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STEREOSELECTIVE SYNTHESIS OF α-L-BICARBOCYCLIC NUCLEOSIDES AS POTENTIAL ANTIVIRAL DRUGS.

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Abstract: Synthesis of hitherto unknown carbocyclic α-L-isomeric bicyclo[3.1.0]hexyl nucleosides (**8-11**) is described. The key intermediate **7** was synthesized in seven steps from the known chiral compound **1** through a stereoselective cyclopropanation under Furukawa conditions. Compounds **8-11** were evaluated as anti-HBV agents in HepG2T14 cells.

Research on the chemistry of the carbocyclic nucleosides, in which the ring oxygen is replaced by a methylene group, has been directed towards the development of agents showing activities against HIV, HSV-1, HSV-2 and HBV.[1-3] Since the discovery of the significant antiviral activity of 3TC[4], the synthesis of the L-forms of other nucleosides has been investigated with renewed urgency.[5,6] Recently, interest in the influence of sugar conformation on biological activity has prompted several studies in which small rings are fused onto the sugar.[7-9] If the orientation of the fused ring is correct, its effect is to 'freeze' the conformation of the 5-membered ring into that required for optimum binding to enzyme substrates and perhaps as a consequence improve the biological activity. In line with this reasoning, carbocyclic nucleosides have been produced, among which the thymidine [(N)-methanocarba-T][10,11] and 2'-deoxycytidine [(N)-2'-deoxymethanocarba-C][12,13] analogues have excited interest as active agents against viruses. As part of our drug discovery program, we have been interested in the synthesis and biological evaluation of L-carbocyclic nucleoside analogues.[14,15] Herein, we wish to report preliminary results of synthesis of new enantiomerically pure bicarbocyclic acyclic pyrimidine α-L-homonucleosides. The choice of the heterocyclic was based on the biological properties of a natural exocyclic amino nucleoside, clitocine, isolated from the mushroom *Clytocybe inversa*[16] and synthesized independently by the working groups of Kamikawa[17] and Moss.[18] The carbocyclic analog of the clitocine was published by Palmer and al.[19] Other acyclic pyrimidine carbocyclic nucleosides have been previously reported.[20] Finally, exocyclic amino nucleosides can be used as a template for potential antiviral purine analogues.

Our synthetic strategy (Scheme 1) utilized the known compound **1**, (*1R,5S*)-2-oxabicyclo[3.3.0]oct-6-en-3-one, which could be prepared in 3 steps from cyclopentadiene.[21] Reduction of the lactone moiety of **1** with diisobutylaluminium hydride afforded diol **2** in 95% yield. One of the most useful features of the Simmons-

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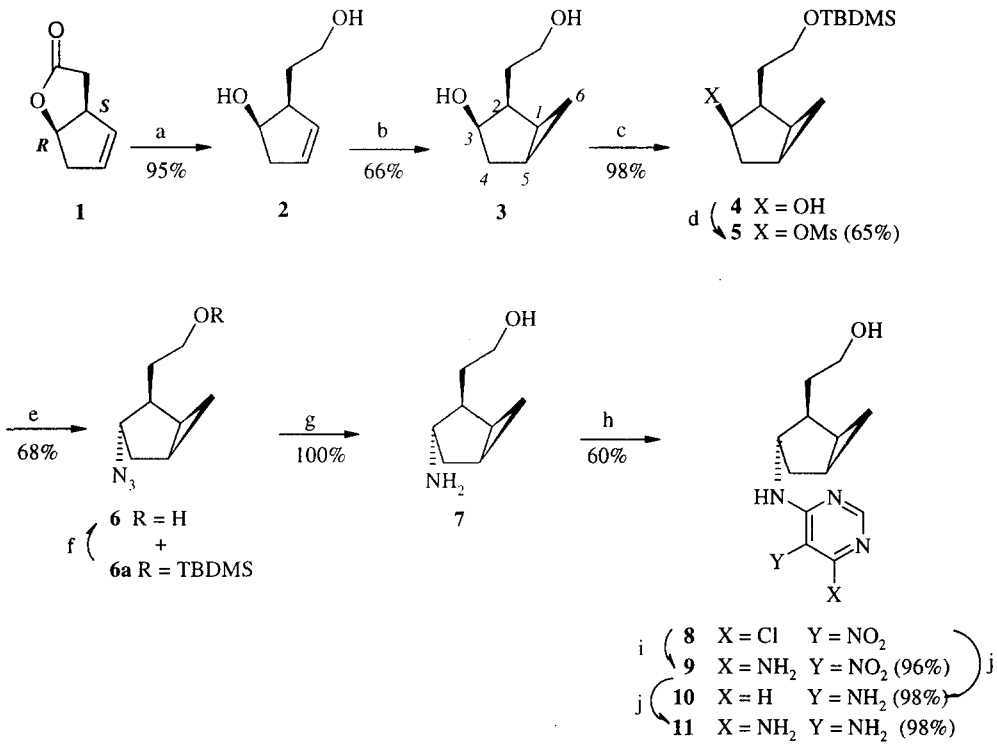
Smith reaction and of its modified versions (Furukawa)[22] is the diastereoselective delivery of the incoming methylene group. We have successfully employed this methodology to the synthesis of bicyclo[3.1.0]hexane template. Thus, the alcohol **2** was treated with $Zn(Et)_2/CH_2I_2$ at 0°C to give regioselectively the (*1S,2R,3R,5S*)-cyclopropyl derivative **3** in 66% yield with 100% diastereomeric excess.[23] The yield and stereoselectivity were not affected by temperature (at -15°C or at rt). In order to obtain the nucleosides, by a linear approach, we decided first to protect the primary alcohol of **3** then to react the heterocycle with the bicyclopentylamine **7**.



