Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Tandem Payne/Meinwald versus Meinwald rearrangement on the α-hydroxy- or α-silyloxy-spiro epoxide skeleton

ELECTRONIC SUPPLEMENTARY INFORMATION (ESI)

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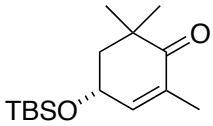
A. Materials and Methods

All experiments were carried out under argon surpressure unless otherwise stated, using oven-dried glassware. Solvents were purified as followed: THF, CH_2Cl_2 and Et_2O were dried on a GT S100 drying station (Glass Technology). DMF, DMSO and *i*-Pr_2NEt were distilled from CaH_2. MeOH was dried with sodium prior distillation. Commercial chemicals were used as received except for $B(C_6F_5)_3$ which was sublimated before use. Purification by flash column chromatography was carried out using Merck Kieselgel 60 silica gel (particle size: 32-63). Thin-layer chromatography (TLC) was performed using Merck pre-coated silica gel 60 F-254 sheets.

^1H and ^{13}C NMR spectra were recorded on a Bruker AC-400 spectrometer. Chemical shifts (δ) are indicated in parts per million with tetramethylsilane as internal standard. The following abbreviations were used for signals description: s (singlet), d (doublet), t (triplet), q (quartet), qt (quintuplet), m (multiplet), bs (broad singlet). IR spectra were recorded using a Nicolet Avatar 370 DTGS FT-IR spectrometer. High-resolution mass spectra were determined on a Waters Micromass GCT Premier spectrometer. Melting points were determined on a Büchi B-540 apparatus and are uncorrected. Elemental analyses were performed by the *Service de Microanalyse*, CNRS ICSN, Gif-sur-Yvette.

B. Synthesis of α-hydroxy spiroepoxides (1a) and (1b)

(±) 4-[(tert-butyldimethylsilyl)oxy]-2,6,6-trimethylcyclohex-2-en-1-one

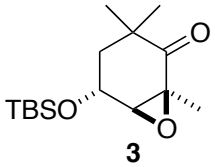


To a solution of phorenol[1] (5.69 g, 37 mmol) and imidazole (6.3 g, 92 mmol, 2.5 equiv) in anhydrous DMF (47 mL), cooled at 0 °C in an ice bath under argon, was added TBSCl (6.7 g, 44.3 mmol, 1.2 equiv). The reaction mixture was stirred for 1 h at 0 °C, then for 16 h at room temperature before hydrolysis by the addition of H_2O (40 mL). The mixture was extracted with Et_2O (3 x 50 mL) and the combined organic phase was washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The oily residue was purified by flash chromatography on silica gel (98:2 to 95:5 cyclohexane/EtOAc) to afford the title compound as a pale yellow oil (8.50 g, 86% yield).

[1] Phorenol was prepared on a multigram-scale in three steps from 4-oxoisophorone, according to a reported procedure: Soukup, M.; Lukac, T.; Zell, R.; Roessler, F.; Steiner, K.; Widmer, E. *Helv. Chim. Acta* **1989**, *72*, 365-369.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.07 (s, 6H), 0.88 (s, 9H), 1.10 (s, 3H), 1.12 (s, 3H), 1.70 (s, 3H), 1.88 (dd, 1H, *J* = 9.7 and 12.9 Hz), 1.98 (ddd, 1H, *J* = 1.8, 5.4 and 12.9 Hz), 4.50 (m, 1H), 6.40 (s, 1H). **^{13}C NMR (100.6 MHz, $CDCl_3$)** δ: -4.6, -4.5, 16.2, 18.1, 24.6, 25.7 (3C), 25.8, 41.8, 47.0, 65.5, 133.2, 147.1, 203.8. **IR (neat)**: 2955, 2927, 2856, 1677, 1384, 1360, 1255, 1102, 870, 833, 773 cm^{-1}. **Elemental analysis** calcd for $C_{15}H_{28}O_2Si$: C 67.11, H 10.51; found: C 67.04, H 10.61.

(±) (1*S*, 5*R*, 6*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-1,3,3-trimethyl-7-oxabicyclo[4.1.0]hepta-2-one **(3)**

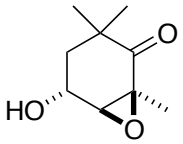


3

To a solution of (±) 4-[(*tert*-butyldimethylsilyl)oxy]-2,6,6-trimethylcyclohex-2-en-1-one (7.91 g, 29.5 mmol) in THF (75 mL), cooled to 0 °C in an ice bath, was added dropwise, *via* a dropping funnel, *tert*-butyl hydroperoxide (70% weight in H_2O, 40.3 mL, 295 mmol, 10 equiv) and then Triton B (40% weight in MeOH, 2.6 mL, 5.9 mmol, 0.2 equiv). The reaction mixture was stirred for 1 h at 0 °C and for 16 h at room temperature before the addition of saturated aqueous NH_4Cl (20 mL). After 10 min stirring, saturated aqueous Na_2SO_3 (50 mL) was added to the mixture and stirring was continued for 1 h. The mixture was then extracted with Et_2O (3 x 75 mL). The combined organic layer was washed successively with saturated aqueous $NaHCO_3$ (50 mL) and brine (75 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. The oily residue was purified by flash chromatography on silica gel (93:7 cyclohexane/EtOAc) to afford **3** as a colorless oil (7.19 g, 86% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.07 (s, 3H), 0.08 (s, 3H), 0.86 (s, 9H), 1.09 (s, 3H), 1.17 (s, 3H), 1.42 (s, 3H), 1.59 (ddd, 1H, *J* = 1.1, 3.2 and 14.4 Hz), 1.96 (dd, 1H, *J* = 3.2 and 14.4 Hz), 3.28 (dd, 1H, *J* = 1.1 and 3.2 Hz), 4.40 (q, 1H, *J* = 3.2 Hz). **^{13}C NMR (100.6 MHz, $CDCl_3$)** δ: -4.7, -4.6, 16.4, 18.2, 25.9 (3C), 27.8, 29.1, 40.8, 41.0, 59.1, 65.0, 66.7, 210.6. **IR (neat)**: 2956, 2930, 1707, 1472, 1385, 1361, 1257, 1085, 1060, 838 cm^{-1}. **HRMS (FI$^+$/GC)** calcd for $C_{15}H_{29}O_3Si$ ($[M+H]^+$): 285.1886, found 285.1871.

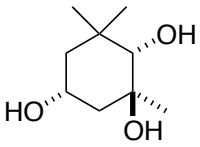
(±) (1*S*, 5*R*, 6*S*)-5-hydroxy-1,3,3-trimethyl-7-oxabicyclo[4.1.0]hepta-2-one



To a solution of compound **3** (5.92 g, 20.8 mmol) in anhydrous THF (125 mL) under argon was added TBAF (1 M in THF, 22 mL, 22.9 mmol, 1.1 equiv). The reaction mixture was stirred at room temperature for 1 h. EtOAc (60 mL) was then added, followed by H_2O (60 mL). The aqueous phase was extracted with EtOAc (3 x 40 mL) and the combined organic layer was washed with brine (100 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. The oily residue was purified by flash chromatography on silica gel (4:1 to 1:1 cyclohexane/EtOAc) to afford the title compound (3.35 g, 94% yield) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.13 (s, 3H), 1.20 (s, 3H), 1.46 (s, 3H), 1.70 (ddd, 1H, *J* = 1.1, 3.5 and 14.6 Hz), 1.91 (bs, 1H), 2.05 (dd, 1H, *J* = 3.5 and 14.6 Hz), 3.44 (dd, 1H, *J* = 1.1 and 2.9 Hz), 4.53 (m, 1H). **^{13}C NMR (100.6 MHz, $CDCl_3$)** δ: 16.1, 27.4, 28.9, 40.8, 40.9, 59.0, 64.5, 65.8, 210.3. **IR (neat)**: 3459, 2974, 2933, 1697, 1471, 1447, 1384, 1359, 1142, 1057, 859 cm^{-1}. **HRMS (FI$^+$/GC)** calcd for $C_9H_{14}O_3$ ($[M]^+$): 170.0943, found 170.0941.

(±) (1*S*, 2*S*, 4*R*)-2,6,6-trimethylcyclohexane-1,2,4-triol **(4)**



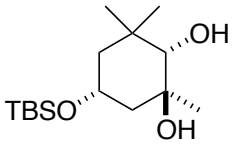
4

To a solution of (±) (1*S*, 5*R*, 6*S*)-5-hydroxy-1,3,3-trimethyl-7-oxabicyclo[4.1.0]hepta-2-one (3.34 g, 19.6 mmol) in anhydrous THF (200 mL) under argon was added dropwise $LiAlH_4$ (2.4 M in THF, 32.7 mL, 78.4 mmol, 4 equiv). The reaction mixture was stirred at room temperature for 16 h and was quenched at 0 °C by careful, dropwise addition of EtOAc (40 mL). After 5 min stirring were successively added, dropwise, H_2O (3 mL), 15% weight aqueous NaOH (3 mL) and H_2O (3 x 3 mL). The reaction mixture was stirred at room temperature for 1 h and filtered on a pad of Celite®. Aluminium salts were triturated and rinsed several times with THF before the filtrate was concentrated under reduced pressure to afford the triol **4** (3.07 g, 90% yield) as a white-off solid.

^{1}H NMR (400 MHz, CD_3OD) δ: 0.98 (s, 3H), 1.06 (s, 3H), 1.18 (dd, 1H, *J* = 11.5 and 12.6 Hz), 1.22 (s, 3H), 1.31 (dd, 1H, *J* = 11.5 and 13.2 Hz), 1.72 (ddd, 1H, *J* = 3.2, 4.2 and 12.6 Hz),

2.02 (ddd, 1H, *J* = 3.2, 4.2 and 13.2 Hz), 2.98 (s, 1H), 3.99 (tt, 1H, *J* = 4.2 and 11.5 Hz). **^{13}C NMR (100.6 MHz, CD_3OD)** δ: 21.3, 29.6, 32.0, 37.6, 48.3, 49.6, 64.7, 74.7, 81.4. **IR (KBr)**: 3358, 2965, 1460, 1385, 1365, 1260, 1151, 1133, 1058, 959, 814 cm^{-1}. **Mp**: 136.3-137.3 °C. **HRMS (Cl^+NH_3/GC)** calcd for $C_9H_{22}NO_3$ ($[M+NH_4]^+$): 192.1600, found 192.1607.

