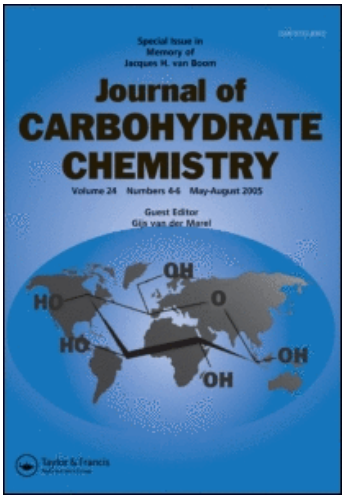

Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

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To cite this Article Lucas, Susana Dias , Rauter, Amélia Pilar and Wessel, Hans Peter(2008) 'Synthesis of 3-Methoxyoxetane δ-Amino Acids with D-*lyxo*, D-*ribo*, and D-*arabino* Configurations', Journal of Carbohydrate Chemistry, 27: 3, 172 — 187
To link to this Article: DOI: 10.1080/07328300802061717
URL: http://dx.doi.org/10.1080/07328300802061717

Journal of Carbohydrate Chemistry, 27:172–187, 2008

ISSN: 0732-8303 print 1532-2327 online
DOI: 10.1080/07328300802061717

Synthesis of 3-Methoxyoxetane δ-Amino Acids with D-*lyxo*, D-*ribo*, and D-*arabino* Configurations

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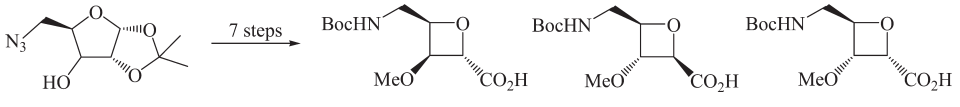
Starting from 1,2-isopropylidene-D-xylose (**1**), 3-methoxyoxetane δ-amino acids with D-*lyxo*, D-*ribo,* and D-*arabino* configurations were synthesized. The early introduction of an azide function at C-5 of **1** shortened the synthetic pathway. Ring contraction of the intermediate D-xylono-1,4-lactone **6** via triflation and treatment with base led to the corresponding 3-methoxyoxetane δ-amino ester with D-*lyxo* configuration **7**. The analogous procedure for D-ribono-1,4-lactone **16** furnished a mixture of D-*ribo* and D-*arabino* esters **17** and **18**. Hydrolysis of the methyl esters **7**, **17**, and **18** to their corresponding δ-amino acids was successful with LiOH in THF, in contrast to that of their 3-hydroxy analog **11**.



Keywords Carbohydrate amino acids, δ-Amino acids, Oxetanes, Carbohydrate scaffolds

Received November 23, 2007; accepted March 17, 2008.
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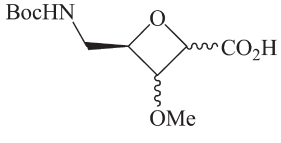
INTRODUCTION

Carbohydrate amino acids (CAAs) are attractive building blocks for the synthesis of biologically active peptide analogs. Their rings induce specific conformations for peptide mimetics[1] and for the synthesis of oligomeric saccharide-peptide hybrids.[2] The highly functionalized CAAs are promising scaffolds for the generation of structurally diverse combinatorial libraries.[3] CAAs have been described as dipeptide isosteres mainly in furanose and pyranose forms. The analogous four-membered rings confer more rigidity to the building blocks and well-defined exit vectors that may orient substituents into specific locations in space. A number of contributions were made concerning the synthesis of carbohydrate-derived β-oxetane amino acids[4] and oxetane δ-amino acids.[5]

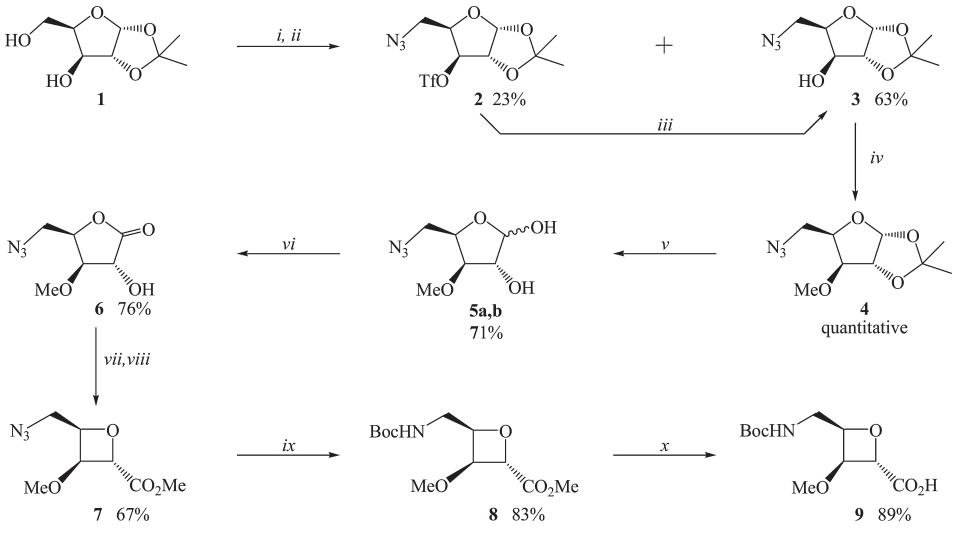
We report herein a successful approach to 3-methoxyoxetane δ-amino acids (Sch. 1) starting from 1,2-*O*-isopropylidene-α-D-xylofuranose and taking advantage of the stability of a primary azide function introduced early in order to avoid protection/deprotection steps over the synthetic pathway. This strategy led to the efficient synthesis of 3-methoxyoxetane δ-amino acids with D-*lyxo*, D-*ribo,* and D-*arabino* configuration in good overall yield.

RESULTS AND DISCUSSION

Starting from commercially available 1,2-*O*-isopropylidene-α-D-xylofuranose (**1**), treatment with triflic anhydride followed by displacement with sodium azide furnished the overtriflated by-product **2,** isolated in 23% yield, together with the desired primary azide **3** in 63% yield (Sch. 2). These results compete favorably with syntheses via a tosylate[6–8] or introduction of the azide from **1** via a zinc salt mediated Mitsonobu reaction.[9] Treatment of the triflate **2** with MeONa/MeOH at rt for 24 h aiming at nucleophilic substitution by the methoxide failed but quantitatively yielded the D-*xylo*-azide **3** instead, thus increasing the overall yield of the desired azide **3**. Methylation of **3** by a standard procedure using iodomethane and sodium hydride in THF gave **4**[6] in quantitative yield. Hydrolysis of the isopropylidene group was achieved with 30% aqueous acetic acid to give a 2:1 α/β-anomeric mixture of 5-azido-3-*O*-methyl-α,β-D-xylofuranose in 88% yield. Selective anomeric oxidation with bromine was performed employing the conditions previously



Scheme 1: Structure of targeted 3-methoxy oxetane δ-amino acids.

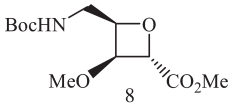
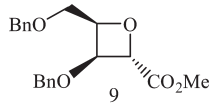
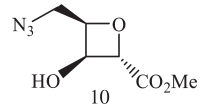
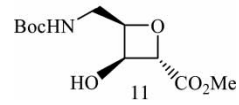


Scheme 2: (*i*) Tf_2O, CH_2Cl_2, Py, −12°C, 30 min; (*ii*) NaN_3, acetone, rt, overnight; (*iii*) MeOH/MeOH, rt, 24 h; (*iv*) MeI, NaH, DMF, 1.5 h; (*v*) AcOH 30%, reflux, 2 h; (*vi*) Br_2, $BaCO_3$, H_2O/dioxane 2:1, rt, 4 h; (*vii*) Tf_2O, CH_2Cl_2, Py, −12°C, 15 min; (*viii*) K_2CO_3, MeOH, −12–0°C, 1 h; (*ix*) H_2, Pd/C, EtOAc, Boc_2O, rt, 3 h; (*x*) LiOH 1N, 0–5°C, 1 h.

