Studies Related to Anthracyclines. Part 3.[1] Stereoselective Synthesis of (+)-Daunomycinone†

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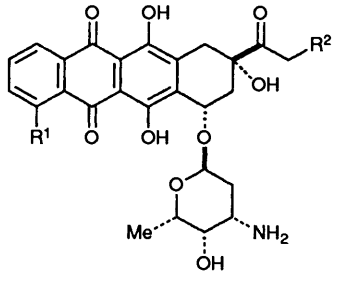
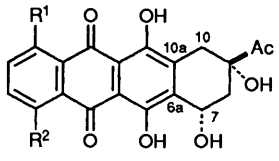
The title compound **2b** was prepared by a seven-step sequence from (±)-4a,9a-epoxy-4a,9a-dihydro-5-methoxyanthracene-1,4,9,10-tetraone **3b/3c** and (*E*)-1-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-3-trimethylsilyloxybuta-1,3-diene **4**. Acidic hydrolysis of the crude Diels–Alder cycloadducts of compounds **3b/3c** and **4** led, after fractional crystallisation, to the isolation of (5a*S*,6a*R*,7*S*,10a*R*,11a*R*)-5a,11a-epoxy-4-methoxy-5a,6a,7,8,9,10,10a,11a-octahydro-7-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyloxy)naphthacene-5,6,9,11,12-pentaone **6b**. The last-cited compound was transformed into (+)-daunomycinone **2b** by reduction, ethynylation, oxidation, hydrolysis and hydration steps.

The potent antitumour properties of daunomycin **1a** and adriamycin **1b**—members of the anthracycline class of antibiotics—have stimulated an enormous interest in the synthesis of these compounds and their relatives. As well as providing structurally modified anthracyclines possessing chemotherapeutic improvements, *e.g.* idarubicin **1c**, this effort has led to the development of an impressive array of new synthetic strategies and methodologies.[2,3]



1

a; R^1 = MeO, R^2 = H
b; R^1 = MeO, R^2 = HO
c; R^1 = R^2 = H



2

a; R^1 = R^2 = H
b; R^1 = H, R^2 = MeO
c; R^1 = MeO, R^2 = H

Our work has focussed upon developing the Diels–Alder strategy, involving construction of the 6a,7- and 10,10a-bonds, to assemble the tetracyclic precursors of the aglycones. Some time ago, we prepared (+)-4-demethoxydaunomycinone **2a**—the aglycone of idarubicin **1c**—by this approach (Scheme 1).[4] Thus, the epoxytetraone **3a** underwent reaction with the diene **4** in benzene at 5 °C to give mainly the cycloadduct **5a**. Under mild acidic conditions, the last-cited compound was hydrolysed to the epoxypentaone **6a** which underwent reduction to the dihydroxytrione **7a**. By ethynylation and oxidation steps, the dihydroxytrione **7a** was transformed into the anthracycline **8a**. Acidic hydrolysis of compound **8a** afforded the anthracyclinone **9a** which underwent hydration to give (+)-4-demethoxydaunomycinone **2a**.

In principle, a regio- and stereo-selective synthesis of (+)-daunomycinone **2b** should be achievable, using the reaction sequence shown in Scheme 1, by starting with the epoxymethoxytetraone **3b**. Before embarking on the synthesis of the starting material **3b** (or an equivalent compound) in enantiomerically pure form, we decided to undertake a feasibility study with racemic material (*i.e.* **3b/3c**). We now report on the findings of this study which have led to a stereoselective synthesis of (+)-daunomycinone **2b**.