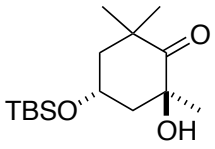
(±) (1*S*, 2*S*, 5*R*)-5-[(*tert*-butyldimethylsilyl)oxy]-1,3,3-trimethylcyclohexane-1,2-diol



To a solution of **4** (3.05 g, 17.5 mmol) and imidazole (4.02 g, 59.1 mmol, 3.4 equiv) in anhydrous DMF (150 mL), cooled at 0 °C in an ice bath under argon, was added TBSCl (5.28 g, 35 mmol, 2 equiv). The reaction mixture was stirred for 1 h at 0 °C and for 16 h at room temperature before hydrolysis by the addition of H_2O (75 mL). The mixture was extracted with Et_2O (3 x 75 mL) and the combined organic layer was washed with brine (100 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. The oily residue was purified by flash chromatography on silica gel (9:1 to 8:2 cyclohexane/EtOAc) to afford the title compound as a white solid (4.37 g, 87% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.00 (s, 6H), 0.82 (s, 9H), 0.92 (s, 3H), 0.98 (s, 3H), 1.18 (s, 3H), 1.19 (dd, 1H, *J* = 11.9 and 12.2 Hz), 1.32 (dd, 1H, *J* = 11.2 and 13.5 Hz), 1.60 (ddd, 1H, *J* = 3.1, 3.6 and 12.2 Hz), 1.76 (d, 1H, *J* = 7.0 Hz), 1.94 (ddd, 1H, *J* = 3.1, 4.3 and 13.5 Hz), 2.98 (d, 1H, *J* = 7.0 Hz), 3.98-4.06 (m, 1H). **^{13}C NMR (100.6 MHz, $CDCl_3$)** δ: -6.7, -6.6, 16.1, 18.4, 23.8 (3C), 27.4, 29.0, 34.4, 45.5, 46.7, 62.5, 71.7, 78.2. **IR (KBr)**: 3433, 2954, 2859, 1476, 1387, 1364, 1258, 1150, 1073, 837 cm^{-1}. **Mp**: 89.0-89.4 °C. **Elemental analysis** calcd for $C_{15}H_{32}O_3Si$: C 62.45, H 11.18; found: C 62.18, H 11.21.

(±) (2*R*,4*S*)-4-[(*tert*-butyldimethylsilyl)oxy]-2-hydroxy-2,6,6-trimethylcyclohexanone **(5)**



5

To a solution of (±) (1*S*, 2*S*, 5*R*)-5-[(*tert*-butyldimethylsilyl)oxy]-1,3,3-trimethylcyclohexane-1,2-diol (2 g, 6.94 mmol) in EtOAc (47 mL, C = 0.14 M), was added IBX[2] (9.2 g, 32.9 mmol, 4.75 equiv). The resulting suspension was heated for 20 h at 80 °C in an oil bath under vigorous magnetic stirring (TLC control). The reaction mixture was then cooled to room temperature and filtered through a glass frit. The solid was washed with EtOAc and the combined filtrates were concentrated *in vacuo* to afford **5** as a pale yellow oil (1.84 g, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.07 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 1.16 (s, 3H), 1.28 (s, 3H), 1.47 (s, 3H), 1.83-1.86 (m, 2H), 2.06 (d, 2H, *J* = 5.3 Hz), 3.31 (bs, 1H, OH), 4.23 (qt, 1H, *J* = 5.3 Hz). **^{13}C NMR (100.6 MHz, $CDCl_3$)** δ: -4.7, -4.6, 18.3, 26.0 (3C), 28.1 (2C), 29.1, 43.5, 47.1, 47.4, 65.3, 75.1, 218.2. **IR (neat)**: 3450, 2930, 2857, 1711, 1472, 1384, 1255, 1165, 1030, 998 cm^{-1}. **HRMS (EI$^+$/GC)** calcd for $C_{15}H_{30}O_3Si$ ([M]$^+$): 286.1964, found 286.1964.

Access to α-hydroxyepoxides (1a) and (1b) from ketone (5)

Epoxidation protocol using trimethylsulfoxonium ylide

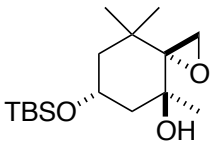
To a suspension of NaH (60% in oil, 705 mg, 17.5 mmol, 10 equiv) in anhydrous DMSO (28 mL), under argon, was added trimethylsulfoxonium iodide (5.76 g, 26.2 mmol, 15 equiv). The reaction mixture was stirred at room temperature for 1 h. THF (28 mL) and LiI (2.81 g, 21 mmol, 12 equiv) were added and stirring was continued for 1 h. After cooling to 0 °C, a solution of **5** (500 mg, 1.75 mmol) in DMSO/THF: 1/1 (28 mL) was added and the reaction mixture was heated at 50 °C for 16 h (TLC control). The reaction was quenched with Et_2O/H_2O: 1/1 (50 mL) and the mixture was extracted with Et_2O (3 x 50 mL). The combined organic layer was washed with brine (2 x 100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The mixture of **1a** and **1b** (82:18 dr) was separated by chromatography on silica gel (95:5 cyclohexane/EtOAc) to afford **1a** as a pale yellow oil (285 mg, 55% yield) and **1b** as white crystals (99 mg, 18% yield).

[2] IBX was prepared according to the literature: Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537.

Epoxidation protocol using trimethylsulfonium ylide

A suspension of NaH (60% in oil, 340 mg, 5.1 mmol, 3 equiv) in anhydrous DMSO (12 mL) was stirred for 1 h at 70 °C under argon atmosphere. After cooling to room temperature, THF (12 mL) was added and the reaction mixture was cooled to 0 °C before the addition of a solution of trimethylsulfonium iodide (1.04 g, 5.1 mmol, 3 equiv) in DMSO (12 mL). The reaction mixture was stirred at 0° C for 15 min and a solution of **5** (500 mg, 1.75 mmol) in THF (5 mL) was added. Stirring was continued for 3 h at 0 °C (TLC control). The reaction was quenched with Et_2O/H_2O: 1/1 (50 mL) and the mixture was extracted with Et_2O (3 x 50 mL). The combined organic phase was washed with brine (2 x 100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The mixture of **1a** and **1b** (14:86 dr) was separated by chromatography on silica gel (95:5 cyclohexane/EtOAc) to afford **1a** as a pale yellow oil (45 mg, 9% yield) and **1b** as white crystals (340 mg, 65% yield).

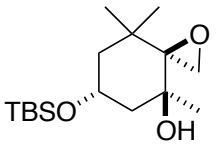
(±) (3*R*, 4*S*, 6*R*) 6-[(*tert*-butyldimethylsilyl]oxy]-4,8,8-trimethyl-1-oxaspiro[2.5]octan-4-ol **(1a)**



1a

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.06 (s, 6H), 0.76 (s, 3H), 0.88 (s, 9H), 1.07 (s, 3H), 1.25 (s, 3H), 1.49 (dd, 1H, *J* = 12.6 and 11.1 Hz), 1.59 (dd, 1H, *J* = 13.4 and 11.1 Hz), 1.63 (ddd, 1H, *J* = 12.6, 4.2 and 2.5 Hz), 1.90 (ddd, 1H, *J* = 13.4, 4.2 and 2.5 Hz), 2.64 (d, 1H, *J* = 4.1 Hz), 2.76 (d, 1H, *J* = 4.1 Hz), 4.19 (tt, 1H, *J* = 11.1 and 4.2 Hz). **^{13}C NMR (100.6 MHz, $CDCl_3$)** δ: -4.4, -4.3, 18.4, 26.1 (3C), 26.2, 26.3, 27.3, 35.3, 45.0, 48.4, 48.5, 62.6, 64.8, 75.6. **IR (neat)**: 3509, 2927, 2856, 1472, 1376, 1252, 1084, 1069, 832 cm^{-1}. **HRMS (GC/CI$^+$$NH_3$)** calcd for $C_{16}H_{33}O_3Si$ ($[M+H]^+$): 301.2199, found 301.2210.

(±) (3*S*, 4*S*, 6*R*) 6-[(*tert*-butyldimethylsilyl]oxy]-4,8,8-trimethyl-1-oxaspiro[2.5]octan-4-ol **(1b)**



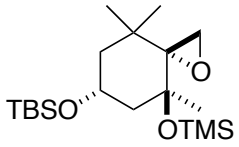
1b

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.06 (s, 6H), 0.88 (s, 9H), 0.98 (s, 3H), 1.06 (s, 3H), 1.22 (s, 3H), 1.47 (dd, 1H, *J* = 13.3 and 7.9 Hz), 1.65 (dd, 1H, *J* = 13.6 and 7.9 Hz), 1.72 (ddd, 1H, *J* = 13.6, 4.1 and 1.9 Hz), 1.92 (ddd, 1H, *J* = 13.3, 4.1 and 1.9 Hz), 2.01 (sl, 1H, OH), 2.81 (d,

1H, *J* = 4.2 Hz), 2.82 (d, 1H, *J* = 4.2 Hz), 4.21 (tt, 1H, *J* = 7.9 and 4.1 Hz). **^{13}C NMR (100.6 MHz, $CDCl_3$)** δ: -4.6 (2C), 18.3, 26.1 (3C), 26.2, 27.2, 28.6, 34.7, 47.5, 47.6, 49.5, 65.8, 65.9, 72.0. **IR (neat)**: 3479, 2925, 2855, 1459, 1370, 1248, 1065, 827 cm^{-1}. **Mp**: 73.7-74.2 °C. **HRMS (CI^+NH_3)** calcd for $C_{16}H_{33}O_3Si$ ($[M+H]^+$): 301.2199, found 301.2203. **Elemental analysis** calcd for $C_{16}H_{32}O_3Si$: C 63.95, H 10.73; found: C 63.86, H 10.67.

C. Synthesis of α-silyloxy spiroepoxides (2a) and (2b)

(±) (3*R*, 4*S*, 6*R*) 6-[(*tert*-butyldimethylsilyl]oxy]-4-[(trimethylsilyl)oxy]-4,8,8-trimethyl-1-oxaspiro[2.5]octane **(2a)**

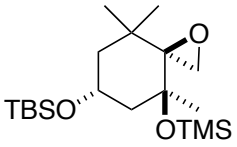


2a

To a solution of **1a** (100 mg, 0.33 mmol) and imidazole (57 mg, 0.84 mmol, 2.5 equiv) in anhydrous DMF (2 mL), cooled at 0 °C in an ice bath under argon, was added TMSCl (50 μL, 0.34 mmol, 1.2 equiv). The reaction mixture was stirred for 4 h at room temperature before hydrolysis by the addition of H_2O (2 mL). The mixture was extracted with Et_2O (3 x 2 mL) and the combined organic phase was washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. The oily residue was purified by flash chromatography on silica gel (7:3 cyclohexane/EtOAc) to afford **2a** as a colorless oil (100 mg, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.06 (s, 6H), 0.10 (s, 9H), 0.73 (s, 3H), 0.88 (s, 9H), 1.09 (s, 3H), 1.21 (s, 3H), 1.41-1.53 (m, 2H), 1.60 (ddd, 1H, *J* = 12.6, 4.0 and 2.6 Hz), 1.89 (ddd, 1H, *J* = 13.0, 4.0 and 2.6 Hz), 2.62 (d, 1H, *J* = 4.1 Hz), 2.69 (d, 1H, *J* = 4.1 Hz), 4.17 (tt, 1H, *J* = 11.2 and 4.0 Hz). **^{13}C NMR (100.6 MHz, $CDCl_3$)** δ: -4.3, -4.2, 2.7 (3C), 18.4, 24.6, 26.2 (3C), 26.5, 27.5, 35.4, 45.6, 48.5, 49.9, 62.6, 65.2, 78.2. **IR (neat)**: 2956, 2929, 1250, 1128, 1070, 832, 772 cm^{-1}. **HRMS (FI^+/GC)** calcd for $C_{19}H_{40}O_3Si_2$ ($[M]^+$): 372.2516, found 372.2498.

