

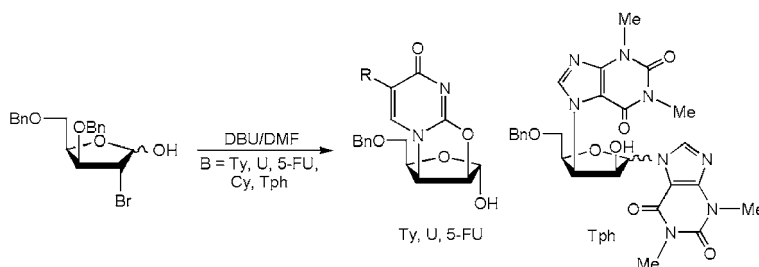
Convenient Synthesis of Nucleoside and Isonucleoside Analogues

Luis Álvarez de Cienfuegos,[†] Antonio J. Mota,[‡] and Rafael Robles**Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Granada, Campus de Fuentenueva 18071, Granada, Spain*

rrobles@ugr.es

Received March 8, 2005

ABSTRACT



A very simple methodology to stereoselectively achieve tricyclic isonucleosides (nucleobase = thymine, uracil, and 5-fluorouracil) and 3'-C-branched nucleosides (nucleobase = theophylline) was performed by means of a DBU-mediated addition process using a readily available 2-bromo sugar. The mechanism for these transformations implies the loss of both substituents at C-2 and C-3 on the sugar moiety, and although it seems that DBU is probably involved, its involvement has not yet been ascertained. Cytosine did not react under these conditions.

Nucleoside derivatives are the predominant molecular target prodrugs for the clinical therapy of AIDS.¹ Unfortunately, several problems concerning the development of resistance against these drugs,² their cytotoxicity,³ and their glycosidic bond cleavage⁴ or enzymatic deamination⁵ processes have led to the synthesis of new families of these compounds. In this manner, the synthesis of nucleoside analogues in which

the sugar and/or the heterocyclic moiety have been modified has received much attention as a consequence of their general biological activity and the potential use of such molecules as antiviral and antineoplastic therapeutic agents.⁶ In particular, isomeric nucleosides (isonucleosides) have revealed significant antiviral activities,⁷ and their syntheses are currently receiving much attention.⁸ In the past few years, we have developed new methods for the stereoselective synthesis of nucleosides by means of furanoid glycals⁹ or 1,2-thiocarbonate sugars.¹⁰ New strategies have also been performed concerning the synthesis of isonucleoside analogues and *seco*-nucleosides through exocyclic methylene furanoid-like sugars.¹¹ In this study, we present a simple way

[†] Current address: Prof. A. Klibanov Laboratory, Department of Chemistry, Massachusetts Institute of Technology, Room 56-570, 77 Massachusetts Avenue, Cambridge, MA 02139–4307.

[‡] Current address: Laboratoire de Chimie Quantique, Institut Le Bel, Université Louis Pasteur, 4, rue Blaise Pascal, 67000-Strasbourg, France.

(1) (a) Mitsuya, H.; Yarchoan, R.; Broder, S. *Science* **1990**, *249*, 1533–544. (b) Herdewijn, P. A. M. *Antiviral Res.* **1992**, *19*, 1–14.

(2) (a) St. Clair, M. H.; Martin, J. L.; Tudor-Williams, G.; Bach, M. C.; Vavro, C. L.; King, D. M.; Kellam, P.; Kemp, S. D.; Larder, B. A. *Science* **1991**, *253*, 1557–1559. (b) De Clercq, E. *Biochem. Pharmacol.* **1994**, *47*, 155–169.

(3) (a) Chen, C.-H.; Cheng, Y.-C. *J. Biol. Chem.* **1989**, *264*, 11934–11937. (b) Chen, C.-H.; Valquez-Padua, M.; Cheng, Y.-C. *Mol. Pharmacol.* **1991**, *39*, 625–628.

(4) (a) York, J. L. *J. Org. Chem.* **1981**, *46*, 2171–2173. (b) Nair, V.; Buenger, G. S. *J. Org. Chem.* **1990**, *55*, 3695–3697.

