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New synthesis of 3′-deoxypurine nucleosides using samarium(III) iodide complex

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Abstract—Regio- and stereoselective iodinative cleavage of 2′,3′-anhydropurine nucleosides was achieved with samarium diiodide and ethyl bromoacetate to produce the corresponding 3′-iodopurine nucleosides, which were then converted to 3′-deoxypurine nucleosides including the natural product cordycepin.

The anti-proliferation activity of nucleosides containing 3′-deoxyribose moiety has been noted in several bacterial and carcinoma cell lines.[1] The wide spectrum of inhibitory activity is likely due to the lack of 3′-hydroxyl group on the ribose sugar. Incorporation of the 3′-deoxyribonucleotides of natural bases by RNA polymerases terminates RNA synthesis.[2] Also, 2′,5′-linked 3′-deoxyoligonucleotides have been utilized as probes for structure and mechanism elucidation.[3] Recent studies have revealed that they selectively bind to complementary RNA (not DNA) and are stable against common cellular nucleases that hydrolyze natural DNA, making them potential candidates for both diagnostic and therapeutic antisense applications.[4]

As a result, the synthesis of 3′-deoxynucleosides has been investigated in many laboratories. Procedures have usually involved either (i) superhydride- or LAH-reduction for ring opening of the anhydronucleoside,[5] (ii) Bu_3SnH/AIBN-mediated deoxygenation for ring opening of the cyclic thiocarbonate[6] or 3′-*O*-thiocarbonate, or (iii) a modified Moffatt reaction followed by Bu_3SnH/AIBN reductive elimination.[7] However, reductive cleavage of the cyclic thiocarbonate proceeds in low yield to afford a mixture of 2′- and 3′-deoxynucleosides, which are difficult to separate. Still other methods involved reductive elimination of the halogenated carbohydrate ring[8] but also resulted in a mixture of 2′- and 3′-deoxy isomers.

Recently we have reported a new method for regio- and stereoselective synthesis of α- and β-hydroxy iodohydrins from α- and β-hydroxy epoxides, respectively with SmI_2 in the presence of ethyl bromoacetate.[9] However, the reaction with δ-hydroxy epoxide produced two regioisomers, and the lack of regioselectivity was probably due to that the hydroxyl group is located too far away from the epoxide ring to form an intermediate important for the regioselectivity.[9]

It led us to expand the utility and scope of the method towards the regio- and stereoselective synthesis of 3′-iodopurine nucleosides. In this paper, we describe a facile method for the synthesis of 3′-deoxypurine nucleosides through the regio- and stereoselective iodination at the C-3′ position of 2′,3′-anhydropurine nucleosides.

The starting material **1a** was readily prepared from guanosine.[5] A solution of **1a** (370 mg, 0.85 mmol) and ethyl bromoacetate (142 mg, 0.85 mmol) in dry THF (3 ml) was reacted with SmI_2 (1.7 mmol) at −78°C for 1 h and further stirred at room temperature for another 1 h to yield **2a** (387 mg, 81%). Only one diastereoisomer of

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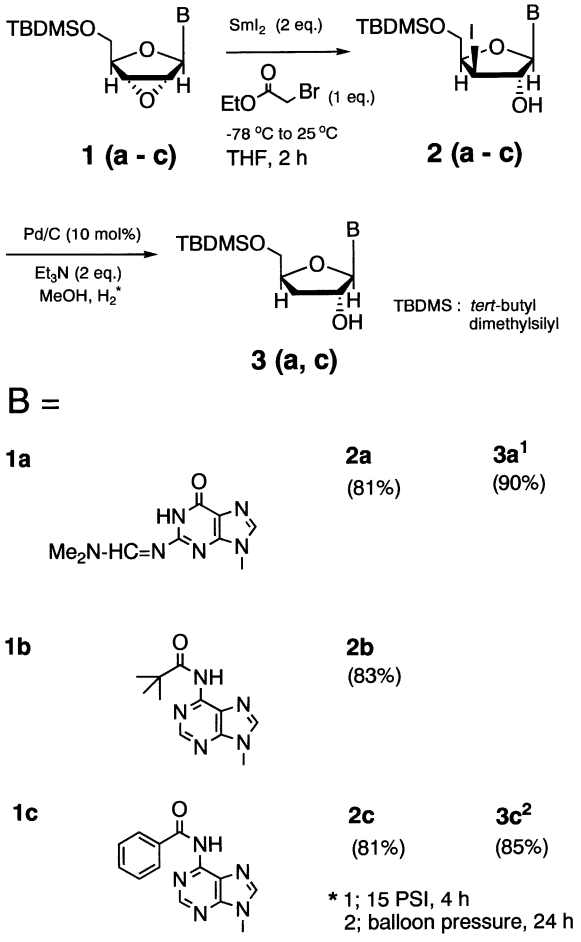
2′-hyroxyl-3′-iodo **2a**† was producted. The coupling constant of H_1' signal ($J=5.4$ Hz) at δ 5.69 ppm showed the *trans*-diaxial arrangement of the substituents at C-1′ and C-2′,[10] and no signals other than H_1', H_2', and H_3' signals were observed in ^{1}H NMR spectra between δ 5.69 and 4.46 ppm. The same reaction of 2′,3′-anhydroadenosine (**1b**)[5] from adenosine gave **2b**† in 83% yield and proceeded with complete regio- and stereoselectivity (Scheme 1).



