THE CONVERGENT AB + CD ROUTE TO 9-ACETYL-7,8,9,10-TETRAHYDRONAPHTHACENEDIONE

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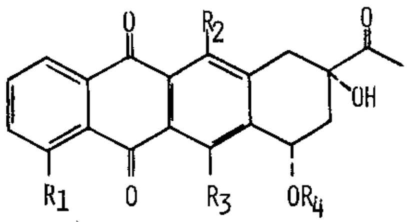
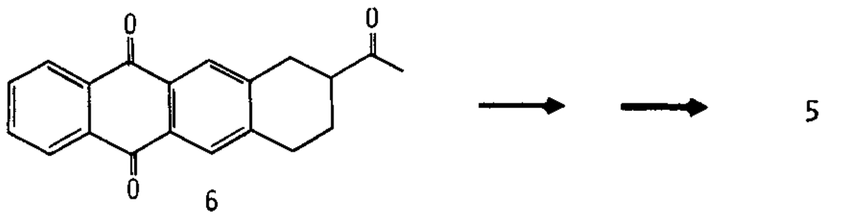
Abstract - The annelated sulfolene derivative (9) has been used as an "AB" synthon in a convergent AB + CD route to 9-acetyl-7,8,9,10-tetrahydro-5,12-naphthacenedione (6), a key precursor to the highly deoxygenated anthracyclinone 4-demethoxy-6,11-dideoxydaunomycinone (5).

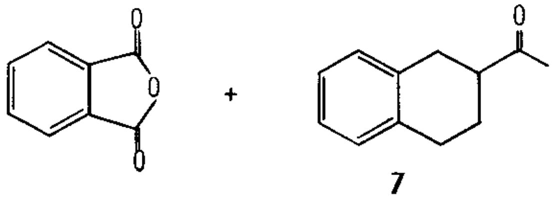
Synthetic anthracycline antibiotics may be an exception to the general concept[1] that a synthetic analog of a natural antibiotic is unlikely to be more active than the parent structure. Indeed, the totally synthetic 4-demethoxydaunomycin (2) has been found to be more active[2] than daunomycin (1); and the less oxygenated analog 4-demethoxy-11-deoxydaunomycin (4) is more effective[3] than 3.



1 R_1=OMe, R_2=R_3=OH, R_4=daunosaminyl
2 R_1=H, R_2=R_3=OH, R_4=daunosaminyl
3 R_1=OMe, R_2=H, R_3=OH, R_4=daunosaminyl
4 R_1=R_2=H, R_3=OH, R_4=daunosaminyl
5 R_1=R_2=R_3=R_4=H

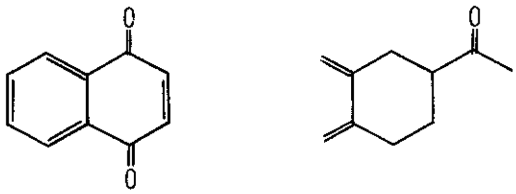
In this regard, we recently reported the first synthesis of 4-demethoxy-6,11-dideoxydaunomycinone (5), the least oxygenated anthracyclinone structure which still contains an unchanged A ring.[4] In this synthesis the key intermediate 9-acetyl-7,8,9,10-tetrahydro-5,12-naphthacenedione (6) was obtained by a "DCB + A" construction from an anthraquinone precursor.



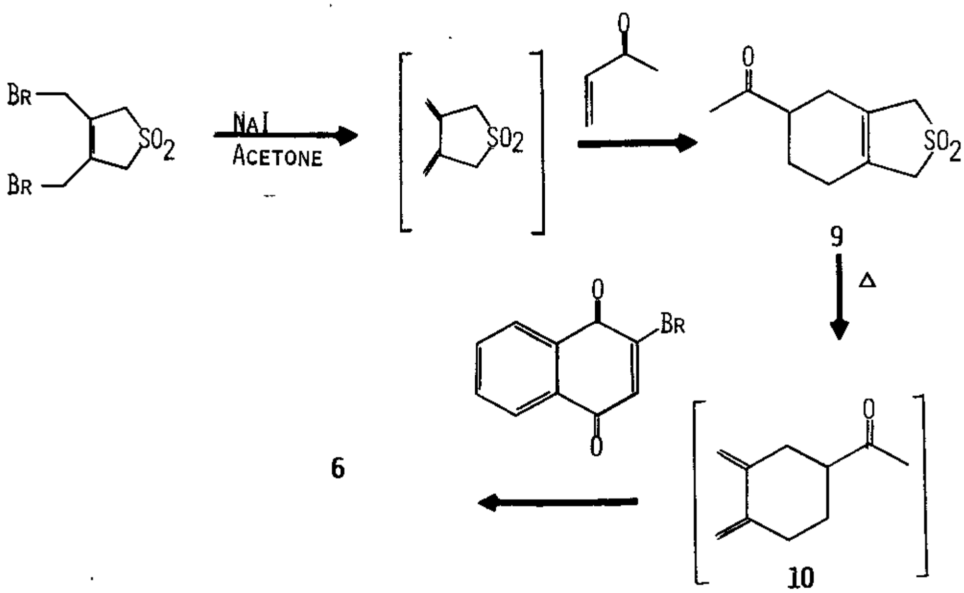


Eq. 1

OR



Eq. 2



We now report the synthesis of 6 by a convergent DC + BA route utilizing the annelated sulfolene 9 as the AB source. This approach has been previously unexplored in anthracycline chemistry.[5] We reasoned that sulfone 9 should be an ideal AB precursor since the cis diene 10 resulting from its thermally induced extrusion of SO_2 should react in a [4 + 2] cycloaddition with an appropriate naphthoquinone derivative [Eq. 2].