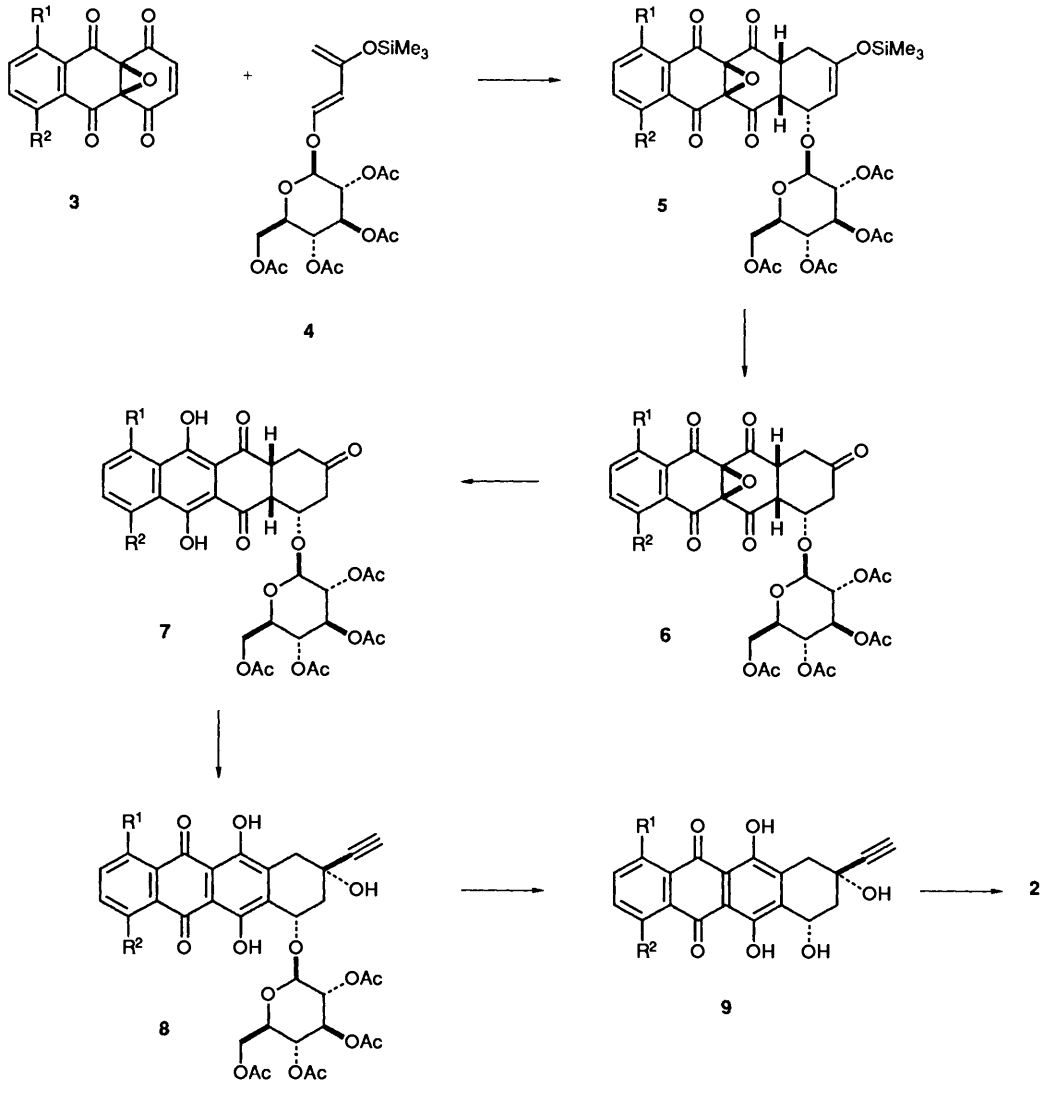
Results and Discussion

Earlier, we had prepared the epoxytetraone **3a** by oxidation of the diquinone **10a** [available from quinizarin **11a** by the action of $Pb(OAc)_4$] with *m*-chloroperoxybenzoic acid (MCPBA).[5] Subsequently, Preston and his co-workers obtained the (±)-epoxymethoxytetraone **3b/3c** from the diquinone **10b** in a similar manner.[6] The last-cited compound was prepared from 1,4-dihydroxy-5-methoxyanthraquinone **11b** [again, by the action of $Pb(OAc)_4$] which, in turn, was derived from 1,4,5-trimethoxyanthraquinone **11c** (by the action of BF_3·Et_2O followed by MeOH).[7] We used Preston's procedure to prepare the (±)-epoxymethoxytetraone **3b/3c** but acquired the methoxydiquinone **10b** from compound **11c** by Kende's method (oxidative de-*O*-methylation using AgO–HNO_3).[8] The overall yield of the (±)-epoxymethoxytetraone **3b/3c** from compound **11c** was *ca.* 22%.

The outcome of the reaction of the (±)-epoxymethoxytetraone **3b/3c** and the diene **4**[4,9] was somewhat variable and, on occasions, only de-*O*-silylation of the diene occurred (to give the butenone **12**[4]). However, by using good-quality samples of the reactants and acetone as the solvent, the aforecited reaction could be partly suppresssed. In general, mainly a 1:1:1 mixture of the (±)-epoxymethoxytetraone **3b/3c**, the butenone **12**, and the cycloadducts **5b/5c** (present in a 1.5–2:1 ratio) was produced according to 300 MHz ^{1}H NMR spectroscopic analysis; no material could be crystallised from the mixture. However, subjection of the mixture to the action of dilute hydrochloric acid in tetrahydrofuran (THF) afforded a product from which a pale-yellow solid could be isolated by crystallisation. The solid comprised a 2.5–3:1 mixture of the epoxymethoxypentaones **6b/6c**. The major component, assigned the regio- and stereo-structure **6b** on the basis of subsequent reactions, was isolated in a pure state in 8–11% yield after 2–3 recrystallisations.

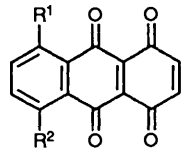
Previously, both sodium dithionite in aqueous methanol and activated zinc in acetic acid and THF were effective in promoting the **6a** ⟶ **7a** transformation.[4] However, neither reagent was satisfactory in inducing the corresponding reaction of compound **6b**, the dihydroxymethoxytrione **7b** being

† To facilitate comparisons, the Brockmann system of numbering and lettering (H. Brockmann, *Fortschr. Chem. Org. Naturst.*, 1963, **21**, 121), which is commonly adopted for anthracyclines and anthracyclinones, is used in this paper to describe anthracyclinone precursors.



a; $R^1 = R^2 = H$ **b**; $R^1 = H$, $R^2 = OMe$ **c**; $R^1 = OMe$, $R^2 = H$

Scheme 1



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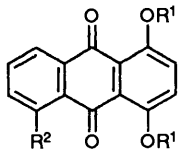
a; $R^1 = R^2 = H$
b; $R^1 = H$, $R^2 = MeO$



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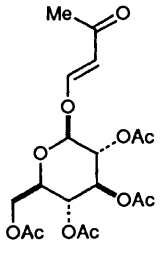
a; $R^1 = R^2 = H$
b; $R^1 = H$, $R^2 = MeO$
c; $R^1 = Me$, $R^2 = MeO$
d; $R^1 = H$, $R^2 = HO$



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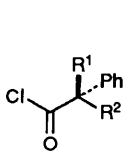
contaminated with by-products which were difficult to remove. After some experimentation, it was found that zinc in a 7:1 mixture of dichloromethane and acetic acid at 0 °C brought about the conversion of compound **6b** into the dihydroxymethoxytrione **7b** (68% yield after recrystallisation).

