A Synthesis of (±)-Demethoxydaunomycinone

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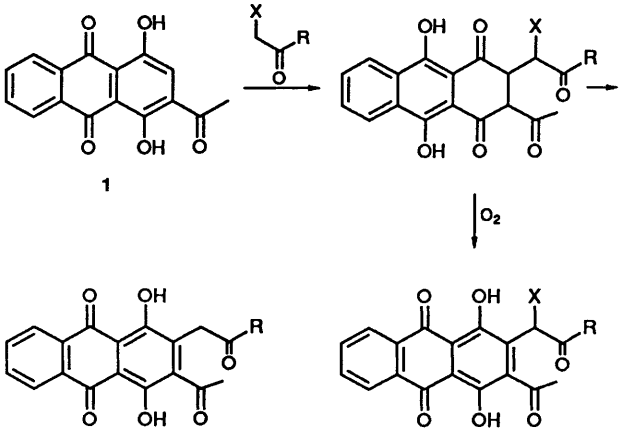
2-Acetyl-1,4-dihydroxyanthracene-9,10-dione **1** is converted into (±)-demethoxydaunomycinone by substitution with 3,3-dimethoxy-1-nitrobutan-2-one, aldol cyclisation, reduction and hydrolysis. The chiral inductions at C-10 realised on cyclisation of **5** and **8** are reported and the predominant chirality established.

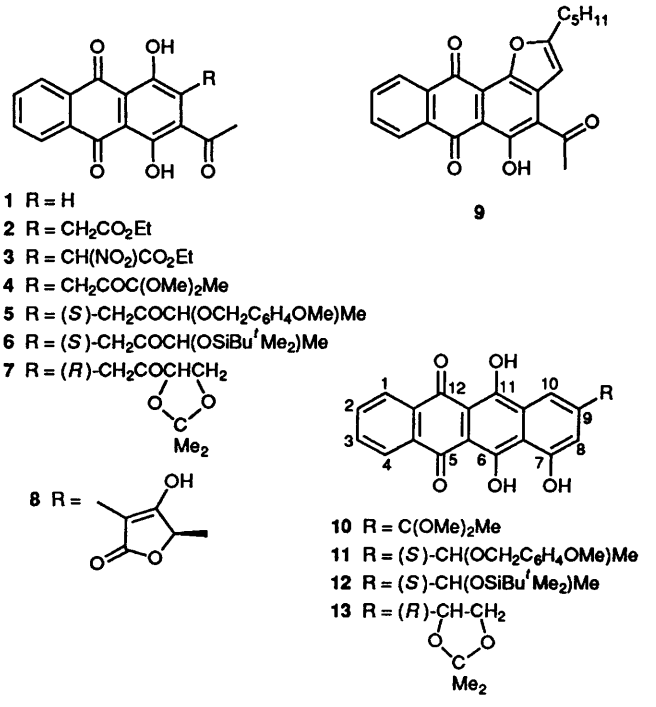
In previous work we have shown that 1,4,5-trihydroxy- and 1,4-dihydroxy-anthracene-9,10-diones undergo Michael addition with certain stabilised carbanions at C-2 and, where the stabilising group is a good leaving group, it is eliminated.[1] β-Keto ester anions also add in a facile manner to 2-acetyl-1,4-dihydroxyanthracene-9,10-dione **1** with the intermediate leuco-compound being oxidised if the reaction is carried out in an air atmosphere.[2] In this paper we describe the results of treating 2-acetyl-1,4-dihydroxyanthracene-9,10-dione **1** with β-keto phosphonate, phosphorane, sulfoxide, sulfone, and nitro compounds in the hope of achieving the reactions shown in Scheme 1.



Scheme 1

In the event neither sulfoxide nor sulfone gave an alkylation product when treated with **1** in Et_3N–MeOH;† however 2-oxoheptylphosphonate gave the furan **9** (24%); under these conditions (2-oxopropyl)triphenylphosphorane was unreactive. Ethyl nitroacetate reacted in the presence of air to give the nitro ester **3** (56%), but in an inert atmosphere the ester **2** was formed (76%). These results encouraged us to investigate a demethoxydaunomycin synthesis based on this approach and to this end 3,3-dimethoxy-1-nitrobutan-2-one was synthesised (73%) from ethyl 2,2-dimethoxypropionate and the dianion of nitromethane using the Seebach method.[3] Attempts to effect a one-pot addition–cyclisation as in our previous work[2] with β-keto esters using amines in MeOH were unsuccessful for reasons that will become apparent; however reaction of the nitro ketone and the quinone **1** in CH_2Cl_2 containing 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) gave the adduct **4** (87%), ν_{max}/cm^{-1} 1735 and 1700, δ_H 1.40 (3 H, s), 2.56 (3 H, s), 3.25 (6 H, s),

† The methyl ether of 3-acetyl-3-mercaptoanthracene-9,10-dione was isolated from the products, presumably from reaction of the quinone with methylthiol generated in a Pummer-type process.



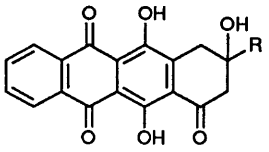
1 R = H
2 R = CH_2CO_2Et
3 R = $CH(NO_2)CO_2Et$
4 R = $CH_2COC(OMe)_2Me$
5 R = (*S*)-$CH_2COCH(OCH_2C_6H_4OMe)Me$
6 R = (*S*)-$CH_2COCH(OSiBu^tMe_2)Me$
7 R = (*R*)-$CH_2COCHCH_2$ (O, C, O; Me_2)

8 R = (OH)

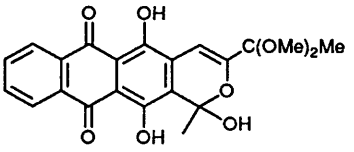
9

10 R = $C(OMe)_2Me$
11 R = (*S*)-$CH(OCH_2C_6H_4OMe)Me$
12 R = (*S*)-$CH(OSiBu^tMe_2)Me$
13 R = (*R*)-$CH\text{-}CH_2$ (O, C, O; Me_2)

