Stereoselective Synthesis of the Spirocyclic Core of 13-Desmethyl Spirolide C using an aza-Claisen Rearrangement and an *exo*-selective Diels-Alder Cycloaddition

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Supporting Information

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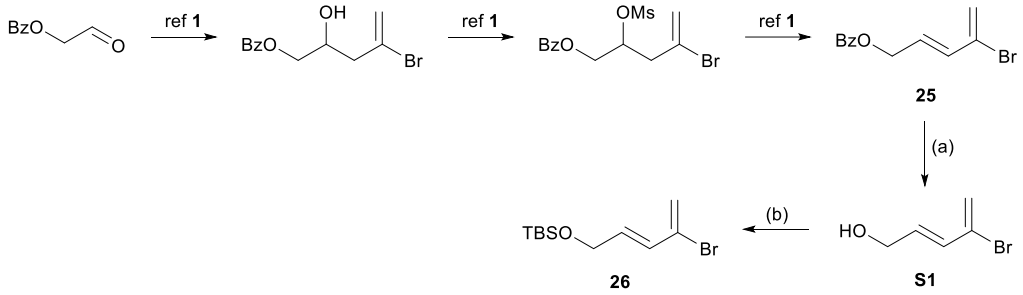
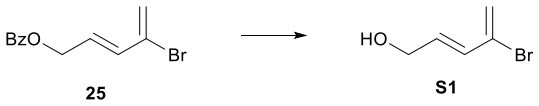
Synthesis of bromodiene 26



Scheme S1. Synthesis of bromodienes **25**[1] and **26**. *Reagents and conditions*: (a) K_2CO_3, MeOH, rt, 30 min, 90%; (b) TBSCl, imidazole, CH_2Cl_2, rt, 5 h, 92%.

Experimental Procedures

Alcohol S1



To a solution of benzoate **25**[1] (1.85 g, 6.93 mmol) in MeOH (50 mL) was added K_2CO_3 (2.87 g, 20.8 mmol) at room temperature and the resulting mixture stirred for 30 min before sat. aq. NH_4Cl (25 mL) was added. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (pet. ether-Et_2O, 4:1) to afford free alcohol **S1** (1.04 g, 90%) as a pale yellow oil.

R_f: 0.26 (pet. ether-Et_2O, 4:1);

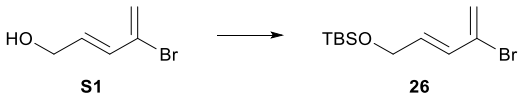
ν_{max}/cm^{-1}**:** 3407, 1718, 1588, 1095, 955;

^{1}H NMR (500 MHz; $CDCl_3$): δ 6.29 (d, *J* = 14.9 Hz, 1H), 6.22 (dt, *J* = 14.8, 4.7 Hz, 1H), 5.82 (s, 1H), 5.64 (s, 1H), 4.32 (d, *J* = 3.3 Hz, 2H), 1.54 (s, 1H);

^{13}C NMR (125 MHz; $CDCl_3$): δ 136.1, 129.4, 128.7, 120.2, 62.4;

HRMS (ESI^+) *m*/*z*: $[M + Na]^+$ calculated for C_5H_7BrNaO: 186.0019; found 186.0015.

Diene 26



To a stirred solution of alcohol **S1** (50 mg, 0.31 mmol) and imidazole (25 mg, 0.37 mmol) in CH_2Cl_2 (2 mL) was added TBSCl (56 mg, 0.37 mmol) at room temperature. The resulting mixture was stirred for 5 h before sat. aq. NH_4Cl (5 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*.

Purification by flash chromatography (pet. ether-Et_2O, 19:1) afforded silyl-protected alcohol **26** (79 mg, 92%) as a colourless oil.

R_f: 0.52 (pet. ether-Et_2O, 19:1);

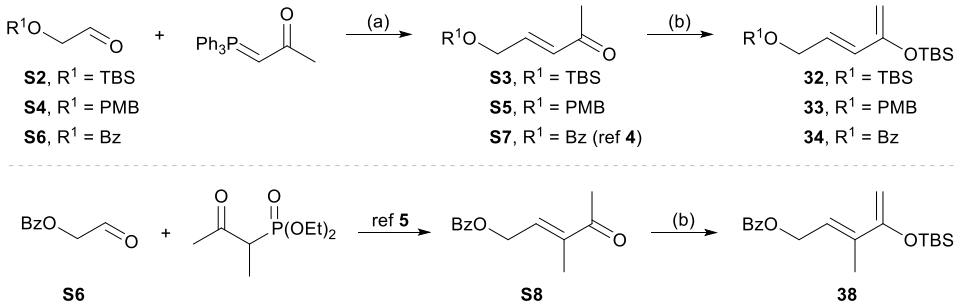
ν_{max}/cm^{-1}: 2956, 2930, 2857, 1258, 1129, 1102, 1011, 834, 802, 775;

^{1}H NMR (500 MHz; $CDCl_3$): δ 6.27 (dt, *J* = 14.7, 1.7 Hz, 1H), 6.15 (dt, *J* = 14.6, 4.2 Hz, 1H), 5.77 (s, 1H), 5.59 (s, 1H), 4.33–4.32 (m, 2H), 0.92 (s, 9H), 0.08 (s, 6H);

^{13}C NMR (125 MHz; $CDCl_3$): δ 136.9, 129.9, 127.4, 119.3, 62.6, 26.1, 18.6, –5.2;

HRMS (ESI$^+$) *m/z*: $[M + Na]^+$ calculated for $C_{11}H_{21}BrNaOSi$: 299.0437; found 299.0435.

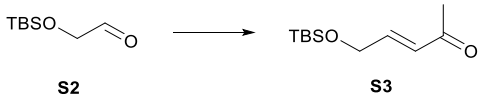
Synthesis of silyl enol ether dienes 32–34 and 38



Scheme S2. Synthesis of silyl enol ether dienes **32**–**34** and **38**. *Reagents and conditions*: (a) THF, rt, 2 h, 66%–71%; (b) TBSOTf, Et_3N, CH_2Cl_2, rt, 1–3 h, 92–98%.

Experimental Procedures

Enone S3



To a stirred solution of aldehyde **S2**[2] (1.00 g, 5.74 mmol) in THF (57 mL) at room temperature was added 1-(triphenylphosphoranylidene)-2-propanone (1.92 g, 6.02 mmol) and the reaction stirred for 2 h. The reaction mixture was then concentrated *in vacuo* and the crude residue was purified by flash chromatography (pet. ether-EtOAc 4:1) to afford the enone product (**S3**, 0.99 g, 71%) as a colourless oil.

R_f = 0.64 (pet. ether-EtOAc, 7:3);

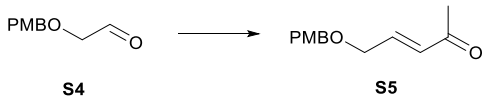
ν_{max}/cm^{-1}: 2955, 2930, 2886, 2857, 1679, 1360, 1252, 1135, 836;

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 6.82 (dt, *J* = 15.6, 3.6 Hz, 1H), 6.34 (dt, *J* = 15.9, 2.1 Hz, 1H), 4.36 (dd, *J* = 3.6, 2.2 Hz, 2H), 2.27 (s, 3H), 0.92 (s, 9H), 0.08 (s, 6H);

^{13}C NMR (100 MHz, $CDCl_3$): *δ* 198.6, 146.4, 128.9, 62.3, 27.5, 26.0, 18.5, −5.3.

HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{11}H_{22}NaO_2Si$, 237.1281; found, 237.1286.

Enone S5



S4 **S5**

To a stirred solution of aldehyde **S4**[3] (0.500 g, 2.77 mmol) in THF (27.7 mL) at room temperature was added 1-(triphenylphosphoranylidene)-2-propanone (0.928 g, 2.91 mmol) and the reaction stirred for 2 h. The reaction mixture was then concentrated *in vacuo* and the residue was purified by flash chromatography (pet. ether-EtOAc 4:1) to afford the enone product (**S5**, 0.404 g, 66 %) as a colourless oil.

R_f = 0.45 (pet. ether-EtOAc, 4:1);

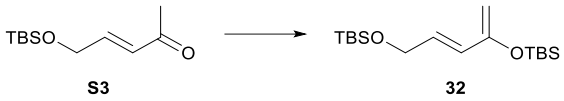
ν_{max}/cm^{-1}: 2937, 2912, 2838, 1674, 1611, 1513, 1247, 1032;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.25 (m, 2H), 6.90–6.88 (m, 2H), 6.79 (dt, J = 16.0, 4.5 Hz, 1H), 6.33 (dt, J = 16.0, 1.9 Hz, 1H), 4.50 (s, 2H), 4.17 (dd, J = 4.5, 1.9 Hz, 2H), 3.81 (s, 3H), 2.26 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 159.5, 143.3, 130.5, 129.8, 129.5, 114.0, 72.8, 68.7, 55.4, 27.4;

HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{13}H_{16}NaO_3$, 243.0992 ; found, 243.0986.

Diene 32



S3 **32**

To a stirred solution of enone **S3** (0.200 g, 0.933 mmol) in CH_2Cl_2 (9 mL) at 0 °C, was added Et_3N (0.2 mL, 1.5 mmol) and TBSOTf (0.3 mL, 1.5 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 1.5 h before water (9 mL) was added, the layers were separated, and the aqueous layer extracted with CH_2Cl_2 (2 × 9 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (pet. ether-Et_2O 19:1, 1% Et_3N) afforded the silyl enol ether product (**32**, 0.285 g, 96%) as a colourless oil.

R_f = 0.88 (pet. ether-EtOAc, 7:3);

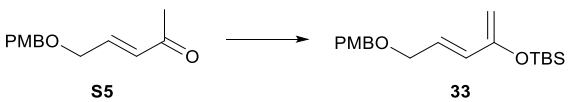
ν_{max}/cm^{-1}: 2956, 2930, 2887, 2858, 1593, 1472, 1463, 1313, 1253, 1131, 1074, 1023, 963, 834, 811, 777;

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.11–6.01 (m, 2H), 4.28 (s, 2H), 4.26 (d, J = 3.6 Hz, 2H), 0.97 (s, 9H), 0.91 (s, 9H), 0.18 (s, 6H), 0.07 (s, 6H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.0, 130.1, 127.4, 95.3, 63.2, 26.1, 26.0, 18.5, 18.4, −4.5, −5.1;

HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{17}H_{36}NaO_2Si_2$, 351.2146; found, 351.2140.

Diene 33



S5 **33**

To a stirred solution of enone **S5** (0.200 g, 0.908 mmol) in CH_2Cl_2 (9 mL) at 0 °C, was added Et_3N (0.2 mL, 1.5 mmol) and TBSOTf (0.3 mL, 1.5 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 2.5 h before water (9 mL) was added, the layers were separated, and the aqueous layer extracted with CH_2Cl_2 (2 × 9 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*.

Purification by flash chromatography (pet. ether-Et_2O 19:1, 1% Et_3N) afforded the silyl enol ether product (**33**, 0.280 g, 92%) as a colourless oil.

R_f = 0.39 (pet. ether-EtOAc, 19:1);

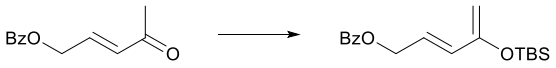
ν_{max}/cm^{-1}: 2959, 2931, 2857, 1679, 1612, 1513, 1248, 1025, 826;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.26 (m, 2H), 6.89–6.87 (m, 2H), 6.14–6.04 (m, 2H), 4.46 (s, 2H), 4.31 (d, J = 2.6 Hz, 2H), 4.07 (d, J = 4.5 Hz, 2H), 3.81 (s, 3H), 0.97 (s, 9H), 0.19 (s, 6H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 154.7, 130.5, 130.2, 129.5, 127.1, 113.9, 95.9, 71.9, 69.8, 55.4, 26.0, 18.4, −4.5;

HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{19}H_{30}NaO_3Si$, 357.1856; found, 357.1848.

Diene 34



S7 **34**

To a stirred solution of enone **S7**[4] (0.500 g, 2.45 mmol) in CH_2Cl_2 (25 mL) at 0 °C, was added Et_3N (0.55 mL, 3.9 mmol) and TBSOTf (0.9 mL, 3.9 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 1.5 h before water (12 mL) was added, the layers were separated, and the aqueous layer extracted with CH_2Cl_2 (2 × 12 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (pet. ether-Et_2O 19:1, 1% Et_3N) afforded the silyl enol ether product (**34**, 0.796 g, 98%) as a colourless oil.

R_f = 0.53 (pet. ether-EtOAc, 19:1);

ν_{max}/cm^{-1}: 2956, 2931, 2886, 2858, 1721, 1314, 1266, 1109, 1025, 826, 710;

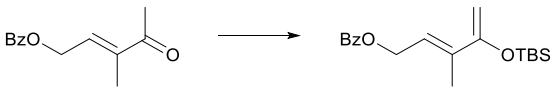
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08–8.05 (m, 2H), 7.58–7.54 (m, 1H), 7.47–7.43 (m, 2H), 6.24–6.12 (m, 2H), 4.89 (d, J = 5.4 Hz, 2H), 4.37 (d, J = 1.5 Hz, 2H), 0.98 (s, 9H), 0.19 (s, 6H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 154.3, 133.1, 131.7, 130.4, 129.8, 128.5, 124.1, 96.9, 64.7, 26.0, 18.4, −2.8, −4.5;

HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{18}H_{26}NaO_3Si$, 341.1543; found, 341.1540.

The analytical data were in agreement with those reported in the literature.[4]

Diene 38



S8 **38**

To a stirred solution of enone **S8**[5] (0.100 g, 0.458 mmol) in CH_2Cl_2 (5 mL) at 0 °C, was added Et_3N (0.10 mL, 0.73 mmol) and TBSOTf (0.17 mL, 0.73 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 2 h before water (2.5 mL) was added, the layers were separated, and the aqueous layer extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (pet. ether-Et_2O 19:1, 1% Et_3N) afforded the silyl enol ether product (**38**, 0.148 g, 97 %) as a colourless oil.

R_f = 0.79 (pet. ether-EtOAc, 19:1);

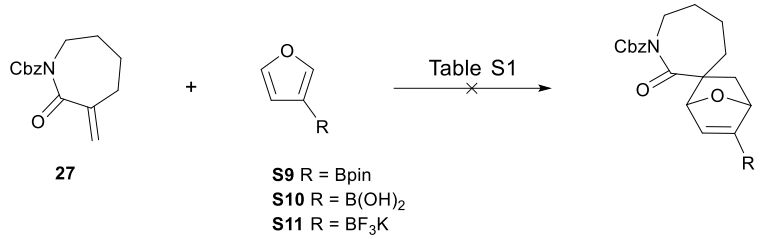
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06–8.03 (m, 2H), 7.55 (tt, J = 7.6, 2.0 Hz, 1H), 7.46–7.42 (m, 2H), 6.26–6.23 (m, 1H), 4.97 (d, J = 7.0 Hz, 2H), 4.56 (d, J = 1.4 Hz, 1H), 4.38 (s, 1H), 1.89 (s, 3H), 0.97 (s, 9H), 0.18 (s, 6H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 156.5, 135.8, 132.9, 130.4, 129.6, 128.3, 121.4, 93.2, 62.0, 25.9, 18.3, 13.6, −4.7.

The analytical data were in agreement with those reported in the literature.[5]

Reactions of lactams 27 and 28 with boron-substituted furans S9–S11

All of the following reaction conditions returned only unreacted starting materials, except for Table S1, entry 5, wherein partial alcoholysis of **S9** was observed.

Table S1. Diels-Alder cycloaddition of *N*-Cbz lactam **27** with 2-boron-substituted furans **S9**–**S11**.

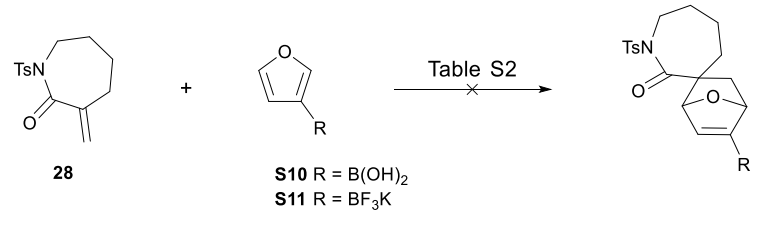


27

S9 R = Bpin
S10 R = $B(OH)_2$
S11 R = BF_3K

Entry	R	Conditions
1	Bpin	toluene/acetonitrile (2:1), 80 °C, 18 h
2		$Mg(OTf)_2$, toluene/acetonitrile (2:1), 80 °C, 18 h
3		p-xylene, 165 °C, 18 h
4		$Mg(OTf)_2$, p-xylene, 165 °C, 18 h
5		ethanol, 100 °C, 54 h
6		toluene/acetonitrile (2:1), 50 °C, 72 h
7	$B(OH)_2$	toluene/acetonitrile (2:1), 80 °C, 18 h
8	BF_3K	acetonitrile, rt, 18 h
9		acetonitrile, 80 °C, 18 h

Table S2. Diels-Alder cycloaddition of *N*-Ts lactam **28** with 2-boron-substituted furans **S10** and **S11**.



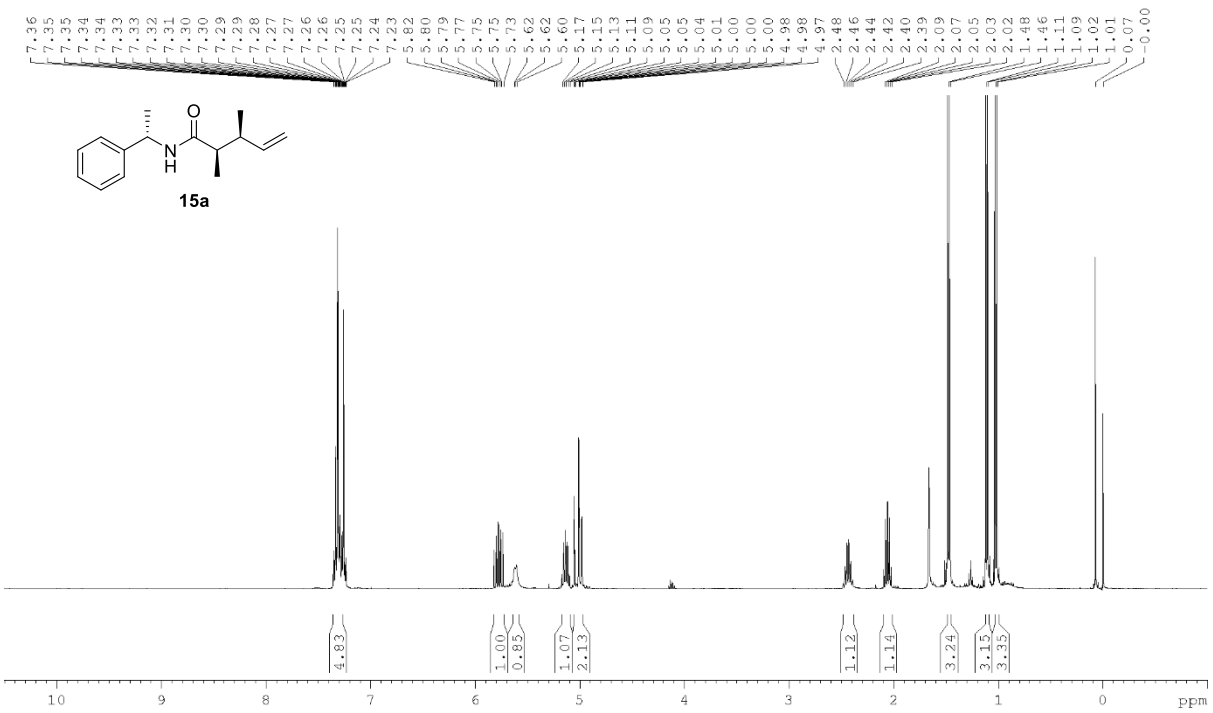
28

S10 R = $B(OH)_2$
S11 R = BF_3K

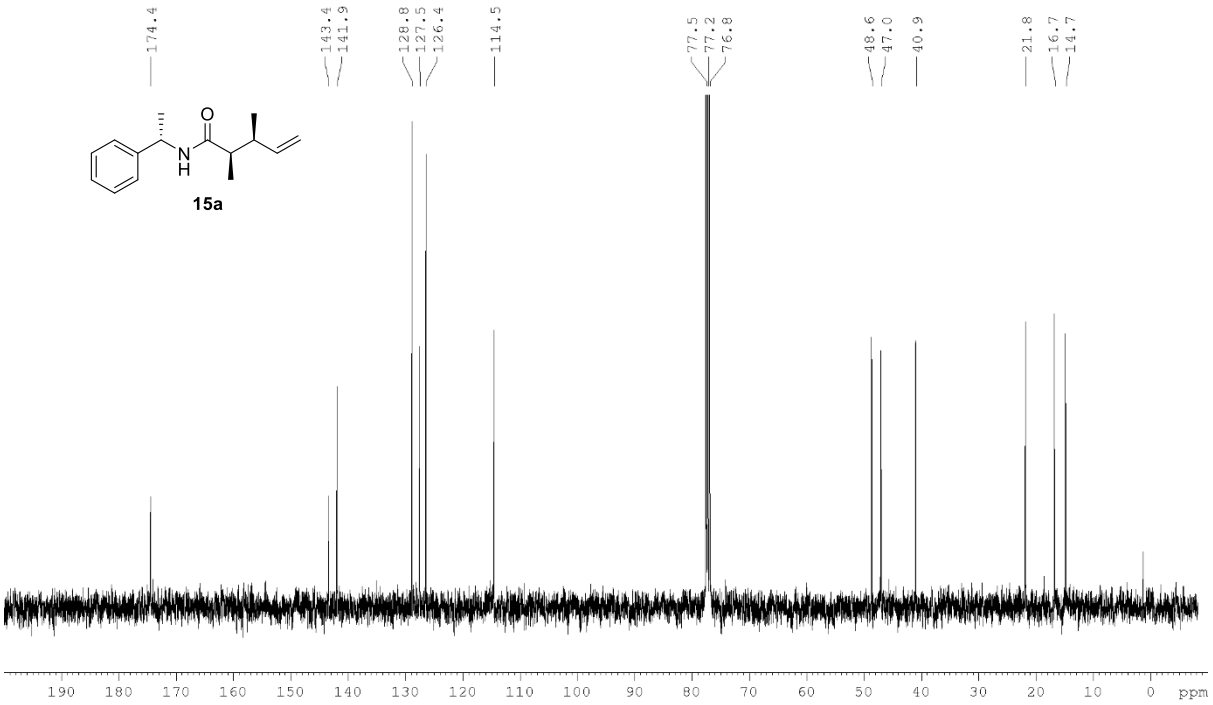
Entry	R	Conditions
1	$B(OH)_2$	Toluene/acetonitrile (2:1), 80 °C, 18 h
2	BF_3K	acetonitrile, rt, 18 h
3		acetonitrile, 80 °C, 18 h

