Studies Related to Anthracyclines. Part 2.[1] Synthesis of (±)-4-Demethoxydaunomycinone[2]†

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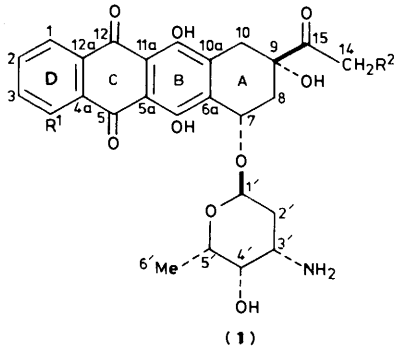
A chromatography-free, six-step, diastereocontrolled synthesis of (±)-4-demethoxy-7-*O*-methyldaunomycinone (**3b**) is described. The tetracyclic carbon skeleton is elaborated by a Diels–Alder strategy in which the 6a,7 and 10,10a bonds are constructed, the epoxytetraone (**5**) and the diene (**10a**) serving as precursors. Hydrolysis of the cycloadduct (**11a**) leads to the epoxypentaone (**12a**), the structure of which is confirmed by *X*-ray crystallography. The diastereocontrol is achieved in the reaction of the dihydroxytrione (**13a**) [obtained by reduction of the epoxypentaone (**12a**)] with ethynylmagnesium bromide or lithium acetylide, the reagents attacking the 9-carbonyl group from the face away from that bearing the 7-methoxy group to give the ethynyldione (**14a**). Although epimerisation of the dihydroxytrione (**13a**) at the 10a-position is a competing reaction when high concentrations of the metal acetylides are employed, the ethynyldione produced, *i.e.* (**20**), still possess the *trans* arrangement of the 7-methoxy and 9-ethynyl groups. The ethynyldiones (**14a**) and (**20**) are converted into compound (**3b**) by an oxidative isomerisation–hydration sequence.

An attempt to effect the de-*O*-methylation of compound (**3b**), by the action of trimethylsilyl iodide, failed; a mixture of 4-demethoxy-7-deoxydaunomycinone (**22b**) and its 9-deoxy derivative (**22a**) resulted. The conversion of compound (**3b**) into the title compound (**3a**) is brought about by a trifluoroacetolysis–ammonolysis sequence.

The conformation of the A ring of the anthracyclinones (**3a**) and (**3b**) and their precursors, as determined by high-field ^{1}H n.m.r. spectroscopy, is discussed.

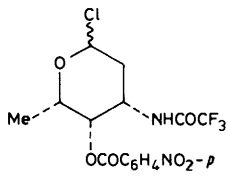
Daunomycin (**1a**), adriamycin (**1b**), and carminomycin (**1c**) are of substantial interest because of their potent antitumour properties.[3] Unfortunately, the clinical utility of these anthracyclines is limited by their cardiotoxicity. In the hope of defining structure–activity–toxicity relationships, a considerable effort is currently being devoted to the synthesis of structurally modified compounds. One of the most promising analogues to emerge from these studies is 4-demethoxydaunomycin (**1d**); besides being orally effective, it is as active as its natural counterpart (**1a**) at 4—8 times lower doses.[4] At present, 4-demethoxydaunomycin (**1d**) is obtained, following deprotection, by the glycosidation of a L-daunosamine derivative, *e.g.* (**2**), with 4-demethoxydaunomycinone (**3a**) (available, as yet, only by total synthesis).[4,5]

In principle, a simple approach to precursors of the anthracyclinone (**3a**) involves the cycloaddition of an appropriate 1,3-diene to the 2,3-positions of the tetraone (**4**). In practice, however, this route is limited by the tendency of many dienes to react preferentially with the 4a,9a-double bond. Recently, we described a solution to this problem.[1] Thus the oxirane (**5**), prepared from quinizarin (**6**) by sequential reactions with lead(IV) acetate and *m*-chloroperoxybenzoic acid, underwent cycloaddition reactions with isoprene, cyclopentadiene, and cyclohexa-1,3-diene. The derived cycloadducts, *e.g.* (**7**), could be reduced to *leuco*-compounds, *e.g.* (**8**), which were converted into anthracyclinone-like products, *e.g.* (**9**), by an oxidation–isomerisation sequence. We now wish to further demonstrate the value of this methodology by describing its application to the synthesis of (±)-4-demethoxydaunomycinone (**3a**).

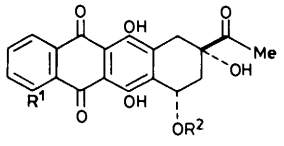


(**1**)

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

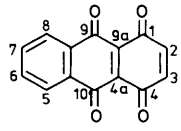


(**2**)



(**3**)

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

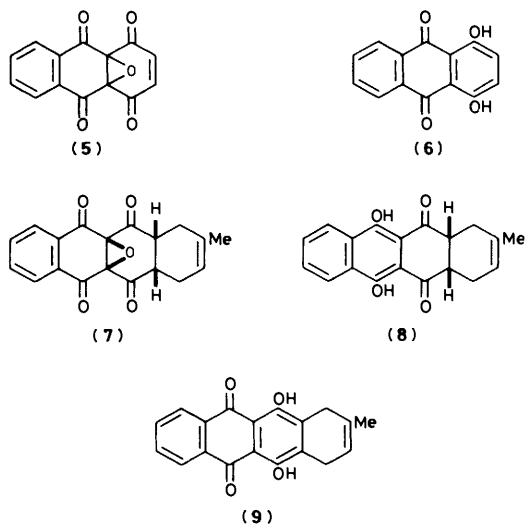


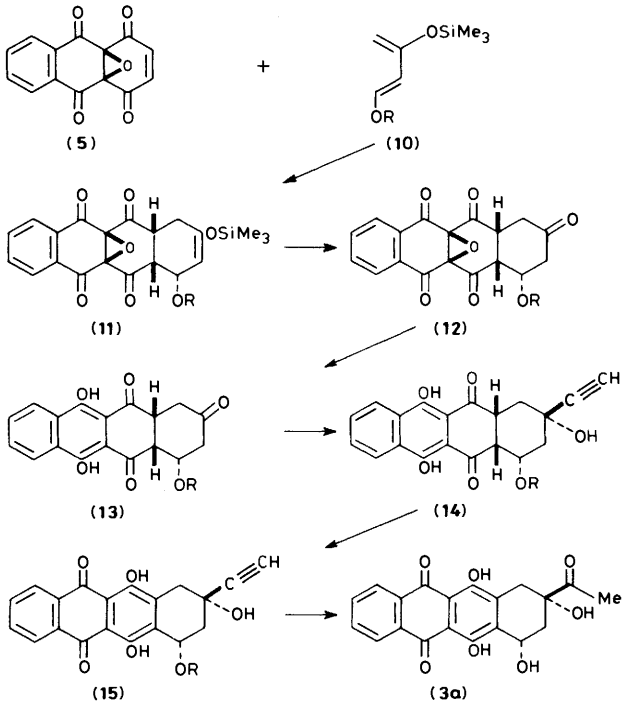
(**4**)

Results and Discussion

Our planned route to the aglycone (**3a**) is outlined in Scheme 1. A ketone of the type (**13**) was considered to be a key intermediate in the sequence because it was hoped that reaction with a metal acetylide would occur with high site- and diastereoselectivity to give a hydroxyacetylene of the type (**14**). By an

† 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 also used in this paper to describe anthracyclinone precursors.





Scheme 1.

oxidation–isomerisation sequence, such a hydroxyacetylene should be convertible into a compound of the type (**15**) which, after hydration of the triple bond and removal of the alcohol-protecting group, should afford (±)-4-demethoxydaunomycinone (**3a**). Hopefully, a ketone of the type (**13**) would be available from the oxirane (**5**) and a diene of the type (**10**), by way of intermediates of the types (**11**) and (**12**).

