SUPPORTING INFORMATION

Diastereoselective reduction of the tricarbonyl moiety in bicyclic tetramates giving pyroglutamates

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1. SYNTHETIC METHODS

1.1 General methods and materials

All reagents were obtained from Sigma Aldrich, Alfa Aesar, Apollo Scientific or Acros Organics and used without further purification. All reactions were conducted in oven-dried glassware under an inert atmosphere of nitrogen unless not using anhydrous solvents. Anhydrous solvents were dried by pre-storing them over activated 3 Å molecular sieves before being passed through an activated alumina column on a solvent tower under N_2 pressure. 'Petrol' refers to light petroleum ether of boiling point 40-60 °C and was used as purchased. Solvents were evaporated at 40 °C under reduced pressure on a Büchi R-114 rotatory evaporator attached to a Vacuubrand CVC2 pump and a pressure control system. Concentrations (*c*) in the general procedures refer to the limiting reagent and are given in mmol/mL.

Analytical thin layer chromatography (TLC) was carried out on Merck aluminium foil backed sheets precoated with 0.2 mm Kielselgel 60 F_{254}. The eluent used is specified in each case. The spots were visualised by UV irradiation (λ 254 nm) and by staining with a $KMnO_4$ solution followed by heating. Retention factors (R_f) are quoted to the nearest 0.01. *Flash* column chromatography was performed on Kielselgel 60 silica gel (230-400 mesh particle size). The eluents are specified in each case.

Optical rotations were recorded at 25 °C on a Perkin-Elmer 241 polarimeter or Unipol L 2000 using the D line of sodium (589 nm) and a path length of 1 dm. Concentrations (*c*) are given in g/100 mL and specific rotations ($[\alpha]_D^{20}$) are quoted in 10^{-1} deg cm^2 g^{-1}.

Melting points were measured using a Stuart Scientific SMP1 melting point instrument and are uncorrected.

Infrared spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer equipped with an attached Pike Miracle attenuated total reflectance (ATR) module. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}) and only selected peaks are reported.

^{1}H NMR spectra were recorded on the following instruments: AVIII HD 400 (400 MHz) and AVII 500 (500 MHz). Chemical shifts (δ_H) are reported in parts per million (ppm) downfield from TMS and are referenced to the residual ^{1}H solvent peak. Coupling constants (*J*) are quoted in Hz. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet), coupling constant, and assignment. Two-dimensional COSY spectra were recorded on Bruker AVIII HD 400 (400 MHz) and AVII 500 (500 MHz) spectrometers, and NOE experiments were performed on a Bruker AVII 500 (500 MHz).

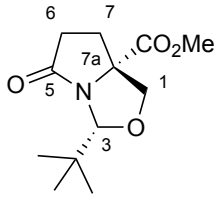
^{13}C NMR spectra were recorded on a Bruker AVIII HD 400 at 100.6 MHz and AVII 500 at 125.8 MHz with proton decoupling. Chemical shifts (δ_C) are reported in ppm downfield from TMS and are referenced to the residual ^{13}C solvent peak. Assignments of the spectra were made with HSQC and HMBC experiments, which were performed on a Bruker AVII 500 spectrometer.

Low resolution mass spectra (*m/z*) were recorded on a Fison Platform spectrometer using electrospray ionisation (ESI). Selected peaks are reported in Daltons and their intensities given as percentages of the base peak. High resolution mass spectra (HRMS) were recorded on a Bruker microTOF (ESI) or on an Agilent 7200 Q-TOF (CI). LC/MS spectra were recorded on a Bruker 9.4T FT-ICR-MS (ESI).

Crystals for X-ray crystallography were grown from slow vapour diffusion of petrol into a solution of the compound in EtOAc at room temperature.

1.2 Numbering

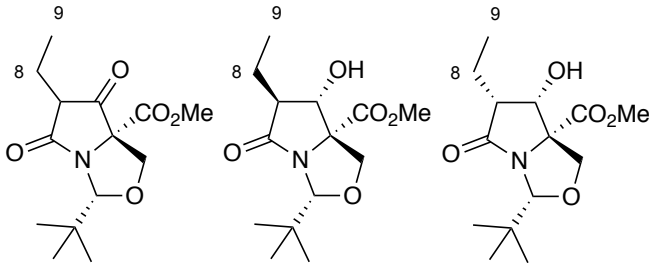
The following IUPAC numbering has been used for the nomenclature and characterisation of the bicyclic pyroglutamates.



1.2 Synthetic procedures

Previously reported compounds **1**,[1] **4**,[2,3] **5**,[4,5] **9**[5] and **16**[5] were prepared using the reported methods.

Methyl (3*R*,7a*R*)-3-(*tert*-butyl)-6-ethyl-5,7-dioxodihydro-1*H*,3*H*-pyrrolo[1,2-c]oxazole-7a(5*H*)-carboxylate (6),
Methyl (3*R*,6*R*,7*S*,7a*R*)-3-(*tert*-butyl)-6-ethyl-7-hydroxy-5-oxodihydro-1*H*,3*H*-pyrrolo[1,2-c]oxazole-7a(5*H*)-carboxylate (7) and
Methyl (3*R*,6*S*,7*S*,7a*R*)-3-(*tert*-butyl)-6-ethyl-7-hydroxy-5-oxodihydro-1*H*,3*H*-pyrrolo[1,2-c]oxazole-7a(5*H*)-carboxylate (7')



$NaBH_4$ (20 mg, 0.53 mmol) was added portionwise at 0 °C to a solution of acetyltetramate **5** (75 mg, 0.25 mmol) and acetic acid (130 μL, 2.27 mmol) in anhydrous DCM (1.2 mL). The reaction mixture was stirred at 0 °C for 15 min and at room temperature for 2 h, quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the first crude product. The aqueous phase was acidified with 2 M aqueous HCl, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the second crude product. The first crude product was purified by *flash* column chromatography (50% EtOAc in petrol) to give alcohols **7** (7 mg, 0.02 mmol, 10%) and **7'** (7 mg, 0.02

mmol, 10%) as colourless oils. The second crude product was purified by *flash* column chromatography (50% EtOAc in petrol to EtOAc) to give tetramate **6** (17 mg, 0.060 mmol, 24%) as an orange oil.

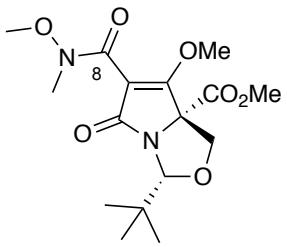
Tetramate (**6**): R_f (EtOAc) 0.15; $[\alpha]_D^{20}$ +64.7 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 2962 (C-H), 1749 (C=O), 1643 (C=O); δ_H (400 MHz, $CDCl_3$) 0.90 (9H, s, C(C*H*$_3$)$_3$), 0.95 (3H, t, *J* 7.4, C(9)*H*$_3$), 1.84-1.91 (2H, m, C(8)*H*$_2$), 3.47 (1H, d, *J* 9.0, C(1)*H*$_A$H$_B$), 3.54 (1H, t, *J* 5.3, C(6)*H*), 3.81 (3H, s, CO_2CH_3), 4.80 (1H, d, *J* 9.0, C(1)H$_A$*H*$_B$), 5.06 (1H, s, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 11.1 (*C*(9)), 17.5 (*C*(8)), 24.8 (C(*C*H$_3$)$_3$), 35.7 (*C*(CH$_3$)$_3$), 53.8 (CO_2CH_3), 55.0 (*C*(6)), 68.0 (*C*(1)), 79.1 (*C*(7a)), 98.2 (*C*(3)), 167.1 (CO_2CH_3), 175.1 (*C*(5)), 201.4 (*C*(7)); *m/z* (ESI$^-$) 282.1 (M-H$^-$, 100%); HRMS (ESI$^-$) found 282.13430, $C_{14}H_{20}NO_5$ (M-H$^-$) requires 282.13470.

Alcohol *R* (**7**): R_f (50% EtOAc in petrol) 0.32; $[\alpha]_D^{20}$ +51.2 (*c* 0.7, $CHCl_3$); ν_{max}/cm^{-1} 3400 (O-H), 2959 (C-H), 1742 (C=O), 1688 (C=O); δ_H (500 MHz, $CDCl_3$) 0.89 (9H, s, C(C*H*$_3$)$_3$), 1.10 (3H, t, *J* 7.5, C(9)*H*$_3$), 1.91 (1H, quint, *J* 7.5, C(8)*H*$_2$), 2.59 (1H, d, *J* 5.4, O*H*), 2.70 (1H, dt, *J* 9.0, 7.5, C(6)*H*), 3.40 (1H, d, *J* 8.6, C(1)*H*$_A$H$_B$), 3.80 (3H, s, CO_2CH_3), 4.53-4.55 (1H, m, C(7)*H*), 4.85 (1H, s, C(3)*H*), 4.90 (1H, d, *J* 8.6, C(1)H$_A$*H*$_B$); δ_C (125 MHz, $CDCl_3$) 11.3 (*C*(9)), 21.2 (*C*(8)), 24.9 (C(*C*H$_3$)$_3$), 36.2 (*C*(CH$_3$)$_3$), 52.8 (CO_2CH_3), 53.2 (*C*(6)), 74.1 (*C*(1)), 75.4 (*C*(7a)), 79.3 (*C*(7)), 96.3 (*C*(3)), 171.0 (CO_2CH_3), 176.5 (*C*(5)); *m/z* (ESI$^+$) 286.2 (MH$^+$, 100%), 308.2 (MNa$^+$, 91%); HRMS (ESI$^+$) found 286.16497, $C_{14}H_{24}NO_5$ (MH$^+$) requires 286.16490.

