Synthesis and Redox Properties of Chromophore Modified Glycosides Related to Anthracyclines

J. William Lown,* Sham M. Sondhi, Sukhendu B. Mandal, and John Murphy

Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2

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Synthetic schemes outlining a general approach to chromophores of the anthracycline antibiotics in which the quinone ring C is replaced by a γ-pyrone are described. Synthesis of several xanthone analogues of 4-demethoxydaunorubicin are given in addition to the coupling of a protected sugar moiety to the 7-position of selected aglycons. Successful separation of the regioisomeric 7-glucosylated xanthone containing chromophores as well as their structural assignment is discussed. These modified anthracycline structures that were synthesized on the premise that resistance to enzymatic chromophore reduction may contribute to the understanding of their mechanism of action exhibit substantially diminished activity toward hepatic microsomal activation and consequent oxygen consumption in comparison with the parent antibiotics.

The anthracycline antitumor antibiotics, including daunorubicin (**1**), 4-demethoxydaunorubicin (**2**), and adriamycin (**3**), have an established place in the clinical treatment of malignant diseases.[1,2] Their chemotherapeutic importance has attracted considerable interest on the part of organic chemists and many elegant total syntheses of the parent antibiotics have been reported.[3] The anthracyclines suffer from two clinical disadvantages in often displaying dose-related cardiotoxicity[4-7] and a tendency to undergo enzymatic reductive deglycosidation to the inactive 7-deoxy aglycons.[1,2,8] In these antibiotics as in others including mitomycin C,[9,10] streptonigrin,[11] and saframycin A[12,13] the quinone moiety is directly implicated or may contribute to their biochemical action. While the intercalative binding of the anthracycline chromophore as a whole to DNA appears to correlate with their anticancer properties,[1,2] it is not at all clear to what extent the presence of the quinone moiety is advantageous or deleterious. Initial one-electron reduction of the quinone may be the triggering event leading to covalent attachment to DNA,[14] but on the other hand there is accumulating evidence that links their risk of cardiotoxicity to the ability of the anthracycline chromophore to undergo microsomal enzymatic one-electron reduction with the concomitant generation of reactive oxygen species.[15-19] The latter may lead to lipid peroxidation[20] and DNA lesions[21,22] in cardiac tissue, which is susceptible to such damage owing to the suppressed levels of superoxide dismutase and catalase in this organ.[23,24] Efforts to test this hypothesis have concentrated on direct chemical modification of the native anthracyclines,[18,19,25,26] permitting in favorable cases a 20-fold improvement in cardiotoxic properties with no sacrifice in antitumor properties.[19] In contrast, very few efforts have been reported to date that are directed toward the synthesis of anthracyclines involving modifications within the quinone ring. One notable attempt, namely, to produce phenazine derived N-isosteres of the chromophore, encountered severe synthetic obstacles.[27]

We report approaches to the synthesis of certain xanthone-containing anthracyclines. The rationale was that the γ-pyrone moiety in, e.g., **4**, **5**, **6**, and **30** should be much more resistant to reduction but should retain some of the planar, spatial, and electronic characteristics of the parent quinonoid system necessary for molecular recognition and intercalative binding.[1,2,28] In this paper we address certain questions including development of useful routes to the four-ring xanthone chromophores (**4a,b**) and of effective means of coupling of selected examples to model sugars (**30a,b**) as well as proof of orientation of the latter glycosylated chromophores. In view of the synthetic difficulties encountered with the aforementioned modified chromophores,[27] it was considered appropriate to resolve these questions before embarking on regiospecific and stereospecific synthetic schemes. Accordingly, we report the results of our synthetic studies as well as the microsomal redox characteristics of the new chromophore modified anthracycline derivatives to date so as to assist other efforts to explore the chemistry of coupling of radically modified anthracycline chromophores to different sugar units.

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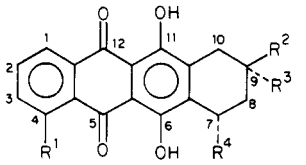
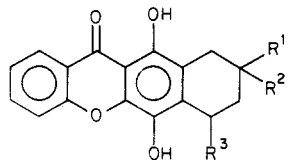
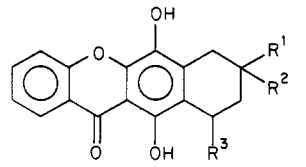
Scheme I[a]



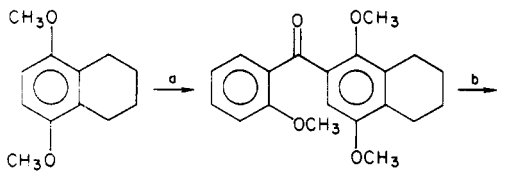
1, $R^1 = OCH_3$; $R^2 = COCH_3$; $R^3 = OH$; R^4 = daunosaminyl
2, $R^1 = H$; $R^2 = COCH_3$; $R^3 = OH$; R^4 = daunosaminyl
3, $R^1 = OCH_3$; $R^2 = COCH_2OH$; $R^3 = OH$; R^4 = daunosaminyl



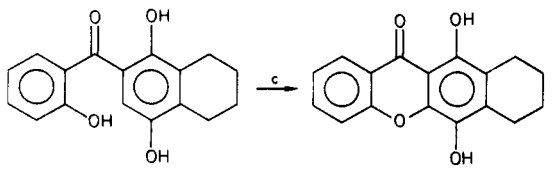
4a, $R^1 = R^2 = H$; $R^3 = OH$
5a, $R^1 = COCH_3$; $R^2 = H$; $R^3 = OH$
6a, $R^1 = COCH_3$; $R^2 = OH$; $R^3 = OH$



4b, $R^1 = R^2 = H$; $R^3 = OH$
5b, $R^1 = COCH_3$; $R^2 = H$; $R^3 = OH$
6b, $R^1 = COCH_3$; $R^2 = OH$; $R^3 = OH$



7 8



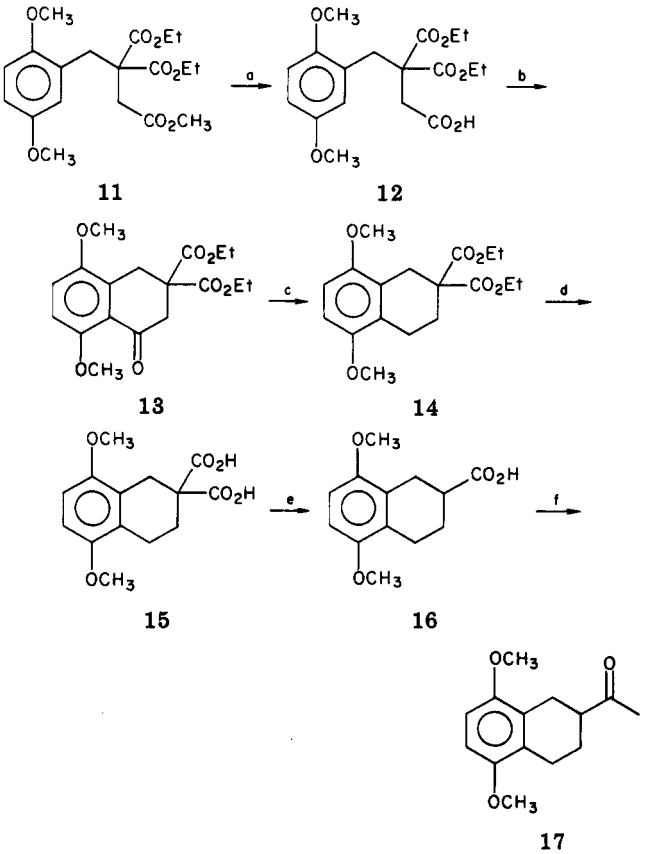
9 10

[a] Reaction conditions: (a) *o*-methoxybenzoyl chloride, $SnCl_4$, CH_2Cl_2, 12 h; (b) $AlCl_3$, C_6H_6, N_2, 65 °C, 12 h; (c) DDQ, C_6H_6, CH_3OH, 25 °C, 24 h.

