## Supporting information

# The first syntheses of the 1-oxo-2-oxa-5-azaspiro[3.4]octane ring system found in oxazolomycin.

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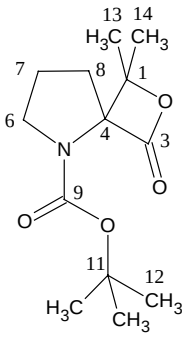
**General.**

All reactions were performed under an inert atmosphere and were magnetically stirred. All reactions requiring anhydrous conditions were conducted in flame-dried apparatus. Where appropriate, solvents were dried by distillation from the usual drying agent prior to use: THF and diethyl ether (ether) from sodium and benzophenone, dichloromethane from calcium hydride. Petroleum ether refers to the fraction with a 40-60ºC boiling point. Commercially available reagents were used without further purification unless otherwise stated. The concentration of alkyllithium reagents was determined by titration against diphenylacetic acid.

Reactions were monitored by TLC with Merck silica gel $60F_{254}$ pre-coated aluminium foil sheets, layer thickness 0.25mm. Compounds were visualised with UV light at 254 nm, followed by development using ninhydrin or phosphomolybdic acid. Column chromatography was carried out using flash silica gel 60, 35-70 μ from Fluorochem Ltd. at increased pressure (hand-held bellows).

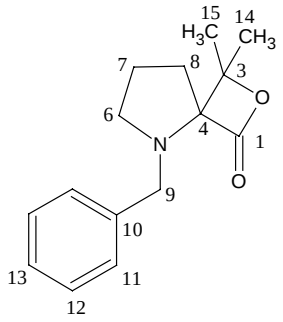
Melting points were recorded on an Electrothermal 9100 and are uncorrected. Infra-red (IR) spectra were recorded as a thin neat film on an ATI Mattson Genesis FT-IR spectrometer. $^{1}$H-NMR and $^{13}$C-NMR spectra were recorded using a Jeol EX270 spectrometer at 270 MHz and 67.9 MHz respectively. Chemical shifts (δ) are quoted in ppm on the scale using residual solvent as internal standard. Coupling constant values (*J*) are given in Hz. Multiplicities are described using the following abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. Low and high resolution mass spectra were recorded using a Fisons analytical Autospec instrument in chemical ionisation (CI) mode. Ion mass (m/z) signals are reported as values in atomic mass units followed, in parentheses, by the peak intensity relative to the base peak (100%). Combustion analyses were performed by the Chemical Analytical Services Unit at the University of Newcastle using a Carlo Erba 1106 Elemental analyser. Optical rotations were recorded on a JASCO DIP-370 DIGITAL polarimeter at r.t.

