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Note

Synthesis of new enantiomerically pure polyhydroxylated azetidines from monosaccharides

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Abstract

Catalytic hydrogenation of O-protected galactopyranoside-fused azetidines led to enantiomerically pure polyhydroxylated azetidines possessing four chiral centers. © 1997 Elsevier Science Ltd.

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In a previous paper [1] we reported the synthesis of monosaccharide derivatives bearing an azetidine ring fused on C-4 and C-6 of the pyranose ring. As azetidines themselves represent an interesting class of heterocycles with biological interest [1], it was important to demonstrate the potential of using these monosaccharides for an access to new functionalized enantiopure azetidines, thus opening a route for further structural modifications.

We describe herein the transformation of benzyl 2,3-di-*O*-benzyl-4,6-dideoxy-4,6-methylimino-α,β-D-galactopyranosides (**1**) and benzyl 2,3-di-*O*-benzyl-4,6-*tert*-butylimino-4,6-dideoxy-α,β-D-galactopyranosides (**2**) into azetidines substituted at C-2 and C-3 by a trihydroxylated chain and a hydroxyl group, respectively. As the ring opening of these pyranosides led to the loss of chirality at C-1, it is thus possible to perform the hydrogenolysis from either pure anomers or their mixtures.

Classical treatment of benzyl 2,3-di-*O*-benzyl-4,6-dideoxy-4,6-methylimino-α,β-D-galactopyranosides (**1**) with hydrogen under a pressure of 50 psi in the presence of 10% palladium-on-charcoal catalyst failed, and the starting material remained unchanged after several days. This could be explained by the presence of a tertiary amino group in the substrate, which has been described in some instances preventing catalytic hydrogenolysis of *O*-benzyl ethers [2]. Treatment of **1** under catalytic hydrogen-transfer conditions using 10% palladium-on-charcoal and ammonium formate in refluxing methanol led to a complex mixture of polar compounds that was not further investigated. Debenzylation of **1** was finally performed by hydrogenolysis in ethyl acetate–methanol at room temperature under a pressure of hydrogen (50 psi) in the presence of 20% palladium hydroxide-on-charcoal. TLC indicated complete cleavage of the *O*-benzyl ether after 24 hours, and (2*S*,3*R*)-1-methyl-2-[(1*S*,2*S*)-1,2,3-trihydroxypropyl]-3-hydroxyazetidine (**3**) was obtained. The pure azetidine **3** (Scheme 1) was obtained by recrystallization from methanol (yield 24%). The compound gave elemental analysis data in good agreement with the expected formula, and its

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[1] See references cited in ref. [1].

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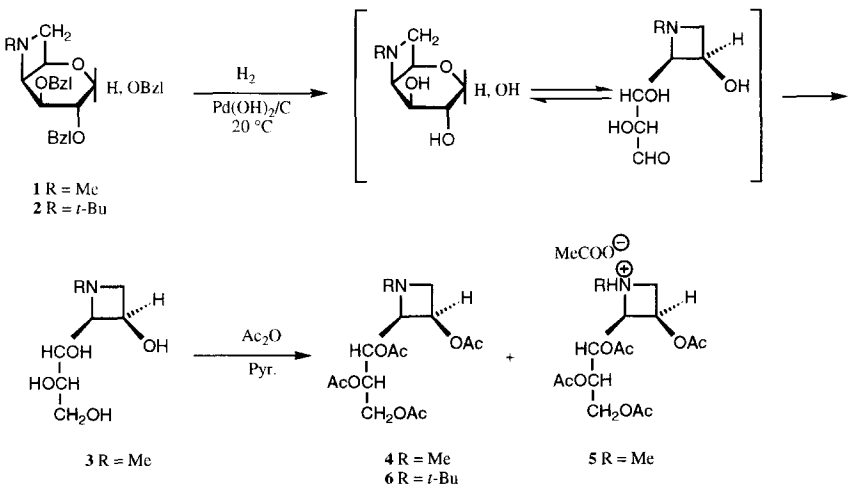
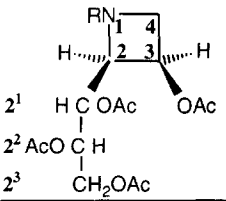


Scheme 1.

structure was confirmed by ^{1}H and ^{13}C NMR spectroscopy (see Tables 1 and 2).

