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Asymmetric Synthesis of Carbocyclic C-Nucleoside, (-)-9-Deazaaristeromycin

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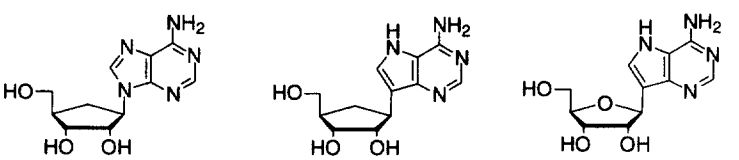
Abstract: Enantiomeric synthesis of a carbocyclic C-nucleoside, 9-deazaaristeromycin (**1**) was achieved *via* the key intermediate **6**, which was prepared stereoselectively using Bu_3SnH and subsequent DIBAL-H reduction from the intermediate **4**.

Keyword: Carbocyclic C-nucleoside

Extensive efforts in the search of chemotherapeutic agents against cancers and viral infectious diseases have led to the discovery of a variety of biologically active nucleoside analogs, including carbocyclic nucleosides[1] (i.e., carbovir) and C-nucleosides[2] (i.e., 9-deazaadenosine). Carbocyclic C-nucleosides possessing the structural features of both carbocyclic nucleosides and C-nucleosides have been paid relatively little attention although they are chemically challenging and may possess interesting biological activity. Most of the known carbocyclic C-nucleosides have been synthesized as racemic mixtures[3] although a few examples of asymmetric synthesis have been reported.[4] Therefore, it was of interest to synthesize optically active carbocyclic C-nucleosides. A hybrid nucleoside **1**, which contains the features of biologically active aristeromycin[1a-c] and 9-deazaadenosine,[2f] was selected as the first target compound (Figure 1). Herein, we wish to report the results on the synthesis of a carbocyclic C-nucleoside **1** (Scheme 1).

Figure 1.



Aristeromycin **1** 9-Deazaadenosine

The major obstacle of the synthesis was the stereoselective preparation of the intermediate **5a**. Initially, a stereospecific side chain extension was attempted on the intermediate **3** by using a nucleophile, such as sodium ethyl cyanoacetate, without success. Our alternative approach was to utilize the intermediate **4** which was expected to be stereoselectively reduced to the desired intermediate **5a** by appropriate reduction conditions despite unfavorable stereoelectronic effects of the isopropylidene group. The intermediate **4** was readily obtained by treating the intermediate **2**[5] with ethyl cyanoacetate and KO*t*-Bu in EtOH in 76% yield. Several reduction conditions from **4** to **5** were investigated as indicated in Scheme 1, among which the Bu_3SnH method provided the best result in terms of obtaining the desired β product **5a**.