Amide 15a

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

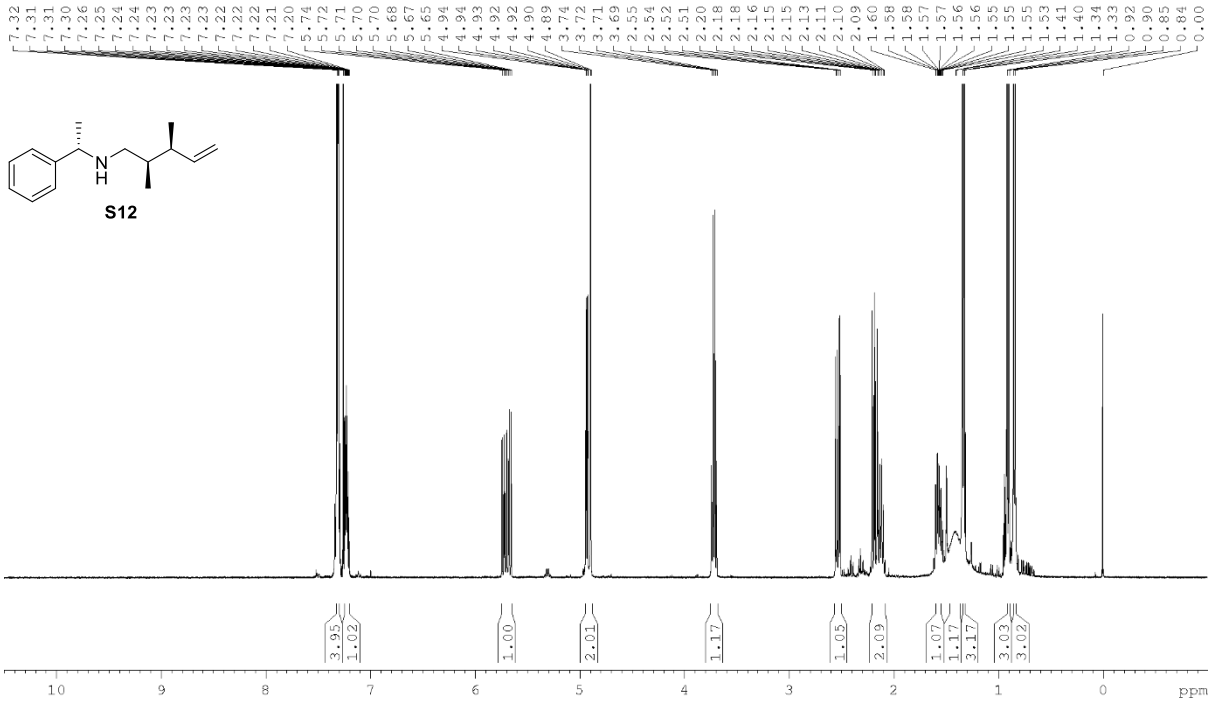


^{13}C NMR (100 MHz, $CDCl_3$)

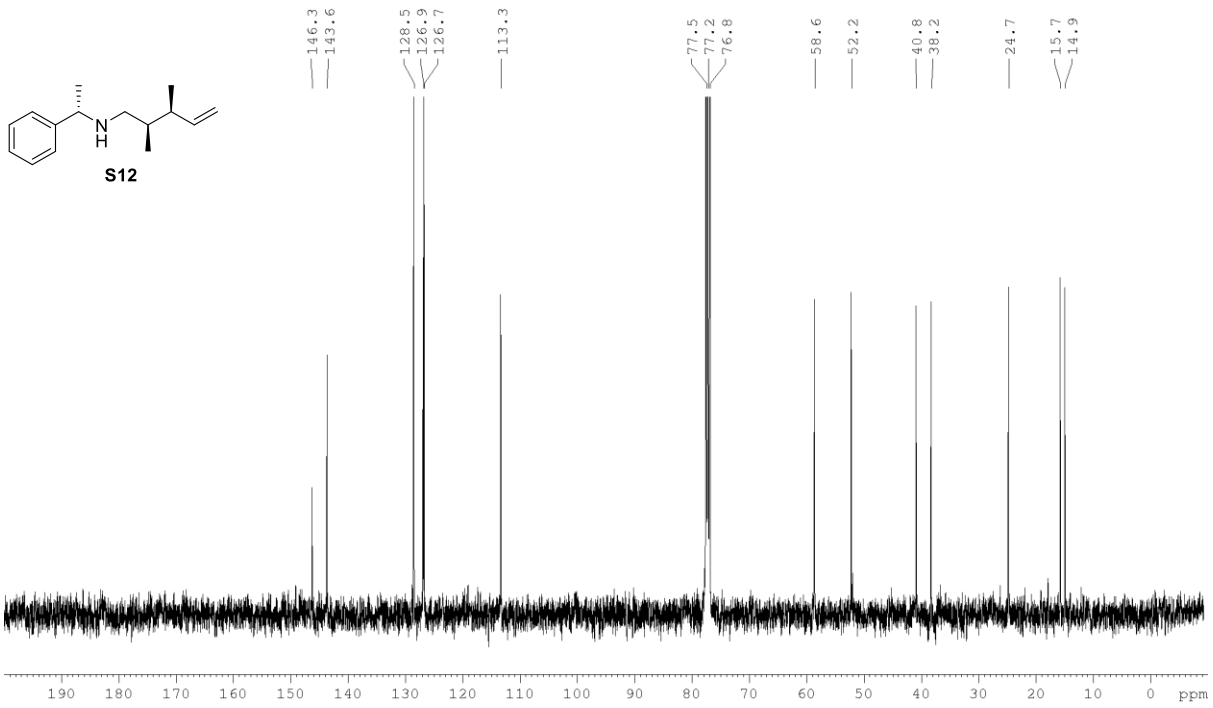


Amine S12

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

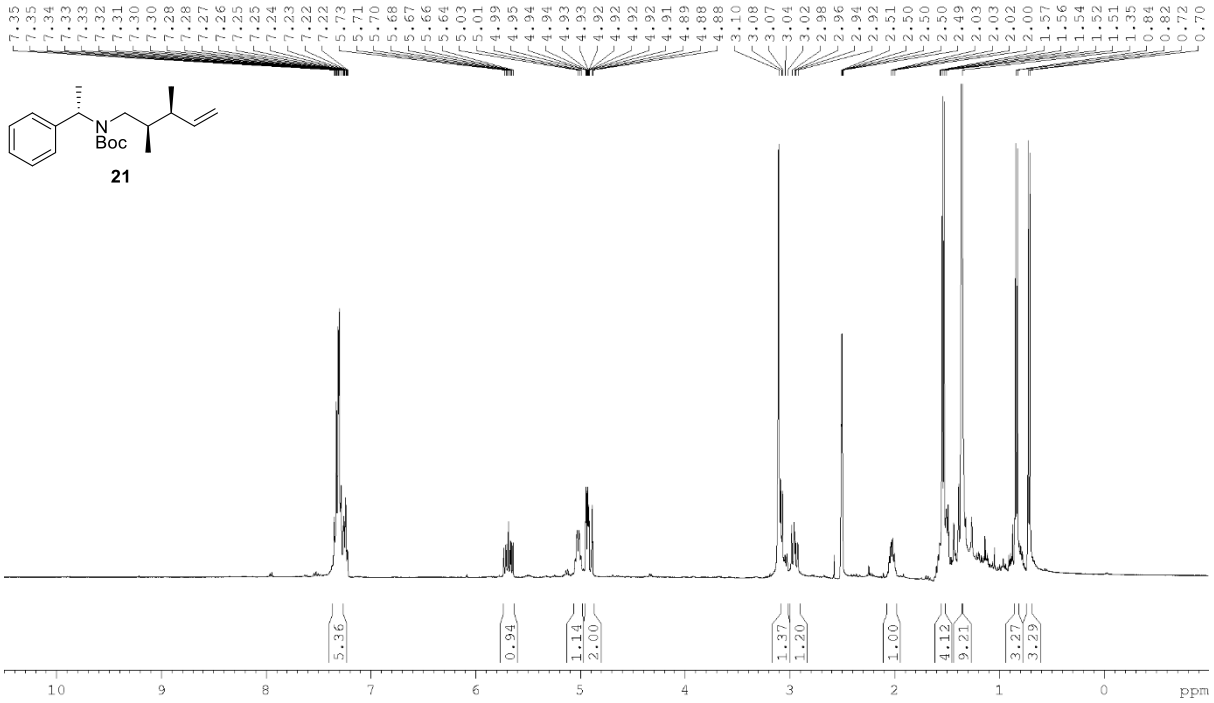


^{13}C NMR (100 MHz, $CDCl_3$)

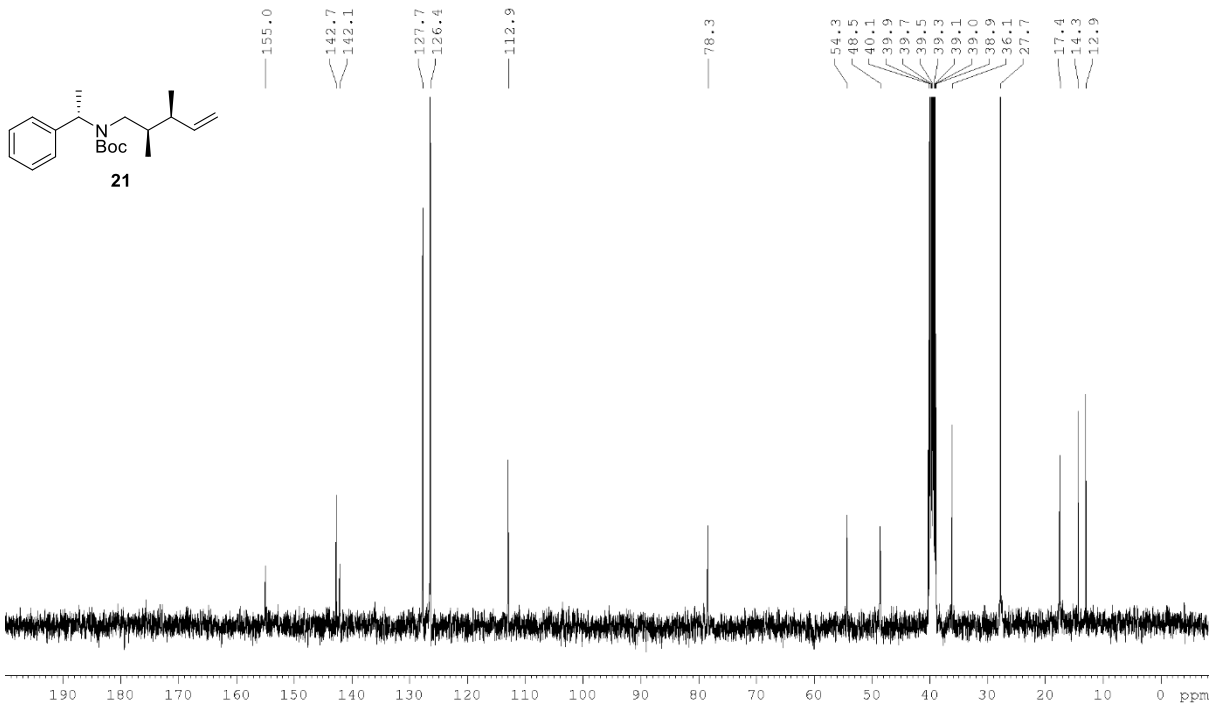


***N*-Boc-amine 21**

^{1}H NMR (400 MHz, DMSO-d_6, 340 K)

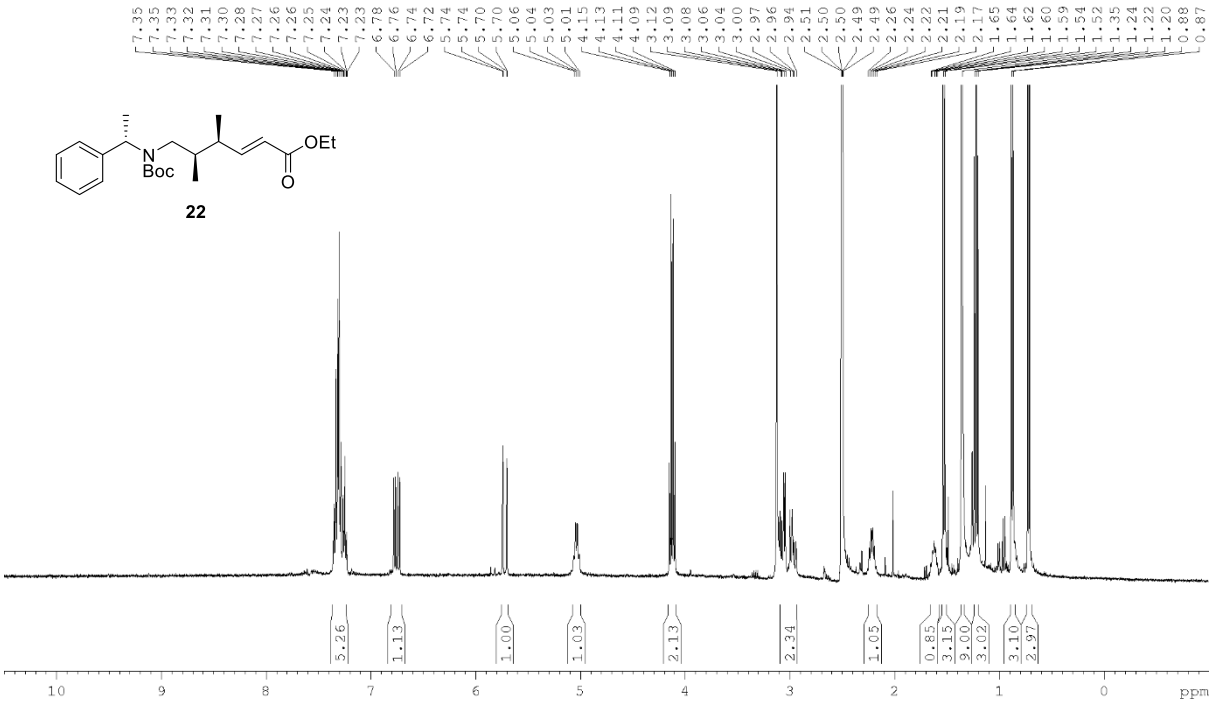


^{13}C NMR (100 MHz, DMSO-d_6, 340 K)

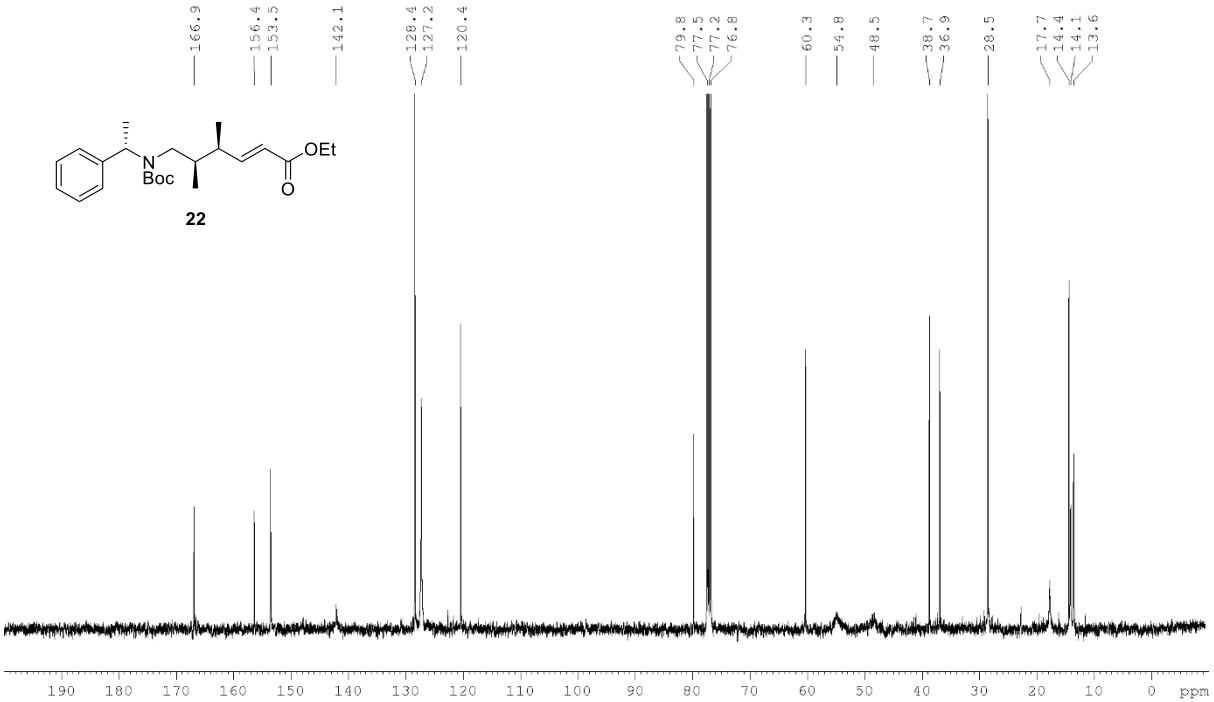


α,β-Unsaturated ester 22

^{1}H NMR (400 MHz, DMSO-d_6, 340 K)



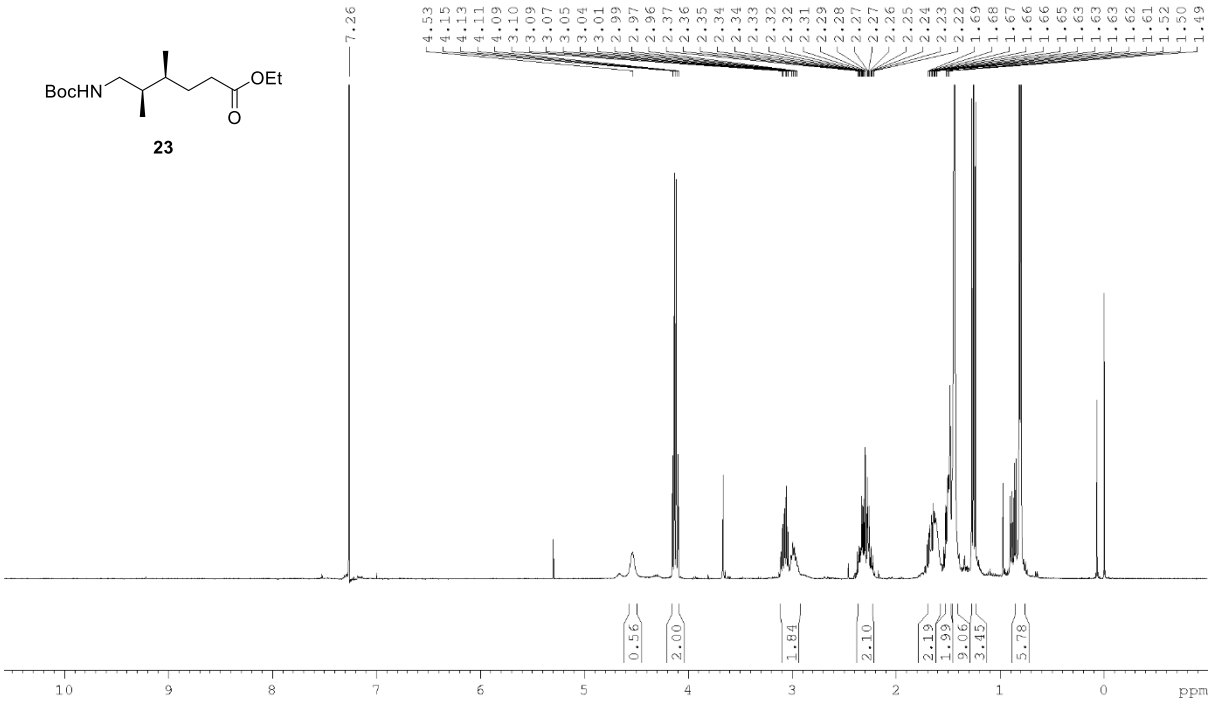
^{13}C NMR (100 MHz, $CDCl_3$, 300K)



