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Benzyl 2,3-*O* -isopropylidene-β-D-ribo-1,4-pentodialdofuranoside as a D-Ribose Chiron for the Synthesis of Terpenyl Tetraols and Aminotriols[1]

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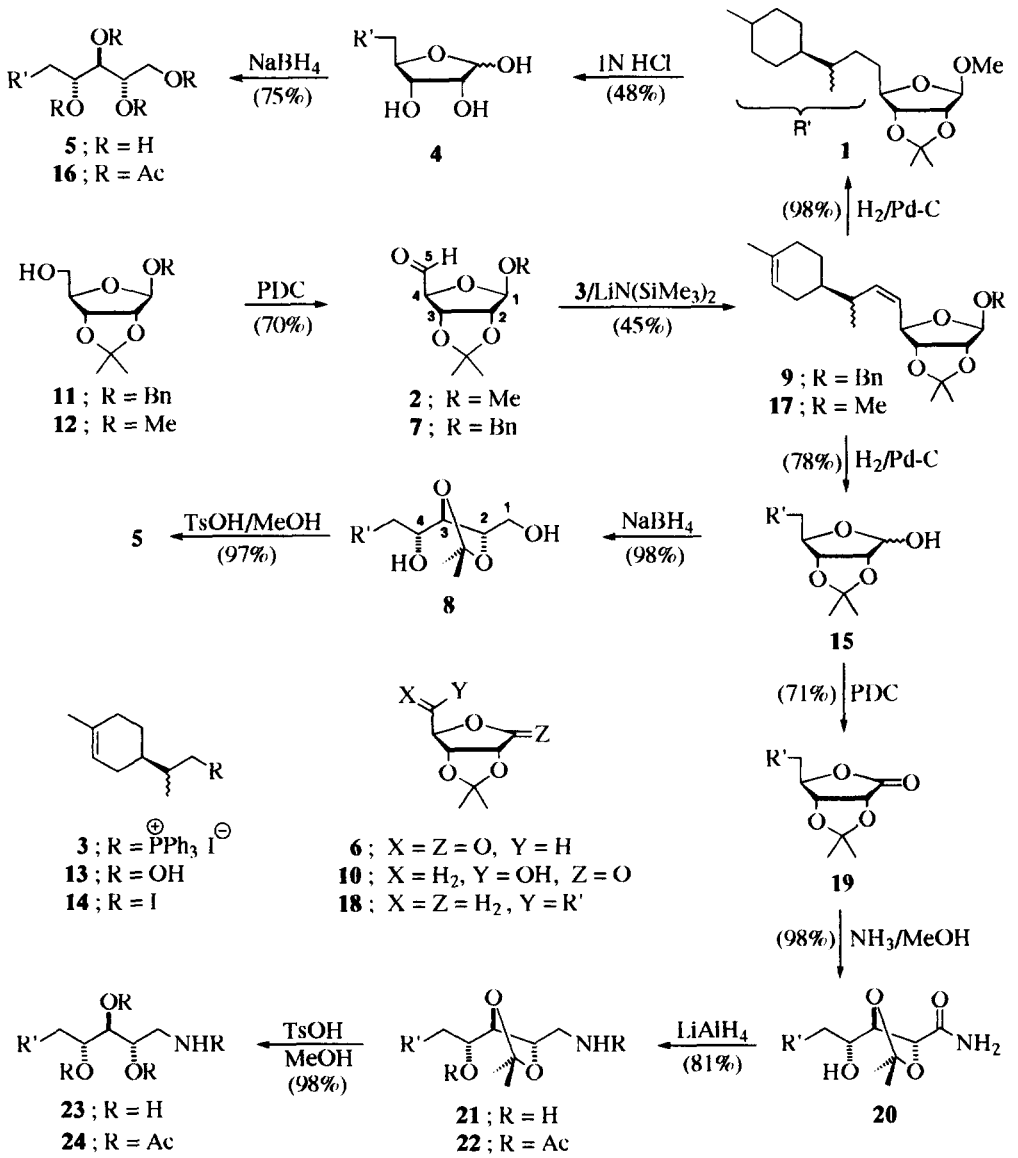
Abstract: Wittig condensation of title compound with a phosphorane derived from *R* -(+)-limonene followed by catalytic hydrogenation, provided a C-5 extended ribofuranose derivative, a model intermediate for the synthesis of terpenyl tetraols, *via* $NaBH_4$ reduction, and terpenyl aminotriols *via* sequential pyridinium dichromate oxidation, ammonolysis and $LiAlH_4$ reduction.

We have recently shown that a variety of C-5 chain-extented D-ribose derivatives, *e.g.* **1**, can be easily accessible using as key-step a Wittig condensation of the D-ribose chiron **2** and the appropriate phosphonium salt, *e.g.* **3**, obtained from a suitable naturally occurring terpene, followed by catalytic hydrogenation.[2] However, deprotection of such derivatives by heating with aqueous HCl in dioxane, *i.e.* using conditions precognized to effect complete deprotection of the sugar moiety of similar substrates,[3] was accompanied by moderate yields[4] to give *e.g.* furanoside **4**. This compound, upon $NaBH_4$ reduction, provided unexceptionally tetraol **5**, a simple structural analog of hopanepolyols. Hopanepolyols, aminohopanepolyols and their derivatives are well-represented bacterial triterpenoids.[5] We now wish to communicate our findings on the development of alternative D-ribose chirons which do not require strong acid conditions for glycoside bond hydrolysis and thus preserve the acetonide protection.

