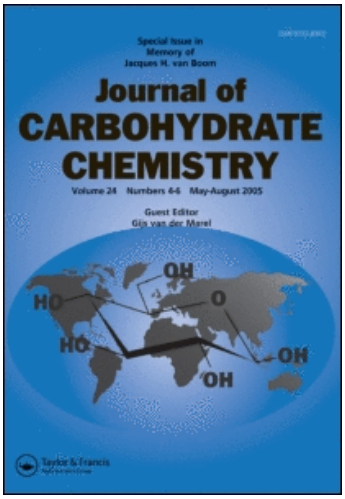

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SYNTHESIS OF 6-HYDROXY-L-DAUNOSAMINE AND L-DAUNOSAMINE DERIVATIVES

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ABSTRACT

Methyl 3-trifluoroacetamido-2,3-dideoxy-α-L-*lyxo*-hexopyranoside (**19**) has been synthesized from D-glucose derivatives following two pathways. The first one involving 1,2:5,6-di-*O*-isopropylidene-α-D-glucopyranose as starting material is mainly based upon azidation at C-3, inversion of configuration at C-5 and then radical deoxygenation at C-2 (13 steps and 10% overall yield). This pathway also afforded methyl *N*-trifluoroacetyl-α-L-daunosamine **22**. The second pathway, which started from tri-*O*-acetyl-D-glucal, relied essentially upon Michael addition of N_3H on the corresponding hex-2-enose and glycosidation of the two pivaloyl compounds **33** and **34**. After the β-D-*ribo* isomer **34** was subsequently converted into its β-methyl glycoside **28b**, inversion of configuration at C-5 was carried out *via* the formation of the 6-bromo-sugar **36**, followed by formation of the hex-5-enopyranoside **37**. Hydroboration of **37** stereoselectively afforded **38**, followed by catalytic hydrogenation and trifluoroacetylation to give **19**.

INTRODUCTION

3-Amino-2,3,6-trideoxy-L-hexopyranoses are of great interest as they have been isolated from a large number of biologically active molecules such as anthracyclines[1] and glycopeptide antibiotics.[2] In relation with their biological importance, their syntheses are well documented.[3] Most of the syntheses have been undertaken in order to obtain novel semi-synthetic anthracyclines with lower cytotoxicity and enhanced activity against cancer cells but also, more recently, in view of overcoming the main problem of multidrug

resistance.[4] In contrast, relatively few publications have appeared concerning the synthesis of the corresponding 6-hydroxy analogs such as 6-hydroxy-L-daunosamine or related diastereoisomers.[5] In addition, one of the procedures started from very expensive L-glucose whereas the other, which was based on the use of L-arabinose, required a multistep procedure.

In connection with our general program aimed at the synthesis of new anthracyclines,[6] including 3-amino-2,3,6-trideoxy-L-hexoses or 3-amino-2,3-dideoxy-L-hexoses, but also in order to explore the potentialities of such sugars as carriers of cytotoxic drugs,[7] we report herein two syntheses of the title compounds, one originating from 1,2:5,6-di-*O*-isopropylidene-α-D-glucopyranose and the other from tri-*O*-acetyl-D-glucal.

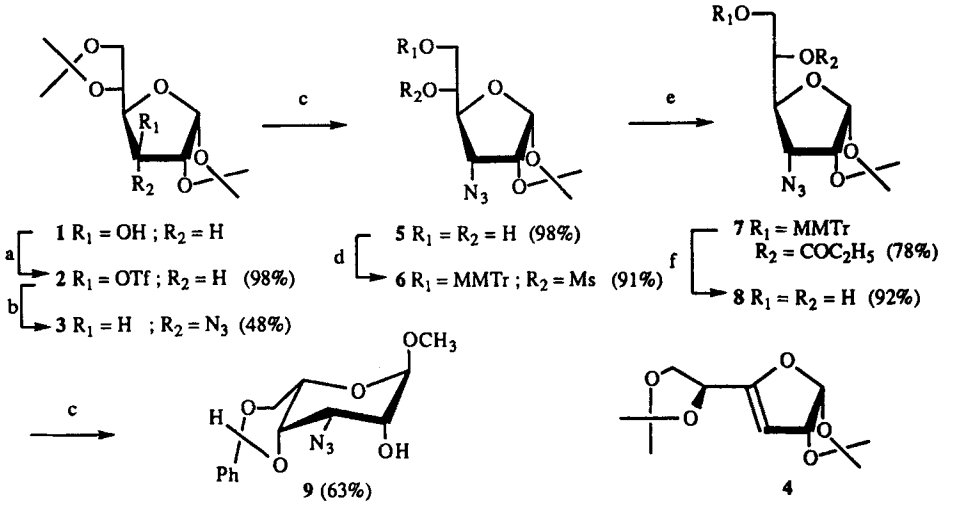
RESULTS AND DISCUSSION

a) from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose. It has been shown that displacement of the *p*-toluenesulfonyl group in 1,2:5,6-di-*O*-isopropylidene-3-*O*-tosyl-D-glucofuranose is difficult to achieve with anionic nucleophiles in DMF[8] or HMPT,[9] even under drastic conditions. In contrast, inversion of configuration at C-3 to give allofuranose derivatives occurs more readily with ammonia[10] and hydrazine.[11] However, as marked enhanced reactivity of secondary triflates *versus* secondary tosylates has been underlined recently in several recent reports,[12] our first objective was to introduce the nitrogen function at C-3 *via* the triflate **2**.[13]

Thus, azidolysis of compound **2** to give **3** was studied under various conditions (see Table 1). However, 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enofuranose **4**[14] was also formed (1:1) in these reactions as a by-product resulting from a base-induced elimination of TfOH from **2**. In our hands, the best conditions (48% isolated yield) involved reaction of **2** with NaN_3 in DMF at 50 °C (entry 5) for 24 h. During completion of this work, Baer and Gan[15] showed that an improved yield (62%) could be obtained using tetramethylguanidinium azide in DMF at 25 °C for 6 h but considerable proportions of **4** still arose as a by-product.

After selective hydrolysis of the 5,6-isopropylidene acetal in acidic medium (98% yield), '"one-pot" treatment of the monoacetonide **5**[16] with 4-methoxyphenyldiphenylmethyl chloride (or MMTrCl) in pyridine (1.2 equiv), followed by addition of methanesulfonyl chloride led to compound **6** in 91% overall yield.

The C-5 configurational inversion was achieved at this stage using cesium propionate[17] in DMF to afford cleanly (78% yield) the L-talofuranose derivative **7**.



a : Tf_2O, pyridine, CH_2Cl_2 ; b: NaN_3, DMF ; c : AcOH/MeOH/H_2O ; d : MMTrCl, pyridine then MsCl ;
e : C_2H_5COOCs, DMF ; f : i : APTS, CH_2Cl_2/MeOH ; ii : MeONa, MeOH ; g : i : HCl, MeOH ; ii : PhCHO, $ZnCl_2$.

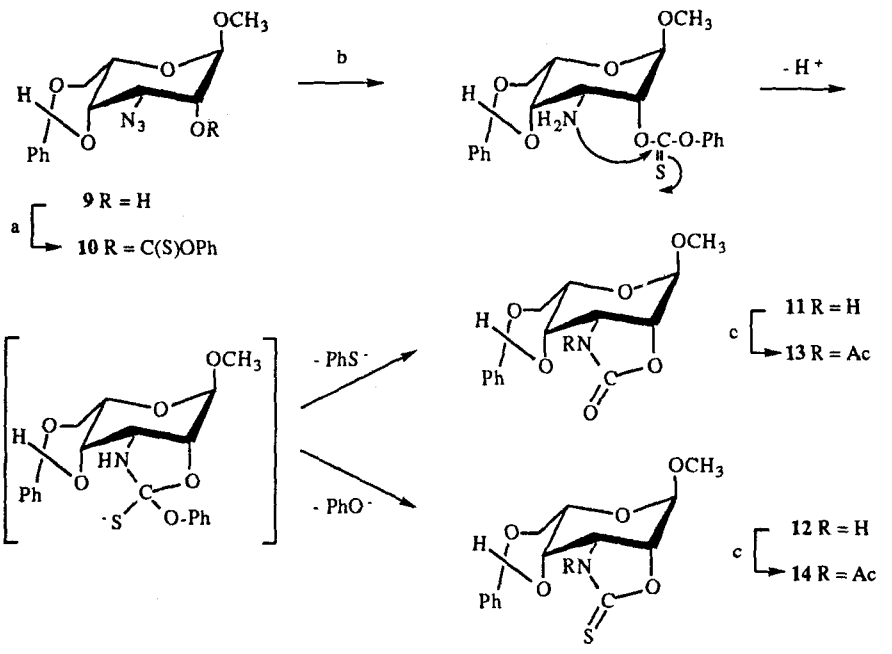
Scheme 1

Table 1. Azidolysis of compound **2**.

Entries	Reagent	Equiv.	Solvent	T °C	Time (h)	Ratio **3/4**	Isolated **3** Yield (%)
1	NaN_3	3	DMF	20	48	55/45	-
2	NaN_3	3	DMF	50	3.5	52/48	-
3	NaN_3	3	DMF	80	1.5	54/46	39
4	LiN_3	3	DMF	50	2.5	59/41	-
5	NaN_3	2	DMF	50	24	-	48
6	NaN_3	2	HMPT	50	1	-	45

Stepwise removal of the 4-methoxyphenyldiphenylmethyl group and of the propionic ester led to **8** in 92% overall yield.

The benzylidene derivative **9** was obtained (63%) by hydrolysis of **8** with methanolic hydrogen chloride under thermodynamic conditions (75 °C, 9 h), and treatment of the resulting mixture with benzaldehyde in the presence of $ZnCl_2$ as the catalyst.

