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A GENERAL AND REGIOSPECIFIC ROUTE TO TETRACYCLIC ALKENES IN THE 11-DEOXYANTHRACYCLINONE SERIES[1]

APPLICATION TO THE TOTAL SYNTHESIS OF (±)-AURAMYCINONE

JEAN-PIERRE GESSON,* JEAN-CLAUDE JACQUESY and BRIGITTE RENOUX
Laboratoire de Chimie XII, E.R.A. 556 "Synthèse et Réactivité de Produits Naturels", Faculté des Sciences-40, Avenue du Recteur Pineau-86022 Poitiers Cedex (France)

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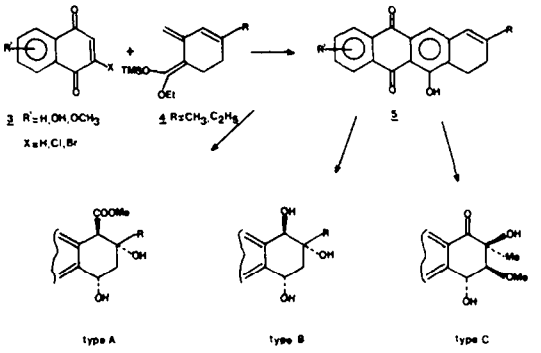
Abstract—Starting from Hagemann's ester the preparation of new ketene acetals **4a** and **4b** and their cycloaddition with juglone derivatives to give 11-deoxytetracyclic alkenes **20** and **21** are described. Furthermore the first total synthesis of (±)-auramycinone (**8**) has been completed from **20** in only nine overall steps from juglone.

The present interest in anthracycline chemistry stems from the discovery of the broad antitumor activity and high clinical efficiency of daunorubicin **1a** and doxorubicin **1b**.[2] However as most cytotoxic agents they are not devoid of side effects and especially show a severe dose-related cardiotoxicity. This may be in part explained by the easy one-electron reduction of these compounds to the corresponding radical anion able to react with oxygen to afford toxic species such as $O_2^{\cdot-}$, $HO^{\cdot}$ or H_2O_2[3]. Modification of the redox potential may thus be of prime importance to get more information about structure activity relationships.

The recent discovery of new biosynthetic anthracyclines such as aclacinomycin A (**2**) in 1975[4] and 11-deoxydaunorubicin (**1c**) in 1980[5] which both show a reduced cardiotoxicity[6] has stimulated the development of new routes toward such 11-deoxy aglycones. Several total synthesis of 11-deoxydaunomycinone,[7] the aglycone of **1c**, and of aklavinone,[8] the aglycone of **2**, have been recently published. This latter compound may then be enzymatically glycosidated in high yield, as shown by Oki.[9]†

We wish now to describe a flexible and regiospecific approach toward aglycones like aklavinone (type A) and also to 11-deoxy analogs of rhodomycinone (type B) or to steffimycinone (type C), thereby extending our recently published synthesis of 11-deoxydaunomycinone and analogs.[11] For this purpose cycloaddition of ketene acetals **4** with naphthoquinones **3** will provide tetracyclic alkenes **5** which may be considered as convergent intermediates whose ring D substitution will be controlled by the starting naphthoquinone while the choice of R (Me, Et . . .) in **4** will provide the required C_9 alkyl substituent (Scheme 1).



Scheme 1.

Such a methodology will provide access to ring D analogs of aklavinone like 2-hydroxyaklavinone (**6**),[12] ε pyrromycinone (**7**)[8i] or to ring A analogs such as auramycinone (**8**) or eventually to more complex aglycones like nogalamycinone (**9**).[13]

Preparation of ketene acetals **4**

These alkyl trimethylsilyl ketene acetals may be *a priori* prepared from the corresponding dienoic esters by initial exocyclic deprotonation followed by

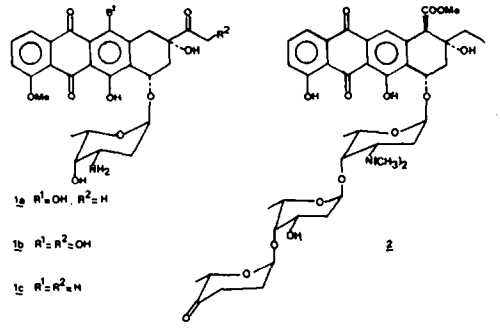


Fig. 1.

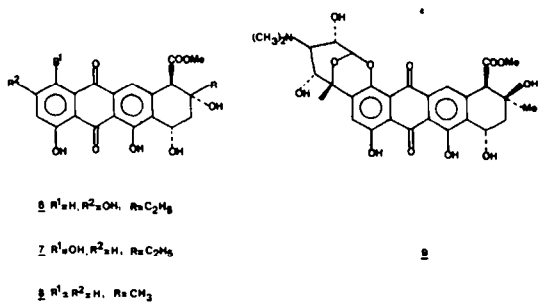
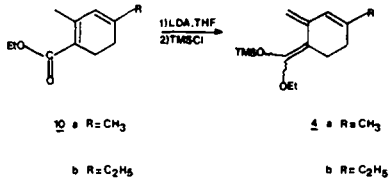


Fig. 2.

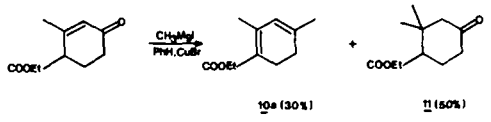
† This process may be applied to a large number of related aglycones and even racemic compounds.[10]

quenching with trimethylchlorosilane (TMSCl)[14] and therefore compounds **10a** and **10b** were chosen as starting material (Scheme 2).



Scheme 2.

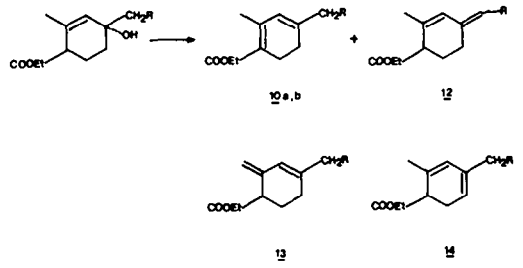
Fortunately **10a** has been previously obtained by Julia[15] in 30% yield together with **11** by adding CH_3MgI, in presence of CuBr, to Hagemann's ester (Scheme 3).



Scheme 3.

Without CuBr only **10a** (50%) is isolated together with starting material arising from the easy enolization of this vinylogous β ketoester. The use of less polar solvents (i.e. benzene) instead of diethylether does not improve the addition/enolization ratio.

