C-Alkylation of Methyl *leuco*-6-Deoxykermesate by Aldol Reactions and its Application to Synthesis of Carminic Acid

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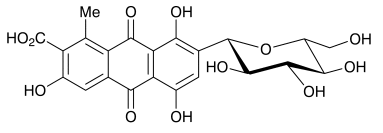
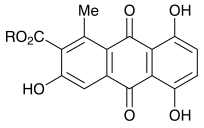
In a non-aqueous medium in the presence of piperidinium acetate, methyl *leuco*-6-deoxykermesate reacts in aldol fashion with aldehydes regioselectively to give 6-alkyl products while under aqueous alkaline conditions over a prolonged time, 7-alkyl compounds are selectively formed; the structures of the 6-alkyl series was confirmed by an X-ray crystal structure determination of the 6-methyl member, namely methyl 3,5,8-trihydroxy-1,6-dimethylanthra-9,10-quinone-2-carboxylate; in aqueous alkaline conditions during a short mild reaction period, intermediate 7-α-hydroxyalkyl compounds can be isolated, and in an application to a synthesis of 6-deoxycarminic acid, the aldol reaction of 2,3,4,5,6-penta-*O*-benzyl-D-glucose with methyl *leuco*-6-deoxykermesate was examined.

C-Glycosides[1] can be prepared, for example, in the case of carminic acid[2] by the use of a cyclic or with an open chain D-glucopyranose derivative the product from which was subsequently capable of facile cyclisation as with tri-*O*-methylvitexin.[3] In the synthesis of carminic acid (the colourant principle of cochineal) **1a** the 7-C-alkylation step had been effected on alkyl 1-methyl-3,4,8,9,10-pentamethoxyanthracene-2-carboxylates which were obtained from the corresponding alkyl 1-methyl-3,5,8-trihydroxyanthra-9,10-quinone-2-carboxylate, **2b**.

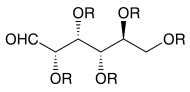
For a simplified synthesis towards 6-deoxycarminic acid **1b** (the precursor of **1a**) the aldol reaction of the free acid **2a** previously synthesised,[7] or the methyl ester **2b**, both in the *leuco* form, with the open-chain derivative, 2,3,4,5,6-penta-*O*-benzyl-D-glucose **3a** or the methyl analogue **3b** were examined.



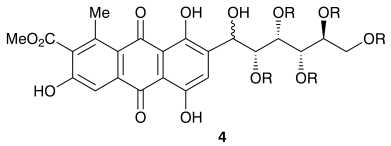
1
a: R = OH
b: R = H



2
a: R = H
b: R = Me



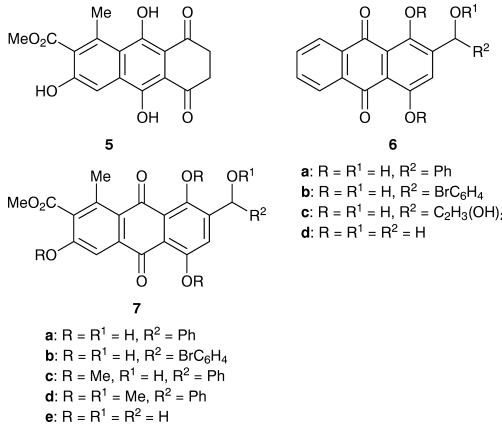
3
a: R = Bn
b: R = Me



4
a: R = Bn
b: R = Me

With *leuco*-quinizarin (from 1,4-dihydroxy-9,10-dioko-anthracene) aldol reactions have been carried out under either aqueous[10] or non-aqueous conditions[11] and the site of aldol addition to the *leuco* form was immaterial. However in the case of 5-hydroxyquinizarin regioselectivity operated[13] and it was found that prolonged aqueous and non-aqueous conditions resulted in 2- and 3-alkyl substitution, respectively. In the case of *leuco* compounds from **2a** or **2b** it was thus imperative to find the appropriate aldol condition for obtaining 7- rather than 6-substitution for the synthesis of **4a** or **4b**.

