Unsaturated Carbohydrates. Part 25.[1] Abbreviated Synthesis of the Insect Pheromone (+)-*exo*-Brevicomin from a Nona-3,8-dienulose Derivative

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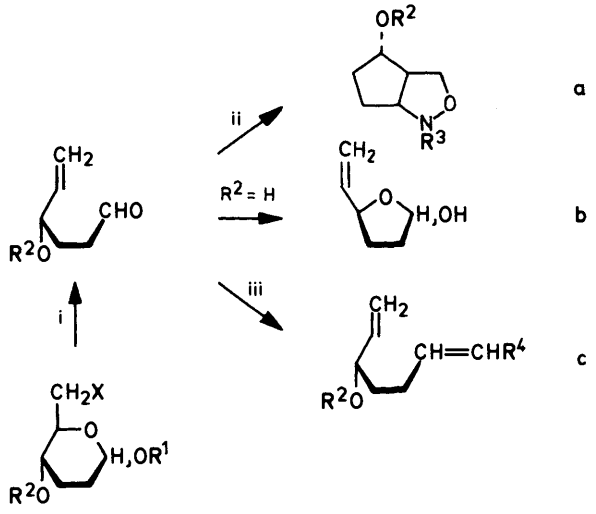
The insect pheromone (+)-*exo*-brevicomin (9) has been synthesised from the methyl 6-deoxy-6-iodo-α-D-glucopyranoside derivative (1) in 54% yield by way of the dienone (5) from which the ketone (7) was obtained by concurrent hydrogenation of the double bonds and hydrogenolysis of the allylic ester group.

Treatment of 6-deoxy-6-halogenohexopyranosyl derivatives in ethanol with metallic zinc offers an efficient and simple means of producing 5,6-dideoxyhex-5-enoses [2] which have found use as precursors of valuable functionalised cyclopentanes [1-3] (Scheme 1a). In addition, members having unsubstituted hydroxy groups at C-4 offer good access to 5,6-dideoxyhex-5-enofuranoses and their derivatives [4] (Scheme 1b). We now demonstrate that an enose formed in this manner can be chain-extended by application of phosphorus-bonded carbanion reagents (Scheme 1c) and we illustrate the use of a derived nona-3,8-dienulose in the synthesis of (+)-*exo*-brevicomin which is the principal sex attractant of the female Western pine beetle (*Dendroctonus brevicomis*).[5]

In a review article [6] Fraser-Reid and Anderson have pointed out that the pheromone (9) is the 2,7-anhydro derivative of 1,3,4,5,8,9-hexadeoxy-α-D-*threo*-2-nonulopyranose [(8), Scheme 2], and they proposed a synthesis of the latter from a 5,6-dideoxy-D-*xylo*-hex-5-enofuranose by a procedure which involves use of a propanone-based Wittig reagent.† Prior to this step, however, they planned a specific deoxygenation step applied at C-2. Our procedure, while following the rationale outlined by Fraser-Reid and Anderson,[6] obviates the need for this potentially troublesome requirement.

exo-Brevicomin has been synthesised in racemic form by several routes,[7-9] but because the natural product is the (+)-enantiomer,[10] and because the biological activity is dependent upon the enantiomeric form,[11] specific attention has been directed toward the separate isomers. Syntheses of the (+)-form from an asymmetric tartaric acid derivative [12] and from a resolved 2-hydroxybutanal derivative [13] have been reported, and a further approach involved partial resolution of an intermediate in a synthesis from other aliphatic compounds.[7] The present procedures (Scheme 2) afford this optically pure natural product in good yield. Preparations of the (−)-enantiomer also utilised tartaric acid derivatives.[12,14]

Treatment of the readily available 6-iodohexopyranoside [15] (1) with zinc in ethanol gave the enal (2) which, with the ylide (3) derived from bromoacetone and triphenylphosphine,[16] was converted into the crystalline dienone (5) together with similar proportions of a chromatographically more mobile syrupy product which, from its ^{1}H n.m.r. spectrum, was assigned the trienone structure (6) with, like compound (5), the (*E*)-configuration at the C-3 double bond. Variation of the solvent for the reaction did not lead to higher proportions of the dienone (5), and therefore the corresponding phosphonate



