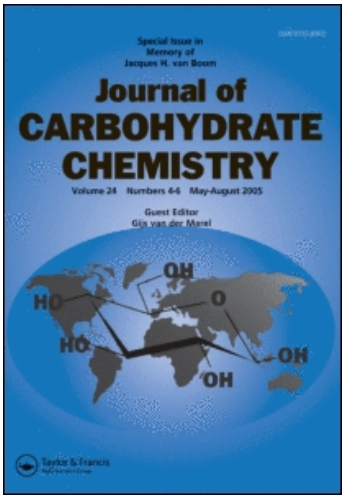

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Synthesis and Structural Assignment of 1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-4-(thymin-1-yl)-α-l-lyxofuranose

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COMMUNICATION

SYNTHESIS AND STRUCTURAL ASSIGNMENT OF 1-*O*-ACETYL-2,3,5-TRI-*O*-BENZOYL-4-(THYMIN-1-YL)-α-L-LYXOFURANOSE

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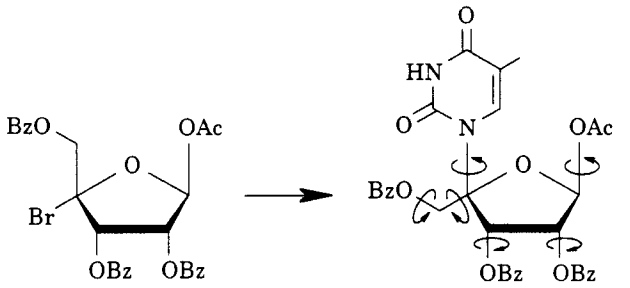
Analogues of nucleosides in which the nucleobase is fixed onto the C-4 of the sugar moiety are generally prepared either from 4,5-unsaturated sugar derivatives or *via* a formaldehyde condensation.[1] We tested the furanosyl bromide reactivity of **1**[2] towards a series of nucleophiles, mostly azides or cyanides, without success. Conversely, the nucleosidation of **1** using 5-methyl-2,4-bis(trimethylsilyloxy)pyrimidine in the presence of stannic chloride took place at the second anomeric position (C-4) and led to the isolation in acceptable yield (47%) of a unique anomer **2** (Scheme 1).

The presence in the ^{1}H NMR spectrum of **2** of an acetyl signal and the small value of $J_{1,2}$ established that the reaction indeed took place exclusively on C-4. A NOESY experiment indicated a strong through-space interaction between H-6' of the nucleobase and the acetyl group, no interaction between H-6' and H_2-5, small interactions between H-6' and both H-1 and H-3, and no interaction between H-6' and H-2. These observations were in favor of an α-L-*lyxo* configuration but could not be considered as constituting a definitive configurational assignment. To confirm this attribution, we resorted to molecular mechanics. For both 4-epimers



1 2

Scheme 1

of **2** (α-L-*lyxo* and β-D-*ribo* configurations), a Monte Carlo conformational search using the MM2 force field included in the Macro Model Software[3] (version 4.5) was performed. For each epimer, rotations around the bonds indicated by curved arrows on Scheme 1 were applied. Three thousand conformers were generated and minimized for each epimer using the continuum solvent model[4] with the chloroform parameters to approximate the solvent effect on the relative conformational energies and allow reliable comparisons with experimental ^1H NMR data (Table). Owing to the steric encumbrance of the benzoyl groups, the rotations performed can be expected to insure a complete coverage of the conformational energy hypersurface of all the molecule including the furanose ring. From the structures and energies of the generated conformers, the Boltzmann averaged coupling constants were calculated using the Imai and Osawa's equation[5] as implemented in a QCPE program[6] we slightly modified to interface it with Macro Model. The results are collected in the Table together with an estimation of some interprotonic distances based on the average values from the two or three more stable conformers corresponding to more than 90% of the overall conformational equilibrium. Such a Monte Carlo search taking into account a large number of conformers (ca. 60) is almost antinomic with the application of the pseudorotation treatment. However, a plain geometry optimization of **2** indicated a prefered 3'-*endo* conformation.

Examination of the data of the Table indicates an almost perfect fit between the experimental values and those computed for **2** (α-L-*lyxo* configuration). This indicates that the 3-benzoyloxy group participates in the S_N displacement at C-4.

TABLE. Selected ^{1}H NMR Data Relative to Nucleoside **2**.

Parameter	Exp. NMR	Molecular mechanics (Monte Carlo)	
		α-L-*lyxo*	β-D-*ribo*
$J_{1,2}$ (Hz)	0.7	0.7	2.8
$J_{2,3}$ (Hz)	5.1	5.0	4.4
H-1...H-6' (Å)	NOESY +	4.1	4.2
H-2...H-6' (Å)	NOESY -	5.3	5.4
H-3...H-6' (Å)	NOESY +	4.2	4.9

Moreover, both the ^{1}H NMR experiments and the molecular modeling of **2** are in favor of an orientation of the nucleobase in which C-6' faces the sugar ring.

