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Synthesis and structure determination of some nonanomerically C–C-linked serine glycoconjugates structurally related to mannojirimycin

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Abstract—The Bucherer–Bergs reaction of methyl 2,3-*O*-isopropylidene-α-D-*lyxo*-hexofuranosid-5-ulose gave (4′*S*)-4′-carbamoyl-4′-[methyl (4*R*)-2,3-*O*-isopropylidene-β-L-erythrofuranosid-4-*C*-yl]-oxazolidin-2′-one instead of expected hydantoins. A mixture of hydantoins—(5′*R*)-triphenylmethoxymethyl-5′-[methyl (4*R*)-2,3-*O*-isopropylidene-β-L-erythrofuranosid-4-*C*-yl]-imidazolidin-2′,4′-dione and (5′*S*)-triphenylmethoxymethyl-5′-[methyl (4*R*)-2,3-*O*-isopropylidene-β-L-erythrofuranosid-4-*C*-yl]-imidazolidin-2′,4′-dione was obtained from the 5-ulose having protected primary OH group at C-6. The 4′-*S* configuration of **2** as well as 5′-*S* configuration of (5′*S*)-hydroxymethyl-5′-[methyl (4*R*)-2,3-*O*-isopropylidene-β-L-erythrofuranosid-4-*C*-yl]-imidazolidin-2′,4′-dione (**9**) was confirmed by X-ray crystallography. Corresponding α-amino acid—methyl (5*S*)-5-amino-5-*C*-carboxy-5-deoxy-α-D-*lyxo*-hexofuranoside (alternative name: 2-[methyl (4*R*)-β-L-erythrofuranosid-4-*C*-yl]-L-serine) (**11**) was obtained from the hydantoin **9** by acid hydrolysis of the isopropylidene and trityl groups followed by basic hydrolysis of the hydantoin ring. Analogous derivatives with 5-*R* configuration, formed in a minority, were also isolated and characterised.

Keywords: Sugar amino acids; Hydantoins; Serine; Bucherer–Bergs reaction; Mannojirimycin; X-ray crystallography; Conformation

1. Introduction

Sugar amino acids represent highly substituted polyfunctionalised building blocks, which can be used in the preparation of very useful glycomimetic and peptidomimetic libraries. Carbohydrate moieties of glycoproteins and glycolipids play an important role in a variety of biological events, especially in recognition phenomena and immune response.[1] Their decisive influence on conformation, solubility and stabilisation of proteins is also known.[2] The use of synthetic glycopeptide model compounds became attractive for understanding of the mutual interactions between both moieties with the aim to develop new powerful glycosidase inhibitors and effective compounds for drug design. To improve the metabolic stability of these potential drugs, a lot of more stable C–C-linked analogues have been synthesised during the past two decades.[3–21] In this respect, α,α-disubstituted sugar α-amino acids are subjects of exceptional interest because an additional substituent at the α-position sterically constrains the free rotation or conformation flexibility of their side chain or strictly fixes conformation by a saccharide ring. Incorporation of such sugar amino acids into a peptide imparts well-defined conformational constraints to a peptide backbone preferring folded conformation, inducing α-helical secondary structures and stabilising the neighbouring peptide bond against chemical or enzymatic hydrolysis due mainly to steric reasons.[22,23]

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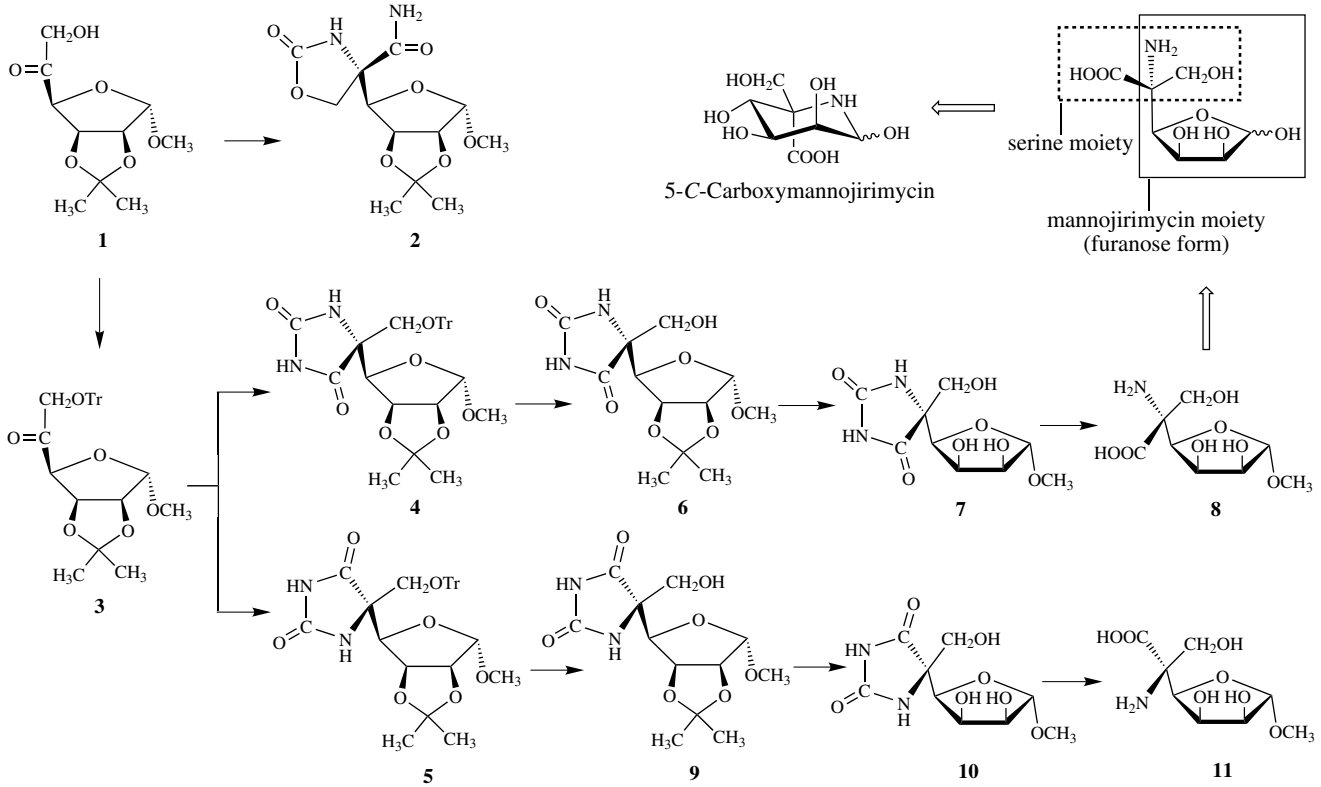
Hydrolysis of hydantoins provides a suitable route for the preparation of sugar α-amino acids.[24–27] Although starting hydantoins can be obtained conveniently by the Bucherer–Bergs reaction (or its modification according to Hoyer), only a few papers on the application of this reaction to a carbohydrate derivative have been reported till now.[26–34] Recently, we have published[31–34] the synthesis of some sugar α-amino acids via corresponding hydantoin derivatives starting from methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-*lyxo*-hexopyranosid-4-ulose, methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hexofuranosid-5-ulose, methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-*lyxo*-hexofuranosid-5-ulose and methyl 6-deoxy-6-isopropyl-2,3-*O*-isopropylidene-α-D-*lyxo*-hexofuranosid-5-ulose. In these cases, with exception of starting hexopyranosid-4-ulose, the prepared glycoconjugate model compounds have C-2-linked α-amino acid attached to a furanoside moiety in the C-4 position, while C-2 atom of α-amino acid coincides with C-5 atom of sugar backbone (C-5–C-2 fused sugar α-amino acid). In this paper we present the synthesis and structure determination of some serine derivatives branched at C-2 atom with a saccharide moiety, obtained from suitably 6-*O*-protected methyl α-D-*lyxo*-hexofuranosid-5-ulose. Further studies on the preparation of analogous glycoconjugates related to phenylalanine or aspartic acid branched with a glucose or mannose moiety, respectively, are in progress.