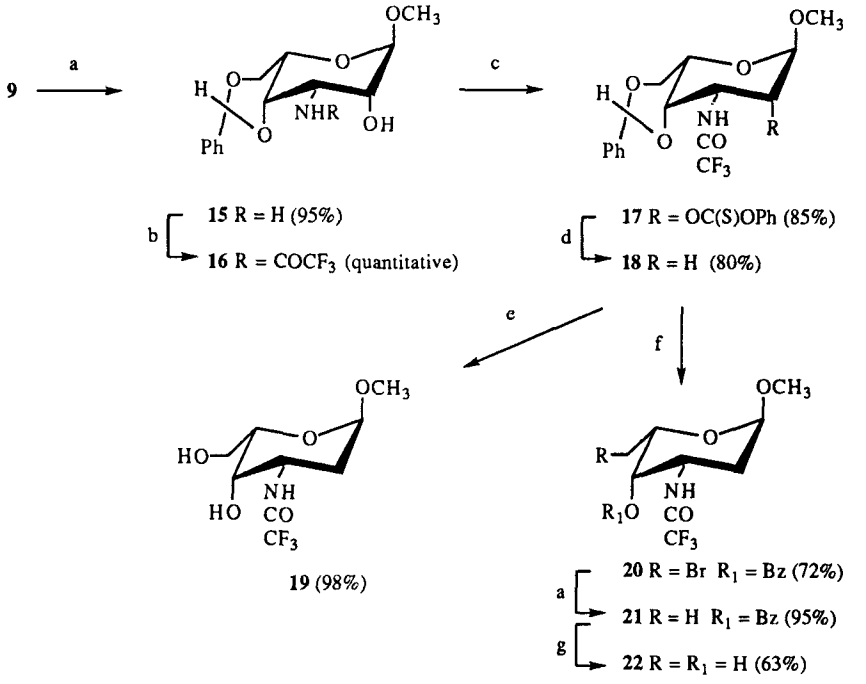


a : PhOC(S)Cl, pyridine ; b Bu_3SnH, $PhCH_3$; c : MeONa, MeOH

Scheme 2

Radical deoxygenation was attempted at this stage by treatment with tributyltin hydride[19] of the phenoxythiocarbonyl derivative **10**.[18] In fact, this afforded the oxazolidinone **11** along with the corresponding thiaoxazolidinone **12** (ratio 1:1) which were separated after *N*-acetylation. The structures of the corresponding acetamides **13** and **14** were deduced from mass spectra (CI, NH_3), IR and from NMR data. Formation of **11** and **12** can be explained (Scheme 2) by initial reduction of the azido-group and subsequent nucleophilic attack of the nitrogen on the vicinal thiocarbonyl with loss of PhS^- or PhO^-, respectively. Such a hypothesis is supported by the known reduction of the azide function by Bu_3SnH,[20] but also by analogy with a known formation of an oxazolidinone ring from an amino-β-benzoyl ester, as reported by Sato *et al.*[21]

Studying carefully the literature, we found that such an unsuccessful reductive deoxygenation of a phenoxythiocarbonate in the presence of a vicinal azide was previously reported by Sakai *et al.*[22] This failure was ascribed to the presence of the azido group but the resulting complex mixture was not further analyzed in their case.

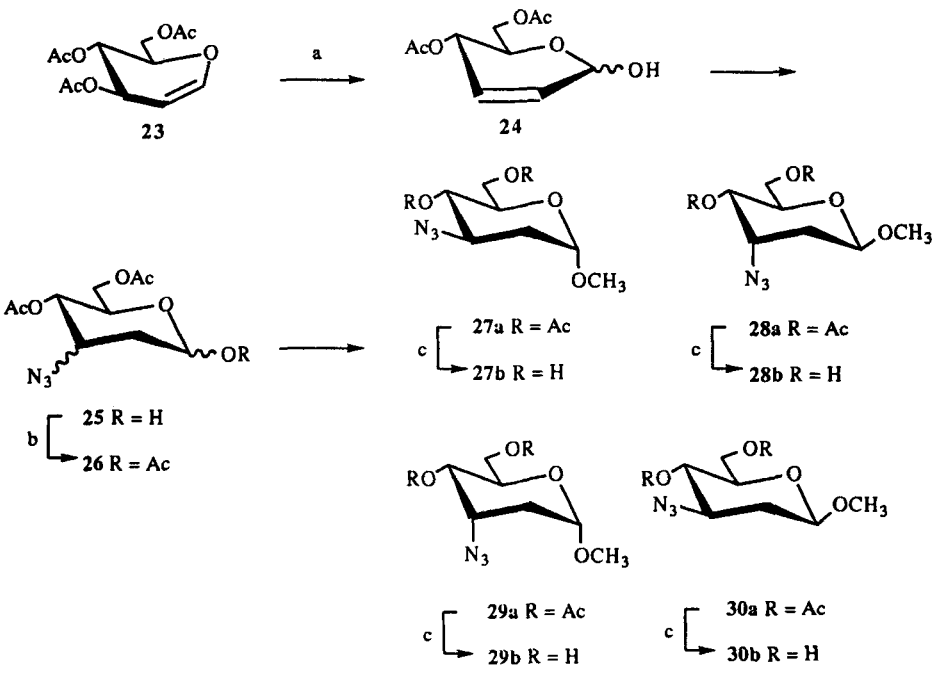


a : H_2 Pd/C ; b : $(CF_3CO)_2O$, Et_3N ; c : PhOC(S)Cl, pyridine ; d : Bu_3SnH, $PhCH_3$;
e : CH_3COCl/MeOH ; f : NBS, $BaCO_3$; g : MeONa, MeOH

Scheme 3

Eventually, in order to avoid this side-reaction, a slightly modified route (Scheme 3) was investigated like that of these latter authors. This consisted in the reduction of the azide and protection of the amine prior to the deoxygenation-step. Therefore, **9** was hydrogenated (95%) and the amino-sugar **15** was trifluoroacetylated ($(CF_3CO)_2O$, CH_2Cl_2), producing **16** in almost quantitative yield.

Deoxygenation was then successfully achieved by conversion of **16** into its phenyl thiocarbonate **17** (85%) which was reacted with Bu_3SnH to give **18** (80% yield). Finally, the α-methyl glycoside of *N*-trifluoroacetyl-6-hydroxy-L-daunosamine **19**[5a] (98%) was isolated after treatment with methanolic hydrogen chloride. On the other hand, methyl 2,3,6-trideoxy-3-trifluoroacetamido-α-L-*lyxo*-hexopyranoside **22** (or methyl *N*-trifluoroacetyl-α-L-daunosaminide)[23] was synthesized *via* **20** resulting from opening the acetal group in the presence of *N*-bromosuccinimide.[24] Catalytic hydrogenolysis of **20** and *O*-deprotection of **21** using sodium methoxide in methanol led to **22**.

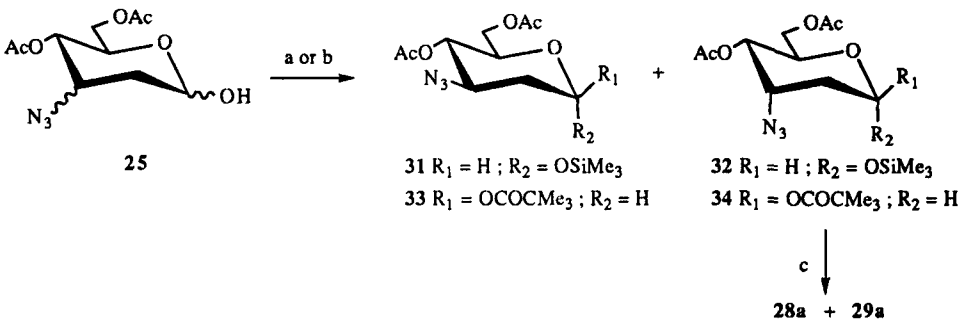


a : i H_2O, 80 °C ; ii : NaN_3, AcOH ; b : Ac_2O, pyridine ; c : MeONa, MeOH

Scheme 4

b) from tri-*O*-acetyl-D-glucal 26. Several years ago, we reported[25] a convenient and stereoselective synthesis of methyl (or benzyl) 3-amino-2,3,6-trideoxy-L-*arabino*-hexopyranoside (or 4-*epi*-L-daunosaminide). This synthesis proceeded *via* addition of hydrazoic acid to a hex-2-enopyranose resulting from the conversion of di-*O*-acetyl-L-rhamnal by simple heating in the presence of water. This was also extended with success for preparing 4-*epi*-L-daunosamine-containing disaccharides[26] and subsequently for new disaccharide-containing anthracycline.[27]

Thus, using a similar sequence as in the L-series,[25-27] tri-*O*-acetyl-D-glucal **23** was heated at 80 °C for 3 h in water and then, without isolation of the hex-2-enopyranose **24**, was reacted with NaN_3 in the presence of AcOH ("one-pot"). This reaction afforded a crude mixture (**25**) which was acetylated to give **26** as a mixture of four diastereisomers (Scheme 4). Four methyl glycosides were formed by treatment of **26** with MeOH *plus* K10 Montmorillonite as catalyst.



a : TMSCl, imidazole ; b : pivaloyl chloride, Et_3N ; c : K-10 Montmorillonite, MeOH

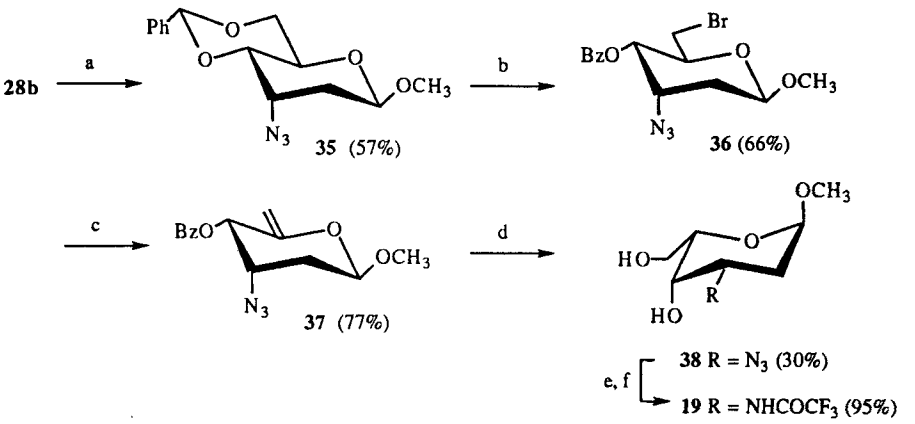
Scheme 5

In a first attempt, flash chromatography of the crude mixture of glycosides afforded two fractions (A and B), homogenous on TLC. Their ^1H NMR indicated that each of them is, in fact, a mixture containing two compounds. The first fraction (A) obtained from the column was an inseparable mixture of **27a** and **28a** while the second fraction (B) contained **29a** and **30a.**

Complete separation of the four components was efficient only after transesterification of the separated fractions A and B. Thus, transesterification of fraction A, followed by column chromatography, afforded the α-D-*arabino* **27b** and the β-D-*ribo* **28b** isomers in a 3:1 ratio. For their part, α-D-*ribo* **29b** and β-D-*arabino* **30b** isomers were obtained in a 1:2 ratio from fraction B following the same procedure.

