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SYNTHESIS OF BENZYL AND METHYL 3-BENZAMIDO-2,3,6-TRIDEOXY-2-FLUORO-β-L-GALACTOPYRANOSIDE: PROTECTED C-2 FLUORO ANALOGUES OF DAUNOSAMINE

LUCIA HELENA BRITO BAPTISTELLA, ANITA JOCELYNE MARSAIOLI,
Universidade Estadual de Campinas, Instituto de Quimica, C.P. 6154, 13100 Campinas, S.P. (Brazil)

JOSE DIAS DE SOUZA FILHO, GEOVANE GERALDO DE OLIVEIRA, ALAIDE BRAGA DE OLIVEIRA,
Universidade Federal de Minas Gerais, Instituto de Ciencias Exatas, 30.000 Belo Horizonte, M.G. (Brazil)

AIMEE DESSINGES, SERGIO CASTILLON, ALAIN OLESKER, TON THAT THANG, AND GABOR LUKACS
Institut de Chimie des Substances Naturelles du C.N.R.S., 91190 Gif-sur-Yvette (France)
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ABSTRACT

The reaction of benzyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-tosyl-α-D-glucopyranoside or benzyl 4,6-*O*-benzylidene-2,3-benzoylepimino-2,3-dideoxy-α-D-allopyranoside with anhydrous tetrabutylammonium fluoride in hexamethylphosphoric triamide gave ~40% of benzyl 3-benzamido-4,6-*O*-benzylidene-2,3-dideoxy-2-fluoro-α-D-altropyranoside (**6a**). Transformation of **6a** into benzyl 3-benzamido-2,3,6-trideoxy-2-fluoro-α-D-*arabino*-hex-5-enopyranoside (**13a**) was carried out by well-established methodology. Hydrogenation of the double bond in **13a** furnished the title compound in good yield. Methyl 3-benzamido-2,3,6-trideoxy-2-fluoro-β-L-galactopyranoside was also prepared in nine steps from 2-amino-2-deoxy-D-glucose.

INTRODUCTION

The antibiotics daunorubicin (**1**) and doxorubicin (**2**), which are effective in the treatment of human tumors[1], are anthracycline glycosides. Analogues in which the configuration of the sugar moiety is changed from L-*lyxo* to L-*arabino* and L-*ribo* display high activity against experimental tumors in mice[2]. As part of a programme on the synthesis of analogues of **1** and **2** modified in the amino sugar moiety[3], we now report the synthesis of benzyl (**14a**) and methyl 3-benzamido-2,3,6-trideoxy-2-fluoro-β-L-galactopyranoside (**14b**), which are protected analogues of daunosamine having an equatorial fluorine substituent at position 2.

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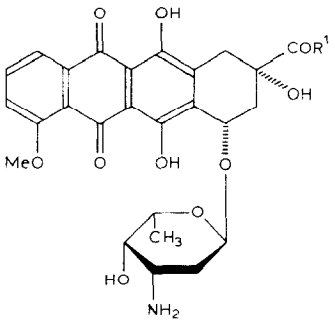


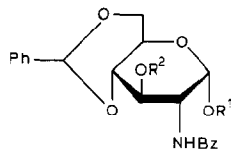
1 R^1 = Me
2 R^1 = CH_2OH

RESULTS AND DISCUSSION

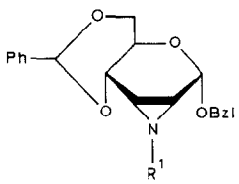
The synthesis scheme was based on the recently discovered[4], easy transformation of methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-tosyl-α-D-glucopyranoside (**4b**) into methyl 3-benzamido-4,6-*O*-benzylidene-2,3-dideoxy-2-fluoro-α-D-altropyranoside (**6b**). Treatment of **6b** with *N*-bromosuccinimide gave the 6-bromo derivative **8**, dehydrobromination of which followed by saponification of the 4-benzoate group and then catalytic hydrogenation (Pd/C) of the double bond in the product **13b** afforded **14b** (~35% from **6b**).

The stability towards acid of alkyl 2-deoxy-2-fluoroglycosides is well known[5] and benzyl glycosides were therefore used in the present work. Tosylation of benzyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside[6] (**3**) afforded 75% of crystalline 3-tosylate **4a**, reaction of which in hexamethylphosphoric triamide at 85° with 7.5 mol. equiv. of anhydrous tetrabutylammonium fluoride furnished 40% of the 2-fluoro derivative **6a**. Reduction of the proportion of tetrabutylammonium fluoride lowered the yield of **6a**. In large-scale experiments, **4a** was first treated with alkali to give the *N*-benzoylepimine **5b**, reaction of which (in hexamethylphosphoric triamide at 80°) with 1.5 mol. equiv. of anhydrous tetrabutylammonium fluoride afforded a mixture from which were isolated **6a** (38%), the epimine **5a** (40%), **5b** (11% which could be recycled), and the 3-fluoro derivative **7** (resulting from diequatorial opening of the epimine ring in **5b**).

