Pergamon

Tetrahedron Letters, Vol. 38, No. 27, pp. 4795-4798, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01035-6

Synthesis of 9-[2',3'-Dideoxy-2',3'-bis-*C*-hydroxymethyl-α-L-threofuranosyl] Adenine and its 4'-Thio Analog as Potential Antiviral Agents

Yoshiko Kikuchi, Hiroko Kurata, Shigeru Nishiyama, and Shosuke Yamamura

Department of Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Yokohama 223, Japan

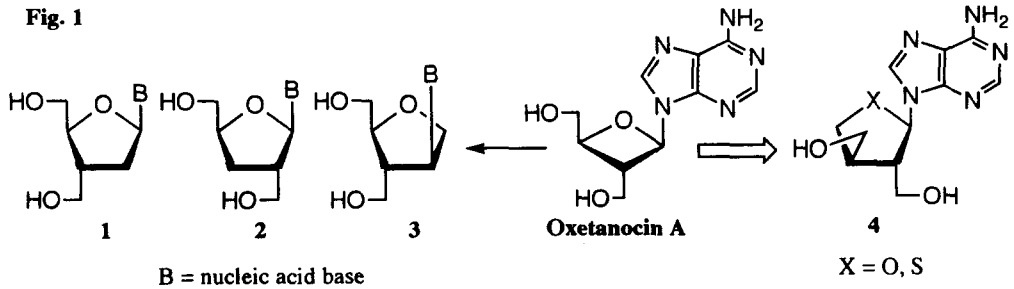
Kuniki Kato*

Research Laboratories, Pharmaceuticals Group, Nippon Kayaku Co. Ltd., Shimo, Kita-ku, Tokyo 115, Japan

Abstract: The enantiomerically pure synthesis of 9-[2',3'-dideoxy-2',3'-bis-*C*-hydroxymethyl-α-L-threofuranosyl]adenine and its 4'-thio analog was achieved *via* coupling of silylated 6-chloropurine with 1-*O*-acetylfuranose derivative **17** and its 4'-thio analog **24**, respectively, prepared from (+)-diethyl L-tartrate.© 1997 Elsevier Science Ltd.

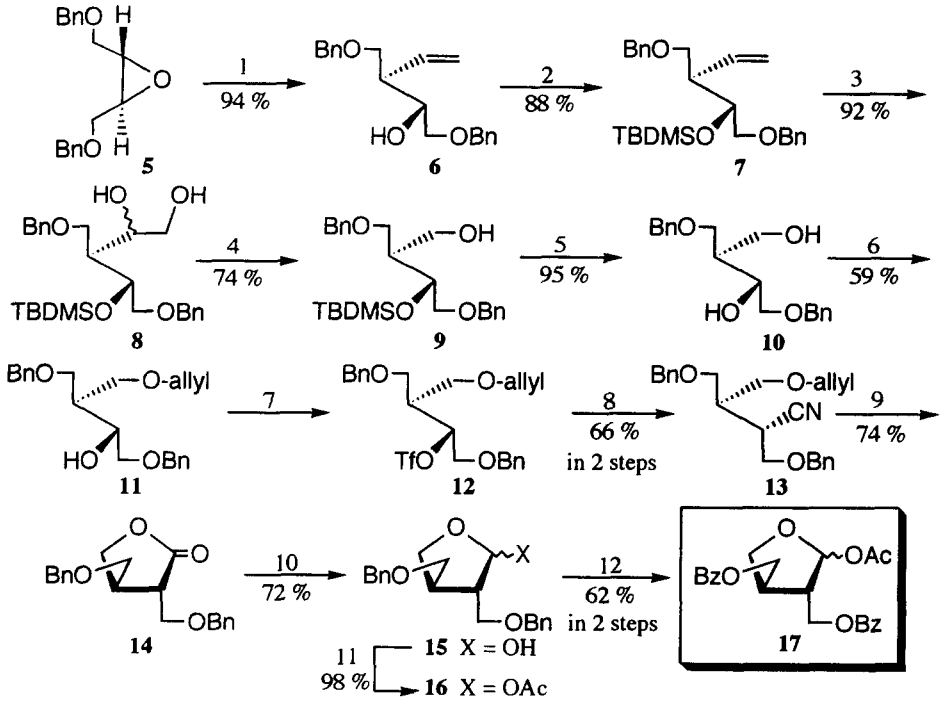
Various nucleoside compounds have been reported as potent and selective inhibitors of human immunodeficiency virus (HIV) targeted at the virus-encoded reverse transcriptase. In the search for effective, selective, and nontoxic antiviral agents, a variety of strategies have been devised to design nucleoside analogs. These strategies have involved several formal modifications of the naturally occurring nucleosides, especially, alternation of the carbohydrate moiety.[1] Since the naturally occurring purine nucleoside analog oxetanocin A and its derivatives have been found to be effective as anti-HIV-1 and anti-herpes virus agents,[2] the syntheses of different types of hydroxymethyl-branched nucleosides (the so-called ring-enlarged oxetanocin A analogs) have been reported (Fig.1: e.g. type **1**[3], type **2**[4], and type **3**[5]). Furthermore, 4'-thionucleosides have received some attention in recent years mostly because of the reported anti-HIV activity of the 2'-deoxy analogs.[6] To further evaluate the structure-activity relationship of hydroxymethyl-substituted nucleosides, we have accomplished the first synthesis of 9-[2',3'-dideoxy-2',3'-bis-*C*-hydroxymethyl-α-L-threofuranosyl]adenine and its 4'-thio analog **4**.

