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The First Total Synthesis of Carminic Acid

Pietro Allevi,*[a] Mario Anastasia,[a] Pierangela Ciuffreda,[a] Alberto Fiecchi,[a] Antonio Scala,[a] Steve Bingham,[b] Max Muir[b] and John Tyman*[b]

[a] *Department of Medical Chemistry and Biochemistry, Faculty of Medicine, University of Milan, I-20133, Milano, Italy*
[b] *Department of Chemistry, Brunel University, Uxbridge, Middlesex UB8 3PN, UK*

The first synthesis of carminic acid (7β-D-glucopyranosyl-1-methyl-3,5,6,8-tetrahydroxy-9,10-anthraquinone-2-carboxylic acid), was accomplished by direct *C*-glucosylation of ethyl 3,5,8,9,10-pentamethoxy-1-methylanthracene-2-carboxylate, here synthesized, which affords ethyl 7-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-3,5,8,9,10- pentamethoxy-1-methylanthracene-2-carboxylate and carminic acid by regeneration of the masked functionalities.

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We report the first total synthesis of carminic acid **1a** (7β-D-glucopyranosyl-1-methyl-3,5,6,8-tetrahydroxy-9,10-anthraquinone-2-carboxylic acid), the colourant principle of cochineal, obtained from the dried female bodies of the insect species *Dactylopius coccus* Costa which feeds on the wild cactus *Nopalea coccinellifera*.[1,2] The structure of carminic acid has long been established by the researches of Dimroth[3] with later modifications by others,[4–6] while the β stereochemistry of the *C*-glucosidic bond was more recently proved and confirmed by chemical and physical methods.[7,8] Although the synthesis of its aglycone, kermesic acid **2a**, has been described[9,10] that of carminic acid has not been reported. An attempted synthesis by direct *C*-glucosylation of a conveniently masked kermesic acid (obtained by synthesis or by degradation of carminic acid[11]) was unsuccessful, but in these studies some new *C*-glucosylation methodology was developed.[12,13] We have reached the goal by performing the first direct *C*-glucosylation of an anthracene nucleus, a synthon of the 6-deoxykermesic acid **2b**,[14] obtained by total synthesis, and by subsequent introduction of the 6-hydroxy group.

Thus the first target molecule of this objective was 6-deoxycarminic acid **1b**, a compound obtained originally by the reduction of carminic acid and capable of conversion into the parent compound.[15]

Diels–Alder reaction of 2-chloronaphthazarin†**4** with an *E*–*Z* mixture of the pentadiene‡ **5** in refluxing toluene for 8 h provided, after desilylation with warm moist methanol, ethyl 6-deoxykermesate **2c** in 75% yield (m.p. 219–221 °C from methanol). Treatment of compound **2c** with dimethyl sulphate in acetone containing potassium carbonate afforded **2d** in 85% yield (m.p. 188–189 °C from diisopropyl ether). By reductive methylation[16] of **2d** [$Na_2S_2O_4$–NaOH–Me_2SO_4–tetrahydrofuran (THF)], the ester **3** was obtained (a glass which resisted all efforts at crystallization). *C*-Glucosylation of **3** was unsucessful under a variety of conditions, but was realized in acetonitrile[13] utilizing tetra-*O*-benzyl-β-D-glucopyranose activated as the 1β-*O*-trifluoroacetate and $BF_3{\cdot}Et_2O$ catalysis, to afford the ester **6** in 40% yield (glass; $[\alpha]_D$ 29.2°, $CHCl_3$, *c* 1)§ accompanied only by some anthrones.

