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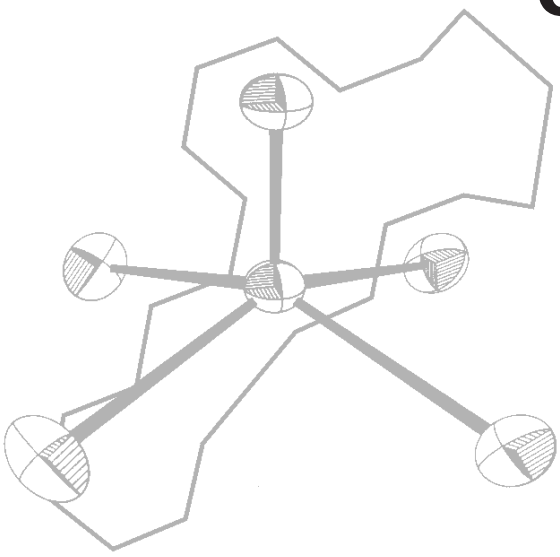

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# Synthesis of 2,3-Dioxy-1,4-anthraquinones Related to Tetracenomycins C and X

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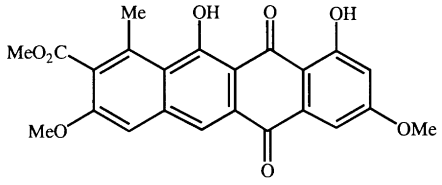
The 2,3-dioxy-1,4-anthraquinones (6) and (7) have been synthesized from the 9,10-anthraquinone (19), through the anthrone (18). Quinones (6) and (7) respectively possess substituents appropriate for three of the four rings of tetracenomycins C (2) and X (3) but they did not show dienophilic properties towards the reactive diene (5). Interaction with the diene was complicated by transsilylation, as was also observed for the model quinone (25).

## Introduction

The tetracenomycin antibiotics comprise aromatic naphthacenequinones, like tetracenomycin $A_2$ (1), together with a closely related group where one ring is non-aromatic in consequence of a pair of angular dioxy substituents. This latter group, which includes tetracenomycins C (2)[1] and X (3),[2] is biosynthesized from the former by oxidation and hydration.[2,3] Tetracenomycin C possesses significant antileukaemic properties. Its entire biosynthetic gene cluster of polyketide synthase enzymes from *Streptomyces glaucescens* has been sequenced.[4,5]

Earlier work here described the first synthesis of tetracenomycin $A_2$ (1), by cycloaddition of the 1,4-anthraquinone dienophile (4) to the 1,1,3-trioxy diene (5) followed by oxidative aromatization. Other aromatic tetracenomycins were obtained analogously.[6] This paper describes the synthesis of the new 2,3-dioxy-1,4-anthraquinones (6) and (7) to assess their effectiveness as dienophiles analogous to (4), as a potential basis for approaching the angular dioxy system of (2) and (3). This approach was encouraged by recent synthesis of the model tricycle (8) through addition of diene (5) to 2,3-diacetoxy naphthoquinone (9).[7] Despite the yield of (8) being poor, owing to competing Michael addition/elimination, it was considered that the large structural change from a simple dienophile like (9) to the highly functionalized tricyclic systems (6) and (7) warranted independent investigation.

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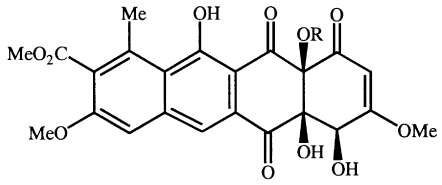
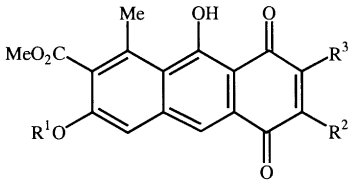
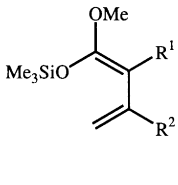



(2) R = H
(3) R = Me




| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| (4) | Me | H | H |
| (6) | Ac | OAc | OAc |
| (7) | Ac | OAc | OMe |
| (23) | H | OH | OMe |
| (24) | H | OH | OH |




| | $R^1$ | $R^2$ |
|---|---|---|
| (5) | H | OMe |
| (22) | OMe | $OSiMe_3$ |
| (26) | H | Me |

## Results and Discussion

At the beginning of this work there was no general method for synthesizing 2,3-dioxy-1,4-anthraquinones. Initial experiments sought to obtain the target system (6) through the 9,10-anthraquinone (10). This would have paralleled efficient synthesis of the 1,4-quinone (4) by deoxygenation of the 9,10-quinone (11) with sodium borohydride. However, synthesis of (10), by cycloaddition of diene (12) to the tautomeric diacetoxy naphthazarin (13), could not be effected. The diacetate (13), which was originally derived by treatment of the tetrol (14)[8] with ketene,[9] was more conveniently obtained by the action of

