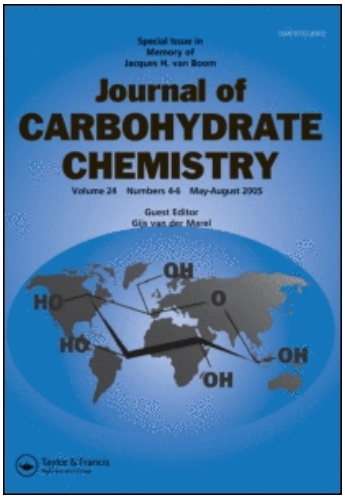

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SYNTHESIS OF EXTREMELY HINDERED DAUNOSAMINE DERIVATIVES

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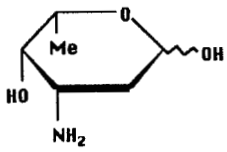
ABSTRACT

The Strecker reaction of methyl 4,6-O-benzylidene-2-deoxy-2-C-dimethyl-α-D-erythro-hexopyranosid-3-ulose gave stereospecifically an α-aminonitrile of ribo configuration. Reductive decyanation of the latter furnished a ribo aminosugar as the exclusive product and key intermediate for the preparation of protected highly hindered daunosamine analogues.

INTRODUCTION

Considerable interest was devoted in recent years towards the synthesis of daunosamine,[1] the amino sugar constituent of the clinically useful antineoplastic agents daunomycin[2] and adriamycin.[2] As part of a program aimed at preparing chemically challenging analogues of daunosamine 1[3-8] we report here the synthesis of extremely hindered derivatives of this important aminosugar. In the new analogues both neighbours of the amine bearing carbon became quaternary sites. A daunosamine derivative containing three contiguous quaternary centers at C-2, C-3 and C-4 has also been synthesized.



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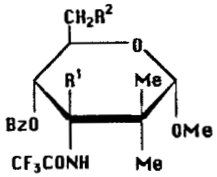
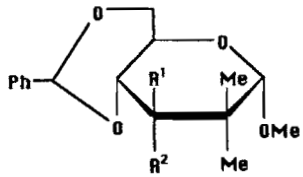


11 $R^1 = H; R^2 = Br$

12 $R^1 = H; R^2 = I$

19 $R^1 = CN; R^2 = Br$

20 $R^1 = CN; R^2 = I$



2 $R^1 = R^2 = O$

3 $R^1 = R^2 = N\text{-}OH$

4 $R^1 = H; R^2 = NH_2$

5 $R^1 = NH_2; R^2 = H$

6 $R^1 = H; R^2 = OH$

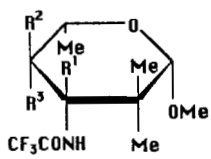
7 $R^1 = CN; R^2 = NH_2$

8 $R^1 = OH; R^2 = CN$

9 $R^1 = CN; R^2 = OH$

10 $R^1 = H; R^2 = NHCOCF_3$

18 $R^1 = CN; R^2 = NHCOCF_3$



14 $R^1 = R^2 = H; R^3 = OBz$

15 $R^1 = R^2 = H; R^3 = OH$

16 $R^1 = H; R^2 = R^3 = O$

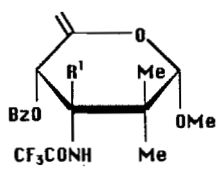
17 $R^1 = H; R^2 = Me; R^3 = OH$

22 $R^1 = CN; R^2 = H; R^3 = OBz$

23 $R^1 = CN; R^2 = H; R^3 = OH$

24 $R^1 = CN; R^2 = R^3 = O$

25 $R^1 = CN; R^2 = Me; R^3 = OH$



13 $R^1 = H$

21 $R^1 = CN$

RESULTS AND DISCUSSION

In connection with another project related to the synthesis of branched-chain carbohydrates by means of organopalladium chemistry, we have reported the preparation of the oxime of methyl 4,6-O-benzylidene-2-deoxy-2-C-dimethyl-α-D-erythro-hexopyranosid-3-ulose 3.[9] Lithium aluminium hydride reduction of 3 appeared to be the obvious method to prepare the corresponding aminosugar with the ribo configuration 4. Surprisingly, the major aminosugar product from the reaction (5, 80%) proved to be of arabino configuration. An attempt to reduce the oxime of 3 with sodium bis(2-methoxy-ethoxy)aluminium hydride failed.[10] When the ketone 2, from which the oxime 3 was obtained, was reduced by sodium borohydride in methanol the ribo derivative 6 was the exclusive product of the reaction. No explanation can be put forward at the moment to explain the contrasting behaviour of ketone 2 and oxime 3 upon metal hydride reduction.

In order to find a satisfactory method for the preparation of aminosugar 4, the Strecker α-aminonitrile route followed by decyanation was planned.[11,12] When methyl 4,6-O-benzylidene-2-deoxy-2-C-dimethyl-α-D-erythro-hexopyranosid-3-ulose 2 was treated in methanol solution saturated with ammoniac gas and in the presence of ammonium chloride and potassium cyanide at 22° C for one week, a single crystalline aminonitrile of ribo stereochemistry 7 was obtained in 74% yield.

The configuration of aminonitrile 7 was established unambiguously by spectral comparison with the two isomeric cyanohydrins 8 and 9 which were also prepared. Cyanohydrins appear to be intermediates in the Strecker aminonitrile synthesis.[13] When the reaction, as described above for the preparation of 7 from 2, was conducted only overnight, it furnished a single cyanohydrin of arabino stereochemistry 8 in 75% yield. The isomeric cyanohydrin 9 having the ribo configuration, the kinetic product, was prepared in 90% yield as a single derivative upon treatment of ketone 2 in dry pyridine solution with hydrocyanic acid. Spectral differentiation between these two cyanohydrins was performed by inspec-

tion of the structurally diagnostic C-5 chemical shifts of these compounds.[3] The ^{13}C NMR spectrum of the ribo 9 and arabino 8 isomers exhibited resonances for C-5 at 59.3 and 61.9 ppm respectively. This difference is due to a greater steric compression effect for the ribo product between the axial H-5 and the axial carbon-oxygen bond at C-3 than in the arabino derivative where the axial C-3 linkage involves a carbon-carbon bond. Since the α-aminonitrile 7 indicated its C-5 resonance at 58.7 ppm, we could conclude that the configuration of this branched-chain carbohydrate is ribo.

