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3-Azidoazetidines as the first scaffolds for β-amino azetidine carboxylic acid peptidomimetics: azetidine iminosugars containing an acetamido group do not inhibit β-*N*-acetylhexosaminidases

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ABSTRACT

Stable amides and oligopeptides derived from methyl *trans,trans*-3-azido-4-hydroxymethyl-L-azetidine carboxylate, prepared in 19% yield from diacetone allose, is the first example of a β-amino-azetidine carboxylic acid incorporated into peptidomimetics and provides a scaffold for investigating secondary structure induced by a novel β-amino acid. A number of azetidine iminosugars containing a NHAc substituent were prepared but none of them were β-*N*-acetylhexosaminidase inhibitors.

1. Introduction

The predisposition of conformationally restricted cyclic non-proteinogenic amino acids to induce a wide variety of secondary structural motifs is well established.[1] In particular, the different helical structures adopted by short β-amino acid oligomers[2] encouraged interest in the efficient syntheses of building blocks for alicyclic[3] and heterocyclic[4] β-amino acids.[5] Oxetane β-amino acid oligomers have a predisposition to induce a distinctive range of helical structures.[6] The four-membered ring azetidine carboxylic acid (Aze) **1**, first isolated from *Convallaria majalis*[7] but widely distributed in many plants including sugar beet,[8] can be mis-incorporated for L-proline **2** in proteins.[9] (Fig. 1) Aze alters the α-helix of the polypeptide chain to a smaller angle than that of L-proline and thus leads to changes in secondary and tertiary structures of proteins compared with their proline analogues.[10] Aze is a well-recognized pharmacophore.[11] Although 3-toslyamido-Aze derivatives such as **3** have been described,[12] it was not possible to remove the tosyl protecting group to give the free amine **4** [Fig. 1] and there are no prior examples of β-amino azetidine carboxylic acids as peptidomimetics.

Iminosugars, sugar mimics in which the ring oxygen has been replaced by nitrogen, comprise a large family of glycosidase inhibitors;[13] polyhydroxylated azetidines have been found to inhibit a number of glycosidases[14] as well as possessing other biological activities.[15] Naturally occurring β-*N*-acetylhexosaminidase (hexNAcase) inhibitors with nanomolar K_i include siastatin,[16] pochonicine[17] and nagstatin.[18] Many synthetic monocyclic sugar mimics with an NHAc attached to the ring show potent hexNAcase inhibition[19] including: azepanes such as **5**,[20] piperidines[21] such as DNJNAc **6**[22] and DGJNAc **7**,[23] and pyrrolidines such as LABNAc **8**[24] and XYLNAc **9**.[25] Examples of submicromolar inhibition of attached exocyclic NHAc groups include the pyrrolidine ADMDP **10** together with several stereoisomers,[26] and the homoDMDP analog **11**.[27] The azetidine analog **12** is a weak hexNAcase inhibitor.[28] The pipecolic acid amide **13**[29] and the proline amide **14**[30] have nanomolar K_i for HexNAcase inhibition. The ring contracted azetidine amide **15** was the first reported micromolar azetidine inhibitor of hexNAcases but was vulnerable to reverse aldol ring cleavage to **16** at pH >8 (Scheme 1).[31]

This paper reports the synthesis of the *trans*-3-azido Aze **19** as the first building block for the incorporation of β-amino-Aze derivatives into peptides, exemplified by the tripeptide **24** (Scheme 1). The azetidine bisamide **22** was stable to both acid and base in marked contrast to the oxetane hydroxyAze amide **15**; oxygenated azetidine peptides are susceptible to fragmentation.[32] The azetidines **20**, **21**, **22** and **23** containing an NHAc substituent on the azetidine ring were assayed as potential

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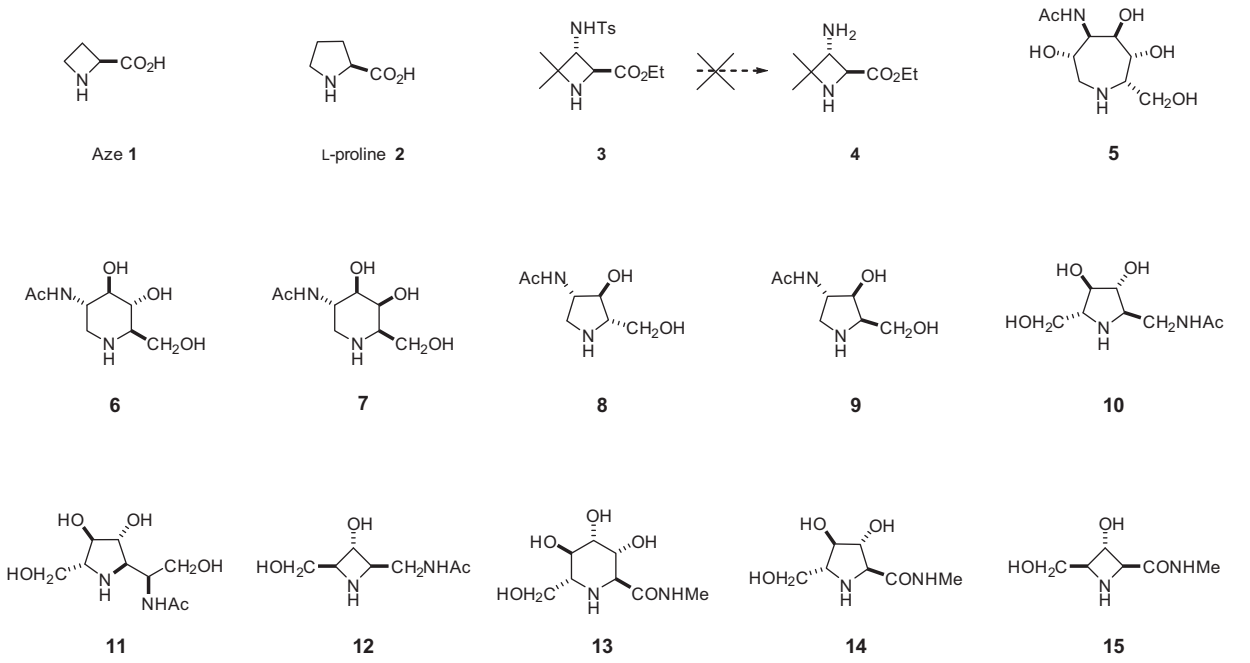
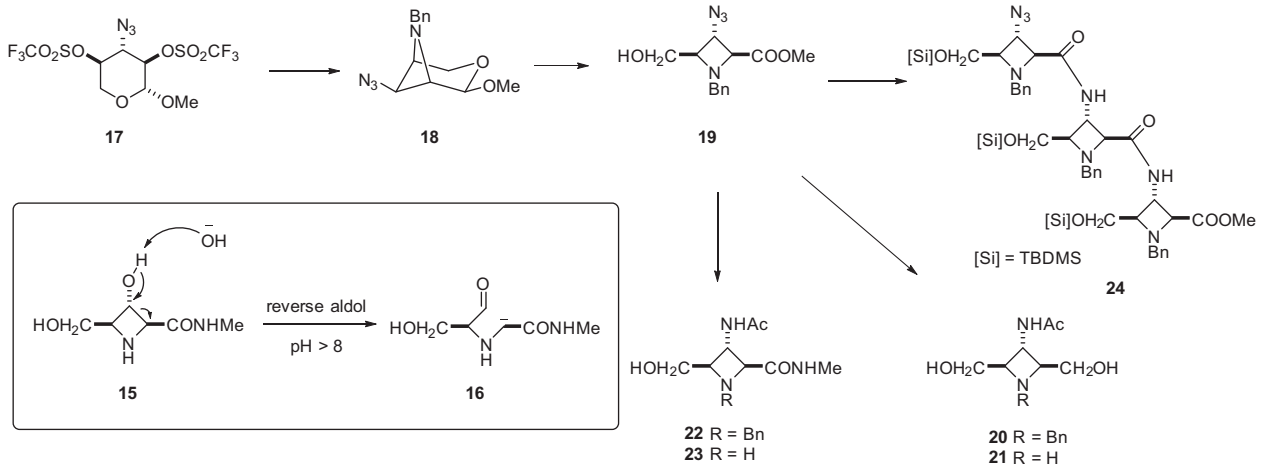


Figure 1. Azetidine structures and monocyclic iminosugar hexNAcase inhibitors.