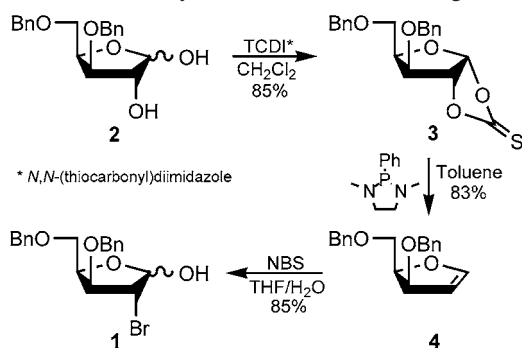
(5) (a) Bloch, A.; Robins, M. J.; McCarthy, J. R. *J. Med. Chem.* **1967**, *10*, 908–912. (b) Cooney, D. A.; Ahluwalia, G.; Mitsuya, H.; Fridland, A.; Johnson, M.; Hao, Z.; Dajal, M.; Balzarini, J.; Broder, S.; Johns, D. G. *Biochem. Pharmacol.* **1987**, *36*, 1765–1768. (c) Nair, V.; Sells, T. B. *Biochim. Biophys. Acta* **1992**, *1119*, 201–204.

(6) (a) Herdewijn, P.; Balzarini, J.; De Clercq, E.; Pauwels, R.; Baba, M.; Broder, S.; VanderHeghe, H. *J. Med. Chem.* **1987**, *30*, 1270–1278. (b) Mitsuya, H.; Yarchoan, R.; Broder, S. *Science* **1990**, *249*, 1533–1544. (c) De Clercq, E. *Design of Anti-AIDS Drugs*; Elsevier: New York, 1990. (7) (a) Huryn, D. M.; Sluboski, B. C.; Tam, S. Y.; Weigle, M.; Sim, I.; Anderson, B. D.; Mitsuya, H.; Broder, S. *J. Med. Chem.* **1992**, *35*, 2347–2354. (b) Verheggen, I.; Van Aerschot, A.; Van Meervelt, L.; Rozenski, J.; Wiebe, L.; Snoeck, R.; Andrei, G.; Balzarini, J.; Claes, P.; De Clercq, E.; Herdewijn, P. *J. Med. Chem.* **1995**, *38*, 826–835. (c) Nair, V.; Jahnke, T. S. *Antimicrob. Agents Chemother.* **1995**, *39*, 1017–1029. (d) Yu, H.-W.; Zhang, L.-R.; Zhou, J.-C.; Ma, L.-T.; Zhang, L.-H. *Bioorg. Med. Chem.* **1996**, *4*, 609–614. (e) Wang, J.-F.; Yang, X.-D.; Zhang, L.-R.; Yang, Z.-J.; Zhang, L.-H. *Tetrahedron* **2004**, *60*, 8535–8546.

to access tricyclic 2,2'-*anhydro*-3-deoxy-3-isonucleosides and their corresponding open forms (3-deoxy-3-isonucleosides), along with a 3'-C-branched nucleoside derivative incorporating two units of theophylline.

Our key starting material is the 2-bromo sugar **1** (Scheme 1), which is readily available from the 1,2-diol **2** through

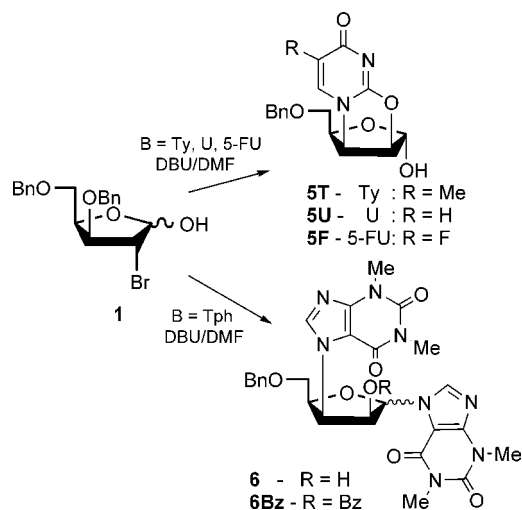
Scheme 1. Synthesis of the 2-Bromo Sugar **1**



the formation of the 1,2-thiocarbonate sugar **3** and the furanoid glycal **4**.¹² The latter quickly reacts with NBS in aqueous THF^{9a,13} to afford compound **1** in high yield.¹⁴

