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Carbon-branched δ-tetrahydrofuran sugar amino acids (SAAs) as dipeptide isostere scaffolds

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ABSTRACT

The synthesis of the first branched sugar amino acid (SAA) scaffolds [methyl (3*R*,4*R*,5*R*)-5-azidomethyl-3,4-dihydroxy-tetrahydrofuran-3-carboxylate and methyl (3*R*,4*R*,5*S*)-5-azidomethyl-3,4-dihydroxy-tetrahydrofuran-3-carboxylate] by an efficient intramolecular displacement of a highly hindered neopentyl triflate allows access to enantiopure THF derivatives which have carbon substituents.

1. Introduction

Sugar amino acids (SAAs) constitute a major class of peptidomimetics providing a set of monomers for both combinatorial synthesis and drug design.[1] Oligomers of SAAs frequently adopt secondary structures in relatively short sequences;[2] many have a predisposition to adopt secondary structural motifs, giving rise to a large family of foldamers.[3] In particular, a number of cyclic δ-amino acids containing an oxygen heterocyclic ring have been shown to act as dipeptide isosteres (Fig. 1) including saturated[4] and unsaturated[5] pyranose, furanose[6] and oxetanose[7] amino acids. All δ-SAAs previously described have linear carbon chains. This paper describes the first example of δ-SAA furanoses with a branched-carbon chain; some of this work has been reported in a preliminary publication.[8]

2-*O*-Triflates of suitably protected 1,4-sugar lactones **1** in methanol give base-catalyzed contraction of the five-membered lactone ring to an oxetane carboxylic ester **2** in which the substituent at C-3 is *trans* to the carboxylate, regardless of the configuration at C-2 of the original γ-lactone.[9] This has allowed the preparation of a wide range of azidooxetane carboxylates that have shown their value in inducing secondary structures.[10] Thus, **1** undergoes nucleophilic ring opening of the lactone to give the open chain ester **2** which closes by displacement of the triflate at C-2 by C-4 OH to the oxetane **3** (Scheme 1).

2-*O*-Triflates of both 1,4-sugar lactones **4** and 1,5-sugar lactones give high yields of tetrahydrofuran (THF) carboxylates under catalysis by *either* acid or base, and *always* with inversion of configuration at C-2 of the original hydroxy lactone;[11] many α-,[12] β-,[13] γ-[14] and δ-[15] amino acid building blocks have been prepared by this strategy. In this case, the lactone **4** is opened to the acyclic triflate **5** in which the C-5 OH displaces the triflate to give the THF carboxylate **6**. The formation of both oxetane and THF rings both involves ring closure by intramolecular nucleophilic displacement of a leaving group α to the ester carbonyl, where nucleophilic attack is facile—but will only produce linear carbon chains in the THF.

This report extends the range of THF rings that may be formed by this methodology by the synthesis of the *trans*- **17** and *cis*- **18** azidomethyl δ-THF carboxylates to provide the first examples of THF SAAs, which contain a branched carbon chain (Scheme 2). The epimeric D-ribono-**7** and L-lyxono-**8** lactones were converted to the corresponding azidolactoses **9** and **10**. The branched carbon chain was then introduced by a Ho[16] crossed aldol reaction between formaldehyde and the open form of **9** and **10** to afford the branched azidolactols **11** and **12**, which were converted to the corresponding triflates **13** and **14**. Treatment of **13** and **14** with methanolic hydrogen chloride resulted in removal of the acetonide and methanolysis of the ring to give the open esters **15** and **16** which subsequently close by nucleophilic attack of the C-4 OH group onto the 2C′ triflate to give the branched SAA scaffolds **17** and **18**. This unexpectedly efficient intramolecular displacement of a highly hindered neopentyl triflate should allow convenient access to complex THF systems which contain quaternary carbons. The syntheses of **17** and **18** reported in this paper are on a suitable scale for the preparation of their homooligomers; the structure of these oligomers has been studied by NMR and circular dichroism and compared with unbranched δ-THF SAAs.

2. Synthesis

2.1. Synthesis of a branched *trans*-azidomethyl carboxylate - THF SAA 17

The protected ribonolactone **7**, readily available from D-ribose by an *Organic Syntheses* procedure,[17] was esterified by triflic anhy-

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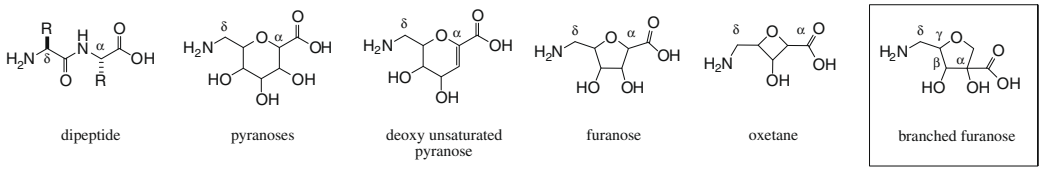
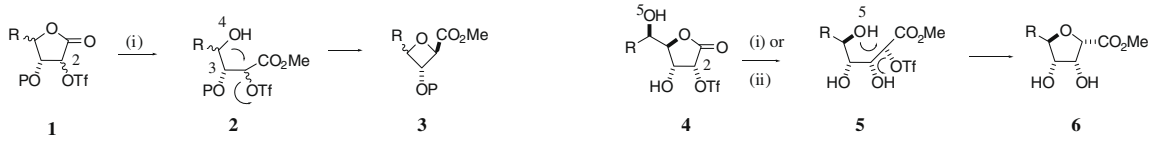
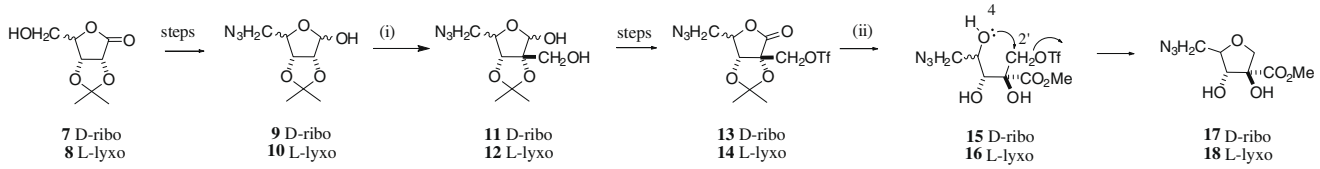


Figure 1. SAA dipeptide isosteres.



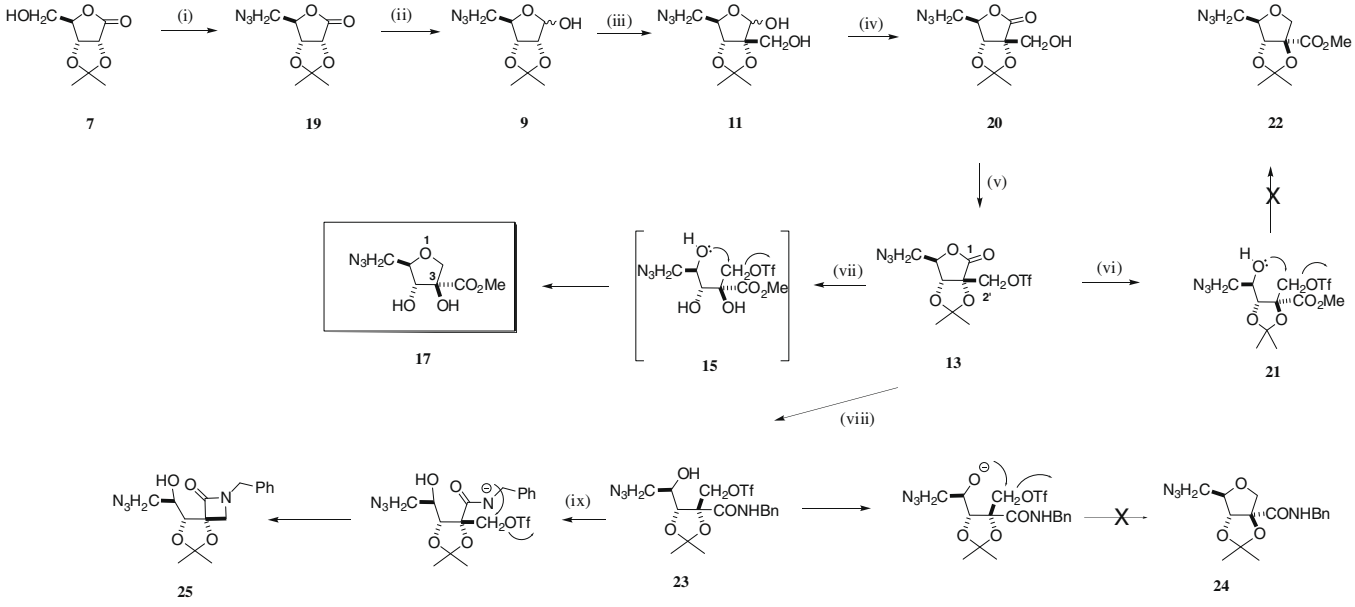
Scheme 1. (i) K_2CO_3, MeOH (ii) H^+, MeOH.