Methyl *leuco*-6-deoxykermesate **5** (methyl 2,3-dihydro-7,9,10-trihydroxy-5-methylanthracene-1,4-dione-2-carboxylate) was prepared either by reduction of **2b** with sodium dithionite in aqueous methanolic sodium hydroxide or by catalytic reduction in tetrahydrofuran containing palladised charcoal. The benzyl ester analogue of **2b** gave the *leuco* free acid.[7]



5

6
a: R = R^1 = H, R^2 = Ph
b: R = R^1 = H, R^2 = BrC$_6$H$_4$
c: R = R^1 = H, R^2 = C$_2$H$_3$(OH)$_2$
d: R = R^1 = R^2 = H

7
a: R = R^1 = H, R^2 = Ph
b: R = R^1 = H, R^2 = BrC$_6$H$_4$
c: R = Me, R^1 = H, R^2 = Ph
d: R = R^1 = Me, R^2 = Ph
e: R = R^1 = R^2 = H

Model experiments with *leuco*-quinizarin (2,3-dihydro-9,10-dihydroxyanthracene-1,4-dione) with benzaldehyde, with 4-bromobenzaldehyde and with 2,3-dihydroxypropanal under mild conditions, gave the α-hydroxyalkyl aldol product, **6a**, **6b** and **6c**, respectively, in good yields. Compound **5** with benzaldehyde and with 4-bromobenzaldehyde afforded single products, the crystalline compounds formulated as the 7-α-hydroxy, **7a** and **7b**, respectively, although the position of substitution was not known. Spectroscopic examination on either compound proved inconclusive for structural elucidation and **7b** was not suitable for X-ray structural study, although from electronic considerations,[2] reaction at the 7-rather than the 6-position appeared more likely in both compounds. Methylation of **7a** afforded the trimethyl ether **7c** in 51% yield accompanied unexpectedly by the tetramethyl ether **7d** in 29% yield; however, like the parent phenolic compounds, these crystalline derivatives also proved unsuitable for X-ray examination.

To determine the position of addition whether at the 6- or 7-position it was proposed to convert the methylol com-

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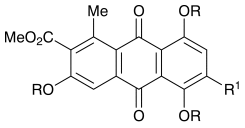
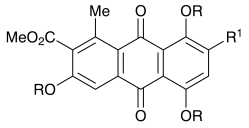
pound formulated as **7e** (from the reaction of formaldehyde with **5**), by oxidation to the aldehyde **9a**, thence by the Dakin reaction to the phenol **9b**, which by permethylation would afford the known[7] methyl isokermesate tetramethyl ether **9c** if the methylol group were at position 7; whereas methyl kermesate tetramethyl ether **8d** would result if the methylol group occupied the 6-position. However, to resolve the structural problem a comparative series of aldol reactions with compound **5** were conducted by the aqueous Marschalk and by non-aqueous Lewis conditions over a pronged reaction time to ensure that in both media the alkyl product would result. In both sets, formaldehyde, propanal, hexanal and benzaldehyde were used and thus the products would each have at the 6- or 7-position methyl, *n*-propyl, *n*-hexyl or benzyl groups.



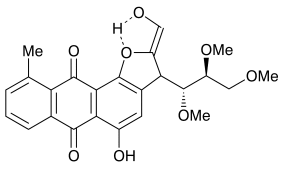
8

a: R = H, R^1 = CH_2OH
b: R = H, R^1 = CHO
c: R = H, R^1 = OH
d: R = H, R^1 = OMe
e: R = H, R^1 = Me
f: R = H, R^1 = Pr
g: R = H, R^1 = C_6H_{11}
h: R = H, R^1 = Bn
i: R = R^1 = Me
j: R = Me, R^1 = Pr
k: R = Me, R^1 = C_6H_{11}
j: R = Me, R^1 = Bn



9

a: R = H, R^1 = CHO
b: R = H, R^1 = OH
c: R = Me, R^1 = OMe
d: R = R^1 = Me
e: R = Me, R^1 = Pr
f: R = Me, R^1 = C_6H_{11}
g: R = Me, R^1 = Bn