(±) (3*S*, 4*S*, 6*R*) 6-[(*tert*-butyldimethylsilyl]oxy]-4-[(trimethylsilyl)oxy]-4,8,8-trimethyl-1-oxaspiro[2.5]octane **(2b)**



2b

To a solution of **1b** (390 mg, 1.29 mmol) and imidazole (224 mg, 3.30 mmol, 2.54 equiv) in anhydrous DMF (2 mL), cooled at 0 °C in an ice bath under argon, was added dropwise TMSCl (250 μL, 1.94 mmol, 1.5 equiv). The reaction mixture was stirred for 4 h at room temperature before hydrolysis by the addition of H_2O (6 mL). The mixture was extracted with Et_2O (3 x 2 mL) and the combined organic phase was washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. The oily residue was purified by flash chromatography on silica gel (7:3 cyclohexane/EtOAc) to afford the title compound as a colorless oil (380 mg, 79% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.07 (s, 6H), 0.11 (s, 9H), 0.73 (s, 3H), 0.89 (s, 9H), 1.08 (s, 3H), 1.21 (s, 3H), 1.36-1.44 (m, 2H), 1.77 (ddd, 1H, *J* = 12.8, 4.0 and 3.2 Hz), 2.03 (ddd, 1H, *J* = 12.9, 4.0 and 3.2 Hz), 2.57 (d, 1H, *J* = 4.2 Hz), 2.73 (d, 1H, *J* = 4.2 Hz), 4.23 (tt, 1H, *J* = 4.0 and 10.9 Hz). **^{13}C NMR (100.6 MHz, $CDCl_3$)** δ: -4.4 (2C), 2.8 (3C), 18.5, 25.7, 26.2 (4C), 28.9, 35.2, 49.9, 50.0, 51.2, 64.6, 65.1, 77.4. **IR (neat)**: 2954, 2928, 1370, 1250, 1128, 1076, 1011, 832, 773 cm^{-1}. **HRMS (FI$^+$/GC)** calcd for $C_{19}H_{40}O_3Si_2$ ($[M]^+$): 372.2516, found 372.2538.

D. Acid-induced rearrangements protocols on compounds (1) and (2)

$SnCl_4$ and $BF_3.OEt_2$ protocol

To a stirred solution of **1** or **2** (100 mg) in anhydrous CH_2Cl_2 (10 mL/mmol), cooled to -78 °C under argon surpressure, was added dropwise the Lewis acid (see tables 1 and 2). The reaction mixture was stirred at -78 °C and the temperature was increased to -20°C if required (TLC monitoring). The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with Et_2O (3 x 5 mL). The combined organic phase was washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. When the product **6** was formed during the reaction, the crude product was purified by chromatography on silica gel (95:5 cyclohexane/EtOAc) to afford **6** as a colorless oil.

$Yb(OTf)_3$ protocol

To a stirred solution of **1** or **2** (100 mg) in anhydrous CH_2Cl_2 (5 mL/mmol), at room temperature and under argon surpressure, was added anhydrous $Yb(OTf)_3$ (0.2 equiv). The

mixture was stirred at room temperature and the temperature was increased to reflux if required (TLC monitoring). The reaction mixture was quenched with H_2O (3 mL) and extracted with Et_2O (3 x 5 mL). The combined organic phase was washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. When the product **6** was formed during the reaction, the crude product was purified by chromatography on silica gel (97:3 cyclohexane/EtOAc) to afford **6** as a colorless oil.

MABR protocol

To a degassed solution of 4-bromo-2,6-di-*tert*-butylphenol (4 equiv) in anhydrous CH_2Cl_2 (2,5 mL/mmol), under argon, was added under magnetic stirring a 1M hexane solution of Me_3Al (2 equiv). After 1 h stirring at room temperature, the reaction mixture was cooled to -78 °C and a solution of **1** or **2** (100 mg, 1 equiv) in anhydrous CH_2Cl_2 (10 mL/mmol) was added dropwise. The mixture was stirred at -78 °C and the temperature was increased to -20 °C if required (TLC monitoring). The reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (99:1 to 95:5 cyclohexane/EtOAc).

$B(C_6F_5)_3$ protocol

To a stirred solution of **1** or **2** in anhydrous THF (0.15 M), cooled to -20 °C under argon surpressure, was added $B(C_6F_5)_3$ (0.1 equiv). The reaction mixture was warmed to room temperature and stirred for 1 h or 15 h (see tables 1 and 2). The temperature was then raised to 60°C and stirring was continued for 12 h or 15 h. The reaction mixture was quenched with $NaHCO_3$ and the aqueous layer was extracted with Et_2O (3 x). The combined organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*.

***t*-$BuMe_2SiOTf$/*i*-Pr_2NEt protocol on substrate 1 (Jung's protocol[3])**

To a solution of **1** in anhydrous CH_2Cl_2 (0.1 M) was successively added activated powdered 4Å molecular sieves (0.1 g/mmol of substrate) and *i*-Pr_2NEt (1.8 equiv). After cooling to -50 °C, *t*-$BuMe_2SiOTf$ was introduced (1.7 equiv) and the reaction mixture was stirred at this temperature for 1 h. The temperature was allowed to warm to 0 °C and stirring was continued for 1 h. *I*-Pr_2NEt (1.2 equiv) and *t*-$BuMe_2SiOTf$ (1.2 equiv) were then successively added and stirring was continued for 15 h. The reaction mixture was quenched with H_2O and the

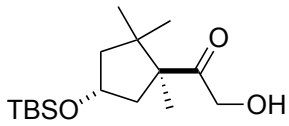
[3] Jung, M. E.; Allen, D. A. *Org. Lett.* **2008**, *10*, 2039.

aqueous layer was extracted with Et_2O (3x). The combined organic layer was washed with brine (1x), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to afford the unchanged substrate **1**.

Me_3SiOTf/*i*-Pr_2NEt protocol on substrate 2 (Jung's protocol)

To a solution of **2** in anhydrous CH_2Cl_2 (0.1 M) was successively added activated powdered 4Å molecular sieves (0.1 g/mmol of substrate) and *i*-Pr_2NEt (1.8 equiv). After cooling to -50 °C, Me_3SiOTf was introduced (1.7 equiv) and the temperature was allowed to warm to -35 °C. After a total 1 h stirring, no substrate was remaining from TLC analysis. The reaction mixture was quenched with H_2O and the aqueous layer was extracted with Et_2O (3x). The combined organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*, affording a complex mixture of products as an oily residue.

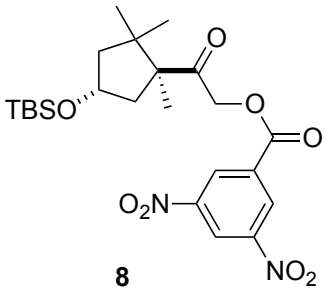
(±) 1-((1*S*, 4*R*)-4-((*tert*-butyldimethylsilyl)oxy)-1,2,2-trimethylcyclopentyl)-2-hydroxyethanone **(6)**



6

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0,00 (s, 6H), 0.77 (s, 3H), 0.84 (s, 9H), 1.12 (s, 3H), 1.25 (s, 3H), 1.49 (dd, 1H, *J* = 14.0 and 3.0 Hz), 1.64 (dd, 1H, *J* = 13.6 and 4.2 Hz), 1.93 (dd, 1H, *J* = 13.6 and 7.8 Hz), 2.64 (dd, *J* = 14.0 and 8.2 Hz), 3.28 (bs, 1H, OH), 4.20 (d, 1H, *J* = 18.9 Hz), 4.28 (d, 1H, *J* = 18.9 Hz), 4.39 (tdd, 1H, *J* = 8.0, 4.2 and 3.0 Hz). **^{13}C NMR (100.6 MHz, $CDCl_3$)** δ: -4.6, -4.5, 18.1, 20.2, 25.1, 26.0, 26.1 (3C), 44.8, 45.5, 51.3, 57.8, 67.0, 70.8, 214.7. **IR (neat)**: 3781, 2928, 2857, 1698, 1380, 1360, 1255 cm^{-1}. **HRMS (GC/CI$^+$$NH_3$)** calcd for $C_{16}H_{33}O_3Si$ ($[M+H]^+$): 301.2199, found 301.2215.

(±) 2-((1*S*, 4*R*)-4-((*tert*-butyldimethylsilyl)oxy)-1,2,2-trimethylcyclopentyl)-2-oxoethyl 3,5-dinitrobenzoate **(8)**

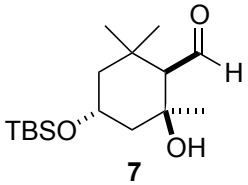


8

To a solution of alcohol **6** (100 mg, 0.33 mmol) in anhydrous CH_2Cl_2 (1.5 mL), under argon, were successively added *i*-Pr_2NEt (174 µL, 1 mmol, 3.0 equiv), 3,5-dinitrobenzoyl chloride (152 mg, 0.66 mmol, 2.0 equiv) and 4-DMAP (10 mg, 0.08 mmol, 0.25 equiv). The reaction mixture was stirred at room temperature for 4 h (TLC control) and quenched with saturated aqueous $NaHCO_3$ (2.5 mL). After 10 minutes stirring at room temperature, the mixture was extracted with CH_2Cl_2 (3 x 3 mL) and the combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The brown residue was purified by flash chromatography on silica gel (9:1 cyclohexane/EtOAc) to afford the title compound as white crystals (273 mg, 71% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.00 (s, 3H), 0.01 (s, 3H), 0.86 (s, 9H), 0.94 (s, 3H), 1.18 (s, 3H), 1.39 (s, 3H), 1.55 (dd, 1H, *J* = 14.0 and 2.9 Hz), 1.68 (dd, 1H, *J* = 13.7 and 4.2 Hz), 1.96 (dd, 1H, *J* = 13.7 and 7.6 Hz), 2.70 (dd, 1H, *J* = 14.0 and 8.1 Hz), 4.39 (m, 1H), 5.08 (d, 1H, J = 16.5 Hz), 5.19 (d, 1H, J = 16.5 Hz), 9.18 (d, 2H, *J* = 2.1 Hz), 9.22 (t, 1H, *J* = 2.1 Hz). **^{13}C NMR (100.6 MHz, $CDCl_3$)** δ: -4.6 (2C), 18.1, 20.4, 25.1, 25.8, 26.0 (3C), 44.9, 45.7, 51.3, 58.6, 69.0, 70.6, 122.8, 129.8, 133.5, 148.9, 162.2, 205.9. **IR (neat)**: 2928, 2855, 1736, 1715, 1542, 1344, 1253, 1056, 832, 772 cm^{-1}. **Mp**: 102.9-103.3. **Elemental analysis** calcd for $C_{23}H_{34}N_2O_8Si$: C 55.85, H 6.93, N 5.66; found: C 55.82, H 6.72, N 5.60.