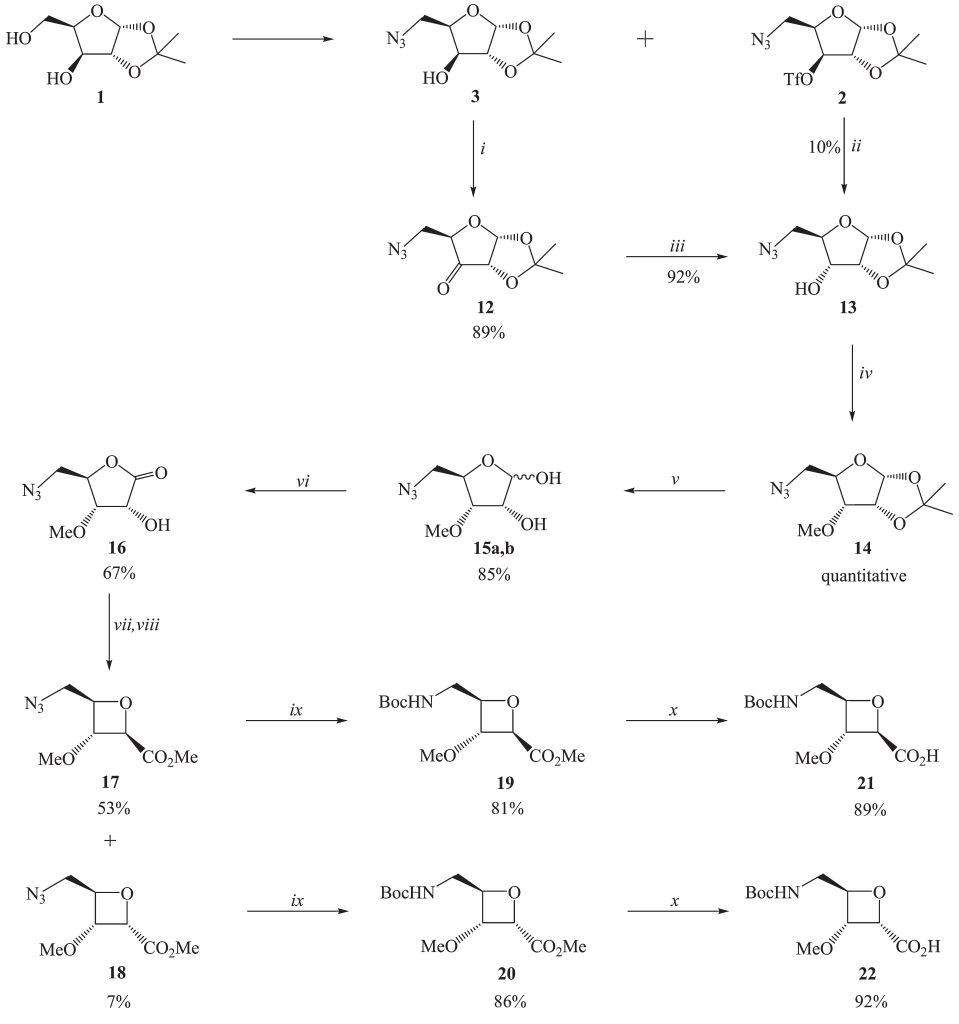
optimized by our group[5b] to give the lactone **6** in 76% yield. Using the methodology described by Witty et al.[10] for the ring contraction of pentano-1,4-lactones to oxetane carboxylic esters, we obtained the oxetane **7** in 67% yield. Hydrogenolysis of the azide in the presence of *tert*-butoxycarbonyl anhydride gave the protected amine **8** in 83% yield.

Saponification with lithium hydroxide allowed the synthesis of the oxetane δ-amino acid **9** in a very good yield (89%). When compared to our previous work on the synthesis of 2,4-anhydro-5-*N*-(*t*-butoxycarbonyl)amino-D-lyxonic acid,[5b] where attempted basic saponification led to complete degradation (Table 1), these results suggest that the free hydroxyl group was indeed responsible for the failure of this reaction, rather than the presence of the amino function, probably due to deprotonation and further intra- or intermolecular reactions resulting in the decomposition of the material. Consistently, basic treatment of **10** or **11** gave complex mixtures, which could not be characterized by NMR.

Table 1: Comparative results for the saponification of oxetane substrates.

			
8	9	10	11
Yield 89%	Quantitative[5b]	Decomposition[5b]	Decomposition[5b]

For the synthesis of the 5-*N*-(*tert*-butoxycarbonyl)amino-3-*O*-methyl-D-ribonic acid starting from the azide **3** (Sch. 3), we made use of a well-established oxidation/reduction sequence.[11] Oxidation with pyridinium dichromate (PDC) of **3** under reflux conditions led to the keto sugar **12** in 89% yield. In comparison, the use of PDC at rt was reported to furnish **12** in 80% yield,[12] while ruthenium dioxide–sodium periodate oxidizing conditions gave 71% of **12**.[8] This keto sugar was reduced with sodium borohydride to give the D-*ribo*-derivative **13**[12] in 92% yield. Attempted inversion of configuration via triflate **2** using sodium trifluoroacetate led to a poor 10% yield of **13**.



Scheme 3: (*i*) PDC, Ac_2O, CH_2Cl_2, reflux, 3 h; (*ii*) CF_3COONa, butanone, rt, overnight; (*iii*) $NaBH_4$, EtOH/H_2O 6:1, rt, overnight; (*iv*) MeI, NaH, DMF, 1 h; (*v*) AcOH 30%, reflux, 1 h; (*vi*) Br_2, $BaCO_3$, H_2O/dioxane 2:1, rt, 1.5 h; (*vii*) Tf_2O, CH_2Cl_2, Py, −12°C, 15 min.; (*viii*) K_2CO_3, MeOH, −12–0°C, 1 h; (*ix*) H_2, Pd/C, EtOAc, Boc_2O, rt, 2 h; (*x*) LiOH 1N, HCl 1N, 0–5°C, 1 h.

The following reactions were carried out as described above. Methylation of 5-azido-5-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranose (**13**) gave the fully protected **14**[6] in quantitative yield and was followed by isopropylidene hydrolysis with 30% aqueous acetic acid to afford the free furanose **15** in 85% yield. Selective anomeric oxidation by bromine gave the ribonolactone **16** in 67% yield. The ring contraction reaction of compound **16** led to a mixture of isomeric D-*ribo*- and D-*arabino*-oxetanes **17** and **18** isolated in 53% and 7% yield, respectively. The stereochemical assignment was possible on the basis of their ^{1}H NMR spectra following the observation that, for similar oxetane systems, *trans*-oriented vicinal protons of the oxetane ring exhibit coupling constants in the range of 4.6 to 6.3 Hz and the corresponding *cis*-oriented vicinal protons coupling constants in the range of 6.2 to 7.9 Hz. Some of the structural assignments have been confirmed by X-ray crystallography.[4a,5b,13] 2D-NOESY ^{1}H-NMR spectra of compounds **19** showed a cross-peak between H-2 and H-4 and between H-2 and the 3-methoxy protons; corresponding cross-peaks were not detected for compound **20**. These stereochemical assignments are in agreement with those reported by Witty et al.[10] for the ring contraction of a different ribono-1,4-lactone.