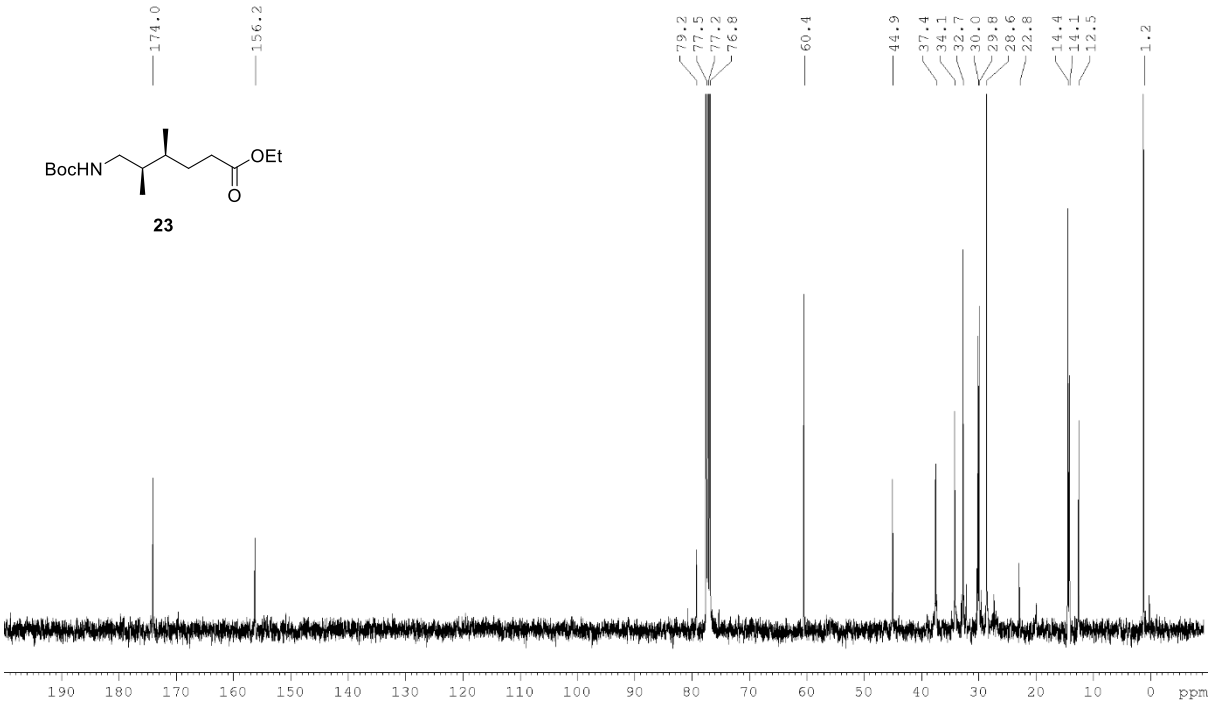
Significant signal broadening was observed in the ^{13}C NMR spectrum due to the presence of rotamers. Attempts to obtain a clear ^{13}C NMR at 340K were not successful, as degradation of α,β-unsaturated ester **22** occurred during the experiment before resolution of rotamers.

_N_-Boc-aminoester 23

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

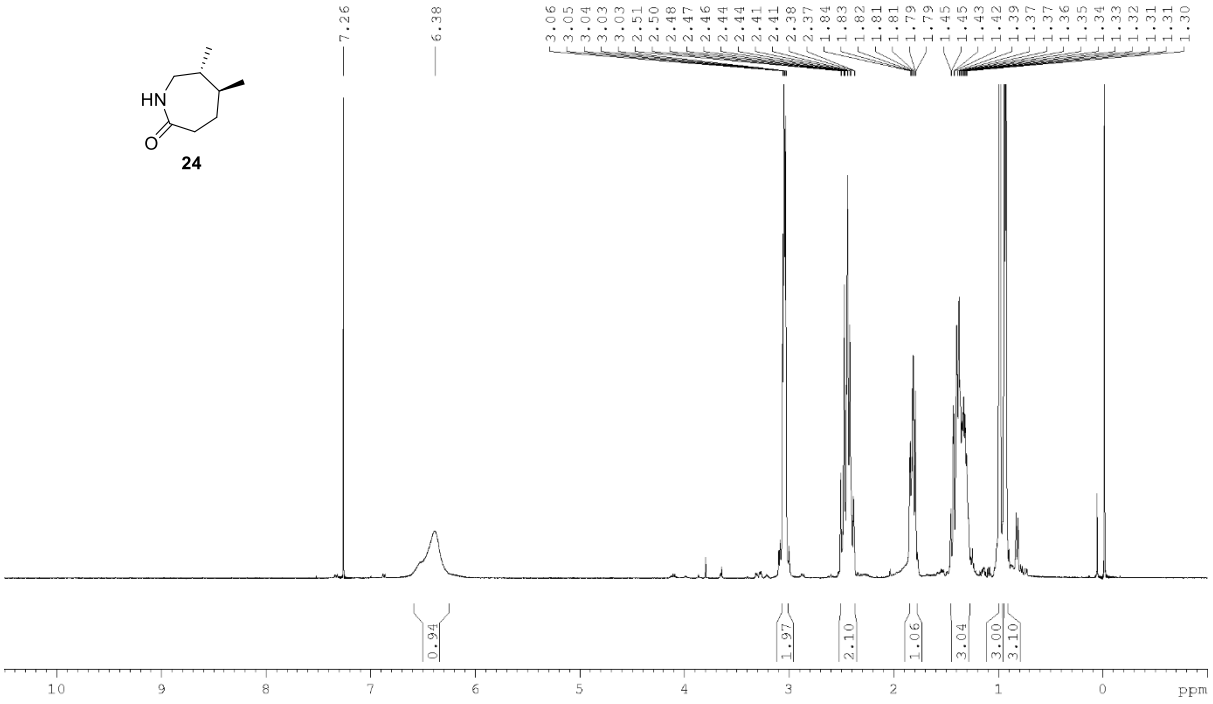


^{13}C NMR (100 MHz, $CDCl_3$)

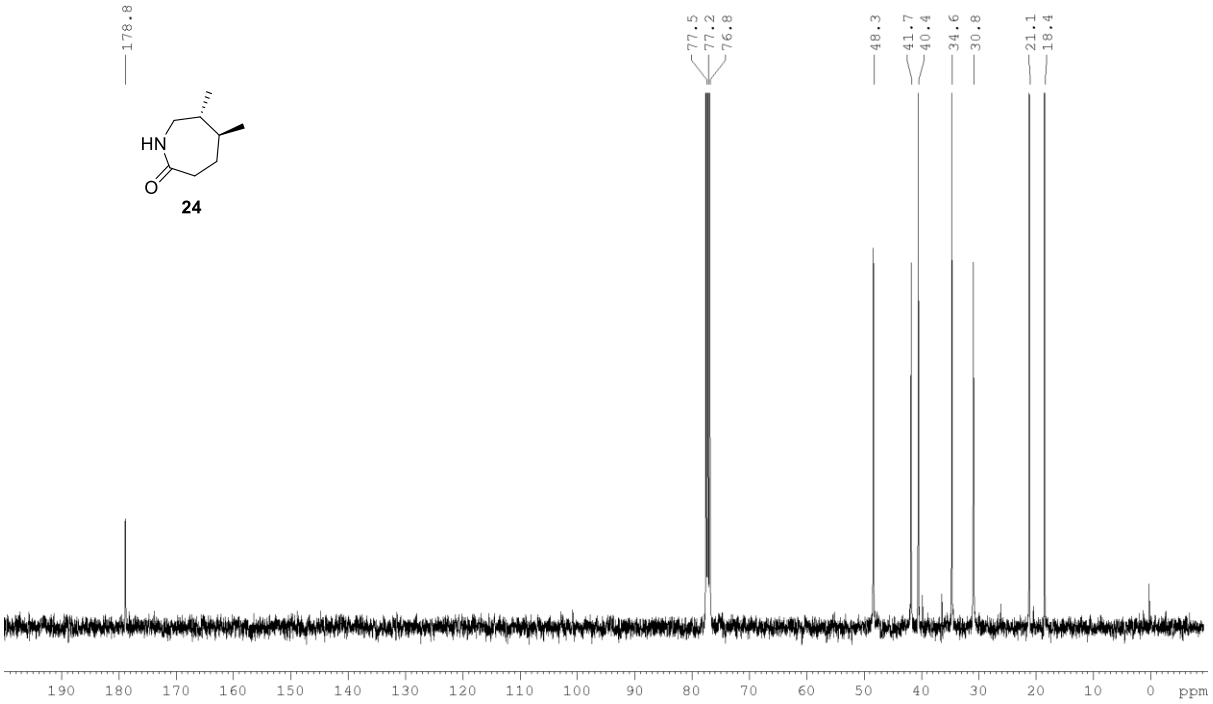


Lactam 24

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

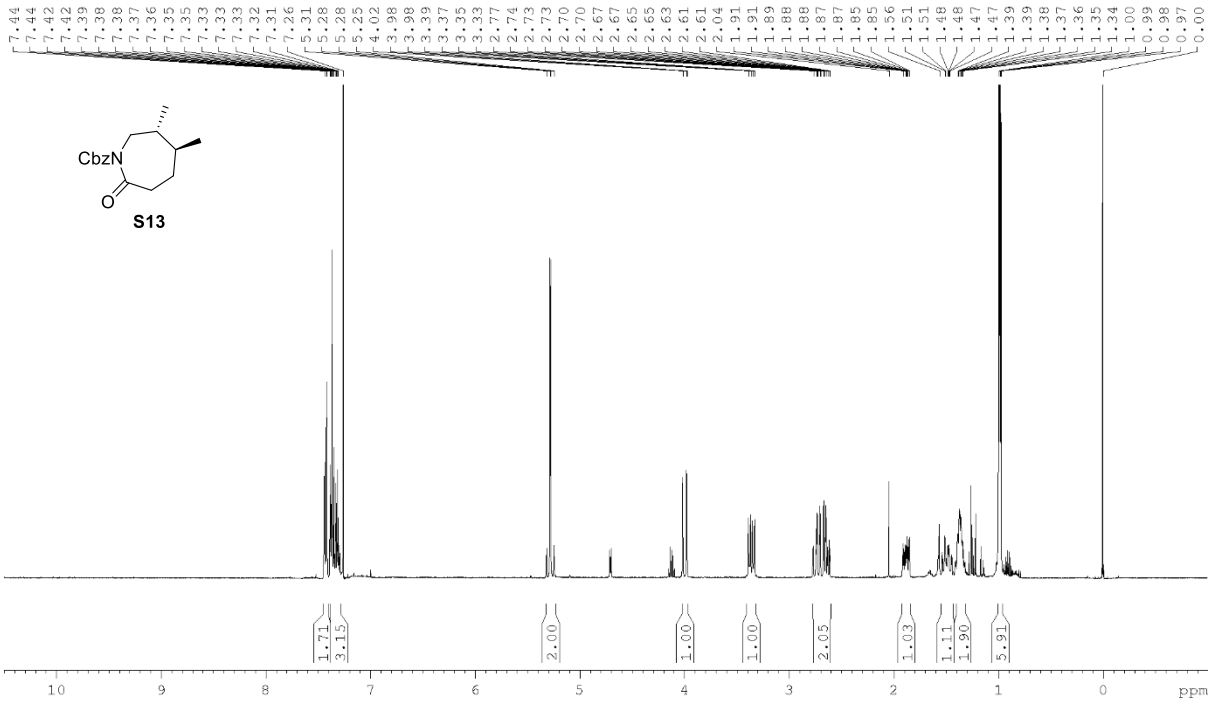


^{13}C NMR (100 MHz, $CDCl_3$)

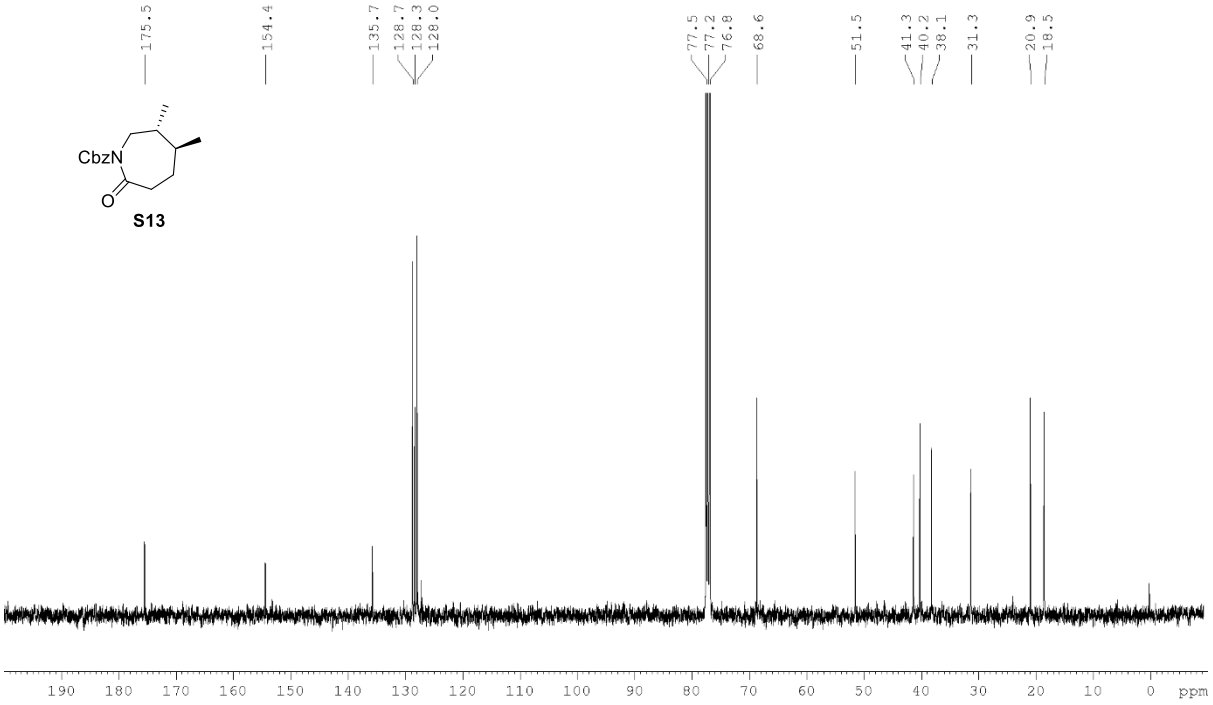


***N*-Cbz-lactam S13**

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

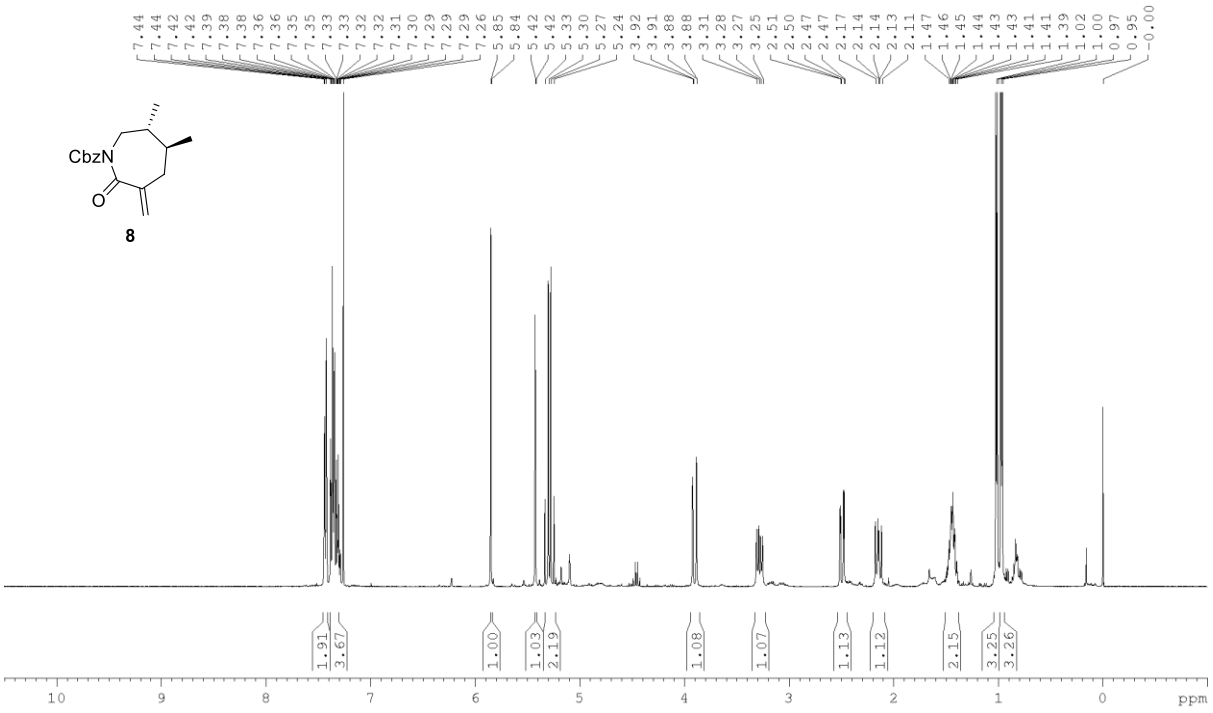


^{13}C NMR (100 MHz, $CDCl_3$)

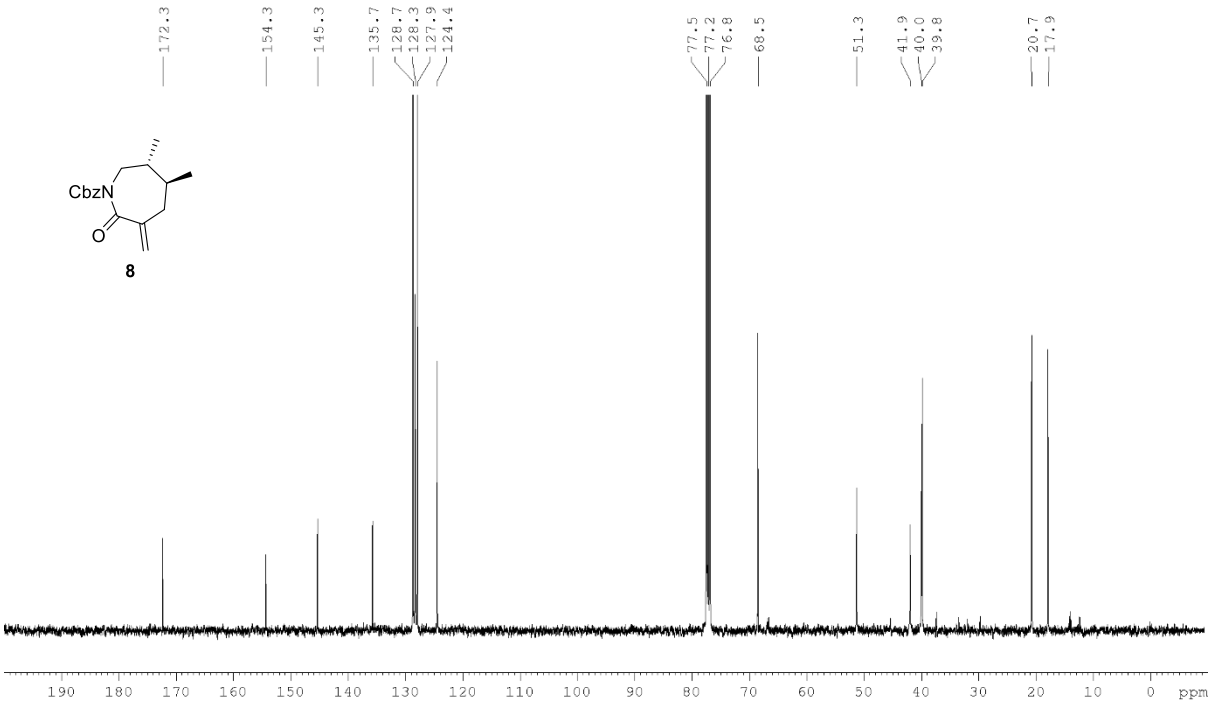


***α-Exo*-methylene lactam 8**

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

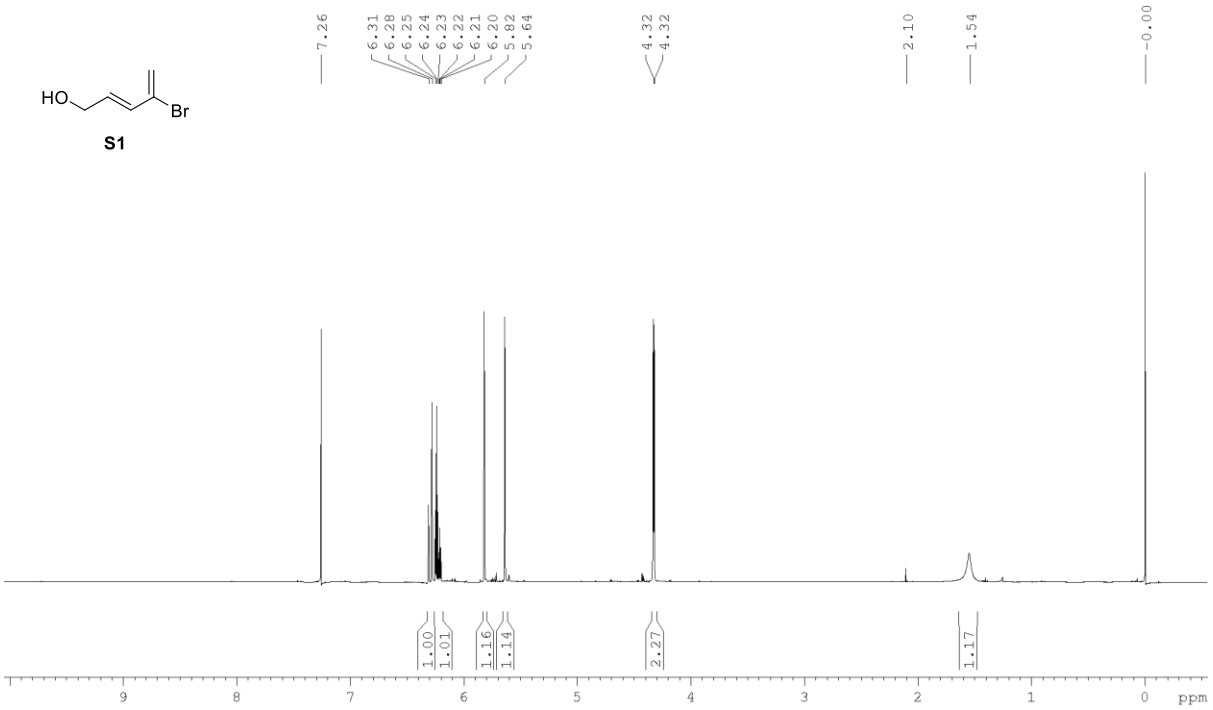


^{13}C NMR (100 MHz, $CDCl_3$)