(±) (2*S*, 4*R*) 4-[(*tert*-butyldimethylsilyl)oxy]-2-hydroxy-2,6,6-trimethylcyclohexane-1-carbaldehyde **(7)**



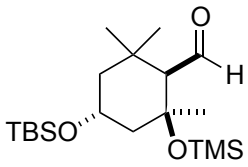
7

To a solution of compound **9** (60 mg, 0.17 mmol) in anhydrous MeOH (1 mL), under argon, was added PPTS (43 mg, 0.17 mmol, 1 equiv).The reaction mixture was stirred for 4 h at room temperature before hydrolysis with a saturated $NaHCO_3$ aqueous solution. The reaction mixture was extracted with Et_2O (3x) and the combined organic layer was washed with brine,

dried over $MgSO_4$ and concentrated under reduced pressure. The oily residue was purified by flash chromatography on silica gel (9:1 cyclohexane/EtOAc) to afford the title compound as a pale yellow oil (15 mg, 30% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.03 (s, 6H), 0.84 (s, 9H), 1.11 (s, 3H), 1.12 (s, 3H), 1.15-1.27 (m, 2H), 1.19 (s, 3H), 1.61 (ddd, 1H, *J* = 12.7, 4.1 and 2.0 Hz), 1.87 (ddd, 1H, *J* = 13.3, 4.1 and 2.0 Hz), 2.10 (d, 1H, *J* = 2.6 Hz), 2.85 (bs, 1H), 4.06 (tt, 1H, *J* = 11.2 and 4,1 Hz), 10.02 (d, 1H, *J* = 2.6 Hz). **^{13}C NMR (100.6 MHz, $CDCl_3$)** δ: -4.4 (2C), 18.3, 23.9, 26.1 (3C), 31.1, 32.3, 36.4, 49.6, 51.4, 64.3, 64.8, 73.4, 209.0. **Mp**: 74.5-75 °C. **IR (neat)**: 3430, 2954, 2925, 2854, 1705, 1384, 1248, 1180, 1064, 830, 776 cm^{-1}. **HRMS (GC/CI^+NH_3)** calcd for $C_{16}H_{33}O_3Si$ ($[M+H]^+$): 301.2199, found 301.2206.

(±) (1*R*,4*R*,6*S*)-4-((*tert*-butyldimethylsilyl)oxy)-2,2,6-trimethyl-6-((trimethylsilyl)oxy) cyclohexanecarbaldehyde **(9)**

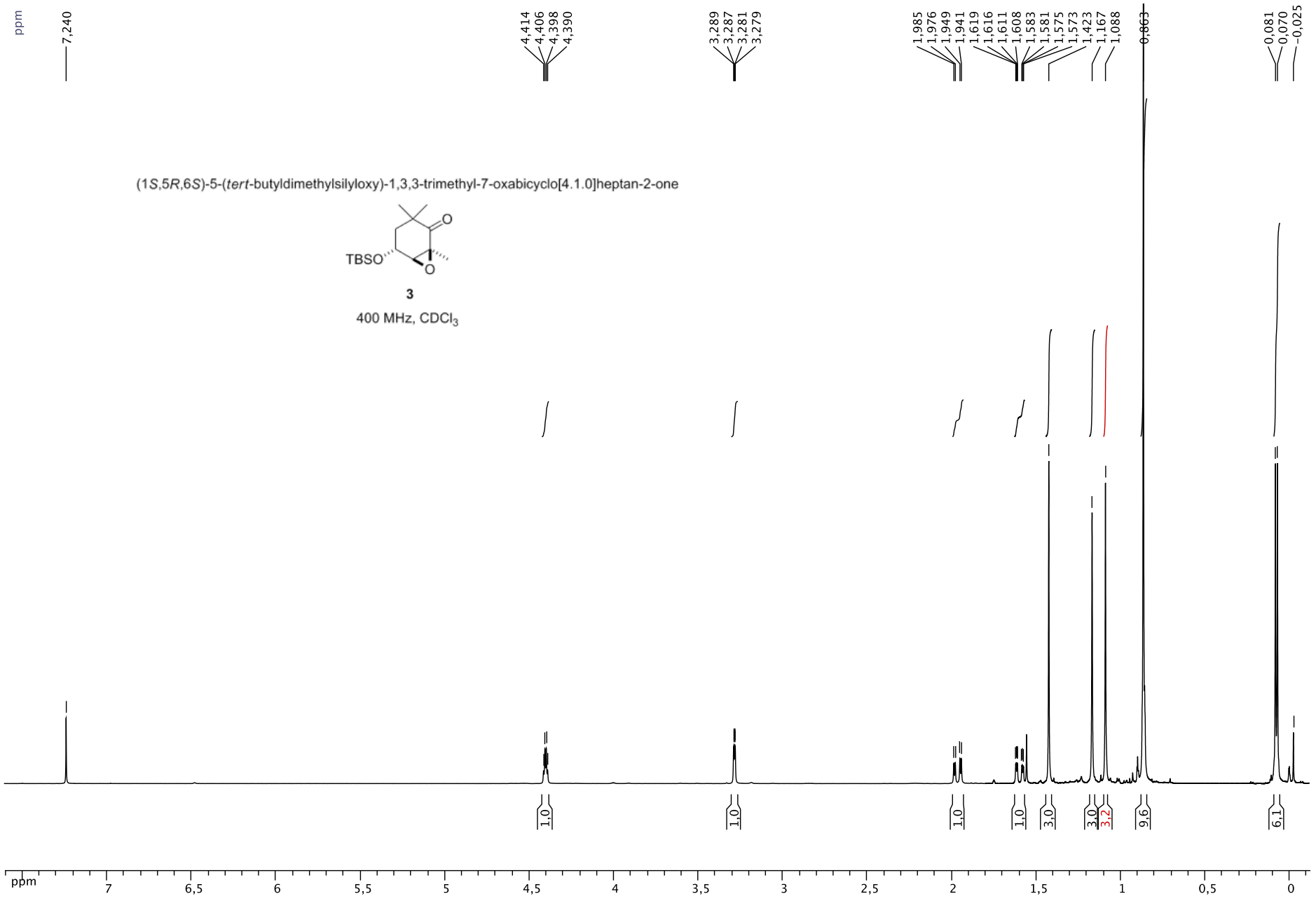


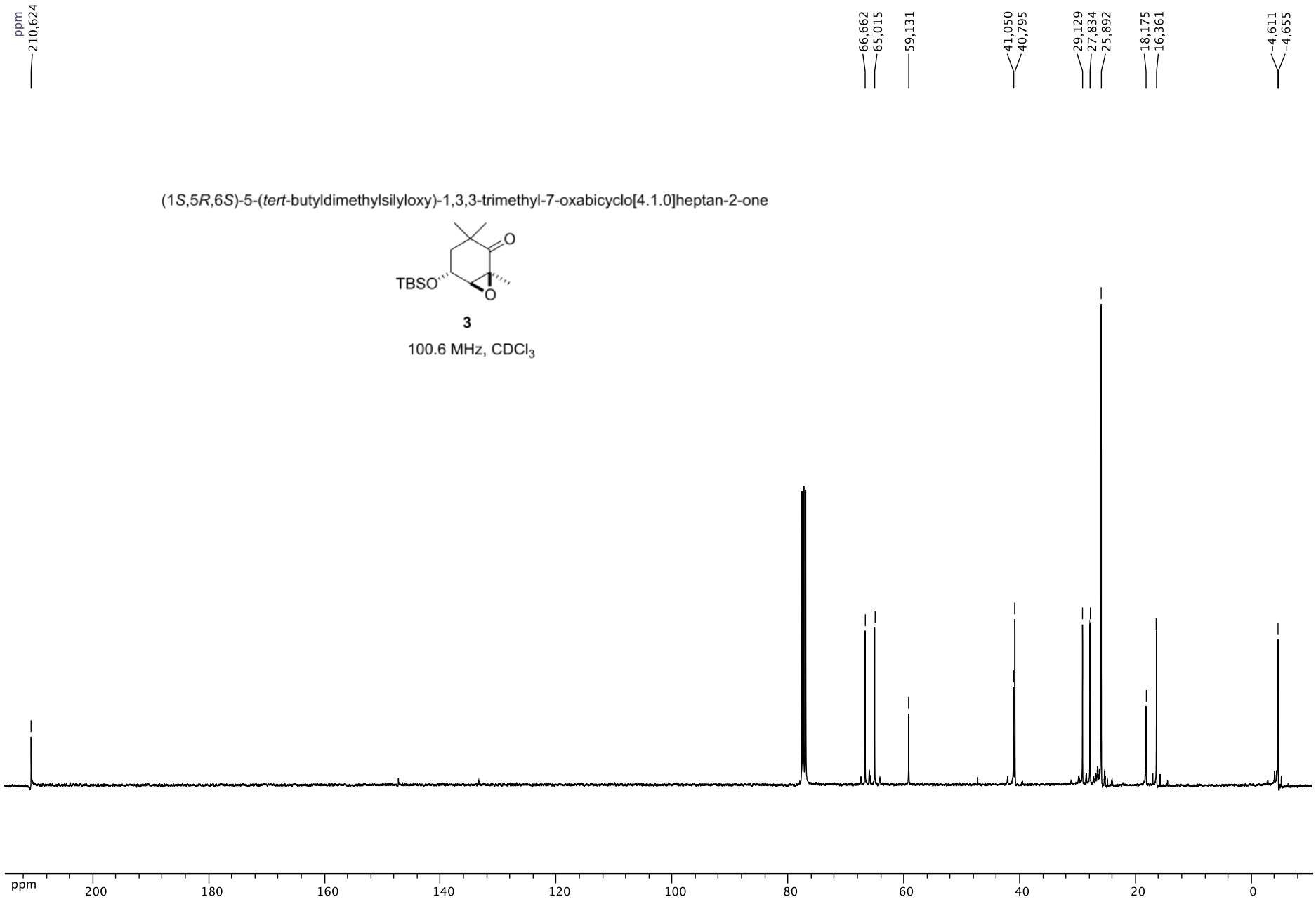
9

The MABR protocol was applied to substrate **2a** (100 mg, 0.27 mmol). The reaction was performed at - 78 °C during 1 h to afford aldehyde **9** as a colorless oil after chromatography (98 mg, 98% yield).

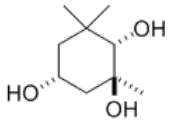
^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.07 (s, 6H), 0.14 (s, 9H), 0.88 (s, 9H), 0.89 (s, 3H), 1.11-1.22 (m, 2H), 1.22 (s, 3H), 1.24 (s, 3H), 1.50 (d, 1H, *J* = 5.1 Hz), 1.61 (ddd, 1H, *J* = 12.8, 4.0 and 2.0 Hz), 1.98 (ddd, 1H, *J* = 13.3, 4.0 and *J* = 2.0 Hz), 4.11 (tt, 1H, *J* = 11.2 and 4.0 Hz), 9.86 (d, 1H, *J* = 5.1 Hz). **^{13}C NMR (100.6 MHz, $CDCl_3$)** δ: -4.3, -4.2, 2.6 (3C), 18.3, 23.3, 26.1 (3C), 30.5, 32.4, 35.8, 50.0, 51.2, 65.3, 66.0, 76.5, 208.9. **IR (neat)**: 2955, 2928, 1718, 1472, 1378, 1250, 1063 1005, 832, 773 cm^{-1}. **HRMS (CI^+/GC)** calcd for $C_{19}H_{41}O_3Si_2$ ($[M+H]^+$): 373.2594 found 373.2591.

