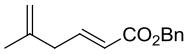
Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supporting Information

Using Singlet Oxygen to Synthesise the CDE-Ring System of the Pectenotoxins

Antonia Kouridaki, Tamsyn Montagnon, Dimitris Kalaitzakis and Georgios Vassilikogiannakis*

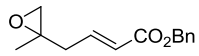
Department of Chemistry, University of Crete, Vasilika Vouton, 71003 Iraklion, Greece. Fax: +30 2810 545166; Tel: +30 2810 545074; E-mail: vasil@chemistry.uoc.gr



2

A stirred solution of IBX (6.66 g, 23.8 mmol) in dry DMSO (50 mL) was cooled to 0 – 5 ^{o}C (ice-water bath) for the slow addition of 3-methyl-3-buten-1-ol (2.00 mL, 1.71 g, 19.9 mmol) over 10 minutes. Following completion of the addition the ice bath was removed and the reaction mixture allowed to warm to room temperature. After 90 minutes of stirring a white precipitate had formed and tlc (using $KMnO_4$ stain to visualize) indicated consumption of the alcohol was complete. CH_2Cl_2 (50 mL) was added to the reaction mixture and stirring continued for 10 minutes. The reaction mixture was then filtered through a coarse sinter funnel to remove the precipitated by-products of the oxidation (IBA) and the resultant solution was then washed with H_2O (3× 75 mL) and brine (75 mL). The solution was then dried (Na_2SO_4). The resultant CH_2Cl_2 solution of the volatile aldehyde product was not concentrated; instead, the ylide $PhCH_2OCOCH{=}PPh_3$ (previously prepared by the method of Aitken and co-workers,[1] 8.94 g, 21.8 mmol) was added directly and the new reaction solution stirred overnight at room temperature (light, which caused the reaction solution to darken from light yellow/orange to dark brown/orange, was excluded during this period by wrapping the reaction vessel in aluminium foil). The reaction mixture was then concentrated to one third of its volume and petroleum ether (75 mL) added to aid the precipitation of $O{=}PPh_3$. The mixture was then filtered through a coarse sinter funnel and the filtrate concentrated and added directly onto the top of a previously readied column for purification by flash column chromatography (silica gel, petroleum ether:EtOAc 50:1 → 40:1). *trans*-Diene **2** (3.57 g, 83%) was isolated with only very minor contamination by the analogous *cis*-isomer.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (m, 5H), 7.03 (dt, J_1 = 15.6 Hz, J_2 = 7.1 Hz, 1H), 5.91 (dt, J_1 = 15.6 Hz, J_2 = 1.4 Hz, 1H), 5.19 (s, 2H), 4.83 (s, 1H), 4.75 (s, 1H), 2.89 (d, J = 7.1 Hz, 2H), 1.74 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 146.9, 142.0, 136.1, 128.5 (2C), 128.2 (2C), 128.1, 122.3, 112.6, 66.1, 40.5, 22.4 ppm.

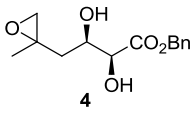


3

A solution of the olefin **2** (3.00 g, 13.9 mmol) in CH_2Cl_2 (50 mL) was slowly introduced, over 20 minutes, into a cooled (ice bath) flask containing a mixture of $NaHCO_3$ (2.56 g, 30.5 mmol) and *m*-CPBA (75% purity by weight such that the 3.51 g used represents *m*-CPBA 2.63 g,

15.3 mmol) in CH_2Cl_2 (100 mL). The solution was then warmed to room temperature and stirred for 30 minutes. Thereafter, it was re-cooled to 0 ^oC and *m*-CPBA (75% purity by weight such that the 1.74 g used represents *m*-CPBA 1.31 mg, 7.6 mmol) was added. After a further 3.5 hours of stirring at room temperature, the resultant suspension was washed with H_2O (80 mL). The phases were separated and the organic layer was re-washed with saturated aq. $Na_2S_2O_5$ (3× 80 mL), saturated aq. $NaHCO_3$ (80 mL) and brine (80 mL). The organic phase was then dried (Na_2SO_4) and concentrated *in vacuo*. The desired epoxide **3** was isolated (3.03 g, 94%) following flash column chromatography (silica gel, petroleum ether:EtOAc = 30:1 → 5:1).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.36 (m, 5H), 6.95 (dt, J_1 = 15.7 Hz, J_2 = 7.4 Hz, 1H), 5.96 (dt, J_1 = 15.7 Hz, J_2 = 1.3 Hz, 1H), 5.18 (s, 2H), 2.65 (d, J = 4.7 Hz, 1H), 2.61 (d, J = 4.7 Hz, 1H), 2.50 (dd, J_1 = 14.9 Hz, J_2 = 7.4 Hz, 1H), 2.42 (ddd, J_1 = 14.9 Hz, J_2 = 7.4 Hz, J_3 = 1.3 Hz, 1H), 1.34 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 143.7, 135.9, 128.5 (2C), 128.2 (3C), 124.0, 66.1, 55.7, 53.0, 39.4, 21.1 ppm; HRMS (TOF ESI): calcd for $C_{14}H_{16}O_3Na$: 255.0992 $[M + Na]^+$; found: 255.0988.

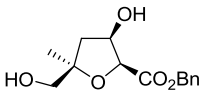


4

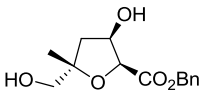
To a solution of the epoxide **3** (3.00 g, 12.9 mmol) in *t*-BuOH:H_2O (1:1, 100 mL) at room temperature, methanesulfonamide (MSA, 1.23 g, 12.9 mmol) and AD-mix-β (19.32 g, 1.5 g per mmol of substrate) were added. The former was added in one portion from the beginning, the latter was added in seven portions over seven hours (1× 2.76 g portion per hour). After the mixture had been stirred for a total of 24 hours, Na_2SO_3 (29.0 g) was added and the stirring was continued for a further 1 hour. NaCl was then added up to the point at which it no longer readily dissolved and the mixture was stirred for 10 minutes. The mixture was then carefully extracted with hot EtOAc (4× 75 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 2:1 → 1:2) to afford the desired diol **4** (2.13 g, 62%, 1:1 mixture of diastereoisomers) and recovered starting material, epoxide **3** (480 mg, 16%).

4 (1:1 mixture of diastereoisomers): ^1H NMR (300 MHz, MeOD) *for both diastereoisomers*: δ = 7.42 - 7.31 (m, 5H for both diastereoisomers), 5.26 (d, J = 12.3 Hz, 1H for both diastereoisomers), 5.18 (d, J = 12.3 Hz, 1H for one diastereoisomer), 5.17 (d, J = 12.3 Hz, 1H for one diastereoisomer), 4.59 (s, -OH), 4.14 (m, 2H for one

diastereoisomer plus 1H for the other), 4.04 (m, 1H for one diastereoisomer), 2.75 (d, *J* = 4.9 Hz, 1H for one diastereoisomer), 2.71 (d, *J* = 4.9 Hz, 1H for one diastereoisomer), 2.62 (d, *J* = 4.9 Hz, 1H for one diastereoisomer), 2.58 (d, *J* = 4.9 Hz, 1H for one diastereoisomer), 2.01 - 1.69 (m, 2H for both diastereoisomers), 1.35 (s, 3H for one diastereoisomer), 1.34 (s, 3H for one diastereoisomer) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) *for both diastereoisomers*: δ = 172.8, 172.7, 135.1, 135.0, 128.6 (4C), 128.5 (2C), 128.3 (4C), 73.7, 73.6, 69.7, 69.5, 67.6, 67.5, 56.3, 55.6, 53.6, 53.4, 39.3, 38.4, 22.1, 21.2 ppm; HRMS (TOF ESI): calcd for $C_{14}H_{18}O_5Na$: 289.1046 [M + Na]$^+$; found: 289.1031.



5a

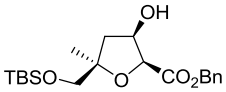


5b

To a solution of the diol **4** (2.00 g, 7.5 mmol, 1:1 mixture of diastereoisomers), prepared above, in EtOAc:CH_2Cl_2 (1:1, 30 mL), at room temperature, PPTS (188 mg, 0.75 mmol) was added and the reaction mixture stirred for 30 minutes. Thereafter, the solution was extracted with saturated aq. $NaHCO_3$ (12 mL) and the two phases were separated. The organic phase was washed with brine (15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silica gel, petroleum ether:EtOAc = 2:1 → 1:2) afforded the cyclised diastereoisomers **5a** (880 mg, 44%) and **5b** (875 mg, 44%) separately.

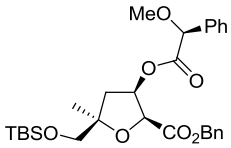
5a: $[a]^{20}_D$ = -10.4 (c = 6.67, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (m, 5H), 5.30 (d, *J* = 12.2 Hz, 1H), 5.17 (d, *J* = 12.2 Hz, 1H), 4.71 (d, *J* = 4.7 Hz, 1H), 4.57 (m, 1H), 3.71 (d, *J* = 12.0 Hz, 1H), 3.43 (d, *J* = 12.0 Hz, 1H), 2.17 (m, 2H), 1.25 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.9, 135.3, 128.5 (2C), 128.3 (3C), 85.5, 83.4, 74.2, 68.6, 67.0, 44.6, 24.3 ppm; HRMS (TOF ESI): calcd for $C_{14}H_{19}O_5$: 267.1227 [M + H]$^+$; found: 267.1220.

5b: $[a]^{20}_D$ = -16.3 (c = 4.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34 (m, 5H), 5.24 (d, *J* = 12.5 Hz, 1H), 5.20 (d, *J* =12.5 Hz, 1H), 4.68 (m, 1H), 4.58 (d, *J* = 4.6 Hz, 1H), 3.50 (d, *J* = 11.6 Hz, 1H), 3.36 (d, *J* = 11.6 Hz, 1H), 2.38 (brs, 2 -OH), 2.30 (dd, J_1 = 13.5 Hz, J_2 = 6.0 Hz, 1H), 1.83 (dd, J_1 = 13.5 Hz, J_2 = 2.3 Hz, 1H), 1.39 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0, 135.4, 128.5 (2C), 128.4, 128.3 (2C), 85.4, 82.7, 74.3, 68.6, 66.8, 41.2, 24.0 ppm; HRMS (TOF ESI): calcd for $C_{14}H_{18}O_5Na$: 289.1046 [M + Na]$^+$; found: 289.1031.



To a solution of the alcohol **5a** (70 mg, 0.26 mmol) in dry DMF (3 mL) at room temperature, imidazole (32 mg, 0.47 mmol), TBSCl (59 mg, 0.39 mmol) and 4-DMAP (5 mg, 0.04 mmol) were added. After 1 hour of stirring at the same temperature, MeOH (0.3 mL) was added and the reaction mixture was left to stir for a further 1 hour. Thereafter, the mixture was diluted with EtOAc (7 mL) and washed with H_2O (4× 4 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 20:1 → 4:1) to afford the desired mono-protected alcohol (62 mg, 63%).

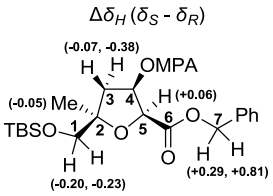
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39-7.31 (m, 5H), 5.31 (d, *J* = 12.4 Hz, 1H), 5.15 (d, *J* = 12.4 Hz, 1H), 4.66 (d, *J* = 11.1 Hz, 1H), 4.49-4.42 (m, -OH plus 1H), 3.75 (d, *J* = 10.5 Hz, 1H), 3.44 (d, *J* = 10.5 Hz, 1H), 2.19 (d, *J* = 14.0 Hz, 1H), 2.02 (dd, J_1 = 14.0 Hz, J_2 = 4.9 Hz, 1H), 1.21 (s, 3H), 0.91 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.6, 135.8, 128.4 (2C), 128.2 (2C), 128.1, 84.3, 82.8, 74.3, 69.5, 66.4, 43.4, 25.8 (3C), 24.3, 18.4, -5.6, -5.8 ppm; HRMS (TOF ESI): calcd for $C_{20}H_{32}O_5SiNa$: 403.1917 $[M + Na]^+$; found: 403.1906.



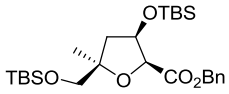
To a solution of the monoprotected diol prepared above (62 mg, 0.16 mmol) in dry CH_2Cl_2 (4 mL) at 0 °C, was added DCC (108 mg, 0.52 mmol), (*S*)-MPA acid (80 mg, 0.48 mmol) and a catalytic amount of 4-DMAP (2 mg, 10 mol%). The reaction mixture was left to stir for a total of 72 hours, before being filtered through a short pad of celite. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 4:1 → 1:1) to afford the desired (*S*)-MPA ester (61 mg, 72%) as a mixture of two diastereoisomers in 5:1 ratio which represents the enantiomeric ratio for the Sharpless asymmetric dihydroxylation of olefin **3**. The above procedure was repeated for the analogous (*R*)-MPA acid coupling, although in this case a shorter reaction time (15 hours) was required for the formation of the (*R*)-MPA ester (79 mg, 93%).

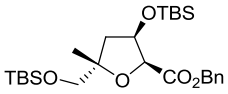
Mixture of two diastereoisomers in 5:1 ratio.^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34 (m, 10H for major plus 8H for minor), 7.09 (m, 2H, minor), 5.65 (q, *J* = 4.6 Hz, 1H, major), 5.63 (q, *J* = 4.4 Hz, 1H, minor), 5.17 (d, *J* = 12.1 Hz, 1H, major), 4.92 (d, *J* = 12.1 Hz, 1H, major), 4.88 (d, *J* = 12.0 Hz, 1H, minor), 4.70 (d, *J* = 4.6 Hz, 1H,

major), 4.64 (d, J = 4.4 Hz, 1H, minor), 4.64 (s, 1H, minor), 4.43 (s, 1H, major), 4.11 (d, J = 12.0 Hz, 1H, minor), 3.69 (d, J = 9.6 Hz, 1H, minor), 3.62 (d, J = 9.6 Hz, 1H, minor), 3.49 (d, J = 9.6 Hz, 1H, major), 3.39 (d, J = 9.6 Hz, 1H, major), 3.35 (s, 3H, minor), 3.29 (s, 3H, major), 2.33 (dd, J_1 = 14.6 Hz, J_2 = 1.6 Hz, 1H, minor), 2.02 (d, J = 14.6 Hz, 1H, minor), 1.95 (m, 2H, major), 1.28 (s, 3H, minor), 1.23 (s, 3H, major), 0.91 (s, 9H, minor), 0.85 (s, 9H, major), 0.09 (s, 6H, minor), 0.01 (s, 3H, major), -0.03 (s, 3H, major) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) for major diastereoisomer: δ = 169.5, 168.1, 135.6, 135.4, 128.8, 128.6 (2C), 128.5 (4C), 128.4, 127.1 (2C), 84.7, 82.1, 79.1, 75.8, 68.9, 66.6, 57.2, 40.7, 25.7 (3C), 24.1, 18.1, -5.4, -5.5 ppm; HRMS (TOF ESI): calcd for $C_{29}H_{41}O_7Si$: 529.2621 $[M + H]^+$; found: 529.2613; ^{13}C NMR (75 MHz, $CDCl_3$) for minor diastereoisomer: δ = 169.4, 167.4, 135.7, 135.2, 128.9, 128.7 (2C), 128.4 (2C), 128.2, 128.1 (2C), 127.4 (2C), 85.0, 82.4, 77.2, 76.3, 68.8, 66.3, 53.3, 40.9, 25.8 (3C), 24.3, 18.2, -5.4, -5.5 ppm; HRMS (TOF ESI): calcd for $C_{29}H_{40}O_7SiNa$: 551.2441 $[M + Na]^+$; found: 551.2437.



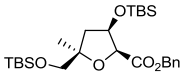
According to Mosher's model,[2] C-4 was assigned as having the *R*-configuration, since the signs of $\Delta\delta_H$ (δ_S – δ_R) were positive for H-5 (+ 0.06), H-7 (+ 0.29, + 0.81) and negative for H-1 (–0.20, –0.23), Me-2 (–0.05) and H-3 (–0.07, –0.38).



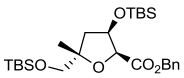


To a solution of the alcohol **5a** or **5b** (800 mg, 3.0 mmol) in dry DMF (15 mL) at room temperature, imidazole (700 mg, 10.5 mmol), TBSCl (1.35 g, 9.0 mmol) and 4-DMAP (55 mg, 0.45 mmol) were added. In the case of substrate **5a**, after the mixture had been stirred for 12 hours at this temperature, the reaction was quenched with MeOH (1.0 mL). Whilst the reaction of substrate **5b** was not completed in this time, so imidazole (700 mg, 10.5 mmol), TBSCl (1.35 g, 9.0 mmol) and 4-DMAP (55 mg, 0.45 mmol) were added again, and the mixture was left to stir for further 12 hours, before MeOH (1 mL) was added. The stirring for both mixtures continued for 1 hour after the addition of MeOH, after which time the mixtures were partitioned between EtOAc (30 mL) and H_2O (4× 10 mL). The organic phases were dried (Na_2SO_4) and the solvent was removed *in vacuo*. In the case where **5a** was the substrate, the product was pure enough to be used in the

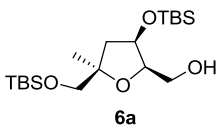
following step without chromatographic purification (1.38 g, 93%). The *bis*-TBS protected product of the **5b** substrate (681 mg, 46%) was isolated by flash column chromatography (silica gel, petroleum ether:EtOAc = 20:1 → 10:1). The reason for the lower yield obtained for the double protection of **5b** (in comparison to that for **5a**'s double protection) was not investigated because it was of little consequence since this compound was required only for NOE studies and not for progression of the synthesis itself.



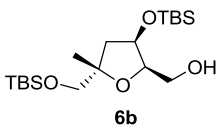
$[a]^{20}_D$ = -3.9 (c = 4.94, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 (m, 5H), 5.36 (d, *J* = 12.4 Hz, 1H), 4.94 (d, *J* = 12.4 Hz, 1H), 4.66 (m, 2H), 3.82 (d, *J* = 9.2 Hz, 1H), 3.59 (d, *J* = 9.2 Hz, 1H), 2.22 (dd, J_1 = 13.4 Hz, J_2 = 2.2 Hz, 1H), 1.78 (dd, J_1 = 13.4 Hz, J_2 = 5.1 Hz, 1H), 1.26 (s, 3H), 0.88 (s, 9H), 0.85 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.00 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.5, 135.6, 128.4 (2C), 128.3 (2C), 128.1, 85.3, 82.6, 74.7, 69.0, 66.4, 43.1, 25.8 (3C), 25.6 (3C), 24.8, 18.1, 17.8, -3.0, -4.8, -5.4, -5.5 ppm; HRMS (TOF ESI): calcd for $C_{26}H_{47}O_5Si_2$: 495.2962 $[M + H]^+$; found: 495.2945.



$[a]^{20}_D$ = + 7.9 (c = 3.63, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34 (m, 5H), 5.35 (d, *J* = 12.4 Hz, 1H), 4.96 (d, *J* = 12.4 Hz, 1H), 4.77 (q, *J* = 5.7 Hz, 1H), 4.61 (d, *J* = 5.7 Hz, 1H), 3.51 (d, *J* = 10.2 Hz, 1H), 3.38 (d, *J* = 10.2 Hz, 1H), 2.32 (dd, J_1 = 12.6 Hz, J_2 = 6.3 Hz, 1H), 1.80 (dd, J_1 = 12.6 Hz, J_2 = 4.8 Hz, 1H), 1.38 (s, 3H), 0.89 (s, 9H), 0.86 (s, 9H), 0.06 (s, 3H), 0.04 (s, 6H), 0.01 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 135.8, 128.4 (2C), 128.2 (2C), 128.0, 85.2, 83.0, 74.7, 70.1, 66.2, 42.1, 25.9 (3C), 25.6 (3C), 24.2, 18.2, 17.9, -4.9, -5.2, -5.4, -5.6 ppm; HRMS (TOF ESI): calcd for $C_{26}H_{46}O_5Si_2Na$: 517.2782 $[M + Na]^+$; found: 517.2765.



6a



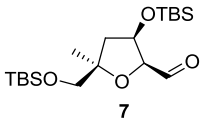
6b

To a solution of the *bis*-TBS protected product derived from the double protection of **5a** (see above, 800 mg, 1.61 mmol) in dry CH_2Cl_2 (15 mL), at -78 ^{o}C, Dibal-H (3.6 mL of 1.0 M in hexane, 3.6 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and was then stirred for 30 minutes, before the addition of a saturated aqueous solution of Rochelle's salt (10 mL) followed by 1 hour

stirring, until the organic phase became completely clear. The phases were separated and the organic layer was washed with brine (10 mL) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 20:1 → 10:1) to afford the alcohol **6a** (512 mg, 82%). This exact procedure was repeated for the product of the double protection of **5b**, albeit on a reduced scale (*bis*-TBS protected substrate derived from **5b**, 600 mg, 1.21 mmol) to afford **6b** (421 mg, 89%).