Fig. 1



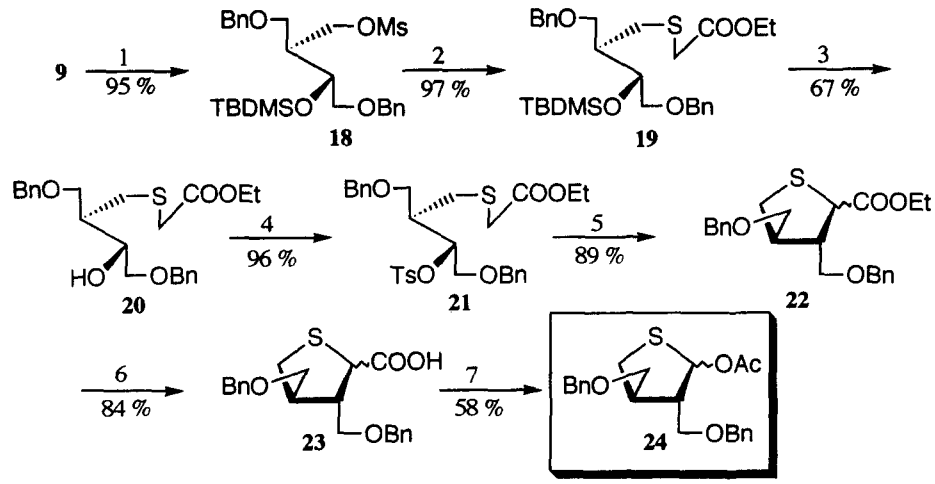
As shown in Scheme 1, the synthesis of key intermediate lactone **14** began with (*S*, *S*)-1,4-bis(benzyloxy)-2,3-epoxybutane **5** prepared from (+)-diethyl L-tartrate according to the protocol of Nicolaou *et al.*.[7] Reaction of **5** with vinylmagnesium bromide in the presence of CuI gave vinylalcohol **6**. After protection of the hydroxyl group in **6** with *tert*-butyldimethylsilyl chloride, the resulting **7** was then *cis*-dihydroxylated

using OsO_4 and *N*-methylmorpholine *N*-oxide as reoxidant to give diol **8**. Oxidative cleavage of vicinal hydroxyls in **8** with $NaIO_4$ followed by *in situ* reduction of the aldehyde with $NaBH_4$ afforded alcohol **9**. Compound **9** was transformed to nitrile **13** by a four-step sequence in 37 % overall yield: (1) desilylation by nBu_4NF, (2) selective protection of the primary alcohol with allyl bromide,[8] (3) preparation of the triflate with triflic anhydride, (4) substitution reaction with LiCN. Naturally, key lactone compound **14** could be obtained under a deprotection procedure of the allyl group of **13** in 74 % yield. Reduction of **14** with DIBAL-H followed by acetylation yielded 1-*O*-acetate **16**. Then, hydrogenolysis of **16** and subsequent benzoylation of the diol gave **17** (1:1 mixture of anomers).[11]



