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Synthesis of *cis*-(±)–2-Hydroxymethyl-5-(Cytosine-1′-yl)-1,3-Oxathiolane (BCH-189)

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Abstract: The target compound BCH-189 was synthesized with high yield *via* four steps from benzoyloxy acetylaldehyde and *p*-dithiane-2,5-diol as starting materials. The synthetic route is preferable to what literature reported.

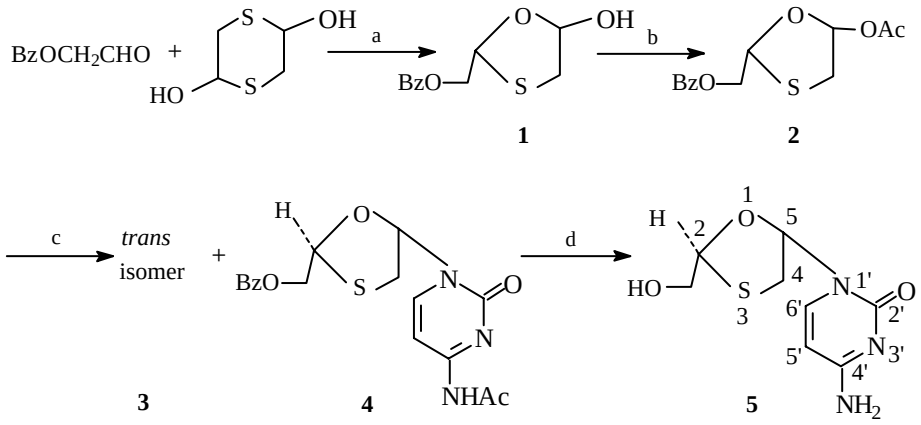
Keywords: Anti-HIV, total synthesis, BCH-189.

cis-BCH-189 are potent anti-HIV agents and have been synthesized from mannose[1] galactose[2] or glucose[3] *etc*. Owing to so many synthetic steps, it is difficult and expensive to obtain a few grams. In this paper, we have designed new route and promoted the reaction conditions for the synthesis of this nucleoside *cis*- (±)- BCH-189 from cheap starting material *via* a four step route as shown in **Scheme 1**. By this method, a series of derivatives of title compound can be synthesized conviniently for finding new prodrug.

A mixture of benzoyloxy acetylaldehyde (4.2 g, 27.5 mmol) and *p*-dithiane-2, 5-diol (8.3 g, 50 mmol) in CH_3CN (200 mL) and a catalytic amount of *p*-TsOH was refluxed for 8 h under N_2. Evaporated CH_3CN and neutralized with saturated $NaHCO_3$ solution, extracted with EtOAc (150 mL × 3) and washed with saturated NaCl solution, then dried over anhydrous $MgSO_4$, filtered, after solvent was evaporated, the colorless syrup **1** was obtained. **1** reacted with acetyl chloride (5.34 mL, 75 mmol) in the presence of Et_3N (10.4 mL, 75 mmol) at 0^oC for 1 h and then kept at room temperature over night, CH_2Cl_2 (50 mL) was added and washed with saturated $NaHCO_3$ and NaCl solution successively, dried over $MgSO_4$, filtered and evaporated solvent, the residue was purified by silica gel column with eluent (petroleum/acetate = 50/1 ~ 30/1) to afford product **2** as colorless syrup 7.85 g (two steps total yield 55.7%). Under Ar atmosphere, at 0-5^oC, solution of **2** (23.54 g, 83.5 mmol) in anhydrous CH_2Cl_2 (50 mL) and Lewis acid $SnCl_4$ (19.5 mL, 167 mmol) were added by turn through syringe to the silylated N_4-acetyl-cytosine (22.6 g, 100.2 mmol) in the same solvent, the mixture was stirred over night at room temperature, the organic solution was washed with saturated $NaHCO_3$ solution, extracted with CH_2Cl_2 and dried over $MgSO_4$, after solvent evaporation, the residue was purified and separated by silica gel column using EtOAc/MeOH (100/1) as

eluent yielding *trans* isomer **3** 4.34 g (mp 158-160°C) and *cis* isomer **4** as a white powder 13.0 g (mp 150-152°C) (combined yield 55.3%). **4** (5.63 g, 15 mmol) was deprotected with K_2CO_3 (2.07 g, 15 mmol) in methol (100 mL) at ambient temperature stirred for about 4 h, the resulting clear solution was filtered, after solvent evaporation, the product was purified by silica gel column using EtOAc/MeOH (6/1) as eluent to afford white powder of target compound **5** 3.37 g (mp 171-173°C) (yield 98.1%). All the solvent were removed under reduced pressure. The structures of all the compounds were characterized by ^{1}H-NMR and ^{13}C-NMR using a varian unity 400 spectrometer.

Scheme 1 The synthetic route of *cis*-BCH-189



a) *p*-TsOH, CH_3CN, reflux; b) CH_3COCl, Et_3N, 0°C-rt; c) N_4-silylated-acetyl-cytosine, $SnCl_4$, CH_2Cl_2, 0°C-rt; d) K_2CO_3, MeOH, rt.

References and Notes

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4. Data of compound 5: ^{1}H-NMR (DMSO, δ ppm, J (Hz)): 7.94 (d, 1H, J = 7.6, H-6'), 7.35 (d, 2H, J = 24.4, NH_2), 6.32 (t, 1H, J = 5.2, H-5), 5.85 (d, 1H, J = 7.2, H-5'), 5.43 (t, 1H, J = 6.0, CH_2OH), 5.28 (t, 1H, J = 4.8, H-2), 3.85 (m, 2H, CH_2OH), 3.51 (dd, 1H, J = 7.6, J = 4.8, H-4), 3.16 (dd, 1H, J = 6.4, J = 5.2, H-4); ^{13}C-NMR (DMSO): 165.7 (C-4'), 154.85 (C-2'), 141(C-6'), 94 (C-5'), 86.68 (C-5), 85.93 (C-2), 62.96 (CH_2OH), 36.38 (C-4).

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