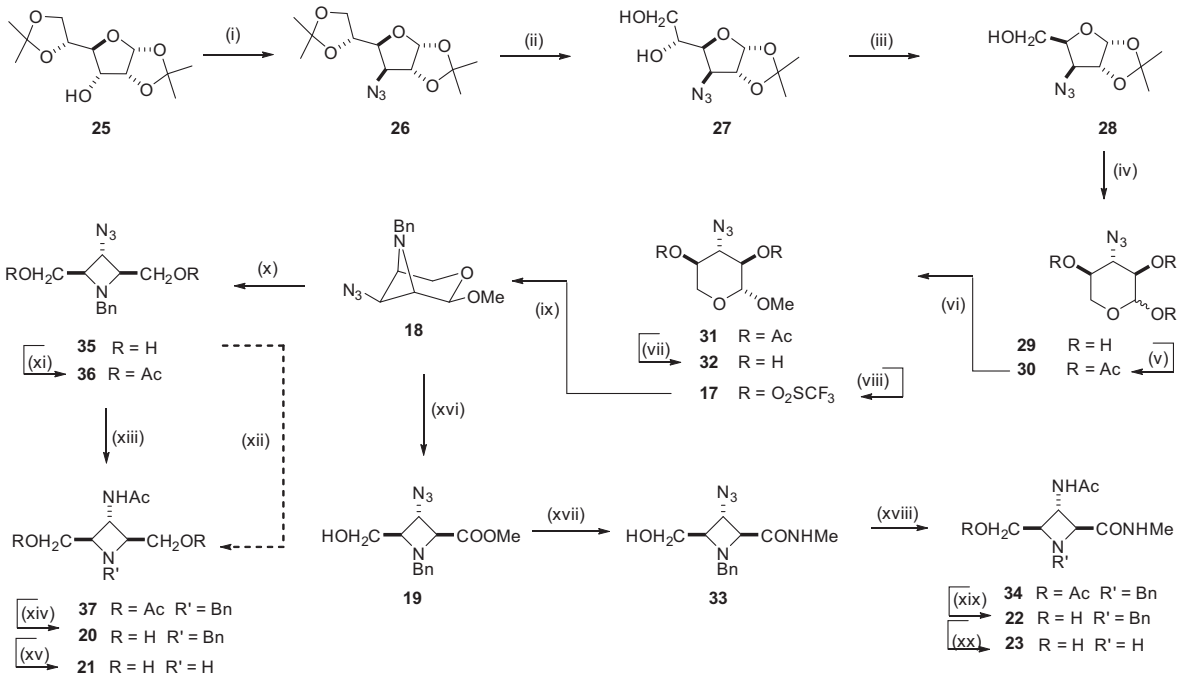


Scheme 1. Synthetic strategy for the synthesis of β-amino-Aze and related iminosugars.

inhibitors of glycosidases. Treatment of 1,3-ditriflates[33] derived from sugars with primary amines is a successful strategy for the synthesis of highly functionalised azetidines. In particular, the reaction of benzylamine with 2,4-di-*O*-triflates of pyranosides in which all the substituents are equatorial give excellent yields of bicyclic azetidines:[34] the key step in the synthesis of the 3-azido azetidine **19** is the reaction of the pyranose ditriflate **17** with benzylamine to give the bicyclic azetidine **18**.

2. Synthesis

Diacetone allose **25** was esterified with triflic anhydride in dichloromethane in the presence of pyridine (Scheme 2); the resulting triflate was treated with sodium azide in DMF to give the *gluco*-azide **26** on a multigram scale (78% over two steps). Selective hydrolysis of the side chain acetonide in **26** by aqueous acetic acid gave diol **27** (60%) which, on periodate cleavage and subsequent borohydride reduction, afforded the *xylo*-azide **28** (96%). Hydrolysis of **28** by DOWEX® 50 W X8-200 resin (H^+ form) in water gave an anomeric mixture of 3-azidoxylose **29** (100%). Acetylation of **29** in the presence of pyridine gave the triacetate **30** as an anomeric mixture (α:β, 10:3) in 98% yield. Treatment of the triacetate **30** with HBr in acetic acid, followed by reaction of the anomeric bromides with silver carbonate in methanol gave the β-methyl pyranoside **31** in a poor yield (30%, 2 steps). A higher yield was achieved using an alternative bromination procedure:[35] **30** was reacted with bismuth(III) bromide in the presence of bromotrimethylsilane to form the crude bromides which, on treatment with silver carbonate in methanol, gave the β-methyl azidopyranoside **31** in a yield of 74% (2 steps). Methanolysis of the acetates in **31** with sodium methoxide in methanol gave the diol **32**. Esterification of **32** with triflic anhydride in the presence of pyridine in DCM gave the crude ditriflate **17**; subsequent reaction of **17** with benzylamine in acetonitrile formed the bicyclic azetidine **18** in 71% over 3 steps. Hydrolysis of **18** in aqueous acid with subsequent oxidation of the lactol by iodine in methanol[36] gave the



Scheme 2. Reagents and conditions: (i) Tf_2O/pyridine, CH_2Cl_2, −30 °C; then NaN_3, DMF, 78% (2 steps); (ii) CH_3COOH/water (7:3), 60%; (iii) $NaIO_4$, water then $NaBH_4$, EtOH, 96% (2 steps); (iv) DOWEX® 50WX8-200, 1,4-dioxane/water (1:1), 80 °C, 100%; (v) Ac_2O/pyridine, 98%; (vi) $BiBr_3$, TMSBr, CH_2Cl_2, then Ag_2CO_3, $CaSO_4$, 74%; (vii) NaOMe, MeOH, 40 °C, 100%; (viii) Tf_2O/pyridine, CH_2Cl_2, −30 °C; (ix) $BnNH_2$, acetonitrile, 70 °C, 71% (2 steps); (x) HCl (2 M, aq)/1,4-dioxane (5:1), 40 °C; then $NaBH_4$, MeOH; (xi) Ac_2O/pyridine, 76% (3 steps from **18**); (xii) zinc powder, $CuSO_4$, THF/AcOH/Ac_2O, 24% (3 steps from **18**); (xiii) zinc powder, $CuSO_4$, THF/AcOH/Ac_2O, 100%; (xiv) MeONa, MeOH, 60 °C, 79%; (xv) Pd/C, H_2, water, 73%; (xvi) HCl (2 M, aq)/1,4-dioxane (5:1), 40 °C; then I_2, K_2CO_3, 81% (2 steps); (xvii) $MeNH_2$, $CaCl_2$, 80%; (xviii) Zinc powder, $CuSO_4$, THF/AcOH/Ac_2O; (xix) then MeONa, MeOH, 85% (2 steps); (xx) Pd/C, H_2, water/1,4-dioxane (1:2), 72%.

methyl Aze ester **19** (85%, 2 steps). The β-azido Aze **19**, the first building block for the incorporation of β-amino Aze into peptides, was formed in an overall yield of 19% from diacetone allose **25**.

Treatment of the ester **19** with methylamine and calcium chloride gave methyl amide **33** (80%).[37] Reductive acetylation with zinc powder and copper sulfate in THF/acetic acid/acetic anhydride formed **34**.[38] Methanolysis of the *O*-acetyl group in **34** gave **22** (85%, 2 steps from **33**); subsequent hydrogenolysis of the *N*-benzyl group in **22** afforded the diamide **23** (9% from **25**). **22** and **23** are the equivalent of a β -amino Aze fragment in a peptide and establish the stability of such moieties as peptidomimetics.

The 3-acetamidoazetidine diols **20** and **21** were also prepared as potential hexNAcase inhibitors. Acidic hydrolysis of **18**, followed by the reduction of the lactol with sodium borohydride, gave the crude diol **35**. Purification of diol **35** with DOWEX resin (H^+ form) column or flash column chromatography was not effective; reductive acetylation of crude azide **35** with zinc powder in the presence of copper sulfate in a mixture of THF/acetic acid/acetic anhydride formed triacetate **37** in a low yield of 24% (3 steps from bicycle **18**). In contrast, initial acetylation of diol **35** gave the easily purified diacetate **36** (76% from bicycle **18**). Subsequent reductive acetylation of **36** by zinc powder gave triacetate **37** (100%). Removal of the *O*-acetate in **37** with methoxide gave **20** (79%) which, on *N*-benzyl deprotection by hydrogenolysis, formed the 3-acetamidoazetidine diol **21** (10% from **25**).

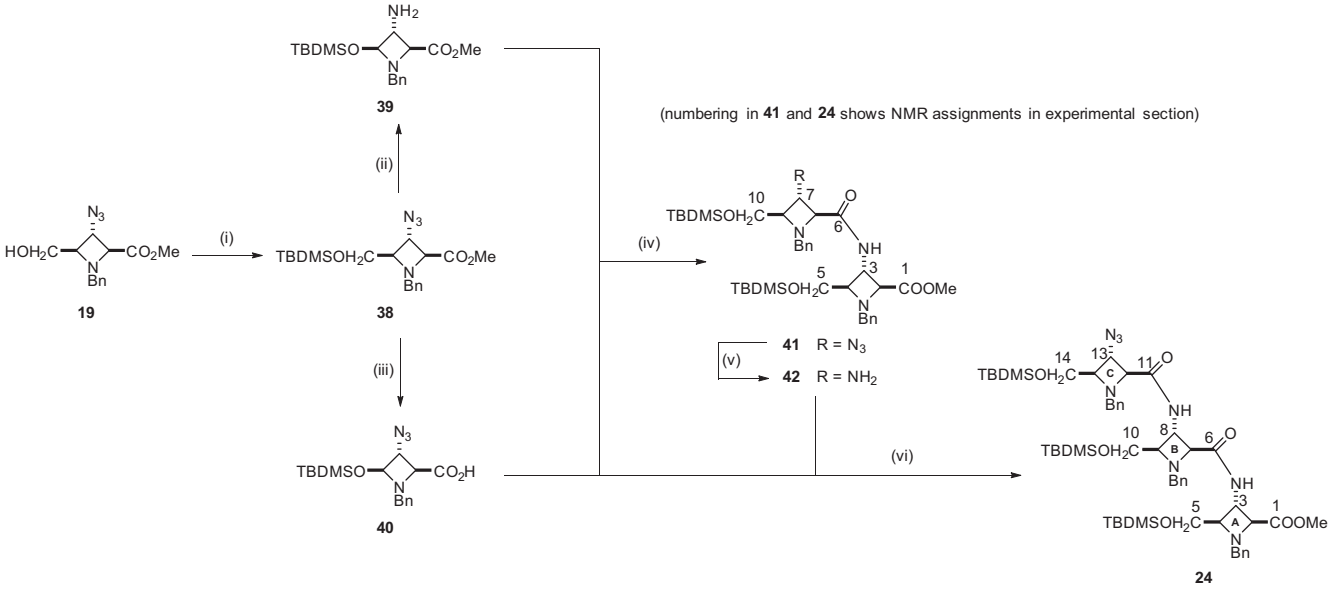
In order to establish the viability of using **19** as a β-amino Aze scaffold, the dipeptide **41** and the tripeptide **24** were prepared as peptidomimetics (Scheme 3). The protection of the primary hydroxyl in methyl ester **19** with *tert*-butyldimethylsilyl chloride (TBDMSCl) in the presence of imidazole gave **38** in a yield of 96%. Hydrolysis of **38** with potassium carbonate in aqueous 1,4-dioxane afforded free acid **40** used without purification. Hydrogenation of another portion of **38** for a short time (30 min) generated the primary amine **39** without affecting the *N*-benzyl group. Then the primary amine **39** and acid **40** were treated with *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uranium hexafluorophosphate (HBTU) in DMF to yield the stable dipeptide **41** (78% from **38**). An iterative procedure gave the tripeptide **24**. After the hydrogenation of dipeptide **41** for 3 h, the free amine dipeptide **41** was coupled with free acid **40** in the presence of HBTU in DMF to afford tripeptide **24** in high yield (72% from dipeptide **41**). Heteronuclear multiple-bond correlation relationship (HMBC) confirmed the ring connections in **24**. Unlike 3-hydroxy azetidine carboxylic acid derivatives, the corresponding amides are not vulnerable to ring fragmentation. It is likely that such moieties will lead to interesting secondary structural features.

