Synthesis and Conformational Investigation of Methyl 4a-Carba-D-arabinofuranosides

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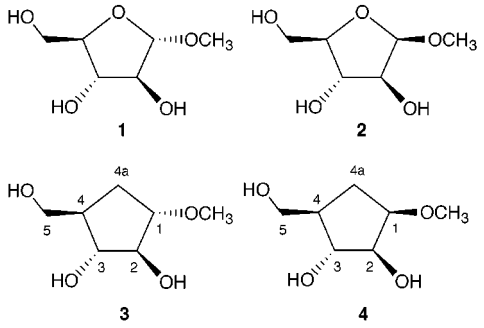
The synthesis of carbasugar analogues of methyl α-D-arabinofuranoside and methyl β-D-arabinofuranoside (**3** and **4**) is reported. The route developed involves the conversion of D-mannose into a suitably protected diene (**13**), which is then cyclized via olefin metathesis. The resulting cyclopentene (**14**) is stereoselectively hydrogenated to provide an intermediate that can be used for the synthesis of both targets. Through the use of NMR spectroscopy, we have probed the ring conformation of **3** and **4**, as well as the rotamer populations about the C_4-C_5 and C_1-O_1 bonds. These studies have demonstrated that there are differences in ring conformation between these carbasugars and their glycoside parents (**1** and **2**). However, only minor differences are seen in the rotameric equilibrium about the C_4-C_5 bond in **3** and **4** relative to **1** and **2**. In regard to the C_1-O_1 bond, NOE data from **3** and **4** suggest that the favored position about this bond is similar to that in the glycosides; that is, the methyl group is anti to C_2. However, confirmation of this preference through measurement of $^3J_{C,C}$ between the methyl group and C_2 or C_{4a} was not successful.

Introduction

Carbasugars are analogues of monosaccharides in which the ring oxygen has been replaced with a methylene group. There has been increasing interest in the synthesis of "glycoconjugates" containing carbasugar residues for use as potential therapeutic agents.[1] It is believed that such species will be more efficacious than their glycoside counterparts due to increased acid and metabolic stability. This approach has already been validated in that many carbasugar-containing nucleoside analogues have been demonstrated to possess antiviral activity.[2] Among these is Abacavir, a drug recently approved for the treatment of HIV.[3]

Over the past few years, our group has been interested in identifying inhibitors of the arabinosyltransferases that are involved in the assembly of two mycobacterial cell wall polysaccharides. Such compounds are likely to be of use in the treatment of mycobacterial infections, including those leading to tuberculosis and leprosy, diseases that are again becoming serious health threats in the industrialized world.[4] Although the natural substrates for these glycosyltransferases are large polysaccharides, recent work has demonstrated that small oligosaccharide fragments (e.g., disaccharides) are also glycosylated by these enzymes.[5] Given that oligosaccharide analogues containing carbasugar residues have been shown to be competent glycosyltransferase substrates,[6] we postulated that arabinosyltransferase inhibitors containing carbasugar residues would be attractive synthetic targets. Toward this end, in an earlier communication,[7] we described a novel route for the preparation of the carbocyclic analogues of methyl α-D-arabinofuranoside (**1**, Chart 1) and methyl β-D-arabinofuranoside (**2**), namely, methyl 4a-carba-α-D-arabinofuranoside (**3**) and methyl 4a-carba-β-D-arabinofuranoside (**4**). We report here a full account of an improved synthesis of **3** and **4**, as well as NMR studies focused on understanding the solution conformation of these carbasugars.

Chart 1



Results and Discussion

Synthesis. The synthesis of cyclopentane and cyclohexane rings in which each carbon atom bears a hydroxyl group (e.g., inositols) has been well studied.[8] Similarly,

(1) (a) Vogel, P. *Chimia* **2001**, *55*, 359. (b) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229. (c) De Clercq, E. *Nucleosides Nucleotides* **1998**, *17*, 625. (d) Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611.

(2) (a) Tan, X.; Chu, C. K.; Boudinot, F. D. *Adv. Drug Delivery Rev.* **1999**, *39*, 117. (b) Mansour, T. S.; Storer, R. *Curr. Pharm. Des.* **1997**, *3*, 227. (c) Marquez, V. E. *Adv. Antiviral Drug Des.* **1996**, *2*, 89.

(3) (a) Hervey, P. S.; Perry, C. M. *Drugs* **2000**, *60*, 447. (b) De Clercq, E. *Pure Appl. Chem.* **2001**, *73*, 55.

(4) (a) Dolin, P. J.; Raviglione, M. C.; Kochi, A. *Bull. World Health Org.* **1994**, *72*, 213. (b) Bloom, B. R.; Murray, C. J. L. *Science* **1992**, *257*, 1055.

(5) (a) Ayers, J. D.; Lowary, T. L.; Morehouse, C. B.; Besra, G. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 437. (b) Lee, R. E.; Brennan, P. J.; Besra, G. S. *Glycobiology* **1997**, *7*, 1121.

(6) (a) Kajihara, Y.; Hashimoto, H.; Ogawa, S. *Carbohydr. Res.* **2000**, *323*, 44. (b) Ogawa, S.; Matsunaga, N.; Li, H.; Palcic, M. M. *Eur. J. Org. Chem.* **1999**, 631. (c) Ogawa, S.; Furuya, T.; Tsunoda, H.; Hindsgaul, O.; Stangier, K.; Palcic, M. M. *Carbohydr. Res.* **1995**, *271*, 197.

(7) Callam, C. S.; Lowary, T. L. *Org. Lett.* **2000**, *2*, 167.

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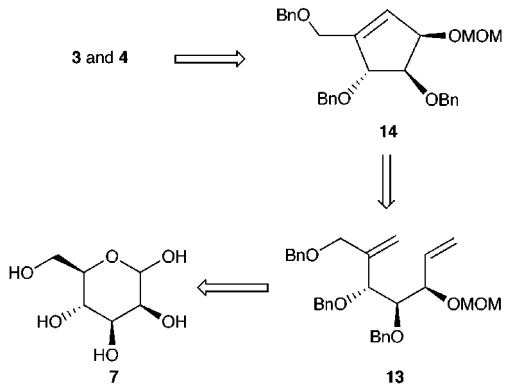


Figure 1. Retrosynthetic analysis of **3** and **4**.

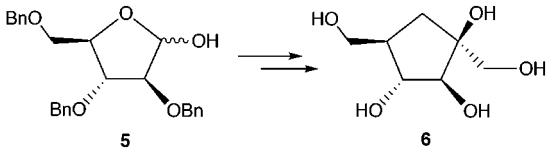


Figure 2.

many methods are available for the preparation of carbasugar analogues of monosaccharides in the pyranose ring form.[9] In contrast, far fewer routes have been developed for the preparation of carbafuranoses.[10] Our approach to **3** and **4** (Figure 1) has, as key steps, a ring-closing metathesis reaction (RCM) of diene **13**, followed by a stereoselective hydrogenation of the resulting cyclopentene, **14**. The preparation of a carbasugar analogue of β-D-fructofuranose (**6**) from 2,3,5-tri-*O*-benzyl-D-arabinofuranose (**5**) via an analogous pathway has been reported recently (Figure 2).[11]

The synthesis of **3** and **4** began with D-mannose, **7** (Scheme 1). Conversion of this monosaccharide into the known[12] protected thioglycoside **8** was readily achieved. We have modified the route to **8** such that a number of the intermediates in this sequence are crystalline, which allows the facile preparation of this thioglycoside in multigram quantities. Details on the conversion of **7** into **8**, which proceeded in 58% yield over six steps, are given in the Supporting Information. The 2-OH group in **8** was next protected as a MOM ether giving **9** in 88% yield. Subsequently, the thioglycoside was hydrolyzed upon reaction with *N*-iodosuccinimide and silver triflate in wet acetonitrile, which afforded hemiacetal **10** in 90% yield. The first alkene moiety was installed via a Wittig reaction by treatment of **10** with methylenetriphenylphosphorane, which was freshly prepared from methyltriphenylphosphonium bromide and *n*-butyllithium. This reaction provided **11** in 78% yield. Our initial attempts to perform this conversion resulted in significant amounts of diene **20** (Chart 2) being produced in addition to the desired alkene. The formation of this elimination byproduct could be suppressed by treatment of **10** with 1 equiv of *n*-butyllithium for 10 min at 0 °C prior to the addition of the phosphorane at −78 °C.[13] When carried out in this fashion, the reaction afforded alkene **11** as the major product, with only traces of **20** being detected by TLC. Oxidation of the hydroxyl group in **11** was achieved with pyridinium chlorochromate buffered with sodium acetate[14] in dichloromethane. Ketone **12** was produced in 93% yield, with no epimerization of the adjacent stereocenter. Attempted oxidation of alcohol **11** under Swern conditions afforded a mixture of products. The second olefin was introduced, in 77% yield, upon reaction of **12** with methylenetriphenylphosphorane. In contrast to the transformation of **10** into **11**, the preparation of **13** from **12** did not require pretreatment of the substrate with *n*-butyllithium. However, to prevent enolization of the ketone during the reaction, it was necessary to ensure that an excess of methyltriphenylphosphonium bromide relative to the *n*-butyllithium was used in the formation of the ylide.[15]

With diene **13** in hand, the key RCM reaction was explored. Our initial attempts involved the use of the first generation Grubbs catalyst (**21**, Chart 2).[16] However, under a range of conditions only poor yields of **14** were produced (Table 1, entries 1−3). These results are consistent with previous investigations,[17] which have demonstrated that **21** does not usually provide good yields of trisubstituted olefins. Significantly better results were obtained (Table 1, entry 4) with the Schrock catalyst (**22**), which is known to provide tri- and tetrasubstituted olefins in good yields from dienes.[18] Cyclization of **13** mediated by **22** in a glovebox gave **14** in 74% yield. We subsequently found that catalysts **23**[19] and **24**[20] (Chart 2) cyclized **13** into **14** in 78% and 74% yield, respectively.

(8) Reviews: (a) Dalko, P. I.; Sinaÿ, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 773. (b) Hudlicky, T.; Enwistle, D. A.; Pitzer, K. K.; Thorpe, A. J. *Chem. Rev.* **1996**, *96*, 1195. (c) Pingli, L.; Vandewalle, M. *Synlett* **1994**, 228. (d) Martínez-Grau, A.; Marco-Contelles, J. *Chem. Soc. Rev.* **1998**, *27*, 155.