Numerous attempts were made to convert the dihydroxymethoxytrione **7b** into the anthracycline **8b** by the ethynylation–oxidation sequence. Initially, the best results were achieved by addition of a large excess (*ca.* 25–30 mol equiv.) of ethynylmagnesium bromide in THF[10] to a solution of the dihydroxymethoxytrione **7b** in THF and oxidation of the product with lead(IV) acetate in acetic acid; following recrystallisation, the anthracycline **8b** was isolated in 11% yield. Subsequently, it was found that the addition of a large excess (*ca.* 30–35 mol equiv.) of ethynylmagnesium chloride in THF[11] to a solution of the dihydroxymethoxytrione **7b** in THF and oxidation of the product as before gave, after work-up (in which Et_2NOH was added to compensate for any over-oxidation) and recrystallisation, mainly the anthracycline **8b** in *ca.* 26% yield.

Acidic hydrolysis (boiling ethanolic hydrochloric acid) of the anthracycline **8b** and subjection of the product to the action of mercury(II) oxide and sulphuric acid gave, after recrystallisation, a red solid in 65% yield. According to Krohn and Tolkiehn,[12] daunomycinone **2b** and isodaunomycinone **2c** can be distinguished by ^1H NMR spectroscopy: the 6- and 11-hydroxy groups absorb ($CDCl_3$) at δ 13.29 and 14.00 in the former compound and at δ 13.57 and 13.70 in the latter compound. In



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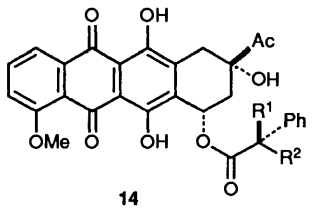
a; R^1 = MeO, R^2 = CF_3
b; R^1 = CF_3, R^2 = MeO



14

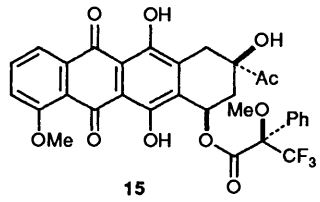
a; R^1 = MeO, R^2 = CF_3
b; R^1 = CF_3, R^2 = MeO

the 300 MHz ^{1}H NMR spectrum of our material, the 6- and 11-hydroxy groups appeared at δ 13.26 and 13.94. Moreover, the spectrum matched that of authentic (+)-daunomycinone **2b**[13] (prepared by acidic hydrolysis of daunomycin **1a**); it was also identical with that of a 1:1 mixture of synthetic and 'natural' material. Although our product showed a somewhat lower optical rotation {$[\alpha]_D$ +162 (dioxane)} than that reported for 'natural' daunomycinone **2b** {$[\alpha]_D$ +193 (dioxane)}[13] and for other synthetic material {$[\alpha]_D$ +175 (dioxane)},[14] it was clearly the natural antipode. In consequence, the regio- and stereo-structure **6b** can be confidently assigned to the crystalline product isolated from the (±)-epoxymethoxytetraone **3b/3c** and the diene **4** by the cycloaddition–hydrolysis sequence.

The discrepancy in the optical rotation of our synthetic daunomycinone **2b** compared with the literature value for 'natural' daunomycinone **2b** (which we corroborated) was a matter of some concern. To determine whether our product was enantiomerically pure, we decided to apply the Mosher method.[15] Preliminary studies with 'natural' daunomycinone **2b** and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride **13a*** revealed that it was necessary to use a large excess of the acid chloride to deplete the reactant. Under these conditions, the product was mainly the desired ester **14a** together with a second compound (presumed to be a diester); careful chromatography was needed to obtain the ester **14a** in a pure state. The use of 2 molar equivalents of the acid chloride **13a** proved to be more convenient for the analysis. It led to the production of only the ester **14a** (44% yield) which was easily separated from the starting material **2b** by chromatography. The aforecited conditions were adopted for the reaction of 'natural' daunomycinone **2b** with (*R*)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride **13b**, resulting in the isolation of the ester **14b** (64% yield after chromatography).

The diastereoisomeric esters **14a** and **b** were readily distinguished by 300 MHz ^{1}H NMR spectroscopy; in particular, the 5- and 11-hydroxy groups of the former material appeared as sharp singlets at δ 13.24 and 13.74 whereas those of the latter material resonated as sharp singlets at δ 13.20 and 13.94.

