Supporting Information for

Total Synthesis of (–)-Domoic Acid, A Potent Ionotropic Glutamate Receptor Agonist and the Key Compound in Oceanic Harmful Algal Blooms

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Contents

1. General

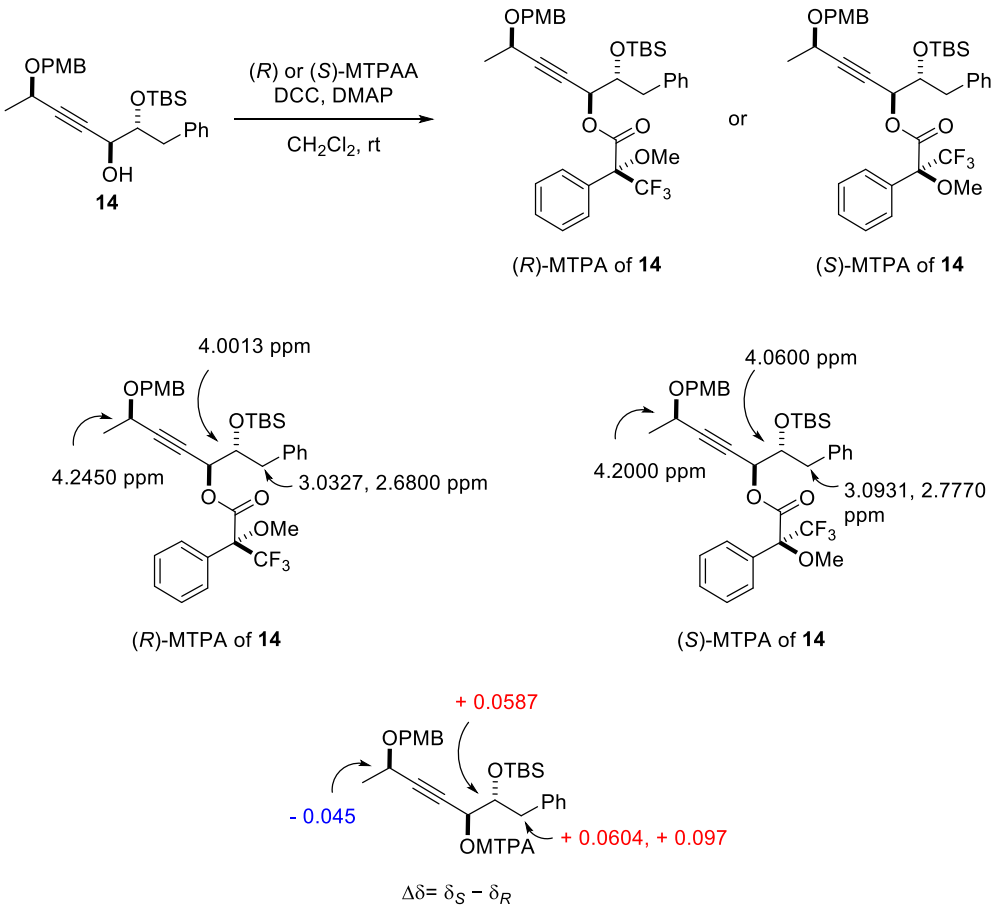
Nuclear magnetic resonance (NMR) spectra were obtained on a JEOL ECZ-500 spectrometer (^{1}H NMR: 500 MHz, ^{13}C{^{1}H} NMR: 126 MHz). Chemical shifts are expressed as δ (ppm) values, and coupling constants are expressed in hertz (Hz). ^{1}H and ^{13}C{^{1}H} NMR spectra were referenced to tetramethylsilane or the solvent residual signals. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), multiplet (m), and broad singlet (br-s). Infrared (IR) spectra were obtained on a JASCO FT/IR-4700 or an Agilent Cary 630 FTIR with an ATR attachment (diamond). High resolution mass spectra (HRMS) were measured on a Bruker micrOTOF spectrometer (ESI). Optical rotations were measured on a JASCO P-2200 Polarimeter at room temperature using the sodium D line.

Analytical thin layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F_{254}. Normal-phase column chromatography separations were performed on Fuji Sylysia silica gel PSQ 100B or PSQ 60B.

All chemicals were of reagent grade and used as received. Anhydrous solvents were purchased from KANTO Chemical Co.,Inc. and further dried over MS4A (CH_2Cl_2, tetrahydrofuran, and toluene) or MS3A (methanol and acetonitrile) prior to use. Unless otherwise noted, air- and moisture-sensitive reactions were performed under an argon atmosphere.

2. Supplementary data

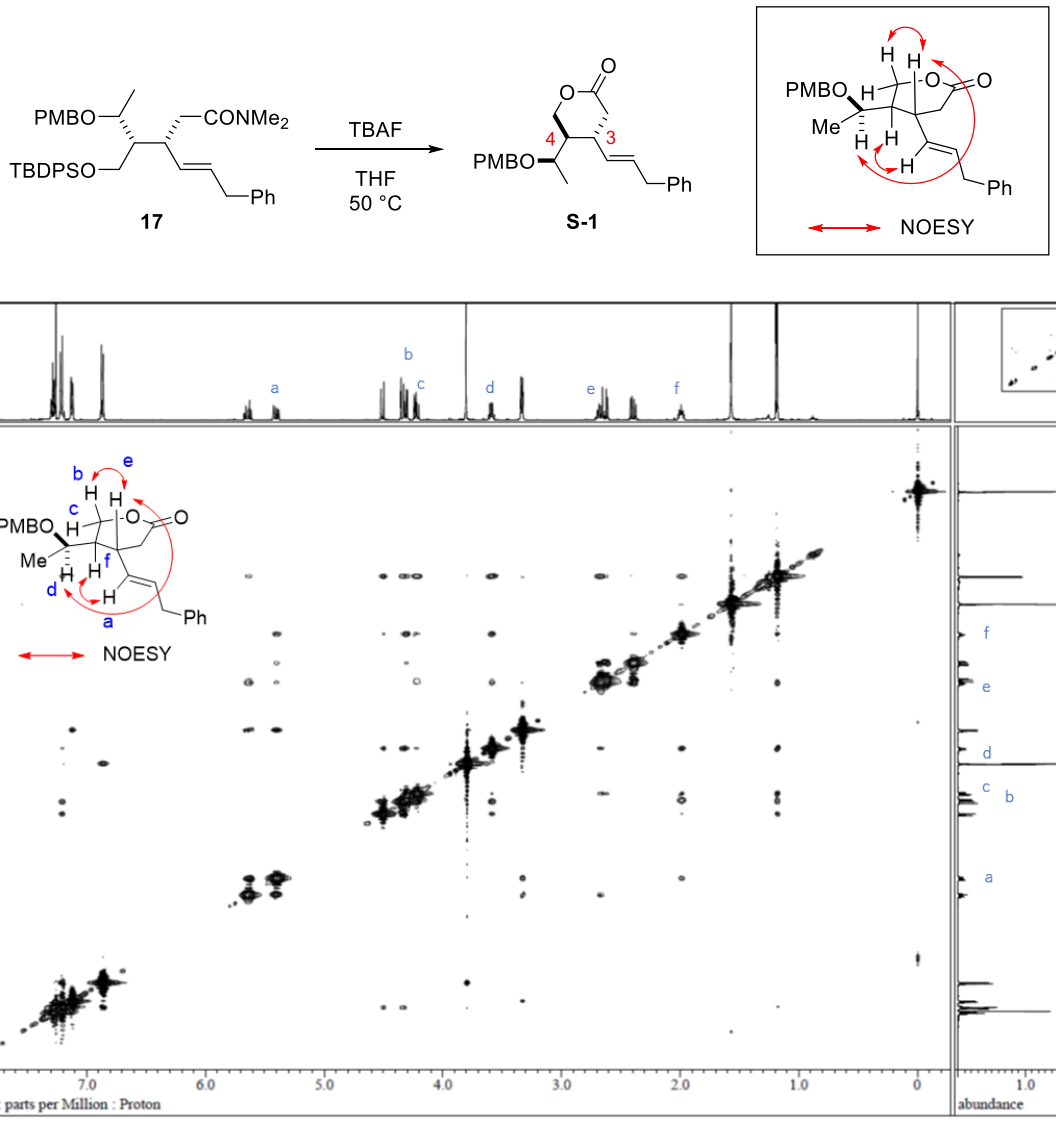
2-1. Determination of the absolute configuration of 14 by the advanced Mosher's method



Scheme S1. The chemical shifts of the Mosher's esters of **14** to determine the absolute configuration.

The absolute configuration of secondary alcohol **14** was determined by the advanced Mosher's method.[S1] The $\Delta\delta$ (= δ_S–δ_R) values from the ^{1}H NMR spectra of MTPA esters revealed that the configuration of the secondary alcohol was found to be (*S*)-form (as illustrated in **Scheme S1**). The determined stereochemistry is consistent with the postulated selectivity in the nucleophilic addition of **12** with the lithiated **13** to afford **14**, as predicted by the Felkin-Anh model.

2-2. Determination of the relative configuration of 17

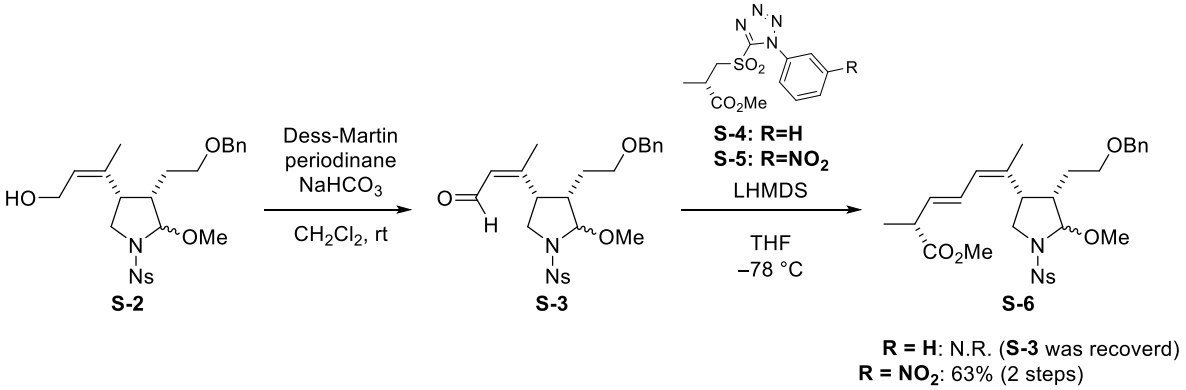


Scheme S2. The NOESY spectrum of **S-1**.

Upon the conversion of **17** into the corresponding lactone **S-1**, a NOESY analysis was conducted (as depicted in **Scheme S2**), indicating that the substituents at the β and γ positions of the lactone ring were positioned in the *trans* cofiguration. These stereocenters correspond to the 3 and 4 positions of pyrrolidine ring core of DA.

This lactone **S-1** was obtained from **17** in our initial investigations, when we examined the deprotection of TBDPS group in the presence of amide group. In order to avoid the unwanted lactone formation, the amide moiety was reduced before the introduction of nitrogen functionality.

2-3. Utility of the modified Julia-Kocieński reaction



Scheme S3. The Julia-Kocieński reaction with the model substrate **S-3**.

With the model aldehyde substrate **S-3**, we examined the Julia-Kocieński reaction for the introduction of the C4-side chain. The use of phenyltetrazolyl sulfone (PT-sulfone) **S-4**[S2] resulted in the failure of C–C bond formation and the recovery of **S-3**. In contrast, this transformation using *m*-nitrophenyltetrazolyl sulfone **S-5**[S3] smoothly proceeded, and the desired diene product **S-6** was obtained in a good yield (63% for 2 steps, **Scheme S3**). These findings demonstrate the superior reactivity of *m*-nitrophenyltetrazolyl sulfone reagents compared to their phenyltetrazolyl sulfone counterparts in the introduction of the C4-side chain.

2-4. HPLC analysis of deprotection of methyl ester S-7 and allyl ester 24

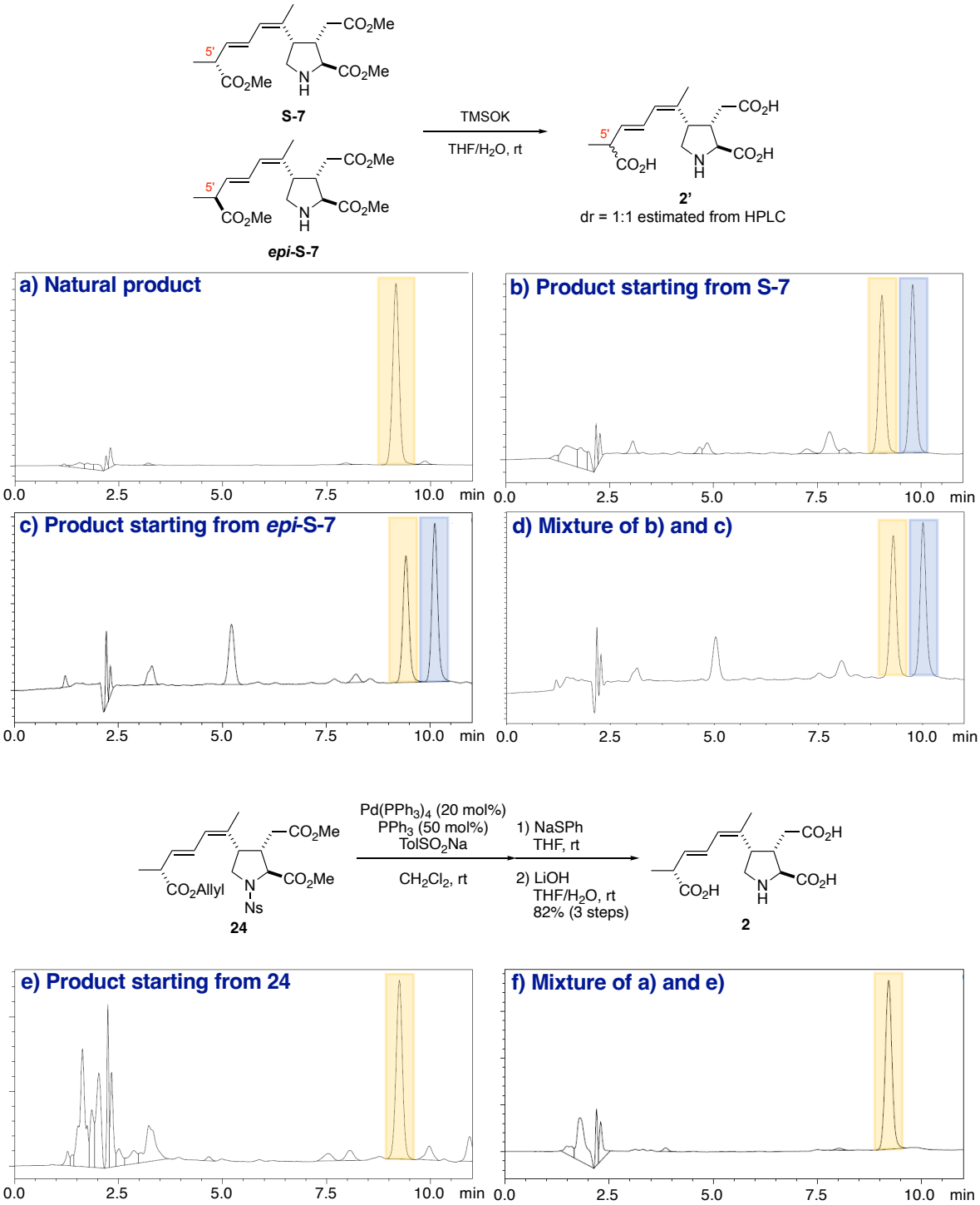


Figure S1. HPLC analysis of deprotected products starting from methyl ester **S-7** and allyl ester **24**.

<HPLC conditions> column: Inertsil ODS-3, 3 μm, 4.6 x 150 mm, GL Science,

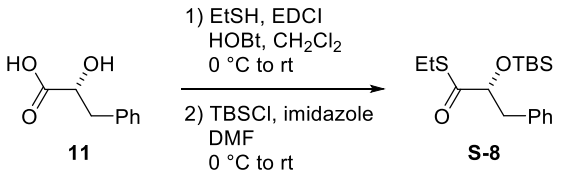
eluent: A) H_2O/0.1% AcOH, B) MeCN/0.1% AcOH, gradient from A/B = 90/10 to 70/30.

Saponification of **S-7**, a compound possessing three methyl ester groups, including one at the C5' position, was carried out under basic conditions (depicted at the top of **Figure S1**). HPLC analysis of

the product indicated the generation of two products (b), one of which was identified as natural product **2** (a). The other byproduct was assigned as the C5'-epimer of **2** when the reaction was performed using ***epi*-S-7** at the C5' position as the starting compound (c, d). These results demonstrated that the reactions of both **S-7** and ***epi*-S-7** afforded both **2** and its C5'-epimer in an almost 1:1 ratio, suggesting that the stereochemistry of the C5' position should be unstable under these conditions. In contrast, the deprotection sequence of the allyl ester **24** resulted in the exclusive production of **2** as a single stereoisomer (e, f).

3. Experimental details and characterization of the products

Thioester S-8

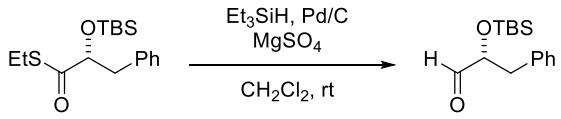


To a solution of **11** (5.0 g, 30 mmol) in CH_2Cl_2 (100 mL) were added EtSH (7.0 mL, 95 mmol), HOBt (6.0 g, 39 mmol), and EDCI (5.3 g, 39 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 19 hours. Then the reaction mixture was quenched with H_2O, filtered through a pad of Celite and extracted with EtOAc. The organic layer was washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was used in the following reaction without further purification.

To a stirred solution of the crude material in DMF (100 mL) were added TBSCl (5.5 g, 36 mmol) and imidazole (2.8 g, 41 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 7 hours. Then the reaction mixture was diluted with Et_2O and quenched with saturated aqueous NH_4Cl. After the separation of the two layers, the organic layer was washed with H_2O and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, *n*-hexane/Et_2O = 95/5) to give **S-8** (8.0 g, 82%, 2 steps) as a colorless oil.

$[\alpha]^{23}_D$ +141.4 (*c* 1.03, $CHCl_3$).
IR (ATR, cm^{-1}): 2952, 2935, 2856, 1681, 1255, 1126, 983, 838, 778.
^1H NMR (500 MHz, $CDCl_3$) δ: 7.28-7.26 (m, 2H), 7.22-7.20 (m, 3H), 4.29 (dd, *J* = 8.8, 3.4 Hz, 1H), 3.05 (dd, *J* = 13.5, 3.4 Hz, 1H), 2.87-2.78 (m, 3H), 1.22 (t, *J* = 7.4 Hz, 3H), 0.86 (s, 9H), –0.07 (s, 3H), –0.40 (s, 3H).
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ: 205.0, 137.0, 130.1, 128.1, 126.6, 79.9, 42.5, 25.7, 22.4, 18.1, 14.6, –5.3, –5.8.
HRMS (ESI (+)): Calcd for $C_{17}H_{28}O_2SSiNa^+$ $[M+Na]^+$ 347.1471, found 347.1474.

Aldehyde 12

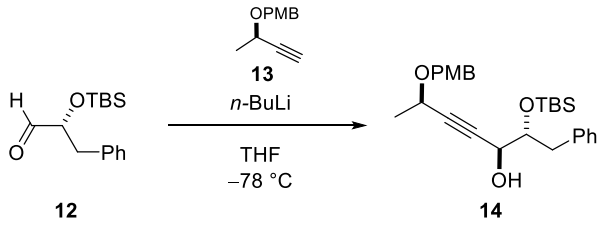


S-8 **12**

To a solution of **S-8** (25.6 g, 78.9 mmol) in CH_2Cl_2 (800 mL) were added 5% Pd/C (2.5 g) and $MgSO_4$ (20 g, 166 mmol) at room temperature. Then to the solution was added triethylsilane (38 mL, 239 mmol) over a period of 20 minutes. The resulting mixture was stirred at the same temperature for 16 hours. Then the reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, *n*-hexane/Et_2O = 97/3 to 95/5) to give **12** (20.7 g, 99%) as a colorless oil.

$[\alpha]^{24}_D$ +61.8 (*c* 1.14, $CHCl_3$).
IR (ATR, cm^{-1}): 2952, 2928, 2857, 1736, 1471, 1254, 1110, 940, 836, 777, 699.
^1H NMR (500 MHz, $CDCl_3$) δ: 9.66 (d, *J* = 1.6 Hz, 1H), 7.29 (t, *J* = 7.0 Hz, 2H), 7.24-7.20 (m, 3H), 4.13 (ddd, *J* = 9.1, 3.9, 1.6 Hz, 1H), 3.00 (dd, *J* = 13.6, 3.9 Hz, 1H), 2.77 (dd, *J* = 13.6, 9.1 Hz, 1H), 0.83 (s, 9H), –0.12 (s, 3H), –0.25 (s, 3H).
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ: 203.7, 136.8, 129.9, 128.3, 126.7, 79.0, 39.1, 25.6, 18.1, –5.2, –5.5.
HRMS (ESI (+)): Calcd for $C_{15}H_{24}O_2SiNa^+$ $[M+Na]^+$ 287.1438, found 287.1434.

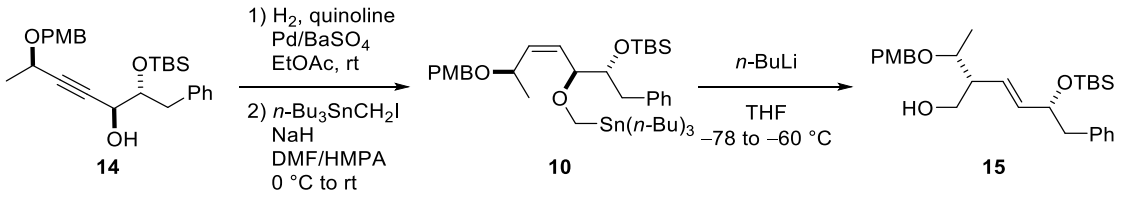
Alcohol 14



To a stirred solution of **13** (26.0 g, 137 mmol) in THF (200 mL) were added *n*-BuLi (50 mL, 2.54 M in *n*-hexane, 127 mmol) at –78 °C. After being stirred for 10 minutes, the resulting solution was transferred via a cannula to another flask that contained a stirred solution of **12** (23.6 g, 89.4 mmol) in THF (300 mL) at –78 °C. After being stirred at the same temperature for 30 minutes, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, *n*-hexane/EtOAc = 10/1 to 5/1) to give **14** (24.3 g, 60%, dr=7:1) as a yellow oil. This material was used as the diastereomixture in the subsequent three steps.

$[\alpha]^{24}_D$ +41.9 (*c* 1.05, $CHCl_3$).
IR (ATR, cm^{-1}): 2965, 2950, 2929, 2853, 1514, 1250, 1220, 1101, 1035, 835, 774, 700.
^1H NMR (500 MHz, $CDCl_3$) δ: 7.33-7.28 (m, 5H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.76 (d, *J* = 11.3 Hz, 1H), 4.49 (d, *J* = 11.3 Hz, 1H), 4.39-4.35 (m, 1H), 4.29 (dddd, *J* = 7.0, 6.5, 6.5, 1.2 Hz, 1H), 4.00-3.96 (m, 1H), 3.80 (s, 3H), 3.04 (dd, *J* = 13.6, 5.1 Hz, 1H), 2.86 (dd, *J* =13.5, 8.0 Hz, 1H), 2.40 (d, *J* = 5.9 Hz, 1H), 1.49 (d, *J* = 6.6 Hz, 3H), 0.86 (s, 9H), –0.02 (s, 3H), –0.26 (s, 3H).
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ: 159.2, 138.1, 129.9, 129.7, 129.6, 128.3, 126.4, 113.7, 86.8, 82.7, 76.5, 70.1, 65.8, 64.0, 55.2, 39.0, 25.7, 22.2, 18.0, –4.9, –5.1.
HRMS (ESI (+)): Calcd for $C_{27}H_{38}O_4SiNa^+$ $[M+Na]^+$ 477.2432, found 477.2416.

