Available online at www.sciencedirect.com
SCIENCE DIRECT®
Carbohydrate Research 338 (2003) 1917–1924
CARBOHYDRATE RESEARCH
www.elsevier.com/locate/carres

Characterisation and X-ray crystallography of products from the Bucherer–Bergs reaction of methyl 2,3-*O*-isopropylidene-α-D-*lyxo*-pentodialdo-1,4-furanoside

Júlia Mičová,[a] Bohumil Steiner,[a] Miroslav Kóš,[a,*] Vratislav Langer,[b] Dalma Gyepesová[c]

[a] *Institute of Chemistry, Slovak Academy of Sciences, Dúbravská cesta 9, SK-84538 Bratislava, Slovakia*
[b] *Department of Environmental Inorganic Chemistry, Chalmers University of Technology, SE-41296 Gothenburg, Sweden*
[c] *Institute of Inorganic Chemistry, Slovak Academy of Sciences, Dúbravská cesta 9, SK-84536 Bratislava, Slovakia*

Received 9 May 2003; accepted 21 June 2003

Abstract

Methyl 2,3-*O*-isopropylidene-α-D-mannofuranosidurononitrile [alternative name: methyl (5*R*)-5-*C*-cyano-2,3-*O*-isopropylidene-α-D-lyxofuranoside] (**2**), methyl 2,3-*O*-isopropylidene-α-D-mannofuranosiduronamide [methyl (5*S*)-5-*C*-carbamoyl-2,3-*O*-isopropylidene-α-D-lyxofuranoside; methyl (5*S*)-2,3-*O*-isopropylidene-α-D-*lyxo*-hexofuranosiduronamide] (**3**), methyl 2,3-*O*-isopropylidene-α-D-mannofuranosiduronic acid [methyl (5*S*)-2,3-*O*-isopropylidene-α-D-*lyxo*-hexofuranosiduronic acid] (**4**), methyl 5-deoxy-2,3-*O*-isopropylidene-5-ureido-β-L-gulofuranosiduronamide [methyl (5*R*)-5-deoxy-2,3-*O*-isopropylidene-5-ureido-α-D-*lyxo*-hexofuranosiduronamide (**5**), and (4*S*,5*S*,6*R*)-5,6-dihydro-6-hydroxy-4,5-isopropylidenedioxy-4*H*-pyrido[2,1-*e*]imidazolidine-2′,4′-dione [IUPAC name: (3a*S*,4*R*,8a*S*)-4-hydroxy-2,2-dimethyl-3a,8a-dihydro-4*H*-1,3-dioxa-4a,6-diaza-*s*-indacene-5,7-dione] (**6**), instead of the expected hydantoin derivative, were obtained from the Bucherer–Bergs reaction of methyl 2,3-*O*-isopropylidene-α-D-*lyxo*-pentodialdo-1,4-furanoside (**1**). The structure of **6** was deduced from NMR and mass spectral data and confirmed by X-ray crystallography. The configuration at C-5 in **2**–**5** was confirmed by establishing the 5*S* configuration of **3** by X-ray crystallography. Conformations of the six- and five-membered rings in **3** and **6** are also discussed.

Keywords: Bucherer–Bergs reaction; Pentodialdo-1,4-furanoside; Pyrido[2,1-*e*]imidazolidine; Furanosiduronamide; X-ray crystallography; Conformation

1. Introduction

Although the Bucherer–Bergs reaction[1] is generally well known and a large number of hydantoins have been prepared in this way, application of this reaction (or its modification[1c] according to Hoyer) to a carbohydrate derivative has been described only a few times till now.[2–10] Recently, a modification utilizing stereoselective preformed α-aminonitrile intermediates, has been applied by Postel and coworkers[11] to some starting sugar uloses. In the last two decades, several spironucleosides derived from sugar hydantoins exhibiting significant biological activity have been reported (e.g., the (+)-hydantocidin,[12] a furanoid spirohydantoin with potent herbicidal and regulatory plant growth activities and low toxicity for mammals, its rhamnose and mannose analogues[13] or hydantoin analogue[5] of Showdomycin).

It has been demonstrated that depending on structure and the type of protective groups of starting keto or aldehydo sugars, unexpected products of simultaneous rearrangement on sugar ring[7] as well as corresponding 4-carbamoyl-2-oxazolidinones (instead of hydantoins) C-4-linked with a saccharide moiety can be also prepared applying the Bucherer–Bergs reaction.[9] These possibilities and susceptibility of both heterocyclic (either hydantoin or 2-oxazolidinone) and carbohydrate

* Corresponding author. Tel.: +421-2-59410254; fax: +421-2-59410222.
E-mail address: chemmiro@savba.sk (M. Kóš).

0008-6215/03/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0008-6215(03)00307-0

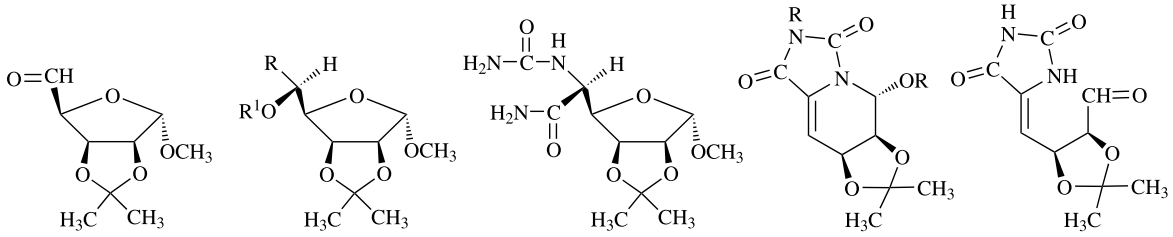
parts of compounds obtained from the Bucherer–Bergs reaction to further transformations affording new model aminosugar glycoconjugate mimetics (or their potential intermediates), makes this reaction still attractive for organic synthetic chemists, despite generally known low stereoselectivity of this reaction.