3. Glycosidase inhibition assays

The azetidine iminosugars **20**, **21**, **22** and **23** were evaluated as inhibitors of a number of hexNAcases and other glycosidases; details of the assays have been described elsewhere.[39] There was no significant inhibition of any hexNAcase (Table 1); the azetidine amides **22** and **23** caused weak inhibition of α-galactosidase (48% and 41%, respectively, at 1 mM concentration).

4. Summary

Methyl *trans*,*trans*-3-azido-4-hydroxymethyl-L-azetidine carboxylate **19** is the first example of a scaffold for introduction of β-amino-Aze fragments into peptidomimetics. Although amides of β-oxetane carboxylic acids fragment by a retroaldol reaction, amides and oligopeptides derived from **19** are stable. This will enable the potential of β-amino-Aze to induce secondary structures in oligopeptides to be investigated. A number of azetidine iminosugars containing a NHAc substituent were prepared but none of them acted as hexNAcase inhibitors.



Scheme 3. Reagents and conditions: (i) TBDMSCl, imidazole, DMF, 96%; (ii) Pd/C, H_2, water/1,4-dioxane, 1:1; (iii) K_2CO_3, water/1,4-dioxane, 1:1; (iv) **39**, **40**, HBTU, DMF, 78% from **38**; (v) Pd/C, H_2, water; (iv) **41**, **40**, HBTU, DMF, 72% from **41.**

5. Experimental

5.1. General experimental

All commercial reagents were used as supplied. Solvents were used as supplied (Analytical or HPLC grade), without prior purification. Thin layer chromatography (TLC) was performed on aluminium sheets coated with 60 F_{254} silica. Plates were visualised using a 0.2% w/v cerium(IV) sulfate and 5% ammonium molybdate solution in 2 M sulfuric acid. Melting points were recorded on a Kofler hot block and are uncorrected. Optical rotations of the protected sugars were recorded on a Perkin-Elmer 241 polarimeter with a path length of 1 dm; optical rotation are quoted in 10^3 · deg cm^2 g^{-1} at concentrations (*c*) in g 100 mL^{-1}. Infrared spectra were recorded on a Perkin-Elmer 1750 IR Fourier Transform spectrophotometer using thin films on a diamond ATR surface (thin film). Only the characteristic peaks are quoted. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AMX 500 (^{1}H: 500 MHz and ^{13}C: 125.7 MHz) or Bruker AVIII 400 HD nanobay and Bruker DQX 400 (^{1}H: 400 MHz, ^{13}C: 100.6 MHz) spectrometers in the deuterated solvent stated. ^{1}H and ^{13}C NMR spectra were assigned by utilizing 2D COSY, HSQC and HMBC spectra. All chemical shifts (δ) are quoted in ppm and coupling constants (*J*) in Hz. Residual signals from the solvents were used as an internal reference. For solutions in D_2O acetonitrile was used as an internal reference. HRMS measurements were made using a microTOF mass analyzer using electrospray ionization (ESI).

5.1.1. 3-Azido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose 26

Triflic anhydride (10.2 mL, 59.0 mmol) was added dropwise to a stirred solution of diacetone allose **25** (11.8 g, 45.4 mmol) and pyridine (0.3 mL) in dichloromethane (40 mL) at −30 °C. The mixture was stirred at −30 °C for 2 h until TLC analysis (cyclohexane/ethyl acetate, 2:1) indicated the complete conversion of starting material (R_f 0.40) to product (R_f 0.70). The reaction mixture was diluted with dichloromethane (10 mL), washed successively with HCl (2 M, aq, 10 mL) and sodium bicarbonate (satd, aq, 50 mL), dried and concentrated in vacuo to afford the crude triflate. Sodium azide (3.9 g, 60.5 mmol) was added to a solution of the crude triflate in DMF (30 mL) at room temperature and stirred overnight. TLC analysis (cyclohexane/ethyl acetate, 2:1) showed one major product formed (R_f 0.75). The reaction mixture was diluted with ethyl acetate (30 mL), washed with brine/water (1:1, 2 × 30 mL). The aqueous layers were combined and extracted with ethyl acetate (2 × 20 mL). The organic extracts were combined, dried, and concentrated in vacuo. Flash column chromatography (cyclohexane/ethyl acetate 10:1) gave the azide **26** as a colorless oil. Proton NMR signals showed the existence of small amount of impurities. Column chromatography in less polar solvents (toluene/acetone, 100:1) afforded the pure product (10.1 g, 78%) as a colorless syrup.

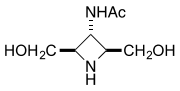
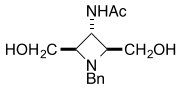
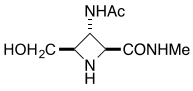
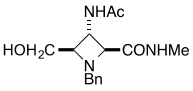
HRMS (ESI+ve): found 308.1214 [M+Na^+]; $C_{12}H_{19}N_3NaO_5^+$ requires 308.1217; $[\alpha]_D^{20}$ = −47.5 (*c* 1.2, $CHCl_3$); [lit.[40] $[\alpha]_D^{22}$ = −36 (*c* 0.65, $CHCl_3$)]; ν_{max} (thin film): 2105 (s, N_3); δ_H ($CDCl_3$, 400 MHz): 1.33–1.58 (12H, 4 × s, CH_3); 3.99 (1H, dd, H6, $J_{6,5}$ 4.8, J_{gem} 8.8), 4.09–4.11 (2H, m, H3 H4), 4.15 (1H, dd, H6′, $J_{6',5}$ 6.0, J_{gem} 8.8), 4.25 (1H, m, H5), 4.64 (1H, d, H2, $J_{2,1}$ 3.6), 5.87 (1H, d, H1, $J_{1,2}$ 3.6); δ_C ($CDCl_3$, 100 MHz): 25.1 (CH_3), 26.2 (CH_3), 26.6 (CH_3), 26.9 (CH_3), 66.3 (C4), 67.6 (C6), 73.0 (C5), 80.4 (C3), 83.4 (C2), 105.0 (C1), 109.6 ($C(CH_3)_2$), 112.3 ($C(CH_3)_2$); *m*/*z* (ESI+ve): 308 ([M+Na^+], 100%).

5.1.2. 3-Azido-3-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose 27

The diacetonide **26** (10.1 g, 35.3 mmol) was dissolved in 7:3 acetic acid/water (30 mL) and stirred for 40 h at room temperature. TLC analysis (cyclohexane/ethyl acetate, 2:1) indicated the formation of a major product (R_f 0.35) and the complete disappearance of starting material (R_f 0.75). The reaction mixture was concentrated in vacuo and purified by column chromatography (cyclohexane/ethyl acetate 2:1) to afford the monoacetonide **27** (5.2 g, 60%) as a white solid.

HRMS (ESI+ve): found 268.0903 [M+Na^+]; $C_9H_{15}N_3NaO_5^+$ requires 268.0904; mp: 80-82 °C; [lit.[41] mp 86 °C]; $[\alpha]_D^{20}$ = −32.7 (*c* 0.47 in $CHCl_3$); [lit.[42] $[\alpha]_D^{20}$ = −41.8 (*c* 4.3 in $CHCl_3$)]; ν_{max} (thin film): 3396 (br, OH), 2106 (s, N_3); δ_H ($CDCl_3$, 400 MHz): 1.34–1.52 (6H, 2 × s, CH_3); 3.76 (1H, dd, H6, $J_{6,5}$ 5.0, J_{gem} 11.1), 3.90 (1H, dd, H6′, $J_{6',5}$ 3.3, J_{gem} 11.1), 3.95 (1H, m, H5), 4.17 (1H, d, H3, $J_{3,4}$ 2.8), 4.20 (1H, dd, H4, $J_{4,3}$ 3.0, $J_{4,5}$ 8.1), 4.66 (1H, d, H2, $J_{2,1}$ 3.7), 5.89 (1H, d, H1, $J_{1,2}$ 3.7); δ_C ($CDCl_3$, 100 MHz): 26.2 (CH_3),

Table 1
Concentration of iminosugars giving 50% inhibition of various glycosidases

	IC_{50} (μM)			
				
