Synthesis of a Bicyclic Analogue of AZT Restricted in an Unusual O4′-*Endo* Conformation

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The [3.2.0]bicyclic β-nucleoside analogue **5** has been designed as a conformationally restricted analogue of the anti-HIV drug AZT. The synthesis of **5** as well as its α-anomer **29** is hereby described. The synthesis was accomplished from D-arabinose *via* a modified Corey−Link procedure stereoselectively incorporating the azide moiety as well as a methyl ester function. When the *tert*-butyldiphenylsilyl group was used as a permanent protecting group, a selective formation of an oxetane ring failed. When using the *p*-methoxyphenyl group as a permanent protecting group, **5** and **29** were efficiently obtained *via* a selective reduction of the ester, a nucleobase coupling followed by separation of the anomers and ring-closing procedures. The nucleoside **5** is conformationally restricted in an unusual O4′-*endo* (East) conformation, which is an intermediate between the North- and South-type conformations. Nevertheless, neither **5** nor **29** displayed any anti-HIV activity.

Introduction

In the treatment of AIDS, 2′,3′-dideoxynucleosides are very important drugs that are used in monotherapy as well as in combination therapy with other types of drugs.[1,2] These nucleoside analogues are phosphorylated in vivo to give their 5′-*O*-triphosphates, which are effective inhibitors of the HIV-encoded enzyme HIV-1 reverse transcriptase (HIV-1 RT).[1,2] The first drug to be approved for the treatment of AIDS was 3′-azido-3′-deoxythymidine (AZT, **1**, Figure 1).[1] However, this and other 2′,3′-dideoxynucleoside analogues have toxic side effects and lead to the emergence of resistance.[1] Therefore, there is a continuous need for improved anti-HIV drugs and for new insight into the structure−activity relations between different nucleoside analogues and their pharmacological effects.

Recently, conformationally restricted nucleoside analogues have received considerable attention as monomers in oligonucleotide sequences with enhanced affinities for complementary nucleic acid sequences[3] as well as in studies on the interactions of nucleoside/nucleotide substrates with corresponding receptors and enzymes.[4,5] Furthermore, a plethora of conformationally restricted nucleosides has been synthesized for potential antiviral activity.[4,6]

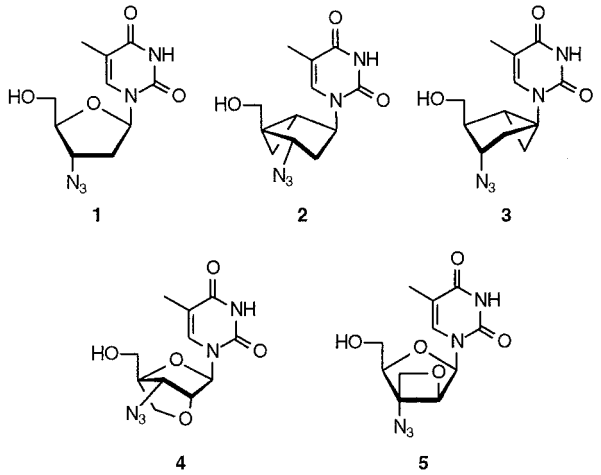

Figure 1. Chemical structures of AZT and related bicyclic analogues.

The conformational behavior of natural as well as modified nucleosides is of immense importance for their biological activities.[7,8] The puckering of the furanose rings of nucleosides can be described by the pseudorotational cycle (Figure 2),[7,9] which correlates all possible twist (T) and envelope (E) conformations of the furanose to the so-called pseudorotational angle *P*.[7,9] Thus, unmodified

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(9) For definitions, nomenclature, and conformational behavior of nucleosides and nucleotides, see ref 7 as well as: (a) Altona, C.; Sundaralingam, M. *J. Am. Chem. Soc.* **1972**, *94*, 8205. (b) Altona, C.; Sundaralingam, M. *J. Am. Chem. Soc.* **1973**, *95*, 2333.

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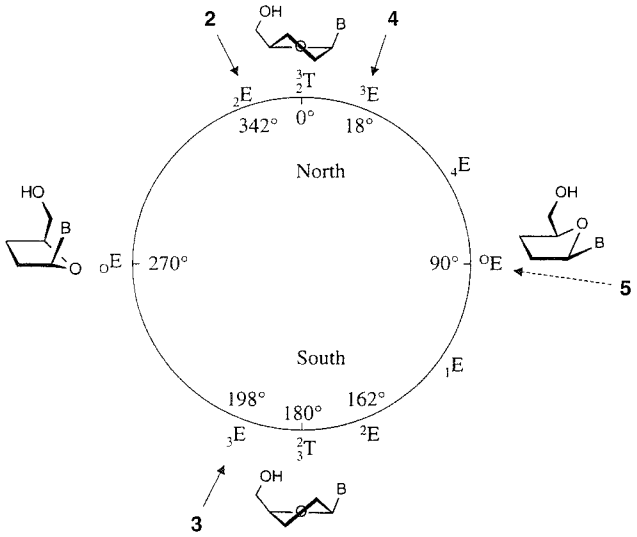

Figure 2. Pseudorotational cycle of the furanose ring in nucleosides (E = envelope, T = twist).

nucleosides are known to exist in an equilibrium between two major conformational ranges, the C-3′-*endo* conformations centered around $P = 18°$ and the C-2′-*endo* conformations centered around $P = 162°$.[7] Due to their positions in the pseudorotational cycle, these are known as North (N) and South (S) conformations, respectively (Figure 2).[7,9] The same equilibrium between N- and S-conformations, driven by the interplay of stereoelectronic effects, exists for most 2′,3′-dideoxynucleosides.[10] Thus, AZT has been shown to crystallize in a high S-type conformation with $P = 215°$,[11] while a study on the interaction between the triphosphate of AZT (AZTTP) and the target viral enzyme HIV-1 RT has shown AZTTP to bind to the enzyme with a pseudorotational angle P around 60°.[12] The natural substrate thymidine triphosphate (TTP) binds with P around 55°,[12] and both of these are C-4′-*exo* conformations that in a broad definition can be recognized as N-type conformations (Figure 2).

Recently, Marquez et al. have presented a comprehensive study on two analogues of AZT that are conformationally restricted due to the replacement of the furanose rings with bicyclic moieties.[4] Thus, the analogue **2** (Figure 1) can be considered as a good mimic of AZT in an N-type conformation as P has been established to be approximately 342° corresponding to a C-2′-*exo* conformation (Figure 2). On the other hand, **3** is an S-type conformational mimic with $P \approx 198°$ i.e., a C-3′-*exo* conformation (Figures 1 and 2). Neither **2** nor **3** display any antiviral activity.[4] However, when transformed into the corresponding triphosphates, **2** shows an inhibition of HIV-1 RT comparable to that observed for unmodified AZTTP, whereas the triphosphate of **3** remains inactive. These results confirm the postulate of Van Roey et al. that the biotransformation of nucleoside drugs into the active triphosphates demands S-type conformations[13] and leads to the conclusion that active anti-HIV nucleoside analogues must display an appropriate flexibility in order to adopt an S-type conformation for phosphorylation and an N-type conformation for inhibiting HIV-1 RT.[4]

Very recently, Obika et al.[14] and Olsen et al.[15] independently synthesized the AZT analogue **4** (Figure 1), which is a perfect N-type conformational mimic.[14,15] Thus, this bicyclic nucleoside adopts a C-3′-*endo* conformation with $P = 18°$ (Figure 2) as determined by NMR[16b] and X-ray crystallography[16c] for the original LNA monomer.[16] In line with the former results, this compound shows no antiviral activity, perhaps due to its very inflexible structure.[15]

To obtain further insight into the relationship between the conformation of the furanose ring and biological activity, we decided to synthesize a bicyclic analogue of AZT that is conformationally restricted into a conformational range on the path between the N- and S-type conformations. On the basis of a [3.2.0]bicyclic structure, the nucleoside **5** would be a 3′-azido-3′-deoxy analogue of a bicyclic nucleoside, which has been suggested to have an O4′-*endo* or East (E)-type conformation with a pseudorotational angle P around 90° (Figures 1 and 2).[17] Due to the constrained bicyclic structure, **5** would be an analogue of AZT prevented from taking a conformation resembling any of the two low-energy N- or S-type conformations. Therefore, this molecule might give further and valuable insight into the structure−activity relationships of the involved enzymes and to the postulated demand for conformational flexibility for anti-HIV nucleoside analogues. On the other hand, it cannot be precluded in advance that this E-type conformational mimic of AZT will be recognized by phosphorylating enzymes and/or as its triphosphate by HIV-1 RT, thus revealing a new potent anti-HIV drug. Thus, in the related anti-HIV drug 2′,3′-didehydro-2′,3′-dideoxythymidine (d4T)[1] the C1′−C2′−C3′−C4′ moiety adopts a similar inflexible planarity.[18]

