Regiospecific Synthesis of Redox Inactive Ring C Modified Aglycones Related to Anthracyclines. Application of Photo-Fries Rearrangement and Novel Nucleophile-Catalyzed Rearrangements Leading to the Xantho[2,3-*g*]tetralin and Xantho[2,3-*f*]tetralin Systems

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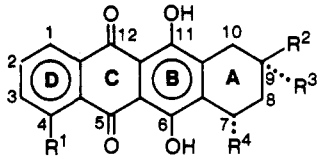
Regiospecific synthetic routes have been developed to chromophores of the anthracycline antibiotics in which the quinone ring C is replaced by a γ-pyrone. Such structures are potentially less cardiotoxic than the parent antibiotics because of their very low in vitro redox activity and low hepatic microsomal oxygen consumption. Initial exploratory studies revealed the characteristic sensitivity of ring A of the xantho[2,3-*g*]tetralin and xantho[3,2-*g*]tetralin systems toward elimination and guided subsequent synthetic strategy. Photo-Fries rearrangement of an acylated and doubly protected tetralin set up the required xantho[2,3-*g*]tetralin framework regiospecifically. While Lewis acid catalyzed dealkylation caused extensive elimination, sodium thiocresolate induced dealkylation of the intermediate protected benzoyltetralin initially resulted primarily in rearrangement to the xantho[2,3-*f*]tetralin systems, producing six products in all. Examination of the factors controlling the formation of the six products in the latter reaction and a consequent change in reaction conditions permitted optimization of the yield of the desired xantho[2,3-*g*]tetralin precursor. Controlled acid deprotection and equilibration of the 4,5-acetonide of the intermediate benzoyltetralin affords the desired trans 7,9-stereochemistry with an axially oriented hydroxyl. 9-Hydroxylation which was followed by controlled acid deprotection afforded the target aglycone 9-acetyl-6,7α,9α,11-tetrahydroxyxantho[2,3-*g*]tetralin.

Introduction

The anthracycline antitumor antibiotics, including daunorubicin (I), 4-demethoxydaunorubicin (II), and doxorubicin (III) are used widely in the clinical treatment of a range of human malignancies.[1-3] However their



I $R^1 = OCH_3$; $R^2 = COCH_3$; $R^3 = OH$; R^4 = daunosaminyl
II $R^1 = H$; $R^2 = COCH_3$; $R^3 = OH$; R^4 = daunosaminyl
III $R^1 = OCH_3$; $R^2 = COCH_2OH$; $R^3 = OH$; R^4 = daunosaminyl

principal clinical limitation is the severe risk of cardiotoxicity attending their administration.[4-7] Because of this side effect recent efforts in the anthracycline area have focused on elucidating the molecular origin of the cytotoxicity[8-10] and cardiotoxicity[8-15] and in structural modification to minimize or eliminate the side effect while retaining the antitumor properties.[14,15] There is accumulating evidence that relates the onset of cardiotoxicity to the property of the anthracycline chromophore to undergo microsomal enzymatic reduction with the concomitant generation of reactive oxygen species.[8,12-15] The latter may lead to lipid peroxidation[12,13] in cardiac tissue which is susceptible to such damage owing to the suppressed levels of catalase[16,17] and possibly superoxide dismutase[12,18] in this organ. Structural modification of the chromophore in a series of daunorubicin derivatives so as to suppress the tendency toward reductive activation is reflected in a progressive reduction in cardiotoxicity in animals with no sacrifice in antitumor properties.[14,15]

Prompted by these encouraging results we recently described the synthesis of ring C chromophore modified aglycones and glycosides related to the anthracyclines.[19] The lead compounds of 9-acetyl-6,9,11-trihydroxyxantho-[2,3-*g*]tetralin and -[3,2-*g*]tetralins and glycosides of 6,9,11-trihydroxyxantho[2,3-*g*]tetralin and -[3,2-*g*]tetralins showed the desired low hepatic microsomal oxygen consumption indicative of minimal in vitro redox activity.[19] Because of these findings we now report on regiospecific syntheses of these parent chromophores and describe the new chemistry necessary for the further development of these novel agents.

Synthesis

(a) Initial Approaches. Since our previous experience of the xantho[2,3-*g*]tetralin and -[3,2-*g*]tetralin[19] demon-

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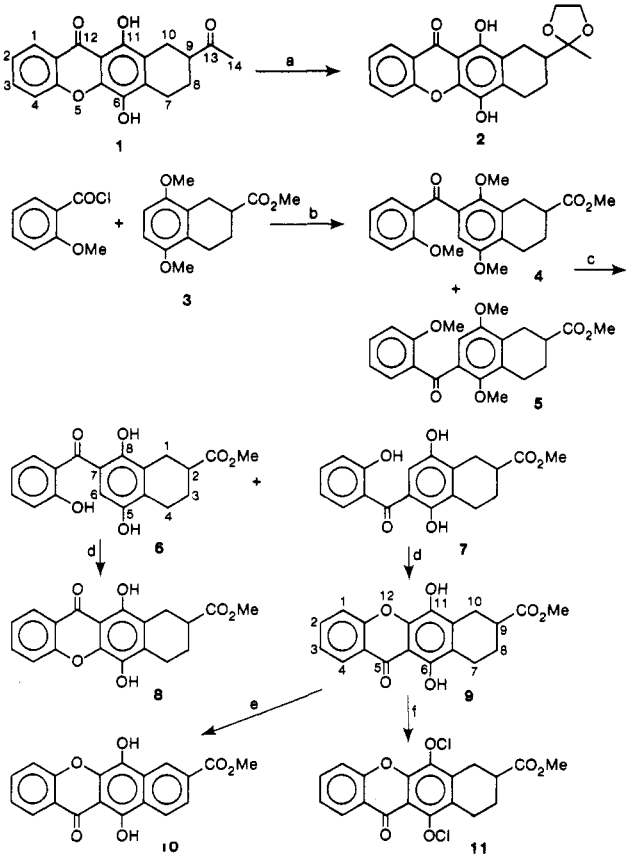
Scheme I[a]

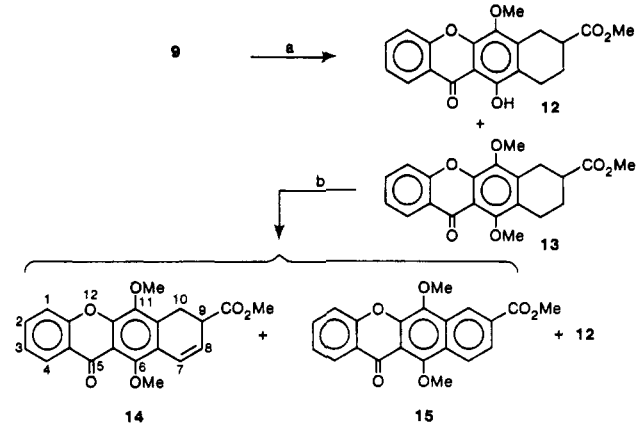


[a] Reaction conditions: (a) ethylene glycol, C_6H_6, *p*-TSA, Δ, 6 h; (b) CH_2Cl_2, $SnCl_4$, 0 °C, 8 h; (c) C_6H_6, $AlCl_3$, nitrogen atmosphere, 50–55 °C, 12 h; (d) C_6H_6, DDQ, nitrogen atmosphere, room temperature for 4 h then MeOH for 12 h; (e) NBS, dibenzoyl peroxide, CCl_4, nitrogen atmosphere, Δ, 4 h then room temperature for 12 h; (f) NCS, dibenzoyl peroxide, CCl_4, nitrogen atmosphere, Δ, 4 h then room temperature for 12 h.

strated substantially different chemical properties from the daunomycinone chromophore, some exploratory reactions were deemed necessary before embarking on a regiospecific synthetic scheme. In particular it was necessary to establish the effects of 9-substitution on, for example, the tendency for elimination and on conformational control. The acetyl group in the compound 9-acetyl-6,11-dihydroxy-12-oxoxantho[2,3-*g*]tetralin (**1**) was converted into the acetal **2** and several attempts were made to introduce a C_7-hydroxyl group. These methods included treatment with *N*-bromosuccinimide and benzoyl peroxide, or azobis(isobutyronitrile) and bromine. In each case either no reaction ensued or a complex mixture of products resulted. Subsequent results confirmed our experience that, in this chromophoric system, the nature of the C_9-functional group exerts an influence on the course of attempted C_7-hydroxylation. At this stage the effects of a C_9-carbomethoxy group were explored. Friedel–Crafts coupling of 5,8-dimethoxy-2-carbomethoxytetralin (**3**) with *o*-methoxybenzyl chloride in the presence of stannic chloride afforded the mixture of regioisomers **4** and **5** (Scheme I).

Demethylation of **4** and **5** by Lewis acid catalysis gave **6** and **7** which were readily separable. Their regioisomeric assignment could be made on the basis of their ^1H NMR. Thus one isomer showed C_5–OH and C_8–OH as singlets at δ 9.04 and 11.99, respectively, and in the other isomer they appeared at δ 11.93 and 9.09, respectively. The slight shift to low field in each case is attributed to the adjacent C_2–CO_2CH_3 function,[20] so that the former set of signals is

Scheme II[a]



[a] Reaction conditions: (a) NaH, THF, nitrogen atmosphere, Δ, 2.5 h, then MeI at 40 °C for 12 h; (b) NBS and dibenzoyl peroxide, $CHCl_3$, Δ, 1.5 h.

ascribed to regioisomer **6** and the latter pair of signals to **7**. The orientation of the 6,11-dihydroxyxantho[2,3-*g*]-tetralin has been confirmed by X-ray diffraction in the case of a glycoside derivative.[21]

Subsequent oxidative ring closure of **6** with DDQ in a mixture of benzene and methanol under nitrogen gave compound **8**. Similar treatment of the regioisomeric tetralin **7** gave compound **9**. Trial experiments were performed with **9** in attempts to functionalize at C_7. However a C_9-carbomethoxy group in this system evidently renders further ring A substituents susceptible to elimination. Thus, treatment of **9** with *N*-bromosuccinimide and benzoyl peroxide resulted in aromatization of ring A to give **10**. It was considered that a less reactive leaving group than bromine at C_7, e.g., Cl, might be more suitable. However, treatment of the four-ring chromophore **9** with *N*-chlorosuccinimide afforded only the dioxy chloro derivative **11** (Scheme I).

To avoid complications, the phenolic hydroxyl groups in **9** were methylated by treatment with methyl iodide in tetrahydrofuran in the presence of sodium hydride. These reaction conditions led to a mixture of compounds **12** and **13**. The position of methylation in compound **12** was evident from the ^1H NMR of the phenolic OH which appeared at δ 12.55 characteristic of the strongly chelated proton at position C_6.[20] The formation of **12** indicates that the C_{11} phenolic group is more readily methylated than the C_6 and (as was subsequently shown) is the more difficult to liberate. Attempts at this point to functionalize at C_7 in compound **13** by *N*-chlorosuccinimide and benzoyl peroxide yielded only unreacted starting material whereas *N*-bromosuccinimide catalyzed by benzoyl peroxide afforded a mixture of compounds **12**, **14**, and **15** (Scheme II), which were readily separable by preparative TLC. The structures were established by ^1H NMR and by mass spectrometry. The fact that in compound **12** the 6-OMe group has been demethylated rather than the 11-OMe was confirmed by the characteristic intramolecular hydrogen bond to the pericarbonyl group.[19] The formation of **12** indicates that the 6-OMe is more readily demethylated (in accord with the relative difficulty of methylation of the 6-OH compared to the 11-OH).

In compound **14** the position of the olefinic double bond at C_7–C_8, (rather than at C_8–C_9 or C_9–C_{10}) is apparent

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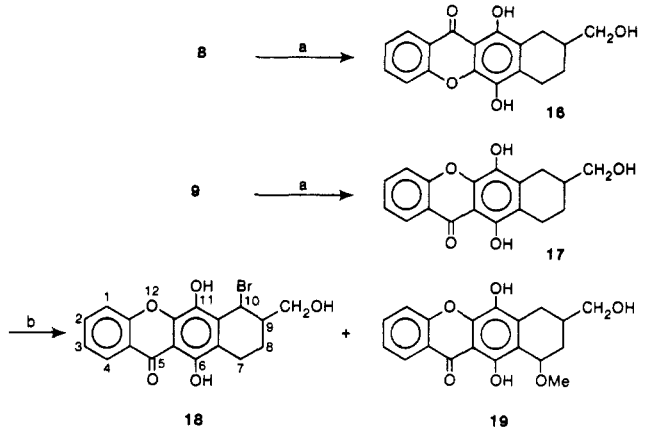
Scheme III[a]



[a] Reaction conditions: (a) $LiAlH_4$, THF, room temperature, 12 h; (b) 1, NBS, dibenzoyl peroxide, $CHCl_3$, nitrogen atmosphere, Δ, 1.5 h, 2, MeOH, nitrogen atmosphere, Δ, 12 h.

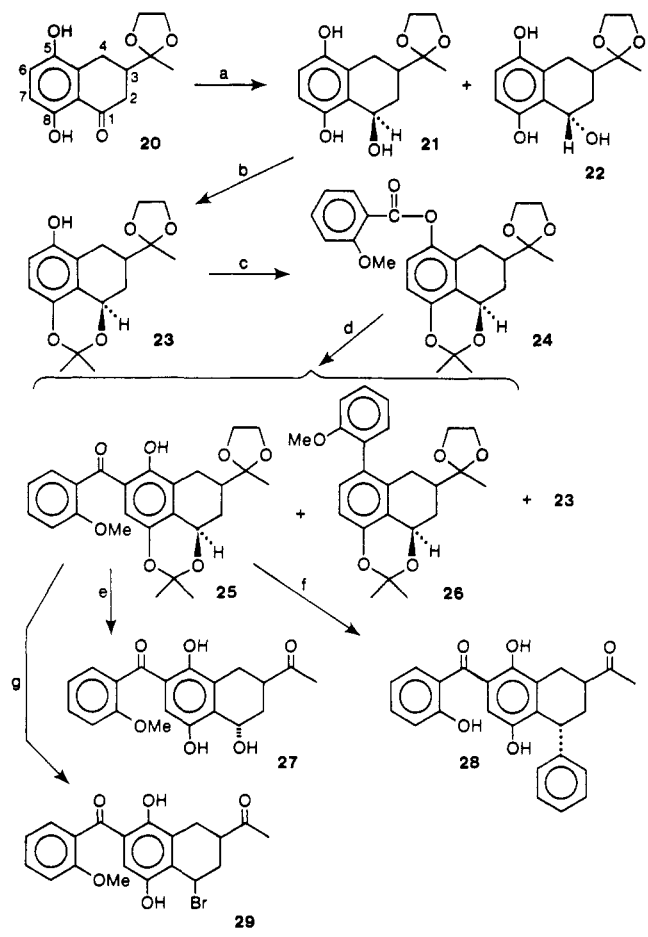
because two vinylic protons are observed in the ^1H NMR at δ 6.18 and 6.88. It is evident from the formation of **14** and **15** that elimination and/or aromatization in ring A is especially facile in this ring system. With a C_9-carbomethoxy substituent monobromination (at C_7) predominates over dibromination (at C_7 and C_{10}) because **14** is a major product compared with **15** (7:1). However, elimination of a C_7-Br group is too facile to permit profitable synthetic development.

The marked influence of the nature of the C_9-substituent led to examination of the behavior of the hydroxymethyl side chain obtained by reduction of the ester side chain in **8** to give **16** and in the regioisomer **9** to give **17** (Scheme III). Subsequent functionalization by treatment of **17** with *N*-bromosuccinimide followed by stirring in methanol was successful in affording **18** and **19**. In the ^1H NMR of **18** in $CDCl_3$ after deuterium oxide exchange, the C_{10}–H appears at δ 5.62 as a doublet with $J_{9,10}$ = 5.5 Hz. Spin decoupling of the C_{10}–H signal shows that it is coupled with only one proton, i.e., C_9–H at δ 2.25, which confirms the position of the Br group at C_{10} rather than C_7. The ^1H NMR of **19** in $CDCl_3$ shows the C_7–H as a triplet at δ 4.88 with $J_{7e',8a'} = J_{7e',8e'}$ = 3.5 Hz which indicates a C_7–OMe having a pseudoaxial orientation.

It seems likely that in the reaction of **17** bromination occurs at both positions C_7 and C_{10} but that the C_7–Br is more readily displaced by methanol. Preferential reaction of *N*-bromosuccinimide at C_7 in the comparable daunomycinone has been attributed to the steric hindrance afforded by the 9-$COOCH_3$ group to possible substitution at C_{10}.[22] Changing the oxidation level of the C_9-substituent has had the desired effect of disfavoring elimination in ring A following C_7-bromination. However, the low yields of **17** from **9** and of **18** and **19** from **17** rendered this approach impractical as a projected regiospecific synthesis of the target molecule bearing in mind the additional steps required. The information gained on the unique chemistry of this system was then used to redesign the synthetic strategy.