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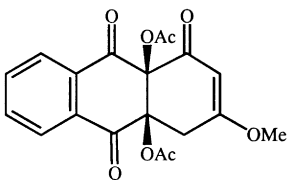

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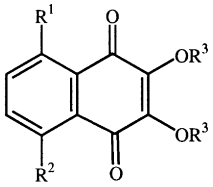
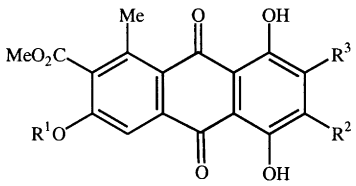
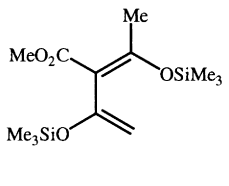


| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| (9) | H | H | Ac |
| (13) | OH | OH | Ac |
| (14) | OH | OH | H |
| (15) | OH | OAc | Ac |



| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| (10) | H | OAc | OAc |
| (11) | Me | H | H |



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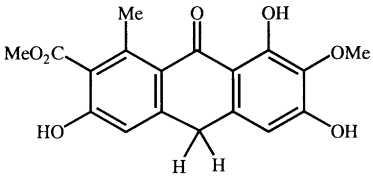

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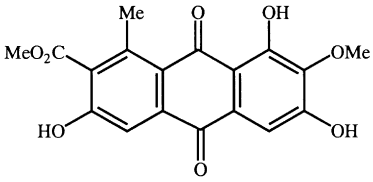

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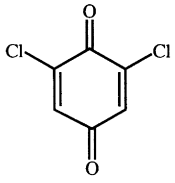

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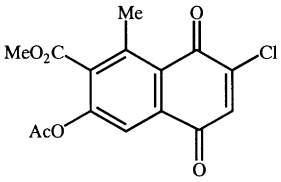

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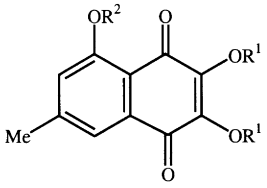
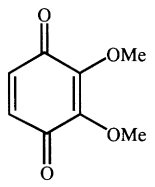


| | $R^1$ | $R^2$ |
|---|---|---|
| (25) | Ac | H |
| (28) | Me | H |
| (29) | H | H |
| (30) | Ac | $SiMe_3$ |



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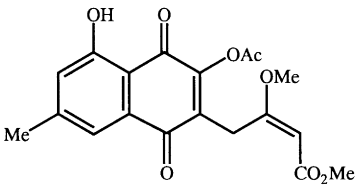

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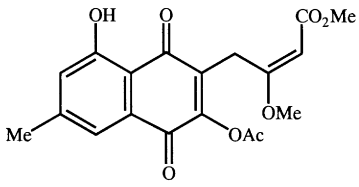
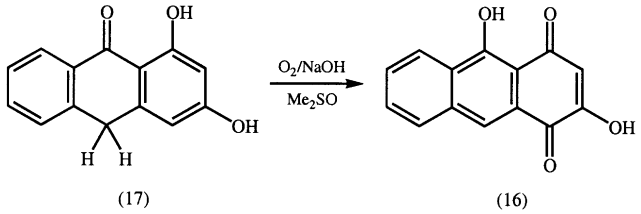


(32)

acetic anhydride/pyridine in cold tetrahydrofuran. Alternative acetylation of (14) catalysed by sulfuric acid gave the new triacetate (15), another potentially tautomeric system through acyl migration,[10–13] which also was found to be unreactive towards diene (12). Its $^1$H n.m.r. spectrum showed one chelated hydroxy resonance (δ 11.97) and three acetate resonances (δ 2.39, 2.38, 2.37). Chlorination of (13) and (15), in an effort to improve their dienophilicity, led only to decomposition.

