The synthesis of kermesic acid and isokermesic acid derivatives and of related dihydroxyanthraquinones

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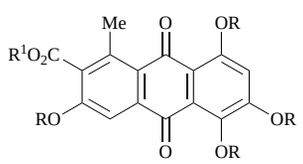
Cochinellic anhydride methyl, ethyl and benzyl esters (4-methoxy-4-ethoxy- and 4-benzyloxy-carbonyl-5-hydroxy-3-methylphthalic anhydrides) have been prepared by a single stage Diels–Alder reaction of 2-bromomaleic anhydride with 3-alkoxycarbonyl-2,4-bis(trimethylsilyloxy)penta-1,3-dienes. The corresponding 5-methyl ether ethyl ester has been obtained by a similar addition reaction but with 3-ethoxycarbonyl-2-methoxy-4-trimethylsilyloxypenta-1,3-diene. The synthesis of methyl 6-deoxykermesate by the acylation of 1,4-dimethoxybenzene in the presence of boron trifluoride–diethyl ether with cochinellic anhydride methyl ester is unsuccessful. The preferred route is by the Diels–Alder addition of 3-alkoxycarbonyl-2,4-bis(trimethylsilyloxy)penta-1,3-dienes to naphthazarin (or 2-chloronaphthazarin). Lead tetraacetate oxidation of methyl 6-deoxykermesate affords a bis(quinone), Thiele acetoxylation of which gives after hydrolysis and permethylation, a mixture of derivatives of kermesic and isokermesic acids in equal proportions. The Diels–Alder addition of 3-chlorojuglone and 3-alkoxycarbonyl-2,4-bis(trimethylsilyloxy)penta-1,3-dienes has led to an improved synthesis of aloesaponarin-I (3,8-dihydroxy-2-methoxycarbonyl-1-methylanthra-9,10-quinone), while juglone itself affords an isomer which may be the 3,5-dihydroxy compound.

Introduction

Kermesic acid **1a** the colouring matter of kermes, obtained from *Kermococcus illicis*, is a dyestuff of antiquity[1] and is mentioned[2] as probably the earliest dye on which records exist. Through early studies[3] and later refinements[4,5,6] the structure **1a** was fully established during which time cochinellic acid



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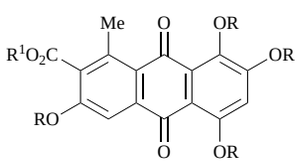

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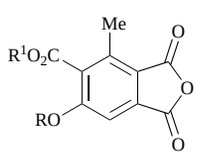
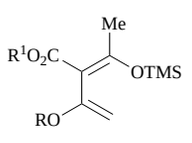
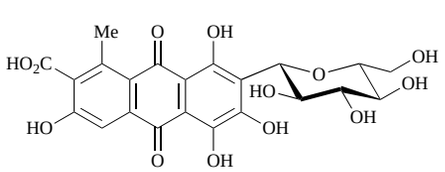
1, 2a R = R^1 = H
b R = R^1 = Me
c R = OAc, R^1 = Me



3 a R = R^1 = Me
b R = Me, R^1 = Et
c R = TMS, R^1 = Me
d R = H, R^1 = Me
e R = H, R^1 = Et
f R = H, R^1 = Bn
g R = Me, R^1 = H



5 a R = TMS, R^1 = Me
b R = TMS, R^1 = Et
c R = TMS, R^1 = Bn
d R = R^1 = Me



4

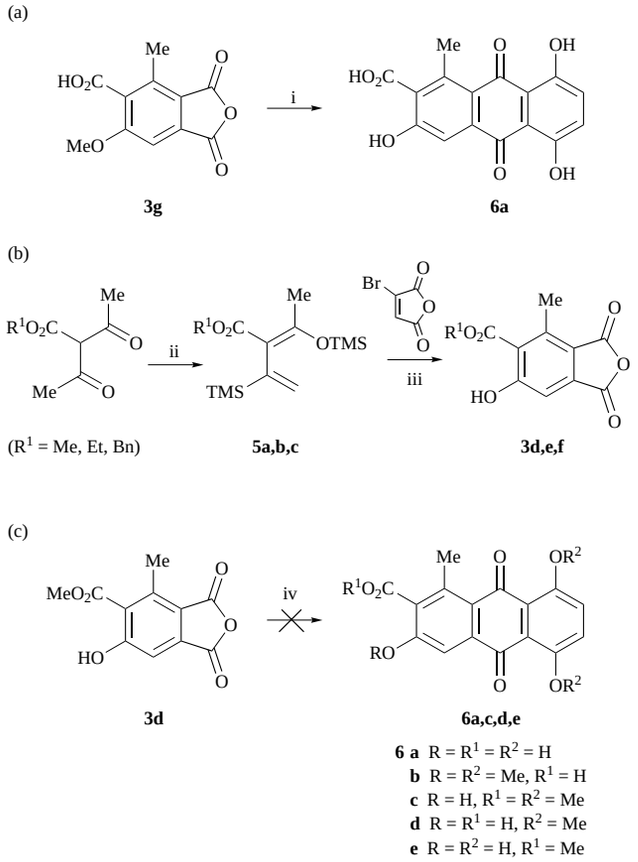
TMS = $SiMe_4$

methyl ester methyl ether (the phthalic anhydride corresponding to **3a**) emerged as an important oxidation product of methyl tetramethylkermesate and also a key substance in the structural work on carminic acid **4**. Two different lengthy syntheses[5,6] to confirm the structural studies were devised for cochinellic acid methyl ether (the phthalic acid corresponding to **3g**). Later, in synthetic work[2] directed towards kermesic acid itself, the anhydride **3g** was condensed with 2-methoxyhydroquinone and the product was briefly reported, with no details, to be isokermesic acid **2a**, an unnatural compound. Reference was made to the fact that, 'the synthesis of kermesic acid was in progress'. In an eventual review[7] this first synthesis was outlined as commencing with the acylation of 1,4-dimethoxybenzene with cochinellic anhydride methyl ether **3g** in an aluminium chloride–sodium chloride melt and was stated to give 2-carboxy-3,5,8-trihydroxy-1-methylanthra-9,10-quinone **6a** [Scheme 1(a)]. Methylation with diazomethane then afforded the 3-methoxy-2-methoxycarbonyl compound which gave, with lead tetraacetate, 3-methoxy-2-methoxycarbonyl-1-methylanthra-5,8,9,10-diquinone and thence by Thiele reaction a major proportion, after permethylation, of the tetramethyl ether methyl ester of kermesic acid **1b** and a minor proportion of **2b**. Experimental details have never appeared in the literature.

