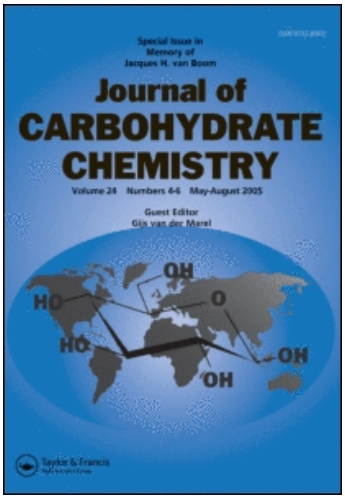

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Oxetane δ-Amino Acids: Chemoenzymatic Synthesis of 2,4-Anhydro-5-*N*-(*t*-butoxycarbonyl)amino-D-lyxonic Acid

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Oxetane δ-Amino Acids: Chemoenzymatic Synthesis of 2,4-Anhydro-5-*N*-(*t*-butoxycarbonyl)amino-D-lyxonic Acid

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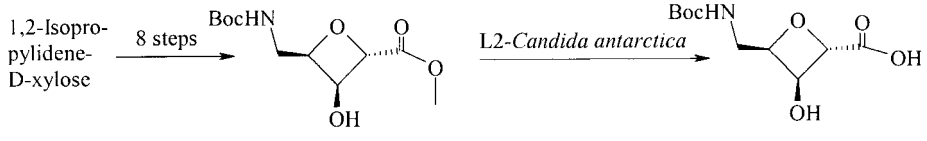
Starting from 1,2-*O*-isopropylidene-D-xylose, methyl 2,4-anhydro-3,5-di-*O*-benzyl-D-lyxonate (**4**) was synthesized. Debenzylation and transformation of the primary hydroxyl group yielded methyl 2,4-anhydro-5-*N*-(*t*-butoxycarbonyl)amino-D-lyxonate (**9**). While transesterification of **4** under basic reaction conditions was straightforward, an analogous reaction with **9** was not successful. After screening of several lipases, the enzymatic transesterification of **9** was achieved with lipase L2 from *Candida antarctica* to furnish the title compound 2,4-anhydro-5-*N*-(*t*-butoxycarbonyl)amino-D-lyxonic acid in excellent yield. The stereochemistry at the oxetane ring was proven by an x-ray structure of the intermediate methyl 2,4-anhydro-5-azido-D-lyxonate.



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

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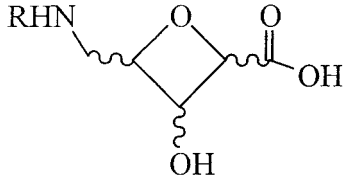
INTRODUCTION

Carbohydrate amino acids (CAAs) are interesting building blocks that have been employed as rigid templates to induce specific conformations in peptide mimetics[1] or to synthesize oligomeric carbohydrate-peptide hybrids.[2] Moreover, they are useful scaffolds for parallel chemistry approaches.[3] While there is ample precedence for pyranose and furanose scaffolds, there are no reports on oxetane-based libraries. The four-membered ring has little flexibility, and thus well-defined exit vectors that may orient substituents into specific locations in space. Oxetane derivatives as shown in Scheme 1 are conformationally restricted δ-amino acids with three different functional groups for further extension. Strategically, we targeted the free carboxylic acid to allow the coupling of the building blocks to a solid-phase carrier using standard methodology.

Here we describe the synthesis of the D-*lyxo* configured CAA and in particular address the problem to prepare the free carboxylic acid by employing a chemoenzymatic approach.

