Synthesis of heterodisaccharide-containing peptides, fragments of actinoidin antibiotics

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Prototypes corresponding to glycopeptide fragments of actinoidin antibiotics have been synthesized using an L-acosaminyl-D-glucose-containing heterodisaccharide linked to 4-hydroxyphenylglycine as pivotal synthon. This latter compound has been obtained by coupling of a suitably protected D-glucopyranosyl bromide with the blocked amino acid, followed by selective deprotection of the glucopyranosyl moiety at C-2 and subsequent stereospecific attachment of the acosaminyl unit.

Introduction

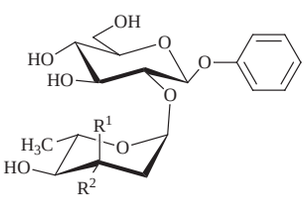
Glycopeptide antibiotics such as vancomycin[1] and, more recently, teicoplanin[1] are widely used in the treatment of staphylococcal infections and considerable interest has been devoted to their structural elucidation and synthesis.[2,3] Although improvements have been registered[4] in recent years in the total synthesis of the peptide-antibiotic aglycons, total syntheses of the carbohydrate portion are rather scarce. Many of these representative antibiotics present a common structural feature which is a heterodisaccharide side-chain. Thus, the central phenolic ring of the peptide-based aglycons is bound through a β-linkage to a glucosyl residue which is, in turn, attached through a (2→1) α-linkage to an aminodeoxy sugar. However the aminodeoxy sugar varies in the individual antibiotics, mainly in the stereochemistry and substitution at C-3 and C-4.

A first paper appeared in 1986 from Bognar's group,[5] related to the synthesis of phenyl β-acobioside **1**, a derivative which simulated the aryloxycarbohydrate domain of actinoidins. More recently, in collaboration with this group, but using a different strategy, we achieved the synthesis[6] of a prototype corresponding to avoparcins, namely phenyl β-avobioside **2**. Simultaneously, Dushin and Danishefsky published[7] a stereospecific synthesis of fully protected aryl β-glucosides such as compounds **3** and **4** simulating the heterodisaccharide part of vancomycin. Closely related, these two last syntheses were based upon the formation of an aryl β-glucoside selectively deprotected at C-2 and upon a subsequent attachment of a ristosamine- (for compound **2**) or a vancosamine-based glycal (for compounds **3** and **4**) as glycosyl donors, in the presence of trimethylsilyl triflate and camphorsulfonic acid as catalyst, respectively.

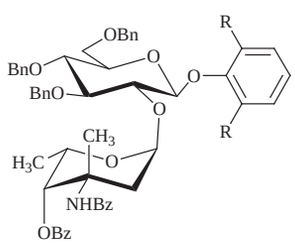
The purpose of the present investigation was to attempt progress in the synthesis of prototypes corresponding to more complex glycopeptide fragments of these antibiotics, in order to examine subsequently their interaction with the model peptide-ligand (diacetyl-L-lysyl-D-alanyl-D-alanine, DALAA) which correlated[8] with the antibacterial potency of close analogues of vancomycin.

Results and discussion

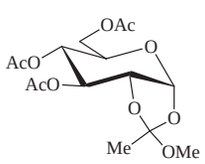
We decided first to use the same successful strategy we developed in our previous approach, *i.e.* coupling of the orthoester **6**[9] readily prepared from triacetate **5**[10] by exchange



1 $R^1 = NH_2$, $R^2 = H$
2 $R^1 = H$, $R^2 = NH_2$



3 R = H
4 R = OCH_3



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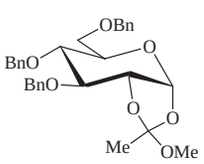

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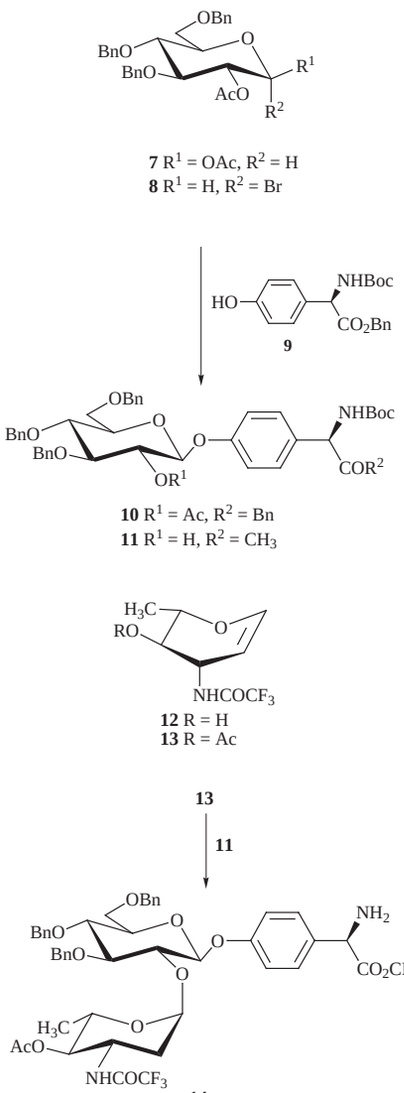
of the protecting groups or of the 1,2-*trans*-di-*O*-acetyl-glucopyranoside **7**[11] with a phenol. However, whereas we succeeded in coupling both glucose derivatives with phenol itself, no glycosidation occurred with the aryloxyhydroxy moiety as present in the glycine derivative **9**. Therefore diacetate **7** was converted into the glucopyranosyl bromide **8** by a known procedure[12] and identified with literature data.[13] Glycosylation of compounds **8** with **9** was achieved in acceptable yield (47%) under phase-transfer conditions ($BnEt_3NBr$, aq. KOH, $CHCl_3$)[14] to give compound **10**.