A good stereoselectivity of the 1,4-addition of N_3H to the hex-2-enopyranose **24** was thus observed as previously with the corresponding 6-deoxy-L-analog, since the ratio of compound having the azido group equatorially oriented, namely the L-*arabino* isomers **27a** (or **b**) and **30a** (or **b**), *versus* the *ribo* isomers **28a** (or **b**) and **29a** (or **b**) was 5:2. However, the lack of stereoselectivity noted during the glycosidation-step which afforded a mixture of α- and β-methylglycosides, as well as the laborious isolation of pure compounds, were not quite satisfactory. Therefore, we turned our attention towards another procedure in order to avoid the formation of an anomeric mixture and achieve stereoselective glycosylation.

We began with the synthesis of 1-*O*-trimethylsilyl-α-D-glucopyranosides (Scheme 5). Treatment of the mixture of 1-*O*-unprotected azido-sugar **25** with trimethylsilyl chloride afforded a mixture of α- and β-anomers. Fortunately, column chromatography allowed us to recover, in almost quantitative yields, only the

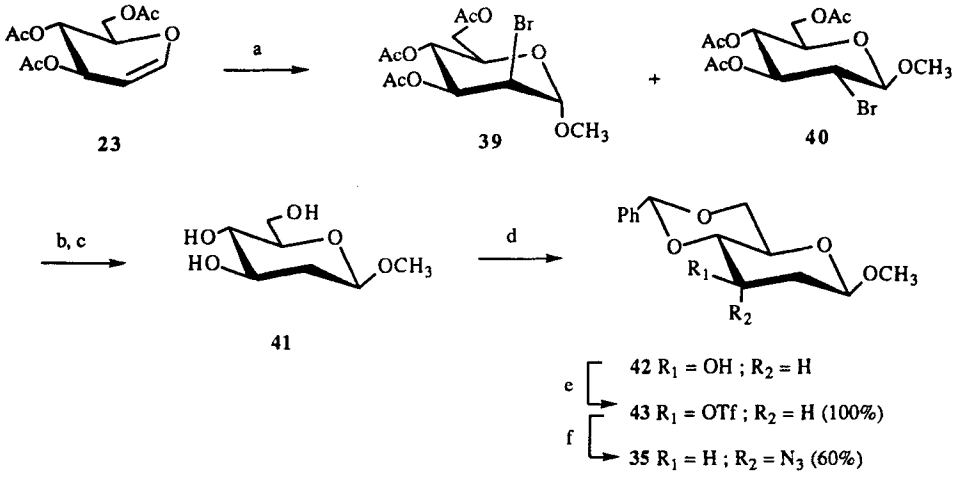


a: α, α-dimethoxytoluene, APTS ; b : NBS, $BaCO_3$; c : AgF, pyridine ;
d : 9-BBN then H_2O_2 ; e : H_2 Pd/C ; f : $(CF_3CO)_2O$, Et_3N

Scheme 6

corresponding α–anomers of *arabino* and *ribo* configurations, **31** and **32,** respectively. Such an anomerization of acetyl-protected β-trimethylsilyl glucoside into the corresponding α-anomer had been reported by Tietze *et al.*,[26] but in the presence of trimethylsilyl trifluoromethanesulfonate. The easier transformation, as observed here, may be attributed to the 2-deoxy feature of **25**. Unfortunately, all attempts to remove the ester functions in **31** and **32** resulted in more or less complete decomposition of the products.

Consequently, we turned our attention towards the formation of 1-*O*-pivaloyl derivatives, since it has been reported[29] that the use of pivaloyl chloride, pyridine and DMAP in dichloromethane stereoselectively afforded the β-D-anomer of a glucopyranuronic acid even in the presence of a non-participating group at C-2. The diastereocontrol of anomeric *O*-alkylation of pyranoses has been explained[30] in terms of enhanced nucleophilicity of the equatorial oxygen atoms. Indeed, treatment of **25** under the above conditions resulted in the exclusive formation of **33** and **34**, these compounds being separated by chromatography and isolated in 73% overall yield. Further treatment of compound **34** with MeOH in the presence of K10-Montmorillonite led to a mixture of β– and α-anomers **28a** and **29a** (66% overall yield and a 2:1.ratio). Next, steps towards the 6-hydroxy-L-daunosamine included inversion of configuration at C-5 in **28b** *via* the formation of a 5-enose. To this end, transesterification of the β-D-*ribo* isomer **28a** was followed by treatment of the resulting **28b** with α,α-dimethoxytoluene to give **35** (Scheme 6). The benzylidene ring, as present in **35**, was opened with



a : NBS, MeOH ; b : MeONa, MeOH ; c : H_2 Ni/Raney ; d : α, α-dimethoxytoluene, APTS ; e : Tf_2O, pyridine ; f : NaN_3, DMF

Scheme 7

N-bromosuccinimide according to Hanessian and Hullar,[24] giving the bromo compound **36** (Scheme 6). Treatment of **36** with silver fluoride led to **37**, which was treated in a subsequent step with 9-borabicyclo[3.3.1]nonane (9-BBN), then with $NaOH\text{-}H_2O_2$ to afford the 6-hydroxy-L-sugar **38**. The latter was converted in two steps (H_2 Pd/C; $(CF_3CO)_2O$) into the corresponding *N*-trifluoroacetyl-6-hydroxy-α-L-daunosamine **19**.[5a]

Compound **35** could finally be prepared by a more direct route, starting from tri-*O*-acetyl-D-glucal **23** (Scheme 7).

Treatment of **23** with *N*-bromosuccinimide and MeOH[31] led to a mixture of α– and β–anomers **39** and **40**. However, the pure β-anomer **40** could be separated (28% yield) by crystallization from methanol, whereas the α–anomer was purified by flash chromatography of the mother-liquors and isolated in 70% yield. The β-anomer **40** was subsequently converted into the methyl 2-deoxy-β-D-glucopyranoside **41** by transesterification and hydrogenolysis. Benzylidenation of **41** by the exchange method of Evans[32] gave the acetal derivative **42**. Activation of **42** as a trifluoromethanesulfonyl derivative **43**, followed by azidolysis of **43**, could be performed under mild conditions (DMF at room temperature) allowing access to **35** in a rather good yield (60%).

In conclusion, methylglycosides of *N*-trifluoroacetyl-6-hydroxy-L-daunosamine **19** and of *N*-trifluoroacetyl-L-daunosamine **22** have been conveniently prepared in 13 and

15 steps (12% and 5.2% yields, respectively) from 1,2:5,6-di-*O*-isopropylidene-D-glycofuranose. Although the synthetic route to **19** is not attractive (9 steps, but less than 1% overall yield), the glycal-based route (2 steps and 45% overall yield) represents an easy access to the glycosyl donor, trimethylsilyl 3-azido-2,3-dideoxy-D-*arabino*-hexopyranoside **31**, useful precursor of the nitrosoureido sugar, ecomustine.[7] Coupling reactions of **31** with biologically relevant molecules has been undertaken and will be reported later.

EXPERIMENTAL

General methods. Melting points are reported uncorrected. IR spectra were recorded in chloroform solution using a PERKIN-ELMER 1710 spectrophotometer, calibrated against a polystyrene film and are expressed in cm^{-1}. Optical rotations have been determined with a PERKIN-ELMER 241 polarimeter (589 nm), at 20 °C, with a concentration expressed in g/100 mL. ^1H NMR spectra were recorded using Bruker HX 270 (270 MHz), 250 MHz and 100 MHz and VARIAN EM390 (90 MHz) spectrophotometers. Chemical shifts are expressed in ppm downfield from internal Me_4Si with the notations indicating the multiplicity of the signal (s, singlet; d, doublet; dd, doublet of doublet; t, triplet and m, multiplet). The coupling constants are expressed as J values in units of Hertz. Mass spectra (CI, NH_3) were recorded with a Nermag R10-10C. TLC was performed on Silica gel $60F_{254}$ (Merck) using the following solvent systems: A = cyclohexane/EtOAc: 4/1; B = cyclohexane/EtOAc: 2/1; C = cyclohexane/EtOAc: 1/1; D = cyclohexane/EtOAc: 1/2; E = CH_2Cl_2/MeOH: 99/1; F = CH_2Cl_2/MeOH: 98/2; G = CH_2Cl_2/MeOH : 95/5. Silica gel (Merck, particle size 0.040-0.063 nm) was used for flash chromatography.[33]

1,2:5,6-Di-*O*-isopropylidene-3-*O*-triflyl-α-D-allofuranose (2). To a cooled solution (- 10 °C) of **1** (10 g, 38,4 mmol) in dry dichloromethane (800 mL) kept under argon atmosphere, were successively added anhydrous pyridine (12 mL) then, dropwise, trifluoromethanesulfonic anhydride (7.1 mL, 42.3 mmol). After stirring at - 10 °C for 1.5 h, the crude mixture was poured into ice and saturated aqueous solution of $NaHCO_3$ (800 mL) and the aqueous layer was extracted with dichloromethane. After usual work-up, compound **2** was obtained (15.3 g, 98%), pure enough for the next step; R_f 0.74 (system B); ^1H NMR (90 MHz, $CDCl_3$) δ 5.85 (d, 1H, H-1), 5.20 (dd, 1H, H-3), 4.70 (d, 1H, H-2), 4.20-3.80 (m, 4H, H-4, H-5, H-6, H-6'). These values are in agreement with literature data.[12]

3-Azido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (3). To a solution of **2** (21.25 g, 54.16 mmol) in anhydrous DMF (80 mL), sodium azide (7.04 g, 108 mmol) was added and the mixture was heated at 50 °C under argon atmosphere for 24 h. After cooling to room temperature, the mixture was poured into water (150 mL) and extraction was conducted with EtOAc (150 mL). Usual work-up was followed by flash chromatography with cyclohexane-EtOAc (6:1, then 4:1 and 1:1). Thus, the unsaturated compound **4** (6 g, 39%), and azido-sugar **3** (7.43 g, 48%) were successively eluted and samples of both compounds were recrystallized from hexane.

Compound **3**: R_f 0.56 (system B); mp 39 °C; $[\alpha]_D^{20}$ +72° (*c* 1, chloroform) [Lit.[8b] mp 38-39 °C, $[\alpha]_D^{20}$ +72° (*c* 1, chloroform)]; IR 2115 (N_3) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.78 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 4.73 (dd, 1H, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 4.3 Hz, H-2), 4.21-3.97 (m, 4H, H-4, H-5, H-6, H-6'), 3.40 (dd, 1H, $J_{3,4}$ = 9 Hz, $J_{2,3}$ = 4.3 Hz, H-3).