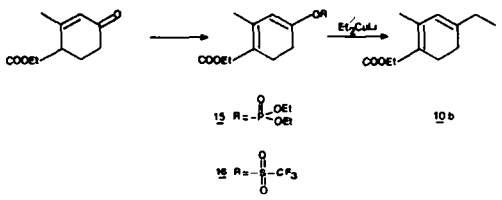
Similar reaction with C_2H_5MgBr affords a mixture of dienes which could not be isomerized in presence of acid, base or organometallics to the desired ester **10b**. This may reflect the relative stabilities of the expected dienes **10a**, **10b**, **12–14** (Scheme 4).



Scheme 4.

When R = H **10a** is the thermodynamically more stable isomer, however when R = CH_3 the $E+Z$ mixture **12** may be present at the equilibrium.† Rhoads *et al.*[16] have shown that the stabilization of a diene by a methyl group ($\Delta\Delta G = -2{,}2$ Kcal/mol) is only moderately lower than that of a carbomethoxy group ($\Delta\Delta G = -2.6$ Kcal/mol (in the case of **10a** and **10b** a *cis* destabilizing interaction ($\Delta\Delta G = 1.3$ Kcal/mol) may also be noted). Dienes **13** and **14**, not observed when R = H, should not be present at equilibrium when R = CH_3 (similar relative stabilities) and furthermore they may be discarded on the basis of Rhoads[16] values.

Nevertheless displacement of enolphosphate **15** (easily prepared from Hagemann's ester) with diethyl copper lithium[17] affords in a moderate yield (30%) the desired pure ester **10b** (Scheme 5) after a rapid silica gel chromatography to separate some dialkylated product.



Scheme 5.

This may be explained by the low reactivity of enolphosphate **15** and hence the use of excess cuprate. As a consequence enoltriflate **16** was prepared in high yield† from Hagemann's ester and then easily displaced by 1.2 eq. of diethyl copper lithium[18] to afford **10b** in 90% after SiO_2 filtration. Similar results were obtained with Me_2CuLi and so the use of more complex cuprates may be considered.

Deprotonation of **10a** and **10b** and quenching of the corresponding enolate with trimethylchlorosilane was then studied (Scheme 2).

Starting from **10b**, **4b** (90%) was isolated after non aqueous work-up. The NMR spectrum fully confirms the expected exocyclic deprotonation on the basis of signals at 4.74 ppm (d, J = 2 Hz, 1H), 5.07 ppm (d, J = 2 Hz, 1H) and 5.67 ppm (s, W_H = 4 Hz, 1H). Similarly from **10a** a 77% yield of a ketene acetal was obtained. One may note in the NMR spectrum the presence of a single vinylic methyl group at 1.70 ppm (s, 3H) and olefinic signals at 4.73 ppm (s, with shoulder, 1H), 5.03 ppm (d, J = 2 Hz, 1H) and 5.67 ppm (s, 1H). The great similarity between these signals and those of **4b** strongly suggests that **4a** is the correct one, although **18** cannot be totally ruled out.

However cycloaddition of this material with naphthoquinones (*vide supra*) will definitely confirm structure **4a**. This selective kinetic deprotonation of the methyl group *cis* to the carbomethoxy group may be explained by the initial coordination of the base cation (Li) with the carbonyl oxygen. This assumption has been recently demonstrated by Weiler using deuterated α,β-unsaturated esters.[20]

In either case (**4a** or **4b**) the NMR spectrum strongly suggests the presence of one single isomer whose stereochemistry (i.e. the respective position of —OTMS and $-OC_2H_5$ groups) cannot be determined, although recent results[19] demonstrate quenching of the *E* dienolate.

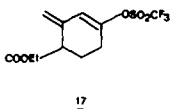


Fig. 3.

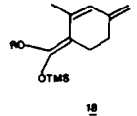


Fig. 4.

† NMR spectra of such mixtures are complex. Attempts to separate components by silica gel chromatography were unsuccessful.

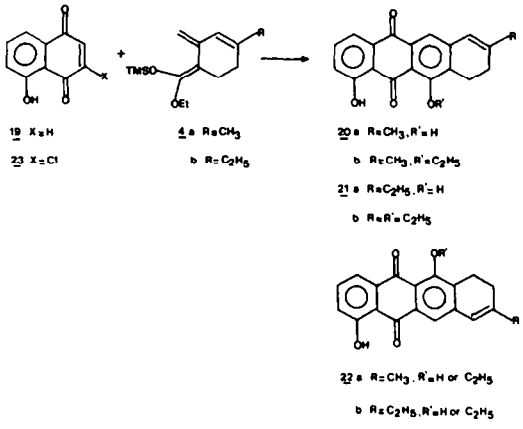
† In presence of triflic anhydride and pyridine at 20°C enoltriflate **17** is kinetically formed and then slowly isomerizes to the more stable **16**.

Cycloaddition with juglone and derivatives

Earlier results from this laboratory[11] as well as others[19] have amply demonstrated that appropriately substituted ketene acetals do rapidly add at room temperature to various naphthoquinones. Recalling the initial objectives, commercially available juglone **19** and derivatives were chosen as quinone partners for **4a** and **4b**.

Condensation of **19** with 1.1 eq. of **4a** (or **4b**) occurs at 0–20° in anhydrous solvents (CH_2Cl_2, THF, Benzene) to give after aqueous work-up a mixture of olefins **20a** and **20b** (or **21a** and **21b**) in a 1:4 ratio as judged by NMR (Scheme 6). Without separation either mixture was treated with excess $AlCl_3$ (10 eq.) in refluxing CH_2Cl_2 to afford in 60% overall yield from juglone **20a** as an orange powder, m.p. 174–176° (or **21a**, orange powder, m.p. 145–147°).

Structures proposed for **20a** and **20b** were fully confirmed by spectroscopic and physical data consistent with those reported by Krohn for **20a** (m.p. lit.[21] = 177°) and for **21a** (m.p. lit.[22] = 147°). It should be emphasized that olefins **22a** and **22b** which would have arisen from less favorable orientation of **19** and **4a** and **4b** were not detected (Scheme 6).



Scheme 6.