Next, in order to obtain access to the heterodisaccharide unit, selective 2-*O*-deprotection of compound **10** was realized under Zemplen conditions (NaOMe–MeOH). This led to ester **11** in 83% yield, resulting from concomitant replacement of the benzyl ester as present in **10** by methyl ester. At the same time, the acosamine-based glycal **13** was obtained from the trifluoroacetamido precursor **12**, which was synthesized in a few steps from di-*O*-acetyl-L-rhamnal by our own procedure.[15] Glycosylation of alcohol **11** with compound **13** [trimethylsilyl trifluoromethanesulfonate (TMSOTf), CH_2Cl_2 and then Et_3N] afforded the glycopeptide **14** in 85% yield, having the amino function of the amino acid moiety selectively deprotected in the course of the reaction. Coupling of compound **14** with *N*-Boc-L-phenylalanine **15** was effected by 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) and *N*-methylmorpholine activation,[16] using one molar equivalent of each component. This led to

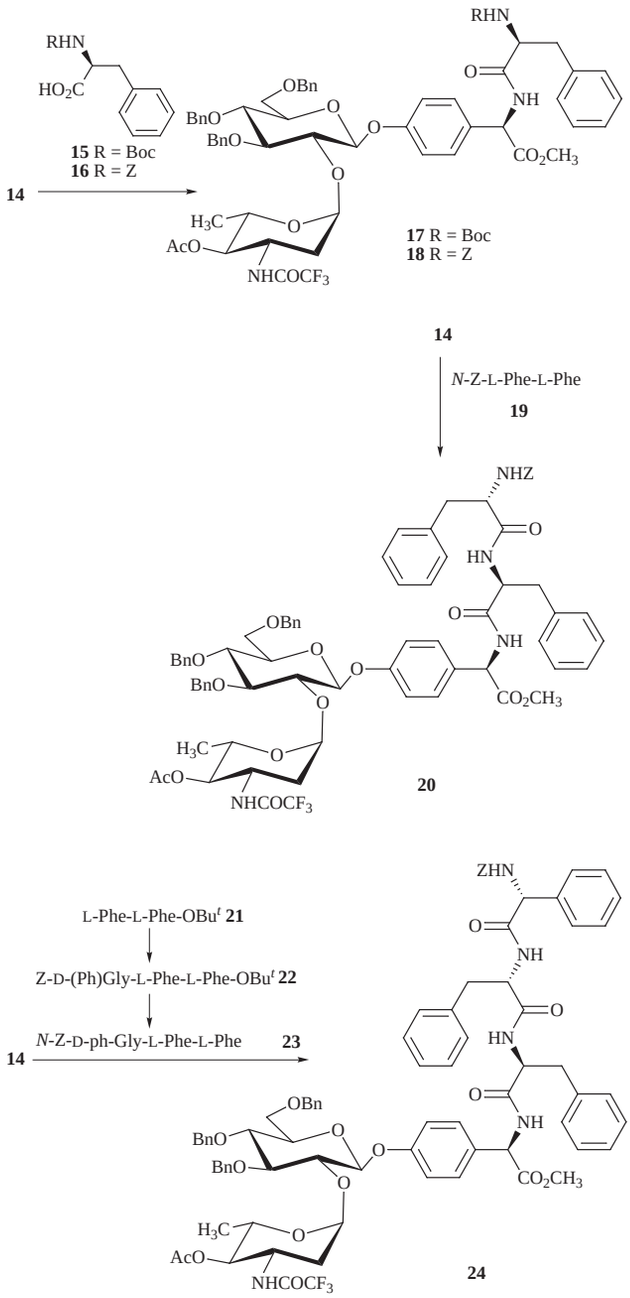
compound **17** in 86% yield, isolated as a crystalline compound. However, since cleavage of the *tert*-butylcarbamate protection of the terminal amino acid proved to be relatively difficult and led to side-products when drastic conditions were attempted, repetitive coupling of compound **14** was carried out with the corresponding *N*-Z-L-phenylalanine **16**. This coupling was performed in the presence of 1-hydroxybenzotriazole (HOBT) and 3-ethyl-1-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI) to give the disaccharide-dipeptide **18** in high yield (84%).

Access to more complex glycopeptides was then attempted in experiments using the glycopeptide **14** as pivotal synthon. For instance, compound **14** was first condensed with *N*-Z-L-phenylalanyl-L-phenylalanine[17] **19** in the presence of HOBT and EDCI, to afford the glycopeptide **20** in 78% yield.



The second target **24** was a tetrapeptide derivative of the heterodisaccharide. This compound was obtained in good yield (83%) by coupling of compound **14** with the tripeptide *N*-Z-D-phenylglycyl-L-phenylalanyl-L-phenylalanine **23** under the same conditions as above. For its part, free acid **23** was synthesized in three steps and 73% overall yield from *N*-Z-L-phenylalanyl-L-phenylalanine *tert*-butyl ester:[18] (i) hydrogenolysis; (ii) condensation of the resulting dipeptide **21** with *N*-Z-D-phenylglycine[19] (EDCI, HOBT); (iii) acid hydrolysis of *N*-Z-D-phenylglycyl-L-phenylalanyl-L-phenylalanine *tert*-butyl ester **22**.

In summary, an efficient synthesis of a prototype of an actinoidin fragment of a glycopeptide antibiotic has been achieved. So far, this represents, to our knowledge, the first



example of a glycopeptide synthesis involving an aminodeoxy sugar unit. This strategy based upon the stereospecific glycosylation of an acosamine derivative with a suitably protected D-4-hydroxyphenylglycyl glucoside may allow access to a large series of glycopeptide-containing heterodisaccharides.

Experimental

Mps were taken on a hot plate Reichert microscope. Optical rotations were measured on a Perkin-Elmer 241 polarimeter and values ($[\alpha]_D^{20}$) are given in units of 10^{-1} deg cm^2 g^{-1}. IR were recorded on a Perkin-Elmer 1600 FT-IR spectrometer. ^{13}C NMR spectra were recorded at 75 MHz and ^{1}H NMR spectra were recorded at 300 MHz using a Bruker AC 300 spectrometer. Coupling constants (J) are given in Hz. Protons and carbons of phenylglycine, 4-hydroxyphenylglycine and phenylalanine of compounds **10**, **11**, **14**, **17**, **18**, **20** and **24** are referred to as **P**, **P′**, $\mathbf{F_1}$ and $\mathbf{F_2}$, respectively in the NMR descriptions of those compounds. Chemical ionization mass spectra (CI-MS; NH_3, positive-ion mode) were recorded on a Nermag R 10-10C spectrometer. Electrospray ionization mass spectra (ESI-MS) were acquired with a quadrapole instrument with a mass of charge

(*m*/*z*) range of 2000. The Nermag R 10-10 mass spectrometer used was equipped with an analytical atmospheric pressure electrospray source. Microanalyses were performed by the 'Service de Microanalyse ICSN-CNRS-91198 Gif sur Yvette' (France).

