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

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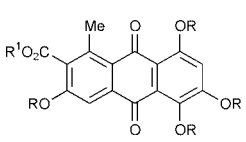
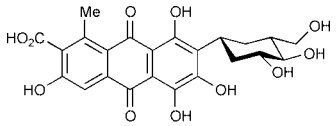
6-Chloro-2,5,8-trihydroxynaphtho-1,4-quinone does not undergo cycloaddition reactions but the 1,2-diacetate, 2-chloro-5,6-diacetoxy-8-hydroxynaphtho-1,4-quinone, formed by acetylation-aided tautomerism added (*E*)- and (*Z*)-3-alkoxycarbonyl-2,4-bis(trimethylsiyloxy)penta-1,3-diene to afford kermesic acid after hydrolysis.

Kermesic acid **1a**, the red colourant component of kermes, a dyestuff of great antiquity and probably the earliest of which



1a R = R^1 = H
b R = H; R^1 = Me
c R = R^1 = Me



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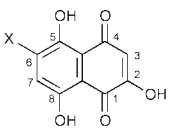
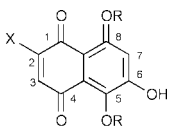
there is a record,[1] is also the aglycone of carminic acid[2] **2**, the colourant principle of cochineal.

Although carminic acid historically, through its brilliant range of red hues, superseded kermesic acid, dyeing with kermes is still active.[3] Nevertheless, the natural source of kermesic acid, for example from the wingless insect *Kermes illicis* which infects the kermes oak, is not abundant, and it was of interest to devise a synthetic approach that could provide an intermediate from which, by different strategies, either kermesic or carminic acid could be obtained. It was desirable to avoid penultimate tricyclic intermediates having an halogeno group requiring difficult hydrolysis[4,5] to the required hydroxy group and in another method[6] the simultaneous formation of isokermesic acid. Therefore, effort was focused on the preparation of 2-halogeno-5,6,8-trihydroxynaphtho-1,4-quinone **3**,



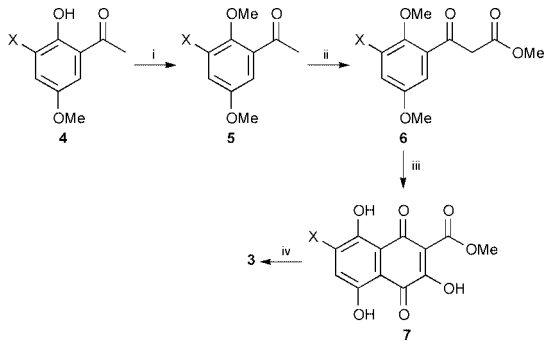
3 (form 1)



3 (form 2)

(form 2) which, as with naphthazarins generally, could be expected to exist as the 6-halogeno-2,5,8-trihydroxynaphtho-1,4-quinone tautomer **3** (form 1) where the halogeno atom is required to aid subsequent cycloaddition.

The starting point of the synthesis (Scheme 1) was 3-bromo-2-hydroxy-5-methoxyacetophenone[7] **4** (X = Br), and its chloro-analogue **4** (X = Cl), prepared 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 DMS in acetone containing K_2CO_3 afforded **5** (X = Br) 82% and **5** (X = Cl) 81%. Reaction of each with dimethyl carbonate in methanolic sodium methoxide gave the β-ketoesters **6** (X = Br, Cl), both in quantitative yield which by treatment with oxalyl chloride in nitromethane containing anhydrous aluminium chloride, a process used to prepare



4 **5** **6** **7**

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

unhalogenated naphthoquinones,[8] afforded the two 3-carbonylmethoxy-6-halogeno-2,5,8-trihydroxynaphth-1,4-quinones **7** (X = Br) 48% and **7** (X = Cl) 56% together with some partially demethylated quinones. Hydrolysis of the trihydroxyquinone esters with either aqueous sodium hydroxide followed by acidification, or with hot acetic acid containing hydrochloric acid (the preferred method) then gave the parent compounds **3** (X = Br) 69% and **3** (X = Cl) 53%.