Hydrogenolysis of the azide **17** in the presence of Boc_2O gave the protected amine **19** in 81% yield. The same procedure was used to transform **18** to **20** in 86% yield. Lithium hydroxide was again very efficient for the saponification of **19** and **20**, which occurred in 89% and 92% yield, to give the final oxetane δ-amino acids **21** and **22**, respectively.

The stability of the 5-azide function along the chosen approach (Sch. 2 and 3) allowed a straightforward synthesis of the three new methoxyoxetane δ-amino acids **9**, **21**, and **22** with different stereochemistry and well-defined exit vectors with different orientations in space particularly interesting for further derivatization.

EXPERIMENTAL

General Methods

All reactions were monitored by TLC (silica gel 60 F_{254}, Merck) with detection by UV light and/or by dipping the chromatograms into a 10% solution of H_2SO_4 in MeOH followed by heating with a heat gun. Solutions were concentrated on a rotary evaporator under reduced pressure below 40°C. Column chromatography (CC) was performed on silica gel 60 G (0.040–0.063 mm, E. Merck). Melting points were determined with an Electrothermal 9100 instrument and are uncorrected. Proton and carbon NMR spectra, COSY, and HMQC experiments were recorded using a Bruker Avance 400 spectrometer operating at 400.13 MHz for ^{1}H or 100.62 MHz for ^{13}C and at a

constant temperature of 298°K at FCUL. Chemical shifts are expressed in parts per million downfield from TMS. Optical rotations were registered on a Perkin Elmer 343 polarimeter at FCUL. High-resolution mass spectra were recorded on a Finnigan LTQ FT from Thermo for positive (ESI) and negative (NSI) electrospray ionization at F. Hoffmann-La Roche, Basel. Elemental analyses were performed at Solvias AG, Basel, Switzerland.

5-Azido-5-deoxy-1,2-*O*-isopropylidene-3-*O*-trifluoromethanesulfonyl-α-D-xylofuranose (2) and 5-Azido-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (3)

A solution of 1,2-*O*-isopropylidene-D-xylofuranose (5.0 g, 26.3 mmol) and pyridine (3.8 mL, 47.3 mmol) in anhydrous CH_2Cl_2 (75 mL) was cooled to −12°C in a MeOH/ice bath. Trifluoromethanesulfonic anhydride (4.5 mL, 27.6 mmol) was added dropwise, and the reaction mixture was stirred for 30 min until complete consumption of starting material was observed by TLC. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed once with a saturated solution of $NaHCO_3$ (100 mL) and once with 2 M hydrochloric acid (100 mL) to remove the pyridine. The aqueous layers were further extracted with CH_2Cl_2, and the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue (assumed 26.3 mmol) was used for the next reaction without further purification due to the low stability of the triflate. To a solution of the crude residue in acetone (250 mL) was added sodium azide (10.25 g, 157 mmol). After stirring overnight at rt the reaction mixture was concentrated, and ice water was added (150 mL). The product was extracted with *tert*-butyl methyl ether (3 × 200 mL), and the combined organic layers were washed with brine (200 mL), dried with $MgSO_4$, filtered, and concentrated. Chromatography (EtOAc/cyclohexane 1:2) of the residue furnished compound **2** as a colorless oil (1.45 g, 23%) followed by the pure product **3** as a colorless solid (3.51 g, 63%).

Physical data of **2**: ^{1}H NMR ($CDCl_3$): δ 6.02 (d, 1H, $J_{1,2} = 3.6$ Hz, H-1), 5.18 (d, 1H, $J_{3,4} = 1.8$ Hz, H-3), 4.76 (d, 1H, $J_{2,3} \approx 0$ Hz, H-2), 4.43 (ddd ≈ td, 1H, H-4), 3.73, 3.70 (each *d*, part AX of ABX, 1H, $J_{4,5a} = 7.0$ Hz, $J_{5a,5b} = 12.6$ Hz, H-5a), 3.51, 3.48 (each *d*, part B of ABX, 1H, $J_{4,5b} = 6.1$ Hz, H-5b), 1.53 (s, 3H, Me-*i-prop*), 1.35 (s, 3H, Me-*i-prop*); ^{13}C NMR ($CDCl_3$): δ 120.1 (CF_3), 113.4 (Cq *i-prop*), 104.7 (C-1), 87.9 (C-3), 83.2 (C-2), 77.3 (C-4), 48.6 (C-5), 26.6 (Me-*i-prop*), 26.4 (Me-*i-prop*).

Physical data of **3**: m.p. 59.8–60.2°C (lit.[8] m.p. 60°C, lit.[14] m.p. 64°C); $[\alpha]_D^{20}$ −36° (*c* 1.0, $CHCl_3$) [lit.[14]: $[\alpha]_D^{25}$ −36.3° (c 1.0, $CHCl_3$)]; ^{1}H and ^{13}C NMR were in agreement with literature data.[8,14]

Anal. Calcd. for $C_8H_{13}N_3O_4$ (215.21): C, 44.65; H, 6.09; N, 19.53. Found: C, 44.48; H, 5.92; N, 19.33.

5-Azido-5-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose (4)

Sodium hydride (60% dispersion in mineral oil, 1.2 g, 30 mmol) was added to a solution of 5-azido-5-deoxy-1,2-*O*-isopropylidene-D-xylofuranose (**3**) (3 g, 13.8 mmol) in anhydrous THF (90 mL) at rt, and the mixture was stirred for 30 min. Methyl iodide (1.8 mL, 28.9 mmol) was added, and the suspension was further stirred at rt for 1 h. After quenching excess NaH with MeOH, the reaction mixture was diluted with EtOAc (ca. 150 mL), washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. Column chromatography with EtOAc/cyclohexane 1:3 gave compound **4**[6] as colorless oil in quantitative yield (1.3 g); $[\alpha]_D^{20}$ −37° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 5.90 (d, 1H, $J_{1,2} = 3.8$ Hz, H-1), 4.60 (d, 1H, $J_{2,3} \approx 0$ Hz, H-2), 4.30 (ddd ≈ dt, 1H, H-4), 3.73 (d, 1H, $J_{3,4} = 3.1$ Hz, H-3), 3.54, 3.51 (each *d*, part AX of ABX, 1H, $J_{4,5a} = 6.8$ Hz, $J_{5a,5b} = 12.4$, H-5a), 3.50, 3.47 (each *d*, part BX of ABX, 1H, $J_{4,5b} = 6.3$ Hz, H-5b), 3.43 (s, 3H, OCH_3), 1.51 (s, 3H, Me-*i*-prop), 1.33 (s, 3H, Me-*i-prop*); ^{13}C NMR ($CDCl_3$): δ 112.0 (Cq *i-prop*), 105.2 (C-1), 83.9 (C-3), 81.5 (C-2), 78.8 (C-4), 57.8 (OMe), 49.0 (C-5), 26.9 (Me-*i-prop*), 26.4 (Me-*i-prop*).

Anal. Calcd. for $C_9H_{15}N_3O_4$ (229.24): C, 47.16; H, 6.60; N, 18.33. Found: C, 47.27; H, 6.51; N, 18.31.

