Synthesis of carminic acid, the colourant principle of cochineal

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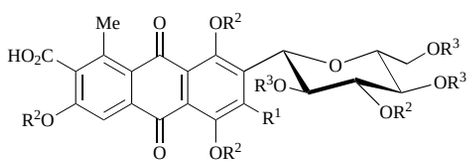
The first synthesis of carminic acid (7β-D-glucopyranosyl-3,5,6,8-tetrahydroxy-1-methyl-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid) is described. Selective *C*-glycosylation at the 7-position of ethyl and benzyl 3,5,8,9,10-pentamethoxy-1-methylanthracene-2-carboxylates with 2,3,4,6-tetra-*O*-benzyl-1-trifluoroacetyl-α-D-glucopyranose afforded intermediates which were oxidised to ethyl and benzyl 3,5,8-trimethoxy-1-methyl-9,10-dioxo-7-(2′,3′,4′,6′-tetra-*O*-benzyl-β-D-glucopyranosyl)-9,10-dihydroanthracene-2-carboxylate respectively. The benzyl compound was hydrogenolysed and the ethyl analogue hydrogenolysed and hydrolysed to give the same product, which was tetraacetylated and demethylated to afford 6-deoxycarminic acid tetraacetate, 3,5,8-trihydroxy-1-methyl-9,10-dioxo-7-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-9,10-dihydroanthracene-2-carboxylic acid. The pentamethoxy intermediates were obtained from 2-chloronaphthazarin by Diels–Alder addition to 3-alkoxycarbonyl-2,4-bis(trimethylsiloxy)penta-2,4-dienes to give alkyl 6-deoxykermesates. Methylation afforded the corresponding trimethyl ethers, which by reductive methylation gave the required pentamethoxy compounds. By known steps 6-deoxycarminic acid tetraacetate was converted into the 5,8,9,10-bisquinone, acetoxylation of which gave carminic acid octaacetate. Acidic hydrolysis afforded carminic acid.

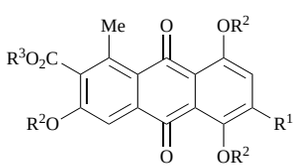
Introduction

Carminic acid[1,2] **1a**, the oldest known and first structurally recognised[3] member of the *C*-glycosides,[4] is obtained from the dried bodies of females of the scale insect species *Dactylopius coccus* Costa which feeds on wild cacti, *Opuntia* spp. and *Nopallea coccinellifera* indigenous to Peru, Mexico and the Canary Islands. It was first isolated in crystalline form in 1858 and the structure was established by Dimroth[5] with modifications by others[6–8] while the β stereochemistry of the *C*-glucosidic bond was assigned later and confirmed by chemical and spectroscopic methods.[9,10] Our first synthesis has been reported[11] and more recently other retrosynthetic schemes have been described.[12] Carminic acid is reputed to possess anticancer activity[13,14] and it is a distant relative of the antibiotics carminomycin and carminomycinone. Its usefulness as a colourant of antiquity is based on the carmines which are the aluminium and calcium lakes. The cochineal extract of commerce is known as Colour Index (CI) No. 75740 and the permitted colour E120.



1

a; R^1 = OH, R^2 = R^3 = H
b; R^1 = R^2 = R^3 = H
c; R^1 = OAc, R^2 = R^3 = Ac
d; R^1 = R^3 = H, R^2 = Me
e; R^1 = H, R^2 = Me, R^3 = Ac
f; R^1 = R^2 = H, R^3 = Ac
g; R^1 = H, R^2 = R^3 = Ac



2

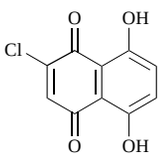
a; R^1 = OH, R^2 = R^3 = H
b; R^1 = R^2 = R^3 = H
c; R^1 = R^2 = H, R^3 = Me
d; R^1 = R^2 = H, R^3 = Et
e; R^1 = R^2 = H, R^3 = Bn
f; R^1 = H, R^2 = R^3 = Me
g; R^1 = H, R^2 = Me, R^3 = Et
h; R^1 = H, R^2 = Me, R^3 = Bn

Results and discussion

Kermesic acid **2a**, the aglycone of carminic acid, has been synthesised[15,16] and its use or that of its methyl ester tetramethyl ether appeared initially to be a simple approach to the synthesis of carminic acid. However, an appropriately masked kermesic acid failed completely to undergo *C*-glycosylation, a result attributable to steric hindrance at the 7-position. It was feasible that 6-deoxykermesic acid **2b** would be free of this restriction and thus responsive to glycosylation although this might occur at either the 6- or 7-position or both, to afford 6-deoxycarminic acid or 7-deoxycarminic acid. This approach was of particular interest since 6-deoxycarminic acid **1b** had been obtained by degradation and reconverted into carminic acid earlier this century[17] by Thiele acetoxylation. Thus 6-deoxycarminic acid **1b** was an appropriate target molecule, with final introduction of the 6-hydroxy group.

In a review,[18] the preparation of 6-deoxykermesic acid **2b** was described by the Friedel–Crafts acylation of 1,4-dimethoxybenzene with 5-methoxy-4-methoxycarbonyl-3-methylphthalic anhydride in an aluminium chloride/sodium chloride melt. However, no practical details were given and the anhydride required a six-stage synthesis. Although we were able to obtain 5-hydroxy-4-methoxycarbonyl-3-methylphthalic anhydride in

one step by a Diels–Alder reaction[19] we were not able to use it for the acylation of 1,4-dimethoxybenzene and therefore sought an alternative method for synthesis of quinone **2b**. A simpler methodology seemed to lie in the Diels–Alder reactions of naphthazarins, particularly of 2-chloronaphthazarin[20–23] **3**, since 2,6-dichloronaphthazarin had been employed earlier[15] in a synthesis of kermesic acid.



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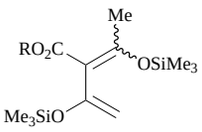
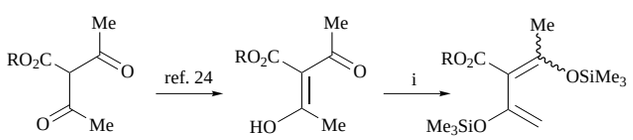


4

a; R = Me
b; R = Et
c; R = Bn

For Diels–Alder reactions we used first the diene from the trimethylsilylation of (*E*)/(*Z*)-3-ethoxycarbonyl-4-methoxypent-3-en-2-one[15] but its protracted preparation led us to employ next the readily prepared bis(trimethylsilyl) ethers of methyl, ethyl and benzyl diacetylacetates which were obtained by acetylation[24] of the corresponding alkyl acetoacetate. By trimethylsilylation with chlorotrimethylsilane (TMSCl) in the presence of triethylamine (as depicted in Scheme 1) a mixture



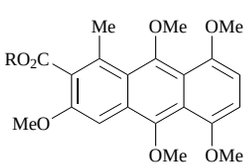
4a–c

Scheme 1 *Reagents:* (i) method (A) *N*,*O*-bis(trimethylsilyl)acetamide, Et_2O. Method (B) Et_3N, Me_3SiCl, PhH.

of *E* and *Z* isomers of the respective 3-alkoxycarbonyl-2,4-bis(trimethylsiloxy)penta-1,3-diene **4a**–**c** was obtained. By contrast, with *N*,*O*-bis(trimethylsilyl)acetamide in dry diethyl ether, compounds **4a** and **4c** were obtained as *Z*-isomers while compound **4b** was obtained as a mixture.[25]

Diels–Alder addition of 2-chloronaphthazarin **3** in refluxing toluene to the dienes **4a**–**c**, either as *E*/*Z* mixture or in the *Z* form, afforded the corresponding alkyl 6-deoxykermesate **2c**–**e** in excellent yield after desilylation in warm, damp tetrahydrofuran (THF) (see Scheme 2).