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-diene[2] **8a**. This was attributed primarily to the intramolecular hydrogen bonding[9] of the 2-OH group thus inhibiting the normal tautomerism of the naphthazarin system and locking the structure in form 1. Further support for this exclusive structure was provided by an X-ray structure determination (Fig. 1)† and that, under mild conditions, **3** (X = Cl) readily underwent: (a) Michael addition at the 3-position and (b) selective O-methylation in 77% yield at the 2-OH with BF_3·MeOH which then removed the impediment to tautomerism and was expected to assist cycloaddition.

Acetylation of **3** (X = Cl) in dichloromethane with pyridine–acetic anhydride afforded the triacetoxy-compound in 91% yield as a 2:1 mixture (confirmed by NMR) of 6-chloro-2,5,8-triacetoxynaphtho-1,4-quinone and 2-chloro-5,6,8-triacetoxynaphtho-1,4-quinone. However, upon heating **3** (X = Cl) in acetic anhydride alone at 100 °C the 2-chloro-5,6-diacetoxy

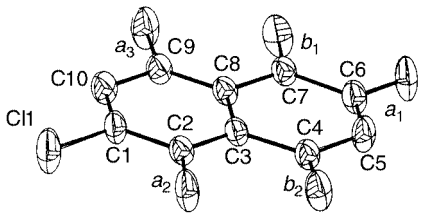


Fig. 1 X-Ray crystal structure of 6-chloro-2,5,8-trihydroxynaphtho-1,4-quinone; C–OH: a_1, a_2, a_3 = 1.33, 1.34, 1.35 Å; C=O: b_1, b_2 = 1.22, 1.24 Å.

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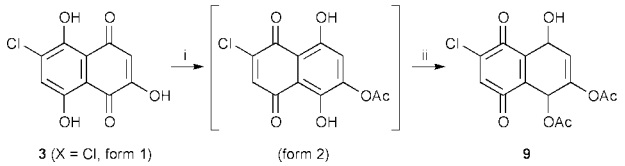


Scheme 2 *Reagents and conditions*: i, ii, Ac_2O, 100 °C, 3 h; vac. to dryness.

compound **9** resulted quantitatively. It is believed (Scheme 2) that acetylation of the 2-OH occurs first allowing tautomerism to form 2 to take place and is then followed by acetylation at the 5-position which locks the structure as form 2. It is conjectural that since hydrogen-bonded OH groups are more difficult to acetylate, migration of the 6-acetyl group to the 5-position may possibly occur enabling the more susceptible 6-OH group to then react. This tentative notion may explain the non-acetylation of the hydrogen-bonded 8-OH although we have no distinct evidence to support this pathway. X-Ray crystallography provided confirmation of the structure of the 5,6-diacetoxy compounds (Fig. 2).†

The diacetyl compound **9** readily underwent cycloaddition with (*E*)- and (*Z*)-3-methoxycarbonyl-2,4-bis(trimethylsilyloxy)penta-1,3-diene **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, with definitive proof of structure being provided by an X-ray study (Fig. 3).† The isopropyl analogue **8b** reacted similarly in 64% yield.

2-Chloro-6-methoxy-5,8-dihydroxynaphtho-1,4-quinone **11**, in which normal naphthazarin tautomerism is able to operate, although the structure is not locked as with the diacetate, also underwent cycloaddition with the diene **8a** in boiling toluene to afford after work-up, methyl 6-methoxy-3,5,8-trihydroxy-1-methylanthra-9,10-quinone-2-carboxylate **12** in 42% yield. Possibly both forms 1 and 2 are present owing to the fact that 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** quantitatively and thence by refluxing in acetic acid containing hydrochloric acid, kermesic acid **1a** was obtained (Scheme 3). Methylation of

