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NOVEL C-NUCLEOSIDE ANALOGS OF 1,3-DIOXOLANE: SYNTHESIS OF ENANTIOMERIC (2'R,4'S)- AND (2'S,4'R)-2-[4-(HYDROXYMETHYL)-1,3-DIOXOLAN-2-YL]-1,3-THIAZOL-4-CARBOXAMIDE

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Abstract. Novel C-nucleosides (2'R,4'S)-and (2'S,4'R)-2-[4-(hydroxymethyl)-1,3-dioxolan-2-yl]-1,3-thiazole-4-carboxamide have been synthesized from stereoselectively induced condensation of optically active triols (S or R) with a 1,3-thiazole-4-carboxamide derivative.

Since the anti-HIV activity of (±)-dioxolane-thymine has been reported by Belleau et al,[1] a number of 1,3-dioxolane nucleosides have been synthesized as potential anti-HIV and anti-HBV agents.[2-10] Among the dioxolane nucleosides, (-)-(2'R,4'R)-(dioxolan-4-yl)-guanine (DG) and (-)-(2'R,4'R)-(dioxolan-4-yl)-2,6-diaminopurine (DAPD)[4] are currently undergoing preclinical evaluations as anti-HIV and anti-HBV agents, respectively. These nucleosides are enantiomerically pure compounds which have been synthesized from carbohydrate chiral templates with a defined stereochemistry. Tiazofurin, 2-(ß-*D* -ribofuranosyl)-1,3-thiazol-4-carboxamide[11-13] is an interesting synthetic C-nucleoside which has demonstrated potent antitumor activity against several murine tumors and antiviral activities *in vitro*. It has been undergoing phase I[12] and phase II[13] clinical trials as an antitumor agent against lung cancer. Therefore, in this communication, we wish to report a novel class of dioxolane C-nucleosides as analogs of tiazofurin.

Due to previous difficulties experienced in building up a heterocyclic moiety from a dioxolane ring for C-nucleosides, our strategy in the current synthesis was to construct C-nucleosides by direct condensation of an appropriate heterocyclic base containing dimethylacetal with a chiral triol such as **5** for the construction of the dioxolane ring. Thus, 1,3-thiazole derivative **4** was prepared from commercially available 2,2-diethoxyacetamide in a one-pot reaction (three steps) in overall yield of 26%. 2,2-Diethoxyacetamide **1** was sulfurized by P_2S_5 in 1,4-dioxolane at room temperature for 30 min to give the intermediate **2** (Scheme 1), which was immediately separated by a short silica gel column to avoid polymerization. The separated intermediate **2** was treated immediately with ethyl bromopyruvate in refluxing ethanol for 4 h to obtain 1,3-thiazole intermediate **3**. Due to difficulties in isolating the pure product **3** from the reaction mixture, the crude product **3** was used directly for the amination reaction. After amination of the compound **3** in saturated methanolic ammonia at room temperature for 24 h, the desired compound **4** could be readily separated by silica gel column chromatography. Upon recrystallization from ethyl acetate and hexanes, pure compound **4** was obtained as a light yellow solid. The asymmetrically induced condensation was accomplished by refluxing a mixture of **4** and an optically active triol (S-configuration) **5** with TsOH in benzene, during which one-half of the solvent was distilled out. The condensation gave a mixture of α and ß-isomers (78%) in a ratio of 1:4 based on ^{1}H NMR spectroscopy, in

