ORGANIC LETTERS

2006
Vol. 8, No. 3
491−494

Synthesis and Conformational Analysis of New Cyclobutane-Fused Nucleosides†

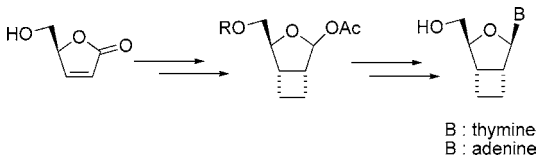
Ramon Alibés,* Angel Alvárez-Larena,‡ Pedro de March, Marta Figueredo, Josep Font,* Teodor Parella,§ and Albert Rustullet

Universitat Autònoma de Barcelona, Departament de Química, 08193 Bellaterra, Spain

ramon.alibes@uab.es

Received November 18, 2005

ABSTRACT



A stereselective synthesis of 3-oxabicyclo[3.2.0]heptane nucleoside analogues, which were designed as conformational mimics of the anti-HIV agents 2′,3′-didehydro-2′,3′-dideoxythimidine (stavudine, d4T) and 2′,3′-didehydro-2′,3′-dideoxyadenosine (d4A), is described. The target compounds were prepared by condensation of a common intermediate bicyclic acetate, derived from a homochiral 2(5*H*)-furanone, with pyrimidine and purine bases under modified VorbrUggen conditions. The conformational behavior of the synthesized nucleoside analogues was studied by NMR spectroscopy and X-ray crystallography.

For the past decade, the considerable attention that has been focused by medicinal chemists to find new potent and selective antiviral agents has been rewarded with the discovery of many 2′,3′-dideoxynucleosides, which exhibit excellent antiviral activities against human immunodeficiency virus type 1 (HIV-1).[1] 3′-α-Azido-2′,3′-dideoxythymidine (AZT, zidovudine),[2] 2′,3′-dideoxycytidine (ddC, zalcibatine),[3] 2′,3′-dideoxyinosine (ddI, didadenosine),[4] and 2′,3′-didehydro-2′,3′-dideoxythymidine (d4T, stavudine)[5] were among the earlier examples (Figure 1). However, the long-term usefulness of these and other 2′,3′-dideoxynucleoside analogues is limited because of their toxicity and viral resistance development. For this reason, efforts to identify new agents with activity against drug-resistance of HIV-1 and low toxicity are still warranted.[6]

During the past few years, the search for structurally modified nucleosides with enhanced chemotherapeutical potential has been devoted to the preparation of bicyclic

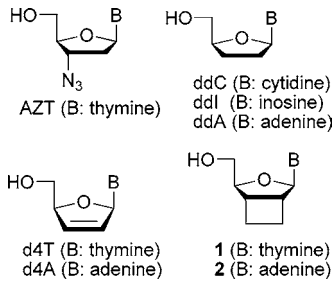


Figure 1. Bioactive 2′,3′-dideoxynucleosides and newly synthesized 2′,3′-dideoxy-2′,3′-α-ethano nucleosides **1** and **2**.

† Dedicated to Prof. Josep Castells on his 80th birthday.

‡ Unitat de Cristal·lografia, Universitat Autònoma de Barcelona, 08193 Bellaterra, Spain.

§ Servei de Ressonància Magnètica Nuclear, Universitat Autònoma de Barcelona, 08193 Bellaterra, Spain.

(1) (a) Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745−1768. (b) Herderwijn, P. *Drug Discov. Today* **1997**, *2*, 235−242. (c) Agrofoglio, L. A.; Challand, S. R. *Acyclic, Carbocyclic and L-Nucleosides;* Kluwer Academic Publisher: Dordrecht, Boston, London, 1998.

(2) Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; St. Clair, M. H.; Lehrman, S. N.; Gallo, R. C.; Bolognesi, D.; Barry, D. W.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 7096−7100.