Synthesis. We have modeled the synthesis of the xanthone compounds on 4-demethoxydaunorubicin (**2**) rather than daunorubicin (**1**) since the former exhibits superior activity.[2,29] 5,8-Dimethoxytetralin (**7**) was prepared in four steps in 66% overall yield from 1,4-dimethoxybenzene. Friedel–Crafts acylation of **7** with *o*-methoxybenzoyl chloride in the presence of $SnCl_4$ afforded the ketone **8**. This was converted to the quinol **9** by demethylation with $AlCl_3$ in benzene. Oxidation of the quinol **9** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[30] and treatment of the resulting quinone in situ with CH_3OH yielded the xanthone **10** as shown in Scheme I.

The synthesis of the ring A acetyl substituted xanthones **25a,b** and **26a,b** required the initial preparation of the acetyltetralin **11**. The route used is shown in Scheme II.

Scheme II[a]



11 12 13 14 15 16 17

[a] Reaction conditions: (a) THF, CH_3OH, H_2O (1:1:1), 1.3 equiv of KOH, 36 h, room temperature; (b) TFAA–TFA (3:2), room temperature, 14 h; (c) H_2–Pd/C, EtOH, HCl; (d) KOH, aqueous EtOH (1:2), 90 °C, 3 h; (e) AcOH, piperidine, 120–25 °C, 1 h; (f) CH_3Li (3 equiv), THF/Et_2O (1:1), −10 °C, 6 h.

Selective hydrolysis of the methyl ester in **11**[31] with 1.3 equiv of KOH afforded the diester carboxylic acid **12**, which on cyclization with $(CF_3CO)_2O$ and CF_3CO_2H (3:2) gave the tetralone **13**, and then reduction gave the tetralin **14**. Hydrolysis to **15** and decarboxylation afforded the monoacid **16** in 85% overall yield from **11**. The acid **16** was converted to the ketone **17** in 98% yield on treatment with 3 equiv of CH_3Li. This procedure, different in approach from reported methods,[31,32] has the advantage of high yields in each step.

The xanthones **25a,b** were then prepared as shown in Scheme III. Condensation of *o*-methoxybenzoyl chloride with the tetralins **17** afforded the diketones **18a** and **18b** in 60% yield. The presence of the two regioisomers was evident in ^1H NMR (400 MHz), which showed two acetyl singlets at δ 2.26 and 2.27 in a 1:1 ratio. Treatment of **18** with $AlCl_3$ gave the trihydroxy compounds **22a** and **22b** in 50% yield. During demethylation of **18** an intermediate could be isolated in minor proportion, which was identified from its ^1H NMR, MS, and IR spectra as compound **23**. The phenolic protons in **23** appear at δ 10.20 and 12.10, which are shifted downfield compared to the third phenolic OH (in the case of **22a** and **22b**), which appears at δ 9.2. The phenolic signals at δ 10.20 disappear following oxidative cyclization to **25** (qv) from which it may be concluded that the two methoxy groups adjacent to the aryl

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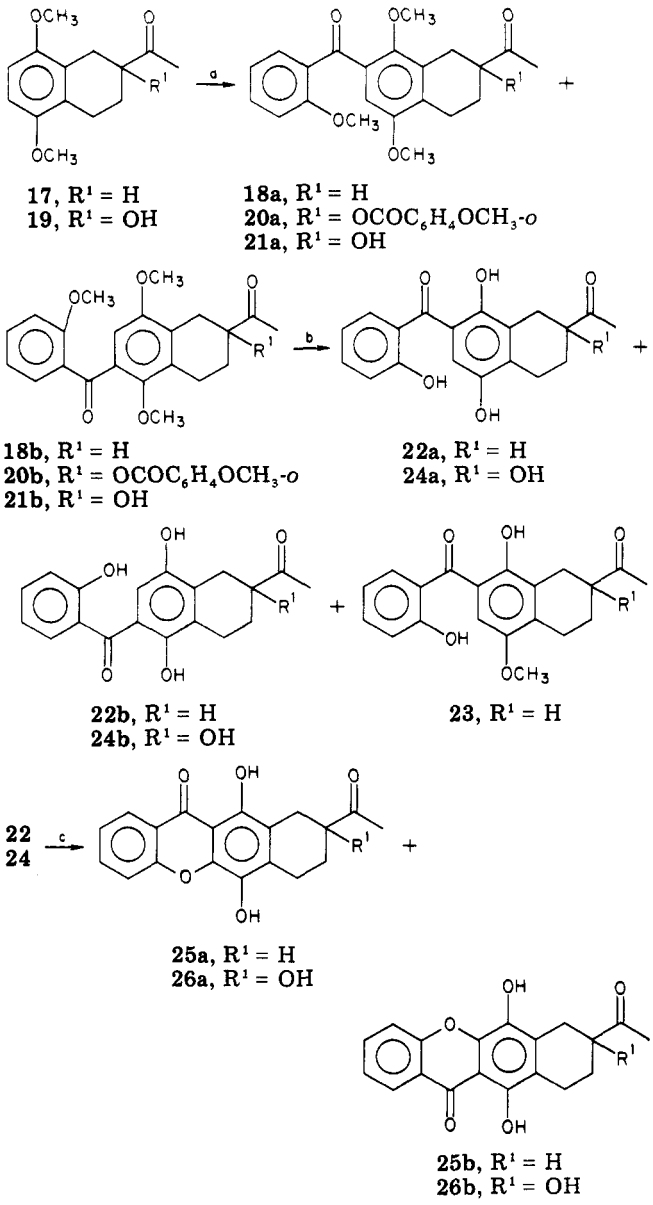
Scheme III[a]



[a] Reaction conditions: (a) (R^1 = H) *o*-methoxybenzoyl chloride, $SnCl_4$, CH_2Cl_2, 0 °C then 12 h at room temperature; (R^1 = OH) *o*-methoxybenzoyl chloride, $AlCl_3$, CH_2Cl_2 room temperature, 12 h, then 8% KOH in aqueous EtOH (1:2), 80 °C 3 h; (b) $AlCl_3$, C_6H_6, N_2, 50–60 °C, 12 h; (c) DDQ C_6H_6, CH_3OH, 50 °C.

carbonyl group in **18** are demethylated preferentially by $AlCl_3$.

Similar treatment of tetralin **19** (prepared from **17** by Wong's oxidative procedure[32]) with *o*-methoxybenzoyl chloride gave the esterified diketones **20a,b**, which were immediately subjected to base hydrolysis to give a mixture of monohydroxy ketones **21** in 51–55% yield. The latter were demethylated with $AlCl_3$ to give the tetrahydroxy compounds **24** in 51% yield. Oxidative cyclization using DDQ[30] in CH_3OH afforded the target xanthones **26a** and **26b** in 55% yield as shown in Scheme III. Functionalization of the modified anthracycline chromophore at the 7-position is crucial for further development and has caused problems in previously reported total syntheses.[2,3]

Treatment of the xanthone **10** with *N*-bromosuccinimide in $CHCl_3$ afforded the seven or ten bromo derivatives. These benzylic halides are known to be unstable[2,3] and therefore these derivatives were immediately converted to the corresponding methoxy or hydroxy derivatives by methanolysis (**27a,b**) or hydrolysis (**4a,b**), respectively (Scheme IV).

