The Use of 3-Acetoxy-1-trimethylsilylbutadiene in the Synthesis of Anthracyclinone Derivatives

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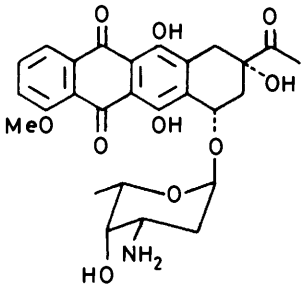
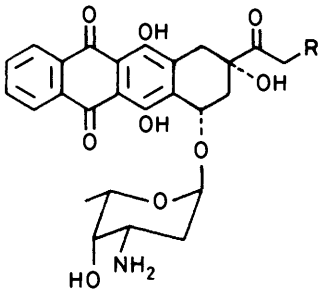
The Diels–Alder reaction of quinizarin quinone (**14**) with 3-acetoxy-1-trimethylsilylbutadiene (**15**) affords a tetracyclic adduct, (±)-3-acetoxy-1,4,4aα,12aα-tetrahydro-1β-trimethylsilylnaphthacene-5,6,11,12-tetraone (**16**) in excellent yield. The simultaneous introduction of the C-7 trimethylsilyl substituent in this process allowed later ready conversion into a C-7 acetoxy group by treatment with lead tetra-acetate. The tetracyclic compound (**16**) was converted in a convenient multistep process into 4-demethoxydaunomycinone (**51**) in 41% overall yield from (**14**). Compound (**51**) was further elaborated to 14-acetoxy-4-demethoxydaunomycinone (**4**) by standard reactions, again in good yield (70% overall).

As part of a continuing programme of anthracyclinone synthesis we sought routes which would allow rapid and efficient construction of the tetracyclic skeleton common to the antitumour compound daunorubicin (**1**). The route needed to be amenable to substrate modification and it was hoped would permit the preparation of several grammes of material.



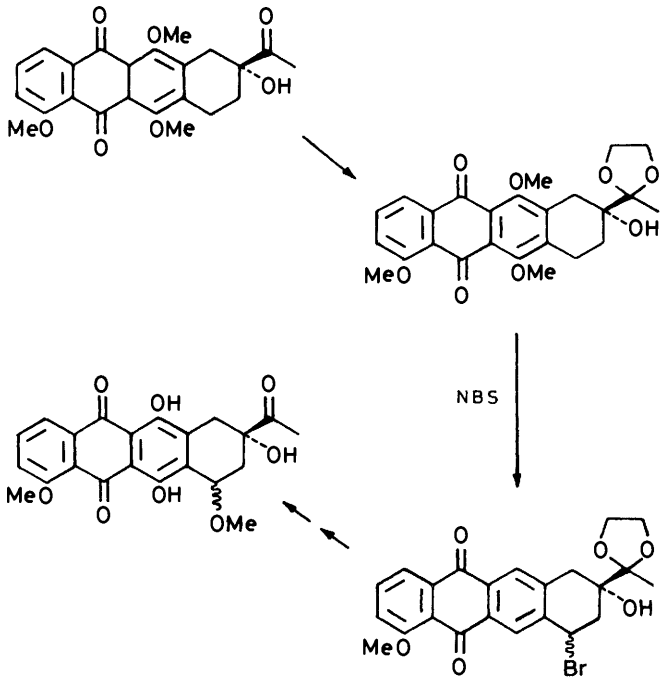
(**1**)



(**2**) R = H
(**3**) R = OH

In view of reports that 4-demethoxydaunorubicin (**2**) and 4-demethoxyadriamycin (**3**) show increased potency [1] over their natural counterparts and are more easily prepared, our attention was focused on these derivatives.

Although many general synthetic schemes to anthracyclinone derivatives are now known [2–5] very few properly address the problem of the introduction of the C-7 functional group. Most rely upon the inefficient process of benzylic bromination



Scheme 1.

followed by nucleophilic displacement and equilibration first introduced by Wong in 1971 [3] (Scheme 1).

The major experimental difficulty associated with any form of early C-7 oxygenation is that of ready A-ring aromatisation as soon as the natural C-7,9 dioxygenated pattern is obtained.[4]

In a communication in 1978 Garland and Pappo reported the use of the trimethylsilyl grouping as an elegant form of latent C-7 oxygenation.[5] The overall route afforded considerable scope for modification and improvement, and could also provide an entry into the rhodomycinone and 11-deoxyanthracyclinone series which are currently being recognised as potential replacements for adriamycin-derived drugs.[6]

In conjunction with G. D. Searle Limited, we have reinvestigated this approach and herein report full experimental details and new modifications for the preparation of 4-demethoxyadriamycinone 14-acetate (**4**) and the elucidation of a number of previously unidentified reaction products.

Hence, reaction of butyn-3-ol with two equivalents of freshly generated ethylmagnesium bromide in tetrahydrofuran (THF) afforded the dianion as the pale grey THF 'ate' complex.

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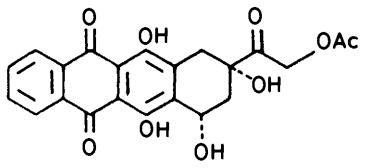
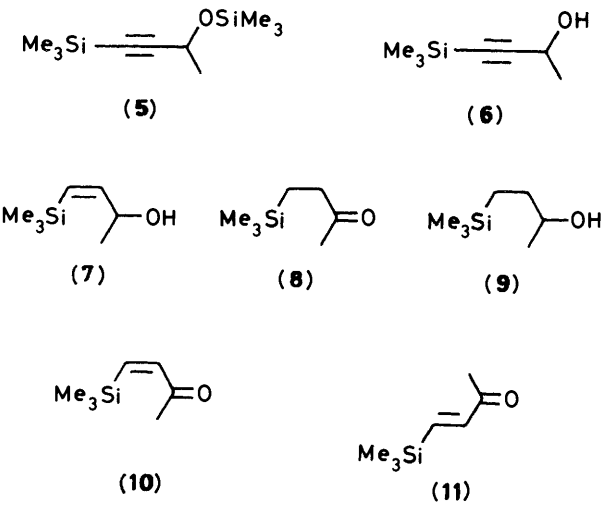


(4)

Quenching of this intermediate with two equivalents of chlorotrimethylsilane allowed isolation of the bis-silylated material (**5**). Alternatively, addition of water and separation of the organic layer followed by treatment with aqueous acid and ethereal extraction led to the trimethylsilylacetylene (**6**).

Partial catalytic hydrogenation of (**6**) over pre-activated palladium–barium sulphate until one equivalent of hydrogen was absorbed resulted in formation of the *cis*-olefin (**7**). Immediate removal of the catalyst on completion of the reaction was necessary in order to avoid isomerisation to (**8**). An authentic sample of (**8**) was prepared by exhaustive catalytic hydrogenation of the triple bond of (**6**) to afford (**9**) which easily underwent Jones oxidation to give (**8**). Jones oxidation of alcohol (**7**) in acetone–water led to the volatile enone (**10**). Optimum yield of this material was obtained by ethereal extraction followed by removal of the solvent by careful fractional distillation. Enone (**10**) was invariably contaminated with the isomeric enone (**11**)[7,8] as evidenced by high-field ^{1}H n.m.r. spectroscopy, due to the acidic reaction conditions. Indeed, extended reaction times allowed isolation of (**11**) as the major product with only traces of (**10**) remaining. Alternatively, immediate work-up followed by double-bond isomerisation in acidic aqueous propan-2-ol also gave (**11**).

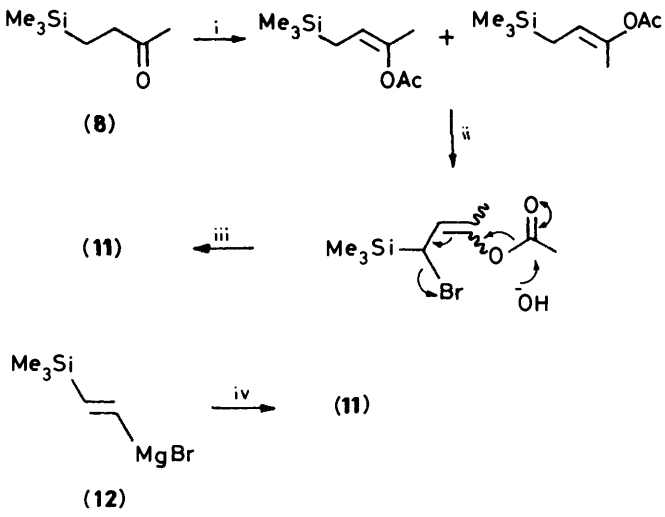
Two other routes to (**11**) are available in the literature: from Grignard reagent (**12**)[7] and from ketone (**8**)[8] (Scheme 2).



(5) (6) (7) (8) (9) (10) (11)

Lithium aluminium hydride is well known to reduce allyl alcohols to hydroxyalkanes[9] and simple propargyl alcohols to *trans*-olefins.[10] Alcohol (**6**) was subjected to this reaction with the intention of avoiding the *cis–trans* isomerisation step and subsequent tedious work-up. However, although (**13**) was obtained as the major product, *cis*-analogue (**7**) was also present [(**13**):(**7**) 5:1].

Quinizarin quinone (**14**) was obtained in 61% yield from commercial quinizarin by the method of Dimroth and Hilcken[11] conveniently carried out on a 100 gramme scale. Bifunctionalised diene (**15**) was prepared in 78% yield from



Scheme 2. *Reagents:* i, Ac_2O–H^+ (30%); ii, NBS; iii, ^-OH; iv, Ac_2O (66%)

enone (**11**) by reaction with neat anhydrous isopropenyl acetate in the presence of an acid catalyst. Cycloaddition of freshly doubly distilled (**15**) with quinone (**14**) at 50 °C in benzene solution produced, in 96% yield, the pale golden tan cycloadduct (**16**) which is stable in the diketo form in the absence of base.

Treatment of this adduct with dilute aqueous sodium hydroxide followed by acidification afforded ketone (**17**) which, in accord with the earlier report,[5] did not undergo Grignard ethynylation presumably because of extensive enolisation of the C-2 carbonyl group.

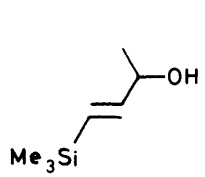
Catalytic reduction of (**16**), however, afforded the orange *leuco*-quinizarin (**18**) in excellent yield. Acidic methanolysis of the vinyl acetate moiety of (**18**) under vigorous reflux afforded acetal (**19**), isolated in 95% yield by filtration of the well chilled solution as a bright yellow feathery solid, from which ketone (**20**) was quantitatively obtained after hydrolysis in strongly acidic conditions.

Up to this stage the best results were obtained by using the compounds as first isolated without further purification. However, (**20**) was routinely purified by crystallisation since the subsequent Grignard reaction proved sensitive to minor impurities.

In order to investigate whether a compound such as (**21**) could be formed directly from (**16**), thus avoiding the *leuco* intermediate, cycloadduct (**16**) was subjected to similar acidic methanolysis conditions as for (**18**) above in the hope of isolating the acetal (**22**) or (**23**). Remarkably the only product observed, in 65% yield, was acetal (**19**). This reductive transformation can perhaps be explained on the basis that the necessary molecule of hydrogen was derived from the solvent possibly *via* a radical process. No such solvent-mediated reduction of a quinone diketone 'iso-quinizarin' to a *leuco*-quinizarin seems to have been previously reported. That such a reaction should take place rather than ring-B isomerisation is noteworthy.