4.19 (2 H, s), 7.85 (2 H, m), 8.36 (2 H, m), 13.25 (1 H, s) and 13.28 (1 H, s); δ_C 19.89, 31.56, 36.17, 49.79, 102.91, 202.32, 204 and 88, and 14 signals for the aromatic fragment. When attempts were made to convert the dione into the tetracycle by aldol cyclisation using R_3N–MeOH or Lewis acids–CH_2Cl_2 the dione was converted into a more polar compound which reverted to starting material on attempted isolation. It was also found that this material formed on dissolution of the dione **4** in Me_2NCHO and the ^1H NMR spectrum of the isolated material in dry, acid free $CDCl_3$ showed it to be a 1:2 mixture of the dione and a compound showing δ_H 1.58 (3 H, s), 2.18 (3 H, s), 3.30 (3 H, s), 3.31 (3 H, s) and 6.83 (1 H, s), and the usual aromatic signals. These results suggested that an enol derivative containing a chiral centre was being formed and, together with the absence of IR absorption above 1625 cm^{-1} in the carbonyl region, supported the enol ether structure **17**. When the dione **4** was hydrolysed with CF_3CO_2H–water a stable enolic ether, ν_{max}/cm^{-1} 1680, δ_H 2.23 (3 H, s), 2.51 (3 H, s), 7.37 (1 H, s), 7.93 (2 H, m), 8.44 (2 H, m), 13.46 (1 H, s) and 14.17 (1 H, s) was formed. It was now obvious that the aldol reaction (and the one-pot process) was being foiled by enol formation and subsequent cyclisation. It is known that the enol content of acetoacetic ester is minimal in water, so the finely powdered dione **4** was suspended in water containing Pr^iNEt which minimised formation of the unproductive **17** and gave the ketone **14** (46%),



14 R = $C(OMe)_2Me$
15 R = (*S*)-$CH_2CH(OCH_2C_6H_4OMe)Me$
16 R = (*S*)-$CH_2CH(OSiBu^tMe_2)Me$



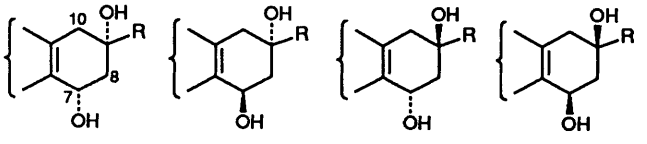
17

δ_H 1.44 (3 H, s), 2.91 (3 H, s), 3.13 (1 H, d, *J* 19),* 3.41 (3 H, s), 3.42 (1 H, d, *J* 19), 3.43 (3 H, s). A small quantity of the naphthacene **10** was also formed and it became the major product if DBU was used as the base.

Reduction of the ketone **14** with $NaBH_4$–$CeCl_3$–Pr^iOH[4] followed by treatment of the mixture with 3 mol dm^{-3} HCl gave a mixture of diols (56%) which was conveniently separated by formation of the boronates (59%) of the *cis*-diols **20a** + **23a**. Cleavage of the boronates gave (±)-demethoxydaunomycinone **20a** + **23a** (87%) identical with an authentic sample.

With the completion of this work we examined possible enantioselective syntheses based on this general approach. There are two obvious ways in which chirality can be introduced: by use of a chiral acetal or by replacement of the acetal function by a chiral secondary alcohol. The latter option was chosen and ethyl (*S*)-lactate used to prepare chiral side chain units. (*S*)-γ-Methyltetronic acid was synthesised[5] and gave the adduct **8** (80%) on reaction with **1** and quinuclidine in CH_2Cl_2; however all attempts to hydrolyse and decarboxylate **8** were unsuccessful. The same adduct was formed (60%) on reaction of **1** with α-bromo-γ-methyltetronic acid; presumably dehydrobromination of the intermediate leuco-addition product to give **8** was faster than its aerial oxidation.

Other means of hydroxy protection were examined. The MEM ether of ethyl (*S*)-lactate was prepared,[6] but its condensation with the nitromethane dianion gave low yields of nitro ketone. The *p*-methoxybenzyl ether was satisfactory in this

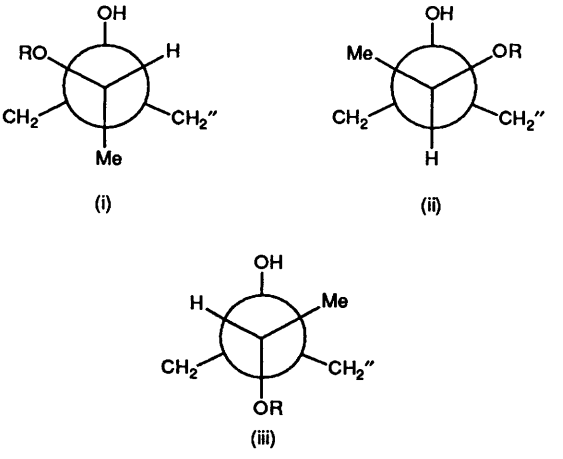


20 **21** **22** **23**

a R = COMe; **b** R = (*S*)-$CH(OCH_2C_6H_4OMe)Me$;
c R = (*S*)-$CH(OSiMe_2Bu^t)Me$; **d** R = (*S*)-CH(OH)Me

respect giving the (*S*)-3-*p*-methoxybenzyloxy-1-nitrobutan-2-one (48%) which reacted with the quinone **1** in Et_3N–CH_2Cl_2 forming the dione **5** (90%). Reaction of the dione **5** with EtN-(c-C_6H_{12})$_2$–MeOH gave the naphthacene **11** (15%), starting material (20%), and the ketols **15** (50%) as a 4:1 mixture. The ^1H NMR spectrum of the mixture of ketols showed the protons of both isomers resonated at identical chemical shifts except for the methoxy resonances.

There are few models for predicting the favoured enantiomer formed in such intramolecular aldol condensations. If a model cyclisation is considered the three possible rotamers around the 11,9 exocyclic C–C bond are shown in Scheme 2. Bond formation can involve the CH_2 or CH_2'' branches; in conformers (i) and (ii) bonding from the CH_2'' face would be favoured, the reverse would be true for (iii) if the steric bulk of Me > OR. Assuming a 'product-like' transition state formation



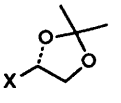
(i) (ii) (iii)

Scheme 2

of conformer (i) would be preferred giving rise to the 'unnatural' 8-*R* isomer of **14**. This preference would be reinforced in a cyclic model where the oxygen atoms are constrained in a ring by coordination with a metal atom. To this end the cyclisation of **5** was investigated with a variety of metal derivatives. With $Mg(OMe)_2$–MeOH or $Ti(OPr)_4$–MeOH the naphthacene **11** was formed. The organometallics in Et_2O or CH_2Cl_2 as solvent were unreactive, but addition of EtN(c-C_6H_{12})$_2$ led to aromatisation of **5**. Similar results were obtained with $Mg(OAc)_2$–MeOH. $Ca(OAc)_2$ or $Ba(OAC)_2$ in MeOH converted the dione into an enol ether (*cf.* **17**). Evidently the organometallics in protic solvents lead to β-elimination and aromatisation being faster than aldol condensation.