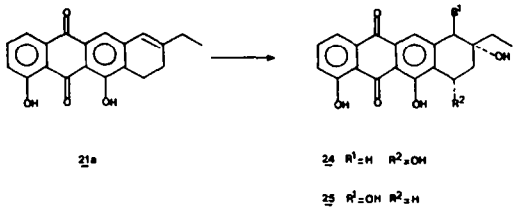
Similarly chloronaphthoquinones rapidly combine with **4a** and **4b** to afford only the corresponding tetracyclic phenol. Thus 3-chloro juglone **23** available in 70% yield from juglone **19** through chlorination-dehydrochlorination[23] and **4a** (1.1 eq.) give only **20a** in 55% yield. Similarly other quinones react with these new ketene acetals and this has been used in an approach toward steffimycinone.[24]

Although the overall condensation of these with quinones may be considered as a classical Diels–Alder reaction we do prefer a Michaël-type condensation of ketene acetals to quinones followed by a rapid cyclisation. The preferred formation of phenol ether **20b** (or **21b**) over phenol **20a** (or **21a**) has been already discussed.[11]

Thus the required alkenes **20a** and **21a** are easily prepared from juglone and Hagemann's ester in only five different operations. This process represents a great improvement over known methods[8e,21,22,25] due to its shortness and versatility.

Synthesis of Auramycinone

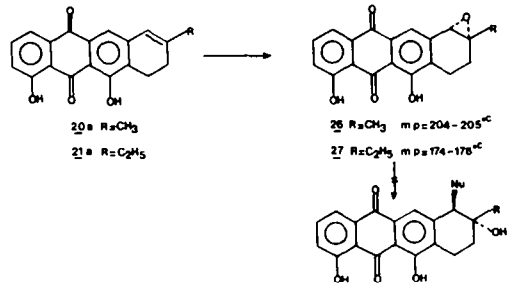
Tetracyclic alkene **20a** has already been used by Krohn[21] in an approach toward aranciamycinone and alkene **21a** by Kende[25] and Krohn[22] to prepare respectively decarbomethoxyaklavinone (**24**) isolated from *Micromonospora peucetica* by Arcamone[26] and β_1 citromycinone (**25**) isolated from a *streptomyces* species (ETH 9386) by Waenheldt[27] (Scheme 7).



Scheme 7.

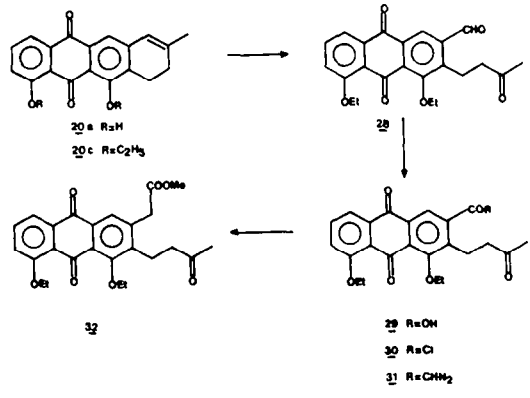
The easy preparation of **20a** and **21a** strongly suggests their use to synthesize more interesting aglycones such as auramycinone (**8**) and aklavinone, aglycone of **2**.

The first investigated route was based on the possible nucleophilic opening of epoxides **26** and **27** prepared in 80% yield from **20a** and **21a** with m-chloroperoxybenzoïc acid (Scheme 8).



Scheme 8.

However numerous attempts using cyanide anion, cyanotrimethylsilane, metal-catalyzed carbonylation, organocuprates, and lithiated anions were unsuccessful due to lack of reactivity or to reduction processes. Similar results have also been quoted by Boeckmann.[8e] These observations led us to use a ring cleavage-homologation-cyclization sequence whose last step has already been used by Krohn[8k], Kishi[8b,f] and Boeckmann[8e] in their aklavinone synthesis (Scheme 9).



Scheme 9.

We now describe the preparation (±) auramycinone **8** from **20a** although aklavinone may be similarly obtained from **21a**. For this purpose phenol groups were first protected by base catalyzed ethylation of the **20a** + **20b** mixture obtained by cycloaddition to afford **20c** in 60% overall yield from juglone. Reductive ozonolysis (O_3, CH_2Cl_2, −78° then KI, H_2O) of **20c**† proceeds cleanly to give ketoaldehyde **28** (90%) as a yellow powder, m.p. 184–186°, characterized in NMR by the presence of deshielded singlets at 8.85 ppm (s, $C_{11}H$) and 10.26 ppm (s, —CHO).

Here again numerous efforts to achieve a carbonyl homologation to prepare keto ester **32** from **28** were disappointing: these include for example cyanohydrin or protected cyanhydrin formation, selective Wittig reaction as described by Mitscher *et al.*[28] for a related aldehyde-ester, or carbonylation of a benzylic bromide derived from the aldehyde function. Finally only Arndt–Eistert homologation (already used by Boeckmann in his aklavinone synthesis[8e]) does proceed in reasonable yield: oxidation of ketoaldehyde **28** with Jones reagent affords ketoacid **29** in 59% yield which is then converted with oxalyl chloride‡ to the corresponding acid chloride **30**. The latter reacts with excess diazomethane to give the intermediate diazoketone **31** rapidly purified by silica gel chromatography§ before treatment in anhydrous methanol with freshly prepared silver oxide.

In this way ketoester **32**, m.p. 126–127°, is obtained in 58% overall yield from acid **29**.

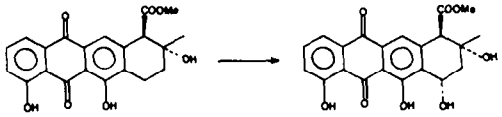
The cyclization step was then first performed with Triton B in MeOH—CH_2Cl_2 as done earlier by Krohn,[21] Boeckmann[8e] and Hauser[8i] to give after 2 hr at −20° a mixture of *cis* hydroxyester **33a** (39%) and *trans* hydroxyester **34a** (43%). Structure and stereochemistry of these esters were proposed on account of their TLC behaviour and spectroscopic data (see experimental section and Scheme 10).

Isomerization of the unwanted isomer **33a** may be carried out at 20° in CH_2Cl_2 in the presence of DBN[29] (48 hr) or Et_3N[8e] (72 hr) to give a 1 : 1 ratio of **33a** to **34a** as judged by HPLC.† This result is similar to the 1.1 : 1 ratio observed in the above cyclization of **32** and is identical to the result obtained by Hauser[8i] in his aklavinone synthesis.

