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Warren J. Ebenezer [a]

[a] Department of Chemistry , University of Nottingham , University Park Nottingham, NG7 2RD, England

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COLABOMYCIN CO-METABOLITES.

SYNTHESIS OF 2880-II, A METABOLITE RELATED TO FERULIC ACID

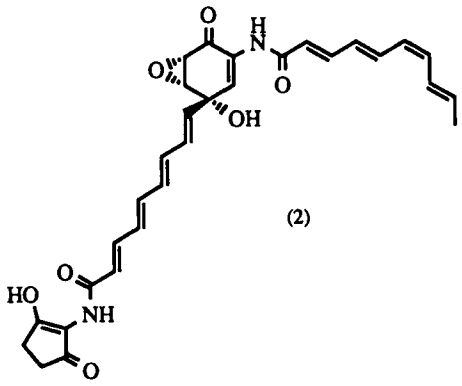
Warren J. Ebenezer

Department of Chemistry, University of Nottingham, University Park, Nottingham NG7 2RD, England

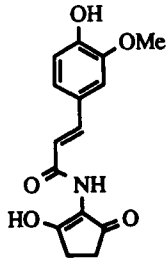
Abstract: A synthesis of 2880-II (**1**), a co-metabolite of colabomycin A (**2**) from *Streptomyces griseoflavus*, is described.

The unusual cinnamoyl substituted 2-amino-3-hydroxycyclopent-2-enone (**1**), known as substance 2880-II has recently been isolated along with colabomycin A (**2**) from the mycelium of *Streptomyces griseoflavus* (strain Tü 2880).[1] Colabomycin A[2] is a member of the manumycin group of antibiotics[3] and is active against Gram-positive bacteria and L-1210 leukemia stem cells. Reductiomycin,[4] moenomycin[5,6] and bafilomycin B_1[7] are other examples of

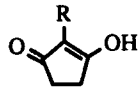
naturally occurring antibiotics which exhibit the 2-amino-3-hydroxycyclopent-2-enone moiety.



(2)

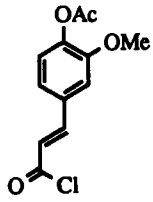


(1)

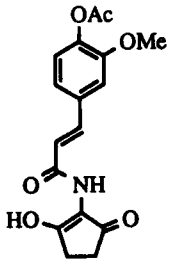


(3)

a) R = NO_2
b) R = NH_3Cl



(4)



(5)

In conjunction with synthetic work towards the manumycin family of natural products, we now report a synthesis of substance 2880-II.

Thus, nitration of 1,3-cyclopentanedione in diethyl ether with dry nitrogen dioxide gas first led to the nitro derivative (**3a**; 93%) which upon hydrogenation in acetic acid, in the presence of hydrochloric acid, using Adams' catalyst next provided the highly unstable amine hydrochloride salt (**3b**).[6]

Treatment of the amine salt (**3b**) with the acid chloride (**4**) derived from ferulic acid [Ac_2O-C_5H_5N, then $(COCl)_2$-DMF] in pyridine then led to the amide (**5**) as a pale yellow powder, m.p. 234-5°C.

Deprotection of (**5**) using ammonia in methanol finally gave the metabolite 2880-II (**1**) as an attractive primrose yellow powder, which showed spectroscopic characteristics identical to those of the naturally derived material.

Experimental

Melting points were recorded on a Köfler hot stage apparatus and are uncorrected. Infra-red spectra were recorded on a Perkin-Elmer 1720X FT spectrometer. Ultraviolet spectra were recorded on a Pye Unicam SP800 spectrometer. N.M.R. spectra were recorded on a Bruker WP8OSY PFT, WM250 PFT or an AM400 PFT spectrometer. For n.m.r. spectra, deuteriochloroform was used as solvent and tetramethylsilane as internal standard unless otherwise stated. Mass spectra were recorded on an AEI MS 902, or a VG 7070E spectrometer. Microanalytical

data were obtained on a Perkin Elmer 240B elemental analyser.

