Carbohydrate Research 346 (2011) 508–511

Contents lists available at ScienceDirect

Carbohydrate Research

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

Note

Synthesis of a protected trihydroxyindolizidine 3-carboxylate via a hetero-Diels–Alder addition of ethyl 2-nitrosoacrylate to a D-ribose-derived *exo*-glycal

Zoe S. Massen, Evdoxia Coutouli-Argyropoulou, Vassiliki C. Sarli, John K. Gallos *

Department of Chemistry, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece

ARTICLE INFO

Article history:
Received 9 December 2010
Received in revised form 28 December 2010
Accepted 29 December 2010
Available online 3 January 2011

Keywords:
Polyhydroxylated indolizidine alkaloids
Ethyl bromopyruvate
Ethyl 2-nitrosoacrylate
Hetero-Diels–Alder cycloaddition
exo-Glycals
Catalytic hydrogenation

ABSTRACT

A protected trihydroxyindolizidine 3-carboxylate was prepared by a 6-*endo* epoxide cleavage, which in turn was intermediately formed from the hetero-Diels–Alder adduct of ethyl 2-nitrosoacrylate to a D-ribose-derived *exo*-glycal.

Alkaloids mimicking the structures of monosaccharides are widespread in plants and microorganisms; among them, those with nitrogen in the ring (also called aza-sugars) can be classified into five structural classes: pyrrolidines, piperidines, pyrrolizidines, indolizidines and nortropanes.[1] Many of them exhibit specific glycosidase and glycosyltranferase inhibition, being thus potential therapeutical agents.[2] Glycosidases and glycosyltransferases are involved in a variety of important biological processes, such as intestinal digestion, post-translational processing of glycoproteins and the lysosomal catabolism of glycoconjugates, and it has been shown that their inhibition is related to many diseases, such as viral and microbial infection, cancer metastasis, diabetes and other metabolic disorders.

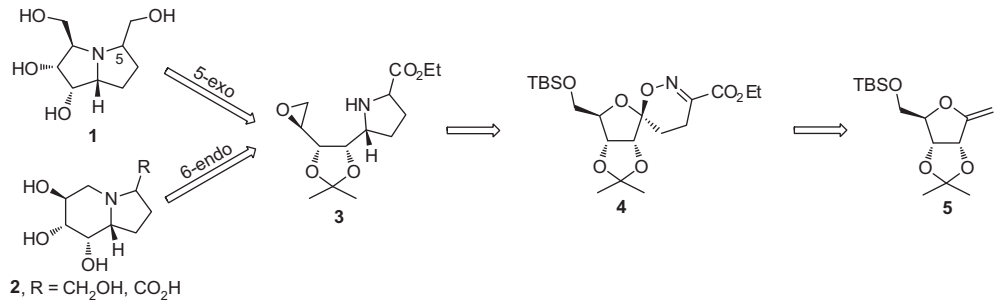
Among the plethora of pyrrolizidine alkaloids, the members of hyacinthacine family[3] such as *hyacinthacine* B_1 [(5*R*)-**1**] and *hyacinthacine* B_2 [(5*S*)-**1**] (Scheme 1), with a carbon branch both at C-3 and C-5 positions, were isolated from the bulbs of *Muscari armenicum* and *Hyacinthoides non-scripta*, and some of them act as inhibitors against a variety of glycosidases. Because of their current interest as potential drugs, pyrrolizidine alkaloids have become popular synthetic targets[4] and a number of new synthetic analogues have been prepared. Also, polyhydroxylated indolizidine alkaloids,[5] such as the well known (−)-swainsonine and (+)-castanospermine, exhibit effective glycosidase inhibition and potential therapeutic applications as antidiabetic, antiviral, anticancer and antimetastatic immunoregulating agents. In addition, aza-glycuronic acid mimetics and related compounds have been found to show glycosidase inhibitory activities.[6]

