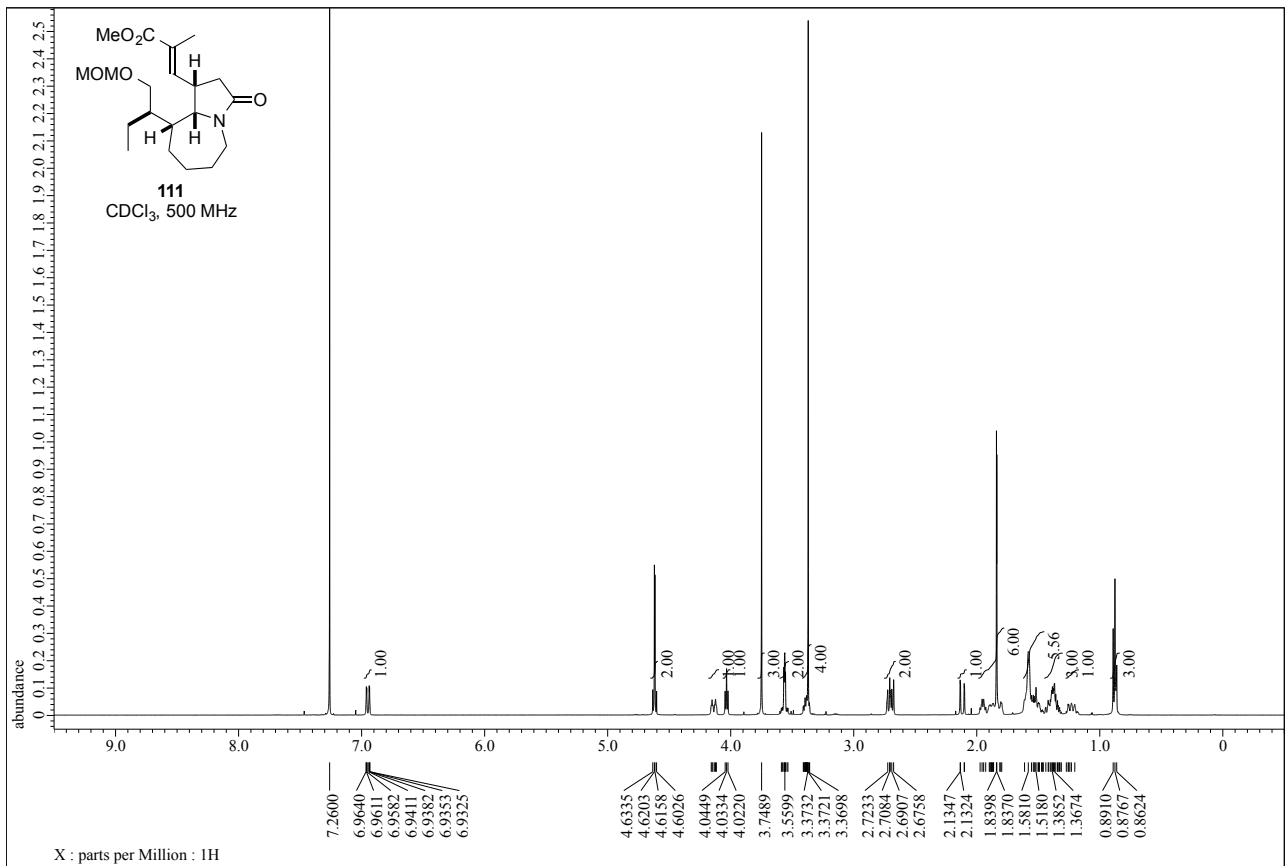


