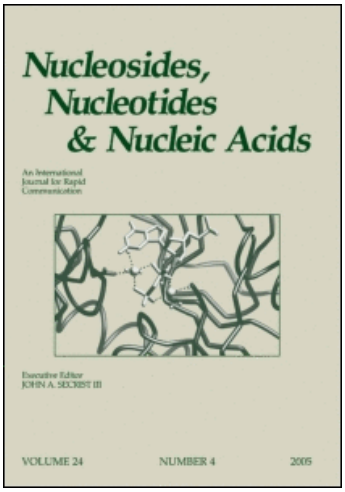

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Asymmetric Synthesis of Optically Active 1,3-Oxathiolane Nucleoside Analogues

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ASYMMETRIC SYNTHESIS OF OPTICALLY ACTIVE 1,3-OXATHIOLANE NUCLEOSIDE ANALOGUES

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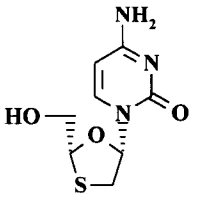
ABSTRACT. A ready asymmetric synthesis of 3'-oxa-4'-thionucleosides has been accomplished in three main steps from benzoyloxyethanal. The synthesis is characterized by high overall yield and appreciable enantiomeric excesses. It represents a general synthetic scheme to prepare a wide range of heterosubstituted sulfur-containing nucleoside analogues.

Acquired Immunodeficiency Syndrome (AIDS) has become a modern day scourge and, clearly, the need for new drugs effective in anti-HIV therapies is of the utmost importance.

Nucleoside analogues have long been known as antiviral agents because of their ability to interfere with DNA synthesis by inhibiting DNA polymerase[1]. Large numbers of analogues have been synthesized and tested, but very few have been approved for clinical testing, either for lack of activity or for excessive toxicity. Recently[2], several members of the heterosubstituted 2',3'-dideoxynucleoside analogues class were discovered to be active against HIV and hepatitis-B viruses *in vitro*. Their common structural characteristic is the presence of a heteroatom which replaces the 3' ribose carbon. An outstanding clinical candidate emerged from these compounds is β-L-(-)-2'-

deoxy-3'-thiacytidine[3] (lamivudine, 3TC™) (**1**) that was recently approved by FDA for the treatment of AIDS.



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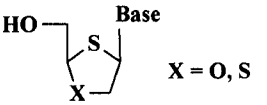


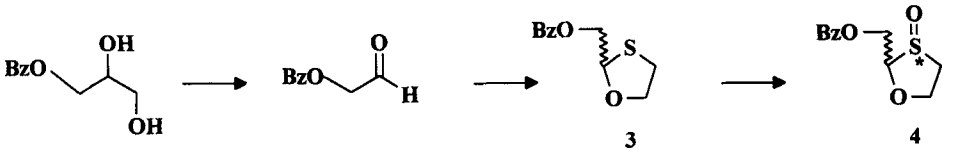
2

It is noteworthy[4] that this compound showed much lower cytotoxicity than its antipode, the D-enantiomer, although both of them were almost equipotent against the replication of HIV-1 and -2 *in vitro*. 4'-Thianucleosides like **2**, possessing a second heteroatom such as oxygen or sulfur at the 3' position, were also reported[5] to have good to excellent antiviral activity.