In search of more selective base-catalyzed conditions, we have found that tBuOK (in tBuOH–THF) rapidly leads to a 2 : 1 mixture of **33a** and **34a** at −20° (30 min). However, this ratio is 1 : 1 after 90 min and 1 : 2 after 3 hr. This clearly demonstrates under these conditions a rapid preferential kinetic cyclization to **33a** followed by a slow epimerization to **34a**. This result is also reached after 15 min at room temperature.

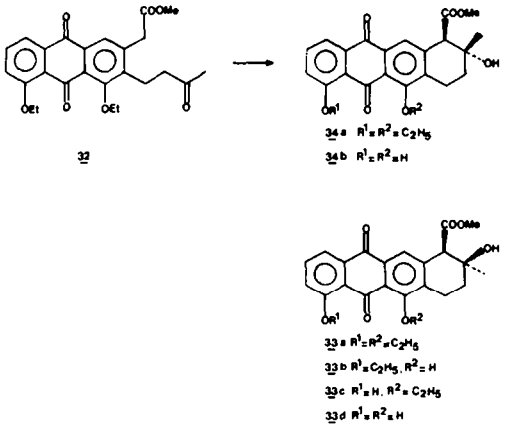
Dealkylation of diether **34a** is done with excess $AlCl_3$ in dichloromethane at 20° to give synthetic (±)-7-deoxyauramycinone (**34b**), m.p. 200–201°, whose spectroscopic properties are in agreement with those reported by Fujiwara.[30]

Finally benzylic hydroxylation at C_7 proceeds in high yield (Br_2—AIBN—CCl_4 then $NaHCO_3$—H_2O) to afford (±)-auramycinone (**8**), m.p. 157° (93%), identical in all respects (TLC, MS, NMR, and UV spectra) with authentic (+)-auramycinone kindly furnished by Prof. Fujiwara (Scheme 11).



Scheme 11.

This regiospecific synthesis of (±) auramycinone is thus completed in only nine steps from juglone and the above methodology appears to provide wide possibilities for the preparation of new anthracyclinones.



Scheme 10.

EXPERIMENTAL

Melting points were determined on a Tottoli Büchi 510 melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Beckman Acculab 2 or 4250 and are reported in wavenumbers (cm^{-1}). Nuclear magnetic resonance (NMR) spectra were recorded on Jeol PMX 60 or FT 60 spectrometers. Chemical shifts are reported in ppm downfield relative to tetramethylsilane (Me_4Si) as standard. Low resolution mass spectra were obtained on a Kratos MS 25 spectrometer. (Relative peak heights are given in brackets for each *m/z*).

High resolution mass spectra were performed by the "Service Central d'Analyse du CNRS de Lyon".

All reactions were run under an inert atmosphere of N_2 and reactions requiring anhydrous conditions were performed in oven-dried apparatus. Solvents and anhydrous reagents were dried according to established procedures by distillation under nitrogen using an appropriate drying agent; benzene, ether, THF, (Na, benzophenone), CH_2Cl_2 (P_2O_5), methanol (Mg), pyridine (KOH), diisopropylamine (CaH_2).

† Similar reaction with **20a** gives a moderate 65% yield of the corresponding ketoaldehyde, m.p. 201–202°.

‡ Similar experiment with $SOCl_2$ affords a mixture of compounds.

§ In our hand this purification appears critical for the success of the subsequent step.

† A small amount of a less polar compound is detected under these equilibration conditions. Its MS and NMR spectra are in agreement with structure **33b** (or **33c**). Stereochemistry is confirmed by quantitative dealkylation to **33d**.

Advancement of reactions and control of purity were performed on silica gel plates (Kieselgel 60 F_{254}, 0.2 mm) or with a Waters HPLC (column Lichrosorb Si 60–5 μm, 250 × 4.6 mm).

Separations and purifications were carried out by column chromatography on SiO_2 (Merck Kieselgel 60 (0.063–0.2 mm)), by medium pressure chromatography on SiO_2 (Merck Kieselgel 60 Type H) with a Jobin–Yvon Chromatospac Prep 10 apparatus or by preparative TLC (Merck, Silica) using plates coated with silica gel (60 F_{254}, 1 mm).

Ethyl 2,4-*dimethyl*-1,3-*cyclo*-*hexadienecarboxylate* (**10a**)

To a soln, under N_2 and at 0°, of Hagemann's ester (18.2 g; 0.1 mol) in anhyd benzene (80 ml) was slowly added a suspension of MeMgI (1.6 eq.) in benzene (120 ml). (This soln was prepared by addition of Me_3I (10 ml; 0.16 mol) in anhyd ether (110 ml) to a suspension of Mg (3.88 g; 0.16 mol) in anhyd ether (10 ml). After removal of ether, the mixture was taken up in anhyd benzene).

The reaction mixture was then kept at 0° during one hour before warming to room temperature, then poured into a soln of saturated NH_4Cl and extracted with ether. The combined extracts were dried over Na_2SO_4 and, after removal of the solvent, the residue was distilled under reduced pressure to afford a mixture of olefins where **10a** was the major product (90%) as judged by NMR. Chromatography over SiO_2 (Eluent: Petroleum ether/ether 95/5; v/v) gave a mixture of olefins (inseparable by chromatography) in 53% yield (9.54 g; 0.053 mol).

Isomerization was performed in benzene (70 ml) with a catalytic amount of paratoluenesulfonic acid at reflux for 2 hr.

After hydrolysis, neutralization and extraction with ether, the residue was rapidly filtered over SiO_2 (Eluent: Petroleum ether/ether; 95/5, v/v) to give pure **10a** (9.03 g; 50%) as a colorless oil. NMR ($CDCl_3$): 1.28 ppm (t, J = 7 Hz, 3H); 1.86 ppm (s, 3H); 2.13 ppm (s, 3H); 4.20 ppm (q, J = 7 Hz, 2H); 5.68 ppm (s, W_H = 4 Hz, 1H).

Ethyl 4-*ethyl*-2-*methyl*-1,3-*cyclohexadienecarboxylate* (**10b**)

Preparation of enolphosphate (**15**). To a suspension of NaH (50% in oil) (4.8 g; 0.1 mol) in anhydrous benzene (100 ml) was slowly added a solution of Hagemann's ester (18.2 g; 0.1 mol) in anhyd benzene (10 ml).

After stirring at room temp for 30 min one equivalent (17.25 g) of diethyl chlorophosphate was added dropwise and stirring was continued for 1 hr.