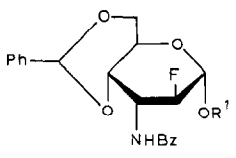
Acid-catalysed debenzylidenation of **6a** gave **9** in quantitative yield. Partial mesylation or tosylation of **9** and treatment of the resulting sulphonate (**10a** or **10b**) with sodium iodide gave the 6-deoxy-6-iodo derivative **11**. Reaction of **11** with silver fluoride afforded the unsaturated compound **13a**. The double bond in **13a** was saturated without cleavage of the benzyl group by rapid hydrogenation (10% Pd/C, triethylamine, methanol), to give benzyl 3-benzamido-2,3,6-trideoxy-2-fluoro-β-L-galactopyranoside (**14a**, 58%) and benzyl 3-benzamido-2,3,6-trideoxy-2-fluoro-α-D-altropyranoside (**15**, 8%). The conversion **13a**→**14a** was also carried out using 5% Rh/Al_2O_3 as catalyst[7].



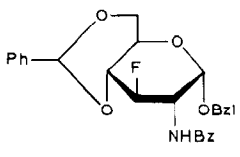
3 R^1 = Bzl, R^2 = H
4a R^1 = Bzl, R^2 = Ts
4b R^1 = Me, R^2 = Ts



5a R^1 = H
5b R^1 = Bz



6a R^1 = Bzl
6b R^1 = Me



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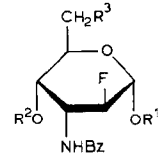
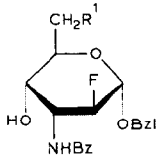
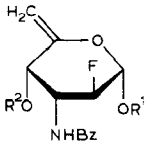


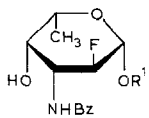
8 R^1 = Me, R^2 = Bz, R^3 = Br
15 R^1 = Bzl, R^2 = R^3 = H



9 R^1 = OH
10a R^1 = OMs
10b R^1 = OTs
11 R^1 = I



12a R^1 = Me, R^2 = Bz
13a R^1 = Bzl, R^2 = H
13b R^1 = Me, R^2 = H



14a R^1 = Bzl
14b R^1 = Me

The configurations of **14a** and **15** were ascertained on the basis of ^{1}H- and ^{13}C-n.m.r. data. The 400-MHz ^{1}H-n.m.r. spectrum of solutions of **14a** in various solvents showed second-order effects which precluded complete analysis of the spectrum. A solution in C_6D_6 showed a signal at δ 2.98 (J 7 Hz) for H-5 which indicated HO-4 to be axial. The L configuration of **14a** was further substantiated by the relatively low-field chemical shift (71.8 p.p.m.) of its C-5 resonance, consistent only with equatorial substituents at C-1 and C-3. The ^{1}H-n.m.r. spectrum of **14b** in $CDCl_3$ contained a sharp signal at δ 4.32 (q, J 7 Hz) in agreement with the L configuration of this compound.

The ^{1}H-n.m.r. spectrum of **15** contained overlapping signals, but that for H-2 was clearly resolved at δ 4.12 (dt, $J_{2,F}$ 45, $J_{1,2} = J_{2,3} = 2$ Hz) and the small values of $J_{1,2}$ and $J_{2,3}$ were indicative of equatorial protons. The D configuration of **15** was also evident from its ^{13}C-n.m.r. spectrum, which contained a signal at 65.4 p.p.m. for C-5 in agreement with axial substituents at C-1 and C-3. The chemical shift

difference of 6.4 p.p.m. for the signals of C-5 in **14a** and **15** reflects the two 1,3-diaxial interactions in which H-5 of **15** is involved. Catalytic hydrogenation of **11** afforded **15**.

EXPERIMENTAL

General methods. — 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 optical rotations. ^{1}H-N.m.r. spectra (internal Me_4Si) were recorded with Bruker WM-80 and WM-400 MHz spectrometers, and ^{13}C-n.m.r. spectra (100.62 MHz) were recorded with a Bruker WM-400 spectrometer. Microanalyses were performed by the Service Central de Microanalyse du C.N.R.S. Silica gel 60 G (Merck) activated at 120° was used for t.l.c.

