# An Organocatalytic Approach to the Core of Eunicellin

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## Supplementary Material

## General Experimental Techniques

$^1$H NMR spectra were recorded on Brucker DRX-400 (400 MHz), DRX-500 (500 MHz) and DRX-700 (700 MHz) spectrometers. Chemical shifts are quoted in ppm relative to tetramethylsilane ($\delta$=0 ppm) and referenced to the solvent residual. For convenience, the following abbreviations are used; s – singlet, d – doublet, t – triplet, q – quartet, qn – quintet, m – multiplet, dd – doublet of doublets etc. Coupling constants (*J*) are given in Hz. Where useful, the FID was zero filled (128 K) and sine-bell shifted (SSB = 30) prior to Fourier Transformation in order to provide baseline resolved multiplets and, as a result, easily identifiable and measurable coupling constants. Two dimensional (2D) spectra were recorded on Bruker DRX-500 (500 MHz) and DRX-400 (400 MHz) spectrometers, fitted with gradient coils. Double Quantum Filtered (DQF) and magnitude COSY spectra were typically acquired with 256 slices in $F_1$ and 2048 in $F_2$ (acquisition time approximately 20 min). 1D nOe spectra were acquired using standard Gauss selective pulses and mixing times ($\tau_m$) of the order of 1.2 s. $^{13}$C NMR spectra were recorded on Bruker DRX-400 (400 MHz) and DRX-500 (500 MHz) spectrometers in the solvent indicated with proton decoupling. Chemical shifts are quoted relative to tetramethylsilane ($\delta$=0 ppm). The attached proton tests (APT) were used to assign signals in particular cases.

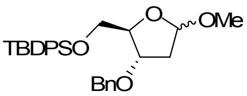
Infrared spectra were recorded on a Perkin-Elmer 1600 FTIR spectrometer or on a Perkin-Elmer Spectrum One ATR-FTIR spectrometer coupled to a universal sampling accessory. The sample was prepared as a thin liquid film, a KBr disc or as a solution in the solvent indicated. Calibration was relative to polystyrene at 1603 $cm^{-1}$.

Mass spectra were carried out at the EPSRC Mass Spectrometry Service Centre, University of Swansea or at the Cambridge University Chemical Laboratory. In Swansea Electron Impact (EI) and Chemical Ionisation (CI) low resolution mass spectra were recorded on a VG model 12-253 under ACE conditions and a Quattro II low resolution triple quadrupole MS. Accurate mass measurements for EI and CI were performed on +VG ZAB-E and Finnigan MAT 900 XLT instruments. In Cambridge, EI and CI, low resolution and accurate mass spectra, were performed on a KRATOS MS-890. Electrospray spectra were determined with an ES Bruker FTICR.

Optical rotations were measured using a Perkin-Elmer 241 polarimeter, in a cell of 1 dm path length. The concentration (c) is expressed in g / 100 $cm^{-3}$ (equivalent to g / 0.1 $dm^{-3}$). Specific rotations denoted as $[\alpha]_D^T$, imply units of dm2$g^{-1}$ (T = temp °C). Non-aqueous reactions were carried out under an atmosphere of dry argon unless indicated to the contrary. Dry THF was distilled from potassium in a recycling still using benzophenone ketyl as indicator. Other dry solvents were purified by standard techniques.[1] Ether refers to diethyl ether. Light petroleum refers to the fraction boiling between 40 °C and 60 °C. Brine refers to a saturated solution of sodium chloride in water. Analytical thin layer chromatography (tlc) was carried out on Merck pre-coated 0.25 mm thick plates of Kieselgel 60 $F_{254}$. Flash chromatography[2] was carried out using Merck Kieselgel 60 (230-400 mesh).

The following compounds were prepared according to literature procedures: the ylid $Ph_3P=C(CH_3)CHO$[3]; the selenoacetal $PhSeCH_2CH(OEt)_2$[4]; the acetals **7**[5]; the imidazolidinones **18**[6]; the platinum(0) catalyst *t*$Bu_3PPt[(CH_2CHSiMe_2)_2O]$.[7]

**(2*R*,3*R*,5*S*)- and (2*R*,3*S*,5*S*)-3-Benzyloxy-2-(*tert*-butyldiphenylsilanyloxymethyl)-5-methoxy-2,3,4,5-tetrahydrofuran 8.**

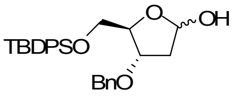


A 60% dispersion of NaH (2.08 g, 52.2 mmol) was washed with hexane (2 × 10 mL), and dried *in vacuo*. THF (300 mL) was added and the resulting suspension cooled to 0 °C. A solution of the furanosides **7** (14.4 g, 37.3 mmol) in THF (50 mL, 5 × 10 mL rinse) was added dropwise, and the reaction stirred at ambient temperature for 1 h. To the solution was added benzyl bromide (5.77 mL, 48.5 mmol) and TBAI (2.75 g, 7.4 mmol). The reaction was stirred at room temperature for 21 h before being quenched by the addition of saturated ammonium chloride (20 mL) and the THF was removed *in vacuo.* Water (150 mL) and ether (150 mL) were. The layers were separated and the aqueous phase was extracted with ether (2 × 150 mL) and the organic extracts were washed with brine (150 mL) The combined organic portions were dried ($MgSO_4$) and solvent was removed *in vacu*o and the resultant pale yellow oil (17.7 g) was used in the next reaction without further purification. For analytical purposes the mixture of anomers could be partially separated by flash chromatography (hexane:ether, 9:1) to furnish the title compounds **8** as clear, colourless oils.

Data for the less polar diastereomer $R_f$ 0.72 (hexane:ether, 1:1); (Found C, 73.0; H, 7.9. $C_{29}H_{36}O_4Si$ requires C, 73.07; H, 7.61%); $[\alpha]_D^{20}$ +56.8 (*c* 0.565 in $CHCl_3$), $R_f$ 0.66 (PE:ether, 3:1); $\nu_{max}$ (film)/cm$^{-1}$ 3080; $\delta_H$(250 MHz; $CDCl_3$) 7.68-7.60 (4H, m, ArH), 7.42-7.28 (11H, m, ArH), 5.08 (1H, dd, *J* 5.3, 1.4, 5-H), 4.56 (1H, d, *J* 12.5, OC*H*HPh), 4.52 (1H, d, *J* 12.5, OCH*H*Ph), 4.22 (1H, q, *J* 4.1, 2-H), 4.10 (1H, ddd, *J* 7.4, 3.4, 2.4, 3-H), 3.72 (1H, dd, *J* 11.4, 4.0, C*H*HOSi), 3.67 (1H, dd, *J* 11.4, 4.4, CH*H*OSi), 3.41 (3H, s, OC3-H), 2.21 (1H, ddd, *J* 14.0, 7.4, 5.3, 4-H), 2.07 (1H, ddd, *J*14.0, 2.4, 1.4, 4-H'), 1.04 [9H, s, (C3-H)$_3$C)Si]; $\delta_H$(100 MHz; $CDCl_3$) 138.2, 135.61, 135.56, 133.3, 129.7, 128.3, 127.7, 127.5, 105.4, 84.2, 78.6, 71.4 ($CH_2$), 64.3, 55.1 ($OCH_3$), 38.9 ($CH_2$), 26.8 [$SiC(CH_3)_3$], 19.2 [$SiC(CH_3)_3$]; *m/z*(CI, $NH_3$) 494 ($[M+NH_4]^+$, 4%), 91 (100); Found $[M+NH_4]^+$ 494.2727. $C_{29}H_{40}NO_4Si$ requires 494.2727.

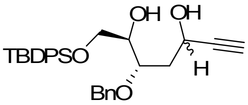
Data for more polar diastereomer R$_f$ 0.66 (hexane:ether, 1:1); $[\alpha]^{16}_{D}$ -39.7 (*c* 0.325 in $CHCl_3$); *R$_f$* 0.64(PE:ether, 3:1); $\delta_H$(250 MHz; $CDCl_3$) 7.72-7.64 (4H, m, ArH), 7.44-7.27 (11H, m, ArH), 5.10 (1H, t, *J* 4.1, 5-H), 4.55 (1H, d, *J* 12.0, OC*H*HPh), 4.48 (1H, d, *J* 12.0, OCH*H*Ph), 4.28-4.16 (2H, m, 2-H, 3-H), 3.74 (1H, dd, *J* 10.9, 5.4, C*H*HOSi), 3.65 (1H, dd, *J* 10.9, 7.1, CH*H*OSi), 3.26 (3H, s, OC3-H), 2.16 (2H, dd, *J* 5.8, 3.8, 4-H, 4-H'), 1.07 [9H, s, (C3-H)$_3$C)Si]; $\delta_C$(62.5 MHz; $CDCl_3$) 138.1, 135.8, 135.6, 133.5, 133.4, 129.7, 129.7, 128.4, 127.7, 127.6, 127.6, 105.5 (C-2), 84.5, 79.9, 71.5, 65.0, 55.0, 39.2, 26.9, 19.2; *m/z*(ES) 494 ($[M+NH_4]^+$, 100%); Found $[M+NH_4]^+$ 494.2731. $C_{29}H_{40}NO_4Si$ requires 494.2727.

**(2*R*,3*R*,5*S*)- and (2*R*,3*S*,5*S*)-3-Benzyloxy-2-(*tert*-butyldiphenylsilanyloxymethyl)-5-hydroxy-2,3,4,5-tetrahydrofurans 9.**[8]



To a mechanically stirred solution of the partially purified furanosides **8** from the previous reaction (17.7 g) in ether (640 mL) was added $BCl_3•SMe_2$ (37.3 mL of a 2.0 mol $dm^{-3}$ solution in $CH_2Cl_2$, 74.6 mmol). After 10 min a saturated aqueous solution of $Na_2CO_3$ (350 mL), and THF (250 mL) were. The resultant mixture was stirred vigorously for 1.5 h. The layers were separated and the aqueous layer was extracted with ether (2 × 200 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$) and the solvent was removed *in vacuo*. Purification by flash chromatography (hexane:ether, 6:4→9:11) yielded the anomeric lactols **9** as a pale yellow oil (13.74 g, 30.9 mmol, 83% from the glycosides **7**) identical to known material;[8] R$_f$ 0.20 (hexane:ether, 3:1); (Found C, 72.7; H, 7.5. $C_{28}H_{34}O_4Si$ requires C, 72.7; H, 7.4%); $[\alpha]^{24}_{D}$ +20.6 (*c* 1.85 in MeOH); *R$_f$* 0.29 and 0.21 (PE:ether, 1:1); $\nu_{max}$ ($CCl_4$)/$cm^{-1}$ 3590, 3520; $\delta_H$(400 MHz; $CDCl_3$) 7.61-7.65 (4H, m, Ar), 7.31-7.43 (11H, m, Ar), 5.54-5.58 (1H, m), 5.43 (1H, dd, *J* 11.0, 4.2, 5-H), 4.61 (1H, d, *J* 11.9, OC*H*HPh), 4.58 (1H, d, *J* 11.9, OCH*H*Ph), 4.43-4.48 (2H, m), 4.29-4.35 (1H, m), 4.16-4.22 (1H, m), 3.78-3.82 (1H, m), 3.59-3.72 (2H, m), 3.45-3.49 (1H, m), 3.28 (1H, d, *J* 7.3), 2.18-2.25 (2H, m), 2.04-2.13 (2H, m), 1.07 [9H, s, C(C$H_3$)$_3$]; $\delta_C$(100 MHz; $CDCl_3$) 137.5, 135.7, 135.6, 135.5, 133.0, 130.0, 129.9, 129.8, 128.54, 128.45, 127.9, 127.79, 127.76, 127.7, 99.5, 99.2, 84.6, 84.0, 80.2, 79.1, 71.5, 71.3, 65.1, 64.1, 41.5, 39.0, 26.9, 26.8, 19.2; *m/z* (CI, $NH_3$) 463 ($[M+H]^+$, 5%), 196 (100); Found $[M+NH_4-H_2O]^+$ 462.2479. $C_{28}H_{36}NO_3Si$ requires 462.2464.

### *(2*R*,3*R*,5*S*)- and (2*R*,3*S*,5*S*)-3-Benzyloxy-1-(*tert*-butyldiphenylsilanyloxy)-hept-6-yne-2,5-diol* **10.**

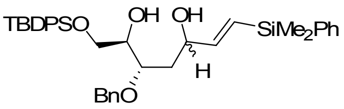


To a stirred solution of lactols **9** (4.3 g, 9.3 mmol) in THF (30 mL) at 0 °C was added ethynylmagnesium bromide (40.9 mL of a 0.5 mol $dm^{-3}$ solution in THF, 20.4 mmol) and the solution was stirred for a further 2 h at 0 °C. The reaction was warmed to RT and additional ethynylmagnesium bromide (9.3 mL, 4.65 mmol) was added. After 1 h, a saturated aqueous solution of $NH_4Cl$ (20 mL) was added and the layers were separated. The aqueous phase was extracted with ether (2 × 20 mL) and the combined organic portions were washed with brine (50 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo*, and purification by flash chromatography (2:1, ether:hexane) furnished the *title compounds* **10** as a white solid (mp 79-82 °C) and a clear colourless oil respectively (3.11 g, 69%).

Data for less polar diastereomer, solid: $R_f$ 0.37 (ether:hexane, 2:1); $[\alpha]_D^{25}$ -43.3 (*c* 0.3 in $CHCl_3$); Found: C, 73.55; H, 7.40; $C_{30}H_{36}O_4Si$ requires C, 73.73; H, 7.43%; $\nu_{max}$ (neat)/$cm^{-1}$ 3310w (OH), 3299m (alkyne H), 2930m, 2858m, 1428s, 1113s; $\delta_H$ (500 MHz, $CDCl_3$) 7.67-7.69 (5H, m, Ar), 7.21-7.47 (10H, m, Ar), 4.64 (1H, m, CHOBn), 4.56 (1H, d, *J* 11, OC*H*HPh), 4.51 (1H, d, *J* 11, OCH*H*Ph), 3.79-3.88 (4H, m, $CH_2OSi$ and 2 × C*H*OH), 3.34 (1H, d, *J* 5.5, OH), 2.79 (1H, d, *J* 3.5, OH), 2.49 (1H, d, *J* 2.2, alkyne-H), 2.01-2.22 (2H, m, 2 × 4-H), 1.09 [9H, s, C($CH_3$)$_3$]; $\delta_C$ (125 MHz, $CDCl_3$) *Note:* the terminal carbon of the acetylene was not visible in the $^{13}C$ NMR spectrum: 137.7, 135.8, 135.5, 132.9, 132.8, 129.9, 128.4, 127.9, 127.8, 127.7, 127.4 (Aromatic), 84.6 (C), 73.1 and 72.9 (CH), 72.1, 64.4 (CH$_2$), 60.0 (CH), 38.4 (CH$_2$), 27.0 (CH$_3$), 19.2 (C); *m*/*z* (CI, NH$_3$) 506 [(M+NH$_4$)$^+$, 100%] and 489 (MH$^+$, 40).

Data for more polar diastereomer, oil: R$_f$ 0.26 (ether:hexane, 2:1); $[\alpha]_D^{25}$ +30.7 (*c* 0.7 in CHCl$_3$); $\nu_{max}$ (neat)/cm$^{-1}$ 3307w, 2931m, 1427s, 1365s, 1217s and 1110s; $\delta_H$ (500 MHz, CDCl$_3$) 7.69-7.75 (5H, m, Ar), 7.30-7.47 (10H, m, Ar), 4.72 (1H, d, *J* 11.7, OC*H*HPh), 4.56 (1H, d, *J* 11.7, OCH*H*Ph), 4.53 (1H, m, CHOBn), 4.19 (1H, m, C*H*OH), 3.47-3.52 (3H, m, CH$_2$OSi and C*H*OH), 2.72 (1H, d, *J* 5, OH), 2.29 (1H, d, *J* 2.2, alkyne-H), 1.94-2.00 (2H, m, 4-H) and 1.10 (9H, s, C(CH$_3$)$_3$]; $\delta_C$ (125 MHz, CDCl$_3$) 137.8, 136.1, 136.0, 135.9, 133.5, 133.0, 130.1, 130.0, 128.5, 128.4, 127.9, 127.8, 127.7 and 127.6 (Ar), 84.4 (C), 82.7 (CH), 72.9 (CH$_2$), 70.8 (CH), 61.5 (CH$_2$), 58.7 (CH), 41.5 (CH$_2$), 27.0 (CH$_3$) and 19.4 (C); *m*/*z* (CI, NH$_3$) 506 [(M+NH$_4$)$^+$, 100%], 489 (MH$^+$, 50), 480 (25) and 474 (19); [*m*/*z* (ES) Found: 506.2727 (M+NH$_4$)$^+$, C$_{30}$H$_{40}$O$_4$NSi requires 506.2721].

### *(2*R*,3*R*,5*S*)- and (2*R*,3*S*,5*S*)-3-Benzyloxy-1-(*tert*-butyldiphenylsilanyloxy)-7-(dimethyl phenylsilanyl)-hept-6-ene-2,5-diols* **11.**



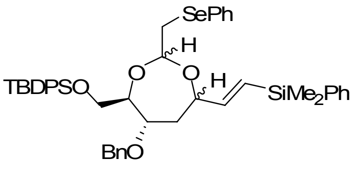
*By the method of Panek:*[9] To a solution of phenyldimethylsilane (34 μL, 0.22 mmol) in THF (0.5 mL) was added *t*Bu$_3$PPt[(CH$_2$CHSiMe$_2$)$_2$O].[7, 10] (4.5 μL of a 0.01 mol dm$^{-3}$ solution in xylenes, 0.005 mmol). A solution of alkynes **11** (50 mg, 0.1 mmol) in THF (2.5 mL) was added dropwise at RT. The reaction was stirred at RT for 3 h after which time, a saturated aqueous solution of NH$_4$Cl (1 mL) was added. The layers were separated and the aqueous phase was extracted with ether (2 × 2 mL). The combined organic portions were washed with brine (2 mL) and dried (MgSO$_4$). The solvent was removed *in vacuo*, and purification by flash chromatography (1:1, ether:hexane) furnished the *title compounds* **11** as clear, colourless oils (60 mg, 97%).

Data for less polar diastereomer: R$_f$ 0.31 (ether:hexane, 2:1); $[\alpha]_D^{25}$ -8.0 (c 1.2 in CHCl$_3$); $\nu_{max}$ (neat)/cm$^{-1}$ 3380w (OH), 2955w, 2858w, 1428s, 1248m, 1112s; $\delta_H$ (400 MHz, CDCl$_3$) 7.18- 7.69 (20H, m, Ar), 6.04-6.10 (1H, dd, *J* 18.6 and 4.4, 6-H), 5.99 (1H, d, *J* 18.6, 7-H), 4.55 (1H, d, *J* 11.5, OC*H*HPh), 4.49 (1H, d, *J* 11.5, OCH*H*Ph), 4.34 (1H, q, *J*

5.8, C*H*OBn), 3.89 (1H, q, *J* 5.4, C*H*OH), 3.75-3.79 (3H, m, C*H*OH and $CH_2OSi$), 3.26 (1H, br. s, OH), 2.76 (1H, br. s, OH), 1.79 (2H, t, *J* 6, 2 × 4-H), 1.07 [9H, s, $C(CH_3)_3$] and 0.33 and 0.32 (2 × 3H, s, 2 × $CH_3Si$); $\delta_C$ (125 MHz, $CDCl_3$) 149.9, 138.5, 137.6, 135.5, 133.8, 132.9, 129.9, 129.8, 128.9, 128.5, 128.0, 127.9, 127.8, 127.7 and 126.7 (Ar), 78.4, 72.9 and 72.1 (CH), 71.9, 64.4 and 36.8 ($CH_2$), 26.9 ($CH_3$), 19.2 (C), -2.6 ($CH_3$); *m*/*z* (ES, MeOH) 624 ($M^+$, 18%), 623 [$(M-H)^+$, 37), 485 (42), 255 (31), 195 (68), 151 (43) and 126 (100%); [*m*/*z* (ES) Found: 642.3449 $(M+NH_4)^+$, $C_{38}H_{52}O_4NSi_2$ requires 642.3429].

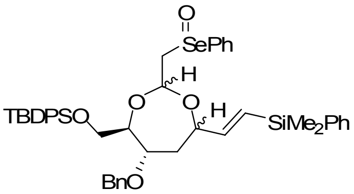
Data for more polar diastereomer: $R_f$ 0.27 (ether:hexane, 2:1); $[\alpha]_D^{25}$ +8.2 (c 0.7 in $CHCl_3$); $\nu_{max}$ (neat)/$cm^{-1}$ 3406w (OH), 2956m, 2858m, 1428s, 1248m, 1112s; $\delta_H$ (500 MHz, $CDCl_3$) 7.69-7.74 (5H, m, Ar), 7.28-7.47 (15H, m, Ar), 5.83 (1H, dd, *J* 18.6 and 4.1, 6-H), 5.75 (1H, d, *J* 18.6, 7-H), 4.77 (1H, d, *J* 11.7, OC*H*HPh), 4.57 (1H, d, *J* 11.7, OCH*H*Ph), 4.28 (1H, m, CHOBn), 4.18 (1H, m, C*H*OH), 3.64-3.74 (3H, m, $CH_2OSi$ and C*H*OH), 2.71 (1H, d, *J* 3.2, OH), 1.91 (1H, br. s, OH), 1.58-1.69 (2H, m, 2 × 4-H), 1.11 [3H, s, $C(CH_3)_3$] and 0.30 (2 × 3H, s, 2 × $CH_3Si$); $\delta_C$ (125 MHz, $CDCl_3$) 149.8, 136.2, 136.1, 136.0, 135.9, 135.7, 133.8, 133.7, 129.9, 128.9, 128.5, 127.9, 127.8, 127.7, 126.2 (Aromatic), 82.8 (CH), 73.0 ($CH_2$), 71.3 and 69.7 (CH), 61.6 and 40.3 ($CH_2$), 27.0 ($CH_3$), 19.3 (C), -2.7 and -2.6 ($CH_3$); *m*/*z* (CI, $NH_3$) 642 [$(M+NH_4)^+$, 35%), 625 ($MH^+$, 40), 624 ($M^+$, 68), 607 (87) and 341 (100); [*m*/*z* (ES) Found: 642.3429 $(M+NH_4)^+$, $C_{38}H_{52}O_4NSi_2$ requires 642.3429].