(9) Reviews: (a) Suami, T.; Ogawa, S. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 21. (b) Suami, T. *Topics Curr. Chem.* **1990**, *154*, 257. (c) Ogawa, S. *Carbohydr. Mimics* **1998**, 87.

(10) Representative syntheses of furanose carbasugar analogues: (a) Gallos, J. K.; Dellios, C. C.; Spata, E. E. *Eur J. Org. Chem.* **2001**, 79. (b) Gathergood, N.; Knudsen, K. R.; Jorgensen, K. A. *J. Org. Chem.* **2001**, *66*, 1014. (c) Horneman, A. M.; Lundt, I. *J. Org. Chem.* **1998**, *63*, 1919. (d) Désiré, J.; Prandi, J. *Tetrahedron Lett.* **1997**, *38*, 6189. (e) Yoshikawa, M.; Yokokawa, Y.; Inoue, Y.; Yamaguchi, S.; Murakami, N.; Kitagawa, I. *Tetrahedron* **1994**, *50*, 9961. (f) Yoshikawa, M.; Murakami, N.; Inoue, Y.; Hatekeyama, S.; Kitagawa, I. *Chem. Pharm. Bull.* **1993**, *41*, 636. (g) Shoberu, K. A.; Roberts, S. M.; *J. Chem. Soc., Perkin Trans. 1* **1992**, *18*, 2419. (h) Parry, R. J.; Haridas, K.; DeJong, R.; Johnson, C. R. *Tetrahedron Lett.* **1990**, *31*, 7549. (i) Marschner, C.; Penn, G.; Griengl, H. *Tetrahedron Lett.* **1990**, *31*, 2873. (j) Marschner, C.; Baumgartner, J.; Griengl, H. *J. Org. Chem.* **1995**, *60*, 5224. (k) Tadano, K.-I.; Hakuba, K.; Kimura, H.; Ogawa, S. *J. Org. Chem.* **1989**, *54*, 276. (l) Yoshikawa, M.; Cha, B. C.; Okaichi, Y.; Kitagawa, I. *Chem. Pharm. Bull.* **1988**, *36*, 3718. (m) Tadano, K.-I.; Maeda, H.; Hoshino, M.; Iimura, Y.; Suami, T. *Chem. Lett.* **1986**, 1081. (n) Tadano, K.-I.; Kimura, H.; Hoshino, M.; Ogawa, S.; Suami, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3673. (o) Tadano, K.-I.; Maeda, H.; Hoshino, M.; Iimura, Y.; Suami, T. *J. Org. Chem.* **1987**, *52*, 1946. (p) Wilcox, C. S.; Guadino, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 3102.

(11) Seepersaud, M.; Al-Abed, Y. *Org. Lett.* **1999**, *1*, 1463.

(12) (a) Paulsen, H.; Heume, M.; Nürnberger, H. *Carbohydr. Res.* **1990**, *200*, 127. (b) Barresi, F.; Hindsgaul, O. *Can. J. Chem.* **1994**, *72*, 1447.

(13) Oshitari, T.; Shibasaki, M.; Yoshizawa, T.; Tomita, M.; Takao, K.-I.; Kobayashi, S. *Tetrahedron* **1997**, *53*, 10993.

(14) Lubineau, A.; Billault, I. *J. Org. Chem.* **1998**, *63*, 5668.

(15) An analogue of **13** in which the methoxymethyl ether is replaced by a *p*-methoxybenzyl ether has been synthesized from 2,3,5-tri-*O*-benzyl arabinofuranose **5**: Seepersaud, M.; Al-Abed, Y. *Tetrahedron Lett.* **2000**, *41*, 7801.

(16) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426.

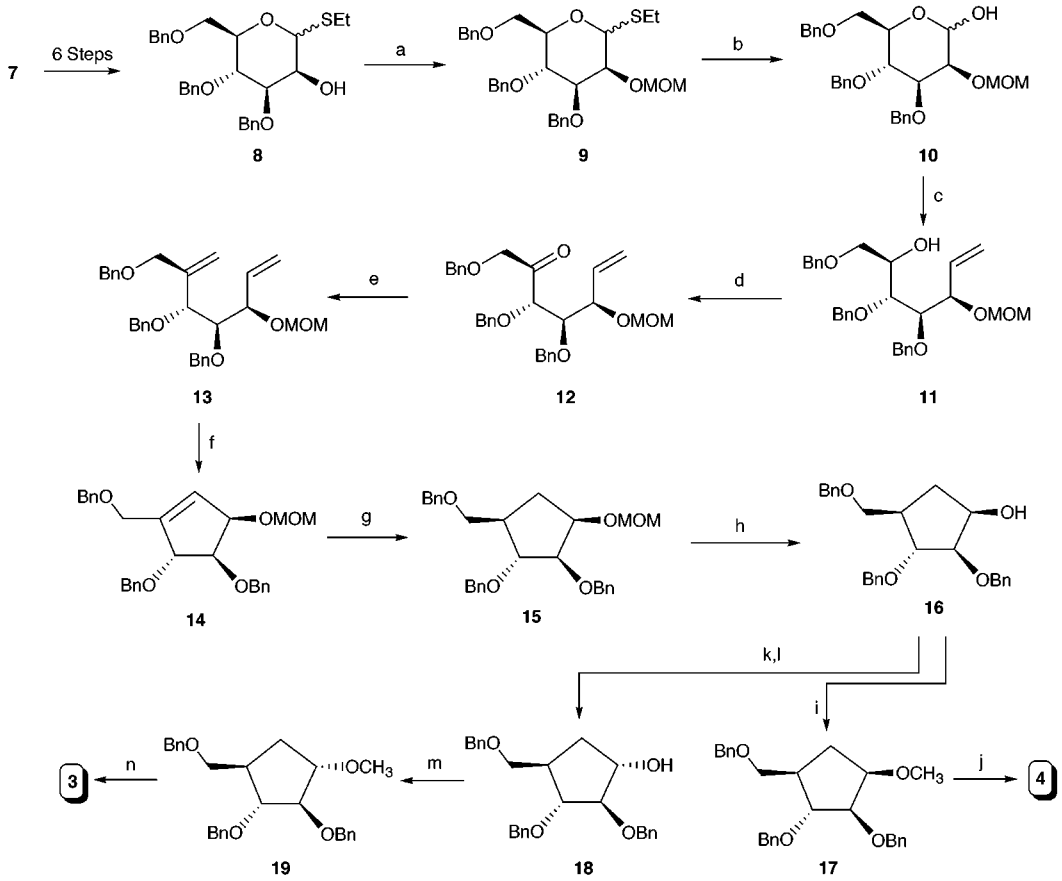
(17) (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2037. (b) Schamlz, H.-G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1833.

(18) Armstrong, S. K.*J. Chem. Soc., Perkin Trans. 1* **1998**, 371.

(19) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. This catalyst is now commercially available from Strem.

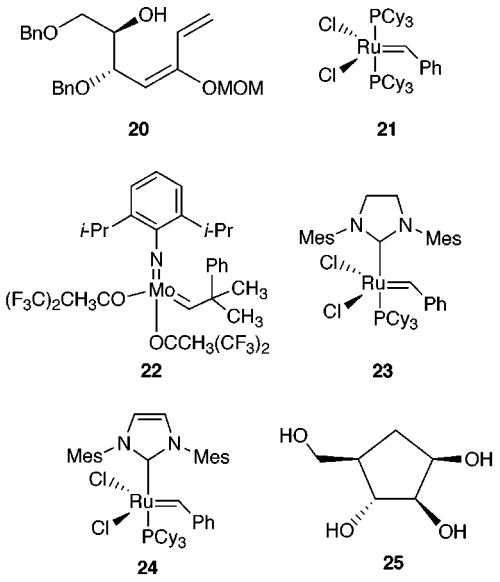
(20) (a) Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674. (b) Huang J., Schanz, H.-J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **1999**, *18*, 5375. (c) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204. (d) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247.

Scheme 1[a]



[a] (a) MOMCl, NaH, THF, rt, 88%; (b) NIS, AgOTf, CH_3CN, H_2O (5 equiv), rt, 90%; (c) Ph_3PCH_3Br, *n*-BuLi, THF, −78 °C → rt, 78%; (d) PCC, NaOAc, 4 Å molecular sieves, CH_2Cl_2, rt, 93%; (e) Ph_3PCH_3Br, *n*-BuLi, THF, −78 °C → rt, 77%; (f) **23** (20 mol %), toluene, 60 °C, 78%; (g) $(Ph_3P)_3RhCl$, (30 mol %), H_2, toluene, rt, 88%; (h) trace concentrated HCl, CH_3OH, rt, 95%; (i) CH_3I, NaH, THF, rt; (j) Pd/C, H_2, CH_3OH, AcOH, rt, 94% (from **16**); (k) DEAD, PPh_3, *p*-$O_2NC_6H_4CO_2H$, toluene, rt; (l) $NaOCH_3$, CH_3OH, rt, 84%, (from **16**); (m) CH_3I, NaH, THF, rt; (n) Pd/C, H_2, CH_3OH, AcOH, rt, 87% (from **18**).

Chart 2



Relative to the Schrock catalyst, both **23** and **24** are more convenient to use in that they are substantially more air stable, thus eliminating the need for a glovebox. When choosing between **23** and **24**, we prefer the former. Both can be conveniently prepared from **21**; however, we have found the ligand required for the synthesis of **24** more difficult to access than the one needed for the preparation of **23**.

Table 1. Conversion of 13 into 14 by Ring-Closing Metathesis

entry	catalyst/ mol %	conditions	yield, %[a]
1	**21**/5%	CH_2Cl_2, rt, 24 h	12
2	**21**/10%	toluene, 60 °C, 33 h	19
3	**21**/10%	xylenes, reflux, 48 h	0
4	**22**/20%	toluene, 60 °C, 2 h[b]	74
5	**23**/10%	toluene, 60 °C, 2 h	78
6	**24**/10%	toluene, 60 °C, 1.5 h	74

[a] Isolated yield. [b] Reaction carried out in a glovebox.