In order to test whether any racemisation of the original chiral centre had occurred and that our analysis of the diastereoselection was correct correlation with a compound of established chirality was required. The Hassall group[7] has characterised the isopropylidene derivatives **18** and **19**; so we

18 **19**



24 X = CHO
25 X = CO_2H
26 X = $CHOHCH_2NO_2$
27 X = CO_2Me
28 X = $COCH_2NO_2$

attempted to correlate our products with these. Reduction of the ketols with $NaBH_4$–$CeCl_3$–Pr^iOH gave a mixture of four diols (81%) in a ratio of 66:20:8:6. Repetitive PTLC separated the mixture into two fractions (60% and 10%). Reaction of the major fraction with $PhB(OH)_2$ gave the phenylboronate of **23b** (74%) and a *trans*-diol **22b** (24%). The minor fraction (2:1 mixture) could also be partly converted into the phenylboronate of **20b**. The initial reduction mixture could also be separated into a mixture of *cis*-diols **20b** and **23b** and a mixture of *trans*-diols *via* phenylboronate formation. All that was now required for the correlation was cleavage of the *p*-methoxybenzyl group

* *J* Values are given in Hz throughout.

and acetonide formation, but we were unable to effect cleavage to the triols **20b** and **23b** under a variety of conditions.

The protecting group was now changed to Bu^tMe_2Si and (*S*)-3-(*tert*-butyldimethylsiloxy)-1-nitrobutan-2-one prepared. Reaction with the quinone **1** gave the dione **6** which was cyclised using $EtN(c\text{-}C_6H_{12})_2$–MeOH to give the diastereoisomeric ketols **15** (5:1). Reduction of the ketols with $NaBH_4$–$CeCl_3$–Pr^iOH gave a diol mixture which with 2,2-dimethoxypropane gave the unchanged *trans*-diols **21c** and **22c** and the 7,9-isopropylidene ethers of **20c** and **23c** (6:1). Both protecting groups were cleaved with $BF_3{\cdot}Et_2O$–$CHCl_3$ to give an intractable triol which was transformed into a mixture (10:1) of the ethers **18** and **19** or their enantiomers. On recrystallisation the major isomer was obtained pure and its ^1H NMR spectrum was identical to that reported for **18** which has $[\alpha]_D$ +97.* Our material showed $[\alpha]_D \approx -80$ so it is enantiomeric to **18**. We found it difficult to obtain reproducible readings for $[\alpha]_D$ on the highly coloured solutions so are uncertain whether some racemisation of the original chiral centre has occurred during the first three steps of the synthesis. The crude triol could also be converted into a boronate with the expected selectivity for reaction with the 1,3-diol system. All attempts to oxidise it to the demethoxydaunomycinone derivative failed.

Use of (*R*)-lactate would give an excess of the required enantiomer, however in an attempt to improve the enantioselection in the cyclisation we decided to prepare the dione **7** as it has been reported[8] that while 2-benzyloxypropanal shows no selectivity in intermolecular reactions with enolates, the aldehyde **24** does. Attempts to prepare the ester **27** from the aldehyde *via* the acid **25** gave very poor yields, so we prepared a mixture of diastereoisomeric nitro alchols **26** by condensation of the aldehyde with CH_3NO_2–NaOH.[9] We were unable to oxidise the alcohols to the required nitro ketone using a variety of methods. However application of the direct RCHO→ RCO_2R' conversion[10] utilising Bu_3SnOMe–N-bromosuccinimide gave the methyl ester **27** (56%) and this was converted into the nitro ketone **28** (29%) by the Seebach method. The nitro ketone reacted smoothly with the quinone **1** to give the dione **7** (88%) which was transformed into the naphthacene **13** (88%) with Pr^i_2NEt–MeOH. No intermediate could be detected by TLC. A variety of bases in MeOH and water were also treated with the dione with similar results; in some cases transient formation of a polar compound with properties similar to that of the enol ether **17** was observed. It is apparent from these and other results that the nature of the substituents at C-11 has a significant influence on the relative rates of the aldol condensation and the β-elimination reactions. The exact nature of these effects is not obvious.

The poor enantioselection and difficult separations did not encourage us to continue with this approach; however it does provide an efficient route to naphthacenequinone derivatives.

Experimental

NMR spectra were measured in $CDCl_3$ at 300 MHz (*J* values in Hz), IR spectra as thin films, and UV spectra in EtOH. 'Usual work-up' implies extractions with an organic solvent, washing the combined extracts with brine, drying the organic solvent over Na_2SO_4, and concentration of the extract under reduced pressure. Aromatic ^1H NMR signals are not reported. $[\alpha]_D$ (given in units of 10^{-1} deg cm^2 g^{-1}) and λ_{max} values are measured in $CHCl_3$ unless indicated otherwise.

Ethyl 2-(3-*Acetyl*-1,4-*dihydroxy*-9,10-*dioxo*-9,10-*dihydro*-2-*anthryl*)-2-*nitroacetate* **3**.—To a stirred suspension of the ketone **1** (29 mg) and in MeOH (5 cm^3) containing Et_3N (29 mm^3), ethyl nitroacetate (57 mm^3) was added and the mixture was left at room temperature for 18 h. The dark red solution was neutralised by the addition of 2 drops of 2 mol dm^{-3} HCl and extracted with CH_2Cl_2 (3 × 10 cm^3). Usual work-up and recrystallisation of the crude product gave the *nitro ester* **3** (32 mg) as a red solid, m.p. 123–124 °C (hexane–CH_2Cl_2); λ_{max}/nm 478 (ε 6500), 340 (2000), 283 (7200) and 253 (18 400); ν_{max}/cm^{-1} 1760 and 1705; δ_H 1.32 (3 H, t, *J* 6.5), 2.68 (3 H, s), 4.32 (2 H, q, *J* 6.5), 6.41 (1 H, s), 7.85 (2 H, m) and 8.26 (2 H, m); *m/z* (Cl; NH_3) 431.

Ethyl 2-(3-*Acetyl*-1,4-*dihydroxy*-9,10-*dioxo*-9,10-*dihydro*-2-*anthryl*)*acetate* **2**.—To a stirred suspension of the ketone **1** (33 mg) and ethyl nitroacetate (66 mm^3) in MeOH (6 cm^3) under an atmosphere of N_2 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (36 mm^3) was added and the mixture was left at room temperature for 18 h. Neutralisation by the addition of 4 drops of 2 mol dm^{-3} HCl led to the formation of an orange precipitate which was extracted into CH_2Cl_2 (4 × 10 cm^3). Work-up in the usual way followed by dry column chromatography on silica (CH_2Cl_2) gave the *ester* **2** (25 mg) as an orange solid, m.p. 176–178 °C (CH_2Cl_2); λ_{max}/nm 485 (ε 7000), 325 (1500), 287 (7400) and 249 (18 400); ν_{max}/cm^{-1} 1730 and 1705; δ_H 1.28 (3 H, t, *J* 6.5), 2.63 (3 H, s), 3.81 (2 H, s) and 4.14 (2 H, q, *J* 6.5) (Found: M$^+$, 368.0901. $C_{20}H_{16}O_7$ requires *M*, 368.0896).