2. Results and discussion

According to our previously published[35] results, the Bucherer–Bergs reaction of the known methyl 2,3-*O*-isopropylidene-α-D-*lyxo*-hexofuranosid-5-ulose (**1**)[36–39] did not afford expected corresponding hydantoin derivatives **4** and **5** but (4′*S*)-4′-carbamoyl-4′-[methyl (4*R*)-2,3-*O*-isopropylidene-β-L-erythrofuranosid-4-*C*-yl]-oxazolidin-2′-one (**2**) was preferentially formed via ring closure including unprotected primary hydroxyl group at C-6 atom of the starting 5-ulose **1** (Scheme 1). Therefore, its initial protection is crucial to avoid such undesired cyclisation and we have used *O*-tritylation for this purpose. Thus, application of the Bucherer–Bergs reaction to methyl 2,3-*O*-isopropylidene-6-*O*-triphenylmethyl-α-D-*lyxo*-hexofuranosid-5-ulose (**3**)[39] gave a mixture of (5′*R*)-triphenylmethoxymethyl-5′-[methyl (4*R*)-2,3-*O*-isopropylidene-β-L-erythrofuranosid-4-*C*-yl]-imidazolidin-2′,4′-dione (**4**) and (5′*S*)-triphenylmethoxymethyl-5′-[methyl (4*R*)-2,3-*O*-isopropylidene-β-L-erythrofuranosid-4-*C*-yl]-imidazolidin-2′,4′-dione (**5**) (Scheme 1). The stereoselectivity of this reaction was almost 60% (ee, based on the analysis of NMR spectra of the reaction mixture) in favour of the hydantoin **5** having *S* configuration at C-5 (with respect to both carbohydrate and hydantoin atoms numbering) unlike alanine and leucine analogues[32,34] (6-deoxy or 5-isobutyl derivatives) where 5-*R* derivatives were favoured. This can be probably



Scheme 1.

due to higher steric influence of bulky 6-*O*-trityl group as well as higher polarity of hydroxymethyl group in comparison with methyl or isobutyl. Although selective acid hydrolysis of 6-*O*-trityl protective group to afford relatively low yields of **6** and **9** is possible, for preparative purposes, the one-step acid hydrolysis (to increase the solubility of the products in water for the next reaction step) of both 6-*O*-trityl and 2,3-*O*-isopropylidene protective group in **4** and **5** is more convenient because of higher overall yields of **7** and **10**. Subsequent basic hydrolysis of the hydantoin ring in **7** and **10** afforded the desired α-amino acids **8** and **11**, respectively. Because, in this case, terminal CH_2OH group of parent saccharide molecule became a part of serine moiety and the quaternary C-5 atom of a saccharide moiety coincides with the α-carbon atom of serine, in addition to methyl (5*S*)-5-amino-5-*C*-carboxy-5-deoxy-α-D-*lyxo*-hexofuranoside (according to carbohydrate nomenclature), compound **11** can be alternatively named as 2-[methyl (4*R*)-β-L-erythrofuranosid-4-*C*-yl]-L-serine. In conclusion, compound **8** (after deprotection) structurally represents the 5-*C*-carboxymannojirimycin (see Scheme 1).

The *S* configuration at C-4′ in oxazolidin-2′-one **2** was confirmed by X-ray crystallography. Analogously, the configuration at C-5 of compounds **3**–**11** was confirmed by unambiguously establishing the 5-*S* configuration (relatively to known configuration at C-2, C-3 and C-4) of compound **9** using X-ray analysis. Figures 1 and 2 show molecule and the numbering scheme of compounds **2** and **9**, respectively. The H-positions have been put at calculated positions and were during refinement riding on their respective pivot atoms. The relevant crystallographic data for **2** and **9** are given in Table 1. A list of selected torsion angles is given in Table 2.

The presence of a 1,3-dioxolane ring fused to a furanose ring at the 2,3-position and the α-glycosidic methyl

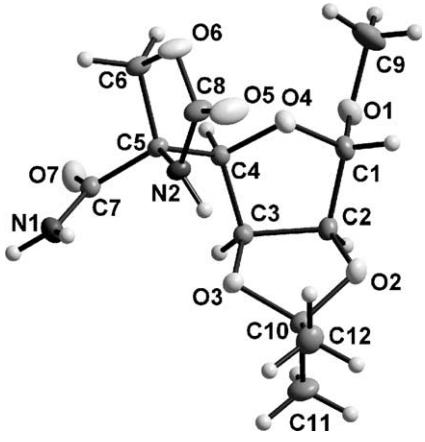


Figure 1. Numbering scheme and atomic displacement ellipsoids at 50% probability level of compound **2**.