A more effective approach to 1,4-anthraquinones (6) and (7) was based on earlier work here, typified by formation of the quinone (16) as the major product from treatment of 1,3-dihydroxy-9-anthrone (17) with oxygen under alkaline conditions (Scheme 1).[14] Establishing whether such chemistry could be applied to synthesizing the highly functionalized



(17) (16)

Scheme 1

1,4-quinones (6) and (7) required access to the new anthrone (18). This was expected to be derivable by regioselective reduction of the 9,10-anthraquinone (19). Protection of the central oxygen of the pyrogallol system of (18) was incorporated to avoid unwanted formation of a 1,2-anthraquinone during oxidation.[14]

Synthesis of the anthraquinone (19) paralleled the procedure employed earlier for the corresponding ethyl ester.[15] This entailed cycloaddition of the diene (12) to 2,6-dichloro-1,4-benzoquinone (20), followed by aromatization and acetylation to give the protected naphthoquinone (21). A second cycloaddition involving the tetraoxy diene (22), followed by aromatization and hydrolysis then gave (19) (86%). Its $^1$H n.m.r. spectrum showed singlet resonances appropriate to the α- and two β-hydroxy protons (δ 13.25, 11.65, 10.97), the two aromatic protons (δ 7.58, 7.17) and the two methoxy groups (δ 3.86, 3.83).

Reduction of (19) with tin(II) chloride in ethanol/hydrochloric acid gave the desired anthrone (18) (82%). The expected regiochemistry was confirmed by retention of a chelated hydroxy resonance (δ 13.60) in its $^1$H n.m.r. spectrum, together with considerable shielding of the two aromatic protons (δ 6.81, 6.40), whose signals were

broadened through benzylic coupling with the new methylene protons (δ 4.24).

Treatment of this anthrone (18) with oxygen in dimethyl sulfoxide containing methanolic sodium methoxide pleasingly gave the 1,4-anthraquinone (23) (54%), accompanied by minor reoxidation to its 9,10-isomer (19) (11%). The former quinone showed characteristic long-wavelength electronic absorption ($\lambda_{max}$ 496 nm), together with strongly deshielded hydroxy and aromatic resonances (δ 15.12, 7.87) for the protons of the central ring. The course of oxidation was base-dependent, sodium hydroxide favouring formation of (19) and other bases (lithium diisopropylamide, sodium hydride, potassium t-butoxide) giving sub-optimal ratios of the two quinones. All oxidations were accompanied by formation of polar, dark red by-products, which increased with reaction time.

Cleavage of the quinonoid methoxy group of (23) with aluminium trichloride in boiling dichloromethane yielded the tetrahydroxy quinone (24) (64%). Survival of the methyl ester was indicated by an appropriate $^1$H n.m.r. resonance (δ 3.85). Similarly hindered ester groups in 9,10-anthraquinones are known to be resistant to hydrolysis.[15]

Selective acetylation of the respective 1,4-anthraquinones (24) and (23) was effected by boiling with acetic anhydride in tetrahydrofuran, giving the target triacetate (6) and diacetate (7). The $^1$H n.m.r. spectrum of the former product showed three new acetate resonances (δ 2.43, 2.40, 2.32), while retaining a chelated hydroxy resonance (δ 14.37). For (7) the two acetate groups resonated at δ 2.41, 2.32 and the hydroxy at δ 14.64.

However, the two quinones (6) and (7) proved to be ineffective as dienophiles. When separately treated with diene (5) in benzene, their orange solutions became yellow with unexpected ease but nothing useful could be isolated from them. Though complex, the $^1$H n.m.r. spectra of the crude products conspicuously lacked any chelated hydroxy resonance. This suggested that interaction with the diene was complicated by transsilylation of this group, an outcome that would not only reduce dienophilicity but would nullify the important directive role the hydroxy group was expected to play in any successful cycloaddition.

To obtain a better perspective for assessing possible transsilylation from diene (5) onto the α-hydroxy group of (6) and (7), we sought a less highly functionalized model system. Apart from possessing an α-hydroxy group, this was to resemble the parent 2,3-diacetoxy naphthoquinone (9) as closely as possible. This resulted in synthesis of the hydroxy diacetate (25).

Access to (25) began with cycloaddition of the diene (26)[16] to 2,3-dimethoxy-1,4-benzoquinone (27)[17] and oxidative aromatization, initially affording the dimethoxy naphthoquinone (28). Its $^1$H n.m.r. spectrum was consistent with the assigned structure, in particular containing two methoxy resonances (δ 4.10, 4.09) and an α-hydroxyl (δ 11.85). On demethylation with aluminium trichloride in boiling dichloromethane it gave the sparingly soluble trihydroxy quinone (29). The latter underwent selective acetylation with acetic anhydride in boiling tetrahydrofuran to give (25). Its $^1$H n.m.r. spectrum contained a sharp α-hydroxy resonance (δ 11.47) and two acetate resonances (δ 2.40, 2.39) as well as other signals supporting the assigned structure.

