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Synthesis of monosaccharide-fused azetidines [1]

Thierry Michaud, Josette Chanet-Ray, Sithan Chou, Jacques Gelas *

Ecole Nationale Supérieure de Chimie de Clermont-Ferrand, B.P. 187, 63174 Aubière Cedex, France

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Abstract

Primary amines reacted upon 4,6-ditosylates of glucopyranosides to give an azetidine ring fused on C-4 and C-6 of the pyranose ring. On the other hand, the 4,6-ditosylate of benzyl mannopyranoside led to the 4,6-diamino-4,6-dideoxy derivative in a good yield. All the compounds and their precursors were identified by ^{1}H and ^{13}C NMR spectroscopy. Assignments of proton signals were made unambiguously using homodecoupling experiments.

Keywords: Tosylate; Nucleophilic substitution; Monosaccharide; Azetidine

1. Introduction

Synthetic routes to five- and six-membered polyhydroxylated aza-heterocycles have been the subject of a considerable number of studies during the last decade, as these compounds are potential glycosidase inhibitors. Fewer examples of analogous four-membered heterocycles (azetidines) are available. Penaresidine A and B have been extracted recently from marine sponge [1] and exhibit actymyosin–ATPase inhibitory activity. Some natural products, such as 3-hydroxymugineic acid (a phytosiderophore), possess a hydroxylated azetidine ring in their structures [2]. Until the discovery of an azetidinone unit in penicillins, few workers had dealt with this kind of compound, because of the difficulties encountered in building such a strained heterocycle. Since then, several methods have been proposed [3], concerning, however, mostly achiral compounds or racemates. The necessity for having optically pure derivatives for pharmaceutical purposes induced chemists to use optically pure chirons [4] such as those derived from carbohydrates, which are a cheap and easily available source of asymmetric carbon centers with a well defined stereochemistry. Within a program of synthesis of saturated nitrogen-containing heterocycles, we aimed to prepare enantiomerically pure polyhydroxylated azetidines from monosaccharides. We started from the pioneering work of Hall and Inch [5] that described the unexpected synthesis of an azetidine fused to a galactopyranoside during the preparation of a diamine through the treatment of 4,6-ditosylates of glucopyranosides with methylamine.

2. Results and discussion

Preparation of ditosylates.—The fused azetidines have been synthesized from several 4,6-ditosylates of glucopyranosides prepared according to the following general sequence shown in Scheme 1, based on known

* Corresponding author.

[1] This work is taken from the Thesis of T. Michaud (Ref. [6a]) and a preliminary account has been presented (Ref. [6b]).

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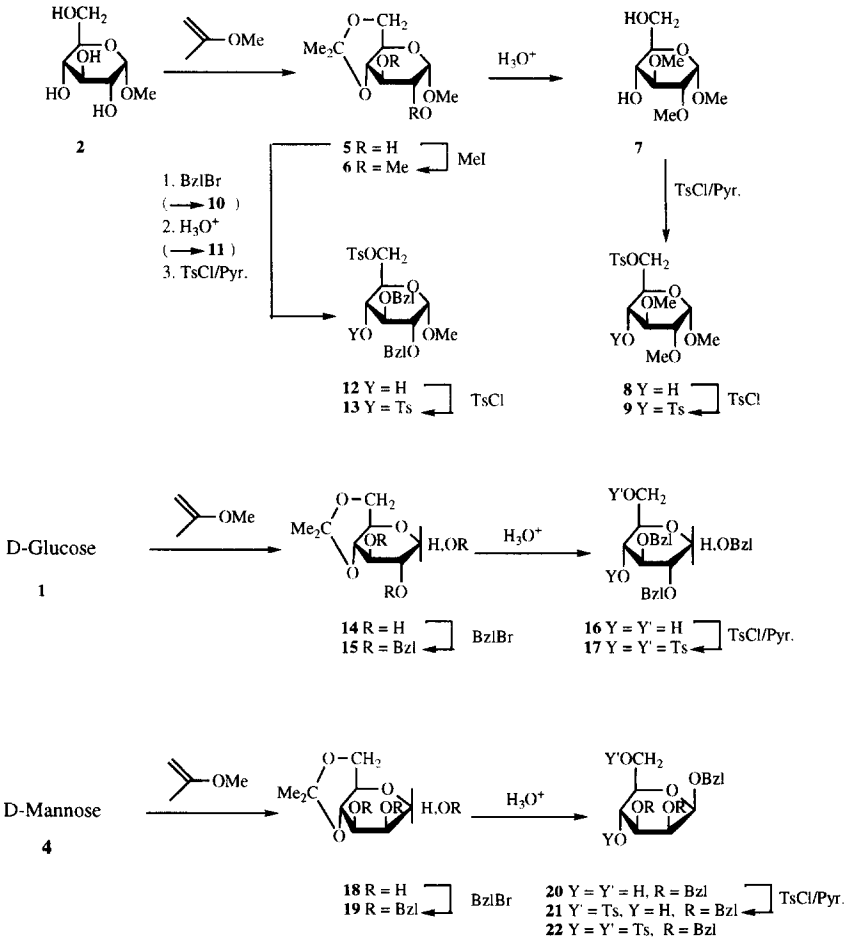
procedures (yields generally were not optimized). The structures assigned to the compounds were consolidated by detailed ^{1}H (Table 1) and ^{13}C (Table 2) NMR spectral studies at high field with complete assignment of proton signals by homodecoupling experiments. D-glucose (**1**) or methyl (**2**α) and benzyl α-D-glucosides (**3**α), and D-mannose (**4**) were utilized in these sequences.

Kinetic acetonation of methyl α-D-glucopyranoside (**2**α) with 2-methoxypropene led [7] to the methyl 4,6-*O*-isopropylidene-α-D-glucopyranoside (**5**α) (Scheme 1), which was subsequently methylated by Hakomori's method, as modified by Phillips and Fraser [8]. Hydrolysis of the permethylated acetal **6**α by an aqueous solution of acetic acid readily gave the methyl 2,3-di-*O*-methyl-α-D-glucopyranoside (**7**α), which was treated with *p*-toluenesulfonyl chloride to furnish the methyl 2,3-di-*O*-methyl-6-*O*-tosyl-α-D-glucopyranoside (**8**α) and/or the methyl 2,3-di-*O*-methyl-4,6-di-*O*-tosyl-α-D-glucopyranoside (**9**α) according to the duration of the reaction. The related methyl 2,3-di-*O*-benzyl-4,6-di-*O*-tosyl-α-D-glucopyranoside (**13**α) has also been prepared from the acetal **5**α by successive benzylation (**10**α), hydrolysis (**11**α), and tosylation via the intermediary monotosylate **12**α, which was not isolated.

A mixture of the two benzyl 2,3-di-*O*-benzyl-4,6-di-*O*-tosyl-α,β-D-glucopyranoside anomers (**17**$\alpha + \beta$) has been prepared by acetonation of D-glucose (**1**) under kinetic conditions [7], which gave the 4,6-*O*-isopropylidene-D-glucopyranose (**14**) in a good yield, followed by benzylation using benzyl bromide in Me_2SO in the presence of powdered potassium hydroxide [9]. The benzyl 2,3-di-*O*-benzyl-4,6-*O*-isopropylidene-α,β-D-glucopyranosides (**15**$\alpha + \beta$) were obtained in a 1:4 ratio (^{1}H NMR) of the two anomers, which were not separable by column chromatography on silica gel. Acidic hydrolysis of their mixture readily gave the corresponding benzyl 2,3-di-*O*-benzyl-α,β-D-glucopyranosides (**16**$\alpha + \beta$), subsequent tosylation of which gave the ditosylates **17**$\alpha + \beta$. The pure diol **16**β can be isolated by recrystallization from ethyl acetate–cyclohexane. The pure anomer **16**α had been prepared by repeating the previous



Scheme 1. Synthesis of the ditosylates **9**, **13**, **17** and **22**.

sequence (acetonation–benzylation–hydrolysis–tosylation) starting from benzyl α-D-glucopyranoside (**3**α), obtained by a known procedure [10] using alcoholysis of β-D-glucopyranose pentaacetate.

Kinetic acetonation of D-mannose (**4**) [11] gave essentially the 4,6-*O*-isopropylidene-D-mannopyranose (**18**α + β), only contamined by traces of the 2,3-*O*-isopropylidene mannofuranose isomer. Benzylation of the crude acetals led to benzyl 2,3-di-*O*-benzyl-4,6-*O*-isopropylidene-α,β-D-mannopyranosides (**19**α + β) (with a strong preponderance of the β anomer), which were separated by chromatography on silica gel. Subsequent hydrolysis, followed by tosylation of the benzyl 2,3-di-*O*-benzyl-β-D-mannopyranoside (**20**β) with *p*-toluenesulfonyl chloride successively gave the benzyl 2,3-di-*O*-benzyl-6-*O*-tosyl-β-D-mannopyranoside (**21**β) and the benzyl 2,3-di-*O*-benzyl-4,6-di-*O*-tosyl-β-D-mannopyranoside (**22**β) according to the duration of the reaction.