3,4,6-Tri-*O*-acetyl-1,2-*O*-(1-methoxyethylidene)-α-D-glucopyranose[10] 5

To a solution of α-acetobromoglucose (6.2 g, 15 mmol) and TBAB (7.3 g, 22.5 mmol) in anhydrous dichloromethane was added, under argon, DMF dimethyl acetal (3 cm^3, 22.5 mmol). After being stirred at 40 °C for 24 h, the reaction mixture was diluted with chloroform (100 cm^3) and washed with a mixture of water–triethylamine (99 : 1 v/v) (50 cm^3). The organic layer was dried ($MgSO_4$), evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel (35–70 μm) using cyclohexane–ethyl acetate–triethylamine (60 : 40 : 1 v/v/v) as eluent to give 3,4,6-tri-*O*-acetyl-1,2-*O*-(1-methoxyethylidene)-α-D-glucopyranose **5** as 6 : 1 (NMR) *exo*/*endo* mixture, as a pale yellow oil (5.3 g, 96%), ν_{max}(film)/cm^{-1} 2952, 1747 (C=O), 1436, 1370, 1228 and 1041 (C–O); δ_H($CDCl_3$) 1.55 (3 H, s, *endo*-CH_3), 1.70 (3 H, s, *exo*-CH_3), 2.08 (9 H, 3s, 3 × $OCOCH_3$), 3.27 (3 H, s, *exo*-OCH_3), 3.44 (3 H, s, *endo*-OCH_3), 3.93 (1 H, dt, $J_{5,4}$ 9, $J_{5,6}$ 4.5, 5-H), 4.18 (2 H, d, $J_{6,5}$ 4.5, 6-H_2), 4.31 (1 H, ddd, $J_{2,1}$ 5, $J_{2,3}$ 3, $J_{2,4}$ 1, 2-H), 4.88 (1 H, ddd, $J_{4,5}$ 9, $J_{4,3}$ 3, $J_{4,2}$ 1, 4-H), 5.18 (1 H, t, $J_{3,4} = J_{3,2} = 3$, 3-H), 5.65 (1 H, d, $J_{1,2}$ 5, *endo*-1-H) and 5.70 (1 H, d, $J_{1,2}$ 5, *exo*-1-H); δ_C($CDCl_3$) 20.0 (CH_3), 20.7 ($OCOCH_3$), 50.9 (OCH_3), 63.0 (6-C), 66.9 (5-C), 68.1 (4-C), 70.0 (3-C), 73.0 (2-C), 96.8 (1-C), 121.5 (*C*-Me), 169.1 and 169.6 and 170.6 (3 × $OCOCH_3$); *m*/*z* (CI) 363 $(M + H)^+$ and 380 $(M + NH_4)^+$.

3,4,6-Tri-*O*-benzyl-1,2-*O*-(1-methoxyethylidene)-α-D-glucopyranose (*exo*-orthoester)[9] 6

A solution of 3,4,6-*tri*-*O*-acetyl-1,2-*O*-methoxyethylidene-α-D-glucopyranose **5** (5.3 g, 14.5 mmol) in dry methanol was treated with anhydrous sodium methoxide (2.4 g, 43.5 mmol) at rt for 1 h. The reaction mixture was then concentrated under reduced pressure. To a solution of the residue in DMF (200 cm^3) was added portionwise sodium hydride (1.75 g, 72.5 mmol). After complete liberation of hydrogen, benzyl bromide (6.9 cm^3, 58 mmol) was added dropwise and the reaction mixture was stirred at rt for 3 h. The excess of reagents was destroyed by careful treatment with methanol (60 cm^3). After being stirred at rt for 16 h, the reaction mixture was concentrated under reduced pressure and the residue was diluted with water (400 cm^3) and extracted with diethyl ether (3 × 200 cm^3). The combined extracts were successively washed with saturated aq. sodium hydrogen carbonate (200 cm^3) and water (200 cm^3), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (35–70 μm) with cyclohexane–ethyl acetate–triethylamine (85 : 15 : 1 v/v/v) as eluent to give 3,4,6-tri-*O*-benzyl-1,2-*O*-(1-methoxyethylidene)-α-D-glucopyranose **6** as a pale yellow oil (6.0 g, 82%), $[\alpha]_D^{20}$ +38 (*c* 1, $CHCl_3$) {lit.,[9] $[\alpha]_D^{20}$ +36 (*c* 1, $CHCl_3$)}; ν_{max}(film)/cm^{-1} 3030, 2869, 1758 (C=O), 1496, 1453, 1366, 1236 and 1059 (C–O); δ_H($CDCl_3$) 1.70 (3 H, s, CH_3), 3.31 (3 H, s, OCH_3), 3.69 (2 H, d, $J_{6,5}$ 3, 6-H_2), 3.75 (1 H, dd, $J_{4,5}$ 9, $J_{4,3}$ 4, 4-H), 3.84 (1 H, dt, $J_{5,4}$ 9, $J_{5,6}$ 3, 5-H), 3.92 (1 H, t, $J_{3,4} = J_{3,2} = 4$, 3-H), 4.47 (1 H, dd, $J_{2,1}$ 5, $J_{2,3}$ 4, 2-H), 4.40–4.80 (6 H, m, 3 × CH_2Ph), 5.82 (1 H, d, $J_{1,2}$ 5, 1-H) and 7.20–7.40 (15 H, m, ArH); δ_C($CDCl_3$) 21.2 (CH_3), 50.5 (OCH_3), 69.1 (6-C), 70.4 (5-C), 71.8 and 72.9 and 73.3 (3 × *C*H_2Ph), 74.8 (4-C), 75.8 (2-C), 78.6 (3-C), 97.7 (1-C), 121.3 (*C*Me), 127.6–128.3 (Ar-C), 137.6 and 137.8 and 137.9 (Ar-C); *m*/*z* (CI) 475, 492 and 524 $(M + NH_4)^+$.

N-Boc-4-(2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyloxy)-D-phenylglycine benzyl ester 10

To a stirred solution of *N*-(*tert*-butoxycarbonyl)-4-hydroxy-D-phenylglycine benzyl ester **9** (629 mg, 1.76 mmol) and 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl bromide **8** (940 mg, 1.76 mmol) in chloroform (10 cm^3) was added a solution of benzyltriethylammonium bromide (480 mg, 1.76 mmol) in 1.25 M aq. potassium hydroxide (6 cm^3). The reaction mixture was vigorously stirred under reflux for 15 h. After cooling to rt it was diluted with water (80 cm^3) and extracted with chloroform (100 cm^3). The organic layer was washed with 1.25 M aq. potassium hydroxide (2 × 90 cm^3), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (20–45 μm) with cyclohexane–ethyl acetate (85 : 15 v/v) as eluent to give the benzyl ester **10** as a pale yellow oil (693 mg, 47%), $[\alpha]_D^{20}$ −9 (*c* 0.9, $CHCl_3$); ν_{max}(film)/cm^{-1} 3429 (NH), 2944, 1748 (C=O), 1509, 1222 and 1162 and 1068 (C–O); δ_H($CDCl_3$) 1.46 (9 H, s, Bu^t), 2.00 (3 H, s, $OCOCH_3$), 3.64–3.86 (5 H, m, 3-, 4- and 5-H, 6-H_2), 4.50–4.90 (6 H, m, 3 × CH_2Ph), 4.96 (1 H, d, $J_{1,2}$ 8, 1-H), 5.17 [1 H, d, $J_{A,B}$ 12, $H_A(CO_2CH_2)$], 5.27 (2 H, m, 2-H and CH**P**), 5.36 [1 H, d, $J_{A,B}$ 12, $H_B(CO_2CH_2)$], 5.61 (1 H, d, $J_{NH,CHP}$ 7, NH), 7.00 (2 H, d, $J_{5',2'} = J_{3',6'} = 8$, 3′- and 5′-H**P**) and 7.20–7.40 (22 H, m, ArH); δ_C($CDCl_3$) 20.7 ($OCOCH_3$), 28.2 [(CH_3)$_3$C], 57.0 (CH**P**), 67.1 (CO_2CH_2), 68.5 (6-C), 72.7 (2-C), 73.4 (CH_2Ph), 75.0 (2 × CH_2Ph), 75.3 (5-C), 77.7 (4-C), 80.0 [(CH_3)$_3$*C*], 82.6 (3-C), 99.1 (1-C), 117.0 (3′- and 5′-C**P**), 127.6–128.3 (Ar-C), 131.1 (1′-C**P**), 135.0 (1″-C**P**), 137.3 and 137.6 [Cq(Ph)], 154.6 (4′-C**P**), 157.2 (OCONH) and 169.3 and 170.9 (O*C*OMe and CO_2Bn); *m*/*z* (ES) 854 $(M + Na)^+$.