Scheme 2. (i) CH_2O, HO^- (ii) H^+, MeOH.

dride in dichloromethane to give the corresponding triflate which was immediately treated with sodium azide in DMF to afford the azido lactone **19** in 76% overall yield (Scheme 3). Reduction of the azidolactone by DIBAL-H in toluene gave the corresponding aldose **9** (93% yield) which underwent a highly efficient Ho[16] crossed aldol reaction with aqueous formaldehyde to form the branched azido lactol **11** (94% yield). Oxidation of the lactol **11** with bromine in the presence of barium carbonate gave the lactone **20** (82% yield) which was esterified to the stable triflate **13** (97% yield).

Treatment of **13** with methoxide in methanol did not give any product as the formation of the THF ring **22** from the open chain acetonide **21** would introduce a *trans*-acetonide protecting group. When the triflate **13** was treated with benzylamine in dioxane, the open chain triflate amide **23** was formed—again there was no indication of cyclization of **23** to the THF benzylamide **24** which again would require the formation of a strained protecting group. When the open chain triflate **23** was stirred in THF in the presence of potassium carbonate, cyclization to the β-lactam **25** was observed; the IR spectrum of **25** shows the appearance of a strong, sharp peak at 1745 cm^{-1}, consistent with the lactam structure. The ^1H NMR spectrum of **25** shows a free hydroxyl as a doublet which couples to proton H-4 in the COSY spectrum; the HMBC spectrum showed some long range correlations (Fig. 2).



Scheme 3. (i) Tf_2O, pyridine, CH_2Cl_2, −25 °C; then NaN_3, EtOAc, 76% (over two steps); (ii) DIBAL-H, CH_2Cl_2, −78 °C, 93%; (iii) 38% aq CH_2O, K_2CO_3, MeOH, 50 °C, 24 h, 94%; (iv) Br_2, $BaCO_3$, H_2O, 0 °C, 82%; (v) Tf_2O, pyridine, CH_2Cl_2, −25 °C, 97%; (vi) MeOH, MeONa; (vii) MeOH/AcCl (1:1), 87%. (viii) $BnNH_2$, 1,4-dioxane; (ix) K_2CO_3, THF, 8 days, 89%.

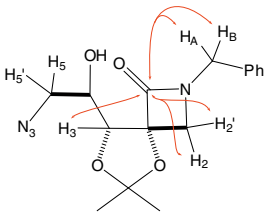


Figure 2. ^{1}H–^{13}C Correlations obtained from the 500/125 MHz HMBC spectrum of lactam **25** in $CDCl_3$ at 298 K.

It was, therefore, evident that it was necessary to remove the acetonide to allow the THF ring to be formed; when the triflate **13** was treated with methanolic hydrogen chloride (prepared from a 1:1 mixture of acetyl chloride and methanol), the target THF carboxylate was produced in 87% yield. The strong acid conditions cause ring opening of the lactone to the methyl ester as well as removal of the acetonide; the open chain deprotected triflate **15** can then cyclize to the THF, even though an S_N2 reaction at a very hindered carbon is necessary. It is noteworthy that **15** does not decompose by any other pathway. The overall yield of the scaffold **17** from the protected ribonolactone **7** is 36% over 6 steps.

2.2. Synthesis of a branched *cis*-azidomethyl carboxylate -THF SAA 18

2,3-*O*-Isopropylidene-L-lyxono-1,4-lactone **8**, readily available from D-ribono-1,4-lactone,[18] has been converted to the azido lactone **27** on a 200 kg scale[19] by the method first described to prepare the enantiomer.[20] Esterification of the alcohol in **8** with triflic anhydride in dichloromethane in the presence of pyridine gave the triflate **26** which on reaction with sodium azide in acetone gave the azide **27** in 86% yield over the two steps. Reduction of the lactone **27** with DIBAL-H in dichloromethane afforded the lactol **10** in 99% yield. Monitoring the conversion of the triflate **26** to the azide **27** by TLC. analysis was difficult as the two compounds co-spotted. If some of triflate **26** remained in the DIBAL-H reduction, the tricyclic compound **31** was formed, presumably by initial reduction of **26** to the lactol **30** and subsequent ring closure; the structure of **31** was firmly established by X-ray crystallographic analysis.[21]

The azidolactol **10** underwent an efficient Ho crossed aldol condensation with aqueous formaldehyde to form the branched lactol **12** in 88% yield (based on recovered starting material). Oxidation of the lactol **12** gave the corresponding lactone **28** (in 87% yield) which was esterified with triflic anhydride in dichloromethane to give the stable triflate **14** in 99% yield.

Treatment of the triflate **14** with dilute hydrogen chloride in methanol provided the methoxymethyl lactone **29**; the structure of which was determined by NMR, IR and high resolution mass spectroscopy. In the ^{1}H NMR spectrum of lactone **29,** the OMe singlet was present at 3.39 ppm; in the HMBC spectrum ^{3}J couplings arose from H-3 to C=O and C-2′, from C-2′ to OCH_3 and from C=O to H-2 and H-2′; the IR spectrum showed the presence of a lactone at 1789 cm^{-1}. The exclusive production of **29** was probably realized due to the difficulty of the removal of the acetonide group under the milder acidic conditions (MeOH/HCl (99:1)). Specifically, consistent with our prior observations (Scheme 3), THF formation through the corresponding open-chain ester of compound **14** failed due to the presence of the acetonide, and direct intermolecular displacement of the triflate group by methanol was favoured. Under more aggressive acidic conditions (MeOH/HCl (2:3)), hydrolysis of the acetonide group occurred faster than nucleophilic displacement of the triflate by methanol; **18** was successfully produced through the open-chain ester intermediate **16**. Under these conditions, the *cis*-substituted SAA scaffold **18** was isolated in 57% yield. It is noteworthy that in the synthesis of unbranched carbon chain, the THF ring is formed under treatment with dilute methanolic hydrogen chloride with no intermolecular nucleophilic triflate displacement by methanol.[11–15] The overall yield of the scaffold **18** from the protected L-lyxonolactone **8** was 37% over 7 steps.

3. Summary

Both *trans*-**17** and *cis*-**18** azidomethyl-THF carboxylates can be readily synthesized suitable for incorporation as dipeptide equivalents in amino acid sequences. NMR and circular dichroism studies on homooligomers of **17** and **18** have allowed the evaluation of their predisposition to induce secondary structures in short sequences.[22]

4. Experimental

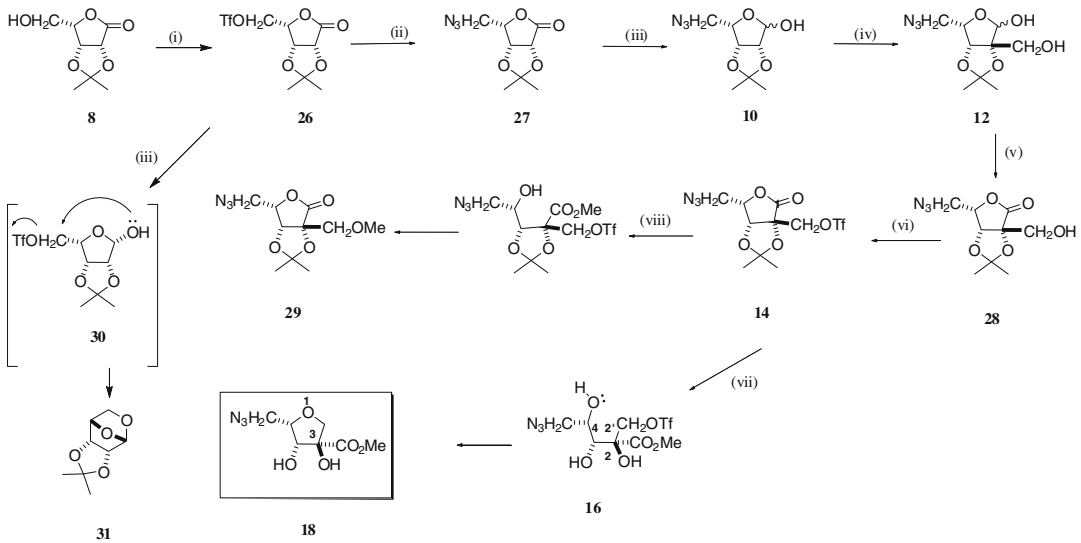
Tetrahydrofuran was purchased dry from the Aldrich Chemical Company in sure-seal™ bottles. Water was distilled. All other solvents were used as supplied without further purification (Analytical or HPLC grade). Reactions were performed under an atmosphere of nitrogen or argon and were maintained by an inflated balloon. Thin layer chromatography (TLC.) was performed on alumnum sheets coated with 60 F_{254} silica, visualized using a spray of 0.2% w/v cerium (IV) sulfate and 5% ammonium molybdate in 2 M sulfuric acid. Purification via flash column chromatography was performed on Sorbsil C60 40/60 silica. Melting points were recorded on a Kofler hot block. Nuclear magnetic resonance (NMR) spectra were recorded on Bruker AMX 500, DRX 500, DPX 400 or DQX 400 spectrometers in the deuterated solvent stated. Chemical shifts (δ) are quoted in ppm and coupling constants (J) in Hertz and residual solvent signals were used as an internal reference. The assignments of the ^{1}H and ^{13}C NMR spectra were made using the results obtained from 2D methods such as COSY, HMQC, HMBC, HSQC and DEPT correlations. Infra red (IR) spectra were recorded on a Perkin-Elmer 1750 IR Fourier Transform spectrophotometer and on a Bruker Tensor 27 FT-IR spectrophotometer using thin films. Only the characteristic peaks are quoted and in units of cm^{-1}. Optical rotations were measured on a Perkin–Elmer 241 polarimeter with a path length of 1.0 dm and concentrations are quoted in g/100 mL. Low resolution mass spectra were recorded using electrospray ionization (ES) or chemical ionization (CI, NH_3), and were measured on Micromass BioQ II-ZS, Micromass 500 OAT, Micromass TofSpec 2E, Micromass GCT, or Micromass Platform 1 mass spectrometers. High resolution mass spectra (HRMS) were measured on a Micromass 500 OAT spectrometer by CI or on a Waters 2790-Micromass LCT by ES. Elemental analyses were performed by the microanalysis service of the Inorganic Chemistry Laboratory, University of Oxford, Oxford.