Inspired from these structures, we considered that *hyacinthacines* B_1 and B_2 (**1**) and the indolizidine analogues **2** could be prepared from D-ribose via epoxide **3** as the crucial reactive intermediate. Intramolecular 5-*exo* epoxide opening[7] could lead to hyacinthacines **1**, whereas a 6-*endo* process will afford the respective indolizidine **2** precursors. Compound **3**, in turn, could be prepared from D-ribose-derived *exo*-glycal **5** by adding ethyl 2-nitrosoacrylate (in situ generated from the oxime of ethyl bromopyruvate) to give **4** and further proper manipulation. Some years ago, we efficiently synthesised enantiomerically pure unnatural hydroxylated pyrrolizidines[8] by stereoselective hetero-Diels–Alder addition of ethyl 2-nitrosoacrylate to easily prepared pent-4-enofuranosides and further manipulations of adducts.

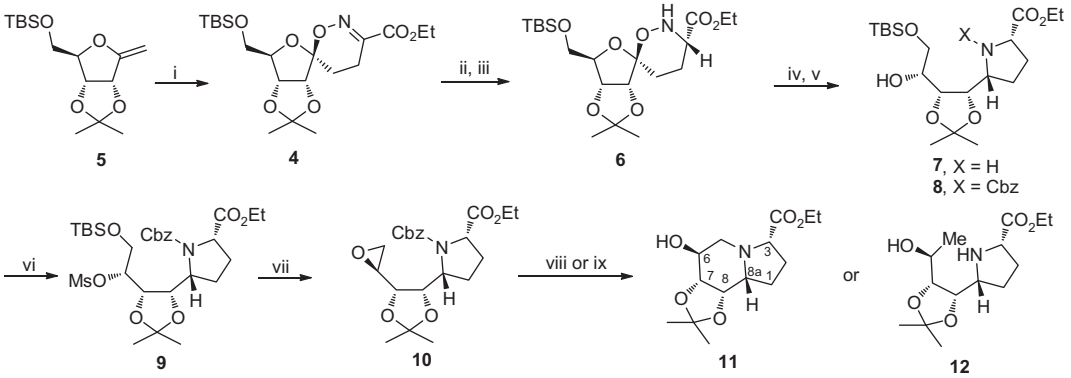
In a recent publication we reported the addition of ethyl 2-nitrosoacrylate to *exo*-glycal **5**[9] as indicated in Scheme 2. The resulting cycloadduct **4** was then firstly reduced by $NaCNBH_3$ to give a mixture of **6** and its epimer in very good yield, but with poor diastereoselectivity, and then this mixture was epimerised by Et_3N to the thermodynamically more stable isomer **6**. In fact, the oxazine ring of this epimer adopts a chair-like conformation that brings the CO_2Et group equatorial and the ribose O-substituent axial, the latter being favoured by the anomeric effect. N–O Bond scission in this compound by hydrogenation with H_2 over Raney

* Corresponding author. Tel.: +30 2310 997714; fax: +30 2310 997679.
E-mail address: igallos@chem.auth.gr (J.K. Gallos).

0008-6215/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2010.12.022



Scheme 1. Retrosynthetic analysis of hyacinthacines **1** and indolizidines **2**.



Scheme 2. Reagents and conditions: (i) $BrCH_2C(NOH)CO_2Et$ (2 equiv), Na_2CO_3 (5 equiv), CH_2Cl_2, 20 °C, 24 h, 64%; (ii) $NaCNBH_3$ (4 equiv), AcOH glacial, 20 °C, 24 h; (iii) $CHCl_3$, Et_3N (cat.), reflux, 30 min, 80% from **4**; (iv) Raney Ni, H_2, MeOH, H_3BO_3, reflux, 75%; (v) Cbz-Cl, Et_3N, MeOH, 0–20 °C, 8 h, 50% (35% of **7** recovered); (vi) MsCl, DMAP, pyridine, 0 °C, 90 min, 74%; (vii) TBAF, THF, 0 °C, 12 h, 80%; (viii) Pd/C, 1,4-cyclohexadiene, EtOH, 20 °C, 1 h, 73% to **11**; (ix) Pd/C, H_2, MeOH, 20 °C, 2 h, 86% to **12**.