E. ^{1}H and ^{13}C spectra for compounds 3, 4, 5, 1a, 1b, 2a, 2b, 6, 8, 7, 9



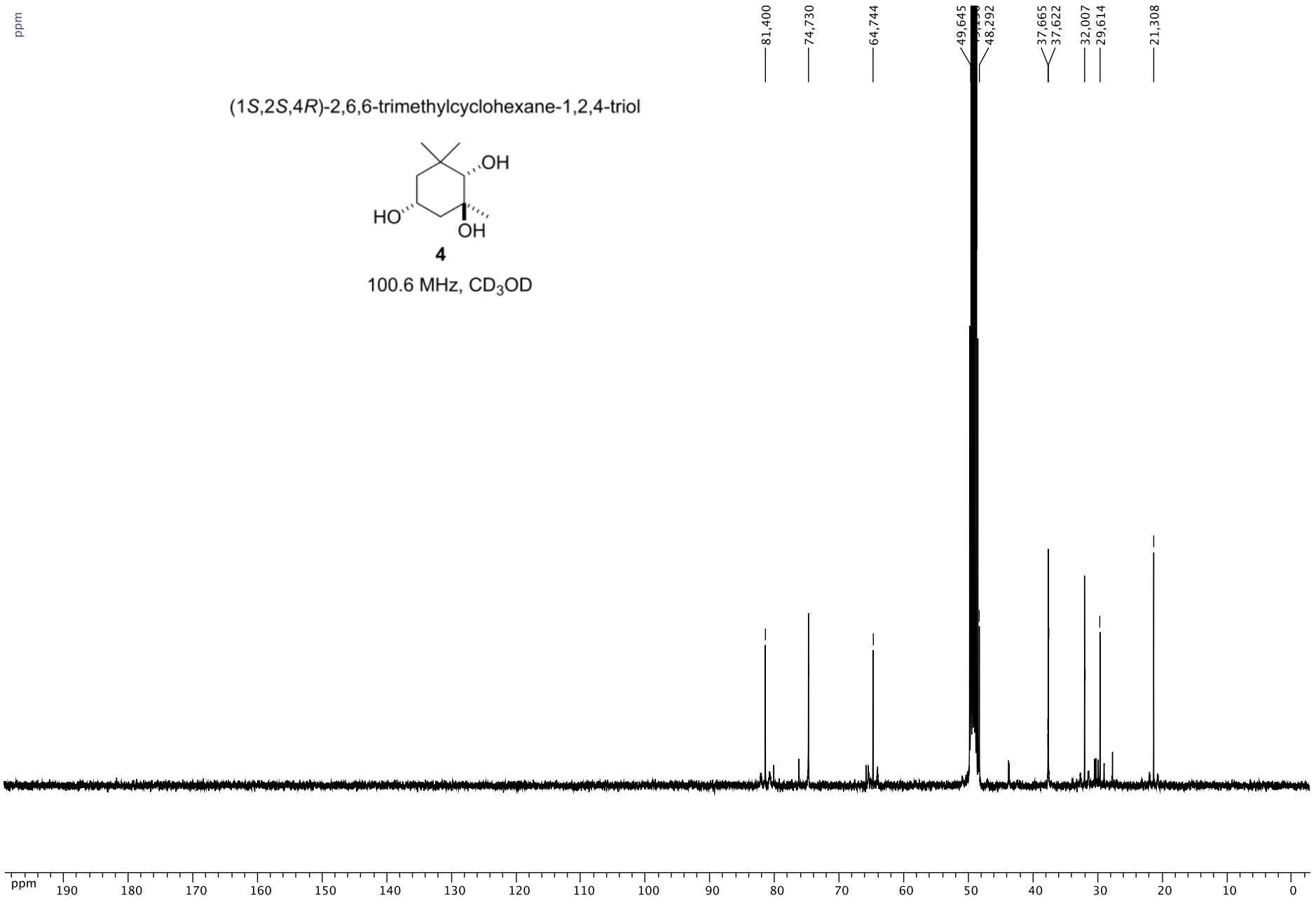


(1*S*,2*S*,4*R*)-2,6,6-trimethylcyclohexane-1,2,4-triol

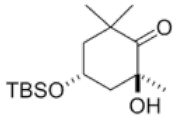


4

400 MHz, CD_3OD

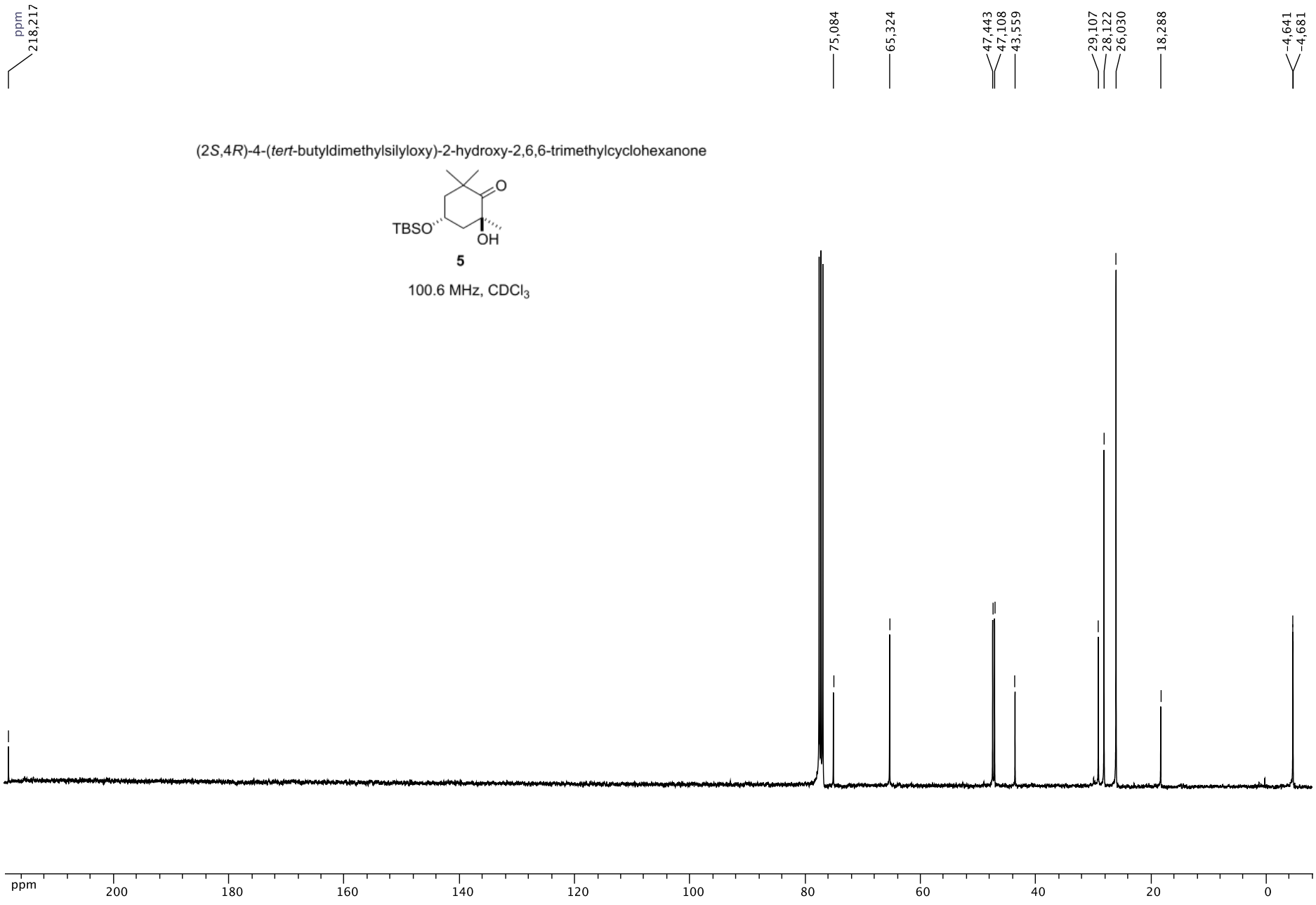


(2*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)-2-hydroxy-2,6,6-trimethylcyclohexanone

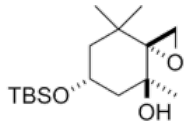


5

400 MHz, $CDCl_3$

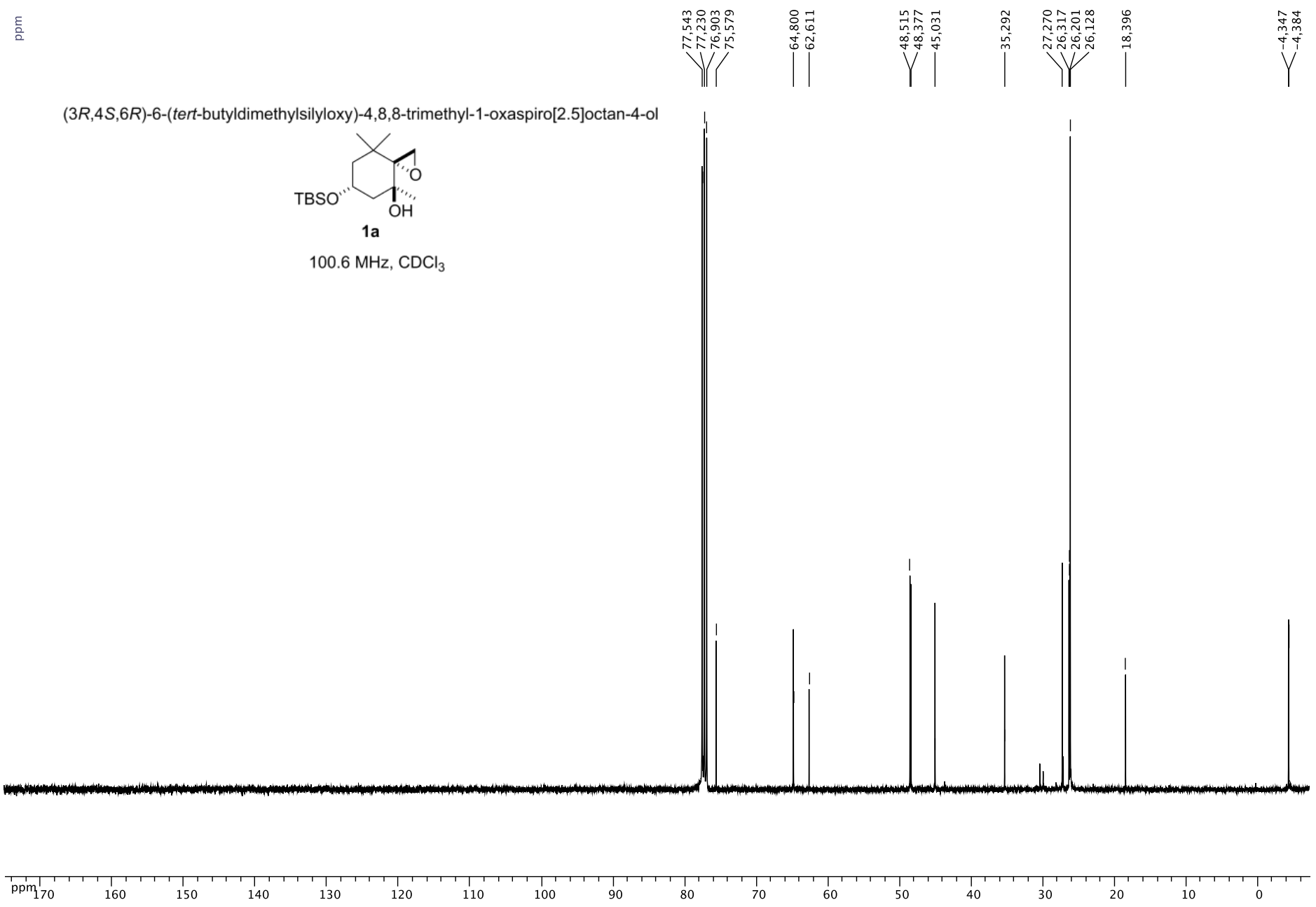


(3*R*,4*S*,6*R*)-6-(*tert*-butyldimethylsilyloxy)-4,8,8-trimethyl-1-oxaspiro[2.5]octan-4-ol