2. Results and discussion

Recently, we have described[8] the reaction products from the Bucherer–Bergs reaction of methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hexofuranosid-5-ulose. In this case, corresponding 5*R* and 5*S* C-5–C-5′-fused sugar-hydantoins were isolated and characterised. In the present work, we have started from the known methyl 2,3-*O*-isopropylidene-α-D-*lyxo*-pentodialdo-1,4-furanoside (**1**).[14,15] Application of the Bucherer–Bergs reaction conditions to this aldehyde led to the formation of several products. In addition to cyanohydrin **2**, hexuronamide **3**, hexuronic acid **4**, and 5-deoxy-5-ureidohexuronamide derivative **5**, corresponding to the side-products of the normal reaction course, the unusual pyrido[2,1-*e*]imidazolidine derivative **6** (Fig. 1) was isolated instead of the expected hydantoin derivative. The proportional representation of these products depends on reaction time and temperature. Compound **2** was isolated as a main product in all experiments. In addition, higher yields of compounds **2**–**4** resulted at lower temperature and prolonged reaction time (method A, see Section 3) while compounds **5** and **6** were preferentially formed under higher temperature and shorter reaction time (method B). In this respect, a noticeable difference is evident especially for compound **6** (3 versus 19% for methods A and B, respectively). The products **2**–**6** as well as *N*,*O*-diacetyl derivative **8** and *O*-acetyl derivative **9** (prepared by acetylation of **6** and **3**, respectively, under usual conditions) were identified by their analytical and spectroscopic properties. The structure of **3** and **6** was confirmed also by X-ray crystallography.

Kuszmann and coworkers[4] presented formation of similar products starting from 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-pentodialdo-1,4-furanose. The anomalous Bucherer–Bergs reaction giving rise to unexpected pyrido[2,1-*e*]imidazolidine derivative they explained by the formation of corresponding cyanohydrin, subsequent removal of H-5 under basic reaction conditions, leading simultaneously to *trans* elimination of O-4, yielding an unsaturated intermediate, from which the *O*-isopropylidene group is removed. According to this hypothesis, our unexpected product **6** could be formed by elimination of only methoxyl group at C-1 (without loss of isopropylidene group, i.e., without deprotection at O-2 as in the case of analogous product reported by Kuszmann) in the final step of the above proposed reaction mechanism, affording an intermediate **7** (Fig. 1) which undergoes spontaneous intramolecular cyclisation to give isopropylidenated pyrido[2,1-*e*]imidazolidine **6**.

The configuration at C-5 position of compounds **2**–**5** and **9** was confirmed by establishing the 5*S* configuration of hexuronamide **3** by X-ray crystallography (Table 1) and by comparison of their NMR data (especially the relevant $J_{4,5}$ coupling constant) and values of optical rotation with those given for very similar structures having identical configuration at C-5 atom). Thus, considering that configuration at C-1, C-2, C-3 and C-4 is known and does not change, almost identical values of $[\alpha]_D$ and $J_{4,5}$ for **2** and methyl 5-cyano-6-deoxy-2,3-*O*-isopropylidene-β-L-gulofuranoside[16] (having the 5*R* configuration) indicate the 5*R* configuration of **2**. The 5*S* configuration results for **4** when compared the corresponding data of **2**–**4**. Analogously, almost identical values of $[\alpha]_D$ and $J_{4,5}$ for **5** and methyl (5*R*)-5-acetamido-5-deoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hexofuranosiduronamide[17] are indicative of the 5*R* configuration of **5**. These observations as well as absence of 5*S* analogue of cyanohydrin **2** among the isolated products also suggest some stereoselectivity of the first reaction step **1** → **2** and that reaction pathways **2** → **3** → **4** and **2** → **3** → **5** had to be involved. Because the column chroma-



1 **5** **7**

2: R = CN, R^1 = H
3: R = $CONH_2$, R^1 = H
4: R = COOH, R^1 = H
9: R = $CONH_2$, R^1 = $COCH_3$

6: R = H
8: R = $COCH_3$

Fig. 1. The products from the Bucherer–Bergs reaction of **1**.

Table 1
Crystallographic and experimental data for compounds **3** and **6** [a]

	3	**6**
Empirical formula	$C_{10}H_{17}NO_6$	$C_{10}H_{12}N_2O_5$
Formula weight	247.25	240.22
Temperature, T (K)	183(2)	183(2)
Wavelength, λ (Å)	0.71073	0.71073
Crystal system	monoclinic	monoclinic
Space group	$P2_1$	$P2_1$
Unit cell dimensions		
a (Å)	7.5891(2)	6.59860(10)
b (Å)	6.5802(2)	9.40970(10)
c (Å)	12.1441(3)	17.37360(10)
β (°)	93.0290 (10)	90.16
Unit-cell volume V (Å^3)	605.60(3)	1078.74(2)
Formula per unit cell, Z	2	4
D_{calcd} (g/cm^3)	1.356	1.479
Radiation	Mo K_α	Mo K_α
Absorption coefficient, μ (mm^{-1})	0.112	0.120
$F(000)$	264	504
Crystal size (mm^3)	$0.75 \times 0.18 \times 0.06$	$0.46 \times 0.42 \times 0.34$
Diffractometer	Siemens SMART CCD	Siemens SMART CCD
θ Range (°)	2.69–32.97	2.16–32.82
Index ranges	$-11 \le h \le 11$, $-9 \le k \le 9$, $-18 \le l \le 18$	$-9 \le h \le 10$, $-14 \le k \le 13$, $-25 \le l \le 25$
Reflections	10843	17850
Independent reflections	4277 (R_{int} = 0.0295)	7390 (R_{int} = 0.0303)
Refinement method	full-matrix least-squares on F^2	full-matrix least-squares on F^2
Data/parameters	4277/175	7390/338
Goodness-of-fit (all)	1.044	1.048
Final R indices $[I > 2\sigma(I)]$	$R_1 = 0.0417$, $wR_2 = 0.1051$	$R_1 = 0.0389$, $wR_2 = 0.0980$
R indices (all data)	$R_1 = 0.0505$, $wR_2 = 0.1123$	$R_1 = 0.0398$, $wR_2 = 0.0996$
Largest difference peak and hole (e/Å^3)	0.302 and −0.155	0.434 and −0.219

[a] Standard deviations in parentheses.

tography and subsequently a crystallisation step was involved in the purification of reaction products, the more detailed data on stereoselectivity are not given.

The presence of 1,3-dioxolane ring fused to a furanose ring at the 2,3-position and the α-glycosidic methyl group imposes some conformational rigidity on compounds **2**–**5** and **9**. For compound **3**, the puckering parameters[18] $Q = 0.355(1)$ Å and $\Phi = 359.5(2)^\circ$ and the values of relevant dihedral angles (see Table 2) are indicative of almost perfect $^\circ E$ conformation for five-membered furanoside ring (O4–C1–C2–C3–C4) with C-1, C-2, C-3, C-4 atoms almost in a plane and O-4 directed *endo* to this plane (Fig. 2). Analogously, the puckering parameters $Q = 0.307(1)$ Å and $\Phi = 145.8(2)^\circ$ and the values of relevant torsion angles (Table 2) indicate almost perfect $^{C\text{-}8}E$ conformation for five-membered 1,3-dioxolane ring (O2–C2–C3–O3–C8) with C-8 atom lying in the *endo* direction with respect to the plane defined by the atoms O-2, C-2, C-3, and O-3.