4-*Acetyl*-5-*hydroxy*-2-*pentylfuro*[2,3-a]*anthracene*-6,11-*dione* **9**.—DBU (31 mm^3) was added to a stirred suspension of the ketone **1** (29 mg) in MeOH (5 cm^3) under an atmosphere of N_2. After 5 min dimethyl (2-oxoheptyl)phosphonate (107 mm^3) was added and the mixture was left at room temperature for 18 h. Water (5 cm^3) was added followed by 5 drops of 2 mol dm^{-3} HCl and the mixture was extracted with CH_2Cl_2. Work-up in the usual way followed by dry column chromatography on silica (CH_2Cl_2) afforded the *furan* (9 mg) as an orange solid, m.p. 137–138 °C (hexane–CH_2Cl_2); λ_{max}/nm 442 (ε 5500), 290 (9400) and 267 (15 000); ν_{max}/cm^{-1} 1670; δ_H 2.76 (3 H, s), 6.97 (1 H, br s), 7.73 (2 H, m) and 8.22 (2 H, m) (Found: M$^+$, 376.1343. $C_{23}H_{20}O_5$ requires *M*, 376.1311).

3,3-*Dimethoxy*-1-*nitrobutan*-2-*one*.—BuLi (1.6 mol dm^{-3} in hexane; 11 cm^3) was added to a cooled (−90 °C), stirred solution of dry CH_3NO_2 (380 mm^3) in dry tetrahydrofuran (THF) (33 cm^3) and $(Me_2N)_3PO$ (7 cm^3) under N_2. The resulting yellow mixture was allowed to warm to −40 °C over a period of 3 h. After re-cooling (−90 °C), methyl 2,2-dimethoxypropanoate (821 mg) was added slowly and the mixture was once again allowed to warm to −40 °C, this time over 2 h. The reaction was quenched at −90 °C by the addition of AcOH (2.5 cm^3) and allowed to warm to room temperature. Et_2O (75 cm^3) was added and the solution was washed with saturated aqueous NaCl (100 cm^3) and worked-up in the usual way. Dry column chromatography of the product on silica (Et_2O) gave the 3,3-*dimethoxy*-1-*nitrobutan*-2-*one* (717 mg). Distillation under reduced pressure provided an analytically pure sample as a colourless mobile oil, b.p. 115 °C/0.2 mmHg; λ_{max}/nm 339 (ε 900) and 236 (950); ν_{max}(cm^{-1} 1755; δ_H 1.45 (3 H, s), 3.26 (6 H, s) and 5.49 (2 H, s) (Found: C, 40.6; H, 6.3; N, 8.0. $C_6H_{11}NO_5$ requires C, 40.7; H, 6.3; N, 7.9%).

2-*Acetyl*-1,4-*dihydroxy*-3-(3,3-*dimethoxy*-2-*oxobutyl*)*anthracene*-9,10-*dione*.—A solution of the ketone **1** (110 mg), Et_2N (120 mm^3) and 3,3-dimethoxy-1-nitrobutan-2-one (400 mg) in CH_2Cl_2 (60 cm^3) was heated under reflux for 18 h under N_2. After cooling the solution was worked-up in the usual way and the product purified by dry column chromatography on silica (CH_2Cl_2) to give the *diketone* **4** (140 mg) as a red solid, m.p. 153–155 °C (CH_2Cl_2); λ_{max}/nm 485 (ε 5700), 287 (5600) and

* $[\alpha]_D$ Values are given in 10^{-1} deg cm^2 g^{-1}.

253 (20 600); ν_{max}/cm^{-1} 1735 and 1700; δ_H 1.40 (3 H, s), 2.56 (3 H, s), 3.25 (6 H, s), 4.19 (2 H, s), 7.85 (2 H, m) and 8.36 (2 H, m); δ_C 19.89, 31.56, 36.17, 49.79, 102.91, 112.02, 112.45, 127.06, 132.99, 133.19, 133.52, 134.68, 13.71, 141.01, 154.19, 155.91, 186.60, 186.81, 202.32 and 204.88 (Found: C, 63.8; H, 4.9. $C_{22}H_{20}O_8$ requires C, 64.1; H, 4.9%).

Hydrolysis of **4** with aqueous CF_3CO_2H gave an *enol hemiacetal*, m.p. 290–294 °C (EtOAc–CH_2Cl_2); λ_{max}/nm 541 (ε 7900), 289 (9700) and 259 (21 700); ν_{max}/cm^{-1} 1685; δ_H 2.23 (3 H, s), 2.51 (3 H, s), 7.37 (1 H, s), 7.93 (2 H, m) and 8.44 (2 H, m); *m/z* ($ClNH_3$) 384, 367.

Dissolution of **4** in Me_2NCHO transformed it into the unstable *enol ether* **17**, λ_{max}/nm 552 (ε 6500), 516 (9500), 298 (7000), 279 (16 000), 260 (12 000) and 252 (11 500); ν_{max}/cm^{-1} 3360 and 1624; δ_H 1.58 (3 H, s), 2.18 (3 H, s) and 6.83 (1 H, s).

Cyclisation of Dione **4**.—The dione **4** (24 mg), finely powdered, was suspended in water (10 cm^3). Pr^{i}NEt (17 mm^3) was added and the mixture was stirred vigorously at room temperature for 3 h. The purple solution was extracted with CH_2Cl_2 (4 × 5 cm^3) and worked up in the usual way. TLC of the product on silica (CH_2Cl_2–EtOAc, 9:1) gave the 4,5,12-*trihydroxy*-3-(1,1-*dimethoxyethyl*)-3,4-*dihydronaphthacene*-1-(2H),6,11-*trione* **14** (11 mg) as a red solid, m.p. 230–232 °C (CH_2Cl_2–EtOAc); λ_{max}/nm 497 (ε 5900), 299 (6500) and 256 (21 000); ν_{max}/cm^{-1} 3490 and 1700; δ_H 1.44 (3 H, s), 2.91 (2 H, br s), 3.13 (1 H, d, *J* 19), 3.41 (3 H, s), 3.42 (1 H, d, *J* 19) and 3.43 (3 H, s) (Found: C, 63.8; H, 4.9. $C_{22}H_{20}O_8$ requires C, 64.1; H, 4.9%).

