Tetrahedron 64 (2008) 9989–9991

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

New approach to (−)-polyoxamic acid and 3,4-diepipolyoxamic acid from D-lyxono-1,4-lactone

Céline Falentin, Daniel Beaupère, Gilles Demailly, Imane Stasik *

Laboratoire des Glucides, UMR 6219, Université de Picardie Jules Verne, 33 Rue Saint-Leu, F-80039 Amiens, France

ARTICLE INFO

Article history:
Received 24 June 2008
Received in revised form 21 July 2008
Accepted 22 July 2008
Available online 26 July 2008

ABSTRACT

The non-natural enantiomer of polyoxamic acid (**1**) and 3,4-diepipolyoxamic acid (**2**) was synthesized in four steps from D-lyxono-1,4-lactone (**4**). Regioselective bromination of unprotected D-lyxono-1,4-lactone with HBr/AcOH led to 2-bromo-2-deoxy-D-xylono-1,4-lactone (**5**). This intermediate was treated with NaN_3 to give 2-azido-2-deoxy-D-lyxono and xylono-1,4-lactones. Saponification of the obtained 2-azido derivatives gave the corresponding 2-azido-2-deoxyaldonic acids salt which, after neutralization followed by reduction, led to the expected compounds: (−)-polyoxamic acid (**3**) and 3,4-diepipolyoxamic acid (**2**) in 38% and 29% overall yields.

1. Introduction

Polyoxins[1] are a group of unusual peptidyl nucleosidic antibiotics isolated from the culture broths of *Streptomyces cacoi* var. *asoensis*. They have been characterized by Isono and co-workers about 40 years ago.[1e] The polyoxins incorporate carbamoylated polyoxamic acid linked to the sugar moiety by an amide bond. They act against the pathogenic fungus that causes the sheath blight disease of the rice plant by inhibiting membrane bound enzyme chitin synthase.[2] They are also therapeutically useful against *Candida albicans*, a fungal pathogen that affects humans.[3] Saponification of polyoxins results in several products, one of which has been identified as (+)-polyoxamic acid (**1**) (Fig. 1).

The sphingofungins (Fig. 2) are a new family of antifungal agents, isolated by Merck group in 1992.[4a] They inhibit serinepalmitoyl transferase,[4] also consist of 3,4-diepipolyoxamic acid **2** head groups.

Interests in the field of chemistry and biology have led to the development of a number of syntheses of polyoxamic acid and its isomers, such as its non-natural enantiomer (**3**) or its stereoisomer 3,4-diepipolyoxamic acid (**2**)[5] (Fig. 1) over the past 20 years. A variety of chemical syntheses are based on the use of chiral auxiliaries or on carbohydrate chemistry.[6] However, most of them involve a large number of steps and, therefore, a practical short route to these amino acids still remains of interest.

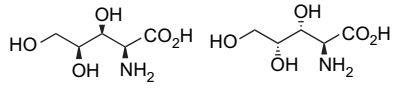
Herein, we describe a concise synthetic route to polyhydroxy amino acids: 3,4-diepipolyoxamic acid (**2**) and (−)-polyoxamic acid (**3**), from unprotected D-lyxono-1,4-lactone (**4**), in four steps (Scheme 1).

2. Results and discussion

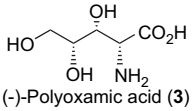
D-Lyxono-1,4-lactone was used as the key starting material for the synthesis of 3,4-diepipolyoxamic acid (**2**) and (−)-polyoxamic acid (**3**). For the synthesis of D-lyxono-1,4-lactone, which was not commercially available like other aldopentonolactones of the D-series, we oxidized D-lyxose, using a modified procedure, and obtained the title product, which was isolated in quantitative yield (bromine water in the presence of sodium hydrogencarbonate).[7]

The selective bromination of D-lyxolono-1,4-lactone (**4**) using HBr in acetic acid (HBA) gave the 2-bromo-2-deoxy-D-xylono-1,4-lactone (**5**) (90%), contaminated with a small amount of 2,5-dibromo derivative (10%).