The requirements of the group R are deserving of comment. In addition, of course, to being compatible with all the reactions required in the assembly of the target, the group should ideally be removable with rupture of the O–R bond. However, before meeting the last-mentioned requirement, it was decided to test the overall strategy using the methyl group. This decision meant that Danishefsky's diene (**10a**),[6] which is commercially

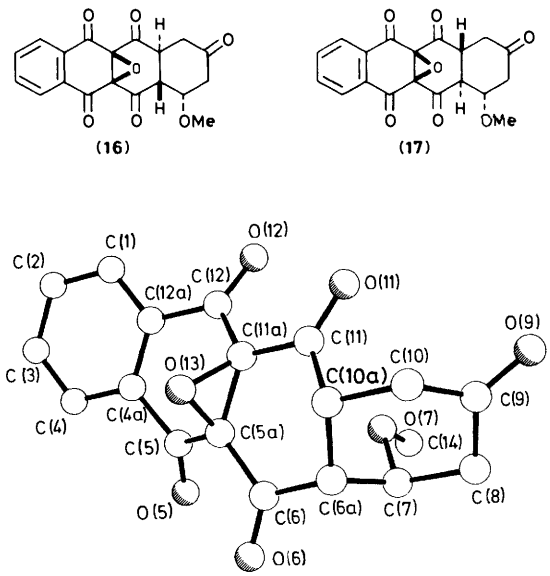


Figure 1. The molecular structure of the epoxypentaone (**12a**)

available, could be employed in the initial cycloaddition reaction.

The diene (**10a**) reacted with the oxirane (**5**) in dichloromethane to give a crystalline cycloadduct in 86% yield. That the cycloadduct, which was obtained as a single diastereoisomer, possessed the stereostructure (**11a**) was inferred on the expectation that the Diels–Alder reaction had occurred by way of the least-hindered *endo* transition state.

The conversion of the silyl enol ether (**11a**) into the ketone (**12a**) presented problems owing to the instability of the product. However, when the hydrolysis was effected in tetrahydrofuran (THF) containing a small amount of 0.1M-hydrochloric acid,[7] a product was isolated in 83% yield after recrystallisation. Although it was assumed that the product was the ketone (**12a**), it should be noted that hydrolysis of the silyl enol ether (**11a**) may be accompanied by an epimerisation at the 6a- or 10a-position. Consequently, the structures (**16**) and (**17**) represented alternative possibilities for the hydrolysis product. Whereas the latter structure was eliminated on the basis of ^{1}H n.m.r. spectroscopy, a distinction between the possibilities (**12a**) and (**16**) was not unequivocal. An *X*-ray analysis of the hydrolysis product was therefore undertaken.

The *X*-ray structure was readily solved using direct methods (see Experimental section for crystal data and other information). The molecular structure, with its crystallographic numbering system, is shown in Figure 1; refined atomic co-ordinates are included in Table 1; bond lengths and angles are available as a supplementary publication (see Experimental section). Clearly, the product possessed the stereostructure (**12a**) and no epimerisation had accompanied the hydrolysis reaction.

On the basis of the *X*-ray evidence, the stereostructure (**11a**) was established for the precursor silyl enol ether. As expected, the cycloaddition reaction between the diene (**10a**) and the oxirane (**5**) had occurred by way of the least-hindered *endo* transition state.

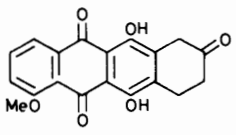
Previously, it was shown that sodium dithionite in aqueous methanol or zinc in acetic acid effected the reduction of the oxirane (**7**) to the *leuco*-compound (**8**).[1] Both reagents promoted the corresponding reduction of the oxirane (**12a**) to the *leuco*-compound (**13a**) in high yield.

At the outset of our work, Kende and his co-workers had effected the conversion of the ketone (**18**) into the ketol (**19**) by

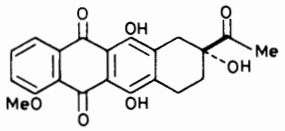
Table 1. Fractional atomic co-ordinates (× 10^4) and temperature factors (Å^2) (× 10^3)

Atom	*x*	*y*	*z*	*U**
C(1)	7 344(3)	8 934(2)	200(2)	50(1)
C(2)	7 004(3)	8 889(3)	−814(2)	58(1)
C(3)	6 130(3)	8 076(2)	−1 135(2)	59(1)
C(4)	5 592(3)	7 307(2)	−473(2)	49(1)
C(4a)	5 928(3)	7 362(2)	539(2)	41(1)
C(5)	5 416(3)	6 515(2)	1 259(2)	40(1)
O(5)	5 222(2)	5 537(2)	1 040(1)	59(1)
C(5a)	5 182(2)	6 961(2)	2 313(2)	37(1)
C(6)	4 455(2)	6 246(2)	3 073(2)	38(1)
O(6)	3 779(2)	5 478(2)	2 790(1)	54(1)
C(6a)	4 643(3)	6 492(2)	4 174(2)	43(1)
C(7)	5 615(3)	5 642(2)	4 568(2)	52(1)
O(7)	6 772(2)	5 831(2)	4 009(2)	61(1)
C(8)	5 856(4)	5 787(3)	5 699(2)	72(1)
C(9)	6 163(3)	6 986(3)	5 976(2)	58(1)
O(9)	7 041(2)	7 218(2)	6 547(2)	81(1)
C(10)	5 289(3)	7 869(3)	5 540(2)	57(1)
C(10a)	5 057(3)	7 714(2)	4 402(2)	44(1)
C(11)	6 233(3)	8 046(2)	3 801(2)	39(1)
O(11)	7 189(2)	8 460(2)	4 159(1)	54(1)
C(11a)	6 102(2)	7 872(2)	2 678(2)	37(1)
C(12)	7 167(2)	8 203(2)	1 948(2)	42(1)
O(12)	8 244(2)	8 440(2)	2 231(1)	63(1)
C(12a)	6 799(2)	8 182(2)	873(2)	40(1)
O(13)	4 821(2)	8 137(1)	2 321(1)	38(1)
C(14)	7 562(5)	4 888(4)	3 888(5)	117(2)

* Equivalent isotropic *U* defined as one third of the trace of the orthogonalised U_{ij} tensor.



(18)



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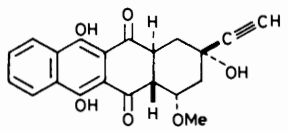

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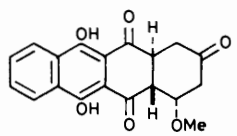


(21)

an ethynylation–hydration sequence.[8] During the course of these studies, other workers have shown the value of acetylene as an acetyl anion equivalent in systems closely related to the ketone (**13a**).[7,9,10]

When treated with an excess of ethynylmagnesium bromide (*ca.* 4 mol equiv.) in THF at 0 °C, the ketone (**13a**) was converted into the crystalline hydroxyacetylene (**14a**). Unfortunately, this reaction was somewhat unreliable and the yield of the product declined as the scale was increased. Thus, although 70% conversions were routinely achieved on a 1.0-g scale only 30—40% yields were observed on a 5-g scale. On the latter occasions, significant amounts of the starting material remained; moreover, when such mixtures were resubjected to the reaction conditions, aromatised products resulted.

In the hope of improving the (**13a**)→(**14a**) transformation, the use of lithium acetylide was examined. After several exploratory experiments, it was found that an excess of this reagent (*ca.* 10 mol equiv. of a 0.1M-solution) in THF at −78 °C reacted with the ketone (**13a**) to give the hydroxyacetylene (**14a**). Interestingly, when the reaction was conducted under similar conditions but using a *ca.* 0.3M-solution of lithium acetylide, a 2:1 mixture of products resulted. On the basis of ^{1}H n.m.r. spectroscopy, the minor product was the hydroxyacetylene (**14a**). Repeated recrystallisation of the mixture afforded the major product, which was clearly a diastereoisomer of the hydroxyacetylene (**14a**). On the basis of subsequent chemistry and its ^{1}H n.m.r. spectroscopic properties, the diastereoisomer was assigned the stereostructure (**20**).

