Short Communication

Approaches to the Synthesis of Terpenyl Carbohydrates

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Hopanepolyols occur widely in prokaryotes where they apparently serve as cholesterol surrogates and their role in these organisms as membrane stabilisers has been accepted.[1] Since the importance of the terpenyl moiety is unknown, it was decided to develop a synthesis accommodating such variation. Based on the proposed hopanetetraol biosynthesis and successful synthesis by others[2] of long-chain polyols by means of Wittig reaction, condensation of the D-ribose derivative **1**[3] with a variety of terpenyl phosphonium salts was attempted. Synthesis could then be completed by reduction of the double bond. Unknown to us another group was working along similar lines.[1]

Model studies were conducted using the phosphonium salt **2d**, obtained in 30 % overall yield in a seven-step reaction sequence as outlined in the Experimental section, and the aldehyde **1**. Although a variety of bases and reaction conditions were tried for the coupling of **2d** to **1**, the only successful method involved lithium hexamethyldisilazide (LHMDS)[4] and provided **2e** as an inseperable mixture of *Z*- and *E*-olefins. Hydrogenation of **2e** for 8 h at room temperature in the presence of 10 % Pd on C completed the projected synthesis and gave the protected *C*-alkylated carbohydrate **2f** in quantitative yield.

This methodology was then extended to the naturally occurring terpenes (+)-(*R*)-limonene (**3a**), valencene (**4a**), diploptene (**5a**) and β-lupeol (as the *O*-benzyl derivative **6a**). These compounds were converted into the required phosphonium salts in a three-step sequence. The alkenes (**3a–6a**) underwent hydroboration with diborane under suitable conditions to provide the corresponding primary alcohols (**3b–6b**). The alcohols were subsequently converted into the corresponding iodides **3c–6c** in yields in the range 85–95 % in a single step by means of a modification of the Mitsunobu reaction employing the system triphenylphosphine/diethyl azodicarboxylate/MeI (TPP/DEAD/MeI).[5] The iodides **3c–5c** when held in a PPh_3 melt for 12 h gave 75–95 % yields of the phosphonium salt **3d–5d**. The iodide **6c**, however, provided only a 35 % yield of **6d** after prolonged reaction (48 h). In every case a preference for one of the two epimeric salts was shown (NMR) and in the case of **6d** only one epimer was detected.

Wittig reaction of these phosphonium salts with **1** was then examined (yields and *Z*–*E* ratios are given in the Experimental section). The lack of product from the salt **6d**, like its sluggish preparation, may be attributed to severe steric hindrance. The diastereoselection apparent in phosphonium salt formation was even more pronounced in the olefinic products **3e–5e** and varied from 1:6 to 1:9 (GC). Examination by NMR spectroscopy of the olefins **2e–5e** or indeed their hydrogenation products **2f–5f** provided no evidence of epimerisation at C-4. Hydrogenation of **3e–5e** proceeded unexceptionally under the circumstances employed for **2e** and produced quantitative yields of the end-products **3f–5f**. The skeletal double bonds present in **3e** and **4e** were, of course, hydrogenated under these conditions and are thus missing in **3f** and **4f**.

The considerably better yields recorded here for the Wittig reaction, as compared with 8 % previously reported[1] for the pure 22*S*-isomer of **5d**, may be attributed to the use of the bulky, less basic and non-nucleophilic base LHMDS. These improved yields together with the established deprotection[2] of similar D-ribosyl derivatives to the free tetraols makes this an attractive route for the synthesis of a variety of terpenepolyols.

Experimental

General. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AM400 spectrometer using $CDCl_3$ as the solvent and Me_4Si as an internal standard. Mass spectra were recorded at 70 eV on a JEOL JMS D-100 instrument to which was coupled a Hewlett-Packard 5710A gas chromatograph. GC was carried out on OV-101 or Silar S9CP columns (stainless steel, 1/8″ × 6′, helium 20 ml min^{-1}).

Alkylation of the sodium salt of diethyl methylmalonate with cyclohexyl bromide, followed by partial saponification (1.5 mol KOH in refluxing 75 % ethanol) and decarboxylation at 170 °C gave ethyl 2-cyclohexylpropionate (b.p. 108–

110 °C, 13 mmHg). Lithium aluminium hydride (LAH) reduction of the latter gave the alcohol **2b** (b.p. 101–103 °C, 13 mmHg) which on tosylation (TsCl/Pyr, 0 °C) and NaI displacement (DMF at 80 °C) provided the iodide **2c** (b.p. 116–120 °C, 13 mmHg). The iodide **2c** is highly hindered and could be converted into the phosphonium salt **2d** only by keeping it in a TPP melt at 110 °C. Full details of this preparation may be obtained from the authors on request.