Trione (**20**) could be selectively ethynylated at C-2 to give an 8.3:1 mixture of isomers, using cold ethynylmagnesium bromide in THF as solvent. A high yield of the carbinols (**24**) was isolated and the isomers could be separated by chromatography or by difficult fractional crystallisation. The major isomer (**25**) was acetylated under acidic conditions providing the monoacetate (**26**).

Stoodley has reported the direct conversion of the *leuco*-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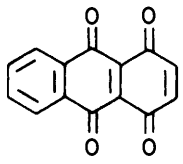
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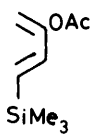
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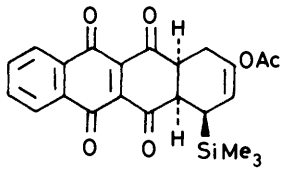
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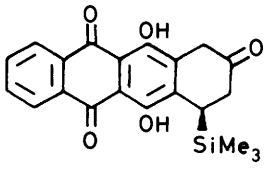
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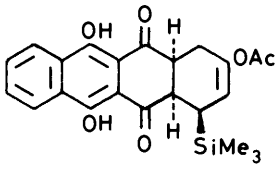
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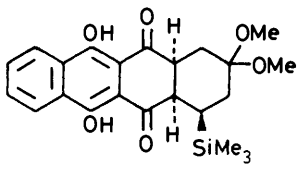
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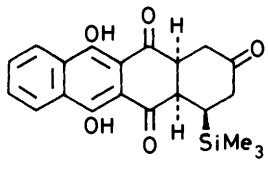
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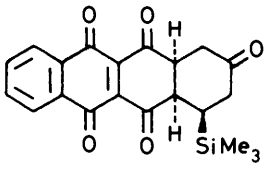
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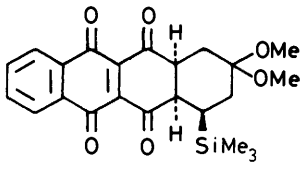
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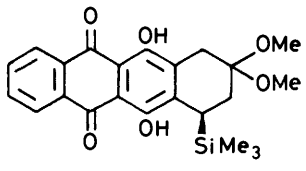
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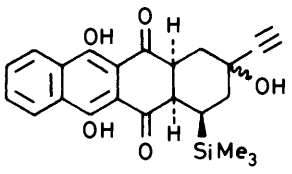
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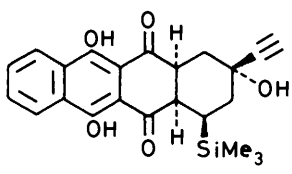
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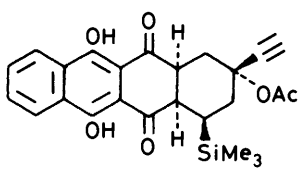
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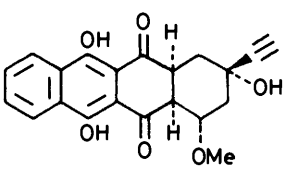
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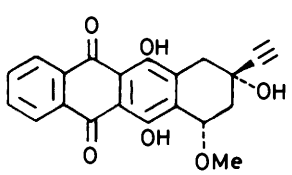
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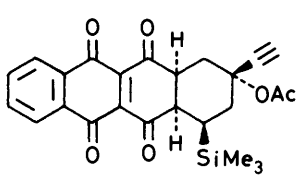
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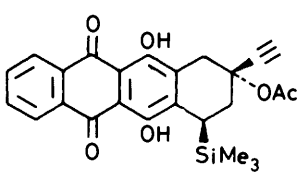
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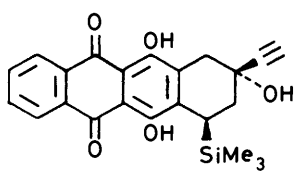
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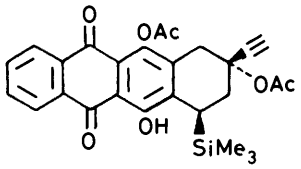
quinizarin (**27**) into the quinizarin (**28**) in the presence of lead tetra-acetate.[12] In our hands, however, (**26**) gave only the stable bright pink quinone diketone (**29**) on oxidation with this reagent at room temperature. Ring-B isomerisation to afford (**30**) as highly crystalline red plates was accomplished by treatment with potassium acetate in a minimum volume of acetic acid at 100 °C. Chromatography of the mother liquors afforded a further sample of (**30**) and also a small quantity of (**26**) despite use of a considerable excess of lead tetra-acetate in the oxidation step. All attempts to convert the tertiary alcohol (**25**) directly into the quinizarin (**31**) were unsuccessful. Similar reactions of trione (**20**) led cleanly to (**17**) *via* (**21**) in 21% yield.

A major strength of the above synthesis lies in the use of inherent C-7 functionalisation. The novel use of the trimethylsilyl moiety as a potential hydroxy group avoids the possibility of elimination to afford a fully aromatic bisanhydro species, and could be a useful process in other systems. A report by Kalman in 1972 noted that aryl trimethylsilanes could be converted into the corresponding aryl trifluoroacetates by treatment with lead tetrakistrifluoroacetate.[13] Garland and Pappo discovered that benzyltrimethylsilane underwent a comparable reaction although neither of these reactions occurred with lead tetra-acetate even in refluxing acetic acid.[5] However, reaction of diacetate (**32**) with lead tetra-acetate in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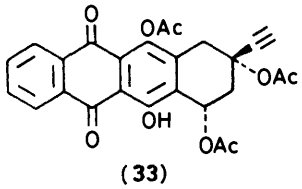
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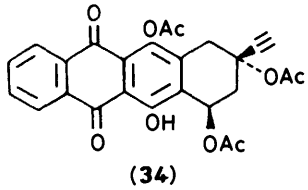
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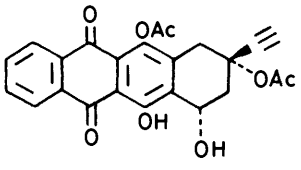
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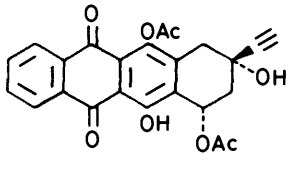
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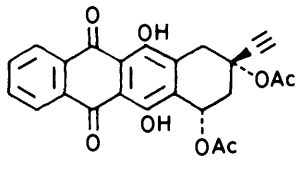
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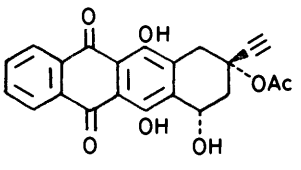
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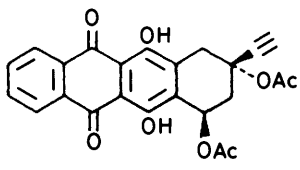
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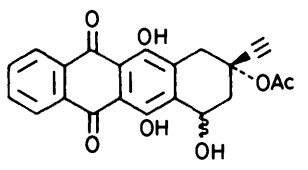
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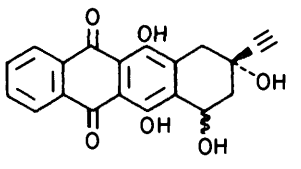
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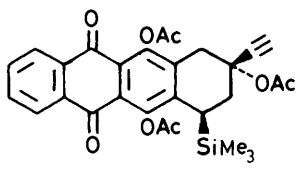
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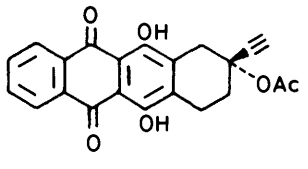
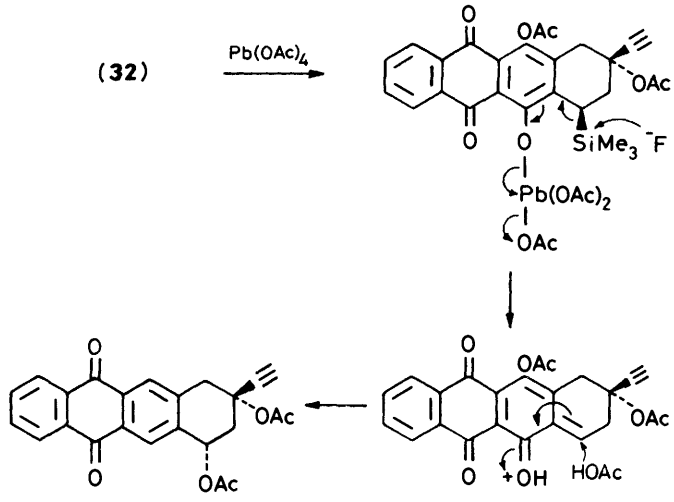

(43)

acetic acid, with a trace of water as catalyst, led to a mixture of the four compounds (**33**)—(**36**). Further, reaction of acetate (**30**) under similar conditions caused rapid B-ring oxidation followed by slow silyl displacement, accelerated by the addition of fluoride ion, to afford (**37**) and (**38**) after metabisulphite reduction of the diquinone moiety in 79 and 7% yield respectively. In our hands this reaction provided the bright orange diacetate (**37**) in 71% yield, and the C-7 epimeric acetate (**39**) in 1—2% yield, monoacetates (**40**) in 4% yield, and diols (**41**) in up to 1.5% yield.

An important mechanistic consideration is that neither (**42**) nor (**43**) reacted in this way with lead tetra-acetate.

A possible rationale for the reaction of (**32**) is shown in Scheme 3. Attack by water rather than by acetic acid in the third step accounts for the proportion of alcohols observed. Assuming that the acetoxy group dominates the stereochemistry of ring A, steric congestion as shown may be the cause of the large proportion of 'incorrect' isomer, with a *trans* arrangement of C-7 and C-9 substituents, found in the product mixture. It should be noted that benzylsilanes are normally quite unreactive towards electrophiles.[14] In the case of compound (**30**) oxidation to the diquinone occurs as the first step preventing *O*-metallation by lead tetra-acetate as proposed in Scheme 3. Nucleophilic attack of intermediate (**44**) by acetic acid, as in the previous mechanism, would not account for the observed diquinone oxidation state of the product. Steric congestion in (**44**) would be lessened by comparison with the 11-acetoxy species which explains the higher stereoselectivity observed. The small quantities of C-7 alcohols found are presumably formed in this case by hydrolysis (Scheme 4).