N-Boc-4-(3,4,6-tri-*O*-benzyl-β-D-glucopyranosyloxy)-D-phenylglycine methyl ester 11

A solution of benzyl ester **10** (692 mg, 0.83 mmol) in dry methanol was treated with anhydrous sodium methoxide (67 mg, 1.25 mmol) at rt for 16 h. The reaction mixture was neutralized by addition of Amberlite® IRC 50H^+ resin. The solution was filtered and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (20–45 μm) with cyclohexane–ethyl acetate (80 : 20 v/v) as eluent to give the methyl ester **11** as a powder (493 mg, 83%), which was recrystallized from cyclohexane, mp 64–65 °C; $[\alpha]_D^{20}$ −2 (*c* 1, $CHCl_3$) (Found: C, 68.8; H, 6.7. Calc. for $C_{41}H_{47}NO_{10}$: C, 68.97; H, 6.64%); ν_{max}(film)/cm^{-1} 3432 (NH), 2869, 1740 and 1714 (C=O), 1610, 1509, 1454, 1234 and 1163 and 1067 (C–O); δ_H($CDCl_3$) 1.44 (9 H, s, Bu^t), 3.71 (3 H, s, OCH_3), 3.60–3.89 (6 H, m, 2-, 3-, 4- and 5-H, 6-H_2), 4.49–4.63 (4 H, m, 2 × CH_2Ph), 4.84–5.01 (3 H, m, CH_2Ph and 1-H), 5.29 (1 H, d, $J_{2P,NH}$ 7, CH**P**), 5.55 (1 H, d, $J_{NH,CHP}$ 7, NH), 7.05 (2 H, d, $J_{5',6'} = J_{3',2'} = 8$, 3′- and 5′-H**P**), 7.20–7.43 (17 H, m, ArH); δ_C($CDCl_3$) 28.3 [(CH_3)$_3$C], 52.6 (OCH_3), 56.9 (CH**P**), 68.7 (6-C), 73.4 and 75.0 and 75.2 (3 × *C*H_2Ph), 74.3 and 75.3 and 77.3 (2-, 4- and 5-C), 80.1 [(CH_3)$_3$*C*], 84.3 (3-C), 100.7 (1-C), 117.2 (3′- and 5′-C**P**), 127.7–128.4 (Ar-C), 131.1 (1′-C**P**), 137.9 and 138.4 [Cq(Ph)], 152.7 (4′-C**P**), 157.2 (OCONH) and 167.0 (CO_2Me); *m*/*z* (ES) 736 $(M + Na)^+$.

4-*O*-Acetyl-1,5-anhydro-2,3,6-trideoxy-3-trifluoroacetamido-L-*arabino*-hex-1-enitol 13

1,5-Anhydro-2,3,6-trideoxy-3-trifluoroacetamido-L-*arabino*-hex-1-enitol[15] **12** (344 mg, 1.60 mmol) was treated with acetic anhydride (2 cm^3) in pyridine at rt for 16 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate (25 cm^3). The organic layer was washed successively with cold 1 M sulfuric acid (25 cm^3), water (25 cm^3) and saturated aq. sodium hydrogen carbonate (25 cm^3). The solvent was removed under reduced pressure to give 4-*O*-acetyl-1,5-anhydro-2,3,6-trideoxy-3-trifluoroacetamido-L-*arabino*-hex-1-enitol **13** (366 mg, 85%) as a powder, which was recrystallized from cyclohexane–ethyl acetate (85 : 15 v/v), mp 169–170 °C; $[\alpha]_D^{20}$ −81 (*c* 0.5, $CHCl_3$) (Found: C, 45.05; H, 4.5. Calc. for $C_{10}H_{12}F_3NO_4$: C, 44.95; H, 4.53%); ν_{max}(film)/cm^{-1} 3290 (NH), 1729 (C=O), 1650 and 1455; δ_H($CDCl_3$) 1.30 (3 H, d,

$J_{6,5}$ 6, 6-H), 2.12 (3 H, s, $OCOCH_3$), 4.07 (1 H, dq, $J_{5,4}$ 9, $J_{5,6}$ 6, 5-H), 4.66 (1 H, dd, $J_{2,1}$ 6, $J_{2,3}$ 2, 2-H), 4.78 (1 H, ddt, $J_{3,4}$ 9, $J_{3,NH}$ 7, $J_{3,2} = J_{3,1} = 2$, 3-H), 4.91 (1 H, t, $J_{4,5} = J_{4,3} = 9$, 4-H), 6.42 (1 H, dd, $J_{1,2}$ 6, $J_{1,3}$ 2, 1-H) and 6.85 (1 H, d, J 7, NH); $\delta_C(CDCl_3)$, 16.9 (6-C), 20.5 ($OCOCH_3$), 49.2 (3-C), 72.8 and 73.0 (4- and 5-C), 99.0 (2-C), 115.6 (q, J 279, CF_3), 146.0 (1-C), 152.7 (NHCO) and 171.1 ($OCOMe$); *m/z* (CI) 285 $(M + NH_4)^+$.

