Appendix

Asymmetric Synthesis of Quaternary Centers. Total Synthesis of (-)-Malyngolide

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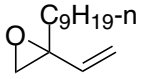
Experimental procedures:

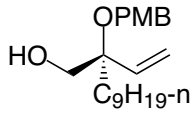
1. 2-Nonyl-2-vinyl-oxirane (**4**)



4

To a solution of 1-bromoundecan-2-one (2.0 g, 8.0 mmol) in 80 ml of absolute DME was added vinylmagnesiumbromide(10.4ml, 8.0 mmol, 0.77M in THF) at -50°C. The solution was allowed to warm from -50°C to room temperature with stirring over 3h and then filtered through Celite. The pad was washed with diethyl ether (30ml) and the solvent was evaporated under vacuum. Flash chromatography (petroleum ether / diethyl ether 50:1 to 30:1) yielded 1.03g (65%) product as a clear oil. IR (film) 2926, 2855, 1466, 987, 923, 668 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.76 (dd, J=10.8Hz, J=17.4Hz, 1H), 5.32 (d, J=17.4Hz, 1H), 5.19 (d, J=10.8Hz, 1H), 2.79 (d, J=5.1Hz, 1H), 2.66 (d, J=5.4Hz, 1H), 1.66 (m, 2H), 1.43-1.26 (m, 14H), 0.87(t, J=6.5Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 132.78, 111.54, 53.96, 50.25, 28.70, 27.08, 24.92, 24.74, 24.51, 20.27, 17.88, 9.32. HRMS: Calcd for $C_{13}H_{23}O$ (M^+-1): 195.1742. Found: 195.1760.

2. 2-(4-Methoxybenzyl)-2-nonyl-but-3-en-1-ol (**3**)

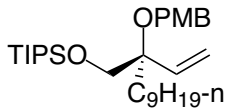


3

To a oven dried flask was given p-methoxybenzyl alcohol (240mg, 1.74mmol), $Pd_2(dba)_3$•$CHCl_3$ (18mg, 0.017mmol) and (R,R) ligand (**6**) (36mg, 0.052mmol). The flask was evacuated and filled with Argon (3x). Then freshly distilled methylene chloride

(17ml) was added. The solute was stirred for 10 min. The color of the solution changed from red to orange. Then a solution of tritheyl borane (17.4μl, 0.017mmol, 1M in THF) was added. After 5 min, neat epoxide (341mg, 1.74mmol) was added. Upon completion (TLC) the yellow solution turned back to orange (24 h). The solvent was evaporated *in vacuo* and the yellow oil was purified via flash chromatography (petroleum ether / diethyl ether 3:1 to 2:1) to yield 409mg (70%) of **3** as colorless oil. IR (film): 3446, 2926, 2854, 1614, 1514, 1465, 1418, 1378, 1302, 1249, 1173, 1109, 1038, 927, 822 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.26 (d, J=8.1Hz, 2H), 6.88 (d, J=8.1Hz, 2H), 5.86 (dd, J=17.9Hz, 11.3Hz, 1H), 5.32 (m, 2H), 4.34 (s, 2H), 3.80 (s, 3H), 3.69-3.56 (m, 2H), 1.84 (t, J=6.3Hz, 1H), 1.68 (m, 2H), 1.44-1.22 (m, 14H), 0.88 (t, J=6.0Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 159.00, 139.16, 131.04, 128.94, 116.95, 113.78, 80.04, 65.08, 63.86, 55.22, 33.06, 31.86, 30.16, 29.55, 29.29, 23.19, 22.64, 14.08. HRMS Calcd for $C_{21}H_{34}O_3$ (M^+): 334.2508. Found: 334.2502. ee%=99% (HPLC, AS, heptane:*iso*-propanol=99:1) Rf=11.43 (S), Rf=21.22 (R). $[\alpha]_D$= -1.64 (c=5.0, THF).