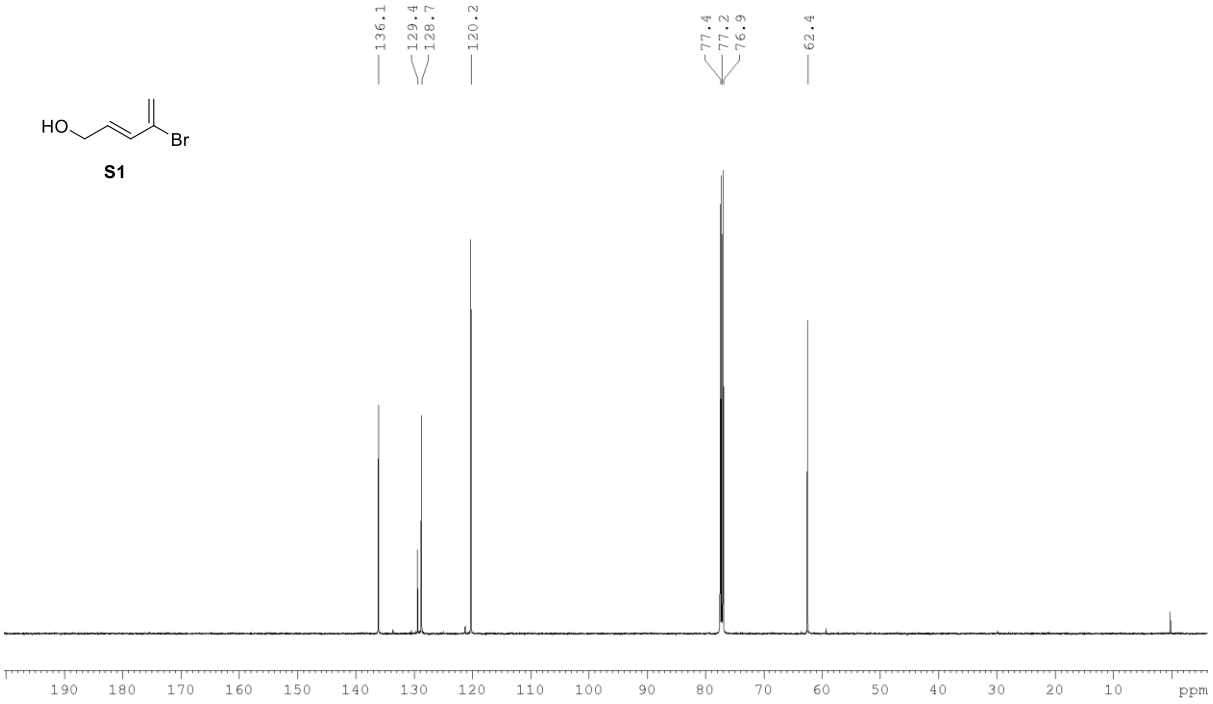


Alcohol S1

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

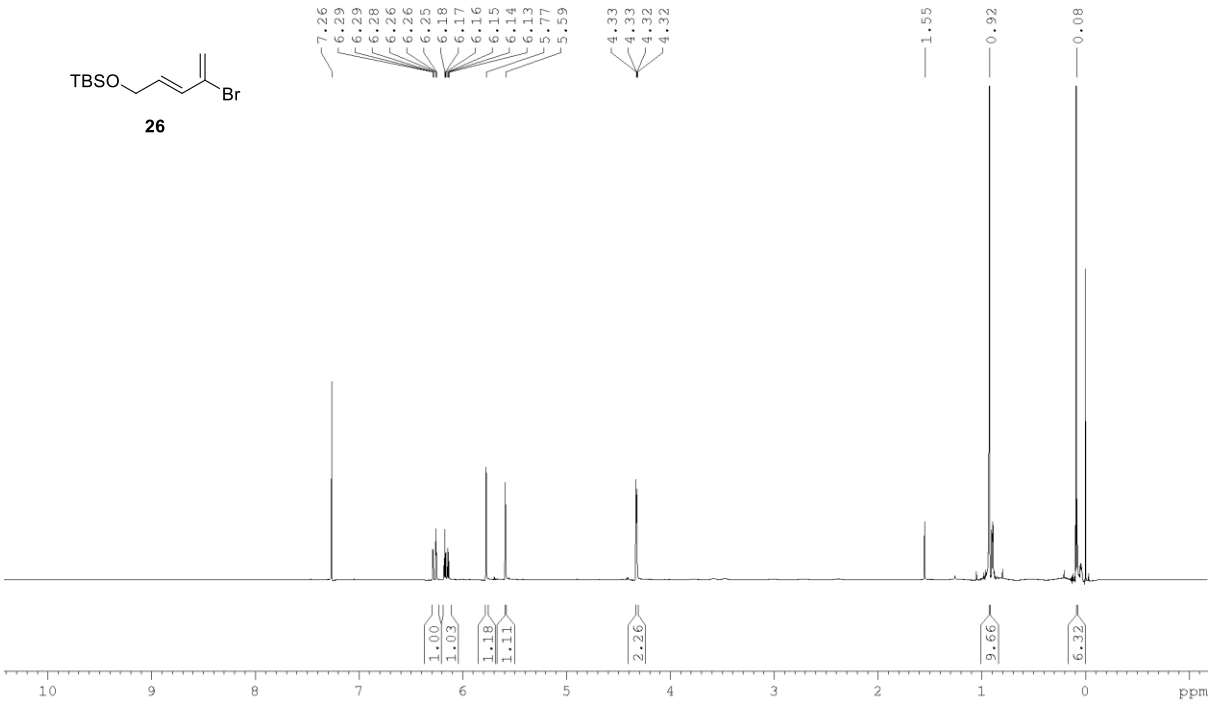


^{13}C NMR (125 MHz, $CDCl_3$)

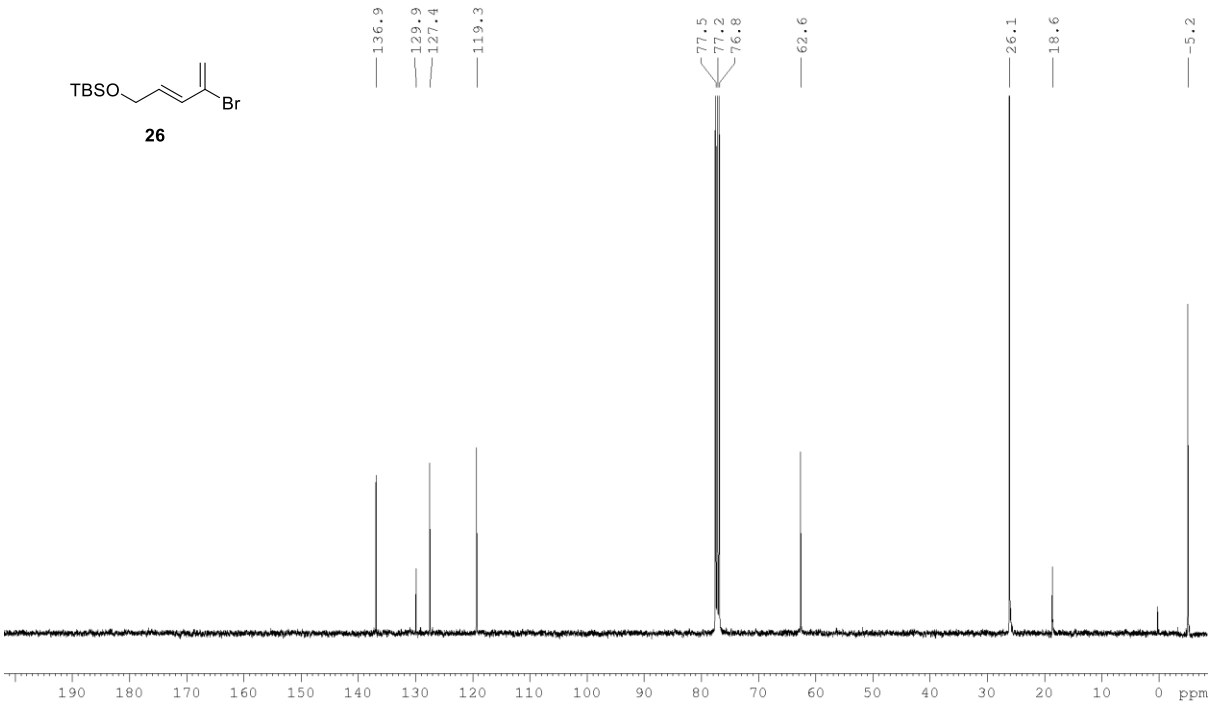


Bromodiene 26

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

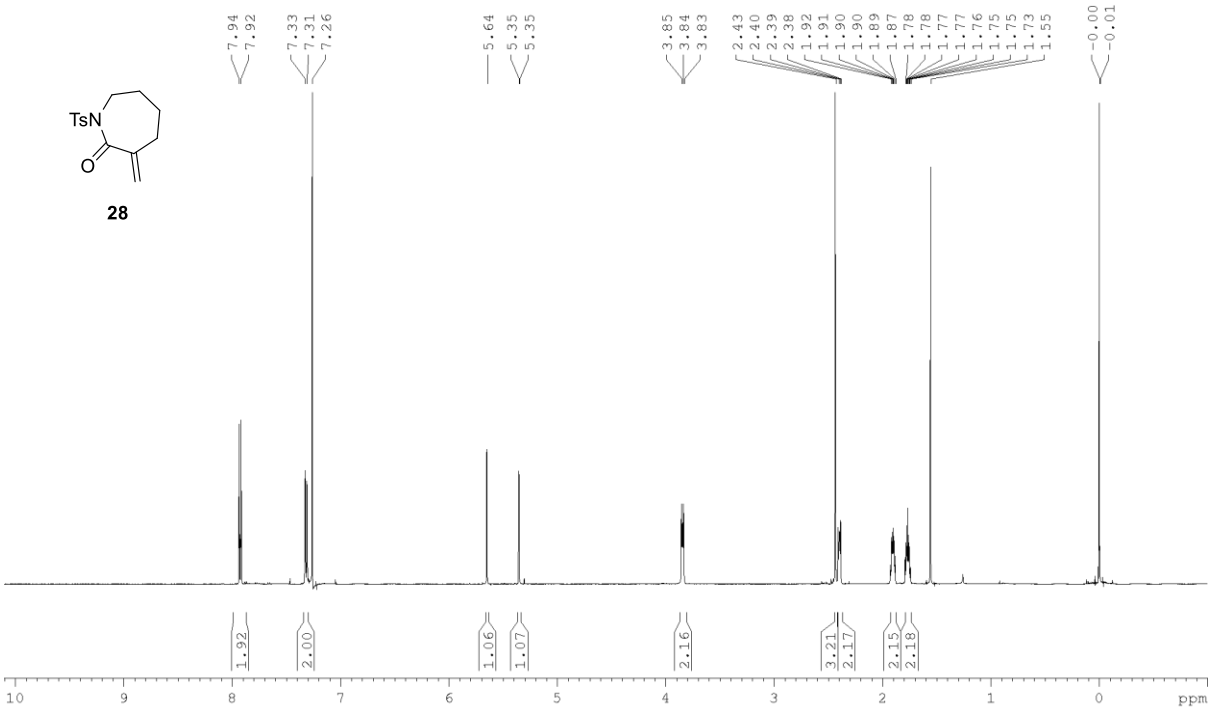


^{13}C NMR (125 MHz, $CDCl_3$)

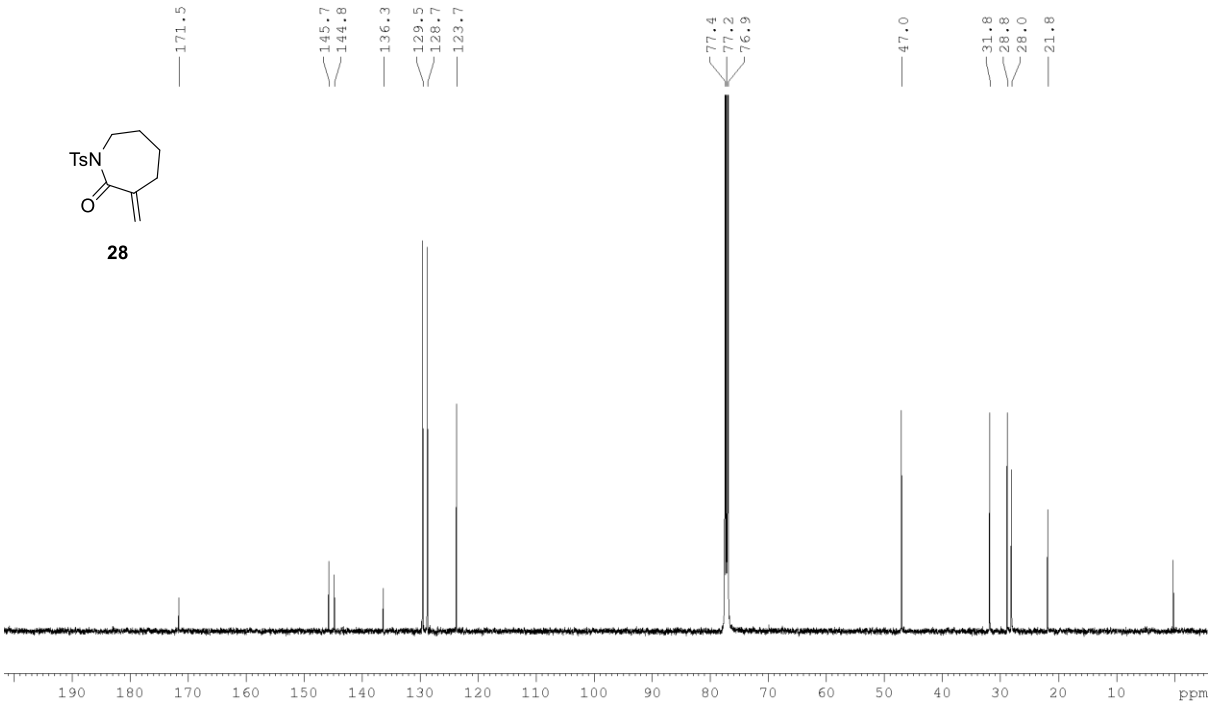


***α-Exo*-methylene lactam 28**

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

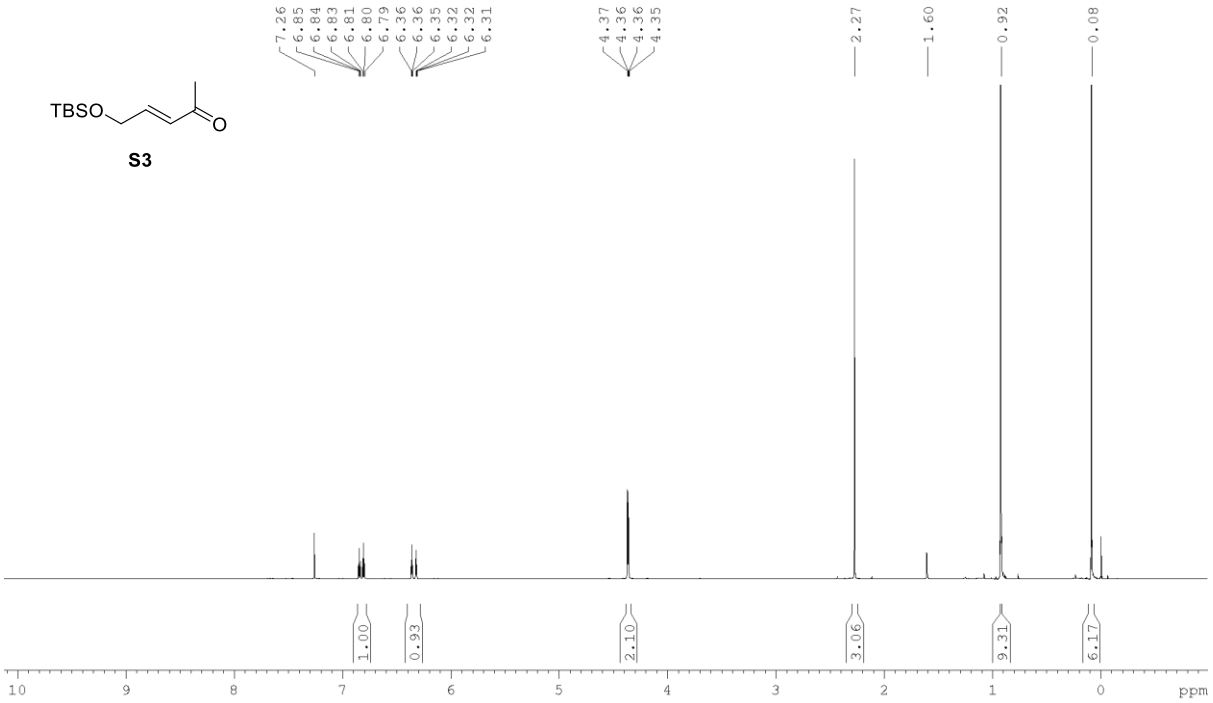


^{13}C NMR (125 MHz, $CDCl_3$)

