Synthetic Approaches to the Angucycline Antibiotics: A Concise Entry to the Ring System of PD 116740 and TAN 1085

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The angucycline antibiotics have attracted a great deal of attention in the past decade due to their interesting biological properties. Although several procedures for the synthesis of individual angucyclines have been reported, an efficient general asymmetric method has yet to be developed. We have recently reported a synthesis of the racemic forms of rubiginone B1 (1) and B2 (2), emycin A (3), and ochromycinone (4), which were synthesized from the common intermediate (±)-5a, formed from the highly stereoselective tetra-O-acetyl diborate promoted Diels-Alder reaction of juglone (5-hydroxy-1,4-naphthoquinone) and the diene (±)-6a. In an extension of this work, the reaction of juglone with diene (±)-6b promoted by a Lewis acid derived from (S)-(−)-3,3′-diphenyl-1,1′-binaphthalene-2,2′-dil and BH3-THF gave cycloadduct (+)-5b (ee > 98%). Modification of (+)-5b resulted in the syntheses of 3 and 4 in enantiomerically pure form.

In an attempt to extend the versatility of this Diels-Alder strategy our attention turned toward angucyclines possessing aromatic A ring and hydroaromatic B ring functionality. We felt that intermediates similar to (+)-5b could serve as precursors to PD 116740 (7), which has been shown to exhibit in vitro activity against L1210 lymphocytic leukaemia and HCT-8 human colon adenocarcinoma cell lines, and the aglycon of TAN 1085 (8), which shows angiogenesis inhibition.

The easily accessible Diels-Alder cycloadduct (±)-9 would serve as an appropriate model to ascertain the viability of our approach. Our synthetic strategy is outlined in Scheme 1. We felt protected trans diol functionality at C-5 and C-6 could be introduced by epoxidation of the C-4a-C-5 double bond. Examination of the crystal structure of a closely related cycloadduct indicated that oxidation would occur from the face of the alkene anti to the C-6 methoxyl group. A neutral oxidant would be required as cycloadduct 9 is unstable under

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acids under acidic and basic conditions. A subsequent oxidation of the C-1 hydroxyl group would facilitate opening of the epoxide to give the required functionality at C-5 and C-6 with the correct relative stereochemistry.

Treatment of 9 with dimethyldioxirane gave epoxide 10 in a 96% yield. Oxidation of 10 at this point in the sequence proved necessary and was effected using activated manganese dioxide to give the quinone 11 in an 83% yield.

An initial investigation of the oxidation of the C-1 hydroxyl group of 11 using chromium-based oxidizing agents proved problematical. Oxidation to the ketone 12 was achieved with limited success using Collins reagent and PDC. Unfortunately, 12 proved labile under the reaction conditions and ultimately afforded aromatic ring B products. PCC provided a route to 12; however, yields were low. Swern oxidation also provided complex mixtures of reaction products. Smooth conversion of 11 to 12 was achieved by oxidation using a slight molar excess of the Dess–Martin periodinane in a yield of 87%. The facile epoxide opening of 12 was effected by adsorption onto silica gel to give 13 in 89% yield.

Having established the correct ring B configurational requirements exhibited by 7 and 8 our attention was focused on methods for the aromatization of the A ring. In an attempt to dehydrogenate ring A of adduct 13, we felt that the existing conjugation could be utilized. Successive enolization of protons at C-4, C-3, and C-2 of 13 would give a net transformation resulting in the aromatization of ring A. A possible pathway is depicted in Scheme 2. Treatment of 13 with acetic anhydride in pyridine furnished the acetylated hydroquinone 14 in excellent yield (95%). Oxidation of 14 with ceric ammonium nitrate in aqueous acetonitrile afforded the target adduct 15 (91%).

This short synthesis, and the availability of a method for the preparation of enantiomerically pure starting materials, firmly demonstrates the potential of the present strategy in the synthesis of angucyclidines and angucyclines possessing aromatic A ring and hydroaromatic B ring functionality. Furthermore, the introduction of protected trans 5,6-diol was achieved with high stereoselective control. Investigations into the asymmetric syntheses of 7 and 8 using this method are currently being pursued.


Experimental Section

General Methods. For general experimental methods refer to ref 2m.