Ni in MeOH in the presence of boric acid[10] gave in a highly stereoselective manner the proline derivative **7** in 75% yield. In the next step, the amino group was protected with Cbz (50% yield and 35% of **7** recovered) and the free hydroxyl group was mesylated to give **9** in 74% yield. Removal of the TBS group with TBAF in THF afforded spontaneously the epoxide **10** with inversion of C-4 configuration (ribose numbering).

Deprotection of amino group, which activates the pyrrolidine nitrogen towards nucleophilic substitution, was found to be quite tricky. Removal of Cbz group by hydrogenation with H_2 over Pd/C caused the epoxide reduction and compound **12** was prepared in 86% yield. After several attempts, we found that hydrogenation over Pd/C with cyclohexadiene as a hydrogen donor, afforded indolizidine **11** by a 6-*endo* mode as the sole product in 73% yield.

The proton signal assignment of compound **11** was made by H,H-COSY and decoupling experiments. The proposed stereochemistry of compound **11** was supported by NOE measurements performed in $CDCl_3/C_6D_6$ 5/1 solution, where some of the signals useful for stereochemical assignment could appear separately. Significant NOE enhancements were observed between the bridged 8a-H (δ 2.46) and the 3-H (δ 3.19) of the indolizidine frame (5% enhancement of 3-H upon saturation of the bridged proton and 4% enhancement of the 8a-H upon saturation of the 3-H). A remarkable through space interaction was also noted between one of the 1-H protons (δ 1.65) and 6-H proton (δ 4.06) (2% enhancement of 6-H upon saturation of the 1-H and 1.5% enhancement of 1-H upon saturation of 6-H). These findings are in accordance with the proposed structure bearing the bridgehead and the 3-H pyrrolidine protons in cis-arrangement and the three rings in a concave disposition, which allows the approach of 1-H and 6-H protons. As it comes out from molecular models, in the concave arrangement of the three rings only an *endo* 6-H can have a through space interaction with an *endo* 1-H that of δ 1.65. The other 1-H is hidden in multiplet centred at δ 2.05. An *exo* 6-H should be far off both 1-H.

Our attention was then turned to efforts for converting epoxide **10** into a pyrrolizodine ring. However, despite our attempts, we could not find experimental conditions leading to 5-*exo* products, probably because the C-4 (ribose numbering) is strongly hindered by the acetonide group. In a different way leading to *epi*-hyacinthcine B_2, we attempted cyclisation of **9**. Removal, however, of the Cbz group with H_2 over Pd/C gave a complex mixture of products, where no pyrrolizidine ring was identified. Taking into account the possibility that the overcrowded environment of the mesyloxy group did not allow approach of the amino group, we attempted to remove the TBS and acetonide protecting groups. By treatment, however, of **9** with PPTS at rt, the TBS group was firstly removed, but under reflux, compound was decomposed.

Considering, finally, that mesyloxy was not a good leaving group, compound **9** was treated with TBAI in refluxing acetonitrile or benzene in order to substitute this group by iodide in a S_N2 reaction, but without success. Alternatively, the free hydroxyl group in compound **8** was triflated and then iodide was successfully introduced upon treatment with TBAI. Surprisingly, however, we were then unable to deprotect the amino group of this product although several hydrogenation conditions were applied.

In conclusion, we have successfully applied the hetero-Diels–Alder 2-nitrosoacrylate cycloaddition reaction to a D-ribose-derived *exo*-glycal in order to prepare a new protected trihydroxyindolizidine derivative (**11**) by a 6-*endo* epoxide opening, intermediately formed. Several attempted 5-*exo* openings of this epoxide were unsuccessful. In addition, interesting proline derivatives branched with polyhydroxylated chains like **7** and **12** were formed.