RESULTS AND DISCUSSION

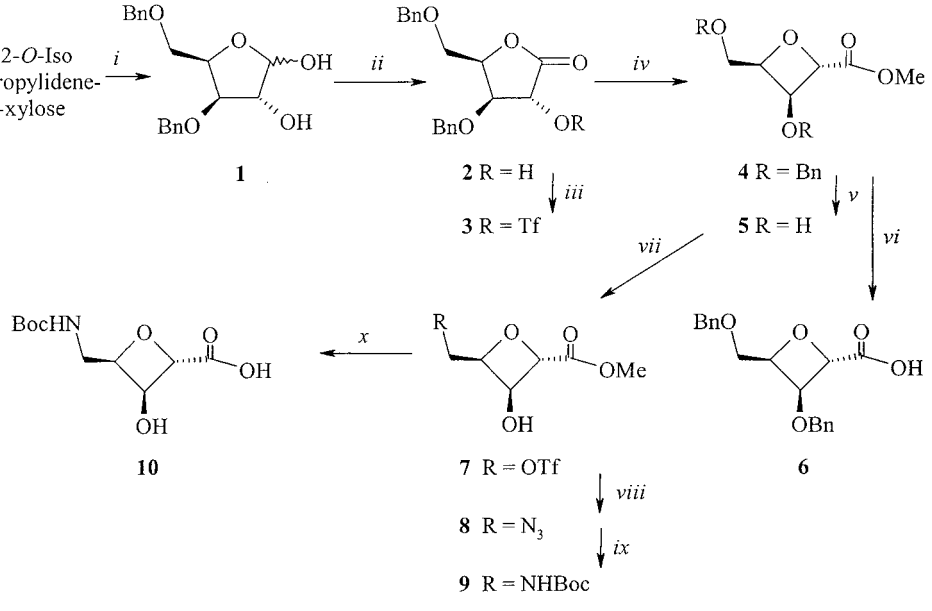
Starting from commercial 1,2-*O*-isopropylidene-D-xylose, 3,5-di-*O*-benzyl-D-xylose (**1**)[4] was prepared in a well-established benzylation/deisopropylidenation sequence. For the acetal cleavage the use of 30% acetic acid gave the best results, conditions that had been employed in the *arabino* series.[5] Oxidation of **1** with bromine furnished the known[6] 3,5-di-*O*-benzyl-D-xylono-γ-lactone (**2**). It was important to carry out this reaction in the dark to avoid radical-mediated debenzylation. By optimizing the water/dioxane ratio, the yield could be improved to reach 73%. Triflation of **2** furnished lactone **3**, which was subjected to treatment with potassium carbonate in methanol leading to ring contraction and formation of the oxetane carboxylic acid ester **4** as described by Witty et al.[6] At this stage we tested whether ester cleavage of the oxetane carboxylic ester was feasible. Indeed, treatment of ester **4** with lithium hydroxide gave the free carboxylic acid **6**[7] in a clean reaction and in excellent yield.



Scheme 1: Carbohydrate-derived oxetane δ-amino acids.

Palladium-catalyzed hydrogenation of **4** yielded the debenzylated oxetane derivative **5**. For this central intermediate an alternative synthetic approach via 3,5-di-*O*-benzylidene-D-xylono-γ-lactone was described recently.[8] For the activation of the primary hydroxyl group we reacted **5** with triflic anhydride in diethyl ether/dichloromethane in the presence of dry molecular sieves; this methodology[9] allows triflation under nonbasic reaction conditions plus facile and mild work-up. Best results were obtained in this case when the reaction mixture was concentrated in the presence of molecular sieves. The triflate **7** was obtained in pure form as judged by TLC, and the residue was reacted without further purification. Crude **7** was then reacted with lithium azide in acetone to furnish azide **8** in 65% yield over the two steps (Scheme 2).

The ring contraction of D-γ-xylono-lactones had been described to result in D-*lyxo* configurated oxetanes.[6] The observation of long-range coupling constants in the resulting derivatives **4** ($J_{2,4} = 0.4$ Hz) and **6** ($J_{2,4} = 0.8$ Hz) did not seem to be in keeping with this configuration as $^{[4]}J$ coupling constants in sterically fixed systems are usually indicative of a W-configuration.[10] Thus, with the observation of a $^{[4]}J_{2,4}$ longe-range coupling, both protons H-2 and H-4 might be expected to be on the same side of the oxetane ring. Therefore, the crystalline azide **8** was subjected to X-ray crystallographic



Scheme 2: *i*) NaH, DMF, rt, 2.5 h, BnBr, 2.5 h; AcOH 30%, reflux, 3 h, 88%; *ii*) Br_2, $BaCO_3$, H_2O/dioxane 2:1, rt, 4 h, 73%; *iii*) Tf_2O, CH_2Cl_2, pyridine, −17°C, 40 min; *iv*) K_2CO_3, MeOH, −12°C, 30 min, 90%; *v*) H_2, Pd/C, MeOH/dioxane, rt, 40 min, 85%; *vi*) 1 N LiOH, THF, 0–5°C, 30 min, quant.; *vii*) Tf_2O, Et_2O/CH_2Cl_2 5:1, 4 Å molecular sieves, −15°C, 50 min; *viii*) LiN_3, acetone, rt, 30 min, 65%; *ix*) H_2, Pd/C, EtOAc, Boc_2O, rt, 2 h, 88%; *x*) L2- *Candida antarctica*, ^{t}BuOMe/H_2O, 45°C, 3 d, 95%.