(1R*,4aS*,5R*,6S*,6aS*,12aS*,12bS*)-4a,5-Epoxy-2,3,4,5,6,12a,12b-octahydro-1,8-dihydoxy-6-methoxy-1H-benzo[a]anthracene-7,12-dione (10). Cycloadduct 9 (200 mg, 0.609 mmol) was added to a stirred solution of moist dimethyldioxirane in acetone (50 mL, ca. 5 mmol) at ambient temperature, and the resultant mixture was stirred for a further 60 min prior to drying (MgSO4), filtration, and removal of solvents in vacuo. The crude reaction product was crystallized and then recrystallized from diethyl ether and dichloromethane to give the title compound 10 as clear crystals (201 mg, 96%): mp 132 °C; m/z (ESI) 342 (M+), 294 (M+ - C9H8O6), 256 (M+ - C10H8O6), 218 (M+ - C11H8O6), 180 (M+ - C12H8O6), 142 (M+ - C13H8O6), 104 (M+ - C14H8O6), 66 (M+ - C15H8O6), 31 (M+ - C9H8O4), 25 (M+ - C8H8O4), 19 (M+ - C7H8O4), 13 (M+ - C6H8O4), 7 (M+ - C5H8O4), 1 (M+ - C4H8O4). Anal. Calcd for C38H24O7: C, 73.3; H, 4.1. Found: C, 73.3; H, 4.1.

(1R*,4aS*,5R*,6S*,6aS*,12aS*,12bS*)-4a,5-Epoxy-2,3,4,5,6,12,12b-octahydro-1,8-dihydoxy-6-methoxy-1H-benzo[a]anthracene-7,12-dione (11). Activated MnO2 (1.5 g) was added to a stirred solution of 10 (250 mg, 0.731 mmol) in anhydrous dichloromethane (100 mL) and the resultant suspension vigorously stirred at ambient temperature for a further 5 min. The mixture was filtered through a pad of Celite and washed thoroughly with diethyl ether. Removal of the organic solvents in vacuo and crystallization from diethyl ether and dichloromethane gave the title compound 11 as orange crystals (206 mg, 83%): mp 169 °C; m/z (ESI) 340 (M+), 292 (M+ - C9H8O6), 254 (M+ - C10H8O6), 216 (M+ - C11H8O6), 178 (M+ - C12H8O6), 140 (M+ - C13H8O6), 102 (M+ - C14H8O6), 64 (M+ - C15H8O6), 26 (M+ - C9H8O4), 20 (M+ - C8H8O4), 14 (M+ - C7H8O4), 8 (M+ - C6H8O4), 2 (M+ - C5H8O4). Anal. Calcd for C37H22O7: C, 74.4; H, 4.0. Found: C, 74.5; H, 4.0.

Notes
in vacuo to yield crude 13. Crystallization and recrystallization of this residue from diethyl ether and petroleum ether gave the title compound 13 as orange crystals (98 mg, 89%): mp 169 °C; UV(CHCl3) λmax 420 (ε = 5150), 300 (ε = 7320); νmax (KBr)/cm\(^{-1}\) 3342 (OH), 1671, 1659, 1647, 1643, 1606, 1576 (C=O, C=C), 1455 (C=C); δH (300 MHz, CDCl3) 11.89 (1H, s), 7.57 (1H, t, J = 8.0, 8.0 Hz), 7.49 (1H, dd, J = 7.5, 1.1 Hz), 7.21 (1H, dd, J = 8.5, 1.1 Hz), 4.69 (1H, d, J = 2.3 Hz), 4.32 (1H, dd, J = 8.0, 2.3 Hz), 3.45 (3H, s), 2.89 (1H, dt, J = 8.0, 17.6 Hz), 2.58 (1H, m), 2.56 (1H, d, J = 19.3 Hz), 2.42 (2H, m), 2.40 (1H, d, J = 17.6 Hz), 2.21–1.90 (2H, m); upon the addition of D2O the δ at δ 2.40 disappeared and the dd at δ 4.32 collapsed to a 1H d with J = 8.0 Hz; δC (75 MHz, CDCl3) 195.2, 188.7, 183.3, 161.9, 141.9, 138.0, 136.5, 133.0, 129.6, 124.2, 124.1, 119.3, 114.6, 72.2, 69.8, 58.5, 37.7, 29.9, 21.9; m/z (EI) 340 (M\(^+\), 10), 311 (M\(^+\) – CHO, 90). Anal. Calcd for C\(_{23}\)H\(_{23}\)O\(_6\): C, 67.1; H, 4.7. Found: C, 66.8; H, 4.8.