Separation of the regioisomers was not attempted at this stage until the conditions for the critical glycosidation step were established. In the event it proved possible to separate readily the regioisomeric analogues of daunorubicin at this latter stage. An initial attempt to couple the chromophore to a protected sugar moiety (in the example acetobromoglucose) in the presence of Ag_2CO_3[33] resulted only in the oxidation of ring B so that the xanthoquinones **28** were the only isolable products. A similar attempt to effect coupling under Koenig's Knorr conditions[34] employing mercuric bromide and mercuric cyanide as catalysts in the presence of protected sugars effected only elimination of the chromophore to produce **29**. Another trial condensation of triacetylglucal[43] with the xanthone chromophore in benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid again led to dehydration of the chromophore to **29**. However, coupling of the new chromophores to protected sugar could be effected by using $CdCO_3$[35,36] in place of silver carbonate to afford **30a** and **30b**. In this reaction ring A is especially prone to dehydration so that the elimination product **29** is also formed in substantial quantity.

It was possible to separate and assign the configurations of each isomeric product **30a** and **30b** after glycosidation. The structures of the regioisomers could be assigned on the basis of the high-field ^1H NMR spectra. The C_6-hydroxyl proton in the case of **30a** exhibited a downfield shift of 0.76 ppm as compared with the corresponding C_{11}-hydroxyl of the regioisomer **30b**. This characteristic chemical shift difference is attributed in the case of **30a** to strong intramolecular hydrogen bonding between the C_6-OH and the adjacent C_7-oxygen, whereas in contrast the corresponding C_{11}-OH in **30b** is not hydrogen bonded. In addition a downfield shift of the C_6-OH in **30b** was observed (0.05 ppm) compared with the corresponding C_{11}-OH in the regioisomer **30a**. This small chemical shift difference may be attributed to the additional flanking hydrogen bonding to the C_7-oxygen that obtains in the case of compound **30b**.

The configurations of the sugar moieties in **30a** and **30b** are assigned β on the basis of the ^1H NMR $J_{1'2'}$ coupling constants of the anomeric protons of 8.4 and 8.2 Hz, respectively, characteristic of trans diaxial coupling.[37] These configurations are anticipated since reaction of α-acetobromoglucose (anomeric coupling 4.0 Hz) by S_N2 displacement with the aglycon or by way of the orthoester[38,39] intermediate should result in inversion of configuration at the anomeric center.

Electron-impact or even chemical-ionization mass spectrometry unfortunately frequently fails to reveal the molecular ion peak in the case of anthracyclines[2,3] or similar large and fragile molecules. In the present work application of field desorption (FD)[40] mass spectrometry

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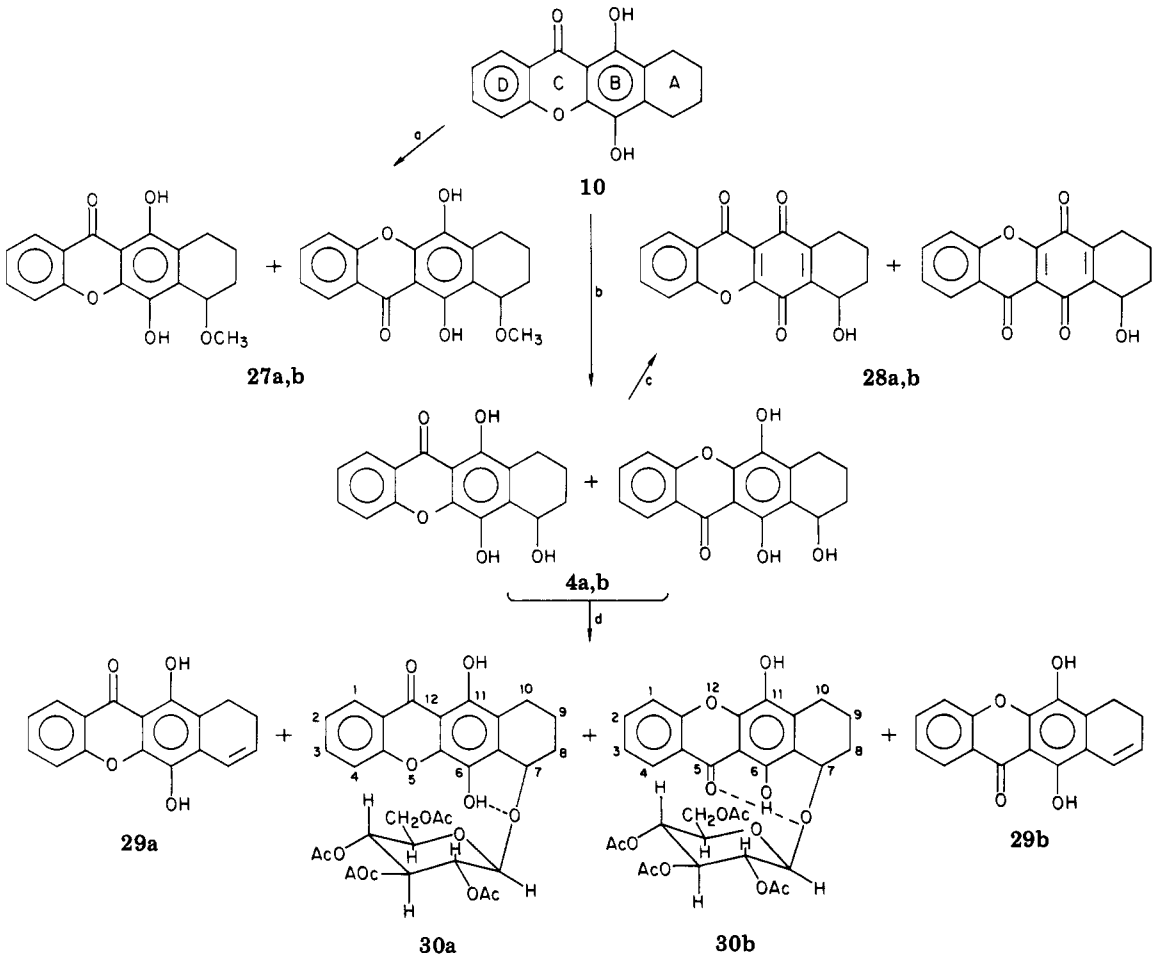
Scheme IV[a]



[a] Reaction conditions: (a) NBS, benzoyl peroxide, $CHCl_3$, 65 °C, followed by MeOH at 65 °C; (b) NBS, benzoyl peroxide, $CHCl_3$, 65 °C, followed by THF/H_2O, room temperature, 12 h; (c) acetobromoglucose, Ag_2CO_3, $CaSO_4$, CH_2Cl_2, 55 °C; (d) acetobromoglucose, $CdCO_3$, $CaSO_4$, CH_2Cl_2, 55 °C.

permitted the observation of the parent molecular ions of both regioisomers **30a** together with their characteristic fragmentation patterns.

Redox Characteristics of Xanthone Chromophore Modified Anthracycline Derivatives. Polarographic studies on xanthones **10**, **25**, **26**, **30a**, and **30b** showed that the chromophore as anticipated was extremely difficult to reduce, $E_{1/2}$ = −1.27 to −1.422 V vs. SCE compared with $E_{1/2}$ = −0.66 V for daunorubicin or adriamycin. Oxygen uptake by these compounds under activation with rat liver microsomal preparations was also very low **10**, **25**, **26**, **30a**, and **30b** were 8%, 12%, 10%, 12%, and 12% of the activity of adriamycin, respectively.[41] Therefore, compounds of this type would not be expected to give rise to significant amounts of oxygen radicals in vivo. Further work directed toward regiospecific and stereospecific synthesis of radically modified chromophores together with the means to couple them effectively to protected daunosamine therefore would seem to be justified in order to determine the characteristics of their binding to DNA. The marked effects on the properties of anthracyclines in which the chromophore is coupled to one, two, or three sugar moieties[2] suggests coupling of these radically modified chromophores to different types of sugars should also be explored. Efforts directed to both these objectives will be reported subsequently.

