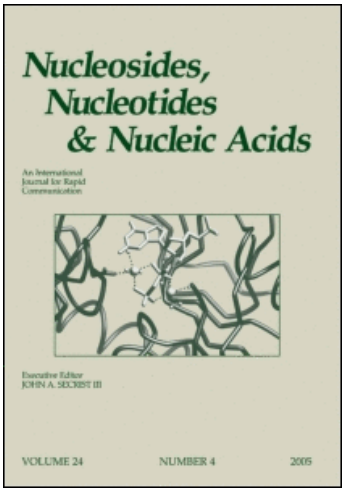

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MODEL SYNTHESES OF THIAZOLIDINE NUCLEOSIDE ANALOGUES

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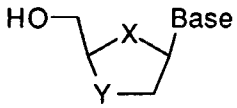
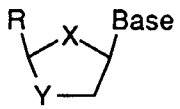
Abstract: The syntheses of racemic thiazolidinyl thymine and cytosine derivatives **6a** and **6b**, and **10a** and **10b**, prototypes of a novel family of heterosubstituted nucleosides, have been achieved from rhodanine (**3**) or thiazolidine (**7**) by a short sequence of steps. The key reaction involved efficient coupling of silylated thymine and cytosine to *N*-Boc-protected 4- and 5-acetoxythiazolidines, **5** and **9**, assisted by *tert*-butyldimethylsilyl trifluoromethanesulfonate.

In the past few years, heterosubstituted nucleoside analogues of type **1** containing two oxygen and sulfur atoms in the carbohydrate ring have revealed significant biological profiles, including anti-HIV and anti-HBV activities.[1,2] Among these compounds, (-)-β-L-(2*R*,5*S*)-1,3-oxathiolanylcytosine (lamivudine; type **1a**, base = cytosine) has emerged as an outstanding clinical candidate exhibiting potent anti-HIV-1 activity (EC_{50} = 0.0018 μM in human PMB cells) associated with strongly reduced cytotoxicity.[3,4]

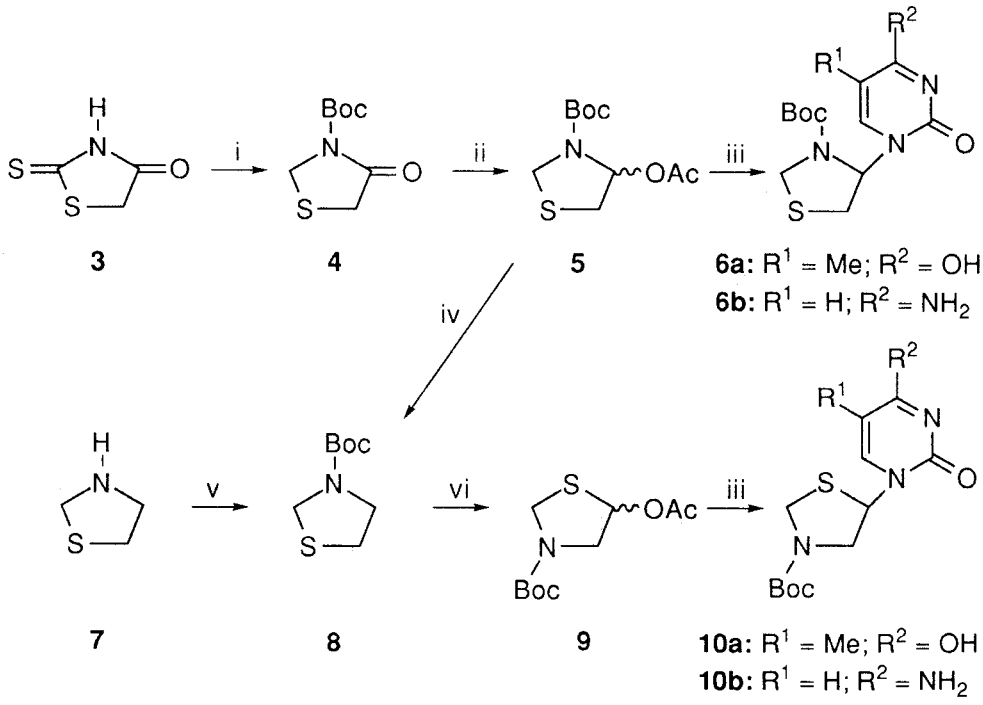


1a: X = O; Y = S
1b: X = S; Y = O



2a: X = NR'; Y = S
2b: X = S; Y = NR'

