Tetrahedron Vol. 40, No. 22, pp. 4657 to 4667, 1984
Printed in Great Britain.

0040-4020/84 $3.00 + .00
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AN EFFICIENT ENANTIOCONTROLLED SYNTHESIS OF (+)-4-DEMETHOXYDAUNOMYCINONE†[1]

RAMESH C. GUPTA, PHILIP A. HARLAND and RICHARD J. STOODLEY*
Department of Organic Chemistry, The University, Newcastle upon Tyne, NE1 7RU, U.K.

(*Received in USA* 10 *May* 1984)

Abstract—A chromatography-free, seven-step synthesis of the title compound (**3**) is described. The tetracyclic carbon skeleton is elaborated by a Diels–Alder strategy in which the 6a,7- and 10,10a-bonds are constructed, the epoxy-tetrone (**9**) and the D-glucose-derived diene (**10b**) serving as precursors. Interestingly, the cycloaddition reaction leads mainly to the "desired" cycloadduct (**11b**), revealing a notable diastereofacial reactivity of the diene (**10b**). Hydrolysis of the cycloadduct (**11b**) leads to the epoxy-pentone (**12b**) which is reduced to the dihydroxy-trione (**13b**). The reaction of the last-cited compound with ethynylmagnesium bromide affords a mixture of the ethynyl-diones (**20b**) and (**21b**), the latter compound arising from the precursor (**13b**) by a prior epimerisation at the 10a-position. The mixture of ethynyl-diones (**20b**) and (**21b**) is converted into the anthracycline (**14b**) by the action of lead (IV) acetate. By a hydrolysis-hydration sequence, the anthracycline (**14b**) is transformed into (+)-4-demethoxydaunomycinone (**3**).

DAUNOMYCIN (**1a**)[2] was the first clinically effective member of the anthracycline class of antibiotics, being used principally in the treatment of acute leukemia. Its 14-hydroxy derivative (**1b**), known as adriamycin,[2] possesses important chemotherapeutic advantages and, currently, is the leading anticancer drug, capturing *ca* 21% of the market.[3] Carminomycin (**1c**)[2] represents a further natural anthracycline that is also of clinical value in the treatment of cancers.

The quest for improved anticancer drugs has, inevitably, led to a world-wide interest in the total synthesis of anthracyclines. As well as supplying a stimulus for the development of new strategies and methodologies, this effort has provided structurally modified anthracyclines that are unavailable from the natural compounds. Examples of such modified anthracyclines, which are endowed with chemotherapeutic improvements, are 4-demethoxydaunomycin (**1d**), 4-demethoxyadriamycin (**1e**) and 4-demethoxy-4′-epiadriamycin.[2]

To date, all syntheses of anthracyclines have relied upon the glycosidation of a sugar with an anthracyclinone. Although this strategy has obvious flexibility, it is not without its problems. For example, 4-demethoxydaunomycin (**1d**) is prepared from L-daunosamine (**2**) and 4-demethoxydaunomycinone (**3**).[4,5] To effect the coupling reaction, it is necessary to protect and activate the sugar, *e.g.* by conversion into the chloride (**4**).[5] After the glycosidation step, the protecting groups are removed and the anthracycline (**1d**) is isolated as its hydrochloride. Although the required α-glycoside is formed preferentially, the overall yield for the **3** → **1d** transformation is not high [*ca* 29% for the route involving the chloride (**4**)[5]] and a chromatographic purification step appears to be necessary.

4-Demethoxydaunomycinone (**3**) is an important synthetic anthracyclinone. As well as being used in the preparation of 4-demethoxydaunomycin (**1d**), it serves as a precursor of 4-demethoxyadriamycin (**1e**) and 4-demethoxy-4′-epiadriamycin.[2,4] Although a large number of endeavours have been devoted to the derivation of this anthracyclinone in racemic form, only three syntheses of the optically active material have been reported.

In the Farmitalia route,[4] which is modelled upon that pioneered by Wong's group,[6] the tetralin (**5**)† [obtained by resolution of its racemate with (−)-phenylethylamine] is treated with phthalic anhydride under Friedel-Craft conditions. The product (**6a**)‡ is then converted, *via* its methylated dioxolan derivative, into a mixture of **6b** and its 7-epimer (introduction of the 7-methoxy group is achieved by bromination and methanolysis steps). The synthesis is completed by a trifluoroacetolysis-ammonolysis sequence—an inefficient process that requires a chromatographic purification step. The overall yield of 4-demethoxydaunomycinone (**3**) is *ca* 20%, based upon the tetralin (**5**) (several steps are required to assemble the last-cited compound).

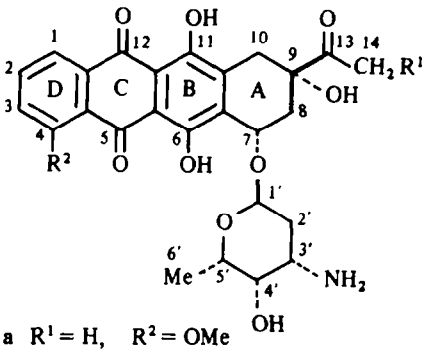
Terashima's group, having developed an efficient asymmetric synthesis[7] of the tetralin (**5**),§ uncovered a further problem with the Farmitalia route. Partial racemisation occurs in the annulation reaction and the tetracycle (**6a**) is obtained with an enantiomeric excess of *ca* 71%; several recrystallisations are required to

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

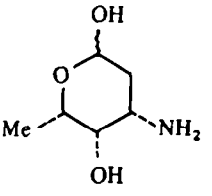
† This compound has also been obtained from its racemate using a microbial resolution [S. Terashima and K. Tamoto, *Tetrahedron Lett.* **23**, 3715 (1982)].

‡ The tetracycle (**6a**) has also been prepared in optically active form by resolution of its racemate [S. Terashima, K. Tamoto and M. Sugimori, *Tetrahedron Lett.* **23**, 4107 (1982); D. Dominguez, R. J. Ardecky and M. P. Cava, *J. Am. Chem. Soc.* **105**, 1608 (1983)] and by an asymmetric synthesis [D. Dominguez and M. P. Cava, *J. Org. Chem.* **48**, 2820 (1983)].

§ Other asymmetric syntheses of this compound [S.-s. Jew, S. Terashima and K. Koga, *Chem. Pharm. Bull. Tokyo* **27**, 2351 (1979); S. Terashima, N. Tanno and K. Koga, *Tetrahedron Lett.* **21**, 2753 (1980); A. V. Rama Rao, J. S. Yadav, K. Bal Reddy and A. R. Mehendale, *J. Chem. Soc.* Chem. Commun. 453 (1983)] and its relatives [R. N. Warrener, P. S. Gee and R. A. Russell, *J. Chem. Soc.* Chem. Commun. 1100 (1981)] have been reported.



1a $R^1 = H$, $R^2 = OMe$
1b $R^1 = OH$, $R^2 = OMe$
1c $R^1 = H$, $R^2 = OH$
1d $R^1 = H$, $R^2 = H$
1e $R^1 = OH$, $R^2 = H$



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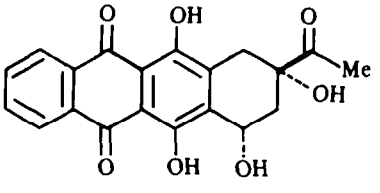

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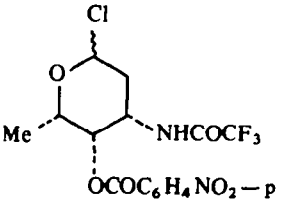

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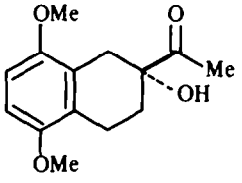
restore the optical purity of the compound. The overall yield of 4-demethoxydaunomycinone (3) is *ca* 10%, based upon the tetralin (5).

The Roche group[5] employed the Diels–Alder reaction to construct the tetracycle (7). Thus the diene obtained by thermolysis of *trans*-1,2-diacetoxybenzocyclobutene is intercepted by the quinone (8). A five-step sequence is then used to convert the tetracycle (7) into 4-demethoxydaunomycinone (3). Although the synthesis is of note in that the A-ring functionality is established at an early stage, a lengthy sequence, which includes a resolution step, is needed to generate the precursor. The overall yield of 4-demethoxydaunomycinone (3) is *ca* 27%, based upon the quinone (8).

From the foregoing discussion, it is clear that no efficient synthesis of 4-demethoxydaunomycinone (3) is so far available.

