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STEREOCHEMICAL STUDIES OF THE SYNTHESIS OF α-AMINONITRILES RELATED TO LINCOSAMINE*

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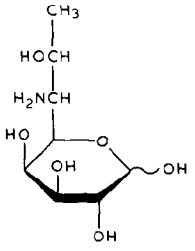
ABSTRACT

The syntheses of 6-amino-6-deoxyheptopyranurononitriles related to lincosamine by cyano-amination of 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose (**2**) is reported. The procedure described allowed direct cyano-amination in good yield under mild conditions. The high diastereofacial selectivity of the reaction is discussed. Indirect cyano-amination by activation of the corresponding cyanohydrins followed by displacement with an amine was also studied. Epimerization occurred at C-6 and the resulting aminonitriles were formed under thermodynamic control. From these chain extensions, precursors of lincosamine and analogues were obtained.

INTRODUCTION

The existence of many naturally occurring higher-carbon carbohydrates[1] has stimulated the search for new methods of chain extension of pentoses and hexoses[2]. The main problem is the transfer of the ring chirality to the emerging side chain[3]. We have described[4] a high-yielding cyano-amination method of protected dialdo sugars under mild conditions in which high diastereofacial selectivity was achieved. We now report details of this work and its application to the synthesis of lincosamine precursors.



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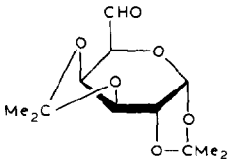

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*Chain-Extension of Carbohydrates, Part III. Communicated in part at the XIIIth International Carbohydrate Symposium, Ithaca, NY, August, 1986. For preceding paper, see ref. 4.

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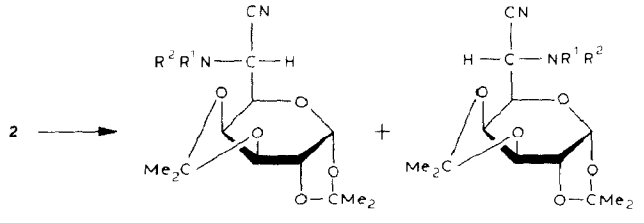
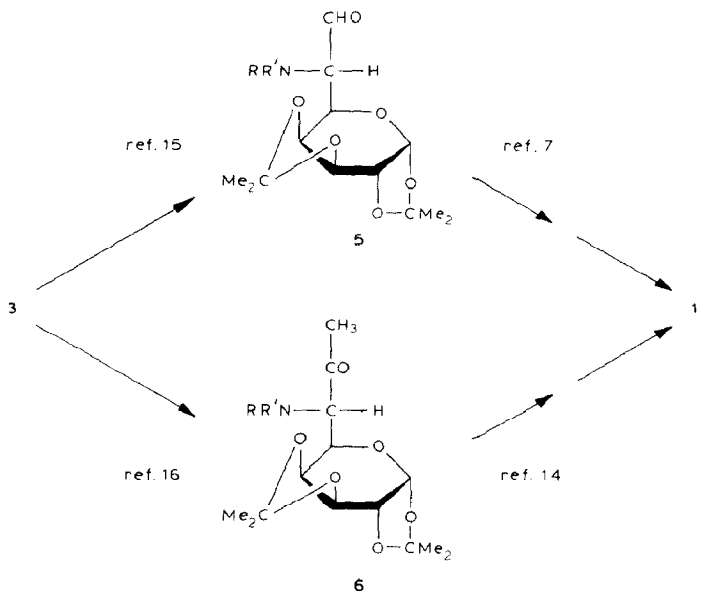
Lincosamine (**1**), an amino-octose, is the sugar moiety of the clinically important antibiotic lincomycin[5]. The synthesis of **1** from D-galactose has been the object of extensive research[6–14]. Generally, low steric control is achieved in introducing an amino function at C-6 in the D-*glycero* configuration[6–12].