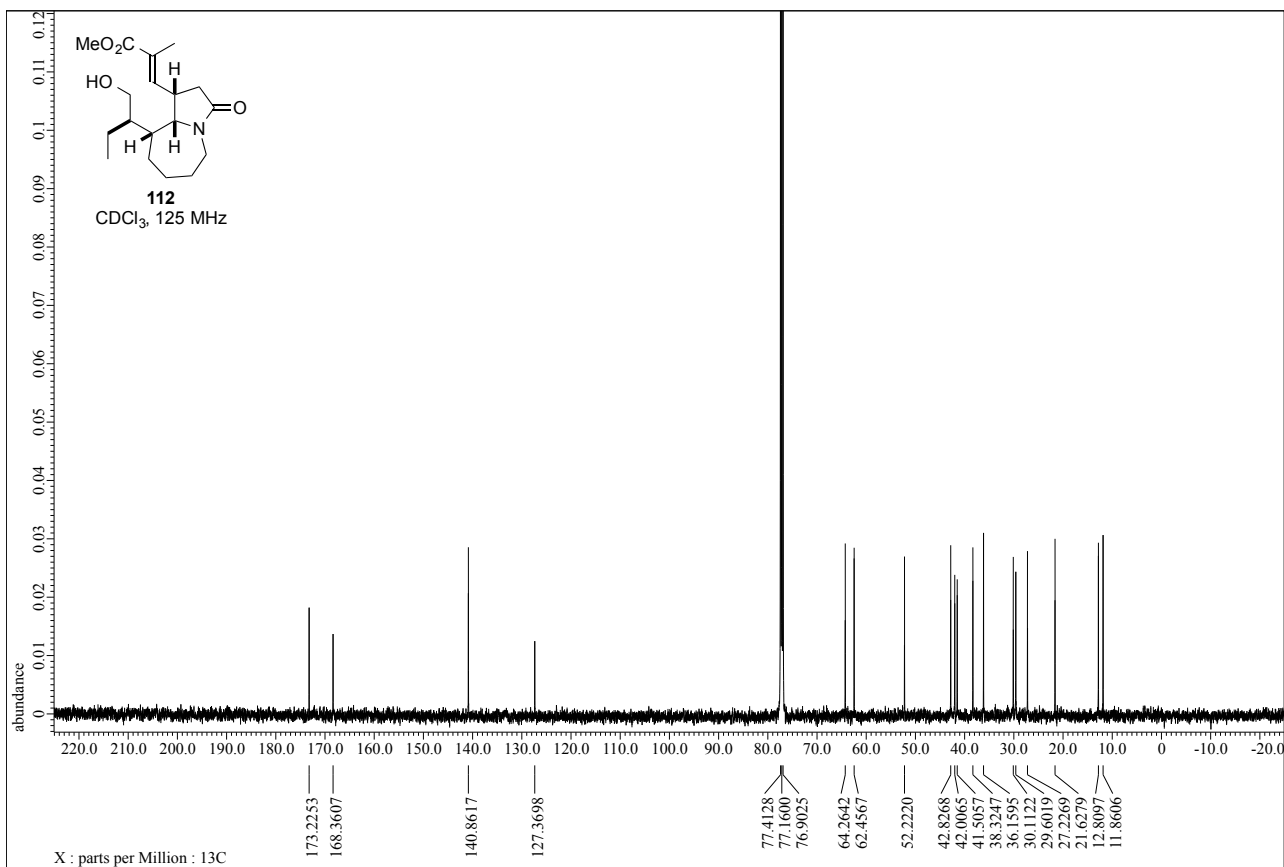
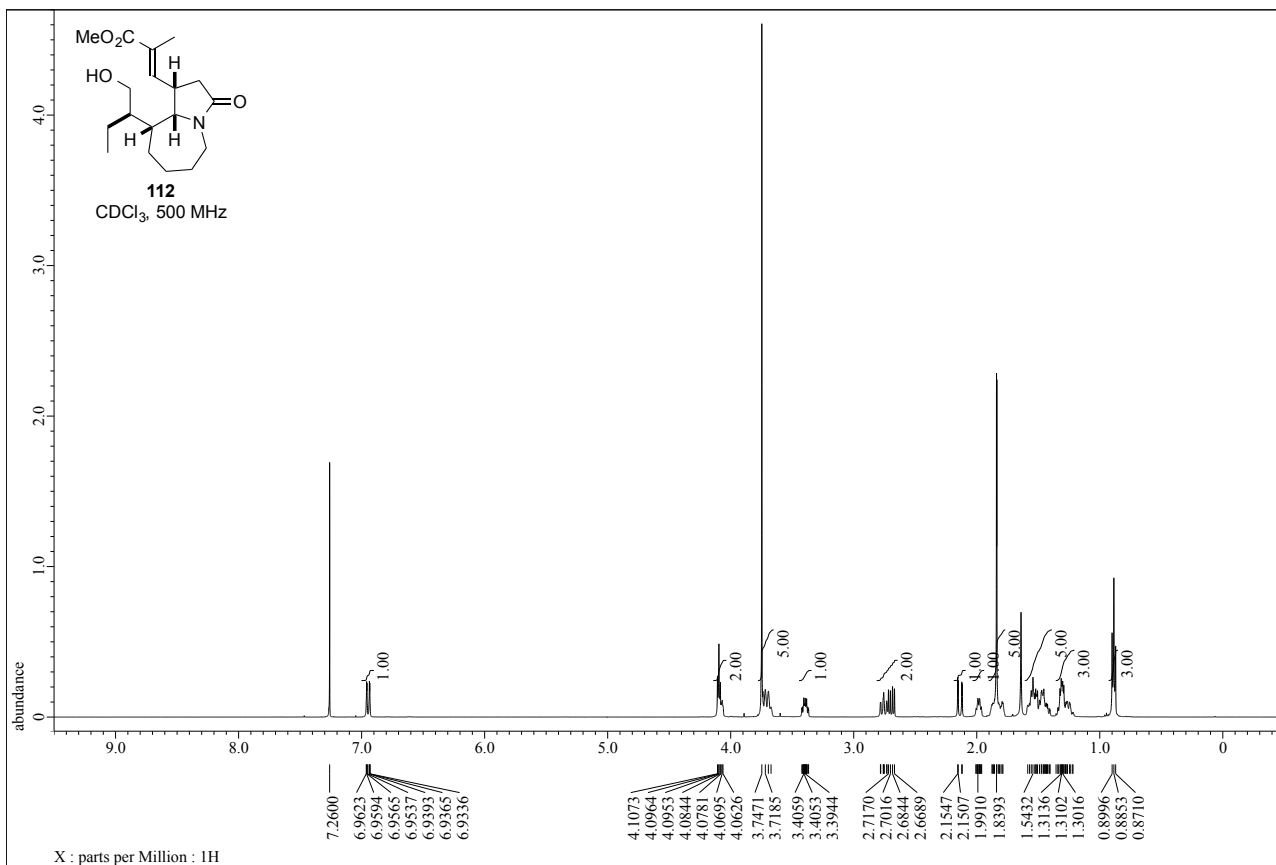


