Stereoselective Synthesis of Rare (D and L) Saccharides by a Facile Intramolecular Rearrangement of Hemiacetal Heptanolactone Alcohols†

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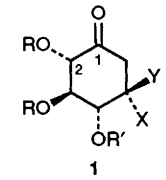
The hemiacetal heptanolactone alcohols **2a, b, c** and **d** undergo a facile acid catalysed, stereospecific intramolecular rearrangement to yield the rare D and L saccharides **3, 4, 5** and **6** respectively.

Stereoselective synthesis of oligosaccharides continues to command interest owing to their significant role in bio-regulatory processes.[1] In spite of the availability of several methods for this specific purpose there still exists ample scope for the development of new methods.[2] Our continued interest in this direction resulted in the development of a general route for the synthesis of rare (D and L) saccharides wherein the hemiacetal heptanolactone alcohols **B** undergo a facile intramolecular nucleophilic displacement to form D- and or L-furanosaccharides **C** (Scheme 1). Lactone alcohols **B** themselves are easily accessible by regio- and stereo-specific oxidation of the cyclohexanone alcohol **A**. Steps i and ii have been found to be highly stereospecific leading to the formation of rare saccharides that are hitherto difficult to synthesize.[3]

Thus, Baeyer-Villiger oxidation of 2*S*,3*R*,4*S*,5*S*/5*R*-tribenzyloxy-5-hydroxycyclohexanones (**1a** and **b**)[4] with *m*-chloroperbenzoic acid (MCPBA) at room temperature afforded the crystalline hemiacetal lactone alcohols **2a** (m.p. 95 °C) and **2b** (m.p. 84 °C) respectively in high yields (89–92%) due to the stereospecific migration of the C–C bond



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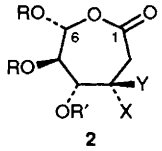

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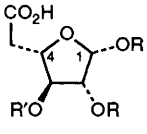
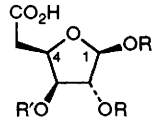
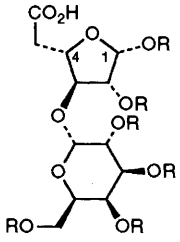


3 R = R′ = CH_2Ph

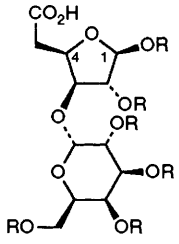
a; R = R′ = CH_2Ph, X = OH, Y = H
b; R = R′ = CH_2Ph, X = H, Y = OH
c; R = CH_2Ph, R′ = 2, 3, 4, 6 -tetra-*o*-benzyl-α-D-galactopyranosyl, X = OH, Y = H
d; R = CH_2Ph, R′ = 2, 3, 4, 6 -tetra-*o*-benzyl-α-D-galactopyranosyl, X = H, Y = OH



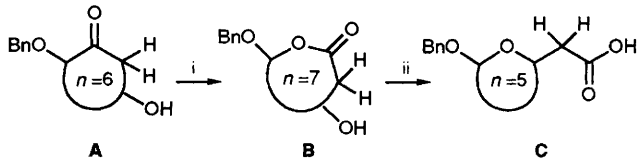
4 R = R′ = CH_2Ph



5 R = CH_2Ph

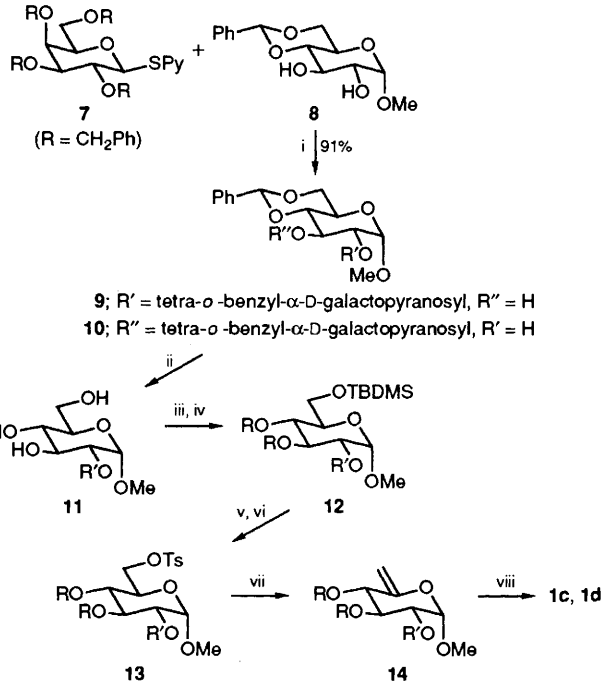


6 R = CH_2Ph



A **B** **C**

Scheme 1 *Reagents and conditions*: i, MCPBA–CH_2Cl_2, room temp., *ii* TsOH–CH_2Cl_2, room temp., (*n* = ring size, Bn = benzyl)



7 (R = CH_2Ph) **8**

9; R′ = tetra-*o*-benzyl-α-D-galactopyranosyl, R″ = H
10; R″ = tetra-*o*-benzyl-α-D-galactopyranosyl, R′ = H