Hydrolysis and extraction afforded the crude enolphosphate which was filtered on SiO_2 (Eluent: Petroleum ether/ether 90/10, v/v) to yield pure **15** as an oil (28.6 g; 90%). NMR ($CDCl_3$): 1.36 ppm (m, 9H); 2.16 ppm (s, 3H); 4.16 ppm (m, 6H); 5.73 ppm (s, 1H).

Preparation of lithium diethyl cuprate. Under a N_2 atm. a chloroethane (32.5 g; 0.5 mol) soln in anhyd benzene (100 ml) was added with stirring to small chips of Li (6.4 g; 1 mol) in anhyd benzene (300 ml).

After the reaction was complete, LiCl settled at the bottom of the flask and the resulting supernatant solution was titrated by 0.1N H_2SO_4 (Yield: 75%). This EtLi soln was then slowly added to a suspension of CuI (39.30 g; 0.2 mol) in anhydrous ether (about 100 ml), kept at −78° under N_2.

The mixture was then stirred for 30 min at this temp.

Preparation of **10b**. To the above soln of lithium diethyl cuprate (1.6 eq., 0.187 mol) at −78° under N_2, was slowly added the enolphosphate previously prepared (37.2 g; 0.117 mol). The mixture was then stirred overnight and allowed to warm to room temp.

Neutralization with a soln of sat NH_4Cl and extraction as usual afforded the crude product **10b** which was purified by filtration on SiO_2 (Eluent: Petroleum ether/ether 80/20, v/v) to give pure **10b** as a colorless oil (6.8 g; 30%). NMR ($CDCl_3$): 1.10 ppm (t, J = 7 Hz, 3H); 1.30 ppm (t, J = 7 Hz, 3H); 2.15 ppm (s, 3H); 4.15 ppm (q, J = 7 Hz, 2H); 5.60 ppm (s, W_H = 4 Hz, 1H).

Preparation of enoltriflates **16, 17**

To a solution of Hagemann's ester (3 g; 0.0165 mol) in CH_2Cl_2 (10 ml, distilled over P_2O_5) under N_2 was added pyridine (1.1 eq.; 1.5 ml) and trifluoromethanesulfonic anhydride (1.2 eq.; 3.3 ml).

The mixture was stirred overnight at room temp.

After hydrolysis and extraction as usual, a mixture of two isomers **16** and **17** was obtained.

Separation by chromatography on SiO_2 (Eluent: Petroleum ether/ether 90/10 v/v) afforded *endo* isomer **16** (3.22 g; 62%) and *exo* isomer **17** (0.94 g; 18%) in a 3.5 to 1 ratio.

After a reaction time of 1 hr, the **16/17** ratio was about 1/1.

Quick degradation of isomer **17** at room temp was observed.

Compound **16** NMR ($CDCl_3$): 1.28 ppm (t, J = 7 Hz, 3H); 2.15 ppm (s, 3H); 2.6 ppm (m, 4H); 4.16 ppm (q, J = 7 Hz, 2H); 5.86 ppm (s, 1H).

Compound **17**: 1.24 ppm (t, J = 7 Hz, 3H); 2.18 ppm (m, 2H); 2.48 ppm (m, 2H); 4.15 ppm (q, J = 7 Hz, 2H); 5.15 ppm (s, 2H); 6.18 ppm (s, 1H).

Ethyl 2,4-*dimethyl*-1,3-*cyclohexadienecarboxylate* (**10a**) *from enoltriflate* **16**

Preparation of lithium dimethyl cuprate. Under N_2 at 0°, a 1.6 M soln of MeLi in ether (0.00318 mol, 2 ml) was slowly added by means of a syringe to a suspension of CuI (0.00189 mol; 0.357 g) in anhyd ether (6 ml) to afford a clear soln. The mixture was stirred for 30 min at the same temp.

Displacement of enoltriflate **16** *by lithium dimethylcuprate.* The above soln of lithium dimethylcuprate was cooled at −40° and enoltriflate **16** (0.421 g; 0.00134 mol) in soln in ether (2 ml) was added.

Under stirring, the reaction mixture was allowed to warm to room temp.

After hydrolysis and extraction as usual (with ether), the crude product was chromatographed on SiO_2 (Eluent: Petroleum ether/ether 95/5, v/v) to afford **10a** (0.155 g; 64%).

Ethyl 4-*ethyl*-2-*methyl*-1,3-*cyclohexadienecarboxylate* (**10b**) *from enoltriflate* **16**

A soln of **16** (1 g; 0.00318 mol) in anhyd ether (8 ml) was added at −78° under N_2 to a soln of lithium diethylcuprate (1.60 eq.).

The mixture was stirred overnight while slowly warming to room temp. After hydrolysis and extraction as usual, the crude product was rapidly filtered on SiO_2 (Eluent: Petroleum ether/ether 90/10, v/v) to afford pure **10b** as a colorless oil (0.5016 g; 81%).

1-*Methyl* 3-*methylene*-4-(*ethoxytrimethylsilyloxymethylene*)-1-*cyclohexene* (**4a**)

To a soln of lithium diisopropylamide previously prepared at 0° from diisopropylamine (2.5 ml; 17.7 mmol) and n-BuLi (11.45 ml of a 1.55 M soln in hexane) in anhyd THF (8.3 ml), were successively added at −78° under N_2 a soln of **10a** (3 g; 16.66 mmol) in anhyd THF (1 ml) and chlorotrimethylsilane (4.4 ml; 45 mmol).

The mixture was then stirred, progressively warming to room temp overnight.

After removal of solvent, the residue was taken up in hexane (about 20 ml), and centrifuged. Evaporation of hexane afforded acetal **4a** (3.25 g, 77%) as a slightly yellow oil which was used in the next step without purification. NMR (CCl_4): 0.17 ppm (s, 9H); 1.23 ppm (t, J = 7 Hz, 3H); 1.7 ppm (s, 3H); 3.77 ppm (q, J = 7 Hz, 2H); 4.73 ppm (s, with shoulder, 1H); 5.03 ppm (d, J = 2 Hz, 1H); 5.67 ppm (s, 1H).

1-*Ethyl*-3-*methylene*-4-(*ethoxytrimethylsilyloxymethylene*)-1-*cyclohexene* (**4b**)

Under the same conditions, **10b** (350 mg; 1.8 mmol) afforded acetal **4b** (430 mg; 90%) as a yellow oil used without purification in the next reaction. NMR (CCl_4): 0.17 ppm (s, 9H); 3.77 ppm (q, J = 7 Hz, 2H); 4.74 ppm (d, J = 2 Hz, 1H); 5.07 ppm (d, J = 2 Hz, 1H); 5.67 ppm (s, W_H = 4 Hz, 1H).

