Carbohydrates to carbocycles: an expedient synthesis of pseudo-sugars

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A short and versatile synthesis of pseudo-sugars from sugars utilizing the Claisen rearrangement as the key step is described.

Conversion of sugars into carbocycles is an area which has attracted considerable attention in recent times.[1] Some important methodologies for achieving this are (i) Ferrier's mercuric ion mediated conversion of 6-deoxyhex-5-enopyranosyl compounds to deoxyinososе derivatives,[2] (ii) the radical cyclization approach of RajanBabu[3] and (iii) the zirconium mediated ring contraction of carbohydrate derivates to carbocycles by Taguchi.[4]

Pseudo-sugars are 2,3,4,5-tetrahydroxy-1-(hydroxymethyl)cyclohexanes, in which the ring oxygen atom of a sugar has been replaced by a methylene group. Pseudo-D-glucose, pseudo-D-galactose and pseudo-D-fructose have been suggested as replacements for their sugar counterparts as non-nutritive sweeteners.[5] Amino pseudo-sugars, which form the aglycon part of many aminoglycoside antibiotics, have chemotherapeutic potential as glycosidase inhibitors.[6] Pseudo-sugars and some related carbocyclic compounds are components of some antibiotics (validamycins) and enzyme inhibitors (adiposins).[7]

The biological significance of pseudo-sugars has led to the development of several approaches for their synthesis in optically pure form from various chiral sources. A comprehensive review on pseudo-sugars has been published.[8] Pseudo-β-D-altro-, pseudo-α-L-manno- and pseudo-β-D-gluco-pyranoses have been synthesized by Hudlicky[9] from homochiral microbial metabolites. Vandewalle[10] prepared eight pseudo-sugars belonging to the allo, gulo, manno and talo series which possess 2,3-*cis*-diol units from (1*R*,2*S*,3*R*,4*S*)-4-butyryloxy-2,3-(propane-2,2-diyldioxy)cyclohex-5-en-1-ol. The synthetic versatility of quinic acid was demonstrated by Shing in his synthesis of pseudo-β-D-manno-,[11] pseudo-β-D-fructo-,[11] pseudo-α-D-gluco-[12] and pseudo-α-D-manno-pyranoses.[12] Ferrier prepared crystalline pseudo-α-D-glucopyranose[13] from 2-deoxyinososе.

It occurred to us (as shown in the retrosynthesis in Scheme 1), that controlled hydroxylation of cyclohexene **1** should lead to the four pseudo-sugars, pseudo-α-D-glucopyranose, pseudo-α-D-mannopyranose, pseudo-β-D-glucopyranose and pseudo-β-D-mannopyranose. The conversion of **2** to **1** involves transformation of a glycal derivative into a cyclohexene, prototypes of which have been reported earlier by Büchi.[14] Compound **1** in turn can be readily derived from D-glucose *via* **2** and **3**. We describe here the successful realization of this strategy.

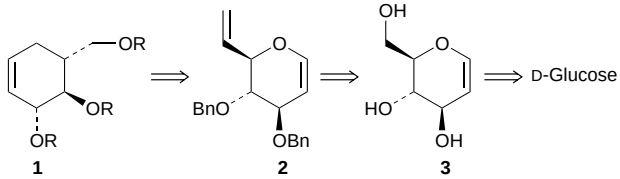
The primary hydroxy group in **4** was oxidized using pyridinium dichromate (PDC) to the aldehyde **5**, which was used without purification.[15] In order to introduce the C6–C7 double bond in **2**, methylenation of **5** was investigated under various conditions. Treatment of **5** with methyltriphenylphosphonium iodide and Bu^{n}Li led to a complex mixture. Wittig olefination of **5** with formylmethylene(triphenyl)-phosphorane and decarbonylation of the resultant unsaturated aldehyde with Wilkinson's catalyst gave **2** in very low yield. Finally, a combination of methyltriphenylphosphonium iodide and sodamide gave **2** in 40% overall yield from **4**.

Heating **2** in a sealed tube in *o*-dichlorobenzene at 240 °C afforded the rearranged chiral carbocycle **6** in 84% yield, based on recovered starting material (4%). The product **6**, being unstable, was subjected to $NaBH_4$ reduction without purification to give **1**.‡ The IR spectrum of **1** showed an olefin band at 1643 cm^{-1} and the presence of a hydroxy absorption at 3445 cm^{-1}. Unlike **2**,§ which showed the presence of five olefinic protons in its ^{1}H NMR spectrum, the rearranged carbocycle **1** exhibited only two olefinic protons as a multiplet at δ 5.74–5.78. The presence of the double bond in **1** was further confirmed from its ^{13}C NMR spectrum, which displayed resonances at δ 125.95 and 138.42 (Scheme 2).

