A Tandem Non-Aldol Aldol Mukaiyama Aldol Reaction

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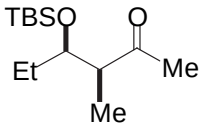


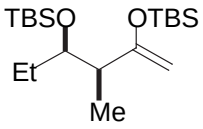
(3*S*,4*R*)-4-(1,1-dimethylethyldimethylsilyloxy)-3-methyl-hexan-2-one (6)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.86 (1H, m), 2.64 (1H, td, *J* = 7.0, 4.8 Hz), 2.18 (3H, s), 1.50 (1H, m), 1.39 (1H, m), 1.06 (3H, d, *J* = 7.0 Hz), 0.88 (9H, s), 0.87 (3H, t, *J* = 7.4 Hz), 0.06 (3H, s), 0.04 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 211.7, 74.7, 51.5, 30.0, 27.4, 25.8(3C), 18.1, 11.5, 9.8, -4.3, -4.6.

IR(neat):2957, 2859, 1713, 1464, 1258, 1045 cm^{-1}.

HRMS (EI, *m/z*): 187.115784, calc for $C_9H_{19}O_2Si$ (M - *t*Bu)$^+$ 187.115433.



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(3*S*,4*R*)-2,4-Bis-(1,1-dimethylethyldimethylsilyloxy)-3-methyl-hex-1-ene (7)

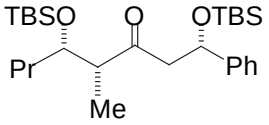
^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.02 (1H, d, *J* = 0.8 Hz), 3.96 (1H, d, *J* = 0.8 Hz), 3.73 (1H, m), 2.18 (1H, td, *J* = 6.9, 6.9 Hz), 1.54 (2H, m), 1.02 (3H, d, *J* = 6.8 Hz), 0.92 (9H, s), 0.89 (9H, s), 0.86 (3H, t, *J* = 7.4 Hz), 0.17 (3H, s), 0.16 (3H, s), 0.03 (3H, s), 0.02 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 161.5, 89.1, 73.9, 44.6, 27.7, 26.0, 25.7, 18.2, 18.1, 14.6, 8.5, -4.3, -4.6, -4.8, -4.9.

IR (neat): 2930, 1620, 1474, 1256.

General procedure for the non-aldol aldol Mukaiyama reaction and non-enolizable aldehydes

In an oven dried 10 mL flask was placed the epoxy alcohol **8** (1eq.), dichloromethane (0.1 M) and powdered 4Å molecular sieves. The solution was cooled to –40 ºC and *i*Pr_2NEt (1.35 eq.) followed by *t*-butyldimethylsilyl triflate (1.3 eq.) were added. The reaction mixture was stirred at –40 ºC for 2 h and the temperature was allowed to rise to –20 ºC. The flask was then left in the freezer overnight. The reaction mixture was cooled to –78 ºC and the aldehyde (2 eq.) and *t*-butyldimethylsilyl triflate (5 mol%) were added. The reaction was allowed to warm to 21 ºC over 5 h. The reaction was quenched with pH 7 buffer, extracted with dichloromethane, washed with pH 7 buffer and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated under vacuo to give a yellowish liquid. The crude ketone was purified by flash column chromatography (SiO_2, pentane/ether: 99/1 to 98/2).



(1*S*,4*R*,5*S*)-1,5-Bis-(1,1-dimethylethyldimethylsilyloxy)-4-methyl-1-phenyl-octan-3-one (10)

Started with the epoxide **8** (500 mg, 1.94 mmol) and obtained the protected 1,5-diol in 63% yield with a 4/1 syn/anti diastereomeric ratio.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.29 (4H, m), 7.23 (1H, m), 5.18 (1H, dd, *J* = 7.8, 4.7 Hz), 3.82 (1H, m), 3.11 (1H, dd, *J* = 16.7, 7.9 Hz), 2.64 (1H, dd, *J* = 16.7, 4.7 Hz), 2.48 (1H, m), 1.30 (4H,

m), 0.95 (3H, d, *J* = 7.0 Hz), 0.87 (9H, s), 0.85 (3H, t, *J* = 7.2 Hz), 0.83 (9H, s), 0.04 (3H, s), 0.03 (3H, s), 0.02 (3H, s), -0.18 (3H, s).

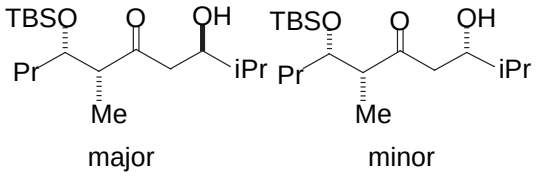
^{13}C NMR (126 MHz, $CDCl_3$) δ: 210.7, 145.0, 128.2(2C), 127.2, 126.0(2C), 73.5, 70.9, 53.8, 52.2, 36.8, 25.9(3C), 25.8(3C), 18.6, 18.1, 14.2, 12.0, -4.37, -4.42, -4.8, -5.1/ (one upfield carbon not observed).

IR (neat): 3032, 2957, 2859, 1715, 1464, 1258 cm^{-1}.