investigation, (Unit cell parameters: a 7.2699(15) b 21.683(4) c 5.5554(11), space group P212121. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and was allocated the deposition number CCDC 289842. CCDC 289842 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.) which clearly showed the D-*lyxo* configuration with the protons H-2 and H-4 on opposite faces of the oxetane ring (Fig. 1). While the oxetane ring has a relative high pucker angle of 13.5°, this could not account for a W-configuration. Thus, in this case the "W-rule" for ^{1}H NMR longe-range couplings does not apply. X-ray structures of related nonannelated oxetane derivatives prepared by Paternò-Büchi reactions[11] or ring contraction reactions[12] have been described.

The azide **8** was reduced by hydrogenolysis in the presence of Boc anhydride to the protected amine **9** in a very good yield of 88%. To our surprise and in contrast to our experience with the conversion of ester **4** to acid **6**, the transesterification of **9** under basic reaction conditions was not successful in our hands. As interference of the amino group might be expected, the transesterification of azide **8** under basic reaction conditions was investigated, but also led to compound mixtures.

Mild cleavage of the methyl ester **9** could be achieved with pig liver esterase (PLE) under pH control in aqueous reaction media. However, a simple acidic extractive isolation led to degradation of **10**. To avoid the aqueous reaction

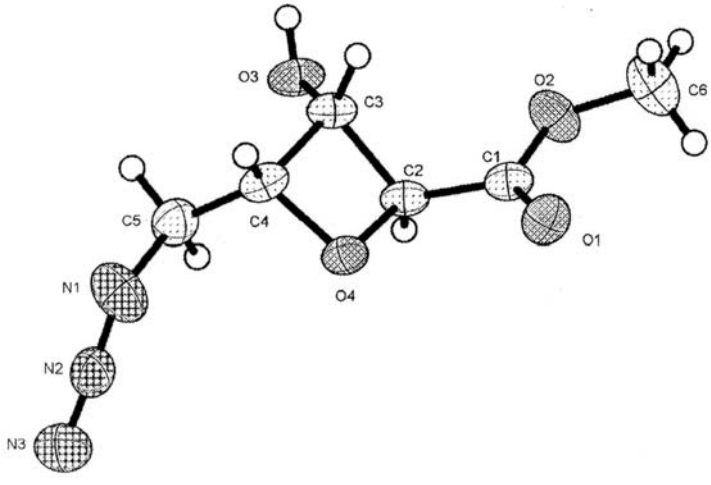


Figure 1: Ortep plot of compound **8**.

media, an enzyme screening for the ester hydrolysis of **9** in micro aqueous systems—organic solvents containing small water contents—was carried out. Several lipases from different microorganisms such as *Candida antarctica, Candida rugosa, Arthobacter ureafaciens, Rhizomucor miehei, Burkholderia cepacia, Thermomyces lanuginose*, or *Aspergillus oryzae* and the polyethylene glycol co-lyophilized esterases[13] from pig liver and *Mucor miehei* displayed hydrolysis activity. The highest activity was shown by lipase L2 from *Candida antarctica*. The product isolation from microaqueous reaction systems could be achieved by simply filtering off the enzyme and evaporation of the organic solvent. Application of the immobilized form of the lipase facilitated the reuse of the enzyme. On a gram scale the free acid **10** was obtained in 91% to 95% yield as a hydroscopic white foam, without purification containing ca. 3% to 4% of the ester **9** and ca. 5% tertiary butyl methyl ether (TBME).