5-Azido-5-deoxy-3-*O*-methyl-α,β-D-xylofuranose (5a,b)

A suspension of xylofuranose **4** (3.0 g; 13.1 mmol) in acetic acid (30% in H_2O, 100 mL) was stirred at reflux (ca. 112°C) over 2 h. The acetic acid was evaporated under reduced pressure. After chromatography with EtOAc/cyclohexane 1:1, the product was obtained as a mixture of anomers (2.18 g, 88%, α/β ca. 2.3:1 by NMR integration) as a colorless oil; ^{1}H NMR ($CDCl_3$): δ 5.50 (d, 1H, $J_{1\alpha,2\alpha} = 4.0$ Hz, H-1α), 5.10 (d, 1H, $J_{1\beta\text{-OH}} = 9.6$ Hz, $J_{1\beta,2\beta} \approx 0$ Hz, H-1β), 4.46–4.38 (m, 2H, H-4α, H-4β), 4.31 (br s, 1H, H-2β), 4.22 (br t, 1H, H-2α), 3.83 (dd, 1H, $J_{2\alpha,3\alpha} = 3.1$ Hz, $J_{3\alpha,4\alpha} = 5.1$ Hz, H-3α), 3.79 (d, 1H, $J_{3\beta,4\beta} = 4.4$ Hz, H-3β), 3.57–3.38 (m, 4H, H-5aα, H-5bα, H-5aβ, H-5bβ, OH-1β), 3.50 (s, 3H, OMeβ), 3.46 (s, 3H, OMeα); ^{13}C NMR ($CDCl_3$): δ 103.4 (C-1β), 96.1 (C-1α), 85.4, 84.6 (C-3α, C-3β), 80.8, 77.4 (C-4α, C-4β, C-2β), 75.4 (C-2α), 58.6, 58.0, 50.7, 50.4 (C-5aα, C-5bα, C-5aβ, C-5bβ, OMeα, OMeβ).

Anal. Calcd. for $C_6H_{11}N_3O_4$ (189.17): C, 38.10; H, 5.86; N, 22.21. Found: C, 38.07; H, 5.58; N, 22.32.

5-Azido-5-deoxy-3-*O*-methyl-D-xylono-1,4-lactone (6)

To a solution of xylofuranose **5** (2.0 g, 10.56 mmol) in dioxane (35 mL) was added water (70 mL) and barium carbonate (2.84 g, 14.37 mmol). Then bromine (4.2 mL, 81.4 mmol) was added dropwise at 0°C. After stirring at rt for 4 h in the dark, the reaction mixture was cooled to 10°C and neutralized with sodium carbonate. Sodium thiosulfate was added until a white precipitate appeared. The reaction mixture was filtered over Celite and the solvents evaporated under reduced pressure. Addition of water (100 mL) was followed by product extraction with EtOAc (3 × 150 mL). The organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated. The residue was column chromatographed with EtOAc/cyclohexane 1:1 to give the desired product **6** (1.50 g; 76%) as a colorless oil; $[\alpha]_D^{20}$ +47° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$; COSY): δ 4.73 (ddd ≈ td, 1H, $J_{4,3} = 7.6$ Hz, $J_{4,5a} \approx J_{4,5b} \approx 3.7$ Hz, H-4), 4.66 (d, 1H, $J_{2,3} = 7.6$ Hz, H-2), 4.20 (t, 1H, $J_{3,4} \approx J_{2,3}$, H-3), 3.66–3.64 (m, 2H, H-5a, H-5b), 3.56 (s, 3H, OMe), 2.97 (br s, 1H, OH-2); ^{13}C NMR ($CDCl_3$): δ 174.9 (C=O), 81.6 (C-3), 76.8 (C-4), 71.9 (C-2), 58.6 (OMe), 50.0 (C-5).

Anal. Calcd. for $C_6H_9N_3O_4$ (187.16): C, 38.51; H, 4.85; N, 22.45. Found: C, 38.53; H, 4.77; N, 22.49.

Methyl 2,4-Anhydro-5-azido-5-deoxy-3-*O*-methyl-D-lyxonate (7)

A solution of γ-lactone **6** (1.0 g, 5.34 mmol) and pyridine (0.73 mL, 9.05 mmol) in CH_2Cl_2 (40 mL) was cooled to −12°C in a MeOH/ice bath. Trifluoromethanesulfonic anhydride (1.0 mL, 6.0 mmol) was added dropwise. The reaction mixture was stirred for 15 min at −12°C, when one major product was formed. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed once with a saturated aqueous solution of $NaHCO_3$ (150 mL) and once with 2 M hydrochloric acid (150 mL). The aqueous layers were further extracted with CH_2Cl_2 and the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. This yielded crude 5-azido-3-*O*-methyl-2-*O*-trifluoromethanesulfonyl-D-xylono-1,4-lactone, which was used for the next reaction without purification.

A solution of the crude 5-azido-3-*O*-methyl-2-*O*-trifluoromethanesulfonyl-D-xylono-1,4-lactone (assumed 5.34 mmol) in MeOH (45 mL) was cooled to −12°C in a MeOH/ice bath. Potassium carbonate (755 mg, 5.34 mmol) was added in one portion, and the reaction mixture was stirred for 1 h while the temperature was allowed to reach 0°C. After that time, complete conversion to one major product was observed and the reaction mixture was filtered over Celite, concentrated, and chromatographed (EtOAc/cyclohexane 1:2) to give the desired oxetane (720 mg, 67% yield) as a colorless oil; $[\alpha]_D^{20}$ −51°

(*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.04 (dd, 1H, $J_{2,3} = 4.8$ Hz, $J_{2,4} = 0.7$, H-2), 4.42 (dd, 1H, $J_{3,4} = 6.6$ Hz, H-3), 4.91 (ddd, 1H, H-4), 3.84 (s, 3H, OMe), 3.69, 3.66 (each *d*, part AX of ABX, 1H, $J_{4,5a} = 6.1$ Hz, $J_{5a,5b} = 13.2$ Hz, H-5a), 3.64, 3.66 (each *d*, part BX of ABX, 1H, $J_{4,5b} = 6.3$ Hz, H-5b), 3.41 (s, 3H, OMe); ^{13}C NMR ($CDCl_3$): δ 170.7 (C-1), 84.0 (C-2), 82.5 (C-4), 77.1 (C-3), 57.5 (OMe), 52.6 (OMe COOMe), 50.4 (C-5).

Anal. Calcd. for $C_7H_{11}N_3O_4$ (201.18): C, 41.79; H, 5.51; N, 20.89. Found: C, 42.05; H, 5.32; N, 20.58.

Methyl 2,4-Anhydro-5-*N*-(*tert*-butoxycarbonyl)amino-3-*O*-methyl-D-lyxonate (8)

A suspension of Pd/C (10%, 80 mg) in a solution of the azide **7** (766 mg, 3.8 mmol) EtOAc (30 mL) was stirred vigorously for 30 min under hydrogen atmosphere. A solution of Boc_2O (1.0 g, 4.56 mmol) in EtOAc (30 mL) was then added. The resulting mixture was stirred for 2 h and filtered, and the solvent was evaporated.

Chromatography of the residue over silica gel (EtOAc/cyclohexane 1:2) gave the pure product **8** (871 mg; 83%) as a colorless oil. $[\alpha]_D^{20}$ -35° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 4.99 (d, 1H, $J_{2,3} = 4.9$ Hz, H-2), 4.96–4.76 (m, 2H, H-4, NH), 4.39 (dd, 1H, $J_{3,4} = 6.5$ Hz, H-3), 3.83 (s, 3H, OMe), 3.61 (ddd, 1H, $J_{5a,5b} = 12.8$ Hz, $J_{5a,NH} \approx J_{4,5a} \approx 6.8$ Hz, H-5a), 3.56–3.49 (m, 4H, H-5b, OMe), 1.44 (s, 9H, Boc); ^{13}C NMR ($CDCl_3$): δ 170.8 (C=O COOMe), 155.9 (C=O Boc), 83.7 (C-2), 82.4 (C-4), 77.4 (C-3), 57.6 (OMe COOMe), 52.5 (OMe), 40.5 (C-5), 28.4 (3Me *t*-Bu).