General procedure for the Mukaiyama aldol using dimethylphenylsilyllithium

Preparation of the dimethylphenylsilyllithium: In an oven dried 25 mL flask was placed litium shots (81.5 mg, 11.75 mmol) and dry hexane (4 mL). The suspension was stirred under argon for 10 min and then sonicated for 5 min and the hexane was removed *via* syringe. To the activated lithium was added tetrahydrofuran (3.36 mL). The suspension was cooled to 0 ºC, dimethylphenylchlorosilane (839 µL, 5 mmol) was added and the reaction was stirred at 0 ºC for 6 h. The deep red solution was kept in the freezer overnight. The solution was titrated with HCl (0.102 M) and was found to be 0.86 M.

In an oven dried 10 mL flask was placed the silyl enol ether **9** (100 mg, 0.27 mmol), C_6D_6 (150 µL) and tetrahydrofuran (1 mL). The dimethylphenylsilyllithium (2 eq.) was added and the deep red solution was stirred for 2 min and then the reaction was allowed to sit for 4 h. The reaction mixture turned yellow and was cooled to –78 ºC. The aldehyde (2 eq.) was added and the reaction was stirred for 30 min. The reaction was quenched by pouring it into sat. NH_4Cl (1.5 mL). The mixture was extracted with diethyl ether, the combined organic phase was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow liquid. The crude ketol was purified by flash column chromatrography (SiO_2, pentane/ether: 9/1 to 85/15).



7-(1,1-dimethylethyldimethylsilyloxy)-3-hydroxy-2,6-dimethyl-decan-5-one (11a)

Major isomer:

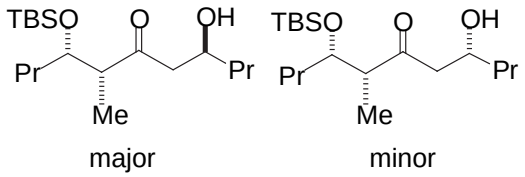
^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.88 (1H, m), 3.77 (1H, m), 3.17 (1H, d, *J* = 3.1 Hz), 2.67 (1H, qd, *J* = 7.0, 4.4 Hz), 2.63 (2H, m), 1.66 (1H, m), 1.32 (4H, m), 1.05 (3H, d, *J* = 7.0 Hz), 0.93 (3H, d, *J* = 6.8 Hz), 0.90 (3H, d, *J* = 6.8 Hz), 0.88 (9H, s), 0.87 (3H, m), 0.06 (3H, s), 0.05 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 215.4, 73.7, 72.1, 52.1, 46.3, 36.5, 32.9, 25.8(3C), 18.9, 18.4, 18.0, 17.8, 14.1, 11.6, -4.39, -4.43.

Minor isomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.85 (1H, m), 3.81 (1H, m), 3.12 (1H, d, *J* = 2.8 Hz), 2.83 (1H, dd, *J* = 18.0, 2.0 Hz), 2.67 (1H, qd, *J* = 7.0, 4.3 Hz), 2.46 (1H, dd, *J* = 18.0, 10.0 Hz), 1.67 (1H, m), 1.40 (2H, m), 1.26 (2H, m), 1.05 (3H, d, *J* = 7.0 Hz), 0.93 (3H, d, *J* = 6.8 Hz), 0.90 (3H, d, *J* = 6.8 Hz), 0.88 (9H, s), 0.89 (3H, *J* = 7.0 Hz), 0.06 (3H, s), 0.05 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 215.1, 73.8, 72.1, 52.4, 46.3, 36.6, 32.9, 25.8(3C), 19.0, 18.3, 18.1, 17.8, 14.2, 11.7, -4.37, -4.42.



4-(1,1-dimethylethyldimethylsilyloxy)-8-hydroxy-5-methyl-undecan-6-one (11b)

Major isomer:

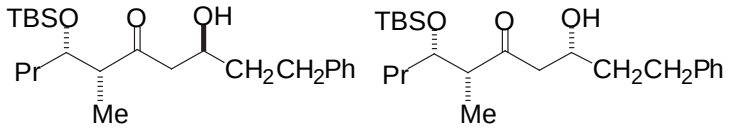
^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.02 (1H, m), 3.88 (1H, m), 3.19 (1H, d, *J* = 3.0 Hz), 2.64 (3H, m), 1.38 (8H, m), 1.05 (3H, d, *J* = 7.0 Hz), 0.92 (3H, t, *J* = 7.1 Hz), 0.89 (3H, m), 0.88 (9H, s), 0.06 (3H, s), 0.05 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 215.2, 73.6, 67.2, 51.9, 49.3, 38.5, 36.6, 25.8(3C), 18.8, 18.6, 18.0, 14.1, 14.0, 11.5, -4.36, -4.44.