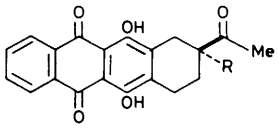
The formation of the hydroxyacetylene (**20**) may be accounted for in two ways: either the hydroxyacetylene (**14a**) undergoes an epimerisation at the 10a-position or the starting ketone (**13a**) is converted into its epimer (**21**) which then affords the product. That the latter explanation was the correct one was inferred from the observation that the hydroxyacetylene (**14a**) was unchanged when resubjected to the action of lithium acetylide. It is interesting to note therefore that in *both* the ketones (**13a**) and (**21**) there is a strong preference for the acetylide to attack the 9-carbonyl group from the face away from the 7-methoxy moiety.

Although lithium acetylide proved to be a reliable reagent for effecting the ethynylation of the ketone (**13a**), the procedure was experimentally less convenient than that employing ethynylmagnesium bromide. A further study with the latter reagent revealed that the ethynylation was efficiently achieved by employing a large excess of ethynylmagnesium bromide (*ca.* 34 mol equiv.) in THF at 0 °C. Under the aforecited conditions, a 1:1 mixture of the hydroxyacetylenes (**14a**) and (**20**) was produced.

Previously, it was reported that the *leuco*-compound (**8**) could be converted into the anthracyclinone-like product (**9**) by sequential reactions with lead(IV) acetate and triethylamine.[1] In the case of the hydroxyacetylene (**14a**), the oxidation–isomerisation sequence was conveniently effected by using lead(IV) acetate in acetic acid at room temperature; compound (**15a**) crystallised from the reaction mixture in 73% yield. Slightly more severe conditions (heating at 50—60 °C) were required to effect the corresponding reaction sequence with a mixture of the hydroxyacetylenes (**14a**) and (**20**). The product, isolated in 69% yield after recrystallisation [based on (**13a**)], was identical with compound (**15a**). This result confirmed that the hydroxyacetylenes possessed identical stereochemistries at the 7- and 9-positions.

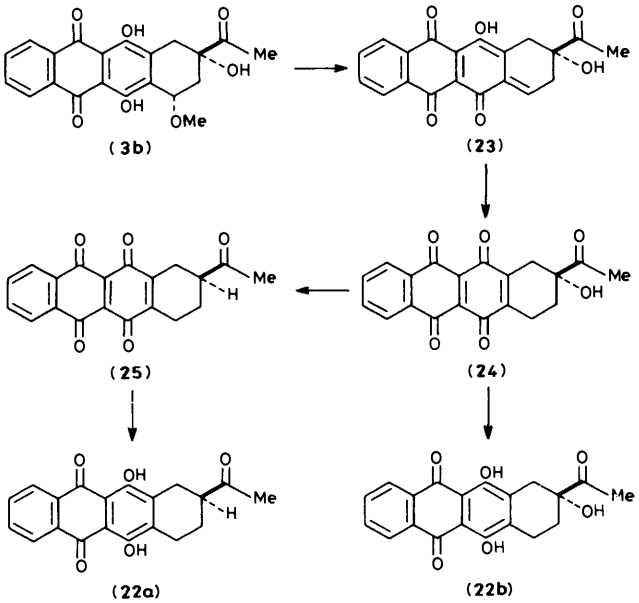
When a mixture of compound (**15a**), mercury(II) oxide, and 7% sulphuric acid was heated in acetone, the anthracyclinone (**3b**) was produced in 90% yield. Although the melting point of the sample (m.p. 230—234 °C) was substantially lower than the literature value (m.p. 250—254 °C),[11] the compound showed spectroscopic properties that were in good agreement with those reported.

Ideally, to complete the synthesis of (±)-4-demethoxydaunomycinone (**3a**), we needed to effect the selective cleavage of the O–Me bond of compound (**3b**). Although attempts to achieve this objective with trimethylsilyl iodide, a reagent that has been effectively employed in the demethylation of methyl



(22)

a; R = H
b; R = OH

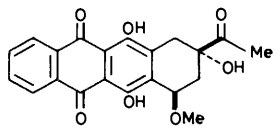


Scheme 2.

ethers,[12] were unsuccessful, the outcome of the reaction was surprising. Two new materials, which were separated by preparative t.l.c., were produced. The more mobile material, isolated in 23% yield, was considered to be the ketone (**22a**)[13] on the basis of its melting point and spectroscopic properties. The less mobile material, obtained in 9% yield, was formulated as the ketol (**22b**); although its melting point (m.p. 196—198 °C) differed from those reported in the literature (m.p. 160—162 °C,[14] 210—211 °C[15]), its spectroscopic properties were in agreement with those published.[15] Furthermore, the ketol (**22b**) was identical with the product obtained from compound (**3b**) by reduction with sodium dithionite. Interestingly, when resubjected to the action of trimethylsilyl iodide, the ketol (**22b**) was recovered unchanged, suggesting that it was not a precursor of the ketone (**22a**).

A possible pathway to account for the formation of compounds (**22a**) and (**22b**) from the anthracyclinone (**3b**) is outlined in Scheme 2. Thus the species (**23**), obtained from compound (**3b**) by the elimination of methanol, may tautomerise to the diquinone (**24**) which may then be reduced by hydrogen iodide to either the ketol (**22b**) or the ketone (**25**); further reduction of the last-cited compound by hydrogen iodide may then lead to the ketone (**22a**). There is precedent for the conversion of α-ketols into ketones by trimethylsilyl iodide.[16]

In view of the failure to convert compound (**3b**) into (±)-4-demethoxydaunomycinone (**3a**) by cleavage of the O–Me bond, attention was turned to the introduction of the 7-hydroxy function by cleavage of the C(7)–O bond. Arcamone and his co-workers reported that compound (**26**) could be converted into the anthracyclinone (**3a**) by treatment with trifluoroacetic acid



(26)

followed by ammonium hydroxide.[4] Although no yield was quoted by the Italian workers, Swenton's group reported a 33% yield for the transformation (using racemic material and effecting the hydrolysis step with $NaHCO_3$ solution).[17] In both cases, it was necessary to purify the product by silica-gel chromatography. When treated with trifluoroacetic acid followed by ammonium hydroxide, the methyl ether (**3b**) gave an impure product from which (±)-4-demethoxydaunomycinone (**3a**) was isolated in 42% yield after silica-gel chromatography. Although the melting point of the sample (m.p. 160—164 °C) was lower than those reported in the literature (m.p. 167—170 °C,[9] 173—175 °C,[18] 180 °C,[7] 183—185 °C[17]), its spectroscopic properties were in agreement with those published.

The present synthesis of compound (**3b**) is of interest in a number of respects. Thus the diastereocontrol achieved augurs well for future studies; providing the substituent R (Scheme 1) is chosen so that the O–R bond can be cleaved, a diastereocontrolled synthesis of the (±)-anthracyclinone (**3a**) will emerge. Surprisingly, in spite of the vast number of studies directed towards the synthesis of the last-cited compound, few[7,9,15] have addressed the diastereocontrol challenge. In the large majority of cases, the tetracycle (**22b**) is assembled which is subsequently functionalised by a bromination–methanolysis (hydrolysis) sequence.[4,11,14,18] Usually, little selectivity is achieved in the oxygenation reaction and the mixture of oxy derivatives is then treated with trifluoroacetic acid to give (after solvolysis of the intermediate trifluoroacetates) predominantly the anthracyclinone (**3a**). As already indicated, modest yields and the need for a chromatographic purification step are unwelcome features of this procedure.

Another point of note in respect of the present synthesis of the anthracyclinone (**3b**) is that no chromatographic purification step is involved. Moreover, the six-step sequence, which can be effected from the oxirane (**5**) and the diene (**10a**) without the purification of any of the intermediates, provides compound (**3b**) in *ca.* 36% overall yield [based on (**10a**)].

Finally, it should be pointed out that a number of the intermediates generated in this work offer considerable prospect for further chemical manipulation. In consequence, there is the opportunity of deriving new anthracyclinones, and hence novel anthracyclines, which will allow a further appraisal of structure–activity–toxicity relationships.

Conformational Considerations.—The aforementioned synthetic work provided the opportunity of assessing the conformation of the A ring of compounds (**3a**), (**3b**), (**11a**)—(**15a**), and (**20**) in deuteriochloroform solution. The results, which held some surprises, will now be considered.