Anal. Calcd. for $C_{12}H_{21}NO_6$ (275.30): C, 52.35; H, 7.69; N, 5.09. Found: C, 51.86; H, 7.31; N, 5.31.

2,4-Anhydro-5-*N*-(*tert*-butoxycarbonyl)amino-3-*O*-methyl-D-lyxonic Acid (9)

To a solution of methyl ester **8** (500 mg, 1.82 mmol) in THF (10 mL) was added 1 N LiOH (6.5 mL) at 0 to 5°C, and the mixture was stirred until complete consumption of starting material (30 min). Still at 0 to 5°C, 6.5 mL of 1 N HCl was added, and the mixture was stirred for 30 min. Brine was added (20 mL), and the product was extracted with *tert*-butyl methyl ether (3×40 mL). The organic layers were combined, dried over $MgSO_4$, and filtered, and the solvent was evaporated to give the product **9** as a colorless hygroscopic foam (424 mg, 89%). ^1H NMR (acetone-d_6): δ 5.82 (brs, 1H, NH), 4.93 (d, 1H, $J_{2,3} = 4.7$ Hz, H-2), 4.79 (q, 1H, $J_{3,4} \approx J_{4,5a} \approx J_{4,5b} \approx 6.5$ Hz, H-4), 4.46 (dd, 1H, $J_{3,4} = 6.3$ Hz, H-3), 3.56–3.40 (m, 2H, H-5a, H-5b), 3.39 (OMe), 1.40 (s, 9H, Boc); ^{13}C NMR (acetone-d_6): δ 170.2 (COOH), 156.7 (C=O Boc), 83.7 (C-2), 82.2 (C-4), 77.9 (C-3), 78.8 (Cq Boc), 57.3 (OMe), 40.9 (C-5),

28.3 (3Me *t*-Bu). HRMS (NSI) *m/z* 260.11397 $[M-H]^-$, calcd. 260.11396 for $C_{11}H_{18}NO_6$.

5-Azido-5-deoxy-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranos-3-ulose (12)

To a solution of 5-azido-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose **3** (2.71 g, 12.6 mmol) in anhydrous CH_2Cl_2 (45 mL) was added PDC (3.32 g, 8.8 mmol) and Ac_2O (3.6 mL, 38.1 mmol), and the mixture was stirred for 3 h under reflux. Diethyl ether was added (100 mL), and the brown suspension was filtered over a Florisil column (Supelco/Sigma-Aldrich, 100–200 mesh) eluting with diethyl ether. The product was crystallized with CH_2Cl_2/cyclohexane to give a colorless solid (2.392 g, 11.2 mmol, 89% yield). m.p. 54.2–55.0°C. $[\alpha]_D^{25}$ +187° (*c* 1.0, $CHCl_3$), (lit.[12] $[\alpha]_D^{25}$ +185.2° (*c* 1.1, $CHCl_3$). NMR data were in full agreement with the literature.[8]

5-Azido-5-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranose (13)

Treatment of the ulose **12** with $NaBH_4$ in $EtOH/H_2O$[8] gave the desired product **13** as a colorless oil in 94% yield. $[\alpha]_D^{25}$ +63° (*c* 1.0, $CHCl_3$), (lit.[8] $[\alpha]_D^{20}$ +65.5° (*c* 0.5, $CHCl_3$). NMR data were in full agreement with the literature.[8]

5-Azido-5-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-ribofuranose (14)

To a solution of 5-azido-5-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranose (**13**, 1.98 g, 9.2 mmol) in THF (60 mL) was added NaH (60% dispersion in mineral oil, 0.756 g, 18.1 mmol), and the solution was stirred for 30 min. MeI (1.18 mL, 18.9 mmol) was then added, and the reaction mixture was stirred again for 30 min. After quenching excess of NaH with MeOH, the reaction mixture was diluted with EtOAc (75 mL), washed with H_2O (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. Column chromatography eluting with EtOAc/cyclohexane 1:4 to 1:2 gave the known product **14**[6] as colorless oil (2.18 g, quantitative). $[\alpha]_D^{25}$ +161° (*c* 1.0, $CHCl_3$),^{1}H NMR ($CDCl_3$): δ 5.80 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 4.71 (t, 1H, H-2), 4.14 (ddd ≈ dt, 1H, H-4), 3.74, 3.70 (each *d*, part AX of ABX, 1H, $J_{4,5a}$ = 2.5 Hz, $J_{5a,5b}$ = 13.5 Hz, H-5a), 3.65 (dd, 1H, $J_{2,3}$ 4.1 Hz, $J_{3,4}$ = 8.0 Hz, H-3), 3.50 (s, 3H, OMe), 3.34, 3.30 (each *d*, part BX of ABX, 1H, $J_{4,5b}$ = 3.8 Hz, H-5b), 1.59 (s, 3H, Me-*i*-prop), 1.38 (s, 3H, Me-*i*-prop); ^{13}C NMR ($CDCl_3$): δ 113.4 (Cq *i-prop*), 104.1 (C-1), 80.6 (C-3), 77.4 (C-4), 77.0 (C-2), 58.6 (OMe), 50.7 (C-5), 26.9 (Me-*i-prop*), 26.5 (Me-*i-prop*). HRMS (ESI) *m/z* 247.14007 $[M + NH_4]^+$, calcd. 247.14008 for $C_9H_{19}N_4O_4$.

Anal. Calcd. for $C_9H_{15}N_3O_4$ (229.24): C, 47.16; H, 6.60; N, 18.33. Found: C, 47.17; H, 6.52; N, 18.46.

5-Azido-5-deoxy-3-*O*-methyl-α,β-D-ribofuranose (15a,b)

A suspension of 5-azido-5-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-ribofuranose (**14**, 2.0 g, 8.7 mmol) in AcOH (30% in H_2O, 75 mL) was stirred under reflux over 1 h. The acetic acid was coevaporated with toluene. Column chromatography eluting with EtOAc/cyclohexane 1:1 gave the desired product **15a**,**b** as a colorless oil (1.42 g, 7.5 mmol, 86% yield). ^{1}H NMR ($CDCl_3$): δ 5.37–5.32 (m, 2H, H-1α, H-1β), 4.21 (ddd $\approx$ q, 1H, H-4α), 4.18 (br t, 1H, $J_{1\alpha,2\alpha} \approx J_{2\alpha,3\alpha} \approx 4.5$ Hz, H-2α), 4.15–4.11 (m, 2H, H-2β, H-4β), 4.00 (dd, 1H, $J_{2\beta,3\beta} = 4.6$ Hz, $J_{3\beta,4\beta} = 6.9$ Hz, H-3β), 3.70 (dd $\approx$ t, 1H, $J_{2\alpha,3\alpha} = 5.0$ Hz, $J_{3\alpha,4\alpha} = 5.5$ Hz, H-3α), 3.63, 3.59 (each *d*, part AX of ABX, 1H, $J_{4\beta,5a\beta} = 3.7$ Hz, H-5aβ), 3.58, 3.54 (each *d*, part AX of ABX, 1H, $J_{4\alpha,5a\alpha} = 4.0$ Hz, H-5aα), 3.49 (s, 3H, OMeα), 3.46 (s, 3H, OMeβ), 3.41, 3.38 (each *d*, part BX of ABX, 1H, $J_{4\beta,5b\beta} = 5.2$ Hz, $J_{5a\beta,5b\beta} = 13.1$ Hz, H-5bβ), 3.34, 3.31 (each *d*, part BX of ABX, 1H, $J_{4\alpha,5b\alpha} = 3.9$ Hz, $J_{5a\alpha,5b\alpha} = 13.2$ Hz, H-5bα); ^{13}C NMR ($CDCl_3$): δ 102.3 (C-1β), 97.1 (C-1α), 81.1 (C-3β), 80.4 (C-3α), 80.0 (C-4β), 79.1 (C-4α), 73.2 (C-2β), 70.1 (C-2α), 58.9 (OMeα), 58.6 (OMeβ), 53.3 (C-5β), 52.2 (C-5α). HRMS (ESI) m/z 248.08925 $[M + OAc]^+$, calcd. 248.08881 for $C_8H_{14}N_3O_6$.