***Tert*-butyl-1, 1-dimethyl-3-oxo-2-oxa-5-azaspiro[3.4]octan-5-carboxylate (13)**



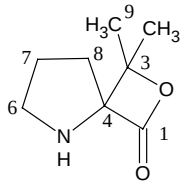
To a solution of diisopropylamine (437 mg, 4.32 mmol) in dry THF (8 $cm^3$) at -90°C was added n-BuLi (1.73 $cm^3$, 2.5M in hexanes, 4.32 mmol). The solution was allowed to warm up to 0°C over 10 min and recooled to -90°C before 1-tert-butyl 2-phenyl 1,2-pyrrolidinedicarboxylate (**6**) (1.50 g, 3.93 mmol) in dry THF (2 $cm^3$) was added dropwise over 45 min. The mixture was allowed to react at -90°C for 20 min and then a solution of freshly distilled acetone (217 mg, 3.74 mmol) in dry THF (1.3 $cm^3$) was added dropwise over 20 min. The solution was stirred at -90°C for 30 min and allowed to warm to r.t. over 4 h, whereupon it was quenched by adding aqueous 1M NaOH. The two layers were separated and the aqueous phase was extracted with ether. The combined organic phases were washed with 1M NaOH ($2 \times 1$ $cm^3$), brine ($2 \times 1$ $cm^3$), dried over $Na_2SO_4$ and the solvent evaporated. The residue was purified by column chromatography (petroleum ether-ethyl acetate = 7:3) to give *tert*-butyl-1, 1-dimethyl-3-oxo-2-oxa-5-azaspiro[3.4]octan-5-carboxylate **13** (186 mg, 0.73 mmol, 19 %) as a solid. Recrystallization from ether-hexane (1:1) afforded colourless needles; mp 100-104 °C (Found: C, 61.3; H, 8.4; N, 5.6. $C_{13}H_{21}NO_4$ requires C, 61.2; H, 8.3; N, 5.5%); $R_f$ 0.48 (petroleum ether-ethyl acetate, 1:1); $\upsilon_{max}/cm^{-1}$ 1828, 1699; $\delta_H$ (DMSO, 80°C) 1.42 (9 H, s, H-12), 1.48 (3 H, s, H-13), 1.54 (3 H, s, H-14), 1.59-1.78 (1 H, m, H-7), 1.84-1.99 (2 H, m, H-7, H-8), 2.37-2.45 (1 H, m, H-8), 3.28-3.47 (2 H, m, H-6); $\delta_C$ ($CDCl_3$) (2 rotamers), 22.0/22.1 (C-13), 22.4/23.4 (C-7), 23.9/24.0 (C-14), 27.9/28.2 (C-12), 30.4/31.3 (C-8), 47.3/47.5 (C-6), 80.8 (C-11), 82.5 (C-4), 86.4/86.6 (C-1), 153.5/154.2 (C-9), 170.3/170.4 (C-3); *m/z* 273 ($MNH_4^+$, 4), 256 ($MH^+$, 2), 156 ([MH-BOC]$^+$, 10), 112 ([MH-$CO_2$-BOC]$^+$, 100); (Found: $MH^+$, 256.1547. $C_{13}H_{21}NO_4$ requires *MH*: 256.1549, 3.5 ppm error).

**5-Benzyl-3,3-dimethyl-2-oxa-5-azaspiro[3.4]octan-1-one (16)**



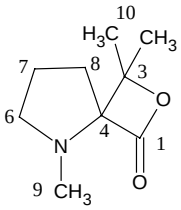
To a solution of diisopropylamine (120 mg, 1.19 mmol) in dry THF (2 $cm^3$) at -78°C was added n-BuLi (750 μl, 1.6M in hexanes, 1.20 mmol). The solution was allowed to warm up to 0°C over 10 min and recooled to -78°C before phenyl (2S) 1-benzyl-2-pyrrolidine carboxylate (**15**) (304 mg, 1.08 mmol) in dry THF (1 $cm^3$) was added dropwise over 5 min. The mixture was allowed to react at -78°C for 30 min and then a solution of freshly distilled acetone (64 mg, 1.08 mmol) in dry THF (0.5 $cm^3$) was added over 5 min. The solution was stirred at -78°C for 15 min whereupon it was quenched by adding saturated aqueous $NH_4Cl$ and allowed to warm up to r.t. The two layers were separated and the organic phase was washed with saturated aqueous $Na_2CO_3$ (2 × 1 $cm^3$), brine (2 × 1 $cm^3$), dried over $Na_2SO_4$ and evaporated. The residue was purified by column chromatography (petroleum ether-ether = 85:15) to give 5-benzyl-3,3-dimethyl-2-oxa-5-azaspiro[3.4]octan-1-one **16** (160 mg, 0.65 mmol, 62 %) as a solid. Recrystallization from cyclohexane afforded white prisms; mp 56-58°C (Found: C, 73.5; H, 7.7; N, 5.7. $C_{15}H_{19}NO_2$ requires C, 73.4; H, 7.8; N, 5.7%); $R_f$ 0.38 (petroleum ether-diethyl ether, 7:3); $\upsilon_{max}/cm^{-1}$ 1809 (C=O); $\delta_H$ ($CDCl_3$), 1.52 (3 H, s, H-14), 1.64 (3 H, s, H-15), 1.59-1.73 (1 H, m, H-7), 1.83-1.95 (1 H, m, H-7), 2.25 (1 H, ddd, *J* 13.5, 11.0, 7.0, H-8), 2.36 (1 H, ddd, *J* 13.5, 7.0, 3.0, H-8), 2.50 (1 H, dt, *J* 9.0, 6.0, H-6), 3.00 (1 H, ddd, *J* 9.0, 6.0, 2.5, H-6), 3.94 (1 H, d, *J* 14.5, H-9), 4.21 (1 H, d, *J* 14.5, H-9), 7.22-7.40 (5 H, m, H-Ar); $\delta_C$ ($CDCl_3$), 23.0 (C-15), 24.2 (C-7), 24.3 (C-14), 31.3 (C-8), 54.2 (C-6), 57.9 (C-9), 82.0 (C-4), 87.5 (C-3), 127.0 (C-12), 127.6 (C-11), 129.1 (C-13), 139.1 (C-10), 174.0 (C-1); *m/z* 246 ($MH^+$, 48), 202 ($[MH\text{-}CO_2]^+$, 29), 91 ($PhCH_2^+$, 100); (Found: $MH^+$, 246.1483. $C_{15}H_{19}NO_2$ requires *MH*: 246.1494, 4.6 ppm error).

