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SYNTHESIS OF NEW BRANCHED-CHAIN AMINODEOXYHEXOSES RELATED TO DAUNOSAMINE (3-AMINO-2,3,6-TRIDEOXY-L-*lyxo*-HEXOSE)

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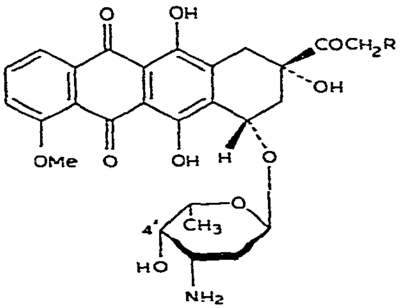
ABSTRACT

Addition of methylmagnesium iodide to methyl 2,3,6-trideoxy-3-trifluoroacetamido-α-L-*threo*-hexopyranosid-4-ulose (**3**) gave methyl 2,3,6-trideoxy-4-*C*-methyl-3-trifluoroacetamido-α-L-*lyxo*-hexopyranoside (**4**) and its L-*arabino* analogue, depending upon the reaction temperature and the solvent. The corresponding 4-*O*-methyl derivatives were obtained by treatment of **4** and **5** with diazomethane in the presence of boron trifluoride etherate. Treatment of **4** with thionyl chloride, followed by an alkaline work-up, gave methyl 2,3,4,6-tetradeoxy-4-*C*-methylene-3-trifluoroacetamido-α-L-*threo*-hexopyranoside (**8**), which was stereoselectively reduced to methyl 2,3,4,6-tetradeoxy-4-*C*-methyl-3-trifluoroacetamido-α-L-*arabino*-hexopyranoside. Epoxidation of **8** with 3-chloroperoxybenzoic acid gave the corresponding $4,4^1$-anhydro-4-*C*-hydroxymethyl-L-*lyxo* derivative (**10**), which was also prepared by treatment of **3** with diazomethane. Azidolysis of **10**, followed by catalytic hydrogenation and *N*-trifluoroacetylation, gave methyl 2,3,6-trideoxy-3-trifluoroacetamido-4-*C*-trifluoroacetamidomethyl-α-L-*lyxo*-hexopyranoside.

INTRODUCTION

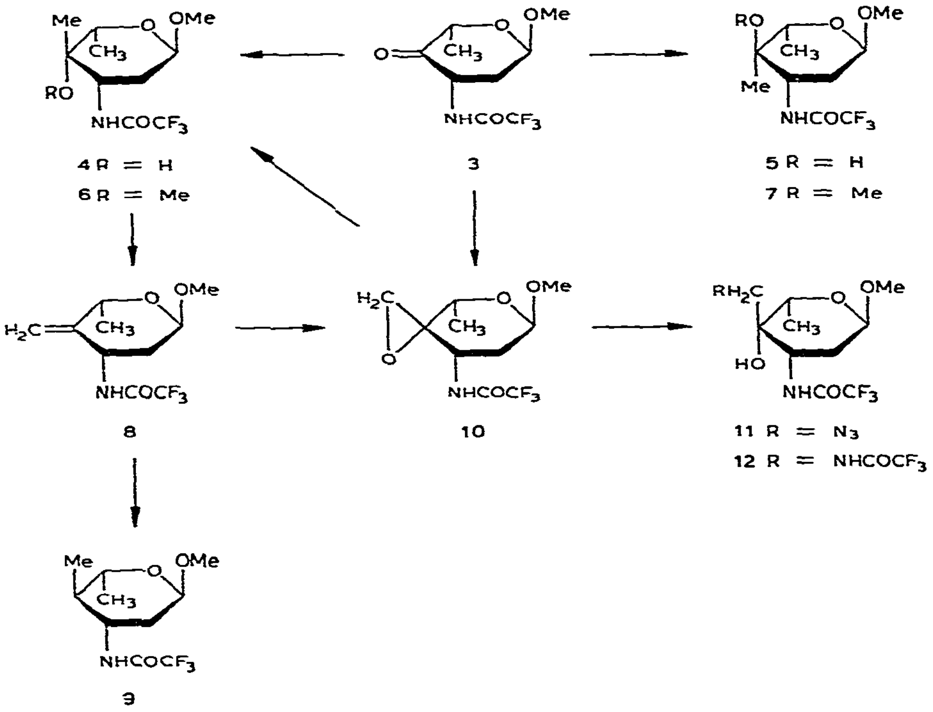
Daunosamine (3-amino-2,3,6-trideoxy-L-*lyxo*-hexose)[1] is the amino sugar constituent of the anthracycline antibiotics daunorubicin (**1**) and doxorubicin (Adriamycin, **2**), which are clinically useful as cancer chemotherapeutic agents. Many analogues of **1** and **2** has been synthesised and some promising congeners have modifications of the sugar moiety[2]. The remarkable anti-tumour activity and pharmacological potential of semi-synthetic anthracyclines modified at position 4 of the amino sugar, such as 4′-epi-, 4′-deoxy-, 4′-*O*-methyl-, and 4′-*O*-tetrahydropyranyl-doxorubicin[3–6], prompted the synthesis of new analogues of daunosamine with other functional modifications at position 4. To our knowledge, none of the natural and semi-synthetic anthracyclines contains branched-chain amino sugars, although garosamine (3-deoxy-4-*C*-methyl-3-methylamino-L-*arabinose*)[7], L-vancosamine (3-amino-2,3,6-trideoxy-3-*C*-methyl-L-*lyxo*-hexose)[8,9], 3-amino-2,3,6-trideoxy-3-*C*-methyl-L-*xylo*-hexose[10], and sibirosamine (4,6-dideoxy-3-*C*-methyl-4-methyl-



