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Synthesis of 4-aminomethyl-tetrahydrofuran-2-carboxylates with 2,4-*cis* and 2,4-*trans* relationships

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Abstract—Templated tetrahydrofuran-based γ-azido esters were prepared with the C-2 and C-4 functionalities in cis and trans relative configurations. This was achieved by ring contraction of the suitably protected 2-*O*-triflates of pentono-1,5-lactones (D-ribose and L-arabinose) with subsequent introduction of the azide via the 4-*O*-triflate. Access to a corresponding β-azido ester was achieved in good yield. Little elimination product was observed by introduction of the azide via the 3-*O*-triflate. These azido esters are scaffolds, which may be predisposed to adopt secondary structural motifs, for example, for use as peptidomimetics; they may also be utilised for the preparation of stereodiverse compound libraries.

1. Introduction

Improvement of the pharmacological properties of natural peptides has focused on the structural modification of the constituent amino acids.[1,2] Both β- and γ-peptides (Fig. 1) have been shown to be stable to common proteases.[3] γ-Peptides have been less extensively studied than their β-counterparts.[4–8] Nonetheless, γ-amino acids (both acyclic and cyclic) have been found to adopt secondary structures akin to those observed for α-peptides.

Vinylogous (α,β-unsaturated) γ-peptides adopt parallel sheet structures; with the insertion of a Pro-Gly unit into the backbone, they also adopt novel helical conformations with 10- and 12-membered hydrogen bonded rings.[9] Conformational searching of a γ-hexapeptide and corresponding vinylogous analogue[10] have since been reported and vinylogous peptides identified as a source for γ-peptide foldamers.[11,12] Hanessian and Seebach[13] have prepared an extensive set of acyclic γ-peptides and related substitution patterns and stereochemistry to secondary structural preference for βII′-type turns[14,15] and left and right handed 14-helices.[16–18] The biological importance of such systems has been highlighted by analogues of a γ-dipeptide, which exhibited submicromolar affinities for human somatostatin receptors.[19] Oligomers of ureas, carbamates, phosphodiesters and vinylogous sulfonamidopeptides have also been prepared as γ-peptide analogues.[20]

Rigid cyclic γ-amino acids have been employed in the formation of parallel sheet structures[21] and in the formation of potent γ-amino butyric acid (GABA) antagonists.[22] Several conformationally restricted γ-amino acids have

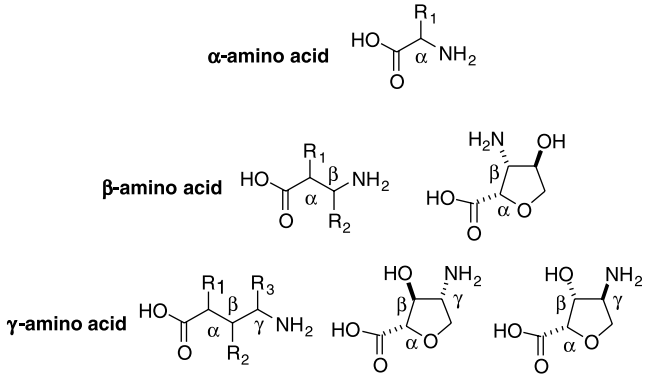

Figure 1. Homologues of α-amino acids.

Keywords: Sugar amino acids; Peptidomimetics; Scaffolds; Gamma amino acids.
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been prepared recently.[23–28] This paper describes the synthesis of conformationally restricted γ-amino acids from sugar starting materials. Sugar amino acids (SAAs) have been frequently employed as peptidomimetic foldamers[29–33] and as library scaffolds with their potential for host–guest chemistry recently explored.[34–38] Compared to δ-SAAs, there are relatively few examples of γ-sugar amino acids (γ-SAAs) in literature.[22,39–45] A pyranose based γ-SAA, which predetermines a β-turn conformation in synthetic peptides has been described.[41] Additionally, a heterooligomer composed of a furanose γ-SAA and GABA exhibited no stable conformation in solution.[44] Furanose and pyranose based γ-SAAs have been utilised to prepare 99-member and 384-member libraries, respectively.[43,46] This paper reports the full synthesis of templated tetrahydrofuran-based γ-azido esters (**1** and **2**) and β-azido ester **3** as SAA precursors for subsequent study of foldamer preference.[47]

2. Results and discussion

2.1. Strategy

Two different synthetic strategies could be employed for the preparation of γ-azido ester **4** as the azide function can be introduced either before of after ring contraction of the activated pentono-1,5-lactone **5** (Fig. 2). This paper reports the synthesis of two γ-azido esters (**1** and **2**) via strategy 1. The key step in the synthesis of γ-azido ester **4** was the ring contraction of a trifluoromethanesulfonyl ester (triflate), from a suitably protected pentono-1,5-lactone (**5**), to form the diol **6**. This method of ring contraction, using either acidic or basic conditions, has been established for the formation of related tetrahydrofuran-2-carboxylates.[48,49] Activation of the C-4 hydroxyl via a sulfonyl ester with subsequent azide displacement from **6** would yield the desired γ-azido ester **4**.

L-Arabinose and D-ribose stereochemistries were employed to give access to γ-azido esters **1** and **2**, which were related at C-2 and C-4 positions by cis and trans stereochemistries, respectively (Fig. 3). The stereochemical relationship between the acid and amine functions of related δ-azido esters has been found to be important in subsequent investigation of conformational preference.[29,30,50,51] Poor selectivity of the C-3 hydroxyl over that at C-4 in **7** generated a suitable precursor (**8**) for synthesis of the corresponding β-azido ester **3**. The β-azido ester **3** has the amine and acid functions in a cis configuration. During synthesis, the methyl ester was converted to the more hindered isopropyl ester where convenient. This was to prevent uncontrolled oligomer and/or lactam formation resulting from nucleophilic attack of the carbonyl group by

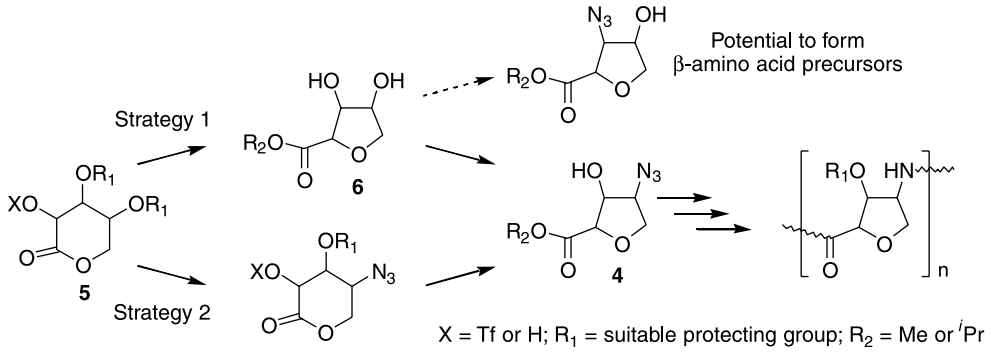


Figure 2. Synthetic strategy for the formation of γ-azido ester **4**.

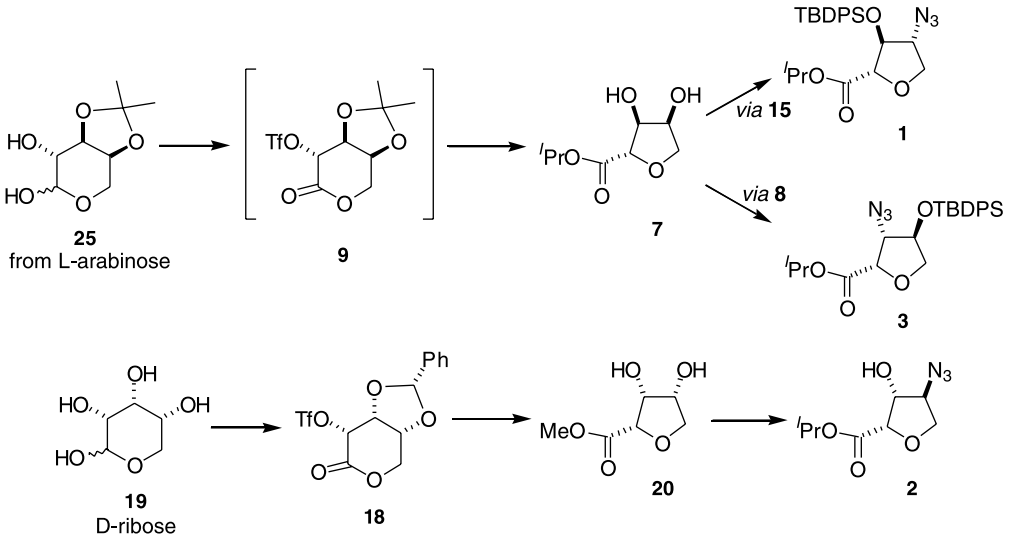


Figure 3. Strategy 1 applied to the formation of **1** and **2**.