Reagents and conditions : (a) DIBAL-H, THF, -78°C to rt ; (b) $ZnEt_2$, CH_2I_2, CH_2Cl_2, 0 °C to rt; (c) TBDMSCl, imidazole, THF, 0 °C; (d) MsCl, pyridine, 50 °C; (e) NaN_3, DMF, 70 °C; (f) nBu$_4$NF/MeOH, rt; (g) H_2, Pd/C, MeOH; (h) 4,6-dichloro-5-nitropyrimidine, Et_3N, CH_2Cl_2, 0 °C; (i) MeOH/NH_3, rt; (j) H_2, Pd/C, MeOH.

Thus, selective protection of the primary alcohol was achieved by reacting **3** with *tert*butyldimethylsilyl chloride in THF in the presence of imidazole to give **4** in 98% yield. The bicyclopentenol **4** was mesylated to **5** (65%) by the usual procedures. The desired stereochemistry in the synthesis of the title nucleosides was achieved by nucleophilic substitution of the mesylate **5** by NaN_3, inducing a partial desilylation, to provide a mixture of **6** and **6a** (68% overall yields). The mixture was treated with a solution of nBu$_4$NF/MeOH[24] and the bicyclo[3.1.0]hexylazide **6** was reduced by hydrogenation to provide the amine **7**. The amine **7** was coupled with 4,6-dichloro-5-nitropyrimidine to afford **8**[25] (60%). The substitution of the aromatic chlorine in **8** with methanolic ammonia gave **9**[26] in 86% yield. Finally, hydrogenation of **8** and **9** gave quantitatively two new

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acyclic pyrimidine bicarbocyclic nucleosides **10**[27] and **11**,[28] respectively.[29] The anti-HBV activity of the synthesized nucleosides was evaluated *in vitro* in hepatitis B virus DNA transfected HepG2 cells, by Dot-blot procedure,[30] at concentrations up to 100 ng/ml and all compounds were found to be inactive and except for compound **8** which exhibited a high toxicity on HepG2 cells.

In summary, the enantioselective synthesis of several acyclic pyrimidine α-L-bicarbocyclic nucleosides **8-11**, has been accomplished from (*1S,2R,3R,5S*)-2-(3-hydroxybicyclo[3.1.0]hex-2-yl)ethanol **3** *via* the key intermediate **7**. Further syntheses of other enantiomerically pure α-L-bicarbocyclic purines *via* compound **8** and pyrimidines are underway.