(5R,6R\(^{+}\))-1,5,7,8,11-Pentaacetoxy-5,6-dihydro-6-methoxybenzo[a]anthracene (14). Quinone 13 (213 mg, 0.626 mmol) and DMAP (ca. 5 mg) were added to a mixture of acetic anhydride (2.5 mL) and pyridine (2.5 mL). The resultant mixture was stirred under an atmosphere of nitrogen for 3 h prior to evaporation of the solvents in vacuo. Purification of the residue by silica gel column chromatography (ethyl acetate/hexanes 1:4 as eluent) and crystallization from diethyl ether and petroleum ether gave the title compound 14 as white crystals (328 mg, 95%): mp 204 °C; UV(CHCl3) λmax 404 (ε = 1010), 344 (ε = 2130), 327 (ε = 2470), 300 (ε = 12 910); νmax (KBr)/cm\(^{-1}\) 3490 (OH), 1770, 1741 (C=O, C=C), 1366 (C=C), 1290 (C=O); δH (200 MHz, CDCl3) 7.86 (1H, d, J = 8.0 Hz), 7.56 (1H, t, J = 8.0, 8.0 Hz), 7.44–7.30 (3H, m), 7.22 (1H, d, J = 8.4 Hz), 5.89 (1H, br s), 4.76 (1H, br s), 3.32 (3H, s), 2.44 (6H, s), 2.31 (3H, s), 2.23 (3H, s), 1.79 (3H, s); δC (75 MHz, CDCl3) 170.9, 169.3, 168.0, 147.5, 145.6, 142.9, 142.4, 134.5, 131.1, 129.4, 128.0, 127.6, 124.8, 124.0, 122.8, 121.9, 121.6, 120.6, 71.0 (br), 57.0, 21.6, 21.3, 20.8, 20.6; m/z (EI) 550 (M\(^+\), 4), 434 (M\(^+\) – C\(_2\)H\(_2\)O\(_3\)), 20. Anal. Calcd for C\(_{25}\)H\(_{20}\)O\(_{11}\): C, 67.1; H, 4.7. Found: C, 66.8; H, 4.8.

(5R,6R\(^{+}\))-1,5,8-Triacetoxy-5,6-dihydro-6-methoxybenzo[a]anthracene-7,12-dione (15). A solution of ceric ammonium nitrate (140 mg, 0.257 mmol) in water (ca. 2 mL) was added to a stirred solution of 14 (47 mg, 0.11 mmol) in acetonitrile (1 mL) and the resultant mixture stirred at ambient temperature for 70 min. The reaction mixture was poured into water (5 mL) and extracted with dichloromethane (3 × 3 mL). The combined organic fractions were dried (MgSO\(_4\)) and the solvents removed in vacuo. Crystallization from diethyl ether and petroleum ether yielded the title compound 15 as yellow crystals (36 mg, 91%): mp 169 °C; UV(CH\(_2\)Cl\(_2\)) λmax 404 (ε = 1010), 370 (ε = 6090), 288 (ε = 7730), 260 (ε = 17 250); νmax (KBr)/cm\(^{-1}\) 1770, 1759, 1670, 1660, 1464 (C=O, C=C), 1192 (C=O); δH (300 MHz, CDCl3) 8.00 (1H, d, J = 7.8 Hz), 7.78 (1H, t, J = 8.1, 8.1 Hz), 7.53–7.42 (2H, m), 7.43 (1H, d, J = 8.3 Hz), 7.33–7.27 (1H, m), 6.05 (1H, d, J = 2.9 Hz), 4.83 (1H, d, J = 2.4 Hz), 3.41 (3H, s), 2.48 (3H, s), 2.21 (3H, s), 1.92 (3H, s); m/z (EI) 464 (M\(^+\), 4), 422 (M\(^+\) – C\(_2\)H\(_2\)O\(_2\)), 20. Anal. Calcd for C\(_{25}\)H\(_{22}\)O\(_{9}\): C, 64.7; H, 4.3. Found: C, 64.7; H, 4.3.

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Supporting Information Available: \(^1\)H NMR spectra for compounds 10–15 (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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