were made based on extensive ^1H NMR NOE experiments as well as by comparison of ^1H NMR spectra with that reported previously.[12] Weinreb amidation[20] of lactone 2 with benzylamine (2 equiv) and trimethylaluminum (2 equiv) in methylene chloride (23 °C for 10 min, then 40 °C for 3 h) afforded hydroxyamide 14 (74% yield, mp 179–182 °C) after silica gel chromatography.[21] Lactone 2 was converted to potent and selective inhibitors of HIV-1 protease according to the previous literature procedure.[4]

In conclusion, an efficient, stereocontrolled, and economical synthetic route to dipeptide isostere 1 has been developed. Since the starting material of this synthesis is D-mannose rather than an amino acid, the present methodology should provide convenient access to other dipeptide isosteres with a great deal of structural diversity at C-2 and C-5 positions. Synthesis of a number of HIV-1 protease inhibitors containing hydroxyethylene isosteres and their biological evaluation is currently under investigation.

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Supplementary Material Available: Experimental procedures and spectral data for compounds 5–14 (7 pages). Ordering information is given on any current masthead page.

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Enantiomeric Synthesis of (+)-BCH-189 [(+)-(2*S*,5*R*)-1-[2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine] from D-Mannose and Its Anti-HIV Activity

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Summary: Enantiomerically pure (+)-BCH-189 has been synthesized from D-mannose via 1,6-thioanhydro-D-mannose and its anti-HIV activity has been determined in peripheral blood mononuclear cells.

Since the discovery of AZT[1] as a potent anti-HIV agent, a number of nucleosides have been identified as potentially useful antiviral agents for AIDS and AIDS-related complex.[2-4] More recently several unusual types of nucleosides have been shown to be potent anti-HIV agents, including (±)-BCH-189,[5] dioxolane-T,[5,6] 6-(phenylthio)acyclonucleosides (HEPT),[7,8] and 4′-azidothymidine.[9]

Dioxolane-T and BCH-189 are particularly interesting in that the 3′-CH_2 groups of the 2′,3′-dideoxyribose moieties are replaced by oxygen and sulfur atoms, respectively (Figure 1). (±)-Dioxolane-T[5,6] has been reported to exhibit a moderate anti-HIV activity (EC_{50} = 20 μM) in ATH8 cells as a racemic mixture. Recently, we have synthesized the enantiomerically pure (−)-β-dioxolane-T and evaluated the anti-HIV activity in human peripheral blood mononuclear cells (PBM).[10] In contrast to the previous report of (±)-dioxolane-T in the ATH8 cells,[6] the enantiomerically pure (−)-β-D-dioxolane-T exhibited a potent anti-HIV activity (EC_{50} = 0.3 μM) in human PBM cells.[10] (±)-BCH-189 is a promising nucleoside with potent anti-HIV activity and low toxicity in vitro. (±)-BCH-189 is currently undergoing preclinical toxicology and is expected to undergo clinical trials in the near future. Thus, it was of interest to synthesize the enantiomerically pure form of BCH-189 and determine its anti-HIV activity. We report here the first asymmetric synthesis of enantiomerically pure (+)-BCH-189 and its anti-HIV activity in human PBM cells.

Retrosynthetic analysis of BCH-189 suggests that 1,6-thioanhydro-D-mannose (5) can serve as a chiral intermediate for the synthesis of enantiomerically pure BCH-189. The 1,6-thioanhydro-D-mannose (5) was prepared in five steps from D-mannose (1) (Scheme I). Selective tosylation of the primary hydroxyl group of D-mannose followed by acetylation gave 1,2,3,4-tetra-*O*-acetyl-6-*O*-tosyl-D-mannose (2) in 96.7% yield as a foam, which, without further purification, was converted to the bromo sugar 3 (97.6%) by treatment with 2 molar equiv of HBr/HOAc (45% w/v) using acetic acid as solvent. The bromo sugar 3 was treated with 3 molar equiv of potassium *O*-ethylxanthate in DMF using a similar methodology as used previously by Akagi et. al.[11] and Whistler and Seib[12]