Minor isomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.03 (1H, m), 3.86 (1H, m), 3.21 (1H, s), 2.84 (1H, dd, *J* = 18.1, 2.3 Hz), 2.66 (1H, m), 2.47 (1H, dd, *J* = 18.1, 9.5 Hz), 1.35 (8H, m), 1.04 (3H, d, *J* = 7.0 Hz), 0.93 (3H, t, *J* = 7.1 Hz), 0.90 (3H, t, *J* = 7.1 Hz), 0.89 (9H, s), 0.07 (6H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 214.9, 73.7, 67.2, 52.2, 49.3, 38.4, 36.6, 25.8(3C), 18.9, 18.6, 18.0, 14.2, 14.0, 11.6, -4.37, -4.4.



major minor

7-(1,1-dimethylethyldimethylsilyloxy)-3-hydroxy-6-methyl-1-phenyl-decan-5-one (11c)

Major isomer:

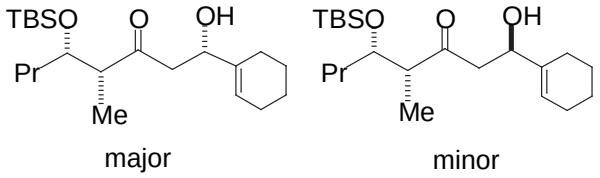
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.27 (4H, m), 7.21 (1H, m), 4.03 (1H, m), 3.87 (1H, m), 3.36 (1H, s), 2.73 (1H, dd, *J* = 18.2, 9.2 Hz), 2.68 (1H, m), 2.63 (1H, dd, *J* = 18.2, 2.4 Hz), 1.84 (1H, m), 1.70 (1H, m), 1.33 (6H, m), 1.05 (3H, d, *J* = 7.0 Hz), 0.90 (3H, m), 0.90 (9H, s), 0.08 (3H, s), 0.05 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 215.1, 141.9, 128.6(2C), 128.3(2C), 125.8, 73.6, 66.8, 51.9, 49.3, 38.0, 36.5, 31.7, 25.8(3C), 18.8, 18.0, 14.1, 11.4, -4.4, -4.5.

Minor isomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.27 (4H, m), 7.21 (1H, m), 4.03 (1H, m), 3.86 (1H, m), 3.36 (1H, s), 2.87 (1H, dd, *J* = 18.1, 2.3 Hz), 2.68 (1H, m), 2.52 (1H, dd, *J* = 18.2, 9.5 Hz), 1.84 (1H, m), 1.70 (1H, m), 1.33 (6H, m), 1.04 (3H, d, *J* = 7.0 Hz), 0.90 (3H, m), 0.90 (9H, s), 0.08 (3H, s), 0.06 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 214.7, 141.9, 128.6(2C), 128.3(2C), 125.8, 73.7, 66.8, 52.2, 49.3, 37.9, 36.5, 31.7, 25.8(3C), 18.9, 18.0, 14.0, 11.6, -4.4, -4.5.



5-(1,1-dimethylethyldimethylsilyloxy)-1-cyclohex-1-enyl-1-hydroxy-4-methyl-octan-3-one (11d)

Major isomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.71 (1H, s), 4.41 (1H, m), 3.86 (1H, m), 3.11 (1H, s), 2.86 (1H, dd, *J* = 17.7, 2.6 Hz), 2.68 (1H, m), 2.65 (1H, dd, *J* = 17.7, 9.6 Hz), 2.02 (3H, m), 1.93 (1H, m), 1.59 (4H, m), 1.39 (4H, m), 1.04 (3H, d, *J* = 7.0 Hz), 0.90 (3H, t, *J* = 7.0 Hz), 0.89 (9H, s), 0.07 (6H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 214.5, 138.2, 122.9, 73.7, 71.6, 52.3, 48.0, 36.6, 25.8(3C), 24.8, 24.2, 22.54, 22.47, 18.9, 18.0, 14.1, 11.6, -4.4, -4.4.

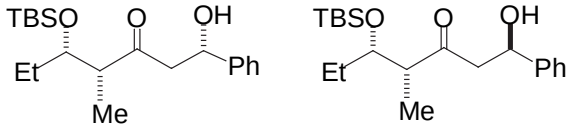
Minor isomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.71 (1H, s), 4.38 (1H, m), 3.90 (1H, m), 3.11 (1H, s), 2.82 (1H, dd, *J* = 17.7, 9.5 Hz), 2.68 (1H, m), 2.66 (1H, dd, *J* = 17.7, 2.6 Hz), 2.02 (3H, m), 1.93 (1H, m), 1.59 (4H, m), 1.39 (4H, m), 1.06 (3H, d, *J* = 7.0 Hz), 0.89 (3H, m), 0.89 (9H, s), 0.07 (3H, s), 0.06 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 214.9, 138.1, 123.0, 73.6, 71.7, 52.0, 47.9, 36.6, 25.8(3C), 24.8, 24.3, 22.54, 22.47, 18.8, 18.0, 14.1, 11.5, -4.4, -4-4.

General procedure for the non-aldol aldol Mukaiyama reaction with BF_3·OEt_2

In an oven dried 10 mL flask was placed the epoxy alcohol **5'** (50 mg), dichloromethane (2 mL) and powdered 4Å molecular sieves. The solution was cooled to –40 ºC and *i*Pr_2NEt (1.35 eq.) was added followed by *t*-butyldimethylsilyl triflate (1.3 eq.). The reaction mixture was stirred at –40 ºC for 2 h and the temperature was allowed to rise to –20 ºC. The flask was then left overnight in the freezer at –16 ºC. The reaction was cooled to –78 ºC and the aldehyde (1.5 eq.) and BF_3·OEt_2 (1.5 eq.) were added. The reaction was stirred 30 min at –78 ºC and was quenched at that temperature with sat. $NaHCO_3$. It was extracted with dichloromethane and washed with sat. $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellowish liquid. The crude ketone was purified by flash column chromatography (SiO_2, pentane/ether: 9/1 to 85/15 to 4/1).