### *(*2R,4R*)-5-Benzyloxy-4-(*tert*-butyldiphenylsilanyloxymethyl)-7-[2-(dimethylphenylsilanyl)-vinyl]-2-phenylselanylmethyl-[1,3]-dioxepanes* **12.**



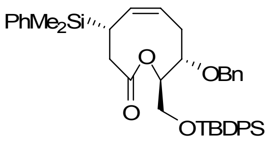
To a stirred solution of diols **11** (250 mg, 0.40 mmol) in toluene (20 mL) was added PPTS (5 mg, 0.02 mmol, 5 mol %) and 2-phenylselanyl acetaldehyde diethylacetal[4] (131 mg, 0.48 mmol). The reaction mixture was heated to reflux under Dean-Stark conditions for 1.5 h. After being allowed to cool to ambient temperature, the mixture was quenched by the addition of water (5 mL). The layers were separated and the aqueous phase extracted with ether (2 × 10 mL). Finally, the organic portions were washed with brine (15 mL) and dried ($MgSO_4$), and the solvent was removed *in vacuo*. The resulting brown oil was purified by flash chromatography (10:1, hexane:ether) to furnish an inseparable mixture of a number of diastereomers of the title compounds **12** as a pale yellow oil (230 mg, 71%) which was used in the next reaction without further characterisation; $R_f$ 0.44 (hexane:ether, 10:1); [*m/z* (ES) Found: 824.3062 $(M+NH_4)^+$, $C_{46}H_{58}O_4NSeSi_2$ requires 824.3064].

### *(2R,4R)-5-Benzyloxy-4-(tert-butyldiphenylsilanyloxymethyl)-7-[2-(dimethylphenylsilanyl)-vinyl]-2-phenylselanyloxy methyl-[1,3]dioxepanes*



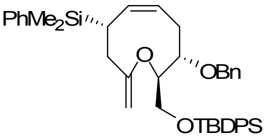
The selenoacetals **12** (2.69g, 3.34 mmol) were dissolved in $CH_2Cl_2$ (50 mL) and MeOH (200 mL). Water (50 mL) was added until the material began to precipitate. To this cloudy mixture was added $NaHCO_3$ (340 mg, 4.01 mmol) and $NaIO_4$ (2.15 g, 10.01 mmol) thus forming a cream/white suspension. After 3 h, the reaction was quenched by the addition of water (50 mL). The organic phase was isolated and the aqueous phase extracted with $CH_2Cl_2$ (4 × 40 mL). The combined organic portions were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the title selenoxides (2.64 g, 96%) which were used in the next reaction without further purfication. TLC showed only base-line material (hexane:ether, 10:1).

### *(4S,5Z,8S,9R)-8-Benzyloxy-9-(tert-butyldiphenylsilanyloxymethyl)-4-(dimethylphenylsilanyl)-4,7,8,9-tetrahydro-3H-oxonin-2-one* **4.**



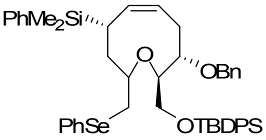
To a stirred solution of the selenoxides prepared above (214 mg, 0.26 mmol) in toluene (25 mL) was added DBU (0.1 mL, 0.78 mmol), and the reaction was heated to reflux under Dean-Stark conditions for 19 h. After being allowed to cool to ambient temperature, the solvent was removed *in vacuo* and the material purified by flash chromatography (hexane:ether, 10:1). The lactone **4** was isolated as a clear, colourless oil (105 mg, 62%); R$_f$ 0.22 (hexane:ether, 10:1); $[\alpha]_D^{25}$ +22.9 (*c* 5.1 in CHCl$_3$); $\nu_{max}$ (neat)/cm$^{-1}$ 3049w, 2956m, 2857m, 1739s (C=O), 1428s, 1269m, 1249m, 1230m; $\delta_H$ (500 MHz, CDCl$_3$) 7.27-7.64 (20H, m, Ar), 5.74 (1H, dt, *J* 11.4 and 4.7, 6-H), 5.50 (1H, t, *J* 11.4, 5-H), 4.65 (1H, d, *J* 11.7, OCH*H*Ph), 4.63 (1H, m, 9-H), 4.42 (1H, d, *J*, 11.7, OC*H*HPh), 4.14 (1H, m, CHOBn), 3.85 (2H, m, CH$_2$OSi), 2.66-2.71 (2H, m, 2 × 3-H), 2.46-2.50 (1H, dd, *J* 13.8 and 5.7, 7-H), 2.37 (1H, m, 4-H), 2.15 (1H, t, *J* 13.8, 7-H), 1.05 [9H, s, C(CH$_3$)$_3$], 0.35 and 0.33 (2 × 3H, s, 2 × CH$_3$Si); $\delta_C$ (125 MHz, CDCl$_3$) 173.9 (C=O), 136.7, 135.8, 135.7, 135.6, 134.9, 133.9, 130.9, 129.6, 129.5, 129.4, 128.3, 127.9, 127.8, 127.7, 127.6, 127.5, 126.6 (Aromatic), 78.4, 76.8 and 76.5 (CH), 71.2 and 64.1 (CH$_2$), 35.2 (CH$_2$), 26.9 (CH$_2$), 26.8 (CH$_3$), 24.1 (CH), 19.3 (C), -4.6 and -5.3 (CH$_3$); *m/z* (CI, NH$_3$) 666 [(M+NH$_4$)$^+$, 100%] and 649 (MH$^+$, 87); [*m/z* (ES) Found: 666.3445 (M+NH$_4$)$^+$, C$_{40}$H$_{52}$O$_4$NSi$_2$ requires 666.3429].

***(2*R*,3*S*,5*Z*,7*S*)-3-Benzyloxy-2-(*tert*-butyldiphenylsilanyloxymethyl)-7-(dimethylphenylsilanyl)-9-methylene-2,3,4,7,8,9-hexahydrooxonine* 13.**



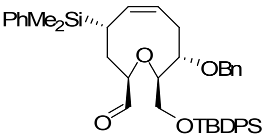
A solution of lactone **4** (350 mg, 0.54 mmol) and DMAP (76 mg, 0.7 mmol) in THF (5 mL) was freeze-thaw degassed three times. The solution was cooled to -40 °C and Tebbe reagent (1.19 mL of a 0.5 mol dm$^{-3}$ solution, 0.59 mmol) was added dropwise. The solution was stirred at -40 °C for 0.5 h before being warmed to RT over 0.5 h. The reaction was re-cooled to -10 °C and a saturated aqueous solution of NaOH was added dropwise until effervescence ceased. The reaction was warmed to RT and then the diluted with ether (20 mL) before being filtered through Celite™. The solution was dried (MgSO$_4$) and the solvent removed *in vacuo*. The crude material was purified by flash chromatography (Brockmann grade II-III alumina deactivated with 6% *w*/*w* H$_2$O, with a layer of HYFLO at the top, 10:1, hexane:ether) to yield the title compound **13** as a clear colourless oil (277 mg, 79%); R*f* 0.64 (10:1, hexane:ether); *m/z* (CI, $NH_3$) 647 [$(M+H)^+$, 100%], 646 ($M^+$, 5%); [*m/z* (ES) Found: $(M+H)^+$, 647.3376. $C_{41}H_{51}O_3Si_2$ requires 647.3371]. Full characterisation was not possible due to the instability of this material.

***(2*R*,3*S*,5Z,7*S*)-3-Benzyloxy-2-(*tert*-butyldiphenylsilanyloxymethyl)-7-(dimethylphenylsilanyl)-9-phenylselanylmethyl-2,3,4,7,8,9-hexahydro-oxonine* 14.**



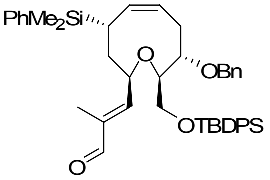
A solution of phenylselenenyl chloride (163 mg, 0.83 mmol) in THF (2 mL) was added dropwise to a stirred solution of enol ether **13** (210 mg, 0.33 mmol) in THF (3 mL) at -78 °C. After the addition was complete, the solution was stirred for a further 1 min, before the dropwise addition of $LiAlH_4$ (0.85 mL of a 1 mol $dm^{-3}$ solution in THF, 0.85 mmol) over 5 min. After 25 min at -78 °C, the reaction was allowed to warm to ambient temperature over 1.5 h, before being quenched by the addition of saturated $NH_4Cl$ (2 mL) and water (5 mL). The layers were separated, and the aqueous phase was extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). Purification by flash chromatography (Brockmann grade II-III alumina deactivated with 6% *w*/*w* $H_2O$, with a layer of HYFLO at the top, 100% hexane) furnished the selenide **14** as a colourless oil (145 mg, 54%); R*f* 0.41 (hexane:ether, 3:1); Found: C, 70.10; H, 6.97%; $C_{47}H_{56}O_3SeSi_2$ requires C, 70.21; H, 7.02%; *m/z* (CI, $NH_3$) 822 [$(M+NH_4)^+$, 72%], 805 [$(M+H)^+$, 53%], 727 (100); [*m/z* (ES) Found: $(M+NH_4)^+$, 822.3270. $C_{47}H_{60}NO_3SeSi_2$ requires 822.3271]. Full characterisation was not possible due to the instability of this material in solution in a number of solvents.

### *(2*R*,4*S*,5Z,8*S*,9*R*)-8-Benzyloxy-9-(*tert*-butyl-diphenyl-silanyloxymethyl)-4-(dimethyl-phenyl-silanyl)-2,3,4,7,8,9-hexahydro-oxonine-2-carbaldehyde* **15.**



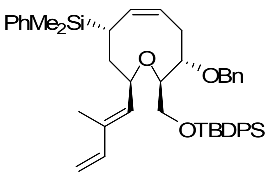
To a stirred solution of selenide **14** (100 mg, 0.12 mmol) in $CH_2Cl_2$ (4 mL) and MeOH (8.5 mL) was added water (1.5 mL) dropwise until precipitation was observed. $NaHCO_3$ (13 mg, 0.16 mmol) and $NaIO_4$ (77 mg, 0.36 mmol) were added and the cloudy suspension was stirred for 2 h. After this time, the layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (2 × 10 mL), dried ($MgSO_4$), and the solvent was removed *in vacuo*. The selenoxides were dried under high vacuum for 1 h and then re-dissolved in THF (5 mL) and cooled to -78 °C. NaOAc (30 mg, 0.36 mmol) and $Ac_2O$ (55 μL, 0.6 mmol) were added and the reaction was stirred for 5 min at -78 °C before being warmed to RT over 0.5 h. The reaction was heated to reflux for 1.5 h and then cooled to RT before being quenched by the addition of water (5 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic portions were washed with brine (10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude material was dissolved in MeOH (2 mL) and $CH_2Cl_2$ (1 mL) and $K_2CO_3$ (100 mg) was added. The reaction was stirred for 18 h at RT and then filtered through Celite™. The solvent was removed *in vacuo* and the crude material was purified by flash chromatography (25% ether:hexane) to furnish the title compound **15** as a clear colourless oil (60 mg, 75%); $R_f$ 0.17 (hexane:ether, 3:1); $[\alpha]_D^{25}$ +83.3 (*c* 1.0 in $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2930m, 2857m, 1729s (C=O), 1474m, 1428s, 1112s and 1071s; $\delta_H$ (500 MHz; $CDCl_3$) 9.85 (1H, d, *J* 1.9, CHO), 7.61-7.68 (5H, m, Ar), 7.49-7.53 (2H, m, Ar), 7.20-7.46 (11H, m, Ar), 7.04-7.09 (2H, m, Ar), 5.77 (1H, dt, *J* 11.4 and 5, 6-H), 5.52 (1H, t, *J* 11.4, 5-H), 4.56 (1H, d, *J* 11.4, OC*H*HPh), 4.23 (1H, d, *J* 11.4, OCH*H*Ph), 3.54 (1H, dt, *J* 9.1, 3.0), 3.48 (1H, ddd, *J* 8.8, 7.5, 1.9), 3.69-3.81 (3H, m), 2.85 (1H, dt, *J* 3.5, 11.9, 7-H), 2.52 (1H, m, 4-H), 2.32 (1H, dt, *J* 13.9 and 3.5, 7-H), 1.72 (2H, t, *J* 9.1, 2 × 3-H), 1.09 [9H, s, $C(CH_3)_3$], 0.32 and 0.31 (2 × 3H, s, 2 × $CH_3Si$); $\delta_C$ (125 MHz; $CDCl_3$) 206.2 (CHO), 126.7-137.8 (Ar), 88.0 and 87.4 (CH), 78.8 (CH), 71.1 and 66.6 ($CH_2$), 29.8 ($CH_2$), 26.7 ($CH_3$), 26.1 ($CH_2$), 21.9 (CH), 19.0 (C), -4.55 and -4.96 [$(CH_3)_2Si$]; *m/z* (ES-) 661 [$(M-H)^+$, 25%], 589 [M-$(CH_3)_3Si$, 32] and 481 (100); [*m/z* (ES) Found: $(M+H)^+$, 663.3322. $C_{41}H_{51}O_4Si_2$ requires 663.3320].

### *(2***R***,4***S***,5Z,8***S***,9***R***)-2-((E)-2'-Carbaldehyde-propenyl)-8-benzyloxy-9-(1,1-dimethyl) ethyldiphenylsilanyloxymethyl-2,3,4,7,8,9-hexahydro-oxonine*



A solution of aldehyde **15** (40 mg, 0.06 mmol) in toluene (5 mL) was added to a stirred suspension of 2-(triphenylphosphoranylidene)propionaldehyde (58 mg, 0.18 mmol) in toluene (5 mL), and the mixture was heated to reflux. After 21 h, the orange reaction mixture was allowed to cool to ambient temperature before being filtered through a plug of silica, which was then flushed with $CH_2Cl_2$ (10 mL). The solvent was removed *in vacuo*. Purification by flash chromatography ($CH_2Cl_2$:ether, 2:1) yielded the title compound as a clear, colourless oil (29 mg, 67%); $R_f$ 0.32 ($CH_2Cl_2$:hexane, 2:1); $[\alpha]_D^{25}$ +18.7 (*c* 0.8 in $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2930s, 2857m, 2326m, 1692s, 1428s, 1113s and 823m; $\delta_H$ (400 MHz; $CDCl_3$) 9.04 (1H, s, CHO), 7.58-7.65 (5H, m, Ar), 7.46-7.52 (2H, m, Ar), 7.17-7.43 (13H, m, Ar), 6.25 [1H, dd, *J* 8 and 1.4, C*H*=C($CH_3$)], 5.76 (1H, dt, *J* 10.8 and 5.4, 6-H), 5.50 (1H, t, *J* 10.8, 5-H), 4.62 (1H, d, *J* 11.3, OC*H*HPh), 4.36 (1H, d, *J* 11.3, OCH*H*Ph), 4.31 (1H, m, 2-H), 3.88 (1H, dt, *J* 7.1, 3.3, 8-H) 3.74 (1H, dd, *J* 10.9 and 4.5, CH*H*OSi), 3.65 (1H, dd, *J* 10.9 and 2.8, C*H*HOSi), 3.25 (1H, m, 9-H), 2.86 (1H, dt, *J* 3, 11.7, 7-H), 2.62 (1H, ddd, *J* 11.8 and 4.7, 7-H'), 2.34 (1H, dt, *J* 13.9 and 4.7, 4-H), 1.60 (1H, m, 3-H), 1.55 (3H, s, $CH_3$), 1.44, (1H, m, 3-H'), 1.01 [9H, s, $C(CH_3)_3$], 0.30 and 0.28 (2 × 3H, s, 2 × $CH_3Si$); $\delta_C$ (125 MHz; $CDCl_3$) 194.9 (CHO), 155.9 (CH), 137.4 (CH, 136.8, 135.7, 135.6, 133.9, 133.4, 133.3, 131.3, 129.6, 129.1, 128.3, 128.3, 128.2, 127.8, 127.7, 127.6, 127.5 and 126.9 (Ar and olefinic), 84.4, 78.8 and 78.5 (CH), 71.5, 65.2 ($CH_2$), 32.7 ($CH_2$), 29.7 ($CH_2$), 27.0 ($CH_3$), 21.9 (CH), 19.2 (C), 9.3 ($CH_3$), -4.5 and -5.1 [$(CH_3)_2Si$]; *m/z* (CI, $NH_3$) 703 [$(M+H)^+$, 100%], 701 (55) and 625 (90); [*m/z* (ES) Found: $(M+NH_4)^+$, 720.3900. $C_{44}H_{58}O_4NSi_2$ requires 720.3899].

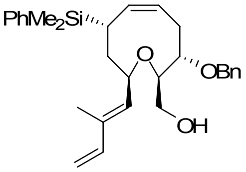
### *(2*R*,4*S*,8*S*,9*R*,*Z*)-8-(Benzyloxy)-9-[(*tert*-butyldiphenylsilyloxy)methyl]-4-(dimethylphenylsilyl)-2-[(*E*)-2-methylbuta-1,3-dienyl]-2,3,4,7,8,9-hexahydrooxonine* **16.**



To a stirred suspension of methyltriphenylphosphonium bromide (221 mg, 0.60 mmol) in THF (7 mL) at -78 °C, was added *n*-butyllithium (0.38 mL of a 1.6 mol dm$^{-3}$ solution in hexanes, 0.60 mmol) dropwise over a period of 5 min. After 3 min, the reaction was allowed to warm to ambient temperature. After a further 1 h, the mixture was cooled to -78 °C, and after 5 min, a solution of the α,β-unsaturated aldehyde prepared above (220 mg, 0.30 mmol) in THF (4 mL) was added dropwise over 5 min. After 45 min, the reaction was quenched by the addition of saturated aqueous $NH_4Cl$ (10 mL), the layers were separated, and the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic portions were washed with brine (10 mL) and dried ($MgSO_4$). No purification was required, and the product **16** was isolated as a clear, colourless oil (179 mg, 81%); R$_f$ 0.4 (hexane:$CH_2Cl_2$, 1:1); $[\alpha]^{25}_{D}$ +32.5 (*c* 0.8 in $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/cm$^{-1}$ 3070w, 2929, 1428s, 1248m and 1112s; $\delta_H$ (500 MHz; $CDCl_3$) 7.63-7.73 (5H, m, Ar), 7.48-7.56 (2H, m, Ar), 7.20-7.44 (12H, m, Ar), 6.20 (1H, dd, *J* 17.4 and 10.6, C*H*=CH$_2$), 5.75 (1H, dt, *J* 11.3 and 5.4, 5-H), 5.51 (1H, t, *J* 11.3, 6-H), 5.39 (1H, d, *J* 8.4, C*H*=CMe), 5.07 (1H, d, *J* 17.4, MeCH=H*H*$_{trans}$), 4.95 (1H, d, *J* 10.6, MeCH=H*H*$_{cis}$), 4.63 (1H, d, *J* 11.5, OC*H*HPh), 4.40 (1H, d, *J* 11.5, OCH*H*Ph), 4.22 (1H, dt, *J* 4.5 and 10.2, 2-H), 4.00 (1H, m, 8-H), 3.75 (1H, dd, *J* 10.8 and 3.8, CH*H*OSi), 3.70 (1H, dd, *J* 10.8 and 3.2, C*H*HOSi), 3.29 (1H, m, 9-H), 2.88 (1H, ddd, *J* 13.6, 11.5 and 2.3, 7-H), 2.65 (1H, dt, *J* 4.7 and 11.9, 4-H), 2.33 (1H, dt, *J* 4.7 and 13.6, 7-H), 1.65 (1H, m, 3-H), 1.58 (3H, s, $CH_3$), 1.42 (1H, dt, *J* 4.5 and 14.1, 3-H), 1.05 [9H, s, C($CH_3$)$_3$] and 0.30 (6H, s, 2 × $CH_3$Si); $\delta_C$ (125 MHz; $CDCl_3$) 141.1, 137.9, 135.8, 135.6, 135.5, 135.4, 134.0, 133.7, 133.0, 131.6, 129.5, 129.4, 128.9, 128.3, 127.6, 127.5, 127.4, 127.3 and 126.7 (Ar and olefinic), 111.9 ($CH_2$), 83.3, 79.2 and 78.1 (CH), 71.4 and 64.8 ($CH_2$), 33.9 ($CH_2$), 29.7 ($CH_2$), 26.9 ($CH_3$), 22.1 (CH), 19.3 (C), 12.0 ($CH_3$), -4.5 and -4.7 ($CH_3$Si); *m/z* (CI, $NH_3$)

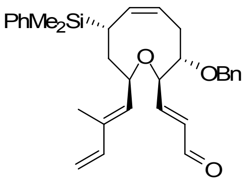
719 [$(MH+NH_4)^+$, 80%], 718 [$(M+NH_4)^+$, 100] and 701 ($MH^+$, 65); [*m/z* (ES) Found: $(M+NH_4)^+$, 718.4105. $C_{45}H_{60}O_3NSi_2$ requires 718.4106].

