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

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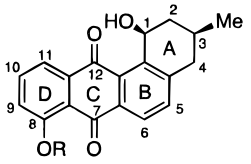
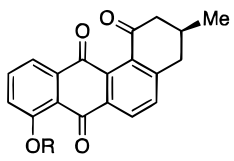
The angucycline antibiotics have attracted a great deal of attention in the past decade due to their interesting biological properties.[1] Although several procedures for the synthesis of individual angucyclines have been reported,[2] an efficient general asymmetric method has yet to be developed. We have recently reported a synthesis of the racemic forms of rubiginone B_1 (**1**) and B_2 (**2**), emycin A (**3**), and ochromycinone (**4**),[2i,j,m] 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′-diol and BH_3·THF gave cycloadduct (+)-**5b** (ee >98%). Modification of (+)-**5b** resulted in the syntheses of **3** and **4** in enantiomerically pure form.[3]

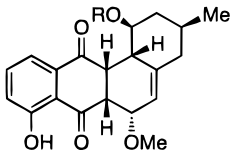
In an attempt to extend the versatility of this Diels−Alder strategy our attention turned toward angucyclines possessing aromatic A ring and hydroaromatic B ring functionality. We felt that intermediates similar to (+)-**5b** could serve as precursors to PD 116740[4] (**7**), which has been shown to exhibit *in vitro* activity against L1210 lymphocytic leukaemia and HCT-8 human colon adenocarcinoma cell lines, and the aglycon of TAN 1085[5] (**8**), which shows angiogenesis inhibition.



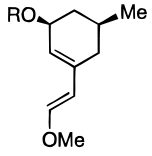
1 R = Me
3 R = H



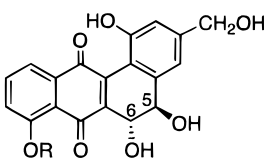
2 R = Me
4 R = H



5a R = Ac
5b R = H

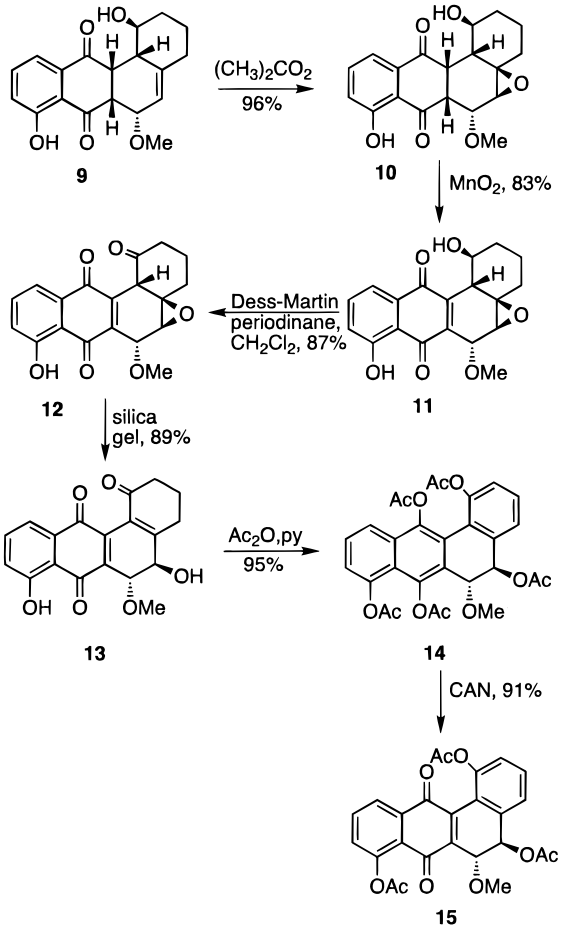


6a R = Ac
6b R = H



7 R = Me (PD 116740)
8 R = H (aglycone of TAN 1085)

Scheme 1



The easily accessible Diels−Alder cycloadduct (±)-**9**[2m] 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[3] 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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(5) JP 009 263/1990 and JP 2 289 532/1990. *Chem. Abstr.* **1991**, *115*, 47759*n*.