Reaction of the quinone (25) with an excess of diene (5) at room temperature was monitored by $^1$H n.m.r. spectroscopy. After 7 h in ($D_6$)benzene the quinone was consumed, with formation of a single major product. Its spectrum lacked an α-hydroxy resonance and, apart from an appropriate overlapping resonance (δ 1.80) for the two acetate groups, it showed aromatic (δ 7.47, 6.64) and *C*-methyl (δ 1.72) signals different from those of (25). It was inferred to be the trimethylsilyl ether (30) but it could not be purified because of rapid desilylation and its spectrum reverted to that of (25) on addition of trifluoroacetic acid to the reaction solution.

After the mixture of (25) and (5) was heated at 50° for 4 days, the major component recoverable by chromatography, again, was (25) (44%). The only identifiable new product (18%) was a 3 : 1 mixture of regioisomers (31) and (32), corresponding to Michael addition/elimination; like (25), they probably derived from hydrolysis of their *O*-silyl derivatives during chromatography.

Their regiochemistry was assigned on the basis of the expected greater deshielding of the α-hydroxy resonance of (32) (δ 11.93) relative to (31) (δ 11.51), through conjugative electron donation from the acetoxy group of the former, to the chelated carbonyl.[7] Crystallization of the isomeric mixture gave pure (31), its $^1$H n.m.r. spectrum showing aromatic (δ 7.50, 7.06), olefinic (δ 5.12), methylene (δ 4.25), and other signals consistent with the assigned structure. Its mass spectrum contained an appropriate molecular ion (*m/z* 374).

These observations militate against 2,3-dioxy-1,4-anthraquinones serving as synthetic sources of tetracenomycins C (2) or X (3). Apart from the problem of competing Michael chemistry, their weak dienophilicity, even towards a reactive 1,1-dioxy diene like (5), exceptionally allows transsilylation of the regiocontrolling α-hydroxy group to supervene. This stands to reduce dienophilicity still further and compromise regiocontrol.

## Experimental

*General*

Melting points were determined on a Kofler hot stage and are uncorrected. Microanalyses were carried out by National Analytical Laboratories, Melbourne, or Chemical and Microanalytical Services, Geelong. Electronic spectra were recorded in ethanol containing 1% formic acid (v/v), unless otherwise stated, on a Varian Superscan 3 spectrophotometer. Infrared spectra were recorded on a Perkin Elmer 983-G grating spectrophotometer. Solids were recorded as potassium bromide disks and liquids as films between sodium chloride plates. Proton nuclear magnetic resonance ($^1$H n.m.r.) spectra were recorded at 399.65 MHz on a JEOL JNM-GX400 spectrometer. The solvent was (D)chloroform unless otherwise stated. High- and low-resolution mass spectra were recorded by using a V.G. Micromass 7070F instrument or a JEOL JMS-AX505H mass spectrometer at 70 eV, unless otherwise stated. In general, only peaks greater than 20% are quoted. Analytical and preparative thin-layer chromatography (t.l.c.) were carried out on glass plates coated with a layer of silica gel [Merck Kieselgel 60 $GF_{254}$ or Merck Kieselgel 60 $GF_{254}$ containing 2% oxalic acid (oxalated silica)]. The separated components were extracted from the silica by using ethyl acetate or dichloromethane. Oxalic acid was removed by

washing the extracts with water and then drying over magnesium sulfate prior to evaporation. Flash chromatography was carried out using Merck Kieselgel No. 9385. All solvents were of A.R. grade or were redistilled prior to use. Petrol refers to the hydrocarbon fraction boiling in the range 60–80°. All diene preparations and reactions were performed under dry nitrogen in flame-dried glassware. Acid-sensitive cycloadditions were performed in glassware which had been previously washed with aqueous ammonia solution followed by distilled water. Organic extracts were generally dried over magnesium sulfate before evaporation at reduced pressure.

*2,3-Diacetoxy-5,8-dihydroxy-1,4-naphthoquinone (13)*

Prepared according to the literature, quinone (14) had m.p. >267° (dec.) (lit.[8] 265°). δ [$(CD_3)_2SO$] 12.12, s, 5-OH, 8-OH; 10.52, br s, 2-OH, 3-OH; 7.25, s, 2×ArH. To a solution of this quinone (14) (105 mg) in tetrahydrofuran (3 $cm^3$) was added acetic anhydride (1 $cm^3$) and the mixture was cooled in an ice/salt bath. Pyridine (2 drops) was added and the mixture was stirred for 10 min. Ice-cold 1 M hydrochloric acid (20 $cm^3$) was then added and the mixture was stirred vigorously for 15 min and extracted into ethyl acetate (2×50 $cm^3$). The extract was washed with water (100 $cm^3$), brine (100 $cm^3$), and then dried and evaporated. The residue was subjected to preparative t.l.c. on oxalated silica, with ether/petrol (1 : 1) as eluent. The major red band gave the diacetoxy naphthoquinone (13) (69 mg, 50%) as red bars from dichloromethane, m.p. 151–163° (lit.[9] 158–60°). δ 12.07, s, 2×OH; 7.29, s, 2×ArH; 2.40, s, 2×OAc. *m/z* 306 (M, 4%), 222 (100), 194 (65), 165 (21), 108 (27).

