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EXPEDITIOUS PREPARATION OF (-)-2'-DEOXY-3'-THIACYTIDINE (3TC)

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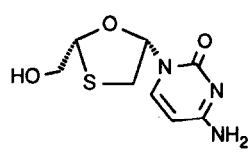
Summary : The title compound has been prepared in enantiomerically pure form in four steps from (+)-thiolactic acid.

2'-Deoxy-3'-thiacytidine (BCH 189)[1] is a nucleoside analogue in which the ribose is replaced by a 1,3-oxathiolane ring. It has been shown that both enantiomers of this structurally interesting compound are equipotent against human immunodeficiency virus types 1 and 2 *in vitro*. However, the (-)-enantiomer (1) (absolute configuration as shown) is considerably less cytotoxic than the (+)-enantiomer[2], and is currently undergoing clinical evaluation.

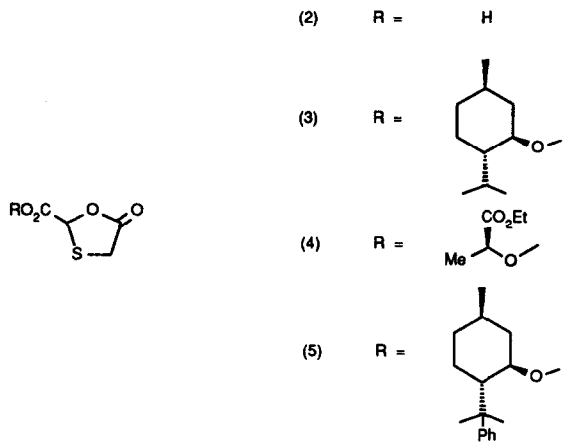
The racemic compound represents a significant challenge to the synthetic chemist, requiring control of relative stereochemistry of two potentially epimerizable acetal centres. Considerable progress has been achieved in developing conditions for high β-stereoselectivity in glycosylation reactions[3]. However, the maintenance of optical purity in a chiral synthesis of 3TC (1) requires that no epimerization of the O,S acetal occurs during coupling, as this would lead to a racemic product. The recent reports of the syntheses of the (+) enantiomer from D-mannose[4] (21 steps) or D-galactose[5] (18 steps) and of the (-)-enantiomer from L-gulose[6] (16 steps) prompt us to disclose our own efforts directed towards the synthesis of the clinically significant (-) enantiomer (3TC).



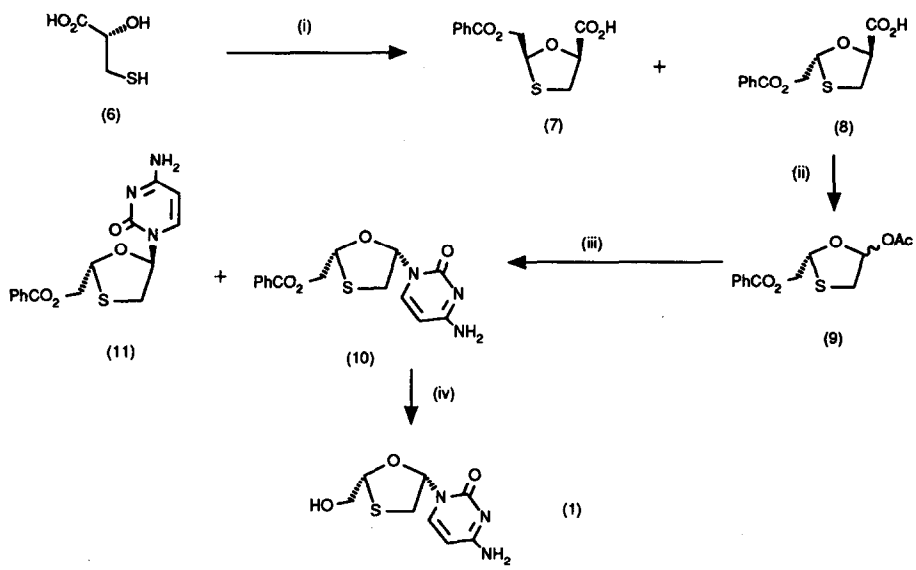
(1) **3TC**

Following resolution of chiral esters (3)-(5) derived from acid (2), initial attempts to prepare benzoate (9) by reduction failed owing to racemization and ring opening under the conditions used[7].

In a successful approach, condensation[8] of (+)-thiolactic acid (6)[9] with 2-benzoylacetaldehyde occurred upon exposure to boron trifluoride etherate, to give a 1:2 mixture of diastereomeric oxathiolane acids (7) and (8) in 75% yield (Scheme 1). The less polar acid (8)[10] (96%ee, m.pt. 105-106°C, $[\alpha]_D^{22}$+66.4°(c=1.0,$CHCl_3$))[11] separated by chromatography on silica gel, was treated with lead tetraacetate in dimethyl formamide to furnish an anomeric mixture (2:1) of the *anti* and *syn* acetates (9) in 64% yield[12].