For the *C*-glycosylation of compounds **2c**–**e** by a substitution reaction, protection of the phenolic system was necessary and a more activated tricyclic structure was desirable. Therefore we prepared first the trimethoxy compounds **2f**–**h** from the alkyl 6-deoxykermesates by methylation with dimethyl sulfate (DMS) in acetone solution containing potassium carbonate, and the number of methoxy groups in these compounds was also increased by reductive methylation. The phase-transfer method[26] with the respective trimethoxy compound **2f**–**h** and sodium dithionite afforded the corresponding 9,10-dianion, which was methylated with dimethyl sulfate to give pentamethoxy series **5a**–**c**. Their solutions were sensitive to light in the



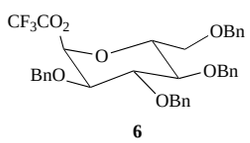
5

a; R = Me
b; R = Et
c; R = Bn

presence of air or water, with partial formation of the 9,10-quinone. For the synthesis of *C*-glycosides, methoxy-, dimethoxy- and polymethoxy-benzenes have been treated with a wide variety of 1-substituted 2,3,4,6-tetra-*O*-benzyl-D-glucose derivatives including the fluoride, chloride, bromide, 4-nitrobenzoate, 3,5-dinitrobenzoate, 2-pyridylthio, trichloroimidate and the trifluoroacetate under Friedel–Crafts conditions.[4]

In earlier work with methoxybenzenes[27] the 1-trifluoroacetate **6** of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose had been used for *C*-glycosylation. Initially for the formation of compound **6** in high yield, 2,3,4,6-tetra-*O*-benzyl-D-glucose in dichloromethane was allowed to react with a large excess of trifluoroacetic anhydride (TFAA) although subsequently a moderate excess (4 mol) was used over a longer reaction time with spectral monitoring of the reaction mixture. Compound **6** was found to be an easily hydrolysable oil which was best prepared as required, and from its ^{1}H NMR spectrum was the α isomer [$\delta_H(CDCl_3)$ 6.37, $J_{1,2}$ 3.5 Hz].

Our first experiments on the *C*-glycosylation of the pentamethoxy compound **5b** with compound **6** were carried out in



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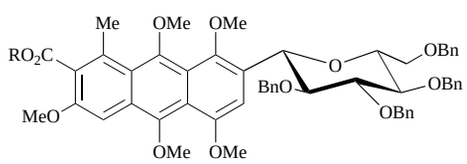
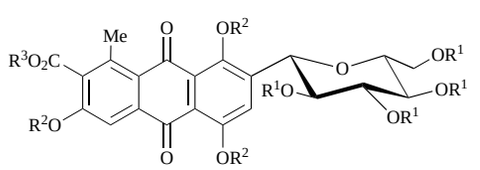


7

a; R = Et
b; R = Bn

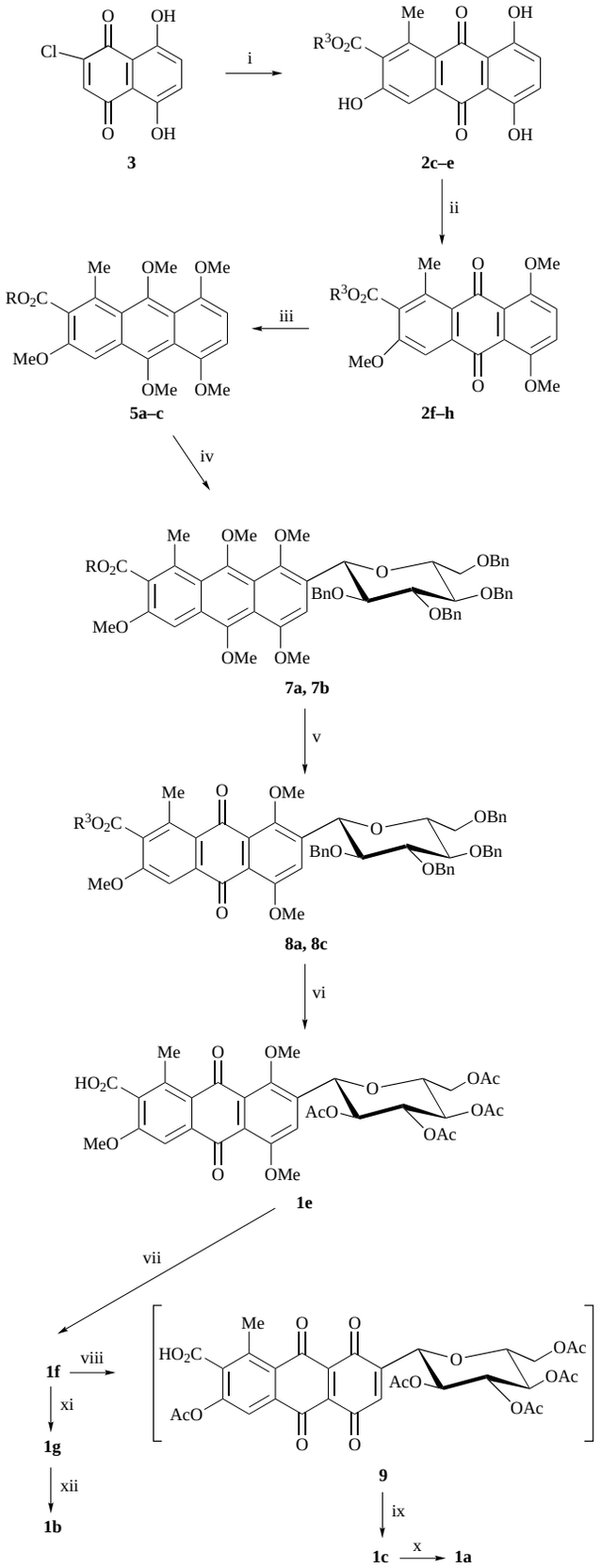


8

a; R^1 = Bn, R^2 = Me, R^3 = Et
b; R^1 = H, R^2 = Me, R^3 = Et
c; R^1 = R^3 = Bn, R^2 = Me

acetonitrile solution in the presence of boron trifluoride–diethyl ether at ambient temp. Thus ethyl 3,5,8,9,10-pentamethoxy-1-methyl-7-(2′,3′,4′,6′-tetra-*O*-benzyl-β-D-glucopyranosyl)anthracene-2-carboxylate **7a** was obtained in 40% yield from reagents **6** and **5b**. By-products were present due to the action of trifluoroacetic acid (TFA) and boron trifluoride–diethyl ether at this temp. Under milder conditions of reaction in dichloromethane solution over a period of 24 hours from −40 °C to ambient temp. the benzyl compound **7b** was obtained in 78% yield without by-product formation from substrates **6** and **5c**.

The chemical shifts in the aromatic region of the ^{1}H NMR [400 MHz, chemical-shift correlation (COSY)] spectrum of the products **7a** and **7b** indicated that only one structural isomer was present through substitution at the 7-position. *C*-Glycosylation of compounds **5b**,**5c** would be expected at this site due to its activation by the 3-methoxy group since the 2-alkoxycarbonyl group would deactivate the 6-position (as depicted in Fig. 1). It was indeed predicted from quantum mechanical calculations that the electron density at the 7-position would be 40% greater than at the 6-position. The 4-position for steric reasons would be likely to be inert towards glycosylation.



Scheme 2 *Reagents and conditions:* (i) (for **2c**), **4a**, MePh, reflux; THF–water and similarly with **4b** (for **2d**) and with **4c** (for **2e**); (ii) Me_2CO, DMS, K_2CO_3; (iii) $Na_2S_2O_4$, HO^-, Bu_4N^+ Br^-, N_2, DMS; (iv) (for **7a**), **6**, MeCN; $BF_3{\cdot}Et_2O$, room temp., 30 min (for **7b**), **6**, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 24 h, −40 °C to room temp.; (v) (for **8a**) Jones reagent (for **8c**) PCC; (vi) (from **8a**) Pd–C, H_2, $MeOH^-$ AcOH; HO^-, MeOH; H_3O^+; Ac_2O, C_5H_5N, DMAP (from **8c**), Pd–C, H_2, THF, HCl; Ac_2O, C_5H_5N, DMAP, CH_2Cl_2 (cat.); (vii) BBr_3, CH_2Cl_2, −80 °C to room temp., 24 h; (viii) Ac_2O, reflux, 1 h; $Pb(OAc)_4$; (ix) H_2SO_4 cat.; (x) EtOH, HCl, reflux 1 h; (xi) Ac_2O, cat. H_2SO_4, room temp.; (xii) MeOH, HCl, reflux

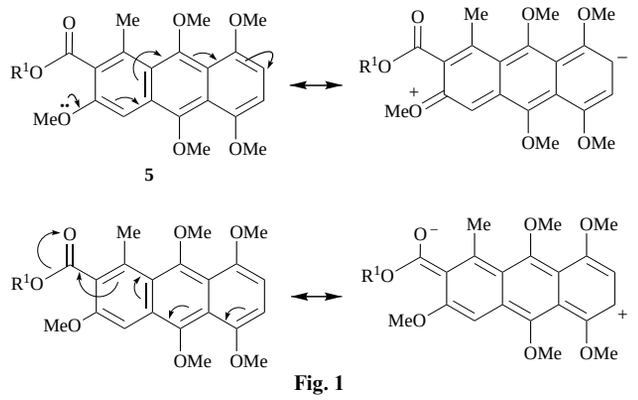


Fig. 1

Compound **7a** was selectively oxidised to the 9,10-quinone **8a** with Jones reagent[28] and oxidation of compound **7b** with pyridinium chlorochromate (PCC)[29] gave the 9,10-quinone **8c** without formation, in either case, of the isomeric 5,8-quinone.

