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Tetrahedron
Tetrahedron 64 (2008) 3471–3476
www.elsevier.com/locate/tet

The synthesis of kermesic acid by acetylation-aided tautomerism of 6-chloro-2,5,8-trihydroxynaphtho-1,4-quinone

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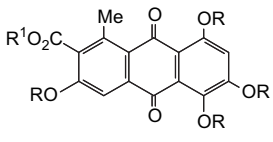
Received 19 November 2007; received in revised form 4 February 2008; accepted 7 February 2008
Available online 9 February 2008

Abstract

Methodology has been sought towards obtaining a 2-chloro-1,4-naphthoquinone bearing hydroxyl groups in the adjoining ring for obtaining either kermesic or carminic acids. In the first of these objectives, kermesic acid has been synthesised from 6-chloro-2,5,8-trihydroxynaphtho-1,4-quinone by the regioselective cycloaddition of the 1,2-diacetate formed by its acetylation-aided tautomerism and cycloaddition with (*E*)- and (*Z*)-3-alkoxycarbonyl-2,4-bis(trimethylsilyloxy)penta-1,3-dienes. The parent unacetylated quinone resists cycloaddition.

1. Introduction

Kermesic acid **1a** is the red colourant component of kermes, a dyestuff of great antiquity and most probably the earliest for which records exist.[1] Kermesic acid is the aglycone of carminic acid **2**, the colourant principle of cochineal.[2] A preliminary communication[3] has appeared and the isomer, isokermesic acid, 1-methyl-3,5,7,8-tetrahydroxyanthra-9,10-quinone-2-carboxylic acid, has been synthesised.[4]



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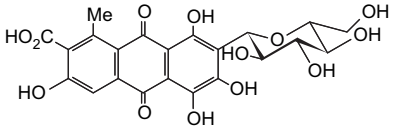


2

1a R = R^1 = H

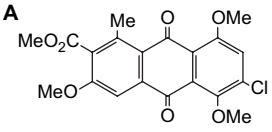
b R = H, R^1 = Me

c R = R^1 = Me

Formulae 1 and 2

Carminic acid **2**, is an abundant indigenous but expensive product from Peru, Mexico and the Canary Islands, and historically superseded kermesic acid through its brilliant red hues, although dyeing with kermes is still practised.[5] By contrast, the natural European source of kermesic acid from the insect *Kermes illicis*, which infects the kermes oak is not widespread. Thus, it was of interest to devise a synthesis that could provide a tricyclic intermediate capable of obtaining either kermesic or carminic acid, which did not contain a halogeno group that is hydrolysed with difficulty as in precursors A and B involved in previous syntheses,[6,7] respectively.

A



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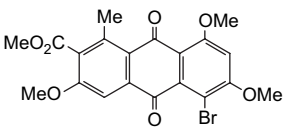

Therefore, effort was directed towards the preparation of 2-halogeno-5,6,8-trihydroxynaphtho-1,4-quinone **3** (form 2), which, like naphthazarins in general, could exist as the tautomers **3** (forms 1 and 2) and contain the prerequisite hydroxyl at positions 2 (form 2) and 6 (form 1). The halogen at 2-position (form 2) would serve to both direct Diels–Alder addition in the correct manner and facilitate aromatisation to the required anthraquinone at the next stage.

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0040-4020/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.02.018

2. Results and discussion

The starting point of the synthesis (Scheme 1), 3-chloro-2-hydroxy-5-methoxyacetophenone **4** was prepared as for the bromo analogue[8] in 80% yield by selective chlorination of 2-hydroxy-5-methoxyacetophenone with *N*-chlorosuccinimide (NCS) in acetic acid containing $Mg(OAc)_2$. Methylation of **4** with dimethyl sulfate in acetone containing potassium carbonate afforded **5** (X=Cl) in 81% and **5** (X=Br) in 82% yield. Reaction of the respective acetophenones with dimethyl carbonate in methanolic sodium methoxide gave the β-ketoesters **6** in quantitative yields, which upon treatment with oxalyl chloride in nitromethane containing anhydrous aluminium chloride, a method used previously for unhalogenated naphthoquinones,[9] afforded the two 3-methoxycarbonyl-6-halogeno-2,5,8-trihydroxynaphtho-1,4-quinones **7** (X=Br) in 48% and **7** (X=Cl) in 56% yields, respectively, together with some partially demethylated material. Hydrolysis of the trihydroxyquinone esters with either aqueous sodium hydroxide followed by acidification or preferably with hot acetic acid containing hydrochloric acid gave **3** (X=Cl) in 53% yield and the bromo analogue in 69% yield. Under a variety of conditions **3** (X=Cl) failed to undergo Diels–Alder cycloaddition with the dienes (*E*)- and (*Z*)-3-methoxycarbonyl-2,4-bis(trimethylsilyloxy)penta-1,3-dienes **8a**. This was attributed primarily to intramolecular hydrogen bonding of the 2-OH group[10] thus inhibiting tautomerism of the naphthazarin system and locking the structure in form 1.