When the bromo derivative **1** was treated with pyrimidinic bases [thymine (Ty), uracil (U), 5-fluoruracil (5-FU), and cytosine (Cy)] in the presence of DBU, the corresponding tricyclic sugars **5** were formed (as tricyclic isonucleosides analogues),¹⁵ with cytosine being the only exception for which we were not able to obtain the corresponding isonucleoside derivative (Scheme 2, Table 1).

Scheme 2. Synthesis of Tricyclic Isonucleosides **5** and 3'-C-Branched Nucleoside **6**



It is noteworthy that nucleobases do not have a preference for either the anomeric position or the C-2 position. These positions are a priori highly sensitive to a possible nucleophilic attack. Conversely, they enter at the C-3 position on

Table 1. Yields Obtained for the Addition Process via Scheme 2

entry	nucleobase used	compound formed (yield %) ^a
1	thymine (Ty)	5T (71)
2	uracil (U)	5U (73)
3	5-fluoruracil (5-FU)	5F (58)
4	cytosine (Cy)	5C (na) ^b
5	theophylline (Tph)	6 (50) ^c

^a Optimized yield. ^b No reaction was observed. ^c Mixture of isomers (~9:1).

the sugar in a highly stereoselective fashion, with the loss of both substituents at C-2 and C-3, the anomeric position remaining unreacted. On the other hand, when theophylline (Tph) was used as a nucleobase,¹⁶ a different final product was observed: a 3'-C-theophyllinyl nucleoside (**6**).

The structure of compounds **5** has been unambiguously secured by X-ray diffraction for the thymine derivative **5T** (CCDC 250080, see Supporting Information), which presents unique NMR patterns clearly recognizable on all the other tricyclic derivatives. Unfortunately, we have not achieved good crystals for **6** (or its benzoylated derivative **6Bz**) in attempts to ascertain its structure. Nevertheless, after an extensive NMR study, we can conclude that structural differences from compounds **5** are due to the insertion of a new nucleobase unit at the anomeric position, not being a tricycle derivative. This is possible since theophylline does

(8) (a) Jung, M. E.; Nichols, C. J. *J. Org. Chem.* **1998**, *63*, 347–355. (b) Díaz, Y.; Bravo, F.; Castillón, S. *J. Org. Chem.* **1999**, *64*, 6508–6511. (c) Bera, S.; Nair, V. *Tetrahedron Lett.* **2001**, *42*, 5813–5815. (d) Lei, Z.; Zhang, L.; Zhang, L.-R.; Chen, J.; Min, J.-M.; Zhang, L.-H. *Nucleic Acids Res.* **2001**, *29*, 1470–1475. (e) Chattopadhyay, A.; Salaskar, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 785–789. (f) Nair, V.; Chun, B.-K. *Arkivoc* **2003**, *i*, 9–21.

(9) (a) Robles, R.; Rodríguez, C.; Izquierdo, I.; Plaza, M. T.; Mota, A. *Tetrahedron: Asymmetry* **1997**, *8*, 2959–2965. (b) Álvarez de Cienfuegos, L.; Mota, A. J.; Rodríguez, C.; Robles, R. *Tetrahedron Lett.* **2005**, *46*, 469–473.

(10) (a) Álvarez de Cienfuegos, L.; Rodríguez, C.; Mota, A. J.; Robles, R. *Org. Lett.* **2003**, *5*, 2743–2745. (b) Robles, R.; Rodríguez, C.; Álvarez de Cienfuegos, L.; Mota, A. J. *Tetrahedron: Asymmetry* **2004**, *15*, 831–838.

(11) Robles, R.; Izquierdo, I.; Rodríguez, C.; Plaza, M. T.; Mota, A. J.; Álvarez de Cienfuegos, L. *Tetrahedron: Asymmetry* **2002**, *13*, 399–405.

