Unsaturated Carbohydrates. Part 27.[1] Synthesis of (−)-*exo*-Brevicomin from a Nona-3,8-dienulose Derivative

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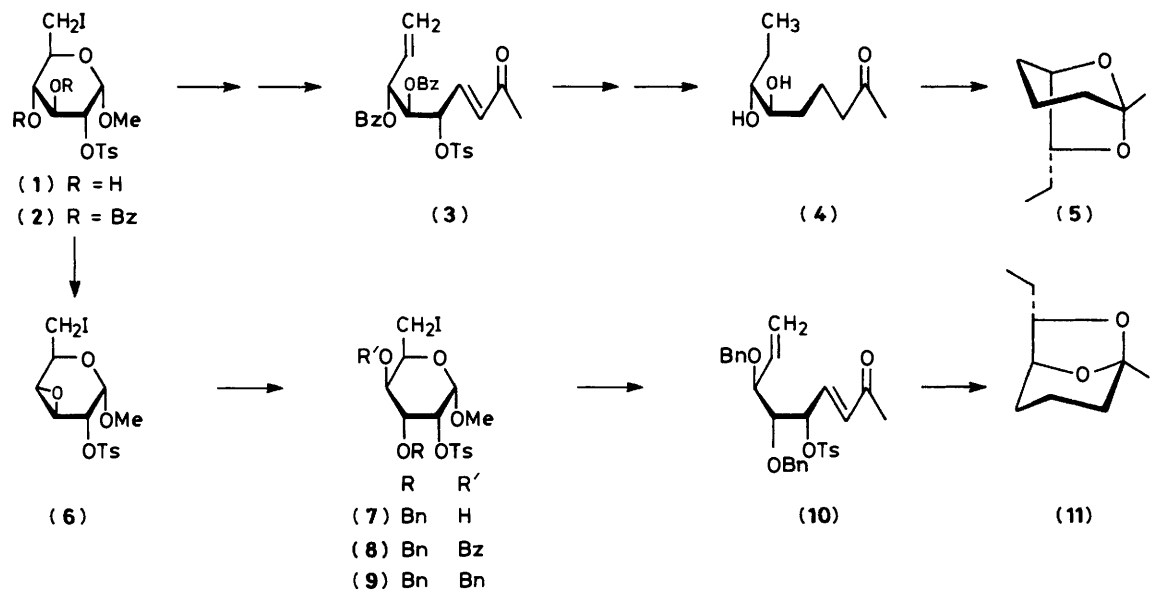
The (−)-enantiomer (**11**) of the insect pheromone (+)-*exo*-brevicomin has been synthesized directly by hydrogenation–hydrogenolysis of the L-*lyxo*-nona-3,8-dienulose derivative (**10**). Epoxide ring opening of the methyl 3,4-anhydro-D-galactopyranoside (**6**), which was readily obtained from methyl α-D-glucopyranoside, permitted the required configurational inversions at C-3 and C-4.

In a recent report[2] we have described the synthesis of (+)-*exo*-brevicomin, which is the principal sex attractant of the female Western pine beetle (*Dendroctonus brevicomis*), from methyl α-D-glucopyranoside, using an abbreviated form of the Sherk and Fraser-Reid approach.[3] In order to provide the enantiomer for biological studies which are based on the probability that various insects will show different responses to the two enantiomers,[4] we have now developed a route (Scheme) to the (−)-isomer from the same starting material. Since our earlier manuscript was submitted, continued interest in brevicomin synthesis has been demonstrated by further reports of the preparation of the racemate[5] and of specific enantiomers produced by use of chiral, non-carbohydrate starting materials[6] or by procedures involving chiral induction.[4,7] In particular, the (−)-isomer has been synthesized by application of the Sharpless asymmetric epoxidation reaction;[4] previously it had been obtained from optically pure, non-carbohydrate compounds such as (+)-diethyl tartrate.[8]