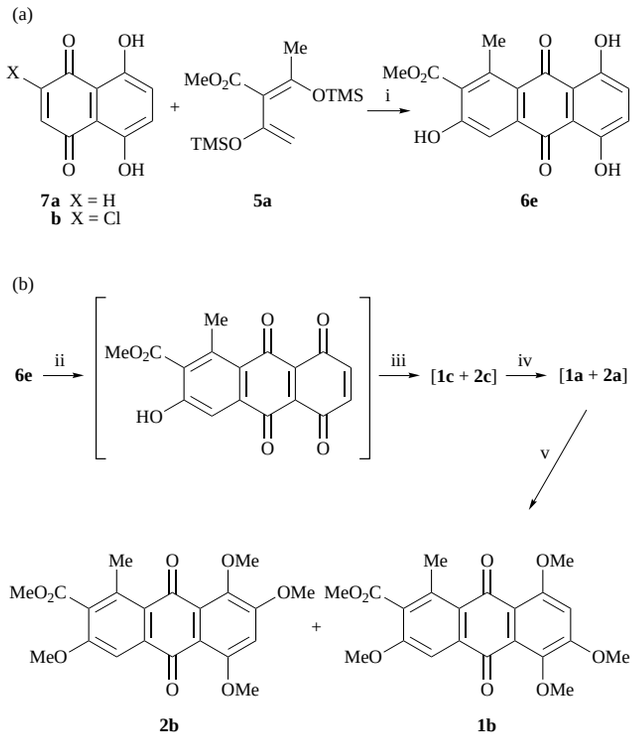
Subsequently, two independent regiospecific syntheses of kermesic acid **1a** were described[8,9] and in one[9] the earlier work[7] was dismissed for its lack of specificity.

We became interested in the availability of both kermesic and isokermesic acids for *C*-glycosylation studies in work generally directed towards the synthesis[10] of carminic acid **4**. In this proposed route by the *C*-glycosylation of 6-deoxykermesic acid **6a** the formation of 6- and/or 7-substituted compounds appeared possible. The final step of Thiele acetoxylation was then expected to result in a 7-*C*-glycosyl derivative of kermesic acid or a 6-*C*-glycosyl isomer in the isokermesic series.

In our first approach to 6-deoxykermesic acid, cochinellic anhydride methyl, ethyl and benzyl esters (**3d–f**) were synthesised by the Diels–Alder addition of the 3-alkoxycarbonyl-2,4-bis(trimethylsilyloxy)penta-1,3-dienes (**5a–c**) to 2-bromomaleic anhydride [Scheme 1(b)] rather than by the previous lengthy routes.[5,6] The bis(trimethylsilyl) esters (**5a–c**) were in turn derived by the silylation of the corresponding alkyl diacetylacetates.[10] Throughout our work we found it more suitable to always use the 2,4-bis(trimethylsilyloxy) dienes (**5a–c**)



Scheme 1 *Reagents and conditions*: i, $AlCl_3$–NaCl, 1,4-$(OMe)_2C_6H_4$; ii, TMSCl, Et_3N; iii, heat, MePh; iv, 1,4-$(OMe)_2C_6H_4$, boron trifluoride–diethyl ether



Scheme 2 *Reagents and conditions*: i, heat, MePh; H_2O–THF; air; ii, Ac_2O, $Pb(OAc)_4$; iii, H_2SO_4; iv, K_2CO_3, H_2O–EtOH; iv, Me_2CO, Me_2SO_4, K_2CO_3

rather than the 2-methoxy-4-trimethylsilyloxy compound[8] **5d** on account of the troublesome separation required by fractional distillation of the *C*- and *O*-methyl compounds both of which are formed in the methylation of alkyl diacetylacetates prior to the final mono-trimethylsilylation.

However in an attempted acylation procedure of 1,4-dimethoxybenzene [Scheme 1(c)] in the presence of boron trifluoride–diethyl ether with the phenolic compound, 4-methoxycarbonyl-5-hydroxy-3-methylphthalic anhydride **3d**, in place of the methyl ether **3g**, we were not able to obtain either 2-carboxy-5,8-dimethoxy-3-hydroxy-1-methylanthra-9,10-quinone **6d**, 5,8-dimethoxy-3-hydroxy-2-methoxycarbonyl-1-methylanthra-9,10-quinone **6c**, the 3,5,8-trihydroxy analogue **6e**, or the corresponding free acid **6a**. The Friedel–Crafts reaction with boron trifluoride–diethyl ether rather than with aluminium chloride–sodium chloride was used since this had been employed[2] in the reaction of cochinellic anhydride methyl ether with 2-methoxyhydroquinone. Although this compound is more activated towards acylation than 1,4-dimethoxybenzene, our negative result with **3d** is attributed to its extensive competing self-polymerisation. There is little doubt that the original work[7] produced 6-deoxykermesic acid in low yield since the melting point given of the derivative 2-methoxycarbonyl-1-methyl-3,5,8-trimethoxyanthra-9,10-quinone agreed with our own for this compound synthesised[10] from **5a** and 2-chloronaphthazarin followed by methylation of the product.

For obtaining the kermesates we therefore turned to the use of alkyl 6-deoxykermesates obtainable[10] from 2-chloronaphthazarin **7b** by Diels–Alder addition of (**5a**–**c**) and in this way obtained 2-methoxycarbonyl-1-methyl-3,5,8-trihydroxyanthra-9,10-quinone and the ethyl and benzyl esters respectively. We found that in the Diels–Alder reaction, commercially-available naphthazarin **7a**, which is the precursor of synthetic 2-chloronaphthazarin, can also be employed as shown in [Scheme 2(a)].

6-Deoxykermesic acid **6a** was obtained from the benzyl 6-deoxykermesate[10] by hydrogenolysis during which time the 9,10-dihydroxy compound (the leuco form) was formed. Aerial oxidation readily gave the required final product.