(b) Regiospecific Synthesis. A more satisfactory and ultimately successful approach was to introduce the C_7–OH function in the initial synthon. The side chain acetal-protected 5,8-dihydroxytetralone **20** was reduced with sodium borohydride[26] to the mixture of epimeric trihydroxy derivatives **21** and **22**. These were readily separable by column chromatography on silica gel and the stereochemistries were assigned by ^1H NMR. After D_2O exchange of the ^1H NMR of **21** and C_1-methine appeared as a quartet with $J_{1a',2a'}$ = 12 Hz and $J_{1a',2e'}$ = 4 Hz which implies that C_1–H is pseudoxial and therefore C_1–OH is pseudoequatorial. Because it is known that large β-substituents in tetralin systems prefer to adopt an equatorial position,[23-25] the C_1–OH and C_3-ketal groups are cis to one another. Similarly, the C_1-methine of **22** appears as a narrow triplet after D_2O exchange and with $J_{1e',2a'}$ = 6.5 Hz and $J_{1e',2e'}$ = 6.5 Hz, confirming that in compound **22** the C_1–OH and C_3-ketal groups are trans to each other[20] (Scheme IV).

Scheme IV[a]



[a] Reaction conditions: (a) $NaBH_4$, THF, nitrogen atmosphere, Δ, 12 h; (b) 2,2-dimethoxypropane, *p*-TSA, room temperature, 8 h; (c) *o*-methoxybenzoic acid, *p*-toluenesulfonyl chloride, pyridine, 0 °C, 30 min, add **23**, 0 °C for 2 h, then room temperature for 12 h; (d) dry dioxane, irradiation with Hanovia 450-W medium-pressure UV lamp at room temperature for 16 h; (e) THF, HCl, water, room temperature for 12 h; (f) anhydrous $AlCl_3$, C_6H_6, nitrogen atmosphere, 45–50 °C for 23 h; (g) BBr_3, CH_2Cl_2 at −60 °C for 1 h, then 0 °C for 1 h.

The cis epimer **21** was converted into the epimerically pure and stereochemically defined acetonide **23** [i.e., $J_{1a',2a'}$ = 11 Hz, $J_{1a',2e'}$ = 4.5 Hz, $J_{4a',3a'}$ = 11 Hz, $J_{4e',3a'}$ = 6 Hz indicate **23** to be the cis pseudodiequatorial acetonide] and acylated at the phenolic OH by *o*-methoxybenzoic acid and *p*-toluenesulfonyl chloride in pyridine to give **24**. Com-

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pound **24** loses a molecule of acetone readily and therefore does not give a molecular ion peak in the EI mass spectrum. However the molecular ion peak was detected by chemical-ionization MS establishing the molecular composition.

Irradiation of compound **24** in dioxane solution at 260 nm with a medium-pressure 450-W UV lamp afforded a mixture of the photo-Fries rearrangement[26] products **25** and **26** and some regenerated **23**, which was recycled. Compound **25** shows the characteristic intramolecular hydrogen bonding between the carbonyl and phenolic OH group[19] confirming the ortho disposition of these groups. A structural isomer of **25**, namely compound **36**, was available for spectral comparison. The ^1H coupling constants of **25** at $J_{1a',2a'}$ = 11 Hz, $J_{1a',2e'}$ = 5 Hz, $J_{4a',3a'}$ = 10.5 Hz, $J_{4e',3a'}$ = 6.5 Hz, and $J_{4,4'}$ = 18 Hz indicate a cis pseudodiequatorial relationship between the C_3-ketal and C_1-acetonide.

The structure of the photodecarboxylation product **26** was established by spectral means, principally by its ^1H NMR spectrum which shows doubling of the C_3–CH_3 and CH_3O signals at ambient temperatures, which at this stage was tentatively ascribed to hindered rotation about the biphenyl system. Confirmatory evidence was obtained by ^1H NMR. The spectrum in Me_2SO-d_6 at room temperature shows a doublet for C_3–CH_3, a singlet for the OCH_3, a dd at δ 6.7, and a doublet at δ 6.86, each corresponding to one proton. At 80 °C the doublet due to the C_3–CH_3 and the dd at δ 6.7 collapse to a singlet and doublet, respectively. At intermediate temperatures of 60–70 °C the C_3–CH_3 signal begins to broaden. This behavior is characteristic of restricted rotation about a hindered biphenyl system.[20] The clearer spectrum obtainable at 80 °C showed that the δ 6.7 and 6.86 doublets represent an AB pattern due to the C_6- and C_7-protons, thereby confirming the position of attachment of the methoxyphenyl ring as C_5–$C_{1'}$. The structure of **26** is therefore in accord with the mechanism of coupling of the radicals produced upon photoextrusion of carbon dioxide.

The initial attempts at demethylation of **25** prior to the projected oxidative cyclization employed mild Lewis acid treatment.[19] This offered an advantage in that before proceeding with the synthesis it was necessary to investigate the configurational fate of the C_1–OH under the mild acid conditions which would be required for selective deprotection and, more particularly, the sensitivity to (C_1–C_2) elimination to which this system is prone. Mild acid treatment of **25** at room temperature afforded **27** as a single product. The ^1H NMR of **27** in $CDCl_3$ after deuterium oxide exchange showed a triplet at δ 5.12 with $J_{1e',2a'} = J_{1e',2e'}$ = 4 Hz, $J_{4a',3a'}$ = 10.5 Hz, $J_{4e',3a'}$ = 4.5 Hz, and $J_{4,4'}$ = 17.5 Hz, which indicates that the C_1–OH is pseudoaxial and the C_3–$COCH_3$ is pseudoequatorial.[20] Therefore these groups have a trans relationship and the acid-catalyzed deprotection has proceeded with inversion at C_1 to afford the more stable epimer (see below). Treatment of compound **25** with aluminum chloride in benzene under an atmosphere of nitrogen at 45–50 °C afforded the deprotected and demethylated but phenylated product **28** in which, by ^1H NMR evidence, the 7-phenyl group is pseudoaxial. The alternative use of boron tribromide to attempt demethylation instead gave the deprotected and 7-bromo-substituted product **29**.

Because Lewis acid catalyzed conditions posed these problems, nucleophilic demethylation was employed with sodium thiocresolate in HMPA–toluene under an atmosphere of nitrogen.[27] These conditions afforded the desired selectively demethylated product **33** in 14% yield but a greater proportion (44% yield) of the angular cyclized product **32** was obtained. The orientation of the angular xanthone moiety in **32** follows unambiguously from the mode of formation (see below). The synthetic strategy at this point posed the problem of establishing a balance of conditions to favor formation of **33** over **32**. It appeared likely that the product **32** was formed by generation of a phenoxide anion in the tetralin moiety and subsequent ring closure by nucleophilic aromatic substitution of the methoxy group promoted by the adjacent acyl group. Treatment of **36** with sodium thiocresolate in HMPA–toluene[27] in fact gives **33** exclusively (see below) (Scheme V).

Acetylation of the phenolic OH group in **25** gave compound **30** in which, by ^1H NMR evidence, the configuration of the protected secondary alcohol is retained. Treatment of **30** with the sodium thiocresolate demethylating reagent led to the exclusive formation of the angular product **32**. The phenolic OH in compound **25** was then methylated with methyl iodide and sodium hydride to give **31** with retention of configuration and a small amount (~1%) of the angular product **32**. The sodium thiocresolate, HMPA reaction conditions with **31** now afforded the desired compound **33**. It is evident from the ^1H coupling constants that **33** has the C_1- and C_3-substituents in the cis pseudodiequatorial arrangement (see Experimental Section). Compound **33** was produced in 37% yield in addition to the angular product **32** (28% yield) and minor amounts of compounds **34** (0.6%), **35** (0.3%), **36** (6.5%), and **37** (trace). The structure of **35** follows from the ^1H NMR which shows $OCH(CH_3)$ as a doublet at δ 1.60 and OCH-CH_3 as a quartet at δ 4.72. Spin decoupling of the OCH signals causes the collapse of the δ 1.60 signal to a singlet. Similarly, the structure of the minor product **37** is proven by the presence of an ethyl side chain at C_3 of the naphthalene moiety together with the molecular formula of **37** from mass spectrometry.

It is plausible that the minor angular products **34**, **35**, and **37** arise from **25** by initial formation of **32** which undergoes dehydrogenation to give **34** followed by thiocresolate-induced dealkylative or reductive cleavage of the ketal to give **35** and finally **37**.

The isolated and purified compound **36** when treated with sodium thiocresolate in HMPA–toluene afforded only the desired compound **33** (76% isolated yield). It is evident therefore that the angular product **32** is formed by attack of the phenoxide anion in the tetralin moiety displacing a leaving group in the substituted benzoyl moiety and not in the reverse direction. This explains why the relative yield of **33** increases in the demethylation reaction of compound **31** compared to **25** and can be attributed to the intermediate formation of **36** during the former reaction. Compound **33** was deprotected by using dilute hydrochloric acid in aqueous THF at ambient temperatures and afforded a mixture of the epimers **39** and **40** (2:1) and the minor elimination product **41**, all of which could be separated readily by column chromatography. Compound **41** arises from deprotection, elimination at the 3- or 4-positions and air oxidation of the 5 and 8 phenolic OH's to the quinone. The configurations at C_1 in **39** and **40** were established by ^1H NMR. After D_2O exchange the NMR of **39** showed $J_{1e',2a'} = J_{1e',2e'}$ = 4.2 Hz and $J_{4a',3a'}$ = 10 Hz, $J_{4e',3a'}$ = 4.5 Hz which clearly indicate that C_1–H is pseudoequatorial and therefore C_1–OH is pseudoaxial.[20] Similarly

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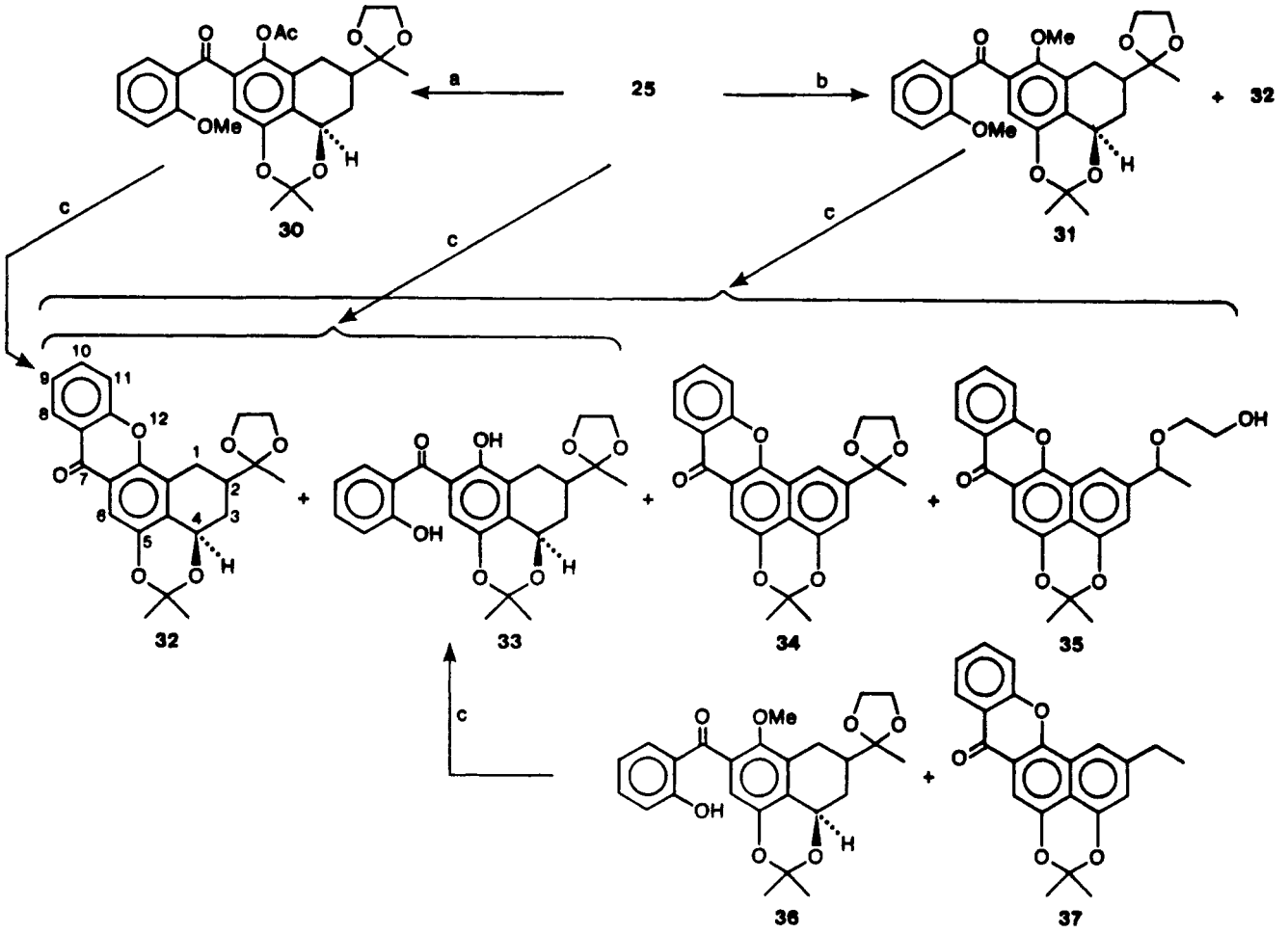
Scheme V[a]



[a] Reaction conditions: (a) Ac_2O, dry pyridine, 0 °C for 2 h then room temperature for 12 h; (b) NaH, THF in nitrogen atmosphere, 1.5 h, then CH_3I, 40 °C 12 h; (c) sodium thiocresolate, HMPA, nitrogen atmosphere, Δ, 16 h.

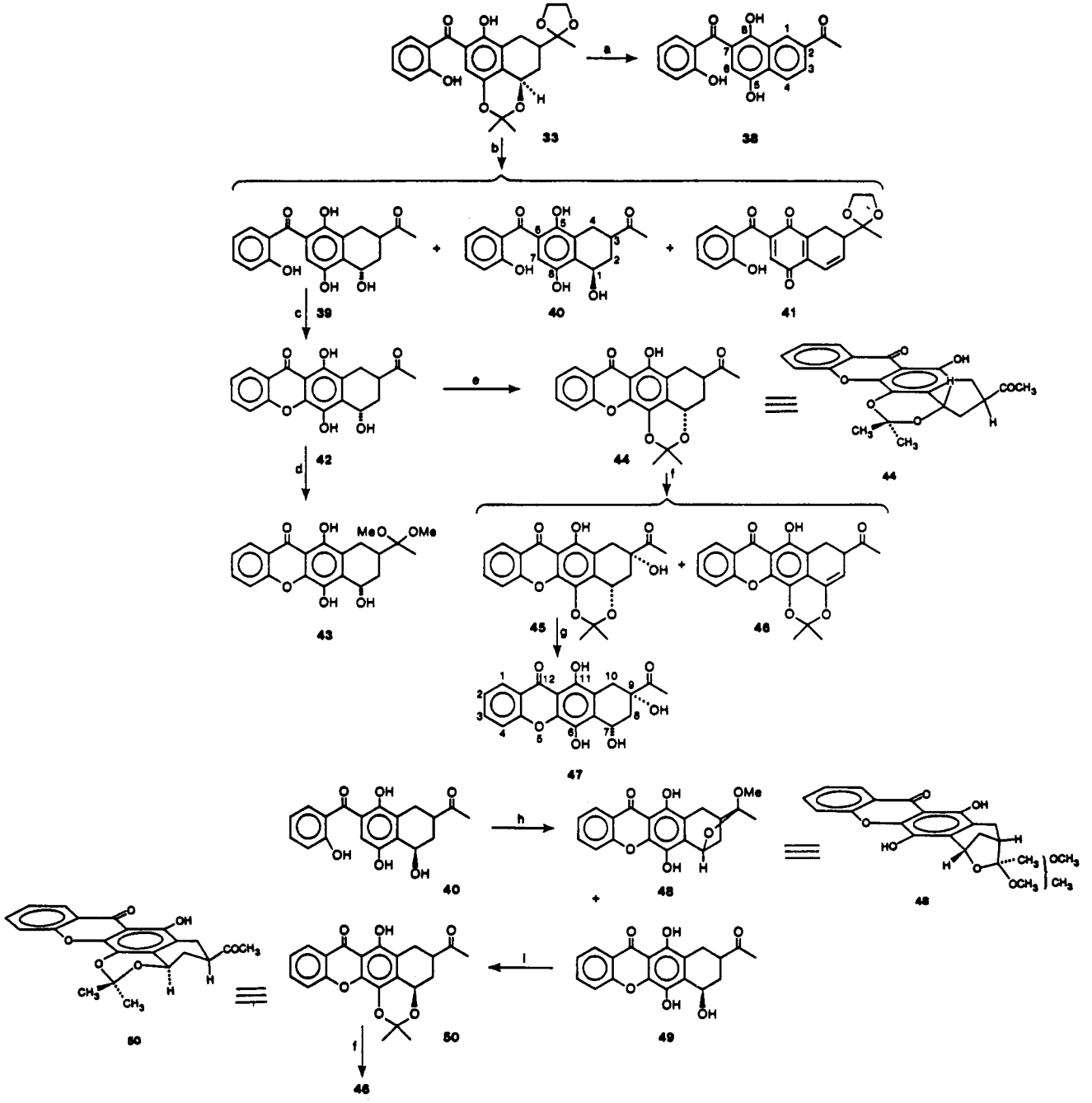
C_3–H is pseudoaxial and hence C_3-acetyl is pseudoequatorial which establishes that C_1–OH (pseudoaxial) and C_3-acetyl (pseudoequatorial) have a trans relationship.

