A New Strategy for the Asymmetric Synthesis of 1,3-Oxathiolane-Based Nucleoside Analogues

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Dedicated to the memory of Professor Fulvio Di Furia

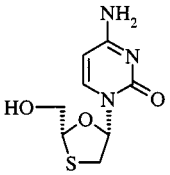
Keywords: Nucleoside analogues / 1,3-Oxathiolanes / Chiral sulfoxides / Heterocycles / Antiviral agents

A ready asymmetric synthesis of 3′-oxathionucleosides has been accomplished in three main steps from benzoyloxyethanal. The synthesis is characterized by high overall yield and considerable enantiomeric excesses. It represents a general synthetic path to prepare a wide range of heterosubstituted sulfur-containing nucleoside analogues.

Introduction

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 the DNA synthesis by inhibiting DNA polymerase[1]. Large numbers of analogues have been synthesized and tested, but only very few have been approved for clinical testing, either due to their poor in vitro activity or to their excessive toxicity. Recently[2], several members of the heterosubstituted 2′,3′-dideoxynucleoside analogues class have been discovered to be active against the 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 has recently been approved by the FDA for the treatment of AIDS.



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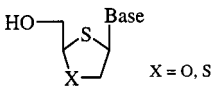

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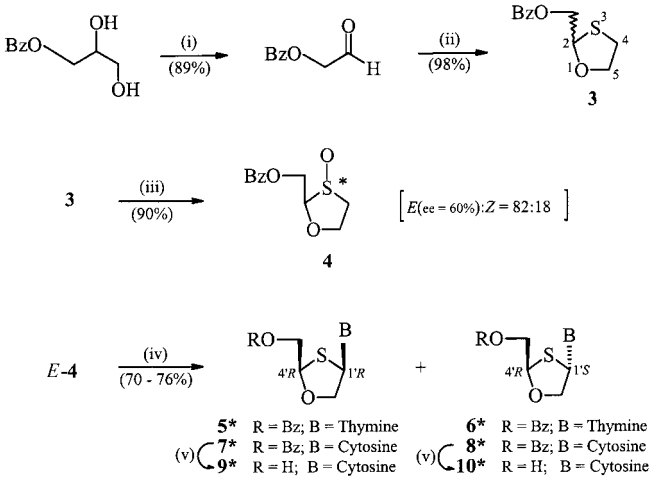
It is noteworthy[4] that this compound has shown much lower cytotoxicity than the D-enantiomer, although both of them were almost equipotent against the replication of HIV-1 and HIV-2 in vitro. Thionucleosides like **2**, possessing a second heteroatom such as oxygen[5a] or sulfur[5b] at the 3′ position,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

Several methods[5][6] are available in the current literature for synthesizing the heterosubstituted nucleoside analogues: notwithstanding, the real bottleneck of their preparation is represented by the difficulty of furnishing such compounds in an optically pure form. To the best of our knowledge, the asymmetric syntheses reported so far are very limited in number and characterized by numerous steps[7][8]. In fact, the enantiomerically pure compounds needed[4] are mostly obtained by resolution of racemic mixtures[9].

Results and Discussion

Under these circumstances, a new general approach to asymmetric syntheses of chiral 3′-oxathionucleosides (2,4-disubstituted 1,3-oxathiolanes) with a good enantiomeric excess, in four main steps starting from 1-*O*-benzoylglycerol[10], seems to be of some interest.

The key step of our approach is actually represented by the preparation of the chiral sulfoxide **4** (Scheme 1).



Scheme 1. (i) $NaIO_4$; (ii) PPh_3/I_2, mercaptoethanol; (iii) *t*BuOOH, (+)-L-DET, $Ti(OiPr)_4$; (iv) TMSOTf, Et_3N, N^4-acetylcytosine or thymine; (v) MeONa, MeOH, 90%; * only the predominant enantiomer shown.

