A stereoselective synthesis of 6,6,6-trifluoro-L-daunosamine and 6,6,6-trifluoro-L-acosamine†

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A short synthesis of 6,6,6-trifluoro-L-acosamine **15** and 6,6,6-trifluoro-L-daunosamine **19** has been accomplished. The pyranose ring system of these carbohydrate analogues was formed by a hetero-Diels–Alder reaction of vinylogous imide **11** and ethyl vinyl ether which gave adduct **12a** in 40% yield. Hydroboration gave **13** and subsequent hydrogenolytic removal of the (*R*)-2-phenylethyl chiral auxiliary gave ethyl 6,6,6-trifluoro-L-acosaminide **14**. Acid hydrolysis furnished target **15**. Glycoside **13** was *N*-trifluoroacetylated to give **16**, the structure was confirmed by single crystal X-ray diffraction. The C-4 stereochemistry of **16** was inverted by Swern oxidation of the 4-OH group, and subsequent borohydride reduction to give **17**. Hydrogenolytic removal of the auxiliary gave ethyl-6,6,6-trifluoro-L-daunosaminide **18**. Acid hydrolysis provided **19**.

Introduction

Takagi *et al.*[1–3] have reported the syntheses of several trifluorinated analogues of daunomycin **1** and adriamycin **2** which have shown good antitumour activities. The analogues, **3**–**5**, incorporated 2,6-dideoxy-6,6,6-trifluoro-L-*lyxo*-hexopyranosyl and 2,3,6-trideoxy-3-amino-6,6,6-trifluoro-L-*lyxo*-hexopyranosyl (6,6,6-trifluoro-L-daunosamine) residues as the carbohydrate moiety. They reasoned that the strongly electron-withdrawing C-5 trifluoromethyl group of the sugar would stabilise the glycosidic bond against acid hydrolysis and, due to its high lipophilicity, would facilitate cellular uptake of the compound. Anthracycline **3** showed stronger activity than adriamycin **1** against murine leukaemia L1210 *in vivo* in the low dose range[1] and both **4** and **5** showed 60 to 70 fold stronger activity against human epitheliod carcinoma (HeLa) and human leukaemia (HL60) *in vitro*.[2]

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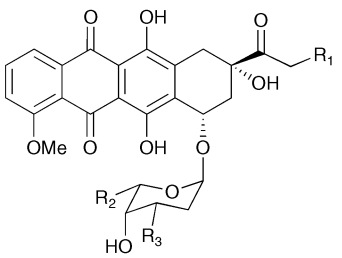
† Electronic supplementary information (ESI) available: HPLC data, NMR spectra, molecular structures, and tables of bond lengths and angles. See DOI: 10.1039/b606055b

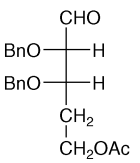
The synthesis of the carbohydrate moiety of **3** involved modification of a tosylated methyl L-*lyxo*-hexopyranoside derivative using an eleven-step reaction sequence where trifluoromethylation was effected by a fluoride catalysed addition of $TMSCF_3$ to the intermediary aldehyde **6**.[1] In a similar fashion, Takagi *et al.*[2] developed a synthesis of a glycosyl donor for the preparation of **4** and **5** from carbohydrate-derived intermediate **7** in a multi-step sequence.

In earlier work, Taguchi *et al.*[4] have reported the synthesis of the *p*-nitrobenzoyl glycoside of a protected 6,6,6-trifluoro-L-daunosamine derivative starting from 2,3-*O*-cyclohexylidene-L-glyceraldehyde, also in eleven steps. The critical trifluoromethylation of the glyceraldehyde was achieved upon treatment with trifluoromethyl iodide and zinc dust.

Tietze *et al.*[5] have reported a hetero-Diels–Alder approach to racemic 3-amino-carbohydrate derivatives and we have previously described the syntheses of 2,6-dideoxy-6,6,6-trifluoro-D- and L-*arabino*-hexose using the Diels–Alder reaction of hetero-diene **8** and ethyl vinyl ether.[6,7] We now report on a short and efficient synthesis of 6,6,6-trifluoro-L-acosamine and 6,6,6-trifluoro-L-daunosamine derivatives using an adaptation of this method.



1 R_1 = H, R_2 = CH_3, R_3 = NH_2
2 R_1 = OH, R_2 = CH_3, R_3 = NH_2
3 R_1 = OH, R_2 = CF_3, R_3 = OH
4 R_1 = H, R_2 = CF_3, R_3 = NH_2
5 R_1 = OH, R_2 = CF_3, R_3 = NH_2



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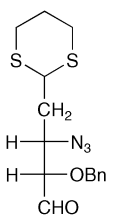

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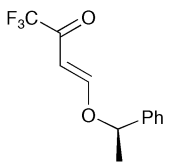

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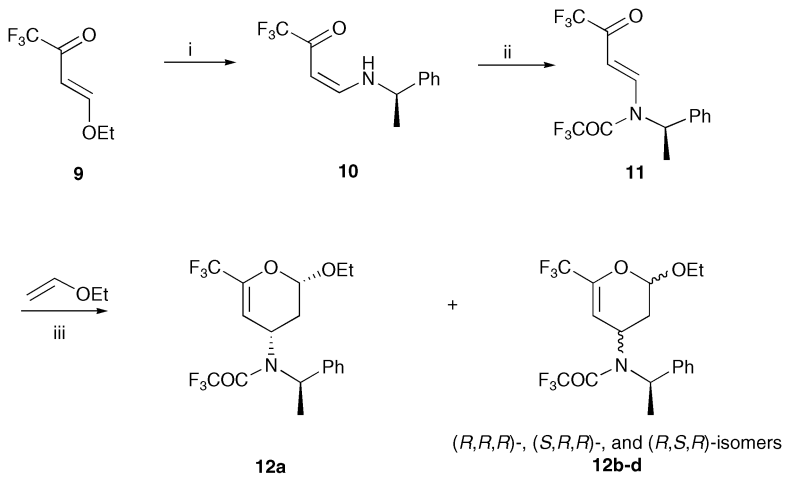


