Synthesis of the Putative Structure of (-)-Oryzoxymycin

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Experimental Section

All new stable compounds have satisfactory spectral and analytical data. Yields refer to pure isolated products.

Ethyl (+)-6-tert-butoxycarbonylamino-5-hydroxy-1,3-cyclohexadiene-1-carboxylate 10a

To a solution of KHMDS (530 mg, 2.64 mmol) in THF (10 cm³) at -50 °C was added a solution of ester (-)-**9a** (250 mg, 0.88 mmol) in THF (2.5 cm³). The solution was then warmed up to room temperature (15 minutes) and quenched with a mixture of ethyl acetate and ethanol (50 cm³, 19:1). The mixture was washed with sat. NH₄Cl (25 cm³), dried (MgSO₄) and concentrated under reduced pressure. The resulting residue was purified by flash chromatography eluting with petroleum ether/ethyl acetate mixture (7:3) to give cyclohexadiene **10a** (178 mg, 71%) as a pale yellow semi solid. $[\alpha]_D^{21} +266$ (c = 1, CHCl₃). Found: C, 59.20, H, 7.53; N, 4.80. C₁₄H₂₁NO₅ requires C, 59.35, H, 7.47, N, 4.94. $\nu_{\max}$ (KBr): 3400 (br), 2979, 2931, 1716, 1700, 1584, 1514, 1392, 1366, 1245, 1169, 1079, 1017, 915, 737cm⁻¹; δ_H (500 MHz, CDCl₃): 1.28 (3H, t, J = 7.0 Hz, OCH₂CH₃), 1.42 (9H, s, OC(CH₃)₃), 4.20 (2H, q, J = 7.0 Hz, OCH₂CH₃), 4.36 (1H, s, H-5), 4.48 (1H, br, NH), 4.76(1H, m, H-6), 6.26 (2H, m, H-3 and 4), 7.17 (1H, d, J = 4.8 Hz); δ_C (125 MHz, CDCl₃): 14.1 (OCH₂CH₃), 28.3 (OC(CH₃)₃), 50.0 (C-6), 60.8 (OCH₂CH₃), 67.7(C-5), 80.0 (OC(CH₃)₃), 124.5 (C-3), 132.6 (C-2), 133.5 (C-4), 155.4 (NCO₂), 165.9 (CO₂C₂H₅); m/z (CI): 284 (MH⁺). The major by-product of the reaction was *ethyl 2-hydroxybenzoate* identified by comparison with an authentic sample.¹

tert-Butyl (2'S,5R,6R)-(+)-2'-[6-*tert*-butoxycarbonylamino-5-hydroxycyclohexa-1,3-diene-1-carbonyloxy]propionate **16a**

CsF (240 mg, 1.57 mmol) was dried under vacuum at 150°C for 5 hours. A suspension of the dried CsF in DMF (5 cm³) was stirred at 25°C for 30 minutes. To this suspension was added acid **15a** (200 mg, 0.78 mmol) and the mixture was stirred at 25°C for 30 minutes. (R)-MsOCH(CH₃)CO₂^tBu was then added and the reaction mixture was stirred at 50°C. After 24 hours the reaction mixture was partitioned between ethyl acetate (3 x 50 cm³) and water (50 cm³). The combined organic extracts were washed with brine, dried (MgSO₄) and concentrated under reduced pressure to give a yellow oil. Purification by column chromatography eluting with petrol/ethyl acetate (6:4) gave **16a** as a yellow gum (205 mg, 68%); [α]_D^{21.6} -171 (c 1, CHCl₃); δ_H (500 MHz, CDCl₃): 1.43 and 1.46 (18H, s, 2 x OC(CH₃)₃), 1.51 (3H, d, J = 6.9 Hz, H-3), 2.90 (1H, br, OH), 4.55 (1H, br, H-5'), 4.76 (1H, m, H-6'), 5.06 (1H, q, J = 6.9 Hz, H-2), 6.30 (2H, m, H-3' and 4'), 7.22 (1H, d, J = 5.5 Hz, H-2'); δ_C (125 MHz, CDCl₃): 17.1 (C-3), 28.2 and 28.4 (2 x OC(CH₃)₃), 51.2 (C-6'), 68.9 (C-5'), 69.4 (C-2), 80.2 and 80.4 (2 x OC(CH₃)₃), 125.3 (C-3'), 125.3 (C-1'), 133.5 (C-4'), 152.1 (NCO₂), 169.4 and 170.1 (2 x CO₂); MS m/z (ES⁺): 406 (MNa)⁺.

tert-Butyl (2'S,5S,6S)-(+)-2'-[6-*tert*-butoxycarbonylamino-5-hydroxycyclohexa-1,3-diene-1-carbonyloxy]propionate **16b**