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The racemic 2-[(phenylcarbonyloxy)methyl]-1,3-oxathiolane (**3**) is obtained in very high yield (98%) by treatment of benzoyloxyethanal (from monobenzoylglycerol) with mercaptoethanol in the presence of the polystyryl diphenylphosphane−iodine complex, which acts as a Lewis acid as well as a dehydrating agent, according to a procedure[11] formerly developed in our lab. The conversion of **3** into the chiral sulfoxide **4** is then performed by a modified Sharpless oxidation[12], by *tert*-butyl hydroperoxide and L-diethyl tartrate in the presence of Ti^{IV} isopropoxide as catalyst. The oxidation leads in high yield (90%) to a mixture of the diastereomeric (*E*) and (*Z*) pairs in an 82:18 ratio. After the chromatographic separation, the more abundant (*E*) pair exhibited an ee of 60%, as determined by ^{1}H-NMR analysis using Eu(hfc)$_3$ (Aldrich) chiral shift reagent[12][13]. The replacement of L-diethyl tartrate with its D-enantiomer leads to the same diastereomeric mixture (81:19) and to 60% reverse ee. This enables the synthesis of nucleoside analogues belonging to both D and L series.

However, the (*E*) pair of the chiral sulfoxide **4** was then coupled with N^4-acetylcytosine under Pummerer rearrangement conditions[5a] via acetate. Unfortunately, the reaction led to poor results (49% α + β pair overall yield) and the coupling was better achieved by direct treatment of the base with the chiral sulfoxide (*E*)-**4** in the presence of trimethylsilyltriflate and triethylamine[14].

The chromatographic separation of the coupling reaction products **7** and **8** led to the diastereomeric α and β pairs, approximately in 1:1 ratio (70% overall yield). The chiral column HPLC analysis[15] of both pairs showed that during the coupling no racemization had occurred at the C-2 position of the chiral 1,3-oxathiolane sulfoxide **4**.

The absolute configuration to the exceeding enantiomer in the final mixture could be assigned, in the cytosinyl series, by comparison of the rotation sign of the fully deprotected modified nucleosides with those reported in the literature for the pure compounds. In fact the modified nucleosides **9** and **10** are known and accurately described,[7] consequently we could confidently attribute to our compounds the configurations (1′*R*,4′*R*) and (1′*S*,4′*R*), respectively.

The coupling of the chiral sulfoxide (*E*)-**4** with thymine led to analogous results: the coupling products **5** and **6** were in fact obtained in 1:1 ratio and 76% overall yield.

This new approach to the asymmetric synthesis of heterosubstituted nucleoside analogues may represent a rapid entry to optically pure material that is potentially amenable to the preparation of multi-gram quantities of these important compounds. Some preliminary results showed that the ee is affected by the nature of the hydroxymethyl-protecting group. As an example, the replacement of the benzoyl group with the *tert*-butyl diphenyl silyl group led to the disappearance of any enantiomeric excess[13].

Work is also in progress to prepare, by the same strategy, new optically pure nucleoside analogues containing a second sulfur atom in the ring.

Experimental Section

General: ^{1}H NMR spectra: Bruker AM-250 and DRX-400 spectrometers, $CDCl_3$ as solvent unless otherwise specified, chemical shifts in ppm (δ), TMS as internal standard. − Optical rotations: Perkin−Elmer 141 polarimeter (1.0 dm cell length), MeOH unless otherwise specified. − HPLC analyses: Gynkotek M480 chromatograph equipped with UVD 160S detector. − Combustion analyses: Perkin−Elmer Series II 2400, CHNS analyzer. − TLC analyses: silica gel Merck 60 F_{254} plates (0.2 mm layer tickness). − Column chromatography: Merck Kieselgel 60 (70−230 mesh). − Dry solvents were distilled immediately before use.

2-[(Phenylcarbonyloxy)methyl]-1,3-oxathiolane (3): To a magnetically stirred suspension of polystyryl diphenylphosphane-iodine complex (22.6 mmol − iodine units; prepared in situ) in anhydrous acetonitrile (150 mL), at room temp. and under dry nitrogen atmosphere, was added in one portion by syringe a solution of benzoyloxyethanal[10] (3.71 g, 22.6 mmol) in the same solvent (25 mL). After 10 min, 1 M 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 then filtered. The residual solid was washed with chloroform (3× 100 mL) and the combined filtrates, after shaking with 5 N aq. sodium thiosulfate (50 mL) and water until neutral, were evaporated under reduced pressure to leave a residue consisting of virtually pure **3** (4.95 g, 98%), oil. − $C_{11}H_{12}O_3S$ (224,3): calcd. C 58.91, H 5.39; found C 59.21, H 5.28. − ^{1}H NMR (400 MHz) δ = 3.01−3.10 (m, 2 H, CH_2S), 3.99−4.04 (m, 1 H, H-5a), 4.26−4.31 (m, 1 H, H-5b), 4.40 (dd, *J* = 3.8 Hz, 11.7 Hz, 1 H, H-6a), 4.51 (dd, *J* = 7.3 Hz, 11.7 Hz, 1 H, H-6b), 5.48 (dd, *J* = 3.8 Hz, 7.3 Hz, 1 H, H-2), 7.41−7.48 (m, 2 H, aromatic H), 7.54−7.59 (m, 1 H, aromatic H), 8.07 (d, *J* = 8.0 Hz, 2 H, aromatic H).