Our route to the (+)-enantiomer utilised the methyl 6-deoxy-6-iodo-2-*O*-(*p*-tolylsulphonyl)-α-D-glucopyranoside (**1**), the dibenzoate (**2**) of which was ring opened by treatment with zinc in ethanol to give the acyclic 5,6-dideoxyald-5-enose.[9] Chain extension by the Wittig procedure gave compound (**3**) which on hydrogenation–hydrogenolysis underwent reductive removal of the sulphonyloxy group to give a dibenzoate from which compound (**4**), which readily cyclises to (+)-*exo*-brevicomin (**5**), was obtained. To adapt this approach to afford the (−)-enantiomer it was necessary to use a glycoside derivative which had inverted stereochemistry at C-3 and C-4, and therefore the initial diol (**1**) was converted into the 3,4-anhydro-D-galactoside derivative (**6**). This was obtained in 56% yield from crude iodide (**1**) which was made without purification from the 2,6-ditosylate which, in turn, was produced by direct tosylation of methyl α-D-glucopyranoside. Di-isopropyl azodicarboxylate and triphenylphosphine were used to effect the dehydration following the initial observation by Mitsunobu *et al.* that such reagents convert vicinal *trans*-diols into epoxides.[10] This procedure has proved of considerable value in carbohydrate chemistry[11] and, in particular, Brandstetter and Zbiral have shown that 2,6-disubstituted derivatives of methyl α-D-glucopyranoside react to give mainly 3,4-anhydrides with the α-D-*galacto*-configuration.[12]

When treated with benzyl alcohol in the presence of boron trifluoride–diethyl ether the anhydride (**6**) gave as main product the monobenzyl ether (**7**) from which the monobenzoate (**8**) was derived. Coupling analysis in the ^{1}H n.m.r. spectrum of this latter compound showed that the proton on the ring carbon atom carrying the benzoyloxy group was adjacent to 5-H and, consequently, that the benzyl alcohol nucleophile had attacked C-3 of the anhydride. Coupling analysis also indicates that compounds (**7**) and (**8**) and the derived dibenzyl ether (**9**) have the D-*gulo*-configuration, and this is borne out by the ultimate production of (−)-brevicomin. It is thus established that the anhydride did have the α-D-*galacto*-structure and, as was to be expected,[13] opened preferentially in the diaxial sense.

The dibenzyl ether (**9**) on reaction with zinc in aqueous



Scheme. Bn = benzyl, Bz = benzoyl, Ts = tosyl

ethanol[9] afforded the corresponding enal which, with the anion derived from diethyl 2-oxopropylphosphonate,[14] gave the dienone (**10**). A convenient feature of the present synthesis was that this product, on hydrogenation, gave the required enantiomer of compound (**4**) directly; reaction over palladium–charcoal in ethyl acetate containing triethylamine caused partial reaction, assumed by analogy[2] to be hydrogenolysis of the allylic ester group, and hydrogenation of the alkene groups, and change of solvent to ethanol resulted in cleavage of the benzyl ether groups. The product was indistinguishable from (+)-brevicomin by ^{1}H n.m.r. analysis.

Experimental

The n.m.r. spectra were measured in deuteriochloroform on a Varian FT 80A spectrometer using $SiMe_4$ as internal standard. Unless otherwise stated optical rotations are for chloroform solutions with concentrations within the range 1—2%.

Methyl 3,4-*Anhydro*-6-*deoxy*-6-*iodo*-2-O-(p-*tolylsulphonyl*)-α-D-*galactopyranoside* (**6**).—Crude methyl α-D-glucopyranoside 2,6-di-O-tosylate (41 g), made by direct esterification of the glycoside, was heated in refluxing butan-2-one (300 ml) with sodium iodide (30 g) for 2 h. After filtration, the solvent was removed, the residue was extracted with chloroform, and the extract was filtered, washed successively with water, aqueous sodium thiosulphate, and again with water, and was dried (Na_2SO_4) and the chloroform removed. The crude syrup was dissolved in toluene (150 ml) and the solution was added to a solution of triphenylphosphine (27.4 g) and di-isopropyl azodicarboxylate (21 g) in toluene (100 ml) and the solution was heated at 90 °C for 2 h. After the mixture had cooled, silica gel (100 g; Riedel-de-Haën, A.G. 'S'; 0.063—0.1 mm) was added and the solvent was removed under reduced pressure. The free flowing residue was applied to a column of similar silica gel (100 g) which was then eluted with ethyl acetate–dichloromethane–light petroleum (b.p. 60—80 °C) (1:4:10) to give the crude product. Further column chromatography using the above conditions and crystallisation from diethyl ether–light petroleum gave the *epoxide* (**6**) (20.1 g, 56% from the ditosylate), m.p. 84 °C; $[\alpha]_D$ + 59° (*c* 1 in $CHCl_3$) (Found C, 38.3; H, 4.1; S, 7.4. $C_{14}H_{17}IO_6S$ requires C, 38.2; H, 3.9; S, 7.3%); δ_H ($CDCl_3$) 2.45 (3 H, s, $C_6H_4CH_3$), 3.4—2.9 (7 H, m, OMe, 3-, 4-, 6-, and 6′-H), 4.09 (1 H, t, $J_{5,6} = J_{5,6'} = 7$ Hz, 5-H), 4.42 (1 H, d, $J_{1,2}$ 4.3 Hz, 2-H), 4.58 (1 H, d, 1-H), 7.36 (2 H, d, *J* 8.1 Hz, ArH), and 7.83 (2 H, d, ArH).