The ribo stereochemistry of the α-aminonitrile appeared particularly attractive for a reductive decyanation reaction to be attempted. It has been shown previously that in such reactions the mechanism implies the prior formation of an imminium ion by elimination of the cyano group and subsequent approach of hydride ion from the less hindered side of the molecule.[11] As a consequence of the α-anomeric substituent an aminosugar of ribo configuration was the exclusive product of the decyanation allowing stereospecific access to our key intermediate 4, unstable and characterized as its N-trifluoroacetyl derivative 10.

The transformation of 4 into the desired highly hindered protected L-daunosamine derivative 17 proceeded uneventfully applying well-established methodology[1] involving the following steps: a) trifluoroacetylation of the amine; b) N-bromosuccinimide induced opening of the benzylidene acetal ring; c) exchange of the bromine at C-6 with iodine followed by dehydrohalogenation; d) stereospecific hydrogenation of the resulting unsaturated sugar to a carbohydrate of the L-series; e) liberation of the hydroxy group at C-4 followed by its oxidation; f) introduction of the branched-chain by stereospecific reaction of the C-4 ketone with methyllithium.

An analogous series of reactions has permitted the transformation of α-aminonitrile 7 into the highly hindered protected L-daunosamine derivative 25 containing three contiguous quaternary centers at C-2, C-3 and C-4.

In order to establish the required β-L-lyxo stereochemistry of our final products 17 and 25, a ^{13}C NMR spectroscopic investigation was initiated. Although, in the methyllithium addition step the desired lyxo configuration was expected in view of the directing effect of the axially disposed C-methyl group at C-2, the stereochemistry at C-4 in 17 and 25 could be rigorously demonstrated in spite of the absence of proton-proton coupling constants.

The four C-methyl resonances in the spectrum of 17 at 13.7, 14.8, 21.8 and 24.1 ppm (14.0, 16.0, 21.3 and 23.8 ppm in the spectrum of 25) respectively, could be easily assigned to $C\text{-}2Me_{ax}$, C-6, $C\text{-}2Me_{eq}$ and C-4Me. These assignments were based on a spectral comparison of all of our intermediates. The chemical shift of 15.5 ± 1.0 ppm is highly characteristic of C-6 in all 6-deoxy sugars present in various antibiotics.[14] The above indicated 8 ppm chemical shift difference between the axial and equatorial C-methyl at C-2 is the result of the steric relationship of these methyls relative to their immediate neighbours. The axial methyl is considerably shielded with respect to its equatorial counterpart. This is because the former is involved in two cis-type gauche interactions with the C-1 and C-3 substituents while the latter suffers two trans-type effects with the same substituents. Since the C-4Me signal of 17 shows up at 23.8 ppm, it is obvious that the C-4Me is involved in two trans-type interactions with the substituents of the pyranose ring at C-3 and at C-5. As a consequence, the β-L-lyxo stereochemistry can be attributed to 17 and 25. It is of interest to note that the small cyano group has no influence on the chemical shift of C-4Me in the ^{13}C NMR spectrum of 25.

Transformation of these highly hindered daunosamine derivatives into the corresponding daunomycins, including a study on the stereochemical outcome of the glycosylation of C-2 gem-disubstituted sugars, will be reported later.

EXPERIMENTAL

General Procedures. The melting points were determined with a Büchi apparatus and are uncorrected. A Perkin-Elmer Model 141 MC polarimeter and 1-dm tubes were used for measurement of specific rotations. ^{1}H NMR spectra were recorded in chloroform-d solution at 400 MHz. The ^{13}C NMR spectra were measured in chloroform-d solution at 50.31 MHz with a Bruker WP-200 spectrometer. Chemical shifts are given in parts per million, and tetramethylsilane was the internal standard (δ 0.000). Carbon-13 chemical shifts for aromatic carbons are not given. Mass spectra were measured with a AEI MS9 apparatus. Microanalyses were performed by the Service Central de Microanalyse du CNRS. Silica gel 60 PF_{254} (Merck) activated at 120 °C was the support for TLC and for column chromatography.

Methyl 3-Amino-4,6-O-benzylidene-3-C-cyano-2,3-dideoxy-2-C-dimethyl-α-D-ribo-hexopyranoside (7). To a solution of the ketone 2 (2.5 g, 8.56 mmol) in methanol (100 mL) were added ammonium chloride (7 g, 130 mmol) and potassium cyanide (8 g, 123 mmol) in a stainless pressure bottle. The mixture was cooled to -78 °C and under an ammonia gas stream the mixture was stirred for 30 min. The bottle was then closed with precaution and the mixture was stirred for 1 week. The methanol was evaporated, the mixture was dissolved in methylene chloride and filtered. Flash chromatography using methylene chloride/hexane/ethyl acetate = 80:19:1 afforded the pure crystalline aminonitrile 7 (2 g, 73%): mp 152-154 °C; $[\alpha]_D^{22}$ = + 32° (c = 1.21, chloroform); mass spectrum (chemical ionization) (isobutane) (M^+ + H) 319; ^{1}H NMR δ: 7.5 and 7.38 (m, 5H, Ph); 5.7 (s, 1H, H-7); 4.35 (q, 1H, $J_{6ax,6eq}$ = 10 Hz, $J_{5,6eq}$ = 5 Hz, H-6eq); 4.30 (s, 1H, H-1); 4.04 (d, 1H, $J_{4,5}$ = 10 Hz, H-4); 4.0 (m, 1H, H-5); 3.85 (t, 1H, $J_{6ax,6eq}$ = $J_{5,6ax}$ = 10 Hz, H-6ax); 3.37 (s, 3H, OMe); 2.21 (bs, 1H, NH); 1.4 (s, 3H, C-2Me_{ax}); 1.26 (s, 3H, C-2Me_{eq}); ^{13}C NMR δ: 119.8 (CN); 105.5 (C-1); 101.8 (C-7); 78.2 (C-4); 68.9 (C-6); 58.7 (C-5); 56.1 (OMe); 41.9 (C-2); 25.1 (C-2Me_{ax}); 20.5 (C-2Me_{eq}).