Alcohol *S* (**7'**): R_f (50% EtOAc in petrol) 0.44; $[\alpha]_D^{20}$ +30.6 (*c* 0.6, $CHCl_3$); ν_{max}/cm^{-1} 3430 (O-H), 2960 (C-H), 1745 (C=O), 1691 (C=O); δ_H (500 MHz, $CDCl_3$) 0.87 (9H, s, C(C*H*$_3$)$_3$), 1.06 (3H, t, *J* 7.5, C(9)*H*$_3$), 1.54-1.63 (1H, m, C(8)*H*$_A$H$_B$), 1.80-1.89 (1H, m, C(8)H$_A$*H*$_B$), 2.61 (1H, s, O*H*), 3.07 (1H, dt, *J* 10.4, 6.4, C(6)*H*), 3.49 (1H, d, *J* 8.7, C(1)*H*$_A$H$_B$), 3.82 (3H, s, CO_2CH_3), 4.16 (1H, d, *J* 10.4, C(7)*H*), 4.87 (1H, s, C(3)*H*), 4.91 (1H, d, *J* 8.7, C(1)H$_A$*H*$_B$); δ_C (125 MHz, $CDCl_3$) 12.6 (*C*(9)), 19.7 (*C*(8)), 25.1 (C(*C*H$_3$)$_3$), 35.7 (*C*(CH$_3$)$_3$), 52.7 (CO_2CH_3), 52.9 (*C*(6)), 72.7 (*C*(7)), 74.6 (*C*(1)), 77.7 (*C*(7a)), 97.1 (*C*(3)), 171.1 (CO_2CH_3), 180.1

(*C*(5)); *m/z* (ESI$^+$) 308.2 (MNa$^+$, 11%); HRMS (ESI$^+$) found 308.14704, $C_{14}H_{23}NNaO_5$ (MNa$^+$) requires 308.14684.

Methyl (3*R*,7a*R*)-3-(*tert*-butyl)-7-methoxy-6-(methoxy(methyl)carbamoyl)-5-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7a(5*H*)-carboxylate (10)

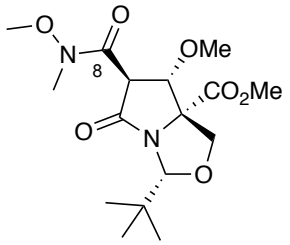


Diisopropyl azodicarboxylate (260 μL, 1.32 mmol) was added to a solution of Weinreb amide **9** (410 mg, 1.20 mmol), methanol (54 μL, 1.3 mmol) and triphenylphosphine (346 mg, 1.32 mmol) in anhydrous THF (13 mL) at 0 °C. The mixture was stirred at room temperature for 13 h and then concentrated under reduced pressure. The crude residue was purified by *flash* column chromatography (25% EtOAc in DCM) to give the methyl ether **10** (342 mg, 0.960 mmol) as a colourless oil. R_f (25% EtOAc in DCM) 0.41; $[\alpha]_D^{20}$ +74.6 (*c* 1.1, DCM); ν_{max}/cm^{-1} 2959 (C-H), 1752 (C=O), 1719 (C=O), 1650 (C=O); δ_H (500 MHz, $CDCl_3$, 4:1 mixture of rotamers, major A and minor B) 0.89 (9H, s, C(CH_3)$_3$), 3.29 (3H, s, NCH_3 A), 3.33 (3H, s, NCH_3 B), 3.51 (1H, d, *J* 8.5, C(1)H_AH$_B$), 3.71 (3H, s, NOCH_3 A), 3.79 (3H, s, CO_2CH_3), 3.87 (3H, s, NOCH_3 B), 3.93 (3H, s, C(7)OCH_3 A), 4.02 (3H, s, C(7)OCH_3 B), 4.70 (1H, s, C(3)*H*), 4.79 (1H, d, *J* 8.5, C(1)H$_A$$H_B$); δ_C (125 MHz, $CDCl_3$) 24.7 (C(*C*H$_3$)$_3$), 32.5 (N*C*H$_3$), 35.2 (*C*(CH$_3$)$_3$), 53.4 (CO_2CH_3), 60.2 (C(7)O*C*H$_3$), 61.9 (NO*C*H$_3$), 69.5 (*C*(1)), 74.4 (*C*(7a)), 97.3 (*C*(3)), 105.0 (*C*(6)), 163.0 (*C*(8)), 168.3 (CO_2CH_3), 169.7 (*C*(7)), 174.9 (*C*(5)); *m/z* (ESI$^+$) 357.1 (MH$^+$, 100%), 379.1 (MNa$^+$, 51%); HRMS (ESI$^+$) found 357.16506, $C_{16}H_{25}N_2O_7$ (MH$^+$) requires 357.16563.

General procedure A: Hydrogenation of *C*(6)-acyltetramates

A suspension of the *C*(6)-acyltetramate (1.0 eq) and PtO_2 (0.2 eq) in EtOAc (*c* 0.02) was stirred at room temperature under an atmosphere of H_2 for 3 h. The mixture was filtered through Celite and concentrated under reduced pressure to give the hydrogenated product.

Methyl (3*R*,6*S*,7*S*,7a*R*)-3-(*tert*-butyl)-7-methoxy-6-(methoxy(methyl)carbamoyl)-5-oxodihydro-1*H*,3*H*-pyrrolo[1,2-c]oxazole-7a(5*H*)-carboxylate (12)



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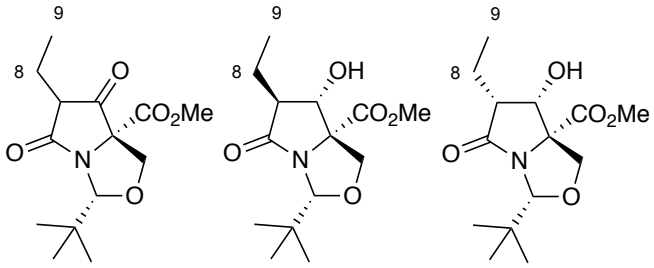
Methyl (3*R*,6*R*,7*S*,7a*R*)-3-(*tert*-butyl)-6-ethyl-7-hydroxy-5-oxodihydro-1*H*,3*H*-pyrrolo[1,2-c]oxazole-7a(5*H*)-carboxylate (7) and
Methyl (3*R*,6*S*,7*S*,7a*R*)-3-(*tert*-butyl)-6-ethyl-7-hydroxy-5-oxodihydro-1*H*,3*H*-pyrrolo[1,2-c]oxazole-7a(5*H*)-carboxylate (7')



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chromatography (50% EtOAc in petrol) to give alcohols **7** (7 mg, 0.02 mmol, 10%) and **7'** (7 mg, 0.02 mmol, 10%) as colourless oils. The second crude product was purified by *flash* column chromatography (50% EtOAc in petrol to EtOAc) to give tetramate **6** (17 mg, 0.060 mmol, 24%) as an orange oil.

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Alcohol *S* (**7'**): R_f (50% EtOAc in petrol) 0.44; $[\alpha]_D^{20}$ +30.6 (*c* 0.6, $CHCl_3$); ν_{max}/cm^{-1} 3430 (O-H), 2960 (C-H), 1745 (C=O), 1691 (C=O); δ_H (500 MHz, $CDCl_3$) 0.87 (9H, s, C(C*H*$_3$)$_3$), 1.06 (3H, t, *J* 7.5, C(9)*H*$_3$), 1.54-1.63 (1H, m, C(8)*H*$_A$H$_B$), 1.80-1.89 (1H, m, C(8)H$_A$*H*$_B$), 2.61 (1H, s, O*H*), 3.07 (1H, dt, *J* 10.4, 6.4, C(6)*H*), 3.49 (1H, d, *J* 8.7, C(1)*H*$_A$H$_B$), 3.82 (3H, s, CO_2CH_3), 4.16 (1H, d, *J* 10.4, C(7)*H*), 4.87 (1H, s, C(3)*H*), 4.91 (1H, d, *J* 8.7, C(1)H$_A$*H*$_B$); δ_C (125 MHz, $CDCl_3$) 12.6 (*C*(9)), 19.7 (*C*(8)), 25.1 (C(*C*H$_3$)$_3$), 35.7 (*C*(CH$_3$)$_3$),

52.7 (CO_2CH_3), 52.9 (*C*(6)), 72.7 (*C*(7)), 74.6 (*C*(1)), 77.7 (*C*(7a)), 97.1 (*C*(3)), 171.1 (CO_2CH_3), 180.1 (*C*(5)); *m/z* (ESI^+) 308.2 (MNa^+, 11%); HRMS (ESI^+) found 308.14704, $C_{14}H_{23}NNaO_5$ (MNa^+) requires 308.14684.

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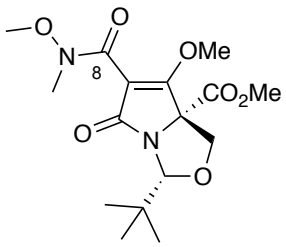
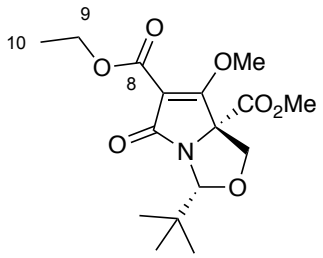


Diisopropyl azodicarboxylate (260 μL, 1.32 mmol) was added to a solution of Weinreb amide **9** (410 mg, 1.20 mmol), methanol (54 μL, 1.3 mmol) and triphenylphosphine (346 mg, 1.32 mmol) in anhydrous THF (13 mL) at 0 °C. The mixture was stirred at room temperature for 13 h and then concentrated under reduced pressure. The crude residue was purified by *flash* column chromatography (25% EtOAc in DCM) to give the methyl ether **10** (342 mg, 0.960 mmol) as a colourless oil. R_f (25% EtOAc in DCM) 0.41; $[\alpha]_D^{20}$ +74.6 (*c* 1.1, DCM); ν_{max}/cm^{-1} 2959 (C-H), 1752 (C=O), 1719 (C=O), 1650 (C=O); δ_H (500 MHz, $CDCl_3$, 4:1 mixture of rotamers, major A and minor B) 0.89 (9H, s, C(CH_3)$_3$), 3.29 (3H, s, NCH_3 A), 3.33 (3H, s, NCH_3 B), 3.51 (1H, d, *J* 8.5, C(1)H_AH_B), 3.71 (3H, s, NOCH_3 A), 3.79 (3H, s, CO_2CH_3), 3.87 (3H, s, NOCH_3 B), 3.93 (3H, s, C(7)OCH_3 A), 4.02 (3H, s, C(7)OCH_3 B), 4.70 (1H, s, C(3)*H*), 4.79 (1H, d, *J* 8.5, C(1)H_AH_B); δ_C (125 MHz, $CDCl_3$) 24.7 (C(CH_3)$_3$), 32.5 (NCH_3), 35.2 (*C*(CH_3)$_3$), 53.4 (CO_2CH_3), 60.2 (C(7)OCH_3), 61.9 (NOCH_3), 69.5 (*C*(1)), 74.4 (*C*(7a)), 97.3 (*C*(3)), 105.0 (*C*(6)), 163.0 (*C*(8)), 168.3 (CO_2CH_3), 169.7 (*C*(7)), 174.9 (*C*(5)); *m/z* (ESI^+) 357.1 (MH^+, 100%), 379.1 (MNa^+, 51%); HRMS (ESI^+) found 357.16506, $C_{16}H_{25}N_2O_7$ (MH^+) requires 357.16563.