Methyl 3-O-*Benzyl*-6-*deoxy*-6-*iodo*-2-O-(p-*tolylsulphonyl*)-α-D-*gulopyranoside* (**7**).—A solution of the epoxide (**6**) (6 g) in dichloromethane (40 ml) was stirred, under nitrogen, with benzyl alcohol (2.3 g, 1.6 mol equiv.) and boron trifluoride–diethyl ether (0.55 ml). After 3 days at 18 °C a similar volume of catalyst was added and after a further 2 days the starting material had undergone complete reaction. The solution was washed successively with aqueous sodium hydrogen carbonate, then water, and, after being dried, the solvent was removed. Column chromatography gave a minor, relatively mobile product (presumably the 4-*O*-benzyl-D-*gluco*-isomer) and then the 3-O-*benzyl*-D-*guloside* (**7**) (4.85 g, 61%), $[\alpha]_D$ +43° (Found: C, 46.4; H, 4.7; S, 6.1. $C_{21}H_{25}IO_7S$ requires C, 46.0; H, 4.6; S, 5.9%); δ_H 2.20 (1 H, m, OH), 2.42 (3 H, s, $C_6H_4CH_3$), 3.16 (2 H, d, $J_{5,6} = J_{5,6'} = 7.7$ Hz, 6- and 6′-H), 3.35 (1 H, m, 4-H), 3.37 (3 H, s, OMe), 3.75 (1 H, m, 3-H), 4.27 (1 H, t, 5-H), 4.3—4.85 (4 H, m, 1- and 2-H, and $PhCH_2$), 7.30 (2 H, d, *J* 8.3 Hz, ArH), 7.31 (5 H, s, Ph), and 7.77 (2 H, d, ArH).

Methyl 4-O-*Benzoyl*-3-O-*benzyl*-6-*deoxy*-6-*iodo*-2-O-(p-*tolylsulphonyl*)-α-D-*gulopyranoside* (**8**).—The alcohol (**7**) (0.58 g) was benzoylated with pyridine (5 ml) and benzoyl chloride (0.18 ml) at 0 °C. Usual work-up and purification by flash chromatography[15] gave the *monobenzoate* (**8**) (0.58 g, 84%), $[\alpha]_D$ +54° (Found: C, 51.2; H, 4.6; S, 5.5. $C_{28}H_{29}IO_8S$ requires C, 51.5; H, 4.5; S, 4.9%); δ_H 2.30 (3 H, s, $C_6H_4CH_3$), 3.13, (2 H, d, $J_{5,6} = J_{5,6'}$ 7.1 Hz, 6- and 6′-H), 3.48 (3 H, s, OMe), 3.64 (1 H, dt, $J_{1,3}$ 0.7, $J_{2,3}$ 4.0, $J_{3,4}$ 3.5 Hz, 3-H), 4.48 (1 H, dt, $J_{4,5}$ 1.1 Hz, 5-H), 4.57 (1 H, t, $J_{1,2}$ 4.0 Hz, 2-H), 4.69 (2 H, s, $PhCH_2$), 4.82 (1 H, dd, 1-H), 5.26 (1 H, dd, 4-H), and 7.0—8.0 (14 H, m, ArH).

