JOC Article
pubs.acs.org/joc

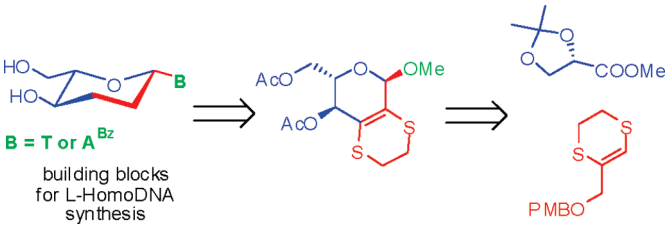
Toward L-Homo-DNA: Stereoselective de Novo Synthesis of β-L-*erythro*-Hexopyranosyl Nucleosides

Daniele D'Alonzo,*[,†] Annalisa Guaragna,[†] Arthur Van Aerschot,[‡] Piet Herdewijn,[‡] and Giovanni Palumbo[†]

[†]*Dipartimento di Chimica Organica e Biochimica, Università di Napoli Federico II, via Cinthia 4, I-80126 Napoli, Italy, and* [‡]*Katholieke Universiteit Leuven, Rega Institute for Medical Research, Minderbroederstraat 10, B-3000 Leuven, Belgium*

dandalonzo@unina.it

Received April 9, 2010



A novel route to 2′,3′-dideoxy-β-L-*erythro*-hexopyranosyl nucleosides equipped with a 1′-(N^6-benzoyl-adenin-9-yl) or a 1′-(thymin-1-yl) moiety has been developed. Synthesis of the enantiopure sugar moiety was carried out by a de novo approach based on a domino reaction as the key step. *N*-Glycosidation was explored via either nucleobase-transfer mechanism (B = T) or in situ anomerization (B = A or T), affording target nucleosides with high overall stereoselectivity.

Introduction

In the search for nucleic acid analogues to be used in therapy, diagnostics, synthetic biology, and etiology-oriented research, a wide variety of oligonucleotide architectures have been devised over the years, exploiting the well-known concept of conformational restriction of the corresponding monomeric units to improve binding efficiencies.[1] Among the numerous examples of constrained oligonucleotides endowed with hybridization potential, those bearing a D- or L-six-membered ring as sugar moiety (Figure 1) cover a privileged position. Owing to the higher conformational rigidity compared to furanoses, oligonucleotides with a six-membered "carbohydrate" mimic in the backbone[1,2] have displayed in most cases either excellent self-hybridization properties[3] or a notable capacity for cross-communication with natural and/or modified complements.[4] The strong self-pairing aptitudes, combined with the natural abundance of pento- and hexopyranoses, have stimulated questions on Nature's choice for pentose over hexose nucleic acids.[3,5] Among the many nucleic acid alternatives with prebiotic relevance, the so-called "β-HomoDNA" (a DNA analogue comprised of (4′→6′)-linked 2′,3′-dideoxy-β-D-*erythro*-hexopyranosyl nucleotides, Figure 1) represented a long investigated synthetic model system, because of its intriguing structure[6] and pairing properties.[7] On the other hand, depending on the ability to cross-communicate with natural/modified complements, applications by six-membered oligonucleotides in gene expression inhibition (D-HNA,[8] D-ANA,[9] D-CeNA[10]),

*To whom correspondence should be addressed. Phone/Fax: +39 081 674119.

(1) (a) Leumann, C. J. *Bioorg. Med. Chem.* **2002**, *10*, 841–854. (b) Zhou, C.; Chattopadhyaya, J. *Curr. Opin. Drug Discovery Dev.* **2009**, *12*, 876–898. (c) Herdewijn, P. *Chem. Biodiversity* **2010**, *7*, 1–59.

(2) Lescrinier, E.; Froeyen, M.; Herdewijn, P. *Nucleic Acids Res.* **2003**, *31*, 2975–2989.

(3) Beier, M.; Reck, F.; Wagner, T.; Krishnamurthy, R.; Eschenmoser, A. *Science* **1999**, *283*, 699–703.

(4) Kerremans, L.; Schepers, G.; Rozenski, J.; Busson, R.; Van Aerschot, A.; Herdewijn, P. *Org. Lett.* **2001**, *3*, 4129–4132.

(5) Eschenmoser, A. *Science* **1999**, *284*, 2118–2124.

(6) (a) Egli, M.; Lubini, P.; Pallan, P. S. *Chem. Soc. Rev.* **2007**, *36*, 31–45. (b) Egli, M.; Pallan, P. S. *Annu. Rev. Biophys. Biomol. Struct.* **2007**, *36*, 281–305.

(7) Eschenmoser, A. *Chimia* **2005**, *59*, 836–850.

(8) (a) Hendrix, C.; Rosemeyer, H.; Verheggen, I.; Seela, F.; Van Aerschot, A.; Herdewijn, P. *Chem.—Eur. J.* **1997**, *3*, 110–120. (b) Kang, H.; Fisher, M. H.; Xu, D.; Miyamoto, Y. J.; Marchand, A.; Van Aerschot, A.; Herdewijn, P.; Juliano, R. L. *Nucleic Acids Res.* **2004**, *32*, 4411–4419.

(9) (a) Allart, B.; Khan, K.; Rosemeyer, H.; Schepers, G.; Hendrix, C.; Rothenbacher, K.; Seela, F.; Van Aerschot, A.; Herdewijn, P. *Chem.—Eur. J.* **1999**, *5*, 2424–2431. (b) Fisher, M.; Abramov, M.; Van Aerschot, A.; Xu, D.; Juliano, R. L.; Herdewijn, P. *Nucleic Acids Res.* **2007**, *35*, 1064–1074. (c) Fisher, M.; Abramov, M.; Van Aerschot, A.; Rozenski, J.; Dixit, V.; Juliano, R. L.; Herdewijn, P. *Eur. J. Pharmacol.* **2009**, *606*, 38–44.

Published on Web 09/08/2010 DOI: 10.1021/jo100691y

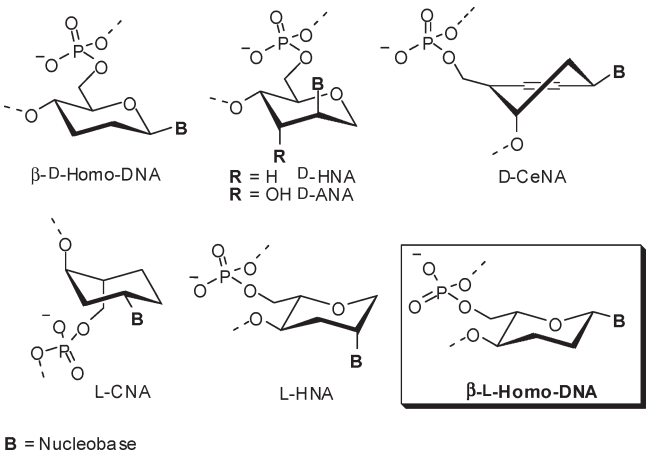
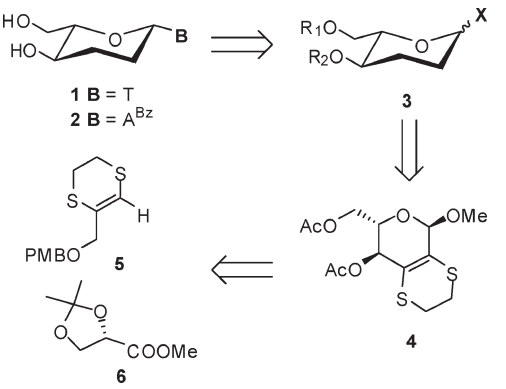


FIGURE 1. Six-membered D- and L-oligonucleotide analogues.

DNA-based diagnostics (D-HNA and D-ANA,[11] β-D-HomoDNA[12]), and chiral and conformational selection of oligonucleotides (D- and L-CNA[13]) have also been found. Recently, incorporation of D-hexopyranosyl nucleotides into a natural DNA duplex mediated by *vent*-DNA polymerase was reported,[14] demonstrating that the six-membered sugar ring of hexopyranosyl nucleosides can be recognized by the binding cavity of some enzymes. Also, the capability of mirror images of hexitol nucleic acids (L-HNA) to form heterochiral duplexes with enantiomeric D-complements was pointed out.[15] On the basis of these remarks, our ongoing interest in sugar-modified oligonucleotides prompted us to examine other potential base-pairing systems, such as the 2′,3′-dideoxy-β-L-*erythro*-hexopyranosyl nucleic acids (β-L-HomoDNA) (Figure 1). In this paper, attention was primarily given to the synthesis of the corresponding nucleoside building blocks, for which a highly stereoselective de novo synthetic approach has been described.