(3) (a) Mitsuya, H.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 1911−1915. (b) Kim, C.-H.; Marquez, V. E.; Broder, S.; Mitsuya, H.; Driscoll, J. *J. Med. Chem.* **1987**, *30*, 862−866. (c) Yarchoan, R.; Thomas, R. V.; Allain, J.-P.; McAtee, N.; Dubinsky, R.; Mitsuya, H.; Lawley, T. J.; Safai, B.; Myers, C. E.; Pemo, C. F.; Klecker, R. W.; Wills, R. J.; Fischl, M. A.; McNeely, M. C.; Pluda, J. M.; Leuther, M.; Collins, J. M.; Broder, S. *Lancet* **1988**, *331*, 76−81.

10.1021/ol052794y CCC: $33.50
Published on Web 01/05/2006

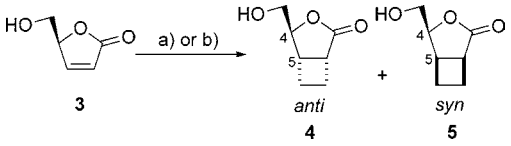
dideoxy nucleoside analogues. This work has led to a variety of novel [3.1.0]-2′,3′-fused bicyclic nucleosides, some of which have shown weak antiviral activity.[7] Conformational studies of these bicyclic nucleosides have shown that the sugar moiety is rigidly fixed outside the pseudorotational range[8] characteristic of active nucleosides, and it has also been suggested that a certain degree of conformational flexibility on the furanose ring is required for potent antiviral activity.[1b,9]

Conversely, [3.2.0]-2′,3′-fused bicyclic nucleosides have received little attention,[10] and to the best our knowledge, an example with the glycone moiety conformationally restricted by a two-carbon chain between positions 2′ and 3′ has never been described. We felt it was of interest to synthesize the 2′,3′-fused bicyclic nucleosides 2′,3′-dideoxy-2′,3′-α-ethanothymidine, **1**, and 2′,3′-dideoxy-2′,3′-α-ethanoadenosine, **2**, to explore the effect of the cyclobutane ring on the conformational mobility of the furanose moiety. Compounds **1** and **2** can be viewed as analogues of the well-known antiviral 2′,3′-didehydro-2′,3′-dideoxynucleosides (d4N), such as d4A and d4T.[11] It was expected that the fusion to a cyclobutane would flatten the furanose ring and impart a significant rigidity to the resulting nucleosides, to a level comparable to that of d4T and d4A. Furthermore, these analogues should be more resistant to hydrolytic processes[12] and have enhanced lipophilicity, which is potentially beneficial for increasing oral bioavailability and cell-wall penetration.

Herein, we describe the synthesis, stereochemical assignment, and conformational analysis of the novel [3.2.0]-heptane-type nucleosides **1** and **2** starting from commercially available (*S*)-5-hydroxymethyl-2(5*H*)-furanone, **3**.

First, we intended the diastereoselective construction of the cyclobutane ring through the photochemical [2 + 2] cycloaddition of ethylene to lactone **3**, following our previous described methodology (Table 1).[13] Thus, irradiation of an

Table 1. Photochemical Reactions



3 *anti* **4** *syn* **5**

conditions	yield (%)	anti/syn (%)
(a) *hν*, ethylene, acetone, −20 °C	66	66:34
(b) (1) *hν*, (*Z*)-1,2-dichloroethylene, CH_3CN, −40 °C; (2) Bu_3SnH, AIBN, toluene, relux	73	90:10

acetone solution of **3** saturated with ethylene for 5.5 h furnished a separable mixture of the cyclobutane diastereomers **4** and **5** in 66% yield in a ratio of 66:34. The relative configuration of the cycloadducts could be determined by the value of the coupling constant between H-4 and H-5, which is smaller for the anti isomer (1.3 Hz) than for the syn isomer (5.6 Hz).[13]

Although the chemical yield was acceptable, the low stereoselectivity achieved on this photochemical reaction prompted us to examine a different approach. We have recently described that cyclobutane derivatives can be efficiently prepared in a highly stereoselective manner by a two-step procedure that involves the photochemical reaction of 2(5*H*)-furanones with (*Z*)-1,2-dicloroethylene in acetonitrile, followed by a dihydrodehalogenation reaction with tri-*n*-butyltin hydride and AIBN in refluxing toluene.[14] Thus, under these conditions, the expected cyclobutanes **4** and **5** were obtained in 73% overall yield with an excellent diastereoselectivity (90:10).