Methyl 3,4-*Di*-O-*benzyl*-6-*deoxy*-6-*iodo*-2-O-(p-*tolylsulphonyl*)-α-D-*gulopyranoside* (**9**).—Sodium hydride (0.07 g) was added portionwise to a solution of the alcohol (**7**) (1.0 g) in tetrahydrofuran (20 ml) at 0 °C under nitrogen. The mixture was stirred for 5 min and benzyl bromide (0.25 ml) and tetrahexylammonium iodide (0.175 g) were added.[16] The mixture was stirred at 0 °C for 1 h and for a further 3 h while the mixture attained room temperature. The product was purified on a column of silica gel to give the *diether* (**9**) (1.04 g, 89%), $[\alpha]_D$ + 25° (Found: C, 52.8; H, 4.8; S, 5.1. $C_{28}H_{31}IO_7S$ requires C, 52.7; H, 4.9; S, 5.0%); δ_H 2.42 (3 H, s, $C_6H_4CH_3$), 2.95 (1 H, dd, $J_{6,6'}$ 10, $J_{5,6}$ 5.8 Hz, 6-H), 3.20 (1 H, d, 6′-H), 3.37 (3 H, s, OMe), 3.50 (1 H, dd, $J_{3,4}$ 3, $J_{4,5}$ 1.0 Hz, 4-H), 3.81 (1 H, t, $J_{2,3}$ 3 Hz, 3-H), 4.15 (1 H, dd, 5-H), 4.10, 4.20, 4.45, and 4.75 (4 H, 4 d, *J* 12 Hz, 2 × $PhCH_2$), 4.65 (1 H, t, $J_{1,2}$ 3 Hz, 2-H), 4.50 (1 H, d, 1-H), and 7.0—7.75 (14 H, m, ArH).

(1S,5R,7S)-7-*Ethyl*-5-*methyl*-6,8-*dioxabicyclo*[3.2.1]*octane* [(−)-*exo*-*Brevicomin*] (**11**).— A solution of the dibenzyl ether (**9**) (3.3 g) in aqueous ethanol (60 ml; 10%) was heated under reflux with zinc dust (10 g) for 1.5 h. The mixture was cooled, the solids were removed, and the solvent was distilled off to give a residue which was extracted with chloroform. Removal of the solvent from the extract gave a syrup which was dissolved in toluene (10 ml) and the solution was added dropwise to the anion derived from diethyl 2-oxopropylphosphonate[14] [prepared by the addition a solution of the phosphonate (1.3 g) in toluene (3 ml) to a suspension of sodium hydride (0.2 g) in toluene (15 ml) at 0 °C under nitrogen, the mixture then being stirred for 0.5 h]. The mixture was stirred at 0 °C for 0.5 h and allowed to warm to 20 °C during 3 h, water was added, the solids were removed, and the product was isolated in the usual way from the organic phase. Purification by column chromatography gave the unstable dienone (**10**) (0.87 g, 32%), $[\alpha]_D$ +17°; δ_H 2.08 (3 H, s, 1-H_3), 2.40 (3 H, s, $C_6H_4CH_3$), 3.7—3.9 (2 H, m, 6- and 7-H), 4.27 (1 H, d, *J* 12 Hz, PhC*H*H), 4.55 (1 H, d, Ph:CH:*H*), 4.63 (2 H, s, $PhCH_2$), 5.1—5.6 (4-H, m, 5-, 8-, 9-, and 9′-H), 6.00 (1 H, dd, $J_{3,4}$ 16.2, $J_{3,5}$ 1.1 Hz, 3-H), 6.65 (1 H, dd, $J_{4,5}$ 6.2 Hz, 4-H), and 7.10—7.7 (14 H, m, ArH).

A solution of dienone (**10**) (1.1 g) in ethyl acetate (30 ml) containing triethylamine (0.3 ml) was shaken in an atmosphere of hydrogen with palladium–charcoal (0.1 g; 10%) for 3 h to give a chromatographically more mobile product. When the catalyst and solvent were removed and the residue was dissolved in ethanol (30 ml) and shaken with hydrogen over more of the same catalyst (0.1 g) for 2 h a more polar compound was produced. Removal of the catalyst and evaporation of the solvent with several portions of hexane at 0 °C then gave a very non-polar compound. Purification by flash chromatography[15] gave (−)-*exo*-brevicomin (**11**) (0.15 g, 45%), $[\alpha]_D$ −73° (*c* 2 in diethyl ether) (lit.,[8a] −80°,[8b] −67°,[8c] −66°). The ^{1}H n.m.r spectrum was identical with that of the (+)-enantiomer.

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