*2,3,5-Triacetoxy-8-hydroxy-1,4-naphthoquinone (15)*

To a solution of quinone (14) (112 mg) in tetrahydrofuran (7 $cm^3$) was added acetic anhydride (1 $cm^3$) and the mixture was cooled in an ice/salt bath. Sulfuric acid (1 drop) was added and the mixture was stirred for 10 min. Ice-cold water was added and the mixture was stirred vigorously for 20 min and then extracted with dichloromethane (2×20 $cm^3$). The extract was washed with water (50 $cm^3$), brine (50 $cm^3$), and then dried and evaporated. The residue was subjected to preparative t.l.c on oxalated silica, with ethyl acetate/petrol (2 : 5) as eluent. The major band gave the *triacetoxy naphthoquinone* (15) (78 mg, 44%) as yellow needles from ethyl acetate/petrol, m.p. 153–155° (Found: C, 55.0; H, 3.2. $C_{16}H_{12}O_9$ requires C, 55.2; H, 3.5%). $\lambda_{max}$ (log ε) ($CHCl_3$) 274, 433 nm (4.07, 3.64). $\nu_{max}$ 1789, 1677, 1644 $cm^{-1}$. δ 11.97, s, OH; 7.32, ABq, *J* 9.1 Hz, H 6, H 7; 2.39, 2.38, 2.37, s, s, s, 3×OAc. *m/z* (20 eV) 222 (100), 194 (35).

*Methyl 3,6,8-Trihydroxy-7-methoxy-1-methyl-9,10-dioxo-9,10-dihydroanthracene-2-carboxylate (19)*

To a solution of the naphthoquinone (21)[18] (470 mg), prepared as for the corresponding ethyl ester,[15] in dry tetrahydrofuran (2 $cm^3$) was added freshly prepared diene (22) (1.20 g) and the mixture was stirred at room temperature for 3 days. The temperature was raised to 50° and the mixture was stirred for a further 24 h. Ethanol (20 $cm^3$) and sodium acetate (1 g) were then added and the mixture was boiled for 15 min. Concentrated hydrochloric acid (10 $cm^3$) was added and boiling was continued for 15 min. The mixture was cooled, diluted with water (200 $cm^3$) and extracted with ethyl acetate (3×100 $cm^3$). The extract was washed with water (2×100 $cm^3$), brine (100 $cm^3$), and then dried and evaporated. The residue was crystallized from ethyl acetate to give the *anthraquinone* (19) (451 mg, 86%) as orange needles, m.p. 254–260° (Found: C, 60.0; H, 3.9. $C_{18}H_{14}O_8$ requires C, 60.3; H, 3.9%). $\lambda_{max}$ (log ε) 283, 346, 416 nm (4.64, 3.72, 3.80). $\nu_{max}$ 3324, 1711, 1649, 1622, 1575 $cm^{-1}$. δ [$(CD_3)_2SO$] 13.25, s, 8-OH; 11.65, 10.97, br s, br s, 2×β-OH; 7.58, s, H 4; 7.17, s, H 5; 3.86, 3.83, s, s, 2×OMe; 2.59, s, ArMe. *m/z* 358 (M, 67%), 326 (49), 311 (28), 309 (21), 308 (100), 283 (38), 280 (21), 250 (37), 227 (24).

*Methyl 3,6,8-Trihydroxy-7-methoxy-1-methyl-9-oxo-9,10-dihydroanthracene-2-carboxylate (18)*

Quinone (19) (1.60 g) was dissolved in boiling acetic acid (300 $cm^3$) and a hot solution of tin(II) chloride (34 g) in concentrated hydrochloric acid (85 $cm^3$) was added carefully. The mixture was then boiled for 30 min. An equal volume of hot water was added slowly and the mixture was allowed to cool. The pale brown needles which precipitated were filtered off and washed with water to give the *anthrone* (18) (1.27 g, 82%). An analytical sample was recrystallized from ethyl acetate/petrol as buff needles, m.p. 125-129° (dec.) (Found: C, 62.8; H, 4.6. $C_{18}H_{16}O_7$ requires C, 62.8; H, 4.7%). $\lambda_{max}$ (log ε) 210, 277, 323 nm (4.62, 4.15, 4.46). $\nu_{max}$ 3555, 3489, 1665, 1620, 1565 $cm^{-1}$. δ [$(CD_3)_2SO$] 13.60, s, 8-OH; 11.03, 10.33, s, s, 2×β-OH; 6.81, s, H 4; 6.40, s, H 5; 4.24, s, $CH_2$; 3.86 3.83, s, s, 2×OMe; 2.57, s, ArMe. *m/z* 345 (M+1, 20%), 344 (M, 100), 313 (21), 312 (74), 297 (54), 294 (33).