The reaction of synthetic daunomycinone **2b** with (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride **13a** (2 mol equiv.) led, after chromatography, to the isolation of two fractions. The ^{1}H NMR spectrum of the first-eluted material matched that of the ester **14a**; there was no evidence for the presence of the ester **15**.† The second fraction was identified as daunomycinone **2b** by ^{1}H NMR spectroscopy; significantly, the optical rotation of the sample {$[\alpha]_D$ +165 (dioxane)} was essentially unchanged, reassuring us that no kinetic resolution



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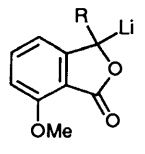
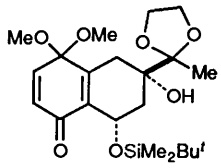


16

a; R = CN
b; R = SO_2Ph



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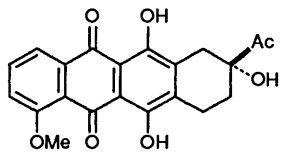

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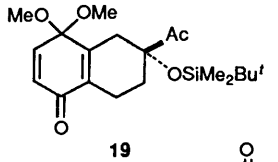

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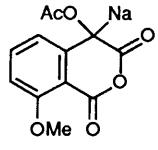

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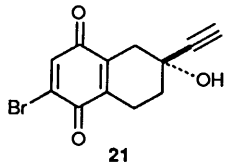

21

had occurred. Clearly our synthesis had led to enantiomerically pure (+)-daunomycinone **2b**.

Since the pioneering studies of Wong[16] in 1973, the synthesis of daunomycinone **2b** has been the objective of numerous investigations. Although many inventive routes have been devised,[2,3] few have addressed the enantioselectivity issue. Indeed, we are aware of only one other reported synthesis of (+)-daunomycinone **2b**. Thus, Swenton's group[14] coupled the salt **16a** with compound **17** in a key operation; a resolution step was involved in the generation of the AB-ring synthon **17**. The synthesis of (−)-7-deoxydaunomycinone **18** [the racemate of which has been converted[8,17] into (±)-daunomycinone **2b**] has been described by two groups. In the approach developed by Russell *et al.*[18] the salt **16b** was coupled with the quinone acetal **19**; the condensation of the salt **20** with the quinone **21** featured in the route reported by Fujioka's group.[19] Asymmetric syntheses were employed in the elaboration of the AB-ring synthons **19** and **21**.

Experimental

Dry solvents, referred to in the ensuing experiments, were prepared as follows: acetone was dried over calcium sulphate, distilled, and stored over 3 Å molecular sieves; THF (tetrahydrofuran) was dried over calcium hydride and distilled from sodium–benzophenone immediately prior to use; pyridine was distilled from potassium hydroxide pellets. Light petroleum refers to the fraction of b.p. 30–40 °C.

Optical rotations were measured at *ca.* 20 °C using either a Thorn Automation Type 243 polarimeter or an Optical Activity 1000 polarimeter and are given in 10^{-1} deg cm^2 g^{-1}. IR Spectra were determined using a Perkin-Elmer 783 spectrometer. Either a Cary 118 or a Perkin-Elmer Lambda 15 was used to record UV–VIS spectra. ^{1}H NMR Spectra were measured at 300 MHz with either a Varian XL300 spectrometer or a Bruker AC 300. *J* Values are given in Hz. FAB Mass spectra were recorded using either a VG ZAB-E or a Kratos Concept 1S

* It should be noted that this acid chloride is prepared from (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid.

† Compounds **15** and **14b**, being enantiomerically related, would be expected to possess identical NMR spectra. In a mixture of the esters **14a** and **b**, we were able to detect <5% of the latter material by 300 MHz ^{1}H NMR spectroscopy.

spectrometer. For chromatographic and other instrumental details, see Part 1.[5]

Preparation of (±)-4a,9a-*Epoxy*-4a,9a-*dihydro*-5-*methoxyanthracene*-1,4,9,10-*tetraone* **3b**/**3c**.—1,4,5-Trihydroxyanthraquinone **11d** (16.4 g, 64 mmol) was converted into the trimethyl ether **11c** by the method of Preston.[7] After recrystallisation from chloroform–light petroleum, compound **11c** (11.1 g, 58%) was obtained as a yellow solid with m.p. 204–208 °C (lit.,[7] 208–209 °C).

A stirred mixture of 1,4,5-trimethoxyanthraquinone **11c** (4.28 g, 14.3 mmol) and silver(II) oxide (9.30 g, 75 mmol) in acetone (400 cm^3) was heated to *ca.* 50 °C and then treated cautiously with nitric acid (6 mol dm^{-3}; 19 cm^3); after a few minutes, the mixture was ice-cooled and stirred for 1.5 h.[8] The mixture was concentrated (to *ca.* half its volume) and the insoluble material collected by filtration, washed with water and dried (*in vacuo*, P_2O_5). The resultant brown powder (2.63 g, *ca.* 68%) was identified as the methoxyanthraquinone **10b**; δ(300 MHz; $CDCl_3$) 4.00 (3 H, s, MeO), 6.88 (2 H, ABq, *J* 10, separation of inner lines 3 Hz, 2- and 3-H), 7.33 and 7.63 (each 1 H, dd, *J* 8 and 1, 6- and 8-H) and 7.73 (1 H, t, *J* 8, 7-H).

ca. 85% *m*-Chloroperoxybenzoic acid (MCPBA) (3.30 g, *ca.* 16 mmol) was added in portions over 20 min to a stirred ice-cooled solution of the diquinone **10b** (2.50 g, 9.3 mmol) in dry dichloromethane (125 cm^3). After 0.5 h, the mixture was allowed to warm to room temperature and left to stir for 30 h. The insoluble material was removed by filtration and washed well with dichloromethane. The filtrate and washings were combined and washed quickly with ice-cold 5% aqueous sodium hydrogen carbonate followed by ice-cold water. Evaporation of the dried ($MgSO_4$) organic phase (to *ca.* 30 cm^3) and addition of light petroleum to the concentrate induced the precipitation of the title compound **3b**/**3c** as a pale-orange solid. After recrystallisation from dichloromethane–diethyl ether, the sample (0.860 g, 32%), obtained as a yellow solid, showed m.p. 210–215 °C (decomp.; with darkening at *ca.* 180 °C) [lit.,[6] 205–220 °C (decomp.)]; δ(300 MHz; $CDCl_3$) 3.97 (3 H, s, MeO), 6.73 (2 H, s, 2- and 3-H), 7.30 and 7.48 (each 1 H, dd, *J* 8 and 1, 6- and 8-H) and 7.70 (1 H, t, *J* 8, 7-H).

