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Synthesis of 4′-thionucleosides by 1,3-dipolar cycloadditions of the simplest thiocarbonyl ylide with alkenes bearing electron-withdrawing groups

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Abstract—Reactions of the simplest thiocarbonyl ylide with a variety of appropriate alkenes bearing electron-withdrawing substituents afforded the corresponding tetrahydrothiophenes, which could be easily elaborated into hydroxy and hydroxymethyl derivatives and then coupled with nucleobases to produce different 4′-thionucleosides. Particularly, α- and β-anomers of 1-[3,4-bis(hydroxymethyl)tetrahydro-2-thienyl]-thymine, -cytosine, -uracil and -fluorouracil were prepared with dimethyl fumarate and maleate, while 1-[4-(hydroxymethyl)tetrahydro-2-thienyl]- and 1-[4-(hydroxymethyl)tetrahydro-3-thienyl]-thymine, -cytosine, -uracil and -fluorouracil were prepared with a chiral α,β-unsaturated amide. These processes, simple in the experimental conditions and large availability of the starting materials, affording moderate to good yields of 4′-thionucleosides, represent an optimum alternative to those, already known, based on sugars, which often have the drawbacks of a higher number of steps and lower yields.

In the past 15 years, a wide variety of nucleoside analogues, modified in the carbohydrate moiety and/or in the nucleobase, have been prepared and tested for antiviral and antitumoural activities.[1] One of the first modifications was the isosteric substitution of the oxygen atom with a sulfur atom in furanonucleosides of adenine affording the corresponding 4′-thio-derivatives.[2] These 4′-thionucleosides showed potent anti-herpes activities, and several other analogues, such as 4′-thiothymidine and 2′-deoxy-4′-thiocytidine, exhibited potent cytotoxicity. On a chemical level, it was envisaged that this modification would modulate stereoelectronic and steric effects in the tetrahydrothiophene moiety. Evidences were accumulating that the presence of a sulfur atom in the sugar ring stabilized the N-glycosidic bond with respect to phosphorolysis.[3] Thus 4′-thioinosine was known to be resistant to phospholytic cleavage, which is a normal pathway in nucleoside catabolism. This is a major advantage of 4′-thionucleosides, since several '4′-oxy' antivirals have a drawback with regard to their metabolic stability caused by nucleoside phosphorylases. In addition, the potent antiviral activity and cytotoxicity of 4′-thionucleosides suggest that they are well recognized as substrates by both viral and host cell kinases.

Frequently, synthetic approaches to 4′-thionucleosides have made use of displacement reactions of a sugar leaving group with a sulfur-containing nucleophile, followed by ring closure or ring contraction,[4] acetolysis of a sugar γ,γ-diethoxy episulfide, or ring closure of sugar dialkyl dithioacetal,[5] since the initial stereochemistry of sugars directly controls that one of the final products through stereo-specific or -selective steps.

In addition to sugars or their derivatives, only a few non-sugar starting materials, such as protected thiophenes,[6] L-glyceraldehyde,[7] chiral thiolactones,[8] or (*S*)-(−)-glycitol,[9] have been used.

However, since tetrahydrothiophene syntheses starting from sugars have often met various difficulties, among

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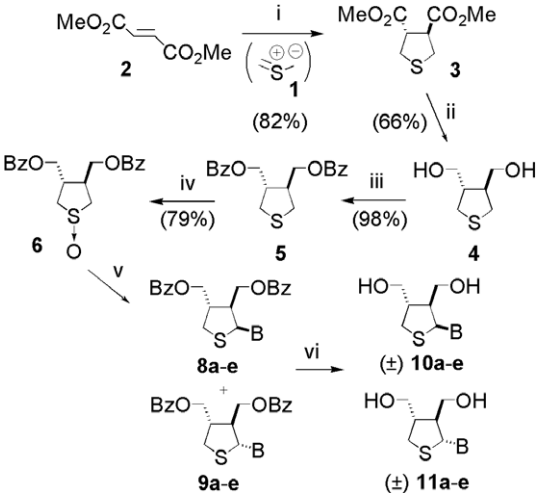
which, for example, the frequent involvement of many steps, and on the basis of our experiences on the nitrile oxide and nitrone chemistry in the construction of N,O-nucleosides,[10] we planned to synthesize the tetrahydrothiophene moiety via a practical method involving the 1,3-dipolar cycloaddition of the simplest thiocarbonyl ylide **1**,[11] to a variety of appropriate alkenes bearing electron-withdrawing substituents such as commercially available methyl fumarate **2** and maleate **12**. From their tetrahydrothiophene adducts **3** and **13**,[12] 4′-thionucleosides were then constructed by conventional synthetic methods, among which the coupling reaction of the corresponding sulfoxides with a persilylated nucleobase is largely applied in most approaches.[13] This thioglycosylation reaction is based on the sila-Pummerer-type reaction,[14] even if it presents the drawback of the poor β-selectivity. The undesired α-isomer is, almost always, the main product, while the β-anomer is formed in excess only in the presence of a neighbouring group of an adjacent acyloxy or benzyloxy group.[15] In addition, by using (*E*)-3-benzoyloxypropenoyl-(1*S*)-camphorsultam **19** with **1**, tetrahydrothiophene rings **20** and **21**[16] were obtained, from which the construction of the desired 4′-thionucleosides bearing the nucleobase and the hydroxymethyl group in positions 3 and 4 or 2 and 4, respectively, was achieved. As first noted, besides thymine and cytosine, uracil and its 5-fluoro derivative were also used as nucleobases.