6a: $[a]^{20}_D$ = -10.9 (c = 3.90, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.51 (q, J = 5.2 Hz, 1H), 4.03 (q, J = 5.2 Hz, 1H), 3.76 (dd, J_1 = 11.6 Hz, J_2 = 5.2 Hz, 1H), 3.71 (dd, J_1 = 11.6 Hz, J_2 = 5.2 Hz, 1H), 3.60 (d, J = 9.6 Hz, 1H), 3.48 (d, J = 9.6 Hz, 1H), 2.11 (dd, J_1 = 13.1 Hz, J_2 = 4.5 Hz, 1H), 2.09 (brs, -OH), 1.81 (dd, J_1 = 13.1 Hz, J_2 = 6.1 Hz, 1H), 1.20 (s, 3H), 0.90 (brs, 18H), 0.08 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H), 0.05 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 82.7, 81.1, 74.3, 69.5, 62.7, 42.9, 25.9 (3C), 25.7 (3C), 24.8, 18.3, 18.0, -4.6, -5.2, -5.4, -5.5 ppm; HRMS (TOF ESI): calcd for $C_{19}H_{43}O_4Si_2$: 391.2700 $[M + H]^+$; found: 391.2685.

6b: $[a]^{20}_D$ = -5.7 (c = 1.46, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.58 (q, J = 5.5 Hz, 1H), 4.03 (q, J = 5.0 Hz), 3.76 (dd, J_1 = 11.8 Hz, J_2 = 4.9 Hz, 1H), 3.71 (dd, J_1 = 11.8 Hz, J_2 = 4.9 Hz, 1H), 3.46 (d, J = 10.1 Hz, 1H), 3.36 (d, J = 10.1 Hz, 1H), 2.31 (dd, J_1 = 12.8 Hz, J_2 = 6.5 Hz, 1H), 1.66 (dd, J_1 = 12.8 Hz, J_2 = 4.6 Hz, 1H), 1.27 (s, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.08 (s, 6H), 0.04 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 82.8, 82.0, 75.0, 70.2, 63.2, 43.3, 25.9 (3C), 25.7 (3C), 24.9, 18.2, 17.9, -4.7, -5.2, -5.4, -5.5 ppm; HRMS (TOF ESI): calcd for $C_{19}H_{43}O_4Si_2$: 391.2700 $[M + H]^+$; found: 391.2691.

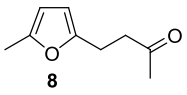


7

IBX (448 mg, 1.6 mmol) was added portionwise to a solution of the alcohol **6a** (312 mg, 0.80 mmol) in dry DMSO (10 mL), at room temperature. After 3 hours stirring, the reaction mixture was diluted with EtOAc (25 mL) and extracted with saturated aq. $NaHCO_3$ (8 mL). The phases were separated and the organic layer was washed with H_2O (4× 10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford pure product (304 mg, 98%).

$[a]^{20}_D$ = -38.7 (c = 3.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.54 (d, J = 2.2 Hz, 1H), 4.69 (td, J_1 = 5.4 Hz, J_2 = 1.7 Hz, 1H), 4.23 (dd, J_1 = 4.7 Hz, J_2 = 2.2 Hz, 1H), 3.73 (d, J = 9.4 Hz, 1H), 3.60 (d, J = 9.4 Hz, 1H), 2.16 (dd, J_1 = 13.6 Hz, J_2 = 1.9 Hz,

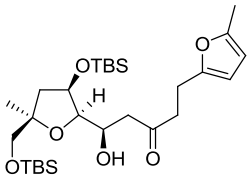
1H), 1.78 (dd, J_1 = 13.6 Hz, J_2 = 5.4 Hz, 1H), 1.25 (s, 3H), 0.87 (s, 9H), 0.82 (s, 9H), 0.04 (s, 3H), 0.02 (s, 6H), -0.01 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.2, 86.8, 86.0, 76.2, 69.0, 43.7, 25.8 (3C), 25.5 (3C), 24.6, 18.2, 17.8, -4.9, -5.4, -5.5, -5.5 ppm; HRMS (TOF ESI): calcd for $C_{19}H_{41}O_4Si_2$: 389.2543 $[M + H]^+$; found: 389.2530.



8

A solution of methyl furan (1.1 mL, 12.2 mmol), methyl vinyl ketone (0.5 mL, 6.1 mmol) and hydroquinone (13 mg, 0.12 mmol) in H_2O:CH_3COOH (10:1, 8.8 mL) was heated in a sealed tube at 130 °C for 40 minutes. The reaction mixture was left to cool to room temperature and saturated aq. $NaHCO_3$ (3 mL) and Et_2O (15 mL) were then added and the mixture stirred for a further 15 minutes. The phases were separated and the organic layer was washed with saturated aq. $NaHCO_3$ (3× 3 mL) and dried (Na_2SO_4). The solvent was evaporated *in vacuo* and the resulting substituted furan **8** (882 mg, 95%) was used in the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.84 (d, J = 3.0 Hz, 1H), 5.82 (brs, 1H), 2.84 (m, 2H), 2.75 (m, 2H), 2.22 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.5, 152.6, 150.5, 105.8, 105.7, 41.8, 29.8, 22.2, 13.4 ppm.

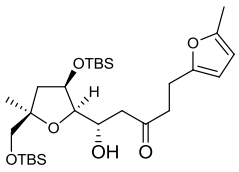


9

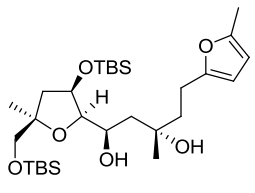
To a flame dried flask, under an inert argon atmosphere, was added anhydrous diisopropylamine (153 μL, 1.09 mmol) in anhydrous THF (2.5 mL). The solution was cooled to 0 °C and *n*-BuLi (0.6 mL, 1.6 M in hexane, 0.96 mmol) was added and the reaction mixture was stirred for 20 minutes at the same temperature. In this way the requisite LDA was generated. The flask was then cooled to –78 °C and a solution of ketone **8** (146 mg, 0.96 mmol) in dry THF (2 mL) was added dropwise. After 30 minutes stirring at this temperature, a solution of the aldehyde **7** (250 mg, 0.64 mmol) in THF (3 mL) at –78 °C was cannulated into the reaction mixture. The reaction mixture was stirred for a further 30 minutes at –78 °C. The reaction was quenched with saturated aq. NH_4Cl (3 mL) whilst still at –78 °C and the mixture was then allowed to warm to room temperature, before being partitioned between saturated aq. NH_4Cl (3 mL) and EtOAc (5 mL). The phases were separated and the organic layer was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, petroleum

ether:EtOAc = 60:1 → 5:1) afforded the desired product **9** (220 mg, 64%) accompanied by small amounts of the undesired diastereoisomer (22 mg, 6%) and trace amounts of the product of self-condensation of ketone **8**.

$[a]^{20}_D$ = -2.9 (c = 5.54, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.83 (d, *J* = 3.0 Hz, 1H), 5.81 (d, *J* = 3.0 Hz, 1H), 4.48 (m, 1H), 4.26 (td, J_1 = 8.6 Hz, J_2 = 2.7 Hz, 1H), 3.68 (dd, J_1 = 8.2 Hz, J_2 = 4.0 Hz, 1H), 3.54 (d, *J* = 9.4 Hz, 1H), 3.43 (d, *J* = 9.4 Hz, 1H), 2.85 (m, 3H), 2.77 (m, 2H), 2.62 (dd, J_1 = 17.0 Hz, J_2 = 9.0 Hz, 1H), 2.22 (s, 3H), 2.06 (dd, J_1 = 13.5 Hz, J_2 = 2.8 Hz, 1H), 1.77 (dd, J_1 = 13.5 Hz, J_2 = 5.4 Hz, 1H), 1.18 (s, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.09 (s, 6H), 0.02 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.4, 152.6, 150.4, 105.8, 105.7, 83.2, 83.0, 73.5, 69.6, 66.6, 46.5, 43.3, 41.8, 25.8 (3C), 25.7 (3C), 24.6, 21.9, 18.2, 17.9, 13.4, -4.7, -5.3, -5.4, -5.5 ppm; HRMS (TOF ESI): calcd for $C_{28}H_{53}O_6Si_2$: 541.3380 $[M + H]^+$; found: 541.3365.



$[a]^{20}_D$ = -3.5 (c = 2.07, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.87 (d, *J* = 2.9 Hz, 1H), 5.82 (d, *J* = 2.9 Hz, 1H), 4.46 (m, 1H), 4.11 (m, 1H), 3.70 (dd, J_1 = 8.2 Hz, J_2 = 3.7 Hz, 1H), 3.54 (d, *J* = 9.4 Hz, 1H), 3.46 (d, *J* = 9.4 Hz, 1H), 3.22 (m, 1H), 3.08 – 2.89 (m, 3H), 2.22 (s, 3H), 2.03 (dd, J_1 = 13.6 Hz, J_2 = 2.2 Hz, 1H), 1.77 (dd, J_1 = 13.6 Hz, J_2 = 5.3 Hz, 1H), 1.29 – 1.20 (m, 2H), 1.17 (s, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.10 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 212.9, 151.6, 150.6, 106.9, 106.0, 83.1, 81.0, 73.8, 69.7, 69.4, 53.5, 43.6, 30.4, 25.8 (3C), 25.7 (3C), 24.9, 24.4, 18.2, 17.9, 13.4, -4.5, -5.2, -5.3, -5.4 ppm; HRMS (TOF ESI): calcd for $C_{28}H_{53}O_6Si_2$: 541.3380 $[M + H]^+$; found: 541.3364.



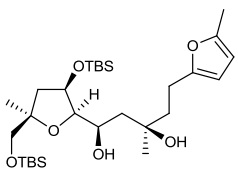
10

Methylation of ketone **9** was accomplished using the method as that first developed and used by Pihko and co-workers.[3]

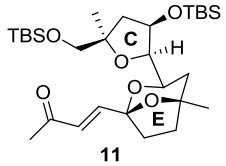
To a flask containing titanium (IV) isopropoxide (2.68 mL, 9.00 mmol) at –5 °C, was added dropwise titanium tetrachloride (0.32 mL, 3.00 mmol). The mixture was left to warm to room temperature and stirred for 5 minutes, before being diluted with Et_2O (13.5 mL). The stirring was then continued at the same temperature for 30 minutes. Thereafter the mixture was cooled to 0 °C, MeLi (1.6 M in Et_2O, 7.5 mL, 12.00 mmol) was added dropwise and the mixture was left to stir at this temperature for 1 hour. A portion of the triisopropoxymethyltitanium solution (0.5 M, 5.6 mL, 2.80 mmol) was

transferred to another flask and cooled to –78 °C. A solution of ketone **9** (110 mg, 0.20 mmol) in Et_2O (4.0 mL) was added dropwise and the reaction mixture was stirred at –78 °C for 10 minutes. It was then warmed to 0 °C and left to stir for a further 30 minutes. The reaction mixture was then diluted with Et_2O (2.5 mL) and a solution of HCl (0.5 M, 2.5 mL) was added dropwise. The mixture was left to stir until both phases were clear. The layers were then separated and the organic phase was washed with brine (3 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Desired diol **10** (72 mg, 65%) was furnished after purification by flash column chromatography (silica gel, petroleum ether:EtOAc = 20:1 → 4:1) as the major diastereoisomeric product. The minor diastereoisomer (19 mg, 17%) was also isolated.

Major diastereoisomer **10**: $[a]^{20}_D$ = -12.3 (c = 3.97, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.83 (brs, 2H), 4.59 (q, J = 4.5 Hz, 1H), 4.23 (ddd, J_1 = 10.3 Hz, J_2 = 7.3 Hz, J_3 = 2.9 Hz, 1H), 3.68 (dd, J_1 = 7.3 Hz, J_2 = 4.5 Hz, 1H), 3.55 (d, J = 9.4 Hz, 1H), 3.45 (d, J = 9.4 Hz, 1H), 3.45 (brs, 2 -OH), 2.66 (m, 2H), 2.24 (s, 3H), 2.09 (dd, J_1 = 13.5 Hz, J_2 = 3.7 Hz, 1H), 2.03-1.67 (m, 5H), 1.22 (s, 3H), 1.20 (s, 3H), 0.91 (s, 9H), 0.87 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H), 0.02 (s, 3H), 0.02 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.5, 150.1, 105.7, 104.9, 83.1, 82.8, 74.5, 72.3, 69.7, 68.8, 43.9, 43.0, 39.0, 27.8, 25.8 (3C), 25.7 (3C), 24.6, 23.2, 18.2, 17.8, 13.4, -4.3, -5.2, -5.4, -5.5 ppm; HRMS (TOF ESI): calcd for $C_{29}H_{57}O_6Si_2$: 557.3693 $[M + H]^+$; found: 557.3680.



Minor diastereoisomer: $[a]^{20}_D$ = -10.3 (c = 2.66, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.83 (brs, 2H), 4.58 (q, J = 4.6 Hz, 1H), 4.25 (ddd, J_1 = 12.7 Hz, J_2 = 7.6 Hz, J_3 = 3.0 Hz, 1H), 3.68 (dd, J_1 = 7.6 Hz, J_2 = 4.5 Hz, 1H), 3.55 (d, J = 9.5 Hz, 1H), 3.47 (d, J = 9.5 Hz, 1H), 3.38 (brs, 2 -OH), 2.69 (m, 2H), 2.23 (s, 3H), 2.09 (dd, J_1 = 14.2 Hz, J_2 = 3.6 Hz, 1H), 1.85 – 1.72 (m, 5H), 1.30 (s, 3H), 1.19 (s, 3H), 0.92 (s, 9H), 0.89 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H), 0.04 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.6, 150.0, 105.7, 104.9, 83.2, 82.8, 74.5, 72.4, 69.7, 69.0, 43.0, 42.8, 42.2, 26.1, 25.8 (3C), 25.7 (3C), 24.5, 22.5, 18.2, 17.8, 13.4, -4.3, -5.2, -5.3, -5.4 ppm; HRMS (TOF ESI): calcd for $C_{29}H_{56}O_6Si_2Na$: 579.3513 $[M + Na]^+$; found: 579.3503.



11

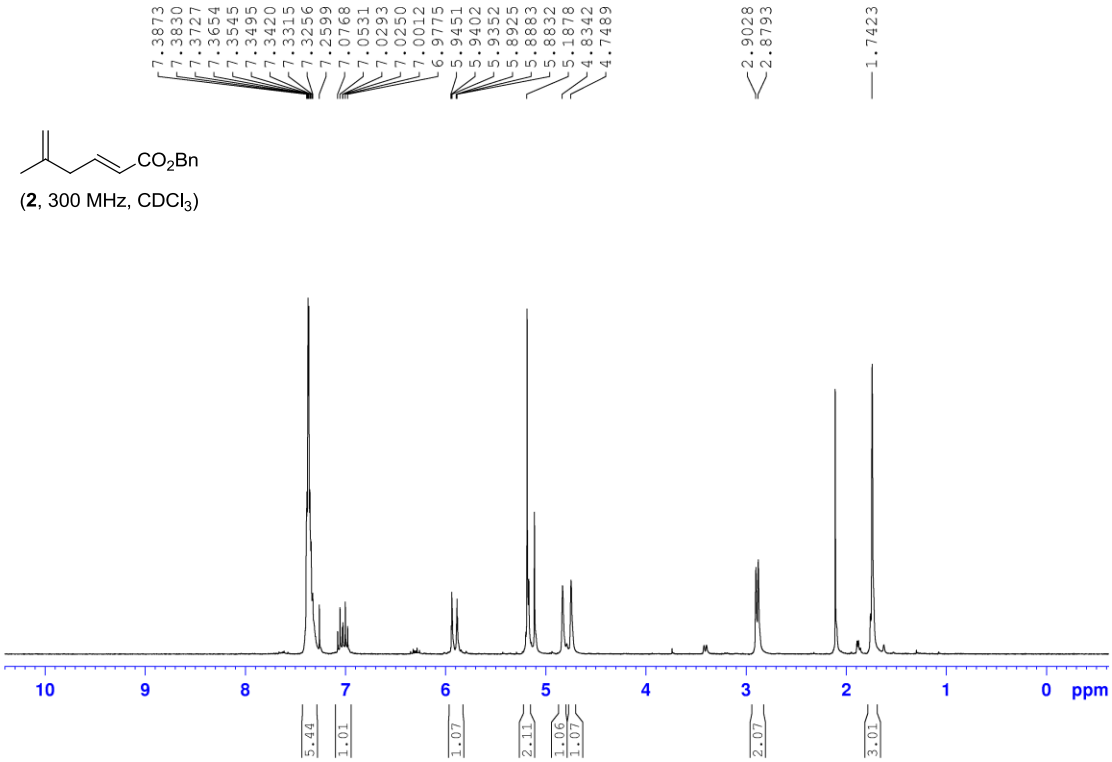
A solution of furan **10** (40 mg, 0.072 mmol) in CH_2Cl_2 (3 mL), contanining Methylene Blue (10^{-4} M) as photosensitizer, was

placed in a test tube and cooled to 0 ^{o}C. Oxygen was gently bubbled through the solution whilst it was irradiated with a xenon Variac Eimac Cermax 300 W lamp for 1 min (still at 0 ºC). The reaction mixture was then transferred to a flask covered with aluminum foil and treated with an excess of dimethyl sulphide (50 μL) at room temperature. After the solution had been stirred for 12 hours, a catalytic amount of *p*-TsOH (5 mg) was added and the stirring was continued for a further 20 minutes at the same temperature. The reaction mixture was extracted with saturated aq. $NaHCO_3$ (1 mL), the layers separated and the organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. The desired product **11** (33 mg, 82%) was isolated by flash column chromatography (silica gel, petroleum ether:EtOAc = 30:1 → 10:1). This photooxygenation could also be conducted with water replacing the CH_2Cl_2 (in this case, however, rose Bengal was used as photosensitiser, not methylene blue). After the initial photooxygenation step the intermediate was extracted into CH_2Cl_2 before the addition of the excess of DMS. The ensuing operations were undertaken exactly as described above for the reaction done entirely in CH_2Cl_2 to ultimately furnish the product with a yield of 74%.

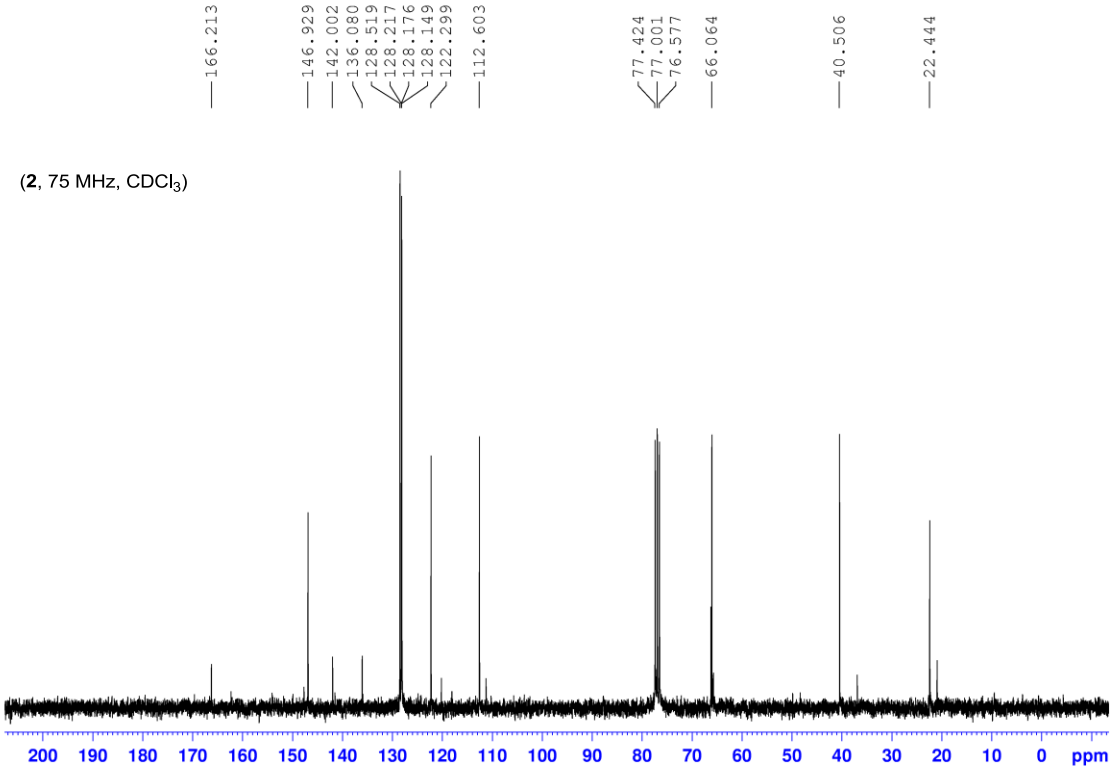
[a]$^{20}_{D}$ = -25.3 (c = 3.55, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.64 (d, *J* = 16.1 Hz, 1H), 6.40 (d, *J* = 16.1 Hz, 1H), 4.34 (dd, J_1 = 4.6 Hz, J_2 = 2.9 Hz, 1H), 4.14 (q, *J* = 7.8 Hz, 1H), 3.64 (dd, J_1 = 8.3 Hz, J_2 = 2.9 Hz, 1H), 3.56 (d, *J* = 9.1 Hz, 1H), 3.47 (d, *J* = 9.1 Hz, 1H), 2.26 (s, 3H), 2.22 (m, 1H), 2.05 (d, *J* = 13.8 Hz, 1H), 2.06 - 1.94 (m, 2H), 1.80 – 1.67 (m, 3H), 1.72 (dd, J_1 = 13.8 Hz, J_2 = 4.6 Hz, 1H), 1.39 (s, 3H), 1.19 (s, 3H), 0.90 (s, 9H), 0.87 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.5, 143.5, 130.5, 103.7, 85.1, 82.9, 81.7, 72.3, 69.7, 67.0, 43.9, 40.4, 36.1, 34.4, 27.2, 26.0, 25.8 (6C), 24.6, 18.2, 17.9, -4.6, -4.9, -5.3, -5.4 ppm; HRMS (TOF ESI): calcd for $C_{29}H_{55}O_6Si_2$: 555.3537 $[M + H]^+$; found: 555.3518.

