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A New Short Synthesis of Deoxyhydantocidin Derivatives

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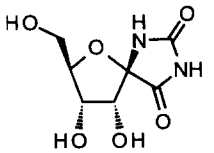
Abstract: Using erythronolactol **8** as chiral C_4 synthon, a new short synthetic pathway was developed to obtain two hydantoin 2'-deoxyribonucleoside epimer derivatives **15a** and **15b**.

Study of spiro nucleosides[1] has gained a new insight with the isolation of (+)-hydantocidin **1**[2] from fermentation broth of *Streptomyces hygroscopicus* SANK 63584. This compound exhibits unique herbicidal activity and is devoid of animal toxicity. We became interested in this kind of constrained nucleoside in another context. While many modified nucleosides have been used as building blocks for oligonucleotide synthesis in the antisense and antigene strategies[3], spiro nucleosides have never been examined for this purpose.

We chose the spiro hydantoin derivative **2b** (dH_β) and its C-1' epimer **2a** (dH_α) as the first target units to be incorporated in oligonucleotides[4,5]. The resulting oligomers containing such units might present, as indicated by molecular modeling, favorable geometry and binding properties owing to the blocked N-glycosidic bond as well as to the thymidine mimicking hydrogen bonding sites of the hydantoin ring[6].



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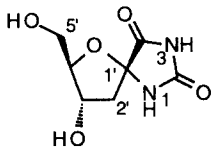
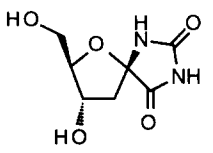


2a (dH_α)



2b (dH_β)

The spiro nucleoside dH_β **2b** was first synthesized using a described method[7] bringing several improvements (Scheme 1). Condensation of the protected hydantoin **4** with the Mukaiyama's aldehyde **3**[8] gave (Z)-diol **5** after acid catalyzed deprotection. While transformation of (Z)-diol **5** to the spiro hydantoins **6a/6b** was precedently achieved in two steps by NBS treatment followed by reductive debromination in 33% yield, we found that cyclization to the spiro nucleosides **6a/6b** (1:3) could be achieved in one step under basic conditions in 90% yield[9]. The inversion of the 3'-OH configuration was accomplished by using a successive oxidation-reduction sequence[7a,9] affording compound **7** which was finally deprotected to give the nucleoside