*Benzyl 2-benzamido-4,6-O-benzylidene-2-deoxy-3-O-toluene-*p*-sulphonyl-α-*D*-glucopyranoside* (**4a**). — A solution of benzyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (**3**; 14 g, 30.4 mmol) in dry pyridine (200 mL) was treated at 0° with toluene-*p*-sulphonyl chloride (17.4 g, 91 mmol) and then stored for 3 days at room temperature. The mixture was poured into ice–water, and the crystalline precipitate was recrystallised from ethanol to give **4a** (14.0 g, 75%), m.p. 215°, $[\alpha]_D^{22}$ +48° (*c* 0.47, chloroform). Mass spectrum: *m/z* 524 ($M^+ - C_7H_7$). ^{1}H-N.m.r. data ($CDCl_3$): δ 5.37 (s, 1 H, H-7), 5.19 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1).

Anal. Calc. for $C_{34}H_{33}NO_8S$: C, 66.34; H, 5.37; N, 2.28; S, 5.20. Found: C, 66.15; H, 5.36; N, 2.55; S, 5.21.

*Benzyl 3-benzamido-4,6-O-benzylidene-2,3-dideoxy-2-fluoro-α-*D*-altropyranoside* (**6a**). — (*a*) A solution of **4a** (612 mg, 1 mmol) and anhydrous tetrabutylammonium fluoride (1.96 g, 7.5 mmol) in hexamethylphosphoric triamide (2.5 mL) was heated at 85° for 6 h and then poured into water. The solid was collected, and a solution in ethyl acetate (50 mL) was washed with water, dried, and concentrated. Preparative t.l.c. (dichloromethane–methanol, 97:3) of the residue gave **6a** (188 mg, 40%), m.p. 144–146° (from hexane–ether), $[\alpha]_D^{22}$ +79° (*c* 0.9, chloroform). Mass spectrum: *m/z* 464 (MH^+), 373 ($MH^+ - C_7H_7$). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.50–7.20 (m, 15 H), 7.00 (d, 1 H, $J_{NH,3}$ 7 Hz, NH), 5.67 (s, 1 H, H-7), 5.14 (m, 1 H, H-3), 5.12 (d, 1 H, $J_{1,F}$ 8.5 Hz, H-1), 4.83 and 4.56 (2 d, 2 H, J_{gem} 11 Hz, CH_2Ph), 4.77 (dd, 1 H, $J_{2,F}$ 44, $J_{2,3}$ 1 Hz, H-2), 4.37 (dd, 1 H, $J_{5,6}$ 4, $J_{6,6'}$ 10 Hz, H-6), 4.17 (ddd, 1 H, $J_{4,5}$ 10, $J_{3,4}$ 4.5, $J_{4,F}$ 2.5 Hz, H-4), 4.11 (td, 1 H, $J_{5,6}$ 4, $J_{4,5}$ 10, $J_{5,6'}$ 10 Hz, H-5), 3.92 (t, 1 H, $J_{5,6'} = J_{6,6'} = 10$ Hz, H-6').

Anal. Calc. for $C_{27}H_{26}FNO_5$: C, 69.98; H, 5.61; F, 4.10; N, 3.02. Found: C, 69.75; H, 5.59; F, 3.99; N, 3.18.

(*b*) To a solution prepared from dry 1-propanol (150 mL) and sodium (0.5 g) was added **4a** (2 g, 4.9 mmol). The solution was boiled under reflux for 1 h, filtered, and concentrated. A solution of the residue in dichloromethane (100 mL) was washed with water (200 mL) and concentrated to give benzyl 4,6-*O*-benzylidene-2,3-dideoxy-2,3-epimino-α-D-allopyranoside (**5a**; 1 g, 91%), m.p. 172–175°. Mass

spectrum: *m/z* 339 (M^+). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.70–7.25 (m, 11 H, 2 Ph, NH), 5.62 (s, 1 H, H-7), 5.10 (d, 1 H, $J_{1,2}$ 3 Hz, H-1), 4.85 and 4.65 (2 d, 2 H, J_{gem} 11 Hz, CH_2Ph), 4.22–3.60 (m, 4 H, H-4,5,6,6'), 2.77–2.70 (m, 2 H, H-2,3).