When 2-bromo-2-deoxy-D-xylono-1,4-lactone (**5**) was treated, in the same conditions as the ones we have used for azidation of hexono or pentonolactones, with sodium or lithium azide in *N*,*N*-dimethylformamide,[7,8] a complex mixture was obtained. NMR



(+)-Polyoxamic acid (**1**) 3,4-Diepipolyoxamic acid (**2**)



(-)-Polyoxamic acid (**3**)

Figure 1.

* Corresponding author. Tel.: +33 3 22 82 75 66; fax: +33 3 22 82 75 60.
E-mail address: imane.Stasik@sc.u-picardie.fr (I. Stasik).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.07.095

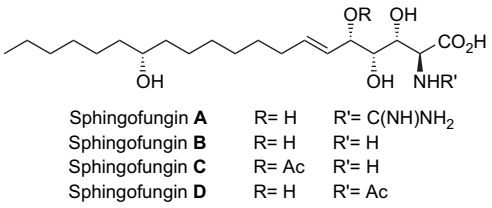


Figure 2.

analysis showed that this mixture contains predominantly four compounds: the compound **5**, its 2-epimer, 2-azido-2-deoxy-D-lyxono-1,4-lactone (**6**) and 2-azido-2-deoxy-D-xylono-1,4-lactone (**7**). We had previously observed such epimerisation, due to C-2 and C-3 configuration, during azidation and thioetherification of 5-bromo-5-deoxy-D-ribono-1,4-lactone.[8,9] However, treatment of 2-bromo-2-deoxy-D-xylono-1,4-lactone (**5**) with sodium azide in acetone or acetonitrile gave 1:1 mixture of (**6**) and (**7**). The obtained residue was chromatographed on silica gel to yield the pure isomers **6** and **7** in 32% and 42% yields, respectively.

When 2-azido-2-deoxy-D-lyxono-1,4-lactone (**6**) was treated with NaOH (1 equiv), in EtOH/water at room temperature for 1 h, a partial epimerization at the level of position 2 takes place and mixture (1:1) of 2-azido-2-deoxy-D-lyxonic acid sodium salt and 2-azido-2-deoxy-D-xylonic acid sodium salt was obtained in quantitative overall yield. When saponification of **6** was performed with LiOH instead of NaOH, 2-azido-2-deoxy-D-lyxonic acid lithium salt was obtained as the only product as seen from the ^{13}C NMR spectrum.

Treatment with acidic resin (Amberlite IR-120H$^+$) of 2-azido-2-deoxy-D-lyxonic acid lithium salt gave 2-azido-2-deoxy-D-lyxonic acid (**8**). Catalytic hydrogenation of **8** over palladium on charcoal (10%), in water at room temperature for 2 h, produced after filtration and concentration the desired 3,4-diepipolyoxamic acid (**2**).

Treatment of 2-azido-2-deoxy-D-xylono-1,4-lactone (**7**) with LiOH as in the case of **6** followed by addition of the acidic resin afforded 2-azido-2-deoxy-D-xylonic acid (**9**) in quantitative yield. Catalytic hydrogenation of **9** gave the target product (−)-polyoxamic acid (**3**) in quantitative yield.

In summary, we have reported a rapid and direct synthesis of non-natural enantiomer of polyoxamic acid (**3**) and 3,4-di-epipolyoxamic acid (**2**), which was synthesized in four steps in 38% and 29% overall yields, respectively, from D-lyxono-1,4-lactone.

