Synthesis of (±)-Secosyrin 1 and a Formal Synthesis of (-)-Secosyrin 1

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Supplementary material

(±)-2-(4-Methoxybenzyl)-2,5-dihydrofuran-2-carboxylic acid amide **5**

Sodium (1.0 g, 45 mmol), ammonia (200 mL, distilled from Na/FeCl₃) and dry THF (50 mL) were combined in a 500 mL flask under an argon atmosphere at -78°C. To the resulting solution was slowly added a solution of **4** (2.5 g, 15 mmol) in THF (10 mL) over 5 min. The reaction was stirred for 10 min then isoprene (5 mL) was added, followed by 4-methoxybenzyl bromide (3.25 mL, 22.5 mmol). After stirring at -78°C for 10 min the reaction was allowed to warm to -40°C then saturated aqueous NH₄Cl (10 mL) was added. Ammonia was evaporated overnight and the residue was taken up in EtOAc (100 mL) and washed with 1M HCl (50 mL) and brine (50 mL). The organic layer was dried over MgSO₄ and concentrated *in vacuo*. Chromatography on silica gel using 1:1 EtOAc:petrol as eluant afforded **5** (3.2 g, 13.8 mmol, 92%) as an off white solid, mp 135-137 °C; R_f(1:1 Pentane:EtOAc) 0.18; ν_{max}/cm⁻¹ 1665 (C=O) and 1248 (ArOMe); δ_H(400MHz; CDCl₃) 7.17-7.13 (2 H, m, ArH_A), 6.82-6.78 (2 H, m, ArH_B), 6.58 (1 H, br s, NH_AH_B), 5.96 (1 H, dt, *J* 6.2 and 2.5, CCH=CH), 5.83 (1 H, dt, *J* 6.0 and 1.5, CCH=CH), 5.46 (1 H, br s, NH_AH_B), 4.67 (1 H, ddd, *J* 13.0, 2.4 and 1.6, OCH_AH_B), 4.48 (1 H, ddd, *J* 13.0, 2.5, 1.5, OCH_AH_B), 3.78 (3 H, s, OMe), 3.19 (1 H, d, *J* 14.0, CH_AH_BAr), 3.01 (1 H, d, *J* 14.0, CH_AH_BAr); δ_C(CDCl₃) 175.7+, 158.3+, 131.4-, 129.7-, 128.1+, 127.4-, 113.2-, 95.1+, 76.1+, 55.1-, 42.1+; *m/z* (ESI) 254 (100%, M+Na⁺), 234 (42, M+H), 189 (44, M-CONH₂); (Found: M+H⁺, 234.1140. C₁₃H₁₆NO₃ requires *M*, 234.1130)(Found: C, 66.9; H, 6.6; N, 5.8. C₁₃H₁₅NO₃ requires C, 66.9; H, 6.5; N, 6.0%).

(±)-[2-(4-Methoxybenzyl)-2,5-dihydrofuran-2-yl]-methanol **6**

A suspension of **5** (6.1 g, 26.3 mmol) in 1M HCl (150 mL) was heated to reflux for 2 h. After cooling the resultant mixture was extracted with EtOAc (2 × 50 mL). Combined organic extracts were dried over MgSO₄ and concentrated *in vacuo* to yield the crude *acid* as a brown solid, mp 84-87 °C. This material was dissolved in dry THF (50 mL) at room temperature and slowly added to a suspension of LiAlH₄ (1.9 g, 50 mmol) in dry THF (100 mL) under argon. After stirring overnight 1M HCl was carefully added drop wise until effervescence ceased. The organic layer was separated and the aqueous layer extracted with 2 portions of EtOAc (50 mL). Combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. Silica gel chromatography using 60:40 pentane:EtOAc as eluant gave the *alcohol* (5.1 g, 88%); R_f(3:2 pentane:EtOAc) 0.24; ν_{max}/cm⁻¹ 3432 br (OH) and 1246 (ArOMe); δ_H(400MHz; CDCl₃) 7.15-7.10 (2 H, m, ArH_A), 6.83-6.79 (2 H, m, ArH_B), 5.88 (1 H, dt, *J* 6.5 and 1.7, CCH=CH), 5.83 (1 H, dt, *J* 6.2 and 2.4, CCH=CH), 4.60 (1 H, ddd, *J* 12.9, 2.3 and 1.8, OCH_AH_B), 4.38 (1 H, ddd, *J* 12.9, 2.5, 1.6, OCH_AH_B), 3.80 (3 H, s, OMe), 3.63 (1 H, d, *J* 11.3, CH_AH_BOH), 3.58 (1 H, d, *J* 11.3, CH_AH_BOH), 2.88 (1 H, d, *J* 13.6, CH_AH_BAr), 2.82 (1 H, d, *J* 13.6, CH_AH_BAr); δ_C(CDCl₃) 158.8+, 131.26-, 129.3-, 129.0+, 128.6-, 113.3-, 93.8+, 75.7+, 67.2+, 55.2-, 41.3+; *m/z* (CI) 238 (100%, M+NH₄⁺), 221 (48, M+H), 203 (31, M-CH₃)(Found: M+NH₄⁺, 238.1444. C₁₃H₂₀NO₃ requires *M*, 238.1443).