Anal. Calcd for: $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.96; N, 8.79. Found: C, 64.30; H, 7.09; N, 8.67.

Methyl 3-Amino-4,6-O-benzylidene-2,3-dideoxy-2-C-dimethyl-3-trifluoroacetamido-α-D-ribo-hexopyranoside (10). To a solution of the aminonitrile 7 (750 mg, 1.81 mmol) in ethanol (500 mL) was added sodium borohydride (1 g, 26 mmol). The mixture was stirred under reflux overnight. The pH was adjusted to 7 by dropwise addition of a 15% aqueous solution of acetic acid, followed by the evaporation of the ethanol. The mixture was diluted with methylene chloride, filtered, washed with water, dried over magnesium sulfate and concentrated *in vacuo* giving the unstable amine 4 (475 mg, 90%). Dry pyridine (3 mL) and trifluoroacetic anhydride (680 μL, 4.86 mmol) were successively added to a stirred solution of amine 4 (475 mg, 1.62 mmol) in ether (20 mL) at -40 °C. After 5 h at 0 °C, the ethereal layer was washed and extracted. Flash chromatography, using hexane/ethyl acetate = 6:4, gave pure 10 (600 mg, 95%), as a syrup; $[\alpha]_D^{22}$ = -11° (c = 1.6, chloroform); mass spectrum (chemical ionization) (isobutane) (M^+ + H) 390; ^{1}H NMR δ: 7.62 (d, 1H, $J_{3\text{-NH}}$ = 10 Hz, NH); 7.41-7.33 (m, 5H, Ph); 5.60 (s, 1H, H-7); 4.32 (m, 2H, H-4 and H-6_{eq}); 4.28 (s, 1H, H-1); 4.07 (m, 1H, H-5); 3.87 (m, 2H, H-3 and H-6_{ax}); 3.43 (s, 3H, OMe); 1.27 (s, 3H, C-2Me_{ax}); 1.07 (s, 3H, C-2Me_{eq}); ^{13}C NMR δ: 157.6 (CO); 105.6 (C-1); 101.6 (C-7); 74.9 (C-4); 69.2 (C-6); 59.4 (C-5); 55.8 (OMe); 53.4 (C-3); 38.6 (C-2); 25.1 (C-2Me_{ax}); 22.2 (C-2Me_{eq}).

Anal. Calcd for $C_{18}H_{22}F_3NO_5$: C, 55.52; H, 5.69; N, 3.59; F, 14.64. Found: C, 55.75; H, 5.82; N, 3.48; F, 14.58.

Methyl 3-Amino-4,6-O-benzylidene-2,3-dideoxy-2-C-dimethyl-α-D-arabino-(5)-and-ribo-hexopyranoside (4). To a suspension of lithium aluminium hydride (100 mg, 2.6 mmol) in anhydrous tetrahydrofuran (10 mL) was added the oxime 3 (180 mg, 0.586 mmol) dissolved in tetrahydrofuran. The solution was stirred under an argon atmosphere at room temperature overnight. The reaction was quenched by adding dropwise a saturated aqueous solution of ammonium chloride. Filtration followed by standard extraction gave,

after chromatography, the unstable amine 5 (145 mg, 83%) and 4 (30 mg, 17%) which after trifluoroacetylation was identical with 10 obtained from 7 as described above. For 5: ^{1}H NMR δ: 7.48-7.36 (m, 5H, Ph); 5.55 (s, 1H, H-7); 4.25 (q, 1H, $J_{6ax,6eq}$ = 10 Hz, $J_{5,6eq}$ = 5 Hz, H-6eq); 3.82 (m, 1H, H-5); 3.76 (t, 1H, $J_{4,5}$ = $J_{3,4}$ = 10 Hz, H-4); 3.56 (s, 3H, OMe); 3.50 (t, 1H, $J_{6ax,6eq}$ = $J_{5,6ax}$ = 10 Hz, H-6ax); 3.14 (d, 1H, $J_{3,4}$ = 10 Hz, H-3); 1.07 (s, 3H, C-2Me$_{ax}$); 1.02 (s, 3H, C-2Me$_{eq}$); ^{13}C NMR δ: 106.5 (C-1); 102.0 (C-7); 80.7 (C-4); 69.3 (C-6); 66.2 (C-5); 55.1 (OMe); 54.0 (C-3); 40.1 (C-2); 23.1 (C-2Me$_{eq}$); 19.2 (C-2Me$_{ax}$).

Methyl 4,6-O-Benzylidene-3-C-cyano-2-deoxy-2-C-dimethyl-α-D-arabino-hexopyranoside (8). To a solution of the ketone 2 (100 mg, 0.34 mmol) in anhydrous methanol saturated with ammonia (6 mL), were added ammonium chloride (200 mg, 3.2 mmol) and potassium cyanide (200 mg, 3.07 mmol). The mixture was stirred overnight at room temperature. The methanol was evaporated (without warming) and the mixture was filtered over celite in methylene chloride solution. Thin layer chromatography using methylene chloride/hexane/ethyl acetate = 80:19:1 afforded pure 8 as a crystalline product (80 mg, 73%); mp = 170-172 °C; $[\alpha]_D^{22}$ = + 84° (c = 0.6, chloroform); mass spectrum (chemical ionization) (isobutane) (M^+ + H) 320; ^{1}H NMR δ: 5.57 (s, 1H, H-7); 4.32 (m, 2H, H-1 and H-6eq); 4.12 (m, 1H, H-5); 3.82 (d, 1H, $J_{4,5}$ = 10 Hz, H-4); 3.79 (t, 1H, $J_{6ax,6eq}$ = $J_{5,6ax}$ = 10 Hz, H-6ax); 3.41 (s, 3H, OMe); 1.32 (s, 3H, C-2Me$_{ax}$); 1.2 (s, 3H, C-2Me$_{eq}$); ^{13}C NMR δ: 118.2 (CN); 105.6 (C-1); 102.8 (C-7); 79.5 (C-4); 76.5 (C-3); 68.9 (C-6); 61.9 (C-5); 55.8 (OMe); 44.1 (C-2); 21.0 (C-2Me$_{ax}$); 20.9 (C-2Me$_{eq}$).

Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.93; H, 6.63; N, 4.38. Found: C, 64.13; H, 6.78; N, 4.30.

Methyl 4,6-O-Benzylidene-3-C-cyano-2-deoxy-2-C-dimethyl-α-D-ribo-hexopyranoside (9). A solution of the ketone (200 mg, 0.68 mmol) in methylene chloride (1 mL) and pyridine (1 mL) was saturated at + 5° C with a stream of hydrocyanic acid [prepared from saturated aqueous potassium cyanide (6 g) and a 50% aqueous

solution of sulfuric acid (10 mL)]. After stirring for 24 h at room temperature the solvent was evaporated under vacuo. Crystallization using methylene chloride/hexane afforded pure 9 (190 mg, 87%), mp 237-239°C, $[\alpha]_D^{22}$ = + 26° (c = 1.17, chloroform); mass spectrum (chemical ionization) (isobutane) (M^+ + H) 320; ^{1}H NMR δ: 7.5 and 7.39 (m, 5H, Ph); 5.69 (s, 1H, H-1); 4.37 (s, 1H, H-1); 4.35 (q, 1H, $J_{6ax,6eq}$ = 10 Hz, $J_{5,6eq}$ = 5 Hz, H-6eq); 4.05 (m, 1H, H-5); 3.95 (d, 1H, $J_{4,5}$ = 10 Hz, H-4); 3.84 (t, 1H, $J_{5,6ax}$ = $J_{6ax,6eq}$ = 10 Hz, H-6ax); 3.42 (s, 3H, OMe); 1.37 (s, 3H, C-2Me$_{ax}$); 1.28 (s, 3H, C-2Me$_{eq}$); ^{13}C NMR δ: 117.68 (CN); 105.6 (C-1); 102.3 (C-7); 78.0 (C-4); 68.9 (C-6); 59.3 (C-5); 56.4 (OMe); 43.1 (C-2); 24.5 (C-2Me$_{ax}$); 20.2 (C-2Me$_{eq}$).

Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.93; H, 6.63; N, 4.38. Found: C, 63.88; H, 6.71; N, 4.42.

Methyl 4-O-Benzoyl-6-bromo-2-C-dimethyl-2,3,6-trideoxy-3-trifluoroacetamido-α-D-ribo-hexopyranoside (11). A suspension of 10 (600 mg, 1.54 mmol), N-bromosuccinimide (329 mg, 1.85 mmol) and barium carbonate (440 mg, 2.23 mmol) in anhydrous carbon tetrachloride (25 mL) was refluxed for 4 h under an argon atmosphere. When the reaction was completed, the mixture was cooled, filtered over celite and washed with methylene chloride. The organic layer was washed successively with a solution of sodium thiosulfate (10% aqueous), a saturated solution of sodium hydrogen carbonate, water and dried over magnesium sulfate. Concentration in vacuo gave a crude material which was further purified by flash chromatography (hexane/ethyl acetate = 7:3) affording pure 11 as a syrup (600 mg, 83%); $[\alpha]_D^{22}$ = + 26° (c = 1.7, chloroform); mass spectrum (chemical ionization) (isobutane) (M^+ + H) 468-470; ^{1}H NMR δ: 7.91, 7.56 and 7.4 (m, 6H, Ph and NH); 5.45 (dd, 1H, $J_{4,5}$ = 10 Hz Hz, $J_{3,4}$ = 4 Hz, H-4); 4.95 (dd, 1H, $J_{3,4}$ = 4 Hz, $J_{3,NH}$ = 10 Hz, H-3); 4.40 (s, 1H, H-1); 4.08 (m, 1H, H-5); 3.64 (m, 1H, H-6); 3.54 (s, 3H, OMe); 3.5 (m, 1H, H-6'); 1.32 (s, 3H, C-2Me$_{ax}$); 1.07 (s, 3H, C-2Me$_{eq}$); ^{13}C NMR δ: 165.0 (OCOPh); 105.4 (C-1); 67.4 (C-4); 65.5 (C-5); 56.1 (OMe); 53.9 (C-3); 38.2 (C-2); 32.3 (C-6); 24.5 (C-2Me$_{ax}$); 21.9 (C-2Me$_{eq}$).

Anal. Calcd for $C_{18}H_{22}BrF_3NO_5$: C, 46.16; H, 4.52; Br, 17.06; F, 12.17; N, 2.99. Found: C, 45.92; H, 4.61; Br, 17.21; F, 12.01; N, 2,78.

Methyl 4-O-Benzoyl-2-C-dimethyl-6-iodo-2,3,6-trideoxy-3-trifluoroacetamido-α-D-ribo-hexopyranoside (12). A mixture of 11 (600 mg, 1.28 mmol) and tetrabutylammonium iodide (1.42 g, 3.48 mmol) in acetonitrile (60 mL) was refluxed for 48 h. The solvent was evaporated and the residue dissolved in methylene chloride filtered on a silica gel column using hexane/ethyl acetate = 7:3. Pure syrup 12 was obtained, (500 mg, 76%), $[\alpha]_D^{22}$ = + 10° (c = 1.4, chloroform); mass spectrum (chemical ionization) (isobutane) (M^+ + H) 516; ^{1}H NMR δ: 7.88, 7.56 and 7.41 (m, 5H, Ph); 5.33 (dd, 1H, $J_{3,4}$ = 4 Hz, $J_{4,5}$ = 10 Hz, H-4); 4.38 (dd, 1H, $J_{3,NH}$ = 10 Hz, $J_{3,4}$ = 4 Hz, H-3); 4.37 (s, 1H, H-1); 3.82 (m, 1H, H-5); 3.55 (s, 3H, OMe); 3.45 (m, 1H, H-6); 3.27 (m, 1H, H-6'); 1.32 (s, 3H, C-2Me$_{ax}$); 1.05 (s, 3H, C-2Me$_{eq}$); ^{13}C NMR δ: 165.1 (OCOPh); 105.6 (C-1); 69.2 (C-4); 65.6 (C-5); 56.3 (OMe); 54.0 (C-3); 38.4 (C-2); 24.6 (C-2Me$_{ax}$); 21.9 (C-2Me$_{eq}$); 5.4 (C-6).