(12) Robles Díaz, R.; Rodríguez Melgarejo, C.; Izquierdo Cubero, I.; Plaza López-Espinosa, M. T. *Carbohydr. Res.* **1997**, *300*, 375–380.

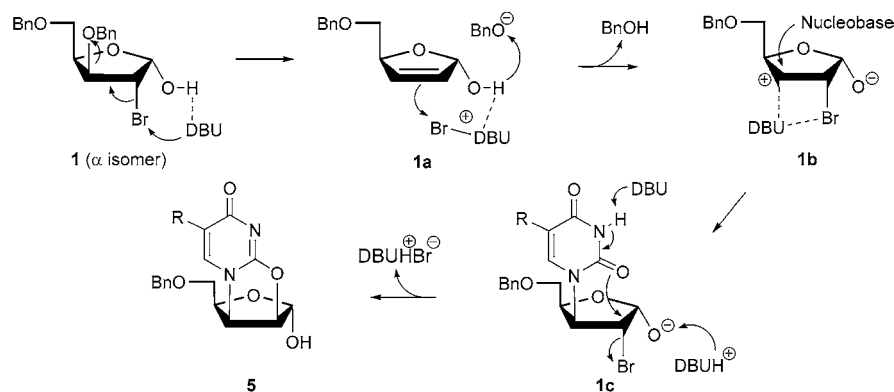
(13) Robles-Díaz, R.; Rodríguez Melgarejo, C.; Plaza López-Espinosa, M.-T.; Izquierdo Cubero, I. *J. Org. Chem.* **1994**, *59*, 7928–7929.

(14) Compound **4** (1 mmol) in THF (10 mL) was treated with NBS (1.1 mmol) and H₂O (1 mL). After 10 min, TLC (ether) revealed that the reaction was finished, showing a lower-running product. The mixture was concentrated under reduced pressure, and the residue was purified by column chromatography (1:1 ether/hexane), yielding **1** (0.85 mmol, 85%) as a mixture of anomers.

(15) To a solution of the corresponding nucleobase (Ty, U, 5-FU, or Tph, 2 mmol) in dry DMF (15 mL) containing DBU (3.2 mmol) was added **1** (1 mmol), and the mixture was stirred for 10 min. After this time, TLC (20:1 Cl₂CH₂/MeOH) showed that the reaction was finished (a lower-running product appeared). An aqueous solution of KHSO₄ (10%) was then added until the pH became slightly acidic. The solution was evaporated under reduced pressure, and the residue was extracted with Cl₂CH₂–H₂O. The organic layer was dried (MgSO₄ anhydrous), filtered, and evaporated under reduced pressure until dryness. The residue was purified by column chromatography (20:1 Cl₂CH₂/MeOH) to yield respectively **5T**, **5U**, **5F**, and **6**, the latter being a ~9:1 mixture of isomers (see Table 1).

(16) Theophylline was chosen as a base because the absence of hydrogens should prohibit the tricycle formation, as it has been experimentally proved.

Scheme 3. Proposed Mechanism to Obtain Derivatives **5**



not allow the tricyclic formation (it has no hydrogens on the nitrogens). The stereochemistry at C-3' for the major isomer in **6** can be deduced from the ^1H NMR couplings, since the key J values (in hertz) are $J_{\text{H}2',\text{H}3'} = 6.0$ (7.8 in **6Bz**) and $J_{\text{H}3',\text{H}4'} = 8.8$, both indicative of an all-2,3,4-*cis* arrangement. At the anomeric position, a $J_{\text{H}1',\text{H}2'}$ value of 1.5 Hz points to an α stereochemistry. These conclusions follow the general behavior of the other bases employed. Nevertheless, with regard to the minor isomer, the ^1H NMR coupling constants are not conclusive, and it cannot be concluded that this compound corresponds to the β anomer. In any case, AM1 semiempirical calculations¹⁷ show that the α anomer is thermodynamically more stable than the β isomer by 3.5 kcal/mol (see Supporting Information). Moreover, calculations also point out a theophylline unit bonding the sugar by the sterically less hindered N-7 position (preferred by 14.7 kcal/mol according to AM1). The isomeric N-9 bonding generates a bigger steric hindrance caused by the methyl group at N-3 (see Supporting Information).