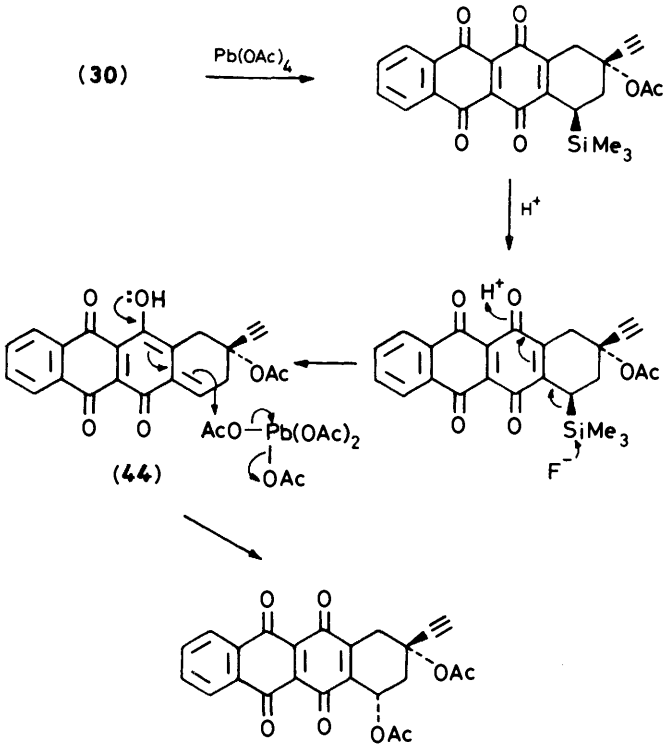
From the foregoing discussion it is clear that the tedious



Scheme 3.

separation of ethynyl epimers of (**24**) proposed by Garland and Pappo is quite unnecessary; whatever the stereochemical outcome of the Grignard reaction the stereochemistry of the final product will be determined only by the silyl displacement reaction.

Accordingly, the mixture of epimers (**24**) obtained from the ethynylation reaction was converted without separation *via* acetates (**45**) and quinizarins (**46**) into the desired oxygenated product (**37**) in 66% overall yield. An attempt was made to convert the quinizarin (**17**) into the oxygenated species (**47**) as



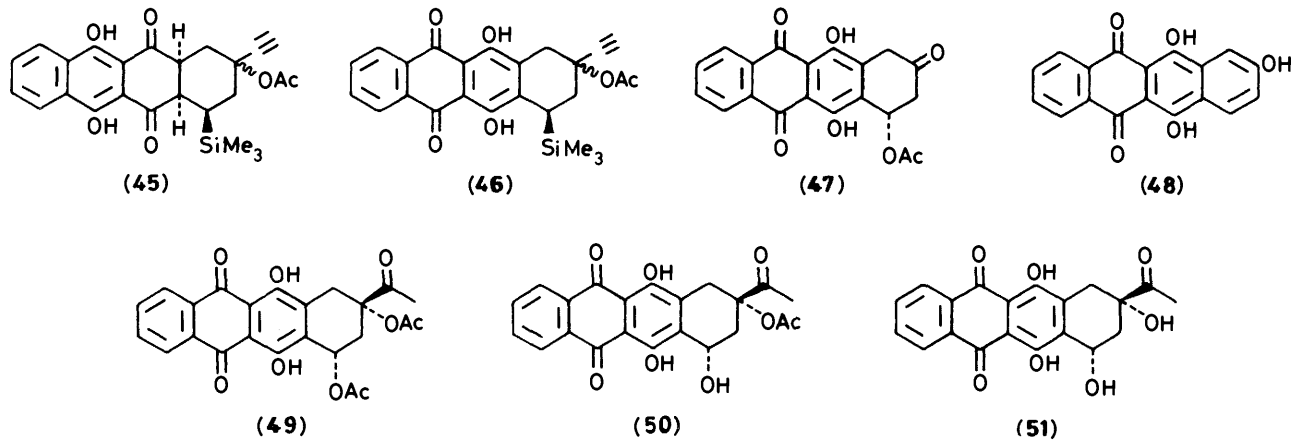
Scheme 4.

demethoxydaunomycinone (**51**) was completed by straightforward acid hydrolysis of (**49**) in aqueous propan-2-ol in 97% yield, and in an overall yield of 41% from (**6**).

In an effort to develop novel anthracyclinone C-9 side-chains and to improve further the Pappo route the addition of a vinyl substituent as opposed to the normal ethynyl grouping was investigated. It was anticipated that the vinyl unit would be more readily modified either by Wacker-type oxidation or by a *cis*-hydroxylation procedure. However, it was shown that addition of vinylmagnesium bromide to ketone (**20**) was less regioselective and also less stereoselective than the corresponding reaction with acetylene Grignard reagent. Thus the two epimers (**52**) and (**53**) were obtained in approximately equal proportions together with a number of more polar materials presumaby resulting from a second addition of the reagent to the C-5 or C-12 carbonyl groups. Acetylation of the mixture of (**52**) and (**53**) as before afforded the acetates (**54**); however, upon reaction of (**54**) with lead tetra-acetate and potassium fluoride a number of products were formed.

In a model study for side-chain elaboration the mixture of (**52**) and (**53**) was subjected to Wacker oxidation conditions; however, none of the desired methyl ketone derivative could be obtained.

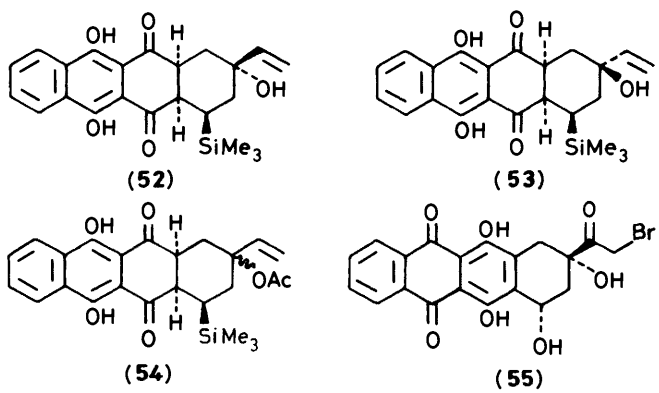
Conversion of (±)-4-demethoxydaunomycinone (**51**) into the adriamycinone series was next examined. Arcamone has reported the conversion of (+)-daunomycinone, derived from the natural product, into (+)-adriamycinone in a three-step sequence[16] and a similar conversion of daunorubicin into adriamycin.[17] Russian workers have also reported an analogous transformation in the carminomycinone series.[18]



this could conceivably allow the addition to (**47**) of carbanion units containing rather more labile functional groups that would normally be destroyed by acid or lead tetra-acetate. In the event, however, (**17**) underwent very rapid conversion into the fully aromatic bisanhydro species (**48**) in good yield. Compound (**48**) was identified by its comparatively non-polar t.l.c. behaviour, physical appearance, and examination of the 250 MHz ^{1}H n.m.r. spectrum which shows only aromatic protons and the loss of the characteristic ring A high-field signals.

Hydration of the triple bond of diacetate (**37**) could be achieved using the method of Stavely[15] [mercury(II) chloride, aniline, and water in refluxing benzene] to give a variable mixture of diacetate (**49**) and monoacetate (**50**) in 87% combined yield. Alternatively this reaction could be accomplished using the well known mercury(II) oxide–sulphuric acid–acetone method in 82% yield without any deprotection of the secondary acetate unit being observed. The synthesis of (±)-4-

The synthetic (±)-4-demethoxydaunomycinone (**51**) obtained as described above was accordingly transformed into the



14-bromide (**55**) by treatment with one equivalent of bromine in chloroform solution in 84% yield. Conversion of (**54**) into (±)-4-demethoxyadriamycinone 14-acetate (**4**) was straightforward and was achieved in 70% yield. The best conditions were found to be reaction of (**55**) with excess of freshly fused sodium acetate in boiling acetone for 30—45 min. These yields are noticeably higher than those for the corresponding transformations in the natural series.

Experimental

M.p.s were determined on a Kofler hot-stage apparatus. I.r. spectra were recorded on Perkin-Elmer 197 and 298 spectrophotometers as thin films for liquids and Nujol mulls for solids. ^{1}H N.m.r. spectra were determined on Varian EM-360A, XL-100, and Bruker WM 250 instruments using Me_4Si as internal standard. Mass spectra were recorded on a V.G. Micromass 7070 spectrometer at 70 eV. Column chromatography was performed under pressure using silica gel (Merck 9385). All solvents were purified and dried by standard methods. Ether is diethyl ether.

Preparation of 4-*Trimethylsilylbut*-3-*yn*-2-*ol* (**6**).—Magnesium turnings (39 g) were placed in a dry 2 l three-neck flask and sufficient dry ether or dry freshly distilled THF to cover the magnesium was added. A solution of ethyl bromide (154 g, 1.41 mol) in ether (or THF) (100 ml) was added dropwise to the stirred mixture at such a rate as to maintain gentle boiling. (Some external cooling was necessary.) After complete formation of the Grignard reagent, but-3-yn-2-ol (40 g, 0.57 mol) was added dropwise to the stirred mixture to cause precipitation of the dimetallated species as a grey solid in THF or as a black highly viscous syrup in ether. A solution of chlorotrimethylsilane (200 g, 1.84 mol) in ether or THF (200 ml) was added dropwise to the stirred mixture which was then stored overnight. After filtration the solid collected was washed very thoroughly with ether and the combined organic solutions were washed in turn with water, dil. hydrochloric acid, and water, and dried over $MgSO_4$. The solution was concentrated to ≃200 ml, methanol (100 ml) and dil. hydrochloric acid (100 ml) were added, and the solution was stirred at room temperature for 1 h. Water (400 ml) was added and the solution was extracted with ether. The extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was distilled to give 4-*trimethylsilylbut*-3-*yn*-2-*ol* (**6**) (66 g, 81%), as an oil, b.p. 54—56 °C at 0.5 mmHg; $\nu_{max.}$ 3 340, 2 980, 2 960, 2 930, 2 900, 2 175, 1 250, 1 115, 1 075, and 1 045 cm^{-1}; δ(CCl_4; 60 MHz) 4.55 (1 H, q, *J* 7 Hz), 2.6 (1 H, br s), 1.5 (3 H, d, *J* 7 Hz), and 0.2 (9 H, s) (Found: C, 59.0; H, 10.1. $C_7H_{14}OSi$ requires C, 59.10; H, 9.92%).

Preparation of 4-*Trimethylsilylbutan*-2-*ol* (**9**).—4-Trimethylsilylbut-3-yn-2-ol (**6**) (6.50 g, 45.8 mmol) was added to benzene (40 ml) and the solution was agitated under slight positive pressure of hydrogen in the presence of palladium–barium sulphate (0.65 g; 5%) as a catalyst until the absorption of gas ceased. The catalyst was removed by filtration and the solution was evaporated under reduced pressure. The residue was purified by chromatography to give 4-trimethylsilylbutan-2-ol (**9**) as an oil (6.39 g, 96%), b.p. 50—52 °C at 0.35 mmHg; $\nu_{max.}$ 3 340, 2 950, 2 900, 1 410, 1 325, 1 300, 1 260, and 1 180 cm^{-1}; δ ($CDCl_3$; 250 MHz) 3.59—3.73 (1 H, m), 2.16 (1 H, br s), 1.30—1.47 (2 H, m), 1.15 (3 H, d, *J* 6 Hz), 0.34—0.62 (2 H, m), and 0.05 (9 H, s).