We conceived that two such obvious chirons would be the D-ribonolactone acetonide **6** and the benzyl riboside **7**. It was thus anticipated that Wittig reaction of **6** with *e.g.* **3**, followed by catalytic hydrogenation and $LiAlH_4$ reduction, would provide the acetonide **8**. On the other hand, use of riboside **7** in the Wittig reaction, would lead to the alkene **9** which by simultaneous catalytic hydrogenation of the double bonds and benzylic hydrogenolysis, followed by $NaBH_4$ reduction, would lead to the same acetonide **8**. Acetonide deprotection with MeOH/TsOH[6] at RT is a well-established mild method suitable to complete nicely the proposed syntheses. This partially protected tetraol derivative **8** was simultaneously projected as a key-intermediate for the synthesis of terpenyl aminotriol derivatives.

However, preliminary experiments aiming to obtain pure aldehyde **6** by oxidizing the alcohol **10**,

easily accessible from the commercially available D-ribonolactone through ketalisation with acetone,[7] using the Swern and Moffatt-Pfitzner oxidations as well as pyridinium dichromate (PDC)[8] were unsuccessful.[9] On the other hand, oxidation of the sugar alcohol **11** with PDC proceeded in the same manner as with the corresponding methyl riboside **12**,[8] giving a 70% yield of the expected aldehyde **7**.[10] Alcohol **11**, was in turn readily obtained from D-ribose in 50% yield by reacting the latter with an excess of benzyl alcohol in acetone in the presence of conc. H_2SO_4.[11]



The applicability of this aldehyde to the assembly of the required terpenyl carbohydrate skeleton was tested by its condensation with the phosphonium salt **3**. This salt had been earlier obtained in 29% overall yield from R-(+)-limonene through hydroboration-oxidation, followed by Mitsunobu-type iodination and reaction with triphenylphosphine (TPP).[2] At this stage we decided to improve this low overall yield which was mainly due to the inefficient hydroboration of R-(+)-limonene. Thus, by changing the diborane to the bulky and therefore more regioselective 9-BBN, a 92% yield of the alcohol **13** was secured. ^{1}H-NMR examination of this alcohol showed the presence of the two expected epimers at the newly formed chiral center in the ratio 2:1. Using diborane, this ratio was found to be 1:1. Alcohol **13** was then converted to the iodide **14** which upon reaction with TPP in a melt, as described earlier,[2] produced a 92% yield (85% overall yield) of the phosphonium salt **3**. Wittig reaction of this salt with aldehyde **7**, also in the way described earlier,[2] produced the expected Wittig adduct (only the major *Z*-isomer **9** is shown here) in 45% yield, as a mixture of isomers.

Simultaneous catalytic hydrogenation and hydrogenolysis of the latter mixture of isomeric alkenes was performed in glacial AcOH in the presence of 10% Pd-C to produce a 78% yield of the lactol **15**. This was then reduced unexceptionally with $NaBH_4$ in MeOH to provide the diol **8** in 98% yield. Finally, transketalisation of **8** with MeOH/TsOH for 18 h at RT completed the synthesis of the tetraol **5** in 97% yield. Tetraol **5** was best characterized as the corresponding tetraacetate **16.** For comparison, the same tetraol was obtained from the alternative Wittig adduct **17** by catalytic hydrogenation (98% yield), aqueous HCl mediated hydrolysis (48% yield) and finally $NaBH_4$ reduction (75% yield). Adduct **17** had been prepared earlier[2] in 42% yield through Wittig condensation of aldehyde **2** with phosphonium salt **3**. Attempts to convert diol **8** to the amino analog **21**, either through its reaction with the system TPP/ diethyl azodicarboxylate/ phthalimide,[12] followed by hydrazinolysis, or *via* selective protection of the secondary hydroxy function were unsuccessful. In particular, the only product isolated from the attempted direct phthalimidation of **8** was the tetrahydrofuran derivative **18**, from an intramolecular redox dehydration. However, oxidation of the lactol **15** with PDC in CH_2Cl_2[2] produced a 71% yield of the lactone **19**. Routine ammonolysis of the latter, in MeOH for 12 h at RT, produced the amide **20**, in 98% yield, which upon $LiAlH_4$ reduction for 6 h in refluxing THF provided the partially protected aminotriol **21** in 81% yield. Acetonide **21** was deprotected with MeOH/TsOH, in 98% yield, to afford the aminotriol **23**. Acetonide **21** and aminotriol **23** were best characterized as the diacetate **22** and tetraacetate **24**, respectively. Application of the present synthetic protocol to the synthesis of aminohopanetriol as well as its amino acid derivatives is now in progress.