On the basis of high-field ^1H n.m.r. spectroscopy, the A ring of the epoxytetraone (**11a**) was considered to adopt the sofa-like geometry (**27**). Thus the 10β,10a- and 10α,10a-protons showed coupling constants of 6.7 and 0 Hz, suggestive[19,20] of dihedral angles of *ca.* 25 and 95° respectively. The coupling constants of 5.5 and 4.2 Hz, observed for the 6a,10a- and 6a,7-protons, respectively, were indicative of dihedral angles of *ca.* 35 and 45°.

The coupling constants of the protons associated with the A rings of compounds (**12a**), (**13a**), (**14a**), and (**20**) are summarised in Table 2. In all the examples, there appeared to be *gauche*-like relationships between the 7,8α-, 7,8β-, and 6a,7-protons, requiring axial-like dispositions of the methoxy groups.

Table 2. Coupling constants (Hz) of the protons associated with the A rings of compounds (**12a**), (**13a**), (**14a**), and (**20**) ($CDCl_3$)

Compound	$J_{7,8\alpha}$	$J_{7,8\beta}$	$J_{8\alpha,8\beta}$	$J_{8\alpha,10\alpha}$	$J_{10\alpha,10\beta}$	$J_{10\alpha,10a}$	$J_{10\beta,10a}$	$J_{6a,10a}$	$J_{6a,7}$
(**12a**)	2.5	2.5	17	1	15.5	5.5	7.5	9	2.5
(**13a**)	3.2	2.6	15.1	2.2	15.5	1.7	7.7	6.8	2.2
(**14a**)	*ca.* 3	*ca.* 3	*ca.* 14		14.5	*ca.* 3	6.0	*ca.* 6	*ca.*3
(**20**)	2.8	2.3	14.9	2.8	14.1	2.9	12.0	13.5	2.5

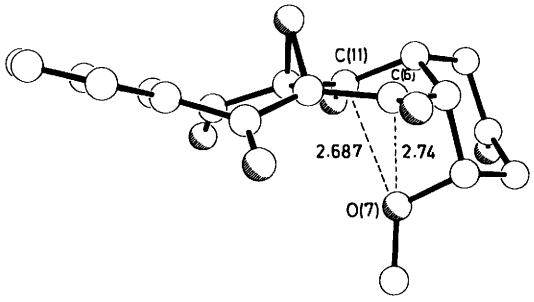


Figure 2. View of the epoxypentaone (**12a**) illustrating the chair-like conformation of the A ring and the close approach of the O(7)–C(11) and O(7)–C(6) atoms

Although *X*-ray crystallography showed that the A ring of the epoxypentaone (**12a**) adopted the chair-like geometry (**28**) in the crystal state (Figure 2), this was not borne out by the coupling constants for the 10α,10a-, 10β,10a-, and 6a,10a-protons (*J* 5.5, 7.5, and 9 Hz, respectively) measured in deuteriochloroform solution. The values were more consistent with the sofa-like geometry (**29**). Furthermore, the geminal coupling constant of the 8-protons (*J* 17 Hz) was noticeably different from that of the 10-protons (*J* 15.5 Hz), implying a difference in their orientation with respect to the 9-carbonyl group. It should be noted that the (**28**)→(**29**) distortion imposes a conformational change of the B ring of compound (**12a**) from half-chair-like to boat-like geometry. A comparison of the pertinent torsion angles of compound (**12a**), obtained by *X*-ray analysis ‡ and calculated from spin-spin coupling constants, is made in Table 3.

In the case of the dihydroxytrione (**13a**), the coupling constants were in moderate agreement with its A ring adopting the chair-like geometry (**28**). The similarity of the geminal coupling constants of the 8-protons (*J* 15.1 Hz) and of the 10-protons (*J* 15.5 Hz) together with the sizable long-range coupling constant between the 8α- and 10α-protons (*J* 2.2 Hz) (which possess a W-configuration[20]) were in support of this interpretation.

A precise evaluation of the coupling constants associated with the A ring protons of the ethynyldione (**14a**) was not possible because of the broadness of some of the signals. However, on the basis of width-at-half-height (w_H) measurements,[20] approximate coupling constants were determined. The values suggested that the A ring of compound (**14a**) adopted the chair-like geometry shown in structure (**30**).

The coupling constants observed for the ethynyldione (**20**) revealed that its A ring preferred the chair-like geometry (**31**). In particular, the values of 12.0 and 13.5 Hz observed for the 10β,10a- and 6a,10a-protons established their *trans* diaxial relationships. Again, the geminal coupling constants of the 8-protons (*J* 14.9 Hz) and of the 10-protons (*J* 14.1 Hz) and the

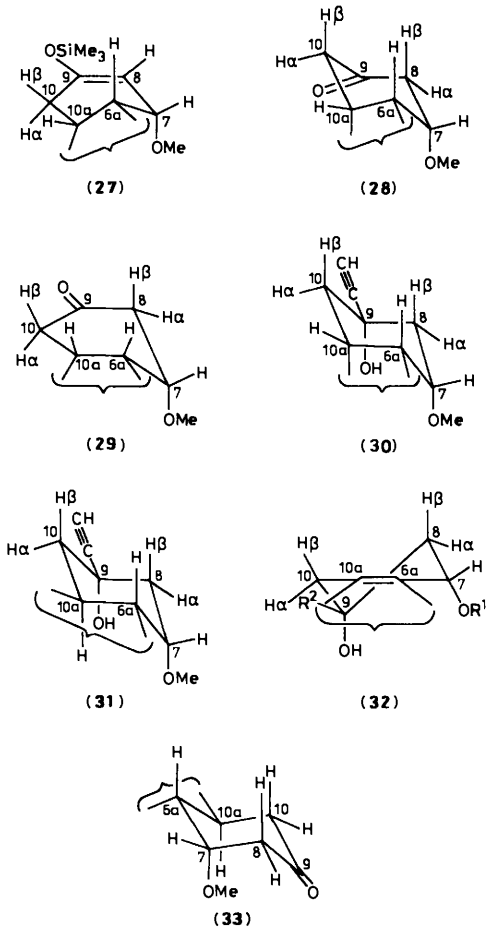
‡ The torsion angles are based on calculated hydrogen positions that were fixed by reference to the refined 'heavy' atom co-ordinates.

Table 3. Selected torsion angles (°) of compound (**12a**) determined from *X*-ray analysis and *J* values

	Angle (from *X*-ray)	Angle (from *J*)
H(7)–C(7)–C(8)–H(8α)	68	58
H(7)–C(7)–C(8)–H(8β)	51	58
H(10α)–C(10)–C(10a)–H(10a)	71	36
H(10β)–C(10)–C(10a)–H(10a)	48	18
H(6a)–C(6a)–C(10a)–H(10a)	54	0
H(6a)–C(6a)–C(7)–H(7)	58	58

Table 4. Coupling constants (Hz) of the protons associated with the A rings of compounds (**15a**), (**3b**), and (**3a**) ($CDCl_3$)

Compound	$J_{7,8\alpha}$	$J_{7,8\beta}$	$J_{8\alpha,8\beta}$	$J_{8\beta,10\beta}$	$J_{10\alpha,10\beta}$
(**15a**)	2.1	3.7	14.8	1.9	19.1
(**3b**)	2.2	3.2	15	2.0	19.0
(**3a**)	2.0	4.9	14.5	2.0	18.6



a; R^1 = Me, R^2 = C≡CH
b; R^1 = Me, R^2 = COMe
c; R^1 = H, R^2 = COMe

large long-range coupling constant between the 8α- and 10α-protons (*J* 2.8 Hz) consolidated this viewpoint.

Table 4 summarises the coupling constants of the protons associated with the A rings of compound (**15a**), (**3b**), and (**3a**). The values, which were quite similar, implied that the half-chair conformers (**32a**)—(**32c**) were adopted.