Each tosylation occurred via the intermediary 6-*O*-tosyl derivative (slower migrating compound on TLC), which was the major compound formed after six hours of reaction. In some examples, **8**α and **21**β were isolated.

The ^{1}H NMR spectra of monotosylates **8**α and **21**β showed, in particular, low-field chemical shifts for H-6 and H-6′ signals (≈ 4.4 ppm) which proved that the sulfonyloxy group was carried by C-6. The ^{1}H NMR spectra of ditosylates (**9**α, **13**α, **17**α, **17**β, and **22**β) showed two singlets (3 H each) near 2.4 ppm for the two methyl groups of the tosyloxy functions and multiplets centered around 7.8 and 7.0 ppm for the aromatic protons. The signals of the H-6, H-6′ and H-4 protons were both deshielded by the sulfonyloxy groups, compared to those of the corresponding diols. The β-configuration of **22**β was assigned by the value [9] of the coupling constant $J_{C\text{-}1\text{-}H\text{-}1}$ 156.55 Hz.

The ^{13}C NMR (JMOD) spectra of ditosylates showed characteristic signals near 145 ppm and 133 ppm for the quaternary carbon atoms of the tosyloxy groups, while their methyl groups appeared at ≈ 21.6 ppm.

Preparation of fused azetidines from ditosylates.—Three compounds can be obtained when primary amines react upon 4,6 ditosylates of glucopyranosides, according to Hall and Inch [5]: the intermediate 6-substituted, the 4,6-disubstituted product, and the expected 4,6 fused azetidine (Scheme 2).

Reaction of the ditosylate **9**α with ethanolic methylamine in an autoclave at 120 °C gave, after inversion of the configuration on C-4, the methyl 4,6-dideoxy-2,3-di-*O*-methyl-4,6-methylimino-α-D-galactopyranoside (**23**α) in 30% yield, as previously described by Hall and Inch [5]. The azetidine **23**α was accompanied by a side product isolated in a 15% yield. This product was not the methyl 4,6-dideoxy-2,3-di-*O*-methyl-4,6-bis(methylamino)-α-D-galactopyranoside (**24**α) isolated by Hall and Inch [5] in a 30% yield, but was identified as the methyl 6-deoxy-2,3-di-*O*-methyl-6-methylamino-4-*O*-tosyl-α-D-glucopyranoside (**25**α).

In a similar manner, the ditosylate **13**α, treated with methylamine for ten hours, gave a syrup for which TLC (8:1 EtOAc–MeOH) revealed two products having R_f 0.22 and 0.55, respectively. The crude product was purified by column chromatography on silica gel. The less polar compound was isolated as a clear oil in a 35% yield and identified as the methyl 2,3-di-*O*-benzyl-4,6-dideoxy-4,6-methylimino-α-D-galactopyranoside (**26**α). The more polar compound, which was isolated as an oil in a 4% yield, was identified as the methyl 2,3-di-*O*-benzyl-4,6-dideoxy-4,6-bis(methylamino)-α-D-galactopyranoside (**27**α) on the basis of its ^{1}H NMR spectrum (Table 5).

Reaction of the ditosylates **17**α + β with methylamine at 120 °C for four hours gave a syrup for which TLC (ether) revealed mainly two compounds having R_f 0.50 and 0.15. The major product (R_f 0.50) was obtained as an oil in 61% yield. It was identified as a mixture of the two benzyl 2,3-di-*O*-benzyl-4,6-dideoxy-4,6-methylimino-α,β-D-galactopyranosides (**28**α + β), which were not separable by column chromatography. The minor product **30**β (R_f 0.15) was shown not to be identical to the benzyl 2,3-di-*O*-benzyl-4,6-dideoxy-4,6-dimethylamino-α-D-galactopyranoside (**29**α) obtained by Hall and Inch [5] as determined by NMR spectroscopy. Its ^{1}H NMR spectrum (Table 5) showed the persistence of the protons of the pyranoside ring, while the signals of the tosyloxy groups had been replaced by two singlets at 2.55 and 2.23 ppm (N–CH_3) and two signals at 3.41 and 2.60 ppm (1 H each) having a geminal coupling constant (J 10.2. Hz). Moreover, one of these protons (δ 3.41 ppm) showed a weak coupling (J 1.4 Hz) with a C-6 proton. The ^{13}C NMR spectrum (Table 6) showed a signal at 71.20 ppm that can be attributed to a methylene group geminal to two nitrogen atoms as in hexahydro- pyrimidine and triazine [12a]. These spectroscopic and analytical data were compatible [12] with a galactopyranoside-fused hexahydropyrimidine structure **30**β. No other example of such a product has been described. Its forma-

Table 1
^{1}H NMR data for compounds **5**α, **6**α, **8**α, **9**α, **13**α, **15**β, **16**α, **17**, **20**, **19**, **21**β, and **22**β

Compound	Chemical shifts in ppm (J in Hz)											
	H-1	H-2	H-3	H-4	H-5	H-6	H-6′	O–Me or O–CH_2Ph or OH			Me or OH	Ph
5α [a]	d 4.73 $J_{1,2}$ 3.9	m 3.55 $J_{2,3}$ 9.3	t 3.76 $J_{3,4}$ 9.1	m 3.50 $J_{4,5}$ 9.4	td 3.60 $J_{5,6}$ 5.1 $J_{5,6'}$ 9.8	dd 3.84 $J_{6,6'}$ 10.5	t 3.72	s 3.39	sl 3.73 (OH)	d 3.18 (OH)	s 1.50 s 1.43	–
6α [b]	d 4.78 $J_{1,2}$ 3.8	dd 3.22 $J_{2,3}$ 9.0	t 3.69		m 3.64–3.56 $J_{5,6}$ 4.5	dd 3.83 $J_{6,6'}$ 9.8	3.54–3.46	s 3.55	s 3.50	s 3.39	s 1.48 s 1.40	–
8α [c]	d 4.70 $J_{1,2}$ 4.0	← m 2.80–3.90 →				m 4.45–4.10		s 3.60	s 3.50	s 3.40	s 2.40	m 8.00–7.10
9α [a]	d 4.74 $J_{1,2}$ 3.6	dd 3.13 $J_{2,3}$ 9.6	t 3.39 $J_{3,4}$ 9.8	dd 4.32 $J_{4,5}$ 10.2	ddd 3.87 $J_{5,6}$ 2.1	dd 4.38 $J_{6,6'}$ 11.2	dd 4.09	s 3.42	s 3.36	s 3.00	s 2.43 s 2.42	m 7.85–7.74 m 7.40–7.28
13β [b]	d 4.49 $J_{1,2}$ 3.6	dd 3.47 $J_{2,3}$ 9.6	m 3.86 $J_{3,4}$ 9.4	m 4.52 $J_{4,5}$ 11.9	ddd 3.93 $J_{5,6}$ 2.0 $J_{5,6'}$ 6.7	dd 4.38 $J_{6,6'}$ 11.1	dd 4.06	d 4.72 d 4.39 J_{gem} 11.1	d 4.68 d 4.51 J_{gem} 11.8	s 3.34	s 2.46 s 2.31	m 7.45–7.20 m 7.81–m 7.71 m 7.18–m 7.10
15β [a]	d 4.66 $J_{1,2}$ 7.6	m 3.56 $J_{2,3}$ 8.8	t 3.66 $J_{3,4}$ 8.9	t 3.82 $J_{4,5}$ 9.2	td 3.32 $J_{5,6}$ 5.4 $J_{5,6'}$ 10.1	dd 4.04 $J_{6,6'}$ 10.8	t 3.90	d 5.00 d 4.73 J_{gem} 11.8	d 4.96 d 4.83 J_{gem} 10.8	d 4.93 d 4.84 J_{gem} 11.5	s 1.58 s 1.52	m 7.50–7.30
16β [d]	d 4.44 $J_{1,2}$ 7.7	dd 3.62 $J_{2,3}$ 9.0	m 3.48 J_{34} 9.0	m 3.78 $J_{4,5}$ 9.7	td 3.16 $J_{5,6}$ 3.6 $J_{5,6'}$ 3.6	ABX 3.90 $J_{6,6'}$ 12.1		d 5.04 d 4.72 J_{gem} 11.3	d 4.99 d 4.83 J_{gem} 11.7	d 4.86 d 4.49 J_{gem} 12.1	sl 3.44 (OH) sl 3.00 (OH)	m. 7.50–7.00
17α [b]	d 4.73 $J_{1,2}$ 3.7	dd 3.48 $J_{2,3}$ 9.5	t 3.93 $J_{3,4}$ 9.5	m 4.55 $J_{4,5}$ 9.7	m 3.99 $J_{5,6}$ 1.8 $J_{5,6}$ 6.7	dd 4.32 $J_{6,6'}$ 10.6	dd 4.08	d 4.74 d 4.39 J_{gem} 12.4	d 4.67 d 4.49 J_{gem} 12.7	d 4.54 d 4.42 J_{gem} 12.2	s 2.45 s 2.30	m 7.45–7.00 m 7.84–m 7.72

