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An Efficient Synthesis of Enantiomerically Pure (+)-(2S,5R)-1-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine [(+)-BCH-189] from D-Galactose

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Key Words: Enantiomeric Synthesis; Anti-HIV; D-Galactose; D-Mannose; (+)-BCH-189

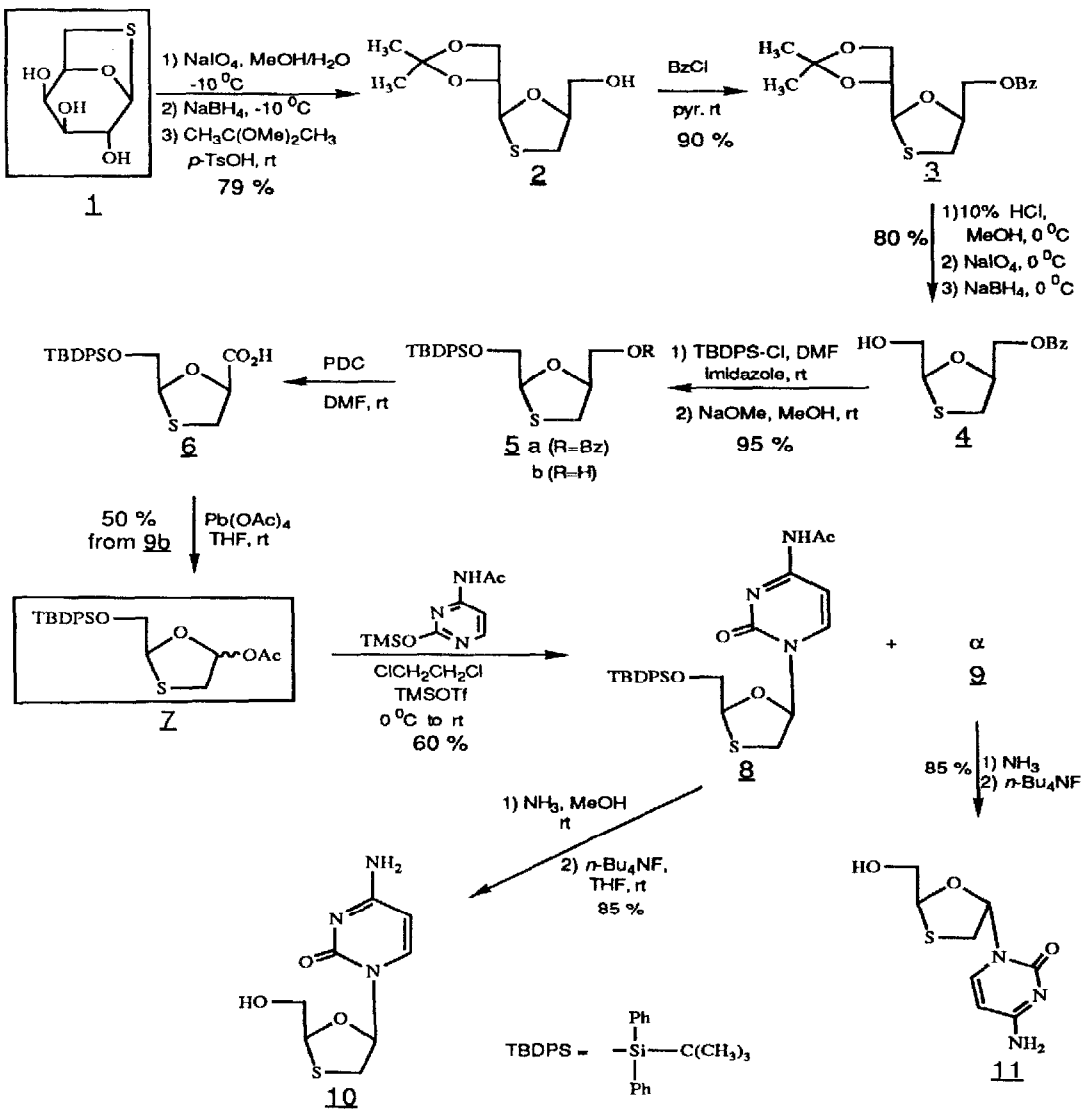
Abstract: *An efficient and short synthesis of enantiomerically pure (+)-BCH-189 has been accomplished from D-galactose via 1,6-thioanhydro-D-galactose.*

