A Novel Approach for the Synthesis of Purine Acyclonucleosides Using 9-D-Ribitylpurines as a Chiral Pool

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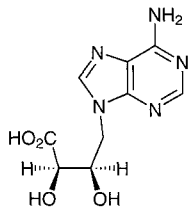
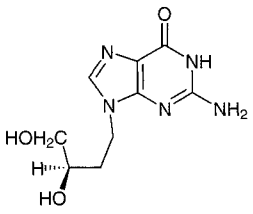
Abstract: Facile syntheses of L-eritadenine (**8a**), (2*S*,3*R*)-9-(2,3,4-trihydroxybutyl)purines (**4a** and **4b**), and (2*S*,3*S*)-9-(2,3,4-trihydroxybutyl)adenine (**6a**) were achieved by using 9-D-(2,3-*O*-isopropylideneribityl)purines (**1a** and **1b**) as a chiral pool.

Much attention has been devoted to the synthesis and biological properties of acyclonucleosides since acyclovir and ganciclovir were developed as antiviral agents for the treatment of certain herpes virus infections.[1] Several purine acyclonucleosides having chiral centers in the N_9-hydroxyalkyl chain such as D-eritadenine[2,3] and buciclovir[4] have been shown to possess antiviral activity. Most synthetic methods for the preparation of such acyclonucleosides have involved the condensation of purine bases with chiral side-chain moieties.[5] These methods, however, incur some difficulties in stereoselective synthesis of the side-chain moiety and/or regioselective condensation of the base moiety with the side-chain moiety. On the other hand, no synthetic methods starting from commercially available nucleosides such as guanosine and adenosine have been reported except for an example of the oxidative cleavage of the 2', 3'-*cis*- diol portion of ribonucleosides with $NaIO_4$.[6]



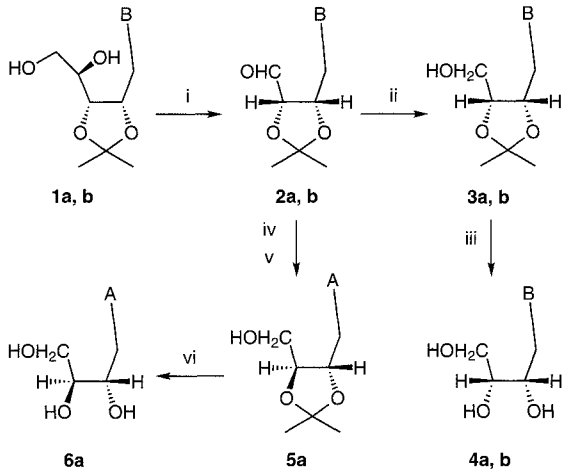
D-eritadenine



buciclovir

Previously we have reported a facile, synthetic method for the preparation of acyclonucleosides, 9-D-ribitylpurines, by the reductive cleavage of the ribofuranosyl ring of purine nucleosides with diisobutylaluminum hydride (DIBAL-H).[7] In this paper, we wish to describe the asymmetric construction of L-eritadenine (**8a**), (2*S*,3*R*)-9-(2,3,4-trihydroxybutyl)purines (**4a** and **4b**), and (2*S*,3*S*)-9-(2,3,4-trihydroxybutyl)adenine (**6a**) as potential antiviral agents by taking advantage of the two chiral carbons in the 9-ribitylpurines (**1a** and **1b**).