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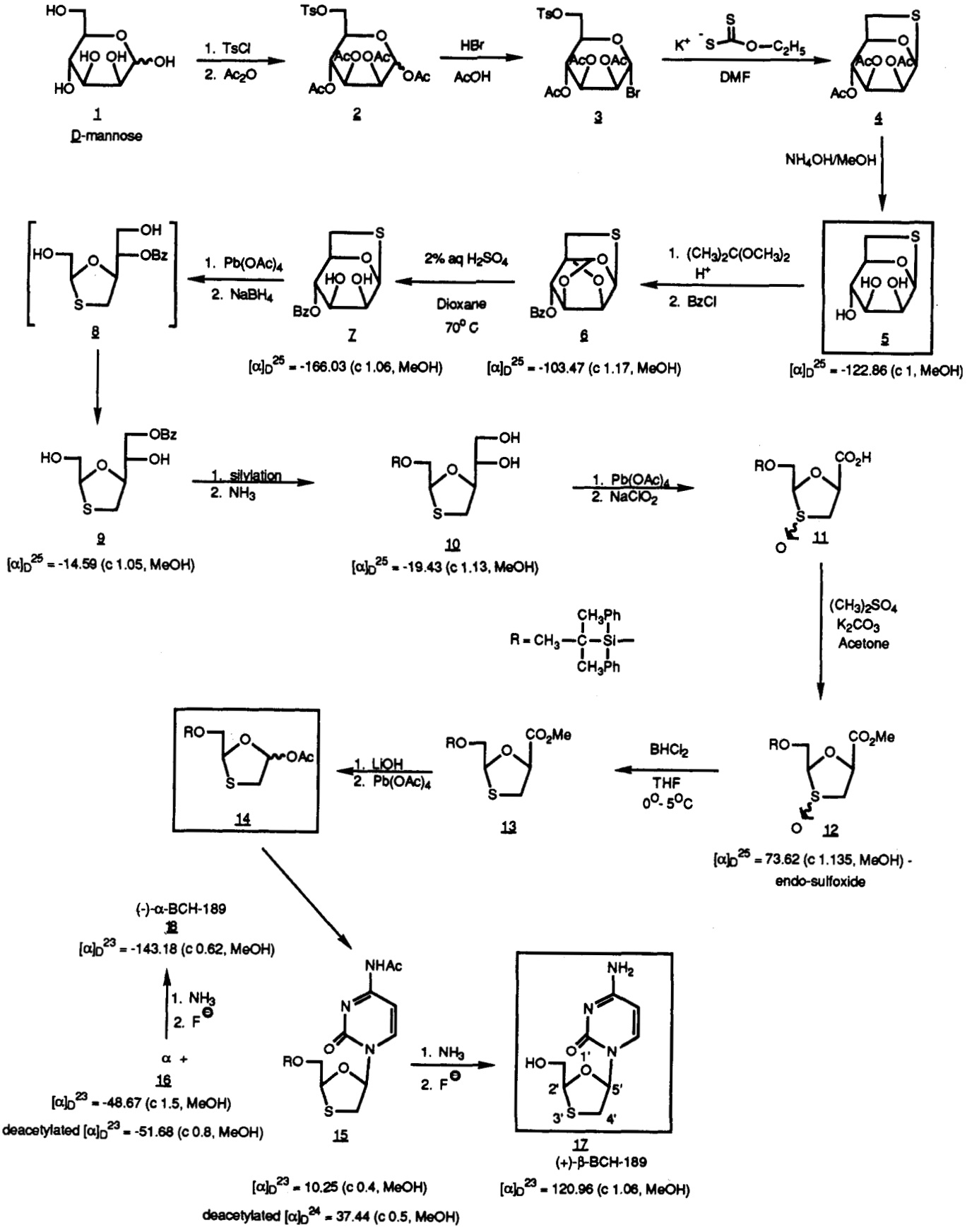
Scheme I



for the synthesis of 1,6-thioanhydroglucose and 1,6-thioanhydrogalactose, respectively, to give 2,3,4-triacetyl-1,6-thioanhydro-D-mannose (4). Compound 4 could be isolated but was usually converted to 1,6-thioanhydro-D-mannose

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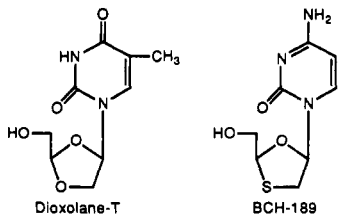

Figure 1.

