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Highly efficient synthesis of 2′,3′-didehydro-2′,3′-dideoxy-β-nucleosides through a sulfur-mediated reductive 2′,3′-*trans*-elimination. From iodomethylcyclopropanes to thiirane analogs

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Abstract—Taking into account the thiophilic properties of iodine, a very simple methodology to achieve 2′,3′-didehydro-2′,3′-dideoxy-β-nucleosides in high yield was performed, using mild, and inexpensive conditions, by means of the treatment of 2′-deoxy-3′,5′-dibenzoyl-2′-iodo-β-nucleoside derivatives with NaHS. The process has shown to be highly dependent of the relative geometry between the iodine atom and the adjacent leaving group. In this way, different essays carried out with pyranose derivatives have concluded in no reaction when the vicinal groups to eliminate do not adopt a *trans*-diaxial disposition. In addition, the treatment of 2-iodomethyl-cyclopropane-1,1-dicarboxylic acid diethyl ester under the same conditions softly and readily leads to the obtention of a mixture of the expected 2-allyl-malonic acid diethyl ester (as the minor product) and the thiirane derivative 2-thiiranylmethyl-malonic acid diethyl ester (as the major product). In this case, the responsible of the reaction progress are the nucleophilic properties of the sulfur atom rather than the thiophilic character of the iodine atom.
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The synthesis of nucleoside analogs in which the sugar and/or the heterocyclic moiety have been modified have received much attention as a consequence of their general biological activity and the potential use of such molecules as antiviral and antineoplasic therapeutic agents.[1] Particularly, 2′,3′-didehydro-2′,3′-dideoxy nucleoside derivatives constitute noteworthy compounds with anti-HIV activity,[2] which compared with AZT[3] display a lower toxicity toward bone marrow.[4]

Among the different methodologies used in the synthesis of the title compounds, they could be highlighted those employing 2′-deoxy-[5] or 2′,3′-dideoxynucleosides,[6] 2′,3′-diprotected ribonucleosides (cyclic orthoester,[7] cyclic thiocarbonate,[7b,8] *bis*-xanthate[8b]) or the more simple unprotected diol,[9] 2,2′-anhydro-nucleosides,[10] and unsaturated acyclic nucleosides.[11] Nevertheless, the most popular methodology is based on the use of 2′-deoxy-2′-halo-3′-leaving-group (or vice versa) through a *cis* or *trans* reductive elimination process.[12] Unfortunately, it has been frequently observed a partial decomposition of the nucleoside through a retro-addition process finishing with the loss of the pyrimidinic base. Since multigram quantities of these unsaturated nucleoside analogs are required for advanced biological studies, methods that facilitates their synthesis in a more general and economical manner than the preparations previously described has been explored.

Iodine atom has been probed to have excellent thiophilic properties. Therefore, the formation of glycosidic bonds from the corresponding alkyl- or phenyl-thio glycosides using NIS (or I_2 in some cases) as thiophilic agent has became one of the most successful methods.[13] Moreover, the reaction between NIS and thioglycosides[14] or thiocarbonates[15] has been shown as highly adequate for the synthesis of nucleoside derivatives.

Considering the thiophilic character of iodine, we present in this work a very simple methodology for the synthesis of 2′,3′-didehydro-2′,3′-dideoxy-β-nucleosides in high yield (90% → quantitative) from their corresponding 2′-deoxy-2′-iodo analogs (**4**) (Scheme 1).[16] In addition, some experiments carried out in order to study

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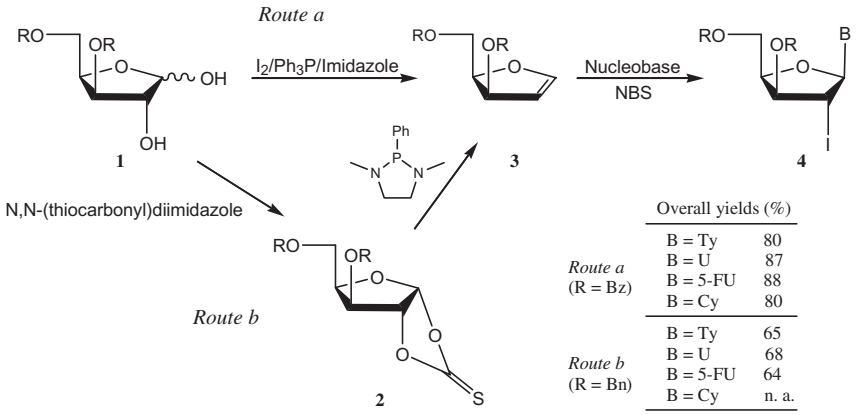