Reduction of the Ketone **14**.—To a stirred solution of the ketone **14** (28 mg) in Pr^{i}OH (6 cm^3) was added $CeCl_3$·7H_2O (40 mg) and $NaBH_4$ (12 mg). After 15 min the reaction was quenched by the addition of water (5 cm^3) and neutralised with 2 mol dm^{-3} HCl (3 cm^3). After being stirred for 10 min the mixture was extracted with CH_2Cl_2 (4 × 5 cm^3) and worked up in the usual way. PTLC of the crude material on silica (CH_2Cl_2–EtOAc 3:1) gave the 9-*acetyl*-5,7,9,11-*tetrahydroxy*-7,8,9,10-*tetrahydronaphthacene*-5,12-*diones* **20a** and **21a** (10 mg) as a red solid, m.p. 102–103 °C (CH_2Cl_2–EtOAC); λ_{max}/nm 483 (ε 4700), 280 (7850), 256 (15 900) and 245 (20 700); ν_{max}/cm^{-1} 3440 and 1715; **20a** δ_H 2.17 (1 H, dd, *J* 15.5 and 5), 2.33 (1 H, dm, *J* 15.5), 2.42 (3 H, s), 2.95 (1 H, d, *J* 18.5), 3.20 (1 H, dd, *J* 18.5 and 2) and 5.33 (1 H, m); **21a** δ_H 2.11 (1 H, dd, *J* 14 and 5), 2.36 (1 H, dm, *J* 14.5), 2.43 (3 H, s), 2.89 (1 H, d, *J* 19), 3.12 (1 H, dd, *J* 19 and 2) and 5.22 (1 H, m) (Found: M$^+$, 368.0925. $C_{20}H_{16}O_7$ requires *M*, 368.0896).

Phenylboronate of Diol **20a**.—Phenylboronic acid (19 mg) and toluene-4-sulfonic acid (4 mg) were added to a stirred solution of the diol mixture **20a** and **21a** (38 mg) in toluene (15 cm^3). After 18 h at room temperature, the mixture was washed with a 5% aqueous $NaHCO_3$ (2 × 10 cm^3) and water (1 × 10 cm^3). Work-up in the usual way followed by PTLC on silica (CH_2Cl_2–EtOAc, 8:1) afforded the *boronate* (28 mg) as an orange solid, m.p. 231–232 °C (CH_2Cl_2-hexane); λ_{max}/nm 545 (ε 4400), 506 (8800), 487 (9000), 272 (17 900), 258 (31 600) and 251 (32 400); ν_{max}/cm^{-1} 1720; δ_H 2.29 (1 H, dd, *J* 13.5 and 2.5), 2.35 (1 H, dm, *J* 13.5), 2.55 (3 H, s), 3.27 (1 H, d, *J* 20.5), 3.37 (1 H, dd, *J* 20.5 and 1.5) and 5.85 (1 H, t, *J* 2.5) (Found: M$^+$, 454.1229. $C_{26}H_{19}BO_7$ requires *M*, 454.1224).

(±)-*Demethoxydaunomycinone*.—A solution of the boronate of **20a** (20 mg) in CH_2Cl_2 (10 cm^3) containing 2-methylpentane-2,4-diol (2 cm^3) and AcOH (0.5 cm^3) was stirred at room temperature for 35 h. The solution was then washed with water (3 × 10 cm^3) and worked up in the usual way. PTLC of the product on silica (CH_2Cl_2–EtOAc 3:1) afforded (±)-demethoxydaunomycinone **20a** + **23a** (20 mg), m.p. 159–162 °C (lit.,[7] m.p. 160–164 °C), with identical spectroscopic properties to an authentic sample.

Ethyl (S)-2-(4-*Methoxybenzyloxy*)*propanoate*.—NaH (1.02 g of a 60% dispersion in mineral oil) was washed free of oil and tetrahydrofuran (THF) (20 cm^3) and Me_2NCHO (30 cm^3) added under a N_2 atmosphere. Ethyl (*S*)-lactate (3 g) in THF (5 cm^3) was added with stirring over 40 min. After an additional 2.5 h 4-methoxybenzyl chloride (3.98 g) in THF (5 cm^3) was added dropwise. After 24 h the mixture was diluted with water (50 cm^3), extracted with Et_2O (3 × 50 cm^3) and worked-up in the usual way. After chromatography on silica (Et_2O–hexane) *ethyl* (S)-2-(4-*methoxybenzyloxy*)*propanoate* (4.84 g) was obtained as a colourless liquid, $[\alpha]_D$ −7.2 (*c* 0.5); ν_{max}/cm^{-1} 1740; δ_H 1.26 (3 H, t, *J* 7.2), 1.38 (3 H, d, *J* 7.2), 3.76 (3 H, s), 4.00 (2 H, q, *J* 7.2), 4.20 (1 H, q, *J* 7.2), 4.37 (1 H, d, *J* 12), 4.60 (1 H, d, *J* 12), 6.70 (2 H, d, *J* 8.2) and 7.28 (2 H, d, *J* 8.2); *m/z* 238.

3-(4-*Methoxybenzyloxy*)-1-*nitrobutan*-2-*one*.—A similar procedure to that for the preparation of 3,3-dimethoxy-1-nitrobutan-2-one was used. Ethyl (*S*)-2-(4-methoxybenzyloxy)-propanoate (1 g) gave recovered starting material (400 mg) and 3-(4-*methoxybenzyloxy*)-1-*nitrobutan*-2-*one* (510 mg), ν_{max}/cm^{-1} 1740; δ_H 7.10 (2 H, d, *J* 8), 6.72 (2 H, d, *J* 8), 5.45 (1 H, d, *J* 15), 5.20 (1 H, d, *J* 15), 4.50 (1 H, d, *J* 15), 4.25 (1 H, d, *J* 15), 3.95 (1 H, q, *J* 7), 3.62 (3 H, s) and 1.25 (3 H, d, *J* 7); *m/z* 253.

2-*Acetyl*-1,4-*dihydroxy*-3[(S)3-(4-*methoxybenzyloxy*)-2-*oxobutyl*]*anthracene*-9,10-*dione*.—A solution of 3-(4-methoxybenzyloxy)-1-nitrobutan-2-one (269 mg), Et_3N (143 mg), and the quinone **1** (200 mg) in CH_2Cl_2 (80 cm^3) was boiled under reflux in a N_2 atmosphere for 24 h. Work-up in the usual way gave a red solid which was washed with Et_2O to recover unchanged ketone. Chromatography of the residue on silica (CH_2Cl_2) gave the *dione* **5**, m.p. 160–161 °C ($CHCl_3$–hexane); $[\alpha]_D$ −11 (*c* 0.25); λ_{max}/nm 484 (ε 8350), 281 (10 900), 258 (30 000) and 255 (30 900); ν_{max}/cm^{-1} 1725 and 1695; δ_H 4.62 (1 H, d, *J* 11), 4.53 (1 H, d, *J* 11), 4.22 (1 H, d, *J* 18), 4.16 (1 H, d, *J* 18), 4.10 (1 H, q, *J* 7), 3.82 (3 H, s), 2.62 (3 H, s) and 1.42 (3 H, d, *J* 7) (Found: C, 68.5; H, 4.8, M$^+$, 488.1460. $C_{28}H_{24}O_8$ requires C, 68.8; H, 4.9%. *M*, 488.1471).