Preparation of (5aS,6aR,7S,10aR,11aR)-5a,11a-*Epoxy*-5a,6a,7,8,9,10,10a,11a-*octahydro*-4-*methoxy*-7-(2′,3′,4′,6-*tetra*-O-*acetyl*-β-D-*glucopyranosyloxy*)*naphthacene*-5,6,9,11,12-*pentaone* **6b**.—A suspension of the (±)-epoxytetraone **3b**/**3c** (2.56 g, 9.0 mmol) and the diene **4**[4,9] (6.60 g, 13.5 mmol) in dry acetone (400 cm^3) was stirred overnight in the dark. The mixture was filtered and the filtrate evaporated to leave a residue (8.68 g) which comprised mainly a 3:2:1:3 mixture of compounds **3b**/**3c**, **5b**, **5c** and **12** by 300 MHz ^1H NMR spectroscopy [the ratio was estimated from the heights of the singlets at δ 0.27 and 0.26 attributed to the trimethylsilyl groups of the cycloadducts **5b** and **5c**, the integral of the doublet (*J* 12.5) at δ 5.82 ascribed to the 3-H of the butenone **12**, and the height of the singlet at δ 6.72 assigned to the 2- and 3-H of the oxirane **3b**/**3c**].

The residue was dissolved in a mixture of THF (180 cm^3) and hydrochloric acid (0.1 mol dm^{-3}; 15 cm^3). After 2 h, dichloromethane was added and the mixture was washed with water. Evaporation of the dried ($MgSO_4$) organic layer left a brown residue (8.05 g) from which a cream-coloured solid (0.792 g, 13%) was isolated after crystallisation from dichloromethane–methanol. The material comprised a 3:1 mixture of the title compound **6b** and its diastereoisomer **6c** by 300 MHz ^1H NMR spectroscopy [the ratio was estimated from the heights of the double doublets (each *J* 18 and 2) at δ 2.92 and 2.94 ascribed to the 8α-hydrogen atoms of the epoxypentaones **6c** and **6b**].

Three recrystallisations of the aforecited mixture from dichloromethane–methanol gave the *title compound* **6b** (0.490 g, 8%) as a pale-yellow solid in a pure state; m.p. 191–192 °C (decomp.); $[\alpha]_D$ −35 (1% in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1750 and 1740sh (ester C=O), 1720 and 1690 (ketone C=O); λ_{max}(EtOH)/nm 240 (ε 11 000) and 354 (4300); δ(300 MHz; $CDCl_3$) 1.80, 1.92, 2.02 and 2.13 (each 3 H, s, 4 × $MeCO_2$), 2.30 (1 H, dd, *J* 18 and 2, 8-Hβ), 2.36 (1 H, dd, *J* 16 and 8, 10-Hβ), 2.94 (1 H, dd, *J* 18 and 2, 8-Hα), 3.22 (1 H, dd, *J* 11 and 2, 6a-H), 3.37 (1 H, dd, *J* 16 and 8, 10-Hα), 3.63–3.71 (1 H, m, 5′-H), 4.00 (3 H, s, MeO), 4.01 (1 H, dt, *J* 11, 8 and 8, 10a-H), 4.10 (1 H, dd, *J* 12 and 3, 6′-H), 4.15 (1 H, dd, *J* 12 and 5, 6′-H), 4.57 (1 H, d, *J* 8, 1′-H), 4.70 (1 H, dd, *J* 9 and 8, 2′-H), 4.80–4.83 (1 H, m, 7-H), 4.95 (1 H, t, *J* 9, 4′-H), 5.13 (1 H, t, *J* 9, 3′-H), 7.32–7.38 (1 H, m, 1- or 3-H) and 7.69–7.77 (2 H, m, 2- and 3- or 1-H); *m*/*z* (EI) 336 ($M^+ - C_{14}H_{20}O_{11}$) and 43 ($C_2H_3O^+$, base peak) (Found: C, 56.4; H, 4.5. $C_{33}H_{32}O_{17}$ requires C, 56.55; H, 4.60%).

