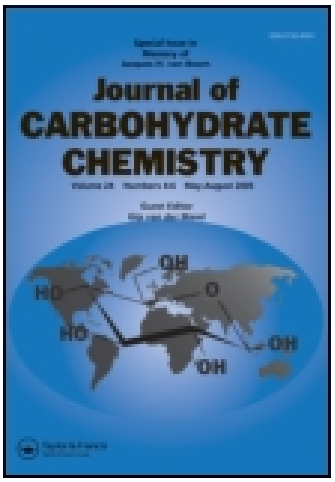

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Entry to the 2,5-Epoxyimidazo[1,5-a][1,3]Diazocine and 5,8-Epoxy[1,2,3]Triazolo[1,5-a][1,3]Diazocine Systems : Novel Reversed Cyclonucleoside Analogues

D.F. Ewing , G. Goethals , G. Mackenzie , P. Martin , G. Ronco , L. Vanbaelinghem & P. Villa

[a] School of Chemistry , University of Hull , Hull HU6 7RX, UK

[b] Laboratoire de Chimie Organique et Cinétique , Université de Picardie Jules Verne , 80039 Amiens, France

[c] School of Chemistry , University of Hull , Hull HU6 7RX, UK

[d] Laboratoire de Chimie Organique et Cinétique , Université de Picardie Jules Verne , 80039 Amiens, France

[e] Laboratoire de Chimie Organique et Cinétique , Université de Picardie Jules Verne , 80039 Amiens, France

[f] Laboratoire de Chimie Organique et Cinétique , Université de Picardie Jules Verne , 80039 Amiens, France

[g] Laboratoire de Chimie Organique et Cinétique , Université de Picardie Jules Verne , 80039 Amiens, France

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ENTRY TO THE 2,5-EPOXYIMIDAZO[1,5-*a*][1,3]DIAZOCINE AND 5,8-EPOXY[1,2,3]TRIAZOLO[1,5-*a*][1,3]DIAZOCINE SYSTEMS : NOVEL REVERSED CYCLONUCLEOSIDE ANALOGUES.

D.F. Ewing,[a] G. Goethals,[b] G. Mackenzie,*[a] P. Martin,[b] G. Ronco,[b] L. Vanbaelinghem,[b] and P. Villa*[b]

[a] School of Chemistry, University of Hull, Hull HU6 7RX, UK

[b] Laboratoire de Chimie Organique et Cinétique, Université de Picardie Jules Verne, 80039 Amiens, France

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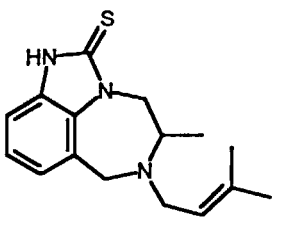
ABSTRACT

5-Azido-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose was used to obtain two reversed nucleoside analogues with either the 5-aminoimidazol-4-carboxamide or 5-amino-1,2,3-triazol-4-carboxamide groups attached, through the N1 site, to the C5' site of the sugar. When deprotected these two compounds cyclised spontaneously and regiospecifically to form a bond between the exocyclic nitrogen and the anomeric carbon of the sugar. These reversed cyclonucleoside analogues are respectively members of the 2,5-epoxyimidazo[1,5-*a*][1,3]diazocine and 5,8-epoxy[1,2,3]triazolo[1,5-*a*][1,3]diazocine systems, novel ring systems with therapeutic potential. The shape of the cyclised imidazole compound and its immediate precursor has been studied by molecular modelling.

INTRODUCTION

Although many key antiviral compounds are closely related to nucleosides, antiviral activity is also known for diverse non-nucleoside compounds. For example species with fused heterocyclic systems such as TIBO (**1**) and compound (**2**) are important inhibitors of HIV reverse transcriptase and compound (**3**) suppresses the function of an HIV regulatory protein.[1] Given the general interest in diazepines and their wide availability it is perhaps not surprising that screening programs have discovered examples of antiviral activity in this class of compound but there appears to be no reported work aimed at potentially interesting compounds based on the diazocine ring system.