RESULTS AND DISCUSSION

The C-6 amino function was introduced at the beginning of the synthesis by cyano-amination of the protected dialdo sugar **2**, readily prepared in high yield from D-galactose[4]. The further chain elongation of the resulting D-*glycero*-D-*galacto* aminonitrile **3** could be achieved by known procedures[15,16] *via* the intermediates **5** and **6** which have been transformed into lincosamine[7,14].



a $R^1 = Me, R^2 = H$
b $R^1 = R^2 = Me$
c $R^1 = Bn, R^2 = H$
d $R^1 = R^2 = Bn$
e $R^1 = (S)PhCHMe, R^2 = H$
f $R^1 = (S)PhCHMe, R^2 = H$
g $R^1 = Bz, R^2 = Bn$



When **2** was treated under the standard conditions of the Strecker reaction[17] (NH_4Cl, NaCN, H_2O), a mixture of the two epimeric cyanohydrins **7a** and **8a** was obtained. Cyano-amination of **2** with sodium hydrogensulfite, a non-tertiary amine, and sodium cyanide at 35° gave a mixture of the epimeric α-aminonitriles **3** and **4** in excellent yield (Table I). The ratios of **3** and **4** were determined by integration of the signals for H-1 and/or H-5 which were well resolved in the ^{1}H-n.m.r. spectra of the crude mixtures (Table II).

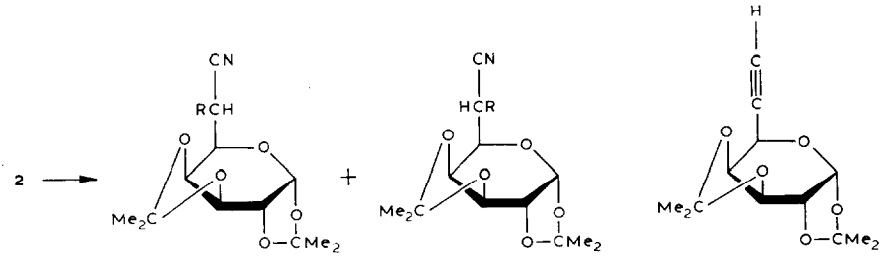
Several primary and secondary amines were used and the lower yield obtained with methylamine could be due to its volatility. Except for the mixtures of **3** and **4a,b,** and **e,** the α-aminonitriles were isolated by column chromatography or crystallization (see Experimental). Several attempts were made to correlate the configuration of **3** and **4** with known compounds. Since the methanesulfonates **7b** and **8b** of the cyanohydrins **7a** and **8a** are known[18], they were used as reference starting materials.

TABLE I

DIASTEREOFACIAL SELECTIVITY IN THE CYANO-AMINATION OF **2**

Entry[a]	*Yield*[b] (%)	*Ratio [yield*[c]*(%)]*	
		3	**4**
a	60	1	6.1
b	86	1	10.1(17)
c	94	1	10.1(71)
d	100	1(3)	4(43)
e	92	1	4.55
f	100	1	5.6(49)

[a]See formulae **3** and **4** for identification of **a–f**. [b]Crude yield of the mixture. [c]Yield of isolated pure epimer.



a R = OH
b R = Ms
c R = N_3
d R = $OSiMe_3$
e R = OSO_2CF_3

TABLE II

^{1}H-N.M.R. DATA[a] FOR NEW COMPOUNDS

Compound	*H-1* *d* ($J_{1,2}$)	*H-2* *dd* ($J_{2,3}$)	*H-3* *dd* ($J_{3,4}$)	*H-4* *dd* ($J_{4,5}$)	*H-5* *dd* ($J_{5,6}$)	*H-6* *d*	*>CMe$_2$*	*Others*
3c	5.58 (4.75)	4.35 (2.75)	4.63 (7.75)	4.34 (2.5)	3.93 (6.5)	3.83	1.53 1.46 1.35	NH 2.07, Ph m 7.4–7.25 PhCH$_2$ ABq 3.99 (12.5)
4c	5.56 (5.0)	4.38 (2.37)	4.69 (7.75)	4.44 (1.6)	4.0 (8.0)	3.90	1.54 1.46 1.34	NH 1.87, Ph m 7.37–7.25 PhCH$_2$ ABq 3.94 (13.0)
3d	5.52 (4.87)	4.28 (2.37)	4.55 (7.75)	4.24 (1.75)	4.04 (7.5)	3.97	1.55 1.40 1.29 1.27	Ph m 7.36–7.23 PhCH$_2$ ABq 3.72 (13.75)
4d	5.65 (5.0)	4.37 (2.5)	4.65 (7.75)	4.36 (1.75)	4.15 (10.0)	4.06	1.45 1.34 1.27 1.17	Ph m 7.44–7.20 PhCH$_2$ ABq 3.70 (13.5)
3f	5.53 (5.0)	4.33 (2.5)	4.60 (8.0)	4.41 (2.0)	3.78 (8.0)	3.61	1.50 1.40 1.38	Ph bs 7.30, NH 1.90 PhC*H*Me q 4.09 (6.5) PhCHCH_3 d 1.35
4f	5.53 (4.75)	4.36 (2.75)	4.65 (7.5)	4.41 (2.0)	3.83 (8.0)	3.61	1.50 1.41 1.39	Ph bs 7.30, NH 2.04 PhC*H*Me q 4.09 (6.5) PhCHCH_3 d 1.33
7e	5.56 (4.75)	4.41 (2.75)	4.73 (7.75)	4.42 (2.0)	4.16 (9.15)	5.44	1.55 1.48 1.35	
8e	5.58 (4.75)	4.41 (2.75)	4.71 (7.75)	4.29 (2.0)	4.20 (7.8)	5.46	1.55 1.46 1.35	