5-(1,1-dimethylethyldimethylsilyloxy)-1-hydroxy-4-methyl-1-phenyl-octan-3-one (12a)

Major isomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 (4H, m), 7.27 (1H, m), 5.14 (1H, ddd, *J* = 12.2, 9.5, 2.6 Hz), 3.87 (1H, dd, *J* = 10.8, 5.9Hz), 3.51 (1H, bs), 3.00 (1H, dd, *J* = 18.0, 9.5 Hz), 2.84 (1H, dd, *J* = 18.0, 2.9 Hz), 2.66 (1H, qd, *J* = 7.0, 4.7 Hz), 1.50 (1H, m). 1.37 (1H, m), 1.07 (3H, d, *J* = 7.0 Hz), 0.88 (9H, s), 0.84 (3H, t, *J* = 7.4 Hz), 0.07 (3H, s), 0.05 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 214.3, 142.9, 128.5(2C), 127.5, 125.7(2C), 74.7, 69.9, 51.4, 51.1, 27.3, 25.8(3C), 18.0, 11.3, 9.8, -4.3, -4.5.

Minor isomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 (4H, m), 7.27 (1H, m), 5.14 (1H, m), 3.85 (1H, dd, *J* = 10.8, 5.8 Hz), 3.47 (1H, bs), 3.02 (1H, dd, *J* = 17.9, 2.7 Hz), 2.83 (1H, dd, *J* = 18.0, 8.9 Hz), 2.66 (1H, m), 1.50 (1H, m). 1.37 (1H, m), 1.06 (3H, d, *J* = 6.8 Hz), 0.87 (9H, s), 0.84 (3H, t, *J* = 7.5 Hz), 0.06 (3H, s), 0.05 (3H, s).

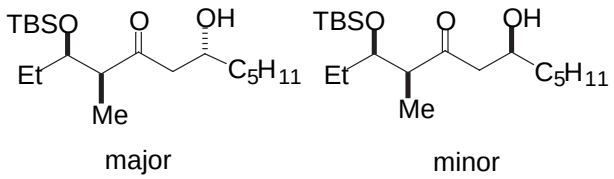
^{13}C NMR (126 MHz, $CDCl_3$) δ: 213.9, 142.9, 128.5(2C), 127.5, 125.6(2C), 74.8, 69.8, 51.8, 51.1, 27.3, 25.8(3C), 18.0, 11.4, 9.9, -4.3, -4.5.

For the mixture of diastereomer:

IR (neat): 3470, 2958, 2930, 2857, 705, 1462, 1255, 836 1cm^{-1}.

HRMS (EI + voltage, *m/z*): 351.234827, calc for $C_{20}H_{35}O_3Si$ $(M + H)^+$ 351.235549.

LRMS (EI, *m/z*): 293, 107.



3-(1,1-dimethylethyldimethylsilyloxy)-7-hydroxy-4-methyl-dodecan-5-one (12b)

Major isomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.00 (1H, m), 3.83 (1H, m), 3.18 (1H, d, *J* = 3.1 Hz), 2.66 (1H, qd, *J* = 6.9, 4.8 Hz), 2.64 (2H, m), 1.48 (2H, m), 1.28 (8H, m), 1.06 (3H, d, *J* = 7.0 Hz), 0.89 (9H, s), 0.89 (3H, m), 0.86 (3H, t, *J* = 7.5 Hz), 0.06 (3H, s), 0.05 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 215.3, 74.9, 67.5, 51.5, 49.2, 36.3, 31.8, 27.2, 25.8(3C), 25.1, 22.6, 18.1, 14.0, 11.5, 9.9, -4.3, -4.5.

IR (neat): 3473, 2931, 1704, 1463, 1256 cm^{-1}.

$[\alpha]_D^{20}$ = + 7.0º (c = 1.0, $CHCl_3$).

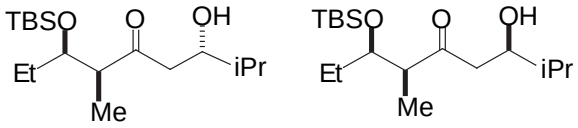
Minor isomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.02 (1H, m), 3.81 (1H, m), 3.16 (1H, d, *J* = 3.1 Hz), 2.83 (1H, dd, *J* = 18.1, 2.3 Hz), 2.67 (1H, qd, *J* = 7.0, 4.8 Hz), 2.47 (1H, dd, *J* = 18.1, 9.5 Hz), 1.40 (10H, m), 1.04 (3H, d, *J* = 7.0 Hz), 0.89 (9H, s), 0.89 (3H, m), 0.86 (3H, m), 0.06 (3H, s), 0.06 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 214.9, 74.9, 67.5, 51.8, 49.2, 36.3, 31.8, 27.2, 25.9(3C), 25.1, 22.6, 18.1, 14.0, 11.7, 10.0, -4.3, -4.5.

IR (neat): 3458, 2930, 1705, 1463, 1256 cm^{-1}.