17β [d]	d 4.26 $J_{1,2}$ 7.4	m 3.35 $J_{2,3}$ 9.0	m 3.31	m 4.64 $J_{4,5}$ 10.0	ddd 3.42 $J_{5,6}$ 2.1 $J_{5,6}$ 7.0	dd 4.72 $J_{6,6'}$ 11.5	dd 4.27	d 4.83 d 4.48 J_{gem} 11.2	d 4.74 d 4.47 J_{gem} 11.7	d 4.63 d 4.33 J_{gem} 11.4	s 1.85 (2.45) [b] s 1.80 (2.30) [b]	m 7.35–7.00 m 7.92–m 7.75 m 6.79–m 6.63
19α [d]	d 4.92 $J_{1,2}$ 1.6	dd 3.85 $J_{2,3}$ 3.3	dd 4.02 J_{34} 9.8	t 4.56 $J_{4,5}$ 9.8		← m 3.95–3.82 →		d 4.76 d 4.49 J_{gem} 12.1	d 4.69 d 4.48 J_{gem} 11.9	d 4.47 d 4.17 J_{gem} 12.0	s 1.43 sl.22	m 7.40–6.95
19β [a]	d 4.48 $J_{1,2}$ 0.8	dd 3.92 $J_{2,3}$ 3.1	dd 3.44 $J_{3,4}$ 9.7	t 4.28	m 3.18 $J_{5,6'}$ 5.6	dd 4.00 $J_{6,6'}$ 10.8	dd 3.97	AB 5.01 J_{AB} 12.4	d 4.98 d 4.58 J_{gem} 11.9	AB 4.63 J_{AB} 12.6	s 1.58 s 1.47	m 7.55–7.25
19β [d]	s 4.15	d 3.82 $J_{2,3}$ 3.2	dd 3.33 $J_{3,4}$ 9.7	t 4.50 $J_{4,5}$ 9.6	m 3.11 $J_{5,6}$ 5.3 $J_{5,6'}$ 10.1	dd 3.91 $J_{6,6'}$ 10.6	dd 3.99	d 5.12 d 4.96 J_{gem} 12.0	d 4.91 d 4.41 J_{gem} 12.0	d 4.75 d 4.62 J_{gem} 12.5	s 1.52 s 1.25	m 7.59–7.05
20β [d]	d 4.21 $J_{1,2}$ 0.5	dd 3.76 $J_{2,3}$ 3.0	dd 3.10 $J_{3,4}$ 9.5	t 4.27 $J_{4,5}$ 9.0	m 3.24 $J_{5,6}$ 3.5 $J_{5,6'}$ 4.4	ABX 4.06–3.95 $J_{6,6'}$ 11.6		d 5.10 d 4.85 J_{gem} 12.2	d 4.91 d 4.44 J_{gem} 12.0	d 4.40 d 4.25 J_{gem} 12.0	sl 2.90 (OH) sl 2.70 (OH)	m 7.55–7.10
21β [d]	sl 4.00 $J_{1,2}$ 0.5	dd 3.54 $J_{2,3}$ 2.9	dd 2.79 $J_{3,4}$ 9.3	td 3.76 $J_{4,5}$ 9.3 $J_{4,OH}$ 2.00	m 3.25 $J_{5,6}$ 7.1 $J_{5,6'}$ 1.80	dd 4.16 $J_{6,6'}$ 10.8	dd 4.46	d 4.88 d 4.57	d 4.70 d 4.30	d 4.12 d 3.92	d 2.17 (OH) s 1.65	m 7.70–6.90
22β [a]	s 4.39 $J_{1,2}$ 0.0	d 3.78 $J_{2,3}$ 2.9	dd 3.39 $J_{3,4}$ 9.1	t 4.81 $J_{4,5}$ 9.3	m 3.67 $J_{5,6}$ 2.6 $J_{5,6'}$ 8.1	dd 4.53 $J_{6,6'}$ 11.1	dd 4.17	d 4.88 d 4.54 J_{gem} 11.9	d 4.87 d 4.67 J_{gem} 12.3	d 4.22 d 4.10 J_{gem} 12.1	s 2.42 s 2.35	m 7.40–7.00 m 7.82–m 7.70

[a] $CDCl_3$, 400 MHz.
[b] $CDCl_3$, 300 MHz.
[c] $CDCl_3$, 60 MHz.
[d] C_6D_6, 400 MHz.

Table 2
^{13}C NMR data ($CDCl_3$) for compounds **5**α, **6**α, **9**α, **13**α, **15**, **16**, **17**, **19**, **20**, **21**β, and **22**β

Compound	C-1	C-2	C-3	C-4	C-5	C-6	O–Me or O–CH_2Ph			Ph (quat.)		Ph	CMe_2	Me (a, e or Ts)
										Ts	Bzl			
5α [a]	100.02	72.91	71.55	73.65	63.29	62.34	–	–	55.28	–	–	–	99.70	29.02 19.09
6α [a]	98.47	81.72 *	80.15 *	74.65	63.24	62.63	60.72	59.29	55.18	–	–	–	99.40	29.24 19.15
9α [b]	96.84	81.72 *	80.01 *	77.55 *	67.35 *	68.27	60.58	58.95	55.49	144.84 134.04 132.88		129.79–127.93 129.57 128.05	–	21.62
13α [b]	97.56	79.52 *	78.41 *	77.37 *	67.41 *	68.32	75.08	73.63	55.60	144.97 144.89 133.72 132.90	138.24 137.58	129–128.11 129.73–127.69 128.54–127.31 128.17–127.20 128.14	–	21.72 21.66
15α [b]	96.58	79.25 *	79.15 *	75.46 *	63.58 *	62.68	75.16	73.53	69.17		139.45 138.71 137.29	128.50–128.03 128.35–127.96 128.29–127.70 128.17–127.57	99.37	29.25 19.22
15β [b]	103.04	82.12 *	81.41 *	74.31 *	66.92 *	62.29	75.39	74.84	71.46		138.85 138.41 137.18	128.44–127.89 128.29–127.77 128.24–127.64 128.11–127.52 127.96	99.28	29.20 19.15
16α [a]	95.62	81.43 *	79.85 *	75.00 *	71.19 *	62.21	75.37	72.74	69.22		138.87 138.09 137.15	128.57–128.13 128.50–127.89 128.37–127.72	–	–
16β [b]	102.95	84.03 *	81.99 *	75.02 *	70.48 *	62.66	75.29	74.83	71.64		138.56 138.32 137.30	128.66–128.43 127.78–128.18 128.54–127.99	–	–
17α [a]	94.79	79.65 *	78.40 *	77.48 *	67.78 *	68.28 *	74.98	73.19	69.40 * *	144.94 144.87 133.83 133.07	138.37 137.64 136.55	129.82–127.96 129.76–127.54 128.54–127.20 128.44 128.11	–	21.66

17β [a]	101.72	81.98 *	81.07 *	77.48 *	71.96 *	68.58	75.04	74.98	71.09	145.18 144.95 133.66 133.06	138.01 137.64 136.55	129.93–128.13 129.85–127.82 128.57–127.36 128.45–127.21 128.36	–	21.69
19α [b]	98.62	76.95 *	76.39 *	71.80 *	65.29 *	62.42	73.46	73.05	68.95		139.08 138.14 137.07	128.45–127.75 128.32–127.68 128.20–127.36 128.04–127.31 127.84	99.68	29.37 19.43
19β [b]	100.94	78.66 *	75.90 *	71.40 *	68.69 *	62.25	74.68	72.30	71.04		138.63 138.53 137.31	128.67–128.08 128.44–127.87 128.28–127.42	99.75	29.34 19.48
20β [b]	100.69	81.65 *	75.98 *	67.56 *	73.42 *	63.06	74.21	71.21	71.17		138.49 137.68 137.37	128.56–127.95 128.50–127.85 128.39–127.73 128.23–127.60 127.92	–	-
21β [b]	100.08	81.37 *	74.26 *	66.52 *	73.07 *	69.95	74.14	71.06	70.76	144.78 133.00	133.80 133.45 132.99	129.84–12804 128.58–127.88 128.48–127.78 128.33–127.59 128.23		21.63
22β [b]	99.15	78.16 *	76.08 *	72.90 *	74.40 *	69.10 * *	74.16	71.53	70.70 * *	144.95 144.90 133.33 132.79	138.33 137.26 136.84	129.91–128.00 129.59–127.95 128.49–127.68 128.27–127.53 128.13	–	21.71