The ^{1}H NMR spectrum in dimethyl sulfoxide-d_6 showed particularly a singlet at 2.28 ppm, attributed to the N-methyl protons, two broad signals (2 H) at 5.04 and 4.00 ppm and a large signal (5 H) from 3.90 to 3.25 ppm. The two first signals disappeared after addition of deuterium oxide, while signals (3 H) remained in place for the latter, thus confirming the presence of four hydroxyl groups. The ^{13}C NMR

Table 1
^{1}H NMR data ($CDCl_3$, 400 MHz) for compounds **4**, **5** and **6**



Compound	Chemical shifts in ppm (J in Hz) [a]									
	H-2	H-3	H-4	H-4′	H-2^1	H-2^2	H-2^3	H-$2^{3'}$	OAc	R
4 R = Me	ddd 3.41 $J_{2,2'}$ 9.4 $J_{2,3}$ 6.3 $J_{2,4}$ 1.5	td 5.29 $J_{3,4}$ 1.5 $J_{3,4'}$ 6.4	td 3.45 $J_{4,4'}$ 9.6	dd 3.16	dd 5.46 $J_{2^1,2^2}$ 1.9	m 5.23 $J_{2^2,2^3}$ 5.5 $J_{2^2,2^{3'}}$ 6.5	dd 4.27 $J_{2^3,2^{3'}}$ 11.6	dd 3.94	s 2.11 s 2.06 s 2.04 s 2.03	s 2.22
5 R = Me	dd 5.22 $J_{2,2'}$ 11.0 $J_{2,3}$ 3.0	m 5.33 $J_{3,4}$ 3.9 $J_{3,4'}$ 7.9	dd 3.59 $J_{4,4'}$ 12.0	dd 3.33	dd 5.42 $J_{2^1,2^2}$ 1.7	ddd 5.10 $J_{2^2,2^3}$ 4.3 $J_{2^2,2^{3'}}$ 8.0	dd 4.25 $J_{2^3,2^{3'}}$ 11.7	dd 3.72	s 2.10 s 2.07 s 2.04 s 2.00 s 1.97	s 3.02
6 R = *t*-Bu	ddd 3.75 $J_{2,2'}$ 4.7 $J_{2,3}$ 8.1 $J_{2,4'}$ 0.9	td 5.24 $J_{3,4}$ 8.2 $J_{3,4'}$ 5.4	dd 3.52 $J_{4,4'}$ 10.2	ddd 3.28	dd 5.33 $J_{2^1,2^2}$ 5.4	td 5.44 $J_{2^2,2^3}$ 4.4 $J_{2^2,2^{3'}}$ 5.9	dd 4.36 $J_{2^3,2^{3'}}$ 11.9	dd 4.02	s 2.07 (6 H) s 2.04 s 2.03	s 0.93

[a] Chemical shifts are in δ (ppm) from Me_4Si referenced to the $CHCl_3$ resonance at 7.27 ppm.

Table 2
^{13}C NMR data (JMOD, $CDCl_3$, 100 MHz) for compounds **3**, **4**, **5**, and **6** [a]

Compound	R	C-2[3]	C-2[2] [b]	C-2[1] [b]	C-2	C-3 [b]	C-4	R	O–C=O	CH_3(OAc)
3	Me	62.61	72.34	69.92	66.26	62.97	61.96	43.22	–	–
4	Me	62.11	68.85	68.88	65.47	68.09	59.86	44.71	170.73–170.06 170.46–169.83	20.98–20.76 20.78–20.69
5	Me	62.87	70.65	67.55	50.95	67.24	43.84	32.92	172.50–170.43 170.68–169.79 170.62	21.71–20.73 20.97–20.70 20.81
6	*t*-Bu	62.78	71.16	69.52	60.52	64.87	52.13	25.20 52.26	170.52–170.03 170.12	20.99–20.75 20.90

[a] Chemical shifts are in δ (ppm) downfield from Me_4Si (referenced to resonance for $CDCl_3$ at 77.1 ppm).
[b] These assignments may be interchanged.

(JMOD) spectrum showed in particular two peaks at 62.61 and 61.96 ppm that can be attributed to methylenic carbon atoms. The absence of any C-anomeric signal near 100 ppm indicated that the pyranose ring has been opened. Additional chemical evidence for the structure was provided by acetylation of **3** to the corresponding (2*S*,3*R*)-1-methyl-2-[(1*S*,2*S*)-1,2,3-triacetoxypropy]-3-acetoxyazetidine (**4**). The ^1H NMR spectrum in chloroform showed in particular a singlet at 2.22 ppm and four singlets near 2 ppm corresponding respectively to the N-methyl group and the four acetoxyl groups. The H-4, H-4′, and H-2 protons, α to a nitrogen atom, appeared upfield relative to H-3 and the acyclic-chain protons that are α to an oxygen atom. A four-bond 'W' coupling (J 1.5 Hz) between the ring protons H-2 and H-4 suggests that the azetidine ring adopts a rigid conformation. The ^{13}C NMR spectrum was likewise in agreement with the proposed structure. The acetoxyl groups gave four signals near 20 ppm and four signals near 170 ppm. The chemical shift of carbon atom signals linked to a nitrogen atom (N–CH_3, C-2 and C-4) appeared at higher field than those α to an oxygen atom.

