Supporting Information

Simple and Efficient Synthesis of (+)-Methyl 7-Benzoylpederate, a Key Intermediate toward the mycalamides

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Compound 8.

To a stirring solution of **7** (1.194 g, 6.45 mmol) in CH_2Cl_2 (13 mL) at -78 °C was slowly added Bu_2BOTf (12.0 mL, 1 M in CH_2Cl_2, 12.0 mmol), followed after 10 min by the dropwise addition of Et_3N (2.20 mL, 15.8 mmol). The solution was stirred for 1 h at -78 °C and for 100 min at 0 °C, recooled to -78 °C, and a -78 °C solution of freshly distilled acetaldehyde (3.6 mL, 64.4 mmol) in CH_2Cl_2 (3.6 mL) was added slowly. After stirring for 2 h at -78 °C and for 90 min at 0 °C, 1.0 M pH 6.86 phosphate buffer (40 mL) and MeOH (40 mL) were added, and the resulting mixture was stirred vigorously in an ice bath as 30% H_2O_2 (20 mL) was added dropwise. After 30 min at ~ 10 - 15 °C, the solvent was removed in vacuo and the residue was partitioned between saturated $NaHCO_3$ and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with saturated $NaHCO_3$, dried ($MgSO_4$), and evaporated. The oily residue was chromatographed [53 g Mallinckrodt silica gel, 100-200 mesh, Type 60 Å Special; 1:4 to 2:5 EtOAc/hexane] giving the starting material **7** (23.7 mg, 2%) followed by aldol adduct **8** (1.350 g, 91%) as a colourless oil. ^{1}H NMR analysis of **8** indicated a diastereoisomer ratio of 98:2: $[\alpha]^{28}_D$ +75.7 (c 1.05, $CHCl_3$); IR (film) 3505 (br), 1780, 1696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, 3H, J = 6.8 Hz), 0.91 (d, 3H, J = 6.8 Hz), 1.17 (d, 3H, J = 6.3 Hz), 1.24 (d, 3H, J = 6.8 Hz), 2.33 (qqd, 1H, J = 6.8, 6.8, 3.9 Hz), 2.98 (d, 1H, J = 2.4 Hz), 3.73 (qd, 1H, J = 7.1, 2.7 Hz), 4.10-4.18 (m, 1H), 4.20 (dd, 1H J = 9.2, 3.4 Hz), 4.28 (t like, 1H, J = 8.5 Hz), 4.42-4.50 (m, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 10.7, 14.7, 17.8, 19.5, 28.3, 43.1, 58.2, 63.3, 67.3, 153.6, 177.6; HRMS m/z for $C_{11}H_{20}NO_4$ (MH^+) calcd 230.1392, found 230.1388. Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.74; H, 8.42; N, 6.05.

Compound 6.

To a stirring solution of **8** (3.198 g, 14.0 mmol) in anhydrous methanol (30 mL) at 0 °C was added sodium methoxide (0.879 g, 16.3 mmol) in one lot, and the resulting solution was stirred for 25

min at 0 °C. Following neutralisation upon addition of Muromac 50W-X8 (H) 100-200 mesh ion exchange resin, the mixture was filtered and the filtrate concentrated in vacuo (pressure ~ 90 mmHg; rt). Vacuum distillation of the condensate gave **6** (1.294 g, 70%) as a colourless oil. ^{1}H NMR analysis of **6** indicated a diastereoisomer ratio of 98:2: bp 62 °C /10 mmHg (Lit.,[17] 75 °C/15 mmHg); $[\alpha]^{29}_D$ +11.8 (c 1.66, MeOH) [lit.,[17] $[\alpha]^{20}_D$ +14.3 (c 5, MeOH)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (d, 3H, J = 6.4 Hz), 1.18 (d, 3H, J = 6.8 Hz), 2.51 (qd, 1H, J = 7.2, 4.0 Hz), 2.56 (br s, 1H), 3.70 (s, 3H), 4.02-4.10 (m, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 11.0, 19.7, 45.4, 51.7, 68.0, 176.3.

Compound 9.