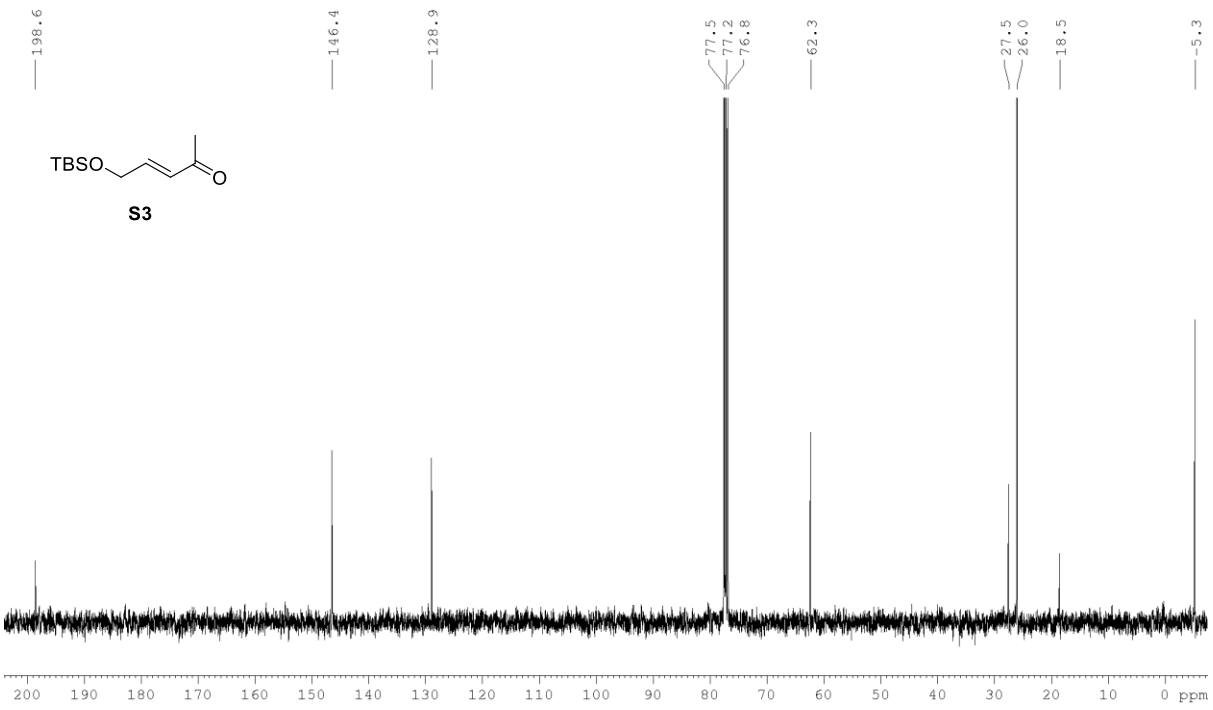


Enone S3

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

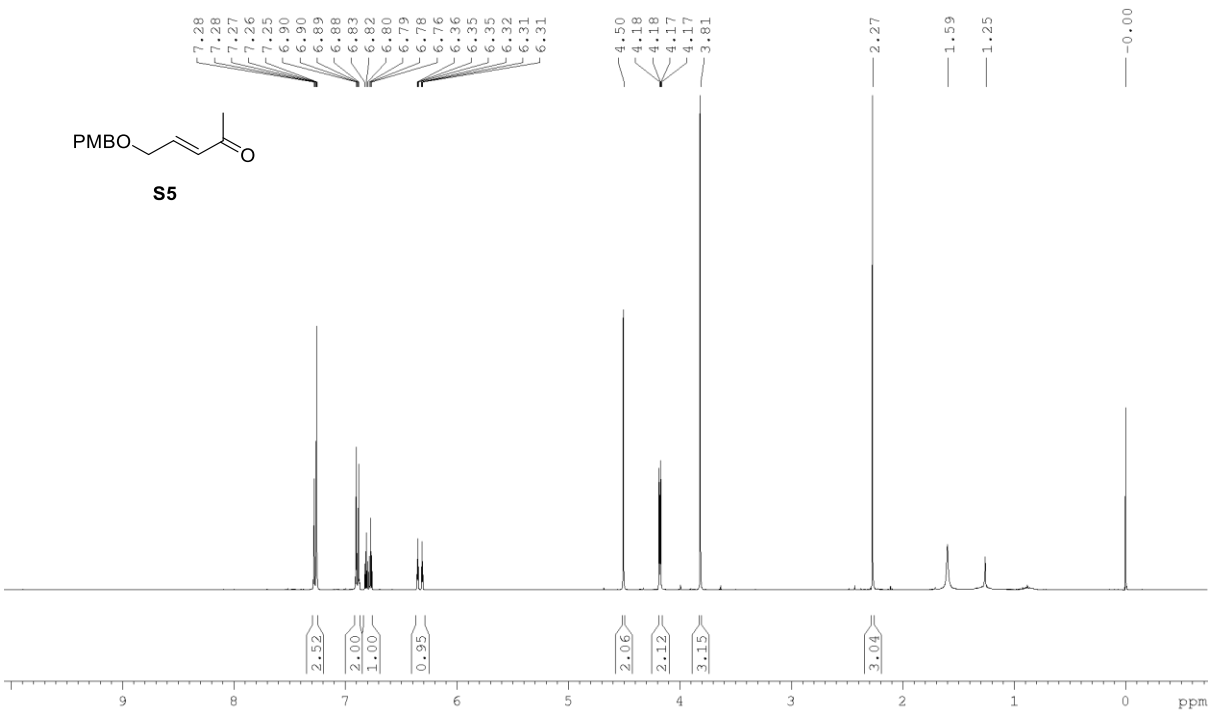


^{13}C NMR (100 MHz, $CDCl_3$)

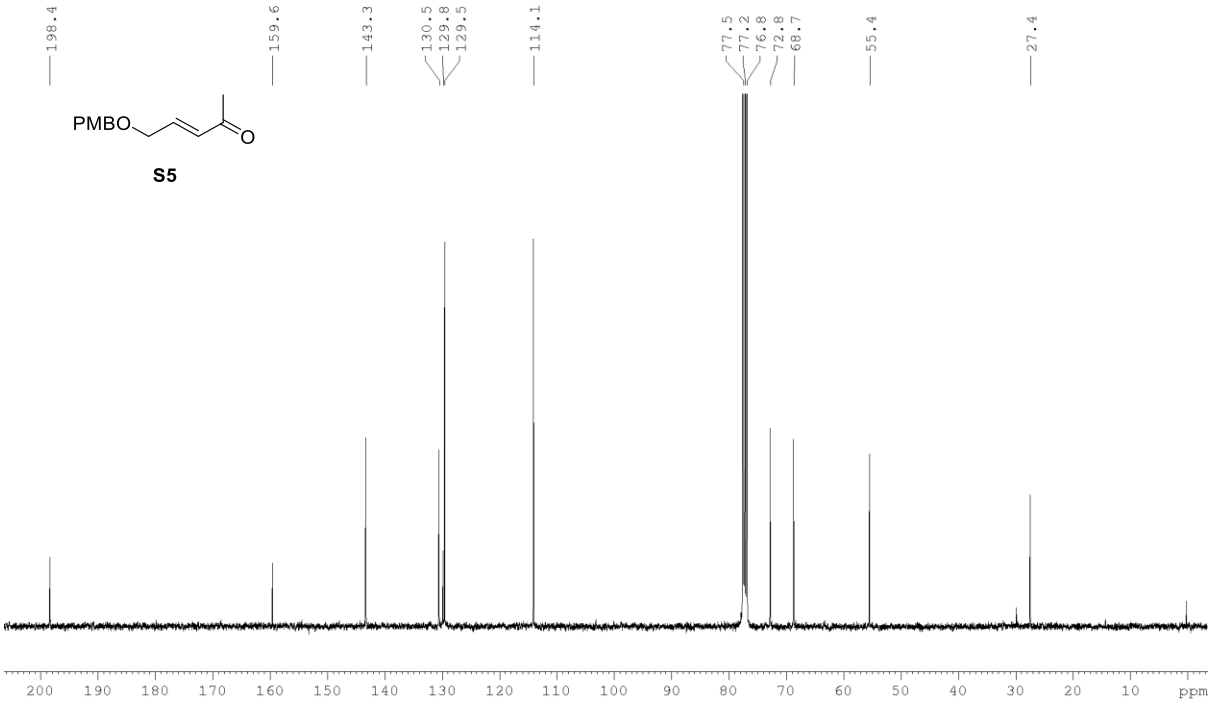


Enone S5

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

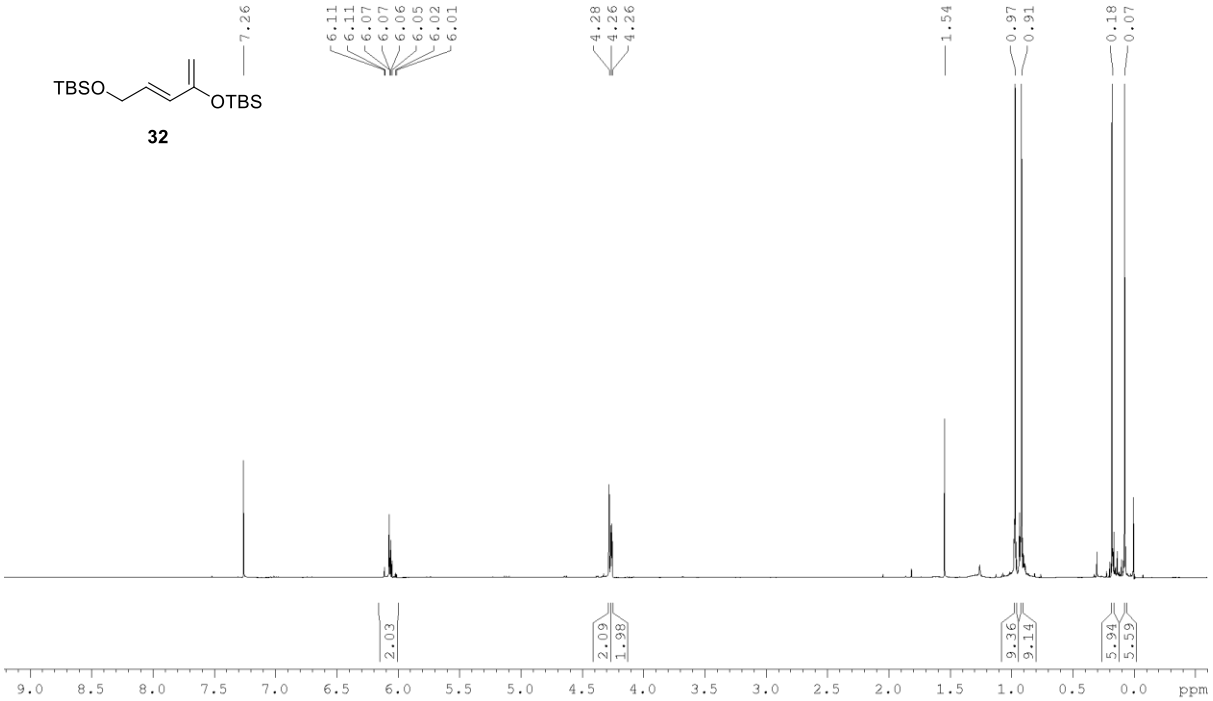


^{13}C NMR (100 MHz, $CDCl_3$)

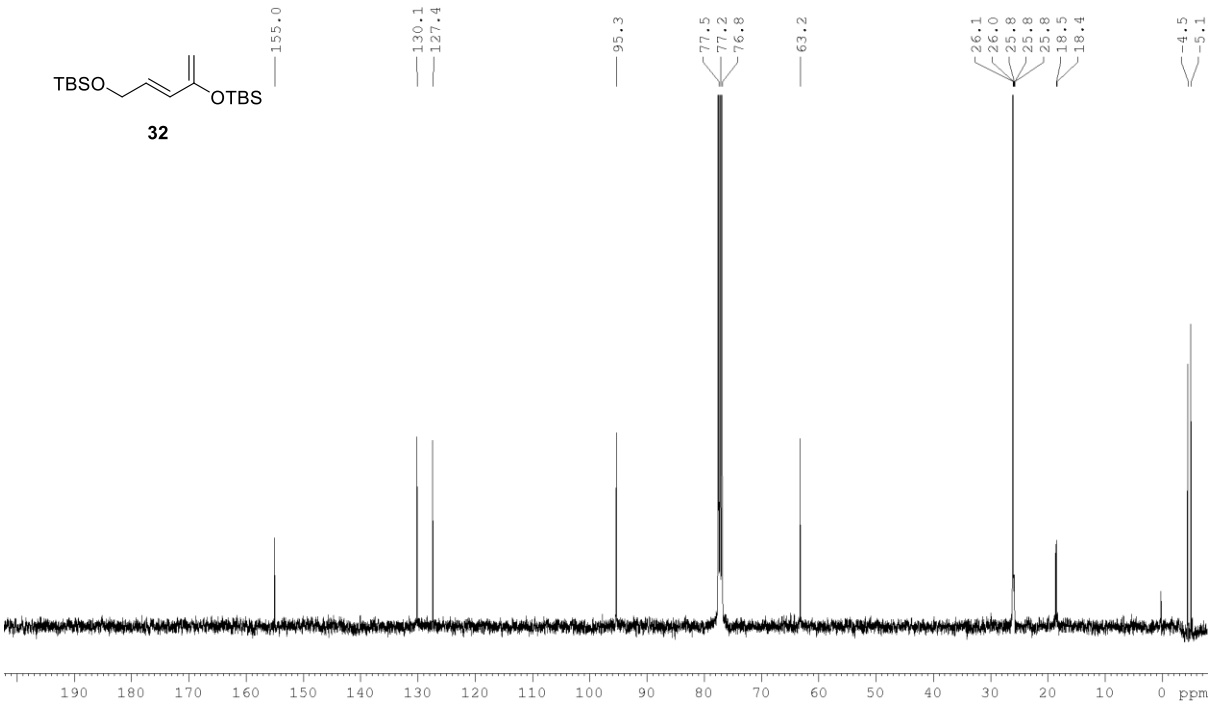


Diene 32

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

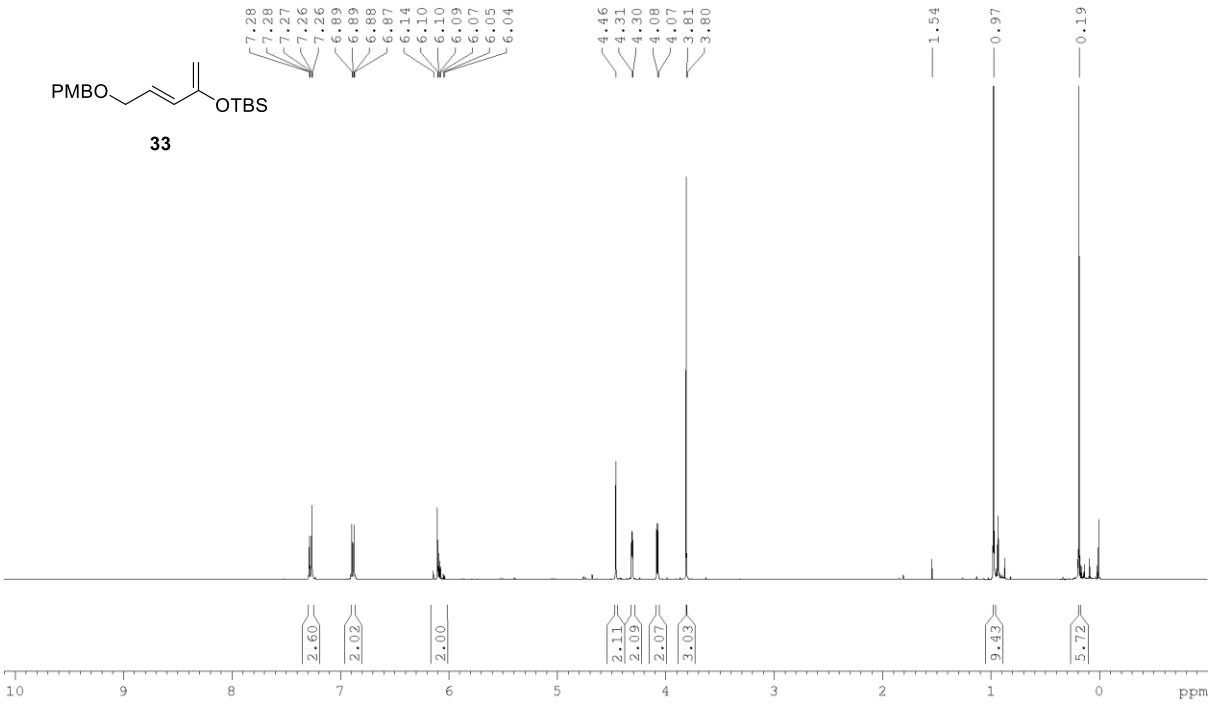


^{13}C NMR (100 MHz, $CDCl_3$)

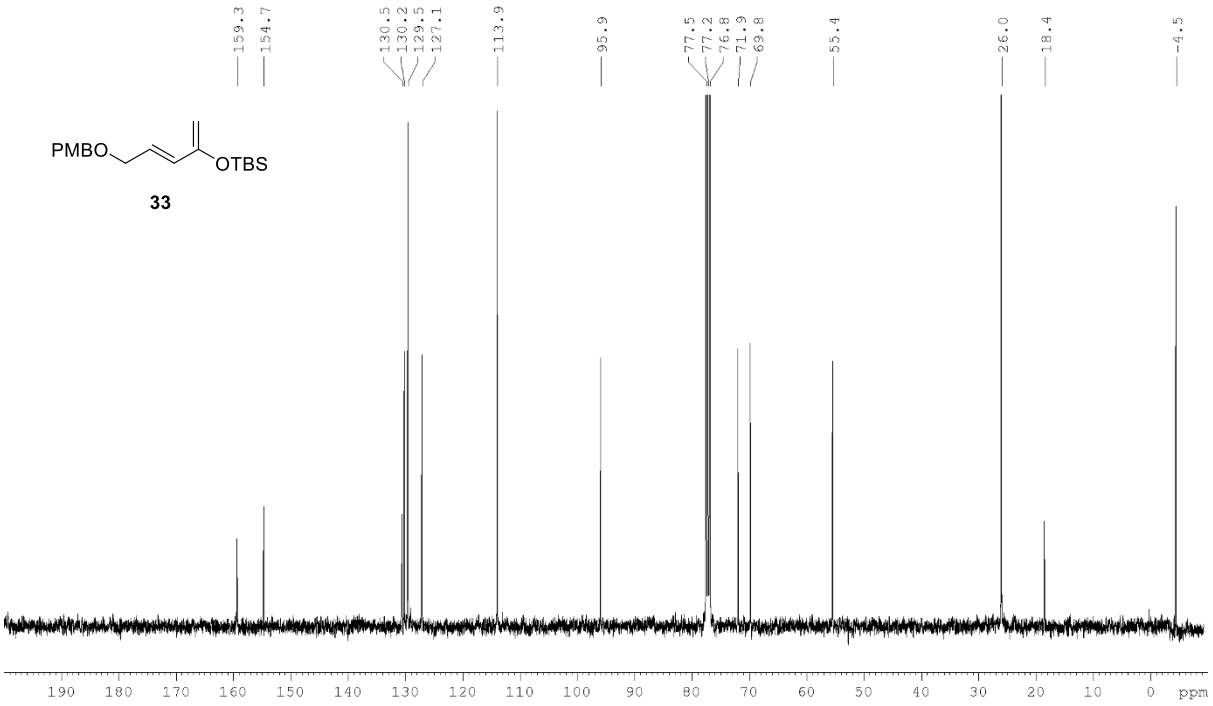


Diene 33

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



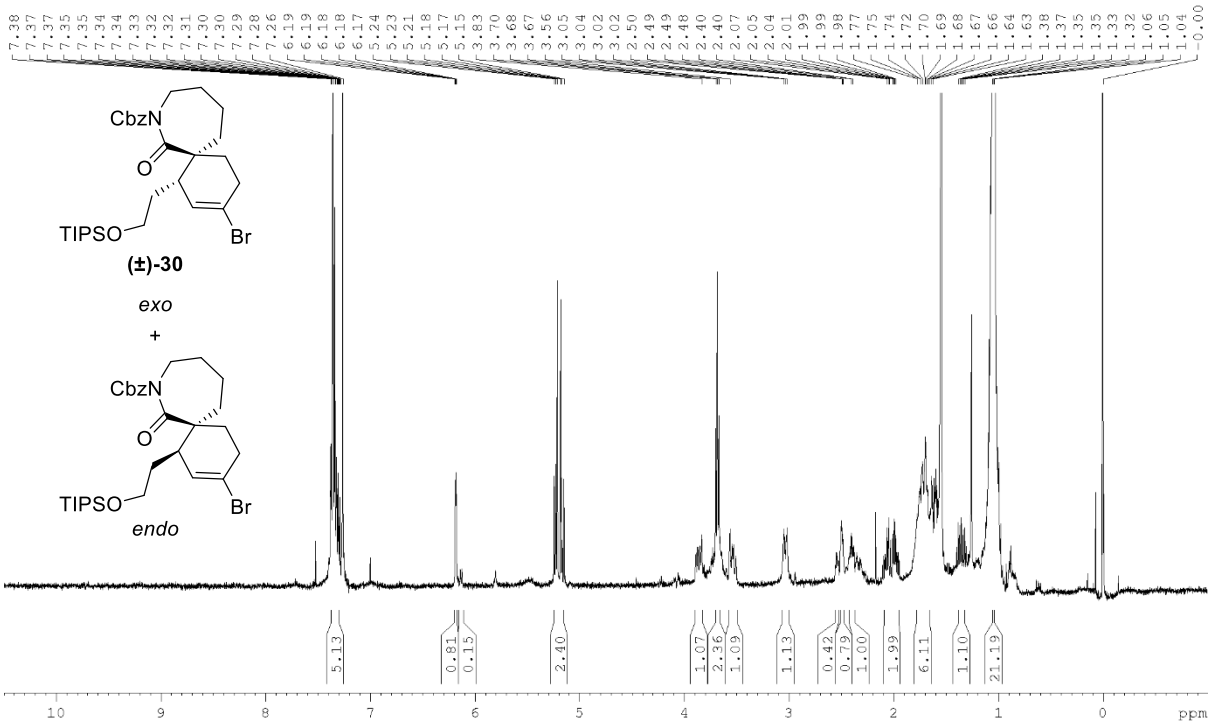
^{13}C NMR (100 MHz, $CDCl_3$)



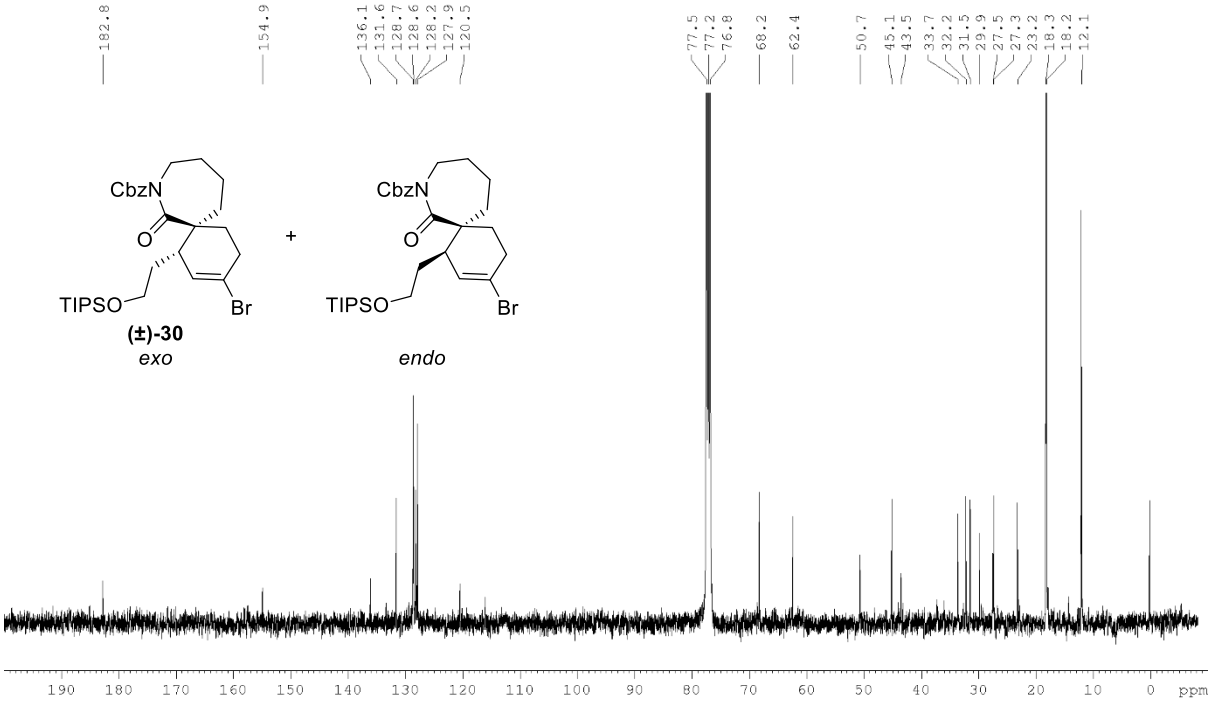
Cycloadduct (±)-30

The product was isolated as a 5:1 mixture of inseparable *exo* and *endo* diastereomers.