Acid **15b** when subjected to the same conditions as above gave ester **16b** as white gum white solid (89%). (204 mg, 68%); [α]_D^{21.6} +181 (c 1, CHCl₃); δ_H (500MHz, CDCl₃): 1.43 and 1.46 (18H, s, 2 x OC(CH₃)₃), 1.49 (3H, d, J = 6.9 Hz, H-3'), 2.78 (1H, br, OH), 4.40 (1H, br, NH), 4.52 (1H, br, H-5), 4.78 (1H, m, H-6), 5.04 (1H, q, J = 6.9 Hz, H-2'), 6.27 (2H, m, H-3 and 4), 7.24 (1H, d, J = 5.5 Hz, H-2); δ_C (125 MHz, CDCl₃): 17.2 (C-3'), 28.2 and 28.6 (2 x OC(CH₃)₃), 50.6 (C-6), 68.4 (C-5), 69.7 (C-2), 80.2 and 82.3 (2 x OC(CH₃)₃), 124.6 (C-3), 125.2 (C-1), 133.5 (C-4), 134.5 (C-2), 152 (NCO₂), 170.0 and 170.1 (CO₂); m/z (ES⁺): 406 (MNa)⁺.

(2'S,5R,6R) 2'-[6-amino-5-hydroxy-1,3-cyclohexadiene-1-carbonyloxy]propionic acid • trifluoroacetic acid salt (ent - 'oryzoxymycin' trifluoroacetic acid salt) **17a**:

To a solution of ester **16a** (140 mg, 0.37 mmol) in dichloromethane (5 cm³) was added trifluoroacetic acid (112 µl, 1.46 mmol). This mixture was then stirred until all the starting material was consumed (TLC ca. 12 h). The solvent was removed under reduced pressure to give a brown gum which was dissolved in water (20 cm³) and washed with ethyl acetate (20 cm³). The aqueous phase was concentrated under reduced pressure to the title salt **17b** as a yellow gum (75 mg, 89%); $[\alpha]_D^{20.8} -199$ (c 1, H₂O); HRMS (ES⁺) Found M⁺-H₂O, 209.0690. C₁₀H₁₁NO₄ requires M, 209.0688; $\nu_{\max}$ (KBr): 3413, 3550-2800(br), 1726 (shoulder), 1679, 1580, 1271, 1202, 1137, 1095, 1044 cm⁻¹; δ_H (500 MHz, D₂O): 1.57 (3H, *d*, J = 7.2 Hz, H-3), 4.42 (1H, *m*, H-6'), 4.45 (1H, *d*, J = 1.2 Hz, H-5'), 5.16 (1H, *q*, J = 7.2 Hz, H-2), 6.49 (2H, *m*, H-3' and H-4'), 7.57 (1H, *d*, J = 1.5 Hz, H-2'); δ_C (125 MHz, D₂O): 16.4 (C-3), 48.4 (C-6'), 63.9 (C-5'), 71.2 (C-2), 121.2 (C-1'), 125.3 (3'), 132.5 (C-4'), 138.8 (C-2'), 166.2 (CO₂), 176.3 (C-1), MS m/z (CI): 228 (MH⁺).

(2*S*,5*S*,6*S*) 2'-[6-amino-5-hydroxy-1,3-cyclohexadiene-1-carbonyloxy]propionic acid • trifluoroacetic acid salt **17b**:

Ester **16b** when subjected to the same conditions as above gave acid **16b** as white solid (89%); m.p. 106-108°C, $[\alpha]_D^{21} +165$ (c = 1, CHCl₃). Found: C, 46.60, H, 5.34; N, 4.64. C₁₀H₁₃NO₅•C₂H₃O₂F₃ requires C, 46.61, H, 4.96, N, 4.53. $\nu_{\max}$ (KBr): 3425, 3550-2800(br), 2927, 1703, 1677, 1589, 1276, 1201, 1138, 1099, 1044 cm⁻¹; δ_H (500 MHz, D₂O): 1.55 (3H, *d*, J = 7.0 Hz, H-3'), 4.39 (1H, *d*, J = H-6), 4.43 (1H, *dd*, J = 3.0 and 1.5 Hz, H-5), 5.18 (1H, *q*, J = 7.0 Hz, H-2'), 6.47 (2H, *m*, H-3 and 4), 7.55 (1H, *d*, J = 5.5 Hz, H-2); δ_C (125 MHz, D₂O): 16.2 (C-3'), 48.5 (C-6), 63.9 (C-5), 70.5 (C-2'), 121.0 (C-1), 125.3 (C-3), 132.8 (C-4), 139.1 (C-2), 166.1 (CO₂H), 175.3 (C=O); m/z (CI/NH₃): 228 (MH⁺, 100%), 210 (96), 138 (42).

(1) Perkins, M. V.; Kitching, W.; Drew, R. A. I.; Moore, C. J.; Konig, W. A. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1111-1117.