Anal. Calcd. for $C_6H_{11}N_3O_4$ (189.17): C, 38.10; H, 5.86; N, 22.21. Found: C, 38.10; H, 5.78; N, 21.99.

5-Azido-5-deoxy-3-*O*-methyl-D-ribono-1,4-lactone (16)

To a solution of **15** (1.33 g, 7.0 mmol) in dioxane/H_2O 1:2 (75 mL) was added $BaCO_3$ (1.94 g, 9.8 mmol). The temperature was decreased to 0°C, and bromine (2.9 mL, 56 mmol) was added dropwise. The reaction mixture was stirred for 1.5 h in the dark while it was allowed to reach rt. The mixture was then cooled to 10°C and neutralized with Na_2CO_3. To destroy the bromine, $Na_2S_2O_3$ was added until a white precipitate was formed. The reaction mixture was filtered over Celite, and the solvents were evaporated. The residue was dissolved in EtOAc and washed with brine, dried over $MgSO_4$, filtered, and concentrated. Column chromatography with EtOAc/cyclohexane 1:1 gave the desired product **16** in 67% yield. $[\alpha]_D^{25} + 60^\circ$ (*c* 1.0, $CHCl_3$), ^{1}H NMR ($CDCl_3$): δ 4.63 (d, 1H, $J_{2,3} = 5.9$ Hz, H-2) 4.55 (dd $\approx$ t, 1H, H-4), 3.90 (d, 1H, $J_{3,4} \approx 0$ Hz, H-3), 3.75, 3.73 (each *d*, part AX of ABX, 1H, $J_{4,5a} = 4.3$ Hz, $J_{5a,5b} = 13.4$ Hz, H-5a), 3.66, 3.63 (each *d*, part BX of ABX, 1H, $J_{4,5b} = 3.7$ Hz, H-5b), 3.52 (s, 3H, OMe); ^{13}C NMR ($CDCl_3$): δ 174.50 (C=O), 79.35 (C-4), 77.96 (C-3), 68.14 (C-2), 58.45 (OMe), 51.91 (C-5). HRMS (ESI) m/z 246.07358 $[M + OAc]^+$, calcd. 246.07316 for $C_8H_{12}N_3O_6$.

Anal. Calcd. for $C_6H_9N_3O_4$ (187.16): C, 38.51; H, 4.85; N, 22.45. Found: C, 38.46; H, 4.89; N, 22.07.

Methyl 2,4-Anhydro-5-azido-5-deoxy-3-*O*-methyl-D-ribonate (17) and Methyl 2,4-Anhydro-5-azido-5-deoxy-3-*O*-methyl-D-arabinonate (18)

A solution of the lactone **16** (812 mg, 4.34 mmol) and pyridine (0.6 mL, 7.44 mmol) in CH_2Cl_2 (30 mL) was cooled to -12°C in a MeOH/ice bath. Trifluoromethanesulfonic anhydride (0.8 mL, 4.8 mmol) was added dropwise. The reaction mixture was stirred for 15 min at -12°C, when one major product was formed. The reaction mixture was diluted with CH_2Cl_2 (75 mL) and washed once with a saturated aqueous solution of $NaHCO_3$ (100 mL) and once with 2 M hydrochloric acid (100 mL). The aqueous layers were further extracted with CH_2Cl_2, and the organic layers were combined, dried over $MgSO_4$, and concentrated. This yielded crude 5-azido-3-*O*-methyl-2-*O*-trifluoromethanesulfonyl-D-xylono-1,4-lactone, which was used for the next reaction without purification.

A solution of the crude 5-azido-3-*O*-methyl-2-*O*-trifluoromethanesulfonyl-D-xylono-1,4-lactone (assumed 4.34 mmol) in MeOH (35 mL) was cooled to -12°C in a MeOH/ice bath. Potassium carbonate (614 mg, 4.34 mmol) was added in one portion, and the reaction mixture was stirred for 1 h while the temperature was allowed to reach 0°C and the reaction mixture was filtered over Celite, concentrated, and chromatographed (EtOAc/cyclohexane 1:3) to furnish compound **17** (465.5 mg, 53% yield) followed by compound **18** (61.0 mg, 7% yield).

Data of compound **17**: Colorless oil, $[\alpha]_D^{25}$ $+140^\circ$ (*c* 1.0, $CHCl_3$),^{1}H NMR ($CDCl_3$): δ 4.95 (d, 1H, $J_{2,3} = 5.1$ Hz, H-2) 4.72 (bq, 1H, H-4), 4.27 (t, 1H, $J_{2,3} \approx J_{3,4} \approx 5.0$ Hz, H-3), 3.84 (s, 3H, COOMe), 3.63, 3.59 (each *d*, part AX of ABX, 1H, $J_{4,5a} = 4.0$ Hz, $J_{5a,5b} = 13.8$ Hz, H-5a), 3.45, 3.42 (each *d*, part BX of ABX, 1H, $J_{4,5b} = 4.0$ Hz, H-5b), 3.40 (s, 3H, OMe); ^{13}C NMR ($CDCl_3$): δ 170.2 (C═O), 84.2 (C-4), 81.7 (C-2), 78.4 (C-3), 57.1 (OMe), 52.7 (C-5), 52.5 (OMe(COOMe)). HRMS (ESI) *m/z* 219.10882 $[M + NH_4]^+$, calcd. 219.10878 for $C_7H_{15}N_4O_4$.

Anal. Calcd. for $C_7H_{11}N_3O_4$ (201.18): C, 41.79; H, 5.51; N, 20.89. Found: C, 41.44; H, 5.42; N, 20.87.

Data of compound **18**: Colorless oil, $[\alpha]_D^{25}$ $+68^\circ$ (*c* 1.0, $CHCl_3$), ^{1}H NMR ($CDCl_3$): δ 5.17 (d, 1H, $J_{2,3} = 6.9$ Hz, H-2) 4.95 (bddd, 1H, H-4), 4.51(dd, 1H, $J_{3,4} = 5.5$ Hz, H-3), 3.86 (s, 3H, COOMe), 3.67, 3.63 (each *d*, part AX of ABX, 1H, $J_{4,5a} = 3.7$ Hz, $J_{5a,5b} = 13.9$ Hz, H-5a), 3.41, 3.37 (each *d*, part BX of ABX, 1H, $J_{4,5b} = 3.4$ Hz, H-5b), 3.35 (s, 3H, OMe); ^{13}C NMR ($CDCl_3$): δ 169.8 (C═O), 87.5 (C-4), 81.4 (C-2), 75.9 (C-3), 58.4 (OMe), 52.8 (C-5), 52.4 (OMe(COOMe)). HRMS (ESI) *m/z* 219.10884 $[M + NH_4]^+$, calc. 219.10878 for $C_7H_{15}N_4O_4$.