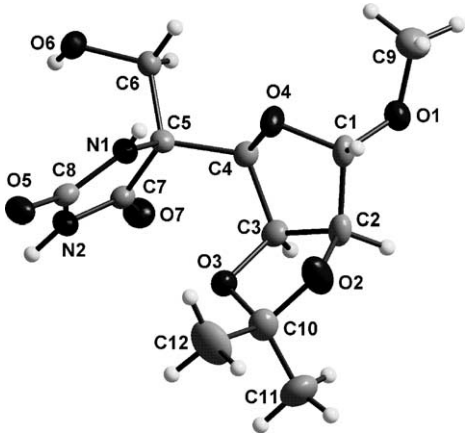


Figure 2. Numbering scheme and thermal ellipsoids at 50% probability level of compound **9**.

group can impose some conformational rigidity on compounds **2**, **4**–**6** and **9**. For compound **2**, the values of relevant torsion angles O4–C1–C2–C3 = 22.90(7)°, C1–C2–C3–C4 = 0.03(9)°, C2–C3–C4–O4 = −22.67(7)°, C3–C4–O4–C1 = 38.73(7)°, C4–O4–C1–C2 = −38.69(7)° and puckering parameters[40] $Q = 0.361(1)$ Å, $\Phi = 359.74(12)°$ indicate that O4–C1–C2–C3–C4 furanose ring adopts almost ideal ^{O}E conformation. Analogously, the puckering parameters $Q = 0.321(1)$ Å, $\Phi = 148.55(13)°$ and the relevant dihedral angles O2–C2–C3–O3 = −2.73(7)°, C2–C3–O3–C10 = −18.57(7)°, C3–O3–C10–O2 = 33.36(7)°, O3–C10–O2–C2 = −35.43(7)°, C10–O2–C2–C3 = 23.48(7)° are indicative of $^{C\text{-}10}E$ conformation slightly distorted to the $^{C\text{-}10}T_{O\text{-}2}$ direction for five-membered 1,3-dioxolane ring (O2–C2–C3–O3–C10) with C-10 atom lying in the *endo* and O-2 *exo* direction with respect to the C3–O3 reference bond. The five-membered oxazolidine ring (O6–C6–C5–N2–C8) adopts almost ideal $^{C\text{-}5}E$ conformation, considering the puckering parameters $Q = 0.211(1)$ Å, $\Phi = 72.6(2)°$ and the relevant torsion angles O6–C6–C5–N2 = 19.84(7)°, C6–C5–N2–C8 = −21.36(8)°, C5–N2–C8–O6 = 15.19(9)°, N2–C8–O6–C6 = −0.67(9)° and C8–O6–C6–C5 = −12.72(8)°.

Similarly for compound **9**, based on the values of relevant torsion angles and puckering parameters [$Q = 0.340(3)$ Å, $\Phi = 0.7(5)°$ and $Q = 0.311(3)$ Å, $\Phi = 149.7(5)°$, respectively], the ideal ^{O}E conformation for O4–C1–C2–C3–C4 furanose ring and $^{C\text{-}10}E$ conformation slightly distorted to the $^{C\text{-}10}T_{O\text{-}2}$ direction for O2–C2–C3–O3–C10 five-membered 1,3-dioxolane ring, was observed. In contrast with our previously published[32–34] planar conformation for five-membered hydantoin rings, in this case, the puckering parameters $Q = 0.082(2)$ Å, $\Phi = 31.1(17)°$ as well as relevant dihedral angles N1–C5–C7–N2 = 7.8(2)°, C5–C7–N2–C8 = −4.6(3)°, C7–N2–C8–N1 = −0.9(3)°, N2–C8–N1–C5 = 6.5(3)°, C8–N1–C5–C7 = −8.8(3)° are indicative of

Table 1. Crystallographic and experimental data for compounds **2** and **9**[a]

	Compound **2**	Compound **9**
Empirical formula	$C_{12}H_{18}N_2O_7$	$C_{12}H_{18}N_2O_7$
Formula weight	302.28	302.28
Temperature, T (K)	183(2)	183(2)
Wavelength, λ (Å)	0.71073	0.71073
Crystal system	Tetragonal	Orthorhombic
Space group	$P4_3$	$P2_12_12_1$
Unit cell dimensions		
a (Å)	9.050	6.19520(10)
b (Å)	9.050	15.3460(2)
c (Å)	17.3645(2)	15.43380(10)
Unit-cell volume V (Å^3)	1422.321(16)	1467.32(3)
Formula per unit cell, Z	4	4
D_{calcd} (g/cm^3)	1.412	1.368
Radiation	Mo K$_\alpha$	Mo K$_\alpha$
Absorption coefficient, μ (mm^{-1})	0.117	0.113
F(000)	640	640
Crystal size (mm)	0.60 (max)	0.95 (max)
	0.35 (min)	0.04 (min)
Diffractometer	Siemens SMART CCD	Siemens SMART CCD
θ Range (°)	2.25–32.81	2.64–26.43
Range of h	$-13 \rightarrow 13$	$-7 \rightarrow 7$
Range of k	$-13 \rightarrow 13$	$-19 \rightarrow 19$
Range of l	$-26 \rightarrow 26$	$-19 \rightarrow 19$
Reflections	25114	17408
Independent reflections	5053 (R_{int} = 0.0225)	1761 (R_{int} = 0.0621)
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	5053/1/214	1761/0/212
Goodness-of-fit on F^2	1.053	1.091
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0263, wR_2 = 0.0714	R_1 = 0.0367, wR_2 = 0.0777
R indices (all data)	R_1 = 0.0276, wR_2 = 0.0728	R_1 = 0.0484, wR_2 = 0.0828
Largest difference peak and hole (e/Å^3)	0.240 and −0.196	0.194 and −0.173

[a] Standard deviations in parentheses.