The reaction of **1**, generated by CsF decomposition[17] of the very easy to synthesize chloromethyltrimethylsilylmethyl sulfide,[18] with methyl fumarate (**2**) afforded *trans*-dimethyl tetrahydrothiophene-3,4-dicarboxylate (**3**),[8] which was reduced to diol **4** by $LiAlH_4$, and then converted into **5** by protection with benzoyl chloride (Scheme 1).



Scheme 1. Reagents and conditions: (i) $Me_3SiCH_2SCH_2Cl$, CsF, CH_3CN, 0 °C, overnight; (ii) $LiAlH_4$, THF, 0 °C, 1 h; (iii) BzCl, Py, rt, 2 h; (iv) *m*-CPBA, CH_2Cl_2, −40 °C; (v) silylated nucleobase (**7a–e**), TMSOTf, Et_3N, CH_2Cl_2, PhMe, rt, overnight; (vi) NH_3 concd, MeOH, rt, 12 h.

Table 1. Yields[a] (%) and anomeric ratios[b] of **8**, **9a–d** and **10**, **11a–d**

Nucleobase	**8**+**9**	**8**:**9**	**10**	**11**
Thymine **7a**	78.0	1:18	4.0	73.5
Cytosine **7b**[c]	72.0	1:15	4.0	67.5
Uracil **7c**	80.0	1:20	3.0	76.0
5-F-Uracil **7d**	79.0	1:18	4.0	74.0
Adenine **7e**[d]	68.0	1:12	5.0	62.5

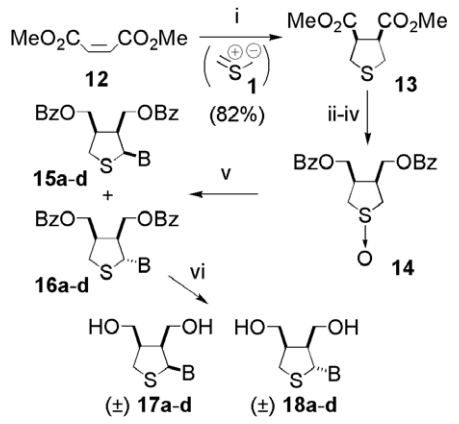
[a] Isolated yields based on **6**.
[b] Determined by ^1H NMR spectroscopy.
[c] Cytosine was used as *N*-benzoyl derivative until the last step.
[d] Adenine was used as 6-chloro derivative, which was aminated in the last step.

After the oxidation of 3,4-dibenzoyltetrahydrothiophene derivative **5** with *m*-CPBA into sulfoxide **6**, the subsequent Pummerer-type reaction performed in the presence of nucleobases **7a–d**, as silylated derivatives, trimethylsilyl triflate and triethylamine, provided a mixture of corresponding 4′-thionucleosides **8a–d** and **9a–d** with the prevalence of β-anomers[9] **9a–d** for which a control attributable to the participation of the neighbouring benzoyloxy group can be invoked, while α-anomers[9] **8a–d** were obtained in very low yields (Table 1). The purification of anomeric mixture by means of preparative HPLC and subsequent deprotection of hydroxyl groups with methanolic ammonia gave β-anomers **11a–d** in moderate to good yields (Table 1). The structures and stereochemistry of **10a–d** and **11a–d** were assigned on the basis of their analytical data and ^1H and ^{13}C NMR spectra. Particularly, NOE experiments easily allowed the assignation of their anomeric configurations. Irradiation of 2-H proton in β-anomers **11a–d** gave a NOE enhancements (1.3–1.6%) on methylene protons of C_4-hydroxymethyl groups, while no NOE effect was observed on the same experiments about α-anomers **10a–d**.