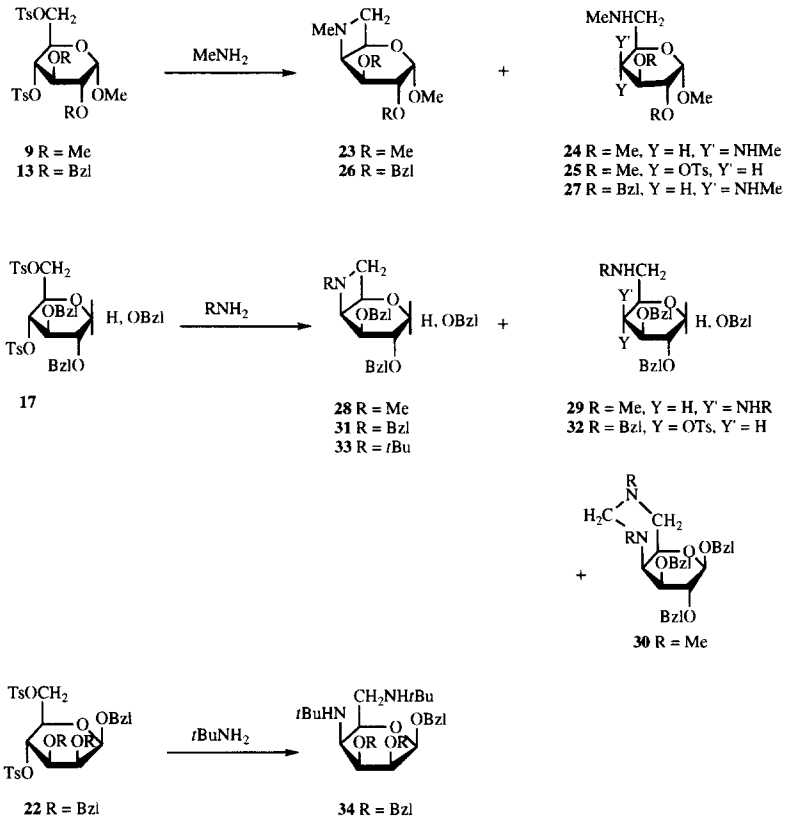
*, * * Assignments may be interchanged.
[a] 75.47 MHz.
[b] 100 MHz.

tion was not explained. The fused azetidines **28**α and **28**β were obtained pure starting from their respective ditosylate precursor **17**α and **17**β. Thus, reaction of the ditosylate **17**α with ethanolic methylamine at 120 °C for four hours gave a crude product for which TLC (ether) revealed a major compound having R_f 0.50. Purification by chromatography on silica gel gave benzyl 2,3-di-*O*-benzyl-4,6-dideoxy-4,6-methylimino-α-D-galactopyranoside (**28**α) in 45% yield, which was identical to the product obtained in 63% yield by Hall and Inch [5]. The ^{1}H and ^{13}C NMR spectroscopic data (Tables 3 and 4) of this compound have been completely described.

When a mixture of ditosylates **17**$\alpha + \beta$ was heated at 120 °C for sixteen hours with benzylamine, a complex mixture of products was obtained. The crude product was purified by column chromatography and furnished two fractions. The less polar fraction (major), (TLC 4:3:2 hexane–$CHCl_3$–AcOEt; one spot R_f 0.66), was in fact constituted of three derivatives in a 60:25:15 ratio (^{1}H NMR). The major products were identified as the benzyl 2,3-di-*O*-benzyl-4,6-benzylimino-4,6-dideoxy-α,β-D-galactopyranosides (**31**$\alpha + \beta$), contaminated by the tosylate of benzylamine. Compounds **31**α and **31**β were isolated as a mixture. The structure of the more polar compound (R_f 0.26) was assigned on the basis of its NMR spectral data and identified to the benzyl 2,3-di-*O*-benzyl-6-benzylamino-6-deoxy-4-*O*-tosyl-α-D-glucopyranoside (**32**α).

The reaction of the ditosylates **17**$\alpha + \beta$ with *tert*-butylamine at 120 °C for six hours afforded only the two benzyl 2,3-di-*O*-benzyl-4,6-*tert*-butylimino-4,6-dideoxy-α,β-D-galactopyranosides (**33**$\alpha + \beta$) (93% yield), which were separated by column chromatography. The two fused azetidines were obtained as a syrup in 65% and 11% yield for the anomers **33**β and **33**α, respectively.

When the ditosylate **22**β was similarly treated with *tert*-butylamine at 120 °C for six hours, the reaction did not afford the expected fused azetidine. Only one syrupy product was isolated by column chromatography in a 74% yield from the crude mixture. It was identified as the benzyl 2,3-di-*O*-benzyl-4,6-bis(*tert*-butylamino)-4,6-dideoxy-β-D-talopyranoside (**34**β).



Scheme 2. Synthesis of azetidines.

Table 3
^{1}H NMR data of fused azetidines **23**α, **26**α, **28**α, **31**, and **33**

Compound	Chemical shifts in ppm (J in Hz)											
	H-1	H-2	H-3	H-4	H-5	H-6	H-6′	O–Me or O–CH_2Ph			Ph	N–R
23α [a]	d 4.85 $J_{1,2}$ 3.0	dd 3.72 $J_{2,3}$ 9.5	dd 3.49 $J_{3,4}$ 5.0	t 3.34 $J_{5,6}$ 8.0 $J_{5,6'}$ 5.0	td 4.15	dd 3.28	dd 2.76	s 3.52	s 3.44	s 3.38		s 2.37
26α [b]	d 4.74 $J_{1,2}$ 2.8	dd 4.08 $J_{2,3}$ 9.4	dd 3.87 $J_{3,4}$ 5.2	t 3.31 $J_{4,5}$ 4.7	t 4.15 $J_{5,6}$ 0.0 $J_{5,6'}$ 4.7	d 3.30 $J_{6,6'}$ 8.3	dd 2.78	AB 4.79 J_{gem} 12.0	AB 4.75 J_{gem} 12.0	s 3.38	m 7.40–7.25	s 2.45
28α [b]	d 4.98 $J_{1,2}$ 2.9	dd 4.12 $J_{2,3}$ 9.4	dd 3.98 $J_{3,4}$ 5.3	t 3.38 $J_{4,5}$ 4.7	t 4.22 $J_{5,6}$ 0.0 $J_{5,6'}$ 4.7	d 3.43 $J_{6,6'}$ 8.2	dd 2.81	d 4.83 d 4.74 J_{gem} 11.9	d 4.79 d 4.62 J_{gem} 11.9	d 4.70 d 4.58 J_{gem} 12.5	m 7.50–7.25	s 2.44
28β [b]	d 4.43 $J_{1,2}$ 7.5	dd 4.08 $J_{2,3}$ 9.0	dd 3.53 $J_{3,4}$ 5.2	t 3.23 $J_{4,5}$ 4.4	t 4.29 $J_{5,6}$ 0.0 $J_{5,6'}$ 4.8	d 3.50 $J_{6,6'}$ 8.3	dd 2.84	d 5.01 d 4.79 J_{gem} 10.9	d 4.98 d 4.65 J_{gem} 12.1	d 4.78 d 4.72 J_{gem} 12.0	m 7.42–7.26	s 2.45
31α [c]	d 5.00 $J_{1,2}$ 2.7	dd 4.44 $J_{2,3}$ 9.4	dd 4.06 $J_{3,4}$ 5.1	t 3.22 $J_{4,5}$ 4.7	t 3.92 $J_{5,6}$ 0.0 $J_{5,6'}$ 4.7	d 3.21 $J_{6,6'}$ 7.4	dd 2.44		4.71–4.31		m 7.42–6.90	d 4.25 d 3.12 J_{gem} 12.9
31β [c]	d 4.40 $J_{1,2}$ 7.1	dd 4.45 $J_{2,3}$ 8.8	dd 3.35 $J_{3,4}$ 4.7	t 3.06 $J_{4,5}$ 4.6	t 3.77 $J_{5,6}$ 0.0 $J_{5,6'}$ 5.0	d 3.32 $J_{6,6'}$ 8.1	dd 2.43	d 5.15 d 4.70 J_{gem} 11.4	d 4.85 d 4.48 J_{gem} 12.2	AB 4.60 J_{gem} 12.2	m 7.42–6.90	d 4.27 d 3.15 J_{gem} 12.9
33α [b]	d 5.08 $J_{1,2}$ 3.0	dd 4.17 $J_{2,3}$ 10.0	dd 3.94 $J_{3,4}$ 4.5	t 3.78 $J_{4,5}$ 4.5	t 4.12 $J_{5,6}$ 0.0 $J_{5,6'}$ 4.6	d 2.99 $J_{6,6'}$ 7.8	dd 3.10	d 4.84 d 4.78 J_{gem} 11.7	d 4.79 d 4.65 J_{gem} 12.0	d 4.79 d 4.62 J_{gem} 12.5	m 7.50–7.25	s 1.05
33β [b]	d 4.90 $J_{1,2}$ 5.1	dd 4.57 $J_{2,3}$ 9.9	dd 3.48 $J_{3,4}$ 3.6	dd 3.91 $J_{4,5}$ 7.3	m 4.41 $J_{5,6}$ 2.8 $J_{5,6'}$ 7.5	dd 3.53 $J_{6,6'}$ 9.0	dd 3.36	AB 4.83 J_{gem} 11.4	d 4.93 d 4.64 J_{gem} 12.1	AB 4.77 J_{gem} 12.2	m 7.50–7.25	s 1.03