References:

[1] R. A. Aitken, J. M. Armstrong, M. J. Drysdale, F. C. Ross, B. M. Ryan, *J. Chem. Soc. Perkin Trans. 1* 1999, 593.
[2] J. M. Seco, E. Quiñoá, R. Riguera, *Chem. Rev.*, 2004, **104**, 17 and references therein.
[3] J. E. Aho, E. Salomäki, K. Rissanen, P. M. Pihko, *Org. Lett.*, 2008, **10**, 4179.



(**2**, 300 MHz, $CDCl_3$)



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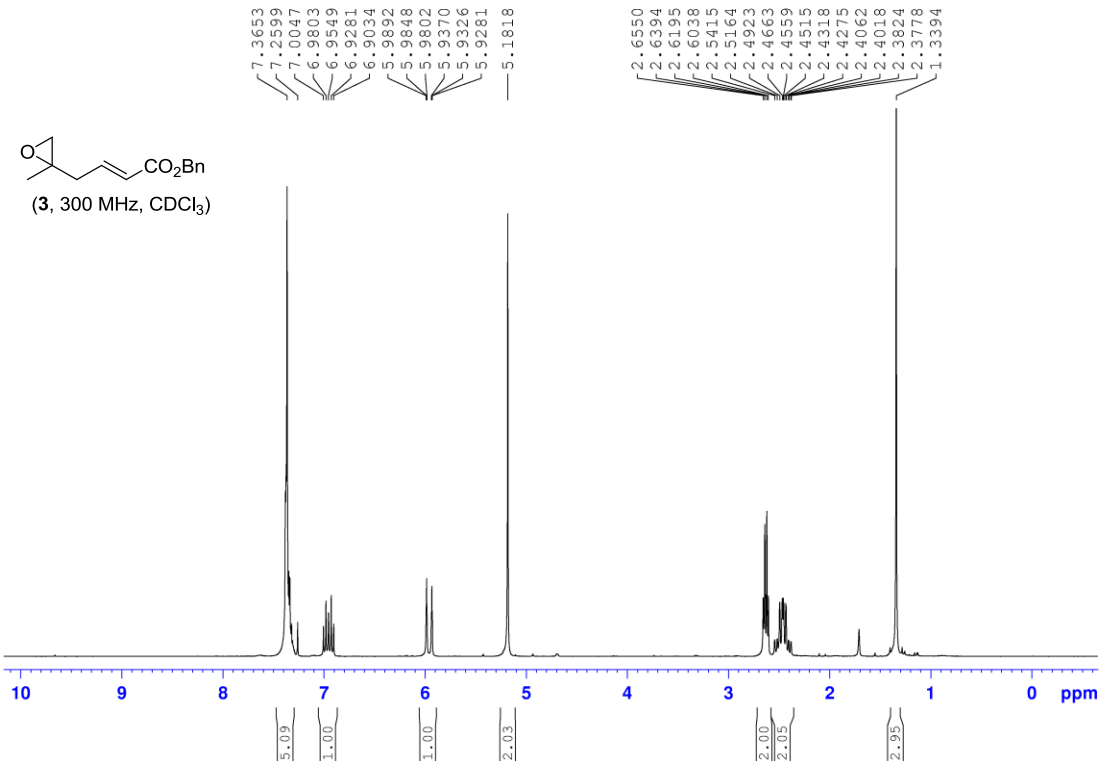

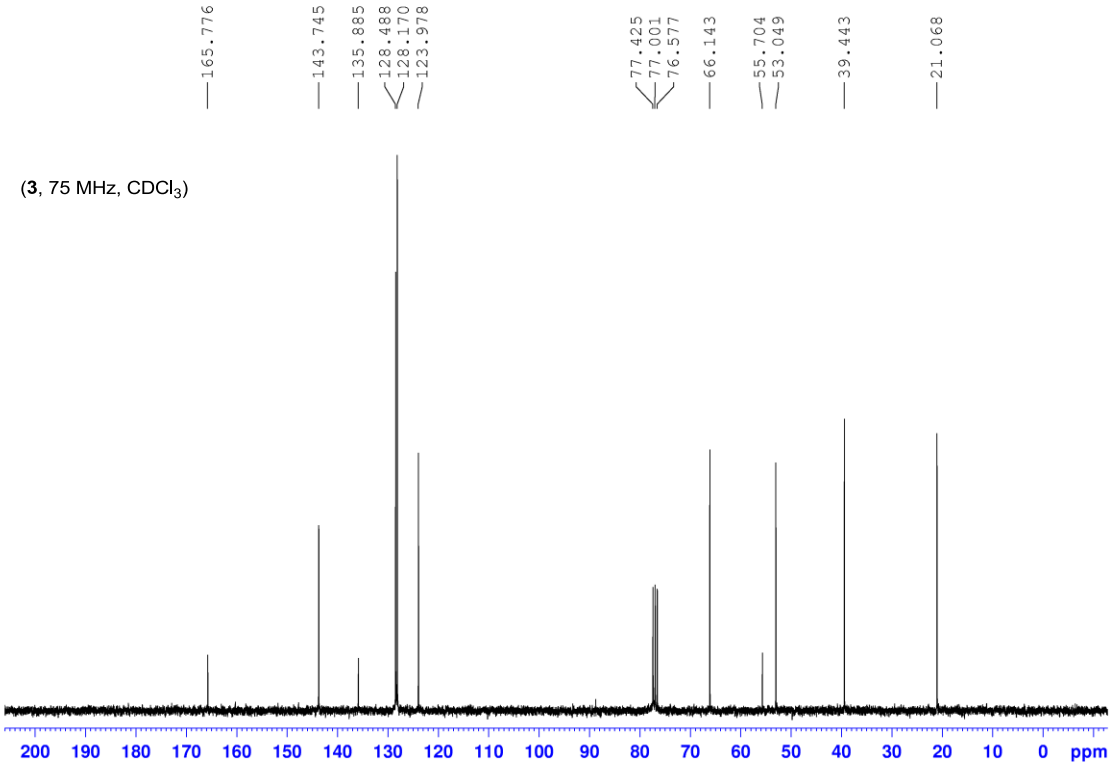

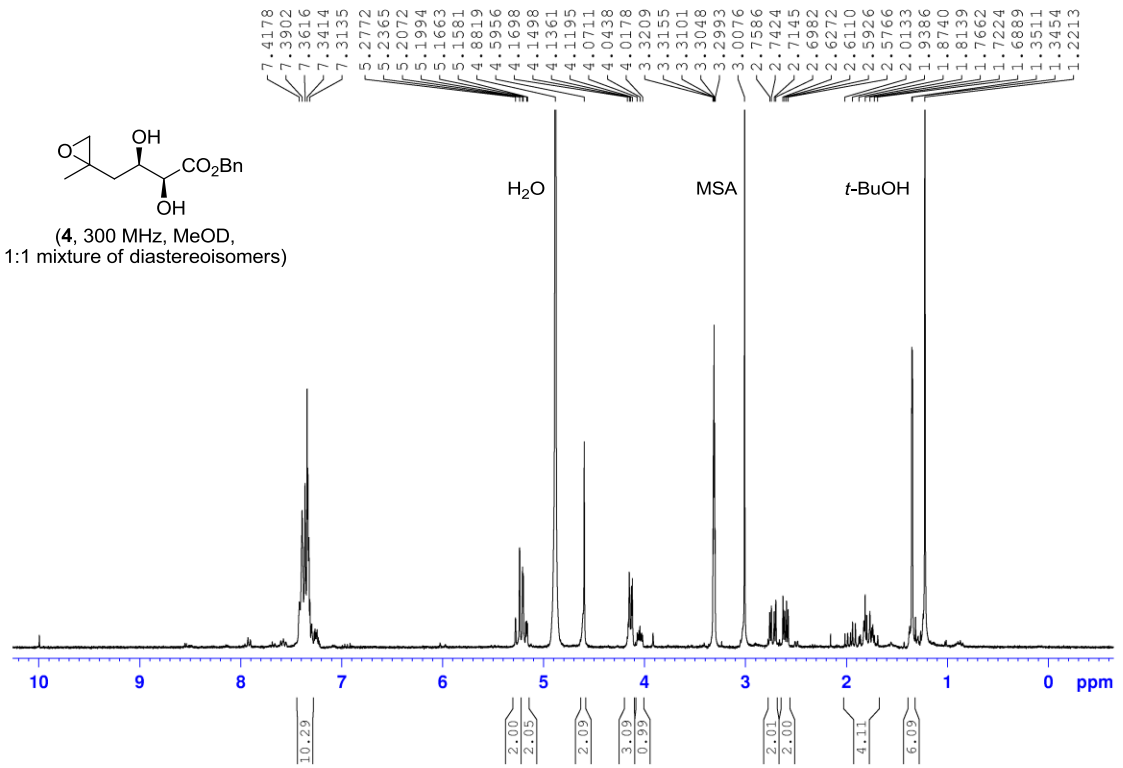
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(4, 300 MHz, MeOD,
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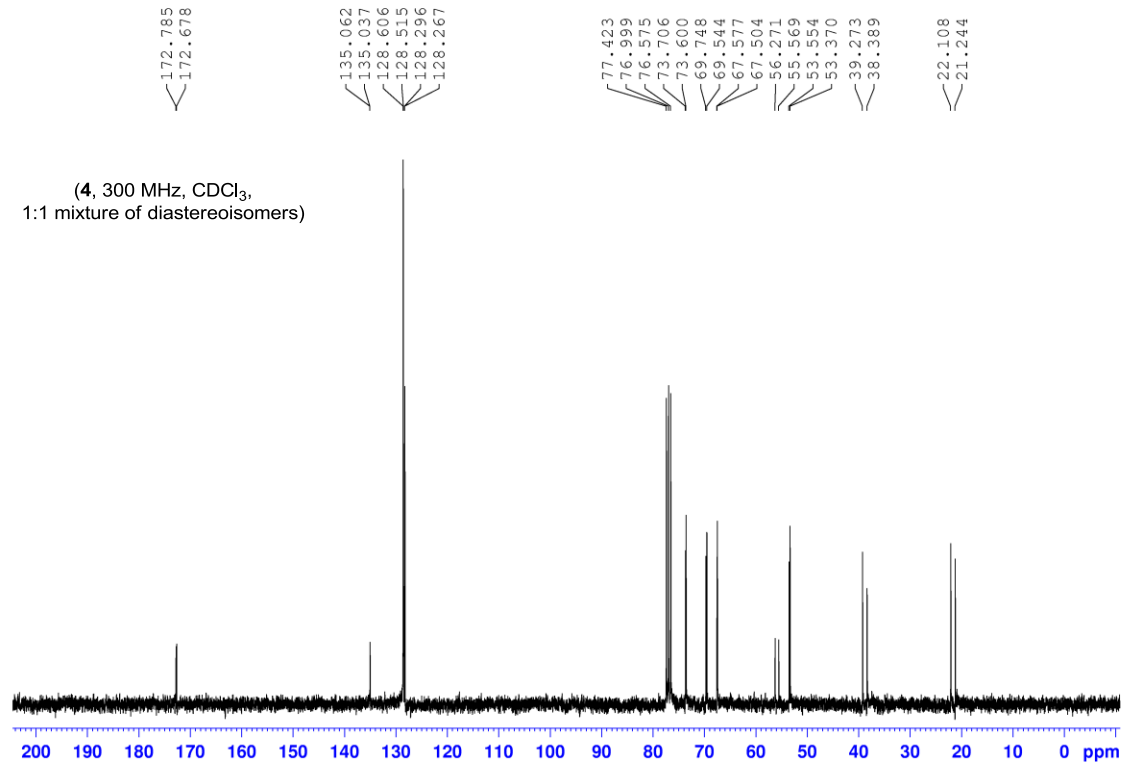
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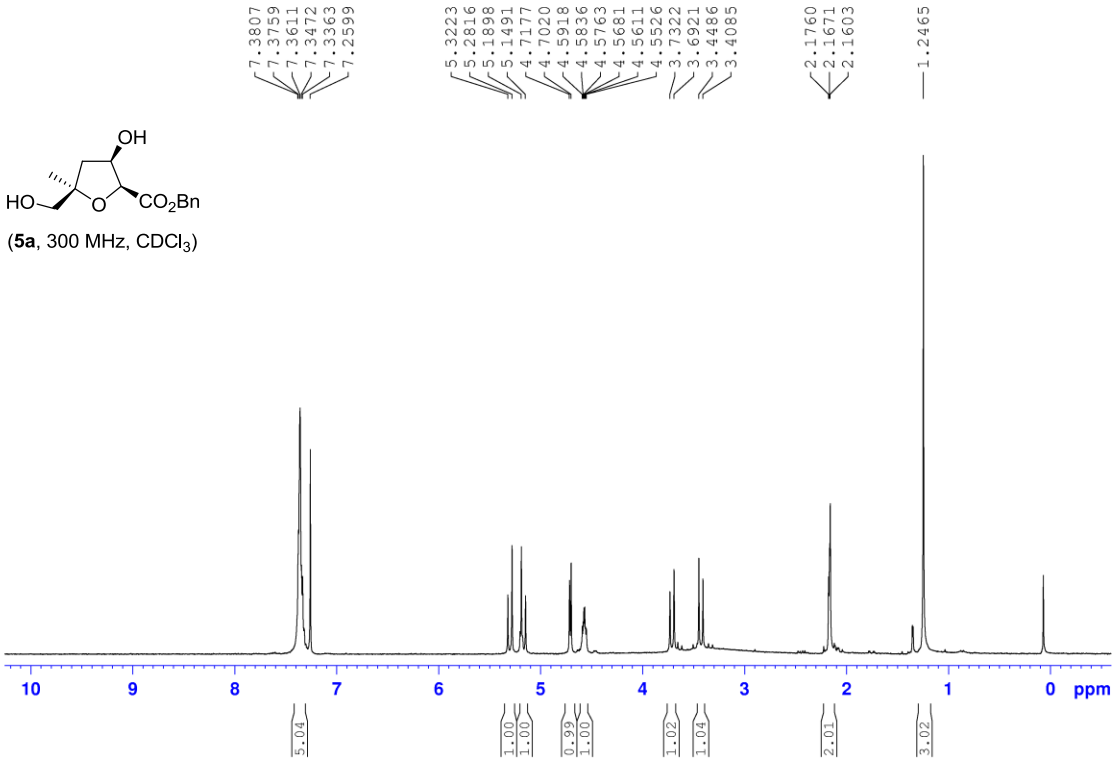
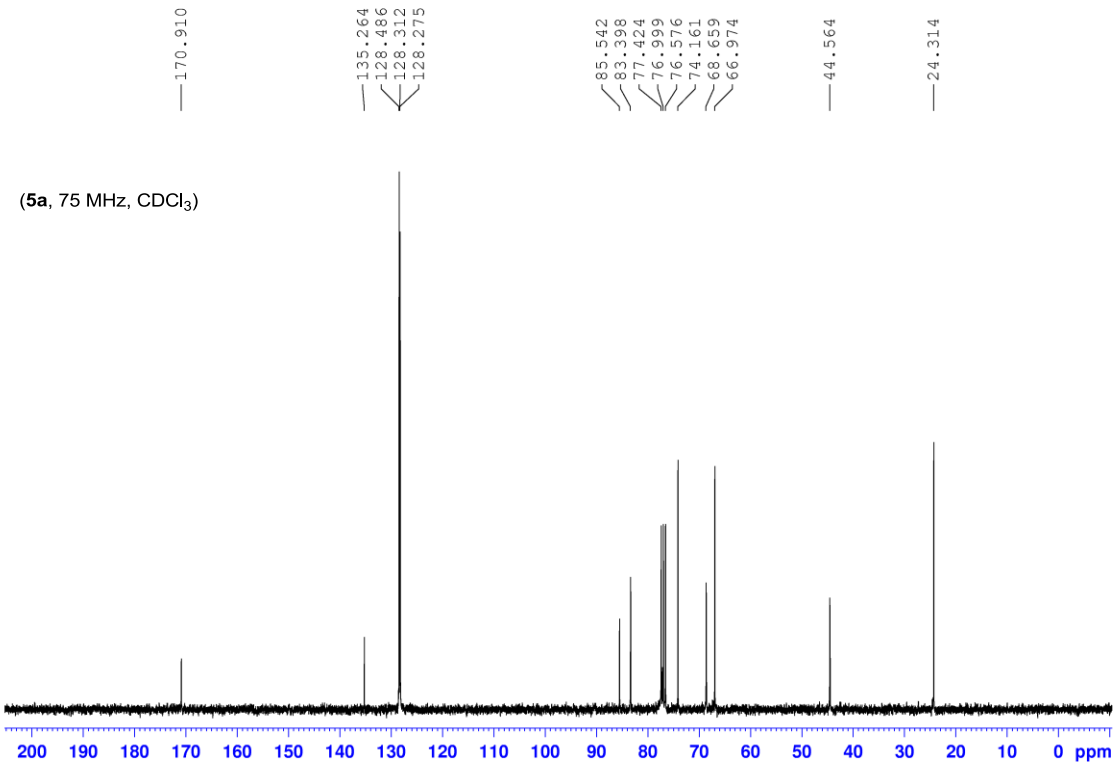
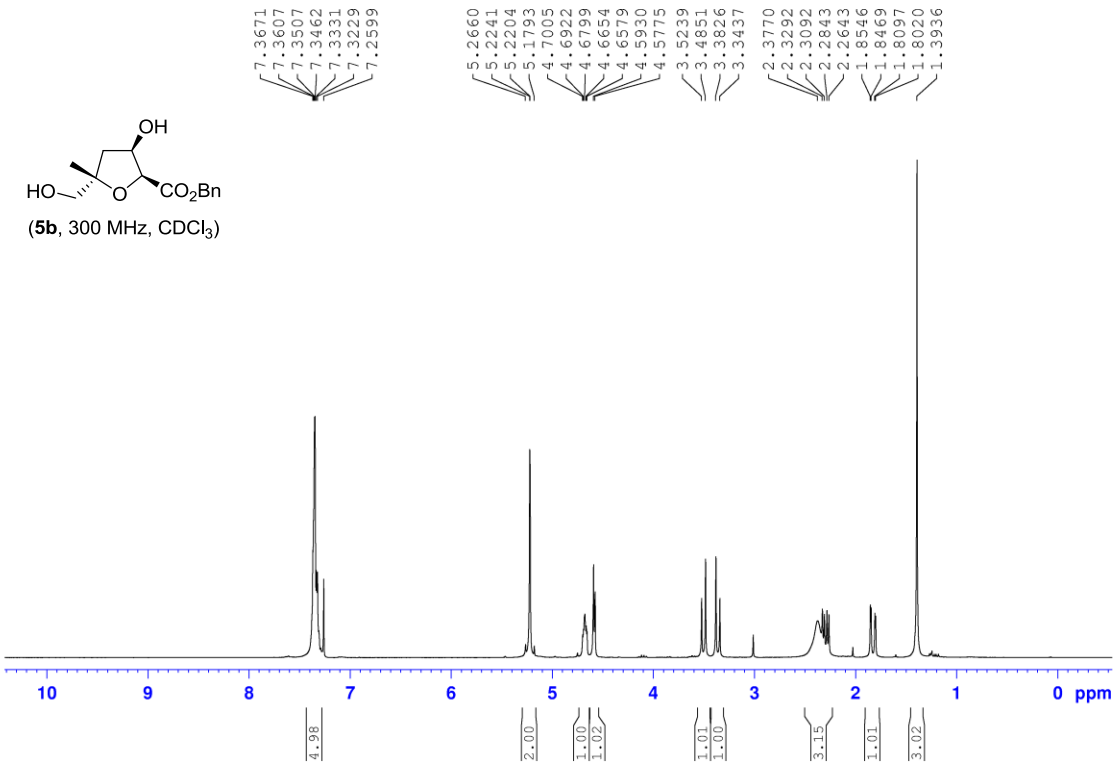
0
ppm