Results

Retrosynthetic Considerations. For the construction of the bicyclic skeleton of **5**, an oxetane ring should be connected to a furanose ring with a 3′-azido moiety. The oxetane ring formation should be relatively straightforward from a furanose substrate with the 2′-OH group preorganized for nucleophilic attack on the 3′-C methylene group connected to a good leaving group like a methylsulfonic ester (**a**, Figure 3).[17] The ring formation should await the nucleobase coupling in order to avoid any Lewis acid mediated ring opening of the strained [3.2.0]bicyclic ring system.[19] However, the compound **a** could have both arabino and ribo configurations, as the

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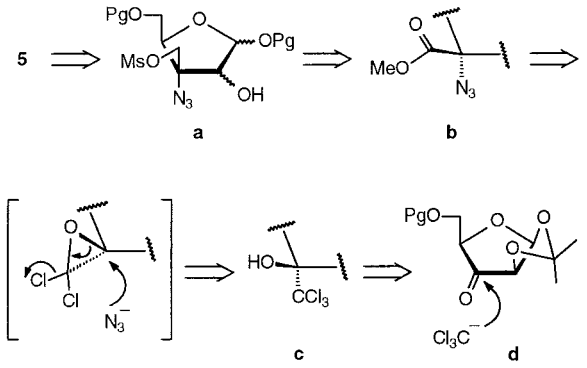
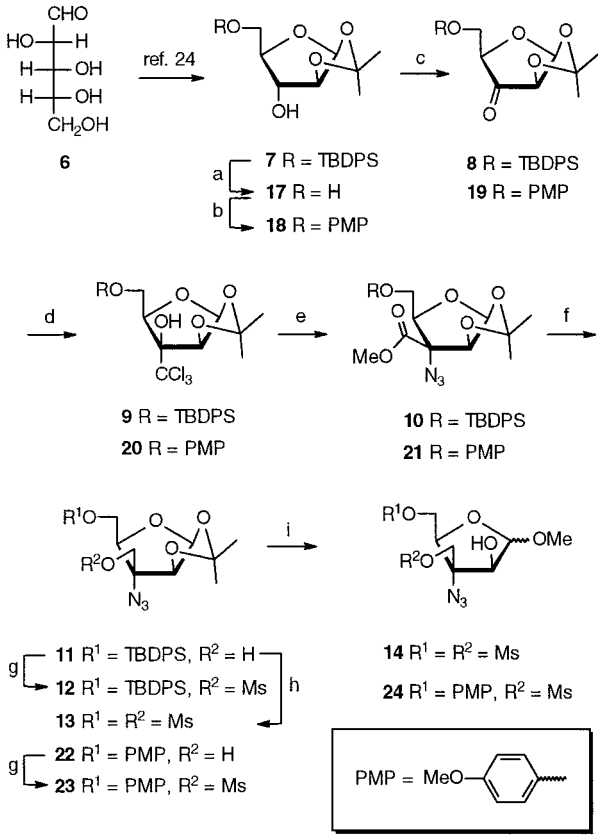


Figure 3. Retrosynthetic considerations. Pg = varying protecting groups.

C-2′ configuration might be easily converted from ribo to arabino taking advantage of the pyrimidine nucleobase in the so-called anhydro approach.[17,20] The 3′-C-hydroxymethyl group in **a** might be obtained by reduction of an ester group. The α-azido ester moiety in **b** can be obtained by a modification of the Corey−Link amino acid synthesis[21] developed by Dominguez et al.[22] Thus, a basic azide treatment of a trichloromethyl-substituted tertiary alcohol **c** should give **b** in a single step with inversion of configuration due to the illustrated mechanism (Figure 3). The alcohol **c** should be obtained from a ketone using a simple reaction with the trichloromethyl anion. Stereoselective control of this reaction can only be obtained on a sterically constrained substrate like **d** where the isopropylidine group directs the nucleophile to attach from the α-face of the furanose ring. Thus, an arabino- or lyxo-configured furanose derivative was preferred as the starting material. In the end, this would give a sugar **a** with arabino configuration, and after nucleobase coupling, two anomeric nucleoside products should be expected.

Chemical Synthesis. As an appropriate carbohydrate precursor possessing the preferred stereochemistry, D-arabinose **6** was chosen as a very cheap starting material (Scheme 1). As a conveniently protected arabinofuranose derivative, the isopropylidene-protected silyl ether **7** has been well described in the literature.[23,24] Thus, **6** has been converted to **7** using two subsequent protecting steps[23] or, alternatively, three steps including a diethyl mercaptal intermediate.[24] The latter method[24] was superior in our hands, and we chose to investigate the feasibility of the silyl group as a permanent protecting group in our synthetic strategy. Thus, a chromium-mediated oxidation of **7** afforded the ketone **8**[24] in a high yield. The reaction with the trichloromethyl anion was accomplished using a strong base, and the product **9** was obtained in a reasonable yield and with absolute stereoselectivity.[25] Following the reported modification of the Corey−Link reaction,[22] **9** was converted to the β-azido methyl ester

Scheme 1[a]



[a] Reagents: (a) KF, 18-crown-6, H_2O, DMF; (b) *p*-methoxyphenol, DEAD, Ph_3P, THF, (63%, two steps); (c) CrO_3, Ac_2O, pyridine, CH_2Cl_2 (**8**: 90%; **19**: 99%); (d) $CHCl_3$, LHMDS, THF (**9**: 54%; **20**: 74%); (e) NaN_3, 18-crown-6, DBU, MeOH (**10**: 68%; **21**: 87%); (f) $NaBH_4$, THF (**11**: 66%) or $NaBH_4$, THF, EtOH (**22**: 80%); (g) MsCl, pyridine (**12**: 77%; **23**: 87%); (h) (i) TBAF, THF, (ii) MsCl, pyridine (96%); (i) HCl, MeOH, H_2O, CH_2Cl_2 (**14**: 79%) or AcCl, MeOH, H_2O, CH_2Cl_2 (**24**: 94%). TBDPS = *tert*-butyldiphenylsilyl.

10 in good yield, taking advantage of the in situ formation of a dichloroepoxide, the reaction with the azide ion and the methanolysis of the intermediate acyl chloride (Figure 3). The reaction was absolutely stereoselective, and only one compound was obtained. However, the absolute configuration was not exclusively verified at this stage. Selective reduction of the methyl ester without simultaneous reduction of the azide was accomplished using a cold treatment with sodium boronhydride[26] affording the primary alcohol **11** in a good yield. As a preparation for the formation of the oxetane ring, the alcohol group was subsequently converted to a leaving group. Hence, the methanesulfonic ester **12** was obtained, and at this stage the expected C-3 configuration was confirmed using NOE-difference spectroscopy. Thus, a mutual NOE-contact was observed between the H-1′ signal of the methylene group and one of the H-5 signals and not the H-4 signal, hereby confirming this group (C-1′) to be at the concave site (the β-face) of the bicyclic structure.

Nevertheless, the isopropylidene group could not be removed without affecting the silyl ether and, therefore, the silyl protecting group had to be exchanged at this stage. However, all attempts to replace the silyl group

(19) Lewis acid mediated ring opening reactions in connection to nucleobase couplings have been reported with a [3.2.0]bicyclic methyl furanoside: (a) Obika, S.; Morio, K.; Hari, Y.; Imanishi, T. *Chem. Commun.* **1999**, 2423. With a [2.2.1]bicyclic methyl furanoside: (b) Nielsen, P.; Wengel, J. *Chem. Commun.* **1998**, 2645.

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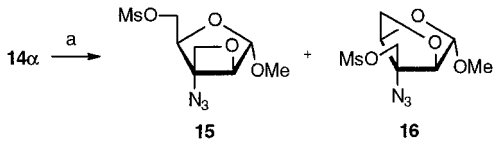
Scheme 2[a]



[a] Reagents: (a) NaH, DMF (**15**: 12% and **16**: 57%).

with alternative protecting groups without affecting the sulfonic ester of **12** or, alternatively, the ester of **10**, failed, and we decided to explore another strategy. Thus, the preference for the formation of four-membered rings over five-membered rings has been observed on related structures in the construction of other [3.2.0]bicyclic nucleoside analogues.[19a,27] Therefore, we converted **11** to the bismethanesulfonic ester **13** in two very efficient steps. Treatment with methanolic hydrochloric acid afforded the two separated anomeric methyl furanosides **14** in a good yield. The elucidation of the anomeric configurations were performed by ^{13}C NMR by comparing the signals of C-1 with known methyl furanosides,[28] as well as from the $^3J_{H1'H2'}$ coupling constants, as the geometry forces the θ_{H1H2} torsion angle of the α-anomer to be near 90° and, thus, $^3J_{H1H2}$ to be ∼0 Hz. To explore the selectivity in a ring-closing procedure, the major α-anomer of **14** was treated with a strong base affording two bicyclic methyl furanosides **15** and **16** in a 1:5 ratio (Scheme 2). These were separated and analyzed by ^{1}H NMR. The major isomer displayed very small $^3J_{H4H5}$ coupling constants (<1 Hz) corresponding to the [2.2.1]-bicyclic system in **16**, whereas the minor isomer displayed larger $^3J_{H4H5}$ coupling constants (4.7 and 6.5 Hz) corresponding to the [3.2.0]bicyclic system in **15**. Furthermore, in ^{13}C NMR the C-2′ signal has shifted downfield to 91 ppm for **15** as observed for the similar [3.2.0]bicyclic system in the original nucleoside analogue[17] compared to 78 ppm for C-2′ in **16**. Thus, the preferred formation of an oxetane ring was disfavored in this case, and in a preliminary similar experiment also the β-anomer of **14** gave two bicyclic products. As nucleoside derivatives potentially obtained by coupling of, e.g., thymine to **14** are expected to behave similarly, we decided to reconsider the entire strategy.