Anal. Calcd. for $C_7H_{11}N_3O_4$ (201.18): C, 41.79; H, 5.51; N, 20.89. Found: C, 41.65; H, 5.72; N, 20.74.

Methyl 2,4-Anhydro-5-*N*-(*tert*-butoxycarbonyl)amino-3-*O*-methyl-D-ribonate (19)

A suspension of Pd/C (10%, 30 mg) in a solution of the azide **17** (330 mg, 1.64 mmol) in EtOAc (15 mL) was stirred vigorously for 30 min under hydrogen atmosphere. A solution of Boc_2O (376 g, 1.76 mmol) in EtOAc (15 mL) was then added. The resulting mixture was stirred for 2 h and filtered, and the solvent was evaporated. Chromatography of the residue over silica gel (EtOAc/cyclohexane 1:2) gave the pure product **8** (390 mg; 81%) as a colorless oil. $[\alpha]_D^{25}$ +3° (*c* 1.0, $CHCl_3$), ^{1}H NMR ($CDCl_3$): δ 5.31 (bs, 1H, NH), 4.93 (d, 1H, $J_{2,3}$ 5.0 Hz, H-2), 4.70 (bq, 1H, $J \approx 4.9$ Hz, H-4), 4.13 (t, 1H, $J_{2,3} \approx J_{3,4} \approx 4.8$ Hz, H-3), 3.84 (s, 3H, COOMe), 3.52 (bddd, 1H, H-5a), 3.37 (s, 3H, OMe), 3.33 (dt, 1H, $J_{4,5b} \approx J_{5b,NH} \approx 3.9$ Hz, $J_{5a,5b} = 15.1$, H-5b), 1.45 (s, 9H, Boc); ^{13}C NMR ($CDCl_3$): δ 170.1 (C═O), 155.8 (C═O Boc), 85.7 (C-4), 81.6 (C-2), 79.1 (Cq Boc), 78.7 (C-3), 57.3 (OMe), 52.6 (OMe(COOMe)), 42.8 (C-5), 27.9 (3Me-Boc). HRMS (ESI) m/z 293.17071 $[M + NH_4]^+$, calcd. 293.17071 for $C_{12}H_{25}N_2O_6$.

Anal. Calcd. for $C_{12}H_{21}NO_6$ (275.30): C, 52.35; H, 7.69; N, 5.09. Found: C, 52.09; H, 7.41; N, 5.30.

Methyl 2,4-Anhydro-5-*N*-(*tert*-butoxycarbonyl)amino-3-*O*-methyl-D-arabinonate (20)

A suspension of Pd/C (10%, 15 mg) in a solution of the azide **18** (125 mg, 0.62 mmol) in EtOAc (5 mL) was stirred vigorously for 30 min under hydrogen atmosphere. A solution of Boc_2O (143 mg, 0.65 mmol) in EtOAc (5 mL) was then added. The resulting mixture was stirred for 2 h and filtered, and the solvent was evaporated. Chromatography of the residue over silica gel (EtOAc/cyclohexane 1:2) gave the pure product **20** (147 mg; 86%) as a colorless oil. $[\alpha]_D^{25}$ +112° (*c* 1.0, $CHCl_3$), ^{1}H NMR ($CDCl_3$): δ 5.09 (d, 1H, $J_{2,3} = 7.2$ Hz, H-2), 4.93 (bs, 1H, NH), 4.85 (bq, $J = 4.7$ Hz, H-4), 4.36 (dd, 1H, $J_{3,4} = 5.9$ Hz, H-3), 3.85 (s, 3H, COOMe), 3.50 (ddd, 1H, $J_{5a,5b} = 15.0$ Hz, $J_{5a,NH} = 7.0$ Hz, $J_{4,5a} = 4.5$ Hz, H-5a), 3.39 (dt, 1H, $J_{4,5b} \approx J_{5b,NH} \approx 4.5$ Hz, H-5b), 3.33 (s, 3H, OMe), 1.46 (s, 9H, Boc); ^{13}C NMR ($CDCl_3$): δ 169.9 (C═O COOMe), 156.1 (C═O Boc), 88.2 (C-4), 81.0 (C-2), 79.8 (Cq Boc), 75.8 (C-3), 58.0 (OMe), 52.2 (OMe(COOMe)), 42.8 (C-5), 28.3 (3Me-Boc). HRMS (ESI) m/z 293.17060 $[M + NH_4]^+$, calcd. 293.17071 for $C_{12}H_{25}N_2O_6$.

Anal. Calcd. for $C_{12}H_{21}NO_6$ (275.30): C, 52.35; H, 7.69; N, 5.09. Found: C, 51.86; H, 7.31; N, 5.31.

2,4-Anhydro-5-*N*-(*tert*-butoxycarbonyl)amino-3-*O*-methyl-D-ribonic Acid (21)

To a solution of methyl ester **19** (60 mg, 0.22 mmol) in THF (3.75 mL) was added 1 N LiOH (0.65 mL) at 0 to 5°C, and the mixture was stirred until complete consumption of starting material (30 min). Still at 0 to 5°C, 1 N HCl (0.65 mL) was added, and the mixture was stirred for 30 min. Brine was added (10 mL), and the product was extracted with *tert*-butyl methyl ether (3 × 20 mL). The organic layers were combined, dried over $MgSO_4$, and filtered, and the solvent was evaporated to give the product **21** as a colorless waxy solid (50.6 mg, 89%).^{1}H NMR (acetone-d_6): δ 6.96 (brs, 1H, NH), 5.59 (d, 1H, $J_{2,3} = 4.7$ Hz, H-2), 5.31 (q, 1H, $J_{3,4} \approx J_{4,5a} \approx J_{4,5b} \approx 4.9$ Hz, H-4), 4.92 (t, 1H, H-3), 3.21–4.04 (m, 5H, H-5a, H-5b, OMe), 1.42 (s, 9H, Boc); ^{13}C NMR (acetone-d_6): δ 171.5 (COOH), 157.1 (C═O Boc), 85.6 (C-4), 81.6 (C-2), 80.2 (C-3), 79.1 (Cq Boc), 56.6 (OMe), 43.3 (C-5), 28.4 (3Me *t*-Bu). HRMS (NSI) *m/z* 260.11406 [M-H]$^-$, calcd. 260.11396 for $C_{11}H_{18}NO_6$.

2,4-Anhydro-5-*N*-(*tert*-butoxycarbonyl)amino-3-*O*-methyl-D-arabinonic Acid (22)

To a solution of methyl ester **20** (60 mg, 0.22 mmol) in THF (3.75 mL) was added 1 N LiOH (0.65 mL) at 0 to 5°C, and the mixture was stirred until complete consumption of starting material (30 min). Still at 0 to 5°C, 0.65 mL of 1 N HCl was added, and the mixture was stirred for 30 min. Brine was added (10 mL), and the product was extracted with *terc*-butyl methyl ether (3 × 20 mL). The organic layers were combined, dried over $MgSO_4$, and filtered, and the solvent was evaporated to give the product **22** as a colorless waxy solid (52.3 mg, 92%). ^{1}H NMR (acetone-d_6): δ 5.18 (d, 1H, $J_{2,3} = 7.3$ Hz, H-2), 4.81 (q, 1H, $J_{3,4} \approx J_{4,5a} \approx J_{4,5b} \approx 5.3$ Hz, H-4), 4.54 (dd, 1H, H-3), 3.47 (d, 2H, H-5b, $J_{4,5a} = J_{4,5b} = 5.0$ Hz, H-5a), 3.41 (s, 3H, OMe), 1.39 (s, 9H, Boc); ^{13}C NMR (acetone-d_6): δ 171.5 (COOH), 157.1 (C═O Boc), 85.6 (C-4), 81.6 (C-2), 80.2 (C-3), 79.1 (Cq Boc), 56.8 (OMe), 43.3 (C-5), 28.4 (3Me *t*-Bu). HRMS (NSI) *m/z* 260.11403 [M-H]$^-$, calcd. 260.11396 for $C_{11}H_{18}NO_6$.