To a stirring solution of diisopropylamine (6.64 mL, 47.4 mmol) in THF (22 mL) at 0 °C was slowly added n-BuLi (29.9 mL, 1.53 M in hexane, 45.8 mmol). After stirring for 30 min at the same temperature, the solution was cooled to -78 °C and t-butyl acetate (6.34 mL, 47.1 mmol) was added dropwise to the mixture. After stirring for a further 75 min, a solution of **6** (1.040 g, 7.87 mmol) in THF (3.5 mL) was added dropwise at -78 °C and the resulting solution was stirred for 2.5 h, then for 50 min at ca. -15 °C. Following cooling to -78 °C and stirring for 30 mins, the solution was quenched with saturated NH_4Cl, and extracted with EtOAc. The combined organic layers were washed with aqueous NH_4Cl, saturated $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated. Purification of the residue by chromatography (65 g silica gel, 6-12% EtOAc/hexane) gave an inseparable 10:1 mixture of β-keto ester **9** and its tautomer (1.601 g, 94%) as a colourless oil: $[\alpha]^{28}_D$ -7.3 (c 1.15, $CHCl_3$); IR (film) 3458 (br), 1732, 1709, 1153 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$; underlined values refer to distinct peaks assignable to its tautomer) δ 1.12 (d, 3H, J = 7.3 Hz), 1.14 (d, 3H, J = 6.4 Hz), 1.43 (s, 9H), <u>1.46</u> (s, 9H), 2.57-2.80 (m, 2H), 3.41 and 3.44 (AB quartet, 2H, J = 15.6 Hz), 4.07-4.18 (m, 1H), <u>4.90</u> (s, 1H), <u>12.4</u> (br s, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 9.9, <u>12.1</u>, 19.9, <u>20.5</u>, 27.9, <u>28.2</u>, <u>46.1</u>, 49.9, 51.8, 67.3, <u>69.2</u>, <u>81.0</u>, 82.1, <u>90.7</u>, 166.5, <u>179.4</u>, 207.7; HRMS m/z for $C_{11}H_{20}O_4Na$ (MNa^+) calcd 239.1259, found 239.1219.

Compound 5.

To a stirring solution of a 10:1 mixture of β-keto ester **9** and its tautomer (182 mg, 0.84 mmol) in CH_2Cl_2 (5 mL) at ca. -40 °C were added boron trifluoride etherate (0.53 mL, 4.21 mmol) and 1,2-ethanedithiol (0.212 mL, 2.53 mmol). The solution was allowed to warm slowly to room temperature and stirred for ca. 120 h. Chromatography of the orange-coloured solution (46 g silica gel, 1:19 - 2:3 EtOAc/hexane) yielded a 17:1 mixture of **5** and its C3-epimer (0.164 g, 90%) as a morphous white solid. Slow crystallisation from EtOAc/hexane afforded pure **5** as colourless prisms: mp 77-78 °C; $[\alpha]^{27}_D$ +106.7 (c 1.10, $CHCl_3$); IR (film) 1723, 1236 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (d, 3H, J = 7.3 Hz), 1.37 (d, 3H, J = 6.3 Hz), 2.16 (qdd, 1H, J = 7.1, 2.7, 1.0 Hz), 3.07 (d [B of AB], 1H, J = 18.5 Hz), 3.11 (dd [A of AB], 1H, J = 18.5, 1.0 Hz), 3.24-3.44

(m, 4H), 4.88 (qd, 1H, J = 6.5, 2.7 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 11.3, 18.8, 39.4 (2x), 43.5, 44.0, 68.0, 78.4, 168.0; HRMS m/z for $C_9H_{14}O_2S_2Na$ (MNa^+) calcd 241.0333, found 241.0332. Anal. Calcd for $C_9H_{14}O_2S_2$: C, 49.51; H, 6.46; S, 29.37. Found: C, 49.75; H, 6.52; S, 29.33.

Compound 10a.