4′-Thioadenosine β-**11e** was also synthesized (Scheme 1) in order to compare the results of our method with that one of Kato and co-workers,[19] who, starting from (+)-diethyl L-tartrate, synthesized (*S*,*S*)-1,4-bis(benzoyloxy)-2,3-epoxy-butane according to the protocol of Nicolaou et al.[20] and from this latter, β-**11e**, but through 13 steps and in a low yield (38%).

By following the same sequence of reactions, but with methyl maleate **12**[21] instead of fumarate **2** (Scheme 2), mixtures of isomers **15a–d** and **16a–d** were obtained in a good yield (Table 2). Their separation by means of HPLC and finally their hydrolysis with methanolic ammonia gave **17a–d** and **18a–d** in the yields reported in Table 2.

NOE experiments allowed to achieve, also in this case, the stereochemistry of isolated nucleosides **17a–d** and **18a–d**: the irradiation of H-3 protons caused the enhancement of H-2 and H-1 protons in **17a–d**, and the enhancement of only H-2 proton in **18a–d**. The α-anomers[9] **18a–d** were isolated as prevalent anomers because of the participation of the neighbouring benzoyloxy group, which directs the attack to their opposite ring face.



Scheme 2. Reagents and conditions: (i) $Me_3SiCH_2SCH_2Cl$, CsF, CH_3CN, 0 °C, overnight; (ii) $LiAlH_4$, THF, 0 °C, 1 h; (iii) BzCl, Py, rt, 2 h; (iv) *m*-CPBA, CH_2Cl_2, −40 °C; (v) silylated nucleobase (**7a–d**), TMSOTf, Et_3N, CH_2Cl_2, PhMe, rt, overnight; (vi) NH_3 concd, MeOH, rt, 12 h.

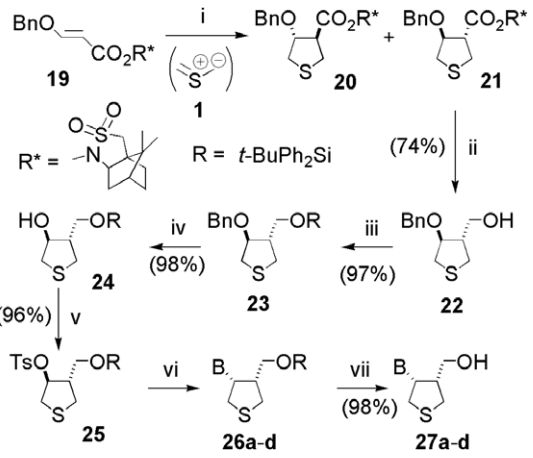
Table 2. Yields[a] (%) and anomeric ratios[b] of **15**, **16a–d** and **17**, **18a–d**

Base	15+16	15:16	17	18
Thymine **7a**	80.0	1:18	75.0	4.0
Cytosine **7b**[c]	74.0	1:16	69.0	4.0
Uracil **7c**	83.0	1:20	79.0	3.0
5-F-Uracil **7d**	81.0	1:18	76.0	4.0

[a] Isolated yields based on **14**.
[b] Determined by ^1H NMR spectroscopy.
[c] Cytosine was used as *N*-benzoyl derivative until the last step.

The generation of thiocarbonyl ylide **1** in the presence of the enantiopure (*E*)-3-benzoyloxypropenoyl-(1*S*)-camphorsultam **19** afforded the two diastereomeric adducts **20** and **21** in excellent yield (92%) and high diastereoselectivity (**20**:**21** = 1:9).[12] The two adducts were separated by silica gel column chromatography, and then the chiral camphorsultam inductor was removed from **21** by reduction with $LiAlH_4$ at 0 °C to give **22**, which was protected with *tert*-butyldiphenylsilyl chloride (TBDPSCl) affording **23**. The debenzylation of **23** into **24** and subsequent activation of the hydroxy group for S_N2 displacement gave tosylate **25**. Reactions of **25** with anions[22] of nucleobases **7a–d** afforded protected nucleosides **26a–d** which, finally, were desilylated with TBAF/THF to give enantiopure thionucleosides **27a–d** (Scheme 3, Table 3). The structure of **27a–d** was confirmed from analytical and spectroscopic data and stereochemistry was assigned with the aid of NOE experiments, which indicated an enhancement of 14.5% between H-3 and H-4 protons.