Although many structural congeners of lamivudine have now been synthesized and evaluated, with variations in the furanose ring substituents and changes in the nucleobase moiety,[2,4] the incorporation of nitrogen into the modified sugar framework leading to thiazole-based analogues of type **2** has been scantly investigated.[5] Filling this void, we want to report herein model syntheses of four thiazolidinyl compounds of type **2** (R = H; R' = Boc), namely deshydroxymethyl thymidine and cytidine analogues **6a** and **6b**, and



Reagents: i, Zn dust, AcOH; then Boc_2O, MeCN, DMAP; ii, $LiEt_3BH$, THF, -78°C; then Ac_2O, pyridine, DMAP; iii, for **6a**, silylated thymine, TBDMS-OTf, CH_2Cl_2, 5°C; for **6b**, silylated 4-*N*-acetylcytosine, TBDMS-OTf, CH_2Cl_2, 5°C; then K_2CO_3, MeOH; iv, TMS-OTf, Et_3SiH; v, Boc_2O, MeCN, DMAP; vi, MCPBA, CH_2Cl_2; then Ac_2O, NaOAc, toluene, 115°C.

Scheme 1

10a and **10b**, which can be envisioned as simplified prototypes of a novel progeny of nitrogenous nucleoside mimics.[6] For 3'-thia-4'-aza-derivatives **6a** and **6b**, the opening move was the preparation of activated azasugar-like compound **5** to be coupled, in the final stage of the sequence, with the suitable nucleobases. Thus, as shown in Scheme 1, readily available rhodanine (**3**) was first converted to protected thiazolidinone **4** (79% yield) via selective reduction of the thiocarbonyl function (zinc dust, acetic acid)[7] and subsequent *N*-protection (Boc_2O, DMAP).

Clean and almost quantitative reduction of the lactam carbonyl within **4** was attained upon exposure to lithium triethylborohydride in THF and yielded a carbinol intermediate, which upon acetylation (acetic anhydride, pyridine, DMAP) afforded 4-acetoxythiazolidine **5** in 63% yield. The coupling of **5** with persilylated thymine and 4-*N*-acetylcytosine was

finally conducted according to a Vorbrüggen-type protocol.[8] In order to obtain optimal yields, we required a Lewis acid of sufficient strength to promote the reaction, but not to decompose the delicate N,S heterocycle of **5**. We found that *tert*-butyldimethylsilyl trifluoromethanesulfonate was the ideal Lewis acid candidate allowing preservation of the integrity of the five-membered ring and the *N*-Boc protective group within **5**. Thus, the reaction of **5** with bis-trimethylsilylthymine was run in CH_2Cl_2 at 5°C for few minutes and produced the desired crystalline nucleoside **6a** in 71% isolated yield (35% overall yield from **3**). In an analogous manner, coupling of **5** with silylated 4-*N*-acetylcytosine afforded, after base-promoted (K_2CO_3, methanol) deacetylation of the crude reaction product, pure cytidine congener **6b** in 70% yield (34% yield from **3**).

The synthesis of isomeric 3'-aza-4'-thionucleosides **10a** and **10b** called for 5-acetoxy-derivative **9** as the immediate precursor. According to a divergent plan, thiazolidine **8** was thus prepared in 83% yield from the same key intermediate **5** of the previous synthesis, via trimethylsilyl trifluoromethanesulfonate-promoted deoxygenation in neat triethylsilane.[2,9] Alternatively and conveniently, **8** was also obtained by direct protection (Boc_2O, pyridine, DMAP) of commercially available thiazolidine (**7**) (89% yield). Protected compound **8** was then subjected to oxidation with *m*-chloroperbenzoic acid to afford a sulfoxide intermediate (not shown) which underwent Pummerer rearrangement in the presence of acetic anhydride and sodium acetate in refluxing toluene.[2,10] In the event, the precursor **9** was generated in 58% yield, accompained by *ca.* 30% of an undesired open-chain by-product.[11] The coupling reactions between **9** and persilylated thymine and 4-*N*-acetylcytosine were rapidly carried out as described for **6a** and **6b**, and afforded the nucleoside models **10a** and **10b** in 61% and 53% isolated yields, respectively (32% and 27% overall yields from **7**).