Table 2. Selected torsion angles (°) for compounds **2** and **9**[a]

	Compound **2**	Compound **9**
C1–C2–C3–C4	0.03(7)	−0.7(3)
O4–C1–C2–C3	22.90(7)	22.3(3)
C2–C3–C4–O4	−22.67(7)	−21.1(2)
C1–O4–C4–C3	38.73(7)	36.5(2)
C4–O4–C1–C2	−38.69(7)	−36.8(3)
O2–C2–C3–O3	−2.73(7)	−3.2(3)
C10–O3–C3–C2	−18.57(7)	−17.8(3)
C3–O3–C10–O2	33.36(7)	32.4(3)
C2–O2–C10–O3	−35.43(7)	−34.8(3)
C10–O2–C2–C3	23.48(7)	23.2(3)
O1–C1–C2–O2	152.46(6)	150.9(2)
O1–C1–O4–C4	78.26(7)	80.5(3)
C1–C2–C3–O3	−116.78(6)	−118.3(2)
O2–C2–C3–C4	114.09(6)	114.5(2)
O4–C4–C5–C6	61.93(7)	82.9(2)
C7–C5–C6–O6	140.80(6)	58.6(3)
N2–C5–C6–O6	19.84(7)	
C8–O6–C6–C5	−12.72(8)	
C6–O6–C8–N2	−0.67(9)	
C5–N2–C8–O6	15.19(9)	
C8–N2–C5–C6	−21.36(8)	
C8–N1–C5–C7		−8.8(3)
C8–N2–C7–C5		−4.6(3)
N1–C5–C7–N2		7.8(2)
C5–N1–C8–N2		6.5(3)
C7–N2–C8–N1		−0.9(3)

[a] Standard deviations in parentheses.

$E_{C\text{-}5}$ conformation for N1–C5–C7–N2–C8 hydantoin ring.

Analysis of the molecular packing in the unit cell of compound **2** revealed four principal hydrogen bonds and three weak hydrogen bonds of C–H···O type (Table 3), which give rise to a number of interactions in many directions. Two of them, [c] and [d], are intramolecular, while the other are intermolecular (Fig. 3). The first level descriptors based on the graph-set theory[41] include intramolecular strings S1,1(6) formed by bond [c] and S1,1(5) formed by bond [d], chains C1,1(7), formed by bond [a], C1,1(8) (bonds [b] and [e]), C1,1(5) (bond [f]) and C1,1(9) (bond [g]). The second level comprises: chains C2,2(6) (bonds [b] and [c], [b] and [e]), C2,2(15) (bonds [a] and [b], [a] and [e]), C2,2(11) (bonds [a], [b]; [b], [e]; [b], [f] and [b], [g]), C1,2(9) (bonds [a], [e]), C2,2(9) (bonds [a] and [f]), C2,2(12) (bonds [a], [f]; [e], [f] and [e], [g]), C2,2(14) (bonds [a], [g] and [f], [g]), C2,2(16) (bonds [a], [g] and [b], [e]), C2,2(17) (bonds [b], [g] and [e], [g]), C2,2(13) (bonds [e], [f]) and C1,2(10) (bonds [f], [g]; also R2,2(13) ring defined by the hydrogen bonds [b] and [f] was found. Assignment of the H-bond descriptors, based on the graph-set theory[41] was obtained using the program PLUTO.[42] For convenience, the notation Xa,d(n) has also been adopted in

Table 3. Hydrogen bond geometry in compound **2**[a]

Notation	X–H···Y	Symmetry code	X–H (Å)	H···Y (Å)	X···Y (Å)	X–H···Y (°)
a	N1–H1A···O5^{ii}	$y, -x, z+1/4$	0.88	2.06	2.9345(10)	172.1
b	N1–H1B···O1^{i}	$-y+1, x, z-1/4$	0.88	2.23	3.0365(10)	151.7
c	N2–H2···O3		0.875(14)	2.199(14)	2.7958(9)	125.2(12)
d	N1–H1B···N2		0.88	2.39	2.7815(10)	107.6
e	C2–H2A···O5^{iii}	$-x, -y+1, z+1/2$	1.00	2.56	3.4298(11)	145.0
f	C6–H6B···O7^{i}	$-y+1, x, z-1/4$	0.99	2.48	3.3913(10)	153.0
g	C12–H12A···O7^{iv}	$x-1, y, z$	0.98	2.60	3.5076(12)	154.5

[a] Standard deviations in parentheses.

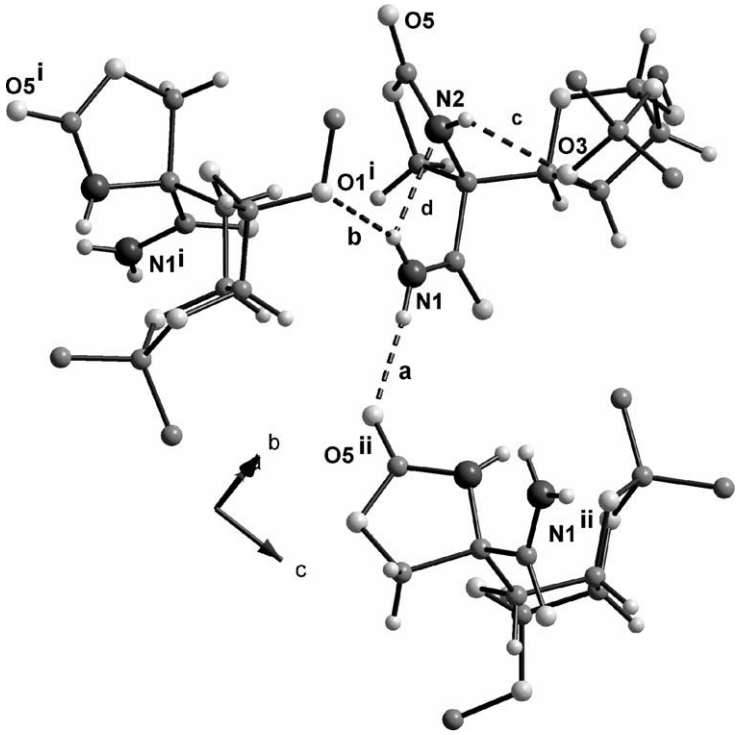


Figure 3. Hydrogen bonding in compound **2**. Methyl hydrogen atoms are omitted for clarity. For symmetry codes and notation, see Table 3.