(2RS,3RS,4RS)-2-Hydroxymethyl-2-(4-methoxybenzyl)-tetrahydrofuran-3,4-diol syn-7 and (2RS,3SR,4SR)-2-Hydroxymethyl-2-(4-methoxybenzyl)-tetrahydrofuran-3,4-diol anti-7

Conditions (i): 4-Methylmorpholine-N-oxide (240 mg, 2 mmol) was added to a stirred solution of **6** (150 mg, 0.68 mmol) in acetone (20 mL) and water (5 mL) at room temperature, followed by quinuclidine (5 mg, 7 mol%) and OsO₄ (5 mg, 3 mol%). The reaction mixture was stirred overnight then acetone was removed *in vacuo* and EtOAc (20 mL) and brine (20 mL) were added. The organic layer was separated, dried over MgSO₄ and concentrated *in vacuo*. HPLC analysis of the crude material showed a 68:32 mixture of diastereomers in favour of syn-7. Purification by column chromatography using 95:5 DCM:IPA as eluant gave anti-7 (41 mg, 24%) as cubes, mp 103-105 °C, and syn-7 (89 mg, 52%) as cubes, mp 93-95 °C; R_f(95:5 DCM:IPA) 0.26; $\nu_{\max}/\text{cm}^{-1}$ 3232 br (OH) and 1249 (ArOMe); δ (400MHz; CD₃OD) 7.20-7.16 (2 H, m, ArH_A), 6.85-6.81 (2 H, m, ArH_B), 4.04 (1 H, d, *J* 5.3, CHOH), 3.81 (1 H, dd, *J* 8.3 and 4.7, OCH_AH_B), 3.76 (3 H, s, OMe), 3.71-3.61 (3 H, m, OCH_AH_B, OCH₂CHOD and CH_AH_BOH) 3.52 (1 H, d, *J* 11.4, CH_AH_BOH), 2.81 (1 H, d, *J* 13.9, CH_AH_BAr), 2.71 (1 H, d, *J* 13.9, CH_AH_BAr); δ_{C} (CD₃OD) 158.9+, 131.7-, 129.1+, 113.5-, 85.4+, 75.2-, 71.9+, 71.8-, 64.3+, 54.6-, 40.2+; *m/z* (ESI) 277 (100%, M+Na⁺)(Found: M+Na⁺, 277.1046. C₁₃H₁₈O₅Na requires *M*, 277.1046)(Found: C, 61.37; H, 7.16. C₁₃H₁₈O₅ requires C, 61.41; H, 7.14%).