2-Ethyl 5,7-dihydroxy-3,4-dihydro-6,11-naphthacenedione (**21a**)

At 0° and under N_2 a soln of **4b** (500 mg, 1.8 mmol) in THF (5 ml) was added to a soln of juglone (290 mg, 1.7 mmol) in THF (about 50 ml). The mixture was stirred overnight at room temp.

After acidic hydrolysis (0.1 N HCl) and extraction with CH_2Cl_2, the resulting mixture was readily purified on SiO_2 (Eluent: CH_2Cl_2) to give a mixture of **21a** and **21b** (0.384 g); this mixture was taken up in CH_2Cl_2 (~150 ml) and heated at reflux for 12 hr with 10 eq. of $AlCl_3$ (1.6 g).

After hydrolysis, extraction and purification on SiO_2 (Eluent: CH_2Cl_2), pure **21a** was obtained as an orange powder (326 mg, 60%). F = 145–147°, F = 147°.[22] NMR ($CDCl_3$): 6.20 ppm (s, 1H); 7.10–7.7 ppm (m, 4H); 12.07 ppm (s, 1H); 12.2 ppm (s, 1H). IR (CH_2Cl_2): 3420, 1670, 1640, 1620, 1590 cm^{-1}. MS: *m/z* = 320 (69); 318 (11); 303 (34); 291 (100).

5,7-Dihydroxy-2-methyl-3,4-dihydro-6,11-naphthacenedione (**20a**) *from juglone* (**19**)

Under the same conditions reaction of acetal **4a** (2.12 g; 8.4 mmol) with juglone (1.22 g; 7 mmol) afforded after dealkylation and purification **20a** as an orange powder (1.28 g; 60%). F = 174–176°, F = 177°.[21] NMR ($CDCl_3$): 2.00 ppm (s, 1H); 2.40 ppm (t, J = 7 Hz, 2H); 2.86 ppm (t, J = 7 Hz, 2H); 6.30 ppm (s, 1H); 7.25–7.74 ppm (m, 4H); 11.9 ppm (s, 1H), 12.01 ppm (s, 1H). IR (CH_2Cl_2): 3420, 1680, 1640, 1620, 1590 cm^{-1} (s, 1H). MS: *m/z* = 306 (100), 304 (70), 291 (94), 288 (31), 202 (29), 189 (38.4), 153 (36), 121 (17).

5,7-Dihydroxy-2-methyl-3,4-dihydro-6,11-naphthacenedione (**20a**) *from 3-chlorojuglone* (**23**)

Condensation of ketene acetal (0.95 g, 0.0038 mol) **4a** with **23** (1.2 eq.; 0.66 g) was carried out under identical conditions as for juglone.

After hydrolysis, extraction and rapid filtration over SiO_2, olefin **20a** was obtained, m.p. 174–176° (0.56 g; 58%).

(±) *1,2-Epoxy-2-ethyl-5,7-dihydroxy-1,2,3,4-tetrahydro-6,11-naphthacenedione* (**27**)

At 0°, a soln of metachloroperoxybenzoïc acid (0.344 g; 2 mmol) in CH_2Cl_2 (5 ml) was added to a soln of **21a** (0.32 g; 1 mmol). The mixture was stirred at room temp for 12 hr. After hydrolysis with a sat Na_2SO_3 aq and extraction with CH_2Cl_2, the crude product was chromatographed on SiO_2 (Eluent: CH_2Cl_2) to yield **27** as a yellow powder (0.268 g; 80%). F = 174–176°, F = 173–175°.[25] NMR ($CDCl_3$): 3.4 ppm (s, 1H); 7.1–7.7 ppm (m, 4H); 12.07 ppm (s, 1H); 12.2 ppm (s, 1H). IR (CH_2Cl_2): 3430, 3020, 1680, 1620, 1390, 1280 cm^{-1}. MS: *m/z* = 336 (40), 308 (100), 307 (64), 293 (17), 291 (28).

(±) *1,2-Epoxy-5,7-dihydroxy-2-methyl-1,2,3,4-tetrahydro-6,11-naphthacenedione* (**26**)

Under the same reaction conditions and starting from **20a** (0.5 g; 1.6 mmol) and after chromatography on SiO_2 (Eluent: CH_2Cl_2) epoxide **26** was obtained in an 80% yield (0.42 g). F = 204–205°, F = 205°.[21] NMR ($CDCl_3$): 1.58 ppm (s, 3H); 3.7 ppm (s, 1H); 7.12–7.7 ppm (m, 4H); 12.01 ppm (s, 1H); 12.33 ppm (s, 1H). IR (CH_2Cl_2): 3450, 3030, 1680, 1620, 1380, 1280, 1150 cm^{-1}. MS: *m/z* = 322 (55), 307 (22), 294 (100), 279 (48), 254 (35), 205 (32), 176 (27).

5,7-Diethoxy-2-methyl-3,4-dihydro-6,11-naphthacenedione **20c**

To a soln of a mixture **20a** and **20b** (prepared as above from acetal **4a** (2.12 g; 8.4 mmol) and juglone (1.22 g; 7 mmol)) in acetone (~400 ml) was added diethylsulfate (1.617 g; 10.5 mmol) and K_2CO_3 (2.9 g; 21 mmol). The mixture was heated at reflux for 12 hr.

After hydrolysis and extraction as usual the residue was chromatographed on SiO_2 (Eluent: CH_2Cl_2). Compound **20c** was isolated as a yellow powder (1.52 g; 60% overall from juglone). F = 152–153°. NMR ($CDCl_3$): 1.5–1.53 ppm (t, J = 7 Hz, 6H); 1.95 ppm (s, 3H); 2.28 ppm (m, 2H); 2.98 ppm (m, 2H), 4.15 ppm (q, J = 7 Hz, 4H), 6.30 ppm (s, 1H); 7.16–7.73 ppm (m, 4H). IR (CH_2Cl_2): 3020, 2990, 2900, 1675, 1640, 1580, 1440, 1310, 1110 cm^{-1}. MS: *m/z* = 362 (3), 347 (4), 333 (100), 305 (11). High resolution MS: Found: 362.1515. Calc for $C_{23}H_{22}O_4$: 362.1518.