An interesting feature of the conformational studies concerns the axial-like orientation of the methoxy group in compounds (**11a**)—(**14a**). In such a situation, the 7-methoxy function experiences a 1,3-diaxial interaction with the 11-carbonyl group (such an interaction is absent in the alternative conformers in which the methoxy group is equatorial). We suggest that the *syn* diaxial relationship benefits from the donation of the electron pairs from the methoxy oxygen atom to the antibonding π* orbitals of the 11- and 6- carbonyl groups. The presence of such a stabilising interaction in compound (**12a**) is implied by the *X*-ray structure (Figure 2), which reveals that the O(7)–C(11) and O(7)–C(6) interatomic distances are 2.687 and 2.74 Å, respectively. Related effects have been noted on previous occasions.[21]

The preference for the half-chair geometry (**32**; R^2 = COMe) for the A ring of daunomycin (**1a**) and its aglycone has been discussed previously and attributed to a H-bonding interaction between the 9-hydroxy and 7-oxy groups.[22] A similar explanation accounts for the adoption of the conformers (**32a—c**) by the A ring of compounds (**15a**), (**3b**), and (**3a**), respectively.

Finally, on the basis of the conformational results, it is possible to understand the diastereoselectivity achieved in the ethynylation reactions. Evidently, the dihydroxytrione (**13a**) reacts by way of the thermodynamically more stable conformer in which the A ring adopts the geometry (**28**); the acetylide then attacks the 9-carbonyl group from its least-hindered face [to give the ethynyldione (**14a**)]. Presumably, the A ring of the dihydroxytrione (**21**) adopts the geometry (**33**); its 9-carbonyl group is again attacked from the least-hindered face [resulting in the production of the ethynyldione (**20**)].

Experimental

Dry solvents, referred to in the ensuing experiments, were prepared as follows: dichloromethane was stored over calcium chloride flakes; THF was stored over calcium hydride and, immediately prior to use, was distilled from lithium aluminium hydride. For chromatographic and instrumental details, see Part 1.[1] High-field ^{1}H n.m.r. spectroscopy was carried out at 300 or 360 MHz using Bruker WM-300 WB or WH-360 spectrometers.

Reaction of the Epoxytetraone (**5**) *with the Diene* (**10a**).—To a stirred solution of the epoxytetraone (**5**) (4.50 g, 17.7 mmol) in dichloromethane (125 cm^3) at 0 °C was added the diene (**10a**) (3.40 g, 19.8 mmol). After 5 min, the solution was allowed to warm to room temperature in the dark and, after a further 60 min, evaporated. Addition of diethyl ether to the residue and filtration gave (5aSR,6aRS,7SR,10aRS,11aRS)-5a,11a-*epoxy*-5a,6a,7,10,10a,11a-*hexahydro*-7-*methoxy*-9-*trimethylsilyloxy*-*naphthacene*-5,6,11,12-*tetraone* (**11a**) (6.50 g, 86%). A sample recrystallised from benzene–diethyl ether, showed the following properties: m.p. 162—164 °C (decomp.); $\nu_{max.}$(KBr) *inter alia* 1 755, 1 735, 1 695, and 1 660 (ketone C=O), and 1 595 cm^{-1}; δ (300 MHz; $CDCl_3$) 0.30 (9 H, s, $SiMe_3$) 2.15 (1 H, dd, *J* 18.0 and 6.7 Hz, 10-H_β), 2.80 (1 H, d, *J* 18.0 Hz, 10-H_α), 3.10 (3 H, s, OMe), 3.14 (1 H, dd, *J* 5.5 and 4.2 Hz, 6a-H), 3.59 (1 H, t, apparent *J* 6.5 and 6.5 Hz, 10a-H), 4.32 (1 H, t, apparent *J* 5 and 5 Hz, 7-H), 5.13 (1 H, d, *J* 5.5 Hz, 8-H), and 7.80—7.90 and 8.00—8.15 (each 2 H, m, 1-, 2-, 3-, and 4-H) [irradiation at 5.13 caused the signal at 4.32 to collapse to a d (*J* 4 Hz)]; *m/z inter alia* 426 (M^+) (Found: C, 62.0; H, 5.2. $C_{22}H_{22}O_7Si$ requires C, 62.00; H, 5.20%).

Reaction of the Silyl Enol Ether (**11a**) *with Hydrochloric Acid.*—To a solution of the silyl enol ether (**11a**) (6.50 g, 15.3 mmol) in THF (300 cm^3) was added 0.1M-hydrochloric acid (20 cm^3). The reaction was monitored by t.l.c. and, when no starting material remained (*ca.* 1.5 h), the mixture was diluted with dichloromethane (300 cm^3) and washed with water. Evaporation of the dried ($MgSO_4$) organic layer and crystallisation of the residue from chloroform gave (5aSR,6aRS,7SR,10aRS,11aRS)-5a,11a-*epoxy*-5a,6a,7,10,10a,11a-*hexahydronaphthacene*-7-*methoxy*-5,6,9,11,12(8H)-*pentaone* (**12a**) (4.50 g, 83%). A sample, after a further crystallisation from chloroform, showed the following properties: m.p. 173—176 °C (decomp.); $\nu_{max.}$(KBr) *inter alia* 1 730br and 1 695 (ketone C=O) and 1 597 cm^{-1}; $\lambda_{max.}$(EtOH) 210sh (ε 8 700), 230 (15 100), 257 (5 200), 263sh (4 600), and 310 nm (1 300); δ (360 MHz; $CDCl_3$) 2.30 (1 H, dd, *J* 17 and 2.5 Hz, 8-H_β), 2.35 (1 H, dd, *J* 15.5 and 7.5 Hz, 10-H_β), 2.83 (1 H, ddd, *J* 17, 2.5, and 1 Hz, 8-H_α), 3.17 (3 H, s, OMe), 3.20 (1 H, ddd, *J* 15.5, 5.5, and 1 Hz, 10-H_α), 3.30 (1 H, dd, *J* 9 and 2.5 Hz, 6a-H), 3.94 (1 H, ddd, *J* 9, 7.5, and 5.5 Hz, 10a-H), 4.32 (1 H, q, apparent *J* 2.5, 2.5, and 2.5 Hz, 7-H), and 7.80—7.82 and 8.0—8.12 (each 2 H, m, 1-, 2-, 3-, and 4-H); *m/z inter alia* 354 (M^+, base peak) (Found: C, 64.1; H, 4.0%; M^+ 354.0733. $C_{19}H_{14}O_7$ requires C, 64.40; H, 4.00%; *M*, 354.0739).

X-Ray Crystal Structure Data.—$C_{19}H_{14}O_7$, *M*, 354.3. Orthorhombic, a = 10.330(2), b = 11.800(2), c = 13.294(4) Å, U = 1.620 Å^3, space group $P2_12_12_1$, Z = 4, D_c = 1.46 g cm^{-3}. Refined unit cell parameters were obtained by centering 18 reflections on a Nicolet R3m diffractometer. 1 276 Independent reflections (θ ≤ 58°) were measured with Cu-K_α radiation (graphite monochromator) using the ω-scan measuring routine. Of these, 1 234 had $|F_o| > 3\sigma(|F_o|)$ and were considered to be observed. The net count of two check reflections (the 121 and 212), measured every 50 reflections during the data collection, did not change significantly, indicating that no deterioration of the crystal had occurred. The data were brought to a uniform arbitrary scale by use of these reflections and Lorentz and polarisation corrections applied; no absorption corrections were applied.

The structure was solved by direct methods. A starting set, comprising the three principal contributors to the list of negative quartets and six automatically selected magic integer phases, was used for the initial phase expansion. The solution with the highest N_{quest} (−0.22) had poor associated values of R_α and produced a featureless *E* map. The next solution (N_{quest} = −0.12) had significantly better values of R_α and the resulting *E* map gave the positions of all the non-hydrogen atoms.

