

Stereoselective Synthesis of the γ -Lactam Hydrolysate of the Thiopeptide Cyclothiazomycin

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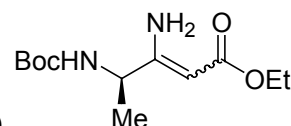
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Materials and Methods

Commercially available reagents were used as received without further purification; solvents were dried by standard procedures. Light petroleum refers to the fraction with b.p. 40-60 °C and ether refers to diethyl ether. Unless otherwise stated, reactions were performed under an atmosphere of dry nitrogen. Flash chromatography was carried out using Merck Kieselgel 60 H silica or Matrex silica 60. Analytical thin layer chromatography was carried out using aluminium-backed plates coated with Merck Kieselgel 60 GF₂₅₄ that were visualised under UV light (at 254 and/or 360 nm). Preparative thin layer chromatography was carried out using aluminium-backed plates coated with Merck Kieselgel 60 GF₂₅₄. Visualisation was achieved by UV light (at 254 and/or 360 nm) and/or potassium permanganate stain.

Fully characterised compounds were chromatographically homogeneous. Melting points were determined on a Kofler hot stage apparatus. Infra-red spectra were recorded in the range 4000-600 cm⁻¹ on a Perkin-Elmer 1600 series FT-IR spectrometer either as a KBr disk, nujol mull, in solution in dry dichloromethane or as a thin film between NaCl plates, as indicated. NMR spectra were recorded using a Bruker DPX 400 instrument operating at 400 MHz for ¹H spectra and 100 MHz for ¹³C spectra (internal standard TMS); *J* values were recorded in Hz and multiplicities were expressed by the usual conventions. Low-resolution mass spectra were determined using a Fisons VG Platform II Quadrupole instrument using atmospheric pressure chemical ionisation (APCI) or electron ionisation (EI), as stated. High-resolution mass spectra were obtained courtesy of the EPSRC Mass Spectrometry Service at University College of Wales, Swansea, UK using atmospheric pressure chemical ionization (APCI) or electron ionization (EI). Calculated accurate masses of parent compounds denote the mass of the ion

(mass of electron is 0.00055 Da) except where indicated. Microanalyses were recorded using a Perkin-Elmer 240C Elemental Analyzer in-house, or courtesy of Warick Analytical Services Ltd at University of Warwick Science Park, UK using an Exeter 440 Elemental Analyser. Chiral compounds were analysed using a AA-1000 Polarimeter apparatus from Optical Activity LTD., using the sodium D line and at the indicated temperature, and are given in $\text{deg cm}^3\text{g}^{-1}\text{dm}^{-1}$ for $[\alpha]$ and 10^{-2}gcm^{-3} for c . HPLC was carried out using a HP-1100 HPLC machine equipped with a variable wavelength UV detector and variable flow pump. Microwave experiments were carried out in a CEM Discover™ microwave synthesiser at the temperature and initial power stated.

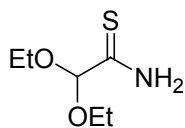


(R)-Ethyl 3-amino-4-(N-tert-butoxycarbonyl)aminopent-2-enoate (6)

A mixture of (*R*)-ethyl 4-(*N*-tert-butoxycarbonyl)amino-3-oxopentanoate (**9**)¹ (994 mg, 3.8 mmol) and ammonium acetate (1.47 g, 19.0 mmol) in ethanol (30 mL) was stirred at room temperature for 4 h and concentrated. The residue was partitioned between ethyl acetate (60 mL) and saturated aqueous sodium hydrogen carbonate solution (60 mL). The aqueous layer was further extracted with ethyl acetate (60 mL) and the organic layers were combined, washed sequentially with saturated aqueous sodium hydrogen carbonate solution (60 mL), and brine (60 mL), dried (Na_2SO_4), evaporated *in vacuo*, and purified by flash chromatography on silica, eluting with light petroleum-ethyl acetate (7:3), to give the *title compound*² (687 mg, 70%) as a colourless oil: $[\alpha]_{\text{D}}^{25} +17.0$ (c 2.50, CHCl_3); IR (KBr) 3458, 3365, 3320, 2983, 2937, 1683, 1612, 1522, 1365, 1310, 1274, 1162, 1042, 861, 792 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.75 (1 H, br s, $\text{NH}(\text{Boc})$), 4.54 (1 H, s, $=\text{CH}$), 4.13 (1 H, q, $J = 7.0$, CHMe), 4.04 (2 H, q, $J = 7.1$, OCH_2Me), 1.37 (9 H, s, CMe_3), 1.28 (3 H, d, $J = 7.0$, CHMe), 1.19 (3 H, t, $J = 7.1$, OCH_2Me); ^{13}C NMR (100 MHz, CDCl_3) δ 170.5 (C), 164.7 (C), 155.6 (C), 81.0 (CH), 80.3 (C), 58.7 (CH_2), 49.7 (CH), 28.3 (Me), 19.6 (Me), 14.5 (Me); MS (APCI) m/z (relative intensity) 259 (MH^+ , 100%), 203 (55), 160 (23); HRMS calcd for $\text{C}_{12}\text{H}_{23}\text{N}_2\text{O}_4$ (MH) 259.1652, found 259.1648.