To a solution of **5a** (285 mg, 0.84 mmol) in dry pyridine (4 mL) at 0° was added benzoyl chloride (0.2 mL, 2 mmol). The solution was kept overnight at room temperature and then poured into ice–water, and the crystalline precipitate was recrystallised from ethanol to give benzyl 4,6-*O*-benzylidene-2,3-benzoylepimino-2,3-dideoxy-α-D-allopyranoside (**5b**; 329 mg, 88%), m.p. 175–180°, $[\alpha]_D^{22}$ +67° (*c* 1.6, chloroform). Mass spectrum: *m/z* 443 (M^+). ^{1}H-N.m.r. data ($CDCl_3$): δ 8.48–7.20 (m, 15 H, 3 Ph), 5.62 (s, 1 H, H-7), 5.15 (d, 1 H, $J_{1,2}$ 3 Hz, H-1), 4.82 and 4.62 (2 d, 2 H, J_{gem} 11 Hz, CH_2Ph), 4.80–3.70 (m, 4 H, H-4,5,6,6'), 3.32 (dd, 1 H, $J_{1,2}$ 4, $J_{2,3}$ 7 Hz, H-2), 3.01 (dd, 1 H, $J_{2,3}$ 7, $J_{3,4}$ 2 Hz, H-3).

Anal. Calc. for $C_{27}H_{25}NO_5$: C, 73.14; H, 5.64; N, 3.16. Found: C, 72.86; H, 5.75; N, 3.14.

To a solution of anhydrous tetrabutylammonium fluoride (20 g, 60 mmol) in hexamethylphosphoric triamide (50 mL) at 80° was added, dropwise, a solution of **5b** (11.5 g, 26 mmol) in hexamethylphosphoric triamide (150 mL). The mixture was stirred at 80° for 1 h and then poured into ice–water, and the crystalline precipitate was collected. A solution of the crystals in ethyl acetate (300 mL) was washed with water (500 mL) and concentrated, and the residue was subjected to column chromatography (dichloromethane–ethyl acetate, 99:1) to give **5b** (1.3 g, 11%) (R_F 0.75), **6b** (4.6 g, 38%) (R_F 0.64), **7** (0.8 g, 7%) (R_F 0.56), and **5a** (3.5 g, 40%) (R_F 0.14). Benzyl 2-benzamido-4,6-*O*-benzylidene-2,3-dideoxy-3-fluoro-α-D-glucopyranoside (**7**) had m.p. 223–226°, $[\alpha]_D^{22}$ +94° (*c* 0.96, chloroform). Mass spectrum: *m/z* 463 (M^+). N.m.r. data ($CDCl_3$): ^{1}H, δ 7.72–7.20 (m, 15 H, 3 Ph), 6.38 (s, 1 H, NH), 5.05 (dd, 1 H, $J_{1,2}$ 4, $J_{1,3}$ 3 Hz, H-1), 4.78 (qd, 1 H, $J_{2,3}$ 9, $J_{3,F}$ 60, $J_{3,4}$ 10 Hz, H-3), 4.72 and 4.50 (2 d, 2 H, J_{gem} 12 Hz, CH_2Ph), 4.28 (qd, 1 H, $J_{6,6'}$ 10, $J_{5,6}$ 4, $J_{6,F}$ 2 Hz, H-6), 3.97–3.88 (m, 3 H, H-2,4,5), 3.85 (t, 1 H, $J_{6,6'} = J_{5,6'} = 10$ Hz, H-6'); ^{13}C (C_5D_5N), δ 168.7 (C=O), 102.1 (C-7), 99.0 (d, $J_{1,F}$ 9 Hz, C-1), 89.5 (d, $J_{3,F}$ 191.0 Hz, C-3), 80.9 (d, $J_{4,F}$ 16.5 Hz, C-4), 70.7 (*C*H_2Ph), 69.2 (C-6), 63.4 (d, $J_{5,F}$ 7.5 Hz, C-5), 54.5 (d, $J_{2,F}$ 17.1 Hz, C-2).

Anal. Calc. for $C_{27}H_{26}FNO_5$: C, 69.98; H, 5.61; F, 4.10; N, 3.02. Found: C, 70.02; H, 3.08; F, 3.97; N, 3.08.

Benzyl 3-benzamido-2,3-dideoxy-2-fluoro-α-D-altropyranoside (**9**). — A solution of **6a** (84 mg, 0.18 mmol) in ethanol (10 mL) containing hydrochloric acid (0.1M) was stirred at room temperature for 12 h, neutralised to pH 5 by dropwise addition of cold, saturated, aqueous sodium hydrogencarbonate, filtered, and concentrated. A solution of the residue in ethyl acetate (50 mL) was washed with water (2 × 50 mL), dried, and concentrated to give **9** (68 mg, 99%), m.p. 164–168°, $[\alpha]_D^{22}$ +83° (*c* 0.66, methanol). Mass spectrum: *m/z* 376 (MH^+). ^{1}H-N.m.r. data (pyridine-d_5): δ 8.10 (d, 1 H, $J_{NH,3}$ 7 Hz, NH), 7.85–7.20 (m, 10 H, 2 Ph), 5.51 (m, 1 H, H-3), 5.42 (dd, 1 H, $J_{1,2}$ 1, $J_{1,F}$ 9.5 Hz, H-1), 5.14 (ddd, 1 H, $J_{1,2}$ 1, $J_{2,3}$ 4, $J_{2,F}$ 44 Hz, H-2), 5.01 and 4.61 (2 d, 2 H, J_{gem} 12 Hz, CH_2Ph), 4.81 (m, 1 H, H-4), 4.60–4.34 (m, 3 H, H-5,6,6').