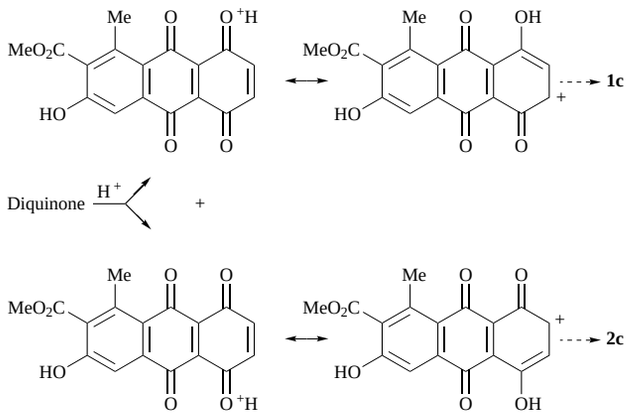
Prior to Thiele reactions with methyl 6-deoxykermesate **6e** we prepared the model compound anthra-1,4,9,10-diquinone from quinizarin (1,4-dihydroxyanthra-9,10-quinone) in much improved yield compared with the original[11] and more recent procedures.[12,13] Thiele reaction both of the isolated diquinone and of quinizarin afforded 1,2,4-triacetoxyanthra-9,10-quinone (purpurin triacetate) in high yield.

By reaction of methyl 6-deoxykermesate **6e** in acetic anhydride with lead tetraacetate under similar conditions to those for the model compound, 3-hydroxy-2-methoxycarbonyl-1-methylanthra-5,8,9,10-diquinone was formed [Scheme 2(b)] and after addition of sulfuric acid, the crude acetate products (**1c** and **2c**) were hydrolysed with aqueous potassium carbonate under inert conditions to give the potassium salts (of **1a** and **2a**). The dried mixture was permethylated and found from preparative TLC separation to consist of a mixture of methyl kermesate **1b** and isokermesate **2b** in equal proportions. The former was identical with a sample prepared previously[8] and kindly made available by Professor Brassard.

The Thiele reaction in the present work resulted in an equal mixture of kermesic and isokermesic acid derivatives whereas the original reference[7] instanced that the former predominated. On mechanistic grounds it seems most likely that the methoxycarbonyl and hydroxy groups would exert a negligible electronic influence on the intermediate diquinone and that the 5- and 8-quinone carbonyl groups would be equally available for protonation leading in turn to 7- and 6-carbocations as transient intermediates (Scheme 3).

The other of our products, methyl isokermesate tetra-*O*-methyl ether was obtained with mp 213–214 °C compared with 182 °C reported[2] for this compound. No spectroscopic or other physical data were listed.

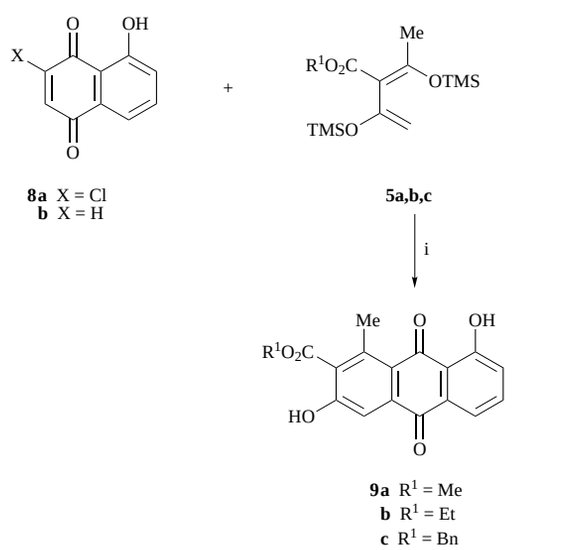
Since 3,8-dihydroxy-2-methoxycarbonyl-1-methylanthra-9,10-quinone **9a** appeared to offer another potential route to methyl-6-deoxykermesate **6e** by hydroxylation at the 5-position,



Scheme 3

its preparation was examined by the Diels–Alder addition of 3-chlorojuglone **8a** to the 3-alkoxycarbonyl-2.4-bis(trimethylsilyloxy)penta-1,3-dienes (**5a**–**c**).

3-Chlorojuglone[14] **8a**, prepared from juglone **8b**, with the diene **5a** gave 3,8-dihydroxy-2-methoxycarbonyl-1-methylanthra-9,10-quinone **9a** in good yield as shown in Scheme 4.

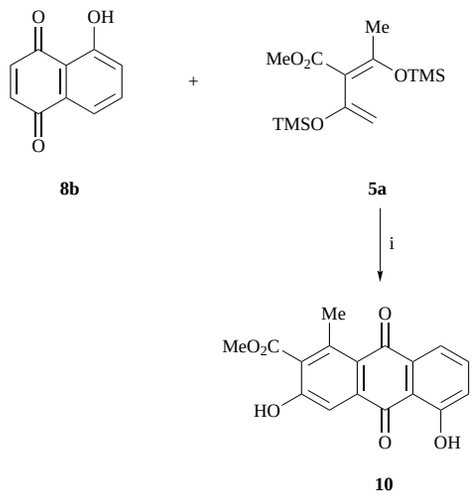


Scheme 4 *Reagents and conditions*: i, heat, MePh; then H_2O–THF

The ethyl and benzyl ester analogues **9b** and **9c** respectively were obtained similarly.

The methyl compound **9a** was identical in melting point and in its ^{1}H NMR spectrum with those of synthetic[9] aloesaponarin-I or with the natural product from *Aloe saponaria* Haw.[15] The synthetic aloesaponarin-I **9a** had been obtained[9] in a circuitous way by the Diels–Alder addition of 3-ethoxycarbonyl-2-methoxy-4-trimethylsilyloxypenta-1,3-diene to 3-chlorojuglone **8a** and had afforded a mixture of the 3-methoxy-8-hydroxy (69%) and the 3,8-dihydroxy (21%) compounds. The former was demethylated in 82% yield with aluminium chloride–sodium chloride and the resultant hydroxy acid then esterified with methanolic boron trifluoride to afford the methyl ester in 67% yield, giving an overall yield of 38%. The single stage reaction of 3-chlorojuglone **8a** with **5a** affords directly a considerably better yield (82%).

The reaction of the methoxycarbonyl diene **5d** with juglone **8b** was described[9] as yielding a mixture of the dihydroxy compound, aloesaponarin-I (in unstated yield, but 6.5% after TLC purification) and the 3-methoxy-8-hydroxy compound (33%). By contrast, in our hands the diene **5a** with juglone **8b** gave a product (33%) (Scheme 5) which appeared from its spectral data to be an isomer, 3,5-dihydroxy-2-methoxycarbonyl-1-methylanthra-9,10-quinone **10**.