*Oxidation of Anthrone (18)*

A solution of anthrone (18) (255 mg) in dimethyl sulfoxide (50 $cm^3$) was purged with nitrogen for 5 min before addition of sodium methoxide in methanol (10% w/v, 2 $cm^3$). The stream of nitrogen was continued for 3.5 min, after which a strong stream of oxygen was passed through the solution for a further 3.5 min. The mixture was then quickly poured into 1 M hydrochloric acid (300 $cm^3$) and extracted with ethyl acetate (2×100 $cm^3$). The extract was washed with water (300 $cm^3$), brine (300 $cm^3$), and then dried and evaporated. The residue was subjected to column chromatography, with an acetone/toluene/acetic acid (10 : 89 : 1 → 30 : 69 : 1) solvent gradient as eluent.

The more mobile, yellow fraction gave the anthraquinone (19) (31 mg, 11%), identical to material described previously.

The less mobile, orange-red fraction gave *methyl 3,6,9-trihydroxy-7-methoxy-1-methyl-5,8-dioxo-5,8-dihydroanthracene-2-carboxylate* (23) (145 mg, 54%) as red needles from ethyl acetate, m.p. 258–267° (dec.) (Found: C, 60.7; H, 3.9. $C_{18}H_{14}O_8$ requires C, 60.3; H, 3.9%). $\lambda_{max}$ (log ε) 231, 248, 329, 434, 496 nm (4.44, 4.44, 4.25, 3.61, 3.66). $\nu_{max}$ 3297br, 1728, 1648, 1581 $cm^{-1}$. δ [$(CD_3)_2SO$] 15.12, s, 9-OH; 11.18, 11.07, s, br s, 2×β-OH; 7.87, s, H 10; 7.32, s, H 4; 3.90, 3.85, s, s, 2×OMe; 2.71, s, ArMe. *m/z* 358 (M, 55%), 327 (25), 326 (100).

*Methyl 3,6,7,9-Tetrahydroxy-1-methyl-5,8-dioxo-5,8-dihydroanthracene-2-carboxylate (24)*

To a solution of the quinone (23) (9 mg) in dichloromethane (25 $cm^3$) under nitrogen was added aluminium trichloride (100 mg) and the mixture was stirred vigorously for 24 h. Aqueous oxalic acid solution (5% w/v, 150 $cm^3$) was added and stirring was continued for a further 1 h. The mixture was then extracted with ethyl acetate (2×150 $cm^3$) and the combined extracts were washed with water (150 $cm^3$), brine (150 $cm^3$), and then dried and evaporated. The residue was subjected to preparative t.l.c. on oxalated silica, with toluene/acetone (7 : 2) as eluent. The mobile orange band gave the *tetrahydroxy anthraquinone* (24) (6 mg, 64%) as red needles, m.p. >180° (dec.) (Found: C, 59.2; H, 3.4. $C_{17}H_{12}O_8$ requires C, 59.3; H, 3.5%). $\lambda_{max}$ (log ε) 234, 244, 286, 329sh, 404, 435, 490 nm (4.40, 4.40, 4.44, 4.14, 3.86, 3.69, 3.69). $\nu_{max}$ 3337br, 1714, 1666, 1648, 1630sh, 1577 $cm^{-1}$. δ [$(CD_3)_2SO$] 14.76, s, 9-OH; 11.14, 10.33, br s, br s, 2×β-OH; 7.81, s, H 10; 7.30, s, H 4; 3.85, s, $CO_2Me$; 2.72, s, ArMe. *m/z* 344 (M, 54%), 313 (25), 312 (100), 256 (24), 115 (20).

*Methyl 3,6,7-Triacetoxy-9-hydroxy-1-methyl-5,8-dioxo-5,8-dihydroanthracene-2-carboxylate (6)*