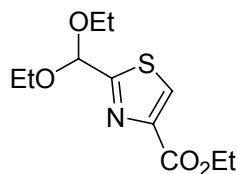
¹ (a) Honoré, T.; Hjeds, H.; Krogsgaard-Larsen, P.; Christiansen, T. R. *Eur. J. Med. Chem.* **1978**, *13*, 429. (b) Kim, H.-O.; Olsen, R. K.; Choi, O.-S. *J. Org. Chem.* **1987**, *52*, 4531.

² HPLC: ee = 92%; Chiralpak AD, hexane-propan-2-ol (95:5), $\lambda_{\text{max}} = 273$ nm, 1.0 mL min^{-1} , $R_{\text{T}} = 15.1$ min (*S*-isomer has $R_{\text{T}} = 18.0$ min).



2,2-Diethoxythioacetamide

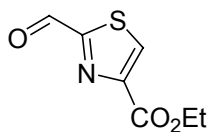
According to a modified literature procedure,³ phosphorus pentasulphide (15.0 g, 34.0 mmol) was added to a solution of 2,2-diethoxyacetamide (10.0 g, 68.0 mmol) in dichloromethane (125 mL). The mixture was stirred for 2 h at 0 °C, the resulting dark purple mixture was filtered through Celite®, washed with dichloromethane (2 x 10 mL) and concentrated *in vacuo*. Purification by flash chromatography on silica, eluting with light petroleum-ethyl acetate (1:1), followed by recrystallisation from light petroleum-ether (7:3) gave the *title compound* (2.5 g, 23%) as a brown solid, mp 93-94 °C (from light petroleum-ether) (lit.³ mp 81-82 °C): IR (nujol) 3310, 3180, 1645, 1258, 1142, 1102, 1057, 981, 886, 836, 715 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.95 (1 H, bs, NH), 7.90 (1 H, bs, NH), 4.98, (1 H, s, CH), 3.66 (2 H, q, *J* = 7.1, CH₂Me), 3.59 (2 H, q, *J* = 7.1, CH₂Me), 1.19 (6 H, app t, *J* = 7.1, CH₂Me); ¹³C NMR (100 MHz, CDCl₃) δ 202.2 (C), 103.0 (CH), 62.9 (CH₂), 15.1 (Me); MS (APCI) *m/z* (relative intensity) 164 (MH⁺, 7%), 118 (100), 90 (14); Anal. Calcd for C₆H₁₃NO₂S: C, 44.1; H, 8.0; N, 8.6. Found: C, 44.1; H, 8.0; N, 8.6.