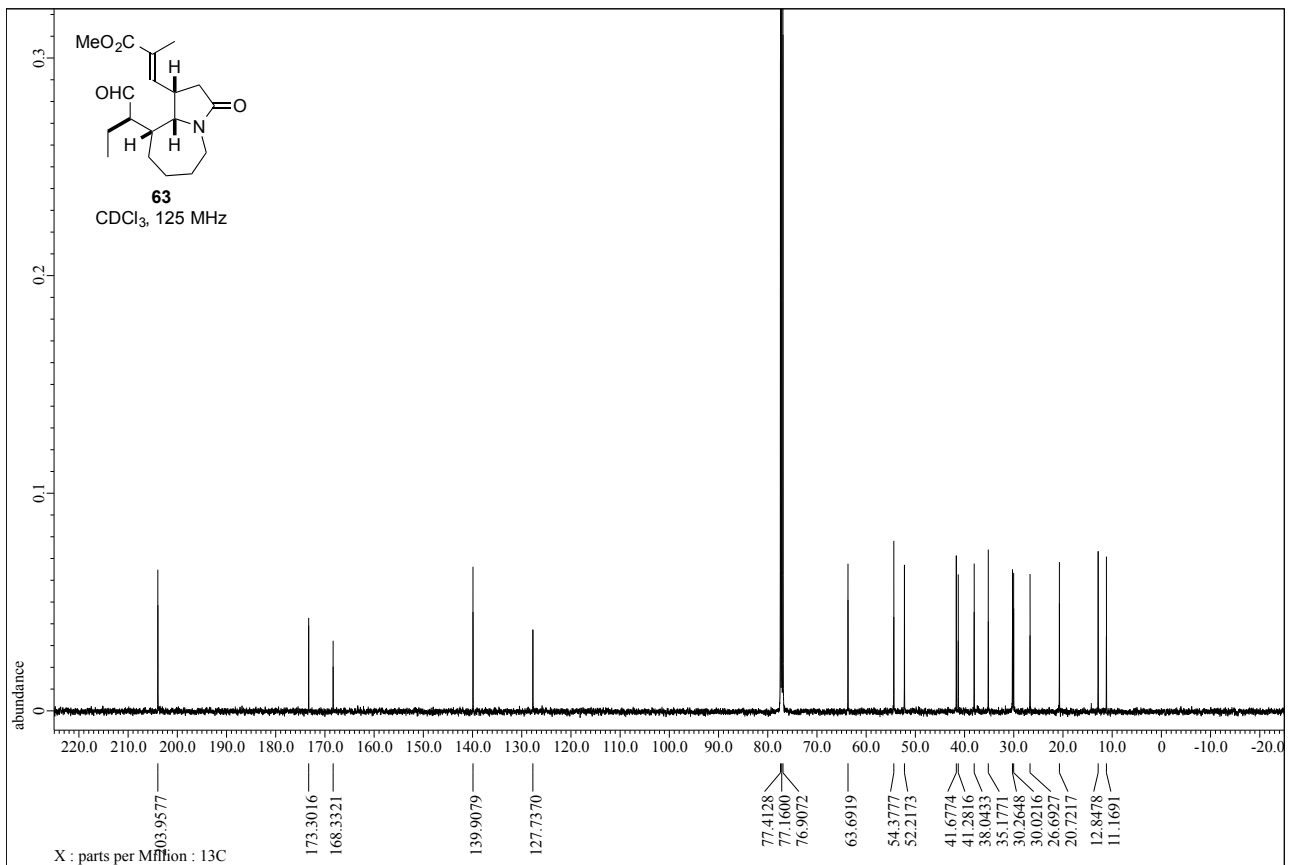