11 **12** **13** **14**

Scheme 2 *Reagents and conditions*: i, MeI, CH_2Cl_2, 4 Å molecular sieves, 50 °C, 48 h;[2] ii, TsOH–acetone–water, room temp., 6 h; iii, *tert*-butyldimethylsilyl chloride (TBDMSCl)–pyridine (py), room temp., 4 h; iv, BnBr–NaH–dimethylformamide, 0–25 °C; v, Bu_4NF–tetrahydrofuran, room temp., 2 h; vi, TsCl–py, room temp., 6 h; vii, NaI–dimethyl sulfoxide–1,8-diazabicyclo[5.4.0]undec-7-ene;[6] viii, $Hg(OCOCF_3)_2$–acetone–H_2O (2 : 1), room temp., 18 h

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attached to the electron rich benzyloxy substituent at C-2. Formation of **2a** and **b** was evident from the appearance of H-2 as a doublet at *ca.* δ 5.31 ($J_{2,3}$ 7.5 Hz) in the ^{1}H NMR spectra (200 MHz). Treatment of **2a** and **b** separately with a catalytic amount of toluene-*p*-sulfonic acid (TSOH) in dichloromethane at room temperature gave the β-L- and D-5-deoxy-*xylo*hexofuranosiduronic acid derivatives **3** and **4** in 89–91% yields. Compounds **3** and **4** were characterised from ^{1}H and ^{13}C NMR spectra.‡[5] For a greater refinement of this process the 4-*O*-α-galactosyl substituted cyclohexanones **1c** and **d** were converted to the lactone alcohols **2c** and **d** (step ii, 87% yield) and were rearranged efficiently to give the rare β-L and D-disaccharides **5** and **6** respectively (80–82% yield).§[5] **1c** and **d** were synthesized as outlined in Scheme 2. The reaction of **7** and **8** with activation by methyl iodide[2] provided the 1,2-*cis* linked saccharides **9** and **10**, which were separated by column chromatography and characterized. Compound **9** was processed further to the 5,6-enosaccharide **14** by standard functional group chemistry (Scheme 2). Ferrier rearrangement[4] of the labile **14** with catalytic amount of $Hg(OCOCF_3)_2$ in acetone and water (2:1) at room temperature for 18 h gave **1c** and **d** in a ratio of 2:1 in an overall yield of 34% from **9**. The ease of variation of the stereocentres and glycosyl substitution in preparing analogues of **1** by Scheme 3 is evident, thus, indicating the scope and utility of this reaction for obtaining several other saccharides.

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‡ *Spectroscopic data*: ^{1}H NMR (200 MHz), ^{13}C NMR (50 MHz), $CDCl_3$: For **3** $[\alpha]^{25}_D$ −56.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 2.58 (dd, 1H, $J_{5a,5b}$ 13.4 Hz, $J_{4,5a}$ 8.1 Hz, H-5a), 2.69 (dd, 1H, $J_{4,5b}$ 5.4 Hz, H-5b), 3.75 (ddd, 1H, $J_{3,4}$ 2.95 Hz, H-4), 4.04 (dd, 1H, $J_{1,2}$ 0.8 Hz, H-2), 4.3–4.8 (m, 7H, H-3 and benzylic), 5.05 (d, 1H, H-1), 7.15–7.40 (arom.), (CO_2H not observed); ^{13}C NMR δ 104.9 (C-1), 169.1 (CO_2H); IR ν/cm^{-1} ($CHCl_3$) 1705. For **4** $[\alpha]^{25}_D$ −16.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 2.6–2.85 (m, 2H, H-5a, 5b), 4.02–4.20 (m, 2H, H-2, 4), 4.35–4.85 (m, 7H, H-3 and benzylic), 5.10 (d, 1H, $J_{1,2}$ 1.5 Hz, H-1), 7.2–7.4 (arom.) (CO_2H not observed); ^{13}C NMR δ 105.8 (C-1), 168.5 (CO_2H); IR ν/cm^{-1} ($CHCl_3$) 1701.

§ *Spectroscopic data* for **5**: $[\alpha]^{25}_D$ +6.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 2.74 (dd, 1H, $J_{5a,5b}$ 13.6 Hz, $J_{4,5a}$ 5.4 Hz, H-5a), 2.88 (dd, 1H, $J_{4,5b}$ 8.4 Hz, H-5b), 3.65–3.75 (m, 2H, H-6′a, 6′b), 3.8–4.9 (m, 22H, H-2/4, H-1′/5′ and benzylic), 4.98 (d, 1H, $J_{1',2'}$ 4.4 Hz, H-1′), 5.06 (s, 1H, H-1), 7.15–7.3 (arom.) (CO_2H not observed); ^{13}C NMR δ 99.3 (C-1′), 105.3 (C-1), 173.5 (CO_2H); IR ν/cm^{-1} ($CHCl_3$) 1710. For **6** $[\alpha]^{25}_D$ +28.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 2.65–2.8 (m, 2H, H-5a, 5b), 3.38–3.55 (m, 2H, H-6′a, 6′b), 3.8–4.85 (m, 22H, H-2/4, H-2′/5′ and benzylic), 4.89 (d, 1H, $J_{1',2'}$ 4.9 Hz, H-1′), 5.03 (s, 1H, H-1), 7.1–7.3 (arom.) (CO_2H not observed); ^{13}C NMR δ 99.4 (C-1′), 105.6 (C-1), 171.2 (CO_2H); IR ν/cm^{-1} ($CHCl_3$) 1702.

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