Anal. Calcd for $C_{18}H_{22}F_3INO_5$: C, 41.96; H, 4.11; F, 11.06; I, 24.63; N, 2.72. Found: C, 42.21; H, 4.19; F, 10.88; I, 24.49; N, 2,60.

Methyl 4-O-Benzoyl-2-C-dimethyl-2,3,6-trideoxy-3-trifluoroacetamido-α-D-erythro-hex-5-enopyranoside (13). A mixture of 12 (500 mg, 0.97 mmol) and silver fluoride (860 mg, 6.8 mmol) in dry pyridine (50 mL) was stirred in the dark overnight. The resulting mixture was diluted with diethyl ether, filtered over celite and concentrated in vacuo. The residue was purified by flash chromatography, using hexane/ethyl acetate = 3:1 to afford pure 13 as a syrup (300 mg, 79%). $[\alpha]_D^{22}$ = -5° (c = 1.3, chloroform); mass spectrum (chemical ionization) (isobutane) (M^+ + H) 388; ^{1}H NMR δ: 8.02, 7.58 and 7.45 (m, 5H, Ph); 7.77 (bd, 1H, $J_{3,NH}$ = 10 Hz, NH); 5.96 (m, 1H, H-4); 4.9 (s, 1H, H-6); 4.78 (s, 1H, H-6'); 4.47 (s, 1H, H-1); 4.43 (dd, 1H, $J_{3,NH}$ = 10 Hz, $J_{3,4}$ = 5 Hz, H-3); 3.52(s, 3H, OMe); 1.4 (s, 3H, C-2Me$_{ax}$); 1.06 (s, 3H,

C-2Me$_{eq}$); ^{13}C NMR δ: 164.8 (OCOPh); 149.1 (C-5); 98.5 (C-1); 88.9 (C-6); 66.4 (C-4); 56.1 (OMe); 55.0 (C-3); 38.5 (C-2); 24.5 (C-2Me$_{ax}$); 22.0 (C-2Me$_{eq}$).

Anal. Calcd for $C_{18}H_{20}F_3NO_5$: C, 55.81; H, 5.20; F, 14.71; N, 3.61. Found: C, 55.96; H, 5.34; F, 14.59; N, 3.58.

Methyl 4-O-Benzoyl-2-C-dimethyl-2,3,6-trideoxy-3-trifluoroacetamido-β-L-lyxo-hexopyranoside (14). A mixture of the unsaturated sugar 13 (250 mg, 0.64 mmol) and 5% palladium on activated carbon (40 mg) in methanol (50 mL) was stirred under a hydrogen atmosphere overnight. Filtration over celite and concentration in vacuo gave a crude reaction mixture (170 mg, 68%) consisting of 14 and most probably a product (15%) of D-absolute configuration. The NMR spectrum of 14 was recorded in the presence of the minor product. ^{1}H NMR δ: 8.1, 7.62 and 7.47 (m, 5H, Ph); 6.3 (d, 1H, $J_{3,NH}$ = 10 Hz); 5.32 (d, 1H, $J_{3,4}$ = 4 Hz, H-4); 4.22 (q, 1H, $J_{3,NH}$ = 10 Hz, $J_{3,4}$ = 4 Hz, H-3); 4.18 (s, 1H, H-1); 3.9 (q, 1H, $J_{5,C\text{-}5Me}$ = 7 Hz, H-6); 3.56 (s, 3H, OMe); 1.28 (s, 3H, $J_{5,6}$ = 7 Hz, H-6); 1.18 (s, 3H, C-2Me$_{ax}$); 1.0 (s, 3H, C-2Me$_{eq}$); ^{13}C NMR δ: 166.4 (OCOPh); 108.0 (C-1); 71.1 (C-5); 71.0 (C-4); 57.3 (OMe); 55.2 (C-3); 38.9 (C-2); 22.6 (C-2Me$_{eq}$); 16.4 (C-6); 14.9 (C-2Me$_{ax}$).

Methyl 2-C-Dimethyl-2,3,6-trideoxy-3-trifluoroacetamido-β-L-lyxo-hexopyranoside (15). To a solution of crude 14 (140 mg, 0.36 mmol) in methanol (25 mL) a 0.1N solution of sodium hydroxyde (25 mL) was added dropwise and the mixture was stirred for 3 h at room temperature. The reaction was quenched by adding dropwise a 0.5N solution of hydrochloric acid until pH 7. The solvent was evaporated without warming and the solution was diluted with methylene chloride. The organic layer was washed with water, evaporated and concentrated in vacuo. The crude material was further purified by flash chromatography (hexane/ethyl acetate = 7:3) to afford 15 as a pure product, crystallized using methylene chloride/hexane (70 mg, 68%); mp 121-123 °C; $[\alpha]_D^{22}$ = + 35° (c = 0.51, chloroform); mass spectrum (chemical ionization) isobutane (M^+ + H) 286; ^{1}H NMR δ: 6.93 (d, 1H, $J_{3,NH}$ = 10 Hz, NH); 4.1

(s, 1H, H-1); 3.93 (q, 1H, $J_{3,NH}$ = 10 Hz, $J_{3,4}$ = 4 Hz, H-3); 3.72 (q, 1H, $J_{5,6}$ = 8 Hz, $J_{4,5}$ = 2 Hz, H-5); 3.53 (m, 4H, H-4 and OMe); 1.35 (d, 3H, $J_{5,6}$ = 8 Hz, H-6); 1.27 (s, 3H, C-2Me_{ax}); 1.0 (s, 3H, C-2Me_{eq}); ^{13}C NMR δ: 108.2 (C-1); 71.9 (C-5); 70.3(C-4); 57.2 (OMe); 56.1 (C-3); 39.4 (C-2); 23.4 (C-2Me_{eq}). 16.0 (C-6); 15.2 (C-2 Me_{ax}).