Homoallylic alcohol 15



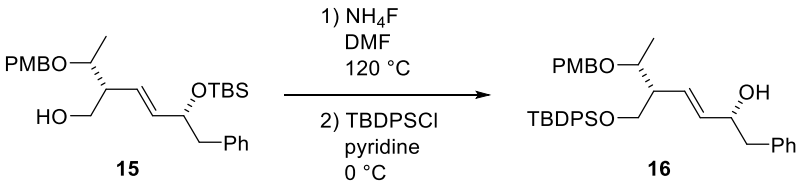
To a stirred solution of **14** (30.5 g, 67.1 mmol) in EtOAc (700 mL) were added 5% $Pd/BaSO_4$ (3.0 g) and quinoline (0.8 mL, 6.75 mmol). The resulting mixture was stirred under a hydrogen atmosphere (balloon) at room temperature for 1 hour. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. The crude material was used in the following reaction without further purification.

To a solution of the crude material and Bu_3SnCH_2I (34.0 g, 79 mmol) in DMF (220 mL) were added HMPA (120 mL) and NaH (3.52 g, 60% oil suspension, 141 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 1 hour. Then the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O. Then the organic layer was washed with H_2O and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was used in the following reaction without further purification.

To a solution of the crude material in THF (670 mL) was added *n*-BuLi (50 mL, 2.69 M in hexane, 135 mmol) at –78 °C. The resulting mixture was stirred at –60 °C for 1.5 hours. Then the reaction mixture was quenched with MeOH and saturated aqueous NH_4Cl. Then the solution was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, *n*-hexane/EtOAc = 5/1) to give **15** (12.6 g, 40%, 3 steps, a single diastereomer) as a yellow oil. The minor diastereomer of **10** would also undergo the rearrangement reaction, and the corresponding minor product was removed during the purification.

$[\alpha]^{24}_{D}$ –9.0 (*c* 0.96, $CHCl_3$).
IR (ATR, cm^{-1}): 2952, 2928, 2853, 1514, 1248, 1038, 834, 773, 700.
^1H NMR (500 MHz, $CDCl_3$) δ: 7.28-7.24 (m, 4H), 7.21-7.16 (m, 3H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.58 (dd, *J* = 15.5, 6.1 Hz, 1H), 5.46 (dd, *J* = 15.6, 8.9 Hz, 1H), 4.53 (d, *J* = 11.3 Hz, 1H), 4.36 (d, *J* = 11.3 Hz, 1H), 4.29 (dd, *J* = 6.1, 6.1 Hz, 1H), 3.82 (s, 3H), 3.75-3.66 (m, 2H), 3.61-3.56 (m, 1H), 2.78 (dd, *J* = 6.0, 2.5 Hz, 2H), 2.45-2.40 (m, 1H), 2.22 (dd, *J* = 6.4, 5.5 Hz, 1H), 1.65-1.63 (m, 1H), 1.08 (d, *J* = 6.4 Hz, 3H), 0.84 (s, 9H), –0.08 (s, 3H), –0.17 (s, 3H).
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ: 159.1, 138.5, 137.0, 130.5, 129.9, 129.2, 128.0, 126.7, 126.1, 113.8, 75.9, 74.5, 70.2, 63.9, 55.2, 49.4, 45.2, 25.8, 18.2, 16.1, –4.7, –5.2.
HRMS (ESI (+)): Calcd for $C_{28}H_{42}O_4SiNa^+$ $[M+Na]^+$ 493.2745, found 493.2754.

Allyl alcohol 16

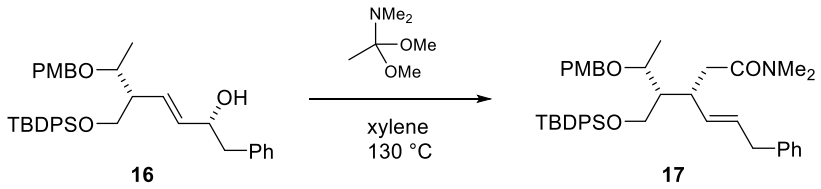


To a stirred solution of **15** (6.03 g, 12.8 mmol) in DMF (65 mL) was added NH_4F (1.4 g, 38 mmol) at room temperature. The resulting mixture was stirred at 120 °C for 24 hours. Then the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was used in the next step without further purification.

To a stirred solution of the crude material in pyridine (60 mL) was added TBDPSCl (5.3 mL, 20.6 mmol) at 0 °C. The resulting mixture was stirred at the same temperature for 4 hours. Then the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, *n*-hexane/EtOAc =10/1 to 5/1) to give **16** (7.11 g, 93%, 2 steps) as a yellow oil.

$[\alpha]^{24}_D$ +13.5 (*c* 1.04, $CHCl_3$).
IR (ATR, cm^{-1}): 2959, 2926, 2856, 2359, 1514, 1248, 1220, 1112, 772, 702, 505.
^1H NMR (500 MHz, $CDCl_3$) δ: 7.64-7.62 (m, 4H), 7.43-7.32 (m, 6H), 7.23-7.27 (m, 2H), 7.25 (d, *J* = 7.5 Hz, 1H), 7.18 (m, 5H), 6.84 (d, *J* = 9.0 Hz, 2H), 5.54-5.52 (m, 2H), 4.48 (d, *J* = 11.0 Hz, 1H), 4.31 (d, *J* = 11.5 Hz, 1H), 4.28 (dt, *J* = 5.5, 1.5 Hz, 1H), 3.88-3.83 (m, 1H), 3.81 (dd, *J* = 10.0, 8.0 Hz, 1H), 3.79 (s, 3H), 3.60 (dd, *J* = 10.0, 6.0 Hz, 1H), 2.80 (dd, *J* = 5.5, 2.5 Hz, 2H), 2.28-2.25 (m, 1H), 1.04 (s, 9H).
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ: 158.9, 137.9, 135.6, 135.5, 133.7, 131.2, 129.6, 129.6, 129.1, 129.0, 128.4, 127.6, 126.4, 113.6, 73.6, 73.2, 70.6, 64.3, 55.2, 51.3, 43.9, 26.9, 19.3, 17.6.
HRMS (ESI (+)): Calcd for $C_{38}H_{46}O_4SiNa^+$ $[M+Na]^+$ 617.3058, found 617.3061.

Amide 17

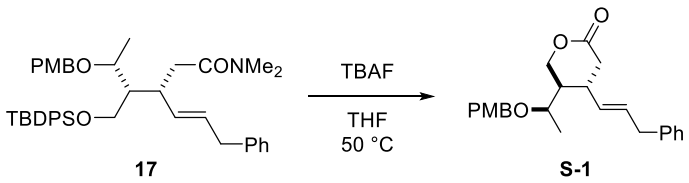


16 17

To a stirred solution of **16** (13.4 g, 22.5 mmol) in xylene (110 mL) was added *N*,*N*-dimethyl acetamide dimethylacetal (6.5 mL, 44.4 mmol) at room temperature. The resulting mixture was stirred at 130 °C for 19 hours. Then the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, *n*-hexane/EtOAc =4/1 to 1/1) to give **17** (11.9 g, 80%) as a yellow oil.

$[\alpha]^{24}_{D}$ –5.59 (*c* 1.13, $CHCl_3$).
IR (ATR, cm^{-1}): 2930, 2891, 2857, 1645, 1513, 1427, 1394, 1248, 1111, 1071, 1037, 822, 741, 702, 504.
^1H NMR (500 MHz, $CDCl_3$) δ: 7.66-7.63 (m, 4H), 7.42-7.38 (m, 2H), 7.37-7.31 (m, 4H), 7.24-7.16 (m, 5H), 7.09 (d, *J* = 6.9 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 5.52 (dt, *J* = 15.3, 7.0 Hz, 1H), 5.40 (dd, *J* = 15.3, 8.4 Hz, 1H), 4.44 (d, *J* = 11.1 Hz, 1H), 4.25 (d, *J* = 11.1 Hz, 1H), 3.83 (dd, *J* = 10.5, 4.6 Hz, 1H), 3.79 (s, 3H), 3.78-3.69 (m, 2H), 3.27 (d, *J* = 6.7 Hz, 2H), 3.07-3.04 (m, 1H), 2.82 (s, 3H), 2.76 (s, 3H), 2.60 (dd, *J* = 14.7, 4.1 Hz, 1H), 2.40 (dd, *J* = 14.7, 10.2 Hz, 1H), 1.82 (quin, 5.5 Hz, 1H), 1.12 (d, *J* = 6.3 Hz, 3H), 1.04 (s, 9H).
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ: 172.5, 158.9, 140.8, 135.6, 133.5, 131.1, 129.7, 129.61, 129.58, 129.2, 128.5, 128.3, 127.6, 125.8, 113.6, 73.9, 70.0, 62.2, 55.2, 49.6, 39.0, 38.7, 37.3, 36.3, 35.3, 26.9, 19.2, 16.7.
HRMS (ESI (+)): Calcd for $C_{42}H_{53}NO_4SiNa^+$ $[M+Na]^+$ 686.3636, found 686.3697.

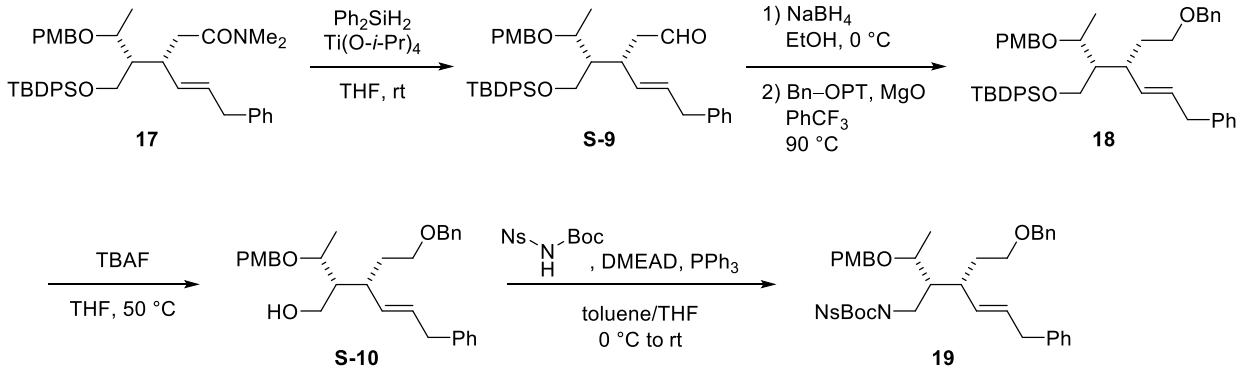
Lactone S-1



To a stirred solution of **17** (4.2 mg, 6.3 μmol) in THF (0.1 mL) was added TBAF (20 μL, 1 M in THF, 20 μmol) at room temperature. The resulting mixture was stirred at 50 °C for 22 hours. Then, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (*n*-hexane/EtOAc =2/1) to give **S-1** (2.2 mg, 80%) as a colorless oil.

$[\alpha]^{22}_D$ –16.5 (*c* 0.23, $CHCl_3$).
IR (ATR, cm^{-1}): 2967, 2906, 2360, 2341, 1748, 1613, 1513, 1248, 1220, 1034, 768.
^1H NMR (500 MHz, $CDCl_3$) δ: 7.29 (t, *J* = 7.4 Hz, 2H), 7.21 (d, *J* = 8.6 Hz, 2H), 7.12 (d, *J* = 7.4 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.64 (dt, *J* = 15.3, 6.9 Hz, 1H), 5.40 (dd, *J* = 15.3, 7.8 Hz, 1H), 4.51 (d, *J* = 10.9 Hz, 1H), 4.34 (d, *J* = 11.5 Hz, 1H), 4.30 (d, *J* = 5.2 Hz, 1H), 4.22 (dd, *J* = 12.0, 8.0 Hz, 1H), 3.80 (s, 3H), 3.61-3.57 (m, 1H), 3.33 (d, *J* = 6.9 Hz, 2H), 2.70-2.61 (m, 2H), 2.39 (dd, *J* = 15.7, 4.4 Hz, 1H), 2.02-1.97 (m, 1H), 1.19 (d, *J* = 6.3 Hz, 3H).
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ: 172.1, 159.2, 139.9, 133.1, 130.4, 130.2, 129.2, 128.5, 128.4, 126.2, 113.8, 73.5, 70.3, 68.0, 55.3, 43.4, 38.7, 35.7, 35.1, 15.8.
HRMS (ESI (+)): Calcd for $C_{24}H_{29}O_4^+$ $[M+H]^+$ 381.2060, found 381.2068.

Imide 19



To a stirred solution of **17** (6.85 g, 10.3 mmol) in THF (50 mL) were added Ph_2SiH_2 (3.8 mL, 20.6 mmol) and Ti(O-*i*-Pr)$_4$ (6.0 mL, 20.5 mmol) at room temperature. The resulting mixture was stirred at the same temperature for 5 hours. Then, the reaction mixture was quenched with 1 M aqueous HCl and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was used in the next step without further purification.

To a stirred solution of the crude material in EtOH (100 mL) was added $NaBH_4$ (200 mg, 5.29 mmol) at 0 °C and stirred for 1 hour at the same temperature. Then the reaction mixture was quenched with acetone and concentrated under reduced pressure. The residue was dissolved with EtOAc and saturated aqueous NH_4Cl and the layers were separated. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved with EtOAc, filtered through a pad of silica gel and concentrated under reduced pressure. The crude material was used in the following reaction without further purification.

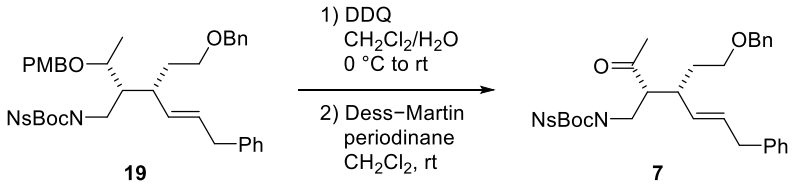
To a stirred solution of the crude material in benzotrifluoride (100 mL) were added BnOPT (11.2 g, 32.1 mmol) and MgO (1.28 g, 31.8 mmol) at room temperature. The resulting mixture was stirred at 90 °C for 22 hours. Then, the reaction mixture was filtered through Celite and concentrated under reduced pressure. The crude material was used in the following reaction without further purification.

To a stirred solution of crude material in THF (20 mL) was added TBAF (30 mL, 1 M in THF, 30 mmol) at 0 °C. The resulting mixture was stirred at 50 °C for 14 hours. Then the reaction mixture was quenched with brine and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was roughly purified by column chromatography (SiO_2, benzene/acetone = 3/1 to 2/1). This material was used in the following reaction without further purification.

To a stirred solution of the resultant material in a 1:1 mixture of toluene and THF (total 40 mL) were added NsBocNH (4.91 g, 16.2 mmol) and PPh_3 (6.06 g, 23.1 mmol) at room temperature. Then to the resulting mixture was added DMEAD (5.46 g, 23.3 mmol) portionwise at 0 °C. The resulting mixture was stirred at room temperature for 4 hours. The reaction mixture was quenched with H_2O and extracted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, *n*-hexane/EtOAc =3/1 to 2/1 to 1/1) to give **19** (2.69 g, 46%, 5 steps) as a yellow oil.

$[\alpha]^{24}_D$ –6.1 (*c* 0.55, $CHCl_3$).
IR (ATR, cm^{-1}): 2959, 2925, 2853, 2359, 1717, 1542, 1450, 1362, 1275, 1169, 1070, 963, 750.
^1H NMR (500 MHz, $CDCl_3$) δ: 8.31 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.76-7.66 (m, 3H), 7.32-7.24 (m, 9H), 7.19-7.13 (m, 3H), 6.83 (d, *J* = 8.6 Hz, 2H), 5.61 (dt, *J* = 15.2, 6.7 Hz, 1H), 5.39 (dd, *J* = 15.2, 9.5 Hz, 1H), 4.45-4.33 (m, 4H), 4.05 (dd, *J* = 14.8, 7.8 Hz, 1H), 3.83 (dd, *J* = 14.8, 5.8 Hz, 1H), 3.77 (s, 3H), 3.71 (dd, *J* = 6.2, 4.3 Hz, 1H), 3.47-3.37 (m, 2H), 3.31 (d, *J* = 6.7 Hz, 2H), 2.47-2.44 (m, 1H), 2.15-2.08 (m, 2H), 1.63-1.61 (m, 1H), 1.28 (s, 9H).
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ: 158.8, 150.4, 147.5, 140.8, 138.8, 133.9, 133.8, 133.4, 132.9, 131.7, 131.3, 130.4, 129.3, 128.5, 128.3, 128.2, 127.7, 127.3, 125.8, 124.3, 113.5, 84.8, 74.4, 72.4, 70.1, 68.6, 55.2, 47.2, 47.0, 39.0, 38.5, 31.9, 27.8, 16.7.
HRMS (ESI (+)): Calcd for $C_{42}H_{50}N_2O_9SNa^+$ $[M+Na]^+$ 781.3129, found 781.3133.

Ketone 7

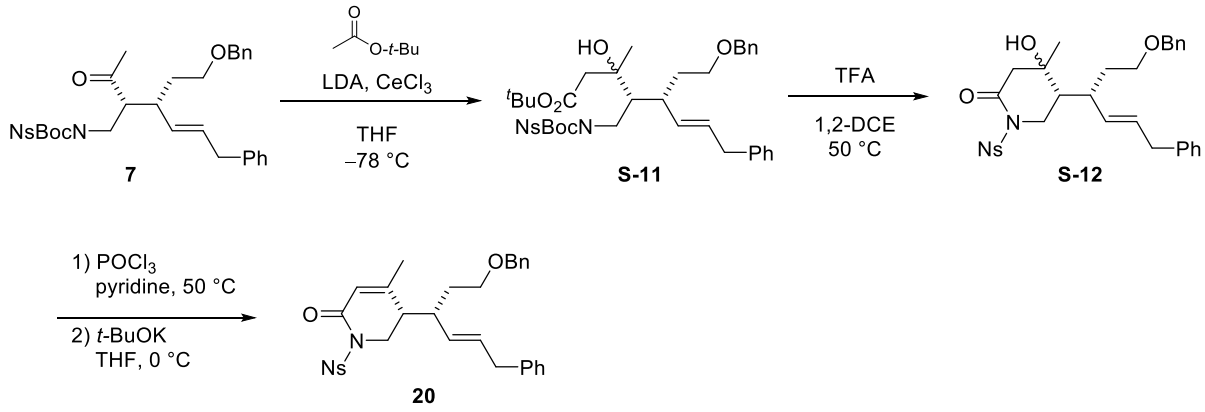


To a stirred solution of **19** (2.69 g, 3.54 mmol) in a 50:1 mixture of CH_2Cl_2 and H_2O (total 35.7 mL) was added DDQ (901 mg, 3.97 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 2 hours. Then the reaction mixture was quenched with saturated aqueous $NaHCO_3$, filtered through Celite and extracted with EtOAc. The organic layer was washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was used in the following reaction without further purification.

To a stirred solution of crude material in CH_2Cl_2 (18 mL) was added Dess-Martin periodinane (2.23 g, 5.26 mmol) at room temperature. The resulting mixture was stirred at the same temperature for 14 hours. Then the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, *n*-hexane/EtOAc = 4/1 to 2/1) to give **7** (1.87 g, 76%, 2 steps) as a yellow oil.

$[\alpha]^{24}_D$ –53.7 (*c* 0.145, $CHCl_3$).
IR (ATR, cm^{-1}): 3027, 2977, 2920, 2847, 1730, 1542, 1362, 1292, 1256, 1149, 1121, 740, 699, 576.
^1H NMR (500 MHz, $CDCl_3$) δ: 8.27-8.31 (m, 1H), 7.72-7.78 (m, 3H), 7.26-7.35 (m, 7H), 7.18 (dd, *J* = 7.5, 7.3 Hz, 1H), 7.14 (d, *J* = 6.9 Hz, 2H), 5.61 (dt, *J* = 15.3, 7.0 Hz, 1H), 5.32 (dd, *J* = 15.0, 10.0 Hz, 1H), 4.42 (dd, *J* = 18.5, 11.5 Hz, 2H), 4.15 (dd, *J* = 14.9, 9.7 Hz, 1H), 3.86 (dd, *J* = 15.1, 3.7 Hz, 1H), 3.50-3.47 (m, 1H), 3.42-3.38 (m, 1H), 3.32 (m, 2H), 3.08-3.04 (m, 1H), 2.54-2.52 (m, 1H), 2.17 (s, 3H), 2.03-1.98 (m, 1H), 1.33 (s, 9H), 1.27-1.24 (m, 1H).
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ: 210.0, 150.1, 147.6, 140.3, 138.4, 134.2, 133.6, 133.4, 132.6, 131.8, 130.5, 128.5, 128.4, 128.3, 127.8, 127.5, 126.0, 124.5, 85.5, 73.0, 67.7, 57.3, 47.9, 40.9, 38.9, 32.1, 29.7, 27.7.
HRMS (ESI (+)): Calcd for $C_{34}H_{40}N_2O_8SNa^+$ $[M+Na]^+$ 659.2398, found 659.2388.

α, β-Unsaturated lactam 20



To a solution of diisopropylamine (1.0 mL, 7.12 mmol) in THF (5.0 mL) was added *n*-BuLi (2.6 mL, 2.69 M in *n*-hexane, 6.99 mmol) at –78 °C and the resulting mixture was stirred at 0 °C for 10 minutes. Then the resulting LDA solution was added *tert*-butyl acetate (1.0 mL, 7.66 mmol) at –78 °C, and stirred at the same temperature for 1 hour. The resulting solution was transferred via a cannula to another flask that contained anhydrous $CeCl_3$ (2.14 g, 8.68 mmol) and stirred for 1.5 hours at –78 °C. To the reaction mixture was added a solution of ketone **7** (1.70 g, 2.67 mmol) in THF (25 mL) and stirred at the same temperature for 30 minutes. Then the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered through a pad of silica gel, and concentrated under reduced pressure. The crude material was used in the following reaction without further purification.

To a stirred solution of the crude material in 1,2-dichloroethane (27 mL) was added TFA (5.0 mL, 65.3 mmol) at room temperature. The resulting mixture was stirred at 50 °C for 17 hours. Then the reaction mixture was concentrated under reduced pressure. The residue was dissolved with EtOAc, filtered through a pad of silica gel, and concentrated under reduced pressure. The crude material was used in the following reaction without further purification.

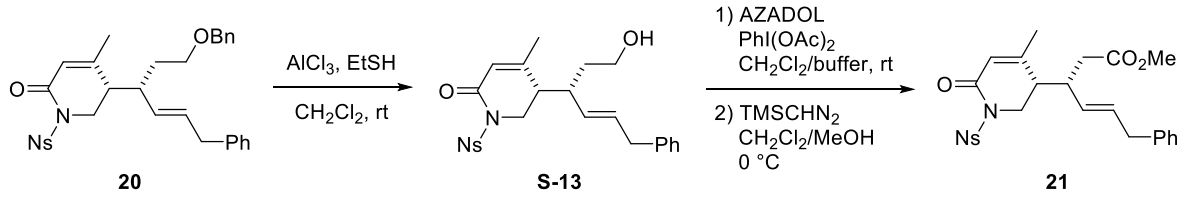
To a stirred solution of the crude material in pyridine (27 mL) was added $POCl_3$ (0.9 mL, 9.68 mmol) at room temperature. The resulting mixture was stirred at 50 °C for 16 hours. Then the reaction mixture was quenched with H_2O and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was used in the following reaction without further purification.

To a stirred solution of the crude material in THF (27 mL) was added *t*-BuOK (79.2 mg, 0.706 mmol) at 0 °C. The resulting mixture was stirred at the same temperature for 30 minutes. Then the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced

pressure. The residue was purified by column chromatography (SiO_2, *n*-hexane/EtOAc = 2/1) to give **20** (938 mg, 63%, 4 steps) as a yellow oil.