HRMS (EI, *m/z*): 345.282598, calc for $C_{19}H_{40}O_3Si$ $(M + H)^+$ 345.282499.



major minor

7-(1,1-dimethylethyldimethylsilyloxy)-3-hydroxy-2,6-dimethyl-nonan-5-one (12c)

Major isomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.83 (1H, m), 3.78 (1H, m), 3.14 (1H, d, *J* = 3.1 Hz), 2.68 (1H, qd, *J* = 7.0, 4.8 Hz), 2.64 (1H, d, *J* = 4.7 Hz), 2.63 (1H, d, *J* = 7.3 Hz), 1.67 (1H, m), 1.49 (1H,

m), 1.37 (1H, m), 1.06 (3H, d, J = 7.0 Hz), 0.93 (3H, d, J = 6.8 Hz), 0.91 (3H, d, J = 6.8 Hz), 0.89 (9H, s), 0.87 (3H, J = 7.5 Hz), 0.06 (3H, s), 0.05 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 215.5, 75.0, 72.1, 52.6, 46.2, 32.9, 27.1, 25.8(3C), 18.4, 18.1, 17.8, 11.6, 9.9, -4.3, -4.5.

IR (neat): 3508, 2959, 1703, 1464, 1255 cm^{-1}.

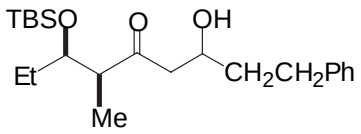
HRMS (EI, *m/z*): 259.1733, calc for $C_{13}H_{27}O_3Si$ (M - *t*Bu)$^+$ 259.1729.

Minor isomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.81 (2H, m), 3.10 (1H, s), 2.81 (1H, dd, J = 17.9, 2.0 Hz), 2.68 (1H, qd, J = 7.0, 4.6 Hz), 2.47 (1H, dd, J = 17.9, 9.9 Hz), 1.67 (1H, m), 1.50 (1H, m), 1.31 (1H, m), 1.05 (3H, d, J = 7.0 Hz), 0.93 (3H, d, J = 6.8 Hz), 0.91 (3H, d, J = 6.8 Hz), 0.89 (9H, s), 0.88 (3H, m), 0.06 (6H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 215.1, 75.0, 72.1, 52.0, 46.2, 32.9, 27.2, 25.8(3C), 18.4, 18.1, 17.8, 11.7, 10.0, -4.3, -4.5.

IR (neat): 3484, 2960, 1705, 1464, 1256 cm^{-1}.



7-(1,1-dimethylethyldimethylsilyloxy)-3-hydroxy-6-methyl-1-phenyl-nonan-5-one (12d)

NMR of mixture:

Major isomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.27 (2H, m), 7.18 (3H, m), 4.04 (1H, m), 3.82 (1H, m), 3.28 (1H, bs), 2.81 (1H, m), 2.70 (1H, m), 2.62 (1H, dd, J = 18.2, 2.7 Hz), 1.81 (1H, m), 1.68 (1H,

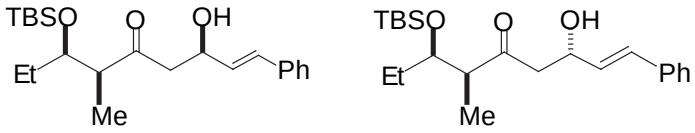
m), 1.49 (1H, m), 1.36 (1H, m), 1.05 (3H, d, J = 7.0 Hz), 0.89 (9H, s), 0.88 (3H, t, J = 7.5 Hz), 0.06 (3H, s), 0.04 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 215.1, 142.0, 128.5(2C), 128.4(2C), 125.8, 74.9, 66.8, 51.5, 49.2, 38.0, 31.7, 27.1, 25.8(3C), 18.0, 11.5, 9.9, -4.3, -4.5.

Minor isomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.27 (2H, m), 7.18 (3H, m), 4.04 (1H, m), 3.80 (1H, m), 3.28 (1H, bs), 2.84 (1H, dd, J = 18.2, 2.3 Hz), 2.70 (1H, m), 2.55 (1H, dd, J = 18.2, 9.5 Hz), 1.81 (1H, m), 1.68 (1H, m), 1.49 (1H, m), 1.36 (1H, m), 1.04 (3H, d, J = 7.0 Hz), 0.89 (9H, s), 0.88 (3H, m), 0.06 (3H, s), 0.04 (3H, s).

IR (neat): 3458, 3062, 3027, 2930, 1702, 1455, 1255 cm^{-1}.



major minor

7-(1,1-dimethylethyldimethylsilyloxy)-3-hydroxy-6-methyl-1-phenyl-non-1-en-5-one (12e)

Major isomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.37 (2H, m), 7.30 (2H, m), 7.25 (1H, m), 6.64 (1H, d, J = 15.9 Hz), 6.20 (1H, dd, J = 15.9, 6.0 Hz), 4.73 (1H, m), 3.85 (1H, m), 3.33 (1H, d, J = 3.5 Hz), 2.87 (1H, dd, J = 18.0, 8.8 Hz), 2.79 (1H, dd, J = 17.9, 3.2 Hz), 2.70 (1H, m), 1.51 (1H, m), 1.38 (1H, m), 1.08 (3H, d, J = 7.0 Hz), 0.89 (9H, s), 0.87 (3H, t, J = 7.4 Hz), 0.07 (6H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 214.3, 136.7, 130.25, 130.20, 128.5(2C), 127.6, 126.5(2C), 74.8, 68.4, 51.5, 49.1, 27.2, 25.9(3C), 18.1, 11.5, 9.8, -4.3, -4.5.