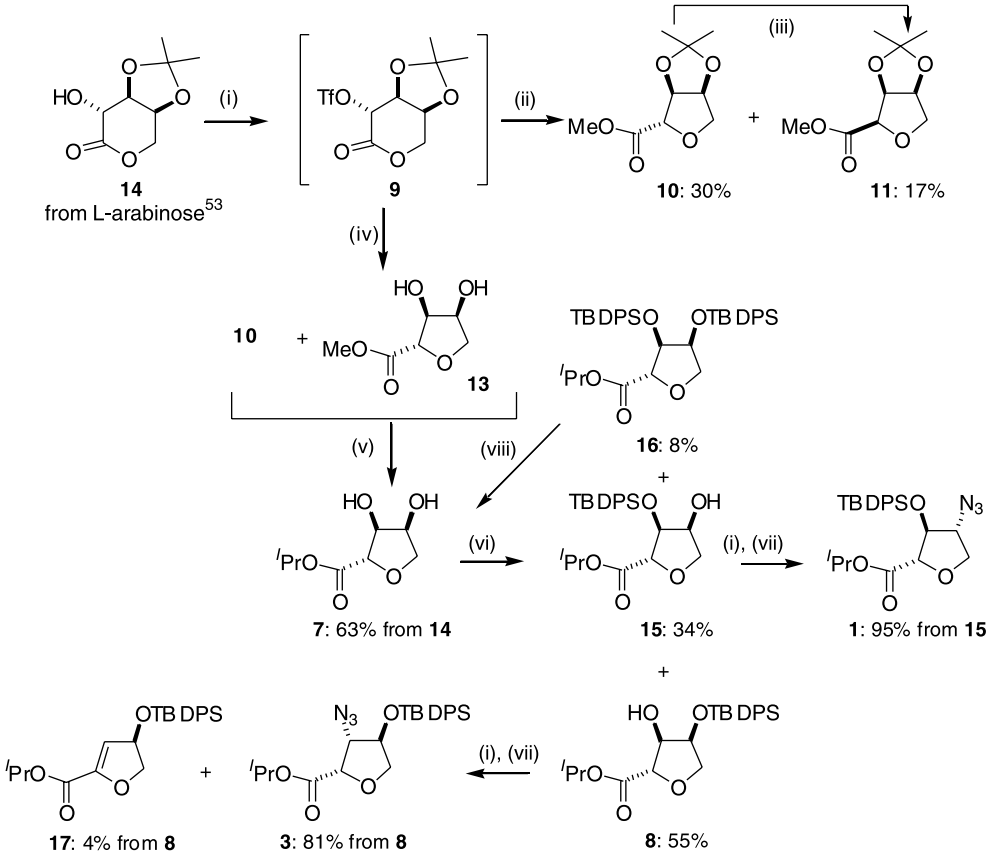
the amine function (by reduction of the azide in later synthesis).[52]

2.2. Synthesis of the β- and γ-azido esters (1 and 3) from L-arabinose stereochemistry

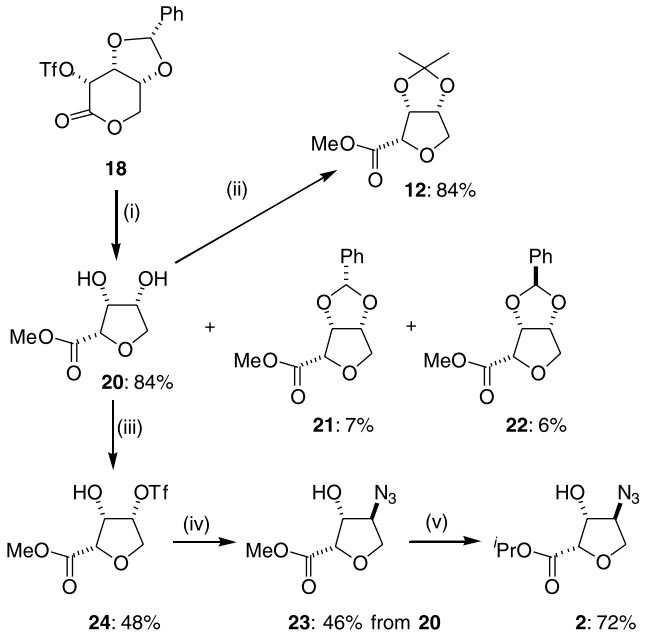
The 2-*O*-trifluoromethanesulfonyl pentono-1,4-lactone (triflate) **9** can be prepared from L-arabinose in three steps using known literature procedures.[53] It was anticipated that the triflate **9** would smoothly undergo the key ring contraction reaction to form **10** upon treatment with methanol in the presence of anhydrous potassium carbonate (K_2CO_3), Scheme 1. However, when the triflate **9** was subjected to basic conditions, the desired product **10** was isolated in 30% yield and a second product **11** in 17% yield, by the K_2CO_3-mediated epimerisation at C-2; in order to confirm this assumption an independent experiment was carried out by the treatment of **10** with methanol containing K_2CO_3. After 13 h, the majority of **10** had been consumed and the more thermodynamically stable C-2 epimer **11** isolated in 89% yield. The stereochemistry of **11** was confirmed by comparison to the physical data of the enantiomer **12** (Scheme 2).

In contrast to basic conditions, acidic conditions obviated epimerisation. Analysis of the reaction mixture by TLC revealed formation of the acetonide **10** (R_f 0.70, ethyl acetate/pet. ether 1:1) together with a second product (R_f 0.20, ethyl acetate/pet. ether 1:1), the diol **13** formed by the deprotection of the acetonide. To achieve complete deprotection of the acetonide to generate the desired diol **13**, hydrochloric acid was added and the reaction mixture warmed to 70 °C. It was convenient at this point to convert the methyl ester to the more sterically hindered isopropyl ester to prevent potential lactone formation. Therefore, the crude diol **13** was subjected to acid-catalysed transesterification with HCl in propan-2-ol (5% v/v) to afford the isopropyl ester **7** as a colourless oil in an overall yield of 63% (over four steps from lactone **14**). Selective reaction of the diol **7** would provide an efficient route to both the γ- and β-azido ester (Fig. 2).

The introduction of azido group at the γ-position, with respect to the carboxyl function on the THF framework, of **7** was investigated. Initial efforts to esterify the C-4 hydroxyl of **7** met with failure as the desired product was found to be highly unstable. It was necessary to protect the free hydroxyls prior to formation of the sulfonyl ester. Introduction of the silyl protecting group was achieved by treatment of the diol **7** with a single equivalent of *tert*-butyl diphenylsilyl chloride (TBDPS-Cl) with imidazole in dimethylformamide. Little selectivity was observed for the hydroxyl at C-3 over that at C-4 giving both the 3-*O*-TBDPS ether **15** and the 4-*O*-TBDPS silyl ether **8** in 34 and 55% yield, respectively. The regio-isomers were easily distinguished from each other by 2D correlated spectroscopy in DMSO-d_6. The formation of the 4-*O*-TBDPS silyl ether **8**, although not part of the desired synthesis for the γ-azido



Scheme 1. Reagents and conditions: (i) Tf_2O, pyridine, DCM, −20 °C; (ii) 1.1 equiv K_2CO_3, MeOH, 0 °C, 1.3 h; (iii) 0.3 equiv K_2CO_3, MeOH, rt, 14 h; (iv) 1% v/v AcCl in MeOH, rt, 13 h; (v) 2 N HCl, 70 °C, 3 h then 5% v/v AcCl in propan-2-ol, 80 °C, 48 h; (vi) TBDPSCl, imidazole, DMF, 0 °C to rt, 10 h; (vii) 4 equiv NaN_3, DMF, rt, 10 h; (viii) 3 equiv TBAF, THF, rt, 14 h.