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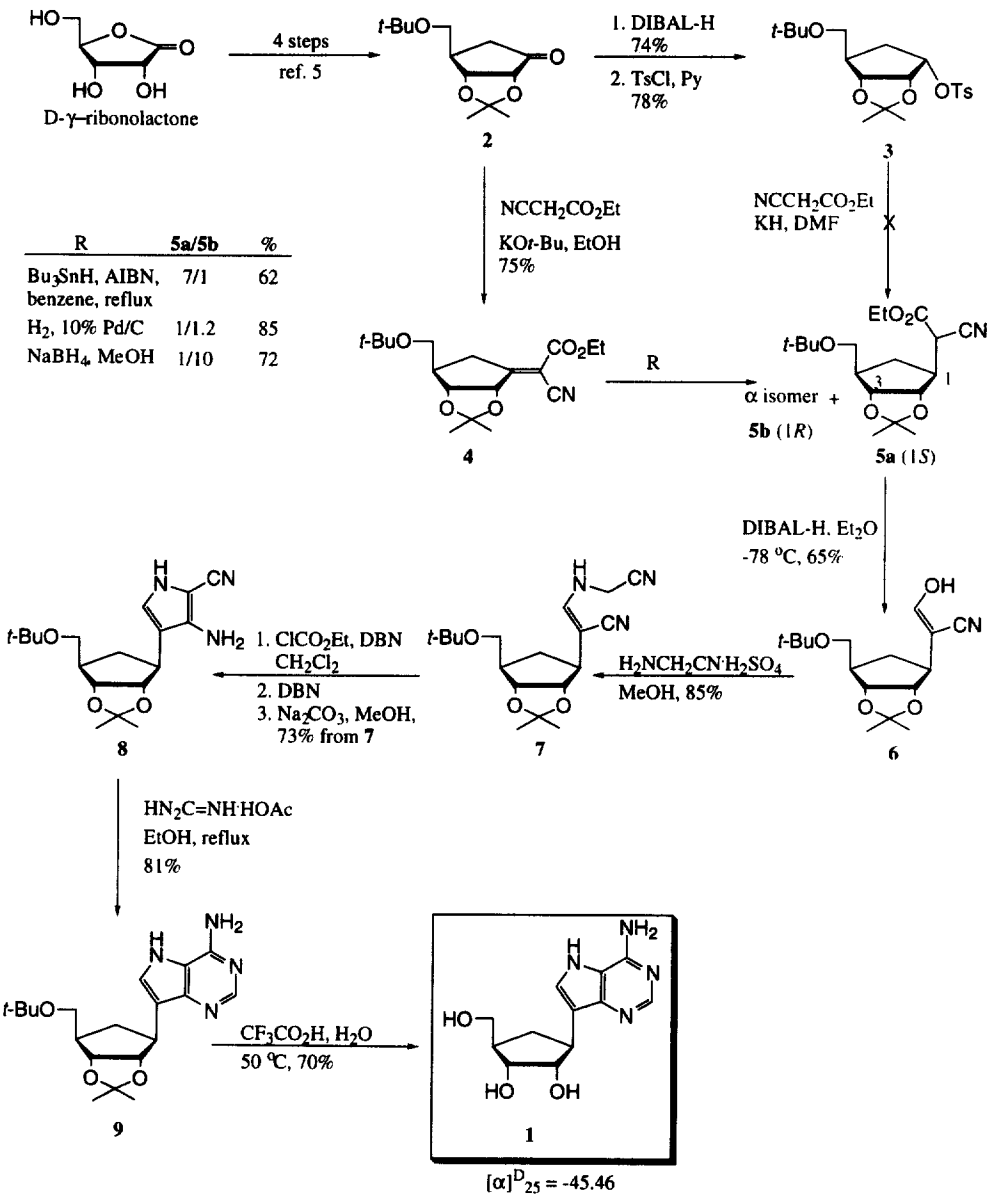
Scheme 1.

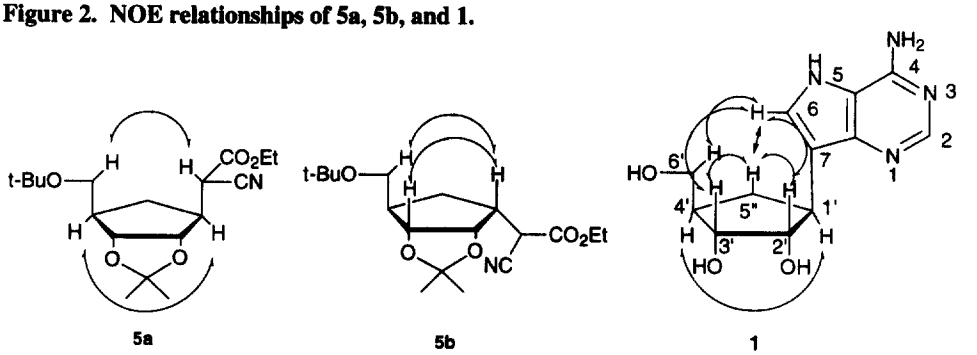


R	5a/5b	%
Bu_3SnH, AIBN, benzene, reflux	7/1	62
H_2, 10% Pd/C	1/1.2	85
$NaBH_4$, MeOH	1/10	72

Thus, treatment of **4** with Bu_3SnH-AIBN in benzene under refluxing conditions gave the desired β isomer **5a**[6] with high stereoselectivity (**5a/5b**=7/1) in moderate yield (62%). Although Bu_3SnH reduction of the α, β-unsaturated carbonyl compound is well known,[7] few studies on the stereochemistry of the reaction have been reported. The stereoselectivity of the radical reduction of **4** to **5a** may be explained by a thermodynamically stable transition state, in which the 1-substituent and the isopropylidene group are in the *trans* relationship to minimize the sterically unfavorable interactions between the two groups. The stereochemistry of each isomer was determined by NOESY experiments (Figure 2). The $NaBH_4$ and H_2-Pd/C method produced more α isomer as the major product due to the stereoelectronic effects of the isopropylidene group, which is consistent with previously reported results.[8, 9]

The desired intermediate **5a** was selectively reduced to the versatile intermediate **6** by DIBAL-H in ether at -78 °C in 65% yield. A treatment of the intermediate **6** with $HN_2CH_2CN{\cdot}H_2SO_4$ in MeOH gave an intermediate **7** which was subsequently protected with EtO_2CCl, cyclized with DBN, and deprotected with Na_2CO_3 to afford a pyrrole **8** in 73% yield. The intermediate **8** was then converted to a protected 9-deazaaristeromycin (**9**)[10] by treating with $HN_2C{=}NH{\cdot}HOAc$ in EtOH under refluxing condition in 81% yield.[2f] Deprotection of **9** with CF_3CO_2H provided free 9-deazaaristeromycin (**1**)[10] in 70% yield.[5a] The NOESY study confirmed the stereochemistry of **1** which was determined from the intermediate **5a** (Figure 2).