Scheme 5 *Reagents and conditions*: i, heat, MePh; then H_2O–THF

The possible formation of this isomeric compound appears puzzling although reversal of addition of the dienophile by reaction in the presence of Lewis acids has been observed.[16] In the present case it is suggested that in the Diels–Alder reaction with 3-chlorojuglone the hydrogen chloride evolved could function in this way whereas it was absent in the case of the reaction with juglone. Although the product, methyl 6-deoxykermesate, resulted in the case of the reaction of **5a** with 2-chloronaphthazarin or with naphthazarin (due to their symmetry) it is feasible that there is a similar reversal of the addition in these two reactions.

Experimental

Spectroscopy

Infrared spectra in the range 600–4000 cm^{-1} were obtained on a Perkin-Elmer 1420 spectrophotometer and electronic spectra in the range 200–600 nm were recorded on a Perkin-Elmer Lambda 9 spectrophotometer. ^{1}H NMR spectra in deuterated solvents with Me_4Si as internal standard were obtained on Varian T 60, CFT-20 and JEOL FX 200 instruments at 60, 80 and 200 MHz respectively. When necessary, ^{13}C and high resolution ^{1}H NMR spectra were obtained at 400 MHz through the SERC facility on a Bruker WM 400 at the University of Warwick. *J* Values are given in Hz. Low resolution EI–MS were obtained on a modified AEI MS902 mass spectrometer and high resolution spectra, FAB spectra and accurate mass determinations were determined through the SERC MS facility at University College of Swansea.

Chromatography

Analytical TLC was effected on commercial plates (Camlab, 0.25 mm with fluorescent indicator UV_{254nm}. Kieselgel 60 (Merck, 40–60 μm) was employed for flash chromatography and Merck silica gel 7734 for gravity columns. GLC was carried out with a Hewlett-Packard 402 chromatograph equipped with FID, glass columns (152 cm × 2.5 mm i.d.) containing 100–120 BSS mesh acid washed Celite and the stationary phase 5% OV17 at 200 °C with nitrogen as carrier gas.

General

Melting points were recorded with an electrothermal digital mp apparatus and are uncorrected. Elemental analyses were carried out by Medac Ltd, Brunel University and at Butterworth Laboratories, Teddington. Solvents and reagents were purified (where necessary) by standard techniques.[17] Starting materials were obtained from Aldrich Chemical Co. Alkyl diacetylacetates were synthesised broadly as described[18] although the analytical and spectral data on all three esters are given for the first time. All existed in the enolic form.

Methyl diacetylacetate was obtained as a clear oil, bp 63–65 °C/0.3 mmHg, which solidified at 4 °C (Found: C, 53.1; H, 6.4 Calc. for $C_7H_{10}O_4$: C, 53.2; H, 6.4%); ν_{max}(film)/cm^{-1} 3000 (C-H, adj. to CO), 2960 (CH), 1715 (α,β unsat. ester), 1560br (C=C, conj.), 1405br (OH), 1215 and 1170 (C-O, ester); δ_H($CDCl_3$) 2.34 (6H, s, 2 × CH_3), 3.77 (3H, s, CH_3, ester), 17.8 (1H, s, OH, exch. D_2O); *m*/*z* 158 (M^+, 28%), 143 (25), 85 (19), 43 (100).

Ethyl diacetylacetate was obtained as a clear oil, bp 48–50 °C/0.2 mmHg (Found: C, 55.8; H, 7.1. Calc. for $C_8H_{12}O_4$: C, 55.8; H, 7.0%); ν_{max}(film)/cm^{-1} 2950 (C-H), 1690 (C=O, ester), 1540br (C=C, conj. with ester), 1405br (O-H), 1215 and 1170 (C-O, ester); δ_H($CDCl_3$) 1.30 (3H, t, *J* 9, CH_3, ester), 2.33 (6H, s, 2 × CH_3), 4.23 (2H, q, *J* 9, OCH_2, ester), 17.7 (1H, s, OH, exch. D_2O); *m*/*z* 172 (M^+, 25%), 157 (20), 127 (24), 98 (23), 85 (25), 43 (100).

Benzyl diacetylacetate was obtained with bp 100–110 °C/0.7 mmHg (Found: C, 66.6; H, 6.1. $C_{13}H_{14}O_4$ requires C, 66.7; H, 6.0%); ν_{max}(film)/cm^{-1} 3050w (C-H, arom.), 2950 (C-H, aliph.), 1700 (C=O, ester), 1550br (C=C, conj.), 1420br (O-H), 1260 and 1060 (C-O, ester), 750 (C-H, arom.); δ_H($CDCl_3$) 2.33 (6H, s, 2 × CH_3), 5.22 (2H, s, OCH_2Ph), 7.33 (5H, s, C_6H_5), 17.8 (1H, s, OH, exch. D_2O); *m*/*z* 234 (M^+, 7%), 127 (24), 100 (11), 91 (100), 85 (8), 43 (15).

The bis(trimethylsilyl) derivatives, **5a**, **5b** and **5c** were obtained[10] as a mixture of (*E*)- and (*Z*)-isomers from reaction with either (i) bis(trimethylsilyl)acetamide or (ii) with chlorotrimethylsilane and triethylamine as described. (*E*)- and (*Z*)-3-Ethoxycarbonyl-4-methoxypent-3-en-2-one was synthesised by the methods of Roberge and Brassard[8] and of Barnes *et al.*[19] and trimethylsilylated to give **5d** according to Cameron *et al.*[9] Juglone (5-hydroxynaphtho-1,4-quinone) **8b**, mp 153–154 °C, was prepared in 68% yield by the oxidation of 1,5-dihydroxynaphthalene in aqueous suspension with sodium dichromate in aqueous sulfuric acid, a method based on a early procedure.[20] 3-Chlorojuglone (3-chloro-5-hydroxynaphtho-1,4-quinone) **8a** was prepared in 78% yield, by addition of chlorine to juglone **8b** in acetic acid and dehydrochlorination of the dichloro adduct in refluxing ethanol to give orange needles, mp 165–166 °C (lit.,[14] 166 °C) (Found: C, 57.48; H, 2.42. Calc. for $C_{10}H_5O_3Cl$: C, 57.58; H, 2.42%); ν_{max}(KBr)/cm^{-1} 3050 (arom. C-H), 1660, 1640 (quin. C=O), 1580 (aryl); δ_H(80 MHz, $CDCl_3$), 7.16 (1H, s, H-2), 7.24–7.66 (3H, m, H-6, H-7 and H-8), 11.60 (1H, s, exch. D_2O, 5-OH); *m*/*z* 210 (M^+, 29%), 208 (M^+, 89), 145 (100), 120 (20), 92 (30), 89 (36), 63 (50), 53 (20).