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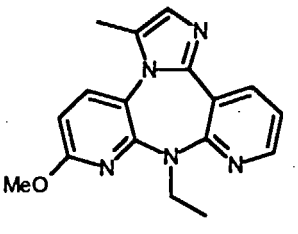

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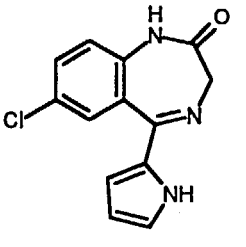

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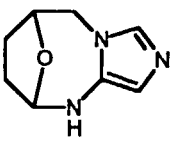

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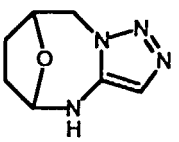

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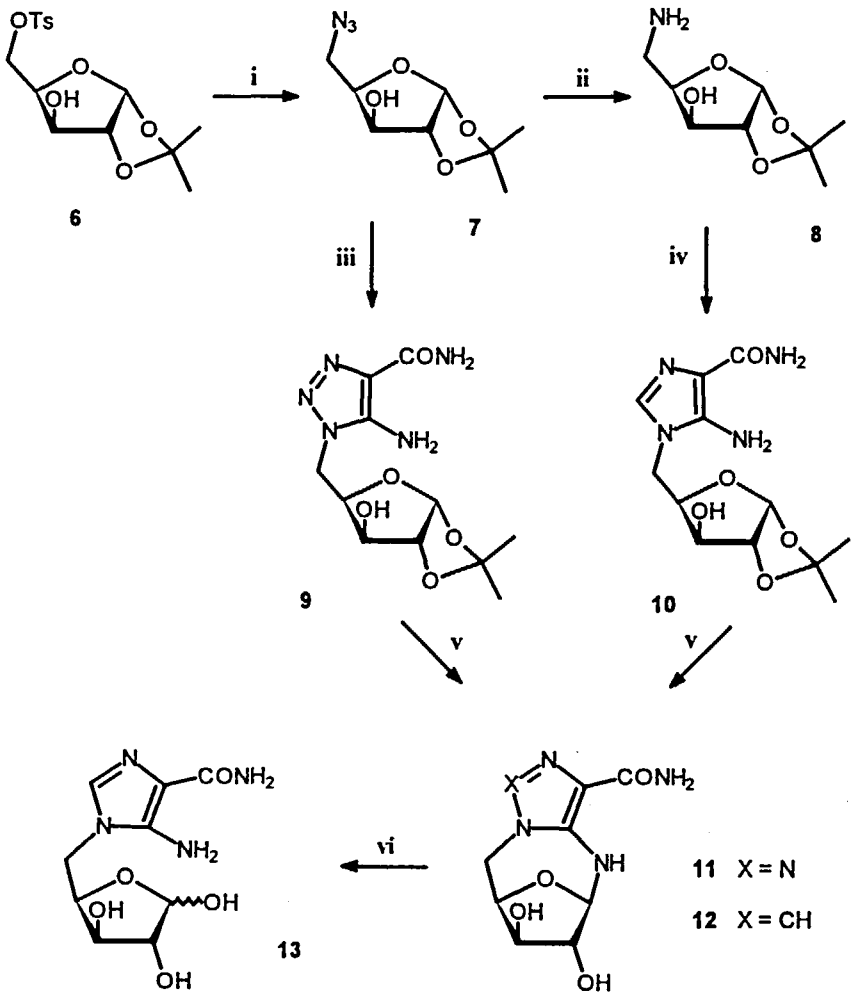
We have developed an entry into the 2,5-epoxyimidazo[1,5-*a*][1,3]-diazocine (**4**) and 5,8-epoxy[1,2,3]triazolo[1,5-*a*][1,3]diazocine (**5**) systems which is based on nucleoside chemistry. The two new compounds contain a fused azole-diazocine ring system (thus showing structural similarity to the antivirals **1–3**), but are also reversed cyclonucleoside analogues (thus retaining direct potential for interaction at the nucleic acid level). Synthetic strategies for cyclonucleosides usually start from a conventional

nucleoside with the heterocyclic base attached at the anomeric position of the sugar moiety. The present strategy starts from a reverse nucleoside with an azole base attached conventionally through an endocyclic nitrogen to the C-5 site on the sugar.[2] Cyclisation is then induced between the anomeric position and an exocyclic amino group on the base.