Belleau and coworkers[1] reported the synthesis and anti-HIV activity of an unusual class of nucleosides, (±)-dioxolane-thymine and (±)-BCH-189 in which C-3' positions of these nucleosides have been replaced by oxygen and sulfur atom, respectively. Norbeck et al.[2] also reported the synthesis of (±)-dioxolane-thymine which was found to exhibit a moderate anti-HIV activity. Thus, it was of interest to synthesize an enantiomerically pure isomer of (±)-dioxolane-thymine. Recently, we have reported asymmetric synthesis of (-)-dioxolane-thymine from 1,6-anhydro-**D**-mannose as a chiral template.[3] We found that the enantiomerically pure isomer was a potent anti-HIV agent in human peripheral blood mononuclear (PBM) cells. However, it was found that the (-)-isomer was somewhat less potent than the racemic mixture. The implication of this difference in activity is under investigation.

Since BCH-189 is expected to undergo clinical trials in patients with AIDS and AIDS-related complex, it was of interest to synthesize the enantiomerically pure isomer of BCH-189. Recently, we have completed the synthesis of (+)-BCH-189 from **D**-mannose in 20 steps via 1,6-thioanhydro-**D**-mannose.[4] Although the procedure resulted in an enantiomerically pure form of (+)-BCH-189, the synthetic steps were too lengthy and the overall yield was not sufficiently high enough for large scale synthesis.

Thus, we wish to report more efficient and shorter synthetic route to (+)-BCH-189 from 1,6-thioanhydro-**D**-galactose (**1**)[5] (scheme 1).The preparation of **1** was more straightforward and gave excellent yield, compared to that of 1,6-thioanhydro-**D**-mannose. Furthermore, all intermediates during the preparation of **1** could be purified by recrystallization, while those in the synthesis of 1,6-thioanhydro-**D**-mannose were purified by silica gel chromatography which makes a large scale preparation difficult.

Scheme 1



The selective oxidative cleavage of 1,6-thioanhydro-D-galactose **1** by $NaIO_4$ to corresponding aldehyde, reduction with $NaBH_4$ followed by protection of resulting diol with 2,2-dimethoxypropane as isopropylidene derivative gave 1,3-oxathiolane derivative **2** (79 % from **1**). The primary hydroxyl group of **2** was benzoylated to give benzoate **3** (90 %) which was converted to **4** by deprotection of isopropylidene group with 10 % HCl in MeOH (v/v) at 0 °C, oxidative cleavage of resulting diol by $NaIO_4$ to corresponding aldehyde followed by reduction with $NaBH_4$ (80 % from **3**). Silyl protection of **4** followed by debenzoylation of **5a** with NaOMe in MeOH gave a silyl derivative **5b** (95 % from **4**). The treatment of **5b** with pyridinium dichromate (PDC) in

DMF[6] at room temperature gave crude acid **6** without oxidizing the sulfur of the ring, unlike $NaClO_2$ oxidation which had given a mixture of sulfoxides in the previously reported synthesis.[4] Without further purification, acid **6** was converted into the key intermediate **7** by $Pb(OAc)_4$/pyridine[2,4,7] in anhydrous THF (50 % from **5b**). Condensation of **7** with silylated N-acetylcytosine in dry 1,2-dichloroethane in the presence of trimethylsilyl triflate[8] gave a mixture of **8** (43 %) and **9** (20 %), which was purified by silica gel column chromatography. Deacetylation of **8** and **9** with NH_3 in MeOH followed by desilylation with tetra-*n*-butylammonium fluoride produced the desired (+)-BCH-189 **10** and its α-isomer **11**, respectively.[9]