Work at Newcastle has focussed upon developing the Diels–Alder strategy, involving constructions of the 6a,7- and 10,10a-bonds, for the synthesis of anthracylinones. A key feature of this approach is the expectation that 1,4-dihydroxyanthraquinone (quinizarin)—a cheap tonnage chemical used in the dyestuff industry—will serve as the BCD-ring synthon. Having established that the oxirane (9) [readily



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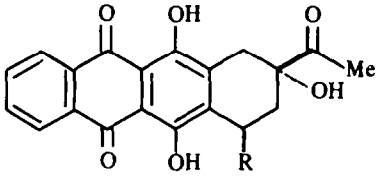

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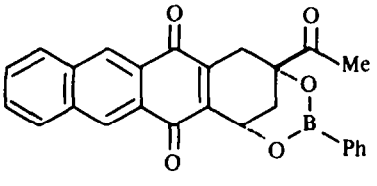
6a R = H
6b R = OMe



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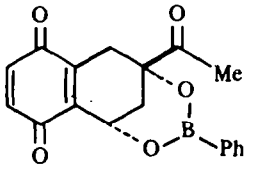

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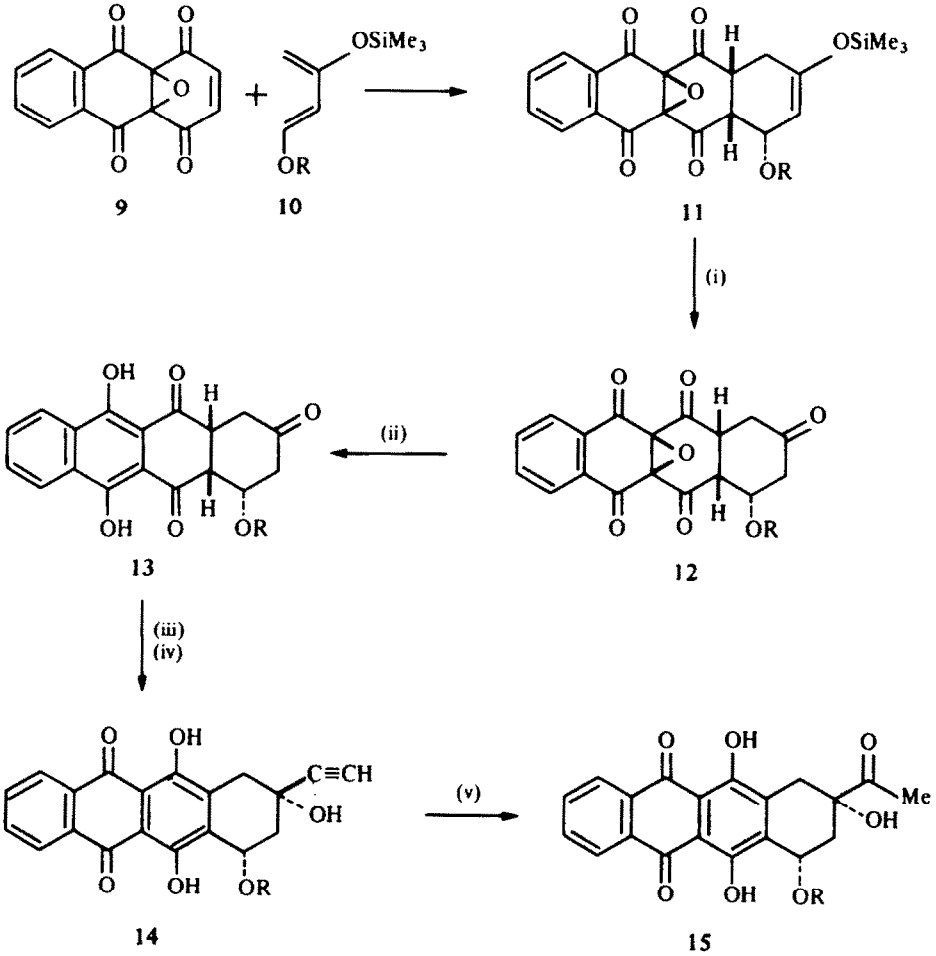
prepared from quinizarin by sequential reactions with lead(IV) acetate and *m*-chloroperoxybenzoic acid] was an excellent dienophile,[8] a diastereocontrolled synthesis of (±)-4-demethoxy-7-O-methyldaunomycinone (**15a**) was developed.[9] In the synthesis, which is summarised in Scheme 1, the oxirane (**9**) is treated with the diene (**10a**) to give the cycloadduct (**11a**). X-ray analysis of the hydrolysis product of the cycloadduct established[10] the stereostructure (**12a**), confirming that the cycloaddition occurs by way of the least-hindered *endo* transition state and that no epimerisation accompanies the hydrolysis reaction. When treated with ethynylmagnesium bromide followed by lead(IV) acetate, the dihydroxy-trione (**13a**) [obtained from the epoxy-pentone (**12a**) by reduction with zinc-acetic acid or sodium dithionite] is converted into the ethynyl-dione (**14a**). Mercury(II)-catalysed hydration of the last-mentioned compound provides the acetyl-dione (**15a**).

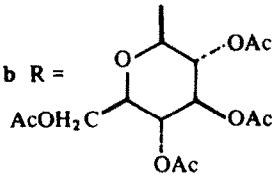
RESULTS AND DISCUSSION

With a view to achieving an enantiocontrolled synthesis of 4-demethoxydaunomycinone (**3**), using the approach depicted in Scheme 1, an analogue of Danishefsky's diene (**10a**) was sought in which the O-Me group was replaced by an enantiomerically pure ligand. To be of value, such a diene had to satisfy four requirements. First, it should be easily prepared from readily available and inexpensive starting materials. Secondly, it should undergo the cycloaddition reaction with the dienophile (**9**) to give predominantly the desired cycloadduct, *i.e.* one of type **11** rather than of type **16**. Thirdly, its ligand should be compatible with the reagents to be used in the subsequent steps of the synthesis. Fourthly, its ligand should be removable from the 7-O-substituted 4-demethoxydaunomycinone of type **15** (or a precursor) without cleavage of the C(7)-O bond.



Reagents: (i) H^+ (ii) Zn–HOAc or $Na_2S_2O_4$ (iii) HC≡CMgBr (iv) $Pb(OAc)_4$ (v) HgO–H_2SO_4

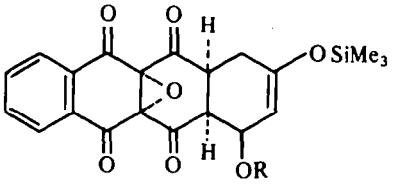
a R = Me b R =



Scheme 1

The diene (**10b**) was selected for an initial study. It is noteworthy that if the cycloaddition reaction and functionalisation steps were to be successful, a new strategy for the synthesis of anthracyclines would emerge. Furthermore, if the diastereoselection turned out to be the opposite of that required, there would be the possibility of remedying the situation by the use of a wide range of other sugars, including those of the L-series.

In the expectation that it would be convertible into the diene (**10b**), efforts were made to prepare the enone (**17**). Treatment of a solution of the bromide (**18**)[11] in dimethyl sulphoxide with the sodium salt (**19**)[12] afforded a mixture of products from which the desired enone (**17**) was isolated in a pure state in 31% yield by direct crystallisation.



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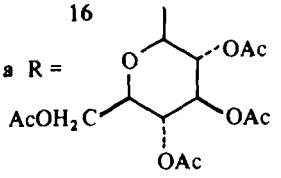

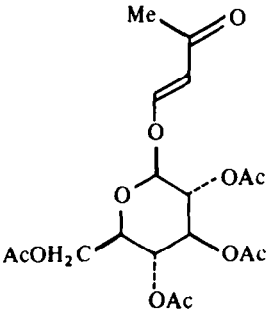

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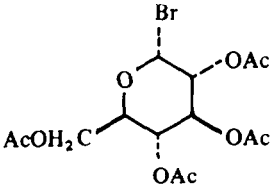

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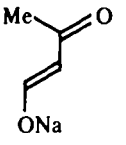

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That compound **17** possessed the β-configuration at its glycosidic centre was established by high-field ^{1}H-NMR spectroscopy ($CDCl_3$); thus the anomeric proton resonated as a doublet at δ 4.91 (J = 8 Hz). It is well established that D-glucopyranosides adopt $^4C_1$ conformations in which the 2-, 3-, 4- and 5-protons are axially orientated. In the case of β-glycosides, the anomeric proton (which bears an *anti*-periplanar relationship to the 2-proton) typically exhibits J = 7 Hz; with α-glycosides, the anomeric proton (which bears a *gauche* relationship to the 2-proton) shows J = 3 Hz.[13] The (*E*)-geometry of the olefinic linkage of **17** was also evident from NMR spectroscopy. Thus the olefinic signals appeared as doublets (J = 12.5 Hz) at δ 5.82 and 7.41. Typically, alkenes bearing oxygen and carbon substituents show J_{cis} = 6.5 Hz and J_{trans} = 12.3 Hz.[14]

The procedure devised by Danishefsky[15] was used to convert the enone (**17**) into the diene (**10b**). Thus when a mixture of the enone (**17**), trimethylsilyl chloride, triethylamine and zinc chloride was heated in benzene, the crystalline diene (**10b**) was isolated as an off-white solid in 78% yield. An analytically pure sample of the diene (**10b**) was obtained as needles after two recrystallisations.