RESULTS AND DISCUSSION

Our strategy requires the synthesis of a reversed nucleoside in which the heterocyclic ring has an amino group in the 5-position and the sugar has the α-configuration. A structure of this type could allow the amino group to approach close enough to the anomeric site to result in cyclisation by S_N displacement of the anomeric hydroxyl group. Xylose was chosen as the sugar since it can be maintained in the α-configuration *via* the 1,2-*O*-isopropylidene derivative. To access the required reversed nucleoside we synthesised a 5-azidoxylose derivative as a suitable precursor for both imidazole and triazole ring systems (Scheme 1). 1,2-*O*-Isopropylidene-5-*O*-tosyl-α-D-xylose[3] (**6**) proved to be an attractive substrate for the synthesis of the corresponding 5-azido derivative (**7**) by treatment with sodium azide, giving a clean product in high yield (86%). Similar yields were obtained starting from the less convenient 5-iodoxylose[3] or 3,5-*O*-disulphenylxylose derivatives.[4] The azide **7** was treated with cyanoacetamide in presence of strong base to give a high yield of the 1,2,3-triazolyl derivative (**9**) by 1,3-cycloaddition.[5] Reduction of the azido group in (**7**) with triphenylphosphine[6] gave 5-amino-1,2-*O*-isopropylidene-α-D-xylofuranose (**8**) which was then converted to the imidazo derivative (**10**) by the Shaw methodology.[7]

Both of the reversed nucleoside analogues **9** and **10** have an amino group in the required position and cyclisation occurs spontaneously when the isopropylidene protecting group is removed from the xylofuranose moiety under acidic conditions. This cyclisation reaction is regioselective since the only isolated product was the cyclonucleoside corresponding to displacement of the anomeric hydroxyl group (*ca.*



Scheme 1 *Reagents and conditions:* i, NaN_3, DMF, 2 h at 90 °C; ii, PPh_3, aqueous THF, 1 h at rt; iii, $CNCH_2CONH_2$, KOH in aqueous DMF, 24 h at rt; iv, aminocyanoacetamide in MeCN, reflux 45 min; v, aqueous TFA, 6 h at rt; vi, 0.1 M H_2SO_4, 6 h at 65 °C.

62% yield in both cases). There is no evidence of reaction at the C-2' site. The two new tricyclic compounds,[8] 1,5'-cyclo-5-(5'-deoxy-β-D-xylofuranosylamino)-1,2,3-triazol-4-carboxamide (**11**) and 1,5'-cyclo-5-(5'-deoxy-β-D-xylofuranosylamino)imidazol-4-carboxamide (**12**) are examples of new ring systems which have an azole ring fused to a diazocine ring.

The structures of the cyclised products were easily confirmed by standard NMR techniques. The formation of a xylofuranosylamine by cyclisation of the anomeric carbon on to the 5-amino group is confirmed by the C-1 chemical shift. The β-configuration of the sugar ring is confirmed by the magnitude of the coupling between H1' and H2'. A value for $J_{1',2'}$ ~0° Hz shows that the torsion angle ϕ(H1',H2') is *ca.* 90°. Coupling between H2' and H3' is 3.0 Hz showing that this end of the molecule adopts an eclipsing conformation, *i.e.*, ϕ(H2',H3') is *ca.* 120°. The *xylo* configuration is confirmed by the large coupling between H3' and H4' ($J_{3',4'}$ 7.8 Hz). There are no significant NOESY contacts apart from those between vicinal protons. We have shown previously[2] that the fused imidazole system **12** is stable in water at room temperature and hence these new compounds have interesting potential for therapeutic development.

Molecular modelling.

The reactivity of the 5-amino group in compounds **9** and **10** is less than that of a simple primary amine, and the facility with which the ring closure reaction occurs must be due to favourable juxtaposition of the reaction centres. Molecular modelling studies were made of compound **10** in its α-configuration. The approach to the S_N transition state for reaction at C1' requires the imidazole 5-amino group to lie close to the β-face of the xylose ring. Compound **10** (without the protecting group) has a stable conformation in which the C5'–N1 bond is gauche to the C4'–C3' and C4'–O4' bonds (**Fig 1**). The other two conformations of the C4'–C5' bond, which place the heterocyclic ring distant from the xylose ring are both much higher in energy (>5 kJ mol^{-1}). The conformation shown in Fig. 1 places the 5-amino group close enough to the xylose ring to form a hydrogen bond N5–H···O4' (separation *ca.* 2 Å). It is notable that the other N5–H is hydrogen bonded to the amide carbonyl, and this interaction may be a significant stabilising factor.