1 R = H (daunorubicin)
2 R = OH (doxorubicin)

amino-D-altrose)[11] occur in Nature as components of some antibacterial and cytotoxic antibiotics.

We now report on the synthesis of derivatives of new 4-*C*-branched-chain 3-amino-2,3,6-trideoxy-L-hexoses related to L-daunosamine, namely methyl 2,3,6-trideoxy-4-*C*-methyl-3-trifluoroacetamido-α-L-*lyxo*-hexopyranoside (**4**), the L-*arabino* isomer (**5**), their 4-methyl ethers (**6**, **7**), methyl 2,3,4,6-tetradeoxy-4-*C*-methylene-3-trifluoroacetamido-α-L-*threo*-hexopyranoside (**8**), methyl 2,3,4,6-tetradeoxy-4-*C*-methyl-3-trifluoroacetamido-α-L-*arabino*-hexopyranoside (**9**), methyl $4,4^1$-anhydro-2,3,6-



trideoxy-4-*C*-hydroxymethyl-3-trifluoroacetamido-α-L-*lyxo*-hexopyranoside (**10**), and methyl 2,3,6-trideoxy-3-trifluoroacetamido-4-*C*-trifluoroacetamidomethyl-α-L-*lyxo*-hexopyranoside (**12**). These new compounds are useful intermediates for the synthesis of new anthracycline glycosides displaying activity against experimental tumours in mice[12–14].

DISCUSSION

The starting compound for the synthesis of the above-mentioned derivatives was methyl 2,3,6-trideoxy-3-trifluoroacetamido-α-L-*threo*-hexopyranosid-4-ulose (**3**), obtained in 60% yield and in three steps from L-daunosamine[3]. Since the steric course of the addition of Grignard reagents and/or alkyl-lithiums to oxo sugars

TABLE I

PRODUCTS RESULTING FROM THE REACTION OF METHYL-LITHIUM AND METHYLMAGNESIUM IODIDE WITH 3

Reagent	*Solvent*	*Temperature (degrees)*	*Time (h)*	*Yields (%)*		
				Total	*Isolated products*	
					L-lyxo (**4**)	L-arabino (**5**)
MeLi[a]	THF[b,c]	−78	2	55	55	—
MeMgI	THF	reflux	3	90	15	75
MeMgI	THF	−20	3	95	38	57
MeMgI	Et_2O	−20	3	92	74	18
MeMgI	Et_2O	−78	3	98	95	traces

[a]6 Equiv. in Et_2O. [b]THF, tetrahydrofuran. [c]60 ml/mmol of **3**.