Enzyme	**20**	**21**	**22**	**23**
α-Glucosidase				
Rice	[a] NI [b] (21.8%)	NI (1.6%)	NI (4.0%)	NI (10.1%)
β-Glucosidase				
Bovine liver	NI (17.2%)	NI (3.9%)	NI (18.3%)	NI (4.4%)
α-Galactosidase				
Coffee beans	NI (23.5%)	NI (3.7%)	NI (48.1%)	NI (41.4%)
α-Mannosidase				
Jack bean	NI (1. 9%)	NI (0%)	NI (0%)	NI (0%)
β-Mannosidase				
Snail	NI (0.368%)	NI (0%)	NI (0%)	NI (0%)
α-L-Fucosidase				
Bovine kidney	NI (1.5%)	NI (0%)	NI (0%)	NI (10.7%)
α-L-Rhamnosidase				
Penicillium decumbens	NI (6.1%)	NI (6.3%)	NI (4.1%)	NI (0%)
Amyloglucosidase				
A.niger	NI (7.1%)	NI (3.8%)	NI (6.4%)	NI (3.4%)
β-*N*-Acetylglucosaminidase				
Human placenta	NI (11.7%)	NI (26.5%)	NI (6.0%)	NI (22.6%)
Bovine kidney	NI (18.6%)	NI (26.5%)	NI (9.0%)	NI (28.2%)
Jack bean	NI (9.5%)	NI (0.7%)	NI (2.9%)	NI (15.2%)
HL60	NI (16.6%)	NI (28.4%)	NI (3.9%)	NI (14.5%)
Aspergillus oryzae	NI (3.9%)	NI (3.9%)	NI (0%)	NI (3.7%)
α-*N*-Acetylgalactosaminidase				
Chicken liver	NI (0%)	NI (0%)	NI (0%)	NI (15.5%)
β-*N*-Acetylgalactosaminidase				
HL60	NI (7.7%)	NI (11.6%)	NI (3.9%)	NI (1.1%)
Aspergillus oryzae	NI (2.3%)	NI (3.8%)	NI (1.3%)	NI (1.3%)
β-Glucuronidase				
E.coli	NI (3.6%)	NI (5.2%)	NI (30.1%)	NI (11.0%)
Bovine liver	NI (13.6%)	NI (6.9%)	NI (11.8%)	NI (20.4%)

[a] NI: No inhibition (<50% inhibition at 1000 μM).
[b] (): Inhibition % at 1000 μM.

26.6 (CH_3), 64.2 (C6), 66.4 (C3), 69.6 (C5), 78.9 (C4), 83.2 (C2), 104.9 (C1), 112.3 ($C(CH_3)_2$); *m/z* (ESI+ve): 268 ([M+Na^+], 59%), 513 ([2 M+Na^+], 100%).

5.1.3. 3-Azido-3-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose 28

Sodium periodate (5.4 g, 25.4 mmol) was added to the diol **27** (5.2 g, 21.2 mmol) in water (30 mL). The reaction mixture was stirred at room temperature for 4 h when TLC analysis (cyclohexane/ethyl acetate, 2:1) showed the complete conversion of starting material (R_f 0.25) to a single product (R_f 0.50). Ethanol (20 mL) was added to the mixture and a white suspension was formed after 20 min stirring. The reaction mixture was filtered and the filter pad washed with ethanol (25 mL). $NaBH_4$ (801 mg, 21.2 mmol) was added portionwise to the filtrate and the mixture was stirred again for 1.5 h. Analysis by mass spectrometry indicated the completion of the reaction ([M+Na]$^+$ 238). Acetic acid was added to adjust the solution to pH 7. The mixture was then concentrated in vacuo and co-evaporated with ethanol to afford a yellow solid that was purified by flash column chromatography (cyclohexane/ethyl acetate 3:1) to afford the azide **28** as a white crystalline solid (4.38 g, 96%).

HRMS (ESI+ve): found 238.0796 [M+Na^+]; $C_8H_{13}N_3NaO_4^+$ requires 238.0798; mp 68–70 °C; $[\alpha]_D^{20} = -57.8$ (*c* 0.38, $CHCl_3$); [lit.[43] (no melting point in report) $[\alpha]_D^{26} = -36.6$ (*c* 1.6, $CHCl_3$)]; υ_{max} (thin film): 3448 (br, OH), 2103 (s, N_3); δ_H ($CDCl_3$, 400 MHz): 1.27–1.45 (6H, 2 × s, CH_3); 3.78 (1H, dd, H5, $J_{5,4}$ 6.1, J_{gem} 11.5), 3.86 (1H, dd, H5′, $J_{5',4}$ 6.4, J_{gem} 11.5), 3.96 (1H, d, H3, $J_{3,4}$ 3.4), 4.30 (1H, ddd, H4, $J_{4,3}$ 3.4, $J_{4,5}$ 6.1, $J_{4,5'}$ 6.4), 4.62 (1H, d, H2, $J_{2,1}$ 3.8), 5.87 (1H, d,

H1, $J_{1,2}$ 3.8); δ_C ($CDCl_3$, 100 MHz): 26.3 (CH_3), 26.6 (CH_3), 60.9 (C5), 66.1 (C3), 79.4 (C4), 83.6 (C2), 104.7 (C1), 112.3 ($C(CH_3)_2$); *m*/*z* (ESI +ve): 238 ([M+Na$^+$], 100%).

5.1.4. 3-Azido-3-deoxy-D-xylopyranose 29

DOWEX® 50WX8-200 (1.00 g) was added to a solution of monoacetonide **28** (4.38 g, 20.4 mmol) in 1,4-dioxane/water (1:1, 40 mL). The reaction mixture was stirred at 80 °C for 20 h after which TLC analysis (cyclohexane/ethyl acetate, 2:1) indicated the disappearance of starting material (R_f 0.50) and the formation of a single product (R_f 0.10). The reaction mixture was filtered and the solvent removed in vacuo to give a residue that was purified by column chromatography (cyclohexane/ethyl acetate, 1:1 to 10% methanol in ethyl acetate) to give a mixture of pyranoside **29** (3.57 g, 100%) as a white solid.

HRMS (ESI+ve): found 198.0479 [M+Na$^+$]; $C_{12}H_{19}N_3NaO_5^+$ requires 198.0485; mp 72–74 °C; υ_{max} (thin film): 3336 (br, OH), 2107 (s, N_3); δ_H ($CDCl_3$, 400 MHz): 3.38 (1H, dd, H5β, $J_{5,4}$ 9.0, J_{gem} 11.9), 3.55 (1H, t, H5α, $J_{gem} = J_{5,4}$ 11.0), 3.67 (1H, t, H3β, $J_{3,2} = J_{3,4}$ 9.4), 3.87 (1H, dd, H5α′, $J_{5',4}$ 5.9, J_{gem} 11.0), 3.92 (1H, d, H3α, $J_{3,2}$ 10.2), 4.09 (1H, dd, H5β′, $J_{5',4}$ 5.1, J_{gem} 11.9), 4.78–4.82 (3H, m, H2α, H4α, H4β), 4.89 (1H, dd, H2β, $J_{2,1}$ 7.4, $J_{2,3}$ 9.6), 5.57 (1H, d, H1β, $J_{1,2}$ 7.3), 6.16–6.17(1H, d, H1α, $J_{1,2}$ 3.7); δ_C ($CDCl_3$, 100 MHz): 60.4 (C3α), 60.6 (C5α), 62.9 (C3β), 63.8 (C5β), 69.1, 69.2, 69.8, 70.0 (C2α, C4α, C2β, C4β), 88.7 (C1α), 92.4 (C1β); *m*/*z* (ESI+ve): 198 ([M+Na$^+$], 100%).

5.1.5. 3-Azido-3-deoxy-1,2,4-tri-*O*-acetyl-D-xylopyranose 30

A solution of the azide **29** (3.78 g, 21.6 mmol) in acetic anhydride/pyridine (1:1, 20 mL) was stirred at room temperature overnight. TLC analysis (cyclohexane/ethyl acetate, 1:1) indicated the complete conversion of starting material (R_f 0.05) to product (R_f 0.90). Removal of the solvent in vacuo gave a residue that was purified by flash column chromatography (cyclohexane/ethyl acetate, 4:1) to afford an α:β mixture of the anomers **30** (6.38 g, 98%) in a ratio of 10:3 as indicated by NMR.

HRMS (ESI+ve): found 324.0804 [M+Na$^+$]; $C_{11}H_{15}N_3NaO_7^+$ requires 324.0802; mp 46–48 °C; υ_{max} (thin film): 2106 (s, N_3), 1752 (s, C=O); β anomer: δ_H ($CDCl_3$, 400 MHz): 3.44 (1H, dd, H5′, $J_{5',4}$ 9.1 J_{gem} 11.9); 3.74 (1H, t, H3, $J_{3,2} = J_{3,4}$ 9.3); 4.14 (1H, dd, H5, $J_{5,4}$ 5.0 J_{gem} 11.9); 4.83 (1H, m, H4); 4.96 (1H, dd, H2, $J_{2,1}$ 7.3 $J_{2,3}$ 9.6); 5.64 (1H, d, H1, $J_{1,2}$ 7.3); δ_C ($CDCl_3$, 100 MHz): 62.8 (C3), 63.7 (C5), 69.2 (C4), 69.7 (C2), 92.3 (C1), 170.4 (C=O), 170.8 (C=O), 171.2 (C=O); *m*/*z* (ESI+ve): 324 ([M+Na$^+$], 100%).

5.2. Methyl 3-azido-3-deoxy-2,4-di-*O*-acetyl-β-D-xylopyranoside 31

5.2.1. Method 1

HBr (33% in acetic acid, 1.23 mL, 7.1 mmol) was added dropwise to a solution of triacetate **30** (789 mg, 2.62 mmol) in acetic acid/dichloromethane (7:3, 20 mL) at 10 °C. The reaction mixture was stirred under 5 °C for 4 h when TLC analysis (cyclohexane/ethyl acetate 2:1) showed complete conversion of starting material (R_f 0.53) to a product (R_f 0.62). The reaction mixture was then diluted with dichloromethane (20 mL) and poured into ice-water (40 mL). The organic layer was firstly washed with cold sodium bicarbonate (satd, aq, 2 × 40 mL) and then with ice-water (20 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo to afford crude bromide. The crude bromide was dissolved in anhydrous methanol (10 mL) in a foil-wrapped flask. Silver carbonate was added and reaction stirred at room temperature overnight. TLC (cyclohexane/ethyl acetate, 2:1) showed the complete conversion of starting material (R_f 0.62) to product (R_f 0.26). The reaction mixture was then filtered through celite and the filter-pad washed with dichloromethane (10 mL) and finally concentrated to dryness in vacuo. Flash chromatography (cyclohexane/ethyl acetate, 4:1) gave the β-pyranoside **31** as a colorless oil (230 mg, 30%).