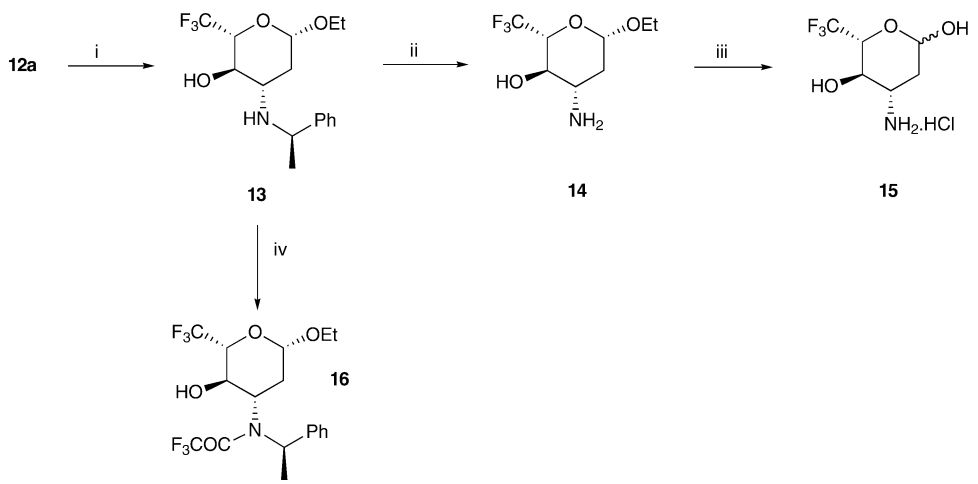
Scheme 1 Reagents and conditions: (i) (*R*)-α-methylbenzylamine; CH_2Cl_2, 0 °C; (ii) TFAA, py, CH_2Cl_2, 0 °C (96% from **9**); (iii) 60–65 °C, 42 h (40% of **12a**).

Discussion

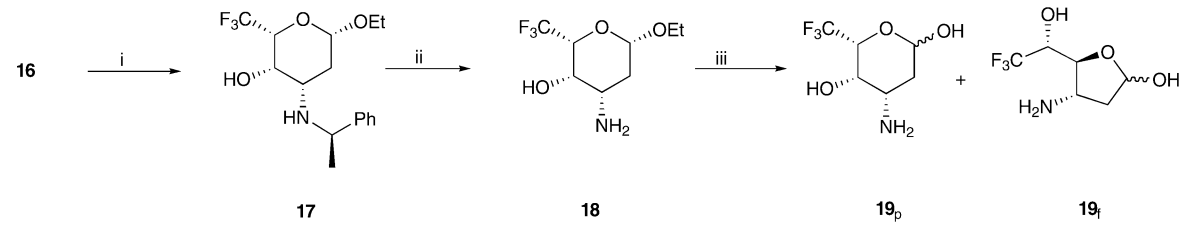
Reaction of trifluorinated vinylogous ester **9** with (*R*)-α-methylbenzylamine gave vinylogous amide **10** (Scheme 1). Treatment with trifluoroacetic anhydride and pyridine gave the heterodiene **11** in 96% yield for the two steps. The thermal Diels–Alder reaction of **11** and ethyl vinyl ether proceeded slowly and, after 2 d, the reaction was close to completion. The ^{1}H NMR spectrum of the crude reaction product gave little information on its composition due to peak overlap and signal broadening presumably due to amide isomerism. The crude product was found to contain a mixture of four cycloadducts **12a**–**d** in an approximately 8 : 3 : 1 : 1.5 ratio based upon integration of the resonances for the trifluoromethyl and C-5 trifluoromethyl groups in the ^{19}F NMR spectrum and analysis by reverse phase (C-18) HPLC. Partial separation of two of the minor isomers, **12c** and **12d** by preparative HPLC aided these analyses. Purification of the crude product by column chromatography and crystallisation gave the major cycloadduct **12a** in 40% yield in multigram quantities. The spectral and analytical data were consistent with **12a** and its absolute structure was determined by a crystallographic study of a derivative (*vide supra*).‡ The signals in the ^{1}H NMR spectrum of **12a** were also broadened and the ^{19}F NMR spectrum showed that **12a** existed as an approximately 9 : 1 mixture of isomers about the amide bond. Attempts were unsuccessfully made to remove the trifluoroacetamido moiety to simplify the structural analysis by NMR. Unfortunately, this group was remarkably resilient to both acid and base promoted hydrolysis.

Hydroboration of **12a** gave, after workup with alkaline hydrogen peroxide, ethyl glycoside **13** in 37% yield (69% corrected yield) along with 48% recovered starting material (Scheme 2). Concomitant hydrolysis of the amide occurred under the reaction conditions, presumably due to participation of the C-4 hydroxyl group. Attempts to optimise the conversion of **12a** to **13** by increasing the reaction time for the hydroboration resulted in a

‡ CCDC reference number 605958. For crystallographic data in CIF format see DOI: 10.1039/b606055b



Scheme 2 Reagents and conditions: (i) $BH_3{\cdot}SMe_2$, CH_2Cl_2, 4 °C, 42 h then H_2O_2, 3 M NaOH, THF, MeOH (69% corrected); (ii) H_2, 10% Pd on C, EtOAc, 17 h (100%); (iii) aqueous 0.5 M HCl, 100 °C (100%); (iv) TFAA, py then IRA 400 (OH) resin, MeOH (84%).



Scheme 3 Reagents and conditions: (i) *a.* DMSO, $(COCl)_2$, −60 °C, **16**, 2 h, *b.* NEt_3, rt, *c.* $NaBH_4$, IPA, rt (78%); (ii) H_2, 10% Pd on C, EtOAc (85%); (iii) aqueous 0.5 M HCl, 100 °C (100%).

complex mixture of products due to a combination of reduction of the trifluoroacetamido and loss of the 2-phenethyl groups.