**3, 3-Dimethyl-2-oxa-5-azaspiro[3.4]octan-1-one (19)**



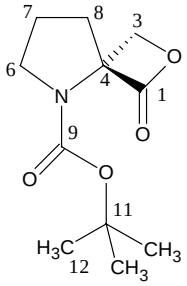

A flask containing **16** (60 mg, 0.24 mmol) and 10% Pd/C (26 mg, 25 μmol) was flushed with $H_2$. Ethyl acetate (10 $cm^3$) was added and the suspension was stirred for 30 min under $H_2$ at atmospheric pressure (balloon). The mixture was filtered through celite and the solvent was removed *in vacuo* to give 3, 3-dimethyl-2-oxa-5-azaspiro[3.4]octan-1-one **19** (38 mg, 0.24 mmol, 100%) as a white solid; mp 31-33°C (Found: $MH^+$, 156.1030. $C_8H_{13}NO_2$ requires *MH*: 156.1025, 3.5 ppm error); $R_f$ 0.16 (petroleum ether-ethyl acetate = 1:1); $\upsilon_{max}/cm^{-1}$ 1807 (C=O); $\delta_H$ ($CDCl_3$) 1.47 (6 H, s, H-9), 1.70-2.17 (4 H, m, H-7, H-8), 2.29 (1 H, s, H-5), 2.94-3.02 (1 H, m, H-6), 3.14-3.22 (1 H, m, H-6); $\delta_C$ ($CDCl_3$) 23.2 (C-9), 23.3 (C-9), 25.1 (C-7), 30.0 (C-8), 46.6 (C-6), 78.3 (C-4), 85.8 (C-3), 176.3 (C-1); *m/z* 156 ($MH^+$, 29), 112 ($[MH\text{-}CO_2]^+$, 100).

**3, 3, 5-Trimethyl-2-oxa-5-azaspiro[3.4]octan-1-one (20)**



To a stirred solution of **19** (49 mg, 0.32 mmol) and anhydrous potassium carbonate (131 mg, 0.95 mmol) in anhydrous DMF (3 $cm^3$) was added methyl iodide (182 mg, 1.28 mmol). The mixture was stirred at 30ºC for 3 h whereupon a further excess of methyl iodide (182 mg, 1.28 mmol) was added. After 22 h, the solvent was removed *in vacuo* and the residue was redissolved in DCM, filtered and the solid washed with DCM. The combined filtrate and washings were concentrated and the residue was purified by column chromatography (petroleum ether-ethyl acetate = 7:3) to afford 3, 3, 5-trimethyl-2-oxa-5-azaspiro[3.4]octan-1-one **20** (50 mg, 0.29 mmol, 93%) as a colourless oil (Found: $MH^+$, 170.1180, $C_9H_{15}NO_2$ requires *MH*: 170.1181, 0.6 ppm error); $R_f$ 0.50 (ethyl acetate); $\upsilon_{max}/cm^{-1}$ 1809 (C=O); $\delta_H$ ($CDCl_3$) 1.45 (3 H, s, H-10), 1.53 (3 H, s, H-10), 1.57-1.72 (1 H, m, H-7), 1.80-1.91 (1 H, m, H-7), 2.10 (1 H, ddd, *J* 13.5, 11.5, 7.0, H-8), 2.28 (1 H, ddd, *J* 13.5, 7.0, 2.5, H-8), 2.62-2.71 (1 H, m, H-6), 2.64 (3 H, s, H-9), 3.09-3.16 (1 H, m, H-6); $\delta_C$ ($CDCl_3$) 22.5 (C-10), 24.2 (C-7), 24.5 (C-10), 31.2 (C-8), 40.2 (C-9), 57.3 (C-6), 82.2 (C-4), 87.1 (C-3), 173.8 (C-1); *m/z* 170 ($MH^+$, 100), 126 ([$MH-CO_2$]$^+$, 35).