In contrast the coupling constants for **40** after D_2O exchange are $J_{1,2a'}$ = 7 Hz, $J_{1,2e'}$ = 5 Hz, and $J_{4a',3}$ = 6 Hz, $J_{4e',3}$ = 4.5 Hz. These values indicate that neither C_1–OH nor C_3–$COCH_3$ in **40** exist in pure axial or equatorial positions owing to distortions in the half-chair cyclohexene ring in **40**.[20] Nevertheless the cis relationship of the two C_1 and C_3 substituents in **40** follows from its epimeric relationship to **39** and is confirmed by formation of the cyclic ketal **48** during oxidative cyclization of **40**. No such cyclic ketal is formed from **39** or **42** (see below). When compound **40** was stirred with dilute hydrochloric acid in THF at room temperature for 3 h and worked up it gave compound **39** and **40** in the ratio of 2:1 (Scheme VI). Thus compound **40** can be converted into **39** under mild acidic conditions which indicates that the configuration acquired by **39** is more stable than that of **40**. This observation is consistent with the preferred configuration in the parent antibiotic.

The sensitivity of the cyclohexenyl ring in **33** toward elimination and/or dehydrogenation was again demonstrated by maintaining **33** in the same dilute HCl/aqueous THF deprotection medium for 10 days where only the aromatized benzoylnaphthalene **38** was formed. When the 7,9-trans epimer **39** was treated with DDQ in methanol–benzene (2:1), oxidative cyclization afforded the chromophore **42** with no trace of cyclic acetal formation (i.e., no **48**). However traces of the dimethyl acetal **43** were formed. The formation and structure of the latter were confirmed by independent reaction of **42** with methanol using acid catalysis. The C_7–H in **42** and **43** appear as narrow triplets with $J_{7e',8a'} = J_{7e',8e'}$ = 3.5 and 3.0 Hz, respectively. This is consistent with a common configuration at C_7. Therefore, because compound **42** is stereochemically pure and epimeric with **49** and because no trace of **48** is observed, the C_7–OH retains its pseudoaxial configuration in the xantho[2,3-*g*]tetralin chromophore both in the oxidative cyclization of **39** and in the mild acid treatment of **42** to give **43**. This is in contrast to the deprotection step of the tetralins **25** and **33** where there is inversion of the initially equatorially oriented C_7–OH to the more stable axial orientation that exists in the parent anthracycline antibiotics.[2] The preference for a more stable 7-axial orientation appears to be general for the benzoyltetralins and xantho[2,3-*g*]tetralins bearing a dominating 9-equatorial substituent as in the examples of **19**, **27**, **28**, **39**, **42**, **43**, and **47**.

The adjacent 6- and 7-hydroxy groups in **42** were then protected by treatment with dimethoxypropane to give the single compound **44**, the ^1H NMR of which showed $J_{9,10}$ = 7.5 Hz, $J_{9,10'}$ = 6 Hz, $J_{7a',8e'}$ = 6 Hz, and $J_{7a',8a'}$ = 11 Hz. In contrast, the 7-epimer **50** shows $J_{10a',9a'}$ = 9.5 Hz, $J_{10e',9a'}$ = 6 Hz, $J_{7a',8a'}$ = 11 Hz, and $J_{7a',8e'}$ = 5 Hz. It is clear from the values of the above coupling constants that the acetonide link at C_7 adopts a pseudoequatorial orientation in both **44** and **50**. The coupling constants for **50** indicate the C_9–H is pseudoaxial and therefore the C_9-acetyl group is pseudoequatorial. Therefore in **50** the C_7 and C_9 substituents retain their cis relationship. In **44** by way of

Scheme VI[a]



[a] Reaction conditions: (a) THF, HCl, H_2O, room temperature for 10 days; (b) THF, HCl, H_2O, room temperature for 3 h; (c) DDQ MeOH, C_6H_6, nitrogen atmosphere at room temperature for 12 h; (d) MeOH, HCl, room temperature, 22 h; (e) 2,2-dimethoxy-propane, THF, *p*-TSA, room temperature, 3 h; (f) K-*t*- OBu, *t*-BuOH, DMF, nitrogen atmosphere, room temperature for 30 min, then triethyl phosphite, O_2, −15 to −25 °C for 2 h; (g) THF, HCl, H_2O, room temperature, 6 h; (h) DDQ, C_6H_6, MeOH, nitrogen atmosphere, room temperature, 12 h; (i) 2,2-dimethoxypropane, THF, *p*-TSA, room temperature for 5 h.

contrast in which the C_7 and C_9 are trans, the steric constraints involved in the acetonide formation and transmitted into the cyclohexenyl ring force the 9-acetyl group into an intermediate orientation between equatorial and axial as indicated by the magnitudes of the coupling constants.

The final functionality, the 9-hydroxy group, was introduced by sequential treatment of **44** with potassium *tert*-butoxide in *tert*-butyl alcohol followed by reaction with molecular oxygen in the presence of triethyl phosphite and dimethylformamide[28] affording a mixture of the desired product **45** and the C_7–C_8 elimination product **46**. Compound **46** may arise from hydroxylation at C_7 during the reaction followed by elimination. The C_8–H appears at δ 7.85 as a doublet and is coupled to C_9–H at δ 2.30 as confirmed by spin decoupling.[20] The basic reaction conditions employed in the C_9-hydroxylation are not expected to alter the configurational integrity at position 7 and this is confirmed by the ^{1}H NMR spectrum (see Experimental Section). In addition, the reaction conditions used to introduce the 9-OH group are expected to proceed with retention[28] so that tentatively the relative stereochemistry of the 7- and 9-substituents in **45** may be assigned as shown.

Controlled deprotection of **45** with dilute HCl in aqueous

(28) Gardner, J. N.; Carlon, F. E.; Gnoj, O. *J. Org. Chem.* **1968**, *33*, 3294.

THF at room temperature for 6 h afforded the final target chromophore **47**. The coupling constant for the C_7 proton after D_2O exchange is $J_{7e',8a'} = J_{7e',8e'} = 5.0$ Hz. Such small values for these coupling constants are characteristic of the value given by natural daunomycinone δ 5.33 ($\nu_{1/2} \approx$ 7 Hz)[1,2] and indicates a pseudoequatorial C_7-hydrogen in both cases.

The epimeric substituted benzoyltetralin **40** was similarly subjected to oxidative cyclization with DDQ in methanol to give a mixture of the expected product **49** and the cyclic acetal **48**. The coupling constants for C_7–H in **49** are $J_{7a',8a'} = 9$ Hz, $J_{7a',8e'} = 5.5$ Hz which indicate that the C_7–OH in **49** is pseudoequatorial. For comparison the coupling constants in **42** for C_7–H are $J_{7e',8a'} = J_{7e',8e'} = 3.5$, characteristic of an axially oriented OH group. The product **48** consisted of a ca. 1:1 mixture of diastereomers arising from the two possible orientations of the groups at C_{13}. Formation of the latter compound **49** requires the 9-acetyl and the 7-hydroxy groups to bear a cis relationship in ring A of the chromophore. The xantho[2,3-*g*]tetralin **49** was then converted into the acetonide **50** by treatment with dimethoxypropane to give **50** which is stereochemically pure and an epimer of **44**. When compound **50** was treated under precisely the same conditions used to introduce the 9-hydroxy group into **44**[28] (to produce **45**) only compound **46** was obtained in 30% yield. It may be noted that in **50** the carbanion is more readily generated at C_7 than at C_9. This may explain why C_7 is hydroxylated and then dehydrated to give **46**. The spectral data showed that compound **46** obtained from **50** was identical with that from **44**.

The coupling of chromophore **47** in glycosides and the further development of the chemistry of this system designed to explore in vivo redox inactive and potentially less cardiotoxic anthracyclines will be reported in due course.

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 in appropriate deuterated solvents with tetramethylsilane as internal standard. Line positions are recorded in ppm from the reference. Electron-impact mass spectra were determined on an Associated Electrical Industries (AEI) MS-9 double-focussing high-resolution mass spectrometer and chemical-ionization mass spectra were recorded on an AEI MS-12 with 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 15 000. Kiesel gel DF-5 (Camag, Switzerland) and Eastman Kodak precoated sheets were used for thin-layer chromatography. TLC grade GF silica (Sigma) was used for column chromatography. In the text as well as in the Experimental Section e′ and a′ represents pseudoequatorial and pseudoaxial protons, respectively.

Ethylene Glycol Ketal of 9-Acetyl-6,11-dihydroxy-12-oxoxantho[2,3-*g*]tetralin and -[3,2-*g*]tetralin (2). A solution of 9-acetyl-6,11-dihydroxy-12-oxoxantho[2,3-*g*]tetralin and -[3,2-*g*]tetralin (**1**)[19] (1.62 g, 5 mmol) in 250 mL of dry benzene and 5 mL of ethylene glycol with *p*-toluenesulfonic acid (200 mg) was heated at reflux in a Dean–Stark apparatus for 6 h when a quantitative release of water was effected. The solvents were removed under reduced pressure, the residual solid was taken up in 25 mL of ethyl acetate, and the solution washed with sodium hydrogen carbonate solution, then water, and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a yellow solid which was recrystallized from benzene: 1.50 g (81.3% yield); mp 205–207 °C; ^1H NMR ($CDCl_3$) δ 1.40 (m + s, 4 H, 1 H + CH_3), 1.95 (m, 1 H), 2.18 (m, 1 H), 2.55 (m, 2 H), 3.15 (m, 2 H), 4.1 (m, 4 H, CH_2CH_2), 5.25 (d, 1 H, OH), 7.40 (m, 2 H, aryl), 7.75 (dt, 1 H, aryl), 8.30 (dd, 1 H, aryl), 12.12 (d, 1 H, chelated OH) (the doublet for phenolic protons indicates the presence of the two regioisomers); IR ($CHCl_3$) ν_{max} 3350 (phenolic OH), 1650 (γ-pyrone), 1605, 1575 cm^{-1} (aryl); MS, *m/z* (% relative intensity) 368.12490 (55) [calcd for $C_{21}H_{20}O_6$ 368.12501], 281,0809 (36.5, $M^+ - C_4H_7O_2$), 87.0433 (100, $C_4H_7O_2$). Anal. Calcd for $C_{21}H_{20}O_6$: C, 68.5; H, 5.4. Found: C, 68.4; H, 5.5.

6- and 7-(2-Methoxybenzoyl)-2-carbomethoxy-5,8-dimethoxytetralin (4 and 5). Stannic chloride (3.12 g, 12 mmol) was added in portions to a solution of 2-carbomethoxy-5,8-dimethoxytetralin (2.50 g, 10 mmol) [prepared from 5,8-dimethoxytetralin-2-carboxylic acid, mp 60 °C][19] and *o*-methoxybenzoyl chloride (1.76 g, 11 mmol) in 40 mL of dry dichloromethane at 0 °C. When the addition was completed the reaction mixture was 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 to give a thick syrup which was purified by column chromatography to give **4** and **5**: 3.5 g (90% yield); ^1H NMR ($CDCl_3$) δ 1.8 (m, 1 H), 2.22 (m, 1 H), 2.6–2.82 (m, 3 H), 2.95 (m, 1 H), 3.10 (m, 1 H), 3.48 (s, 3 H, $COOCH_3$), 3.76 (d, 6 H, 2 OCH_3), 3.81 (s, 3 H, OCH_3), 6.9, 6.95 (2 s, 1 H, aryl), 6.98 (q, 2 H, aryl), 7.48 (m, 2 H, aryl); IR (film) ν_{max} 1740 (CO_2CH_3), 1660, 1640 (C=O), 1595 cm^{-1} (aryl); MS, *m/z* (relative intensity) 384.1578 (100) [calcd for $C_{22}H_{24}O_6$ 384.1577], 325.1434 (4.5, $M^+ - C_2H_3O_2$), 277.1045 (6.8, $M^+ - C_7H_7O$), 135.0445 (57.3, $M^+ - C_{14}H_{17}O_4$).

6- and 7-(2-Hydroxybenzoyl)-2-carbomethoxy-5,8-dihydroxytetralin (6 and 7). The 6- and 7-(2-methoxybenzoyl)-2-carbomethoxy-5,8-dimethoxytetralin (**4** and **5**, 3.84 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 50–55 °C for 12 h under nitrogen. The reaction mixture was poured onto an ice–hydrochloric acid mixture and the benzene layer was removed, washed successively with aqueous sodium bicarbonate and water, and dried (Na_2SO_4). Removal of the solvent in vacuo gave a thick syrup which was taken up in ether and kept at 0 °C for 12 h during which time a solid separated which was collected and washed with warm ether to give **7**. The filtrate was again concentrated and subjected to column chromatography with ether–petroleum ether (1:1) as eluant. Removal of the solvent from the main fraction gave an oil which was taken up in ether and kept at 0 °C for 10 h during which time more of **7** separated and was collected. The filtrate was concentrated and the residue taken up in dry ether and chilled, affording a mixture of **6** and **7**. Repetition of this process resulted in the separation of compounds **6** and **7** which were finally purified by crystallization from ether–petroleum ether and THF–ether, respectively, to give 0.68 g of **6** (20% yield), mp 158–160 °C, and 0.85 g of **7** (25% yield), mp 228–30 °C. Compound **6**: ^1H NMR (Me_2SO-d_6) δ 1.70 (m, 1 H), 2.12 (m, 1 H), 2.45–3.00 (m, 5 H), 3.72 (s, 3 H, CO_2CH_3), 6.70 (s, 1 H, aryl), 7.00 (m, 2 H, aryl), 7.25 (dd, 1 H, aryl), 7.40 (m, 1 H, aryl), 9.04 (s, 1 H, C_5-OH), 10.02 (s, 1 H, exchange OH), 11.99 (s, 1 H, exchange C_8-OH); IR (Nujol) ν_{max} 3440–3300 (phenolic OH), 1710 (CO_2CH_3), 1610 (C=O), 1570 cm^{-1} (aryl); MS, *m/z* (relative intensity) 342.1105 (100) [calcd for $C_{19}H_{18}O_6$ 342.1105], 325,1073 (51.39, M^+ – OH), 283.0960 (10.09, $M^+ - COOCH_3$), 249.0732 (8.96, $M^+ - C_6H_5O$), 248.0686 (43.15 $M^+ - (C_6H_5O + H)$), 162.0677 (7.57, $M^+ - (COOCH_3 + C_7H_5O_2)$), 121.0290 (54.95, $M^+ - C_{12}H_{13}O_4$). Compound **7**: ^1H NMR (Me_2SO-d_6) δ 1.70 (m, 1 H), 2.10 (m, 1 H), 2.50–3.00 (m, 5 H), 3.68 (s, 3 H, CO_2CH_3), 6.68 (s, 1 H, aryl), 6.98 (m, 2 H, aryl), 7.25 (dd, 1 H, aryl), 7.40 (m, 1 H, aryl), 9.09 (s, 1 H, exchange C_8-OH), 10.02 (s, 1 H, exchange OH), 11.93 (s, 1 H, exchange C_5-OH); IR (Nujol) ν_{max} 3500 (phenolic OH), 1713 (CO_2CH_3), 1610 (C=O), 1585 cm^{-1} (aryl); MS, *m/z* (relative intensity) 342.1099 (100) [calcd for $C_{19}H_{18}O_6$ 342.1099], 325.1073 (54.3, M^+ – OH), 283.0957 (11, $M^+ - CO_2CH_3$), 249.0727 (11.4, $M^+ - C_6H_5O$), 248.0682 (48.5, $M^+ - (C_6H_5O + H)$), 162.0672 (7.8, $M^+ - (CO_2CH_3 + C_7H_5O_2)$), 121.0291 (45, $M^+ - C_{12}H_{13}O_4$).