The second key step was the stereoselective hydrogenation of **14**. This reduction was successfully carried out in 88% yield upon reaction of **14** with Wilkinson's catalyst ($(Ph_3P)_3RhCl$) under an atmosphere of hydrogen. Determining the stereochemistry in the product, **15**, was achieved by global deprotection of the benzyl ethers (H_2, Pd/C) affording 4a-carba-β-D-arabinofuranose (**25**). Comparison of the ^1H and ^{13}C NMR spectra of **25** with that previously reported for the racemate[10j] showed them to be identical. None of the other stereoisomeric reduction product, which possesses the L-*xylo* stereochemistry, was isolated.

The final steps of the synthesis involved first the removal of the MOM ether to give, in 95% yield, alcohol **16**.[21] The β-glycoside analogue **4** was prepared in two steps from **16**, by methylation (yielding **17**) and then

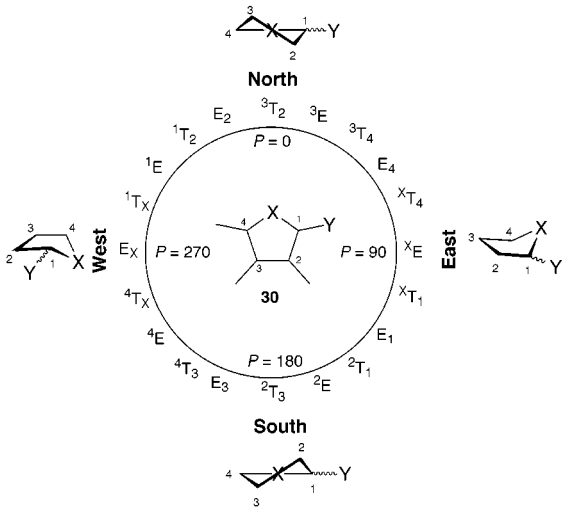


Figure 3. Pseudorotational wheel for a five-membered ring.

hydrogenation of the benzyl protecting groups (94%, two steps). Alternatively, reaction of **16** with *p*-nitrobenzoic acid, triphenylphosphine, and DEAD, followed by deacylation with sodium methoxide in methanol provided the C_1 inverted alcohol **18** in 84% yield (two steps). The synthesis of **3** from **18** was achieved in two steps and 87% yield, as described for the conversion of **16** into **4**.

Conformation. Five-membered rings are flexible entities that can adopt a wide range of envelope and twist conformations. These conformers can be conveniently visualized using the pseudorotational wheel (Figure 3).[22] The standard method used to assess the solution conformation of furanose rings (**30**, X = O; Y = OR, NR) assumes an equilibrium between two low-energy structures. One of these conformers lies in the northern hemisphere of the pseudorotational wheel (the N conformer) and the other in the southern hemisphere (the S conformer).

An increasing number of investigations have demonstrated that the conformational preferences of furanose rings play an important role in their biological function. For example, biasing (or locking) the conformation of the sugar ring of a nucleoside often significantly influences its recognition by various processing enzymes.[23] Similarly, nucleic acids composed of nucleosides in which the sugar rings are locked into a single conformation often bind to complementary sequences of DNA and RNA with increased affinity relative to the unlocked parent structures.[24]

For a given furanose ring, the two conformers that contribute to the equilibrium mixture in solution can be determined by NMR spectroscopy, through measurement of the ring $^3J_{H,H}$. Analysis of these experimental data, which are an average of the coupling constants arising from all solution conformers, can be done with the program PSEUROT.[25] This program assumes the two-state model described above and provides the conformers (and their populations) that best fit the NMR data. Although the PSEUROT method has been most widely used for the conformational analysis of furanose rings,[26] it can be applied to any five-membered ring. This approach has previously been used for assessing the conformation of pyrrolidines,[27] 4-thiofuranose derivatives,[28] and cyclopentanes (e.g., carbocyclic nucleosides).[29]

The identity and relative populations of the N and S conformers for a particular furanose ring are influenced not only by the steric demands of the substituents, but also by stereoelectronic effects. These effects have been most thoroughly explored in nucleosides and nucleotides;[30] however, they are also important in furanose *O*-glycosides. Of particular importance are the anomeric effect and favorable gauche interactions[31] between the ring oxygen and the hydroxyl groups at C_2 and C_3. In carbafuranoses such as **3** and **4**, there is no endocyclic oxygen, and therefore all of the stereoelectronic effects present in the furanose parent structures are absent. The $O \rightarrow CH_2$ replacement may therefore substantially alter the conformational equilibrium of **3** and **4** relative to **1** and **2**, and such changes will likely have important implications in the development of carbafuranose-based enzyme inhibitors. Consequently, we viewed it as important to probe the solution conformation of **3** and **4** in order to determine how closely the conformation of these species resembled that of **1** and **2**. It is somewhat surprising that, despite the synthesis of a number of carbacyclic nucleoside analogues, the conformation of the five-membered rings in these species has been relatively unexplored.[29] Furthermore, although conformational investigations of carbapyranose *O*-glycoside analogues have been described,[32] similar studies on carbafuranoses have not been reported.

Of additional interest was the rotameric equilibrium about the C_4-C_5 and C_1-O_1 bonds (see Chart 1 for atom numbering scheme). In furanose rings, rotamer populations about these bonds are also influenced by the ring oxygen. For the C_4-C_5 bond,[33] a gauche interaction

(21) Attempted removal of the MOM ether prior to reduction of the double bond under a variety of conditions led to very low yields of the desired allylic alcohol and the formation of a number of unidentified byproducts.

(22) Altona, C.; Sundaralingam, M. *J. Am. Chem. Soc.* **1972**, *94*, 8205.

(23) (a) Ford, H., Jr; Dai, F.; Mu, L.; Siddiqui, M. A.; Nicklaus, M. C.; Anderson, L. Marquez, V. E.; Barchi, J. J., Jr. *Biochemistry* **2000**, *39*, 2581. (b) Wang, P.; Brank, A. S.; Banavali, N. K.; Nicklaus, M. C.; Marquez, V. E.; Christman, J. K.; MacKerell, A. D., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 12422. (c) Mu, L.; Sarafianos, S. G.; Nicklaus, M. C.; Russ, P.; Siddiqui, M. A.; Ford, H., Jr.; Mitsuya, H.; Le, R.; Kodama, E.; Meier, C.; Knispel, T.; Anderson, L.; Barchi, J. J., Jr.; Marquez, V. E. *Biochemistry* **2000**, *39*, 11205.

(24) (a) Meldgaard, M.; Wengel, J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3539. (b) Herdewijn, P. *Liebigs Ann.* **1996**, 1337.

(25) (a) PSEUROT 6.2, Gorlaeus Laboratories, University of Leiden. (b) de Leeuw, F. A. A. M.; Altona, C. *J. Comput. Chem.* **1983**, *4*, 428. (c) Altona, C. *Recl. Trav. Chem. Pays-Bas* **1982**, *101*, 413.

(26) For some examples, see: (a) Hoffman, R. A.; Van Wijk, J.; Leeflang, B. R.; Kamerling, J. P.; Altona, C.; Vliegenthart, J. F. G. *J. Am. Chem. Soc.* **1992**, *114*, 3710. (b) Rickel, L. J.; Altona, C. *J. Biomol. Struct. Dyn.* **1987**, *4*, 621. (c) van Wijk, J.; Huckriede, B. D.; Ippel, J. H.; Altona, C. *Methods Enzymol.* **1992**, *211*, 286.

(27) (a) de Leeuw, F. A. A. M.; Altona, C.; Kessler, H.; Bermal, W.; Friedrich, A.; Krack, G.; Hull. W. *J. Am. Chem. Soc.* **1983**, *105*, 2237. (b) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; de Leeuw, H. P. M.; Altona, C. *Biopolymers* **1981**, *20*, 1211.

(28) Crnugelj, M.; Dukhan, D.; Barascut, J.-L.; Imbach, J.-L.; Plavec, J. *J. Chem. Soc., Perkin Trans. 2* **2000**, 255.

(29) Thibaudeau, C.; Kumar, A.; Bekiroglu, S.; Matsuda, A.; Marquez, V. E. Chattopadhyaya, J. *J. Org. Chem.* **1998**, *63*, 5447.

(30) (a) Thibaudeau, C.; Chattopadhyaya, J. *Stereoelectronic Effects in Nucleosides and Nucleotides and their Structural Implications*; Uppsala University Press: Uppsala, Sweden, 1999. (b) Thibaudeau, C.; Chattopadhyaya, J. *Nucleosides Nucleotides* **1997**, *16*, 523. (c) Plavec, J.; Thibaudeau, C.; Chattopadhyaya, J. *Pure Appl. Chem.* **1996**, *68*, 2137. (d) Thibaudeau, C.; Plavec, J.; Chattopadhyaya, J. *J. Am. Chem. Soc.* **1994**, *116*, 8033. (e) Thibaudeau, C.; Plavec, J.; Garg, N.; Papchikhin, A.; Chattopadhyaya, J. *J. Am. Chem. Soc.* **1994**, *116*, 4038. (f) Plavec, J.; Thibaudeau, C.; Chattopadhyaya, J. *J. Am. Chem. Soc.* **1994**, *116*, 6558. (g) Plavec, J.; Tong, W.; Chattopadhyaya, J. *J. Am. Chem. Soc.* **1993**, *115*, 9734.

(31) Wolfe, S. *Acc. Chem. Res.* **1972**, *5*, 102.

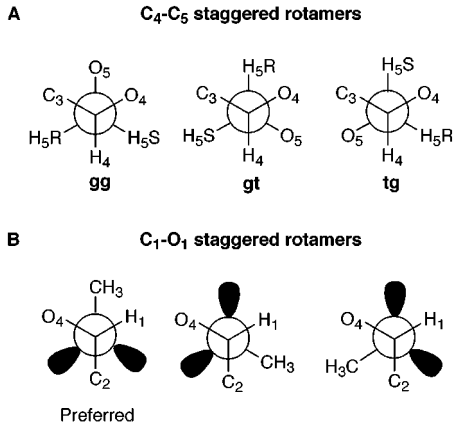


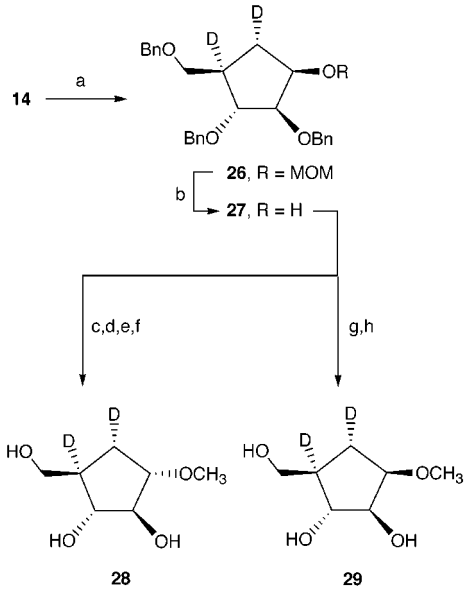
Figure 4. Staggered rotamers about the C_4-C_5 and C_1-O_1 bonds.

between OH_5 and the endocyclic oxygen stabilizes the gt and gg rotamers relative to the tg counterpart where such a stabilizing interaction is absent (See Figure 4A for rotamer definitions). In the case of the C_1-O_1 bond, the exo-anomeric effect and steric effects dictate that the preferred conformation about this bond is the one in which the methyl group is antiperiplanar to C_2 (Figure 4B).[34] However, the preferred orientation about either of these bonds in **3** and **4** is unknown. Discussed below are investigations directed toward determining the ring conformers adopted by **3** and **4** in solution, as well as the preferred orientation about the C_4-C_5 and C_1-O_1 bonds.