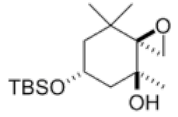


1a

400 MHz, $CDCl_3$

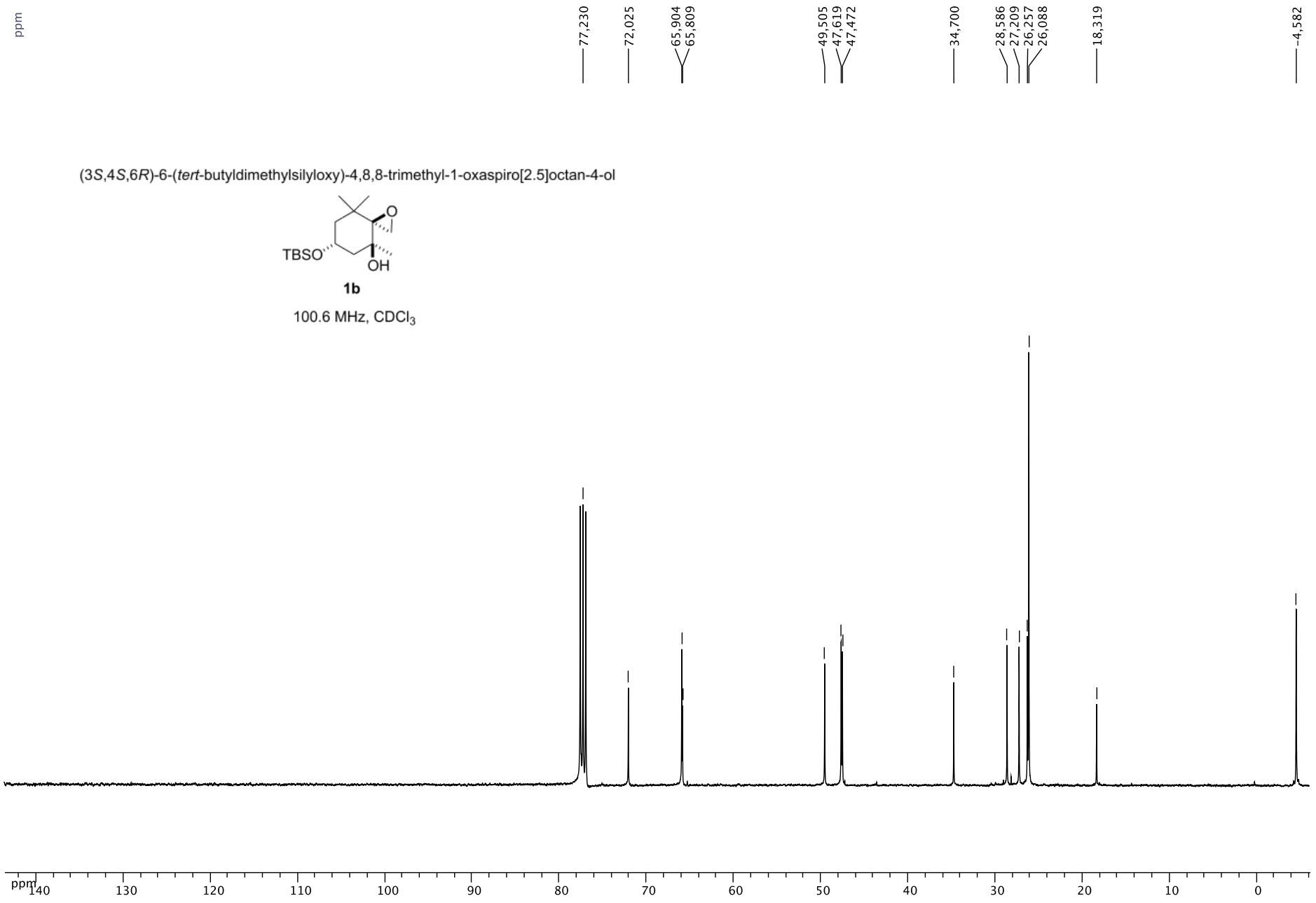


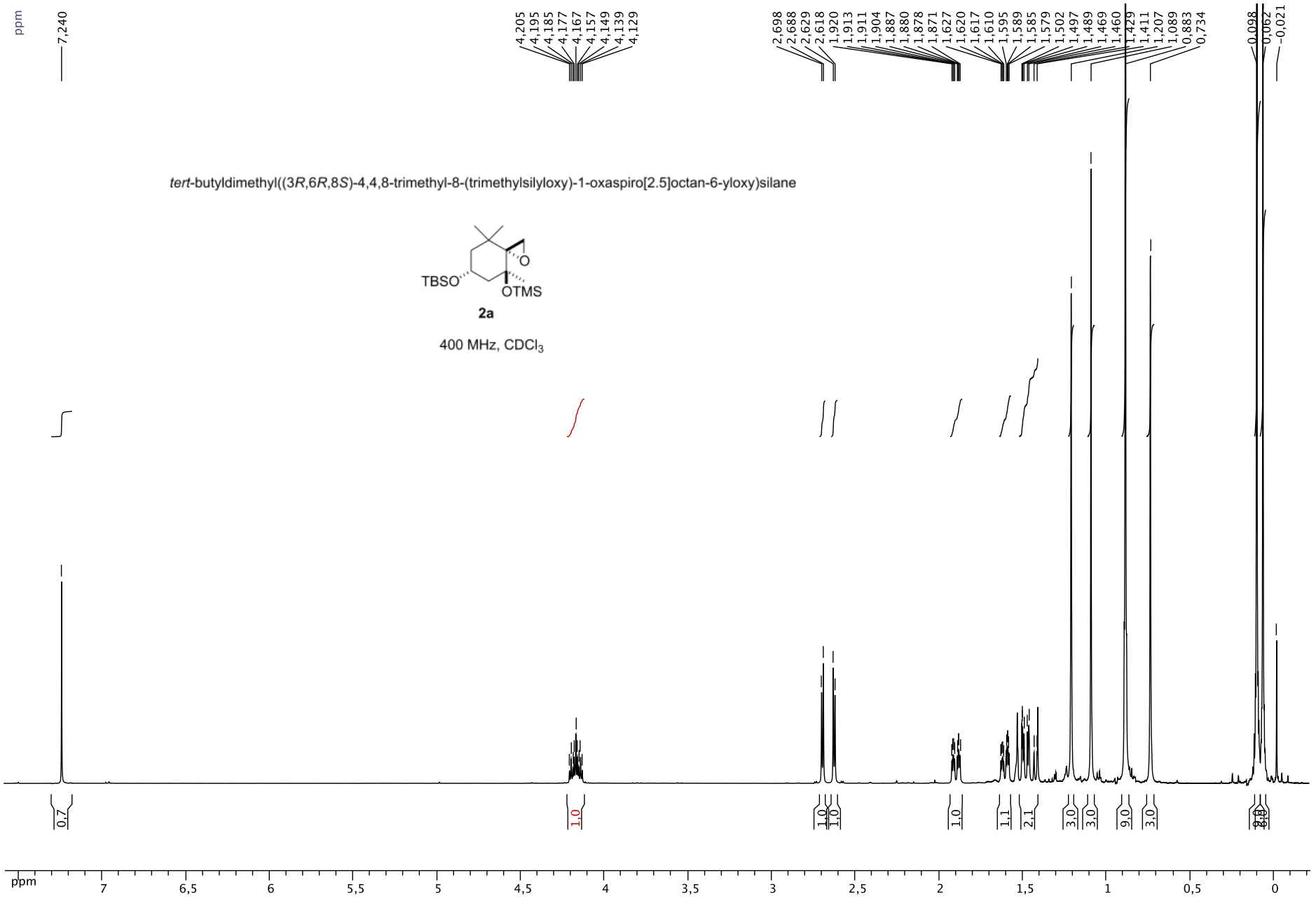
(3*S*,4*S*,6*R*)-6-(*tert*-butyldimethylsilyloxy)-4,8,8-trimethyl-1-oxaspiro[2.5]octan-4-ol