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References and Notes

1. Agrofoglio, L. A.; Challand, S. R. in "*Acyclic, Carbocyclic and L-Nucleosides*" Kluwer Academic Publishers, Dordrecht, **1998**.
2. Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611-10670.
3. Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571-623.
4. Belleau, B.; Dixit, D.; Nguyen-Ba, N.; Krans, J. L. *Fifth International Conference on AIDS*, Montreal, Canada, June 4-9, **1989**, paper No. T.C.O.I.
5. Kim, H. O.; Ahn, S. K.; Alves, A. J.; Beach, J. W.; Jeong, L. S.; Choi, B. G.; Van Roey, P.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **1992**, *35*, 1987-1995.
6. (a) Lin, T. S.; Luo, M. Z.; Liu, M. C.; Pai, S. B.; Dutschman, G. E.; Cheng, Y.-C. *J. Med. Chem.* **1994**, *37*, 798-803. (b) Faraj, A.; Agrofoglio, L. A.; Wakefield, J. K.; McPherson, S.; Morrow, C. D.; Gosselin, G.; Mathe, C.; Imbach, J.-L.; Schinazi, R. F.; Sommadossi, J.-P. *Antimicrob. Agents Chemother.* **1994**, *38*, 2300-2305.
7. Okabe, M.; Sun, R.-C. *Tetrahedron Lett.* **1989**, *30*, 2203-2206.
8. Rodriguez, J. B.; Marquez, V. E.; Nicklaus, M. C.; Mitsuya, H.; Barchi, J. Jr. *J. Med. Chem.* **1994**, *37*, 3389-3399.
9. Chao, Q.; Nair, V. *Tetrahedron* **1997**, *53*, 1957-1970.
10. (a) Ezzitouni, A.; Marquez, V. E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1073-1078. (b) Marquez, V. E.; Siddiqui, M. A.; Ezzitouni, A.; Russ, P.; Wang, J.; Wagner, R. W.; Matteucci, M. D. *J. Med. Chem.* **1996**, *39*, 3739-3747.
11. (a) Altmann, K.-H.; Kesselring, R.; Francotte, E.; Rihs, G. *Tetrahedron Lett.* **1994**, *35*, 2331-2334. (b) Altmann, K.-H.; Imwinkelried, R.; Kesselring, R.; Rihs, G. *Tetrahedron Lett.* **1994**, *35*, 7625-7628.
12. Siddiqui, M. A.; Ford, H.; George, C.; Marquez, V. E. *Nucleosides Nucleotides* **1996**, *15*, 235-250.
13. O-Yang, C.; Kurz, W.; Eugui, E. M.; McRoberts, M. J.; Verheyden, J. P. H.; Kurz, L. J.; Walker, K. A. *Tetrahedron Lett.* **1992**, *33*, 41-44.