[a] δ_H in p.p.m. downfield from internal Me_4Si in $CDCl_3$, *J* in Hz.

The displacement of the mesyloxy group in **7b** or **8b** with a primary amine did not occur at low temperature and only degradation was observed under forcing conditions. When displacement by azide ion[19,20] was attempted on **7b** and **8b**, using sodium azide in *N,N*-dimethylformamide, the α-azidonitriles **7c** and **8c** were not obtained, but the alkyne **9** was formed after substitution and subsequent decomposition[21]. The L-*glycero* configuration at C-6 in **4c** was determined by X-ray crystallography[22].

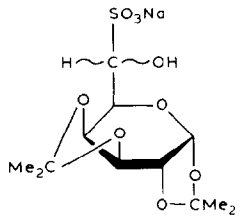
Since the marked diastereoselectivity in the above reactions was not affected

significantly by the nature of the amine, the L-*glycero* configuration of C-6 in the α-aminonitriles **4a–f** was expected. In fact, the H-5 signal in the ^{1}H-n.m.r. spectra of **4** and **8e** (L-*glycero*) appeared at lower field than the corresponding signals for **3** and **7e** (D-*glycero*). However, there was an inversion of the chemical shifts of the H-1 signals of the dibenzylaminonitriles **3d** and **4d** and also for the resonances of C-7. In order to verify the stereochemical course of the reaction leading to **3d** and **4d**, the configurations were correlated with that of the major benzylaminonitrile **4c** of known configuration.

Benzoylation of **4c** (C-7, δ 118.0) gave crystalline **4g** which could not be reduced to **4d** (C-7, δ 115.8) with sodium borohydride–acetic acid, a reagent claimed to reduce amide to amine[23]. Treatment of **4c** with benzyl bromide in ethanol gave a dibenzylaminonitrile, the ^{13}C-n.m.r. spectrum of which was identical with that of the major dibenzylaminonitrile **4d** obtained by cyano-amination of **2** in the presence of dibenzylamine.

Thus, the steric course of reaction was independent of the amine and, even with chiral α-methylbenzylamines, the stereochemical outcome was not modified significantly. That the reaction was not under thermodynamic control was verified by the fact that the minor α-aminonitrile **3c** was not affected under the reaction conditions which led to its formation.

Due to the fact that this cyano-amination procedure involves preliminary formation of the bisulfite adduct of **2** followed by introduction of the amine and subsequent reaction with sodium cyanide, the α-aminosulfonates **11** may be envisaged as intermediates. Such compounds have been prepared by reaction of simple aldehydes with sodium hydrogensulfite and primary amines[24]. However, when **2** reacted with sodium hydrogensulfite and benzylamine in the absence of sodium cyanide, 53% of the imine was isolated. Thus, the α-aminosulfonates **11** were precluded as major intermediates. The basic character of benzylic type amines



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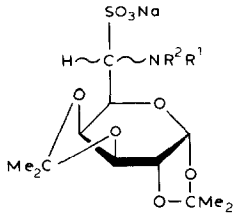

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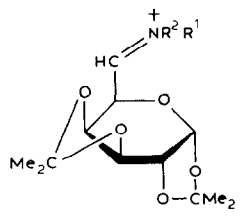

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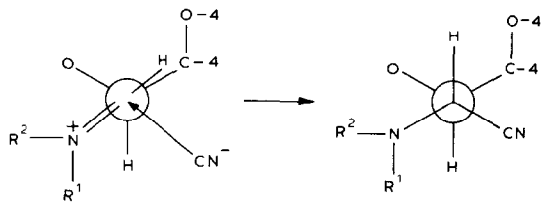

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could induce progressive release of **2** from its bisulfite adduct **10** rather than substitution at congested C-6. Subsequent formation under the mild conditions of the imine (or iminium ion with secondary amines) then allowed reaction with cyanide to yield the α-aminonitriles **3** and **4**.