The mechanism involved in these transformations has not been ascertained, and other experiments have been carried out with derivatives chemically related with **1** in order to

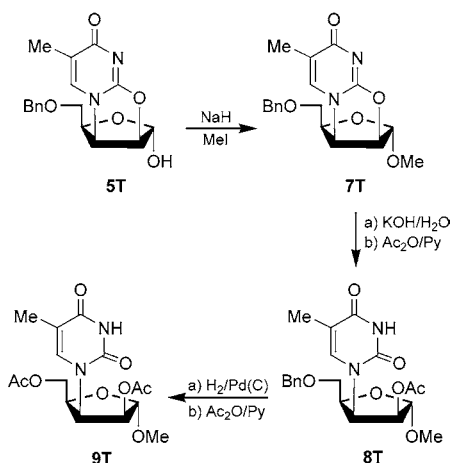
clarify it (see Supporting Information). As a result, an attempted mechanism based on a cascade reaction, in which DBU is actively involved, is proposed in Scheme 3. It should be noted that DBU not only acts to catalyze the process but also controls the stereochemistry of the addition. The regiochemistry, however, is controlled by the intermediate **1b**. Thus, the positive charge is necessarily placed on C-3 in order to avoid the vicinity of the δ^+ anomeric carbon. All these polar species are assumed to be significantly stabilized by the solvent (DMF).

We have also carried out several modifications over the tricyclic derivative **5T** oriented to the synthesis of its corresponding 3-deoxy-3-isonucleoside by regio- and stereospecific ring-opening of the tricyclic system (Scheme 4). In this manner, derivatives **7T**, **8T**, and **9T** have been obtained following common protocols (see Supporting Information). It should be noted that the **7T** \rightarrow **8T** transformation takes place with retention of the configuration on C-2', because it does not go through an $\text{S}_{\text{N}}2$ process at this position but instead goes through an OH^- addition (alkaline hydrolysis) at C-2 of the pyrimidine.¹⁸

In summary, we have developed a very simple methodology to stereoselectively achieve tricyclic isonucleosides and 3'-C-branched nucleoside derivatives by means of a DBU-mediated addition process using the readily available 2-bromo sugar **1**. The reaction conditions are soft, and we can quickly provide the valuable title compounds in a few steps. The stereochemistry of the tricyclic derivatives has been ascertained by X-ray diffraction for the thymine derivative and correlated to the other derivatives by finding similar NMR patterns. The regio- and stereospecific ring-opening of the tricyclic derivative **5T** afforded the corresponding 3-deoxy-3-isonucleoside.

Acknowledgment. We thank the Universidad de Granada for the grant to L. Álvarez de Cienfuegos and for providing funds for this work, along with the Junta de Andalucía for the research contract to A. J. Mota.

Scheme 4. Chemical Modifications on the Tricyclic Sugar Derivative **5T**



(17) Hyperchem, release 7.5; Hypercube, Inc.: Gainesville, FL.

(18) (a) Thedford, R.; Fleysher, M. H.; Hall, R. H. *J. Med. Chem.* **1965**, *8*, 486-491. (b) Robles, R.; Rodríguez, C.; Izquierdo, I.; Plaza, M. T.; Mota, A.; Álvarez de Cienfuegos, L. *Tetrahedron: Asymmetry* **2000**, *11*, 3069-3077.

Supporting Information Available: Complete physical data (IR, α_D , HMRS, and ^1H and ^{13}C NMR) of compounds **1**, **5T**, **5U**, **5F**, **6**, **6Bz**, **7T**, **8T**, and **9T**; the X-ray structure for derivative **5T**; AM1 structures, energies, and Cartesian coordinates of the calculated structures;

additional experiments carried out in order to ascertain the mechanism; and the protocols followed in the **5T** \rightarrow **9T** transformations. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL050496V