A Simple Approach to 1′,1′a-Methano Carbocyclic Thymidine

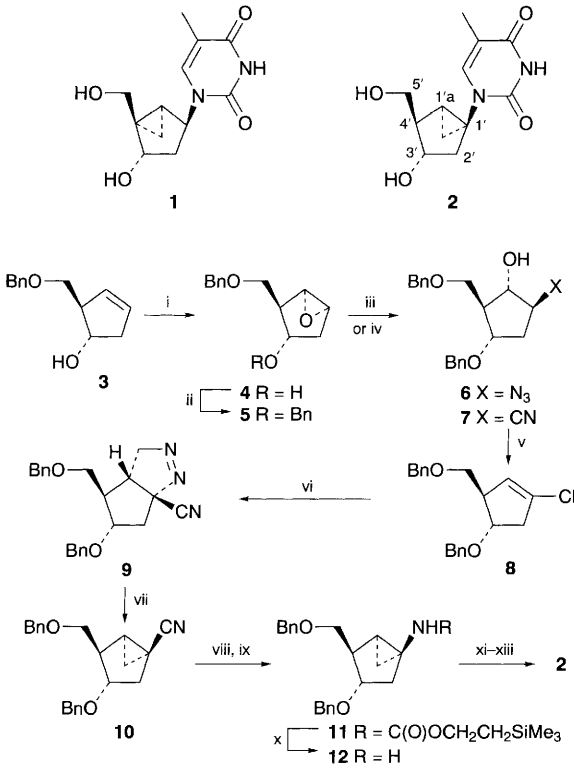
Abdallah Ezzitouni, Joseph J. Barchi, Jr. and Victor E. Marquez*

Laboratory of Medicinal Chemistry, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, NIH, Bethesda, MD 20892, USA

An enantioselective synthesis of 1′,1′a-methano carbocyclic thymidine, a rigid molecule that mimics thymidine's 2′-*endo*/3′-*exo* (South) conformation, is efficiently synthesized from chiral 2-benzyloxymethylcyclopent-3-enol.

The cyclopentane ring in carbocyclic nucleosides exists in an unusual 1′-*exo* conformation which is relatively far from the typical 2′-*exo*/3′-*endo* (North) or 2′-*endo*/3′-*exo* (South) conformations of nucleosides.[1] Such a conformational difference could explain in part why most carbocyclic nucleosides are generally biologically less effective than their nucleoside counterparts.[2] The removal of the furan oxygen completely abolishes the important anomeric effect, as well as *gauche* interactions between the oxygen and the 2′- and 3′-hydroxy groups. The result from the interplay of these forces normally determines the direction of equilibrium in solution between North and South conformations in conventional nucleosides.[3,4]

Recently, some new carbocyclic nucleosides built on a rigid bicyclo[3.1.0]hexane system have been shown to have ring conformations that mimic very well the North and South conformers of conventional nucleosides.[5–8] A series of 2′,3′-dideoxy-4′,1′a-methano carbocyclic nucleosides,[5,7] as well as 4′,1′-methano carbocyclic thymidine **1**,[6] have rigid North conformations corresponding to a 2′-*exo*/3′-*endo* form of ring pucker, while the isomeric 1′,1′a-methano carbocyclic thymidine analogue **2**[8] has the opposite 2′-*endo*/3′-*exo* ring pucker corresponding to a South conformer.[9] An enantioselective synthesis of the important South conformer **2** was reported recently,[8] but the process was rather lengthy and required the initial separation of diastereoisomeric (−)-ephedrine salts of the starting tetrahydrophthalic acid monomethyl ester.[10] Although the reported yields were excellent, we wished to simplify the process by starting from a simpler homochiral starting material **3** that has been developed as a versatile synthon for accessing a variety of carbocyclic nucleosides (Scheme 1).[11,12] This compound was obtained as described in optically pure form (e.e. > 98%), and following Sharpless epoxidation and protection of the free hydroxy group as a benzyl ether, the corresponding known epoxide **5** was obtained.[12] Nucleophilic opening of the epoxide ring occurred with high regioselectivity to afford either the azido **6**[12] or cyano **7** analogue. Compound **6** was the most desirable intermediate, but unfortunately the intermediate thiocarbonylimidazolide formed with *N*,*N*′-thiocarbonyldiimidazole (Im_2CS) did not give the desired *syn*-β-elimination product even under forcing conditions. On the other hand, the thiocarbonylimidazolide from the cyano intermediate **7** was smoothly converted to the desired alkene **8** in excellent yield. The mechanism of this reaction is similar to the well known Chugaev reaction,[13] and the utility of this type of *syn*-elimination reaction of thiocarbonylimidazolides recently has been applied to the synthesis of 2′-*C*-cyano-2′,3′-didehydro-2′,3′-dideoxynucleosides.[14] Subsequent 1,3-dipolar addition of diazomethane to alkene **8** proceeded with exquisite regio- and stereo-chemical selectivity to give exclusively the five-membered *cis*-fused pyrazoline intermediate **9**. The stereofacial selectivity of this reaction is probably controlled by the