$[\alpha]^{25}_D$ +272.6 (*c* 0.13, $CHCl_3$).
IR (ATR, cm^{-1}): 3024, 2921, 2859, 1687, 1542, 1363, 1173, 767, 749.
^1H NMR (500 MHz, $CDCl_3$) δ: 8.55 (dd, *J* = 7.0, 2.0 Hz, 1H), 7.78-7.72 (m, 3H), 7.38-7.27 (m, 7H), 7.20 (m, 1H), 7.15 (dd, *J* = 8.2, 7.1 Hz, 2H), 5.71 (d, *J* = 1.2 Hz, 1H), 5.66 (dt, *J* = 15.0, 7.0 Hz, 1H), 5.41 (dd, *J* = 15.2, 9.0 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.40 (d, *J* = 12.5 Hz, 1H), 4.31 (dd, *J* = 13.3, 3.9 Hz, 1H), 3.99 (dd, *J* = 13.3, 4.5 Hz, 1H), 3.53-3.49 (m, 1H), 3.40 (ddd, *J* = 9.0, 5.5, 3.5 Hz, 1H), 3.36 (d, *J* = 6.7 Hz, 2H), 2.70-2.64 (m, 1H), 2.45 (dd, *J* = 10.0, 4.4 Hz, 1H), 1.96 (s, 3H), 1.92-1.86 (m, 1H), 1.70-1.63 (m, 1H).
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ: 163.6, 161.8, 148.6, 140.8, 139.2, 135.7, 135.0, 133.8, 133.3, 132.6, 131.8, 129.2, 129.1, 129.0, 128.3, 128.2, 126.7, 124.7, 121.6, 73.5, 68.3, 47.2, 45.3, 40.9, 39.6, 31.6, 23.8.
HRMS (ESI (+)): Calcd for $C_{31}H_{32}N_2O_6SNa^+$ $[M+Na]^+$ 583.1873, found 583.1884.

Ester 21



20 **S-13** **21**

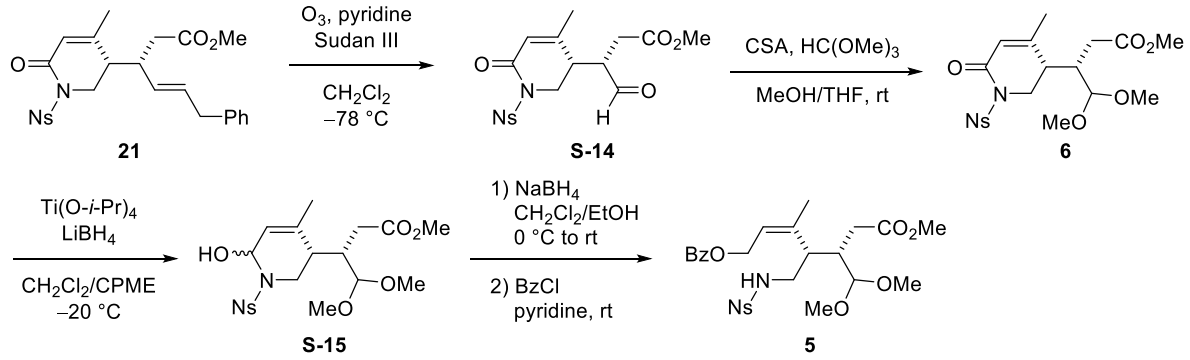
To a stirred solution of **20** (54.1 mg, 96.4 μmol) in CH_2Cl_2 (1 mL) were added EtSH (20 μL, 277 μmol) and $AlCl_3$ (35 mg, 262 μmol) at room temperature. The resulting mixture was stirred at the same temperature for 2 hours. Then the reaction mixture was quenched with 1 M aqueous HCl and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was used in the following reaction without further purification.

To a stirred solution of the crude material in a 1:1 mixture of CH_2Cl_2 and pH 6.4 phosphate buffer solution (total 1.0 mL) were added AZADOL (3.2 mg, 21 μmol) and $PhI(OAc)_2$ (95 mg, 295 μmol) at room temperature. The resulting mixture was stirred at the same temperature for 11 hours. Then the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was used in the following reaction without further purification.

To a stirred solution of the crude material in a 1:1 mixture of CH_2Cl_2 and MeOH (total 0.1 mL) was added $TMSCHN_2$ (0.3 mL, 0.6 M in *n*-hexane, 0.18 mmol) at 0 °C. The resulting mixture was stirred at the same temperature for 5 minutes. Then the reaction mixture was quenched with a few drops of AcOH and concentrated under reduce pressure. The residue was purified by column chromatography (SiO_2, *n*-hexane/EtOAc = 3/1 to 1/1) to give **21** (40.0 mg, 83%, 3 steps) as a yellow oil.

$[\alpha]^{22}_D$ +337.3 (*c* 0.24, $CHCl_3$).
IR (ATR, cm^{-1}): 3024, 2947, 2850, 1733, 1686, 1542, 1363, 1173, 773, 741.
^1H NMR (500 MHz, $CDCl_3$) δ: 8.55 (dd, *J* = 6.9, 1.7 Hz, 1H), 7.79-7.73 (m, 3H), 7.30 (t, *J* = 7.3 Hz, 2H), 7.19 (dd, *J* = 7.5, 7.2 Hz, 1H), 7.15 (d, *J* = 6.8 Hz, 1H), 5.77 (dt, *J* = 15.4, 7.7 Hz, 1H), 5.73 (d, *J* = 1.7 Hz, 1H), 5.55 (dd, *J* = 15.5, 7.9 Hz, 1H), 4.31 (dd, *J* = 13.5, 3.2 Hz, 1H), 3.97 (dd, *J* = 13.7, 4.6 Hz, 1H), 3.62 (s, 3H), 3.39-3.37 (m, 2H), 3.00-2.98 (m, 1H), 2.62 (dd, *J* = 15.4, 9.5 Hz, 1H), 2.58-2.55 (m, 1H), 2.53 (dd, *J* = 15.4, 3.9 Hz, 1H), 1.99 (d, *J* = 1.1 Hz, 3H).
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ: 172.3, 162.7, 160.5, 147.7, 139.8, 135.1, 134.4, 133.0, 132.6, 132.0, 130.2, 128.5, 128.4, 126.1, 124.1, 121.2, 51.7, 46.4, 43.3, 40.0, 38.8, 35.8, 23.2.
HRMS (ESI (+)): Calcd for $C_{25}H_{26}N_2O_7SNa^+$ $[M+Na]^+$ 521.1353, found 521.1342.

Amide 5



To a stirred solution of **21** (36.4 mg, 73.0 μmol) in CH_2Cl_2 (1.5 mL) were added pyridine (30 μL, 372 μmol) and sudan III (0.2 mg) at room temperature. The resulting mixture was stirred with O_3 bubbling at –78 °C until the solution color turned to yellow. After purging unreacted O_3 with argon gas, the reaction mixture was filtered thought a pad of silica gel and concentrated under reduced pressure. The crude material was used in the following reaction without further purification.

To a stirred solution of the crude material in a 10:1 mixture of THF and MeOH (total 0.77 mL) were added $HC(OMe)_3$ (160 μL, 1.46 mmol) and CSA (15.2 mg, 65.3 μmol) at room temperature. The resulting mixture was stirred at the same temperature for 18 hours. Then, the reaction mixture was quenched with a few drops of Et_3N and concentrated under reduced pressure. The residue was dissolved with EtOAc, filtered through a pad of silica gel, and concentrated under reduced pressure. The crude material was used in the following reaction without further purification.

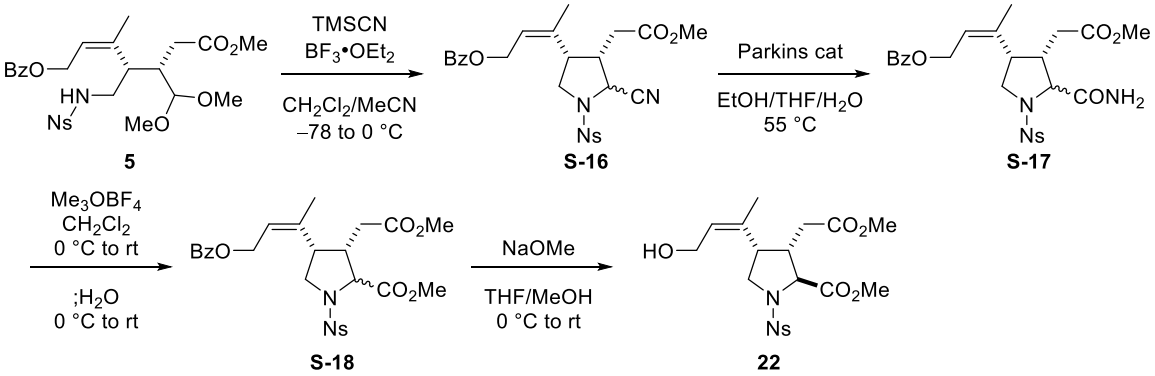
To a suspension of $LiBH_4$ (7.2 mg, 0.33 mmol) in CPME (1.1 mL) was added Ti(O-*i*-Pr)$_4$ (0.1 mL, 0.34 mmol) at room temperature. After being stirred for 1 hour at the same temperature, a portion of the resulting solution (0.5 mL, ca. 150 μmol) was transferred to another flask that contained a solution of crude material in CH_2Cl_2 (1.4 mL) at –20 °C. After being stirred 1 hour at the same temperature, the reaction mixture was quenched with acetone and saturated aqueous Rochelle salt and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was used in the following reaction without further purification.

To a stirred solution of crude material in CH_2Cl_2 (0.7 mL) was added $NaBH_4$ (6.9 mg, 0.182 mmol) in EtOH (0.7 mL) at 0 °C. After being stirred for 16 hours at room temperature, the reaction mixture was quenched with acetone and concentrated under reduced pressure. The residue was dissolved with EtOAc and saturated aqueous NH_4Cl, and the layer were separated. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was used in the following reaction without further purification.

To a stirred solution of crude material in pyridine (0.3 mL) was added BzCl (25 μL, 0.217 mmol) at room temperature. After being stirred for 2 hours at the same temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc, the organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, *n*-hexane/EtOAc = 5/1 to 2/1) to give **5** (26.2 mg, 64%, 5 steps) as a yellow oil.

$[\alpha]^{25}_D$ −21.0 (*c* 0.20, $CHCl_3$).
IR (ATR, cm^{-1}): 3291, 2956, 2923, 2856, 1717, 1542, 1450, 1362, 1275, 1169, 1070, 750, 715.
^1H NMR (500 MHz, $CDCl_3$) δ: 8.11-8.07 (m, 3H), 7.81-7.79 (m, 1H), 7.73-7.71 (m, 2H), 7.56 (ddd, *J* = 7.4, 7.4, 1.3 Hz, 1H), 7.45 (dd, *J* = 7.9, 7.6 Hz, 2H), 5.72-5.69 (m, 2H), 4.96 (dd, *J* = 12.6, 8.6 Hz, 1H), 4.64 (ddd, *J* = 12.7, 5.9, 1.1 Hz, 1H), 3.98 (d, *J* = 2.8 Hz, 1H), 3.66 (s, 3H), 3.304(s, 3H), 3.300 (s, 3H), 3.20-3.17 (m, 1H), 3.06-3.02 (m, 2H), 2.72 (dd, *J* = 16.9, 5.6 Hz, 1H), 2.40-2.35 (m, 1H), 2.17 (dd, *J* = 16.9, 5.8 Hz, 1H), 1.65 (s, 3H).
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ: 174.0, 167.0, 148.2, 138.3, 133.5, 133.2, 133.1, 132.5, 131.1, 130.0, 129.8, 128.4, 125.8, 125.1, 106.1, 60.7, 56.0, 55.9, 51.9, 43.2, 40.8, 37.9, 31.0, 18.2.
HRMS (ESI (+)): Calcd for $C_{26}H_{32}N_2O_{10}SNa^+$ $[M+Na]^+$ 587.1670, found 587.1685.

Allyl alcohol 22



To a stirred solution of **5** (60.1 mg, 108 μmol) in a 10:1 mixture of CH_2Cl_2 and MeCN (total 1.1 mL) was added TMSCN (70 μL, 560 μmol) at room temperature. Then to the resulting mixture was added $BF_3{\cdot}OEt_2$ (40 μL, 318 μmol) at –78 °C and allowed to warm gradually to 0 °C over 2 hours. Then the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was used in the following reaction without further purification.

To a stirred solution of the crude material in a 10:1 mixture of EtOH and THF (total 1.0 mL) and H_2O (10 μL, 1.1 mmol) was added Parkins catalyst (9.2 mg, 21 μmol) at room temperature. The resulting mixture was stirred at 55 °C for 24 hours. Then the reaction mixture was filtered through a pad of Celite and silica gel and concentrated under reduced pressure. The crude material was used in the following reaction without further purification.

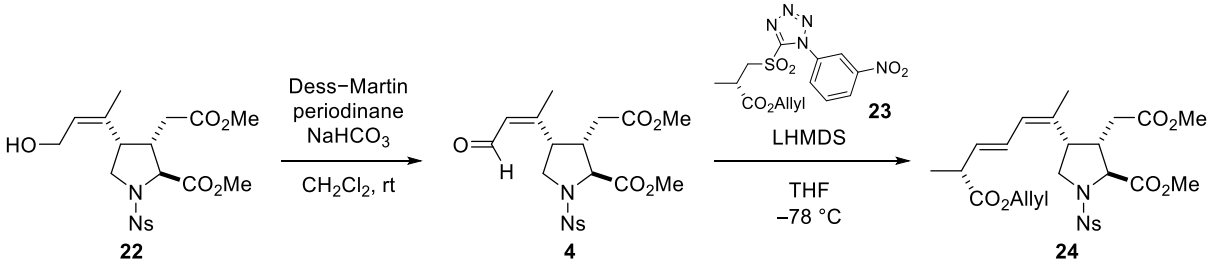
To a stirred solution of the crude material in CH_2Cl_2 (1.0 mL) was added Me_3OBF_4 (32 mg, 216 μmol) at 0 °C, and resulting mixture was stirred at room temperature for 24 hours. Then to the reaction mixture was added H_2O (0.1 mL) at 0 °C and the resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was used in the following reaction without further purification.

To a stirred solution of the crude material in THF (0.8 mL) and MeOH (0.2 mL) was added NaOMe (11.5 mg, 213 μmol) at 0 °C. The resulting mixture was stirred at room temperature for 20 minutes. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, *n*-hexane/EtOAc

= 3/1 to 1/1) to give **22** (18.1 mg, 37%, 4 steps) as a colorless oil.

$[\alpha]^{23}_{D}$ −54.7 (*c* 0.41, $CHCl_3$).
IR (ATR, cm^{-1}): 3565, 2954, 2921, 1736, 1544, 1438, 1372, 1172, 782, 615.
^1H NMR (500 MHz, $CDCl_3$) δ: 8.08-8.06 (m, 1H), 7.72-7.66 (m, 3H), 5.57 (t, *J* = 6.8 Hz, 1H), 4.38 (d, *J* = 5.9 Hz, 1H), 4.04 (d, *J* = 7.0 Hz, 2H), 3.82 (dd, *J* = 10, 2, 7.4 Hz, 1H), 3.75 (dd, *J* = 10.2, 5.4 Hz, 1H), 3.67-3.62 (m, 7H), 2.99-2.93 (m, 1H), 2.48 (dd, *J* = 17.0, 6.8 Hz, 1H), 2.42 (dd, *J* = 17.0, 8.1 Hz, 1H), 1.68 (d, *J* = 1.1 Hz, 3H).
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ: 172.3, 171.4, 148.0, 134.1, 133.7, 132.9, 131.7, 131.0, 130.1, 124.2, 65.3, 58.3, 52.7, 52.1, 50.9, 44.1, 40.4, 32.9, 22.2.
HRMS (ESI (+)): Calcd for $C_{19}H_{24}N_2O_9SNa^+$ $[M+Na]^+$ 479.1095, found 479.1071.

Diene 24

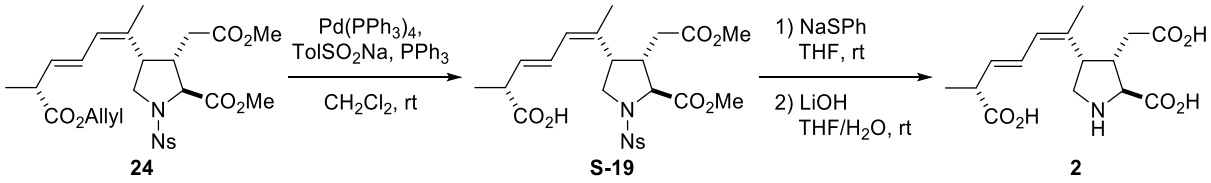


To a stirred solution of **22** (2.3 mg, 5.0 μmol) in CH_2Cl_2 (0.5mL) were added Dess–Martin periodinane (3.0 mg, 5.9 μmol) and $NaHCO_3$ (1.7 mg, 20.2 μmol) at room temperature. The resulting mixture was stirred at the same temperature for 10 minutes. Then the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ and extracted with EtOAc. The organic layer was filtered through a pad of silica gel and concentrated under reduced pressure. The crude material was used in the following reaction without further purification.

To a stirred solution of the crude material and **23** (5.8 mg, 15.2 μmol) in THF (0.1 mL) was added LHMDS (10 μL, 1 M in toluene, 10 μmol) at –78 °C. The resulting mixture was stirred at the same temperature for 10 minutes. Then the reaction mixture was quenched with 1 M AcOH in THF, diluted with saturated aqueous $NaHCO_3$, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC (*n*-hexane/Et_2O = 1/2) to give **24** (1.8 mg, 64%, 2 steps) as a colorless oil.

$[\alpha]^{23}_D$ –93.2 (*c* 0.215, $CHCl_3$).
IR (ATR, cm^{-1}): 2952, 1734, 1543, 1438, 1372, 1170, 773.
^1H NMR (500 MHz, $CDCl_3$) δ: 8.09-8.07 (m, 1H), 7.73-7.66 (m, 3H), 6.19 (dd, *J* = 14.9, 11.9 Hz, 1H), 5.96 (d, *J* = 10.5 Hz, 1H), 5.90 (ddd, *J* = 11.3, 5.8, 5.8 Hz, 1H), 5.69 (dd, *J* = 14.9, 7.8 Hz, 1H), 5.30 (ddd, *J* = 17.2, 1.6, 1.5 Hz, 1H), 5.23 (dd, *J* = 10.5, 1.3 Hz, 1H), 4.58 (d, *J* = 5.7 Hz, 2 H), 4.39 (d, *J* = 6.3 Hz, 1H), 3.85-3.73 (m, 2H), 3.71-3.61 (m, 7H), 3.20 (t, *J* = 7.2 Hz, 1H), 3.01 (t, *J* = 7.1 Hz, 1H), 2.45 (dd, *J* = 17.1, 7.4 Hz, 1H), 2.36 (dd, *J* = 17.0, 7.7 Hz, 1H), 1.70 (s, 3H), 1.28 (d, *J* = 6.9 Hz, 3H).
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ: 173.9, 171.8, 171.4, 148.0, 133.6, 133.0, 132.7, 132.6, 132.1, 131.6, 131.0, 130.2, 126.0, 124.2, 118.2, 65.3, 65.2, 52.6, 51.9, 51.1, 44.1, 42.9, 40.6, 32.6, 22.1, 17.0.
HRMS (ESI (+)): Calcd for $C_{26}H_{32}N_2O_{10}SNa^+$ $[M+Na]^+$ 587.1670, found 587.1648.

Domoic acid 2



To a stirred solution of **24** (2.2 mg, 4.0 μmol) in CH_2Cl_2 (0.1 mL) were added $Pd(PPh_3)_4$ (0.5 mg, 0.6 μmol), $TolSO_2Na$ (2.1 mg, 12 μmol) and PPh_3 (0.5 mg, 1.9 μmol) at room temperature. The resulting mixture was stirred at the same temperature for 2 hours. Then the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was used in the following reaction without further purification.

To a stirred solution of the crude material in THF (0.1 mL) was added NaSPh (2.8 mg, 21 μmol) at room temperature. The resulting mixture was stirred at the same temperature for 11 hours. Then the reaction mixture was charged onto a column containing Amberlite-IR120B hydrogen form. After washing the resin with H_2O and MeOH, the product was eluted with 25% aqueous NH_3. The eluate was concentrated under reduced pressure. The crude material was used in the following reaction without further purification.

To a stirred solution of crude material in THF (50 μL) was added 1 M aqueous LiOH (30 μL) at room temperature. The resulting mixture was stirred at the same temperature for 3 hours. Then the reaction mixture was charged onto a column containing Amberlite-IR120B hydrogen form. After washing the resin with H_2O and MeOH, the product was eluted with 25% aqueous NH_3. The eluate was concentrated under reduced pressure to give free amino acid **2** (1.0 mg, 83%, 3 steps) as a colorless solid.

$[\alpha]^{23}_D$ –115.3 (*c* 0.04, H_2O).

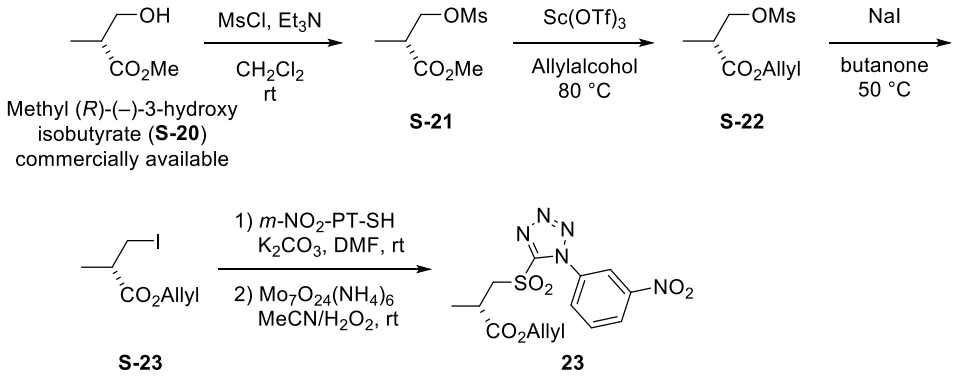
IR (ATR, cm^{-1}): 3358, 3198, 2978, 1710, 1618, 1565, 1457, 1387, 1327, 1170, 1036, 969, 921, 783, 667.

^1H NMR (500 MHz, D_2O) δ: 6.14 (dd, *J* = 14.9, 11.0 Hz, 1H), 5.93 (d, *J* = 11.0 Hz, 1H), 5.58 (dd, *J* = 15.0, 7.9 Hz, 1H), 3.76 (d, *J* = 8.2 Hz, 1H), 3.63 (ddd, *J* = 8.1, 7.8, 7.5 Hz, 1H), 3.50 (dd, *J* = 11.2, 7.8 Hz, 1H), 3.29 (dd, *J* = 12.3, 7.2 Hz, 1H), 3.05-3.02 (m, 1H), 2.87-2.81 (m, 1H), 2.51 (dd, *J* = 16.7, 5.8 Hz, 1H), 2.27 (dd, *J* = 16.6, 9.1 Hz, 1H), 1.61 (s, 3H), 1.05 (d, *J* = 7.0 Hz, 3H).

$^{13}C\{^1H\}$ NMR (126 MHz, D_2O) δ: 181.1, 176.0, 173.0, 133.8, 131.3, 130.7, 64.8, 46.8, 43.8, 42.7, 40.5, 33.7, 25.0, 21.4, 16.7.

HRMS (ESI (+)): Calcd for $C_{15}H_{21}NO_6Na^+$ $[M+Na]^+$ 334.1261, found 334.1258.

Sulfone 23



To a stirred solution of methyl (*R*)-(–)-3-hydroxyisobutyrate (**S-20**) (0.2 mL, 1.81 mmol) in CH_2Cl_2 (9 mL) were added Et_3N (0.4 mL, 2.87 mmol) and MsCl (170 μL, 2.20 mmol) at room temperature. The resulting mixture was stirred at the same temperature for 2 hours. Then the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was used in the following reaction without further purification.