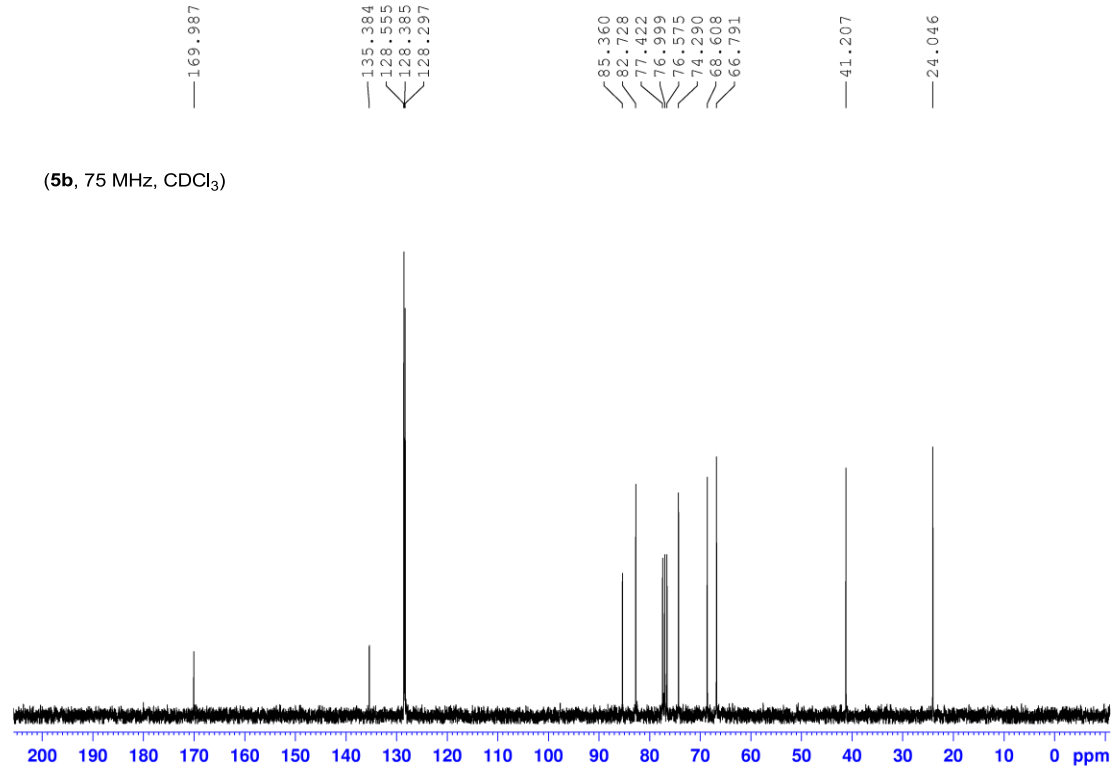
(**5a**, 300 MHz, $CDCl_3$)



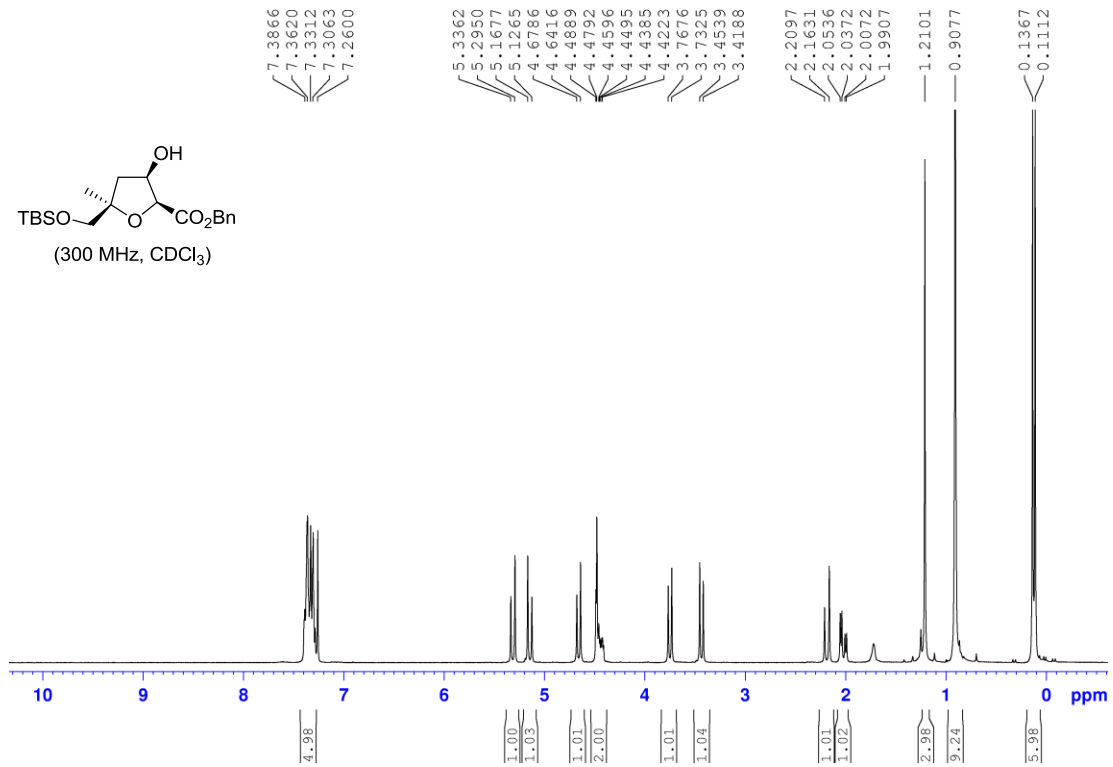
(**5a**, 75 MHz, $CDCl_3$)

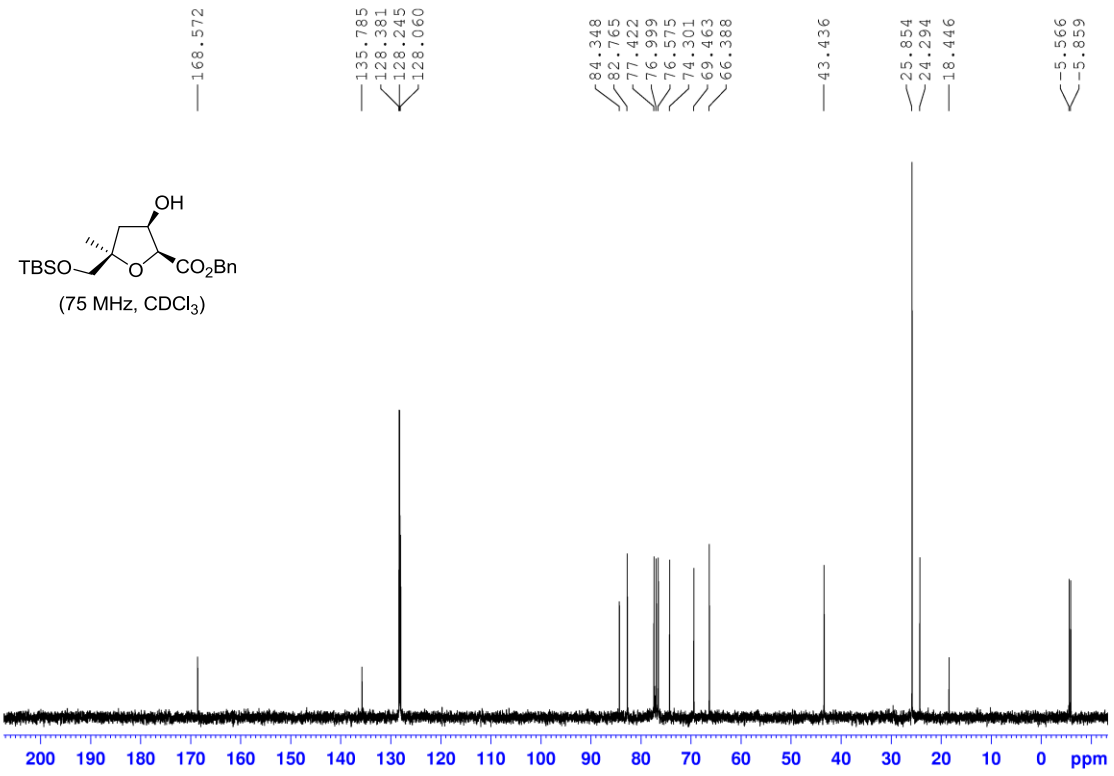


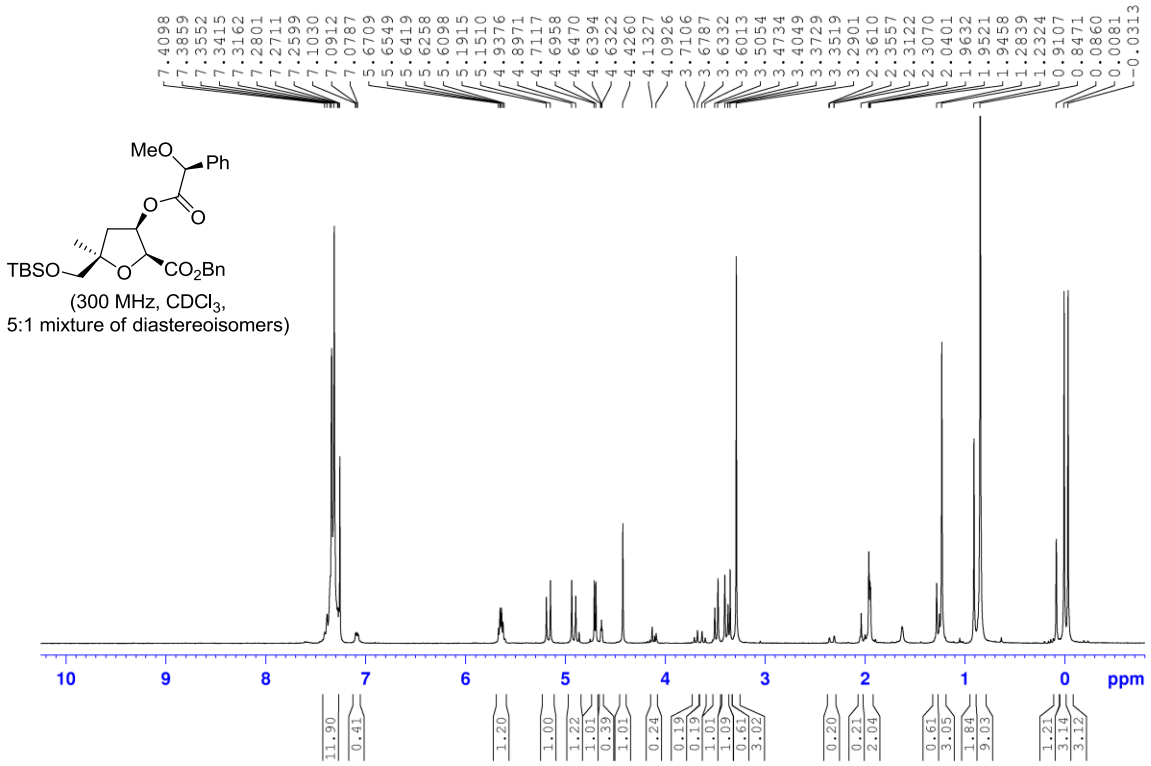
(**5b**, 300 MHz, $CDCl_3$)

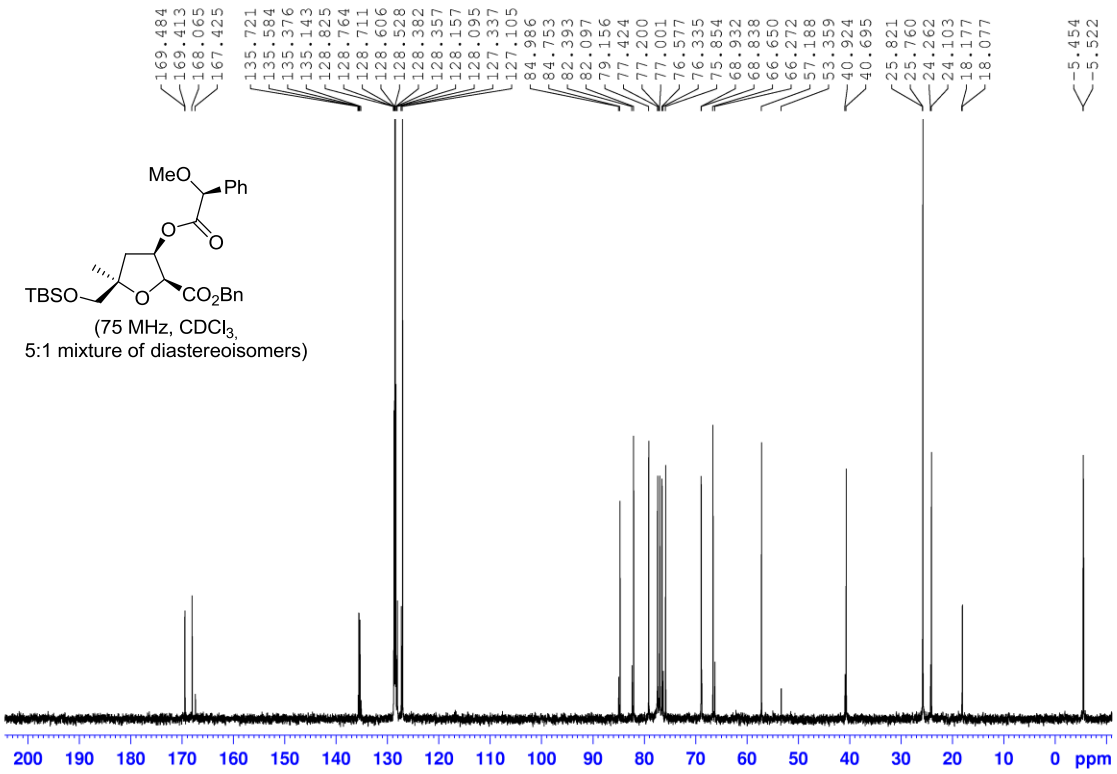


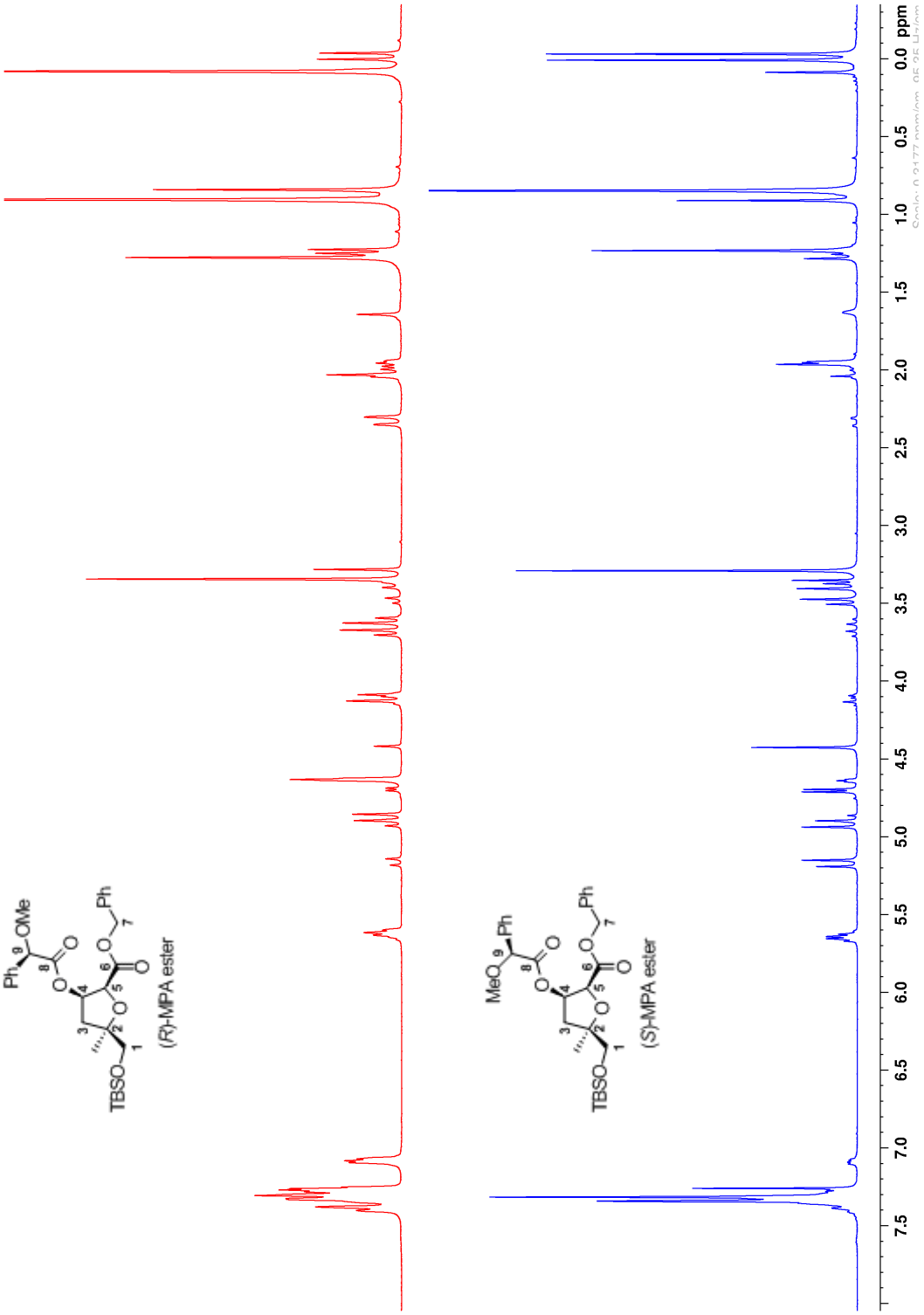
(**5b**, 75 MHz, $CDCl_3$)