Catalytic hydrogenolysis of the ethyl compound **8a** with Pd–C in methanol containing acetic acid afforded compound **8b** in 83% yield. Saponification of ethyl ester **8b** with methanolic sodium hydroxide gave a 75% yield of the corresponding acid **1d**, which was acetylated to give tetraacetate **1e** in 65% yield.

The tetraacetate **1e** was also isolated in 41% yield together with partially acetylated material (26%) and an impurity (24%) by acetylation of the tetraol product **1d** (after re-formation of the 9,10-quinone from the intermediate leuco compound) from catalytic hydrogenolysis of the benzyl compound **8c** in THF containing Pd–C and some hydrochloric acid.

By examination of the ^{1}H NMR spectrum of the acetate **1e** rather than those of its tetra-*O*-benzyl precursors **8a** and **8c**, clearer signals were obtained for the pyranose protons at C-1′, C-2′, C-3′ and C-4′. The β-configuration at C-1 in these compounds was readily apparent from the *J*-values of the respective axial pyranose ring protons in the ^{1}H NMR spectra (500 and 400 MHz, COSY respectively) by comparison with known reference compounds and reported values.[27,30]

By demethylation of compound **1e** in dichloromethane with boron tribromide[31–33] at 0 °C over a period of 24 h the 3,5,8-trihydroxy compound **1f** was obtained in 72% yield. Peracetylation of compound **1f** gave 6-deoxycarminic acid heptaacetate **1g** which was identical in mp, mixed mp, ^{1}H NMR and IR spectra with a sample prepared from carminic acid[17] **1a** by reduction in acetic acid with zinc dust followed by peracetylation.

The 2′,3′,4′,6′-tetraacetate **1f** was converted into the 2′,3,3′,4′,6′-pentaacetate by acetylation at 100 °C with acetic anhydride. Oxidation of this pentaacetate with lead tetraacetate then afforded the bis-quinone **9**, which by reaction *in situ* with a small quantity of sulfuric acid underwent Thiele acetoxylation[17,34] to give, in 82% yield, carminic acid octaacetate **1c**, identical in mp and mixed mp with the octaacetate of natural carminic acid. Carminic acid **1a**, which crystallised as deep red prisms from methanol, was obtained by hydrolysis of the octaacetate with ethanolic hydrochloric acid.

From the 2D-COSY-45 spectrum of the glucose ring of the octaacetate **1c** it was apparent that rotation around the *C*-glycosidic bond is restricted by the 2′-acetoxy group and that the two participant rotamers are distinguishable.

Experimental

IR spectra were recorded in the range 600–4000 cm^{-1} on a Perkin-Elmer 1420 spectrometer, and electronic spectra in the range 200–600 nm were determined in spectroscopic grade methanol on a Perkin-Elmer Lambda 9/UV/VIS/NIR spectrophotometer. ^{1}H NMR spectra were recorded in deuteriated solvents at 60, 80, 200 and 500 MHz on Varian T60, CFT-20, Jeol FX200 and Bruker AM-500 spectrometers with tetra-

methylsilane as internal standard. Coupling constants (J) are in Hz. Certain ^{13}C and high-resolution ^{1}H NMR spectra were obtained at 400 MHz through the SERC facility at the University of Warwick. Election-impact mass (EIMS) spectra were recorded at 70 eV with a direct-insertion probe or septum inlet. Fast-atom bombardment mass spectra (FAB-MS) (low and high resolution) and accurate mass determinations were carried out by the SERC Centre at the University College of Swansea. Optical rotations were measured on a Perkin-Elmer 141 spectrometer, with $[\alpha]_D$-values given in units of 10^{-1} deg cm^2 g^{-1}. TLC was performed on commercial silica gel$_{254}$ plates (0.25 mm). Kieselgel 60 (40–60 μm) was used for flash chromatography and silica gel for column chromatography. GLC was carried out on glass columns (2.5 mm × 76 cm) at 200 °C with 5% OV17 on Celite (100–120 BSS mesh) with nitrogen as carrier gas.

Mps (uncorrected) were determined using an electrothermal digital apparatus. Elemental analyses were carried out by Butterworth Labs. and by Medac Ltd., Brunel University. Solvents and reagents were purified where necessary by standard techniques.[35] Jones reagent refers to an aqueous solution of chromium trioxide (267 g) with sulfuric acid (230 cm^3) made up to 1 dm^3. Light petroleum refers to the fraction with distillation range 60–80 °C.

Molecular-modelling calculations were made on a Vax computer through CHEM-X in which structure full optimisation was effected with the minimal neglect of differential overlap (MNDO) molecular orbital method from the MOPAC quantum mechanics package.

Alkyl diacetylacetates

Methyl, ethyl and benzyl diacetylacetates were prepared by acetylation of alkyl acetoacetates.[25] They existed (from their ^{1}H NMR spectral data) in 100% enol form.

3-Alkoxycarbonyl-2,4-bis(trimethylsiloxy)penta-1,3-dienes 4a–c

Method A. To a stirred solution of the alkyl or aralkyl diacetylacetate (0.05 mol) in dry diethyl ether (25 cm^3) was added *N*,*O*-bis(trimethylsilyl)acetamide (30 g, 0.15 mol) and following the initial exothermic reaction the mixture was kept for 100 h, when GLC indicated complete reaction. The faintly orange solution was distilled to remove, first, solvent, and then *N*,*O*-bis(trimethylsilyl)acetamide *in vacuo*, to leave a light orange oil in quantitative yield in each case. This method is stated to result in the more thermodynamically stable *Z* form.[36]

(*Z*)-3-*Methoxycarbonyl*-2,4-*bis*(*trimethylsiloxy*)*penta*-2,4-*diene* **4a**.—^{1}H NMR data showed *compound* **4a** to consist of the *Z*-form (Found: C, 51.1; H, 8.5. $C_{13}H_{26}O_4Si_2$ requires C, 51.6; H, 8.6%); ν_{max}(film)/cm^{-1} 3120 (=C–H) 2960s (C–H), 1710 (C=O, ester) and 1630 and 1605s (diene); δ_H($CDCl_3$) 0.11 (9 H, s, Me_3Si), 0.18 (9 H, s, Me_3Si), 2.17 (3 H, s, Me), 3.6 (3 H, s, OMe) and 4.16 and 4.35 (2 H, 2 s, $=CH_2$); *m*/*z* 302 (M^+, 33%).

(*E*)- *and* (*Z*)-3-*Ethoxycarbonyl*-2,4-*bis*(*trimethylsiloxy*)*penta*-1,3-*diene* **4b**.—The spectral data obtained in our work on this compound agreed with those of a previous preparation.[25]

(*Z*)-3-*Benzyloxycarbonyl*-2,4-*bis*(*trimethylsiloxy*)*penta*-1,3-*diene* **4c**.—The ^{1}H NMR spectrum indicated that *product* **4c** was the *Z*-isomer (Found: C, 60.4; H, 7.85. $C_{19}H_{30}O_4Si_2$ requires C, 60.3; H, 8.0%); *m*/*z* 287 ($M^+ - Bn$, 34%), 197 (17), 91 (100), 73 (62) and 43 (15).