2-(3-Oxo-butyl)-1,8-diethoxy-3-formyl-9,10-anthracenedione (**28**)

A stream of O_3 (Labo 66 apparatus, 50 W power, stream: 60 L of air per hr) was maintained during 30 min in a soln of **20c** (500 mg; 1.4 mmol) in CH_2Cl_2 (~40 ml) cooled to −78°. The reaction was stopped when TLC indicated consumption of starting material (~30 min). After successive washings with a 1% soln of KI, sat $Na_2S_2O_3$ aq, water and drying over Na_2SO_4, the residue was chromatographed on SiO_2 (Eluent: CH_2Cl_2) to give keto-aldehyde **28** (500 mg; 90%). F = 184–186°. NMR ($CDCl_3$): 1.5 ppm (t, J = 7 Hz, 6H); 2.15 ppm (s, 3H); 2.76 ppm (m, 2H); 3.33 ppm (m, 2H); 4.15 ppm (q, J = 7 Hz, 4H); 7.2–7.8 ppm (m, 3H); 8.35 ppm (s, 1H); 10.26 ppm (s, 1H). IR (CH_2Cl_2): 3000, 2940, 1710, 1700, 1680, 1585, 1440, 1250 cm^{-1}. MS: *m/z* = 394 (12), 365 (100), 351 (7), 347 (18), 337 (11), 323 (10), 305 (11), 295 (13). High resolution MS: Found: C, 70.09; H, 5.53. Calc for $C_{23}H_{22}O_6$: C, 70.04; H, 5.62).

2-(3-Oxo-butyl)3-carboxy-5,7-diethoxy-9,10-anthracenedione (**29**)

To a soln of **28** (3 g; 7.6 mmol) in acetone (~600 ml) under N_2, was added Jones reagent (2 eq., 6 ml). The mixture was stirred overnight at room temp. After hydrolysis and extraction as usual acid **29** was isolated together with some unreacted **28**. Chromatography on SiO_2 gave **29** (1.8 g; 58%). F = 165–170° (dec). NMR ($CDCl_3$): 1.53 ppm (t, J = 7 Hz, 6H); 2.2 ppm (s, 3H); 2.9 ppm (m, 2H); 3.25 ppm (m, 2H); 4.16 ppm (q, J = 7 Hz, 4H); 7.2–7.76 ppm (m, 3H); 8.46 ppm (s, 1H); 10.25 ppm (s, 1H). IR (CH_2Cl_2): 3200–2600 (broad band), 1730, 1710, 1680, 1585, 1430, 1260–1220 (broad band), 1060 cm^{-1}. MS: *m/z* = 410 (4), 409 (24), 392 (5), 381 (26), 364 (29), 363 (100), 361 (19), 337 (15), 321 (75), 293 (16). High resolution MS: (Found: C, 67.32; H, 5.25. Calc for $C_{23}H_{22}O_7$: C, 67.31; H, 5.40).

Methyl (2-(3-oxo-butyl)-1,8-diethoxy-9,10-anthracenedione-3-yl)Acetate (**32**)

Under N_2, acid **29** (0.266 g; 0.65 mmol) was dissolved in anhyd benzene (25 ml) in presence of a catalytic amount of pyridine (0.08 ml). Oxalyl chloride (0.2 ml, 1.9 mmol) was added and the resulting mixture was stirred at room temp for 3 hr.

Reaction was followed by TLC and showed the formation of a slightly less polar product.

After removal of solvent, the residue was taken up in anhyd THF (20 ml) and added at 0° under N_2 to a soln of diazomethane (10 eq., 59 ml of a 0.11 N soln in ether). The resulting mixture was stirred at 0° for 1 hr and then at room temp for 1 hr. After evaporation of THF and excess diazomethane, the residue was chromatographed on Florisil (Eluent: CH_2Cl_2, hexane, Et_2O 2/1/1) to separate diazoketone **31** (197 mg, 70%) from some ester (57 mg, 20%) arising from esterification of unreacted starting acid **10**.

Diazoketone **31** was dissolved in anhyd MeOH (20 ml, distilled on Mg, I_2) in the presence of freshly prepared Ag_2O (0.1 eq., 10 mg). This mixture was heated at reflux for 1 hr and then filtered to remove Ag-salts.

Purification on SiO_2 (Eluent: CH_2Cl_2, hexane, Et_2O 2/1/1) afforded the desired ketoester **32** (164 mg; 58% from **29**). F = 126–127°. NMR ($CDCl_3$): 1.48 ppm (t, J = 7 Hz, 3H); 1.51 ppm (t, J = 7 Hz, 3H); 2.13 ppm (s, 1H); 2.9 ppm (m, 4H); 3.71 ppm (s, 3H); 3.85 ppm (s, 2H); 4.15 ppm (q, 4H); 7.2–7.81 ppm (m, 4H). IR (CH_2Cl_2): 3060, 3000, 1735, 1715, 1675, 1585, 1440, 1265 (broad band), 1170 cm^{-1}. MS: *m/z* = 438 (5), 422 (8), 410

(35), 409 (100), 391 (16), 376 (12), 307 (10), 279 (18). High resolution MS: Found: 438.1680. Calc for $C_{25}H_{26}O_7$: 438.16784.

(±)-1α-Carbomethoxy-5,7-diethoxy-2α-hydroxy-2β-methyl-1,2,3,4-tetrahydro-6,11-naphthacenedione (**33a**) *and (±)-1β-carbomethoxy-5,7-diethoxy-2α-hydroxy-2β-methyl-1,2,3,4-tetrahydro-6,11-naphthacenedione or (±)-7-deoxy-5,7-di-O-ethyl auramycinone* (**34a**)

To a soln of **32** (0.026 g; 0.059 mmol) in MeOH–CH_2Cl_2 (2:1) (2.6 ml) kept at −20° under N_2, was added Triton B (0.2 ml of a 40% soln in MeOH).

The mixture was stirred at −20° for 2 hr. At this point HPLC analysis (Eluent: CH_2Cl_2, EtOAc 80/20, v/v) showed total disappearance of starting material (retention time: 6.11 min) and formation of two compounds in a 54/45 ratio (**34a**: 9.7 min; **33a**: 8.79 min). After hydrolysis, neutralization by 2N HCl (4.3 ml) and extraction, the two products (R_f: 0.5 and 0.4; CH_2Cl_2, hexane, Et_2O 2/1/1) were separated by preparative TLC, in the same solvent system: **33a** (R_f: 0.5) with a yield of 39% and **34a** (R_f = 0.4) with a yield of 43%.