The primary hydroxyl group of the major isomer **4** was protected as the *tert*-butyldimethylsilyl ether and then the lactone function was reduced by treatment with DIBAL-H in toluene to provide the corresponding lactol, which was acetylated to furnish the *β* anomeric acetate **7** in 79% yield for the three steps (Scheme 1).

This acetate was then used as a common glycosyl donor for coupling reactions with protected nucleobases, under modified Vorbrüggen conditions.[15] Thus, the condensation reaction of **7** with silylated thymine furnished a chromatographically separable 45:55 mixture of the α- and *β*-anomers **8** and **9** in 85% yield (Scheme 1). The α/*β* configuration of each epimer was elucidated by ^{1}H NMR analysis, including

(4) Yarchoan, R.; Mitsuya, H.; Thomas, R. V.; Pluda, J. M.; Hartman, N. R.; Perno, C.-F.; Marczyk, K. C.; Allain, J. P.; Johns, D. G.; Broder, S. *Science* **1989**, *246*, 412−415.

(5) Lin, T.-S.; Schinazi, R. F.; Prusoff, W. H. *Biochem. Pharmacol.* **1987**, *36*, 2713−2718.

(6) Rando, R. F.; Nguyen-Ba, N. *Drug Discov. Today* **2000**, *5*, 465−476.

(7) 2′,3′-Cyclopropane nucleosides: (a) Okabe, M.; Sun, R.-C. *Tetrahedron Lett.* **1989**, *30*, 2203−2206. (b) Beard, A. R.; Butler, P. I.; Mann, J.; Parlett, N. K. *Carbohydr. Res.* **1990**, *205*, 87−91. (c) Wu, J.-C.; Chattopadhyaya, J. *Tetrahedron* **1990**, *46*, 2587−2592. (d) Koole, L. H.; Neidle, S.; Crawford, M. D.; Krayevsji, A. A.; Gurskaya, G. V.; Sandström, A.; Wu, J. C.; Tong, W.; Chattopadhyaya, J. *J. Org. Chem.* **1991**, *56*, 6884−6892. (e) Sard, H. *Nucleosides Nucleotides* **1994**, *13*, 2321−2328. (f) Hong, J. H.; Chun, B. K.; Chu, C. K. *Tetrahedron Lett.* **1998**, *39*, 225−228. (g) Lescop, C.; Huet, F. *Tetrahedron* **2000**, *56*, 2995−3003. (h) Chun, B. K.; Olgen, S.; Hong, J. H.; Newton, M. G.; Chu, C. K. *J. Org. Chem.* **2000**, *65*, 685−693. For 2′,3′-fused byciclic nucleosides with a skeleton different of a cyclopropane ring see for example: (i) Miah, A.; Reese, C. B.; Song, Q. *Chem. Commun.* **1997**, 407−408. (j) Porcari, A. R.; Ptack, R. G.; Borysko, K. Z.; Breitenbach, J. M.; Vittori, S.; Wotring, L. L.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **2000**, *43*, 2438−2448. (k) Callam, C. S.; Gadikota, R. R.; Lowary, T. L. *Synlett* **2003**, 1271−1274.

(8) Altona, C.; Sundaralingam, M. *J. Am. Chem. Soc.* **1972**, *94*, 8205−8212.

(9) Wang, J.; Froeyen, M.; Hendrix, C.; Andrei, G.; Snoeck, R.; de Clercq, E.; Herdewijn, P. *J. Med. Chem.* **2000**, *43*, 736−745.