4-[2-*O*-(4-*O*-Acetyl-2,3,6-trideoxy-3-trifluoroacetamido-α-L-*arabino*-hexopyranosyl)-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyloxy]-D-phenylglycine methyl ester 14

A solution of *N*-Boc-4-(3,4,6-tri-*O*-benzyl-β-D-glucopyranosyloxy)-D-phenylglycine methyl ester **11** (929 mg, 1.30 mmol) and 4-*O*-acetyl-1,5-anhydro-2,3,6-trideoxy-3-trifluoroacetamido-L-*arabino*-hex-1-enitol **13** (348 mg, 1.30 mmol) in anhydrous dichloromethane (5 cm^3) containing powdered molecular sieves 4 Å was stirred under argon for 1 h at rt. The reaction mixture was then cooled to −45 °C and stirred for 15 min, and then TMSOTf (252 mm^3, 1.30 mmol) was added dropwise. The mixture was stirred at −45 °C for 45 min and allowed to warm to rt gradually overnight. After the reaction had been quenched by addition of triethylamine (500 mm^3), the solution was filtered and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (35–70 μm) with dichloromethane–methanol (97:3 v/v) as eluent to give title compound **14** as a powder (980 mg, 85%), which was recrystallized from dichloromethane, mp 174–175 °C; $[a]_D^{20}$ −56 (*c* 0.1, $CHCl_3$) (Found: C, 62.55; H, 5.8. Calc. for $C_{46}H_{51}F_3NO_{12}$: C, 62.72; H, 5.83%); ν_{max}(film)/cm^{-1} 3315 (NH), 2927, 2857, 1737 (C=O), 1509, 1454, 1376, 1238 and 1162 and 1066 (C–O); $\delta_H(CDCl_3)$ 1.21 (3 H, d, $J_{6',5'}$ 6, 6′-H_3), 1.58 (1 H, m, 2′-H^{eq}), 1.91 (2 H, s, NH_2), 2.06 (3 H, s, $OCOCH_3$), 2.09 (1 H, m, 2′-H^{ax}), 3.72 (3 H, s, OCH_3), 3.61–3.83 (5 H, m, 3-, 4- and 5-H, 6-H_2), 3.93 (1 H, t, $J_{2,1} = J_{2,3} = 8$, 2-H), 4.27–4.44 (2 H, m, 3′- and 5′-H), 4.61 (1 H, s, CH**P**), 4.49–5.02 (7 H, m, 3 × CH_2Ph and 4′-H), 4.99 (1 H, d, $J_{1,2}$ 8, 1-H), 5.34 (1 H, dd, $J_{1',2'ax}$ 3, $J_{1',2'eq}$ 1, 1′-H), 6.79 (1 H, d, J 8, NH), 7.01 (2 H, d, $J_{5'P,6'P} = J_{3'P,2'P} = 9$, 3′- and 5′-H**P**) and 7.16–7.40 (17 H, m, ArH); $\delta_C(CDCl_3)$ 17.5 (6′-C), 20.6 ($OCOCH_3$), 35.5 (2′-C), 48.0 (3′-C), 52.4 (OCH_3), 58.1 (CH**P**), 65.7 (5′-C), 68.5 (6-C), 73.5 (4′-C), 75.0 and 75.2 (3 × CH_2Ph), 76.6 (2-C), 75.6 and 78.2 (4- and 5-C), 85.8 (3-C), 96.6 (1′-C), 99.0 (1-C), 116.7 (3′- and 5′-C**P**), 127.4–128.5 (Ar-C), 134.4 and 137.6 and 137.9 [Cq(Ph)], 156.7 (4′-C**P**) and 172.1 and 174.5 (CO_2Me and $OCOMe$); *m/z* (ES) 881 $(M + Na)^+$.

***N*-(*N*-Boc-L-phenylalanyl)-4-[2-*O*-(4-*O*-acetyl-2,3,6-trideoxy-3-trifluoroacetamido-α-L-*arabino*-hexopyranosyl)-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyloxy]-D-phenylglycine methyl ester 17**

Activation. *N*-Methylmorpholine (NMM) (12.8 mm^3, 0.11 mmol) was added dropwise to a stirred solution of CDMT (20 mg, 0.11 mmol) and *N*-Boc-L-phenylalanine **15** (31 mg, 0.11 mmol) in dichloromethane (10 cm^3) at −5 to 0 °C. The reaction mixture was stirred for 2.5 h at 0 °C until complete consumption of CDMT (checked by TLC).

Coupling. A solution of compound **14** (100 mg, 0.11 mmol) and NMM (12.5 mm^3, 0.11 mmol) in dichloromethane (5 cm^3) was added to the crude solution obtained as described above at −5 to 0 °C. The reaction mixture was stirred for 3 h at 0 °C, then for 16 h at rt. The solvent was removed under reduced pressure and the residue was suspended in ethyl acetate (30 cm^3). The suspension was washed successively with water (10 cm^3), 1 M hydrochloric acid (10 cm^3), saturated aq. sodium hydrogen carbonate (10 cm^3) and water (10 cm^3). The organic layer was dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (35–70 μm) with dichloromethane–methanol (99:1 v/v) as eluent to give title compound **17** (110 mg, 86%) as a powder, which was recrystallized from methanol, mp 203 °C, $[a]_D^{20}$ −44 (*c* 0.9, $CHCl_3$) (Found: C, 63.8; H, 6.1. Calc. for $C_{60}H_{68}F_3NO_{15}$: C, 63.87; H, 6.08%); ν_{max}(film)/cm^{-1} 3341 (NH), 1725 and 1670 (C=O), 1509, 1239 and 1165 and 1065 (C–O); $\delta_H(CDCl_3)$ 1.22 (3 H, d, $J_{6',5'}$ 6, 6′-H_3), 1.38 and 1.41 and 1.44 (9 H, s, Bu^t), 1.62 (1 H, m, 2′-H^{eq}), 1.74 (1 H, s, NH), 1.91 (1 H, s, NH), 2.02 (3 H, s, $OCOCH_3$), 2.08 (1 H, m, 2′-H^{ax}), 3.09 (2 H, m, $CH_2\mathbf{F}_1$), 3.70 (3 H, s, OCH_3), 3.58–3.82 (5 H, m, 3-, 4- and 5-H, 6-H_2), 3.93 (1 H, t, $J_{2,1} = J_{2,3} = 8$, 2-H), 4.27–4.42 (2 H, m, 3′- and 5′-H), 4.53 (1 H, d, $J_{1,2}$ 2, $CH\mathbf{F}_1$), 4.96 (1 H, d, $J_{1,2}$ 8, 1-H), 4.47–5.04 (7 H, m, 3 × CH_2Ph and 4′-H), 5.34 (1 H, m, 1′-H), 5.47 (1 H, m, CH**P**), 6.84 (1 H, d, J 8, NH), 6.94–7.40 (24 H, m, ArH); $\delta_C(CDCl_3)$ 17.5 (6′-C), 20.6 ($OCOCH_3$), 28.2 [$(CH_3)_3C$], 35.4 (2′-C), 38.5 ($CH_2\mathbf{F}_1$), 47.8 (3′-C), 52.7 (OCH_3), 55.7 (CH**P**), 65.7 (5′-C), 68.4 (6-C), 74.9 and 73.4 (2 × CH_2Ph), 75.2 (4′-C and $CH\mathbf{F}_1$), 75.6 (CH_2Ph), 76.5 (2-C), 76.1 and 78.1 (4- and 5-C), 80.5 [$(CH_3)_3C$], 85.7 (3-C), 96.4 (1′-C), 98.9 (1-C), 116.9 (3′- and 5′-C**P**), 126.9–130.0 (Ar-C), 136.4 and 137.6 and 137.9 [Cq(Ph)], 157.0 (OCONH) and 170.5 and 170.7 and 172.1 (CO_2Me, $OCOMe$ and NHCO); *m/z* (ES) 1150 $(M + Na)^+$.