1. Experimental

1.1. General

Optical rotations were determined at room temperature on an A. Krüss P3000 Automatic Digital Polarimeter. The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, on a Bruker 300 AM spectrometer, with tetramethylsilane (TMS) as internal standard. High-resolution mass spectra (HRMS) were obtained on a VG ZAB-ZSE mass spectrometer under fast-atom bombardment (FAB) conditions with nitrobenzyl alcohol (NBA) as the matrix or on an IONSPEC FTMS spectrometer (matrix-assisted laser-desorption ionisation, MALDI) with 2,5-dihydroxybenzoic acid (DHB) as matrix. Compounds **4**, **5** and **6** were prepared according to published procedures.[9]

1.2. (2*S*,5*R*)-Ethyl 5-((4*S*,5*R*)-5-((*R*)-2-(*tert*-butyldimethylsilyloxy)-1-hydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pyrrolidine-2-carboxylate (7)

To a stirred solution of **6** (0.67 g, 1.55 mmol) in MeOH (40 mL) were added H_3BO_3 (1.92 g, 31 mmol), $MgSO_4$ (2.0 g) and catalytic amount of Raney Ni, and the mixture was refluxed under H_2 atmosphere for 4 h. The H_3BO_3 was then neutralised by saturated aqueous Na_2CO_3, the mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the organic layer was dried over Na_2SO_4. The solvent was then removed on a rotary evaporator and the residue was chromatographed on a column of silica gel with hexane/ethyl acetate as the eluent to give 485 mg of **7** (75%) as an oil. $[\alpha]_D^{25}$ +3.3 (*c* 3.2, $CHCl_3$), FTIR (film) 3442, 2924, 2852, 1742, 1460, 1377, 1250, 1219, 1048, 830, 783 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.17 (q, *J* = 7.0 Hz, 2H), 3.85 (m, 3H), 3.75 (m, 2H), 3.62 (m, 1H), 3.55 (br, 2H, OH, NH), 3.35 (m, 1H), 2.00 (m, 4H), 1.36 (s, 3H), 1.35 (s, 3H), 1.27 (t, *J* = 7.0 Hz, 3H), 0.91 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 108.5, 83.1, 79.6, 73.5, 65.0, 61.5, 61.0, 60.2, 29.9, 29.3, 27.0, 26.9, 26.0, 18.5, 14.1, −5.3, −5.4; HRMS (*m*/*z*) calcd for $C_{20}H_{40}NO_6Si$ [(M+H)$^+$] 418.26249, found 418.26254.

1.3. (2*S*,5*R*)-1-Benzyl 2-ethyl 5-((4*S*,5*R*)-5-((*R*)-2-(*tert*-butyldimethylsilyloxy)-1-hydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pyrrolidine-1,2-dicarboxylate (8)

To a stirred solution of **7** (0.25 g, 0.60 mmol) and dry Et_3N (0.68 ml, 8 equiv) in MeOH (8 mL) were added dropwise 0.256 ml Cbz-Cl (3 equiv) at 0 °C under argon atmosphere. The mixture was then stirred at room temperature for 8 h, the volatiles were removed on a rotary evaporator, and the residue was chromatographed on a column of silica gel with hexane/ethyl acetate (5:1) as the eluent to give 160 mg of **8** (50%) as an oil. FTIR (film) 3471, 2929, 2856, 1730, 1708, 1453, 1412, 1350, 1252, 1211, 1108, 836, 776 cm^{-1}; $[\alpha]_D^{25}$ +4.3 (*c* 0.62, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (br s, 5H), 5.15 (d, *J* = 12.3 Hz, 1H), 5.11 (d, *J* = 12.3 Hz, 1H), 4.40–3.60 (m, 7H), 3.35 (d, *J* = 3.1 Hz, 1H, OH), 2.20 (m, 3H), 1.90 (m, 1H), 1.39 (s, 3H), 1.36 (s, 3H), 1.33 (s, 2H), 1.27 (t, *J* = 7.0 Hz, 3H), 0.91 (s, 9H), 0.09 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 155.0, 136.3, 128.3, 127.9, 127.8, 109.3, 80.6, 78.5, 73.8, 67.3, 64.6, 61.0, 60.6, 60.1, 29.4, 27.5, 27.2, 25.9, 18.3, 14.0, −5.3. HRMS (*m*/*z*) calcd for $C_{28}H_{46}NO_8Si$ [(M+H)$^+$] 552.29872, found 552.29817.