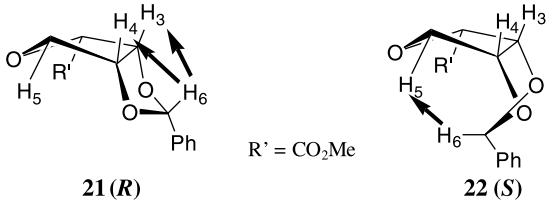
Scheme 2. Reagents and conditions: (i) 5% v/v AcCl in MeOH, rt to 70 °C, 3 h then aq HCl added, 70 °C, 15 h; (ii) CSA, acetone, rt, 24 h; (iii) 1.5 equiv Tf_2O, pyridine, DCM, −25 °C, 4 h then rt, 48 h; (iv) 5 equiv NaN_3, DMF, rt then 85 °C for 15 h; (v) *p*-toluenesulfonic acid, propan-2-ol, 80 °C, 24 h.

ester **1**, was advantageous as the ether **8** is an ideal precursor for the formation of the β-azido ester **3**. A small amount of the disubstituted silyl derivative **16** was isolated (8% yield) and was easily converted back to the diol **7**, albeit in moderate yield (50%), by treatment with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran. A single crystal X-ray structure of **16** was obtained,[54] confirming that ring contraction occurred with complete inversion of configuration at C-2 and thus the relative stereochemistry of the diol.

The 3-*O*-TBDPS ether **15** was esterified using trifluoromethanesulfonic anhydride with pyridine in dichloromethane and was reacted without purification. The 4-*O*-triflate was treated with excess sodium azide in dimethylformamide to yield the γ-azido ester **1** in 95% yield (from **15**) with inversion of configuration at C-4. Following similar protocols, the β-azido ester **3** was obtained via the 3-*O*-triflate in good yield (81% from **8**) together with a small amount (4%) of the β-eliminated product **17**. The effective substitution (with little elimination) is in stark contrast to a related synthesis previously reported.[39]

2.3. Synthesis of γ-azido ester 2 from D-ribose stereochemistry

The 2-*O*-triflate of 3,4-*O*-benzylidene-D-ribono-1,5-lactone (**18**) can be prepared using literature procedures, in three steps starting from D-ribose **19**.[55,56] The preparation of diol **20** from the triflate **18** was achieved by acid-catalysed ring contraction with subsequent deprotection (Scheme 2). Reaction of the crude triflate gave a more complex reaction mixture. Treatment of the recrystallised triflate **18** with methanolic hydrogen chloride (5% v/v) gave the desired ring contraction products and subsequent heating at 70 °C with further addition of hydrochloric acid afforded the unprotected diol **20**, the (*R*)-benzylidene **21** and the (*S*)-benzylidene **22** in 84, 7 and 6% yields, respectively. The stereochemistry of the epimeric centre of the benzylidene group in **21** and **22** was assigned on the basis of NOESY cross-peaks between each benzylidine methane proton and protons of the THF ring (Fig. 4). The diol **20** was treated with acetone and DL-camphor-10-sulfonic acid to yield the acetonide **12** in 83% yield. The formation of **12** confirmed the diol had cis configuration and the physical data is in agreement with the enantiomer **11** (Scheme 1).



21 (*R*) **22 (*S*)**

nOe	21 (*R*)	22 (*S*)
H-6 ↔ H-3	Yes	No
H-6 ↔ H-4	Yes	No
H-6 ↔ H-5	No	Yes

Figure 4. Assignment of *R* and *S* configurations of **21** and **22**.

The preparation of the 4-azido derivative **23** was achieved via S_N2 displacement with sodium azide after selective activation of the C-4 hydroxyl of **20**. The activated ester **24** was obtained in 48% yield by treatment of **20** with trifluoromethanesulfonic anhydride and pyridine in dichloromethane at −25 °C although was observed to be unstable on silica (by 2D TLC). Reaction of the crude triflate **24** with sodium azide in dimethylformamide afforded the azide **23** in 46% yield (over two steps from **20**). Finally, the methyl azido ester **23** was converted to the isopropyl ester **2** in 72% yield by treatment with *p*-toluenesulfonic acid in propan-2-ol at 80 °C.

3. Conclusion

This paper reports the efficient preparation of two diastereomeric γ-azido esters (**1** and **2**) and a β-azido ester **3**. The γ-amino acid precursors have been studied for conformational preference to assess their future role as peptidomimetic foldamers; these results will be published shortly. The efficient displacement of the β-triflate by sodium azide will provide easy access to a range of THF templated β-amino acid building blocks. Furthermore, these orthogonally protected γ- and β-amino acids may be employed for the preparation of novel stereodiverse compound libraries.

4. Experimental

4.1. General

All commercial reagents were used as supplied. *N*-*N*-Dimethylformamide (DMF) was purchased dry from the Aldrich chemical company in sure-seal bottles. All other solvents were used as supplied (Analytical or HPLC grade),

without prior purification. Petroleum ether (pet. ether) refers to the fraction of petroleum ether that boils in the range 40–60 °C and hexane refers to the fraction of petroleum ether that boils in the range 60–80 °C. Reactions were performed under an atmosphere of nitrogen or argon. Thin-layer chromatography (TLC) was performed on aluminium or plastic sheets coated with 60 F_{254} silica. Sheets were visualised using a spray of 0.2% w/v cerium (IV) sulfate and 5% ammonium molybdate in 2 M sulfuric acid. Flash chromatography was performed on Sorbsil C60 40/60 silica. Melting points were recorded on a Kofler hot block and are uncorrected. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a path length of 1 dm. Concentrations are quoted in g $100\,mL^{-1}$. Elemental analyses were performed by the microanalysis service of the Dyson Perrins Laboratory, Oxford or the Inorganic Chemistry Laboratory, Oxford. Infra-red (IR) spectra were recorded on a Perkin–Elmer 1750 IR Fourier Transform spectrophotometer using thin films on NaCl plates (film) or KBr discs. Only the characteristic peaks are quoted and in units of cm^{-1}. Low resolution mass spectra (*m/z*) were recorded on VG MassLab 20-250, Micromass BIOQ-II, Micromass Platform 1, Micromass TofSpec 2E, or Micromass Autospec 500 OAT spectrometers and high resolution mass spectra (HRMS *m/z*) on a Micromass Autospec 500 OAT spectrometer. Techniques used were chemical ionization (CI NH_3), or atmospheric pressure chemical ionization (APCI). Nuclear magnetic resonance (NMR) spectra were recorded on Bruker AMX 500 and DRX 500 spectrometers (^1H: 500 MHz and ^{13}C: 125.7 MHz), a Bruker DPX 400 spectrometer (^1H: 400 MHz and ^{13}C: 100.6 MHz) and a Bruker DPX 200 spectrometer (^1H: 200 MHz and ^{13}C: 50.3 MHz) in the deuterated solvent stated. All chemical shifts (δ) are quoted in parts per million and coupling constants (*J*) given in Hz. Residual signals from the solvents were used as an internal reference. ^{13}C multiplicities were assigned using a DEPT sequence. 3,4-Isopropylidene-L-arabinose **25** was provided by CMS chemicals and the selectively protected lactone **14** prepared according to a literature procedure.[53] 3,4-*O*-Benzylidene-2-*O*-trifluoromethanesulfonyl-D-ribono-1,5-lactone **18** was prepared in three steps from D-ribose using literature procedures.[55,56]