Method B. To a mixture of dry triethylamine (25.3 g, 0.25 mol) and TMSCl (38.0 g, 0.25 mol) in sodium-dried benzene (100 cm^3) was added a solution of methyl diacetylacetate (15.9 g, 0.10 mol) in benzene (50 cm^3) and the mixture was stirred for 24 h at ambient temp., when GLC showed complete silylation. Removal of excess of TMSCl and benzene *in vacuo* left a pale orange liquid, which was distilled, bp 70–71 °C at 0.35 mmHg, to give compound **4a** as a faintly yellow oil (28.4 g, 94%) (Found: C, 51.1; H 8.5%); the δ_H values showed the product to be a mixture of *E* and *Z* forms in the ratio 3:4 respectively.

2-Chloro-5,8-dihydroxynaphtho-1,4-quinone (2-chloronaphthazarin) 3

(i) From 1,5-dinitronaphthalene.[20,21]. Naphthazarin was obtained as a deep purple-red solid (39%), mp 238 °C (lit.,[21,22] 235–237 °C); ν_{max}(KBr)/cm^{-1} 3060w (=C–H), 1610 (C=O) and 1578 (aryl); δ_H(80 MHz; $CDCl_3$) 7.13 (4 H, s, 2-, 3-, 6-, 7-H) and 12.37 (2 H, s, 5- and 8-OH, exch. D_2O); *m*/*z* 190 (M^+, 100%), 189 (29), 134 (11) and 108 (14).

Chlorination[20] gave the yellow-red adduct, 2,3-dichloro-5,8-dihydroxy-2,3-dihydronaphtho-1,4-quinone (99%), mp 200–202 °C; ν_{max}(KBr)/cm^{-1} 3300 (O–H), 3060 (C–H, arom), 2980w (C–H, aliph), 1645 (C=O) and 1575 (aryl); δ_H(80 MHz; $CDCl_3$) 4.70 (2 H, s, 2- and 3-H), 7.31 (2 H, s, 6- and 7-H) and 11.25 (2 H, s, 5- and 8-OH, exch. D_2O); *m*/*z* 264 (M^+, 3%) and 262 (M^+, 16).

The adduct obtained by ethanolic dehydrochlorination gave 2-chloronaphthazarin **3** as purple-black needles with a green metallic lustre (85%), mp 182 °C (lit.,[20] 176 °C) (Found: C, 53.7; H, 2.3. Calc. for $C_{10}H_5ClO_4$: C, 53.5; H, 2.2%); ν_{max}(KBr)/cm^{-1} 3460br (O–H), 3060w (C–H, arom), 1620 (C=O, quinone) and 1565 (aryl); δ_H($CDCl_3$) 7.18 (2 H, s, 6-H and 7-H), 7.25 (1 H, s, 3-H) and 12.28 and 12.33 (2 H, 2 s, 5- and 8-OH, exch. D_2O); *m*/*z* 226 (M^+, 32%) and 224 (M^+, 100).

(ii) Similarly to other naphthazarins.[23] Compound **3** was obtained in low yield by the reaction of 2-chloro-1,4-dihydroxybenzene with maleic anhydride in an aluminium/sodium chloride melt, as a purple-black substance having similar spectral properties to the product from method (i), above.

Reaction of (*E*)- and (*Z*)-3-alkoxycarbonyl-2,4-bis(trimethylsiloxy)penta-1,3-dienes with 2-chloronaphthazarin 3 to give alkyl 6-deoxykermesates 2c–e

To a refluxing solution of 2-chloronaphthazarin **3** (0.01 mol) in sodium-dried toluene (50 cm^3) was slowly added a solution of the appropriate 3-alkoxycarbonyl-2,4-bis(trimethylsiloxy)-penta-1,3-diene (0.02 mol) in dry toluene (20 cm^3) dropwise over a period of 8 h and the mixture was then refluxed for a further 16 h. The solvent was then removed *in vacuo*, and the residue was dissolved in tetrahydrofuran (THF) containing 1% water and left for 24 h, after which silica gel (18 g) was added and the mixture was evaporated to dryness *in vacuo*. The silica gel containing the crude product was added to the top of a column of silica gel and the product was eluted with chloroform. Evaporation of the eluate afforded the crude product, which was then recrystallised.

Methyl 3,5,8-trihydroxy-1-methyl-9,10-dioxo-9,10-dihydroanthracene-2-carboxylate 2c. 2-Chloronaphthazarin **3** (0.200 g, 0.89 mmol) and (*E*)- and (*Z*)-3-methoxycarbonyl-2,4-bis(trimethylsiloxy)penta-1,3-diene **4a** (0.538 g, 1.78 mmol) were refluxed together in dry toluene (6 cm^3), and after chromatography *title compound* **2c** (0.227 g, 78%) was obtained as orange needles with a golden lustre, mp 263–264 °C (from nitrobenzene) (Found: C, 62.5; H, 3.7. $C_{17}H_{12}O_7$ requires C, 62.2; H, 3.7%); ν_{max}(KBr)/cm^{-1} 3220br (O–H), 2980, 2960w (C–H, aliph), 1680 (C=O, ester), 1620 (C=O, quinone) and 1575 aryl; δ_H($CDCl_3$) 2.98 (3 H, s, 1-Me) 4.04 (3 H, s, CO_2Me), 7.23 and 7.24 (2 H, 2 s, 6- and 7-H), 7.82 (1 H, s, 4-H), 10.27 (1 H, s, 3-OH, D_2O exch.), 12.60 (1 H, s, 5-OH, D_2O exch.) and 13.08 (1 H, s, 8-OH, D_2O exch.); *m*/*z* 328 (M^+, 53%).

Ethyl 3,5,8-trihydroxy-1-methyl-9,10-dioxo-9,10-dihydroanthracene-2-carboxylate 2d. *Compound* **2d** was obtained as an orange solid (76%), giving orange needles with a golden lustre on crystallisation, mp 230–231 °C (from benzene) (Found: C, 62.9; H, 4.1. $C_{18}H_{14}O_7$ requires C, 63.1, H, 4.1%); ν_{max}(KBr)/cm^{-1} 3220br (O–H), 2980 and 2960w (C–H, aliph), 1680 (C=O, ester), 1620 (C=O, quinone) and 1575 (aryl); δ_H($CDCl_3$) 1.48 (3 H, t, *J* 9, $CO_2CH_2CH_3$), 3.01 (3 H, s, 1-Me), 4.55 (2 H, q, *J* 9,

$CO_2CH_2CH_3$), 7.28 (2 H, s, 6- and 7-H), 7.85 (1 H, s, 4-H) 10.41 (1 H, s, 3-OH, D_2O exch.), 12.67 (1 H, s, 5-OH, D_2O exch.) and 13.15 (1 H, s, 8-OH, D_2O exch.); *m/z* 342 (M^+, 100%).

Benzyl 3,5,8-trihydroxy-1-methyl-9,10-dioxo-9,10-dihydroanthracene-2-carboxylate 2e. *Compound* **2e** resulted as an orange solid (0.25 g, 72%), which gave dark red plates, mp 176 °C (from benzene) (Found: C, 68.1; H, 4.1. $C_{23}H_{16}O_7$ requires C, 68.3; H, 4.0%); ν_{max}(KBr)/cm^{-1} 3270br (O–H), 2980, 2960w (C–H, aliph), 1700 (C=O, ester), 1620 (C=O, quinone) and 1570 (aryl); δ_H($CDCl_3$) 2.94 (3 H, s, 1-Me), 5.48 (2 H, s, CO_2CH_2Ph), 7.43 (5 H, s, Ph), 7.8 (1 H, s, 4-H), 10.41 (1-H, s, 3-OH, D_2O exch.), 12.67 (1 H, s, 5-OH, D_2O exch.) and 13.15 (1 H, s, 8-OH, D_2O exch.); *m/z* 404 (M^+, 8%).

Methyl 3,5,8-trimethoxy-1-methyl-9,10-dioxo-9,10-dihydroanthracene-2-carboxylate 2f. *Compound* **2f** was prepared similarly to the benzyl and ethyl compounds (**2g**,**h**) and was obtained as an off-yellow solid in 82% yield, R_f 0.29 ($CHCl_3$), which was recrystallised (EtOAc) to give fine yellow needles, mp 249–250 °C (Found: C, 64.65; H, 5.05. $C_{20}H_{18}O_5$ requires C, 64.85; H, 4.90%); ν_{max}(film)/cm^{-1} 2940 and 2840 (C–H, aliph), 1730 (C=O, ester), 1660 (C=O, quinone) and 1580 (aryl); λ_{max}(MeOH)/nm (log ε) 222, (4.49), 267 (4.51) and 419 (3.78); δ_H(80 MHz; $CDCl_3$) 2.62 (3 H, s, 1-Me), 3.93 and 3.95 (12 H, 2 s, CO_2Me, 3-, 5- and 8-OMe), 7.23 (2 H, s, 6- and 7-H) and 7.51 (1 H, s, 4-H); *m/z* 370 (M^+, 46%).