Preparation of 4-*Trimethylsilylbutan*-2-*one* (**8**).—4-Trimethylsilylbutan-2-ol (**9**) (6.0 g, 41.1 mmol) was dissolved in acetone (100 ml), and one molar equivalent of Jones reagent [formed from chromium trioxide (4.15 g), water (30 ml), and sulphuric acid (4 ml)] was added slowly to the stirred solution, the internal temperature being maintained below 10 °C by ice-bath cooling. After completion of the reaction the solution was decanted and the inorganic residues washed with ether. Water (50 ml) was added to the combined organic solutions and the mixture was extracted with ether (3 × 100 ml). The combined organic layers were washed with water and dried over $MgSO_4$ and the solvents removed by distillation. The residue was purified by chromatography to give 4-*trimethylsilylbutan*-2-*one* (**8**) (4.8 g, 81%) as an oil, b.p. 171—174 °C; $\nu_{max.}$ 2 950, 2 920, 2 895, 1 720, 1 410, 1 360, 1 250, 1 220, 1 190, and 1 040 cm^{-1}; δ ($CDCl_3$; 250 MHz) 2.35—2.45 (2 H, m), 2.15 (3 H, s), 0.7—0.8 (2 H, m), and 0.05 (9 H, s) (Found: C, 58.4; H, 11.3. $C_7H_{16}OSi$ requires C, 58.26; H, 11.17%).

Preparation of (Z)-4-*Trimethylsilylbut*-3-*en*-2-*ol* (**7**).—(*a*) Palladium–barium sulphate catalyst was placed in a 1 l flask together with benzene (300 ml) and the mixture was shaken under slight positive pressure of hydrogen until absorption of gas ceased. Quinoline (2.5 ml) was added followed by 4-trimethylsilylbut-3-yn-2-ol (**6**) (50 g, 0.35 mol) and the mixture was agitated under slight positive pressure of hydrogen until 8 450 ml of gas had been absorbed. The catalyst was removed and the filtrate washed in turn with dil. hydrochloric acid (200 ml) and water (200 ml), and dried over $MgSO_4$. The solvent was removed under reduced pressure and the yellow oily residue distilled to give 4-*trimethylsilylbut*-3-*en*-2-*ol* (**7**) (47.5 g, 94%), as an oil, b.p. 34—38 °C at 0.3 mmHg; $\nu_{max.}$ 3 340, 2 955, 2 920, 2 870, 2 850, 1 620, 1 450, 1 370, 1 250, 1 110, and 1 050 cm^{-1}; δ ($CDCl_3$; 250 MHz) 6.25 (1 H, dd, *J* 9 and 14 Hz), 5.60 (1 H, dd, *J* 1 and 14 Hz), 4.45 (1 H, ddq, *J* 1, 6, and 9 Hz), 2.2 (1 H, br s), 1.25 (3 H, d, *J* 6 Hz), and 0.15 (9 H, s); *m*/*z* 144 (Found: C, 58.2; H, 11.3. $C_7H_{16}OSi$ requires C, 58.27; H, 11.18%).

Preparation of (Z)- *and* (E)-4-*Trimethylsilylbut*-3-*en*-2-*ol* (**7**) *and* (**13**).—(*b*) 4-Trimethylsilylbut-3-yn-2-ol (**6**) (1.10 g, 7.75 mmol) was added to anhydrous THF (10 ml) and the mixture was cooled to 0 °C. Lithium aluminium hydride (300 mg, 7.8 mmol) was added slowly and the mixture was stirred until effervescence ceased. After the solution had been cooled to −50 °C, dil. hydrochloric acid (2 ml) was added and the mixture was filtered. The filtrate was evaporated and redissolved in ether (25 ml) and the ethereal solution was washed with water (25 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by flash column chromatography to afford a mixture of double-bond isomers of 4-trimethylsilylbut-3-en-2-ol (**7**) and (**13**) (635 mg, 57%) in a *Z*:*E* ratio of 1:5. For the (*E*)-compound, $\nu_{max.}$ 3 340, 2 950, 2 920, 2 870, 2 850, 1 610, 1 370, 1 250, 1 110, and 1 070 cm^{-1}; δ ($CDCl_3$; 60 MHz) 5.7—6.0 (2 H, m) 3.2—3.6 (1 H, m), 2.6 (1 H, br s), 1.2 (3 H, d, *J* 6 Hz), and 0.1 (9 H, s).

Preparation of (Z)- *and* (E)-*4-Trimethylsilylbut*-3-*en*-2-*one* (**10**) *and* (**11**).—(*Z*)-4-Trimethylsilylbut-3-en-2-ol (**7**) (47.5 g, 0.33 mol) was dissolved in acetone (400 ml) and the solution cooled using an ice–salt bath. Jones reagent [1 mol equiv., prepared from chromium trioxide (35 g), water (250 ml), and sulphuric acid (30 ml)] was added at such a rate as to maintain the internal temperature below 10 °C. Working up at this point gave largely (*Z*)-4-trimethylsilylbut-3-en-2-one (**10**). Alternatively, after addition was complete the mixture was stirred overnight, water (500 ml) added, and the solution extracted with ether (2 × 400 ml). The combined extracts were washed with water, dried over $MgSO_4$, and the solvents removed by distillation at atmospheric pressure. Propan-2-ol (150 ml) and conc. hydrochloric acid (5 ml) were added to the residue and the mixture was stirred overnight at room temperature. Ether

(1 500 ml) was added and the solution was washed three times with water. The combined aqueous extracts were washed with ether and the combined ethereal extracts dried over $MgSO_4$. The solvents were removed by distillation at atmospheric pressure and the residue distilled to give (E)-4-*trimethylsilylbut*-3-*en*-2-*one* (**11**) (31.5 g, 67%), as an oil, b.p. 165—169 °C; $\nu_{max.}$ 3 000, 2 960, 2 900, 1 680, 1 420, 1 360, 1 250, 1 220, and 1 190 cm^{-1}; δ ($CDCl_3$; 60 MHz) 7.0 (1 H, d, *J* 20 Hz), 6.35 (1 H, d, *J* 20 Hz), 2.3 (3 H, s), and 0.2 (9 H, s) (Found: C, 58.9; H, 10.2. $C_7H_{14}OSi$ requires C, 59.10; H, 9.92%). For (*Z*)-enone, δ ($CDCl_3$; 60 MHz) 6.85 (1 H, d, *J* 14 Hz), 6.25 (1 H, d, *J* 14 Hz), 2.3 (3 H, s), and 0.2 (9 H, s).

Preparation of (E)-3-*Acetoxy*-1-*trimethylsilylbuta*-1,3-*diene* (**15**).—Benzene (120 ml) and toluene-*p*-sulphonic acid hydrate (1.6 g) were placed in a 250 ml flask and about 80 ml of solvent was removed by distillation at atmospheric pressure. Isopropenyl acetate (120 ml) was added and the distillation was resumed until the boiling point reached 96 °C. The solution was allowed to cool under a dry argon atmosphere and (*E*)-4-trimethylsilylbut-3-en-2-one (**11**) (20.0 g, 141 mmol) was added. The flask was placed in an oil-bath maintained at 85—90 °C and the contents were stirred for 24 h. The solvents were removed under reduced pressure and the residue distilled to give (*E*)-1-trimethylsilyl-3-acetoxybuta-1,3-diene (**15**) (20.3 g, 78%), as an oil, b.p. 42—48 °C at 0.15 mmHg; $\nu_{max.}$ 2 950, 1 760, 1 675, 1 630, 1 580, 1 420, 1 365, 1 250, 1 200, 1 185, and 1 015 cm^{-1}; δ ($CDCl_3$; 60 MHz) 6.3 (1 H, d, *J* 20 Hz), 5.8 (1 H, d, *J* 20 Hz), 4.8—5.0 (2 H, m,), 2.2 (3 H, s), and 0.1 (9 H, s).

Preparation of Anthracene-1,4,9,10-*tetraone* (**14**).—Quinizarin (100 g, 0.42 mol), glacial acetic acid (250 ml), and lead tetra-acetate (200 g) were placed in a mortar and ground together for 15 min during which time the mixture darkened to a dark red-brown and became viscous. The syrupy mixture was filtered at the pump and the solid washed thoroughly with water and air-dried. The brown solid was dissolved in hot nitrobenzene (1 350 ml) and the solution filtered at the pump while hot. After the mixture had cooled, carbon disulphide (2 700 ml) was added to the filtrate and the mixture was stirred and kept for 2 h at room temperature after which the crystalline solid was removed by filtration and washed with carbon disulphide to give anthracene-1,4,9,10-tetraone (quinizarin quinone) (**14**) as yellow-brown needles (60.1 g, 61%), $\nu_{max.}$ 2 950, 2 920, 2 840, 1 680, 1 640, 1 620, 1 590, 1 465, 1 375, 1 280, 1 260, and 1 140 cm^{-1}; δ ($CDCl_3$; 250 MHz) 8.05—8.15 (2 H, m), 7.8—7.9 (2 H, m), and 6.95 (2 H, s); *m/z* 240 (M^+ + 2).

Preparation of (±)-3-*Acetoxy*-1,4,4aα,12aα-*tetrahydro*-1β-*trimethylsilylnaphthacene*-5,6,11,12-*tetraone* (**16**).—Anthracene-1,4,9,10-tetraone (**14**) (8.97 g, 37.7 mmol) was dissolved in benzene (250 ml) and about 20 ml of solvent was removed by distillation at atmospheric pressure to remove water azeotropically. The solution was cooled under dry argon to about 50 °C and freshly prepared (*E*)-1-trimethylsilyl-3-acetoxybuta-1,3-diene (**15**) (5.4 g, 29.4 mmol) was added. The reaction vessel was placed in an oil-bath maintained at 55 °C and the contents were stirred for 4 d. The reaction mixture was allowed to cool whilst being stirred overnight, cyclohexane (25 ml) was added, and the mixture was chilled to −10 °C. Filtration through a sintered glass funnel provided golden-tan crystals of (±)-3-*acetoxy*-1,4,4aα,12aα-*tetrahydro*-1β-*trimethylsilylnaphthacene*-5,6,11,12-*tetraone* (**16**) (11.9 g, 96%), which could be recrystallised from benzene, m.p. 196—199 °C; $\nu_{max.}$ 2 950, 2 920, 2 850, 1 740, 1 720, 1 705, 1 665, 1 590, 1 460, 1 370, 1 270, 1 245, and 1 210 cm^{-1}; δ ($CDCl_3$; 250 MHz) 8.05—8.15 (2 H, m), 7.80—7.90 (2 H, m), 5.48 (1 H, br s), 3.75 (1 H, dd, *J* 5 and 5 Hz), 3.44—3.57 (1 H, m), 2.19—2.53 (2 H, m), 2.10 (3 H, s), 1.86—1.94 (1 H, m), and 0.2 (9 H, s); *m/z* 424 (M^+ + 2) (Found: C, 65.3; H, 5.1. $C_{23}H_{22}O_6Si$ requires C, 65.38; H, 5.25%).