The assignment of the regioisomers to structures **6** and **7** is discussed in the text.

9-Carbomethoxy-6,11-dihydroxy-12-oxoxantho[2,3-*g*]tetralin (8). Compound **6** (3.42 g, 10 mmol) was suspended in 100 mL of dry benzene and a solution of 2,3-dichloro-5,6-dicyano-

1,4-benzoquinone (DDQ, 2.27 g, 10 mmol) in 80 mL of dry benzene with stirring under N_2. Stirring was continued for 4 h and the solution was filtered to remove the precipitated hydroquinone. The filtrate was concentrated in vacuo at room temperature and the residue taken up in 50 mL of warm dry methanol and stirred mechanically at ambient temperature under a nitrogen atmosphere for 12 h. The solvent was removed in vacuo and the residue subjected to column chromatography with ether as eluant. The product (**8**) was further purified by recrystallization from THF–ether (1:1) to afford 1.7 g (50% yield): mp 238–240 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.72 (m, 1 H), 2.17 (m, 1 H), 2.67 (m, 3 H), 2.97 (m, 2 H), 3.70 (s, 3 H, CO_2CH_3), 7.50 (t, 1 H, aryl), 7.65 (d, 1 H, aryl), 7.93 (m, 1 H, aryl), 8.20 (dd, 1 H, aryl), 9.08 (s, 1 H, C_6-OH), 12.18 (s, 1 H, C_{11}-OH); IR (Halo oil) ν_{max} 3400 (phenolic OH), 1710 (CO_2CH_3), 1640 (γ-pyrone), 1600 cm^{-1} (aryl); MS, m/z (relative intensity) 340.0948 (100) [calcd for $C_{19}H_{16}O_6$ 340.0948], 281.0806 (67, $M^+ - COOCH_3$), 280.0726 (50.3, $M^+ - (COOCH_3 + H)$).

9-Carbomethoxy-6,11-dihydroxy-5-oxoxantho[3,2-*g*]tetralin (9). Compound **9** was prepared from **7** following the same procedure used for the preparation of **8** in 75% yield: mp 250 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.70 (m, 1 H), 2.14 (m, 1 H), 2.55 (m, 1 H), 2.78 (m, 3 H), 3.10 (q, 1 H), 3.70 (s, 3 H, CO_2CH_3), 7.45 (t, 1 H, aryl), 7.60 (d, 1 H, aryl), 7.90 (m, 1 H, aryl), 8.15 (dd, 1 H, aryl), 9.05 (s, 1 H, C_{11}-OH), 12.15 (s, 1 H, C_6-OH); IR (Nujol) ν_{max} 3200–3400 (phenolic OH), 1705 (CO_2CH_3), 1620 (γ-pyrone), 1605, and 1585 cm^{-1} (aryl); MS, m/z (relative intensity) 340.0946 (100) [calcd for $C_{19}H_{16}O_6$ 340.0946], 281.0795 (33.8, $M^+ - C_2H_3O_2$), 280.0733 (78.7, $M^+ - (C_2H_3O_2 + H)$), 279.0646 (28.6, $M^+ - (C_2H_3O_2 + 2\ H)$).

9-Carbomethoxy-6,11-dihydroxy-5-oxoxantho[3,2-*g*]naphthalene (10). Compound **9** (170 mg, 0.5 mmol) was suspended in 100 mL of carbon tetrachloride and *N*-bromosuccinimide (178 mg, 1 mmol) and benzoyl peroxide (20 mg) were added. The reaction mixture was heated at reflux with stirring under an atmosphere of N_2. After 3 h of reflux, additional *N*-bromosuccinimide (125 g, 0.7 mmol) was added and stirring was continued for 12 h at room temperature. The solution was refluxed for 1 h, the solvent was removed under reduced pressure, and the residual solid was taken up in 50 mL of 50% aqueous THF and stirred for 12 h. The solvent was removed in vacuo, the residue taken up in ethyl acetate, and the extract washed with water and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave **10** which was purified by recrystallization from THF to afford 60 mg (35% yield): mp 266–270 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.96 (s, 3 H, $COOCH_3$) 7.64 (m, 1 H, Ar) 7.94 (m, 2 H, Ar), 8.20 (m, 2 H, Ar), 8.56 (m, 2 H, Ar); IR (MeOH cast) 1725 ($COOCH_3$) 1635 (C=O) 1610, 1605 (Ar); MS, m/z (relative intensity) 336.0624 (44.4) [calcd for $C_{19}H_{12}O_6$ 336.0625], 335, 0515 (25.0, $M^+ - H$), 334.0474 (100, $M^+ - 2$ H), 305.0406 (38, $M^+ - OCH_3$) 303.0290 (67.9, $M^+ - (2\ H + OCH_3)$), 277.0494 (16.6, $M^+ - COOCH_3$), 276.0394 (8, $M^+ - (H + COOCH_3)$), 275.0341 (28.6, $M^+ - (COOCH_3 + 2\ H)$).

9-Carbomethoxy-6,11-dichloroxy-5-oxoxantho[3,2-*g*]tetralin (11). To a suspension of compound **9** (170 mg, 0.5 mmol) in 100 mL of carbon tetrachloride was added *N*-chlorosuccinimide (80 mg, 0.6 mmol) and benzoyl peroxide (20 mg) and the mixture were heated under reflux in a N_2 atmosphere with stirring for 3 h. Additional *N*-chlorosuccinimide (53 mg, 0.4 mmol) and benzoyl peroxide (10 mg) were added and the reaction mixture was stirred at room temperature for 12 h and then refluxed for 1.5 h. The solvent was removed under reduced pressure and the residue taken up in 40 mL of 50% aqueous THF and stirred at room temperature for 12 h. The solvent was removed in vacuo, the residue taken up in ethyl acetate, the extract washed with water and dried (Na_2SO_4). Removal of the solvent and column chromatography of the residue with ether–petroleum ether (1:1) as eluant gave **11** (22 mg, 11% yield): mp 180 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.85 (m, 1 H), 2.2–2.74 (m, 5 H), 2.97 (m, 1 H), 3.76 (s, 3 H, CO_2CH_3), 7.7 (dt, 1 H, aryl), 8.0 (m, 2 H, aryl), 8.18 (dd, 1 H, aryl); IR (Nujol) ν_{max} 1730 (CO_2CH_3), 1660 (γ-pyrone), 1600 cm^{-1} (aryl); MS, m/z (relative intensity) 410.0145 (22.4) [calcd for $C_{19}H_{14}O_6{}^{37}Cl^{35}Cl$ 410.0144], 408.0173 (35.4) [calcd for $C_{19}H_{14}O_6{}^{35}Cl_2$ 408.0173], 375.0441 (28.93, $M^+ - {}^{35}Cl$), 373.0470 (91.42, $M^+ - {}^{37}Cl$), 313.0224 (100, 373.0470 – ($COOCH_3$ + H)).

9-Carbomethoxy-11-methoxy-6-hydroxy-5-oxoxantho[3,2-*g*]tetralin (12) and 9-Carbomethoxy-6,11-dimethoxy-5-oxoxantho[3,2-*g*]tetralin (13). Sodium hydride (270 mg, 80% dispersion in oil, 9 mmol) was added in portions to a solution of **9** (1.02 g, 3 mmol in THF) and the reaction mixture was heated under reflux for 2.5 h under an atmosphere of N_2. The solution was cooled to room temperature, 2 mL of methyl iodide was added, and the mixture was maintained at 40 °C for 12 h.

The solvent was removed in vacuo and the residue taken up in 1:1 ethyl acetate–water and acidified with dilute hydrochloric acid. The organic layer was removed, washed successively with water, sodium hydrogen carbonate, and water, and dried (Na_2SO_4). Removal of the solvent and column chromatography with ether–petroleum ether (1:3) as eluant afforded **12** as a yellow solid which was purified by recrystallization from 1:1 THF–petroleum ether to afford 50 mg (5% yield): mp 174 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.75 (m, 1 H), 2.12 (m, 1 H), 2.55–3.20 (m, 5 H), 3.68 (s, 3 H, CO_2CH_3), 3.90 (s, 3 H, OCH_3), 7.50 (t, 1 H, aryl), 7.72 (d, 1 H, aryl), 7.92 (t, 1 H, aryl), 8.18 (d, 1 H, aryl), 12.55 (s, 1 H, C_6-OH); IR (Nujol) ν_{max} 3400 (OH), 1725 (CO_2CH_3), 1635 (γ-pyrone), 1600 cm^{-1} (aryl); MS, m/z (relative intensity) 354.1103 (100) [calcd for $C_{20}H_{18}O_6$ 354.1103], 339.0857 (42.4, $M^+ - CH_3$), 295.0945 (8.5, $M^+ - CO_2CH_3$).

Further elution with 1:1 THF–ether gave a dimethoxy derivative **13** which was further purified by crystallization from 1:1 THF–ether to give 820 mg (80% yield): mp 160 °C; ^{1}H NMR (CF_3CO_2D) δ 2.70 (m, 1 H), 3.05 (m, 1 H), 3.70–4.25 (m, 5 H), 4.56 (s, 3 H, CO_2CH_3), 4.85 (s, 3 H, OCH_3), 4.93 (s, 3 H, OCH_3), 8.5 (t, 1 H, aryl), 8.65 (d, 1 H, aryl), 8.95 (t, 1 H, aryl), 9.25 (d, 1 H, aryl); IR (Nujol) ν_{max} 1725 (CO_2CH_3), 1655 (γ-pyrone), 1590 cm^{-1} (aryl); MS, m/z (relative intensity) 368.1262 (100) [calcd for $C_{21}H_{20}O_6$ 368.1262], 353.1025 (55.2, $M^+ - CH_3$), 309.1121 (18.7, $M^+ - CO_2CH_3$).

9-Carbomethoxy-6,11-dimethoxy-5-oxo-9,10-dihydroxantho[3,2-*g*]naphthalene (14), 12, and 9-Carbomethoxy-6,11-dimethoxy-5-oxoxantho[3,2-*g*]naphthalene (15). A solution of **13** (368 mg, 1 mmol) in 200 mL of chloroform was treated with *N*-bromosuccinimide (196 mg, 1.1 mmol) and benzoyl peroxide (20 mg). The reaction mixture was heated under reflux for 90 min, the solvent was removed in vacuo, the residue was taken up in ethyl acetate, and the extract washed with water and dried (Na_2SO_4). The solvent was removed in vacuo and the residue subjected to column chromatography with ether–petroleum ether (1:3) as eluant affording **12**, which was purified by crystallization from 1:1 THF–petroleum ether: 24 mg (yield 7%); mp 174 °C.

Further elution with ether–petroleum ether (1:3) gave **15** which was further purified by crystallization from 1:1 THF–petroleum ether to afford 8 mg (yield 2.2%): mp 228–230 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.96 (s, 3 H, OCH_3), 4.04 (s, 3 H, OCH_3), 4.20 (s, 3 H, CO_2CH_3), 7.45 (t, 1 H, aryl), 7.70 (d, 1 H, aryl), 7.90 (m, 1 H, aryl), 8.03 (dd, 1 H, aryl), 8.20 (dd, 1 H, aryl), 8.45 (d, 1 H, aryl), 8.82 (s, 1 H, aryl); IR (Halo oil) ν_{max} 1725 (CO_2CH_3), 1660 (γ-pyrone), 1590 cm^{-1} (aryl); MS, m/z (relative intensity) 364.0946 (63.4) [calcd for $C_{21}H_{16}O_6$ 364.0946], 349.0719 (100, $M^+ - CH_3$).

Further elution of the column with ether gave **14** which was further purified by crystallization from 1:1 THF–ether to afford 48 mg (yield 14%): mp 138–140 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.85 (m, 1 H), 3.16 (m, 2 H), 3.68 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.98 (s, 3 H, CO_2CH_3), 6.18 (q, 1 H, C_8-H), 6.88 (dd, 1 H, C_7-H), 7.45 (t, 1 H, aryl), 7.68 (d, 1 H, aryl), 7.85 (m, 1 H, aryl), 8.16 (dd, 1 H, aryl); IR (Nujol) ν_{max} 1710 (CO_2CH_3), 1640 (γ-pyrone), 1565 cm^{-1} (aryl); MS, m/z (relative intensity) 366.1104 (100) [calcd for $C_{21}H_{18}O_6$ 366.1104], 351.0884 (14.7, $M^+ - CH_3$), 307.0969 (47.5, $M^+ - COOCH_3$), 306.0883 (3.7, $M^+ - (COOCH_3 + H)$).

9-(Hydroxymethyl)-6,11-dihydroxy-12-oxoxantho[2,3-*g*]tetralin (16). Lithium aluminum hydride (152 mg, 4 mmol) was added to a solution of **8** (340 mg, 1 mmol) in 100 mL of dry THF and the mixture was stirred at room temperature for 12 h. The solution was then chilled and decomposed by careful addition of cold water and then 10 mL of 5% hydrochloric acid. The solution was filtered and the solid was washed thorougly with THF. The filtrate was concentrated in vacuo, the residue was taken up in ethyl acetate, and the extract was dried (Na_2SO_4). Concentration of the extract and column chromatography of the residue with ether–petroleum ether (1:1) as eluant gave **16** which was purified by crystallization from 1:1 THF–petroleum ether to afford 22 mg (7% yield): mp 180 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.30 (m, 1 H), 1.75 (m, 1 H), 2.00 (m, 1 H), 2.15 (q, 1 H), 2.60 (m, 1 H), 2.85

(m, 1 H), 3.05 (m, 1 H), 3.45 (t, 2 H), 4.64 (bs, 1 H, OH), 7.45 (m, 1 H, aryl), 7.65 (d, 1 H, aryl), 7.90 (m, 1 H, aryl), 8.18 (dd, 1 H, aryl), 9.00 (s, 1 H, C_6-OH), 12.40 (s, 1 H, C_{11}-OH); IR (KBr disk) ν_{max} 3400 (OH), 1650 (γ-pyrone), 1610, 1595 cm^{-1} (aryl); MS, m/z (relative intensity) 312.0996 (100) [calcd for $C_{18}H_{16}O_5$ 312.0996], 281.0812 (55, $M^+ - CH_2OH$) 280.0719 (5.6, $M^+ - (CH_2OH + H)$), 254.0576 (12.2, $C_{15}H_{10}O_4$, retro-Diels–Alder scission).

9-(Hydroxymethyl)-6,11-dihydroxy-5-oxoxantho[3,2-*g*]tetralin (17). Compound **17** was prepared from **9** following a similar procedure as described for **16**. Elution in the column chromatographic separation was performed with 1:1 ether–petroleum ether and **17** was purified by crystallization from THF and ether: yield 21%; mp 240 °C; ^1H NMR (Me_2SO-d_6) δ 1.30 (m, 1 H), 1.75 (m, 1 H), 2.00 (m, 1 H), 2.35 (m, 2 H), 2.95 (m, 2 H), 3.45 (t, 2 H), 4.65 (bs, 1 H, OH), 7.50 (t, 1 H, aryl), 7.65 (d, 1 H, aryl), 7.91 (m, 1 H, aryl), 8.18 (dd, 1 H, aryl), 9.03 (s, 1 H, C_{11}-OH), 12.20 (s, 1 H, C_6-OH); IR (Nujol) ν_{max} 3400 (OH), 1640 (γ-pyrone), 1605 cm^{-1} (aryl); MS, m/z (relative intensity) 312.1000 (100) [calcd for $C_{18}H_{16}O_5$ 312.1000], 281.0807 (20.9, $M^+ - CH_2OH$) 280.0705 (7.1, $M^+ - (CH_2OH + H)$) 254.0567 (9.59, $C_{15}H_{10}O_4$, retro-Diels–Alder scission).