Table 2
Selected torsion angles (°) for compounds **3** and **6** [a]

	3	**6**	**6** (A)
C1–C2–C3–C4	0.19(12)	−41.49(18)	−41.74(19)
C2–C3–C4–O4	−22.43(12)		
C3–C4–O4–C1	38.46(12)		
C4–O4–C1–C2	−38.45(12)		
O4–C1–C2–C3	22.65(12)		
O1–C1–C2–O2	151.90(9)	−179.90(14)	177.97(14)
O1–C1–C2–C3	−96.49(11)	−66.33(17)	−68.13(17)
C2–C3–C4–C5		13.7(2)	15.0(2)
C3–C4–C5–N5		1.1(2)	0.8(2)
C4–C5–N5–C1		12.8(2)	11.0(2)
C5–N5–C1–C2		−38.67(19)	−35.6(2)
N5–C1–C2–C3		52.59(18)	51.15(19)
C2–O2–C8–O3	−33.56(14)	−16.79(17)	−17.58(17)
O2–C8–O3–C3	32.97(14)	−11.10(18)	−9.98(17)
C8–O3–C3–C2	−19.48(14)	32.10(16)	31.42(16)
O3–C3–C2–O2	−1.01(13)	−41.50(14)	−41.07(14)
C3–C2–O2–C8	21.01(13)	35.89(15)	35.97(15)

[a] Standard deviations in parentheses.

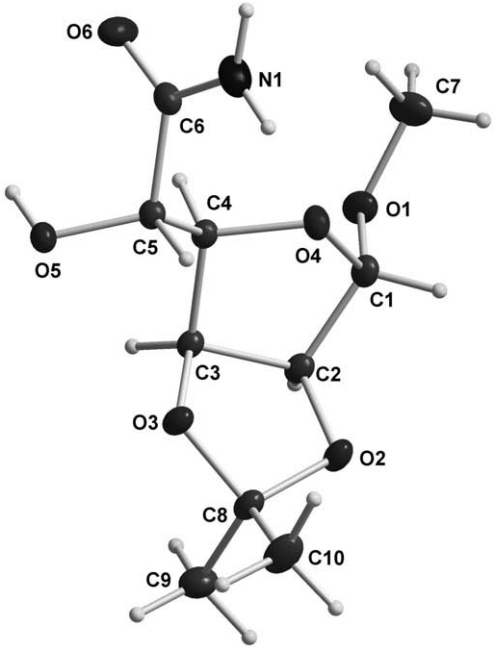


Fig. 2. Numbering scheme for **3**. Thermal ellipsoids are shown at 30% probability level.

Based on spectral and X-ray crystallographic data, the structure of (4*S*,5*S*,6*R*)-5,6-dihydro-6-hydroxy-4,5-isopropylidenedioxy-4*H*-pyrido[2,1-*e*]imidazolidine-2′,4′-dione [IUPAC name: (3a*S*,4*R*,8a*S*)-4-hydroxy-2,2-dimethyl-3a,8a-dihydro-4*H*-1,3-dioxa-4a,6-diaza-*s*-indacene-5,7-dione] was identified for compound **6**. In carbohydrate terminology, compound **6** is a 5-amino-5-deoxy-2,3-*O*-isopropylidene-hex-4-enopyranose fused (at C-5 and N) with hydantoin ring (at C-5′ and N-1). From this point of view, the values of relevant torsion angles O1–C1–C2–O2 = −179.90(14)°, N5–C1–C2–O2 = −60.98(17)° and O1–C1–N5–C7 = −79.71(19)° [for the second independent molecule: O1A–C1A–C2A–O2A = 177.97(14)°, N5A–C1A–C2A–O2A = −62.74(17)° and O1A–C1A–N5A–C7A = −77.0(2)°] as well as coupling constant $J_{1,2} = \sim 0$ Hz indicate β-L configuration (with respect to the position of hydroxyl groups at C-1 and C-3 to the plane of ring) of the 5-deoxy-5-aminopyranose, because the configuration at C-2 and C-3 was known and did not change (Fig. 3). The presence of 1,3-dioxolane and hydantoin rings fused to a 5-deoxy-5-aminopyranose ring imposes some conformational rigidity on **6**. The values of relevant torsion angles (see Table 2) and puckering parameters $Q = 0.422(2)$ Å, $\Theta = 51.0(3)°$, $\Phi = 93.7(3)°$ [$Q = 0.410(2)$ Å, $\Theta = 50.9(3)°$, $\Phi = 97.6(3)°$ for the second independent molecule] indicate that N5–C1–C2–C3–C4–C5 six-membered ring adopts the $^{C\text{-}2}H_{C\text{-}1}$ conformation. Analogously, the puckering parameters $Q = 0.396(2)$ Å and $\Phi = 230.0(2)°$ [$Q = 0.393(2)$ Å, $\Phi = 228.8(2)°$ for the second independent molecule] and the relevant dihedral angles are indicative of $^{C\text{-}2}T_{C\text{-}3}$ conformation slightly distorted to the $^{C\text{-}2}E$ direction for five-membered 1,3-dioxolane ring (O2–C2–C3–O3–C8). The five-membered fused hydantoin ring (N5–C7–N6–C6–C5) is almost planar as all relevant torsion angles are close to zero.

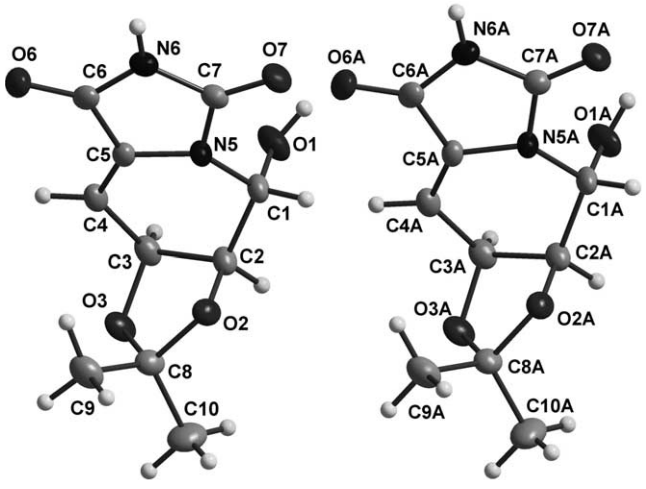


Fig. 3. Numbering scheme and thermal ellipsoids on 50% probability level for compound **6**.