3,5,12-*Trihydroxy*-3-[(S)-2-(4-*methoxybenzyloxy*)*propyl*]-3,4-*dihydronaphthacene*-1(2H),6,11-*trione* **15**.—$EtN(C_6H_{11})_2$ (84 mg) was added dropwise to a stirred solution of dione **5** (100 mg) in MeOH (80 cm^3) under an N_2 atmosphere. The mixture was stirred at room temperature for 2.5 h, acidified with 10 mol dm^{-3} HCl, diluted with water (100 cm^3) and extracted with CH_2Cl_2 (2 × 30 cm^3). Work-up in the usual way, followed by chromatography on silica (2.5 g) (CH_2Cl_2–EtOAc, 10:1) afforded unchanged dione (20 mg), *aromatic tetracycle* **11** (15 mg), m.p. 142–144 °C; λ_{max}/nm 531 (ε 800), 495 (23 650), 464 (13 050), 272 (49 900) and 243 (25 800); δ_H 7.99 (1 H, d, *J* 1.5), 7.38 (1 H, d, *J* 1.5), 4.64 (1 H, q, *J* 6.5), 4.52 (1 H, d, *J* 11), 4.36 (1 H, d, *J* 11), 3.84 (3 H, s) and 1.52 (3 H, d, *J* 6.5) (Found: M$^+$, 470.1360. $C_{28}H_{22}O_7$ requires *M*, 470.1365), and a mixture of *tetracyclic ketones* **15** (50 mg), m.p. 90–92 °C; λ_{max}/nm 497 (ε 10 900), 284 (12 350) and 256 (38 600); ν_{max}/cm^{-1} 3490 and 1695; δ_H 4.70 (1 H, d, *J* 11), 4.40 (1 H, d, *J* 11), 3.76 (3 H, s), 3.54 (1 H, q, *J* 7), 3.37 (1 H, d, *J* 19), 3.05 (1 H, d, *J* 19), 2.86 (2 H, s) and 1.30 (3 H, d, *J*); *m/z* 470.

Reduction of the Tetracyclic Ketones **15**.—To a stirred solution of the ketones **15** (50 mg) in Pr^{i}OH (70 cm^3) was added $CeCl_3$·7H_2O (57 mg) and $NaBH_4$ (12 mg) at 0 °C under an N_2 atmosphere. After 24 h, the solution was acidified with 2 mol dm^{-3} HCl and extracted with CH_2Cl_2 (2 × 50 cm^3). Work-up in the usual way followed by PTLC on silica (CH_2Cl_2–EtOAc,

15:1; triple elution) gave the *diols* **22b** and **23b** (1:3) (30 mg) and the *diols* **20b** and **21b** (2:1) (5 mg).

The major fraction (27 mg) was treated with $PhB(OH)_2$ as described previously and work-up followed by PTLC on silica (CH_2Cl_2–EtOAc, 19:1) gave the diol **22b** (7 mg), m.p. 82–84 °C; $[\alpha]_D$ −38 (*c* 0.42); λ_{max}/nm 519 (ε 5200), 485 (4600), 284 (10 900) and 252 (40 000); δ_H 5.34 (1 H, $W_{\frac{1}{2}}$ 18), 4.68 (1 H, d, *J* 11), 4.41 (1 H, d, *J* 11), 3.74 (3 H, s), 3.54 (1 H, q, *J* 6.5), 2.98 (1 H, dd, *J* 18 and 2.3), 2.84 (1 H, d, *J* 18), 2.38 (1 H, ddd, *J* 12.7, 6.5 and 2.3), 1.82 (1 H, dd, *J* 12.7 and 9.7) and 1.29 (3 H, d, *J* 6.5) (Found: M^+, 490.1628. $C_{28}H_{26}O_8$ requires *M*, 490.1628), and the *boronate* of **23b**, m.p. 213–215 °C; λ_{max}/nm 521 (ε 4050), 487 (6600), 284 (6950) and 253 (26 400); δ_H 5.80 (1 H, $W_{\frac{1}{2}}$ 6), 4.73 (1 H, d, *J* 11.5), 4.48 (1 H, d, *J* 11.5), 3.78 (3 H, s), 3.65 (1 H, q, *J* 6.5), 3.26 (1 H, dd, *J* 20 and 1.5), 3.13 (1 H, d, *J* 20), 2.38 (1 H, dd, *J* 14.5 and 2.5), 2.09 (1 H, ddd, *J* 14.5, 2.5 and 1.5) and 1.54 (3 H, d, *J* 6.5) (Found: M^+, 576.1966. $C_{34}H_{29}BO_8$ requires *M*, 576.1955).

Using the method described previously the boronate (15 mg) was cleaved to the *diol* **23b** (10 mg), m.p. 78–80 °C; $[\alpha]_D$ −42.6 (*c* 0.5); λ_{max}/nm 520 (ε 5200), 485 (8650), 284 (10 950) and 253 (34 000); δ_H 5.25 (1 H, $W_{\frac{1}{2}}$ 11), 4.70 (1 H, d, *J* 11), 4.44 (1 H, d, *J* 11), 3.35 (1 H, dd, *J* 19 and 2), 2.66 (1 H, d, *J* 19), 2.27 (1 H, ddd, *J* 15, 2 and 2), 2.00 (1 H, dd, *J* 15 and 5) and 1.32 (3 H, d, *J* 6.5) (Found: M^+, 490.1626. $C_{28}H_{26}O_8$ requires *M*, 490.1628).

Ethyl (S)-2-tert-*Butyldimethylsilyloxypropanoate*.—(*S*)-Ethyl lactate (3.022 g), *tert*-butyldimethylsilyl chloride (4.86 g) and imidazole (3.967 g) were dissolved in dry Me_2NCHO (10 cm^3) and stirred at room temperature for 2 h. The mixture was diluted with water (20 cm^3) and extracted with Et_2O (3 × 20 cm^3). Work-up in the usual way followed by chromatography on silica (50 g) (b.p. 40–60 °C light petroleum–Et_2O, 2:1) gave the *silyl ether* as a colourless oil (4.75 g), δ_H 4.07 (2 H, q, *J* 7.3), 4.07 (1 H, m), 1.31 (3 H, d, *J* 6.5), 1.20 (3 H, t, *J* 7.3), 0.85 (9 H, s) and 0.05 (6 H, s) (M^+, 233.1573. $C_{12}H_{25}O_3Si$ requires *M*, 233.1573).

3-tert-*Butyldimethylsilyloxy*-1-*nitrobutan*-2-*one*.—A stirred solution of CH_3NO_2 (265 mg) in dry THF (34 cm^3) containing $(Me_2N)_3PO$ (5 cm^3) was cooled to −90 °C and BuLi (6 cm^3; 1.6 mol dm^{-3} in hexane) added dropwise at such a rate that the temperature remained below −90 °C. The resulting mixture was warmed to −40 °C over 3 h, cooled to −90 °C again and ethyl 2-*tert*-butyldimethylsilyloxypropanoate (0.98 g) added dropwise. After warming to −40 °C over 2 h, AcOH (2.0 g) was added and the mixture warmed to room temperature. The resulting yellow solution was diluted with Et_2O (25 cm^3) and worked-up in the usual way. Flash chromatography of the product on silica (50 g) (b.p. 40–60 °C light petroleum–Et_2O 2:1) gave 3-tert-*butyldimethylsilyloxy*-1-*nitrobutan*-2-*one* as a yellow oil (0.6 g), ν_{max}/cm^{-1} 1750; δ_H 5.59 (1 H, d, *J* 16), 5.47 (1 H, d, *J* 16), 4.38 (1 H, q, *J* 7), 1.39 (3 H, d, *J* 7), 0.91 (9 H, s), 0.13 (3 H, s), 0.12 (3 H, s) ($[M + NH_4]^+$ 265.1586. $C_{10}H_{25}NO_4Si$ requires *M*, 265.1584).