Ring Conformation. Before applying the PSEUROT method for the analysis of **3** and **4**, it was important to determine the validity of the two-state N/S model for these ring systems. Although this had been previously done for carbacyclic nucleosides,[29] we verified this for **3** and **4** through a series of density functional theory calculations. Using a protocol previously used by us[35,36] and others,[37] all 10 idealized envelope conformers for each ring system were optimized. These calculations demonstrated (see Supporting Information for data) that for both **3** and **4**, the two-state N/S model is valid. A full account of these calculations will be reported separately.[38]

The $^3J_{H,H}$ used in the PSEUROT calculations were measured from ^{1}H NMR spectra obtained from samples dissolved in D_2O. For many of the resonances in the spectrum of **3** and **4**, there was sufficient spectral resolution that all coupling constants could be conveniently and unambiguously extracted from the simple 1D

Scheme 2[a]



[a] (a) $(Ph_3P)_3RhCl$, (30 mol %), D_2, toluene, rt, 82%; (b) trace concentrated HCl, CH_3OH, rt, 95%; (c) DEAD, PPh_3, *p*-$O_2NC_6H_4CO_2H$, toluene, rt; (d) $NaOCH_3$, CH_3OH, rt; (e) CH_3I, NaH, THF, rt; (f) Pd/C, H_2, CH_3OH, AcOH, rt, 64% (from **27**); (g) CH_3I, NaH, THF, rt; (h) Pd/C, H_2, CH_3OH, AcOH, rt, 94% (from **27**).

^{1}H NMR spectra. However, substitution of the ring oxygen for the methylene group significantly increases the complexity of the signals arising from H_1 and H_4, which in turn complicates measurement of the $^3J_{H,H}$ involving these hydrogens. Two approaches were used in order to confirm these coupling constants. First, the Bruker program NMRSim[39] was used to simulate the ^{1}H NMR spectrum of both **3** and **4**. Second, we synthesized analogues of these compounds that were deuterated at the C_4 and C_{4a} carbons, which in turn simplified the coupling patterns of H_1. These compounds (**28** and **29**) were readily prepared as outlined in Scheme 2.[40]

The $^3J_{H,H}$ and $^2J_{H,H}$ for **3**, **4**, **28**, and **29** measured from spectra recorded at 298 K are presented in Table 2, as are the coupling constants used in the simulation of the ^{1}H NMR spectrum of **3** and **4**. PSEUROT 6.2 analysis of these data gave the results shown in Table 3, which are compared to those previously reported for **1** and **2**.[36,41]

The ability of the PSEUROT program to effectively treat these systems can be assessed by consideration of the RMS errors of these calculations. When the $^3J_{H,H}$ measured from the spectra of **3** and **4** are used, these errors are reasonably low, 0.45 and 0.38 Hz, respectively. Nevertheless, these errors are higher than those normally seen in analysis of coupling constants from furanose rings.[36,41] In a previous conformational analysis of carbacyclic nucleosides by Chattopadhyaya and co-workers, relatively high RMS errors in PSEUROT calculations were ascribed to the poor parametrization of the program

(32) (a) Carpintero, M.; Fernández-Mayoralas, A.; Jiménez-Barbero, J. *Eur. J. Org. Chem.* **2001**, 681. (b) Montero, E.; García-Herrero, A.; Asensio, J. L.; Hirai, K.; Ogawa, S.; Santoyo-González, Cañada, F. J.; Jiménez-Barbero, J. *Eur. J. Org. Chem.* **2000**, 1945. (c) Duus, J. Ø.; Bock, K.; Ogawa, S. *Carbohydr. Res.* **1994**, *252*, 1. (d) Bock, K.; Guzmán, J. F. B.; Duus, J. Ø.; Ogawa, S. Yokoi, S. *Carbohydr. Res.* **1991**, *209*, 51. (e) Bock, K.; Ogawa, S.; Orihara, M. *Carbohydr. Res.* **1989**, *191*, 357. (f) Bock, K.; Guzmán, J. F. B.; Ogawa, S. *Carbohydr. Res.* **1988**, *174*, 354.

(33) (a) Rockwell, G. D.; Grindley, T. B. *J. Am. Chem. Soc.* **1998**, *120*, 10953. (b) Bock, K.; Duus, J. Ø. *J. Carbohydr. Chem.* **1994**, *13*, 513.

(34) Lemieux, R. U.; Koto, S. *Tetrahedron* **1974**, *30*, 1933.

(35) Gordon, M. T.; Lowary, T. L.; Hadad, C. M. *J. Am. Chem. Soc.* **1999**, *121*, 9682.

(36) Gordon, M. T.; Lowary, T. L.; Hadad, C. M. *J. Org. Chem.* **2000**, *65*, 4954.

(37) (a) Cloran, F.; Carmichael, I.; Serianni, A. S. *J. Am. Chem. Soc.* **2001**, *123*, 4781. (b) Church, T. J.; Carmichael, I.; Serianni, A. S. *J. Am. Chem. Soc.* **1997**, *119*, 8946.

(38) Callam, C. S.; Lowary, T. L.; Hadad, C. M. Manuscript in preparation.

(39) NMRSim Version 2.5, Bruker Analytik GmbH, Silberstreifen, D-76287 Rheinstetten, Germany.

(40) We tried, unsuccessfully, to synthesize analogues that were monodeuterated at C_{4a} via hydroboration of **14** and subsequent treatment with CD_3CO_2D. Although a number of borane reagents were explored, the regioselectivity of the hydroboration was poor, and separation of the C_{4a} [^{2}H] and C_4 [^{2}H]-labeled isomers was, as expected, impossible.

(41) D'Souza, F. W.; Ayers, J. D.; McCarren, P. R.; Lowary, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 1251.

Table 2. $^3J_{H,H}$ and $^2J_{H,H}$ in 3, 4, 28, and 29[a,b]

$^3J_{H,H}$	**3**	**28**	**3**[c]	**4**	**29**	**4**[c]
$^3J_{1,2}$	6.2	6.2	6.20	5.1	5.1	5.10
$^3J_{2,3}$	7.5	7.4	7.48	6.6	6.4	6.51
$^3J_{3,4}$	8.4	NA	8.35	6.8	NA	6.70
$^3J_{4,4a}$[d]	8.4	NA	8.33	7.5	NA	7.52
$^3J_{4,4a'}$[d]	9.8	NA	9.72	9.3	NA	9.30
$^3J_{1,4a}$[d]	8.4	NA	8.38	4.9	NA	4.85
$^3J_{1,4a'}$[d]	5.4	5.3	5.36	6.2	6.0	6.11
$^3J_{4,5R}$	4.7	NA	4.71	5.8	NA	5.81
$^3J_{4,5S}$	6.8	NA	6.84	7.5	NA	7.46
$^2J_{4a,4a'}$	14.1	NA	14.15	13.9	NA	13.93
$^2J_{5R,5S}$	11.1	11.8	11.11	10.9	12.1	10.88

[a] See Chart 1 for atom numbering scheme. [b] Coupling constants are in hertz. [c] Values used for simulation of ^{1}H NMR spectra using NMRSim. [d] The 4a and 4a′ hydrogens are trans and cis, respectively, to the hydroxymethyl group at C_4.

Table 3. Ring Conformers of 1−4, 28, and 29[a,b]

compound	**3**	**3**[c]	**28**	**1**[e]	**4**	**4**[c]	**29**	**2**[f]
P_N (deg)[d]	15	21	16	72	2	10	7	339
N conformer	^{3}E	^{3}E	^{3}E	^{O}T$_4$	^{3}T$_2$	^{3}T$_2$	^{3}T$_2$	E$_2$
X_N (%)	86	83	82	56	75	77	73	99
P_S (deg)[d]	161	166	165	183	158	160	159	162
S conformer	^{2}E	^{2}E	^{2}E	^{2}T$_3$	^{2}E	^{2}E	^{2}E	^{2}E
X_S (%)	14	17	18	41	25	23	27	1
RMS (Hz)	0.45	0.16	0.20	0.01	0.38	0.17	0.24	0.00

[a] Calculated using a constant $\tau_m = 40°$. [b] See Figure 3 for assignment of conformers. [c] Coupling constants from simulated spectra were used. [d] P = Altona-Sundaralingam pseudorotational phase angle as defined in ref 22. [e] Taken from ref 41. [f] Taken from ref 36.

for cyclopentane systems.[29] In that study, reparamerization of the Karplus equation used by the program provided results with lower RMS errors. However, the outcome of the calculations (e.g., conformer identities and populations) were unchanged relative to the default equation. We have not, therefore, reparamatarized this equation for **3** and **4**.

Another potential source of error is the inability to accurately measure all ring $^3J_{H,H}$ in **3** and **4**. Given the number of hydrogens coupled to H_1 and H_4, accurate measurement of these coupling constants is particularly challenging and may be the cause of some of the error. This postulate has been validated in that when $^3J_{H,H}$ from the simulated spectra or the deuterated compounds (**28**/**29**) are used in the PSEUROT calculations, the RMS errors are lower and more in line with those obtained with furanose rings. However, as is clear from the data presented in Table 3, neither the identity of the equilibrium conformers nor their populations are dependent upon the data set used. The N:S ratio for **3**/**28** ranges from 82:18 ^{3}E:^{2}E to 86:14 ^{3}E:^{2}E, while for **4**/**29** a 73:27 ^{3}T$_2$:^{2}E to 75:25 ^{3}T$_2$:^{2}E ratio is predicted.