(41) We are indebted to Dr. J. H. Peters of SRI International, Menlo Park, CA, for these data.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. The IR spectra were recorded on a Nicolet 7199 FT spectrophotometer, and only the principal sharply defined peaks are reported. The ^1H NMR spectra were recorded on Perkin-Elmer 90 and Varian HA-100 analytical spectrometers or on Bruker WH-200 and WH-400 spectrometers. The spectra were recorded on approximately 5–15% (w/v) solutions, depending upon the spectrometers, in appropriate deuterated solvents with tetramethylsilane as internal standard. Line positions are recorded in parts per million from the reference. Electron-impact and field-desorption mass spectra were determined on an Associated Electrical Industries (AEI) MS-9 double-focusing high-resolution mass spectrometer and chemical-ionization mass spectra were recorded on an AEI MS-12 instrument using ammonia as reagent gas. The ionization energy, in general, was 70 eV. The peak measurements were made by comparison with perfluorotributylamine at a resolving power of 15000. Kieselgel DF-5 (Camag, Switzerland) and Eastman Kodak precoated sheets were used for thin-layer chromatography. In the workup procedures reported for the various syntheses described, solvents were removed with a rotary evaporator under reduced pressure without heating. Kieselgel (Fluka, Switzerland) was used for column chromatography. Electrochemical measurements of redox potentials were made as described previously.[18,19]

6-(2-Methoxybenzoyl)-5,8-dimethoxytetralin (8). Stannic chloride (3.12 g, 12 mmol) was added in portions to a solution of 5,8-dimethoxytetralin (**7**;[42,44] 1.92 g, 10 mmol) and *o*-meth-

(42) Livingstone, R.; Whiting, M. C. *J. Chem. Soc.* **1955**, 3631.
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oxybenzoylchloride (1.76 g, 11 mmol) in 40 mL of dry dichloromethane at 0 °C. When the addition was completed, the reaction mixture was stirred at room temperature for 12 h and then the reaction mixture treated with 50 mL of water and 5 mL of concentrated hydrochloric acid. The organic layer was washed with 8% aqueous sodium hydroxide solution and water and then dried (Na_2SO_4). The solvent was removed in vacuo and the residual solid purified by recrystallization from ether/petroleum ether (1:1), giving **8**: 3.09 g (95% yield); mp 85 °C; ^1H NMR ($CDCl_3$) δ 1.60–1.90 (m, 4 H), 2.55–2.80 (m, 4 H), 3.42 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 6.85 (s, 1 H, aryl), 6.88–7.06 (dt, 2 H, aryl), 7.30–7.50 (dt, 2 H, aryl); MS, *m/e* 326.1517 (34; calcd for $C_{20}H_{22}O_4$ 326.1518), 135.0449 (100, $M^+ - C_{12}H_{15}O_2$); IR ($CHCl_3$) 1650 (>C=O) cm^{-1}. Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.6, H, 6.7. Found: C, 73.6, H, 6.7.

6-(2-Hydroxybenzoyl)-5,8-dihydroxytetralin (9). A solution of 6-(2-methoxybenzoyl)-5,8-dimethoxytetralin (**8**; 3.26 g, 10 mmol) in 50 mL of dry benzene was treated with anhydrous aluminum chloride (4.0 g, 30 mmol) in portions and then heated at 65–60 °C overnight under an atmosphere of nitrogen. The reaction mixture was then poured onto an ice–hydrochloric acid mixture and the benzene layer removed, washed successively with aqueous sodium bicarbonate solution, and water, and then dried (Na_2SO_4). Removal of the solvent in vacuo gave a solid residue that was purified by column chromatography on silica gel. Elution with petroleum ether/ether (4:1) allowed separation of the desired trihydroxy ketone **9**, which was purified by recrystallization from benzene/petroleum ether: 1.28 g (45% yield); mp 128 °C; ^1H NMR ($CDCl_3$) δ 1.76–1.88 (m, 4 H), 2.66–2.78 (m, 4 H), 4.64 (s, 1 H, OH), 6.84 (s, 1 H, aryl), 6.86–6.92 (t, 1 H, aryl), 7.04–7.08 (d, 1 H, aryl), 7.42–7.50 (t, 1 H, aryl), 7.58–7.62 (d, 1 H, aryl), 10.46 (s, exchangeable 1 H, OH), 10.84 (s, exchangeable 1 H, OH); IR ($CHCl_3$) 3440 (OH), 1620 (>C=O) cm^{-1}; MS, *m/e* 284.1050 (100; calcd for $C_{17}H_{16}O_4$ 284.1049), 267.1018 (82.6, $M^+ - OH$), 191.0697 (24.5, $M^+ - C_6H_5O$), 121.0290 (58.2, $M^+ - C_{10}H_{11}O_2$). Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.8; H, 5.6. Found: C, 71.9; H, 5.7.

6,11-Dihydroxyxantho[2,3-*g*]tetralin (10). A solution of 6-(2-hydroxybenzoyl)-5,8-dihydroxytetralin (**9**; 2.84 g, 10 mmol) in 80 mL of dry benzene was added to a solution of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ; 2.27 g, 10 mmol) in 80 mL of benzene with stirring under a nitrogen atmosphere. After several seconds the DDQ–hydroquinone precipitated. The reaction mixture was stirred for a further 10 min and then filtered. The filtrate was concentrated in vacuo and the residue triturated with warm methanol. The solution was set aside at room temperature for 24 h when dihydroxyxanthotetralin (**10**) precipitated as a yellow solid, which was purified by recrystallization from tetrahydrofuran: 1.83 g (65% yield); mp 270 °C; ^1H NMR [$(CD_3)_2SO$] δ 1.75, (s, 4 H), 2.65 (s, 2 H), 2.78 (s, 2 H), 7.45–7.52 (t, 1 H, aryl) 7.6–7.66 (d, 1 H, aryl), 7.88–7.94 (t, 1 H, aryl), 8.14–8.22 (d, 1 H, aryl), 9.01 (s, 1 H, OH), 12.21 (s, 1 H, OH); IR ($CHCl_3$) 3420 (OH), 1650 (γ-pyrone) cm^{-1}; MS *m/e* 282.0893 (100; calcd for $C_{17}H_{14}O_4$ 282.0892). Anal. Calcd for $C_{17}H_{14}O_4$: C, 72.3; H, 5.0. Found: C, 72.4; H, 5.0.

