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Synthesis of 2,3-dihydro-1,4-dithiinyl nucleosides via Pummerer-type glycosidation

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ABSTRACT

A straightforward procedure for the preparation of nucleoside analogue **1** and its regioisomer **2** containing a dihydro-1,4-dithiin as sugar moiety has been accomplished in four steps by our readily available heterocyclic system **5**. Nucleobase insertion was carried out by direct addition of N^4-acetylcytosine to sulfoxide derivatives via Pummerer-type glycosidation reaction.

1. Introduction

The structural requirements of antiviral and antitumour nucleosides to be recognized by cellular/viral enzymes rely on three key elements: (a) the hydroxymethyl group, necessary for nucleoside phosphorylation, (b) the heterocyclic base moiety, involved in the main recognition processes through specific hydrogen bonds, and (c) the sugar moiety, which can be considered as a spacer to connect the hydroxymethyl group and the nucleobase in the correct orientation. A wide number of structural modifications at the carbohydrate moiety have been devised, with the aim to replace the furanose ring with units resembling the conformational features of natural nucleosides.[1] Particularly, replacement of the sugar skeleton with acyclic moieties, *n*-membered rings (with $n = 3–7$), equipped in some cases with *exo*- or *endo*-cyclic double bonds, has been reported.[2] Such systems quite often contain carbon, one or more heteroatoms[3] in place of/or along with *endo*-cyclic oxygen, resulting in major functional changes in the nucleoside subunits. Such a wide structural diversity in nucleoside architectures has led, over the years, to the development and approval of several molecules on the antiviral market in both racemic and enantiomerically pure form (Chart 1).[4]

In this context, our interest in sulfur-containing nucleosides[5] and six-membered nucleoside analogues[6] took us to open up a synthetic study on the preparation of heterocyclic nucleosides **1** and **2**, in which the sugar moiety is substituted by a 5,6-dihydro-1,4-dithiine ring (Fig. 1). Such a system has long been at the centre of our investigations regarding the development of novel de novo synthetic methodologies for the preparation of natural and unnatural compounds by three-carbon homologation of various

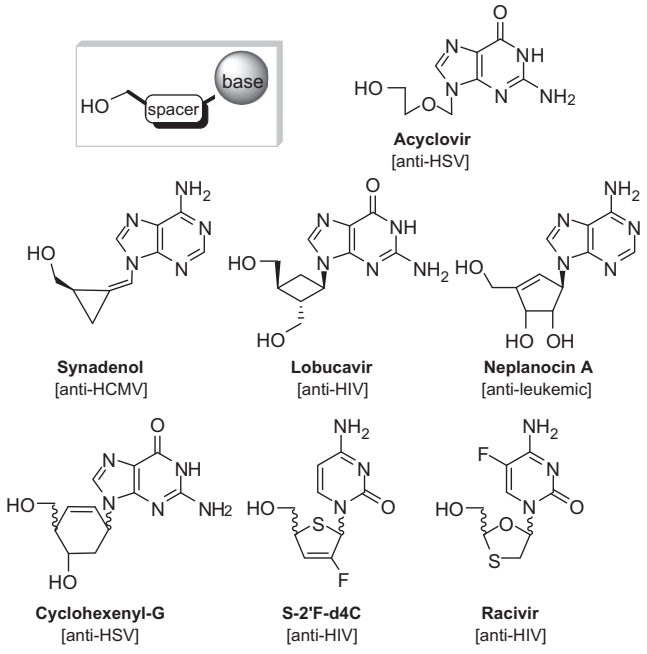

Chart 1. Sugar-modified nucleoside analogues with antiviral activity.

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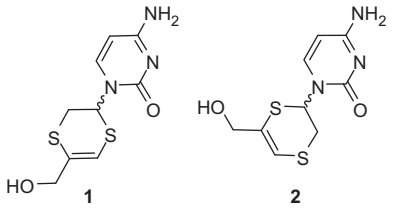


Figure 1. Dithiine nucleoside analogues **1** and **2**.

electrophiles.[7] Differently from its common employ as elongating system,[7,8] herein we report the use of dithiinyl moiety as sugar scaffold in place of the furan ring of natural nucleosides to produce novel analogues endowed with potential antiviral activity.