Benzyl 3-benzamido-2,3-dideoxy-2-fluoro-6-O-methanesulfonyl-α-D-altropyranoside (**10a**). — To a solution of **9** (33 mg, 0.088 mmol) in dry pyridine (3 mL) at 0° was added methanesulfonyl chloride (0.007 mL, 0.096 mmol). The mixture was stirred at room temperature for 1.5 h, then poured into ice–water, and extracted with dichloromethane. The extract was concentrated and the residue was purified by preparative t.l.c. (hexane–ethyl acetate, 1:2) to afford syrupy **10a** (30 mg, 76%), $[\alpha]_D^{22}$ +22° (*c* 2.8, chloroform). Mass spectrum: *m/z* 454 (MH^+). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.60–7.15 (m, 11 H, 2 Ph, NH), 5.19 (dd, 1 H, $J_{1,2}$ 1, $J_{1,F}$ 7.5 Hz, H-1), 4.97 (m, 1 H, H-3), 4.92 and 4.62 (2 d, 2 H, J_{gem} 12 Hz, CH_2Ph), 4.72 (ddd, 1 H, $J_{1,2}$ 1, $J_{2,3}$ 4, $J_{2,F}$ 45 Hz, H-2), 4.64 (dd, 1 H, $J_{5,6}$ 1.5, $J_{6,6'}$ 11 Hz, H-6), 4.49 (dd, 1 H, $J_{5,6'}$ 5.5, $J_{6,6'}$ 11 Hz, H-6'), 4.20–4.00 (m, 2 H, H-4,5), 3.72 (s, 1 H, OH), 3.16 (s, 3 H, $MeSO_2$).

Benzyl 3-benzamido-2,3-dideoxy-2-fluoro-6-O-toluene-p-sulphonyl-α-D-altropyranoside (**10b**). — To a solution of **9** (8.5 g, 22.7 mmol) in dry pyridine (100 mL) at 0° was added tosyl chloride (4.75 g, 25 mmol). The mixture was stirred at room temperature for 24 h and then poured into ice–water. The crystalline precipitate was collected, and a solution in dichloromethane (300 mL) was washed with water (500 mL) and then concentrated to give **10b** (8.4 g, 70%), m.p. 158° (from ethyl acetate–hexane), $[\alpha]_D^{22}$ +19° (*c* 0.97, chloroform). Mass spectrum: *m/z* 529 (M^+). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.83–7.15 (m, 14 H, 2 Ph, $OSO_2C_6H_4Me$), 5.06 (dd, 1 H, $J_{1,F}$ 8, $J_{1,2}$ 1 Hz, H-1), 4.87 (m, 1 H, H-3), 4.82 and 4.50 (2 d, 2 H, J_{gem} 10 Hz, CH_2Ph), 4.62 (ddd, 1 H, $J_{2,F}$ 45, $J_{1,2}$ 1, $J_{2,3}$ 3 Hz, H-2), 4.45 (dd, 1 H, $J_{5,6}$ 1.5, $J_{6,6'}$ 10 Hz, H-6), 4.20 (dd, 1 H, $J_{5,6'}$ 11, $J_{6,6'}$ 10 Hz, H-6'), 4.03–3.95 (m, 2 H, H-4,5), 3.37 (d, 1 H, $J_{4,OH}$ 3 Hz, OH), 2.38 (s, 3 H, $OSO_2C_6H_4Me$).

Anal. Calc. for $C_{27}H_{28}FNO_7S$: C, 61.25; H, 5.29; N, 2.65. Found: C, 60.35; H, 5.67; N, 2.59.