All experiments were conducted under an atmosphere of argon and THF was distilled from sodium/benzophenone. (+)-(*R*)-limonene, valencene and β-lupeol were purchased from Roth (Karlsruhe, FRG) and diploptene isolated from *Polypodium vulgare*.[6] All compounds were purified by distillation or by flash chromatography (FC) on Merck silica gel 60 (230–400 mesh) and had spectral and analytical data in accordance with the proposed structures.

General procedure for hydroboration. The alkene (5 mmol) was dissolved in THF (15 ml) and borane–THF complex (1 M in THF) added. The amounts of reagent and reaction temperatures required reflected increasing molecular complexity: **3a** (0.4 mol equiv., 0 °C), **4a** (0.7 mol equiv., 0 °C), **5a** (1 mol equiv., ambient) and **6a** (1 mol equiv., ambient). After the reaction had been stirred for 5 h excess 3 M NaOH and then excess 30 % H_2O_2 were added and the mixture stirred for 3 h at 50 °C. The product was recovered by extraction with diethyl ether and purified by FC (eluant: petroleum ether b.p. 40–60 °C containing increasing amounts [0–10 %] of diethyl ether). The products, **3b** (20 % yield), **4b** (70 % yield), **5b** (75 % yield) and **6b** (81 % yield), were obtained as inseperable mixtures (1:2 to 1:1) epimeric at the resulting tertiary C-atom.

General procedure for iodination. The alcohol (2 mmol) and TPP (3 mmol) were dissolved in THF (10 ml). DEAD (3.3 mmol) was added dropwise to the stirred solution at room temperature. After 5 min MeI (3.3 mmol) was added and stirring was continued until completion of the reaction (0.5 h or less). The solvent was removed under reduced pressure and the product isolated by FC (eluant: petroleum ether b.p. 40–60 °C containing increasing amounts of diethyl ether). Nearly quantitative yields of the iodides **3c–6c** were obtained from the alcohols **3b–6b**.

General procedure for Wittig salt formation. The iodide (3 mmol) was intimately mixed with ground TPP (20 mmol) and held at 110 °C for 12 h. After this time the reaction mixture was allowed to cool, $CHCl_2$ (5 ml) added and the product recovered by trituration with ethyl ether. The iodides **3c–5c** provided 75–95 % yields of the corresponding phosphonium salts **3d–5d** by this procedure. Even after prolonged reaction (48 h) the iodide **6c** provided only a 35 % yield of **6d**.

General procedure for the Wittig reaction. To a cooled solution (−15 °C) of phosphonium salt (2.5 mmol) in THF (5 ml) was added dropwise a solution (2.5 ml) of LHMDS (1

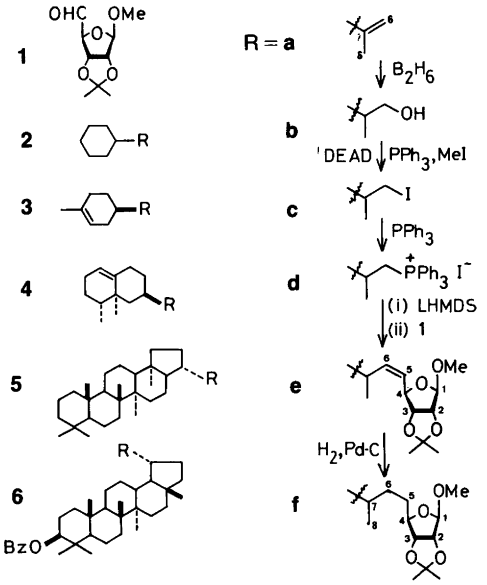

Fig. 1. Outline of the reaction sequence for the conversion of terpenes into terpenyl carbohydrates.

molar in THF). The resultant deep red mixture was stirred at −15 °C for 15 min and then allowed to attain 0 °C. The sugar derivative **1** (2.7 mmol) was added in a single portion and the resulting solution held at 0 °C for 5 min and then allowed to come to room temperature where it was kept for 15 min. (The phosphoranes from **5d** and **6d** were generated *in situ* and reacted with **1** at room temperature). After this time a saturated aqueous solution of NH_4Cl was added and the mixture extracted twice with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), evaporated under reduced pressure and the residue subjected to FC (eluant: petroleum ether b.p. 40–60 °C/diethyl ether = 9:1 or 95:5) to provide pure *Z–E* mixtures of C-7 epimeric alkenes **2e–5e**. Yields and *Z–E* ratios (GC) were as follows: **2e** 64 % (7:1), **3e** 43 % (9:1), **4e** 32 % (6:1) and **5e** 36 % (6:1). Since the reduced products lack the double bond no attempt was made to separate these isomers prior to catalytic hydrogenation which proceeded quantitatively.