2. Results and discussion

In spite of the unusual shape of the dithiine skeleton, we evaluated its capacity to work as a good spacer to place the nucleobase and the hydroxymethyl group in the appropriate orientation and distance for recognition by viral/cellular enzymes. With this aim, some preliminary Hyperchem calculations[9] were carried out, overlapping the structures of nucleosides **1** and **2** with those of natural nucleosides, as well as of other potent antiviral agents. The 1,4-dithiinyl system demonstrated to possess fairly good structural features, showing the best superimposition of both the hydroxymethyl group and the nucleobase when cytosine analogue (*S*)-**2** was overlapped with the potent antiretroviral agent lamivudine (3TC, **3**) frozen in its bioactive N conformation[10] (Fig. 2).

Such studies prompted us to evaluate the biological properties of such nucleoside and to develop an expeditious procedure for its preparation as well as that of its regioisomer **1** (Fig. 1). Moreover, given the relaxed enantioselectivity displayed by some key enzymes involved in the activation of deoxycytidine analogues,[11] a comparable activity of both enantiomers should be expected. In this letter, the synthesis of target compounds **1** and **2** as *R*/*S* mixture has been performed, as the antiviral evaluation of the racemic nucleosides would give results regarding both enantiomers in one procedure.

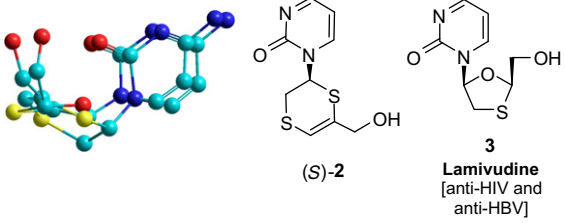


Figure 2. Superimposed structures of analogue (*S*)-**2** and lamivudine (**3**).

Synthesis of dithiinyl nucleosides **1** and **2** was envisioned to be carried out through a Pummerer-type glycosylation reaction on sulfoxides **8** and **9**, in turn obtained from our bis-thioenolether **5** (Scheme 1). As already documented,[7] preparation of the 5,6-dihydro-1,4-dithiine ring was easily carried out in four steps from methyl pyruvate **4** (Scheme 1).

The synthesis began with the protection of free alcohol **5** (Ac_2O, pyridine) and subsequent thioether oxidation of the acetate **6** with *m*-CPBA in CH_2Cl_2 to give a 55:45 mixture of two regioisomers **8b** and **9b** in 78% yield.

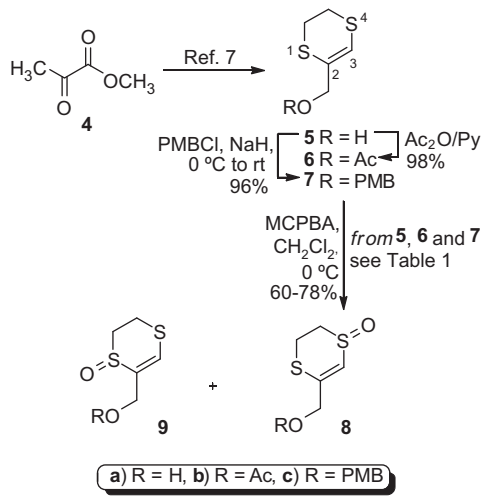
Sulfoxidation reaction was also attempted using dithiin **5** and its derivative **7** in presence of various oxidizing agents.[12,13] As shown in Table 1, the use of *m*-CPBA gave similar results on all substrates, affording the two regioisomeric sulfoxides **8a** and **9a** in approximatively 1:1 mixture (R = H) with a slight prevalence for **8** over **9** when R = Ac or PMB. The preference for the oxidation at *S*-4 of the dithiine ring was observed in most cases; only the use of a bulkier oxidizing agent, such as pyridinium dichromate (PDC), in the oxidation of dithiin **7** led to a greater excess of regioisomer **8c** (entry 2). Even the use of Kagan–Modena sulfoxidation conditions[14] (L-DET or D-DET/*t*BuOOH/Ti(*O*-*i*Pr)$_4$) did not affect the reaction outcome (entries 4 and 5). Sulfoxidation reaction seemed to be essentially driven by steric hindrance reasons at allylic position, even though an additional electronic contribute was found.[15] Indeed, energy calculation (B3LYP/6-31G*)[16] performed on **6** and **7** provided consistent explanation for the greater oxidability of *S*-4 compared to *S*-1. For both **6** and **7**, the HOMO molecular orbital is more localized on *S*-4 rather than on *S*-1 and coefficient value difference is grater in **7** (Table 2).