(2*S*,3*S*)-4-(Adenin-9-yl)-2,3-dihydroxy-2,3-*O*-isopropylidenebutanal (**2a**)[8] was prepared quantitatively from 9-D-(2,3-*O*-isopropylideneribityl)adenine (**1a**)[7] by $NaIO_4$ oxidation as a chiral key intermediate for the preparation of acycloadenosines. Reduction of **2a** with $NaBH_4$ afforded the primary alcohol (**3a**) in 78% yield, which was converted into the corresponding (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetate (MTPA ester).[9] ^{19}F NMR analyses of the ester showed no formation of any detectable epimeric isomer. This fact evidently indicates that the formation of **2a** and **3a** proceeds with complete retention of steric configuration. The alcohol **3a** smoothly underwent removal of the isopropylidene protection with 80% AcOH to afford (2*S*,3*R*)-9-(2,3,4-trihydroxybutyl)adenine(**4a**),[10,11] quantitatively. On the other hand, the inversion at the 2-position of the aldehyde **2a** was achieved under strong basic conditions with NaOMe to give (2*R*)-epimer of **2a** and subsequent reduction with $NaBH_4$ gave the corresponding alcohol **5a** in 66% yield.[12] Deprotection of **5a** afforded (2*S*,3*S*)-9-(2,3,4-trihydroxybutyl)adenine (**6a**)[11] in 60% yield (Scheme 1). It is noteworthy that the stereochemistry at the 3'-position of acyclonucleosides (**4a** and **6a**) could be easily controlled by the use of the aldehyde **2a** as a chiral pool.

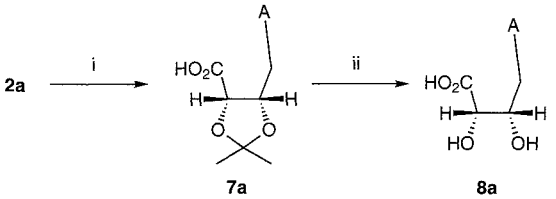


a series : B = adenin-9-yl (= **A**)

b series : B = guanin-9-yl

Scheme 1 Reagents and conditions: (i) *for* **2a**, $NaIO_4$ (1.5 equiv.), H_2O, 0 °C, 1 h; *for* **2b**, $NaIO_4$ (1.5 equiv.), pH 4, 0 °C, 1.5 h. (ii) *for* **3a**, $NaBH_4$ (5 equiv.), H_2O, pH 8, 0 °C, 1.5 h; *for* **3b**, $NaBH_3CN$ (15 equiv.), pH 4, r. t., 27 h. (iii) *for* **4a**, 80% AcOH, 60 °C, 5 h; *for* **4b**, 80% AcOH 70 °C, 4.5 h. (iv) NaOMe (1.5 equiv.), MeOH, r. t., 11h. (v) $NaBH_4$ (5 equiv.), H_2O, r. t., 1.5 h. (vi) 80% AcOH, 70 °C, 19 h.

The aldehyde **2a** was utilized as a novel approach for the synthesis of L-eritadenine (**8a**), which is an enantiomer of naturally occurring D-eritadenine.[2] Our first attempt for the preparation of **8a**, the oxidation of **2a** with $KMnO_4$ in alkaline aqueous solution, resulted in the formation of an epimeric mixture of the corresponding carboxylic acid **7a** (*erythro*) and its (2*R*)-isomer (*threo*) in 63% yield (*erythro*/*threo* = 32 : 68).[13] On the other hand, the Pt/C catalyzed oxidation of **2a** under O_2 atmosphere afforded **7a** in 46% yield without any detectable epimerization. Deprotection of **7a** with 10% AcOH led to the quantitative formation of **8a**, whose optical activity, $[\alpha]_D^{26}$(*c* 0.07, 1M HCl) = -14.3, was identical with that reported by Holy and coworkers (Scheme 2).[3]



Scheme 2 Reagents and conditions: (i) Pt/C, O_2, H_2O, 45 °C, 49 h. (ii) 10% AcOH, 65 °C, 4 h.

This methodology was applied to the synthesis of acycloguanosine. Treatment of 9-D-(2,3-*O*-isopropylideneribityl)guanine (**1b**), obtained by the DIBAL-H reduction of 2',3'-*O*-isopropylideneguanosine, with $NaIO_4$ in a sodium acetate buffer (pH 4) gave the aldehyde (**2b**) as a hydrate in 87% yield. Reduction of **2b** with $NaBH_3CN$ in the acidic medium led to the formation of the alcohol **3b** in a good yield without epimerization.[14] Deprotection of **3b** by 80% AcOH afforded (2*S*,3*R*)-9-(2,3,4-trihydroxybutyl)guanine (**4b**) in 93% yield (Scheme 1).