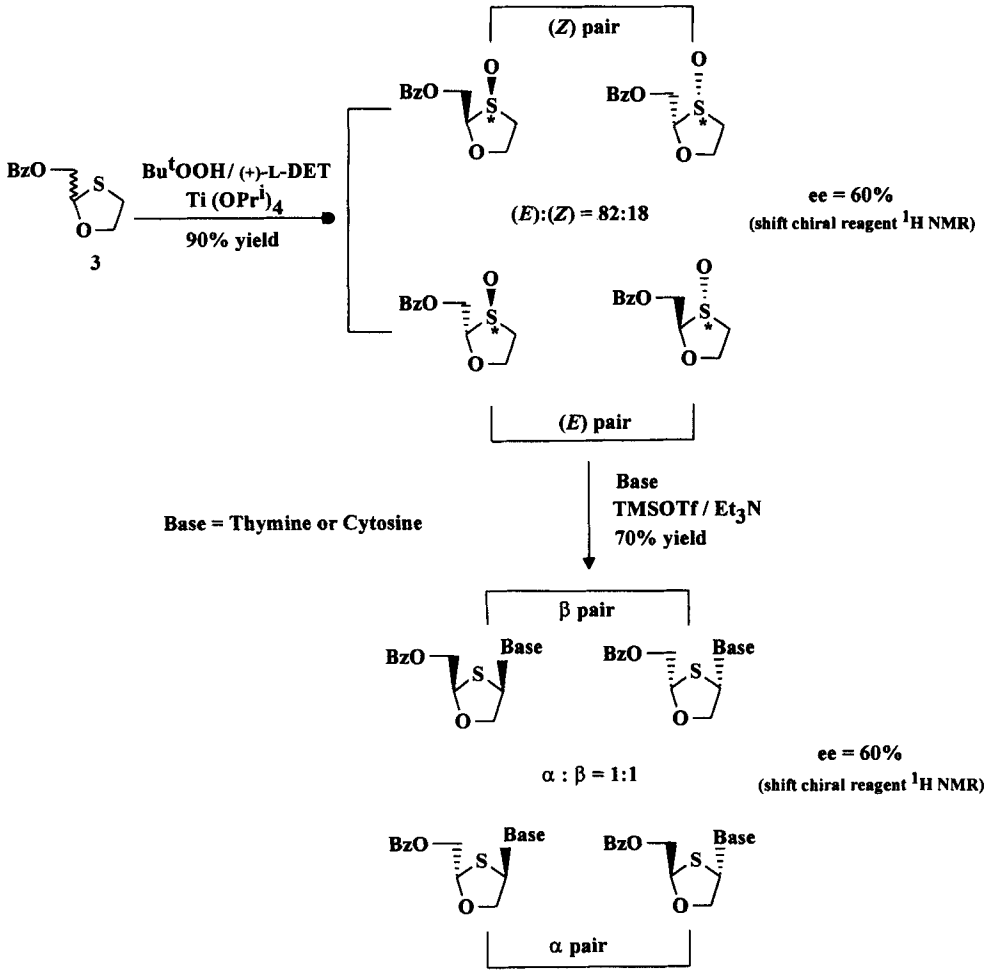
Several methods[6] are available from the current literature to synthesize heterosubstituted nucleoside analogues. Notwithstanding, the real bottle-neck of their preparation is represented by the difficulty of achieving such compounds in optically pure form. This is, in fact, mostly performed by resolution of their racemic mixtures[5].

We are now approaching a new asymmetric synthesis to achieve chiral 3'-oxa-4'-thionucleosides (2,4-disubstituted 1,3-oxathiolanes) in enantiomerically pure forms from 1-*O*-benzoylglycerol[7].

The key step of our procedure was the preparation of the chiral sulfoxide **4** (Scheme 1). Racemic 2-[(phenylcarbonyloxy)methyl]-1,3-oxathiolane **3** was obtained in very high yield (98%) by treatment of benzoyloxyethanal (from benzoylglycerol) with mercaptoethanol in presence of polystyryl diphenylphosphine-iodine complex, which acted as Lewis acid and dehydrating agent as well, according to a procedure[8] developed in our lab. The conversion of **3** into the chiral sulfoxide **4** was then performed *via* a modified Sharpless oxidation[9] by *t*-butyl hydroperoxide and L-diethyl tartrate in presence of Ti^{IV} isopropoxide as catalyst (Scheme 2). The oxidation led in high yield (90%) to a mixture of the diastereomeric (*E*) and (*Z*) pairs in a 82:18 ratio. After



Scheme 1- Synthesis of the chiral sulfoxide 4 from benzoylglycerol.



Scheme 2- Conversion of 1,3-oxathiolane 3 into 3'-oxa-4'-thionucleosides *via* chiral sulfoxide 4.

chromatographic separation, both (*E*) and (*Z*) pairs exhibited e.e.= 60% by ^{1}H NMR analysis using Eu(hfc)$_3$ (Aldrich) as chiral shift reagent.

The more abundant (*E*) pair of the chiral sulfoxide **4** was then treated with a suitable base (thymine or cytosine) under Pummerer rearrangement conditions[10] in presence of trimethylsilyl triflate and Et_3N. The chromatographic separation of the reaction mixture led to the diastereomeric α and β pairs, approximately in 1:1 ratio (70% overall yield). The ^{1}H NMR analysis of both α and β pairs, using Eu(hfc)$_3$ shift reagent, showed that no racemization occurred at 4' position during the coupling reaction of the base with the chiral sulfoxide.

