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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**.

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 analogs[2] as well as the emergence of drug resistant viral strains[3] 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-thymidine[7] and 4'-azido-thymidine[8]) as well as 4'-fluoro-nucleoside (nucleocidin[9]), 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 nucleosides[12] 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-glyceraldehyde[17] was immediately subjected to Wittig reaction with ethoxycarbonyl ethylidene(triphenyl)-phosphorane in methylene chloride to give the α,β-unsaturated ethyl

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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*-butyldimethysilyl group to yield compound **5** in 91.9% yield. Subsequently, Johnson-Claisen rearrangement[19] 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 $BF_3/(C_2H_5)_2O$ 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 A) in acetonitrile[22] 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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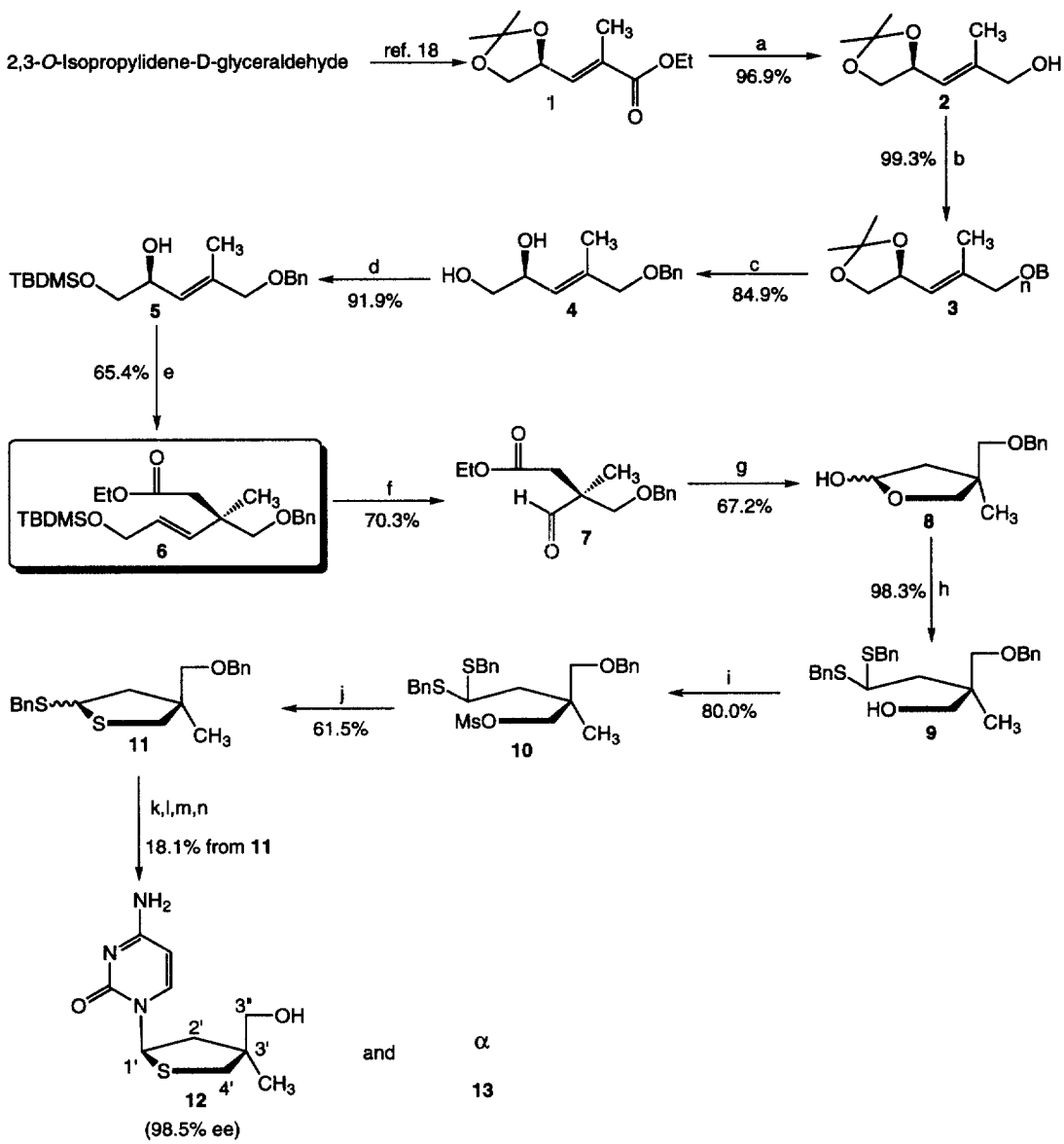
23. **1-[3-*C*-(Hydroxymethyl)-3-deoxy-3-methyl-4-thio-β-D-erythro-tetrafuranosyl] cytosine (12):** mp 182-184 °C; $[\alpha]^{26}_{D}$ -12.6 (*c* 0.33%, CH_3OH); UV (H_2O) λ_{max} 270.5 (*e* 10 123) (pH 7), 277.0 (*e* 12 210) (pH 2), 271.0 (*e* 10 490), (pH 11); ^1H NMR (DMSO-d_6) δ 7.95 (d, *J* = 7.5 Hz, 1 H), 7.34, 7.23 (br s, 2 H, D_2O 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, D_2O 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); ^{13}C 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 $C_{10}H_{15}N_3O_2S$: 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-tetrafuranosyl] cytosine (13):** mp 176-178 °C; $[\alpha]^{26}_{D}$ +13.8 (*c* 0.47%, CH_3OH); UV (H_2O) 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, D_2O exchangeable), 6.24 (t, *J* = 6.5 Hz, 1 H), 5.85 (d, *J* = 7.5 Hz, 1 H), 4.92 (s, 1 H, D_2O 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); ^{13}C 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 $C_{10}H_{15}N_3O_2S$: 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, $BF_3/(C_2H_5)_2O$, CH_2Cl_2. i) Methanesulfonyl chloride, pyridine. j) TBAI, $BaCO_3$, Py, reflux. k) N^4-benzoylcytosine, *N*-iodosuccinimide (NIS), 4 A molecular sieve, acetonitrile. l) Separation of anomers using silica gel column chromatography. m) NH_3/MeOH. n) BCl_3/CH_2Cl_2, -78 °C.