The success achieved with the preparation of deshydroxymethyl nucleoside models **6** and **10** will undoubtedly prompt investigations to broaden the scope of this strategy en route to various hydroxymethylene-substituted N,S-analogues of type **2** (R = CH_2OH), and to study the structure-activity relationships of these novel nucleosides series.

EXPERIMENTAL

***N*-(*tert*-Butoxycarbonyl)thiazolidin-4-one (4).** To a stirred mixture of zinc dust (3.27 g, 50 mmol) in acetic acid (15 mL) was added rhodanine **3** (1.33 g, 10 mmol) in four portions over a period of 30 min. After being refluxed for 10 h, the mixture was cooled, filtered over a Celite pad, and concentrated in vacuo. To the crude product, dissolved in acetonitrile (30 mL), di-*tert*-butyldicarbonate (2.18 g, 10 mmol), and *N,N*-dimethylaminopyridine (DMAP, 0.06 g, 0.5 mmol) were added under stirring. The

mixture was stirred at room temperature for 3 h, evaporated in vacuo and flash chromatographed on silica gel eluting with 70:30 hexane-EtOAc to afford pure **4** (1.6 g, 79%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54 (9H, s), 3.62 (2H, s), 4.72 (2H, s); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 27.6 (3C), 33.4, 45.8, 83.7, 148.9, 169.8.

Anal. Calcd for $C_8H_{13}NO_3S$: C, 47.28; H, 6.45; N, 6.90. Found: C, 47.12; H, 6.24; N, 6.71.

(±)-*N*-(*tert*-Butoxycarbonyl)-4-acetoxythiazolidine (5). To a solution of **4** (1.4 g, 6.9 mmol) in dry THF (15 mL) was added a 1 M solution of $LiEt_3BH$ in THF (8.97 mL, 8.97 mmol) under nitrogen at -78°C. The solution was stirred at this temperature for 2 h, then the reaction was quenched with CH_3OH (20 mL). After ambient temperature was reached, the resulting mixture was extracted with EtOAc (3x20 mL), the solvent was evaporated off and the crude product was purified by flash chromatography on silica gel eluted with 70:30 hexane-EtOAc. This compound (1.3 g, 6.3 mmol), dissolved in pyridine (5 mL), was treated with acetic anhydride (15 mL, 15.8 mmol), and DMAP (0.01 g, 0.8 mmol) at room temperature under nitrogen. The solution was stirred for 1 h, then quenched with H_2O (20 mL) and extracted with CH_2Cl_2 (3x15 mL). The extracts were evaporated and the crude product was purified by flash chromatography on silica gel eluting with 80:20 hexane-EtOAc to afford compound **5** (1.0 g, 63%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (9H, s), 2.09 (3H, s), 3.00 (1H, bd, J = 12.0), 3.31 (1H, bd, J = 12.0), 4.54 (2H, m), 6.73 (1H, bs).

Anal. Calcd for $C_{10}H_{17}NO_4S$: C, 48.57; H, 6.93; N, 5.66. Found: C, 48.37; H, 6.77; N, 5.48.

(±)-1-[*N*-(*tert*-Butoxycarbonyl)thiazolidin-4-yl]thymine (6a). A mixture of thymine (0.9 g, 7.2 mmol), hexamethyldisilazane (50 mL) and ammonium sulfate (catalytic amount) was refluxed for 2 h and the resulting solution was concentrated in vacuo under anhydrous conditions to yield silylated thymine as a colorless oil. Silylated thymine in anhydrous 1,2-dichloroethane (35 mL) was treated with **5** (0.9 g, 3.6 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.65 mL, 7.2 mmol) at 5°C, and the reaction was stirred for 15 min under nitrogen. The reaction mixture was quenched by saturated $NaHCO_3$ (50 mL) and stirred for additional 15 min at room temperature. The reaction mixture was extracted with CH_2Cl_2 (3x20 mL) and dried ($MgSO_4$). After filtration, the filtrate was concentrated and flash chromatographed on silica gel eluting with 50:50 hexane-EtOAc to afford pure compound **6a** (0.8 g, 71%) as colorless crystals, m.p. 215°C (decomp.): ^{1}H NMR (300 MHz, DMSO, 80°C) δ 1.36 (9H, s), 1.79 (3H, d, J = 1.2), 3.12 (1H, dd, J = 12.0, 2.7), 3.47 (1H, dd, J = 12.0, 5.7), 4.50 (1H, d, J = 9.0), 4.73 (1H, d, J = 9.0), 6.21 (1H, dd, J = 5.7, 2.7), 7.39 (1H, d, J = 1.2), 11.0 (1H, bs);

^{13}C NMR (75.4 MHz, DMSO, 80°C) δ 11.4, 27.4 (3C), 36.0, 48.8, 70.1, 80.6, 108.0, 136.1, 149.8, 151.6, 163.3.