When reconsidering the synthetic strategy, it appeared obvious that a more stable permanent protecting group for the 5′-hydroxy group was needed. Thus, a group that is less labile toward both basic and acidic conditions, compared to the silyl ether, might form the basis of successful synthesis of the target bicyclic nucleoside. Furthermore, some of the modest yields obtained with the silyl ether might be improved (e.g., the conversions of **8** to **11**). The protecting group should also be stable toward oxidative and reductive conditions, and as it should be removable without affecting the azide moiety, a benzyl ether could be excluded. Therefore, we chose the *p*-methoxyphenyl ether as this can be selectively reacted with primary alcohols, removed with mild oxidation using cerium(IV) ammonium nitrate (CAN), and fulfills all other criteria.[29] To our knowledge, this protecting group has been used in the construction of only few other nucleoside derivatives.[30]

As the first step, **7** was desilylated to give the known arabinose derivative **17**[31,32] and then directly reacted with *p*-methoxyphenol under Mitsunobu conditions to give the *p*-methoxyphenyl ether **18** in a reasonable overall yield (Scheme 1). We still consider the present route as superior even though **17** has also been obtained through other 5′-O-protected compounds.[31] The new arabinose derivative **18** was oxidized quantitatively to give the ketone **19** and subsequently reacted with chloroform to give the alcohol **20**. The same modified Corey−Link procedure[22] was applied giving **21** in a high yield, and mild reduction gave efficiently the primary alcohol **22**. In all the four latter steps, the yields were improved compared to the steps converting **7** to **11**. In the reaction of **19** with chloroform, the probable explanation was a very slow addition of the strong base.[25] Esterification of **22** to give **23** and treatment with methanolic hydrochloric acid gave the mixture of methyl furanosides **24** in a high yield.

At this stage, two options appeared possible. Thus, cyclization of **24** would give two bicyclic methyl furanosides (similar to α- and β-analogues of **15**) on which a coupling reaction with a nucleobase following a modified Vorbrüggen method might give the target α- and β-anomeric bicyclic nucleosides. However, as similar conditions have been reported to afford ring-opening reactions (vide supra),[19] we decided to perform the coupling reaction before the ring closure. Thus, with a protocol used successfully with similar methyl furanosides,[33] simultaneous trimethylsilylation of the secondary alcohol of **24** and thymine and subsequent coupling of these with TMS-triflate as a Lewis acid catalyst, after separation afforded the two anomeric nucleosides **25** and **26** in good yields and in an almost equimolar ratio (Scheme 3). As the α-anomer might be a very useful side product, we did not investigate a variety of solvents and Lewis acids in order to change this ratio in favor of the β-anomer. Instead, both anomers were reacted with a strong base to give the bicyclic nucleosides **27** and **28**. Finally, the deprotections using CAN[30] afforded smoothly the target nucleoside **5** as well as its α-anomer **29**.

The anomeric configurations of the two products were elucidated using NOE-difference spectroscopy in addition to the information covered in the $^3J_{HH}$ coupling constants. Thus, for the two anomers **25**/**26** the $^3J_{H1'H2'}$ coupling constants were <1 Hz and 3.3 Hz, respectively. For both compounds, C-2′-*endo* conformations are expected, due to the preference of the 2′-OH group for adopting a pseudoaxial position and the 3′-carbon substituent for adopting a pseudoequatorial position. Therefore, the isomer with the very small $^3J_{H1'H2'}$ constant can be deduced to the α-anomer **26**, as in this case a torsion angle $\theta_{H1'H2'}$ very close to 90° is expected. The coupling constants for the bicyclic compounds further verified these assignments as the α-anomers **28** and **29** displayed very small coupling constants $^3J_{H1'H2'}$ < 1 Hz, whereas the β-anomers **27** and **5** displayed larger $^3J_{H1'H2'}$ coupling constants, 2.4 and 2.7 Hz, respectively. The characteristic ^{13}C chemical shifts for the C-2′ between 86 and 92 ppm

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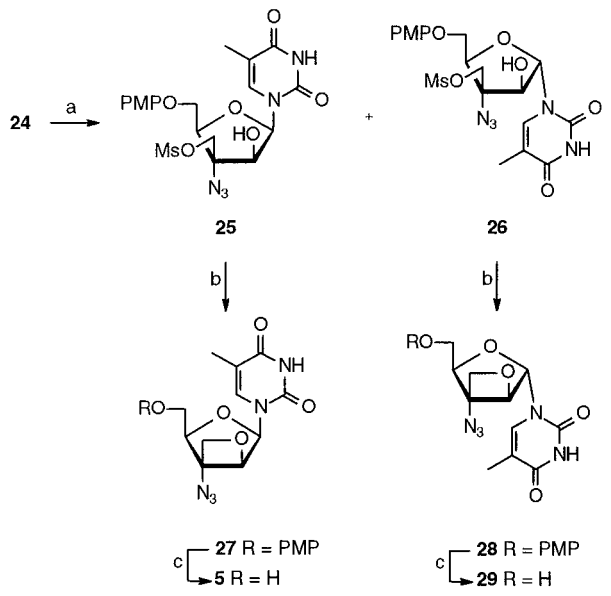
Scheme 3[a]



[a] Reagents: (a) thymine, TMS-Cl, bis(trimethylsilyl)acetamide, TMS-OTf, CH_3CN (**25**: 32% and **26**: 35%); (b) NaH, DMF (**27**: 79%; **28**: 93%); (c) CAN, CH_3CN, H_2O (**5**: 96%; **29**: 80%). PMP = *p*-methoxyphenyl.

were observed for all the four bicyclic nucleosides. Finally, mutual NOE contacts were seen for **5** between the oxetane H-1″ and the thymine H-6 (3%), between H-1′ and H-4′ (4%), and between H-1″ and H-5′ (3%). These contacts verify the β-configuration of the nucleoside as well as the position of the oxetane ring on the β-face of the furanose moiety. For **29**, the mutual NOE contacts between H-1″ and H-5′ (2%) as well as the lack of contacts between H-1″ and H-6 and between H-1′ and H-4′ indicate the corresponding α-configuration. Finally, the strong NOE contacts between the oxetane H-1″ and the thymine H-6 for **5** indicate an anti conformation[7] of the nucleobase moiety.

Discussion

The present synthesis of the target bicyclic derivative **5** has been accomplished in 6.4% overall yield from the starting material **7** taking advantage of the *p*-methoxyphenyl protecting group. In addition, the same reaction sequence afforded the α-anomer **29** in a similar 6.8% overall yield. Thus, the yield limiting step toward **5** was the nucleobase coupling reaction giving a mixture of anomeric nucleosides. All other steps were performed in satisfying yields. According to the retro-synthetic strategy (Figure 3), the addition of a trichloromethyl group and the subsequent Corey−Link-type reaction were performed in high yields and with perfect stereoselectivity. Furthermore, all other steps were performed successfully setting up a convenient substrate **24** for nucleobase coupling reactions. The key point in the synthesis has been the choice of the *p*-methoxyphenyl ether as a permanent protecting group for the primary alcohol moiety. To our opinion, this simple ether group deserves much greater attention in carbohydrate and nucleoside chemistry as a very stable, easily removable, and selective protecting group for primary hydroxyl groups.

The conformational restriction of **5** in an O4′-endo conformation can be confirmed by simple modeling and NMR. Thus, the presence of the oxetane ring demands the torsion angle ν_2 describing the C2′−C3′ torsion to be relatively close to 0°. Hereby, the pseudorotation angle *P* must be near 270° or 90° (Figure 2).[7,9] From a generalized Karplus equation, the relation between *P* and the coupling constant $^3J_{H1'H2'}$ can be found.[34] Thus, for **5,** our experimental coupling constant $^3J_{H1'H2'} = 2.7$ Hz, confirms a conformation with $P \sim 90°$ as a conformation with $P \sim 270°$ would demand a $^3J_{H1'H2'} \sim 7$ Hz. Nevertheless, some flexibility in an oxetane ring can be expected. However, from vibrational spectroscopy on simple oxetane this ring type has been reported to be essentially planar in contrast to the cyclobutane ring.[35] Thus, for the simple oxetane molecule the O−C−C−C torsion angle has been estimated to be a maximum of 2.5°.[35] Therefore, as a supposition we can claim that $\nu_2 \leq \pm 7°$. From the definitions of $\nu_2 = \Phi_{max} \cos P$, where Φ_{max} is the puckering amplitude,[7,9] this suggests that *P* can be found in the following interval [90 ± 11°] if $\Phi_{max} = 36°$ as standard for unmodified nucleosides[7] and if compensated by a lower puckering amplitude, e.g., $\Phi_{max} = 20°$, the interval is enlarged to [90 ± 20°]. Therefore, the bicyclic nucleosides **5** and **29** are in all probability restricted in conformations very close to pure E-type (O4′-*endo*) conformations. Furthermore, an ab initio calculation was performed on **5**, i.e., a geometry optimization at the 6-31G* level using the Gaussian94 program.[36] This confirmed the bicyclic nucleoside to adopt an E-conformation with $P = 91.4°$ ($\nu_2 = -1.1°$) and $\Phi_{max} = 46.8°$. The $\theta_{H1'H2'} = 38.7°$ is in perfect agreement[34] with our experimental coupling constant $^3J_{H1'H2'} = 2.7$ Hz.