6,11-Dihydroxy-7- and -10-methoxyxantho[2,3-*g*]tetralin (27a,b). A suspension of 6,11-dihydroxyxantho[2,3-*g*]tetralin (**10**; 0.282 g, 1 mmol) in 20 mL of dry chloroform was brought to reflux under an atmosphere of nitrogen and a mixture of *N*-bromosuccinimide (0.18 g, 1 mmol) and benzoyl peroxide (3 mg) was added, and the reaction contents were stirred under reflux for 1.5 h. The solvent was removed under reduced pressure and the residue taken up in absolute methanol (20 mL) and the solution heated under reflux with stirring under nitrogen for 12 h. The solvent was removed in vacuo and the residue taken up in ethyl acetate. The ethyl acetate solution was washed with water and dried (Na_2SO_4). Removal of the solvent in vacuo gave **27** as a yellow solid, which was purified by column chromatography on silica eluted with 1:1 petroleum ether/ether. The 6,11-dihydroxy-7-methoxyxantho[2,3-*g*]tetralins (**27a,b**) were purified by recrystallization from tetrahydrofuran ether: 156 mg (50% yield); mp 160–166 °C; ^1H NMR ($CDCl_3$) δ 1.66–1.80 (m, 1 H), 1.9–2.10 (m, 2 H), 2.14–2.26 (m, 1 H), 2.60–2.72 (m, 1 H), 2.76–2.90 (m, 1 H), 3.55 (s, 3 H, OCH_3), 5.88–5.98 (dt, 1 H, C_7-H), 7.34–7.40 (dt, 1 H, aryl), 7.54–7.58 (dd, 1 H, aryl), 7.70–7.77 (dt, 1 H, aryl), 7.86 (s, 1 H, OH), 8.24–8.30 (d, 1 H, aryl), 12.24 (s, 1 H, OH); MS, *m/e* 312.0993 (6.4; calcd for $C_{18}H_{16}O_5$ 312.0998), 281.0768 (21.7, $M^+ - OCH_3$), 280.0726 (100, $M^+ - CH_3OH$); CIMS (NH_3 reagent gas) *m/e* 313 (67.3, $M^+ + 1$) 281 (34.9, $M^+ + 1 - CH_3OH$). Anal. Calcd for $C_{18}H_{16}O_5$: C, 69.2; H, 5.1. Found: C, 69.3; H, 5.2.

6,11-Dihydroxy-7- and -10-hydroxyxantho[2,3-*g*]tetralin (4a,b). A similar *N*-bromosuccinimide bromination of the 6,11-dihydroxy-7-methoxyxantho[2,3-*g*]tetralin (**10**) and using the same quantities was carried out and the product obtained after removal of the chloroform was stirred with 20 mL of 50% aqueous tetrahydrofuran at room temperature for 12 h. The solvent was removed under reduced pressure and the residue washed thoroughly with water and then with chloroform. Column chromatography of the product on silica with elution by 1:1 ether/petroleum ether to elute unreacted starting material followed by elution with 1:9 tetrahydrofuran/ether gave the 7-hydroxy derivatives **4a,b**. This was further purified by recrystallization from THF/ether: 200 mg (67% yield); mp 182–187 °C; ^1H NMR [$(CD_3)_2SO$] δ 1.68 1.78 (m, 1 H), 1.84–1.94 (m, 1 H), 1.96–2.06 (m, 1 H), 2.06–2.16 (m, 1 H), 2.60–2.80 (m, 2 H), 5.08–5.16 (dd, 1 H, C_7-H), 5.62–5.66 (d, 1 H, exchangeable C_7OH), 7.36–8.28 (m, 4 H, aryl), 9.18 (s, 1 H, exchangeable OH), 12.20 (s, 1 H, exchangeable OH); MS, *m/e* 298.0825 (5.4; calcd for $C_{17}H_{14}O_5$ 298.0841), 280.0724 (100, $M - H_2O$); CIMS (NH_3 reagent gas), *m/e* 299 (41.6, $M^+ + 1$), 281 (100, $M^+ + 1 - H_2O$). Anal. Calcd for $C_{17}H_{14}O_5$: C, 68.5; H, 4.7. Found: C, 68.5; H, 4.8.

4-(2,5-Dimethoxyphenyl)-3,3-dicarbethoxybutanoic Acid (12). A solution of the triester **11** (3.82 g, 10 mmol) in 30 mL of 1:1:1 tetrahydrofuran/methanol/water containing potassium hydroxide (0.728 g, 1.3 equiv) was stirred at room temperature for 36 h. The organic solvents were removed in vacuo at 25 °C and the aqueous layer acidified with hydrochloric acid. The product was extracted with chloroform, washed with water, and dried (Na_2SO_4). Removal of the solvent afforded the diethyl ester monoacid **12** (3.1 g, 84% yield), which was purified by recrystallization from methanol: mp, 121–122 °C; ^1H NMR ($CDCl_3$) δ 1.22 (t, 6 H, $2CO_2CH_2CH_3$), 2.90 (s, 2 H, CH_2CO_2H), 3.45 (s, 2 H, benzylic), 3.66 (s, 3 H, OCH_3), 3.69 (s, 3 H, OCH_3), 4.20 (q, 4 H, $2CO_2CH_2CH_3$), 6.60 (d, 1 H, aryl), 6.78 (d, 2 H, aryl), 10.85 (br s, 1 H, CO_2H, exchangeable); MS *m/e* 368.1471 (59%; calcd for $C_{18}H_{24}O_8$ 368.1471); IR ($CHCl_3$) 1755, 1735 (ester CO), 1710 (acid CO) cm^{-1}.

3,3-Dicarbethoxy-5,8-dimethoxy-1-tetralone (13). A solution of the dicarbethoxy monoacid **12** (3.68 g, 10 mmol) in 14.8 mL of trifluoroacetic acid and 22.2 mL of trifluoroacetic anhydride (3:2) was stirred at room temperature for 14 h. The reaction mixture was poured into ice water, the product isolated by chloroform extraction, and the extract washed with water and dried (Na_2SO_4). The product tetralone **13** was purified by recrystallization from aqueous ethanol: 3.4 g (97% yield); mp 90–94 °C; ^1H NMR ($CDCl_3$) δ 1.12 (t, 6 H, $2CO_2CH_2CH_3$), 3.06 (s, 2 H, $COCH_2$), 3.42 (s, 2 H, benzylic), 3.80 (s, 6 H, $2OCH_3$), 4.14 (q, 4 H, $2CO_2CH_2CH_3$), 6.92 (q, 2 H, aryl); MS, (*m/e*) 350.1366 (51; calcd for $C_{18}H_{22}O_7$ 350.1366), 277.1076 ($M^+ - CO_2C_2H_5$, 100); IR ($CHCl_3$) 1750 (ester), 1685 (>C=O), 1585 (aryl) cm^{-1}.

2,2-Dicarbethoxy-5,8-dimethoxytetralin (14). A solution of the tetralone **13** (3.5 g, 10 mmol) in 125 mL of 95% ethanol containing 2 mL of concentrated hydrochloric acid was hydrogenated under atmospheric pressure in the presence of 5% palladium on charcoal until consumption of hydrogen ceased. The filtered solution was concentrated in vacuo to give 2,2-dicarbethoxy-5,8-dimethoxytetralin (**14**) as a low-melting solid: 3.36 g (100% yield); mp 49–50 °C; ^1H NMR ($CDCl_3$) δ 1.18 (t, 6 H, $2CO_2CH_2CH_3$), 2.25 (t, 2 H), 2.67 (t, 2 H), 3.14 (s, 2 H), 3.72 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 4.15 (q, 4 H, $2CO_2CH_2CH_3$), 6.62 (s, 2 H, aryl); MS, *m/e* 336.1571 (99.4; calcd for $C_{18}H_{24}O_6$ 336.1572); IR ($CHCl_3$) 1735 (ester), 1600 (aryl) cm^{-1}.

2,2-Dicarboxy-5,8-dimethoxytetralin (15). A solution of 2,2-dicarbethoxy-5,8-dimethoxytetralin (**14**; 3.36 g, 10 mmol) in 75 mL of (1:2) aqueous ethanol containing 1.2 g of potassium hydroxide was heated at 90 °C for 3 h. Removal of the solvent in vacuo and acidification with concentrated hydrochloric acid caused precipitation of the product diacid **15**, which was purified by recrystallization from acetone: 2.68 g (96% yield); mp 166–170 °C; ^1H NMR [$(CD_3)_2CO$] δ 2.24 (t, 2 H, CH_2), 2.72 (t, 2 H, CH_2),

(44) Royer, R.; Bisagni, E.; Menichi, G. *Bull Soc. Chim. Fr.* **1964**, 2112.