Support for this exclusive formulation was provided physically by an X-ray structure determination (Fig. 1), and chemically by (a) its ready Michael addition under mild conditions at the 3-position with (*E*)- and (*Z*)-3-ethoxycarbonyl-3-penten-2-ones to give **13**, and (b) selective O-methylation in 77% yield at the 2-position with $BF_3 \cdot MeOH$, the product of which removed the impediment to tautomerism and facilitated cycloaddition.

Acetylation of **3** in dichloromethane with pyridine/acetic anhydride afforded triacetoxy compounds in 91% yield as a 2:1 mixture (from NMR analysis) of 6-chloro-2,3,8-triacetoxynaphtho-1,4-quinone and 2-chloro-5,6,8-triacetoxynaphtho-1,4-quinone. However, heating **3** with acetic anhydride alone at 100 °C afforded the 2-chloro-5,6-diacetoxy compound (**9**, R=R′=Ac) in quantitative yield. It is postulated (Scheme 2) that acetylation of the 2-OH group occurs first allowing tautomerism to give form 2, which is then followed by acetylation at the 5-position thus locking the structure to that form. It is conjectured that since hydrogen-bonded OH groups are more difficult to acetylate, migration of the 6-acetyl group

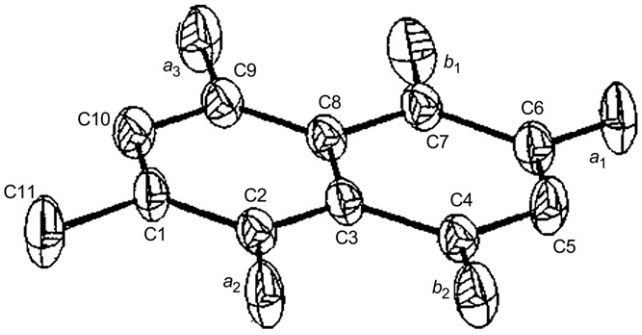
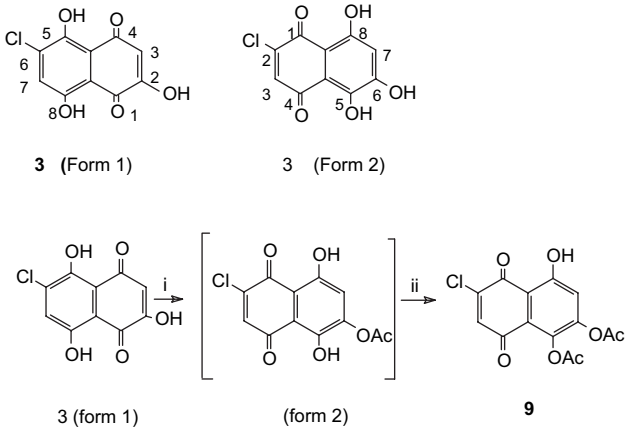


Figure 1. X-ray crystal structure of 6-chloro-2,5,8-trihydroxynaphtho-1,4-quinone; C–OH: a_u, a_2, a_3=1.33, 1.34, 1.35 Å; C=O: b_u, b_2=1.22, 1.24 Å.

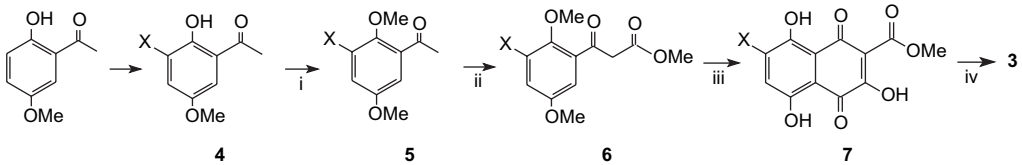
to the 5-position in form 2 may possibly occur enabling the more susceptible 6-OH to subsequently react. Such a mechanism may explain non-acetylation of the hydrogen-bonded 8-OH. There is no further information currently available to support this hypothesis. An X-ray structure determination of 3-chloro-5,6-diacetoxy-8-hydroxynaphtho-1,4-quinone (Fig. 2) provided definitive confirmation of its structure.



Scheme 2. *Reagents and conditions*: (i) Ac_2O, 100 °C, 3 h; (ii) vacuum to dryness.

The diacetoxy compound readily underwent cycloaddition with (*E*)- and (*Z*)-3-methoxycarbonyl-2,4-bis(trimethylsilyloxy)penta-1,3-dienes **8a** followed by aromatisation in boiling toluene to afford **10**, methyl 5,6-diacetoxy-3,8-dihydroxy-1-methylanthra-9,10-quinone-2-carboxylate in 87% yield after column chromatography. Definitive proof of structure was provided by an X-ray structural study (Fig. 3). The isopropyl analogue **8b** reacted similarly in 64% yield to give **12b**.