Compound **4**: R_f 0.68 (system B); mp 50 °C; $[\alpha]_D^{20}$ +24° (*c* 1.2, ethanol); [Lit.[14] mp 51 °C; $[\alpha]_D^{20}$ +24° (*c* 1.1, ethanol)]; IR 1668 (C=C) cm^{-1}.

3-Azido-3-deoxy-1,2-*O*-isopropylidene-α-D-allofuranose (5). The azido-sugar **3** (7.33 g, 25.7 mmol) was added to a mixture of AcOH/MeOH/H_2O 4:5:6 (90 mL). After stirring at 50 °C for 17 h, the crude mixture was cooled to 20 °C, then poured into EtOAc (200 mL). The organic phase was washed with a saturated $NaHCO_3$ aqueous solution (60 mL). Concentration under reduced pressure, led to **5** (6.20 g, 98%) as a syrup; R_f 0.31 (system D); mp 76 °C (cyclohexane/EtOAc); $[\alpha]_D^{20}$ +127° (*c* 0.88, chloroform)(Lit. [16a]: mp 76-77 °C, $[\alpha]_D^{20}$ +111° (*c* 1.5, $CHCl_3$); [16b]: mp 73-75 °C, $[\alpha]_D^{20}$ +76.0° (*c* 1.02, acetone); IR ($CDCl_3$) 3597 (OH), 2113 (N_3) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.80 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 4.76 (dd, 1H, $J_{2,1}$ = 3.7 Hz, $J_{2,3}$ = 4.5 Hz, H-2), 4.09 (dd, 1H, $J_{4,5}$ = 4 Hz, $J_{4,3}$ = 9 Hz, H-4), 4.00 (m, 1H, H-5), 3.76 (d, 2H, H-6, H-6'), 3.59 (dd, 1H, $J_{3,2}$ = 4.5 Hz, $J_{3,4}$ = 9 Hz, H-3), 2.33-2.28 (m, 2H, OH exchangeable with D_2O).

3-Azido-3-deoxy-1,2-*O*-isopropylidene-5-*O*-mesyl-6-*O*-(4-methoxyphenyldiphenylmethyl)-α-D-allofuranose (6). To a cooled solution (0 °C) of diol **5** (6.03 g, 24.6 mmol) in dry pyridine (60 mL), 4-methoxyphenyldiphenylmethyl chloride (MMTrCl) (9.11 g, 29.52 mmol) was added under argon atmosphere. After stirring for 0.5 h at 0 °C, then for 3.5 h at 20 °C, an additional amount (2.27 g, 7.38 mmol) of MMTrCl was poured into the mixture with additional stirring for 2.5 h at 20 °C. The reaction mixture was then cooled to 0 °C and methanesulfonyl chloride (2.29 mL, 29.52 mmol) was added under argon. After stirring for 0.5 h at 0 °C, then for 16 h at 20 °C, the organic layer was poured into water (60 mL). The aqueous phase was extracted with ethyl acetate (2 x 60 mL). The organic phases were combined, dried over Na_2SO_4, concentrated

under reduced pressure and chromatographed on silica gel (cyclohexane/EtOAc/Et_3N 75:25:1, 66:34:1 and 50:50:1) to give **6** (13.41 g, 91%); R_f 0.56 (system F); mp 64 °C (EtOAc); $[\alpha]_D^{20}$ +55° (*c* 1.7, dichloromethane); IR ($CDCl_3$) 3597 (OH), 2113 (N_3) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.45-6.80 (m, 14H, H_{Ar}), 5.74 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 5.01 (m, 1H, H-5), 4,70 (dd, 1H, $J_{2,1}$ = 3.7 Hz, $J_{2,3}$ = 4.2 Hz, H-2), 4.31 (dd, 1H, $J_{4,5}$= 3.5 Hz, $J_{4,3}$ = 9.5 Hz, H-4), 3.79 (s, 3H, CH_3-O-Ph), 3.52-3.35 (m, 3H, H-3, H-6, H-6'), 3.03 (s, 3H, CH_3-SO_3).

Anal. Calcd for $C_{30}H_{33}N_3O_8S$: C, 60.49; H, 5.58; N, 7.05. Found: C, 60.53; H, 5.71; N, 7.15.

3-Azido-3-deoxy-1,2-*O*-isopropylidene-5-*O*-propionyl-6-*O*-(4-methoxyphenyldiphenylmethyl-α-L-talofuranose (7). Cesium propionate (1.23 g, 5.98 mmol) was added to a solution of **6** (2.97 g, 4.98 mmol) in anhydrous DMF (40 mL). After stirring for 72 h at 120 °C, the crude material was cooled to 20 °C, poured into water (25 mL) and extracted with ethyl acetate (50 mL). The organic layers were washed with water (7 x 10 mL) and reextracted with ethyl acetate (30 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. Chromatography (cyclohexane/ethyl acetate/triethylamine 80:20:1) yielded **7** (2.25 g, 78%) and recovered starting material (0.28 g, 10%); R_f 0.52 (system B); mp. 68 °C (EtOAc/cyclohexane); $[\alpha]_D^{20}$ +39° (*c* 1.5, chloroform); ^1H NMR (250 MHz, $CDCl_3$) δ 7.45-6.81 (m, 14H, H_{Ar}), 5.74 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 5.27 (m, 1H, H-5), 4.69 (dd, 1H, $J_{2,1}$ = 3.6 Hz, $J_{2,3}$ = 4.4 Hz, H-2), 4.32 (dd, 1H, $J_{4,5}$ = 3 Hz, $J_{4,3}$ = 9.8 Hz, H-4), 3.79 (s, 3H, CH_3-O-Ph), 3.37-3.27 (d, 2H, H-6, H-6'), 3.30 (dd, 1H, $J_{3,2}$ = 4.4 Hz, $J_{3,4}$ = 9.8 Hz, H-3), 2.42 (q, 2H, CH_2), 1.17 (t, 3H, CH_3); LRMS (CI/NH_3): *m/z* 591 $[M + NH_4]^+$.

3-Azido-3-deoxy-1,2-*O*-isopropylidene-α-L-talofuranose (8). The propionate **7** (2.40 g, 4.1 mmol) in a solution (50 mL) of *p*-toluenesulfonic acid (2% in CH_2Cl_2/MeOH 7:3) was stirred for 1.5 h at 20 °C. The crude mixture was poured into CH_2Cl_2 (50 mL). The organic layer was washed successively with a saturated aqueous $NaHCO_3$ solution (30 mL), then with a saturated aqueous NaCl solution (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was immediately dissolved in anhydrous methanol (40 mL) and a solution of 1M sodium methoxide in methanol (2 mL) was added under argon atmosphere. After reacting for 1 h at 20 °C, the organic layer was neutralized by addition of H^+ (Amberlite CG 50) resin. The crude mixture was filtered and concentrated under reduced pressure to give **8** (0.94 g, 92%); R_f 0.24 (system D); mp 92 °C; $[\alpha]_D^{20}$ +142° (*c* 0.8, chloroform); IR ($CDCl_3$) 3571 (OH), 2112 (N_3) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.82 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 4.75 (dd, 1H, $J_{2,1}$ = 3.7 Hz, $J_{2,3}$ = 4.2 Hz, H-2), 4.08 (dd, 1H, $J_{4,5}$ = 1.6 Hz, $J_{4,3}$ = 9.6 Hz,

H-4), 3.87-3.78 (m, 3H, H-5, H-6, H-6'), 3.71 (dd, 1H, $J_{3,2}$ = 4.2 Hz, $J_{3,4}$ = 9.6 Hz, H-3), 2.25 (massif, 2H, OH, exchangeable with D_2O).

Anal. Calcd for $C_9H_{15}F_3N_3O_5$: C, 44.08; H, 4.16; N, 17.13. Found: C, 44.15; H, 4.10; N, 17.25.

Methyl 3-Azido-3-deoxy-4,6-*O*-benzylidene-α-L-talopyranoside (9). To a solution of the diol **8** (0.102 g, 0.042 mmol) in anhydrous methanol (15 mL) was added concentrated hydrochloric acid (0.3 mL) under argon. After reacting for 9 h at 75 °C, the mixture was cooled to 20 °C, concentrated under reduced pressure and treated with benzaldehyde (5 mL) in the presence of zinc chloride (0.073 g). After reacting for 9.5 h at 20 °C, the reaction medium was poured into EtOAc (20 mL). The organic layer was washed successively with a $NaHCO_3$ saturated aqueous solution (2 x 20 mL, pH = 9) and with water (2 x 20 mL, pH = 7). The organic phase was dried over Na_2SO_4, concentrated under reduced pressure and flash chromatographed (hexane/EtOAc 10:1 then 2:1) to give **9** as a syrup (0.081 g, 63%); R_f 0.56 (system C); $[\alpha]_D^{20}$ -85° (*c* 1.4, chloroform); ^1H NMR (100 MHz, $CDCl_3$) δ 7.60-7.40 (m, 5H, H_{Ar}), 5.50 (s, 1H, H-Ph), 4.89 (d, 1H, H-1), 4.41 (m, 1H, H-4), 4.32 (d, 1H, H-6), 4.17 (d, 1H, H-6'), 3.85 (m, 1H, H-2), 3.68 (m, 1H, H-5), 3.50-3.42 (m, 4H, H_3, CH_3-O); LRMS (CI/NH_3): *m/z* 325 $[M + NH_4]^+$.

Methyl 3-Azido-4,6-*O*-benzylidene-3-deoxy-2-*O*-phenoxythiocarbonyl-α-L-talopyranoside (10). Phenoxythiocarbonyl chloride (0.32 mL, 2.28 mmol) was added, under argon, to a (0 °C) cooled solution of azidosugar **9** (0.352 g, 1.14 mmol) in anhydrous pyridine (5 mL). After stirring for 15 min at 0 °C, then for 2 h at 20 °C, the mixture was poured into ethyl acetate (100 mL). The organic layer was washed with water (3 x 8 mL), dried over $MgSO_4$, concentrated under reduced pressure and the residue was flash chromatographed (hexane/CH_2Cl_2 1:9 then CH_2Cl_2) to give **10** (0.403 g, 80%); R_f 0.83 (system C); mp 181 °C; $[\alpha]_D^{20}$ -118° (*c* 1, chloroform); ^1H NMR (100 MHz, $CDCl_3$) δ 7.72-7.14 (m, 10H, H_{Ar}), 5.73 (m, 1H, H-2), 5.66 (s, 1H, H-Ph), 5.58 (d, 1H, H-1), 4.41 (m, 1H, H-4), 4.33 (d, 1H, H-6), 4.24 (d, 1H, H-6'), 3.73 (m, 1H, H-5), 3.64 (dd, 1H, H-3), 3.43 (s, 3H, CH_3-O).