When hydrogenolysis of **1** was immediately followed by acetylation with an excess of acetic anhydride in pyridine, a syrup was obtained for which TLC (2:1 EtOAc–hexane) revealed two products having R_f 0.23 and 0.43, respectively. Chromatographic separation of the mixture gave successively the pure (2*S*,3*R*)-1-methyl-2-[(1*S*,2*S*)-1,2,3-triacetoxypropyl]-3-acetoxyazetidinium acetate (**5**) and (2*S*,3*R*)-1-methyl-2-[(1*S*,2*S*)-1,2,3-triacetoxypropyl]-3-acetoxyazetidine (**4**), both of which were identified by NMR spectroscopy. The more polar compound showed ^1H and ^{13}C NMR spectra (see Tables 1 and 2) in accordance with the structure of the peracetylated azetidine **4**. The stucture of the fast-migrating product **5** (R_f 0.43) was assigned on the basis of its NMR spectral data. The ^1H NMR spectrum (Table 1) resembled closely that of the azetidine **4**. However, it revealed in particular the presence of six singlets (3 H for each). The singlet at 3.02 ppm was attributed to the N-methyl group, and the other signals near 2 ppm represented five acetoxyl groups. We can observe that the signals for H-2, H-4, H-4′ and N–CH_3 were strongly deshielded compared to those of **4** (respectively +1.81, +0.14, +0.17 and +0.80 ppm). The chemical shift of the N-methyl group was in agreement with those reported for the N-methyl groups in azetidinium derivatives [3]. The presence of five acetoxyl groups was also confirmed by the number of signals in the ^{13}C NMR spectrum (Table 2). The C-2, C-4 and N–CH_3 signals were strongly shielded compared to those of **4** (respectively −14.52, −16.02 and −11.79 ppm). We thus propose an azetidinium acetate structure for compound **5**, although it has not been possible to obtain correct elemental analytical data for the compound.

Under conditions similar to those used for hydrogenolysis of **1**, benzyl 2,3-di-*O*-benzyl-4,6-*tert*-butylimino-4,6-dideoxy-α,β-D-galactopyranosides (**2**) were hydrogenated, and the crude product was directly acetylated in the usual way to give the (2*S*,3*R*)-1-*tert*-butyl-2-[(1*S*,2*S*)-1,2,3-triacetoxypropyl]-3-acetoxyazetidine (**6**). The pure compound was obtained by flash chromatography on silica gel as a syrup in a 35% yield. This azetidine **6** was identified from NMR spectroscopy data and from the compari-

son of these with data of the peracetylated azetidine **4**. The ^{1}H NMR spectrum (Table 1) showed, in particular, a singlet (9 H) at 0.93 ppm, attributed to the N-*t*-Bu group, and three singlets (6 H, 3 H, 3 H) corresponding to four acetoxyl groups. We observed some significant differences in the coupling constants compared with those of azetidine **4** for ring protons H-2, H-3 and H-4, indicating a change of conformation probably due to the effect of the bulky N-*t*-Bu group. Also the ^{13}C NMR spectrum (Table 2) showed in particular only three signals near 20 ppm and three signals near 170 ppm for the carbon atoms of four acetoxyl groups due to the overlapping of two peaks.

1. Experimental

General methods.—Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. Evaporations were performed under reduced pressure. Optical rotations were measured at room temperature on a Perkin–Elmer 241 polarimeter (path length 1 dm). Column chromatography was carried out using Silica Gel 60 (E. Merck 70–230 mesh) or 60A (E. Merck 35–70 mesh). TLC were performed on precoated plates (E. Merck 5724), and compounds were visualised with a spray of 30% aqueous sulfuric acid or a solution of phosphomolybdic acid (25 g) in ethanol (500 mL), followed by heating. All organic solvents were dried and distilled. Pyridine was dried and distilled under diminished pressure. Either anhydrous Na_2SO_4 or $MgSO_4$ were used to dry organic extracts. ^{1}H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) spectra were recorded on a Bruker MSL 300 or AC 400 spectrometer; the residual absorption of the NMR solvent was taken as the internal reference. Chemical shift data are given in δ-units (ppm), and spin–spin coupling are in Hz. Elemental analyses were performed by the Service Central d'Analyse du CNRS, Vernaison (France).