EXPERIMENTAL

General Methods

Solvents and reagents were bought from Fluka; 1,2-*O*-isopropylidene-D-xylose was purchased from Senn Chemicals. Lipase L2 from *Candida antarctica* was purchased from Boehringer Mannheim as lyophilisate (Chirazyme L-2, lyo., BM; 1836021) and in an immobilized form (Chirazyme L2, c.-f. C2, lyo.; 1816969). Solutions were concentrated below 50°C in vacuo on a Büchi rotary evaporator. Qualitative TLC was performed on precoated silica gel 60F-254 plates (Merck); compounds were detected by UV light (254 nm) and spraying with a 10% solution of concd sulfuric acid in methanol or with a cerium sulfate solution followed by heating. Column chromatography was carried out on silica gel (63-200, 60 Å) from Chemie Brunschwig. Melting points were determined with a Büchi 510 capillary apparatus and are uncorrected. Optical rotations were measured on a Perkin Elmer 241 spectrometer in a 1 dm cell at 20°C. ^{1}H NMR spectra were recorded in $CDCl_3$ on Bruker spectrometers Avance 300 (300 MHz) and AM 400 (400 MHz) with an Aspect 3000 and process controller. Chemical shifts are given in ppm relative to tetramethylsilane. Mass spectra were recorded on API III Sciex, Perkin Elmer for negative (ISN) and positive (ISP) electrospray ionization. For the single crystal structure analysis a single crystal was mounted in a loop and cooled to 150 K in a nitrogen stream; data were collected on a STOE Imaging Plate Diffraction System (STOE, Darmstadt) with Mo-radiation (0.71 Å) and data processed with STOE IPDS-software; the crystal structure was solved and refined with ShelXTL (Bruker AXS, Karlsruhe).

3,5-Di-*O*-benzyl-D-xylofuranose (**1**). A suspension of 3,5-di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-xylofuranose[4,5] (43.9 g, 118.5 mmol) in aqueous acetic

acid (30%, 1400 mL) was stirred at reflux (≈112°C) over 3 h. The acetic acid was evaporated under high vacuum. Chromatography with cyclohexane/EtOAc (2:1, 1:1, 2:3) gave **1** (34.63 g, 88%) as a mixture of isomers ($\alpha/\beta = 4{:}1$). α − Isomer: $[\alpha]_D = +5^\circ$ ($c = 0.5$; $CHCl_3$). ^{1}H NMR (COSY, 400 MHz, $CDCl_3$) δ 7.38–7.26 (m, 10H, 2Ph), 5.50 (t, 0.75H, $J_{1\alpha,2\alpha} = 4.8$ Hz, H-1α), 5.10 (d, 0.25H, $J_{,1\beta\text{-OH}} = 11.5$ Hz, $J_{1\beta,2\beta} \sim 0$ Hz, H-1β), 4.71–4.47 (m, 4.25H, 2 OCH_2, H-4β), 4.42 (q, 0.75H, H-4α), 4.26 (dd ∼ t, 0.25 H, $J_{2\beta,3\beta} = 2.4$ Hz, $J_{3\beta,4\beta} = 5.0$ Hz, H-2β), 4.22 (br ddd, 0.75 H, $J_{2\alpha,3\alpha} = 2.4$ Hz, H-2α), 4.02 (dd, 0.25 H, $J_{3\beta,4\beta} = 5.0$ Hz, H-3β), 4.00 (dd ∼ t, 0.75H, $J_{3\alpha,4\alpha} = 5.0$ Hz, H-3α), 3.86 (d, 0.25H, OH-1β), 3.78 (dd, 0.75H, $J_{4\alpha,5a\alpha} = 5.0$ Hz, $J_{5a\alpha,5b\alpha} = 9.8$ Hz, H-5aα), 3.73 (dd, 0.75H, $J_{4\alpha,5b\alpha} = 4.8$ Hz, H-5bα), 3.68 (dd, 0.25H, $J_{4\beta,5a\beta} = 5.5$ Hz, $J_{5a\beta,5b\beta} = 7.0$ Hz, H-5aβ), 3.67 (dd, 0.25H, $J_{4\beta,5b\beta} = 3.8$ Hz, H-5bβ), 3.63 (d, 0.75H, OH-1α), 2.80 (d, 0.75H, $J_{2\alpha,\ 2\alpha\text{-OH}} = 6.0$ Hz, OH-2α), 2.13 (d, 0.25H, $J_{2\beta,\ \text{OH-}2\beta} = 6.0$ Hz, OH-2β).