The non-hydrogen atoms were refined anisotropically. The positions of the C(14) methyl hydrogen atoms were obtained from a Δ*F* map and the group refined as a rigid body. The positions of the other hydrogen atoms were idealised (C–H = 0.96Å), assigned isotropic thermal parameters, U(H) = $1.2U_{eq}$(C), and allowed to ride on their parent carbons. Refinement was by block-cascade full-matrix least-squares to R = 0.030, R_w = 0.035 ($w^{-1} = \sigma^2(F) + 0.00048F^2$). The maximum residual electron density in the final Δ*F* map was 0.14 e Å^{-3}. Computations were carried out on an Eclipse S140 computer using the SHELXTL program system.[23]

The fractional co-ordinates of the hydrogen atoms and their isotropic thermal parameters, the bond lengths and bond angles, and the anisotropic thermal parameters of the non-hydrogen atoms have been deposited as a Supplementary Publication (SUP No. 56132, 5pp.).* Tables of observed and

* For details of the Supplementary Publications Scheme, see Instructions for Authors (1985) in *J. Chem. Soc., Perkin Trans. 1*, 1985, Issue 1.

calculated structure factors are available on request from the editorial office.

Reaction of the Epoxypentaone (**12a**) *with Sodium Dithionite.*—A solution of sodium dithionite (85%, 8.00 g, 39.2 mmol) in water (100 cm^3) was added in drops to a stirred solution of the epoxypentaone (**12a**) (4.50 g, 12.7 mmol) in methanol (450 cm^3). The mixture became bright yellow in colour and a yellow precipitate was deposited. When no starting material remained (*ca.* 1 h, t.l.c.), the mixture was diluted with dichloromethane and water. The aqueous layer was separated and extracted twice with dichloromethane. The combined organic layers were dried ($MgSO_4$) and evaporated. Crystallisation of the residue from acetone gave (6aRS,7SR,10aRS)-6a,7,10,10a-*tetrahydro*-5,12-*dihydroxy*-7-*methoxynaphthacene*-6,9,11(8H)-*trione* (**13a**) (3.53 g, 82%) as a mustard-coloured solid. A sample, obtained as a bright-yellow solid after crystallisation from acetone, showed the following properties: m.p. 171—173 °C (decomp. with darkening above 150 °C); $\nu_{max.}$(KBr) *inter alia* 3 440 (OH), 1 715, 1 645, 1 635, and 1 615 (C=O), and 1 587 cm^{-1}; $\lambda_{max.}$(EtOH) 238 (ε 21 600), 250sh (19 300), 278 (19 100), 287 (18 300), 380sh (6 200), 398 (10 300), and 418 nm (9 500); δ (360 MHz; $CDCl_3$) 2.45 (1 H, dd, *J* 15.5 and 7.7 Hz, 10-H_β), 2.54 (1 H, dd, *J* 15.1 and 2.6 Hz, 8-H_β), 2.90 (1 H, ddd, *J* 15.1, 3.2, and 2.2 Hz, 8-H_α), 3.00 (3 H, s, OMe), 3.47 (1 H, dd, *J* 6.8 and 2.2 Hz, 6a-H), 3.55 (1 H, dt, apparent *J* 15.5, 2, and 2 Hz, 10-H_α), 3.67 (1 H, dt, apparent *J* 7.3, 7.3, and 1.7 Hz, 10a-H), 4.23 (1 H, q, apparent *J* 2, 2, and 2 Hz, 7-H), 7.71—7.78 and 8.41—8.47 (each 2 H, m, 1-, 2-, 3-, and 4-H), and 12.94 and 13.72 (each 1 H, s, 5- and 12-OH) (addition of D_2O caused the signals at δ 12.94 and 13.72 to disappear); *m/z inter alia* 340 (M^+) and 240 (base peak) (Found: C, 67.15; H, 4.7%; M^+, 340.0957. $C_{19}H_{16}O_6$ requires C, 67.05; H, 4.75%; *M*, 340.0947).

Reaction of the Epoxypentaone (**12a**) *with Zinc–Acetic Acid.*—To a stirred solution of the epoxypentaone (**12a**) (0.100 g, 0.28 mmol) in dry THF (4 cm^3) at 0 °C was added activated zinc[24] (0.100 g, 0.28 mmol) and acetic acid (2 cm^3). After 3 min, water (15 cm^3) was added and the resultant mixture was extracted (2 ×) with dichloromethane. The organic extract, after washing with water, aqueous sodium hydrogen carbonate, and water, was dried ($MgSO_4$) and evaporated. Recrystallisation of the residue from methanol gave a material (0.075 g, 78%) that was identical (m.p. and ^1H n.m.r. spectroscopy) with the dihydroxytrione (**13a**) obtained by reduction of the epoxypentaone (**12a**) with sodium dithionite.

Reaction of the Dihydroxytrione (**13a**) *with Ethynylmagnesium Bromide.*—(*a*) To a vigorously stirred solution of the dihydroxytrione (**13a**) (1.00 g, 2.94 mmol) in dry THF (40 cm^3) at 0 °C under argon was added, in drops, a THF solution of *ca.* 1M-ethynylmagnesium bromide[25] (12 cm^3, *ca.* 12 mmol). After being warmed to 25 °C, the mixture was stirred for 14 h and then diluted with dichloromethane and saturated aqueous ammonium chloride. Evaporation of the dried ($MgSO_4$) organic layer and recrystallisation of the residue from chloroform gave (6aRS,7SR,9SR,10aRS)-9-*ethynyl*-6a,7,8,9,-10,10a-*hexahydro*-5,9,12-*trihydroxy*-7-*methoxynaphthacene*-6,11-*dione* (**14a**) (0.753 g, 70%) as yellow needles showing the following properties: m.p. 176—178 °C (decomp. with softening at 170 °C); $\nu_{max.}$(KBr) *inter alia* 3 520 and 3 440br (OH), 1 640 and 1 607 (C=O), and 1 580 cm^{-1}; $\lambda_{max.}$(EtOH) 239 (ε 22 200), 255 (21 000), 279 (18 200), 287 (16 400), 380sh (6 800), 400 (11 500), and 409 nm (11 800); δ (300 MHz; $CDCl_3$) 1.89br (1 H, d, apparent *J* 14 Hz, 8-H_β), 1.99 (1 H, dd, *J* 14.5 and 6.0 Hz, 10-H_β), 2.54 (1 H, s, C≡CH), 2.64br (1 H, d, apparent *J* 14 Hz, 8-H_α), 3.16 (3 H, s, OMe), 3.16—3.22br (2 H, m, 10-H and 6a-H), 3.39 (1 H, dt, apparent *J* 6, 6, and 3 Hz, 10a-H), 3.68br (1 H, s, 9-OH), 4.03br (1 H, s, w_H 10 Hz, 7-H), 7.74—7.82 and 8.44—8.51 (each 2 H, m, 1-, 2-, 3-, and 4-H), and 13.25 and 13.80 (each 1 H, s, 5- and 12-OH) (addition of D_2O caused the signals at δ 3.68, 13.25, and 13.80 to disappear) (irradiation at δ 1.89 caused the signal at 2.64 to collapse to a br s and that at 4.03 to sharpen; irradiation at 1.99 caused the signal at δ 3.39 to sharpen; irradiation at δ 4.03 caused the signal at δ 3.16—3.22 to sharpen); *m/z inter alia* 366 (M^+, base peak) (Found: C, 68.9; H, 4.8%; M^+, 366.1120. $C_{21}H_{18}O_6$ requires C, 68.85; H, 4.95%; *M*, 366.1103).

(*b*) To a stirred solution of the dihydroxytrione (**13a**) (1.80 g, 5.29 mmol) in dry THF (140 cm^3) at 0 °C was added a THF solution of *ca.* 1M-ethynylmagnesium bromide[25] (180 cm^3, *ca.* 180 mmol). After 25 min, the mixture was poured into saturated aqueous ammonium chloride (400 cm^3) and extracted with dichloromethane (2 × 300 cm^3). After washing with water and drying ($MgSO_4$), the organic extract was evaporated to leave a solid residue which, on the basis of 300 MHz ^1H n.m.r. spectroscopy, was a *ca.* 1:1 mixture of the ethynyldiones (**14a**) and (**20**).