2-Chloro-6-methoxy-5,8-dihydroxynaphtho-1,4-quinone **11**, in which normal naphthazarin tautomerism is able to operate



Scheme 1. *Reagents and conditions*: **4** (X=Cl) (i) NCS, HOAc, $Mg(OAc)_2$, rt, 24 h; DMS, Me_2CO, K_2CO_3, heat, 24 h; (ii) NaOMe, MeOH, $(MeO)_2CO$, heat; (iii) $(COCl)_2$, $MeNO_2$, $AlCl_3$, 0–80 °C, 3 h; (iv) 10% concd HCl–HOAc, 100 °C, 5 h.

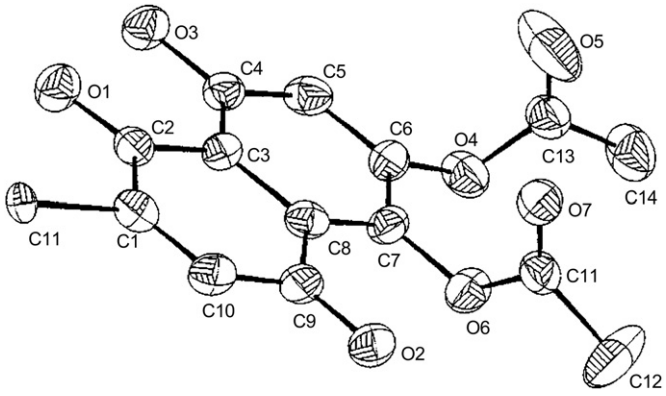


Figure 2. X-ray crystal structure of 2-chloro-5,6-diacetoxy-8-hydroxynaphtho-1,4-quinone.

(although the structure is not locked as with the diacetate), also underwent cycloaddition with the diene **8a** in boiling toluene to give after work-up methyl 6-methoxy-3,5,8-trihydroxy-1-methylanthra-9,10-quinone-2-carboxylate **12a** in 42%yield. This observation is consistent with the previously observed[2] cycloaddition of 2-chloronaphthazarin with diene **8a**.

Possibly forms of both type 1 and 2 are present with the methoxy compound **11** since there is no locking of the structure in this compound.

Hydrolysis of **10** in 1% methanolic sodium carbonate followed by acidification gave methyl kermesate **1b** in quantitative yield, and hence by refluxing in acetic acid containing hydrochloric acid, kermesic acid was derived (Scheme 3). Methylation of methyl kermesate **1b** with dimethyl sulfate in acetone solution containing potassium carbonate gave methyl 3,5,6,8-tetramethoxy-1-methylanthraquinone-2-carboxylate **1c**, which was identical with an authentic sample kindly made available by Prof. P. Brassard.

It is believed that **3** has the potential to facilitate access to carminic acid. For this, **3** (form 1) appears to be an ideal candidate by way of Michael and enamine reactions from initial work. Such chemical approaches using kermesic acid itself as an intermediate to carminic acid have not, so far, been successful although this or xanthokermesic are the likely biosynthetic precursors.

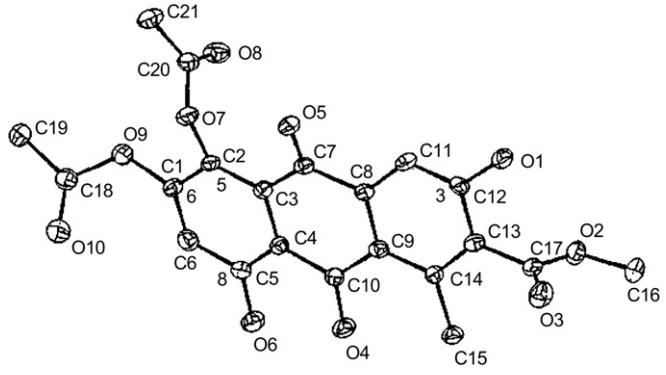


Figure. 3. X-ray crystal structure of methyl 5,6-diacetoxy-3,8-dihydroxy-1-methylanthra-9,10-quinone-2-carboxylate.

3. Experimental

3.1. 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. ^1H 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 (J values are given in hertz). When necessary, ^{13}C and high resolution ^1H NMR spectra were obtained at 400 MHz through the SERC facility, on a Bruker WM 400 at the University of Warwick.

Low resolution EIMS were obtained on a modified AEI MS902 and high resolution, FAB spectra and accurate mass determinations through the SERC facility at University of Wales, Swansea.