Ethyl 2-(diethoxymethyl)thiazole-4-carboxylate

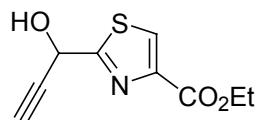
Ethyl bromopyruvate (2.2 mL, 15.4 mmol) was added to a mixture of 2,2-diethoxythioacetamide (2.3 g, 14.0 mmol) and 4Å molecular sieves (4 g) in ethanol (30 mL) and the mixture heated at reflux for 1 h. The solution was cooled, filtered through Celite® and evaporated *in vacuo*. Purification by flash chromatography on silica, eluting with light petroleum-ethyl acetate (3:1), gave the *title compound*³ (2.5 g, 68%) as a pale yellow oil: IR (film) 3111, 2980, 2936, 2885, 1732, 1489, 1368, 1313, 1241, 1206, 1093, 1062, 1020, 760 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.14 (1 H, s, 5-H), 5.64 (1 H, s, CH), 4.36 (2 H, q, *J* = 7.1, CH₂Me), 3.69 (2 H, q, *J* = 7.1, OCH₂Me), 3.58 (2 H, q, *J* = 7.1, OCH₂Me), 1.33 (3 H, t, *J* = 7.1, CH₂Me), 1.19 (6 H, app t, *J* = 7.1, OCH₂Me); ¹³C NMR (100 MHz, CDCl₃) δ 170.1 (C), 161.4 (C), 147.1 (C), 128.5 (CH), 98.8 (CH), 62.8 (CH₂), 61.5 (CH₂), 15.1 (Me), 14.4 (Me); MS (APCI) *m/z* (relative intensity) 261 (M⁺, 67%), 215 (100); HRMS calcd for C₁₁H₂₁N₂O₄S (MNH₄) 277.1222, found 277.1218.

³ Inami, K.; Shiba, T. *Bull Chem. Soc. Jpn.* **1985**, 58, 352.



Ethyl 2-formylthiazole-4-carboxylate

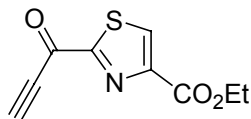
A solution of ethyl 2-(diethoxymethyl)thiazole-4-carboxylate (2.11 g, 8.14 mmol) was heated at reflux in acetone (175 mL) with aqueous 2 N hydrochloric acid (17 mL) for 1 h, cooled, evaporated *in vacuo* and extracted with chloroform (100 mL). The aqueous layer was further extracted with chloroform (2 x 70 mL) and the combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. Purification by flash chromatography on silica, eluting with light petroleum-ethyl acetate (3:2), gave the *title compound* (1.39 g, 92%) as a pale yellow solid, mp 64.3-65.6 °C (from light petroleum) (lit.³ mp 67-68 °C). IR (nujol) 3103, 1723, 1706, 1324, 1214, 1100, 1022, 946, 879, 767 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 10.01 (1 H, d, *J* = 1.2, CHO), 8.52 (1 H, d, *J* = 1.2, 5-H), 4.42 (2 H, q, *J* = 7.2, CH₂Me), 1.37 (3 H, t, *J* = 7.2, CH₂Me); ¹³C NMR (100 MHz, CDCl₃) δ 183.7 (CH), 166.1 (C), 160.6 (C), 149.5 (C), 133.1 (CH), 62.1 (CH₂), 14.3 (Me); MS (APCI) *m/z* (relative intensity) 186 (MH⁺, 100%), 171 (40), 158 (12), 140 (24); HRMS calcd for C₇H₈NO₃S (MH) 186.0225, found 186.0219. Anal. Calcd for C₇H₇NO₃S: C, 45.5; H, 3.8; N, 7.6. Found: C, 45.5; H, 3.8; N, 7.5.



Ethyl 2-(1-hydroxyprop-2-ynyl)thiazole-4-carboxylate

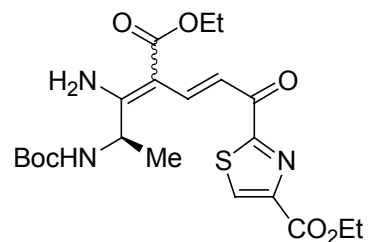
A solution of ethynyl magnesiumbromide in tetrahydrofuran (0.5 M; 14.1 mL, 7.07 mmol) was added dropwise over 5 min to a solution of ethyl 2-formylthiazole-4-carboxylate (1.31 g, 7.07 mmol) in tetrahydrofuran (50 mL) at 0 °C and the mixture was stirred for 30 min at this temperature. A further aliquot of ethynyl magnesiumbromide in tetrahydrofuran (0.5 M; 2.8 mL, 1.41 mmol) was added and the solution stirred for a further 20 min. Saturated aqueous ammonium chloride solution (30 mL) was added and the mixture was concentrated *in vacuo* and partitioned between water (30 mL) and chloroform (60 mL). The aqueous layer was further extracted with chloroform (2 x 30 mL) and the combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. Purification by flash chromatography on silica, eluting with light petroleum-ethyl acetate (2:3), gave the *title compound* (1.09 g, 73%) as a brown oil: IR (film) 3290, 3122, 2981, 2121, 1714, 1486, 1371, 1221, 1174, 1100, 1020, 958, 922, 878, 758 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.11 (1 H, s, 5-H), 5.70, (1 H, m, CHOH), 5.14, (1 H, bm, OH), 4.30 (2 H, q, *J* = 7.2, CH₂Me), 2.69 (1 H, d, *J* = 1.9, CCH), 1.29 (3 H, t, *J* = 7.2, CH₂Me); ¹³C NMR (100 MHz, CDCl₃) δ 172.3 (C), 161.3 (C), 146.6 (C), 128.6 (CH), 81.3 (C), 75.5 (CH), 61.7 (CH₂), 61.3 (CH), 14.3 (Me); MS (EI) *m/z* (relative intensity) 211 (M⁺, 20%), 182 (74),