3.15 (s, 2 H, benzylic), 3.75 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 6.70 (s, 2 H, aryl); MS, *m/e* 280.0948 (54.7; calcd for $C_{14}H_{16}O_6$ 280.0949), 236.1047 (100, $M^+ - CO_2$); IR ($CHCl_3$) 1690 (acid CO); 1600 (aromatic) cm^{-1}.

5,8-Dimethoxytetralin-2-carboxylic Acid (16). The 2,2-dicarboxy-5,8-dimethoxytetralin (**15**; 2.8 g, 10 mmol) was decarboxylated by heating with a mixture of 20 mL of acetic acid and 4 mL of piperidine at 120–125 °C for 1 h. The reaction mixture was diluted with water and extracted with chloroform. The usual workup procedure afforded the tetralin acid **16** which was purified by recrystallization from acetone: 2.26 g (96% yield); mp 176–177 °C; ^1H NMR [$(CD_3)_2CO$] δ 1.68 (m, 1 H), 2.16 (m, 1 H), 2.58 (m, 3 H), 2.85 (dq, 1 H), 3.00 (m, 1 H), 3.75 (s, 6 H, $2OCH_3$), 6.70 (s, 2 H, aryl); MS, *m/e* 236.1049 (100; calcd for $C_{13}H_{16}O_4$ 236.1049); IR ($CHCl_3$) 1690 (acid CO), 1600 (aromatic) cm^{-1}.

2-Acetyl-5,8-dimethoxytetralin (17). An ether solution of methyllithium (28.1 mL, 45 mmol) was added dropwise with stirring at −10 °C to a solution of 5,8-dimethoxytetralin-2-carboxylic acid (**16**; 3.54 g, 15 mmol) in 150 mL of (1:1) tetrahydrofuran–ether. During the addition of lithium salt of the acid separated as a white precipitate and redissolved as the addition was continued. Stirring was continued for a further 6 h and then the reaction mixture was poured on to an ice–hydrochloric acid mixture. The product was extracted with chloroform, and the extract was washed with sodium bicarbonate solution and dried (Na_2SO_4). Removal of the solvent afforded 2-acetyl-5,8-dimethoxytetralin (**17**), which was purified by recrystallization from chloroform–petroleum ether; 3.45 g (98% yield); mp 82–83 °C; ^1H NMR ($CDCl_3$) δ 1.62 (m, 1 H), 2.15 (m, 1 H), 2.25 (s, 3 H, $COCH_3$), 2.55 (m, 3 H), 3.00 (m, 2 H), 3.80 (s, 6 H, $2OCH_3$), 6.65 (s, 2 H, aryl); MS, *m/e* 234.1256 (100; calcd for $C_{14}H_{18}O_3$ 234.1256), 219.1021 ($M^+ - CH_3$, 30); 191.1069 (46, $M^+ - COCH_3$); IR ($CHCl_3$) 1700 ($COCH_3$) cm^{-1}.

2-Acetyl-5,8-dimethoxy-2-hydroxyetetralin (19). Compound **19** was prepared from 2-acetyl-5,8-dimethoxytetralin (**17**), employing a published oxidative procedure.[32]

6- and 7-(2-Methoxybenzoyl)-2-acetyl-5,8-dimethoxytetralin (18a,b). The Friedel–Crafts condensation of *o*-methoxybenzyl chloride and the 2-acetyl-5,8-dimethoxytetralin (**17**) was carried out as described for the preparation of **8**. The product was purified by column chromatography on silica with elution by ether to give the tetralins **18a** and **18b** in 60% yield as an oil. The ratio of the regioisomers **18a** and **18b** was 1:1 as shown by the two ^1H NMR acetyl signals at δ 2.26 and 2.27: ^1H NMR ($CDCl_3$) δ 1.60–1.74 (m, 2 H), 2.22–2.28 (d, 3 H, $COCH_3$), 2.55–2.75 (m, 3 H), 2.90–3.08 (m, 2 H), 3.45 (s, 3 H, OCH_3), (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 6.88 (d, 1 H, aryl), 6.94–7.02 (q, 2 H, aryl), 7.42–7.50 (dq, 2 H, aryl; MS, *m/e* 368.1626 (100; calcd for $C_{22}H_{24}O_5$ 368.1624), 261.1120 (12.8, $M^+ - C_7H_7O$), 233.1181 (6.5, $M^+ - C_8H_7O_2$), 135.0448 (91.8, $M^+ - C_{14}H_{17}O_3$); IR ($CHCl_3$) 1705 (acetyl CO), 1650 (diaryl CO), 1600 (aromatic) cm^{-1}. Anal. Calcd for $C_{22}H_{24}O_5$: C, 71.7, H, 6.5. Found: C, 71.6; H, 6.7.

6- and 7-(2-Methoxybenzoyl)-2-acetyl-2-hydroxy-5,8-dimethoxytetralin (21a,b). When the Friedel–Crafts condensation of *o*-methoxybenzoyl chloride and 2-acetyl-2-hydroxy-5,8-dimethoxytetralin (**19**) was initially carried out as described for the preparation of **18a,b**, the products isolated were the 2-esters of **21**, i.e., **20a,b** formed by reaction with the aryl chloride. Ultimately, compounds **21a,b** were prepared by using 5 equiv of *o*-methoxybenzoyl chloride under otherwise similar conditions for the preparation of **18**. The product esters **20** were hydrolyzed by heating with an 8% aqueous ethanolic (1:2) solution of potassium hydroxide at 80–90 °C for 3 h. The ethanol was removed in vacuo and the aqueous layer extracted with ethyl acetate. The organic layer was washed with water and dried (Na_2SO_4). Removal of the solvent gave the benzoyltetralins **21a** and **21b**, which were purified by column chromatography on silica in 51.5% yield: ^1H NMR ($CDCl_3$) δ 1.94 (m, 2 H), 2.34 (s, 3 H, $COCH_3$), 2.82 (m, 2 H), 3.00 (m, 2 H), 3.44 (s, 3 H, OCH_3), 3.58 (s, 1 H, OH), 3.74 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 6.92 (s, 1 H, aryl), 7.00 (q, 2 H, aryl), 7.50 (m, 2 H, aryl); MS, *m/e* 384.1574 (68.1; calcd for $C_{22}H_{24}O_6$ 384.1574), 366.1467 (4.7, $M^+ - H_2O$), 135.0447 (100, $M^+ - C_{14}H_{17}O_4$); IR ($CHCl_3$) 1708 ($COCH_3$), 1655 (aryl CO) cm^{-1}.