Benzyl 2,3-di-*O*-benzyl-4,6-dideoxy-4,6-methylimino-α,β-D-galactopyranosides (**1**) and benzyl 2,3-di-*O*-benzyl-4,6-*tert*-butylimino-4,6-dideoxy-α,β-D-galactopyranosides (**2**) were prepared by the reaction of benzyl 2,3-di-*O*-benzyl-4,6-di-*O*-tosyl-α,β-D-glucopyranosides with methylamine or *tert*-butylamine respectively [1].

(2S,3R)-1-Methyl-2-[(1S,2S)-1,2,3-trihydroxypropyl]-3-hydroxyazetidine (**3**).—A solution of **1** (1.80 g, 4 mmol) in 1:1 EtOAc–EtOH (15 mL) was shaken under a pressure of hydrogen of 50 psi in the presence of 20% $Pd(OH)_2/C$ (3.6 g). TLC (MeOH) indicated the disappearance of starting material and formation of a component having *Rf* 0.33 after 24 h. The catalyst was removed by filtration and washed several times with EtOH. The combined filtrates were concentrated to give a solid mixed with a syrup (0.98 g). Recrystallization from MeOH gave **3** as a white solid (0.17 g, 24%); **3** can also be purified by column chromatography on silica gel (MeOH): mp 188 °C (turns yellow before melting); $[\alpha]_D^{21}$ −66.3° (*c* 1.01, H_2O); R_f 0.33 (MeOH). Anal. Calcd for $C_7H_{15}NO_4$: C, 47.45; H, 8.53; N, 7.90; O 36.12. Found: C, 47.19; H, 8.95; N, 7.87; O, 35.72.

(2S,3R)-1-Methyl-2-[(1S,2S)-1,2,3-triacetoxypropyl]-3-acetoxyazetidine (**4**) *and (2S,3R)-1-methyl-2-[(1S,2S)-1,2,3-triacetoxypropyl]-3-acetoxyazetidinium acetate* (**5**).—The fused azetidine **1** (700 mg, 1.57 mmol) was first hydrogenated as described above. After evaporation of the solvent, the crude mixture (214 mg) was dissolved in anhydrous pyridine and acetylated overnight with acetic anhydride (1.0 g). The reaction mixture was then poured onto ice containing sodium carbonate and stirred vigorously. The product was extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were washed with satd aq sodium hydrogen carbonate and water and then dried. Evaporation of the solvent and chromatography of the resulting syrup (216 mg) on silica gel (2:1 EtOAc–hexane) afforded two compounds: azetidine **4** as a syrup (65 mg, 12%) and azetidinium derivative **5** as a white solid (106 mg, 17%). **4**: R_f 0.23 (2:1 EtOAc–hexane). **5**: mp 150–151 °C (95% ethanol); $[\alpha]_D^{25}$ −26.2° (*c* 1.00, $CHCl_3$); R_f 0.43 (2:1 EtOAc–hexane). For ^{1}H and ^{13}C NMR spectra, see Tables 1 and 2.

(2S,3R)-1-tert-butyl-2-[(1S,2S)-1,2,3-triacetoxypropyl]-3-acetoxyazetidine (**6**).—To a solution of the fused azetidine **2** (1.3 g, 2.7 mmol) in 1:1 EtOAc–EtOH (15 mL) was added 20% palladium hydroxide-on-charcoal (2.5 g). The mixture was hydrogenated at 50 psi for 5 h, and the catalyst was removed by filtration and washed several times with EtOH. The solvent was removed under diminished pressure to give a syrup (0.67 g) that was dissolved in anhydrous pyridine and treated overnight with acetic anhydride (2.2 g). The reaction mixture was then treated as described above. Flash chromatography (1:1 EtOAc–cyclohexane) of the residue on silica gel afforded azetidine **6** (0.36 g, 35%) as a viscous syrup: $[\alpha]_D^{18}$ −35.4° (*c* 1.06, $CHCl_3$); R_f 0.39 (1:1 EtOAc–cyclohexane). Anal. Calcd for $C_{18}H_{29}NO_8$: C, 55.80; H, 7.54; N, 3.62; O, 33.04. Found: C, 55.46; H, 7.62; N, 4.00; O, 33.32. For ^{1}H and ^{13}C NMR spectra, see Tables 1 and 2.

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