To a -78 °C cooled solution of LDA, prepared from diisopropylamine (0.55 mL, 3.95 mmol) and nBuLi (2.50 mL, 1.53 M in hexane, 3.83 mmol) in THF (8 mL) at -78 °C, was slowly added methyl O-(2-methoxy-2-propyl)-glycolate (0.62 mL, 3.96 mmol). After 1 h at -78 °C, HMPA (1.00 mL, 5.75 mmol) was added and the solution stirred for 15 min, followed by the slow addition of zinc chloride (3.96 mL, 1.00 M in ether, 3.96 mmol), and a further 75 min stirring at this same temperature. A solution of **5** (76 mg, 0.35 mmol) in THF (2 mL) was added dropwise and the solution was stirred for 2 h at -78 °C followed by 17 h at ca. -40 °C. The mixture was quenched with saturated NH_4Cl and extracted with Et_2O, and the combined organic layers were washed with saturated NH_4Cl, aqueous $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated to leave a residue (0.578 g) which was employed in the subsequent step without purification. To a solution of the above residue in CH_2Cl_2/MeOH (1:1v/v; 8 mL) at room temperature were added trimethyl orthoformate (1.60 mL, 14.6 mmol) and 10-camphorsulfonic acid monohydrate (112 mg, 0.45 mmol). After stirring for 2 h, the deep purple-coloured solution was poured into water and extracted with Et_2O, and the combined organic layers were washed with aqueous $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated. Chromatography of the oily residue (50 g silica gel, 1:4-1:1 EtOAc/hexane) resulted in the elution of starting lactone **5** (5.7 mg, 8%), followed by desired product **10a** (91.5 mg, 82% for 2 steps) as a pale yellow oil: $[\alpha]^{28}_D$ +102.8 (c 1.04, $CHCl_3$); IR (film) 3448 (br), 1741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, 3H, J = 6.8 Hz), 1.16 (d, 3H, J = 6.8 Hz), 1.65 (br q, 1H, J = 6.8 Hz, 2.23 (dd [B of AB], 1H, J = 14.6, 1.0 Hz), 2.29 (d [A of AB], 1H, J = 14.5 Hz), 2.85 (d, 1H, J = 5.9 Hz), 3.06-3.34 (m, 4H), 3.29 (s, 3H), 3.78 (s, 3H), 4.25 (d, 1H, J = 5.4 Hz), 4.34 (qd, 1H, J = 6.6, 1.8 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 9.7, 18.6, 37.3, 37.8, 39.3, 45.7, 48.1, 52.5, 68.3, 69.3, 72.6, 98.9, 172.1; HRMS m/z for $C_{13}H_{22}O_5S_2Na$ (MNa^+) calcd 345.0806, found 345.0805. Anal. Calcd for $C_{13}H_{22}O_5S_2$: C, 48.42; H, 6.88. Found: C, 48.15; H, 6.89.

Compound 10b.

To a solution of **10a** (208 mg, 0.64 mmol) in pyridine (7 mL) at 0 °C were added benzoyl chloride (0.50 mL, 4.31 mmol) and a few crystals of DMAP, and the resulting mixture was stirred at room temperature for 13 h. The reaction was quenched at 0 °C by addition of 10% (w/v) aqueous tartaric acid and stirring vigorously for ca. 10 min. The mixture was extracted with Et_2O and the combined organic layers were washed with 10% (w/v) aqueous tartaric acid, saturated $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated. Purification of the oily residue by chromatography (50 g

silica gel, 2:5 EtOAc/hexane) afforded **10b** (270.6 mg, 98%) as a white foam: $[\alpha]^{28}_D$ +87.9 (c 1.29, $CHCl_3$); IR (film) 1750, 1728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (d, 3H, J = 6.8 Hz), 1.17 (d, 3H, J = 6.3 Hz), 1.67 (br q, 1H, J = 7.0 Hz), 2.38 (dd [X of AX], 1H, J = 14.6, 1.0 Hz), 2.82 (d [A of AX], 1H, J = 14.6 Hz), 3.09-3.34 (m, 4H), 3.28 (s, 3H), 3.77 (s, 3H), 4.38 (qd, 1H, J = 6.4, 1.8 Hz), 5.36 (s, 1H), 7.43 (t, 2H, J = 7.6 Hz), 7.54-7.58 (m, 1H), 8.05 (dd, 2H, J = 8.1, 1.2 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 9.7, 18.6, 37.3, 37.9, 39.2, 45.7, 47.7, 52.3, 68.1, 69.4, 71.8, 98.5, 128.4, 128.8, 130.0, 133.5, 165.4, 168.3; HRMS m/z for $C_{20}H_{26}O_6S_2Na$ (MNa^+) calcd 449.1069, found 449.1062. Anal. Calcd for $C_{20}H_{26}O_6S_2$: C, 56.32; H, 6.14. Found: C, 56.14; H, 6.12.

Compound 4. To a stirred solution of **10b** (95 mg, 0.22 mmol) in acetonitrile/water (8:1v/v; 5.6 mL) at ca. -5 °C was added bis(trifluoroacetoxy)iodobenzene (293 mg, 97%, 0.66 mmol). In the absence of light the mixture was stirred for 2 h at ca. -5 °C, then at room temperature for 1 h. The solution was poured into saturated $NaHCO_3$ and extracted with Et_2O, and the ethereal extracts were washed with saturated $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated. Purification of the residue by chromatography (50 g silica gel, 1:3 - 1:1 EtOAc/hexane) gave **4** (62.5 mg, 80%) as a colourless oil: $[\alpha]^{28}_D$ +114.4 (c 1.23, $CHCl_3$); IR (film)1749, 1725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (d, 3H, J = 6.8 Hz), 1.24 (d, 3H, J = 6.3 Hz), 2.34 (br qd, 1H, J = 7.2, 2.1 Hz), 2.64 (dd [X of AX], 1H, J = 15.6, 1.0 Hz), 3.25 (d [A of AX] , 1H, J = 15.6 Hz), 3.27 (s, 3H), 3.82 (s, 3H), 4.18 (qd, 1H, J = 6.5, 2.7 Hz), 5.48 (s, 1H), 7.45 (t, 2H, J = 7.8 Hz), 7.57-7.61 (m, 1H), 8.04 (dd, 2H, J = 8.3, 1.5 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 9.7, 16.8, 41.8, 48.5, 48.8, 52.5, 68.0, 70.9, 100.8, 128.5, 129.9 (2x), 133.7, 165.2, 168.4, 208.6; HRMS m/z for $C_{18}H_{22}O_7Na$ (MNa^+) calcd 373.1263, found 373.1279. Anal. Calcd for $C_{18}H_{22}O_7$: C, 61.71; H, 6.33. Found: C, 61.72; H, 6.53.