The bicyclic nucleosides **5** and **29** were evaluated for antiviral activity against HIV-1 in MT-4 cells (HIV-IIIB) as described previously.[37] Unfortunately, both compounds were inactive against HIV-1 at 300 μM. Thus, the conformational restriction of the furanose moiety of AZT by the [3.2.0]bicyclic structure of **5** is unfavorable for anti-HIV activity. This might be due to a decreased biotransformation of **5** into its corresponding triphosphate or, alternatively, to a low affinity of the triphosphate for HIV-1 RT. Hence, these results confirm the results of Marquez et al. suggesting that the conformational flexibility is essential for the activity of AZT.[4] Thus, the lack of anti-HIV activity of **5** is not opposed to the results with other bicyclic analogues of AZT (vide supra),[4,15] confirming that the viral enzyme binds AZT in an N-conformation,[12] whereas the enzymes performing the phosphory-

(34) The Karplus relationship correlating $^3J_{H1'H2'}$ and the pseudorotational angle *P* was constructed employing a generalised Karplus equation for nucleosides developed by Altona and co-workers, which accounts for the electronegativity of substituents: (a) Donders, L. A.; de Leeuw F. A. A. M.; Altona, C. *Magn. Reson. Chem.* **1989**, *27*, 556. (b) Altona, C.; Ippel, J. H.; Westra Hoekzema, A. J. A.; Erkelens, C.; Groesbeek, M.; Donders, L. A. *Magn. Res. Chem.* **1989**, *27*, 564. (c) Altona, C.; Francke, R.; de Haan, R.; Ippel, J. H.; Daalmans, G. J.; Westra Hoekzema, A. J. A.; van Wijk, J. *Magn. Reson. Chem.* **1994**, *32*, 670.

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lation reactions recognize the substrates in S-conformations.[13] On the other hand, the well-established anti-HIV activity of d4T[1] indicates that some conformational restriction in a conformation between N- and S-type conformations can be accepted. Therefore, the inactivity of **5** might be due to the molecular geometry, e.g., the sterical effect of the oxetane ring, more than the conformationally constrained structure. In forthcoming biological studies, we might be able to deduce the low anti-HIV activity to either low affinity for the target viral enzyme or to insufficient biotransformation. Hence, **5** might be a very important compound in the understanding of the conformational preferences of these important enzymes.

Finally, we plan to use compounds **5** and **29** in our ongoing study of conformationally restricted oligonucleotide analogues.[3,16,17,33] Thus, oligonucleotide sequences with so-called N3′−P5′-phosphoramidite internucleotide linkages have revealed very promising results concerning the recognition of complementary RNA sequences.[38] As the azide moiety of **5** and **29** should be easily converted to a primary amine, these bicyclic nucleosides will be very useful building blocks for the construction of conformationally restricted oligonucleotide sequences with N3′−P5′-phosphoramidite linkages and evaluated with both the α- and β-geometry for their properties in nucleic acid recognition.

Conclusion

The synthesis of a bicyclic AZT analogue **5** and its anomer **29** has been successfully accomplished using, e.g., a modified Corey−Link procedure. The nucleoside analogue **5** is conformationally restricted in the unusual E-type (O4′-*endo*) conformation but inactive against HIV-1 in MT-4 cells. These results are in line with the results by Marquez et al.[4] indicating that conformational flexibility is essential for the anti-HIV activity of 2′,3′-dideoxynucleoside analogues. On the other hand, the inactivity of **5** might also be due to steric effects. In general, the present [3.2.0]bicyclic structure might find wider applicability in other nucleoside analogues for the study of the correlation between conformational behavior of nucleoside substrates and their affinity for nucleoside/nucleotide converting enzymes and receptors.

Experimental Section

Reactions were performed under an atmosphere of nitrogen when anhydrous solvents were used. Column chromatography was carried out on glass columns using silica gel 60 (0.040−0.063 mm). Chemical shifts are reported in ppm relative to tetramethylsilane as internal standard for ^{1}H NMR (250, 300, or 500 MHz) and ^{13}C NMR (62.5 or 75 MHz). ^{1}H NOE difference spectra were recorded for compounds **12**, **5**, and **29**. Assignments of NMR spectra when given are based on 2D spectra and follow standard carbohydrate and nucleoside style; i.e., the carbon atom next to a nucleobase is assigned C-1′, etc. In nucleosides, C-1″ designates the carbon atom in the 3′-C branch; otherwise, C-1′ designates the carbon atom in the 3-C branch. Compound names given in this section for the bicyclic compounds are given according to the von Baeyer nomenclature. Fast-atom bombardment mass spectra (FAB-MS) were recorded in positive-ion mode. Microanalyses were performed at The Microanalytical Laboratory, Department of Chemistry, University of Copenhagen.

5-*O*-*tert*-Butyldiphenylsilyl-1,2-*O*-isopropylidene-β-D-arabinofuran-3-ulose (8).[24] To a mixture of anhydrous pyridine (15 mL, 187 mmol) and anhydrous CH_2Cl_2 (150 mL) was added CrO_3 (9.4 g, 94 mmol), and the mixture was stirred for 15 min. After the mixture was cooled to 0 °C, a solution of the secondary alcohol **7** (10 g, 23 mmol) in CH_2Cl_2 (70 mL) was added dropwise. Acetic anhydride (9.0 mL, 94 mmol) was added, and the mixture was stirred for 30 min. The mixture was poured into a mixture of toluene and ethyl acetate (500 mL, 1:4 (v/v)), stirred for 20 min, and filtered through a layer of silica. The filter was rinsed three times with ethyl acetate, and the filtrate was evaporated under reduced pressure to give the ketone **8** (8.70 g, 90%) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.74−7.68 (4H, m), 7.43−7.37 (6H, m), 6.03 (1H, d, *J* 4.5 Hz), 4.39 (1H, d, *J* 4.5 Hz), 4.30 (1H, t, *J* 4.6 Hz), 3.96−3.93 (2H, m), 1.38 (3H, s), 1.36 (3H, s), 1.07 (9H, s); ^{13}C NMR ($CDCl_3$) δ 207.11, 135.72, 132.93, 129.73, 127.70, 114.74, 102.57, 82.29, 76.73, 64.47, 27.43, 26.59, 19.20.

5-*O*-*tert*-Butyldiphenylsilyl-3-*C*-trichloromethyl-1,2-*O*-isopropylidene-β-D-lyxofuranose (9). The ketone **8** (2.5 g, 5.9 mmol) was dissolved in anhydrous THF (25 mL) and anhydrous $CHCl_3$ (2.6 mL, 32 mmol). The solution was stirred at −78 °C, and a 1 M solution of LiHMDS in THF (21.3 mL, 21.3 mmol) was added slowly. The solution was stirred at −78 °C for 3 h, and the reaction was poured into an ice-cold saturated aqueous solution of $NaHCO_3$. The mixture was extracted with CH_2Cl_2, and the combined organic phases were dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using hexanes/ethyl acetate (9:1 (v/v)) as eluent affording the tertiary alcohol **9** (1.72 g, 54%) as an oil after evaporation of the solvents: FAB-MS *m*/*z* 487 [M − *t*-Bu]$^+$; ^{1}H NMR ($CDCl_3$) δ 7.73−7.71 (4H, m, Ph), 7.43−7.36 (6H, m, Ph), 5.95 (1H, d, *J* 4.3 Hz, 1-H), 4.80 (1H, d, *J* 4.3 Hz, 2-H), 4.64 (1H, dd, *J* 4.7, 7.3 Hz, 4-H), 4.36 (1H, s, OH), 4.09 (1H, dd, *J* 4.7, 11.1 Hz, 5-H), 3.93 (1H, dd, *J* 7.3, 11.1 Hz, 5-H), 1.49 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.10 (9H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 135.73, 135.61, 133.16, 132.86, 129.68, 129.71, 127.67, 114.14, 105.54, 103.90, 87.50, 84.28, 82.17, 65.13, 27.06, 26.82, 19.16.