3-[4-(Acetyloxy)-3-methoxyphenyl]-2-propenoic acid: Acetic anhydride (0.37ml, 1.2 equiv.) was added dropwise over 5 minutes to a stirred solution of 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid (0.64g) and a catalytic amount of DMAP in dry pyridine (2ml), at 0°C under an atmosphere of nitrogen. The mixture was stirred at 23°C for 4.5hrs and then diluted with water (15ml) and extracted with dichloromethane (3 × 20ml). The combined organic extracts were washed successively with 2N HCl, water and brine, then dried and evaporated to give the acetate (0.66g, 85%) m.p. 199-201°C (from MeOH); (Found: C, 61.0; H, 5.2%. $C_{12}H_{12}O_5$ requires C, 61.0; H, 5.1%.); $\lambda_{max.}$ (1,4-dioxane) 226 (15200), 229 inf. (14800), 279 (19200), 307 inf. (10600) nm.; $\nu_{max.}$ (KBr) 1755, 1682, 1620, 1600 and 1507 cm^{-1}; δ_H (d_6-DMSO) 2.3 (s, O*Ac*), 3.8 (s, O*Me*), 6.5 (d, *J*15.9Hz, H8), 7.2 (m, 2 × Ar*H*), 7.6 (m, H7 + Ar*H*) p.p.m.; δ_C (d_6-DMSO) 20.4 (q, CO*Me*), 55.9 (q, O*Me*), 111.7 (d, C2), 119.5/121.2/123.1 (3 × d, C5+C6+C8), 133.3 (s, C1), 140.9 (s, C4), 143.2 (d, C7), 151.2 (s, C3), 167.6 (s, C9), 168.2 (s, *C*OMe) p.p.m.; m/z (EI) 236 (M^+, 14%), 194 (100), 179 (46) and 133 (29).

3-[4-(Acetyloxy)-3-methoxyphenyl]-2-propenoyl chloride (4): Oxalyl chloride (0.96ml, 5 equiv.) was added dropwise over 10 minutes to a stirred suspension of 3-[4-(acetyloxy)-3-methoxyphenyl]-2-propenoic acid (0.43g) and a catalytic amount of DMF in dry dichloromethane (50ml), at 0°C under an atmosphere of nitrogen. The mixture was allowed to warm to 23°C over 3.5hrs, and the colourless solution was then evaporated *in vacuo* to leave the acid

chloride as a pale yellow solid; $\nu_{max.}$ (KBr) 1750, 1634, 1610, 1600, 1585 and 1510 cm^{-1}; δ_H ($CDCl_3$) 2.3 (s, O*Ac*), 3.9 (s, O*Me*), 6.9 (d, *J*15.5Hz, H8), 7.1 (m, 3 × Ar*H*), 7.8 (d, *J*15.5Hz, H7) p.p.m. which was used without further purification.

3-Hydroxy-2-nitro-2-cyclopenten-1-one (3a): A suspension of 1,3-cyclopentanedione (0.57g) in dry diethyl ether (50ml) was stirred at 23°C while dry nitrogen dioxide gas was passed through the mixture over 10 minutes. The diethyl ether containing excess nitrogen dioxide was then evaporated by passing nitrogen through the mixture leaving a solid residue. The solid was washed with copious amounts of diethyl ether to leave the nitro compound (0.77g, 93%) m.p. 168°C dec. (from MeOH); (Found: C, 42.0; H, 3.6; N, 9.6%. $C_5H_5NO_4$ requires C, 42.0; H, 3.5; N, 9.8%.); $\lambda_{max.}$ (H_2O) 228 (16500), 237 inf. (16100), 317 (9000) nm.; $\nu_{max.}$ (KBr) 1665, 1575, 1545, 1495, 1443, 1417 and 1385 cm^{-1}; δ_H (d_6-DMSO) 2.5 (s, 2 × C*H*$_2$), 9.2 (s, O*H*) p.p.m.; δ_C (d_6-DMSO) 29.4 (t, C4+C5), 126.3 (s, C2), 191.2 (s, C1 + C3) p.p.m.; m/z (EI) 143 (M^+, 100%), 126 (63) and 110 (20). (Found: M^+, 143.0197. $C_5H_5NO_4$ requires 143.02185.)

2-Amino-3-hydroxy-2-cyclopenten-1-one hydrochloride (3b): A mixture of 3-hydroxy-2-nitro-2-cyclopenten-1-one (138mg), platinum dioxide (30mg), 2N HCl (3ml) and glacial acetic acid (25ml) was exposed to hydrogen gas at atmospheric pressure until 134ml had been taken up. The mixture was filtered and the resulting colourless solution was then evaporated (azeotroping with toluene) to leave the very unstable amine hydrochloride salt as a dark solid;

$\nu_{max.}$ (KBr) 3410, 2940, 2886, 1725 and 1645cm^{-1}; δ_H (d_4-MeOH) 2.7 (s, 2 × CH_2) p.p.m. which was used without further purification.