The conformation of the cyclised product (**12**) was also investigated by molecular modelling. The eight-membered ring adopts a distorted boat conformation with the imidazole ring essentially coplanar with the end face of the boat. The angle between the bottom face and the end face attached to the imidazole ring is *ca.* 140°. The oxygen bridge is on the bottom face of the boat. The two hydroxyl groups are unencumbered by

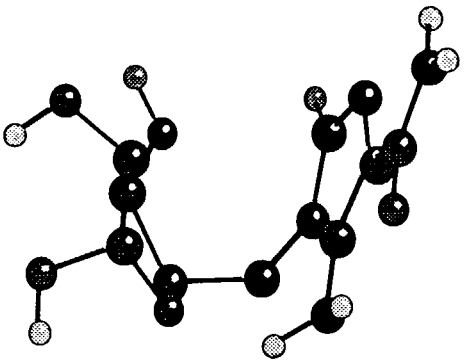


Figure 1. Conformation of the reversed nucleoside **10** with the protecting group removed to promote cyclisation. (Xylose backbone hydrogen atoms are omitted for clarity).

the heterocyclic ring and will be amenable to phosphorylation. Variation in the position of the hydroxyl groups gives rise to a range of conformational energies (*ca.* 13 kJ mol^{-1}).[2] The two lowest energy forms have the 2'-OH group in either of the *gauche* conformations with respect to the C2'–C1' bond with the 3'-OH group in the *trans* position with respect to bond C3'–C4'. The amide group adopts the conformation which permits a hydrogen bond to the N5–H group. A stereoscopic pair of images is shown in **Fig. 2**.

Compound **12** can also exist with the eight-membered ring in a distorted chair conformation. In this case the face with the imidazole ring attached is placed cis to the oxygen bridge and it makes an angle with the bottom face of *ca.* 140°. However this conformation is about 12 kJ mol^{-1} higher in energy and will not be significantly populated. Compound **12** can be regarded as a bridged sugar, a geometric modification which restricts the conformational freedom of the sugar ring. The normal North ↔ South equilibrium cannot occur and the attached atoms at C2 and C3 are nearly eclipsing.

EXPERIMENTAL

General methods. Melting points were determined on an electrothermal automatic apparatus, and are uncorrected. Optical rotations, for solutions in $CHCl_3$ or

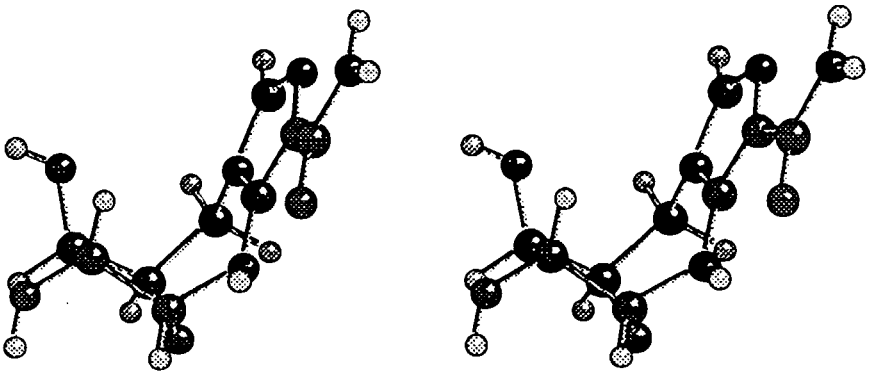


Figure. 2 Stereoscopic pair of images for compound **12.**

MeOH, were measured with a digital polarimeter JASCO model DIP-370 at 25 °C. NMR spectra were recorded with JEOL Lambda 400 or BRUKER WP-300 instruments for solutions in $CDCl_3$ or $(CD_3)_2SO$ (DMSO). Assignments were confirmed by standard correlation methods. Elemental analyses were performed on a Fisons EA 1108 instrument. Reactions were monitored by TLC on aluminium plates of silica gel (Kieselgel 60 F_{254}) and spots were detected by spraying with an ethanolic solution of phosphomolybdic acid-sulfuric acid. Column chromatography was performed on silica gel (60 mesh, Matrex). Molecular modelling calculations were carried out with the Nemesis package using a PC (166MHz). The standard parameterisation of the Cosmic force field was used throughout.