3,5-Di-*O*-benzyl-D-xylono-γ-lactone (**2**). To a solution of **1** (57.3 g; 0.173 mol) in dioxane (550 mL) was added water (1,100 mL) and barium carbonate (47.93 g; 0.243 mol). Then bromine (71.4 mL; 1.39 mol) 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 sodium carbonate was added. Sodium thiosulfate was added until a white precipitate appeared. The reaction mixture was then filtered over Speedex. The filtrate was concentrated under high vacuum, and after the addition of water (250 mL) the product was extracted with EtOAc (3 × 500 mL). The organic phases were washed with brine and after drying with Mg_2SO_4, filtration, and concentration, the product was crystallized from a mixture of ether and hexane to give colorless crystals of **2** (41.5 g; 73%), mp = 64–65°C, lit.:[6] mp = 70°C. $[\alpha]_D = +54^\circ$ (c 0.5, $CHCl_3$), lit.:[6] $[\alpha]_D = +40.0^\circ$ (c 1.00, $CHCl_3$); MS (ionspray): m/z 346.1 $[M+ NH_4]^+$, 351.3 $[M + Na]^+$. ^{1}H NMR (COSY, 400 MHz, $CDCl_3$): δ 7.39–7.29 (m, 10H, 2Ph), 4.83, 4.66 (2d, 2H, $J_{a,b}$ 12.0 Hz, OCH_aH_bPh), 4.81 (dd, 1H, $J_{2,3}$ 8.0 Hz, H-2), 4.58 (ddd ∼ dt, 1H, $J_{4,5a}$ 2.2 Hz, H-4), 4.58, 4.52 (2d, 2H, $J_{a',b'}$ 12.0 Hz, $OCH_{a'}$-$H_{b'}Ph$), 4.37 (dd ∼ t, 1H, $J_{3,4}$ 8.0 Hz, H-3), 3.79 (dd, 1H, $J_{5a,5b}$ 11.0 Hz, H-5a); 3.71 (dd, 1H, $J_{4,5b}$ 2.8 Hz, H-5b).

3,5-Di-*O*-benzyl-2-*O*-trifluoromethanesulfonyl-D-xylono-γ-lactone(**3**). To a solution of **2** (27 g; 82.2 mmol) in dichloromethane (460 mL) was added pyridine (11.9 mL; 147.9 mmol). Then trifluoromethanesulfonic anhydride (29.8 mL; 139.7 mmol) was added dropwise at −17°C. After stirring for 40 min under argon, trimethanesulfonic acid was neutralized by aqueous sodium carbonate solution (200 mL). The organic layer was extracted three times with dichloromethane and washed with a saturated solution of sodium carbonate. After drying the organic phases with $MgSO_4$, filtration, and concentration of the filtrate, the product was immediately used for the next reaction

step without further purification. MS (ionspray): m/z 478.1 $[M+ NH_4]^+$, 483.3 $[M + Na]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.26 (m, 10H, Ph), 5.89 (d, 1H, $J_{2,3} = 7.9$ Hz, H-2), 4.79, 4.59 (2d, 2H, $J_{a,b} = 11.8$ Hz, OCH_aH_bPh), 4.59, 4.52 (2d, 2H, $J_{a',b'} = 11.8$ Hz, $CH_{a'}H_{b'}Ph$); 4.56 (dd ∼ t, 1H, $J_{3,4} = 7.9$ Hz, H-3), 4.51 (ddd, 1H, $J_{4,5a} = 1.2$ Hz, H-4), 3.74 (dd, 1H, $J_{5a,5b} = 11.0$ Hz, H-5a), 3.66 (dd, 1H, $J_{4,5b} = 2.4$ Hz, H-5b).