To a stirred solution of crude material in allyl alcohol (6 mL) was added $Sc(OTf)_3$[S4] (214 mg, 0.435 mmol) at room temperature. After being stirred for 15 hours at 80 °C, the resulting mixture was added further $Sc(OTf)_3$ (202 mg, 0.410 mmol) and stirred for 24 hours at same temperature. Then, the reaction mixture was concentrated under reduced pressure. The residue was dissolved with EtOAc, filtered through a pad of silica gel, and concentrated under reduced pressure. The crude material was used in the following reaction without further purification.

To a stirred solution of crude material in butanone (6 mL) was added NaI (814 mg, 5.43 mmol) at room temperature. The resulting mixture was stirred at 50 °C for 24 hours. Then the reaction mixture was quenched with H_2O and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was used in the following reaction without further purification.

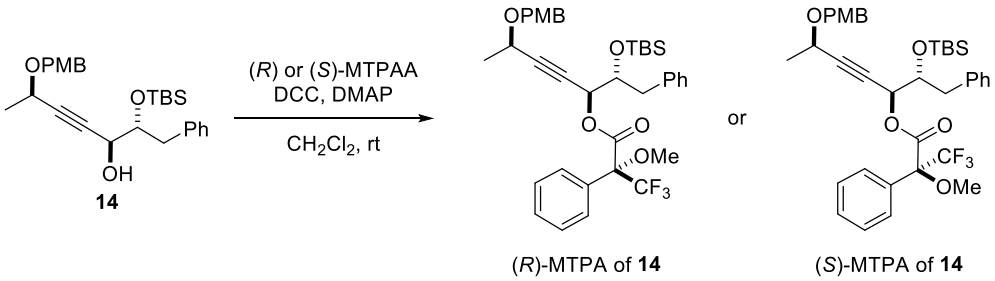
To a stirred solution of crude material in DMF (10 mL) were added *m*NPTSH[S3] (510 mg, 2.20 mmol) and K_2CO_3 (350 mg, 2.53 mmol) at room temperature. The resulting mixture was stirred at the same temperature for 2 hours. Then the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was used in the following reaction without further purification.

To a stirred solution of crude material in MeCN (10 mL) were added H_2O_2 (9.8 M in H_2O, 3.5

mL 34.3mmol) and $Mo_7O_{24}(NH_4)_6$ (235 mg, 0.190 mmol) at room temperature. The resulting mixture was stirred at the same temperature for 24 hours. Then the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, *n*-hexane/EtOAc = 2/1) to give **23** (282 mg, 41%, 5 steps) as a yellow oil.

$[\alpha]^{24}_D$ –4.5 (*c* 0.78, $CHCl_3$).
IR (ATR, cm^{-1}): 3091, 2979, 2938, 1733, 1536, 1151, 765.
^1H NMR (500 MHz, $CDCl_3$) δ: 8.62 (t, *J* = 2.1 Hz, 1H), 8.51 (ddd, *J* = 8.3, 2.1, 0.9 Hz, 1H), 8.07 (ddd, *J* = 8.1, 2.1, 0.9 Hz, 1H), 7.83 (t, *J* = 8.2 Hz, 1H), 5.88 (ddt, *J* = 17.2, 10.5, 5.8 Hz, 1H), 5.31(dq, *J* = 17.2, 1.5 Hz, 1H), 5.26 (dq, *J* = 10.4, 1.2 Hz , 1H), 4.62-4.55 (m, 2H), 4.29 (dd, *J* = 15.1, 8.6 Hz, 1H), 3.84 (dd, *J* = 15.1, 4.2 Hz, 1H), 3.31-3.27 (m, 1H), 1.46 (d, *J* = 7.3 Hz, 3H).
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ: 172.5, 153.7, 148.5, 133.7, 131.3, 131.0, 130.8, 126.2, 120.9, 119.1, 66.4, 58.5, 35.0, 17.6.
HRMS (ESI (+)): Calcd for $C_{14}H_{15}N_5O_6SNa^+$ $[M+Na]^+$ 404.0635, found 404.0640.

MTPA esters derived from 14



To a solution of **14** (6.3 mg, 13.9 μmol) in CH_2Cl_2 (0.1 mL) were added (*R*)-MTBAA (7.3 mg, 31.2 μmol), DCC (10.4 mg, 50.4 μmol) and DMAP (1.5 mg, 12 μmol) at room temperature. The resulting mixture was stirred at the same temperature for 17 hours. Then the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (*n*-hexane/EtOAc = 9/1) to give (*R*)-MTPA of **14** (9.4 mg, quant.) as a colorless oil.

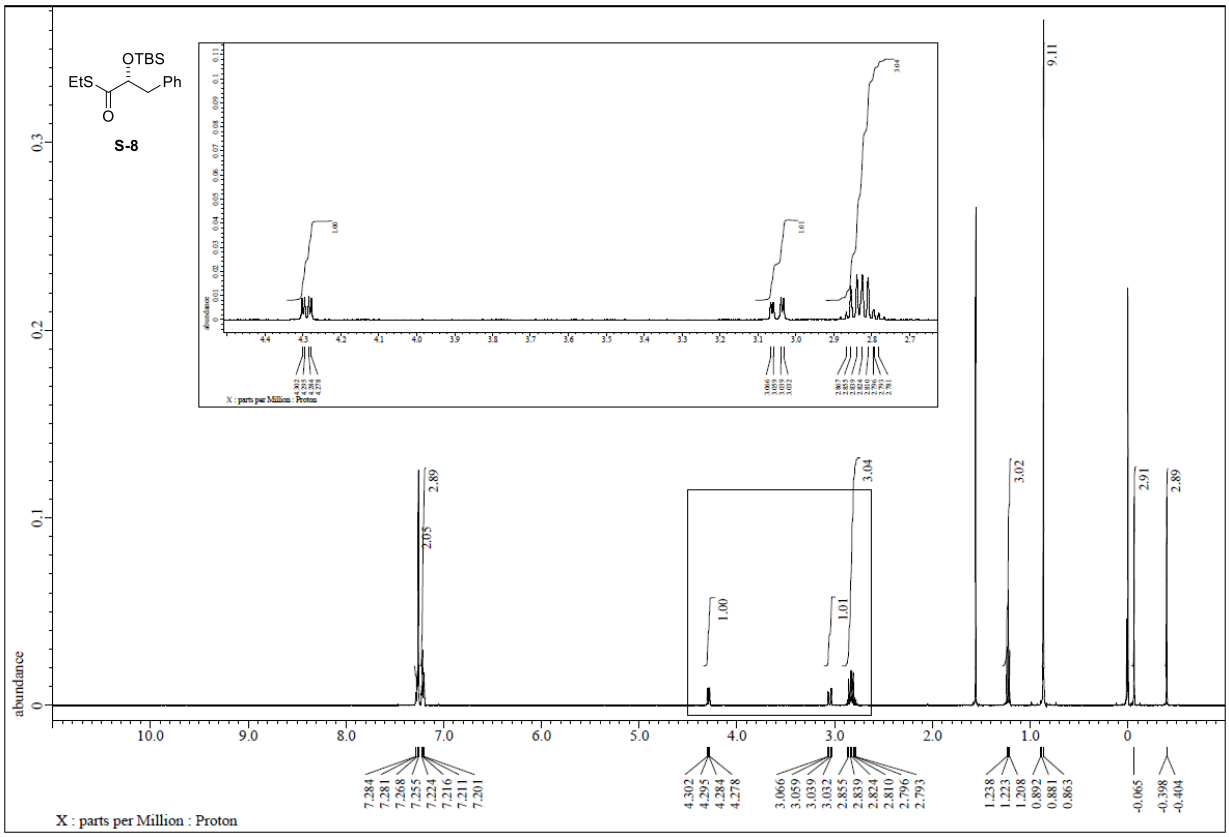
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.62-7.60 (m, 2H), 7.43-7.38 (m, 3H), 7.28-7.26 (m, 4H), 7.22-7.19 (m, 1H), 7.12 (d, *J* = 6.9 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.70 (s, 1H), 4.70 (d, *J* = 10.6 Hz, 1H), 4.44 (d, *J* = 11.5 Hz, 1H), 4.24 (q, *J* = 6.5 Hz, 1H), 4.00 (td, *J* = 5.9, 2.9 Hz, 1H), 3.80 (s, 3H), 3.62 (s, 3H), 3.03 (dd, *J* = 13.5, 3.7 Hz, 1H), 2.68 (dd, *J* = 13.5, 8.9 Hz, 1H), 1.46 (d, *J* = 6.9 Hz, 3H), 0.78 (s, 9H), –0.13 (s, 3H), –0.47 (s, 3H).

To a solution of **14** (6.2 mg, 13.6 μmol) in CH_2Cl_2 (0.1 mL) were added (*S*)-MTBAA (8.4 mg, 35.9 μmol), DCC (9.2 mg, 44.6 μmol) and DMAP (1.3 mg, 10.6 μmol) at room temperature. The resulting mixture was stirred at the same temperature for 17 hours. Then the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC (*n*-hexane/EtOAc = 9/1) to give (*S*)-MTPA of **14** (6.7 mg, 74%) as a colorless oil.

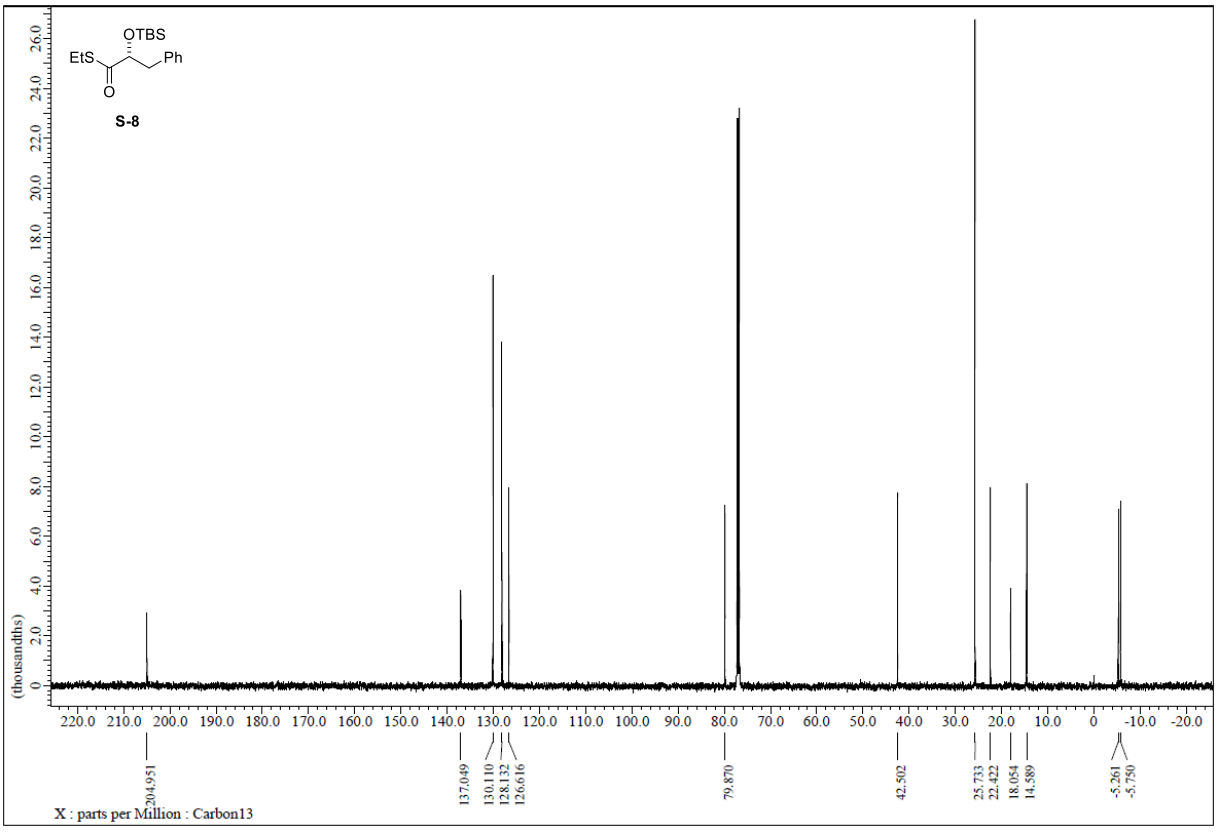
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.63 (d, *J* = 7.4 Hz, 2H), 7.39-7.37 (m, 3H), 7.28-7.25 (m, 4H), 7.21-7.19 (m, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.86 (d, *J* = 7.4 Hz, 2H), 5.76 (t, *J* = 1.1 Hz, 1H), 4.67 (d, *J* = 10.9 Hz, 1H), 4.39 (d, *J* = 11.5 Hz, 1H), 4.20 (q, *J* = 6.7 Hz, 1H), 4.07-4.05 (m, 1H), 3.79 (d, *J* = 1.1 Hz, 3H), 3.63 (s, 3H), 3.09 (dd, *J* = 13.5, 3.2 Hz, 1H), 2.78 (dd, *J* = 13.7, 9.2 Hz, 1H), 1.43 (d, *J* = 6.9 Hz, 3H), 0.75 (s, 9H), –0.11 (s, 3H), –0.42 (s, 3H).

4. Copies of NMR spectra

^{1}H NMR



^{13}C{^{1}H} NMR



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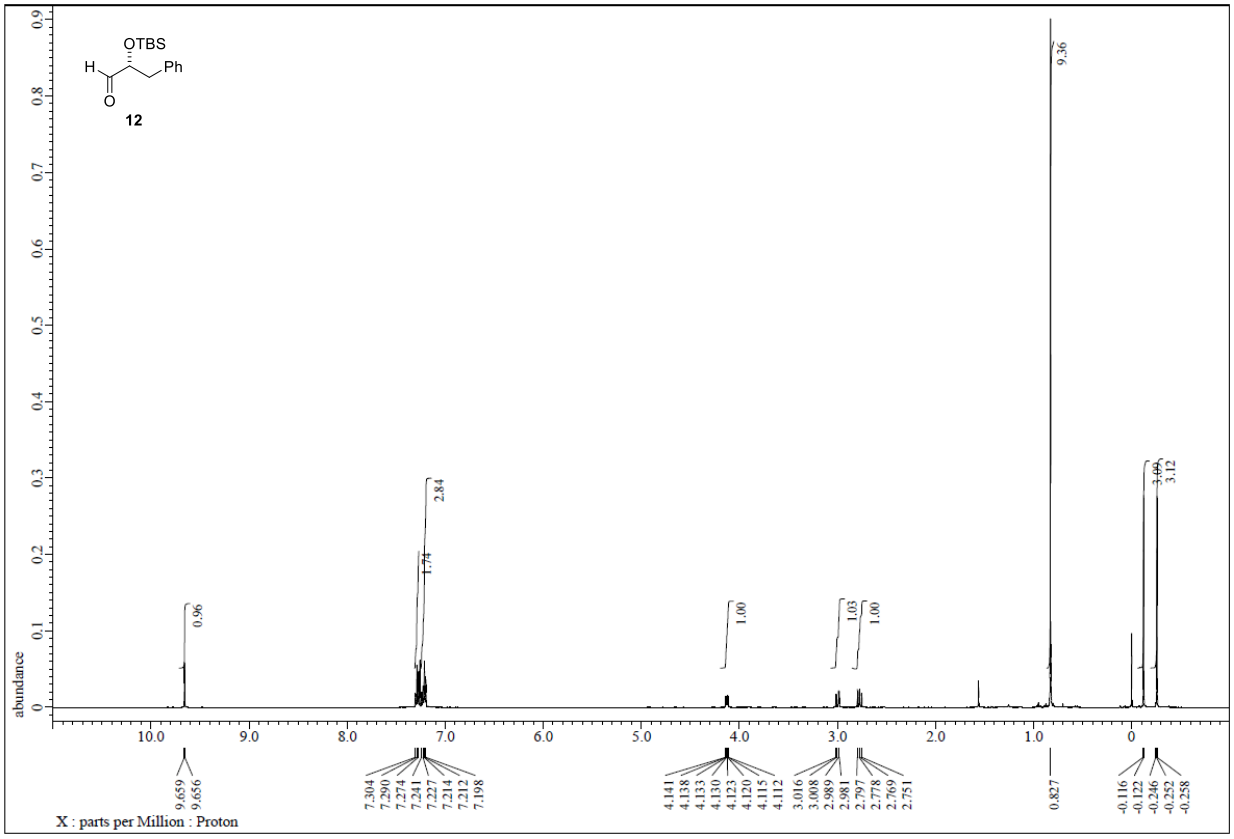

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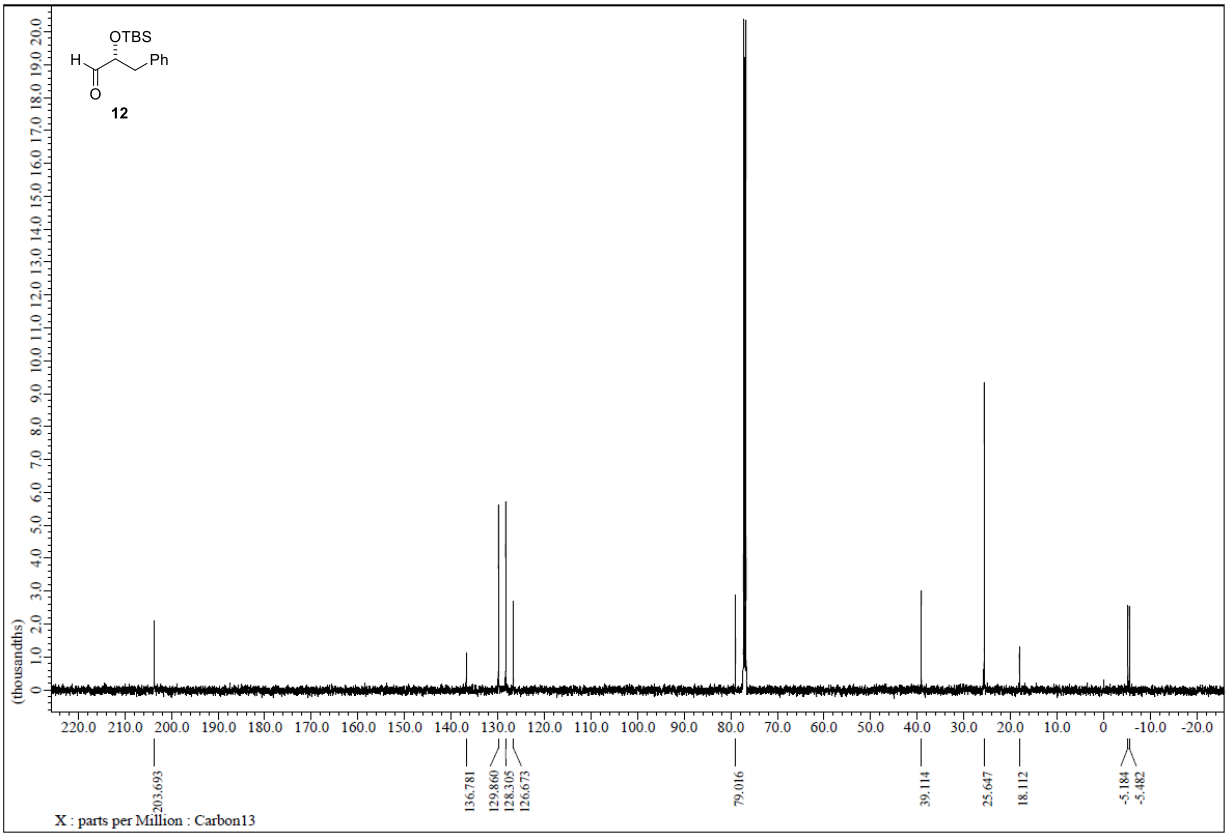

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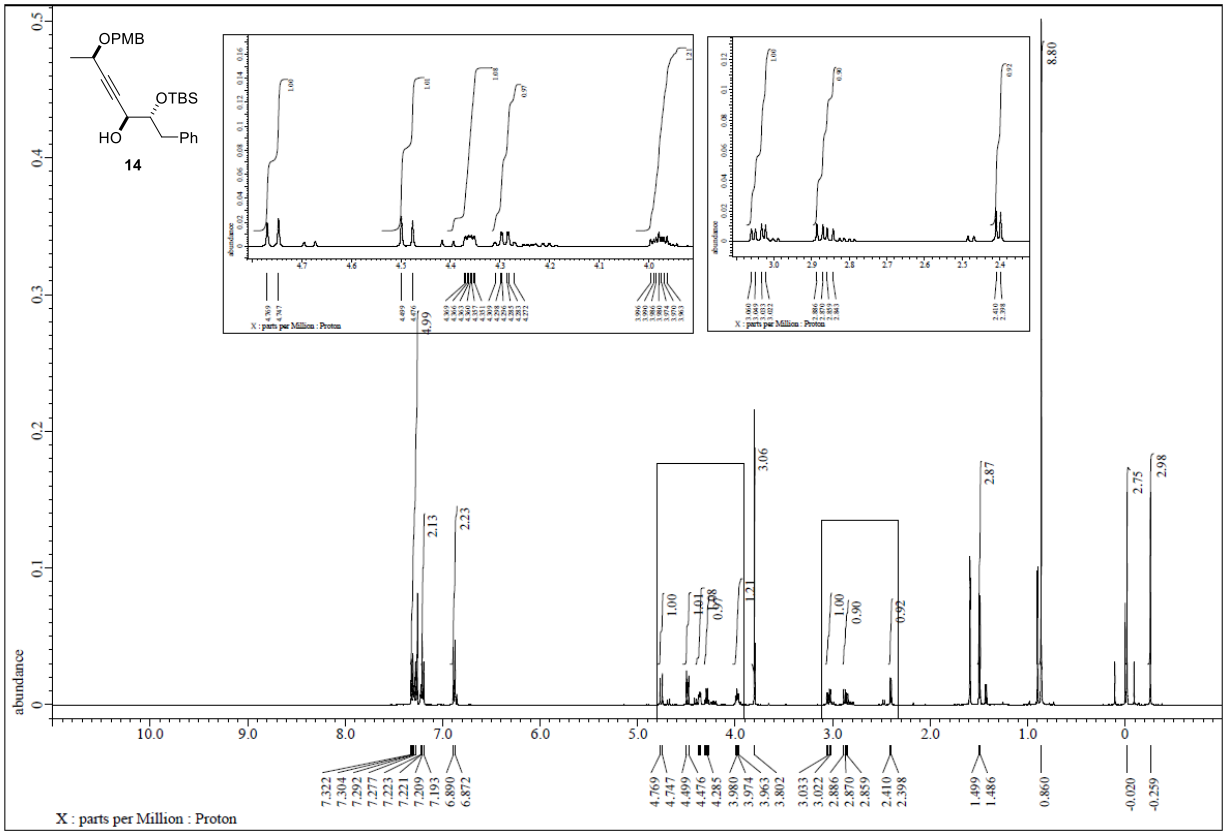