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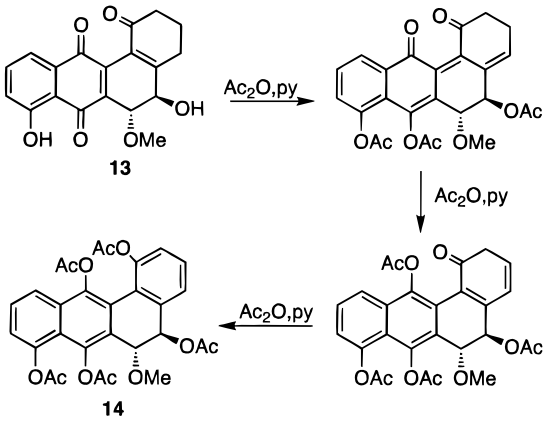
Scheme 2



acidic and basic conditions.[2m] A subsequent oxidation of the C-1 hydroxyl group would facilitate opening of the epoxide to realize 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[6] 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[3] for the preparation of enantiomerically pure starting materials, firmly demonstrates the potential of the present strategy in the synthesis of angucyclinones and angucyclines possessing aromatic A ring and hydroaromatic B ring functionality. Furthermore, the introduction of protected *trans* 5,6-diol was achieved with high stereochemical control. Investigations into the asymmetric syntheses of **7** and **8** using this method are currently being pursued.

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Experimental Section

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

(1*R,4a*S**,5*R**,6*S**,6a*S**,12a*S**,12b*S**)-4a,5-Epoxy-2,3,4,5,6,6a,12a,12b-octahydro-1,8-dihydroxy-6-methoxy-1*H*-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 ($MgSO_4$), 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; ν_{max} (KBr)/cm^{-1} 3514 (OH), 1698, 1692, 1644, 1582 (C=O, C=C), 1455 (C=C), 1072 ($COCH_3$); δ_H (300 MHz, $CDCl_3$) 12.00 (1H, s), 7.60 (1H, t, J = 7.8, 7.8 Hz), 7.36 (1H, dd, J = 7.6, 1.2 Hz), 7.18 (1H, dd, J = 8.5, 1.2 Hz), 4.84 (1H, tdd, J = 10.7, 10.7, 5.7, 5.4 Hz), 4.12 (1H, dd, J = 4.4, 2.0 Hz), 3.55 (1H, t, J = 5.4, 5.4 Hz), 3.20 (1H, t, J = 4.9, 4.9 Hz), 3.14 (1H, m, 5-H), 3.10 (3H, s), 2.26 (1H, ddd, J = 14.2, 11.2, 6.4 Hz), 2.20−2.07 (1H, m), 2.02−1.78 (2H, m), 1.56−1.40 (m, 2H), 1.27 (1H, dt, J = 14.1, 4.8, 4.8 Hz). Upon the addition of D_2O the tdd at δ4.84 collapsed to a 1H dt (J = 10.7, 10.7, 5.7 Hz); δ_C (75 MHz, $CDCl_3$) 204.4, 197.8, 161.4, 138.3, 136.8, 122.6, 118.5, 116.8, 66.7, 61.4, 59.8, 58.4, 51.2, 46.5, 43.1, 31.7, 29.3, 17.5; m/z (EI) 344 (M^+, 10), 294 ($M^+ - CH_3OH - H_2O$, 50). Anal. Calcd for $C_{19}H_{20}O_6$: C, 66.3; H, 5.9. Found: C, 66.2; H, 6.1.

(1*R,4a*S**,5*R**,6*S**,12b*S**)-4a,5-Epoxy-2,3,4,5,6,12b-hexahydro-1,8-dihydroxy-6-methoxy-1*H*-benzo[*a*]anthracene-7,12-dione (11).** Activated MnO_2 (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; ν_{max} (KBr)/cm^{-1} 3478 (OH), 1673, 1644, 1614 (C=O, C=C), 1454 (C=C), 1066 ($COCH_3$); δ_H (300 MHz, $CDCl_3$) 12.03 (1H, s), 7.64 (1H, br d, J = 7.6 Hz), 7.60 (1H, t, J = 7.3, 7.3 Hz), 7.27 (1H, dd, J = 7.3, 1.8 Hz), 5.07 (1H, d, J = 3.0 Hz), 3.74−3.59 (1H, m), 3.58 (3H, s), 3.43 (1H, d, J = 9.8 Hz), 3.32 (1H, dd, J = 3.0, 1.2 Hz), 2.24−1.90 (5H, m), 1.68−1.38 (2H, m); δ_C (75MHz, $CDCl_3$) 189.3, 185.7, 161.4, 145.6, 138.9, 136.3, 131.9, 124.7, 119.7, 114.7, 76.2, 70.2, 59.5, 58.9, 57.2, 44.9, 36.2, 32.1, 21.1; m/z (EI) 342 (M^+, 60), 310 ($M^+ - CH_3OH$, 30). Anal. Calcd for $C_{19}H_{18}O_6$: C, 66.7; H, 5.3. Found: C, 66.7; H, 5.4.