Conditions (ii): Trimethylamine-N-oxide dihydrate (5.7 g, 51 mmol) was added to a stirred solution of **6** (3.78 g, 17.2 mmol) in DCM (200 mL) at room temperature. OsO₄ (50 mg, ~1 mol%) was added and the mixture stirred overnight. Saturated aqueous sodium sulfite (20 mL) was added and the mixture stirred for 20 minutes further. The organic layer was separated, dried over MgSO₄ and concentrated *in vacuo*. HPLC analysis showed a 87:13 ratio of diastereomers in favour of syn-7. Column chromatography using 95:5 DCM:IPA as eluant gave anti-7 (0.45 g, 10%) and syn-7 (3.04 g, 70%)

Conditions (iii): In a solution of **6** (100 mg, 0.45 mmol) in DCM (15 mL) was suspended **8** (100 mg, ~10 mol% OsO₄) at room temperature. Trimethylamine-N-oxide dihydrate (150 mg, 1.4 mmol) was added and the mixture was agitated overnight. The polymer was then removed by filtration and the filtrate was concentrated *in vacuo*. HPLC analysis showed a 88:12 ratio of diastereomers in favour of syn-7. Chromatography using 95:5 DCM:IPA as eluant gave anti-7 (12 mg, 10%) and syn-7 (85 mg, 74%).

Conditions (iv): A solution of **6** (100 mg, 0.45 mmol) in DCM (40 mL) was cooled to -78 °C under an argon atmosphere. N,N,N,N-tetramethylethylenediamine (72 μ L, 0.48 mmol) was added followed by OsO₄ (120 mg, 0.48 mmol) and the mixture was stirred for 2 h then allowed to warm to room temperature. DCM was removed *in vacuo* and the residue was taken up in MeOH (20 mL) and 10 M HCl was added (3 drops). After stirring overnight, the solvent was removed *in vacuo*. HPLC analysis showed a 99:1 ratio of diastereomers in favour of syn-7. Chromatography using 95:5 DCM:IPA as eluant gave syn-7 (93 mg, 82%).

(2RS,3RS,4RS)-4-(tert-butyldimethylsilanyloxy)-2-(tert-butyldimethylsilanyloxymethyl)-2-(4-methoxybenzyl)-tetrahydrofuran-3-ol 9

A solution of syn-7 (2.6 g, 10 mmol) in THF (150 mL) was cooled to -78 °C under an argon atmosphere. 2,6-lutidine (3.0 mL, 26 mmol) was added followed by TBDMSOTf (4.7 mL, 20.5 mmol). The reaction mixture was allowed to slowly warm to room temperature overnight. Silica gel (ca. 1 g) was added and the mixture was concentrated *in vacuo*.

Chromatography using 97:3 petrol:EtOAc gave the *bis-silyl ether* (4.56 g, 92%); R_f (97:3 petrol:EtOAc) 0.14; $\nu_{\max}/\text{cm}^{-1}$ 3534 br (OH) and 1250 (ArOMe); δ_H (400MHz; CDCl_3) 7.20-7.16 (2 H, m, ArH_A), 6.84-6.80 (2 H, m, ArH_B), 3.95 (1 H, d, J 10.2, $\text{CH}_A\text{H}_B\text{OSi}$), 3.83-3.76 (1 H, m, CHOSi), 3.78 (3 H, s, OCH₃), 3.70 (1 H, dd, J 11.1 and 5.7, OCH_AH_B), 3.58 (1 H, d, J 9.8, $\text{CH}_A\text{H}_B\text{OSi}$), 3.57 (1 H, dd, J 8.6 and 5.8), 3.05 (1 H, d, J 4.7, CHOH), 2.88 (1 H, d, J 14.1, $\text{CH}_A\text{H}_B\text{OSi}$), 2.82 (1 H, d, J 13.6, $\text{CH}_A\text{H}_B\text{OSi}$), 0.94 (9 H, s, $\text{SiC}(\text{CH}_3)_3$), 0.84 (9 H, s, $\text{SiC}(\text{CH}_3)_3$), 0.09 (6 H, s, SiMe), -0.01 (3 H, s, SiMe), -0.03 (3 H, s, SiMe); δ_C (CDCl_3) 158.1+, 131.4-, 129.2-, 113.4-, 85.6+, 74.9-, 72.3-, 71.4+, 65.0+, 55.4-, 40.3+, 26.1-, 25.9-, -4.8-, -5.2-; m/z (ESI) 505 (100%, $\text{M}+\text{Na}^+$)(Found: $\text{M}+\text{H}^+$, 483.2939. $\text{C}_{25}\text{H}_{47}\text{O}_5\text{Si}_2$ requires M , 483.2957).