5.2.2. Method 2

$BiBr_3$ (475 mg, 1.06 mmol) and Me_3SiBr (11.2 mL, 84.4 mmol) were added portionwise to a stirred solution of triacetate compound **30** (6.38 g, 21.1 mmol) in dichloromethane (30 mL). The reaction mixture was stirred at room temperature for 4 h until TLC analysis (cyclohexane/ethyl acetate, 2:1) showed the complete conversion of starting material (R_f 0.53) to product (R_f 0.62). Reaction mixture was poured into cold sodium bicarbonate (satd, aq, 30 mL) and extracted twice with dichloromethane (2 × 30 mL). The organics were combined, dried ($MgSO_4$) and concentrated in vacuo. Crude bromide was dissolved in dichloromethane /MeOH (1:1, 30 mL) in a foil-wrapped flask. Silver carbonate (9.79 g, 42.2 mmol) and $CaSO_4$ (5.74 g, 42.2 mmol) were added. The reaction was stirred at room temperature for 1 h and mixture filtered through Celite and washed with dichloromethane (30 mL). Column chromatography (cyclohexane/ethyl acetate, 6:1) afforded the β-pyranoside **31** (4.25 g, 74%) as a colorless oil.

HRMS (ESI+ve): found 296.0848 [M+Na$^+$]; $C_{10}H_{15}N_3NaO_6^+$ requires 296.0853; $[\alpha]_D^{20} = -65.0$ (*c*, 0.72 $CHCl_3$); υ_{max} (thin film): 2105 (s, N_3), 1743 (C=O); δ_H ($CDCl_3$, 400 MHz): 2.12–2.14 (6H, 2 × s, CH_3), 3.31 (1H, dd, H5, $J_{5,4}$ 9.1 J_{gem} 11.9), 3.33 (3H, s, OCH_3), 3.67 (1H, t, H3, $J_{3,2} = J_{3,4}$ 9.3), 4.14 (1H, dd, H5′, $J_{5',4}$ 5.3 J_{gem} 11.9), 4.81–4.85 (2H, m, H2, H4). δ_C ($CDCl_3$, 100 MHz): 20.7 (2 × CH_3), 56.6 (OCH_3), 62.8 (C5), 63.0 (C3), 69.6 (C4), 70.7 (C2), 101.8 (C1), 169.3 (C=O), 169.7 (C=O); *m*/*z* (ESI+ve): 296 ([M+Na$^+$], 70%), 569 ([2M+Na$^+$], 100%).

5.3. Methyl 3-azido-3-deoxy-β-D-xylopyranoside 32

Sodium methoxide (84.2 mg, 1.56 mmol) was added to a solution of diacetate **31** (4.25 g, 15.6 mmol) in anhydrous methanol (40 mL) at 40 °C and stirred for 15 h until TLC analysis (cyclohexane/ethyl acetate, 1:3) indicated the complete conversion of starting material (R_f 0.2) to product (R_f 0.4). The reaction mixture was neutralized with 2 M HCl, diluted with ethyl acetate (40 mL), washed with water (2 × 40 mL) and the combined aqueous layers extracted with ethyl acetate (2 × 40 mL). The combined organics were washed with brine (2 × 40 mL) and dried ($MgSO_4$), filtered and concentrated in vacuo to obtain a residue that was purified by flash column chromatography (cyclohexane/ethyl acetate, 3:1) yielding the azide **32** (2.95 g, 100%) as a pale yellow solid.

HRMS (ESI+ve): found 212.0638 [M+Na]$^+$; $C_6H_9N_3NaO_3^+$ requires 212.0642; $[\alpha]_D^{20} = -31.1$ (*c*, 0.55 $CHCl_3$); υ_{max} (thin film): 2106 (s, N_3); mp 48–50 °C; δ_H (CD_3OD, 400 MHz): 3.14 (1H, dd, H2, $J_{2,1}$ 7.6, $J_{2,3}$ 9.8), 3.23 (1H, dd, H3, $J_{3,2}$ 10.3 $J_{3,4}$ 9.3), 3.26 (1H, dd, H5′, $J_{5',4}$ 7.8, J_{gem} 10.9), 3.34 (3H, s, OCH_3), 3.46 (1H, m, H4), 3.88 (1H, dd, H5, $J_{5,4}$ 5.3 J_{gem} 10.9); 4.15 (1H, d, H1, $J_{1,2}$ 7.6). δ_C (CD_3OD, 100 MHz): 56.3 (OCH_3), 66.7 (C4), 69.0 (C5), 70.0 (C3), 72.7 (C2), 105.0 (C1); *m*/*z* (ESI+ve): 212 (100%, [M+Na]$^+$).

5.4. Methyl 3-azido-*N*-benzyl-2,4-imino-2,3,4-trideoxy-β-L-riboside 18

Triflic anhydride (7.1 mL, 63.2 mmol) was added dropwise to a stirred solution of diol **32** (3.0 g, 15.8 mmol) and pyridine (5.6 mL, 94.8 mmol) in anhydrous dichloromethane (30 mL). The mixture was stirred at −30 °C for 2 h until TLC analysis (cyclohexane/ethyl acetate, 2:1) indicated the disappearance of starting material (R_f 0.1). Then the mixture was diluted with dichloromethane (10 mL) and successively washed with HCl (aq, 2 M, 2 × 40 mL) and sodium bicarbonate (satd, aq, 40 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo to afford the

crude ditriflate **17** which was used without further purification. Benzylamine (6.6 ml, 79.0 mmol) was added to a solution of crude triflate in acetonitrile (30 mL). The reaction mixture was stirred at 70 °C with a condenser attached for 2 h until mass spectrometry analysis showed the formation of desired product ([M+H]$^+$ 261). Then the reaction mixture was cooled and concentrated in vacuo to give a residue that was purified by flash column chromatography (cyclohexane/ethyl acetate, 7:1) to afford the bicyclic azetidine **18** as a yellow oil (2.90 g, 71% (2 steps)).

HRMS (ESI+ve): found 261.1344 [M+H]$^+$; $C_{13}H_{17}N_4O_2^+$ requires 261.1346; $[\alpha]_D^{20} = -47.4$ (*c* 0.72, $CHCl_3$); ν_{max} (thin film): 2099 (s, N_3); δ_H (CD_3CN, 400 MHz): 3.32 (3H, s, OCH_3), 3.41 (1H, s, H3), 3.52 (2H, m, H4, H2), 3.69 (1H, dd, H5, $J_{5,4}$ 1.2, J_{gem} 11.2), 3.93 (1H, d, CH_2Ph, J_{gem} 14.2), 4.02 (1H, d, CH_2Ph, J_{gem} 14.2); 4.26 (1H, dd, H5′, $J_{5',4}$ 1.5, J_{gem} 11.2); 4.61 (1H, s, H1); 7.12–7.30 (5H, m, Ar); δ_C (CD_3CN, 100 MHz): 51.1 (CH_2Ph), 55.6 (OCH_3), 61.0 (C3), 61.1 (C5), 65.3 (C4), 67.4 (C2), 100.3 (C1), 126.8, 128.3, 128.4, 138.8 (Ar); *m*/*z* (ESI+ve): 261 (100%, [M+H]$^+$).

5.5. Methyl 3-azido-*N*-benzyl-2,4-imino-2,3,4-trideoxy-L-ribonate [methyl *trans,trans*-3-azido-4-hydroxymethyl-L-azetidine carboxylate] 19

The bicycle **18** (250 mg, 0.96 mmol) was dissolved in 1,4-dioxane/HCl (2 M, aq.) (1:5, 10 mL) at 40 °C overnight. TLC analysis (cyclohexane/ethyl acetate, 2:1) indicated the complete conversion of starting material (R_f 0.70) to product (R_f 0.05). The mixture was diluted with ethyl acetate (15 mL) and washed with sodium bicarbonate (satd, aq, 2 × 10 mL). The aqueous layers were combined and extracted with ethyl acetate (2 × 10 mL). The organics were combined, dried ($MgSO_4$) and concentrated in vacuo to afford the crude lactol which was dissolved in anhydrous MeOH (10 mL) at 0 °C and K_2CO_3 (265 mg, 1.92 mmol). A solution of iodine (291 mg, 1.15 mmol, dissolved by sonication) in anhydrous methanol (5 mL) was then added dropwise to the reaction mixture which was stirred at 0 °C for 1 h when mass spectrometry showed the formation of desired product ([M+H]$^+$ 277) and TLC (cyclohexane/ethyl acetate, 2:1) showed the formation of one major spot (R_f 0.50). Excess iodine was quenched with sodium sulfite (satd, aq.) until a white precipitate appeared. The reaction mixture was diluted with excess water to dissolve all the precipitate and extracted with diethyl ether (4 × 20 mL). The organics were combined, dried and concentrated in vacuo to give a crude product which was purified by flash column chromatography (cyclohexane/ethyl acetate, 3:1 to 1:1) to afford the ester **19** as a yellow oil (214 mg, 81%).