9-(Hydroxymethyl)-6,11-dihydroxy-10-bromo-5-oxoxantho[3,2-*g*]tetralin (18) and 9-(Hydroxymethyl)-6,11-dihydroxy-7-methoxy-5-oxoxantho[3,2-*g*]tetralin (19). *N*-Bromosuccinimide (302 mg, 1.1 mmol) and benzoyl peroxide (30 mg) were added to a solution of **17** (322 mg. 1 mmol) in 25 mL of $CHCl_3$. The reaction mixture was heated under reflux in a nitrogen atmosphere for 1.5 h, the solvent was removed in vacuo, and then the residual solid was taken up in dry methanol and stirred under reflux in a nitrogen atmosphere for 12 h. The solvent was removed, the residue was extracted with ethyl acetate, and the extract was washed with water and dried (Na_2SO_4). Removal of the solvent under reduced pressure and column chromatography with ether–petroleum ether (1:1) as eluant afforded **18** which was purified by crystallization from THF to afford 30 mg (8% yield): mp 238–240 °C; ^1H NMR ($CDCl_3$) δ 1.95 (d, 1 H), 2.24 (m, 1 H, C_9–H), 2.84–3.00 (m, 3 H), 3.85 (d, 1 H), 4.10 (m, 1 H), 5.65 (t, 2 H, C_{10}–H and C_{11}–OH) (the triplet at δ 5.65 after D_2O exchange changes to a doublet counting for one proton, i.e., C_{10}–H, $J_{10,9}$ = 5.5 Hz), 7.5 (m, 2 H, aryl), 7.78 (m, 1 H, aryl), 8.30 (dd, 1 H, aryl), 12.03 (s, 1 H, exchange C_6-OH); IR (Nujol) ν_{max} 3300 (OH), 1640 (γ-pyrone), 1605 cm^{-1} (aryl); MS, m/z (relative intensity) 310.0844 (100) [calcd for $C_{18}H_{14}O_5$ 310.0844 (M^+ – HBr)].

Further elution of the column with ether gave some starting material **17** (15 mg) and then compound **19** which was purified by recrystallization from 1:1 THF–ether to give **19**: 23 mg (7% yield); mp 188 °C; ^1H NMR ($CDCl_3$) δ 2.15–2.45 (m, 4 H) 3.08 (d, 1 H), 3.60 (s, 3 H, OCH_3), 3.65–3.86 (m, 3 H), 4.88 (t, 1 H, C_7–$H_{e'}$, $J_{7e',8a'} = J_{7e',8e'}$ = 3.5 Hz), 6.47 (s, 1 H, exchange C_{11}–OH), 7.42 (m, 1 H, aryl), 7.57 (d, 1 H, Ar), 7.78 (m, 1 H, Ar), 8.32 (dd, 1 H, aryl), 12.24 (s, 1 H, exchange C_6-OH); IR (Nujol) 3400 (b, OH), 1640 (γ-pyrone), 1600 cm^{-1} (aryl); MS, m/z (relative intensity) 342.1103 (5) [calcd for $C_{19}H_{18}O_6$ 342.1103], 311.0883 (20, $M^+ - OCH_3$), 310.0883 (100, $M^+ - CH_3OH$), 279.0659 (64.8, 310 – CH_2OH).

Ethylene Glycol Ketals of 3-Acetyl-1,5,8-trihydroxytetralin (*cis*-21 and *trans*-22). A solution of the 3-ethylene glycol ketal of 3-acetyl-5,8-dihydroxy-1-tetralone (2.66 g, 10 mmol) in 125 mL of dry THF was treated wth sodium borohydride (529 mg, 14 mmol) and the reaction mixture was heated under reflux in a N_2 atmosphere for 12 h. The solvent was removed under reduced pressure, the residue was taken up in water and acidified with cold 10% sulfuric acid, and the solution was saturated with sodium chloride and extracted with ethyl acetate. The extract was washed with water, then aqueous sodium hydrogen carbonate, and then water and dried (Na_2SO_4). The solvent was removed in vacuo and the residual syrup subjected to column chromatography and eluted with ether–petroleum ether (80:20) to afford **21**[26] which was purified by crustallization from 1:1 THF–petroleum ether to give 1.07 g (40% yield): mp 120–123 °C;[26] ^1HNMR (Me_2SO-d_6) δ 1.26 (s, 3 H, CH_3), 1.35 (q, 1 H), 1.86 (m, 1 H), 2.2 (m, 1 H), 2.8 (dd, 1 H), 3.90 (d, 4 H, CH_2CH_2), 4.86 (quintet, 1 H, C_1-$H_{a'}$, after D_2O exchange gives a quartet with couplings $J_{1a',2a'}$ = 12 Hz, $J_{1a',2e'}$ = 4 Hz), 5.98 (d, 1 H, exchange C_1-OH, $J_{1H,10H}$ = 5 Hz), 6.40 (d, 1 H, aryl, $J_{6,7}$ = 8 Hz), 6.55 (d, 1 H, aryl), $J_{6,7}$ = 8 Hz), 8.60 (s, 1 H, exchange OH), 8.90 (s, 1 H, exchange OH).

Further elution of the column with ether gave **22** as a white solid which was purified by recrystallization from THF–ether to give 0.8 g (30% yield): mp 160–162 °C; ^1H NMR (Me_2SO-d_6) δ 1.25–1.4 (dd + s, 4 H, CH_3, 1 H), 2.09 (m, 3 H), 2.80 (dd, 1 H), 3.88 (m, 4 H, CH_2CH_2), 4.38 (d, 1 H, exchange C_1-OH, $J_{1H,10H}$ = 4.5 Hz), 4.84 (bd, 1 H, C_1-H, $\nu_{1/2}$ = 9.5 Hz, after D_2O exchange a triplet $J_{1e',2a'} = J_{1e',2e'}$ = 6.5 Hz), 6.48 (q, 2 H, C_6-H, C_7–H), 8.45 (2 s, 2 H, exchange C_5-OH, C_8-OH); IR (Nujol) ν_{max} 3470, 3390, 3200 cm^{-1} (phenolic, alcoholic OH); MS, m/z (relative intensity) 266.1149 (2) [calcd for $C_{14}H_{18}O_5$ 266.1149], 248.1048 (2.8 $M^+ - H_2O$), 161.0601 (11.2, $M^+ - (C_4H_7O_2 + H_2O)$), 87.0449 (100, $C_4H_7O_2$).

Ethylene Glycol Ketal of *cis*-3-Acetyl-1,5,8-trihydroxytetralin 1,8-Acetonide (23).[26] A solution of **21** (2.66 g, 10 mmol) in 25 mL of 2,2-dimethoxypropane containing 5 mg of *p*-toluenesulfonic acid was stirred at room temperature for 8 h. [If a larger proportion of *p*-TSA is used the dimethoxypropane tends to polymerize, which reduces the yield substantially.] The solvent was removed in vacuo, the residue was taken up in ethyl acetate, and the extract was washed thoroughly with aqueous sodium hydrogen carbonate and then water and dried (Na_2SO_4). The solvent was removed and the residue subjected to column chromatography with ether-petroleum ether (1:1) as eluant to give **23**[26] as a white solid which was further purified by crystallization from 1:1 ether–petroleum ether to give 2.10 g (68.6% yield): mp 143 °C;[26] ^1H NMR ($CDCl_3$) δ 1.35 (s, 3 H, CH_3), 1.43–1.60 (m, d, 7 H, CH_3, CH_3, H), 2.25 (m, 2 H), 2.50 (q, 1 H, C_4-$H_{a'}$, $J_{4a',3a'}$ 11 Hz, $J_{4,4'}$ = 18 Hz), 2.84 (q, 1 H, C_4-$H_{e'}$, $J_{4e',3a'}$ = 6 Hz, $J_{4,4'}$ = 18 Hz), 3.98 (m, 4 H, CH_2CH_2), 4.40 (s, 1 H, exchange C_5–OH), 4.76 (q, 1 H, C_1-$H_{a'}$, $J_{1a',2a'}$ = 11 Hz, $J_{1a',2e'}$ = 4.5 Hz), 6.52 (q, 2 H, aryl); IR (Halo oil) ν_{max} 3360 cm^{-1} (b, OH); MS, m/z (relative intensity) 306.1475 (4.6) [calcd for $C_{17}H_{22}O_5$ 306.1474], 248.1056 (14.5, $M^+ - C_3H_6O$), 87.0454 (53.4, $C_4H_7O_2$), 58.0445 (0.8, C_3H_6O).

Ethylene Glycol Ketal of *cis*-3-Acetyl-5-((*o*-methoxybenzoyl)oxy)-1,8-dihydroxytetralin 1,8-Acetonide (24). A solution of *o*-methoxybenzoic acid (3.04 g, 20 mmol) in dry pyridine (25 mL) was cooled in an ice bath, then *p*-toluenesulfonyl chloride (1.90 g, 10 mmol) was added, and the solution was stirred at 0 °C for 30 min. Compound **23** (3.06 g, 10 mmol) was added to the solution and the reaction mixture was stirred at 0 °C for 2 h then at room temperature for 12 h. The pyridine was removed under vacuum at ambient temperature, the residue was taken up in ethyl acetate, the extract washed thoroughly with aqueous sodium hydrogen carbonate and then water and dried (Na_2SO_4). Removal of the solvent left a thick syrup which upon trituration with ether gave **24** as a white crystalline solid which was further purified by crystallization from 1:1 THF–ether to give 2.75 g (62.5% yield): mp 122 °C; ^1H NMR ($CDCl_3$) δ 1.32 (s, 3 H, CH_3), 1.55 (m, s, 7 H, CH_3, CH_3, H), 2.30 (m, 2 H), 2.62 (q, 1 H, C_4-$H_{a'}$, $J_{4,4'}$ = 18 Hz, $J_{4a',3a'}$ = 11 Hz), 2.90 (q, 1 H, C_4-$H_{e'}$, $J_{4,4'}$ = 18 Hz, $J_{4e',3a'}$ = 7 Hz), 3.95 (m, s, 7 H, CH_2CH_2, OCH_3), 4.85 (q, 1 H, C_1-$H_{a'}$, $J_{1a',2a'}$ = 11 Hz, $J_{1a',2e'}$ = 4.5 Hz), 6.65 (d, 1 H, aryl), 7.02 (m, 3 H, aryl), 7.55 (m, 1 H, aryl), 7.95 (dd, 1 H, aryl); IR (Nujol)ν_{max} 1740 (ester), 1600 cm^{-1} (aryl); MS, m/e (relative intensity) 382.1416 (5.8, $M^+ - C_3H_6O$), 135.0447 (100, $C_8H_7O_2$), 87.0449 (25.3, $C_4H_7O_2$), 58.0443 (0.7, C_3H_6O); CIMS, m/z (relative intensity) 459 (18, $M^+ + 1 + H_2O$), 458 (64, $M^+ + H_2O$), 441 (2.5, $M^+ + 1$), 440 (7, M^+), 400 (100, 458 – C_3H_6O).

Ethylene Glycol Ketals of *cis*-3-Acetyl-6-(*o*-methoxybenzoyl)-1,5,8-trihydroxytetralin 1,8-Acetonide (25) and 3-Acetyl-5-(*o*-methoxyphenyl)-1,8-dihydroxytetralin 1,8-Acetonide (26). Compound **24** (4.0 g, 9 mmol) was dissolved in 350 mL of dioxane (freshly distilled from sodium metal) and photolyzed at room temperature (in a vertical photolysis apparatus equipped with water cooling) with a 450-W medium-pressure Hanovia lamp for 16 h.[26] The solvent was then removed under reduced pressure and the residual yellow syrup was subjected to column chromatography with ether–petroleum ether (1:3) as eluant to give in the first fraction compound **26** as a white solid which was further purified by crystallization from 1:1 THF–ether to give 180 mg (5% yield): mp 140 °C; ^1H NMR (Me_2SO-d_6) δ 1.1 (d, 3 H, CH_3, this doublet changes to a singlet at 80 °C), 1.30 (m, 1 H), 1.55 (d, 6 H, 2 × CH_3), 2.05–2.45 (m, 4 H), 3.6–3.90 (m, s, 7 H, CH_3 + CH_2CH_2), 4.90 (bd, 1 H, C_1-$H_{a'}$ changes to a quartet at 80 °C, $J_{1a',2a'}$ = 12 Hz, $J_{1a',2e'}$ = 5 Hz), 6.60 (dd, 1 H, aryl, changes to a doublet at 80 °C), 6.88 (d, 1 H, aryl, $J_{6,7}$ = 8.7 Hz at 80 °C),

7.05 (m, 3 H, Ar), 7.35 (m, 1 H, Ar). The doublet signals observed for the ketal CH_3 and the dd at δ 6.60 which change to singlets and doublets, respectively, at 80 °C suggest that **26** exists in rotameric forms in solution at room temperature arising from the restricted rotation about the biphenyl system: IR (Nujol) ν_{max} 1590 cm^{-1} (aryl); MS, m/z (relative intensity) 396.1938 (3.9) [calcd for $C_{24}H_{28}O_5$ 396.1938], 338.1519 (16.9, $M^+ - C_3H_6O$), 87.0449 (81.6, $C_4H_7O_2$), 58.0440 (1.1, C_3H_6O).

Further elution of the column with ether–petroleum ether (1:3) afforded **25** as a yellow solid which was further purified by crystallization from 1:1 THF–ether to afford 1 g (25% yield): mp 172 °C; ^1H NMR ($CDCl_3$) δ 1.40 (s, 3 H, CH_3), 1.55 (m, d, 7 H, 2 CH_3, 1 H), 2.30 (m, 2 H), 2.65 (q, 1 H, C_4-$H_{a'}$, $J_{4a',3a'}$ = 10.5 Hz, $J_{4,4'}$ = 18 Hz) 3.02 (q, 1 H, C_4-$H_{e'}$, $J_{4e',3a'}$ = 6.5 Hz, $J_{4,4'}$ = 18 Hz) 3.78 (s, 3 H, OCH_3), 4.0 (m, 4 H, CH_2CH_2), 4.82 (q, 1 H, C_1-$H_{a'}$, $J_{1a',2a'}$ = 11 Hz, $J_{1a',2e'}$ = 5 Hz), 6.62 (s, 1 H, aryl), 7.0 (m, 2 H, aryl), 7.25 (dd, 1 H, aryl), 7.45 (dt, 1 H, aryl), 12.10 (s, 1 H, chelated OH exchangeable); IR ($CHCl_3$) ν_{max} 1620 (CO), 1600 cm^{-1} (aryl); MS, m/z (relative intensity) 440.1833 (3.3) [calcd for $C_{25}H_{28}O_7$ 440.1833], 382.1418 (20.7, $M^+ - C_3H_6O$), 135.0447 (50.9, $C_8H_7O_2$), 87.0449 (88.5, $C_4H_7O_2$), 58.0443 (1.9, C_3H_6O).

Further elution with ether–petroleum ether (1:3) gave compound **23**: mp 143 °C mmp 143 °C; 1 g (36% yield). Further elution of the column with ether gave 300 mg (7.5% yield) of unreacted starting compound **24**.

3-Acetyl-6-(*o*-methoxybenzoyl)-1,5,8-trihydroxytetralin (27). A mixture of concentrated hydrochloric acid (2 mL) and water (2 mL) was added to a solution of **25** (50 mg) in 10 mL of THF and the mixture was stirred for 12 h at ambient temperature. The solution was diluted with 100 mL of water and extracted with ethyl acetate. The organic layer was washed with sodium bicarbonate solution and then water and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue subjected to column chromatography with ehter as eluant to afford **27** which was purified by crystallization from 1:1 THF–ether affording 9 mg (23% yield): mp 165–167 °C; ^1H NMR ($CDCl_3$) δ 2.02 (m, 1 H), 2.16–2.40 (m, s, 5 H, $COCH_3$ + 1 H + C_1-OH, one exchange proton with D_2O), 2.63 (q, 1 H, C_4-$H_{a'}$, $J_{4a',3a'}$ = 10.5 Hz, $J_{4,4'}$ = 17.5 Hz), 2.95 (m, 1 H), 3.22 (q, 1 H, C_4-$H_{e'}$, $J_{4e',3a'}$ = 4.5 Hz, $J_{4,4'}$ = 17.5 Hz), 3.78 (s, 3 H, OCH_3), 5.12 (t, 1 H, C_1-$H_{e'}$, after D_2O exchange $J_{1e',2a'}$ = $J_{1e',2e'}$ = 4.0 Hz), 5.95 (s, 1 H, C_8–OH), exchange), 6.70 (s, 1 H, aryl), 7.02 (m, 2 H, aryl), 7.25 (dd, 1 H, aryl), 7.45 (dt, 1 H, aryl), 12.18 (s, 1 H, C_5–OH, exchange); IR (Nujol) ν_{max} 3520 and 3300–3200 (OH function) 1675 (C(=O)CH_3), 1615 (C=O) 1580 (Ar); MS, m/z (relative intensity) 356.1264 (13.81) [calcd for $C_{20}H_{20}O_6$ 356.12636], 339.1185 (3.58, M^+ – OH), 338.1153 (16.28, $M^+ - H_2O$) 295.0969 (24.20, $M^+ - (H_2O + COCH_3)$) 294.0886 (4.30, 295 – H) 187.0386 (9.27, 294 – C_7H_5O) 159.0444 (2.94, 294 – $C_8H_7O_2$) 135.04446 (100, $C_8H_7O_2$).