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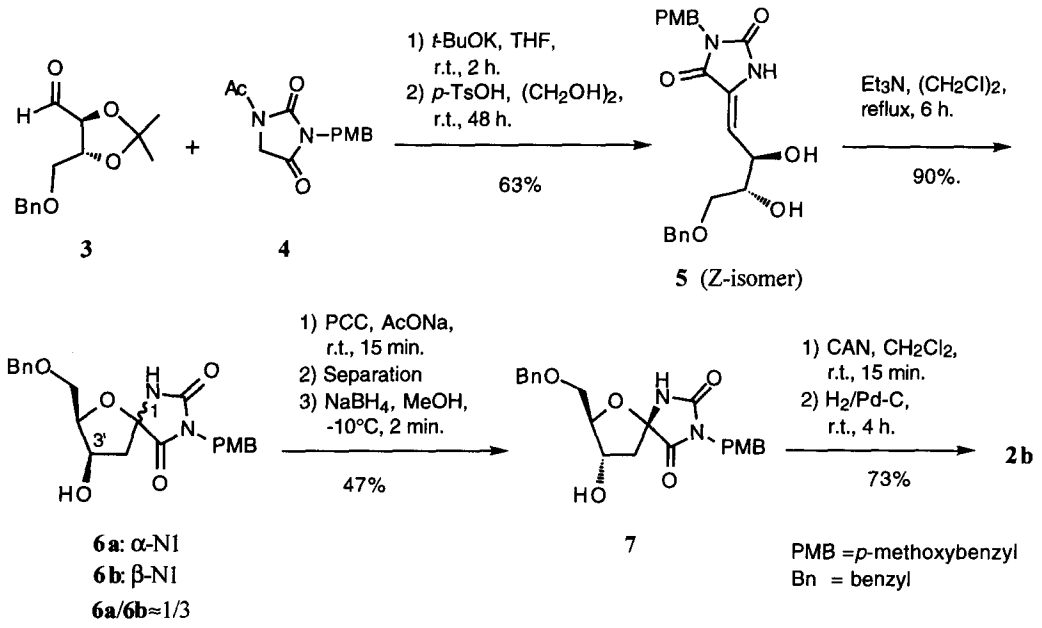
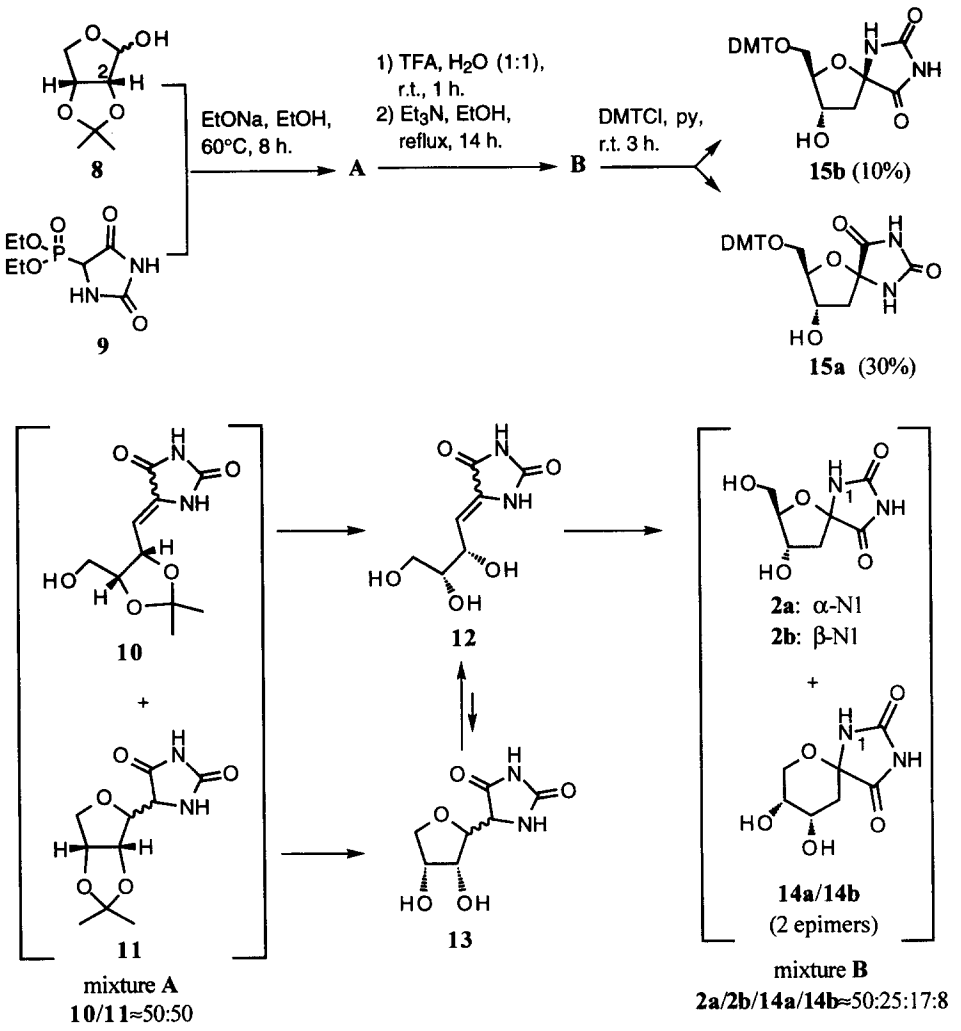
dH_β **2b**. Although improvements have been brought to the original synthetic scheme, notably in the cyclization step (**5**→**6**), the overall yield in dH_β **2b** obtained in six steps from **3** does not exceed 19%. We thus developed a new short and efficient synthesis which afforded not only this dH_β but also the dH_α epimer.



Scheme 1

Erythronolactol **8** is a readily available C_4 chiral synthon[10]. Unlike aldehyde **3**, this cyclic hemiacetal possesses the required stereochemistry at C-2, thus avoiding the inversion steps involved in scheme 1. Horner-Emmons condensation of lactol **8** with phosphonate **9**[11] afforded a complex mixture **A** containing as indicated by NMR analysis[12] the desired hydroxyolefins **10** (2 isomers) accompanied by the hydantoins **11** (4 isomers) resulting from Michael cyclization of **10** (**10/11**≈50:50). This reaction mixture was treated successively, without intermediate separation of the components, by trifluoroacetic acid to remove the acetonide protection (giving derivatives **12** and **13**) and by refluxing triethylamine to catalyze spiro cyclization of **12** to the 2'-deoxyhydantocidins **2** assuming that the intermediate hydantoins **13** undergo retro Michael ring opening to triols **12** in the cyclization conditions. High field NMR analysis of the resulting mixture **B** indicated the presence of the desired 2'-deoxyhydantocidins **2** as the major components (~75%) accompanied by the isomeric pyranosyl hydantoins **14** (**2a/2b/14a/14b**≈50:25:17:8)[13]. Treatment of the mixture by dimethoxytrityl chloride selectively derivatized the deoxyhydantocidins **2** allowing their convenient separation from the hydantoin derivatives **14**. The two epimers DMT-dH_α **15a** and DMT-dH_β **15b** were obtained pure by liquid-liquid chromatography[14].

This synthetic route constitutes a convenient and efficient preparation of the new spiro deoxyribose derivatives **15a** and **15b** that are obtained in 10% and 30% overall yields respectively (from **8**).