3. TIPS protected ether (**7**)

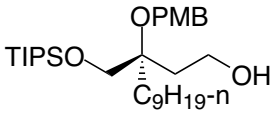


7

To a solution of the alcohol **3** (476mg, 1.42mmol) in 12ml of methylene chloride was added dropwise at 0°C triethyl amine (219ul, 1.57mmol) followed by triisopropylsilyl triflate (422 μL, 1.57 mmol). The solution was stirred at 0°C for 45 min and then it was given 6 ml of water. The aqueous layer was extracted with methylene chloride (3x20ml) and the combined organic layer was dried over magnesium sulfate. The solvent was

evaporated *in vacuo* and the resulting oil was purified by flash chromatography (Petroleum ether / diethyl ether 40:1, Rf=0.3) to yield 654mg (94%) of **7** as colorless oil. IR(film): 2926, 2866, 1615, 1588, 1514, 1465, 1381, 1301, 1248, 1172, 1120, 1070, 1041, 997, 921, 882, 806, 681. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.27 (d, J=8.1Hz, 2H), 6.86 (d, J=8.1Hz, 2H), 5.85 (dd, J=17.3Hz, J=10.7Hz, 1H), 5.29 (d, J=5.1Hz, 1H), 5.24 (s, 1H), 4.38 (s, 2H), 3.80 (s, 3H), 3.82 (d, J=9.9Hz, 1H), 3.65 (d, J=9.6, 1H), 1.82-1.66 (m, 2H), 1.36-0.96 (m, 35H), 0.88 (t, J=6.3Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 154.02, 136.31, 126.99, 124.06, 111.02, 108.88, 75.41, 62.11, 59.25, 50.49, 27.36, 27.13, 25.42, 24.88, 24.82, 24.56, 18.01, 17.93, 13.23, 9.35, 7.18. $[\alpha]_D$=-6.84 (c=5.0, THF). Anal. Calcd for $C_{30}H_{54}O_3Si$: C, 73.41%; H, 11.09%. Found: C, 73.39%; H, 10.87%.

4. Alcohol (**13**).

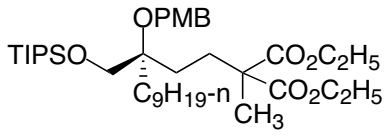


13

To a solution of Alkene **7** (480mg, 0.98mmol) and Wilkisnson's catalyst (36mg, 0.04mmol) in THF (15ml), a solution of 9-BBN (5.9ml, 2.94mmol, 0.5M in THF) was added. The reaction mixture was stirred at room temperature for 24 h. Then sodium hydroxide solution (7ml, 3M in water) was added. Hydrogen peroxide (15ml, 30% in water) was added in several portions at 50 °C during 5 h period. The aqueous solution was saturated by potassium carbonate and extracted by diethyl ether (3x40ml). The combined organic layer was dried over magnesium sulfate. Flash chromatography eluting with petroleum ether / diethyl ether (3:1, Rf=0.3) afforded colorless oil 447mg (90%).

IR (film) 3440, 2927, 2866, 1614, 1514, 1464, 1249, 1115, 1069, 1040, 882, 804, 692, 660 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$): δ 7.24 (d, J=8.4Hz, 2H), 6.85 (d, J=8.4Hz, 2H), 4.46 (s, 2H), 3.79 (m, 7H), 3.00 (t, J=5.4Hz, 1H), 1.90 (m, 2H), 1.70 (m, 2H), 1.40-0.95 (m, 35H), 0.89 (t, J=6.0Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 154.22, 126.26, 124.22, 109.03, 75.83, 61.84, 59.99, 54.43, 50.48, 30.95, 28.39, 27.10, 25.45, 24.83, 24.79, 24.53, 18.31, 17.89, 13.25, 9.34, 7.17. $[\alpha]_D$= +3.63 (c=4.0, THF). Anal. Calcd for $C_{30}H_{56}O_4Si$: C, 70.81%; H, 11.09%. Found: C, 70.87%; H, 11.07%.