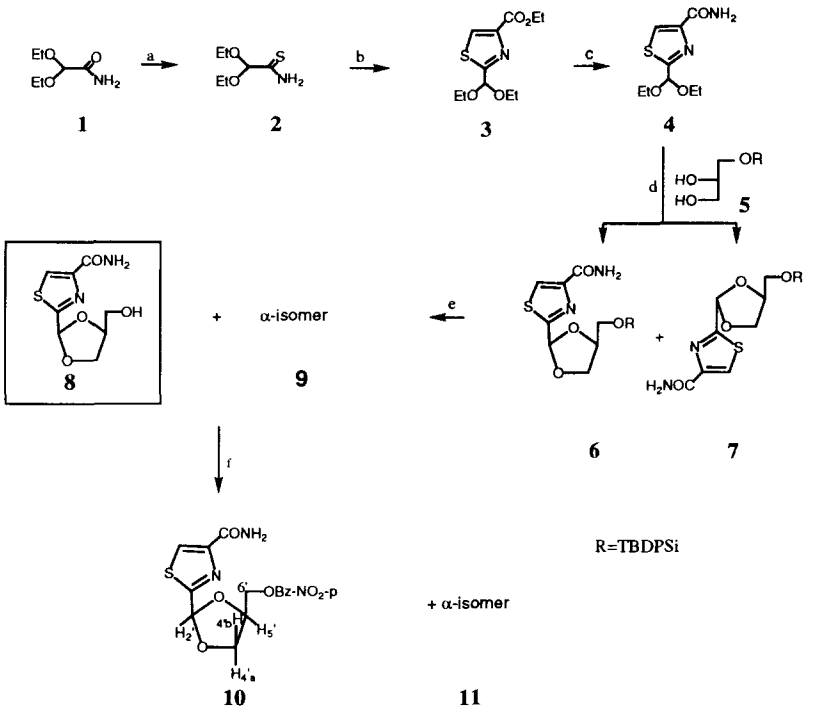
which the major compound (ß-isomer) **6** showed the upfield shift for H-2'(δ 6.08), compared to the minor compound (α-isomer) **7** for H-2'(δ 6.20). Based on the above differences in chemical shifts of H-1'(H-2' in thiazole C-nucleosides) in C-nucleosides,[14-15] we assigned the ß –and α–anomeric configuration for **6** and **7**, respectively. The mixture of **6** and **7** gave only one spot on a silica gel TLC plate in various solvent systems. Therefore, the mixture could not be separated into single isomers at this stage. The mixture of **6** and **7** was treated with n-Bu_4NF in THF at room temperature for 1h to give a mixture of free nucleosides **8** and **9** as a syrup in 92% yield. Again, the mixture could not be separated on a silica column due to the overlapping R_f values on a TLC plate in various conditions. According to ^1H NMR spectroscopy, the ratio of the major product to the minor compound was 4:1. On the basis of the difference in chemical shift of H-2', we assigned the major compound as the β-configuration, which exhibited upfield chemical shifts of H-2' (δ6.03), compared to the minor compound (the α-isomer) with the chemical shift of H-2' (δ 6.20), which is consistent with the previous assignment of the anomeric configurations of **6** and **7**. Fortunately, the major compound **8**[16] could be separated by the careful recrystallization of the mixture of **8** and **9** from methanol and diethyl ether (1:1) at low temperature (0° C). The minor α-isomer could not be isolated as a pure product. Due to the failure of isolating the major compound **8** in our earlier experiment, we reprotected the nucleoside mixture of **8** and **9** with 4-nitrobenzoyl chloride in CH_2Cl_2 to obtain 4-nitrobenzoylated derivatives, which could be recrystallized from methanol to give the pure isomer **10**[17] as a white solid. Again, the α-isomer could not be isolated as a single product. The configuration of compound **10** was assigned based on two dimensional NOESY NMR experiments, in which the strong NOE of H-2' and H-4", and H-2' and H-5'$_a$ were observed. Based on these results, we unambiguously assigned the compound **10** as the ß-isomer, which is consistent with the previous assignment for the major compound **8** as the ß-isomer.

Optically pure (2'S,4'R)-2-[4-(hydroxymethyl)-1,3-dioxolan-2-yl]thiazole-4-carboxamide **14**[18], an enantiomer of **8** was also synthesized from a similar procedure as described above (Scheme 2). The condensation of **4** with an optically pure triol (R-configuration) **12** gave a mixture of α- and ß-isomers in 81% yield with a ratio of 1:4 according to ^1H NMR spectroscopy. The mixture was deprotected and recrystallized from methanol and diethyl ether (1:1) at 0° C to obtain the pure compound **14** (46%). ^1H NMR spectroscopy confirmed the compound **13** as the ß–isomer, which exhibits nearly the identical chemical shifts as well as the pattern of the ß–*L*-isomer **8**.

In summary, we have synthesized a hitherto unknown dioxolane C-nucleosides **8** (*L*-form) and its enantiomer **14** (*D*-form) from the condensations of the 1,3-thiazole-4-carboxamide derivative **4** with an optically active *D* (or S)- **5** and *L* (or R)- **12** triols, respectively. The above described synthetic strategy of dioxolane C-nucleosides should be applicable for the synthesis of various pyrimidine and purine dioxolane-C-nucleosides, of which efforts are currently in progress in our laboratory.