General procedure for hydrogenation. The alkene (2 mmol, **2e–5e**) was dissolved in 30 ml methanol/ethyl acetate (3:7) and hydrogenated under an atmosphere of H_2 in the presence of 10 % Pd–C (100 mg). After 5–10 h, the mixture was filtered and the solvent removed under reduced pressure. FC as above gave quantitative yields of **2f–5f**.

While the progress of the synthesis could be monitored by mass spectrometry, the most significant spectroscopic evidence for the nature of the products was derived from the changes observed in the appropriate ^1H and ^{13}C NMR resonances. This is illustrated by the typical spectral extracts given below for compounds in the hopane series.

Alcohol (**5b**). MS [*m/z* (% rel. int.)]: 428 (8, *M*), 413 (5, *M*−15), 369 (17, *M*−side chain), 191 (100, ring C cleavage). ^{1}H NMR: δ 3.744 and 3.631 (1 H, 2 × dd, *J* 3.5 and 10.5 Hz; 3.2 and 10.6 Hz, H-6), 3.384 and 3.344 (1 H, 2 × dd, *J* 6.8 and 10.6 Hz; 7.3 and 10.5 Hz, H-6), 0.718 and 0.716 (3 H, 2 × d, *J* 4.2 Hz, H-8). ^{13}C NMR: δ 68.071 and 67.767 (C-7).

Wittig salt (**5d**). ^{1}H NMR: δ 4.224 and 4.130 (1 H, 2 × dt, *J* 15.4 and 11.1 Hz, H-6), 3.306 and 3.043 (1 H, 2 × t, *J* 15.4 Hz, H-6), 1.026 and 0.932 (3 H, 2 × d, *J* 6.5 Hz, H-8). ^{13}C NMR: δ 29.587 and 29.455 (d, *J* 46.0 Hz, C-7).

Wittig product (**5e**). MS [*m/z* (% rel. int.)]: 596 (7, *M*), 581 (21, *M*−15), 565 (29, *M*−31), 549 (12, *M*−15−32), 478 (19, *M*−58−60), 369 (38, *M*−side chain), 191 (100, ring C cleavage). NMR data for major component: ^{1}H NMR: δ 5.336 (1 H, t, *J* 10.4 Hz, H-5), 5.213 (1 H, t, *J* 10.4 Hz, H-6), 4.959 (1 H, s, H-1), 4.887 (1 H, d, *J* 10.1 Hz, H-4), 4.626 (1 H, d, *J* 5.9 Hz, H-3), 4.531 (1 H, d, 5.9 Hz, H-2), 3.314 (3 H, s, OMe), 2.657 (1 H, m, H-7), 1.315 and 1.501 (2 × 3 H, s, acetonide), 0.803 (3 H, d, *J* 8.9 Hz, H-8). ^{13}C NMR: δ 140.003 (C-5), 125.765 (C-6), 112.177 (Me_2C), 109.135 (C-1), 85.874, 85.457 and 83.061 (C-2, C-3, C-4).

Hydrogenation product (**5f**). MS [*m/z* (% rel. int.)]: 598 (3, *M*), 583 (28, *M*−15), 567 (26, *M*−31), 551 (*M*−15−32), 480 (24, *M*−58−60), 369 (27, *M*−side chain), 191 (100, ring C cleavage). NMR data for major component: ^{1}H NMR: δ 4.932 (1 H, s, H-1), 4.595 (1 H, d, *J* 6.0 Hz, H-2), 4.508 (1 H, d, *J* 6.0 Hz, H-3), 4.088 (1 H, br t, *J* 7.6 Hz, H-4), 3.343 (3 H, s, OMe), 1.477 and 1.317 (2 × 3 H, s, acetonide), 0.803 (3 H, d, *J* 9.2 Hz, H-8). ^{13}C NMR: δ 112.161 (Me_2C), 109.448 (C-1), 87.868, 85.629 and 84.328 (C-2, C-3, C-4).

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References

1. Bisseret, P. and Rohmer, M. *J. Org. Chem. 54* (1989) 2958 and refs. therein.
2. Kjær, A., Kjær, D. and Skrydstrup, T. *Tetrahedron 42* (1986) 1439.
3. Papaioannou, D., Francis, G. W., Aksnes, D. W., Brekke, T. and Maartmann-Moe, K. *Acta Chem. Scand. 44* (1990) 90.
4. Moustakis, C. A., Viala, J., Capdevilla, J. and Falck, J. R. *J. Am. Chem. Soc. 107* (1985) 5283.
5. Loibner, H. and Zbiral, E. *Helv. Chim. Acta 59* (1976) 2100.
6. Berti, G. and Bottari, F. 'Constituents of Ferns'. In: Reinhold, L. and Liwschitz, Y., Eds., *Progress in Phytochemistry,* Interscience, New York 1968, Vol. 1, p. 589 and refs. therein.

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