General procedure A (from **10**); yield quant. (440 mg); white solid; m.p. 178 °C. R_f (50% EtOAc in petrol) 0.24; $[\alpha]_D^{20}$ -39.0 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 2960 (C-H), 1748 (C=O), 1718 (C=O), 1668 (C=O);

δ_H (500 MHz, $CDCl_3$) 0.87 (9H, s, C(CH_3)$_3$), 3.29 (3H, s, NCH_3), 3.30 (3H, s, C(7)OCH_3), 3.72 (1H, d, *J* 8.5, C(1)H_AH_B), 3.81 (3H, s, NOCH_3), 3.83 (3H, s, CO_2CH_3), 4.61 (1H, d, *J* 10.2, C(7)*H*), 4.73 (1H, d, *J* 10.2, C(6)*H*), 4.86 (1H, s, C(3)*H*), 4.98 (1H, d, *J* 8.5, C(1)H_AH_B); δ_C (125 MHz, $CDCl_3$) 25.0 (C(CH_3)$_3$), 32.4 (NCH_3), 36.2 (C(CH_3)$_3$), 52.9 (CO_2CH_3), 54.8 (C(6)), 59.1 (C(7)OCH_3), 62.1 (NOCH_3), 73.7 (C(1)), 74.7 (C(7a)), 84.5 (C(7)), 96.2 (C(3)), 167.5 (C(8)), 170.1 (CO_2CH_3), 170.4 (C(5)); *m/z* (ESI^+) 359.2 (MH^+, 59%), 381.2 (MNa^+, 100%); HRMS (ESI^+) found 359.18165, $C_{16}H_{27}N_2O_7$ (MH^+) requires 359.18128.

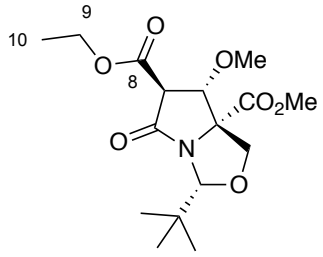
6-Ethyl 7a-methyl (3*R*,7a*R*)-3-(*tert*-butyl)-7-methoxy-5-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6,7a(5*H*)-dicarboxylate (14)



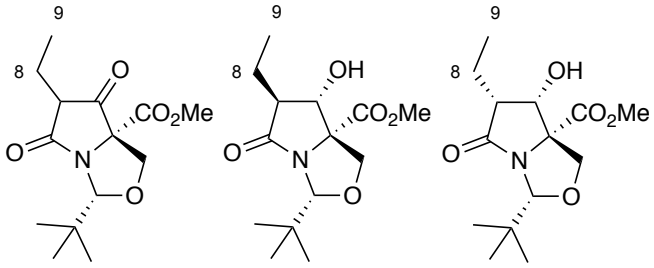
To a solution of tetramic acid **1** (432 mg, 1.69 mmol) and DMAP (465 mg, 3.81 mmol) in anhydrous DCM (34 mL) was added ethyl chloroformate (195 µL, 2.04 mmol). The solution was stirred at room temperature for 19 h, acidified with 2 M aqueous HCl and extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resultant residue was dissolved in anhydrous THF (17 mL), and triphenylphosphine (488 mg, 1.86 mmol) and methanol (75 µL, 1.9 mmol) were added. DEAD (292 µL, 1.86 mmol) was then added dropwise at 0 °C and the mixture was stirred at room temperature for 24 h before concentrating it under reduced pressure. The crude product was purified by *flash* column chromatography to give methylated ethyl ester **14** (198 mg, 0.580 mmol, 34%) as a light yellow oil. R_f (40% EtOAc in petrol) 0.52; $[\alpha]_D^{20}$ +106.6 (*c* 0.7, $CHCl_3$); ν_{max}/cm^{-1} 2959 (C-H), 1742 (C=O), 1717 (C=O), 1643 (C=O); δ_H (400 MHz, $CDCl_3$) 0.88 (9H, s, C(CH_3)$_3$), 1.35 (3H, t, *J* 7.1, C(10)H_3), 3.47 (1H, d, *J* 8.5, C(1)H_AH_B), 3.78 (3H, s, CO_2CH_3), 4.06 (3H, s, C(7)OCH_3), 4.32 (2H, q, *J* 7.1, C(9)H_2), 4.72 (1H, s, C(3)*H*), 4.81 (1H, d, *J* 8.5, C(1)H_AH_B); δ_C (100 MHz, $CDCl_3$) 14.3 (C(10)), 24.7 (C(CH_3)$_3$), 35.2 (C(CH_3)$_3$), 53.5 (CO_2CH_3), 61.9 (C(9)), 62.0 (C(7)OCH_3), 69.5

(*C*(1)), 74.1 (*C*(7a)), 97.6 (*C*(3)), 103.6 (*C*(6)), 162.1 (*C*(8)), 167.9 (CO_2CH_3), 174.0 (*C*(7)), 174.1 (*C*(5)); *m/z* (ESI^+) 342.2 (MH^+, 54%), 364.2 (MNa^+, 100%); HRMS (ESI^+) found 342.15484, $C_{16}H_{24}NO_7$ (MH^+) requires 342.15473.

6-Ethyl 7a-methyl (3*R*,6*S*,7*S*,7a*R*)-3-(*tert*-butyl)-7-methoxy-5-oxodihydro-1*H*,3*H*-pyrrolo[1,2-c]oxazole-6,7a(5*H*)-dicarboxylate (15)



Methyl (3*R*,7a*R*)-3-(*tert*-butyl)-6-ethyl-5,7-dioxodihydro-1*H*,3*H*-pyrrolo[1,2-c]oxazole-7a(5*H*)-carboxylate (6),
Methyl (3*R*,6*R*,7*S*,7a*R*)-3-(*tert*-butyl)-6-ethyl-7-hydroxy-5-oxodihydro-1*H*,3*H*-pyrrolo[1,2-c]oxazole-7a(5*H*)-carboxylate (7) and
Methyl (3*R*,6*S*,7*S*,7a*R*)-3-(*tert*-butyl)-6-ethyl-7-hydroxy-5-oxodihydro-1*H*,3*H*-pyrrolo[1,2-c]oxazole-7a(5*H*)-carboxylate (7')



$NaBH_4$ (20 mg, 0.53 mmol) was added portionwise at 0 °C to a solution of acetyltetramate **5** (75 mg, 0.25 mmol) and acetic acid (130 μL, 2.27 mmol) in anhydrous DCM (1.2 mL). The reaction mixture was stirred at 0 °C for 15 min and at room temperature for 2 h, quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the first crude product. The aqueous phase was acidified with 2 M aqueous HCl, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the second crude product. The first crude product was purified by *flash* column

chromatography (50% EtOAc in petrol) to give alcohols **7** (7 mg, 0.02 mmol, 10%) and **7'** (7 mg, 0.02 mmol, 10%) as colourless oils. The second crude product was purified by *flash* column chromatography (50% EtOAc in petrol to EtOAc) to give tetramate **6** (17 mg, 0.060 mmol, 24%) as an orange oil.

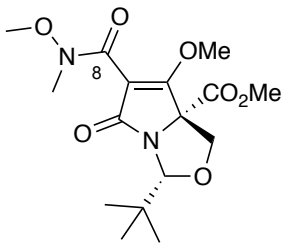
Tetramate (**6**): R_f (EtOAc) 0.15; $[\alpha]_D^{20}$ +64.7 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 2962 (C-H), 1749 (C=O), 1643 (C=O); δ_H (400 MHz, $CDCl_3$) 0.90 (9H, s, C(C*H*$_3$)$_3$), 0.95 (3H, t, *J* 7.4, C(9)*H*$_3$), 1.84-1.91 (2H, m, C(8)*H*$_2$), 3.47 (1H, d, *J* 9.0, C(1)*H*$_A$H$_B$), 3.54 (1H, t, *J* 5.3, C(6)*H*), 3.81 (3H, s, CO_2CH_3), 4.80 (1H, d, *J* 9.0, C(1)H$_A$*H*$_B$), 5.06 (1H, s, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 11.1 (*C*(9)), 17.5 (*C*(8)), 24.8 (C(*C*H$_3$)$_3$), 35.7 (*C*(CH$_3$)$_3$), 53.8 (CO_2CH_3), 55.0 (*C*(6)), 68.0 (*C*(1)), 79.1 (*C*(7a)), 98.2 (*C*(3)), 167.1 (CO_2CH_3), 175.1 (*C*(5)), 201.4 (*C*(7)); *m/z* (ESI$^-$) 282.1 (M-H$^-$, 100%); HRMS (ESI$^-$) found 282.13430, $C_{14}H_{20}NO_5$ (M-H$^-$) requires 282.13470.