		Overall yields (%)
Route a (R = Bz)	B = Ty	80
	B = U	87
	B = 5-FU	88
	B = Cy	80
Route b (R = Bn)	B = Ty	65
	B = U	68
	B = 5-FU	64
	B = Cy	n. a.

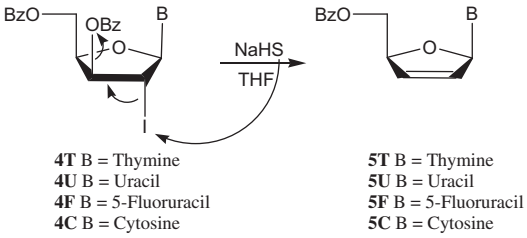
Scheme 1. The synthesis of the 2′-deoxy-2′-iodo-β-nucleoside derivatives.

the stereochemistry of the elimination process have led to the easily conversion of iodomethylcyclopropanes in thiiranes.

Thus, the treatment of **4** (R = Bz, Bn) with NaHS[17] leads to the expected 2,3-didehydro-pent-2-enofuranosyl nucleoside derivatives (**5**) only for R = Bz, while compounds with R = Bn remained unreacted (Scheme 2). This fact is not only due to the greater leaving-group character of benzoate substituent but also to the formation of a more stable sodium benzoate salt.

Presumably, the attack of HS^- to iodine leads to the formation of the IHS species, which likely reacts with another NaHS molecule to give the most stable NaI + H_2S_2 system. Reactions are completely clean at room temperature, leading after 1 h to the corresponding 2′,3′-didehydro-2′,3′-dideoxy derivatives (**5**) in very high yield (Table 1).

We believe that the elimination process presents an E2-like stereochemistry. Thus, when compounds 1-(3,4,6-tri-*O*-acetyl-2-deoxy-2-iodo-β-D-*gluco*-pyranosyl)thymine (**6a**) and 1-(3,4,6-tri-*O*-acetyl-2-deoxy-2-iodo-α-D-*manno*-pyranosyl)thymine (**6b**)[19] have been treated under the same conditions, no reaction was observed.



Scheme 2. The formation of the enofuranosyl nucleoside derivatives.

Table 1. 2′,3′-Didehydro-2′,3′-dideoxy-β-nucleoside derivatives produced via Scheme 2[18]

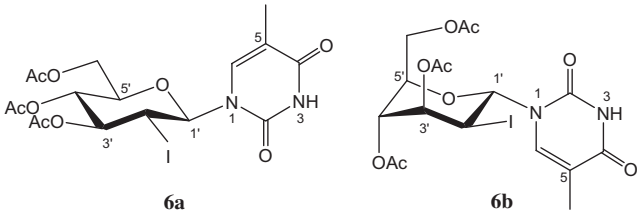
Entry	Nucleobase	Enofuranosyl nucleoside (Yield %)
1	Thymine	**5T** (Quantitative)
2	Uracil	**5U** (92)
3	5-Fluoruracil	**5F** (90)
4	Cytosine	**5C** (90)

It can be seen that derivative **6a** presents a *trans*-diequatorial relation between iodine and the acetyl group present at C-3′, while in the case of **6b** the disposition is *cis*-axial/equatorial for the same substituents (Scheme 3).

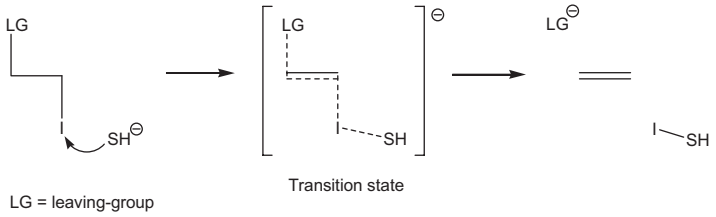
Both dispositions are inadequate for the elimination since the new π bond is formed by overlap of the σC–I bond with the σ*C-LG antibonding orbital, which must be co-planar in order to facilitate the stereoelectronic interaction between them. That allows populating the antibonding orbital in an effective manner giving rise to the elimination process (Scheme 4).