4-Ethoxycarbonyl-5-methoxy-3-methylphthalic anhydride 3b (cochinellic anhydride methyl ether ethyl ester) and the 5-hydroxy analogue 3e (cochinellic anhydride ethyl ester)

Bromomaleic anhydride (0.200 g, 1.13 mmol) and (*E*)- and (*Z*)-3-ethoxycarbonyl-2-methoxy-4-trimethylsilyloxypenta-1,3-diene (0.583 g, 2.26 mmol) in sodium-dried toluene (5 cm^3) were refluxed for 24 h. After removal of the solvent, the residue in damp tetrahydrofuran (20 cm^3) was treated with silica gel (5 g), the solvent was evaporated and the residue added to the top of a column of silica gel (Merck 7734) which was then eluted with chloroform to afford two products; 4-ethoxycarbonyl-5-hydroxy-3-methylphthalic anhydride **3e** (cochinellic anhydride ethyl ester), R_f 0.31 (chloroform), (73 mg, 26%) was isolated as white needles (from ethanol), mp 95–96 °C (Found: C, 57.90; H, 4.10. $C_{12}H_{10}O_6$ requires C, 57.60; H, 4.03%); ν_{max}(KBr)/cm^{-1} 3320w (OH), 3020w (arom. C-H), 2060 (aliph. C-H), 1835, 1765 (anhydr. C=O), 1670 (ester C=O); δ_H(80 MHz, $CDCl_3$) 1.49 (3H, t, *J* 9, 4-$CO_2CH_2CH_3$), 2.97 (3H, s, 3-CH_3), 4.56 (2H, q, *J* 9, 4-$CO_2CH_2CH_3$), 7.40 (1H, s, H-6), 12.16 (1H, s, exch. D_2O, 5-OH); *m*/*z* 250 (M^+, 32%), 222 (24), 204 (100), 160 (93), 132 (54), 64 (31); and 4-ethoxycarbonyl-5-methoxy-3-methylphthalic anhydride, R_f 0.20 (chloroform), (92 mg, 31%) was obtained as white cubes (from ethanol), mp 142 °C (Found: C, 59.10; H, 4.60. $C_{13}H_{12}O_6$ requires C, 59.1; H, 4.58%); ν_{max}(KBr)/cm^{-1} 3020w (arom. C-H), 2960w (aliph. C-H), 1835, 1765 (anhydr. C=O), 1690 (ester C=O); δ_H(80 MHz, $CDCl_3$) 1.39 (3H, t, *J* 9, 4-$CO_2CH_2CH_3$), 2.61 (3H, s, 3-CH_3), 3.96 (3H, s, OCH_3), 4.43 (2H, q, *J* 9, 4$CO_2CH_2CH_3$), 7.28 (1H, s, H-6); *m*/*z* 264 (M^+, 44%), 220 (31), 219 (100), 218 (69), 192 (10), 147 (19), 99 (21), 76 (11), 64 (18), 63 (23).

4-Methoxycarbonyl-5-hydroxy-3-methylphthalic anhydride 3d (cochinellic anhydride methyl ester)

Bromomaleic anhydride (0.200 g, 1.13 mmol) and (*E*)- and (*Z*)-3-methoxycarbonyl-2,4-bis(trimethylsilyloxy)penta-1,3-diene (0.683 g, 2.26 mmol) in dry toluene (5 cm^3) were refluxed for 24 h. The solvent was removed, the crude product was dissolved in damp tetrahydrofuran, silica gel (30 equiv.) was then added and after evaporation of the mixture to dryness, the residue was added to the top of a column of silica gel (Merck 7734). Elution with chloroform gave 4-methoxycarbonyl-5-hydroxy-3-methylphthalic anhydride which was obtained as a white solid (0.123 g, 46%), R_f 0.29 (chloroform) which recrystallised as needles (from ethanol), mp 146 °C (Found: C, 56.11; H, 3.42. $C_{11}H_8O_6$ requires C, 55.94; H, 3.41%); ν_{max}(KBr)/cm^{-1} 3320w (O-H), 3020w (arom. C-H), 2960w (aliph. C-H), 1835, 1765 (anhydr. C=O), 1670 (ester C=O), 1620 (aryl); λ_{max}(MeOH)/nm (log ε), 221 (4.31), 254 (4.30), 3.29 (3.56); δ_H(80 MHz, $CDCl_3$), 2.95 (3H, s, 3-CH_3), 4.07 (3H, s, 4-CO_2CH_3), 7.37 (1H, s, H-6), 12.0 (1H, s, exch. D_2O, 5-OH); *m*/*z* 236 (M^+, 30%), 204 (50), 160 (33), 132 (26), 58 (41), 43 (100).

4-Ethoxycarbonyl-5-hydroxy-3-methylphthalic anhydride 3e (cochinellic anhydride ethyl ester)

Bromomaleic anhydride (0.200 g, 1.13 mmol) and (*E*)- and (*Z*)-3-ethoxycarbonyl-2,4-bis(trimethylsilyloxy)penta-1,3-diene (0.714 g, 2.26 mmol) were refluxed in dry toluene (5 cm^3) during 24 h to afford the product (0.090 g, 32%), after work-up as before and chromatography, with mp 96 °C and identical spectroscopically (IR and ^{1}H NMR) with the alcohol product **2** obtained from the 2-methoxy-4-trimethylsilyloxydiene.

4-Benzyloxycarbonyl-5-hydroxy-3-methylphthalic anhydride 3f (cochinellic anhydride benzyl ester)

Bromomaleic anhydride (0.200 g, 1.13 mmol) and (*E*)- and (*Z*)-3-benzyloxycarbonyl-2,4-bis(trimethylsilyloxy)penta-1,3-diene (0.854 g, 2.26 mmol) were reacted and worked-up similarly to give 4-benzyloxycarbonyl-5-hydroxy-3-methylphthalic anhydride (0.042 g, 12%) which crystallised as needles (from ethanol), mp 95–96 °C; R_f 0.30 (chloroform) (Found: C, 65.12; H, 3.66. $C_{17}H_{12}O_6$ requires C, 65.39; H, 3.87%); ν_{max}(KBr)/cm^{-1} 3320 (O-H), 3020 (arom. C-H), 1835, 1765 (anhydr. C=O), 1670 (ester C=O); δ_H(80 MHz, $CDCl_3$) 2.91 (3H, s, 3-CH_3), 5.47 (2H, s, 4-CO_2CH_2Ph), 7.39 (5H, m, 4-$CO_2CH_2C_6H_5$ and H-6), 1.98 (1H, s, exch. D_2O, 5-OH); *m*/*z* 312 (M^+, 7%), 92 (20), 91 (100), 65 (14), 57 (6), 51 (7), 43 (6).