[a] $CDCl_3$, 300 MHz.
[b] $CDCl_3$, 400 MHz.
[c] C_6D_6, 400 MHz.

Table 4
^{13}C NMR data (JMOD, $CDCl_3$, 100 MHz) of azetidines **23**α, **26**α, **28**, **31**, **33**

Compound	C-1	C-2 *	C-3 *	C-4	C-5 *	C-6	O–Me or O–CH_2Ph			N–R	Ph	Ph (CH)
23α	98.03	79.32	76.67	64.96	65.59	59.08	58.53	57.70	55.29	45.49		
26α	99.36	79.32	75.42	65.50	67.07	59.60	73.70	72.76	55.76	46.16	138.95 138.71	128.35–127.65–127.44 128.29–127.92–127.42
28α	96.54	79.21	75.58	65.84	67.12	59.68	73.27	72.86	69.08	46.22	139.10 138.80 137.60	128.50–128.13–127.58 128.40–127.88–127.52 128.36–127.74–127.38 128.30–127.72 128.28–127.63
28β	101.26	81.05	79.16	67.14	67.31	60.06	74.91	72.83	70.46	46.30	138.88 138.68 137.70	128.57–128.08–127.56 128.33–127.83–127.50 128.28–127.61
31α	96.65	79.03	75.84	64.77	66.07	57.23	73.11	72.94	68.99	62.53	138.88 138.76 137.96 137.67	128.85–127.81–127.14 128.71–127.71–126.97 128.58–127.61–126.82 128.48–127.55
31β	101.84	81.26	79.48	64.77	67.46	57.87	74.80	72.94	70.50	62.53	138.88 138.76 138.04 137.67	128.30–127.48 128.24–127.41 128.09–127.37
33α	97.16	78.07	78.00	61.09	65.21	51.35	73.80	73.13	68.99	52.09 25.79	138.92 137.84	128.35–127.84–127.43 128.26–127.69–127.34 128.22–127.60
33β	104.43	81.36	77.99	59.46	67.26	52.68	74.20	73.04	69.50	51.71 25.59	138.96 138.00	128.41–127.98–127.35 128.25–127.42 128.01–127.64

* Assignments may be interchanged.

The difference in behaviour between the *gluco* and the *manno* derivatives can be explained by the following considerations: in order to permit the substitution of the 4-*O*-tosyl group according to a S_N2 process, the intermediate 6-*tert*-butylamino-6-deoxy derivative, initially formed, must adopt a boat-like conformation (Scheme 3).

In this conformation, we can see on the *manno* derivative that the *O*-benzyl group at C-2 creates steric hindrance that prevents the approach of the nitrogen electronic doublet on C-4. In this case, a substitution by a second molecule of amine is favoured. On the other hand, this hindrance does not exist in the *gluco* derivative, and the intramolecular substitution is kinetically favoured, leading mainly to the fused azetidine compounds.

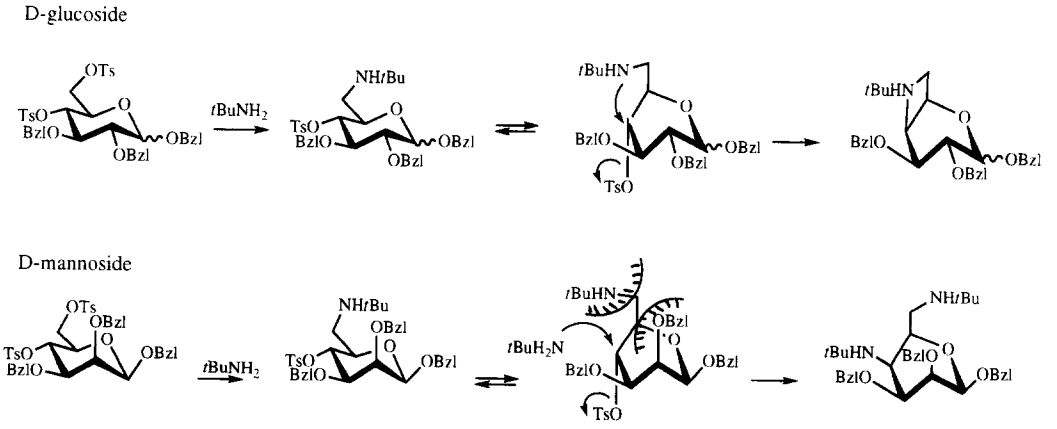
All these compounds were identified on the basis of their NMR spectroscopic data. As a general rule for all the fused azetidines, the H-6, H-6′ and H-4 signals were shielded by about 1 ppm compared to those of the ditosylate precursors, indicating that double substitution occurred. This was confirmed by the disappearance of the signals of the tosyloxy protons. The coupling constants $J_{4e,3a}$ and $J_{4e,5a} \approx 5.0$ Hz established the galactopyranoside configuration. For each couple of anomers **28**, **31** and **33**, H-1 appears as a doublet at lower field and with a smaller coupling constant for the α anomer (2.7 to 3.0 Hz) than for the β anomer (5.1 to 7.5 Hz). The ^{1}H NMR spectra of azetidines **23**α, **26**α, **28**α and **28**β (Table 3) showed, in particular, one singlet (3 H) at ≈ 2.4 ppm corresponding to the N-methyl group. Azetidines **23**α and **26**α showed a second singlet (3 H) near 3.4 ppm for the anomeric methoxy group.

The ^{1}H NMR spectra of the monosubstituted compounds **25**α and **32**α (Table 5) showed the persistence of the signals of one tosyloxy group, in particular one singlet at ≈ 2.40 ppm (3 H). The chemical shift of H-4 (almost unchanged compared to the spectra of the ditosylates **9**α and **17**α), the coupling constant $J_{4a,3a} \approx 9.7$ Hz and the shielding of the signal of H-6 and H-6′ confirmed that the remaining tosyloxy group was carried by C-4; the singlet at 2.42 ppm (3 H) for the N-methyl group (**25**α), and the well-resolved AB system (δ 3.75 ppm, J 13.3 Hz), corresponding to the methylene of the benzylamino group (**32**α), proved the substitution of the C-6 tosyloxy group.

The ^{1}H NMR spectrum of the disubstituted compound **27**α showed, in particular, three singlets (3 H each) at 2.26, 2.53 and 3.43 ppm attributed to the two N-methyl and the methoxy groups, respectively. The ^{1}H NMR spectrum of disubstituted compound **34**β (Table 5) showed, in particular, a singlet at 1.05 ppm (18 H, N-*tert*-Bu), and two broad signals (1 H each, N–H) near 2.70–2.20 ppm, which disappeared after the addition of deuterium oxide. The coupling constant value $J_{4,3}$ (4.0 Hz) indicated a *talo* configuration which, with the disappearance of the two tosyloxy groups, confirmed the structure.

The ^{13}C NMR spectra of fused azetidines **23**α, **26**α, **28**, **31** and **33** (Table 4) showed, in particular, the signals of a single N-alkyl group; the chemical shift of anomeric carbon appears at higher field for the α anomer ($\approx$ 97 to 99 ppm) than for β anomer ($\approx$ 101 to 104 ppm). The comparison with ^{13}C NMR spectra of ditosylates (Table 2) showed a strong shielding (≈ -10 ppm) for the C-6 signal of azetidines.

The ^{13}C NMR spectrum of the disubstituted com-



Scheme 3.