Preparation of (6aR,7S,10aR)-6a,7,8,9,10,10a-*Hexahydro*-5,12-*dihydroxy*-4-*methoxy*-7-(2′,3′,4′,6′-*tetra*-O-*acetyl*-β-D-*glucopyranosyloxy*)*naphthacene*-6,9,11-*trione* **7b**.—Glacial acetic acid (5 cm^3) and activated zinc dust (0.490 g, 7.5 mmol) were added to a stirred ice-cooled solution of the epoxypentaone **6b** (0.343 g, 0.49 mmol) in dichloromethane (35 cm^3). After 3 h, the mixture was filtered and the filtrate partitioned between dichloromethane and water. After having been washed with saturated aqueous sodium hydrogen carbonate and brine, the organic phase was dried ($MgSO_4$) and evaporated. Recrystallisation of the residue (0.308 g) from ethanol gave the *title compound* **7b** (0.228 g, 68%) as a yellow solid; m.p. 132–134 °C (decomp.); $[\alpha]_D$ +139 (0.25% in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1760br (ester C=O) and 1610 (chelated C=O); λ_{max}(EtOH)/nm 208 (ε 11 700), 242 (24 500), 270 (24 500), 399 (7500) and 410 (13 200); δ(300 MHz; $CDCl_3$) 1.36, 1.81, 1.94 and 2.13 (each 3 H, s, 4 × $MeCO_2$), 2.47 (1 H, dd, *J* 17 and 8, 10-Hβ), 2.53 (1 H, dd, *J* 17 and 3, 8-Hβ), 3.03 (1 H, br d, separation 17, 8-Hα), 3.41 (1 H, dd, *J* 8 and 2, 6a-H), 3.51–3.58 (2 H, m, 10-Hα and 5′-H), 3.65 (1 H, dt, *J* 8, 8 and 3, 10a-H), 4.04 (3 H, s, MeO), 4.07 (1 H, dd, *J* 13 and 3, 6′-H), 4.14 (1 H, dd, *J* 13 and 6, 6′-H), 4.38 (1 H, d, *J* 8, 1′-H), 4.49–4.53 (1 H, m, 2′-H), 4.70–4.73 (1 H, m, 7-H), 4.87–4.93 (2 H, m, 3′- and 4′-H), 7.16 (1 H, d, *J* 8, 1- or 3-H), 7.73 (1 H, t, *J* 8, 2-H), 8.13 (1 H, d, *J* 8, 3- or 1-H) and 12.94 and 14.88 (each 1 H, s, 5- and 12-OH); *m*/*z* (EI) 340 ($M^+ - C_{14}H_{18}O_{10}$) and 43 ($C_2H_3O^+$, base peak) (Found: C, 57.4; H, 5.1. $C_{33}H_{34}O_{16}$ requires C, 57.7; H, 5.00%).

Preparation of (7S,9S)-9-*Ethynyl*-7,8,9,10-*tetrahydro*-6,9,11-*trihydroxy*-4-*methoxy*-7-(2′,3′,4′,6′-*tetra*-O-*acetyl*-β-D-*glucopyranosyloxy*)*naphthacene*-5,12-*dione* **8b**.—(*a*) A solution of ethynylmagnesium bromide in THF[10] (*ca.* 1 mol dm^{-3}; 6 cm^3, *ca.* 6 mmol) was added to a stirred solution of the dihydroxytrione **7b** (0.150 g, 0.22 mmol) in dry THF (10 cm^3). After 3 h, the mixture was poured onto saturated aqueous ammonium chloride at 0 °C and extracted (×2) with chloroform. The organic layer was washed with water, dried ($MgSO_4$) and evaporated. The residue was dissolved in glacial acetic acid (5 cm^3) and to the stirred solution was added lead(IV) acetate (0.110 g, 0.25 mmol). After 15 h, the mixture was diluted with water and extracted (×2) with chloroform. Evaporation of the dried ($MgSO_4$) organic layer and recrystallisation of the product from dichloromethane–methanol gave the *title compound* **8b** (0.018 g, 11%) as red crystals; m.p. 292–295 °C; ν_{max}(KBr)/cm^{-1} 3500 (OH), 3300 (chelated OH), 1750 (ester C=O) and 1620 (chelated C=O); λ_{max}(EtOH, saturated solution)/nm 219sh, 234, 252 and 280; δ(300 MHz; $CDCl_3$) 1.85, 1.98, 2.05 and 2.16 (each 3 H, s, 4 × $MeCO_2$), 2.22 (1 H, dd, *J* 16 and 4, 8-Hβ), 2.54 (1 H, s, C≡CH), 2.92 (1 H, br d, *J* 16, 8-Hα), 2.93 (1 H, d, *J* 19, 10-Hβ), 3.58 (1 H, br d, *J* 19, 10-Hα), 3.81–3.87 (1 H, m, 5′-H), 3.93 (1 H, br s, 9-OH), 4.09 (3 H, s,

MeO), 4.22–4.32 (2 H, m, 6′-H_2), 4.92 (1 H, dd, *J* 10 and 8, 2′-H), 5.08 (1 H, d, *J* 8, 1′-H), 5.10 (1 H, t, *J* 10, 4′-H), 5.25 (1 H, t, *J* 10, 3′-H), 5.28–5.32 (1 H, m, 7-H), 7.40 (1 H, d, *J* 8, 1- or 3-H), 7.79 (1 H, t, *J* 8, 2-H), 8.05 (1 H, d, *J* 8, 3- or 1-H) and 13.26 and 14.05 (each 1 H, s, 6- and 11-OH); *m/z* (EI) 364 ($M^+ - C_{14}H_{18}O_{10}$) and 43 ($C_2H_3O^+$, base peak) (Found: C, 59.0; H, 4.6. $C_{35}H_{34}O_{16}$ requires C, 59.15; H, 4.80%).