TABLE II

^{13}C-N.M.R. CHEMICAL SHIFTS (δ)[a]

Carbon atom	*Compounds*		
	4[b]	**5**[b]	**11**[c]
C-1	96.8	96.5	97.2
C-2	30.8	33.7	32.2
C-3	49.7	51.8	46.3
C-4	69.8	71.4	71.9
C-5	69.5	69.8	66.1
CH_3O	53.8	53.7	55.0
CH_3-C-4	21.3	13.2	—
CH_2-C-4	—	—	52.4
CH_3-C-5	13.9	13.6	13.8

[a]Assignments based on the data reported in ref. 20 for daunosamine. [b]In $(CD_3)_2SO$. [c]In $CDCl_3$.

cannot be reliably predicted[15] and depends upon such factors as reaction temperature, solvent, and the nature of the halogen atom[16,17], the addition of methylmagnesium iodide and methyl-lithium to **3** was studied by using ^{13}C-n.m.r. spectroscopy for configurational assignments at the branch point. After the reaction of **3** in tetrahydrofuran with ethereal methyl-lithium at −78°, only methyl 2,3,6-trideoxy-4-*C*-methyl-3-trifluoroacetamido-α-L-*lyxo*-hexopyranoside (**4**, 55%) was isolated crystalline. The stereochemistry of the addition of methylmagnesium iodide was dependent on the reaction temperature and the solvent (see Table I). The ^{13}C-n.m.r. spectrum of **4** showed a signal for Me-4 at 21.3 p.p.m., whereas, for the *arabino* epimer **5**, it was observed at 13.2 p.p.m. These chemical shifts (see Table II) are characteristic for equatorial and axial methyl groups, respectively, in C-4 branched-chain hexopyranosides[16]. Glycosides **4** and **5** were treated with diazomethane in dry dichloromethane at −70° and in the presence of boron trifluoride etherate, to give the syrupy 4-*O*-methyl derivatives **6** and **7**, respectively, in yields of 65 and 75%.

Another synthesis objective (aimed at the introduction of other branched chains) was the 4-*C*-methylene derivative **8**, which was obtained from **4** by a sequential esterification–elimination reaction[18]. Treatment of **4** with thionyl chloride in boiling anhydrous benzene[19] followed by reaction with aqueous sodium hydrogencarbonate gave crystalline **8** (87%), the structure of which was established on the basis of ^{1}H-n.m.r. data (the broad signal at δ 4.83 indicated two vinylidene protons). On the other hand, treatment of the 4-*C*-methyl-L-*arabino* analogue **5** under similar conditions gave a saturated furanoside derivative in which HO-5 apparently had been replaced by chlorine. The structure of this compound is presently under investigation.

Catalytic hydrogenation of **8** proceeded stereoselectively, to give the 4-deoxy-4-*C*-methyl-L-*arabino*-hexopyranoside **9** (95%). The stereochemistry at C-4 and C-5 of **9** was determined on the basis of the value (8.5 Hz) for $J_{4,5}$ (obtained by spin-decoupling experiments at 270 MHz), which indicated H-4,5 to be *trans*-diaxial. Epoxidation of **8** with 3-chloroperoxybenzoic acid in 1,2-dichloroethane gave 92% of a spiro-epoxide (**10**) that was also obtained, in a comparable yield, by treatment of **3** in methanol with diazomethane in dichloromethane. The configuration of **10** was established by its conversion into the 4-*C*-methyl-L-*lyxo*-glycoside **4** by catalytic reduction in the presence of Raney nickel. Azidolysis of **10** in aqueous 1,4-dioxane in the presence of ammonium chloride gave the crystalline azido derivative **11** (95%). That **11** was methyl 4-*C*-azidomethyl-2,3,6-trideoxy-3-trifluoroacetamido-α-L-*lyxo*-hexopyranoside was indicated by ^{1}H- and ^{13}C-n.m.r., i.r., and mass-spectral data. Catalytic hydrogenation of **11**, followed by *N*-trifluoroacetylation, gave methyl 2,3,6-trideoxy-3-trifluoroacetamido-4-*C*-trifluoroacetamidomethyl-α-L-*lyxo*-hexopyranoside (**12**).

EXPERIMENTAL

General methods. — The chemical and physical data for the new compounds were determined on unrecrystallised samples unless stated otherwise. Melting points