10

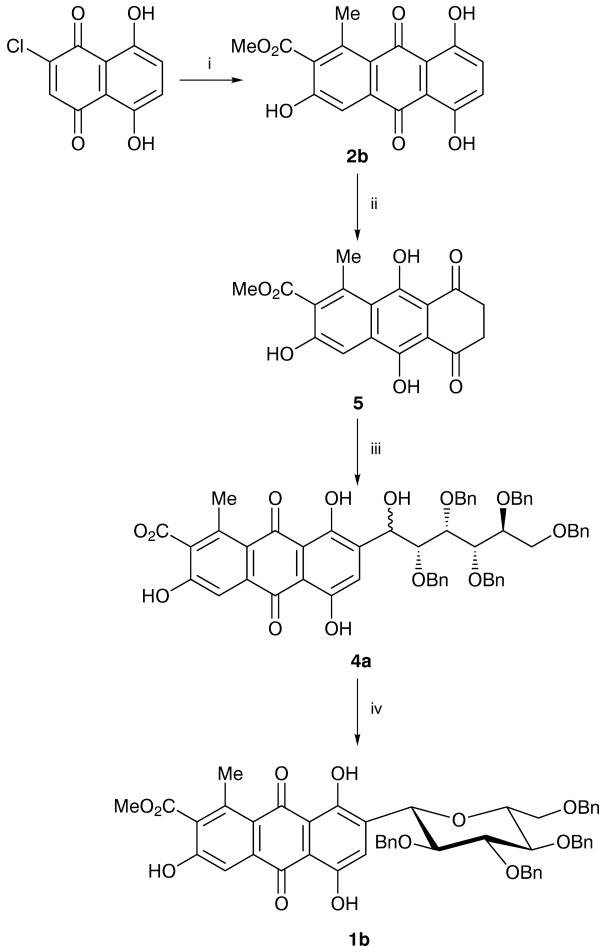
The products from the Lewis series with **5** were formulated as **8e**, **8b**, **8g** and **8h**, respectively, and methylation afforded the trimethyl ethers **8i**, **8j**, **8k** and **81**.

The Marschalk conditions gave less complete reaction and to separate the four products from unchanged **5**, all were methylated to give the trimethyl ethers designated as **9d**, **9e**, **9b** and **9g**. Compound **8e** in the Lewis series proved amenable to X-ray structural determination[33] which showed that it was methyl 3,5,8-trihydroxy-1,6-dimethylanthra-9,10-quinone-2-carboxylate as depicted in Fig. 3 (see full text). Thus, under non-aqueous Lewis conditions, regioselective reaction occurred at the 6-position and the aqueous medium of the Marschalk conditions regioselectively affords products at the 7-position.

Accordingly, the reaction of either **3a** or **3b** with compound **5** under mild aqueous alkaline reaction conditions in order to afford the corresponding α-hydroxyalkyl product, appeared to be a feasible route towards the open-chain glucosidic derivative **4a** or **4b**, a precursor of 6-deoxycarminic acid **1b** (Scheme 4). It was anticipated that cyclisation of **4a** could be effected by catalytic hydrogenolysis in methanolic acetic acid.[3]

The aldol reaction of **5** with 2,3,4,5,6-penta-*O*-benzyl-D-glucose **3a** (which was prepared in improved yield compared with an earlier route[3]), appears to proceed to give **4a** although this product was not fully characterised and its formation is speculative. The untimely conclusion of this work unfortunately precluded further study.

For the reaction of **5** with the glucose derivative **3b**, it seems most probable that β-elimination complicated the course of reaction. A model reaction of *leuco*-quinizarin with **3b** gave a number of products of which it is hypothesised that the normal aldol product by 1,2-addition, the analogue from β elimination of a methoxyl group and the major product, one of Michael addition of this elimination compound followed by cyclisation resulting in **10**. Some spectral evidence supports this although the formulation is speculative.



Scheme 4 *Reagents and conditions*: i, ref. 2; ii, $Na_2S_2O_4$, aq. NaOH; iii, 2,3,4,5,6-penta-*O*-Bn-D-glucose, KOH, air, column chromatography; iv, Pd-C, H_2, MeOH,EtOAc,AcOH as in ref. 3 (this stage was not completed)

Techniques used: ^{1}H NMR, MS, TLC, column chromatography X-ray crystallography

Schemes: 4 Figures: 3 Refs: 36 Appendix: crystal data

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