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

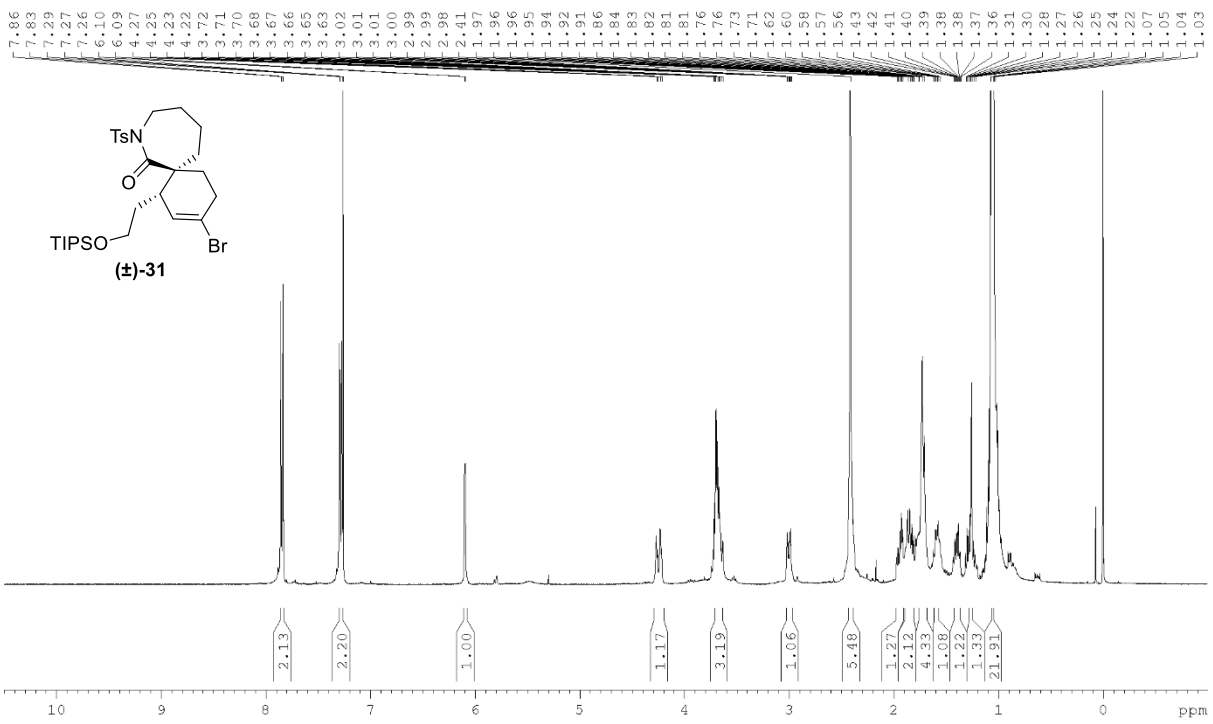


^{13}C NMR (100 MHz, $CDCl_3$)

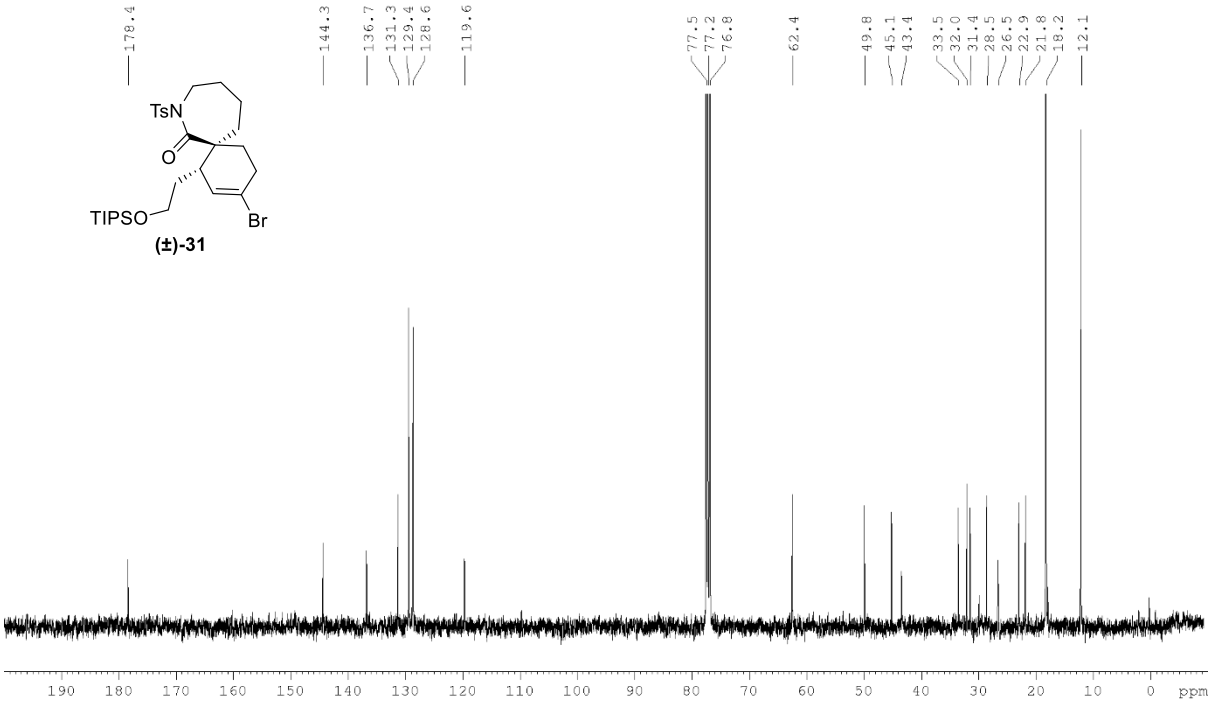


Cycloadduct (±)-31

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

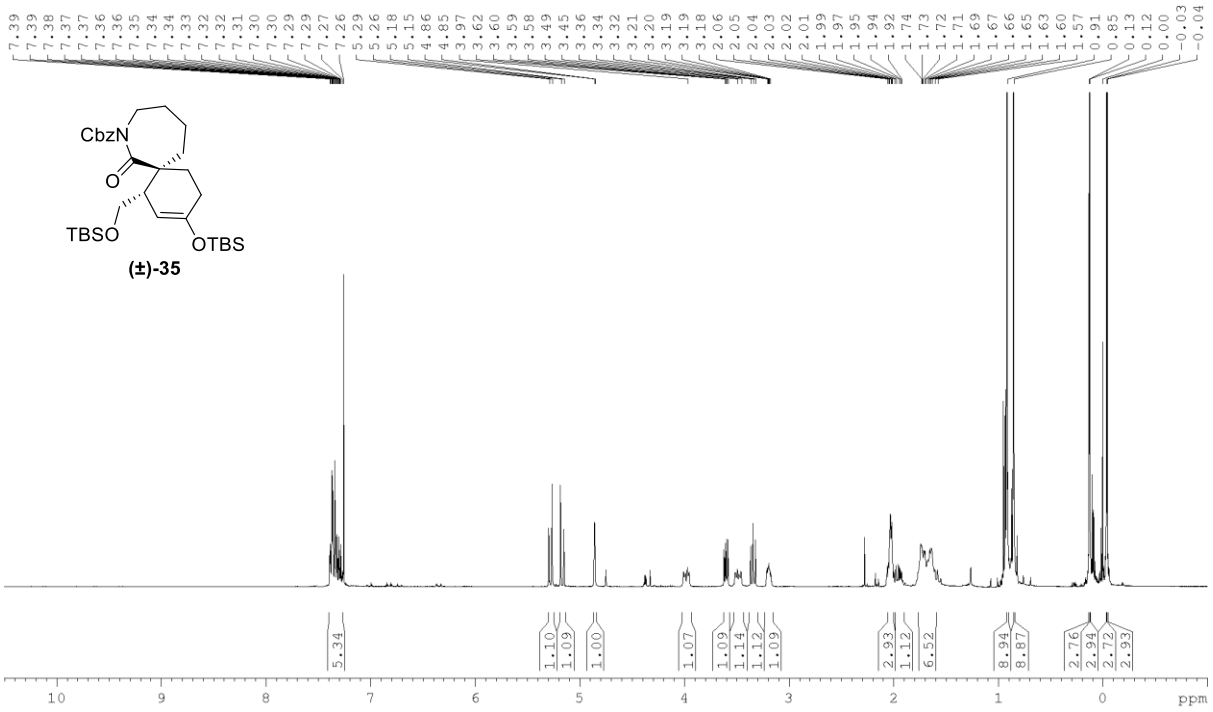


^{13}C NMR (100 MHz, $CDCl_3$)

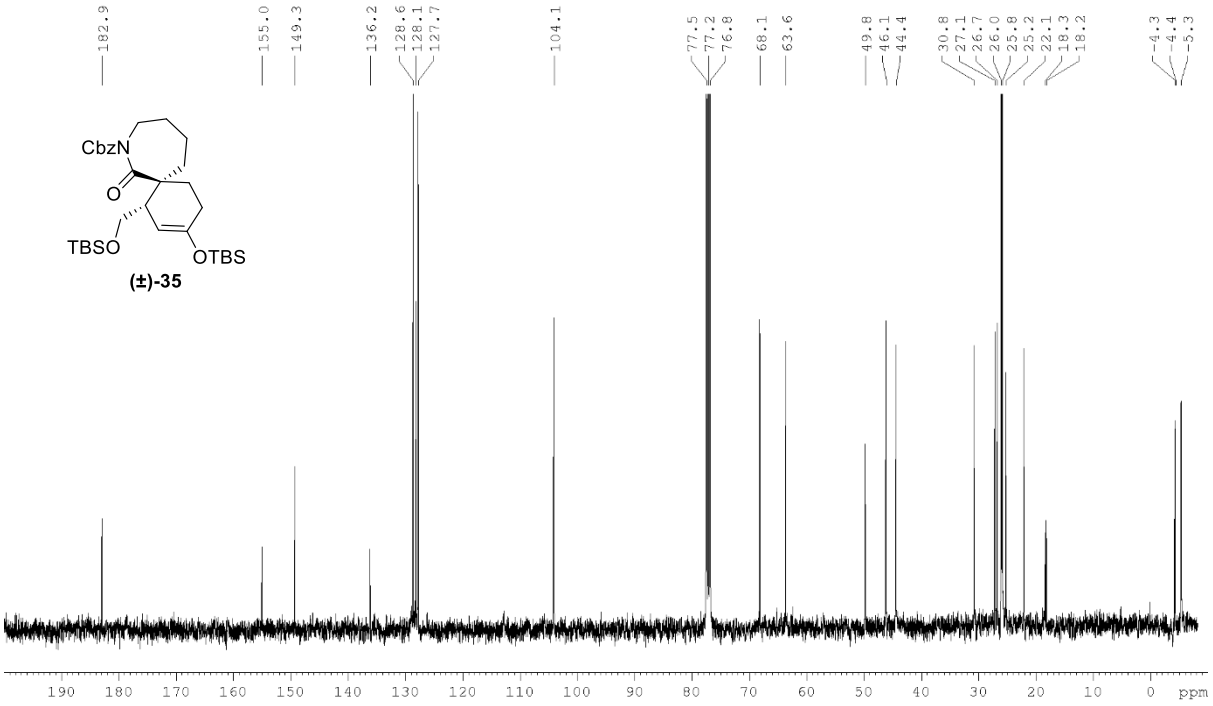


Cycloadduct (±)-35

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

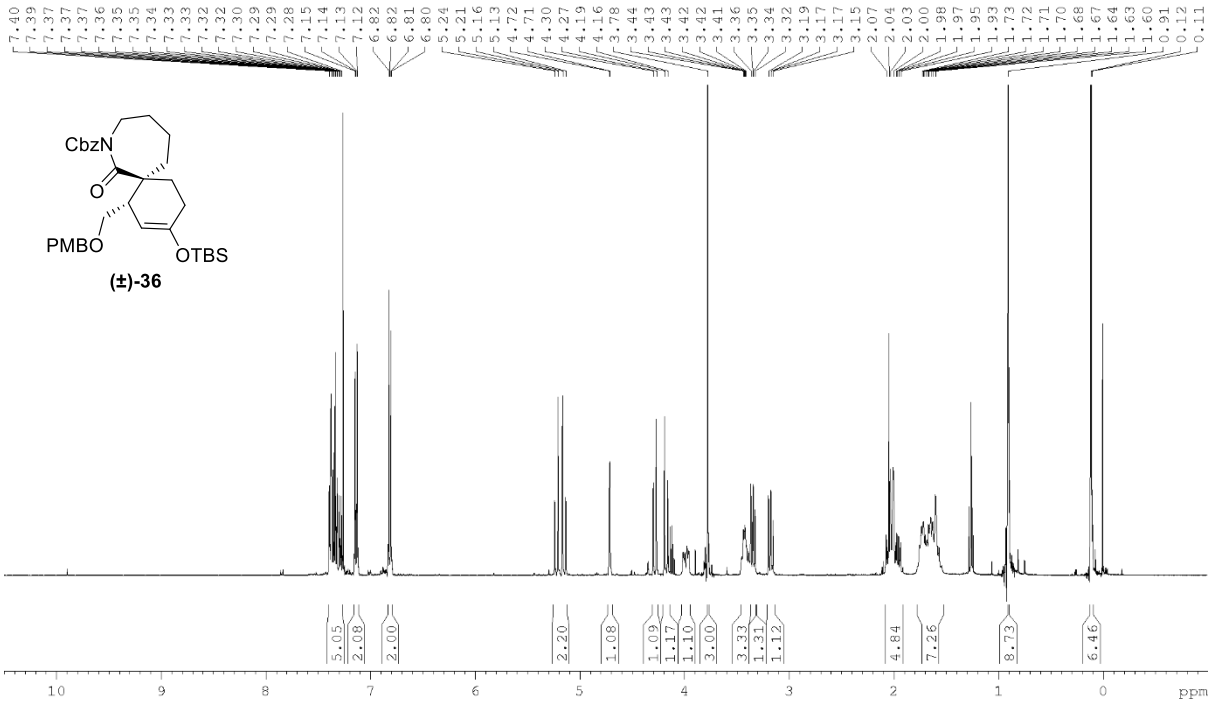


^{13}C NMR (100 MHz, $CDCl_3$)

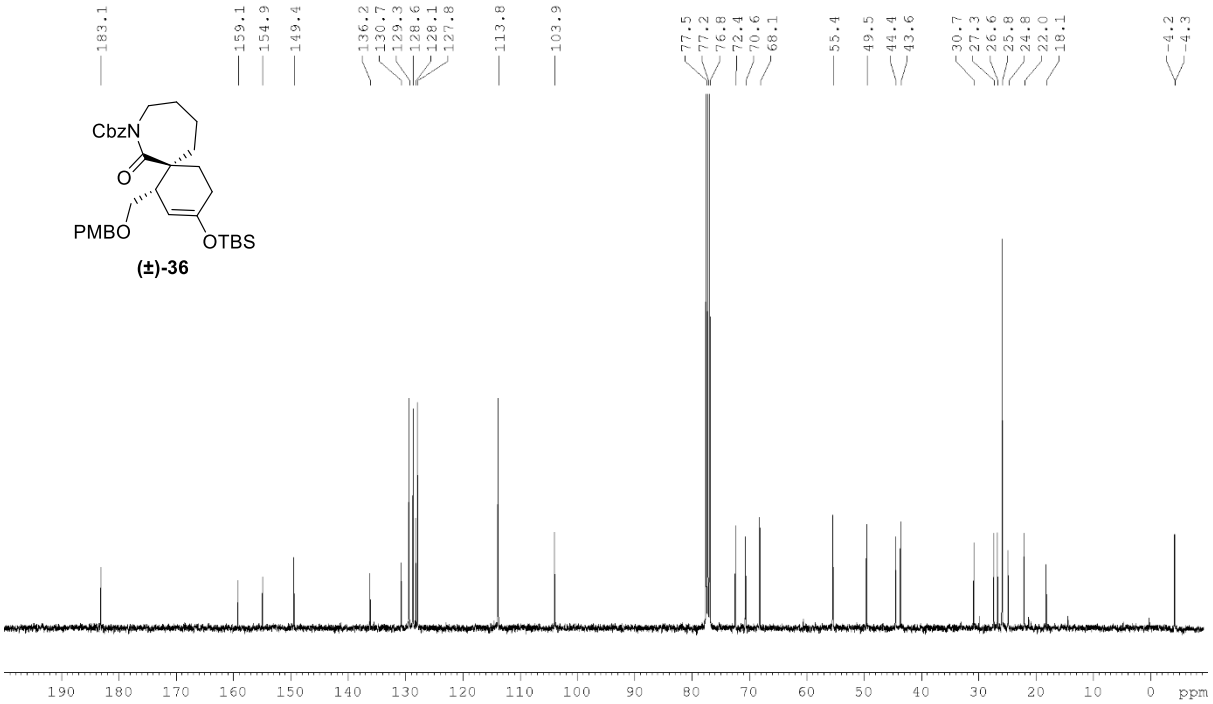


Cycloadduct (±)-36

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

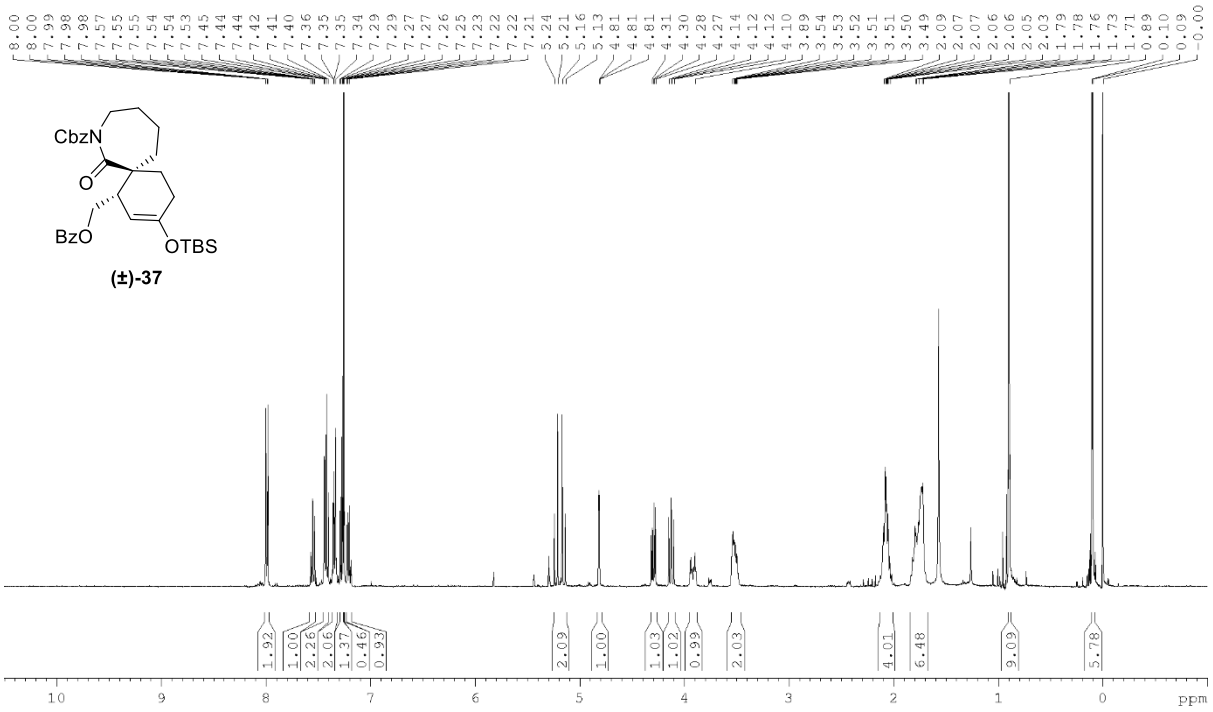


^{13}C NMR (100 MHz, $CDCl_3$)