As sulfoxides **8** and **9** were obtained, preparation of target nucleoside analogues was carried out by a Pummerer-type glycosidation reaction. First attempts carried out on sulfoxide **8c**, under the same conditions previously reported[5] with N^4-acetylcytosine, TMSOTf and TEA in CH_2Cl_2, led as the only product of the reaction to the unexpected α,β-unsaturated aldehyde **10**. This is probably the result of an intramolecular oxido-reduction process and, as depicted in Scheme 2, it can be conjectured to occur after PMB protecting group removal, sulfoxide trimethylsilylation, thionum ion

Table 1
Sulfoxidation of dithiins **5**–**7**

Entry	Conditions[a]	**8**/**9** Ratio (% yield)		
		R = H	R = Ac	R = PMB
1	*m*-CPBA (1.0 equiv), −20 °C	50:50 (60)	55:45 (78)	60:40 (74)
2	PDC (1.0 equiv), −20 °C	ND[b]	65:35 (82)	85:15 (84)
3	PDC (1.0 equiv), rt	ND[b]	65:35 (80)	—[c] (41)
4	L-DET/*t*BuOOH/Ti(*O*-*i*Pr)$_4$, (2:1.2:1.0 equiv), −20 °C	50:50 (87)	60:40 (90)	65:35 (85)
5	D-DET/*t*BuOOH/Ti(*O*-*i*Pr)$_4$, (2:1.2:1.0 equiv), −20 °C	50:50 (89)	57:43 (91)	68:32 (86)

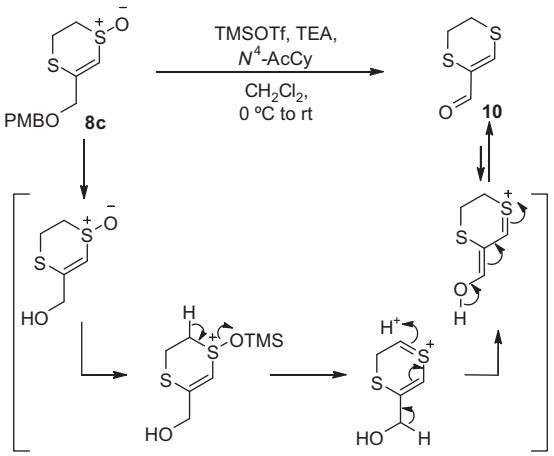
[a] CH_2Cl_2 used as solvent in all reactions.
[b] ND: not determined (concurrent oxidation of primary hydroxyl group occurred).
[c] Further *S*-4 oxidation led to formation of a sulfone as the only product of the reaction.



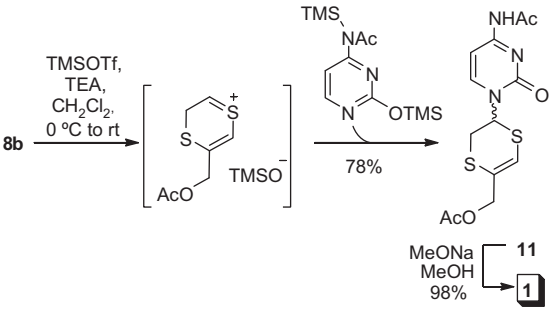
Scheme 1. Synthesis of sulfoxides **8**–**9**.

Table 2
Homo coefficients in **6** and **7**

Atom	Dithiin **6**	Dithiin **7**
S-1	0.36824	0.28018
S-4	0.44799	0.40612



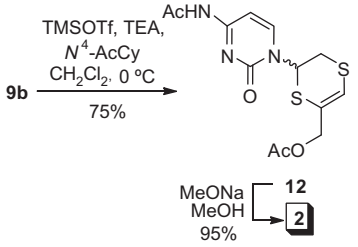
Scheme 2. α,β-Unsaturated aldehyde formation.



Scheme 3. Dihydrodithiinyl nucleoside **1** via Pummerer-type glycosidation of **8b**.

formation by TEA-mediated elimination and concurred oxidation of free hydroxyl group, to give aldehyde **10**.

On the other hand, as depicted in Scheme 3, under the same conditions the use of the more stable acetylated sulfoxide **8b** allowed to obtain the desired dihydrodithiine nucleoside derivative **11**[17] as a racemic mixture and in good yield (78%). Similarly to what observed in Scheme 2, the reaction proceeds through thionum ion intermediate mediated by TMSOTf and TEA and subsequent attack of silylated nucleobase on thionum ion. Replacement of CH_2Cl_2 with CH_3CN led to the final product with approximately the same yield, but prolonged reaction times were required.



