Supporting Information

Synthesis of Optically Active Constrained 2-Substituted Norstatines: a Straightforward Application of Seebach's "SRS" Synthetic Principle

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List of Contents

General

^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer with Me_4Si or $CHCl_3$ (in $CDCl_3$) as internal standards. Mass spectra were recorded on an ion trap spectrometer with an ionization potential of 70 eV. Gas chromatography (GC) was carried out on a GC–mass spectrometer (ion trap, 70 eV). Infrared spectra were recorded on a Fourier-transform IR spectrometer. The HPLC system consisted of a solvent delivery system, multiwavelength detector connected to a computer station. A Rheodyne injector with a 20 μL loop was used. Chiralcel OJ column (250 x 4.6 mm, i.dwas used for the enantioselective HPLC analysis of compounds **8**, **9**, **12**, and **13**, eluent n-hexane/2-propanol (80/20, v/v), 1 ml/min; a Chiralpack OD column (250 x 4.6 mm, i.d.) was used for the enantioselective HPLC analysis of compounds **16** and **17**, eluent n-hexane/2-propanol (90/10, v/v), 1 ml/min; a CapCell Pak C8 SG120 (250 x 4.6 mm, i.d.) was used for the determination of the stereoisomeric ratio of compounds **18** and **19**, eluent $MeOH/H_3PO_4$ buffer pH = 4 (60/40, v/v), 1 ml/min. The dioxolanones **1-3** were prepared according to the literature and were purified by distillation under vacuum. N-BOC aldimines **4-5** were prepared according to literature procedures.

Synthesis of (2*S*,5*R*,1'*R*)- and (2*S*,5*R*,1'*S*)-2-(*tert*-Butyl)-5-(1'-*tert*-butoxycarbonylamino-1'-(2-thienyl)methyl)-2,5-dimethyl-1,3-dioxolan-4-ones [(2*S*,5*R*,1'*R*)-10 and (2*S*,5*R*,1'*S*)-11]. 0.350 g (2.00 mmol) of **1** (93:7 mixture), and imine **5** gave a 1: 4.6 mixture of **10**/**11**. Chromatography (SiO_2, cyclohexane/Et_2O/$CHCl_3$, 13:0.5:6.5) gave 0.115 g (0.30 mmol, 15 %) of (2*S*,5*R*,1'*R*)-**10** and 0.522 g (1.36 mmol, 68 %) of (2*S*,5*R*,1'*S*)-**11**. (2*S*, 5*R*, 1'*R*)-**10**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20-7.25 (m, 1 H), 7.00-7.05 (m, 1 H), 6.95-7.00 (m, 1 H), 5.30-5.45 (b, 1 H), 5.20 (bd, 1 H, *J* = 11.0 Hz), 1.53 (s, 3 H), 1.40 (s, 9 H, 3 Me), 1.10 (s, 3 H, Me), 1.00 (s, 9 H, 3 Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.1, 154.6, 141.2, 127.4, 127.0, 125.6, 116.5, 82.8, 80.6, 56.2, 39.3, 28.5, 25.5, 23.5, 22.2. $[\alpha]^{20}_D$ + 33.0 (*c* 0.7, $CHCl_3$); IR (nujol, cm^{-1}): 3345,1790, 1720, 1480, 1368, 1152; MS *m/z* 384, 328, 284, 212, 156, 113; Anal. Calcd. for $C_{19}H_{29}NO_5S$: C. 59.51; H, 7.62; N, 3.65. Found: C. 59.65; H, 7.74; N, 3.61. (2*S*, 5*R*, 1'*S*)-**11**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.18-7.22 (m, 1 H), 6.95-7.05 (m, 2 H), 5.40 (bd, 1 H, *J* = 9.5 Hz), 5.26 (bd, 1 H, *J* = 9.5.0 Hz), 1.45-1.49 (b, 3 H), 1.43-1.47 (b, 9 H, 3 Me), 1.10 (bs, 3 H), 0.97 (s, 9 H, 3 Me); ^{13}C NMR ($CDCl_3$) δ 173.4, 155.3, 141.2, 127.4, 127.0, 125.6, 116.5, 82.8, 80.6, 56.2, 39.3, 28.5, 25.5, 23.5, 22.2. $[\alpha]^{20}_D$ + 38.0 (*c* 0.7, $CHCl_3$); IR (nujol, cm^{-1}): 3350,1795, 1710, 1485, 1368, 1152; MS *m/z* 384, 328, 284, 212, 156, 113; Anal. Calcd. for $C_{19}H_{29}NO_5S$: C, 59.51; H, 7.62; N, 3.65. Found: C, 59.30; H, 7.72; N, 3.72.