Although the overall yield of the crude crystalline diene (**10b**) was only *ca* 20% based upon D-glucose, the synthesis was a straightforward one and involved no chromatography. It was conveniently and routinely operated to give 20 g batches of the diene (**10b**).

The pure diene (**10b**) reacted with the epoxy-tetrone (**9**) in benzene at 5° to give a product which, by 300 MHz ^{1}H-NMR spectroscopy, comprised mainly a 4:1 mixture of cycloadducts. This analysis was based upon the integrals for the two doublets (J = 18 Hz) at δ 2.73 and 2.84, attributed to the 10α-protons of the cycloadducts, and of the two double doublets (J = 7.5 and 4 Hz) at δ 3.07 and 3.10, assigned to the 6a-protons of the cycloadducts. Addition of diethyl ether to the mixture induced the crystallisation of the major cycloadduct as an off-white solid in *ca* 74% yield; an analytically pure sample of the material was obtained after two recrystallisations. On the assumption that the cycloadditions had occurred by way of the least-hindered *endo* transition states, the stereostructures (**11b**) and (**16a**) are permissible for the cycloadducts. That the major cycloadduct possessed the former structure was inferred on the basis of subsequent chemistry. Hydrolysis of the crude cycloadduct in THF containing a small amount of 0.1 M-HCl provided the crystalline epoxy-pentone (**12b**). The yield of the last-mentioned compound, after recrystallisation, was 57% [based upon the diene (**10b**)].

It was convenient to conduct the aforementioned cycloaddition-hydrolysis sequence on the crude crystalline diene (**10b**). The yield of the recrystallised epoxy-pentone (**12b**) was then 45%, based upon the starting diene.

Reduction of the epoxy-pentone (**12b**) to the dihydroxy-trione (**13b**) was achieved by using either sodium dithionite in aqueous methanol or zinc in acetic acid. The latter procedure, which gave the dihydroxy-

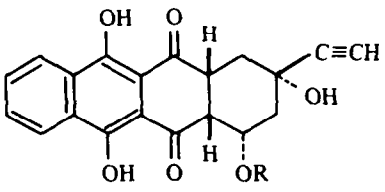
trione (**13b**) in 71% yield after recrystallisation, was preferable.

Previously, it was observed that the outcome of the reaction of the dihydroxy-trione (**13a**) with metal acetylides was dependent upon the reaction conditions.[10] At 0° in THF containing *ca* 4 mol equiv of ethynylmagnesium bromide, the ethynyl-dione (**20a**) was produced, whereas a 1 : 1 mixture of the ethynyl-diones (**20a**) and (**21a**) resulted when *ca* 34 mol equiv of the reagent was employed. The use of 0.1 M-lithium acetylide (*ca* 10 mol equiv) in THF at −78° afforded the ethynyl-dione (**20a**) whereas a threefold increase in the concentration of the reagent gave a 1 : 2 mixture of the ethynyl-diones (**20a**) and (**21a**). Since a control experiment established that the ethynyl-dione (**20a**) was stable in the presence of 0.3 M-lithium acetylide in THF at −78°, it was inferred that the dihydroxy-trione (**13a**) underwent a competing epimerisation at the 10a-position. Evidently, there is a strong preference for a metal acetylide to attack the 9-CO group of **13a** and its 10a-epimer from the face away from the 7-OMe group.

When treated with *ca* 30 mol equiv of ethynylmagnesium bromide in THF at 0°, the dihydroxy-trione (**13b**) was converted into a 3 : 1 mixture of the ethynyl-diones (**20b**) and (**21b**). Repeated crystallisation of the mixture provided the ethynyl-dione (**20b**) in a pure state and the ethynyl-dione (**21b**) in a *ca* 70% pure state. When resubjected to the ethynylation conditions, the former compound was recovered unchanged, indicating that the ethynyl-dione (**21b**) arose from the dihydroxy-trione (**13b**) by way of the 10a-epimer (**22**).

In earlier work,[9,10] it was shown that lead(IV) acetate in acetic acid was an effective reagent for bringing about the oxidative isomerisation of the ethynyl-diones (**20a** and **21a**) to the anthracyclinone (**14a**). When similarly treated, the crude 3 : 1 mixture of the ethynyl-diones (**20b** and **21b**) was transformed into the anthracycline (**14b**) [77% yield after recrystallisation based upon the dihydroxy-trione (**13b**)].

Hydrolysis of the glycosidic linkage of the anthracycline (**14b**) was effected by hot ethanolic hydrochloric acid to give the ethynyl-dione (**23**) in 89% yield after recrystallisation. The spectroscopic properties of the material were in good agreement with those reported for the racemate.[16]



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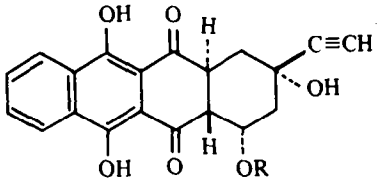

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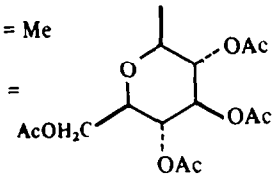
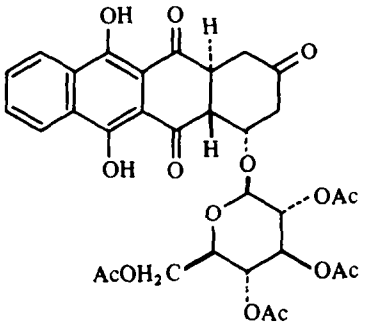
a R = Me

b R =





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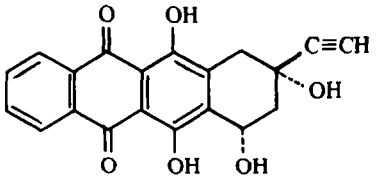

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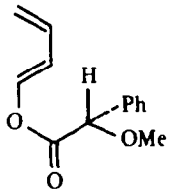

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When a mixture of **23**, mercury(II) oxide and 7% sulphuric acid was heated in acetone, 4-demethoxydaunomycinone (**3**) was produced in 75% yield after recrystallisation. The m.p., optical rotation and spectroscopic properties of the product were in accord with those published.[4,5,7]

Hydration of the acetylenic linkage of **14b** could be achieved without glycoside hydrolysis by using the aforementioned procedure. The resultant anthracycline (**15b**) was obtained in 88% yield after recrystallisation.

The foregoing results are significant in several respects. First, they show that the Diels–Alder strategy involving the construction of the 6a,7- and 10,10a-bonds, which hitherto has played an important role in the elaboration of anthracyclinones,[9,10,17] can be used for the synthesis of anthracyclines. Secondly, they disclose a practical route to 4-demethoxydaunomycinone (**3**), which is exceptional in that no resolution step or chromatography is involved. Thirdly, it should be noted that a number of the intermediates generated

Table 1. Coupling constants (Hz) of the protons associated with the A-ring of compounds **11a** and **11b**

Compound	$J_{6a,7}$	$J_{7,8}$	$J_{10\alpha,10\beta}$	$J_{10\alpha,10a}$	$J_{10\beta,10a}$	$J_{10a,6a}$
11a	4.2	5.5	18.0	0	6.7	5.5
11b	3.9	6.1	18.3	1	8.3	7.6

Table 2. Coupling constants (Hz) of the protons associated with the A-ring of compounds **12a,b**, **13a,b** and **21a,b**

Compound	$J_{6a,7}$	$J_{7,8\alpha}$	$J_{7,8\beta}$	$J_{8\alpha,8\beta}$	$J_{8\alpha,10a}$	$J_{10\alpha,10\beta}$	$J_{10\alpha,10a}$	$J_{10\beta,10a}$	$J_{10a,6a}$
12a	2.5	2.5	2.5	17	1	15.5	5.5	7.5	9
12b	2	2.5	4	18	0	16.5	8.5	8	11
13a	2.2	3.2	2.6	15.1	2.2	15.5	1.7	7.7	6.8
13b	2.2	3	2.8	16.2	2	16.4	2.8	8.1	7.5
21a	2.5	2.8	2.3	14.9	2.8	14.1	2.9	12.0	13.5
21b	2	3	—	14	3	14	3	14	13

in this work offer considerable prospect for further manipulation. Fourthly, the diastereoselection observed in the cycloaddition of the epoxy-tetrone (**9**) and the diene (**10b**) is interesting. With some exceptions[18,19] particularly Trost's diene (**24**), chiral dienes have had only a modest record of diastereodifferentiation.[20] Finally, in view of the repertoire of Danishefsky's diene (**10a**),[21] which continues to be enlarged,[22] the diene (**10b**) would appear to have a promising future in organic synthesis.