Scheme 1. *Reagents:* i, Zn, EtOH; ii, R^3NHOH; iii, $\geqslant P{=}CHR^4$

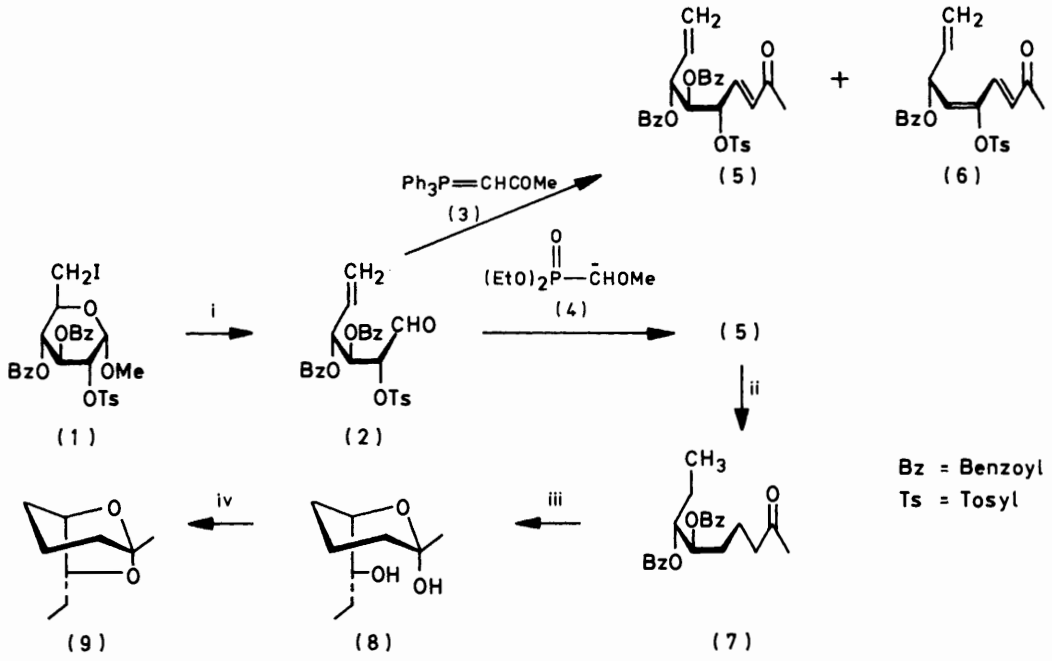
(4),[17] which affords a more nucleophilic and less basic carbanionic reagent,[18] was employed. With it, less β-elimination occurred and the dienone (5) was isolated in 66% yield.

Attempts to displace the allylic tosyloxy group of compound (5) with iodide and benzenethiolate anions in a variety of solvents caused extensive degradation, but when compound (5) was hydrogenated in ethyl acetate containing triethylamine over palladium–charcoal the detosylated ketone (7) was obtained in almost quantitative yield. Hydrogenolysis of allylic ester groups is well known,[19] and the concurrent saturation of the alkene groups and removal of the sulphonyloxy group permit the preparation of the required diester (7) in two steps from the readily available enal (2).

Base-catalysed hydrolysis of the ester groups gave a polar product [presumably the hemiacetal (8)] which was completely converted into the chromatographically more mobile (+)-*exo*-brevicomin (9) on slight acidification of the solution. As soon as this compound had been initially isolated from natural sources and characterised its relationship to anhydrosugars was recognised,[5] and the ready anhydride ring closure [(8)] ⟶ (9)] is analogous to that which occurs in the generation of 1,6-anhydroaldoses from the parent sugars under acid conditions.[20]

The yield of the final product represents a 54% conversion from the readily available iodide (1), the only step having less than almost quantitative efficiency being the chain-extension reaction (2) ⟶ (5).

† Since this paper was completed A. E. Sherk and B. Fraser-Reid have published their brevicomin synthesis (*J. Org. Chem.*, 1982, **47**, 932).



Scheme 2. *Reagents:* i, Zn, EtOH; ii, H_2, Pd–C; iii, OH^-; iv, H^+

Experimental

The n.m.r. spectra were measured in deuteriochloroform on a Varian FT 80A spectrometer and the mass spectrum on the Micromass 12F instrument. Optical rotations are for chloroform solutions unless otherwise noted (concentrations 1 ± 0.5%). Light petroleum refers to that fraction boiling in the range 60—80 °C.