5-Azido-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose 7. NaN_3 (1.9 g, 29 mmol) was added to a solution of 5-*O*-tosyl-1,2-*O*-isopropylidene-α-D-xylofuranose[3] (5 g, 14 mmol) in DMF (50 mL) and the mixture heated at 90 °C for 2 h. The solvent was removed under vacuum, the residue dissolved in toluene and washed twice with water. The organic phase was concentrated under reduced pressure and the crude product purified by column chromatography (acetone–hexane, 2:8) to afford the 5-azidoxylose derivative 7 (2.7 g, 86%): mp 64 °C (lit.[9] 61–63 °C); $[\alpha]_D^{25}$ –36.3° (*c* 1.0, $CHCl_3$), $[\alpha]_D^{25}$ – 40.6° (*c* 0.8, MeOH); ^1H NMR ($CDCl_3$): δ 5.88 (1H, d, $J_{1,2}$ 3.6, H-1), 4.45 (1 H, d, $J_{2,3}$ 0, H-2), 4.21 (1 H, m, $J_{4,5a}$ 6.2, H-4), 4.16 (1 H, d, $J_{3,4}$ 2.8, H-3), *ca.*3.53 (2 H, m, $J_{4,5b}$ 6.2, $J_{5a,5b}$ 10.1, H_{5a}, H_{5b}), 2.70 (1 H, d, $J_{3,OH}$ 4.9, OH), 1.44, 1.26 (6 H, 2 s, Me);

^{13}C NMR ($CDCl_3$) δ 111.9, 26.6, 26.1(isopropylidene), 104.7, (C-1), 85.2 (C-2), 78.4 (C-4), 74.9 (C-3), 49.1 (C-5).

Anal. Calcd for $C_8H_{13}N_3O_4$ (215.21): C 44.65; H 6.05; N 19.53. Found C 44.82; H 5.97; N 19.62.

5-Amino-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose 8. PPh_3 (2.7 g, 10.2 mmol) was added to a solution of 7 (2 g, 9.3 mmol) in THF–H_2O (4:1, 20 mL) and the mixture stirred for 1 h. The THF was removed by evaporation and the residue extracted twice with Et_2O. The aqueous phase was concentrated under reduced pressure. The 5-aminoxylose (**8**) was isolated after crystallisation in Et_2O, (1.6 g, 92%), mp 106 °C (lit.[10] 92–93 °C); $[\alpha]_D^{24}$ –4.3° (*c* 0.36, $CHCl_3$), $[\alpha]_D^{24}$ –17.6° (*c* 0.56, MeOH), {lit.[10] $[\alpha]_D^{24}$ –12.5 (MeOH)}; ^1H NMR ($CDCl_3$): δ 5.94 (1 H, d, $J_{1,2}$ 3.6, H-1), 4.46 (1 H, d, H-2), 4.28 (1 H, d, $J_{3,4}$ 2.9, H-3), 4.09 (1 H, m, $J_{4,5a}$ 3.6, H-4), 3.49 (1 H, dd, $J_{5a,5b}$ 13.4, H-5a), 3.13 (1 H, dd, $J_{4,5b}$ 1.7, H-5b), 1.45, 1.30 (6 H, 2 s, Me); ^1H NMR (CD_3OD): δ 5.87 (1 H, d, $J_{1,2}$ 3.9, H-1), 4.46 (1 H, d, H-2), 4.08–4.12 (2 H, m, H-3, H-4), 2.91 (2 H, d, $J_{4,5}$ 5.6, H-5), 1.44, 1.30 (6 H, 2 s, Me);^{13}C NMR ($CDCl_3$): 111.2, 26.7, 26.0 (isopropylidene), 104.9 (C-1), 86.0 (C-2), 78.2 (C-3), 77.1 (C-4), 40.8 (C-5).

Anal. Calcd for $C_8H_{15}NO_4$ (189.21): C 50.78; H 7.99; N 7.40. Found: C 50.89; H 7.94; N 7.27.