Scheme 1 *Reagents and conditions*: i, and ii, ref. 12; iii, KCN, $LiClO_4$, MeCN, 70 °C, 24 h (**7**, 75%); iv, ref. 12 (**6**); v, Im_2CS, DMAP, DMF, room temp., 12 h then heating at 80 °C, 2 h (84%); vi, CH_2N_2, Et_2O, 0 °C to room temp., 3 d (94%); vii, *hν* (250–400 nm), benzophenone, benzene–MeCN (1 : 1), 2 h (79%); viii, NaOH, EtOH, reflux, 36 h (62%); ix, DPPA, Et_3N, toluene, room temp., 4 h then Me_3SiCH_2 CH_2OH and heating at 80 °C (56%); x, Bu^t_4NF, THF, 70 °C (used as a crude product in the following step); xi, MeOCH=C(Me)C(O)NCO, toluene, room temp., 24 h (55%); xii, HCl–EtOH, reflux, 20 h (84%); xiii, BCl_3, CH_2Cl_2, −78 °C (72%)

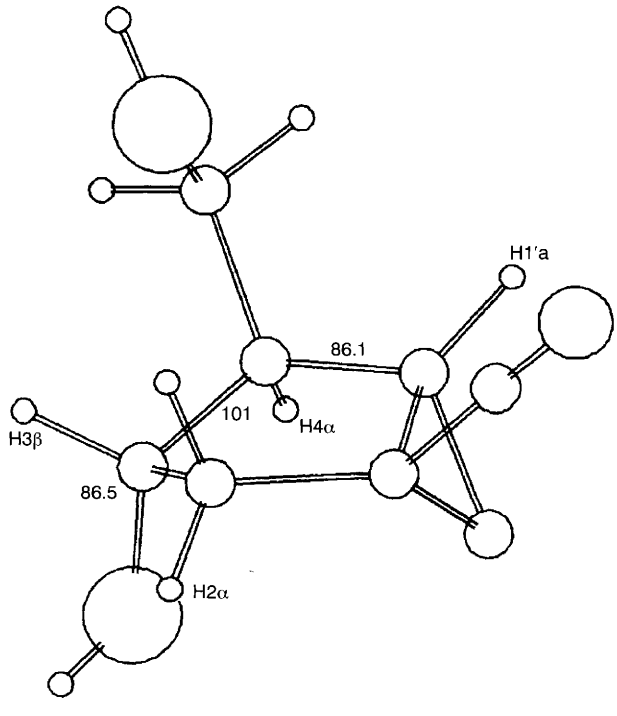


Fig. 1 The pseudo-boat conformation of **10** depicting the dihedral angles described in the text (benzyl protecting groups have been omitted for simplicity)

stereochemistry of the benzyloxymethyl group which blocks nucleophilic attack from the β-face. Photolysis of this intermediate gave the key bicyclo[3.1.0]hexane **10** with the desired β-CN group. Since bicyclo[3.1.0]hexane systems are quite rigid and exist exclusively in a pseudo-boat conformation,[15] the ^{1}H NMR spectrum of **10** was very informative. Consistent with an α-fused cyclopropane ring, the following dihedral angles approached 90°: $H_{2\alpha}$–C_2–C_3–$H_{3\beta}$ (86.5°), $H_{3\beta}$–C_3–C_4–$H_{4\alpha}$ (101.0°), and $H_{4\alpha}$–C_4–$C_{1'a}$–$H_{1'a}$ (86.1°) (Fig. 1). These values indeed helped explain the multiplicities observed for the signals corresponding to H_3 (d, J = 6.4 Hz), H_4 (t, J = 6.5 Hz), and $H_{1'a}$ (dd, J = 8.5, 5.0 Hz).