***(2*R*,4*S*,8*S*,9*R*,Z)-8-(Benzyloxy)-4-(dimethylphenylsilyl)-9-hydroxymethyl-2-[(*E*)-2-methylbuta-1,3-dienyl]-2,3,4,7,8,9-hexahydrooxonine* 17.**



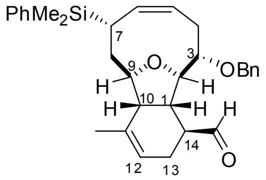
HF•pyridine (0.7 mL) was added dropwise to a solution of silyl ether **16** (320 mg, 0.46 mmol) in THF (3 mL) and pyridine (0.5mL) at RT. The reaction was stirred for 3 h after which time a saturated aqueous solution of $NaHCO_3$ was added cautiously until effervescence ceased. The mixture was extracted with ether (3 × 10 mL) and the combined organic portions were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography furnished the title compound **17** as a clear, colourless oil (198 mg, 93%); $R_f$ 0.2 (hexane:ether, 1:1); $[\alpha]_D^{25}$ +51.4 (*c* 0.7 in $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/cm$^{-1}$ 3468m (OH), 2919m, 1427m, 1248s and 1107s; $\delta_H$ (500 MHz; $CDCl_3$) 7.47-7.51 (2H, m, Ar), 7.26-7.36 (8H, m, Ar), 6.29 (1H, dd, *J* 17.4 and 10.6, C*H*=$CH_2$), 5.76 (1H, dt, *J* 11.1 and 5.2, 6-H), 5.52 (1H, t, *J* 11.1, 5-H), 5.40 (1H, d, *J* 8.8, C*H*=CMe), 5.16 (1H, d, *J* 17.4, MeC=CH$H_{trans}$), 5.03 (1H, d, *J* 10.6, MeC=CH$H_{cis}$), 4.67 (1H, d, *J* 11.2, OCH*H*Ph), 4.43 (1H, d, *J* 11.2, OC*H*HPh), 4.12 (1H, ddd, *J* 10.8, 8.9 and 4.6, H2), 3.74 (1H, dt, *J* 3.1 and 8.6, 8-H), 3.60 (1H, br. d, *J* 11.3, C*H*HOH), 3.52 (1H, br d, *J* 11.3, CH*H*OH), 3.22 (1H, dt, *J* 3.8 and 8.6, 9-H), 2.83 (1H, m, 7-H), 2.59 (1H, ddd, *J* 12.2 and 5.2, 7-H), 2.33 (1H, dt, *J* 13.0 and 4.0, 4-H), 1.86 (1H, br s, OH), 1.69 (3H, d, *J* 1.2, $CH_3$), 1.56 (1H, m, 3-H), 1.46 (1H, m, 3-H), 0.31 and 0.30 (2 × 3H, s, 2 × $CH_3Si$); $\delta_C$ (125 MHz; $CDCl_3$) 140.7, 138.1, 137.6, 134.5, 134.0, 133.9, 131.8, 129.0, 128.4, 127.9, 127.7, 127.6 and 126.3 (Ar and olefinic), 113.3 ($CH_2$), 84.7, 79.8 and 79.4 (CH), 71.5, 63.6, 34.2 and 26.5 ($CH_2$), 22.7 (CH), 12.1 ($CH_3$), -4.5 and -4.9 ($CH_3Si$); *m/z* (CI, $NH_3$) 719 [$(MH+NH_4)^+$, 80%], 718 [$(M+NH_4)^+$, 100] and 701 ($MH^+$, 65); [*m/z* (ES) Found: $(M+NH_4)^+$, 480.2930. $C_{29}H_{42}O_3NSi$ requires 480.2928].

### *(2*R*,4*S*,8*S*,9*R*,Z)-8-(Benzyloxy)-9-[(E)2-carbaldehyde-ethenyl)]-4-(dimethylphenylsilyl)-2-[(*E*)-2-methylbuta-1,3-dienyl]-2,3,4,7,8,9-hexahydrooxonine* 3



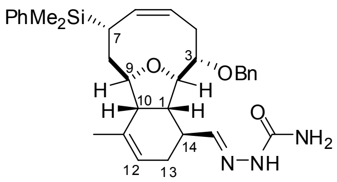
A flask was charged with DMSO (12.8 µL, 0.18 mmol) in $CH_2Cl_2$ (1 mL) and cooled to -78 °C. To this was added $(COCl)_2$ (12.2 µL, 0.14 mmol) dropwise, and the reaction stirred for 0.5 h at -78 °C. A solution of alcohol **17** (40 mg, 0.09 mmol) in $CH_2Cl_2$ (1 mL) was added dropwise and the solution stirred for 45 minutes at -78 °C. $Et_3N$ (63 µL, 0.45 mmol) was added and the reaction was stirred at -78 °C for 15 minutes before being warmed to RT over 1 h. The reaction was cooled to 0 °C and a solution of (triphenylphosphoranyliden)-acetaldehyde (104 mg, 0.27 mmol) in $CH_2Cl_2$ (1 mL) was added dropwise. The reaction was stirred at RT for 24 h before being quenched by the addition of a saturated aqueous solution of $NH_4Cl$ (5 mL), extracted with ether (3 × 10 mL) and dried ($MgSO_4$). The solution was concentrated under reduced pressure to yield the crude aldehyde, which was purified by flash chromatography (hexane:ether, 5:1). Aldehyde **3** was isolated as a colourless oil (37 mg, 84% from **17**); $R_f$ 0.18 (hexane:ether, 5:1); $[\alpha]_D^{25}$ +44.3 (*c* 1.9 in $CHCl_3$); $\nu_{max}/cm^{-1}$ (thin film) 2971m, 1691s (C=O), 1249m and 1106s; $\delta_H$ (500 MHz; $CDCl_3$) 9.41 (1H, d, *J* 7.9, CHO), 7.50-7.53 (2H, m, Ar), 7.29-7.38 (8H, m, Ar), 6.80 (1H, dd, *J* 15.7 and 4.3, C*H*=CHCHO), 6.26 (1H, dd, *J* 17.3 and 10.8, C*H*=$CH_2$), 6.25 (1H, ddd, *J* 15.7, 7.9 and 1.6, C*H*CHO), 5.78 (1H, td, *J* 11.0 and 5.2, 5-H), 5.60 (1H, t, *J* 11.0, 6-H), 5.39 (1H, d, *J* 9.1, C*H*=CMe), 5.12 (1H, d, *J* 17.3, $CHH_{trans}$), 5.01 (1H, d, *J* 10.8, $CHH_{cis}$), 4.70 (1H, d, *J* 11.6, OCH*H*Ph), 4.41 (1H, d, *J* 11.6, OC*H*HPh), 4.09 (1H, ddd, *J* 14.7, 9.2 and 4.7, H2), 3.86 (1H, ddd, *J* 8.9, 4.3 and 1.6, 9-H), 3.60 (1H, dt, *J* 8.9 and 3.1, 8-H), 2.94 (1H, ddd, *J* 14.1, 11.6 and 3.5, 7-H), 2.59 (1H, dt, *J* 12.1 and 5.2, 4-H), 2.37 (1H, ddd, *J* 14.1, 4.9 and 2.6, 7-H), 1.67 (1H, ddd, *J* 15.4, 10.2 and 5.2, 3-H), 1.62 (3H, s, $CH_3$), 1.51 (1H, ddd, *J* 14.1, 12.1 and 4.6, 3-H), 0.31 and 0.31 (2 × 3H, s, 2 × $CH_3Si$); $\delta_C$ (125 MHz; $CDCl_3$) 193.6 and 157.8 (C), 140.6 (CH), 137.7 and 137.4 and 134.2 (C), 134.0, 133.1, 133.0, 131.2, 129.1, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7 and 125.3 (CH), 113.2 ($CH_2$), 82.6, 82.3 and 80.2 (CH), 71.6, 34.1 and 26.6 ($CH_2$), 22.6, 12.1 ($CH_3$), -4.6 and -4.9 ($CH_3Si$); *m/z* (ES) 509 [$(M+Na)^+$, 15%], 478 (100) and 438 (30); [*m/z* (ES) Found: $(M+Na)^+$, 509.2498. $C_{31}H_{38}O_3NaSi$ requires 509.2488].

### ***(1S,2R,3S,5Z,7S,9R,10R,11Z,14S)-3-(Benzyloxy)-7-dimethyl(phenyl)silyl-14-formyl-cladiella-5(6),11(12)-diene exo-2.***



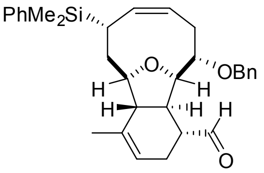
To a stirred solution of **(*S*)-18** (0.3 mg, 0.001 mmol) in MeCN/$H_2O$ (1 mL, 95/5 *v*/*v*) was added the α,β-unsaturated aldehyde **3** (10 mg, 0.02 mmol). The reaction was stirred for 16 h after which time it was diluted by the addition of ether (5 mL), washed with $H_2O$ (5 mL) and brine (5 mL). The organic portion was dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography ($CH_2Cl_2$) yielded the title cycloadduct ***exo*-2** (6.0 mg, 62%) as a single diastereoisomer; R*f* 0.33 ($CH_2Cl_2$); $[\alpha]_D^{25}$ +45.0 (*c* 0.45 in $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2918s, 2850s, 1723m (C=O), 1427m 1248m, and 1067s; $\delta_H$ (500 MHz; $CDCl_3$) 9.65 (1H, s, CHO), 7.51-7.57 (2H, m, Ar), 7.31-7.42 (8H, m, Ar), 5.74 (1H, dt, *J* 10.8 and 5.8, 5-H), 5.59 (1H, t, *J* 10.8, 6-H), 5.41 (1H, br, 12-H), 4.67 (1H, d, *J* 12.5, OCH*H*Ph), 4.60 (1H, d, *J* 12.5, OC*H*HPh), 4.23 (1H, br dd, *J* 4.2 and 1.7, 2-H), 4.15 (1H, br t, *J* 4.8, 9-H), 3.48 (1H, d, *J* 6.8, 3-H), 2.72 (1H, dd, *J* 14.6 and 9.8, 4-H), 2.62 (1H, m, 10-H), 2.30-2.43 (4H, m, 1-H, 4-H', 13-H and 14-H), 2.29 (1H, t, *J* 11.4, 7-H), 2.09 (1H, m, 13-H'), 1.92 (1H, ddd, *J* 14.8, 11.5 and 4.4, 8-H), 1.47 (1H, d, *J* 14.7, 8-H'), 1.25 (3H, s, $CH_3$), 0.34 and 0.30 (2 × 3H, s, 2 × $CH_3Si$); $\delta_C$ (125 MHz; $CDCl_3$) 203.6 (C=O), 138.7, 137.7 and 135.0 (C), 134.0, 132.5, 129.1, 128.2, 127.8, 127.7, 127.6, 127.4, 125.5, 119.2 (CH, Ar and olefinic), 87.1 and 86.1 (CH), 76.9 (CH), 70.6 ($CH_2$), 48.1, 43.8 and 40.8 (CH), 31.5, 25.9 and 23.1 ($CH_2$), 22.2 and 20.9 (CH or $CH_3$), -4.40 and -6.11 ($CH_3Si$); *m/z* (ES) 509 [$(M+Na)^+$, 25%], 504 [$(M+NH_4)^+$, 100], 487 [$(M+H)^+$, 10] and 143 (35); [*m/z* (ES) Found: $(M+H)^+$, 487.2668. $C_{31}H_{39}O_3Si$ requires 487.2668].

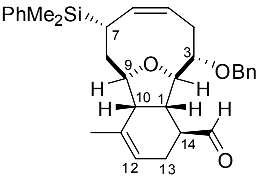
### ***(1*S*,2*R*,3*S*,5*Z*,7*S*,9*R*,10*R*,11*Z*,14*S*)-3-(Benzyloxy)-7-dimethyl(phenyl)silyl-cladiella-5(6),11(12)-diene-(E)-semicarbazide 19.***



To a solution of aldehyde ***exo*-2** (2 mg, 0.004 mmol) in MeOH (0.5 mL) and pyridine (2 drops) was added semicarbazide hydrochloride (0.4 mg, 0.004 mmol). The mixture was heated to 60 °C for 10 minutes and then stirred at RT for an additional 16 h. The solvent was removed *in vacuo* to yield a white residue. EtOAc (1 mL) was added and the mixture was filtered through a plug of silica (eluting with EtOAc). The product **19** was isolated as clear oil (2 mg, 90%) which solidified under reduced pressure; R$_f$ 0.45 (EtOAc); $[\alpha]_D^{25}$ +19.5 (*c* 0.1 in $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/cm$^{-1}$ 3473w, 3189br, 2920m, 1692s (C=O), 1578s, 1426s, and 1114m; $\delta_H$ (125 MHz; $CDCl_3$) 7.97 (1H, s, NH), 7.50-7.55 (2H, m, Ar), 7.31-7.39 (8H, m, Ar), 6.83 (1H, dd, *J* 5.5 and 0.8, CH=N), 5.68 (1H, m, 5-H), 5.55 (1H, t, *J* 10.7, 6-H) , 5.37 (1H, m, 12-H), 4.66 (1H, d, *J* 12.5, OCH*H*Ph), 4.53 (1H, d, *J* 12.5, OC*H*HPh), 4.25 (1H, t, *J* 2.9, H2), 4.13-4.17 (1H, m, 9-H), 3.52 (1H, dd, *J* 7.8 and 3.0, 3-H), 2.68 (1H, dd, *J* 15.3 and 8.4, 4-H), 2.63 (1H, t, *J* 8.1, 10-H), 2.30-2.39 (2H, m, 4-H and 14-H), 2.27 (1H, t, *J* 11.4, 7-H), 2.14-2.21 (2H, m, 13-H, 8-H), 1.86-1.97 (2H, m, 8-H' and 13-H'), 1.18 (3H, s, $CH_3$), 0.34 and 0.31 (2 × 3H, s, 2 × $CH_3Si$); $\delta_C$ (125 MHz; $CDCl_3$) 156.4 (C=O), 146.2 (CH), 138.4 and 137.6 (CH), 134.0 (C), 133.1 (CH), 131.4, 129.1, 128.4, 128.3, 127.8, 127.7, 126.0 and 120.3 (CH, Ar and olefinic), 86.7 and 86.0 (CH), 77.1 (CH), 70.4 ($CH_2$), 44.0, 43.3 and 38.3 (CH), 31.0, 28.2 ($CH_2$), 22.3 and 20.8 (CH or $CH_3$), -4.4 and -6.1 ($CH_3Si$); *m/z* (ES); 567 [(MH+Na)$^+$, 45%], 544 [(M+H)$^+$, 100] and 380 (50); [*m/z* (ES) Found: (M+H)$^+$, 544.3004. $C_{32}H_{42}N_3O_3Si$ requires 544.2995].

### (*1*R,*2*R,*3*S,*5*Z,*7*S,*9*R,*10*R,*11*Z,*14*R)-*3-(Benzyloxy)-7-dimethyl(phenyl)silyl-14-formyl-cladiella-5(6),11(12)-diene endo*-2 *and* (*1*S,*2*R,*3*S,*5*Z,*7*S,*9*R,*10*R,*11*Z,*14*S)-*3-(benzyloxy)-7-dimethyl(phenyl)silyl-14-formyl-cladiella-5(6),11(12)-diene exo*-2.

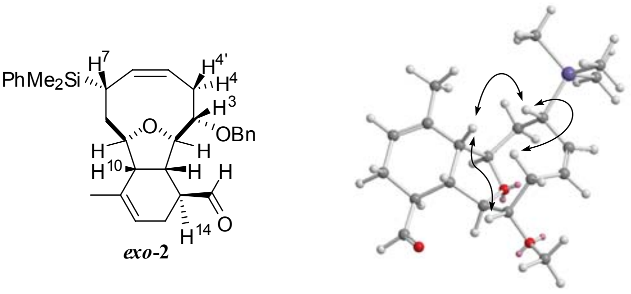




To a stirred solution of ***(R)*-18** (0.3 mg, 0.001 mmol) in MeCN/$H_2O$ (1 mL, 95/5 *v*/*v*) was added the α,β-unsaturated aldehyde **3** (10 mg, 0.02 mmol). The reaction was stirred for 16 h after which time it was diluted by the addition of ether (5 mL), washed with $H_2O$ (5 mL) and brine (5 mL). The organic portion was dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography ($CH_2Cl_2$) yielded the *title cycloadduct*s (6.7 mg, 67%, 15:1 mixture of ***endo*-2**:***exo*-2** as determined by $^1$H NMR spectroscopy); Data for ***endo*-2:** $R_f$ 0.25 ($CH_2Cl_2$); $[\alpha]_D^{25}$ +7.0 (*c* 0.28 in $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/cm$^{-1}$ 2912m, 2849s, 1721m (C=O), 1071 and 808m; $\delta_H$ (500 MHz; $CDCl_3$) 9.55 (1H, d, *J* 2.5, CHO), 7.52-7.55 (2H, m, Ar), 7.32-7.38 (8H, m, Ar), 5.72 (1H, dt, *J* 10.6 and 5.7, 5-H), 5.58 (1H, t, *J* 10.6, 6-H), 5.23 (1H, s, 12-H), 4.56 (2H, s, $OCH_2Ph$), 4.53 (1H, dd, *J* 7.9 and 2.2, H2), 4.06 (1H, ddd, *J* 10.4, 4.1 and 1.7, 9-H), 3.45 (1H, d, *J* 7.9, 3-H), 2.81 (1H, t, *J* 10.4, 10-H), 2.65 (1H, m, 14-H), 2.55 (1H, dd, *J* 15.0 and 9.3, 4-H), 2.33-2.46 (3H, m, H1, 4-H' and 13-H), 2.23 (1H, t, *J* 11.3, 7-H), 2.12 (1H, m, 13-H'), 1.94 (1H, ddd, *J* 15.1, 12.2 and 4.1, 8-H), 1.58 (1H, m, 8-H'), 1.28 (3H, s, $CH_3$), 0.35 and 0.31 (2 × 3H, s, 2 × $CH_3Si$); $\delta_C$ (125 MHz; $CDCl_3$) *Note: one of the CO carbons is obscured by solvent:* 202.1 (C=O), 138.4, 137.5, 134.8 (C), 134.0, 130.8, 129.1, 128.2, 127.8, 127.7, 127.4, 126.6 and 119.9 (CH, Ar and olefinic), 81.6 and 74.7 (CH), 70.3 ($CH_2$), 47.9, 45.2 and 42.8 (CH), 29.8, 29.2 and 26.8 ($CH_2$), 20.6 and 20.2 (CH or $CH_3$), -4.4 and -6.1 ($CH_3Si$); *m/z* (ES) 995 [(2M+Na)$^+$, 100%], 509 [(M+Na)$^+$, 86] and 504 [(M+$NH_4$)$^+$, 100]; [*m/z* (ES) Found: (M+Na)$^+$, 509.2487. $C_{31}H_{38}O_3NaSi$ requires 509.2488].

## Stereochemical Determination of *exo*-2

Detailed 2D $^1$H NMR experiments indicated that the stereochemistry of the cycloadduct is as shown in Scheme 4. The key transannular $^1$H NMR nOe interactions observed are shown in Figure 2. Particularly noteworthy are the $^1$H NMR nOes between 7-H and 10-H, and between 10-H and the formyl proton which are consistent with the 'natural' eunicellin configuration ***exo*-2**. However the resonances corresponding to 14-H and H1 were obscured by other additional signals, appearing as a complex multiplet [$\delta_H$ 2.29-2.43 (4H, m, H1, 14-H, 13-H and 7-H)]. Attempts to separate the multiplet into the individual component signals by recording the spectrum in d$_6$-benzene proved unsuccessful. Therefore it was necessary to obtain proof of stereochemistry by X-ray crystallography

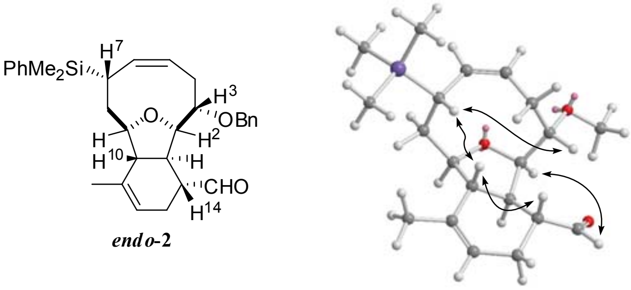


*Key transannular nOes*

Stereochemical assignment of adduct ***exo*-2** – the molecular model was generated from a MonteCarlo conformation search[11] using the MM2* forcefield[12] as implemented in MacroModel v. 8.0. Macromodel is available from Schrodinger (www.schrodinger.com).

## Stereochemical Determination of *endo*-2

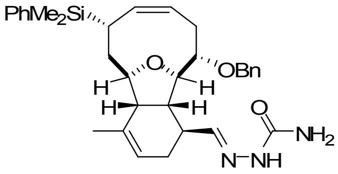
Detailed $^1$H NMR analysis of the cycloadduct isolated from the reaction suggests that the structure is that shown in Figure 5.9. The $^1$H NMR NOESY spectrum shows clear transannular nOes between 10-H and 14-H on the top face of the molecule and H2 and the formyl proton on the lower face. This is consistent with the product ***endo*-2** arising from an *endo*-transition state (*vide infra*).