166 (58), 158 (22), 139 (51), 121 (26), 112 (82), 84 (34), 55 (100), 45 (58); HRMS calcd for C₉H₁₀NO₃S (MH) 212.0381, found 212.0380.



Ethyl 2-(propynoyl)thiazole-4-carboxylate (10)

Activated manganese(IV) oxide (69 mg, 0.71 mmol) was added to a solution of ethyl 2-(1-hydroxyprop-2-ynyl)thiazole-4-carboxylate (28 mg, 0.14 mmol) in dichloromethane (2 mL). After stirring for 10 min at room temperature, a further aliquot of activated manganese(IV) oxide (69 mg, 0.71 mmol) was added and the mixture was stirred for a further 10 min. The resulting mixture was filtered through Celite[®], washed with dichloromethane (1 mL) and evaporated without heat under a nitrogen atmosphere to give the *title compound* (28 mg, 100%) as a pale yellow solid that was used without further purification, mp 101-102 °C (from dichloromethane): IR (CH₂Cl₂) 3054, 2984, 2103, 1732, 1650, 1447, 1367, 1334, 1222, 1104, 1020, 969, 932 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.44 (1 H, s, 5-H), 4.40 (2 H, q, *J* 7.1 CH₂Me), 3.66 (1 H, s, CCH), 1.40 (3 H, t, *J* 7.1, CH₂Me); ¹³C NMR (100 MHz, CDCl₃) δ 169.5 (C), 166.5 (C), 161.0 (C), 149.0 (C), 134.0 (CH), 85.4 (CH), 79.3 (C), 62.5 (CH₂), 14.7 (Me); MS (APCI) *m/z* (relative intensity) 210 (MH⁺, 100%); HRMS calcd for C₉H₈NO₃S (MH) 210.0225, found 210.0224.

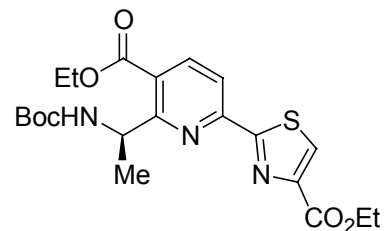


(*R,4E*)-Ethyl 2-[5-amino-6-(*N*-tert-butoxycarbonyl)amino-4-(ethoxycarbonyl)hepta-2,4-dienoyl]-thiazole-4-carboxylate (11)

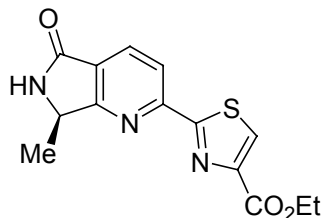
To a solution of ethyl 2-(propynoyl)thiazole-4-carboxylate (**10**) (29 mg, 0.14 mmol) in ethanol (5 mL) was added (*R*)-ethyl 3-amino-4-(*N*-tert-butoxycarbonyl)aminopent-2-enoate (**6**) (41 mg, 0.16 mmol). The reaction mixture was stirred at 50 °C for 10 min and concentrated *in vacuo*. Purification by flash chromatography on silica, eluting with light petroleum-ethyl acetate (1:1), gave the *title compound* (53 mg, 82%) as a yellow solid, mp 176-178 °C (from methanol): [α]_D²⁵ -153.3 (*c* 1.25, CHCl₃); IR (KBr) 3424, 2976, 1720, 1654, 1559, 1509, 1458, 1368, 1328, 1278, 1222, 1022 cm⁻¹; ¹H NMR (400 MHz, *d*₆-DMSO) δ 9.77 (1 H, br s, *N*HH), 8.82 (1 H, s, SCH), 8.25 (1 H, d, *J* = 15.0, 3-H), 8.18 (1 H, br s, *N*HH), 7.59 (1 H, d, *J* = 15.0, 2-H), 7.38 (1 H, d, *J* = 5.6, *N*H*Boc*), 4.96 (1 H, m, *CH*Me), 4.34 (2 H, q, *J* = 7.1, OCH₂Me), 4.25 (2 H, q, *J* = 7.1, OCH₂Me), 1.40 (3 H, t, *J* = 7.1, OCH₂Me), 1.39 (9 H, s, CMe₃), 1.33 (3 H, t, *J* = 7.1, OCH₂Me), 1.33 (3 H, d, *J* = 6.7, *CH*Me); ¹³C NMR (100 MHz, *d*₆-DMSO) δ 177.6 (C), 172.0 (C), 167.9 (C), 166.4 (C), 158.3 (C), 152.4 (C), 144.9 (C), 139.6 (CH), 131.8 (CH),