(*b*) A solution of ethynylmagnesium chloride in THF[11] (*ca.* 1.2 mol dm^{-3}; 25 cm^3, *ca.* 30 mmol) was added to a stirred ice-cooled solution of the dihydroxy trione **7b** (0.576 g, 0.84 mmol) in dry THF (50 cm^3). After 2 h, the mixture was poured onto ice-cold saturated aqueous ammonium chloride and extracted (× 2) with dichloromethane. The organic layer was washed with water, dried ($MgSO_4$) and evaporated. The residue was dissolved in glacial acetic acid (25 cm^3) and to the stirred solution was added lead(IV) acetate (0.420 g, 0.95 mmol). After 15 h, the mixture was diluted with water and extracted with ethyl acetate. The organic phase was washed with saturated aqueous sodium hydrogen carbonate, treated with *N,N*-diethylhydroxyamine (3 cm^3), and then quickly washed with dilute hydrochloric acid, brine and water. Evaporation of the dried ($MgSO_4$) organic layer left a residue which was recrystallised from dichloromethane–methanol. The resultant red solid (0.156 g, *ca.* 26%) comprised an 8:1 mixture of the title compound **8b** and an unidentified material by ^1H NMR spectroscopy.

Purification of a portion (0.070 g) of the aforecited material by HPLC gave the title compound **8b** (0.040 g) in a pure state by ^1H NMR spectroscopy; m.p. >230 °C; $[\alpha]_D$ +130 (0.2% in $CHCl_3$).

Preparation of (+)-*Daunomycinone* **2b**.—A suspension of the ethynyldione **8b** (0.038 g, 0.054 mmol) in ethanol (10 cm^3) and hydrochloric acid (1 mol dm^{-3}; 10 cm^3) was heated under reflux for 15 h. The mixture was then cooled, diluted with water and extracted with ethyl acetate. After having been washed with brine, the organic extract was dried ($MgSO_4$) and evaporated to leave a red solid which was predominantly (7*S*,9*S*)-9-ethynyl-7,8,9,10-tetrahydro-6,7,9,11-tetrahydroxy-4-methoxynaphthacene-5,12-dione **9b** (0.022 g); δ(300 MHz; $CDCl_3$) *inter alia* 2.30 (1 H, dd, *J* 14.5 and 5, 8-Hβ), 2.58 (1 H, s, C≡CH), 2.64 (1 H, ddd, *J* 14.5, 3 and 2, 8-Hα), 3.02 (1 H, d, *J* 18.5, 10-Hβ), 3.48 (1 H, dd, *J* 18.5 and 1.5, 10-Hα), 3.64 (1 H, s, 9-OH), 3.68 (1 H, d, *J* 3.5, 7-OH), 4.10 (3 H, s, MeO), 5.28–5.34 (1 H, m, 7-H), 7.40 (1 H, d, *J* 8, 3-H), 7.80 (1 H, t, *J* 8, 2-H), 8.06 (1 H, d, *J* 8, 1-H) and 13.28 and 14.08 (each 1 H, s, 6- and 11-OH).

A suspension of the ethynyldione **9b** (0.022 g) and red mercury(II) oxide (0.117 g, 0.540 mmol) in acetone (10 cm^3) and 7% sulphuric acid (10 cm^3) was heated under reflux for 3 h. The mixture was then cooled, diluted with hydrochloric acid (1 mol dm^{-3}) and extracted with ethyl acetate. After having been washed with water and brine, the organic phase was dried ($MgSO_4$) and evaporated to leave a red solid (0.020 g), which was predominantly the title compound **2b**. Recrystallisation of the material from dichloromethane–hexane gave pure (+)-daunomycinone **2b** (0.014 g, 65% based upon **8b**); m.p. 208–210 °C (lit., 213–214 °C[13] and 210–212 °C[14]); $[\alpha]_D$ +162 (0.1% in dioxane) [lit., +193 (dioxane)[13] and +175 (dioxane)[14]]; ν_{max}(KBr)/cm^{-1} 3440br (OH), 1710 (ketone C=O), 1620 (chelated C=O) and 1580; λ_{max}(EtOH)/nm 205 (ε 19 600), 234 (34 000), 251 (25 800), 290 (8800), 481 (12 300), 496 (12 800) and 532 (7100); δ(300 MHz; $CDCl_3$) 2.16 (1 H, dd, *J* 14.5 and 4.5, 8-Hβ), 2.34 (1 H, dt, *J* 14.5, 2 and 2, 8-Hα), 2.44 (3 H, s, MeCO), 2.92 (1 H, d, *J* 18.5, 10-Hβ), 3.18 (1 H, dd, *J* 18.5 and 2, 10-Hα), 3.74 (1 H, br s, 7-OH), 4.08 (3 H, s, MeO), 4.58 (1 H, s, 9-OH), 5.32 (1 H, br d, *J* 4, 7-H), 7.40 (1 H, d, *J* 8, 3-H), 7.78 (1 H, t, *J* 8, 2-H), 8.02 (1 H, d, *J* 8, 1-H) and 13.26 and 13.94 (each 1 H, s, 6- and 11-OH) [the spectrum was identical with that of a sample of (+)-daunomycinone **2b** obtained from daunomycin **1a** by acidic hydrolysis; it was also unchanged when diluted with the 'natural' sample].