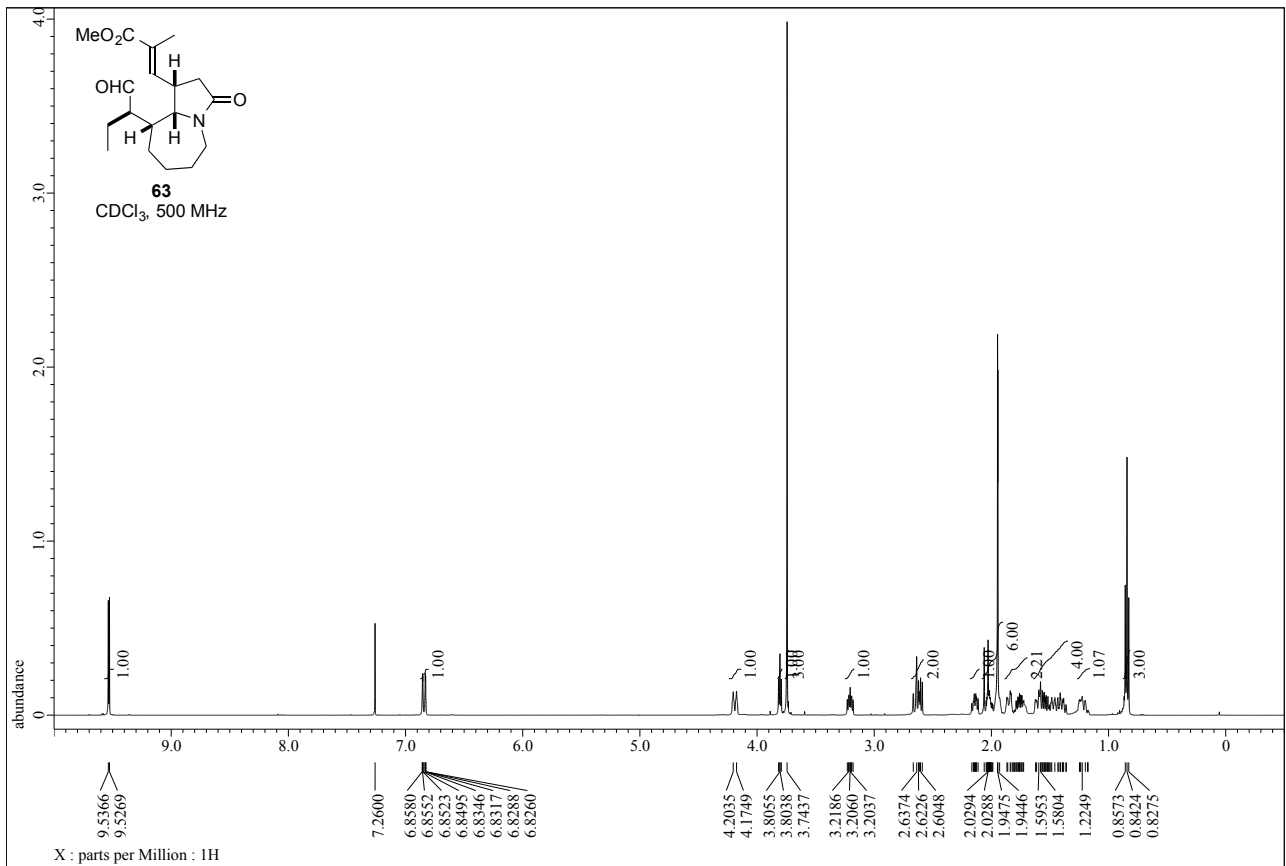