The stereocontrolled synthesis of 2′-deoxy- or 2′,3′-dideoxy-β-D- and β-L-nucleosides is a difficult task and a challenging synthetic target, due to the lack of control elements at the *C*-2′ position. Investigations have mainly been focused on 2′-deoxy-furanosyl nucleosides and their analogues, as a consequence of the great interest aroused by antiviral research.[16] For such a purpose, use of glycosyl halides[17] and sulfides[18] or the participation of a *C*-3′ group[19] have been employed to control anomeric β-stereochemistry. On the other hand, a few stereoselective approaches have been devised for the preparation of pyranosyl nucleosides, which are mainly restricted to those belonging to the D-series, owing to the wide availability of the corresponding starting materials.[20] To the best of our knowledge, the only asymmetric route to deoxy-hexopyranosyl nucleosides belonging to the L-series, limited to adenine and 6-chloropurine analogues, has been recently achieved by Pd-catalyzed *N*-glycosylation reaction carried out on an unsaturated L-pyranone.[21] The lack of methodologies toward 2′-deoxy- and 2′,3′-dideoxy-L-hexopyranosyl nucleosides are mainly due to the synthetic difficulty to have easy access to deoxy-hexoses belonging to the rare L-series in enantiomeric pure form. In this paper, the stereoselective synthesis of nucleosides **1** and **2**, as building blocks for β-L-HomoDNA synthesis, was envisioned through the use of bicyclic intermediate **4** (Scheme 1). Reactivity of the latter has long been at the core of our investigations on the total synthesis of L-hexoses.[22]

SCHEME 1. Access to β-L-*erythro*-Hexopyranosyl Nucleosides: Retrosynthetic Analysis



Results and Discussion

The synthesis began with the three-carbon homologation of methyl α,β-isopropylidene-L-glycerate (**6**) (Scheme 2). As the coupling reaction between **5** and **6** was accomplished, acetate *anti*-**8b** was obtained in a stereoselective manner, as previously described.[22b] Treatment of the latter with DDQ in CH_2Cl_2/MeOH smoothly afforded bicycle **4a** as an anomeric mixture (α/β = 85/15). This reaction can be regarded as a domino process,[23,24] since several synthetic transformations (PMB group removal, oxidation of the resulting primary alcohol, isopropylidene group removal, and subsequent

(10) (a) Wang, J.; Verbeure, B.; Luyten, I.; Lescrinier, E.; Froeyen, M.; Hendrix, C.; Rosemeyer, H.; Seela, F.; Van Aerschot, A.; Herdewijn, P. *J. Am. Chem. Soc.* **2000**, *122*, 8595–8602. (b) Nauwelaerts, K.; Fisher, M.; Froeyen, M.; Lescrinier, E.; Van Aerschot, A.; Xu, D.; DeLong, R.; Kang, H.; Juliano, R. L.; Herdewijn, P. *J. Am. Chem. Soc.* **2007**, *129*, 9340–9348.

(11) (a) Abramov, M.; Schepers, G.; Van Aerschot, A.; Van Hummelen, P.; Herdewijn, P. *Biosens. Bioelectron.* **2008**, *23*, 1728–1732. (b) Wang, G.; Bobkov, G. V.; Mikhailov, S. N.; Schepers, G.; Van Aerschot, A.; Rozenski, J.; Van der Auweraer, M.; Herdewijn, P.; De Feyter, S. *ChemBioChem* **2009**, *10*, 1175–1185.

(12) Crey-Desbiolles, C.; Ahn, D.-R.; Leumann, C. J. *Nucleic Acids Res.* **2005**, *33*, e77.

(13) (a) Maurinsh, Y.; Rosemeyer, H.; Esnouf, R.; Medvedovici, A.; Wang, J.; Ceulemans, G.; Lescrinier, E.; Hendrix, C.; Busson, R.; Sandra, P.; Seela, F.; Van Aerschot, A.; Herdewijn, P. *Chem.—Eur. J.* **1999**, *5*, 2139–2150. (b) Froeyen, M.; Morvan, F.; Vasseur, J.-J.; Nielsen, P.; Van Aerschot, A.; Rosemeyer, H.; Herdewijn, P. *Chem. Biodiversity* **2007**, *4*, 803–817.

(14) Renders, M.; Abramov, M.; Froeyen, M.; Herdewijn, P. *Chem.—Eur. J.* **2009**, *15*, 5463–5470.

(15) (a) D'Alonzo, D.; Guaragna, A.; Van Aerschot, A.; Herdewijn, P.; Palumbo, G. *Tetrahedron Lett.* **2008**, *49*, 6068–6070. (b) D'Alonzo, D.; Van Aerschot, A.; Guaragna, A.; Palumbo, G.; Schepers, G.; Capone, S.; Rozenski, J.; Herdewijn, P. *Chem.—Eur. J.* **2009**, *15*, 10121–10131.

(16) Mehellou, Y.; De Clercq, E. *J. Med. Chem.* **2010**, *53*, 521–538.

(17) For a recent example, see: Arico, J. W.; Calhoun, A. K.; McLaughlin, L. W. *J. Org. Chem.* **2010**, *12*, 120–122.

(18) Sugimura, H.; Osumi, K.; Kodaka, Y.; Sujino, K. *J. Org. Chem.* **1994**, *59*, 7653–7660.

(19) (a) Young, R. J.; Shaw-Ponter, S.; Hardy, G. W.; Mills, G. *Tetrahedron Lett.* **1994**, *35*, 8687–8690. (b) Choi, W.-B.; Wilson, L. J.; Yeola, S.; Liotta, D. C.; Schinazi, R. F. *J. Am. Chem. Soc.* **1991**, *113*, 9377–9379.

(20) For early results, see for example: Nord, L. D.; Dalley, N. K.; McKerman, P. A.; Robins, R. K. *J. Med. Chem.* **1987**, *30*, 1044–1054.

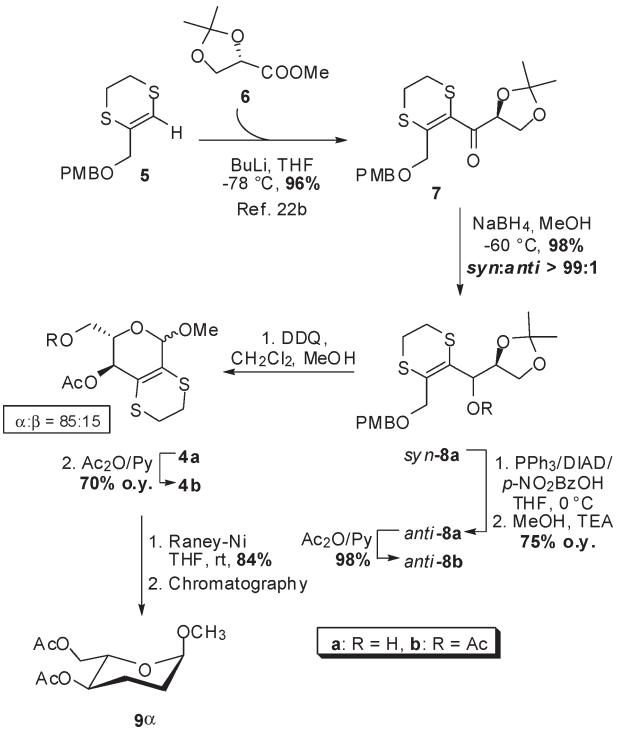
(21) Guppi, S. R.; Zhou, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 293–296.

(22) (a) D'Alonzo, D.; Guaragna, A.; Palumbo, G. *Curr. Org. Chem.* **2009**, *13*, 71–98. (b) Guaragna, A.; D'Alonzo, D.; Paolella, C.; Napolitano, C.; Palumbo, G. *J. Org. Chem.* **2010**, *75*, 3558–3568.

(23) See: *Domino Reactions in Organic Synthesis*; Tietze, L. F., Brasche, G., Gericke, K. M., Eds.; Wiley-VCH: Weinheim, Germany, 2006.

(24) D'Alonzo, D.; Guaragna, A.; Napolitano, C.; Palumbo, G. *J. Org. Chem.* **2008**, *73*, 5636–5639.

SCHEME 2. De Novo Synthesis of Intermediate 9 from Thioenol Ether 5

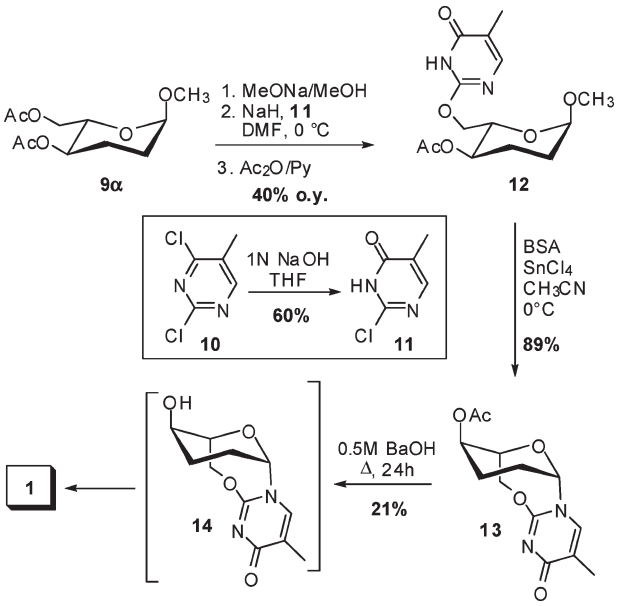


cyclization) took place in a single step. Bicycle **4a** was directly subjected to acetylation (to avoid any further cyclization),[24] obtaining diacetate **4b**. Treatment of the latter with Ni/Ra afforded methyl glycosides **9α**/***β*** (84% yield), the major α-anomer being easily separated from the corresponding *β*-component.