When this mixture (9) was treated with silylated cytosine in the presence of stannic chloride[13], (10) and (11) were obtained in a 10:1 ratio. However, the products were racemic as judged by chiral HPLC of the debenzoylated material[14]. This result is in agreement with the recent findings of Chu and co-workers[6]. One possible explanation for this is opening and closing of the oxathiolane ring under the reaction conditions; this may preclude the use of such Lewis acids in the preparation of chiral oxathiolane surrogates of nucleosides.



(i) $PhCO_2CH_2CHO$, $BF_3.Et_2O$, CH_3CN. (ii) $Pb(OAc)_4$, DMF. (iii) Silylated Cytosine, TMSI, $C_2H_4Cl_2$ (iv) Amberlite IRA400(OH), EtOH, Δ.

Scheme 1

In order to overcome this limitation, we have applied a direct coupling technique using silylated cytosine and (9) in the presence of iodotrimethylsilane (1.1 equivalents). From this reaction, the nucleoside products (10) and (11) were isolated in 83% yield in a ratio of 1.3:1. After chromatographic separation, the enantiomeric purity of (10) was determined by NMR spectroscopy using the chiral shift reagent (R)-2,2,2-trifluoro-1-(9-anthryl)ethanol. Thus by comparison with a racemic sample the compound (10) was judged to be of 96%ee. It is not yet known if the glycosylation reaction passes through the intermediacy of an oxonium ion or an anomeric iodide species.

That TMSI is a suitable catalyst for this reaction is interesting in view of its ability to open oxathiolane rings[15]. Clearly under these conditions, no loss of thioacetal integrity is seen. Final deprotection to 3TC (1) was accomplished by treatment of (10) with basic resin in boiling ethanol, to furnish the enantiomerically pure crystalline product (m.pt. 160-2°C, $[\alpha]_D^{21}$-135° (c=0.38, MeOH))[14].

In conclusion, the route to (-)-3TC we present here represents a rapid entry to enantiomerically pure material, which is potentially amenable to the preparation of multi-gram quantities of this important nucleoside analogue.

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7. Acid (2) (m.p. 140-143°C) was prepared by a modification of the literature procedure. J. L. Kraus and G. Attardo, *Synthesis*, 1991, 1046.

   (3): m.pt. 71-72°C, $[\alpha]_D^{22}$+22.5° (c=1, $CHCl_3$), ^1H NMR ($CDCl_3$) δ 0.75 (d, 3H, 6Hz), 0.85-1.12 (m, 9H), 1.50 (m, 2H), 1.70 (bd, 2H), 1.92 (m, 1H), 2.05 (m, 1H), 3.56 (d, 1H, 17Hz), 3.82 (d, 1H, 17Hz), 4.78 (dt, 1H, 8Hz, 4Hz), 5.63 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 16.74, 21.25, 22.49, 23.86, 26.69, 30.06, 31.97, 34.59, 41.10, 47.64, 74.26, 77.73, 168.10, 172.86.

   (4): m.pt. 74-75°C, $[\alpha]_D^{22}$+98.3° (c=1, $CHCl_3$), ^1H NMR ($CDCl_3$), δ 1.30 (t, 3H, 7Hz), 1.56 (d, 3H, 7Hz), 3.58 (d, 1H, 16Hz), 3.89 (d, 1H, 19Hz), 4.24 (q, 2H, 7Hz), 5.22 (q, 1H, 7Hz), 5.75 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.62, 17.35, 28.90, 62.44, 70.87, 74.05, 167.60, 170.12, 172.80.

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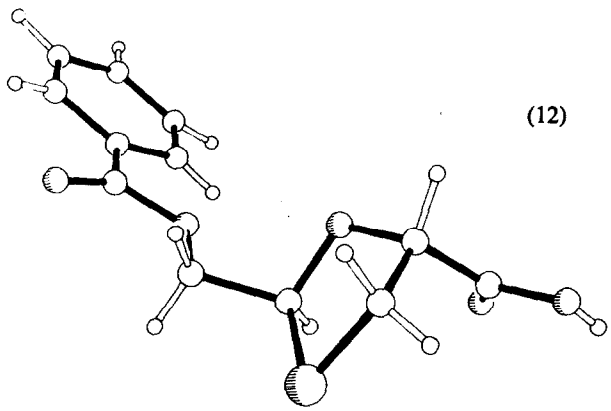
10. Relative and absolute stereochemistry of the less polar acid was confirmed by a single crystal X-ray diffraction study of its enantiomer (12) prepared analogously from (-)-thiolactic acid.



(12)

11. (+)-Enantiomer: R_t= 21.0 min., (-)-enantiomer: R_t = 26.8 min., Column: Techocel OA 2500, 250x4.6mm.,Eluant: 20mM NH_4OAc in methanol, Flow: 1.0ml/min., Detection at 230nm.
12. No sulfoxides corresponding to (9) were observed.
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14. (-)-3TC: R_t = 6.46 min., (+)-3TC: R_t = 6.98 min., Column: Astec cyclobond acetyl, 250x4.6mm., Eluant: 0.2% triethylammonium acetate, Flow: 1.0ml/min., Detection at 235nm.
15. G. E. Keyser, J. P. Bryant and J. R. Barrio, *Tetrahedron Lett.*, 1979, *20*, 3236.

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