3-*C*-Azido-5-*O*-*tert*-butyldiphenylsilyl-1,2-*O*-isopropylidene-3-*C*-methoxycarbonyl-β-D-arabinofuranose (10). The tertiary alcohol **9** (2.9 g, 5.3 mmol) was dissolved in anhydrous MeOH (25 mL), and NaN_3 (1.04 g, 16.0 mmol) and 18-crown-6 (15 mg, 0.057 mmol) were added. DBU (4.00 mL, 26.7 mmol) was added dropwise, and the mixture was stirred at 50 °C for 1 h and poured into a saturated aqueous solution of NH_4Cl (50 mL). The mixture was extracted with ether, and the combined organic extracts were dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using hexanes/ethyl acetate (9:1 (v/v)) as eluent affording the azido ester **10** (1.83 g, 68%) as an oil after evaporation of the solvents: FAB-MS *m*/*z* 496 [M − Me]$^+$; IR (KBr) 2114, 1756 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.69−7.65 (4H, m, Ph), 7.42−7.35 (6H, m, Ph), 5.84 (1H, d, *J* 3.5 Hz, 1-H), 4.50 (1H, d, *J* 3.5 Hz, 2-H), 4.25 (1H, t, *J* 6.2 Hz, 4-H), 4.09 (1H, dd, *J* 6.2, 10.4 Hz, 5-H), 3.95 (1H, dd, *J* 6.5, 10.4 Hz, 5-H), 3.74 (3H, s, OCH_3), 1.36 (3H, s, CH_3), 1.30 (3H, s, CH_3), 1.06 (9H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 166.04 (1′-C), 135.60, 135.49, 133.27, 132.96, 129.70, 129.68, 127.68, 127.67 (Ph), 114.77 ($C(CH_3)_2$), 105.20 (1-C), 85.78 (4-C), 84.95 (2-C), 73.59 (3-C), 63.27 (5-C), 52.71 (OCH_3), 26.73 (CH_3), 26.35 (CH_3), 19.14 ($C(CH_3)_3$).

3-*C*-Azido-5-*O*-*tert*-butyldiphenylsilyl-1,2-*O*-isopropylidene-3-*C*-hydroxymethyl-β-D-arabinofuranose (11). The azido ester **10** (1.75 g, 3.42 mmol) was dissolved in 96% EtOH (25 mL), and the solution was stirred at 0 °C. $NaBH_4$ (0.26 g, 6.8 mmol) was added, and the mixture was stirred at 5 °C for 12 h and poured into an ice-cold saturated aqueous solution of $NaHCO_3$. The mixture was extracted with CH_2Cl_2, and the combined organic extracts were dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using hexanes/ethyl acetate (9:1 (v/v)) as eluent affording the primary alcohol **11** (1.08 g, 66%) as a white solid after evaporation of the solvents: FAB-MS *m*/*z* 484 [M + H]$^+$; IR (KBr) 3446, 2114 cm^{-1}; ^{1}H NMR ($CDCl_3$)

(38) For a review, see: Gryaznov, S. M. *Biochim. Biophys. Acta* **1999**, *1489*, 131.

δ 7.68−7.62 (4H, m, Ph), 7.46−7.37 (6H, m, Ph), 5.80 (1H, d, *J* 3.9 Hz, 1-H), 4.40−4.29 (3H, m, 2-H, 4-H, 1′−H), 4.15−4.01 (2H, m, 5-H, 1′−H), 3.73 (1H, dd, *J* 3.8, 10.6 Hz, H-5), 3.13 (1H, dd, *J* 4.1, 10.1 Hz, OH), 1.25 (3H, s, CH_3), 1.21 (3H, s, CH_3), 1.08 (9H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 135.47, 135.44, 132.06, 131.61, 130.20, 128.01, 128.00, 112.86, 105.82, 85.36, 84.11, 74.60, 64.01, 62.56, 26.79, 26.12, 25.42, 19.03. Anal. Calcd for $C_{25}H_{33}N_3O_5Si$: C, 62.09; H, 6.88; N, 8.69. Found: C, 61.99; H, 6.92; N, 8.47.

3-*C*-Azido-5-*O*-*tert*-butyldiphenylsilyl-1,2-*O*-isopropylidene-3-*C*-methansulfonyloxymethyl-*β*-D-arabinofuranose (12). The primary alcohol **11** (300 mg, 0.62 mmol) was dissolved in anhydrous pyridine (5 mL) and the solution was stirred at 0 °C. Methanesulfonyl chloride (0.1 mL, 1.2 mmol) was added and the mixture was stirred at room temperature for 1 h and evaporated to dryness under reduced pressure. The residue was redissolved in CH_2Cl_2 and washed with a saturated aqueous solution of $NaHCO_3$. The organic phase was dried (Na_2SO_4), and evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using CH_2Cl_2/MeOH (98:2 (v/v)) as eluent affording the sulfonic ester **12** (227 mg, 77%) as an white solid after evaporation of the solvents: FAB-MS *m*/*z* 466 $[M - MsO]^+$; ^{1}H NMR ($CDCl_3$) δ 7.69−7.64 (4H, m, Ph), 7.48−7.41 (6H, m, Ph), 5.88 (1H, d, *J* 3.8 Hz, 1-H), 4.67 (2H, s, 2 × 1′-H), 4.54 (1H, d, *J* 3.8 Hz, 2-H), 4.24 (1H, dd, *J* 4.5, 10.1 Hz, 4-H), 3.94 (1H, t, *J* 10.2 Hz, 5-H), 3.78 (1H, dd, *J* 4.4, 10.4 Hz, 5-H), 3.03 (3H, s, SO_2CH_3), 1.26 (6H, s, CH_3), 1.09 (9H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 135.55, 135.47, 132.40, 132.11, 130.03, 130.00, 127.95, 127.89 (Ph), 112.95 ($C(CH_3)_2$), 105.60 (1-C), 85.75 (4-C), 82.97 (2-C), 72.09 (3-C), 67.98 (1′-C), 62.93 (5-C), 37.26 (SO_2CH_3), 26.81 ($C(CH_3)_3$), 25.96 (CH_3), 25.56 (CH_3), 19.00 ($C(CH_3)_3$).

3-*C*-Azido-5-*O*-methansulfonyl-1,2-*O*-isopropylidene-3-*C*-methansulfonyloxymethyl-*β*-D-arabinofuranose (13). The primary alcohol **11** (300 mg, 0.62 mmol) was dissolved in anhydrous THF (5 mL), and a 1 M solution of TBAF in THF (0.68 mL, 0.68 mmol) was added. The mixture was stirred at room temperature for 30 min and evaporated to dryness under reduced pressure. The residue was redissolved in anhydrous pyridine (2 mL), and methanesulfonyl chloride (0.2 mL, 2.5 mmol) was added. The mixture was stirred at room temperature for 30 min and evaporated to dryness under reduced pressure. The residue was redissolved in CH_2Cl_2 and washed with a saturated aqueous solution of $NaHCO_3$. The organic phase was dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using CH_2Cl_2 as eluent affording the sulfonic ester **13** (240 mg, 96%) as an off-white solid after evaporation of the solvents: FAB-MS *m*/*z* 402 $[M + H]^+$; ^{1}H NMR ($CDCl_3$) δ 6.00 (1H, d, *J* 3.5 Hz), 4.58−4.40 (6H, m), 3.15 (6H, s), 1.63 (3H, s), 1.33 (3H, s); ^{13}C NMR ($CDCl_3$) δ 113.79, 106.06, 83.26, 82.41, 71.37, 67.32, 66.65, 38.07, 37.68, 25.88, 25.33.

Methyl 3-*C*-Azido-5-*O*-methansulfonyl-1,2-*O*-isopropylidene-3-*C*-methansulfonyloxymethyl-D-arabinofuranoside (14). The sulfonic ester **13** (276 mg, 0.69 mmol) was dissolved in CH_2Cl_2 (1 mL). MeOH (2.6 mL) and water (1.4 mL) were added, and the mixture was stirred at 0 °C. A solution of HCl in MeOH (7 mL, 26% (w/w)) was added, and the reaction mixture was stirred at room temperature for 16 h. Water (5 mL) was added, and the mixture was neutralized by $NaHCO_3$(s) and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using CH_2Cl_2/MeOH (98:2 (v/v)) as eluent affording the two anomeric methyl furanoside **14**α (153 mg, 59%) and **14**β (51 mg, 20%) as clear oils after evaporation of the solvents. **14**α: FAB-MS *m*/*z* 376 $[M + H]^+$; ^{1}H NMR ($CDCl_3$) δ 4.99 (1H, s, H-1), 4.68 (1H, d, *J* 11.1 Hz, H-1′), 4.49−4.32 (5H, m, H-2, 2 x H-5, H-1′ og H-4), 3.44 (3H, s, OCH_3), 3.16 (3H, s, SO_2-CH_3) 3.11 (3H, s, SO_2-CH_3); ^{13}C NMR ($CDCl_3$) δ 108.86 (C-1), 80.87 (C-4), 79.89 (C-2), 70.17 (C-3), 67.38, 67.04 (C-5, C-1′), 55.83 (OCH_3), 37.82, 37.58 (2 × SO_2CH_3). **14**β: FAB-MS *m*/*z* 376 $[M + H]^+$; ^{1}H NMR ($CDCl_3$) δ 5.17 (1H, d, *J* 4.5 Hz, H-1), 4.65 (1H, d, *J* 11.1 Hz, H-1′), 4.57, (1H, d, *J* 11.1 Hz, H-1′), 4.41 (2H, d, *J* 5.9 Hz, 2 x H5), 4.29 (1H, m, H-4), 4.19 (1H, m, H-2), 3.59 (3H, s, OCH_3), 3.14 (3H, s, SO_2CH_3) 3.09 (3H, s, SO_2CH_3); ^{13}C NMR ($CDCl_3$) δ 102.89 (C-1), 80.13 (C-4), 75.93 (C-2), 71.00 (C-3), 67.57, 66.79 (C-5, C-1′), 56.92 (OCH_3), 37.70, 37.60 (2 × SO_2CH_3).