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 **9** (see Table 4) three strong hydrogen bonds of types O–H···O and N–H···O are present together with one weak hydrogen bond of C–H···O. The first-level descriptors based on the graph-set theory[41] include chains C1,1(7), formed by hydrogen bonds [a], C1,1(5) ([b]) (Fig. 4), C1,1(6) ([c]) and C1,1(8) ([d]). The second-level comprises: chains C2,2(10) (bonds [a], [b] and [b], [c]), C2,2(11) (bonds [a], [b]; [b], [d] and [c], [d]), C2,2(6) (bonds [a] and [c] (Fig. 5), C2,2(15) (bonds [a] and [d]), C1,2(9) (bonds [a] and [d]), C2,2(12) (bonds [b] and [d]) and C2,2(14) (bonds [e] and [d]). Also a ring R2,2(13), formed by bonds [a] and [c], has been identified.

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 (equipped with gradient-enhanced spectroscopy kit GRASP for generation of *Z* gradient up to 50 G/cm) 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. When reporting assignments of NMR signals, data for the oxazolidine and hydantoin

Table 4. Hydrogen bond geometry in compound **9**[a]

Notation	X–H···Y	Symmetry code	X–H (Å)	H···Y (Å)	X···Y (Å)	X–H···Y (°)
a	O6–H6···O5^{ii}	$x+1/2, -y+3/2, -z$	0.84	1.83	2.667(3)	174.2
b	N1–H1···O7^{i}	$x-1, y, z$	0.88	2.10	2.905(3)	151.5
c	N2–H2···O6^{ii}	$x+1/2, -y+3/2, -z$	0.88	1.94	2.801(3)	164.2
d	C2–H2A···O5^{iii}	$-x+1/2, -y+1, z+1/2$	1.00	2.50	3.454(3)	158.7

[a] Standard deviations in parentheses.

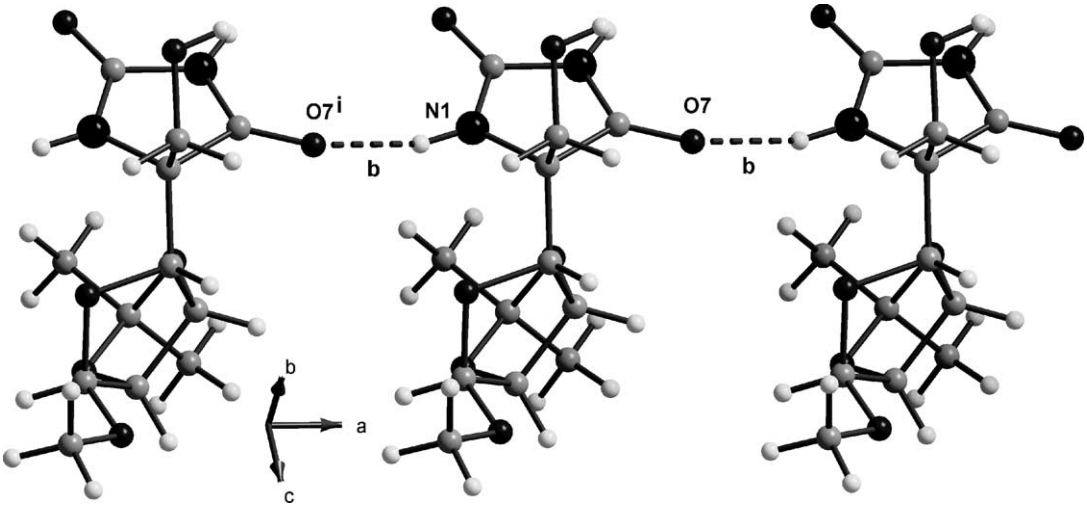


Figure 4. A chain parallel with *b*-axis of hydrogen bonds of N1···O7 type in compound **9**. For symmetry code and notation, see Table 4.

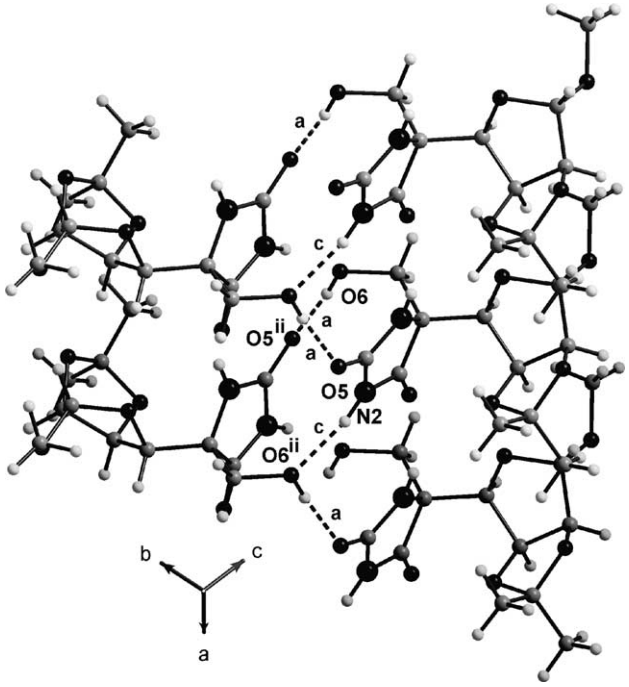


Figure 5. Chains and rings of hydrogen bonds of type N2···O6 and O6···O5 in compound **9**. For symmetry code and notation, see Table 4.

residue are identified by a prime and those for the phenyls by a double prime. The EI and CI (using pyridine as a reactive agent) mass spectra (70 eV) were obtained on a Finnigan MAT SSQ 710 instrument. Specific rotations 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. All reactions were monitored by TLC on Silica Gel 60 plates (E. Merck) using the following solvents: 2:3 EtOAc–hexane (eluent A), 10:1 $CHCl_3$–MeOH (eluent B), 4:1 $CHCl_3$–MeOH (eluent C), 8:1 $CHCl_3$–MeOH (eluent D), 7:3 MeOH–water (eluent E). Visualisation was affected with iodine vapour or H_2SO_4. Column chromatography was performed as flash chromatography on Silica Gel 60 (E. Merck, 0.063–0.200 mm).