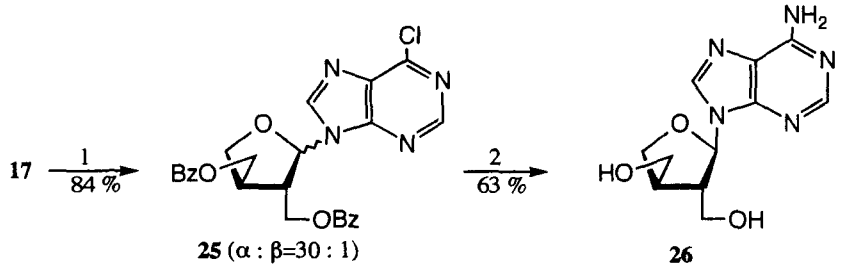
Scheme 1 *Reagents and Conditions*: 1) CH_2=CHMgBr, CuI, Et_2O, -10 °C, 4.5 h; 2) TBDMSCl, imidazole, DMF, rt, 15 h; 3) OsO_4, NMO, H_2O-acetone, rt, 16 h; 4) a: $NaIO_4$, H_2O-MeOH, rt, 3 h; b: $NaBH_4$, MeOH, 0 °C, 0.5 h; 5) nBu_4NF, THF, rt, 3 h; 6) allyl bromide, NaH, THF, rt, 18 h; 7) Tf_2O, pyridine, -40 °C, 0.5 h; 8) LiCN, THF-HMPA, -40 °C, 18 h; 9) a: $RhCl(PPh_3)_3$, H_2O-EtOH, reflux, 1 h, b: c-HCl, THF, rt, 40 h; 10) DIBAL-H, THF-toluene, -78 °C, 1.5 h; 11) Ac_2O, pyridine, rt, 18 h; 12) a: Pd-black, H_2, EtOAc, rt, 4 h; b: PhCOCl, pyridine, rt, 2 h.

To obtain key compound **24** as depicted in Scheme 2, alcohol **9** was mesylated to give **18**. Then, **18** was reacted with sodium ethyl mercaptoacetate to afford ester **19**. Desilylation of **19** by nBu_4NF and subsequent tosylation provided **21**. Treatment of **21** with NaH in THF at room temperature gave tetrahydrothiophene **22** in 89 % yield. Hydrolysis of **22** with LiOH followed by modified Hunsdiecker reaction of the carboxyl group of **23** using $Pb(OAc)_4$ afforded **24** (2:3 mixture of anomers).[9, 11] Several attempts to remove the benzyl protecting groups of **24** by using conventional methods to exchange with benzoyl groups resulted in a very low yield.



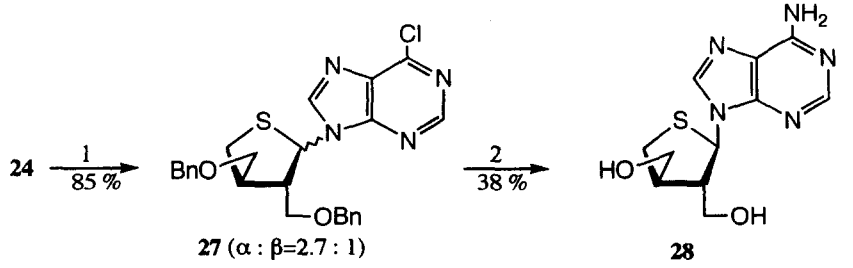
Scheme 2 *Reagents and Conditions*: 1) MsCl, Et_3N, CH_2Cl_2, rt. 2 h; 2) $HSCH_2COOEt$, NaH, THF, reflux, 2 h; 3) nBu_4NF, THF, rt, 3 h; 4) TsCl, pyridine, DMAP, rt, 12 h; 5) NaH, THF, rt, 12 h; 6) LiOH, H_2O, rt, 12 h; 7) $Pb(OAc)_4$, pyridine, EtOAc, rt, 0.5 h.