9-Acetyl-6-methoxy-2-phenyl-*m*-dioxino[4',5':5,6]pyrano[4,3-*d*]oxazol-8(*9H*)-one (13) and 9-acetyl-6-methoxy-2-phenyl-*m*-dioxino[4',5':5,6]pyrano[4,3-d]oxazol-8(*9H*)-thione (14). Tributyltin hydride (0.836 mL, 3.11 mmol) and AIBN (0.073 g, 0,44 mmol) were added successively, under argon, to a solution of **10** (0.4 g, 0.88 mmol) in toluene (5 mL) at 20 °C. After stirring for 1 h at 70 °C, the mixture was cooled to 20 °C and concentrated under reduced pressure. The residue was dissolved in pyridine (2 mL) and acetic anhydride (1 mL) was added. After stirring for 19.5 h, the mixture was extracted with ethyl acetate (2 x10 mL). The combined

organic layers were washed successively with a saturated aqueous solution of $NaHCO_3$ and with water. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Chromatography on silica gel (hexane/ethyl acetate 2:1, then 1:1) gave **13** and **14** as a syrup.

Compound **13** (108 mg, 30%): R_f 0.49 (system F); mp 152 °C; $[\alpha]_D^{20}$ -230° (*c* 0.6, chloroform); IR ($CDCl_3$) 1782 (NHCO), 1703 (C=O) cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 7.43-7.27 (m, 5H, H_{Ar}), 5.50 (s, 1H, H-Ph), 5.18 (s, 1H, H-1), 4.75 (dd, 1H, H-3), 4.44 (dd, 1H, H-4), 4.34-4.26 (m, 2H, H-2, H-6), 4.15 (d, 1H, H-6'), 3.73 (m, 1H, H-5), 3.43 (s, 3H, CH_3-O), 2.47 (s, 3H, CH_3CO); LRMS (CI, NH_3) : *m/z* 367 $[M + NH_4]^+$, 350 $[M + H]^+$.

Compound **14** (98 mg, 30%): R_f 0.66 (system F); mp 164 °C; $[\alpha]_D^{20}$ -140° (*c* 0.9, chloroform); IR ($CDCl_3$) 1709 (C=O) cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 7.46-7.28 (m, 5H, H_{Ar}), 5.50 (s, 1H, H-Ph), 5.21 (s, 1H, H-1), 5.01 (dd, 1H, H-3), 4.45-4.37 (m, 4H, H-2, H-4, H-6, H-6'), 3.70 (dd, 1H, H-5), 3.44 (s, 3H, CH_3-O), 2.77 (s, 3H, CH_3CO); LRMS (CI, NH_3): *m/z* 383 $[M + NH_4]^+$, 366 $[M + H]^+$.

Methyl 3-Amino-4,6-*O*-benzylidene-3-deoxy-α-L-talopyranoside (15). The azido-sugar **9** (0.72 g, 2.33 mmol) in solution in anhydrous ethanol containing triethylamine (0.1 mL) and 10% Pd/C (0.012 g) was stirred under hydrogen atmosphere (1 atm.) for 4 h at 20 °C. After filtration and concentration under reduced pressure, the amino-sugar **15** was obtained (0.62 g, 95%) and recrystallized from dichloromethane/pentane; R_f 0.32 (CH_2Cl_2/MeOH/Et_3N : 95/5/1); mp 135 °C; $[\alpha]_D^{20}$ -71° (*c* 1.1, chloroform); IR ($CDCl_3$) 3690 (NH_2, OH), 1703 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.50-7.35 (m, 5H, H_{Ar}), 5.50 (s, 1H, H-Ph), 4.75 (d, 1H, $J_{1,2}$ = 1.5 Hz, H-1), 4.40-3.90 (m, 3H, H-4, H-6, H-6'), 3.60 (s, 1H, H-5), 3.50 (m, 1H, H-2), 3.40 (s, 3H, CH_3-O), 3.10 (m, 1H, H-3).

Anal. Calcd for $C_{14}H_{19}NO_5$: C, 59.78; H, 5.81; N, 14.98. Found: C, 60.01; H, 45.95; N, 4.87.

Methyl 3-Trifluoroacetamido-4,6-*O*-benzylidene-3-deoxy-α-L-talopyranoside (16). To the amino-sugar **15** (0.608 g, 2.16 mmol) in solution in dichloromethane, Et_3N (0.75 mL) and trifluoroacetic anhydride (0.67 mL) were successively added under argon at 0 °C. After reacting for 0.5 h at 0 °C, the mixture was concentrated under reduced pressure (T < 30 °C), treated with anhydrous methanol (10 mL), stirred for 0.5 h, concentrated again under reduced pressure and poured into CH_2Cl_2 (10 mL). The organic layer was washed with water (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give **16** (0.821 g, quantitative yield) which was recrystallised from dichloromethane/pentane; R_f 0.64 (system C); mp 77 °C; $[\alpha]_D^{20}$ -144 (*c* 1.1, chloroform); IR ($CDCl_3$) 3517, 3422 (NH, OH), 1724 (C=O) (cm^{-1}); ^1H

NMR (300 MHz, $CDCl_3$) δ 7.46-7.30 (m, 5H, H_{Ar}), 7.09 (d, 1H, NH), 5.50 (s, 1H, H-Ph), 4.90 (d, 1H, $J_{1,2}$ = 1.5 Hz, H-1), 4,45 (m, 1H, H-3), 4.38-4.33 (m, 2H, H-4, H-6), 4.09 (dd, 1H, $J_{6',5}$ = 1.5 Hz, $J_{6',6}$ = 12.5 Hz, H-6'), 3.78 (d, 1H, $J_{5,6'}$ = 1.5 Hz, H-5), 3.64 (t, 1H, $J_{2,1}$ = 1.5 Hz, H-2), 3.46 (s, 3H, CH_3-O).

Anal. Calcd for $C_{16}H_{18}F_3NO_6$: C, 50.93; H, 4.81; N, 3.71. Found: C, 50.87; H, 4.98; N, 3.65.

Methyl 3-Trifluoroacetamido-4,6-*O*-benzylidene-3-deoxy-2-*O*-phenoxythiocarbonyl-α-L-talopyranoside (17). Compound **16** (0.20g, 0.53 mmol) was dissolved in anhydrous pyridine (2 mL) and cooled to 0 °C under argon atmosphere. Phenoxythiocarbonyl chloride (0.15 mL, 1.06 mmol) was added and the mixture was stirred for 20 min at 0 °C, for 19 h at 20 °C and then poured into ethyl acetate (15 mL). The organic layer was washed with water (2 x 15 mL) and dried over Na_2SO_4, concentrated under reduced pressure and chromatographed on silica gel (cyclohexane/CH_2Cl_2 1:3, 1:5 then CH_2Cl_2) to give **17** (0.23 g, 85%); R_f 0.67 (system E); mp 122 °C; $[\alpha]_D^{20}$ -18° (*c* 1.29, chloroform); IR ($CDCl_3$) 1731 (C=O) (cm^{-1}); ^1H NMR (300 MHz, $CDCl_3$) δ 7.66-6.81 (m, 10H, H_{Ar}), 5.57 (s, 1H, H-Ph), 5.50 (d, 1H, J = 3.5 Hz, H-2), 5.25 (s, 1H, H-1), 4.85 (m, 1H, H-3), 4.37 (d, 1H, J = 12.5 Hz, H-6), 4.18-4.14 (m, 2H, H-4, H-6'), 3.50 (s, 3H, CH_3-O); LRMS (CI, NH_3): *m/z* 514 $[M + H]^+$.

Methyl 3-Trifluoroacetamido-4,6-*O*-benzylidene-2,3-dideoxy-α-L-*lyxo*-hexopyranoside (18). Tributyltin hydride (0.134 mL, 0.49 mmol) and AIBN (0.027 g, 0.16 mmol) were successively added under argon to a solution of compound **17** (0.17 g, 0.33 mmol) in toluene (5 mL) at 20 °C. After reacting for 1.5 h at 60 °C, the mixture was cooled to 20 °C and concentrated under reduced pressure. After chromatography on silica gel (hexane/EtOAc 3:1 then 2:1), **18** was obtained as crystals (0.095 g, 80%) and recrystallized in Et_2O/pentane; R_f 0.40 (system E); mp 252 °C; $[\alpha]_D^{20}$ -137° (*c* 1.05, chloroform); IR ($CDCl_3$) 3428 (NH), 1726 (C=O) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.46 (m, 1H), 7.33 (m, 1H), 7.21 (s, 1H, H_{Ar}), 6.61 (m, 1H, NH), 5.57 (s, 1H, H-Ph), 4.95 (br s, 1H, H-1), 4.64 (m, 1H, H-3), 4.30 (dd, 1H, $J_{6,6'}$ = 13 Hz, $J_{6,5}$ = 1 Hz, H-6), 4.10 (dd, 1H, $J_{6',6}$ = 13 Hz, $J_{6',5}$ = 1 Hz, H-6'), 4.07 (br d, 1H, H-4), 3.73 (d, 1H, H-5), 3.37 (s, 3H, CH_3-O), 2.02 (m, 1H, $J_{2a,2e}$ = 13 Hz, $J_{2a,3}$ = 12 Hz, $J_{2a,1}$ = 3 Hz, H-2a), 2.02 (m, 1H, $J_{2e,2a}$ = 13 Hz, $J_{2e,3}$ = 4 Hz, $J_{2e,1}$ < 1 Hz, H-2e); LRMS (CI, NH_3): *m/z* 379 $[M + NH_4]^+$.

Anal. Calcd for $C_{16}H_{17}F_3NO_5$: C, 53.17; H, 5.02; N, 3.87. Found: C, 53.25; H, 5.00; N, 3.95.