2-[(Phenylcarbonyloxy)methyl]-1,3-oxathiolan-3-one (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 temp. After 10 min, the resulting yellow homogeneous solution was cooled to −20°C. *tert*-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 maintained at −20°C under stirring for 14 h, then quenched with water (30 mL), warmed to room temp. and filtered on Celite. The inorganic layer was extracted with dichloromethane (2× 50 mL) and the combined dichloromethane layers, after washing 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%). Higher R_f (*E*)-**4** (0.43 g), m.p. 89−91°C (from hexane/benzene). − $[\alpha]_D^{25}$ = −72.4 (*c* = 1.1, $CHCl_3$). − $C_{11}H_{12}O_4S$ (240.3): calcd. C 54.99, H 5.03; found C 54.71, H 4.96. − ^{1}H NMR (400 MHz): δ = 2.68−2.77 (m, 1 H, H-4a), 3.14 (dd, *J* = 3.5 Hz, 13.5 Hz, 1 H, H-4b), 4.41−4.48 (m, 1 H, H-5a), 4.64−4.72 (m, 1 H, H-5b), 4.72−4.85 (m, 3 H, H-2 and H-6), 7.41−7.47 (m, 2 H, aromatic H), 7.52−7.61 (m, 1 H, aromatic H), 7.98 (d, *J* = 8.2 Hz, 2 H, aromatic H). Lower R_f sulfoxide (*Z*)-**4**: (0.09 g), oily. − $[\alpha]_D^{25}$ = −87.7 (*c* = 2.6, $CHCl_3$). − $C_{11}H_{12}O_4S$ (240.3): calcd. C 54.99, H 5.03; found C 55.15, H 5.10. − ^{1}H NMR (400 MHz): δ = 3.05−3.14 (m, 1 H, H-4a), 3.20−3.28 (m, 1 H, H-4b), 4.08−4.13 (m, 1 H, H-5a), 4.65−4.72 (m, 4 H, H-2, H-5b, H-6), 7.41−7.47

(m, 2 H, aromatic H), 7.51−7.59 (m, 1 H, aromatic H), 8.04 (d, 2 H, J = 8.2 Hz, aromatic H).