To a solution of the quinone (24) (40 mg) in tetrahydrofuran (8 $cm^3$) was added acetic anhydride (1 $cm^3$) and the mixture was boiled for 5 h. The solvent was evaporated and the mixture was subjected to preparative t.l.c. on oxalated silica, with ethyl acetate/toluene (1 : 9) as eluent. The mobile orange band gave the *triacetoxy anthraquinone* (6) (21 mg, 38%) as orange-red crystals from dichloromethane/petrol, m.p. 209–212° (Found: C, 58.8; H, 3.8. $C_{23}H_{18}O_{11}$ requires C, 58.7; H, 3.9%). $\lambda_{max}$ (log ε) ($CHCl_3$) 250, 284, 494 nm (4.77, 4.16, 3.99). $\nu_{max}$ 1791, 1772, 1719, 1670, 1600, 1648, 1605 $cm^{-1}$. δ 14.37, s, 9-OH; 8.03, s, H 10; 7.65, s, H 4; 3.98, s, $CO_2Me$; 2.92, s, ArMe; 2.43, 2.40, 2.32, s, s, s, 3×OAc. δ ($C_6D_6$) 14.83, s, 9-OH; 7.73, s, H 10; 7.05, s, H 4; 3.49, s, $CO_2Me$; 2.80, s, ArMe; 1.84, 1.83, 1.78, s, s, s, 3×OAc. *m/z* 470 (M, 1%), 469 (M – 1, 4), 386 (21), 345 (36), 344 (100), 313 (31), 312 (82), 283 (32), 256 (25), 199 (25), 198 (22), 171 (22), 143 (23), 115 (41).

*Methyl 3,6-Diacetoxy-9-hydroxy-7-methoxy-1-methyl-5,8-dioxo-5,8-dihydroanthracene-2-carboxylate (7)*

To a solution of the quinone (23) (29 mg) in tetrahydrofuran (3 $cm^3$) was added acetic anhydride (0.5 $cm^3$) and the mixture was boiled for 8.5 h. The solvent was evaporated and the solid was crystallized from dichloromethane/petrol to give the *diacetoxy anthraquinone* (7) (9 mg, 23%) as orange needles, m.p. 210–213° (Found: C, 59.7; H, 4.0. $C_{22}H_{18}O_{10}$ requires C, 59.7; H, 4.1%). $\lambda_{max}$ (log ε) ($CHCl_3$) 245, 287, 477 nm (4.59, 4.50, 4.00). $\nu_{max}$ 1771, 1726, 1657, 1600, 1565 $cm^{-1}$. δ 14.64, s, 9-OH; 7.98, s, H 10; 7.61, s, H 4; 4.23, 3.96, s, s, 2×OMe; 2.41, 2.32, s, s, 2×OAc. *m/z* 442 (M, 1%), 441 (M – H, 3), 399 (26), 357 (64), 343 (26), 326 (29), 325 (100).

*5-Hydroxy-2,3-dimethoxy-7-methyl-1,4-naphthoquinone (28)*

To a solution of 2,3-dimethoxy-1,4-benzoquinone (27)[17] (1.37 g) in benzene (10 $cm^3$) was added diene (26)[16] (2.26 g) and the mixture was stirred at room temperature for 2 h. The solvent was then evaporated and the residue was dissolved in tetrahydrofuran (10 $cm^3$) and concentrated hydrochloric acid (5 $cm^3$). The mixture was stirred in air for 5 h, poured into water (100 $cm^3$) and extracted with ethyl acetate (2×75 $cm^3$). The extract was washed with water (100 $cm^3$), brine (100 $cm^3$), and then dried and evaporated. The residue was subjected to flash chromatography in ethyl acetate/petrol (1 : 1) to give the *naphthoquinone* (28) (0.98 g, 49%) as orange needles from ethyl acetate/petrol, m.p. 139–140° (Found: C, 62.8; H, 5.0. $C_{13}H_{12}O_5$ requires C, 62.9; H, 4.9%). $\lambda_{max}$ (log ε) ($CHCl_3$) 253, 296, 421 nm (4.14, 4.10, 3.63). $\nu_{max}$ 1673, 1625, 1606 $cm^{-1}$. δ 11.85, s, OH; 7.63, d, *J* 1.2 Hz, H 8; 7.02, br s, H 6; 4.10, 4.09, s, s, 2×OMe; 2.40, s, ArMe. *m/z* 248 (M, 95%), 233 (100), 219 (23), 203 (58), 177 (33), 135 (35), 134 (62), 106 (51), 77 (25).