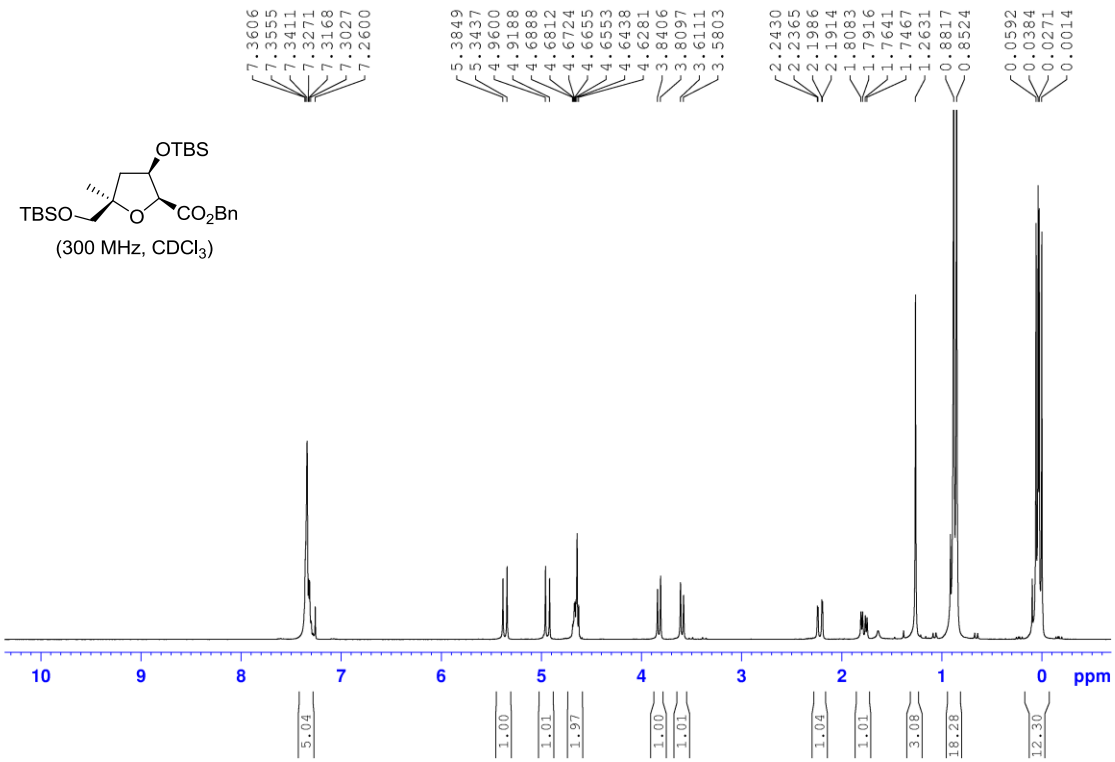


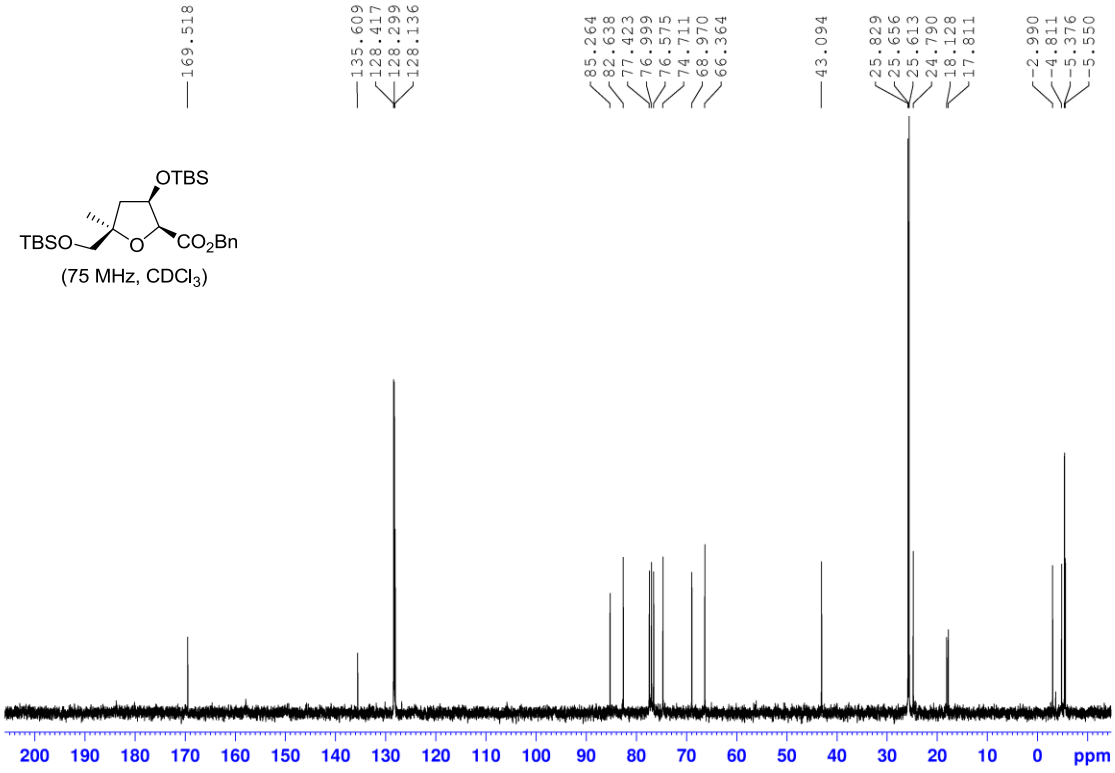


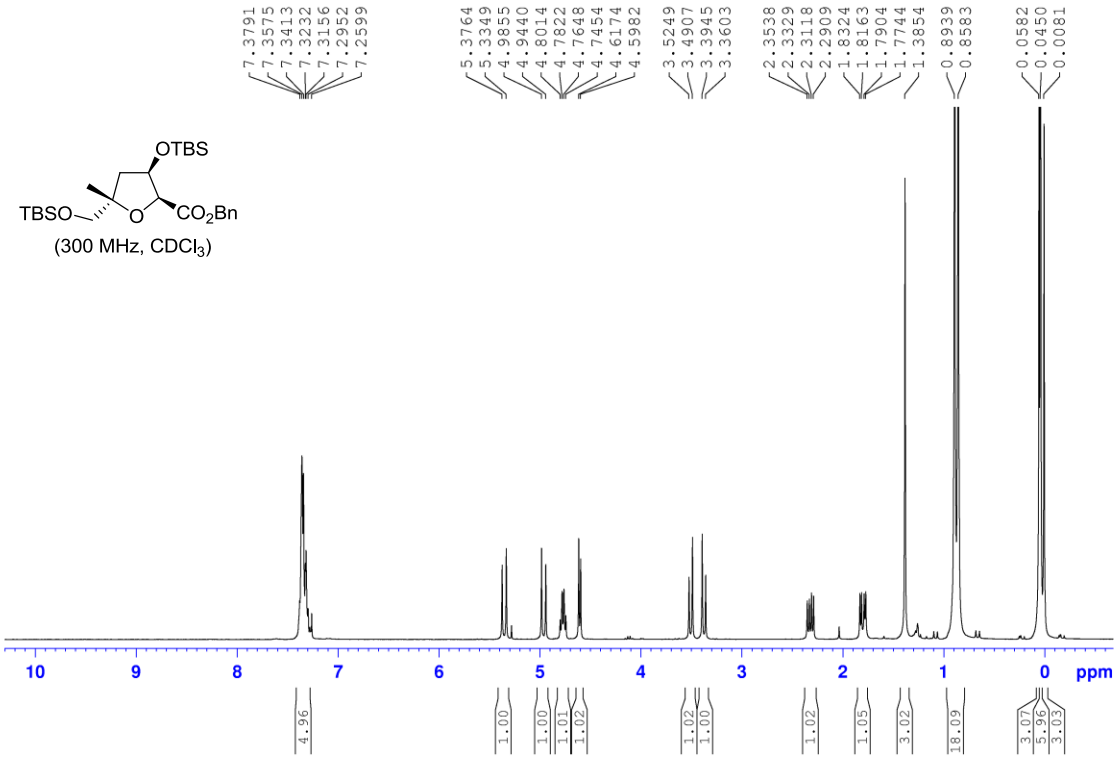

MeO
Ph
O
O
TBSO
O
CO2Bn
(300 MHz, CDCl3,
5:1 mixture of diastereoisomers)
ppm

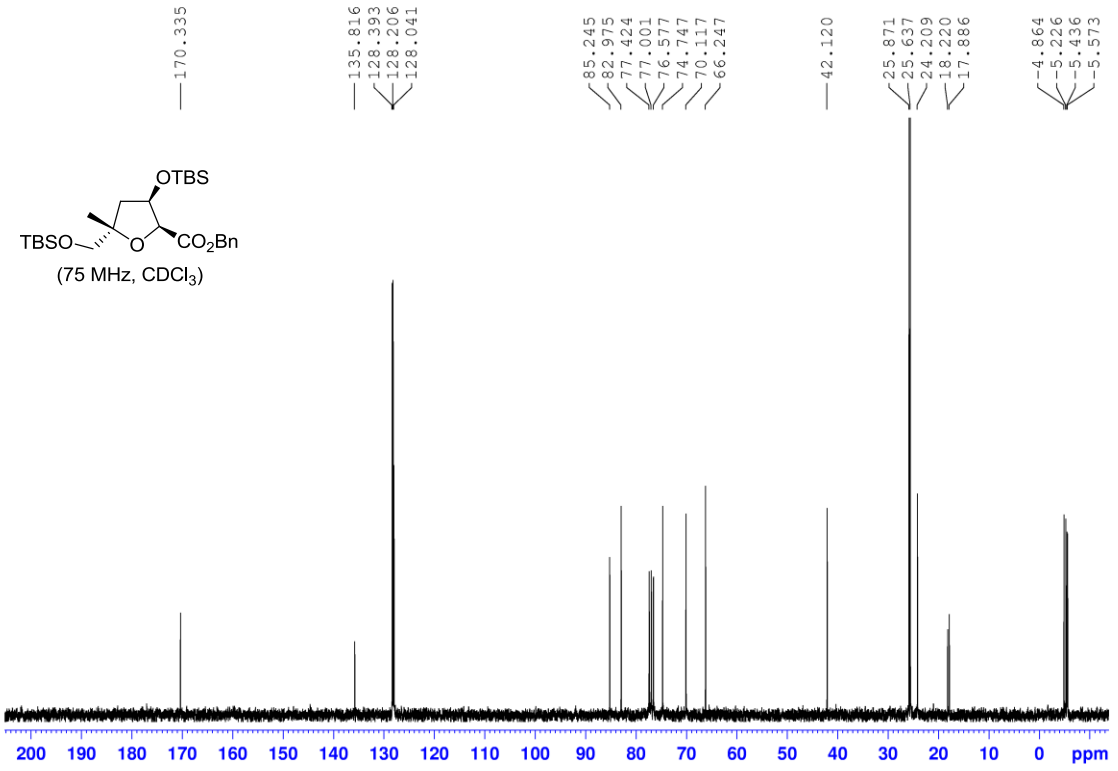

MeO
Ph
O
O
TBSO
O
CO2Bn
(75 MHz, CDCl3,
5:1 mixture of diastereoisomers)
ppm

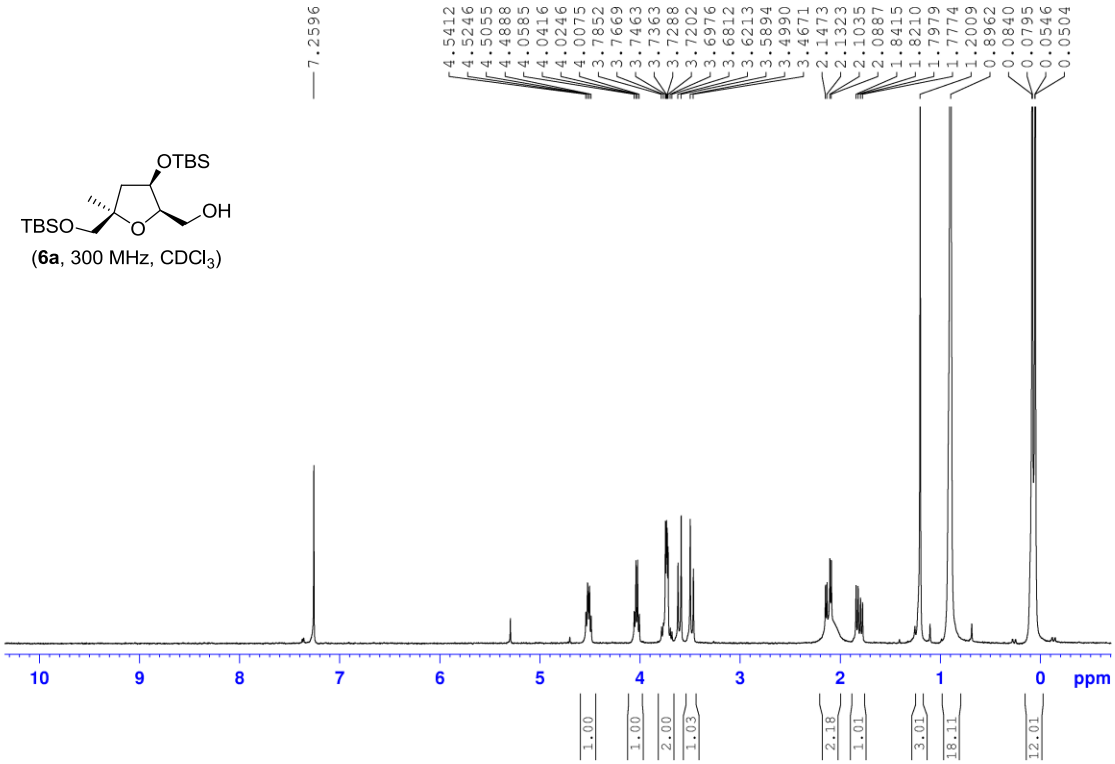

(R)-MPA ester
(S)-MPA ester
ppm



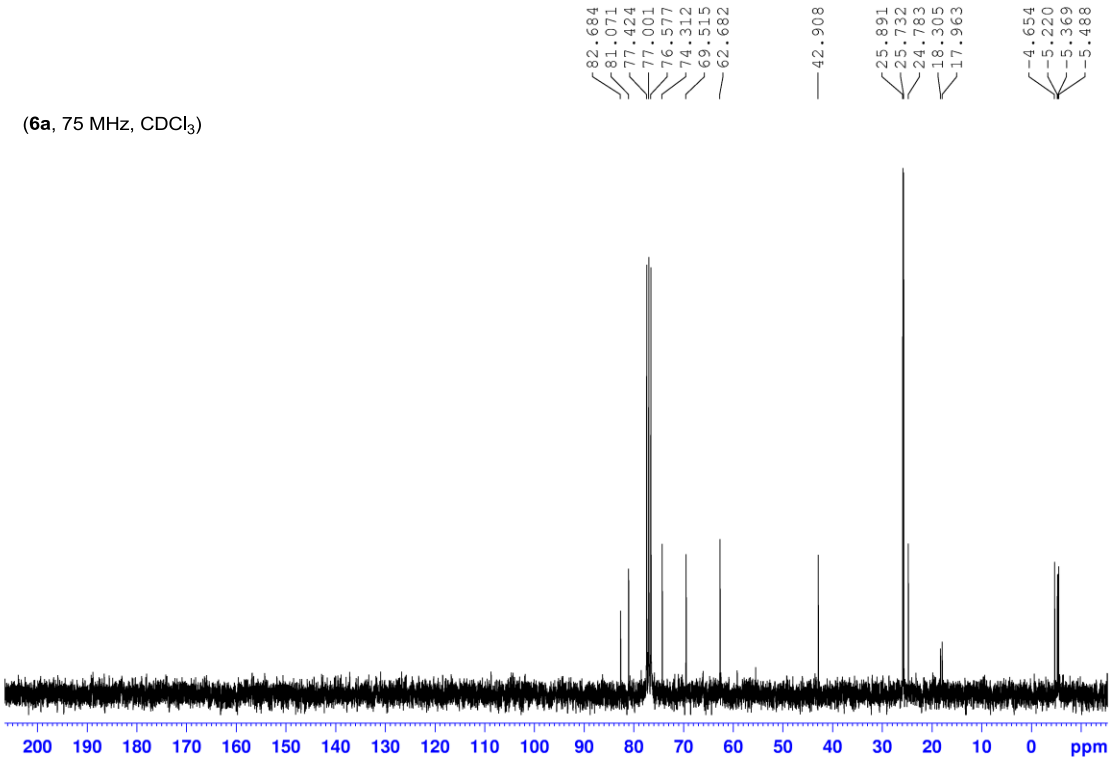



7.3791
7.3575
7.3413
7.3232
7.3156
7.2952
7.2599
5.3764
5.3349
4.9855
4.9440
4.8014
4.7822
4.7648
4.7454
4.6174
4.5982
3.5249
3.4907
3.3945
3.3603
2.3538
2.3329
2.3118
2.2909
1.8324
1.8163
1.7904
1.7744
1.3854
0.8939
0.8583
0.0582
0.0450
0.0081
OTBS
TBSO
O
CO2Bn
(300 MHz, CDCl3)
10
9
8
7
6
5
4
3
2
1
0
ppm
4.96
1.00
1.00
1.01
1.02
1.02
1.00
1.02
1.05
3.02
18.09
3.07
5.96
3.03

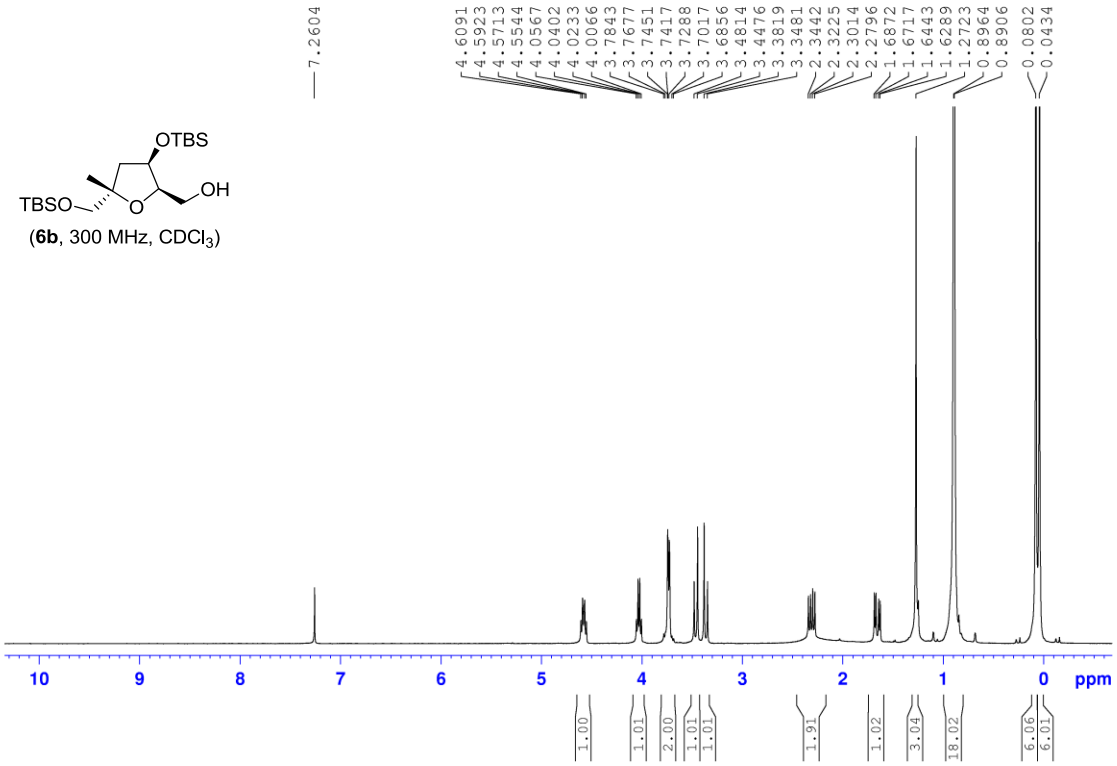

170.335
135.816
128.393
128.206
128.041
85.245
82.975
77.424
77.001
76.577
74.747
70.117
66.247
42.120
25.871
25.637
24.209
18.220
17.886
-4.864
-5.226
-5.436
-5.573
OTBS
TBSO
O
CO2Bn
(75 MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



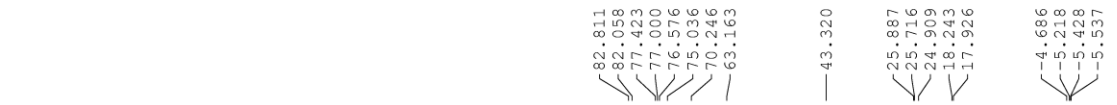
(**6a**, 300 MHz, $CDCl_3$)



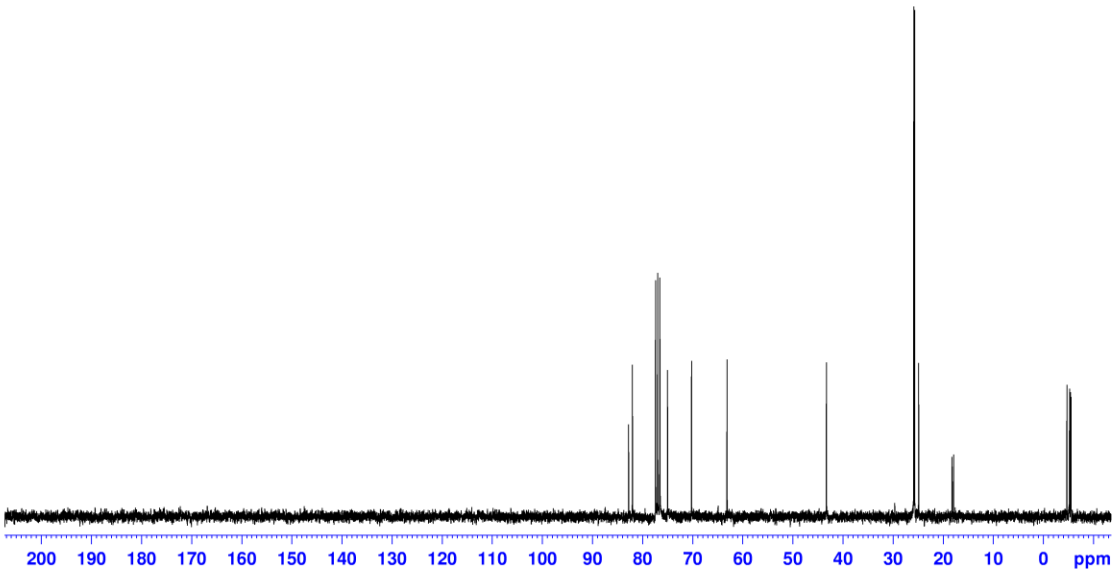
(**6a**, 75 MHz, $CDCl_3$)