3. Experimental

3.1. General

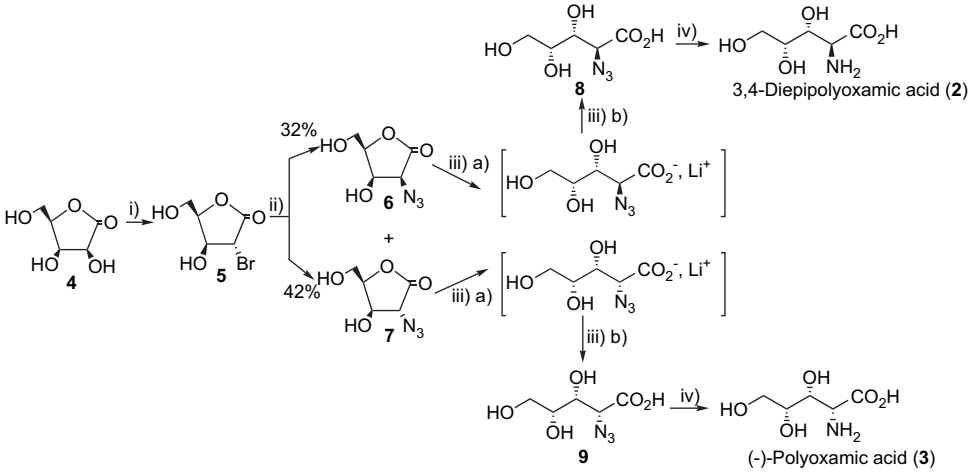
Melting points were determined on a Büchi 535 apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-370 digital polarimeter, using a sodium lamp (λ=589 nm) at 20 °C. ^1H and ^{13}C NMR spectra were recorded in D_2O or in DMSO-d_6 on a Bruker 300 MHz spectrometer; Me_4Si was used as an internal standard. Mass spectra were recorded on a Q-TOF Global mass spectrometer in ESI mode. Thin-layer chromatography (TLC) was performed on E. Merck glass plates silica gel sheets (Silica Gel F_{254}) and stained with cerium molybdate acid/aq H_2SO_4 solution. Column chromatography was carried out on silica gel (E. Merck 230–400 mesh). All solvents were purified in a conventional manner.

3.1.1. D-Lyxono-1,4-lactone (**4**)

To a solution of D-lyxose (3 g, 20 mmol) and sodium hydrogencarbonate (5.96 g, 30 mmol) in distilled water (25 mL) cooled at 0 °C, bromine (3×0.38 mL, 22 mmol) was added at 20 min interval. The reaction mixture was stirred at this temperature for 1 h and then for 3 h at room temperature. Sodium thiosulfate was added to destroy the excess of bromine. The solvent was removed in vacuo to give white solid. The white solid was extracted twice by boiling acetone (250 mL). The mixture was filtered and the filtrate was concentrated in vacuo to give quantitatively **4** as colourless oil; $[\alpha]_D^{20}$ +76 (*c* 1.4, MeOH); lit.[10] $[\alpha]_D^{20}$ +72.9 (*c* 4, H_2O); ^1H NMR (300 MHz, DMSO-d_6) δ 4.42 (d, 1H, *J*=4.7 Hz), 4.30 (m, 1H), 4.20 (dd, 1H, *J*=3.0 Hz), 3.67 (dd, 1H, *J*=7.1 Hz), 3.59 (dd, 1H, *J*=12 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 176.1, 80.4, 70.3, 68.9, 59.3; ESIMS: *m*/*z* calcd $[M+Na]^+$ for $C_5H_8O_5$: 171, found: 171.

3.1.2. 2-Bromo-2-deoxy-D-xylono-1,4-lactone (**5**)

A solution of D-Lyxono-1,4-lactone (500 mg, 3.38 mmol) in HBA (5 mL) was kept for 1 h at room temperature. Methanol (10 mL) was then added and the solution was kept overnight and then concentrated. The resulting syrup was dissolved in chloroform (20 mL) and the solution was extracted with water (6×10 mL). The combined extracts were concentrated. Flash chromatography (EtOAc/cyclohexane, 1:1) gave 2-bromo-2-deoxy-D-xylono-1,4-lactone (**5**) (660 mg, 90%) as white solid; $[\alpha]_D^{20}$ +36 (*c* 0.22, water); mp 80–82 °C; lit.[11] $[\alpha]_D^{20}$ +26 (*c* 2.5, AcOEt); mp 86.5–87.5 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 4.62 (q, 1H, *J*=8.8 Hz), 4.52 (d, 1H, *J*=4.5 Hz,), 4.48 (t, 1H, *J*=4.8 Hz), 3.70 (m, 2H); ^{13}C NMR (75 MHz,



Scheme 1. Reagents and conditions: (i) HBr/AcOH, rt, 90%; (ii) NaN_3, CH_3CN, 95 °C, 6 h, 80%; (iii) (a) LiOH, EtOH/H_2O, rt, 100%; (b) Amberlite IR-120H$^+$, 100%; (iv) H_2/Pd/C, H_2O, rt, 2 h, 100%.