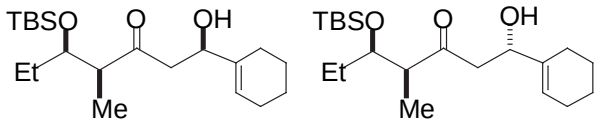
Minor isomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.37 (2H, m), 7.30 (2H, m), 7.25 (1H, m), 6.64 (1H, d, *J* = 15.9 Hz), 6.20 (1H, dd, *J* = 15.9, 6.0 Hz), 4.73 (1H, m), 3.85 (1H, m), 3.30 (1H, d, *J* = 3.4 Hz), 2.96 (1H, dd, *J* = 17.9, 2.9 Hz), 2.71 (1H, dd, *J* = 17.9, 8.9 Hz), 2.70 (1H, m), 1.51 (1H, m), 1.38 (1H, m), 1.07 (3H, d, *J* = 7.1 Hz), 0.89 (9H, s), 0.87 (3H, t, *J* = 7.4 Hz), 0.06 (6H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 213.9, 136.7, 130.27, 130.15, 128.5(2C), 127.6(2C), 126.5, 74.8, 68.3, 51.8, 49.1, 27.2, 25.9(3C), 18.1, 11.6, 10.0, -4.3, -4.4.

IR (neat): 3427, 3027, 1705, 1255 cm^{-1}.

HRMS (EI, *m/z*): 376.24255, calc for $C_{22}H_{36}O_3Si$ $(M)^+$ 376.24337.



major minor

5-(1,1-dimethylethyldimethylsilyloxy)-1-cyclohex-1-enyl-1-hydroxy-4-methyl-heptan-3-one (12f)

NMR of mixture:

Major isomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.71 (1H, s), 4.39 (1H, m), 3.84 (1H, m), 3.14 (1H, d, *J* = 3.0 Hz), 2.80 (1H, dd, *J* = 17.8, 9.6 Hz), 2.67 (2H, m), 2.06 (3H, m), 1.92 (1H, m), 1.56 (3H, m), 1.27 (3H, m), 1.06 (3H, d, *J* = 7.0 Hz), 0.89 (9H, s), 0.87 (3H, t, *J* = 7.3 Hz), 0.06 (6H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 214.9, 138.3, 123.0, 74.8, 71.7, 51.6, 47.8, 27.2, 25.8(3C), 24.9, 24.26, 22.6, 22.3, 18.1, 9.9, -4.3, -4.5.

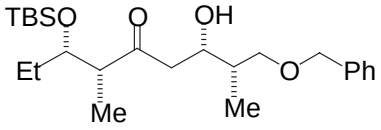
Minor isomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.71 (1H, s), 4.39 (1H, m), 3.81 (1H, m), 3.03 (1H, d, *J* = 3.0 Hz), 2.84 (1H, dd, *J* = 17.7, 2.5 Hz), 2.67 (2H, m), 2.02 (3H, m), 1.92 (1H, m), 1.56 (3H, m), 1.27 (3H, m), 1.04 (3H, d, *J* = 7.0 Hz), 0.89 (9H, s), 0.87 (3H, t, *J* = 7.4 Hz), 0.06 (6H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 214.5,138.2, 122.9, 74.9, 71.6, 51.9, 47.9, 27.17, 25.8, 24.9, 24.31, 22.5, 18.1, 11.6, -4.3, -4.5.

IR (neat): 3462, 2930, 1705, 1463, 1255 cm^{-1}.

HRMS (EI + volt scan, *m/z*): 354.2598, calc for $C_{20}H_{38}O_3Si$ $(M)^+$ 354.2590.

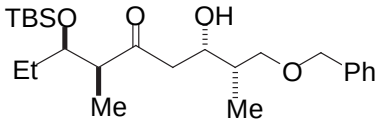


(2*S*,3*R*,6*R*,7*S*)-1-Benzyloxy-3,7-dihydroxy-2,6-dimethyl-7-(1,1-dimethylethyl-dimethylsilyloxy)-nonan-5-one (14)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 (4H, m), 7.29 (1H, m), 4.51 (2H, s), 4.22 (1H, m), 3.80 (1H, m), 3.51 (1H, dd, *J* = 9.1, 6.5 Hz, 3.47 (1H, dd, 9.1, 5.2 Hz), 3.16 (1H, d, *J* = 3.3 Hz), 2.71 (1H, dd, *J* = 17.6, 3.1 Hz), 2.68 (1H, m), 2.63 (1H, d, *J* = 17.6, 9.2 Hz), 1.85 (1H, m), 1.49 (1H, m), 1.32 (1H, m), 1.03 (3H, t, *J* = 7.0 Hz), 0.95 (3H, d, *J* = 7.0 Hz), 0.89 (9H, s), 0.86 (3H, t, *J* = 7.4 Hz), 0.06 (3H, s), 0.05 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 214.2, 138.3, 128.4(2C), 127.6(3C), 74.9, 73.6, 73.3, 68.8, 51.8, 46.9, 38.0, 27.2, 25.8(3C), 18.1, 11.7, 11.3, 9.9, -4.3, -4.5.

$[\alpha]_D^{20}$ = -45º (c = 0.6, $CHCl_3$).