Searching for new stereospecific evidences and applications for this process, 2-iodomethyl-cyclopropane-1,1-dicarboxylic acid diethyl ester (**7**)[20] was treated with NaHS as before (Scheme 5).[21] The readily available compound **7** was chosen because the iodine atom is placed in an open-chain sector (avoiding in this manner the use of other rigid systems as in derivatives **4**) and presents a bond on the cyclopropane ring in *trans* position with respect to the iodine atom acting as living group.

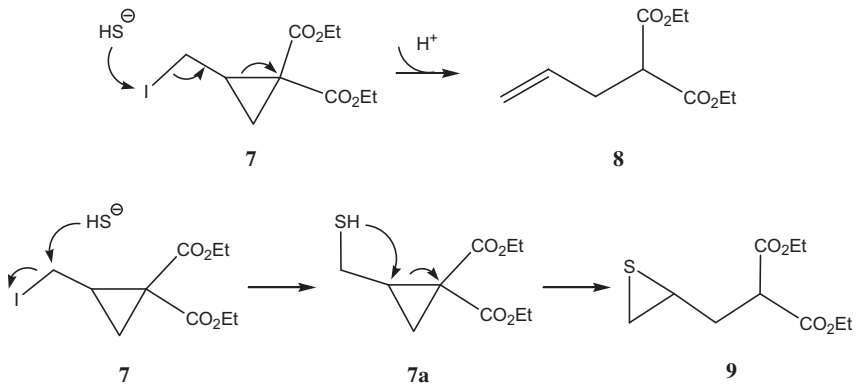
Therefore, considering the thiophilic aptitude of the iodine atom, it was expected that the reaction takes place via Scheme 5 leading to the alkene **8**. Nevertheless, this compound was only found in a poor yield (22%). In fact, the major product (46%) has been identified as the thiirane derivative **9** (Scheme 5).



Scheme 3. *Gluco* (**6a**) and *manno* (**6b**) 2′-iodo-nucleoside derivatives shown unreacted after the treatment with NaHS.



Scheme 4. Geometrical requirements for the leaving-groups.



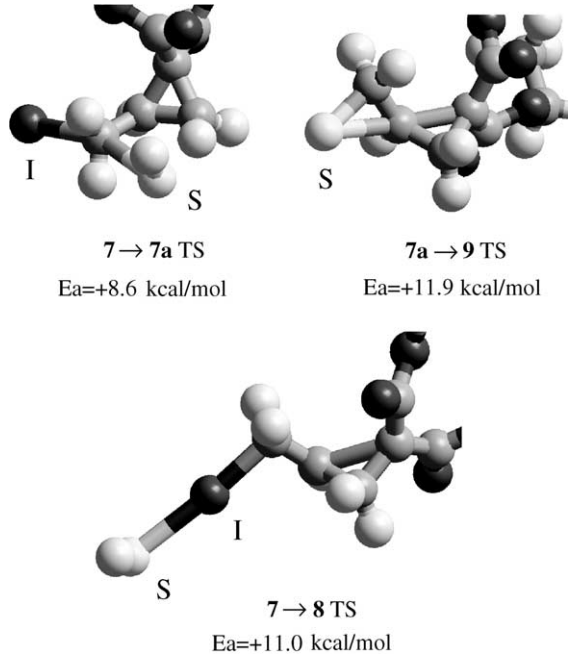
Scheme 5. Schematic mechanism for the transformation of **7** in the presence of NaHS.

PM3 semiempirical calculations[22] show low energy transition states for the **7** → **7a** → **9** sequence, competing with the activation energy for the **7** → **8** transformation (Scheme 6). From a qualitative point of view, that would mean that the weight of the thiophilic character of the iodine atom is approximately the same as the nucleophilic character of the sulfur atom.