Conformational considerations

The aforementioned synthetic work provided the opportunity of assessing the conformation of the A-ring of compounds **11b**–**15b** and **21b** in deuteriochloroform solution. The results, which held some surprises, will now be considered.

In Table 1, the coupling constants associated with the A-ring protons of the cycloadduct (**11b**) are compared with those of the cycloadduct (**11a**).[10] The values reveal that the A-ring geometry of both compounds is quite similar. Moreover, on the basis of the Karplus relationship,[14] the dihedral angles of the 6a,7-, 10α, 10a-, 10β, 10a- and 10a,6a-protons are *ca* 45°, 110°, 10° and 20°, respectively. These angles are consistent with the adoption of a sofa-like conformation of type **25** for the A-ring of the cycloadducts.

The coupling constants of the A ring-associated protons of **12b**, **13b** and **21b** are compared with those of **12a**, **13a** and **21a**[10] in Table 2. In all pairs of compounds, the A-ring geometry is reasonably similar. Moreover, in all the examples, there appears to be a *gauche*-like relationship between the 6a,7-, 7,8α- and 7,8β-protons, requiring an axial-like orientation of the 7-oxy substituent.

Although X-ray crystallography showed that the A-ring of the epoxy-pentone (**12a**) adopted a chair-like geometry of type **26** in the crystal state, this was not born out by the coupling constants of the 10α,10a-, 10β,10a-, and 10a,6a-protons of it[10] or its relative **12b** in deuteriochloroform solution. The values were more consistent with a sofa-like conformation of type **27**. Furthermore, the geminal coupling constants of the 8-protons were noticably different from those of the 10-protons, implying a difference in their orientation with respect to the 9-carbonyl group. It should be noted that the **26** → **27** distortion imposes a conformational change on the B-ring of **12a** and **12b** from half chair-like to boat-like geometry.

In the case of the dihydroxy-triones (**13a**[10] and **13b**), the coupling constants were in reasonable agreement with the A-ring adopting a chair-like geometry of type **26**. The similarity of the geminal constants of the 8- and 10-protons together with the sizable long-range coupling constant between the 8α- and 10α-protons, for which a W-pathway is available, were in support of this interpretation.

An evaluation of the coupling associated with the A-ring protons of the ethynyl-dione (**20b**) was not possible because of the broadness of some of the signals and their overlapping nature. Earlier, however, on the basis of width-at-half-height (W_H) measurements, the ethynyl-dione (**20a**) was considered[10] to favour a chair-like geometry of type **28**.

The coupling constants observed for the ethynyl-diones (**21a**[10] and **21b**)† indicated that their A-rings adopted a chair-like geometry of type **29**. In particular, the *trans*-diaxial relationship between the 10β,10a- and between the 10a,6a-protons was revealed by the coupling constants of 12–14 Hz. Again, the similar values observed for the geminal coupling constants of the 8- and 10-protons, together with the substantial long-range coupling constant between the 8α- and 10α-protons, consolidated this viewpoint.

Table 3 summarises the coupling constants associated with the A-ring protons of **14b** and **15b** and compares them with those of their relatives **14a** and **15a**.[10] The values, which are quite similar, imply that half-chair conformations of types **30a** and **30b** are favoured.

An interesting feature arising from the conformational studies concerns the axial-like disposition of the 7-oxy group in **11a,b**, **12a,b**, **13a,b** and **20a**. In such a situation, the group experiences a 1,3-diaxial interaction with the 11-CO group (such an interaction is absent in the alternative conformers in which the oxy group is equatorial). We suggest that the *syn*-diaxial relationship benefits from the donation of an electron-

† The possibility that these compounds were the 6a-epimers of the epoxy-diones (**20a** and **20b**) was excluded by the values of the coupling constants.

Table 3. Coupling constants (Hz) of the protons associated with the A-ring of compounds **14a,b** and **15a,b**

Compound	$J_{7,8a}$	$J_{7,8\beta}$	$J_{8a,8\beta}$	$J_{8\beta,10\beta}$	$J_{10a,10\beta}$
14a	2.1	3.7	14.8	1.9	19.1
14b	*ca* 3	4.4	15.0	*ca* 2	19.0
15a	2.2	3.2	15	2.0	19.0
15b	⟵ *ca* 8 ⟶		15	*ca* 2	19.0

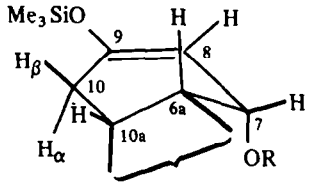
pair from the oxy O-atom to the antibonding π^* orbital of the 11-CO group. Such transannular effects have been noted on previous occasions.[23]

The preference for the A-ring of daunomycin (**1a**) and its aglycone to adopt a half chair-like geometry of type **30b** has been discussed previously[24] and attributed to a H-bonding interaction between the 9-hydroxy and 7-oxy groups. A similar explanation accounts for the adoption of conformers of types **30a** and **30b** by the A-ring of **14a,b** and **15a,b**, respectively.

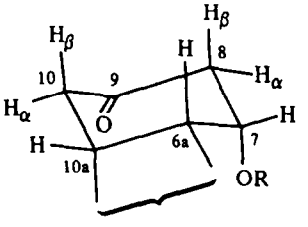
EXPERIMENTAL

Dry solvents, referred to in the ensuing experiments, were prepared as follows: C_6H_6 was stored over Na wire; THF was stored over CaH_2 and, prior to use, was distilled from $LiAlH_4$; Me_2SO was stored over 4A molecular sieves. Light petroleum refers to that fraction boiling in the range 40–60°.

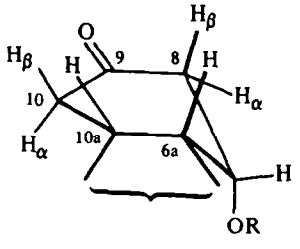
TLC was performed on Schleicher and Schull plastic sheets coated with SiO_2 (F1500 LS 254); the plates were initially examined under UV light and the spots were then visualised with I_2 vapour. Column chromatography was effected, under pressure, using Merck Keiselgel H (Type 60).



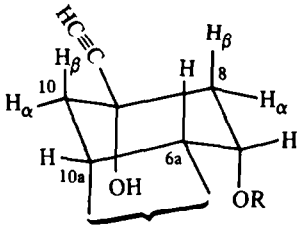
25



26



27



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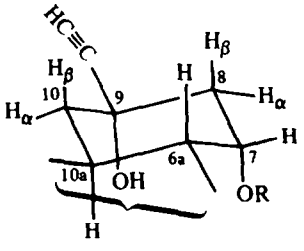

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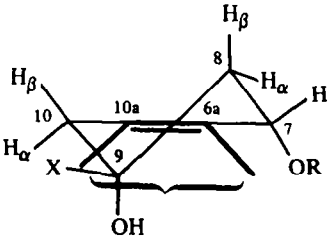

30a X = C≡CH
30b X = COMe

Evaporations were carried out using a Buchi rotary evaporator. M.ps were determined using a Kofler hot-stage apparatus and were uncorrected. Optical rotations were measured at ambient temp (*ca* 20°) using a Type 243 Thorn Automation automatic polarimeter. IR spectra were recorded using a Hilger and Watts Infrascan. A Unicam SP 800 spectrometer was employed to determine UV spectra. ^{1}H-NMR spectra were run using Me_4Si as an internal standard; spectra were measured at 60 MHz with either a Varian EM 360 or a Hitachi Perkin-Elmer R24 spectrometer, at 300 MHz with a Bruker WM-300 WB spectrometer, or at 360 MHz with a Bruker WH-360 spectrometer. MS were determined using an A.E.I. MS9 instrument operating at 70 eV. Microanalyses were performed with a Carlo-Erba 1106 Elemental Analyser.