Analysis of the molecular packing in the unit cell of **3** revealed five principal interactions (Table 3), which give rise to a number of interactions in many directions. One of them, [*a*], is intramolecular, while the other four, [*b*], [*c*], [*d*] and [*e*] are intermolecular. The hydrogen bonds are forming an infinite sheet of molecules in the plane (*a*,*b*) (Fig. 4(a)), while the fifth, [*e*], is making a chain together with [*b*] in the *a*-direction (Fig. 4(b)). The first-level descriptors based on the graph-set theory[19] include intramolecular string S1,1(5) formed by bond [*a*], chains C1,1(5), formed by bonds [*b*], [*c*] and [*e*], respectively and a chain C1,1(4), formed by bond [*d*]. The second-level comprises: R2,2(9) ring defined by the hydrogen bonds [*b*] and [*d*], chains C2,2(6) (bonds [*b*] and [*c*], [*b*] and [*e*]), C2,2(10) (bonds [*b*] and [*c*], [*b*] and [*e*] and [*c*] and [*e*]), C1,2(7) (bonds [*b*], [*d*] and [*d*], [*e*]), C2,2(9) (bonds [*c*], [*d*] and [*d*], [*e*]), C2,1(5) (bonds [*c*] and [*e*]) and C1,2(4) (bonds [*c*] and [*e*]). Assignment of the H-bond descriptors, based on the graph-set theory[19] was obtained using the program PLUTO.[20] For convenience, the notation X*a*,*d*(*n*) has also been adopted in this paper, in which (X) is the pattern descriptor, (*a*) is number of acceptors, (*d*) is number of donors and (*n*) is the number of atoms comprising the pattern. For compound **6** (see Table 4) four strong hydrogen bonds of types O–H···O and N–H···O are present together with two weak, bifurcated, hydrogen bonds of C–H···O type between the molecules of the same type (denoted as A). This is an explanation why there are two independent types of molecules in the structure. Molecules of **6** form an infinite layer in (*a*,*c*)-plane, formed by hydrogen bonds [*a*]–[*e*] (Fig. 5(a)), while the last one, [*f*], is weaving the molecules together in the *b*-direction (Fig. 5(b)). The first-level descriptors based on the graph-set theory[19] include chains C1,1(7), formed by hydrogen bonds [*a*] and [*b*], C1,1(6) ([*e*]) and C1,1(5) ([*f*]) and dimers D1,1(2) formed by bonds [*c*] and [*d*], respectively. The second-level comprises: dimers D3,3(13) ([*a*] and [*c*], [*a*] and [*d*], [*b*] and [*c*], [*b*] and [*d*] and [*c*] and [*e*]), D3,3(14) ([*c*] and [*f*] and [*d*] and [*e*], and D3,3(15) ([*d*] and [*f*], ring R2,2(7) defined by the hydrogen bonds [*b*] and [*e*], chains C2,2(13) (bonds [*b*] and [*e*]), C2,2(10) (bonds [*b*] and [*f*]), C1,2(14) (bonds [*b*] and [*f*]), C2,2(8) (bonds [*c*] and [*d*]), C2,2(11) (bonds [*e*] and [*f*]) and C2,1(5) (bonds [*e*] and [*f*]).

In conclusion, six products were isolated and fully characterised from the Bucherer–Bergs reaction of methyl 2,3-*O*-isopropylidene-α-D-*lyxo*-pentodialdo-1,4-furanoside. Five of them are side-products of the normal reaction course and one product is unexpected isopropylidenated pyrido[2,1-*e*]imidazolidine derivative. Formation of such compounds, especially fused pyrido[2,1-*e*]imidazolidines, from analogous starting methyl 2,3-*O*-isopropylidene-pentodialdo-1,4-furanosides can give rise of further interesting sugar derivatives useful as a model compounds.

Table 3
Hydrogen bond geometry in compound **3** [a]

Notation	X–H···Y	Symmetry code	X–H (Å)	H···Y (Å)	X···Y (Å)	X–H···Y (°)
a	O5–H5···O6		0.84	2.46	2.7982(15)	104.8
b	O5–H5···O6	$-x+2, y+1/2, -z+2$	0.84	1.95	2.7240(16)	153.5
c	N1–H1A···O5	$x, y-1, z$	0.88	2.50	3.2055(17)	137.2
d	N1–H1A···O6	$-x+2, y-1/2, -z+2$	0.88	2.37	3.185(2)	154.8
e	N1–H1B···O5	$-x+1, y-1/2, -z+2$	0.88	2.61	3.3981(19)	149.0

[a] Standard deviations in parentheses.

3. Experimental

3.1. General methods

The ^{1}H and ^{13}C NMR spectra (in $CDCl_3$ unless specified other, internal standard Me_4Si) were recorded on a Bruker Avance DPX 300 instrument operating at 300.13 and 75.46 MHz working frequencies, respectively. For the assignments of signals, 1D NOESY and C–H heterocorrelated experiments were used. The quaternary carbon atoms were identified on the basis of a semiselective INEPT experiment and a 1D INADEQUATE pulse sequence technique. The EI and CI (using Py as a reactive agent; only one peak, characteristic of the molecular weight of compound, is registered by this method[21]) mass spectra (70 eV) were obtained on a Finnigan MAT SSQ 710 instrument. Specific rotations (at 20 °C) were determined on a Perkin–Elmer 241 polarimeter (10 cm cell). Microanalyses were performed on a Fisons EA 1108 analyser. Melting points were determined with a Boetius PHMK 05 microscope. The analytical thin-layer chromatography (TLC) was performed on Silica Gel plates (E. Merck) using following solvents: 3:1 (v/v) EtOAc–hexane (eluent A) and 8:1 $CHCl_3$–MeOH (eluent B). Visualisation was affected with iodine vapour or H_2SO_4 charring. Column chromatography was carried out as flash chromatography on Silica Gel 60 (E. Merck, 230–400 mesh).

3.2. General procedure for the preparation of compounds 2–6 applying the Bucherer–Bergs reaction

A mixture of methyl 2,3-*O*-isopropylidene-α-D-*lyxo*-pentodialdo-1,4-furanoside (**1**) (4.04 g, 20 mmol), KCN (2.60 g, 40 mmol), and $(NH_4)_2CO_3$ (7.69 g, 80 mmol) in 50% aq EtOH (50 mL) was stirred either at 45 °C for 5 h (method A) or at 60 °C for 2 h (method B). Ethanol was then evaporated and the product extracted thoroughly with $CHCl_3$. After complete solvent removal in vacuo, the residue was chromatographed on a column of silica gel using first eluent A and then eluent B. The corresponding fraction were collected and the solvent evaporated in vacuo to afford pure products which were recrystallised from the appropriate solvent.