Anal. Calcd for $C_{11}H_{18}F_3NO_4$: C, 46.31; H, 6.35; F, 19.97; N, 4.91. Found: C, 46.26; H, 6.28; F, 19.70; N, 4.65.

Methyl 2-C-Dimethyl-2,3,6-trideoxy-3-trifluoroacetamido-β-L-threo-hexopyranoside-4-ulose (16). The alcohol 15 (26 mg, 0.09 mmol) was added to a suspension of pyridium chlorochromate (58 mg, 0.27 mmol) with molecular sieve powder 3Å (2 g per mmol of starting material) in methylene chloride (2 mL). The reaction was stirred in the darkness for 3 h. Diethyl ether was added (6 mL) and the solution was filtered over Fluorisil. Concentration in vacuo gave the pure crystalline ketone 16 (24 mg, 95%); mp 89-91 °C; $[\alpha]_D^{22}$ = + 95° (c = 2, chloroform); mass spectrum (chemical ionization) (isobutane) $(M^+ + H)$ 284, $(MH-MeOH)^+$ 252; ^{1}H NMR δ: 6.76 (d, 1H, $J_{3,NH}$ = 10 Hz, NH); 4.67 (s, 1H, H-1); 4.66 (d, 1H, $J_{3,NH}$ = 10 Hz, H-3); 4.16 (q, 1H, $J_{5,6}$ = 7 Hz, H-5); 3.58 (s, 3H, OMe); 1.37 (d, 3H, $J_{5,6}$ = 7 Hz, H-6); 1.07 (s, 3H, C-2Me_{ax}); 0.82 (s, 3H, C-2Me_{eq}); ^{13}C NMR δ: 201.7 (C-4); 106.2 (C-1); 69.9 (C-5); 62.6 (C-3); 57.6 (OMe); 42.6 (C-2); 21.7 (C-2Me_{eq}). 14.3 (C-2Me_{ax} and C-6).

Anal. Calcd for $C_{11}H_{16}F_3NO_4$: C, 46.64; H, 5.69; F, 20.12; N, 4.94. Found: C, 46.88; H, 5.50; F, 20.28; N, 4.98.

Methyl 2-C-Dimethyl-4-C-methyl-2,3,6-trideoxy-3-trifluoroacetamido-β-L-lyxo-hexopyranoside (17). To a solution of the ketone 16 (17 mg, 0.06 mmol) in anhydrous tetrahydrofuran (4 mL) were added at -78 °C 4 eq. of a solution 1.6M of methyllithium (150 μL). The temperature was allowed to rise to -30 °C and the mixture was stirred for 5 h under an argon atmosphere. The reaction was quenched by adding a saturated solution of ammonium chloride and the organic layer was extracted with ethyl acetate and washed with water. Drying over magnesium sulfate and concen-

tration in vacuo gave a crude material which was further purified by thin layer chromatography using hexane/ethyl acetate = 7:3 to afford pure 17 as a syrup (12 mg, 67%); $[\alpha]_D^{22}$ = + 43° (c = 0.2, chloroform); mass spectrum (chemical ionization) (isobutane) $(M^+ + H)$ 300, $(MH-MeOH)^+$ 268; ^1H NMR δ: 6.82 (d, 1H, $J_{3,NH}$ = 10 Hz, NH); 4.17 (s, 1H, H-1); 3.77 (d, 1H, $J_{3,NH}$ = 10 Hz, H-3); 3.57 (m, 4H, H-5 and OMe); 1.32 (d, 3H, $J_{5,6}$ = 7 Hz, H-6); 1.03 (s, 3H, C-4Me); 0.98 (s, 3H, C-2Me$_{ax}$); 0.96 (s, 3H, C-2Me$_{eq}$); ^{13}C NMR δ: 108.2 (C-1); 76.2 (C-4); 72.4 (C-5); 60.0 (C-3); 57.2 (OMe); 40.5 (C-2); 24.1 (C-4Me); 21.8 (C-2Me$_{eq}$); 14.8 (C-6); 13.72 (C-2Me$_{ax}$).

Anal. Calcd for $C_{12}H_{20}F_3NO_4$: C, 48.15; H, 6.73; F, 19.04; N, 4.67. Found: C, 48.30; H, 6.66; F, 18.77; N, 4.41.

Methyl 4,6-O-Benzylidene-3-C-cyano-2,3-dideoxy-2-C-dimethyl-3-trifluoroacetamido-α-D-ribo-hexopyranoside (18). Dry pyridine (12 mL) and trifluoroacetic anhydride (2.6 mL, 18.6 mmol) were successively added to a stirred solution of the aminonitrile 7 (2 g, 6.2 mmol) in ether (80 mL) at -40 °C. After 2 h at 0 °C the ethereal layer was washed with water and extracted. Filtration on silica gel using methylene chloride followed by crystallization using ethyl acetate/hexane afforded pure 18 (1.9 g, 74%); mp 202-204 °C; $[\alpha]_D^{22}$ = -29° (c = 1.24, chloroform); mass spectrum (chemical ionization) (isobutane) $(M^+ + H)$ 415; ^1H NMR δ: 8.33 (bs, 1H, NH); 7.5 and 7.42 (m, 5H, Ph); 5.71 (s, 1H, H-7); 4.5 (s, 1H, H-1); 4.36 (q, 1H, $J_{5,6eq}$ = 4 Hz, $J_{6ax,6eq}$ = 10 Hz, H-6eq); 4.27 (d, 1H, $J_{4,5}$ = 10 Hz, H-4); 3.89 (m, 2H, H-5 and H-6ax); 3.52 (s, 3H, OMe); 1.52 (s, 3H, C-2Me$_{ax}$); 1.3 (s, 3H, C-2Me$_{eq}$); ^{13}C NMR δ: 114.3 (CN); 104.7 (C-1); 102.0 (C-7); 78.4 (C-4); 68.3 (C-6); 60.0 (C-5); 58.0 (C-3); 56.2 (OMe); 42.9 (C-2); 23.7 (C-2Me$_{ax}$); 20.5 (C-2Me$_{eq}$).