Reaction of the Dihydroxytrione (**13a**) *with Lithium Acetylide.*—(*a*) In a flame-dried apparatus under nitrogen, lithium acetylide (*ca.* 12 mmol) was prepared by bubbling acetylene for 1 h into a hexane solution of 1.55M-n-butyl-lithium (8 cm^3, 12.4 mmol) and dry THF (30 cm^3) at −78 °C. To this stirred solution was added a solution of the dihydroxytrione (**13a**) (0.400 g, 1.18 mmol) in THF (5 cm^3) in one portion under an atmosphere of acetylene. After 1 h, the mixture was allowed to warm to room temperature and poured into saturated aqueous ammonium chloride (30 cm^3). The mixture was extracted with chloroform and the extract was dried ($MgSO_4$) and evaporated to leave a *ca.* 1:2 mixture of compounds (**14a**) and (**20**) (0.360 g). Repeated recrystallisation of the mixture from chloroform provided (6aRS,7SR,9SR,10aSR)-9-*ethynyl*-6a,7,8,9,10,10a-*hexahydro*-5,9,12-*trihydroxy*-7-*methoxynaphthacene*-6,11-*dione* (**20**), as pale-yellow crystals, which showed the following properties: m.p. 207—210 °C (decomp.); $\nu_{max.}$(KBr) *inter alia* 3 420 (OH), and 1 635 and 1 613 cm^{-1} (C=O); $\lambda_{max.}$(EtOH) 237 (ε 21 000), 250 (20 200), 276 (16 800), 284 (14 900), 378sh (6 100), 396 (10 200), 414 (10 100), and 418sh nm (9 200); δ (360 MHz; $CDCl_3$) 1.74 (1 H, dd, *J* 14.9 and 2.3 Hz, 8-H_β), 1.89 (1 H, dd, *J* 14.1 and 12.0 Hz, 10-H_β), 2.52 (1 H, s, C≡CH), 2.61 (1 H, dt, apparent *J* 14.9, 2.8, and 2.8 Hz, 8-H_α), 2.82 (1 H, dd, *J* 13.5 and 2.5 Hz, 6a-H), 2.94 (1 H, dt, apparent *J* 14.1, 2.9, and 2.9 Hz, 10-H_α), 3.52 (1 H, ddd, *J* 13.5, 12.0, and 2.9 Hz, 10a-H), 3.57 (3 H, s, OMe), 4.49 (1 H, q, apparent *J* 2.5, 2.5, and 2.5 Hz, 7-H), 4.71 (1 H, s, 9-OH), 7.74—7.78 and 8.42—8.45 (each 2 H, m, 1-, 2-, 3-, and 4-H), and 13.44 and 13.66 (each 1 H, s, 5- and 12-OH); *m/z inter alia* 366 (M^+) (Found: C, 68.8; H, 4.75. $C_{21}H_{18}O_6$ requires C, 68.85; H, 4.95%.

(*b*) The foregoing reaction was repeated but the concentration of lithium acetylide was reduced three-fold. Work-up as before gave the ethynyldione (**14a**). After recrystallisation from chloroform, the sample (m.p. 174—176 °C) was identical (n.m.r. spectroscopy) with that obtained from the reaction of the dihydroxydione (**13a**) with ethynylmagnesium bromide.

Reaction of the Ethynyldiones (**14a**) *and* (**20**) *with Lead*(IV) *Acetate.*—(*a*) A mixture of the ethynyldione (**14a**) (0.450 g, 1.23 mmol) and lead(IV) acetate (0.650 g, 1.5 mmol) in acetic acid (10 cm^3) was stirred and, after 24 h, the orange-red precipitate was collected by filtration, washed with water, and dried (*in vacuo*; $CaCl_2$). The derived (7SR,9SR)-9-*ethynyl*-7,8,9,10-*tetrahydro*-6,9,11-*trihydroxy*-7-*methoxynaphthacene*-5,12-*dione* (**15a**) (0.330 g, 73%) was recrystallised from chloroform and the sample, obtained as shiny-red plates, showed the following properties: m.p. 228—236 °C (decomp.); $\nu_{max.}$(KBr) *inter alia* 3 430 and 3 260 (OH), 1 625 (C=O), and 1 590 cm^{-1}; $\lambda_{max.}$-

(EtOH) 209 (ε 15 000), 252 (38 000), 256sh (34 100), 286 (7 700), 466sh (8 200), 480 (9 100), and 515 nm (5 700); δ (300 MHz; $CDCl_3$) 2.06 (1 H, dd, *J* 14.8 and 3.8 Hz, 8-H_β), 2.58 (1 H, s, C≡CH), 2.84 (1 H, dt, apparent *J* 14.8, 2.0, and 2.0 Hz, 8-H_α), 2.96 (1 H, d, *J* 19.1 Hz, 10-H_β), 3.64 (3 H, s, OMe), 3.66 (1 H, dd, *J* 19.1 and 1.9 Hz, 10-H_α), 4.87 (1 H, dd, *J* 3.6 and 2.2 Hz, 7-H), 5.02 (1 H, s, 9-OH), 7.83—7.86 and 8.35—8.38 (each 2 H, m, 1-, 2-, 3-, and 4-H), and 13.34 and 13.58 (each 1 H, s, 6- and 11-OH) (addition of D_2O caused the signals at δ 5.02, 13.34, and 13.58 to disappear); *m/z inter alia* 364 (M^+) and 332 ($M^+ - CH_4O$, base peak) (Found: C, 69.1; H, 4.25%; M^+, 364.0950. $C_{21}H_{16}O_6$ requires C, 69.25; H, 4.45%; *M*, 364.0947).

(*b*) A *ca.* 1:1 mixture of the ethynyldiones (**14a**) and (**20**) [obtained from the reaction of the dihydroxytrione (**13a**) (1.80 g, 5.29 mmol) with excess HC≡CMgBr] was stirred with lead(IV) acetate (2.35 g, 5.30 mmol) and acetic acid (35 cm^3), at 50—60 °C for 2 h and at room temperature for 24 h. Water (100 cm^3) was added to the mixture which was then extracted (3 ×) with dichloromethane. After washing with water, aqueous sodium hydrogen carbonate, and water, the organic extract was dried ($MgSO_4$) and evaporated. Recrystallisation of the residue from chloroform–methanol gave a material [1.32 g, 69% based on (**13a**)] that was identical (m.p. and ^1H n.m.r. spectroscopy) with the ethynyldione (**15a**) obtained in procedure (*a*).

Reaction of the Ethynyldione (**15a**) *with Mercury*(II) *Oxide–Sulphuric Acid.*—A vigorously stirred mixture of the ethynyldione (**15a**) (0.140 g, 0.38 mmol), red mercury(II) oxide (0.210 g, 0.97 mmol), acetone (25 cm^3), and 7% sulphuric acid (14 cm^3) was briefly heated under reflux and allowed to cool to room temperature. The mixture was then diluted with *ca.* 1M-hydrochloric acid (20 cm^3) and extracted with dichloromethane (50 cm^3). After washing with water, the organic extract was dried ($MgSO_4$) and evaporated to leave (±)-4-demethoxy-7-*O*-methyldaunomycinone (**3b**) (0.131 g, 90%) as a red solid. A sample, after recrystallisation from chloroform, showed the following properties: m.p. 230—234 °C (lit.,[11] 250—254 °C); $\nu_{max.}$(KBr) *inter alia* 3 400 (OH), 1 715 and 1 625 (C=O), and 1 590 cm^{-1}; $\lambda_{max.}$(EtOH) 207 (ε 8 200), 235sh (7 400), 252 (18 600), 257sh (16 400), 285 (14 000), 458 (3 800), 480 (4 600), 500sh (3 300), and 514 nm (2 700); δ (360 MHz; $CDCl_3$) 1.96 (1 H, dd, *J* 15 and 3.2 Hz, 8-H_β), 2.43 (3 H, s, COMe), 2.43 (1 H, dt, apparent *J* 15, 2.2, and 2.2 Hz, 8-H_α), 2.98 (1 H, dd, *J* 19.0 and 0.6 Hz, 10-H_β), 3.27 (1 H, dd, *J* 19.0 and 2.0 Hz, 10-H_α), 3.63 (3 H, s, OMe), 4.93 (1 H, ddd, *J* 3.2, 2.2, and 0.6 Hz, 7-H), 5.09 (1 H, s, 9-OH), 7.82—7.85 and 8.34—8.37 (each 2 H, m, 1-, 2-, 3-, and 4-H), and 13.32 and 13.57 (each 1 H, s, 6- and 11-OH) (addition of D_2O caused the signals at δ 5.09, 13.32, and 13.57 to disappear); *m/z inter alia* 382 (M^+) and 307 ($M^+ - C_3H_7O_2$, base peak) (Found: M^+, 382.1062. Calc. for $C_{21}H_{18}O_7$: *M*, 382.1052. Found: C, 64.05; H, 4.7. Calc. for $C_{21}H_{18}O_7$ 0.5 H_2O. C, 64.45; H, 4.85%).