In addition, the tosyl derivative **25** was subjected to an other process including the elimination of the tosylate group with NaH in DMF to produce the protected 4-hydroxymethyl thioglycal **28**. The addition of phenylselenyl chloride and nucleobases **7a–d**, as silylated derivatives, to **28** provided adducts **29** and **30** as anomeric mixtures in satisfying yield from which subsequently the phenylselenyl substituent was eliminated to give **31** and **32** by radical reduction with tributyltin

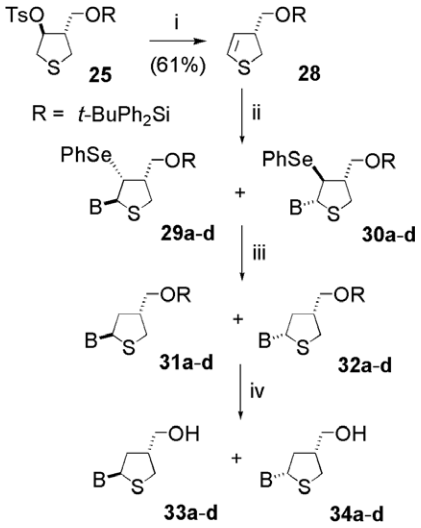


Scheme 3. Reagents and conditions: (i) $Me_3SiCH_2SCH_2Cl$, CsF, CH_3CN, 0 °C, overnight; (ii) $LiAlH_4$, THF, 0 °C, 1 h; (iii) TBDPSCl, DMAP, Et_3N, rt, 12 h; (iv) H_2, Pd/C, AcOEt, rt, 4 h; (v) TsCl, Py, rt, 24 h; (vi) silylated nucleobase (**7a–d**), 18-Crown-6, K_2CO_3, DMF, 100 °C, 18 h; (vii) TBAF, THF, rt, 1 h.

Table 3. Yields[a] (%) of enantiomerically pure protected nucleosides **26a–d**

Base	26
Thymine **7a**	46.0
Cytosine **7b**[b]	45.0
Uracil **7c**	38.0
5-F-Uracil **7d**	40.0

[a] Isolated yields based on **25**.
[b] Cytosine was used as *N*-benzoyl derivative until the last step.



Scheme 4. Reagents and conditions: (i) NaH, DMF, 0 °C–rt, 3 h; (ii) PhSeCl, silylated nucleobase (**7a–d**), CH_3CN, 0 °C, 3 h; (iii) TBAF, THF, rt, 30 min; (iv) Bu_3SnH, Et_3B, O_2, PhMe, rt, 12 h.

hydride and triethyl borane at −78 °C in the presence of a continuous flow of oxygen (Scheme 4). In this way, desired α- and β-thioapionucleosides **33** and **34**[23] (Table 4) were obtained with good diastereoselectivity accord-

Table 4. Yields[a] (%) and anomeric ratios[b] of **29**, **30a–d**, **31**, **32a–d** and **33**, **34a–d**

Nucleobase	**29+30**	**29:30**	**31+32**	**31:32**	**33**	**34**
Thymine **7a**	82.0	1:10	64.0	1:9	4.0	47.0
Cytosine **7b**[c]	74.0	1:6	61.0	1:6	5.0	36.0
Uracil **7c**	84.0	1:12	69.0	1:10	5.0	52.0
5-F-Uracil **7d**	80.0	1:8	66.0	1:8	4.0	45.0

[a] Isolated yields based on **28**.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Cytosine was used as *N*-benzoyl derivative until the last step.

ing to Haraguchi et al.[24] and then with a process that registers a minor number of simpler steps with respect to that one of Jeong and co-workers.[25]

In conclusion, this strategy of thiocarbonyl ylide cycloadditions leading to suitable tetrahydrothiophene rings, which are coupled with a nucleobase, provides an unprecedented and convenient route to different 4′-thionucleosides. It is based on the ready accessibility of the starting materials for the thiocarbonyl ylide preparation, and, above all, for the simplicity of the moderate to good conversion of [3+2] cycloadditions. Investigations on the antiviral and antitumoural activities of these and several other nucleosides will be the object of a next work. Particularly, in addition to reactions with alkenes bearing other different electron-withdrawing groups, reactions of the α-hydroxymethyl substituted thiocarbonyl ylide will be investigated in order to examine the stereochemical outcome due to a chiral 1,3-dipole, if necessary in the presence of chiral auxiliaries, by which the control of the stereochemistry can be effected.

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