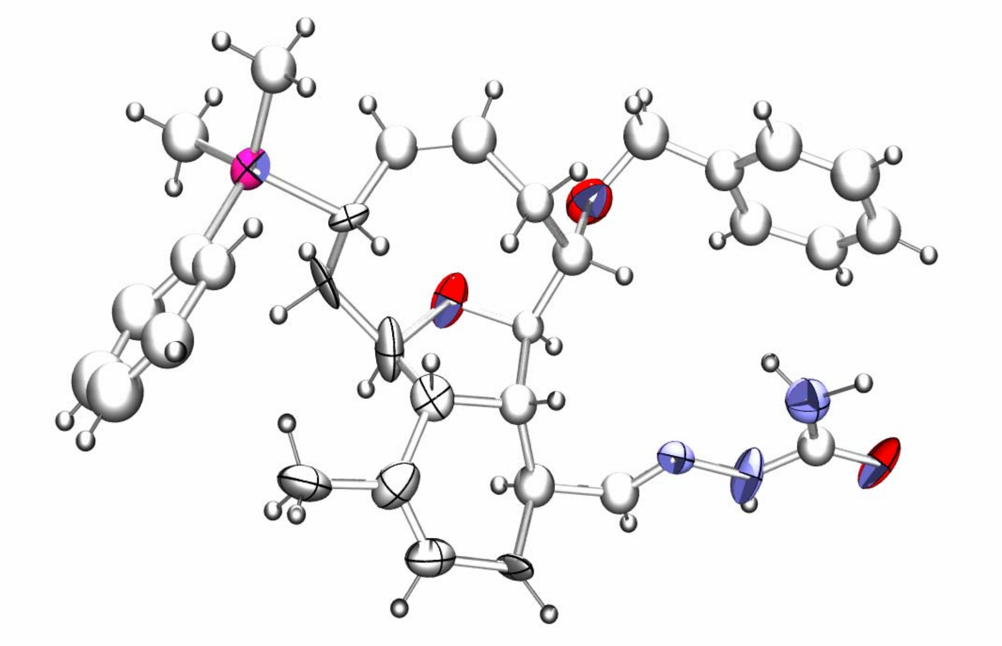


*key transannular nOes*

**Figure 5.9** Stereochemical assignement of adduct ***endo*-2** – the molecular model was generated from a MonteCarlo conformation search[11] using the MM2* forcefield[12] as implemented in MacroModel v. 8.0. Macromodel is available from Schrodinger (www.schrodinger.com).

## X-Ray Data for 19.





An Organocatalytic Approach to the Core of Eunicellin

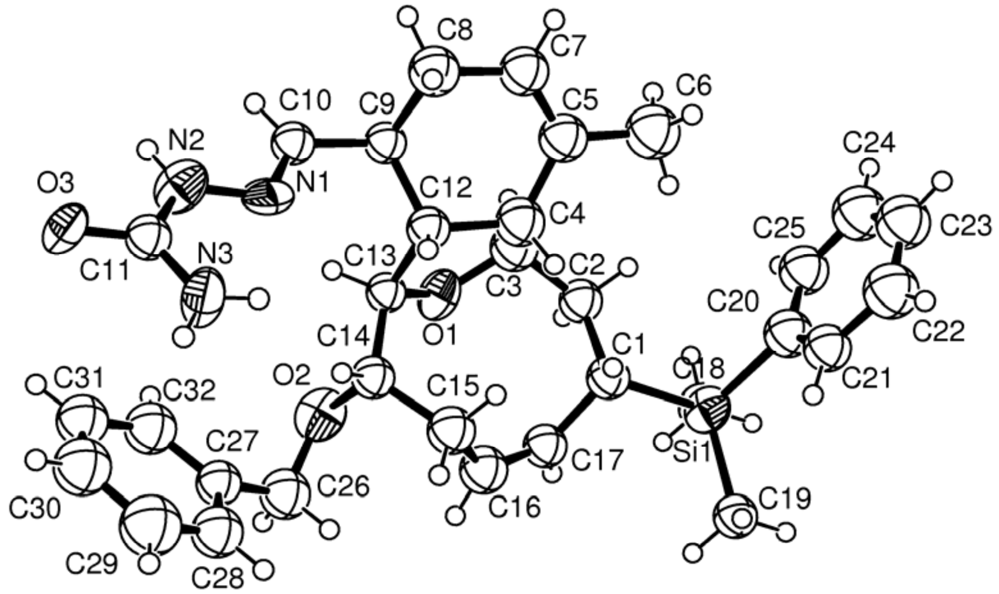
**Table 1.** Crystal data and structure refinement for **19**.

| | | |
|---|---|---|
| Identification code | **19** | |
| Empirical formula | C32 4-H1 N3 O3 Si | |
| Formula weight | 543.77 | |
| Temperature | 150(2) K | |
| Wavelength | 84.640 pm | |
| Crystal system | Monoclinic | |
| Space group | $P2_1$ | |
| Unit cell dimensions | a = 1563.0(5) pm | $\alpha$= 90.000°. |
| | b = 664.9(5) pm | $\beta$= 117.866(5)°. |
| | c = 1586.2(5) pm | $\gamma$ = 90.000°. |
| Volume | 1.4573(13) $nm^3$ | |
| Z | 2 | |
| Density (calculated) | 1.239 $Mg/m^3$ | |
| Absorption coefficient | 0.118 $mm^{-1}$ | |
| F(000) | 584 | |
| Crystal size | 40 x 40 x 10 $\mu m^3$ | |
| Theta range for data collection | 4.04 to 22.62°. | |
| Index ranges | -14<=h<=12, 0<=k<=6, 0<=l<=14 | |
| Reflections collected | 1273 | |
| Independent reflections | 1273 [R(int) = 0.0000] | |
| Completeness to theta = 22.62° | 99.3 % | |
| Absorption correction | None | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 1273 / 1 / 193 | |
| Goodness-of-fit on $F^2$ | 1.024 | |
| **Final R indices [I>2sigma(I)]** | **R1 = 0.0902, wR2 = 0.2370** | |
| R indices (all data) | R1 = 0.1224, wR2 = 0.2507 | |
| Absolute structure parameter | -0.2(9) | |
| Largest diff. peak and hole | 0.273 and -0.329 e.$Å^{-3}$ | |

An Organocatalytic Approach to the Core of Eunicellin

Data collection details: synchrotron X-ray diffraction data were collected at Station 16.2SMX at CCLRC Daresbury Laboratory, on a Bruker Nonius D8 diffractometer with an APEXII detector. Data were corrected for beam decay and absorption by an empirical method based on equivalents. Friedel opposites were merged as there is no significant anomalous dispersion. N,O, Si atoms were refined with anisotropic displacement parameters. Carbon atoms were refined with isotropic parameters. Hydrogen atoms were placed using geometric considerations and refined using a riding model.

---



**ORTEP plot of 19 showing 50% probability ellipsoids**

## checkCIF/PLATON report

```
Bond precision:      C-C = 0.0320 A              Wavelength=0.84640
```

```
Cell:   a=15.630(5)     b=6.649(5)      c=15.862(5)

        alpha=90        beta=117.866(5) gamma=90

                  Calculated                     Reported

Volume            1457.3(13)                     1457.3(13)

Space group       P 21                           P 21

Hall group        P 2yb                          P 2yb

Moiety formula    C32 4-H1 N3 O3 Si              C32 4-H1 N3 O3 Si

Sum formula       C32 4-H1 N3 O3 Si              C32 4-H1 N3 O3 Si

Mr                543.77                         543.77

Dx,g cm-3         1.239                          1.239

Z                 2                              2

Mu (mm-1)         0.240                          0.118

F000              584.0                          584.0

F000'             583.90

h,k,lmax          14,6,14                        14,6,14

Nref              1282( 2279)                    1273

Tmin,Tmax         0.000,0.000                    0.910,1.000

Tmin'             0.000

Correction method= 'MULTI-SCAN'

Data completeness= 0.99(0.56)  Theta(max)= 22.620

R(reflections)= 0.0902( 776)      wR2(reflections)= 0.2507( 1273)

S = 1.024             Npar= 193


THETM01_ALERT_3_A  The value of sine(theta_max)/wavelength is less than
0.550
            Calculated sin(theta_max)/wavelength =    0.4544
PLAT027_ALERT_3_A _diffrn_reflns_theta_full (too) Low ............
22.62 Deg.
PLAT201_ALERT_2_A Isotropic non-H Atoms in Main Residue(s) .......
32
RFACR01_ALERT_3_C  The value of the weighted R factor is > 0.25
            Weighted R factor given   0.251
```

An Organocatalytic Approach to the Core of Eunicellin

Data were extremely weak and were curtailed at 1.1Å (2 $_{\text{max}}$ = 45.2 º).

Despite the limited data, it was possible to solve the structure by direct methods. These low angle data allow a reliable determination of the atom arrangement but provide little information about the thermal motion of the atoms. Only the heavier atoms (Si, O, N) are refined with anisotropic displacement parameters. Refining the carbon atoms in a similar way led to physically unrealistic adps. Therefore all carbon atoms are treated as isotropic. These factors lead to wR somewhat larger than would be the case for a strongly diffracting crystal.

```
PLAT340_ALERT_3_B Low Bond Precision on C-C bonds (x 1000) Ang ...
32
PLAT089_ALERT_3_C Poor Data / Parameter Ratio (Zmax .LT. 18) .....
6.60
REFNR01_ALERT_3_C  Ratio of reflections to parameters is < 8 for a
            non-centrosymmetric structure, where ZMAX < 18
            sine(theta)/lambda               0.4544
            Proportion of unique data used    1.0000
            Ratio reflections to parameters   6.5959
```

The weakness and limited number of data lead to relatively low bond precision and data to parameter ratio.

```
STRVA01_ALERT_4_C          Flack test results are meaningless.
           From the CIF: _refine_ls_abs_structure_Flack   -0.200
           From the CIF: _refine_ls_abs_structure_Flack_su    0.900
REFLT03_ALERT_4_G  WARNING: Large fraction of Friedel related reflns
may
                     be needed to determine absolute structure
           From the CIF: _diffrn_reflns_theta_max           22.62
           From the CIF: _reflns_number_total               1273
           Count of symmetry unique reflns         1282
           Completeness (_total/calc)             99.30%
           TEST3: Check Friedels for noncentro structure
           Estimate of Friedel pairs measured         0
           Fraction of Friedel pairs measured     0.000
           Are heavy atom types Z>Si present        yes
PLAT030_ALERT_1_C _diffrn_reflns_number .LE.  _reflns_number_total
?
```

```
PLAT032_ALERT_4_C Std. Uncertainty in Flack Parameter too High ...
0.90
```

Preliminary refinements with all data (Friedel opposites not merged) led to an unsuitably large error on the Flack parameter. In the final refinement Friedel opposites were merged, hence the calculated Flack parameter is meaningless. Using the fairly short wavelength of the synchrotron radiation, it is not surprising there is little amomalous dispersion in a sample containing only light atoms.

```
PLAT241_ALERT_2_C Check High      Ueq as Compared to Neighbors for
C29
```

Inspection of the ORTEP plot reveals no serious problem with the thermal parameter for C29.

## Alert level G

```
  ABSMU_01  Radiation type not identified. Calculation of
            _exptl_absorpt_correction_mu not performed.
```

Fails because radiation source is a synchrotron.

```
PLAT035_ALERT_1_A No _chemical_absolute_configuration info given .
?
PLAT791_ALERT_1_G Confirm the Absolute Configuration of C1     = .
S
PLAT791_ALERT_1_G Confirm the Absolute Configuration of C3     = .
R
PLAT791_ALERT_1_G Confirm the Absolute Configuration of C4     = .
R
PLAT791_ALERT_1_G Confirm the Absolute Configuration of C9     = .
S
PLAT791_ALERT_1_G Confirm the Absolute Configuration of C12    = .
R
PLAT791_ALERT_1_G Confirm the Absolute Configuration of C13    = .
R
PLAT791_ALERT_1_G Confirm the Absolute Configuration of C14    = .
S
```

Stereochemical information obtained from the crystal structure solution concurs with the structure expected synthetically.

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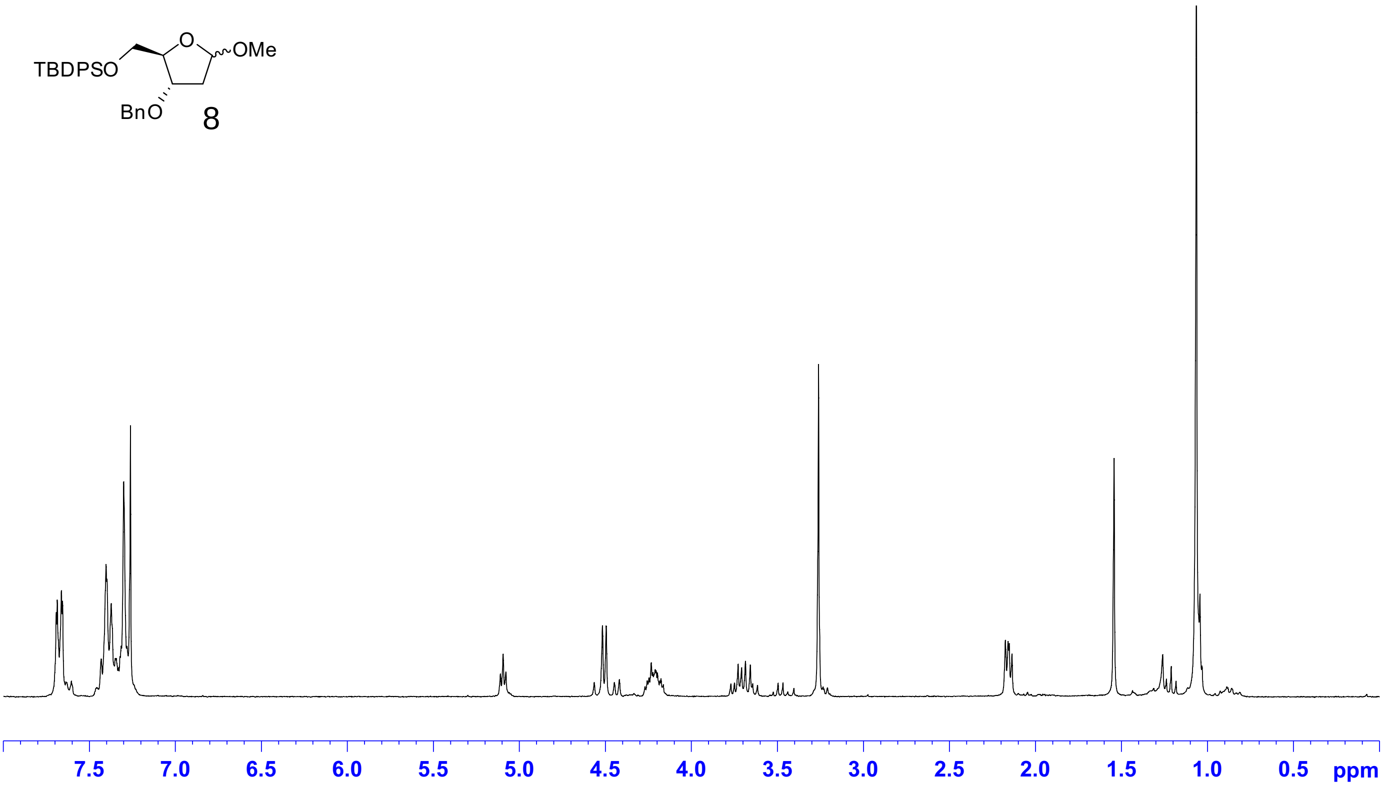
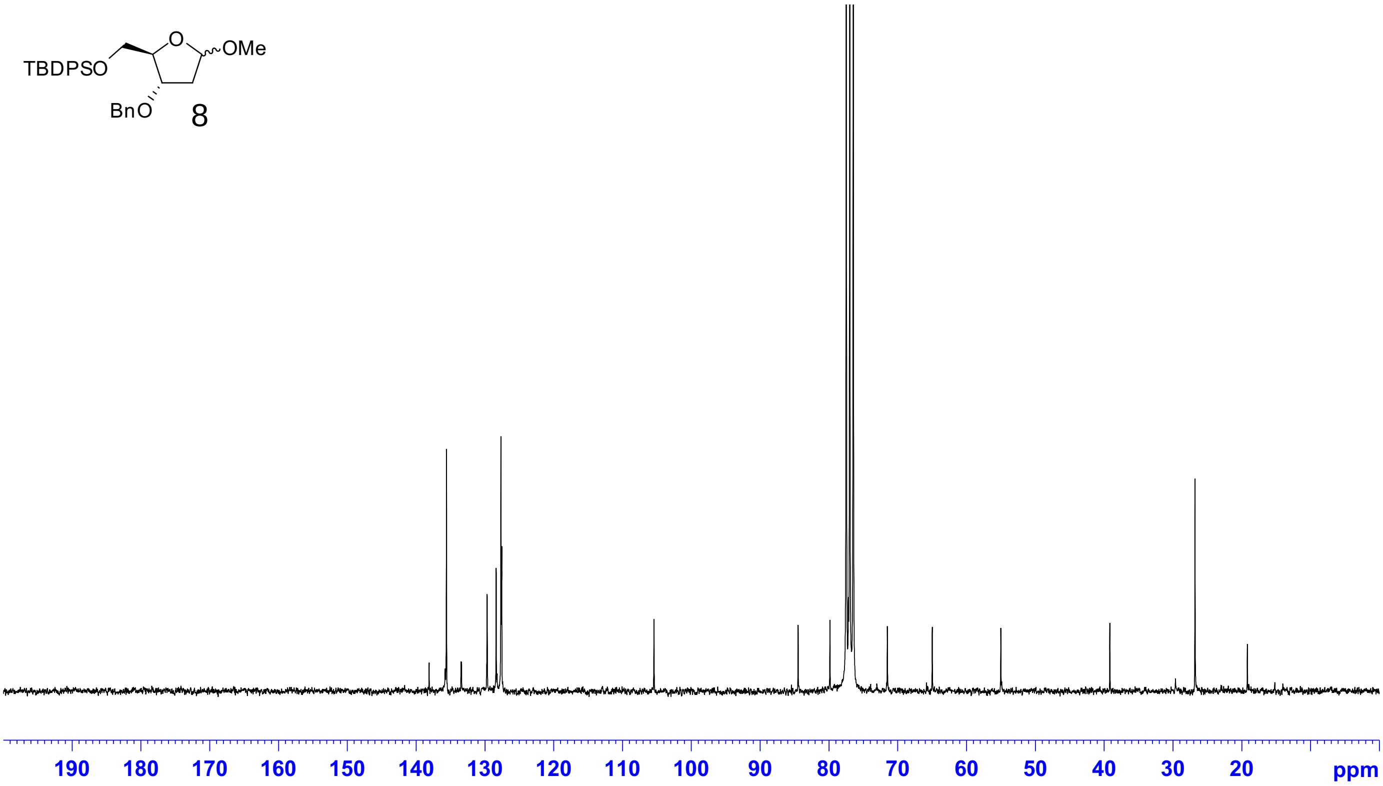
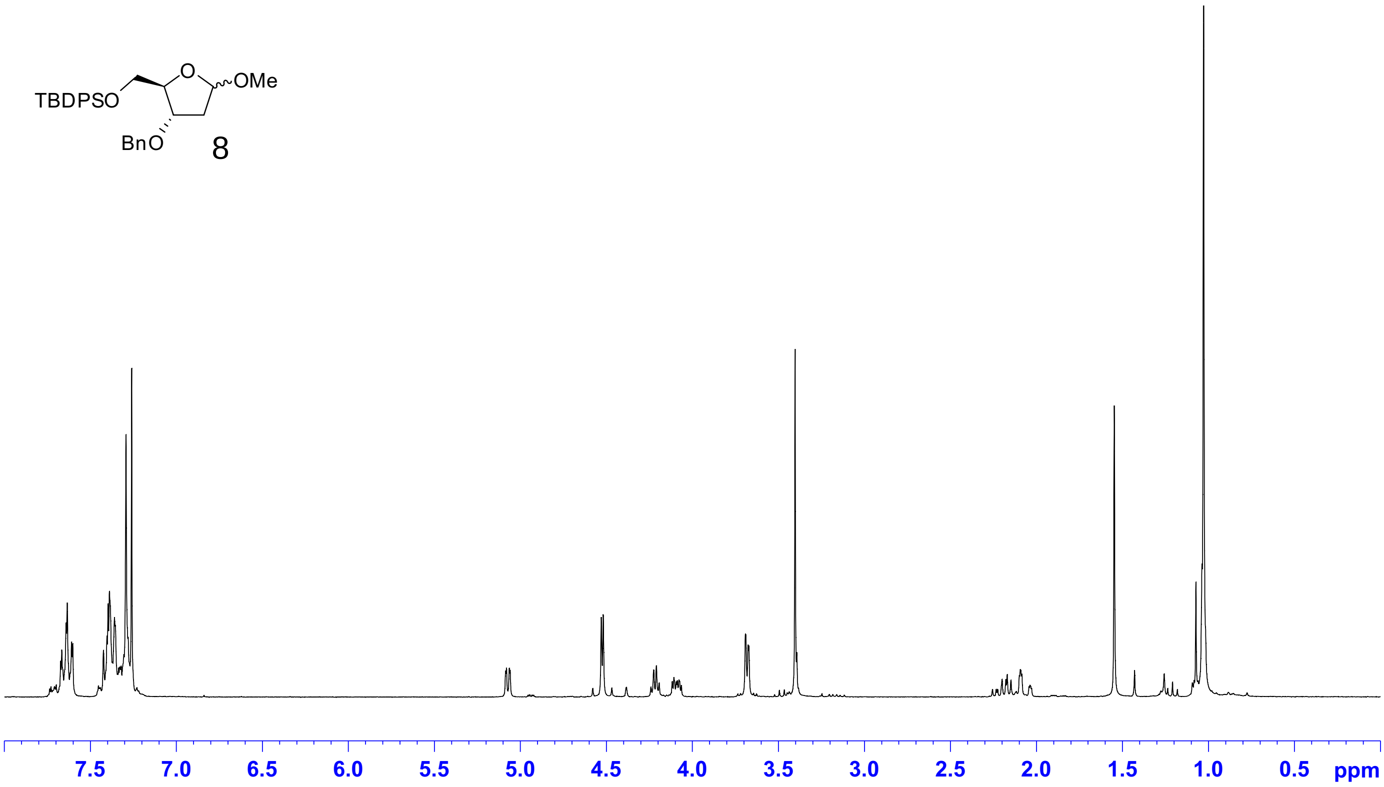
1H NMR (250 MHz, CDCl3): methylglycoside, less polar diastereomer