Reaction of the Methyl Ether (**3b**) *with Trimethylsilyl Iodide.*—A suspension of the methyl ether (**3b**) (0.070 g, 0.19 mmol) in redistilled chloroform (1 cm^3) was treated with trimethylsilyl iodide (0.068 cm^3, 0.48 mmol). After 15 min, the brown mixture was treated with methanol (1 cm^3) and the crimson solution was diluted with chloroform and washed twice with aqueous sodium thiosulphate. Evaporation of the dried ($MgSO_4$) solution left a red solid (0.065 g) which contained three major components (t.l.c.); these were separated by preparative t.l.c. [$CHCl_3$–light petroleum b.p. 40—60 °C) (4:1) as eluant].

The least polar material, isolated as a red solid (0.016 g, 23%), was considered to be (±)-4-demethoxy-7,9-dideoxydaunomycinone (**22a**). A sample, recrystallised from chloroform–diethyl ether, showed the following properties: m.p. 183—185 °C (lit.,[13] 180—182 °C); $\nu_{max.}$(KBr) *inter alia* 1 710 and 1 622 (C=O), and 1 593 cm^{-1}; $\lambda_{max.}$(EtOH) 207 (ε 10 600), 230sh (8 100), 253 (24 200), 257sh (23 700), 288 (4 700), 454 (4 600), 480 (5 400), 500 (3 400), and 512 nm (3 400); δ (360 MHz; $CDCl_3$) 1.71—1.82 and 2.21—2.30 (each 1 H, m, 8-H_2), 2.30 (3 H, s, COMe), 2.64—2.86 and 3.00—3.14 (3 H and 2 H, each m, 9-H, 7- and 10-H_2), 7.78—7.83 and 8.30—8.34 (each 2 H, m, 1-, 2-, 3-, and 4-H), and 13.45 and 13.49 (each 1 H, s, 6- and 11-OH) (addition of D_2O caused the signals at δ 13.45 and 13.49 to disappear); *m/z inter alia* 336 (M^+, base peak) (Found: M^+, 336.0998. Calc. for $C_{20}H_{16}O_5$: *M*. 336.0997).

The material of intermediate polarity, obtained as a red solid (0.006 g, 9%), was identical (t.l.c. and n.m.r. spectroscopy) with the starting methyl ether (**3b**).

The most polar material, isolated as a red solid (0.006 g, 9%), was (±)-4-demethoxy-7-deoxydaunomycinone (**22b**). The sample, recrystallised from chloroform, showed m.p. 196—198 °C (lit., 160—162 °C[14] and 210—211 °C[15]). It was identical (i.r., u.v., and mass spectroscopy) with the material obtained by reduction of the methyl ether (**3b**) with sodium dithionite.

Reaction of the Methyl Ether (**3b**) *with Sodium Dithionite.*—To a stirred mixture of the methyl ether (**3b**) (0.350 g, 0.92 mmol) in a 1:1 mixture of THF–methanol (14 cm^3) was added potassium carbonate (1.26 g, 9.16 mmol) followed, after 5 min, by a solution of sodium dithionite (85%, 0.58 g, 2.8 mmol) in water (5 cm^3) (added in drops). When no starting material remained (*ca.* 15 min, t.l.c.), the mixture was diluted with *ca.* 1M-hydrochloric acid (20 cm^3) when a red solid precipitated. The solid was extracted into dichloromethane and the solution was washed with *ca.* 0.1M-hydrochloric acid followed by water. Evaporation of the dried ($MgSO_4$) organic layer gave (±)-4-demethoxy-7-deoxydaunomycinone (**22b**) (0.280 g, 86%) as a red solid. The sample, after recrystallisation from chloroform, showed the following properties: m.p. 196—198 °C (lit., 160—162 °C[14] and 210—211 °C[15]); $\nu_{max.}$(KBr) 3 500 (OH), 1 700 and 1 620 (C=O), and 1 588 cm^{-1}; $\lambda_{max.}$(EtOH) 207 (ε 10 300), 230sh (7 800), 253 (23 500), 288 (4 500) 320sh (1 800), 454sh (4 400), 480 (5 500), 500 (3 700), and 512 nm (3 700); δ (360 MHz; $CDCl_3$) 1.89—2.05 (2 H, m, 8-H_2), 2.39 (3 H, s, COMe), 2.83—3.12 (4 H, m, 7- and 10-H_2), 3.79br (1 H, s, 9-OH), 7.76—7.82 and 8.25—8.30 (each 2 H, m, 1-, 2-, 3-, and 4-H), and 13.36 (2 H, s, 6- and 11-OH) (addition of D_2O caused the signals at δ 3.79 and 13.36 to disappear); *m/z inter alia* 352 (M^+) and 309 ($M^+ - C_2H_3O$, base peak) (Found: M^+, 352.0952. Calc. for $C_{20}H_{16}O_6$: *M*, 350.0947).

Reaction of the Methyl Ether (**3b**) *with Trifluoroacetic Acid–Ammonia.*—A solution of the methyl ether (**3b**) (0.200 g, 0.52 mmol) in trifluoroacetic acid (5 cm^3) was left at room temperature. When the starting material had disappeared (*ca.* 24 h, n.m.r. spectroscopy), the solution was evaporated to a red gum which was treated with 2M-ammonium hydroxide solution (50 cm^3). After extraction with dichloromethane, the organic layer was washed with dilute hydrochloric acid and water, dried ($MgSO_4$), and evaporated. Fractionation of the product by silica-gel chromatography [$CHCl_3$–light petroleum (b.p. 40—60 °C) (1:1) as eluant] gave (±)-4-demethoxydaunomycinone (**3a**) (0.080 g. 42%) as a red solid. The sample, recrystallised from benzene, showed the following properties: m.p. 160—164 °C (lit., 167—170 °C,[9] 173—175 °C,[18] 183 °C,[7] 183—185 °C[17]); $\nu_{max.}$(KBr) 3 450br (OH), 1 715 and 1 625 (C=O), and 1 585 cm^{-1}; $\lambda_{max.}$(EtOH) 208 (ε 16 400), 237sh (15 600), 252 (35 000), 257sh (30 700), 285 (7 000), 325sh (2 000), 465sh (6 400), 480 (7 700), 500sh (5 100), and 514 nm (5 100); δ (360 MHz; $CDCl_3$) 2.18 (1 H, dd, *J* 14.5 and 4.9 Hz, 8-H_β), 2.34 (1 H, dt, apparent *J* 14.5, 2.0, and 2.0 Hz, 8-H_α), 2.42 (3 H, s, COMe), 2.96 (1 H, d, *J* 18.6 Hz, 10-H_β), 3.20 (1 H, dd, *J* 18.6 and 2.0 Hz, 10-H_α), 3.77 (1 H, d, *J* 5.7 Hz, 7-OH), 4.53 (1 H, s, 9-OH), 5.30—5.34 (1 H, m, 7-

H), 7.83—7.85 and 8.33—8.36 (each 2 H, m, 1-, 2-, 3-, and 4-H), and 13.31 and 13.59 (each 1 H, s, 6- and 11-OH) [addition of D_2O caused the signals at 3.77, 4.53, 13.31, and 13.59 to disappear and those centred at 5.32 to simplify to a dd (*J* 4.9 and 2 Hz)]; *m/z inter alia* 368 (M^+, base peak) (Found: C, 65.5; H, 4.1%; M^+, 368.0919. Calc. for $C_{20}H_{16}O_7$: C, 65.20; H, 4.40%; *M*, 368.0896).

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