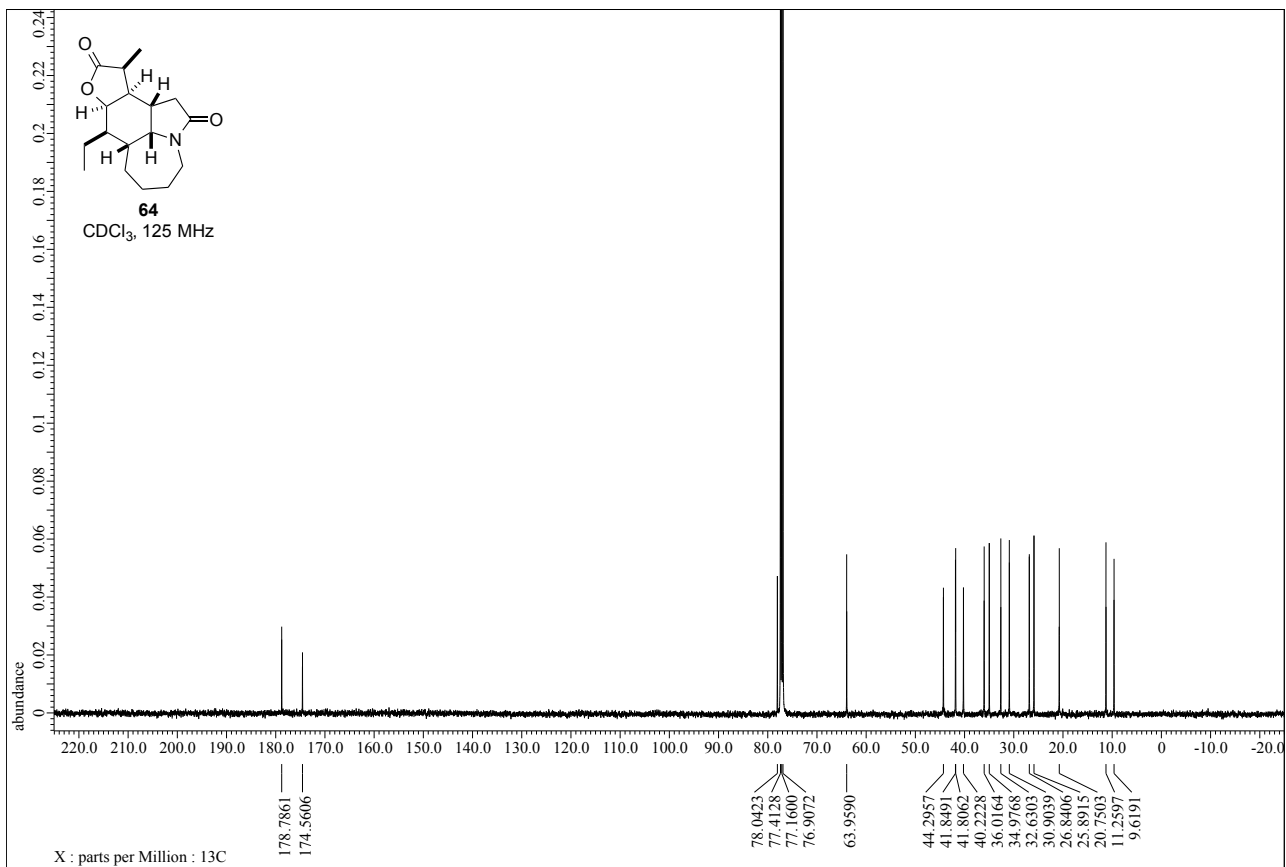
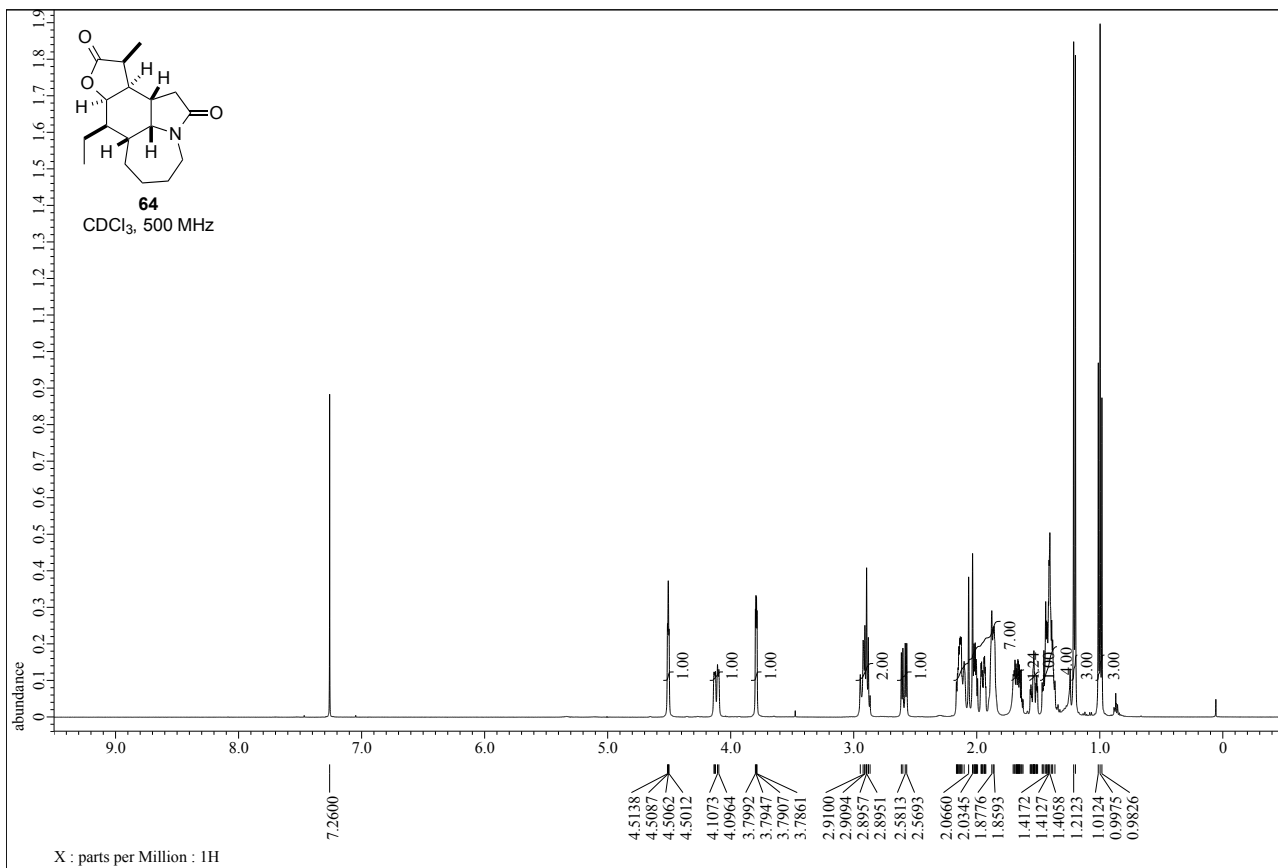