TABLE III

^{1}H-N.M.R. DATA

Compound	Chemical shifts (δ)[a,b]												
	H-1 ($J_{1,2a}$)	*H-2e* ($J_{1,2e}$)	(J_{gem})	*H-2a* ($J_{1,2a}$)	*H-3*	*H-4*	*H-5* ($J_{5,6}$)	*MeO-1*	*MeO-4*	*Me-4*	*Me-5* ($J_{5,6}$)	*NH*	*Others*
6	4.77 bs (W_H6.5)	← 1.3–2.5 m →			3.9–4.6 m	—	3.77 q (6.5)	3.33 s	3.48 s	1.22 s	1.28 d (6.5)	6.54 vbs	
7	4.66 bs (W_H7.5)	1.83 dd (4.0)	(11.5)	2.20 dd (5.6)	4.3–4.9 m	—	4.12 q (6.5)	3.33 s	3.22 s	1.12 s	1.17 d (6.5)	6.20 vbs	
8	4.95 bs (W_H7.0)	← 1.2–2.3 m →			3.2–3.7 m	—	4.37 q (6.0)	3.37 s	—	—	1.35 d (6.5)	6.61 vbs	4.83 bs (exocyclic methylene)
9[c]	4.87 bd (3.0)	← 1.5–2.2 m →			4.0–4.3 m	1.0–1.5 m	3.70 dq (6.0; $J_{4,5}$ 8.5)	3.36 s	—	0.92 d (6.0)	1.23 d (6.0)	6.40 vbs	
10	4.85 bs (W_H7.0)	← 1.6–2.2 m →			4.5–5.1 m	—	4.40 q (6.5)	3.42 s	—	—	1.07 d (6.5)	6.32 vbs	2.66 d, 2.72 d (oxirane methylene) (3.5)
11	4.76 bs (W_H6.5)	← 1.5–2.4 m →			4.2–4.8 m	—	4.08 q (6.5)	3.39 s	—	—	1.23 d (6.5)	6.50 vbs	3.2–3.6 (exocyclic methylene); 2.58 s (OH)
12	4.73 bs (W_H6.0)	← 1.7–2.3 m →			4.2–4.6 m	—	3.88 q (6.5)	3.36 s	—	—	1.32 d (6.5)	7.04 vbs, 7.75 vbs	2.94 d, 3.78 d (exocyclic methylene); 2.90 s (OH) (3.15)

[a] Signal shapes: bs, broad signal; m, multiplet; q, quartet; d, doublet; vbs, very broad signal; dd, pair of doublets; s, singlet; bd, broad doublet; dq, pair of quartets. [b] First-order couplings or half-band widths (Hz) in parentheses. [c] Spectrum recorded at 270 MHz (Bruker WH 270 spectrometer).

were determined with an SMP-20 apparatus (Büchi) and are uncorrected. A Perkin–Elmer Model 141 polarimeter and 1-dm tubes were used for measurement of specific rotations. ^{13}C-N.m.r. spectra (20 MHz, internal Me_4Si) were recorded with a Varian CFT-20 spectrometer, by broad-band proton decoupling and single-frequency off-resonance decoupling. Chemical shifts are listed in Table II. ^{1}H-N.m.r. spectra (60 MHz, internal Me_4Si) were recorded with Varian A-60-A or EM-360 spectrometers for solutions in $CDCl_3$ unless stated otherwise. Chemical shifts and J values are listed in Table III. The mass spectra of **4**, **6**, and **8** were obtained with a Perkin–Elmer 270 mass spectrometer, and of other compounds with a Varian MAT-311-A mass spectrometer equipped with a combined e.i./f.i./f.d. ion-source. E.i. mode: electron energy, 70 eV; direct-inlet temperature, 40–60°; ion-source temperature, 200–250°. F.d. mode: accelerating voltage, 3 kV; extraction-plate voltage, 6 kV; ion-source temperature, 150°; emitter heating-current, 5–15 mA. T.l.c. was performed on silica gel HF (Merck) with detection by u.v. light or charring with sulphuric acid. Column chromatography was conducted with silica gel (70–230 mesh, ASTM Merck).

*Reactions of methyl 2,3,6-trideoxy-3-trifluoroacetamido-α-*L-threo-*hexopyranosid-4-ulose* (**3**). — (*a*) *With methyl-lithium*. To a solution of **3** (0.255 g, 1 mmol) in anhydrous tetrahydrofuran (60 ml) at −78° was added ethereal methyl-lithium (3 ml; 2M, LiBr-free), and the mixture was stirred for 2 h at −78°. After addition of water (60 ml), the aqueous layer was extracted with ether (3 × 30 ml), and the combined extracts and ether layer were washed with saturated, aqueous NaCl, dried (Na_2SO_4), and concentrated. The white, amorphous residue (0.15 g, 0.55 mmol) gave a single spot in t.l.c. (R_F 0.2; chloroform–methanol, 9:1) and, after crystallisation from ether–hexane, methyl 2,3,6-trideoxy-4-*C*-methyl-3-trifluoroacetamido-α-L-*lyxo*-hexopyranoside (**4**) was obtained; m.p. 133–134°, $[\alpha]_D^{23}$ −128° (*c* 1, chloroform). Mass spectrum (e.i.): *m/z* 240 ($M^{+\cdot}$ — OMe).