4.1.1. Methyl 2,5-anhydro-3,4-*O*-isopropylidene-L-ribonate 10 and methyl 2,5-anhydro-3,4-*O*-isopropylidene-L-arabinoate 11. Trifluoromethanesulfonic anhydride (0.6 mL, 3.67 mmol) was added dropwise to a stirred solution of the lactone **14** (460 mg, 2.40 mmol) in dichloromethane (5 mL) with freshly distilled pyridine (0.32 mL, 3.90 mmol) at −20 °C. After 40 min, TLC (ethyl acetate/pet. ether, 1:1) showed the absence of starting material (R_f 0.45) and the formation of a single product (R_f 0.73). The reaction mixture was diluted with dichloromethane (10 mL), and then washed sequentially with brine (10 mL), citric acid (1 M aq, 10 mL) and water (10 mL). The organic layer was concentrated in vacuo at low temperature (0–5 °C) to obtain a yellow solid (**9**), which was used without further purification. The triflate **9** was dissolved in methanol (10 mL) containing anhydrous potassium carbonate (360 mg, 2.64 mmol) and stirred at 0–5 °C. After 1.3 h, TLC (ethyl acetate/pet. ether, 1:1) showed the absence of the triflate **9** (R_f 0.73) and the formation of a major (R_f 0.70) and minor (R_f 0.38) product. The reaction mixture was filtered and the residue washed with methanol (2×5 mL). The filtrate was concentrated in vacuo and purified by flash chromatography (ethyl acetate/pet. ether, 1:4) to afford the desired product **10** (150 mg, 30%) as a colourless oil and the C-2 epimer **11** (82 mg, 17%) as a solid.

Compound **10**. $[\alpha]_D^{23}$ +64.6 (*c* 1.2 in $CHCl_3$); (HRMS (CI+): Found 203.092464. $C_9H_{14}O_5$ ($M+H^+$) requires *m/z*, 203.091949); ν_{max} (thin film)/cm^{-1} 1741 (C=O, ester); δ_H ($CDCl_3$, 200 MHz) 1.32 (3H, s, $C(CH_3)_2$), 1.50 (3H, s, $C(CH_3)_2$), 3.75 (3H, s, CO_2CH_3), 4.02 (1H, dd, $J_{5,4}$= 4.3 Hz, $J_{5,5'}$=11.0 Hz, H-5), 4.15 (1H, d, $J_{5',5}$=11.0 Hz, H-5′), 4.60 (1H, br s, H-2), 4.83 (1H, m, H-4), 4.95 (1H, m, H-3); δ_C ($CDCl_3$, 50.3 MHz) 24.8 (q, $C(CH_3)_2$), 26.3 (q, $C(CH_3)_2$), 52.2 (q, CO_2CH_3), 74.0 (t, C-5), 80.7 (d, C-4), 83.2 (d, C-3), 83.9 (d, C-2), 113.1 (s, $C(CH_3)_2$), 170.8 (s, C=O); *m/z* (APCI+): 203.01 ($M+H^+$, 33), 148.88 (100%).

Compound **11**. Mp 61–62 °C; $[\alpha]_D^{23}$ +88.5 (*c* 1.1 in $CHCl_3$): (HRMS (CI+): Found 203.092171. $C_9H_{14}O_5$ ($M+H^+$) requires *m/z*, 203.091949); ν_{max} (thin film)/cm^{-1} 1765 (C=O, ester); δ_H (C_6D_6, 500 MHz) 1.13 (3H, s, $C(CH_3)_2$), 1.48 (3H, s, $C(CH_3)_2$), 2.90 (1H, dd, $J_{5,4}$=4.1 Hz, $J_{5,5'}$= 10.2 Hz, H-5), 3.45 (3H, s, CO_2CH_3), 3.73 (1H, d, $J_{2,3}$= 3.9 Hz, H-2), 3.95 (1H, d, $J_{5',5}$=10.2 Hz, H-5′), 4.05 (1H, m, H-4), 4.43 (1H, m, H-3); δ_C (C_6D_6, 50.3 MHz) 25.7 (q, $C(CH_3)_2$), 26.5 (q, $C(CH_3)_2$), 51.5 (q, CO_2CH_3), 73.0 (t, C-5), 80.9 (d, C-4), 81.9 (d, C-3), 82.2 (d, C-2), 113.30 (s, $C(CH_3)_2$), 168.5 (s, C=O); *m/z* (APCI+): 203.03 ($M+H^+$, 100%).

4.1.2. Conversion of methyl 2,5-anhydro-3,4-*O*-isopropylidene-L-ribonate 10 to methyl 2,5-anhydro-3,4-*O*-isopropylidene-L-arabinoate 11. A catalytic amount of anhydrous potassium carbonate (3 mg, 0.025 mmol) was added to a stirred solution of acetonide **10** (18 mg, 0.089 mmol) in dry methanol (0.5 mL) at room temperature. After 14 h, TLC (ethyl acetate/pet. ether, 1:1) showed the formation of a major product (R_f 0.45) and a trace of starting material (R_f 0.70). The reaction mixture was filtered, concentrated in vacuo and the residue was purified by flash chromatography (ethyl acetate/pet. ether, 1:4) to obtain the *C*-2 epimer **11** (16 mg, 89%); data given above.

4.1.3. Isopropyl 2,5-anhydro-L-ribonate 7. Trifluoromethanesulfonic anhydride (11.6 mL, 70.9 mmol) was added slowly over a period of 15 min to a stirred solution of the lactone **14** (9.52 g, 50.6 mmol) in freshly distilled dry dichloromethane (100 mL) containing dry pyridine (6.13 mL, 75.9 mmol) at −20 °C. After 40 min, TLC (ethyl acetate/pet. ether, 1:1) showed the absence of starting material (R_f 0.45) and the formation of a single product (R_f 0.73). The reaction mixture was diluted with dichloromethane (100 mL), washed sequentially with brine and concentrated in vacuo at low temperature (0–5 °C). The residue (triflate **9**) was dissolved in methanolic hydrogen chloride (1% v/v, 100 mL) and stirred at room temperature. After 13 h, TLC (ethyl acetate/pet. ether, 1:1) showed the absence of the triflate **9** (R_f 0.73) and the formation of two products; R_f 0.70 (**10**) and R_f 0.20 (**13**). Hydrochloric acid

(2 N aq, 15 mL) was added and the reaction mixture warmed to 70 °C. After 3 h, TLC (ethyl acetate/pet. ether, 1:1) indicated the absence of **10** (R_f 0.70). The reaction mixture was concentrated in vacuo and co-evaporated with toluene. The residue was dissolved in 5% v/v HCl in propan-2-ol (100 mL) and heated to 80 °C. After 48 h, TLC (ethyl acetate) showed the formation of a major product (R_f 0.55). The reaction mixture was neutralised by careful addition of solid sodium hydrogen carbonate (30 g) until no more effervescence was observed. The reaction mixture was filtered and the filtrate concentrated in vacuo to obtain an oil, which was purified by flash chromatography (ethyl acetate/pet. ether, 2:3) to afford the title product **7** (6.10 g, 63%) as a colourless oil: $[\alpha]_D^{23}$ +44.3 (*c* 1.01 in $CHCl_3$); (HRMS (CI+): Found 208.118100. $C_8H_{14}O_5$ ($M+NH_4^+$) requires *m/z*, 208.118498); ν_{max} (thin film)/cm^{-1} 3436 (OH) and 1724 (C=O, ester); δ_H ($CDCl_3$, 500 MHz) 1.32 (6H, d, $J=6.3$ Hz, $CH(CH_3)_2$), 3.13 (2H, br s, O*H*), 3.92 (1H, dd, $J_{5,4}=2.7$ Hz, $J_{5,5'}=10.0$ Hz, H-5), 4.16 (1H, dd, $J_{5',4}=4.5$ Hz, $J_{5',5}=10.0$ Hz, H-5′), 4.10 (2H, m, H-2 and H-3), 4.35 (1H, m, H-4), 5.15 (1H, sept, $J=6.3$ Hz, $CH(CH_3)_2$); δ_C ($CDCl_3$, 125.3 MHz) 21.6 (q, $CH(CH_3)_2$), 69.3 (d, $CH(CH_3)_2$), 70.9 (d, C-4), 73.4 (t, C-5), 75.1 (d, C-3), 80.8 (d, C-2), 171.1 (s, C=O); *m/z* (CI+): 208.3 ($M+NH_4^+$, 100%).