(2RS,4RS)-4-(tert-butyldimethylsilyloxy)-2-(tert-butyldimethylsilyloxymethyl)-2-(4-methoxybenzyl)-dihydrofuran-3-one 11

Dess-Martin periodinane (1.06 g, 2.5 mmol) was added to a solution of **9** (1.0 g, 2.1 mmol) at room temperature in dry DCM (50 mL) and the mixture was stirred overnight under argon. The solvent was removed *in vacuo* and chromatography using 97:3 petrol:EtOAc yielded the *ketone* (970 mg, 97%) as a white solid, mp 65-66 °C; R_f (97:3 petrol:EtOAc) 0.18; $\nu_{\max}/\text{cm}^{-1}$ 1769 (C=O) and 1246 (ArOMe); δ_H (400MHz; CDCl_3) 7.17-7.11 (2 H, m, ArH_A), 6.90-6.87 (2 H, m, ArH_B), 4.23 (1 H, dd, J 8.6 and 8.2, OCH_AH_B), 4.05 (1 H, d, J 10.5, $\text{CH}_A\text{H}_B\text{OSi}$), 4.00 (1 H, dd, J 10.1 and 8.2, OCH_AH_B), 3.87 (3 H, s, OCH₃), 3.77 (1 H, d, J 11.4, $\text{CH}_A\text{H}_B\text{OSi}$), 3.37 (1 H, dd, J 10.1 and 9.4, CHOSi), 2.80 (1 H, d, J 13.6, $\text{CH}_A\text{H}_B\text{Ar}$), 2.75 (1 H, d, J 13.7, $\text{CH}_A\text{H}_B\text{Ar}$), 0.96 (9 H, s, $\text{SiC}(\text{CH}_3)_3$), 0.90 (9 H, s, $\text{SiC}(\text{CH}_3)_3$), 0.15 (3 H, s, SiCH₃), 0.14 (3 H, s, SiCH₃), 0.11 (3 H, s, SiCH₃), 0.00 (3 H, s, SiCH₃); δ_C (CDCl_3) 215.2+, 158.4+, 131.4-, 127.4+, 113.5-, 85.7+, 73.0-, 69.9+, 68.2-, 55.2-, 38.5+, 25.7-, 25.6-, 18.1+, -4.72-, -5.46-, -5.60-, -5.72-; m/z (ESI) 503 (100%, $\text{M}+\text{Na}^+$)(Found: $\text{M}+\text{H}^+$, 481.2792. $\text{C}_{25}\text{H}_{45}\text{O}_5\text{Si}_2$ requires M , 481.2800)(Found: C, 62.51; H, 9.30. $\text{C}_{25}\text{H}_{45}\text{O}_5\text{Si}_2$ requires C, 62.45; H, 9.22%).

(2RS,3SR,4RS)-4-(tert-butyldimethylsilyloxy)-2-(tert-butyldimethylsilyloxymethyl)-2-(4-methoxybenzyl)-tetrahydrofuran-3-ol 12