Benzyl 3-benzamido-2,3,6-trideoxy-2-fluoro-6-iodo-α-D-altropyranoside (**11**). — To a solution of **10a** (0.29 g, 0.69 mmol) in butanone (30 mL) was added sodium iodide (0.62 g, 4.14 mmol). The mixture was boiled under reflux for 15 h and then concentrated, and a solution of the residue in hexane–ethyl acetate (1:2, 50 mL) was filtered through a short column of Silica gel 60 G to give **11** (0.30 g, 99%), m.p. 148–150° (from hexane–ether), $[\alpha]_D^{22}$ −43° (*c* 1, chloroform). Mass spectrum: *m/z* 456 (M^+). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.60–7.15 (m, 11 H, 2 Ph, NH), 5.20 (dd, 1 H, $J_{1,2}$ 1, $J_{1,F}$ 7.5 Hz, H-1), 5.10 and 4.62 (2 d, 2 H, J_{gem} 11 Hz, CH_2Ph), 4.92 (m, 1 H, H-3), 4.70 (ddd, 1 H, $J_{1,2}$ 1, $J_{2,3}$ 3.5, $J_{2,F}$ 43 Hz, H-2), 3.99 (ddd, 1 H, $J_{4,5}$ 10, $J_{3,4}$ 2.5, $J_{4,F}$ 2 Hz, H-4), 3.87 (td, 1 H, $J_{4,5}$ 10, $J_{5,6}$ 2, $J_{5,6'}$ 9 Hz, H-5), 3.76 (dd, 1 H, $J_{5,6}$ 2, $J_{6,6'}$ 11 Hz, H-6), 3.60 (s, 1 H, OH), 3.32 (dd, 1 H, $J_{5,6'}$ 9, $J_{6,6'}$ 11 Hz, H-6').

Anal. Calc. for $C_{20}H_{21}FINO_4$: C, 49.48; H, 4.33; F, 3.92; I, 26.20; N, 2.88. Found: C, 49.60; H, 4.37; F, 3.81; I, 26.54; N, 2.85.

Benzyl 3-benzamido-2,3,6-trideoxy-2-fluoro-α-D-arabino-hex-5-enopyranoside (**13a**). — To a solution of **11** (24 mg, 0.049 mmol) in dry pyridine (5 mL) was added silver fluoride (38 mg, 0.3 mmol). The mixture was stirred in the dark at

room temperature for 24 h, then diluted with ether (50 mL), filtered through a column of Silica gel 60 G, and concentrated. Preparative t.l.c. (hexane–ethyl acetate, 1:2) of the residue gave **13a** (9 mg, 53%), m.p. 180–183°, $[\alpha]_D^{22}$ +12° (*c* 1, chloroform). Mass spectrum: *m/z* 358 (M^+). ^{1}H-N.m.r. data (C_6D_6): δ 7.60–6.85 (m, 11 H, 2 Ph, NH), 5.18 (s, 1 H, H-6), 5.10 (m, 1 H, H-3), 4.90 (s, 1 H, H-6'), 4.81 (m, 1 H, H-4), 4.74 (dd, 1 H, $J_{1,2}$ 1, $J_{1,F}$ 8 Hz, H-1), 4.61 and 3.87 (2 d, 2 H, J_{gem} 10.5 Hz, CH_2Ph), 4.25 (ddd, 1 H, $J_{1,2}$ 1, $J_{2,3}$ 2.5, $J_{2,F}$ 45 Hz, H-2).

Anal. Calc. for $C_{20}H_{20}FNO_4$: C, 67.23; H, 5.60; F, 5.32; N, 3.92. Found: C, 66.98; H, 5.69; F, 5.73; N, 4.17.

*Benzyl 3-benzamido-2,3,6-trideoxy-2-fluoro-β-*L*-galactopyranoside* (**14a**) *and benzyl 3-benzamido-2,3,6-trideoxy-2-fluoro-α-*D*-altropyranoside* (**15**). — (*a*) A stirred solution of **13a** (404 mg, 1.13 mmol) in methanol (100 mL) containing triethylamine (0.3 mL, 2 mmol) was hydrogenated for 25 min in the presence of 10% Pd/C (400 mg) at normal pressure, then filtered through Kieselguhr (Merck), and concentrated. The residue was purified by preparative t.l.c. (dichloromethane–ethyl acetate, 9:1) to give **14a** (234 mg, 58%), R_F 0.28, and **15** (30 mg, 8%), R_F 0.47. Compound **14a** had m.p. 126–128°, $[\alpha]_D^{22}$ −11.5° (*c* 0.5, chloroform). Mass spectrum: *m/z* 360 (MH^+). N.m.r. data (C_6D_6): ^{1}H, δ 7.52–6.82 (m, 10 H, 2 Ph), 6.45 (d, 1 H, $J_{NH,3}$ 7 Hz, NH), 4.83 and 4.51 (2 d, 2 H, J_{gem} 11 Hz, CH_2Ph), 4.60–4.30 (m, 3 H, H-1,2,3), 3.24 (m, 1 H, H-4), 2.98 (q, 1 H, $J_{5,6}$ 7 Hz, H-5), 0.94 (d, 1 H, $J_{5,6}$ 7 Hz, H-6); ^{13}C ($CDCl_3$), δ 167.9 (C=O), 137.0, 134.0, 131.8, 128.6, 128.5, 128.0, 127.3 (CH_2Ph, NHCOPh), 100.3 (d, $J_{1,F}$ 22.8 Hz, C-1), 89.6 (d, $J_{2,F}$ 187.4 Hz, C-2), 72.0 (d, $J_{4,F}$ 8.1 Hz, C-4), 71.8 (C-5), 54.0 (d, $J_{3,F}$ 17.8 Hz, C-3), 16.1 (C-6).