***N*-(*N*-Z-L-phenylalanyl)-4-[2-*O*-(4-*O*-acetyl-2,3,6-trideoxy-3-trifluoroacetamido-α-L-*arabino*-hexopyranosyl)-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyloxy]-D-phenylglycine methyl ester 18**

To an ice-cooled solution of compound **14** (300 mg, 0.34 mmol), 1-hydroxybenzotriazole (HOBT) (51 mg, 0.37 mmol), *N*-Z-L-phenylalanine **16** (102 mg, 0.34 mmol) and triethylamine (57 mm^3, 0.41 mmol) in dry DMF (20 cm^3) was added EDCI (78 mg, 0.41 mmol). The reaction mixture was stirred for 1.5 h at 0 °C then for 16 h at rt. The solvent was removed under reduced pressure and the residue was suspended in dichloromethane (50 cm^3). The suspension was washed successively with 1 M hydrochloric acid (40 cm^3), saturated aq. sodium hydrogen carbonate (40 cm^3) and brine (40 cm^3). The organic layer was dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (35–70 μm) with dichloromethane–methanol (99:1 v/v) as eluent to give title compound **18** (333 mg, 84%) as a powder, which was recrystallized from methanol, mp 217–219 °C; $[a]_D^{20}$ −45 (*c* 0.5, $CHCl_3$) (Found: C, 65.0; H, 5.7. Calc. for $C_{63}H_{66}F_3N_3O_{15}$: C, 65.11; H, 5.72%); ν_{max}(film)/cm^{-1} 3314 (NH), 3064, 2948, 1742–1708 and 1678 (C=O), 1530, 1511, 1376, 1241–1166 and 1060 (C–O); $\delta_C(CDCl_3)$ 1.22 (3 H, d, $J_{6',5'}$ 6, 6′-H_3), 1.62 (1 H, m, 2′-H^{eq}), 1.94 (1 H, s, NH), 2.02 (3 H, s, $OCOCH_3$), 2.08 (1 H, m, 2′-H^{ax}), 3.08 (2 H, m, $CH_2\mathbf{F}_1$), 3.70 (3 H, s, OCH_3), 3.59–3.83 (5 H, m, 3-, 4- and 5-H, 6-H_2), 3.93 (1 H, t, $J_{2,1} = J_{2,3} = 8$, 2-H), 4.27–4.43 (2 H, m, 3′- and 5′-H), 4.53 (1 H, m, $CH\mathbf{F}_1$), 4.97 (1 H, d, $J_{1,2}$ 8, 1-H), 4.47–5.05 (9 H, m, 3 × CH_2Ph, 4′-H and CH_2OCO), 5.34 (1 H, m, 1′-H), 5.43 (1 H, d, $J_{2P,NH}$ 7, CH**P**), 6.83 (1 H, d, J 8, NH), 6.94 (1 H, m, NH), 6.90–7.40 (29 H, m, ArH); $\delta_C(CDCl_3)$ 17.6 (6′-C), 20.6 ($OCOCH_3$), 35.5 (2′-C), 38.8 ($CH_2\mathbf{F}_1$), 47.9 (3′-C), 52.8 (OCH_3), 55.8 (CH**P** and $CH\mathbf{F}_1$), 65.7 (5′-C), 67.0 (CH_2OCO), 68.4 (6-C), 73.4 and 74.9 (2 × CH_2Ph), 75.2 (4′-C), 76.6 (2-C), 75.6 and 78.1 (4- and 5-C), 85.8 (3-C), 96.7 (1′-C), 98.9 (1-C), 116.8 (3′- and 5′-C**P**), 126.9–129.9 (Ar-C), 136.5 and 137.6 and 137.9 [Cq(Ph)], 157.0 (OCONH) and 170.1 and 170.8 and 172.2 (CO_2Me, $OCOMe$ and NHCO); *m/z* (ES) 1184 $(M + Na)^+$.

***N*-(*N*-Z-L-phenylalanyl-L-phenylalanyl)-4-[2-*O*-(4-*O*-acetyl-2,3,6-trideoxy-3-trifluoroacetamido-α-L-*arabino*-hexopyranosyl)-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyloxy]-D-phenylglycine methyl ester 20**

Synthesized by a procedure essentially similar to that described for the synthesis of compound **18**. To an ice-cooled solution of compound **14** (350 mg, 0.40 mmol), HOBT (65 mg, 0.44 mmol), *N*-Z-L-phenylalanyl-L-phenylalanine[16] **19** (177 mg, 0.40 mmol) and triethylamine (66 mm^3, 0.48 mmol) in dry DMF (30 cm^3) was added EDCI (91 mg, 0.48 mmol). The reaction mixture was stirred for 1.5 h at 0 °C then for 16 h at rt. The solvent was removed under reduced pressure and the residue was suspended in dichloromethane (50 cm^3). The suspension was