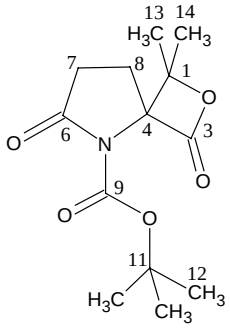
***Tert*-butyl (4S)-1-oxo-2-oxa-5-azaspiro[3.4]octan-5-carboxylate (28)**



A solution of triphenylphosphine (103 mg, 0.39 mmol) in dry THF (2 $cm^3$) was cooled down to -78°C. Freshly distilled dimethylazadicarboxylate (60 mg, 0.41 mmol) was added and a pale yellow slurry was formed. After 15 min, a solution of (2S)-1-(tert-butoxycarbonyl)-2-(hydroxymethyl)-2-pyrrolidinecarboxylic acid (**27**) (74 mg, 0.30 mmol) in dry THF (600 µl) was added over 5 min and the mixture was stirred for a further 10 min at -78°C whereupon the mixture was allowed to warm up to r.t. and the solvent evaporated *in vacuo*. The residue was purified by column chromatography (petroleum ether-ethyl acetate = 7:3) to afford *tert*-butyl (4S)-1-oxo-2-oxa-5-azaspiro[3.4]octan-5-carboxylate **28** (59 mg, 0.26 mmol, 86%) as a colourless oil that crystallises upon standing; mp 53-57°C (Found: $MNH_4^+$, 245.1509, $C_{11}H_{17}NO_4$ requires *MNH4*: 245.1501, 3.2 ppm error); $[\alpha]_D^{20}$ –5.6 (*c* 1.6, $CHCl_3$); $R_f$ 0.55 (ethyl acetate); $\upsilon_{max}/cm^{-1}$ 1830, 1693 (C=O); $\delta_H$ ($CDCl_3$) (2 rotamers), 1.45 (~3 H, s, H-12, 1 rotamer), 1.46 (~6 H, s, H-12, other rotamer), 1.75-2.05 (2 H, m, H-7), 2.20-2.49 (2H, m, H-8), 3.42

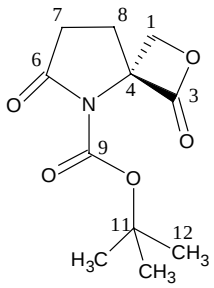
(0.6 H, dd, *J* 8.0, 5.5, H-6, 1 rotamer), 3.48 (0.4 H, dd, *J* 8.0, 5.5, H-6, other rotamer), 4.12 (~0.3 H, d, *J* 4.5, H-3, 1 rotamer), 4.15 (~0.7 H, d, *J* 4.5, H-3, 1 rotamer), 4.57 (~0.7 H, d, *J* 4.5, H-3', other rotamer), 4.77 (~0.3 H, d, *J* 4.5, H-3', other rotamer); $\delta_C$ ($CDCl_3$) (2 rotamers), 23.0/23.6 (C-7), 28.0/28.2 (C-12), 34.0/35.2 (C-8), 47.3/47.4 (C-6), 71.5/72.8 (C-3), 74.7/74.9 (C-4), 81.1/82.2 (C-11), 152.8/153.4 (C-9), 172.4/172.5 (C-1); *m/z* 245 ($MNH_4^+$, 57), 184 ($[MH\text{-}CO_2]^+$, 8), 156 (100).