Preparation of 2,3,4,6-*tetra*-O-*acetyl*-α-D-*glucopyranosyl bromide* (**18**)

D-Glucose (200 g) was converted into **18** (370 g, 81%, after recrystallisation from Et_2O-light petroleum) using the lit. procedure.[11] The recrystallised material, which could be stored for several weeks at −15°, showed the following properties: m.p. 88° (lit.[11] 88–89°); $[\alpha]_D$ +191° (*c* = 1.0, $CHCl_3$) [lit.[11] +198° ($CHCl_3$)]; ^{1}H-NMR (300 MHz, $CDCl_3$) 2.04, 2.06, 2.10 and 2.11 (each 3H, s, 4 × $MeCO_2$), 4.13br (1H, d, separation 11 Hz, 6-H), 4.27–4.37 (2H, m, 5- and 6-H), 4.84 (1H, dd, J = 10 and 4 Hz, 2-H), 5.17 (1H, t, J = 10 and 10 Hz, 4-H), 5.55 (1H, t, J = 10 and 10 Hz, 3-H) and 6.62 (1H, d, J = 4 Hz, 1-H).

Preparation of (*E*)-4-*hydroxybut*-3-*en*-2-*one sodium salt* (**19**)

Using the lit. procedure[12] and operating on a 2 mol scale, the title **19** was isolated as an off-white powder (189 g, 88%) which showed the following properties: IR(KBr) *inter alia* 1620 cm^{-1} (vinylogous carboxylate CO); δ (60 MHz, D_2O) (the spectrum was recorded immediately after dissolution) 2.00 (3H, s, 1-H_3), 5.10 (1H, d, J = 12 Hz, 3-H) and 8.77 (1H, d, J = 12 Hz, 4-H).

Reaction of the bromide **18** *with the sodium salt* **19**

To a stirred soln of **18** (120 g, 0.29 mol) in dry Me_2SO (400 ml) was added the Na salt **19** (47.2 g, 0.44 mol). After 1 hr, the mixture was poured into ice-cold H_2O (500 ml) and extracted with CH_2Cl_2 (4 ×). The organic layer was washed with H_2O (4 ×), dried ($MgSO_4$) and evaporated. Addition of Et_2O followed by light petroleum to the syrupy product gave a soln which deposited (*E*)-4-[(2′,3′,4′,6′-*tetra*-O-*acetyl*-β-D-*glucopyranosyl*)*oxy*]*but*-3-*en*-2-*one* **17** (37.5 g, 31%) as fine needles. A sample, recrystallised from Et_2O showed the following properties: m.p. 149–150°; $[\alpha]_D$ −20° (*c* = 1.0, EtOH); IR(KBr) *inter alia* 1750 and 1740 (ester CO), 1650 (vinylogous ester CO), and 1622 cm^{-1} (C=C); UV (EtOH) 237 nm (ε 16,000); ^{1}H-NMR (360 MHz, $CDCl_3$) 2.00, 2.02, 2.04 and 2.07 (each 3H, s, 4 × $MeCO_2$), 2.17 (3H, s, 1-H_3) 3.78–3.83 (1H, m, 5′-H), 4.12 (1H, dd, J = 12.5 and 2 Hz, 6′-H), 4.26 (1H, dd, J = 12.5 and 5 Hz, 6′-H), 4.91 (1H, d, J = 8 Hz, 1′-H), 5.11 (1H, t, J = 9 and 9 Hz, 4′-H), 5.13 (1H, dd, J = 8 and 9 Hz, 2′-H), 5.23 (1H, t, J = 9 and 9 Hz, 3′-H), 5.82 (1H, d, J = 12.5 Hz, 3-H) and 7.41 (1H, d, J = 12.5 Hz, 4-H) [irradiation at 3.80 caused the dd at 4.12 and 4.26 to collapse to d (J = 12.5 Hz) and the t at 5.11 to collapse to a d (J = 9 Hz)]; MS *inter alia* 331 ($C_{14}H_{19}O_9^+$), 169, 109, and 43 ($C_2H_3O^+$, base peak). (Found: C, 51.9; H, 5.70. Calc for $C_{18}H_{24}O_{11}$: C, 51.90; H, 5.75%).

Preparation of the diene **10b**

To a stirred mixture of fused $ZnCl_2$ (2.40 g, 17.6 mmol) and Et_3N (60 ml^3, 430 mmol) was added a slurry of the enone **17** (24.0 g, 57.7 mmol) in dry C_6H_6 (360 ml^3) followed by Me_3SiCl (30 ml^3, 236 mmol). The mixture was stirred at 50–55° for 40 hr. Following evaporation, Et_2O (300 ml) was added to the residue and the mixture was filtered. The filtered material was washed with Et_2O (2 × 100 ml). The combined filtrates were washed with H_2O (2 × 200 ml), dried ($MgSO_4$) and evaporated. Recrystallisation of the residue from Et_2O-light petroleum gave (*E*)-1-[(2′,3′,4′,6′-*tetra*-O-*acetyl*-β-D-*glucopyranosyl*)*oxy*]-3-*trimethylsilyloxybuta*-1,3-*diene* **10b** (21.9 g, 78%) as an off-white solid. A sample of **10b** (1.00 g), after two further recrystallisations from CH_2Cl_2-light petroleum, was obtained as white needles (0.554 g) with the following properties: m.p. 104–106°; $[\alpha]_D$ −19° (*c* = 0.5, EtOH); ν_{max} (KBr) *inter alia* 1755 and 1740 cm^{-1} (ester CO); λ_{max} (EtOH) 211 sh (ε 6000) and 237 nm (14,400); δ (360 MHz, $CDCl_3$) 0.22 (9H, s, $SiMe_3$), 2.00, 2.02, 2.03 and 2.06 (each 3H, s, 4 × $MeCO_2$), 3.75–3.82 (1H, m, 5′-H), 4.13 (1H, dd, J = 12.5 and 2.5 Hz, 6′-H), 4.14 (2H, s, 4-H_2), 4.24 (1H, dd, J = 12.5 and 5 Hz, 6′-H), 4.77 (1H, d, J = 8 Hz, 1′-H), 5.09 (1H, dd, J = 9 and 8 Hz, 2′-H), 5.09 (1H, t, J = 9 and 9 Hz, 4′-H), 5.22 (1H, t, J = 9 and 9 Hz, 3′-H), 5.63 (1H, d, J = 12 Hz, 2-H) and 6.66 (1H, d, J = 12 Hz, 1-H); MS *inter alia* 473 ($M^+ - CH_3$) and 331 ($C_{14}H_{19}O_9^+$, base peak). (Found: C, 51.5; H, 6.45%. Calc for $C_{21}H_{32}O_{11}Si$: C, 51.65; H, 6.55%).

Reaction of the epoxy-tetrone **9** *with the diene* **10b**

A soln of **9** (0.508 g, 2 mmol) and pure **10b** (0.976 g, 2 mmol) in dry C_6H_6 (30 ml) was left at 5° for 48 hr. Evaporation left a residue which was predominantly a 4:1 mixture of the cycloadducts **11b** and **16a**; δ (300 MHz, $CDCl_3$) *inter alia* 2.73 and 2.84 (0.2 and 0.8H, each d, J = 18 Hz, 10-Hα), 3.07 and 3.10 (0.8 and 0.2H, each dd, J = 7.5 and 4 Hz, 6a-H).