*2,3,5-Trihydroxy-7-methyl-1,4-naphthoquinone (29)*

To a solution of the quinone (28) (103 mg) in dry dichloromethane (25 $cm^3$) was added aluminium trichloride (0.5 g) and the mixture was stirred vigorously at reflux for 20 h. Aqueous oxalic acid solution (5% w/v; 50 $cm^3$) was then added and stirring was continued for a further 30 min, after which time the purple colour was discharged and an orange precipitate had formed. The mixture was poured into water (100 $cm^3$) and extracted into ethyl acetate (2×75 $cm^3$). The extract was washed with water (150 $cm^3$), brine (150 $cm^3$), and then dried and evaporated to give the *trihydroxy naphthoquinone* (29) (92 mg, 100%) as a red solid, m.p. >220° (subl.) (Found: $M^{+\bullet}$, 220.0374. $C_{11}H_8O_5$ requires $M^{+\bullet}$, 220.0372). $\lambda_{max}$ (log ε) 237sh, 260, 297, 402, 445 nm (3.98, 4.24, 4.04, 3.66, 3.45). $\nu_{max}$ 3299br, 1674, 1648, 1615 $cm^{-1}$. δ [$(CD_3)_2SO$] 11.73, br s, 5-OH; 10.23, br s, 2-OH, 3-OH; 7.29, d, *J* 1.2 Hz, H 8; 7.05, br s, H 6; 2.35, s, ArMe. *m/z* 220 (M, 59%), 192 (100), 118 (20).

*2,3-Diacetoxy-5-hydroxy-7-methyl-1,4-naphthoquinone (25)*

To a solution of the quinone (29) (63 mg) in tetrahydrofuran (7 $cm^3$) was added acetic anhydride and the solution was boiled for 3 h. It was then evaporated and subjected to preparative t.l.c., with ethyl acetate/petrol (2 : 5) as eluent, to give the *diacetoxy naphthoquinone* (25) (28 mg, 32%) as yellow needles from ethyl acetate/petrol, m.p. 148–149° (Found: C, 59.1; H, 3.7. $C_{15}H_{12}O_7$ requires C, 59.2; H, 4.0%). $\lambda_{max}$ (log ε) ($CHCl_3$) 251, 257sh, 278, 432 nm (3.86, 3.85, 3.93, 3.49). $\nu_{max}$ 1782, 1675, 1656sh, 1635 $cm^{-1}$. δ 11.47, s, 5-OH; 7.49, br d, *J* 1.3 Hz, H 8; 7.09, br s, H 6; 2.43, br s, ArMe; 2.40, 2.39, s, s, 2×OAc. δ ($C_6D_6$) 11.72, s, 5-OH; 7.17, d, *J* 1.4 Hz, H 8; 6.55, br s, H 6; 1.79, 1.78, s, s, 2×OAc; 1.63, br s, ArMe. *m/z* 304 (M, 4%), 262 (24), 220 (100), 192 (53).

*Reaction of Diene (5) with Quinone (25)*

To a solution of the naphthoquinone (25) (32 mg) in benzene (1 $cm^3$) was added diene (5) (109 mg) and the mixture was stirred at room temperature for 24 h. The temperature was raised to 50° and stirring was continued for a further 24 h. More diene (385 mg) was added and the mixture was stirred at 50° for another 48 h, then evaporated and subjected to preparative t.l.c., with ethyl acetate/petrol (2 : 5) as eluent. The more mobile yellow band gave starting quinone (14 mg, 44%). The less mobile yellow band gave a 3 : 1 mixture of Michael adducts (31) and (32) (7 mg, 18%). Recrystallization of this material from ethyl acetate/petrol afforded *methyl 4-(3′-acetoxy-5′-hydroxy-7′-methyl-1′,4′-dioxo-1′,4′-dihydronaphthalen-2′-yl)-3-methoxybut-2-enoate* (31) as yellow needles, m.p. 183–190° (Found: $M^{+\bullet}$, 374.1007. $C_{19}H_{18}O_8$ requires $M^{+\bullet}$, 374.1002). $\lambda_{max}$ (log ε) ($CHCl_3$) 241, 276sh, 427 nm (4.35, 4.13, 3.73). $\nu_{max}$ 1772, 1701, 1670, 1619 $cm^{-1}$. δ 11.51, s, 5′-OH; 7.50, d, *J* 1.3 Hz, H 8′; 7.05, br s, H 6′; 5.12, s, H 2; 4.25, s, $CH_2$; 3.72, 3.55, s, s, 2×OMe; 2.43, br s, ArMe; 2.31, s, OAc. *m/z* 374 (M, 38%), 332 (43), 301 (32), 300 (56), 273 (100), 272 (32).

The $^1H$ n.m.r. spectrum of an unrecrystallized sample of the less mobile band showed additional, minor resonances attributed to methyl 4-(3′-acetoxy-8′-hydroxy-6′-methyl-1′,4′-dioxo-1′,4′-dihydronaphthalen-2′-yl)-3-methoxybut-2-enoate (32). δ 11.93, s, 8′-OH; 7.46, d, *J* 1.3 Hz, H 5′; 7.08, br s, H 7′; 5.13, s, H 2; 4.26, s, $CH_2$; 3.72, 3.56, s, s, 2×OMe; 2.42, br s, ArMe; 2.31, s, OAc.

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