11 (750 mg, 1.56 mmol) was dissolved in THF (60 mL) and cooled to -78 °C under an atmosphere of argon. Lithium aluminium hydride (1M in THF, 3.1 mL) was slowly added over 5 minutes and the resulting reaction mixture was stirred for 4 hours at -78 °C. Saturated aqueous NH₄Cl was added and the reaction mixture was allowed to warm to room temperature. The mixture was diluted with EtOAc (50 mL) and brine (50 mL) and the organic layer was separated, dried over MgSO₄ and concentrated *in vacuo*. HPLC on the crude mixture showed a ratio for **9:12** of 7:93. Chromatography using 9:1 petrol:EtOAc afforded **12** (467 mg, 62%); R_f (9:1 petrol:EtOAc) 0.25; $\nu_{\max}/\text{cm}^{-1}$ 3466 br (OH) and 1250 (ArOMe); δ_H (400MHz; CDCl_3) 7.24-7.21 (2 H, m, ArH_A), 6.84-6.81 (2 H, m, ArH_B), 4.12-3.99 (3 H, m, OCH_AH_B , CHOH and CHOSi), 3.80 (3 H, s, OCH₃), 3.57 (1 H, dd, J 8.7 and 5.1, OCH_AH_B), 3.46 (1 H, d, J 9.3, $\text{CH}_A\text{H}_B\text{OSi}$), 3.41 (1 H, d, J 9.6, $\text{CH}_A\text{H}_B\text{OSi}$), 2.84 (1 H, d, J 13.9, $\text{CH}_A\text{H}_B\text{Ar}$), 2.79 (1 H, d, J 13.9, $\text{CH}_A\text{H}_B\text{Ar}$), 0.93 (9 H, s, $\text{SiC}(\text{CH}_3)_3$), 0.87 (9 H, s, $\text{SiC}(\text{CH}_3)_3$), 0.06 (3 H, s, SiCH₃), 0.05 (6 H, s, SiCH₃), 0.03 (3 H, s, SiCH₃); δ_C (CDCl_3) 158.1+, 131.8-, 129.3+, 113.3-, 84.7+, 82.5-, 77.6-, 71.3+, 66.3-, 55.2-, 35.3+, 25.9-, 25.8-, -5.44-; m/z (ESI) 505 (100%, $\text{M}+\text{Na}^+$)(Found: $\text{M}+\text{H}^+$, 483.2955. $\text{C}_{25}\text{H}_{47}\text{O}_5\text{Si}_2$ requires M , 483.2962)(Found: C, 62.29; H, 9.67. $\text{C}_{25}\text{H}_{46}\text{O}_5\text{Si}_2$ requires C, 62.19; H, 9.60%).

(2RS,3SR,4RS)-Hexanoic acid-4-(tert-butyldimethylsilanyloxy)-2-(tert-butyldimethylsilanyloxymethyl)-2-(4-methoxybenzyl)-tetrahydrofuran-3-yl ester 13

Hexanoic anhydride (0.66 mL, 2.85 mmol) was slowly added to a solution of **12** (460 mg, 0.95 mmol), Et₃N (0.4 mL, 2.85 mmol) and DMAP (5 mg, ~4 mol%) in THF (25 mL) at 0 °C under an argon atmosphere. The reaction was stirred at 0 °C for 30 min then warmed to room temperature and stirred for 2 h further. Solvent was removed *in vacuo* and the material was purified by column chromatography using 97:3 petrol:EtOAc as eluant, to yield the *ester* (535 mg, 97%), R_f (3%EtOAc/Petrol) 0.79; ν_{max}/cm⁻¹ 1743 (C=O) and 1249 (ArOMe); δ_H(400MHz; CDCl₃) 7.27-7.22 (2 H, m, ArH_A), 6.83-6.80 (2 H, m, ArH_B), 5.28 (1 H, d, *J* 2.6, CHOCO), 4.14-4.11 (1 H, m, CHOSi), 4.01 (1 H, dd, *J* 9.4, 5.0, OCH_AH_B), 3.79 (3 H, s, OCH₃), 3.70 (1 H, dd, *J* 9.4 and 3.4, OCH_AH_B), 3.53 (1 H, d, *J* 9.6, CH_AH_BOSi), 3.37 (1 H, d, *J* 9.8, CH_AH_BOSi), 2.82 (1 H, d, *J* 13.8, CH_AH_BAr), 2.70 (1 H, d, *J* 13.8, CH_AH_BAr), 2.41-2.37 (2 H, m, OCOCH₂), 1.72-1.65 (2 H, m, OCOCH₂CH₂), 1.37-1.31 (4 H, m, CH₂Et and CH₂Me), 0.93 (9 H, s, SiC(CH₃)₃), 0.92 (3 H, m, CH₃), 0.86 (9 H, s, SiC(CH₃)₃), 0.08 (3 H, s, SiCH₃), 0.04 (3 H, s, SiCH₃), 0.03 (6 H, s, SiCH₃); δ_C(CDCl₃) 172.5+, 158.1+, 131.8-, 129.2+, 113.2-, 85.8+, 81.4-, 77.5-, 72.7+, 63.8-, 55.2-, 35.5+, 34.4+, 31.3+, 25.9-, 25.7-, 24.7+, 22.3+, 18.1+, 18.0+, 13.9-, -5.2-, -5.5-; *m/z* (APCI) 581 (100%, M+H⁺)(Found: M+H⁺, 581.3688. C₃₁H₅₇O₆Si₂ requires *M*, 581.3688)(Found: C, 64.04; H, 9.80. C₃₁H₅₆O₆Si₂ requires C, 64.09; H, 9.72%).

