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THE CHEMICAL RESOLUTION OF RACEMIC *CIS*-2-HYDROXYMETHYL-5-(CYTOSINE-1′-YL)-1,3-OXATHIOLANE (BCH-189)—ONE DIRECT METHOD TO OBTAIN LAMIVUDINE AS ANTI-HIV AND ANTI-HBV AGENT

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ABSTRACT

Racemic *cis*-BCH-189 can be resolved to (−)-enantiomer (lamivudine) and (+)-enantiomer by esterification of *cis*-2-hydroxymethyl-5-(N_4'-acetylcytosine-1′-yl)-1,3-oxathiolane and (+)-menthyl chloroformate in CH_3CN with pyridine as base. The two diastereomers of ester were seperated by recrystallization in methanol at 0°C. Lamivudine was obtained by deprotection of (−)-diastereomer with high yield.

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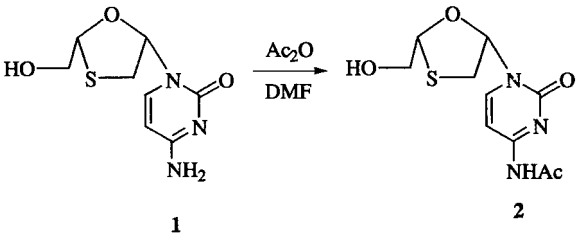
2-Hydroxymethyl-5-(cytosine-1′-yl)-1,3-oxathiolane (BCH-189) has potential biological activity as anti-HIV and anti-HBV agent, among the four enantiomers, the β-L-(−)-enantiomer (lamivudine) is considerably less toxic than other three corresponding ones.[1,2] Numerous efficient methods of optical resolution of *cis*-BCH-189 by biological enzyme using such as specially Mucor miehei lipase etc. have been reported.[3,4] However, these multistep procedures are time consuming and proceed in low yields or low enantiomer purity.

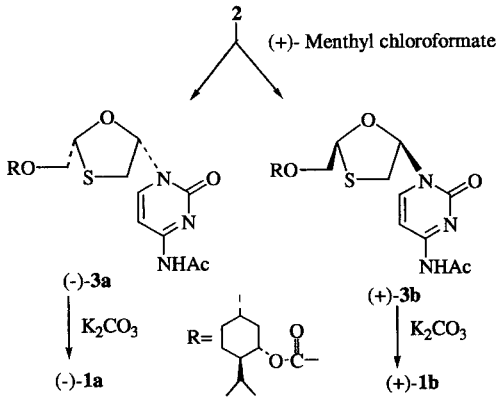
In this article, we report a new, inexpensive, practical, and efficient method for the resolution of racemic *cis*-BCH-189, (−)-camphanic acid chloride and (+)-menthyl chloroformate were chosen as resolving agents. We found that the former almost has no effect for the resolution but the latter is an excellent resolving agent for resolution of racemic *cis*-BCH-189 in the solvent of methanol.

The NH_2 group of racemic *cis*-BCH-189 was firstly protected by acetylation using the equivalent molar Ac_2O in DMF at room temperature to afford the corresponding N_4-acetyl-BCH-189 (**2**) in 95% chemical yield as shown in Scheme 1. Racemic compound **2** reacts with (+)-menthyl chloroformate in presence of 3 equivalent molar pyridine to give a mixture of two diastereomers of (−)-**3a** and (+)-**3b**. Complete seperation of the two diastereomers was achieved in a single recrystallization from methanol at 0°C. The (−)-**3a** crystallized firstly in needle form, the diastereoisomer (+)-**3b** crystallized by concentration of the mother liquor followed by cooling to 0°C for one day. After deprotection of (−)-**3a** and (+)-**3b**, the enantiomers of (−)-**1a** (lamivudine) and (+)-**1b** were obtained with yield 45.7 and 73.6%, respectively, from **1** as shown in Scheme 2. The specific rotation of lamivudine thus obtained was $[\alpha]_D^{20} - 137^\circ$ (c 0.21, MeOH), comparing with that reported in literatures showing $[\alpha]_D^{22} - 135^\circ$ (c 1.01, MeOH)[5] and $[\alpha]_D^{21} - 135^\circ$ (c 0.38, MeOH) in 96% ee,[6] the lamivudine obtained in this word should have the optical purity >97% and (+)-enantiomer $[\alpha]_D^{20} + 34.1^\circ$ (c 0.20, MeOH) should have the optical purity only 29% relative to lamivudine.



1 2

Scheme 1.



Scheme 2.

In conclusion, the present work offers a simpler resolution method of racemic *cis*-BCH-189 to enantiomerically pure lamivudine. So, it is conveniently to prepare multi-gram quantities of this important nucleoside analogue.