(2*R*,3*R*)-3-(*tert*-Butoxycarbonylamino)-2-hydroxy-2-methyl-3-(2-thienyl)propionic acid methyl ester [(2*R*,3*R*)-12]. 0.10 g (0.26 mmol) of (2*S*,5*R*,1'*R*)-**10** (93:7 mixture) gave (2*R*,3*R*)-**12** (0.072 g, 0.23 mmol, 90 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22-7.27 (m, 1 H), 7.09-7.12 (m, 1 H), 6.94-6.97 (m, 1 H), 5.28-5.35 (b, 2 H), 3.82 (s, 3 H), 1.38 (s, 9 H), 1.29 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ176.4, 154.8, 140.1, 127.6, 126.5, 125.9, 80.1, 77.0, 56.3, 53.6, 28.4, 23.6. $[\alpha]^{20}_{D}$ + 11.0 (*c* 0.4, $CHCl_3$); IR (nujol, cm^{-1}): 1720, 3360; MS *m/z* 316, 260, 212, 199, 156, 139; Anal. Calcd. for $C_{14}H_{21}NO_5S$: C, 53.32; H, 6.71; N, 4.44. Found C, 53.17; H, 6.69; N, 4.50.

(2*R*,3*S*)-3-(*tert*-Butoxycarbonylamino)-2-hydroxy-2-methyl-3-(2-thienyl)propionic acid methyl ester (2*R*,3*S*)-13. 0.115 g (0.3 mmol) of (2*S*,5*R*,1'*S*)-**11** (93:7 mixture) gave (2*R*,3*S*)-**13** (0.084 g, 0.27 mmol, 91 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.17-7.20 (m, 1 H), 6.9-6.95 (m, 2 H), 5.38 (bd, 1 H, *J* = 10.0 Hz), 5.38 (bd, 1 H, *J* = 10.0 Hz), 3.67 (s, 3 H), 3.40-3.55 (b, 1 H), 1.54 (s, 3 H), 1.42 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 175.4, 155.6, 141.0, 126.6, 126.1, 125., 80.2, 77.7, 56.1, 53.2, 28.5, 23.4. $[\alpha]^{20}_{D}$ - 30.0 (*c* 0.4, $CHCl_3$); IR (nujol, cm^{-1}): 1711, 3370; MS *m/z* 316, 260, 212, 199, 156, 139; Anal. Calcd. for $C_{14}H_{21}NO_5S$: C, 53.32; H, 6.71; N, 4.44. Found C, 53.53; H, 6.77; N, 4.33.

(Synthesis of (2*S*,5*R*,1'*R*)- and (2*S*,5*R*,1'*S*)-2-(*tert*-Butyl)-5-(1'-*tert*-butoxycarbonylamino-1'-(2-thienyl)methyl-5-phenyl-1,3-dioxolan-4-ones [(2*S*,5*R*,1'*R*)-14 and (2*S*,5*R*,1'*S*)-15]. 0.200 g of pure dioxolanone **2** (0.91 mmol) and imine **5** gave a 3.6: 1.0 mixture of (2*S*, 5*R*, 1'*R*)-**14**/(2*S*, 5*R*, 1'*S*)-**15**. Chromatography (SiO_2, cyclohexane/Et_2O/$CHCl_3$, 13:0.5:6.5) gave 0.246 g (0.57 mmol, 63 %) of (2*S*,5*R*,1'*R*)-**14** and 0.069 g (0.16 mmol, 18 %) of (2*S*,5*R*,1'*S*)-**15**. The mixture of 1'amino dioxolanones was purified by chromatography (SiO_2, *n*hexane/EtOAc, 2:1. Overall Yield (**14** + **15**) 81 %. IR (nujol, cm^{-1}): 3253, 2975,1794, 1698, 1483, 1366; MS *m/z* 431, 376, 315, 173, 156,112; Anal. Calcd. for $C_{23}H_{29}NO_5S$: C, 64.01; H, 6.77; N, 3.25. Found: C, 63.83; H, 6.64; N, 3.31. (2*S*, 5*R*, 1'*R*)-**14**: ^{1}H NMR ($CDCl_3$, 400 MHz δ 7.61-7.70 (d, 2 H, arom), 7.22-7.55 (m, 4 H), 6.90- 6.95 (m, 2 H), 5.56 (bd, 1 H), 5.49 (bd, 1 H, *J* = 9.5 Hz), 4.95 (bs, 1 H), 1.30 (s, 9 H, 3 Me), 0.82 (s, 9 H, 3 Me); ^{13}C NMR ($CDCl_3$)) relevant resonances at δ 172.0, 154.5, 139.7, 136.3, 128.6, 128.4, 127.0, 126.7, 125.9, 125.7, 111.4, 84.4, 80.5, 57.8, 35.6, 28.4, 23.6. (2*S*, 5*R*, 1'*S*)-**15**: ^{1}H NMR ($CDCl_3$, 400 MHz δ 7.78-7.82 (d, 2 H), 7.09 (d, 1 H), 7.0 (m, 1 H), 6.95 (m, 1 H), 5.65 (bd, 1 H, *J* = 10.0 Hz), 5.16 (bd, 1 H, *J* = 10.0 Hz), 4.62 (bs, 1 H), 1.20 (s, 9 H, 3 Me), 0.85 (s, 9 H, 3 Me); ^{13}C NMR ($CDCl_3$)) relevant resonances at δ 171.3, 151.0, 111.2, 35.4, 27.8, 23.7 23.6.