Methyl 3-Trifluoroacetamido-2,3-dideoxy-α-L-*lyxo*-hexopyranoside (19). *From* **18:** To a solution of the acetal **18** (34 mg, 0.09 mmol) in anhydrous methanol (15 mL) was added acetyl chloride (18 μL). After reacting for 19 h, the reaction mixture was neutralized by addition of sodium hydrogencarbonate, filtered and concentrated under reduced pressure. Chromatography on silica gel (system G) gave **19** (25 mg, 98%); R_f 0.32 (system G); mp 187 °C; $[\alpha]_D^{20}$ -187° (*c* 1, methanol) [Lit.[5a] mp 190 °C, $[\alpha]_D^{20}$ -186° (*c* 1; methanol)]; LRMS (CI, NH_3): *m/z* 293 $[M + NH_4]^+$, 274 $[M + H]^+$.

From **38:** A solution of **38** (55 mg, 0.27 mmol) in ethanol (10 mL) was stirred for 2 h at room temperature in the presence of Pd/C 10% (10 mg) under hydrogen atmosphere. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was dissolved in dichloromethane (10 mL) before Et_3N (0.16 mL, 1.2 mmol) and trifluoroacetic anhydride (0.15 mL, 1.1 mmol) were added. After additional stirring for 1.5 h at 0 °C, the solvents were removed under reduced pressure and the residue was co-evaporated twice with methanol (2 x 15 mL), affording pure **19** (52 mg, 70%) after flash chromatography (system G).

Methyl 6-Bromo-4-*O*-benzoyl-3-trifluoroacetamido-2,3,6-trideoxy-α-L-*lyxo*-hexopyranoside (20). To a solution of the acetal **18** (0.13 g, 0.36 mmol) in carbon tetrachloride (5 mL), *N*-bromosuccinimide (77 mg), barium carbonate (106 mg) and AIBN (29 mg) were added successively at 20 °C under argon. After refluxing for 1.5 h (80 °C), the crude mixture was poured into CH_2Cl_2 (10 mL) filtered and washed with water (10 mL). The organic layer was dried over Na_2SO_4, concentrated under reduced pressure and chromatographed on silica gel (cyclohexane/EtOAc 4:1), thus giving **20** (0.12 g, 72%); R_f 0.41 (system E); mp 141 °C; $[\alpha]_D^{20}$ -135° (*c* 0.8, chloroform); ^1H NMR (270 MHz, DMSO-d_6) δ 9.48 (d, 1H, NH), 8.02-7.98, 7.73-7.64, 7.59-7.51 (m, 5H, H_{Ar}), 5.50 (s, 1H, H-4), 5.01 (d, 1H, H-1), 4.36 (m, 1H, H-3), 4.14 (m 1H, H-5), 3.53 (dd, 1H, H-6), 3.39-3.35 (m, 4H, H-6', CH_3-O), 2.24 (m, 1H, H-2a), 1.70 (m, 1H, H-2e); LRMS (CI, NH_3): *m/z* 458 $[M + NH_4]^+$.

Anal. Calcd for $C_{16}H_{17}BrF_3NO_5$: C, 43.63; H, 3.86; N, 3.18. Found: C, 44.08; H, 3.91; N, 3.16.

Methyl 4-*O*-Benzoyl-3-trifluoroacetamido-2,3,6-trideoxy-α-L-*lyxo*-hexopyranoside (21). The bromosugar **20** (50 mg, 0.11 mmol) in solution in anhydrous ethanol (5 mL) containing Et_3N (100 μL) was hydrogenated in the presence of Pd/C 10% (26 mg) for 24 h at 20 °C. After filtration, concentration under reduced pressure and chromatography on silica gel, **21** was obtained (39 mg, 95%); R_f 0.48 (system B); IR ($CDCl_3$) 3439 (NH), 1730 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.21-8.10, 7.66-

7.61, 7.52-7.47 (m, 10H, H_{Ar}), 6.45 (bd, 1H, NH), 5.33 (s, 1H, H-4), 4.93 (d, 1H, H-1 J < 1 Hz), 4.70 (m, 1H, H-3), 4.19 (m, 1H, H-5), 3.40 (s, 3H, CH_3-O), 2.01 (m, 2H, H-2a, H-2e), 1.21 (d, 3H, CH_3); LRMS (CI, NH_3): *m/z* 379 $[M + NH_4]^+$, 362 $[M + H]^+$

Methyl 3-Trifluoroacetamido-2,3,6-trideoxy-α-L-*lyxo*-hexopyranoside (22). To a solution of the benzoate **21** (49 mg, 0.13 mmol) in anhydrous methanol (5 mL), a 1M solution of sodium methanolate (3 mL) was added. After stirring for 2 h at 0 °C, the mixture was neutralized by addition of Amberlite IRC 50H$^+$, filtered and concentrated under reduced pressure to give the trifluoroacetamido-sugar **22** (22 mg, 63%); R_f 0.83 (system E); mp 110 °C; $[\alpha]_D^{20}$ -142° (*c* 0.5, chloroform) [Lit.[23] mp 108-109 °C; $[\alpha]_D^{20}$ -148° (*c* 0.5, chloroform)]; LRMS (CI, NH_3): *m/z* 275 $[M + NH_4]^+$, 258 $[M + H]^+$.

Preparation of the 1,4,6-tri-*O*-acetyl-3-azido-2,3-dideoxy-D-hexopyranoses (26). Tri-*O*-acetyl-D-glucal **23** (10 g, 36 mmol) was suspended in water (50 mL) and the mixture was heated at 95-100 °C for 4 h. After cooling the resulting solution to room temperature, acetic acid (10 mL) and sodium azide (10 g, 153 mmol) were added and stirring was maintained for 18 h. Extraction with ethyl acetate (400 mL) and washings with water and with brine afforded **25** (9.4 g, 90%) after drying over $MgSO_4$ and concentration under reduced pressure. This compound was dissolved in dichloromethane (100 mL) and stirred for 24 h at room temperature in the presence of pyridine (10 mL) and acetic anhydride (25 mL). After dilution with dichloromethane (200 mL), the organic solution was washed with a cold 1N aqueous H_2SO_4 solution, with water, with brine and dried over $MgSO_4$. Concentration under reduced pressure led to 11 g of crude compounds. Flash chromatography (cyclohexane-EtOAc : 5:1) provided the azido-sugars **26** (7.9 g, 61%) as a mixture.

Glycoside formation of 26 with MeOH in the presence of K10 Montmorillonite. The mixture of the azido-sugars **26** (7 g) in a benzene solution (200 mL) was refluxed for 18 h in the presence of MeOH (6 mL) and K10 montmorillonite (8 g). After cooling and filtration, the filtrate was concentrated under reduced pressure and the residue (5.65 g) was chromatographed. Elution with cyclohexane-EtOAc (5:1) as eluent afforded two fractions, homogenous on TLC (Fraction A = 1.68 g and fraction B = 0.75 g). Fraction A (1.6 g) was dissolved in methanol (50 mL) and stirred for 18 h at room temperature in the presence of 1M sodium methoxide in methanol (5 mL) to give, after neutralization with Amberlite IRC 50H$^+$, filtration and concentration, 0.9 g of crude residue. Chromatography (system B) gave **27b** (338 mg) and **28b** (112 mg). Similar treatment of fraction B led to **29b** (60 mg) and **30b** (140 mg).

Methyl 3-Azido-2,3-dideoxy-α-D-*arabino*-hexopyranoside (27b): mp 120-121 °C; $[\alpha]_D^{20}$ +160° (*c* 1, methanol) [Lit.[7a] mp 120-122 °C, $[\alpha]_D^{20}$ +162.5° (*c* 1, methanol)].

Methyl 3-Azido-2,3-dideoxy-β-D-*ribo*-hexopyranoside (28b): syrup; R_f 0.28 (system C); $[\alpha]_D^{20}$ +10° (*c* 0.7, chloroform); ^1H NMR (300 MHz, $CDCl_3$) δ 4.67 (dd, 1H, $J_{1,2e}$ = 2 Hz, $J_{1,2a}$ = 9 Hz, H-1), 4.13 (q, 1H, $J_{3,2e}$ = 3.5 Hz, $J_{3,2a}$ = 3.5 Hz, $J_{3,4}$ = 3.5 Hz, H-3), 3.90-3.79 (m, 3H, H-4, H-6, H-6'), 3.68 (m, 1H, H-5), 3.49 (s, 3H, CH_3-O), 2.12 (ddd, 1H, $J_{2e,2a}$ = 14 Hz, $J_{2e,1}$ = 2 Hz, $J_{2e,3}$ = 3.5 Hz, H-2e), 1.77 (ddd, 1H, $J_{2a,2e}$ = 14 Hz, $J_{2a,1}$ = 9 Hz, $J_{2a,3}$ = 3.5 Hz, H-2a); LRMS (CI, NH_3): *m/z* 221 $[M + NH_4]^+$, 204 $[M + H]^+$.

Anal. Calcd for $C_7H_{13}N_3O_4$: C, 41.38; H, 6.45; N, 20.67. Found: 41.70; H, 6.42; N, 20.34.

Methyl 3-Azido-2,3-dideoxy-α-D-*ribo*-hexopyranoside (29b): R_f 0.32 (system C); mp 100-102 °C (hexane-acetone); $[\alpha]_D^{20}$ +252° (*c* 1, chloroform); IR 3629 (OH), 3564 (OH), 2127 (N_3) (cm^{-1}); ^1H NMR (300 MHz, $CDCl_3$) δ 4.73 (d, 1H, $J_{1,2a}$ = 4 Hz, H-1), 4.10 (q, 1H, $J_{3,2e}$= 4 Hz, $J_{3,2a}$ = 4 Hz, $J_{3,4}$ = 4 Hz, H-3), 3.85-3.72 (m, 4H, H-4, H-5, H-6, H-6'), 3.37 (s, 3H, CH_3-O), 2.22 (m, 1H, $J_{2e,2a}$ = 15 Hz, $J_{2e,3}$ = 4 Hz, H-2e), 2.01 (m, 1H, $J_{2a,2e}$ = 15 Hz, $J_{2a,1}$ = 4 Hz, $J_{2a,3}$ = 4 Hz, H-2a).

Methyl 3-Azido-2,3-dideoxy-β-D-*arabino*-hexopyranoside (30b): mp 92-93 °C (hexane-acetone); $[\alpha]_D^{20}$ - 40° (*c* 1, chloroform); ^1H NMR (300 MHz, $CDCl_3$) δ 4.43 (dd, 1H, $J_{1,2a}$ = 9.5 Hz, $J_{1,2e}$ = 2 Hz, H-1), 3.95 (m, 2H, H-6, H-6'), 3.44 (s, 3H, CH_3-O), 3.52-3.32 (m, 2H, H-3, H-4), 3.28 (m, 1H, H-5), 2.30 (m, 1H, H-2e), 1.70 (m, 1H, H-2a); LRMS (CI, NH_3): *m/z* 221 $[M + NH_4]^+$, 204 $[M + H]^+$.