EXPERIMENTAL SECTION

Measurements and Materials

^{1}H-NMR spectra were recorded on a VARIAN UNITY 400. The chemical values δ were expressed in ppm relative to tetramethylsilane. Elemental analysis were performed using Vario EL apparatus. The melting points were determined on a RY-1 apparatus and were uncorrected. The optical rotation readings were obtained on a 341LC polarimeter. All solvents used in reactions dried and distilled before use according to standard procedures. (+)-Menthyl chloroformate was bought from ACROS. *Cis*-BCH-189 was synthesized in our laboratory according to the literature.[7]

Preparation of *cis*-2-Hydroxymethyl-5-(N_4'-acetylcytosine-1′-yl)-1,3-oxathiolane (2)

Ac_2O (0.1 mL) was added drop by drop to **1** (0.229 g, 1.0 mmol) in anhydrous DMF (10 mL) with stiring at room temperature under N_2

protection, the mixture was kept over night. Then, solvent evaporated under vacuo and toluene (5 mL) was added to the mixture and evaporated under the same conditions. The product was obtained by silica gel column chromatography using EtOAc and MeOH (5 : 1) as eluent yielding white powder 0.26 g, yield 95%. M.p. 164°C (dec). ^{1}H-NMR (DMSO) δ: 2.21 (s, 3H), 3.30–3.33 (dd, 1H), 3.65–3.69 (dd, 1H), 3.92–3.95 (m, 2H), 5.37 (t, 1H), 5.56 (t, 1H), 6.32 (t, 1H), 7.31 (d, 1H), 8.51 (d, 1H), 11.01 (s, 1H). Anal. calcd for $C_{10}H_{13}O_4N_3S$: C, 44.28; H, 4.80; N, 15.50; S, 11.81; Found: C, 44.35; H, 4.91; N, 15.40; S, 11.75.

Preparation of Diasteromerically Pure Menthyl Esters (3)

(+)-Menthyl chloroformate (3 mL, 13.6 mmol) was dripped to the solution of **2** (3.70 g, 13.6 mmol) in CH_3CN (100 mL) and pyridine (3.5 mL, 40 mmol) with stirring at 0°C under N_2, then kept for 48 h. Removal of the solvent under vacuo condition gave the light yellow residue, purified through silica gel column with ethyl acetate as eluent to afford white solid (±)-**3** 4.50 g in a 73% chemical yield. ^{1}H-NMR ($CDCl_3$) δ: 0.78 (d, 3H), 0.81 (d, 3H), 0.91 (d, 3H), 0.86–2.06 (m, 10H), 2.28 (s, 3H), 3.19–3.23 (dd, 1H), 3.61–3.65 (dd, 1H), 4.51–4.65 (m, 2H), 5.41 (s, 1H), 6.34 (s, 1H), 7.46 (dd,1H), 8.22 (dd, 1H), 9.47 (s, 1H). Anal. calcd for $C_{21}H_{31}O_6N_3S$: C, 55.60; H, 6.84; N, 9.27; S, 7.06; Found: C, 55.41; H, 6.50; N 9.18; S, 7.32.

Preparation of Diasteromers of (−)-3a and (+)-3b

Menthyl esters (±)-**3** (4.50 g) in methanol (100 mL) refluxed for 0.5 h under N_2 and then kept in refrigerator for one day, filtered, and the solid was recrystallized from methanol (50 mL) two times, the (−)-**3a** was obtained as white needle crystals 1.56 g, theory yield 50.6%. M.p. 186–188°C. $[\alpha]_D^{20} - 12.5^\circ$ (c 0.01, $CHCl_3$).

All the filtrate were collected and concentrated to a quarter volume, and cooled at 0°C, white solid (+)-**3b** was obtained 2.51 g, theory yield 81.5%. M.p. 136–138°C. $[\alpha]_D^{20} + 56.3^\circ$ (c 0.01, $CHCl_3$).

Preparation of the Enantiomers of (−)-1a (Lamivudine) and (+)-1b

A mixture of (−)-**3a** (0.6 g, 1.32 mmol) and K_2CO_3 (0.54 g, 3.97 mmol) in MeOH (50 mL) was stirred at 0°C for about 10 h. The resulting clear solution was filtered and after solvent evaporation, the product was purified

by silica gel column chromatography with EtOAc and MeOH (6 : 1) as eluent yielding white solid 0.29 g, yield 95%. M.p. 156°C (dec). $[\alpha]_D^{20} - 137^\circ$ (c 0.21, MeOH). ^{1}H-NMR (DMSO) δ: 3.01–3.05 (dd, 1H), 3.32–3.42 (dd, 1H), 3.70–3.74 (m, 2H), 5.16 (t, 1H), 5.29 (t, 1H), 5.73 (dd, 1H), 6.20 (t, 1H), 7.17–7.22 (dd, 2H), 7.81 (dd, 1H). Anal. calcd for $C_8H_{11}O_3N_3S$: C, 41.91; H, 4.84; N, 18.33; S, 13.99. Found: C, 41.81; H, 4.98; N, 18.25; S, 13.72.

(+)-**3b** was deprotected according to the above method to afford white solid (+)-**1b** also in 95% yield. M.p. 153°C (dec). $[\alpha]_D^{20} + 34.1^\circ$ (c 0.20, MeOH), optical purity 29%. ^{1}H-NMR (DMSO) δ: 3.01–3.05 (dd, 1H), 3.32–3.42 (dd, 1H), 3.70–3.74 (m, 2H), 5.16 (t, 1H), 5.29 (t, 1H), 5.73 (dd, 1H), 6.20 (t, 1H), 7.17–7.22 (dd, 2H), 7.81 (dd, 1H). Anal. calcd for $C_8H_{11}O_3N_3S$: C, 41.91; H, 4.84; N, 18.33; S, 13.99. Found: C, 41.85; H, 4.78; N, 18.25; S, 14.11.

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