Since the reaction conditions are mild, the stereochemical outcome of the reaction could be rationalized in terms of the attack of cyanide ion on the imine or iminium intermediate. By analogy[25], the favoured conformation of these intermediates will then be **13** in which there is a *s-cis* arrangement between the double bond of the imine (or iminium) and the C-5–O-5 bond of the pyranose ring. The cyanide ion will then react predominantly from the less-hindered face to afford the L-*glycero*-α-aminonitriles **4** as major products.

Although high diastereocontrol was achieved during the reaction, the configuration of the major α-aminonitrile was not that required for lincosamine; hence, indirect cyano-amination was investigated.

Since the L-*glycero* isomer **8a** was the major component in the mixture of cyanohydrins obtained by Yoshimura *et al.*[18], its transformation into the D-*glycero*-α-aminonitrile **3c** by activation followed by S_N2 displacement was studied using the trimethylsilyloxy derivatives[26]. A mixture of **7d** and **8d** was prepared in good yield from the mixture of the cyanohydrins **7a** and **8a**[18], using chlorotrimethylsilane–hexamethyldisilazane in dichloromethane. Treatment of **7d** and **8d** with benzylamine in methanol afforded the L-*glycero*-α-benzylaminonitrile **4c** in high yield (t.l.c., ^{1}H- and ^{13}C-n.m.r. spectra).

Finally, a mixture of the trifluoromethanesulfonates **7e** and **8e**, prepared in good yield from **7a** and **8a**, was stable enough for chromatography, but the two epimers could not be separated. The ^{1}H-n.m.r. (250 MHz) signal for H-1 of **7e** was a doublet at δ 5.56 ($J_{1,2}$ 4.75 Hz) integrating for 30%, and the corresponding signal of **8e** was slightly downfield (δ 5.58, $J_{1,2}$ 4.75 Hz; 70%) as observed usually in the series **7** and **8** (Table II, see also the values for H-5). These data clearly establish that the percentages of **7e** and **8e** in the mixture were similar to those (27 and 73%) of **7a** and **8a** in the starting mixture of cyanohydrins. The displacement of the triflate by benzylamine afforded 83% of a mixture of the α-benzylaminonitriles **3c** and **4c**. The ^{1}H-n.m.r. spectrum of the mixture revealed 65% of **4c**, indicating that epimerization has occurred during the transformation. Similar results were obtained when milder conditions were used.

Although rather low (35%), the yield of D-*glycero* epimer obtained at this stage of our work compares favorably with that (~10%) of the previous work[6–12] as far as stereocontrol is concerned. Since thermodynamic control was operative, it was not possible to increase the amount of the desired epimer and this approach was not investigated further.

EXPERIMENTAL

General methods. — Melting points were determined with a Thomas–Hoover

apparatus and are uncorrected. I.r. spectra (film or KBr pellets) were recorded with a Unicam SP3-300 spectrophotometer. Optical rotations were measured with a Perkin–Elmer 141 polarimeter. ^{1}H- (250 MHz) and ^{13}C- (80 MHz) n.m.r. spectra were recorded in the F.t. mode for solutions in $CDCl_3$ (internal Me_4Si). T.l.c. was performed on Silica Gel 60 F_{254} (Merck) with ether–light petroleum *A*, 2:1; *B*, 3:1; and detection by u.v. light and charring with H_2SO_4. Silica Gel 60 (Merck, 230–400 mesh) was used for flash chromatography, and silica gel (Merck, 70–230 mesh) for column chromatography with an automatic collector ISCO 328 fitted with a u.v. detector and an ISCO UA-5 absorbance monitor. Elemental analyses were performed at the Service de Microanalyse of The University of Paris VI.