(1*R*,2*S*,4*S*,5*S*)-1-Azido-2-methansulfonyloxymethyl-4-methoxy-3,6-dioxabicyclo[3.2.0]heptane (15) and (1*S*,3*S*,-4*S*,7*R*)-7-Azido-7-methansulfonyloxymethyl-3-methoxy-2,5-dioxabicyclo[2.2.1]heptane (16). The methyl furanoside **14**α (69 mg, 0.18 mmol) was dissolved in anhydrous DMF (1 mL), and a 60% oily dispersion of NaH (12.5 mg, 0.31 mmol) was added. The mixture was stirred at room temperature for 30 min, and water (1 mL) was added. The mixture was neutralized with a 0.1 M aqueous solution of HCl and poured into CH_2Cl_2 (10 mL). The organic phase was washed with a saturated aqueous solution of $NaHCO_3$, dried (Na_2SO_4), and evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using hexanes/ethyl acetate (7:3 (v/v)) as eluent affording the bicyclic compounds **15** (6 mg, 12%) and **16** (29 mg, 57%) as clear oils after evaporation of the solvents. **15**: FAB-MS *m*/*z* 280 $[M + H]^+$; ^{1}H NMR ($CDCl_3$) δ 5.01, 5.00 (2H, 2 × s, 1-H, 2-H), 4.76 (1H, d, *J* 7.8 Hz, 1′-H), 4.69 (1H, d, *J* 7.8 Hz, 1′-H), 4.56 (1H, dd *J* 6.5, 11.3 Hz, 5-H), 4.42 (1H, dd *J* 4.7, 11.3 Hz, 5-H), 4.15 (1H, m, 4-H) 3.41 (3H, s, OCH_3), 3.11 (3H, s, SO_2CH_3); ^{13}C NMR ($CDCl_3$) δ 105.86, 91.30, 76.92, 73.07, 67.17, 65.86, 54.93, 37.84. **16**: ^{1}H NMR ($CDCl_3$) δ 5.03 (1H, s, 1-H), 4.56 (1H, s, 4-H), 4.51 (1H, d, *J* 11.0 Hz, 5-H), 4.44 (1H, d, *J* 11.0 Hz, 5-H), 4.10 (1H, s, 2-H), 4.00 (1H, d, *J* 9.3 Hz, 1′-H), 3.87 (1H, d, *J* 9.3 Hz, 1′-H), 3.52 (3H, s, OCH_3), 3.13 (3H, s, SO_2CH_3); ^{13}C NMR ($CDCl_3$) δ 106.82 (1-C), 78.39 (4-C), 77.98 (2-C), 71.21 (1′-C), 69.86 (3-C), 69.39 (5-C), 56.79 (OCH_3), 37.59 (SO_2CH_3).

1,2-*O*-Isopropylidene-5-*O*-*p*-methoxyphenyl-*β*-D-arabinofuranose (18). The silyl ether **7** (20 g, 47 mmol) was dissolved in anhydrous THF (150 mL), and KF (16.2 g, 280 mmol), water (10 mL, 560 mmol), and 18-crown-6 (3.6 g, 14 mmol) were added. The mixture was stirred at room temperature for 18 h and evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using CH_2Cl_2/MeOH (9:1 (v/v)) as eluent affording the dialcohol **17**[32] (7.93 g) as a white solid after evaporation of the solvents. This solid was redissolved in anhydrous THF (50 mL), and triphenylphosphine (14.2 g, 54.1 mmol) and 4-methoxyphenol (14.9 g, 121 mmol) were added. The mixture was stirred at 0 °C, and DEAD (8.5 mL, 54 mmol) was added dropwise. The mixture was stirred at 0 °C for 30 min and at 50 °C for 16 h. The solvent was removed by evaporation under reduced pressure, and the residue was purified by silica gel chromatography using hexanes/ether (1:1 (v/v)) as eluent affording the phenyl ether **18** (8.75 g, 63%) as a white solid after evaporation of the solvents: FAB-MS *m*/*z* 296 $[M]^+$; ^{1}H NMR ($CDCl_3$) δ 6.84 (4H, s), 5.97 (1H, d, *J* 3.8 Hz), 4.60 (1H, d, *J* 3.8 Hz), 4.43 (1H, br s), 4.30 (1H, m), 4.25−4.10 (3H, m), 3.79 (3H, s), 2.46 (1H, br s), 1.55 (3H, s), 1.34 (3H, s); ^{13}C NMR ($CDCl_3$) δ 154.07, 152.52, 115.51, 114.67, 112.71, 105.75, 86.91, 85.56, 76.42, 68.38, 55.67, 26.94, 26.02. Anal. Calcd for $C_{15}H_{20}O_6$: C, 60.81; H, 6.76. Found: C, 61.07; H, 6.76.

1,2-*O*-Isopropylidene-5-*O*-*p*-methoxyphenyl-*β*-D-arabinofuran-3-ulose (19). To a mixture of anhydrous pyridine (2.0 mL, 27 mmol) and anhydrous CH_2Cl_2 (15 mL) was added CrO_3 (1.3 g, 14 mmol), and the mixture was stirred for 15 min. After the mixture was cooled to 0 °C, a solution of the secondary alcohol **18** (1.0 g, 3.4 mmol) in CH_2Cl_2 (10 mL) was added dropwise. Acetic anhydride (1.3 mL, 14 mmol) was added, and the mixture was stirred for 30 min. The mixture was poured into a mixture of toluene and ethyl acetate (50 mL, 1:3 (v/v)), stirred for 20 min, and filtered through a layer of silica. The filter was rinsed three times with ethyl acetate, and the filtrate was evaporated under reduced pressure to give the ketone **8** (0.99 g, 99%) as an oil: ^{1}H NMR ($CDCl_3$) δ 6.88−6.79 (4H, m), 6.08 (1H, d, *J* 4.0 Hz), 4.50−4.48 (2H, m), 4.26−4.15 (2H, m), 3.75 (3H, s), 1.56 (3H, s), 1.42 (3H, s); ^{13}C NMR ($CDCl_3$) δ 207.05, 154.34, 152.29, 116.02, 115.11, 114.60, 102.74, 80.27, 76.67, 68.89, 55.61, 27.43, 26.93.

1,2-*O*-Isopropylidene-5-*O*-*p*-methoxyphenyl-3-*C*-trichloromethyl-*β*-D-lyxofuranose (20). The ketone **19** (0.99 g, 3.4

mmol) was dissolved in anhydrous THF (10 mL) and anhydrous $CHCl_3$ (0.75 mL, 9.3 mmol). The solution was stirred at −78 °C, and a 1 M solution of LiHMDS in THF (6.0 mL, 6.0 mmol) was added slowly. The solution was stirred at −78 °C for 3 h, and the reaction mixture was poured into an ice-cold saturated aqueous solution of $NaHCO_3$. The mixture was extracted with CH_2Cl_2, and the combined organic phases were dried ($MgSO_4$), and evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using CH_2Cl_2 as eluent affording the tertiary alcohol **20** (1.03 g, 74%) as a white solid after evaporation of the solvents: FAB-MS *m/z* 412 $[M]^+$; ^{1}H NMR ($CDCl_3$) δ 6.92−6.81 (4H, m), 6.00 (1H, d, *J* 4.2 Hz), 4.90−4.86 (2H, m), 4.39 (1H, dd, *J* 2.9, 10.8 Hz), 4.16 (1H, dd, *J* 8.2, 10.8 Hz), 4.11 (1H, s), 3.76 (3H, s), 1.66 (3H, s), 1.47 (3H, s); ^{13}C NMR ($CDCl_3$) δ 154.05, 152.66, 115.68, 114.84, 114.59, 105.53, 86.94, 82.76, 82.22, 69.95, 55.69, 27.27, 27.03. Anal. Calcd for $C_{16}H_{19}O_6Cl_3$: C, 46.60; H, 4.61. Found: C, 46.65; H, 4.47.