(5)[13] (39.3% from 3) by treatment with NH_4OH in methanol. To the best of our knowledge, this is the first report of a 1,6-thioanhydro compound in the mannose series. Protection of the 2,3-cis-diol 5 as its isopropylidene followed by benzoylation gave 6. The isopropylidene group was removed using 2% aqueous H_2SO_4 in dioxane at 70 °C to give the diol 7 (85% from 5). Oxidative cleavage of 7 with $Pb(OAc)_4$ followed by reduction with $NaBH_4$ gave 8 as an intermediate. Under the reaction conditions, 8 underwent a secondary to primary benzoyl migration to give 9 (97%). Silylation of 9 using *tert*-butyldiphenylsilyl chloride effected selective primary silylation followed by removal of the benzoyl protection using NH_4OH in methanol gave the diol 10 (83%).

Treatment of diol 10 with $Pb(OAc)_4$ gave the aldehyde, which, without isolation, was further oxidized by treatment with sodium chlorite[14] to give the acid 11 as a crude mixture of endo and exo sulfoxides (~70%). The crude mixture of sulfoxide acids 11 was converted to their corresponding methyl esters 12 by treatment with dimethyl sulfate in order to facilitate the purification as well as sulfoxide reduction to sulfide in organic solvent. The sulfoxide esters 12 were converted to sulfide 13 (80%) by reduction with dichloroborane–dimethylsulfide in dry THF.[15] Hydrolysis of the ester 13 with LiOH in THF/H_2O (4:1) gave the acid, which, without purification, was converted to the acetate 14 (64%) by treatment with $Pb(OAc)_4$/pyridine in EtOAc.[6,16] The crude acetate 14 was isolated by filtration through a short silica gel pad to remove lead salts and used for the next reaction without further purification. Condensation of 14 with *N*-acetylcytosine in 1,2-dichloroethane in the presence of trimethylsilyl triflate[17] gave a β:α mixture (2:1) of 15 and 16 (50%).[18] Separation on a silica gel column followed by deacetylation with NH_3 in methanol and desilyation with tetra-*n*-butylammonium fluoride gave the desired β-17[19] and α-18[20] isomers.

The anti-HIV activity of 17 and 18 was evaluated in human PBM cells. The (+)-β-BCH-189 (17) exhibited potent anti-HIV activity (EC_{50} = 0.32 μM), which suggests that the (+) enantiomer of BCH-189 is slightly less potent than the racemic mixture (EC_{50} = 0.06 μM) in PBM cells.[21] No effect on cell viability was apparent when PBM cells were cultivated for 6 days in the presence of 100 μM of 17. Using a chiral column,[22] the (+) enantiomer of racemic BCH-189 was separated from the (−) enantiomer; the (+) enantiomer had an identical retention time to a sample of 17 obtained from D-mannose, suggesting that it is enantiomerically pure. The activity against HIV-1 of the (+)-β enantiomer obtained by HPLC was similar to that obtained with compound 17. As expected, the (−)-α-BCH-189 (18) did not show any significant anti-HIV activity when tested up to 100 μM. These results have prompted us to synthesize the (−)-β enantiomer by a similar route, which is in progress.

In summary, the synthesis of enantiomerically pure (+)-β-BCH-189 has been accomplished utilizing a carbohydrate chiral template (5).[23] The structure–activity relationships of 1,3-oxathiolanyl nucleosides as anti-HIV agents and exploring this synthetic methodology as a general approach for the synthesis of new classes of enantiomerically pure nucleosides are in progress in our laboratory.

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(13) mp 220 °C dec; ^1H NMR (DMSO-d_6) δ 2.9 (d, J = 12.96 Hz, 1 H, 6a-H), 3.05 (dd, J = 3.5, 12.96 Hz, 1 H, 6b-H), 3.55 (m, 2 H, 2-H and 3-H), 3.8 (m, 1 H, 4-H), 4.3 (d, J = 3.73 Hz, 1 H, OH), 4.65 (m, 1 H, 5-H), 4.8 (d, J = 7.03 Hz, OH), 5.1 (d, J = 4.83 Hz, 1 H, 1-H), 5.2 (d, J = 3.73 Hz, 1 H, OH). $[\alpha]^{25}_D$ = −122.86° (*c* 1.0, MeOH). Anal. Calcd for $C_6H_{10}O_4S$: C, 40.45; H, 5.62; S, 17.97. Found: C, 40.46; H, 5.68; S, 17.91.