(10) (a) Mikhailopulo, I. A.; Poopeiko, N. E.; Tsvetkova, T. M.; Marochkin, A. P.; Balzarini, J.; de Clercq, E. *Carbohydr. Res.* **1996**, *285*, 17−28. (b) Christensen, N. K.; Petersen, M.; Nielsen, P.; Jacobsen, J. P.; Olsen, C. E.; Wengel, J. *J. Am. Chem. Soc.* **1998**, *120*, 5458−5463. (c) Sørensen, M. H.; Nielsen, C.; Nielsen, P. *J. Org. Chem.* **2001**, *66*, 4878−4886. (d) Sharma, P. K.; Petersen, M.; Nielsen, P. *J. Org. Chem.* **2005**, *70*, 4918−4928.

(11) Balzarini, J.; Kang, G.-J.; Dalal, M.; Herdewijn, P.; de Clercq, E.; Broder S.; Johns, D. G. *Mol. Pharmacol.* **1987**, *32*, 162−167.

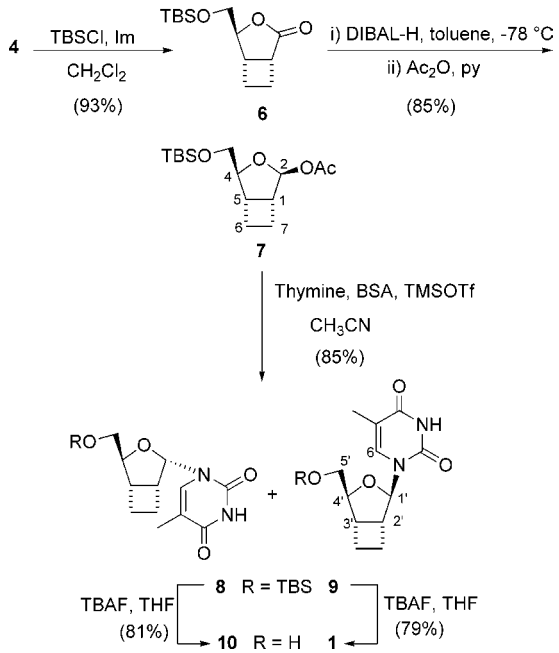
(12) York, J. L. *J. Org. Chem.* **1981**, *46*, 2171−2173.

(13) Alibés, R.; Bourdelande, J. L.; Font, J.; Gregori, A.; Parella, T. *Tetrahedron* **1996**, *52*, 1267−1278.

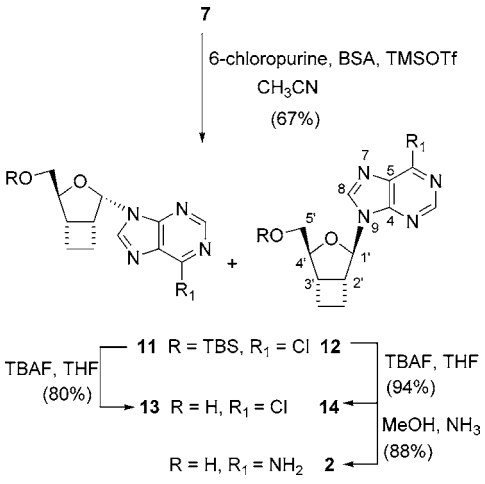
(14) Alibés, R.; de March, P.; Figueredo, M.; Font, J.; Racamonde, M.; Alvarez-Larena, A.; Piniella, J. F.; Parella, T. *Tetrahedron Lett.* **2003**, *44*, 69−71.

(15) For an extensive review of this reaction, see: Vorbrüggen, H.; Ruh-Pohlenz, C. *Handbook of Nucleoside Synthesis*, John Wiley & Sons: New York, 2001.

Scheme 1



Scheme 2



NOE difference experiments.[16] The isomer displaying a small coupling constant $J_{1',2'}$ (1.9 Hz) was assigned as the β-anomer, **9**, whereas **8** with a larger $J_{1',2'}$ (6.0 Hz) was assigned as the α-anomer.[7a,h] Accordingly, for **9**, a significant NOE enhancement of H-5′ signal was observed upon saturation of thymine H-6 proton, while, for **8**, irradiation of H-6 gave NOE interaction with H-4′.[17] Because the α-anomer might be an equally useful product for biological assays, alternative conditions to increase the β-selectivity of the coupling reaction were not investigated. Removal of the silyl protecting group of **9** with TBAF led efficiently to the targeted conformationally restricted nucleoside **1**, while its α-anomer **10** was obtained from **8**.