Anal. Calc. for $C_{10}H_{16}F_3NO_4$: C, 44.28; H, 5.95; F, 21.01; N, 5.16. Found: C, 44.06; H, 5.96; F, 21.00; N, 5.11.

(*b*) *With methylmagnesium iodide*. The yields of products obtained upon addition of methylmagnesium iodide to **3** in tetrahydrofuran and/or ether, at various temperatures, are summarised in Table I. The reactions were performed by using 18 equiv. of magnesium, 24 equiv. of methyl iodide per equiv. of **3**, and relative volumes of solvents similar to those used in the following example.

To a refluxing solution of methylmagnesium iodide (from 3.02 g of Mg and 10.3 ml of methyl iodide) in dry tetrahydrofuran (150 ml) was added, dropwise during 10 min, a solution of **3** (1.76 g, 6.9 mmol) in the same solvent (35 ml). After boiling under reflux for 3 h, the mixture was diluted with chloroform and water, dried (Na_2SO_4), and concentrated to dryness. T.l.c. (chloroform–acetone, 9:1) of the residue revealed two products having R_F 0.20 (minor, **4**) and 0.15 (major, **5**). Elution of the residue (1.85 g) from a column of silica gel with chloroform–acetone (97:3) gave, first, **4**, which, after recrystallisation from ether–hexane, was isolated as white needles (0.28 g, 15%), m.p. 133–134°, identical to the product in (*a*). Eluted second was the major component. Crystallisation from isopropyl ether gave methyl 2,3,6-trideoxy-4-*C*-methyl-3-trifluoroacetamido-α-L-*arabino*-hexopyranoside (**5**; 1.4 g, 75%) as white needles, m.p. 140–141°, $[\alpha]_D^{23}$ −155° (*c* 1.1, chloroform). Mass spectrum (e.i.): *m/z* 240 (M^+ — OMe).

Anal. Calc. for $C_{10}H_{16}F_3NO_4$: C, 44.28; H, 5.95; N, 5.16; F, 21.01. Found: C, 44.63; H, 6.00; N, 5.09; F, 20.89.

*Methyl 2,3,6-trideoxy-4-C-methyl-4-O-methyl-3-trifluoroacetamido-α-*L-lyxo-*hexopyranoside* (**6**). — A solution of **4** (1 g, 3.7 mmol) in dry dichloromethane (10 ml) was treated at −70° with an excess of diazomethane in dichloromethane (100 ml) in the presence of boron trifluoride etherate (0.05 ml). After 1 h at −70°, polymethylene was removed and the filtrate was washed with 10% aqueous sodium hydrogencarbonate and water, dried (Na_2SO_4), and concentrated. The resulting oil (0.9 g) was eluted from a column of silica gel with chloroform–acetone (95:5), to give **6** as a syrup (0.68 g, 65%), $[\alpha]_D^{23}$ −129° (*c* 1.1, chloroform). Mass spectrum (e.i.): *m/z* 254 (M^+ — OMe).

*Methyl 2,3,6-trideoxy-4-C-methyl-4-O-methyl-3-trifluoroacetamido-α-*L-arabino-*hexopyranoside* (**7**). — Treatment of **5** (1.3 g, 4.8 mmol) in dichloromethane with diazomethane–boron trifluoride etherate, as described above, gave **7** as a syrup (1.03 g, 75%), $[\alpha]_D^{23}$ −118° (*c* 1, chloroform).

*Methyl 2,3,4,6-tetradeoxy-4-C-methylene-3-trifluoroacetamido-α-*L-threo-*hexopyranoside* (**8**). — A solution of **4** (1 g, 3.7 mmol) in anhydrous benzene (90 ml) was treated with freshly distilled thionyl chloride (2.75 ml), and the mixture was boiled under reflux for 2 h, washed with water, and stirred with 10% aqueous sodium hydrogencarbonate for 1 h. The organic phase was separated, washed with water, and concentrated to dryness, to give **8** (0.82 g, 87%) as a white solid, m.p. 160–162°, $[\alpha]_D^{23}$ −180° (*c* 1, chloroform). Mass spectrum (f.d.): *m/z* 253 ($M^{+\cdot}$).

Anal. Calc. for $C_{10}H_{14}F_3NO_3$: C, 47.43; H, 5.57. Found: C, 47.21; H, 5.48.