With the aim to find the best conditions for the stereoselective *β*-insertion of the nucleobase in the absence of anchimeric assistance by *C*-2 and *C*-3 groups, *N*-glycosidation reaction starting from methyl glycoside **9** was next studied. To test the breadth of our methodology, insertion of thymine (T) and N^6-benzoyladenine (A^{Bz}) as nucleobases was preliminarily considered.

As far as it concerns T nucleoside synthesis, the opportunity to reach complete stereocontrol by *C*-1′ insertion of the nucleobase through an intramolecular base-transfer glycosidation[25] was initially explored (Scheme 3). Sugimura et al. already reported an application of this methodology, using a D-pyranosyl thioglycoside intermediate.[26] To examine a convenient alternative to such conditions, we studied this reaction directly on methyl 2,3-dideoxy-α-L-*erythro*-hexopyranoside **9α**, using 2-chlorothymine (**11**) as the nucleobase precursor (Scheme 3). Thus, methyl glycoside **9α** was first deacetylated (MeONa), then the resulting diol was treated at 0 °C with NaH and **11** (in turn obtained from 2,4-dichloro-5-methylpyrimidine, **10**). The resulting crude residue was directly acetylated (Ac_2O/Py), achieving 6′-*O*-(thymin-2-yl)-4′-*O*-acetyl-2′,3′-dideoxy-α-L-*erythro*-hexopyranoside (**12**) as the major product (40% yield over three steps). Then, treatment of **12** with $SnCl_4$ and BSA in CH_3CN at 0 °C enabled

SCHEME 3. Synthesis of Thymidine Analogue 1 by Intramolecular *N*-Glycosidation



intramolecular *N*-glycosidation. Differently from previous approaches, which did not allow the isolation of the bridged nucleoside intermediate,[26a] in this case the presence of a 6-*O*-thymine moiety in **12** enabled cyclonucleoside **13** to be obtained smoothly in very good yield (89%).

Unexpectedly, tricycle **13** displayed poor reactivity to the common conditions required for 6′-OH function release.[27] Indeed, treatment of the latter with 1 M NaOH or 0.5 M BaOH furnished target T nucleoside **1** (via intermediate **14**) only after prolonged reaction times (24 h at reflux) and in low yield (Scheme 3). Acidic treatment (aq HCl or aq AcOH) was also ineffective at rt (refluxing conditions only resulted in hydrolysis at the *C*-1′ position). This behavior strongly disagrees with the reactivity of cyclonucleosides **15** and **16** (Figure 2), in which the primary hydroxyl group release has been reported to occur by OH^- attack at the *C*-2 position with moderate to excellent yields even at low temperatures.[26a,28] With the aim to shed light on such contrasting experimental data, a chemical reactivity analysis based on the FMO theory was performed, comparing the energies of LUMO orbitals of compounds **14**, **15**, and **16** calculated by the semiempirical method PM3 (Hyperchem 8.0). As cyclonucleoside **14** bears a different pyrimidine nucleobase (T vs U) compared to **15** and **16**, the effect of the Me group at the *C*-5 position was also calculated.[29] Interestingly, lower LUMO energy values related to compounds **16a**,**b** were found (R = H, −0.352 eV; R = CH_3, −0.312 eV) than those associated to tricycles **14a**,**b** (R = H, −0.297 eV; R = CH_3, −0.259 eV). Far from them, the energy values related to the LUMO of compounds **15a**,**b** were the lowest ones (R = H, −5.388 eV; R = CH_3, −5.284 eV) (Figure 2). On this matter, it must be considered that the total

(25) Sekine, M. In *Glycoscience*; Fraser-Reid, B. O., Tatsuta, K.; Thiem, J., Eds.; Springer: Berlin, Germany, 2001; Chapter 3.6, pp 673−689.

(26) See for example: (a) Sugimura, H. *Nucleosides, Nucleotides Nucleic Acids* **2000**, *19*, 629–635. (b) Watanabe, R.; Sugimura, H. *Nucleic Acids Symp. Ser.* **2004**, *48*, 51–52.

(27) Mieczkowski, A.; Roy, V.; Agrofoglio, L. A. *Chem. Rev.* **2010**, *110*, 1828–1856.

(28) Jung, M. E.; Castro, C. *J. Org. Chem.* **1993**, *58*, 807–808.

(29) Moreover, even though cyclonucleosides **14**, **15**, and **16** differ in the nature of the protective groups at the *C*-3′/*C*-4′ positions and in the configuration of the stereogenic centers, it was calculated that these structural differences did not significantly influence reactivity of the resulting nucleosides (data not shown).

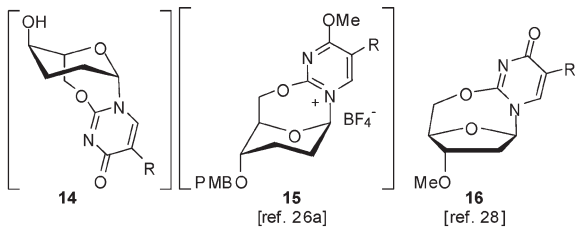
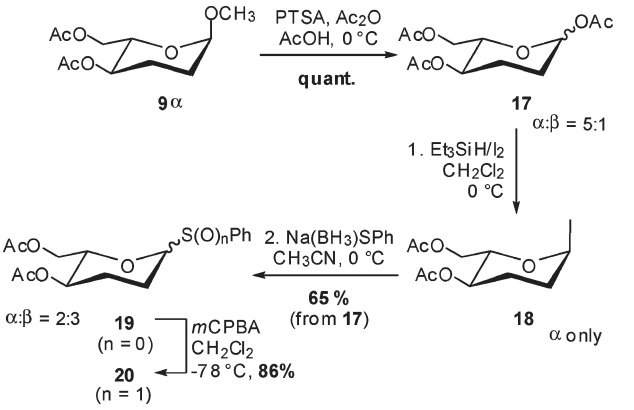


FIGURE 2. LUMO energy values of cyclonucleoside analogues **14**−**16**.

charge distribution in tricycles **15a**,**b** is such that *C*-2 bears a higher positive charge;[30] therefore, a double effect, ruled by both Coulombic and frontier orbital interactions, favors the attack at the *C*-2 position. On the other hand, Coulombic forces associated to both cyclonucleosides **14** and **16** are relatively small,[30] therefore frontier orbital interactions must be considered to only explain their different reactivity. As for compounds **14a**,**b** this interaction is much less effective than that for compounds **16a**,**b**, we can overall conclude that theoretical data are in agreement with the experimental reactivity of the above cyclonucleosides toward alkaline hydrolysis, which follows the order **15** > **16** > **14**.

Because of the poor reactivity displayed by tricycle **13** to common hydrolysis conditions, intramolecular glycosidation as reported in Scheme 3 was not considered of practical interest for the synthesis of thymidine analogue **1**. Therefore, we turned our attention to investigate other stereoselective methods for direct β-*N*-glycosidation starting from methyl glycoside **9α** (Scheme 4). Such approaches resumed previous work on the synthesis of D-hexose oligonucleotides[31] the above mentioned ("β-Homo-DNA"), which made use of the D-enantiomer of **9**. In that case, target D-nucleosides obtained under common Vorbrüggen conditions (HMDS/TMSCl/$SnCl_4$) were endowed with low stereoselectivity[31a] at the anomeric center (B = T, α:β = 18:65; B = A^{Bz}, α:β = 43:57). In an effort to improve the stereoselective outcome of this reaction using our L-hexose derivative, we studied the reactivity of some other glycosyl donors, such as glycosides **17**, **18**, and **20**, prepared from compound **9α** (Scheme 4). Particularly, methyl glycoside **9α** was first converted into the corresponding acetate **17** by mild acetolysis (PTSA/Ac_2O/AcOH), which occurred stereoselectively (α:β = 5:1). Then, treatment of triacetate **17** with Et_3SiH/I_2 in CH_2Cl_2 at 0 °C quantitatively afforded iodide **18** as a single anomer (^{1}H NMR analysis).[32] Reaction of the crude **18** with $Na(BH_3)SPh$, in turn obtained by treatment of PhSSPh with $NaBH_4$,[33] furnished thioglycosides **19** (α:β = 2:3; 65% yield from acetate **17**). Finally, thioether oxidation under common conditions (*m*CPBA) smoothly gave sulfoxides **20** (86%) as a mixture of four diastereomers.