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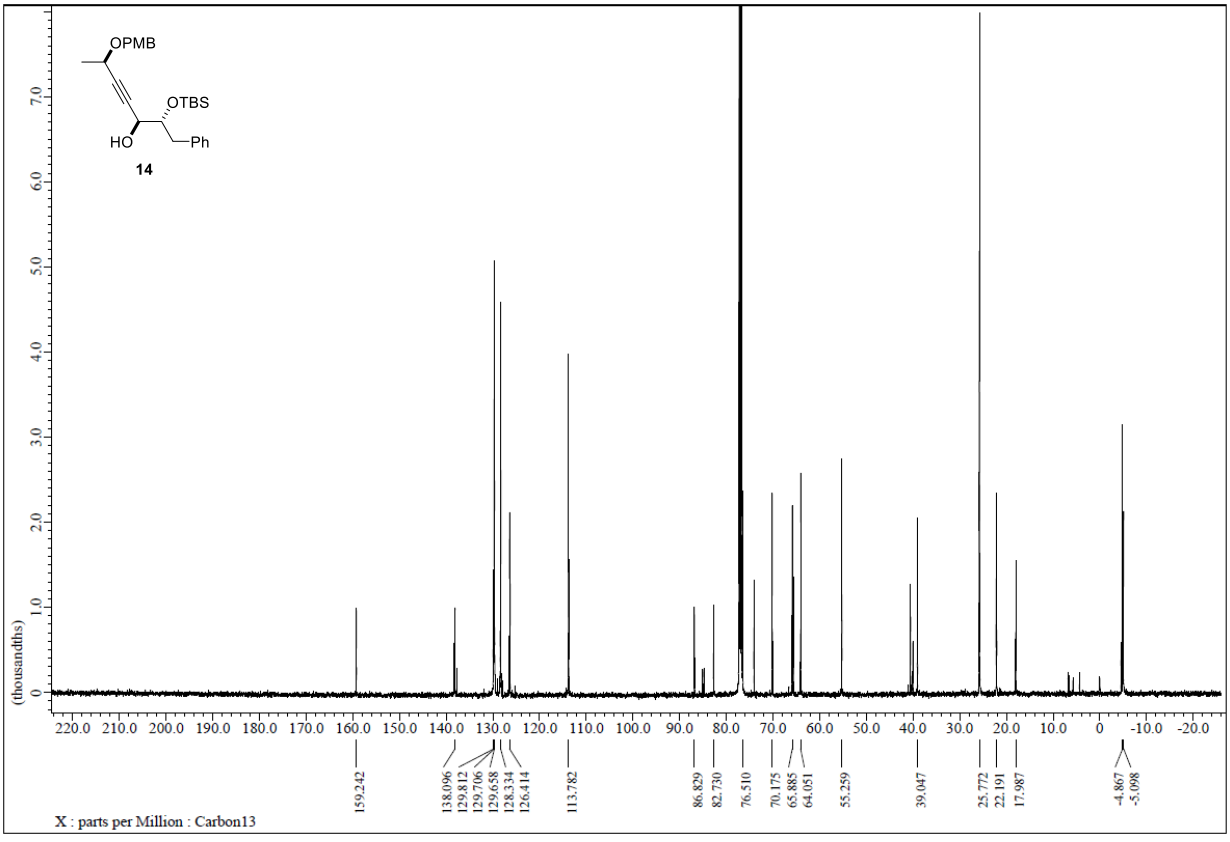

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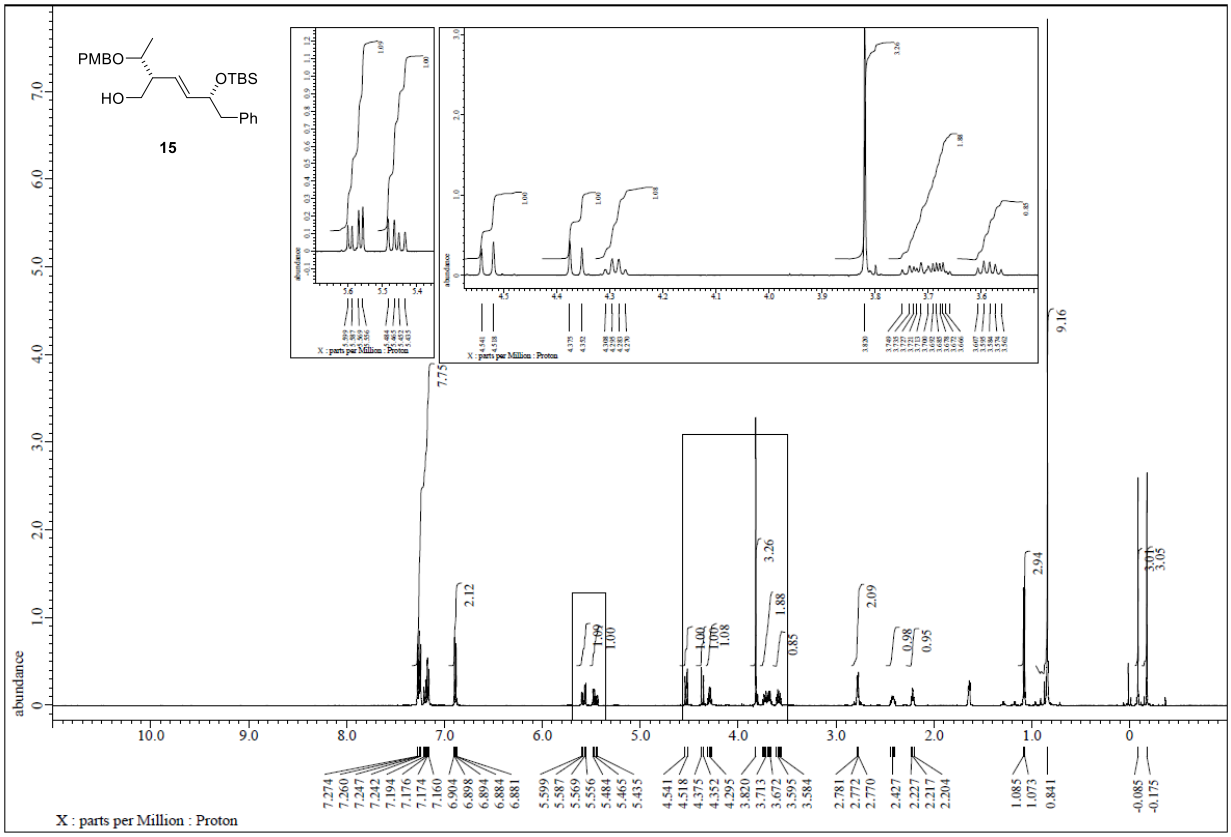

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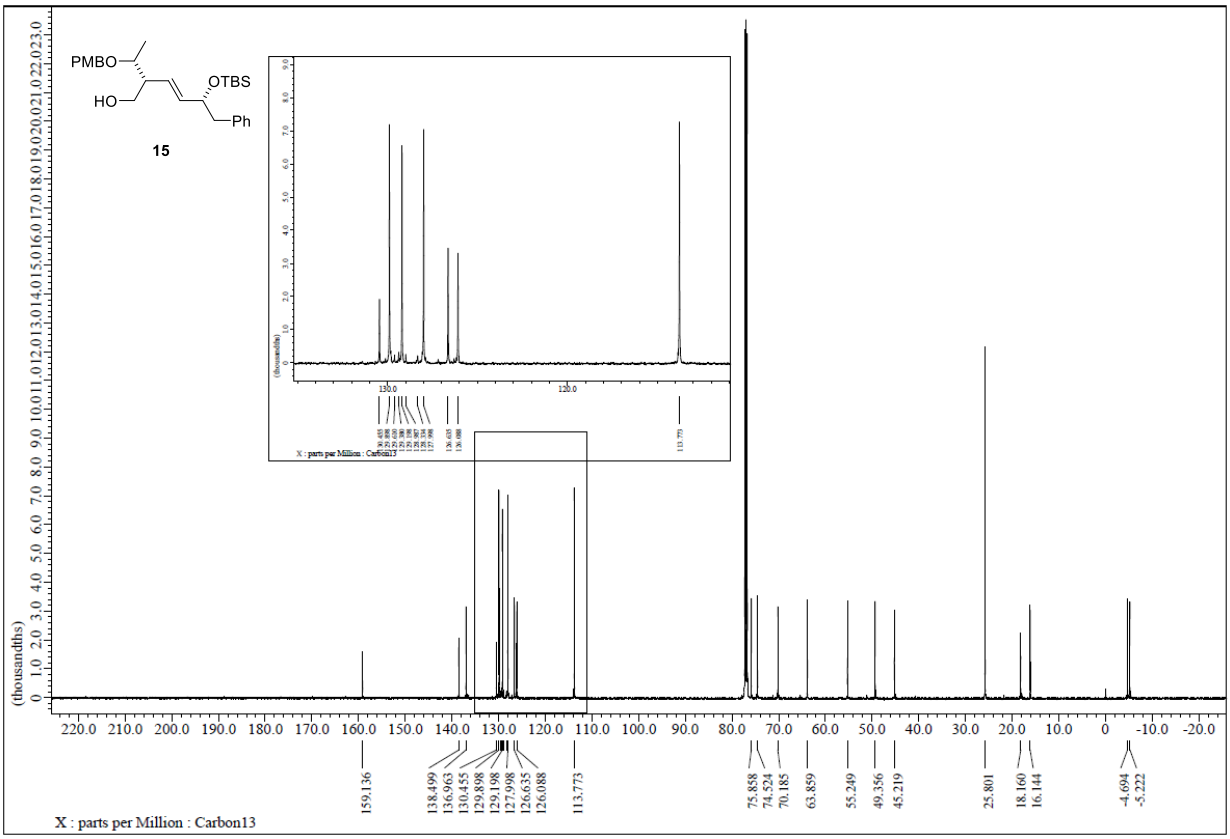

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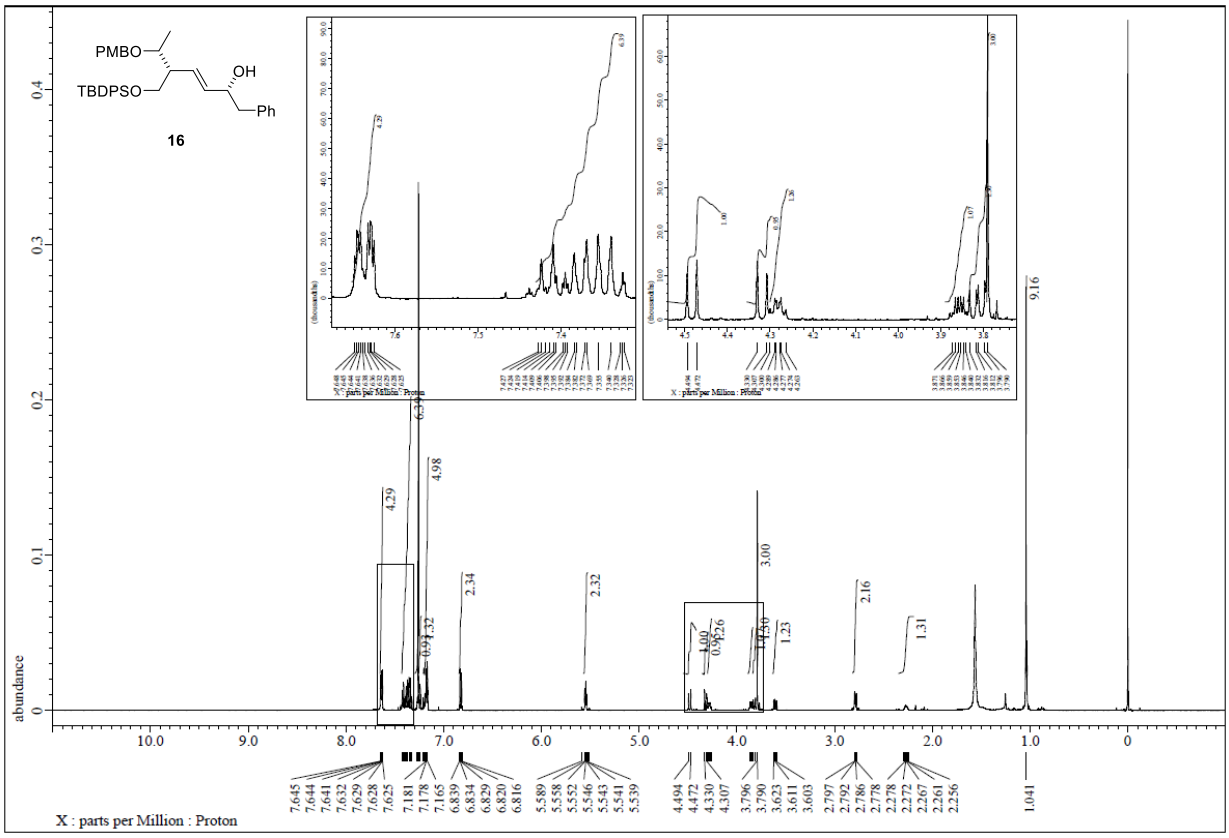

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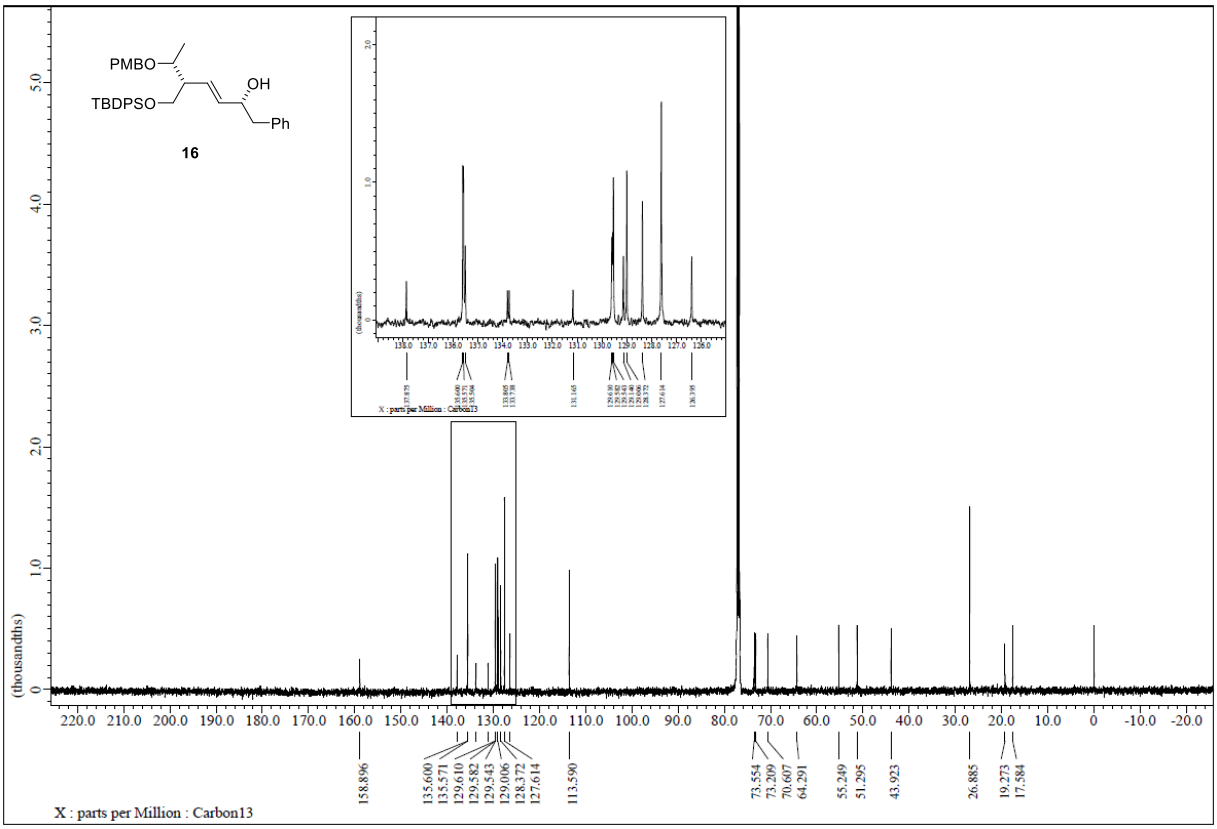

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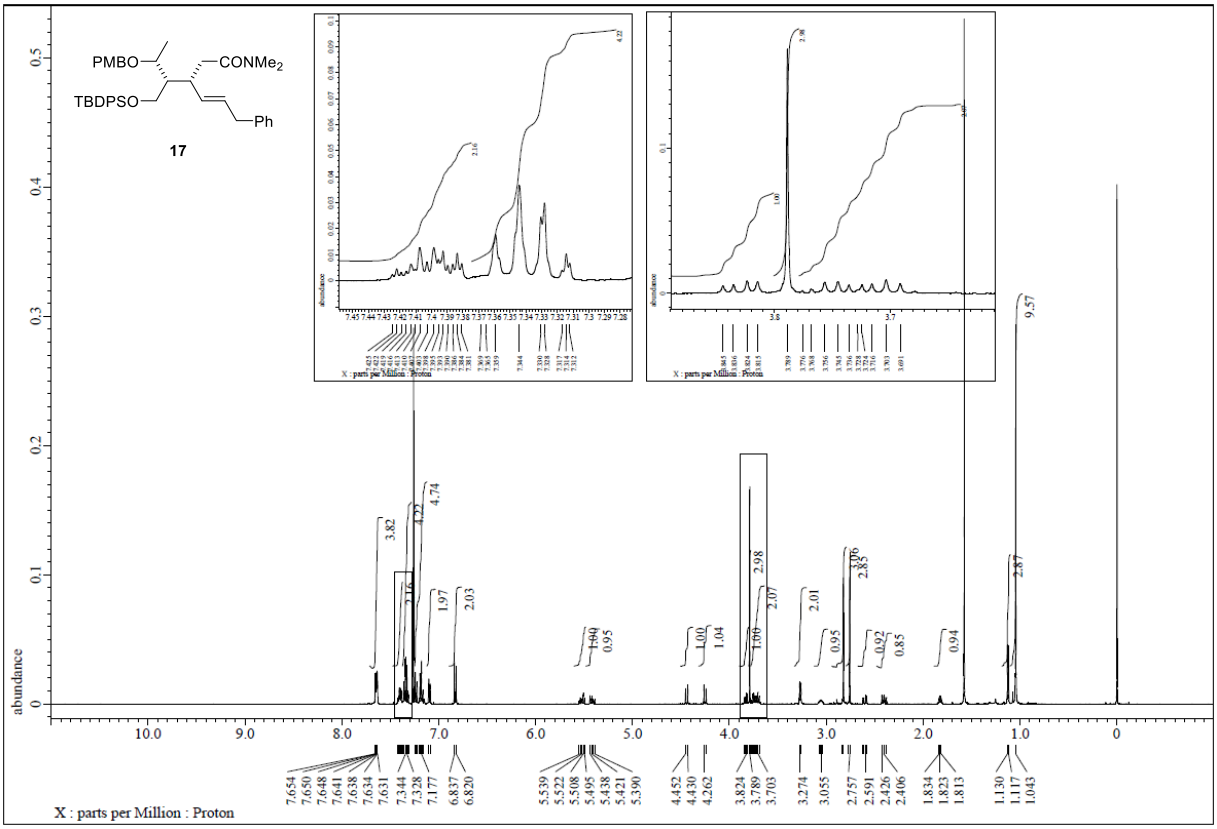

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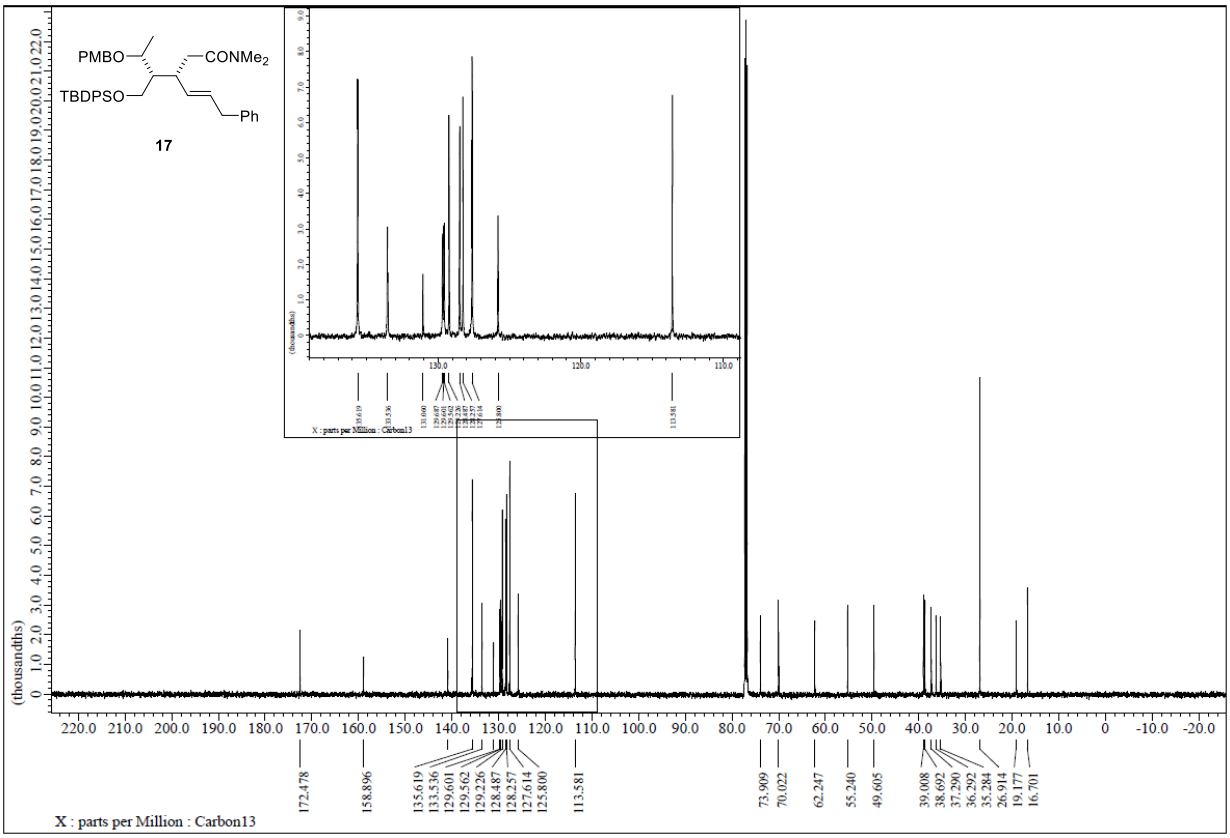

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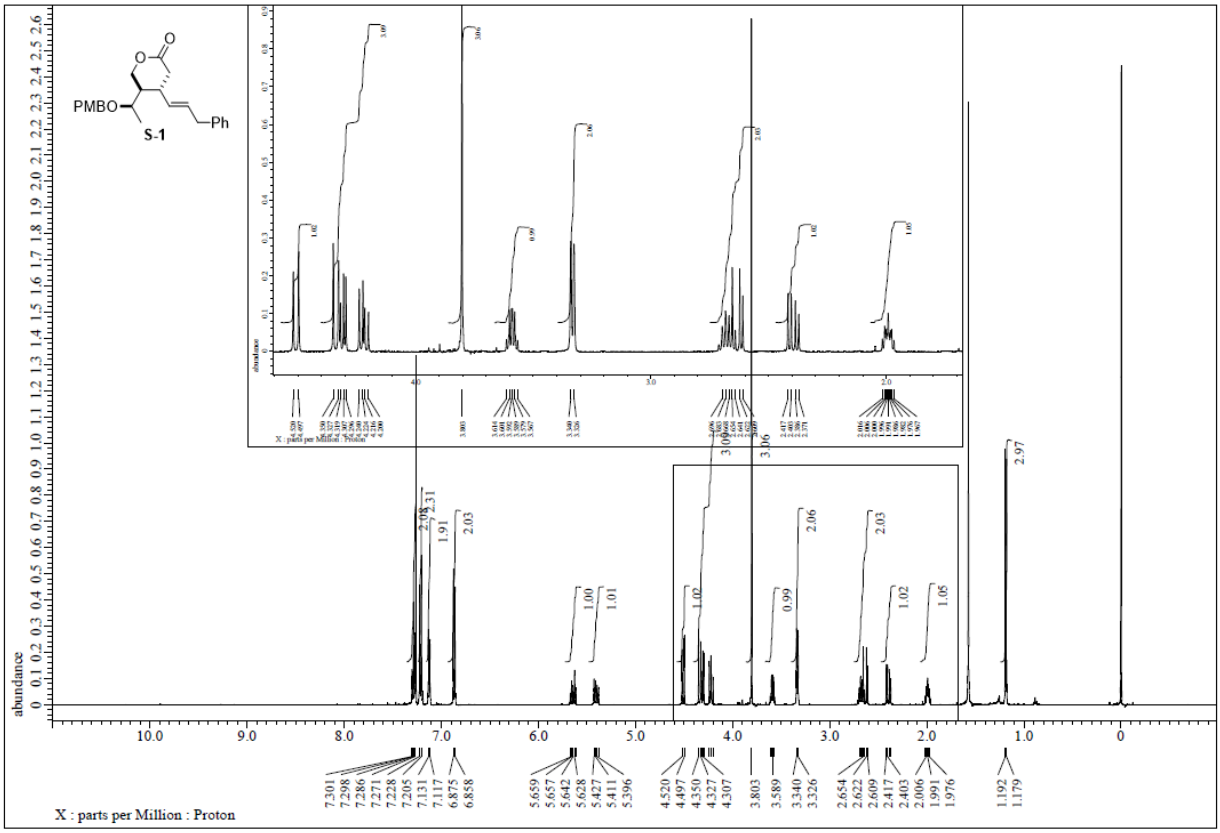