1.4. (2*S*,5*R*)-1-Benzyl 2-ethyl 5-((4*S*,5*R*)-5-((*R*)-2-(*tert*-butyldimethylsilyloxy)-1-mesyloxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pyrrolidine-1,2-dicarboxylate (9)

To a stirred solution of **8** (120 mg, 0.22 mmol) and DMAP (17 mg, 0.5 equiv) in pyridine (4 mL) were added 0.033 ml $MeSO_2Cl$ (1.5 equiv) at 0 °C under argon atmosphere. The mixture was stirred at the same temperature for 90 min, the solvent was removed azeotropically with toluene on a rotary evaporator and the residue was chromatographed on a column of silica gel with hexane/ethyl acetate (5:1) as the eluent to give 102 mg of **9** (74%) as an oil. $[\alpha]_D^{25}$ +7.6 (*c* 1.77, $CHCl_3$); FTIR (film) 2934, 2857, 1744, 1705, 1463, 1409, 1358, 1177, 1112, 920, 838, 777 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5H), 5.12 (s, 2H), 5.03 (m, 1H), 4.40–4.10 (m, 6H), 3.98 (d, *J* = 5.1 Hz, 2H), 3.16 (s, 3H), 2.25 (m, 1H), 2.15 (m, 2H), 1.95 (m, 1H), 1.41 (s, 6H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.9 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 155.3, 136.2, 128.3, 128.0, 127.9, 110.0, 80.2, 78.5, 78.0, 67.6, 61.3, 61.2, 61.0, 60.3, 38.6, 28.9, 27.1, 26.9, 26.5, 25.8, 18.3, 14.0, −5.5, −5.6; HRMS (*m*/*z*) calcd for $C_{29}H_{48}NO_{10}SSi$ [(M+H)$^+$] 630.27627, found 630.27565.

1.5. (2*S*,5*R*)-1-Benzyl 2-ethyl 5-((4*S*,5*S*)-2,2-dimethyl-5-((*S*)-oxiran-2-yl)-1,3-dioxolan-4-yl)pyrrolidine-1,2-dicarboxylate (10)

To a stirred solution of **9** (100 mg, 0.16 mmol) in THF (7 mL) were added dropwise 0.25 mL TBAF 1.0 M in THF (1.5 equiv) at 0 °C under argon atmosphere and the stirring was continued for 1 h. An additional amount of 0.25 mL TBAF 1.0 M in THF (1.5 equiv) were added, the mixture was allowed to warm at room temperature, and stirred for 12 h. Then CH_2Cl_2 (10 mL) and brine (5 mL) were added, the organic layer was dried over Na_2SO_4, the solvent was evaporated off, and the residue was chromatographed on a column of silica gel with hexane/ethyl acetate (2:1) as the eluent to give 55 mg of **10** (80%) as an oil. $[\alpha]_D^{25}$ +1.7 (*c* 1.12, $CHCl_3$); FTIR (film) 2986, 2864, 1748, 1706, 1455, 1405, 1351, 1296, 1183, 1104, 1056 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 5H), 5.17 (d, *J* = 12.2 Hz, 1H), 5.04 (d, *J* = 12.2 Hz, 1H), 4.40–4.15 (m, 4H), 4.09 (q, *J* = 7.3 Hz, 2H), 3.05 (q, *J* = 3.7 Hz, 1H), 2.68 (d, *J* = 3.7 Hz, 2H), 2.40–1.90 (m, 4H), 1.40 (s, 6H), 1.38 (s, 9H), 1.15 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 155.1, 136.0, 128.4, 128.1, 127.7, 109.1, 78.7, 78.2, 67.3, 61.3, 61.1, 60.2, 51.8, 44.7, 28.6, 27.5, 27.1, 26.5, 13.9; HRMS (*m*/*z*) calcd for $C_{22}H_{30}NO_7$ [(M+H)$^+$] 420.20223, found 420.20211.