The NMR spectral data were consistent with the proposed structure of **13**. The doublet at δ −77.7 ppm ($^3J_{F-H}$ 6.1 Hz) in the ^{19}F NMR spectrum confirmed the success of the hydroboration. The coupling constants for the signals assigned to H-1 ($^3J_{1,2ax}$ 9.7 Hz) and H-4 ($^3J_{3,4}$ and $^3J_{4,5}$ 9.3 Hz) indicated that **13** existed in a chair-like conformation. Hydrogenolysis of the α-methylbenzyl group was effected under standard conditions to give ethyl 6,6,6-trifluoro-β-L-acosamidine **14** in quantitative yield. Acosaminide **14** was hydrolysed under acidic conditions to give acosamine **15** which was isolated as the hydrochloride salt. The ^1H NMR spectrum, recorded in D_2O showed that **15** existed as a 1.9 : 1 mixture of the α- and β-pyranose forms.

The structures of **12a**, **13** and **14** and **15** were unambiguously confirmed from the following synthetic sequence (Scheme 2). Trifluoroacetylation of **13** and subsequent hydrolysis of the trifluoroacetate group gave **16** in 84% yield. Single crystals of **16** were obtained from dichloromethane and hexanes and an X-ray diffraction study confirmed its structure and revealed that each of the two unique molecules in the unit cell possessed an L-*arabino*-configuration based upon the (*R*)-phenylethyl chiral auxiliary (Fig. 1).‡ Small differences in the bond distances and angles may be ascribed to crystal packing effects with a significant variation of the ethoxy substituent with C-1–O1–C-1′–C-2′ torsion angles 164.6(2) and 173.48(19)°, respectively.

The next objective of the study was to invert the stereochemistry at C-4 of the acosamine derivative to produce a daunosamine analogue. This was achieved by Swern oxidation of **16** and subsequent reduction of the ketone intermediate with sodium borohydride to give the L-*lyxo* glycoside **17** in 78% yield. As before, removal of the α-methylbenzyl group was effected by catalytic hydrogenolysis which gave ethyl 6,6,6-trifluoro-β-L-daunosaminide **18** in 85% yield (Scheme 3).

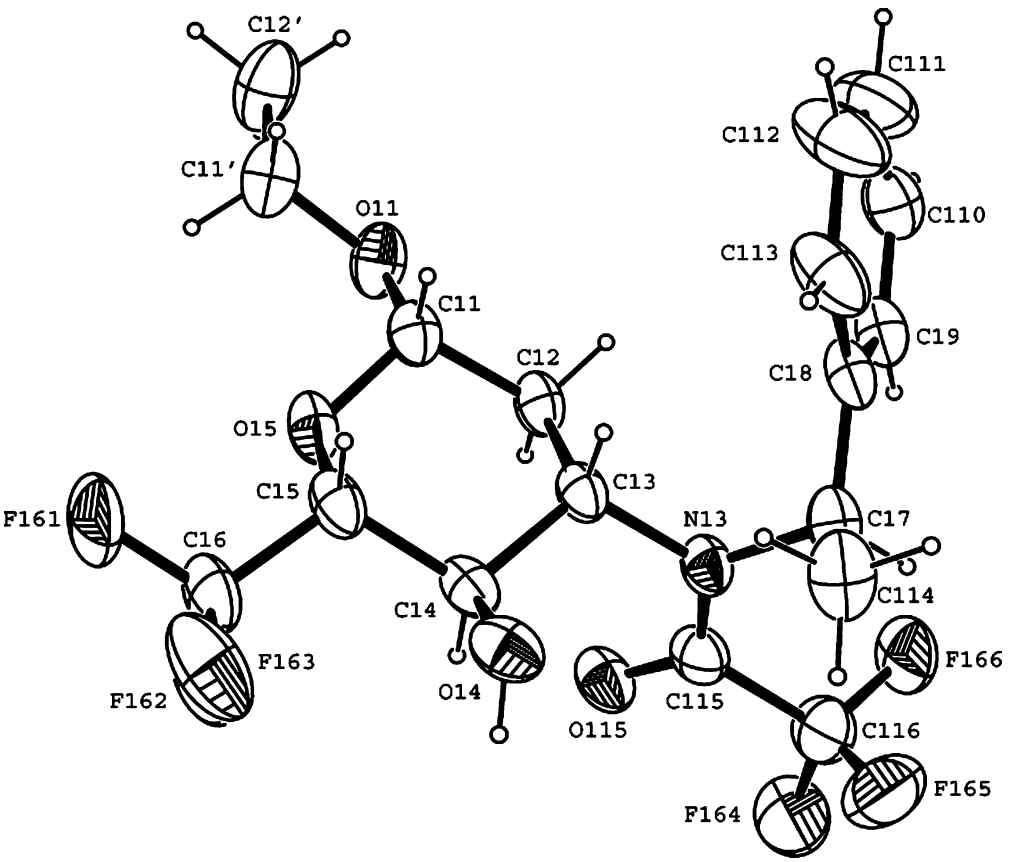


Fig. 1 Perspective view of one of the unique molecules of **16** with displacement ellipsoids drawn at the 50% probability level.

Hydrolysis of **18** in 0.5 M hydrochloric acid gave 6,6,6-trifluoro-L-daunosamine hydrochloride **19** in near quantitative yield. In D_2O **19** existed as an approximately 8 : 4 : 3 : 1 mixture of **19**α_p: **19**β_p: **19**α_f: **19**β_f forms at room temperature based upon its ^1H and ^{19}F NMR spectra. The assignment of anomeric configurations of the pyranose forms of **19** was made by comparison with the chemical shifts and coupling constants of the anomeric protons to those of **15**. The assignment of the anomeric configurations of the furanose forms of **19** are tentative.

In summary, we have reported a short and facile synthesis of 6,6,6-trifluoro-L-acosamine **15** and 6,6,6-trifluoro-L-daunosamine **19** from cheap and readily available starting materials. Other 6,6,6-trifluoro-3-amino-hexoses would be available by minor modifications of this methodology. We are currently utilising these fluorinated carbohydrates for the preparation of a range of anthracycline and angucycline analogues.