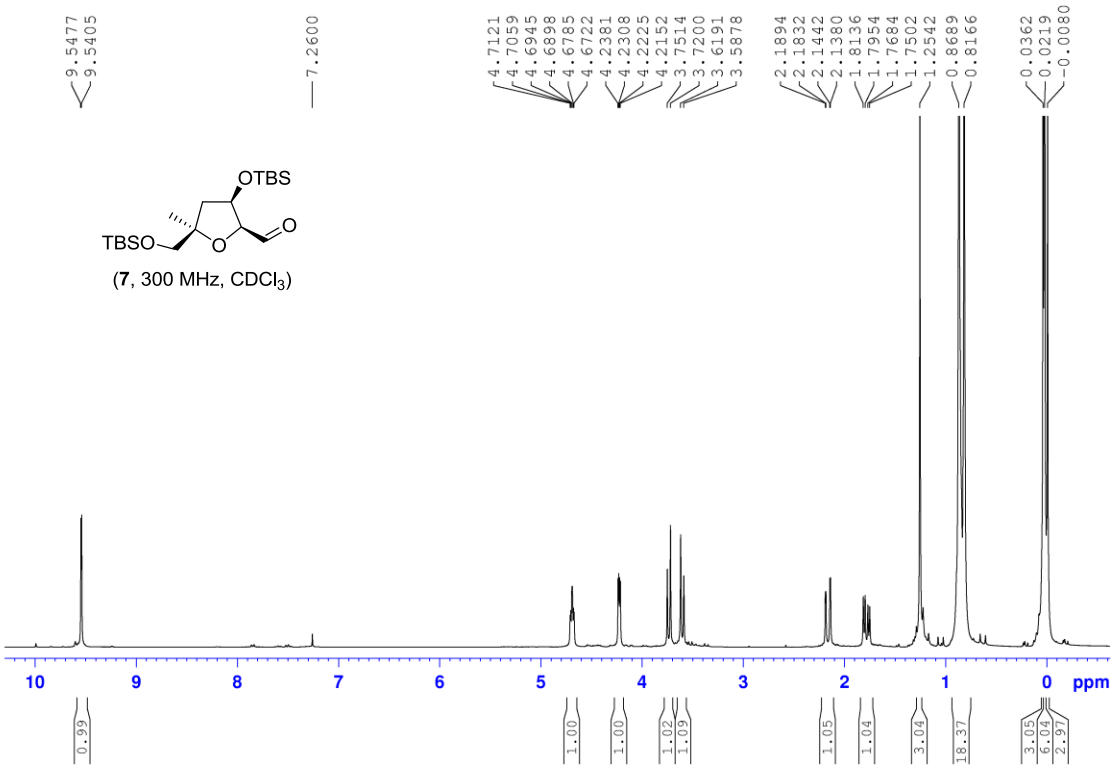


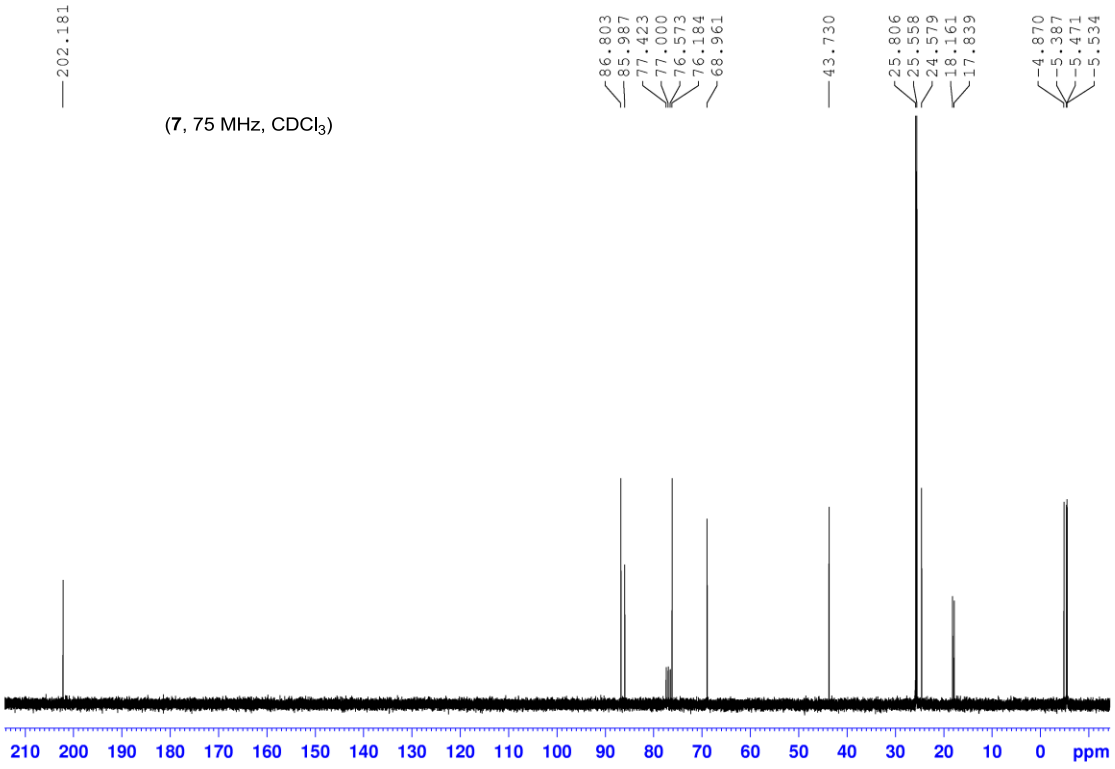
(**6b**, 300 MHz, $CDCl_3$)

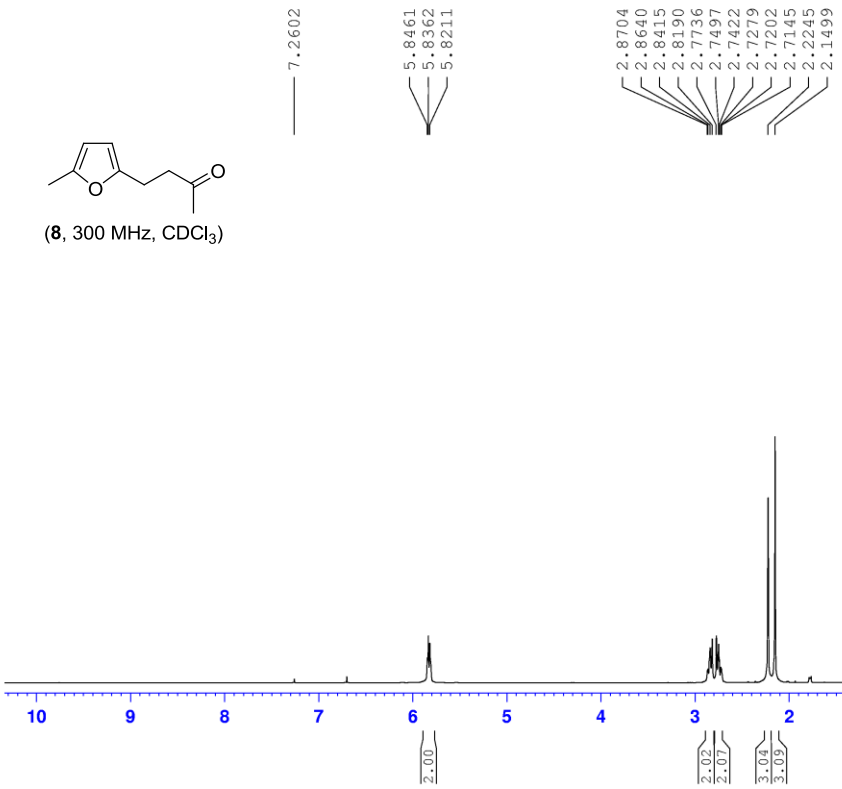


(**6b**, 75 MHz, $CDCl_3$)

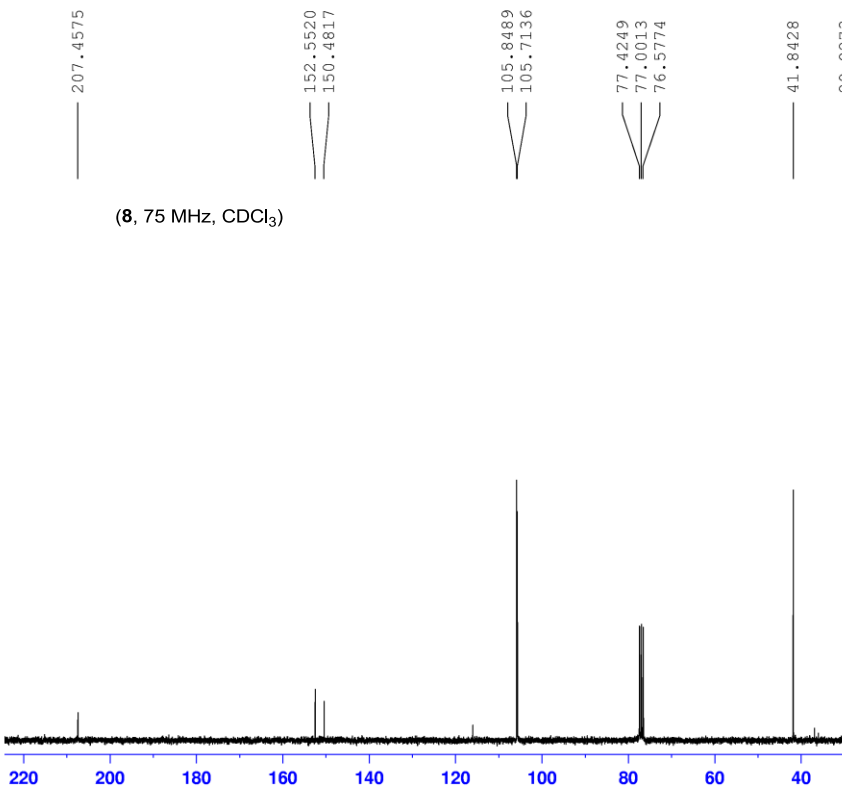



9.5477
9.5405
7.2600
4.7121
4.7059
4.6945
4.6898
4.6785
4.6722
4.2381
4.2308
4.2225
4.2152
3.7514
3.7200
3.6191
3.5878
2.1894
2.1832
2.1442
2.1380
1.8136
1.7954
1.7684
1.7502
1.2542
0.8689
0.8166
0.0362
0.0219
-0.0080
OTBS
TBSO
O
O
(7, 300 MHz, CDCl3)
10
9
8
7
6
5
4
3
2
1
0
ppm
0.99
1.00
1.00
1.02
1.09
1.05
1.04
3.04
18.37
3.05
6.04
2.97

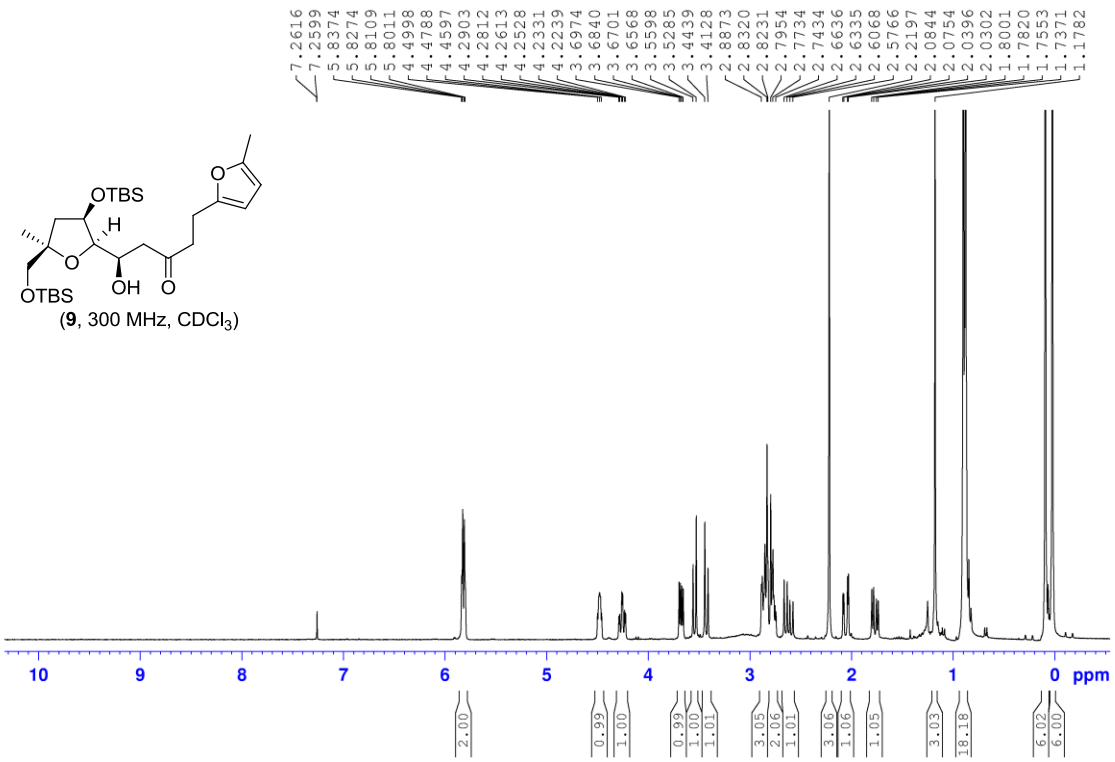

202.181
86.803
85.987
77.423
77.000
76.573
76.184
68.961
43.730
25.806
25.558
24.579
18.161
17.839
-4.870
-5.387
-5.471
-5.534
(7, 75 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



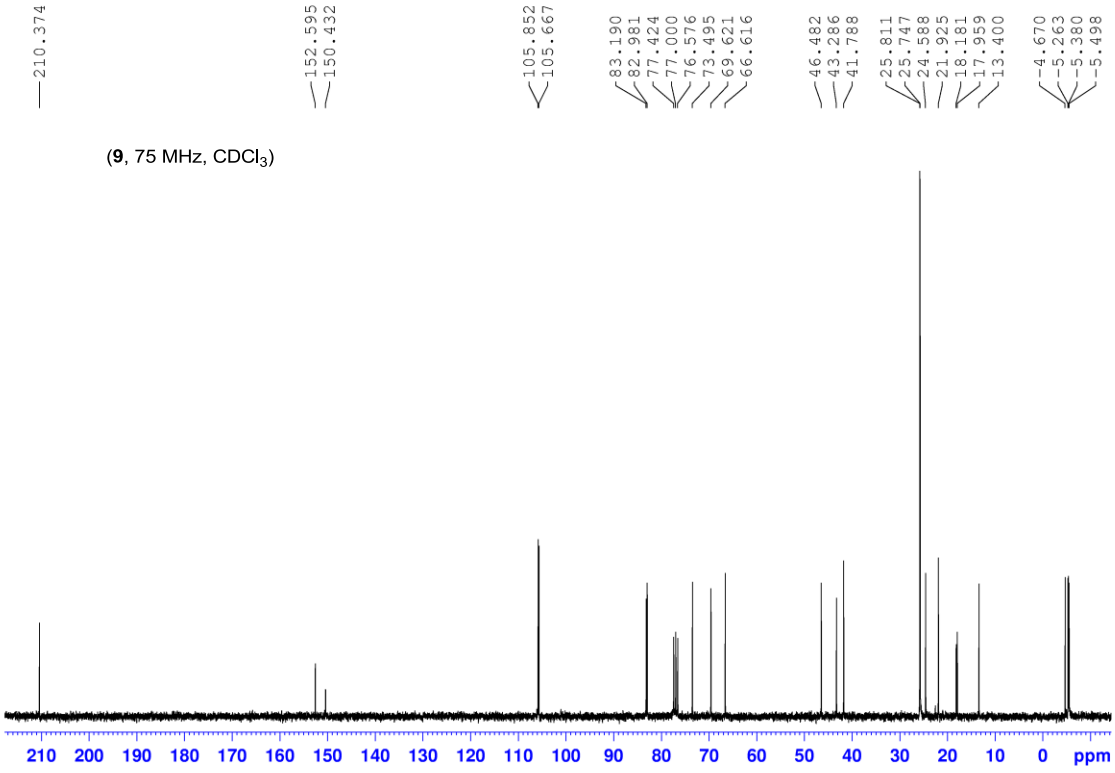
(**8**, 300 MHz, $CDCl_3$)



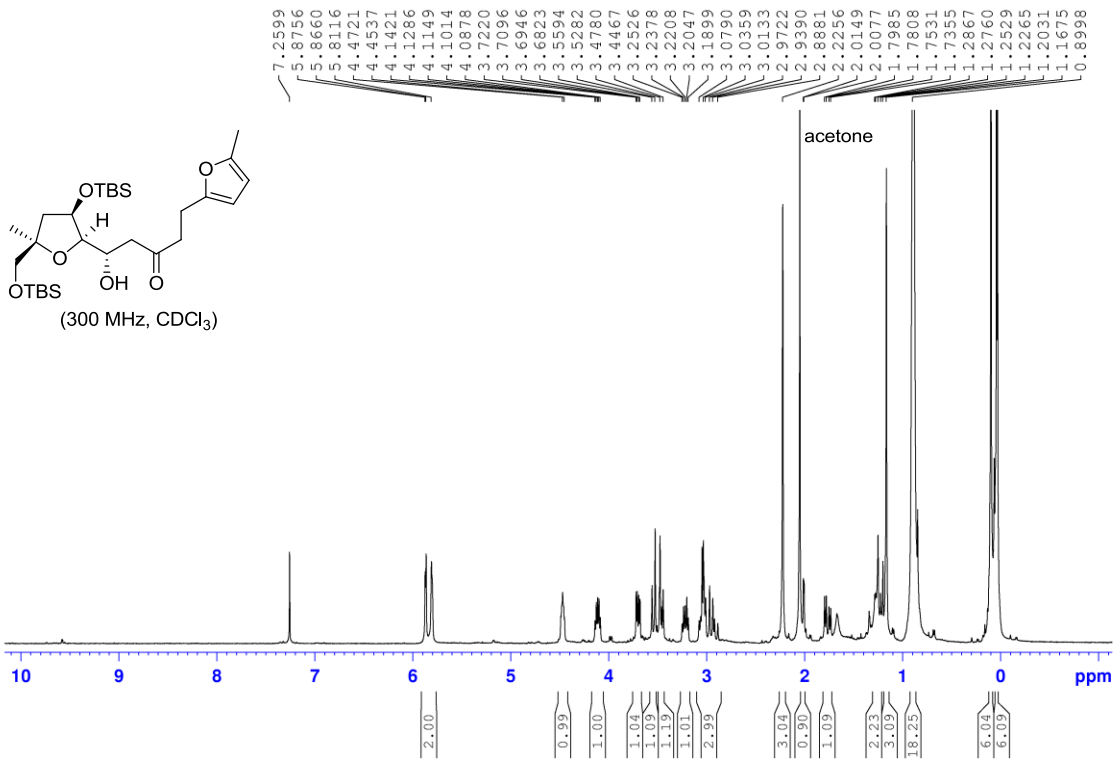
(**8**, 75 MHz, $CDCl_3$)

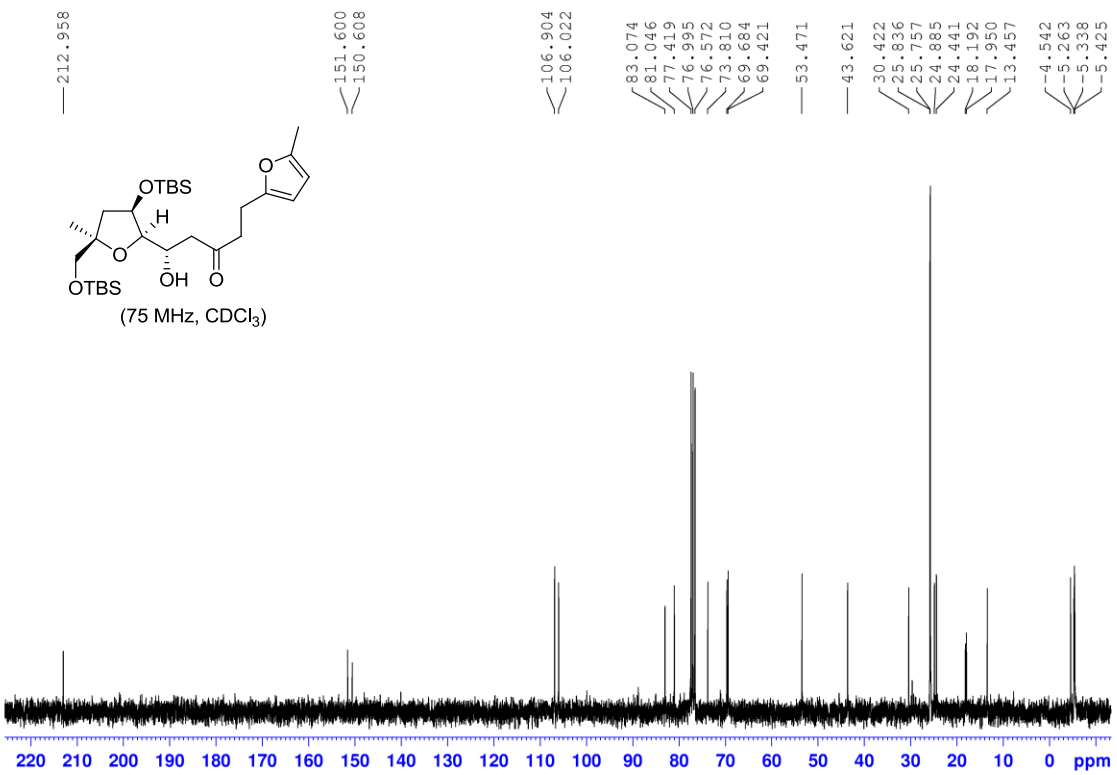


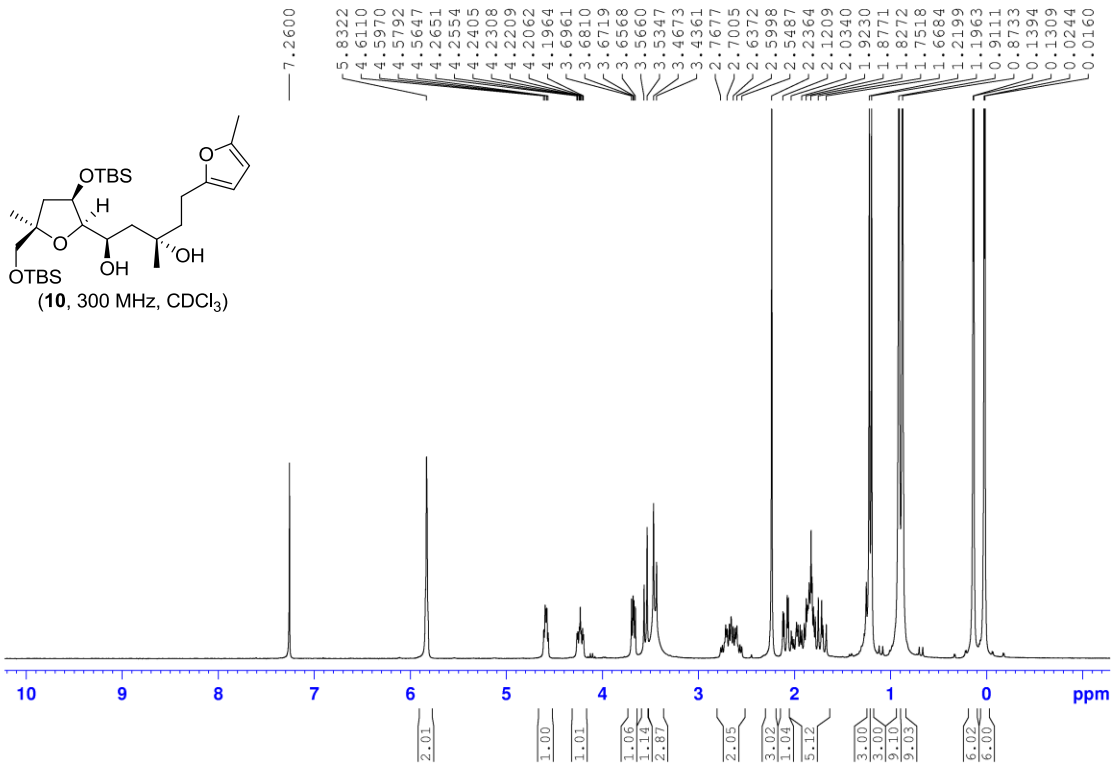
(**9**, 300 MHz, $CDCl_3$)