HRMS (ESI+ve): found 277.1299 [M+H]$^+$; $C_{13}H_{17}N_4O_3^+$ requires 277.1301; $[\alpha]_D^{20} = -39.6$ (*c*, 0.50 in $CHCl_3$); ν_{max} (thin film): 2106 (s, N_3), 1715 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 3.14 (1H, dd, H5, $J_{5,4}$ 2.0, J_{gem} 12.1), 3.18–3.21 (1H, m, H4), 3.35 (1H, dd, H5′, $J_{5',4}$ 2.5, J_{gem} 12.1), 3.64 (1H, d, H2, $J_{2,3}$ 6.3), 3.67 (1H, d, CH_2Ph, J_{gem} 12.4), 3.98 (1H, d, CH_2Ph, J_{gem}12.6), 4.15 (1H, t, H3, $J_{3,2} = J_{3,4}$ 6.3), 7.27–7.34 (5H, m, Ar); δ_C ($CDCl_3$, 100 MHz): 52.3 (CH_3), 54.0 (C3), 60.3 (C5, CH_2Ph), 67.2 (C2), 69.1 (C4), 171.5 (C=O); *m*/*z* (ESI+ve): 277 ([M+H]$^+$, 100%).

5.6. Methyl 3-azido-*N*-benzyl-2,4-imino-2,3,4-trideoxy-L-ribonamide 33

Methylamine (0.45 mL, 3.62 mmol) and calcium chloride (20 mg, 0.18 mmol) were added to a solution of ester **19** (50 mg, 0.181 mmol) in methanol (2 mL) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 4 h until mass spectrometry showed the completion of the reaction ([M+H]$^+$ 276). The reaction mixture was filtered and concentrated to dryness in vacuo to give the amide **33** as a yellow oil (40 mg, 80%).

HRMS (ESI+ve): found 276.1450 [M+H$^+$]; $C_{13}H_{18}N_5O_2^+$ requires 276.1455; $[\alpha]_D^{20} = -10.5$ (*c*, 0.50 in $CHCl_3$); ν_{max} (thin film): 3338 (br, OH), 2105 (s, N_3), 1654 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 2.61–2.63 (3H, d, NHCH_3, *J* 5.1), 3.22 (1H, dt, H4, $J_{4,3}$ 6.1, $J_{4,5} = J_{4,5'}$ 3.0), 3.39 (1H, dd, H5, $J_{5,4}$ 3.3, J_{gem} 12.4), 3.46 (1H, dd, H5′, $J_{5',4}$ 3.3, J_{gem} 12.4), 3.55 (1H, d, H2, $J_{2,3}$ 6.3), 3.71 (1H, d, CH_2Ph, J_{gem} 12.4), 3.75 (1H, d, CH_2Ph, J_{gem} 12.4), 3.87 (1H, t, H3, $J_{3,2} = J_{3,4}$ 6.6), 6.72 (1H, d, N*H*CH_3, *J* 5.0), 7.27–7.36 (5H, m, Ar); δ_C ($CDCl_3$, 100 MHz): 25.7 (CH_3), 55.7 (C3), 61.2 (C6), 61.3 (C5), 69.7 (C4), 69.8 (C2), 128.2, 128.8, 129.3, 136.2 (Ar), 170.8 (C=O); *m*/*z* (ESI+ve): 276 ([M+H]$^+$, 100%).

5.7. Methyl 3-acetamido-*N*-benzyl-2,4-imino-2,3,4-trideoxy-L-ribonamide 22

The azide **33** (20 mg, 0.073 mmol) was suspended in a mixture of THF/AcOH/Ac_2O (3:2:1, 1.2 mL). Zinc powder (95 mg, 1.45 mmol) was added and the mixture was stirred to give a mixture. Then copper sulfate (sat, aq, 0.25 mL) was added dropwise and the reaction mixture was stirred for 1 h at room temperature until TLC analysis (cyclohexane/ethyl acetate, 2:1) showed the complete conversion of starting material (R_f 0.1) to a single product (R_f 0.6). Reaction mixture was filtered, concentrated to dryness to give acetate **34** which was dissolved in methanol (1 mL) and treated with sodium methoxide (2 mg, 0.037 mmol). The reaction mixture was stirred at 40 °C overnight until mass spectrometry showed the formation of desired product ([M+H]$^+$ 292). The mixture was then filtered and concentrated in vacuo to give product **22** as a yellow gum (18 mg, 85%, 2 steps).

HRMS (ESI+ve): found 276.1458 [M+H]$^+$; $C_{15}H_{22}N_3O_3^+$ requires 292.1661; $[\alpha]_D^{20} = +56.4$ (*c*, 0.90 in $CHCl_3$); $[\alpha]_D^{20} = +9.7$ (*c* 0.35, MeOH); ν_{max} 3294 (br, OH), 1650 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 2.59–2.61 (3H, d, CH_3, *J* 4.8), 3.14 (1H, dt, H4, $J_{4,5} = J_{4,5'}$ 3.8, $J_{4,3}$ 6.8), 3.39–3.44 (2H, m, H5, H5′), 3.52 (1H, d, H2, $J_{2,3}$ 7.6), 3.64 (1H, d, CH_2Ph, J_{gem} 12.4), 3.67 (1H, m, H3), 3.74 (1H, d, CH_2Ph, J_{gem} 12.1); δ_C ($CDCl_3$, 100 MHz): 25.7 (CH_3), 50.6 (C3), 61.5 (C6), 63.6 (C5), 67.8 (C2), 72.3 (C4), 170.7 (C=O), 172.1 (C=O); *m*/*z* (ESI+ve): 292 ([M+H]$^+$, 100%).

5.8. Methyl 3-acetamido-2,4-imino-2,3,4-trideoxy-L-ribonamide 23

10% Palladium on charcoal (10% wt., 5 mg) was added to a solution of azetidine **22** (12 mg, 0.04 mmol) in water/1,4-dioxane (2:1, 1.5 mL). The reaction mixture was flushed sequentially with argon and hydrogen. The mixture was stirred for 20 h after which mass spectrometry showed the reaction had gone to completion ([M+H]$^+$ 202). The reaction mixture was filtered and concentrated in vacuo to afford the debenzylated amide **23** (6 mg, 72%) as colorless gum.

HRMS (ESI+ve): found 202.1186 [M+H]$^+$; $C_8H_{16}N_3O_3^+$ requires 202.1186; $[\alpha]_D^{20} = +112.5$ (*c* 0.30, $CHCl_3$); ν_{max} 3303 (br, OH), 1645 (s, C=O); δ_H (CD_3OD, 400 MHz): 2.78 (3H, d, CH_3, *J* 4.8), 3.53–3.56 (2H, m, H5 and H5′), 3.73 (1H, dt, H4, $J_{4,5} = J_{4,5'}$ 3.6, $J_{4,3}$ 7.6), 4.01 (1H, d, H2, $J_{2,1}$ 6.4), 4.24 (1H, m, H3); δ_C (CD_3OD, 100 MHz): 24.9 (CH_3), 49.9 (C3), 62.1 (C2), 62.9 (C4), 63.4 (C5), 170.1 (C=O); *m*/*z* (ESI+ve): 202 ([M+H]$^+$, 100%).

5.9. 3-Azido-*N*-benzyl-2,4-imino-2,3,4-trideoxy-*meso*-ribitol 35

A solution of the bicyclic azetidine **18** (200 mg, 0.76 mmol) in 2 M aq HCl/1,4-dioxane (5:1, 6 mL) was stirred at 40 °C for 18 h after which the consumption of starting material and the formation of product was confirmed by mass spectrometry ([M+MeOH+Na]$^+$ 301). The solvent was removed in vacuo to give a residue that was dissolved in methanol (4 mL) and sodium borohydride

(115 mg, 3.04 mmol) was added. The reaction mixture was stirred at room temperature for 2 h when mass spectrometry showed the completion of reaction ([M+Na]$^+$ 271). The solvent was concentrated in vacuo to obtain a polar residue (320 mg). Purification with a short column of DOWEX® 50WX8-200 or flash column chromatography was not successful. The crude diol **35** was used for the following steps without further purification.

5.10. 3-Azido-*N*-benzyl-1,5-di-*O*-acetyl-2,4-imino-2,3,4-trideoxy-*meso*-ribitol 36

A solution of the diol **35** (320 mg) in acetic anhydride/pyridine (1:1, 4 mL) was stirred at room temperature for 16 h when TLC (cyclohexane/ethyl acetate, 1:1) indicated the formation of the only product (R_f 0.72). The mixture was concentrated in vacuo and the residue purified by flash column chromatography (cyclohexane/ethyl acetate/triethylamine, 6:1:0.01) to obtain the diacetate **36** (191 mg, 76% 3 steps from **18**) as a light yellow oil.

HRMS m/z (ESI+ve): found 355.1372 [M+Na]$^+$; $C_{16}H_{20}N_4NaO_4^+$ requires 355.1377; $[\alpha]_D^{20} = 0$ (c 0.81, $CHCl_3$); ν_{max} (thin film): 2104 (s, N_3), 1742 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 2.03 (6H, s, $2 \times CH_3$), 3.20 (2H, m, H2, H4), 3.67 (1H, t, H3, $J_{3,2} = J_{3,4}$ 6.1), 3.71 (2H, br s, CH_2Ph), 3.82 (2H, dd, H1, H5, $J_{1(5),2(4)}$ 4.29, J_{gem} 11.4), 4.03 (2H, dd, H1′, H5′), $J_{1'(5'),2'(4')}$ 4.29, J_{gem} 11.4), 7.25–7.34 (5H, m, Ar); δ_C ($CDCl_3$, 100 MHz): 20.8 ($2 \times CH_3$), 56.7 (C1, C5), 61.0 (CH_2Ph), 64.4 (C3), 67.2 (C2, C4), 128.5, 129.2, 136.6 (Ar), 170.7 ($2 \times$ C=O); m/z (ESI+ve): 355 ([M+Na]$^+$, 100%).