Ethyl 3,5,8-trimethoxy-1-methyl-9,10-dioxo-9,10-dihydroanthracene-2-carboxylate 2g. *Compound* **2g** was synthesised in a similar way to the methyl and benzyl analogues (**2g**,**h**) and was obtained in 85% yield, mp 188–189 °C (from diisopropyl ether); ν_{max}($CHCl_3$)/cm^{-1} 1725, 1670 and 1580; λ_{max}(EtOH)/nm (log ε) 268 (4.57) and 420 (3.84); δ_H(60 MHz; $CDCl_3$), 1.37 (3 H, t, *J* 7, OCH_2CH_3), 2.65 (3 H, s, 1-Me), 3.93 (9 H, 3s, 3 × OMe), 4.45 (2 H, q, *J* 7, OCH_2CH_3), 7.18 (2 H, s, 6- and 7-H) and 7.57 (1 H, s, 4-H).

Benzyl 3,5,8-trimethoxy-1-methyl-9,10-dioxo-9,10-dihydroanthracene-2-carboxylate 2h. A solution of compound **2e** (8.00 g, 0.02 mol) and DMS (15 cm^3, 20.0 g, 0.16 mol) in acetone (100 cm^3) containing anhydrous potassium carbonate (30.0 g, 0.22 mol) was refluxed for 24 h. The solvent was removed *in vacuo*, water (200 cm^3) was added, and the mixture was extracted with dichloromethane. The combined extracts were dried and evaporated to afford *title compound* **2h** as a brown oil which solidified (8.12 g, 92%), and which was recrystallised (EtOH) to give orange needles, mp 211–212 °C (Found: C, 69.75; H, 4.95. $C_{26}H_{22}O_7$ requires C, 69.95; H, 4.95%); ν_{max}(film)/cm^{-1} 3050 (C–H, arom), 2940 and 2850 (C–H, aliph), 1730 (C=O, ester), 1660 (C=O, quinone) and 1585 (aryl); δ_H(80 MHz; $CDCl_3$) 2.58 (3 H, s, 1-Me), 3.90, 3.93 and 3.95 (9 H, 3 s, 3-, 5- and 8-OMe), 5.37 (2 H, s, CO_2CH_2Ph), 7.23 (2 H, s, 6- and 7-H), 7.54 (5 H, s, CO_2CH_2Ph) and 7.50 (1 H, s, 4-H); *m/z* 446 (M^+, 3%).

Reductive methylation of anthraquinones 2f–h

A mixture of the finely divided quinone (2.0 mmol) in THF (20 cm^3) containing tetrabutylammonium bromide (64 mg, 0.2 mmol) was treated under nitrogen with aq. sodium dithionite (12 mmol in the minimum volume of water), and after 15 min aq. potassium hydroxide (2.58 g, 46 mmol in the minimum of water) was added to the vigorously stirred mixture. After 10 min the mixture was cooled to 0 °C, DMS (4.0 cm^3, 5.3 g, 42 mmol) was added, and the mixture was then stirred for 2 h before being allowed to warm to ambient temperature and extracted with dichloromethane; the extract was washed with water, dried and evaporated, and the residue was purified by chromatography or crystallisation, as follows.

Methyl 3,5,8,9,10-pentamethoxy-1-methylanthracene-2-carboxylate 5a. *Compound* **5a** was obtained as a light brown glass (90%) which failed to crystallise; R_f 0.45 ($CHCl_3$) (Found: M^+, 400.1522. $C_{22}H_{24}O_7$ requires *M*, 400.1522); ν_{max}(film)/cm^{-1} 2950 and 2840 (C–H, aliph), 1740 (C=O, ester) and 1620 (aryl); δ_H(80 MHz; $CDCl_3$) 2.85 (3 H, s, 1-Me), 3.71 (3 H, s, 10-OMe), 3.88 (3 H, s, 9-OMe), 3.94 and 3.95 (12 H, 2 s, CO_2Me and 3-, 5- and 8-OMe), 6.62 and 6.64 (2 H, 2s, 6- and 7-H) and 7.48 (1 H, s, 4-H); *m/z* (401, 16%) and 400 (M^+, 65).

Ethyl 3,5,8,9,10-pentamethoxy-1-methylanthracene-2-carboxylate 5b. *Compound* **5b** was obtained in similar fashion as a glass; ν_{max}/cm^{-1} 1725 cm^{-1} (C=O, ester); λ_{max}(EtOH)/nm (log ε) 253 (4.74), 271 (4.69) and 375 (3.93); δ_H(60 MHz; $CDCl_3$) 1.40 (3 H, t, *J* 7, OCH_2CH_3), 2.90 (3 H, s, 1-Me), 3.73 (3 H, s, OMe), 3.97 (12 H, 4 s, 4 × OMe), 4.50 (2 H, q, *J* 7, OCH_2CH_3), 6.65 (2 H, s, 6- and 7-H) and 7.58 (1 H, s, 4-H).

Benzyl 3,5,8,9,10-pentamethoxy-1-methylanthracene-2-carboxylate 5c. *Compound* **5c** was obtained as a light brown viscous syrup (94%), R_f 0.52 ($CHCl_3$), which was crystallised (from diethyl ether–light petroleum, 1 : 1) as fine, light yellow needles, mp 135–137 °C (Found: M^+, 476.1835. $C_{28}H_{28}O_7$ requires *M*, 476.1835); ν_{max}(film)/cm^{-1} 2960 and 2860 (C–H, aliph), 1740 (C=O, ester) and 1630 (aryl); δ_H(80 MHz; $CDCl_3$) 2.83 (3 H, s, 1-Me), 3.71 (3 H, s, 10-OMe), 3.88 (3 H, s, 9-OMe), 3.92 and 3.96 (9 H, 2 s, 3-, 5- and 8-OMe), 5.42 (2 H, s, CO_2CH_2Ph), 6.63 and 6.65 (2 H, 2 s, 6- and 7-H), 7.30–7.42 (5 H, s, CO_2CH_2Ph) and 7.47 (1 H, s, 4-H); *m/z* 477 (21%) and 476 (M^+, 63).

All the pentamethoxy compounds were highly yellow-green fluorescent in CH_2Cl_2 solution. They were readily oxidisable and sensitive to light in solution.

2,3,4,6-Tetra-*O*-benzyl-1-*O*-trifluoroacetyl-α-D-glucopyranose 6

A stirred suspension of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (1.00 g, 1.85 mmol) in dry 1,2-dichloroethane (10 cm^3) under N_2 was treated with TFAA (1.0 cm^3, 1.4 g, 7.1 mmol). From the solution which soon formed, aliquots were withdrawn for ^{1}H NMR examination under dry conditions after removal of solvent *in vacuo*. After 30 min the reaction was 15–20% complete and 100% conversion was obtained after 4 h; compound **6** had δ_H(80 MHz; $CDCl_3$) 3.60–4.90 (15 H, m, sugar H and OCH_2Ph), 5.67 (1 H, dd, *J* 3.5 and 1.5, 2-H), 6.37 (1 H, *J* 3.5, 1-H) and 7.10–7.40 (20 H, m, OCH_2Ph).