DMSO-d_6): δ 171.9, 82.9, 73.8, 58.7, 44.3; ESIMS: m/z calcd $[M+Na]^+$ for $C_5H_7BrO_4$: 234, found: 234.

*3.1.3. 2-Azido-2-deoxy-D-lyxono (**6**) and 2-azido-2-deoxy-D-xylono-1,4-lactone (**7**)*

To a solution of 2-bromo-2-deoxy-D-xylono-1,4-lactone (**5**) (930 mg, 14.3 mmol) in CH_3CN (10 mL) was added NaN_3 (582 mg, 8.95 mmoL). The mixture was refluxed for 6 h. Filtration and concentration gave a residue, which was chromatographed (EtOAc/cyclohexane, 4:6) to give the *lyxo* isomer (**6**) (240 mg, 32%) as colourless oil; $[\alpha]_D^{20}$+38 (*c* 0.25, water); ^{1}H NMR (300 MHz, D_2O): δ 4.79 (dd, 1H, *J*=4.8 Hz), 4.65 (d, 1H, *J*=3.0 Hz), 4.61 (m, 1H), 3.86 (t, 2H, *J*=6.5 Hz); ^{13}C NMR (75 MHz, D_2O): δ 174.7, 82.9, 69.9, 62.2, 59.5; ESIMS: m/z calcd $[M+Na]^+$ for $C_5H_7N_3O_4$: 196, found: 196. The *xylo* isomer (**7**) was then isolated (320 mg, 42%) as colourless solid; $[\alpha]_D^{20}$ +142 (*c* 0.22, water); mp 80–82 °C; lit.[12] mp 80–82 °C; ^{1}H NMR (300 MHz, D_2O): δ 4.77 (d, 1H, *J*=8.6 Hz), 4.70 (ddd, 1H, *J*=4.6 Hz), 4.60 (dd, 1H, *J*=7.7 Hz), 3.91 (t, 2H, *J*=3.0 Hz); ^{13}C NMR (75 MHz, D_2O): δ 174.2, 81.2, 71.5, 63.1, 58.7; ESIMS: m/z calcd $[M+Na]^+$ for $C_5H_7N_3O_4$: 196, found: 196.

*3.1.4. General procedure for the preparation of 2-azido-2-deoxy-D-lyxonic acid (**8**) and 2-azido-2-deoxy-D-xylonic acid (**9**)*

To a solution of 2-azido-2-deoxy-D-pentonolactones (**6** or **7**) (210 mg, 1.21 mmol) in 3:1 EtOH/water (2 mL) was added LiOH (1 equiv). The reaction mixture was stirred at room temperature for 1 h and EtOH (2 mL) was added. The suspension was filtered and the obtained white solid was washed with 3:1 EtOH/water (2 mL) to give the desired 2-azido-2-deoxy-D-aldonic acid lithium salt. A solution of the obtained 2-azido-2-deoxy-D-pentanoic acid lithium salt in water was treated with Amberlite IR-120H$^+$. The suspension was stirred for 5 min at room temperature, the resin was filtered off and the filtrate was concentrated under diminished pressure to give the desired azido acid **8** or **9**.

*3.1.4.1. 2-Azido-2-deoxy-D-lyxonic acid (**8**).* Yield 250 mg, 100%; white solid; $[\alpha]_D^{20}$ +17 (*c* 0.34, water); mp 120–125 °C; ^{1}H NMR (300 MHz, D_2O): δ 3.93 (d, 1H, *J*=3.2 Hz), 3.71 (dd, 1H, *J*=4.0 Hz), 3.64 (m, 1H), δ 3.57 (m, 2H); ^{13}C NMR (75 MHz, D_2O): δ 175.2, 72.4, 72.2, 66.4, 62.5; ESIMS: m/z calcd $[M+Na]^+$ for $C_5H_9N_3O_5$: 214, found: 214.

*3.1.4.2. 2-Azido-2-deoxy-D-xylonic acid (**9**).* Yield 248 mg, 100%; white solid; $[\alpha]_D^{20}$ −31 (*c* 0.35, water); mp 190–194 °C; ^{1}H NMR (300 MHz, D_2O): δ 4.09 (d, 1H, *J*=6.5 Hz), 3.88 (m, 1H), δ 3.86 (m, 1H), 3.70 (dd, 1H, *J*=5.0 Hz), 3.62 (dd, 1H, *J*=11.0 Hz); ^{13}C NMR (75 MHz, D_2O): δ 175.4, 71.0, 70.9, 66.5, 62.8; ESIMS: m/z calcd $[M+Na]^+$ for $C_5H_9N_3O_5$: 214, found: 214.