Methyl 2,4-Anhydro-3,5-di-*O*-benzyl-D-lyxonate (**4**). To a suspension of triflate **3** (37.8 g; 82 mmol) in absolute methanol (675 mL) at −12°C was added potassium carbonate (11.4 g; 82 mmol). After stirring for 30 min the reaction mixture was filtered over Speedex. The filtrates were concentrated, and the residue was chromatographed (cyclohexane/EtOAc 1:2) to give the expected product as a syrup (25.4 g, 90%); $[\alpha]_D = -18^\circ$ ($c = 0.5$; $CHCl_3$) [lit.:[6] $[\alpha]_D^{20}$ −17.9° (c 1.0, $CHCl_3$)]. MS (ionspray): m/z 360.1 $[M+ NH_4]^+$, 365.3 $[M + Na]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.27 (m, 10H, Ph), 5.06 (dd, 1H, $J_{2,3} = 5.1$ Hz, $J_{2,4} = 0.4$ Hz, H-2), 5.00 (dddd ∼ dq, 1H, $J_{4,5a} = 5.6$ Hz, H-4), 4.62 (dd, 1H, $J_{3,4} = 6.6$ Hz, H-3), 4.60–4.53 (4d, 4H, $J_{a,b} = 12.0$ Hz, $J_{a',b'} = 11.7$ Hz, OCH_aH_bPh), 4.42 (dd, 1H, $J_{5a,5b} = 10.9$ Hz, H-5a), 3.94 (dd, 1H, $J_{4,5b} = 6.0$ Hz, H-5b), 3.81 (s, 3H, CH_3).

Methyl 2,4-Anhydro-D-lyxonate (**5**). To a solution of benzylated **4** (13 g; 38 mmol) in methanol (260 mL) and dioxane (260 mL) was added palladium on charcoal (1.3 g). The reaction mixture was stirred under hydrogen atmosphere for 40 min. The catalyst was then removed by filtration. The filtrate was concentrated and chromatographed over silica gel (EtOAc) to obtain the desired product as syrup (5.24 g, 85%); $[\alpha]_D = -18^\circ$ (c 0.5, $CHCl_3$) [lit.:[7] crystalline solid, $[\alpha]_D^{24}$ −27.1° (c 0.92, $CHCl_3$)]. MS: (ionspray) m/z 180.1 $[M+ NH_4]^+$, 185.3 $[M + Na]^+$. The ^{1}H NMR data were in agreement with published values.[7]

2,4-Anhydro-3,5-di-*O*-benzyl-D-lyxonic acid (6). To a suspension of **4** (100 mg; 0.292 mmol) in THF (5 mL) was added a solution of 1 N LiOH (1 mL; 1 mmol) at 0 to 5°C. After stirring for 30 min, 1 N HCl (1.1 mL; 1.1 mmol) was added, and the reaction mixture was kept at 10°C overnight. The acid was extracted with ethyl acetate. The organic phase was washed with brine, dried, filtered, and concentrated to dryness to obtain after drying overnight under high vacuum the desired compound (95 mg) as a foam, $[\alpha]_D = -10.6^\circ$ (c 1.0, $CHCl_3$). MS: (ionspray) m/z 346.4 $(M + NH_4^+)$, 351.3 $(M + Na^+)$, 674.4 $(2M+ NH_4^+)$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–7.38 (m, 10H, Ph), 5.10 (dd, 1H, $J_{2,3} = 5.1$ Hz, $J_{2,4} = 0.8$ Hz, H-2), 5.03 (dddd ∼ dq, 1H, H-4), 4.64 (dd, 1H, $J_{3,4} = 6.5$ Hz, H-3), 4.62, 4.56 (2d, 2H, $J_{7a,7b} = 11.6$ Hz, CH_2Ph), 4.65, 4.50 (d, 2H, $J_{6a,6b} = 12.0$ Hz, CH_2Ph), 3.96 (d, 1H, $J_{4,5a} = 5.7$ Hz, $J_{5a,5b} = 11.0$ Hz, H-5a), 3.92 (d, 1H, $J_{4,5b} = 6.1$ Hz, H-5b).

Anal. Calcd for $C_{19}H_{20}O_5$ (328.37): C, 69.50; H, 6.14. Found: C, 69.39; H, 6.16.

Methyl 2,4-Anhydro-5-azido-D-lyxonate (**8**). To a suspension of diol **5** (1.014 g; 6.24 mmol) and molecular sieves (4 Å, ca. 1 g) in dry CH_2Cl_2 and dry ether (175 mL; 1:5) at -15°C was added dropwise a solution of trifluoromethanesulphonic anhydride (1.03 mL; 6.55 mmol) in dry ether (175 mL). After stirring for 50 min the mixture was concentrated in a rotary evaporator without heating, and the resulting triflate **7** was used immediately without further purification for the next reaction. MS: m/z 312.0 $[M+ NH_4]^+$, 606.4 $[2M+ NH_4]^+$.