13C NMR (62.5 MHz, CDCl3): methylglycoside, less polar diastereomer



1H NMR (250 MHz, CDCl3): methylglycoside, more polar diastereomer



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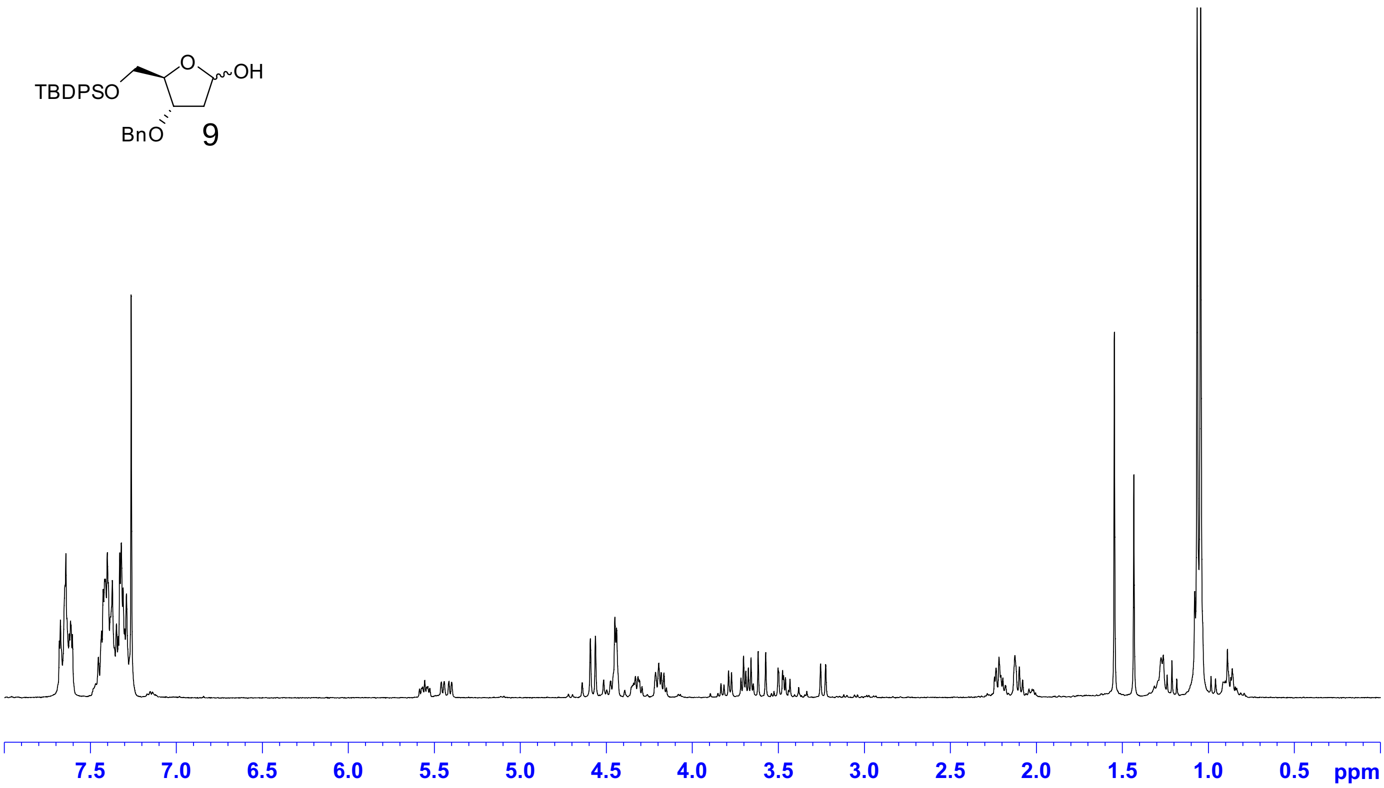
1H NMR (250 MHz, CDCl3): lactols



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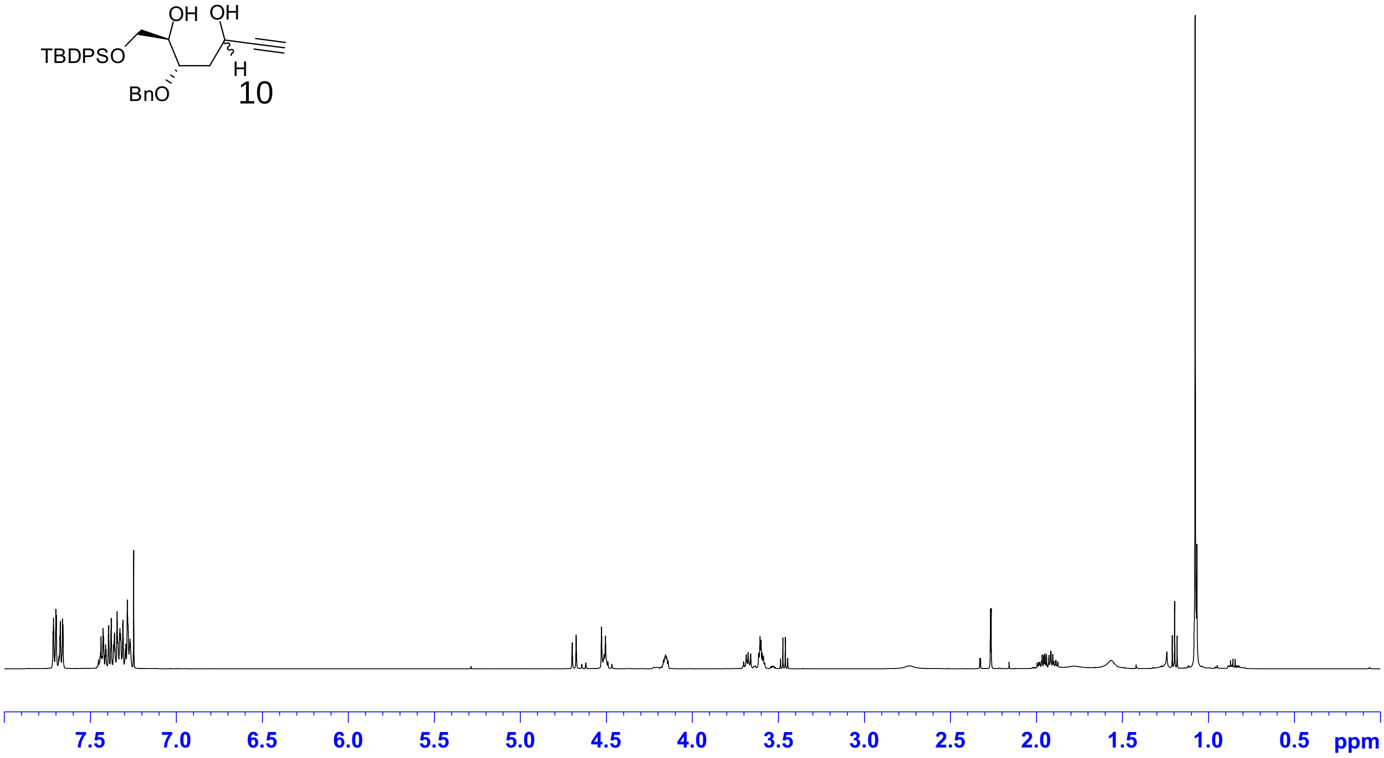
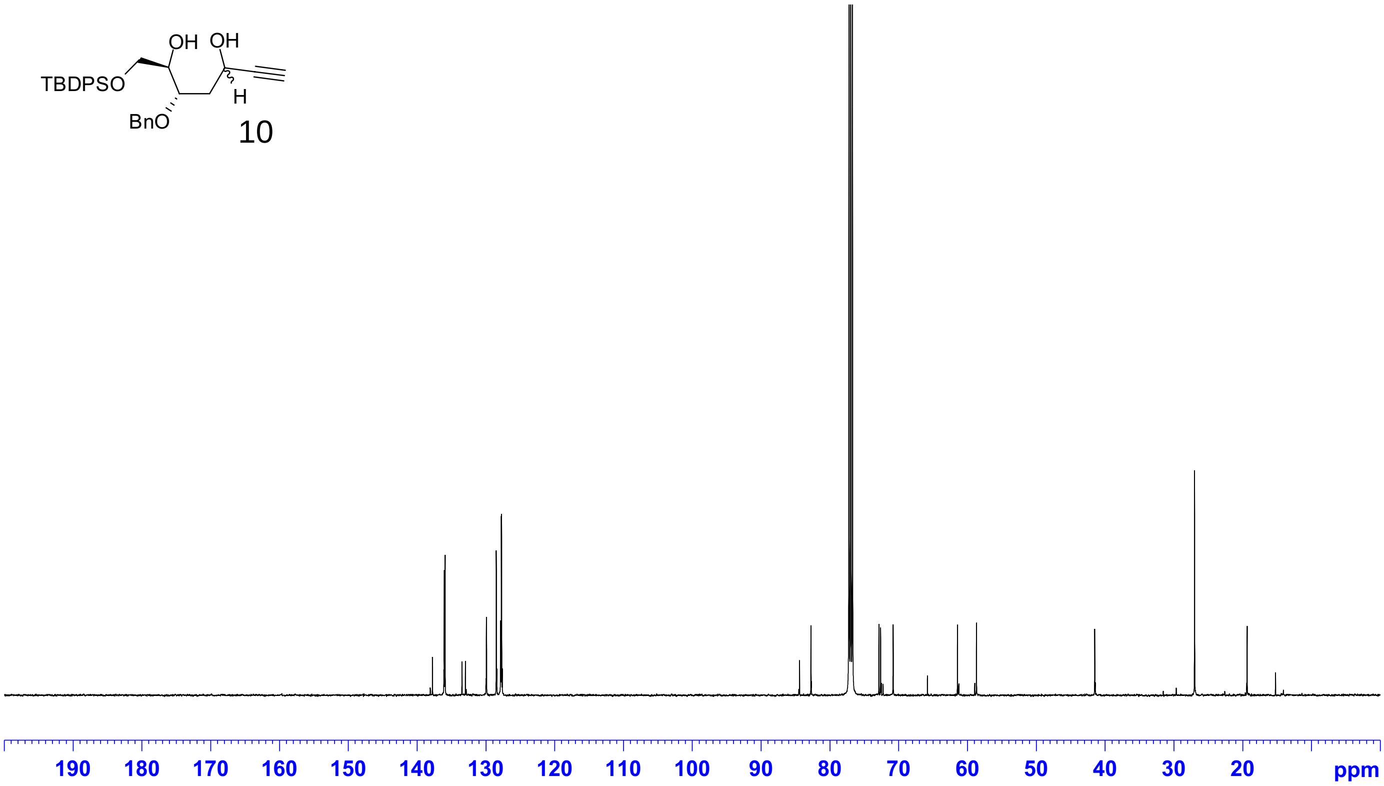
1H NMR (500 MHz, CDCl3): Diol, more polar diastereomer
contains other diastereomer as a slight impurity



13C NMR (125 MHz, CDCl3): Diol, more polar diastereomer
contains other diastereomer as a slight impurity



1H NMR (400 MHz, CDCL3): Diol, less polar diastereomer

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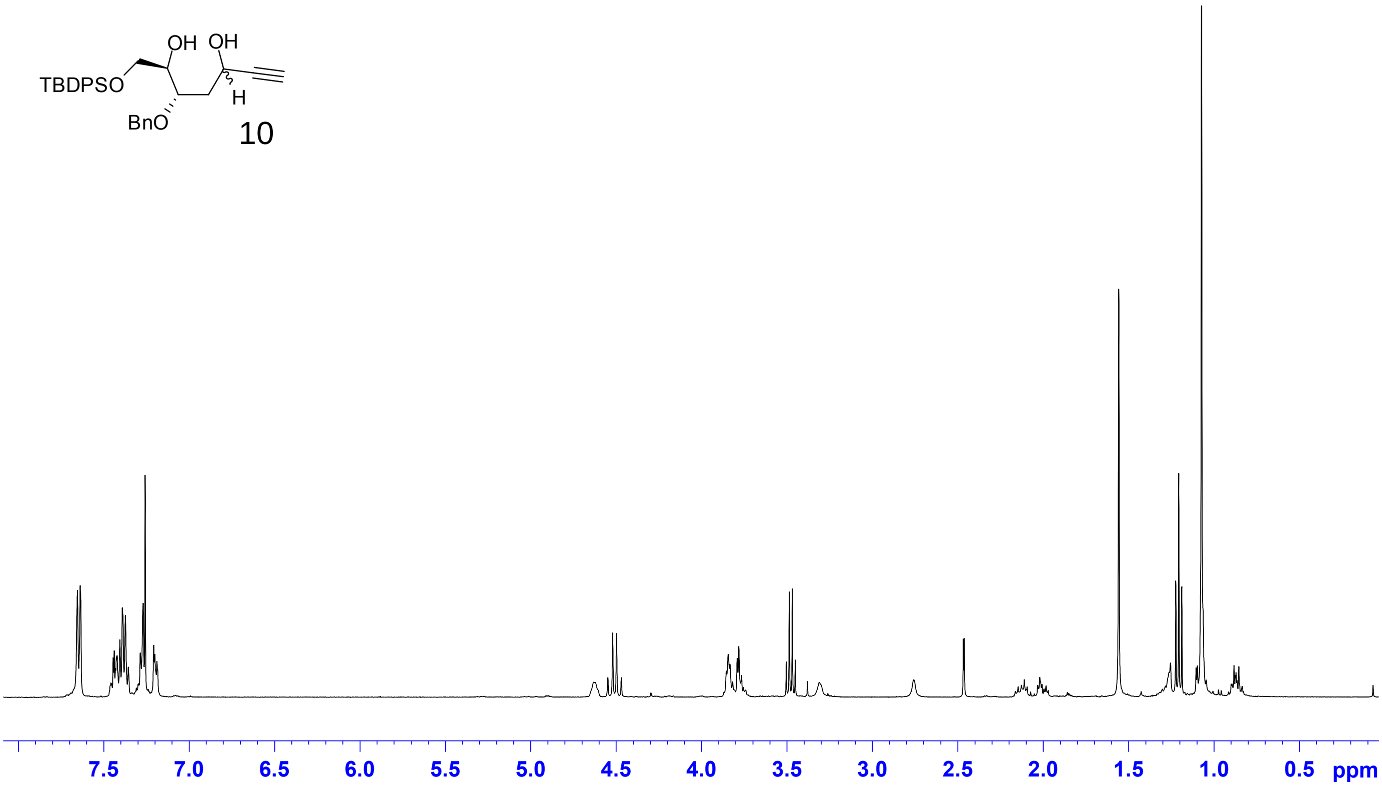

13C NMR (125 MHz, CDCl3): Diol, less polar diastereomer
contains other diastereomer as a slight impurity

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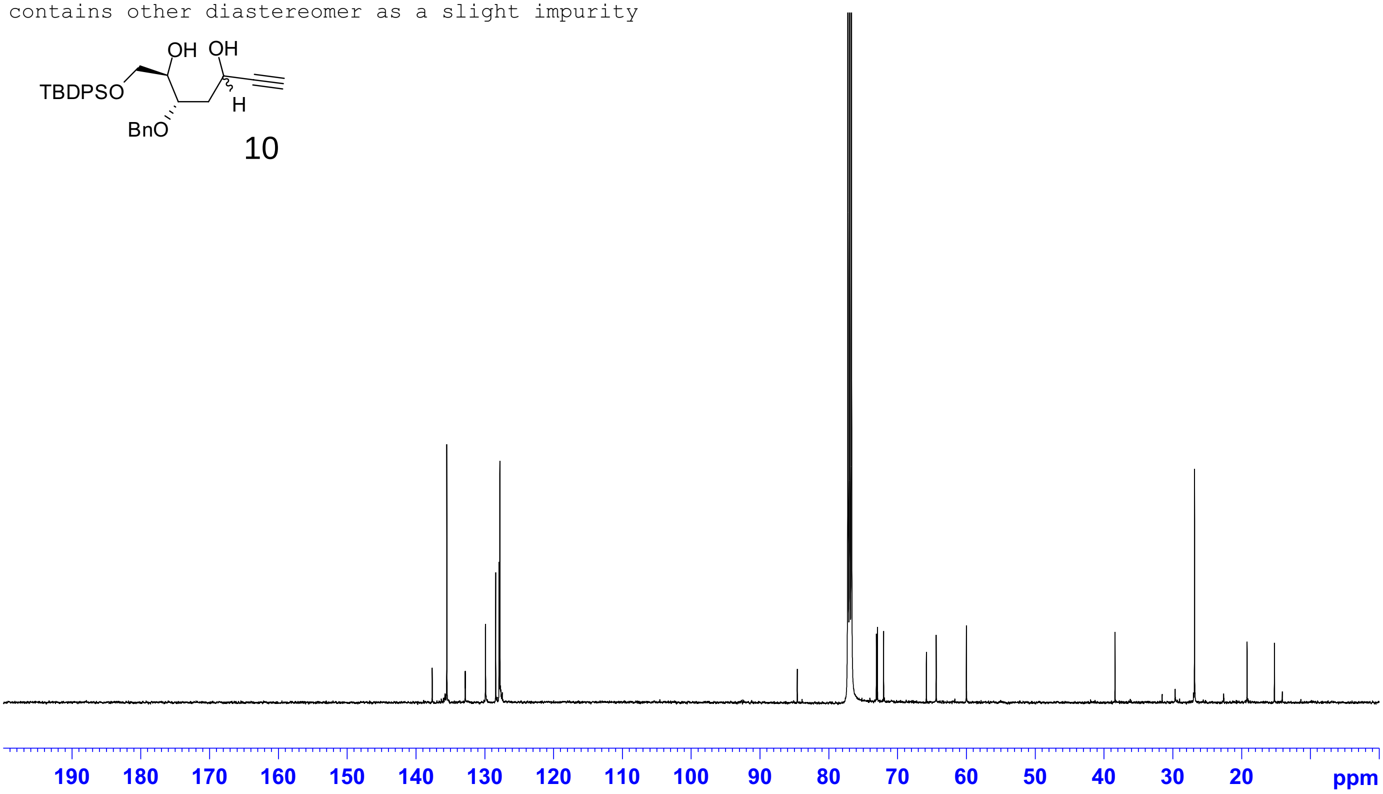
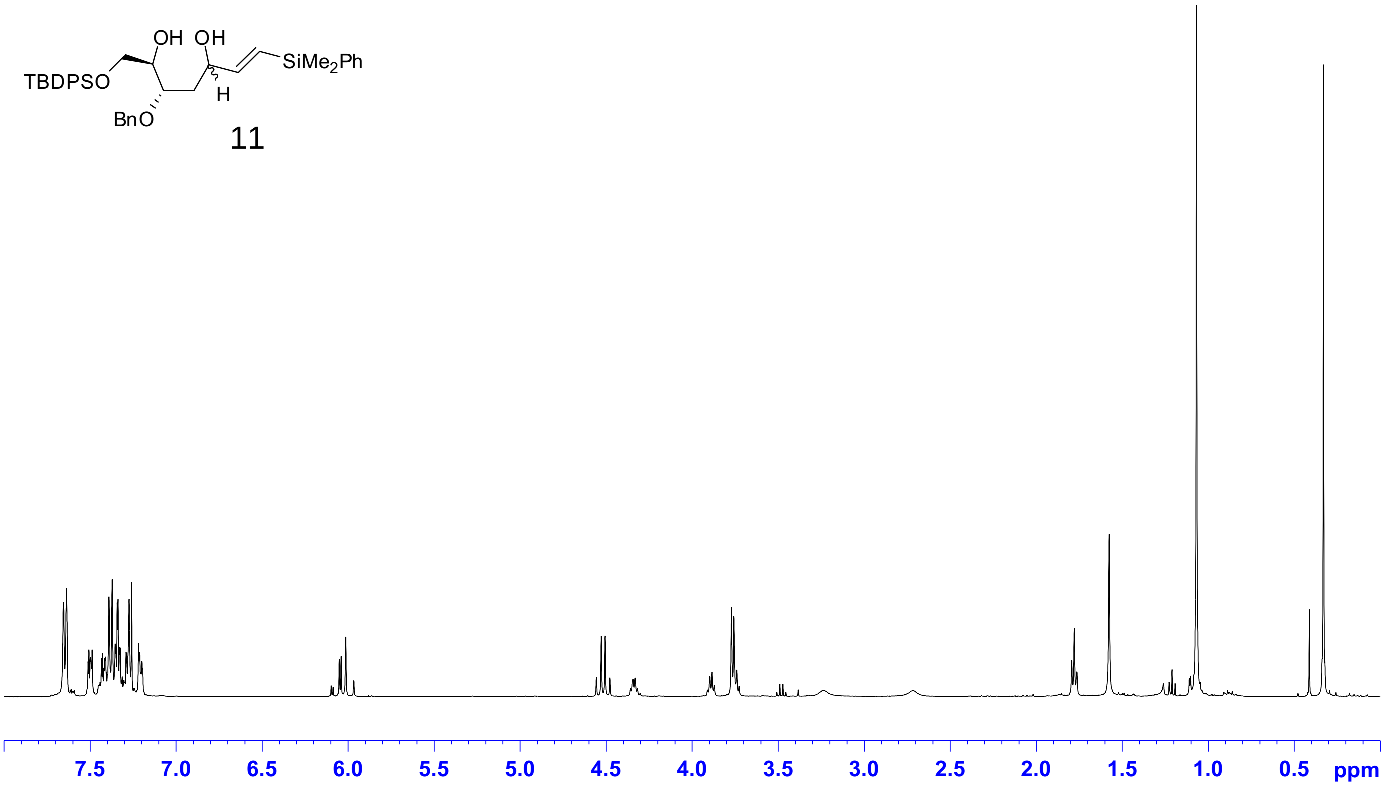
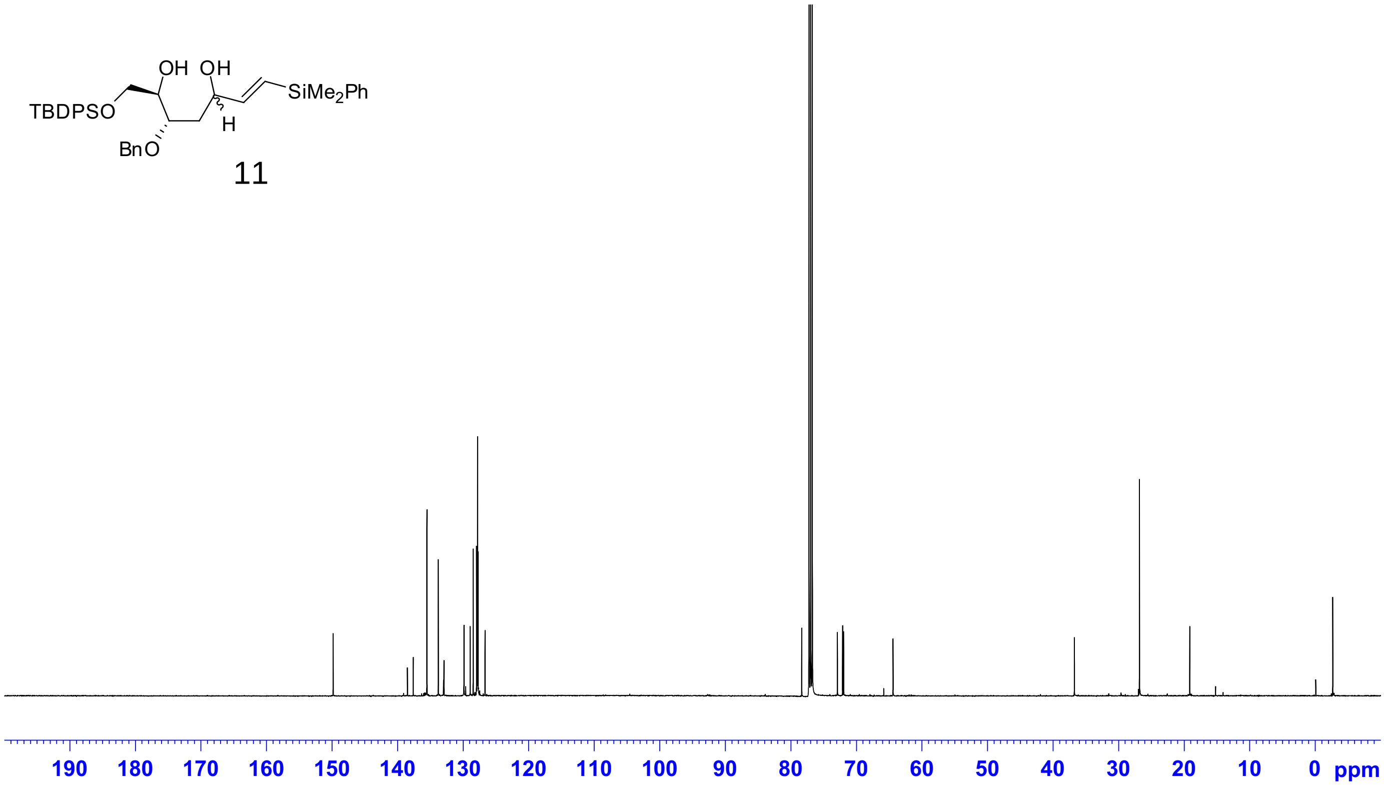