General experimental

Melting points were measured on a Mettler Toledo FP52 melting point apparatus or a Reichardt hot stage and are uncorrected. ^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Varian VXRS300 spectrometer. Chemical shifts are reported as parts per million. Deuteriochloroform samples are referenced to the residual chloroform (δ_H 7.26, δ_C 77.08), and D_2O samples are referenced to dioxane as an internal standard (δ_H 3.74, δ_C 67.4). All ^{19}F spectra are referenced to an external standard of 5% trifluoroacetic acid in $CDCl_3$ (δ_F −78.5). All IR spectra were recorded on a Perkin Elmer Spectrum BX FT-IR spectrophotometer. Optical rotations were recorded on a Jasco DIP-1000 digital polarimeter. Mass spectra (EI) were recorded at the University of Canterbury, New Zealand on a Kratos MS80RFA mass spectrometer operating with an accelerating voltage of 4 kV and an ionisation energy of 70 eV. Electrospray ionisation mass spectra were recorded on a micromass LCT mass spectrometer. Elemental analyses were carried out the Campbell Microanalytical Laboratory, University of Otago, Dunedin, New Zealand. Flash column chromatography was carried out using silica-gel (Merck 60 Å, 230–400 mesh). Thin layer chromatography was performed on silica-gel precoated aluminium plates, (Merck 60 Å, F254, 0.2 mm) and were visualised under a UV lamp and with alkaline $KMnO_4$ or phosphomolybdic acid dips with subsequent heating. Analytical HPLC was performed using a Jasco PU-980 pump and a Jasco UV-975 detector set at 254 nm equipment on a Phenomonex Luna RP-C18 (200 mm × 5 mm) column using 80% aqueous methanol with 0.1% TFA as the mobile phase with a flow rate of 1 ml min^{-1}. Dichloromethane was distilled from P_2O_5. All other solvents and reagents were purified using standard methods.[8]

(*Z*)-4-[(1*R*)-phenethylamino]-1,1,1-trifluorobutenone (10)

(*R*)-α-Methylbenzylamine (7.8 g, 64 mmol) was added to a cold (ice bath) stirred solution of **9** (10.9 g, 65 mmol) in CH_2Cl_2 (50 mL) over a period of 5 min. Concentration under reduced pressure gave the title compound **10** (16.0 g, 100%) as a slightly impure brown oil that was used without further purification; ^1H NMR (200 MHz, $CDCl_3$) *inter alia* 1.64 (3H, d, *J* 7 Hz, CH_3), 4.59 (1H, apparent quin, separation 7 Hz, C*H*(Ph)CH_3), 5.38 (1H, d, *J* 7 Hz, H-3), 7.12 (1H, dd, *J* 7, 13.5 Hz, H-4), 7.25–7.45 (5H, m, Ph), 10.40–10.70 (1H, br s, NH).

(*E*)-4-[(1*R*)-phenethyltrifluoroacetamido]-1,1,1-trifluorobutenone (11)

Trifluoroacetic anhydride (16.2 g, 77 mmol) was added to a cooled (ice bath) stirred solution of **10** (15.5 g, 64 mmol) and pyridine (6.1 g, 77 mmol) in CH_2Cl_2 (40 mL) under a N_2 atmosphere over a period of 10 min. The cooling bath was removed and the reaction mixture was left to stand for 4 h. The reaction mixture was concentrated under reduced pressure and the residue was suspended in hexane (50 mL) and filtered through a sintered glass funnel. Concentration of the filtrate and Kugelrohr distillation (115–120 °C, 0.1 mm Hg) gave the title compound **11** (21.0 g, 96%) as a pale-yellow oil; $[a]_D^{22}$ +56.5 (*c* 1.1, CH_2Cl_2); υ_{max} (neat)/cm^{-1} 3068, 3035, 2990, 2950, 1784 (C=O), 1731 (C=O), 1599; ^1H NMR (300 MHz, $CDCl_3$) δ 1.84 (3H, d, *J* 7.1 Hz, CH_3), 5.89 (1H, q, *J* 7.1 Hz, C*H*(Ph)CH_3), 6.17 (1H, d, *J* 13.8 Hz, H-3), 7.22–7.44 (5H, m, Ph), 7.95 (1H, d, *J* 13.8 Hz, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9 (CH_3), 55.6 (*C*H(Ph)CH_3), 105.7, 115.8 (q, *J* 289 Hz, CF_3), 116.0 (q, *J* 290 Hz, CF_3), 126.2, 128.6, 129.3, 136.7, 142.1, 157.4 (q, *J* 38 Hz, CO), 179.3 (q, *J* = 36 Hz, CO); ^{19}F NMR (282 MHz, $CDCl_3$) δ −81.0 (s, CF_3), −70.3 (s, CF_3); *m*/*z* (EI) 339 (M^+, 58%), 243 (M^+- 96, 54%), 105 (M^+-234, 100%); found: C, 49.86; H, 3.51; N, 4.27; F, 33.81%. $C_{14}H_{11}F_6NO_2$ requires C, 49.57; H, 3.27; N, 4.13; F, 33.6.