Alcohol *R* (**7**): R_f (50% EtOAc in petrol) 0.32; $[\alpha]_D^{20}$ +51.2 (*c* 0.7, $CHCl_3$); ν_{max}/cm^{-1} 3400 (O-H), 2959 (C-H), 1742 (C=O), 1688 (C=O); δ_H (500 MHz, $CDCl_3$) 0.89 (9H, s, C(C*H*$_3$)$_3$), 1.10 (3H, t, *J* 7.5, C(9)*H*$_3$), 1.91 (1H, quint, *J* 7.5, C(8)*H*$_2$), 2.59 (1H, d, *J* 5.4, O*H*), 2.70 (1H, dt, *J* 9.0, 7.5, C(6)*H*), 3.40 (1H, d, *J* 8.6, C(1)*H*$_A$H$_B$), 3.80 (3H, s, CO_2CH_3), 4.53-4.55 (1H, m, C(7)*H*), 4.85 (1H, s, C(3)*H*), 4.90 (1H, d, *J* 8.6, C(1)H$_A$*H*$_B$); δ_C (125 MHz, $CDCl_3$) 11.3 (*C*(9)), 21.2 (*C*(8)), 24.9 (C(*C*H$_3$)$_3$), 36.2 (*C*(CH$_3$)$_3$), 52.8 (CO_2CH_3), 53.2 (*C*(6)), 74.1 (*C*(1)), 75.4 (*C*(7a)), 79.3 (*C*(7)), 96.3 (*C*(3)), 171.0 (CO_2CH_3), 176.5 (*C*(5)); *m/z* (ESI$^+$) 286.2 (MH$^+$, 100%), 308.2 (MNa$^+$, 91%); HRMS (ESI$^+$) found 286.16497, $C_{14}H_{24}NO_5$ (MH$^+$) requires 286.16490.

Alcohol *S* (**7'**): R_f (50% EtOAc in petrol) 0.44; $[\alpha]_D^{20}$ +30.6 (*c* 0.6, $CHCl_3$); ν_{max}/cm^{-1} 3430 (O-H), 2960 (C-H), 1745 (C=O), 1691 (C=O); δ_H (500 MHz, $CDCl_3$) 0.87 (9H, s, C(C*H*$_3$)$_3$), 1.06 (3H, t, *J* 7.5, C(9)*H*$_3$), 1.54-1.63 (1H, m, C(8)*H*$_A$H$_B$), 1.80-1.89 (1H, m, C(8)H$_A$*H*$_B$), 2.61 (1H, s, O*H*), 3.07 (1H, dt, *J* 10.4, 6.4, C(6)*H*), 3.49 (1H, d, *J* 8.7, C(1)*H*$_A$H$_B$), 3.82 (3H, s, CO_2CH_3), 4.16 (1H, d, *J* 10.4, C(7)*H*), 4.87 (1H, s, C(3)*H*), 4.91 (1H, d, *J* 8.7, C(1)H$_A$*H*$_B$); δ_C (125 MHz, $CDCl_3$) 12.6 (*C*(9)), 19.7 (*C*(8)), 25.1 (C(*C*H$_3$)$_3$), 35.7 (*C*(CH$_3$)$_3$),

52.7 (CO_2CH_3), 52.9 (*C*(6)), 72.7 (*C*(7)), 74.6 (*C*(1)), 77.7 (*C*(7a)), 97.1 (*C*(3)), 171.1 (CO_2CH_3), 180.1 (*C*(5)); *m/z* (ESI^+) 308.2 (MNa^+, 11%); HRMS (ESI^+) found 308.14704, $C_{14}H_{23}NNaO_5$ (MNa^+) requires 308.14684.

Methyl (3*R*,7a*R*)-3-(*tert*-butyl)-7-methoxy-6-(methoxy(methyl)carbamoyl)-5-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7a(5*H*)-carboxylate (10)

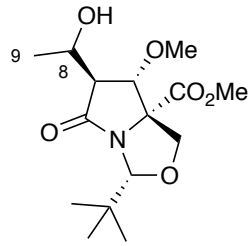


Diisopropyl azodicarboxylate (260 μL, 1.32 mmol) was added to a solution of Weinreb amide **9** (410 mg, 1.20 mmol), methanol (54 μL, 1.3 mmol) and triphenylphosphine (346 mg, 1.32 mmol) in anhydrous THF (13 mL) at 0 °C. The mixture was stirred at room temperature for 13 h and then concentrated under reduced pressure. The crude residue was purified by *flash* column chromatography (25% EtOAc in DCM) to give the methyl ether **10** (342 mg, 0.960 mmol) as a colourless oil. R_f (25% EtOAc in DCM) 0.41; $[\alpha]_D^{20}$ +74.6 (*c* 1.1, DCM); ν_{max}/cm^{-1} 2959 (C-H), 1752 (C=O), 1719 (C=O), 1650 (C=O); δ_H (500 MHz, $CDCl_3$, 4:1 mixture of rotamers, major A and minor B) 0.89 (9H, s, C(CH_3)$_3$), 3.29 (3H, s, NCH_3 A), 3.33 (3H, s, NCH_3 B), 3.51 (1H, d, *J* 8.5, C(1)H_AH_B), 3.71 (3H, s, NOCH_3 A), 3.79 (3H, s, CO_2CH_3), 3.87 (3H, s, NOCH_3 B), 3.93 (3H, s, C(7)OCH_3 A), 4.02 (3H, s, C(7)OCH_3 B), 4.70 (1H, s, C(3)*H*), 4.79 (1H, d, *J* 8.5, C(1)H_AH_B); δ_C (125 MHz, $CDCl_3$) 24.7 (C(CH_3)$_3$), 32.5 (NCH_3), 35.2 (*C*(CH_3)$_3$), 53.4 (CO_2CH_3), 60.2 (C(7)OCH_3), 61.9 (NOCH_3), 69.5 (*C*(1)), 74.4 (*C*(7a)), 97.3 (*C*(3)), 105.0 (*C*(6)), 163.0 (*C*(8)), 168.3 (CO_2CH_3), 169.7 (*C*(7)), 174.9 (*C*(5)); *m/z* (ESI^+) 357.1 (MH^+, 100%), 379.1 (MNa^+, 51%); HRMS (ESI^+) found 357.16506, $C_{16}H_{25}N_2O_7$ (MH^+) requires 357.16563.

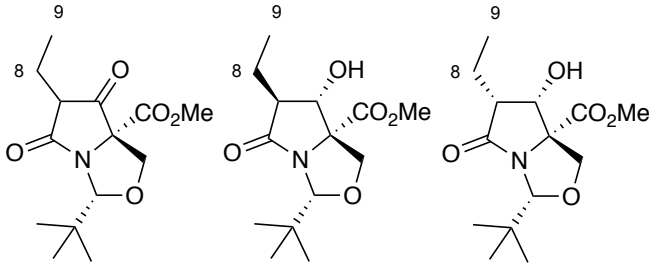
General procedure A (from **14**); yield quant. (66 mg); white solid; m.p. 132 °C. R_f (20% EtOAc in petrol) 0.29; $[\alpha]_D^{20}$ -6.6 (*c* 0.7, $CHCl_3$); ν_{max}/cm^{-1} 2957 (C-H), 1738 (C=O), 1718 (C=O); δ_H (400 MHz,

$CDCl_3$) 0.85 (9H, s, C(CH_3)$_3$), 1.32 (3H, t, *J* 7.2, C(10)H_3), 3.31 (3H, s, C(7)OCH_3), 3.69 (1H, d, *J* 8.7, C(1)H_AH_B), 3.80 (3H, s, CO_2CH_3), 4.23 (1H, d, *J* 10.6, C(6)*H*), 4.25 (1H, dq, *J* 10.8, 7.2, C(9)H_AH_B), 4.31 (1H, dq, *J* 10.8, 7.2, C(9)H_AH_B), 4.45 (1H, d, *J* 10.6, C(7)*H*), 4.87 (1H, s, C(3)*H*), 4.98 (1H, d, *J* 8.7, C(1)H_AH_B); δ_C (100 MHz, $CDCl_3$) 14.3 (*C*(10)), 24.8 (C(CH_3)$_3$), 36.2 (*C*(CH_3)$_3$), 52.9 (CO_2CH_3), 58.2 (*C*(6)), 59.1 (C(7)OCH_3), 62.2 (*C*(9)), 73.6 (*C*(1)), 74.4 (*C*(7a)), 84.9 (*C*(7)), 96.1 (*C*(3)), 167.9 (*C*(8)), 169.2 (*C*(5)), 169.7 (CO_2CH_3); *m/z* (ESI^+) 344.2 (MH^+, 21%), 366.2 (MNa^+, 100%); HRMS (ESI^+) found 344.17060, $C_{16}H_{26}NO_7$ (MH^+) requires 344.17038.

Methyl (3*R*,6*S*,7*S*,7a*R*)-3-(*tert*-butyl)-6-((S)-1-hydroxyethyl)-7-methoxy-5-oxodihydro-1*H*,3*H*-pyrrolo[1,2-c]oxazole-7a(5*H*)-carboxylate (17)



Methyl (3*R*,7a*R*)-3-(*tert*-butyl)-6-ethyl-5,7-dioxodihydro-1*H*,3*H*-pyrrolo[1,2-c]oxazole-7a(5*H*)-carboxylate (6),
Methyl (3*R*,6*R*,7*S*,7a*R*)-3-(*tert*-butyl)-6-ethyl-7-hydroxy-5-oxodihydro-1*H*,3*H*-pyrrolo[1,2-c]oxazole-7a(5*H*)-carboxylate (7) and
Methyl (3*R*,6*S*,7*S*,7a*R*)-3-(*tert*-butyl)-6-ethyl-7-hydroxy-5-oxodihydro-1*H*,3*H*-pyrrolo[1,2-c]oxazole-7a(5*H*)-carboxylate (7')



$NaBH_4$ (20 mg, 0.53 mmol) was added portionwise at 0 °C to a solution of acetyltetramate **5** (75 mg, 0.25 mmol) and acetic acid (130 μL, 2.27 mmol) in anhydrous DCM (1.2 mL). The reaction mixture was stirred at 0 °C for 15 min and at room temperature for 2 h, quenched with saturated aqueous

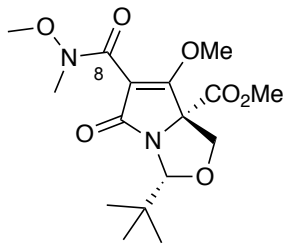
$NaHCO_3$ and extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the first crude product. The aqueous phase was acidified with 2 M aqueous HCl, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the second crude product. The first crude product was purified by *flash* column chromatography (50% EtOAc in petrol) to give alcohols **7** (7 mg, 0.02 mmol, 10%) and **7'** (7 mg, 0.02 mmol, 10%) as colourless oils. The second crude product was purified by *flash* column chromatography (50% EtOAc in petrol to EtOAc) to give tetramate **6** (17 mg, 0.060 mmol, 24%) as an orange oil.