SCHEME 4. Preparation of Dideoxy-L-Glycosides 17, 18, and 20



Our initial attempts at stereoselective *N*-glycosidation were in fact not encouraging. Use of glycosyl iodide **18** under alkaline conditions (NaH/CH_3CN) was primarily examined, with the aim to achieve a direct S_N2 displacement by the nucleobase. To our regret, the anomeric mixture of T and A nucleosides **21** and **22** was formed at 0 °C without selectivity (α:β = 1:1, 38−40% yield; entries 1 and 2). Use of THF in place of CH_3CN (entry 3) did not improve selectivity. In the reaction with A^{Bz}, *N*-isomer nucleosides were also detected (18−20% yield). A lower temperature (−20 °C) led even to a slight preference for the undesired α-anomer (entry 4). In all cases, a large amount of L-glycal[31a] **23** was found (40−47% yield). Importantly, while T nucleoside anomers **21** were easily separable by chromatography, the corresponding anomeric A^{Bz} nucleoside mixture **22** was nearly inseparable under the same conditions. Reactivity of glycosyl sulfoxide **20** was then studied. The anomeric mixture of **20** was envisaged to undergo an S_N2 attack by the nucleobase onto the α-triflate intermediate **24** (Scheme 5), which is usually reported to be formed at low temperatures on similar substrates under common activating conditions (Tf_2O[34] or TMSOTf[35]). In our hands, treatment of T nucleobase with glycoside **20** and BSA/TfOTMS[36] at −100 °C (entry 5) proceeded with fairly high stereoselectivity (α:β = 1:6), even though in low yield (38%). On the other hand, reactions at higher temperatures (−40 or −20 °C) gave better yields (75−81%), but without stereoselectivity (entries 6 and 7). Such contrasting stereoselective outcome could be explained assuming that, at lower temperatures, glycosyl triflate **24**, likely along with the corresponding transient contact ion pair (CIP)[37,34b] **25**, are the most active species, resulting in the high observed selectivity after S_N2 displacement by the nucleobase; conversely, at higher temperatures, the

(30) See the Supporting Information.

(31) (a) Bohringer, M.; Roth, H. J.; Hunziker, J.; Gobel, M.; Krishnan, R.; Giger, A.; Schweizer, B.; Schreiber, J.; Leumann, C.; Eschenmoser, A. *Helv. Chim. Acta* **1992**, *75*, 1416–1477. (b) Augustyns, K.; Vandendriessche, F.; Van Aerschot, A.; Busson, R.; Urbanke, C.; Herdewijn, P. *Nucleic Acids Res.* **1992**, *20*, 4711–4716.

(32) Compare: (a) Lam, S. N.; Gervay-Hague, J. *Org. Lett.* **2003**, *5*, 4219–4222. (b) Adinolfi, M.; Iadonisi, A.; Ravidà, A.; Schiattarella, M. *Synlett* **2002**, 269–270.

(33) Valerio, S.; Iadonisi, A.; Adinolfi, M.; Ravidà, A. *J. Org. Chem.* **2007**, *72*, 6097–6106.

(34) (a) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217–11223. (b) Crich, D. *Acc. Chem. Res.* **2010**, *43*, 1144–1153.

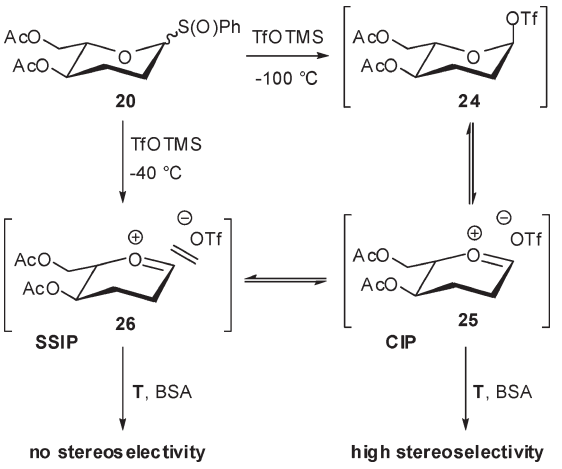
(35) Sliedregt, L. A. J. M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1994**, *35*, 4015–4018. For an application of glycosyl sulfoxides in *N*-glycosidation reactions, see: Chanteloup, L.; Beau, J.-M. *Tetrahedron Lett.* **1992**, *33*, 5347.

(36) Early attempts with Tf_2O gave similar results.

(37) Crich, D.; Chandrasekera, N. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5386–5389.

(38) The authors did not further investigate into the reaction mechanism of the sulfoxide glycosidation at low temperatures, for example, analyzing the formation of the glycosyl sulfenate intermediates (see for example: Gildersleeve, J.; Pascal, R. A., Jr.; Kahne, D. *J. Am. Chem. Soc.* **1998**, *120*, 5961–5969), as the low yield achieved under the best stereoselective conditions (entry 5) does not render the reaction of practical interest for our synthetic purposes.

SCHEME 5. Working Hypothesis for the Sulfoxide *N*-Glycosidation



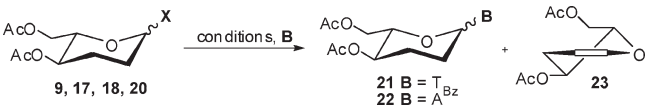
reaction proceeds with the substantial development of a solvent-separated ion pair (SSIP)[34b] **26**, with evident loss of stereoselectivity.[38]

With the aim to improve the anomeric β-selectivity, *N*-glycosidation reactions were also carried out at higher temperatures, providing more promising results. We reasoned that absence of electron-withdrawing substituents on the sugar moiety could promote anomerization reactions, which would be driven toward the thermodynamically more stable β-nucleosides. As a result, an attempt carried out on methyl glycoside **9α**[39] and T with $SnCl_4$/BSA at 40 °C (entry 8) led to an $\alpha{:}\beta$ = 1:4 mixture of nucleosides **21** (75% yield). On the other hand, reaction of **9α** with A^{Bz} (entry 9) afforded a mixture of anomers **22** (45% yield) with lower selectivity ($\alpha{:}\beta$ = 4:6). These results are substantially in line with those found for the corresponding D-nucleosides.[31a] Use of acetate **17** as glycosyl donor was then considered. Treatment of the latter with T nucleobase at rt (entry 10) led to nucleosides **21** with identical selectivity ($\alpha{:}\beta$ = 1:4) as observed for **9α**. The same reaction, carried out with A^{Bz} (entry 11), led to nucleosides **22** with $\alpha{:}\beta$ = 1:3. To our delight, we observed that for both A and T nucleosides anomeric selectivity increased time-dependently when the reaction was warmed to 45−60 °C, which was strongly indicative for a thermodynamically controlled anomerization reaction (entries 12−14).[40] With regards to T nucleosides **21**, after 40 h at 60 °C (entry 13) the anomeric ratio was significantly high (α/β = 1:11, 60% yield), along with a relatively small amount of **23** (25%). On the other hand, in the case of A nucleoside **22**, after 40 h at 60 °C a $\alpha{:}\beta$ = 1:6 mixture of anomers was isolated in 40% yield (entry 14); only a few traces of *N*-regioisomer nucleosides were detected. However, regardless of the good selectivity achieved, the elimination reaction was also fostered, to the extent that glycal **23** was isolated as the main product (47%). In the search for more convenient conditions, we noticed that, when previously silylated base was used, reaction times and temperature could be drastically reduced, hampering formation of **23**. Hence, treatment of acetate **17** with bis-silylated A^{Bz} and TMSOTf in CH_3CN at 30 °C for 3 h (entry 15) afforded **22α/β**

(39) Reaction with the pure **9β** gave nearly the same results.

(40) This reaction augments previous results carried out on similar substrates: Augustyns, K.; Rozenski, J.; Van Aerschot, A.; Busson, R.; Claes, P.; Herdewijn, P. *Tetrahedron* **1994**, *50*, 1189–1198 and references cited therein.

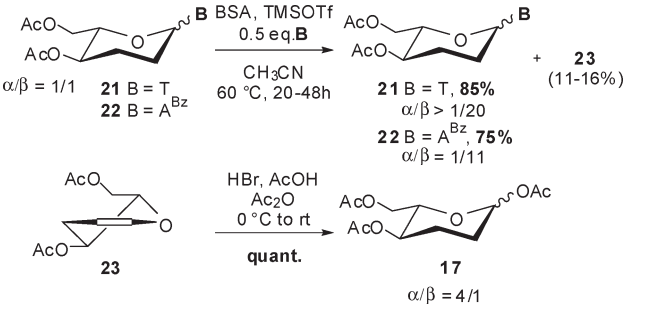
TABLE 1. *N*-Glycosidation Reaction[a]



						yield (%)		
entry	compd	B	T (°C)	t (h)	α/β ratio	**21**	**22**	**23**
1	**18**[b]	T	0	0.5	1:1	38		40
2	**18**[b]	A^{Bz}	0	0.5	1:1		40[c]	45
3	**18**[b,d]	A^{Bz}	0	0.5	1:1		38[c]	44
4	**18**[b]	A^{Bz}	−20	0.5	2:1		37	47
5	**20**[e]	T	−100	0.5	1:6	38		10
6	**20**[f]	T	−40	0.5	1:1	81		< 5
7	**20**	T	−20	0.5	1:1	75		7
8	**9α**[g]	T	40	40	1:4	75		11
9	**9α**[g]	A^{Bz}	40	40	4:6		45[c]	15
10	**17**	T	rt	40	1:4	70		15
11	**17**	A^{Bz}	rt	40	1:3		51[c]	22
12	**17**	T	45	40	1:6	51		22
13	**17**	T	60	40	1:11	60		25
14	**17**	A^{Bz}	60	40	1:6		40	47
15	**17**[h]	A^{Bz}	30	3	1:9		65	11
16	**20**	T	rt	0.5	1:1	79		9
17	**20**	A^{Bz}	rt	0.5	1:1		81	7
18	**20**	T	rt→60	20	1:20	65		11
19	**20**	A^{Bz}	rt→60	48	1:11		70	19

[a]Conditions: BSA/TfOTMS/CH_3CN (unless otherwise specified). [b]Nucleobase activation under alkaline conditions (NaH). [c]Regioisomeric A^{Bz} nucleosides also detected. [d]THF used as solvent. [e]CH_2Cl_2 used as solvent. [f]Use of CH_3CN or CH_2Cl_2 led to similar results. [g]$SnCl_4$ was used in place of TfOTMS. [h]Previously silylated nucleobase was used.