Figure 2. NOE relationships of 5a, 5b, and 1.



In summary, we have developed a stereoselective synthetic methodology for a novel optically active carbocyclic C-nucleoside from 1,4-γ-ribonolactone. The syntheses of related purine and pyrimidine analogs, and their biological evaluations are in progress.

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References and Notes

1. (a) Shealy, Y. F.; Clayton, J. D. *J. Am. Chem. Soc.* **1966**, *88*, 3885; (b) Kusaka, T.; Yamamoto, H.; Shibata, M.; Murai, M.; Kishi, T.; Mizuno, K. *J. Antibiot.* **1968**, *21*, 255; (c) Arita, M.; Adachi, K.; Ito, Y.; Sawai, H.; Ohno, M. *J. Am. Chem. Soc.* **1983**, *105*, 4049; (d) Vince, R.; Hua, M. *J. Med. Chem.* **1990**, *33*, 17; (e) as recent reviews: Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571. Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R. A.; Guedj, R.

Tetrahedron **1994**, *50*, 10611.

2. (a) Davis, F. F.; Allen, F. W. *J. Biol. Chem* **1957**, *227*, 907; (b) Hori, M.; Ito, E.; Takita, T.; Koyama, G.; Tacheuchi, T.; Umezaya, H. *J. Antibiot.* **1964**, *17A*, 96; (c) Chu, C. K.; Wempen, I.; Watanabe, K. A.; Fox, J. J. *J. Org. Chem.* **1976**, *41*, 2793; (d) Liang, C.; Ma, T.; Cooperwood, J. S.; Du, J.; Chu, C. K. *Carbohydr. Res.* **1997**, *303*, 33; (e) Lee, C. S.; Du, J.; Chu, C. K. *Nucleosides & Nucleotides* **1996**, *15*, 1223; (f). Lim, M.; Klein, R. S. *Tetrahedron Lett.* **1981**, *22*, 25; (g) as recent reviews: Watanabe, K. A. In *Chemistry of Nucleosides and Nucleotides* **1994**, vol 3; Townsend, L. B., Ed., Plenum, New York, Chapter 5. Shaban, M. A. E.; Nasr, A. Z. *Adv. Heterocycl. Chem.* **1997**, *68*, 223.
3. (a) Just, G.; Kim, S. *Tetrahedron Lett.* **1976**, 1046; (b) Saksena, A. K.; McPhail, A. T.; Onan, K. D. *Tetrahedron Lett.* **1981**, *22*, 2067; (c) Katagiri, N.; Tomura, M.; Haneda, T.; Kaneko, C. *J. Chem. Soc. Chem. Commun.* **1987**, 1422; (d) Hildbrand, S.; Leuman, C.; Scheffold, R. *Helv. Chim. Acta.* **1996**, *79*, 702.
4. (a) Takahashi, T.; Kotsubo, H.; Koizumi, T. *Tetrahedron: Asymmetry* **1991**, *2*, 1035; (b) Dishington, A. P.; Humber, D. C.; Stoodley, R. J. *J. Chem. Soc. Perkin Trans.* 1 **1993**, 57.
5. (a) Wang, P.; Agrofoglio, L. A.; Newton, M. G.; Chu, C. K. *Tetrahedron Lett.* **1997**, *38*, 4207; (b) Wolfe, M. S.; Borcherding, D. R.; Borchardt, R. T. *Tetrahedron Lett.* **1989**, *30*, 1453; (c) Ali, S. M.; Ramesh, K.; Borchardt, R. T. *Tetrahedron Lett.* **1990**, *31*, 1509.