For both **3**/**28** and **4**/**29**, the conformational equilibrium is biased to the northern conformer. In the major conformer of **3**/**28** (^{3}E), the substituents at C_2, C_3, and C_4 are pseudoequatorially oriented, and there is a gauche relationship between OH_2 and OH_3. This conformer would therefore be expected to be favored over the southern conformer (^{2}E) in which OH_2 and OH_3 are pseudoaxial and hence trans to each other. Furthermore, the methoxy group, while not pseudoequatorial in the ^{3}E conformer, is "less" pseudoaxial than in the southern structure. A similar situation is observed for **4**/**29**. In the northern conformer (^{2}T$_3$), the groups at C_2, C_3, and C_4 are pseudoequatorial, there is a gauche relationship between OH_2 and OH_3, and the methoxy group adopts an orientation intermediate between pseudoaxial and pseudoequatorial. In common with **3**/**28**, the southern conformer of **4**/**29** (^{2}E) is destabilized by the pseudoaxial orientation of the hydroxyl groups at C_2 and C_3. However, in contrast to **3**/**28**, the methoxy group of the ^{2}E conformer in **4**/**29** is oriented in a pseudoequatorial direction and is also gauche to OH_2. This last conformational feature may explain the slightly larger percentage of the southern conformer of **4**/**29** relative to **3**/**28** (27% vs 18%).

To determine the influence of temperature on the conformational equilibrium, we have carried out a series of variable temperature NMR experiments using **28** and **29**. The coupling constants measured from these spectra are given in the Supporting Information; the results of the PSEUROT analysis of these data are provided in Table 4. Over the temperature range investigated (288 K to 328 K), only minor changes in the conformational equilibrium are observed. The same two conformers are present; however, the population of the northern structures is slightly increased (∼5%) at higher temperature.

A comparison of the conformational equilibrium of these carbasugars with that previously reported[36,41] for glycosides **1** and **2** is shown in Table 3. For the α-isomer there is a pronounced shift to the north in the carbasugar. The conformational ensemble of **1** is a 55:45 mixture of ^{O}T$_4$(N) and ^{2}T$_3$(S) conformers;[41] for **3**/**28** an 82:18 ratio of ^{3}E(N) and ^{2}E(S) conformers is present. In the carbasugar, therefore, not only are the identities of the conformers shifted to the north, but also the northern conformer predominates at equilibrium. In the glycoside, both the ^{O}T$_4$ and ^{2}T$_3$ conformers are stabilized by the anomeric effect and, in the case of S conformer, by an attractive gauche interaction between the ring oxygen and the OH_2 and OH_3 groups. In the absence of these stereoelectronic effects (as in **3**/**28**), steric effects as well as gauche interactions between exocyclic hydroxyl groups predominate, and hence northern conformers are favored. From these studies, it is clear that the conformational preferences of **3**/**28** do not closely resemble that of **1**.

On the other hand, for the β-isomer, **4**, the conformer distributions in the carbasugar agree better with the glycoside. Glycoside **2** is a relatively rigid furanose ring. In aqueous solution, a 99:1 mixture of E$_2$(N) and ^{2}E(S) conformers is present at equilibrium.[36] In the E$_2$ conformer of **2**, not only are the substituents at C_2, C_3, and C_4 pseudoequatorial, but the methoxy group is pseudoaxial and hence stabilized by the anomeric effect. In terms of conformer identity, there is good agreement between **2** and **4**/**29**. The carbasugar adopts the same *S* conformer as the glycoside (^{2}E) and the northern conformer adopted by **4**/**29** (^{3}T$_2$) is immediately adjacent on the pseudorotational wheel to that observed for **2** (E$_2$). The equilibrium in both ring systems is also heavily favored toward the north. Therefore, the conformational equilibrium of **4**/**29** approximates **2** fairly closely.

C_4−C_5 Bond Rotamer Populations. We have determined the populations of rotamers about the C_4−C_5 bond in **3** and **4** by analysis of $^3J_{4,5R}$ and $^3J_{4,5S}$ measured from the ^{1}H NMR spectrum of these compounds. These coupling constant data were analyzed using eqs 1−3.

$$2.1X_{gg} + 14.1X_{gt} + 2.2X_{tg} = {}^3J_{4,5R} \quad (1)$$

$$3.4X_{gg} + 3.0X_{gt} + 15.5X_{tg} = {}^3J_{4,5S} \quad (2)$$

$$X_{gg} + X_{gt} + X_{tg} = 1 \quad (3)$$

Table 4. Ring Conformers of 28 and 29 at Various Temperatures[a,b]

compound	**28**					**29**				
temperature	288 K	298 K	308 K	318 K	328 K	288 K	298 K	308 K	318 K	328 K
P_N (deg)[c]	16	16	17	15	15	7	7	5	5	5
N conformer	^{3}E	^{3}E	^{3}E	^{3}E	^{3}E	$^3T_2$	$^3T_2$	$^3T_2$	$^3T_2$	$^3T_2$
X_N (%)	82	82	84	88	88	73	73	74	75	78
P_S (deg)[c]	165	165	166	168	168	159	159	159	159	159
S conformer	^{2}E	^{2}E	^{2}E	^{2}E	^{2}E	^{2}E	^{2}E	^{2}E	^{2}E	^{2}E
X_S (%)	18	18	16	12	12	27	27	26	25	22
RMS (Hz)	0.20	0.20	0.23	0.24	0.24	0.24	0.24	0.23	0.25	0.25

[a] Calculated using a constant $\tau_m = 40°$. [b] See Figure 3 for assignment of conformers. [c] P = Altona-Sundaralingam pseudorotational phase angle as defined in ref 22.

Table 5. Comparison of C_4-C_5 Rotamer Populations in 1–4[a]

compound	**3**	**3**[c]	**1**[d]	**4**	**4**[c]	**2**[e]
X_{gg}(%)[b]	49	49	48	34	34	34
X_{gt} (%)	39	39	38	45	45	55
X_{tg} (%)	12	12	14	21	21	11

[a] See Experimental Section for protocol used for determining percentages. [b] See Figure 4A for rotamer definitions. [c] Coupling constants from simulated spectra were used. [d] Taken from ref 41. [e] Taken from ref 36.

In assigning the chemical shifts arising from the H_{5R} and H_{5S} hydrogens, the assumption was made that H_{5S} resonates downfield relative to H_{5R} as is the case in glycosides **1** and **2**.[42] This approach has been used previously in determining the populations of hydroxymethyl group rotamers in carbapyranose derivatives.[32e,f] The method used for the determination of the coefficients in eqs 1 and 2 is provided in the Experimental Section. The results of these analyses are presented in Table 5 and compared with the rotamer populations found previously for **1** and **2**.[36,41]

In the case of **3**, the rotamer populations about the C_4-C_5 bond are essentially unchanged relative to its glycoside parent structure, **1**. Similar results have been observed previously with carbapyranoses.[32e,f,33b] In **1** and **3**, the favoring of the gg rotamer over the gt and tg forms can be rationalized on the basis of $\sigma_{(C4-H4)} \rightarrow \sigma^*_{(C5-O5)}$ hyperconjugation,[43] which is possible in both the glycoside and the carbasugar. For **1**, the predominance of gt over tg can be ascribed to a gauche effect involving O_4 and O_5. The same trend is seen in **3**, however, it is best rationalized by considering that in the tg rotamer of the major ring conformer (^{3}E), a "1,3-diaxial" interaction between O_5 and O_3 is present.

A comparison of the C_4-C_5 rotamer populations in **2** and **4** reveals that the population of the gg rotamer is unchanged. However, in the carbasugar the amount of the tg rotamer increases at the expense of gt. These trends can be explained as above for **3**, i.e., $\sigma_{(C4-H4)} \rightarrow \sigma^*_{(C5-O5)}$ hyperconjugation in the gg rotamer of both **2** and **4**, and a destabilization of tg relative to gt via "1,3-diaxial" interactions between O_5 and O_3. For **3**, there is an approximately 3:1 gt:tg ratio, while for **4**, this ratio is 2:1. The increase in the tg rotamer in **4** relative to **3**, may be a consequence of the fact that the southern ring conformer (^{2}E) is more populated at equilibrium. For this ring conformer, the tg rotamer no longer places O_5 in a "1,3-diaxial" relationship to O_3.

C_1-O_1 Bond Rotamer Populations. The population of rotamers about the C_1-O_1 bond in **3** and **4** were initially explored through ^{1}H NMR spectroscopy via the measurement of NOE's between the methyl group and the hydrogens on C_2 and C_{4a}. From these experiments, it was demonstrated that for both **3** and **4**, the NOE's were significantly larger to the C_{4a} hydrogens than to the C_2 hydrogen (Figure 5). These data suggest that the preferred orientation about the C_1-O_1 bond is one in which the methyl group is anti to C_2, which is identical to the parent glycoside. To simplify the discussion below, we have designated each staggered rotamer about the C_1-O_1 bond as gg, gt, or tg as defined in Figure 6. Within this reference system, the major rotamer predicted by the NOE experiments is tg.

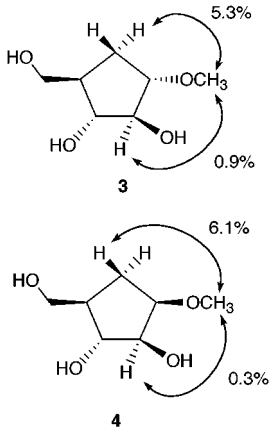


Figure 5. NOE's in **3** and **4**. Only the NOE's involving the methyl group are shown.