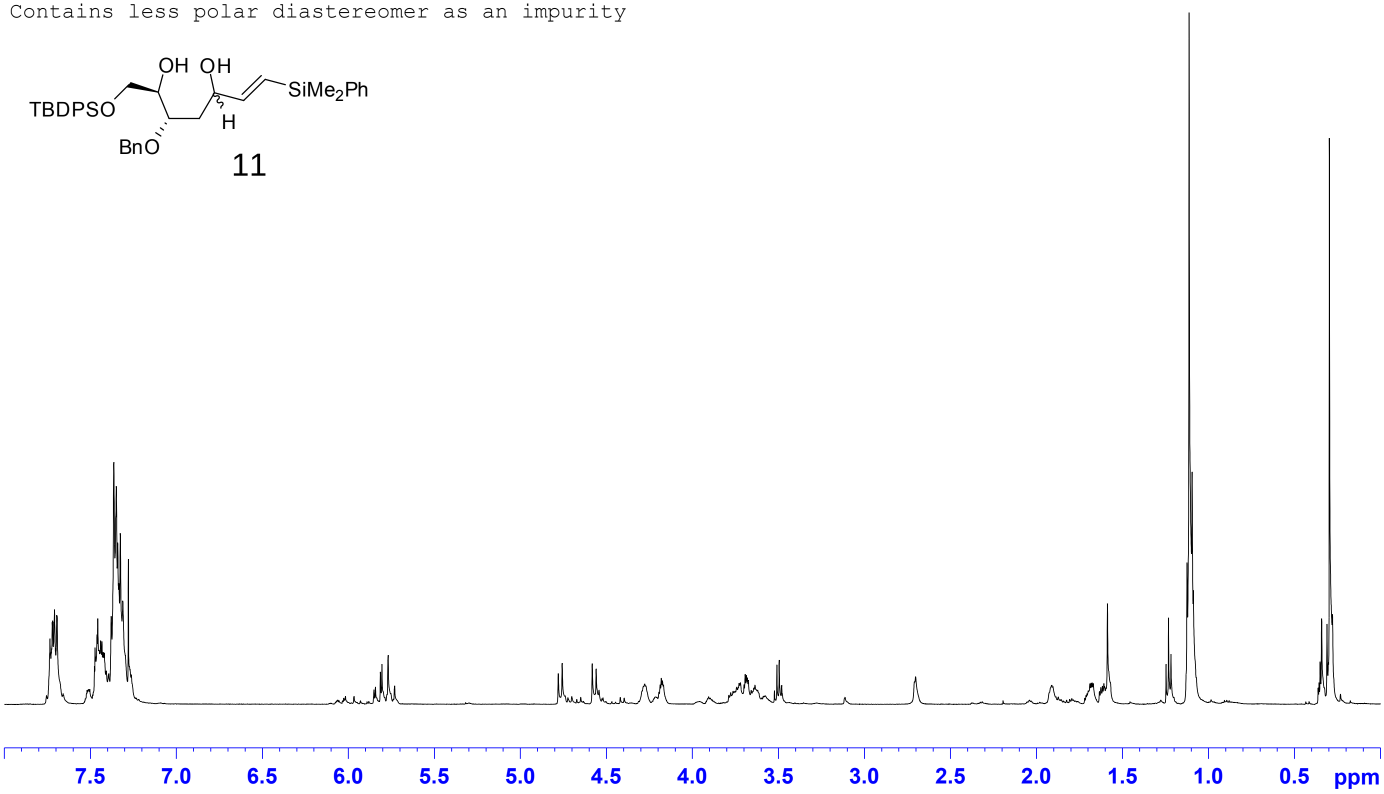
1H NMR (400 MHz, CDCl3): Silane less polar diastereomer



13C NMR (125MHz, CDCl3): Silane less polar diastereomer



1H NMR (500 MHz, CDCl3): Silane more polar diastereomer
Contains less polar diastereomer as an impurity



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13C NMR (125MHz, CDCl3): Silane more polar diastereomer
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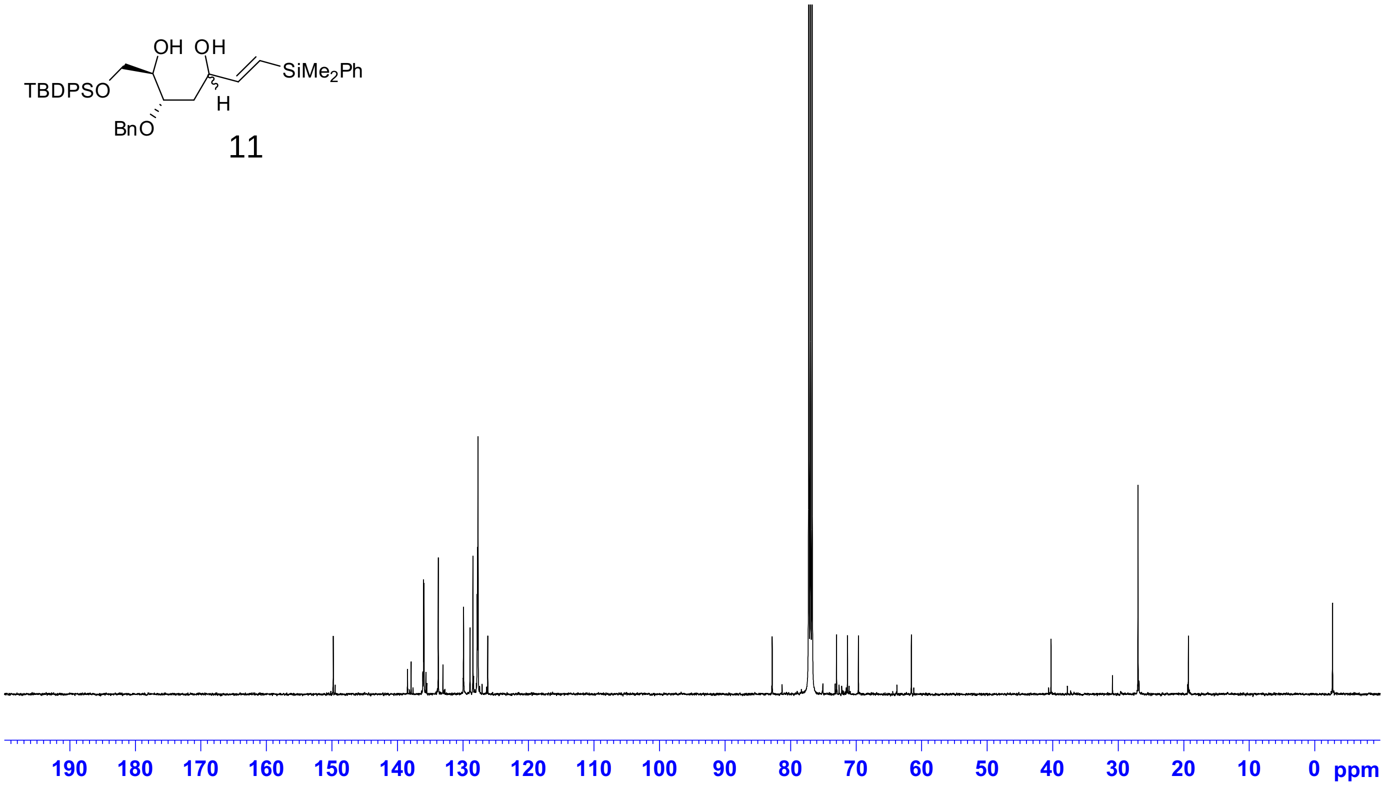

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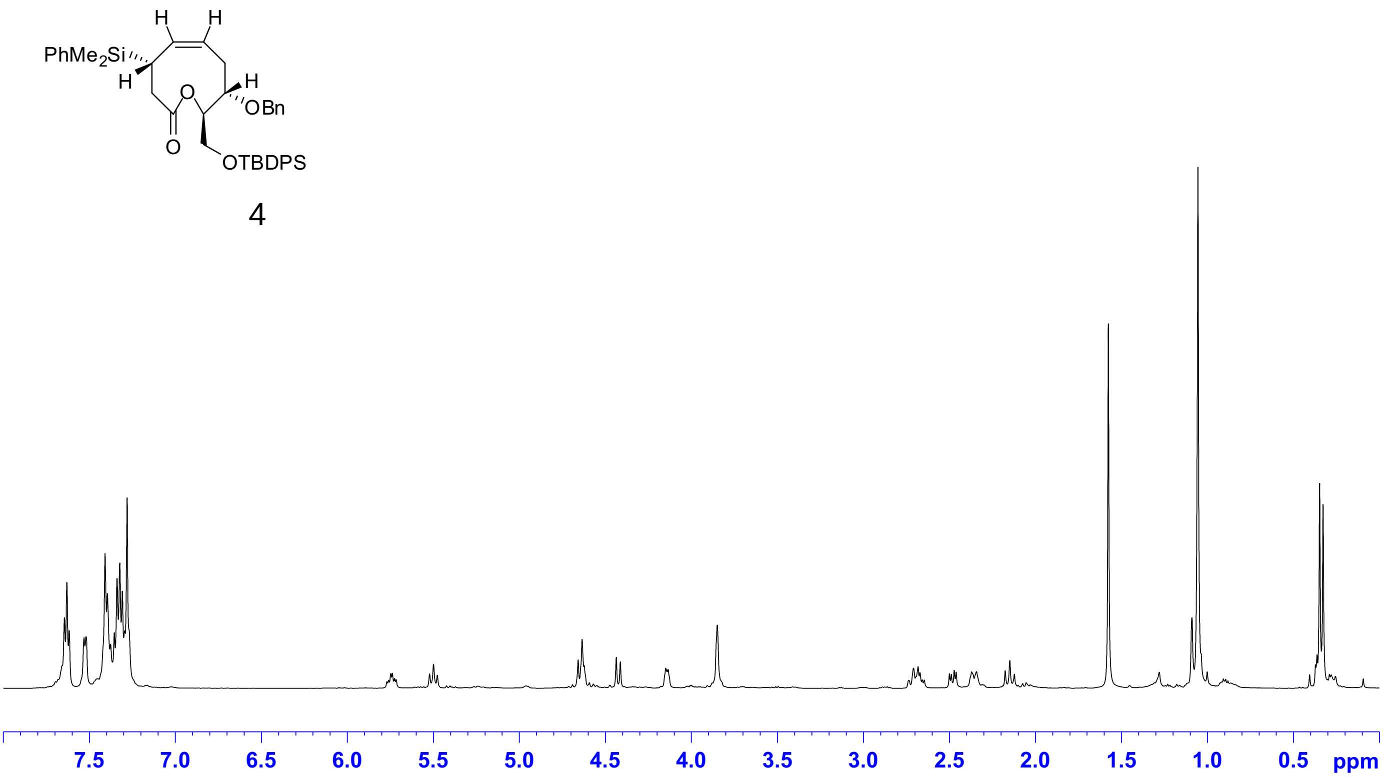
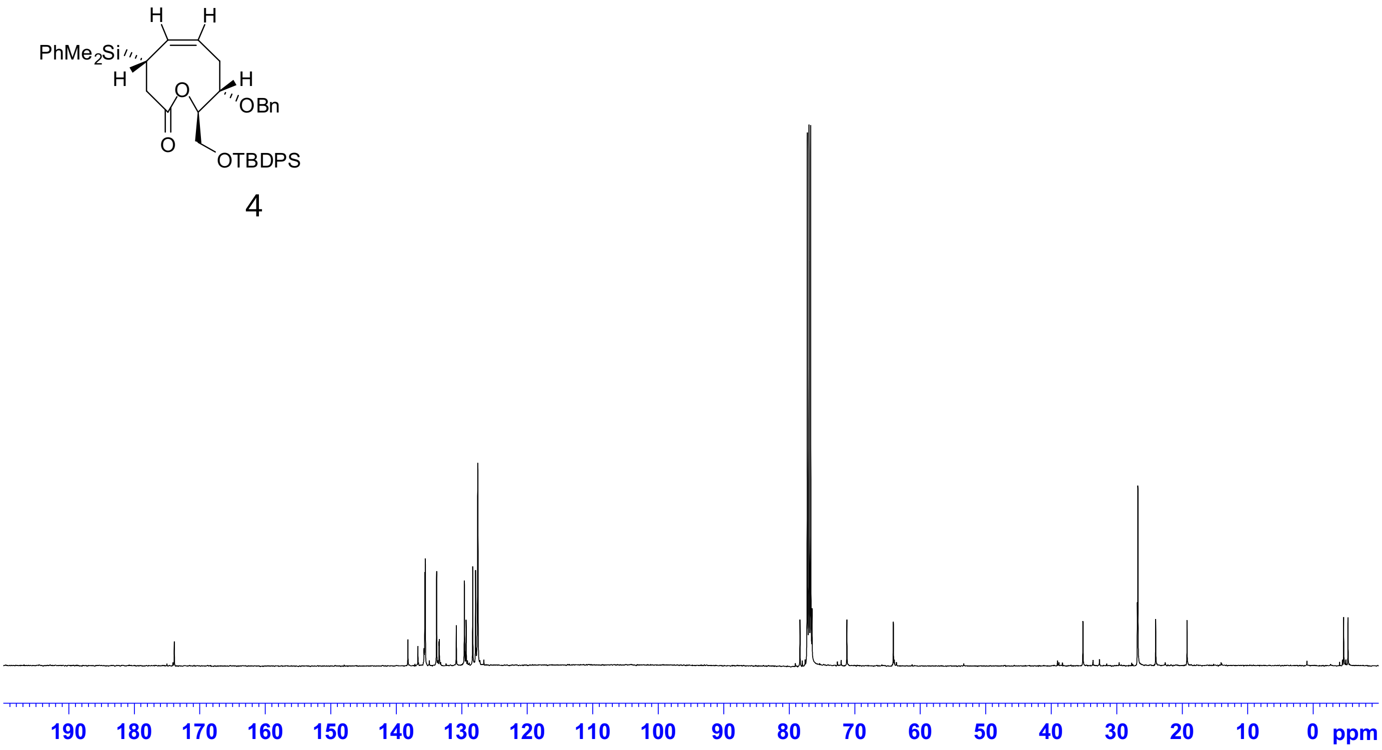
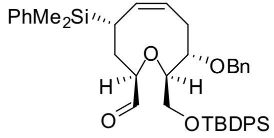
1H NMR (500 MHz, CDCl3): Lactone



13 C NMR (125 MHz, CDCl3): Lactone



1H NMR (500 MHz, CDCl3): Aldehyde



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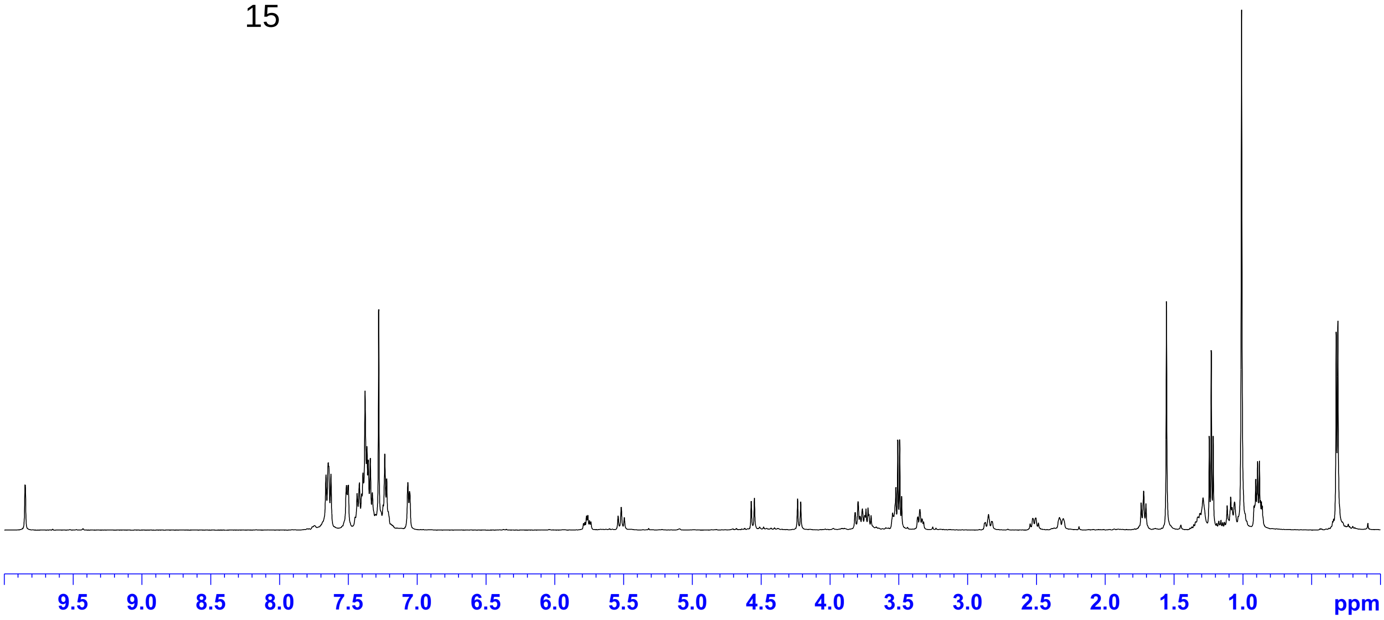
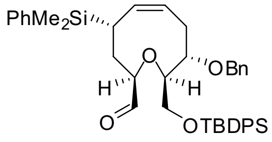