This methodology using 2',3'-*O*-isopropylidene protected 9-D-ribitylpurines as chiral starting materials was shown to be widely applicable to the synthesis of biologically interesting acyclonucleosides. Especially, the aldehydes (**2a** and **2b**) are useful intermediates for the preparation of acyclonucleosides having a chiral glycol moiety at the 2', 3'-positions in the side-chain.

References and Notes

(1) (a) Shaeffer, H. J.; Beauchamp, L.; De Miranda, P.; Elion, G. B.; Bauer, D. J.; Collins, P. *Nature* (London), **1978**, *272*, 583. (b) Remy, R. J.; Secrist III, J. A. *Nucleosides & Nucleotides*, **1985**, *4*, 411.

(2) (a) Rokujo, T.; Kikuchi, H.; Tensho, A.; Tsukitani, Y.; Takenawa, T.; Yoshida, K.; Kamiya, T. *Life Sciences*, **1970**, *9* (II), 379. (b) Chibata, I.; Okamura, K.; Takeyama, S.; Kotera, K. *Experientia*, **1969**, *25*, 1237. (c) Kamiya, T.; Saito, Y.; Hashimoto, M.; Seki, H. *Tetrahedron Lett.*, **1969**, 4729.

(3) Holy, A.; Votruba, I.; De Clercq, E. *Collect. Czech. Chem. Commun.*, **1982**, *47*, 1392.

(4) Larsson, A.; Öberg, B.; Alenius, S.; Hagberg, C.-E.; Johansson, N.-G.; Lindborg, B.; Stening, G. *Antimicrob. Ag. Chemoth.*, **1983**, *23*, 664.

(5) Chu, C. K.; Cutler, S. J. *J. Heterocycl. Chem.*, **1986**, *23*, 289 and references cited therein.

(6) (a) Lerner, L. M. *Carbohydr. Res.*, **1984**, *127*, 141. (b) Bessodes, M.; Antonakis, K. *Tetrahedron Lett.*, **1985**, *26*, 1305.

(7) Kitade, Y.; Hirota, K.; Maki, Y. *Tetrahedron Lett.*, **1993**, *34*, 4835.

(8) The ^1H NMR (DMSO-d_6) spectrum of **2a** exhibited complicated signals at room temperature. Upon raising the probe temperature to 100 °C these signals came to merge into one set, suggesting the existence of a polymer and/or a hydrate of **2a.** Schmid *et al.* have reported D-glyceraldehyde acetonide tended to polymerize and easily form a hydrate in the presence of H_2O: (a) Schmid, C. R.; Bryant, J. D.; Dowlatzedah, M.; Phillips, J. L.; Prather, D. E.; Schantz, R. D.; Sear, N. L.; Vianco, C. S. *J. Org. Chem.*, **1991**, *56*, 4056. (b) Schmid, C. R.; Bryant, J. D. *Org. Synth.*, **1993**, *72*, 6.

(9) (a) Dale, J. A.; Dull, D. L.; Mosher, H.S. *J. Org. Chem.*, **1969**, *34*, 2543. (b) Ward, D. E.; Rhee, C. K. *Tetrahedron Lett.*, **1991**, *32*, 7165.

(10) Ikehara, M.; Ohtsuka, E. *Chem. Pharm. Bull.*, **1963**, *11*, 1095.

(11) Holy, A. *Collect. Czech. Chem. Commun.*, **1982**, *47*, 173.

(12) In a sequence of epimerization and reduction operations, **5a** and **3a** formed in the ratio of 94 : 6. Both epimers were isolated by silica gel column chromatography.

(13) The epimerization of D-eritadenine methyl ester in basic conditions has been described in the literature: Hashimoto, M.; Saito, Y.; Seki, H.; Kamiya, T. *Tetrahedron Lett.*, **1970**, *16*, 1359.

(14) When both oxidation and reduction were carried out in H_2O as a solvent, a diastereomeric mixture of **3b** (*erythro*) and its (3'*S*)-isomer (*threo*) was obtained in the ratio of 83 : 17.