Tetramate (**6**): R_f (EtOAc) 0.15; $[\alpha]_D^{20}$ +64.7 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 2962 (C-H), 1749 (C=O), 1643 (C=O); δ_H (400 MHz, $CDCl_3$) 0.90 (9H, s, C(CH_3)$_3$), 0.95 (3H, t, *J* 7.4, C(9)H_3), 1.84-1.91 (2H, m, C(8)H_2), 3.47 (1H, d, *J* 9.0, C(1)H_AH_B), 3.54 (1H, t, *J* 5.3, C(6)*H*), 3.81 (3H, s, CO_2CH_3), 4.80 (1H, d, *J* 9.0, C(1)H_AH_B), 5.06 (1H, s, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 11.1 (*C*(9)), 17.5 (*C*(8)), 24.8 (C(CH_3)$_3$), 35.7 (*C*(CH_3)$_3$), 53.8 (CO_2CH_3), 55.0 (*C*(6)), 68.0 (*C*(1)), 79.1 (*C*(7a)), 98.2 (*C*(3)), 167.1 (CO_2CH_3), 175.1 (*C*(5)), 201.4 (*C*(7)); *m/z* (ESI^-) 282.1 ($M\text{-}H^-$, 100%); HRMS (ESI^-) found 282.13430, $C_{14}H_{20}NO_5$ ($M\text{-}H^-$) requires 282.13470.

Alcohol *R* (**7**): R_f (50% EtOAc in petrol) 0.32; $[\alpha]_D^{20}$ +51.2 (*c* 0.7, $CHCl_3$); ν_{max}/cm^{-1} 3400 (O-H), 2959 (C-H), 1742 (C=O), 1688 (C=O); δ_H (500 MHz, $CDCl_3$) 0.89 (9H, s, C(CH_3)$_3$), 1.10 (3H, t, *J* 7.5, C(9)H_3), 1.91 (1H, quint, *J* 7.5, C(8)H_2), 2.59 (1H, d, *J* 5.4, O*H*), 2.70 (1H, dt, *J* 9.0, 7.5, C(6)*H*), 3.40 (1H, d, *J* 8.6, C(1)H_AH_B), 3.80 (3H, s, CO_2CH_3), 4.53-4.55 (1H, m, C(7)*H*), 4.85 (1H, s, C(3)*H*), 4.90 (1H, d, *J* 8.6, C(1)H_AH_B); δ_C (125 MHz, $CDCl_3$) 11.3 (*C*(9)), 21.2 (*C*(8)), 24.9 (C(CH_3)$_3$), 36.2 (*C*(CH_3)$_3$), 52.8 (CO_2CH_3), 53.2 (*C*(6)), 74.1 (*C*(1)), 75.4 (*C*(7a)), 79.3 (*C*(7)), 96.3 (*C*(3)), 171.0 (CO_2CH_3), 176.5 (*C*(5)); *m/z* (ESI^+) 286.2 (MH^+, 100%), 308.2 (MNa^+, 91%); HRMS (ESI^+) found 286.16497, $C_{14}H_{24}NO_5$ (MH^+) requires 286.16490.

Alcohol *S* (**7'**): R_f (50% EtOAc in petrol) 0.44; $[\alpha]_D^{20}$ +30.6 (*c* 0.6, $CHCl_3$); ν_{max}/cm^{-1} 3430 (O-H), 2960 (C-H), 1745 (C=O), 1691 (C=O); δ_H (500 MHz, $CDCl_3$) 0.87 (9H, s, C(CH_3)$_3$), 1.06 (3H, t, *J* 7.5, C(9)H_3), 1.54-1.63 (1H, m, C(8)H_AH_B), 1.80-1.89 (1H, m, C(8)H_AH_B), 2.61 (1H, s, O*H*), 3.07 (1H, dt, *J* 10.4, 6.4, C(6)*H*), 3.49 (1H, d, *J* 8.7, C(1)H_AH_B), 3.82 (3H, s, CO_2CH_3), 4.16 (1H, d, *J* 10.4, C(7)*H*), 4.87 (1H, s, C(3)*H*), 4.91 (1H, d, *J* 8.7, C(1)H_AH_B); δ_C (125 MHz, $CDCl_3$) 12.6 (*C*(9)), 19.7 (*C*(8)), 25.1 (C(CH_3)$_3$), 35.7 (*C*(CH_3)$_3$), 52.7 (CO_2CH_3), 52.9 (*C*(6)), 72.7 (*C*(7)), 74.6 (*C*(1)), 77.7 (*C*(7a)), 97.1 (*C*(3)), 171.1 (CO_2CH_3), 180.1 (*C*(5)); *m/z* (ESI^+) 308.2 (MNa^+, 11%); HRMS (ESI^+) found 308.14704, $C_{14}H_{23}NNaO_5$ (MNa^+) requires 308.14684.

Methyl (3*R*,7a*R*)-3-(*tert*-butyl)-7-methoxy-6-(methoxy(methyl)carbamoyl)-5-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7a(5*H*)-carboxylate (10)



Diisopropyl azodicarboxylate (260 μL, 1.32 mmol) was added to a solution of Weinreb amide **9** (410 mg, 1.20 mmol), methanol (54 μL, 1.3 mmol) and triphenylphosphine (346 mg, 1.32 mmol) in anhydrous THF (13 mL) at 0 °C. The mixture was stirred at room temperature for 13 h and then concentrated under reduced pressure. The crude residue was purified by *flash* column chromatography (25% EtOAc in DCM) to give the methyl ether **10** (342 mg, 0.960 mmol) as a colourless oil. R_f (25% EtOAc in DCM) 0.41; $[\alpha]_D^{20}$ +74.6 (*c* 1.1, DCM); ν_{max}/cm^{-1} 2959 (C-H), 1752 (C=O), 1719 (C=O), 1650 (C=O); δ_H (500 MHz, $CDCl_3$, 4:1 mixture of rotamers, major A and minor B) 0.89 (9H, s, C(CH_3)$_3$), 3.29 (3H, s, NCH_3 A), 3.33 (3H, s, NCH_3 B), 3.51 (1H, d, *J* 8.5, C(1)H_AH_B), 3.71 (3H, s, NOCH_3 A), 3.79 (3H, s, CO_2CH_3), 3.87 (3H, s, NOCH_3 B), 3.93 (3H, s, C(7)OCH_3 A), 4.02 (3H, s, C(7)OCH_3 B), 4.70 (1H, s, C(3)*H*), 4.79 (1H, d, *J* 8.5, C(1)H_AH_B); δ_C (125 MHz, $CDCl_3$) 24.7 (C(CH_3)$_3$), 32.5 (NCH_3), 35.2 (*C*(CH_3)$_3$), 53.4 (CO_2CH_3), 60.2 (C(7)OCH_3), 61.9 (NOCH_3), 69.5 (*C*(1)), 74.4 (*C*(7a)), 97.3

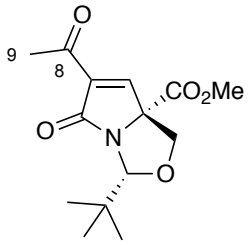
(*C*(3)), 105.0 (*C*(6)), 163.0 (*C*(8)), 168.3 (*C*O_2CH_3), 169.7 (*C*(7)), 174.9 (*C*(5)); *m/z* (ESI^+) 357.1 (MH^+, 100%), 379.1 (MNa^+, 51%); HRMS (ESI^+) found 357.16506, $C_{16}H_{25}N_2O_7$ (MH^+) requires 357.16563.

General procedure A (from **16**); yield 57% (33 mg); white solid; m.p. 121 °C. R_f (50% EtOAc in petrol) 0.27; $[\alpha]_D^{20}$ -7.4 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 3467 (O-H), 2975 (C-H), 2960 (C-H), 1740 (C=O), 1702 (C=O); δ_H (400 MHz, $CDCl_3$) 0.85 (9H, s, C(CH_3)$_3$), 1.27 (3H, d, *J* 6.4, C(9)H_3), 3.13 (1H, dd, *J* 10.7, 7.1, C(6)*H*), 3.30 (3H, s, C(7)OCH_3), 3.56 (1H, d, *J* 8.8, C(1)H_AH_B), 3.69 (1H, d, *J* 10.7, C(7)*H*), 3.80 (3H, s, CO_2CH_3), 3.90-3.94 (1H, m, *C*(8)*H*), 3.97-3.98 (1H, m, O*H*), 4.86 (1H, s, C(3)*H*), 4.97 (1H, d, *J* 8.8, C(1)H_AH_B); δ_C (100 MHz, $CDCl_3$) 20.9 (*C*(9)), 24.8 (C(*C*H_3)$_3$), 36.2 (*C*(CH$_3$)$_3$), 52.9 (CO_2CH_3), 56.5 (*C*(6)), 59.2 (C(7)O*C*H_3), 67.6 (*C*(8)), 73.9 (*C*(1)), 74.7 (*C*(7a)), 86.0 (*C*(7)), 95.6 (*C*(3)), 170.0 (*C*O_2CH_3), 176.0 (*C*(5)); *m/z* (ESI^+) 316.2 (MH^+, 18%), 338.2 (MNa^+, 100%); HRMS (ESI^+) found 338.15733, $C_{15}H_{25}NNaO_6$ (MNa^+) requires 338.15741.