In summary, the enantiomerically pure (+)-BCH-189 has been synthesized from 1,6-thioanhydro-**D**-galactose.[10] This synthetic procedure gives the major advantages, such as easy large scale preparation of key intermediate **1**, selective cleavage of cis-diol and no sulfur oxidation in preparation of acid **6**, compared to the previously published procedure starting from **D**-mannose.[4] Such advantages make this scheme possible as a general approach for the structure-activity relationships of 1,3-oxathiolanyl nucleosides as anti-HIV agents which are in progress in our laboratory.

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9. The spectral data of **10** and **11** were identical with those of authentic samples.

10: mp = 145-147°C; $[\alpha]^{25}_D$ = 123.02 (c 0.24, MeOH); ^{1}H NMR (DMSO-d_6) δ 3.03 (dd, $J_{5,4a}$ = 4.4 Hz, $J_{4a,4b}$ = 11.9 Hz, 1 H, 4-H_a), 3.43 (dd, $J_{5,4b}$ = 5.3 Hz, $J_{4a,4b}$ = 11.9 Hz, 1 H, 4-H_b), 3.80 (pseudo t on D_2O exchange goes to d, $J_{2,2\text{-}CH2\text{-}OH}$ = 4.17 Hz, 2 H, 2-CH_2-OH), 5.27 (t, $J_{2\text{-}CH2,OH}$ = 4.6 Hz, 1 H, 2-CH_2OH), 5.22 (t, $J_{2,2\text{-}CH2\text{-}OH}$ = 4.2 Hz, 1 H, 2-H), 5.88 (d, $J_{5,6}$ = 7.5 Hz, 1 H, H-5), 6.21 (pseudo t, J = 5.1 and 4.8 Hz, 1 H, 5-H), 7.19 (br s, 2 H, NH_2), 7.89 (d, $J_{5,6}$ = 7.5 Hz, 1 H, H-6); UV: H_2O λ_{max} (pH = 7) 270 (ε = 9500), (pH = 2) 279 (ε = 13700), (pH = 11) 270 (ε = 9600).

11: mp = 153-156°C; $[\alpha]^{25}_D$ = -140.15 (c 0.52, MeOH); ^{1}H NMR (DMSO-d_6) δ 3.08 (dd, $J_{5,4a}$ = 2.6

Hz, $J_{4a,4b}$ = 12.1 Hz, 1 H, 4-H_a), 3.46 (dd, $J_{5,4b}$ = 5.1 Hz, $J_{4a,4b}$ = 12.1 Hz, 1 H, 4-H_b), 3.54 (pseudo t on D_2O exchange goes to d, $J_{2,2\text{-}CH2\text{-}OH}$ = 5.1 Hz, 2 H, 2-CH_2-OH), 5.16 (t, $J_{2\text{-}CH2,OH}$ = 5.7 Hz, 1 H, 2-CH_2-O<u>H</u>), 5.53 (t, $J_{2,2CH2\text{-}OH}$ = 5.1 Hz, 1 H, 2-H), 5.83 (d, $J_{5,6}$ = 7.5 Hz, 1 H, H-5), 6.36 (dd, $J_{5,4a}$ = 2.6 Hz, $J_{5,4b}$ = 5.1 Hz, 1 H, 5-H), 7.16 (br s, 2 H, NH_2), 7.63 (d, $J_{5,6}$ = 7.5 Hz, 1 H, H-6); UV: H_2O λ_{max} (pH = 7) 271 (ε = 9800), (pH = 2) 279 (ε = 14000), (pH = 11) 271 (ε = 10.000).

10. All the unknown compounds in scheme 1 gave satisfactory spectroscopic data and correct elemental analyses (± 0.4 %).

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