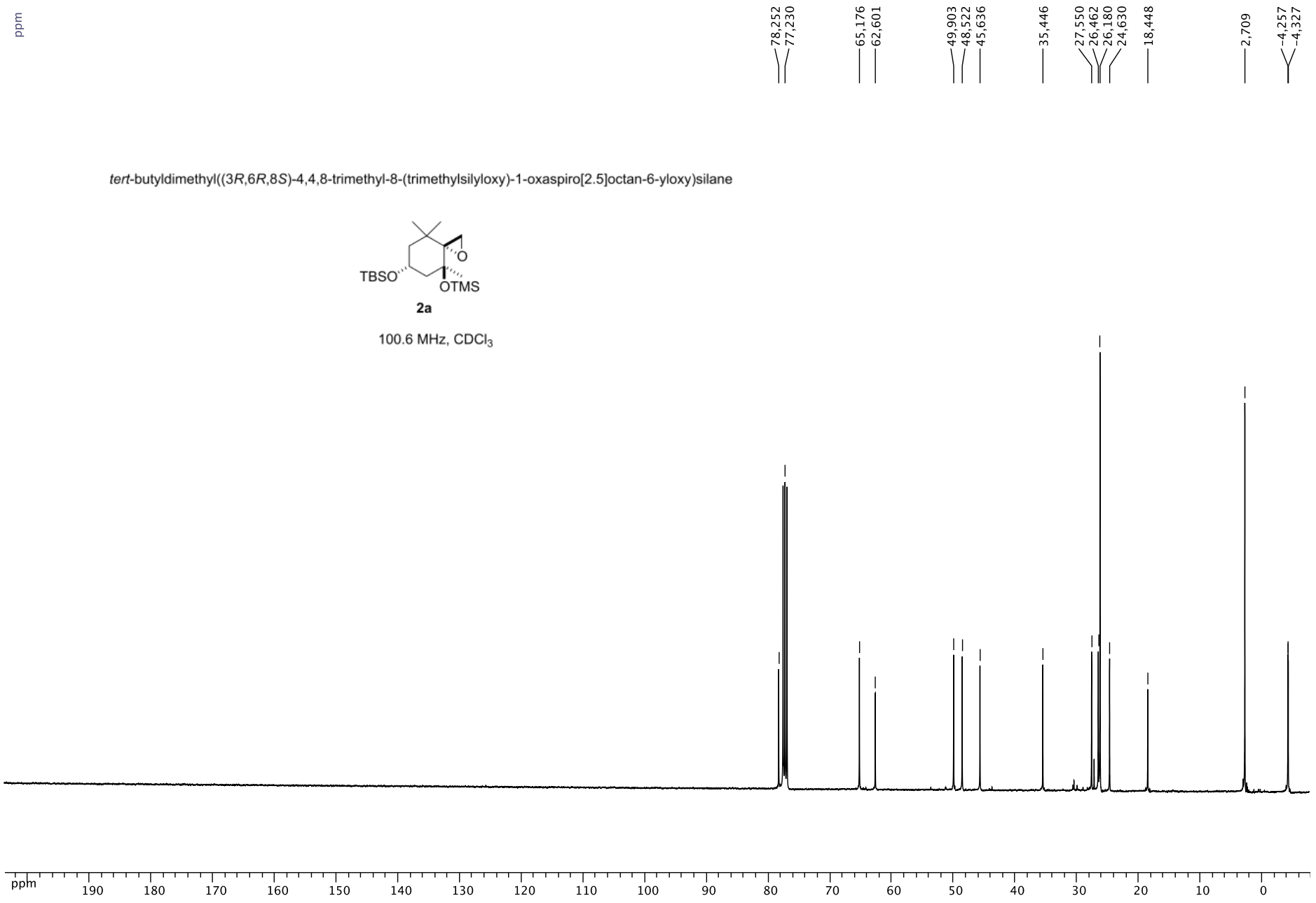


1b

400 MHz, $CDCl_3$





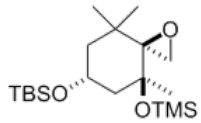


tert-butyldimethyl((3*R*,6*R*,8*S*)-4,4,8-trimethyl-8-(trimethylsilyloxy)-1-oxaspiro[2.5]octan-6-yloxy)silane

2a

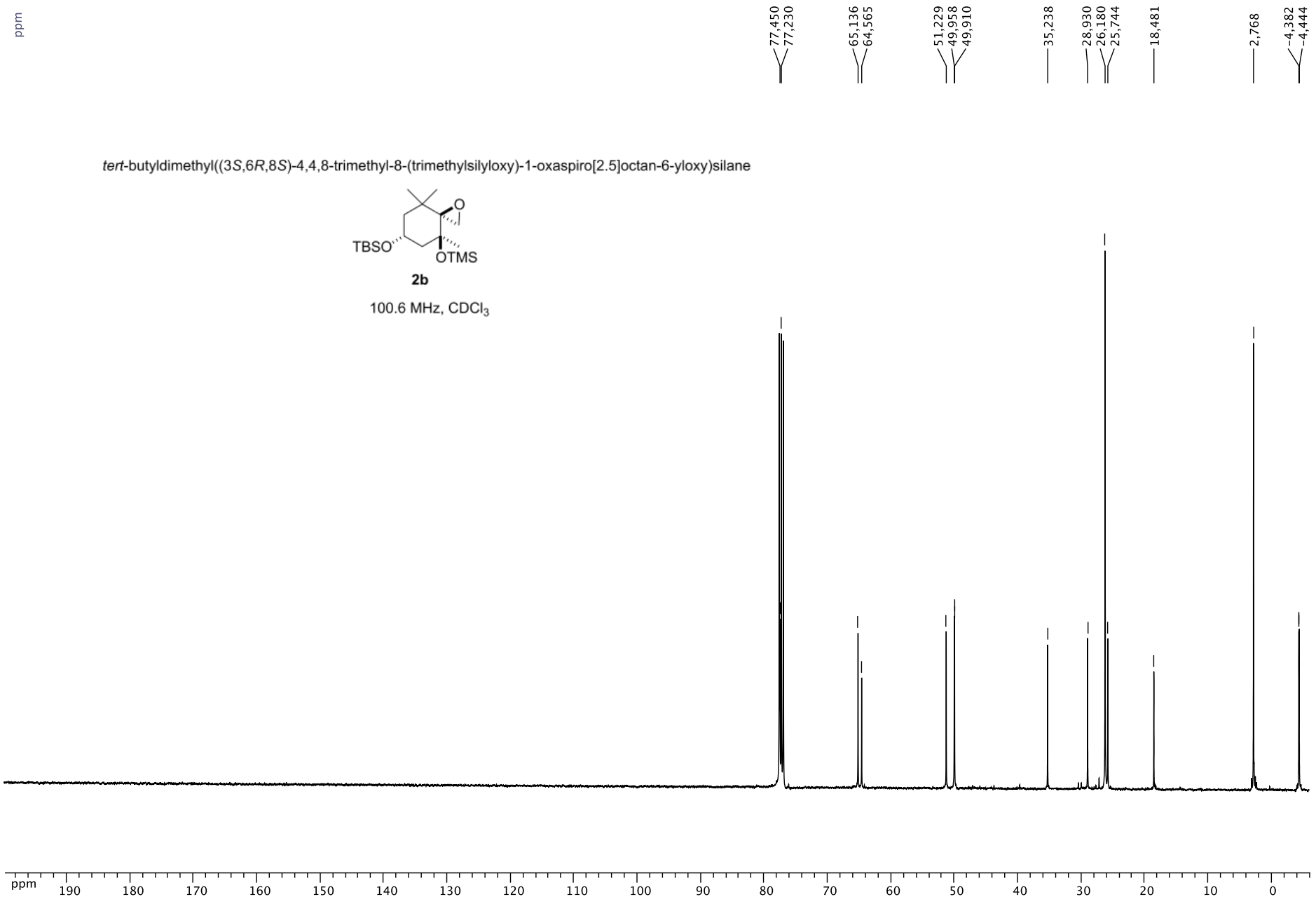
100.6 MHz, $CDCl_3$

tert-butyldimethyl((3*S*,6*R*,8*S*)-4,4,8-trimethyl-8-(trimethylsilyloxy)-1-oxaspiro[2.5]octan-6-yloxy)silane

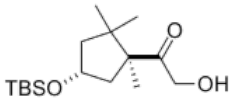


2b

400 MHz, $CDCl_3$

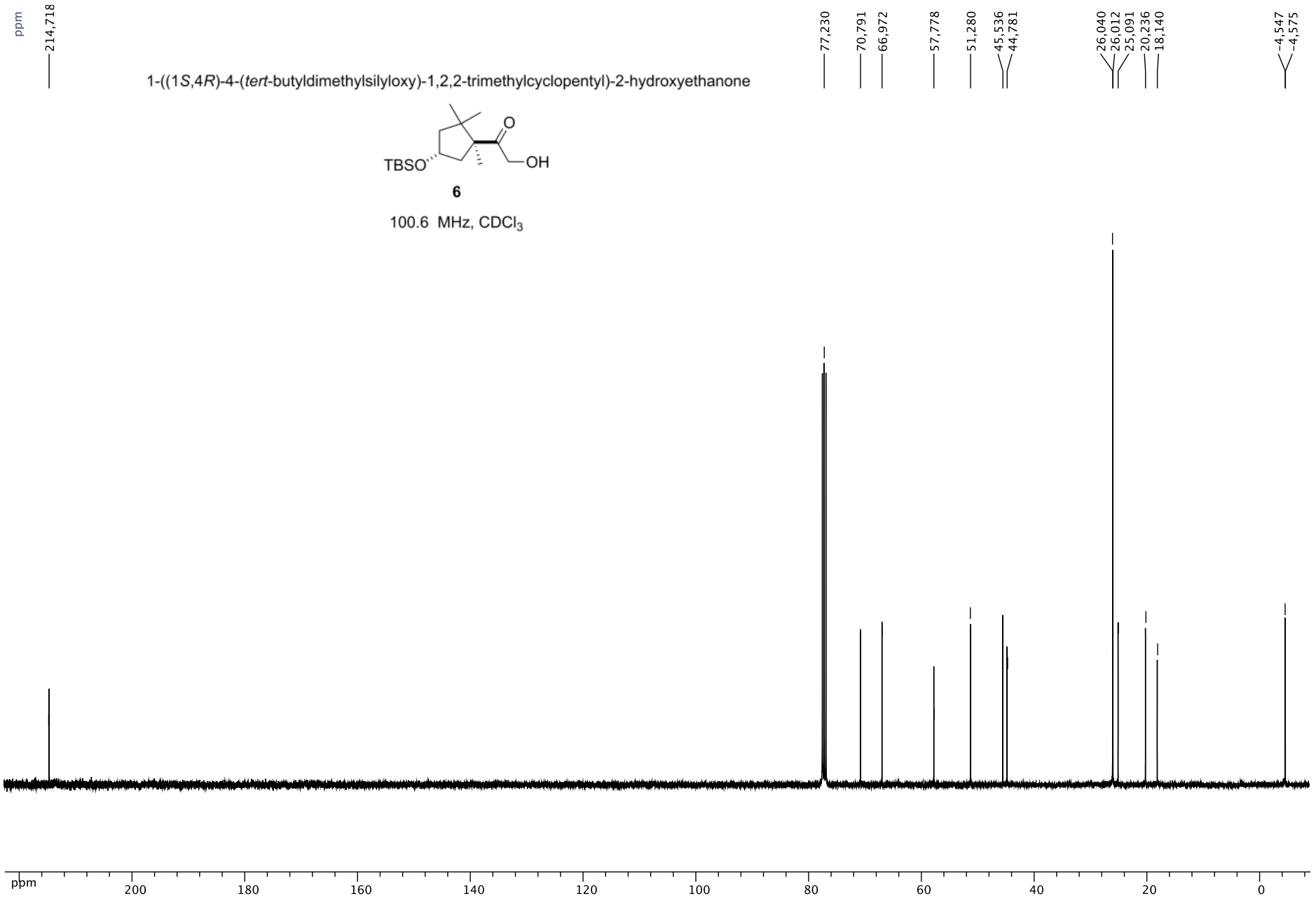


1-((1*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)-1,2,2-trimethylcyclopentyl)-2-hydroxyethanone