General procedure B: Grignard addition to Weinreb amide 12 and elimination

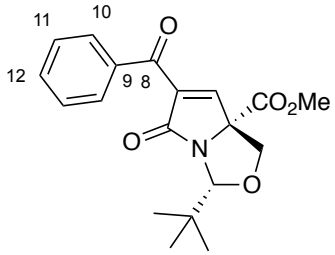
The Grignard reagent (1.2 eq), prepared following the reported method[5] if not commercially available, was added to a solution of Weinreb amide **12** (1.0 eq) in anhydrous THF (*c* 0.2) at -15 °C. The solution was stirred at the same temperature for 1 h, then quenched with aqueous saturated NH_4Cl, extracted with Et_2O, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in DCM (*c* 0.1), stirred with *para*-toluenesulfonic acid monohydrate (0.5 eq) for 24 h and concentrated *in vacuo*. The crude product was purified by *flash* column chromatography to give the enone product.

Methyl (3*R*,7a*S*)-6-acetyl-3-(*tert*-butyl)-5-oxo-1*H*,3*H*-pyrrolo[1,2-c]oxazole-7a(5*H*)-carboxylate (23)



General procedure B (with MeMgBr); yield 48% (18 mg); yellow oil. R_f (20% EtOAc in petrol) 0.20; $[\alpha]_D^{20}$ +187.6 (*c* 0.5, $CHCl_3$); ν_{max}/cm^{-1} 2960 (C-H), 1715 (C=O), 1695 (C=O), 1610 (C=C); δ_H (400 MHz, $CDCl_3$) 0.95 (9H, s, C(CH_3)$_3$), 2.56 (3H, s, C(9)H_3), 3.33 (1H, d, *J* 8.6, C(1)H_AH_B), 3.77 (3H, s, CO_2CH_3), 4.74 (1H, s, C(3)*H*), 4.81 (1H, d, *J* 8.6, C(1)H_AH_B), 7.70 (1H, s, C(7)*H*); δ_C (100 MHz, $CDCl_3$) 24.9 (C(CH_3)$_3$), 29.3 (*C*(9)), 35.5 (*C*(CH_3)$_3$), 53.6 (CO_2CH_3), 70.6 (*C*(1)), 75.2 (*C*(7a)), 97.6 (*C*(3)), 138.7 (*C*(6)), 151.1 (*C*(7)), 168.1 (CO_2CH_3), 173.9 (*C*(5)), 193.3 (*C*(8)); *m/z* (ESI^+) 282.1 (MH^+, 18%), 304.1 (MNa^+, 100%); HRMS (ESI^+) found 282.13377, $C_{14}H_{20}NO_5$ (MH^+) requires 282.13360.

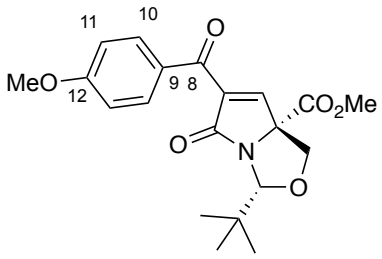
Methyl (3*R*,7a*S*)-6-benzoyl-3-(*tert*-butyl)-5-oxo-1*H*,3*H*-pyrrolo[1,2-c]oxazole-7a(5*H*)-carboxylate (24)



General procedure B (with PhMgBr); yield 68% (31 mg); white solid; m.p. 86 °C. R_f (20% EtOAc in petrol) 0.25; $[\alpha]_D^{20}$ +148.1 (*c* 0.6, $CHCl_3$); ν_{max}/cm^{-1} 3062 (C-H), 2958 (C-H), 1747 (C=O), 1714 (C=O), 1655 (C=O), 1615 (C=C); δ_H (400 MHz, $CDCl_3$) 0.96 (9H, s, C(CH_3)$_3$), 3.48 (1H, d, *J* 8.6, C(1)H_AH_B), 3.81 (3H, s, CO_2CH_3), 4.79 (1H, s, C(3)*H*), 4.86 (1H, d, *J* 8.6, C(1)H_AH_B), 7.42 (1H, s, C(7)*H*), 7.48 (2H, t, *J* 7.6, C(11)*H*), 7.63 (1H, tt, *J* 7.6, 1.2, C(12)*H*), 7.85-7.88 (2H, m, C(10)*H*); δ_C (100 MHz, $CDCl_3$) 24.9 (C(CH_3)$_3$), 35.5 (*C*(CH_3)$_3$), 53.6 (CO_2CH_3), 70.6 (*C*(1)), 75.9 (*C*(7a)), 97.5 (*C*(3)), 128.8 (*C*(11)), 129.7 (*C*(10)), 134.3 (*C*(12)), 135.9 (*C*(9)), 139.9 (*C*(6)), 148.5 (*C*(7)), 168.5 (CO_2CH_3), 173.5 (*C*(5)), 188.5

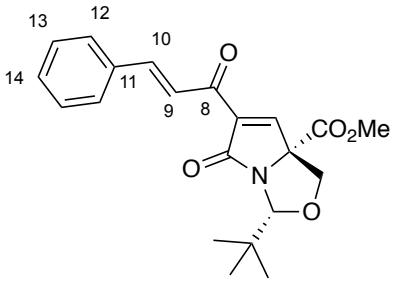
(*C*(8)); *m/z* (ESI$^+$) 366.2 (MNa$^+$, 100%); HRMS (ESI$^+$) found 344.14936, $C_{19}H_{22}NO_5$ (MH$^+$) requires 344.14925.

Methyl (3*R*,7a*S*)-3-(*tert*-butyl)-6-(4-methoxybenzoyl)-5-oxo-1*H*,3*H*-pyrrolo[1,2-c]oxazole-7a(5*H*)-carboxylate (25)



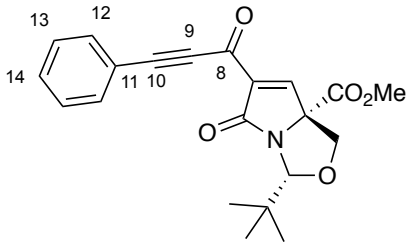
General procedure B (with *p*-MeOPhMgBr); yield 50% (21 mg); yellow solid; m.p. 126 °C. R_f (20% EtOAc in petrol) 0.11; $[\alpha]_D^{20}$ +156.5 (*c* 0.5, $CHCl_3$); ν_{max}/cm^{-1} 2958 (C-H), 1750 (C=O), 1710 (C=O), 1644 (C=O), 1599 (C=C); δ_H (400 MHz, $CDCl_3$) 0.97 (9H, s, C(CH_3)$_3$), 3.47 (1H, d, *J* 8.6, C(1)H_AH_B), 3.81 (3H, s, CO_2CH_3), 3.87 (3H, s, C(12)OCH_3), 4.78 (1H, s, C(3)*H*), 4.85 (1H, d, *J* 8.6, C(1)H$_A$$H_B$), 6.95 (2H, d, *J* 8.9, C(11)*H*), 7.37 (1H, s, C(7)*H*), 7.87 (2H, d, *J* 8.9, C(10)*H*); δ_C (100 MHz, $CDCl_3$) 25.0 (C(*C*H$_3$)$_3$), 35.5 (*C*(CH$_3$)$_3$), 53.6 (CO_2CH_3), 55.7 (C(13)O*C*H$_3$), 70.6 (*C*(1)), 76.0 (*C*(7a)), 97.5 (*C*(3)), 114.1 (*C*(11)), 129.0 (*C*(9)), 132.2 (*C*(10)), 140.5 (*C*(6)), 147.6 (*C*(7)), 164.6 (*C*(12)), 168.6 (*C*O$_2$CH$_3$), 173.9 (*C*(5)), 186.9 (*C*(8)); *m/z* (ESI$^+$) 374.2 (MH$^+$, 38%), 396.2 (MNa$^+$, 100%); HRMS (ESI$^+$) found 374.16002, $C_{20}H_{24}NO_6$ (MH$^+$) requires 374.15981.

Methyl (3*R*,7a*S*)-3-(*tert*-butyl)-6-cinnamoyl-5-oxo-1*H*,3*H*-pyrrolo[1,2-c]oxazole-7a(5*H*)-carboxylate (26)



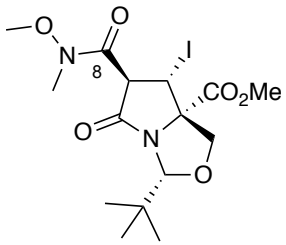
General procedure B (with PhCH=CHMgBr); yield 49% (19 mg); yellow oil. R_f (20% EtOAc in petrol) 0.22; $[\alpha]_D^{20}$ +162.1 (*c* 0.3, $CHCl_3$); ν_{max}/cm^{-1} 3026 (C-H), 2958 (C-H), 1747 (C=O), 1713 (C=O), 1666 (C=O), 1612 (C=C); δ_H (400 MHz, $CDCl_3$) 0.99 (9H, s, C(CH_3)$_3$), 3.39 (1H, d, *J* 8.6, C(1)H_AH_B), 3.78 (3H, s, CO_2CH_3), 4.80 (1H, s, C(3)*H*), 4.85 (1H, d, *J* 8.6, C(1)H_AH_B), 7.37-7.43 (3H, m, C(13)*H* + C(14)*H*), 7.66-7.68 (2H, m, C(12)*H*), 7.84-7.85 (3H, m, C(7)*H* + C(9)*H* + C(10)*H*); δ_C (100 MHz, $CDCl_3$) 25.0 (C(CH_3)$_3$), 35.5 ($C(CH_3)_3$), 53.6 (CO_2CH_3), 70.7 (*C*(1)), 75.3 (*C*(7a)), 97.6 (*C*(3)), 122.7 (*C*(9)), 129.1 (*C*(13)), 129.2 (*C*(12)), 131.3 (*C*(14)), 134.6 (*C*(11)), 139.1 (*C*(6)), 146.0 (*C*(10)), 152.0 (*C*(7)), 168.2 (CO_2CH_3), 174.2 (*C*(5)), 183.7 (*C*(8)); *m/z* (ESI^+) 370.2 (MH^+, 42%), 392.2 (MNa^+, 100%); HRMS (ESI^+) found 370.16495, $C_{21}H_{24}NO_5$ (MH^+) requires 370.16490.