3-Acetyl-6-(*o*-hydroxybenzoyl)-1-phenyl-5,8-dihydroxytetralin (28). Anhydrous aluminum chloride (400 mg, 3 mmol) was added in small portions to a solution of **25** (110 mg, 0.25 mmol) in 25 mL of dry benzene. The reaction mixture was heated at 45–50 °C under a nitrogen atmosphere for 23 h and then poured on a mixture of ice and hydrochloric acid and stirred for 15 min. The reaction mixture was extracted with ethyl acetate and the extract was washed with sodium bicarbonate and then water and dried (Na_2SO_4). Removal of the solvent in vacuo and column chromatography of the residue with ether–petroleum ether (1:3) as eluant gave **28** as a yellow solid which was further purified by crystallization from 1:1 THF–ether to afford 12 mg (12% yield): mp 212–215 °C; ^1H NMR ($CDCl_3$) δ 2.15 (m + s, 5 H, $COCH_3$ + 2 H), 2.72 (m, 2 H), 3.30 (m, 1 H), 4.18 (s, 1 H, exchange C_8-OH), 4.46 (q, 1 H, C_1-$H_{e'}$, $J_{1e',2a'}$ = 5.5, $J_{1e',2e'}$ = 2.0 Hz), 6.94 (t, 2 H, Ar), 7.10 (m, 3 H, Ar), 7.30 (m, 3 H, Ar), 7.50 (m, 1 H, Ar), 7.66 (dd, 1 H, Ar), 10.50 (s, 1 H, exchange OH), 10.87 (s, 1 H, exchange, OH); IR ($CHCl_3$) ν_{max} 3265 (OH), 1697 ($COCH_3$), 1618 (γ-pyrone), 1595 cm^{-1} (aryl); MS, m/z (relative intensity) 402.1471 (100) [calcd for $C_{25}H_{22}O_5$ 402.1471], 281.1161 (1.1, $M^+ - C_7H_5O_2$), 121.0292 (93.3, $C_7H_5O_2$).

3-Acetyl-6-(*o*-methoxybenzoyl)-1-bromo-5,8-dihydroxytetralin (29). A solution of **25** (110 mg, 0.25 mmol) in 20 mL of dichloromethane was cooled to –60 °C and to it was added boron tribromide (500 mg, 0.2 mL, 2 mmol) and the reaction mixture was stirred at –60 °C for 1 h. The solution was allowed to reach 0 °C, then stirred for an additional 1 h, then poured on an ice–hydrochloric acid mixture, stirred for another 20 min, and extracted with chloroform. The chloroform layer was washed with sodium bicarbonate solution and then water and dried (Na_2SO_4). Removal of the solvent under reduced pressure and column chromatography with ether and then THF as eluant gave **29** as a yellow solid which was further purified by crystallization from 1:1 THF–ether giving 16 mg (15% yield): mp 160–167 °C; IR ($CHCl_3$) ν_{max} 3400 (OH), 1710 ($COCH_3$), 1620 (CO), 1580 cm^{-1} (aryl); MS, m/z (relative intensity) 339.1183 (2.5, M^+ – Br), 338.1148 (13.5, M^+ – HBr) [calcd for $C_{20}H_{18}O_5$ 338.1148], 323.0884 (13.6, $M^+ - (HBr + CH_3)$), 307.0965 (15.3, $M^+ - (HBr + OCH_3)$), 135.0446 (38.6, $C_8H_7O_2$); CIMs 420 (11.7, $M^+ + 1$), 421 (3.2, $M^+ + 2$).

Ethylene Glycol Ketal of *cis*-3-Acetyl-5-acetoxy-6-(*o*-methoxybenzoyl)-1,8-dihydroxytetralin 1,8-Acetonide (30). A solution of **25** (440 mg, 1 mmol) in 25 mL of dry pyridine was cooled to 0 °C and treated with acetic anhydride (5 mL), and the mixture was stirred for 2 h at 0 °C and then at room temperature for 12 h. The solvents were removed in vacuo at ambient temperature, the residual solid was taken up in ethyl acetate, and the extract was washed with sodium bicarbonate and then water and dried (Na_2SO_4). The solvent was removed in vacuo and the residual syrup taken up in the minimum of ether, diluted with petroleum ether, and kept at 0 °C for 12 h. The crystalline product **30** which separated was further purified by recrystallization from 1:1 THF–petroleum ether to afford 440 mg (91% yield): mp 118 °C; ^1H NMR ($CDCl_3$) δ 1.34 (s, 3 H, CH_3), 1.55 (m, s, 7 H, 2 CH_3, H) 2.08 (s, 3 H, $OCOCH_3$), 2.25 (m, 2 H), 2.50 (q, 1 H, C_4-$H_{a'}$, $J_{4,4'}$ = 18 Hz, $J_{4a',3a'}$ = 11 Hz), 2.80 (q, 1 H, C_4-$H_{e'}$, $J_{4,4'}$ = 18 Hz, $J_{4e',3a'}$ = 6.5 Hz), 3.74 (s, 3 H, OCH_3), 4.0 (m, 4 H, CH_2CH_2), 4.84 (q, C_1-$H_{a'}$, $J_{1a',2a'}$ = 11 Hz, $J_{1a',2e'}$ = 4.5 Hz), 6.80 (s, 1 H, aryl), 6.96 (m, 2 H, aryl); 7.40 (m, 2 H, aryl); IR ($CHCl_3$) ν_{max} 1765 ($OCOCH_3$), 1670 (CO), 1598, 1580 cm^{-1} (aryl); MS, m/z (relative intensity) 482.1933 (5.2) [calcd for $C_{27}H_{30}O_8$ 482.1934], 424.1515 (39.1, $M^+ - C_3H_6O$), 87.0448 (100, $C_4H_7O_2$).

Ethylene Glycol Ketal of *cis*-3-Acetyl-5-methoxy-6-(*o*-methoxybenzoyl)-1,8-dihydroxytetralin 1,8-Acetonide (31) and Ethylene Glycol Ketal of *cis*-2-Acetyl-4,5-dihydroxy-7-oxoxantho[2,3-*f*]tetralin 4,5-Acetonide (32). A solution of **25** (440 mg, 1 mmol) in 50 mL of dry THF was heated with sodium hydride (120 mg, 80% dispersion in oil, 4 mmol). The reaction mixture was heated under reflux in a nitrogen atmosphere and after 1 h a further 120 mg of sodium hydride was added and refluxing continued for 30 min. The reaction mixture was cooled to room temperature, methyl iodide (2 mL) was added, and the reaction mixture was stirred at 40 °C for 12 h under N_2. The solvent was removed in vacuo and the residue taken up in 100 mL of 1:1 ethyl acetate–water and acidified with dilute hydrochloric acid. The ethyl acetate layer was washed with sodium bicarbonate and then water and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residual oil triturated with ether. The white solid which separated was further purified by crystallization from 1:1 THF–ether to afford **31**: 344 mg (75% yield); mp 120 °C; ^1H NMR ($CDCl_3$) δ 1.38 (s, 3 H, CH_3), 1.56 (m, d, 7 H, 2 CH_3, H), 2.30 (m, 2 H), 2.65 (q, 1 H, C_4-$H_{a'}$, $J_{4,4'}$ = 17 Hz, $J_{4a',3a'}$ = 11 Hz), 3.0 (q, 1 H, C_4-$H_{e'}$, $J_{4,4'}$ = 17 Hz, $J_{4e',3a'}$ = 6.5 Hz), 3.60 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 4.0 (m, 4 H, CH_2CH_2), 4.82 (q, 1 H, C_1-$H_{a'}$, $J_{1a',2a'}$ = 11 Hz, $J_{1a',2e'}$ = 4.5 Hz), 6.74 (s, 1 H, aryl), 6.98 (q, 2 H, aryl), 7.45 (q, 2 H, aryl); IR ($CHCl_3$) ν_{max} 1665 (CO), 1600, 1580 cm^{-1} (aryl); MS, m/z (relative intensity) 454.1992 (1.03) [calcd for $C_{26}H_{30}O_7$ 454.1992], 396.1577 (14.6, $M^+ - C_3H_6O$), 365.1344 (0.16, $M^+ - (C_3H_6O + OCH_3)$), 334.1210 (15.3, $M^+ - (C_3H_6O + 20CH_3)$), 135.0446 (25.3, $C_8H_7O_2$), 87.0455 (100, $C_4H_7O_2$), 58.0449 (2.4, C_3H_6O).

The filtrate, upon column chromatography and elution with ether–petroleum ether (30:70) afforded 5 mg (1% yield) of **32** which was shown to be identical with the authentic sample described below by IR, ^1H NMR, mass spectra, and by mixed melting point.

Ethylene Glycol Ketal of *cis*-2-Acetyl-4,5-dihydroxy-7-oxoxantho[2,3-*f*]tetralin 4,5-Acetonide (32). A solution of **30** (241 mg, 0.5 mmol) in 30 mL of dry toluene was treated with sodium thiocresolate (306 mg, 2.1 mmol) and hexamethylphosphoramide (0.55 ml, 3 mmol). The reaction mixture was refluxed under a N_2 atmosphere for 16 h and then diluted with ethyl acetate (100 mL), and the organic layer washed with 10%

aqueous sodium hydroxide (3 × 20 mL) and then water and dried (Na_2SO_4). Removal of the solvent in vacuo afforded a white crystalline solid which was washed with ether and recrystallized from 1:1 ethyl acetate–ether to afford 122 mg (60% yield) of **32**: mp 202 °C; ^1H NMR ($CDCl_3$) δ 1.48 (s, 3 H, CH_3), 1.65 (m, d, 7 H, 2 CH_3, H), 2.40 (m, 2 H), 2.92 (q, 1 H, C_1-$H_{a'}$, $J_{1,1'}$ = 18 Hz, $J_{1a',2a'}$ = 11 Hz), 3.32 (q, 1 H, C_1-$H_{e'}$, $J_{1,1'}$ = 18 Hz, $J_{1e',2a'}$ = 6 Hz), 4.05 (m, 4 H, CH_2CH_2), 4.95 (q, 1 H, C_4-$H_{a'}$, $J_{4a',3a'}$ = 10 Hz, $J_{4a',3e'}$ = 5 Hz), 7.35 (m, 1 H, aryl), 7.55 (m, 2 H, aryl), 7.74 (m, 1 H, aryl), 8.32 (dd, 1 H, aryl); IR ($CHCl_3$) ν_{max} 1655 cm^{-1} (C=O); MS, m/z (relative intensity) 408.1574 (4.7) [calcd for $C_{24}H_{24}O_6$ 408.1574], 350.1152 (17.2, $M^+ - C_3H_6O$), 263.0705 (29, $M^+ - (C_3H_6O + C_4H_7O_2)$), 87.0447 (69, $C_4H_7O_2$), 58.0440 (1.2, C_3H_6O).

Reaction of Ethylene Glycol Ketal of *cis*-3-Acetyl-6-(*o*-methoxybenzoyl)-1,5,8-trihydroxytetralin 1,8-Acetonide (25) with Sodium Thiocresolate To Afford 32 and 33. A solution of **25** (110 mg, 0.25 mmol) in 10 mL of dry toluene was treated with sodium thiocresolate (146 mg, 1 mmol) and hexamethylphosphoramide (233 mg, 1.3 mmol). The reaction mixture was heated under reflux in a N_2 atmosphere for 16 h and then diluted with ethyl acetate (100 mL). The extract was washed with 10% aqueous sodium hydroxide (4 × 25 mL) and then water and dried (Na_2SO_4). Removal of the solvent in vacuo afforded a solid which was washed with ether and crystallized from ethyl acetate–ether to give 45 mg (44% yield) of **32** as a white crystalline solid: mp 202 °C; mmp (with authentic sample) 202 °C. The IR, ^1H NMR, and mass spectra were identical with those of **32** prepared above.

The aqueous layer was acidified with dilute hydrochloric acid and rapidly extracted with ethyl acetate (3 × 50 mL). The yellow extract was thoroughly washed with water and dried (Na_2SO_4). Removal of the solvent in vacuo gave a yellow solid which was washed with cold ether and recrystallized from 1:1 THF–ether to give 15 mg (14% yield) of **33**: mp 185 °C; ^1H NMR ($CDCl_3$) δ 1.42 (s, 3 H, CH_3), 1.60 (d + m, 7 H, CH_3 + CH_3 + 1 H), 2.32 (m, 2 H), 2.68 (q, 1 H, C_4-$H_{a'}$, $J_{4a',3a'}$ = 11 Hz, $J_{4,4'}$ = 18 Hz), 3.02 (q, 1 H, C_1-$H_{e'}$, $J_{4e',3a'}$ = 6.5 Hz, $J_{4,4'}$ = 18 Hz), 4.04 (m, 4 H, CH_2CH_2), 4.88 (q, 1 H, C_1-$H_{a'}$, $J_{1a',2a'}$ = 11 Hz, $J_{1a',2e'}$ = 4.5 Hz), 6.93 (s, 1 H, Ar), 6.98 (t, 1 H, Ar), 7.08 (d, 1 H, Ar), 7.52 (m, 1 H, Ar), 7.68 (dd, 1 H, Ar) 10.58 (d, 2 H, OH + OH exchange); IR ($CHCl_3$) ν_{max} 3400–3200 (b, OH), 1620 (CO), 1590, 1575 cm^{-1} (aryl); MS, m/z (relative intensity) 426.1673 (3.3) [calcd for $C_{24}H_{26}O_7$ 426.1673], 368.1258 (15.8, $M^+ - C_3H_6O$), 281.0811 (3.9, $M^+ - (C_3H_6O + C_4H_7O_2)$), 121.0292 (29.2, $C_7H_5O_2$), 87.0448 (71.5, $C_4H_7O_2$) 58.0440 (1.5, C_3H_6O).

Reaction of Ethylene Glycol Ketal of *cis*-3-Acetyl-5-methoxy-6-(*o*-methoxybenzoyl)-1,8-dihydroxytetralin 1,8-Acetonide (31) with Sodium Thiocresolate To Afford 32, 33, 34, 35, 36, and 37. A solution of **31** (8 g, 17.6 mmol) in 600 mL of dry toluene was treated with sodium thiocresolate[27] (12 g, 82 mmol) and hexamethylphosphoramide (20 mL, 115 mmol). The reaction mixture was heated under reflux in a N_2 atmosphere for 18 h and then diluted with ethyl acetate (500 mL) and extracted with 10% aqueous sodium hydroxide (6 × 100 mL). The sodium hydroxide extract was acidified and then extracted with ethyl acetate. This extract was washed with cold 5% aqueous hydrochloric acid and then water and dried (Na_2SO_4). The solvent was removed in vacuo and the residual yellow solid washed with ether to give **33** which was further purified by crystallization from 1:1 THF–ether to afford 2.8 g (37.3%) yield): mp 185 °C. This compound was identical with the material prepared from **25**.

The organic layer (toluene and ethyl acetate) was washed with 5% aqueous hydrochloric acid and then water and dried (Na_2SO_4). Removal of the solvent in vacuo and trituration of the residue with ether gave a white solid, which was collected and washed with cold ether and further purified by crystallization from 1:1 ethyl acetate–ether to give 2 g (27.8% yield) of **32**: mp 202 °C; mmp 202 °C (with previously prepared samples).

The filtrate and ether washings from the isolation of **32** were collected and the solvents removed in vacuo. The residue was subjected to column chromatography with ether–petroleum ether (30:70) as eluant. The fractions were monitored by TLC for additional products and combined appropriately. The first group of fractions afforded **37** in trace amounts; it was characterized by mass spectrometry. Both high- and low-resolution mass gave the highest peak m/z 346 which corresponds to the molecular formula $C_{22}H_{18}O_4$: MS, m/z (relative intensity) 346.1211 (1.67) [calcd for $C_{22}H_{18}O_4$ 346.1209]. Further elution gave **34** which was further purified by crystallization from 1:1 THF–ether to afford 40 mg (0.6% yield): mp 215–218 °C; ^1H NMR ($CDCl_3$) 1.70 (s, 6 H, CH_3 + CH_3) 1.78 (s, 3 H, CH_3) 3.90 (q, 2 H, CH_2) 4.15 (q, 2 H, CH_2) 7.30 (m, 1 H, Ar) 7.45 (m, 1 H, Ar) 7.62 (s, 1 H, Ar) 7.75 (m, 2 H, Ar) 8.38 (m, 2 H, Ar); IR ($CHCl_3$) 1655 (C=O), 1610, 1590 cm^{-1} (Ar); MS, m/z (relative intensity) 404.1261 (66.2) [calcd for $C_{24}H_{20}O_6$ 404.1261], 389.1027 (100, $M^+ - CH_3$) 317.0800 (15.3, $M^+ - C_4H_7O_2$) 87.0448 (35.6, $C_4H_7O_2$).