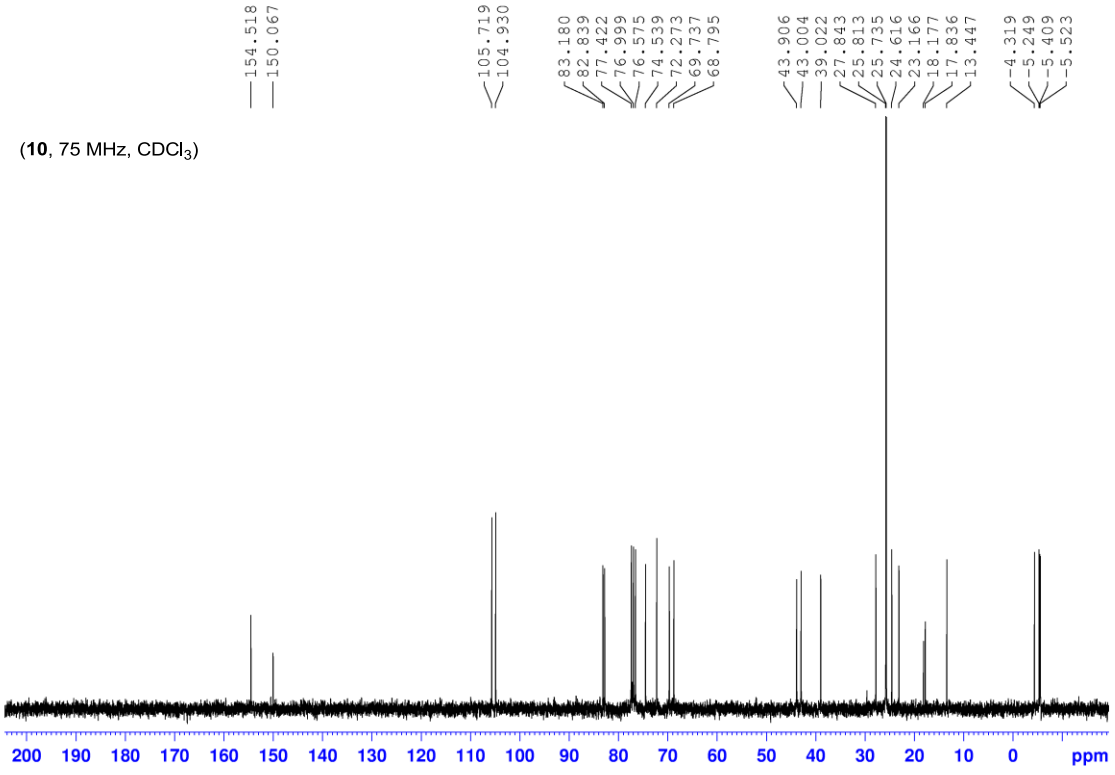


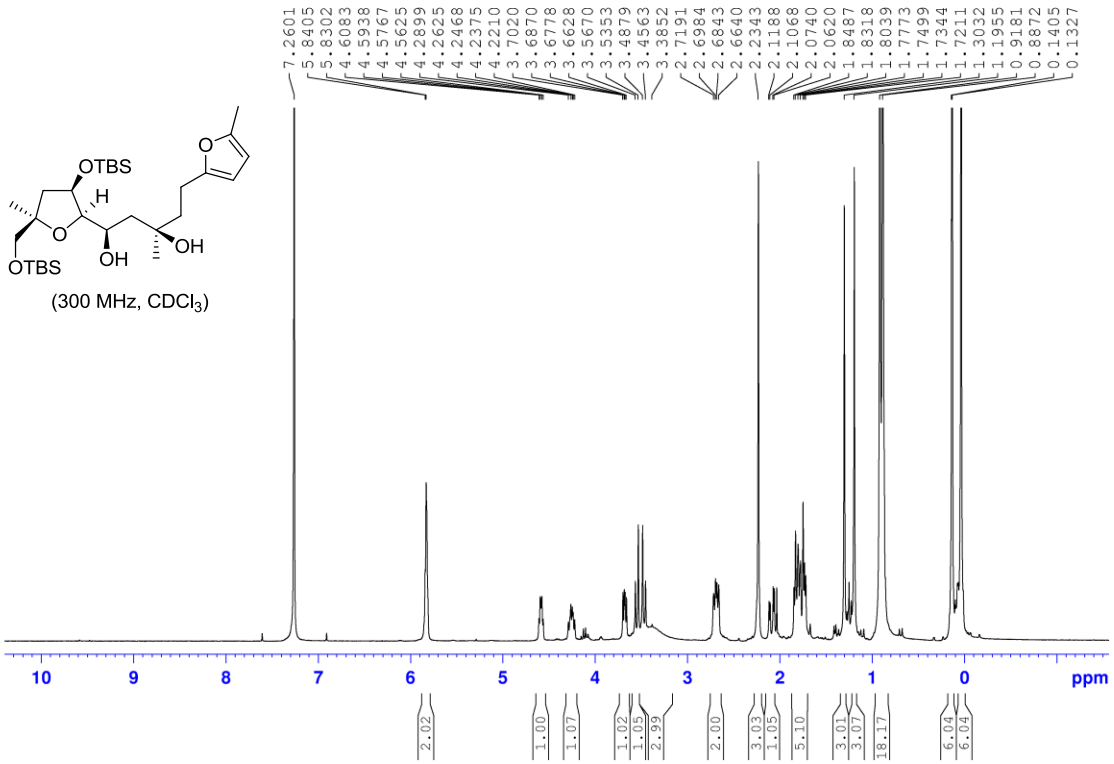
(**9**, 75 MHz, $CDCl_3$)

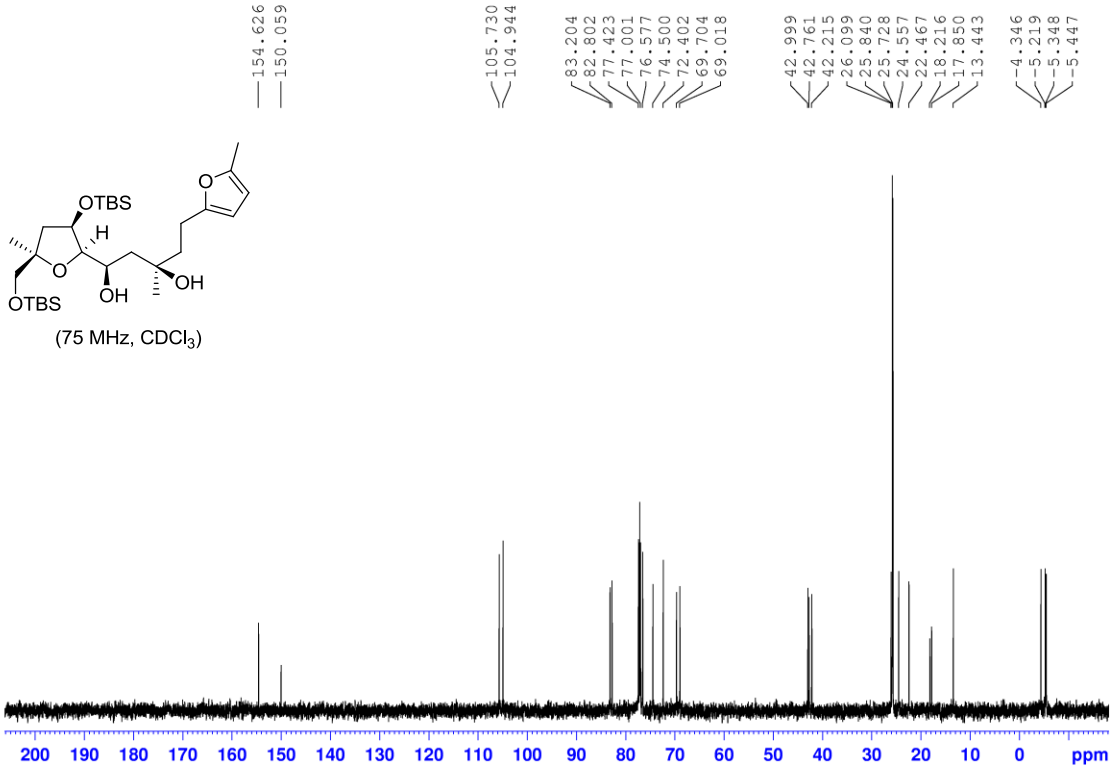


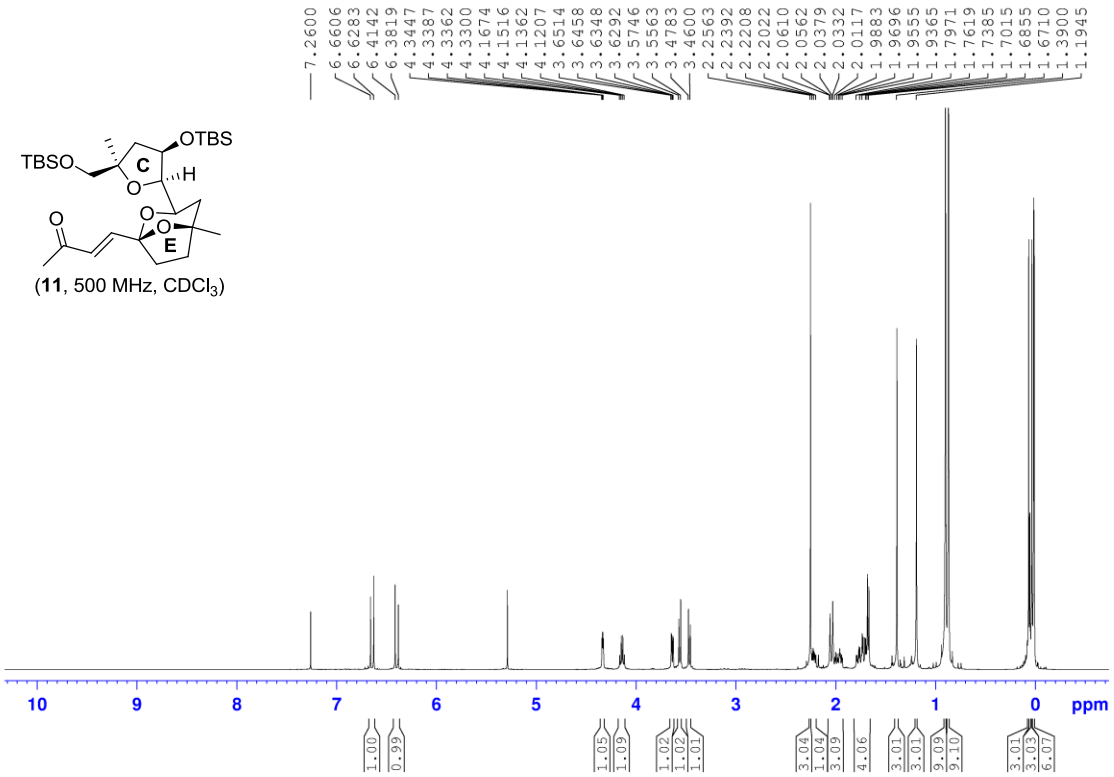




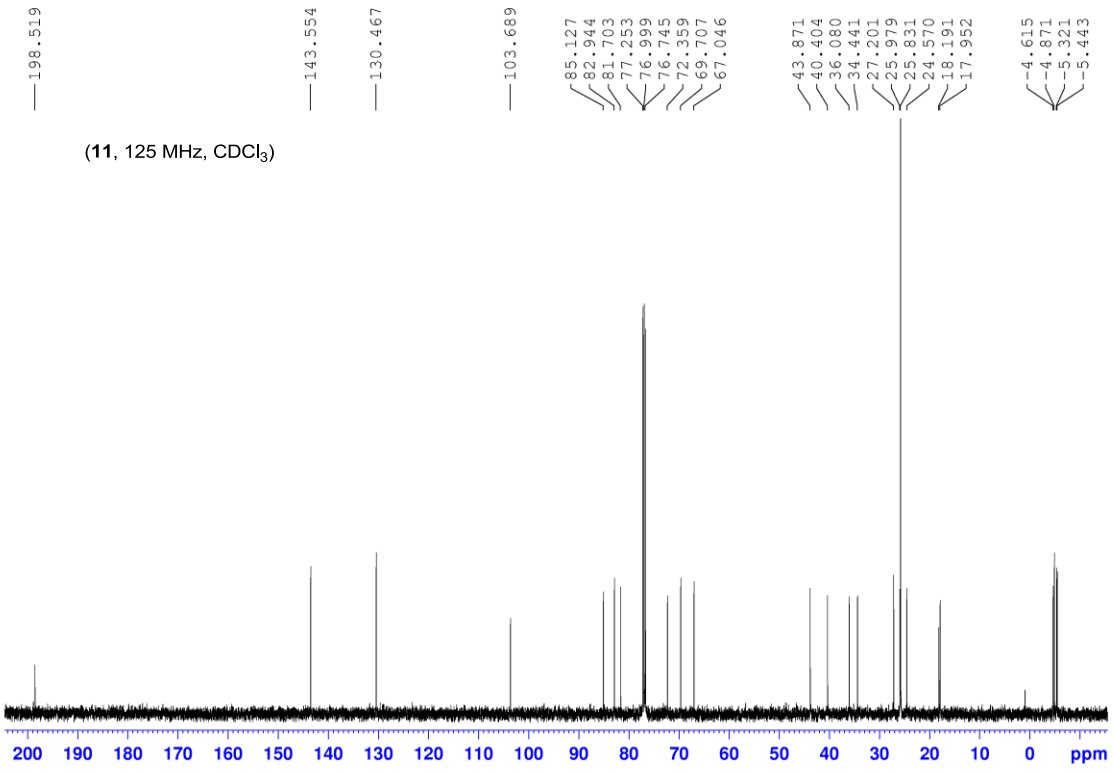



OTBS
H
O
OH
OH
OTBS
O
(300 MHz, CDCl3)
7.2601
5.8405
5.8302
4.6083
4.5938
4.5767
4.5625
4.2899
4.2625
4.2468
4.2375
4.2210
3.7020
3.6870
3.6778
3.6628
3.5670
3.5353
3.4879
3.4563
3.3852
2.7191
2.6984
2.6843
2.6640
2.2343
2.1188
2.1068
2.0740
2.0620
1.8487
1.8318
1.8039
1.7773
1.7499
1.7344
1.7211
1.3032
1.1955
0.9181
0.8872
0.1405
0.1327
10
9
8
7
6
5
4
3
2
1
0
ppm
2.02
1.00
1.07
1.02
1.05
2.99
2.00
3.03
1.05
5.10
3.01
3.07
18.17
6.04
6.04

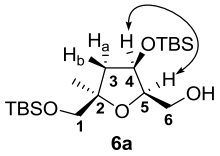

154.626
150.059
105.730
104.944
83.204
82.802
77.423
77.001
76.577
74.500
72.402
69.704
69.018
42.999
42.761
42.215
26.099
25.840
25.728
24.557
22.467
18.216
17.850
13.443
-4.346
-5.219
-5.348
-5.447
OTBS
H
O
OH
OH
OTBS
O
(75 MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



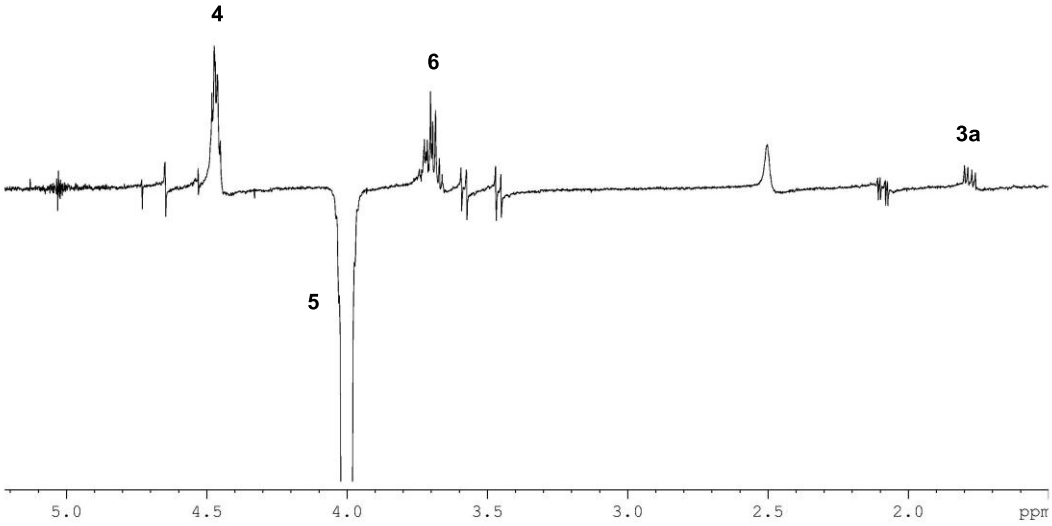
(**11**, 500 MHz, $CDCl_3$)

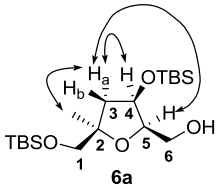


(**11**, 125 MHz, $CDCl_3$)