3.2. X-ray techniques

Crystal and experimental data for **2** and **9** are summarised in Table 1. Preliminary orientation matrix was obtained from the first frames using Siemens SMART software.[43] Final cell parameters were obtained by refinement of 7505 (for **2**) and 8087 (for **9**) reflections using Siemens SAINT software.[43] The data were empirically corrected for absorption and other effects using SADABS program[44] based on the method of Blessing.[45] The structures were solved by direct methods and refined by full-matrix least-squares on all F^2 data using Bruker SHELXTL.[46] The non-H atoms were refined aniso-

tropically. Hydrogen atoms were constrained to the ideal geometry using an appropriate riding model. Molecular graphics were obtained using the program DIAMOND.[47]

3.3. (4′*S*)-4′-Carbamoyl-4′-[methyl (4*R*)-2,3-*O*-isopropylidene-β-L-erythrofuranosid-4-*C*-yl]-oxazolidin-2′-one (2)

To a solution of 5-ulose **1** (6.97 g, 30 mmol) in 50% aqueous EtOH (50 mL) was added KCN (3.90 g, 60 mmol) and $(NH_4)_2CO_3$ (13.45 g, 140 mmol) and the mixture was stirred at 60 °C for 8 h. Ethanol was then evaporated and the product extracted with $CHCl_3$. After complete solvent removal in vacuo, the residue was chromatographed on a column of silica gel with eluent D. The fractions having R_f 0.70 were collected and evaporated to give **2** (3.90 g, 43%). Recrystallisation from EtOAc afforded white needles with mp 235–237 °C; $[\alpha]_D$ +126 (*c* 1, MeOH); NMR: ^{1}H (300 MHz, $CDCl_3$): δ 6.80 and 5.67 (2br s, each 1H, NH_2), 6.09 (br s, 1H, NH), 4.98 (s, 1H, H-1), 4.82 (dd, 1H, $J_{2,3}$ 5.9 Hz, $J_{3,4}$ 3.4 Hz, H-3), 4.57 (d, 1H, H-2), 4.56 and 4.46 (2d of ABq, each 1H, $J_{Ha,Hb}$, 8.8 Hz, CH_2), 4.45 (d, 1H, H-4), 3.35 (s, 3H, OCH_3), 1.54 and 1.28 (2s, each 3H, Me_2C); ^{13}C (75.5 MHz, $CDCl_3$): δ 172.9 ($CONH_2$), 159.1 (CO at C-2′), 113.2 (CMe_2), 106.9 (C-1), 85.1 (C-2), 79.9 (C-3), 78.6 (C-4), 72.6 (CH_2), 64.0 (C-4), 55.0 (OCH_3), 25.8 and 23.9 [$(CH_3)_2C$]; EIMS (70 eV): *m*/*z* 287 $[M-Me]^+$, 258 (100%, $[M-CONH_2]^+$), 226, 170, 134, 75, 53, 40. CIMS: *m*/*z* 382 $(M+C_5H_5NH)^+$. Anal. Calcd for $C_{12}H_{18}N_2O_7$: C, 47.70; H, 6.00; N, 9.27. Found: C, 47.81; H, 6.08, N, 9.20.

3.4. (5′*R*)-Triphenylmethoxymethyl-5′-[methyl (4*R*)-2,3-*O*-isopropylidene-β-L-erythrofuranosid-4-*C*-yl]-imidazolidin-2′,4′-dione (4)

Starting from 5-ulose **3** (14.23 g, 30 mmol) and application of the same reaction procedure as described for the preparation of **2** afforded a mixture of hydantoins **4** and **5**, which were separated on a column of silica gel using solvent A as an eluent. The fractions having R_f 0.59 (eluent A) were collected and evaporated. Recrystallisation of the product from EtOAc–hexane gave pure **4** as white needles (1.80 g, 11% yield); mp 209–210 °C; $[\alpha]_D$ +75 (*c* 1, $CHCl_3$); NMR: ^{1}H (300 MHz, $CDCl_3$): δ 8.80 (br s, 1H, NH), 7.45–7.20 (m, 15H, aromatic), 5.89 (br s, 1H, NH), 4.83 (s, 1H, H-1), 4.61 (dd, 1H, $J_{2,3}$ 5.8 Hz, $J_{3,4}$ 3.2 Hz, H-3), 4.45 (d, 1H, H-2), 4.07 (d, 1H, H-4), 3.52 and 3.41 (2d of ABq, each 1H, $J_{Ha,Hb}$, 9.4 Hz, CH_2), 3.18 (s, 3H, OCH_3), 1.47 and 1.24 (2s, each 3H, Me_2C); ^{13}C (75.5 MHz, $CDCl_3$): δ 173.6 (CO at C-4′), 157.0 (CO at C-2′), 143.1 (C-1″), 128.6 (C-3″ and C-5″), 127.9 (C-2″ and C-6″), 127.2 (C-4′), 112.9 (CMe_2), 106.2 (C-1), 87.4 (CPh_3), 84.8 (C-2), 80.0 (C-3), 77.2 (C-4), 67.6 (C-5′), 63.8 (CH_2), 54.6 (OCH_3), 25.8 and 24.3 [$(CH_3)_2C$]; EIMS (70 eV): *m*/*z* 259, 243 (100%, $[Ph_3C]^+$), 239, 165, 105, 43. Anal. Calcd for $C_{31}H_{32}N_2O_7$: C, 68.40; H, 5.92; N, 5.14. Found: C, 68.43; H, 5.98; N, 5.11.