109.6 (CH), 90.3 (C), 76.6 (C), 58.7 (CH₂), 57.5 (CH₂), 44.9 (CH), 25.8 (Me), 17.5 (Me), 11.8 (Me), 11.7 (Me); MS (APCI) m/z (relative intensity) 468 (MH⁺, 100%); HRMS calcd for C₂₁H₃₀N₃O₇S (MH) 468.1799, found 468.1796.

(R)-Ethyl 6-[4-(ethoxycarbonyl)thiazol-2-yl]-2-[1-(*N*-tert-butoxycarbonyl)aminoethyl]pyridine-3-carboxylate (8a)



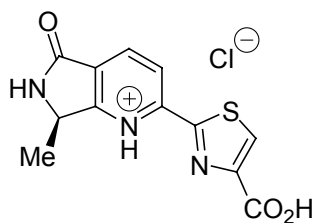
A solution of (*R*)-ethyl 4-(*N*-tert-butoxycarbonyl)amino-3-oxopentanoate (**9**) (107 mg, 0.41 mmol) and ammonium acetate (158 mg, 2.0 mmol) in ethanol (10 mL) was stirred at room temperature for 4 h then a solution of ethyl 2-(propynoyl)thiazole-4-carboxylate (**10**) (69 mg, 0.33 mmol) in ethanol (5 mL) was added. The reaction mixture was stirred at room temperature for 1 h and cooled to 0 °C. *N*-Iodosuccinimide (92 mg, 0.41 mmol) was added portionwise, the mixture was stirred at 0 °C for 15 min and then concentrated. The residue was partitioned between ethyl acetate (15 mL) and saturated aqueous sodium hydrogen carbonate solution (15 mL). The aqueous layer was further extracted with ethyl acetate (10 mL) and the organic layers were combined, washed sequentially with saturated aqueous sodium hydrogen carbonate solution (10 mL), and brine (10 mL), dried (Na₂SO₄), evaporated *in vacuo*, and purified by flash chromatography on silica, eluting with light petroleum-ethyl acetate (7:3), to give the *title compound*⁴ (82 mg, 55%) as a pale yellow oil: $[\alpha]_D^{21} +39.0$ (*c* 1.06, CHCl₃); IR (KBr) 3361, 2983, 2933, 1738, 1723, 1689, 1582, 1528, 1449, 1366, 1336, 1270, 1208, 1174, 1047, 1029, 855, 806, 756 cm⁻¹; ¹H NMR (400 MHz, *d*₆-acetone) δ 8.46 (1 H, s, SCH), 8.31 (1 H, d, *J* = 8.1, PyH), 8.08 (1 H, d, *J* = 8.1, PyH), 6.26 (1 H, d, *J* = 8.2, NH), 5.58 (1 H, m, CHMe), 4.31 (2 H, q, *J* = 7.2, OCH₂Me), 4.26 (2 H, q, *J* = 7.1, OCH₂Me), 1.37 (3 H, d, *J* = 6.8, CHMe), 1.30 (3 H, t, *J* = 7.1, OCH₂Me), 1.26 (3 H, t, *J* = 7.2, OCH₂Me), 1.24 (9 H, s, CMe₃); ¹³C NMR (100 MHz, CDCl₃) δ 168.7 (C), 165.2 (C), 162.9 (C), 161.3 (C), 155.2 (C), 151.7 (C), 148.7 (C), 140.3 (CH), 130.3 (CH), 125.2 (C), 118.1 (CH), 79.3 (C), 61.9 (CH₂), 61.7 (CH₂), 48.7 (CH), 28.4 (Me), 22.9 (Me), 14.4 (Me), 14.2 (Me); MS (APCI) m/z (relative intensity) 450 (MH⁺, 100%), 394 (23), 350 (9); HRMS calcd for C₂₁H₂₈N₃O₆S (MH) 450.1693, found 450.1691.