Anal. Calcd for: $C_{13}H_{19}N_3O_4S$: C, 49.83; H, 6.11; N, 13.41. Found: C, 49.61; H, 6.24; N, 13.54.

(±)-1-[*N*-(*tert*-Butoxycarbonyl)thiazolidin-4-yl]cytidine (6b). A mixture of 4-*N*-acetylcytosine (0.44 g, 2.9 mmol), hexamethyldisilazane (20 mL) and ammonium sulfate (catalytic amount) was refluxed for 2 h and the resulting solution was concentrated in vacuo to afford silylated cytosine as a clear syrup. Silylated cytosine in anhydrous 1,2-dichloroethane (20 mL) was treated with **5** (0.36 g, 1.4 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.66 mL, 2.9 mmol) as described above for **6a**. The crude reaction product so obtained dissolved in methanol (10 mL) was then treated with K_2CO_3 (10 mg) and the mixture was stirred at room temperature for 1 h. The reaction was quenced with water and extracted with ethyl acetate (3x15 mL) and dried ($MgSO_4$). After filtration, the organic layer was concentrated and flash chromatographed on silica gel eluting with 80:18:2 EtOAc-MeOH-30% NH_4OH to afford pure nucleoside **6b** (0.29 g, 70%) as white powder, m.p. > 300°C: ^1H NMR (300 MHz, DMSO, 80°C) δ 1.40 (9H, s), 3.03 (1H, dd, J = 12.3, 2.4), 3.45 (1H, dd, J = 12.3, 5.7), 4.51 (1H, d, J = 8.7), 4.67 (1H, d, J = 8.7), 5.70 (1H, d, J = 7.3), 6.23 (1H, dd, J = 5.7, 2.4), 6.76 (2H, bs), 7.45 (1H, d, J = 7.3); ^{13}C NMR (75.4 MHz, DMSO) δ 27.6 (3C), 37.1, 49.0, 70.7, 71.4, 92.7, 141.5, 151.8, 154.9, 165.7.

Anal. Calcd for: $C_{12}H_{18}N_4O_3S$: C, 48.31; H, 6.08; N, 18.78. Found: C, 48.18; H, 6.24; N, 18.66.

***N*-(*tert*-Butoxycarbonyl)thiazolidine (8). Method A.** To a room temperature solution of **7** (2.0 g, 22.4 mmol) in acetonitrile (40 mL), di-*tert*-butyldicarbonate (4.2 g, 22.4 mmol) and DMAP (0.13 g, 1.1 mmol) were added under stirring. The mixture was stirred at room temperature for 3 h, evaporated in vacuo and flash chromatographed on silica gel eluting with 70:30 hexane-EtOAc to give compound **8** (3.77 g, 89%) as an oil: ^1H NMR (300 MHz, $CDCl_3$) δ 1.47 (9H, s), 2.97 (2H, t, J = 6.3), 3.67 (2H, bt, J = 6.3), 4.43 (2H, bs).

Anal. Calcd for $C_8H_{15}NO_2S$: C, 50.77; H, 7.99; N, 7.40. Found: C, 50.81; H, 8.12; N, 7.20.

Method B. To a solution of **5** (0.05 g, 0.2 mmol) in triethylsilane (2 mL) was added trimethylsilyl trifluoromethanesulfonate (0.04 mL, 0.2 mmol). The solution was strirred at room temperature for 10 h, the solvent was evaporated and the resulting product subjected to chromatographic purification to afford compound **8** (0.031 g, 83%).