With an opposite β-fused cyclopropane ring, no dihedral angle in the molecule would approach 90°, and hence the corresponding proton signals would have been much more complex. For the conversion of the nitrile function into a suitable amine derivative, we utilized the mild Curtius rearrangement of the corresponding carboxylic acid derivative into an isocyanate with diphenylphosphoryl azide (DPPA).[16] The isocyanate intermediate was trapped with 2-(trimethylsilyl)ethanol to give carbamate **11** and removal of the amino protecting group with fluoride ion gave the bicyclic amine from which the thymine base was constructed by a standard methodology.[17] Final deblocking of the *O*-benzyl groups produced the desired compound **2**, mp 206–207 °C (lit.[8] mp 206–206.4 °C), $[\alpha]_D^{25}$ −47.7 (*c* 0.58, MeOH) with identical spectral properties [^{1}H NMR (500 MHz) and MS] to those reported previously.[8] In summary, in addition to achieving an alternate synthesis for the bicyclo thymidine analogue **2**, the stable carbamate **11** constitutes a versatile and very accessible intermediate for the construction of other conformationally rigid carbocyclic nucleosides that mimic conventional nucleosides in the South conformation.

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References

1 A. Kalman, T. Koritsanszky, J. Beres and G. Sagi, *Nucleosides Nucleotides*, 1990, **9**, 235.
2 V. E. Marquez and M.-I. Lim, *Med. Res. Rev.*, 1986, **6**, 1.
3 C. Thibaudeau, J. Plavec, N. Garg, A. Papchikhin and J. Chattopadhyaya, *J. Am. Chem. Soc.*, 1994, **116**, 4038.
4 C. Thibaudeau, J. Plavec and J. Chattopadhyaya, *J. Am. Chem. Soc.*, 1994, **116**, 8033.
5 J. B. Rodriguez, V. E. Marquez, M. C. Nicklaus and J. J. Barchi, Jr., *Tetrahedron Lett.*, 1993, **34**, 6233.
6 K.-H. Altmann, R. Kesselring, E. Francotte and G. Rihs, *Tetrahedron Lett.*, 1994, **35**, 2331.
7 J. B. Rodriguez, V. E. Marquez, M. C. Nicklaus, H. Mitsuya and J. J. Barchi, Jr., *J. Med. Chem.*, 1994, **37** 3389.
8 K.-H. Altmann, R. Imwinkelried, R. Kesselring and G. Rihs, *Tetrahedron Lett.*, 1994, **35**, 7625.
9 The numbering system used conforms to the recommendations for the nomenclature of carbocyclic nucleosides proposed by J. Balzarini, H. Baumgartner, M. Bodenteich, E. De Clercq and H. Griengl, *Nucleosides Nucleotides*, 1989, **8** 855.
10 H.-J. Gais, K. L. Lukas, W. A. Ball, S. Braun and H. J. Lindner, *Liebigs Ann. Chem.*, 1986, 687.
11 K. Biggadike, A. D. Borthwick, A. M. Exall, B. E. Kirk, S. M. Roberts, P. Youds, A. M. Z. Slawin and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1987, 255.
12 K. Biggadike, A. D. Borthwick, D. Evans, A. M. Exall, B. E. Kirk, S. M. Roberts. L. Stephenson and P. Youds, *J. Chem. Soc., Perkin Trans. 1*, 1988, 549.
13 H. R. Nace, *Org. React.*, 1962, **12**, 57.
14 A. Azuma, Y. Kakajima, N. Nishizono, N. Minakawa, M. Suzuki, K. Hanaoka, T. Kobayashi, M. Tanaka, T. Sasaki and A. Matsuda, *J. Med. Chem.*, 1993, **36**, 4183.
15 R. Okazaki, J. Niwa and S. Kato, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 1619.
16 T. Shiori, K. Ninomiya and S. Yamada, *J. Am. Chem. Soc.*, 1972, **94**, 6203.
17 Y. F. Shealy, C. A. O'Dell and M. C. Thorpe, *J. Heterocycl. Chem.*, 1981, **18**, 383.