Methyl (3*R*,7a*S*)-3-(*tert*-butyl)-5-oxo-6-(3-phenylpropioloyl)-1*H*,3*H*-pyrrolo[1,2-c]oxazole-7a(5*H*)-carboxylate (27)



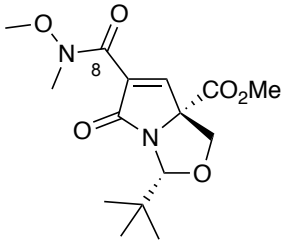
General procedure B (with PhC≡CMgBr); yield 42% (17 mg); orange solid; m.p. 110 °C. R_f (20% EtOAc in petrol) 0.28; $[\alpha]_D^{20}$ +154.5 (*c* 0.5, $CHCl_3$); ν_{max}/cm^{-1} 2955 (C-H), 2204 (C≡C), 1725 (C=O), 1639 (C=O), 1613 (C=C); δ_H (400 MHz, $CDCl_3$) 0.97 (9H, s, C(CH_3)$_3$), 3.41 (1H, d, *J* 8.6, C(1)H_AH_B), 3.79 (3H, s, CO_2CH_3), 4.80 (1H, s, C(3)*H*), 4.86 (1H, d, *J* 8.6, C(1)H_AH_B), 7.41 (2H, t, *J* 7.4, C(13)*H*), 7.50 (1H, tt, *J* 7.4, 1.2, C(14)*H*), 7.66-7.68 (2H, m, C(12)*H*), 7.89 (1H, s, C(7)*H*); δ_C (100 MHz, $CDCl_3$) 25.0 (C(CH_3)$_3$), 35.5 ($C(CH_3)_3$), 53.7 (CO_2CH_3), 70.6 (*C*(1)), 75.0 (*C*(7a)), 87.3 (*C*(9)), 95.3 (*C*(10)), 97.6 (*C*(3)), 119.5 (*C*(11)), 128.9 (*C*(13)), 131.6 (*C*(14)), 133.6 (*C*(12)), 138.0 (*C*(6)), 153.2 (*C*(7)), 168.1 (CO_2CH_3), 170.5 (*C*(8)), 171.9 (*C*(5)); *m/z* (ESI^+) 368.2 (MH^+, 27%), 390.0 (MNa^+, 100%); HRMS (ESI^+) found 368.14939, $C_{21}H_{22}NO_5$ (MH^+) requires 368.14925.

Methyl (3*R*,6*S*,7*S*,7a*S*)-3-(*tert*-butyl)-7-iodo-6-(methoxy(methyl)carbamoyl)-5-oxodihydro-1*H*,3*H*-pyrrolo[1,2-c]oxazole-7a(5*H*)-carboxylate (28)



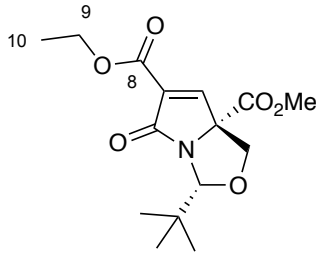
TMSI (25 µL, 0.18 mmol) was added to a solution of methyl ether **12** (53 mg, 0.15 mmol) in anhydrous DCM (740 µL). The solution was stirred at room temperature for 1 h, then diluted with H_2O and extracted with Et_2O. The combined organic exctracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by *flash* column chromatography (30% EtOAc in petrol) to give iodide **28** (39 mg, 0.086 mmol, 59%) as a white solid; m.p. 146 °C (deg). R_f (30% EtOAc in petrol) 0.28; $[\alpha]_D^{20}$ +1.6 (*c* 1.3, $CHCl_3$); ν_{max}/cm^{-1} 2951 (C-H), 1755 (C=O), 1708 (C=O), 1668 (C=O); δ_H (500 MHz, $CDCl_3$) 0.87 (9H, s, C(C*H*$_3$)$_3$), 3.32 (3H, s, NC*H*$_3$), 3.62 (1H, d, *J* 8.9, C(1)*H*$_A$H$_B$), 3.82 (3H, s, NOC*H*$_3$), 3.88 (3H, s, CO_2CH_3), 4.89 (1H, s, C(3)*H*), 4.89 (1H, d, *J* 12.2, C(6)*H*), 4.95 (1H, d, *J* 8.9, C(1)H$_A$*H*$_B$), 4.96 (1H, d, *J* 12.2, C(7)*H*); δ_C (125 MHz, $CDCl_3$) 17.4 (*C*(6)), 24.9 (C(*C*H$_3$)$_3$), 32.5 (NCH$_3$), 36.4 (*C*(CH$_3$)$_3$), 53.1 (CO_2CH_3), 59.1 (*C*(7)), 62.2 (NO*C*H$_3$), 73.4 (*C*(1)), 75.7 (*C*(7a)), 96.9 (*C*(3)), 165.9 (*C*(8)), 170.2 (CO_2CH_3), 170.3 (*C*(5)); *m/z* (ESI$^+$) 455.0 (MH^+, 31%), 477.0 (MNa^+, 100%); HRMS (ESI$^+$) found 455.06721, $C_{15}H_{24}IN_2O_6$ (MH^+) requires 455.06736.

Methyl (3*R*,7a*S*)-3-(*tert*-butyl)-6-(methoxy(methyl)carbamoyl)-5-oxo-1*H*,3*H*-pyrrolo[1,2-c]oxazole-7a(5*H*)-carboxylate (30)



Triethylamine (79 µL, 0.57 mmol) was added to a solution of iodide **28** (39 mg, 0.086 mmol) in anhydrous DCM (1.1 mL). The mixture was then stirred at room temperature for 20 h, diluted with brine and extracted with Et_2O. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by *flash* column chromatography (25% to 60% EtOAc in petrol) to give alkene **30** (13 mg, 0.041 mmol, 48%) as a white solid; m.p. 213 °C (deg). R_f (60% EtOAc in petrol) 0.24; $[\alpha]_D^{20}$ +184.5 (*c* 0.4, $CHCl_3$); ν_{max}/cm^{-1} 2955 (C-H), 1741 (C=O), 1702 (C=O), 1668 (C=O), 1635 (C=C); δ_H (500 MHz, $CDCl_3$) 0.96 (9H, s, C(C*H*$_3$)$_3$), 3.29 (3H, s, NC*H*$_3$), 3.41 (1H, d, *J* 8.6, C(1)*H*$_A$H$_B$), 3.70 (3H, s, NOC*H*$_3$), 3.78 (3H, s, CO_2C*H*_3), 4.73 (1H, s, C(3)*H*), 4.80 (1H, d, *J* 8.6, C(1)H$_A$*H*$_B$), 7.26 (1H, s, C(7)*H*); δ_C (125 MHz, $CDCl_3$) 25.0 (C(*C*H$_3$)$_3$), 32.3 (N*C*H$_3$), 35.5 (*C*(CH$_3$)$_3$), 53.5 (CO_2*C*H_3), 61.8 (NO*C*H$_3$), 70.5 (*C*(1)), 76.2 (*C*(7a)), 97.4 (*C*(3)), 137.7 (*C*(6)), 144.9 (*C*(7)), 162.3 (*C*(8)), 168.7 (*C*O$_2$CH$_3$), 173.3 (*C*(5)); *m/z* (ESI$^+$) 327.2 (MH$^+$, 100%), 349.0 (MNa$^+$, 56%); HRMS (ESI$^+$) found 327.15507, $C_{15}H_{23}N_2O_6$ (MH$^+$) requires 327.15506.

6-Ethyl 7a-methyl (3*R*,7a*S*)-3-(*tert*-butyl)-5-oxo-1*H*,3*H*-pyrrolo[1,2-c]oxazole-6,7a(5*H*)-dicarboxylate (31)



TMSI (10 µL, 0.070 mmol) was added to a solution of methyl ether **15** (20 mg, 0.058 mmol) in anhydrous DCM (300 µL). The solution was stirred at room temperature for 1 h, then diluted with H_2O and extracted with Et_2O. The combined organic exctracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude residue was dissolved in anhydrous DCM (600 µL), and triethylamine (24 µL, 0.17 mmol) was added. The mixture was then stirred at room temperature for 20 h, diluted with brine and extracted with Et_2O. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by

flash column chromatography (10% to 20% EtOAc in petrol) to give alkene **31** (14 mg, 0.044 mmol, 75%) as a yellow oil. R_f (25% EtOAc in petrol) 0.24; $[\alpha]_D^{20}$ +159.2 (*c* 0.4, $CHCl_3$); ν_{max}/cm^{-1} 2960 (C-H), 1730 (C=O), 1627 (C=C); δ_H (400 MHz, $CDCl_3$) 0.94 (9H, s, C(CH_3)$_3$), 1.35 (3H, t, *J* 7.1, C(10)H_3), 3.35 (1H, d, *J* 8.6, C(1)H_AH_B), 3.77 (3H, s, CO_2CH_3), 4.33 (2H, q, *J* 7.1, C(9)H_2), 4.74 (1H, s, C(3)*H*), 4.81 (1H, d, *J* 8.6, C(1)H_AH_B), 7.75 (1H, s, C(7)*H*); δ_C (100 MHz, $CDCl_3$) 14.3 (*C*(10)), 24.9 (C(CH_3)$_3$), 35.5 (*C*(CH_3)$_3$), 53.6 (CO_2CH_3), 61.9 (*C*(9)), 70.5 (*C*(1)), 75.1 (*C*(7a)), 97.6 (*C*(3)), 132.9 (*C*(6)), 152.5 (*C*(7)), 160.7 (*C*(8)), 168.2 (CO_2CH_3), 172.3 (*C*(5)); *m/z* (ESI^+) 334.2 (MNa^+, 100%); HRMS (ESI^+) found 334.12605, $C_{15}H_{21}NNaO_6$ (MNa^+) requires 334.12611.