(2*S*,3*S*,6*S*,7*R*)-1-Benzyloxy-3,7-dihydroxy-2,6-dimethyl-7-(1,1-dimethylethyl-dimethylsilyloxy)-nonan-5-one (15)

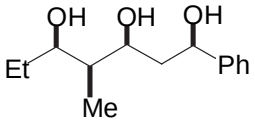
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33 (4H, m), 7.28 (1H, m), 4.50 (2H, s), 4.21 (1H, m), 3.84 (1H, m), 3.51 (1H, dd, *J* = 9.1, 6.6 Hz), 3.45 (1H, dd, 9.1, 5.2 Hz), 3.19 (1H, d, *J* = 3.1 Hz), 2.74 (1H, dd, *J* = 17.7, 9.7 Hz), 2.68 (1H, qd, *J* = 7.0, 4.9 Hz), 2.56 (1H, d, *J* = 17.7, 2.2 Hz), 1.83 (1H, m), 1.49 (1H, m), 1.37 (1H, m), 1.05 (3H, t, *J* = 7.0 Hz), 0.95 (3H, d, *J* = 7.0 Hz), 0.88 (9H, s), 0.86 (3H, t, *J* = 7.4 Hz), 0.06 (3H, s), 0.04 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 214.6, 138.3, 128.4(2C), 127.6(2C), 127.6, 74.7, 73.4, 73.3, 68.6, 51.5, 46.9, 38.1, 27.2, 25.9(3C), 18.1, 11.7, 11.3, 9.8, -4.3, -4.5.

IR (neat): 3501, 3065, 3031, 2931, 1704, 1455, 1255.

$[\alpha]_D^{20}$ = + 9.1º (c = 0.6, $CHCl_3$).

Determination of the stereochemistry:



(1R,3S,4S,5R)-4-Methyl-1-phenyl-heptane-1,3,5-triol (17)

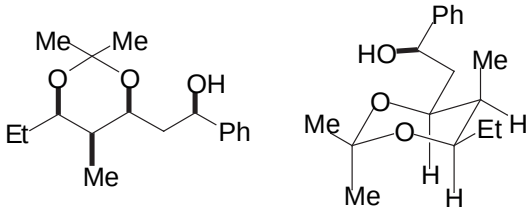
To a 100 mL flask containing the ketone **16** (870 mg, 1.87 mmol) was added a 2 mol% solution of HF/CH_3CN (16 mL). The reaction mixture was stirred at 21º C for 90 min. and more HF/CH_3CN (1 mL) was added. The reaction was stirred at 21º C for 90 min. The reaction was quenched by adding sat. $NaHCO_3$ (5 mL). The milky aqueous phase was extracted with ethyl

acetate (4x), the combined organic phases were washed with brine (5 mL) and the organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellowish liquid. The crude diol was purified by flash column chromatography (SiO_2, pentane/ether: 45/55 to 2/3) to give a colorless liquid in 78% yield as a 4/1 diastereomeric mixture.

To a 100 mL flask containing the diol (150 mg, 0.636 mmol) was added tetrahydrofuran (5.1 mL) and methanol (1.3 mL). The solution was cooled to –78 ºC. Triethylborane-THF complex (1 M in tetrahydrofuran, 699 µL, 0.699 mmol) was added dropwise to the solution and stirred for 35 min followed by sodium borohydride (26 mg, 0.699 mmol). The reaction was stirred for 90 min at –78 ºC and then quenched by adding acetic acid (0.8 mL) and ethyl acetate (80 mL). The organic phase was washed with sat. $NaHCO_3$ (2x 1 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give an oil. The compound was purified by flash column chromatography (SiO_2, pentane/ether: 3/7 to 25/75 to 1/4) to give a colorless gue in 50 % yield (76.5 mg, 0.32 mmol) as one major compound.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35 (4H, m), 7.28 (1H, m), 4.96 (1H, dd, J = 10.3, 2.4 Hz), 4.03 (1H, m), 3.84 (1H, m), 2.02 (1H, m), 1.77 (1H, ddd, J = 14.4, 2.1, 2.1 Hz), 1.53 (6H, m), 0.97 (3H, d, J = 7.1 Hz), 0.93 (3H, t, J = 7.5 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 144.4, 128.5(2C), 127.7, 125.6(2C), 77.3, 75.8, 74.2, 44.1, 41.6, 26.8, 11.1, 10.6.



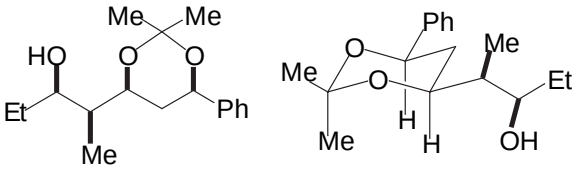
(1*R*,3*S*,4*S*,5*R*)-β-Ethyl-2,2,5-trimethyl-1-phenyl-[1,3]dioxane-4-ethanol (18)