Preparation of (±)-1,2,3,4-*Tetrahydro*-5,12-*dihydroxy*-4-*trimethylsilylnaphthacene*-2,6,11-*trione* (**17**).—(*a*) A suspension of (±)-3-acetoxy-1,4,4aα,12aα-tetrahydro-1β-trimethylsilylnaphthacene-5,6,11,12-tetraone (**16**) (2.0 g, 4.74 mmol) in methanol (100 ml) was stirred and cooled to 0 °C and a solution of sodium hydroxide (300 mg, 7.50 mmol) in methanol (50 ml) was added dropwise. The dark purple solution was stirred overnight at room temperature. Acidification with conc. hydrochloric acid caused formation of a red precipitate which was collected on a sintered glass funnel, washed thoroughly with water, and air-dried to give (±)-1,2,3,4-tetrahydro-5,12-dihydroxy-4-trimethyl silylnaphthacene-2,6,11-trione (**17**) (1.35 g, 75%) as a red solid. $\nu_{max.}$ 2 960, 2 920, 2 850, 1 710, 1 620, 1 580, 1 570, 1 510, 1 500, 1 465, 1 375, 1 360, 1 265, 1 230, 1 210, 1 165, 1 150, and 1 065 cm^{-1}; δ ($CDCl_3$; 100 MHz) 13.71 (1 H, s), 13.55 (1 H, s), 8.28—8.67 (2 H, m), 7.71—8.01 (2 H, m), 3.18—3.63 (2 H, m), 2.38—2.93 (2 H, m), 1.19—1.45 (1 H, m), and 0.15 (9 H, s); *m/z* 380.

Preparation of (±)-3-*Acetoxy*-1,4,4aα,12aα-*tetrahydro*-6,11-*dihydroxy*-1β-*trimethylsilylnaphthacene*-5,12-*dione* (**18**).—(±)-3-Acetoxy-1,4,4aα,12aα-tetrahydro-1β-trimethylsilylnaphthacene-5,6,11,12-tetraone (**16**) (10.0 g, 23.7 mmol) was placed in a 2 l flask and suspended in freshly distilled THF (800 ml). Palladium–barium sulphate catalyst (2.0 g) was added and the mixture was agitated under slight positive pressure of hydrogen until absorption of gas ceased. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The orange-yellow residue was triturated with ethyl acetate (200 ml) and the mixture filtered at the pump to give (±)-3-*acetoxy*-1,4,4aα,12aα-*tetrahydro*-6,11-*dihydroxy*-1β-*trimethylsilylnaphthacene*-5,12-*dione* (**18**) (9.24 g, 92%) as a yellow solid which could be recrystallised from benzene–cyclohexane or benzene–ether, m.p. 219—223 °C (decomp.); $\nu_{max.}$ 2 920, 2 865, 2 850, 1 750, 1 675, 1 640, 1 615, 1 580, 1 495, 1 460, 1 390, 1 370, 1 330, 1 295, 1 285, 1 240, 1 210, 1 160, and 1 150 cm^{-1}; δ ($CDCl_3$; 250 MHz) 13.38 (1 H, s), 13.32 (1 H, s), 8.42—8.54 (2 H, m), 7.71—7.84 (2 H, m), 5.52 (1 H, br s), 3.55 (1 H, dd, *J* 5.2 and 5.2 Hz), 3.26—3.39 (1 H, m), 2.40—2.53 (2 H, m), 2.09 (3 H, s), 1.91—2.00 (1 H, m), and 0.14 (9 H, s); *m/z* 424 (Found: C, 65.2; H, 5.6. $C_{23}H_{24}O_6Si$ requires C, 65.07; H, 5.70%).

Preparation of (±)-1,2,3,4,4aα,12aα-*Hexahydro*-6,11-*dihydroxy*-3,3-*dimethoxy*-1β-*trimethylsilylnaphthacene*-5,12-*dione* (**19**).—(*a*) (±)-3-Acetoxy-1,4,4aα,12aα-tetrahydro-6,11-dihydroxy-1β-trimethylsilylnaphthacene-5,12-dione (**18**) (6.0 g, 14.2 mmol) was suspended in methanol (250 ml) and conc. hydrochloric acid (6.0 ml) was added. The mixture was heated under reflux and vigorously stirred for 4 h, allowed to cool, and chilled to −20 °C. The solid was removed using a sintered glass funnel and washed with cold methanol to give (±)-1,2,3,4,4aα,12aα-*hexahydro*-6,11-*dihydroxy*-3,3-*dimethoxy*-1β-*trimethylsilylnaphthacene*-5,12-*dione* (**19**) (5.78 g, 95%) as yellow flakes which could be recrystallised from benzene or from methylene dichloride–methanol, m.p. 209—211 °C; $\nu_{max.}$ 2 920, 2 840, 1 635, 1 610, 1 570, 1 500, 1 460, 1 395, 1 370, 1 295, 1 250, 1 240, 1 165, 1 150, 1 115, 1 100, and 1 040 cm^{-1}; δ ($CDCl_3$; 250 MHz) 13.64 (1 H, s), 13.61 (1 H, s), 8.41—8.53 (2 H, m), 7.72—7.82 (2 H, m), 3.32 (1 H, dd, *J* 3.8 and 4.2 Hz); 3.10—3.23 (1 H, m), 3.19 (3 H, s), 3.17 (3 H, s), 2.21—2.33 (1 H, m), 1.92—2.04 (1 H, m), 1.49—1.56 (2 H, m), 1.05 (1 H, ddd, *J* 3.3, 3.7, and 13.8 Hz), and 0.15 (9 H, s); *m/z* 428 (Found: C, 64.2; H, 6.55. $C_{23}H_{28}O_6Si$ requires C, 64.46; H, 6.59%).

Preparation of (±)-1,2,3,4,4aα,12aα-*Hexahydro*-6,11-*dihydroxy*-4β-*trimethylsilylnaphthacene*-2,5,12-*trione* (**20**).—(±)-1,2,3,4,4aα,12aα-Hexahydro-6,11-dihydroxy-3,3-dimethoxy-1β-trimethylsilylnaphthacene-5,12-dione (**19**) (12.0 g, 28.0 mmol) was dissolved in neat trifluoroacetic acid (80 ml) under an atmosphere of dry argon, and water (18 ml) was added dropwise to the stirred solution during 1 h using a motorised syringe. Further water (80 ml) was added and the reaction mixture was thoroughly homogenised. After filtration at the pump the solid product was well washed with water and air-dried to give (±)-1,2,3,4,4aα,12aα-*hexahydro*-6,11-*dihydroxy*-4β-*trimethylsilylnaphthacene*-2,5,12-*trione* (**20**) (10.8 g, 100%) which was crystallised from benzene–ether to afford yellow needles, m.p. 205—208 °C; $\nu_{max.}$ 2 920, 2 840, 1 710, 1 635, 1 610, 1 580, 1 500, 1 460, 1 370, 1 285, 1 240, 1 220, 1 180, and 1 145 cm^{-1}; δ ($CDCl_3$; 250 MHz) 13.55 (1 H, s), 13.50 (1 H, s), 8.45—8.57 (2 H, m), 7.74—7.89 (2 H, m), 3.47—3.58 (1 H, m), 3.37 (1 H, ddd, *J* 4.8, 5.8, and 14.4 Hz), 2.31—2.76 (4 H, m), 1.33 (1 H, ddd, *J* 3.8, 3.8, and 14.4 Hz), and 0.17 (9 H, s); *m/z* 382 (Found: C, 66.0; H, 5.8. $C_{21}H_{22}O_5Si$ requires C, 65.94; H, 5.80%).

Preparation of (±)-1,2,3,4,4aα,12aα-*Hexahydro*-6,11-*dihydroxy*-3,3-*dimethoxy*-1β-*trimethylsilylnaphthacene*-5,12-*dione* (**19**).—(*b*) A suspension of (±)-3-acetoxy-1,4,4aα,12aα-tetrahydro-1β-trimethylsilylnaphthacene-5,6,11,12-tetraone (**16**) (1.0 g, 2.37 mmol) in methanol was vigorously stirred and heated under reflux in the presence of conc. hydrochloric acid (0.5 ml) for 15 h. The mixture was chilled to −20 °C, and the solid was collected on a sintered glass funnel and washed with cold methanol to give (±)-1,2,3,4,4aα,12aα-hexahydro-6,11-dihydroxy-3,3-dimethoxy-1β-trimethylsilylnaphthacene-5,12-dione (**19**) (656 mg, 65%), as yellow flakes, identical with previous samples.

Preparation of (±)-3β-*Ethynyl*-1,2,3,4,4aα,12aα-*hexahydro*-3α,6,11-*trihydroxy*-1β-*trimethylsilylnaphthacene*-5,12-*dione* (**25**) *and* (±)-3α-*Ethynyl*-1,2,3,4,4aα,12aα-*hexahydro*-3β,6,11-*trihydroxy*-1β-*trimethylsilylnaphthacene*-5,12-*dione*.—Freshly dried and distilled THF (100 ml) was placed in a dry 500 ml three-neck flask which was externally cooled using an ice-bath. Purified acetylene was bubbled through the solvent for about 2 h and a solution of ethylmagnesium bromide, freshly prepared from magnesium turnings (4.0 g) and ethyl bromide (14.3 g, 131 mmol), was then added dropwise to the reaction flask by syringe with the acetylene still flowing; the formation of a deep red colour was observed. After the addition was complete the temperature was allowed to rise to 10 °C and the flow of acetylene was halted. The flask was cooled to an external temperature of −30 °C causing precipitation of the Grignard reagent THF 'ate' complex as a grey solid. A solution of (±)-1,2,3,4,4aα,12aα-hexahydro-6,11-dihydroxy-4β-trimethylsilylnaphthacene-2,5,12-trione (**20**) (5 g, 13.1 mmol) in THF (200 ml) was added dropwise to the stirred suspension. The mixture was stirred at −20 °C for a further 30 min after the addition was complete and then at 0 °C for 1 h. A saturated aqueous solution of ammonium chloride (50 ml) was added dropwise, followed by a mixture of conc. hydrochloric acid (60 ml) and water (60 ml), and finally water (120 ml). The solution was concentrated under reduced pressure, the residue was extracted with ether, and the extract was dried over $MgSO_4$. The solvent was removed under reduced pressure; crystallisation of the residue from benzene–cyclohexane afforded a 8.3:1 diastereoisomeric mixture of the 3β- and 3α-ethynyl carbinols (**24**) (5.0 g, 94%). Alternatively the residue could be dissolved in the minimum volume of methylene dichloride (30 ml) and twice this volume of cyclohexane was added to give yellow crystals of (±)-3β-ethynyl-1,2,3,4,4aα,12aα-hexahydro-3α,6,11-trihydroxy-1β-trimethylsilylnaphthacene-5,12-dione (**25**) (3.36 g, 63%) which could be recrystallised from methylene dichloride–cyclohexane, benzene–cyclohexane, or ether–light petroleum (b.p. 40—60 °C) to give yellow needles of (**25**), m.p. 205—207 °C; $\nu_{max.}$ 3 530, 3 260, 2 920, 2 840, 1 630, 1 605, 1 500, 1 460, 1 390, 1 370, 1 360, 1 280, 1 240, 1 180, 1 150, and 1 050 cm^{-1}; δ ($CDCl_3$; 250 MHz) 13.64 (1 H, s), 13.60 (1 H, s), 8.42—8.56 (2 H, m), 7.73—7.84 (2 H, m), 3.22—3.38 (2 H, m), 2.63 (1 H, s), 2.20—2.30 (1 H, m), 2.18 (1 H, s), 1.91—2.02 (1 H, m), 1.69—1.79 (1 H, m), 1.61—1.69 (1 H, m), 1.18—1.29 (1 H, m), and 0.14 (9 H, s); *m/z* 408. The mother liquors were evaporated under reduced pressure and the residue crystallised from benzene–cyclohexane to provide a 1.4:1 diastereoisomeric mixture of the 3β- and 3α-ethynyl carbinols (1.13 g, 21%). For the 3α-ethynyl epimer: $\nu_{max.}$ 3 540, 3 300, 2 920, 2 850, 1 635, 1 610, 1 585, 1 500, 1 465, 1 375, 1 360, 1 280, 1 245, 1 190, 1 150, and 1 050, cm^{-1}; δ ($CDCl_3$; 250 MHz) 13.7 (1 H, s), 13.6 (1 H, s), 8.4—8.5 (2 H, m), 7.75—7.85 (2 H, m), 3.3—3.45 (2 H, m), 2.45 (1 H, s), 2.15—2.25 (1 H, m), 1.8—1.9 (1 H, m), 1.6—1.8 (2 H, m), 1.45 (1 H, br s), 1.35—1.45 (1 H, m), and 0.15 (9 H, s).