Anal. Calcd for $C_{19}H_{21}F_3N_2O_5$: C, 55.07; H, 5.10; F, 13.75; N, 6.76. Found: C, 55.28; H, 5.23; F, 13.59; N, 6.81.

Methyl 4-O-Benzoyl-6-bromo-3-C-cyano-2-C-dimethyl-2,3,6-trideoxy-3-trifluoroacetamido-α-D-ribo-hexopyranoside (19). Protected α-aminonitrile 18 (1.8 g, 4.34 mmol) was reacted under the

same conditions described for 10. After 3 h, flash chromatography using hexane/ethyl acetate = 7:3 afforded pure 19 (2 g, 93%) as a crystalline product; mp 54-55 °C; $[\alpha]_D^{22}$ = -6° (c = 0.6, chloroform); mass spectrum (chemical ionization) (isobutane) (M^+ + H) 493-495; ^{1}H NMR δ: 8.7 (bs, 1H, NH); 8.03, 7.67 and 7.5 (m, 5H, Ph); 5.87 (d, 1H, $J_{4,5}$ = 10 Hz, H-4); 4.6 (s, 1H, H-1); 4.06 (m, 1H, H-5); 3.63 (m, 3H, OMe)); 3.55 (bs, 2H, CH_2Br); 1.6 (s, 3H, C-2Me_{ax}); 1.27 (s, 3H, C-2Me_{eq}); ^{13}C NMR δ: 164.6 (OCOPh); 113.5 (CN); 104.3 (C-1); 69.7 (C-4); 66.2 (C-5); 59.2 (C-3); 56.6 (OMe); 42.9 (C-2); 31.2 (C-6); 23.4 (C-2Me_{ax}); 20.1 (C-2Me_{eq}).

Anal. Calcd for $C_{19}H_{20}BrF_3N_2O_5$: C, 46.26; H, 4.08; Br, 16.19; F, 11.55; N, 5.68. Found: C, 46.11; H, 4.13; Br, 16.02; F, 11.39; N, 5.81.

Methyl 4-O-Benzoyl-3-C-cyano-2-C-dimethyl-6-iodo-2,3,6-trideoxy-3-trifluoroacetamido-α-D-ribo-hexopyranoside (20). The brominated sugar 19 (2 g, 4 mmol) was treated as described for 11. Flash chromatography using hexane/ethyl acetate = 3:1 afforded pure 20 as a syrup (1.62 g, 75%). $[\alpha]_D^{22}$ = -23° (c = 1.52, chloroform); mass spectrum (chemical ionization) (isobutane) (M^+ + H) 541; ^{1}H NMR δ: 8.63 (bs, 1H, NH); 7.98, 7.63 and 7.47 (m, 5H, Ph); 5.75 (d, 1H, $J_{4,5}$ = 10 Hz, H-4); 4.56 (s, 1H, H-1); 3.8 (m, 1H, H-5); 3.62 (s, 3H, OMe)); 3.35 (q, 1H, $J_{5,6}$ = 3 Hz, $J_{6,6'}$ = 11 Hz, H-6); 3.26 (q, 1H, $J_{5,6'}$ = 7 Hz, $J_{6,6'}$ = 11 Hz, H-6'); 1.58 (s, 3H, C-2Me_{ax}); 1.32 (s, 3H, C-2Me_{eq}); ^{13}C NMR δ: 164.9 (OCOPh); 113.6 (CN); 104.8 (C-1); 71.4 (C-4); 66.8 (C-5); 59.4 (C-3); 56.9 (OMe); 43.3 (C-2); 23.7 (C-2Me_{ax}); 20.4 (C-2Me_{eq}); 3.6 (C-6).

Anal. Calcd for $C_{19}H_{20}F_3IN_2O_5$: C, 42.24; H, 3.73; F, 10.55; I, 23.49; N, 5.18. Found: C, 42.29; H, 3.85; F, 10.41; I, 23.28; N, 5.06.

Methyl 4-O-Benzoyl-3-C-cyano-2-C-dimethyl-2,3,6-trideoxy-3-trifluoroacetamido-α-D-erythro hex-5-enopyranoside (21). Compound 20 (1.5 g, 2.7 mmol) was treated under the same conditions as 11. Flash chromatography using hexane/ethyl acetate = 3:1 afforded pure 21 as a syrup (870 mg, 78%). $[\alpha]_D^{22}$ = -50° (c = 2.89, chlo-

roform); mass spectrum (chemical ionization) (isobutane) $(M^+ + H)$ 413; $(MH-HCN)^+$ 386; ^1H NMR δ: 8.53 (bs, 1H, NH); 8.13, 7.62 and 7.48 (m, 5H, Ph); 6.18 (bs, 1H, H-4); 4.98 (bs, 1H, H-6); 4.78 (bs, 1H, H-6'); 4.62 (s, 1H, H-1); 3.55 (s, 3H, OMe); 1.62 (s, 3H, C-2Me$_{ax}$); 1.3 (s, 3H, C-2Me$_{eq}$); ^{13}C NMR δ: 164.7 (OCOPh); 147.0 (C-5); 113.9 (CN); 105.5 (C-6); 101.4 (C-1); 69.9 (C-4); 60.0 (C-3); 56.6 (OMe); 43.3 (C-2); 23.4 (C-2Me$_{ax}$); 20.5 (C-2Me$_{eq}$).

Anal. Calcd for $C_{19}H_{19}F_3N_2O_5$: C, 55.34; H, 4.64; F, 13.82; N, 6.79. Found: C, 55.49; H, 4.75; F, 13.67; N, 6.56.