⁴ HPLC: ee = 96%; Chiralpak AD, hexane–propan-2-ol (95:5), λ_{max} = 311 nm, 1.0 mL min⁻¹, *R*_T = 14.8 min (*S*-isomer has *R*_T = 12.4 min).

(R)-2-[4-(Ethoxycarbonyl)thiazol-2-yl]-7-methyl-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine (12)

A solution of (R)-ethyl 6-[4-(ethoxycarbonyl)thiazol-2-yl]-2-[1-(*N*-tert-butoxycarbonyl)aminoethyl]-pyridine-3-carboxylate (**8a**) (93 mg, 0.21 mmol) in aqueous hydrochloric acid (6 N; 10 mL) was stirred at room temperature for 6 h, neutralised to pH 7 with aqueous sodium hydroxide (5 N) and extracted with dichloromethane (3 x 20 mL). The organic layers were combined, dried (Na₂SO₄) and evaporated *in vacuo*. Purification by flash chromatography on silica, eluting with ethyl acetate, gave the *title compound*⁵ (56 mg, 89%) as a colorless solid, mp 236-238 °C (from methanol): [α]_D²⁴ +48.1 (*c* 0.54, CHCl₃); IR (KBr) 3200, 2926, 1700, 1600, 1412, 1247, 1098, 1022, 805 cm⁻¹; ¹H NMR (400 MHz, *d*₆-DMSO) δ 9.14 (1 H, s, NH), 8.79 (1 H, s, SCH), 8.33 (1 H, d, *J* = 8.0, PyH), 8.30 (1 H, d, *J* = 8.0, PyH), 4.83 (1 H, q, *J* = 6.8, CHMe), 4.42 (2 H, q, *J* = 7.1, OCH₂Me), 1.52 (3 H, d, *J* = 6.8, CHMe), 1.41 (3 H, t, *J* = 7.1, OCH₂Me); ¹³C NMR (100 MHz, *d*₆-DMSO) δ 168.9 (C), 168.5 (C), 166.8 (C), 161.0 (C), 152.5 (C), 148.0 (C), 133.9 (CH), 132.6 (CH), 127.3 (C), 119.7 (CH), 61.5 (CH₂), 53.5 (CH), 19.0 (Me), 14.7 (Me); MS (APCI) *m/z* (relative intensity) 304 (MH⁺, 100%); HRMS calcd for C₁₄H₁₄N₃O₃S (MH) 304.0750, found 304.0750.

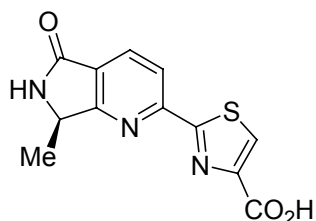


(R)-2-(4-Carboxythiazol-2-yl)-7-methyl-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridinium chloride (13)

Lithium hydroxide monohydrate (25 mg, 0.60 mmol) was added to a solution of (R)-2-[4-(ethoxycarbonyl)thiazol-2-yl]-7-methyl-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine (**12**) (92 mg, 0.30 mmol) in tetrahydrofuran-water (1:1) (30 mL) at room temperature. The solution was stirred for 3 h, evaporated *in vacuo*, and partitioned between water (30 mL) and dichloromethane (30 mL). The aqueous layer was separated, acidified to pH 6 with aqueous hydrochloric acid (3 N) and concentrated. The precipitate was filtered, washed sequentially with water (2 mL) and acetone (5 mL), and dried in a vacuum dessicator for 24 h to give the *title compound* (72 mg, 77%) as a colorless solid that was used without further purification, mp 287 °C dec (from aqueous methanol): [α]_D³⁰ +30.8 (*c* 0.26, MeOH); UV λ_{max} (methanol) 234 nm (ϵ 12400), 314 nm (ϵ 17000); IR (KBr) 3234, 2925, 2517, 1890, 1716,

⁵ HPLC: ee = 94%; Chiralcel OD, hexane–propan-2-ol (90:10), λ_{max} = 314 nm, 1.0 mL min⁻¹, *R*_T = 52.6 min (*S*-isomer has *R*_T = 34.8 min).