ACKNOWLEDGMENTS

The authors would like to thank Siegfried Stolz for recording HRMS spectra and Joseph Schneider for NOESY ^{1}H NMR experiments at F. Hoffmann-La Roche, Basel. S.D. Lucas would like to thank Fundação para a Ciência e Tecnologia for a PhD grant (SFRH/BD/16592/2004).

REFERENCES

[1] (a) Gruner, S.A.W.; Locardi, E.; Lohof, E.; Kessler, H. Carbohydrate-based mimetics in drug design: sugar amino acids and carbohydrate scaffolds. Chem. Rev. **2002**, *102*, 491–514; (b) Jensen, K.J.; Brask, J. Carbohydrates in peptide and protein design. Biopolym. (Peptide Sci.) **2005**, *80*, 747–761.

[2] (a) Wessel, H.P. Non-sugar glycomimetics. In *Glycoscience: Chemistry and Chemical Biology*; Fraser-Reid, B., Tatsuta, K., Thiem, K., Eds.; Springer Verlag: Heidelberg, 2001; Vol. III, 2725–2752; (b) Wessel, H.P. Saccharide-peptide hybrids. In *Oligosaccharides in Chemistry and Biology: A Comprehensive Handbook. Synthesis of Oligosaccharides, Glycoconjugates and Glycomimetics, Part II: Synthesis of Oligosaccharide Mimetics*; Ernst, B., Hart, G., Sinay, P., Eds.; Wiley/VCH: Weinheim, 2000; Vol. I, 565–586.

[3] (a) Peri, F.; Cipolla, L.; Forni, E.; Nicotra, F. Carbohydrate-based scaffolds for the generation of sortiments of bioactive compounds. Monatshefte für Chemie **2002**, *133* (4), 369–382; (b) Chakraborty, T.K.; Jayaprakas, S.; Ghosh, S. Sugar amino acid based scaffolds—novel peptidomimetics and their potential in combinatorial synthesis. Combinatorial Chem. High Throughput Screen **2002**, *5*, 373–387; (c) Edwards, A.A.; Ichihara, O.; Murfin, S.; Wilkes, R.; Whittaker, M.; Watkin, D.J.; Fleet, G.W.J. Tetrahydrofuran-based amino acids as library scaffolds. J. Comb. Chem. **2004**, *6*, 230–238.

[4] (a) Barker, S.F.; Angus, D.; Taillefumier, C.; Probert, M.R.; Watkin, D.J.; Watterson, M.P.; Claridge, T.D.W.; Hungerford, N.L.; Fleet, G.W.J. *cis*- and *trans*-3-Azido-oxetane-2-carboxylate scaffolds: hexamers of oxetane *cis*-β-amino acids. Tetrahedron Lett **2001**, *42*, 4247–4250; (b) Jenkinson (née Barker), S.F.; Harris, T.; Fleet, G.W.J. Oxetane *cis*- and *trans* β-amino-acid scaffolds from D-xylose by efficient S_N2 reactions in oxetane rings: methyl and hydroxymethyl analogues of the antibiotic oxetin, an oxetane β-amino-acid. Tetrahedron Asymm. **2004**, *15*, 2667–2679; (c) Johnson, S.W.; Jenkinson (née Barker), S.F.; Angus, D.; Jones, J.H.; Fleet, G.W.J.; Taillefumier, C. Oxetane *cis*- and *trans* β-amino-acid scaffolds from L-rhamnose by efficient S_N2 reactions in oxetane rings: pseudoenantiomeric analogues of the antibiotic oxetin. Tetrahedron Asymm. **2004**, *15*, 2681–2686.

[5] (a) Johnson, S.W.; Jenkinson (née Barker), S.F.; Angus, D.; Jones, J.H.; Watkin, D.J.; Fleet, G.W.J. Pseudoenantiomeric oxetane δ-amino acid scaffolds derived from L-rhamnose and D-xylose: D/L-alanine-D-serine and glycine-L-serine dipeptide isosteres. Tetrahedron Asymm. **2004**, *15*, 3263–3273; (b) Lucas, S.D.; Iding, H.; Alker, A.; Wessel, H.P.; Rauter, A.P. Oxetane δ-amino acids: chemoenzymatic synthesis of 2,4-anhydro-5-*N*-(*t*-butoxycarbonyl)amino-D-lyxonic acid. J. Carbohydr. Chem. **2006**, *25*, 187–196.

[6] Tulshian, D.B.; Fundes, A.F.; Czarniecki, M. Versatile synthesis of dihydroxy γ- and δ-amino acids from carbohydrates. Bioorg. Med. Chem. Lett. **1992**, *2* (6), 515–518.

[7] Yamashita, M.; Takahashi, C.; Seo, K. Preparation of novel cyclophosphamides derivatives of sugars. Heterocycles **1993**, *36* (4), 651–654.

[8] Kefurt, K.; Kefurtova, Z.; Markova, V.; Slivova, K. Synthesis of 5-amino-5-deoxypentonolactams. Collect. Czech. Chem. Commun. **1996**, *61*, 1027–1036.

[9] Moravcová, J.; Spilová, L.; Capková, J.; Chéry, F.; Rollin, P. Mitsunobu transformations of 1,2-isopropylidene-α-D-pentofuranoses mediated by zinc salts. Collect. Czech. Chem. Commun. **2000**, *65*, 1745–1753.

[10] Witty, D.R.; Fleet, G.W.J.; Vogt, K.; Wilson, F.X.; Wang, Y.; Storer, R.; Myers, P.L.; Wallis, C.J. Ring contraction of 2-*O*-trifluoromethanesulphonates of α-hydroxy-γ-lactones to oxetane carboxylic esters. Tetrahedron Lett. **1990**, *31* (33), 4787–4790.

[11] Baker, D.C.; Horton, D.; Tindall, C.G. Large-scale preparation of D-allose: observations on the stereoselectivity of the reduction of 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose hydrate. Carbohydr. Res. **1972**, *24* (1), 192–197.

[12] Ewing, D.F.; Goethals, G.; Mackenzie, G.; Martin, P.; Ronco, G.; Vanbaelinghem, L.; Villa, P. Novel reversed cyclonucleoside analogues with a D-ribofuranose glycone. Carbohydr. Res. **1999**, *321*, 190–196.

[13] Suzuki, M.; Tomooka, K. Anionic ring-contraction reaction of cyclic acetal system: stereoselective approach to multi-functionalized oxetanes. Synlett **2004**, *4*, 651–654.

[14] Ewing, D.F.; Goethals, G.; Mackenzie, G.; Martin, P.; Ronco, G.; Vanbaelinghem, L.; Villa, P. Entry to the 2,5-epoxymidazo[1,5-α][1,3]diazocine and 5,8-epoxy[1,2,3]-triazolo[1,5-α][1,3]diazocine systems: novel reversed cyclonucleoside analogues. J. Carbohydr. Chem. **1999**, *18* (4), 441–450.