*Methyl 2,3,4,6-tetradeoxy-4-C-methyl-3-trifluoroacetamido-α-*L-arabino-*hexopyranoside* (**9**). — To a solution of **8** (0.506 g, 2 mmol) in methanol (40 ml) was added 20% Pd/C (0.5 g), and the mixture was hydrogenated at 20 atmos. overnight, filtered through kieselguhr, and concentrated to dryness, to give **9** (0.5 g, 98%) as a white solid, m.p. 132–134°, $[\alpha]_D^{23}$ −82° (*c* 0.5, chloroform). Mass spectrum (e.i.): *m/z* 224 (M^+ — OMe).

Anal. Calc. for $C_{10}H_{16}F_3NO_3$: C, 47.06; H, 6.32; N, 5.49. Found: C, 46.99; H, 6.12; N, 5.33.

*Methyl $4,4^1$-anhydro-2,3,6-trideoxy-4-C-hydroxymethyl-3-trifluoroacetamido-α-*L-lyxo-*hexopyranoside* (**10**). — (*a*) A solution of **8** (0.51 g, 2 mmol) and 3-chloroperoxybenzoic acid (0.69 g, 4 mmol) in dry 1,2-dichloroethane (20 ml) was boiled under reflux for 2 days, and then washed with aqueous sodium hydrogencarbonate and water. The organic phase was concentrated, to give **10** (0.5 g, 92%), m.p. 185–186°, $[\alpha]_D^{23}$ −133° (*c* 0.5, chloroform). Mass spectrum (e.i.): *m/z* 238 (M^+ — OMe).

Anal. Calc. for $C_{10}H_{14}F_3NO_4$: C, 44.61; H, 5.24; N, 5.20; F, 21.17. Found: C, 44.60; H, 5.28; N, 5.17; F, 21.04.

(*b*) A solution of **3** (0.51 g, 2 mmol) in methanol (10 ml) was stirred with a solution of diazomethane in dichloromethane (0.64 g in 20 ml) at room temperature overnight. The white, crystalline product (0.5 g, 92%) had physical constants identical with those of **10** described in (*a*).

A solution of **10** (0.27 g, 1 mmol) in methanol (40 ml) was hydrogenated in the presence of Raney nickel at 10 atmos. for 4 h. The mixture was then filtered and concentrated to dryness, and the residue was crystallised, to give white needles (0.24 g, 90%) having physical constants identical with those of **4** described above.

*Methyl 4-C-azidomethyl-2,3,6-trideoxy-3-trifluoroacetamido-α-*L-lyxo-*hexopyranoside* (**11**). — A solution of **10** (0.54 g, 2 mmol) in 1,4-dioxane (15 ml) and water (5 ml) was stirred with sodium azide (0.95 g) and ammonium chloride (0.425 g) and boiled under reflux for 4 h, and then diluted with chloroform and water. The aqueous layer was extracted with chloroform, and the combined organic solutions were washed with water, dried (Na_2SO_4), and concentrated to dryness, to give **11** (0.62 g), m.p. 150–151°, $[\alpha]_D^{23}$ −179° (*c* 1, chloroform); ν_{max}^{film} 3380 (OH) and 2210 (N_3) cm^{-1}. Mass spectrum (f.d.): *m/z* 313 $(MH)^+$.

Anal. Calc. for $C_{10}H_{15}F_3N_4O_4$: C, 38.47; H, 4.84; N, 17.94; F, 18.25. Found: C, 38.55; H, 4.94; N, 17.48; F, 18.37.

*Methyl 2,3,6-trideoxy-3-trifluoroacetamido-4-*C*-trifluoroacetamidomethyl-α-*L-lyxo-*hexopyranoside* (**12**). — To a solution of **11** (0.47 g, 1.5 mmol) in methanol (20 ml) was added 20% Pd/C (0.5 g), and the mixture was hydrogenated at 10 atmos. overnight, filtered, and concentrated to dryness. A solution of the resulting, colourless syrup in anhydrous dichloromethane (15 ml) at 0° was treated with trifluoroacetic anhydride (2 ml). After 30 min, the mixture was concentrated to dryness, to give **12** (0.47 g, 83%) as a white solid, m.p. 165–166°, $[\alpha]_D^{23}$ −59° (*c* 1, chloroform). Mass spectrum (e.i.): *m/z* 351 (M^+ − OMe).

Anal. Calc. for $C_{12}H_{16}F_6N_2O_5$: C, 37.70; H, 4.22; N, 7.33. Found: C, 37.81; H, 4.19; N, 7.13.

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