Ethyl 3,5,8-trimethoxy-1-methyl-9,10-dioxo-7-(2′,3′,4′,6′-tetra-*O*-benzyl-β-D-glucopyranosyl)-9,10-dihydroanthracene-2-carboxylate 8a

2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose (4.05 g, 7.5 mmol) and TFAA (12 cm^3, 82.5 mmol) were allowed to react in dichloromethane (50 cm^3) for 1 h at ambient temp. after which the solvent, excess of anhydride and TFA were removed. To the glassy residue, **5b** (1 g, 2.5 mmol) in acetonitrile (40 cm^3) was added followed by boron trifluoride–diethyl ether (4.7 cm^3). After being stirred for 30 min the reaction mixture was neutralised with saturated aq. sodium hydrogen carbonate and concentrated *in vacuo.* Water was added and the mixture was extracted with dichloromethane. The dried extract was concentrated, and chromatographed on silica gel [hexane–ethyl acetate (7 : 3, v/v)] to afford ethyl 3,5,8,9,10-pentamethoxy-1-methyl-7-(2′,3′4′,6′-tetra-*O*-benzyl-β-D-glucopyranosyl)anthracene-2-carboxylate **7a** (0.930 g, 40%) as a glass, $[\alpha]_D$ +30.6 (*c* 1, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 1715, 1625, 1455 and 1370; λ_{max}(EtOH)/nm (log ε) 274 (4.72) and 375 (3.79); δ_H(500 MHz; $CDCl_3$) 1.432 (3 H, t, *J* 7, OCH_2CH_3), 2.888 (3 H, s, 1-Me), 3.7–4.0 (4 H, overlapping, 1′-, 2′-, 3′- and 4′-H), 3.652 (1 H, ddd, $J_{5',4'}$ 9.0, $J_{5',6'a}$ 3.5 and $J_{5',6'b}$ 1.5), 3.792 (1 H, dd, $J_{6'b,6'a}$ 11 and $J_{6'b,5'}$ 1.5, 6′-H^b), 3.868 (1 H, dd, $J_{6'b,6'a}$ 11 and $J_{6'b,5}$ 3.5, 6′-H^a), 3.944 (6 H, 2 s, 2 × OMe), 3.980 (3 H, s, OMe), 4.168 (1 H, d, *J* 10.5, $OCHAr$), 4.484 (2 H, q, *J* 7, OCH_2CH_3), 4.528 (1 H, d, *J* 12, $OCHAr$), 4.536 (1 H, d, *J* 10.5, $OCHAr$), 4.654 (1 H, d, *J* 12, $OCHAr$), 4.700 (1 H, d, *J* 11, $OCHAr$), 4.912 (1 H, d, *J* 11, $OCHAr$), 4.964 (1 H, d, *J* 11, $OCHAr$), 5.040 (1 H, d, *J* 11, $OCHAr$), 6.732 (1 H, s, 6-H), 6.90–7.37 (20 H, ArH) and 7.546 (1 H, s, 4-H).

A solution of compound **7a** (1 g, 1.07 mmol) in acetone (120 cm^3) at 0 °C was treated with an excess of Jones reagent and, after 5 min, propan-2-ol (2 cm^3) was added. The mixture was

filtered through Celite and the filtrate, after neutralisation with sodium hydrogen carbonate, was concentrated *in vacuo*. The oil recovered by extraction with ethyl acetate was chromatographed (hexane–ethyl acetate, 7:3 v/v) to give the anthraquinone **8a** (0.823 g, 85%) as a glass, $[\alpha]_D^{20}$ +33 (*c* 1, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 1727, 1672, 1584 and 1465; λ_{max}(EtOH)/nm (log ε) 269 (4.472) and 375 (3.77); δ_H(500 MHz; $CDCl_3$) 1.396 (3 H, t, *J* 7, OCH_2CH_3), 2.638 (3 H, s, 1-Me), 3.626 (1 H, ddd, $J_{5',4'}$ 9.5, $J_{5',6'a}$ 4, $J_{5',6'b}$ 2, 5′-H), 3.718 (1 H, dd, $J_{6'b,6'a}$ 11, $J_{6'b,5'}$ 2, 6′-H^b), 3.75–4.00 (4 H, overlapping, 1′-, 2′-, 3′- and 4′-H), 3.776 (1 H, dd, $J_{6'a,6'b}$ 11, *J* 4.0, 6′-H^a), 3.832 (3 H, s, OMe), 3.842 (3 H, s, OMe), 3.996 (3 H, s, OMe), 4.178 (1 H, d, *J* 11, OC*H*Ar), 4.438 (2 H, q, *J* 7, OCH_2CH_3), 4.504 (1 H, d, *J* 12, OC*H*Ar), 4.566 (1 H, d, *J* 11, OC*H*Ar), 4.572 (1 H, d, *J* 12, OC*H*Ar), 4.660 (1 H, d, *J* 10.5, OC*H*Ar), 4.881 (1 H, d, *J* 10.5, OC*H*Ar), 4.937 (1 H, part B of an AB system, *J* 11, OC*H*Ar), 4.962 (1 H, part A of an AB system, *J* 11, OC*H*Ar), 7.136 (1 H, s, 6-H), 6.80–7.35 (20 H, ArH) and 7.572 (1 H, s, 4-H).

Ethyl 7-β-D-glucopyranosyl-3,5,8-trimethoxy-1-methyl-9,10-dioxo-9,10-dihydroanthracene-2-carboxylate 8b

A solution of the ethyl ester **8a** (1 g, 1.2 mmol) in methanol (400 cm^3) containing 10% Pd–C (0.200 g) and acetic acid (1 cm^3) was hydrogenolysed at ambient temperature and pressure during a period of 6 h. Filtration, and evaporation of the solvent, gave the product **8b** (0.510 g, 85%) as a yellow solid (from diisopropyl ether), mp 142–145 °C (decomp.); $[\alpha]_D^{20}$ −23 (*c* 1, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3600, 3420, 1725, 1670, 1585 and 1468; λ_{max}(EtOH)/nm (log ε), 269 (4.39) and 383 (3.72); δ_H(500 MHz, $CDCl_3$) 1.386 (3 H, t, *J* 7, OCH_2CH_3), 2.586 (3 H, s, 1-Me), 3.5–4.0 (6 H, overlapping, 2′-, 3′-, 4′- and 5′-H and 6′-H_2), 3.982 (3 H, s, OMe), 3.941 (3 H, s, OMe), 3.982 (3 H, s, OMe), 4.417 (2 H, q, *J* 7, OCH_2CH_3), 4.779 (1 H, d, *J* 9, 1′-H), 7.352 (1 H, s, 6-H) and 7.535 (1 H, s, 4-H).

Benzyl 3,5,8-trimethoxy-1-methyl-9,10-dioxo-7-(2′,3′,4′,6′-tetra-*O*-benzyl-β-D-glucopyranosyl)-9,10-dihydroanthracene-2-carboxylate 8c

2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose (1.00 g, 1.85 mmol) and TFAA (1.0 cm^3, 1.49 g, 7.1 mmol) were allowed to react in dichloromethane (10 cm^3) to form the trifluoroacetate as described for compound **6**. After removal of excess of reactant *in vacuo*, a solution of the anthracene **5c** (1.76 g, 3.70 mmol) in dichloromethane (5.0 cm^3) was added. The solution was cooled to −40 °C and cold boron trifluoride–diethyl ether (3.55 mmol) added slowly, after which the temperature was allowed to rise to ambient and the reaction mixture was then stirred for 24 h (under N_2). Following monitoring by TLC and work-up (acidification and dichloromethane extraction), the brown viscous syrup (containing *C*-glycoside **7b**) obtained by evaporation of the mixture was dissolved in dichloromethane (50 cm^3) and the solution stirred with PCC (0.80 g, 3.7 mmol) for 15 min. Ethereal extraction, filtration, evaporation and column chromatography on silica gel (diethyl ether–light petroleum) afforded the title anthraquinone **8c** as a brown syrup (1.400 g, 78%) (Found: $[M + H]^+$, 969.3850. $C_{60}H_{57}O_{12}$ requires *m*/*z*, 969.3850); δ_H(200 MHz; $CDCl_3$) 2.56 (3 H, s, 1-Me), 3.78, 3.86 and 3.92 (9 H, 3 s, 3-, 5- and 8-OMe), 3.50–5.00 (15 H, m, 1′-, 2′, 3′-, 4′- and 5′-H, 6′-H_2 and 4 × OCH_2Ph), 5.37 (2 H, s, CO_2CH_2Ph), 6.70–7.50 (26 H, m, 6-H and 5 × *Ph*) and 7.59 (1 H, s, 4-H); *m*/*z* (FAB) 969 ($[M + H]^+$, 24%).

7-β-D-Glucopyranosyl-1-methyl-3,5,8-trimethoxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid 1d

The quinone **8c** (1.240 g, 1.28 mmol) with 10% Pd–C (0.130 g) in THF containing conc. hydrochloric acid (0.65 cm^3) was hydrogenolysed at atmospheric pressure until no further absorption of hydrogen occurred. After filtration, and aerial oxidation of the filtrate, the recovered material was purified by column chromatography on silica gel (chloroform–ethanol) and the tetraol acid **1d** was obtained as a light yellow glass (0.551 g, 83%), which was directly acetylated.