3.2. Chromatography

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

3.3. General

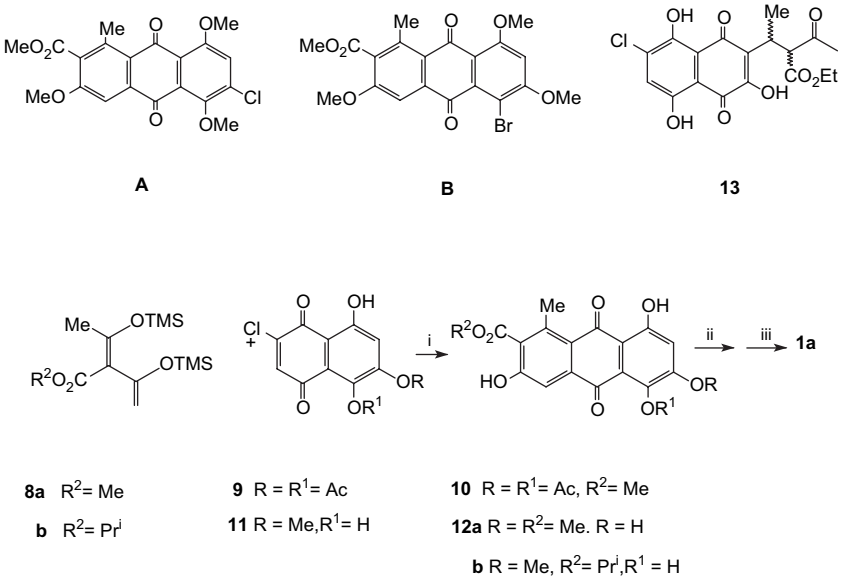
Melting points were recorded with an electrothermal digital melting point apparatus and are uncorrected. Elemental analyses were carried out by Medac Ltd., Brunel University; Butterworth Laboratories, Teddington and NRM Ltd., Bracknell, Berks. Solvents and reagents were purified (where necessary) by standard techniques. Intermediates were obtained from Aldrich Chemical Co. X-ray measurements were effected at the National Crystallographic Service, now at University of Southampton.

3.4. Synthesis of kermesic acid

(*E*)- and (*Z*)-3-methoxycarbonyl-2,4-bis(trimethylsilyloxy)-penta-1,3-dienes, and (*E*)- and (*Z*)-3-isopropoxycarbonyl-2,4-bis(trimethylsilyloxy)penta-1,3-dienes were prepared as described.[2,4]

3.4.1. 3-Chloro-2-hydroxy-5-methoxyacetophenone (*4*, X=Cl)

To a stirred solution of magnesium acetate prepared by dissolving magnesium turnings (4.86 g, 0.20 mol) in glacial acetic acid (300 cm^3), 2-hydroxy-5-methoxyacetophenone (33.24 g, 0.250 mol) was added followed 10 min later by *N*-chlorosuccinimide (33.24 g, 0.250 mol). After 24 h at ambient temperature the brown solution was poured into crushed ice (1250 g) and water (1250 cm^3) and the precipitate filtered,



Scheme 3. For **1a** and **1b**. *Reagents and conditions*: **9** (i) toluene, **8a** heat, 24 h, column chromatography, SiO_2; (ii) MeOH, 1% Na_2CO_3; (iii) HOAc–HCl, heat; (iv) for **1c**, DMS, Me_2CO, K_2CO_3, heat. Compound **11** from **3**, with $BF_3{\cdot}MeOH$; toluene, **8**, heat, column chromatography SiO_2.

washed with water and air dried to give a green-brown solid (32.10 g, 80%), which crystallised (ethanol) as green-yellow needles, mp 78–79 °C (Found: C, 54.11; H, 4.59. C_9H_9ClO requires C, 53.88; H, 4.52%.). δ_H (80 MHz, $CDCl_3$) 2.61 (3H, s, CH_3CO), 3.77 (3H, s, 5-CH_3O), 7.12 (1H, s, 4-H), 7.16 (1H, s, 6-H), 12.24 (1H, s, 2-OH); *m/z* 202 (M^+, 29%), 200 (M^+-2, 87%), 185 (100), 18 (11).

*3.4.2. 3-Bromo-2-hydroxy-5-methoxyacetophenone (**4**, X=Br)*

To a stirred mixture of 2-hydroxy-5-methoxyacetophenone (22.24 g, 0.20 mol) and sodium acetate (17.25 g, 0.21 mol) in glacial acetic acid (500 cm^3), a solution of bromine (33.24 g, 0.21 mol) in glacial acetic acid (340 cm^3) was added dropwise for over 2 h. After 48 h at ambient temperature the brown solution was added to crushed ice (1250 g) and water (1250 cm^3) and the precipitated product collected, washed with water and dried to give a green solid (42.64 g, 87%), which crystallised (ethanol) to afford green/yellow needles, mp 74–77 °C (lit.[8] 76–76.5 °C). δ_H (80 MHz, $CDCl_3$) 2.62 (3H, s, CH_3CO), 3.78 (3H, s, 5-CH_3O), 7.16 (1H, d, *J* 3 Hz, 4-H), 7.35 (1H, d, *J* 3 Hz, H-6), 12.36 (1H, s, 2-OH).