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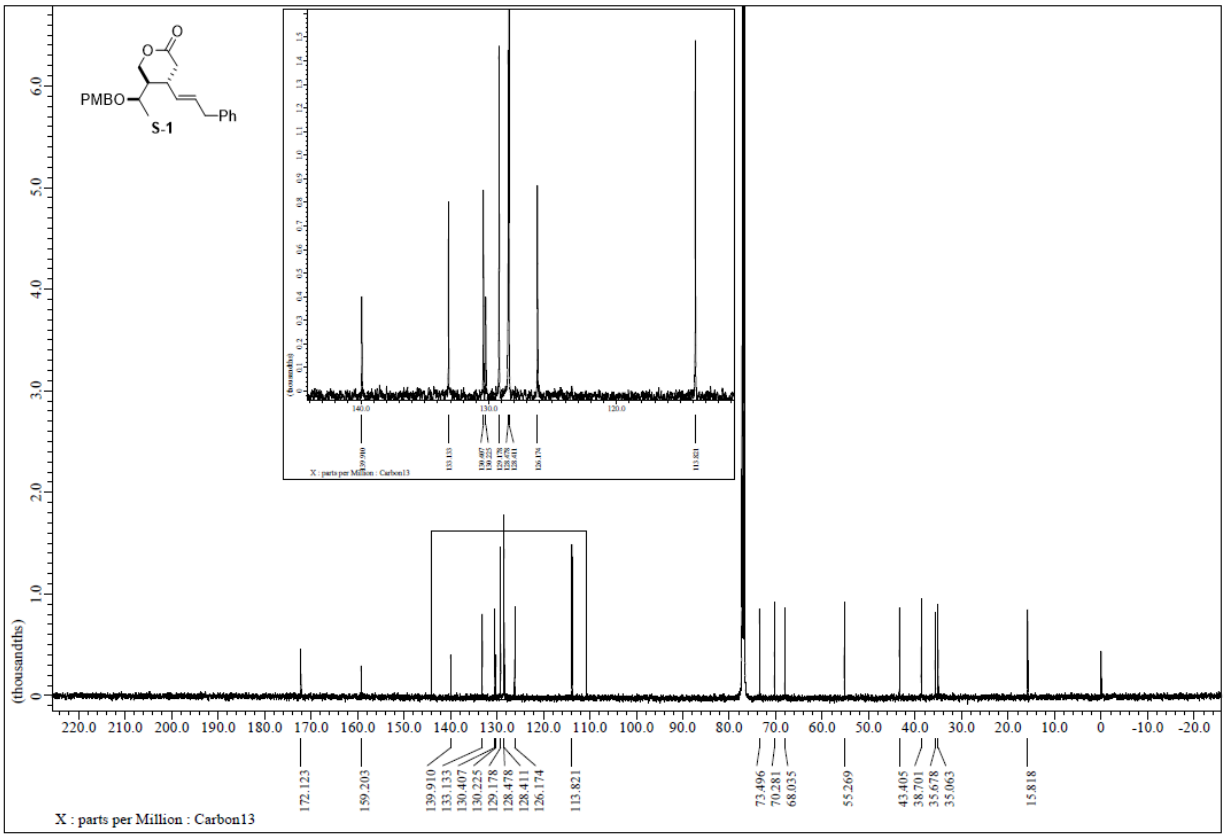

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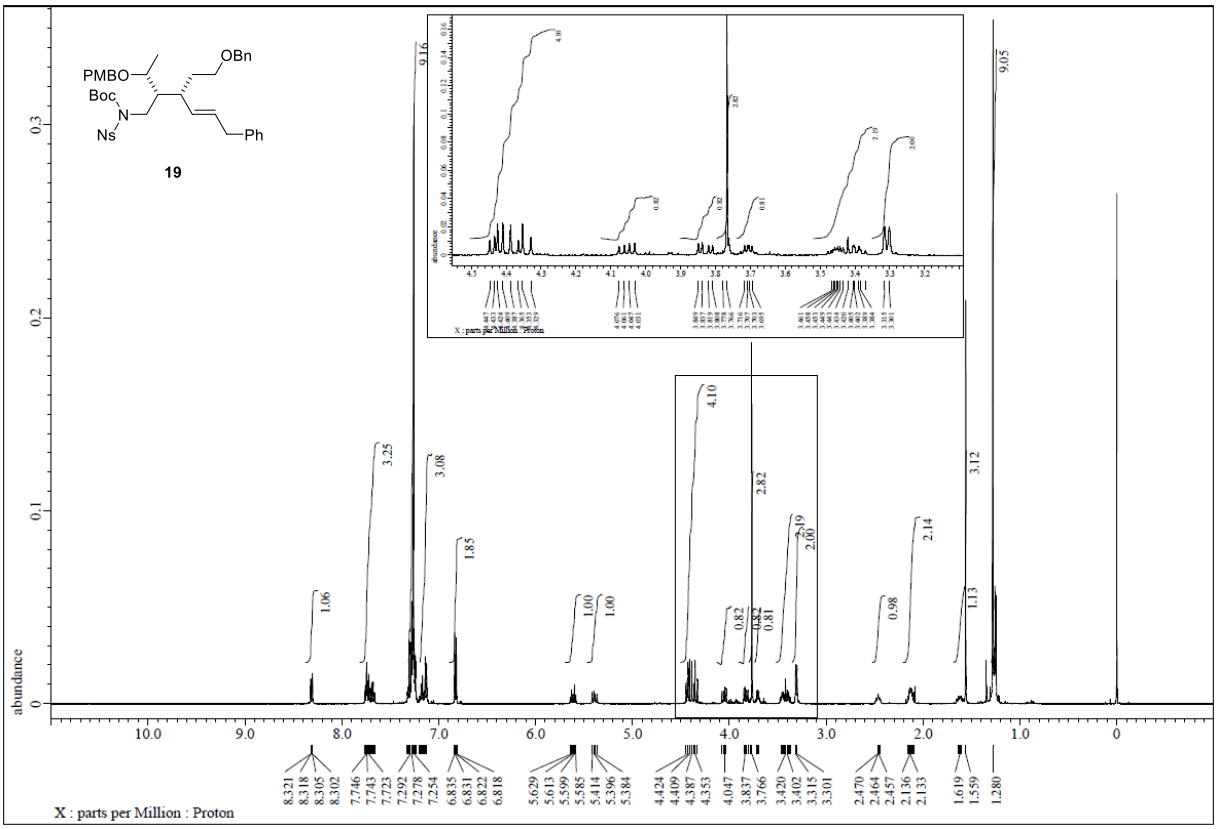

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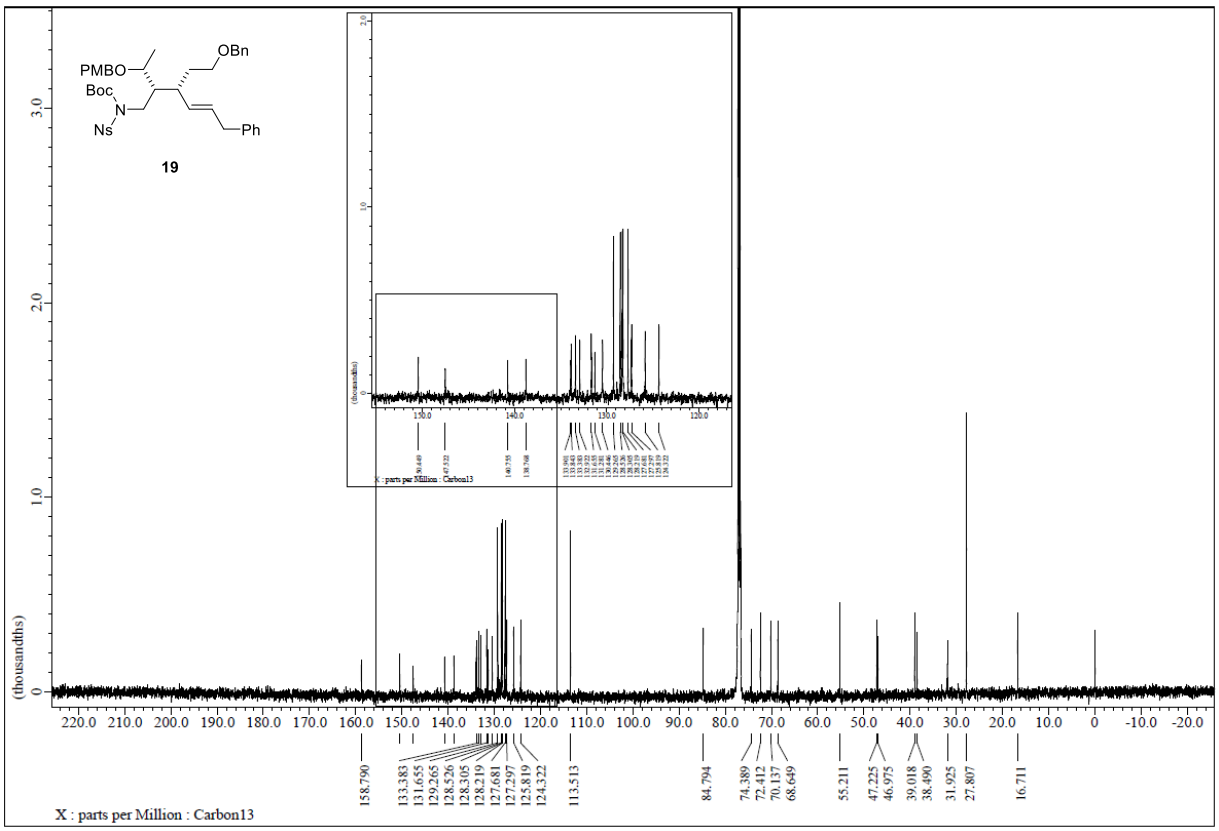

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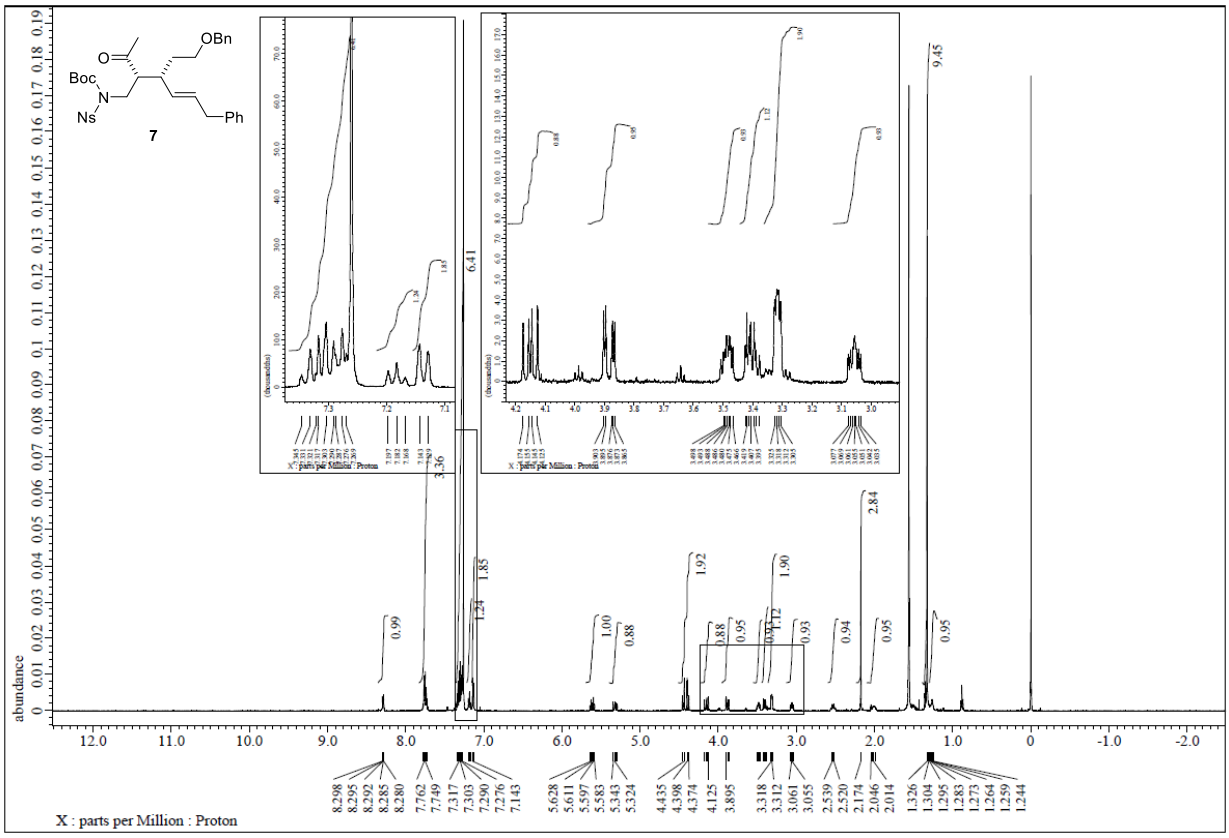

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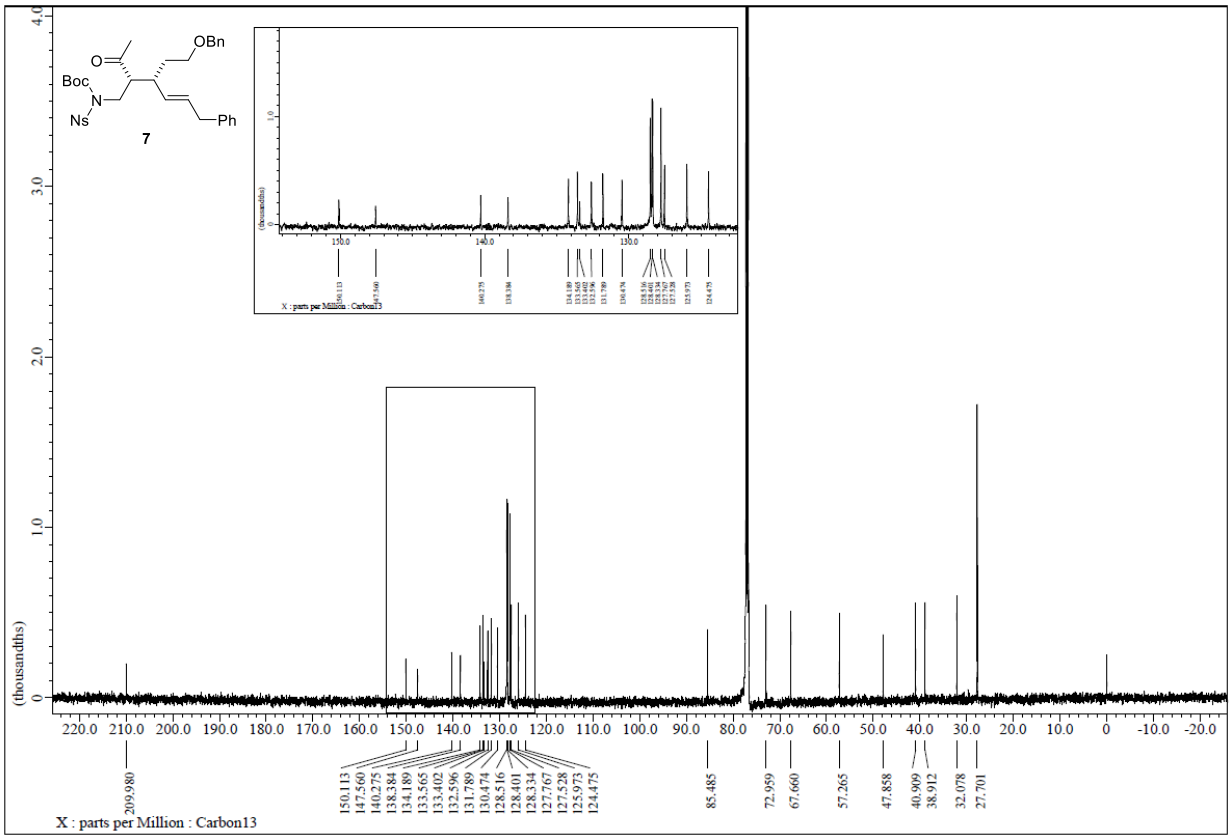

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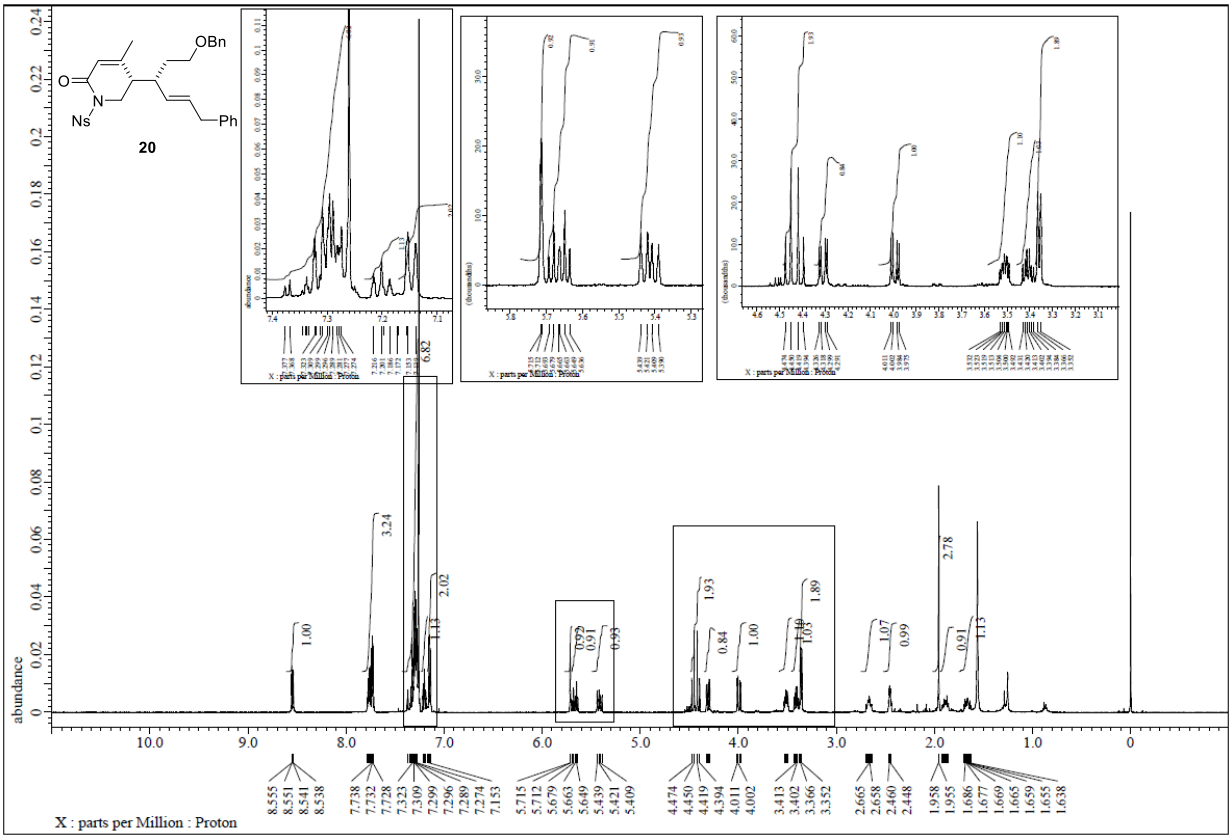

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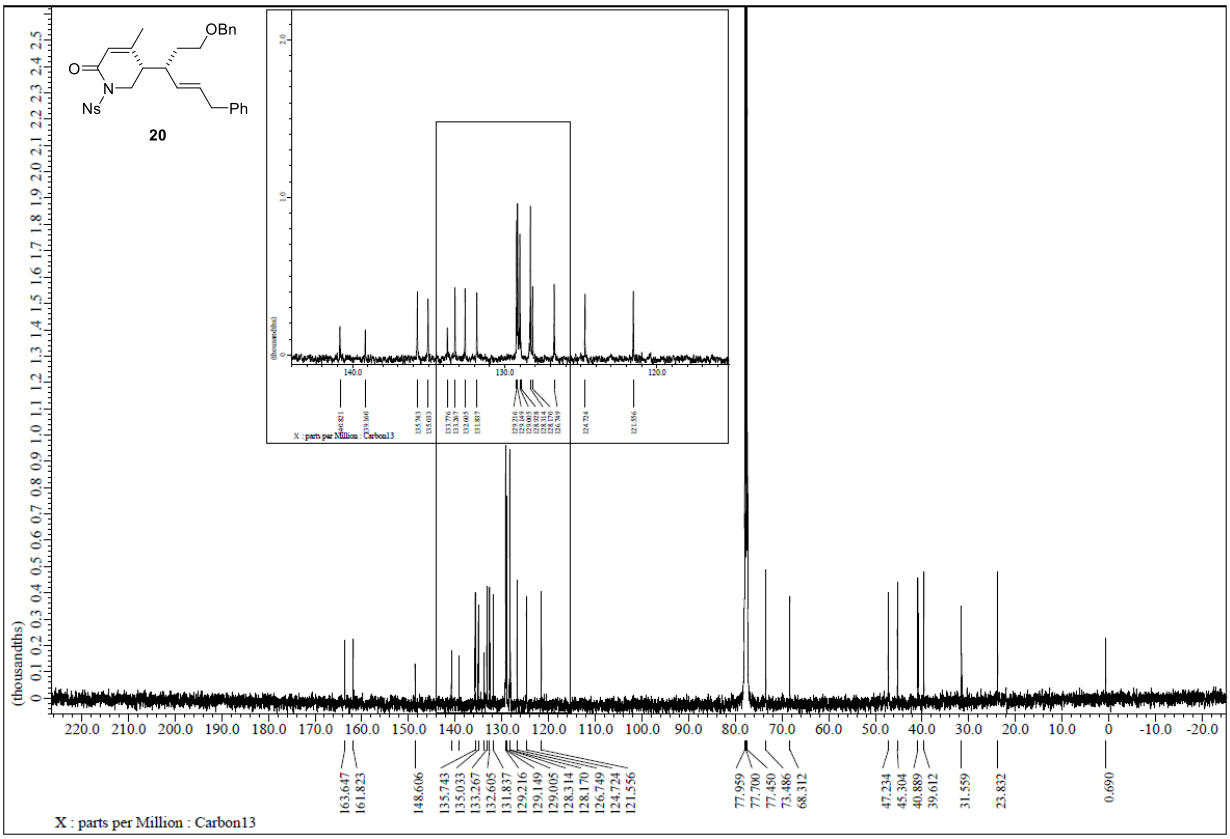