Addition of Et_2O to the residue gave (5a*S*, 6a*R*, 7*S*, 10a*R*, 11a*R*)-5a-11a-*epoxy*-5a, 6a, 7, 10, 10a, 11a-*hexahydro*-7-[(2′,3′,4′,6′-*tetra*-O-*acetyl*-β-D-*glucopyranosyl*)*oxy*]-9-*trimethylsilyloxynaphthacene*-5, 6, 11, 12-*tetrone* **11b** (1.10 g, 74%) as an off-white solid. A sample, after two recrystallisations from CH_2Cl_2-light petroleum, showed the following properties: m.p. 173–174°; $[\alpha]_D$ +92° (*c* = 1.0, EtOH); IR(KBr) *inter alia* 1750 (ester CO), 1685 (ketone CO) and 1595 cm^{-1}; UV (EtOH) 211 (ε 9500), 233 (15,200), 260sh (4900) and 307 nm (1500); ^{1}H-NMR (300 MHz, $CDCl_3$) 0.26 (9H, s, $SiMe_3$), 1.78, 1.86, 1.96 and 2.06 (each 3H, s, 4 × $MeCO_2$) 2.09 (1H, dd, J = 18.3 and 8.3 Hz, 10-Hβ), 2.84br (1H, d, J = 18.3 Hz, 10-Hα), 3.08 (1H, dd, J = 7.6 and 3.9 Hz, 6a-H), 3.54–3.56 (1H, m, 5′-H), 3.96 (1H, dt, J = 8, 8 and 1 Hz, 10a-H), 4.04 (1H, dd, J = 12 and 2.5 Hz, 6′-H), 4.16 (1H, dd, J = 12 and 4.6 Hz, 6′-H), 4.44 (1H, d, J = 8 Hz, 1′-H), 4.56 (1H, dd, J = 9 and 8 Hz, 2′-H), 4.64 (1H, dd, J = 6.1 and 3.9 Hz, 7-H), 4.90 (1H, t, J = 9.5 and 9.5 Hz, 4′-H), 5.04 (1H, t, J = 9.5 and 9.5 Hz, 3′-H), 5.05 (1H, d, J = 6.1 Hz, 8-H), 7.75–7.79, 8.04–8.06 and 8.09–8.12 (2, 1 and 1H, each m, 1-, 2-, 3- and 4-H) [irradiation at 3.55 caused the dd at 4.04 and 4.16 to collapse to d (each J = 12 Hz) and the t at 4.90 to collapse to a d (J = 9.5 Hz)]; MS *inter alia* 540 and 43 ($C_2H_3O^+$, base peak). (Found: C, 56.6; H, 5.05. Calc for $C_{35}H_{38}O_{16}Si$: C, 56.60; H, 5.10%).

Preparation of the epoxy-pentone **12b**

(a) A soln of **9** (1.00 g, 3.9 mmol) and pure **10b** (2.00 g, 4.1 mmol) in dry C_6H_6 (80 ml) was left at 5° for 48 hr. Evaporation, addition of Et_2O and filtration gave **11b** which was dissolved in freshly distilled THF (40 ml) and treated with *ca* 0.1 M-HCl (2 ml). When the hydrolysis was complete (*ca* 3 hr, TLC), the mixture was diluted with CH_2Cl_2 (100 ml), dried ($MgSO_4$) and evaporated. Recrystallisation of the residue from $CHCl_3$—EtOH gave (5a*S*, 6a*R*, 7*S*, 10a*R*, 11a*R*)-5a, 11a-*epoxy*-5a, 6a, 7, 8, 9, 10, 10a, 11a-*octahydro*-7-[(2′,3′,4′,6′-*tetra*-O-*acetyl*-β-D-*glucopyranosyl*)*oxy*]*naphthacene*-5, 6, 9, 11, 12-*pentone* **12b** (1.50 g, 57%) as colourless crystals which possessed the following properties: m.p. 215–220°; $[\alpha]_D$ −34° (*c* = 1.0, $CHCl_3$); IR(KBr) *inter alia* 1750 (ester CO), 1735sh, 1720 and 1690 cm^{-1} (ketone CO); UV(EtOH) 209 (ε 21,600), 233 (26,000), 265sh (20,900) and 415 nm (11,900); ^{1}H-NMR (360 MHz, $CDCl_3$) 1.73, 1.89, 1.98 and 2.09 (each 3H, s, 4 × $MeCO_2$), 2.32 (1H, dd, J = 18 and 4 Hz, 8-Hβ), 2.36 (1H, dd, J = 16.5 and 8 Hz, 10-Hβ), 2.94 (1H, dd, J = 18 and 2.5 Hz, 8-Hα), 3.22 (1H, dd, J = 11 and 2 Hz, 6a-H), 3.36 (1H, dd, J = 16.5 and 8.5 Hz, 10-Hα), 3.62–3.67 (1H, m, 5′-H), 4.04–4.16 (3H, m, 6′-H_2 and 10a-H), 4.53 (1H, d, J = 7.7 Hz, 1′-H), 4.65 (1H, dd, J = 9.5 and 7.7 Hz, 2′-H), 4.83 (1H, q, separation = 8 Hz, 7-H), 4.92 (1H, t, J = 9.5 and 9.5 Hz, 4′-H), 5.10 (1H, t, J = 9.5 and 9.5 Hz, 3′-H), and 7.80–7.86 and 8.15–8.21 (each 2H,

m, 1-, 2-, 3- and 4-H) [irradiation at 3.65 caused the m at 4.04–4.16 to simplify and the t at 4.92 to collapse to a d (J = 9.5 Hz)]; MS *inter alia* 375. (Found: C, 56.9; H, 4.15. Calc for $C_{32}H_{30}O_{16}$: C, 57.30; H, 4.50%).

(b) A soln of **9** (6.00 g, 23.4 mmol) and crude **10b** (12.0 g, 24.6 mmol) in dry C_6H_6 (300 ml) was left at 5° for 3 days. The residue, obtained upon evaporation, was triturated with Et_2O and **11b** was collected by filtration. The cycloadduct **11b** was dissolved in freshly distilled THF (120 ml) and to the soln was added *ca* 0.1 M-HCl (8 ml). When no starting material remained (*ca* 3 hr, TLC), the mixture was diluted with CH_2Cl_2 (120 ml) and washed with wayer. Evaporation of the dried ($MgSO_4$) organic layer and crystallisation of the residue from $CHCl_3$—EtOH gave **12b** (7.40 g, 45%), identical (m.p. and ^{1}H-NMR spectroscopy) with the sample obtained in procedure (a).

Reduction of the epoxy-pentone **12b**

(a) A suspension of **12b** (0.600 g, 0.90 mmol) in MeOH (80 ml) was treated with a soln of 85% $Na_2S_2O_4$ (1.00 g, 4.88 mmol) in H_2O (5 ml) and the mixture was stirred for 4 hr during which time a yellow ppt formed; H_2O (100 ml) was added to the resultant mixture which was then extracted with $CHCl_3$ (3 ×). After washing with H_2O, the organic layer was dried ($MgSO_4$) and evaporated. Crystallisation of the residue from MeOH gave (6a*R*, 7*S*, 10a*R*) - 5,12 - dihydroxy - 6a, 7, 8, 9, 10, 10a - *hexahydro* - 7 - [(2', 3', 4', 6' - *tetra* - O - *acetyl* - *β* - D - *glucopyranosyl)oxy]naphthacene* - 6, 9, 11 - *trione* **13b** (0.300 g, 51%) as pale-yellow needles with the following properties: m.p. 185–188°; $[\alpha]_D$ + 134° (*c* = 1.0, EtOH); IR(KBr) *inter alia* 3440 (OH), 1750 and 1735 (ester CO), 1720sh (ketone CO) and 1640 cm^{-1} (chelated CO); UV(EtOH) 239 (ε 26,200), 250 (26,000), 278 (24,600), 286 (23,400), 378sh (8800), 396 (13,000) and 416 nm (12,600); ^{1}H-NMR (360 MHz, $CDCl_3$) 1.28, 1.79, 1.94 and 2.12 (each 3H, s, 4 × $MeCO_2$), 2.48 (1H, dd, J = 16.4 and 8.1 Hz, 10-H*β*), 2.54 (1H, dd, J = 16.2 and 2.8 Hz, 8-H*β*), 3.03br (1H, d, separation = 16 Hz, 8-H*α*), 3.42 (1H, dd, J = 7.5 and 2.2 Hz, 6a-H), 3.50–3.56 (2H, m, 10-H*α* and 5'-H), 3.64 (1H, dt, J = 8, 8 and 3 Hz, 10a-H), 4.06 (1H, dd, J = 12 and 3 Hz, 6'-H), 4.13 (1H, dd J = 12 and 5 Hz, 6'-H), 4.39 (1H, d, J = 8 Hz, 1'-H), 4.47–4.51 (1H, m, 2'-H), 4.70br (1H, q, separation = 8 Hz, 7-H), 4.89–4.91 (2H, m, 3'- and 4'-H), 7.73 – 7.82 and 8.43–8.50 (each 2H, m, 1-, 2-, 3- and 4-H), and 13.00 and 13.73 (each 1H, s, 5- and 12-OH); MS involatile. (Found: C, 58.3; H, 4.85. Calc for $C_{32}H_{32}O_{15}$: C, 58.55; H, 4.90%).

