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A Stereoselective Approach to Nucleosides and 4′-Thioanalogues from Acyclic Precursors

Daniel Chapdelaine, Benoit Cardinal-David, Michel Prévost, Marc Gagnon, Isabelle Thumin, and Yvan Guindon*

Institut de recherches cliniques de Montréal (IRCM), Bio-organic Chemistry Laboratory, 110 avenue des Pins Ouest, Montréal, Québec, Canada H2W 1R7, Department of Chemistry, Université de Montréal, C.P. 6128, succursale Centre-ville, Montréal, Québec, Canada, H3C 3J7 and Department of Chemistry, McGill University, 801 Sherbrooke Street West, Montréal, Québec, Canada, H3A 2K6

Received July 9, 2009; E-mail: yvan.guindon@ircm.qc.ca

Abstract: D- and L-nucleosides and analogues thereof, including the 4′-thionucleoside series, are one of the most important biological and pharmaceutically active classes of compounds. A novel approach to their synthesis from chiral acyclic thioaminal, bearing the nucleobase, is described.

Introduction

Since endogenous nucleosides are key components of the molecular building blocks of life, one should not be surprised of the critical role that analogues of these compounds play in the treatment of various diseases. For example, three drugs in this compound class decitarabine,[1] clofarabine,[2] and 5-azacytidine[3] (AZT) have been recently approved for the treatment of leukemic and myelodysplastic syndromes. Analogues, such as the 4′-thio-β-D-arabinofuranosyl (4′-thio-Ara-C), have shown improved activity against solid tumors relative to their "*oxa*" counterparts due to an increase in stability toward enzyme-mediated hydrolysis,[4] that results in improved pharmacokinetic properties. Similarly 4′-thio-oligonucleosides form duplexes with similar affinity as that of their "*oxa*" counterparts with the additional benefit of possessing nuclease-promoted strand scission resistance.[5] While most of these analogues exert their effects through termination of DNA elongation, alternate mechanisms also include inhibition of ribonucleotide reductase and DNA methylation.

Nucleoside analogues are also used as antiviral agents[6] (e.g., zidovudine [AZT]).[7] Of particular importance, from a structural standpoint, is the discovery that analogues in the L-series could also be inhibitors of crucial enzymes such as the reverse transcriptase of HIV (e.g., lamivudine [L-3TC]).[7]

A novel approach to the synthesis of nucleoside analogues should therefore take into account the need to access both 4′-*oxa* and 4′-*thio* molecules in D- and L-series. Highlighted in Figure 1 are the 1,2-*cis* isomers which, for steric reasons, are difficult to prepare using the present approaches.

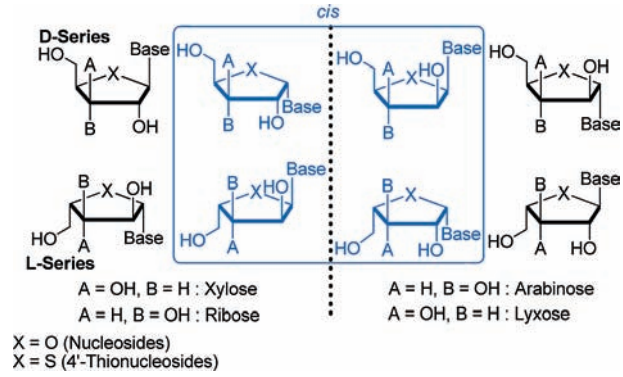

Figure 1. Nucleoside and 4′-thionucleoside analogues in the xylose, ribose, arabinose, and the lyxose series.

We have synthesized 16 of the possible 32 isomers depicted in Figure 1. Two stereoselective cyclizations of acyclic chiral thioaminals bearing a nucleobase at C-1′ are used, a novel approach that is reported herein.