The numbering of all compounds for NMR data is in accordance with carbohydrate nomenclature except the azidomethyl THF SAA **17** and **18** which are numbered as the THF (as indicated in Schemes 3 and 4).

4.1. Synthesis of *trans*-azidomethyl THF SAA 17

4.1.1. 5-Azido-5-deoxy-2,3-*O*-isopropylidene-D-ribono-1, 4-lactone 19

Triflic anhydride (10.9 mL, 64.79 mmol) was added dropwise to a solution of the protected lactone **7** (8.10 g, 43.02 mmol) and pyridine (10 mL) stirring in dichloromethane (325 mL) at −50 °C under an atmosphere of argon. After 30 min, the reaction temperature had risen to −25 °C. TLC. analysis (ethyl acetate/cyclohexane, 1:2) showed the presence of a product (R_f 0.52) and com-



Scheme 4. (i) Tf_2O, pyridine, CH_2Cl_2, −55 °C; (ii) NaN_3, acetone, 60 °C (86% over 2 steps); (iii) DIBAL-H (1.5 M soln in toluene), CH_2Cl_2, −80 °C, 99%; (iv) aq CH_2O soln (38.5%), MeOH, K_2CO_3, 78 °c, 88% (based on recovered starting material); (v) Br_2, $BaCO_3$, H_2O, 0 °c, 87%; (vi) Tf_2O, pyridine, CH_2Cl_2, −55 °C, 99%; (vii) MeOH/HCl (34:23), 57%; (viii) MeOH/HCl (99:1), 24 h, 51% (based on recovered starting material); (ix) DIBAL-H (1.5 M soln in toluene), CH_2Cl_2, −80 °C.

plete consumption of starting material (R_f 0.10). The reaction mixture was washed with aqueous hydrochloric acid solution (1 M, 100 mL), brine (25 mL), dried (magnesium sulfate), filtered and concentrated in vacuo to afford 2,3-*O*-isopropylidene-5-*O*-trifluoromethanesulfonyl-D-ribono-1,4-lactone (13.50 g, 98%) as an unstable white solid. ν_{max} (thin film): 2987 (C–H), 1790 (s, C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.42, 1.50 (2 × 3H, 2 × s, $C(CH_3)_2$), 4.71 (1H, dd, $J_{H\text{-}5,H\text{-}5'}$ 11.2 Hz, $J_{H\text{-}5,H\text{-}4}$ 2.3 Hz, H-5), 4.77 (1H, dd, $J_{H\text{-}5',H\text{-}5}$ 11.2 Hz, $J_{H\text{-}5',H\text{-}4}$ 2.4 Hz, H-5′), 4.79 (1H, m, H-4), 4.81–4.84 (2H, m, H-3 and H-2); δ_C ($CDCl_3$, 100 MHz): 25.5, 26.6 ($C(CH_3)_2$), 74.0 (C-5), 74.7 (C-3), 76.8 (C-2), 78.5 (C-4), 114.5 ($C(CH_3)_2$), 172.0 (C=O). Sodium azide (8.61 g, 132.47 mmol) was added to a stirred solution of the triflate (13.50 g, 42.29 mmol) in acetone (250 mL) and the reaction mixture was stirred at room temperature under an atmosphere of argon. After 22 h 30 min, a white salt had precipitated out of solution and TLC analysis (ethyl acetate/cyclohexane, 1:2) showed the presence of one product (R_f 0.52). The reaction mixture was filtered through Celite (eluent/acetone), dried (magnesium sulfate), filtered and concentrated in vacuo to afford a residue, which was purified by flash column chromatography (ethyl acetate/cyclohexane, 1:2) to give the azide **19** (7.07 g, 78%; 76% over 2 steps) as a pale yellow oil which crystallized on standing. mp 36 °C [Lit.[23] mp 39 °C]. *m/z* (CI^+): 231.2 ($[M+NH_4]^+$, 100%); HRMS (CI^+): found 231.1083 $[M+NH_4]^+$ $C_8H_{15}N_4O_4$ requires 231.1093; $[\alpha]_D^{23} = +18.9$ (*c* 1.66, chloroform) {Lit.[23] $[\alpha]_D = +15.0$ (*c* 1.00, chloroform)}; ν_{max} (thin film): 2990 (C–H), 2113 (s, N_3), 1788 (s, C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.38, 1.48 (2 × 3H, 2 × s, $C(CH_3)_2$), 3.67 (1H, dd, $J_{H\text{-}5,H\text{-}5'}$ 13.2 Hz, $J_{H\text{-}5,H\text{-}4}$ 2.4 Hz,H-5), 3.79 (1H, dd, $J_{H\text{-}5',H\text{-}5}$ 13.3 Hz, $J_{H\text{-}5',H\text{-}4}$ 3.1, H-5′), 4.64 (1H, a-d, *J* 5.5, H-3), 4.67 (1H, m, H-4), 4.86 (1H, d, $J_{H\text{-}2,H\text{-}3}$ 6.0 Hz, H-2); δ_C ($CDCl_3$, 100 MHz): 25.5, 26.6 ($C(CH_3)_2$), 52.5 (C-5), 75.1 (C-3), 78.0 (C-2), 80.0 (C-4), 113.7 ($C(CH_3)_2$), 173.3 (C=O). $C_8H_{11}N_3O_4$ required C, 45.07; H, 5.20; N 19.71. Found: C, 45.09; H, 5.26; N, 19.58.