(E)-N-(3-Hydroxy-1-oxocyclopent-2-en-2-yl)-3-[4-(acetyloxy)-3-methoxyphenyl) propenamide (5): Dry pyridine (2.5ml) was added to a mixture of 3-[4-(acetyloxy)-3-methoxyphenyl]-2-propenoyl chloride (0.33g), 2-amino-3-hydroxy-2-cyclopenten-1-one hydrochloride (0.18g) and a catalytic amount of DMAP, and the resulting dark solution was then stirred at 23°C for 24hrs, before evaporating to dryness. Chromatography of the solid residue on silica using 95:5 dichloromethane-methanol as eluant gave the amide (0.20g,50%) as a pale yellow powder. m.p. 234-5°C (from MeOH); (Found: C, 60.9; H, 5.1; N, 4.2%. $C_{17}H_{17}NO_6$.0.25 H_2O requires C, 60.8; H, 5.3; N, 4.2%.); $\lambda_{max.}$ ($CHCl_3$/MeOH) 277 (21000), 324 (15400) nm.; $\nu_{max.}$ (KBr) 3436, 3254, 1762, 1600, 1554, 1510 and 1302 cm^{-1}; δ_H (d_7-DMF) 2.3 (s, O*Ac*), 2.5 (s, 4'+5' CH_2), 3.9 (s, O*Me*), 7.2 (d, *J*8.1Hz, H5), 7.3 (dd, *J*8.1 and 1.5Hz, H6), 7.4 (d, *J*15.6Hz, H7), 7.5 (d, *J*1.5Hz, H2), 7.7 (d, *J*15.6Hz, H7), 10.0 (s, N*H*), 13.9 (s, O*H*) p.p.m.; δ_C (d_7-DMF) 20.5 (q,CO*Me*), 56.3 (q, O*Me*), 112.6 (d, C2), 115.8 (t, C4'+C5'), 120.1/121.5/124.2 (3 × d,C5+C6+C8), 134.4 (s, C1), 142.2 (s, C4), 142.6 (d, C7), 152.4 (s, C3), 167.0 (s, C9), 169.1 (s, *C*OMe) p.p.m.; m/z (EI) 331 (M^+, 11%), 289 (22), 194 (50) and 177 (100). (Found: M^+, 331.1051. $C_{17}H_{17}NO_6$ requires 331.1056.)

(E)-N-(3-Hydroxy-1-oxocyclopent-2-en-2-yl)-3-(4-hydroxy-3-methoxyphenyl) propenamide.(2880-II) (1): Anhydrous ammonia (8

drops) was added to a stirred suspension of (E)-N-(3-hydroxy-1-oxocyclopent-2-en-2-yl)-3-[4-(acetyloxy)-3-methoxyphenyl) propenamide (80mg) in dry methanol (20ml) at 23°C. The resulting solution was stirred for 0.5hr and then evaporated to dryness *in vacuo* to leave a dark oil. Chromatography on silica using 98:2 chloroform-methanol as eluant gave the phenolic amide (20mg, 29%) as a primrose yellow powder. m.p. 265-8°C (from MeOH), (Grote *et al*[1] quote m.p. 272°C for natural 2880-II); $\nu_{max.}$ 3432, 3255, 2921, 1691, 1604, 1547 and 1514cm^{-1}; δ_H (d_7-DMF) 2.5 (s, 4'+5' CH_2), 3.9 (s, O*Me*), 6.9 (d, *J*8.2Hz, H5), 7.2 (dd, *J*8.2 and 1.9Hz, H6), 7.2 (d, *J*15.6Hz, H8), 7.3 (d, *J*1.9Hz, H2), 7.6 (d, *J*15.6Hz, H7), 9.8 (s, N*H*) p.p.m.; δ_C (d_7-DMF) 56.1 (q, O*Me*), 111.8 (d, C2), 115.9 (s, C2'), 116.37/116.44 (2 × d, C5+C8), 123.4 (d, C6), 127.1 (s, C1), 143.8 (d, C7), 149.0 (s, C4), 150.5 (s, C3), 167.6 (s, C9) p.p.m.; m/z (EI) 289 (M^+, 24%), 177 (100), 145 (25) and 117 (11). (Found: M^+, 289.0947. Calc. for $C_{15}H_{15}NO_5$; M 289.0950.)

Acknowledgements

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