(2*S*,4*S*)-*cis*-2-Ethoxy-4-[(1*R*)-phenethyltrifluoroacetamido]-6-trifluoromethyl-3,4-dihydro-2*H*-pyran (12a)

A solution of **11** (14.9 g, 44 mmol) and ethyl vinyl ether (15 g, 208 mmol) was split into three equal portions and heated in three screw cap test tubes for 42 h in an oil bath maintained between 60–65 °C. The portions were recombined and excess ethyl vinyl ether was removed under reduced pressure. The residue was passed through a silica column (gradient elution, 1 to 2.5% ether–hexanes). Fractions containing the target cycloadducts (R_f = 0.36, 10% ether–hexanes) were collected and concentrated. Crystallisation from hexanes afforded the title compound **12a** (7.3 g, 40%) as a white solid; mp 101 °C; $[a]_D^{21}$ −24.5 (*c* 0.64, CH_2Cl_2); υ_{max} (KBr)/cm^{-1} 3447 (br, OH), 3100, 3072, 3042, 2989 2942, 2904, 1687 (C=O); ^1H NMR (300 MHz, $CDCl_3$, −50 °C) δ *inter alia* 1.04 (0.9H, br dd, *J* 6.6, 11.8 Hz, 0.9 of H-3) 1.14 (3H, t, *J* 7.1 Hz, CH_2CH_3), 1.68 (2.7H, d, *J* 6.7 Hz, CH(Ph)CH_3), 1.80 (0.3H, d, *J* 7.0 Hz, CH(Ph)CH_3), 2.10–2.20 (0.1H, m, 0.1 of H-3), 2.34–2.43 (0.1H, m, 0.1 of 3-H), 2.50 (0.9H, q, *J* 11.3 Hz, 0.9 of H-3), 3.41 (0.9H, qd, *J* 7.1, 9.1 Hz, 0.9 of CH_2CH_3), 3.53–3.63 (0.1H, m, 0.1 of CH_2CH_3), 3.78–4.05 (2H, m, H-4, 1 of CH_2CH_3), 4.54 (0.1H, q, *J* 7.0 Hz, 0.1 of C*H*(Ph)CH_3), 4.70 (0.9H, d, *J* 9.0 Hz, H-2), 4.92–5.02 (0.1H, br s, H-2), 5.18–5.32 (1.8H, m, 0.9 of H-5, 0.9 of C*H*(Ph)CH_3), 7.18–7.42 (5H, m, Ph); ^{19}F NMR (282 MHz, $CDCl_3$) for the major amide isomer/rotamer δ −69.3 (CF_3CO), −73.6 (3F, d, *J* 1 Hz, 6-F_3); for the minor amide isomer/rotamer δ −69.7 (3F, br s, CF_3CO), −73.7 (3F, br s, *J* 1 Hz, 6-F_3); *m*/*z* (EI) 411 (M^+, 9%), 365 (M^+-46, 8%), 339 (M^+-72, 14%), 306 (M^+-105, 68%), 105 (M^+-306, 100%); found: C, 52.42; H, 4.61; N, 3.47; F, 27.94%. $C_{18}H_{19}F_6NO_3$ requires C, 52.56; H, 4.66; N, 3.41; F, 27.71.

Small quantities of **12c** and **12d** were obtained by HPLC separation on a Merck Lichrospher RP18 (10 μ) 250 mm × 20 mm column using 80% aqueous methanol as the mobile phase with a flow rate of 4 ml min^{-1}.

For **12c**, 9 : 1 mixture of amide isomers/rotamers; for the major amide isomer/rotamer ^{19}F NMR (282 MHz, $CDCl_3$) δ −69.1 (3F, s, CF_3CO), −73.7 (3F, d, *J* 2.5 Hz, 6-F_3); for the minor amide isomer/rotamer ^{19}F NMR (282 MHz, $CDCl_3$) δ −70.1 (3F, br s, CF_3CO), −73.9 (3F, br s, *J* 1 Hz, 6-F_3).

For **12d**, 17 : 1 mixture of amide isomers/rotamers; for the major amide isomer/rotamer ^{19}F NMR (282 MHz, $CDCl_3$) δ −69.1 (3F, s, CF_3CO), −73.6 (3F, d, *J* 2.5 Hz, 6-F_3); for the minor amide isomer/rotamer ^{19}F NMR (282 MHz, $CDCl_3$) δ −70.0 (3F, br s, CF_3CO), −73.8 (3F, br s, *J* 1 Hz, 6-F_3).

Ethyl 4-amino-4-*N*-[(1*R*)-phenethyl]-6,6,6-trifluoro-2,3,6-trideoxy-β-L-*arabino*-hexopyranoside (13)

$BH_3{\cdot}S(CH_3)_2$ (3.0 mL, 30 mmol) was added to a cooled (ice-bath) solution of **12a** (5.0 g, 12 mmol) in dry CH_2Cl_2 (200 mL) under an atmosphere of N_2. The reaction was left at 4 °C for 42 h. Methanol (30 mL), THF (80 mL) and 1 : 1 mixture of 3 M NaOH and 30% H_2O_2 (100 mL) were cautiously added and the reaction mixture was stirred vigorously at ambient temperature for 2 h. Potassium carbonate (50 g) was added and the reaction mixture was stirred for a further 5 min, transferred to a separating funnel and diluted with hexane (100 mL). The phase was separated and back extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. Purification by silica-gel column chromatography (2.5–30% ethyl acetate–hexanes as eluent) gave recovered **12a** (2.3 g, 48%) and the title compound **13** (1.5 g, 37%) as a hygroscopic white solid; $[\alpha]_D^{22}$ +147 (*c* 0.30, CH_2Cl_2); υ_{max} (KBr)/cm^{-1} 3846 (OH), 3029, 2979, 2932, 2891; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (3H, t, *J* 7.1 Hz, CH_2CH_3), 1.37 (3H, d, *J* 6.5 Hz, CH(Ph)CH_3), 1.28–1.42 (1H, m, H-2_{ax}), 2.29–2.42 (2H, m, H-2_{eq} and 3-H), 3.40 (1H, t, *J* = 9.3 Hz, H-4), 3.50 and 3.52 (1H each, 2 × overlapping qd, *J* 7.1, 9.5 Hz and *J* 6.1, 9.3 Hz, CH_2CH_3, H-5), 3.92 (1H, qd, *J* 7.1, 9.5 Hz, 1 of CH_2CH_3) overlapping with 3.96 (1H, q, *J* 6.5 Hz, CH(Ph)CH_3), 4.40 (1H, dd, *J* 2.0, 9.7 Hz, H-1), 7.20–7.40 (5H, m, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.1, 25.5, 35.6, 54.2, 55.7, 65.1, 69.1, 74.5 (q, *J* 31 Hz, C-5), 100.8 (C-1), 123.6 (q, *J* 281 Hz, C-6), 126.6, 127.5, 128.8, 140.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −77.7 (d, *J* 6.1 Hz, F-6); *m*/*z* (EI) 333 (M^+, 19%), 318 (M^+-15, 68%), 288 (M^+-45, 44%), 204 (M^+-129, 70%), 105 (M^+-228, 100%); found: C, 57.35; H, 6.50; N, 4.23; F, 16.98%. $C_{16}H_{22}F_3NO_3$ requires C, 57.65; H, 6.65; N, 4.20; F, 17.10.