4.1.2. 5-Azido-5-deoxy-2,3-*O*-isopropylidene-D-ribose 9

Diisobutylaluminum hydride solution (1.5 M in toluene, 14.4 mL, 21.60 mmol) was added dropwise over a period of 30 min to a stirred solution of the azidolactone **19** (4.16 g, 19.51 mmol) in dichloromethane (51 mL) under an atmosphere of argon at −78 °C. The temperature was kept at −78 °C for the duration of the reaction. After 3 h 20 min, TLC analysis (ethyl acetate/dichloromethane, 1:4) showed the presence of a major product (R_f 0.53) and almost complete consumption of the starting material **19** (R_f 0.76). The reaction mixture was quenched by addition of water (10 mL), then diluted with dichloromethane (40 mL), water (30 mL) and extracted with dichloromethane (3 × 250 mL). The organic extracts were combined, dried (magnesium sulfate), filtered and concentrated in vacuo to give a residue, which was purified by flash column chromatography (ethyl acetate/dichloromethane, 1:7) to afford starting material (114 mg) and the lactols **9** (3.80 g, 90%; 93% based on recovered starting material) as a pale yellow oil. *m/z* (ES^-): 214.1 ($[M-H]^-$, 100%); HRMS (ES^-): found 214.0828 $[M-H]^-$ $C_8H_{12}N_3O_4$ requires 214.0822; $[\alpha]_D^{25} = -42.8$ (*c* 0.54, acetonitrile); ν_{max} (thin film): 3434 (br, OH), 2991 (C–H), 2106 (s, N_3) cm^{-1}; δ_H (CD_3CN, 400 MHz), *anomeric ratio:* α:β = 5:4; 1.30, 1.42 (2 × 3H, 2 × s, $C(CH_3)_2$, β), 1.37, 1.43 (2 × 3H, 2 × s, $C(CH_3)_2$, α), 3.30 (1H, dd, $J_{H\text{-}5,H\text{-}5'}$ 12.8 Hz, $J_{H\text{-}5,H\text{-}4}$ 6.0 Hz, H-5, β), 3.53 (1H, dd, $J_{H\text{-}5',H\text{-}5}$ 12.7 Hz, $J_{H\text{-}5',H\text{-}4}$ 8.2, H-5′, β), 3.69 (1H, dd, $J_{H\text{-}5,H\text{-}5'}$ 13.6 Hz, $J_{H\text{-}5,H\text{-}4}$ 3.5 Hz, H-5, α), 3.77 (1H, dd, $J_{H\text{-}5',H\text{-}5}$ 13.5 Hz, $J_{H\text{-}5',H\text{-}4}$ 3.4, H-5′, α), 4.16–4.21 (1H, m, H-4, β), 4.51 (1H, d, $J_{OH\text{-}1,H\text{-}1}$ 4.4 Hz, OH-1, α), 4.57 (1H, d, $J_{H\text{-}2,H\text{-}3}$ 5.9 Hz, H-2, β), 4.65 (1H, dd, $J_{H\text{-}3,H\text{-}2}$ 5.9 Hz, $J_{H\text{-}3,H\text{-}4}$ 1.3 Hz, H-3, β), 4.69 (1H, t, $J_{H\text{-}4,H\text{-}5} = J_{H\text{-}4,H\text{-}5'}$ 3.4 Hz, H-4, α), 4.74 (1H, d, $J_{H\text{-}2,H\text{-}3}$ 5.6 Hz, H-2, α), 4.87 (1H, d, $J_{H\text{-}3,H\text{-}2}$ 5.6 Hz, H-3, α), 5.33 (1H, d, $J_{H\text{-}1,OH\text{-}1}$ 4.4 Hz, H-1, α); δ_C (CD_3CN, 100 MHz): 24.4, 26.2 ($C(CH_3)_2$, β), 24.9, 26.3 ($C(CH_3)_2$, α), 52.5 (C-5, α), 54.1 (C-5, β), 75.3 (C-3, α), 78.5 (C-2, α), 80.9 (C-4, α), 82.5 (C-3, β), 85.6 (C-4, β), 86.4 (C-2, β), 97.5 (C-1, β), 103.2 (C-1, α), 112.5 ($C(CH_3)_2$, α), 113.4 ($C(CH_3)_2$, β).

4.1.3. 5-Azido-5-deoxy-2-*C*-hydroxymethyl-2, 3-*O*-isopropylidene-D-ribose 11

Potassium carbonate (1.98 g, 14.35 mmol) was added, followed by an aqueous solution of formaldehyde (38.5%, 63 mL), to a stirred solution of the lactols **9** (6.16 g, 28.64 mmol) in methanol (168 mL) and the mixture was heated to 50 °C. After 24 h, TLC analysis (ethyl acetate/cyclohexane, 1:1) showed the presence of a product (R_f 0.24) and complete consumption of the starting material (R_f 0.59). The reaction mixture was allowed to cool to room temperature, water was added (200 mL) and the mixture was concentrated until the methanol was completely removed. The aqueous solution was then extracted with diethyl ether (3 × 250 mL). The organic extracts were combined, dried (magnesium sulfate), filtered and

concentrated in vacuo to give a residue, which was purified by flash column chromatography (ethyl acetate/cyclohexane, 1:2 to 1:1) to afford the branched ribose **11** (6.57 g, 94%) as a colourless oil which crystallized on standing, mp 115–117 °C; *m*/*z* (ES^-): 244.4 ($[M-H]^-$, 100%); HRMS (ES^-): found: 244.0929 $[M-H]^-$ $C_9H_{14}N_3O_5$ requires 244.0933; $[\alpha]_D^{25} = +23.1$ (*c* 0.95, acetonitrile); ν_{max} (thin film): 3436 (br s, OH), 2988, 2938 (C–H), 2105 (s, N_3), 1633 (s, CHO) cm^{-1}; δ_H (CD_3CN, 400 MHz): anomeric ratio: β:α = 9:11; 1.39, 1.45 (2 × 3H, 2 × s, $C(CH_3)_2$, α), 1.42, 1.54 (2 × 3H, 2 × s, $C(CH_3)_2$, β), 3.07 (1H, m, OH-2′, α), 3.31 (1H, dd, $J_{H\text{-}5,H\text{-}5'}$ 12.8 Hz, $J_{H\text{-}5,H\text{-}4}$ 6.0, H-5, α), 3.34 (1H, a-t, $J_{OH\text{-}2',H\text{-}2} = J_{OH\text{-}2',H\text{-}2'}$ 5.8 Hz, OH-2′, β), 3.37 (1H, dd, $J_{H\text{-}5,H\text{-}5'}$ 13.2 Hz, $J_{H\text{-}5,H\text{-}4}$ 4.8, H-5, β), 3.45 (1H, dd, $J_{H\text{-}5',H\text{-}5}$ 13.3 Hz, $J_{H\text{-}5',H\text{-}4}$ 6.6 Hz, H-5′, β), 3.55 (1H, dd, $J_{H\text{-}5',H\text{-}5}$ 12.8 Hz, $J_{H\text{-}5',H\text{-}4}$ 8.3 Hz, H-5′, α), 3.66 (1H, dd, $J_{H\text{-}2,H\text{-}2'}$ 12.0 Hz, $J_{H\text{-}2,OH\text{-}2'}$ 6.0 Hz, H-2, β), 3.68 (1H, dd, $J_{H\text{-}2',H\text{-}2}$ 12.0 Hz, $J_{H\text{-}2',OH\text{-}2'}$ 5.6 Hz, H-2′, β), 3.74 (1H, m, H-2, α), 3.77 (1H, dd, $J_{H\text{-}2',H\text{-}2}$ 12.0 Hz, $J_{H\text{-}2',OH\text{-}2'}$ 5.6 Hz, H-2′, α), 4.09 (1H, d, $J_{OH\text{-}1,H\text{-}1}$ 9.2 Hz, OH-1, α), 4.16–4.21 (2H, m, H-4, β and H-4, α), 4.44–4.46 (2H, m, H-3, β and H-3, α), 4.90 (1H, d, $J_{OH\text{-}1,H\text{-}1}$ 4.4 Hz, OH-1, β), 5.09 (1H, d, $J_{H\text{-}1,OH\text{-}1}$ 9.2 Hz, H-1, α), 5.31 (1H, d, $J_{H\text{-}1,OH\text{-}1}$ 4.4 Hz, H-1, β); δ_C (CD_3CN, 100 MHz): 26.8, 27.0 ($C(CH_3)_2$, β), 27.5 (1 × s, $C(CH_3)_2$, α), 51.9 (C-5, β), 53.6 (C-5, α), 62.4 (C-2′, α), 62.5 (C-2′, β), 80.7 (C-4, β), 83.8 (C-3, β), 84.8 (C-4, α), 85.2 (C-3, α), 91.3 (C-2, β), 94.3 (C-2, α), 98.3 (C-1, α), 104.8 (C-1, β), 113.6 ($C(CH_3)_2$, α), 114.8 ($C(CH_3)_2$, β).

4.1.4. 5-Azido-5-deoxy-2-*C*-hydroxymethyl-2,3-*O*-isopropylidene-D-ribono-1,4-lactone 20

Bromine (1.4 mL, 27.26 mmol) was added dropwise over a period of 7 min to the lactol **11** (5.10 g, 20.07 mmol) stirring in water (540 mL) at 0 °C in the presence of barium carbonate (4.97 g, 25.16 mmol). After 2 h and 15 min, TLC analysis (ethyl acetate/cyclohexane, 1:1) showed the presence of a product (R_f 0.34) and almost complete consumption of the starting material (R_f 0.21). The reaction mixture was quenched with sodium thiosulfate and extracted with diethyl ether (3 × 200 mL). The organic extracts were combined, dried (magnesium sulfate), filtered and concentrated in vacuo to afford a residue, which was purified by flash column chromatography (ethyl acetate/cyclohexane, 1:1) to give the branched lactone **20** (4.20 g, 82%) as a white crystalline solid. mp 100.5–102 °C. *m*/*z* (CI^+): 261.0 ($[M+NH_4]^+$, 100%); HRMS (CI^+): found 261.1197 $[M+NH_4]^+$ $C_9H_{17}N_4O_5$ requires 261.1199; $[\alpha]_D^{25} = +11.3$ (*c* 0.31, acetonitrile); ν_{max} (thin film): 3430 (s, OH), 2992, 2954 (C–H), 2129 (s, N_3), 1782 (s, C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.45, 1.47 (2 × 3H, 2 × s, $C(CH_3)_2$), 2.20–2.45 (1H, br s, OH), 3.6–3.71 (2H, m, H-5 and H-5′), 3.94 (1H, d, $J_{H\text{-}2,H\text{-}2'}$ 11.7 Hz, H-2), 4.08 (1H, d, $J_{H\text{-}2',H\text{-}2}$ 11.7 Hz, H-2′), 4.66 (1H, a-t, *J* 5.6 Hz, H-4), 4.64 (1H, a-s, H-3); δ_C ($CDCl_3$, 100 MHz): 26.7, 26.9 ($C(CH_3)_2$), 51.9 (C-5), 61.5 (C-2′), 79.7 (C-3), 81.7 (C-4), 85.3 (C-2), 114.0 ($C(CH_3)_2$), 174.4 (C=O). $C_9H_{13}N_3O_4$ required C, 44.44; H, 5.39; N, 17.28. Found: C, 44.39; H, 5.37; N, 17.32.