In a 25 mL flask the triol **17** (60 mg, 0.25 mmol) was dissolved in dichloromethane (1.5 mL) and 2,2-dimethoxypropane (62 μL, 0.5 mmol) was added to the solution followed by camphorsulfonic acid (cat.). After stirring for 2 h the starting material remained and more 2,2-dimethoxypropane (62 μL, 0.5 mmol) was added followed by camphorsulfonic acid (cat.) This was repeated again after 2 h. The reaction was quenched after 2 hours with a few drops of $NaHCO_3$. The aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over $MgSO_4$, filtrated and concentrated *in vacuo* to give an oil. Two major diastereomers **18** and **19** were isolated by flash column chromatography for analysis.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35 (4H, m), 7.26 (1H, m), 4.98 (1H, m), 4.07 (1H, ddd, *J* = 10.5, 2.2, 2.2 Hz), 3.69 (1H, ddd, *J* = 7.3, 7.1, 2.2 Hz), 3.17 (1H, d, *J* = 5.9 Hz), 2.16 (1H, ddd, *J* = 14.4, 10.5, 3.4 Hz), 1.67 (1H, ddd, *J* = 14.4, 6.7, 2.1 Hz), 1.49 (1H, qdd, *J* = 13.7, 7.4, 7.4 Hz), 1.42 (3H, s), 1.39 (3H, s), 1.34 (1H, qdd, *J* = 13.8, 7.3, 6.4 Hz), 1.23 (1H, qdd, *J* = 6.9, 2.3, 2.2 Hz), 0.86 (3H, d, *J* = 6.9 Hz), 0.84 (3H, t, *J* = 7.4 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 144.7, 128.3(2C), 127.0, 125.6(2C), 99.0, 74.9, 71.5, 70.4, 41.0, 34.8, 30.1, 25.5, 19.8, 9.6, 4.9.

IR (neat): 3444, 3062, 3029, 1455,1199 cm^{-1}.



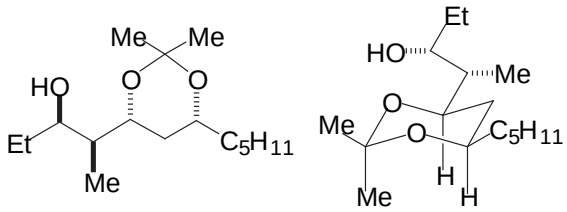
(α*S*,β*R*,4*S*,6*R*)-β-Ethyl-α,2,2-trimethyl-6-phenyl-[1,3]dioxane-4-ethanol (19)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.37 (4H, m), 7.28 (1H, m), 4.92 (1H, dd, *J* = 11.3, 2.9 Hz), 4.08 (1H, ddd, *J* = 11.4, 6.4, 2.6 Hz), 3.75 (1H, m), 2.9 (1H, m), 1.69 (2H, m), 1.58 (1H, m), 1.57 (3H, s), 1.51 (3H, s), 1.45 (2H, m), 0.97 (3H, t, *J* = 7.3 Hz), 0.91 (3H, d, *J* = 7.1 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 142.2, 128.5(2C), 127.7, 125.9(2C), 99.2, 74.0, 73.3, 71.8, 41.9, 37.7, 30.3, 26.5, 19.5, 11.00, 10.98.

IR (neat): 3485, 3064, 3030, 1455, 1380 cm^{-1}.

HRMS (EI, *m/z*): 279.196583, calc for $C_{17}H_{27}O_3$ $(M + H)^+$ 279.196020.

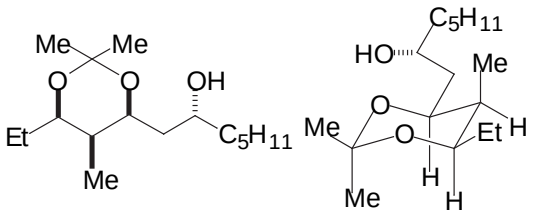


(α*S*,β*R*,4*R*,6*R*)-β-ethyl-6-pentyl-α,2,2-trimethyl -[1,3]dioxane-4-ethanol

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.88 (1H, ddd, *J* = 11.6, 6.2, 2.3 Hz), 3.79 (1H, m), 3.70 (1H, m), 3.05 (1H, bs), 1.62 (1H, m), 1.42 (3H, s), 1.37 (3H, s), 1.35 (12H, m), 0.96 (3H, t, *J* = 7.3 Hz), 0.88 (3H,m), 0.88 (3H, d, *J* = 7.0 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 98.5, 74.1, 73.3, 69.2, 41.9, 36.4, 35.1, 31.8, 30.2, 26.3, 24.6, 22.6, 19.5, 14.0, 11.2, 11.0.

IR (neat): 3521, 2934, 1463, 1380, 1259, 1202 cm^{-1}.



(β*R*,4*S*,5*S*,6R)-6-Ethyl-2,2,5-trimethyl-β-pentyl-[1,3]dioxane-4-ethanol

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.22 (1H, ddd, *J* = 10.3, 2.2, 2.2 Hz), 3.79 (1H, ddd, *J* = 6.9, 6.9, 2.1 Hz), 3.77 (1H, m), 2.09 (1H, s), 1.81 (1H, ddd, *J* = 14.3, 10.3, 3.0 Hz), 1.50 (4H, m), 1.45

(3H, s), 1.39 (1H, m), 1.38 (3H, s), 1.30 (7H, m), 0.89 (3H, t, J = 7.4 Hz), 0.87 (3H, t, J = 7.4 Hz), 0.84 (3H, d, J = 6.9 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 98.8, 75.0, 70.1, 69.1, 39.6, 37.5, 35.0, 31.9, 30.0, 25.6, 25.5, 22.6, 19.7, 14.0, 9.6, 4.8.