In the preparation of furanosyladenine **26**, **17** was condensed with silylated 6-chloropurine in the presence of trimethylsilyl triflate to give glycosylated products **25** with 30:1 or better selectivity for the desired α-anomer.[10, 11] Simultaneous deblocking and amination of **25** (mixture of anomers) with methanolic ammonia provided target compound **26** after purification by preparative reversed-phase HPLC (C-18 column).[12]



Scheme 3 *Reagents and Conditions*: 1) silylated 6-chloropurine, TMSOTf, CH_3CN, rt, 0.5 h; 2) NH_3, MeOH, sealed tube, rt, 15 h.

To obtain 4'-thiofuranosyladenine **28**, coupling of **24** with silylated 6-chloropurine in the presence of trimethylsilyl triflate afforded the glycosylated products **27** with an anomer ratio of α:β = 2.7:1.[11] Debenzylation of **27** (mixture of anomers) with boron trichloride at -78 °C followed by amination provided target compound **28** after purification by preparative reversed-phase HPLC in 38 % overall yield.[12]



Scheme 4 *Reagents and Conditions*: 1) silylated 6-chloropurine, TMSOTf, CH_2Cl_2, rt, 3 h; 2) a: BCl_3, CH_2Cl_2, -78 °C, 3 h; b: NH_3, MeOH, sealed tube, rt, 15 h.

In summary, we have developed the first synthesis of 2',3'-dideoxy-2',3'-bis-*C*-hydroxymethyl-α-L-threofuranosyl and its 4'-thiofuranosyl adenines as novel ring-enlarged analogs of oxetanocin A. The synthetic strategy outlined in this report seems to be efficient and applicable to the chiral synthesis of a number of potential antiviral pyrimidine and purine derivatives of these new classes. Further studies on the synthesis of related compounds, as well as investigation of the biological activities, will be reported in due course.[13]

References and Notes:

1. Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745-1768. De Clercq, E. *Nucleosides and Nucleotides.* **1994**, *13*, 1271-1295.
2. Masuda, A.; Kitagawa, M.; Tanaka, A.; Saito, S.; Shimada, N.; Ikeda, R.; Hoshino, H.; Daikoku, T.; Nishiyama, Y. *J. Antibiot.* **1993**, *46*, 1034-1037.
3. Bamford, M. J.; Coe, P. L.; Walker, R. T. *J. Med. Chem.* **1990**, *33*, 2494-2501. Tseng, C. K-H.; Marquez, V. E.; Milne, G. W. A.; Wysocki, R. J. Jr.; Mitsuya, H.; Shirasaki, T.; Driscoll, J. S. *J. Med. Chem.* **1991**, *34*, 343-349. Svansson, L.; Kvarnstrom, I.; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1991**, *56*, 2993-2997. Sanghvi, Y. S.; Bharadwaj, R.; Debart, F.; Desmaeker, A, D. *Synthesis*, **1994**, 1163-1166. Mann, J.; Weymouth-Wilsson, A. C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3141-3148. Wengel, J.; Schinazi, R. F.; Carathers, M. H. *Bioorg. & Med. Chem.* **1995**, *3*, 1223-1229.
4. Tseng, C. K-H.; Marquez, V. E.; Milne, G. W. A.; Wysocki, R. J. Jr.; Mitsuya, H.; Shirasaki, T.; Driscoll, J. S. *J. Med. Chem.* **1991**, *34*, 343-349. Wolf, J.; Jarrige, J-M.; Florent, J-C.; Grierson, D. S.; Monneret, C. *Synthesis*, **1992**, 773-778.
5. Tino, J. A.; Clark, J. M.; Field, A. K.; Jacobs, G. A.; Lis, K. A.; Michalik, T. L.; McGeever-Rubin, B.; Slusarchyk, W. A.; Spergel, S. H.; Sundeen, J. E.; Tuomari, A. V.; Weaver, E. R.; Young, M. G.; Zahler, R. *J. Med. Chem.* **1993**, *36*, 1221-1229.
6. Dyson, M. R.; Coe, P. L.; Walker, R. T. *J. Med. Chem.* **1991**, *34*, 2782-2786. Secrist III, J. A.; Tiwari, K. N.; Riordan, J. M.; Montgomery, J. A. *J. Med. Chem.* **1991**, *34*, 2361-2366. Van Draanen, N. A.; Freeman, G. A.; Short, S. A.; Harvey, R.; Jansen, R.; Szczech, G.; Koszalka, G. W. *J. Med. Chem.* **1996**, *39*, 538-542. Rahim, S. G.; Trivedi, N.; Bogunovic-Batchelor, M. V.; Hardy, G. W.; Mills, G.; Selway, J. W. T.; Snowden, W.; Littler, E.; Coe, P. L.; Basnak, I.; Whale, R. E.; Walker, R. T. *J. Med. Chem.* **1996**, *39*, 789-795.
7. Nicolaou, K. C.; Papahatjis, D. P.; Claremon, D. A.; Magolda, R. L.; Dolle, R. E. *J. Org. Chem.* **1985**, *50*, 1440-1456.
8. After many trials we decided on the use of an allyl group to effect an inversion reaction *via* a triflate. When an acetyl or MOM (methoxymethyl) group was used as a protecting group, respectively, the triflate was very unstable.
9. Norweck, D. W.; Spanton, S.; Broder, S.; Mitsuya, H. *Tetrahedron Lett.* **1989**, *30*, 6263-6266.
10. The *O*-benzoate group branching out of C-2 in compound **17** is capable of directing a preferred α-face attack *via* a cyclic six-membered 1, 3 ortho ester ion. Similar control of stereochemistry by such participation reaction has been reported by Marquez *et al* (see ref 4).
11. Anomeric composition was confirmed by ^{1}H NMR and/or reversed-phase HPLC.
12. The assignments of the anomeric configurations of compounds **26** and **28** were achieved by comparison with the NMR data reported for 2'-hydroxymethyl-ddA (see ref 4).

    Selected spectroscopic data for **26**: white waxy solid ^{1}H NMR (270 MHz, D_2O) δ 2.51 (1H, m), 2.84 (1H, m), 3.71-3.82 (4H, complex), 4.03 (1H, t , J = 8.4Hz), 4.21 (1H, t, J = 8.4Hz), 6.09 (1H, d, J = 6.4Hz), 8.18 (1H, s), and 8.31 (1H, s); HRMS, m/z 265.1162 cacld for $C_{11}H_{15}N_5O_3$ (M^+), found 265.1148.

    Selected spectroscopic data for **28**: white waxy solid ^{1}H NMR (270 MHz, CD_3OD) δ 2.50 (1H, m), 2.70 (1H, m), 3.09 (1H, dd, J = 6.2, 9.6Hz), 3.41 (1H, t, J = 9.6Hz), 3.62 (2H, complex), 3.69 (1H, dd, J = 6.2, 10.7Hz), 3.80 (1H, dd, J = 4.5, 10.7Hz), 6.20 (1H, d, J = 7.6Hz), 8.20 (1H, s), and 8.41 (1H, s); HRMS, m/z 281.0945 cacld for $C_{11}H_{15}N_5O_2S$ (M^+), found 281.0953.
13. Evaluation of compounds **26** and **28** against HSV-1 and HSV-2 in Vero cells by a plaque reduction assay at concentrations up to 10 μg/ml, and HIV-1 in MT-4 cells by an indirect immunofluorescence assay at concentrations up to 10 μg/ml revealed these compounds to be devoid of antiviral activity and cytotoxicity.

(*Received in Japan* 17 *April* 1997; *revised* 21 *May* 1997; *accepted* 22 *May* 1997)