Scheme 4. Dihydrodithiinyl nucleoside **2** via Pummerer-type glycosidation of **9b**.

Deprotection under common Zemplèn conditions (MeONa/MeOH) afforded the final target compound **1**[18] in 98% yield. Analogously, the same reactions, carried out starting from sulfoxide **9b**, led to the desired nucleoside analogue **2**[18] in 71% overall yield (Scheme 4).

3. Conclusions

In summary, a straightforward procedure for the preparation of dithiinyl nucleoside **1** and **2** has been accomplished in four steps by our readily available heterocyclic system **5**. Regioselectivity of sulfoxidation reaction of bis-thioenolethers **6**–**7** was rationalized on the basis of both steric and electronic effects. Nucleobase insertion was carried out by direct addition of N^4-acetylcytosine to sulfoxide **8b**–**9b** via Pummerer-type glycosidation reaction. Evaluation of racemic **1** and **2** as potential antiviral agents is currently in progress and will be reported elsewhere. In case, further development of asymmetric Pummerer rearrangements[19] and/or enantiomeric resolution of our mixtures by chiral HPLC will be considered to provide enantiopure (*S*)- and (*R*)-**1** as well as their regioisomers (*S*)- and (*R*)-**2**.

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^{1}H and ^{13}C NMR spectra were performed at the 'Centro Interdipartimentale di Metodologie Chimico-Fisiche' (CIMCF), Università di Napoli Federico II.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.060.

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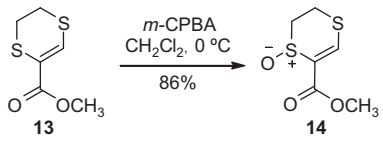
15. A full electronic contribution has been observed when the sulfoxidation reaction was performed on methyl ester derivative **13**, in which the electron withdrawing group at *C*-2 position made *S*-4 atom a weak nucleophile. However **13** could not be used for providing nucleoside **2**, owing to fair instability of sulfoxide **14** to subsequent reaction conditions.