3.5. (5′*S*)-Triphenylmethoxymethyl-5′-[methyl (4*R*)-2,3-*O*-isopropylidene-β-L-erythrofuranosid-4-*C*-yl]-imidazolidin-2′,4′-dione (5)

The fractions having R_f 0.36 (eluent A) from the above column chromatography were collected and evaporated. Recrystallisation of the product from toluene gave pure **5** as white needles (6.86 g, 42% yield); mp 264–265 °C; $[\alpha]_D$ +29 (*c* 1, $CHCl_3$); NMR: ^{1}H (300 MHz, $CDCl_3$): δ 7.78 (br s, 1H, NH), 7.42–7.18 (m, 15H, aromatic), 5.31 (br s, 1H, NH), 4.86 (s, 1H, H-1), 4.73 (dd, 1H, $J_{2,3}$ 5.9 Hz, $J_{3,4}$ 3.8 Hz, H-3), 4.45 (d, 1H, H-2), 3.96 (d, 1H, H-4), 3.54 and 3.45 (2d of ABq, each 1H, $J_{Ha,Hb}$, 9.2 Hz, CH_2), 3.18 (s, 3H, OCH_3), 1.32 and 1.18 (2s, each 3H, Me_2C); ^{13}C (75.5 MHz, $CDCl_3$): δ 173.5 (CO at C-4′), 156.4 (CO at C-2′), 143.3 (C-1″), 128.6 (C-3″ and C-5″), 127.9 (C-2″ and C-6″), 127.2 (C-4′), 113.1 (CMe_2), 106.7 (C-1), 87.0 (CPh_3), 84.3 (C-2), 79.7 (C-3), 77.4 (C-4), 66.4 (C-5′), 65.8 (CH_2), 54.9 (OCH_3), 25.4 and 24.0 [$(CH_3)_2C$]; EIMS (70 eV): *m*/*z* 259, 243 (100%, $[Ph_3C]^+$), 239, 165, 105, 43. Anal. Calcd for $C_{31}H_{32}N_2O_7$: C, 68.40; H, 5.92; N, 5.14. Found: C, 68.41; H, 5.99; N, 5.09.

3.6. (5′*R*)-Hydroxymethyl-5′-[methyl (4*R*)-2,3-*O*-isopropylidene-β-L-erythrofuranosid-4-*C*-yl]-imidazolidin-2′,4′-dione (6)

To a magnetically stirred solution of hydantoin **4** (5.45 g, 10 mmol) in concentrated acetic acid (75 mL) heated at 60 °C, water (50 mL) was slowly added and the solution was stirred at this temperature for 3 h. After cooling to rt, the separated triphenylmethanol was filtered off and the solvent was evaporated on vacuum rotatory evaporator. The crude product (R_f 0.55, eluent B) was recrystallised from EtOAc affording **6** as white needles (1.27 g, 42% yield); mp 187–188 °C; $[\alpha]_D$ +103 (*c* 1, MeOH); NMR: ^{1}H (300 MHz, D_2O): δ 5.03 (s, 1H, H-1), 4.97 (dd, 1H, $J_{2,3}$ 5.9 Hz, $J_{3,4}$ 3.5 Hz, H-3), 4.70 (d, 1H, H-2), 4.23 (d, 1H, H-4), 4.01 and 3.87 (2d of ABq, each 1H, $J_{Ha,Hb}$, 11.8 Hz, CH_2), 3.33 (s, 3H, OCH_3), 1.48 and 1.33 (2s, each 3H, Me_2C); ^{13}C (75.5 MHz, D_2O): δ 177.7 (CO at C-4′), 160.2 (CO at C-2′), 114.7 (CMe_2), 106.9 (C-1), 84.5 (C-2), 79.8 (C-3), 78.8 (C-4), 69.0 (C-5′), 63.1 (CH_2), 55.4 (OCH_3), 25.0 and 24.2 [$(CH_3)_2C$]; EIMS (70 eV): *m*/*z* 287 $[M-Me]^+$, 272, 173, 154, 85, 59, 43 (100%). Anal. Calcd for $C_{12}H_{18}N_2O_7$:

C, 47.70; H, 6.00; N, 9.27. Found: C, 47.78; H, 6.11; N, 9.20.

3.7. (5′*R*)-Hydroxymethyl-5′-[methyl (4*R*)-β-L-erythrofuranosid-4-*C*-yl]-imidazolidin-2′,4′-dione (7)

A magnetically stirred solution of hydantoin **4** (5.45 g, 10 mmol) in diluted acetic acid (75%, 75 mL) was heated at 60 °C for 3 h and then at 70 °C for 16 h. After cooling to rt, the separated triphenylmethanol was filtered off and the solvent was evaporated to dryness under diminished pressure and co-evaporated twice with toluene. The residue was chromatographed on a column of silica gel with eluent C. The fractions having R_f 0.42 were collected and evaporated to give pure **7** (1.65 g, 63% yield). Analytical sample (white needles) was obtained by recrystallisation from EtOH; mp 203–204 °C; $[\alpha]_D$ +93 (*c* 1, H_2O); NMR: ^1H (300 MHz, D_2O): δ 4.97 (d, 1H, $J_{1,2}$ 4.4 Hz, H-1), 4.39 (d, 1H, $J_{3,4}$ 3.8 Hz, H-4), 4.37 (dd, 1H, $J_{2,3}$ 4.4 Hz, H-3), 4.09 (t, 1H, H-2), 3.90 (s, 2H, CH_2), 3.42 (s, 3H, OCH_3); ^{13}C (75.5 MHz, D_2O): δ 178.2 (CO at C-4′), 160.4 (CO at C-2′), 108.9 (C-1), 79.1 (C-4), 76.5 (C-2), 71.5 (C-3), 70.9 (C-5′), 62.0 (CH_2), 57.1 (OCH_3). Anal. Calcd for $C_9H_{14}N_2O_7$: C, 41.20; H, 5.38; N, 10.70. Found: C, 41.09; H, 5.30; N, 10.62.