Further elution of the column with ether–petroleum ether (30:70) gave a thick syrup which upon trituration with ether gave a white crystalline solid which was further purified by crystallization from 1:1 THF–ether to give **36**: 500 mg (6.5% yield); mp 145 °C; ^1H NMR ($CDCl_3$) δ 1.40 (s, 3 H, CH_3), 1.60 (m, s, 7 H, 2 CH_3, H), 2.30 (m, 2 H), 2.70 (q, 1 H, C_4-$H_{a'}$, $J_{4,4'}$ = 17.5 Hz, $J_{4a',3a'}$ = 11 Hz), 3.02 (q, 1 H, C_4-$H_{e'}$, $J_{4,4'}$ = 17.5, $J_{4e',3a'}$ = 6.5 Hz), 3.62 (s, 3 H, OCH_3), 4.02 (m, 4 H, CH_2CH_2), 4.85 (q, 1 H, C_1-$H_{a'}$, $J_{1a',2a'}$ = 11 Hz, $J_{1a',2e'}$ = 4.5 Hz), 6.6 (s, 1 H, aryl), 6.85 (t, 1 H, aryl), 7.04 (d, 1 H, aryl), 7.45 (m, 2 H, aryl), 12.14 (s, 1 H, exchange OH); IR ($CHCl_3$) ν_{max} 1630 (CO), 1610, 1580 cm^{-1} (aryl); MS, m/z (relative intensity) 440.1836 (4.4) [calcd for $C_{25}H_{28}O_7$ 440.1836], 382.1420 (25.4, $M^+ - C_3H_6O$), 353.1360 (0.5, $M^+ - C_4H_7O_2$) 121.0291 (27.2, $C_7H_5O_2$) 87.0450 (100, $C_4H_7O_2$) 58.0442 (1.9, C_3H_6O).

Further elution of the column with ether–petroleum ether (30:70) gave a further 20 mg of **33**. Further elution of the column with the same eluant gave a thick syrup which upon trituration with ether gave **35** as a solid which was purified by crystallization from 1:1 THF–petroleum ether to afford 25 mg (0.35% yield): mp 158 °C; ^1H NMR ($CDCl_3$) δ 1.60 (d, 3 H, $CHCH_3$), 1.73 (s, 6 H, 2 CH_3), 2.08 (t, 1 H, exchange OH), 3.55 (m, 2 H, OCH_2), 3.80 (q, 2 H, CCH_2OH), 4.72 (q, 1 H, $C(=O)CH_3$), 7.16 (d, 1 H, aryl), 7.45 (m, 1 H, aryl), 7.60 (s, 1 H, aryl), 7.86 (m, 2 H, aryl), 8.13 (d, 1 H, aryl), 8.40 (dd, 1 H, aryl). After D_2O exchange the signal at δ 3.80 becomes a triplet instead of a quartet which indicates that CH_2 at δ 3.80 is linked to an OH group. Decoupling of the proton at δ 4.72 converts the doublet at δ 1.6 to a singlet which means CH is coupled with $C(=O)CH_3$ methyl group. IR ($CHCl_3$) ν_{max} 3450 (OH), 1650 cm^{-1} (CO); MS, m/z (relative intensity) 406.1423 (100) [calcd for $C_{24}H_{22}O_6$ 406.1422], 391.1184 (5.9, $M^+ - CH_3$), 348.1023 (3.3, $M^+ - C_3H_6O$), 345.1121 (22.8, $M^+ - C_2H_5O_2$).

Preparation of Ethylene Glycol Ketal of *cis*-3-Acetyl-6-(*o*-hydroxybenzoyl)-1,5,8-trihydroxytetralin 1,8-Acetonide (33) from the Ethylene Glycol Ketal of *cis*-3-Acetyl-5-methoxy-6-(*o*-hydroxybenzoyl)-1,8-dihydroxytetralin 1,8-Acetonide (36). A solution of **36** (440 mg, 1 mmol) in 50 mL of dry toluene was treated with sodium thiocresolate[27] (628 mg, 4.3 mmol) and HMPA (1.1 mL, 6 mmol) and the reaction contents were heated under reflux in a nitrogen atmosphere for 20 h and then diluted with ethyl acetate. The mixture was extracted with 10% aqueous sodium hydroxide (5 × 40 mL), the aqueous layer was extracted rapidly with ethyl acetate, and the combined extracts were dried (Na_2SO_4). Removal of the solvent in vacuo gave a yellow solid which was washed with ether and crystallized from THF–ether to give **33**, 320 mg (76% yield), mp 185 °C, which was identical in all physical and spectral properties to the previously prepared samples from **25** or **31**.

2-Acetyl-7-(*o*-hydroxybenzoyl)-5,8-dihydroxynaphthalene (38). To a solution of **33** (213 mg, 0.5 mmol) in THF (80 mL) was added a cooled mixture of 10 mL of water and 10 mL of concentrated hydrochloric acid and the reaction mixture was set aside at room temperature for 10 days during which time 80 mg of a yellow solid separated and was collected. The filtrate was diluted with 200 mL of water and extracted with ethyl acetate (4 × 50 mL). The combined extracts were washed with water and dried (Na_2SO_4). Removal of the solvent in vacuo gave a further 20 mg of **38**. The combined product was crystallized from 1:1 ethyl acetate–ether to give 100 mg (62% yield): mp 295 °C; ^1H NMR (Me_2SO-d_6) δ 2.74 (s, 3 H, $COCH_3$), 6.88 (s, 1 H, aryl), 6.98 (m, 2 H, aryl), 7.40 (m, 2 H, aryl), 8.18 (d, 2 H, aryl), 8.96 (s, 1 H, aryl), 9.9 (s, 1 H, exchange OH), 10.24 (s, 1 H, exchange OH), 13.22 (s, 1 H, exchange OH); IR ($CHCl_3$) ν_{max} 1660 ($COCH_3$), 1628 (CO), 1585 cm^{-1} (aryl); MS, m/z (relative intensity) 322.0846 (70.3) [calcd for $C_{19}H_{14}O_5$ 322.0846], 305.0802 (21.7, M^+ – OH), 279.0654 (2.26, $M^+ - COCH_3$), 229.0466 (17.4, $M^+ - C_6H_5O$), 228.0424 (100, 229 – H) 121.0292 (26.6, $C_7H_5O_2$), 93.0340 (8.5, C_6H_5O).

***trans*-3-Acetyl-6-(*o*-hydroxybenzoyl)-5,8-dihydroxytetralin (39), *cis*-3-Acetyl-6-(*o*-hydroxybenzoyl)-1,5,8-trihydroxytetralin (40), and Ethylene Glycol Ketal of 2-Acetyl-7-(*o*-hydroxybenzoyl)-1,2-dihydronaphtho-5,8-quinone (41).** A solution of **33** (426 mg, 1 mmol) in 100 mL of THF was treated with 10 mL of 50% aqueous hydrochloric acid and the reaction mixture was stirred at room temperature for 3 h and then neutralized carefully with aqueous sodium bicarbonate. The THF was removed in vacuo and the residue extracted with ethyl acetate (4 × 30 mL). The organic layer was washed with sodium bicarbonate solution and then water and dried (Na_2SO_4). Removal of the solvent and column chromatography of the residual syrup with ether–petroleum ether (1:1) as eluant afforded a reddish-yellow solid **41**: 2 mg (0.6% yield); mp 238 °C; ^1H NMR ($CDCl_3$) δ 1.46 (s, 3 H, CH_3), 2.44–3.08 (m, 4 H), 3.70 (m, 1 H), 4.02 (m, 4 H, CH_2CH_2), 7.35 (t, 1 H, Ar), 7.52 (d, 1 H, Ar), 7.70 (m, 2 H, Ar), 8.30 (dd, 1 H, Ar), 11.75 (s, 1 H, OH exchange); IR ($CHCl_3$) 1650 (C=O), 1605, and 1580 cm^{-1} (Ar); MS, *m/z* (relative intensity) 366.1094 (26.5) [calcd for $C_{21}H_{18}O_6$ 366.1095], 279.0654 (11.6, $M^+ - C_4H_7O_2$), 278.0580 (2.1, $M^+ - (C_4H_7O_2 + H)$), 87.0447 (100, $C_4H_7O_2$).

Further elution of the column with ether gave a yellow oil which upon trituration with petroleum ether deposited a solid which was collected and purified by recrystallization from 1:1 ether–petroleum ether to give **40**: 126 mg (37% yield); mp 174–175 °C; ^1H NMR ($CDCl_3$) δ 2.30 (m, s, 5 H, $COCH_3$ + C_2-H, H′), 2.90 (q, 1 H, C_4-H, $J_{4,4'}$ = 17 Hz, $J_{4,3}$ = 6 Hz) 3.12–3.25 (quintet, 1 H, C_3-H), 3.25–3.40 (q, 1 H, C_4-H′, $J_{4,4'}$ = 17 Hz, $J_{4',3}$ = 4.5 Hz), 4.75 (d, 1 H, exchange, C_1-OH, $J_{1H,OH}$ = 10 Hz), 4.96 (m, 1 H, C_1-H, after D_2O exchange C_1-H appears as a quartet with coupling constants of 5 and 7 Hz), 6.98 (m, 1 H, aryl), 7.10 (d, 2 H, aryl), 7.55 (m, 1 H, aryl), 7.68 (dd, 1 H, aryl), 7.86 (s, 1 H, exchange C_8-OH), 10.62 (s, 2 H, exchange 2 OH); IR (Nujol) ν_{max} 3500, 3300 cm^{-1} (OH), 1700 (C(=O)CH_3), 1610 (C=O), 1585 cm^{-1} (Ar); MS, *m/z* (relative intensity) 342.1109 (8.5) [calcd for $C_{19}H_{18}O_6$ 342.1109], 324.0994 (19.4, $M^+ - H_2O$), 281.0810 (45, $M^+ - (COCH_3 + H_2O)$), 121.0292 (100, $C_7H_5O_2$), 93.0341 (9.7, C_6H_5O).

Further elution of the column with ether–THF (80:20) gave upon removal of the solvent a yellow colored solid which was purified by recrystallization from 1:1 THF–ether to give **39**: 107 mg (31% yield); mp 166 °C; ^1H NMR ($CDCl_3$) 2.08 (m, 1 H, C_2-H), 2.30 (m + s, 4 H, C_2-H + CH_3), 2.68 (q, 1 H, C_4-$H_{a'}$, $J_{4,4'}$ = 17 Hz, $J_{4a',3a'}$ = 10 Hz), 2.95 (m, 1 H, C_3-$H_{a'}$), 3.25 (q, 1 H, C_4-$H_{e'}$, $J_{4,4'}$ = 17 Hz, $J_{4e',3a'}$ = 4.5 Hz), 5.18 (m, C_1-$H_{e'}$ after D_2O exchange the multiplet became a triplet with coupling constant $J_{1e',2a'} = J_{1e',2e'}$ = 4.2 Hz), 6.22 (s, 1 H, C_8-OH exchange), 6.94 (t, 1 H, Ar), 7.02 (s, 1 H, Ar), 7.08 (d, 1 H, Ar), 7.52 (m, 1 H, Ar), 7.64 (dd, 1 H, Ar), 10.55 (s, 1 H OH exchange), 10.57 (s, 1 H, OH, exchange). When the spectrum is run in $CDCl_3$ with a drop of Me_2SO the signal at δ 5.18, i.e., C_1-$H_{e'}$, appears as a quartet and gives coupling constants $J_{1e',2a'}$ = 4.5 Hz, $J_{1e',2e'}$ = 3 Hz; on adding D_2O this quartet gave a triplet with coupling constant $J_{1e',2a'} = J_{1e',2e'}$ = 4 Hz; IR (Nujol) ν_{max} 3400, 3150, (OH), 1685 ($COCH_3$), 1610 (CO), 1580 cm^{-1} (aryl); MS, *m/z* (relative intensity) 342.1107 (10.5) [calcd for $C_{19}H_{18}O_6$ 342.1107], 324.0997 (21.8, $M^+ - H_2O$), 281.0815 (34.4, $M^+ - (H_2O + COCH_3)$), 121.0294 (100, $C_7H_5O_2$), 93.0344 (9.0, C_6H_5O).

***trans*-9-Acetyl-6,7,11-trihydroxy-12-oxoxantho[2,3-*g*]tetralin (42).** A solution of **39** (1.026 gm, 3 mmol) in 200 mL of dry methanol (freshly distilled from magnesium methanolate) was treated dropwise with a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (678 mg, 3 mmol) in 100 mL of dry benzene in an atmosphere of nitrogen and the mixture was stirred at ambient temperature for 12 h. The solvent was removed under reduced pressure and the residual solid subjected to column chromatography with ether as eluant. The first fractions contained the hydroquinone of DDQ and further elution with ether–THF (3:1) gave compound **42** which after removal of the solvent was washed with ether and purified by recrystallization from 1:1 THF–ether to give 720 mg (74% yield): mp 200 °C dec; ^1H NMR (Me_2SO-d_6 + $CDCl_3$) 1.80 (m, 1 H), 2.30 (m + s, 4 H, CH_3 + H) 2.58 (m, 1 H), 3.15 (m, 2 H), 4.80 (bs, 1 H, C_7–OH), 5.25 (t, 1 H, C_7-$H_{e'}$, $J_{7e',8a'} = J_{7e',8e'}$ = 3.5 Hz), 7.42 (m, 1 H, Ar), 7.60 (d, 1 H, Ar), 7.80 (m, 1 H, Ar), 8.25 (dd, 1 H, Ar), 8.64 (s, 1 H, C_6-OH), 12.28 (s, 1 H, C_{11}-OH); IR (Nujol) 3500–3400 and 3100–3200 (OH function) 1685 ($COCH_3$), 1625 (C=O), 1595, 1580 cm^{-1} (Ar); MS, *m/z* (relative intensity) 340.0944 (2.1) [calcd for $C_{19}H_{16}O_6$ 340.0944], 322.0828 (32.2, $M^+ - H_2O$) 321.0724 (10.0, $M^+ - (H_2O + H)$), 320.0675 (31.9, 322 - 2 H) 279.0647 [100, $M^+ - (H_2O + COCH_3)$), 278.0563 (25.5, 279 - H), 186.0280 (2.7, $C_{11}H_6O_3$ 278 - C_6H_4O), 92.0261 (1.5, C_6H_4O).

Dimethyl Ketal of *trans*-9-Acetyl-6,7,11-trihydroxy-12-oxoxantho[2,3-*g*]tetralin (43). A solution of **42** (34 mg, 0.1 mmol) in 50 mL of methanol containing one drop of concentrated hydrochloric acid was stirred at room temperature for 22 h. After 1.5 h a solid separated. At the end of 22 h the solid was collected and washed with methanol to give **43** which was purified by recrystallization from ethyl acetate to give 28 mg (73% yield): mp 230 °C dec; ^1H NMR (Me_2SO-d_6 + $CDCl_3$) δ 1.20 (s, 3 H, CH_3) 1.35 (m, 1 H), 2.10 (m, 2 H), 2.46 (m, 1 H), 2.88 (m, 1 H), 3.18 (s, 6 H, $2OCH_3$), 5.02 (bs, 1 H, C_7-OH, exchange) 5.12 (bs, 1 H, C_7-$H_{e'}$ this broad singlet after D_2O exchange becomes a triplet with coupling constant $J_{7e',8a'} = J_{7e',8e'}$ = 3 Hz), 7.45 (t, 1 H, aryl), 7.65 (d, 1 H, aryl), 7.90 (m, 1 H, aryl), 8.20 (dd, 1 H, aryl), 9.0 (s, 1 H, exchange C_6-OH), 12.16 (s, 1 H, exchange C_{11}-OH); IR (Nujol) ν_{max} 3400–3200 (OH), 1640 (γ-pyrone), 1600 cm^{-1} (aryl); MS, *m/z* (relative intensity) 386.1365 (1.4) [calcd for $C_{21}H_{22}O_7$ 386.1365], 355.1173 (2, $M^+ - OCH_3$), 338.1110 (10.9, $M^+ - (OCH_3 + OH)$), 337.1041 (27, $M^+ - (OCH_3 + H_2O)$), 336.0998 (100, 337 - H), 279.0649 (74.7, $M^+ - (C_4H_9O_2 + H_2O)$).