Ethyl 3-amino-2,3,6-trideoxy-6,6,6-trifluoro-β−L-*arabino*-hexopyranoside (14)

A mixture of **13** (276 mg, 0.84 mmol) and 10% Pd/C (30 mg) in ethyl acetate (10 mL) was stirred under an atmosphere of H_2 for 17 h. Filtration through a Celite pad and removal of the solvent gave the title compound **14** (190 mg, 100%) as a white solid. A small sample was purified by column chromatography (10% methanol–ethyl acetate) for analysis; $[\alpha]_D^{23}$ +65.4 (*c* 0.65, MeOH); υ_{max} (KBr)/cm^{-1} 3551, 3475, 3412 3340, 3282, 2953, 2895, 2862, 1618; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (3H, t, *J* 7.1 Hz, CH_3), 1.53 (1H, ddd, *J* 9.6, 12.3, 12.8 Hz, H-2_{ax}), 1.62–1.98 (3H, br s, NH_2, OH), 2.13 (1H, ddd, *J* 2.0, 4.4, 12.8 Hz, H-2_{eq}), 2.80 (1H, ddd, *J* 4.4, 9.3, 12.3 Hz, H-3), 3.39 (1H, t, *J* 9.3 Hz, H-4), 3.56 (1H, dq, *J* 9.6, 7.1 Hz, 1 of CH_2CH_3), 3.65 (1H, qd, *J* 6.2, 9.3 Hz, H-5), 3.95 (1H, dq, *J* 9.6, 7.1 Hz, 1 of CH_2CH_3), 4.60 (1H, dd, *J* 2.0, 9.6 Hz, H-1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.1 (CH_3), 39.0 (C-2), 52.6, 65.2 (CH_2CH_3), 70.9, 74.6 (q, *J* 29 Hz, C-5), 100.6 (C-1), 123.8 (q, *J* 281 Hz, C-6); ^{19}F NMR (282 MHz, $CDCl_3$) δ −77.2 (3F, d, *J* 6.2 Hz, F-6); *m*/*z* (ESI) 230 (MH^+, 100%); found: *m*/*z* 2320.0997 (MH^+). $C_8H_{15}NO_3F_3$ requires *m*/*z* 230.1004.

3-Amino-2,3,6-trideoxy-6,6,6-trifluoro-L-*arabino*-hexopyranose hydrochloride (15)

A solution of **14** (220 mg, 1.0 mmol) in 0.5 M HCl (10 mL) was heated over a steam bath for 1 h. Concentration under reduced pressure afforded the title compound **15** (230 mg, 100%) (*α* : *β* 1.9 : 1) as a white powder; $[\alpha]_D^{24}$ −17.2 (*c* 0.4, H_2O, 12 h); υ_{max} (KBr)/cm^{-1} 3384, 2961, 1617, 1598; ^1H NMR (300 MHz, D_2O) δ 1.76 (0.34H, ddd, *J* 9.6, 12.6, 12.7 Hz, β-H-2_{ax}), 1.97 (0.66H, ddd, *J* 3.5, 12.5, 13.4 Hz, α-H-2_{ax}), 2.25 (0.66H, ddd, *J* 1.4, 4.4, 13.4 Hz, α-H-2_{eq}), 2.40 (0.34H, ddd, *J* 2.1, 4.6, 12.7 Hz, β-H-2_{eq}), 3.50 (0.34H, ddd, *J* 4.6, 10.1, 12.6 Hz, β-H-3), 3.65 (0.66H, ddd, *J* 4.4, 10.3, 12.5 Hz, α-H-3), 3.79–3.90 (1H, m, H-4), 4.02 (0.34H, dq, *J* 6.3, 9.4 Hz, β-H-5), 4.39 (0.66H, dq, *J* 6.5, 9.6 Hz, α-H-5), 5.12 (0.34H, dd, *J* 2.1, 9.6 Hz, β-H-1), 5.48–5.18 (0.66H, m, α-H-1); ^{13}C NMR (75 MHz, D_2O) δ 33.9 (α-C-2), 35.7 (β-C-2), 49.8 (α-C-3), 52.1 (β-C-3), 66.8 (β-C-4), 67.0 (α-C-4), 70.0 (q, *J* 29 Hz, α-C-5), 74.1 (q, *J* 30 Hz, β-C-5), 91.2 (α-C-1), 94.5 (β-C-1), 123.9 (q, *J* 280 Hz, β-C-6), 124.6 (q, *J* 280 Hz, α-C-6); ^{19}F NMR (282 MHz, D_2O) δ −77.2 (1F, d, *J* 6.3 Hz, β-F-6), −76.9 (2F, d, *J* 6.5 Hz, α-F-6); *m*/*z* (ESI) 202 (MH^+, 100%), 184 (M^+-OH, 55%); found: *m*/*z* 202.0682 (MH^+). $C_6H_{11}NO_3F_3$ requires *m*/*z* 202.0691.