3.8. Methyl (5*R*)-5-amino-5-*C*-carboxy-5-deoxy-α-D-*lyxo*-hexofuranoside {2-[methyl (4*R*)-β-L-erythrofuranosid-4-*C*-yl]-D-serine} (8)

A mixture of hydantoin **7** (1.31 g, 5 mmol), barium hydroxide octahydrate (4.73 g, 15 mmol) and water (50 mL) was heated under reflux for 6 h. Carbon dioxide gas was then passed to the hot reaction mixture. The separated barium carbonate was removed by filtration and washed with hot water. Carbon dioxide gas was again passed to the hot solution and after cooling to room temperature, another portion of barium carbonate separated. Filtration and decolourising with charcoal gave clear solution. Water was evaporated under diminished pressure and the residual solid was purified on a short column of silica gel (eluent E). Fractions with R_f 0.68 (eluent E) were collected and evaporated to afford **8** (391 mg, 33%). Analytical sample (white solid) was obtained by recrystallisation from water–methanol; mp 107 °C (dec.); $[\alpha]_D$ +124 (*c* 0.4, H_2O); NMR: ^1H (300 MHz, D_2O): δ 5.00 (d, 1H, $J_{1,2}$ 1.4 Hz, H-1), 4.50 (dd, 1H, $J_{2,3}$ 4.3 Hz, $J_{3,4}$ 6.8 Hz, H-3), 4.47 (d, 1H, H-4), 4.06 (dd, 1H, H-2), 3.94 and 3.91 (2d of ABq, each 1H, $J_{Ha,Hb}$, 11.9 Hz, CH_2), 3.36 (s, 3H, OCH_3); ^{13}C (75.5 MHz, D_2O): δ 175.9 (CO), 108.7 (C-1), 79.3 (C-4), 76.4 (C-2), 72.5 (C-3), 67.3 (C-5′), 64.6 (CH_2), 56.7 (OCH_3). Anal. Calcd for $C_8H_{15}NO_7$: C, 40.50; H, 6.37; N, 5.90. Found: C, 40.59; H, 6.44; N, 5.82.

3.9. (5′*S*)-Hydroxymethyl-5′-[methyl (4*R*)-2,3-*O*-isopropylidene-β-L-erythrofuranosid-4-*C*-yl]-imidazolidin-2′,4′-dione (9)

The same reaction procedure as described for the preparation of **6** was applied. The crude product (R_f 0.47, eluent B) was recrystallised from EtOAc–hexane to give pure **9** as white needles (1.33 g, 44% yield); mp 229–230 °C; $[\alpha]_D$ +29 (*c* 1, MeOH); NMR: ^1H (300 MHz, D_2O): δ 5.09 (s, 1H, H-1), 4.91 (dd, 1H, $J_{2,3}$ 6.0 Hz, $J_{3,4}$ 4.2 Hz, H-3), 4.71 (d, 1H, H-2), 4.10 (d, 1H, H-4), 3.95 and 3.89 (2d of ABq, each 1H, $J_{Ha,Hb}$, 11.8 Hz, CH_2), 3.34 (s, 3H, OCH_3), 1.41 and 1.29 (2s, each 3H, Me_2C); ^{13}C (75.5 MHz, D_2O): δ 177.8 (CO at C-4′), 160.4 (CO at C-2′), 114.6 (CMe_2), 106.6 (C-1), 84.8 (C-2), 80.2 (C-3), 77.8 (C-4), 69.0 (C-5′), 65.0 (CH_2), 55.4 (OCH_3), 25.2 and 24.2 [$(CH_3)_2C$]; EIMS (70 eV): *m*/*z* 287 $[M-Me]^+$, 272, 173, 154, 85, 59, 43 (100%). Anal. Calcd for $C_{12}H_{18}N_2O_7$: C, 47.70; H, 6.00; N, 9.27. Found: C, 47.61; H, 6.06; N, 9.19.

3.10. (5′*S*)-Hydroxymethyl-5′-[methyl (4*R*)-β-L-erythrofuranosid-4-*C*-yl]-imidazolidin-2′,4′-dione (10)

The same reaction procedure as described for the preparation of **7** was applied. The fractions having R_f 0.32 (eluent C) from the column chromatography were collected and evaporated. Recrystallisation of the product from EtOH gave pure **10** as white needles (1.70 g, 65% yield); mp 36–37 °C; $[\alpha]_D$ +48 (*c* 1, H_2O); NMR: ^1H (300 MHz, D_2O): δ 5.00 (d, 1H, $J_{1,2}$ 3.1 Hz, H-1), 4.42 (t, 1H, $J_{2,3}$ 5.1 Hz, $J_{3,4}$ 5.1 Hz, H-3), 4.32 (d, 1H, H-4), 4.05 (dd, 1H, H-2), 3.91 (s, 2H, CH_2), 3.42 (s, 3H, OCH_3); ^{13}C (75.5 MHz, D_2O): δ 178.1 (CO at C-4′), 160.6 (CO at C-2′), 108.8 (C-1), 78.7 (C-4), 75.5 (C-2), 72.0 (C-3), 69.7 (C-5′), 64.5 (CH_2), 56.7 (OCH_3). Anal. Calcd for $C_9H_{14}N_2O_7$: C, 41.20; H, 5.38; N, 10.70. Found: C, 41.29; H, 5.40; N, 10.66.

3.11. Methyl (5*S*)-5-amino-5-*C*-carboxy-5-deoxy-α-D-*lyxo*-hexofuranoside {2-[methyl (4*R*)-β-L-erythrofuranosid-4-*C*-yl]-L-serine} (11)

Starting from **10** (1.31 g, 5 mmol) and application of the same reaction procedure as described for the preparation of **8** afforded **11** (415 mg, 35%). Analytical sample (white solid) was obtained by recrystallisation from water–methanol; mp 110 °C (dec.); $[\alpha]_D$ +65 (*c* 0.4, H_2O); NMR: ^1H (300 MHz, D_2O): δ 5.02 (d, 1H, $J_{1,2}$ 4.0 Hz, H-1), 4.42 (d, 1H, $J_{3,4}$ 3.0 Hz, H-4), 4.41 (dd, 1H, $J_{2,3}$ 4.0 Hz, H-3), 4.09 (t, 1H, H-2), 3.97 and 3.92 (2d of ABq, each 1H, $J_{Ha,Hb}$, 11.8 Hz, CH_2), 3.45 (s, 3H, OCH_3); ^{13}C (75.5 MHz, D_2O): δ 175.5 (CO), 109.0 (C-1), 78.4 (C-4), 76.2 (C-2), 73.1 (C-3), 66.8 (C-5′), 64.8 (CH_2), 57.0 (OCH_3). Anal. Calcd for $C_8H_{15}NO_7$: C, 40.50; H, 6.37; N, 5.90. Found: C, 40.56; H, 6.45; N, 5.85.

4. Supplementary material

Crystallographic data for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, CCDC Nos 178704 and 231556 for compound **2** and **9**, respectively. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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