Work is now in progress to determine the absolute configurations of the chiral centers in the final products. This new approach to the asymmetric synthesis of heterosubstituted nucleoside analogues may represent a rapid entry to optically pure material which is potentially amenable to the preparation of multi-gram quantities of these important compounds.

EXPERIMENTAL

^{1}H NMR spectra were recorded on Bruker AM-250 and DRX-400 spectrometers on $CDCl_3$ solutions. Chemical shifts were reported in ppm (δ) downfield from internal tetramethylsilane (TMS), and *J* were given in Hz. Optical rotations were measured on a Perkin-Elmer 141 polarimeter (1.0 dm cell lenght) for $CHCl_3$ solutions. Thin layer chromatography (TLC) analyses were performed on silica gel Merck 60 F_{254} plates (0.2 mm layer tickness). Column chromatography was carried out with Merck Kieselgel 60 (70-230 mesh). Dry solvents were distilled immediately before use. Combustion analyses were performed on a Perkin-Elmer Series II 2400 CHNS analyzer.

2-[(Phenylcarbonyloxy)methyl]-1,3-oxathiolane 3.– To a magnetically stirred suspension of polystyryl diphenylphosphine-iodine complex (22.6 mmol - iodine units; prepared *in situ*) in anhydrous acetonitrile (150 mL), at room temperature and under dry nitrogen atmosphere, a solution of benzoyloxyethanal (3.71 g; 22.6 mmol) in the same solvent (25 mL) was added *via* syringe in one portion. After 10 min, 1M mercaptoethanol in anhydrous acetonitrile (23 mL) was also added in one portion. Benzoyloxyethanal was

fully consumed (TLC monitoring) within 2 h. Solid K_2CO_3 (excess) was then added, and the suspension was stirred for a couple of minutes and eventually filtered. The residual solid was washed with chloroform (3 x 100 mL) and the combined filtrates, after shaking with 5N aq sodium thiosulfate (50 mL) and water until neutral, was evaporated under reduced pressure to leave a residue consisting of practically pure **3** (4.95 g, 98%); Elemental analysis, $C_{11}H_{12}O_3S$ requires C, 58.91; H, 5.39: found C, 59.21; H, 5.28%; ^{1}H NMR (400 MHz) δ 3.01-3.10 (2H, m, CH_2S), 3.99-4.04 (1H, m, H-5a), 4.26-4.31 (1H, m, H-5b), 4.40 (1H, dd, J = 3.8, 11.7, H-6a), 4.51 (1H, dd, J = 7.3, 11.7, H-6b), 5.48 (1H, dd, J = 3.8, 7.3, H-2), 7.41-7.48 (2H, m, aromatic H), 7.54-7.59 (1H, m, aromatic H), 8.07 (2H, d, J = 8.0, aromatic H).