Anal. Calcd for $C_7H_{13}N_3O_4$: C, 41.38; H, 6.45; N, 20.67. Found: 41.75; H, 6.35; N, 20.20.

Trimethylsilyl 4,6-Di-*O*-acetyl-3-azido-2,3-dideoxy-α-D-*arabino*-(31) and α-D-*ribo*-hexopyranoside (32). To a cooled solution (-15 °C) of **25** (1.7 g, 6.22 mmol) in anhydrous dichloromethane (40 mL) were added imidazole (634 mg, 9.2 mmol) and trimethylsilyl chloride (1.2 mL, 9.2 mmol). After stirring for 1 h at -15 °C and then for 2 h at room temperature, the mixture was diluted with dichloromethane (≈ 200 mL) and then washed twice with water (2 x 25 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Subsequent flash chromatography (cyclohexane-EtOAc 12:1) successively afforded **31** (1 g, 50%) and **32** (0.5 g, 25%).

Compound **31**: syrup; ^1H NMR (300 MHz, $CDCl_3$) δ 5.24 (dd, 1H, $J_{1,2a}$ = 3 Hz, $J_{1,2e}$ = 1.5 Hz, H-1), 4.78 (dd, 1H, $J_{3,4}$ = $J_{4,5}$ = 10 Hz, H-4), 4.14 (dd, 1H,

$J_{6,5}$ = 5 Hz, $J_{6,6'}$ = 12 Hz, H-6), 3.95-3.85 (m, 3H, H-3, H-5, H-6'), 2.02 (s, 3H, CH_3CO), 2.01-1.95 (m, 1H, H-2e), 1.95 (s, 3H, CH_3CO), 1.65 (m, 1H, $J_{2a,2e}$= $J_{2a,3a}$ = 12 Hz, $J_{2a,1e}$ = 3 Hz, H-2a); LRMS (CI, NH_3): *m/z* 363 $[M + NH_4]^+$.

Compound **32**: syrup; ^1H NMR (300 MHz, $CDCl_3$) δ 5.24 (dd, 1H, $J_{1,2a}$ = 3 Hz, $J_{1,2e}$ = 2 Hz, H-1), 4.82 (dd, 1H, $J_{4,5}$ = 9.5 Hz, $J_{4,3}$ = 3.5 Hz, H-4), 4.41-4.29 (m, 2H, H-5, H-6), 4.19 (ddd, 1H, $J_{3,2a}$ = $J_{3,2e}$ = $J_{3,4}$ = 3.5 Hz, H-3), 4.01 (dd, 1H, $J_{6',6}$ = 12 Hz, $J_{6',5}$ = 2 Hz, H-6'), 2.07 (s, 3H, CH_3CO), 2.03 (s, 3H, CH_3CO), 2.07-2.03 (m, 2H, H-2a, H-2e); LRMS (CI, NH_3: *m/z* 363 $[M + NH_4]^+$.

Pivaloyl 4,6-Di-*O*-acetyl-3-azido-2,3-dideoxy-β-D-*arabino*-hexopyranoside (33) and its β-D-*ribo*-isomer (34). Triethylamine (11.7 mL, 83.7 mmol) and pivaloyl chloride (10.3 mL, 83.7 mmol) were added to a solution of **25** (15.2 g, 55.8 mmol) in anhydrous dichloromethane (150 mL) cooled to 0 °C. After stirring for 15 min at 0 °C, then overnight at room temperature, the crude mixture was poured into water (200 mL). The organic layer was separated and the aqueous layer was extracted twice with dichloromethane (2 x 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure, giving a residue (19.3 g) which was chromatographed (cyclohexane/ethyl acetate 6:1) to give successively the *ribo* isomer **34** (3 g, 20%) and the *arabino* isomer **33** (10.6 g, 53%).

Compound **33**: syrup; R_f 0.43 (system B); IR ($CDCl_3$) 2105 (N_3), 1746 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.71 (dd, 1H, $J_{1,2a}$ = 9.5 Hz, $J_{1,2e}$ = 2 Hz, H-1), 4.92 (t, 1H, $J_{4,3}$ = 9.5 Hz, $J_{4,5}$ = 9.5 Hz, H-4), 4.26 (dd, 1H, $J_{6,5}$ = 5 Hz, $J_{6,6'}$ =12 Hz, H-6), 4.05 (dd, 1H, $J_{6',5}$ = 2.5 Hz, $J_{6',6}$ = 12 Hz, H-6'), 3.69-3.62 (m, 2H, H-3, H-5), 2.25 (ddd, 1H, $J_{2e,1}$ = 2 Hz, $J_{2e,2a}$ = 12.5 Hz, $J_{2e,3}$ = 5 Hz, H-2e), 2.09 and 2.05 (2 s, 6H, CH_3CO), 1.79 (m, 1H, $J_{2a,1}$ = 9.5 Hz, $J_{2a,2e}$ = 12.5 Hz, $J_{2a,3}$ = 12.5 Hz, H-2a), 1.19 (s, 9H, *t*-Bu); LRMS (CI, NH_3): *m/z* 375 $[M + NH_4]^+$.

Anal. Calcd for $C_{15}H_{23}N_3O_7$: C, 50.41; H, 6.20; N, 11.76. Found: C 50.21; H 6.50; N 11.73.

Compound **34**: syrup; R_f 0.52 (system B); IR ($CDCl_3$) 2105 (N_3), 1746 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.94 (dd, 1H, $J_{1,2a}$ = 8.5 Hz, $J_{1,2e}$ = 2.5 Hz, H-1), 4.97 (dd, 1H, $J_{4,3}$ = 3.5 Hz, $J_{4,5}$ = 8.5 Hz, H-4), 4.31-4.11 (m, 4H, H-3, H-5, H-6, H-6'), 2.13-2.05 (m, 7H, H-2e, 2 CH_3CO), 1.94 (ddd, 1H, $J_{2a,1}$ = 8.5 Hz, $J_{2a,2e}$ = 13.5 Hz , $J_{2a,3}$ = 3.5 Hz, H-2a), 1.19 (s, 9H, *t*-Bu).

Anal. Calcd for $C_{15}H_{23}N_3O_7$: C, 50.41; H, 6.20; N, 11.76. Found: C 50.64; H, 6.45; N, 11.55.

Methyl 4,6-Di-*O*-acetyl-2,3-dideoxy-β-D-*ribo* and α-D-*ribo*-hexopyranoside (28a) and (29a). Compound **34** (2.1g, 5.88 mmol) in a benzene

solution (120 mL) was heated under reflux for 60 h in the presence of K10 Montmorillonite and MeOH (7.4 mL). After cooling to rt, filtration, followed by concentration under reduced pressure of the filtrate and flash chromatography (system A), afforded **28a** (0.72g, 42%) and **29a** (0.4 g, 22%).

Compound **28a**: syrup; R_f 0.47 (system B); $[\alpha]_D^{20}$ -11° (*c* 1.2, chloroform); IR ($CDCl_3$) 2114 (N_3), 1758 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.86 (dd, 1H, $J_{4,3}$ = 3.5 Hz, $J_{4,5}$ = 9.5 Hz, H-4), 4.58 (dd, 1H, $J_{1,2e}$ = 2 Hz, $J_{1,2a}$ = 9 Hz, H-1), 4.24 (dd, 1H, $J_{6,5}$ = 5 Hz, $J_{6,6'}$ = 12 Hz, H-6), 4.14 (q, 1H, $J_{3,2e}$ = 3.5 Hz, $J_{3,2a}$ = 3.5 Hz, $J_{3,4}$ = 3.5 Hz, H-3), 4.10 (dd, 1H, $J_{6',5}$ = 2.5 Hz, $J_{6',6}$ = 12 Hz, H-6'), 4.03-3.97 (m, 1H, H-5), 3.40 (s, 3H, CH_3-O), 2.04 (s, 3H, CH_3CO), 2.00 (s, 3H, CH_3CO), 2.00-1.95 (m, 1H, H-2e), 1.75 (ddd, 1H, $J_{2a,2e}$ = 12 Hz, $J_{2a,1}$ = 9 Hz, $J_{2a,3}$ = 3.5 Hz, H-2a); LRMS (CI, NH_3): *m/z* 305 $[M + NH_4]^+$, 288 $[M + H]^+$.

Compound **29a**: syrup; R_f 0.35 (system B); $[\alpha]_D^{20}$ +160° (*c* 1.2, chloroform); IR ($CDCl_3$) 2104 (N_3), 1752 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.90 (dd, 1H, $J_{4,3}$ = 3.5 Hz, $J_{4,5}$ = 9.5 Hz, H-4), 4.71 (d, 1H, $J_{1,2e}$ = 2 Hz, $J_{1,2a}$ = 9 Hz, H-1), 4.33 (dd, 1H, $J_{6,5}$ = 5 Hz, $J_{6,6'}$ = 12 Hz, H-6), 4.28-4.23 (m, 1H, H-5), 4.14 (q, 1H, $J_{3,4}$ = 3.5 Hz, $J_{3,2e}$ = 3.5 Hz, $J_{3,2a}$ = 3.5 Hz, H-3), 4.09 (dd, 1H, $J_{6',5}$ = 5 Hz, $J_{6',6}$ = 12 Hz, H-6'), 3.34 (s, 3H, CH_3-O), 2.11-2.03 (m, 2H, H-2e, H-2a), 2.07 (s, 3H, CH_3CO), 2.04 (s, 3H, CH_3CO); LRMS (CI, NH_3): *m/z* 305 $[M + NH_4]^+$, 288 $[M + H]^+$.

Methyl 3-Azido-4,6-*O*-benzylidene-2,3-dideoxy-β-D-*ribo*-hexo pyranoside (35). *Prepared from* **28b**: α,α-Dimethoxytoluene (0.18 mL, 1.21 mmol) and *p*-TsOH (33 mg, 0.17 mmol) were successively added to a solution of **28b** (0.17 g, 0.87 mmol) in DMF (5 mL) kept under argon. After stirring for 1.5 h at 60 °C under reduced pressure (20 mm Hg), water (20 mL) was added. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with water several times (4 x 10 mL), dried over $MgSO_4$, concentrated under reduced pressure and flash chromatographed (cyclohexane/ethyl acetate 9:1) to give **35** (142 mg, 57%).