REFERENCES AND NOTES

1. New compounds gave analytical and spectral data in agreement with the proposed structures. The PMR spectra were recorded in $CDCl_3$ solutions using TMS as internal standard at 400.13 MHz. Chemical shifts (δ) for the diagnostically most significant sugar part of important intermediates and final products are provided below. Peracetylated compounds showed sharp singlets for each Ac group at *ca.* 2.09-2.07 (AcO) and 1.99-1.97 (AcNH) ppm. *Furanoside* **7** : 9.63 (1H, s, H-5), 7.40-

7.25 (5H, m, Ph-H), 5.27 (1H, d, *J* 0.6 Hz, H-1), 5.10 (1H, d, *J* 5.9 Hz, H-4), 4.83 and 4.61 (2H, two d, *J* 11.9 Hz, $OC\underline{H}_2Ph$), 4.58 (1H, dd, *J* 5.9 and 0.6 Hz, H-3), 4.51 (1H, t, *J* 0.6 Hz, H-2), 1.48 and 1.32 (6H, two s, $C\text{-}C\underline{H}_3$). *Acetonide* **8** : 4.29 (1H, dt, *J* 5.4 and 8.9 Hz, H-2), 3.99 (1H, dd, *J* 7.1 and 8.9 Hz, H-3), 3.84 (1H, dd, *J* 8.9 and 12.5 Hz, H-1a), 3.72 (1H, dd, *J* 5.4 and 12.5 Hz, H-1b), 1.37 and 1.32 (6H, two s, OC-Me).*Tetraacetate* **16** : 5.28 (1H, m, *J* 1.3, 2.4, 5.7 and 6.4 Hz, H-2), 5.24 (1H, ddd, *J* 1.4, 4.3 and 5.7 Hz, H-3), 5.04 (1H, ddd, *J* 1.3, 4.3 and 8.5 Hz, H-4), 4.39 (1H, ddd, *J* 1.4, 2.4 and 12.1 Hz, H-1a), 4.15 (1H, dd, *J* 6.4 and 12.1 Hz, H-1b). *Lactone* **19** : 4.74 (1H, d, *J* 5.3 Hz, H-2), 4.52 (1H, d, *J* 5.3 Hz, H-3), 4.52 (1H, dd, *J* 6.3 and 9.8 Hz, H-4), 1.48 and 1.39 (6H, two s, OCMe). *Acetonide* **22** : 5.80 (1H, br. m, $N\underline{H}Ac$), 4.94 (1H, m, H-4), 4.22-4.10 (2H, m, H-2 and H-3), 3.78 (1H, ddd, *J* 2.9, 8.1 and 13.5 Hz, H-1a), 2.93 (1H, ddd, *J* 3.5, 9.3 and 13.5 Hz, H-1b), 1.44 and 1.34 (6H, two s, OCMe).*Tetraacetate* **24** : 5.77 (1H, m, $N\underline{H}Ac$), 5.17 (1H, ddd, *J* 1.1, 4.1 and 6.1 Hz, H-4), 5.07 (1H, ddd, *J* 3.3, 6.4 and 9.3 Hz, H-2), 5.00 (1H, dd, *J* 4.1 and 9.3 Hz, H-3), 3.69 (1H, ddd, *J* 3.3, 5.9 and 14.8 Hz, H-1a), 3.38 (1H, dt, *J* 6.4 and 14.8 Hz, H-1b).

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10. Furanoside **7** had m.p. 85-88° C (from EtOAc/hexane); $[\alpha]_D^{25}$ -66.9° (c 0.5, $CHCl_3$); FT-IR (KBr) : 1740 cm^{-1}; FAB-MS [m/z (% rel. int.)] : 279 (39, *M*H), 249 (13, [*M*H-H_2CO]), 171(100, [*M*H- BnOH]). This compound has been recently used for the assembly of a tunicamine derivative. Karpiesiuk, W.; Banaszek, A. *Bioorg. & Med. Chem. Lett.* **1994**, 7, 879-882
11. D-ribose (10 mmol), acetone (6 ml), BnOH (10 ml) and conc. H_2SO_4 (0.12 ml) were refluxed for 3h and then neutralized with solid Na_2CO_3. Acetone was evaporated under reduced pressure and the residue was taken up in water and extracted thrice with EtOAc. The organic layers were combined, dried and evaporated and the residue short path distilled at 0.1 mm Hg and 100° C (bath temperature) to remove excess of BnOH. Benzyl 2,3-*O*- isopropylidene-β-D-ribofuranoside (**11**), obtained pure by flash column chromatography (eluent: EtOAc/PhMe ; 1:4), had m.p. 108-110° C (from EtOAc/ hexane); $[\alpha]_D^{25}$ -113° (c 1, $CHCl_3$); FT-IR (KBr) : 3450 cm^{-1} . This compound has been earlier prepared from D-ribose, in *ca.* 30% overall yield, using a two-step synthetic protocol. Rauch, E.M.; Lipkin, D. *J. Org. Chem.* **1962**, *27*, 403-406.
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