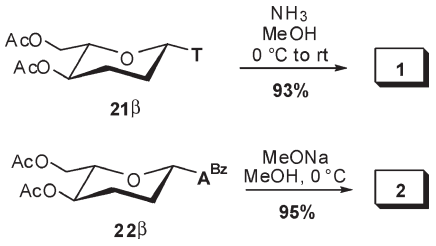
SCHEME 6. Anomerization of Nucleosides 21 and 22



in a satisfying yield (65%) and with a considerably high anomeric ratio ($\alpha{:}\beta$ = 1:9); also, formation of **23** was remarkably reduced (11%). Eventually, use of sulfoxide **20** was investigated. While reactions at rt with T and A^{Bz} (entries 16 and 17) run very quickly (30 min) but without selectivity, the same mixtures, heated to 60 °C (entries 18−19), led, after 20−48 h, to the corresponding nucleosides **21** and **22** with the most preferable selectivities (B = T, $\alpha{:}\beta$ = 1:20, 65% yield; B = A^{Bz}, $\alpha{:}\beta$ = 1:11, 70% yield). A relatively small amount of **23** was detected (11−19%); moreover, in the case of A^{Bz} nucleosides **22**, no regioisomer nucleoside was found.

To further test the anomerization reaction occurring under these conditions, an anomeric mixture of T and A nucleosides **21** and **22** ($\alpha{:}\beta \approx$ 1:1) was treated with BSA/TfOTMS in CH_3CN at 60 °C (Scheme 6). A substoichiometric amount of the nucleobase was also added, as it proved to speed up the reaction. After 20−48 h, an improvement of

SCHEME 7. Deprotection of Nucleosides 21β and 22β



the α/β ratio (B = T, α:β > 1:20; B = A^{Bz}, α:β = 1:11) was observed (75−85% yield). It is worthy to note that results obtained by *N*-glycosidation of sulfoxide **20** with T/A^{Bz} (Table 1) and those obtained by anomerization of T/A^{Bz} nucleosides **21**−**22**α/**β** (Scheme 6) are exactly in line, as reactions with sulfoxide **20** at rt immediately furnished an equimolar α/β mixture of anomeric nucleosides (TLC analysis), which were then subjected to in situ anomerization as temperature was raised to 60 °C.

It is also noteworthy to underline that glycal **23** could be recovered to provide starting material **17**, which could be resubjected to *N*-glycosidation reaction under anomerization conditions to produce more β-nucleosides **21** and **22**, with the advantage of increasing the overall efficiency of the process. As already reported for similar substrates,[32a] treatment of **23** with HBr/AcOH/Ac_2O at 0 °C gave back triacetate **17** with moderate stereoselectivity (α:β = 4:1) (Scheme 6).

Finally, removal of protective groups from β-nucleosides **21** and **22** provided our target nucleosides **1** and **2** (Scheme 7). Particularly, treatment of **21β** with saturated methanolic NH_3 solution easily gave 1′-(thymin-1-yl)-2′,3′-dideoxy-β-L-*erythro*-hexopyranoside (**1**) in 93% yield. Similarly, treatment of **22β** with 0.1 M MeONa led to pure 1′-(N^6-benzoyladenin-9-yl)-2′,3′-dideoxy-β-L-*erythro*-hexopyranoside (**2**) in 95% yield.

Conclusions

In summary, a stereoselective procedure for the synthesis of 2′,3′-dideoxy-β-L-*erythro*-hexopyranosyl nucleosides has been herein developed, starting from our 1,2-bis-thioenol ether synthon **5**, as homologating agent, and methyl α,β-isopropylidene-L-glycerate (**6**), as chiral electrophile. Fast and efficient access to enantiopure sugar scaffold **9** belonging to the L-series has been achieved by a de novo approach based on a domino reaction, which deeply reduces the total number of synthetic steps. *N*-Glycosylation study between glycosyl donors **9**, **17**, **18**, and **20** and A^{Bz}/T (as models of purine/pyrimidine nucleobases) revealed that, in both cases, anomerization reaction toward nucleosides **21β** and **22β** occurred with high stereoselectivity, despite the absence of directing groups at *C*-2 and *C*-3 positions. The reaction is of synthetic relevance especially for A nucleoside **22β**, since its anomeric mixture is not easily separable by common purification techniques. On the other hand, in the case of T nucleoside synthesis, complete stereocontrol has also been explored by intramolecular glycosidation, even though final hydrolysis was complicated by inefficient HOMO−LUMO interactions, as highlighted by semiempirical calculations. Overall, the procedure herein reported enables an effective gram-scale preparation of our target nucleosides, which is a difficult task to reach by common sugar-based approaches, owing to the limited availability of the corresponding L-hexoses as starting materials. Further experiments aimed to incorporate our L-nucleoside building blocks **1** and **2** into natural oligonucleotide sequences as well as to construct fully modified L-oligonucleotide analogues ("β-L-HomoDNA") for hybridization studies with natural and unnatural complements are ongoing and will be published in due course.

Experimental Section

General Methods and Materials. All moisture-sensitive reactions were performed under nitrogen atmosphere, using oven-dried glassware. Solvents were dried over standard drying agents and freshly distilled prior to use. Reactions were monitored by TLC (precoated silica gel plate F_{254}, Merck). Column chromatography: Merck Kieselgel 60 (70−230 mesh); flash chromatography: Merck Kieselgel 60 (230−400 mesh). Melting points are uncorrected and were determined with a Gallenkamp apparatus. Optical rotations were measured at 25 ± 2 °C in the stated solvent. ^{1}H and ^{13}C NMR spectra were recorded on NMR spectrometers operating at 200, 300, 400, or 500 MHz and 50, 75, 100, or 125 MHz, respectively. Combustion analyses were performed with a Perkin−Elmer Series II 2400 CHNS analyzer.

(5*R*,7*S*,8*S*)-5-Methoxy-7-[(methylcarbonyloxy)methyl]-2,3,7,8-tetrahydro-5*H*-[1,4]dithiino[2,3-*c*]pyran-8-yl Acetate (4b). To a stirred 3:1 CH_2Cl_2/CH_3OH solution (15 mL) containing the PMB ether **8b** (2.0 g, 4.6 mmol; prepared according to refs 22b and 24) was added DDQ (1.5 g, 6.8 mmol) in one portion at room temperature. The reaction mixture was stirred at the same temperature for 24 h. Then, H_2O was added and the mixture was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and the solvent evaporated. The crude residue was directly acetylated by addition of pyridine (20 mL) and acetic anhydride (10 mL). The resulting solution was stirred for 4 h. Then solvents were evaporated under diminished pressure. Chromatography of the crude residue (hexane/EtOAc = 7:3) gave **4b** (1.0 g, 70% yield). The anomeric ratio as determined by ^{1}H NMR was α/β = 85:15. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.10 (s, 2.55H), 2.11 (s, 2.55H), 2.12 (s, 0.45H), 2.13 (s, 0.45H), 3.14−3.34 (m, 4H), 3.46 (s, 2.55H), 3.47 (s, 0.45H), 4.06−4.16 (m, 1H), 4.19−4.27 (m, 1H), 4.29−4.33 (m, 1H), 4.77 (s, 0.85H), 4.90 (s, 0.15H), 5.56 (bd, *J* = 9.2 Hz, 1H). ^{13}C NMR (major α-anomer; 50 MHz, $CDCl_3$): δ 20.8 (2C), 27.3, 28.2, 55.6, 62.5, 65.2, 67.3, 97.9, 122.3, 126.3, 169.9, 170.1. Anal. Calcd for $C_{13}H_{18}O_6S_2$: C 46.69, H 5.43, S 19.18. Found: C 46.85, H 5.45, S 19.26.