1-Methyl-3,5,8-trimethoxy-9,10-dioxo-7-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-9,10-dihydroanthracene-2-carboxylic acid 1e

(**i**) The tetraol acid **1d** (0.497 g, 0.959 mmol), pyridine (3.82 g, 3.90 cm^3, 48.2 mmol) and acetic anhydride (0.97 g, 0.90 cm^3, 9.53 mmol) in dry, stirred dichloromethane (50 cm^3) containing 4-(dimethylamino)pyridine (DMAP) (0.012 g, 0.10 mmol) were allowed to react together at ambient temperature until TLC showed absence of **1d**. After work-up [acidification, extraction, and column chromatography on silica gel (gradient elution with chloroform–ethanol)], title acid **1e** was obtained as a pale yellow glass (0.270 g, 41%), R_f 0.45 ($CHCl_3$–MeOH, 4:1) (Found: $[M + H]^+$, 687.1925. $C_{33}H_{35}O_{16}$ requires *m*/*z*, 687.1925); δ_H(400 MHz; $CDCl_3$) 1.779 (3 H, s, 2′-Ac), 1.963, 1.995 and 2.014 (3 × 3 H, 3 s, 3′-, 4′- and 6′-OAc), 2.658 (3 H, s, 1-Me), 3.845, 3.931 and 3.962 (3 × 3 H, 3 s, 3-, 5- and 8-OMe), 3.86–3.90 (1 H, m, 5′-H), 4.07–4.12 (1 H, m, 6′-H^a), 4.17–4.21 (1 H, m, 6′-H^b), 5.00 (1 H, d, *J* 9.7, 1′-H), 5.15–5.20 (1 H, m, 4′-H), 5.35–5.38 (2 H, m, 2′- and 3′-H), 7.275 (1 H, s, 6-H) and 7.499 (1 H, s, 4-H); δ_C(400 MHz; $CDCl_3$) 18.37, 20.38, 20.52 and 20.63 (4 × OAc), 29.57 (1-Me), 56.30, 56.62, 62.28, 63.63, 68.55, 70.86, 74.19, 76.49 and 77.10 (3 × OMe, glucose-H), 106.36, 116.46, 122.22, 126.72, 129.57, 138.57, 139.00, 151.56, 155.61 and 158.80 (C-aryl), 169.25, 169.55, 170.13 and 170.54 (4 × $OCOCH_3$) and 187.50 and 184.34 (quinone C=O); *m*/*z* (FAB) (709 $[M + Na]^+$, 57%) and 687 ($[M + H]^+$, 100).

Other fractions separated were partially acetylated material (0.170 g) and an impurity (0.157 g), R_f 0.98 ($CHCl_3$–MeOH, 4:1), 0.54 ($CHCl_3$–EtOAc, 1:1).

(**ii**) A solution of the ethyl ester **8b** (1 g, 1.83 mmol) in methanol (25 cm^3) was refluxed with 20% aq. sodium hydroxide (25 cm^3) for 6 h. After cooling, the mixture was acidified with conc. HCl, concentrated, extracted with butan-1-ol, and the extracts were evaporated. The residue (crude acid **1d**) was acetylated with acetic anhydride (3 cm^3) in pyridine (6 cm^3) containing DMAP (0.200 g) during 12 h. Work-up afforded the crude acetate, which was crystallised (diisopropyl ether) to give the title acid **1e** (0.815 g, 65%) as a yellow solid, mp 146–148 °C (decomp.); $[\alpha]_D$ −33.3 (*c* 1, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1750, 1675, 1583, 1465, 1370 and 1332; δ_H(500 MHz; $CDCl_3$) 1.818 (3 H, s, OAc), 2.003 (3 H, s, OAc), 2.034 (3 H, s, OAc), 2.054 (3 H, s, OAc), 2.699 (3 H, s, 1-Me), 3.888 (3 H, s, OMe), 3.921 (1 H, ddd, $J_{5',4'}$ 9.5, $J_{5',6'a}$ 5.5, $J_{5',6'b}$ 2.5, 5′-H), 3.970 (3 H, s, OMe), 4.003 (3 H, s, OMe), 4.140 (1 H, dd, $J_{6'b,6'a}$ 12.5, $J_{6'b,5'}$ 2.5, 6′-H^b), 4.234 (1 H, dd, $J_{6'a,6'b}$ 12.5, $J_{6'a,5'}$ 5.5, 6′-H^a), 5.044 (1 H, d, $J_{1',2'}$ 9.5, 1′-H), 5.218 (1 H, dd, $J_{4',5'}$ 9.5, $J_{4',3'}$ 9.5, 4′-H), 5.378 (1 H, dd, $J_{3',2'}$ 9.5, $J_{3',4'}$ 9.5, 3′-H), 5.412 (1 H, dd, $J_{2',3'}$ 9.5, $J_{2',1'}$ 9.5, 2′-H), 7.319 (1 H, s, 6-H) and 7.544 (1 H, s, 4-H).

3,5,8-Trihydroxy-1-methyl-9,10-dioxo-7-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-9,10-dihydroanthracene-2-carboxylic acid (6-deoxycarminic acid tetraacetate) 1f

To a solution of compound **1e** (0.157 g, 0.058 mmol) in dry dichloromethane (10 cm^3) at −80 °C was added M boron tribromide as a solution in dichloromethane (0.60 cm^3, 0.60 mmol) cooled to −80 °C. The temperature of the mixture was allowed to rise slowly to 0 °C and was kept at that value for 24 h. Work-up with 1 M hydrochloric acid, extraction with dichloromethane, drying, filtration and recovery followed by TLC on silica gel ($CHCl_3$–MeOH, 5:1) gave the trihydroxy product **1f**, isolated as an orange-red glass (0.106 g, 72%), R_f 0.26 ($CHCl_3$–MeOH, 5:1) (Found: $[M + H]^+$, 645.1456. $C_{30}H_{29}O_{16}$ requires *m*/*z*, 645.1455); ν_{max}(KBr)/cm^{-1} 3400br (O–H), 2960w and 2840w (C–H, aliph), 1740 and 1630 (C=O), 1570 (aryl), 1430, 1370, 1220 and 1030; δ_H(200 MHz; $CDCl_3$) 1.90 (3 H, s, 2′-OAc), 2.01, 2.02 and 2.12 (3 × 3 H, 3′, 4′ and 6′- OAc), 2.88

(3 H, s, 1-Me), 3.50–5.50 (7 H, m, 7 × glucose-H), 7.37 and 7.51 (2 H, 2 s, 4- and 6-H) and 12.54br and 13.57 (3 H, 3 s, 3-, 5- and 8-OH, exch. D_2O); *m/z* (FAB) 667 ([M + Na]$^+$, 68%) and 645 ([M + H]$^+$, 100).

3,5,8-Triacetoxy-1-methyl-9,10-dioxo-7-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-9,10-dihydroanthracene-2-carboxylic acid (6-deoxycarminic acid heptaacetate) 1g

A solution of the triol acid **1f** (27 mg, 0.042 mmol) in acetic anhydride (2 cm^3) containing conc. sulfuric acid (1 small drop) was stirred for 16 h. The yellow solution was then diluted with dry dichloromethane (20 cm^3), washed with 5% aq. sodium chloride, dried, filtered and evaporated to give a yellow product, which was recrystallised twice (EtOH) to give 6-deoxycarminic acid heptaacetate **1g** (18 mg, 56%) as fine, pale yellow needles, mp 271 °C (decomp.). The mixed mp with 6-deoxycarminic acid heptaacetate, prepared from natural carminic acid, showed no depression. ^{1}H NMR, IR and UV spectral data proved to be identical with that for the compound from the reduction[17] of natural carminic acid with zinc in acetic acid and acetylation of the product ([*a*]$_D$ +87.8, *c* 1, $CHCl_3$). Hydrolysis of the heptaacetate in 0.5 M methanolic hydrochloric acid afforded 7-β-D-glucopyranosyl-3,5,8-trihydroxy-1-methyl-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid (6-deoxycarminic acid) **1b** in 80% yield, mp 286–288 °C (decomp.).

