

Synthesis of Novel 3'-C-Methyl-4'-Thio Apionucleosides *via* Highly Enantioselective Elaboration of Quaternary Carbon by [3,3]-Sigmatropic Rearrangement

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Abstract: Asymmetric synthesis of 3'-C-methyl-4'-thio apionucleosides was accomplished from the chiral intermediate **6**. The chirality of quaternary carbon of the key intermediate **6** was transferred from the chirality of secondary allylic alcohol **5** *via* [3,3]-sigmatropic Claisen rearrangement with high enantiomeric excess (estimated to be 98.5% ee). The thioglycosyl intermediate **11** was condensed with silylated *N*⁴-benzoylcytosine followed by deprotection to give the desired nucleoside **12**.

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A number of nucleosides have been reported as potential antiviral agents against human immunodeficiency virus (HIV) and human hepatitis B virus (HBV).¹ However, toxicities associated with certain nucleoside analogs² as well as the emergence of drug resistant viral strains³ warrant the search for additional novel and structurally diverse compounds with minimally overlapping resistance and toxicity profiles.

Recently, a number of modified nucleosides with dioxolane,⁴ oxathiolane,⁵ apiose (iso),⁶ and 4'-substituted ring systems instead of classical ribose derivatives, have been synthesized and found to show potent antiviral activities. Promising anti-HIV activity of 4'-substituted nucleosides (4'-cyano-thymidine⁷ and 4'-azido-thymidine⁸) as well as 4'-fluoro-nucleoside (nucleocidin⁹), which is a natural anti-trypanosomal agent, have attracted the attention of medicinal chemists. However, only a few examples of C-4'-substituted dideoxynucleosides,^{10,11} or C-4'-alkyl carbocyclic nucleosides¹² of defined absolute stereochemistry are known in the literature. Furthermore, there has been no report on C-4'-alkyl substituted furanose- or its dideoxy analog-containing nucleosides. This may be largely due to the lack of synthetic methodology for elaborating an appropriate chiral quaternary carbon stereocenter.

In the past, a great deal of effort has been devoted to developing more efficient synthetic methods for generating quaternary carbon stereocenters,¹³ particularly in natural product synthesis, as a variety of biologically active compounds contain quaternary carbon atoms in nature.¹⁴ For the construction of asymmetric carbon, intramolecular chirality-transfer reactions with high stereochemical fidelity have often been employed.¹⁵ Recently, we developed a new methodology for the synthesis of tertiary fluorinated compounds with high enantiomeric excess *via* Claisen rearrangement. We successfully adapted this methodology for the synthesis of 3'-fluoro substituted apionucleoside.¹⁶ This synthetic strategy is also useful for the construction of quaternary carbon stereocenter. Herein, we wish to report an efficient synthetic methodology for generating a quaternary carbon atom with high enantiomeric excess. The methodology was utilized for the synthesis of optically active 3'-C-methyl-4'-thio apionucleosides, which is otherwise difficult to synthesize.

Freshly prepared 2,3-*O*-isopropylidene-D-glyceraldehyde¹⁷ was immediately subjected to Wittig reaction with ethoxycarbonyl ethylidene(triphenyl)-phosphorane in methylene chloride to give the α,β -unsaturated ethyl

ester **1** (Scheme 1).¹⁸ Compound **1** was reduced by diisobutylaluminum hydride (DIBAL-H) in methylene chloride to give an allylic alcohol **2**, which was treated with sodium hydride and benzyl bromide to obtain the benzyl protected compound **3**. The isopropylidene group of compound **3** was hydrolyzed to diol **4** using a mixture of 2 N HCl and 1,4-dioxane. The primary hydroxyl group of compound **4** was selectively protected with *tert*-butyldimethylsilyl group to yield compound **5** in 91.9% yield. Subsequently, Johnson-Claisen rearrangement¹⁹ of compound **5** using triethyl orthoacetate at 135 °C in the presence of catalytic amounts of propionic acid yielded γ,δ -unsaturated quaternary carbon ethyl ester **6** in 65.4% yield. The enantiomeric excess of the chirality transfer reaction was calculated at the stage of the final compound **12** by chiral reverse HPLC to be 98.5% (ee).²⁰ The reason for the determination of the enantiomeric excess at the nucleoside stage, instead of compound **6**, was that the availability of a reverse phase column in our laboratory as well as the advantage of UV detection of the cytosine moiety of nucleoside by HPLC vs. benzyl moiety. The double bond of **6** was ozonized to an aldehyde **7** which was subsequently reduced using DIBAL-H in toluene at -78 °C to yield lactol **8** in 47.3% in two steps. The apiose lactol intermediate **8** was treated with excess of benzyl mercaptan in the presence of $\text{BF}_3/(\text{C}_2\text{H}_5)_2\text{O}$ as a Lewis acid.²¹ The resulting dithiane protected alcohol derivative **9** was activated by a methane sulfonate group, which was cyclized in refluxing conditions to give the thio-glycosyl donor **11** as a diastereomeric mixture in the presence of tetrabutylammonium iodide (TBAI) and barium carbonate (BaCO_3). Compound **11** was condensed with *N*⁴-benzoylcytosine in the presence of *N*-iodosuccinimide (NIS) as a Lewis acid and anhydrous molecular sieve (4 Å) in acetonitrile²² to give protected anomeric mixture (1.2/1 = β/α ratio, determined by NMR), which was readily separated by silica gel column chromatography. To obtain the final nucleosides, individual isomers were treated with methanolic ammonia, and subsequently treated with BCl_3 in the methylene chloride at -78 °C to give the final nucleosides **12**²³ and **13**.²⁴ The stereochemical assignment was determined on the basis of 1D and 2D-NMR studies.