1648, 1601, 1412, 1364, 1221, 1099, 1013, 744, 725 cm^{-1} ; ^1H NMR (400 MHz, d_6 -DMSO) δ 9.14 (1 H, s, NH), 8.69 (1 H, s, SCH), 8.34 (1 H, d, $J = 8.0$, PyH), 8.31 (1 H, d, $J = 8.0$, PyH), 4.84 (1 H, q, $J = 6.8$, CHMe), 1.52 (3 H, d, $J = 6.8$, CHMe); ^{13}C NMR (100 MHz, d_6 -DMSO) δ 168.4 (C), 167.6 (C), 166.3 (C), 161.9 (C), 152.2 (C), 148.7 (C), 133.3 (CH), 131.6 (CH), 126.7 (C), 119.2 (CH), 53.0 (CH), 18.5 (Me); MS (ES) m/z (relative intensity) 298 (M - HCl + Na^+ , 100%), 276 (M - HCl + H^+ , 53); HRMS calcd for $\text{C}_{12}\text{H}_{10}\text{N}_3\text{O}_3\text{S}$ (M - HCl + H) 276.0437, found 276.0441.



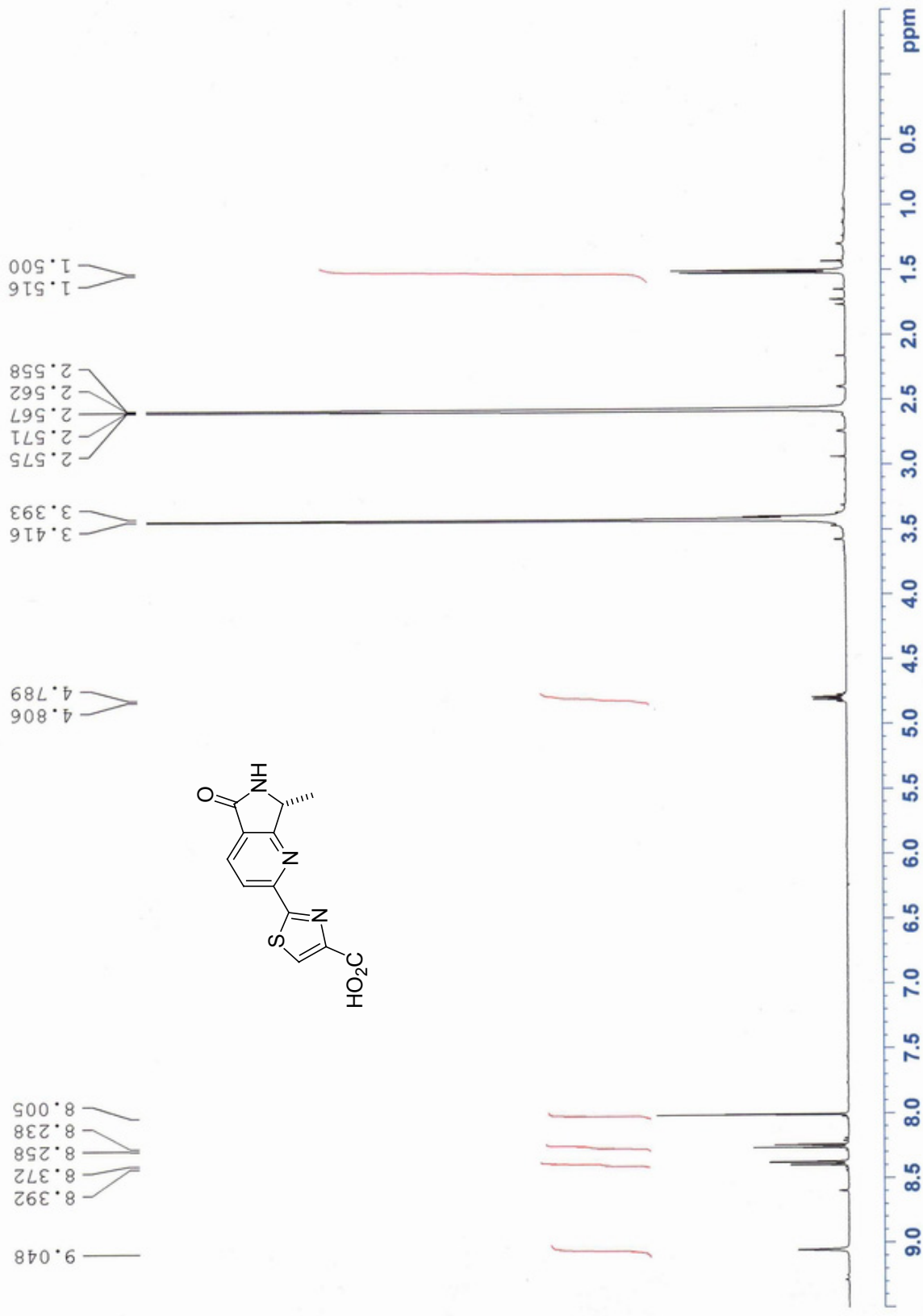
(R)-2-(4-Carboxythiazol-2-yl)-7-methyl-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine (2)