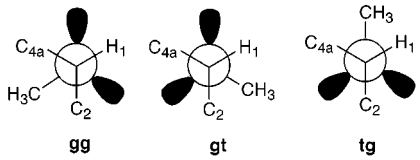
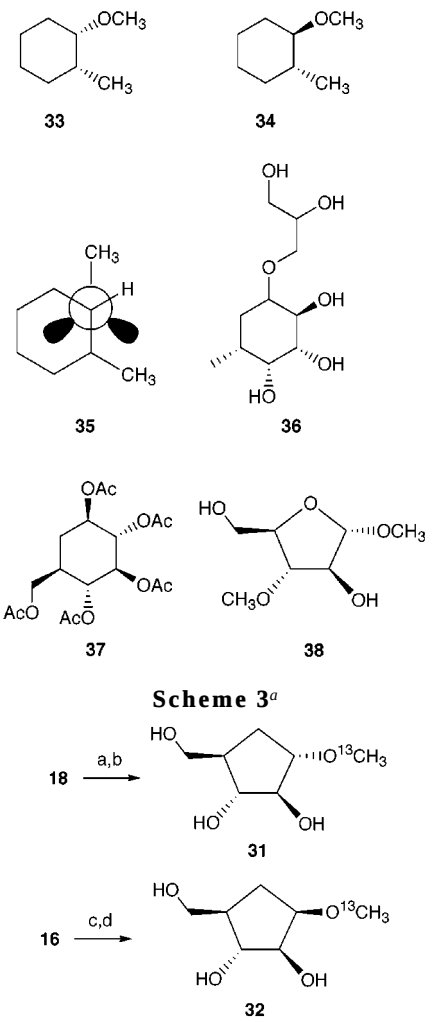


Figure 6. Definition of gg, gt, and tg rotamers about the C_1-O_1 bond in **3** and **4**.

These results are in agreement with previous investigations on substituted methoxycyclohexanes (e.g., **33**, **34**, Chart 3).[44] Through the combined use of NMR spectroscopy and molecular mechanics calculations, it was demonstrated that for both **33** and **34**, the preferred orientation about the C–O bond places the methyl group gauche to the unsubstituted flanking position (**35**). These results are also in good agreement with recent investigations on carbafucose derivative **36** (Chart 3).[32a] By using molecular mechanics calculations and NOE data, it was

(42) Serianni, A. S.; Barker, R. *Can J. Chem.* **1979**, *57*, 3160.
(43) Juaristi, E.; Antúnez, S. *Tetrahedron* **1992**, *48*, 5941.
(44) Anderson, J. E.; Ijeh, A. I. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1965.

Chart 3



Scheme 3[a]

[a] (a) $^{13}CH_3I$, NaH, THF, rt; (b) Pd/C, H_2, CH_3OH, AcOH, rt, 90% (from **18**); (c) $^{13}CH_3I$, NaH, THF, rt; (d) Pd/C, H_2, CH_3OH, AcOH, rt, 94% (from **16**).

Table 6. $^3J_{C,O,C,H}$ and $^3J_{C,O,C,C}$ in 31 and 32[a,b]

	$^3J_{CH3,H1}$	$^3J_{CH3,C2}$	$^3J_{CH3,C4a}$	$^2J_{CH3,C1}$
31	0.7	1.5	1.4	2.1
32	0.6	1.6	1.4	1.9

[a] See Chart 1 for atom numbers. [b] Coupling constants are in hertz.

determined that the favored rotamer about this bond is tg. However, there is also approximately 20% of the gt conformer present. Also consistent with our NOE experiments is the crystal structure of the pentaacetate derivative of 5a-carba-β-D-glucopyranose (**37**) in which the C_1-O_1 bond is oriented tg.[45]

In an effort to probe further the conformation about this bond, we synthesized analogues of **3** and **4** containing a ^{13}C-label in the methyl group (Scheme 3). With these substrates (**31** and **32**) in hand, we were able to easily measure the $^3J_{C,O,C,H}$ and $^3J_{C,O,C,C}$ involving the "aglycone". The data are presented in Table 6.

For both **3** and **4**, the magnitude of $^3J_{CH3,H1}$ is very small, and from these data we can rule out the possibility that the gg rotamer (Figure 6) is significantly populated. Using the Karplus equation for C−O−C−H fragments proposed by Serianni and co-workers[46] ($^3J_{C,O,C,H} = 7.49 \cos^2\theta - 0.96 \cos\theta + 0.15$), it can be predicted that $^3J_{CH3,H1}$ for the gg rotamer should be approximately 8.6 Hz. If this rotamer was a significant contributor to the equilibrium population, the magnitude of this coupling constant should be substantially larger than observed (0.6−0.7 Hz).

We turned next to an analysis of the $^{13}C-^{13}C$ coupling constant data. We initially had hoped that these data would allow us to quantify, at least to some degree, the relative populations of the three rotamers shown in Figure 6. We had previously been successful in doing a similar analysis for the 3-*O*-methyl group in **38** (Chart 3).[47] To that end, the $^3J_{C,O,C,C}$ coupling constants measured from **3** and **4** (Table 6) were analyzed using eqs 4−6.

$$0.4X_{gg} + 4.1X_{gt} + 1.1X_{tg} = {}^3J_{CH3,4a} \quad (4)$$

$$3.0X_{gg} + 0.6X_{gt} + 4.3X_{tg} = {}^3J_{CH3,2} \quad (5)$$

$$X_{gg} + X_{gt} + X_{tg} = 1 \quad (6)$$

Determination of the coefficients for eqs 4 and 5 is provided in the Experimental Section. Unfortunately, no physically reasonable solution to these equations was found; a 112%:36%:−48% gg:gt:tg ratio was calculated. From the $^3J_{C,O,C,H}$ data presented above, we proposed that the population of the gg rotamer is negligible. We therefore considered a two-state model involving only the tg and gt isomers. However, using the limiting $^3J_{C,C}$ magnitudes used in eqs 4 and 5, a two-rotamer model provided no better results.

One interpretation of these results is that a model in which only two or three staggered rotamers about this bond are considered cannot be applied to this system. In this regard we note that previous conformational investigations[48] on furanose *C*-glycosides, which also lack any anomeric effects, have suggested that there is increased flexibility about this bond. Another possible source of error in these analyses is that the angles used for calculating the limiting $^3J_{C,C}$ values which serve as the coefficients in eqs 4 and 5 are incorrect. The equation (eq 8, see Experimental Section) used to determine these coefficients was developed for C−O−C−C fragments involving the anomeric center of glycosides and hence may not be applicable to systems such as **3** and **4**. It is unfortunate that these coupling constant data cannot be reconciled with the NOE experiments, and we are currently further investigating this discrepancy.

Conclusions

In conclusion, we have developed a novel route for the preparation of carbasugar analogues of methyl α-D-arabinofuranoside and methyl β-D-arabinofuranoside (**3** and **4**). Starting from D-mannose, the targets are obtained via a route in which the key steps are (1) a ring-closing metathesis and (2) a subsequent stereoselective hydrogenation. This route can also be applied to the prepara-

(45) Watkins, S. F.; Abboud, K. A.; Nghiem, N. P.; Voll, R. J.; Younathan, E. S. *Carbohydr. Res.* **1986**, *158*, 7.

(46) Cloran, F.; Carmichael, I.; Serianni, A. S. *J. Am. Chem. Soc.* **1999**, *121*, 9843.

(47) Houseknecht, J. B.; McCarren, P. R.; Lowary, T. L.; Hadad, C. M. *J. Am. Chem. Soc.* **2001**, *123*, 8841.

(48) O'Leary, D. J. Kishi, Y. *J. Org. Chem.* **1994**, *59*, 6629.

tion of other carbafuranoses through substitution of D-mannose with other pyranose sugars.

We have also probed the conformation of **3** and **4** by NMR spectroscopy. These studies have demonstrated that for both compounds, the conformational equilibria of ring conformers are biased to northern structures. However, the similarity of the distribution to that observed for the parent glycosides differs for each ring system. For the α-isomers, there are significant differences in ring conformation between glycoside **1** and carbasugar **3**. In contrast, the ring conformation of **4** is similar to its furanoside counterpart, **2**.

In regard to rotamer populations about the C_4-C_5 bond, no significant differences were seen between glycoside **1** and carbasugar **3**. Comparison of these populations in **2** and **4** showed larger, but still small, differences. NOE experiments suggest that the preferred orientation about the C_1-O_1 bond in **3** and **4** is similar to that in the glycosides, i.e., the methyl group is anti to C_2. However, we were unable to confirm this preference through measurement of $^3J_{C,C}$ between the methyl group and C_{4a} and C_2.

We are currently exploring the preparation of "oligosaccharides" of these carbafuranoses with the ultimate goal of identifying inhibitors of the arabinosyltransferases that assemble cell wall polysaccharides in mycobacteria. Conformational investigations of these oligomers are also in progress.

Experimental Section

General. Solvents were distilled from the appropriate drying agents before use. Unless stated otherwise, all reactions were carried out at room temperature under a positive pressure of argon and were monitored by TLC on silica gel 60 F_{254} (0.25 mm, E. Merck). Spots were detected under UV light or by charring with 10% H_2SO_4 in ethanol. Solvents were evaporated under reduced pressure and below 40 °C (bath). Organic solutions of crude products were dried over anhydrous Na_2SO_4. Column chromatography was performed on silica gel 60 (40−60 μM). The ratio between silica gel and crude product ranged from 100 to 50:1 (w/w). Optical rotations were measured at 21 ± 2 °C. Melting points are uncorrected. For the characterization of reaction products, ^{1}H NMR spectra were recorded at 500.12 MHz, and chemical shifts are referenced to either TMS (0.0, $CDCl_3$) or external dioxane (3.75, D_2O). ^{13}C NMR spectra were recorded at 125.75 MHz, and ^{13}C chemical shifts are referenced to $CDCl_3$ (77.00, $CDCl_3$) or external dioxane (68.11, D_2O). Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA. Electrospray mass spectra were recorded on samples suspended in mixtures of THF with CH_3OH and added trifluoroacetic acid or NaCl.