Preparation of (±)-3α-*Acetoxy*-3β-*ethynyl*-1,2,3,4,4aα,12aα-*hexahydro*-6,11-*dihydroxy*-1β-*trimethylsilylnaphthacene*-5,12-*dione* (**26**).—A suspension of (±)-3β-ethynyl-1,2,3,4,4aα,12aα-hexahydro-3α,6,11-trihydroxy-1β-trimethylsilylnaphthacene-5,12-dione (**25**) (3.0 g, 7.35 mmol) in isopropenyl acetate (45 ml) was stirred at room temperature for 24 h in the presence of toluene-*p*-sulphonic acid (150 mg). The solvent was removed under reduced pressure and the residue crystallised from methylene dichloride–ether to give (±)-3α-*acetoxy*-3β-*ethynyl*-1,2,3,4,4aα,12aα-*hexahydro*-6,11-*dihydroxy*-1β-*trimethylsilylnaphthacene*-5,12-*dione* (**26**) (2.69 g, 81%) as yellow needles, m.p. 211—212 °C; $\nu_{max.}$ 3 270, 2 920, 2 850, 1 740, 1 640, 1 610, 1 500, 1 465, 1 370, 1 360, 1 280, 1 235, 1 220, 1 210, 1 170, 1 145, 1 090, and 1 050 cm^{-1}; δ ($CDCl_3$; 250 MHz) 13.61 (1 H, s), 13.59 (1 H, s), 8.40—8.53 (2 H, m), 7.72—7.85 (2 H, m), 3.29—3.43 (2 H, m), 2.68—2.79 (1 H, m), 2.75 (1 H, s), 2.32—2.43 (1 H, m), 1.98 (3 H, s), 1.63—1.85 (2 H, m), 1.26—1.38 (1 H, m), and 0.16 (9 H, s); *m/z* 450 (Found: C, 66.5; H. 5.8. $C_{25}H_{26}O_6Si$ requires C, 66.64; H, 5.82%).

Preparation of (±)-3α-*Acetoxy*-3β-*ethynyl*-1,2,3,4,4aα,12aα-*hexahydro*-1β-*trimethylsilylnaphthacene*-5,6,11,12-*tetraone* (**29**) *and* (±)-9α-*Acetoxy*-9β-*ethynyl*-7,8,9,10-*tetrahydro*-6,11-*dihydroxy*-7β-*trimethylsilylnapthacene*-5,12-*dione* (**30**).—Lead tetra-acetate (3.0 g) was added to a suspension of (±)-3α-acetoxy-3β-ethynyl-1,2,3,4,4aα,12aα-hexahydro-6,11-dihydroxy-1β-trimethylsilylnaphthacene-5,12-dione (**26**) (2.0 g, 4.45 mmol) in glacial acetic acid (30 ml) and the mixture was stirred at room temperature for 30 min. Water (75 ml) was added and the precipitate was immediately collected on a sintered glass funnel, washed with water, and air-dried. The solid was redissolved in methylene dichloride and the solution was filtered at the pump and evaporated to dryness under reduced pressure to afford (±)-3α-acetoxy-3β-ethynyl-1,2,3,4,4aα,12aα-hexahydro-1β-trimethylsilylnaphthacene-5,6,11,12-tetraone (**29**) as a deep pink solid. Without further purification this material was dissolved in glacial acetic acid (20 ml) and a saturated solution of potassium acetate in glacial acetic acid (12 ml) was added. The mixture was maintained at 95 °C over a steam-bath for 3 h and water (2.0 ml) was then added. Filtration through a sintered glass funnel gave dark red crystals of (±)-9α-*acetoxy*-9β-*ethynyl*-7,8,9,10-*tetrahydro*-6,11-*dihydroxy*-7β-*trimethylsilylnaphthacene*-5,12-*dione* (**30**) (1.35 g, 68%), which could be recrystallised from methylene dichloride–ether, m.p. 205—207 °C; $\nu_{max.}$ 3 360, 2 920, 2 860, 1 755, 1 630, 1 615, 1 580, 1 465, and 1 020 cm^{-1}; δ ($CDCl_3$; 250 MHz) 13.72 (1 H, s), 13.58 (1 H, s), 8.27—8.37 (2 H, m), 7.74—7.87 (2 H, m), 3.78 (1 H, ddd, *J* 1, 2.5, and 16.7 Hz), 3.08 (1 H,

dddd, *J* 1.0, 1.7, 8.0, and 8.3 Hz), 2.95 (1 H, dd, *J* 1.7 and 16.7 Hz), 2.74 (1 H, ddd, *J* 2.5, 8.3, and 13.3 Hz), 2.42 (1 H, s), 2.22 (1 H, dd, *J* 8.0 and 13.3 Hz), 2.22 (3 H, s), and 0.1 (9 H, s); *m/z* 448 (Found: C, 66.9; H, 5.3. $C_{25}H_{24}O_6Si$ requires C, 66.94; H, 5.39%).

Preparation of (±)-1,2,3,4-*Tetrahydro*-5,12-*dihydroxy*-4β-*trimethylsilylnaphthacene*-2,6,11-*trione* (**17**).—(*b*) (±)-1,2,3,4,4aα,12aα-Hexahydro-6,11-dihydroxy-4β-trimethylsilylnaphthacene-2,5,12-trione (**20**) (2.0 g, 5.24 mmol) was dissolved in glacial acetic acid (60 ml) and lead tetra-acetate (5.0 g) was added. The mixture was stirred for 30 min, water (75 ml) was added, and the solids were removed by filtration at the pump and air-dried, then redissolved in benzene and the solution was filtered. Removal of the solvent under reduced pressure afforded (±)-1,2,3,4,4aα,12aα-hexahydro-4β-trimethylsilylnaphthacene-2,5,6,11,12-pentaone (**21**) *m/z* 378 ($M^+ - 2$) (Found: $M^+ - 2$, 378.0931. $C_{21}H_{20}O_5Si$ requires $M - 2$, 378.0923) which was dissolved in glacial acetic acid (30 ml). A saturated solution of potassium acetate in acetic acid (3.0 ml) was added and the solution was heated at 95 °C on a steam-bath for 3 h. Water (3.0 ml) was added and the cooled mixture was filtered to give (±)-1,2,3,4-tetrahydro-5,12-dihydroxy-4β-trimethylsilylnaphthacene-2,6,11-trione (**17**) (413 mg, 21%), identical with the previously prepared material.

Preparation of (±)-7α,9α-*Diacetoxy*-9β-*ethynyl*-7,8,9,10-*tetrahydro*-6,11-*dihydroxynaphthacene*-5,12-*dione* (**37**) *and* (±)-7β,9α-*Diacetoxy*-9β-*ethynyl*-7,8,9,10-*tetrahydro*-6,11-*dihydroxynaphthacene*-5,12-*dione* (**39**).—(*a*) Lead tetra-acetate (2.8 g) was added to a suspension of (±)-9α-acetoxy-9β-ethynyl-7,8,9,10-tetrahydro-6,11-dihydroxy-7β-trimethylsilylnaphthacene-5,12-dione (**30**) (1.2 g, 2.68 mmol) in glacial acetic acid (20 ml) and the mixture was stirred for 3 h at room temperature until all the red solid had dissolved. Potassium fluoride, dried *in vacuo*, (0.8 g) was added and the mixture was stirred overnight. Methylene dichloride (190 ml) was added and the mixture was filtered through a Celite pad. Sodium metabisulphite (disodium disulphite) (900 mg) was added to the filtrate and water (90 ml) was added dropwise to the stirred solution. After the addition was complete the organic layer was separated, washed with water, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was triturated with the minimum volume of ether to give (±)-7α,9α-*diacetoxy*-9β-*ethynyl*-7,8,9,10-*tetrahydro*-6,11-*dihydroxynaphthacene*-5,12-*dione* (**37**) (810 mg, 70%) which could be crystallised from methylene dichloride–ether to provide bright orange needles of (**37**), m.p. 265—267 °C; $\nu_{max.}$ 3 290, 2 960, 2 920, 2 850, 1 745, 1 735, 1 620, 1 585, 1 460, 1 400, 1 370, 1 335, 1 305, 1 260, 1 230, 1 210, 1 110, and 1 045 cm^{-1}; δ ($CDCl_3$; 250 MHz) 13.36 (1 H, s), 13.35 (1 H, s), 8.31—8.41 (2 H, m), 7.80—7.92 (2 H, m), 6.40 (1 H, dd, *J* 1.9 and 5.7 Hz), 3.76 (1 H, dd, *J* 2.0 and 18.5 Hz), 3.39 (1 H, ddd, *J* 1.9, 2.0, and 15 Hz), 2.99 (1 H, dd, *J* 0.9 and 18.5 Hz), 2.68 (1 H, s), 2.23 (1 H, ddd, *J* 0.9, 15, and 18.5 Hz), 2.06 (3 H, s), and 1.99 (3 H, s); *m/z* 434 (Found: C, 66.2; H, 4.1. $C_{24}H_{18}O_8$ requires C, 66.36; H, 4.18%). The mother liquors were evaporated and the residue separated by chromatography to give a diastereoisomeric mixture of the above compound and the 7β-acetoxy epimer (**39**) in a 1:1 ratio (30 mg, 2.6%). For the 7β-acetoxy compound: $\nu_{max.}$ 3 295, 2 920, 2 840, 1 740, 1 615, 1 580, 1 460, 1 400, 1 370, 1 335, 1 310, 1 265, 1 220, 1 140, and 1 020 cm^{-1}; δ ($CDCl_3$; 250 MHz) 13.45 (1 H, s), 13.34 (1 H, s), 8.32—8.40 (2 H, m), 7.81—7.90 (2 H, m), 6.41 (1 H, dd, *J* 6 and 6 Hz), 3.67—3.77 (1 H, m), 3.35—3.46 (1 H, m), 2.65—2.69 (2 H, m), 2.62 (1 H, s), 2.12 (3 H, s), and 2.06 (3 H, s). Also isolated was (±)-9α-acetoxy-9β-ethynyl-7,8,9,10-tetrahydro-6,7,11-trihydroxynaphthacene-5,12-dione as a diastereoisomeric mixture (**40**) (37 mg, 3.6%). For the major isomer: δ ($CDCl_3$; 250 MHz) 13.76 (1 H, s), 13.33 (1 H, s), 8.31—8.42 (2 H, m), 7.80—7.92 (2 H, m), 5.28—5.37 (1 H, m), 3.60 (1 H, br s), 3.35—3.45 (2 H, m), 2.86 (1 H, dd, *J* 5 and 14 Hz), 2.62 (1 H, s), 2.55 (1 H, dd, *J* 6 and 14 Hz), and 2.03 (3 H, s).