4.1.4. Isopropyl 2,5-anhydro-3-*O*-*tert*-butyldiphenylsilyl-L-ribonate 15, isopropyl 2,5-anhydro-4-*O*-*tert*-butyldiphenylsilyl-L-ribonate 8 and isopropyl 2,5-anhydro-3,4-di-*O*-*tert*-butyldiphenylsilyl-L-ribonate 16. *tert*-Butyldiphenylsilyl chloride (5.46 mL, 21.0 mmol) was added to a stirred solution of diol **7** (4.00 g, 21.0 mmol) in dry DMF (20 mL) containing imidazole (1.71 g, 25.2 mmol) at 0 °C. The reaction was allowed to warm to room temperature. After 10 h, TLC (ethyl acetate) showed the absence of starting material (R_f 0.55). Elution of the TLC (with ethyl acetate/pet. ether, 1:9) showed the presence of one minor product (R_f 0.65) and two major products, (R_f 0.32) and (R_f 0.20). The reaction mixture was concentrated in vacuo. The residue was dissolved in ethyl acetate (100 mL) and sequentially washed with brine (100 mL), citric acid (1 M aq, 100 mL), saturated aq sodium hydrogen carbonate (100 mL) and water (100 mL) and then concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate/pet. ether, 1:19) to afford 3-*O*-silyl derivative **15** (3.10 g, 34%) as a colourless oil, the 4-*O*-silyl derivative **8** (5.00 g, 55%) as a colourless oil and the disilylated derivative **16** (1.12 g, 8%) as a white solid.

Compound **15**. $[\alpha]_D^{23}$ +28.9 (*c* 1.9 in $CHCl_3$); (HRMS (CI+): Found 446.234455. $C_{24}H_{32}O_5Si$ ($M+NH_4^+$) requires *m/z*, 446.234934); ν_{max} (thin film)/cm^{-1} 3538 (OH) and 1736 (C=O, ester); δ_H ($(CD_3)_2SO$, 200 MHz) 1.10 (15H, m, $CH(CH_3)_2$ and $SiC(CH_3)_3$), 3.72 (1H, m, H-5), 3.92 (2H, m, H-4 and H-5′), 4.25 (2H, m, H-3 and H-2), 4.82 (1H, sept, $J=6.36$ Hz, $CH(CH_3)_2$), 5.05 (1H, d, O*H*), 7.34–7.65 (10H, m, Ar*H*); δ_C ($(CD_3)_2SO$, 50.3 MHz) 19.9 (s, $SiC(CH_3)_3$), 22.1 (q, $CH(CH_3)_2$), 27.6 (q, $SiC(CH_3)_3$), 68.9 (d, $CH(CH_3)_2$), 71.3 (d, C-4), 73.6 (t, C-5), 77.8 (d, C-3), 82.1 (d, C-2), 128.5, 128.6, 130.8 (3×d, 6×Ar*C*H), 133.6, 133.8 (2×d, 2×Ar*C*), 136.2, 136.4 (2×d, 4×Ar*C*H), 171.3 (s, C=O); *m/z* (CI+): 446.4 ($M+NH_4^+$, 100%).

Compound **8**. $[\alpha]_D^{23}$ +16.5 (*c* 1.6 in $CHCl_3$); (HRMS (CI+): Found 446.236835. $C_{24}H_{32}O_5Si$ ($M+NH_4^+$) requires *m/z*, 446.236277); ν_{max} (thin film)/cm^{-1} 3513 (OH) and 1738 (C=O, ester); δ_H ($(CD_3)_2SO$, 400 MHz) 1.05 (9H, s, $SiC(CH_3)_3$), 1.13 (6H, d, $J=6.2$ Hz, $CH(CH_3)_2$), 3.53 (1H, m, H-5), 3.72 (1H, m, H-5′), 3.95 (1H, m, H-3), 4.12 (1H, m, H-4), 4.20 (1H, d, $J=4.8$ Hz, H-2), 4.90 (1H, sept, $J=6.2$ Hz, $CH(CH_3)_2$), 5.55 (1H, d, O*H*), 7.40–7.75 (10H, m, Ar*H*); δ_C ($(CD_3)_2SO$, 50.3 MHz) 19.8 (s, $SiC(CH_3)_3$), 22.2 (q, $CH(CH_3)_2$), 27.6 (q, $SiC(CH_3)_3$), 68.8 (d, $CH(CH_3)_2$), 72.7 (t, C-5), 73.9 (d, C-4), 75.4 (d, C-3), 82.2 (d, C-2), 128.6, 128.7, 130.7 (3×d, 6×Ar*C*H), 133.8, 134.2 (2×s, 2×Ar*C*), 136.1, 136.2 (2×d, 4×Ar*C*H), 171.3 (s, C=O); *m/z* (CI+): 446.3 ($M+NH_4^+$, 100%).

Compound **16**. Mp 135–136 °C (EtOAc/*n*-hexane, 1:4); $[\alpha]_D^{23}$ +15.1 (*c* 0.5 in $CHCl_3$); (HRMS (CI+): Found 684.354410. $C_{40}H_{50}O_5Si_2$ ($M+NH_4^+$) requires *m/z*, 684.354056); ν_{max} (thin film)/cm^{-1} 1743 (C=O, ester); δ_H ($CDCl_3$, 200 MHz) 1.00 (6H, d, $J=6.7$ Hz, $CH(CH_3)_2$), 1.12, 1.15 (18H, 2×s, 2×$SiC(CH_3)_3$), 3.62 (1H, m, H-5), 3.85 (1H, m, H-5′), 4.13 (1H, m, H-4), 4.22 (1H, d, $J=1.8$ Hz, H-2), 4.35 (1H, m, H-3), 4.75 (1H, sept, $J=6.7$ Hz, $CH(CH_3)_2$), 7.23–7.82 (20H, m, Ar*H*); δ_C ($CDCl_3$, 50.3 MHz) 19.2, 19.4 (2×s, 2×$SiC(CH_3)_3$), 21.4 (q, $CH(CH_3)_2$), 26.9, 27.0 (2×q, 2×$SiC(CH_3)_3$), 68.3 (d, $CH(CH_3)_2$), 70.5 (t, C-5), 73.2 (d, C-4), 76.5 (d, C-3), 82.7 (d, C-2), 127.6, 127.7, 127.7, 127.7, 129.7, 129.9, 129.9 (7×d, 12×Ar*C*H), 133.0, 133.1, 133.5 (3×s, 4×Ar*C*), 135.6, 135.7, 136.0, 136.1 (4×d, 8×Ar*C*H), 170.3 (s, C=O); *m/z* (CI+): 684.4 ($M+NH_4^+$, 35), 589.3 (100%).

4.1.5. Conversion of isopropyl 2,5-anhydro-3,4-di-*O*-*tert*-butyldiphenylsilyl-L-ribonate 16 to isopropyl 2,5-anhydro-L-ribonate 7. Tetrabutylammonium fluoride (1 M solution in THF, 2.2 mL, 2.2 mmol) was added to a stirred solution of disilylated derivative **16** (0.50 g, 0.75 mmol) in dry THF (2 mL) at room temperature. After 14 h, TLC (ethyl acetate) showed the formation of a major product (R_f 0.55). The reaction mixture was concentrated in vacuo and the residue purified by flash chromatography (ethyl acetate/pet. ether, 2:3) to afford the diol **7** (70 mg, 50%) as a colourless oil; data given above.

4.1.6. Isopropyl 2,5-anhydro-4-azido-3-*O*-*tert*-butyldiphenylsilyl-4-deoxy-L-ribonate 1. Trifluoromethanesulfonic anhydride (1.72 mL, 10.5 mmol) was added dropwise over a period of 5 min to a stirred solution of 3-*O*-silyl derivative **15** (3.00 g, 7.0 mmol) in dichloromethane (60 mL) containing freshly distilled dry pyridine (0.96 mL, 11.9 mmol) at −20 °C. After 40 min, TLC (ethyl acetate/pet. ether, 1:9) showed the absence of starting material (R_f 0.20) and the formation of a single product (R_f 0.60). The reaction mixture was diluted with dichloromethane (50 mL), then washed sequentially with brine (50 mL), citric acid (1 M aq, 50 mL) and water (50 mL) and concentrated in vacuo at low temperature (0–5 °C). The residue was dissolved in pre-cooled (0 °C) dry DMF (30 mL) containing sodium azide (1.80 g, 28.0 mmol) and stirred under an atmosphere of nitrogen. After 1 h, the ice bath was removed and the reaction mixture stirred at room temperature. After 10 h, TLC (ethyl acetate/pet. ether, 1:9) showed the formation of a single product (R_f 0.63).