The requisite 3,4-bis(bromomethyl)-2,5-dihydrothiophene-1,1-dioxide (8) was easily prepared from the comercially available 2,3-dimethyl-1,3-butadiene by the known procedure.[7] Treatment of 8 wth NaI followed by trapping the resulting diene in situ with methyl vinyl ketone afforded the thermally labile 9 in 60% yield. The structure of 9 was confirmed by its ^1H NMR and IR spectra. Immediate treatment of 9 with an excess of 2-bromo-1,4-naphthoquinone[8] provided the desired ketone 6 (50%), identical in all respects (NMR, MS, mp) with an authentic sample.[4]

For comparison purposes, we also investigated the assembly of 6 by the conventional AB + CD route, (Eq. 1), a strategy analogous to Wong's[6] original approach to 4-demethoxydaunomycinone. Surprisingly the requisite starting material 2-acetyl-1,2,3,4-tetrahydronaphthalene (7) was unknown in the literature; it could be obtained in only poor yield (25%) by the treatment of α,α-dibromo-o-xylene with methyl vinyl ketone and activated zinc dust. Fusion of 7 with an intimate mixture of phthalic anhydride and $AlCl_3$-NaCl at 180°C for 10 min, and treatment of the resultant mass with a saturated solution of oxalic acid directly provided 6, albeit in only 30% yield.

EXPERIMENTAL

General Methods. Melting points (mp) were determined on a Thomas-Hoover apparatus and are uncorrected. Mass spectra were determined on a Hewlett-Packard 5985 A system. ^1H NMR spectra were recorded on a Nicolet NT-200 (200 MHz) spectrometer using Me_4Si as an internal standard and are reported in δ units. Elemental analyses were performed by Atlantic Microlab Inc. All organic extracts were washed and dried over anhydrous Na_2SO_4 prior to filtration and evaporation.

2,3,4,5,6,7-Hexahydro-4-acetylthiophene-1,1-dioxide (9). Compound 8 (0.4 g, 1.32 mmol) dissolved in acetone (15 ml) was added in a dropwise manner to a refluxing solution of methyl vinyl ketone (2.0 ml), sodium iodide (0.4 g) and acetone (10 ml) under N_2 atm. After refluxing for 2 h, the solvent was removed under reduced pressure and the residue was dried under high vacuum (approx. 0.5 torr) to remove all traces of methyl vinyl ketone. Chromatography (SiO_2, 50:50 hexane-EtOAc) afforded 9 (170 mg, 60%) as an unstable solid which was immediately used in the next step.

^1H NMR 1.71 (m, 2H, CH_2), 2.10 (s, 3H, $COCH_3$), 2.20 (m, 4H, $2xCH_2$), 2.80 (m, 1H, CH), 3.80 (m, 4H, $2xCH_2$). IR_{max} 1150, 1295, 1710 cm^{-1}.

2-Acetyl-1,2,3,4-tetrahydronaphthalene (7). Zinc was activated by stirring with a saturated solution of NH_4Cl for 30 min under N_2 atm.

To a stirred suspension of methyl vinyl ketone (3.0 ml) and activated Zn dust (0.4 g) in DMF (25 ml) under N_2 atm, was added a solution of α,α-dibromo-o-xylene (2.0 g, 7.57 mmol) in DMF (25 ml). After stirring at room temperature for 6 h, the Zn dust was filtered and the filtrate diluted with H_2O (250 ml). The resulting white polymeric material was filtered and the clear filtrate was extracted with EtOAc, washed with H_2O and then evaporated under reduced pressure. Chromatography (SiO_2, 80:20 hexane-EtOAc) provided 7 as a colorless oil (0.33 g, 25%), ^1H NMR 1.69 (m, 2H, CH_2), 2.15 (m, 1H, CH), 2.24 (s, 3H, $COCH_3$), 2.90 (m, 4H, benzylic) 7.10 (s, 4H, aromatic) MS = m/z (relative intensity) 174 (M^+, 76.3), 159 (84.1), 131 (100). 2,4-DNP derivative: mp 164°C. Anal. calcd. for $C_{18}H_{18}N_4O_4$: C, 61.02; H, 5.08. Found: C, 60.95, H, 5.15.

9-Acetyl-7,8,9,10-tetrahydrnaphthacenedione (6). a) A mixture of 9 (0.15 g, 0.7 mmol), 2-bromo-1,4-naphthoquinone (0.33 g, 1.4 mmol) and $NaHCO_3$ (25 mg) in DMA (10 ml) was heated for 6 h at 70°C under N_2 atm. After cooling to room temperature, the contents were diluted with H_2O (100 ml) and air bubbled in for 20 min. The solid was filtered and chromatographed (SiO_2, 70:30 hexane-EtOAc) to afford 6 (60 mg, 50%) identical in all respects with an authentic sample.[4]

b) An intimate mixture of 7 (0.15 g, 0.86 mmol), phthalic anhydride (0.25 g, 1.68 mmol), $AlCl_3$ (1.2 g, 9.0 mmol) and NaCl (0.32 g, 5.47 mmol) was heated at 180°C for 5 min. The melt was cooled, a saturated solution of oxalic acid (20 ml) was added and the mixture was warmed on a steam bath for 10 min. The product was extracted into ethyl acetate, which was washed with H_2O and evporated under reduced pressure. Chromatography (SiO_2, 50:50 hexane-CH_2Cl_2) provided 6 as a light yellow solid (80 mg, 30%), identical in all respects with an authentic sample.[4]

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8. It was interesting to note that replacing 2-bromo-1,4-naphthoquinone with 2,3-dichloronaphthoquinone and employing identical experimental conditions did not provide the required 6.

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