Table 5
^{1}H NMR data for compounds **25**α, **27**α, **30**β, **32**α, and **34**β

Compound	Chemical shifts in ppm (J in Hz)													
	H-1	H-2	H-3	H-4	H-5	H-6	H-6′	NH or H-7	Ts or H-7′	N–R	O–Me or O–CH_2Ph			Ph
25α [a]	d 4.77 $J_{1,2}$ 3.5	dd 3.17 $J_{2,3}$ 9.7	t 3.40 $J_{3,4}$ 9.7	dd 4.40 $J_{4,5}$ 10.2	m 3.78 $J_{5,6}$ 3.5 $J_{5,6'}$ 6.5	dd 2.83 $J_{6,6'}$ 12.4	dd 2.75	sl 1.67	s 2.42 *	s 2.40 *	s 3.44	s 3.38	s 2.96	m 7.82–7.27
27α [b]	d 4.82 $J_{1,2}$ 3.6	dd 4.16 $J_{2,3}$ 10.6	dd 4.05 $J_{3,4}$ 3.0	m 2.60–2.43	d 3.60 $J_{5,6}$ 2.0 $J_{5,6'}$ 8.8	dt 2.98 $J_{6,6'}$ 12.0	m 2.60–2.43	m 2.20–2.40 sl 3.81	–	s 2.26 s 2.53	s 3.43	AB 4.76 J_{AB} 12.3	AB 4.75 J_{AB} 12.3	m 7.50–7.15
30β [c]	d 4.38 $J_{1,2}$ 7.3	dd 4.09 $J_{2,3}$ 10.0	dd 3.32 $J_{3,4}$ 3.9	m 2.22 $J_{4,5}$ 1.3	m 2.78 $J_{5,6}$ 1.8 $J_{5,6'}$ 2.6	td 2.89 $J_{6,6'}$ 12.6 $J_{6,7}$ 1.4	dd 2.03	dd 3.41 $J_{7,7'}$ 10.2	d 2.60	s 2.55 s 2.23	d 4.95 d 4.78 J 11.4	d 4.90 d 4.58 J 12.2	AB 4.55 J_{AB} 12.0	m 7.40–7.28 m 7.20–7.00
32α [b]	4.78–4.69 $J_{1,2}$ 3.7	dd 3.54 $J_{2,3}$ 9.6	t 4.00 $J_{3,4}$ 9.4	m 4.78–4.69 $J_{4,5}$ 10.1	m 3.98 $J_{5,6}$ 2.6 $J_{5,6'}$ 6.4	dd 2.83 $J_{6,6'}$ 12.8	dd 2.74	sl 1.77	s 2.30	AB 3.75 J_{AB} 13.3	d 4.80 d 4.48 J 11.0	d 4.77 d 4.53 J 12.2	d 4.60 d 4.48 J 12.0	m 7.73–7.07 m 7.42–7.15
34β [c]	sl 4.18 $J_{1,2}$ 1.2	d 3.63 $J_{2,3}$ 2.9	m 2.96 $J_{3,4}$ 4.0	m 2.71 $J_{4,5}$ 1.6	m 3.15 $J_{5,6}$ 8.5 $J_{5,6'}$ 3.3	dd 3.38 $J_{6,6'}$ 11.2	dd 2.65	sl 2.70–2.20 sl 1.75–1.00	–	s 1.05	d 4.98 d 4.56	d 4.91 d 4.52	AB 4.20 J_{AB} 12.0	m 7.40–6.95

* Assignments may be interchanged.
[a] $CDCl_3$, 300 MHz.
[b] $CDCl_3$, 400 MHz.
[c] C_6D_6, 400 MHz.

Table 6
^{13}C NMR data (JMOD, $CDCl_3$, 100 MHz) for compounds **27α**, **30β**, **32α**, **34β**

Compound	C-1	C-2 *	C-3 *	C-4	C-5 *	C-6	O–Me or O–CH_2Ph			N–R	Ph (quaternary)		Ph (CH)
27α	99.65	79.85	75.11	63.49	65.68	57.62	73.53	73.62	55.38	42.76	138.88		128.51–128.09–127.41
										41.81	138.64		128.34–127.67
30β	104.36	83.62	79.71	62.21	70.47	58.16	80.76	75.79	73.60	42.34	140.45		129.23–128.70–128.36
						71.20				43.90	139.98		129.03–128.46–128.16
						(C-7)					139.33		128.94–128.38
32α	94.97	79.94	79.63	78.73	68.97	53.95	74.92	73.21	69.26	49.11	140.38	144.42	129.54–128.10–127.32
							21.60				138.57	134.57	129.36–128.06–127.20
							(CH_3)				137.80		129.03–128.00–126.92
											136.84		128.50–127.88
											(Bzl)	(Ts)	128.40–127.65
34β	101.05	78.40	77.20	52.44	76.57	44.99	75.09	70.91	70.81	30.99	139.16		128.43–128.06–127.63
										29.34	138.91		128.38–127.72–127.59
										50.28	138.01		128.12–127.67–127.40
										50.16			
34β [a]	100.86	78.66	77.78	52.33	76.92	44.97	74.81	70.84	70.44	31.16	139.53		128.46–128.11–127.59
										29.32	138.37		128.41–127.68–127.35
										49.98	138.47		128.20–127.64
										49.76			

* Assignments may be interchanged.
[a] C_6D_6, 100 MHz.

pounds **27**α and **34**β (Table 6) showed, in particular, the signals of two N-alkyl groups.

3. Conclusions

The reaction of 4,6-ditosylates of glucopyranosides with a primary amine led to a monosaccharide-fused azetidine. The yield of cyclised product is affected to a great extent by the protecting group of the hydroxyl groups and the type of amine. Benzyl ether gave the best results with a bulky primary amine like *tert*-butylamine. When we used a mixture of the two anomeric ditosylates with a given α:β ratio, the two anomeric fused azetidines were obtained in the same ratio, indicating that the anomeric position axial or equatorial of the C-1 substituant does not significantly affect the yield of the cyclisation products.

4. Experimental

General methods.—Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. Evaporations were performed under diminished 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 was performed on precoated plates (E. Merck 5724), and compounds were visualised with a spray of 30% aq sulfuric acid or a solution of phosphomolybdic acid (25 g) in ethanol (500 mL), and heating. All organic solvents were dried and distilled. Pyridine was dried and distilled under diminished pressure. *N*,*N*-Dimethylformamide was stirred over CaH_2 and distilled under reduced pressure. Anhydrous Na_2SO_4 or $MgSO_4$ were either 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. Microanalyses were performed by the Service Central d'Analyse du CNRS, Vernaison (France).

*Preparation of methyl 4,6-*O*-isopropylidene-*α*-*D*-glucopyranoside* (**5**α).—Acetal **5**α was prepared as described [7] from commercial methyl α-D-glucopyranoside (**2**α). Although NMR data were in good agreement with those of literature, the melting point was quite different: mp 116 °C, lit. 84–86 °C [7]; $[\alpha]_D^{22}$ +111° (*c* 1.01, H_2O), lit. $[\alpha]_D^{25}$ +105° (*c* 5.0, H_2O) [7]; R_f 0.32 (EtOAc). For ^{1}H and ^{13}C NMR spectra, see Tables 1 and 2.

*Preparation of methyl 4,6-*O*-isopropylidene-2,3-di-*O*-methyl-*α*-D-glucopyranoside* (**6**α).—Acetal **5**α (5.4 g, 23.0 mmol) was permethylated using a slightly modified Hakomori's method [8]. Compound **6**α was obtained as a crystalline product (5.8 g, 96%), which could be used directly for further transformations: mp 85 °C, lit. 84 °C [13]; $[\alpha]_D^{28}$ +122° (*c* 1.04, $CHCl_3$), lit. $[\alpha]_D^{25}$ +120° (*c* 1.0, $CHCl_3$) [13]; R_f 0.68 (EtOAc). For ^{1}H and ^{13}C NMR spectra, see Tables 1 and 2.

*Preparation of methyl 2,3-di-*O*-methyl-*α*-D-glucopyranoside* (**7**α).—Acetal **6**α (6.2 g, 24.0 mmol) was hydrolysed by heating (50 °C) in a 60:40 aq solution of acetic acid for 1 h (checked by TLC, EtOAc) to give a single product. The water was evaporated under reduced pressure, and acetic acid was eliminated by coevaporation with toluene to afford **7**α (5.0 g, 95%) as a white solid: mp 86 °C, lit. 84 °C [14], 82–85 °C [15].