Preparation of (±)-3-*Acetoxy*-3-*ethynyl*-1,2,3,4,4aα,12aα-*hexahydro*-6,11-*dihydroxy*-1β-*trimethylsilylnaphthacene*-5,12-*dione* (**45**).—A suspension of (±)-3-ethynyl-1,2,3,4,4aα,12aα-hexahydro-3,6,11-trihydroxy-1β-trimethylsilylnaphthacene-5,12-dione as a mixture of diastereoisomers (**24**) (4.5 g, 11.0 mmol) in isopropenyl acetate (60 ml) was stirred at room temperature for 24 h in the presence of toluene-*p*-sulphonic acid (200 mg). The mixture was concentrated to about 20 ml at room temperature and cyclohexane (80 ml) was added. The solid was collected on a sintered glass funnel and washed with cyclohexane. The mother liquors were evaporated to dryness and the residue purified by chromatography to afford unchanged starting material (686 mg, 1.68 mmol) and a further portion of the above solid. The two portions were combined to afford (±)-3-acetoxy-3-ethynyl-1,2,3,4,4aα,12aα-hexahydro-6,11-dihydroxy-1β-trimethylsilylnaphthacene-5,12-dione (**45**) (4.15 g, 99%) as a mixture of diastereoisomers, data for the major isomer (**29**) as given above.

Preparation of (±)-9-*Acetoxy*-9-*ethynyl*-7,8,9,10-*tetrahydro*-6,11-*dihydroxy*-7β-*trimethylsilylnaphthacene*-5,12-*dione* (**46**).—Lead tetra-acetate (9.0 g) was added to a suspension of (±)-3-acetoxy-3-ethynyl-1,2,3,4,4aα,12aα-hexahydro-6,11-dihydroxy-1β-trimethylsilylnaphthacene-5,12-dione as a mixture of diastereoisomers (**45**) (6.0 g, 13.3 mmol) in glacial acetic acid (85 ml) and the mixture was stirred at room temperature for 30 min. Water (220 ml) was added and the precipitate was immediately collected on a sintered glass funnel, washed with water and ether, and air-dried. The solid was redissolved in methylene dichloride and the solution was filtered at the pump and evaporated to dryness under reduced pressure to afford the quinone as a deep pink solid which was immediately redissolved in glacial acetic acid. A saturated solution of potassium acetate in glacial acetic acid (7.0 ml) was added and the mixture was maintained at 95 °C over a steam bath for 3 h. Water (7.0 ml) was added and the cooled mixture was filtered at the pump to give dark red crystals which were washed thoroughly with water and air-dried. Chromatography of the mother liquors afforded unchanged starting material (320 mg, 0.71 mmol) and a further portion of the above product. The two portions were combined to give (±)-9-acetoxy-9-ethynyl-7,8,9,10-tetrahydro-6,11-dihydroxy-7β-trimethylsilylnaphthacene-5,12-dione (**46**) as a mixture of diastereoisomers (4.26 g, 76%).

Preparation of (±)-7α,9α-*Diacetoxy*-9β-*ethynyl*-7,8,9,10-*tetrahydro*-6,11-*dihydroxynaphthacene*-5,12-*dione* (**37**) *and* (±)-7β,9α-*Diacetoxy*-9β-*ethynyl*-7,8,9,10-*tetrahydro*-6,11-*dihydroxynaphthacene*-5,12-*dione* (**39**).—(*b*) Lead tetra-acetate (7.35 g) was added to a suspension of (±)-9-acetoxy-9-ethynyl-7,8,9,10-tetrahydro-6,11-dihydroxy-7β-trimethylsilylnaphthacene-5,12-dione as a mixture of diastereoisomers (**46**) (3.5 g, 7.82 mmol) in glacial acetic acid (60 ml) and the mixture was stirred for 3 h at room temperature until all the red solid had dissolved. Potassium fluoride, dried *in vacuo* (2.1 g), was added and the mixture was stirred overnight. Methylene dichloride (500 ml) was added and the mixture was filtered through a Celite pad. Sodium metabisulphite (disodium disulphite) (2.4 g) was added to the filtrate and water (240 ml) was added dropwise to the vigorously stirred mixture. After the addition was complete the organic layer was separated, washed with water, and dried over $MgSO_4$. The solution was evaporated to dryness and the residue was triturated with ether to give (±)-7α,9α-diacetoxy-9β-ethynyl-7,8,9,10-tetrahydro-6,11-dihydroxynaphthacene-5,12-dione (**37**) (2.73 g, 81%), with

data as described in method (*a*) above. Chromatography of the mother liquors afford a further portion of the above compound in a 1:1 diastereoisomeric mixture with its 7β-acetoxy epimer (**39**) (65 mg, 1.9%), and a sample of the monoacetates (**40**) (37 mg, 1.2%).

Attempted Preparation of 4-*Acetoxy*-1,2,3,4-*tetrahydro*-5,12-*dihydroxynaphthacene*-2,6,11-*trione* (**47**).—Lead tetra-acetate (2.0 g) was added to a suspension of (±)-1,2,3,4-tetrahydro-5,12-dihydroxy-4β-trimethylsilylnaphthacene-2,6,11-trione (**17**) (310 mg, 0.82 mmol) in glacial acetic acid (15 ml) and the mixture was stirred at room temperature for 3 h. Potassium fluoride, dried *in vacuo* (500 mg), was added and the mixture was stirred overnight. Methylene dichloride (120 ml) was added and the solution was filtered through a Celite pad. Sodium metabisulphite (600 mg) was added to the filtrate and water (60 ml) was added dropwise to the stirred mixture. After the addition was complete the organic layer was separated, washed with water, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was triturated with cyclohexane to give only 6,8,11-trihydroxynaphthacene-5,12-dione (**48**) (253 mg, 85%) as an insoluble orange-red solid, m.p. 231—235 °C; $\nu_{max.}$ 2 960, 2 920, 2 850, 1 620, 1 585, 1 570, 1 510, 1 500, 1 460, 1 375, 1 260, 1 230, 1 210, and 1 170 cm^{-1}; δ ($CDCl_3$; 100 MHz) 15.0—15.1 (2 H, s), 8.3—8.8 (4 H, m), 7.65—7.95 (3 H, m), and 5.4 (1 H, s); *m/z* 306, 165, 105, and 77.

Preparation of (±)-7α,9α-*Diacetoxy*-9β-*acetyl*-7,8,9,10-*tetrahydro*-6,11-*dihydroxynaphthacene*-5,12-*dione* (**49**).—(*a*) (±)-7α,9α-Diacetoxy-9β-ethynyl-7,8,9,10-tetrahydro-6,11-dihydroxynaphthacene-5,12-dione (**37**) (2.00 g, 4.61 mmol), mercury(II) chloride (2.8 g), aniline (0.5 ml), water (34 ml), and benzene (170 ml) were mixed in a round bottomed flask and the mixture was heated under reflux and vigorously stirred for 12 h until no starting material remained by t.l.c. After concentration to a small volume the residue was suspended in methylene dichloride (1 500 ml) and dil. hydrochloric acid (10%; 100 ml) was added. The mixture was stirred for 90 min and the organic layer was separated and thoroughly treated with hydrogen sulphide for 30 min. After filtration of the mixture through a Celite pad the filtrate was evaporated to dryness and the residue triturated with ether to give (±)-7α,9α-*diacetoxy*-9β-*acetyl*-7,8,9,10-*tetrahydro*-6,11-*dihydroxynaphthacene*-5,12-*dione* (**49**) (1.81 g, 87%) as a bright orange solid which could be recrystallised from methylene dichloride–ether, m.p. 243—245 °C; $\nu_{max.}$ 2 930, 2 860, 1 735, 1 720, 1 660, 1 625, 1 590, 1 465, 1 415, 1 400, 1 375, 1 335, 1 310, 1 275, 1 260, 1 250, 1 230, 1 165, 1 140, and 1 115 cm^{-1}; δ ($CDCl_3$; 250 MHz) 13.39 (1 H, s), 13.36 (1 H, s), 8.32—8.42 (2 H, m), 7.83—7.91 (2 H, m,), 6.49 (1 H, dd, *J* 1.9 and 5.6 Hz), 3.52 (1 H, dd, *J* 2.5 and 18 Hz), 2.98 (1 H, dddd, *J* 0.9, 1.9, 2.5, and 16 Hz), 2.67 (1 H, dd, *J* 0.9 and 18 Hz), 2.41 (1 H, dd, *J* 5.6 and 16 Hz), 2.27 (3 H, s), 2.07 (3 H, s), and 2.05 (3 H, s); *m/z* 452 (Found: C, 63.5; H, 4.35. $C_{24}H_{20}O_9$ requires C, 63.72; H, 4.46%). Monoacetate (**50**) could be isolated from this reaction if treatment with hydrogen sulphide was insufficiently thorough. For (**50**); δ ($CDCl_3$; 250 MHz) 13.52 (1 H, s), 13.21 (1 H, s), 8.31—8.43 (2 H, m), 7.82—7.92 (2 H, m), 6.66 (1 H, dd, *J* 1.6 and 7.5 Hz), 3.43 (1 H, dd, *J* 1.6 and 19.4 Hz), 2.92—3.04 (1 H, m), 2.61—2.72 (1 H, m), 2.57 (3 H, s), 2.36—2.47 (1 H, m), and 1.99 (3 H, s); *m/z* 332 ($M^+ - 78$).

Preparation of (±)-7α,9α-*Diacetoxy*-9β-*acetyl*-7,8,9,10-*tetrahydro*-6,11-*dihydroxynaphthacene*-5,12-*dione* (**49**).—(*b*) A solution of (±)-7α,9α-diacetoxy-9β-ethynyl-7,8,9,10-tetrahydro-6,11-dihydroxynaphthacene-5,12-dione (**37**) (30 mg, 0.069 mmol) in acetone (14 ml) and dil. sulphuric acid (7 ml; 7%) was heated under reflux for 40 h in the presence of mercury(II) oxide (15 mg). The mixture was concentrated under reduced pressure to remove the acetone, methylene dichloride (25 ml) was added, and after being stirred for 30 min the organic layer was separated and treated with hydrogen sulphide for a further 30 min. The solution was filtered through a Celite pad and the filtrate was dried over $MgSO_4$ and evaporated to dryness. The residue was triturated with ether to give (±)-7α,9α-diacetoxy-9β-acetyl-7,8,9,10-tetrahydro-6,11-dihydroxynaphthacene-5,12-dione (**49**) (25.7 mg, 82%), with data as described above.