washed successively with 1 M hydrochloric acid (40 cm^3), saturated aq. sodium hydrogen carbonate (40 cm^3) and brine (40 cm^3). The organic layer was dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (35–70 μm) with dichloromethane–methanol (99 : 1 v/v) as eluent to give title compound **20** (406 mg, 78%) as a powder, which was recrystallized from methanol, mp 196–197 °C; $[\alpha]_D^{20}$ −47 (*c* 0.5, $CHCl_3$–MeOH 1 : 1 v/v) (Found: C, 66.2; H, 5.8. Calc. for $C_{72}H_{75}F_3N_4O_{16}$: C, 66.04; H, 5.77%); ν_{max}(film)/cm^{-1} 3401 and 3307 (NH), 3060, 3031, 2925, 1734 and 1719 and 1653 (C=O), 1537, 1508, 1374, 1238 and 1162 and 1061 (C–O); δ_H($CDCl_3$) 1.22 (3 H, d, $J_{6',5'}$ 6, 6′-H_3), 1.59 (1 H, m, 2′-H^{eq}), 1.98 (1 H, s, NH), 2.02 (3 H, s, $OCOCH_3$), 2.08 (1 H, m, 2′-H^{ax}), 3.05 (4 H, m, $CH_2\mathbf{F}_1$ and $CH_2\mathbf{F}_2$), 3.70 (3 H, s, OCH_3), 3.54–3.81 (5 H, m, 3-, 4- and 5-H, 6-H_2), 3.92 (1 H, t, $J_{2,1} = J_{2,3} = 8$, 2-H), 4.25–4.43 (3 H, m, 3′- and 5′-H and $CH\mathbf{F}_1$), 4.95 (1 H, d, $J_{1,2}$ 8, 1-H), 4.45–5.08 (10 H, m, 3 × CH_2Ph, 4′-H, $CH\mathbf{F}_2$ and CH_2OCO), 5.34 (1 H, m, 1′-H), 5.41 (1 H, d, *J* 7, CH**P**), 5.46 (1 H, d, *J* 7, NH), 6.50 (1 H, d, *J* 8, NH), 6.57 (1 H, d, *J* 7, NH), 6.87–7.40 (34 H, m, ArH); δ_C($CDCl_3$) 17.6 (6′-C), 20.6 ($OCOCH_3$), 35.5 (2′-C), 38.1 ($CH_2\mathbf{F}_1$ and $CH_2\mathbf{F}_2$), 48.0 (3′-C), 52.8 (OCH_3), 54.1 ($CH\mathbf{F}_2$), 56.1 (CH**P** and $CH\mathbf{F}_1$), 65.7 (5′-C), 67.2 (CH_2OCO), 68.3 (6-C), 73.4 (CH_2Ph), 75.0 (2 × CH_2Ph and 4′-C), 76.6 (2-C), 75.6 and 78.1 (4- and 5-C), 85.7 (3-C), 96.5 (1′-C), 99.2 (1-C), 116.7 (3′- and 5′-C**P**), 127.1–129.7 (Ar-C), 135.9 and 137.6 and 137.9 [Cq(Ph)], 157.0 (OCONH) and 169.5, 170.9 and 172.2 (CO_2Me, OCOMe and NHCO); *m*/*z* (ES) 1331 $(M + Na)^+$.

L-Phenylalanyl-L-phenylalanine *tert*-butyl ester 21

Palladium on activated carbon (10%; 242 mg) was added to a solution of *N*-Z-L-phenylalanyl-L-phenylalanine *tert*-butyl ester[17] (2.42 g, 4.82 mmol) in methanol (25 cm^3). After the reaction mixture had been stirred for 5 h under hydrogen (1 atm.), it was filtered through a Celite pad and the filtrate was evaporated under reduced pressure to give title ester **21** as a powder (1.75 g, 81%), which was recrystallized from cyclohexane, mp 68 °C; $[\alpha]_D^{20}$ +4 (*c* 1, $CHCl_3$) (Found: C, 71.8; H, 7.65; N, 7.6. Calc. for $C_{22}H_{28}N_2O_3$: C, 71.71; H, 7.66; N, 7.60%); ν_{max}(film)/cm^{-1} 3356 (NH), 3025, 2965, 2917, 1733 and 1668 (C=O) and 1497; δ_H($CDCl_3$) 1.40 (9 H, s, Bu^t), 1.47 (2 H, s, NH_2), 2.61 {1 H, dd, *J*[Hb,Ha($CH_2\mathbf{F}_2$)] 13.5, *J*(Hb,$CH_2\mathbf{F}_2$) 9, H^b/$CH_2\mathbf{F}_2$}, 3.07 [2 H, d, *J*(Ha,$CH_2\mathbf{F}_2$) 6, $CH_2\mathbf{F}_1$], 3.17 {1 H, dd, *J*[Ha,Hb(CH_2F_2)] 13.5, *J*(CH,Hb$\mathbf{F}_2$) 4, H^a/$CH_2\mathbf{F}_2$}, 3.61 {1 H, dd, *J*(CH,Ha$\mathbf{F}_2$) 9, *J*[CH,Hb(F_2)] 4, $CH\mathbf{F}_2$}, 4.77 [1 H, td, *J*(CH,NH$\mathbf{F}_1$) 8, *J*(CH,$CH_2\mathbf{F}_1$) 6, $CH\mathbf{F}_1$], 7.06–7.36 (10 H, m, ArH) and 7.77 [1 H, d, *J*(NH,$CH\mathbf{F}_1$) 8, NH]; δ_C($CDCl_3$) 27.8 [(CH_3)$_3$C], 38.1 and 40.6 (2 × $CH_2\mathbf{F}$), 53.0 and 56.0 (2 × CH**F**), 82.2 [(CH_3)$_3$*C*], 126.8–129.4 (Ar-C), 136.1 and 137.5 [Cq(Ph)], 170.6 (NHCO) and 173.9 (CO_2Bu^t); *m*/*z* (CI) 369 $(M + H)^+$ and 386 $(M + NH_4)^+$.

N-Z-D-phenylglycyl-L-phenylalanyl-L-phenylalanine *tert*-butyl ester 22

To an ice-cooled solution of L-phenylalanyl-L-phenylalanine *tert*-butyl ester **21** (1 g, 2.62 mmol), *N*-Z-D-phenylglycine[18] (746 mg, 2.62 mmol) and HOBT (354 mg, 2.62 mmol) in anhydrous DMF containing Et_3N (375 mm^3, 2.62 mmol) was added EDCI (502 mg, 2.62 mmol) portionwise. The reaction mixture was stirred for 1.5 h at 0 °C and then for 16 h at rt. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (100 cm^3). The solution was washed successively with 1 M hydrochloric acid (2 × 50 dm^3) and brine (50 cm^3). The organic layer was dried ($MgSO_4$), and evaporated under reduced pressure to give title compound **22** (1.57 g, 95%) as a powder, which was recrystallized from cyclohexane, mp 188 °C; $[\alpha]_D^{20}$ −18 (*c* 0.5, $CHCl_3$) (Found: C, 71.8; H, 6.5; N, 6.6. Calc. for $C_{38}H_{41}N_3O_6$: C, 71.79; H, 6.50; N, 6.61%); ν_{max}(KBr)/cm^{-1} 3288 (NH), 3061, 2989, 1735 and 1694 and 1644 (C=O) and 1532; δ_H($CDCl_3$) 1.45 (9 H, s, Bu^t), 2.95 (2 H, m, $CH_2\mathbf{F}$), 2.98 [2 H, d, *J*(CH_2,CH**F**) 7, $CH_2\mathbf{F}$], 4.64 [1 H, td, *J*(CH,$CH_2\mathbf{F}$) = *J*(CH, NH**F**) = 7, CH**F**], 4.79 (1 H, m, CH**F**), 5.06 (2 H, s, CH_2OCO), 5.30 [1 H, d, *J*(CH,NH**P**′) 6, CH**P**′], 6.46 (1 H, s, NH), 6.62 (1 H, s, NH), 6.77 [1 H, d, *J*(NH,CH**F**) 7, NH] and 6.98–7.40 (20 H, m, ArH); δ_C($CDCl_3$) 27.8 [(CH_3)$_3$C], 38.0 (2 × $CH_2\mathbf{F}$), 53.7 and 54.0 (2 × CH**F**), 58.7 (CH**P**′), 66.9 (CH_2OCO), 82.3 [(CH_3)$_3$*C*], 126.8–129.4 (Ar-C), 135.6, 135.8, 136.2 and 138.0 [Cq(Ph)], 155.6 (OCONH), 169.6 and 170.1 (CO_2Bu^t and NHCO); *m*/*z* (CI) 636 $(M + H)^+$, 653 $(M + NH_4)^+$.