5.11. 3-Acetamido-*N*-benzyl-1,5-di-*O*-acetyl-2,4-imino-2,3,4-trideoxy-*meso*-ribitol 37

5.11.1. Method 1 (reductive acetylation of 35)

Zinc powder (494 mg, 7.6 mmol) and copper sulfate (sat, aq, 0.95 mL) were added to a solution of crude diol **35** (from **18** (100 mg, 0.38 mmol)) in THF/acetic acid/acetic anhydride (3:2:1, 6 mL). The mixture was stirred at room temperature for 1 h until mass spectrometry showed the formation of desired product ([M+Na]$^+$ 371). Then the mixture was filtered with Celite and the solvent was removed in vacuo to give a residue that was purified by flash column chromatography (ethyl acetate/methanol/triethylamine, 10:1:0.01) to give the protected amide compound **37** (31 mg, 24%, 3 steps from **18**) as a light yellow solid.

5.11.2. Method 2 (reductive acetylation of 36)

Zinc powder (743 mg, 11.4 mmol) and copper sulfate (sat, aq, 1.42 mL) were added to a solution of the diacetate **36** (190 mg, 0.57 mmol) in THF/acetic acid/acetic anhydride (3:2:1, 6 mL). The reaction mixture was stirred at room temperature for 1 hour until mass spectrometry showed the formation of desired product ([M+Na]$^+$ 371). Then the mixture was filtered with celite and solvent was removed in vacuo to give the title compound **37** (202 mg, 100%) as a light yellow solid without further purification.

HRMS m/z (ESI+ve): found 371.1576 [M+Na]$^+$; $C_{18}H_{24}N_2NaO_5^+$ requires 371.1577; $[\alpha]_D^{20} = 0$ (c 1.0, $CHCl_3$); ν_{max} (thin film): 1741 (s, $COCH_3$), 1658 (s, NHCO); δ_H ($CDCl_3$, 400 MHz): 1.94 (3H, s, $NHCOCH_3$), 1.98 (6H, s, $2 \times OCOCH_3$), 3.15 (2H, ddd, H2 and H4, $J_{2(4),1'(5')}$ 4.29, $J_{2(4),1(5)}$ 5.6, $J_{2(4),3}$ 7.1), 3.73 (2H, s, CH_2Ph), 3.90 (2H, dd, H1 and H5, $J_{1(5),2(4)}$ 5.6, J_{gem} 11.9), 4.12 (2H, dd, H1′ and H5′, $J_{1'(5'),2(4)}$ 4.3, J_{gem} 11.9), 5.89 (1H, br s, NH), 7.25–7.33 (5H, m, Ar); δ_C ($CDCl_3$,100 MHz): 20.8 ($2 \times OCOCH_3$), 23.1 ($NHCOCH_3$), 45.9 (C3), 60.8 (CH_2Ph), 65.4 (C1, C5), 67.6 (C2, C4), 127.5, 128.4, 129.3, 137.2 (Ar), 169.7 (NHCO), 170.9 ($2 \times$ OCO); m/z (ESI+ve): 349 ([M+H]$^+$, 100%).

5.12. 3-Acetamido-*N*-benzyl-2,4-imino-2,3,4-trideoxy-*meso*-ribitol 20

Sodium methoxide (3.2 mg, 0.06 mmol) was added to a solution of **37** (200 mg, 0.57 mmol) in methanol (5 mL). The mixture was stirred at 60 °C for 16 h until mass spectrometry indicated the formation of product ([M+H]$^+$ 265). After removal of the solvent in vacuo, the residue was dissolved in ethanol (5 mL) and passed through a glass microfiber filter paper and then loaded with water (~1 mL) onto a short column of DOWEX® 50WX8-200 (pre-washed with water, 1,4-dioxane and water sequentially until the eluent was neutral). The ion exchange column was then washed with water, 1,4-dioxane and then water; the pure product was then eluted with aqueous ammonia (2 M). Removal of solvent in vacuo gave the *meso*-diol **20** (120 mg, 79%) as a light yellow glass.

HRMS m/z (ESI+ve): found 265.1559 [M+H]$^+$; $C_{14}H_{21}N_2O_3^+$ requires 265.1547; $[\alpha]_D^{20} = 0$ (c 1.2, MeOH); ν_{max} (thin film): 1633 (s, NHCO); δ_H (CD_3OD, 400 MHz): 1.92 (3H, s, $NHCOCH_3$), 3.08 (2H, br dt, H2, H4, $J_{2(4),1'(5')} = J_{2(4),1(5)}$ 4.7, $J_{2(4),3}$ 6.9), 3.33 (2H, dd, H1, H5, $J_{1(5),2(4)}$ 4.1, J_{gem} 11.7), 3.37 (2H, dd, H1′, H5′, $J_{1'(5'),2(4)}$ 5.0, J_{gem} 11.7), 3.77 (2H, s, CH_2Ph), 3.89 (1H, t, H3, $J_{3,2} = J_{3,4}$ 6.9), 7.28–7.37 (5H, m, Ar); δ_C (CD_3OD,100 MHz): 21.0 ($NHCOCH_3$), 46.0 (C3), 61.3 (CH_2Ph), 65.4 (C1, C5), 70.5 (C2, C4), 127.5, 128.4, 129.3, 137.2 (Ar), 169.7 (C=O),; m/z (ESI+ve): 265 ([M+H]$^+$, 100%).

5.13. 3-Acetamido-2,4-imino-2,3,4-trideoxy-*meso*-ribitol 21

10% Palladium on charcoal (10% wt., 5 mg) was added to a solution of **20** (40 mg, 0.15 mmol) in 1,4-dioxane/water (1:1, 2 mL). The reaction mixture was flushed with argon and hydrogen., stirred for 20 h when mass spectrometry showed the completion of the reaction, filtered and concentrated in vacuo to give a residue that was purified with a short column of DOWEX® 50WX8-200 (as illustrated above) to yield diol **21** (19 mg, 73%) as a light yellow glass.

HRMS m/z (ESI+ve): found 175.1074 [M+H]$^+$; $C_7H_{15}N_2O_3^+$ requires 175.1075; $[\alpha]_D^{20} = 0$ (c 1.0, H_2O); ν_{max} (thin film): 3283 (br, OH, NH); δ_H (D_2O, 400 MHz): 1.98 (3H, s, $NHCOCH_3$), 3.61 (2H, dd, H1 and H5, $J_{1(5),2(4)}$ 6.4, J_{gem} 11.7), 3.65 (2H, dd, H1′ and H5′, $J_{1'(5'),2(4)}$ 4.9, J_{gem} 11.7), 3.74 (2H, m, H2 and H4), 4.00 (1H, t, H3, $J_{3,2} = J_{3,4}$ 7.3); δ_C (D_2O,100 MHz): 22.3 ($NHCOCH_3$), 48.3 (C3), 62.2 (C1, C5), 64.1 (C2, C4), 174.2 (C=O); m/z (ESI+ve): 175 ([M+H]$^+$, 100%).

5.14. Methyl 3-azido-*N*-benzyl-5-*O*-(*tert*-butyldimethylsilyl)-2,4-imino-2,3,4-trideoxy-L-ribonate 38

tert-Butyldimethylsilyl chloride (90 mg, 0.60 mmol) and imidazole (56 mg, 0.72 mmol) was added to a solution of methyl ester **19** (138 mg, 0.50 mmol) in DMF (3 mL) and the reaction mixture was stirred at room temperature for 2 h when TLC analysis (cyclohexane/ethyl acetate, 1:1) indicated the disappearance of starting material (R_f 0.50) and the formation of a major product (R_f 0.80). The reaction mixture was diluted with ethyl acetate (10 mL) and washed with 1:1 water/brine (satd, aq, 2×10 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent removed in vacuo to yield the silyl ether **38** as a brown oil (188 mg, 96%).

HRMS (ESI+ve): found 413.1978 [M+Na$^+$]; $C_{19}H_{30}N_4NaO_3Si^+$ requires 413.1979; $[\alpha]_D^{20} = +55$ (c 0.36, $CHCl_3$); ν_{max} 2105 (s, N_3), 1747 (s, C=O); δ_H ($CDCl_3$, 400 MHz): 0.00 (6H, s, $2 \times CH_3$), 0.86 (9H, s, $C(CH_3)_3$), 3.13 (2H, ddd, H4, $J_{4,5}$ 5.1, $J_{4,3}$ 6.6, $J_{4,5'}$ 6.9), 3.36 (1H, dd, H5, $J_{5,4}$ 5.1, J_{gem} 10.5), 3.41 (1H, dd, H5′, $J_{5',4}$ 6.9, J_{gem} 10.5), 3.47 (1H, d, H2, $J_{2,3}$ 6.6), 3.7 (3H, s, OCH_3), 3.71 (1H, d, CH_2-Ph, J_{gem} 12.5), 3.90 (1H, t, H3, $J_{3,2} = J_{3,4}$ 6.6), 3.92 (1H, d, CH_2Ph, J_{gem} 12.5); δ_C ($CDCl_3$, 100 MHz): −5.46 ($2 \times CH_3$), 18.3 ($3 \times CH_3$), 25.8 (OCH_3), 52.1 (C3), 56.9 (CH_2Ph), 61.0 (C5), 64.5 (C2), 69.0 (C4),

127.7, 128.3, 129.7, 138.1 (Ar), 171.0 (C=O); *m*/*z* (ESI+ve): 413 ([M +Na$^+$], 100%).

5.15. Methyl 3-(8-azido-*N*-benzyl-10-*O*-(*tert*-butyldimethylsilyl)-7,9-imino-8,7,9-trideoxy-L-ribonamido)-*N*-benzyl-5-*O*-(*tert*-butyldimethylsilyl)-2,4-imino-2,3,4-trideoxy-L-ribonamide 41

Potassium carbonate (27.6 mg, 0.20 mmol) was added to a solution of methyl ester **38** (60 mg, 0.15 mmol) in 1,4-dioxane/water (3 mL, 1:1). The reaction mixture was stirred at 60 °C for 18 h until mass spectrometry indicated completion of the hydrolysis ([M−H]$^-$ 375) and the solvent was removed in vacuo to give the sodium salt **40** (80 mg).