(b) A stirred soln of **12b** (1.50 g, 2.24 mmol) in $MeCO_2H$ (25 ml) was treated with activated Zn[25] (1.50 g, 22.9 g atom) keeping the reaction temp below 20°. After 5 hr, H_2O (300 ml) was added and the mixture was extracted with $CHCl_3$ (2 ×). Evaporation of the dried ($MgSO_4$) organic layer and crystallisation of the residue from MeOH gave **13b** (1.05 g, 71%): m.p. 185–188°.

Reaction of the dihydroxy-trione **13b** *with ethynylmagnesium bromide*

(a) To a stirred soln of **13b** (0.375 g, 0.57 mmol) in dry THF (40 ml) at 0° was added a *ca* 1 M soln of HC≡CMgBr in THF[26] (15 ml, *ca* 30 mol equiv). After 30 min, the mixture was poured into an ice-cold sat of NH_4Cl aq (150 ml) and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried ($MgSO_4$) and evaporated to leave a solid (0.400 g) which was a 3 : 1 mixture of **20b** and **21b**; ^{1}H-NMR (300 MHz, $CDCl_3$) *inter alia* 13.52, 13.56, 13.64 and 13.78br (0.25, 0.75, 0.25 and 0.75H, each s, 5- and 12-OH). Repeated recrystallisation of the mixture from CH_2Cl_2-light petroleum gave the major diastereoisomer in a pure state and the minor diastereoisomer in a *ca* 70% pure state.

The major diastereoisomer, which was (6a*R*, 7*S*, 9*S*, 10a*R*) - 9 - *ethynyl* - 6a,7,8,9,10,10a - *hexahydro* - 7 - [(2',3',4',6' - *tetra* - O - *acetyl* - *β* - D - *glucopyranosyl)oxy*] - 5,9,12 - *trihydroxynaphthacene* - 6,11 - *dione* **20b**, was obtained as yellow crystals with the following properties: m.p. 125–127°; $[\alpha]_D$ + 102° (*c* = 0.1, $CHCl_3$); IR(KBr) *inter alia* 3540 (OH), 3280 (chelated OH), 1750 (ester CO), 1635 and 1610 cm^{-1} (chelated CO); UV (EtOH) 237 (ε 31,300), 253 (29,600), 278 (25,600), 286 (22,200), 380sh (8800), 399 (14,800), 417 (14,500) and 421 nm (13,400); ^{1}H-NMR (360 MHz, $CDCl_3$) 1.57, 1.82, 1.96 and 2.13 (each 3H, s, 4 × $MeCO_2$), 1.85br (1H, d, separation = 15 Hz, 8-H*β*), 2.03–2.15 (1H, m, 10-H*β*), 2.47 (1H, s, C≡CH), 2.64br (1H, d, separation = 15 Hz, 8-H*α*), 3.24–3.33 (3H, m, 6a- and 10a-H and 10-H*α*), 3.40br (1H, s, 9-OH), 3.68–3.72 (1H, m, 5'-H), 4.05 (1H, dd, J = 12 and 6 Hz, 6'-H), 4.17 (1H, d, J = 12 and 2 Hz, 6'-H), 4.41 br (1H, s, 7-H), 4.50–4.60 (2H, m, 1'- and 2'-H), 4.89 (1H, t, J = 9.5 and 9.5 Hz, 4'-H), 4.98 (1H, t, J = 9 and 9 Hz, 3'-H), 7.72–7.80 and 8.43–8.50 (each 2H, m, 1-, 2-, 3- and 4-H), and 13.56 and 13.79br (each 1H, s, 5- and 12-OH) (addition of D_2O caused the s at 3.40 to disappear); MS *inter alia* 334 ($C_{20}H_{14}O_5^+$, base peak). (Found: C, 59.5; H, 4.90. Calc for $C_{34}H_{34}O_{15}$: C, 59.80; H, 5.00%).

The minor diastereoisomer was (6a*R*, 7*S*, 9*S*, 10a*S*) - 9 - ethynyl - 6a,7,8,9,10,10a - hexahydro - 7 - [(2',3',4',6' - tetra - *O* - acetyl - *β* - D - glucopyranosyl)oxy] - 5,9,12 - trihydroxynaphthacene - 6,11 - dione **21b**; ^{1}H-NMR (300 MHz, $CDCl_3$) *inter alia* 1.81, 1.98, 2.05 and 2.16 (each 3H, s, 4 × $MeCO_2$), 2.50 (1H, s, C≡CH), 2.73 (1H, dt, J = 14, 3 and 3 Hz, 8-H*α*), 2.85 (1H, dd, J = 13 and 2 Hz, 6a-H), 3.01 (1H, dt, J = 14, 3 and 3 Hz, 10-H*α*), 3.53 (1H, dt, J = 13, 13 and 3 Hz, 10a-H), 3.82–3.88 (1H, m, 5'-H), 3.90 (1H, s, 9-OH), 4.20 (1H, dd, J = 12 and 5 Hz, 6'-H), 4.28 (1H, dd, J = 12 and 3 Hz, 6'-H), 4.85–4.95 (3H, m, 7-, 1'- and 2'-H), 5.03 (1H, t, J = 9.5 and 9.5 Hz, 4'-H), 5.30 (1H, t, J = 9.5 and 9.5 Hz, 3'-H), 7.76–7.83 and 8.43–8.51 (each 2H, m, 1-, 2-, 3- and 4-H), and 13.52 and 13.65 (each 1H, s, 5- and 12-OH) (the signals for 8-H*β* and 10-H*β*, expected in the 1.80–2.00 region, were obscured by the $MeCO_2$ signals).

Reaction of the dihydroxy-trione **13b** with ethynylmagnesium *bromide followed by lead*(IV) *acetate*

The dihydroxy-trione **13b** (1.00 g, 1.52 mmol) was treated with HC≡CMgBr in THF as described in the previous experiment. The resultant mixture of **20b** and **21b** was dissolved in $MeCO_2H$ (20 ml) and $(MeCO_2)_4Pb$ (0.670 g, 1.51 mmol) was added to the stirred soln. After 24 hr (when, by TLC, no starting material remained and one new product was present), H_2O (40 ml) was added to the mixture. The red ppt, which appeared, was filtered, washed with H_2O and air dried. Recrystallisation of the material from $CHCl_3$—MeOH gave (7*S*,9*S*) - 9 - *ethynyl* - 7 - [(2',3',4',6' - *tetra* - O - *acetyl* - *β* - D - *glucopyranosyl)oxy*] - 7,8,9,10 - *tetrahydro* - 6,9,11 - *trihydroxynaphthacene* - 5,12 - *dione* **14b** (0.800 g, 77% based upon **13b**), as red crystals with the following properties: m.p. 239–241°; $[\alpha]_D$ + 201° (*c* = 0.4, dioxan); IR(KBr) *inter alia* 3500br (OH), 3300 (chelated OH), 1750 (ester CO), 1625 (chelated CO) and 1590 cm^{-1}; UV(EtOH) 208 (ε 16,400), 251 (36,800), 257sh (33,200) and 285 nm (8000); ^{1}H-NMR (360 MHz, $CDCl_3$) 1.85, 1.97, 2.04 and 2.14 (each 3H, s, 4 × $MeCO_2$), 2.23 (1H, dd, J = 15.0 and 4.4 Hz, 8-H*β*), 2.53 (1H, s, C≡CH), 2.90br (1H, d, separation = 15 Hz, 8-H*α*), 2.93 (1H, d, J = 19.0 Hz, 10-H*β*) 3.57br (1H, d, separation = 19 Hz, 10-H*α*), 3.83–3.87 (2H, m, 9-OH and 5'-H), 4.27 (2H, separation 4 Hz, 6'-H_2), 4.92 (1H, dd, J = 9.5 and 8 Hz, 2'-H), 5.07 (1H, t, J = 9.5 and 9.5 Hz, 4'-H), 5.08 (1H, d, J = 8 Hz, 1'-H), 5.22–5.27 (1H, m, W_H = 8 Hz, 7-H), 5.28 (1H, t, J = 9.5 and 9.5 Hz, 3'-H), 7.81–7.85 and 8.30–8.34 (each 2H, m, 1-, 2-, 3- and 4-H), and 13.27 and 13.63 (each 1H, s, 6- and 11-OH); MS *inter alia* 314 ($C_{20}H_{10}O_4^+$, base peak). (Found: C, 59.6; H, 4.55. Calc for $C_{34}H_{32}O_{15}$: C, 60.00; H, 4.70%).