1.6. (3a*R*,4*S*,7*S*,9a*R*,9b*S*)-Ethyl 4-hydroxy-2,2-dimethyl-octahydro-[1,3]dioxolo[4,5-*g*]indolizine-7-carboxylate (11)

To a solution of **10** (30 mg, 0.07 mmol) and 1,4-cyclohexadiene (0.07 mL, 10 equiv) in absolute EtOH (5 mL) catalytic amount of 5% Pd/C was added and the mixture was stirred at room temperature under argon atmosphere for 1 h. The solids then were filtered off, the solvent was removed on a rotary evaporator, and the residue was chromatographed on a column of silica gel with hexane/ethyl acetate (2:1) as the eluent to give 15 mg of **11** (73%) as a colorless oil. $[\alpha]_D^{25}$ +19.1 (*c* 0.18, MeOH); FTIR (film) 3355, 2978, 2935, 2879, 1733, 1451, 1371, 1227, 1147, 1088, 1046, 840 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18 (q, *J* = 7.3 Hz, 1H), 4.10 (m, 1H), 3.35 (m, 3H), 3.21 (dd, *J* = 9.8, 6.4 Hz, 1H), 2.51 (m, 1H), 2.31 (br, 1H, OH), 2.15 (m, 2H), 2.03 (m, 2H), 1.65 (m, 1H), 1.46 (s, 3H), 1.45 (s, 3H), 1.28 (t, *J* = 7.0 Hz, 3H); ^{1}H NMR (300 MHz, $CDCl_3$/C_6D_6, 5/1) δ 4.17 (q, *J* = 7.6 Hz, 2H), 4.06 (m, 1H), 3.32 (m, 3H), 3.19 (dd, *J* = 9.4, 6.2 Hz, 1H), 2.46 (m, 1H), 2.05 (m, 4H), 1.86 (d, *J* = 3.6 Hz, 1H), 1.65 (m, 1H), 1.43 (s, 3H), 1.42 (s, 3H), 1.26 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 109.7, 84.6, 79.0, 68.8, 65.0, 63.3, 60.8, 54.2, 29.8, 28.6, 26.8, 26.7, 14.2; HRMS (*m*/*z*) calcd for $C_{14}H_{24}NO_5$ [(M+H)$^+$] 286.16545, found 286.16538.

1.7. (2*S*,5*R*)-Ethyl 5-((4*S*,5*R*)-5-((*S*)-1-hydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pyrrolidine-2-carboxylate (12)

To a solution of **10** (60 mg, 0.14 mmol) in MeOH (2 mL) catalytic amount of 5% Pd/C was added and the mixture was stirred at room

temperature under H_2 atmosphere for 2 h. The solids then were filtered off, the solvent was removed on a rotary evaporator, and the residue was chromatographed on a column of silica gel with hexane/ethyl acetate (2:1) as the eluent to give 35 mg of **12** (86%) as a thick oil. $[\alpha]_D^{25}$ +15.2 (*c* 0.23, MeOH); FTIR (film) 3335, 2984, 2935, 1733, 1455, 1379, 1241, 1211, 1181, 1098, 1067, 882 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.18 (q, J = 7.3 Hz, 2H), 3.98 (ddd, J = 9.8, 6.7, 3.1 Hz, 1H), 3.85 (m, 3H), 3.28 (m, 1H), 2.86 (br s, 2H, OH, NH), 2.12 (m, 1H), 1.95 (m, 3H), 1.41 (s, 3H), 1.39 (s, 3H), 1.28 (t, J = 7.3 Hz, 3H), 1.26 (d, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 108.7, 83.6, 78.8, 66.6, 61.7, 61.1, 60.3, 29.9, 29.2. 27.3, 27.2, 18.7, 14.2; HRMS (*m*/*z*) calcd for $C_{14}H_{25}NO_5Na$ [$(M+Na)^+$] 310.16249, found 310.16255.