10% Palladium on charcoal (10% wt., 5 mg) was added to a solution of **38** (60 mg, 0.15 mmol) in 1,4-dioxane/water (3 mL, 1:1). The reaction mixture was flushed with argon and hydrogen gas sequentially and then stirred vigorously for 30 min at room temperature under hydrogen until mass spectrometry showed the completion of the reaction ([M+H]$^+$ 365). After filtration, the solvent was removed in vacuo to afford crude amine **39** (60 mg) which was used without further purification.

N,*N*,*N*′,*N*′-Tetramethyl-*O*-(1H-benzotriazol-1-yl)uranium hexafluorophosphate (HBTU, 68 mg, 0.18 mmol) was added to a solution of the crude acid **40** (60 mg) and amine **39** (60 mg) in anhydrous DMF (3 mL). After stirring for 20 min, triethylamine (0.03 mL, 0.21 mmol) was added; the reaction mixture was then stirred at room temperature for a further 20 h until TLC analysis (cyclohexane/ethyl acetate, 1:1) showed the consumption of the starting materials and formation of one major product (R_f 0.78). The reaction mixture was diluted with ethyl acetate (10 mL) and washed with half saturated brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent removed in vacuo to give a residue that was purified by flash column chromatography (cyclohexane/ethyl acetate, 3:1) to give the pure dipeptide **41** as a yellow oil (85 mg, 78%).

HRMS (ESI+ve): found 745.3892 [M+Na]$^+$; $C_{37}H_{58}N_6NaO_5Si_2^+$ requires 745.3899; $[\alpha]_D^{20}$ = +12.9 (*c* 0.92, $CHCl_3$); ν_{max} 2106 (s, N_3), 1744 (s, OCO), 1681 (s, NHCO); δ_H (CD_3CN, 400 MHz): 0.00 (6H, s, CH_3), 0.01 (6H, s, CH_3), 0.88 (9H, s, $C(CH_3)_3$), 0.93 (9H, s, $C(CH_3)_3$), 2.88 (1H, d, H2, $J_{2,3}$ 6.9), 2.88 (1H, dt, H4, $J_{4,5}$ = $J_{4,5'}$ 5.2, $J_{4,3}$ 7.1), 3.21 (1H, dt, H9, $J_{9,10}$ = $J_{9,10'}$ 2.7, $J_{9,8}$ 6.4), 3.42 (1H, dd, H5, $J_{5,4}$ 5.2, J_{gem} 11.0), 3.43 (1H, d, H7, $J_{7,8}$ 6.4), 3.46 (1H, dd, H5′, $J_{5',4}$ 5.2, J_{gem} 11.0), 3.47 (3H, s, OCH_3), 3.57 (1H, d, CH_2Ph, J_{gem} 12.3), 3.58 (1H, dd, H10, $J_{10,9}$ = 2.7, J_{gem} 9.0), 3.61 (1H, dd, H10′, $J_{10',9}$ 2.7, J_{gem} 9.0), 3.67 (1H, t, H8, $J_{8,7}$ = $J_{8,9}$ 6.4), 3.70 (1H, d, CH_2Ph, J_{gem} 13.1), 3.81 (1H, d, CH_2Ph, J_{gem} 13.1), 3.87 (1H, d, CH_2Ph, J_{gem} 13.1), 4.03 (1H, dt, H3, $J_{3,NH}$ = $J_{3,2}$ 6.9, $J_{3,4}$ 7.1), 6.78 (1H, d, NH, $J_{NH,3}$ 6.9), 7.27–7.40 (10H, m, 2 × Ar); δ_C (CD_3CN, 100 MHz): −5.78 (CH_3), −5.8 (CH_3), −5.7 (CH_3), −5.6 (CH_3), 25.7 ($C(CH_3)_3$), 25.8 ($C(CH_3)_3$), 45.7 (C3), 51.5 (OCH_3), 57.4 (C8), 61.1 (CH_2Ph), 61.5 (CH_2Ph), 63.9 (C10), 65.1 (C5), 68.8 (C2), 69.8, 69.9 (C7, C9), 70.0 (C4), 127.7, 128.3, 128.5, 129.2, 129.8, 130.0, 127.7, 127.8 (2 × Ar), 169.7 (C=O), 171.3 (C=O); *m*/*z* (ESI+ve): 745 ([M+Na]$^+$, 100%).

5.16. Methyl *N*-benzyl-3-(*N*-benzyl-8-(13-azido-*N*-benzyl-16-*O*-(*tert*-butyldimethylsilyl)-12,14-imino-12,13,14-trideoxy-L-ribonamido)-10-*O*-(*tert*-butyldimethylsilyl)-7,9-imino-7,8,9-trideoxy-L-ribonamido)-5-*O*-(*tert*-butyldimethylsilyl)-2,4-imino-2,3,4-trideoxy-L-ribonamide 24

Potassium carbonate (27.6 mg, 0.20 mmol) was added to a solution of methyl ester **38** (60 mg, 0.15 mmol) in 1,4-dioxane/water (3 mL, 1:1). The reaction mixture was stirred at 60 °C for 18 h until mass spectrometry indicated completion of the hydrolysis ([M−H]$^-$ 375) and the solvent was removed in vacuo to give the crude acid **40** (90 mg).

10% Palladium on charcoal (10% wt., 5 mg) was added to a solution of dipeptide **41** (80 mg, 0.11 mmol) in 1,4-dioxane/water (3 mL, 1:1). The reaction mixture was flushed with argon and hydrogen gas sequentially and then stirred vigorously for 3 h at room temperature under hydrogen until mass spectrometry showed the completion of reaction ([M+H]$^+$ 697). After filtration, the solvent was removed in vacuo to afford crude amine **42** (70 mg) that was used without further purification.

HBTU (68 mg, 0.18 mmol) was added to a solution of the crude acid **40** (90 mg) and amine **42** (60 mg) in anhydrous DMF (3 mL). After stirring for 20 min, triethylamine (0.03 mL, 0.21 mmol) was added; the reaction mixture was then stirred at room temperature for a further 24 h until TLC analysis (cyclohexane/ethyl acetate, 2:1) showed the formation of one major product (R_f 0.81). The reaction mixture was diluted with ethyl acetate (10 mL) and washed with half saturated brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent removed in vacuo to give a residue that was purified by flash column chromatography (cyclohexane/ethyl acetate, 10:1 to 4:1) to afford the tripeptide **24** as a yellow oil (85 mg, 72%).

$[\alpha]_D^{20}$ = +16.5 (*c* 1.1, $CHCl_3$); ν_{max} 2105 (s, N_3), 1746 (s, OC=O), 1681 (s, NHC=O); δ_H (CD_3CN, 400 MHz): 0.00 (6H, s, CH_3), 0.05 (6H, s, CH_3), 0.06 (6H, s, CH_3), 0.89 (9H, s, $C(CH_3)_3$), 0.90 (9H, s, $C(CH_3)_3$), 0.91 (9H, s, $C(CH_3)_3$), **Ring A**: 2.91 (1H, d, H2, $J_{2,3}$ 6.8), 2.94 (1H, dt, H4, $J_{4,5}$ = $J_{4,5'}$ 5.0, $J_{4,3}$ = 7.1), 3.45 (3H, s, OCH_3), 3.48 (2H, d, H5, $J_{5,4}$ 5.0), 3.96 (1H, ddd, H3, $J_{3,2}$ 6.8, $J_{3,4}$ 7.1, $J_{3,NH}$ 8.1), 7.04 (1H, d, NH, $J_{NH,3}$ 8.1), **Ring B**: 3.03 (1H, d, H7, $J_{7,8}$ 6.9), 3.09 (1H, dt, H9, $J_{9,10}$ = $J_{9,10'}$ 4.7, $J_{9,8}$ 6.9), 3.49–3.51 (2H, m, H10), 3.83 (1H, dt, H8, $J_{8,9}$ = $J_{8,7}$ 6.9, $J_{8,NH}$ 8.5), 7.02 (1H, d, NH, $J_{NH,8}$ 8.5), **Ring C**: 3.22 (1H, dt, H14, $J_{14,15}$ = $J_{14,15'}$ 5.1, $J_{14,13}$ 6.1), 3.43 (1H, d, H12, $J_{12,13}$ 6.4), 3.53 (2H, d, H15, $J_{15,14}$ 5.1), 3.69 (1H, dd, H13, $J_{13,14}$ 6.1, $J_{13,12}$ 6.4), 3.60 (1H, d, CH_2Ph, J_{gem} 12.4), 3.65 (1H, d, CH_2Ph, J_{gem} 13.0), 3.67 (1H, d, CH_2Ph, J_{gem} 12.5), 3.81 (1H, d, CH_2Ph, J_{gem} 12.5), 3.83 (1H, d, CH_2Ph, J_{gem} 13.0), 3.84 (1H, d, CH_2Ph, J_{gem} 12.4), 7.26–7.41 (15H, m, 3 × Ar); δ_C (CD_3CN, 100 MHz): −5.2 to −5.0 (6 × CH_3), 26.27 ($C(CH_3)_3$), 26.31 ($C(CH_3)_3$), 26.38 ($C(CH_3)_3$), **Ring A**: 46.4 (C3), 52.0 (OCH_3), 65.7 (C5), 69.6 (C2), 70.8 (C4), 172.0 (C1), **Ring B**: 47.5 (C8), 65.1 (C10), 70.9 (C9), 71.1 (C7), 171.0 (C6), **Ring C**: 58.3 (C13), 64.6 (C15), 70.3 (C14), 70.4 (C12), 170.8 (C11), 61.8 (CH_2Ph), 61.9 (CH_2Ph), 62.3 (CH_2Ph), 128.2–138.8 (3 × Ar); *m*/*z* (ESI+ve): 528 ([0.5M+H]$^+$, 100%).

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