Ester **33a** m.p.: 164–166°. NMR ($CDCl_3$): 1.33 ppm (s, 3H); 1.51 ppm (t, 6H); 3.85 ppm (s, 3H); 4.13 ppm (q, 4H); 7.15–7.7 ppm (m, 4H). IR (CH_2Cl_2): 1725, 1675, 1585 cm^{-1}. MS: *m/z* = 438 (0.8), 421 (4), 410 (26), 409 (100), 391 (17), 378 (6), 361 (16), 333 (11), 305 (9), 279 (13). High resolution MS: Found: 438.16663. Calc for $C_{25}H_{26}O_7$: 438.16784.

Ester **34a** No m.p. could be reported due to decomposition. NMR ($CDCl_3$): 1.38 ppm (s, 3H); 1.5 ppm (t, 6H); 3.71 ppm (s, 3H); 4.12 ppm (q, 4H); 7.1–7.7 ppm (m, 4H). IR (CH_2Cl_2): 1735, 1675, 1585 cm^{-1}. MS: *m/z* = 438 (1), 421 (3), 410 (26), 409 (100), 391 (20), 362 (11), 333 (8), 306 (10), 297 (11). High resolution MS: Found: 438.16704. Calc for $C_{25}H_{26}O_7$: 438.16784.

Cyclization of **32** *with potassium t.butoxide*

Ketoester **32** (5 mg; 0.011 mmol) was dissolved in a mixture of tertiobutanol-THF (1/1; 2 ml) under N_2. At room temp was added 1.8 eq. of potassium tertiobutylate (1.9 mg). The reaction was followed by HPLC (Eluent: CH_2Cl_2, EtOAc 80/20). After a 15 min reaction time, the **34a/33a** ratio was about 65:35.

Equilibration of ketoester **33a**

Method A (Et_3N). Under N_2, a soln of **33a** (10 mg; 0.02 mmol) in anhyd CH_2Cl_2 (3 ml) was treated by anhyd Et_3N (0.3 ml). The mixture was stirred at room temp and followed by HPLC (Lichrosorb Si 60 5 μm; Eluent CH_2Cl_2, EtOAc 80/20). After a reaction time of 72 hr, the **34a/33a** ratio was 1:1 and did not change anymore. After neutralization and extraction, a mixture of **34a** and **33a** was obtained in a ratio of about 1:1.

Method B (DBN). In a similar way, **33a** (10 mg; 0.02 mmol) was treated with DBN (0.1 ml) in CH_2Cl_2 (3 ml) and the reaction was followed by HPLC. After 48 hr, the same equilibrium was reached and no further evolution was noted. Isomers **34a** and **33a** were isolated in a ratio of 1:1.

(±)-1β-Carbomethoxy-2β-methyl-2α,5,7-trihydroxy-1,2,3,4-tetrahydro-6,11-naphthacene-dione or (±)-7-deoxyauramycinone (**34b**)

Hydroxyester **34a** (0.017 g, 0.038 mmol) was dissolved in anhyd CH_2Cl_2 (3 ml) and added to a suspension of excess $AlCl_3$ (22 eq.; 0.104 g) in CH_2Cl_2 (3 ml).

The reaction mixture was stirred at room temperature under nitrogen for 40 hr. After hydrolysis, extraction as usual and filtration on SiO_2 (Eluent: CH_2Cl_2, Hexane, Et_2O 2/1/1), **34b** was obtained in 93% yield (0.0135 g). F = 200–201°, F = 200°.[30] NMR ($CDCl_3$): 1.46 ppm (s, 3H); 3.71 ppm (s, 3H); 3.86 ppm (s, 1H); 7.3–7.7 ppm (m, 4H); 11.95 ppm (s, 1H); 12.38 ppm (s, 1H). IR (KBr): 3080, 1735, 1680, 1620, 1585, 1290, 1260, 1160 cm^{-1}. MS: *m/z* = 382 (35), 364 (35), 349 (6), 340 (8), 332 (17), 307 (48), 306 (27), 305 (100), 304 (37), 391 (7), 279 (44). High resolution MS: Found: 382.1043. Calc for $C_{21}H_{18}O_7$: 382.10525.

(±)-1β-Carbomethoxy-2β-methyl-2α,4α,5,7-tetrahydroxy-1,2,3,4-tetrahydro-6,11-naphthacenedione or (±)-auramycinone (**8**)

To a soln of **34b** (0.0087 g; 0.0227 mmol) in CCl_4 (38 ml) containing a catalytic amount of AIBN (αα′ azo *bis* isobutyronitrile; one crystal) was slowly added (~1 hr) a soln of bromine (0.045 mmol) in CCl_4 (38 ml). The reaction was followed by TLC (Eluent: CH_2Cl_2/hexane, Et_2O 2/1/1).

When all starting material had disappeared (~1 hr) and after evaporation of solvent, the residue was taken up in a mixture of THF–H_2O (1/1, 3 ml), stirred for 1 hr, then diluted with CH_2Cl_2 (7.6 ml) and poured into a sat $NaHCO_3$ aq (3 ml). Extraction as usual gave a mixture of two products which were separated by preparative TLC (Eluent: CH_2Cl_2/hexane, Et_2O 2/1/1). (±)-**8** (8 mg, 93%) was so obtained as a yellow powder.

A small amount (0.6 mg, 6%) of other compound (7-epi auramycinone ?) was also isolated.

Compound **8** F = 157°. NMR ($CDCl_3$): 1.41 ppm (s, 3H); 3.70 ppm (s, 3H); 4.03 ppm (s, 1H); 5.25 ppm (m, 1H); 7.18–7.73 ppm (m, 4H); 11.85 ppm (s, 1H); 12.60 ppm (s, 1H). IR (KBr): 3250, 2920, 1735, 1680, 1620, 1580, 1480, 1460, 1390, 1290, 1260, 1170, 1125, 760 cm^{-1}. MS: *m/z* = 398 (7), 380 (38), 362 (100), 347 (26), 332 (62), 321 (24), 305 (37), 302 (24), 278 (58). UV (MeOH): λ = 225 nm (log ε = 4.53); 255 nm (log ε = 4.29); 286 nm (log ε = 3.95); 432 nm (log ε = 3.98). (Found: C, 63.22; H, 4.43. Calc for $C_{21}H_{18}O_8$: C, 63.31; H, 4.55).

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