*3.4.3. 3-Chloro-2,5-dimethoxyacetophenone (**5**, X=Cl)*

To 3-chloro-2-hydroxy-5-methoxyacetophenone (20.06 g, 0.10 mol) in dry acetone (200 cm^3) containing potassium carbonate (27.64, 0.20 mol), dimethyl sulfate (15 cm^3 20.0 g, 0.16 mol) was added at ambient temperature and the mixture refluxed for 24 h, after which it was cooled, poured into water (5000 cm^3). After 2 h, the above mixture was extracted with dichloromethane (200 cm^3), the extract dried, filtered, and the filtrate evaporated to afford a clear oil, which was distilled (bp 91 °C/0.1 mm Hg) to give a solid upon refrigeration. δ_H (80 MHz, $CDCl_3$) 2.60 (3H, s, CH_3CO), 3.80 (3H, s, 2-OMe), 3.82 (3H, s, 5-OMe), 6.99, 7.00 (2×1H, 2s, 4-H, 6-H); *m/z* 216 (M^+, 27%), 214 (M^+-2, 79%).

*3.4.4. 3-Bromo-2,5-dimethoxyacetophenone (**5**, X=Br)*

3-Bromo-2-hydroxy-5-methoxyacetophenone (24.51 g, 0.10 mol) treated as for the chloro compound gave the titled product as a clear oil (21.25 g, 82%), bp 110–114 °C/0.5 mm Hg, mp 41–42 °C. δ_H (80 MHz $CDCl_3$) 2.62 (3H, s, $COCH_3$), 3.77 (3H, s, 2-OMe), 3.80 (3H, s, 5-OCH_3), 7.04 (1H, d, *J* 3 Hz, H-4), 7.21 (1H, d, *J* 3 Hz, H-6); *m/z* M^+ found, 257.9892. Required for $C_{10}H_{11}^{79}BrO_3$, 257.9892.

*3.4.5. Methyl 3-(3-chloro-2,5-dimethoxyphenyl)-3-oxopropionate (**6**, X=Cl)*

With rapid stirring under nitrogen, 3-chloro-2,5-dimethoxyacetophenone (21.46 g, 0.10 mol) in dimethyl carbonate (90 cm^3) was added dropwise to a solution of sodium methoxide from sodium (8.46 g, 0.37 mol) in dry methanol (81 cm^3), and the mixture was refluxed with removal of methanol via a fractionating column. After 3 h, the mixture, cooled to ambient temperature, was treated with acetic acid (27 cm^3) in diethyl ether (90 cm^3) followed by water (200 cm^3). The separated organic phase was dried (magnesium sulfate), filtered and concentrated in vacuo to give a light brown oil (27.3 g, 100%). δ_H (80 MHz, $CDCl_3$) 3.72 (3H, s 2-OMe), 3.76 (3H, s, 5-OMe), 3.82 (3H, s, CH_3OCO), 3.99 (2H, s, $OCCH_2CO$), 7.07 (2H, s, 4-H, 6-H); *m/z* 274 (M^+ 20%), 272 (M^+-2, 59%).

*3.4.6. Methyl 3-(3-bromo-2,5-dimethoxyphenyl-3-oxopropionate (**6**, X=Br)*

3-Bromo-2,5-dimethoxyacetophenone treated as for the chloro compound gave the titled product as a light brown oil (31.7 g, 100%), which was used directly. δ_H (60 MHz, $CDCl_3$) 3.72 (3H, s 2-OMe), 3.77 (3H, s, 5-OMe), 3.80 (3H, s, CH_3OCO), 4.00 (2H, s, $OCCH_2CO$), 7.1–7.3 (2H, m, H-4 and H-6); *m/z* 318 (M^+, 89%), 316 (M^+-2, 88%), 286 (56), 285 (20), 261 (24), 260 (24), 259 (23), 258 (30), 256 (20),

246 (23), 245 (96), 244 (29), 243 (100), 241 (27), 230 (32), 228 (34), 165 (21), 58 (28), 43 (51), 18 (23).

3.4.7. Methyl 6-chloro-2,5,8-trihydroxynaphtho-1,4-quinone-3-carboxylate (**7**, X=Cl)

To a stirred solution of aluminium chloride under nitrogen (4.00 g, 0.003 mol) in dry nitromethane (10 cm^3) at 0 °C, methyl 3-(3-chloro-2,5-dimethoxyphenyl)-3-oxopropionate (2.71 g, 0.01 mol) was added followed by oxalyl chloride (0.82 cm^3, 0.01 mol) and the mixture kept at 0 °C for 1 h. It was then allowed to rise to ambient temperature and heated at 80 °C for 1 h after which the cooled dark violet solution was treated with 5% aqueous oxalic acid and extracted with dichloromethane (3×100 cm^3). The combined extracts were washed with 5% sodium carbonate solution (150 cm^3) and the aqueous layer first washed with diethyl ether, before careful acidification with concentrated hydrochloric acid to liberate the product, which was extracted with dichloromethane (3×100 cm^3). The total extracts were dried (magnesium sulfate), filtered and concentrated to afford a dark red solid (1.67 g), which (by TLC) contained some partially methylated material, in addition to the desired product. Crystallisation (toluene) gave fine dark red needles, mp 200–212 °C (sublimes). δ_H (80 MHz, $CDCl_3$) 4.05 (3H, s, CH_3OCO), 7.35 (1H, s, 7-H), 12.01 (1H, s, 8-OH, exch. D_2O), 13.48 (1H, s, 5-OH, exch. D_2O); *m/z* 300 (M^+, 10%), 298 (M^+-2, 28%), 268 (20), 266 (56), 242 (21), 240 (78), 238 (46), 212 (12), 210 (16), 205 (12), 199 (17), 170 (19), 142 (14), 120 (13), 118 (13), 87 (35), 85 (100), 83 (100), 69 (21), 58 (58), 53 (27), 47 (13), 43 (15).