To a stirred solution of (R)-2-(4-carboxythiazol-2-yl)-7-methyl-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridinium chloride (**13**) (25 mg, 0.08 mmol) in dry methanol (50 mL) was added dry polymer-bound 4-(N-benzyl-N-methylamino)pyridine (32 mg, 0.08 mmol) and powdered 4Å molecular sieves (2 g). The reaction mixture was stirred at room temperature for 18 h, filtered through Celite[®], washed with methanol (2 x 20 mL) and concentrated *in vacuo*. Recrystallisation from methanol gave the *title compound*^{6,7} (18 mg, 80%) as a colorless solid, mp 185 °C dec (from methanol): $[\alpha]_{\text{D}}^{28} +22.7$ (c 0.12, MeOH); UV λ_{max} (methanol) 230 nm (ϵ 12200), 321 nm (ϵ 14400); IR (KBr) 3385, 3227, 2925, 1701, 1601, 1485, 1413, 1372, 1289, 1017, 858, 787, 756, 724 cm^{-1} ; ^1H NMR (400 MHz, d_6 -DMSO) δ 9.05 (1 H, s, NH), 8.38 (1 H, d, $J = 8.0$, PyH), 8.25 (1 H, d, $J = 8.0$, PyH), 8.01 (1 H, s, SCH), 4.80 (1 H, q, $J = 6.6$, CHMe), 1.51 (3 H, d, $J = 6.6$, CHMe); ^{13}C NMR (100 MHz, d_6 -DMSO) δ 168.6 (C), 167.1 (C), 165.9 (C), 164.6 (C), 160.4 (C), 153.7 (C), 133.3 (CH), 126.4 (C), 125.1 (CH), 119.7 (CH), 53.5 (CH), 19.1 (Me); MS (ES) m/z (relative intensity) 320 (M - H + 2Na^+ , 100%), 298 (M + Na^+ , 18), 232 (32), 109 (28); HRMS calcd for $\text{C}_{12}\text{H}_8\text{N}_3\text{O}_3\text{S}$ (M - H) 274.0292, found 274.0290.

⁶ HPLC: ee = 88%; Chiralpak OD-R, water–acetonitrile (95:5), $\lambda_{\text{max}} = 321$ nm, 0.5 mL min^{-1} , $R_{\text{T}} = 18.9$ min (*S*-isomer has $R_{\text{T}} = 15.0$ min).

⁷ Literature reported data (ref 6 and 20 in article): FAB mass, positive 276 (M+H)⁺, negative 274 (M-H)⁻; ^1H -NMR (δ ppm DMSO- d_6) 1.45 (3H, d), 4.74 (1H, q), 8.01 (1H, s), 8.18 (1H, d, $J = 8$ Hz), 8.38 (1H, d, $J = 8$ Hz), 9.00 (1H, s, D₂O exchangeable); ^{13}C -NMR 168.2, 166.5, 165.6, 164.3, 159.8, 153.2, 132.7, 126.9, 124.6, 119.3, 53.0, 18.6; UV λ_{max} (methanol) 230 nm (ϵ 12200), 321 nm (ϵ 14400).

¹H NMR spectrum (400 MHz, d₆-DMSO) of γ-lactam **2**



^{13}C NMR spectrum (100 MHz, d_6 -DMSO) of γ -lactam **2**