Hydrolysis of the anthracycline **14b**

To a suspension of **14b** (1.15 g, 1.69 mmol) in EtOH (170 ml) was added *ca* 1 M-HCl (170 ml). The mixture was heated under reflux for 30 hr when it was concentrated and filtered. Recrystallisation of the filtered material from $CHCl_3$-light petroleum gave (7*S*,9*S*) - 9 - *ethynyl* - 7,8,9,10 - *tetrahydro* - 6,7,9,11 - *tetrahydroxynaphthacene* - 5,12 - *dione* **23** (0.525 g, 89%), as red crystals with the following properties: m.p. 215–

218°; $[\alpha]_D$ + 161° (c = 0.5, dioxan); IR(KBr) *inter alia* 3420br (OH), 3300 (chelated OH), 1625 (chelated CO) and 1590 cm^{-1}; UV(EtOH) 206 (ε 28,000), 251 (47,300), 256sh (41,300) and 285 nm (9500); ^{1}H-NMR (360 MHz, $CDCl_3$), 2.28 (1H, dd, J = 14.5 and 5 Hz, 8-Hβ), 2.58 (1H, s, C≡CH), 2.64 (1H, ddd, J = 14.5, 3 and 2 Hz, 8-Hα), 3.00 (1H, d, J = 18.5 Hz, 10-Hβ), 3.48 (1H, dd, J = 18.5 and 1.7 Hz, 10-Hα), 3.57 (1H, s, 9-OH), 3.70 (1H, d, J = 4 Hz, 7-OH), 5.27–5.29 (1H, m, 7-H), 7.80–7.85 and 8.30–8.34 (each 2H, m, 1-, 2-, 3- and 4-H), and 13.26 and 13.60 (each 1H, s, 6- and 11-OH) [addition of D_2O caused the signals at 3.57, 3.70, 13.26 and 13.60 to disappear and those at 5.27–5.29 to collapse to a dd (J = 5 and 3 Hz)]; MS *inter alia* 350 (M^+), 332 ($C_{20}H_{12}O_5^+$, base peak) and 314 ($C_{20}H_{10}O_4^+$). (Found: C, 68.35; H, 3.95. Calc for $C_{20}H_{14}O_6$: C, 68.55; H, 4.00%). Found: M^+, 350.0797. Calc for $C_{20}H_{14}O_6$: *M*, 350.0790.

Hydration of the ethynyl-dione **23**

To a soln of **23** (0.200 g, 0.57 mmol) in Me_2CO (40 ml) was added red HgO (0.600 g, 2.77 mmol) in 7% H_2SO_4 (40 ml). The mixture was heated under reflux for 3 hr and the cooled soln was diluted with *ca* 1 M-HCl (60 ml) and extracted with $CHCl_3$ (2 × 75 ml). The organic extract was washed with H_2O, dried ($MgSO_4$) and evaporated. Recrystallisation of the residue from CH_2Cl_2—Et_2O gave **3** (0.158 g, 75%) as a red solid with the following properties: m.p. 175–178° (lit. 184–186°,[4] 182.5–183°[5] and 183.5–184.5°[7]); $[\alpha]_D$ + 160° (c = 0.5 dioxan) [lit. +170° and 140°,[4] +164.5°[5] and +153° (dioxan)[7]]; IR(KBr) *inter alia* 3400br (OH), 1720 (ketone CO), 1625 (chelated CO) and 1590 cm^{-1}; UV(EtOH) 207 (ε 22,500), 227sh (21,000), 252 (48,900), 257sh (43,700) and 287 nm (11,700); ^{1}H-NMR (360 MHz, $CDCl_3$) 1.58br (> 1H, s, H_2O), 2.17 (1H, dd, J = 14.5 and 5 Hz, 8-Hβ), 2.34br (1H, d, separation = 14.5 Hz, 8-Hα), 2.43 (3H, s, MeCO), 2.95 (1H, d, J = 18.5 Hz, 10-Hβ), 3.18 (1H, dd, J = 18.5 and 2 Hz, 10-Hα), 3.82br (1H, d, J = 5 Hz, 7-OH), 4.56 (1H, s, 9-OH), 5.31br (1H, s, W_H 10 Hz, 7-H), 7.82–7.85 and 8.31–8.34 (each 2H, m, 1-, 2-, 3- and 4-H), 13.26 and 13.55 (each 1H, s, 6- and 11-OH); MS *inter alia* 368 (M^+, base peak). (Found: C, 63.5; H, 4.35. Calc for $C_{20}H_{16}O_7$. 0.5 H_2O: C, 63.65; H, 4.50%). Found: M^+, 368.0890. Calc for $C_{20}H_{16}O_7$: *M*, 368.0896.

Reaction of the ethynyl-dione (**14b**) *with mercury*(II) *oxide-sulphuric acid*

A soln of **14b** (0.200 g, 0.29 mmol) in Me_2CO (25 ml) was treated with red HgO (0.200 g, 0.92 mmol) and 7% aqueous H_2SO_4 (25 ml). The mixture was heated under reflux for 5 min and allowed to cool to room temp. After dilution with *ca* 1 M-HCl (20 ml), the mixture was extracted with CH_2Cl_2 (2 ×). The organic extract was washed with *ca* 0.1 M-HCl, dried ($MgSO_4$) and evaporated to leave a red solid (0.188 g). Purification of the material by SiO_2 chromatography [elution with Et_2O to remove impurities and with Et_2O—EtOAc (1 : 1) to obtain the product] gave (7*S*,9*S*) - 9 - *acetyl* - 7 - [(2′,3′,4′,6′ - *tetra* - O - *acetyl* - β - D - *glucopyranosyl*)*oxy*] - 7,8,9,10 - *tetrahydro* - 6,9,11 - *trihydroxynaphthacene* - 5,12 - *dione* **15b** (0.150 g, 73%) as red crystals. The sample, recrystallised from MeOH, possessed the following properties: m.p. 240–242°; $[\alpha]_D$ + 165° (c = 0.4 dioxan); IR(KBr) *inter alia* 3500 (OH), 1750 (ester CO), 1720sh (ketone CO) 1625 (chelated CO) and 1590 cm^{-1}; UV(EtOH) 207 (ε 13,500), 250 (32,900), 256 (29,700) and 284 nm (7200); ^{1}H-NMR (360 MHz, $CDCl_3$) 1.57br (> 2H, s, H_2O), 1.85, 1.98, 2.05 and 2.10 (each 3H, s, 4 × $MeCO_2$), 2.46 (3H, s, MeCO), 2.68br (1H, d, separation = 15 Hz, 8-Hα), 2.95 (1H, d, J = 19.0 Hz, 10-Hβ), 3.23br (1H, d, separation = 19 Hz, 10-Hα), 3.80–3.87 (1H, m, 5′-H), 4.17 (1H, s, 9-OH), 4.26 (2H, separation = 3 Hz, 6′-H_2), 4.49 (1H, dd, J = 9.5 and 8 Hz, 2′-H), 5.06 (1H, d, J = 8 Hz, 1′-H), 5.08 (1H, t, J = 9.5 and 9.5 Hz, 4′-H), 5.30 (1H, t, J = 9.5 and 9.5 Hz, 3′-H), 5.37br (1H, s, W_H 8 Hz, 7-H), 7.83–7.88 and 8.35–8.40 (each 2H, m, 1-, 2-, 3- and 4-H), and 13.30 and 13.68 (each 1H, s, 6- and 11-OH) (the signals for 8-Hβ, expected in the 1.80–2.00 region, were obscured by the $MeCO_2$ signals); MS *inter alia* 332 ($C_{20}H_{12}O_5^+$) and 43 ($C_2H_3O^+$, base peak). (Found: C, 58.6; H, 4.75. Calc for $C_{34}H_{34}O_{16}$: C, 58.45; H, 4.85%).

Acknowledgements—We thank the S.E.R.C. for a research fellowship (to R.C.G.) and the University of Newcastle upon Tyne for a demonstratorship (to P.A.H.). We are also grateful to Drs. I. Sadler (Edinburgh University) and M. N. S. Hill for recording the 360 and 300 MHz ^{1}H-NMR spectra, respectively, to Messrs. P. Kelly and S. Addison for the determination of the MS, and to Mr. D. Dunbar for measuring the IR spectra and for the microanalytical results.

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