Results and Discussion

The existing paradigm that widely governs the synthesis of nucleosides dictates that a nucleobase (purine or pyrimidine, modified or not) be attached to an activated cyclic glycosyl or thioglycosyl donor in a bimolecular reaction.[8] The stereoselectivities observed in the coupling steps depends either on steric effect, anchimeric participation from a neighboring acyloxy group,[9] 1,3-induction (ribose series),[10] or a concerted stereospecific displacement of an anomeric halide.[11]

Specifically the limits of this approach lie first in the syntheses of the thioglycosyl donors which often are poorly yielded. Second, the synthesis of sterically encumbered analogue mol-

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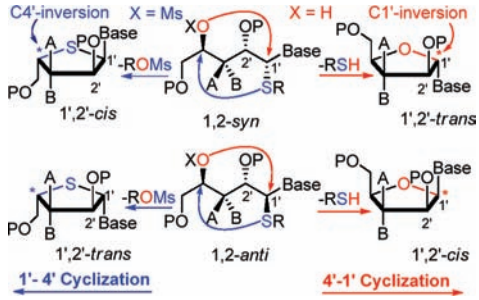
Scheme 1. C4′−C1′ (red arrow) and C1′−C4′ (blue arrow) Cyclization Pathways



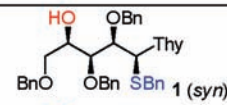
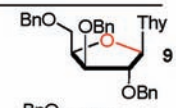
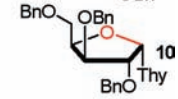
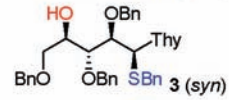
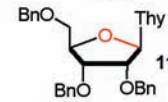
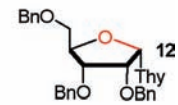
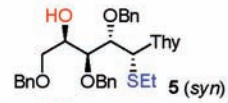
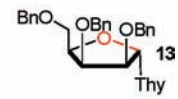
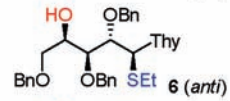
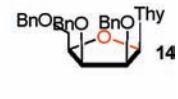
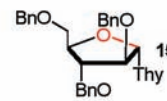
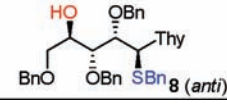
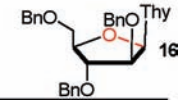
ecules is also difficult as in D- or L- β-arabinosides or lyxosides (see *cis* series, Figure 1). Obviously, the collision of the silylated thymine nucleobase to the more hindered face of the glycosyl or thioglycosyl donor is not favored because of steric factors, thus, the higher energy of the transition states leading to these products.

From a conceptual standpoint, a kinetically controlled cyclization of an acyclic precursor already containing the nucleobase (i.e., formation of the furanose ring downstream from the addition of the nucleobase) may be better suited to create these sterically encumbered molecules than the bimolecular processes currently used. We hypothesized that such cyclizations may involve a stereogenic center (at C1′) bearing the nucleobase and a thioether, which may serve as a leaving group or alternatively as a nucleophile as illustrated in Scheme 1. In order to take advantage of the stereochemistry of the thioaminal at C1′, both types of cyclizations should involve "S_N2-like" nucleophilic displacements. Avoiding the formation of iminium ion[12] (i.e., S_N1-competing mechanism) will therefore be crucial to the success of this strategy. The presence of an alkoxy at C2′ and the chemoselective and soft activation of the thioethers at C1′ by thiophilic Lewis acids such as dimethyl(methylthio)sulfonium tetrafluoroborate[13] should disfavor such intermediates.

The first cyclization protocol will involve the intramolecular displacement of the activated thioalkyl group of the thioaminal at C1′ by the secondary hydroxyl group at C4′ (C4′−C1′ cyclization). This process would lead to the desired nucleosides and analogues thereof with inversion of configuration at C1′, as illustrated in Scheme 1. The acyclic 1,2-*syn* isomer would give the C1′−C2′ *trans* nucleoside series, not withstanding the stereochemistry of the substituent at C3′ and C4′. Similarly, the *anti* thioaminals should lead to the C1′−C2′ *cis* nucleoside series.