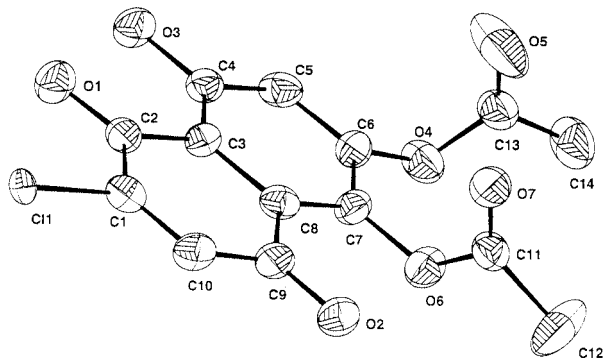


Fig. 2 X-Ray crystal structure of 2-chloro-5,6-diacetoxy-8-hydroxynaphtho-1,4-quinone.

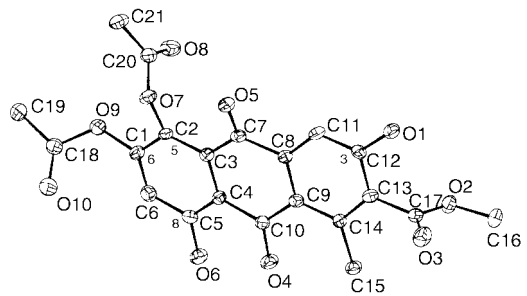
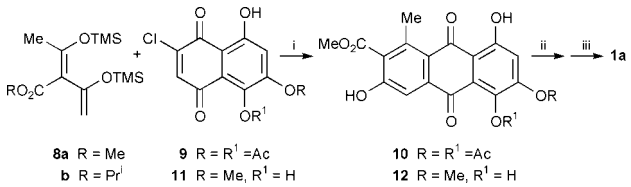


Fig. 3 X-Ray crystal structure of methyl 5,6-diacetoxy-3,8-dihydroxy-1-methylanthra-9,10-quinone-2-carboxylate.

methyl kermesate **1b** with DMS in acetone solution containing potassium carbonate gave methyl 3,5,6,8-tetramethoxy-1-methylanthra-9,10-quinone-2-carboxylate **1c**, which was identical with an authentic sample[4] kindly made available by Paul Brassard. Correct spectroscopic, elemental analysis and mass spectral data were obtained for all compounds.



Scheme 3 *Reagents and conditions*: i, **9**, toluene, **8**, heat, 24 h; col chrom. SiO_2, ii, MeOH, 1% Na_2CO_3; iii, HOAc–HCl, heat; iv, **1b**, DMS, Me_2CO, K_2CO_3, heat **11** from **3** with BF_3·MeOH; toluene, **8**, heat; col. chrom. SiO_2.

Finally, it is believed that **3** (X = Cl) also has the potential utility to facilitate efficient access to carminic acid and work is continuing in this approach.[10]

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Notes and references

† *Crystal data*: **3**: $C_{20}H_{10}Cl_2O_{10}$, *M* 479.16, triclinic, space group $P\bar{1}$, a = 6.756(4), b = 9.329(7), 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.

9: $C_{14}H_9ClO_7$, *M* 324.66, monoclinic, space group *C*2/*c*, a = 16.0510(8), b = 5.5590(8), c = 30.980(8) Å, V = 2743.7(9) Å^3, Z = 8, μ = 0.313 mm^{-1}, 1926 independent reflections: (R_{int} = 0.0742), R indices (all data): R_1 = 0.1202, wR_2 = 0.2532.

10: $C_{21}H_{16}O_{10}$, *M* = 428.34, triclinic, space group $P\bar{1}$, a = 8.295(4), b = 8.8970(10), 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.

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9 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.* δ ($CDCl_3$) (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. 8. In F. Farina, R. Martinez-Utrilla and M. C. Paredes, *Synthesis*, 1981, 300, the authors do not list the 2-OH group in data for 2-hydroxy-5,8-dimethoxynaphtho-1,4-quinone).
10 For this **3** (form 1) appears to be an ideal candidate from initial work on Michael addition and enamine reactions. Chemical approaches to using kermesic acid itself as an intermediate to carminic acid have not so far been successful although this or xanthokermesic acid are the likely biosynthetic precursors.