Scheme 1.

† All new compounds showed satisfactory ^{1}H NMR, HR-FAB-MS, mp and optical rotation data for **2a**–**c**. **2a**: (400 MHz, DMSO-d_6) δ 11.36 (s, 1H), 8.57 (s, 1H), 7.96 (s, 1H), 6.27 (d, $J=5.8$, 1H, OH), 5.69 (d, $J=5.4$, H_1'), 4.90 (m, H_2'), 4.46 (m, H_3'), 4.03 (m, H_4'), 3.90 (m, H_5'), 3.15 (s, 3H), 3.03 (s, 3H), 0.89 (s, 9H), 0.00 (s, 6H); HRMS calcd for $C_{19}H_{31}IN_6O_4Si$ (M+1) 563.1320, found 563.1300; mp 175–178°C; $[\alpha]_D^{21.5}$ +74.5 (*c* 0.5, MeOH). **2b**: (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.58 (br, 1H), 8.27 (s, 1H), 5.90 (d, $J=4.2$ Hz, H_1'), 4.98 (m, H_2'), 4.49 (m, H_3'), 4.30 (m, H_4'), 4.08 (dd, $J=3.3$, 11.3, H_5'), 3.95 (dd, $J=3.5$, 11.3, H_5'), 1.38 (s, 9H), 0.72 (s, 9H), 0.00 (s, 6H); HRMS calcd for $C_{21}H_{34}IN_5O_4Si$ (M+1) 576.1425, found 576.1501; mp 65–68°C; $[\alpha]_D^{27.6}$ +10.2 (*c* 0.9, $CHCl_3$). **2c**: δ 9.26 (br, 1H), 8.71 (s, 1H), 8.31 (s, 1H), 8.01 (m, 2H), 7.60–7.50 (m, 3H), 5.92 (d, $J=4.3$, H_1'), 5.67 (br, 1H, OH), 5.01 (m, H_2'), 4.50 (m, H_3'), 4.30 (m, H_4'), 4.10 (dd, $J=3.0$, 11.2, H_5'), 3.96 (dd, $J=3.4$, 11.3, H_5'), 0.71 (s, 9H), 0.00 (s, 6H); HRMS calcd for $C_{23}H_{30}IN_5O_4Si$ (M+1) 596.1112, found 596.1187; mp 95–98°C (dec.); $[\alpha]_D^{24}$ −15.1 (*c* 2.1, $CHCl_3$).

The assignment of H_2'-up, H_3'-down and H_4'-down configuration was established on the basis of NOE difference spectroscopy ($CDCl_3$, 25°C, 400 MHz)[11] (Fig. 1). Saturation of H_8 of adenosine ring system results in enhancement of NOE's of H_2' signal (2.55%), while H_3' and H_4' signals do not show any significant intensity enhancement (<0.5%). The chemical shifts of H_2' (δ 5.75) and H_3' (δ 4.43) of 3′-bromo adenosine nucleoside[12] show also the similar correlations with **1b** (**1b**: $H_2'=\delta$ 4.97, $H_3'=\delta$ 4.49).