***trans*-9-Acetyl-6,7,11-trihydroxy-12-oxoxantho[2,3-*g*]tetralin 6,7-Acetonide (44).** A solution of **42** (408 mg, 1.2 mmol), dimethoxypropane (40 mL), and *p*-toluenesulfonic acid monohydrate (25 mg) in 200 mL of dry THF was stirred for 3 h at room temperature. The solvent was removed in vacuo, the residue taken up in ethyl acetate, and the extract washed with sodium bicarbonate solution and then water and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a yellow solid which was washed with ether and purified by recrystallization from 1:1 THF–ether to afford 368 mg (81% yield) of **44**: mp 200 °C; ^1H NMR ($CDCl_3$) δ 1.65 (m, 2 × s, 7 H, 2 CH_3, C_8-$H_{a'}$), 2.34 (s, 3 H, $COCH_3$), 2.62 (m, 1 H, C_8-$H_{e'}$), 2.72 (q, 1 H, C_{10}-H, $J_{10,10'}$ = 16 Hz, $J_{10H,9H}$ = 6 Hz), 3.10 (m, 1 H, C_9-H), 3.28 (q, 1 H, C_{10}-H′, $J_{10,10'}$ = 16 Hz, $J_{10H',9H}$ = 7.5 Hz), 4.8 (q, 1 H, C_7-$H_{a'}$, $J_{7a',8a'}$ = 11 Hz, $J_{7a',8e'}$ = 6 Hz), 7.38 (t, 1 H, aryl), 7.58 (d, 1 H, aryl), 7.75 (m, 1 H, aryl), 8.28 (dd, 1 H, aryl), 12.46 (s, 1 H, exchange C_{11}-OH); IR (Nujol) ν_{max} 1695 ($COCH_3$), 1640 (γ-pyrone), 1600 cm^{-1} (aryl); MS, *m/z* (relative intensity) 380.1262 (0.85) [calcd for $C_{22}H_{20}O_6$ 380.12618], 322.0835 (36.5, $M^+ - C_3H_6O$), 321.0722 (8.0, 322 - H), 320.0676 (29.8, 321 - H), 279.0649 (100, $M^+ - (C_3H_6O + COCH_3)$), 278.0565 (37.9, 279 - H), 277.0494 (45.3, 278 - H) 58.0440 (3.0, C_3H_6O).

9-Acetyl-6,7α,9α,11-tetrahydroxy-12-oxoxantho[2,3-*g*]tetralin 6,7-Acetonide (45) and 9-Acetyl-9,10-dihydro-6,7,11-trihydroxy-12-oxoxantho[2,3-*g*]naphthalene 6,7-Acetonide (46). A mixture of dimethylformamide (30 mL, freshly distilled from CaH_2) and dry *tert*-butyl alcohol (12 mL) was treated with potassium *tert*-butoxide (257 mg, 2.3 mmol) and the reaction mixture was stirred at room temperature in a N_2 atmosphere for 30 min and then cooled to −25 °C. Triethyl phosphite[28] (6 mL) and compound **44** (114 mg, 0.3 mmol) were added to the mixture and dry O_2 was bubbled through the solution for 2 h while the temperature was kept between −15 and −25 °C. The reaction mixture was diluted with 200 mL of ice cold water, acidified with dilute hydrochloric acid, and extracted exhaustively with ethyl acetate. The ethyl acetate layer was washed thoroughly with water and dried (Na_2SO_4). Removal of the solvent under reduced pressure and treatment by ether caused a solid to separate which was purified by preparative TLC on silica gel to give 11 mg (10% yield) of **46**: mp >300 °C dec; ^1H NMR ($CDCl_3$) δ 1.60 (s, 3 H, CH_3), 1.74 (s, 3 H, CH_3), 2.30 (m, 1 H, C_9-H), 2.48 (s, 3 H, $COCH_3$), 3.30 (q, 1 H, C_{10}-H, $J_{10,10'}$ = 16 Hz, $J_{10H,9H}$ = 7 Hz), 5.0 (q, 1 H, C_{10}-H′, $J_{10,10'}$ = 16 Hz, $J_{10H',9H}$ = 7 Hz), 7.44 (t, 1 H, Ar), 7.64 (d, 1 H, Ar), 7.76 (dd, 1 H, Ar), 7.85 (d, 1 H, C_8-H, $J_{8H,9H}$ = 2.5 Hz, changes to a singlet on decoupling C_9-H, i.e., δ 2.30), 8.28 (dd, 1 H, Ar), 12.72 (s, 1 H, exchange C_{11}-OH); IR (Nujol) 3500–3300 (OH), 1645 ($COCH_3$), 1615 (γ-pyrone), 1600 (Ar); MS, *m/z* (relative intensity) 378.1087 (0.5) [calcd for $C_{22}H_{18}O_6$ 378.1089], 320.0678 (100, $M^+ - C_3H_6O$), 305.0446 (29.7, $M^+ - (C_3H_6O + CH_3)$), 277.0498 (52.4, $M^+ - (C_3H_6O + COCH_3)$), 276.0416 (4.8, 277 - H), 58.0440 (2.0, C_3H_6O). The solvent was removed in vacuo from the filtrate and the residual solid was subjected to preparative

TLC on silica gel with ether as eluant affording **45** which was further purified by crystallization from 1:1 THF–ether to give 24 mg (20% yield): mp 192–193 °C; ^{1}H NMR ($CDCl_3$) δ 1.63 (s, 3 H, CH_3), 1.78 (m + s, 4 H, C_8-H + CH_3), 2.42 (s, 3 H, $COCH_3$), 2.70 (d, 1 H, C_{10}-H, $J_{10,10'}$ = 15.5 Hz), 2.82 (m, 1 H, C_8-H′), 3.15 (bs + d, 2 H, C_9-OH + C_{10}-H′, $J_{10H',10H}$ = 15.5 Hz, this signal on D_2O exchange gave a doublet for C_{10}-H′), 4.88 (q, 1 H, C_7-Ha′, $J_{7a',8a'}$ = 10 Hz, $J_{7a',8e'}$ = 7.5 Hz), 7.40 (t, 1 H, Ar) 7.60 (d, 1 H, Ar) 7.75 (t, 1 H, Ar) 8.26 (d, 1 H, Ar) 12.42 (s, 1 H, C_{11}-OH, exchange); IR (Nujol) ν_{max} 3500–3400 (OH), 1690 ($COCH_3$), 1640 (γ-pyrone), 1600, 1580 cm^{-1} (aryl); MS, *m/z* (relative intensity) 396.1197 (1.5) [calcd for $C_{22}H_{20}O_7$ 396.1198], 338.0789 (18.5, $M^+ - CH_3COCH_3$), 321.0720 [17.6, $M^+ - (C_3H_6O + OH)$), 320.0684 (85.8, $M^+ - (C_3H_6O + H_2O)$), 295.0604 (83.5, 338.0789 – CH_3CO), 277.0499 (100, $M^+ - (C_3H_6O + CH_3CO + H_2O)$ or 320.0684 – CH_3CO), 58.0440 (8.3, CH_3COCH_3).

9-Acetyl-6,7α,9α,11-tetrahydroxy-12-oxoxantho[2,3-*g*]tetralin (47). A solution of **45** (50 mg, 0.126 mmol) in 100 mL of THF containing concentrated HCl (1 mL) and water (1 mL) was stirred at room temperature for 6 h, then diluted with 200 mL of water, and extracted exhaustively with ethyl acetate. The organic layer was washed with sodium bicarbonate and then water and dried (Na_2SO_4). Removal of the solvent in vacuo gave a yellow solid that was subjected to preparative TLC on silica gel with ether as eluant to give first some unreacted **45** (10 mg) and the slower moving deprotected compound **47** which was crystallized from 1:1 THF–ether to give 20 mg [56% yield on the basis of uncrecovered **45**]: mp 216–220 °C; ^{1}H NMR (Me_2SO-d_6, $CDCl_3$) δ 2.12 (m, 2 H, C_8-$H_{a',e'}$), 2.30 (s, 3 H, $COCH_3$), 2.90 (d, 1 H, C_{10}-H, $J_{10a'e'}$ = 17.5 Hz), 3.10 (d, 1 H, C_{10}-H, $J_{10a'e'}$ = 17.5 Hz) 5.08 (d, 1 H, C_7-OH, exchange $J_{70H,H}$ = 7.5 Hz), 5.28 (m, 1 H, C_7-$H_{e'}$, after D_2O exchange this multiplet changes for a quartet $J_{7e'8e'}$ = 3.5 Hz, $J_{7e',8a'}$ = 5 Hz), 5.6 (s, 1 H, C_9-OH exchange), 7.48 (m, 1 H, aryl), 7.68 (d, 1 H, aryl), 7.88 (m, 1 H, aryl), 8.22 (dd, 1 H, aryl), 8.55 (s, 1 H, exchange C_6-OH), 12.18 (s, 1 H, exchange C_{11}-OH); IR (Nujol) 3400 (OH), 1700 ($COCH_3$), 1625 (γ-pyrone), 1590 cm^{-1} (aryl); MS, *m/z* (relative intensity) (low resolution) 357 (0.1, M^+ + 1) 356 (0.6, M^+), 320 (100, $M^+ - 2H_2O$); (high resolution) 338.0785 (3.2, $M^+ - H_2O$), 320.0683 (55.7, $M^+ - 2H_2O$) 305.0444 (20.9, 320 – CH_3), 295.0605 (100, $M^+ - (COCH_3 + H_2O)$), 277.0497 (41.8, 320 – $COCH_3$).

Cyclic Methyl Ketal of 7,13-*cis*-9-Acetyl-6,7,11-trihydroxy-12-oxoxantho[2,3-*g*]tetralin (48) and *cis*-9-Acetyl-6,7,11-trihydroxy-12-oxoxantho[2,3-*g*]tetralin (49). A solution of **40** (480 mg, 1.4 mmol) in 100 mL of methanol was treated dropwise with a solution of DDQ (316 mg, 1.4 mmol) in 50 mL of dry benzene under an atmosphere of nitrogen and then stirred at room temperature for 12 h. Removal of the solvent under reduced pressure and column chromatography with ether–petroleum ether (2:1) as eluant afforded 70 mg (14% yield) of **48**: mp 245 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.40, 1.50 (2 × s, 3 H, CH_3), 1.90 (q, 1 H), 2.40–3.20 (m, 4 H), 3.24, 3.30 (2 × s, 3 H, OCH_3), 5.34 (d, 1 H, exchange C_6-OH), 5.52, 5.60 (2 × d, 1 H, C_7-H), 7.45 (m, 2 H, aryl), 7.75 (m, 1 H, aryl), 8.26 (m, 1 H, aryl), 11.88, 11.98 (2 × s, 1 H, exchange C_{11}-OH) (as explained in the Discussion the doubling of the signals is due to the existence of the two diastereomeric forms at the C_{13} is ca 1:1 ratio); IR (Nujol) ν_{max} 3300 (b, OH), 1640 (γ-pyrone), 1610, 1580 cm^{-1} (aryl); MS *m/z* (relative intensity) 354.1101 (1.8) [calcd for $C_{20}H_{18}O_6$ 354.1101], 323.0881 (8.3, $M^+ - OCH_3$), 280.0705 (27, $M^+ - CH_3COOCH_3$), 279.0653 (100, 280 – H).

Further elution of the column with ether gave the hydroquinone of DDQ and elution with THF–ether (1:3) gave compound **49**, which was purified by recrystallization from THF to give 170 mg (36% yield): mp 245 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.85 (m, 1 H), 2.30 (m, s, 4 H, OCH_3, H), 2.60–3.0 (m, 3 H), 5.15 (m, 1 H, C_7-$H_{a'}$ after D_2O exchange this signal appears as a quartet with coupling constants $J_{7a',8a'}$ = 9 Hz, $J_{7a',8e'}$ = 5.5 Hz), 6.25 (d, 1 H, exchange, C_7–OH, $J_{7a,70H}$ = 5.5 Hz), 7.50 (t, 1 H, aryl), 7.65 (d, 1 H, aryl), 7.90 (m, 1 H, aryl), 8.20 (dd, 1 H, aryl), 9.45 (s, 1 H, exchange C_6-OH), 12.18 (s, 1 H, exchange, C_{11}-OH); IR (Nujol) ν_{max} 3550, 3220 (b, OH), 1685 ($COCH_3$), 1630 (γ-pyrone), 1600, 1575 cm^{-1} (aryl); MS, *m/z* (relative intensity) 340.0939 (2.4) [calcd for $C_{19}H_{16}O_6$ 340.0940], 322.0828 (35.7, $M^+ - H_2O$), 321.0716 (16.0, $M^+ - (H_2O + H)$), 320.0675 (66.83, $M^+ - (H_2O + 2\ H)$), 279.0649 (100, $M^+ - (H_2O + COCH_3)$), 278.0563 (34.0, 279.0649 – H).

***cis*-9-Acetyl-6,7,11-trihydroxy-12-oxoxantho[2,3-*g*]tetralin 6,7-Acetonide (50).** A solution of **49** (400 mg, 1.17 mmol) in 200 mL of THF was treated with dimethoxypropane (40 mL) and *p*-toluenesulfonic acid (25 mg). The reaction mixture was stirred at room temperature for 5 h, then the solvent removed, and the residual solid was taken up in ethyl acetate. The organic layer was washed with sodium bicarbonate solution and then water and dried (Na_2SO_4). Removal of the solvent in vacuo afforded **50** which was purified by crystallization from 1:1 THF–ether to give 200 mg (47% yield): mp 230 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.68 (d, 6 H, CH_3 + CH_3), 1.80 (m, 1 H, C_8-$H_{a'}$), 2.30 (s, 3 H, $COCH_3$) 2.45 (m, 1 H, C_8-$H_{e'}$), 2.84 (q, 1 H, C_{10}-$H_{a'}$, $J_{10a',10e'}$ = 15 Hz, $J_{10a',9a'}$ = 9.5 Hz), 3.01 (m, 1 H, C_9-$H_{a'}$), 3.13 (q, 1 H, C_{10}-$H_{e'}$, $J_{10a',10e'}$ = 15 Hz, $J_{10e',9a'}$ = 6 Hz), 4.92 (q, 1 H, C_7-$H_{a'}$, $J_{7a',8a'}$ = 11 Hz, $J_{7a',8e'}$ = 5 Hz), 7.40 (m, 1 H, Ar), 7.60 (d, 1 H, Ar), 7.75 (m, 1 H, Ar), 8.30 (dd, 1 H, Ar), 12.38 (s, 1 H, C_{11}-OH, exchange); IR (Nujol) 3500–3300 (b, OH), 1680 ($COCH_3$), 1620 (γ-pyrone), 1600, 1585 (Ar); MS, *m/z* (relative intensity) 380.1259 (0.98) [calcd for $C_{22}H_{20}O_6$ 380.1259], 322.0838 (55, $M^+ - C_3H_6O$), 279.0648 (100, $M^+ - (C_3H_6O + C_2H_3O)$), 278.0567 (40.8, 279 – H), 58.0441 (1.6, C_3H_6O).

Attempted C_9-Hydroxylation of *cis*-9-Acetyl-6,7,11-trihydroxy-12-oxoxantho[2,3-*g*]tetralin 6,7-Acetonide (50). When compound **50** was treated under similar reaction conditions as for **44** (for preparing **45**) and after the usual workup it gave only **46** in 30% yield. The latter was identical in physical and spectral properties with **46** obtained from **44**.

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Registry No. 1 ([2,3-*g*] isomer), 82891-55-2; 1 ([3,2-*g*] isomer), 82891-56-3; 2 ([2,3-*g*] isomer), 90623-58-8; 2 ([3,2-*g*] isomer), 90623-59-9; 3, 90623-60-2; 4, 90623-61-3; 5, 90623-62-4; 6, 90623-63-5; 7, 90623-64-6; 8, 90623-65-7; 9, 90623-66-8; 10, 90623-67-9; 11, 90623-68-0; 12, 90623-69-1; 13, 90623-70-4; 14, 90623-71-5; 15, 90641-21-7; 16, 90623-72-6; 17, 90623-73-7; 18, 90623-74-8; 19, 90623-75-9; 20, 90623-76-0; 21, 90623-77-1; 22, 90623-78-2; 23, 90623-79-3; 24, 90623-80-6; 25, 90623-81-7; 26, 90623-82-8; 27, 90623-83-9; 28, 90623-84-0; 29, 90623-85-1; 30, 90623-86-2; 31, 90641-22-8; 32, 90641-23-9; 33, 90623-87-3; 34, 90623-88-4; 35, 90641-24-0; 36, 90623-89-5; 37, 90623-90-8; 38, 90623-91-9; 39, 90623-92-0; 40, 90623-93-1; 41, 90623-94-2; 42, 90623-95-3; 43, 90623-96-4; 44, 90623-97-5; 45, 87548-95-6; 46, 90623-98-6; 47, 87584-68-7; 48 (isomer 1), 90623-99-7; 48 (isomer 2), 90693-99-5; 49, 90624-00-3; 50, 90624-01-4; *o*-methoxybenzoyl chloride, 21615-34-9; *o*-methoxybenzoic acid, 579-75-9.