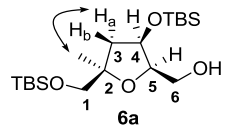


6a

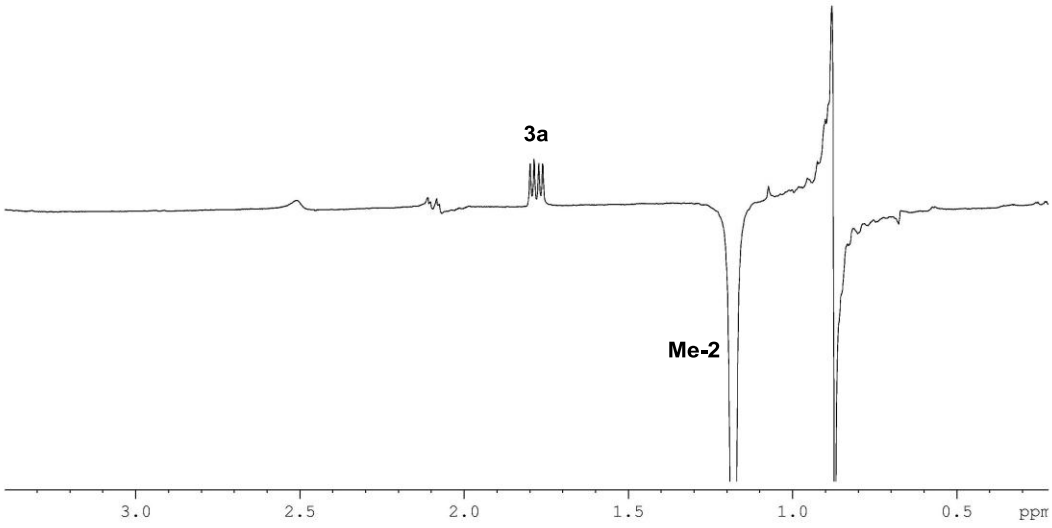


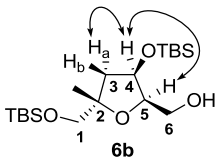


6a

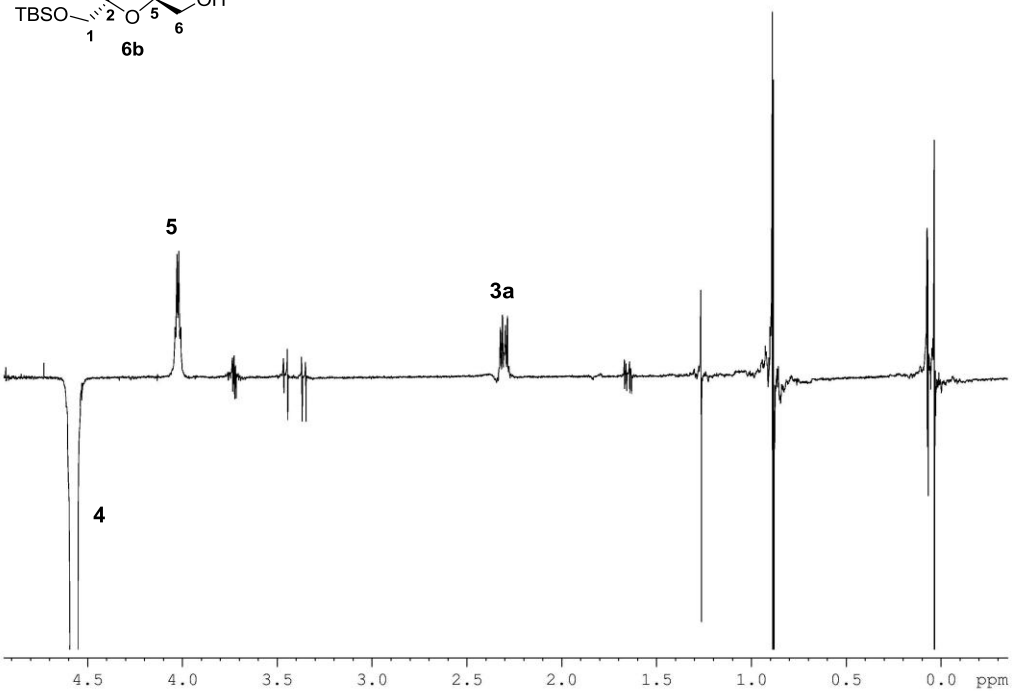


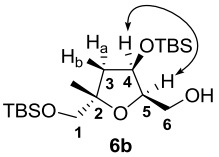
6a



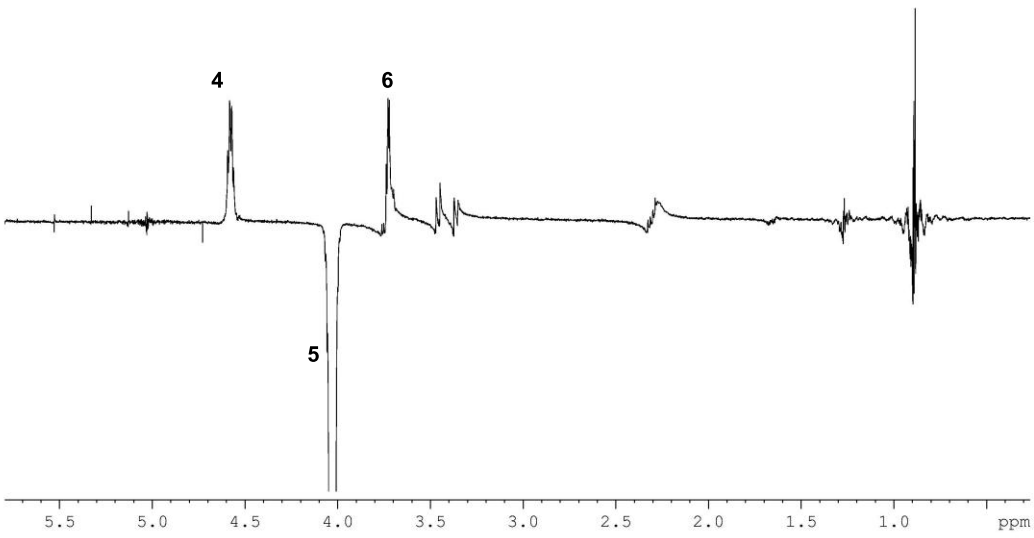


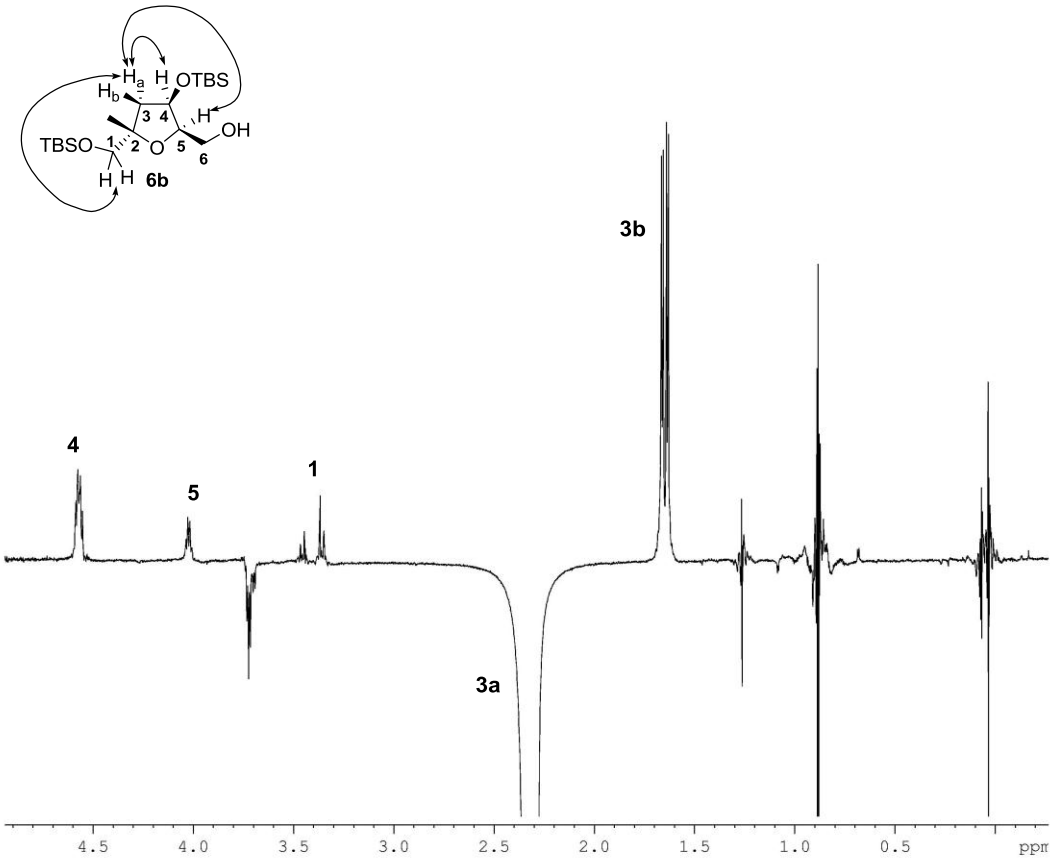
6b

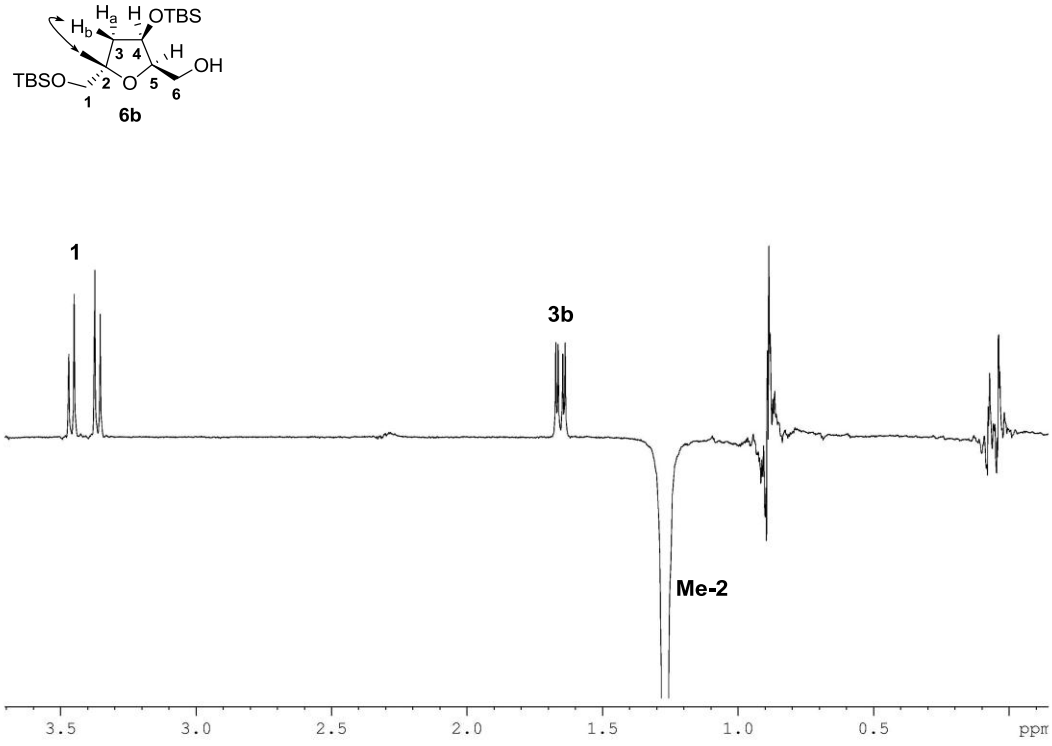


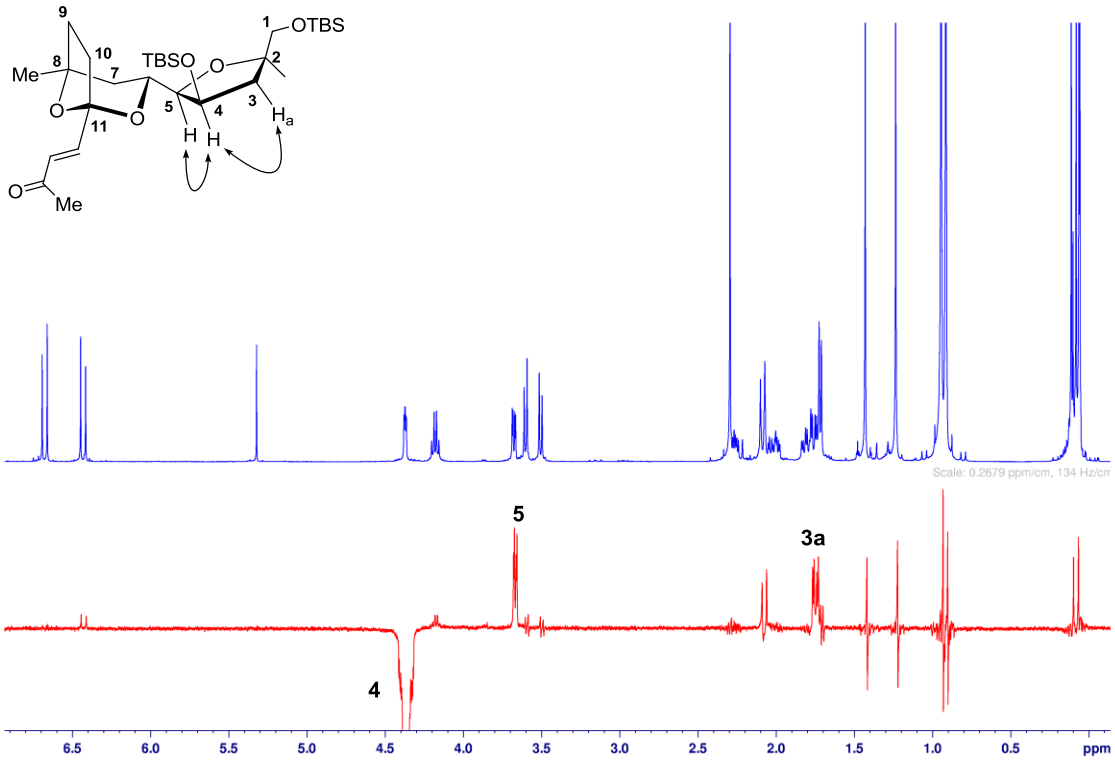


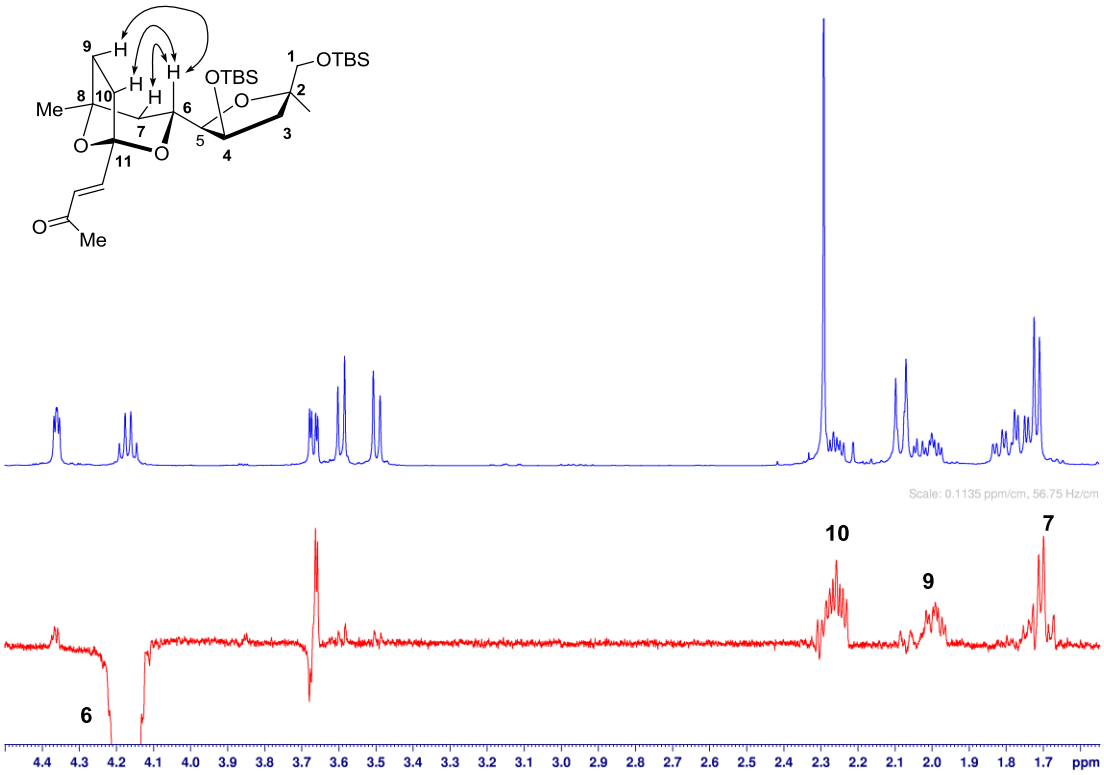
6b

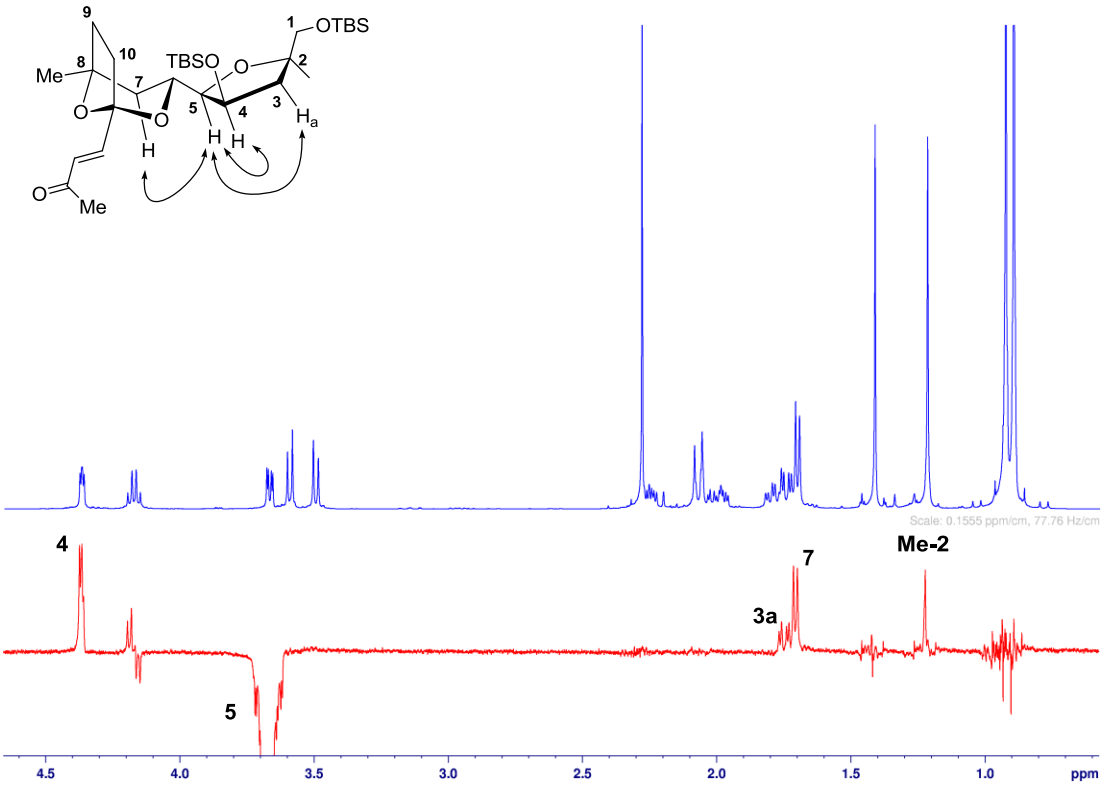


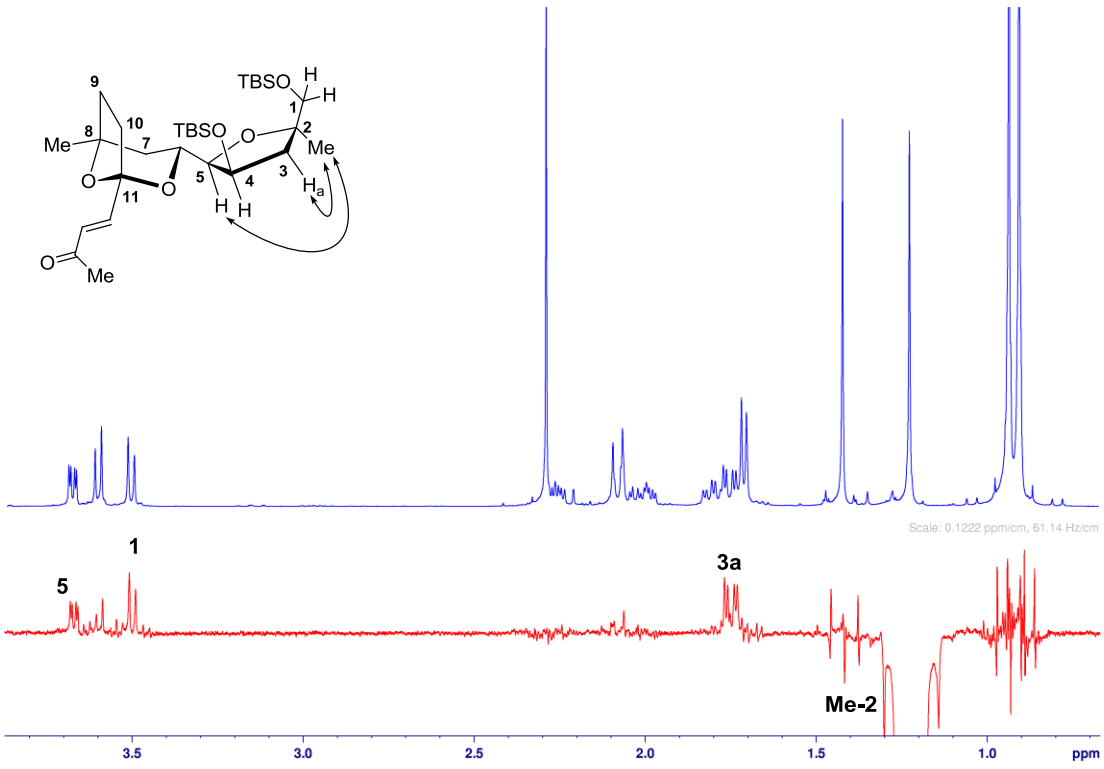









9
1
OTBS
Me
8
10
TBSO
O
2
7
5
4
3
Ha
O
O
H
H
H
O
Me
Scale: 0.1555 ppm/cm, 77.76 Hz/cm
4
7
Me-2
3a
5
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


9
TBSO
H
1
H
10
8
Me
7
TBSO
O
2
Me
O
11
O
5
4
3
Ha
H
H
O
Me
Scale: 0.1222 ppm/cm, 61.14 Hz/cm
1
5
3a
Me-2
3.5
3.0
2.5
2.0
1.5
1.0
ppm