The regio- and stereoselective iodinative cleavage can be rationalized by formation of an intermediate **I** (Fig. 2). Coordination between epoxide ether and silyloxy ether at β-position with samarium iodoenolate (SmI_2L)[9] may form **I** by a strong oxophilicity of Sm. The additive ethyl bromoacetate is essential for the regio- and stereoselective iodinative cleavage of epoxides. When other additives such as I_2 ($2\ SmI_2+I_2\rightarrow 2\ SmI_3$) or *i*-PrOH ($SmI_2+i\text{-PrOH}\rightarrow SmI(i\text{-PrO})_2$) were used in the reaction of **1b** to **2b**, neither chemical yield nor regioselectivity was high. After 6 h reaction at 25°C the former reaction gave only the 2′-hydroxyl-3′-iodo isomer of **2b** but in only ca. 10% yield, and the latter resulted in ca. 40% of yield but in a mixture of the 2′- and 3′-iodo regioisomers in the ratio of 1:5.

Next, deiodination of **2a** could be achieved by treatment with Bu_3SnH (3 equiv.) and AIBN (cat.) in refluxing toluene for 5 h,[6,7] which yielded the protected

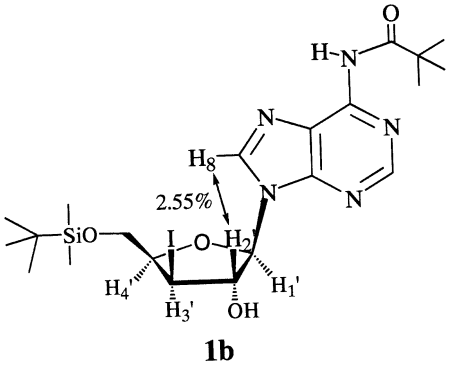


Figure 1.

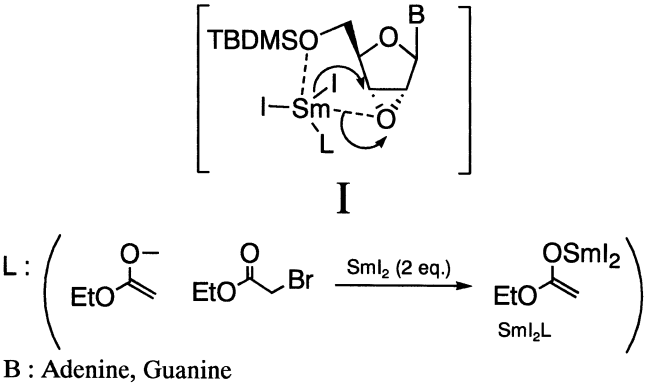
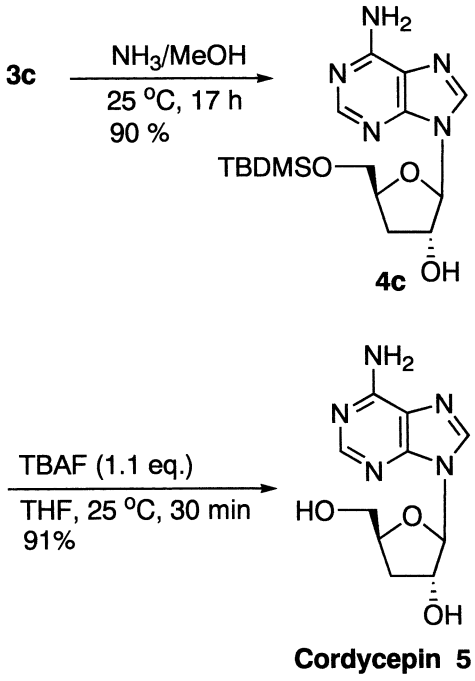


Figure 2.



Scheme 2.

3′-deoxyguanosine **3a** in 89% yield. In order to avoid the use of toxic Bu_3SnH, an alternative method was developed for the deiodination as shown in Scheme 1. The **2a** was readily deiodinated with catalytic Pd/C (10 mol%) catalyst and Et_3N (2 equiv.) in methanol under 15 psi hydrogen pressure for 4 h to yield **3a** (90%). No anomerization occurred at C-1′ in the deiodination step. When KOH (2 equiv.) was used instead of Et_3N, anomerization (5%) occurred with 92% yield (H_1': δ 5.82 and 5.77 ppm for the β- and α-anomers of **3a**, respectively in ^1H NMR spectroscopy[10]).