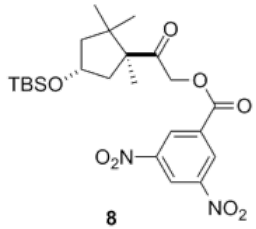


6

400 MHz, $CDCl_3$

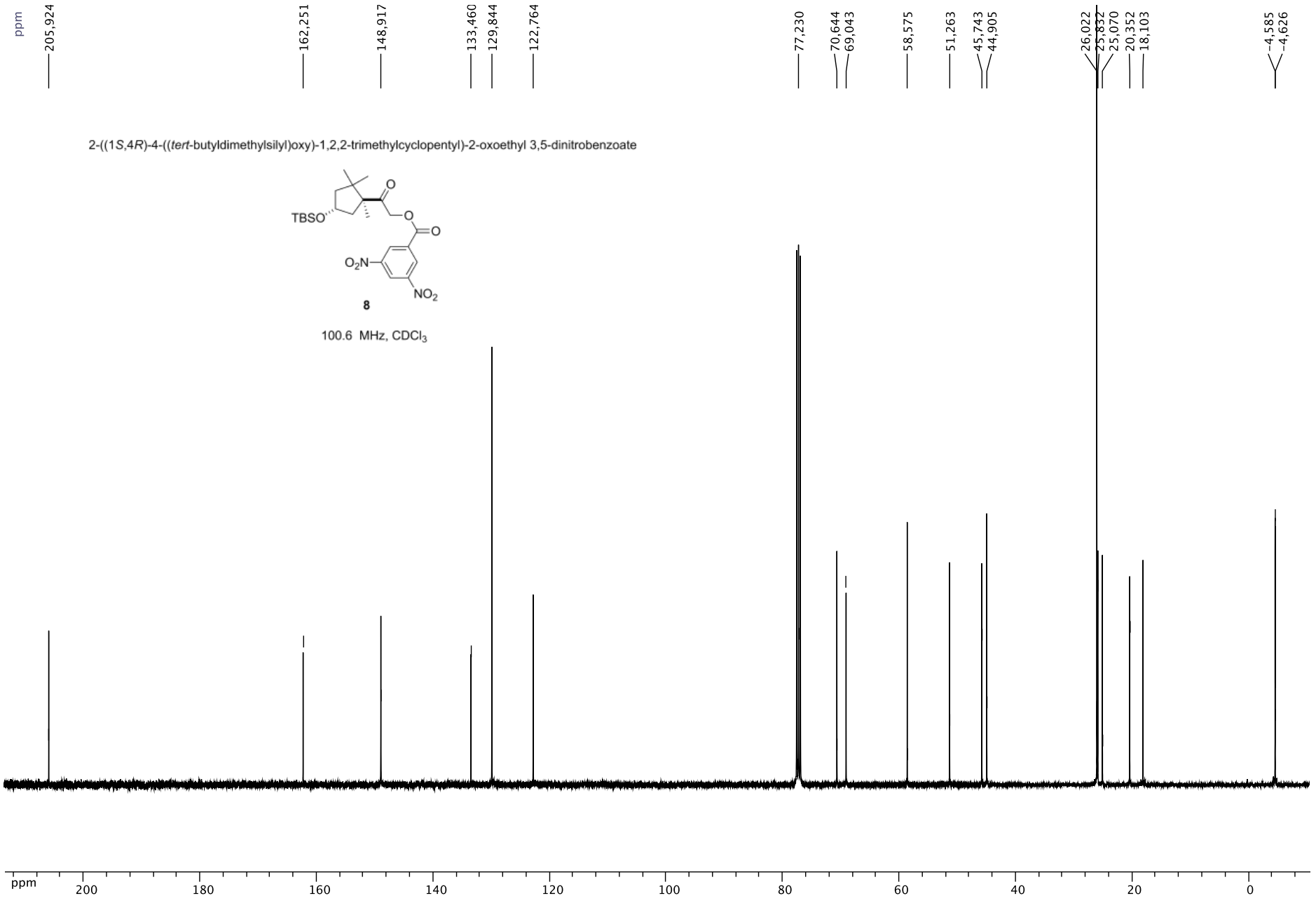


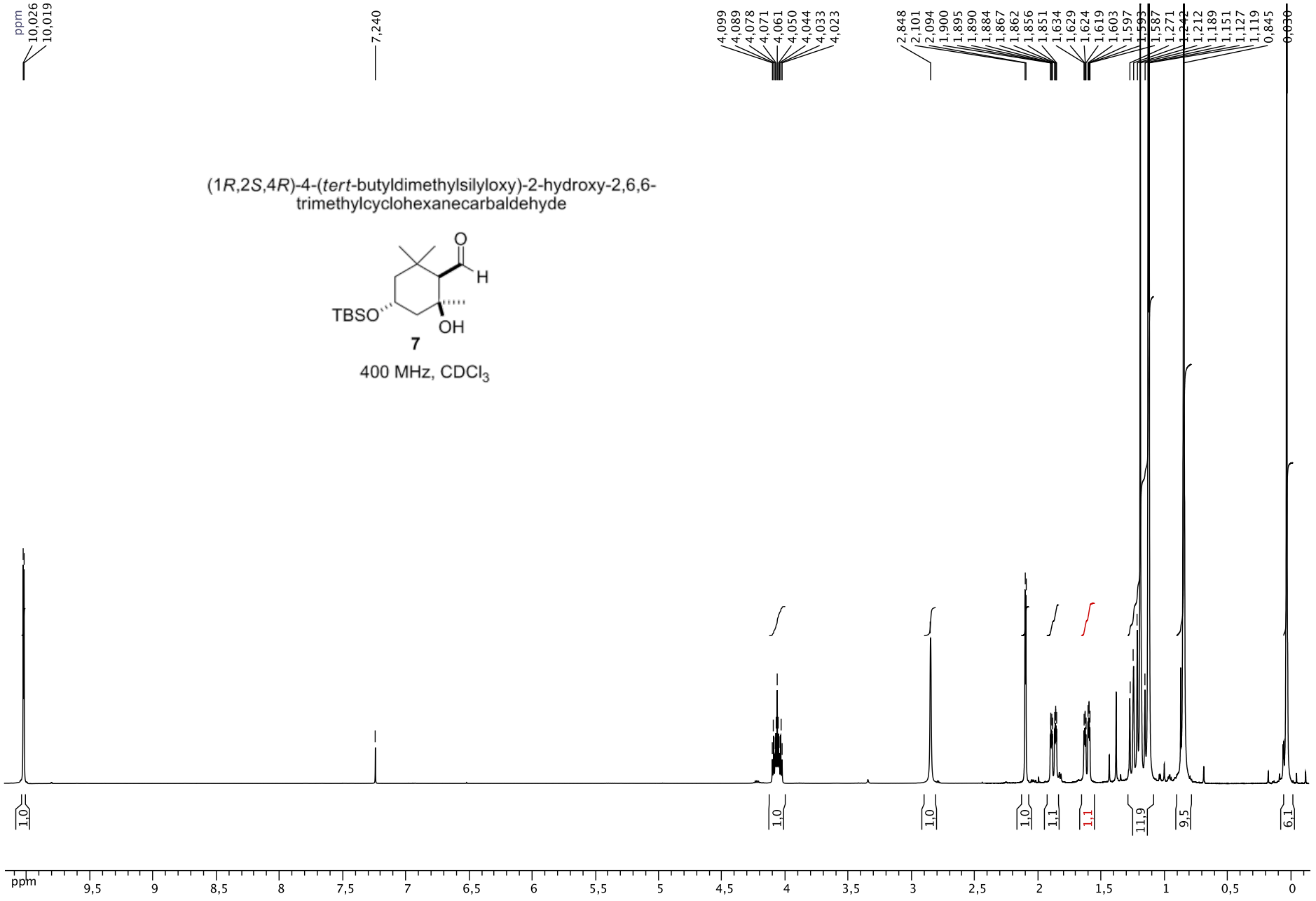
2-((1*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)-1,2,2-trimethylcyclopentyl)-2-oxoethyl 3,5-dinitrobenzoate

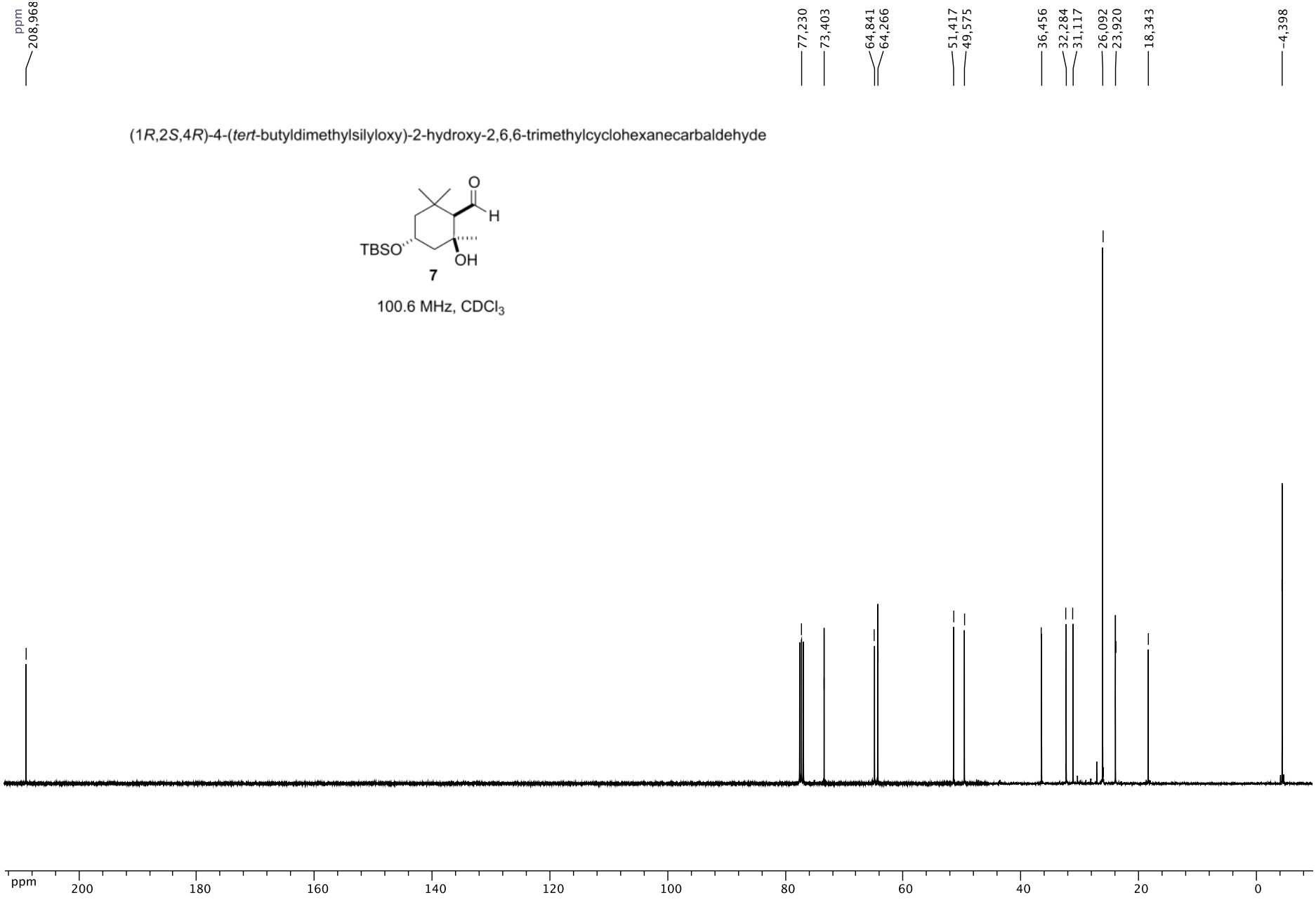


8

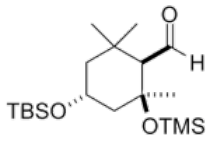
400 MHz, $CDCl_3$







(1*R*,4*R*,6*S*)-4-(*tert*-butyldimethylsilyloxy)-2,2,6-trimethyl-6-(trimethylsilyloxy)cyclohexanecarbaldehyde



9

400 MHz, $CDCl_3$