14. Girard, F.; Lee, M.-G.; Fridland, A.; Agrofoglio, L. A. *J. Heterocyclic Chem.* **1998**, *38*, in press.
15. Wang, P.; Agrofoglio, L. A.; Newton, M. G.; Chu, C. K. *Tetrahedron Lett.* **1997**, *38*, 4207-4210.
16. Kubo, I.; Kim, M.; Wood, W. F.; Naoki, H. *Tetrahedron Lett.* **1986**, *27*, 4277-4280.
17. Kamikawa, T.; Fujie, S.; Yamagiwa, Y.; Kim, M.; Kawaguchi, H. *J. Chem. Soc., Chem. Commun.* **1988**, 195-196.
18. Moss, R. J.; Petrie, C. R.; Meyer, R. B.; Nord, L. D.; Willis, R. C.; Smith, R. A.; Larson, S. B.; Kini, G. D.; Robins, R. K. *J. Med. Chem.* **1988**, *31*, 786-790.
19. Palmer, C. F.; Parry, K. P.; Roberts, S. M. *Tetrahedron Lett.* **1990**, *31*, 279-282.
20. (a) Agrofoglio, L., Condom, R.; Guedj, R.; Challand, S. R.; Selway, J. *Nucleosides Nucleotides* **1994**, *13*, 1147-1160. (b) Eger, K.; Klunder, E. M.; Schmidt, M. *J. Med. Chem.* **1994**, *37*, 3057-3061.
21. (a) Partridge, J. J.; Chadha, N. K.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1973**, *95*, 7171-7172. (b) Tsung-Tee, L.; Lesko, P.; Ellison, R. H.; Subramanian, N.; Fried, J. H. *J. Org. Chem.* **1981**, *46*, 111-115.
22. (a) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* 1968, *24*, 53-58. (b) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256-4264.
23. Compound **3**: white solid. mp 74°C; $[\alpha]^{20}_{D}$ +11.5 (c 10.9, $CHCl_3$); ^{1}H-NMR ($CHCl_3$) δ 4.20 (t, 1H *J*=6.4 Hz), 3.89 (m, 1H), 3.70 (m, 1H), 2.9 (br s, OH, D_2O exchangeable), 2.23 (m, 2H), 1.86 (m, 3H), 1.26 (m, 2H), 0.67 (m, 1H), 0.32 (m, 1H). MS: m/z 143 (M^++1); Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.78; H, 10.03.
24. Zhang, W.; Robins, M. *Tetrahedron Lett.* **1992**, *33*, 1177-1180.
25. Compound **8**: yellow oil. $[\alpha]^{20}_{D}$ +86 (c 9.6, MeOH); UV (MeOH) λmax 351 nm; ^{1}H-NMR (MeOD-*d4*) δ 8.30 (s, 1H), 4.10 (m, 1H), 3.67 (m, 2H), 2.30 (m, 2H), 1.76 (m, 2H), 1.65 (m, 1H), 1.35 (m, 2H), 0.35 (m, 2H). MS: m/z 298 (M^++1); Anal. Calcd for $C_{12}H_{15}ClN_4O_3$. 0.5 EtOAc: C, 49.05; H, 5.58; N, 17.32. Found: C, 49.01; H, 5.50; N, 17.58.
26. Compound **9**: yellow solid. mp 166 °C; $[\alpha]^{20}_{D}$ +134 (c 5.9, MeOH); UV (MeOH) λmax 347 nm; ^{1}H-NMR (MeOD-*d4*) δ 7.93 (s, 1H), 4.11 (m, 1H), 3.70 (m, 2H), 2.33 (m, 2H), 1.77 (m, 2H), 1.63 (m, 1H), 1.48-1.37 (m, 2H), 0.36 (m, 2H). MS: m/z 280 (M^++1); Anal. Calcd for $C_{12}H_{17}N_5O_3$: C, 51.60; H, 6.13; N, 25.07. Found: C, 51.48; H, 6.11; N, 26.97.
27. Compound **10**: brown oil. $[\alpha]^{20}_{D}$ +60 (c 8.6, MeOH); UV (MeOH) λmax 350 nm; ^{1}H-NMR (MeOD-*d4*) δ 8.10 (s, 1H), 7.52 (s, 1H), 4.06 (dd, 1H, *J*=9 Hz, 3Hz), 3.70 (m, 2H), 2.35 (m, 2H), 1.77 (m, 2H), 1.61 (m, 1H), 1.48-1.37 (m, 2H), 0.36 (m, 2H). MS: m/z 235 (M^++1); Anal. Calcd for $C_{12}H_{17}N_4O$: C, 61.78; H, 7.34; N, 24.01. Found: C, 61.69; H, 7.28; N, 23.97.
28. Compound **11**: brown gum $[\alpha]^{20}_{D}$ +56 (c 7.4, MeOH); UV (MeOH) λmax 288 nm; ^{1}H-NMR (MeOD-*d4*) δ 7.70 (s, 1H), 3.73-3.50 (m, 3H), 2.23 (m, 2H), 1.75-1.52 (m, 7H), 0.33 (m, 2H). MS: m/z 250 (M^++1); Anal. Calcd for $C_{12}H_{19}N_5O$: C, 57.81; H, 7.68; N, 28.09. Found: C, 57.79; H, 7.64; N, 27.92.
29. All new compounds **2-11** gave correct elemental analyses (±0.5%). These products were purified by column chromatography and product structures were determined by MS, 250 MHz ^{1}H NMR and ^{13}C NMR.
30. (a) Roingeard, P.; Lu, S.; Sureau, C.; Freschlin, M.; Arbeille, B.; Essex, M.; Romet-Lemonne J.-L. *Hepatology* **1989**, 277-285. (b) Roingeard, P.; Romet-Lemonne, J.-L.; Leturcq, D.; Goudeau, A.; Essex, M. *Virology* **1990**, *179*, 113-120.