(2RS,3SR,4RS)-Hexanoic acid-4-(tert-butyldimethylsilanyloxy)-2-(tert-butyldimethylsilanyloxymethyl)-2-carboxymethyl-tetrahydrofuran-3-yl ester 14

To a suspension of **13** (184 mg, 0.32 mmol) in CCl₄ (2 mL), MeCN (2 mL) and water (3 mL) was added Na₂HPO₄·7H₂O (1.29 g, 4.8 mmol), NaIO₄ (1.03 g, 4.8 mmol) and RuCl₃·H₂O (5 mg, ~8 mol%). The mixture was stirred for 18 h at room temperature then diethyl ether (20 mL) was added and the mixture was stirred for 20 min further. The reaction mixture was filtered through a pad of celite then brine (20 mL) was added. The organic layer was separated, dried over MgSO₄ and concentrated *in vacuo*. Chromatography using 90:10 petrol:EtOAc afforded the *acid* (101 mg, 61 %), R_f(10%EtOAc/Pentane) 0.30; ν_{max}/cm⁻¹ 1744 (C=O ester), 1709 (C=O acid); δ_H(400MHz; CDCl₃) 5.02 (1 H, d, *J* 2.0, CHOCO), 4.19-4.16 (1 H, m, CHOSi), 4.06 (1 H, dd, *J* 9.8, 5.1, OCH_AH_B), 3.74 (1 H, dd, *J* 9.8 and 3.1, OCH_AH_B), 3.74 (2 H, s, CH₂OH), 2.61 (2 H, s, CH₂CO₂H), 2.28-2.24 (2 H, m, OCOCH₂), 1.59-1.51 (2 H, m, OCOCH₂CH₂), 1.28-1.18 (4 H, m, CH₂Et and CH₂Me), 0.82 (12 H, s, SiC(CH₃)₃ and CH₃), 0.81 (9 H, s, SiC(CH₃)₃), 0.04 (3 H, s, SiCH₃), 0.01 (3 H, s, SiCH₃), 0.00 (6 H, s, SiCH₃); δ_C(CDCl₃) 173.1+, 172.3+, 85.4+, 80.7-, 76.8-, 73.9+, 65.9-, 37.0+, 33.9+, 31.3+, 25.9-, 25.8-, 24.5+, 22.4+, 17.9+, 14.0-, -4.6-, -5.3-, -5.0-; *m/z* (ESI) 541 (100%, M+Na⁺)(Found: M+H⁺, 519.3168. C₂₅H₅₁O₇Si₂ requires *M*, 519.3168)(Found: C, 58.05; H, 9.63. C₂₅H₅₀O₇Si₂ requires C, 57.87; H, 9.71%).

(±)-Secosyrin 1

To a solution of **14** (58 mg, 0.11 mmol) in THF (4 mL) under an argon atmosphere was added trifluoroacetic acid (85 μL, 1.1 mmol) and trifluoroacetic anhydride (155 μL, 1.1 mmol). After stirring for 1 h at room temperature, TBAF (1M in THF, 1.1 mL, 1.1 mmol) was added and the mixture was stirred for 2 d. Solvent was removed *in vacuo* and the residue was purified by column chromatography using 70:30 petrol:EtOAc to yield (±)-Secosyrin **1** (22 mg, 73%); δ_H(400MHz; CDCl₃) 4.95 (1 H, d, *J* 2.2), 4.46 (1 H, d, *J* 10), 4.37 (1 H, d, *J* 10),

4.33 (1 H, dd, *J* 5.3 and 2.6), 4.13 (1 H, dd, *J* 10.2 and 5.4), 3.87 (1 H, dd, *J* 10.2 and 2.8), 2.80 (1 H, d, *J* 18), 2.60 (1 H, d, *J* 18), 2.39 (2 H, t, *J* 7.6), 1.69-1.53 (2 H, m), 1.42-1.23 (4 H, m), 0.89 (3 H, t, *J* 6.8); δ_c (CDCl₃) 174.1, 173.7, 86.53, 81.99, 75.88, 75.62, 72.59, 35.37, 34.00, 31.16, 24.46, 22.21, 13.84; *m/z*(ESI) 295 (100%, M+Na⁺).