2. ANTIBACTERIAL ACTIVITY

Antibacterial assays were performed using the hole-plate method with agar plates inoculated with Gram-positive *Staphylococcus aureus* DS267 and Gram-negative *Escherichia coli* X580. Samples were prepared as 4 mg/mL solutions in 1:1 MeOH/DMSO, and diluted to lower concentrations where necessary. A 100 µL aliquot of each solution was loaded into wells of 10 mm of diameter in agar plates and incubated at 37 °C for 16-20 h. The diameters of the resultant inhibition zones were then measured along two perpendicular axes and averaged to obtain the zone of inhibition. The assays were repeated in duplicate, and a negative control was run with solvent alone.

Cephalosporin C (CephC) was used as a standard. Calibration curves were performed at 2-100 µg/mL for *E. coli* and 200-1000 µg/mL for *S. aureus*, and these were collected for each set of bioassays performed.

Table S1 indicates the zone sizes obtained for the compounds tested at the indicated concentration, which are the average of duplicates. The bactericidal effect of the compounds was compared to that of the standard CephC via the relative potency, which corresponds to the equivalent moles of CephC (that would have given the same zone size as the compound) / moles of the compound. The equivalent number of moles of Ceph C was calculated from the calibration curves.

Table S1. Antibacterial activity of synthesised analogues against *E. coli* and *S. aureus* using the hole-plate method. n.a. = not active, 'H' = 'halo' zone of inhibition.

Compound	Concentration [mg/mL]	*E. coli*		*S. aureus*	
		Zone size [mm]	Relative potency	Zone size [mm]	Relative potency
9	4	n.a.	-	n.a.	-
10	4	n.a.	-	n.a.	-
12	4	n.a.	-	n.a.	-
13	4	n.a.	-	13.5	0.08
14	4	n.a.	-	n.a.	-
15	1	21	$8.0 \cdot 10^{-3}$	22	1.30
23	1	27.5	$1.6 \cdot 10^{-2}$	23	1.54
24	1	21.5	$8.4 \cdot 10^{-3}$	27.75	3.42
25	1	18.75	$6.3 \cdot 10^{-3}$	24.5	1.98
26	1	18.75	$6.3 \cdot 10^{-3}$	28.25	3.72
27	1	14.25 H	$3.9 \cdot 10^{-3}$	28.5	3.89
28	1	19.5	$6.8 \cdot 10^{-3}$	14.5 H	0.37
30	1	19.5	$6.8 \cdot 10^{-3}$	14.25 H	0.35
31	1	21	$8.0 \cdot 10^{-3}$	23	1.54

3. ANTICANCER ACTIVITY

H460 and MCF7 cells were purchased from ATCC and cultured in DMEM containing 10% fetal calf serum (FCS) and 1% penicillin-streptavidin (PS), all purchased from Gibco, in a humidified atmosphere at 37°C and 5% CO_2. Hoechst 33342 was purchased from Sigma, and propidium iodide from Biolegend.

Stock solutions of the compounds were prepared at 10 mM in DMSO, stored at -15 °C and defrosted each time before use.

The effect of the compounds on cell viability was analysed by obtaining the total number of live and dead cells per well of a 96-well plate (Corning 3595), using Hoechst 33342 and propidium iodide staining. Cells were seeded at densities of 5,000 cells/well. Cells were incubated in the presence of compound for three cell cycles and then stained and counted using a Celigo imaging cytometer. The IC_{50} (the compound concentration at which cell viability is 50% of that of the control) value for each

compound was determined from a plot of viable cells, expressed as a percentage of the control cell count, against log[compound] in Graphpad Prism v7, using the equation $y = 100/(1 + 10^{(m(\log IC50 - x))})$ in which m is the gradient of the slope.

Table S2. IC_{50} values [μM] of **23-27** against the 2 cell lines tested. The assays were performed in triplicates.

Cell line	Compound				
	23	**24**	**25**	**26**	**27**
MCF7	7.3	2.2	1.3	0.64	16.5
	7.6	2.1	1.1	0.38	9.1
	3.0	1.1	0.72	0.34	9.8
H460	18.1	5.1	3.95	0.57	10.4
	6.5	3.3	2.4	0.48	15.1
	14.4	4.7	4.0	0.78	11.1

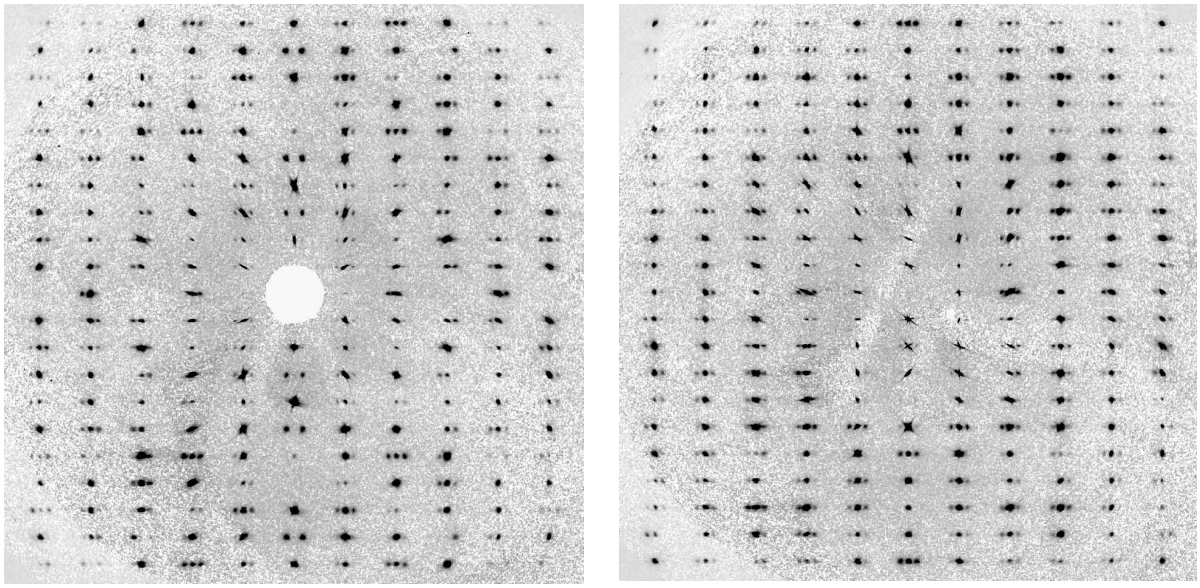
4. X-RAY CRYSTALLOGRAPHIC STUDIES

Low temperature[6] single crystal X-ray diffraction data were collected using a (Rigaku) Oxford Diffraction SuperNova diffractometer. Raw frame data were reduced using CrysAlisPro and the structures were solved using 'Superflip'[7] before refinement with CRYSTALS[8,9] as per the SI (CIF). Full refinement details are given in the Supporting Information (CIF); Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 1817419-20) and can be obtained via www. ccdc.cam.ac.uk/data_request/cif.

Single Crystal Data for **12**: C16H26N2O7, Mr =358.39. 150 K – orthorhombic, P21 21 21, a = 8.5004(2) Å, b = 12.8701(2) Å, c = 16.4218(3) Å, V = 1796.56(6) Å, Data/restraints/parameters – 3739/30/236, Flack = -0.02(13) for 1597 Friedel pairs, Rint = 0.038, Final R1 = 0.0356, wR2 = 0.0950 (I>2σ(I)).

Single Crystal Data for **28**: C15H23I1N2O6, Mr =454.26. 150 K – orthorhombic, P21 21 21, a = 8.55340(10) Å, b = 13.2093(2) Å, c = 16.1337(2) Å, V = 1822.86(4) Å, Data/restraints/parameters – 3811/27/265, Flack = 0.026(6) for 1601 Friedel pairs, Rint = 0.071, Final R1 = 0.0301, wR2 = 0.0803 (I>2σ(I)).

During single crystal X-ray diffraction studies of **28** additional reflections were observed in the diffraction pattern.[10] Upon closer inspection of the diffraction data these additional reflections could be recognised as satellite reflections, see Figure 1. The satellite reflections can be indexed with a *q*-vector of 0.15414(16), 0(2e-004), -1.2e-003(2). These reflections could be observed, but the intensity is so low that they cannot be used meaningfully in a refinement (the average I/sigma ≈ 2.74 and R_{int} ≈ 50% to a resolution of 0.8 Å). By only taking into account the main reflections the structure contain disorder. If the satellite reflections could have been used meaningfully in a refinement it would have been possible to resolve the disorder.



(a) (b)

Figure 1. Reconstructed precession images of (a) the h0l – layer and (b) the h1l –layer for single crystal diffraction data of **28**. Additional weaker reflections are observed close to the main reflections.

5. REFERENCES

(1) Andrews, M. D.; Brewster, A. G.; Crapnell, K. M.; Ibbett, A. J.; Jones, T.; Moloney, M. G.; Prout, K.; Watkin, D. *J. Chem. Soc. Perkin Trans. 1* **1998**, 223.

(2) Andrews, M. D.; Brewster, A. G.; Moloney, M. G. *J. Chem. Soc. Perkin Trans. 1* **2002**, 80.

(3) Josa-Culleré, L.; Moloney, M. G.; Thompson, A. L. *Synlett* **2016**, *27* (11), 1677.

(4) Tan, S. W. B.; Chai, C. L. L.; Moloney, M. G. *Org. Biomol. Chem.* **2014**, *12*, 1711.

(5) Moloney, M. G.; Josa-Culleré, L.; Thompson, A.; Towers, C. *European J. Org. Chem.* **2017**.

(6) Cosier, J.; Glazer, A. M. *J. Appl. Cryst.* **1986**, *19*, 105.

(7) Palatinus, L.; Chapuis, G. *J. Appl. Cryst.* **2007**, *40*, 786.

(8) Parois, P.; Cooper, R. I.; Thompson, A. L. *Chem. Cent. J.* **2015**, *9*, 30.

(9) Cooper, R. I.; Thompson, A. L.; Watkin, D. J. *Chem. Cent. J.* **2010**, *43*, 1100.

(10) Wagner, T.; Schönleber, A. *Acta Crystallogr.* **2009**, *B*, 249.