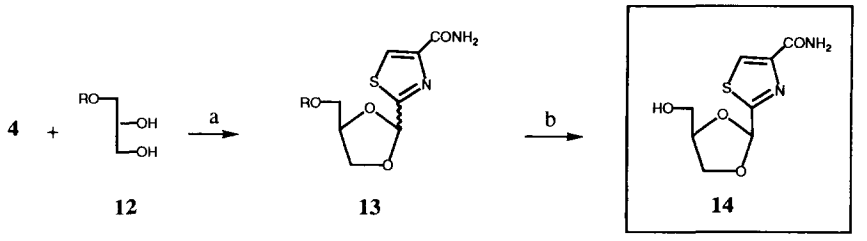
Biological evaluations of the synthesized compounds are in progress and will be reported elsewhere in case of positive data.

Scheme 1



a. P_4S_{10}/Dioxane, r.t., 30min; b. Ethyl bromopyruvate/EtOH, reflux, 5h; c. NH_3/MeOH, r.t., 1h; d. Benzene/TsOH, reflux,3h; e. n-Bu_4NF/THF, r.t.,1h; f. p-NO_2BzCl/Py, r.t., 10h.

Scheme 2



R=TBDPSi

a. Benzene/TsOH, reflux, 2h; b. n-Bu_4NF/THF, r.t., 30min.

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16. Compound **8**: $[\alpha]_D$ +6.0 [c=0.56, MeOH]; UV(H_2O)λ_{max} 238.5 (ε 4870) (pH 2), 239.2 (ε 4120) (pH 7), 237.0 (ε 5650) (pH 11); ^{1}H NMR (DMSO-d_6) δ 8.32 (s, 1H, H-5), 7.76 (bs, 1H, NH), 7.59 (bs, 1H, NH), 6.03 (s, 1H, H-2'), 5.00 (t, J=5.6Hz, 1H, 6-OH), 4.25 (m, 1H, H-4'), 4.09 (t, J=8.0Hz, 1H, H-5'a), 3.90 (dd, J=6.0 and 8.0Hz, 1H, H-5'b), 3.52 (m, 2H, H-6'); Anal calcd for $C_8H_{10}N_2O_4S$ + 0.1Et_2O: C,42.25; H, 4.67; N,11.78. Found: C, 42.32; H,4.90; N, 11.51.
17. Compound **10**: $[\alpha]_D$ +7.2 [c 0.51, MeOH]; ^{1}H NMR (DMSO-d_6) δ 8.14-8.31 (m, 5H, H-5 and Ar), 7.15 (bs, 1H, NH), 6.13 (s, 1H, H-2'), 5.90 (bs, 1H, NH), 4.69 (m, 1H, H-4'), 4.62 (dd, J=4.2 and 7.6Hz, 1H, H-6'), 4.52 (dd, J=5.3 and 11.2Hz, 1H,H-6'), 4.30 (t, J=6.4Hz, 1H, H-5a'), 4.17(dd, J=5.5and 8.5Hz, 1H, H-5b'); Anal calcd for $C_{15}H_{13}N_3O_6S + 0.75H_2O$: C,47.81; H, 3.87; N,11.15. Found: C, 47.49; H,3.55; N, 11.07.
18. Compound **14**: $[\alpha]_D$ -5.6 [c 0.56, MeOH]; UV(H_2O)λ_{max} 238.5 (ε 4670) (pH 2), 239.2 (ε 4320) (pH 7), 237.0 (ε 5850) (pH 11); ^{1}H NMR (DMSO-d_6) δ 8.49 (s, 1H, H-5), 7.87 (bs, 1H, NH), 7.72(bs, 1H,NH), 6.21 (s, 1H, H-2'), 5.12 (t, J=5.0Hz, 1H, 6'-OH), 4.43 (m, 1H, H-4'), 4.28 (t, J=7.2Hz, 1H, H-5'a), 4.09 (dd, J=6.2 and 8.0Hz, 1H, H-5'b), 3.72 (m, 2H, H-6'); Anal calcd for $C_8H_{10}N_2O_4S$: C,41.73; H, 4.37; N,12.17. Found: C, 41.60; H,4.42; N, 12.02.

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