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δ_H (CDCl₃) 4.94 (1 H, d, *J* = 2 Hz), 4.45 (1H, d, *J* = 10 Hz), 4.36 (1 H, d, *J* = 10 Hz), 4.31 (1H, dd, *J* = 5.1, 2.5 Hz), 4.14 (1H, dd, *J* = 10.3, 5.3 Hz), 3.86 (1 H, dd, *J* = 10.2, 2.8 Hz), 2.78 1H, d, *J* = 18 Hz), 2.58 (1H, d, *J* = 18 Hz), 2.38 (1 H, t, *J* = 7.4), 1.63 (2H, m), 1.3 (4 H, m), 0.89 (3H, t, *J* = 6.8 Hz). δ_c (CDCl₃) 174.4, 173.6, 86.61, 81.67, 76.40, 75.85, 72.83, 35.47, 34.01, 31.15, 24.46, 22.19, 13.75 ppm.

(2'R,5'R,2R)-(2',5'-Bismethoxymethylpyrrolidin-1-yl)-[2-(4-methoxybenzyl)-3-trimethylsilanyl-2,5-dihydrofuran-2-yl]-methanone 17

Sodium (64 mg, 2.8 mmol), ammonia (40 mL, distilled from Na/FeCl₃) and dry THF (10 mL) were combined under an argon atmosphere at -78°C. To the resulting solution was slowly added a solution of **16** (300 mg, 0.92 mmol) in THF (5mL) over 1 min. The reaction was stirred for 10 min the isoprene (0.2 mL) was added, followed by 4-methoxybenzyl bromide (0.4 mL, 2.8 mmol). After stirring for 10 min further, saturated aqueous NH₄Cl (1 mL) was added and the reaction warmed to room temperature allowing ammonia to evaporate. The residue was taken up in EtOAc (200 mL) and washed with 1M HCl (20 mL) and brine (20 mL). The organic layer was dried over MgSO₄ and concentrated *in vacuo*. Chromatography using 90:10 Pentane:EtOAc as eluant gave the title compound as an inseparable mixture of diastereomers ($\geq 20:1$, 280 mg, 68%), *R_f*(90:10 Pentane;EtOAc) 0.21; $\nu_{\max}/\text{cm}^{-1}$ 1613 (C=O) and 1246 (ArOMe); δ_H (400MHz; CDCl₃) 7.20-7.16 (2 H, m, ArH_A), 6.77-6.73 (2 H, m, ArH_B), 6.09 (1 H, dd, *J* 1.6 and 1.5, CH=CSi), 4.66-4.61 (1 H, m, NCH_A), 4.57 (1 H, dd, *J* 4.1 and 1.6, OCH_AH_B), 4.41 (1 H, dd, *J* 4.0, 1.2, OCH_AH_B), 4.24-4.19 (1 H, m, NCH_B), 3.76 (3 H, s, ArOCH₃), 3.30-3.27 (2 H, m, NCH_ACH_AH_BOMe and CH_AH_BAr), 3.23 (3 H, s, CH₂OCH₃), 3.21 (3 H, s, CH₂OCH₃), 3.10 (1 H, m, NCH_BCH_AH_BOMe), 2.90 (1 H, dd, NCH_BCH_AH_BOMe), 2.82-2.76 (2 H, m, NCH_ACH_AH_BOMe and CH_AH_BAr), 1.86-1.75 (3 H, m, CH₂CH_AH_B), 1.67-1.62 (1 H, m, CH₂CH_AH_B), 0.22 (9 H, s, Si(CH₃)₃); δ_c (CDCl₃) 171.3+, 158.1+, 146.5-, 137.9-, 132.0-, 129.3+, 112.9-, 101.0+, 75.4+, 74.2+, 71.4+, 58.7-, 58.3-, 57.5-, 57.4-, 55.2-, 45.3+, 27.2+, 23.0+, -0.4-; *m/z* (ESI) 470 (100%, M+Na⁺)(Found: M+Na⁺, 470.2327. C₂₄H₃₇NO₅SiNa requires *M*, 470.2333)(Found: C, 64.34; H, 8.39; N, 3.11. C₂₄H₃₇NO₅Si requires C, 64.40; H, 8.33; N, 3.13 %); $[\alpha]_D$ +110.7 (c. 0.35 in CH₂Cl₂).