Methyl 4,6-Di-*O*-acetyl-2,3-dideoxy-α-L-*erythro*-hexopyranoside (9α). A solution of **4b** (5.0 g, 15 mmol) in THF (120 mL) was added in one portion to a stirred suspension of Raney-Ni (W2) (wet, 50 g) in the same solvent (120 mL) at 0 °C. The resulting suspension was warmed to room temperature and further stirred for 4 h, then the solid was filtered off and washed with EtOAc. The filtrate was evaporated under reduced pressure to afford a crude residue that after chromatography over silica gel (CH_2Cl_2) gave pure **9α** (2.6 g) as a colorless oil, besides a small amount of the corresponding β-anomer **9β** (0.5 g) (84% overall yield). Data for **9α**: oily, $[\alpha]^{25}_D$ −132.7 (*c* 0.8, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.78−1.86 (m, 3H), 1.95−2.01 (m, 1H), 2.05 (s, 3H), 2.09 (s, 3H), 3.38 (s, 3H), 3.90 (ddd, *J* = 2.0, 4.9, 9.8 Hz, 1H), 4.11 (dd, *J* = 2.0, 11.7 Hz, 1H), 4.26 (dd, *J* = 4.9, 11.7 Hz, 1H), 4.70−4.76 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.8, 21.1, 23.9, 28.6, 54.6, 63.2, 67.7, 68.5, 97.5, 170.0, 170.9. Anal. Calcd for $C_{11}H_{18}O_6$: C 53.65, H 7.37. Found: C 53.83, H 7.64.

2-Chlorothymine (11). To a solution of 2,4-dichloro-5-methylpyrimidine (**10**) (1.0 g, 6.17 mmol) in 5 mL of THF was added a 1 N aq NaOH solution (6 mL) at rt. The reaction mixture was

stirred for 16 h at the same temperature; then the reaction mixture was slightly acidified with 1 N HCl and extracted with $CHCl_3$. The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure. Chromatography of the crude residue (CH_2Cl_2) gave the pure **11** (0.53 g, 60% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.38 (s, 3H), 8.40 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.7, 129.0, 158.0, 159.9, 162.4. Anal. Calcd for $C_5H_5ClN_2O$: C 41.54, H 3.49, N 19.38. Found: C 41.58, H 3.47, N 19.52.

Methyl 4′-*O*-Acetyl-6′-*O*-(thymin-2-yl)-2′,3′-dideoxy-α-L-*erythro*-hexopyranoside (12). Diacetate **9α** (0.5 g, 2.0 mmol) was dissolved in a 0.1 M MeONa solution in MeOH (10 mL) and the resulting mixture was stirred at room temperature overnight. Then, a few drops of AcOH were added until neutrality. The crude residue was dissolved in CH_2Cl_2 and filtered through a short pad of silica gel; the resulting filtrate was then concentrated to dryness. The residue was dissolved in anhydrous DMF (10 mL), the mixture was cooled to 0 °C, then NaH (0.15 g, 6.5 mmol) was added in one portion. After 30 min, pyrimidine **11** (0.35 g, 2.4 mmol) was added. The resulting brown suspension was warmed to room temperature and further stirred for 16 h. The mixture was diluted with AcOEt and washed with a saturated $NaHCO_3$ solution and brine. The organic layer was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. Chromatography of the crude residue over silica gel (CH_2Cl_2/MeOH = 97/3) furnished the pure **12** (0.25 g, 40% overall yield from compound **9α**): $[\alpha]^{25}_D$ −42.3 (*c* 0.7, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.78−1.86 (m, 3H), 2.00−2.10 (m, 4H), 2.18 (s, 3H), 3.38 (s, 3H), 4.07 (ddd, J = 2.4, 5.4, 10.3 Hz, 1H), 4.47 (dd, J = 5.4, 11.7 Hz, 1H), 4.51 (dd, J = 2.4, 11.7 Hz, 1H), 4.73 (br s, 1H), 4.83 (dt, J = 4.4, 10.2 Hz, 1H), 8.15 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.0, 21.0, 23.8, 28.5, 54.5, 66.2, 67.7, 68.3, 97.3, 116.9, 157.2, 157.7, 168.5, 169.8. Anal. Calcd for $C_{14}H_{19}N_2O_6$: C 54.01, H 6.15, N 9.00. Found: C 54.19, H 6.14, N 8.96.

Compound 13. To a stirring solution of methyl glycoside **12** (0.15 g, 0.48 mmol) in anhydrous CH_3CN (2.5 mL) under nitrogen stream was added BSA (0.50 mL, 2.0 mmol) at room temperature. After 15 min, the mixture was cooled to 0 °C, and $SnCl_4$ (0.07 mL, 0.58 mmol) was added dropwise. The resulting solution was stirred for 2 h at the same temperature, then the mixture was diluted with AcOEt and washed with a saturated $NaHCO_3$ solution (2 × 50 mL) and brine (2 × 50 mL). The collected organic layers were dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. Chromatography of the crude residue (CH_2Cl_2/MeOH = 97/3) gave the pure **13** (0.12 g, 89% yield). $[\alpha]^{25}_D$ −96.0 (*c* 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.83−2.16 (m, 5H), 2.18 (s, 3H), 2.52 (dt, J = 4.4, 17.1 Hz, 1H), 4.18−4.25 (m, 1H), 4.58 (dd, J = 2.9, 12.0 Hz, 1H), 4.61 (dd, J = 4.9, 12.0 Hz, 1H), 4.71−4.78 (m, 1H), 5.15 (q, J = 7.3 Hz, 1H), 6.38 (d, J = 6.3 Hz, 1H), 8.15 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.1, 21.1, 25.6, 29.7, 65.3, 65.6, 73.8, 97.7, 117.1, 142.7, 158.0, 168.4, 169.9. Anal. Calcd for $C_{13}H_{16}N_2O_5$: C 55.71, H 5.75, N 9.99. Found: C 55.53, H 5.77, N 10.02.

1,4,6-Tri-*O*-acetyl-2,3-dideoxy-L-*erythro*-hexopyranoside (17). Method A: To a stirring solution of methyl glycoside **9α** (5.0 g, 20.5 mmol) in Ac_2O/AcOH (2:1 v/v, 150 mL) at 0 °C was added *p*-toluenesulfonic acid (7.5 g, 41.0 mmol) in one portion. The resulting mixture was stirred for 4 h, keeping the temperature at 0 °C. Then the solution was diluted with AcOEt, warmed to room temperature, and washed with $NaHCO_3$ solution and brine. The organic layer was dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The crude acetyl glycoside **17** was directly engaged in the following step without further purification. The anomeric ratio as determined by ^{1}H NMR was α/β = 5/1. Method B: To a stirring solution of olefin **23** (0.20 g, 0.9 mmol; obtained in significant amount as byproduct during preparation of nucleosides **21*β*** and/or **22*β***, see farther on) in anhydrous CH_2Cl_2 (6 mL) at 0 °C were added a 30% HBr/AcOH solution (50 μL, 0.25 mmol of HBr) and acetic anhydride (4 mL) dropwise. The resulting mixture was stirred for 16 h at 0 °C, then AcONa was added until neutrality. After 15 min, the resulting suspension was filtered and the solid washed with AcOEt. The filtrate was then washed with brine (2 × 150 mL). The organic layer was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude acetyl glycoside **17** was directly engaged in the following step without further purification. The anomeric ratio as determined by ^{1}H NMR was α/β = 4/1. Data for compound **17**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.75−2.02 (m, 4H), 2.06 (s, 0.45H), 2.08 (s, 2.55H), 2.10 (s, 2.55H), 2.11 (s, 0.45H), 2.13 (s, 0.45H), 2.14 (s, 2.55H), 3.80−3.86 (m, 0.15H), 3.98−4.04 (m, 0.85H), 4.11 (dd, J = 2.2, 12.2 Hz, 0.85H), 4.14−4.22 (m, 0.30H), 4.28 (dd, J = 4.8, 12.2 Hz, 0.85H), 4.65−4.77 (m, 0.15H), 4.82 (dt, J = 4.9, 10.5 Hz, 1H), 5.80 (dd, J = 2.4, 8.4 Hz, 0.15H), 6.15 (br s, 0.85H). ^{13}C NMR (major α-anomer; 100 MHz, $CDCl_3$): δ 20.8, 21.0, 21.1, 23.6, 27.6, 62.7, 67.1, 70.8, 90.8, 169.3, 169.8, 170.8. Anal. Calcd for $C_{12}H_{18}O_7$: C 52.55, H 6.62. Found: C 52.75, H 6.65.

4,6-Di-*O*-acetyl-2,3-dideoxy-α-L-*erythro*-hexopyranosyl Iodide (18). To a stirring solution of triacetate **17** (0.5 g, 1.8 mmol) in anhydrous CH_2Cl_2 (5 mL) at 0 °C was added a solution of iodine (0.6 g, 2.2 mmol) in anhydrous CH_2Cl_2 (5 mL) in one portion. After a few minutes, Et_3SiH (0.3 mL, 2.2 mmol) was added at the same temperature. The resulting mixture was stirred for 20 min, then solvent was removed under reduced pressure. Given its low stability to humidity, the crude glycosyl iodide **18** was directly engaged in the following step (i.e., *N*-glycosidation or preparation of thioglycoside **19**) without further purification. Data for compound **18**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.86−1.92 (m, 1H), 2.02−2.12 (m, 8H), 2.28−2.34 (m, 1H), 3.83 (ddd, J = 2.4, 4.9, 10.1 Hz, 1H), 4.13 (dd, J = 1.9, 12.3 Hz, 1H), 4.37 (dd, J = 4.6, 12.3 Hz, 1H), 4.83 (dt, J = 4.9, 10.1 Hz, 1H), 7.14 (d, J = 3.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.7, 21.0, 26.0, 37.1, 61.8, 66.3, 68.2, 75.1, 169.9, 170.7. ESI-MS calcd for $[C_{10}H_{15}IO_5Na]^+$ 364.99, found 364.83. Anal. Calcd for $C_{10}H_{15}IO_5$: C 35.11, H 4.42. Found: C 35.18, H 4.44.