9-[(S)-1-tert-*Butyldimethylsilyloxyethyl*]-6,7,11-*trihydroxy*-*naphthacene*-5,12-*dione* **12**.—A solution of 3-*tert*-butyldimethylsilyloxy-1-nitrobutan-2-one (8 mg) in dry CH_2Cl_2 (2 cm^3), and DBU (51 mm^3) was added to quinone (52 mg) in dry CH_2Cl_2 (10 cm^3). The mixture was heated under reflux in an N_2 atmosphere for 24 h. After dilution with CH_2Cl_2 (20 cm^3) work-up in the usual way and chromatography on silica (25 g) (CH_2Cl_2) gave the *tetracycle* **12** (6 mg), m.p. 161–162 °C; λ_{max}/nm 555 (ε 3100), 525 (6900), 490 (6900), 460 (6300) and 270 (17 200); δ_H 7.90 (1 H, d, *J* 1.4), 7.34 (1 H, d, *J* 1.4), 4.97 (1 H, q, *J* 6.5), 1.47 (3 H, d, *J* 6.5), 0.95 (9 H, s), 0.11 (3 H, s) and 0.05 (3 H, s) (M^+, 465.1744. $C_{26}H_{29}O_6Si$ requires *M*, 465.1733).

2-*Acetyl*-3-[(S)-tert-*butyldimethylsilyloxy*-2-*oxobutyl*]-1,4-*dihydroxyanthracene*-9,10-*dione* **6**.—3-*tert*-Butyldimethylsilyloxy-1-nitrobutan-2-one (77 mg) and Et_3N (44 mg) in dry CH_2Cl_2 (2 cm^3) were added to quinone **1** (50 mg) in CH_2Cl_2 (10 cm^3). The mixture was heated under reflux in a N_2 atmosphere for 24 h. CH_2Cl_2 (20 cm^3) was added and the solution washed with 2 mol dm^{-3} HCl (10 cm^3) and worked-up in the usual way. Chromatography of the product on silica (25 g) (CH_2Cl_2) gave the *dione* **6** (64 mg), m.p. 180–188 °C; λ_{max}/nm 480 (ε 5200), 280 (6400) and 250 (18 500); ν_{max}/cm^{-1} 1725 and 1690; δ_H 4.30 (1 H, q, *J* 6.8), 4.20 (2 H, s), 2.62 (3 H, s), 1.39 (3 H, d, *J* 6.8), 0.97 (9 H, s), 0.16 (3 H, s) and 0.14 (3 H, s) (Found: M^+, 483.1852. $C_{26}H_{31}O_7Si$ requires *M*, 483.1839).

3-[(S)-2-tert-*Butyldimethylsilyloxypropyl*]-3,5,12-*trihydroxy*-3,4-*dihydronaphthacene*-1(2H),6,11-*trione* **16**.—$EtN(C_6H_{11})_2$ (91 mg) was added dropwise to a stirred solution of dione **6** (104 mg) in MeOH (80 cm^3) under an N_2 atmosphere. After 3 h the mixture was acidified with 10 mol dm^{-3} HCl, diluted with water (80 cm^3) and extracted with CH_2Cl_2 (3 × 200 cm^3). Work-up in the usual way, followed by chromatography on silica (25 g) (CH_2Cl_2–EtOAc, 15:1) afforded unchanged dione (60 mg) and an inseparable mixture of diastereoisomeric *tetracyclic ketones* **16** (33 mg), m.p. 77–80 °C; ν_{max}/cm^{-1} 1700; δ_H(major isomer) 3.82 (1 H, q, *J* 6), 3.40 (1 H, d, *J* 19), 2.98 (1 H, d, *J* 19), 2.82 (2 H, s), 1.26 (3 H, d, *J* 6), 0.94 (9 H, s) and 0.14 (6 H, s); (minor isomer) 3.82 (1 H, q, *J* 6), 3.32 (1 H, dd, *J* 19 and 2), 2.95 (1 H, d, *J* 19), 2.91 (1 H, dd, *J* 16 and 2), 2.75 (1 H, d, *J* 16), 1.28 (3 H, d, *J* 6), 0.94 (9 H, s) and 0.15 (6 H, s); *m*/*z* ($CINH_3$) 483.

Reduction of the Tetracyclic Ketones **16**.—The ketones **16** (7 mg) were reduced as described previously with $CeCl_3 \cdot 7H_2O$ and $NaBH_4$. Work-up and PTLC (CH_2Cl_2–EtOAC, 15:1) gave an inseparable mixture of the diastereoisomeric diols **20c**, **21c**, **22c**, **23c** (6 mg), m.p. 45–59 °C; δ_H(major isomer) 5.27 (1 H, br s, $W_{\frac{1}{2}}$ 10), 3.80 (3 H, q, *J* 6.2), 3.23 (1 H, dd, *J* 19 and 1.8), 2.66 (1 H, d, *J* 19), 2.25 (1 H, dm, *J* 14.5), 1.96 (1 H, dd, *J* 14.5 and 5), 1.30 (3 H, d, *J* 6.2), 0.94 (9 H, s) and 0.15 (6 H, s); *m*/*z* ($CINH_3$) 485.

The diol mixture (21 mg) in 1,2-dimethoxyethane (20 cm^3) containing anhydrous toluene-4-sulfonic acid (2 mg) and 2,2-dimethoxypropane (4.24 g) was heated under reflux in an N_2 atmosphere for 1 h. The cooled mixture was diluted with CH_2Cl_2 (20 cm^3) and worked-up in the usual way. Chromatography on silica (25 g) (CH_2Cl_2:EtOAc, 15:1) gave a mixture of the *isopropylidene ethers* of **20c** and **23c** (15 mg), m.p. 147–151 °C; δ_H(major isomer) 5.50 (1 H, t, *J* 3), 3.92 (1 H, q, *J* 6), 3.04 (1 H, dd, *J* 18 and 1.5), 2.88 (1 H, d, *J* 18), 2.36 (1 H, dm, *J* 15), 1.94 (1 H, dd, *J* 15 and 3), 1.50 (3 H, s), 1.31 (3 H, d, *J* 6), 1.07 (3 H, s), 0.90 (9 H, s), 0.16 (3 H, s) and 0.12 (3 H, s) (Found: M^+, 524.2201. $C_{29}H_{36}O_6Si$ requires *M*, 524.2230).