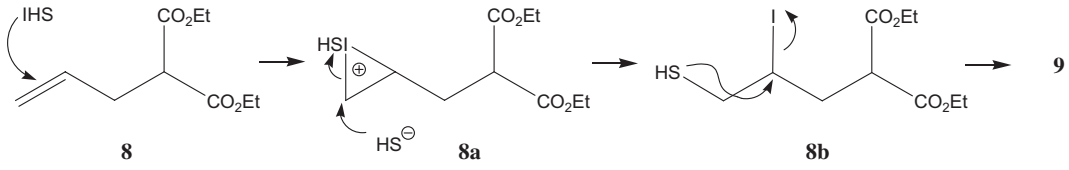
On the other hand, compound **8** could react with the already generated HIS species in order to give also the thiirane **9** (Scheme 7). This fact could then explain the low yield achieved in the synthesis of alkene **8**.

The reason for the different reactivity encountered between the 2′-iodo-nucleosides and the iodomethylcyclopropane derivative probably falls upon the fact that the nucleophilic attack of the sulfur atom on the nucleoside system is sterically hindered. Conversely, for the iodomethylcyclopropane system, the iodine atom is placed on an open-chain fraction, the nucleophilic displacement being more straightforward.

In summary, we have presented an extremely easy and performing way to attain 2′,3′-didehydro-2′,3′-dideoxy-β-nucleosides through a sulfur-mediated reductive



Scheme 6. Transition states involved in the **7** → **9** and **7** → **8** transformations. Carboxylate groups are cut in order to zoom in figures.



Scheme 7. A possible simplified mechanism for the **8** → **9** transformation.

2′,3′-*trans*-elimination, on the basis of the thiophilic character of the iodine atom. The stereochemistry is in all probability *trans*, because experiences carried out with 2′-iodo-nucleosides not having a *trans* relation between the two leaving groups did not react in the same conditions. Moreover, the same protocol applied on the iodomethylcyclopropane **7**, preferentially leads to the formation of the thiirane derivative **9**. This preference can be explained on the basis of the further reaction undergone by derivative **8** to give thiirane **9**, since PM3 semiempirical calculations show similar activation energies for both processes.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.11.087. Complete IR, $[\alpha]_D$, NMR data, and mass spectra of products **5F**, **6a**, **6b**, and **9** along with the energies and Cartesian coordinates of all the calculated structures are available.

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17. Compounds **4T**, **4U**, **4F**, and **4C** (1 mmol) in THF (10 mL) were individually treated with NaHS (260 mg), the suspension being stirred for 1 h at room temperature. After this time, the mixture was concentrated under reduced pressure and the residue was extracted with

Cl_2CH_2–H_2O. The organic layer was dried ($MgSO_4$ anhyd), filtrated, and evaporated under reduced pressure. The residue was purified by column chromatography (Cl_2CH_2–MeOH (20/1)), to yield, respectively, **5T**, **5U**, **5F**, and **5C** (see Table 1).

18. The methodology successfully employed in the synthesis of 4 derivatives (See Ref. 16b) failed in the case of purines because mixtures were obtained (addition by the nitrogens in 9 and 11 positions and further addition of iodine to the purine moiety).
19. See also Ref. 13b: 3,4,6-tri-*O*-acetyl-D-glucal (1 mmol) was treated with persilylated thymine (2 mmol) and NIS (1 mmol) in dried CH_2Cl_2 (30 mL). After 2 h, the solution was successively washed with a 10% aqueous solution of $Na_2S_2O_3$ (20 mL), water, saturated aqueous solution of $NaHCO_3$ and water. The organic layer was dried ($MgSO_4$ anhyd), filtered, and evaporated under reduced pressure until dryness. The residue was purified by column chromatography (Et_2O–hexane (8/1)), to yield first the unreacted starting material (0.34 mmol, 34%), then **6a** (0.21 mmol, 21%), and finally **6b** (0.36 mmol, 36%).
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21. Compound **7** (1.47 mmol) in THF (10 mL) was treated with NaHS (300 mg) as indicated in Ref. 17. The residue was purified by column chromatography (Et_2O–hexane (1/20)), to yield first **8** (0.32 mmol, 22%) and then **9** (0.68 mmol, 46%).
22. Hyperchem Release 7.5, Hypercube, Inc., 1115 NW 4th Street, Gainesville, FL 32601, USA.