2-[(*tert*-Butyldiphenylsilyloxy)methyl]-1,3-oxathiolan-3-one: Preparation from 2-hydroxymethyl-1,3-oxathiolane by oxidation under the same conditions used for the oxathiolane **3.** After workup a mixture of the diastereomeric sulfoxides [(*E*)/(*Z*) = 95:5] was obtained in 92% overall yield. By chromatographic separation on silica gel (CH_2Cl_2) the pure (*E*) pair could be isolated: m.p. 95−97°C (from hexane/light petroleum ether). − $C_{20}H_{26}O_3SSi$ (374.6): calcd. C 64.13, H 7.00; found C 63.90, H 7.05. − ^{1}H NMR (250 MHz): δ = 2.68−2.87 (m, 1 H, H-4a), 3.12 (dd, J = 3.9 Hz, 13.2 Hz, 1 H, H-4b), 3.92 (dd, J = 3.6 Hz, 11.8 Hz, 1 H, H-6a), 4.20 (dd, J = 2.9 Hz, 11.8 Hz, 1 H, H-6b), 4.41−4.55 (m, 1 H, H-5a), 4.63−4.77 (m, 2 H, H-5b and H-2), 7.32−7.52 (m, 6 H, aromatic H), 7.69 (d, J = 7.9 Hz, 4 H, 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, were added dropwise trimethylsilyl triflate (TMSOTf) (0.9 mL, 5.0 mmol) and triethylamine (0.7 mL, 5.0 mmol) in this 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 stirred overnight. After solvent evaporation under reduced pressure the residue was redissolved by EtOAc (15 mL), washed with 5% aq. $NaHCO_3$ (2× 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 petroleum ether, 70:30) two diastereomeric oxathiolanylcytosines (overall yield 0.21 g, 70%) were obtained. Higher R_f α-pair (**8**) (0.11 g), m.p. 205−206°C (from EtOH). − $C_{17}H_{17}O_5N_3S$ (375.4): calcd. C 54.39, H 4.56; found C 54.21, H 4.72. − ^{1}H NMR (250 MHz): δ = 2.28 (s, 3 H, CH_3CO), 4.32 (dd, J = 3.4 Hz, 12.3 Hz, 1 H, H-6′a), 4.38 (m, 2 H, H-2′), 4.67 (dd, J = 8.2 Hz, 12.3 Hz, 1 H, H-6′b), 5.92 (dd, J = 3.3 Hz, 8.2 Hz, 1 H, H-1′), 6.68 (br. s, 1 H, H-4′), 7.42−7.55 (m, 3 H, aromatic H and H-5), 7.58−7.67 (m, 1 H, aromatic H), 8.03−8.20 (m, 3 H, aromatic H and H-6), 9.23 (br. s, 1 H, NH). Lower R_f β-pair (**7**) (0.10 g), m.p. 174−178°C (from EtOH). − $C_{17}H_{17}O_5N_3S$ (375.4): calcd. C 54.39, H 4.56; found C 54.15, H 4.61. − ^{1}H NMR (250 MHz): δ = 2.25 (s, 3 H, CH_3CO), 4.05 (dd, J = 4.1 Hz, 10.5 Hz, 1 H, H-2′a), 4.48 (d, J = 10.5 Hz, 1 H, H-2′b), 4.75 (dd, J = 4.3 Hz, 12.6 Hz, 1 H, H-6′a), 4.86 (dd, J = 3.0 Hz, 12.6 Hz, 1 H, H-6′b), 5.48 (dd, J = 3.0 Hz, 4.3 Hz, 1 H, H-4′), 6.63 (d, J = 4.3 Hz, 1 H, H-1′), 7.40−7.75 (m, 4 H, aromatic H and H-5), 8.08 (d, J = 8.1, 2 H, aromatic H), 8.29 (d, J = 7.5 Hz, 1 H, H-6), 8.89 (br. s, 1 H, NH).

Under the same conditions, the coupling of the sulfoxide (*E*)-**4** with thymine led to a mixture of diastereomeric oxathiolanylthymines (overall yield 75%) separated by silica gel column chromatography (AcOEt/light petroleum ether, 70:30). Higher R_f α-pair (**6**) (0.097 g), m.p. 209−211°C (from MeOH). − $C_{16}H_{16}O_5N_2S$ (348.4): calcd. C 55.16, H 4.63; found C 55.25, H 4.68. − ^{1}H NMR (250 MHz): δ = 1.95 (d, J = 1.3 Hz, 3 H, Me), 4.27 (dd, J = 3.5 Hz, 12.4 Hz, 1 H, H-6′a), 4.32 (m, 2 H, H-2′), 4.62 (dd, J = 8.7 Hz, 12.4 Hz, 1 H, H-6′b), 5.94 (dd, J = 3.5 Hz, 8.7 Hz, 1 H, H-4′), 6.53 (dd, J = 1.9 Hz, 3.7 Hz, 1 H, H-1′), 7.37 (q, J = 1.3 Hz, H-6), 7.47 (m, 2 H, aromatic H), 7.59 (t, J = 7.9 Hz, 1 H, aromatic H), 8.09 (d, J = 7.9 Hz, 1 H, aromatic H), 8.25 (br. s, 1 H, NH). Lower R_f β-pair (**5**) (0.118 g), m.p. 178−180°C (from MeOH). − $C_{16}H_{16}O_5N_2S$ (348.4): calcd. C 55.16, H 4.63; found C 55.31, H 4.58. − ^{1}H NMR (250 MHz): δ = 1.79 (d, J = 1.2 Hz, 3 H, Me), 4.02 (dd, J = 4.9 Hz, 11.0 Hz, 1 H, H-2′a), 4.47 (d, J = 11.0 Hz, 1 H, H-2′b), 4.71 (dd, J = 5.5 Hz, 12.3 Hz, 1 H, H-6′a), 4.82 (dd, J = 3.3 Hz, 12.3 Hz, 1 H, H-6′b), 5.49 (dd, J = 3.3 Hz, 5.5 Hz, 1 H, H-4′), 6.53 (d, J = 4.9 Hz, 1 H, H-1′), 7.48 (m, 2 H, aromatic H), 7.52 (q, J = 1.2 Hz, 1 H, H-6), 7.60 (t, J = 7.5 Hz, 1 H, aromatic H), 8.06 (d, J = 7.5 Hz, 2 H, aromatic H), 8.21 (br. s, 1 H, NH).