$BF_3 \cdot OEt_2$ (0.577 g) was added dropwise to a solution of the isopropylidene ketals (7 mg) in $CHCl_3$ under a N_2 atmosphere. After 20 min water (20 cm^3) was added and the mixture extracted with $CHCl_3$ (3 × 10 cm^3). Work-up in the usual way followed by PTLC (CH_2Cl_2–EtOAc, 5:1) gave the intractable tetracyclic triols (4.5 mg). The triols (6 mg) in dry dimethoxyethane (20 cm^3) were heated under reflux with 2,2-dimethoxypropane (2.12 g) and a catalytic amount of toluene-4-sulfonic acid in an N_2 atmosphere for 1 h. The cooled mixture was diluted with CH_2Cl_2 (20 cm^3) and worked-up in the usual way. PTLC (CH_2Cl_2) gave the 9,13-isopropylidene derivatives (4.5 mg). Recrystallisation from light petroleum (b.p. 40–60 °C)

gave the major isomer (enantiomer of **18**), m.p. 226–229 °C; $[\alpha]_D$ −79 (*c* 0.025, dioxane); δ_H 5.28 (1 H, dm, *J* 10), 4.34 (1 H, d, *J* 10), 4.21 (1 H, q, *J* 6), 3.15 (1 H, dd, *J* 18 and 2), 2.70 (1 H, d, *J* 18), 2.43 (1 H, dm, *J* 18), 1.70 (1 H, dd, *J* 14 and 4), 1.55 (3 H, s), 1.41 (3 H s) and 1.32 (3 H, d, *J* 6) (Found: M^+ − 18 392.1232. $C_{23}H_{20}O_6$ requires *M*, 392.1260).

Isopropylidene Acetal of Methyl (R)-2,3-*Dihydroxypropanoate* **27**.—*N*-Bromosuccinimide (0.81 g) was added to a solution of Bu_3SnOMe (1.46 g) and the aldehyde **24** (0.59 g) in dry CCl_4 (25 cm^3) under an N_2 atmosphere. After 20 h at room temperature the mixture was filtered and the filtrate evaporated under reduced pressure to give an oil which was purified by dry column chromatography (Et_2O–light petroleum b.p. 40–60 °C) to give the *ester* **27** (407 mg), ν_{max}/cm^{-1} 1760 and 1740; δ_H 4.58 (1 H, dd, *J* 7.5 and 5), 4.22 (1 H, dd, *J* 7.5 and 8.5), 4.08 (1 H, dd, *J* 8.5 and 5), 3.76 (3 H, s), 1.45 (3 H, s) and 1.36 (3 H, s); *m*/*z* ($CINH_3$) 178 and 145.

Isopropylidene Acetal of (R)-3,4-*Dihydroxy*-1-*nitrobutan*-2-*one* **28**.—BuLi (4.53 cm^3; 1.6 mol dm^{-3} in hexane) was added dropwise to a stirred solution of CH_3NO_2 (153 mg) and $(Me_2N)_3PO$ (2.5 cm^3) in dry THF (10 cm^3) under N_2 at −90 °C. The mixture was allowed to warm to −40 °C over 3 h. The ester **27** (550 mg) dissolved in dry THF (2.5 cm^3) was added to the mixture at −90 °C and allowed to warm to −40 °C over 2 h. The reaction was quenched by addition of AcOH (0.5 cm^3). Et_2O (25 cm^3) was added and work-up in the usual way gave an oil which was purified by dry column chromatography (Et_2O–light petroleum b.p. 40–60 °C) to give the *nitro ketone* **28** (135 mg), $[\alpha]_D$ +58 (*c* 0.6 in CH_2Cl_2); ν_{max}/cm^{-1} 1750; δ_H 5.58 (1 H, d, *J* 16), 5.51 (1 H, d, *J* 16), 4.65 (1 H, dd, *J* 8 and 4.5), 4.31 (1 H, dd, *J* 9.5 and 8), 4.21 (1 H, dd, *J* 9.5 and 4.5), 1.51 (3 H, s) and 1.38 (3 H, s); *m*/*z* ($CINH_3$) 207, 190.

2-*Acetyl*-1,4-*dihydroxy*-3-[(R)-3,4-*isopropylidenedioxy*-2-*oxobutyl*]*anthracene*-9,10-*dione* **7**.—Et_3N (14 mg) and nitro ketone **28** (60 mg) dissolved in CH_2Cl_2 (1.5 cm^3) were added to a solution of the quinone **1** (18 mg) in CH_2Cl_2 (35 cm^3). The mixture was heated under reflux under N_2 for 20 h. Work-up in the usual way gave a red solid purified by PTLC (EtOAc–CH_2Cl_2, 1:19) to give the *diketone* **7** (24 mg) as orange plates, m.p. 174–177 °C (CH_2Cl_2–light petroleum b.p. 40–60 °C); $[\alpha]_D$ +12.8 (*c* 0.125 in CH_2Cl_2); ν_{max}/cm^{-1} 1725 and 1705; δ_H 4.53 (1 H, dd, *J* 7.7 and 5.5), 4.18 (1 H, dd, *J* 8.5 and 7.7), 4.08 (1 H, dd, *J* 8.5 and 5.5), 4.11 (1 H, d, *J* 18), 4.00 (1 H, d, *J* 18), 2.52 (3 H, s), 1.46 (3 H, s) and 1.34 (3 H, s) (Found: M^+, 424.1135. $C_{23}H_{20}O_8$ requires *M*, 424.1158).

6,7,11-*Trihydroxy*-9[(R)-1,2-*isopropylidenedioxyethyl*]*naphthacene*-5,12-*dione* **13**.—$EtN(C_6H_{11})_2$ (2 drops) was added to a solution of the diketone **7** (5 mg) in MeOH (7 cm^3). After 20 h the mixture was poured into water and extracted with CH_2Cl_2. Work-up in the usual way gave a solid which was purified by PTLC (EtOAc–CH_2Cl_2, 1:19) to give the *naphthacene* **13** (4 mg), m.p. 188–191 °C; δ_H 7.90 (1 H, d, *J* 1.5), 7.34 (1 H, d, *J* 1.5), 5.18 (1 H, m), 4.41 (1 H, dd, *J* 8.5 and 7), 3.72 (1 H, dd, *J* 8.5 and 7.5), 1.52 (3 H, s) and 1.44 (3 H, s) (Found: M^+, 406.1071. $C_{23}H_{18}O_7$ requires *M*, 406.1052).

Acknowledgements

We thank the SERC and the University of Manchester for financial support and Professor R. J. Stoodley, UMIST, for an authentic sample of demethoxydaunomycinone.

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Paper 2/01464E
Received 19*th March* 1992
Accepted 15*th April* 1992