(4a*R,5*S**,6*R**,12b*S**)-4a,5-Epoxy-2,3,4,5,6,12b-hexahydro-8-hydroxy-6-methoxybenzo[*a*]anthracene-1,7,12-trione (12).** Alcohol **11** (80 mg, 0.23 mmol) was added to a solution of freshly prepared Dess−Martin periodinane[7] (130 mg, 0.31 mmol) in anhydrous dichloromethane (7 mL) and the resultant mixture stirred at ambient temperature for 30 h. The solvent was removed *in vacuo* (T < 30 °C) and the residue dissolved in a minimum volume of ethyl acetate (4 mL). The solution was chromatographed on silica gel (ethyl acetate/cyclohexane 1:4 as eluent) to give the title compound **12** as orange crystals (70 mg, 87%): mp 208 °C (dec); ν_{max} (KBr)/cm^{-1} 1713, 1662, 1646, 1621 (C=O, C=C), 1456 (C=C); δ_H (300 MHz, $CDCl_3$) 12.00 (1H, s), 7.64 (1H, br d, J = 7.1 Hz), 7.61 (1H, t, J = 7.4, 7.4 Hz), 7.28 (1H, dd, J = 7.1, 2.5 Hz), 5.10−5.05 (1H, m, 5-H), 4.50 (1H, s), 3.49 (3H, s), 3.42-3.37 (1H, m), 2.66−2.57 (2H, m), 2.55−2.42 (1H, m), 2.26−2.14 (1H, m), 1.90−1.52 (2H, m); δ_C (75 MHz, $CDCl_3$) 202.9, 188.9, 182.8, 161.5, 141.4, 138.6, 136.4, 131.7, 124.5, 119.6, 114.9, 69.1, 59.5, 58.8, 57.7, 51.3, 40.8, 32.0, 20.9; m/z (EI) 340 (M^+, 80), 311 (M^+ − CHO, 70). Anal. Calcd for $C_{19}H_{16}O_6$: C, 67.1; H, 4.7. Found: C, 66.9; H, 4.7.

(5*R,6*R**)-5,8-Dihydroxy-3,4,5,6-tetrahydro-6-methoxy-2*H*-benzo[*a*]anthracene-1,7,12-trione (13).** Epoxide **12** (110 mg, 1.10 mmol) was added to a stirred suspension of silica gel (8 g) in dichloromethane (50 mL) and the resultant mixture stirred at ambient temperature for 30 min. The solvent was removed and the solid residue vigorously stirred under an air atmosphere for a further 30 min. The mixture was washed with diethyl ether and filtered, and the solvents were concentrated

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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(CH_2Cl_2) λ_{max} 420 (ϵ = 5150), 300 (ϵ = 7320); ν_{max} (KBr)/cm^{-1} 3342 (OH), 1671, 1659, 1647, 1643, 1606, 1576 (C═O, C═C), 1455 (C═C); δ_H (300 MHz, $CDCl_3$) 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* = 19.3, 4.3, 4.3 Hz), 2.75 (1H, dt, *J* = 17.6, 5.4, 5.4 Hz), 2.58−2.42 (2H, m), 2.40 (1H, d, *J* = 8.0 Hz), 2.21−1.90 (2H, m); upon the addition of D_2O the d at δ 2.40 disappeared and the dd at δ4.32 collapsed to a 1H d with *J* = 2.3 Hz; δ_C (75 MHz, $CDCl_3$) 195.2, 188.7, 183.3, 161.0, 141.9, 138.0, 136.5, 133.1, 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 $C_{19}H_{16}O_6$: C, 67.1; H, 4.7. Found: C, 66.8; H, 4.8.

(5*R,6*R**)-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(CH_2Cl_2) λ_{max} 404 (ϵ = 1010), 344 (ϵ = 2130), 327 (ϵ = 2470), 300 (ϵ = 12 910); ν_{max} (KBr)/cm^{-1} 3490 (OH), 1770, 1741 (C═O, C═C), 1366 (C═C), 1190 (C═O); δ_H (200 MHz, $CDCl_3$) 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); δ_C (75 MHz, $CDCl_3$) 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^+, 5), 434 ($M^+ - C_5H_8O_3$, 20). Anal. Calcd for $C_{29}H_{26}O_{11}$: C, 63.3; H, 4.8. Found: C, 63.0; H, 4.8.

(5*R,6*R**)-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_2Cl_2) λ_{max} 404 (ϵ = 1010), 370 (ϵ = 6090), 288 (ϵ = 7730), 260 (ϵ = 17 250); ν_{max} (KBr)/cm^{-1} 1770, 1759, 1670, 1660, 1464 (C═O, C═C), 1192 (C═O); δ_H (300 MHz, $CDCl_3$) 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 ($M^+ - C_2H_2O$, 20). Anal. Calcd for $C_{25}H_{20}O_9$: C, 64.7; H, 4.3. Found: C, 64.7; H, 4.3.

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Supporting Information Available: ^1H 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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