3-*C*-Azido-1,2-*O*-isopropylidene-3-*C*-methoxycarbonyl-5-*O*-*p*-methoxyphenyl-*β*-D-arabinofuranose (21). The tertiary alcohol **20** (1.08 g, 2.62 mmol) was dissolved in anhydrous MeOH (15 mL), and NaN_3 (0.42 g, 6.5 mmol) and 18-crown-6 (5 mg, 0.019 mmol) were added. DBU (1.6 mL, 11 mmol) was added dropwise, and the mixture was stirred at 40 °C for 1 h and poured into a saturated aqueous solution of NH_4Cl (25 mL). The mixture was extracted with ether, and the combined organic extracts were dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using CH_2Cl_2 as eluent affording the azido ester **21** (0.87 g, 87%) as a clear oil after evaporation of the solvents: FAB-MS *m/z* 379 $[M]^+$; IR (KBr) 2119, 1751 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.87−6.80 (4H, m, PMP), 5.93 (1H, d, *J* 3.6 Hz, 1-H), 4.59 (1H, d, *J* 3.6 Hz, 2-H), 4.47 (1H, t, *J* 6.1 Hz, 4-H), 4.39 (1H, dd, *J* 5.8, 9.8 Hz, 5-H), 4.29 (1H, dd, *J* 6.7, 9.8 Hz, 5-H), 3.82 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 1.58 (3H, s, CH_3), 1.36 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 165.85 (1′−C), 154.13, 152.24, 115.55, 114.59 (PMP), 114.99 ($C(CH_3)_2$), 105.30 (1-C), 85.07 (2-C), 83.14 (4-C), 73.97 (3-C), 67.50 (5-C), 55.62 (OCH_3), 52.91 (OCH_3), 26.60, 26.34 (CH_3). Anal. Calcd for $C_{17}H_{21}O_7N_3$: C, 53.83; H, 5.54; N, 11.08. Found: C, 53.78; H, 5.50; N, 10.93.

3-*C*-Azido-1,2-*O*-isopropylidene-3-*C*-hydroxymethyl-5-*O*-*p*-methoxyphenyl-*β*-D-arabinofuranose (22). The azido ester **21** (0.91 g, 2.41 mmol) was dissolved in THF (5 mL) and 96% EtOH (15 mL), and the solution was stirred at 0 °C. $NaBH_4$ (0.27 g, 7.22 mmol) was added, and the mixture was stirred at 5 °C for 14 h and poured into an ice-cold saturated aqueous solution of $NaHCO_3$. The mixture was extracted with CH_2Cl_2, and the combined organic extracts were dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using hexanes/ethyl acetate (9:1 (v/v)) as eluent affording the primary alcohol **22** (0.67 g, 80%) as a clear oil after evaporation of the solvents: FAB-MS *m/z* 351 $[M]^+$; IR (KBr) 3440, 2131 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.88−6.82 (4H, m), 5.94 (1H, d, *J* 3.8 Hz), 4.57−4.02 (6H, m), 3.78 (3H, s), 1.57 (3H, s), 1.31 (3H, s); ^{13}C NMR ($CDCl_3$) δ 154.69, 151.45, 115.54, 114.87, 113.10, 105.94, 84.16, 83.07, 74.43, 68.36, 62.29, 55.69, 26.57, 25.45. Anal. Calcd for $C_{16}H_{21}O_6N_3$: C, 54.70; H, 5.98; N, 11.96. Found: C, 54.68; H, 5.87; N, 11.72.

3-*C*-Azido-1,2-*O*-isopropylidene-3-*C*-methansulfonyloxymethyl-5-*O*-*p*-methoxyphenyl-*β*-D-arabinofuranose (23). The primary alcohol **22** (649 mg, 1.85 mmol) was dissolved in anhydrous pyridine (7 mL), and the solution was stirred at 0 °C. Methanesulfonyl chloride (0.43 mL, 5.6 mmol) was added, and the mixture was stirred at room temperature for 1 h and evaporated to dryness under reduced pressure. The residue was redissolved in CH_2Cl_2 and washed with a saturated aqueous solution of $NaHCO_3$. The organic phase was dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using CH_2Cl_2/MeOH (98:2 (v/v)) as eluent affording the sulfonic ester **23** (690 mg, 87%) as a white solid after evaporation of the solvents: FAB-MS *m/z* 429 $[M]^+$; ^{1}H NMR ($CDCl_3$) δ 6.87−6.80 (4H, m, PMP), 5.99 (1H, d, *J* 3.8 Hz, 1-H), 4.66 (1H, d, *J* 10.8 Hz, 1′−H), 4.58 (1H, d, *J* 10.8 Hz, 1′−H), 4.56 (1H, d, *J* 3.8 Hz, 2-H), 4.47 (1H, dd, *J* 5.1, 8.9 Hz, 4-H), 4.24 (1H, t, *J* 9.5 Hz, 5-H), 4.14 (1H, dd, *J* 5.1, 9.9 Hz, 5-H), 3.77 (3H, s, OCH_3), 3.08 (3H, s, SO_2CH_3), 1.58 (3H, s, CH_3), 1.34 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 154.50, 151.68, 115.51, 114.83, 113.37, 105.77, 83.34, 83.22, 71.90, 67.49, 67.38, 55.67, 37.56, 26.42, 25.59.

Methyl 3-*C*-Azido-3-*C*-methansulfonyloxymethyl-5-*O*-*p*-methoxyphenyl-D-arabinofuranoside (24). Anhydrous MeOH (10 mL) was stirred at −30 °C, and acetyl chloride (2 mL) was added slowly. The mixture was stirred at −30 °C for 30 min and warmed to room temperature. A solution of **23** (540 mg, 1.26 mmol) in CH_2Cl_2/MeOH/water (2:2:1 (v/v/v), 12.5 mL) was stirred at 0 °C, and the first solution was added dropwise. The mixture was stirred at room temperature for 16 h, and water (12 mL) was added. The mixture was neutralized with $NaHCO_3$(s) and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using CH_2Cl_2/MeOH (97:3 (v/v)) as eluent affording the anomeric mixture **24** (510 mg, 94%) as a clear oil after evaporation of the solvents: FAB-MS *m/z* 403 $[M]^+$; ^{1}H NMR ($CDCl_3$) δ 6.90−6.83 (m), 5.16 (d, *J* 4.8 Hz), 5.05 (s), 4.72−4.56 (m), 4.45−4.11 (m), 3.77 (s), 3.45 (s), 3.08 (s); ^{13}C NMR ($CDCl_3$) δ 154.94, 154.64, 151.97, 151.35, 116.08, 115.69, 114.86, 114.74, 109.59, 102.65, 82.36, 80.92, 79.33, 76.00, 71.26, 70.83, 68.19, 67.84, 67.81, 67.34, 56.68, 55.78, 55.68, 37.53, 37.46.

1-(3-*C*-Azido-3-*C*-methansulfonyloxymethyl-5-*O*-*p*-methoxyphenyl-α/*β*-D-arabinofuranosyl)thymine (25 and 26). The anomeric mixture of methyl furanosides **24** (320 mg, 0.80 mmol) was coevaporated with anhydrous CH_3CN (3 × 20 mL). Thymine (0.2 g, 1.6 mmol) was added, and the mixture was dried under reduced pressure and dissolved under an Ar atmosphere in anhydrous CH_3CN (4 mL). *N*,*O*-Bis(trimethylsilyl)acetamide (BSA) (1.5 mL, 6.5 mmol) and TMS-Cl (0.10 mL, 0.80 mmol) were added, and the mixture was stirred at 60 °C for 1 h. After the mixture was cooled to 0 °C, TMS-triflate (0.73 mL, 4.0 mmol) was added dropwise, and the mixture was stirred at 70 °C for 24 h. An additional portion of TMS-triflate (0.3 mL, 1.6 mmol) was added, and after being stirred for another 24 h, the mixture was poured into a saturated aqueous solution of $NaHCO_3$ (30 mL). CH_2Cl_2 was added, and the organic phase was washed with a saturated aqueous solution of $NaHCO_3$, dried ($MgSO_4$), and evaporated to dryness under reduced pressure. The residue was redissolved in anhydrous THF (10 mL), and a 1 M solution of TBAF in THF (1.2 mL, 1.2 mmol) was added. The solution was stirred at room temperature for 1 h and diluted with CH_2Cl_2. The mixture was washed with a saturated aqueous solution of $NaHCO_3$ and water, dried ($MgSO_4$), and evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using CH_2Cl_2/MeOH (19:1 (v/v)) as eluent affording the α-anomer **26** (139 mg, 35%) as a white foam and the *β*-anomer **25** (126 mg, 32%) as an oil after evaporation of the solvents. **26**: FAB-MS *m/z* 497 $[M]^+$; ^{1}H NMR ($CDCl_3$) δ 10.45 (1H, s, NH), 7.49 (1H, d, *J* 1.0 Hz, 6-H), 6.90−6.83 (4H, m, PMP), 6.03 (1H, br s, 2′-OH), 5.91 (1H, s, 1′-H), 4.79−4.67 (3H, m, 4′-H, 5′-H′, 1″-H), 4.47 (1H, br s, 2′-H), 4.28−4.24 (2H, m, 5′-H, 1″-H), 3.78 (3H, s, OCH_3) 3.09 (3H, s, SO_2CH_3), 1.95 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 164.73 (4-C), 154.60 (3-C), 151.72, 150.57 (PMP), 135.23 (6-C), 115.70, 114.83 (PMP), 110.36 (5-C), 94.23 (1′-C), 85.23 (4′-C), 78.92 (2′-C), 71.12 (3′-C), 67.55, 67.29 (1″-C, 5′-C), 55.73 (OCH_3), 37.51 (SO_2CH_3), 12.64 (CH_3). Anal. Calcd for $C_{19}H_{23}N_5O_9S$: C, 45.87; H, 4.66; N, 14.08; s, 6.44. Found: C, 45.62; H, 4.52; N, 13.52; S, 6.21. **25**: FAB-MS *m/z* 498 $[M + H]^+$; ^{1}H NMR ($CDCl_3$) δ 11.08 (1H, s, NH), 7.38 (1H, s, 6-H), 6.88 (4H, br s, PMP), 6.26 (1H, d, *J* 2.9 Hz, 1′−H), 5.57 (1H, d, *J* 5.4 Hz, 2′-OH), 4.79−4.63 (3H, m, 2 × 1″-H, 2′-H), 4.44 (1H, t, *J* 6.2 Hz, 4′-H), 4.24 (2H, m, 2 × 5′-H), 3.78 (3H, s, OCH_3), 3.12 (3H, s, SO_2CH_3), 1.58 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 166.01 (4-C), 154.71 (2-C), 151.86, 150.42 (PMP), 138.79 (6-C), 115.84, 114.91 (PMP), 107.95 (5-C), 88.11 (1′-C), 82.39 (4′-C), 73.44 (3′-C), 71.81 (2′-C), 67.34, (1″-C, 5′-C), 55.75 (OCH_3), 37.63 (SO_2CH_3), 12.17 (CH_3).