3.4.8. Methyl 6-bromo-2,5,8-trihydroxynaphtho-1,4-quinone-3-carboxylate (**7**, X=Br)

From methyl 3-(3-bromo-2,5-dimethoxyphenyl)-3-oxopropionate (3.17 g, 0.01 mol) treated as for the chloro analogue, the title compound was obtained (together with some partially demethylated material) as fine dark red needles, after crystallisation (toluene), mp 190 °C (decomp.). Found, M^+ 341.9375. Required for $C_{12}H_7BrO_7$, 341.9375. δ_H (60 MHz, $CDCl_3$) 4.00 (3H, s, CO_2 CH_3), 7.58 (1H, s, H-7), 11.97 (1H, s, 8-OH, D_2O exch.); *m/z* 344 (M^+, 8%), 342 (M^+-2, 10%), 312 (36), 310 (35), 286 (82), 284 (100), 282 (27), 266 (19), 256 (25), 240 (35), 58 (30), 44 (37), 43 (91), 18 (24).

3.4.9. 6-Chloro-2,5,8-trihydroxynaphtho-1,4-quinone (**3**, form 1)

Methyl 6-chloro-2,5,8-trihydroxynaphtho-1,4-quinone-3-carboxylate (1.49 g, 5.0 mmol) in acetic acid (12 cm^3) containing concd hydrochloric acid (1.2 cm^3) was heated at 100 °C for 5 h. The mixture was cooled, poured into water (500 cm^3), extracted with dichloromethane (100 cm^3), the extracts dried (magnesium sulfate) and concentrated in vacuo to give a red-black prisms (0.72 g, 53%), which crystallised (xylene) to afford red-black prisms, mp 202–205 °C (Found: C, 50.20; H, 1.95. $C_{10}H_5ClO_5$ requires, C, 49.89; H, 2.08.). M^+, found, 239.9829, 241.9790. $C_{10}H_5ClO_5$ requires, 239.9826, 241.9796. δ_H (80 MHz, $CDCl_3$) 6.34 (1H, s, 3-H), 7.51 (1H, s, 7-H), 11.27 (1H, s, 2-OH, exch. D_2O), 13.33 (2H, br s, 5- and 8-OH, exch. D_2O).

3.4.10. 2-Chloro-5,6-diacetoxy-8-hydroxynaphtho-1,4-quinone (**9**)

6-Chloro-2,5,8-trihydoxynaphtho-1,4-quinone (1.16 g, 5.0 mmol) in acetic anhydride (10 cm^3) was heated at 120 °C for 5 h and then evaporated to dryness in vacuo to give a solid (1.63 g, 100%), which crystallised (ethanol) as flat orange plates, mp 168–171 °C. δ_H (80 MHz, $CDCl_3$) 2.36, 2.39 (2×3H, 2s, $2CH_3CO$), 6.78 (1H, s, 7-H), 7.43 (1H, s 3-H), 12.92 (1H, s, OH, exch. D_2O); *m/z* 326 (M^+, 14%), 324 (M^+-2, 32%).

3.4.11. Methyl 5,6-diacetoxy-3,8-dihydroxy-1-methylanthra-9,10-quinone-2-carboxylate (**10**, R=R^1=Ac, R^2=Me)

A stirred solution of 2-chloro-5,6-diacetoxy-8-hydroxynaphtho-1,4-quinone under nitrogen (0.56 g, 1.70 mmol) with (*E*)- and (*Z*)-3-methoxycarbonyl-2,4-bis(trimethylsilyloxy)-penta-1,3-dienes (0.79 g, 2.50 mmol) in dry toluene (19 cm^3) was refluxed for 24 h and the mixture then evaporated to dryness. The residue was purified by column chromatography on silica gel (chloroform) to give a yellow-brown solid (0.63 g, 87%), which crystallised (ethanol) as brown prisms, mp 197–200 °C. δ_H (80 MHz, $CDCl_3$) 2.34, 2.43 (2× 3H, 2s, $2CH_3CO_2$), 2.95 (3H, s, 1-CH_3), 4.05 (3H, s, 2-CH_3OC=O), 7.17 (1H, s, 7-H), 7.68 (1H, s, 4-H), 10.43 (1H, s, 3-OH, exch. D_2O), 13.30 (1H, s, 8-OH, exch. D_2O); *m/z* 428 (M^+, 21%), 386 (53), 345 (23), 344 (83), 313 (46), 312 (100), 85 (28), 43 (59), 18 (77).