An analogous condensation of the glycone **7** with N^6-benzoyladenine gave the expected *N*9 α- and β-nucleosides along with the *N*7 coupling products. However, excellent regioselectivity was achieved by coupling of **7** with 6-chloropurine, leading exclusively to a chromatographically separable 35:65 mixture of **11** and **12** in 67% total yield (Scheme 2). The anomeric configuration of **11** and **12** was elucidated by ^{1}H NMR analysis as above, while the site of attachment (*N*7 or *N*9) of the purine base was confirmed by heteronuclear multiple bond correlation (HMBC) experiments, which showed correlation between H-1′ and C4, but not between H-1′ and C5. The adenosine analogue **2** was finally obtained in 82% yield by sequential treatment of **12** with TBAF and ammonia-saturated methanol. Unexpectedly, all attempts of ammonolysis of the desilylated α-anomer **13** led only to degradation products.[18]

The newly synthesized 3-oxabicyclo[3.2.0]heptane adenosine analogue **2** provided adequate crystals for X-ray analysis,[19] which revealed that the furanose ring adopts a C4′endo (^4E) pucker with a pseudorotation phase angle P = 228.1° and a maximum amplitude of puckering ν_{max} = 22.9°.[20] The conformation around the glycosylic bond is anti with a χ value of −157.1°, while the torsion angle γ is 173.8°, indicating that the preferred conformation around the C4′-C5′ bond is trans γ^t.

A comparison between the X-ray structure of **2** and those of d4A and ddA obtained from the Cambridge Crystallographic Database[21] showed that their pseudorotational parameters are similar (Table 2 and Figure 2).[22]

Table 2. Some Conformational Parameters from X-ray Crystallographic Data of **2**, ddA, and d4A

compd	P^a (deg)	$\nu_{max}{}^b$ (deg)	χ^c (deg)	γ^d (deg)	d^e (Å)
2	228.1	22.9	−157.1	173.8	3.7 (4.0)
ddA	190.4	35.7	−95.9	−178.7	3.9 (4.5)
d4A	243.5	7.5	−100.2	179.8	3.9 (4.6)

[a] *P:* pseudorotational phase angle of the sugar moiety. [b] ν_{max}: maximum amplitude of puckering. [c] χ: torsion angle of O4′−C1′−N9−C4. [d] γ: torsion angle of O5′−C5′−C4′−C3′. [e] Distance between C5′ and N9 (distance between O5′ and N9).

The three compounds are located in the Southern *S* hemisphere of the pseudorotational cycle, with **2** being separated 15.4° and 37.7°, respectively, from d4A[23] (P = 243.5°) and ddA[24] (P = 190.4°). In terms of puckering, the

(16) The nucleoside numbering system is utilized to compare the structure of 3-oxabicyclo[3.2.0]heptane nucleosides with regular nucleosides. The systematic numbering for these compounds is used in the Supporting Information.

(17) Rosemeyer, H.; Tóth, G.; Golankiewicz, B.; Kazimierczuk, Z.; Bourgeois, W.; Kretschmer, U.; Muth, H.-P.; Seela, F. *J. Org. Chem.* **1990**, *55*, 5784−5790.

(18) Even on standing at room temperature, compound **13** decomposes slowly.

(19) Crystallographic data for **2** has been deposited with the Cambridge Crystallographic Data Centre as suplementary publication no. 290124.

(20) The Altona pseudorotational parameters were calculated by the Pseudo-Rotational Online Service and Interactive Tool (PROSIT) available at http://cactus.nci.nih.gov/prosit. See: Sun, G. S.; Voight, J. H.; Filipov, I. V.; Marquez, V. E.; Nicklaus, M. C. *J. Chem. Inf. Comput. Sci.* **2004**, *44*, 1752−1762.

(21) Allen, F. H. *Acta Crystallogr., Sect. B* **2002**, *58*, 380−388.