3,5,8-Trihydroxy-2-methoxycarbonyl-1-methylanthra-9,10-quinone 6e (methyl 6-deoxykermesate)

Naphthazarin (0.200 g, 1.05 mmol) and 3-methoxycarbonyl-2,4-bis(trimethylsilyloxy)penta-1,3-diene (0.64 g, 2.10 mmol) were refluxed in dry toluene (5 cm^3) during 24 h. After removal of the solvent the crude residue was dissolved in damp tetrahydrofuran, left for 24 h, silica gel (30 equiv.) added and the mixture evaporated to dryness. The silica was added to the top of a column of silica gel which was eluted with chloroform. The product obtained upon concentration (0.100 g, 29%) was recrystallised from nitrobenzene to give 3,5,8-trihydroxy-2-methoxycarbonyl-1-methylanthra-9,10-quinone **6e**, as orange needles, mp 264 °C identical spectroscopically with the product obtained by using 2-chloronaphthazarin in the Diels–Alder addition.[10] It was characterised as the triacetate.

3,5,8-Triacetoxy-2-methoxycarbonyl-1-methylanthra-9,10-quinone

Methyl 6-deoxykermesate (0.100 g, 0.30 mmol) was stirred with acetic anhydride (5 cm^3) containing 1 drop of conc. sulfuric acid during 24 h at ambient temperature. The resulting yellow suspension was diluted with dichloromethane (100 cm^3), washed with 5% aqueous sodium chloride, dried (Na_2SO_4), filtered and the filtrate evaporated to dryness to give a yellow solid (0.114 g, 82%), which crystallised as yellow needles (from ethyl acetate), mp 268 °C (decomp.) (Found: C, 60.51; H, 3.78. $C_{23}H_{18}O_{10}$ requires C, 60.80; H, 3.99%); ν_{max}(KBr)/cm^{-1} 3690 (aliph. C-H), 1740 (C=O), 1670 (quin. C=O), 1590 (aryl); δ_H(80 MHz, $CDCl_3$) 2.27 (3H, s, 3-OCOCH_3), 2.41, 2.42 (6H, 2s, 5-OCOCH_3 and 8-OCOCH_3), 2.61 (3H, s, 1-CH_3), 3.91 (3H, s, 2-CO_2CH_3), 7.33 (2H, s, H-6, H-7), 7.81 (1H, s, H-4); *m*/*z* 454 (M^+, 1%), 328 (52), 297 (22), 296 (100), 240 (10), 28 (9).

2-Carboxy-3,5,8-trihydroxy-1-methylanthra-9,10-quinone 6a (6-deoxykermesic acid)

Benzyl 6-deoxykermesate[10] (0.050 g, 0.12 mmol) in tetrahydrofuran (10 cm^3) containing 10% Pd–C (0.013 g) was hydrogenolysed with hydrogen at ambient pressure and temperature during 4 h. Filtration of the mixture gave a greenish yellow solid, the leuco compound, 2-carboxy-6,7-dihydro-1-methyl-3,9,10-trihydroxyanthra-5,8-quinone (0.039 g, 100%), mp > 300 °C (Found: M^+, 316.0583. Calc. for $C_{16}H_{12}O_6$: 316.0583); ν_{max}(KBr)/cm^{-1} 3280br (O-H), 1690 (CO_2H), 1610 (dione), 1480, 1380, 1310, 1210, 1170, 1110, 1010, 940, 840, 730; δ_H[80 MHz, $(CD_3)_2SO$] 2.79 (3H, s, 1-CH_3), 3.05 (4H, s, H-2, -2a, -3 and -3a), 7.64 (1H, s, H-6), 10.70 (1H, br s, 7-O*H*), 13.42 (2H, s, exch. D_2O, 9- and 10-H); *m*/*z* 316 (M^+, 23%), 298 (57), 272 (34), 270 (100), 256 (24), 252 (21), 44 (22), 31 (29), 18 (51).

The leuco acid (0.038 g) in tetrahydrofuran (5 cm^3) containing 1 M sodium hydroxide (5 cm^3) was stirred at ambient temperature in air. The brown solution turned to a plum-red colour after 10 min and after acidification with acetic acid the mixture was extracted with dichloromethane from which by evaporation an orange solid **6a** (0.037 g, 96%) was obtained. Crystallisation (methanol–water, 1:1), afforded red–brown flat needles, mp 293–295 °C (sublimes) (Found: C, 61.03; H, 3.22. Calc. for $C_{16}H_{10}O_7$: C, 61.15; H, 3.21%); ν_{max}(KBr)/cm^{-1} 3100br (O-H), 2940, 2670 (arom. C-H), 1700 (CO_2H), 1635 (quin. C=O), 1580 (aryl), 1470, 1400, 1360, 1270, 1225, 1170, 900, 790, 650; δ_H[80 MHz, $(CD_3)_2SO$] 2.82 (3H, s, 1-CH_3), 7.28 (2H, s, H-6, H-7), 7.77 (1H, s, H-4), 12.58, 13.07 (2H, 2s, exch. D_2O); *m*/*z* 314 (M^+ 3%), 271 (22), 270 (100), 252 (23), 224 (9), 149 (19), 126 (10), 98 (12), 91 (13), 85 (9), 71 (10), 57 (1), 55 (12), 44 (80), 43 (44), 36 (46).