(±)-*N*-(*tert*-Butoxycarbonyl)-5-acetoxythiazolidine (9). To a solution of **8** (1.8 g, 9.5 mmol) in dry CH_2Cl_2 (20 mL) was added 3-chloroperoxybenzoic acid (50-

60%, 3.27 g, 9.5 mmol) dissolved in CH_2Cl_2 (20 mL) at -30°C under nitrogen. After the solution was stirred for 1 h, a 10% sodium bisulfite solution and saturated Na_2CO_3 were added and the reaction mixture was extracted with CH_2Cl_2 (3x10 mL). The organic layer was dried over $MgSO_4$ and evaporated. Flash chromatography on silica gel eluting with 50:50:10 CH_2Cl_2-EtOAc-MeOH afforded 1.49 g of the sulfoxide intermediate as an oil which was used as such in the next reaction. A stirred mixture of the sulfoxide, (1.49 g, 7.25 mmol), sodium acetate (1.8 g, 21.7 mmol) and acetic anhydride (19 mL) in toluene (40 mL) was heated at 115°C overnight. The reaction mixture was cooled, concentrated, and flash chromatographed on silica gel eluting with 60:40 hexane-EtOAc to afford compound **9** (1.0 g, 58%): ^{1}H NMR (300 MHz, DMSO, 75°C) δ 1.47 (9H, s), 2.07 (3H, s), 3.66 (1H, dd, J = 14.7, 4.5), 3.82 (1H, dd, J = 14.7, 8.1), 5.30 (2H, ABq, J = 10.8, $\Delta\nu$ = 17.1), 6.01 (1H, dd, J = 8.1, 4.5); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 20.2, 27.5 (3C), 46.0, 49.3, 72.2, 80.2, 153.4, 169.6.

Anal. Calcd for $C_{10}H_{17}NO_4S$: C,48.57; H, 6.93; N, 5.66. Found: C, 48.61; H, 7.14; N, 5.43.

(±)-1-[*N*-(*tert*-Butoxycarbonyl)thiazolidin-5-yl]thymine (10a). Acetoxythiazolidine **9** (0.9 g, 3.64 mmol) was coupled with silylated thymine (from thymine, 0.9 g, 7.3 mmol) by the same procedure as described for **6a** to give compound **10a** (0.7 g, 61%) as a colorless glass: ^{1}H NM R (300 MHz, DMSO, 80°C) δ 1.43 (9H, s), 1.78 (3H, s), 3.65 (1H, dd, J = 14.7, 4.5), 3.80 (1H, dd, J = 14.7, 8.4), 5.26 (2H, ABq, J = 11.0, $\Delta\nu$ = 13.5), 5.98 (1H, dd, J = 8.4, 4.5), 7.38 (1H, s), 11.02 (1H, bs); ^{13}C NMR (75.4 MHz, DMSO, 80°C) δ 11.3, 27.4 (3C), 46.5, 49.3, 67.7, 80.5, 108.2, 140.1, 150.8, 153.8, 163.5.

Anal. Calcd for $C_{13}H_{19}N_3O_4S$: C, 49.83; H, 6.11; N, 13.41. Found: C, 49.81; H, 6.27; N, 13.11.

(±)-1-[*N*-(*tert*-Butoxycarbonyl)thiazolidin-5-yl]cytosine (10b). Acetoxythiazolidine **9** (0.5 g, 2.02 mmol) was coupled with silylated 4-*N*-acetylcytosine (from 4-*N*-acetylcytosine, 0.62 g, 4.04 mmol) by the same procedure as described for **6b** to afford compound **10b** (0.32 g, 53%) as a waxy solid: ^{1}H NMR (300 MHz, DMSO 80°C) δ 1.41 (9H, s), 3.61 (1H, dd, J = 14.7, 4.5), 3.78 (1H, dd, J = 14.7, 8.4), 5.26 (2H, ABq, J = 11.0, $\Delta\nu$ = 13.5), 5.70 (1H, d, J = 7.3), 5.98 (1H, dd, J = 8.4, 4.5), 6.76 (2H, bs), 7.45 (1H, d, J = 7.3); ^{13}C NMR (75.4 MHz, DMSO) δ .27.5 (3C), 46.1, 49.5, 67.9, 80.6, 92.1, 141.3, 148.9, 154.9, 165.2.

Anal. Calcd for $C_{12}H_{18}N_4O_3S$: C, 48.31; H, 6.08; N, 18.78. Found: C, 48.44; H, 6.16; N, 18.61.

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11. An acyclic structure, $AcOCH_2SCH_2CH_2N(Ac)Boc$, was assigned to this compound.

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