4.1.5. 5-Azido-5-deoxy-2-*C*-hydroxymethyl-2,3-*O*-isopropylidene-2′-*C*-trifluoromethanesulfonyl-D-ribono-1,4-lactone 13

Pyridine (1.70 mL) then triflic anhydride (1.50 mL, 8.92 mmol) was added dropwise to a stirred solution of hydroxymethyl lactone **20** (1.40 g, 5.76 mmol) in dichloromethane (110 mL) at −25 °C under an atmosphere of argon. After 15 min, TLC (ethyl acetate/cyclohexane, 1:1) showed the presence of one product (R_f 0.53) and complete consumption of the starting material (R_f 0.32). The reaction mixture was diluted in dichloromethane (70 mL), washed with an aqueous hydrochloric acid solution (1 M, 40 mL), brine (40 mL) and dried (magnesium sulfate). The organic layer was then filtered, concentrated in vacuo to yield the triflate **13** (2.10 g, 97%) as a thick colourless oil. *m*/*z* (ES^+): 439.0 ($[M+NH_4+Na]^+$, 100%); HRMS (MS^+): found 398.0240 $[M+NH_4]^+$ $C_{10}H_{12}F_3N_3NaO_7S$ requires 398.0234; $[\alpha]_D^{21} = +58.9$ (*c* 0.52, dichloromethane); ν_{max} (thin film): 2997 (C–H), 2120 (s, N_3), 1786 (s, C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.46, 1.47 (2 × 3H, 2 × s, $C(CH_3)_2$), 3.79 (1H, dd, $J_{H\text{-}5',H\text{-}5}$ 13.4 Hz, $J_{H\text{-}5',H\text{-}4}$ 2.5 Hz, H-5′), 3.87 (1H, dd, $J_{H\text{-}5,H\text{-}5'}$ 13.4 Hz, $J_{H\text{-}5,H\text{-}4}$ 3.2 Hz, H-5), 4.70 (1H, ddd, $J_{H\text{-}4,H\text{-}5}$ 3.3 Hz, $J_{H\text{-}4,H\text{-}5'}$ 2.6 Hz, $J_{H\text{-}4,H\text{-}3}$ 0.8 Hz, H-4), 4.73 (1H, d, $J_{H\text{-}3,H\text{-}4}$ 0.8 Hz, H-3), 4.83 (1H, d, $J_{H\text{-}2,H\text{-}2'}$ 11.2 Hz, H-2), 4.93 (1H, d, $J_{H\text{-}2',H\text{-}2}$ 11.2 Hz, H-2′); δ_C ($CDCl_3$, 100 MHz): 26.3, 27.0 ($C(CH_3)_2$), 52.2 (C-5), 71.3 (C-2′), 78.9 (C-3), 81.6 (C-4), 83.6 (C-2), 113.7, 116.9, 120.1, 123.3 (1C, q, $J_{C,F}$ −318 Hz, CF_3), 115.2 ($C(CH_3)_2$), 171.1 (C=O). $C_{10}H_{12}F_3N_3O_7S$ required C, 32.00; H, 3.22; N, 11.20. Found: C, 32.09; H, 3.25; N, 11.18.

4.1.6. Methyl (3*R*,4*R*,5*R*)-5-azidomethyl-3,4-dihydroxy-tetrahydrofuran-3-carboxylate 17

A freshly prepared solution of acetyl chloride/methanol (1:1 v/v, 210 mL) was cooled to 0 °C and was added to the crude triflate **13** (2.17 g, 5.78 mmol) and stirred at room temperature under an atmosphere of nitrogen. After 19 h, TLC analysis (ethyl acetate/cyclohexane, 1:1) showed the presence of a major product (R_f 0.18) and complete consumption of the starting material (R_f 0.66). The reaction mixture was diluted in methanol (300 mL), then quenched with anhydrous sodium bicarbonate and adjusted to pH 7. The mixture was filtered (eluent: methanol) and the filtrate concentrated in vacuo to yield a white residue, which was suspended in water (50 mL) and extracted with dichloromethane (2 × 400 mL, 4 × 100 mL). The organic layers were combined, dried (magnesium sulfate), filtered and concentrated in vacuo to yield the title compound **17** (1.09 g, 87%) as a dark yellow viscous oil. *m*/*z* (CI^+): 235.1 ($[M+NH_4]^+$, 28%); HRMS (CI^+): found 235.1048 $[M+NH_4]^+$ $C_7H_{15}N_4O_5$ requires 235.1042; $[\alpha]_D^{21} = +25$ (*c* 4.4, methanol); ν_{max} (thin film): 3428 (br, OH), 2957 (C–H), 2106 (s, N_3), 1735 (C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 3.44 (1H, dd, $J_{H\text{-}6,H\text{-}6'}$ 13.1 Hz, $J_{H\text{-}6,H\text{-}5}$ 5.0 Hz, H-6), 3.60 (1H, dd, $J_{H\text{-}6',H\text{-}6}$ 13.1 Hz, $J_{H\text{-}6',H\text{-}5}$ 3.6 Hz, H-6′), 3.71 (1H, d, $J_{OH\text{-}4,H\text{-}4}$ 5.5 Hz, OH-4), 3.86 (3H, s, CO_2CH_3), 3.96 (1H, d, $J_{H\text{-}2,H\text{-}2'}$ 9.7 Hz, H-2), 4.02–4.08 (1H, m, H-5), 4.18 (1H, a-t, *J* 6.3 Hz, H-4), 4.21 (1H, s, OH-3), 4.26 (1H, d, $J_{H\text{-}2',H\text{-}2}$ 9.7 Hz, H-2′); δ_C ($CDCl_3$, 100 MHz): 51.7 (C-6), 53.4 (CO_2CH_3), 74.5 (C-2), 81.2 (C-4), 82.6 (C-5), 84.0 (C-3), 172.9 (C=O).

4.1.7. *N*-Benzyl 5-azido-5-deoxy-2-*C*-hydroxymethyl-2,3-isopropylidene-2′-*O*-trifluoromethanesulfonyl-D-ribonamide 23

Benzylamine (25 μL, 0.23 mmol) was added dropwise to a solution of the triflate **13** (85 mg, 0.23 mmol) in THF (2 mL) at room temperature under an atmosphere of argon. After 2 h, TLC analysis (ethyl acetate/cyclohexane, 1:1) showed the presence of one major UV-active product (R_f 0.56) and starting material (R_f 0.48). More benzylamine (25 μL) was added and after 3 h and 45 min TLC analysis (ethyl acetate/cyclohexane, 1003A1) showed complete consumption of the starting material (R_f 0.48). The reaction mixture was purified by flash column chromatography (ethyl acetate/cyclohexane, 1:3) to afford the open chain triflate amide **23** (60.6 mg, 55%) as a colourless oil. *m*/*z* (CI^+): 483.1 ($M+H^+$, 100%); HRMS (CI^+): found 483.1154 $[M+H]^+$ $C_{17}H_{22}N_4O_7F_3S$ requires 483.1161; ν_{max} (thin film): 3417 (s, NH, OH), 3033 (ArC-H), 2993, 2939 (C–H), 2106 (s, N_3), 1664 (s, C=ONH, I), 1531 (s, C=ONH, II) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.48, 1.52 (2 × 3H, 2 × s, $C(CH_3)_2$), 3.40 (1H, dd, $J_{H\text{-}5',H\text{-}5}$ 12.7 Hz, $J_{H\text{-}5',H\text{-}4}$ 5.6 Hz, H-5′), 3.52 (1H, dd, $J_{H\text{-}5,H\text{-}5'}$ 12.8 Hz, $J_{H\text{-}5,H\text{-}4}$ 2.6 Hz, H-5), 3.74–3.81 (1H, m, H-4), 4.06 (1H, d, $J_{H\text{-}3,H\text{-}4}$ 9.4 Hz, H-3), 4.51 (1H, dd, $J_{H\text{-}A,H\text{-}B}$ 15.3 Hz, $J_{H\text{-}A,NH}$ 6.2 Hz, CH_AH_BNH), 4.57 (1H, dd, $J_{H\text{-}B,H\text{-}A}$ 15.3 Hz, $J_{H\text{-}B,NH}$ 6.3 Hz, CH_AH_BNH), 4.61 (1H, d, $J_{H\text{-}2,H\text{-}2'}$ 10.7 Hz, H-2), 4.96 (1H, a-s, OH-4), 4.98 (1H, d, $J_{H\text{-}2',H\text{-}2}$ 10.8 Hz, H-2′), 7.24–7.42 (6H, m, NH and 5 × Ar-H); δ_C ($CDCl_3$, 100 MHz): 25.3, 27.2 ($C(CH_3)_2$), 43.8 ($NHCH_2$), 53.5 (C-5), 70.0 (C-4), 77.5 (C-2′), 79.4 (C-3), 84.8 (C-2), 111.9 ($C(CH_3)_2$),