3.2.1. Methyl 2,3-*O*-isopropylidene-α-D-mannofurano-sidurononitrile [methyl (5*R*)-5-*C*-cyano-2,3-*O*-isopropylidene-α-D-lyxofuranoside] (2). Yield 1.24 g (27%, method A) or 0.96 g (21%, method B); white needles (R_f 0.82, eluent A); mp 97–98 °C (from Et_2O–hexane); $[\alpha]_D$ +61° (*c* 1, MeOH); ^{1}H (300 MHz, $CDCl_3$): δ 5.02 (s, 1 H, H-1), 4.86 (dd, 1 H, $J_{2,3}$ 5.9, $J_{3,4}$ 3.8 Hz, H-3), 4.84 (d, 1 H, $J_{4,5}$ 6.8 Hz, H-5), 4.63 (d, 1 H, H-2), 4.20 (dd, 1 H, H-4), 3.37 (s, 3 H, OCH_3), 3.16 (bs, 1 H, OH), 1.52 and 1.32 (2s, each 3 H, Me_2C); ^{13}C (75.5 MHz, $CDCl_3$): δ 117.4 (CN), 113.7 (CMe_2), 107.5 (C-1), 84.8 (C-2), 79.3 (C-4), 79.2 (C-3), 60.7 (C-5), 55.1 (OCH_3), 25.4 and 24.3 [$(CH_3)_2C$]; EIMS (70 eV): *m*/*z* 229 $[M]^+$, 214 $[M-Me]^+$, 185, 173, 114, 87, 73, 43; CIMS: *m*/*z*

Table 4
Hydrogen bond geometry in compound **6** [a]

Notation	X–H···Y	Symmetry code	X–H (Å)	H···Y (Å)	X···Y (Å)	X–H···Y (°)
a	O1–H1···O6	$x-1, y, z$	0.84	1.93	2.767(2)	179.7
b	O1A–H1A1···O6A	$x+1, y, z$	0.84	1.95	2.786(2)	171.0
c	N6–H6···O7A	$-x+2, y+1/2, -z+1$	0.88	2.04	2.880(2)	159.8
d	N6A–H6A···O7	$-x+1, y-1/2, -z+1$	0.88	2.00	2.8278(19)	157.1
e	C4A–H4A···O1A	$x-1, y, z$	0.95	2.59	3.310(2)	133.0
f	C4A–H4A···O2A	$-x+1, y-1/2, -z+1$	0.95	2.51	3.1983(19)	129.7

[a] Standard deviations in parentheses.

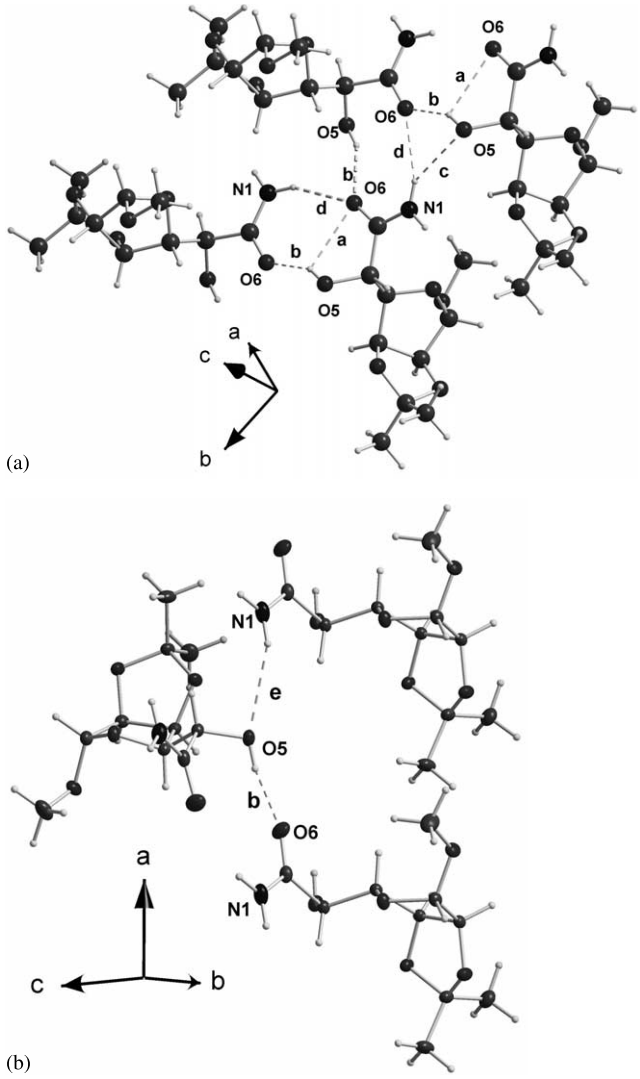


Fig. 4. Hydrogen bonding in compound **3**: (a) the sheet of molecules in the plane (*a*,*b*); (b) H-bond chain in *a*-direction.

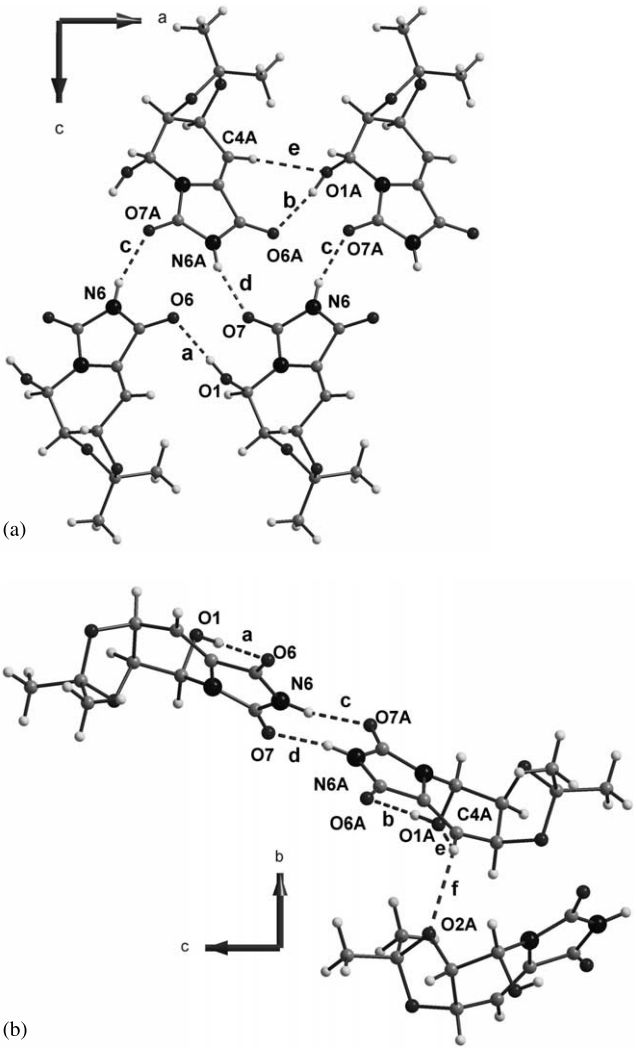


Fig. 5. Hydrogen bonding in compound **6**: (a) the layer of molecules in (*a*,*c*)-plane; (b) H-bonds weaving the molecules together in the *b*-direction.