Ethyl 4-trifluoroacetamido-4-*N*-[(1*R*)-phenethyl]-6,6,6-trifluoro-2,3,6-trideoxy-β-L-*arabino*-hexopyranoside (16)

A stirred solution of **13** (520 mg, 1.6 mmol) and pyridine (190 mg, 2.4 mmol) in CH_2Cl_2 (10 mL) under an N_2 atmosphere was cooled in an ice-water bath. Trifluoroacetic anhydride (980 mg, 4.4 mmol) was added dropwise and the reaction flask was left in the cooling bath for 2 h and then for a further 2 h at ambient temperature. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and poured into a stirring saturated $NaHCO_3$ solution. The organic layer was washed with 1 M HCl, dried (Na_2SO_4) and concentrated under reduced pressure. The resultant oil (800 mg) was dissolved in reagent grade methanol (10 mL) and stirred in the presence of Amberlite® 400 (OH^-) ion exchange resin for 1.75 h. A further 100 mg of fresh resin was added and stirring continued for another 15 min. Filtration and concentration under reduced pressure gave a colourless oil. Purification by column chromatography (10% ethyl acetate–hexanes) gave the title compound **16** (565 mg, 84%) as a white solid; mp 144 °C (CH_2Cl_2/hexanes); $[\alpha]_D^{21}$ +137 (*c* 0.49, CH_2Cl_2); υ_{max} (KBr)/cm^{-1} 3470 (OH), 2989, 1669 (C=O), 1114, 708; ^1H NMR (300 MHz, $CDCl_3$) δ 0.78 (1H, ddd, *J* 2.2, 4.3, 12.7 Hz, H-2_{eq}), 1.09 (3H, t, *J* 7.1 Hz, CH_2CH_3), 1.68 (3H, d, *J* 6.8 Hz, CH(Ph)CH_3), 2.24 br (1H, d, *J* 4.8 Hz, OH), 2.36 (1H, ddd, *J* 9.7, 12.7, 12.7 Hz, H-2_{ax}), 3.06 (1H, ddd, *J* 4.3, 9.7, 12.8 Hz, H-3), 3.34 (1H, qd, *J* 7.1, 9.5 Hz, 1 of CH_2CH_3), 3.52 (1H, qd, *J* 6.1, 9.4 Hz, H-5), 3.77 (1H, qd, *J* 7.1, 9.5 Hz, 1 of CH_2CH_3),

4.02 (1H, dd, *J* 2.2, 9.5 Hz, H-1), 4.81 (1H, ddd, *J* 4.8, 9.4, 9.7 Hz, H-4), 5.32 (1H, q, *J* 6.8 Hz, C*H*(Ph)CH_3), 7.37–7.43 (5H, m, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9, 17.5, 32.7 (C-2), 55.9, 58.1, 62.6, 64.7, 75.2 (q, *J* 29 Hz, C-5), 100.1 (C-1), 116.6 (q, *J* 288 Hz, CF_3), 123.7 (q, *J* 281 Hz, CF_3), 128.1, 129.0, 129.1, 137.2, 156.4 (q, *J* 35 Hz, *C*OCF_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ −76.6 (3F, d, *J* 6.1 Hz, F-6), −70.7 (3F, s, $COCF_3$); *m/z* (EI) 429 (M^+, 13%), 414 (M^+-15, 14%), 383 (69%), 286 (19%), 216 (75%), 105 (100%); found: C, 50.31; H, 4.95; N, 3.36; F, 26.58%. $C_{18}H_{21}F_6NO_4$ requires C, 50.35; H, 4.93; N, 3.26; F, 26.55.

X-Ray data were collected at 153(2)K on a Bruker SMART CCD diffractometer, processed using SAINT, with empirical absorption corrections applied using SADABS.‡ Chemical formula $C_{18}H_{21}F_6NO_4$; formula weight = 429.36; crystal system triclinic, space group P1. Unit cell dimensions: a = 9.499(2) Å, b = 10.601(3) Å, c = 11.958(3) Å, α = 113.345(3)° β = 98.080(3)°, γ = 103.188(3)°; volume 1039.9(4) Å^3, Z = 2, absorption coefficient 0.131 mm^{-1}. Temperature 153(2) K. Reflections collected 13093, independent reflections 7146 [R(int) = 0.0232]. Final R indices [$I > 2\sigma(I)$]: $R1$ = 0.0311, $wR2$ = 0.0757; R indices (all data) $R1$ = 0.0366, $wR2$ = 0.0779.

The structure was solved using SHELXS[9] and refined by full-matrix least-squares using SHELXL-97[10] and TITAN2000.[11] Non-hydrogen atoms were assigned anisotropic temperature factors and the H atoms were included in calculated positions. Tables of bond lengths, bond angles and torsion angles are provided in the ESI.

Ethyl 4-amino-4-*N*-[(1*R*)-phenethyl]-6,6,6-trifluoro-2,3,6-trideoxy-β-L-*lyxo*-hexopyranoside (17)

A two necked 50 mL round bottomed flask containing a stirred solution of CH_2Cl_2 (5 mL) and DMSO (160 μL, 2.2 mmol) under an atmosphere of N_2 was cooled in a −60 °C dry ice–acetone bath. Oxalyl chloride (165 μL,1.9 mmol) was added dropwise and the solution was left to stir for three min before adding **16** (280 mg, 0.65 mmol) in one portion. The stirred mixture was held in the cooling bath for 2 h. Triethylamine (335 μL, 2.4 mmol) was added dropwise and after 5 min the reaction flask was removed from the cooling bath and left to stir for a further 10 min. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with 1 M HCl (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give the ketone intermediate as an impure white solid which was used without purification in the next step; ^{1}H NMR (200 MHz, $CDCl_3$) δ *inter alia* 1.14 (3H, t, *J* 7 Hz, CH_2CH_3), 1.38–1.51 (1H, m, 1 of H-2), 1.64 (3H, d, *J* 8 Hz, CH(Ph)C***H***$_3$), 2.74 (1H, ddd, *J* 9, 13, 13 Hz, 1 of H-2), 3.40 (1H, dq, *J* 7, 9.5 Hz, 1 of C***H***$_2$CH$_3$), 3.59 (1H, dd, *J* 6, 13 Hz, H-3), 3.85 (1H, dq, *J* 7, 9.5 Hz, 1 of C*H*$_2$CH$_3$), 4.37 (1H, q, *J* 8 Hz, C*H*(Ph)CH_3), 4.65 (1H, dd, *J* 4.5, 9 Hz, H-1), 5.41 (1H, q, *J* 7 Hz, H-5), 7.30–7.50 (5H, m, Ph).