Alternatively, the sulfur of the thioaminal can serve as a nucleophile when the C4′ hydroxyl is converted into a leaving group,[14] as illustrated in Scheme 1. The potential concomitant loss of a benzyl halide[15] from benzyl sulfonium would promote such reactions. This would result in the transformation of the thioaminals into 4′-thionucleosides in the L-series with retention

Scheme 2. C4′−C1′ Cyclization*

Entry*	Substrate	Yield%	Product
1	 1 (*syn*)	95	 9
2	 2 (*anti*)	71	 10
3	 3 (*syn*)	95	 11
4	 4 (*anti*)	97	 12
5	 5 (*syn*)	84	 13
6	 6 (*anti*)	98	 14
7	 7 (*syn*)	93	 15
8	 8 (*anti*)	83	 16

* Reagents and conditions: 1.2 equiv $Me_2S(SMe)BF_4$, THF, RT, (1−3 h).

of configuration at C1′ (C1′−C4′ cyclization); the 1,2-*syn* isomers leading to the C1′−C2′ *cis* geometry and the 1,2-*anti* isomers to the C1′−C2′ *trans* geometry. Both types of cyclizations should be stereocontrolled and stereospecific, an exciting strategy not previously exploited.

Our first cyclization strategy was tested on acyclic *syn*- or *anti*-ethylthio- and benzylthio-*N*-thymidine thioaminals. A chemoselective activation of the thioether moiety was achieved by adding 1.1 equiv of dimethyl(methylthio)sulfonium tetrafluoroborate ($Me_2S(SMe)BF_4$) to a tetrahydrofuran (THF) solution of the thioaminal at room temperature.[16] As illustrated in Scheme 2, in all cases the cyclization was diastereospecific, and the final products were obtained in good to excellent yields. An inversion of configuration had occurred at C1′ (products **9**−**16**), suggesting that an "S_N2-like" mechanism was operative. Even highly sterically congested molecules (such as **12** and **14**) were efficiently synthesized, attesting to the potential of this approach. The dependency of the C1′−C2′ relative stereochemistry of the final product to the C1′−C2′ relative stereochemistry of the thioaminal is in sharp contrast to the pioneering work of Liotta[12] who used acyclic hemiaminals in his synthesis of AZT, where strong Brønsted acids were employed and iminium ion intermediates suggested since both C1′ epimers gave the same product.

Our second cyclization strategy was tested on mesyloxy derivatives at C4′ as illustrated in Scheme 3. A solution of a given diastereomerically pure thioaminal in presence of an

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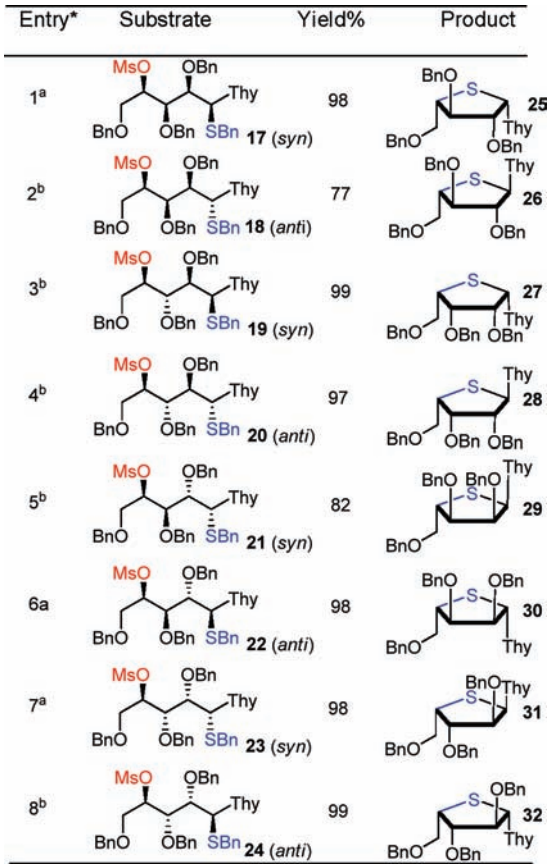
Scheme 3. C1′−C4′ Cyclization*