Preparation of (±)-9β-*Acetyl*-7,8,9,10-*tetrahydro*-6,7α,9α,11-*tetrahydroxynaphthacene*-5,12-*dione* [(±)-4-*Demethoxydaunomycinone*] (**51**).—(±)-7α,9α-Diacetoxy-9β-acetyl-7,8,9,10-tetrahydro-6,11-dihydroxynaphthacene-5,12-dione (**49**) (1.07 g, 3.76 mmol), propan-2-ol (830 ml), water (100 ml), and conc. hydrochloric acid (20 ml) were placed in a flask and the mixture was heated under reflux until the reaction was complete by t.l.c. Water (200 ml) was added and the reaction mixture was concentrated by distillation until about 400 ml remained. The solid was collected on a sintered glass funnel, washed with water, air-dried, and recrystallised in two crops from benzene–ether to give (±)-4-demethoxydaunomycinone (**51**) (1.29 g, 93%), as orange-red needles, m.p. 196—198 °C; $\nu_{max.}$ 2 930, 2 850, 1 705, 1 620, 1 585, 1 465, 1 375, 1 310, 1 265, 1 255, 1 235, 1 200, 1 165, 1 150, 1 130, 1 120, and 1 070 cm^{-1}; δ ($CDCl_3$; 250 MHz) 13.61 (1 H, s), 13.32 (1 H, s), 8.30—8.43 (2 H, m), 7.77—7.93 (2 H, m), 5.32 (1 H, ddd, *J* 1.6, 4.5, and 5.7 Hz), 4.54 (1 H, br s), 3.79 (1 H, d, *J* 5.7 Hz), 3.21 (1 H, dd, *J* 2.0 and 18.1 Hz), 2.96 (1 H, d, *J* 18.1 Hz), 2.45 (3 H, s), 2.36 (1 H, ddd, *J* 1.6, 2.0, and 14.5 Hz), and 2.18 (1 H, dd, *J* 4.5 and 14.5 Hz); *m/z* 368.

Preparation of (±)-1,2,3,4,4aα,12aα-*Hexahydro*-3α,6,11-*trihydroxy*-1β-*trimethylsilyl*-3β-*vinylnaphthacene*-5,12-*dione* (**52**) *and* (±)-1,2,3,4,4aα,12aα-*Hexahydro*-3β,6,11-*trihydroxy*-1β-*trimethylsilyl*-3α-*vinylnaphthacene*-5,12-*dione* (**53**).—Freshly dried and distilled THF (20 ml) and magnesium turnings (1.59 g, 66.3 mg-atom) were placed in a 500 ml flask and a solution of vinyl bromide (7.0 g, 65.4 mmol) in THF (10 ml) was added dropwise to the stirred mixture. A further portion of THF (30 ml) was added to the flask after initiation of the reaction. After complete formation of the Grignard reagent the dark yellow solution was cooled to an external temperature of −30 °C and a solution of (±)-1,2,3,4,4aα,12aα-hexahydro-6,11-dihydroxy-4β-trimethylsilylnaphthacene-2,5,12-trione (**20**) (5.0 g, 13.1 mmol) in THF (200 ml) was added slowly to the stirred mixture. After the addition was complete the mixture was stirred at an external temperature of −20 °C for 30 min and at 0 °C for a further 30 min. Saturated aqueous ammonium chloride (20 ml) was added dropwise followed by a mixture of conc. hydrochloric acid (30 ml) and water (35 ml). Water (130 ml) was then added and the mixture was concentrated at room temperature under reduced pressure to remove the organic solvents, then extracted with methylene dichloride. The organic layer was dried over $MgSO_4$ and evaporated to dryness, and the residue was purified by chromatography to give (±)-1,2,3,4,4aα,12aα-hexahydro-3,6,11-trihydroxy-1β-trimethylsilyl-3-vinylnaphthacene-5,12-dione as a diastereoisomeric mixture of (**52**) and (**53**) in 1.3:1 ratio which was crystallised from benzene–cyclohexane to afford yellow crystals (5.3 g, 99%), m.p. 172—174 °C; $\nu_{max.}$ 3 480, 2 960, 2 920, 2 860, 1 640, 1 605, 1 585, 1 500, 1 465, 1 400, 1 375, 1 365, 1 335, 1 290, 1 240, 1 180, and 1 155 cm^{-1}. This mixture could be further separated by chromatography to give the individual diastereoisomers. For the 3β-vinyl isomer (**52**): δ ($CDCl_3$; 250 MHz) 13.66 (1 H, s), 13.60 (1 H, s), 8.41—8.51 (2 H, m), 7.71—7.83 (2 H, m), 5.87 (1 H, dd, *J* 10.6 and 16.9 Hz), 5.24 (1 H, dd, *J* 0.9 and 16.9 Hz), 5.05 (1 H, dd, *J* 0.9 and 10.6 Hz), 3.36—3.51 (2 H, m), 1.81—1.93 (1 H, m), 1.49—1.77 (4 H, m), 1.42 (1 H, ddd, *J* 3.4, 3.7, and 13.7 Hz), and 0.12 (9 H, s). For the 3α-*vinyl isomer*

(**53**): m.p. 155.5—158 °C; δ ($CDCl_3$; 250 MHz) 13.62 (1 H, s), 13.60 (1 H, s), 8.38—8.51 (2 H, m), 7.70—7.82 (2 H, m), 6.08 (1 H, dd, *J* 10.4 and 17.2 Hz), 5.44 (1 H, d, *J* 17.2 Hz), 5.33 (1 H, d, *J* 10.4 Hz), 3.32 (1 H, dd, *J* 3.7 and 3.9 Hz), 3.02 (1 H, ddd, *J* 3.9, 5.2, and 13.7 Hz), 2.06—2.17 (1 H, m), 1.62—1.91 (4 H, m), 0.93 (1 H, dd, *J* 3.4, 3.7, and 13.3 Hz), and 0.14 (9 H, s) (Found: C, 67.45; H, 6.5. $C_{23}H_{26}O_5Si$ requires C, 67.29; H, 6.38%).

Preparation of (±)-3-*Acetoxy*-1,2,3,4,4aα,12aα-*hexahydro*-6,11-*dihydroxy*-1β-*trimethylsilyl*-3-*vinylnaphthacene*-5,12-*dione* (**54**).—The diastereoisomeric mixture of (±)-1,2,3,4,4aα,12aα-hexahydro-3,6,11-trihydroxy-1β-trimethylsilyl-3-vinylnaphthacene-5,12-diones (**52**) and (**53**) (5.3 g, 12.9 mmol) was added to isopropenyl acetate (50 ml) and the suspension was stirred at room temperature for 24 h in the presence of toluene-*p*-sulphonic acid (100 mg). The solvent was removed under reduced pressure at room temperature and the residue purified by chromatography to give (±)-3-acetoxy-1,2,3,4,4aα,12aα-hexahydro-6,11-dihydroxy-1β-trimethylsilyl-3-vinylnaphthacene-5,12-dione (**54**) as a mixture of diastereoisomers which was recrystallised from methylene dichloride–cyclohexane to afford (**54**) as yellow needles (5.02 g, 86%), m.p. 177—179 °C; $\nu_{max.}$ 2 960, 2 930, 2 860, 1 740, 1 640, 1 605, 1 585, 1 500, 1 465, 1 390, 1 375, 1 360, 1 290, 1 240, 1 170, and 1 155 cm^{-1}; δ ($CDCl_3$; 100 MHz) 13.6—13.65 (2 H, m), 8.4—8.5 (2 H, m), 7.7—7.8 (2 H, m), 6.0—6.3 (1 H, m), 5.15—5.65 (2 H, m), 3.0—3.5 (2 H, m), 1.0—2.2 (5 H, m), 2.0 (3 H, s), and 0.15 (9 H, s).

Preparation of (±)-14-*Bromo*-4-*demethoxydaunomycinone* (**55**).—(±)-4-Demethoxydaunomycinone (**51**) (50 mg, 0.14 mmol) was dissolved in chloroform (5 ml) and mixed with a solution of bromine in chloroform (0.35 ml of a 1:50 v/v solution). The mixture was stirred at room temperature overnight and concentrated under reduced pressure to about 3 ml. The solid was collected on a sintered glass funnel and washed with cold ether to give (±)-14-bromo-4-demethoxydaunomycinone (**55**) as red needles which could be recrystallised from ethyl acetate (50.8 mg, 84%), m.p. 219—224 °C (decomp.); $\nu_{max.}$ 3 520, 3 450, 2 930, 2 850, 1 730, 1 620, 1 580, 1 465, 1 410, 1 395, 1 375, 1 360, 1 340, 1 285, 1 260, 1 240, 1 200, 1 140. 1 095, and 1 075 cm^{-1}; δ ($CDCl_3$; 250 MHz) 13.61 (1 H, s), 13.29 (1 H, s), 8.34—8.43 (2 H, m), 7.80—7.93 (2 H, m), 5.37 (1 H, ddd, *J* 1.0, 2.0, and 5.2 Hz), 4.71 (1 H, br, s), 4.64 (1 H, d, *J* 14.6 Hz), 4.56 (1 H, d, *J* 14.6 Hz), 3.35 (1 H, d, *J* 2.0 Hz), 3.34 (1 H, ddd, *J* 1.0, 2.0, and 18.8 Hz), 3.04 (1 H, d, *J* 18.8 Hz), 2.48 (1 H, ddd, *J* 1.0, 2.0, and 14.5 Hz), and 2.24 (1 H, ddd, *J* 1.0, 5.2, and 14.5 Hz).

Preparation of (±)-14-*Acetoxy*-4-*demethoxydaunomycinone* (**4**).—A suspension of (±)-14-bromo-4-demethoxydaunomycinone (**55**) (95 mg, 0.21 mmol) in dry acetone (50 ml) was stirred vigorously and freshly fused potassium acetate (200 mg) was added. The mixture was heated under reflux and stirred for 30 min, allowed to cool, and filtered at the pump. The filtrate was evaporated to dryness and the residue was recrystallised from ethyl acetate to give dark red crystals of (±)-14-acetoxy-4-demethoxydaunomycinone (**4**) (63.7 mg, 70%), m.p. 230—232 °C; $\nu_{max.}$ 3 520, 3 460, 2 900, 1 745, 1 730, 1 620, 1 580, 1 465, 1 410, 1 375, 1 285, 1 250, 1 230, 1 200, 1 155, and 1 120 cm^{-1}; δ ($CDCl_3$; 250 MHz) 13.60 (1 H, s), 13.27 (1 H, s), 8.30—8.43 (2 H, m), 7.82—7.93 (2 H, m), 5.36—5.44 (1 H, m), 5.37 (1 H, d, *J* 17.7 Hz), 5.15 (1 H, d, *J* 17.7 Hz), 4.65 (1 H, br, s), 3.35 (1 H, br s), 3.33 (1 H, dd, *J* 2.5 and 18.5 Hz), 3.02 (1 H, d, *J* 18.5 Hz), 2.52 (1 H, ddd, *J* 1.6, 2.1, and 14.6 Hz), 2.22 (3 H, s), and 2.15 (1 H, dd, *J* 4.8 and 14.6 Hz); *m/z* 426.

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