*3.1.5. General procedure for the preparation of 3,4-diepipolyoxamic acid (**2**) and (−)-polyoxamic acid (**3**)*

To a solution of the obtained 2-azido-2-deoxy-D-pentanoic acid (100 mg, 0.52 mmol) in water (2.5 mL) was added palladium on charcoal (10%, 34 mg) and the suspension was hydrogenated for 2 h at room temperature. The mixture was filtered through a layer of Celite to give the desired 2-amino-2-deoxy-D-pentanoic acid.

*3.1.5.1. 3,4-Diepipolyoxamic acid (**2**).* Yield 85 mg, 100%; white solid; $[\alpha]_D^{20}$ +12 (*c* 0.23, water); mp 142–145 °C; lit.[5] mp 145–150 °C; ^{1}H NMR (300 MHz, D_2O): δ 4.00 (t, 1H, *J*=7.2 Hz), 3.85 (m, 1H), 3.67 (m, 2H), 3.57 (d, 1H, *J*=3.6 Hz); ^{13}C NMR (75 MHz, D_2O): δ 176.5, 72.9, 70.0, 62.5, 58.0; ESIMS: m/z calcd $[M+Na]^+$ for $C_5H_{11}NO_5$: 188, found: 188.

*3.1.5.2. (−)-Polyoxamic acid (**3**).* Yield 84 mg, 100%; white solid; $[\alpha]_D^{20}$ −7 (*c* 0.22, water); mp 150–155 °C; lit.[6c] mp 151–153 °C; ^{1}H NMR (300 MHz, D_2O): δ 3.86 (m, 1H), 3.82 (dd, 1H, *J* 2.3 Hz), 3.68 (m, 2H), 3.57 (d, 1H, *J* 5.4 Hz); ^{13}C NMR (75 MHz, D_2O): δ 178.5, 71.5, 71.0, 63.0, 58.2; ESIMS: m/z calcd $[M+Na]^+$ for $C_5H_{11}NO_5$: 188, found: 188.

Acknowledgements

We thank the Ministère de la Recherche, the Conseil Régional de Picardie and the CNRS for financial support.