309 $[M+C_5H_5NH]^+$. Anal. Calcd for $C_{10}H_{15}NO_5$: C, 52.40; H, 6.60; N, 6.11. Found: C, 52.29; H, 6.68; N, 6.18.

3.2.2. Methyl 2,3-*O*-isopropylidene-α-D-mannofurano-siduronamide [methyl (5*S*)-5-*C*-carbamoyl-2,3-*O*-isopropylidene-α-D-lyxofuranoside; methyl (5*S*)-2,3-*O*-isopropylidene-α-D-*lyxo*-hexofuranosiduronamide] (3). Yield 0.84 g (17%, method A) or 0.59 g (12%, method B); white plates (R_f 0.58, eluent B); mp 179–181 °C (from EtOAc–hexane); $[\alpha]_D$ +99° (*c* 1, MeOH); ^1H (300 MHz, $CDCl_3$): δ 6.74 and 6.04 (2bs, each 1 H, NH_2), 4.99 (s, 1 H, H-1), 4.90 (dd, 1 H, $J_{2,3}$ 5.8, $J_{3,4}$ 3.4 Hz, H-3), 4.58 (d, 1 H, H-2), 4.42 (d, 1 H, $J_{4,5}$ 7.6 Hz, H-5), 4.11 (dd, 1 H, H-4), 4.05 (bs, 1 H, OH), 3.33 (s, 3 H, OCH_3), 1.51 and 1.34 (2s, each 3 H, Me_2C); ^{13}C (75.5 MHz, $CDCl_3$): δ 174.9 ($CONH_2$), 112.8 (CMe_2), 107.5 (C-1), 84.5 (C-2), 80.2 (C-3), 78.4 (C-4), 69.0 (C-5), 54.7 (OCH_3), 25.8 and 24.3 [$(CH_3)_2C$]; EIMS (70 eV): *m*/*z* 248 $[M+1]^+$, 232 $[M-Me]^+$ or $[M+1-NH_2]^+$, 216, 203, 173, 86, 71, 59, 43; CIMS: *m*/*z* 327 $[M+C_5H_5NH]^+$. Anal. Calcd for $C_{10}H_{17}NO_6$: C, 48.60; H, 6.93; N, 5.67. Found: C, 48.69; H, 6.70; N, 5.61.

3.2.3. Methyl 2,3-*O*-isopropylidene-α-D-mannofurano-siduronic acid [methyl (5*S*)-2,3-*O*-isopropylidene-α-D-*lyxo*-hexofuranosiduronic acid] (4). Yield 0.55 g (11%, method A) or 0.40 g (8%, method B); white needles (R_f 0.53, eluent B); mp 87–89 °C (from EtOAc); $[\alpha]_D$ +61° (*c* 1, MeOH); ^1H (300 MHz, $(CD_3)_2SO$): δ 4.81 (s, 1 H, H-1), 4.65 (dd, 1 H, $J_{2,3}$ 5.8, $J_{3,4}$ 3.1 Hz, H-3), 4.40 (d, 1 H, H-2), 3.66 (d, 1 H, $J_{4,5}$ 8.5 Hz, H-5), 3.59 (dd, 1 H, H-4), 3.17 (s, 3 H, OCH_3), 1.36 and 1.23 (2s, each 3 H, Me_2C); ^{13}C (75.5 MHz, $(CD_3)_2SO$): δ 174.6 (COOH), 111.1 (CMe_2), 106.7 (C-1), 83.7 (C-2), 80.8 (C-4), 80.2 (C-3), 68.7 (C-5), 53.7 (OCH_3), 26.0 and 24.8 [$(CH_3)_2C$].

Anal. Calcd for $C_{10}H_{16}O_7$: C, 48.40; H, 6.50. Found: C, 48.29; H, 6.56.

3.2.4. Methyl 5-deoxy-2,3-*O*-isopropylidene-5-ureido-β-L-gulofuranosiduronamide [methyl (5*R*)-5-deoxy-2,3-*O*-isopropylidene-5-ureido-α-D-*lyxo*-hexofuranosiduronamide] (5). Yield 0.23 g (4%, method A) or 0.35 g (6%, method B); white needles (R_f 0.24, eluent B); mp 179–181 °C (from EtOAc–hexane); $[\alpha]_D$ +62° (*c* 0.5, MeOH); ^{1}H (300 MHz, $(CD_3)_2SO$): δ 7.03 and 6.98 (2bs, each 1 H, $CONH_2$), 6.31 (d, 1 H, $J_{5,NH}$ 7.8 Hz, NH), 5.66 (s, 2 H, $CONH_2$), 4.84 (s, 1 H, H-1), 4.71 (dd, 1 H, $J_{2,3}$ 5.8, $J_{3,4}$ 3.5 Hz, H-3), 4.51 (d, 1 H, H-2), 4.29 (t, 1 H, $J_{4,5}$ 7.8 Hz, H-5), 4.06 (dd, 1 H, H-4), 3.23 (s, 3 H, OCH_3), 1.37 and 1.22 (2s, each 3 H, Me_2C); ^{13}C (75.5 MHz, $(CD_3)_2SO$): δ 172.6 (CO), 158.3 (CO), 111.6 (CMe_2), 105.6 (C-1), 84.2 (C-2), 79.5 (C-3), 78.2 (C-4), 53.8 (OCH_3), 51.9 (C-5), 25.7 and 24.5 [$(CH_3)_2C$]; EIMS (70 eV): *m*/*z* 289 $[M]^+$, 274 $[M-Me]^+$, 245 $[M-CONH_2]^+$, 213, 173, 85, 73, 59, 43; CIMS: *m*/*z* 369 $[M+C_5H_5NH]^+$. Anal. Calcd for $C_{11}H_{19}N_3O_6$: C, 45.70; H, 6.62; N, 14.50. Found: C, 45.61; H, 6.70; N, 14.42.