(3E,5S,6S,7R)-6,7-*Dibenzoyloxy*-5-*tosyloxynona*-3,8-*dien*-2-*one* (5).—A solution of methyl 3,4-di-*O*-benzoyl-6-deoxy-6-iodo-2-*O*-tosyl-α-D-glucopyranoside (1) (10 g) in 95% ethanol was heated under reflux for 1 h in the presence of zinc dust (10 g). The solids were removed and washed and the combined filtrate and washings were evaporated to give a yellow syrup; a solution of this in diethyl ether (40 ml) was added at −70 °C to a solution of the anion (4) derived from diethyl 2-oxopropylphosphonate [17] [the anion was prepared by the addition, at −78 °C under nitrogen, of a solution of the phosphonate (3.5 g, 1.2 mol equiv.) in diethyl ether (10 ml) to a solution of n-butyl-lithium (1.2 mol equiv.) in diethyl ether (40 ml)]. The reaction mixture was allowed to attain room temperature and was then stirred for 6 h before being quenched with water. The organic phase and the ethyl acetate extract of the aqueous phase were combined and dried, and the solvents were removed to leave a brown syrup (10 g) which was passed in chloroform solution through a short column of silica gel (80 g) to give a product (7.68 g) which was predominantly the required *dienone* (5). When recrystallised from ethanol–light petroleum compound (5) (5.4 g, 66%) had m.p. 99—101 °C, $[\alpha]_D$ +85° (Found: C, 65.6; H, 5.3; S, 5.9. $C_{30}H_{28}O_8S$ requires C, 65.7; H, 5.1; S, 5.8%); δ_H 2.02 (3 H, s, 1-H_3), 2.34 (3 H, s, $C_6H_4CH_3$), 5.2—5.9 (6 H, m), 6.16 (1 H, d, $J_{3,4}$ 16 Hz, 3-H), 6.63 (1 H, dd, $J_{4,5}$ 5.6 Hz, 4-H), and 7.10—8.05 (14 H, ArH).

When the above reaction was carried out in benzene, chloroform, 1,2-dichloroethane, or dichloromethane, with the enal (2) prepared from the iodide (2 g), in the presence of the ylide (3),[16] two products were obtained and were resolved on a column of silica gel. The less polar fraction (0.5 g, 39%) was an unstable syrup [δ_H 2.19 (3 H, s, 1-H_3), 2.40 (3 H, s, $C_6H_4CH_3$), 5.15—5.45 (2 H, m), 5.70—5.95 (2 H, m), 6.05—6.30 (2 H, m), 6.94 (1 H, d, $J_{3,4}$ 15.7 Hz, 4-H), and 7.25—8.05 (9 H, ArH)]. On this basis it was assigned the trienone structure (6). The less mobile fraction (0.67 h, 41%) was the dienone (5), m.p. 99—101 °C; $[\alpha]_D$ +85°; ^{1}H n.m.r. spectrum identical to that of the earlier sample.

(6R,7R)-6,7-*Dibenzoyloxynonan*-2-*one* (7).—A solution of the dienone (5) (1.0 g) in ethyl acetate (40 ml) containing triethylamine (0.2 ml) was hydrogenated at atmospheric pressure over palladium–charcoal (0.9 g, 5%) to give, after work-up, the syrupy *saturated ketone* (7) (0.66 g, 95%), $[\alpha]_D$ +58° (Found: C, 72.5; H, 6.8. $C_{23}H_{26}O_5$ requires C, 72.3; H, 6.8%); δ_H 0.98 (3 H, t, $J_{8,9}$, 7 Hz, 9-H_3), 1.6—1.9 (6 H, m, 4-, 5-, and 8-H_2), 2.06 (3 H, s, 1-H_3), 2.45 (2 H, br t, 3-H_2), 5.20—5.55 (2 H, m, 6- and 7-H), and 7.25—8.15 (10 H, ArH); δ_C 9.70, 19.40, 24.09, 29.80, 30.36, and 42.96 (C-1, -3, -4, -5, -8, and -9), 73.81 and 75.78 (C-6, and -7), and 207.96 p.p.m. (C-2), in addition to benzoate-ester signals.

(1R,5S,7R)-7-*Ethyl*-5-*methyl*-6,8-*dioxabicyclo*[3.2.1]*octane* [(+)-exo-*Brevicomin*] (9).—Crushed potassium hydroxide (0.5 g) was added to a stirred solution of the dibenzoate (7) (0.5 g) in 65% aqueous ethanol (20 ml) and the mixture was stirred until conversion into a very polar product was complete. Concentrated hydrochloric acid was added until the mixture was slightly acidic whereupon a much less polar compound was formed; the solution was diluted with water and the product was extracted into dichloromethane. The extract was washed successively with saturated aqueous sodium hydrogen carbonate and water and was then dried and the solvent was carefully removed. Chromatography of the resultant oil on a column of silica gel gave (+)-*exo*-brevicomin (9) as an oil (0.18 g, 88%), $[\alpha]_D$ +82.4° (*c* 1.5 in diethyl ether) [lit.,[12] $[\alpha]_D$ +84° (diethyl ether)]. The i.r.,[12] ^{1}H n.m.r.,[12] and mass spectra [12,21] were identical to those previously reported. Each of the resonances observed in the ^{13}C n.m.r. spectrum was 0.25—0.4 p.p.m. downfield relative

to recorded figures;[22] this is taken as further proof of the assigned structure.

Acknowledgements

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