114.5, 117.1, 119.7, 122.3 (CF_3), 127.3, 128.0, 129.0 (5 × Ar-*C*H), 136.5 (Ar*C*), 169.5 (*C*ONH).

4.1.8. *N*-Benzyl 1,2′-anhydro-5-azido-5-deoxy-2-*C*-hydroxymethyl-2,3-*O*-isopropylidene-D-ribonamide 25

Potassium carbonate (96 mg, 0.70 mmol) was added to a solution of the open chain triflate **23** (63.3 mg, 0.13 mmol) in tetrahydrofuran (13 mL) at room temperature under an atmosphere of argon. After 6 days, TLC (ethyl acetate/cyclohexane, 1:1) showed the presence of one product (R_f 0.64) and complete consumption of the starting material (R_f 0.43). The reaction mixture was filtered through Celite (eluent: ethyl acetate), concentrated in vacuo and purified by flash chromatography (ethyl acetate/cyclohexane, 1:3) to yield *N*-benzyl 1,2′-anhydro-5-azido-5-deoxy-2-*C*-hydroxymethyl-2,3-*O*-isopropylidene-D-ribonamide **25** (39 mg, 89%) as a colourless oil. *m*/*z* (CI^+): 333.3 ($[M+H]^+$, 100%); HRMS (CI^+): found: 333.1572 $[M+H]^+$ $C_{16}H_{21}N_4O_4$ requires 333.1563; $[\alpha]_D^{23} = +25.2$ (*c* 1.76, acetonitrile); ν_{max} (thin film): 3414 (br, OH), 3032 (ArC-H), 2988, 2935 (C–H), 2105 (s, N_3), 1745 (C=O, 4-ring lactam) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.37, 1.52 (2 × 3H, 2 × s, C(CH_3)$_2$), 3.25 (1H, d, $J_{OH\text{-}4,H\text{-}4}$ 5.5 Hz, OH-4), 3.40 (1H, d, $J_{H\text{-}2,H\text{-}2'}$ 5.5 Hz, H-2), 3.43 (1H, d, $J_{H\text{-}2',H\text{-}2}$ 5.6 Hz, H-2′), 3.44 (1H, dd, $J_{H\text{-}5,H\text{-}5'}$ 12.6 Hz, $J_{H\text{-}5,H\text{-}4}$ 5.7 Hz, H-5), 3.59 (1H, dd, $J_{H\text{-}5',H\text{-}5}$ 12.7 Hz, $J_{H\text{-}5',H\text{-}4}$ 2.6 Hz, H-5′), 4.20 (1H, dddd, $J_{H\text{-}4,H\text{-}3}$ 9.4 Hz, $J_{H\text{-}4,H\text{-}5}$ 5.7 Hz, $J_{H\text{-}4,OH\text{-}4}$ 5.5 Hz, $J_{H\text{-}4,H\text{-}5'}$ 2.6 Hz, H-4), 4.25 (1H, d, $J_{H\text{-}3,H\text{-}4}$ 9.4 Hz, H-3), 4.40 (1H, d, $J_{HA,HB}$ 15.1 Hz, NCH_AH$_B$), 4.47 (1H, d, $J_{H\text{-}B,H\text{-}A}$ 15.1 Hz, NCH$_A$$H_B$), 7.23–7.39 (5H, m, 5 × Ar-*H*); δ_C ($CDCl_3$, 100 MHz): 26.1, 27.3 (C(CH_3)$_2$), 46.0 (NCH_2), 54.3 (C-5), 54.5 (C-2′), 70.0 (C-4), 79.4 (C-3), 90.4 (C-2), 111.4 (*C*(CH_3)$_2$), 128.0, 128.1, 128.9 (5 × Ar-*C*H), 134.5 (ArCCH_2), 167.4 (*C*ONH).

4.2. Synthesis of *cis*-azidomethyl THF SAA 18

4.2.1. 5-Azido-5-deoxy-2,3-*O*-isopropylidene-L-lyxono-1,4-lactone 27

Pyridine (2.61 mL) followed by trifluoromethanesulfonic anhydride (5.96 mL, 35.45 mmol) was added dropwise to a solution of the alcohol **8** (6.67 g, 35.45 mmol) stirred in dichloromethane (445 mL) at −50 °C under an atmosphere of nitrogen. After 15 min, TLC analysis (ethyl acetate/cyclohexane, 1:1) showed the presence of one product (R_f 0.57) and complete consumption of starting material (R_f 0.13). The reaction mixture was washed with aqueous hydrochloric acid solution (1 M, 150 mL) and brine (120 mL), dried (magnesium sulfate), filtered and concentrated in vacuo to afford crude triflate **26** as a white hygroscopic amorphous solid (13.17 g, 99%). Sodium azide (6.91 g, 106.34 mmol) was added to a solution of the crude triflate **26** in acetone (54 mL) and was stirred at 65 °C under an atmosphere of nitrogen. After 15 h, a white precipitate had formed in the stirring reaction mixture and TLC analysis (ethyl acetate/cyclohexane, 1:1) showed the presence of one product (R_f 0.57). The reaction mixture was filtered through Celite (eluent/acetone), and the filtrate was dried (magnesium sulfate), filtered and concentrated in vacuo to afford a residue, which was purified by flash column chromatography (ethyl acetate/cyclohexane, 1:1 to ethyl acetate) to give the azido-lactone **27** (6.51 g, 86% over two steps) as pale yellow crystals. mp 72–74 °C [Lit.[20] mp 59.7 °C for the *enantiomer* 5-azido-5-deoxy-2,3-*O*-isopropylidene-D-lyxono-1,4-lactone]; HRMS (FI^+): found 213.0757 $[M]^+$ $C_8H_{11}N_3O_4$ requires 213.0750; $[\alpha]_D^{22} = -75.8$ (*c* 0.52, chloroform) {Lit.[19] $[\alpha]_D = -71.0$ (*c* 2.0, chloroform)}; ν_{max} (thin film): 2992, 2971 (C–H), 2108 (s, N_3), 1790 (C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.39, 1.49 (2 × 3H, 2 × s, C(CH_3)$_2$), 3.66 (1H, dd, $J_{H\text{-}5,H\text{-}5'}$ 12.9 Hz, $J_{H\text{-}5,H\text{-}4}$ 6.3 Hz, H-5), 3.72 (1H, dd, $J_{H\text{-}5',H\text{-}5}$ 13.0 Hz, $J_{H\text{-}5',H\text{-}4}$ 7.1 Hz, H-5′), 4.54–4.59 (1H, ddd, $J_{H\text{-}4,H\text{-}5'}$ 7.1 Hz, $J_{H\text{-}4,H\text{-}5}$ 6.4, $J_{H\text{-}4,H\text{-}3}$ 3.6 Hz, H-4), 4.85 (1H, d, $J_{H\text{-}2,H\text{-}3}$ 10.9 Hz, H-2), 4.85 (1H, a-t, *J* 10.9 Hz, H-3); δ_C ($CDCl_3$, 100 MHz): 25.8, 26.7 (C(CH_3)$_2$), 49.6 (C-5), 75.6 (C-3), 76.0 (C-2), 77.1 (C-4), 114.2 (*C*(CH_3)$_2$), 172.9 (C=O). $C_8H_{11}N_3O_4$ requires C, 45.07; H, 5.20; N, 19.71. Found: C, 45.05; H, 5.22; N, 19.32.