The reaction mixture was filtered and the filtrate concentrated in vacuo and purified by flash chromatography (ethyl acetate/pet. ether, 2:23) to yield the γ-azido ester **1** (3.02 g, 95%) as a colourless oil: $[\alpha]_D^{23}$ +11.3 (*c* 1.15 in $CHCl_3$); (HRMS (CI+): Found 471.242624. $C_{24}H_{31}N_3O_4Si$ ($M+NH_4^+$) requires *m/z*, 471.242759); ν_{max} (thin film)/cm^{-1} 2107 (N_3) and 1753 (C=O, ester); δ_H ($CDCl_3$, 500 MHz) 1.16 (9H, s, $SiC(CH_3)_3$), 1.19 (3H, d, $J=6.2$ Hz, $CH(CH_3)_2$), 1.23 (3H, d, $J=6.2$ Hz, $CH(CH_3)_2$), 3.80 (1H, d, $J=3.5$ Hz, H-4), 4.11 (1H, d, $J_{5,5'}=10.0$ Hz, H-5), 4.30 (1H, dd, $J_{5',4}=4.5$ Hz, $J_{5',5}=10.0$ Hz, H-5′), 4.50 (1H, br s, H-2), 4.58 (1H, br s, H-3), 5.05 (1H, sept, $J=6.2$ Hz, $CH(CH_3)_2$), 7.43–7.67 (10H, m, Ar*H*); δ_C ($CDCl_3$, 50.3 MHz) 19.1 (s, $SiC(CH_3)_3$), 21.6 (q, $CH(CH_3)_2$), 26.8 (q, $SiC(CH_3)_3$), 66.4 (d, $CH(CH_3)_2$), 68.9 (d, C-4), 71.5 (t, C-5), 80.7 (d, C-3), 84.3 (d, C-2), 127.9, 128.0, 130.2, 130.3 (4×d, 6×Ar*C*H), 132.2, 132.7 (2×s, 2×Ar*C*), 135.6, 135.8 (2×d, 4×Ar*C*H), 169.1 (s, C=O); *m/z* (CI+): 471.4 ($M+NH_4^+$, 65), 376.3 (100%).

4.1.7. Isopropyl 2,5-anhydro-3-azido-4-*O*-*tert*-butyldiphenylsilyl-3-deoxy-L-ribonate 3 and isopropyl L-glycero-4-*O*-*tert*-butyldiphenylsilyl-pent-2-enoate 17. Trifluoromethanesulfonic anhydride (1.2 mL, 7.35 mmol) was added dropwise over a period of 5 min to a stirred solution of 4-*O*-silyl derivative **8** (2.10 g, 4.9 mmol) in dichloromethane (60 mL) containing freshly distilled dry pyridine (0.63 mL, 7.8 mmol) at −20 °C. After 40 min, TLC (ethyl acetate/pet. ether, 1:9) showed the absence of starting material (R_f 0.32) and the formation of a single product (R_f 0.58). The reaction mixture was diluted with dichloromethane (50 mL), washed sequentially with brine (50 mL), citric acid (1 M aq, 50 mL) and water (50 mL) and concentrated in vacuo at low temperature (0–5 °C). The residue was dissolved in pre-cooled (0 °C) dry DMF (20 mL) containing sodium azide (1.27 g, 19.6 mmol) and stirred. After 1 h, the ice bath was removed and the reaction mixture stirred at room temperature. After 10 h, TLC (ethyl acetate/pet. ether, 1:9) showed the formation of a minor product (R_f 0.62) and a major product (R_f 0.56). The reaction mixture was filtered and the filtrate concentrated in vacuo and purified by flash chromatography (ethyl acetate/pet. ether, 1:49) to give the β-azido ester **3** (1.80 g, 81%) and the β-elimination product **17** (84 mg, 4%) as colourless oils.

Compound **3**. $[\alpha]_D^{23}$ −12.6 (*c* 1.04 in $CHCl_3$); (HRMS (CI+): Found 471.241851. $C_{24}H_{31}N_3O_4Si$ ($M+NH_4^+$) requires *m/z*, 471.240959); ν_{max} (thin film)/cm^{-1} 2111 (N_3) and 1759 (C=O, ester); δ_H ($CDCl_3$, 500 MHz) 1.15 (9H, s, $SiC(CH_3)_3$), 1.34 (6H, d, $J=6.3$ Hz, $CH(CH_3)_2$), 3.90 (1H, dd, $J_{5,4}=0.9$ Hz, $J_{5,5'}=9.6$ Hz, H-5), 4.03 (1H, t, $J_{3,2}=4.6$ Hz, H-3), 4.08 (1H, dd, $J_{5',4}=3.8$ Hz, $J_{5',5}=9.6$ Hz, H-5′), 4.40 (1H, m, H-4), 4.81 (1H, d, $J_{2,3}=4.6$ Hz, H-2), 5.20 (1H, sept, $J=6.3$ Hz, $CH(CH_3)_2$), 7.42–7.70 (10H, m, 10×Ar*H*); δ_C ($CDCl_3$, 50.3 MHz) 19.0 (s, $SiC(CH_3)_3$), 21.7 (q, $CH(CH_3)_2$), 21.8 (q, $CH(CH_3)_2$), 26.8 (q, $SiC(CH_3)_3$), 69.3 (d, $CH(CH_3)_2$), 69.7 (d, C-4), 74.8 (t, C-5), 77.0 (d, C-3), 79.1 (d, C-2), 128.0, 128.1, 130.2, 130.3 (4×d, 6×Ar*C*H), 132.6 (s, 2×Ar*C*), 135.6 (d, 4×Ar*C*H), 168.3 (s, C=O); *m/z* (APCI+): 454.33 ($M+H^+$, 20), 127.85 (100%).

Compound **17**. $[\alpha]_D^{23}$ −22.3 (*c* 1.75 in $CHCl_3$); (HRMS (TOF MS FI+): Found 410.1973. $C_{24}H_{30}O_4Si$ (M^+) requires *m/z*, 410.1913); ν_{max} (thin film)/cm^{-1} 1737 (C=O, ester); δ_H ($CDCl_3$, 200 MHz) 1.08 (9H, s, $SiC(CH_3)_3$), 1.32 (3H, d, $J=6.3$ Hz, $CH(CH_3)_2$), 1.35 (3H, d, $J=6.3$ Hz, $CH(CH_3)_2$), 4.23 (1H, m, H-5), 4.41 (1H, dd, $J_{5',4}=3.2$ Hz, $J_{5',5}=10.8$ Hz, H-5′), 5.10 (1H, m, H-4), 5.13 (1H sept, $J=6.3$ Hz, $CH(CH_3)_2$), 5.82 (1H, d, $J_{3,4}=2.8$ Hz, H-3), 7.40–7.70 (10H, m, 10×Ar*H*); δ_C ($CDCl_3$, 50.3 MHz) 19.0 (s, $SiC(CH_3)_3$), 21.7 (q, $CH(CH_3)_2$), 26.8 (q, $SiC(CH_3)_3$), 69.2 (d, $CH(CH_3)_2$), 74.8 (d, C-4), 78.4 (t, C-5), 111.5 (d, C-3), 127.7, 127.9, 129.9 (3×d, 6×Ar*C*H), 133.5 (s, 2×Ar*C*), 135.6 (d, 4×Ar-*C*H), 151.0 (s, C-2), 159.9 (s, C=O); *m/z* (TOF MS FI+): 410.19 (M^+, 100%).