Prepared from **42** : To a cooled solution of **42** (1.92 g, 7.2 mmol) in a mixture of CH_2Cl_2 (50 mL) and pyridine (1.17 mL, 14.5 mmol), trifluoromethanesulfonic anhydride (1.46 mL, 8.7 mmol) was added dropwise. After stirring for 0.5 h at -15 °C, water (50 mL) was added. The organic layer was extracted with CH_2Cl_2 (2 x 50 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give **43** as a crude product. This was dissolved in DMF (30 mL) and NaN_3 (0.94 g, 14.5 mmol) was added. After stirring for 5 h at 20 °C, water (80 mL) was added. The residue was extracted with ethyl acetate and washed several times with water (4 x 30 mL). This afforded, after drying over $MgSO_4$, concentration and flash chromatography (cyclohexane/EtOAc 9/1), a crystalline

residue of **35** (1.25 g, 60%, two steps); R_f 0.52 (system B); mp 101 °C (EtOAc); $[\alpha]_D^{20}$ -97° (*c* 1, chloroform); IR ($CDCl_3$) 2110 (N_3) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53-7.49, 7.42-7.37 (m, 5H, H_{Ar}), 5.58 (s, 1H, H-Ph), 4.71 (dd, 1H, $J_{1,2a}$ = 9.5 Hz , $J_{1,2e}$ = 2 Hz, H-1), 4.36 (dd, 1H, $J_{6,5}$ = 5 Hz, $J_{6,6'}$ = 10 Hz, H-6), 4.21 (q, 1H, $J_{3,4}$ = $J_{3,2a}$ = $J_{3,2e}$ = 3.5 Hz, H-3), 4.04-3.96 (m, 1H, H-5), 3.82-3.75 (m, 2H, H-4, H-6'), 3.51 (s, 3H, CH_3-O), 2.06 (m, 1H, H-2e), 1.80 (ddd, 1H, $J_{2a,1}$ = 9.5 Hz, $J_{2a,2e}$ = 13 Hz, $J_{2a,3}$ = 3.5 Hz, H-2a); LRMS (CI, NH_3): *m/z* 309 $[M + NH_4]^+$, 292 $[M + H]^+$.

Methyl 3-Azido-4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-β-D-*ribo*-hexopyranoside (36). To a solution of **35** (1.2 g, 4.1 mmol) in carbon tetrachloride (25 mL) under argon atmosphere, barium carbonate (1.2 g, 6.15 mmol) and *N*-bromosuccinimide (0.87 g, 4.92 mmol) were successively added. After stirring for 1h under reflux, the crude reaction was filtered and the filtrate was diluted with dichloromethane (50 mL). The organic solution was washed twice with water (2 x 15 mL) and dried over $MgSO_4$ before concentration under reduced pressure. Flash chromatography afforded **36** (1 g, 66%) as a syrup; R_f 0.52 (system A); $[\alpha]_D^{20}$ -102° (*c* 1.7, chloroform); IR ($CDCl_3$) 2104 (N_3), 1724 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.08-8.04, 7.63-7.58, 7.50-7.44 (m, 5H, H_{Ar}), 5,15 (dd, 1H, $J_{4,3}$ = 3.5 Hz, $J_{4,5}$ = 9 Hz, H-4), 4.75 (dd, 1H, $J_{1,2a}$ = 8.5 Hz, $J_{1,2e}$ = 2 Hz, H-1), 4.32 (q, 1H, $J_{3,2a}$ = 3.5 Hz, $J_{3,2e}$ = 3.5 Hz, $J_{3,4}$ = 3.5 Hz, H-3), 4.23 (m, 1H, $J_{5,6}$ = 3 Hz, $J_{5,6'}$ = 6 Hz, $J_{5,4}$ = 9 Hz, H-5), 3.60 (dd, 1H, $J_{6,5}$ = 3 Hz, $J_{6,6'}$ = 11 Hz, H-6), 3.53 (s, 3H, CH_3-O), 3.49 (dd, 1H, $J_{6',5}$ = 6 Hz, $J_{6',6}$ = 11 Hz, H-6'), 2.13 (m, 1H, $J_{2e,1}$ = 2 Hz, $J_{2e,2a}$ = 14 Hz, $J_{2e,3}$ = 3.5 Hz, H-2e), 1.92 (m, 1H, $J_{2a,1}$ = 8.5 Hz, $J_{2a,2e}$ = 14 Hz, $J_{2a,3}$ = 3.5 Hz, H-2a); LRMS (CI, NH_3): *m/z* 388 $[M + NH_4]^+$, 371 $[M + H]^+$.

Methyl 3-Azido-4-*O*-benzoyl-2,3,6-trideoxy-β-D-*erythro*-hex-5-eno pyranoside (37). A solution of **36** (1.08 g, 2.91 mmol) in pyridine (10 mL) was stirred in the dark and under argon atmosphere for 4 h at room temperature in the presence of silver fluoride (1.85 g, 14.6 mmol). After dilution of the reaction mixture with diethyl ether (50 mL) and subsequent filtration, the organic layer was concentrated under reduced pressure and the residue was chromatographed (cyclohexane/EtOAc 4:1) to afford **37** (0.65 g, 77%) as a syrup; R_f 0.52 (system A); $[\alpha]_D^{20}$ -133° (*c* 1, chloroform); IR 2105 (N_3), 1723 (C=O), 1669 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.08-8.05, 7.60-7.55, 7.48-7.43 (m, 5H, H_{Ar}), 5.78 (d, 1H, $J_{4,3}$ = 3.5 Hz, H-4), 5.04 (d, 1H, $J_{1,2}$ = 2 Hz, H-1), 4.83 (d, 2H, H-6, H-6', $J_{6,6'}$ = 8 Hz), 4.05 (m, 1H, $J_{3,2a}$ = 3.5 Hz, $J_{3,2e}$ = 3.5 Hz, $J_{3,4}$ = 3.5 Hz, H-3), 3.44 (s, 3H, CH_3-O), 2.42 (m, 1H, $J_{2,1}$ = 3 Hz, $J_{2,2}$ = 12 Hz, $J_{2,3}$ = 12 Hz, H-2), 2.14 (m, 1H, $J_{2,2}$ = 12 Hz, $J_{2,3}$ = 3 Hz, H-2); LRMS (CI, NH_3): *m/z* 307 $[M + NH_4]^+$, 290 $[M + H]^+$.

Methyl 3-Azido-2,3-dideoxy-α-L-*lyxo*-hexopyranoside (38). A solution of azido-sugar **37** (0.29 g, 1 mmol in 10 mL THF) was added to a cooled solution (0 °C) of 9-BBN (0.5 M solution in THF, 11.2 mL, 5 mmol). After stirring at 0 °C for 0.5 h and 1 h at room temperature, the mixture was cooled to 0 °C before successive additions of NaOH (3 M solution, 11.2 mL) and hydrogen peroxide (30% solution in water, 11.2 mL). After additional stirring for 0.5 h at 0 °C and 18 h at 20 °C, the resulting mixture was poured into a 10% solution of sodium bisulfite (30 mL) and subsequently diluted with diethyl ether (100 mL). The L-*lyxo*-derivative **38** was finally obtained (62 mg, 30%) after concentration under reduced pressure and chromatography of the residue; R_f 0.22 (system D); ^1H NMR (90 MHz, $CDCl_3$) δ 4.70 (d, 1H, H-1), 3.70-3.40 (m, 5H, H-3, H-4, H-5, H-6, H-6'), 3.05 (s, 3H, CH_3-O), 1.90 (dd, 1H, H-2), 1.70 (m, 1H, H-2).

Methyl 3,4,6-Tri-*O*-acetyl-2-bromo-2-deoxy-β-D-*arabino*-hexopyranoside (40). Tri-*O*-acetyl-D-glucal **23** (50 g, 183 mmol) in methanolic solution (500 mL) was stirred at 0 °C for 3 h in the presence of *N*-bromosuccinimide (44 g, 240 mmol). The solution was concentrated under reduced pressure (T < 30 °C) to *ca.* 50 mL, diluted with water (≈ 100 mL) and extracted with diethyl ether (≈ 500 mL). The organic layer was washed with a 10% aqueous solution of sodium thiosulfate, with water and dried over $MgSO_4$. This afforded a residue which crystallized from methanol, yielding compound **40** (20 g, 28%); mp 136-137 °C; $[\alpha]_D^{20}$ +54° (*c* 1.85, chloroform) [Lit.[34] mp 135-136 °C, $[\alpha]_D^{20}$ +46° (*c* 2, chloroform)].

Methyl 2-Deoxy-β-D-*arabino*-hexopyranoside (41). To a solution of **40** (10 g) in methanol (120 mL), a 1 M solution of sodium methoxide was added (35 mL). After stirring for 3 h at room temperature, Raney nickel (4.6 g) was added and the suspension was stirred under H_2 atmosphere for 24 h. The catalyst was removed by filtration and the filtrate was neutralized by filtration over Amberlite IRC 50H$^+$ ion-exchange resin. After concentration under reduced pressure, the residue was dissolved in dichloromethane/ethanol (9:1) (≈ 150 mL) and the suspension was filtered. Concentration of the filtrate led to **41** (4.5 g, 96%); mp 120 °C; $[\alpha]_D^{20}$ -54° (*c* 1, methanol) [Lit.[35] mp 122 °C, $[\alpha]_D^{20}$ -48° (H_2O)].

Methyl 4,6-*O*-Benzylidene-2-deoxy-β-D-*arabino*-hexopyranoside (42). To a solution of **41** (4.46 g, 25 mmol) in *N*,*N*-dimethylformamide (60 mL), α,α-dimethoxytoluene (5.8 mL) and *p*-toluenesulfonic acid (0.64 g, 3.37 mmol) were added. The mixture was heated at 60 °C for 3 h under reduced pressure (20 mm Hg). After cooling and addition of saturated aqueous solution of $NaHCO_3$ (20 mL), the resulting mixture was concentrated under reduced pressure. The residue was extracted with ethyl

acetate and washed several times with water. This afforded, after drying and concentration, a crystalline residue (4.33 g, 65%) which was recrystallized from methanol; R_f 0.22 (system B); mp 154 °C; $[\alpha]_D^{20}$ -65° (*c* 1, chloroform) [Lit.[36] mp 155-156 °C; $[\alpha]_D^{20}$ -67° (*c* 1, chloroform)].

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