Typical procedure for the cyano-amination of **2**. — 4M Sodium hydrogensulfite (0.25 mL, 1 mmol) and **2**[4] (258 mg, 1 mmol) were stirred vigorously for 20 min at 35°. A solution of the amine (1.1 mmol) in ethanol (0.2 mL) was added and the mixture was stirred for 20 min at 35°. Sodium cyanide (75 mg, 1.53 mmol) was added and the mixture was stirred at room temperature until t.l.c. (solvent *A*) indicated completion of the reaction (~4 h). The mixture was taken up in chloroform–water (15 mL each) and extracted with chloroform (3 × 15 mL). The combined extracts were washed successively with brine (2 × 10 mL) and water (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford the mixture of epimers (see Table I for the yields) which was analyzed by ^{1}H-n.m.r. spectroscopy after flash chromatography.

The following new compounds were isolated by crystallization and/or column chromatography.

6-Deoxy-6-dimethylamino-1,2:3,4-di-*O*-isopropylidene-α-L-*glycero*-D-*galacto*-heptopyranurononitrile (**4b**), m.p. 103–105°, $[\alpha]_D^{20}$ −78° (*c* 0.97, chloroform); R_F 0.40 (solvent *A*).

Anal. Calc. for $C_{15}H_{24}N_2O_5$ (312.34): C, 57.68; H, 7.74; N, 8.97. Found: C, 57.75; H, 7.75; N, 9.08.

6-Benzylamino-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-L-*glycero*-D-*galacto*-heptopyranurononitrile (**4c**), m.p. 90–91° (from hexane), $[\alpha]_D^{20}$ −41° (*c* 2.4, chloroform); R_F 0.72 (solvent *B*).

Anal. Calc. for $C_{20}H_{26}N_2O_5$ (374.42): C, 64.15; H, 7.01; N, 7.48. Found: C, 64.05; H, 7.35; N, 7.76.

6-Benzylamino-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-L-*glycero*-D-*galacto*-heptopyranurononitrile (**3c**), m.p. 113–115°, $[\alpha]_D^{20}$ −151° (*c* 0.8, chloroform); R_F 0.68 (solvent *B*).

Anal. Calc. for $C_{20}H_{26}N_2O_5$ (374.42): C, 64.15; H, 7.01; N, 7.48. Found: C, 64.21; H, 7.32; N, 7.66.

6-Deoxy-6-dibenzylamino-1,2:3,4-di-*O*-isopropylidene-α-L-*glycero*-D-*galacto*-heptopyranurononitrile (**4d**), m.p. 145–146°, $[\alpha]_D^{20}$ −7.8° (*c* 5.2, chloroform); R_F 0.74 (solvent *A*).

Anal. Calc. for $C_{27}H_{32}N_2O_5$ (464.52): C, 69.81; H, 6.94; N, 6.02. Found: C, 69.63; H, 7.25; N, 5.97.

6-Deoxy-6-dibenzylamino-1,2:3,4-di-*O*-isopropylidene-α-L-*glycero*-D-*galacto*-heptopyranurononitrile (**3d**), oil, $[\alpha]_D^{20}$ −97° (*c* 2, chloroform); R_F 0.70 (solvent *A*).

6-Deoxy-1,2:3,4-di-*O*-isopropylidene-6-(*R*)-(1-phenylethylamino)-α-L-*glycero*-D-*galacto*-heptopyranurononitrile (**4f**), m.p. 125–126°, $[\alpha]_D^{20}$ −8° (*c* 2.7, chloroform); R_F 0.73 (solvent *B*).

Anal. Calc. for $C_{21}H_{28}N_2O_5$ (388.43): C, 64.93; H, 7.27; N, 7.21. Found: C, 64.85; H, 7.31; N, 7.17.

N-*Benzoyl-6-benzylamino-6-deoxy-1,2:3,4-di*-O-*isopropylidene*-α-L-glycero-D-galacto-*heptopyranurononitrile* (**4g**). — Benzoyl chloride (385 μL, 466 mg; 3.3 mmol) and **4c** (1.122 g, 3 mmol) were reacted in pyridine (3 mL) in the presence of 4-dimethylaminopyridine (40 mg, 0.33 mmol) for 2 h. The solvent was evaporated under reduced pressure, and the residue was treated with crushed ice and water (50 mL) and then extracted with chloroform (2 × 25 mL). The combined extracts were washed with aqueous 5% sodium hydrogencarbonate (10 mL) and water (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Recrystallization of the residue from ethanol (10 mL) yielded **4g** (1.125 g, 78.5%), m.p. 171–172°, $[\alpha]_D^{20}$ +7.7° (*c* 1.8, chloroform); R_F 0.47 (solvent *A*), 0.59 (solvent *B*).