4.1.8. Methyl 2,5-anhydro-D-arabinoate 20, methyl 2,5-anhydro-3,4-*O*-(*S*)-benzylidene-D-arabinoate 22 and methyl 2,5-anhydro-3,4-*O*-(*R*)-benzylidene-D-arabinoate 21. 3,4-*O*-Benzylidene-2-*O*-trifluoromethanesulfonyl-D-ribono-1,5-lactone **18** (2.00 g, 5.43 mmol) was dissolved in methanolic hydrogen chloride (5% v/v, 42 mL) and stirred at room temperature. After 1 h, the reaction mixture was heated to 70 °C for 3 h. The reaction mixture was cooled to room temperature, hydrochloric acid (1 M aq, 6 mL) was added and the reaction mixture heated to 70 °C. After 24 h, TLC (chloroform/methanol, 4:1) showed the absence of the starting material (R_f 0.65), the presence of a major product (R_f 0.37) and minor products (R_f 0.71 and 0.68). The reaction mixture was cooled to room temperature and sodium hydrogen carbonate added to neutralize the solution. The mixture was filtered through Celite (eluent: methanol), concentrated in vacuo and purified by flash chromatography (chloroform/methanol, 4:1) to yield the diol **20** (740 mg, 84%) as a white solid. The minor products were purified by further flash chromatography (ethyl acetate/pet. ether, 1:1) to yield the *S*-benzylidene derivative **22** (95 mg, 7%) and the *R*-benzylidene derivative **21** (81 mg, 6%).

Compound **20**. Mp 71–73 °C; $[\alpha]_D^{23}$ +21.7 (*c* 1.0 in $CHCl_3$); (HRMS (CI+ve): Found 163.0614. $C_6H_{11}O_5$ ($M+H^+$) requires *m/z*, 163.0606); (Found C, 44.15; H, 6.52. $C_6H_{10}O_5$ requires C, 44.45; H, 6.22%); ν_{max} (KBr)/cm^{-1} 3491 (OH), 1737 (C=O, ester); δ_H ($CDCl_3$, 400 MHz) 3.31, 3.48 (2H, m, 2×O*H*), 3.81 (3H, s, CO_2CH_3), 4.04–4.07 (2H, m, H-5 and H-5′), 4.26–4.33 (1H, m, H-4), 4.48–4.52 (1H, m, H-3), 4.53 (1H, d, $J_{2,3}=6.4$ Hz, H-2); δ_C ($CDCl_3$, 100 MHz) 53.0 (q, CO_2CH_3), 71.7 (d, C-4), 72.9 (d, C-3), 73.4 (t, C-5), 80.2 (d, C-2), 172.0 (s, C=O); *m/z* (APCI+ve): 163 ($M+H^+$, 80), 103 (100%).

Compound **22**. Mp 125–126 °C; $[\alpha]_D^{24}$ −71.9 (*c* 1.0 in $CHCl_3$): (Found C, 62.55; H, 5.61. $C_{13}H_{14}O_5$ requires C, 62.39; H, 5.64%); ν_{max} (KBr)/cm^{-1} 1756 (C=O, ester); δ_H ($CDCl_3$, 200 MHz) 3.76 (1H, dd, $J_{4,5}=4.0$ Hz, $J_{5,5'}=11.3$ Hz, H-5), 3.84 (3H, s, CO_2CH_3), 4.33 (1H, d, $J_{2,3}=4.3$ Hz, H-2), 4.41 (1H, dd, $J_{4,5'}=0.6$ Hz, $J_{5,5'}=11.3$ Hz, H-5′), 4.98 (1H, ddd, $J_{4,5'}=0.6$ Hz, $J_{4,5}=4.0$ Hz, $J_{3,4}=5.7$ Hz, H-4), 5.08 (1H, dd, $J_{2,3}=4.3$ Hz, $J_{3,4}=5.7$ Hz, H-3), 6.07 (1H, s, Ar-C*H*), 7.35–7.47 (5H, m, 5×Ar*H*); δ_C ($CDCl_3$, 50.3 MHz) 52.6 (q, CO_2CH_3), 74.6 (t, C-5), 80.4 (d, C-4), 81.3 (d, C-3), 82.6 (d, C-2), 106.3 (d, Ar-*C*H), 127.0, 128.6, 129.9, 135.5 (5×d and s, 5×Ar*C*H and Ar*C*), 167.9 (s, C=O); *m/z* (APCI+ve): 121 (100), 251 ($M+H^+$, 35%).

Compound **21**. Mp 79–81 °C: $[\alpha]_D^{23}$ −162.8 (*c* 1.02 in $CHCl_3$): (Found C, 62.19; H, 6.00. $C_{13}H_{14}O_5$ requires C, 62.39; H, 5.64%); ν_{max} (thin film)/cm^{-1} 1764 (C=O, ester); δ_H ($CDCl_3$, 400 MHz) 3.66 (1H, dd, $J_{4,5}=3.5$ Hz, $J_{5,5'}=10.9$ Hz, H-5), 3.78 (3H, s, CO_2CH_3), 4.31 (1H, d, $J_{2,3}=4.3$ Hz, H-2), 4.36 (1H, d, $J_{5,5'}=10.9$ Hz, H-5′), 4.89 (1H, dd, $J_{4,5}=3.5$ Hz, $J_{3,4}=6.3$ Hz, H-4), 5.05 (1H, dd, $J_{2,3}=4.3$ Hz, $J_{3,4}=6.3$ Hz, H-3), 5.76 (1H, s, Ar-CH), 7.37–7.52 (5H, m, 5×ArH); δ_C ($CDCl_3$, 100 MHz) 52.7 (q, CO_2CH_3), 73.0 (t, C-5), 81.6 (d, C-4), 81.9 (d, C-2), 82.3 (d, C-3), 107.1 (d, Ar-CH), 127.8, 128.8, 130.4, 136.0 (5×d and s, 5×ArCH and ArC), 168.1 (s, C=O); *m/z* (APCI+ve): 251 ($M+H^+$, 100%).

4.1.9. Methyl 2,5-anhydro-3,4-*O*-isopropylidene-D-arabinoate 12. DL-Camphor-10-sulfonic acid (182 mg, 0.78 mmol) was added to a stirred solution of the diol **20** (1.27 g, 7.84 mmol) in acetone (6 mL). After 18 h, a white solid had precipitated from solution and TLC (ethyl acetate/hexane, 1:1) showed the absence of starting material (R_f 0.0) and the presence of a major product (R_f 0.2). Sodium hydrogen carbonate was added to the reaction mixture to neutralize the solution and the reaction mixture filtered through Celite (eluent/acetone). The filtrate was concentrated in vacuo and purified by flash chromatography (ethyl acetate/hexane, 1:1) to yield the acetonide **12** (1.19 g, 75%) as a white solid. Mp 60–61 °C; $[\alpha]_D^{23}$ −91.7 (*c* 1.02 in $CHCl_3$): (Found C, 53.48; H, 6.99. $C_9H_{14}O_5$ requires C, 53.46; H, 6.98%); ν_{max} (thin film)/cm^{-1} 1761 (C=O, ester); δ_H (C_6D_6, 400 MHz) 1.13, 1.50 (2×3H, 2×s, $C(CH_3)_2$), 2.85 (1H, dd, $J_{4,5}=3.8$ Hz, $J_{5,5'}=10.6$ Hz, H-5), 3.41 (3H, s, CO_2CH_3), 3.71 (1H, d, $J_{2,3}=4.3$ Hz, H-2), 3.94 (1H, d, $J_{5,5'}=10.6$ Hz, H-5′), 4.04–4.08 (1H, m, H-4), 4.47–4.51 (1H, m, H-3); δ_C (C_6D_6, 100 MHz) 24.9, 25.9 (2×q, $C(CH_3)_2$), 52.2 (q, CO_2CH_3), 72.8 (t, C-5), 80.3 (d, C-4), 81.4 (d, C-3), 81.6 (d, C-2), 113.1 (s, $C(CH_3)_2$), 167.8 (s, C=O); *m/z* (APCI+ve): 203 ($M+H^+$, 100%).