(+)-Methyl 7-Benzoylpederate (3b).

1.Preparation of a Stock Solution of CH_2I_2-Zn-$TiCl_4$ Organometallic 'Methylenation' Reagent ('CH_2'):

Commercial zinc dust (Kanto Chemical Co., Inc.; 10 g) was initially activated by washing it with 10% (v/v) aqueous hydrochloric acid, 1 M aqueous sodium hydroxide, 10% (v/v) aqueous hydrochloric acid again, water, acetone and ether. It was then dried under vacuum at 100 °C for 6 h. A flame-dried 100 mL, three-necked flask was equipped with a magnetic stirring bar, a thermometer, rubber septum and a three-way stopcock. The air in the flask was replaced by argon and charged with zinc dust (1.950 g, 29.8 mmol). The flask was flushed three times with argon, and THF added (4 mL) followed by 1,2-dibromoethane (0.10 mL, 1.16 mmol). The zinc suspension was heated gently with a heat gun until ebullition was observed. The reaction mixture was stirred for a few minutes and heated again. The process was repeated 3 times, after which chlorotrimethylsilane (0.150 mL, 1.18 mmol) was added slowly and the resultant, gently

bubbling mixture was stirred for 30 min. A solution of diiodomethane (1.33 mL, 16.5 mmol) in THF (3 mL) was added dropwise over 40 min between 25 and 40 °C, and the mixture then stirred for 100 min at rt. Following cooling to 0 °C, $TiCl_4$ (3.30 mL, 1.00 M in CH_2Cl_2, 3.30 mmol) was added dropwise, and the dark brown mixture was warmed to room temperature and stirred for a further 40 min. The excess zinc solid was allowed to settle for 1 h and the 'methylenation reagent' stock solution was ready to be employed.

2. Exomethylenation of Ketone 4:

To a stirring solution of **4** (38.5 mg, 0.11 mmol) in THF (2 mL) at room temperature was added the 'methylenation reagent' (1.5 mL) . The light red-coloured solution was stirred for 50 min, then poured into saturated $NaHCO_3$, extracted with EtOAc, and the combined organic layers were washed with saturated $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated. Purification of the residue by chromatography (30 g silica gel, 10-15% EtOAc/hexane) afforded **3b** (30.2 mg, 79%) as a colourless oil. The optical rotation and ^{1}H NMR data of **3b** were in good agreement with the data of authentic sample **3b**: $[\alpha]^{27}_D$ +106.4 (c 0.71, $CHCl_3$) [lit.,[10b] $[\alpha]^{28}_D$ +112.5 (c 0.51, CH_2Cl_2)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, 3H, J = 6.8 Hz), 1.15 (d, 3H, J = 6.8 Hz), 2.23 (qd, 1H, J = 6.9, 2.4 Hz), 2.45 (d [X of AX], 1H, J = 14.6 Hz), 2.90 (ddd [A of AX], 1H, J = 14.4, 2.1, 2.1 Hz), 3.26 (s, 3H), 3.81 (s, 3H), 3.90 (qd, 1H, J = 6.5, 2.6 Hz), 4.80 (t, 1H, J = 2.2 Hz), 4.87 (t, 1H, J = 2.0 Hz), 5.42 (s, 1H), 7.46 (t, 2H, J = 7.8 Hz), 7.57-7.61 (m, 1H), 8.09 (dd, 2H, J = 8.1, 1.2 Hz); ^{13}C (100 MHz, $CDCl_3$) δ 11.5, 17.7, 33.7, 41.4, 48.4, 52.3, 69.3, 72.1, 99.2, 109.9, 128.5, 129.0, 130.0, 133.5, 146.2, 165.6, 168.7.