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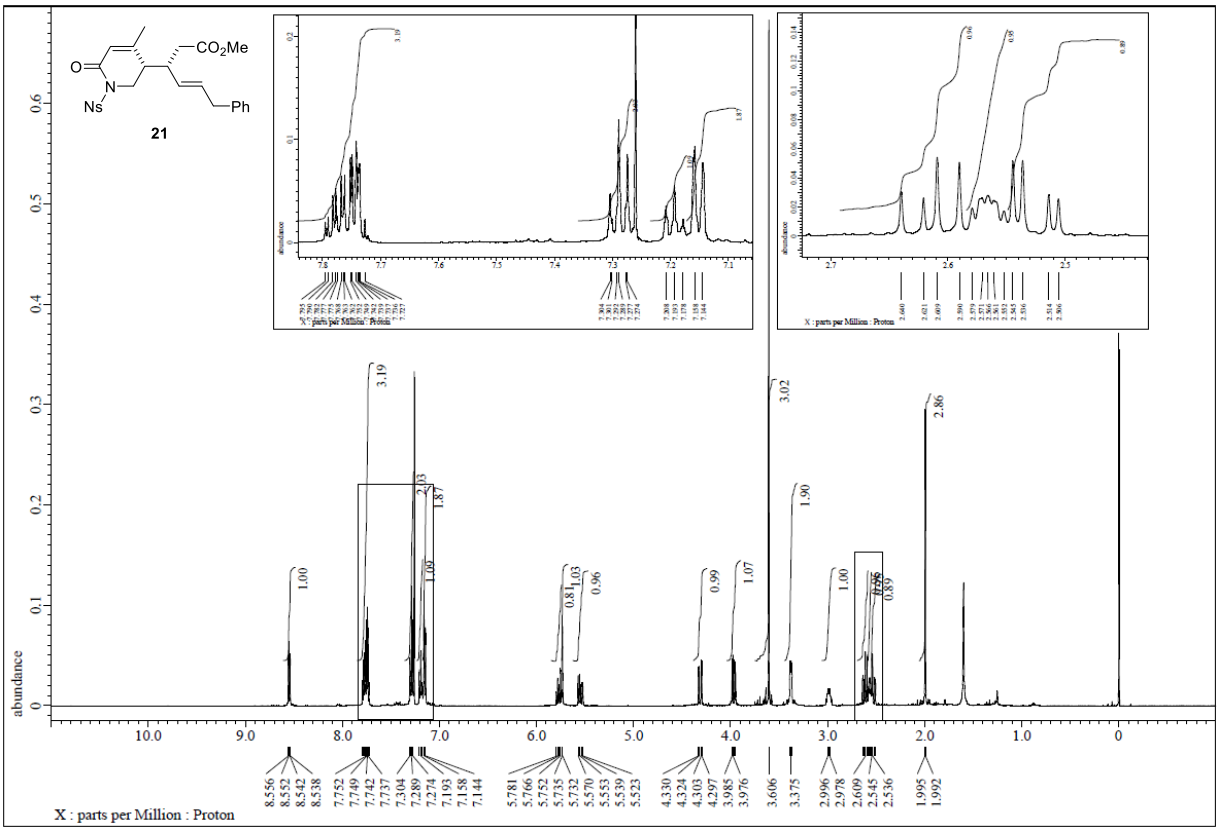

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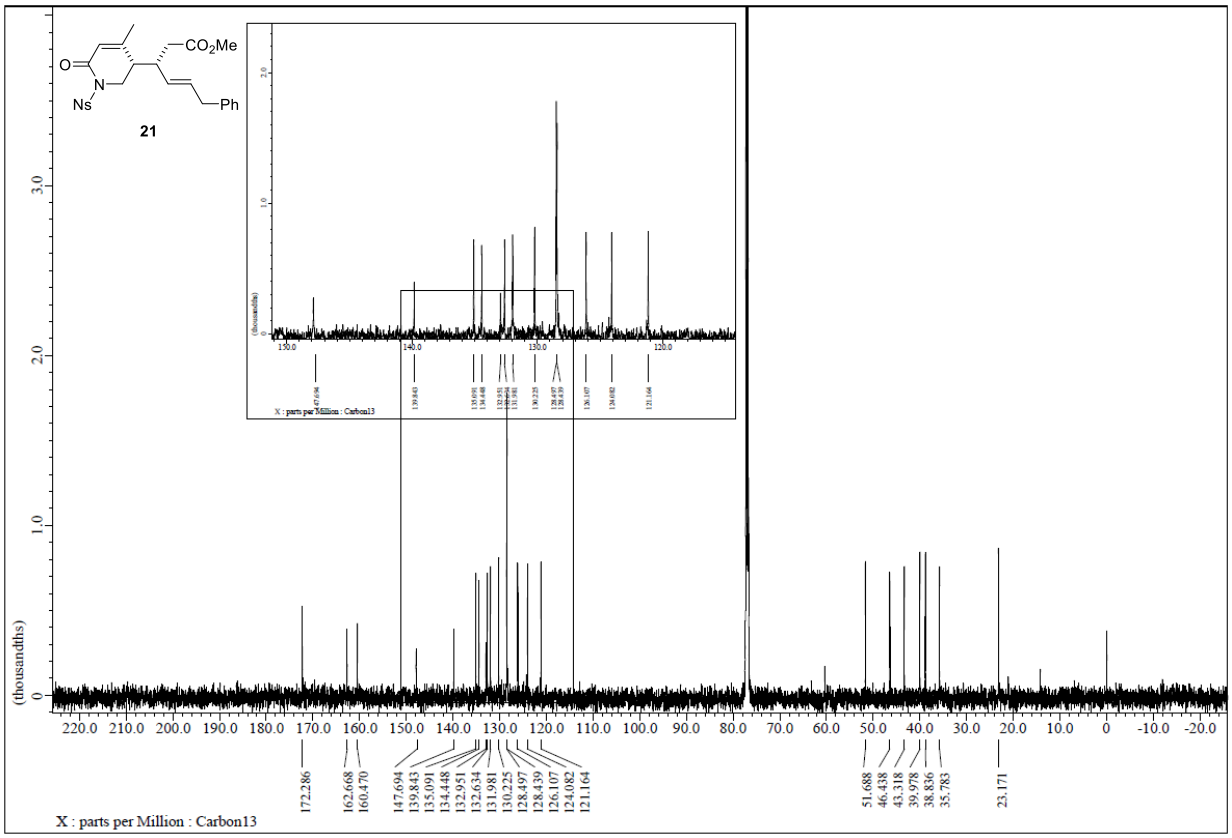

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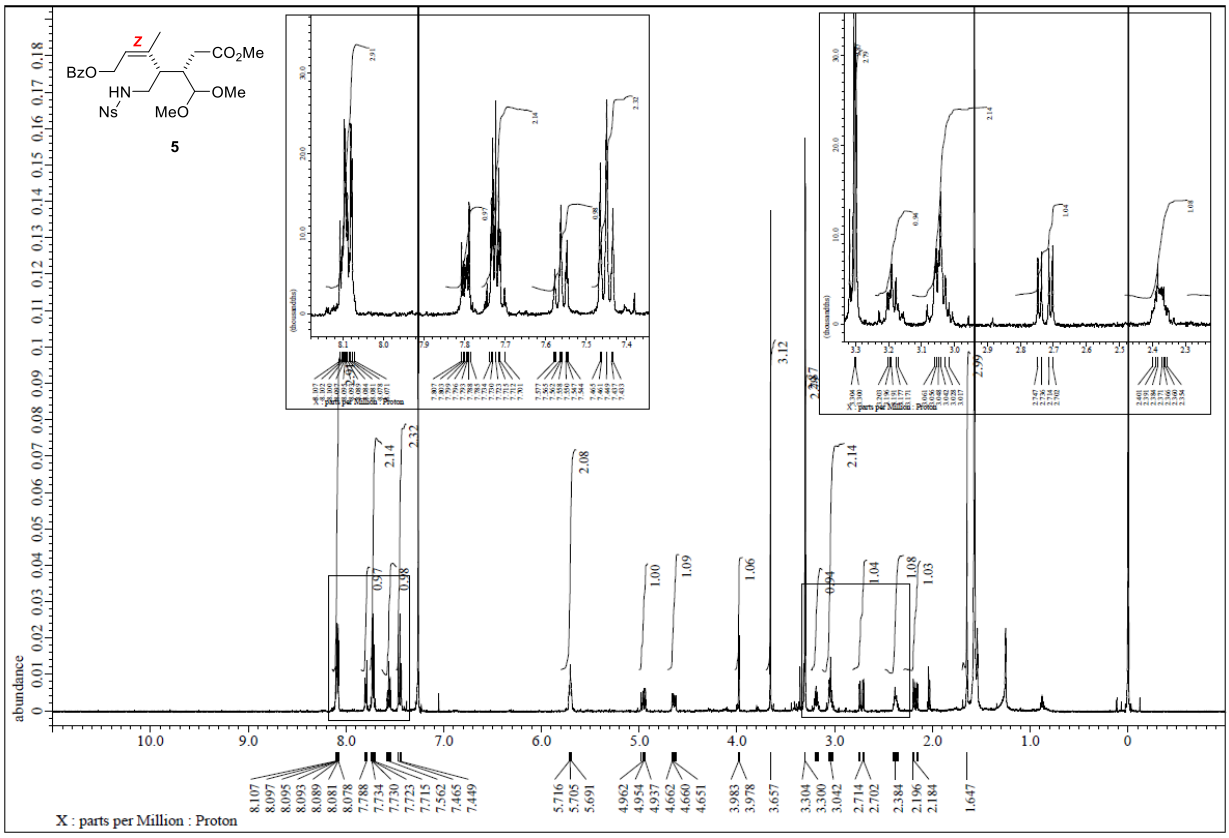
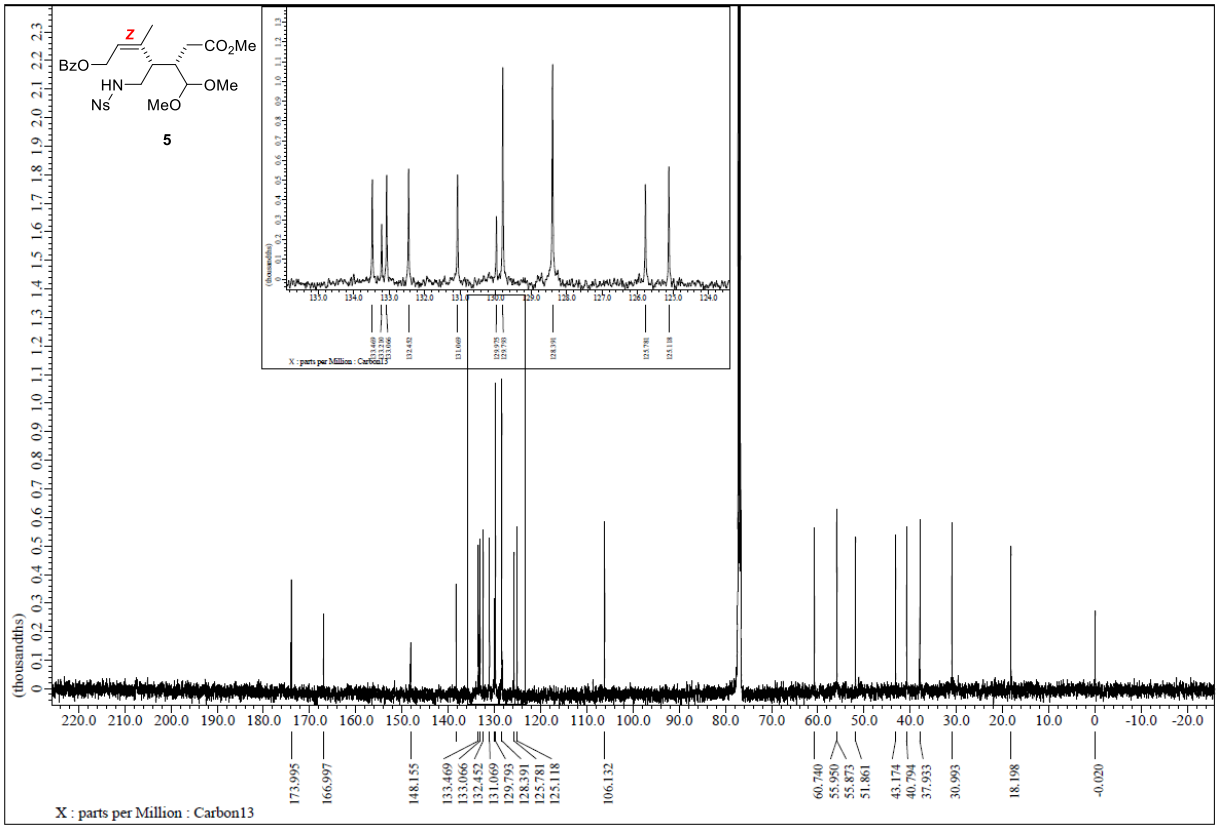


^{13}C{^{1}H} NMR



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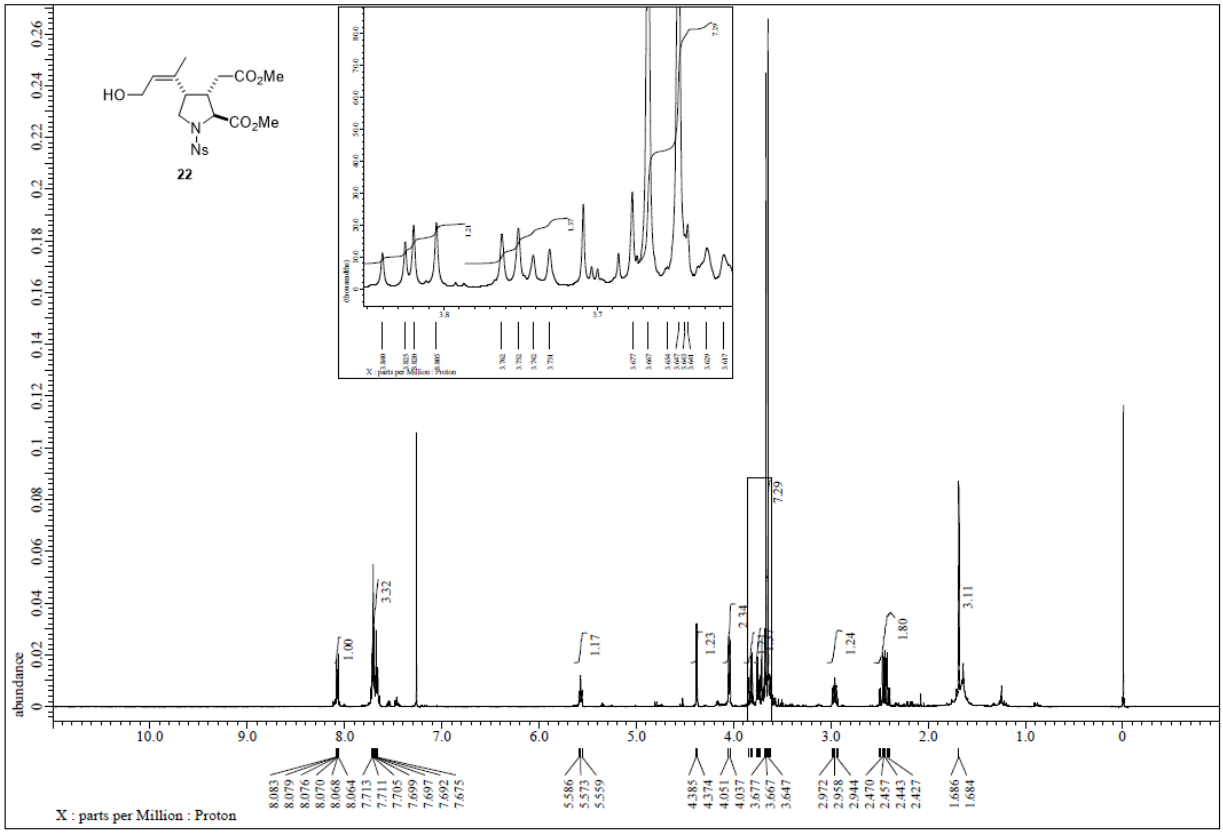

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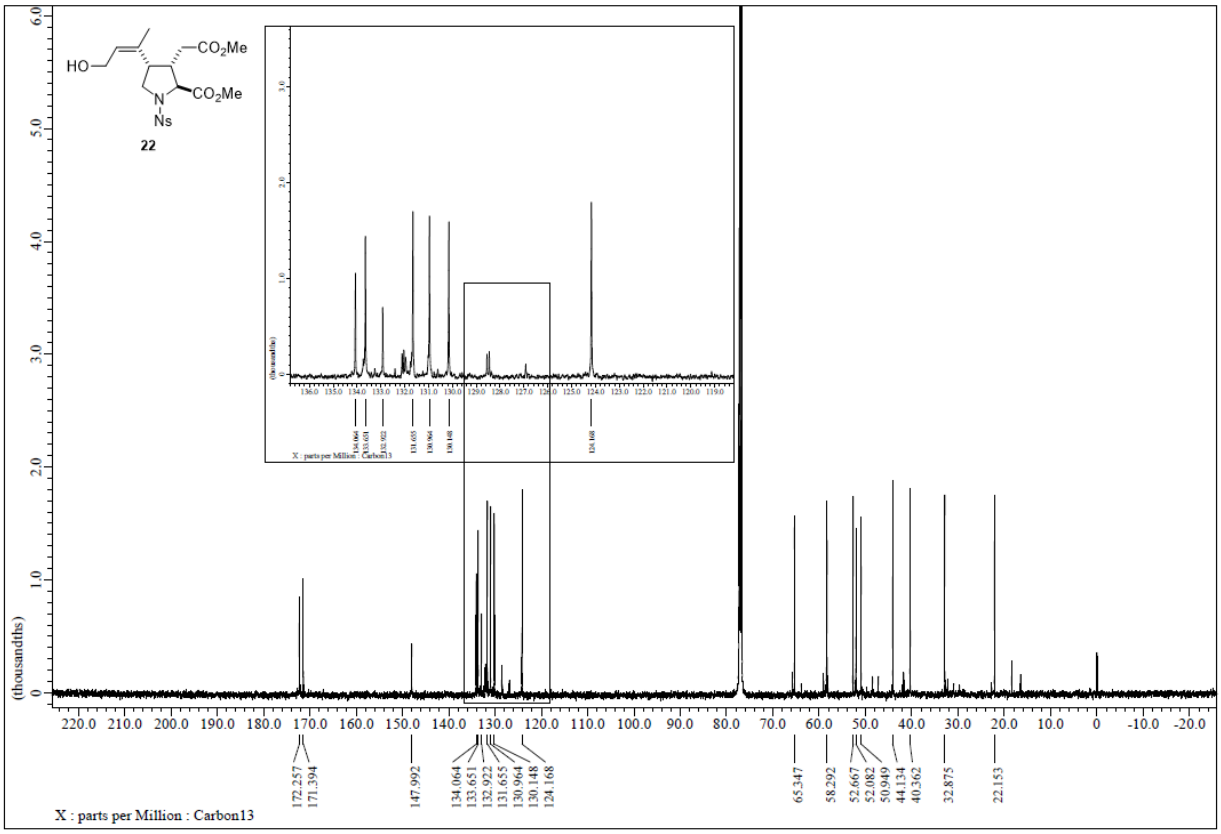
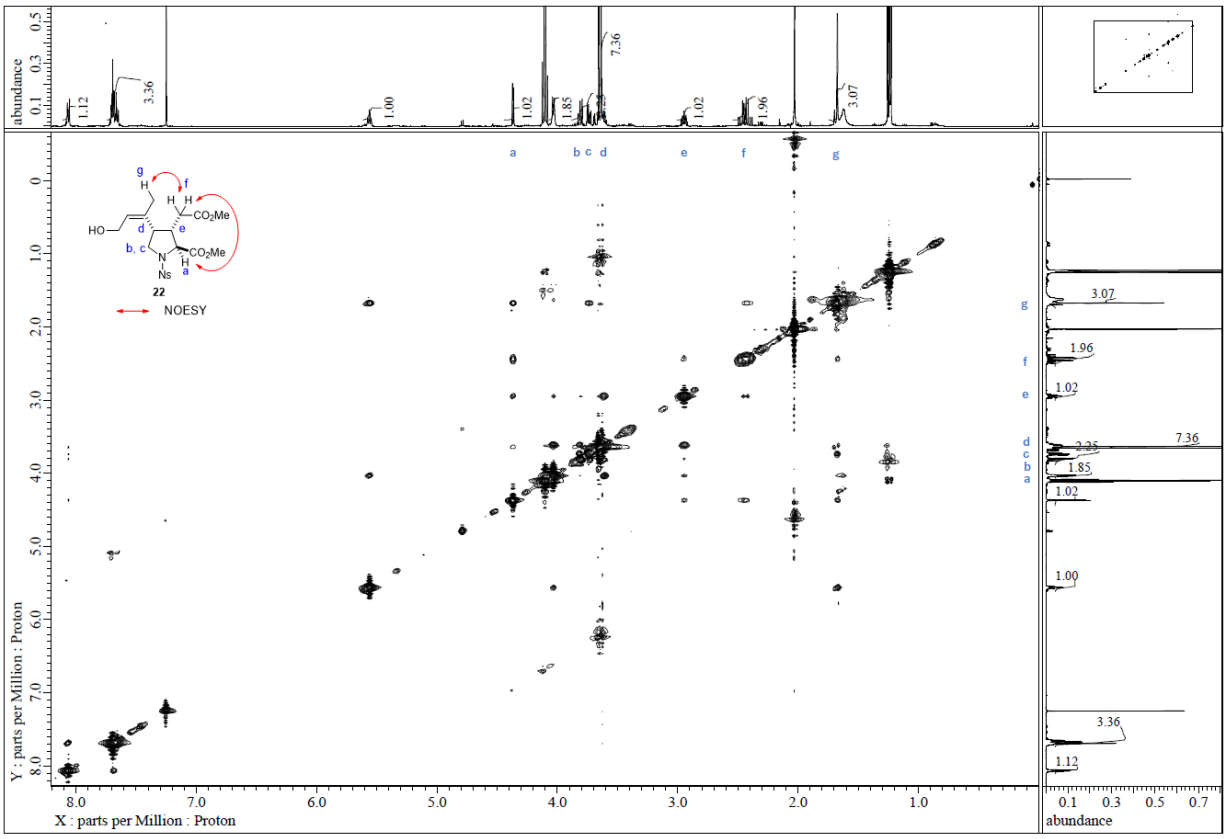
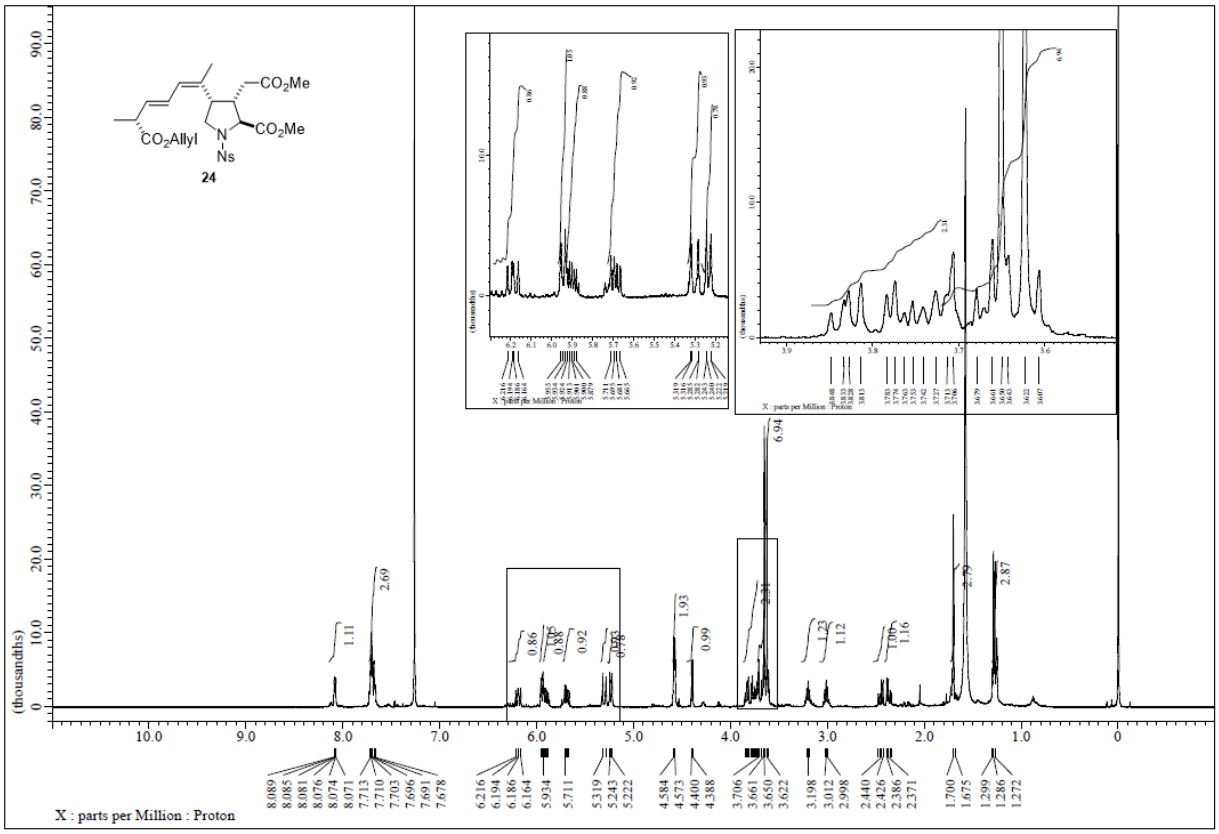