6. **5a**: ^{1}H NMR ($CDCl_3$) δ 4.52-4.41 (m, 2H, H-2, 3), 4.28 (m, 2H, $OC\underline{H}_2CH_3$), 3.86 (d, 0.55H, J = 6.94 Hz, C<u>H</u>CN), 3.77 (m, 0.45H, J = 6.80, C<u>H</u>CN), 3.39 (m, 2H, H-6), 2.60 (m, 1H, H-1), 2.30 (m, 1H, H-4), 2.23 (m, 1H, H-5), 1.53 (m, 1H, H-5'), 1.50-1.53, 1.45-1.15 (m, 18H, $OCH_2C\underline{H}_3$, $(C\underline{H}_3)_2C$, $C\underline{H}_3)_3C$): FABMS *m/z* 340 (M+H)+; Anal. Calcd. For $C_{18}H_{29}NO_5$: C, 63.69; H, 8.61; N, 4.13. Found: C, 63.47; H, 8.52; N, 3.97. **5b**: 1H NMR ($CDCl_3$) δ 4.70-4.48 (m, 2H, H-2, 3), 4.28 (m, 2H, $OC\underline{H}_2CH_3$), 3.72 (d, 0.6H, J = 9.66 Hz, C<u>H</u>CN), 3.53 (m, 0.4H, J = 10.78 Hz, C<u>H</u>CN), 3.24 (m, 2H, H-6), 2.75 (m, 1H, H-1), 2.26 (m, 2H, H-4, 5), 1.98-1.79 (m, 1H, H-5'), 1.45-1.15 (m, 18H, $OCH_2C\underline{H}_3$, $C\underline{H}_3)_2C$, $C\underline{H}_3)_3C$: FABMS *m/z* 340 (M+H)+; Anal. Calcd. For $C_{18}H_{29}NO_5$: C, 63.69; H, 8.61; N, 4.13. Found: C, 63.75; H, 8.52; N, 3.95.
7. Pereyre, M.; Quintard, J.-P.; Rahm, A., Ed. In *Tin in Organic Synthesis* **1987**, Butterworths, London, Chapter 7 and references therein.
8. Xie, M.; Berges, D. A.; Robins, M. J. *J. Org. Chem.* **1996**, *61*, 5178.
9. Huber, R.; Vasella, A. *Tetrahedron* **1990**, *46*, 33.
10. **9**: mp 180°; $[\alpha]^D_{25}$ -43.40 (0.23, MeOH); UV (H_2O) λ_{max} (nm) 234 (ε 17 721), 274 (ε 7 733) (pH 7), 234 (ε 16 623), 273 (ε 6 180) (pH 11), 239 (ε 10 760), 275 (ε 7 953) (pH 2); ^{1}H NMR ($CDCl_3$) δ 8.78 (s, 1H, H-2), 7.60 (bs, 2H, H_2N-4), 7.18 (s, 1H, H-6), 4.66 (t, 1H, J = 6.80, H-2'), 4.42 (m, 1H, H-3'), 3.37 (m, 1H, H-6'), 3.24-3.31 (m, 2H, H-1', H-6"), 2.30 (m, 2H, H-4', H-5'), 1.73 (m, 1H, H-5"); FABMS *m/z* 361 (M+H)+; Anal. Calcd. For $C_{19}H_{28}N_4O_3$ 0.8 MeOH: C, 61.40; H, 8.15; N, 14.51. Found: C, 61.29; H, 7.82; N, 14.64.

    1: mp 240° (decomp.); $[\alpha]^D_{25}$ -45.46 (0.35, MeOH); UV(H_2O) λ_{max}(nm) 234 (ε 16 151), 274 (ε 6 759) (pH 7), 234 (ε 15 675), 273 (ε 5 741) (pH 11), 240 (ε 12 098), 275 (ε 10 285) (pH 2); ^{1}H NMR (DMSO-d_6) δ 10.74 (s, 1H, HN-5, D_2O exchangeable), 8.07 (s, 1H, H-2), 7.30(d, 1H, J = 2.0, H-6), 6.78 (s, 2H, H_2N-4, D_2O exchangeable), 5.78 (bs, 1H, HO, D_2O exchangeable), 4.61 (bs, 1H, HO, D_2O exchangeable), 4.16 (ds, 1H, HO, D_2O exchangeable), 3.87 (m, 1H, H-2'), 3.79 (m, 1H, H-3'), 3.45 (dm, 2H, H-6'), 3.17 (m, 1H, H-1'), 2.18 (m, 1H, H-5'), 2.04 (m, 1H, H-4'), 1.45 (m, 1H, H-5"); FABMS *m/z* 265 (M+H)+; Anal. Calcd. For $C_{12}H_{16}N_4O_3$ 0.3 MeOH: C, 53.94; H, 6.33; N, 20.46. Found: C, 53.67; H, 6.12; N, 20.11.