Reactions of (+)-*Daunomycinone* **2b** *with Mosher's Acid Chlorides* **13a** *and* **b**.—(*a*) A mixture of 'natural' (+)-daunomycinone **2b** (0.100 g, 0.25 mmol) and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride **13a** (0.126 g 0.50 mmol) in dry pyridine (5 cm^3) was stirred for 2 d. The mixture was then diluted with dichloromethane and washed with dilute hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate and brine. Evaporation of the dried ($MgSO_4$) organic phase left a residue (0.132 g) which comprised mainly a 1:1 mixture of the ester **14a** and unchanged daunomycinone **2b**. Purification of a portion (0.128 g) of the material by silica-gel column chromatography [CH_2Cl_2–EtOAc (9:1) as eluant] gave 7-O-[(R)-α-*methoxy*-α-(*trifluoromethyl*)*phenylacetyl*]-*daunomycinone* **14a** (0.068 g, 44%) as a red solid. After recrystallisation from dichloromethane–hexane, the material showed m.p. 190–192 °C (decomp.); $[\alpha]_D$ +220 (0.1% in CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 3460br (OH), 1745 (ester C=O), 1710 (ketone C=O), 1620 (chelated C=O) and 1580; λ_{max}(EtOH)/nm 204 (ε 26 800), 233 (38 100), 252 (23 200), 287 (9200), 481 (12 100), 497 (12 100) and 532 (6600); δ(300 MHz; $CDCl_3$) 2.28–2.40 (2 H, m, 8-H_2), 2.40 (3 H, s, MeCO), 2.98 (1 H, d, *J* 18.5, 10-Hα), 3.24 (1 H, d, *J* 18.5, 10-Hβ), 3.33 (1 H, s, 9-OH), 3.46–3.50 (3 H, m, MeO), 4.10 (3 H, s, 4-MeO), 6.72 (1 H, dd, *J* 4 and 2.5, 7-H), 7.37–7.47 and 7.60–7.68 (4 and 2 H, each m, Ph and 3-H), 7.80 (1 H, t, *J* 8, 2-H), 8.02 (1 H, d, *J* 8, 1-H) and 13.24 and 13.74 (each 1 H, s, 6- and 11-OH); *m/z* (FAB) 615 (MH^+, 3%), 614 (M^+, 8), 321 (68) and 189 ($C_9H_8F_3O^+$, 100) (Found: C, 60.6; H, 4.1; F, 9.3. $C_{31}H_{25}F_3O_{10}$ requires C, 60.60; H, 4.10; F, 9.25%).

(*b*) 'Natural' daunomycinone **2b** (0.100 g, 0.25 mmol) was treated with (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride **13b** (0.126 g, 0.50 mmol) and dry pyridine (5 cm^3) as described in the previous experiment. Work-up as before gave a residue (0.138 g) which comprised mainly a 3:1 mixture of the ester **14b** and unchanged daunomycinone **2b**. Purification of a portion (0.132 g) of the material by silica-gel column chromatography [CH_2Cl_2–EtOAc (9:1) as eluant] gave 7-O-[(S)-α-*methoxy*-α-(*trifluoromethyl*)*phenylacetyl*]*daunomycinone* **14b** (0.098 g, 64%) as a red solid. After recrystallisation from dichloromethane–hexane, the material showed m.p. 106–108 °C (decomp.); $[\alpha]_D$ +342 (0.1% in CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 3480br (OH), 1750 (ester C=O), 1710 (ketone C=O), 1625 (chelated C=O) and 1580; λ_{max}(EtOH)/nm 205 (ε 21 200), 233 (38 700), 252 (22 600), 288 (9000), 480 (12 100), 496 (11 800) and 532 (6200); δ(300 MHz; $CDCl_3$) 2.09 (1 H, dt, *J* 16, 1.5 and 1.5, 8-Hα), 2.20 (1 H, s, 9-OH), 2.23 (3 H, s, MeCO), 2.24 (1 H, dd, *J* 16 and 4.5, 8-Hβ), 2.88 (1 H, d, *J* 18.5, 10-Hβ), 3.16 (1 H, dd, *J* 18.5 and 2, 10-Hα), 3.60–3.64 (3 H, m, MeO), 4.11 (3 H, s, 4-MeO), 6.66 (1 H, dd, *J* 4.5 and 1, 7-H), 7.38–7.48 and 7.56–7.64 (4 and 2 H, each m, Ph and 3-H), 7.80 (1 H, t, *J* 8, 2-H), 8.04 (1 H, d, *J* 8, 1-H) and 13.20 and 13.94 (each 1 H, s, 6- and 11-OH); *m/z* (FAB) 615 (MH^+, 5%), 614 (M^+, 12), 321 (100) and 189 ($C_9H_8F_3O^+$, 35) (Found: C, 60.9; H, 4.4; F, 9.1. $C_{31}H_{25}F_3O_{10}$ requires C, 60.60; H, 4.10; F, 9.25%).

(*c*) A mixture of synthetic daunomycinone **2b** (0.006 g, 0.015 mmol) and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride **13a** (0.008 g, 0.030 mmol) in dry pyridine (0.5 cm^3) was stirred for 3 d. Work-up as before gave a red solid (0.007 g) which was separated into two fractions by silica-gel chromatography. The first fraction (0.005 g, 52%) [eluted with CH_2Cl_2–EtOAc (9:1)] was identified as the ester **14a** by 300 MHz ^1H NMR spectroscopy. The second fraction (0.002 g, 37% recovery) (eluted with EtOAc); $[\alpha]_D$ +165 (0.1% in dioxane), was identified as daunomycinone **2b** by 300 MHz ^1H NMR spectroscopy.

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