Anal. Calc. for $C_{27}H_{30}N_2O_6$ (478.50): C, 67.77; H, 6.32; N, 5.85. Found: C, 67.63; H, 5.84; N, 6.64.

6-Deoxy-6-dibenzylamino-1,2:3,4-di-O-*isopropylidene*-α-L-glycero-D-galacto-*heptopyranurononitrile* (**4d**). — Compound **4c** (374 mg, 1.0 mmol) was treated with benzyl bromide (119 μL, 171 mg; 1.0 mmol) in aqueous 95% ethanol (1.0 mL) at 60°. The reaction was monitored by t.l.c. (solvent *A*) and, when complete (~24 h), a solution of the mixture in ether (25 mL) was washed successively with aqueous 5% sodium hydrogencarbonate (10 mL) and water (2 × 10 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford a thick syrup (422 mg). Column chromatography (ether–light petroleum, with progressive increase of the proportion of ether) of the residue on silica gel (50 g) yielded **4d** (140 mg), m.p. 144–145°. The ^{13}C- and ^1H-n.m.r. spectra of this compound were identical to those of **4d** prepared by cyano-amination of **2**.

1,2:3,4-Di-O-*isopropylidene-6*-O-*trimethylsilyl*-α-D- *and* -L-glycero-D-galacto-*heptopyranurononitriles* (**7d** *and* **8d**) *and their reaction with benzylamine.* — A solution of the crude mixture of cyanohydrins **7a** and **8a** (428 mg, 1.5 mmol), obtained as previously described[21], in dichloromethane (1.5 mL) was added dropwise to a mixture of chlorotrimethylsilane (190 μL, 163 mg; 1.5 mmol), hexamethyldisilazane (380 μL), and pyridine (1.9 mL). After completion of the reaction (monitored by t.l.c., solvent *B*), the white precipitate was removed, the filtrate was concentrated under reduced pressure, and toluene (2 × 5 mL) was evaporated from the residue. To a solution of the resulting crude mixture (455 mg) of trimethylsilyl-cyanohydrins **7d** and **8d** in methanol (1.5 mL) was added benzylamine (170 μL, 137 mg; 1.3 mmol), and the mixture was stirred for 2 h at 60°. T.l.c. then showed a single spot, R_F 0.73 (solvent *B*). Evaporation of the solvent afforded a

thick syrup, the ^{1}H- and ^{13}C-n.m.r. spectra of which were identical to those of L-*glycero*-α-benzylaminonitrile **4c**. Crystallization from hexane yielded **4c** (380 mg, 67.7% from **7a–8a**), m.p. 90–91°.

*1,2:3,4-Di-O-isopropylidene-6-O-trifluoromethylsulfonyl-α-*D- *and* -L-glycero-D-galacto-*heptopyranurononitriles* (**7e** *and* **8e**) *and their reaction with benzylamine.* — A solution of the crude cyanohydrins **7a** and **8a** (325 mg, 1.14 mmol) and pyridine (1.25 equiv., 115 μL) in dry dichloromethane (6 mL) was added dropwise to a mixture of triflic anhydride (190 μL, 321 mg; 1.14 mmol) in dry dichloromethane (6 mL) at −5° under argon. After 30 min at −5°, t.l.c. showed a single spot, R_F 0.81 (solvent *B*). Benzylamine (125 μL, 1.14 mmol) was added, the mixture was stirred at 0° overnight, and more benzylamine (250 μL, 2.2 mmol) was added. The reaction was conducted at room temperature until t.l.c. (solvent *B*) showed the disappearance of the spot at R_F 0.8 (~5 days). A solution of the mixture in chloroform was washed with water (10 mL), the aqueous phase was extracted with chloroform (3 × 10 mL), and the combined organic layers were washed with brine (10 mL) and water (10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. T.l.c. (solvent *B*) of the resulting syrupy mixture (365 mg, 83%) of α-benzylaminonitriles **3c** and **4c** showed two spots R_F 0.71 and 0.67 for **4c** and **3c**, respectively, in the ratio 65:35 from the integration of the H-1 signals in the ^{1}H-n.m.r. spectrum of the mixture. In an alternative experiment, the mixture was quenched after completion of the triflation step by cold aqueous 10% sodium hydrogencarbonate. Conventional work-up afforded the mixture of **7e** and **8e** as an oil (369 mg, 77.5%) in the ratio 30:70.

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