Acknowledgement

This work was co-funded by European Union and National fund PYTHAGORAS—EPEAEK II.

References

1. (a) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680; (b) Winchester, B. G. *Tetrahedron: Asymmetry* **2009**, *20*, 645–651; (c) Davis, B. G. *Tetrahedron: Asymmetry* **2009**, *20*, 652–671; (d) Compain, P.; Chagnault, V.; Martin, O. R. *Tetrahedron: Asymmetry* **2009**, *20*, 672–711.
2. (a) *Iminosugars as Glycosidase Inhibitors, Nojirimycin and Beyond*; Stütz, A. E., Ed.; Wiley-VCH: Weinheim, 1999; (b) *Carbohydrate Mimics, Concepts and Methods*; Chapleur, Y., Ed.; Wiley-VCH: Weinheim, 1998; (c) *Carbohydrates in Drug Design*; Witczak, Z. J., Nieforth, K. A., Eds.; Marcel Dekker, Inc.: New York, 1997; (d) Sinnott, M. L. *Chem. Rev.* **1990**, *90*, 1171–1202; (e) Look, G. C.; Fotsch, C. H.; Wong, C.-H. *Acc. Chem. Res.* **1993**, *26*, 182–190; (f) Bols, M. *Acc. Chem. Res.* **1998**, *31*, 1–8; (g) Heightman, T. D.; Vasella, A. T. *Angew. Chem., Int. Ed.* **1999**, *38*, 750–770; (h) Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2301–2324; (i) Zechel, D. L.; Withers, S. G. *Acc. Chem. Res.* **2000**, *33*, 11–18; (j) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515–553.
3. (a) Kato, A.; Adachi, I.; Miyauchi, M.; Ikeda, K.; Komae, T.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Wormald, M. R.; Fleet, G. W. J.; Asano, N. *Carbohydr. Res.* **1999**, *316*, 95–103; (b) Asano, N.; Kuroi, H.; Ikeda, K.; Kizu, H.; Kameda, Y.; Kato, A.; Adachi, I.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1–8.
4. For a recent review: Wardrop, D. J.; Waidyarachchi, S. L. *Nat. Prod. Rep.* **2010**, *27*, 1431–1468.
5. Fleet, G. W. J.; Fellows, L. E.; Smith, P. W. *Tetrahedron* **1987**, *43*, 979–990.
6. Rassu, G.; Carta, P.; Luigi Pinna, L.; Battistini, L.; Zanardi, F.; Acquotti, D.; Casiraghi, G. *Eur. J. Org. Chem.* **1999**, 1395–1400.
7. Van Ameijde, J.; Horne, G.; Wormald, M. R.; Dwek, R. A.; Nash, R. J.; Jones, P. W.; Evinsonb, E. L.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2006**, *17*, 2702–2712.
8. (a) Gallos, J. K.; Sarli, V. C.; Koftis, T. V.; Coutouli-Argyropoulou, E. *Tetrahedron Lett.* **2000**, *41*, 4819–4822; (b) Gallos, J. K.; Sarli, V. C.; Stathakis, C. I.; Koftis, T. V.; Nachmia, V. R.; Coutouli-Argyropoulou, E. *Tetrahedron* **2002**, *58*, 9351–9357.
9. Massen, Z. S.; Sarli, V. C.; Coutouli-Argyropoulou, E.; Gallos, J. K. *Carbohydr. Res.* **2011**, *346*, 230–237.
10. (a) Gallos, J. K.; Sarli, V. C.; Varvogli, A. C.; Papadoyanni, C. Z.; Papaspyrou, S. D.; Argyropoulos, N. G. *Tetrahedron Lett.* **2003**, *44*, 3905–3909; (b) Gallos, J. K.; Sarli, V. C.; Massen, Z. S.; Varvogli, A. C.; Papadoyanni, C. Z.; Papaspyrou, S. D.; Argyropoulos, N. G. *Tetrahedron* **2005**, *61*, 565–574.