3.4.12. Methyl 3,5,6,8-tetrahydroxy-1-methylanthra-9,10-quinone-2-carboxylate (methyl kermesate) (**1b**)

To methyl 5,6-diacetoxy-3,8-dihydroxy-1-methylanthra-9,10-quinone-2-carboxylate (50 mg, 0.120 mmol) in methanol (5 cm^3) was slowly added 1% aqueous sodium carbonate solution and after 2 h, the purple red solution was carefully acidified with hydrochloric acid to give an orange precipitate, which was filtered, washed with water, dried to give a solid (40 mg, 100%), and crystallised (ethanol) to afford dark red rhomboids, mp 240–241 °C. δ_H (80 MHz, $(CD_3)_2SO$), 2.51 (3H, s, 1-Me), 3.89 (3H, s, MeOCO), 6.71 (1H, s, 7-H), 7.73 (1H, s, 4-H), 11.49 (1H, s, 3-OH, exch. D_2O), 13.69 (1H, s, 8-OH, exch. D_2O); *m/z* 344 (M^+ 59%), 313 (33), 312 (80), 284 (24), 58 (47), 44 (28), 43 (100), 18 (100).

3.5. Kermesic acid

1-Methyl-3,5,6,8-tetrahydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid was obtained by alkaline hydrolysis under stronger conditions, followed by acidification. The product was characterised as the tetramethyl ether.

3.5.1. Methyl 3,5,6,8-tetramethoxy-1-methylanthra-9,10-quinone-2-carboxylate (**1a**, R=R′=Me)

To a suspension of methyl 3,5,6,8-tetrahydroxy-1-methylanthra-9,10-quinone-2-carboxylate (25 mg, 0.073 mmol) in dry acetone (10 cm^3) containing potassium carbonate

(1.00 g, 7.3 mmol) dimethyl sulfate (0.50 cm^3, 0.67 g, 5.3 mmol) was added and the mixture refluxed for 24 h. The cooled mixture was poured into ice-cold water (100 cm^3) and extracted with dichloromethane (30 cm^3), the extract dried, concentrated and the brown solid chromatographed on silica gel (chloroform) to give a yellow solid (26 mg, 89%), mp 196 °C and mixed mp 196 °C (lit.[6] Brassard); R_f 0.60 (silica gel, chloroform–ethyl acetate). δ_H (80 MHz, $CDCl_3$) 2.63 (3H, s, 1-Me), 3.93–3.96 (12H, 4s, 4OMe), 3.97 (3H, s, 2-MeOC=O), 6.76 (1H, s, 7-H), 7.50 (1H, s, 4-H); *m/z* 401 (M^++H, 26%), 400 (M^+, 100%), 386 (47), 385 (77), 383 (26), 371 (64), 369 (25), 354 (24), 353 (23), 339 (21).

3.5.2. 6-Chloro-5,8-dihydroxy-2-methoxynaphtho-1,4-quinone (*11*, R=Me, R′=H)

6-Chloro-2,5,8-trihydroxynaphtho-1,4-quinone (1.36 g, 5.0 mmol) in BF_3·MeOH complex (10 cm^3) was refluxed for 2 h, allowed to cool and then poured into water (100 cm^3). The mixture was carefully treated with sodium carbonate solution until gas evolution ceased, and the suspended solid was filtered, washed and air dried to give a red-black product (0.98 g, 89%), mp 182–186 °C. δ_H (80 MHz, $CDCl_3$) 3.95 (3H, s, 2-Me), 6.19 (1H, s, 3-H), 7.35 (1H, s, 7-H), 12.15 (2H, 2s, 5-OH, 8-OH, exch. D_2O); *m/z* 256 (M^+, 5%), 254 (M^+−2, 100%).

3.5.3. iso-Propyl 6-methoxy-3,4,8-trihydroxy-1-methyl-anthra-9,10-quinone-2-carboxylate (*12b*, R=Me, R^1=H, R^2=^{i}Pr)