4.2.2. 5-Azido-5-deoxy-2,3-*O*-isopropylidene-L-lyxose 10

Diisobutylaluminum hydride (1.7 M in toluene, 12.9 mL, 22.03 mmol) was added dropwise over a period of 15 min to a stirred solution of the azidolactone **27** (4.05 g, 18.99 mmol) in dichloromethane (51 mL) at 78 °C under an atmosphere of argon. After 2.5 h at −78 °C, more diisobutylaluminum hydride (10 mL, 17.00 mmol) was added dropwise to the stirring solution. After 45 min, TLC analysis (ethyl acetate/dichloromethane, 1:4) showed the presence of a major product (R_f 0.47) and complete consumption of the starting material (R_f 0.70). The reaction mixture was quenched by addition of water (25 mL) and extracted with dichloromethane (3 × 100 mL). The organic extracts were combined, dried (magnesium sulfate), filtered and concentrated in vacuo to give the azidolyxose **10** (4.07 g, 99%) as a pale yellow oil. *m*/*z* (CI^+): 233.1 ($[M+NH_4]^+$, 100%); HRMS (CI^+): found 233.1245 $[M+NH_4]^+$ $C_8H_{17}N_4O_4$ requires 233.1250; $[\alpha]_D^{21} = -36.0$ (*c* 0.90, methanol); ν_{max} (thin film): 3423 (br, OH), 2942 (C–H), 2102 (s, N_3) cm^{-1}; δ_H (C_6D_6, 400 MHz): (data for the major anomer α): 1.06, 1.35 (2 × 3H, 2 × s, C(CH_3)$_2$), 2.12 (1H, d, $J_{OH\text{-}1,H\text{-}1}$ 2.8 Hz, OH-1), 3.27 (1H, dd, $J_{H\text{-}5,H\text{-}5'}$ 12.8 Hz, $J_{H\text{-}5,H\text{-}4}$ 4.6 Hz, H-5), 3.50 (1H, dd, $J_{H\text{-}5',H\text{-}5}$ 12.8 Hz, $J_{H\text{-}5',H\text{-}4}$ 8.0 Hz, H-5′), 4.14 (1H, m, H-4), 4.50 (1H, dd, $J_{H\text{-}3,H\text{-}2}$ 6.0 Hz, $J_{H\text{-}3,H\text{-}4}$ 3.6 Hz, OH-1), 4.50 (1H, d, $J_{H\text{-}2,H\text{-}3}$ 5.9 Hz, H-2), 5.30 (1H, d, $J_{H\text{-}1,OH\text{-}1}$ 2.4 Hz, H-1); δ_C (C_6D_6, 100 MHz): 24.5, 26.0 (2 × C(CH_3)$_2$), 50.1 (C-5), 79.0 (C-4), 80.0 (C-3), 85.9 (C-2), 101.4 (C-1), 112.6 (*C*(CH_3)$_2$).

If the azide-triflate displacement reaction was not complete, the triflate **26** was carried through giving an impurity which was reduced to 1,5-anhydro-2,3-*O*-isopropylidene-L-lyxofuranose **31**, a volatile colourless crystalline solid; R_f 0.57 (ethyl acetate: cyclohexane, 1: 1); mp 65–66 °C (recrystallized from ethyl acetate/cyclohexane); HRMS (FI^+): found 172.0732 $[M]^+$ $C_8H_{12}O_4$ requires 172.0736; $[\alpha]_D^{21} = +106.8$ (*c* 0.72, methanol); ν_{max} (thin film): 2992, 2955, 2906 (s, C–H), 1378 (–O–CO–CH), 1291 (C–O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.34, 1.60 (2 × 3H, 2 × s, C(CH_3)$_2$), 3.55 (1H, ddd, $J_{H\text{-}5,H\text{-}5'}$ 6.6 Hz, $J_{H\text{-}5,H\text{-}4}$ 3.5 Hz, $J_{H\text{-}5,H\text{-}3}$ 1.3 Hz, H-5), 4.31 (1H, a-d, *J* 6.8 Hz, H-5′), 4.45 (1H, a-dd, *J* 8.2 Hz, *J* 2.3, H-2), 4.64 (1H, dd, $J_{H\text{-}3,H\text{-}2}$ 8.1 Hz, $J_{H\text{-}3,H\text{-}4}$ 4.6, H-3), 4.72–4.77 (1H, m, H-4), 5.45 (1H, d, $J_{H\text{-}1,H\text{-}2}$ 2.2 Hz, H-1); δ_C ($CDCl_3$, 100 MHz): 25.6, 26.1 (C(CH_3)$_2$), 63.7 (C-5), 76.5 (C-3), 78.8 (C-4), 81.6 (C-2), 100.1 (C-1), 119.7 (*C*(CH_3)$_2$).

4.2.3. 5-Azido-5-deoxy-2-*C*-hydroxymethyl-2,3-*O*-isopropylidene-L-lyxose 12

Potassium carbonate (598 mg, 4.33 mmol), followed by an aqueous solution of formaldehyde (38.5 wt %, 19 mL), was added to a solution of lactol **10** (1.86 g, 8.63 mmol) in methanol (51 mL) and heated at 78 °C. After 22 h, TLC analysis (ethyl acetate/cyclohexane, 1:1) showed the presence of a major product (R_f 0.39) and almost complete consumption of the starting material (R_f 0.56). The reaction mixture was cooled to room temperature, water was added (200 mL) and the mixture was concentrated *in vacuo*; the concentrate was extracted with dichloromethane (3 × 250 mL). The organic extracts were combined, dried (magnesium sulfate), filtered and concentrated in vacuo to give a residue, which was purified by flash column chromatography (ethyl acetate/cyclohexane, 1:1) to give the branched lyxose **12** [1.31 g, 62%; 88% based on recovered starting material (551 mg)] as a pale yellow oil which crystallized on standing, mp 63–65 °C; *m*/*z* (CI^+): 263.1 ($[M+NH_4]^+$, 100%); HRMS (CI^+): found: 263.1362 $[M+NH_4]^+$ $C_9H_{19}N_4O_5$ requires 263.1355; $[\alpha]_D^{22} = -0.2$ (*c* 0.96, chloroform); ν_{max} (thin film): 3423 (br s, OH), 2989, 2939 (s, C–H), 2104 (s, N_3), 1635 (w, CHO) cm^{-1}; $C_9H_{15}N_3O_5$ requires C, 44.08; H, 6.17; N, 17.13. Found: C, 44.18; H, 6.14; N, 17.11.

4.2.4. 5-Azido-5-deoxy-2-*C*-hydroxymethyl-2,3-*O*-isopropylidene-L-lyxono-1,4-lactone 28

Bromine (0.64 mL, 12.49 mmol) was added dropwise at 0 °C to a solution of the azidolyxose **12** (2.00 g, 8.16 mmol) in water (250 mL) in the presence of barium carbonate (2.46 g, 12.47 mmol) over a period of 30 min. After 1 h 30 min, an extra portion of barium carbonate (0.27 g, 1.35 mmol) was carefully added. After 1 h, TLC analysis (ethyl acetate/cyclohexane, 1:1) indicated the presence of a major product (R_f 0.43), and complete consumption of the starting material (R_f 0.27). The reaction mixture was quenched with a saturated solution of sodium thiosulfate and the suspension was extracted with diethyl ether (3 × 250 mL). The organic extracts were combined, dried (magnesium sulfate), filtered and concentrated in vacuo to give a residue, which was purified by flash column chromatography (ethyl acetate) to yield the branched lyxonolactone **28** (1.73 g, 87%) as pale yellow crystals. mp 98–99 °C; *m/z* (CI^+): 261.1 ($[M+NH_4]^+$, 100%); HRMS (CI^+): found 261.1204 $[M+NH_4]^+$ $C_9H_{17}N_4O_5$ requires 261.1199; $[\alpha]_D^{21} = -0.1$ (*c* 0.73, chloroform); ν_{max} (thin film): 3221 (s, OH), 2984, 3040 (C–H), 2101 (s, N_3), 1784 (C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.43, 1.49 (2 × 3H, 2 × s, $C(CH_3)_2$), 2.19–2.25 (1H, dd, $J_{OH,H-2}$ 3.9 Hz, $J_{OH,H-2'}$ 7.6 Hz, OH), 3.65 (1H, dd, $J_{H-5,H-5'}$ 13.1 Hz, $J_{H-5,H-4}$ 6.1 Hz, H-5), 3.73 (1H, dd, $J_{H-5',H-5}$ 13.0 Hz, $J_{H-5',H-4}$ 7.3 Hz, H-5′), 3.94 (1H, dd, $J_{H-2,H-2'}$ 11.4 Hz, $J_{H-2,OH}$ 3.8 Hz, H-2), 4.03 (1H, dd, $J_{H-2',H-2}$ 11.4 Hz, $J_{H-2',OH}$ 7.5 Hz, H-2′), 4.58 (1H, ddd, $J_{H-4,H-5'}$ 7.2 Hz, $J_{H-4,H-5}$ 6.2 Hz, $J_{H-4,H-3}$ 3.5 Hz, H-4), 4.79 (1H, d, $J_{H-3,H-4}$ 3.5 Hz, H-3); δ_C ($CDCl_3$, 125 MHz): 26.4, 26.9 ($C(CH_3)_2$), 49.5 (C-5), 61.4 (C-2′), 77.2 (C-4), 78.4 (C-3), 86.0 (C-2), 114.2 ($C(CH_3)_2$), 174.7 (C=O). $C_9H_{13}N_3O_4$ requires C, 44.44; H, 5.39; N, 17.28. Found: C, 44.41; H, 5.39; N, 17.10.