*Preparation of methyl 2,3-di-*O*-methyl-4,6-di-*O*-tosyl-*α*-D-glucopyranoside* (**9**α).—Diol **7**α (4.8 g, 22.0 mmol) was tosylated for 72 h, using the method described by Kabalka et al. [16]. TLC (1:2 hexane–EtOAc) showed two spots at R_f 0.31 (monotosylate **8**α) and R_f 0.52 (ditosylate **9**α). The crude product was purified by column chromatography to give **9**α (7.5 g, 65%) as a white solid: mp 123 °C, lit. 123–124 °C [14]; $[\alpha]_D^{23}$ +80° (*c* 0.95, $CHCl_3$), lit. $[\alpha]_D^{23}$ +80° (*c* 2, $CHCl_3$) [14]; R_f 0.52 (1:2 hexane–EtOAc). For ^{1}H and ^{13}C NMR spectra, see Tables 1 and 2. If the duration of tosylation was only 6 h, two products were obtained: the monotosylate **8**α (6.3 g, 79%), as a syrup (for ^{1}H NMR spectrum, see Table 1), and the ditosylate **9**α (1.2 g, 10%).

*Preparation of methyl 2,3-di-*O*-benzyl-*α*-D-glucopyranoside* (**11**α).—Acetal **10**α, prepared by benzylation [9] of **5**α (10.6 g, 45.3 mmol), was hydrolysed as described for the acetal **6**α, to give **11**α as a white solid (4.8 g, 28% from **5**α): mp 77 °C, lit. 79–80 °C [17a], 75–76 °C [17b]; $[\alpha]_D^{23}$ +89.4° (*c* 1.01, acetone), $[\alpha]_D^{23}$ +18.4° (*c* 1.01, $CHCl_3$), lit. $[\alpha]_D^{20}$ +88.7° (*c* 1, acetone) [17a], $[\alpha]_D^{20}$ +18.8° (*c* 4.9, $CHCl_3$) [17b].

*Methyl 2,3-di-*O*-benzyl-4,6-di-*O*-tosyl-*α*-D-glucopyranoside* (**13**α).—Diol **11**α (4.8 g, 12.8 mmol), treated as described for diol **7**α, gave **13**α (4.0 g, 46%) as a white solid, which was recrystallized from 95% ethanol; mp 114–115 °C; $[\alpha]_D^{25}$

+15.7° (*c* 1.04, $CHCl_3$); R_f 0.68 (1:1 hexane–EtOAc); Anal. Calcd for $C_{35}H_{38}O_{10}S_2$: C, 61.57; H, 5.61; O, 23.43; S, 9.39. Found: C, 61.64; H, 5.56; O, 23.52; S, 9.53. For ^1H and ^{13}C NMR spectra, see Tables 1 and 2.

Preparation of 4,6-O-isopropylidene-D-glucopyranose (**14**$\alpha+\beta$).—Acetals **14**$\alpha+\beta$ were prepared as described by Wolfrom et al. [7]. They were contamined by a small amount of unreacted glucose and were used without further purification; R_f 0.24 (EtOAc), lit. R_f 0.2 (EtOAc) [7].

Benzyl 2,3-di-O-benzyl-4,6-O-isopropylidene-α,β-D-glucopyranosides (**15**$\alpha+\beta$).—The crude acetals **14**$\alpha+\beta$ (5.4 g, 24.5 mmol) were benzylated using the method described by Decoster et al. [9]. Purification of the resulting yellow oil by column chromatography (eluent: 9:1 hexane–EtOAc) furnished the syrupy acetals **15**$\alpha+\beta$ (5.3 g 42%), contaminated by perbenzylated glucose. Analytically pure anomer **15**β has been thus isolated; $[\alpha]_D^{21}$ −26.2° (*c* 1.06, $CHCl_3$); R_f 0.36 (4:1 hexane–EtOAc); Anal. Calcd for $C_{30}H_{34}O_6$: C, 73.45; H, 6.99. Found: C, 73.28; H, 7.01. For ^1H and ^{13}C NMR spectra, see Tables 1 and 2.

Preparation of benzyl 2,3-di-O-benzyl-α,β-D-glucopyranosides (**16**$\alpha+\beta$).—A solution of 5.0 g of the acetals **15**$\alpha+\beta$ (contaminated by perbenzylated glucose) in a 60:40 aq solution of acetic acid was heated for 1 h at 60 °C. After usual workup, the crude diols **16**$\alpha+\beta$ were purified by column chromatography (1:1 hexane–EtOAc) to give pure diols **16**$\alpha+\beta$ (2.9 g, 64%) as a white solid. Anal. Calcd for $C_{27}H_{30}O_6$: C, 72.02; H, 6.70. Found: C, 72.10; H, 6.72. Pure anomer **16**β was obtained by recrystallization (cyclohexane–EtOAc) from the mixture of the two anomers; mp 112–113 °C, lit. 112–113 °C [18]; $[\alpha]_D^{20}$ −5.4° (*c* 1.06, acetone), $[\alpha]_D^{21}$ −41.3° (*c* 1.06, $CHCl_3$), lit. $[\alpha]_D^{20}$ −6.5° (*c* 2, acetone) [18]; R_f 0.40 (1:1 hexane–EtOAc). For ^1H and ^{13}C NMR spectra, see Tables 1 and 2. The ^{13}C NMR spectrum of **16**α was determined from the mixture.

Benzyl 2,3-di-O-benzyl-4,6-di-O-tosyl-α,β-D-glucopyranosides (**17**$\alpha+\beta$).—Diols **16**$\alpha+\beta$ (4.6 g, 10.2 mmol) were tosylated using the method described by Kabalka et al. [16]. The crude product was purified by column chromatography to give the ditosylates **17**$\alpha+\beta$ (5.7 g, 74%) as a white solid: mp 96 °C; R_f 0.50 (5:3:1 hexane–$CHCl_3$–EtOAc); Anal. Calcd for $C_{41}H_{42}O_{10}S_2$: C, 64.89; H, 5.58; O, 21.00; S, 8.45. Found: C, 65.12; H, 5.75; O, 21.10; S, 8.53. For ^1H and ^{13}C NMR spectra, see Tables 1 and 2. Pure anomer **17**β was obtained from the diol **16**β: mp 97–98 °C; $[\alpha]_D^{25}$ −5.0 (*c* 1.00, $CHCl_3$). Anomer **17**α [5]: $[\alpha]_D^{24}$ +41.6° (*c* 1.11, $CHCl_3$). The ^{13}C NMR spectrum of **17**α was determined from the mixture (see Table 2).

Preparation of 4,6-O-isopropylidene-D-mannopyranose (**18**$\alpha+\beta$).—Acetals **18**$\alpha+\beta$ were prepared as previously described [11]. They have been characterized as their peracetylated derivatives obtained by acetylation of the crude product by usual procedure and separation by column chromatography: *1,2,3-tri-O-acetyl-4,6-O-isopropylidene-α-D-mannopyranose*: mp 44–49 °C, lit. 49 °C [11]; $[\alpha]_D^{20}$ +42° (*c* 1.0, $CHCl_3$), lit. $[\alpha]_D^{20}$ +48° (*c* 1.0, $CHCl_3$) [11]. *1,2,3-tri-O-acetyl-4,6-O-isopropylidene-β-D-mannopyranose*, syrup: lit. mp 53–62 °C [11]; $[\alpha]_D^{20}$ −34° (*c* 1.0, $CHCl_3$), lit. $[\alpha]_D^{20}$ −39° (*c* 1.0, $CHCl_3$) [11].

Benzyl 2,3-di-O-benzyl-4,6-O-isopropylidene-β-D-mannopyranoside (**19**β).—The perbenzylated D-mannopyranoside acetal **19**β was prepared from the crude acetals **18**$\alpha+\beta$ (3.0 g, 13.6 mmol) as described above [9] for the D-glucose derivatives **16**$\alpha+\beta$. Purification of the resulting yellow oil by column chromatography (4:1 hexane–EtOAc) furnished two syrupy fractions: 3.3 g (49%) of the anomer **19**β, and 0.60 g (10%) of the anomer **19**α; **19**β: $[\alpha]_D^{24}$ −75.0° (*c* 1.0, $CHCl_3$); R_f 0.56 (4:1 hexane–EtOAc); **19**α: $[\alpha]_D^{24}$ +74.0° (*c* 1.0, $CHCl_3$); R_f 0.63 (4:1 hexane–EtOAc). For ^1H and ^{13}C NMR spectra, see Tables 1 and 2.

Benzyl 2,3-di-O-benzyl-β-D-mannopyranoside (**20**β).—Acetal **19**β (4.2 g, 8.6 mmol) was treated as described for compounds **15**$\alpha+\beta$. Diol **20**β, thus prepared, was purified by column chromatography (2:1 cyclohexane–EtOAc), and obtained as a white solid (3.6 g, 93%): mp 136–137 °C; $[\alpha]_D^{27}$ −126.7° (*c* 1.01, $CHCl_3$); R_f 0,32 (1:1 cyclohexane–EtOAc); Anal. Calcd for $C_{27}H_{30}O_6$: C, 71.98; H, 6.71; O, 21.31. Found: C, 71.80; H, 6.74. For ^1H and ^{13}C NMR spectra, see Tables 1 and 2.