3.2.5. (4*S*,5*S*,6*R*)-5,6-dihydro-6-hydroxy-4,5-isopropylidenedioxy-4*H*-pyrido[2,1-*e*]imidazolidine-2′,4′-dione [IUPAC name: (3a*S*,4*R*,8a*S*)-4-hydroxy-2,2-dimethyl-3a,8a-dihydro-4*H*-1,3-dioxa-4a,6-diaza-*s*-indacene-5,7-dione] (6). Yield 0.14 g (3%, method A) or 0.91 g (19%, method B); white needles (R_f 0.46, eluent A); mp 174–176 °C (from toluene); $[\alpha]_D$ +89° (*c* 1, MeOH); ^{1}H (300 MHz, $CDCl_3$): δ 8.65 (bs, 1 H, NH), 5.96 (dd, 1 H, $J_{3,4}$ 2.8, $J_{3,5}$ 1.3 Hz, H-3), 5.80 (s, 1 H, H-6), 4.92 (dd, 1 H, $J_{4,5}$ 5.0 Hz, H-4), 4.48 (bs, 1 H, OH), 4.42 (dd, 1 H, H-5), 1.40 and 1.36 (2s, each 3 H, Me_2C); ^{13}C (75.5 MHz, $CDCl_3$): δ 161.7 (C-4′), 153.4 (C-2′), 127.1 (C-2), 110.4 (CMe_2), 109.7 (C-3), 73.6 (C-5), 71.2 (C-6), 69.0 (C-4), 28.1 and 26.4 [$(CH_3)_2C$] (data for the fused hydantoin moiety are identified by a prime); EIMS (70 eV): *m*/*z* 240 $[M]^+$, 225 $[M-Me]^+$, 207 $[M-H_2O]^+$, 165, 154, 136, 122, 83, 55, 43; CIMS: *m*/*z* 320 $[M+C_5H_5NH]^+$. Anal. Calcd for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.04; N, 11.70. Found: C, 49.92; H, 5.09; N, 11.79.

3.2.6. (4*S*,5*S*,6*R*)-6-acetoxy-*N*-3′-acetyl-5,6-dihydro-4,5-isopropylidenedioxy-4*H*-pyrido[2,1-*e*]imidazolidine-2′,4′-dione (8). Acetylation of **6** with Ac_2O in Py under usual conditions afforded diacetate **8** in 85% yield; white needles (R_f 0.72, eluent A); mp 160–162 °C (from EtOAc–hexane); $[\alpha]_D$ +96° (*c* 1, MeOH); ^{1}H (300 MHz, $CDCl_3$): δ 6.84 (d, 1 H, $J_{5,6}$ 2.5 Hz, H-6), 6.06 (dd, 1 H, $J_{3,4}$ 2.8, $J_{3,5}$ 1.3 Hz, H-3), 4.89 (dd, 1 H, $J_{4,5}$ 5.1 Hz, H-4), 4.39 (ddd, 1 H, H-5), 2.62 (s, 3 H, CH_3CON), 2.11 (s, 3 H, CH_3COO), 1.40 and 1.37 (2s, each 3 H, Me_2C); ^{13}C (75.5 MHz, $CDCl_3$): δ 168.4 (CH_3CON), 167.4 (CH_3COO), 158.0 (C-4′), 148.6 (C-2′), 125.0 (C-2), 110.9 (CMe_2), 109.9 (C-3), 71.7 (C-5), 70.6 (C-6), 68.9 (C-4), 28.0 and 26.2 [$(CH_3)_2C$], 26.3 (CH_3CON), 20.6 (CH_3COO) (data for the fused hydantoin moiety are identified by a prime); CIMS: *m*/*z* 404 $[M+C_5H_5NH]^+$. Anal. Calcd for $C_{14}H_{16}N_2O_7$: C, 51.90; H, 4.97; N, 8.64. Found: C, 52.02; H, 5.03; N, 8.59.

3.2.7. Methyl 5-*O*-acetyl-2,3-*O*-isopropylidene-α-D-mannofuranosiduronamide [methyl (5*S*)-5-*O*-acetyl-5-*C*-carbamoyl-2,3-*O*-isopropylidene-α-D-lyxofuranoside; methyl (5*S*)-5-*O*-acetyl-2,3-*O*-isopropylidene-α-D-*lyxo*-hexofuranosiduronamide] (9). Acetylation of **3** with Ac_2O in Py under usual conditions afforded **9** in 81% yield; white needles (R_f 0.56, eluent B); mp 157–158 °C (from EtOAc); $[\alpha]_D$ +84° (*c* 1, MeOH); ^{1}H (300 MHz, $CDCl_3$): δ 6.22 and 5.73 (2bs, each 1 H, NH_2), 5.25 (d, 1 H, $J_{4,5}$ 9.2 Hz, H-5), 4.96 (s, 1 H, H-1), 4.75 (dd, 1 H, $J_{2,3}$ 5.7, $J_{3,4}$ 3.1 Hz, H-3), 4.57 (d, 1 H, H-2), 4.25 (dd, 1 H, H-4), 3.31 (s, 3 H, OCH_3), 2.17 (s, 1 H, CH_3CO), 1.45 and 1.30 (2s, each 3 H, Me_2C); ^{13}C (75.5 MHz, $CDCl_3$): δ 170.1 ($COCH_3$), 169.6 ($CONH_2$), 112.8 (CMe_2), 107.5 (C-1), 84.3 (C-2), 79.5 (C-3), 76.6 (C-4), 70.0 (C-5), 54.8 (OCH_3), 26.0 and 24.7 [$(CH_3)_2C$], 20.6 (CH_3CO); CIMS: *m*/*z* 369 $[M+C_5H_5NH]^+$. Anal. Calcd for $C_{12}H_{19}NO_7$: C, 49.80; H, 6.62; N, 4.48. Found: C, 49.88; H, 6.70; N, 4.51.