3-Oxo-2-[(phenylcarbonyloxy)methyl]-1,3-oxathiolane 4.- To a solution of Ti^{IV} isopropoxide (0.7 mL, 2.4 mmol) in dry dichloromethane (15 mL) L-diethyl tartrate (1.4 mL; 9.6 mmol) dissolved in the same solvent (15 mL) was added under vigorous magnetic stirring at room temperature. After 10 min, the resulting yellow homogeneous solution was cooled to -20° C. *t*-Butyl hydroperoxide (1.6 mL, 5.7 mmol) was then added dropwise, followed after a few minutes by 1,3-oxathiolane **3** (0.54 g; 2.4 mmol) dissolved in dry dichloromethane (20 mL). The reaction mixture was mantained at -20° C under stirring for 14 h, then quenched with water (30 mL), warmed up to room temperature and filtered on Celite. The inorganic layer was extracted with dichloromethane (2 x 50 mL) and the combined dichloromethane layers, after being washed with 10% aq sodium metabisulfite (100 mL), 5% aq sodium hydroxide, and brine until neutral, were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$) and two diastereomeric sulfoxides were separated (overall yield 0.52 g, 90%): (*E*)-**4** (0.43 g); m.p. 89-91° C (from hexane/benzene); $[\alpha]_D$ = -48.3 (c = 1.1); Elemental analysis, $C_{11}H_{12}O_4S$ requires C, 54.99; H, 5.03: found C, 54.71; H, 4.96%; ^{1}H NMR (400 MHz): δ 2.68-2.77 (1H, m, H-4a), 3.14 (1H, dd, J = 3.5, 13.5, H-4b), 4.41-4.48 (1H, m, H-5a), 4.64-4.72 (1H, m, H-5b), 4.34-4.72 (3H, m, H-2 and 2 x H-6), 7.41-7.47 (2H, *m*, aromatic H), 7.52-7.61 (1H, *m*, aromatic H), 7.98 (2H, *d*, J = 8.2, aromatic H). Lower R_f sulfoxide: (*Z*)-**4** (0.09 g); oily; Elemental analysis, $C_{11}H_{12}O_4S$ requires C, 54.99; H, 5.03: found C, 55.15; H, 5.10%; ^{1}H NMR (400 MHz): δ 3.05-3.14 (1H, m, H-4a), 3.20-3.28 (1H, m, H-4b), 4.08-4.13 (1H, m, H-5a), 4.65-4.72 (4H, m, H-2, H-5b, 2 x H-6), 7.41-7.47 (2H, m, aromatic H), 7.51-7.59 (1H, m, aromatic H), 8.04 (2H, d, J = 8.2, aromatic H).

Coupling of the chiral sulfoxide (*E*)-4 with N^4-acetylcytosine. Typical procedure.- To a magnetically stirred suspension of N^4-acetylcytosine (0.13 g, 1.2 mmol) in dry toluene

(15 mL), at 0° C and under nitrogen atmosphere, trimethylsilyl triflate (TMSOTf) (0.9 mL, 5.0 mmol) and triethylamine (0.7 mL, 5.0 mmol) were added dropwise in sequence. After 20 min a suspension of sulfoxide **4** [(*E*) pair] (0.20 g, 0.8 mmol) in the same solvent (5 mL) was also added and the resulting mixture was kept under stirring overnight. After evaporation of the solvent under reduced pressure the residue was redissolved by EtOAc (15 mL), washed with 5% aq $NaHCO_3$ (2 x 10 mL) and then water until neutral, dried (Na_2SO_4), and evaporated under reduced pressure. After purification by silica gel column chromatography (EtOAc/light pet) two diastereomeric oxathiolanylcytosines (overall yield 0.21 g, 70%) were obtained: α pair (0.11 g); m.p. 214-215° C (from ethanol); [found: C, 54.21; H, 4.72%; Elemental analysis, $C_{16}H_{17}O_5N_3S$ requires C, 54.39; H, 4.56]; ^{1}H NMR (250 MHz): δ 2.28 (3H, s, CH_3CO), 4.32 (1H, dd, *J* = 3.4, 12.3, H-6'a), 4.38 (2H, br, 2 x H-5') 4.67 (1H, dd, *J* = 8.2, 12.3, H-6'b), 5.92 (1H, dd, *J* = 3.3, 8.2, H-4'), 6.68 (1H, br, H-2'), 7.42-7.55 (3H, m, 2 x aromatic H and H-5), 7.58-7.67 (1H, m, aromatic H), 8.03-8.20 (3H, m, 2 x aromatic H and H-6), 9.23 (1H, br, NH). Lower R_f β pair (0.10 g); oily; Elemental analysis, $C_{16}H_{17}O_5N_3S$ requires C, 54.39; H, 4.56: found C, 54.15; H, 4.61%; ^{1}H NMR (250 MHz): δ 2.25 (3H, s, CH_3CO), 4.05 (1H, dd, *J* = 4.1, 10.5, H-5'a), 4.48 (1H, d, *J* = 10.5, H-5'b), 4.75 (1H, dd, *J* = 4.3, 12.6, H-6'a), 4.86 (1H, dd, *J* = 3.0, 12.6, H-6'b), 5.48 (1H, dd, *J* = 3.0, 4.3, H-2'), 6.63 (1H, d, *J* = 4.3, H-4'), 7.40-7.75 (4 H, m, 3 x aromatic H and H-5), 8.08 (2H, d, *J* = 8.1, aromatic H), 8.29 (1H, d, *J* = 7.5 H-6), 8.89 (1H, br, NH).

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