Hydrolysis of the Coupling Products 7 and 8: (1′*R*,4′*R*)-2′-Deoxy-3′-oxathiocytidine (9) and its (1′*S*,4′*R*)-Diastereomer (10): To a solution of **7** (0.04 g, 0.1 mmol) in MeOH (5 mL) was added MeONa (5.4 mg, 0.1 mmol) under stirring and under a nitrogen atmosphere at room temp. After 6 h the reaction mixture was quenched with glacial acetic acid excess, MeOH was removed under reduced pressure, and the crude residue chromatographed on silica gel ($CHCl_3$/MeOH, 90:10) to give the pure β-pair **9** (22 mg, 96% yield), m.p. 149°C (*dec.*) (from Et_2O/MeOH). − $[\alpha]_D^{25}$ = +114.1 (c = 0.4). − $C_8H_{11}O_3N_3S$ (229.3): calcd. C 41.91, H 4.84; found C 42.00, H 4.79. − ^{1}H NMR (250 MHz), [D$_6$]DMSO: δ = 3.65−3.85 (m, 2 H, H-2′), 4.08 (d, J = 11.3 Hz, 1 H, H-6′a), 4.20 (d, J = 11.2 Hz, 1 H, H-6′b), 5.10 (t, J = 4.9 Hz, 1 H, OH), 5.48 (t, J = 7.0 Hz, 1 H, H-4′), 5.80 (d, J = 7.4 Hz, 1 H, H-5), 6.33 (d, J = 3.7 Hz, 1 H, H-1′), 7.07−7.28 (m, 2 H, NH_2), 7.75 (d, J = 7.4 Hz, 1 H, H-6).

The coupling product **8** afforded the pure α-pair **10**, under the same conditions: (21 mg, 90% yield), m.p. 190°C (*dec.*) (from Et_2O/MeOH). − $[\alpha]_D^{25}$ = −76.0 (c = 1.1). − $C_8H_{11}O_3N_3S$ (229.3): calcd. C 41.91, H 4.84; found C 42.00, H 4.79. − ^{1}H NMR (250 MHz), [D$_6$]DMSO: δ = 3.68−3.79 (m, 2 H, H-2′), 3.87 (dd, J = 4.2 Hz, 11.0 Hz, 1 H, H-6′a), 4.43 (d, J = 11.0 Hz, 1 H, H-6′b), 4.90 (t, J = 4.6 Hz, 1 H, OH), 5.39 (t, J = 5.3 Hz, 1 H, H-4′), 5.80 (d, J = 7.4 Hz, 1 H, H-5), 6.35 (d, J = 4.2, 1 H, H-1′), 7.12−7.30 (m, 2 H, NH_2), 7.90 (d, J = 7.4 Hz, 1 H, H-6).

Acknowledgments

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[13] Sulfoxide (*E*)-**4**: H-2 proton, from δ = 4.72−4.85 (m) to δ = 5.95 (br. s, 80%) and δ = 6.01 (br. s, 20%); *2-[(tert-butyldiphenylsilyloxy)methyl]-1,3-oxathiolan-3-one*: H-2 proton, from δ = 4.63−4.77 (m) to δ = 5.42 (br. s, 47%) and δ = 5.49 (br. s, 53%).

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[15] Cyclobond I 2000 RSP (250 × 4.6 mm), 50% MeOH in 0.1 M NH_4OAc; β pair **7**: R_t = 14.30 min (81%) and 15.03 min (19%); α pair **8**: R_t = 21.62 min (80%) and 23.15 min (20%).

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