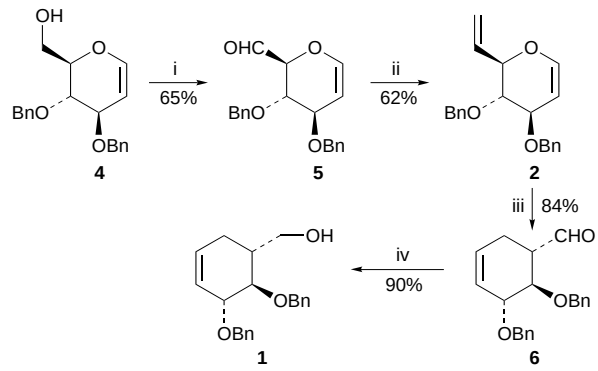
Having synthesized the highly functionalized chiral synthon **1**, attempts were made to prepare the four pseudo-sugars, namely, pseudo-α-D-glucopyranose, pseudo-α-D-mannopyranose, pseudo-β-D-glucopyranose and pseudo-β-D-mannopyranose.

Catalytic OsO_4 dihydroxylation[16] of the double bond in **1** from the less hindered β-face gave the triol **7** in quantitative yield, which on debenzylation with 20% $Pd(OH)_2/C/H_2$ yielded pseudo-α-D-glucopyranose **8**, $[\alpha]_D$ +57.0 (*c* 0.65, H_2O) [lit.,[12] + 63.0 (*c* 0.6, H_2O)].

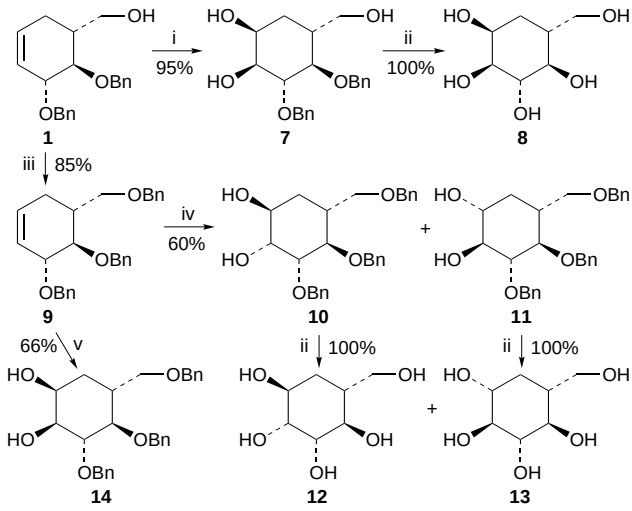
The primary hydroxy group in **1** was protected as the benzyl ether to yield **9**.¶ A mixture of partially benzylated pseudo-α-D-mannopyranose **10** and pseudo-β-D-glucopyranose **11** was obtained in one step from **9** involving a sequence of epoxidation and ring opening using MCPBA, water and 10% H_2SO_4.[17] Purification and separation by preparative TLC of the partially benzylated mixture gave **10** and **11** in 34 and 26% yields, respectively. Deprotection under similar conditions as those for



Scheme 1



Scheme 2 *Reagents and conditions*: i, PDC, 4 Å molecular sieves, CH_2Cl_2, room temp., 10 h; ii, Ph_3MePI, $NaNH_2$, Et_2O, room temp., 30 min; iii, *o*-dichlorobenzene, 240 °C (sealed tube), 1 h; iv, $NaBH_4$, THF, room temp., 10 min



Scheme 3 *Reagents and conditions*: i, OsO_4, $K_3Fe(CN)_6$, K_2CO_3, Bu^{t}OH, H_2O, 24 h; ii, 20% $Pd(OH)_2/C/H_2$, 55 psi, 2 h; iii, NaH, DMF, BnBr, room temp., 10 h; iv, MCPBA, H_2O, 10% H_2SO_4, 48 h; v, aq. AcOH, AgOAc, I_2, Na (cat.), MeOH, 15 h

7 gave pseudo-α-mannopyranose **12**, $[\alpha]_D$ +1.5 (*c* 0.4, MeOH) [lit.,[12] $[\alpha]_D$ +1.9 (*c* 1.0, MeOH)], and pseudo-β-D-glucopyranose **13**, $[\alpha]_D$ +10.0 (*c* 0.3, H_2O) [lit.,[18] $[\alpha]_D$ +10.9 (*c* 0.83, H_2O)], from **10** and **11**, respectively, in quantitative yields (Scheme 3).

cis-Hydroxylation[19] of the alkene **9** under Woodward's conditions gave in 66% yield the tribenzyl diol **14** which on debenzylation afforded only pseudo-α-D-glucopyranose instead of the anticipated pseudo-β-D-mannopyranose, in quantitative yield. This is surprising as Woodward's hydroxylation is expected to give overall *syn*-hydroxylation from the more hindered face, in contrast to the osmium tetroxide hydroxylation.

The ^{1}H NMR spectra of all the pseudo-sugars were in consonance with the data reported in the literature. The structures of all new compounds were unambiguously established from their spectral and analytical data wherever appropriate.