Transformation of **6** into 6-deoxycarminic acid **1b** required in sequence: regeneration of the anthraquinone chromophore

1
a; R^1 = OH, R^2 = H
b; R^1 = R^2 = H
c; R^1 = OAc, R^2 = 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 = Et
d; R^1 = H, R^2 = Me, R^3 = Et

3

4

5

6

7
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 = H, R^2 = Me
d; R^1 = Ac, R^2 = Me, R^3 = H
e; R^1 = Ac, R^2 = R^3 = H
f; R^1 = R^2 = Ac, R^3 = H
Bn = $PhCH_2$

† 2-Chloronaphthazarin **4** was prepared either from the reaction of maleic anhydride with 2-chloro-1,4-dihydroxybenzene (reaction of 2-chloromaleic anhydride with 1,4-dihydrobenzene was also used) in an aluminium chloride–sodium chloride melt or from dehydrochlorination of the dichloro adduct (D. B. Bruce and R. H. Thomson, *J. Chem. Soc.*, 1955, 1089) of naphthazarin (K. Zahn and P. Ochwat, *Liebigs Ann. Chem.*, 1928, **464**, 72). The reaction was performed also with 2-bromonaphthazarin 1,4-diacetate (obtained according to A. S. Wheeler and V. C. Edwards, *J. Am. Chem. Soc.*, 1917, **39**, 2460).

‡ Prepared from ethyl diacetylacetate, chlorotrimethylsilane and triethylamine as an *E*–*Z* mixture (D. W. Cameron, C. Conn and G. I. Feutrill, *Aust. J. Chem.*, 1981, **34**, 1945) (b.p. 85–87 °C at 0.5 mmHg). The methyl and benzyl analogues were prepared similarly.

§ Assignment of structure was by examination of spin–spin coupling constants for the pyranose ring protons in the ^1H NMR spectrum (500 MHz) of the tetraacetate derived by acetylation of the product **7b** and by NOE difference spectroscopy which showed indicative NOEs for the sets: 8-OMe–1-Me, 8-OMe–1′-H, 6-H–5-OMe, 6-H–2′-H, 4-H–3-OMe. Open-chain derivatives of D-glucose (J. H. P. Tyman, S. Ghorbanian, M. Muir, V. Tychopoulous, I. Bruce and I. Fisher, *Synth. Commun.*, 1989, **19**, 179) and other aldehydes were considered to result in 7-substitution in aqueous aldol reactions (M. C. Marschalk, *Bull. Soc. Chim. Fr.*, 1939, **6**, 655). Other methodologies (M. Muir and J. H. P. Tyman, *16th IUPAC Int. Symp. Chem. Nat. Products*, Kyoto 1988, Abs. PB 188) have been used with open-chain derivatives.

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(Jones reagent at 0 °C, to afford **7a** in 85% yield: a glass; $[\alpha]_D$ 34°, $CHCl_3$, *c* 1), debenzylation (H_2–Pd–C–MeOH–AcOH, to give **7b** in 85% yield: m.p. 142–145 °C, from dichloromethane–diisopropyl ether; $[\alpha]_D$ −23°, $CHCl_3$, *c* 1), saponification (2.5 mol dm^{-3} methanolic NaOH at reflux for 6 h, to afford **7c** in 75% yield, used as crude material), acetylation (Ac_2O–pyridine, 12 h at room temperature to give **7d** in 90% yield: m.p. 116–117 °C, sinters, and 146 °C, decomposes, from dichloromethane–diisopropyl ether; $[\alpha]_D$ −33.3°, $CHCl_3$, *c* 1), regeneration of the phenolic groups (BBr_3–CH_2Cl_2, −40 °C, to produce **7e** in 90% yield: this compound was used without purification for successive reaction and characterization as the heptaacetate **7f**), and hydrolysis in acidic medium (0.5 mol dm^{-3} methanolic HCl, reflux) to give **1b** (in 80% yield: m.p. 286–288 °C, decomp.).

The conversion of 6-deoxycarminic acid into carminic acid was described by Dimroth *via* oxidation with lead tetraacetate and Thiele acetylation.[15] Application of this procedure, essentially by the reported conditions, to the tetraacetate **7e** afforded the octaacetate **1c** (in 60% yield: m.p. 168–170 °C, from methanol–diisopropyl ether; $[\alpha]_D$ + 62.3°, $CHCl_3$, *c* 1) which possessed the appropriate physicochemical properties and was identical with a sample obtained from natural carminic acid. Hydrolysis of the acetate groups of **1c** (HCl–EtOH, reflux 1 h) gave carminic acid **1a**, the physicochemical identification of which was verified also by direct comparison with a sample of the natural product.¶

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¶ Satisfactory spectroscopic data and elemental analyses were obtained for all new compounds.

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