Anthra-1,4,9,10-diquinone

Previous preparations have given[12] a 61% yield and in another[13] a 58% yield. To stirred 1,4-dihydroxyanthra-9,10-quinone (quinizarin) (1.00 g, 4.17 mmol) in dry dichloromethane was added lead tetraacetate (2.50 g, 5.64 mmol). The orange solution soon became green–brown and after 2 h at ambient temperature, the suspension was diluted with dichloromethane (30 cm^3), filtered and the filtrate evaporated to dryness. Crystallisation (from ethyl acetate) of the green–brown solid gave straw-yellow needles (0.856 g, 86%), mp 210–212 °C (lit.,[11] 208–210 °C) (decomp.) (lit.,[12] no mp and lit.,[13] 210–212 °C); ν_{max}(KBr)/cm^{-1} 3040 (=C-H), 1690, 1680 (quin. C=O), 1590 (aryl), 1285, 1115, 858, 850, 800, 790, 780, 710; δ_H(80 MHz, $CDCl_3$) 6.86 (2H, s, H-2, H-3), 7.71–7.93 (2H, s, H-6, H-7), 7.95–8.09 (2H, s, H-5, H-8).

1,2,4-Triacetoxyanthra-9,10-quinone

To stirred anthra-1,4,9,10-diquinone (0.010 g, 0.42 mmol) in acetic anhydride (1 cm^3) a drop of conc. sulfuric acid was added. During 2 h the straw colour changed to orange–yellow and after addition of dichloromethane (25 cm^3), the mixture was washed with 5% aqueous sodium chloride, dried (sodium sulfate), filtered and evaporated to afford a yellow solid (0.146 g, 91%) which gave light yellow needles, mp 186–187 °C (from ethanol) (lit.,[21] 200–201 °C); δ_H(80 MHz, $CDCl_3$) 2.33 (3H, s, 2-OCOCH_3), 2.46 (6H, s, 1- and 4-OCOCH_3), 7.32 (1H, s, H-3), 7.63–7.75 (2H, s, H-6 and H-7), 8.05–8.13 (2H, s, H-5 and H-8).

Thiele reaction of quinizarin in acetic anhydride with lead tetraacetate followed by addition of conc. sulfuric acid gave the same product in 84% yield as light yellow needles, mp 187 °C, identical with the preceding product. Peracetylation of commercial 1,2,4-trihydroxyanthra-9,10-quinone (purpurin) afforded the triacetate, mp 184–187 °C.

3,5,6,8-Tetramethoxy-2-methoxycarbonyl-1-methylanthra-9,10-quinone 1b (methyl tetra-*O*-methylkermesate) and 3,5,7,8-tetramethoxy-2-methoxycarbonyl-1-methylanthra-9,10-quinone 2b (methyl tetra-*O*-methylisokermesate)

A stirred suspension of methyl 6-deoxykermesate (0.100 g, 0.030 mmol) in acetic anhydride (5 cm^3) was treated at ambient temperature with lead tetraacetate (0.250 g, 0.56 mmol). A yellow–green precipitate of the anthradiquinone appeared and after 4 h conc. sulfuric acid (5 drops) was added. The mixture was stirred for 24 h and then diluted with dichloromethane, filtered through Celite, washed with 5% aqueous sodium chloride, evaporated to dryness and the residual crude acetates hydrolysed during 2 h under nitrogen with 10% potassium carbonate in aqueous ethanol (25 cm^3, 1:1) at ambient temperature. The red solution was evaporated to dryness and to the residue suspended in dry acetone (25 cm^3) were added potassium carbonate (1.5 g) and dimethyl sulfate (0.6 cm^3). The mixture was refluxed for 24 h, following which it was filtered and the filtrate and washings evaporated to give the permethylated products. Preparative TLC with ethyl acetate–chloroform (1:1) on silica gel afforded 3,5,6,8-tetramethoxy-2-methoxycarbonyl-1-methylanthra-9,10-quinone (methyl tetra-*O*-methylkermesate) as a yellow solid (0.013 g, 11%), R_f 0.60, mp 196 °C (lit.,[2,8] 196 °C) (Found: M^+, 400.1168. Calc. for $C_{21}H_{20}O_8$: 400.1158); ν_{max}(film)/cm^{-1} 2940, 2840 (aliph. C-H), 1725 (ester, C=O), 1660 (quin. C=O), 1580 (aryl), 1460, 1340, 1230, 1210, 1030, 750; λ_{max}(MeOH)/nm (log ε) 229 (4.37), 272 (4.42), 402 (3.81); δ_H(80 MHz, $CDCl_3$) 2.63 (3H, s, 1-CH_3), 3.93, 3.96, 3.97 (15H, 3s, 2-CO_2CH_3, 3,5,6,8-OCH_3), 6.76 (1H, s, H-7), 7.50 (1H, s, H-4); *m*/*z* 401 (26%), 400 (100), 386 (47), 385 (77), 383 (26), 371 (64), 369 (25), 367 (37), 354 (24), 353 (23), 339 (21). The compound was identical in mp and mixed mp with a sample kindly provided by Professor P. Brassard.

The second band was obtained as a yellow solid (methyl tetra-*O*-methylisokermesate) (0.015 g, 12%), R_f 0.52, mp 213–214 °C (lit.,[7] 182 °C) (Found: M^+, 400.1157. Calc. for $C_{21}H_{20}O_8$: M^+, 400.1158); ν_{max}(film)/cm^{-1} 2940, 2840 (aliph. C-H), 1725 (ester, C=O), 1660 (quin; 1660), 1580 (aryl), 1465, 1345, 1290, 1215, 1160, 1085, 750; λ_{max}(MeOH)/nm (log ε) 224 (4.37), 267 (4.42), 411 (3.81); δ_H(80 MHz, $CDCl_3$), 2.60 (3H, s, 1-CH_3), 3.91, 3.97, 3.98 (15H, 3s, 2-CO_2CH_3, 3,5,7-OCH_3), 6.69 (1H, s, H-6), 7.54 (1H, s, H-4); *m*/*z* 400 (M^+, 33%), 386 (34), 353 (32), 43 (51), 41 (26).