In summary, we achieved an efficient synthetic method for a chiral quaternary carbon stereocenter using [3,3]-sigmatropic Claisen rearrangement with high enantiomeric excess, which was applied for the synthesis of novel 3'-C-methyl-4'-thio apionucleosides. Investigation of apio nucleosides with other substitutions on the 3'-position as well as biological evaluation are in progress.

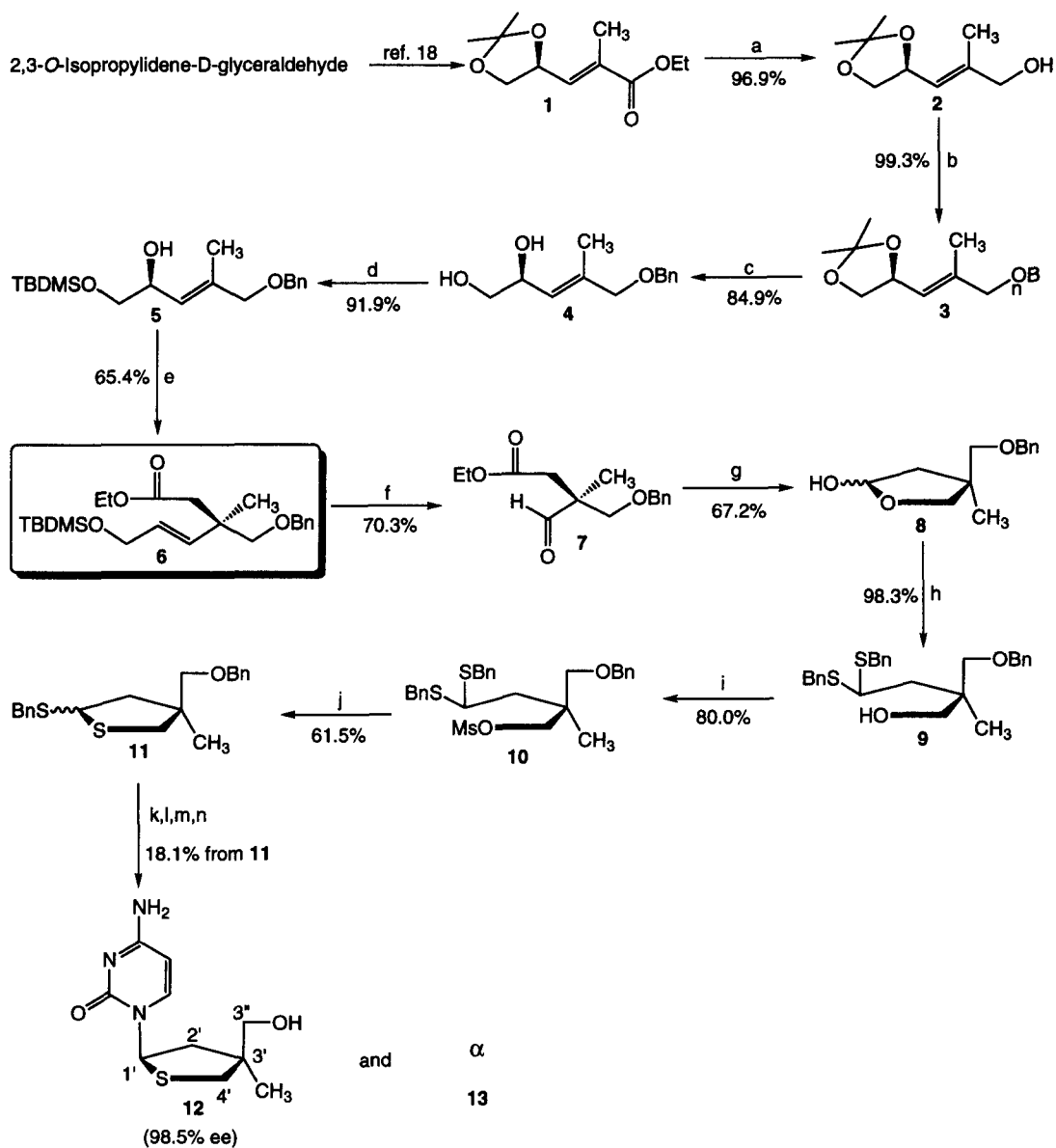
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References:

1. (a) De Clercq, E. *Clin. Microbiol. Rev.* **1997**, *10*, 674-693; (b) Hong, J. H.; Choi, Y.; Chun, B. K.; Lee, K.; Chu, C. K. *Arch. Pharm. Res.* **1998**, *21*, 89-105.
2. Martin, J. L.; Brown, C. E.; Matthews-Davis, N.; Reardon, J. E. *Antimicrob. Agent Chemother.* **1994**, *38*, 2743-2749.
3. Shirasaka, T.; Kavlick, M. F.; Ueno, T.; Gao, W.-Y.; Kojima, E.; Alcaide, M. L.; Chokekuchai, S.; Roy, B. M.; Arnold, E.; Yarchoan, R.; Mitsuya, H. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 2398-2402.
4. Kim, H. O.; Ahn, S. K.; Alves, A. J.; Beach, J. W.; Jeong, L. S.; Choi, B. G.; PanRoey, V.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **1992**, *35*, 1987-1995.

5. Jeong, L. S.; Schinazi, R. F.; Beach, J. W.; Kim, H. O.; Shanmuganathan, K.; Nampalli, S.; Chun, M. W.; Chung, W.-K.; Choi, B. G.; Chu, C. K. *J. Med. Chem.* **1993**, *36*, 2627-2638.
6. Nair, V.; Jahnke, T. S. *Antimicrob. Agent Chemother.* **1995**, *39*, 1017-1029.
7. Oyang, C.; Wu, H. Y.; Fraser-Smith, E. B.; Walker, K. A. M. *Tetrahedron Lett.* **1992**, *33*, 37-40.
8. Maag, H.; Rydzewski, R. M.; McRoberts, M. J.; Crowford-Ruth, D.; Verheyden, J. P. H.; Prisbe, E. J. *J. Med. Chem.* **1992**, *35*, 1440-1451.
9. Jenkins, I. D.; Verheyden, J. P. H.; Moffatt, J. G. *J. Am. Chem. Soc.* **1976**, *98*, 3346-3357.
10. Lipshutz, B. H.; Sharma, S.; Dimock, S. H.; Behling, J. R. *Synthesis* **1992**, 191-195.
11. Arnone, A.; Bravo, P.; Frigerio, M.; Viani, F.; Salani, G.; Zappalà, C. *J. Chem. Research (S)* **1997**, 458-459.
12. Nieto, M. I.; Blanco, J. M.; Caamaño, O.; Fernández, F.; García-Mera, X.; Balzarini, J.; Padalko, E.; Neyts, J.; De Clercq, E. *Nucleosides & Nucleotides* **1998**, *17*, 1255-1266.
13. (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 388-401; (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037-2066.
14. (a) Corey, E. Z.; Guzman-Perez, A.; Lazerwith, S. E. *J. Am. Chem. Soc.* **1997**, *119*, 11769-11776; (b) Corey, E. J.; Roberts, B. E.; Dixon, B. R. *J. Am. Chem. Soc.* **1995**, *117*, 193-196.
15. (a) Bennett, G. B. *Synthesis* **1977**, 589-606; (b) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423-1452; (c) Bleichert, S. *Synthesis* **1989**, 71-82; (d) Schubert, P.; Morris, S. *Aldrichimica Acta* **1993**, *26*, 17-29; (f) Frauenrath, H. in *Houben-Weyl*, Eds. Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaubmann, E.; Thieme Stuttgart-New York, **1995**, 3301-3689.
16. Hong, J. H.; Lee, K.; Choi, Y.; Chu, C. K. *Tetrahedron Lett.* **1998**, *39*, 3443-3446.
17. Hafele, B.; Jager, V. *Liebigs. Ann. Chem.* **1987**, *317*, 85-87.
18. Nemoto, H.; Satoh, A.; Ando, M.; Fukumoto, K. *J. Chem. Soc., Chem. Commun.* **1990**, *15*, 1001-1002.