Methyl 3-C-Cyano-4-O-benzoyl-2-C-dimethyl-2,3,6-trideoxy-3-trifluoroacetamido-β-L-lyxo-hexopyranoside (22). The unsaturated sugar 21 (850 mg, 2.06 mmol) was treated as described for 13. Flash chromatography (hexane/ethyl acetate = 3:1) afforded pure 22 as a syrup (730 mg, 86%); $[\alpha]_D^{22}$ = -39° (c = 1.02, chloroform); mass spectrum (chemical ionization) (isobutane) $(M^+ + H)$ 415; ^1H NMR δ: 8.06, 7.65 and 7.5 (m, 5H, Ph); 6.36 (bs, 1H, NH); 5.9 (d, 1H, $J_{4,5}$ = 3 Hz, H-4); 4.64 (s, 1H, H-1); 4.57 (bq, 1H, $J_{4,5}$ = 3 Hz, $J_{5,6}$ = 7 Hz); 3.62 (s, 3H, OMe); 1.33 (2s, 6H, C-2Me$_{ax}$ and C-2Me$_{eq}$); 1.31 (d, 3H, $J_{5,6}$ = 7 Hz, H-6); ^{13}C NMR δ: 165.0 (OCOPh); 114.8 (CN); 104.7 (C-1); 69.3 (C-4); 69.0 (C-5); 59.5 (C-3); 57.4 (OMe); 41.4 (C-2); 21.2 (C-2Me$_{eq}$); 16.4 (C-6); 15.4 (C-2Me$_{ax}$).

Anal. Calcd for $C_{19}H_{21}F_3N_2O_5$: C, 55.07; H, 5.11; F, 13.75; N, 6.76. Found: C, 55.29; H, 5.25; F, 13.61; N, 6.70.

Methyl 3-C-Cyano-2-C-dimethyl-2,3,6-trideoxy-3-trifluoroacetamido-β-L-lyxo-hexopyranoside (23). Compound 22 (400 mg, 0.97 mmol) was treated as 14. Flash chromatography using hexane/ethyl acetate = 6:4 afforded pure 23 as a syrup (250 mg, 83%). $[\alpha]_D^{22}$ = + 37° (c = 0.56, chloroform); mass spectrum (chemical ionization) (isobutane) $(M^+ + H)$ 311; ^1H NMR δ: 6.98 (bs, 1H, NH); 4.47 (s, 1H, H-1); 4.20 (q, 1H, $J_{5,6}$ = 7 Hz, H-5); 4.05 (bs, 1H, H-4); 3.55 (s, 3H, OMe); 2.70 (bs, 1H, OH); 1.40 (d, 3H, $J_{5,6}$ = 7 Hz, H-6); 1.25 (s, 3H, C-2Me$_{ax}$); 1.10 (s, 3H, C-2Me$_{eq}$); ^{13}C NMR δ: 118.3 (CN); 105.1 (C-1); 71.6 (C-4); 69.7 (C-5);

59.9 (C-3); 57.4 (OMe); 42.9 (C-2); 22.4 (C-2Me$_{eq}$); 16.1 (C-6); 15.5 (C-2Me$_{ax}$).

Anal. Calcd for $C_{12}H_{17}F_3N_2O_4$: C, 46.45; H, 5.52; F, 18.36; N, 9.02. Found: C, 46.69; H, 5.33; F, 18.52; N, 9.13.

Methyl 3-C-Cyano-2-C-dimethyl-2,3,6-trideoxy-3-trifluoroacetamido-β-L-threo-hexopyranosid-4-ulose (24). Compound 23 (250 mg, 0.8 mmol) was treated as 15. Flash chromatography using hexane/ethyl acetate = 3:1 afforded pure 24 as a syrup (235 mg, 94%). $[\alpha]_D^{22}$ = -26° (c = 1.16, chloroform); mass spectrum (chemical ionization) (isobutane) (M^+ + H) 309; ^{1}H NMR δ: 7.20 (bs, 1H, NH); 5.0 (s, 1H, H-1); 4.78 (q, 1H, $J_{5,6}$ = 7 Hz, H-5); 3.6 (s, 3H, OMe); 1.45 (d, 3H, $J_{5,6}$ = 7 Hz, H-6); 1.37 (s, 3H, C-2Me$_{ax}$); 0.9 (s, 3H, C-2Me$_{eq}$); ^{13}C NMR δ: 193.1 (C-4); 112.4 (CN); 103.6 (C-1); 71.8 (C-5); 64.0 (C-3); 57.7 (OMe); 52.0 (C-2); 21.6 (C-2Me$_{eq}$); 14.9 (C-2Me$_{ax}$ + C-6).

Anal. Calcd for $C_{12}H_{15}F_3N_2O_4$: C, 46.75; H, 4.90; F, 18.48; N, 9.08. Found: C, 46.96; H, 4.79; F, 18.45; N, 9.35.

Methyl 3-C-Cyano-2-C-dimethyl-4-methyl-2,3,6-trideoxy-3-trifluoroacetamido-β-L-lyxo-hexopyranoside (25). The ketone 24 (200 mg, 0.7 mmol) was treated under the same conditions as 15, but the temperature of the reaction was kept at -78 °C. Flash chromatography using hexane/ethyl acetate = 6:4 afforded pure 25 as a syrup (185 mg, 80%). $[\alpha]_D^{22}$ = + 62° (c = 1.32, chloroform); mass spectrum (chemical ionization) (isobutane) (M^+ + H) 325; ^{1}H NMR δ: 6.9 (bs, 1H, NH); 4.46 (s, 1H, H-1); 4.02 (q, 1H, $J_{5,6}$ = 7 Hz, H-5); 3.52 (s, 3H, OMe); 2.38 (bs, 1H, OH); 1.37 (s, 3H, C-2Me$_{ax}$); 1.29 (d, 3H, $J_{5,6}$ = 7 Hz, H-6); 1.26 (s, 3H, C-4Me); 1.03 (s, 3H, C-2Me$_{eq}$); ^{13}C NMR δ: 115.7 (CN); 105.3 (C-1); 76.0 (C-4); 73.5 (C-5); 63.2 (C-3); 57.5 (OMe); 45.6 (C-2); 23.8 (C-4Me); 21.3 (C-2Me$_{eq}$); 16.0 (C-6); 14.0 (C-2Me$_{ax}$).

Anal. Calcd for $C_{13}H_{19}F_3N_2O_4$: C, 48.14; H, 5.90; F, 17.57; N, 8.63. Found: C, 48.80; H, 5.96; F, 17.41; N, 8.75.

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