4.1.10. Methyl 2,5-anhydro-4-*O*-trifluoromethanesulfonyl-D-arabinoate 24. Pyridine (374 μL, 4.59 mmol) and trifluoromethanesulfonic anhydride (0.78 mL, 4.64 mmol) were added to a stirred solution of the diol **20** (500 mg, 3.09 mmol) in dichloromethane (25 mL) at −25 °C. The reaction mixture was warmed to room temperature after being stirred for 4 h. After 48 h, TLC (ethyl acetate/pet. ether, 1:1) showed traces of starting material (R_f 0.0) and the presence of a major product (R_f 0.3). The reaction mixture was diluted with dichloromethane (125 mL), washed with hydrochloric acid (1 M aq, 50 mL) and extracted with dichloromethane (3×30 mL). The combined organic extracts were washed with aq buffer (pH 7, 100 mL) and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered, concentrated in vacuo and purified by flash chromatography (ethyl acetate/pet. ether, 1:1) to give the triflate **24** (432 mg, 48%) as a yellow solid. Mp 101–102 °C; $[\alpha]_D^{24}$ −4.6 (*c* 0.53 in $CHCl_3$): (Found C, 28.53; H, 3.11. $C_7H_9F_3O_7S$ requires C, 28.58; H, 3.08%); ν_{max} (thin film)/cm^{-1} 3426 (OH) and 1755 (C=O, ester); δ_H ($(CD_3)_2CO$, 400 MHz) 3.69 (3H, s, CO_2CH_3), 4.22–4.25 (2H, m, H-5 and H-5′), 4.63 (1H, d, $J_{2,3}=6.4$ Hz, H-2), 4.89 (1H, dd, $J_{2,3}=6.4$ Hz, $J_{3,4}=5.4$ Hz, H-3), 5.51–5.55 (1H, m, H-4); δ_C ($(CD_3)_2CO$, 50.3 MHz) 51.6 (q, CO_2CH_3), 69.9 (t, C-5), 71.5 (d, C-3), 79.5 (d, C-2), 86.7 (d, C-4), 119.8 (q, CF_3), 169.5 (s, C=O); *m/z* (TOF CI+ve): 312 ($M+NH_4^+$, 100%).

4.1.11. Methyl 2,5-anhydro-4-azido-4-deoxy-L-xylonate 23. Pyridine (1.0 mL, 12.3 mmol) and trifluoromethanesulfonic anhydride (1.56 mL, 9.23 mmol) were added to a stirred solution of the diol **20** (1.00 g, 6.17 mmol) in dichloromethane (50 mL) at −25 °C. The reaction mixture was warmed to room temperature after being stirred for 4 h. After 48 h, TLC (ethyl acetate/pet. ether, 1:1) showed traces of starting material (R_f 0.0) and the presence of a major product (R_f 0.3). The reaction mixture was diluted with dichloromethane (125 mL), washed with hydrochloric acid (1 M aq, 50 mL) and extracted with dichloromethane (3×30 mL). The combined organic extracts were washed with aq buffer (pH 7, 100 mL) and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo to afford the triflate **24** as a yellow solid, which was used without further purification.

Sodium azide (2.21 g, 34.0 mmol) was added to a stirred solution of the triflate **24** in DMF (95 mL). The reaction mixture was heated to 85 °C after being stirred for 10 h. After 15 h, TLC (ethyl acetate/pet. ether, 1:1) showed the absence of the starting material (R_f 0.3, UV active) and the presence of a major product (R_f 0.3). The reaction mixture was cooled to room temperature and concentrated in vacuo. The resulting residue was dissolved in ethyl acetate (480 mL), washed with water (100 mL) and extracted with ethyl acetate (3×380 mL). The combined organic extracts were dried over magnesium sulfate, filtered, then concentrated in vacuo and purified by flash chromatography (ethyl acetate/pet. ether, 1:1) to yield the title product (528 mg, 46% over two steps) as a white solid. Mp 115–116 °C; $[\alpha]_D^{23}$ +35.9 (*c* 0.99 in $CHCl_3$): (Found C, 38.63; H, 4.82. $C_6H_9O_4N_3$ requires C, 38.51; H, 4.85%); ν_{max} (thin film)/cm^{-1} 3449 (OH), 2127 (N_3) and 1743 (C=O, ester); δ_H ($CDCl_3$, 200 MHz) 2.60 (1H, d, $J=5.0$ Hz, OH), 3.84 (3H, s, CO_2CH_3), 3.95 (1H, dd, $J_{4,5}=2.0$ Hz, $J_{5,5'}=9.8$ Hz, H-5), 4.10–4.15 (1H, m, H-4), 4.35 (1H, dd, $J_{4,5'}=4.9$ Hz, $J_{5,5'}=9.8$ Hz, H-5′), 4.52 (1H, m, H-3), 4.65 (1H, d, $J_{2,3}=4.4$ Hz, H-2); δ_C ($CDCl_3$, 50.3 MHz) 52.7 (q, CO_2CH_3), 66.8 (d, C-4), 71.4 (t, C-5), 76.8 (d, C-3), 80.7 (d, C-2), 170.3 (s, C=O); *m/z* (APCI+ve): 160 ($M-N_2+H^+$, 100%).

4.1.12. Isopropyl 2,5-anhydro-4-azido-4-deoxy-L-xylonate 2. *Method A*. Potassium carbonate (30 mg, 0.22 mmol) was added to a stirred solution of the methyl azido ester **23** (30 mg, 0.16 mmol) in propan-2-ol (2.42 mL). After 72 h, TLC (ethyl acetate/pet. ether, 2:1) showed the absence of the starting material (R_f 0.3) and the presence of a major product (R_f 0.5). The reaction mixture was filtered through Celite (eluent propan-2-ol), concentrated in vacuo and purified by flash chromatography (ethyl acetate/pet. ether, 2:1) to yield isopropyl azido ester **2** (18 mg, 52%) as a white solid.

Method B. *p*-Toluenesulfonic acid monohydrate (160 mg, 0.84 mmol) was added to a stirred solution of methyl azido ester **23** (500 mg, 2.67 mmol) in propan-2-ol (5 mL) at 80 °C. After 24 h, TLC (ethyl acetate/pet. ether, 2:1) showed the absence of the starting material (R_f 0.3) and the presence of a major product (R_f 0.5). The reaction mixture was

cooled to room temperature and sodium hydrogen carbonate added to neutralize the solution. The reaction mixture was filtered, concentrated in vacuo and purified by flash chromatography (ethyl acetate/pet. ether, 2:1) to yield isopropyl azido ester **2** (414 mg, 72%) as a white solid.

Compound **2**. Mp 78–80 °C; $[\alpha]_D^{24}$ +28.9 (*c* 1.07 in $CHCl_3$); (HRMS (CI+ve): Found 216.0987. $C_8H_{14}N_3O_4$ ($M+H^+$) requires *m/z*, 216.0984); ν_{max} (thin film)/cm^{-1} 3431 (OH), 2088 (N_3) and 1728 (C=O, ester); δ_H ($CDCl_3$, 200 MHz) 1.30 (3H, d, $J=6.3$ Hz, $CH(CH_3)_2$), 1.31 (3H, d, $J=6.3$ Hz, $CH(CH_3)_2$), 2.71 (1H, d, $J=5.3$ Hz, OH), 3.92 (1H, dd, $J_{4,5}=2.0$ Hz, $J_{5,5'}=9.9$ Hz, H-5), 4.10–4.13 (1H, m, H-4), 4.34 (1H, dd, $J_{4,5'}=4.7$ Hz, $J_{5,5'}=9.9$ Hz, H-5′), 4.49–4.52 (1H, m, H-3), 4.57 (1H, d, $J_{2,3}=4.4$ Hz, H-2), 5.17 (1H, sept, $J=6.3$ Hz, $CH(CH_3)_2$); δ_C ($CDCl_3$, 50.3 MHz) 22.0 (q, $CH(CH_3)_2$), 66.9 (d, C-4), 69.8 (d, $CH(CH_3)_2$), 71.3 (t, C-5), 76.8 (d, C-3), 80.3 (d, C-2), 169.4 (s, C=O); *m/z* (APCI+ve): 188 ($M-N_2+H^+$, 24), 233 ($M+NH_4^+$, 100%).

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