Thiophenyl 4,6-Di-*O*-acetyl-2,3-dideoxy-L-*erythro*-hexopyranoside (19). To a stirring solution of phenyl disulfide (0.05 g, 0.2 mmol) in anhydrous CH_3CN (3 mL) was added $NaBH_4$ (0.02 g, 0.4 mmol). The mixture was stirred until evolution of hydrogen ceased and then was shortly heated at 50 °C to ensure completion of the reaction. The mixture was then added to a solution of the crude glycosyl iodide **18** (0.1 g, 0.3 mmol) in CH_3CN (2 mL). The resulting solution was stirred at 0 °C for 10 min, then acetic acid was added until neutrality. The mixture was diluted with CH_2Cl_2 and washed with water; then the organic phase was dried and evaporated under vacuum. Chromatography of the crude residue (hexane/EtOAc = 85:15) gave sulfide **19** (0.06 g, 65% yield calculated from triacetate **17**) as a mixture of anomers (α:β = 2:3). Data for compound **19**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.77−1.89 (m, 2H), 1.99 (s, 1.8H), 2.01 (s, 1.2H), 2.02−2.18 (m, 4H), 2.19−2.35 (m, 1H), 3.65 (ddd, J = 4.3, 4.6, 9.7 Hz, 0.6H), 4.08 (dd, J = 2.1, 12.0 Hz, 0.4H), 4.18 (d, J = 4.3 Hz, 1.2H), 4.27 (dd, J = 5.8, 12.0 Hz, 0.4H), 4.43−4.48 (m, 0.4H), 4.68 (ddd, J = 4.8, 9.7, 10.4 Hz, 0.6H), 4.69−4.77 (m, 0.4H), 4.78 (dd, J = 2.0, 11.5 Hz, 0.6H), 5.58 (d, J = 5.2 Hz, 0.4H), 7.20−7.37 (m, 3H), 7.43−7.57 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.6 (2C), 20.8 (2C), 25.3, 29.4 (2C), 30.3, 62.9, 63.3, 67.3, 67.8, 69.0, 77.8, 84.0, 84.4, 127.0, 127.2, 128.6 (2C), 128.7 (2C), 131.2 (4C), 133.9, 134.3, 169.7 (2C), 170.6 (2C). ESI-MS calcd for $[C_{16}H_{20}O_5SNa]^+$ 347.09, found 346.90. Anal. Calcd for $C_{16}H_{20}O_5S$: C 59.24, H 6.21, S 9.88. Found: C 59.46, H 6.23, S 9.92.

4,6-Di-*O*-acetyl-2,3-dideoxy-1-(phenylsulfinyl)-L-*erythro*-hexopyranose (20). To a stirring solution of thioglycoside **19** (0.1 g, 0.3 mmol) in anhydrous CH_2Cl_2 (4 mL) at −78 °C was slowly added a solution of *m*CPBA (0.05 g, 0.3 mmol) at the same temperature.

After 10 min, the resulting mixture was further diluted with CH_2Cl_2 (50 mL), warmed to rt, and washed with sat $NaHCO_3$ and brine. The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure. Flash chromatography of the crude residue (hexane/EtOAc = 85:15) gave sulfoxide **20** (0.09 g, 86% yield) as a mixture of four diastereomers. Data for compound **20**: ^{1}H NMR (major two diastereomers; 500 MHz, C_6D_6): δ 0.86−0.98 (m, 0.5H), 1.31−1.42 (m, 0.5H), 1.52 (s, 1.5H), 1.61 (s, 1.5H), 1.67 (s, 1.5H), 1.68 (s, 1.5H), 1.72−1.97 (m, 2H), 2.43−2.50 (m, 0.5H), 3.01−3.04 (m, 0.5H), 3.78 (dd, J = 3.5, 10.4 Hz, 0.5H), 4.02 (dd, J = 2.2, 11.8 Hz, 0.5H), 4.05−4.21 (m, 2.5H), 4.66−4.78 (m, 1.5H), 7.01−7.12 (m, 3H), 7.58−7.62 (m, 2H). ^{13}C NMR (major two diastereomers; 125 MHz, C_6D_6): δ 20.3, 20.4, 20.5, 21.4, 23.3, 24.9, 27.9, 30.1, 62.8, 62.9, 67.0, 67.1, 74.5, 78.7, 94.2, 94.4, 124.8 (2C), 125.0 (2C), 128.7, 128.9 (2C), 129.0 (2C), 130.9, 142.9, 143.7, 169.0, 169.2, 169.9, 170.0. ESI-MS calcd for $[C_{16}H_{20}O_6SNa]^+$ 363.09, found 362.85. Anal. Calcd for $C_{16}H_{20}O_6S$: C 56.46, H 5.92, S 9.42. Found: C 56.30, H 5.94, S 9.46.

(Thymin-1-yl) 4′,6′-Di-*O*-acetyl-2′,3′-dideoxy-*β*-L-*erythro*-hexopyranoside (21*β*). Method A: To a stirring suspension of acetyl glycoside **17** (3.0 g, 11.0 mmol, α/β = 5/1) and thymine (1.7 g, 13.2 mmol) in anhydrous CH_3CN (150 mL) and under nitrogen atmosphere was added *N*,*N*-bis-trimethylsilylacetamide (BSA, 9.8 mL, 39.6 mmol) and the resulting solution was stirred for 30 min at 60 °C; after a few minutes the solution became homogeneous. Hence, TfOTMS (2.4 mL, 13.2 mmol) was added dropwise in 10 min. The reaction mixture was further stirred for 40 h at 60 °C. Then the solution was diluted with AcOEt and washed with a saturated $NaHCO_3$ solution and brine. The organic layer was dried (Na_2SO_4) and the solvent evaporated under reduced pressure. Chromatography of the crude residue over silica gel (CH_2Cl_2/MeOH = 95/5) gave the pure **21*β*** (2.1 g, 60% yield); a minor amount of anomeric **21α** (0.2 g) was also recovered. In addition, L-glycal **23** (25% yield) was isolated. Method B (anomerization of dideoxythymidine analogue **21**): To a stirring solution of nucleoside **21** (0.1 g, 0.3 mmol, α/β = 1/1) and thymine (0.1 mmol) in anhydrous CH_3CN (4 mL) and under nitrogen atmosphere was added BSA (0.4 mL, 1.0 mmol). The resulting solution was stirred for 30 min at rt. Hence, TfOTMS (0.1 mL, 0.4 mmol) was added in a few minutes. The reaction mixture was warmed to 60 °C and further stirred for 20 h at the same temperature. Then the solution was diluted with AcOEt and washed with a saturated $NaHCO_3$ solution and brine. The organic layer was dried (Na_2SO_4) and the solvent evaporated under reduced pressure. Flash chromatography of the crude residue (CH_2Cl_2/MeOH = 97/3) gave the pure **21*β*** (0.7 g, 85% yield). In addition, L-glycal **23** (11%) was isolated. Data for **21*β***: white foam, $[\alpha]^{25}_D$ −27.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.68−1.89 (m, 2H), 1,97 (s, 3H), 1.70−2.06 (m, 1H), 2.09 (s, 3H), 2.10 (s, 3H), 2.33−2.42 (m, 1H), 3.85 (ddd, J = 2.3, 6.4, 10.3 Hz, 1H), 4.17 (dd, J = 2.2, 12.2 Hz, 1H), 4.25 (dd, J = 6.2, 12.2 Hz, 1H), 4.75 (dt, J = 4.6, 10.3 Hz, 1H), 5.78 (dd, J = 2.5, 10.5 Hz, 1H), 7.19 (s, 1H), 8.82 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.6, 20.8, 21.0, 27.9, 29.3, 62.9, 66.5, 77.9, 81.3, 111.5, 134.9, 150.0, 163.3, 170.0, 170.8. Anal. Calcd for $C_{15}H_{20}N_2O_7$: C 52.94, H 5.92, N 8.23. Found: C 53.12, H 5.90, N, 8.20. Data for **23**: oily. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.01−2.16 (m, 7H), 2,45 (dddd, J = 2.1, 4.8, 6.3, 17.2 Hz, 1H), 4.05 (ddd, J = 3.3, 5.7, 8.7 Hz, 1H), 4.22 (dd, J = 3.3, 12.0 Hz, 1H), 4.31 (dd, J = 5.7, 12.0 Hz, 1H), 4.66−4.76 (m, 1H), 5.02 (ddd, J = 6.0, 7.8, 13.8 Hz, 1H), 6.35 (dt, J = 2.1, 6.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.8, 21.2, 25.8, 62.3, 65.7, 74.0, 97.7, 142.6, 169.9, 170.2. Anal. Calcd for $C_{10}H_{14}O_5$: C 56.07, H 6.59. Found: C 56.23, H 6.56.