Ethyl 3,4,6-Tri-*O*-benzyl-2-*O*-methoxymethyl-1-thio-α/*β*-D-mannopyranoside (9). To a solution of **8**[12] (4.40 g, 8.89 mmol) in DMF (10 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 350 mg, 12.5 mmol). The solution was allowed to stir for 15 min followed by the dropwise addition of chloromethyl methyl ether (840 μL, 11.11 mmol). The reaction mixture was warmed to room temperature and stirred for 1 h, and then CH_3OH /water (1:1, 5 mL) was added. The reaction mixture was extracted with Et_2O, and the organic layer was washed with water and brine and then dried and evaporated. Purification by chromatography (hexanes/EtOAc, 8:1) yielded **9** (4.21 g, 88%) as a colorless oil: R_f 0.44 (hexanes/EtOAc, 6:1); ^{1}H NMR (500 MHz, $CDCl_3$, δ) 7.34−7.18 (m, 15 H), 5.39 (d, 0.9 H, J = 1.1 Hz), 5.00 (d, 0.1 H, J = 0.1 Hz), 4.90−4.50 (m, 8 H), 4.06 (dd, 1 H, J = 0.3, 3.2 Hz), 3.95 (s, 1 H), 3.94−3.68 (m, 4 H), 3.4 (s, 0.3 H), 3.39 (s, 3 H), 2.67−256 (m, 2.2 H), 1.32−1.26 (m, 3.3 H); ^{13}C NMR (125.7 MHz, $CDCl_3$, δ) 138.5, 138.4, 138.3, 138.2, 138.0, 137.8, 128.4, 128.3, 128.2 (2), 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 97.4, 96.3, 84.2, 83.9, 83.1, 80.2, 79.9, 75.1, 75.0, 74.9, 74.7, 73.6, 73.4, 73.2, 72.1, 71.9, 71.8, 69.9, 69.1, 56.5, 55.7, 25.7, 25.3, 15.2, 14.9. Anal. Calcd for $C_{31}H_{38}O_6S$: C, 69.12; H 7.11. Found: C, 69.01; H, 7.13.

3,4,6-Tri-*O*-benzyl-2-*O*-methoxymethyl-α/*β*-D-mannopyranose (10). To a solution of **9** (4.60 g, 9.30 mmol) in CH_3CN/H_2O (5:1, 15 mL) at 0 °C was added NIS (2.62 g, 11.63 mmol). The solution was allowed to stir for 10 min followed by the addition of AgOTf (480 mg, 2.33 mmol). After stirring for 10 min, triethylamine was added to neutralize the reaction. The solution was diluted with CH_2Cl_2 and filtered through Celite (2 cm). The filtrate was washed with saturated aqueous $Na_2S_2O_3$ solution, water, and brine. The organic layer was dried, filtered, and concentrated. The compound was purified by chromatography (hexanes/EtOAc, 4:1) yielding **10** (3.88 g, 90%) as a colorless oil: R_f 0.24 (hexanes/EtOAc, 4:1); ^{1}H NMR (500 MHz, $CDCl_3$, δ) 7.39−7.22 (m, 15 H), 5.34 (s, 0.75 H), 5.29 (d, 0.25 H, J = 4.3 Hz), 4.94−4.53 (m, 7 H), 4.06−4.02 (m, 3 H), 3.85−3.69 (m, 4 H), 3.5 (s, 1 H), 3.43 (s, 3H), 3.19 (d, 1 H, J = 1.0 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$, δ) 138.4, 138.3, 138.2, 138.1, 128.4, 128.3 (2), 128.2 (2), 127.9, 127.8, 127.7. 127.6. 127.5, 127.4, 127.3 (2), 97.9, 96.8, 93.6, 81.9, 79.2, 78.3, 75.5, 75.1, 75.0, 74.9, 74.3, 73.7, 73.4, 73.3, 72.2, 72.1, 71.5, 69.6, 69.0, 56.0, 55.6. Anal. Calcd for $C_{29}H_{34}O_7$: C, 70.43; H 6.93. Found: C, 70.22; H, 6.88.

4,5,7-Tri-*O*-benzyl-1,2-didehydro-1,2-dideoxy-3-*O*-methoxymethyl-D-*manno*-heptitol (11). To a solution of **10** (2.00 g, 4.04 mmol) in THF (30 mL) at 0 °C was added 1.6 M *n*-butyllithium in THF (2.53 mL, 4.04 mmol). The solution was allowed to stir for 10 min at 0 °C followed by cooling to −78 °C. The ylide derived from methyltriphenylphosphonium bromide (3.61 g, 10.1 mmol) and 1. 6 M *n*-butyllithium in THF (6.33 mL, 10.1 mmol) was added dropwise over the course of 1 h. The solution was allowed to stir for 10 h followed by the addition of a saturated aqueous $NaHCO_3$ solution and EtOAc. The organic layer was washed with brine, dried, and concentrated under reduced pressure. The crude oil was purified by chromatography (hexanes/EtOAc, 10:1) yielding **11** (1.55, 78%) as a colorless oil: R_f 0.55 (hexanes/EtOAc, 5:1); $[\alpha]_D$ +23.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ) 7.39−7.30 (m, 15 H), 6.00 (ddd, 1 H, J = 7.2, 14.6, 17.3 Hz), 5.40 (dd, 1 H, J = 14.6, 1.5 Hz), 5.39 (dd, 1 H, J = 17.6 Hz, 1.5 Hz), 4.79 (d, 1 H, 12.2 Hz), 4.74−4.57 (m, 7 H), 4.40 (dd, 1 H, J = 6.6, 7.6 Hz), 4.08 (m, 1 H), 3.91 (dd, 1 H, J = 5.0, 4.0 Hz), 3.83 (dd, 1 H, J = 5.0, 4.0 Hz), 3.70−3.66 (m, 2 H), 3.39 (s, 3 H), 2.78 (d, 1 H, J = 5.5 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$, δ) 138.5, 138.3, 138.0, 135.3, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.5, 127.4, 119.3, 94.1, 81.0, 78.5, 77.8, 74.1, 73.7, 73.4, 71.2, 70.4, 55.8. Anal. Calcd for $C_{30}H_{36}O_6$: C, 73.15; H 7.37. Found: C, 73.02; H, 7.41.

1,3,4-Tri-*O*-benzyl-6,7-didehydro-6,7-dideoxy-5-*O*-methoxymethyl-L-*arabino*-hept-2-ulose (12). To a solution of PCC (591 mg, 3.56 mmol), NaOAc (300 mg, 3.65 mmol), and crushed 4 Å molecular seives in CH_2Cl_2 (10 mL) was added **11** (1.35 g, 2.74 mmol) dissolved in CH_2Cl_2 (5 mL). The reaction mixture was allowed to stir at room temperature for 2 h followed by the addition of hexanes (10 mL) and Et_2O (10 mL). The solution was stirred for 30 min followed by filtration through a 3.0 cm bed of silica gel followed by copious elution with Et_2O. The eluants were evaporated to yield **12** (1.25 g. 93%) as a colorless oil: R_f 0.65 (hexanes/EtOAc, 5:1); $[\alpha]_D$ +43.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ) 7.28−7.21 (m, 15 H), 5.84 (ddd, 1 H, J = 7.2, 14.6, 17.3 Hz), 5.37 (dd, 1 H, J = 14.6, 1.5 Hz), 5.32 (dd, 1 H, J = 17.6 Hz, 1.5 Hz), 4.62−4.22 (m, 12 H), 3.90 (d, 1 H, J = 5 Hz), 3.32 (s, 3 H); ^{13}C NMR (125.7 MHz, $CDCl_3$, δ) 208.3, 137.5, 137.3, 137.0, 135.3, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 119.9, 94.5, 83.7, 81.9, 77.3, 77.2, 74.5, 74.3, 74.2, 73.1, 55.9, Anal. Calcd for $C_{30}H_{34}O_6$: C, 73.45; H 6.99. Found: C, 73.35; H, 7.01.

4,5,7-Tri-*O*-benzyl-1,2-didehydro-1,2,6-trideoxy-3-*O*-methoxymethyl-6-*C*-methylene-D-*arabino*-heptitol (13). The ylide derived from methyltriphenylphosphonium bromide (1.09 g 3.1 mmol) and 1.6 M *n*-butyllithium in THF (1.90 mL, 2.7 mmol) was added dropwise over the course of 1 h to a solution of **12** (1.00 g, 2.03 mmol) in THF (30 mL) at −78 °C.

The solution was allowed to stir for 3 h followed by the addition of a saturated aqueous solution of $NaHCO_3$ and EtOAc. The organic layer was washed with brine, dried, and evaporated under reduced pressure. The crude oil was purified by chromatography (hexanes/EtOAc. 15:1) yielding **13** (0.76 g, 77%) as a colorless oil: R_f 0.57 (hexanes/EtOAc, 6:1); $[\alpha]_D$ +69.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ) 7.39−7.30 (m, 15 H), 5.95 (ddd, 1 H, J = 6.7, 14.6, 17.3), 5.49 (d, 1 H, J = 6.7 Hz), 5.33−5.28 (m, 3 H), 4.81−4.74 (m, 2 H), 4.62−4.57 (m, 4 H), 4.52 (d, 1 H, J = 7.0 Hz), 4.40 (d, 1 H, J = 7.0 Hz), 4.22 (dd, 1 H, J = 7.9, 4.3 Hz), 4.12−4.00 (m, 3 H), 3.85 (dd, 1 H, J = 6.8, 3.7 Hz), 3.31 (s, 3 H); ^{13}C NMR (125.7 MHz, $CDCl_3$, δ) 142.5, 138.9, 138.4, 138.2, 134.5, 128.3, 128.1, 128.0, 127.9 (2), 127.6, 127.5, 127.3, 127.2, 119.5, 116.8, 93.9, 82.6, 82.4, 77.8, 74.9, 72.7, 70.9, 69.7, 55.4. Anal. Calcd for $C_{31}H_{36}O_5$: C, 76.20; H 7.43. Found: C, 76.10; H, 7.40.

2,3,5-Tri-*O*-benzyl-4-dehydro-4-deoxy-1-*O*-methoxymethyl-4a-carba-*β*-D-arabinofuranoside (14). To a solution of **13** (100 mg, 0.204 mmol) in toluene (5 mL) was added **23** (10 mol %). The reaction was allowed to stir for 2.5 h at 60 °C. After cooling to room temperature, the solvent was evaporated and the product purified by chromatography (hexanes/EtOAc, 15:1) to yield **14** (73 mg, 78%) as a colorless oil: R_f 0.77 (hexanes/EtOAc, 6:1); $[\alpha]_D$ +10.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ) 7.44−7.30 (m, 15 H), 6.04 (d, 1 H, J = 1.0 Hz), 4.80−4.53 (m, 10 H), 4.17 (m, 2 H), 4.05 (dd, 1 H, J = 5.4, 5.3 Hz), 3.42 (s, 3 H); ^{13}C NMR (125.7 MHz, $CDCl_3$, δ) 146.4, 138.5, 138.2, 137.9, 128.3, 128.2 (2), 128.0, 127.8, 127.7, 127.6, 127.5 (2), 126.9, 95.9, 85.3, 84.8, 76.0, 72.6, 72.5, 72.0, 66.5, 55.5. Anal. Calcd for $C_{29}H_{32}O_5$: C, 75.63; H 7.00. Found: C, 75.55; H, 7.05.