19. Wipf, P. *Comprehensive Organic Synthesis*: Trost, B. M.; Fleming, I.; Eds.; Pergamon Press; Oxford, **1991**, Vol 5, Chapter 7.2, pp 827-873.
20. Enantiomeric excess (ee %) was calculated by "cyclobond I 2000 RSP" reverse phase chiral HPLC.
21. Bellon, L.; Barascut, J.-L.; Imbach, J.-L. *Nucleosides & Nucleotides* **1992**, *11*, 1467-1479.
22. 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. F.; Walker, R. T. *J. Med. Chem.* **1996**, *39*, 789-795.
23. **1-[3-C-(Hydroxymethyl)-3-deoxy-3-methyl-4-thio-β-D-erythro-tetrafuransyl] cytosine (12)**: mp 182-184 °C; $[\alpha]_D^{26}$ -12.6 (c 0.33%, CH₃OH); UV (H₂O) λ_{max} 270.5 (e 10 123) (pH 7), 277.0 (e 12 210) (pH 2), 271.0 (e 10 490), (pH 11); ¹H NMR (DMSO-*d*₆) δ 7.95 (d, *J* = 7.5 Hz, 1 H), 7.34, 7.23 (br s, 2 H, D₂O exchangeable), 6.41 (dd, *J* = 9.7, 7.1 Hz, 1 H), 5.89 (d, *J* = 7.3 Hz, 1 H), 4.99 (br s, 1 H, D₂O exchangeable), 3.29, 3.22 (s, s, 2 H), 2.56, 2.51 (s, s, 2 H), 2.02 (dd, *J* = 12.7, 7.1 Hz, 1 H), 1.91 (t, *J* = 12.6, 1 H), 1.12 (s, 3 H); ¹³C NMR (DMSO-*d*₆) δ 168.48, 158.71, 145.73, 98.47, 70.83, 70.71, 65.11, 52.52, 47.89, 24.63; Anal. Calcd. for C₁₀H₁₅N₃O₂S: C, 49.77; H, 6.27; N, 17.41. Found: C, 49.56; H, 5.99; N, 17.27; MS (*m/z*): 242 [M+H]⁺.
24. **1-[3-C-(Hydroxymethyl)-3-deoxy-3-methyl-4-thio-α-D-erythro-tetrafuransyl] cytosine (13)**: mp 176-178 °C; $[\alpha]_D^{26}$ +13.8 (c 0.47%, CH₃OH); UV (H₂O) λ_{max} 271.0 (e 9 974) (pH 7), 277.5 (e 13 250) (pH 2), 270.0 (e 11 470) (pH 11); ¹H NMR (DMSO-*d*₆) δ 8.00 (d, *J* = 7.5 Hz, 1 H), 7.46, 7.28 (s, s, 2 H, D₂O exchangeable), 6.24 (t, *J* = 6.5 Hz, 1 H), 5.85 (d, *J* = 7.5 Hz, 1 H), 4.92 (s, 1 H, D₂O exchangeable), 3.28, 3.16 (s, s, 2 H), 3.04, 2.78 (d, d, *J* = 10.5, 10.5 Hz, 2 H), 2.27 (dd, *J* = 12.9, 7.1 Hz, 1 H), 1.69 (dd, *J* = 17.7, 9.6 Hz, 1 H), 1.12 (s, 3 H); ¹³C NMR (DMSO-*d*₆) δ 167.98, 158.08, 146.32, 98.39, 68.47, 68.35, 65.39, 52.59, 47.81, 25.89; Anal. Calcd. for C₁₀H₁₅N₃O₂S: C, 49.77; H, 6.27; N, 17.41. Found: C, 49.91; H, 6.23; N, 17.71; MS (*m/z*): 242 [M+H]⁺.

Scheme 1



Reagents: a) DIBAL-H, CH_2Cl_2 , -78°C . b) BnBr , NaH , THF. c) 2 N HCl. d) TBDMSCl, imidazole, CH_2Cl_2 . e) Triethylortho acetate, propionic acid, 135°C . f) O_3/DMS , MeOH, -78°C . g) DIBAL-H, toluene, -78°C . h) Benzyl mercaptan, $\text{BF}_3/(\text{C}_2\text{H}_5)_2\text{O}$, CH_2Cl_2 . i) Methanesulfonyl chloride, pyridine. j) TBAI, BaCO_3 , Py, reflux. k) *N*⁶-benzoylcytosine, *N*-iodosuccinimide (NIS), 4 Å molecular sieve, acetonitrile. l) Separation of anomers using silica gel column chromatography. m) NH_3/MeOH . n) $\text{BCl}_3/\text{CH}_2\text{Cl}_2$, -78°C .