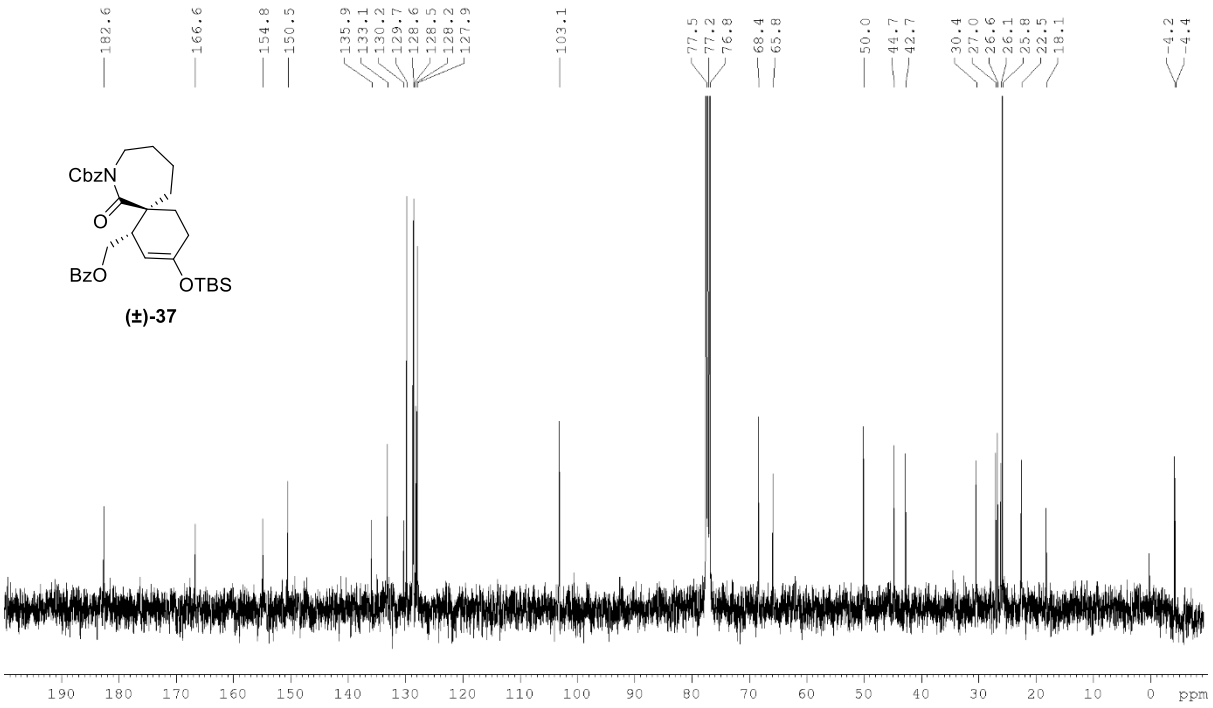


Cycloadduct (±)-37

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

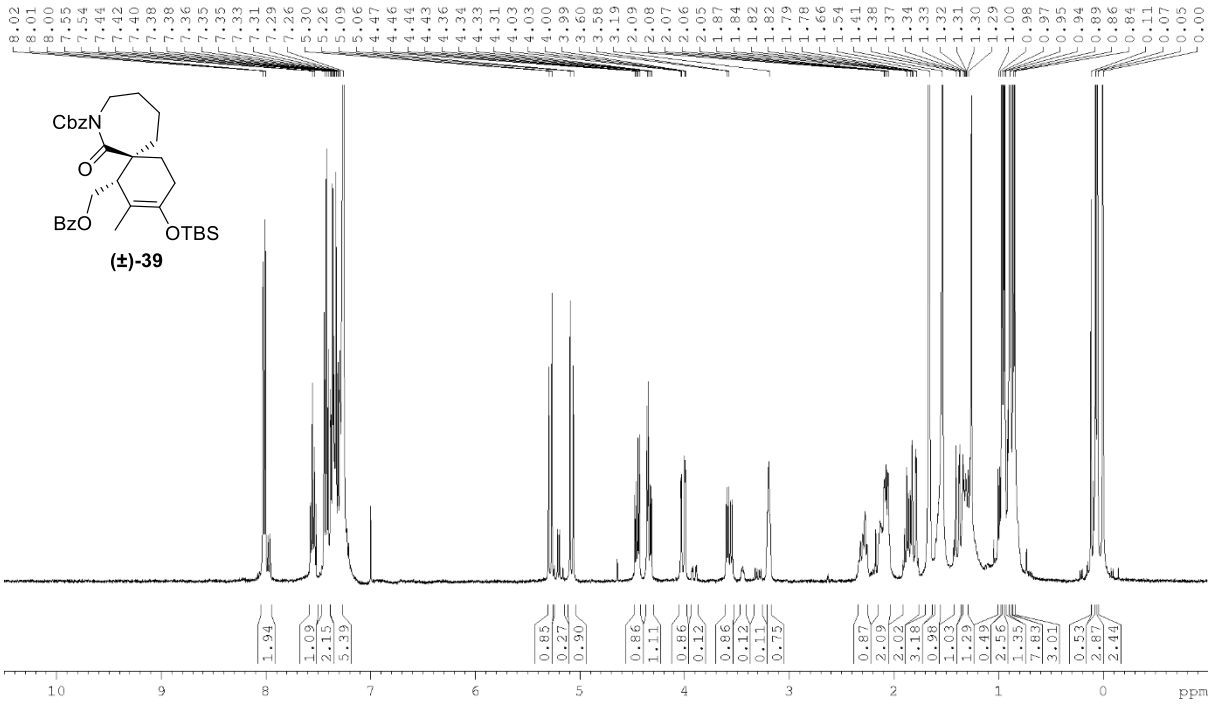


^{13}C NMR (100 MHz, $CDCl_3$)

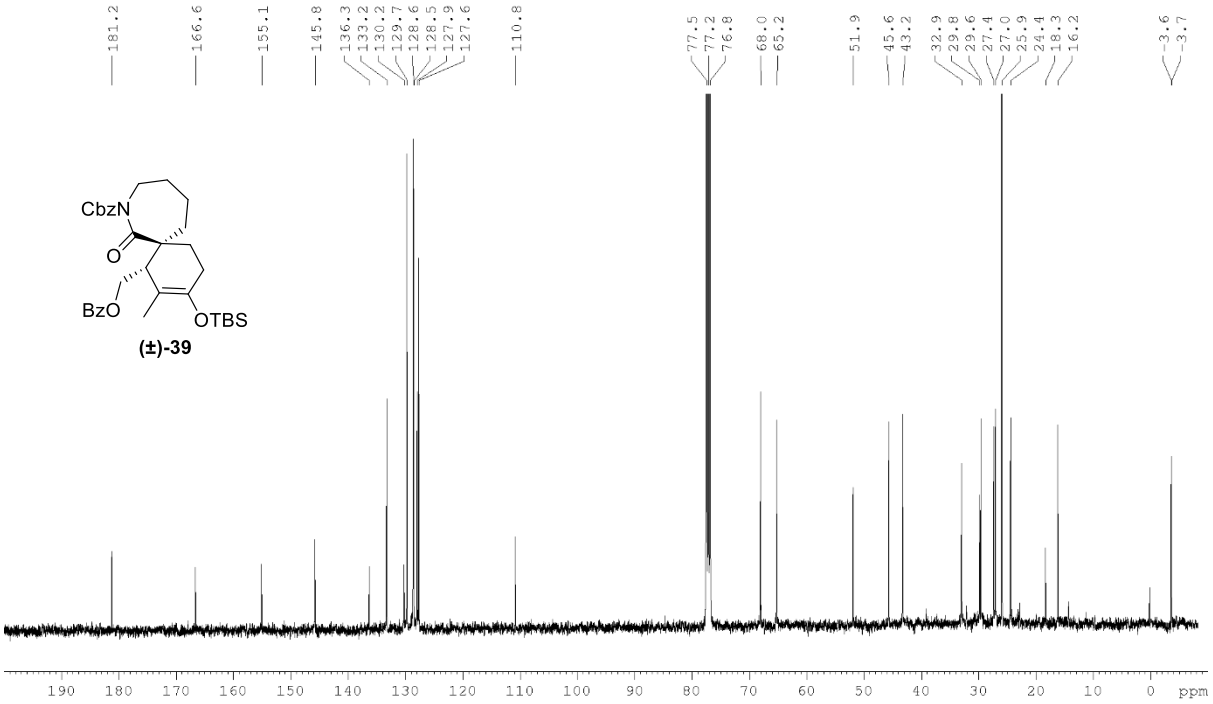


Cycloadduct (±)-39

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

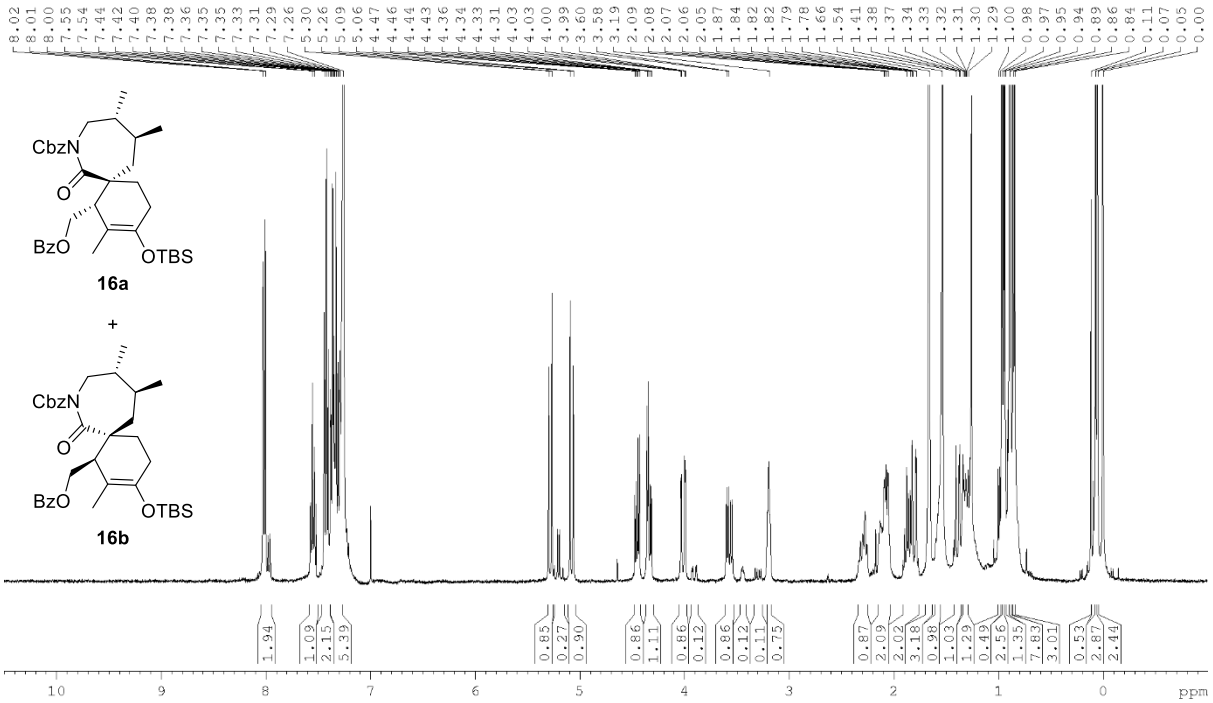


^{13}C NMR (100 MHz, $CDCl_3$)

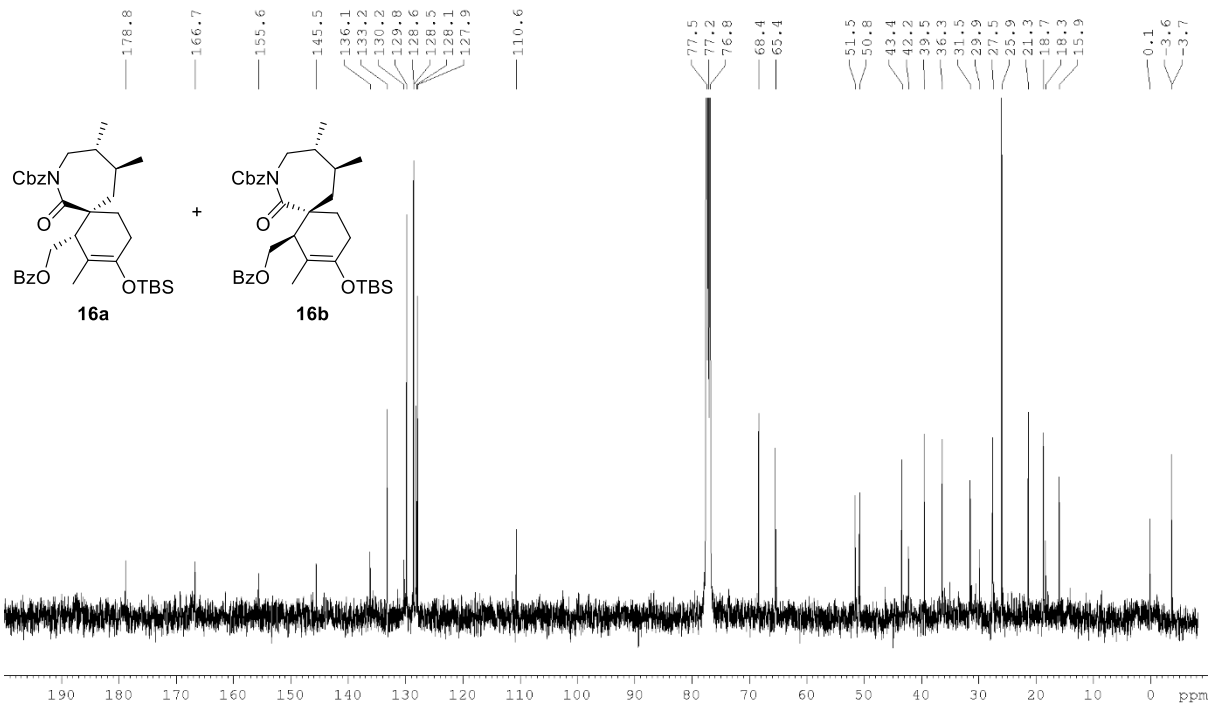


Cycloadducts 16a and 16b

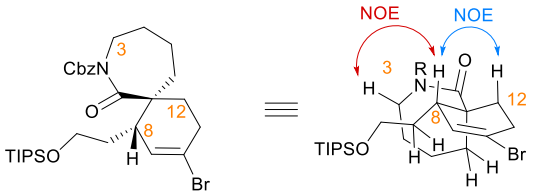
^{1}H NMR (400 MHz, $CDCl_3$)



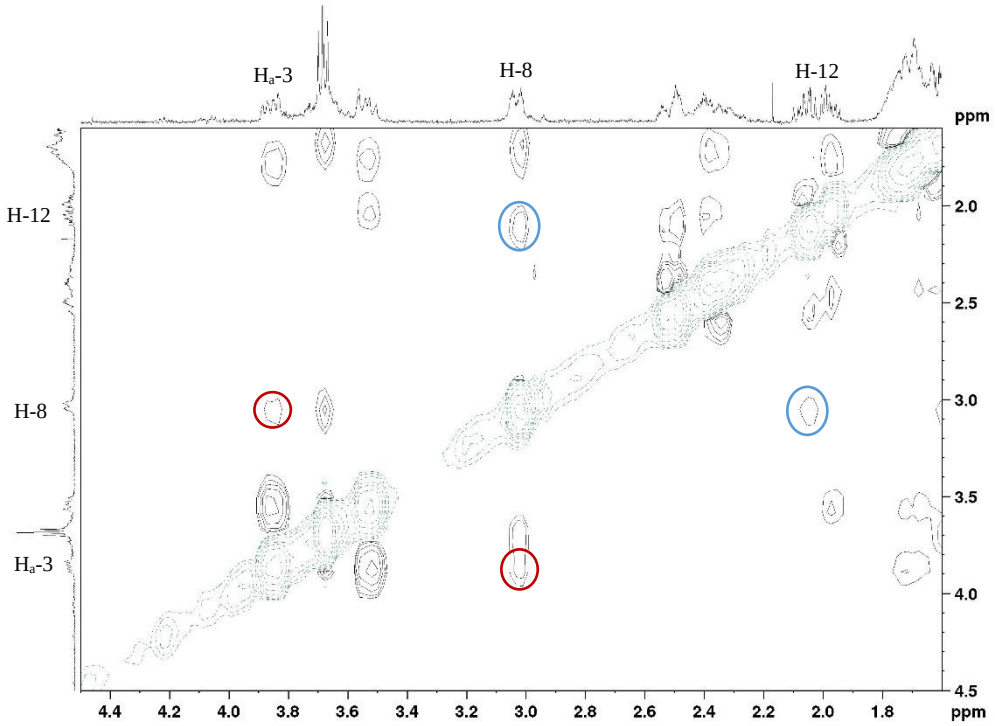
^{13}C NMR (100 MHz, $CDCl_3$)



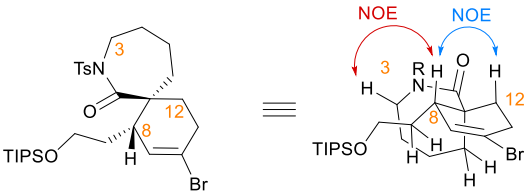
Key NOESY correlations of Cycloadduct (±)-30