References and notes

1. (a) Suzuki, S.; Isono, K.; Mizutani, T.; Kawashima, Y.; Mizuno, T. *J. Antibiot.* **1965**, *A18*, 131–134; (b) Isono, K. *J. Antibiot.* **1988**, *41*, 1711–1739; (c) Isono, K. *Pharmacol. Ther.* **1991**, *52*, 269–286; (d) Isono, K.; Suzuki, S. *Heterocycles* **1979**, *13*, 333–351 (review); (e) Isono, K.; Asahi, K.; Suzuki, S. *J. Am. Chem. Soc.* **1969**, *91*, 7490–7505.
2. Hori, M.; Kakiki, K.; Misato, T. *Agric. Biol. Chem.* **1974**, *38*, 699–705.
3. Shenbagamurthi, P.; Smith, H. A.; Becker, J. M.; Steinfeld, A.; Naider, F. *J. Med. Chem.* **1983**, *26*, 1518–1522.
4. (a) VanMiddlesworth, F.; Giacobbe, R. A.; Lopez, M.; Garrity, G.; Bland, J.; Zweerink, M.; Edison, A. M.; Rozdilsky, W.; Wilson, K. E.; Monaghan, R. A. *J. Antibiot.* **1992**, *45*, 861–867; (b) VanMiddlesworth, F.; Dufresne, C.; Wincott, F. E.; Mosley, R. T.; Wilson, K. E. *Tetrahedron Lett.* **1992**, *33*, 297–300.
5. Li, S.; Hui, X. P.; Yang, S. B.; Jia, Z. J.; Xu, P. F.; Lu, T. J. *Tetrahedron: Asymmetry* **2005**, *16*, 1729–1731.
6. (a) Collet, M.; Génisson, Y.; Baltas, M. *Tetrahedron: Asymmetry* **2007**, *18*, 1320–1329; (b) Enders, D.; Vrettou, M. *Synthesis* **2006**, *13*, 2155–2158; (c) Tarrade, A.; Dauban, P.; Dodd, R. H. *J. Org. Chem.* **2003**, *68*, 9521–9524; (d) Kim, K. S.; Lee, Y. J.; Kim, J. H.; Sung, D. K. *Chem. Commun.* **2002**, 1116–1117; (e) Pepper, A. G.; Procter, G.; Voyle, M. *Chem. Commun.* **2002**, 1066–1067; (f) Bose, A. K.; Banik, B. K.; Mathur; Wagle, C.; Dilip, R.; Manhas, M. S. *Tetrahedron* **2000**, *56*, 5603–5619; (g) Uchida, K.; Kato, K.; Yamaguchi, K.; Akita, H. *Heterocycles* **2000**, *53*, 2253–2260; (h) Ghosh, A. K.; Wang, Y. *Tetrahedron* **1999**, *55*, 13369–13376; (i) Uchida, K.; Kato, K.; Akita, H. *Synthesis* **1999**, 1678–1686; (j) Ghosh, A. K.; Wang, Y. *J. Org. Chem.* **1999**, *64*, 2789–2795; (k) Savage, I.; Thomas, E. J.; Wilson, P. D. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3291–3303; (l) Harwood, L. M.; Robertson, S. M. *Chem. Commun.* **1998**, 2641–2642; (m) Veeresa, G.; Datta, A. *Tetrahedron Lett.* **1998**, *39*, 119–122; (n) Kang, S. H.; Choi, H. W. *Chem. Commun.* **1996**, 1521–1523; (o) Trost, B. M.; Krueger, A. C.; Bunt, R. C.; Zambrano, J. *J. Am. Chem. Soc.* **1996**, *118*, 6520–6521; (p) Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1994**, *35*, 733–735; (q) Chida, N.; Koizumi, K.; Kitada, Y.; Yokoyama, C.; Ogawa, S. J. *J. Chem. Soc., Chem. Commun.* **1994**, 111–113; (r) Jackson, R. F. W.; Palmer, N. J.; Wythes, M. J. *J. Chem. Soc., Chem. Commun.* **1994**, 95–96; (s) Casiraghi, G.; Passu, G.; Spanu, P.; Pinna, L. *Tetrahedron Lett.* **1994**, *35*, 2423–2426; (t) Ariza, J.; Diaz, M.; Font, J.; Ortuno, R. M. *Tetrahedron* **1993**, *49*, 1315–1326; (u) Dondoni, A.; Franco, S.; Metchan, L.; Merino, P.; Tejero, T. *Tetrahedron Lett.* **1993**, *34*, 5475–5478; (v) Banik, B. K.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1993**, *58*, 307–309; (w) Savage, L.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1989**, 717–719; Garner, P.; Park, J. M. *J. Org. Chem.* **1988**, *53*, 2979–2984; (x) Dureault, A.; Careaux, F.; Depezay, J. C. *Tetrahedron Lett.* **1989**, *30*, 4527–4530; (y) Hirama, M.; Hioki, H.; Ito, S. *Tetrahedron Lett.* **1988**, *29*, 3125–3128; (z) Saksena, A. K.; Lovey, R. G.; Girijavallabhan, V. M.; Ganguly, A. K. *J. Org. Chem.* **1986**, *51*, 5024–5028.
7. Chaveriat, L.; Stasik, I.; Demailly, G.; Beaupère, D. *Tetrahedron* **2004**, *60*, 2079–2081.
8. Bouchez, V.; Stasik, I.; Beaupère, D.; Uzan, R. *Tetrahedron Lett.* **1997**, *38*, 7733–7736.
9. Lalot, J.; Manier, G.; Stasik, I.; Demailly, G.; Beaupère, D. *Carbohydr. Res.* **2001**, *335*, 55–61.
10. Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1: Org. Bioorg. Chem.* **1989**, *3*, 665–666.
11. Bock, K.; Lundt, I.; Pedersen, C. *Carbohydr. Res.* **1981**, *90*, 17–26.
12. Bols, M.; Lundt, I. *Acta Chem. Scand.* **1988**, *B42*, 67–74.