N-Z-D-phenylglycyl-L-phenylalanyl-L-phenylalanine 23

To a solution of dry dichloromethane (50 cm^3) and TFA (20 cm^3) was added *N*-Z-D-phenylglycyl-L-phenylalanyl-L-phenylalanine *tert*-butyl ester **22** (1.42 g, 2.24 mmol). The reaction mixture was stirred for 5 h at rt, then was evaporated under reduced pressure to eliminate excess of TFA to give title acid **23** (1.23 g, 95%) as a powder, which was recrystallized from ethyl acetate, mp 220 °C; $[\alpha]_D^{20}$ −33 (*c* 0.5, DMF) (Found: C, 70.5; H, 5.7; N, 7.2. Calc. for $C_{34}H_{33}N_3O_6$: C, 70.75; H, 5.74; N, 7.25%); δ_H($CDCl_3$) 2.69–3.13 (4 H, m, 2 × $CH_2\mathbf{F}$), 4.48 (2 H, m, 2 × CH**F**), 5.03 (2 H, s, CH_2OCO), 5.32 [1 H, d, *J*(CH,NH**P**′) 9, CH**P**′], 6.46 (1 H, s, NH), 6.62 (1 H, s, NH), 6.77 [1 H, d, *J*(NH,CH**F**) 7, NH] and 6.98–7.40 (20 H, m, Ar-H); δ_C($CDCl_3$) 27.8 [(CH_3)$_3$C], 37.9 (2 × $CH_2\mathbf{F}$), 53.7 and 54.0 (2 × CH**F**), 58.7 (CH**P**′), 66.9 (CH_2OCO), 82.3 [(CH_3)$_3$*C*], 126.8–129.4 (Ar-C), 135.6, 135.8, 136.2 and 138.0 [Cq(Ph)], 155.6 (OCONH) and 169.6 and 170.1 (CO_2Bu^t and NHCO); *m*/*z* (CI) 636 $(M + H)^+$ and 653 $(M + NH_4)^+$.

N-(*N*-Z-D-phenylglycyl-L-phenylalanyl-L-phenylalanyl)-4-[2-*O*-(4-*O*-acetyl-2,3,6-trideoxy-3-trifluoroacetamido-α-L-*arabino*-hexopyranosyl)-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyloxy]-D-phenylglycine methyl ester 24

Synthesized by a procedure essentially similar to that described for the synthesis of compound **18**. To an ice-cooled solution of compound **14** (500 mg, 0.57 mmol), HOBT (85 mg, 0.63 mmol), *N*-Z-D-phenylglycyl-L-phenylylalanyl-L-phenylylalanine **23** (329 mg, 0.57 mmol) and triethylamine (95 mm^3, 0.68 mmol) in dry DMF (40 cm^3) was added EDCI (131 mg, 0.68 mmol). The reaction mixture was stirred for 2 h at 0 °C then for 16 h at rt. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (80 cm^3). The solution was washed successively with 1 M hydrochloric acid (50 cm^3), saturated aq. sodium hydrogen carbonate (50 cm^3) and brine (50 cm^3). The organic layer was dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by column chromatography on silica (35–70 μm) with dichloromethane–methanol (99 : 1 v/v) as eluent to give title compound **24** (681 mg, 83%) as a powder, which was recrystallized from methanol, mp 220–222 °C; $[\alpha]_D^{20}$ −38 (*c* 0.5, DMF) (Found: C, 66.5; H, 5.7. Calc. for $C_{80}H_{82}F_3N_5O_{17}$: C, 66.61; H, 5.73%); ν_{max}(film)/cm^{-1} 3302 (NH), 3060, 3025, 2931, 1740–1706 and 1642 (C=O), 1543, 1509, 1376, 1239–1164 and 1064 (C–O); δ_H(CD_3OD) 1.02 (3 H, d, $J_{6',5'}$ 6, 6′-H_3), 1.59 (1 H, m, 2′-H^{eq}), 1.74 (1 H, m, 2′-H^{ax}), 1.80 (3 H, s, $OCOCH_3$), 2.80 (4 H, m, $CH_2\mathbf{F}_1$ and $CH_2\mathbf{F}_2$), 3.50 (3 H, s, OCH_3), 3.39–3.65 (5 H, m, 3-, 4- and 5-H, 6-H_2), 3.73 (1 H, m, 2-H), 4.10–4.27 (2 H, m, 3′- and 5′-H), 4.31–5.05 (13 H, m, 3 × CH_2Ph, 4′-H, $CH\mathbf{F}_1$, $CH\mathbf{F}_2$, CH**P**′, 1-H and CH_2OCO), 5.17 (1 H, m, 1′-H), 5.28 (1 H, d, *J* 3, CH**P**) and 6.78–7.22 (39 H, m, ArH); δ_C(CD_3OD) 17.1 (6′-C), 20.0 ($OCOCH_3$), 34.6 (2′-C), 37.6 ($CH_2\mathbf{F}_1$ and $CH_2\mathbf{F}_2$), 46.4 (3′-C), 52.2 (OCH_3), 54.0 ($CH\mathbf{F}_1$ and $CH\mathbf{F}_2$), 55.6 (CH**P**), 58.3 (CH**P**′), 65.7 (5′-C), 66.7 (CH_2OCO), 68.0 (6-C), 73.1 (CH_2Ph), 74.7 (2 × CH_2Ph and 4′-C), 76.6 (2-C), 75.3 and 77.4 (4- and 5-C), 85.3 (3-C), 96.6 (1′-C), 98.5 (1-C), 116.4 and 116.6 (3′- and 5′-C**P**), 126.4–128.9 (Ar-C), 135.7, 137.3 and 137.6 [Cq(Ph)], 156.9 (OCONH) and 170.3, 171.1, 170.7 and 171.0 (CO_2Me, OCOMe and NHCO); *m*/*z* (ES) 1464 $(M + Na)^+$.

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