13C NMR (125 MHz, CDCl3): Aldehyde



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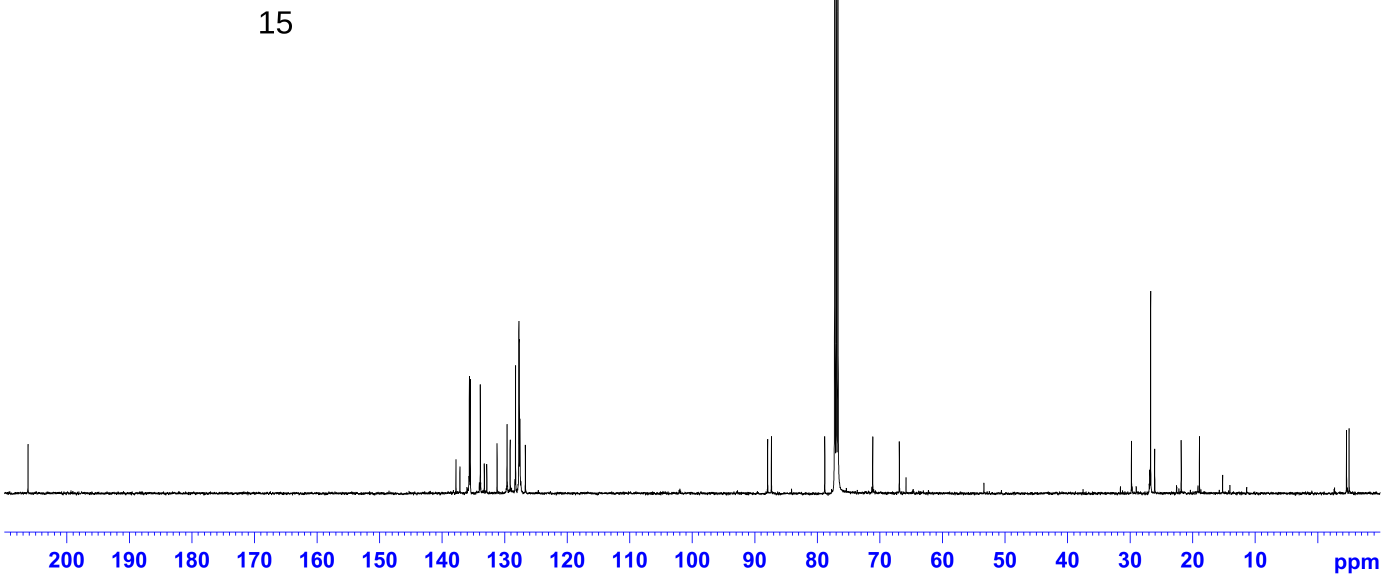
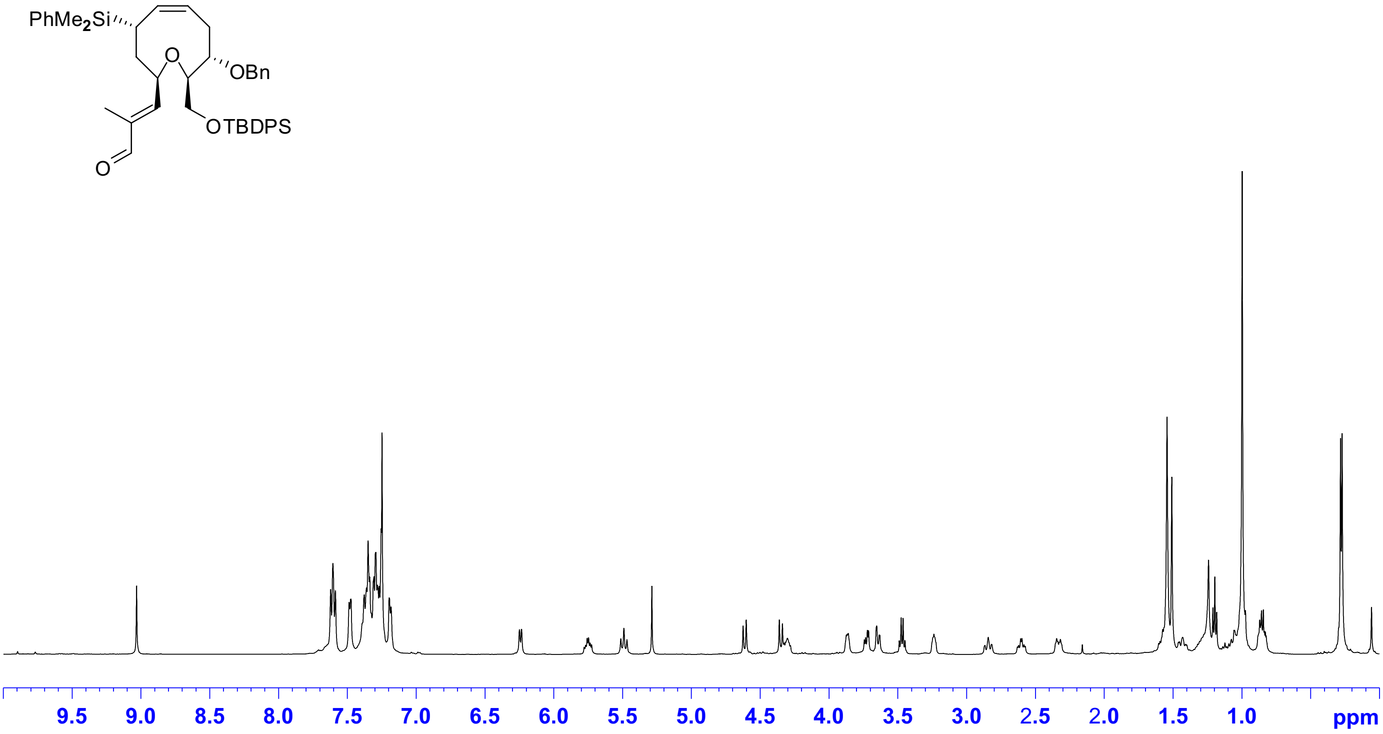
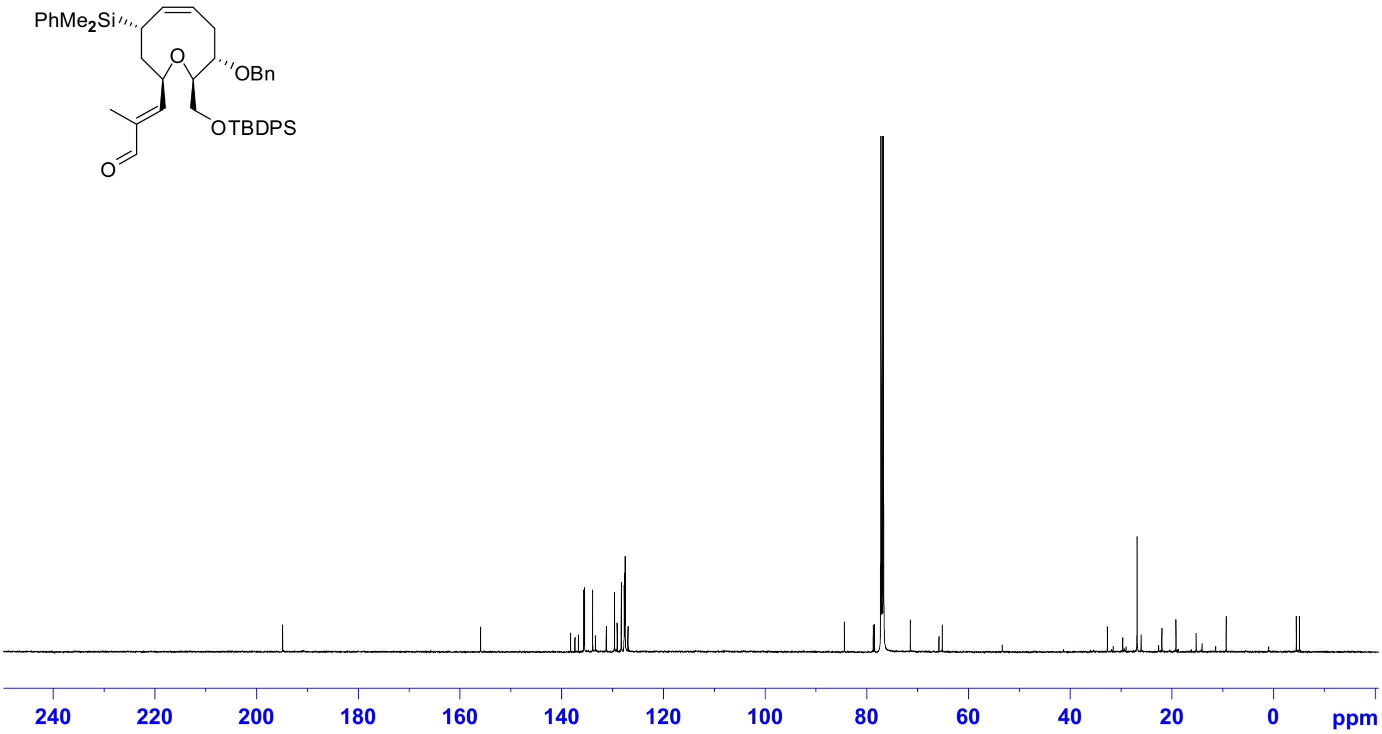


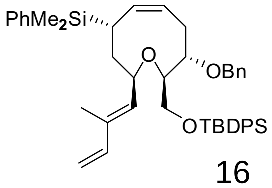
1H NMR (500 MHz, CDCl3): unsturated aldehyde



13 C NMR (125 MHz, CDCl3): unsaturated aldehyde



1H NMR (500 MHz, CDCl3): diene



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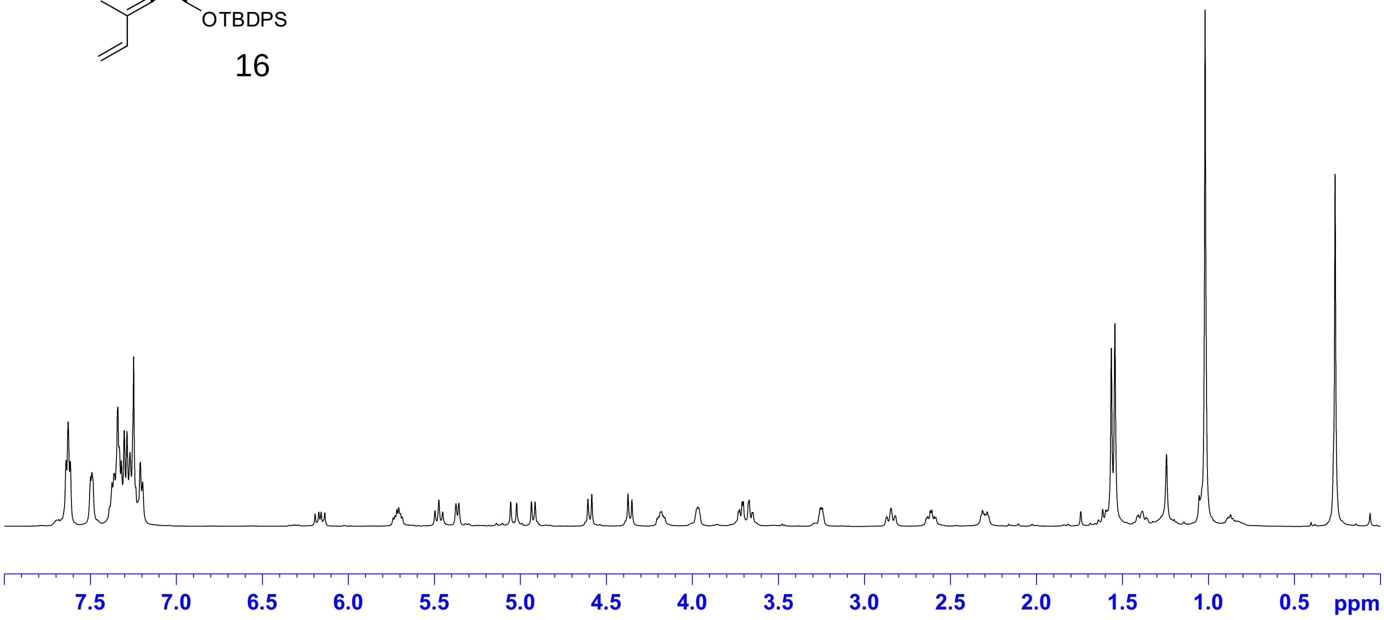
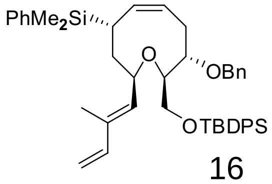


13C NMR (125 MHz, CDCl3): diene



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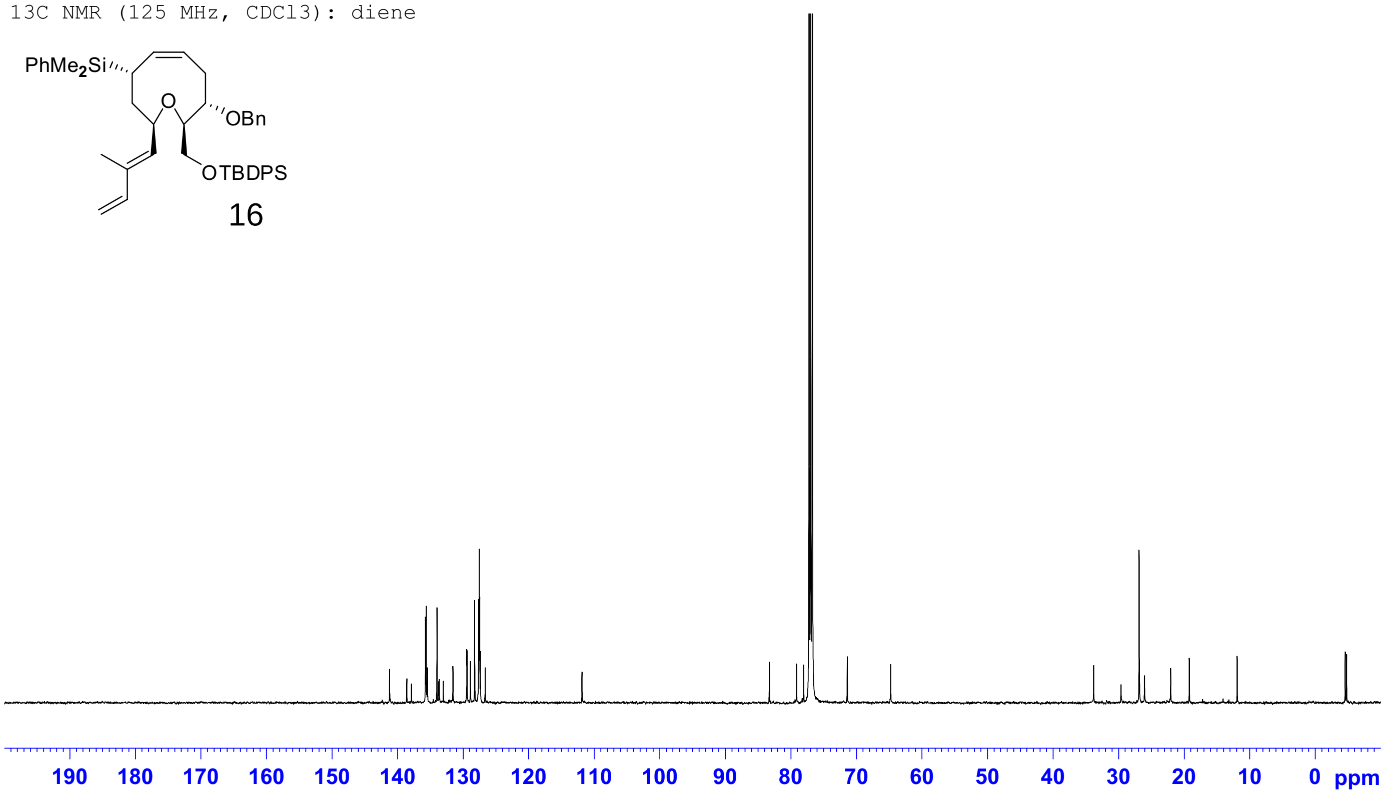
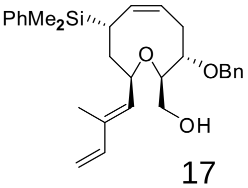


1H NMR (500 MHz, CDCl3): alcohol



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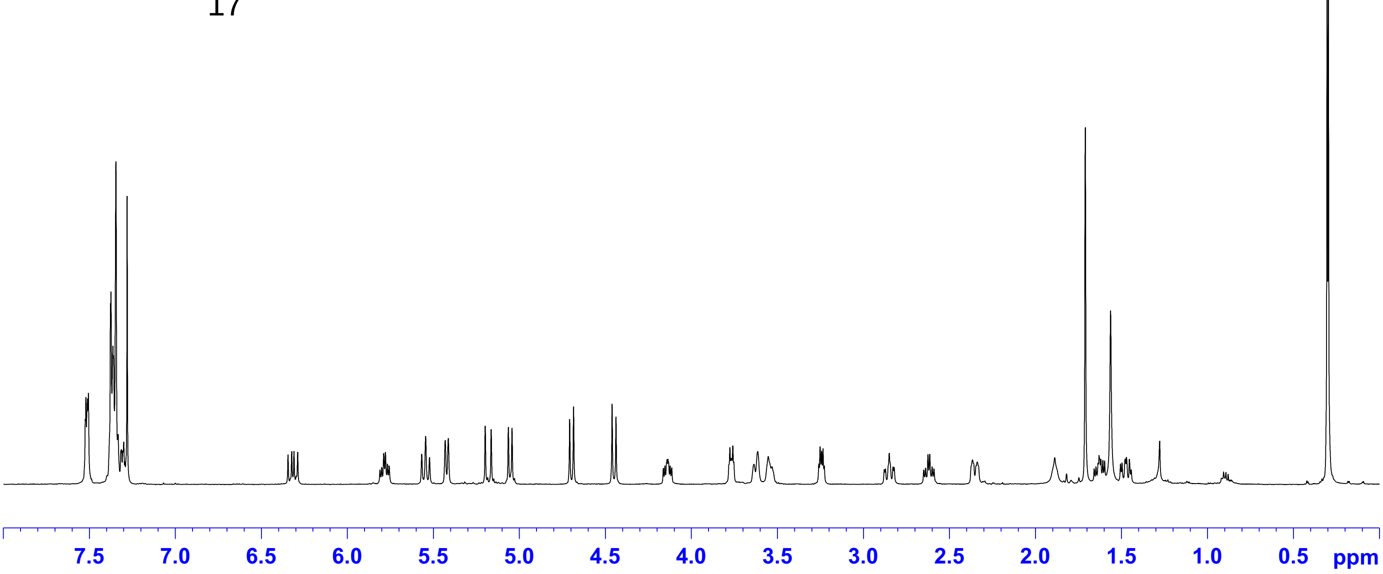
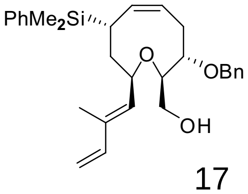


13C NMR (500 MHz, CDCl3): alcohol



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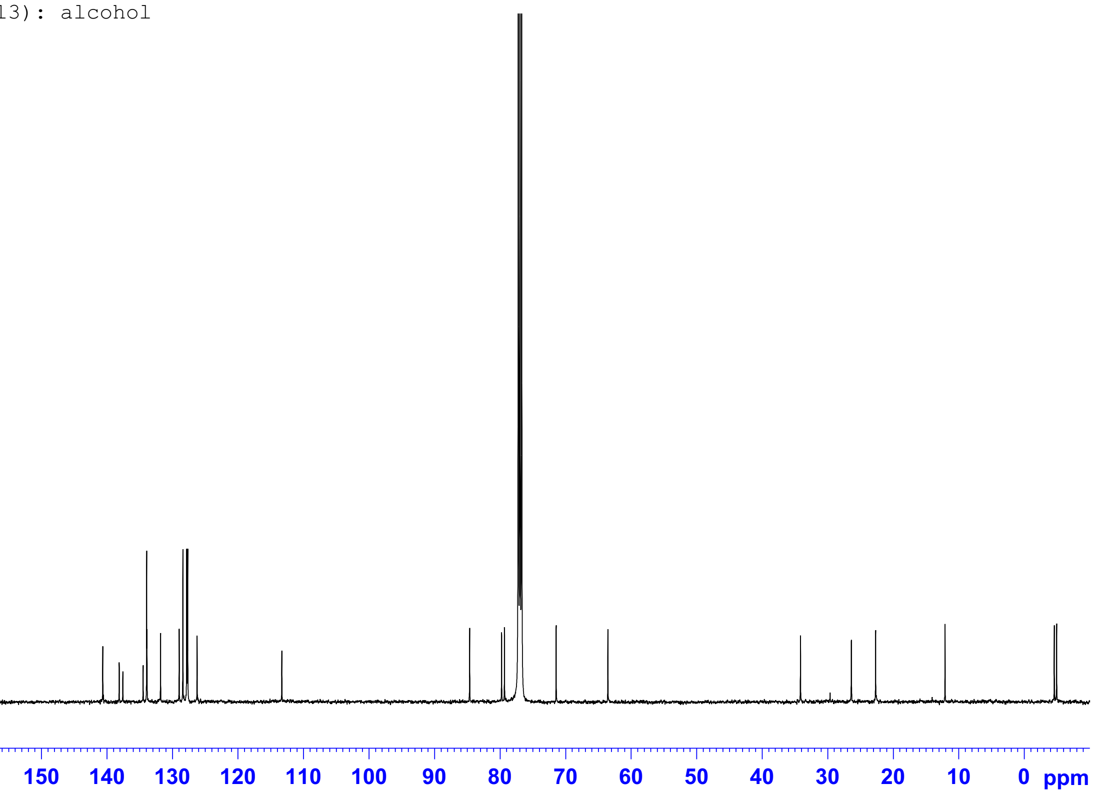
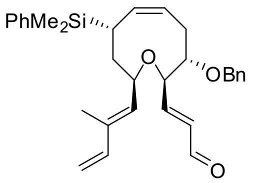