3,5,6,8-Tetraacetoxy-1-methyl-9,10-dioxo-7-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-9,10-dihydroanthracene-2-carboxylic acid (carminic acid octaacetate) 1c

A mixture of compound **1b** (54 mg, 0.084-mmol) in acetic anhydride (3 cm^3) was heated at 100 °C for 1 h to give the 2′,3,3′,4′,6′-pentaacetate and the mixture then allowed to cool to ambient temp. Lead tetraacetate (100 mg, 0.230 mmol) was added and the suspension was stirred for 8 h after which the solution had become greenish-orange due to the presence of the bis-quinone **9**. Conc. sulfuric acid (5 drops) was added, white lead salts soon formed, and the solution became orange coloured. Stirring was continued overnight, dichloromethane (20 cm^3) was added, and the solution was filtered through Celite. The filtrate was washed with 5% aq. sodium chloride, dried and evaporated to give a yellow residue. This was dissolved in ethanol (10 cm^3), the solution was left for 16 h, then filtered to remove traces of lead salts, and the filtrate was evaporated to afford a yellow residue (57 mg, 82%), which was crystallised (EtOH) to give light yellow needles, mp and mixed mp 171 °C with an authentic sample of carminic acid octaacetate **1c**. ^{1}H NMR, IR and UV spectral data proved to be identical with those of a sample of the octaacetate prepared from natural carminic acid.

6-Deoxycarminic acid, obtained by way of the ethyl ester **5b**, gave carminic acid octaacetate **1c**, mp 168–170 °C (from methanol–diisopropyl ether); [*a*]$_D$ +62.3 (*c* 1, $CHCl_3$) in 60% overall yield.

7-β-D-Glucopyranosyl-3,5,6,8-tetrahydroxy-1-methyl-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid, carminic acid 1a

A solution of synthetic carminic acid octaacetate **1c** (25 mg) in ethanol (20 cm^3) containing conc. HCl (1 cm^3) was refluxed for 1 h. The red solution was cooled, then was evaporated to dryness *in vacuo* to give a red glass, which was stored over NaOH pellets for 24 h. Crystallisation (methanol) gave carminic acid **1a** as deep red prisms (15 mg, 100%), mp > 300 °C (lit., no mp) (Found: [M + H]$^+$, 493.0982. $C_{22}H_{21}O_{13}$ requires *m/z*, 493.0982); ^{1}H NMR and IR spectral data proved to be identical with those for the natural product (Merck) which had mp > 300 °C; ν_{max}(KBr)/cm^{-1} 3300br (O–H), 2943w (C–H, aliph), 1693 (C=O), 1635 and 1595; δ_H[400 MHz; $(CD_3)_2SO$] 2.691 (3 H, s, 1-Me), 3.16–3.28 (3 H, m, 3′-H and 6′-H_2), 3.463 (1 H, m, 5′-H), 3.736 (1 H, m, 4′-H), 4.048 (1 H, m, 2′-H), 4.727 (1 H, d, *J* 9.8, 1′-H) and 7.669 (1 H, s, 4-H); δ_C[400 MHz; $(CD_3)_2SO$] 20.24 (1-Me), 61.67 (6′-C), 70.56 (5′-C), 70.73 (2′-C), 73.45 (1′-C), 78.94 (3′-C), 81.99 (4′-C), 111.77 (5-C), 121.46 (2-C), 140.37 (8-C), 147.83 (4-C), 154.32 (3-C), 158.18 (1-C), 160.09 (6-C), 168.49 (2-CO_2H), 186.29 (9-C) and 186.46 (10-C); *m/z* (FAB) 492 ([M + H]$^+$, 25%).

Reduction of natural carminic acid 1a

Carminic acid (Merck) was reduced[17] in acetic acid solution with zinc to give 6-deoxycarminic acid **1b** in 65% yield as a red solid, which gave orange-red needles, mp > 300 °C (from aq. EtOH) contaminated with traces of a persistent nitrogenous impurity (Found: C, 53.3; H, 4.35. Calc. for $C_{22}H_{20}O_{12}$: C, 55.45; H, 4.25%); ν_{max}(KBr)/cm^{-1} 3300br (O–H), 2943w (C–H, aliph), 1740 and 1693 (C=O), 1635 and 1595 (aryl); δ_H(200 MHz; $CDCl_3$) 2.75 (3 H, s, 1-Me), 3.29–3.56 (4 H, m, 3′-, 4′- and 5′-H and 6′-H^a), 3.72–3.81 (1-H, m, 6′-H^b), 3.90–3.99 (1 H, m, 2′-H), 4.78 (1 H, d, *J* 8.8, 1′-H), 7.41 (1 H, s, 6-H) and 7.60 (1 H, s, 4-H); *m/z* (FAB) 499 ([M + Na]$^+$, 5%) and 477 ([M + H]$^+$, 14).

6-Deoxycarminic acid heptaacetate 1g was obtained by peracetylation of 6-deoxycarminic acid **1b** in acetic anhydride, containing a catalytic amount of sulfuric acid, as a yellow solid. Crystallisation (EtOH) gave pale yellow micro-needles (57%), mp 272 °C (decomp.) (lit.,[17] 245–250 °C) (Found: C, 55.9; H, 4.40. Calc. for $C_{36}H_{34}O_{19}$: C, 56.1; H, 4.45%); ν_{max}(KBr)/cm^{-1} 2955 and 2895 (C–H aliph), 1770, 1740, 1675 (C=O), 1600 and 1575 (aryl), 1430, 1415, 1370, 1325, 1285, 1220, 1185, 1100, 1050, 1015, 945, 915, 845 and 825; δ_H(400 MHz; $CDCl_3$) 1.239 (3 H, s, 2′-OAc), 1.991, 2.051 and 2.092 (3 × 3 H, 3 s, 3′-, 4′- and 6′-OAc), 2.307, 2.451 and 2.468 (3 × 3 H, 3 s, 3-, 5- and 8-OAc), 2.64 (3 H, s, 1-Me), 3.870 (1 H, m, 5′-H), 4.094 (1 H, m, 6′-H^a), 4.295 (1 H, m, 6′-H^b), 4.819 (1 H, d, *J* 9.7, 1′-H), 5.164 (2 H, m, 3′- and 4′-H), 5.378 (1 H, m, 2′-H), 7.528 (1 H, s, 6-H) and 7.818 (1 H, s, 4-H); *m/z* (FAB) 793 ([M+Na]$^+$, 100%) and 771 ([M+H]$^+$, 6).

Carminic acid octaacetate **1c**, by similar acetylation, was obtained as a yellow glass which slowly crystallised (EtOH) to give fine, light yellow micro-needles (62%), mp 171 °C (lit.,[37] 155–165 °C) (Found: C, 54.6; H, 4.3. Calc. for $C_{38}H_{36}O_{21}$: C, 55.05; H, 4.4%); ν_{max}(KBr)/cm^{-1} 1780, 1760 and 1680 (C=O), 1570 (aryl), 1440, 1380, 1335, 1230, 1190, 1115, 1040, 920 and 870; δ_H(400 MHz; $CDCl_3$) 1.797 and 1.854 (2 × 3 H, 2 s, 2′-OAc), 2.007, 2.021, 2.044, 2.061 and 2.091 (6 × 3 H, 5 s, 3′-, 4′- and 6′-OAc), 2.199, 2.294, 2.409, 2.439, 2.485 and 2.546 (8 × 3 H, 6 s, 3-, 5-, 6- and 8-OAc), 2.634 and 2.653 (2 × 3 H, 2 s, 1-Me), 3.802 (2 × 1 H, m, 5′-H), 3.985 (2 × 1 H, m, 6′-H^a), 4.429 (2 × 1 H, m, 6′-H^b), 4.760 (1 H, d, *J* 10.3, 1′-H), 4.930 (1 H, d, *J* 8.6, 1′-H), 5.160 (2 × 1 H, m, 4′-H), 5.318 (2 × 1 H, m, 3′-H), 5.607 (1 H, t, *J* 9.5, 2′-H), 5.787 (1 H, t, *J* 9.6, 2′-H) and 7.732 and 7.815 (2 × 1 H, 2 s, 4-H); *m/z* (FAB) 851 ([M + Na]$^+$, 57%) and 829 ([M + H]$^+$, 14).

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