5-(5-Amino-4-carbamoyl-1,2,3-triazol-1-yl)-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose 9. Powdered KOH (1.17 g, 21 mmol) and cyanoacetamide (1.76 g, 21 mmol) were added to a solution of triazole 7 (3 g, 14 mmol) in H_2O-DMF (1:10, 33 mL) and the mixture stirred for 24 h and then filtered and concentrated under reduced pressure. The residue was dissolved in MeOH (60 mL), neutralized with Dowex 50 (H^+) and the solution concentrated and chromatographed (acetone–hexane, 3:2) to give **9** (3.67 g, 88%), mp 190 °C; $[\alpha]_D^{25}$ –23° (*c* 1.0; MeOH); ^1H NMR (DMSO): 7.42, 7.07 (2 H, two br s, $CONH_2$), 6.24 (2 H, br s, NH_2), 5.87 (1 H, d, $J_{1,2}$ 3.5, H-1), 4.46 (1 H, d, H-2), 4.39 (1 H, m, $J_{4,5}$ 4.0, H-4), 4.32 (2 H, d, H-5), 4.08 (1 H, m, $J_{3,OH}$ 4.6, H-3), 1.33, 1.22 (6 H, 2 s, Me); ^{13}C NMR (DMSO): 25.9, 26.5, 110.6 (isopropylidene), 104.3 (C-1), 84.9 (C-2), 77.9 (C-4), 73.4 (C-3), 44.8 (C-5); triazole 121.6 (C-4), 144.8 (C-5), 164.2 ($CONH_2$).

Anal. Calcd for $C_{11}H_{17}N_5O_5$ (299.29): C 44.14; H 5.72; N 23.40. Found: C 44.29; H 5.71; N 23.12.

5-(5-Amino-4-carbamoylimidazol-1-yl)-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose 10. A mixture of triethyl orthoformate (7.9 mL, 47.6 mmol) and amino-cyanoacetamide (4.71 g, 47.6 mmol) in anhydrous MeCN (50 mL) was heated under reflux for 45 min then cooled. A solution of amine **8** (4.5 g, 23.8 mmol) in MeCN (50 mL) was added dropwise. After 15 h at room temperature, the solution was filtered, concentrated under reduced pressure and the residue chromatographed (acetone–hexane, 3:1) to give compound **5** (4.5 g, 63%), mp 130-131 °C; $[\alpha]_D^{25}$ −12° (*c* 1.0; MeOH); ^{1}H NMR (DMSO): 7.07 (1 H, s, imidazole H-2), 6.77, 6.64 (2 H, two br s, $CONH_2$), 5.88 (1 H, d, $J_{1,2}$ 3.7, H-1), 5.78 (2 H, br s, NH_2), 4.46 (1 H, d, H-2), 4.23 (1 H, m, $J_{3,4}$ 3.0, H-4), 4.06 (1 H, d, $J_{4,5a}$ 4.4, $J_{5a,5b}$ 14.6, H-5a), 4.00 (1 H, m, $J_{3,OH}$ 4.9, H-3), 3.94 (1 H, d, $J_{4,5b}$ 8.1, H-5b), 1.34, 1.22 (6 H, 2 s, Me); ^{13}C NMR (DMSO): 26.6, 26.0, 110.6 (isopropylidene), 104.4 (C-1), 85.0 (C-3), 78.4 (C-2), 73.3 (C-4), 51.6 (C-5); imidazole ring 110.7 (C-4), 130.2 (C-2), 142.9 (C-5), 166.6 ($CONH_2$).

Anal. Calcd for $C_{12}H_{18}N_4O_5$ (298.30): C 48.32; H 6.08; N 18.78. Found: C 48.60; H 6.20; N 18.80.

1,5'-Cyclo-5-(5'-deoxy-β-D-xylofuranosylamino)-1,2,3-triazol-4-carboxamide 11. A solution of compound **9** (500 mg, 1.7 mmol) in CF_3COOH–H_2O (9:1, 5 mL) was stirred at room temperature for 6 h. Trifluoroacetic acid was removed by evaporation and the residue chromatographed (acetone–ethanol, 9:1) to give **11** (250 mg, 62%), mp 240-241 °C; $[\alpha]_D^{25}$ 119.8° (*c* 1.0, H_2O); ^{1}H NMR (DMSO): 7.56, 7.17 (2 H, two br s, $CONH_2$), 7.52 (1 H, d, $J_{1',NH}$ 4.4, NH), 5.53 (1 H, d, $J_{3',OH}$ 4.0, OH-3'), 5.48 (1 H, d, $J_{2',OH}$ 4.0, OH-2'), 4.98 (1 H, d, H-1'), 4.81 (1 H, dd, $J_{4',5a'}$ 3.4, $J_{5a',5b'}$ 14.4, H-5a'), 4.65 (1 H, m, $J_{2',3'}$ 3.0, $J_{3',4'}$ 7.8, $J_{4',5b'}$ 1.7, H-4'), 4.14 (1 H, dd, H-5b'), 4.12 (1 H, dd, H-3'), 3.58 (1 H, d, H-2'); ^{13}C NMR (DMSO): 91.6 (C-1'), 83.6 (C-2'), 77.1 (C-3'), 76.7 (C-4'), 51.6 (C-5'), 123.1 (C-4), 144.7 (C-5), 163.9 ($CONH_2$).