3,8-Dihydroxy-2-methoxycarbonyl-1-methylanthra-9,10-quinone 9a

3-Chlorojuglone (0.200 g, 0.96 mmol) and (*E*)- and (*Z*)-3-methoxycarbonyl-2,4-bis(trimethylsilyloxy)penta-1,3-diene (0.579 g, 1.92 mmol) were refluxed in dry toluene (5 cm^3) for 24 h after which the solvent was evaporated and the residue was kept in damp tetrahydrofuran for 24 h. Silica gel (30 equiv.) was then added, the mixture was evaporated to dryness and the residue added to the top of a column of silica gel (Merck 7734) which was eluted with chloroform to afford upon removal of the solvent an orange–red solid (0.245 g, 82%), R_f 0.24 (ethyl acetate–chloroform, 1:1), which crystallised as orange microplates (from ethanol), mp 208–209 °C (lit.,[9] 202.5–206.5 °C;

lit.,[13] 190–203 °C) (Found: C, 65.42; H, 3.80. Calc. for $C_{17}H_{12}O_6$: C, 65.39; H, 3.87%); ν_{max}(KBr)/cm^{-1} 3480br, 3250 (O-H), 2960w (aliph. C-H), 1715s (ester C=O), 1670 and 1630 (quin. C=O), 1560 (aryl); λ_{max}(MeOH)/nm (log ε) 229 (4.47), 260 (4.15), 284 (4.26), 290sh (4.25), 310sh (4.05), 422 (3.82); δ_H(80 MHz, $CDCl_3$) 2.94 (3H, s, 1-CH_3), 4.03 (3H, s, 2-CO_2CH_3), 7.24 (1H, dd, *J* 2.0, 7.5, H-7), 7.55 (1H, t, *J* 7.5, H-6), 7.73 (1H, s, H-4), 7.74 (1H, dd, *J* 2.0, 7.5, H-5), 10.20 (1H, br s, exch. D_2O, 3-O*H*), 12.80 (1H, s, exch. D_2O, 8-O*H*); *m*/*z* 312 (M^+, 61%), 281 (29), 280 (100), 252 (42), 224 (43), 168 (24), 139 (32), 72 (17).

2-Ethoxycarbonyl-3,8-dihydroxy-1-methylanthra-9,10-quinone 9b

3-Chlorojuglone **8a**, (0.200 g, 0.96 mmol) and (*E*)- and (*Z*)-3-ethoxycarbonyl-2,4-bis(trimethylsilyloxy)penta-1,3-diene (0.579 g, 1.92 mmol) were refluxed in dry toluene (5 cm^3) to give after work-up and chromatography an orange–yellow solid (0.263 g, 84%), R_f 0.25 (chloroform), which crystallised as fine orange needles (toluene), mp 202–203 °C (lit.,[9] 193–198 °C) (Found: C, 66.05; H, 4.32. Calc. for $C_{18}H_{14}O_6$: C, 66.26; H, 4.32%); ν_{max}(KBr)/cm^{-1} 3480 and 3250 (O-H), 2960 (aliph. C-H), 1730 (ester, C=O), 1670 and 1630 (quin. C=O), 1560 (aryl); δ_H(80 MHz, $CDCl_3$) 1.48 (3H, t, *J* 9, 2-$CO_2CH_2CH_3$), 7.27 (1H, dd, *J* 2.0, 7.5, H-7), 7.60 (1H, t, *J* 7.5, H-6), 7.77 (1H, s, H-4), 7.77 (1H, dd, *J* 2.0, 7.5, H-5), 10.43 (1H, s, exch. D_2O, 3-O*H*), 12.88 (1H, s, exch. D_2O, 8-O*H*); *m*/*z* 326 (M^+, 47%), 297 (63), 281 (26), 280 (79), 252 (27), 224 (35), 168 (26), 139 (100).

2-Benzyloxycarbonyl-3,8-dihydroxy-1-methylanthra-9,10-quinone 9c

3-Chlorojuglone **8a** (0.200 g, 0.96 mmol) and (*E*)- and (*Z*)-3-benzyloxycarbonyl-2,4-bis(trimethylsilyloxy)penta-1,3-diene (0.725 g, 1.92 mmol) were refluxed in toluene to afford after work-up and chromatography an orange–yellow solid (0.261 g, 70%), R_f (chloroform) 0.25, which crystallised as fine orange micro plates (ethanol), mp 203–204 °C (Found: C, 70.95; H, 4.13. $C_{23}H_{16}O_6$ requires C, 71.13; H, 4.15%); ν_{max}(KBr)/cm^{-1} 3480 and 3250 (O-H), 3020 (arom. C-H), 2960 (aliph. C-H), 1715 (ester, C=O), 1670 and 1630 (quin. C=O), 1560 (aryl); δ_H(80 MHz, $CDCl_3$), 2.92 (3H, s, 1-CH_3), 5.42 (2H, s, 2-CO_2CH_2Ph), 7.24 (1H, dd, *J* 2.0, 7.5, H-7), 7.38 (5H, s, 2-$CO_2CH_2C_6H_5$), 7.54 (1H, t, *J* 7.5, H-6), 7.72 (1H, s, H-4), 7.71 (1H, dd, *J* 2.0, 7.5, H-5), 10.22 (1H, s, exch. D_2O, 3-O*H*), 12.77 (1H, s exch. D_2O, 8-O*H*); *m*/*z* 388 (M^+, <1%), 297 (38), 139 (5), 92 (9), 91 (100), 65 (9).

Reaction of (*E*)- and (*Z*)-3-methoxycarbonyl-2,4-bis(trimethylsilyloxy)penta-1,3-diene with juglone

Juglone **8b** (0.200 g, 1.15 mmol) and 3-methoxycarbonyl-2,4-bis(trimethylsilyloxy)penta-1,3-diene **5a** (0.580 g, 1.92 mmol) were refluxed in dry toluene (20 cm^3) during 24 h. After work-up, consisting of concentration, dissolution in damp tetrahydrofuran and chromatography as before on silica gel with chloroform as eluent, an orange yellow solid (0.114 g, 32%) was obtained, R_f 0.24 (chloroform), which crystallised as green–brown plates (ethanol), mp 247–248 °C; ν_{max}(KBr)/cm^{-1} 3320br (O-H), 2950w (aliph. C-H), 1735 (ester, C=O), 1640 (quin. C=O), 1560 (aryl), 1478, 1451, 1427, 1374, 1340, 1296, 1259, 1163, 1147, 1070, 1020, 956, 889, 839, 770, 720, 708, 640; λ_{max}(MeOH)/nm (log ε) 232 (4.41), 287 (4.45), 402 (3.84); δ_H(80 MHz, $CDCl_3$) 2.93 (3H, s, 1-CH_3), 4.03 (3H, s, 2-CO_2CH_3), 7.26–7.85 (4H, m, H-4, -6, -7 and -8), 10.44 (1H, br s, exch. D_2O, 3-O*H*), 12.20 (1H, s, exch. D_2O, 5-O*H*); *m*/*z* 312 (M^+, 66%), 281 (25), 280 (100), 252 (23), 224 (18), 152 (20). The product may be the isomeric 3,5-dihydroxy-2-methoxycarbonyl-1-methylanthra-9,10-quinone **10**.

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