(2R)-[2-(4-Methoxybenzyl)-2,5-dihydrofuran-2-yl]-methanol 6

A suspension of **17** (0.23 g, 0.52 mmol) in 10M HCl (25 mL) was heated to reflux for 4 h. After cooling the resultant mixture was extracted with DCM (2 × 20 mL). Combined organic extracts were dried over MgSO₄ and concentrated *in vacuo* to yield the crude *acid* as a brown solid, mp 84-87 °C. This material was dissolved in dry THF (50 mL) and slowly added to a suspension of LiAlH₄ (38 mg, 1.0 mmol) in dry THF (5 mL) under argon. After stirring overnight 1M HCl was carefully added drop wise until effervescence ceased. The organic layer was separated and the aqueous layer extracted with 2 portions of EtOAc (10 mL). Combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. Silica gel chromatography using 60:40 pentane:EtOAc as eluant gave the *alcohol* (48 mg, 42%); $[\alpha]_D$ -47.9 (c. 0.14 in CH₂Cl₂); 90% ee measured by HPLC in comparison with a racemic standard.

^1H NMR for secosyrin 1

Secosyrin 1: CDCl_3
at 250 Mhz

CIF for compound syn-7

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F2 > 2sigma(F2) is used
only for calculating R-
factors(gt) etc. and is
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C12 C7 C8 116.84(16) . . ?	? .
C12 C7 C6 121.57(15) . . ?	O1 C1 C2 O2 145.05(10) . . .
C8 C7 C6 121.55(15) . . ?	. ?
C9 C8 C7 121.47(17) . . ?	C5 C1 C2 O2 28.12(15)
C9 C8 H8A 119.3 . . ?	? .
C7 C8 H8A 119.3 . . ?	C6 C1 C2 O2 -96.79(13) . . .
C10 C9 C8 120.23(18) . . ?	. ?
C10 C9 H9A 119.9 . . ?	O1 C1 C2 C3 17.40(12)
C8 C9 H9A 119.9 . . ?	? .
C11 C10 O5 124.72(19) . . ?	C5 C1 C2 C3 -99.53(13) . . .
C11 C10 C9 119.68(17) . . ?	. ?
O5 C10 C9 115.61(18) . . ?	C6 C1 C2 C3 135.56(11) . . .
C10 C11 C12 119.33(18) . . ?	. ?
C10 C11 H11A 120.3 . . ?	O2 C2 C3 O3 -40.41(15) . . .
C12 C11 H11A 120.3 . . ?	. ?
C7 C12 C11 122.43(17) . . ?	C1 C2 C3 O3 86.78(12)
C7 C12 H12A 118.8 . . ?	? .
C11 C12 H12A 118.8 . . ?	O2 C2 C3 C4 -160.89(11) . . .
O5 C13 H13A 109.5 . . ?	. ?
O5 C13 H13B 109.5 . . ?	C1 C2 C3 C4 -33.70(12) . . .
H13A C13 H13B 109.5 . . ?	. ?
O5 C13 H13C 109.5 . . ?	C1 O1 C4 C3 -30.06(14) . . .
H13A C13 H13C 109.5 . . ?	. ?
H13B C13 H13C 109.5 . . ?	O3 C3 C4 O1 -81.10(13) . . .
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	C1 C6 C7 C8 69.91(19)
_geom_torsion_site_symmetry_2	? .
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_geom_torsion_site_symmetry_3	C6 C7 C8 C9 -176.38(16) . . .
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 O5 C10 C11 C12 179.82(17) . .
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 C8 C7 C12 C11 -0.5(3)
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 C6 C7 C12 C11 177.15(16) . .
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 C10 C11 C12 C7 -0.1(3) . . .
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