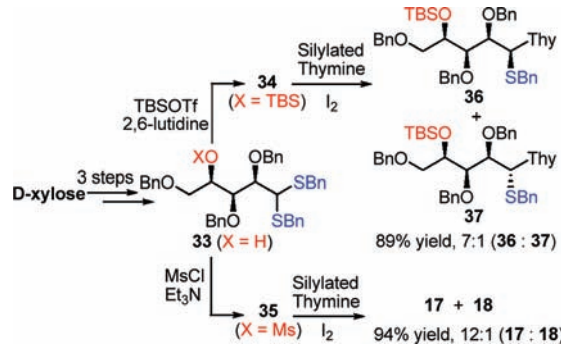


* Reagents and conditions a: NaI, pinacolone, 106°C; b: NaI, 2,6-lutidine, 145°C.

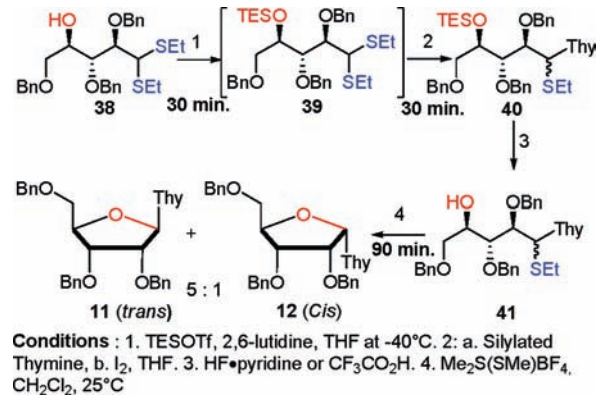
excess of NaI (to debenzylate the putative benzylthio sulfonium intermediate) in pinacolone or in 2,6-lutidine was heated at reflux for 2−5 h. This second cyclization strategy was also successful. This reaction provided direct access to L-4′-thionucleosides in good to excellent yields. The 1,2-*trans* thioaminals gave the respective 1,2-*trans* cyclized products (entries 2, 4, 6, and 8, Scheme 3) while the 1,2-*syn* products gave the 1,2-*cis* thionucleosides (entries 1, 3, 5, and 7). Again, the synthesis of highly sterically congested molecules (**25**, **27**, **29**, and **31**) using this approach with the level of diastereoselectivity was achieved. No displacement of the mesylate by our nucleobase (N-silylated nucleobases) was noted.

In the beginning of our studies both *syn*- and *anti*-thioaminals (**1**−**8**) were prepared as a mixture from the corresponding thioacetals. The exciting results obtained in the cyclization steps now justify that diastereoselective or enantioselective syntheses of acyclic thioaminals bearing nucleobases can be developed. Our first studies aimed at these objectives dealt with simpler models.[16] We reported that good to excellent *syn* diastereoselectivity was obtained when a bulky substituent was present at C2′ of thioacetals activated by the sulfonium salt $Me_2S(SMe)BF_4$ in acetonitrile, or by a combination of $Hg(OAc)_2$/TMSOTf[17] in dichloromethane, in the presence of persilylated nucleobases (thymine, cytosine). We then hypothesized that iodine (this study) could be a more practical and less toxic activating agent. Such an approach

Scheme 4. Synthesis of Acyclic Thioaminals in D-Xylose Series



Scheme 5. One-Pot Sequence (D-Ribose)



Conditions : 1. TESOTf, 2,6-lutidine, THF at -40°C. 2: a. Silylated Thymine, b. I_2, THF. 3. HF•pyridine or CF_3CO_2H. 4. $Me_2S(SMe)BF_4$, CH_2Cl_2, 25°C

was used for the synthesis of the *syn*-thioaminals illustrated in Scheme 4. The dithioacetal **33** was first obtained as described in the literature from D-xylose in three steps.[18] After silylation (**34**) or mesylation (**35**) of the C4′−OH, a solution of the appropriate dithioacetal was exposed to persilylated thymine (2 equiv) and I_2 (2 equiv). Respective ratios of 7:1 and 12:1 (*syn*:*anti*) were obtained for C4′-OTBS (**36**, **37**) and C4′-OMs thioaminals (**17**, **18**) at ambient temperature.