Anal. Calcd for $C_8H_{11}N_5O_4$ (240.22): C 39.83; H 4.60; N 29.04. Found: C 40.07; H 4.66; N 28.79.

1,5'-Cyclo-5-(5'-deoxy-β-D-xylofuranosylamino)imidazol-4-carboxamide 12. Using a similar treatment to that given above, compound **10** (1.00 g, 3.4 mmol) was

converted to **12** (0.49 g, 61%), mp 210 °C; $[\alpha]_D^{25}$ +22° (*c* 0.2, MeOH); ^{1}H NMR (DMSO): 7.23 (1 H, d, $J_{1',NH}$ 4.6, NH), 7.18 (s, 1H, H-2), 6.95 - 6.78 (2 br, 2H, $CONH_2$), 5.49 (1 H, d, $J_{2',OH}$ 4.7, OH-2'), 5.42 (1 H, d, $J_{3',OH}$ 3.9, OH-3'), 4.85 (1 H, d, $J_{1',2'}$ 0, H-1'), 4.45 (m, 1H, H-4'), 4.37 (1 H, d, $J_{4',5a'}$ 0, $J_{5a',5b'}$ 14.3, H-5a'), 4.08 (1 H, d, $J_{3',4'}$ 7.2, H-3'), 3.80 (1 H, d, $J_{4',5b'}$ 1.6, H-5b'), 3.56 (1 H, d, $J_{2',3'}$ 0, H-2'). ^{13}C NMR (DMSO) : 92.1 (C-1'), 82.9 (C-2'), 77.9 (C-3'), 76.8 (C-4'), 49.1 (C-5'), base: 114.8 (C-4), 132.0 (C-2)143.1 (C-5), 166.4 (CO).

Anal. Calcd for $C_9H_{12}N_4O_4$ (240.22): C 45.00; H 5.04; N 23.32. Found: C 45.33; H 5.05; N 23.00.

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REFERENCES AND NOTES

1. E. De Clercq, *J. Med.Chem.*, **38**, 2491 (1995).
2. M.Chabbi, P.Vanlemmens, G. Ronco, G. Goethals, P. Villa, D.F.Ewing and G. Mackenzie, *Collect. Czech. Chem. Commun.*, **61**, S12 (1996).
3. P.A.Levene and A.L.Rymond, *J. Biol. Chem.*, **102**, 317 (1933).
4. P. Martin, Ph.D.Thesis, Université de Picardie Jules Verne, 1993.
5. F. Chretien and B. Gross, *Tetrahedron*, **38**, 103 (1982).
6. N. Knouzi, M. Vaultier and R. Carrie, *Bull. Soc. Chim. Fr.*, **5**, 815 (1985).
7. G. Shaw in *Comprehensive Heterocyclic Chemistry* (A.R. Katritzky and C. W. Rees, Eds), Chap.4.09. Pergamon Press, Oxford 1984.
8. The systematic names of these compounds are (5*R*,6*R*,7*R*,8*R*)-6,7-dihydroxy-4,5,6,7,8,9-hexahydro-5,8-epoxy[1,2,3]triazolo[1,5-*a*][1,3]diazocin-3-carboxamide (**11**) and (2*R*,3*R*,4*R*,5*R*)-3,4-dihydroxy-1,2,3,4,5,6-hexahydro-2,5-epoxy-imidazo[1,5-*a*][1,3]diazocin-10-carboxamide (**12**). These names obscure the similarity of the structures and the nucleoside character and are not used in the text.
9. S. Hanessian, *Chem. Ind.*, 1296 (1965).
10. B. Helferich and M. Burgdorf, *Tetrahedron*, **3**, 274 (1958).