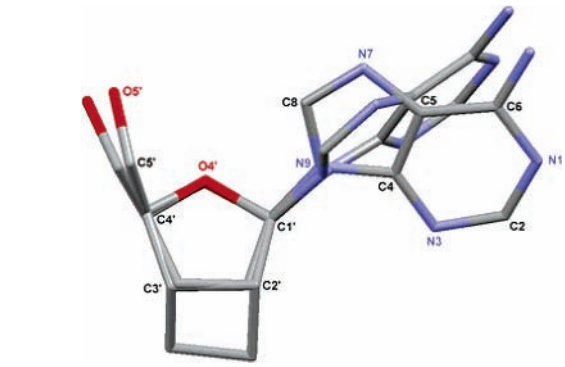


Figure 2. Overlap of **2** and d4A X-ray structures. Numbers correspond to compound **2**.

furanoid ring of **2** is more planar than that of ddA (ν_{max} = 35.7°) but less than that of d4A (ν_{max} = 7.5°). The torsion angles γ are nearly identical (~178°), and their values indicate that in all these nucleosides the conformation around the C4′−C5′ bond is trans. In contrast, the glycosidic link of **2** (χ = −157.1°) is strikingly different to those of d4A (−95.9°) and ddA (−100.2°). The difference is likely caused by the C4′ pucker of the furanose ring because, if the torsion angle was around 100°, H-5′ of the side chain would be very close from H-8 of the purine base. Thus, the rotation of the purine ring about the glycosidic bond relieves the steric interaction. Finally, another important conformational feature of **2** is that the distance between C5′ and N9, a main feature for the recognition by nucleoside kinases,[25] is comparable to those of the anti-HIV active nucleosides ddA and d4A.

The conformations of **1** and **2** in solution were also investigated by 1D and 2D NOESY NMR studies. In compound **1**, thymine H-6 showed a strong interaction with H-2′ and weak correlations with H-1′, H-3′, and H-5′. In contrast, in compound **2**, purine H-8 showed a strong correlation with H-1′ and H-2′, as well as weaker interactions with H-5′ and H-3′. These results indicate that the preferred relative position of the base toward the sugar ring of **2** in solution differs from that determined in the solid state and hence the 2′,3′-cyclobutane fused nucleosides are not completely locked and they have some flexibility.

In summary, the chemistry described here furnishes a facile entry into novel cyclobutane nucleosides analogues. The greater flexibility of the 3-oxabicyclo[3.2.0]heptane nucleosides when compared to the 3-oxabicyclo[3.1.0]hexane analogues may be an important feature for potential antiviral activity. Currently, these nucleosides are undergoing biological evaluation as potential antiviral and anticancer agents.

Acknowledgment. We acknowledge financial support from DGES (CTQ2004-02539/BQU) and CIRIT (2001SGR-00178) and a grant from the Generalitat de Catalunya to (A.R.).

Supporting Information Available: Experimental details and characterization data for all new compounds and X-ray crystallographic information of **2** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL052794Y

(22) For X-ray structure analyses and structure−activity relationship of 2′,3′-dideoxynucleosides, see: Herdewijn, P. A.; Van Aerschot, A.; Balzarini, J.; de Clercq, E.; Everaert, D. H.; de Winter, H. L.; Peeters, O. M.; Blaton, N. M.; de Ranter, C. J. *Med. Chem. Res.* **1991**, *1*, 9−19.

(23) d4A (DHOADS01): Chu, C. K.; Bhadti, V. S.; Doboszewski, B.; Gu, Z. P.; Kosugi, Y.; Pullaiah, K. C.; Van Roey, P. *J. Org. Chem.* **1989**, *54*, 2217−2225.

(24) ddA (GAHHIG): Silverton, J. V.; Quinn, F. R.; Haugwitz, R. D.; Todaro, L. J. *Acta Crystallogr., Sect. C* **1988**, *44*, 321−324.

(25) Taylor, E. W.; Van Roey, P.; Schinazi, R. F.; Chu, C. K. *Antiviral Chem. Chemother.* **1990**, *1*, 163−173.