Anal. Calc. for $C_{20}H_{22}FNO_4$: C, 66.85; H, 6.13; F, 5.29; N, 3.90. Found: C, 66.77; H, 6.25; F, 5.35; N, 4.17.

Compound **15** had m.p. 150–152°, $[\alpha]_D^{22}$ +20° (*c* 1.5, chloroform). Mass spectrum: *m/z* 359 (M^+). N.m.r. data ($CDCl_3$): ^{1}H, δ 7.55–6.83 (m, 11 H, 2 Ph, NH), 4.97 (m, 1 H, H-3), 4.65 (dd, 1 H, $J_{1,F}$ 8, $J_{1,2}$ 2 Hz, H-1), 4.37 and 3.83 (2 d, 2 H, J_{gem} 11 Hz, CH_2Ph), 4.12 (td, 1 H, $J_{2,F}$ 45, $J_{1,2} = J_{2,3}$ = 2 Hz, H-2), 3.97 (m, 1 H, H-4), 3.83 (m, 1 H, H-5), 3.67 (s, 1 H, OH), 3.67 (s, 1 H, OH), 1.43 (d, 1 H, $J_{5,6}$ 7 Hz, H-6); ^{13}C, δ 169.1 (C=O), 136.3, 132.9, 132.0, 129.0, 128.9, 128.8, 128.7, 127.1 (CH_2Ph, NHCOPh), 96.6 (d, $J_{1,F}$ 31 Hz, C-1), 87.2 (d, $J_{2,F}$ 178.6 Hz, C-2), 70.5 and 70.3 (2 C, C-4 and CH_2Ph), 65.4 (C-5), 50.3 (d, $J_{3,F}$ 26.9 Hz, C-3), 17.4 (C-6).

Anal. Found: C, 66.49; H, 6.00; F, 5.41; N, 3.70.

(*b*) A stirred solution of **13a** (50 mg, 0.14 mmol) in tetrahydrofuran (20 mL) was hydrogenated for 2 h in the presence of 5% Rh/Al_2O_3 (15 mg) at normal pressure, filtered through Kieselguhr, and concentrated. The residue was purified by preparative t.l.c. as in (*a*), to give **14a** (39 mg, 80%).

(*c*) A stirred solution of **9** (31 mg, 0.06 mmol) in methanol (5 mL) containing triethylamine (0.01 mL, 0.12 mmol) was hydrogenated for 45 min in the presence of 10% Pd/C (30 mg) at normal pressure, filtered through Kieselguhr, and concen-

trated. The residue was purified by preparative t.l.c. (dichloromethane–ethyl acetate, 9:1) to give **15** (13 mg, 59%).

*Methyl 3-benzamido-4-O-benzoyl-6-bromo-2,3,6-trideoxy-2-fluoro-α-*D*-altropyranoside* (**8**). — A suspension of **6b** (2.02 g, 5.2 mmol), *N*-bromosuccinimide (1.12 g, 6.3 mmol), and barium carbonate (1.5 g, 7.6 mmol) in dry carbon tetrachloride (40 mL) was boiled under reflux for 2 h. Insoluble material was collected and washed with dichloromethane (40 mL), and the combined filtrate and washings were washed with aqueous sodium hydrogencarbonate (100 mL) and water (200 mL), and then concentrated. The residue was crystallised from cyclohexane to give **8** (0.99 g, 41%), m.p. 118–199°, $[\alpha]_D^{22}$ +100° (*c* 1.4, chloroform). Mass spectrum: *m/z* 467 (M^+) and 465. ^{1}H-N.m.r. data ($CDCl_3$): δ 7.98–7.32 (m, 11 H, 2 Ph, NH), 5.40 (ddd, 1 H, $J_{3,4}$ 4.5, $J_{4,5}$ 10, $J_{4,F}$ 2 Hz, H-4), 5.30 (m, 1 H, H-3), 5.03 (bd, 1 H, $J_{1,F}$ 8 Hz, H-1), 4.70 (ddd, 1 H, $J_{1,2}$ 1, $J_{2,3}$ 3.5, $J_{2,F}$ 44.5 Hz, H-2), 4.27 (m, 1 H, H-5), 3.68 (s, 3 H, OMe), 3.55 (m, 2 H, H-6,6′).

