SYNTHESIS OF CABOCYCLIC NUCLEOSIDES OF PHARMACOLOGICAL IMPORTANCE

Prof. Dr. Juan B. Rodriguez
Buenos Aires University, Argentina

The sugar moiety of nucleosides in solution exists in a dynamic equilibrium between the Northern-type geometry and the facing Southern-type geometry according to the concept of the pseudorotational cycle.[1] However, only one of these conformers is found in the crystalline structure, and only the Northern or Southern conformer is exclusively responsible for molecular recognition as well because just one form is present in the drug-enzyme complex. However, as the ribose ring is flexible and the conformation in solution may be unlike than that found in the solid state, any attempt to correlate sugar conformation with biological action would be flawed unless the crystal and the solution conformation are the same. A cyclopropane or an epoxy ring can confer such rigidity to the sugar ring, in which the equilibrium N $\Leftrightarrow$ S is not observed indicating that the solution conformation is virtually the same to that found in the crystal.[2] On the other hand, the conformational restriction induced by an epoxy group at the C-2' and C-3' positions fixes the sugar conformation far away from the Northern or Southern geometry required for biological activity. In carbanucleosides, removal of the oxygen atom of the furanose ring produces significant changes in terms of stereoelectronic effects.[3] Certainly, the lack of an anomeric effect as well as significant gauche interactions between the furanosic oxygen atom and any electronegative substituent at C-2' or C-3' lead to conformers that do not match those found in conventional nucleosides. The naturally occurring carbocyclic nucleoside neplanocin C (1),[4] is a good prototype of a conformationally locked nucleoside analogue. Neplanocin C, isolated from *Ampullariela regularis*, is a minor component of the neplanocin family of antibiotics, which is built on an oxabicyclic[3.1.0]-hexane system that allows this compound to exhibit the typical Northern-type (N) conformation, specifically in the $_2$E geometry. This conformation is very close to a pure $^3T_2$ (P = 0º) geometry as determined by the *P* value of the pseudorotational cycle (P value = 338.03º and $_{max}$ = 21.89º) from the solved X ray structure.[4c] The chemical structure of neplanocin C was taken as lead drug for the design of a substantial number of conformationally restricted carbocyclic nucleosides of biological importance.[5] The enantioselective synthesis of neplanocin C and other closely related carbocyclic nucleosides including their episulfide analogues will be discussed.[6–8] The crucial point in the preparation of neplanocin C was the remarkable stability of the epoxy group under methanolic ammonia at high temperature to convert a 6-chloropurine derivative into an adenosine derivative.[6] This fact had already been described in simpler and closely related carbanucleosides built in a [3.1.0]oxabicyclo systems.[9]

1. Saenger, W. *Principles of Nucleic Acid Structure*; Springer-Verlag: New York, 1984; pp 51–104.
2. Koole, L. H.; Neidle, S.; Crawford, M. D.; Krayevski, A. A.; Gurskaya, G. V.; Sandström, A.; Wu, J.-C.; Tong, W.; Chattopadhyaya, J. *J. Org. Chem*. **1991**, *56*, 6884–6892.
3. Rodriguez, J. B.; Comin, M. J. *Mini Rev. Med. Chem.* **2003**, *3*, 95–114.
4. (a) Yaginuma, S.; Muto, N.; Tsujino, M.; Sudate, Y.; Hayashi, M.; Otani, M. *J. Antibiot.* **1981**, *34*, 359–366; (b) Isono, K. *J. Antibiot.* **1988**, *41*, 1711–1739; (c) Kinoshita, K.; Yaginuma, S.; Hayashi, M.; Nakatsu, K. *Nucleosides Nucleotides*, **1985**, *4*, 661–668.
5. (a) Rodriguez, J. B.; Marquez, V. E.; Nicklaus, M. C.; Barchi, J. J., Jr. *Tetrahedron Lett*. **1993**, *34*, 6233–6236; (b) Rodriguez, J. B.; Marquez, V. E.; Nicklaus, M. C.; Mitsuya, H.; Barchi, J. J., Jr. *J. Med. Chem.* **1994**, *37*, 3389–3399; (c) Marquez, V. E.; Ezzitouni, A.; Russ, P.; Siddiqui, M. A.; Ford, H. Jr.; Feldman, R. J.; Mitsuya, H.; George, C.; Barchi, J. J., Jr. *J. Am. Chem. Soc*. **1998**, *120*, 2780–2789; (d) Marquez, V. E.; Siddiqui, M. A.; Ezzitouni, A.; Russ, P.; Wang, J.; Wagner, R. W.; Mateucci, M. D. *J. Med. Chem.* **1996**, *39*, 3739–3747; (e) Altmann, K. -H.; Kesselring, R.; Francotte, E.; Rihs, G. *Tetrahedron Lett*. **1994**, *35*, 2331–2334; (f) Altmann, K. -H.; Imwinkelried, R.; Kesselring, R.; Rihs, G. *Tetrahedron Lett*. **1994**, *35*, 7265–7268; (g) Joshi, B. V.; Moon, H. R.; Fettinger, J. C.; Marquez, V. E.; Jacobson, K. A. *J. Org. Chem*. **2005**, *70*, 439–447; (h) Jeong, L. S.; Buenger, G.; McCormack, J. J.; Cooney D. A.; Hao, Z.; Marquez, V. E. *J. Med. Chem.* **1998**, *41*, 2572–2578; (i) Moon, H. R.; Ford, H. Jr.; Marquez, V. E. *Org. Lett*. **2000**, *24*, 3793–3796. (j) Shin, K. J.; Moon, H. R.; George, C.; Marquez, V. E. *J. Org. Chem*. **2000**, *65*, 2172–2178. (k) Moon, H. R.; Kim, H. O.; Chun, M. W.; Jeong, L. S.; Marquez, V. E. *J. Org. Chem.* **1999**, *64*, 4733–4741.
6. Comin, M. J.; Rodriguez, J. B. *Tetrahedron* **2000**, *56*, 4639–4649.
7. Comin, M. J.; J. B. Rodriguez, Russ, P.; Marquez, V. E. *Tetrahedron* **2003**, *59*, 295–301.
8. Elhalem, E.; Comin, M. J.; Leitofuter, J. García-Liñares, G.; Rodriguez, J. B. *Tetrahedron : Asymmetry* 2005, *16*, 425–431.
9. Comin, M. J.; Pujol, C. A.; Damonte, E. B.; Rodriguez, J. B.; *Nucleosides Nucleotides* **1999**, *18*, 2219–2231.