Benzyl 2,3-di-O-benzyl-4,6-di-O-tosyl-β-D-mannopyranoside (**22**β).—Diol **20**β (3.0 g, 7.0 mmol) was tosylated as described above for the glucosides derivatives **16**$\alpha+\beta$. The crude product was purified by column chromatography (6:3:1 cyclohexane–$CHCl_3$–EtOAc) to give the ditosylate **22**β (4.9 g, 97%) as a white solid, and traces of the monotosylate **21**β as a syrup. The tosylation of diol **20**β (0.4 g, 0.9 mmol) during only 6 h gave 0.5 g (93%) of the monotosylate **21**β as a syrup; **21**β: $[\alpha]_D^{28}$ −93.8° (*c* 1.00, $CHCl_3$); **22**β: mp 112–113 °C; $[\alpha]_D^{24}$ −121.2° (*c* 1.00, $CHCl_3$); R_f 0.66 (6:3:2 cyclohexane–$CHCl_3$–EtOAc); Anal. Calcd for

$C_{41}H_{42}O_{10}S_2$: C, 64.89; H, 5.58; O, 21.08; S, 8.45. Found: C, 64.80; H, 5.75; O, 20.54; S, 8.50. For ^1H and ^{13}C NMR spectra, see Tables 1 and 2.

General preparation of the fused azetidines.—The ditosylate was heated at 120 °C with the appropriate amine in a sealed autoclave. The crude product was concentrated under diminished pressure, and ethyl acetate was added. A white solid was filtered; the filtrate was concentrated in vacuo, and the resulting syrup was purified by flash chromatography on silica gel.

Methyl 4,6-dideoxy-2,3-di-O-methyl-4,6-methylimino-α-D-galactopyranoside (**23α**).—Ditosylate **9α** (4.0 g, 7.5 mmol) was heated for 4 h with 15 mL of ethanolic methylamine (33%). Purification (eluent: acetone) after workup, as described above, furnished two fractions: the fused azetidine **23α** (0.5 g, 30%) as a pale yellow oil: $[\alpha]_D^{23}$ +205.0° (*c* 0.85, $CHCl_3$), lit. $[\alpha]_D$ +205.0° (*c* 2, $CHCl_3$) [5]; R_f 0.40 (acetone); the monosubstituted compound **25α** (0.5 g, 19%) as an orange oil: $[\alpha]_D^{23}$ +100.0° (*c* 1.02, $CHCl_3$); R_f 0.30 (acetone). For ^1H and ^{13}C NMR spectra, see Tables 3–5.

Methyl 2,3-di-O-benzyl-4,6-dideoxy-4,6-methylimino-α-D-galactopyranoside (**26α**).—Ditosylate **13α** (2.2 g, 3.2 mmol) was heated for 10 h with 10 mL of ethanolic methylamine (33%). Purification (eluent: 10:1 EtOAc–methanol) after workup, as described above, furnished two fractions: the fused azetidine **26α** (0.42 g, 35%) as a clear oil: $[\alpha]_D^{23}$ +69.5° (*c* 1.18, $CHCl_3$); R_f 0.55 (8:1 EtOAc–MeOH); the 4,6-disubstituted compound **27α** (43 mg, 3%) as an orange oil: $[\alpha]_D^{24}$ +27.8° (*c* 1.20, $CHCl_3$); R_f 0.22 (8:1 EtOAc–MeOH). For ^1H and ^{13}C NMR spectra, see Tables 3–6.

Benzyl 2,3-di-O-benzyl-4,6-dideoxy-4,6-methylimino-α,β-D-galactopyranosides (**28α + β**).—Ditosylates **17α + β** (5.1 g, 6.7 mmol) were heated for 4 h with 15 mL of ethanolic methylamine (33%). Purification (eluent: ether) after workup, as described above, furnished two fractions: the two fused azetidines **28α + β** (1.83 g, 61%) and the compound **30β** (0.13 g, 4%); **28α + β**: R_f 0.50 (ether); Anal. Calcd for $C_{28}H_{31}NO_4$: C, 75.48; H, 7.01; N, 3.14; O, 14.36. Found: C, 74.77; H, 7.04; N, 3.94; O, 14.23; **30β**: mp 113–115 °C; $[\alpha]_D^{20}$ −29.8° (*c* 1.07, $CHCl_3$); R_f 0.15 (ether); Anal. Calcd for $C_{30}H_{36}N_2O_4$: C, 73.74; H, 7.43; N, 5.73. Found: C, 73.15; H, 7.63; N, 5.36. For ^1H and ^{13}C NMR spectra, see Tables 3–6.

Benzyl 2,3-di-O-benzyl-4,6-dideoxy-4,6-methylimino-α-D-galactopyranoside (**28α**).—Prepared, as described above, from the anomerically pure ditosylate **17α**: $[\alpha]_D^{25}$ +105.8° (*c* 1.00, $CHCl_3$), lit. +96° (*c* 2, $CHCl_3$) [5]; R_f 0.50 (ether). For ^1H and ^{13}C NMR spectra, see Tables 3 and 4.

Benzyl 2,3-di-O-benzyl-4,6-dideoxy-4,6-methylimino-β-D-galactopyranoside (**28β**).—Prepared, as described above, from the anomerically pure ditosylate **17β**: $[\alpha]_D^{25}$ −33.0° (*c* 1.00, $CHCl_3$). For ^1H and ^{13}C NMR spectra, see Tables 3 and 4.

Benzyl 2,3-di-O-benzyl-4,6-benzylimino-4,6-dideoxy-α,β-D-galactopyranosides (**31α + β**).—Ditosylates **17α + β** (3.0 g, 4.0 mmol) were heated at 120 °C for 16 h with 15 mL of benzylamine. After evaporation of the amine, the crude product was dissolved in ether, filtered and concentrated. Chromatography of the resulting syrup (4:3:2 hexane–$CHCl_3$–EtOAc) gave two fractions: 0.75 g of a syrup containing the two azetidines **31α + β**, contamined by the tosylate of benzylamine (ratio 85:15, determined by the ^1H NMR spectrum); the second fraction contained the pure benzyl 2,3-di-*O*-benzyl-6-benzylamino-6-deoxy-4-*O*-tosyl-α-D-glucopyranoside (**32α**) (0.20 g, 8%) as a syrup: $[\alpha]_D^{20}$ +55.9° (*c* 1.00, $CHCl_3$); R_f 0.26 (4:3:2 hexane–$CHCl_3$–EtOAc). For ^1H and ^{13}C NMR spectra, see Tables 3–6.

*Benzyl 2,3-di-O-benzyl-4,6-*tert*-butylimino-4,6-dideoxy-α,β-D-galactopyranosides* (**33α + β**).—Ditosylates **17α + β** (2.0 g, 2.6 mmol) were heated at 120 °C for 6 h with 10 mL of *tert*-butylamine. Purification after workup, as described above, furnished three fractions: the first contained the pure azetidine **33β** (0.83 g, 65%) as a syrup, the second fraction (0.22 g, 17%) was a mixture of the two azetidine anomers **33α + β**, and the third was the pure azetidine **33α** (0.143 g, 11%); **33β**: $[\alpha]_D^{19}$ −52.1° (*c* 1.04, $CHCl_3$); R_f 0.89 (ether); Anal. Calcd for $C_{31}H_{37}NO_4$: C, 76.35; H, 7.65; N, 2.87; O, 13.12. Found: C, 76.07; H, 7.49; N, 2.97; O, 13.18; **33α**: $[\alpha]_D^{19}$ +119.4° (*c* 1.01, $CHCl_3$); R_f 0.66 (ether). For ^1H and ^{13}C NMR spectra, see Tables 3 and 4.

*Benzyl 2,3-di-O-benzyl-4,6-bis(*tert*-butylamino)-4,6-dideoxy-β-D-talopyranoside* (**34β**).—Ditosylate **22β** (1.9 g, 25.0 mmol) was heated at 120 °C in a sealed autoclave for 6 h with 10 mL of *tert*-butylamine. The crude product was treated as described for the *galacto* derivatives. Column chromatography (2:1 MeOH–$CHCl_3$) of the resulting syrup gave the compound **34β** (1.04 g, 74%) as a viscous syrup: $[\alpha]_D^{22}$ −60.0° (*c* 1.02, $CHCl_3$); R_f 0.25 (2:1 MeOH–$CHCl_3$); Anal. Calcd for $C_{35}H_{48}N_2O_4$: C, 74.96; H, 8.63; N, 5.00; O, 11.41. Found: C, 74.76; H, 8.80; N, 5.20; O, 11.70. For ^1H and ^{13}C NMR spectra, see Tables 5 and 6.

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