3.3. X-ray crystallography

Crystal and experimental data for compounds **3** and **6** are summarised in Table 1. Selected relevant torsion angles are given in Table 2. Preliminary orientation matrices were obtained from the first frames using Siemens SMART software.[22] Final cell parameters were obtained by refinement using Siemens SAINT software.[22] The data were empirically corrected for absorption and other effects using SADABS program[23] based on the method of Blessing.[24] The structures were solved by direct methods and refined by full-matrix least-squares on all F^2 data using Bruker SHELXTL.[25] The non-H atoms were refined anisotropically. Hydrogen atoms were constrained to the ideal geometry using an appropriate riding model. Molecular graphics were obtained using the program DIAMOND.[26]

The diffraction data of **6** showed apparent Laue symmetry *mmm* (R_{merge} = 4.7% after absorption correction) indicating thus the orthorhombic system. Nevertheless, it was difficult to determine the space group due to uncertain extinction conditions. It was possible though to solve the structure in the orthorhombic space group $P2_12_12_1$ (with 35 systematic absence violations), while the refinement of the model did not lead to a satisfactory result (*R*-value of 17.3%, non-positive definite temperature factors). Therefore, a lower symmetry was anticipated and the structure was regarded to be monoclinic, space group $P2_1$, with two crystal-

lographically independent molecules in the crystal lattice. Consequently, the twinning law has been introduced (TWIN 1 0 0 0 -1 0 0 0 -1, BASF 0.534(1), see SHELXTL (Bruker, 2001)) and the refinement of the structure satisfactorily converged (R-value = 3.9%, all temperature factors well behaving).

4. Supplementary material

Crystallographic data for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, CCDC Nos. 206813 and 206814 for compounds **3** and **6**, respectively. Copies of the data may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: + 44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

Acknowledgements

The authors thank K. Paule, G. Košický, A. Karovičová, A. Kanská, and Dr V. Pätoprstý (Institute of Chemistry) for microanalyses, optical rotation, NMR, and mass spectral measurements. Financial support of this work by the Scientific Grant Agency (VEGA, Slovak Academy of Sciences and Ministry of Education, Bratislava, Grant Nos. 2/3077/23 and 2/3104/23) is gratefully appreciated.

References

1. (a) Bucherer, H. T.; Fischbeck, H. T. *J. Prakt. Chem.* **1934**, *140*, 69;
   (b) Bergs, H. Ger. pat. 566,094, 1929.;
   (c) Hoyer, H. L. *Chem. Ber.* **1950**, *83*, 491;
   (d) Ware, E. *Chem. Rev.* **1950**, *46*, 422.
2. Yanagisawa, H.; Kinoshita, M.; Nakada, S.; Umezawa, S. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 246–252.
3. Rosenthal, A.; Dodd, R. R. *J. Carbohydr. Nucleos. Nucleot.* **1979**, *6*, 467–476.
4. Kuszmann, J.; Márton-Merész, M.; Jerkovich, G. *Carbohydr. Res.* **1988**, *175*, 249–264.
5. Lamberth, C.; Blarer, S. *Synlett* **1994**, 489–490.
6. Sano, H.; Sugai, S. *Tetrahedron* **1995**, *51*, 4635–4646.
7. Kóš, M.; Steiner, B.; Langer, V.; Gyepesová, D.; Ďurík, M. *Carbohydr. Res.* **2000**, *328*, 115–126.
8. Kóš, M.; Steiner, B.; Mičová, J.; Langer, V.; Ďurík, M.; Gyepesová, D. *Carbohydr. Res.* **2001**, *332*, 351–361.
9. Mičová, J.; Steiner, B.; Kóš, M.; Langer, V.; Gyepesová, D. *Synlett* **2002**, 1715–1717.
10. Steiner, B.; Mičová, J.; Kóš, M.; Langer, V.; Gyepesová, D. *Carbohydr. Res*., **2003**, *338*, 1349–1357.
11. Postel, D.; Nguyen Van Nhien, A.; Villa, P.; Ronco, G. *Tetrahedron Lett.* **2001**, *42*, 1499–1502.
12. (a) Haruyama, H.; Takayama, T.; Kinoshita, T.; Kondo, M.; Nakajima, M.; Haneishi, T. *J. Chem. Soc. Perkin Trans. 1* **1991**, 1637–1640;
    (b) Nakajima, M.; Itoi, K.; Takamatsu, Y.; Kinoshita, T.; Okazaki, T.; Kawakubo, K.; Shindo, M.; Honma, T.; Tohjigamori, M.; Haneishi, T. *J. Antibiot.* **1991**, *44*, 293–300;
    (c) Nakajima, N.; Matsumoto, M.; Kirihara, M.; Hashimoto, M.; Katoh, T.; Terashima, S. *Tetrahedron* **1996**, *52*, 1177–1194.
13. (a) Estevez, J. C.; Estevez, R. J.; Ardron, H.; Wormald, M. R.; Brown, D.; Fleet, G. W. J. *Tetrahedron Lett.* **1994**, *35*, 8885–8888;
    (b) Estevez, J. C.; Smith, M. D.; Lane, A. L.; Crook, S.; Watkin, D. J.; Besra, G. S.; Brennan, P. J.; Nash, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1996**, *7*, 387–390.
14. Krajewski, J. W.; Gluzinski, P.; Pakulski, Z.; Zamojski, A.; Mishnev, A.; Kemme, A. *Carbohydr. Res.* **1994**, *252*, 97–105.
15. Barton, D. H. R.; Gero, S. D.; Quiclet-Sire, B.; Samadi, M. *Tetrahedron: Asymmetry* **1994**, *5*, 2123–2136.
16. Mičová, J.; Steiner, B.; Kóš, M.; Gajdoš, J.; Langer, V.; Gyepesová, D. *Molecules* **2002**, *7*, 437–446.
17. Mičová, J.; Steiner, B.; Kóš, M.; Langer, V.; Ďurík, M.; Gyepesová, D.; Smrčok, L. *Carbohydr. Res.* **2002**, *337*, 663–672.
18. Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354–1358.
19. Bernstein, J.; Davis, R. E.; Shimoni, L.; Chang, L.-N. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1555–1573.
20. Motherwell, W. D. S.; Shields, G. P.; Allen, F. H. *Acta Crystallogr., Sect. B* **1999**, *55*, 1044–1056.
21. Pätoprstý, V.; Kovácik, V.; Karácsonyi, Š. *Rapid Commun. Mass Spectrom*. **1995**, *9*, 840–844.
22. Siemens AXS. *SMART & SAINT*; Madison, WI, USA, 1995.
23. Sheldrick, G. M. *Program SADABS*; University of Göttingen: Germany, 2001.
24. Blessing, R. H. *Acta Crystallogr., Sect. A.* **1995**, *51*, 33–38.
25. Bruker AXS Inc. *SHELXTL Version 6.10*; Madison, WI, USA, 2001.
26. Brandenburg, K. *DIAMOND: Visual Crystal Structure Information System, Version 2.1d*; Crystal Impact GbR: Bonn, Germany, 2000.