4.2.5. 5-Azido-5-deoxy-2-*C*-hydroxymethyl-2,3-*O*-isopropylidene-2′-*O*-trifluoromethanesulfonyl-L-lyxono-1,4-lactone 14

Pyridine (0.62 mL) then triflic anhydride (1.67 mL, 9.94 mmol) was added dropwise to a stirred solution of lactone **28** (1.42 g, 5.86 mmol) in dichloromethane (95 mL) at −25 °C under an atmosphere of nitrogen. After 20 min, TLC analysis (ethyl acetate/cyclohexane, 1:1) showed the presence of one product (R_f 0.76) and complete consumption of starting material (R_f 0.40). The reaction mixture was diluted with dichloromethane (100 mL), washed with an aqueous solution of HCl (1 M, 90 mL) and then with brine (90 mL). The organic layer was dried (magnesium sulfate), filtered and concentrated in vacuo to yield the azidotriflate **14** as a colourless oil which crystallized on standing (2.17 g, 99%). mp 33–34 °C; *m/z* (CI^+): 393.0 ($[M+NH_4]^+$, 100%); HRMS (CI^+) found: 393.0695 $[M+NH_4]^+$ $C_{10}H_{16}N_4O_7F_3S$ requires 393.0692; $[\alpha]_D^{21} = -29.4$ (*c* 0.70, ethyl acetate); ν_{max} (thin film): 2996 (C-H), 2111 (s, N_3), 1790 (C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.45, 1.51 (2 × 3H, 2 × s, $C(CH_3)_2$), 3.68 (1H, dd, $J_{H-5,H-5'}$ 13.1 Hz,, $J_{H-5,H-4}$ 6.1 Hz, H-5), 3.76 (1H, dd, $J_{H-5',H-5}$ 13.1 Hz, $J_{H-5',H-4}$ 7.2 Hz, H-5′), 4.56 (1H, ddd, $J_{H-4,H-5'}$ 7.2 Hz, $J_{H-4,H-5}$ 6.1 Hz, $J_{H-4,H-3}$ 3.6 Hz, H-4), 4.68 (1H, d, $J_{H-2,H-2'}$ 11.2, H-2), 4.78 (1H, d, $J_{H-2',H-2}$ 11.2 Hz, H-2′), 4.84 (1H, d, $J_{H-3,H-4}$ 3.6 Hz, H-3); δ_C ($CDCl_3$, 100 MHz): 25.9, 26.7 ($C(CH_3)_2$), 49.2 (C-5), 70.6 (C-2′), 77.1 (C-4), 77.4 (C-3), 83.5 (C-2), 113.7, 116.8, 120.0, 123.2 (CF_3) 115.5 ($C(CH_3)_2$), 171.1 (C=O). $C_{10}H_{12}F_3N_3O_7S$ requires C, 32.00; H, 3.22; N, 11.20. Found: C, 32.41; H, 3.32; N, 11.02.

4.2.6. 5-Azido-5-deoxy-2,3-*O*-isopropylidene-2-*C*-methoxymethyl-L-lyxono-1,4-lactone 29

The triflate **14** (70 mg, 0.19 mmol) was dissolved in a methanol/acetyl chloride solution (99:1, 35 mL) and was stirred at room temperature under an atmosphere of nitrogen. The reaction mixture was heated at 52 °C for 15 h. TLC. analysis (ethyl acetate/cyclohexane, 1:1) showed the presence of some starting material (R_f 0.76) and one product (R_f 0.63). The reaction mixture was quenched with anhydrous sodium bicarbonate, filtered through Celite (eluent/methanol) and concentrated in vacuo. The residue was purified by flash column chromatography (ethyl acetate/cyclohexane, 1:3) to give starting material **14** (24 mg) and the methyl ether **29** (16 mg, 33%; 51% based on recovered starting material) as a pale yellow oil. HRMS (FI^+): found 257.1010 $[M]^+$ $C_{10}H_{15}N_3O_5$ requires 257.1012; $[\alpha]_D^{23} = -32.7$ (*c* 0.22, dichloromethane); ν_{max} (thin film): 2941 (C–H), 2109 (s, N_3), 1789 (s, C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.39, 1.48 (2 × 3H, 2 × s, $C(CH_3)_2$), 3.39 (3H, s, $COCH_3$), 3.54 (1H, dd, $J_{H-5,H-5'}$ 12.8 Hz, $J_{H-5,H-4}$ 6.5 Hz, H-5), 3.69 (1H, m, H-5′), 3.68 (1H, d, $J_{H-2,H-2'}$ 8.8 Hz, H-2), 3.77 (1H, d, $J_{H-2',H-2}$ 8.8 Hz, H-2′), 4.53 (1H, ddd, $J_{H-4,H-5'}$ 10.2 Hz, $J_{H-4,H-5}$ 6.7 Hz, $J_{H-4,H-3}$ 3.5 Hz, H-4), 4.72 (1H, d, $J_{H-3,H-4}$ 3.5 Hz, H-3); δ_C ($CDCl_3$, 100 MHz): 26.2, 26.8 ($C(CH_3)_2$), 49.4 ($COCH_3$), 60.0 (C-5), 72.3 (C-2′), 76.2 (C-4), 79.6 (C-3), 84.5 (C-2), 114.1 ($C(CH_3)_2$), 174.8 (C=O).

4.2.7. Methyl (3*R*,4*R*,5*S*)-5-azidomethyl-3,4-dihydroxy-tetrahydrofuran-3-carboxylate 18

A freshly prepared solution of acetyl chloride/methanol (1.5/1.0, 160 mL) was carefully added to a solution of the triflate **14** (1.43 g, 3.81 mmol) stirring in methanol (30 mL) at 0 °C under an atmosphere of nitrogen. The reaction solution was allowed to warm up to room temperature. After 19 h, TLC analysis (ethyl acetate/cyclohexane, 1:1) showed the presence of a major product (R_f 0.23) and complete consumption of the starting material (R_f 0.76). The reaction mixture was quenched with anhydrous sodium bicarbonate, filtered through Celite (eluent : methanol) and concentrated in vacuo. The residue was dissolved in ethyl acetate, filtered through Celite (ethyl acetate), concentrated in vacuo and purified by flash column chromatography (ethyl acetate/cyclohexane, 1:2 to 2:1) to give the *lyxo*-scaffold **18** (470 mg, 57%) as a pale yellow oil. *m/z* (ES^+): 218.0 ($[M+H]^+$, 100%), 235.0 ($[M+NH_4]^+$, 62%); HRMS (CI^+): found 218.0776 $[M+H]^+$ $C_7H_{12}N_3O_5$ requires 218.0777; $[\alpha]_D^{21} = -39.5$ (*c* 0.61, methanol); ν_{max} (thin film): 3418 (br, OH), 2959 (s, C–H), 2107 (s, N_3), 1732 (C=O) cm^{-1}; δ_H (CD_3CN, 400 MHz): 2.85 (1H, dd, $J_{H-6,H-6'}$ 12.8 Hz, $J_{H-6,H-5}$ 5.0 Hz, H-6), 2.92 (1H, dd, $J_{H-6',H-6}$ 12.8 Hz, $J_{H-6',H-5}$ 7.7 Hz, H-6′), 3.18 (1H, d, $J_{H-2,H-2'}$ 9.8 Hz, H-2), 3.19 (3H, s, CO_2CH_3), 3.38 (1H, d, $J_{OH-4,H-4}$ 5.9 Hz, OH-4), 3.50 (1H, dd, $J_{H-4,OH-4}$ 5.8 Hz, $J_{H-4,H-5}$ 3.5 Hz, H-4), 3.65 (1H, m, H-5), 3.79 (1H, d, $J_{H-2',H-2}$ 9.8 Hz, H-2′), 3.80 (1H, a-s, OH-3); δ_C (CD_3CN, 100 MHz): 49.8 (C-6), 51.8 (CO_2CH_3), 73.4 (C-2), 77.9 (C-4), 80.0 (C-5), 84.4 (C-3), 170.9 (C=O).

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