1H NMR (500 MHz, CDCl3): unsaturated aldehyde



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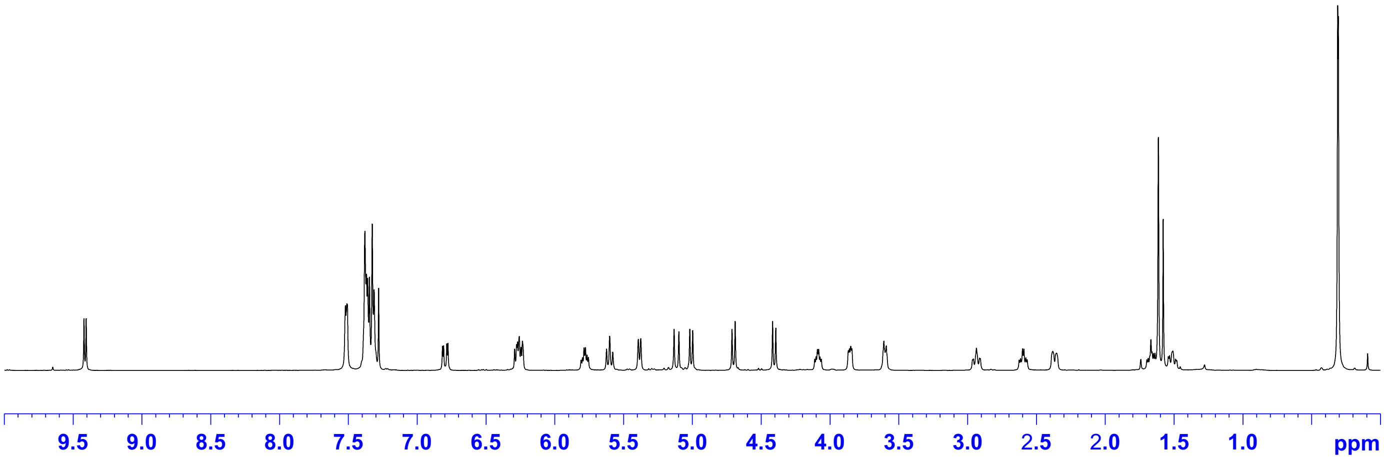
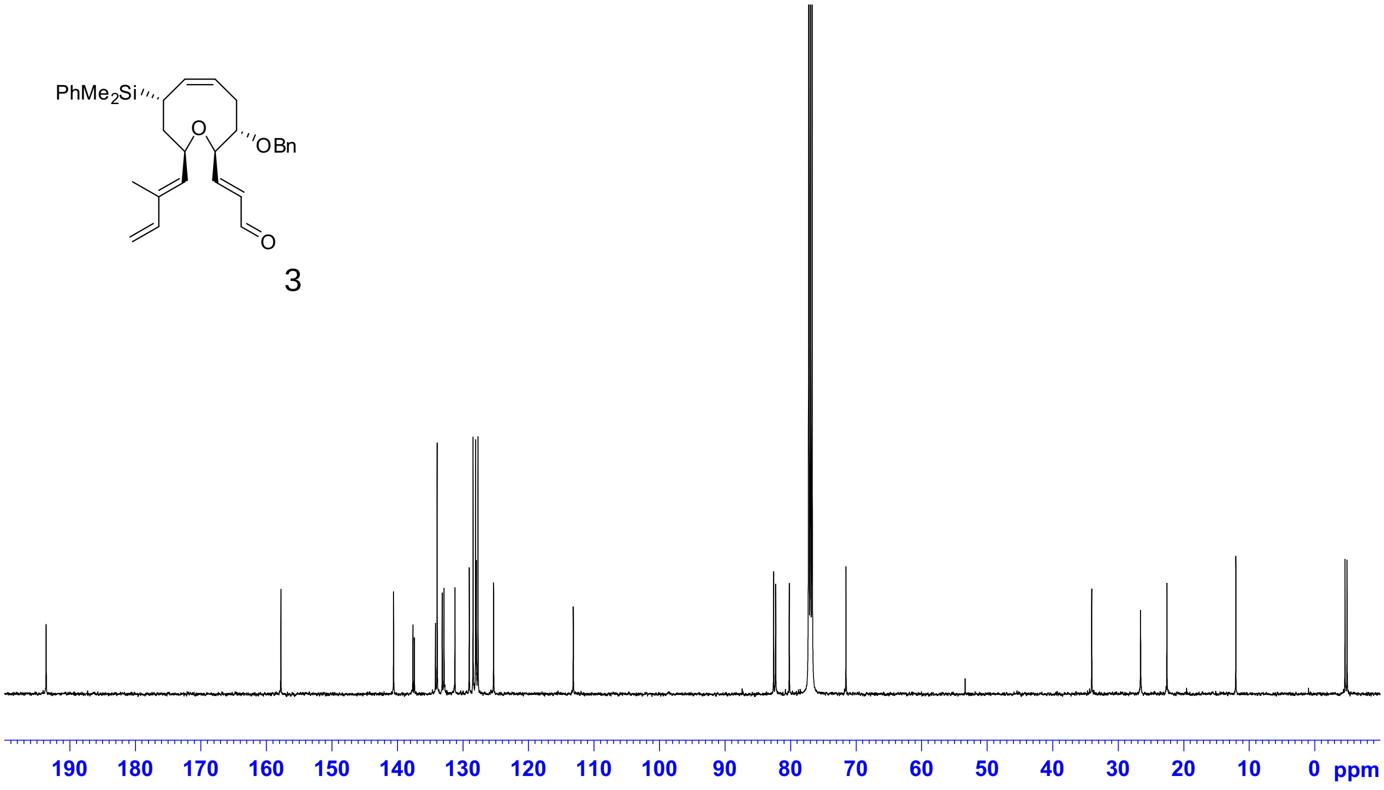


13C NMR (125 MHz, CDCl3): unsaturated aldehyde



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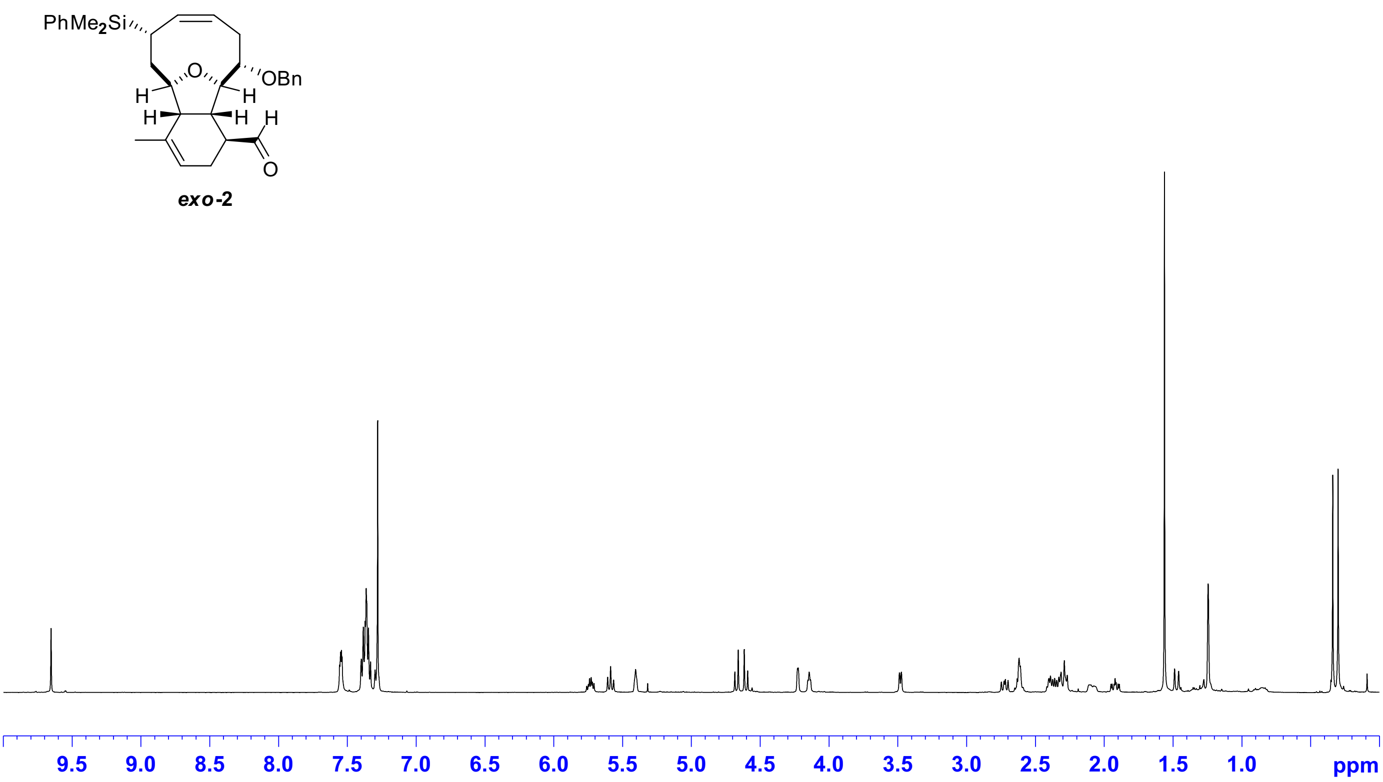
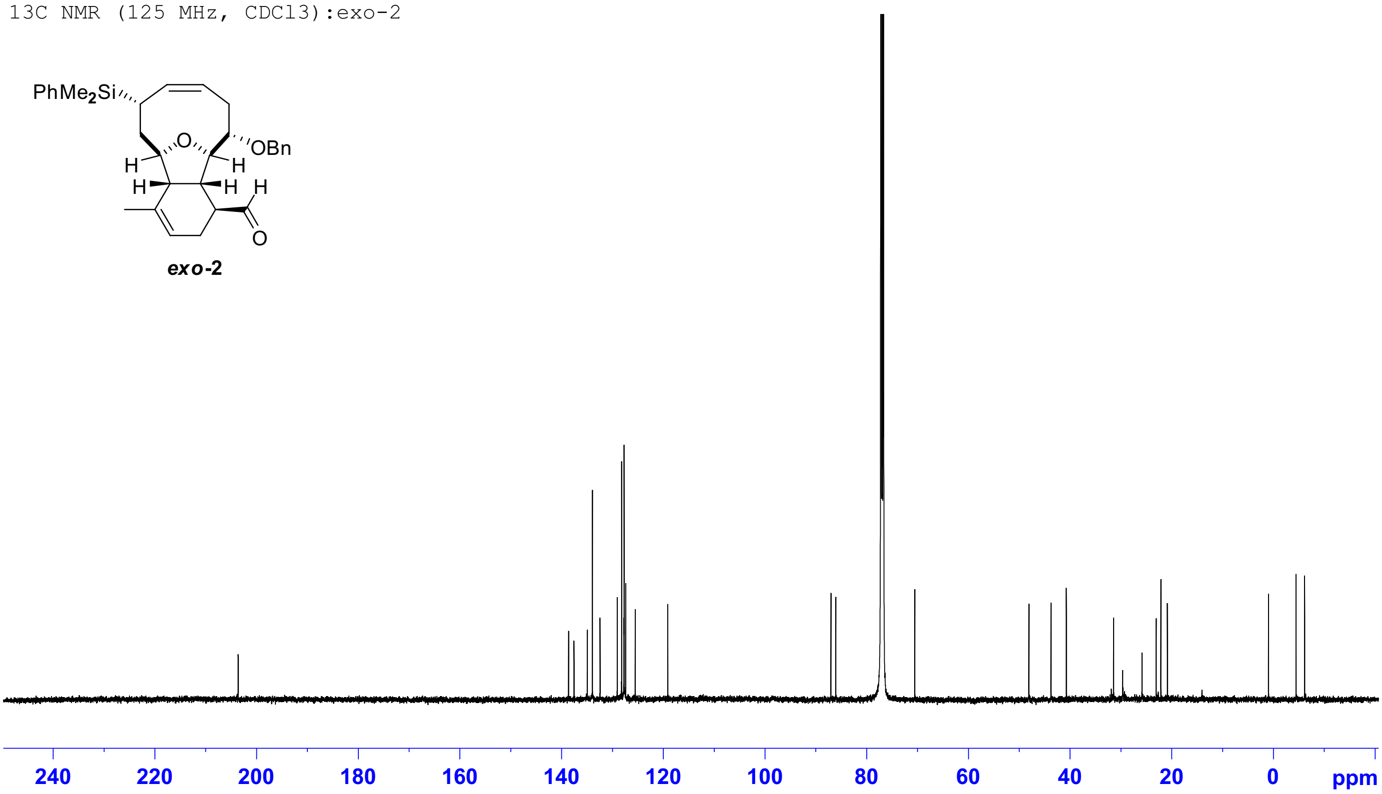
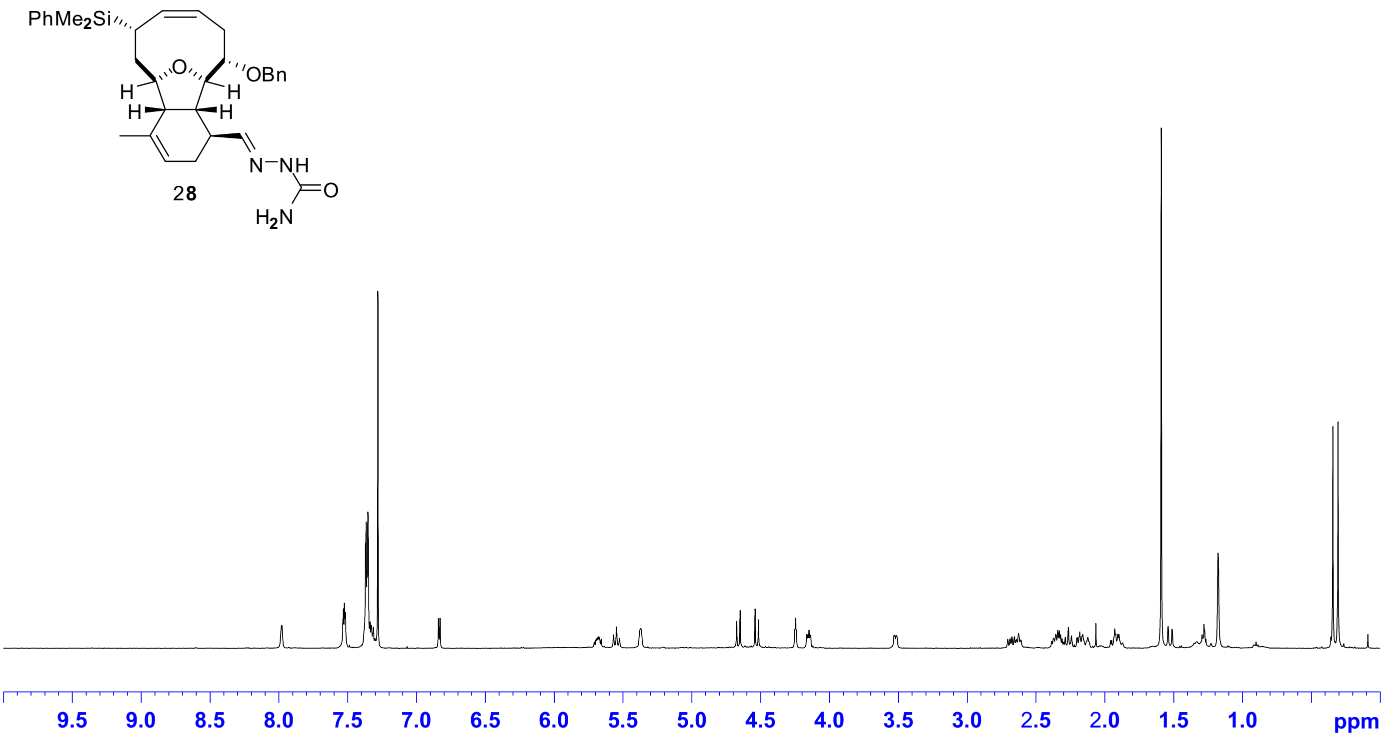
1H NMR (500 MHz, CDCl3): exo-2



13C NMR (125 MHz, CDCl3):exo-2



1H NMR (500 MHz, CDCl3): semicarbazone 28



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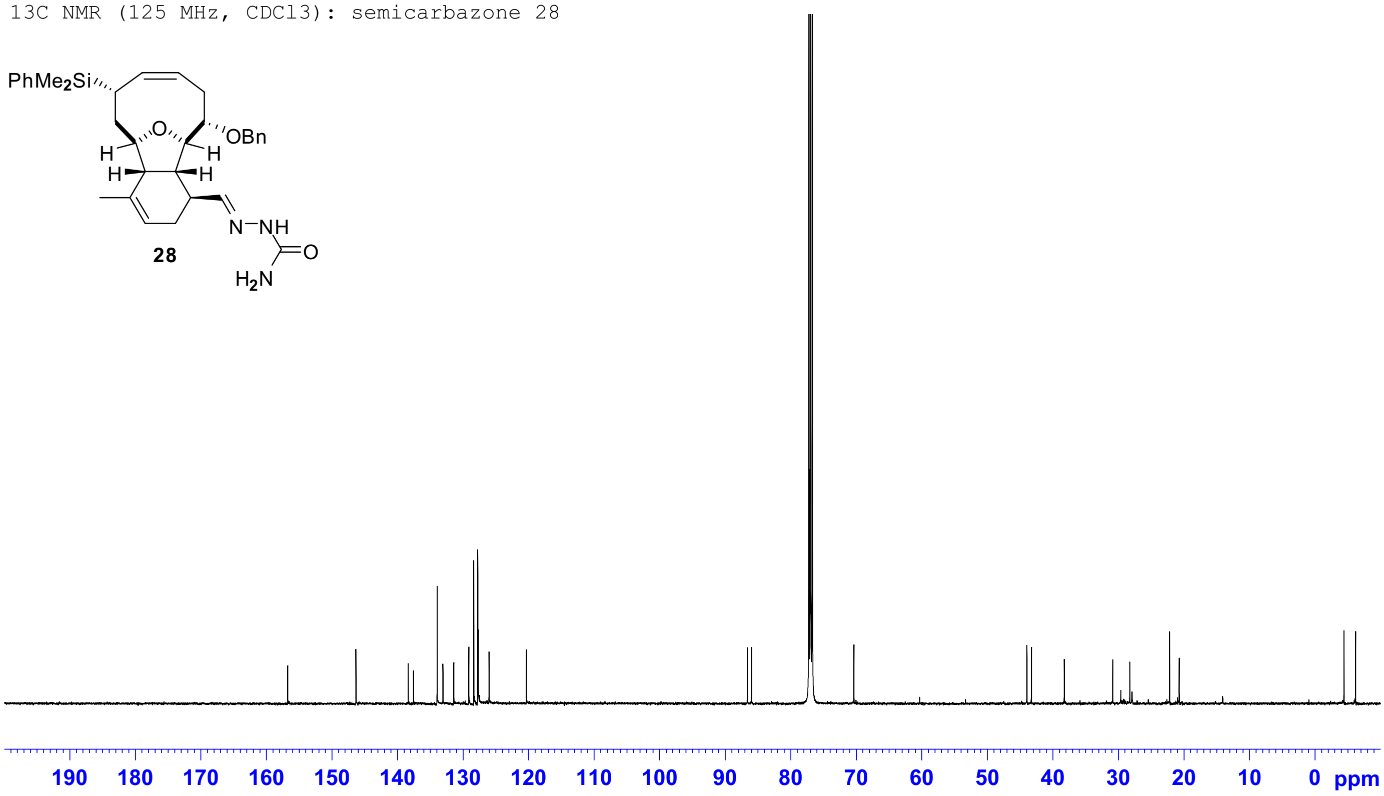

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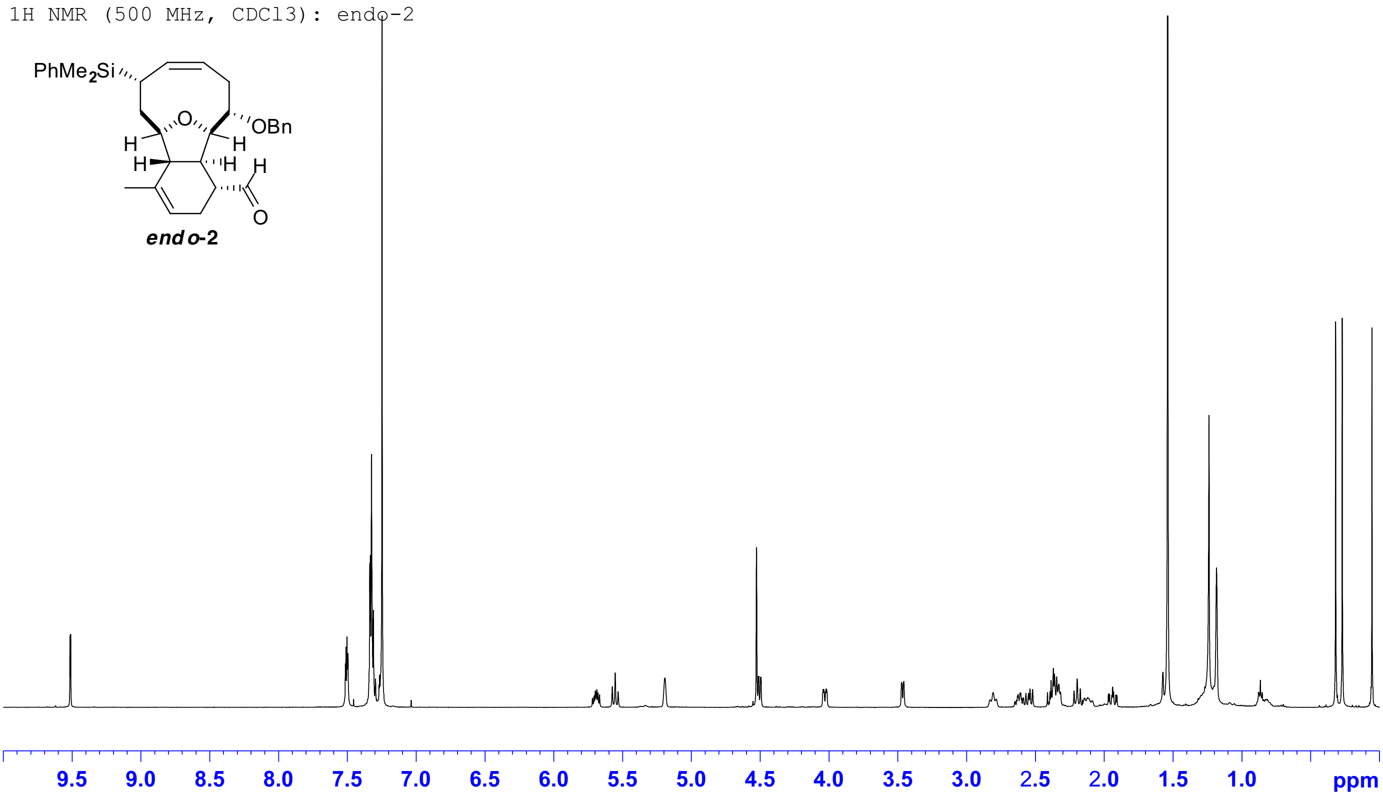

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