Compound **2** was found surprisingly reluctant to undergo either de-*O*-acylation or anomeric substitution reactions. It either lost its nucleobase or did not react at all. It exhibited no activity against either HIV-1 or HIV-2 in human T-lymphocyte (CEM/0) cells. Its cytotoxicity (CC_{50}) against the same cell line was 4.3 ± 0.47 μg/mL.

EXPERIMENTAL

General methods.[7]

Molecular mechanics

The algorithm used for the Monte Carlo search was that developed by Chang et al.[8] The MM2* force field utilised differs from the Allinger's original one[9] by replacement of the dipole-dipole Jones' formulae by the simpler point charge-point charge interaction and of the out-of-plane energy term by an improper torsion term. The geometry optimization criterion was a 0.05 $kJ.A^{-1}.mol^{-1}$ derivative convergence. In the continuum solvent model for chloroform used,[10,11] the point charges were the same as those used in the intramolecular energy expression. The identity criterion used for the reduction of the number of conformers was based on a rigid body superimposition of the heavy atoms of the furanose ring and immediate neighbours (0.25 Å tolerance).

NOESY measurements

The NOESY matrix of **2** was obtained using a standard NOESYPH. AU BRUKER experiment with the following acquisition parameters: AQ = 0.16 s, SW = 3104, SI = 1024, all other parameters as previously described.[12]

1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-4-(thymin-1-yl)-α-L-lyxofuranose (2). To a solution of **1** (205 mg, 0.35 mmol) in anhydrous acetonitrile (2 mL), kept under a dry nitrogen atmosphere, 5-methyl-2,4-bis(trimethylsilyloxy)pyrimidine (212 mg, 0.83 mmol) and stannic chloride (0.2 mL) were added. After 2 h stirring at 25 °C, the reaction mixture was concentrated, dissolved in chloroform (20 mL) and the organic phase, washed with a saturated aqueous sodium hydrogenocarbonate solution (15 mL), was dried ($MgSO_4$), concentrated and submitted to a column chromatography (20:1 CH_2Cl_2/acetone) to afford **2** (103 mg, 47%): syrup, R_F 0.42 (20:1 CH_2Cl_2/acetone); $[\alpha]_D^{25}$ +28.5° (*c* 0.3, $CHCl_3$); λ_{max}^{EtOH} 265 (ε 8900), 230 (34600), and 202 nm (41000). ^1H NMR ($CDCl_3$, 300 MHz): δ 8.81 (*s*, 1 H, NH), 8.0-7.3 (*m*, 16 H, Bz + H-6'), 6.58 (*d*, $J_{1,2}$ ~0.7 Hz, H-1), 6.40 (*d*, $J_{2,3}$ = 5.1 Hz, H-3), 5.80 (*dd*, 1 H, H-2), 5.06 (*m*, 2 H, H_2-5), 2.07 (*s*, 3 H, OAc), and 1.85 (*s*, 3 H, Me-5'). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 169.5 (**CO**Me), 165 (**CO**Ph + C-2'), 150.8 (C-4'), 137.2 (C-6'), 134-129 (Ph), 110.5 (C-5'), 99.1 (C-1), 98.1 (C-4), 78.1 (C-2), 75.4 (C-3), 65.1 (C-5), 21.4 (CO**Me**), and 13.1 (**Me**-5').

Anal. Calcd for $C_{33}H_{28}N_2O_{11}$ (628.61): C, 63.06; H, 4.49; N, 4.46. Found: C, 62.76; H, 4.43; N, 4.41.

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REFERENCES

1. E. J. Prisbe, H. Maag, J. P. H. Verheyden, and R. M. Rydzewski, *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*; C. K. Chu and D. C. Baker, Eds.; Plenum Press, New York, 1993, pp 101.
2. R. J. Ferrier and S. R. Haines, *J. Chem. Soc., Perkin Trans. 1*, 1675 (1984).
3. F. Mohamadi, N. G. J. Richards, W. C. Guida, M. Lipton, C. Caufield, G. Chang, T. Hendrikson and W. C. Still, *J. Comput. Chem.* **11,** 440 (1990).
4. W. C. Still, A. Tempczyk, R. C. Hawley and T. Hendrickson, *J. Am. Chem. Soc.* **112**, 6127 (1990).
5. K. Imai and E. Osawa, *Magn. Reson. Chem.*, **28**, 668 (1990).
6. K. Imai and E. Osawa, 3SHH Program, QCPE 591.
7. V. Buet, A. Grouiller and G. Descotes, *Nucleosides Nucleotides*, **7**, 1651 (1992).
8. G. Chang, W. C. Guida and W. C. Still, *J. Am. Chem. Soc.* **111**, 4379 (1989).

9. N. L. Allinger, *J. Am. Chem. Soc.* **99**, 8127 (1977).
10. W. Hasel, T. F. Hendrickson and W. C. Still, *Tetrahedron Comput. Meth.* **1**, 103 (1988).
11. W. C. Still, A. Tempczyk, R. C. Hawley and T. F. Hendrickson, *J. Am. Chem. Soc.* **112**, 6127 (1990).
12. V. Uteza, G.-R. Chen, J. Le Quan Tuoi, G. Descotes, B. Fenet and A. Grouiller, *Tetrahedron* **49**, 8579 (1993).