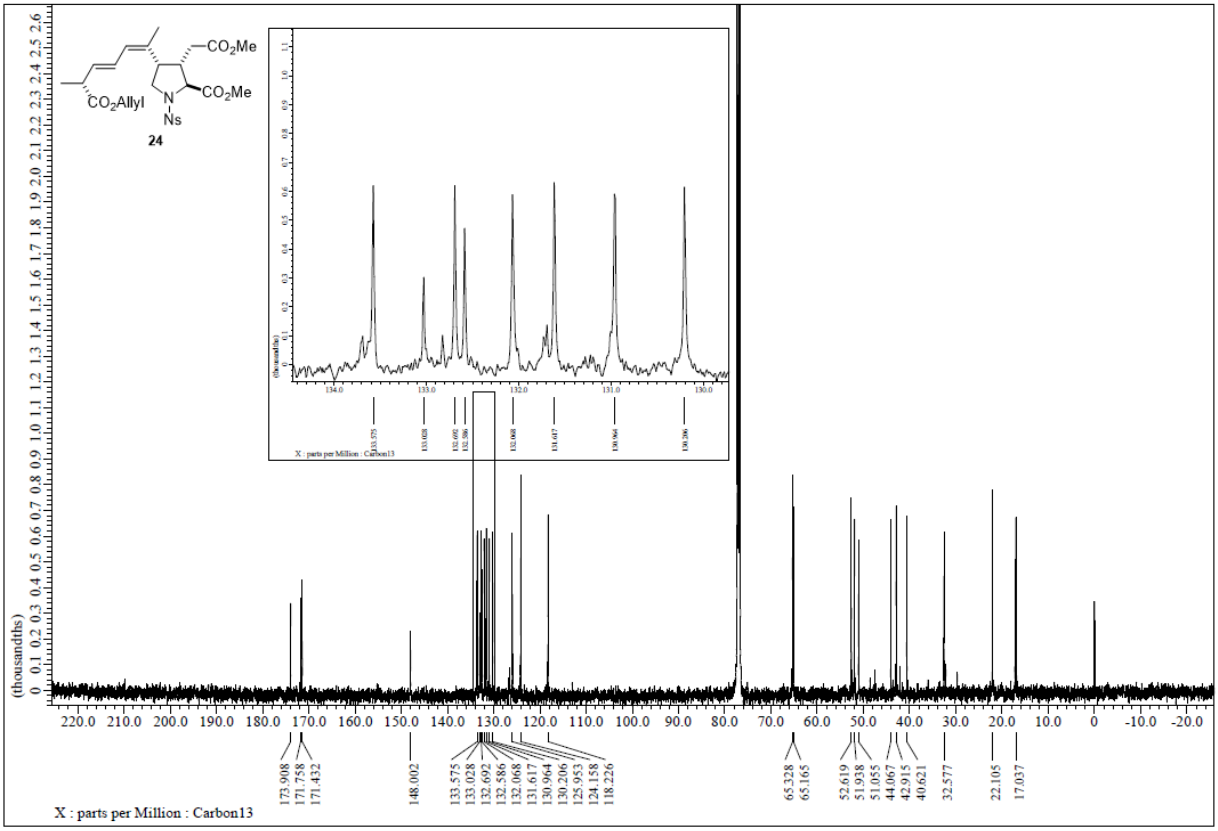
^{1}H-^{1}H NOESY


abundance
1.12
3.36
1.00
1.02
1.85
7.36
1.02
1.96
3.07
a
b c d
e
f
g
HO
CO2Me
CO2Me
Ns
22
NOESY
3.07
1.96
1.02
7.36
2.25
1.85
1.02
1.00
3.36
1.12
Y : parts per Million : Proton
X : parts per Million : Proton
abundance

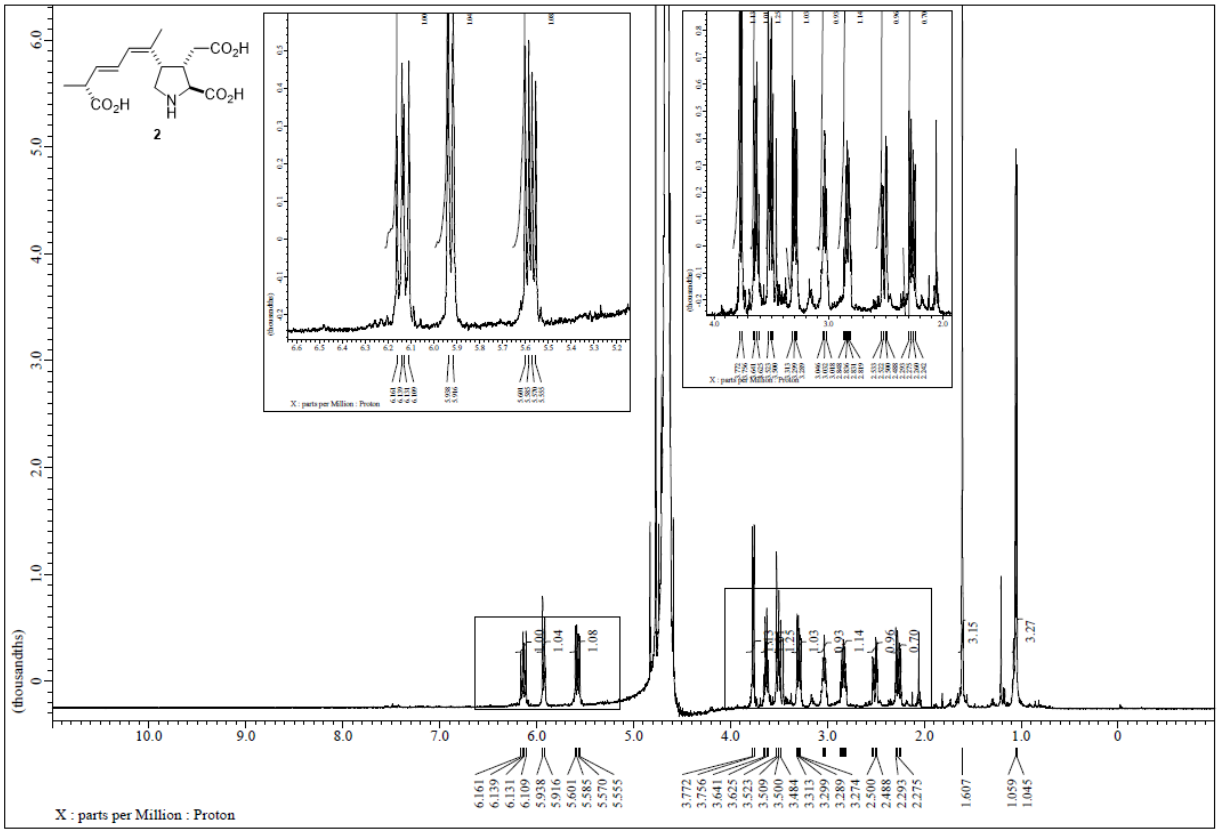
^{1}H NMR



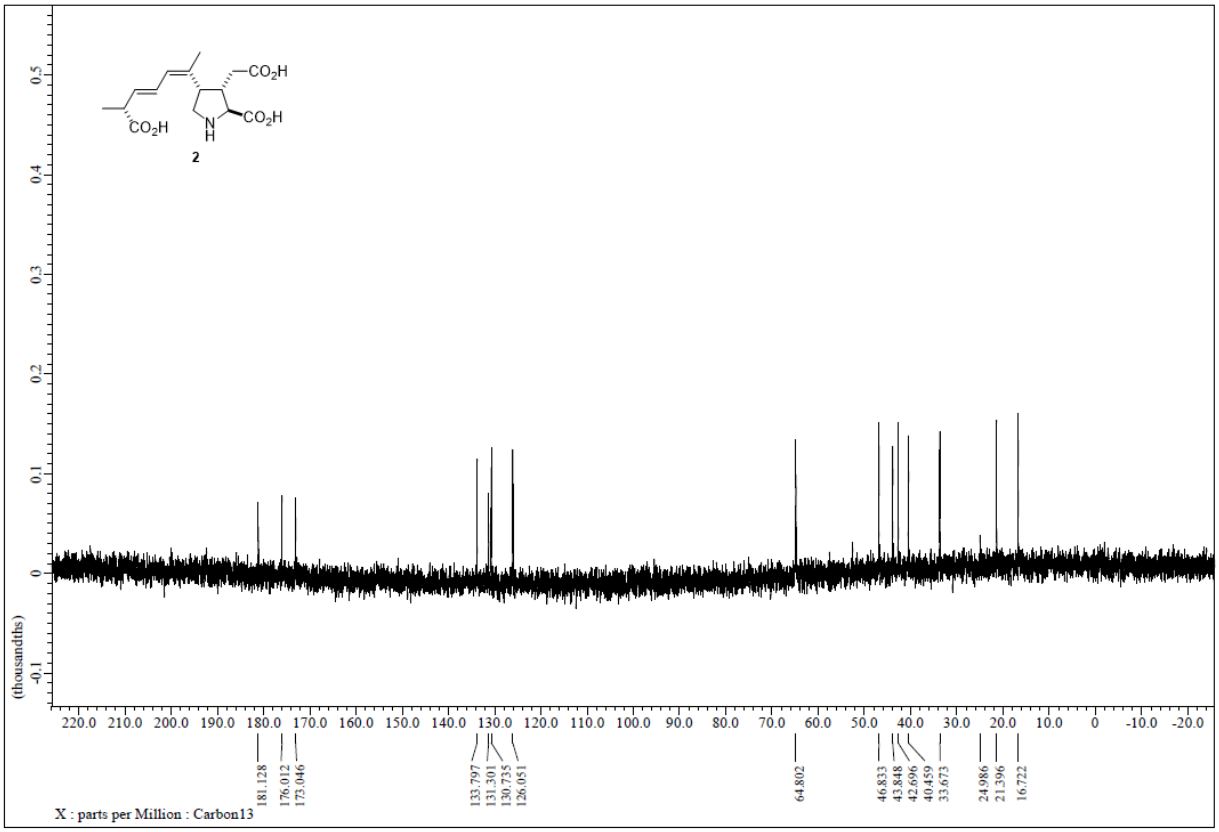
^{13}C{^{1}H} NMR



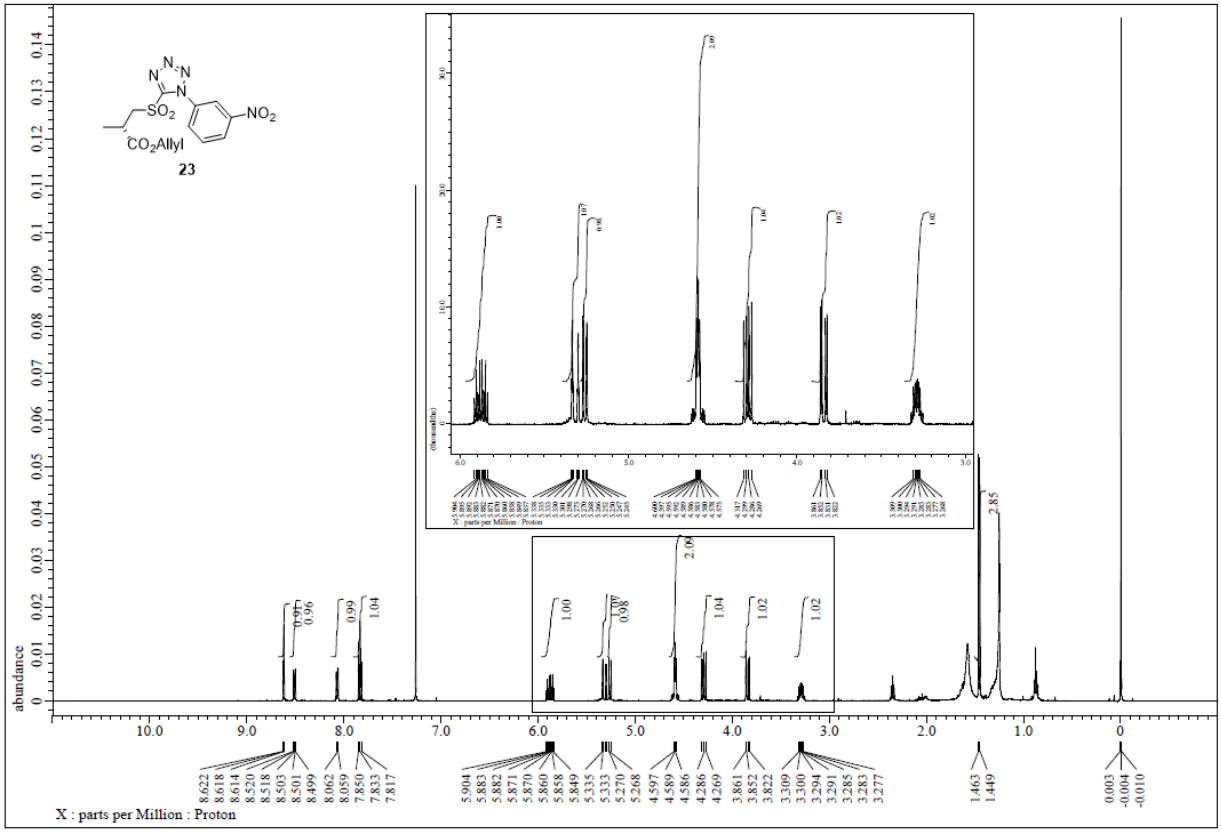
^{1}H NMR



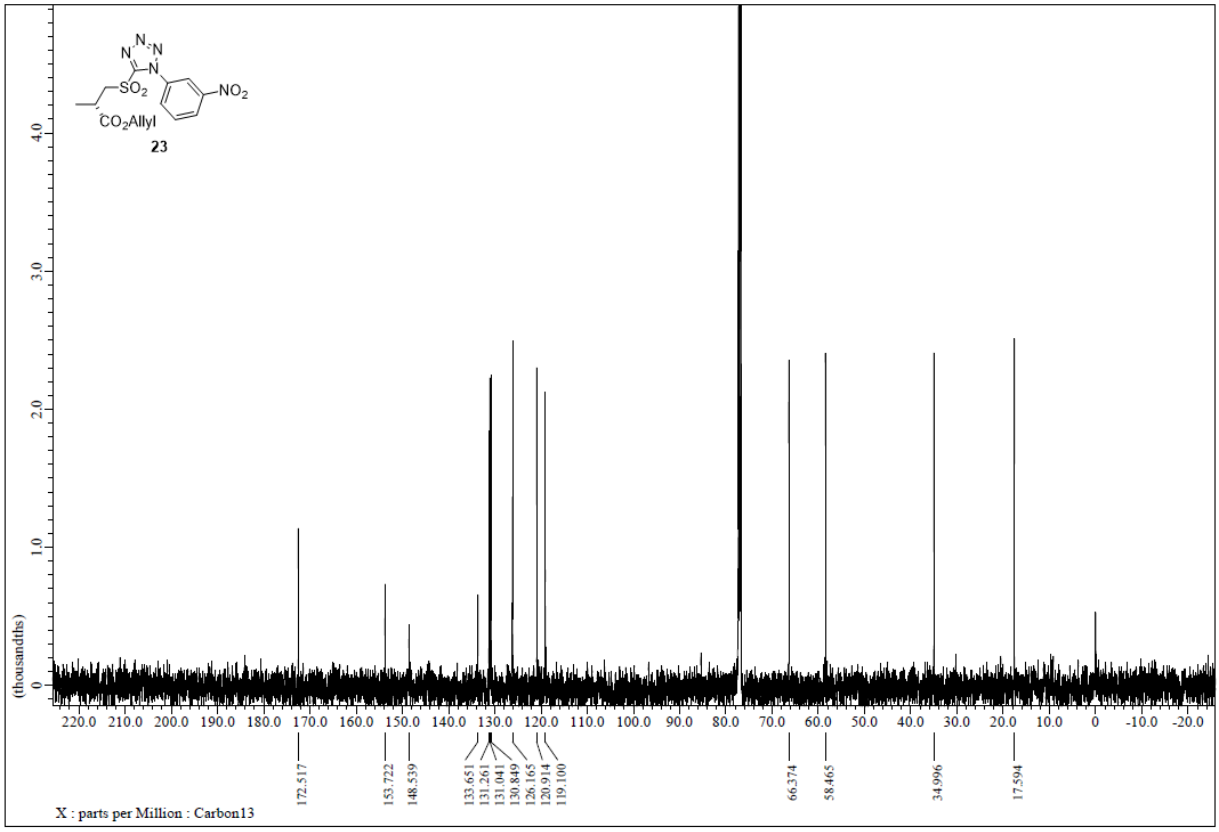
^{13}C{^{1}H} NMR



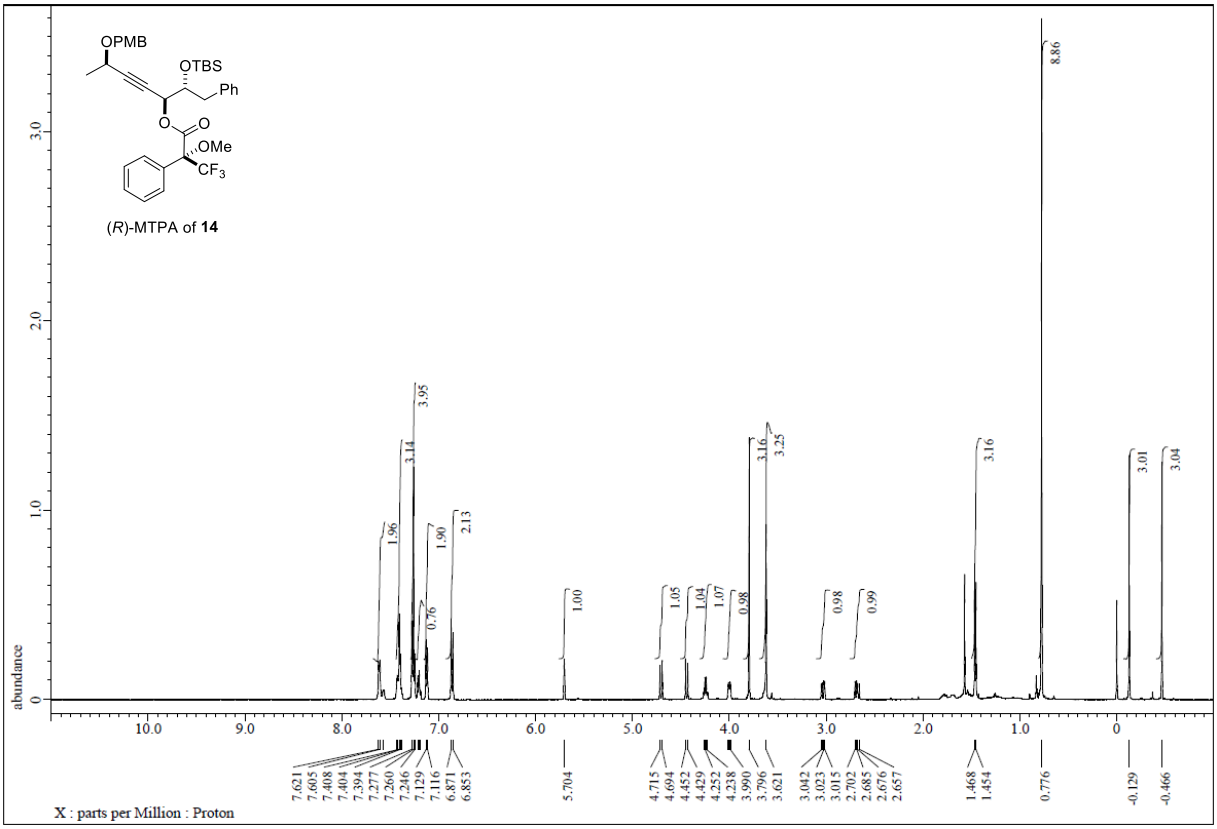
^{1}H NMR



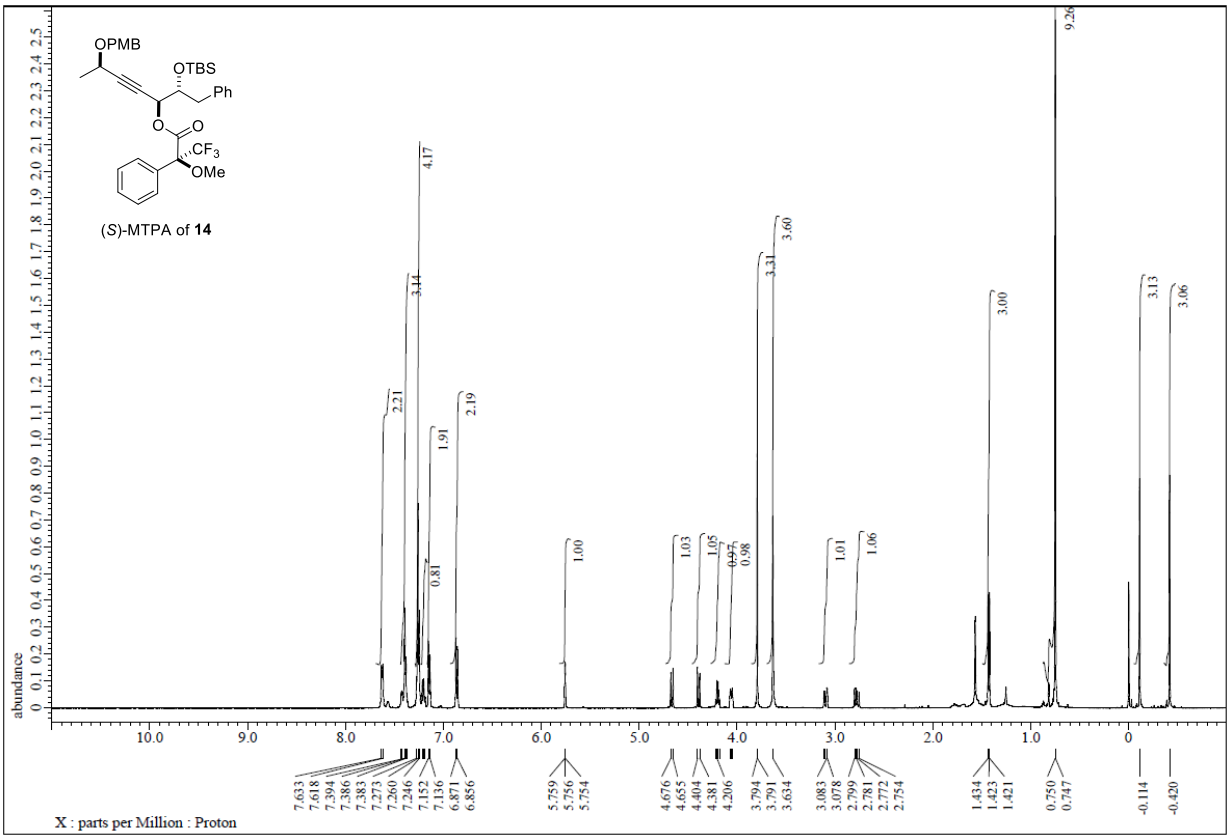
^{13}C{^{1}H} NMR



^{1}H NMR


OPMB
OTBS
Ph
O
O
OMe
CF3
(R)-MTPA of 14
abundance
X : parts per Million : Proton

^{1}H NMR


OPMB
OTBS
Ph
O
O
CF3
OMe
(S)-MTPA of 14
abundance
X : parts per Million : Proton

5. References

S1 (a) J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* 1973, **95**, 512–519. (b) I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc.* 1991, **113**, 4092–4096.

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