Scheme 2

References and Notes

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2. a) Nakajima, M.; Itoi, K.; Takamatsu, Y.; Kinoshita, T.; Okazaki, T.; Kawakubo, K.; Shindo, M. *J. Antibiot.* **1991**, *44*, 293-300. b) Haruyama, H.; Takayama, T.; Kinoshita, T.; Kondo, M.; Nakajima, M.; Haneishi, T. *J. Chem. Soc., Perkin Trans. 1*, **1991**, 1637-1640.
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4. We use the nucleoside numbering system for the hydantocidin derivatives (see figure) in reference to oligonucleotides. Similar numbering was used originally in ref 2b. According to the usual hydantoin numbering, compound **2b** refers as 4-deoxyhydantocidin.
5. dH_β has been previously described and shown to have no herbicidal activity: Mio, S.; Sano, H.; Shindou, M.; Honma, T.; Sugai, S. *Agric. Biol. Chem.* **1991**, *55*, 1105-1109.
6. The preferential binding of hydantoin derivatives with 9-ethyladenine has been described: Yu, N.-T.; Kyogoku, Y. *Biochim. Biophys. Acta,* **1973**, *331*, 21-26.
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9. The two epimers were separated after the oxidation step and only the β-N1 ketone was reduced to alcohol **7**. The reduction of the α-N1 ketone has been shown to afford the starting alcohol **6a**[7a].
10. Cohen, N.; Banner, B. L.; Lopresti, R. J.; Wong, F.; Rosenberg, M.; Liu, Y.-Y.; Thom, E.; Liebman, A. A. *J. Am. Chem. Soc.* **1983**, *105*, 3661-3672.
11. Meanwell, N. A.; Roth, H. R.; Smith, E. C. R.; Wedding, D. L.; Wright, J. J. K. *J. Org. Chem.* **1991**, *56*, 6897-6904.
12. Using TOCSY experiments, the components of the mixture **A** were fully assigned.
13. The stereochemistry of **14a** and **14b** was not determined.
14. Data for **15b**: mp 94-112°C. TLC (acetone/CH_2Cl_2 1:3): R_f 0.37. $[\alpha]_D^{25}$=-3.2 (c=1.1, MeOH). IR (KBr) 3322, 3192, 3067, 2956, 2932, 2869, 2836, 1790, 1739, 1607, 1509, 1463, 1445, 1405, 1305, 1251, 1178, 1154, 1083, 1031, 988, 827, 766 cm^{-1}. ^1H NMR (300MHz, acetone-d_6) δ ppm 2.40 and 2.45 (*ABX*, J_{AX}= 5.7Hz, J_{BX}=6.0Hz, J_{AB}=13.6Hz, H-2' and H-2"); 3.23 (*d*, *J*=4.8Hz, H-5' and H-5"); 3.78 (*s*, MeO); 4.14 (*q*, *J*=4.8Hz, H-4'); 4.33 (*m*, H-3'); 4.5 (*br.s,* OH); 6.75-6.90 (*m*, arom. H); 7.15-7.52 (*m*, arom. H); 7.6 (*br.s,* NH); 9.7 (*br.s,* NH). ^{13}C NMR (75MHz, acetone-d_6) δ ppm 41.4 (C-2'); 55.4 (MeO); 65.2 (C-5'); 72.6 (C-3'); 86.8 (CAr_3); 87.5 (C-4'); 93.1 (C-1'); 113.8, 127.4, 128.5, 128.9, 130.9 (arom. CH); 136.4, 146.0 (arom. C); 155.7, 159.5 (arom. C and C=O of C-2); 175.8 (C=O of C-4). MS (FAB+, nba) m/z: 504 $(M+H)^+$. Anal. calcd. for $C_{28}H_{28}N_2O_7 \cdot 0.5H_2O$: C 65.49, H 5.69, N 5.46; found: C 65.15, H 5.61, N 5.35.

    Data for **15a**: mp 97-112°C. TLC (acetone/CH_2Cl_2 1:3): R_f 0.25. $[\alpha]_D^{25}$=+3.8 (c=1.0, MeOH). IR (KBr) 3427, 3273, 3067, 2958, 2937, 2869, 2836, 1787, 1738, 1610, 1508, 1459, 1445, 1405, 1303, 1251, 1176, 1073, 1034, 831 cm^{-1}. ^1H NMR (300MHz, acetone-d_6) δ ppm 2.14 (*dd*, *J*=3.0, 13.2Hz, H-2'); 2.56 (*dd*, *J*=5.7, 13.2Hz, H-2'); 3.17 (*d*, *J*=5.3Hz, H-5'); 3.78 (*s*, MeO); 4.23 (*m*, H-4'); 4.47 (*m*, H-3'); 5.6 (*br.s,* H-N); 6.71-6.92 (*m*, arom. H); 7.15-7.61 (*m*, arom. H and NH); 9.6 (*br.s*, NH). ^{13}C NMR (75MHz, acetone-d_6) δ ppm 42.1 (C-2'); 55.4 (MeO); 64.8 (C-5'); 73.1 (C-3'); 86.9 (CAr_3); 87.7 (C-4'); 93.7 (C-1'); 113.8, 127.4, 128.5, 129.0, 131.0 (arom. CH); 136.9, 146.2 (arom. C); 155.6, 159.5 (arom. C and C=O of C-2 and); 176.6 (C=O of C-4). MS (FAB+, nba) m/z: 504 $(M+H)^+$. Anal. calcd. for $C_{28}H_{28}N_2O_7 \cdot 0.5H_2O$: C 65.49, H 5.69, N 5.46; found: C 65.66, H 5.82, N 5.46.