***Tert*-butyl-1,1-dimethyl-3,6-dioxo-2-oxa-5-azaspiro[3.4]octan-5-carboxylate (30)**




Acetonitrile (0.2 $cm^3$), carbon tetrachloride (0.2 $cm^3$) and water (0.3 $cm^3$) were added to **13** (25 mg, 0.098 mmol) and $NaIO_4$ (86 mg, 0.401 mmol). The mixture was vigorously stirred and $RuCl_3.xH_2O$ (1 mg, 4.5 μmol) was added in one portion (further addition of 3 portions of $RuCl_3$ was necessary because of the diffusion of the metal out of solution onto the walls of the flask). TLC indicated complete conversion after 30 h and dichloromethane (1 $cm^3$) was added. The two layers were seperated and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried over $Na_2SO_4$ and concentrated *in vacuo* to give a residue that was taken up in ether and filtered over celite. Evaporation of the solvent *in vacuo* afforded *tert*-butyl-1,1-dimethyl-3,6-dioxo-2-oxa-5-azaspiro[3.4]octan-5-carboxylate **30** (26.5 mg, 0.098 mmol, 100%) as a white powder; mp 131-132 °C (Found: $MH^+$, 287.1612 $C_{13}H_{19}NO_5$ requires *MH*: 287.1607, 1.9 ppm error); $R_f$ 0.27 (petroleum ether-ethyl acetate, 1:1); $\upsilon_{max}/cm^{-1}$ 1824, 1762, 1724 (C=O); $\delta_H$ ($CDCl_3$) 1.53 (9 H, s, H-12), 1.61 (3 H, s, H-13), 1.64 (3 H, s, H-14), 2.25-2.59 (4 H, m, H-7, H-8); $\delta_C$ ($CDCl_3$) 22.0 (C-13), 23.6 (C-7), 25.0 (C-14), 27.6 (C-12), 30.2 (C-8), 77.2 (C-4), 85.8 (C-11), 85.9 (C-1), 149.1 (C-9), 167.8 (C-6), 171.9 (C-3); *m/z* 287 ($MNH_4^+$, 15), 226 ($[MH\text{-}CO_2]^+$, 100), 187 ($[MNH_4\text{-BOC}]^+$, 92), 126 ($[MH\text{-}CO_2\text{-BOC}]^+$, 31).

***Tert*-butyl-3,6-dioxo-2-oxa-5-azaspiro[3.4]octan-5-carboxylate (31)**



Acetonitrile (0.23 $cm^3$), carbon tetrachloride (0.23 $cm^3$) and water (0.46 $cm^3$) were added to **28** (24 mg, 0.106 mmol) and $NaIO_4$ (90 mg, 0.422 mmol). The mixture was vigorously stirred and $RuCl_3.xH_2O$ (1.5 mg, 6.7 μmol) was added in one portion (further addition of three portions of $RuCl_3$ was necessary because of the diffusion of the metal out of solution onto the walls of the flask). TLC indicated complete conversion after 25 h and dichloromethane (1 $cm^3$) was added. The two layers were seperated and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried over $Na_2SO_4$ and concentrated *in vacuo* to give a residue that was purified by column chromatography (petroleum ether-ethyl acetate = 7:3) to give *tert*-butyl-3,6-dioxo-2-oxa-5-azaspiro[3.4]octan-5-carboxylate **31** (6.5 mg, 27 μmol, 25%) as a white powder. Recrystallisation from ethyl acetate-hexane afforded tiny needles; mp 146-148 °C (dec.) (Found: $MH^+$, 259.1301 $C_{11}H_{19}N_2O_5$ requires *$MNH_4$*: 259.1294, 2.8 ppm error); $[\alpha]_D^{20}$ +5.1 (*c* 0.16, $CHCl_3$); $R_f$ 0.11 (petroleum ether-ethyl acetate, 1:1); $\upsilon_{max}/cm^{-1}$ 1824, 1798, 1780 (C=O); $\delta_H$ ($CDCl_3$) 1.55 (9 H, s, H-12), 2.33-2.46 (1 H, m, H-7), 2.51-2.67 (3 H, m, H-7, H-8), 4.31 (1 H, d, *J* 5.0, H-1), 4.72 (1 H, d, *J* 5.0, H-1); $\delta_C$ ($CDCl_3$) 25.5 (C-7), 27.7 (C-12), 30.2 (C-8), 72.2 (C-4), 74.2 (C-1), 86.0 (C-11), 148.2 (C-9), 169.7 (C-6), 171.7 (C-3); *m/z* 259 ($MNH_4^+$, 76), 242 ($MH^+$, 7), 159 ($[MNH_4\text{-BOC}]^+$, 100), 142 ($[MH\text{-BOC}]^+$, 20).