Anal. Calc. for $C_{21}H_{21}BrFNO_5$: C, 54.09; H, 4.54; Br, 17.14; F, 4.07; N, 3.00. Found: C, 54.03; H, 4.65; Br, 17.17; F, 4.00; N, 3.14.

*Methyl 3-benzamido-4-O-benzoyl-2,3,6-trideoxy-2-fluoro-α-*D*-*arabino*-hex-5-enopyranoside* (**12**). — To a solution of **8** (0.2 g, 0.43 mmol) in dry pyridine (3.8 mL) was added silver fluoride (0.19 g, 1.5 mmol). The mixture was stirred in the dark at room temperature for 24 h, diluted with ether (10 mL), filtered through a column of silica gel, and concentrated to give **12** (0.15 g, 92%), m.p. 114–115°, $[\alpha]_D^{22}$ +128° (*c* 0.9, chloroform). Mass spectrum: *m/z* 385 (M^+). ^{1}H-N.m.r. data ($CDCl_3$): δ 8.00–7.35 (m, 10 H, 2 Ph), 7.05 (d, 1 H, $J_{NH,3}$ 7 Hz, NH), 6.00 (m, 1 H, H-4), 5.25 (m, 1 H, H-3), 5.02 (bd, 1 H, $J_{1,F}$ 8 Hz, H-1), 4.98 (s, 1 H, H-6), 4.83 (s, 1 H, H-6′), 4.76 (ddd, 1 H, $J_{1,2}$ 1, $J_{2,3}$ 3.5, $J_{2,F}$ 44 Hz, H-2), 3.62 (s, 3 H, OMe).

Anal. Calc. for $C_{21}H_{20}FNO_5$: C, 65.45; H, 5.23; F, 4.93; N, 3.63. Found: C, 65.19; H, 5.34; F, 5.05; N, 3.70.

*Methyl 3-benzamido-2,3,6-trideoxy-2-fluoro-α-*D*-*arabino*-hex-5-enopyranoside* (**13b**). — A solution of **12** (250 mg, 6.5 mmol) in dry methanol (1.5 mL) was treated with methanolic 0.5M sodium methoxide (0.5 mL) at room temperature for 1 h, neutralised with Amberlite IRC-50 (H^+) resin, and concentrated. The solid residue was washed with cyclohexane to give **13b** (157 mg, 86%), m.p. 127–130°, $[\alpha]_D^{22}$ +47° (*c* 1, chloroform). Mass spectrum: *m/z* 281 (M^+). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.77–7.40 (m, 5 H, Ph), 7.13 (d, 1 H, $J_{NH,3}$ 7 Hz, NH), 4.92 (m, 3 H, H-1,6,6′), 4.75 (ddd, 1 H, $J_{1,2}$ 1, $J_{2,3}$ 3.5, $J_{2,F}$ 44 Hz, H-2), 4.68 (m, 1 H, H-4), 3.58 (s, 3 H, OMe), 3.20 (d, 1 H, $J_{OH,H}$ 4 Hz, OH).

Anal. Calc. for $C_{14}H_{16}FNO_4$: C, 59.78; H, 5.74; F, 6.79; N, 4.98. Found: C, 59.88; H, 5.81; F, 7.02; N, 5.23.

*Methyl 3-benzamido-2,3,6-trideoxy-2-fluoro-β-*L*-galactopyranoside* (**14b**). — A solution of **13b** (55 mg, 0.2 mmol) in dry methanol (1.8 mL) was hydrogenated for 24 h at atmospheric pressure in the presence of 10% Pd/C (5.5 mg), filtered, and concentrated. The solid residue was recrystallised from benzene to give **14b** (37 mg, 67%), m.p. 118°, $[\alpha]_D^{22}$ −60° (*c* 1.3, chloroform). Mass spectrum: *m/z* 283

(M^+). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.84–7.40 (m, 5 H, Ph), 6.80 (d, 1 H, $J_{NH,3}$ 7 Hz, NH), 4.50 (m, 3 H, H-1,2,3), 4.32 (q, 1 H, $J_{5,6}$ 7 Hz, H-5), 3.82 (m, 2 H, H-4 and OH), 3.60 (s, 3 H, OMe), 1.32 (d, 3 H, $J_{5,6}$ 7 Hz, H-6).

Anal. Calc. for $C_{14}H_{18}FNO_4$: C, 59.35; H, 6.40; N, 4.94. Found: C, 58.56; H, 6.52; N, 4.90.

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