To the crude triflate **7** (1.836 g) in acetone (300 mL), still in the presence of 4 Å molecular sieves, was added lithium azide (3.06 g; 62.4 mmol). After stirring for 30 min the reaction mixture was concentrated and then washed with 100 mL of iced water. The organic layer was then extracted five times with TBME, washed with brine, dried over Mg_2SO_4, and filtered, and the filtrate was concentrated. Chromatography of the residue over silica gel (ethyl acetate/cyclohexane 1:1) furnished the pure product **8** (766 mg; 65%) as a colorless solid, m.p. 67–70°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ5.08 (d, 1H, $J_{2,3} = 5.3$ Hz, H-2), 4.95 (ddd, 1H, $J_{4,5a}$ 4.3 = Hz, H-4), 4.87 (dd, 1H, $J_{3,4} = 7.0$ Hz, H-3), 3.85 (dd, 1H, $J_{5a,5b} = 13.6$ Hz, H-5a), 3.83 (s, 3H, OCH3), 3.62 (dd, 1H, $J_{4,5b} = 3.3$ Hz, H-5b).

Methyl 2,4-Anhydro-5-*N*-(*t*-butoxycarbonyl)amino-D-lyxonate (**9**). A suspension of palladium-on-charcoal (10%, 100 mg) in EtOAc (20 mL) was vigorously stirred for 30 min under a hydrogen atmosphere. A mixture of azide **8** (510.2 mg; 2.73 mmol) and Boc_2O (705 mg; 3.25 mmol) in EtOAc (15 mL) was added. The reaction mixture was stirred for 2 h and filtered, and the solvent was evaporated. Chromatography over silica gel (EtOAc/cyclohexane 1:2) of the residue gave the pure product **9** (624.8 mg; 88%) as a colorless solid, m.p. 93–96°C. MS: (ionspray) m/z 262.0 $[M + H]^+$; 279.1 $[M+ NH_4]^+$, 280.3 $[M + Na]^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.01 (dd ~ t, 2H, NH and OH), 4.81 (d, 1H, $J_{2,3} = 3.8$ Hz, H-2), 4.79 (ddd, 1H, $J_{4,5b} = 6.2$ Hz, H-4), 4.76 (ddd ~ dd, 1H, $J_{3,4} = 3.2$ Hz, H-3), 3.81 (s, 3H, OCH3), 3.78 (ddd ~ dd, 1H, $J_{4,5a} = 7.1$ Hz, H-5a), 3.30 (ddd ~ dd, 1H, $J_{5a,5b} = 13.4$ Hz, H-5b), 1.44 (s, 9H, Boc).

Anal. Calcd for $C_{11}H_{19}NO_6$ (261.28): C, 50.57; H, 7.33; N, 5.36. Found: C, 50.48; H, 7.36; N, 5.33.

2,4-Anhydro-5-*N*-(*t*-butoxycarbonyl)amino-D-lyxonic Acid (**10**). To a solution of carboxylic ester **9** (1.0 g; 3.645 mmol) in TBME saturated with water (330 mL) was added commercial lipase L2-*Candida antarctica* (500 mg) at 45°C. The reaction mixture was stirred for 3 days. After filtration of the immobilized enzyme the concentration of filtrate gave the crude product **10** as a colorless foam (941 mg, 105%) containing 4.3% ester **9** and 5% TBME.

$[\alpha]_D = -4.7^\circ$ (*c* 1.1, MeOH) MS (ionspray neg.): *m/z* 246.3 $[M\text{-}H]^-$, 493.3 $[2M\text{-}H]^-$, 515.3 $[2M\text{-}H + Na]^-$. ^1H NMR (300 MHz, CD_3OD): δ 4.78 (d, 1H, H-2), 4.64 (dd $\sim$ t, 1H, $J_{2,3} = 5.7$ Hz, $J_{3,4} = 6.9$ Hz, H-3), 4.61 (ddd, 1H, H-4), 3.44 (dd, 1H, $J_{4,5a} = 4.9$ Hz, $J_{5a,5b} = 14.5$ Hz, H-5a), 3.36 (dd, 1H, $J_{4,5b} = 6.2$ Hz, H-5b), 1.34 (s, 9H, Boc).

Anal. Calcd for $C_{10}H_{17}NO_6$ (247.25): C, 48.58; H, 6.93; N, 5.67. Found: C, 49.12; H, 6.92; N, 5.32.

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