Thus, our new SmI_2 mediated regio- and stereoselective iodination of epoxide **1** is successfully applied to the synthesis of 3′-deoxy adenosine **5**, which was initially isolated from the fungus *Cordyceps militaris* and named cordycepin.[1] When **3c** was treated with NH_3/MeOH, debenzoylated product **4c** was produced in good yield (90%). Finally, deprotection of 5′-silyl group was achieved smoothly and the desired compound **5** was obtained, which showed all satisfactory ^1H NMR, 2D NMR (^1H–^1H COSY), ^{13}C NMR, FAB-MS and $[\alpha]_D$ value; $[\alpha]_D^{24.6}$ –41.1 (*c* 0.55, H_2O), lit.[5] $[\alpha]_D^{20}$ –44.0 (*c* 0.5, H_2O) (Scheme 2).

In conclusion, a novel route to the synthesis of 3′-deoxypurine nucleosides is developed by regio- and stereoselective iodinative cleavage of 2′,3′-anhydropurine nucleosides with SmI_2 in the presence of ethyl bromoacetate and the subsequent deiodination under mild conditions without hazardous chemicals. This method could be generally used for the synthesis of various analogues of 3′-deoxypurine nucleosides.

Acknowledgements

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References

1. (a) Cunnigham, K. G.; Hutchinson, S. A.; Manson, W.; Spring, F. S. *J. Chem. Soc.* **1951**, 2299; (b) Jagger, D. V.; Kredich, N. M.; Guarino, A. J. *Cancer Res.* **1961**, *21*, 2156; (c) Kaczka, E. A.; Dulaney, E. L.; Gitterman, C. O.; Woodruff, H. R.; Folkers, K. *Biochem. Biophys. Res. Commun.* **1964**, *14*, 452.
2. Axelrod, V.; Kramer, F. *Biochemistry* **1985**, *24*, 5716.
3. (a) Hashimoto, H.; Switzer, C. J. *J. Am. Chem. Soc.* **1992**, *114*, 6255; (b) Jung, K. E.; Switzer, C. J. *J. Am. Chem. Soc.* **1994**, *116*, 6059.
4. Sheppard, T. L.; Breslow, R. C. *J. Am. Chem. Soc.* **1996**, *118*, 9810.
5. (a) Hansske, F.; Robins, M. J. *Tetrahedron Lett.* **1985**, *26*, 4295; (b) Bazin, H.; Chattopadhyaya, J. *Synthesis* **1985**, 1108; (c) Norbeck, D. W.; Kramer, J. B. *J. Am. Chem. Soc.* **1988**, *110*, 7217; (d) Rizzo, C. J.; Dougherty, J. P.; Breslow, R. *Tetrahedron Lett.* **1992**, *33*, 4129; (e) He, G.-X.; Bischofberger, N. *Tetrahedron Lett.* **1995**, *36*, 6991.
6. (a) Barton, D. H. R.; Subramanian, R. *J. Chem. Soc., Chem. Commun.* **1976**, 867; (b) Nair, V.; Buenger, G. S. *J. Am. Chem. Soc.* **1989**, *111*, 8502.
7. (a) Russell, A. F.; Greenberg, S.; Moffatt, J. G. *J. Am. Chem. Soc.* **1973**, *95*, 4025; (b) Jain, T. C.; Jenkins, I. D.; Russel, A. F.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1974**, *39*, 30; (c) Engels, J. *Tetrahedron Lett.* **1980**, *21*, 4339; (d) Dorland, E.; Serafinowski, P. *Synthesis* **1992**, 477.
8. Mengel, R.; Wiedner, H. *Chem. Ber.* **1976**, *109*, 1395.
9. (a) Kwon, D. W.; Cho, M. S.; Kim, Y. H. *Synlett* **2003**, 59; (b) Kwon, D. W.; Park, H. S.; Kim, Y. H. *Bull. Korean Chem. Soc.* **2002**, *23*, 1185.
10. (a) Okabe, M.; Sun, R.-C.; Tam, S. Y.-K.; Todaro, L. J.; Coffen, D. L. *J. Org. Chem.* **1988**, *53*, 4780; (b) Chu, C. K.; Ullas, G. V.; Jeong, L. S.; Ahn, S. K.; Doboszewski, B.; Lin, Z. X.; Beach, J. W.; Schinazi, R. F. *J. Med. Chem.* **1990**, *33*, 1553.
11. Hong, J. H.; Shim, M. J.; Ro, B. O.; Ko, O. H. *J. Org. Chem.* **2002**, *67*, 6837.
12. Cui, Z.; Zhang, L. *Tetrahedron Lett.* **2001**, *42*, 561.