Water (2 mL) and $NaBH_4$ (100 mg, 2.6 mmol) were added to a solution of **16** in isopropyl alcohol (12 mL), and the mixture was stirred for 10 min. Glacial acetic acid (100 μL) was added and the mixture was concentrated under reduced pressure until most of the isopropyl alcohol had been removed. The resultant syrup was diluted with saturated $NaHCO_3$ solution (10 mL) and extracted twice with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and concentrated. Purification by column chromatography (10–15% ethyl acetate–hexanes) afforded the title compound **17** (169 mg, 78%) as a colourless syrup; $[\alpha]_D^{24}$ +60.8 (*c* 0.49, CH_2Cl_2); υ_{max} (neat)/cm^{-1} 3441 (*br*), 2977, 1144, 897, 763, 704; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (3H, t, *J* 7.1 Hz, CH_2CH_3), 1.37 (3H, d, *J* 6.3 Hz, CH(Ph)C*H*$_3$), 1.63 (1H, ddd, *J* 9.7, 12.4, 12.7 Hz, H-2$_{ax}$), 1.96 (1H, ddd, *J* 2.2, 4.8, 12.7 Hz, H-2$_{eq}$), 2.67 (1H, ddd, *J* 2.9, 4.8, 12.4 Hz, H-3), 3.47–3.65 (3H, m, 1 of C*H*$_2$CH$_3$, H-4, H-5), 3.87–4.02 (2H, m, C*H*(Ph)CH_3, 1 of C*H*$_2$CH$_3$), 4.42 (1H, dd, *J* 2.2, 9.7 Hz, H-1), 7.20–7.38 (5H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.1, 24.6, 32.3, 53.8, 55.0, 64.1, 65.0, 74.0 (q, *J* 31 Hz, C-5), 101.1 (C-1), 123.1 (q, *J* 280 Hz, C-6), 126.5, 127.4, 128.7, 144.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ −76.4 (d, *J* 6.6 Hz, 6-F); *m/z* (EI) 333 (M^+, 22%), 318 (M^+-15, 66%), 288 (M^+-45, 35%), 105 (M^+-228, 100%); found: *m/z* 334.1644 (MH^+). $C_{16}H_{22}F_3NO_3$ requires *m/z* 334.1630.

Ethyl 3-amino-2,3,6-trideoxy-6,6,6-trifluoro-β-L-*lyxo*-hexopyranoside (18)

A mixture of **17** (187 mg, 0.56 mmol) and 10% Pd/C (25 mg) in ethyl acetate (8 mL) was stirred under an atmosphere of H_2 for 5 d. Filtration through a Celite pad and removal of the solvent gave a white solid. Column chromatography (10% methanol–ethyl acetate) gave the title compound **18** (110 mg, 85%) as an amorphous white powder. $[\alpha]_D^{24}$ +25.0 (*c* 0.41, MeOH); υ_{max} (KBr)/cm^{-1} 3420 (br str, OH, NH), 1639, 1188; ^{1}H NMR (300 MHz, D_2O) δ 1.20 (3H, t, *J* 7.1 Hz, CH_3), 1.53 (1H, ddd, *J* 9.9, 12.6, 12.8 Hz, H-2$_{ax}$), 1.89 (1H, ddd, *J* 2.9, 4.5, 12.8 Hz, H-2$_{eq}$), 3.01 (1H, ddd, *J* 3.1, 4.6, 12.6 Hz, H-3), 3.71 (1H, qd, *J*.7.1, 7.8 Hz, 1 of C*H*$_2$CH$_3$), 3.90–4.03 (2H, H-4, 1 of C*H*$_2$CH$_3$), 4.12 (1H, dq, *J* 1.1, 6.8 Hz, H-5), 4.77 (1H, dd, *J* 2.9, 9.9 Hz, H-1); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.0, 34.4, 49.3, 65.6, 66.6, 74.6 (q, *J* 31 Hz, C-5), 101.8 (C-1), 124.0 (q, *J* 280 Hz, C-6); ^{19}F NMR (282 MHz, $CDCl_3$) δ −76.3 (d, *J* 6.8 Hz, 6-F); *m/z* (ESI) 230 (MH^+, 52%), 170 (100%); found: *m/z* 230.1013 (MH^+). $C_8H_{14}F_3NO_3$ requires *m/z* 230.1004.

3-Amino-2,3,6-trideoxy-6,6,6-trifluoro-L-*lyxo*-hexopyranose (19)

A solution of (49 mg, 1.0 mmol) in 0.5 M HCl (10 mL) was heated over a steam bath for 1 h. Concentration under reduced pressure afforded the title compound **19** as a slightly impure white powder (50 mg, 100%).

In D_2O at 25 °C, **19** existed as an 8 : 4 : 3 : 1 (α_p : β_p : α_f : β_f) mixture of pyranose and furanose anomers; ^{1}H NMR (300 MHz, D_2O) δ *inter alia* (0.25H, dd, *J* 2.2, 9.8 Hz, β_p-H-1), 5.54 (0.51H, br d, *J* 2.9 Hz, α_p-H-1), 5.69–5.76 (0.24H, m, α_f- and β_f- H-1); ^{19}F NMR (282 MHz, $CDCl_3$) δ −78.6 (0.54F, d, *J* 7.6 Hz, α_f-6-F), −78.4 (0.18F, d, *J* 7.3 Hz, β_f-F-6), −76.8 (1.53F, d, *J* 6.8 Hz, α_p-F-6), −76.5 (0.75F, d, *J* 6.6 Hz, β_p-F-6); found: *m/z* 202.0682 (MH^+). $C_6H_{11}NO_3F_3$ requires *m/z* 202.0691.

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