6- and 7-(2-Hydroxybenzoyl)-2-acetyl-5,8-dihydroxytetralins (22a,b). The benzoylacetyltetralins **18a** and **18b** were demethylated with aluminum chloride following the same procedure as was used for compound **9**. The product was purified by column chromatography on silica with elution by tetrahydrofuran–ether and finally by recrystallization: mp 175 °C; ^1H NMR [$(CD_3)_2SO$] δ 1.48–1.60 (m, 1 H), 2.04–2.16 (dd, 1 H), 2.18–2.26 (d, 3 H, $COCH_3$), 2.44–2.60 (m, 2 H), 2.70–2.80 (m, 2 H), 2.80–2.90 (dd, 1 H), 6.62 (s, 1 H, aryl), 6.90–7.00 (dq, 2 H, aryl), 7.20–7.24 (dd, 1 H, aryl), 7.32–7.40 (dt, 1 H, aryl), 9.2 (d, 1 H, OH), 10.02 (s, 1 H, OH), 12.00 (s, 1 H, OH); MS, *m/e* 326.1156 (53; calcd for $C_{19}H_{18}O_5$ 326.1157), 309.1127 (29.8, $M^+ - OH$), 121.0291 (57, $M^+ - C_{12}H_{13}O_3$), 205.0851 (6.3, $M^+ - C_7H_5O_2$); IR (KBr disks) 3400 (br, OH), 1700 (acetyl >CO) 1620 (diaryl CO) cm^{-1}. anal. Calcd for $C_{19}H_{18}O_5$: C, 69.9; H, 5.5. Found: C, 70.1; H, 5.6. Column chromatograph permitted the isolation of the partially demethylated product 7-(2-hydroxybenzoyl)-2-acetyl-1-hydroxy-5-methoxytetralin (**23**), purified by recrustallization from tetrahydrofuran–petroleum ether: mp 135 °C; ^1H NMR [$(CD_3)_2SO$] δ 1.52–1.62 (m, 1 H), 2.08–2.19 (m, 1 H), 2.24 (s, 3 H, $COCH_3$), 2.50–2.68 (m, 2 H), 2.70–2.84 (dd, 2 H), 2.85–2.94 (dd, 1 H), 3.58 (s, 3 H, OCH_3), 6.64–7.44 (m, 5 H, aryl), 10.20 (br s, 1 H, exchangeable OH), 12.10 (br s, 1 H, exchangeable OH); MS *m/e* 340.1309 (100; calcd for $C_{20}H_{20}O_5$ 340.1311), 323.1279 (34, M^+ –OH), 297.1128 (13, $M^+ - COCH_3$), 121.0291 (76.8, $M^+ - C_{13}H_{15}O_3$). Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.6; H, 5.9. Found: C, 70.6; H, 5.9.

6- and 7-(2-Hydroxybenzoyl)-2-acetyl-2,5,8-trihydroxytetralin (24a,b). The (2-hydroxybenzoyl)acetyltetralins **21a** and **21b** were demethylated in a similar way as for **8** except that 10 molar equiv of aluminum chloride was used (instead of the 5 molar equiv used for **8**) and the heating was carried out for 30 h. The demethylated product **24a,b** was purified by recrystallization from ether–petroleum ether (40% yield): mp 160–167 °C; IR (KBr disk) 3430 (OH), 1705 ($COCH_3$), 1620 (diaryl CO) cm^{-1}; NMR [$CDCl_3$ + $(CD_3)_2SO$] δ 2.05 (m, 2 H), 2.28 (s, 3 H, $COCH_3$), 2.70–3.00 (m, 4 H), 3.95 (br s, 1 H, OH), 6.85 (t, 1 H, aromatic), 6.91 (s, 1 H, Ar), 6.98 (d, 1 H, Ar), 7.38 (dt, 1 H, Ar), 7.56 (dd, 1 H, Ar), 8.02 (br s, 1 H, OH), 10.68 (s, 1 H, OH), 11.69 (s, 1 H, OH); MS, *m/e* 342.1106 (34.7; calcd for $C_{19}H_{18}O_6$ 342.1103), 324.1002 (4.9, $M^+ - H_2O$), 299.0919 (42.5, $M^+ - COCH_3$), 121.0291 (100, $M^+ - C_{12}H_{13}O_4$).

9-Acetyl-6,11-dihydroxyxantho[2,3-*g*]- and -[3,2-*g*]tetralin (25a,b). A stirred solution of 2,3-dichloro-5,6-dicyanobenzoquinone (113.2 mg, 0.5 mmol) in 3 mL of dry benzene was treated dropwise with a solution of the trihydroxy ketones **22** (163 mg, 0.5 mmol) in 5 mL of warm (50 °C) methanol under a nitrogen atmosphere. The solution was stirred for 8 h at room temperature and then at 40 °C for 15 min. The organic solvents were removed in vacuo, the residue taken up in benzene, and the solution filtered to remove the hydroquinone. The product **25** was isolated by column chromatography on silica by elution with ether. The main fraction gave **25** as a yellow solid: 85 mg (52% yield) which was recrystallized from THF–ether: mp 224–30 °C; ^1H NMR [$(CD_3)_2SO$] δ 1.50–1.64 (m, 1 H), 2.10–2.20 (d, 1 H), 2.24 (d, 3 H, $COCH_3$), 2.44–3.06 (m, 5 H), 7.44–7.52 (t, 1 H), 7.60–7.70 (dd, 1 H), 7.86–7.96 (dt, 1 H), 8.14–8.24 (d, 1 H), 9.04–9.14 (d, 1 H, OH) (from the intensity ratio of the 11-OH signals it could be estimated that the ratio of **26a** to **26b** was 1:2), 12.16–12.26 (d, 1 H, OH); MS, *m/e* 324.0998 (85; calcd for $C_{19}H_{16}O_5$ 324.0998), 309.0772 (45.9, $M^+ - CH_3$), 281.0799 (100, $M^+ - COCH_3$), 254.0571 (20.3, $M^+ - CH_2{=}CHCOCH_3$, due to retro-Diels–Alder cleavage of the parent molecule[2]); IR (KBr disk) 3440 (OH), 1680 ($COCH_3$), 1630 (γ-pyrone) cm^{-1}. Anal. Calcd for $C_{19}H_{16}O_5$: C, 70.4; H, 4.9. Found: C, 70.2; H, 5.1.

9-Acetyl-6,9,11-trihydroxyxantho[2,3-*g*]- and -[3,2-*g*]tetralin (26a,b). The title products were obtained by treatment of tetrahydroxydiketotetralins (**24**) with DDQ following a similar procedure as was described for the preparation of **25**. Compounds **26a,b** were obtained as yellow solids (51% yield): mp 235–239 °C; ^1H NMR [$(CD_3)_2SO$] δ 1.82 (m, 2 H), 2.29 (s, 3 H, $COCH_3$), 2.72–2.90 (m, 4 H), 5.53 (s, 1 H, C_9-OH), 7.49 (dt, 1 H), 7.65 (d, 1 H), 7.92 (dt, 1 H), 8.20 (dd, 1 H, aryl), 9.08 (s, 1 H, OH), 12.20 (s, 1 H, OH); MS, *m/e* 340.0945 (43.4; calcd for $C_{19}H_{16}O_6$ 340.0946), 322.0838 (15, $M^+ - H_2O$), 297.0759 (100, $M^+ - COCH_3$), 279.0657 (24, 297 − H_2O, 322 − $COCH_3$), 254.0573 (10.7, $M^+ - C_4H_6O_2$, retro-Diels–Alder cleavage); IR (KBr disk) 3430 (br, OH), 1705 (s, $COCH_3$) 1645, 1625 (γ-pyrone) cm^{-1}.

7- and 10-Hydroxyxantho[2,3-*b*]-5,6,7,8-tetrahydro-1,4-naphthoquinone (28a,b). A mixture of 6,11-dihydroxy-7- and -10-hydroxyxantho[2,3-*g*]tetralin (4; 149 mg, 0.5 mmol), acetobromoglucose (411 mg, 1 mmol), silver carbonate (275.7 mg, 1 mmol), and calcium sulfate (1 g) in 15 mL of dry methylene chloride was heated at 55 °C with stirring for 5 h. The reaction mixture was diluted with 25 mL of tetrahydrofuran and filtered to remove inorganic material. The solvent was removed under reduced pressure, affording **28** as a yellow solid, which was purified by recrystallization from acetonitrile: 75 mg (50% yield); mp 210–215 °C; ^{1}H NMR [$(CD_3)_2SO$ + $CDCl_3$] δ 1.52–1.64 (t, 1 H), 1.64–2.80 (m, 5 H), 4.85 (s, 1 H, C_7-H), 5.10–5.16 (d, 1 H, C_7-OH exchangeable), 7.5–7.62 (t, 1 H, Ar), 7.7–7.8 (d, 1 H, Ar), 7.84–7.90 (t, 1 H, Ar), 8.16–8.28 (d, 1 H, Ar); IR (KBr disk) 3500 (OH), 1690 (quinone C=O), 1620 (γ-pyrone) cm^{-1}; MS, *m/e* 296.0690 (69.05; calcd for $C_{17}H_{12}O_5$ 296.0695), 278.0568 (29.6, $M^+ - H_2O$). Anal. Calcd for $C_{17}H_{12}O_5$: C, 68.9, H, 4.1. Found: C, 69.0; H, 4.2.