(±)-**30** (±)-**30**
R = Cbz

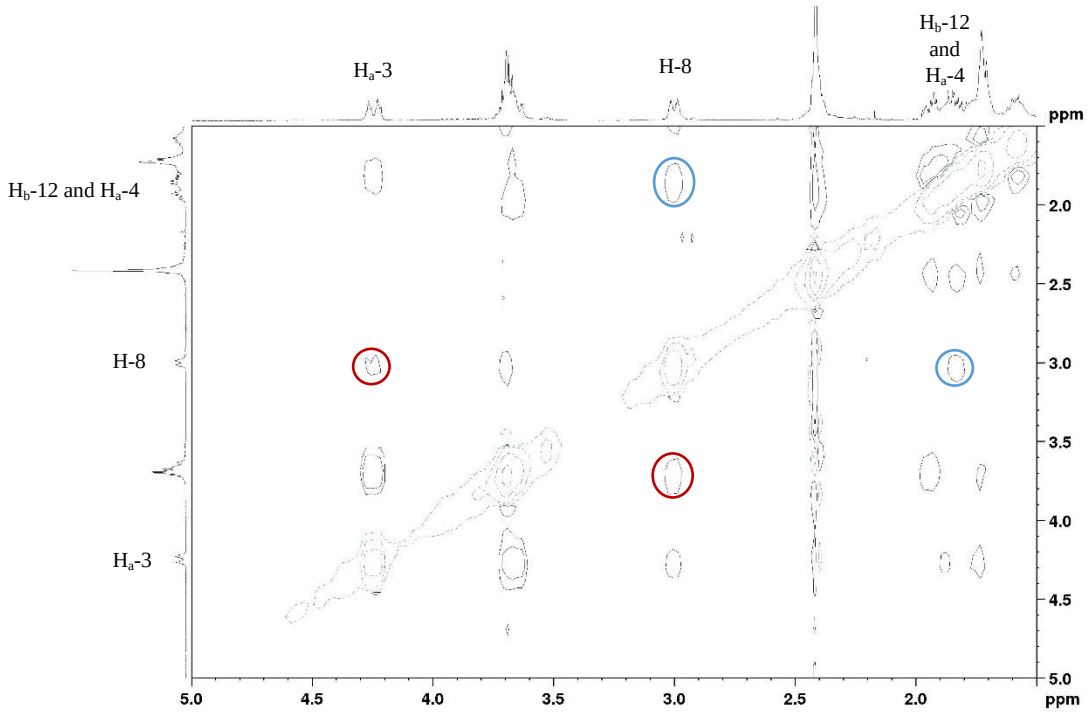


Key NOESY correlations of Cycloadduct (±)-31

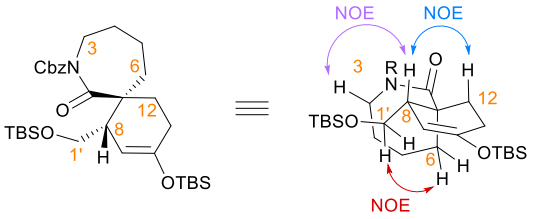


(±)-**31** (±)-**31**

R = Ts

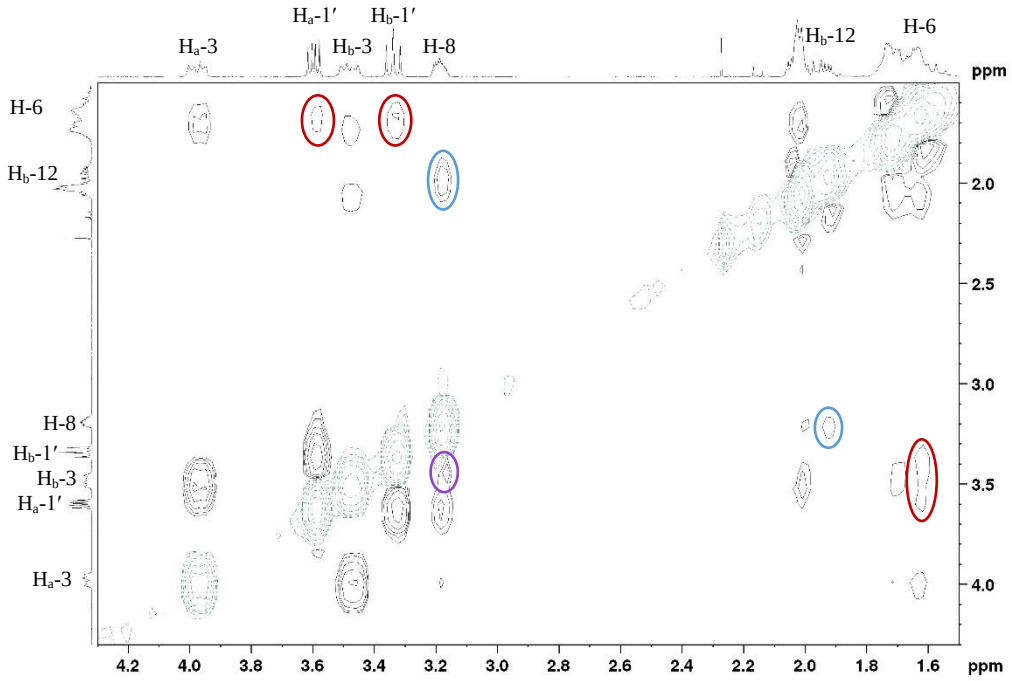


Key NOESY correlations of Cycloadduct (±)-35

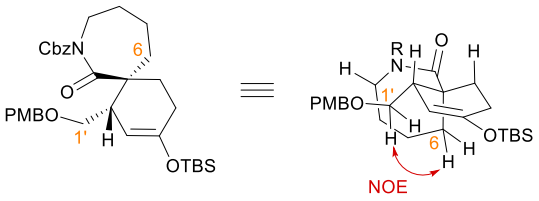


(±)-**35** (±)-**35**

R = Cbz

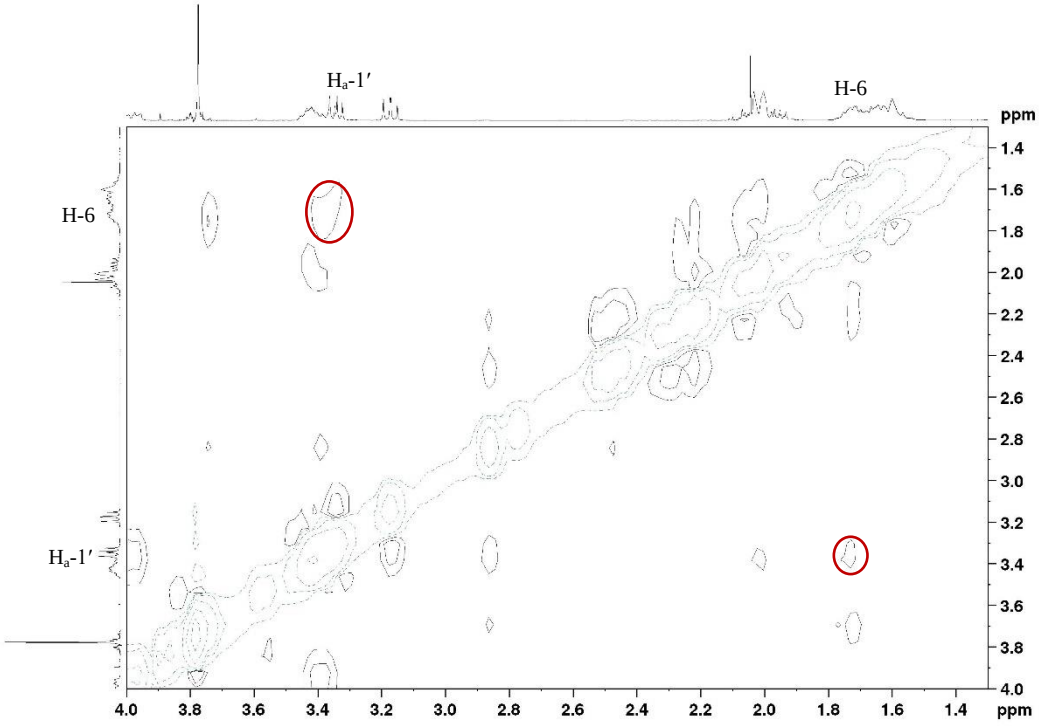


Key NOESY correlations of Cycloadduct (±)-36

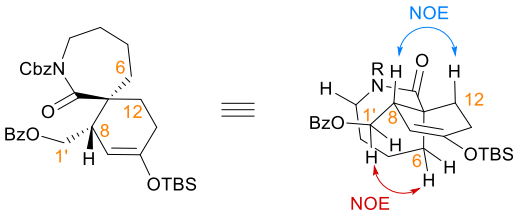


(±)-**36** (±)-**36**

R = Cbz

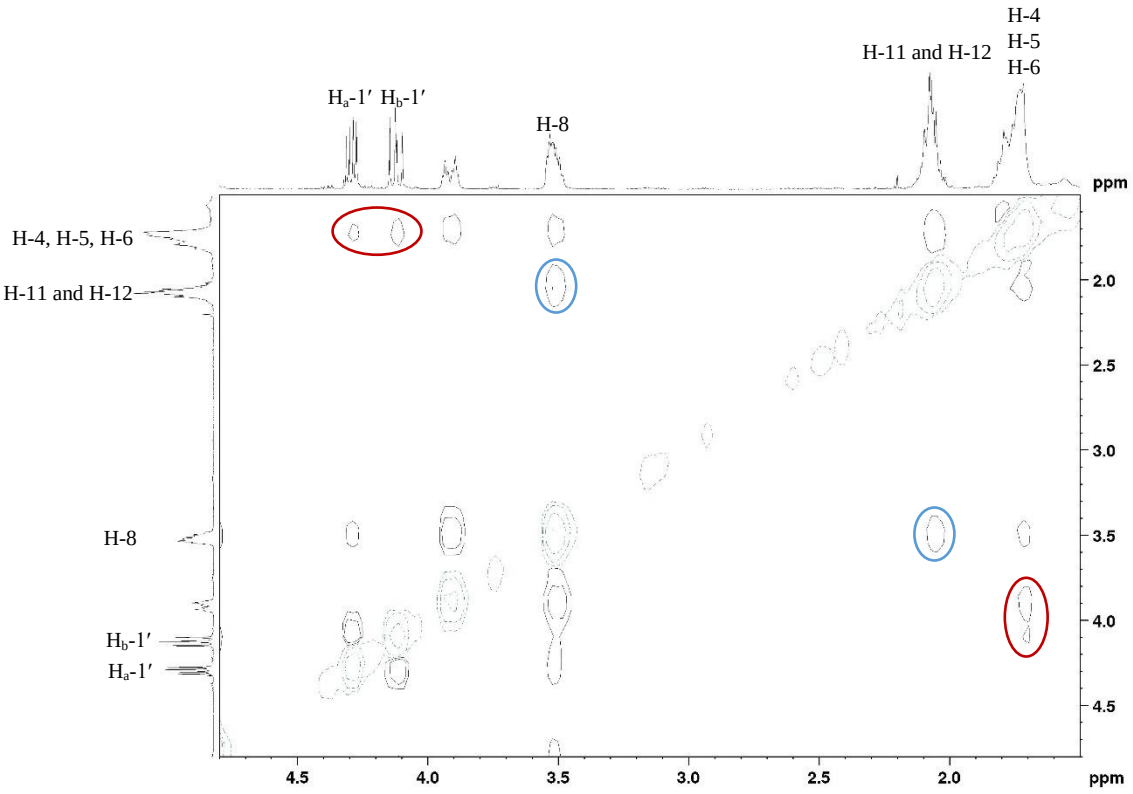


Key NOESY correlations of Cycloadduct (±)-37

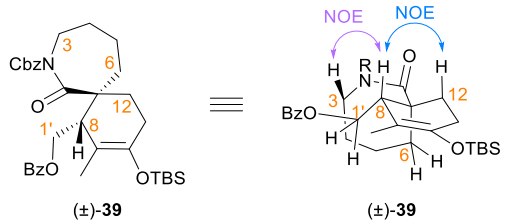


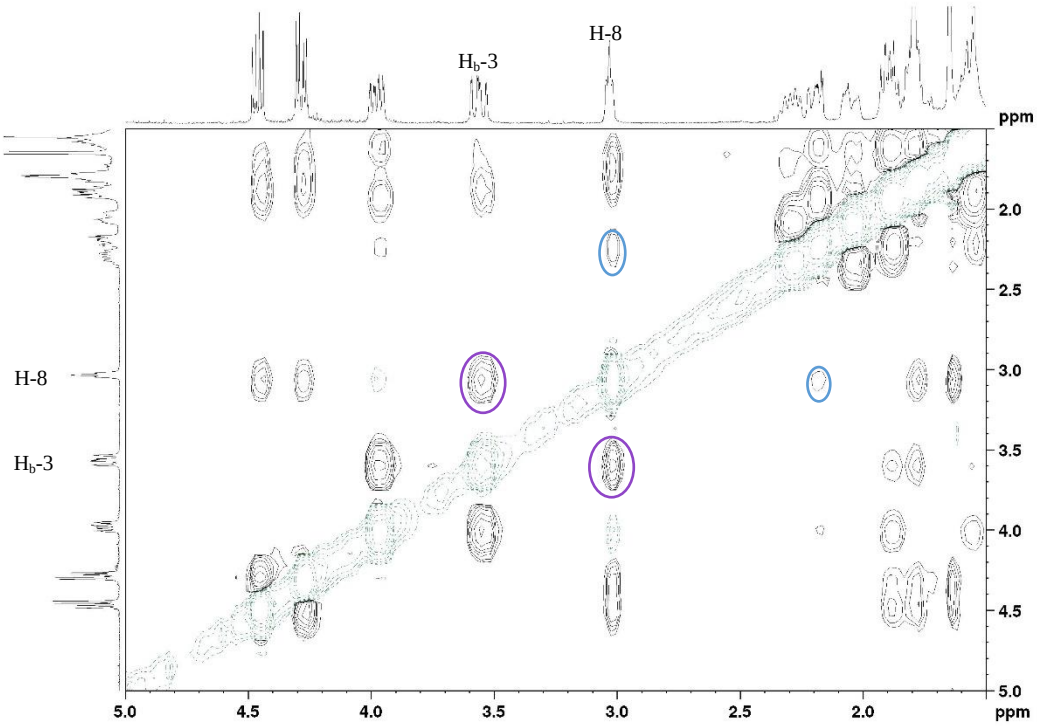
(±)-**37** ≡ (±)-**37**

R = Cbz

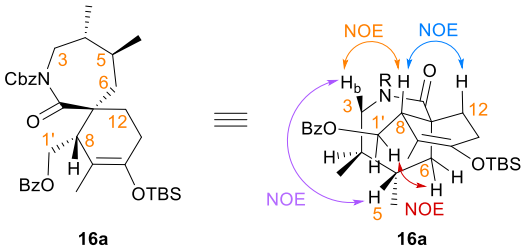


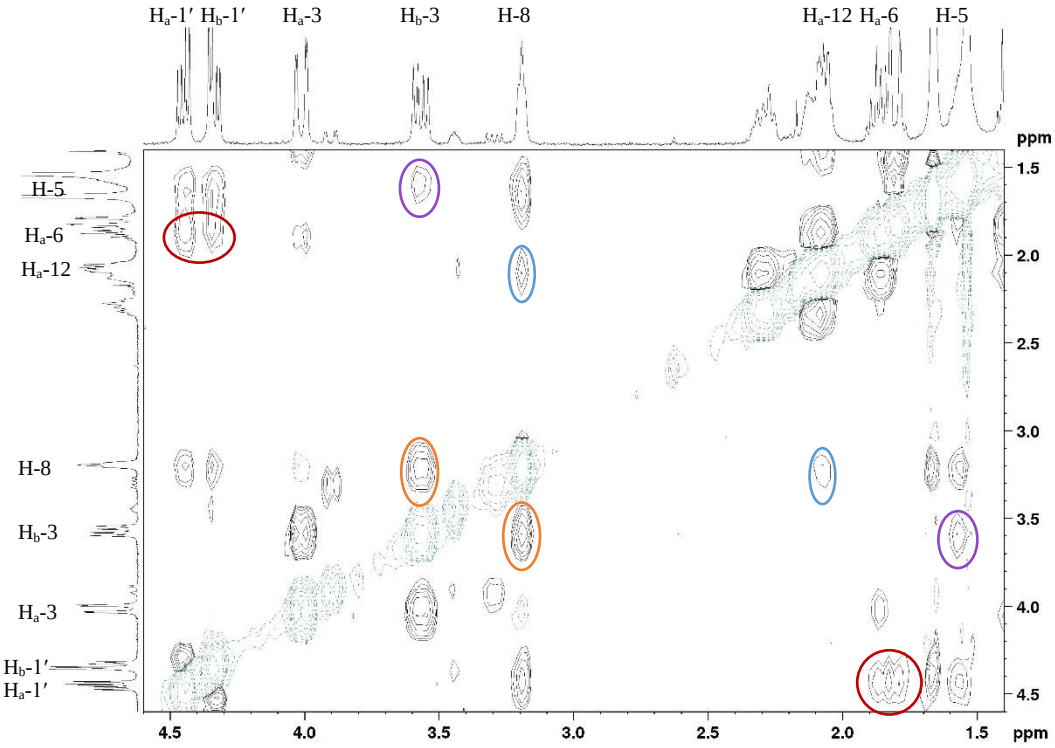
Key NOESY correlations of Cycloadduct (±)-39



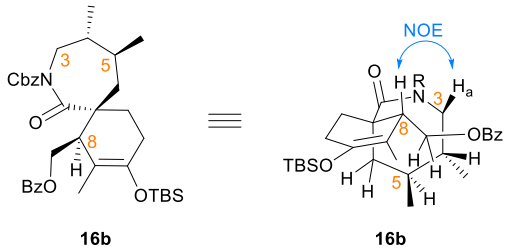


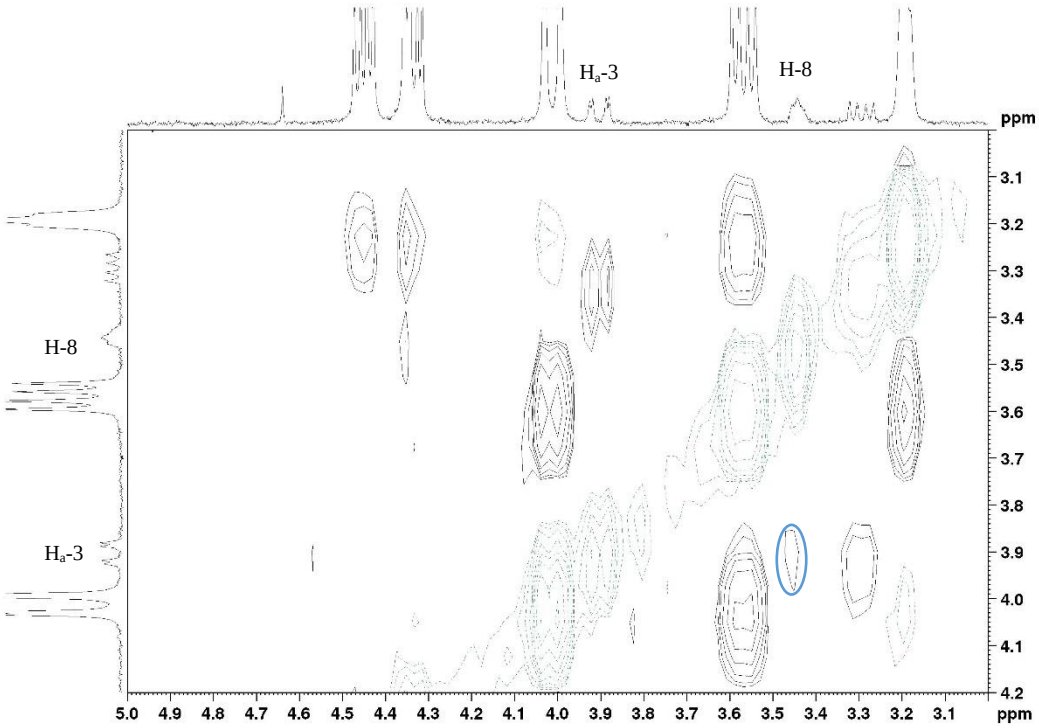
Key NOESY correlations of Cycloadduct 16a





Key NOESY correlations of Cycloadduct 16b





Crystal Structure of Cycloadduct (±)-35 – CCDC 2205771

Crystallisation: Single crystals of cycloadduct (±)-**35** were obtained by slow recrystallisation of a solution of the compound in Pet. Ether:Et_2O (9:1).

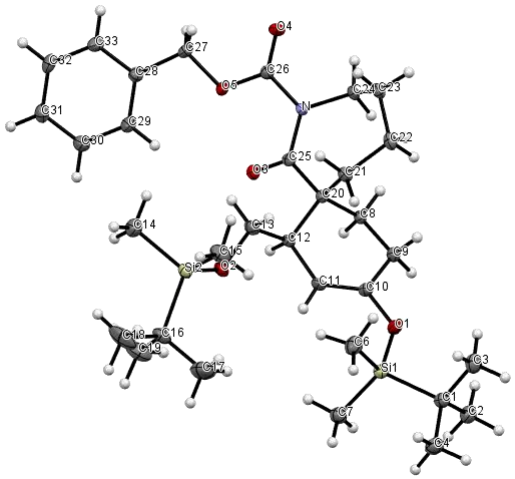


Figure S1. ORTEP diagram drawn with 50% ellipsoid probability of the crystal structure of cycloadduct (±)-**35**

Table S3. Crystal data and structure refinement details for cycloadduct (±)-**35**

Empirical formula	$C_{32}H_{53}NO_5Si_2$
Formula weight	587.93
Temperature (K)	104.3(8)
Wavelength (A)	1.54184
Crystal system	Monoclinic
Space group	P 21
a (Å)	8.01200(10)
b (Å)	11.4236(2)
c (Å)	18.6445(3)
α (°)	90.000
β (°)	101.794(2)
γ (°)	90.000
V ($Å^3$)	1670.43(5)
Z	2
D_c (Mg/m^3)	1.169
F(000)	640
μ (mm^{-1})	1.262
θ_{max} (°)	68.250
Total reflections	21914
Unique reflections	6128
Reflections [$I > 2\sigma(I)$]	6128
Parameters	372
R_{int}	0.0477
Goodness-of-fit on F^2	1.037
R [$F_2 > 2\sigma(F_2)$]	0.0311
wR (F_2, *all data*)	0.0747

References

[1] H. Choi, H. J. Shirley, H. R. M. Aitken, T. Schulte, T. Söhnel, P. A. Hume, M. A. Brimble, D. P. Furkert, *Org. Lett.* **2020**, *22*, 1022–1027.
[2] J. A. Lafontaine, D. P. Provencal, C. Gardelli, J. W. Leahy, *J. Org. Chem.* **2003**, *68*, 4215–4234.
[3] F. Yang, J. J. Newsome, D. P. Curran, *J. Am. Chem. Soc.* **2006**, *128*, 14200–14205.
[4] J. L. Freeman, M. A. Brimble, D. P. Furkert, *Org. Biomol. Chem.* **2019**, *17*, 2705–2714.
[5] Z. Wang, N. Krogsgaard-Larsen, B. Daniels, D. P. Furkert, M. A. Brimble, *J. Org. Chem.* **2016**, *81*, 10366–10375.