(1*R*,2*S*,4*R*,5*S*)-1-Azido-2-(*p*-methoxyphenoxy)methyl-4-(thymin-1-yl)-3,6-dioxabicyclo[3.2.0]heptane (27). The β-nucleoside **25** (181 mg, 0.36 mmol) was dissolved in anhydrous DMF (3 mL), and a 60% oily dispersion of NaH (36 mg, 0.91 mmol) was added. The mixture was stirred at room temperature for 1 h and quenched with water (3 mL). The mixture was neutralized with a 0.1 M aqueous solution of HCl and extracted with CH_2Cl_2 . The organic phase was washed with a saturated aqueous solution of $NaHCO_3$, dried ($MgSO_4$), and evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using CH_2Cl_2/MeOH (97:3 (v/v)) as eluent affording the bicyclic β-nucleoside **27** (115.5 mg, 79%) as a white solid after evaporation of the solvents: FAB-MS *m*/*z* 402 $[M + H]^+$; ^{1}H NMR ($CDCl_3$) δ 8.50 (1H, s, NH), 7.52 (1H, s, 6-H), 6.91−6.85 (4H, m, PMP), 6.03 (1H, d, *J* 2.4 Hz, 1′-H), 5.21 (1H, d, *J* 2.4 Hz, 2′-H), 4.96 (1H, d, *J* 7.8 Hz, 1″-H), 4.88 (1H, d, *J* 7.8 Hz, 1″-H), 4.41 (1H, dd, *J* 5.7, 10.2 Hz, 5′−H), 4.27 (1H, dd, *J* 5.7, 10.2 Hz, 5′-H), 4.18 (1H, t, *J* 5.7 Hz, 4′-H) 3.79 (3H, s, OCH_3) 1.93 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 163.57,154.56, 151.88, 150.20, 137.01, 115.39, 114.75, 110.19, 87.16, 83.41, 78.47, 73.07, 66.90, 65.37, 55.68, 12.54. Anal. Calcd for $C_{18}H_{19}N_5O_6$: C, 53.86; H, 4.77; N, 17.45. Found: C, 53.68; H, 4.85; N, 17.04.

(1*R*,2*S*,4*S*,5*S*)-1-Azido-2-(*p*-methoxyphenoxy)methyl-4-(thymin-1-yl)-3,6-dioxabicyclo[3.2.0]heptane (28). The same procedure as in the preparation of **27** was used applying the α-nucleoside **26** (114 mg, 0.23 mmol), anhydrous DMF (3 mL) and a 60% oily dispersion of NaH (18.4 mg, 0.46 mmol) affording the bicyclic α-nucleoside **28** (85.1 mg, 93%) as a white solid: FAB-MS *m*/*z* 402 $[M + H]^+$;^{1}H NMR ($CDCl_3$) δ 9.39 (1H, s, NH), 7.00 (1H, s, 6-H), 6.84−6.83 (4H, m, PMP), 5.58, 5.56 (2H, 2 × s, 1′-H, 2′-H), 4.91 (1H, d, *J* 7.3 Hz, 1″-H), 4.74 (1H, t, *J* 5.6 Hz, 4′-H), 4.66 (1H, d, *J* 7.3 Hz, 1″-H), 4.27 (1H, dd, *J* 6.0, 10.0 Hz, 5′-H), 4.11 (1H, dd, *J* 6.0, 10.0 Hz, 5′-H), 3.75 (3H, s, OCH_3) 1.92 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 163.84, 154.37, 152.09, 151.01, 139.10, 115.42, 114.65, 111.60, 95.09, 91.82, 82.40, 73.41, 69.70, 66.24, 55.63, 12.28.

(1*R*,2*S*,4*R*,5*S*)-1-Azido-2-hydroxymethyl-4-(thymin-1-yl)-3,6-dioxabicyclo[3.2.0]heptane (5). The nucleoside **27** (58 mg, 0.14 mmol) was dissolved in CH_3CN/water (4:1 (v/v), 3 mL), and the solution was stirred at 0 °C. Cerium(IV)-ammonium nitrate (CAN) (158 mg 0.29 mmol) was added, and after the solution was stirred for 1 h, $MgSO_4$(s) was added. After being stirred for another 30 min, the mixture was filtered and the filtrate evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using CH_2Cl_2/MeOH (19:1 (v/v)) as eluent affording the bicyclic nucleoside **5** (42 mg, 96%) as an off-white solid after evaporation of the solvents: FAB-MS *m*/*z* 296 $[M + H]^+$; HR MALDI FT-MS *m*/*z* 318.0844, calcd 318.0809 $[M + Na^+]$; IR (KBr) 3432, 2115, 1699 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.43 (1H, s, NH), 7.71 (1H, s, 6-H), 6.03 (1H, d, *J* 2.7 Hz, 1′-H), 5.15 (1H, t, *J* 5.6 Hz, 5′-OH) 5.14 (1H, d, *J* 2.7 Hz, 2′-H), 5.00 (1H, d, *J* 7.9 Hz, 1″-H), 4.63 (1H, d, *J* 7.9 Hz, 1″-H), 3.96 (1H, t, *J* 5.7 Hz, 4′-H), 3.87 (1H, m, 5′-H), 3.73 (1H, m, 5′-H), 1.80 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ 163.48 (4-C), 149.90 (2-C), 137.71 (6-C), 108.03 (5-C), 86.73 (2′-C), 82.46 (1′-C), 79.30 (4′-C), 72.87 (3′-C), 66.49 (1″-C), 58.32 (5′-C), 12.07 (CH_3).

(1*R*,2*S*,4*S*,5*R*)-1-Azido-2-hydroxymethyl-4-(thymin-1-yl)-3,6-dioxabicyclo[3.2.0]heptane (29). The same procedure as in the preparation of **5** was used with the nucleoside **28** (39 mg, 0.10 mmol), CH_3CN/water (4:1 (v/v), 2 mL), and CAN (106 mg 0.20 mmol) affording the bicyclic nucleoside **29** (23 mg, 80%) as an off-white solid: FAB-MS *m*/*z* 296 $[M + H]^+$; HR MALDI FT-MS *m*/*z* 318.0846, calcd 318.0809 $[M + Na^+]$; IR (KBr) 3435, 2118, 1690 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.47 (1H, s, NH), 7.57 (1H, s, 6-H), 5.59, 5.56 (2H, 2 × s, 1′-H, 2′-H), 5.06 (1H, t, *J* 5.5 Hz, 5′-OH), 4.82 (1H, d, *J* 7.7 Hz, 1″-H) 4.43 (1H, d, *J* 7.7 Hz, 1″-H), 4.37 (1H, t, *J* 6.0 Hz, 4′-H), 3.77 (1H, m, 5′-H), 3.60 (1H, m, 5′-H), 1.76 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ 163.95, 151.22, 140.31, 109.06, 93.97, 91.59, 83.41, 72.79, 69.07, 59.03, 11.82.

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Supporting Information Available: ^{13}C NMR spectra of compounds **5**, **8**−**10**, **12**−**14**, **16**, **19**, **23**−**25**, **28**, and **29**. ^{1}H NMR spectra of compounds **5** and **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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