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(19) mp, softens at 140 °C and melts at 145–147 °C; $[\alpha]^{23}_D$ = 120.96° (*c* 1.06, MeOH); ^1H NMR (DMSO-d_6) δ 3.03 (dd, $J_{5',4'a}$ = 4.4 Hz, $J_{4'a,4'b}$ = 11.86 Hz, 1 H, 4'a-H), 3.43 (dd, $J_{5',4'b}$ = 5.3 Hz, $J_{4'a,4'b}$ = 11.86 Hz, 1 H, 4'b-H), 3.80 (t on D_2O exchange goes to d, $J_{2',2'\text{-}CH_2OH}$ = 4.17 Hz, 2 H, 2'-CH_2OH), 5.22 (t, $J_{2',2'\text{-}CH_2OH}$ = 4.17 Hz, 1 H, 2'-H), 5.27 (t, $J_{2'\text{-}CH_2OH}$ = 4.6 Hz, 1 H, 2'-CH_2OH), 5.88 (d, $J_{5,6}$ = 7.47 Hz, 1 H, H-5), 6.21 (J = 5.05 and 4.84 Hz, 1 H, 5'-H), 7.19 (br s, 2 H, NH_2), 7.89 (d, $J_{5,6}$ = 7.47 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). Anal. Calcd for $C_8H_{11}O_3N_3S$: C, 41.92; H, 4.8; N, 18.3; S, 13.9. Found: C, 41.71; H, 4.76; N, 18.06; S, 13.83.

(20) mp, softens at 145 °C and melts at 154–156 °C; $[\alpha]^{23}_D$ = −143.18° (*c* 0.62, MeOH); ^1H NMR (DMSO-d_6) δ 3.08 (dd, $J_{5',4'a}$ = 2.64 Hz, $J_{4'a,4'b}$ = 12.08 Hz, 1 H, 4'a-H), 3.46 (dd, $J_{5',4'b}$ = 5.05 Hz, $J_{4'a,4'b}$ = 12.08 Hz, 1 H, 4'b-H), 3.54 (t on D_2O exchange goes to d, $J_{2',2'\text{-}CH_2OH}$ = 5.05 Hz, 2 H, 2'-CH_2OH), 5.16 (t, $J_{2'\text{-}CH_2OH}$ = 5.7 Hz, 1 H, 2'-CH_2OH), 5.53 (t, $J_{2',2'CH_2OH}$ = 5.05 Hz, 1 H, 2'-H), 5.83 (d, $J_{5,6}$ = 7.47 Hz, 1 H, H-5), 6.36 (dd, $J_{5',4'a}$ = 2.64 Hz, $J_{5',4'b}$ = 5.05 Hz, 1 H, 5'-H), 7.16 (br s, 2 H, NH_2), 7.63 (d, $J_{5,6}$ = 7.47 Hz, 1 H H-6); UV H_2O λ_{max} (pH = 7) 271 (9800), (pH = 2) 279 (14000), (pH = 11) 271 (10000). Anal. Calcd for $C_8H_{11}O_3N_3S$: C, 41.92; H, 4.8; N, 18.3; S, 13.9. Found: C, 41.73; H, 4.94; N, 18.08; S, 13.82.

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(22) The enantiomers of (±)-BCH-189 were separated using a Micrometrics (Norcross, GA) HPLC system equipped with a chiral column (Cyclobond I-Ac, Rainin, Woburn, MA, catalog no. AST-41049). An isocratic solvent was used which was composed of 0.5% MeOH in H_2O, at a flow rate of 0.7 mL/min. The material (100–200 μM) was injected into a 10-μL loop and the peaks containing the compounds were detected by UV set at 262 nm. Fractions were collected every 12 s. The retention time for (−)-β and (+)-β enantiomers of BCH-189 were 12.5 min and 13.5 min, respectively.

(23) All the reported compounds in Scheme I gave correct elemental analyses (±, 0.4%) except 14, which is too unstable to be fully characterized.