D-Lyxoside, riboside, and arabinoside dithioacethals were treated similarly with ratios ranging from 4:1 to 15:1 in favor of the *syn* compounds as described in the Supporting Information. A study aimed at defining the reasons at the origin of this diastereoselectivity and at maximizing the ratios through a protecting group strategy is presently underway. The stereoselective synthesis of *anti*-thioaminals awaits further displacement.

Other pyrimidines (e.g., cytosine) or purine (e.g., adenine) derivatives have been tested successfully in the two cyclization protocols; adjustments in the reaction conditions are at times needed and will be reported in separate studies.

The sequence of reactions also has the potential to be combined and realized in the same reaction vessel (Scheme 5). Such an approach has to be considered to minimize the use of solvents, a benefit from an environmental standpoint. We planned to combine four reactions: protection of the hydroxyl at C4 of the thioacetals; the coupling reaction to give the *syn*-thioacetals, the removal of the protecting group at C4, and the cyclization C4′−C1′. We decided first to optimize the coupling step. The diethyl thioacetal **38** was selected as starting material, the yields and reaction time being slightly increased, regardless of the nature of the protecting group at C2′. To achieve our

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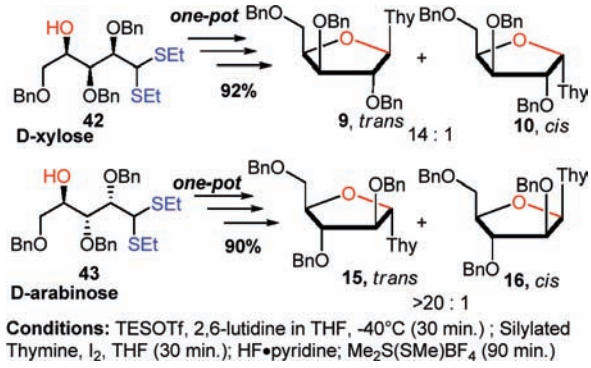
Scheme 6. One-Pot Sequence Case of Conditions of D-Xylose and D-Arabinose



one-pot sequence, we selected to replace the TBS protecting group by a more labile TES. The corresponding thioacetal **38**, with a free hydroxyl group at C4′, was reacted in THF with TESOTf in presence of 2,6-lutidine at −40 °C for a period of 30 min. The silylated thymine and iodine were added to the THF solution stirred at 0 °C until the disappearance of the starting material.

Addition of the HF·pyridine to cleave the TES protecting group for a period of 45 min at room temperature, followed by the addition of the $Me_2S(SMe)BF_4$, led unfortunately to poor yields. Replacing the HF·pyridine by trifluoroacetic acid in the protecting group cleavage step led to impressive results: a ratio (D-arabinose) of 5:1 of the C1′−C2′ *anti* isomer in 90% yield was observed as illustrated in Scheme 6. Similar conditions were used for the thioacetals derived from D-xylose and D-ribose, and the C1′−C2′ *anti* products were obtained in ratio of 14:1 and 20:1 in excellent yields. The yields of the one-pot sequence are similar to the ones obtained in stepwise sequence.

Conclusion

We have shown that the stereocenter at C1′ of acyclic thioaminals bearing a nucleoside can be used to create C4′ thionucleoside analogues in the L-series. The stereochemistry at C1′ was maintained in the final product. Alternatively 4-*oxa* analogues could be constructed using acyclic thioaminal. The stereochemistry at C1 was inverted in the latter cases. The cyclization reactions used are remarkably insensitive to steric effects, as affirmed by some of the final products which are highly sterically stranded. Accessing the L-thioanalogues represents as well an opportunity for drug discovery. The "S_N2-like" displacements (C4′−C1′ and C1′−C4′ cyclization modes) may well represent a novel paradigm particularly useful for the synthesis of sterically encumbered molecules in the 2-*oxy* series. The construction of novel acyclic thioaminal, not derived from the natural pentoses, could also lead to novel scaffolds of medicinal interest. We have already embarked on this project. These new findings will expand our capacity to explore the chemical space of various enzymes or receptors of biological significance.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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