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Notes and References

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‡ *Selected data* for **1**: ν_{max}(neat)/cm^{-1} 3445, 2924, 1454, 1093, 1028, 698; δ_H($CDCl_3$) (200 MHz) 1.81–2.21 (m, 3 H), 2.52–2.66 (br s, 1 H), 3.57–3.71 (m, 3 H), 4.20–4.27 (m, 1 H), 4.67–5.03 (m, 4 H), 5.74–5.78 (m, 2 H), 7.30–7.48 (m, 10 H); δ_C($CDCl_3$; 50 MHz) 138.42, 128.57, 128.48, 128.21, 127.87, 127.72, 125.95, 82.00, 81.15, 74.30, 71.30, 65.53, 40.62, 28.05 (Found: C, 77.80; H, 7.46. Calc. for $C_{21}H_{24}O_3$. C, 77.74; H, 7.46%).

§ *Selected data* for **2**: ν_{max}(neat)/cm^{-1} 3065, 2862, 1643, 1238, 1095, 696; δ_H($CDCl_3$; 200 MHz) 3.58–3.65 (dd, 1 H), 4.21–4.26 (dd, 1 H), 4.30–4.40 (t, 1 H), 4.61–4.92 (m, 4 H), 5.29–5.48 (m, 3 H), 5.94–6.14 (m, 1 H), 6.40–6.45 (d, 1 H), 7.20–7.33 (m, 10 H); δ_C($CDCl_3$; 50 MHz) 144.63, 139.90, 139.82, 134.54, 128.47, 128.02, 127.81, 127.71, 118.23, 100.48, 78.50, 78.11, 75.63, 73.87, 70.74 (Found: C, 78.28; H, 6.85. Calc. for $C_{21}H_{22}O_3$; C, 78.23; H, 6.88%).

¶ *Selected data* for **9**: ν_{max}(neat)/cm^{-1} 3030, 1496, 1454, 1155, 1097, 696; δ_H($CDCl_3$; 200 MHz) 2.02–2.30 (m, 3 H), 3.54–3.75 (m, 3 H), 4.12–4.24 (m, 1 H), 4.50–4.92 (m, 6 H), 5.66–5.85 (m, 2 H), 7.24–7.40 (m, 15 H); δ_C($CDCl_3$; 50 MHz) 139.14, 138.76, 128.52, 128.34, 127.91, 127.78, 127.51, 126.17, 81.11, 79.62, 74.29, 73.17, 71.44, 70.64, 39.47, 28.80 (Found: C, 81.18; H, 7.31. Calc. for $C_{28}H_{30}O_3$: C, 81.12; H, 7.29%).

1 R. J. Ferrier and S. Middleton, *Chem. Rev.*, 1993, **93**, 2779.
2 R. J. Ferrier, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1455.
3 T. V. RajanBabu, *Acc. Chem. Res.*, 1991, **24**, 139.
4 T. Taguchi, H. Ito, Y. Motoki and Y. Hanzawa, *J. Am. Chem. Soc.*, 1993, **115**, 8835.
5 S. Ogawa, Y. Uematsu, S. Yoshida, N. Sesaki and T. Suami, *J. Carbohydr. Chem.*, 1987, **6**, 471.
6 T. K. M. Shing and L. H. Wan, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1643.
7 S. Ogawa, *Yuki. Gosei Kagaku Kyokai Shi*, 1985, **43**, 26.
8 T. Suami and S. Ogawa, *Adv. Carbohydr. Chem. Biochem.*, 1990, **28**, 41.
9 D. A. Entwistle and M. Hudlicky, *Tetrahedron Lett.*, 1995, **36**, 2591.
10 L. Pingli and M. Vandewalle, *Synlett*, 1994, 228.
11 T. K. M. Shing and Y. Tang, *Tetrahedron*, 1991, **47**, 4571.
12 T. K. M. Shing, Y. Cui and Y. Tang, *J. Chem. Soc., Chem. Commun.*, 1991, 756.
13 R. J. Ferrier and R. Blattner, *J. Chem. Soc., Chem. Commun.*, 1987, 1008.
14 G. Büchi and J. E. Powell Jr., *J. Am. Chem. Soc.*, 1967, **89**, 4559.
15 B. Fraser-Reid, R. A. Alonso, G. D. Vite and R. E. McDevitt, *J. Org. Chem.*, 1992, **57**, 573.
16 K. Yamamoto, M. Minato and J. Tsuji, *J. Org. Chem.*, 1990, **55**, 766.
17 F. Fringuelli, R. Germani, F. Pizzo and G. Savelli, *Synth Commun.*, 1989, **19**, 1939.
18 H. Paulsen and W. von Deyn, *Justus Liebigs. Ann. Chem.*, 1987, 125.
19 R. B. Woodward and F. V. Brutcher Jr., *J. Am. Chem. Soc.*, 1958, **80**, 209.

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