16. Theoretical calculations were performed by SPARTAN 08 Quantum mechanics program.
17. *Pummerer-type glycosidation reaction.* Typical procedure: To a suspension of N^4-acetylcytosine (0.30 g, 2.0 mmol) in CH_2Cl_2 (10 mL) TEA (0.8 mL, 6.1 mmol) and TMSOTf (1.1 mL, 6.1 mmol) were added at 0 °C and under N_2 atmosphere. The mixture was left at room temperature for 30 min, after this time the mixture was cooled at 0 °C and a solution of sulfoxide **8b** (0.28 g, 1.36 mmol) was added dropwise. The reaction was warmed at room temperature for 2 h, then saturated aq $NaHCO_3$ was added until neutrality. The mixture was extracted with EtOAc and washed with water; the organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give a crude product whose chromatography afforded the pure {5-[4′-(methylcarboxamido)-2-oxo-1,2-dihydro-1-pyrimidinyl]-5,6-dihydro-1,4-dithiin-2-yl}methyl acetate (**11**) (78% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.11 (s, 3H, $OCOCH_3$), 2.24 (s, 3H, $NHCOCH_3$), 3.26 (dd, J = 2.3, 14.6 Hz, 1H, CH_aS), 3.40 (dd, J = 4.4, 14.6 Hz, 1H, CH_bS), 4.61 (d, J = 12.7 Hz, 1H, CH_aO), 4.65 (d, J = 12.7 Hz, 1H, CH_bO), 6.40 (dd, J = 2.3, 4.4 Hz, 1H, CHS), 6.47 (s, 1H, HC=), 7.44 (d, J = 7.3 Hz, 1H, H-5), 7.84 (d, J = 7.3 Hz, 1H, H-6), 8.42 (s, 1H, NH). ^{13}CNMR (50 MHz, $CDCl_3$): ppm 20.7 (CH_3CO), 24.9 (CH_3CO), 30.6 (CH_2S), 53.0 (CHS), 67.4 (CH_2O), 96.2 (C-5), 114.1 (HC=), 124.3 (C=CH_2), 147.4 (C-6), 155.1 (C=O), 162.5 (C=N), 170.5 (C=O). Anal. calcd for $C_{13}H_{15}N_3O_4S_2$: C, 45.73, H, 4.43, N, 12.31, S, 18.78. Found: C, 45.65, H, 4.44, N, 12.26, S, 18.84. Under the same conditions, starting from **9b** compound **12** was obtained (75% yield). {6-[4′-(Methylcarboxamido)-2-oxo-1,2-dihydro-1-pyrimidinyl]-5,6-dihydro-1,4-dithiin-2-yl}methyl acetate (**12**) ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.13 (s, 3H, $OCOCH_3$), 2.25 (s, 3H, $NHCOCH_3$), 3.26 (dd, 1H, J = 2.0, 13.9 Hz, 1H, CH_aS), 3.35 (dd, 1H, J = 4.6, 13.9 Hz, 1H, CH_bS), 4.70 (d, J = 12.7 Hz, 1H, CH_aO), 4.73 (d, J = 12.7 Hz, 1H, CH_aO), 6.45 (s, 1H, HC=), 6.48 (dd, J = 2.0, 4.6 Hz, 1H, CHS), 7.47 (d, J = 7.5 Hz, 1H, H-5), 7.80 (d, J = 7.5 Hz, 1H, H-6), 8.35 (s, 1H, NH). ^{13}CNMR (50 MHz, $CDCl_3$): ppm 20.8 (CH_3CO), 24.9 (CH_3CO), 28.8 (CH_2S), 53.8 (CHS), 67.2 (CH_2O), 96.4 (C-5), 116.0 (HC=), 123.1 (C=CH_2), 147.2 (C-6), 154.8 (C=O), 162.7 (C=N), 170.6 (C=O). Signal assignments have been unambiguously determined on the basis of 2D experiments. Anal. calcd for $C_{13}H_{15}N_3O_4S_2$: C, 45.73, H, 4.43, N, 12.31, S, 18.78. Found: C, 45.80, H, 4.44, N, 12.28, S, 18.70.
18. *Data for (R/S) 4-amino-1-[5-(hydroxymethyl)-2,3-dihydro-1,4-dithiin-2-yl]-1,2-dihydro-2-pyrimidinone* (**1**): ^{1}H NMR (200 MHz, CD_3OD): δ 3.18–3.25 (m, 2H, CH_2S), 4.12 (dd, J = 0.9, 13.0 Hz, 1H, CH_aOH), 4.21 (dd, J = 0.9, 13.1 Hz, 1H, CH_bOH), 5.87 (d, J = 7.6 Hz, 1H, H-6), 6.34 (dd, J = 2.8, 3.8 Hz, 1H, CHS), 6.39 (d, J = 0.9 Hz, 1H, HC=), 7.66 (d, J = 7.6 Hz, 1H, H-5). ^{13}CNMR (50 MHz, CD_3OD): ppm 30.6 (CH_2S), 55.2 (CHS), 67.2 (CH_2O), 95.5 (C-5), 113.1 (HC=), 130.6 (C=CH_2), 145.2 (C-6), 157.8 (C=O), 167.8 (C=N). Anal. calcd for $C_9H_{11}N_3O_2S_2$: C, 42.01, H, 4.31, N, 16.33, S, 24.92. Found: C, 41.94, H, 4.30, N, 16.28, S, 25.00. *Data for (R/S) 4-amino-1-[6-(hydroxymethyl)-2,3-dihydro-1,4-dithiin-2-yl]-1,2-dihydro-2-pyrimidinone* (**2**): ^{1}H NMR (200 MHz, CD_3OD): δ 3.15-3.34 (m, 2H, CH_2S), 4.05 (d, J = 13.1 Hz, 1H, CH_aOH), .4.07 (d, J = 13.1 Hz, 1H, CH_bOH), 5.84 (d, J = 7.6 Hz, 1H, H-6), 6.25 (dd, J = 2.5, 4.8 Hz, 1H, CHS), 6.46 (d, J = 0.9 Hz, 1H, HC=), 7.63 (d, J = 7.6 Hz, 1H, H-5). ^{13}CNMR (75 MHz, CD_3OD): ppm 31.8 (CH_2S), 54.0 (CHS), 67.2 (CH_2O), 95.3 (C-5), 112.0 (HC=), 130.5 (C=CH_2), 145.4 (C-6), 157.6 (C=O), 167.4 (C=N). Signal assignments have been unambiguously determined on the basis of 2D experiments. Anal. calcd for $C_9H_{11}N_3O_2S_2$: C, 42.01, H, 4.31, N, 16.33, S, 24.92. Found: C, 41.90, H, 4.32, N, 16.37, S, 24.99.
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