Glycosylation of 6,11-Dihydroxy-7- and -10-hydroxyxantho[2,3-*g*]tetralin (4). A mixture of 6,11-dihydroxy-7- and -10-hydroxyxantho[2,3-*g*]tetralins (4; 0.298 g, 1 mmol), acetobromoglucose (0.822 g, 2 mmol), cadmium carbonate[35,36] (0.345 g, 2 mmol), and anhydrous calcium sulfate (2 g) in 20 mL of dry 1,2-dichloroethane was heated at 55 °C with stirring. After 24 h of continuous heating and stirring was added another molar equivalent of acetobromoglucose and the reaction contents heated for a further 66 h. The reaction mixture was then diluted with 25 mL of tetrahydrofuran and filtered. The inorganic material was washed with 20 mL of tetrahydrofuran, and the combined filtrates were concentrated in vacuo to give a yellow syrup, which was subjected to column chromatography on silica.

7,8- and 9,10-Dihydro-6,11-dihydroxyxantho[2,3-*g*]naphthalene (29a,b). The first product eluted with 50:50 ether–petroleum ether was the elimination product **29a,b**, which was purified by recrystallization from tetrahydrofuran and ether: 112 mg (40% yield); mp 235 °C; ^{1}H NMR [$(CH_3)_2SO$] δ 2.26–2.36 (m, 2 H), 2.69–2.78 (t, 2 H), 6.30–6.38 (dt, 1 H), 6.90–6.98 (dd, 1 H), 7.42–7.50 (t, 1 H, aryl), 7.58–7.66 (d, 1 H, aryl), 7.84–7.92 (t, 1 H, aryl), 8.12–8.18 (d, 1 H, aryl), 9.14–9.24 (d, 1 H, exchangeable OH); MS *m/e* 280.0731 (100; calcd for $C_{17}H_{12}O_4$, 280.0735), 263.0686 (18.2, M^+ - OH); IR ($CHCl_3$) 3360 (br, OH), 1655 (γ-pyrone) cm^{-1}. Anal. Calcd for $C_{17}H_{12}O_4C$: 72.8; H, 4.3. Found: C, 72.5; H, 4.6.

7β-(Tetraacetoglucosyl)-6,11-dihydroxyxantho[2,3-*g*]tetralin (30a). Further elution with ether was continued with collection of 25-mL fractions. The early fractions were combined on the basis of monitoring by TLC and evaporated to afford syrup, which was taken up in the minimum of ether and chilled. A yellow solid separated, which was collected and washed with ether to give compound **30a**, which was further purified by recrystallization from tetrahydrofuran and ether: 21 mg (3.5% yield); mp 215 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 1.52–1.64 (t, 1 H), 1.64–1.86 (m, 5 H, CH_2, $OCOCH_3$), 1.90 (s, 3 H, $OCOCH_3$), 1.99 (s, 3 H, $OCOCH_3$), 2.06 (s, 3 H, $OCOCH_3$), 2.20–2.28 (m, 1 H), 2.34–2.46 (m, 1 H), 2.72–2.82 (dd, 1 H), 4.02–4.10 (m, 2 H), 4.20–4.30 (q, 1 H), 4.66–4.74 (q, 1 H), 4.84–4.94 (t, 1 H), 5.02–5.08 (d, 1 H, anomeric proton $J_{1'2'}$ = 8.4 Hz), 5.16–5.20 (t, 1 H, C_7-H), 5.20–5.28 (t, 1 H), 7.46–7.54 (t, 1 H, Ar), 7.64–7.68 (d, 1 H, Ar), 7.90–7.96 (t, 1 H, Ar), 8.16–8.24 (d, 1 H, Ar), 9.30–9.44 (br s, 1 H, exchangeable C_6-OH), 12.10 (s, 1 H, exchangeable C_{11}-OH) [see text for assignment of regiochemistry of chromophore based on ^{1}H NMR evidence]; MS (field desorption;[40] argon–sulfolane) *m/e* 628 (4.3, M^+), 281 [100, $C_{17}H_{13}O_4$, M^+ - (*O*-sugar)], 347 [2.6 (*O*-acetoglucose moiety)], 280 [83.0, $C_{17}H_{12}O_4$, M^+ - (*O*-sugar) - H^+], 297 (25.5, $C_{17}H_{13}O_5$), 331 (8.2, $M^+ - C_{17}H_{13}O_5$); IR (KBr disk) 3420 (br, OH), 1740, 1750 (acetyl C=O) cm^{-1}. Anal. Calcd for $C_{31}H_{32}O_{14}$: C, 59.2; H, 5.1. Found: C, 59.4; H, 5.2.

7β-(Tetraacetoglucosyl)-6,11-dihydroxyxantho[3,2-*g*]tetralin (30b). Concentration of the combined later ether fractions gave a yellow solid, which was collected and purified by recrystallization from tetrahydrofuran–ether: 21 mg (3.5% yield); mp 230–232 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 1.58–1.70 (m, 2 H), 1.72–1.84 (br s, 1 H), 1.94 (s, 3 H, $OCOCH_3$), 2.00 (s, 3 H, $OCOCH_3$), 2.02 (s, 3 H, $OCOCH_3$), 2.05 (s, 3 H, $OCOCH_3$), 2.10–2.22 (br d, 1 H), 2.34–2.46 (m, 1 H), 2.78–2.90 (br d, 1 H), 4.00–4.06 (dd, 1 H), 4.06–4.14 (m, 1 H), 4.20–4.30 (dd, 1 H), 4.70–4.80 (q, 1 H), 4.90–4.98 (t, 1 H), 5.16–5.24 (d, anomeric proton $J_{1'2'}$ = 8.2 Hz, and t, C_7-H, 2 H), 5.30–5.38 (t, 1 H), 7.46–7.54 (t, 1 H, aryl), 7.64–7.70 (d, 1 H, aryl), 7.90–7.98 (t, 1 H, aryl), 8.20–8.22 (d, 1 H, aryl), 8.54–8.64 (s, 1 H, exchangeable C_6-OH), 12.15 (s, 1 H, exchangeable C_{11}-OH) [see text for assignment of regiochemistry of chromophore based on ^{1}H NMR data]; MS (field desorption;[40] argon–sulfolane) *m/e* 628 (5.8, M^+), 281 [100, $C_{17}H_{13}O_4$, M^+ - (*O*-sugar)], 347 (2.2 *O*-acetoglucose moiety), 331 (6.4, $M^+ - C_{17}H_{13}O_5$), 280 [89.2, $C_{17}H_{12}O_4$, M^+ - (*O*-sugar) - H^+)], 297 (14.6, $C_{17}H_{13}O_5$); IR ($CHCl_3$) 3460 (OH), 1750 (acetyl = C=O) cm^{-1}. Anal. Calcd for $C_{31}H_{32}O_{14}$: C, 59.2; H, 5.1. Found: C, 59.3; H, 5.2.

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