A stirred solution of 6-chloro-5,8-dihydroxy-2-methoxynaphtho-1,4-quinone (25 mg, 0.010 mmol) with (*E*)- and (*Z*)-3-isopropoxycarbonyl-2,4-bis(trimethylsilyloxy)penta-1,3-dienes **8b** (66 mg, 0.02 mmol) in dry toluene (5 cm^3) was refluxed for 48 h. The mixture was then evaporated to dryness and purified by column chromatography on silica gel (chloroform) to afford an orange solid (16 mg, 42%), which crystallised (toluene) as orange needles, mp 246–249 °C. δ_H (80 MHz, $CDCl_3$) 1.46 (6H, d, $(CH_3)_2CHOCO$, *J* 6 Hz), 3.00 (3H, s, 1-Me), 3.99 (3H, s, 6-OMe), 5.41 (1H, sept. $OCOCH(CH_3)_2$ *J* 6 Hz), 6.72 (1H, s, 7-H), 7.83 (1H, s, 4-H), 10.31 (1H, s, 3-OH, exch. D_2O), 13.18, 13.82 (2H, 2s, 5-OH, 8-OH, exch. D_2O); *m/z* 387 (M^++H, 11), 386 (M^+, 51%), 344 (19), 343 (20), 328 (11), 327 (60), 326 (100), 298 (14), 58 (14), 43 (40), 18 (10).

3.5.4. 6-Chloro-2,5,8-trihydroxy-3-(1-methyl-2-ethoxy-carbonyl-3-oxobutyl)naphtho-1,4-quinone (*13*)

To a stirred solution of 6-chloro-2,5,8-trihydroxynaphtho-1,4-quinone (0.050 g, 0.180 mmol) and (*E*)- and (*Z*)-3-ethoxycarbonyl-3-penten-2-ones (0.050 g, 0.320 mmol) in DMF (5 cm^3) at ambient temperature, piperidine (1 drop) was added. After 24 h, the mixture was acidified with 0.5 M hydrochloric acid (50 cm^3) and extracted with dichloromethane, and the extracts were dried (magnesium sulfate), filtered and concentrated to give a red solid, which was purified by column chromatography (SiO_2, chloroform) to give a dark red solid (0.067 g, 94%), which crystallised (ethanol) as dark red prisms, mp 134–141 °C. δ_H (80 MHz, $CDCl_3$), 1.28 (3H, d, 1-CH_3, *J* 7 Hz), 1.32 (3H, t, CH_3CH_2OCO, *J* 7 Hz), 2.18 (3H, s, CH_3CO), 4.1–4.5 (4H, 2q and d, CH_3CH_2OCO, 1-H and 2-H, *J* 7 Hz), 7.31 (1H, s, 7-H), 11.30 (1H, s, 8-OH, exch. D_2O); *m/z* 398 (M^+, 66%), 352 (26), 351 (35), 350 (53), 308 (56), 268 (31), 266 (68), 238 (26), 233 (38), 58 (30), 43 (100), 18 (40).

3.6. Crystal data

Compound **3**: $C_{29}H_{10}Cl_2O_{10}$ (reported as dimeric in X-ray examination), *M* 479.16, triclinic, space group *PI*, *a*=6.756(4) Å, *b*=9.329(7) Å, *c*=11.536(9) Å, *V*=676.4(8) $Å^3$, *Z*=3, μ=0.425 mm^{-1}; 1913 independent reflections (R_{int}=0.0484), *R* indices (all data) R_1=0.0894, wR_2=0.1282.

Compound **9**: $C_{14}H_9ClO_7$, *M* 324.66, monoclinic space group *C*2/*c*, *a*=16.0510(8) Å, *b*=5.5590(8) Å, *c*=30.980(8) Å, *V*=27,437(9) $Å^3$, *Z*=8, μ=0.313 mm^{-1}, 1826 independent reflections (R_{int} 0.0742), *R* indices (all data) R_1 0.1202, wR_2=0.2532.

Compound **12a**: $C_{21}H_{16}O_{10}$, *M* 428.34, triclinic, space group *PI*, *a*=8.295(4) Å, *b*=8.8970(10) Å, *c*=12.799(8) Å, *V*=922.0(7) $Å^3$, *Z*=2, μ=0.125 mm^{-1}, 2459 independent reflections (R_{int} 0.0518), *R* indices, all data: R_1=0.0836, wR_2=0.1125.

Acknowledgements

Financial support is acknowledged from the SPUR initiative (DTI) accessed by Mr. M. Armitage of European Colour. We thank Prof. S.M. Roberts (Exeter University) and Prof. M. Hursthouse (University of Wales, Cardiff) for facilitating and effecting X-ray structural determinations. Discussion and critical comments from late Mr. G. Marshall (European Colour) are also greatly appreciated.

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10. The 2-, 5- and 8-OH groups in **3** (form 1) are hydrogen-bonded as seen in the ^{1}H NMR spectrum with δ (DMSO-d_6) at 12.75 (br s), 11.70, 13.35 ppm, respectively, cf. ($CDCl_3$) (Sadtler 19857), 10.34 for lawsone (2-hydroxynaphtho-1,4-quinone and δ Me_2CO (Sadtler 3230), 8.35 for 2-naphthol. No NMR data for the 2-OH are given in Ref. 9 by Farina, F.; Martinez-Utrilla, R.; Parades, M. C. *Synthesis* **1981**, 300 , who do not list the 2-OH group in data for 2-hydroxy-5,8-dimethoxynaphth-1,4-quinone.