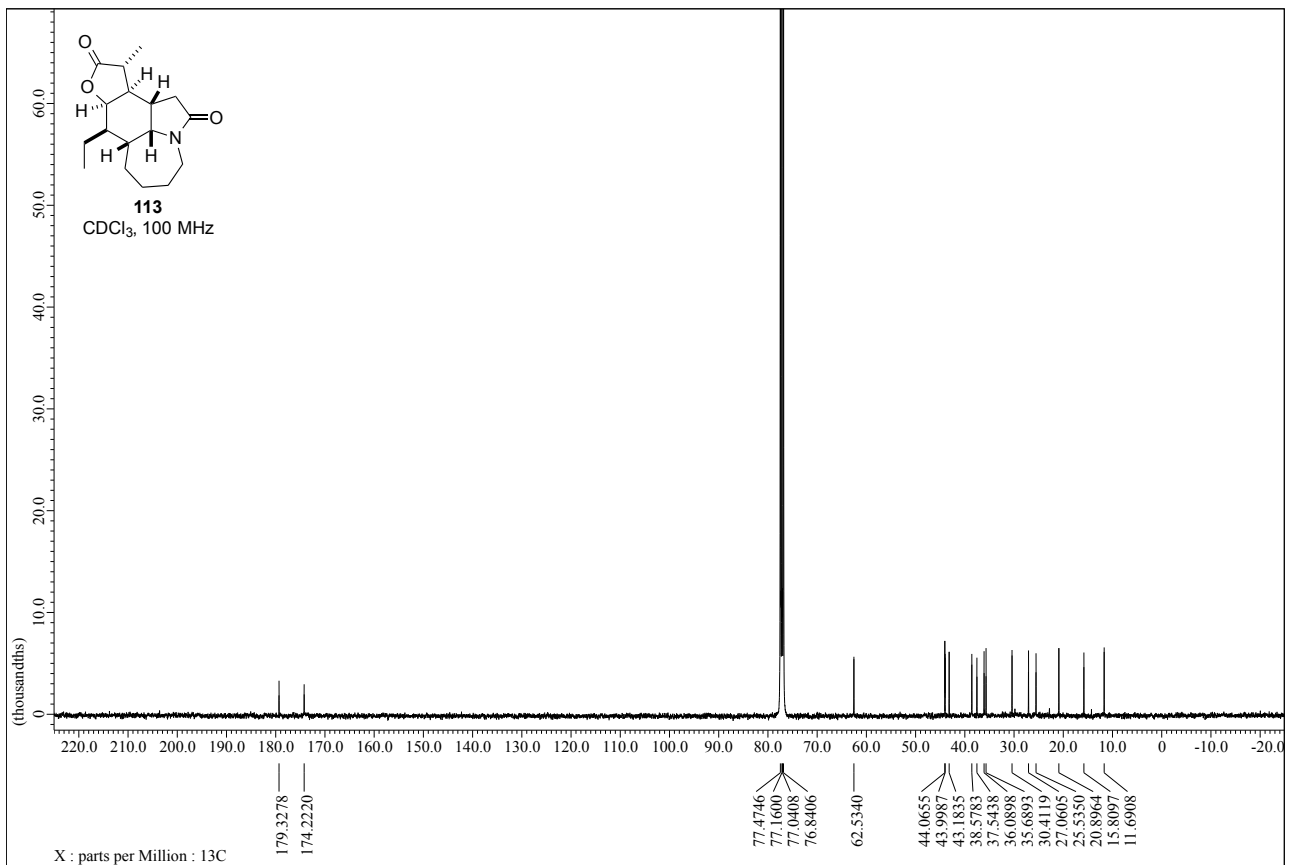
