

The First Total Synthesis of Carminic Acid

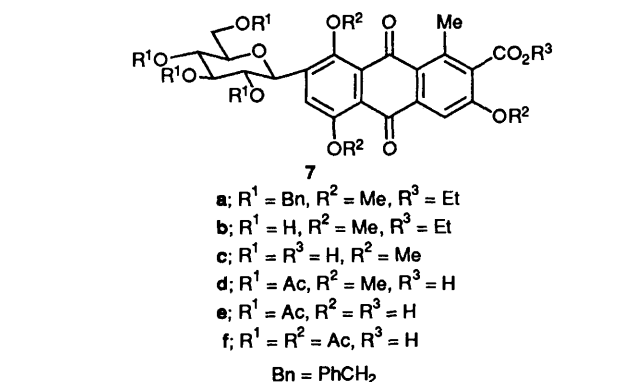
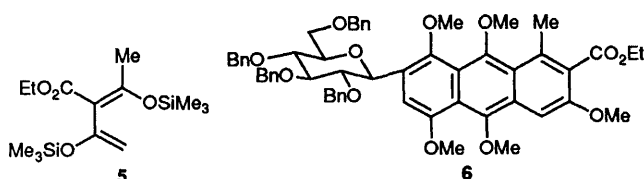
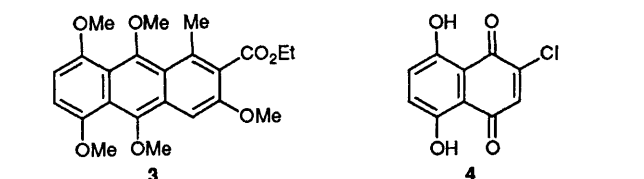
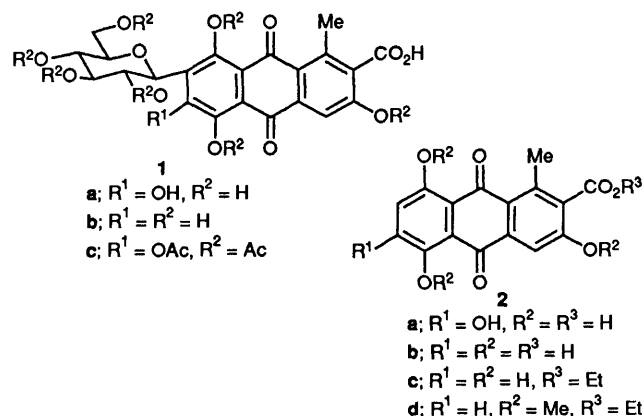
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The first synthesis of carminic acid (7- β -D-glucopyranosyl-1-methyl-3,5,6,8-tetrahydroxy-9,10-anthraquinone-2-carboxylic acid), was accomplished by direct C-glucosylation of ethyl 3,5,8,9,10-pentamethoxy-1-methylantracene-2-carboxylate, here synthesized,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

We report the first total synthesis of carminic acid **1a** (7- β -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 Dimroth³ 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 acid¹¹) 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 methylation¹⁶ of **2d** [Na₂S₂O₄-NaOH-Me₂SO₄-tetrahydrofuran (THF)], the ester **3** was obtained (a glass which resisted all efforts at crystallization). C-Glucosylation of **3** was unsuccessful under a variety of conditions, but was realized in acetonitrile¹³ utilizing tetra-O-benzyl- β -D-glucopyranose activated as the 1 β -O-trifluoroacetate and BF₃·Et₂O catalysis, to afford the ester **6** in 40% yield (glass; [α]_D 29.2°, CHCl₃, c 1)§ accompanied only by some anthrones.

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

† 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-dihydroxybenzene 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. Tychopoulos, 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.

(Jones reagent at 0 °C, to afford **7a** in 85% yield: a glass; $[\alpha]_D^{34}$, CHCl_3 , *c* 1), debenzoylation (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; $[\alpha]_D^{33}$, 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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References

- 1 L. J. Haynes, *Adv. Carbohydr. Chem.*, 1965, **20**, 357.
- 2 A. G. Lloyd, *Food Chem.*, 1980, **5**, 91.
- 3 O. Dimroth and R. Fick, *Liebigs Ann. Chem.*, 1916, **411**, 315.
- 4 J. C. Overeem and G. G. M. van der Kerk, *Recl. Trav. Chim. Pays Bas*, 1964, **83**, 1023.
- 5 S. B. Bhatia and K. Vankateraman, *Indian J. Chem.*, 1965, **3**, 92.
- 6 M. A. Ali and L. J. Haynes, *J. Chem. Soc.*, 1959, 1033.
- 7 A. Fiecchi, M. Anastasia, C. Galli and P. Gariboldi, *J. Org. Chem.*, 1981, **46**, 1511.
- 8 P. Schmitt, H. Günther, G. Hägele and R. Stilke, *Org. Magn. Reson.*, 1984, **22**, 446.
- 9 G. Roberge and P. Brassard, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1041.
- 10 D. W. Cameron, D. J. Deutscher, G. I. Feutrill and P. G. Griffiths, *Aust. J. Chem.*, 1981, **34**, 2401.
- 11 P. Allevi, M. Anastasia, P. Ciuffreda, A. Fiecchi and A. Scala, *J. Org. Chem.*, 1987, **52**, 5469.
- 12 P. Allevi, M. Anastasia, P. Ciuffreda, A. Fiecchi and A. Scala, *J. Chem. Soc., Chem. Commun.*, 1987, 101.
- 13 The reaction conditions were those reported for the *C*-glucosylation of other aglycones by P. Allevi, M. Anastasia, P. Ciuffreda, A. Fiecchi and A. Scala, *J. Chem. Soc., Chem. Commun.*, 1987, 1245, but it was essential to use acetonitrile as solvent in place of the reported dichloromethane.
- 14 A synthesis of 6-deoxykermesic acid was recently reported: J. H. P. Tyman and S. J. Bingham, *Br. Pat. Appl.* 17/08/1990.
- 15 O. Dimroth and H. Kammerer, *Chem. Ber.*, 1920, **53B**, 471; J. F. W. McOmie and J. M. Blatchly, *Org. Reactions*, 1960, **19**, 199.
- 16 G. A. Kraus and T. On Man, *Synth. Commun.*, 1986, **16**, 1037.