(N^6-Benzoyladenin-9-yl) 4′,6′-Di-*O*-acetyl-2′,3′-dideoxy-*β*-L-*erythro*-hexopyranoside (22*β*). Method A: To a stirring suspension of N^6-benzoyladenine (1.6 g, 6.6 mmol) in anhydrous CH_3CN (50 mL) under nitrogen stream was added BSA (5.0 mL, 20 mmol). The resulting suspension was warmed to reflux and stirred for 1 h; after a few minutes, the solution became homogeneous. The solvent was removed under reduced pressure, and the crude residue was coevaporated three times with anhydrous CH_3CN (40 mL). Then, a solution of acetyl glycoside **17** (1.5 g, 5.5 mmol) in anhydrous CH_3CN (50 mL) was added in one portion. Hence, TfOTMS (1.2 mL, 6.6 mmol) was added dropwise in 20 min. The resulting mixture was further stirred for 3 h at 30 °C. Then the solution was diluted with AcOEt and washed with a saturated $NaHCO_3$ solution and brine. The organic layer was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. Flash chromatography of the crude residue (CH_2Cl_2/MeOH = 97/3) gave the pure **22*β*** (1.5 g, 65% yield); a minor amount of **22α** (0.2 g) was also recovered. Moreover, a small quantity of L-glycal **23** (11%) was isolated. Method B: To a stirring suspension of sulfoxide **20** (0.2 g, 0.5 mmol) and N^6-benzoyladenine (0.2 g, 0.6 mmol) in anhydrous CH_3CN (5 mL) under nitrogen atmosphere was added BSA (0.5 mL, 2.0 mmol). The resulting mixture was warmed to 60 °C and stirred for 30 min; after a few minutes the solution became homogeneous. Then the solution was cooled to room temperature, and TfOTMS (0.1 mL, 0.6 mmol) was added dropwise in 10 min. The resulting mixture was further stirred until disappearance of sulfoxide **20** (< 30 min). Then the mixture was warmed to 60 °C and stirred for 48 h at the same temperature. The solution was then diluted with AcOEt and washed with a saturated $NaHCO_3$ solution and brine. The organic layer was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. Flash chromatography of the crude residue (CH_2Cl_2/MeOH = 97/3) gave the pure **22*β*** (0.2 g, 70% yield); a minor amount of anomeric **22α** (0.02 g) was also recovered. In addition, L-glycal **23** (19%) was isolated. Method C (anomerization of dideoxyadenosine analogue **22**): To a stirring suspension of nucleoside **22** (1.0 g, 2.2 mmol, α/β = 1/1) and N^6-benzoyladenine (0.3 g, 1.1 mmol) in anhydrous CH_3CN (40 mL) and under nitrogen atmosphere was added BSA (2.0 mL, 8.0 mmol). The resulting suspension was stirred for 30 min at 60 °C; after a few minutes the solution became homogeneous. Hence, the mixture was cooled to rt and TfOTMS (0.5 mL, 2.6 mmol) was added dropwise in 10 min. The reaction mixture was warmed again to 60 °C and further stirred for 48 h at the same temperature. Then the solution was diluted with AcOEt and washed with a saturated $NaHCO_3$ solution and brine. The organic layer was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. Flash chromatography of the crude residue (CH_2Cl_2/MeOH = 97/3) gave the pure **22*β*** (1.5 g, 75% yield), besides a minor amount of the corresponding α-anomer (0.1 g). In addition, L-glycal **23** (16%) was isolated. Data for compound **22*β***: white foam; $[\alpha]^{25}_D$ −23.6 (*c* 0.8, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.82 (dq, J = 4.8, 13.0 Hz, 1H), 2.06 (s, 3H), 2.10 (s, 3H), 2.26 (dq, J = 3.9, 13.2 Hz, 1H), 2.28−2.36 (m, 1H), 2.43−2.50 (m, 1H), 3.94−3.99 (m, 1H), 4.20 (dd, J = 1.5, 12.2 Hz, 1H), 4.28 (dd, J = 5.4, 12.2 Hz, 1H), 4.88 (dt, J = 4.8, 10.8 Hz, 1H), 5.94 (dd, J = 2.2, 11.0 Hz, 1H), 7.51 (t, J = 7.8 Hz, 2H), 7.60 (t, J = 7.3 Hz, 2H), 8.03 (d, J = 7.3 Hz, 1H), 8.22 (s, 1H), 8.79 (s, 1H), 9.26 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.6, 20.8, 28.1, 30.4, 62.7, 66.7, 78.0, 81.6, 123.2, 127.9 (2C), 128.8 (2C), 132.7, 133.8, 140.4, 149.7, 151.4, 152.7, 164.5, 169.7, 170.5. Anal. Calcd for $C_{22}H_{23}N_5O_6$: C 58.27, H 5.11, N 15.44. Found: C 58.03, H 5.09, N 15.50.

(Thymin-1-yl) 2′,3′-dideoxy-*β*-L-*erythro*-hexopyranoside (1). Deacetylation of nucleoside **21*β*** (2.0 g, 5.8 mmol) was accomplished by treatment with a saturated metanolic NH_3 solution (50 mL) at 0 °C. After stirring for 24 h at room temperature, the solvent was removed. Chromatography of the crude residue (CH_2Cl_2/MeOH = 8:2) gave the pure **1** (1.4 g, 93% yield) as a white solid: mp 199.0−199.8 °C (acetone); $[\alpha]^{25}_D$ −22.0 (*c* 1.0, H_2O). ^{1}H NMR (500 MHz, CD_3OD): δ 1.66 (dq, J = 4.4, 12.7 Hz, 1H), 1.83 (dq, J = 3.9, 12.7 Hz, 1H), 1.87−1.93 (m, 4H), 2.15−2.22 (m, 1H), 3.38−3.44 (m, 1H), 3.56 (dt, J = 4.9, 10.0 Hz, 1H), 3.75 (dd, J = 5.4, 12.0 Hz, 1H), 3.85 (dd, J = 1.5, 12.0 Hz, 1H), 5.66 (dd, J = 2.2, 10.7 Hz, 1H), 7.62 (s, 1H). ^{13}C NMR

(75 MHz, CD_3OD): δ 10.9, 29.0, 31.0, 61.3, 64.3, 81.6, 83.1, 110.0, 136.8, 150.7, 164.9. Anal. Calcd for $C_{11}H_{16}N_2O_5$: C 51.56, H 6.29, N 10.93. Found: C 51.40, H 6.27, N 10.97.

(N^6-Benzoyladenin-9-yl) 2′,3′-Dideoxy-β-L-*erythro*-hexopyranoside (2). Nucleoside **22β** (2.0 g, 4.4 mmol) was treated with a 0.1 M NaOMe solution in MeOH (60 mL) and the mixture was stirred for 2 h at 0 °C. Then, a few drops of acetic acid were added until neutrality. The solvent was evaporated under reduced pressure. Chromatography of the crude residue (CH_2Cl_2/MeOH = 8:2) afforded the pure **2** (1.6 g, 95% yield) as a white solid: mp 202.1−202.9 °C (MeOH); $[\alpha]^{25}_D$ −21.2 (*c* 1.0, DMSO). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.65−1.75 (m, 1H), 2.08−2.20 (m, 2H), 2.42−2.52 (m, 1H), 3.40−3.51 (m, 3H), 3.71 (appdd, J = 6.3, 11.2 Hz, 1H), 4.58 (t, J = 5.9 Hz, 1H), 4.99 (d, J = 4.8 Hz, 1H), 5.88 (dd, J = 1.5, 10.8 Hz, 1H), 7.62 (t, J = 7.8 Hz, 2H), 7.72 (t, J = 7.8 Hz, 1H), 8.07 (d, J = 7.8 Hz, 1H), 8.72 (s, 1H), 8.78 (s, 1H), 11.20 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 29.4, 31.9, 61.2, 64.5, 81.1, 83.7, 125.8, 127.7, 128.8, 132.8, 133.6, 143.1, 150.7, 152.0, 152.2, 166.3. Anal. Calcd for $C_{18}H_{19}N_5O_4$: C 58.53, H 5.18, N 18.96. Found: C 58.73, H 5.20, N 19.02.

Acknowledgment. D.D. is grateful to Prof. B. Doboszewski and Dr. A. Iadonisi for helpful discussions on the *N*-glycosidation reaction. Moreover, the authors wish to thank a reviewer who suggested the use of sulfoxide **20** for nucleoside synthesis. ^{1}H and ^{13}C NMR experiments were performed at the "Centro Interdipartimentale di Metodologie Chimico-Fisiche" (CIMCF), University of Napoli Federico II.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.