5. Diethyl malonate derivative (**15**).

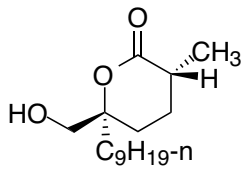


15

To a suspension of sodium hydride (80mg 60% in mineral oil, 2.0mmol) and sodium iodide (30mg, 0.2mmol) in dry toluene (20ml) stirred under argon was added a solution of diethyl methyl malonate (348mg, 2.0mmol). The reaction was stirred at 50°C for 30 min. To the resulting solution was added a solution of mesylate **14** (235mg, 0.40mmol) in 6ml of dry toluene. The reaction mixture was heated at 100°C for 24 h. Then the solution was diluted with diethyl ether and work up with 1N HCl, saturated sodium bicarbonate and brine. The organic layer was dried over magnesium sulfate. Flash chromatography eluting with petroleum ether / diethyl ether (5:1, Rf=0.3) afforded **15** (236mg, 89%) as clear oil. IR (film), 2929, 2866, 1733, 1614, 1514, 1464, 1379, 1302, 1248, 1172, 1109, 1038, 882, 805, 682 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$): δ 7.19 (d, J=8.1Hz, 2H), 6.78 (d, J=8.7Hz, 2H), 4.31 (d, J=10.2Hz, 1H) 4.23 (d, J=10.2Hz, 1H), 4.10 (m, 4H), 3.72 (s, 3H), 3.56 (d, J=3.9Hz, 2H), 2.02-0.95 (m, 50H), 0.81 (t, J=6.3Hz, 3H). ^{13}C NMR (75MHz,

$CDCl_3$): δ 167.78, 167.57, 154.07, 126.68, 124.29, 108.92, 74.21, 60.17, 58.07, 56.32, 50.48, 48.63, 28.46, 27.12, 25.35, 24.88, 24.82, 24.53, 23.94, 22.38, 18.01, 17.89, 15.18, 13.27, 9.34, 9.25, 7.17. $[\alpha]_D$= -0.50 (c=5.3, $CHCl_3$). Anal. Calcd for $C_{38}H_{68}O_7Si$: C, 68.63%; H, 10.31%. Found: C, 68.49%; H, 10.13%.

6. (-)-Malyngolide **1**.



1

To a solution of silyl protected compound **17** (58mg, 0.136mmol) in THF (5ml) was added TBAF (272ul, 0.27mmol, 1M in THF) at 0°C and the solution was continued stirring until the reaction is complete (1 h). After working up with diethyl ether and sat. ammonium chloride, the organic layer was dried over magnesium sulfate. The solvent was evaporated under vacuum. Flash chromatography eluting with 30% ethyl acetate in petroleum ether afforded 37mg (100%) of mixture of malyngolide **1** and *epi*-**1** in 1:1 ratio (based on ^{1}HNMR).

Isomerization of **1** and ***epi*-1**:

n-butyl lithium (0.31ml, 1.6M in hexane, 0.49mmol) was added via syringe to diisopropyl amine (69μl, 0.49mmol) in THF (1ml) at -78°C. The pale yellow solution was stirred at -78°C for 1 h before the addition of 1:1 mixture of **1** and *epi*-**1** (33mg, 0.081mmol) at -78°C. The resulting solution was stirred at -78°C for 1 h, then continue stirring at room temperature for 1h. The dianion solution was canulated into a solution of PPTS (184mg, 0.73 mmol) in CH_3CN (10ml) at -30°C. The whole solution was worked

up with water and diethyl ether. The ether layer was dried over magnesium sulfate. Flash chromatography eluting with 25% ethyl acetate in petroleum ether afforded *epi*-**1** (6.6mg, 20%) and **1** (20.0mg, 61%) and a mixture of two (1.6mg, 5%). (dr is about 3:1 based on crude ^{1}H NMR and isolated yield). (-) Malyngolide **1**: IR (film), 3433, 2927, 2855, 1727, 1460, 1378, 1329, 1253, 1208, 1069 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$): δ 3.65 (d, J=12Hz, 1H) 3.47, (d, J=12Hz, 1H), 2.42 (m, 1H), 2.25 (m, 1H), 2.00-1.80 (m, 2H), 1.80-1.40 (m, 5H) 1.40-1.10 (m, 16H), 0.87 (t, J=6.6Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 170.33, 82.09, 62.94, 31.69, 30.77, 27.03, 25.21, 24.69, 24.64, 24.46, 21.47, 20.40, 18.83, 17.85, 12.31, 9.29. $[\alpha]_D$= -12.8 (c=0.70, $CHCl_3$), [lit.[3] $[\alpha]_D$=-13.0, lit.[5e] $[\alpha]_D$= -12.4, lit.[7a] $[\alpha]_D$=-13.4]. In accordance with literature.[4-7]