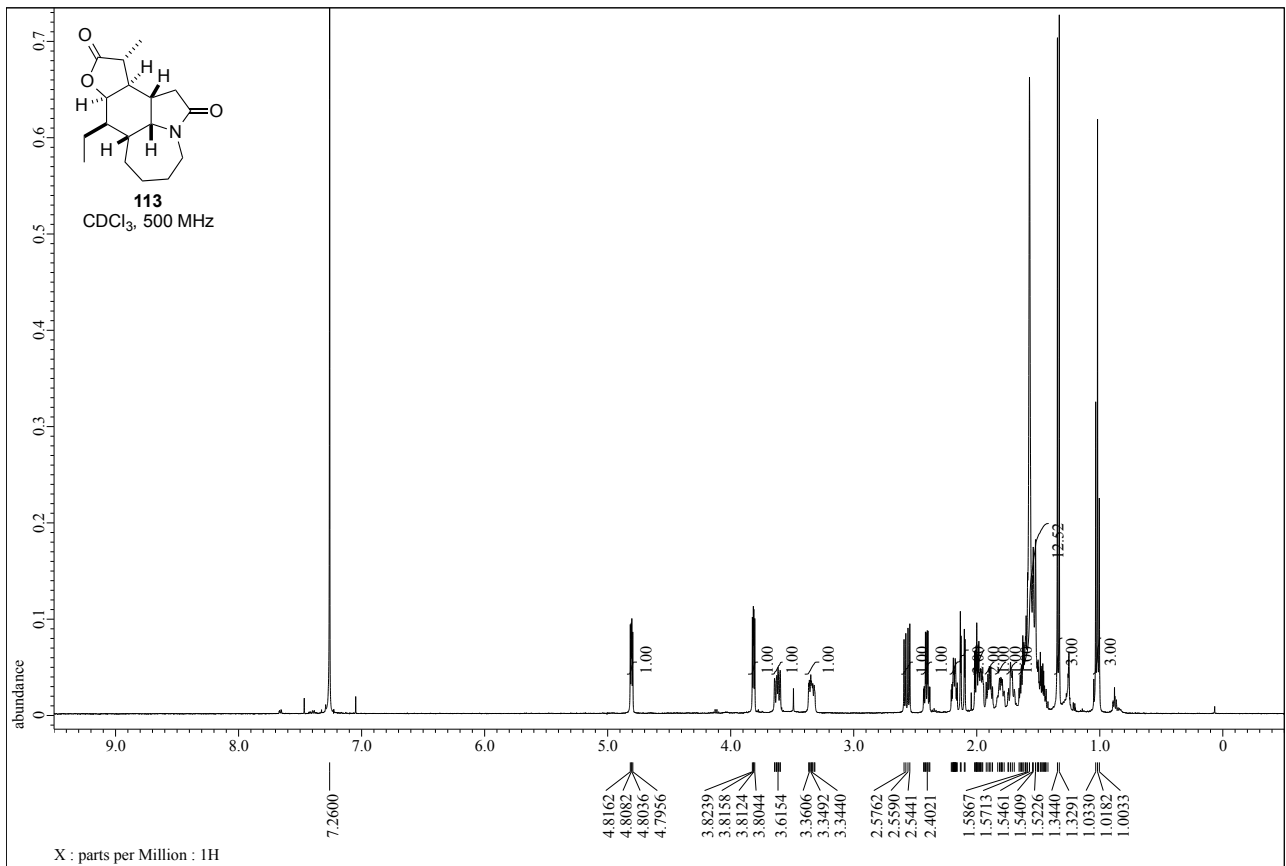














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