(2*R*, 3*R*)- and (2*R*, 3*S*)-3-(*tert*-Butoxycarbonylamino)-2-hydroxy-2-phenyl-3-(2-thienyl)propionic acid methyl esters (2*R*, 3*R*)-16 and (2*R*, 3*S*)-17: 0.120 g (0.278 mmol) of a 3.6:1 mixture of (2*S*, 5*R*, 1'*R*)-**14**/(2*S*, 5*R*, 1'*S*)-**15** gave a 3.6:1 mixture of (2*R*, 3*R*)-**16** and (2*R*, 3*S*)-**17** in (0.12, 0.264 mmol, 95 %). IR (nujol, cm^{-1}): 3450, 1720, 1495, 1251; MS *m/z* 377, 272, 261, 201, 156, 112; Anal. Calcd. for $C_{19}H_{23}NO_5S$: C, 60.46; H, 6.14; N, 3.71. Found C, 60.35; H, 6.15; N, 3.61. (2*R*, 3*R*)-**16**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.59-7.65 (m, 2 H), 7.20-7.38 (m, 3 H), 7.0-7.08 (m, 1 H), 6.7-6.8 (m, 2 H), 5.94 (d, 1 H, *J* = 10.0 Hz), 5.51 (d, 1 H, *J* = 10.0 Hz), 4.3 (bs, 1 H), 3.85 (s, 3 H), 1.42 (s, 9 H); ^{13}C NMR ($CDCl_3$) relevant resonances at δ 174.6, 154.8, 140.2, 138.1, 128.4, 126.4, 126.4, 125.4, 81.5, 80.3, 56.4, 54.0, 28.5. (2*R*, 3*S*)-17 ^{1}H NMR ($CDCl_3$, 400 MHz) relevant resonances at δ 7.75-7.82 (m, 2 H), 7.20-7.20-7.42 (m, 3 H), 6.9-7.0 (m, 1 H), 5.99 (d, 1 H, *J* = 10.0 Hz), 5.32 (d, 1 H, *J* = 10.0 Hz), 4.10 (bs, 1 H), 3.66 (s, 3 H), 1.22 (s, 9 H); ^{13}C NMR ($CDCl_3$) relevant resonances at δ 173.4, 155.1, 141.0, 137.9,126.6, 125.8, 81.3, 79.9, 56.0, 53.7, 28.3.

Synthesis of (2*S*,5*R*,1'*S*)- and (2*S*,5*R*,1'*R*)-2-(*tert*-Butyl)-5-(1'-*tert*-butoxycarbonylamino-1'-(2-thienyl)methyl)-5-carboxyethyl-1,3-dioxolan-4-ones [(2*S*,5*R*,1'*R*)-18 and (2*S*,5*R*,1'*S*)-19]. 0.20 g of pure dioxolanone **3** (0.92 mmol) and imine **5** (0.489 g, 0.23 mmol) LHMDS (3.0 eq) gave a 1.0:1.0 mixture of (2*S*, 5*R*, 1'*R*)-**18**/(2*S*, 5*R*, 1'*S*)-**19**. The reaction was quenched after 82 % (0.75 mmol) conversion. Chromatography (SiO_2, *n*hexane/EtOAc, 2:8) gave a 1:1 mixture of (2*S*,5*R*,1'*R*)-**18** and (2*S*,5*R*,1'*S*)-**19** (0.193 g , 0.467 mmol, 62 % on product conversion). (2*S*, 5*R*, 1'*R*)-**18** and (2*S*, 5*R*, 1'*S*)-**19**: IR (nujol, cm^{-1}): 3420, 2976,1799, 1719, 1484, 1395, 1159; MS *m/z* 413, 358, 295, 212, 157, 112, 84; Anal. Calcd. for $C_{19}H_{27}NO_7S$: C, 55.19; H, 6.58; N, 3.39. Found: C, 55.01; H, 6.50; N, 3.41. ^1H NMR ($CDCl_3$, 400 MHz, T = 55 °C) δ 8.0-8.9 (b, 1 H of **18** and 1 H of **19**), 6.95-7.35 (m, 3 H of **18** and 3 H of **19**), 5.70-5.85 (b, 1 H), 5.40-5.65 (b, 3 H), 4.65 (b, 1 H), 4.18-4.25 (b, 1 H), 3.00 (b, 2 H), 2.90-3.00 (m, 2 H), 1.45 (b, 9 H), 1.43 (b, 9 H), 0.89 (b, 9 H), 0.85 (b, 9 H); ^{13}C NMR ($CDCl_3$) relevant resonances at δ 173.5, 171.8, 155.1, 154.9, 140.1, 139.5, 127.8, 127.5, 126.9, 126.8, 126.3, 125.8, 110.8, 109.8, 83.5, 82.7, 81.9, 81.2, 54.1, 53.6, 39.7, 38.5, 34.6, 28.5, 28.4, 23.7, 23.6.

3-Hydroxy-5-oxo-2-thiophen-2-yl-pyrrolidine-3-carboxylic acid methyl ester (2*R*, 3*S*)-31 and (2*R*, 3*R*)-32. A slightly modified procedure for the methanolysis of (2*S*, 5*R*, 1'*S*)-**29** and (2*S*, 5*R*, 1'*R*)-**30** gave the methyl esters (2*R*, 3*S*)-**31** and (2*R*, 3*R*)-**32**. To a methanol solution of the dioxolanone was added 1.0 eq of a 1.0 M solution of MeONa in MeOH. The reaction was stirred at 20 °C for two hours, quenched with 0.1 N HCl, and extracted with ethyl acetate, dried and the solvent evaporated. Chromatography ethyl acetate/*n*-hexane 3:1 gave 90 and 92 %, respectively, of the esters **31** and **32**

(2*R*, 3*S*)-**31**: $[\alpha]^{20}_{D}$ + 50.0 (*c* 0.4, $CHCl_3$); IR (nujol, cm^{-1}): 3410, 2905,2610, 1712, 1260; MS *m/z* 241, 223, 167, 149, 112; Anal. Calcd. for $C_{10}H_{11}NO_4S$: C. 49.78; H, 4.60; N, 5.81. Found: C. 49.85; H, 4.70; N, 5.75; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 (m, 1 H), 7.04 (m, 2 H), 6.26 (s, 1 H), 5.33 (s, 1 H), 3.88 (s, 3 H), 3.12 (d, 1 H, *J* = 17.0 Hz), 2.92 (b, 1 H), 2.67 (d, 1 H, *J* = 17.0 Hz); ^{1}H NMR (CD_3COCD_3, 400 MHz) relevant resonances at δ 5.44 (s, 1 H), 4.56 (s, 1 H), 2.97 (d, 1 H, *J* = 17.0 Hz), 2.47 (b, 1 H); ^{13}C NMR ($CDCl_3$) δ 173.9, 172.7, 136.6, 127.4, 127.3, 127.2, 78.9, 62.2, 53.7, 42.5. (2*R*, 3*R*)-**32**: $[\alpha]^{20}_{D}$ - 49.0 (*c* 0.4, $CHCl_3$); IR (nujol, cm^{-1}): 3400, 2900-2600, 1705, 1257; MS *m/z* 241, 223, 167, 149, 112; Anal. Calcd. for $C_{10}H_{11}NO_4S$: C. 49.78; H, 4.60; N, 5.81. Found: C. 49.95; H, 4.67; N, 5.73; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27 (m, 1 H), 7.00 (m, 2 H), 6.14 (s, 1 H), 5.09 (s, 1 H), 3.96 (b, 1 H), 3.55 (s, 3 H, OMe), 3.05 (d, 1 H, *J* = 17.0 Hz), 2.73 (d, 1 H, *J* = 17.0 Hz); ^{13}C NMR ($CDCl_3$) δ 173.9, 172.7, 138.9, 127.5, 126.0, 125.8, 81.6, 65.3, 53.4, 41.0.