2,3,5-Tri-*O*-benzyl-1-*O*-methoxymethyl-4a-carba-*β*-D-arabinofuranoside (15). To a solution of **14** (50 mg, 0.110 mmol) in CH_2Cl_2 (10 mL) was added $(Ph_3P)_3RhCl$ (10 mol %, 0.011 mmol). The heterogeneous solution was allowed to stir under an atomsphere of H_2 for 6 h. The solvent was evaporated and the product purified by chromatography (hexanes/EtOAc, 20:1) to give **15** (45 mg, 88%) as a colorless oil: R_f 0.61 (hexanes/EtOAc, 10:1); $[\alpha]_D$ +87.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ) 7.32−7.24 (m, 15 H), 4.68−4.58 (m, 6 H), 4.49 (s, 2 H), 4.15 (dd, 1 H, J = 4.1, 7.6 Hz), 3.86−3.83 (m, 2 H), 3.51 (dd, 1 H, J = 7.7, 8.9 Hz), 3.44 (dd, 1 H, J = 9.0, 7.3 Hz), 3.35 (s, 3 H), 2.24−2.22 (m, 2 H), 2.08 (ddd, 1 H, J = 5.6, 9.4, 13.7 Hz), 1.66 (ddd, 1 H, 5.8, 5.9, 11.6 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$, δ) 138.7, 138.5, 138.3, 128.3, 128.2, 127.6 (2), 127.5 (2), 127.4, 127.3, 95.5, 84.5, 84.3, 75.6, 73.3, 72.9, 71.9, 71.7, 55.5, 41.2, 30.4. Anal. Calcd for $C_{29}H_{34}O_5$: C, 75.30; H 7.41. Found: C, 75.35; H, 7.33.

2,3,5-Tri-*O*-benzyl-4a-carba-*β*-D-arabinofuranose (16). To a solution of **15** (40 mg, 0.086 mmol) in CH_3OH (10 mL) was added concentrated HCl (5 μL). The solution was stirred for 6 h followed by neutralization with basic alumina. The solution was filtered through a bed of Celite and concentrated, and the product was purified by chromatography (hexanes/EtOAc, 8:1) to give **16** (36 mg, 95%) as a colorless oil: R_f 0.21 (hexanes/EtOAc, 8:1); $[\alpha]_D$ +28.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ) 7.35−7.25 (m, 15 H), 4.65−4.60 (m, 4 H), 4.51 (d, 1 H, 12.1 Hz), 4.50 (d, 1 H, J = 12 Hz), 4.15 (dd, 1 H, J = 8.6, 4.3 Hz), 3.92 (dd, 1 H, J = 5.5, 5.4 Hz), 3.83 (dd, 1 H, J = 10.0, 4.7 Hz), 3.51 (m, 2 H), 2.67 (d, 1 H, 5.5 Hz), 2.14−2.10 (m, 1 H), 2.09 (ddd, 1 H, J = 13.7, 9.4, 5.6 Hz), 1.58 (ddd, 1 H, J = 5.9, 5.8, 1.6 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$, δ) 138.7, 138.2, 137.9, 128.4, 128.3, 128.2 (2), 127.8, 127.7 (2), 127.6 (2), 127.5, 86.6, 84.6, 73.1, 73.0, 72.0, 71.9, 70.5, 41.6, 32.9. Anal. Calcd for $C_{27}H_{30}O_4$: C, 77.48; H 7.22. Found: C, 77.30; H, 7.29.

2,3,5-Tri-*O*-benzyl-4a-carba-α-D-arabinofuranose (18). To a solution of **16** (100 mg, 0.238 mmol), *p*-nitrobenzoic acid (52 mg, 0.310 mmol), and triphenylphosphine (84 mg, 0.310 mmol) in toluene (5 mL) at 0 °C was added diethyl azodicarboxylate (54 mg, 0.310 mmol). The solution was allowed to warm to room temperature followed by stirring for 4 h. The solvent was evaporated, and the resulting compound was subsequently dissolved in CH_3OH (5 mL) and treated with a catalytic amount of 1 M $NaOCH_3$ solution (100 μL). The solution was stirred at room temperature for 30 min, neutralized with AcOH, and evaporated under reduced pressure. The product was purified by chromatography (hexanes/EtOAc, 8:1) to give **18** (0.84 g, 84%) as a colorless oil: R_f 0.21 (hexanes/EtOAc, 8:1); $[\alpha]_D$ +18.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ) 7.38−7.30 (m, 15 H), 4.66 (s, 2 H), 4.63 (s, 2 H), 4.55 (s, 2 H), 4.19 (bs, 1 H), 3.90 (dd, 1 H, J = 8.1, 4.1 Hz), 3.86 (dd, 1 H, J = 9.3, 4.6 Hz), 3.48 (d, 2 H), 2.25 (m, 1 H), 2.06 (bs, 1 H), 1.98 (ddd, 1 H, J = 4.7, 8.9, 13.6 Hz), 1.89 (ddd, 1 H, J = 5.0, 6.7, 13.7 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$, δ) 138.4, 138.3, 128.4, 128.3, 127.8, 127.7, 127.6, 127.5, 127.4, 89.9, 84.9, 74.9, 73.0, 72.1, 71.9, 71.7, 41.9, 34.2. Anal. Calcd for $C_{27}H_{30}O_4$: C, 77.48; H 7.22. Found: C, 77.40; H, 7.31,

Methyl-4a-carba-α-D-arabinofuranoside (3). To a solution of **18** (100 mg, 0.238 mmol) in THF (5 mL) at 0 °C was added NaH (18 mg, 0.714 mmol). The solution was stirred for 15 min, and then CH_3I (40 mg, 0.286 mmol) was added dropwise. CH_3OH was added, and the solution was concentrated. The resulting paste was dissolved in CH_2Cl_2, and the organic solution was washed successively with an aqueous saturated solution of $NaHCO_3$, water, and brine. The organic solution was dried and concentrated. The oil was immediately dissolved in CH_3OH/AcOH (5:1, v/v), and Pd/C (50 mg, 10 mol %) was added. The solution was stirred under an atmosphere of H_2 for 4 h. The solution was subsequently filtered through a bed of Celite, washed with CH_3OH, and concentrated. The compound was purified by chromatography ($CHCl_3$/CH_3OH, 20:1) to yield **3** (34 mg, 87%) as a colorless oil: R_f 0.21 ($CHCl_3$/CH_3OH, 10:1); $[\alpha]_D$ +16.1 (*c* 1.0, H_2O); ^{1}H NMR (500 MHz, D_2O, δ) 3.78 (dd, 1 H, J = 6.2, 5.4 Hz), 3.65 (dd, 1 H, J = 11.1, 4.7 Hz), 3.61 (dd, 1 H, J = 6.2, 7.5 Hz), 3.60 (dd, 1 H, J = 7.5, 8.4 Hz), 3.51 (dd, 1 H, J = 6.8, 11.1 Hz), 3.34 (s, 3 H), 2.03 (m, 1 H), 1.83 (ddd, 1 H, J = 8.4, 8.4, 14.1 Hz), 1.77 (ddd, 1 H, J = 5.4, 9.8, 14.1 Hz); ^{13}C NMR (125.7 MHz, D_2O, δ) 83.1, 82.3, 77.0, 63.2, 56.8, 42.9, 28.9. Anal. Calcd for $C_7H_{14}O_4$: C, 51.84; H 8.70. Found: C, 51.64; H, 8.80.

Methyl-4a-carba-*β*-D-arabinofuranoside (4). Conversion of **16** (121 mg, 0.283 mmol) into **4** was carried out as described above for the preparation of **3**. The compound was purified by chromatography ($CHCl_3$/CH_3OH, 20:1) to yield **4** (44 mg, 94%) as a colorless oil: R_f 0.16 ($CHCl_3$/CH_3OH, 8:1); $[\alpha]_D$ +9.1 (*c* 1.0, H_2O); ^{1}H NMR (500 MHz, D_2O, δ) 3.89 (dd, 1 H, J = 5.1, 6.2 Hz), 3.75 (dd, 1 H, J = 5.1, 6.5 Hz), 3.71 (dd, 1 H, J = 6.6, 6.8 Hz), 3.66 (dd, 1 H, J = 5.8, 10.9 Hz), 3.51 (dd, 1 H, J = 7.5, 11.0 Hz), 3.32 (s, 3 H), 2.13 (ddd, 1 H, J = 4.9, 7.5, 13.9 Hz), 1.89 (m, 1 H), 1.48 (ddd, 1 H, 6.2, 9.3, 13.4 Hz); ^{13}C NMR (125.7 MHz, D_2O, δ) 80.2, 78.0, 77.6, 64.5, 57.0, 43.5, 29.3. Anal. Calcd for $C_7H_{14}O_4$: C, 51.84; H 8.70. Found: C, 51.70; H, 8.89.

(4-^{2}H,4a-^{2}H)-1-*O*-Methoxymethyl-2,3,5-tri-*O*-benzyl-4a-carba-*β*-D-arabinofuranoside (26). To a solution of **14** (50 mg, 0.110 mmol) in CH_2Cl_2 (10 mL) was added $(Ph_3P)_3RhCl$ (10 mol %, 0.011 mmol). The heterogeneous solution was stirred under an atomsphere of D_2 for 6 h. The solvent was evaporated and the product purified by chromatography (hexanes/EtOAc, 20:1) to afford **12** (42 mg, 82%) as a colorless oil: R_f 0.61 (hexanes/EtOAc, 10:1); $[\alpha]_D$ +61.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ) 7.32−7,24 (m, 15 H), 4.68−4.58 (m, 6 H), 4.49 (s, 2 H), 4.15 (dd, 1 H, J = 4.1, 7.6 Hz), 3.86−3.83 (m, 2 H), 3.51 (dd, 1 H, J = 7.7, 8.9 Hz), 3.44 (dd, 1 H, J = 9.0, 7.3 Hz), 3.35 (s, 3 H), 1.66 (d, 1 H, J = 5.8 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$, δ) 138.7, 138.5, 138.3, 128.3, 128.2, 127.6 (2), 127.5 (2), 127.4, 127.3, 95.5, 84.5, 84.3, 75.6, 73.3, 72.9, 71.9, 71.7, 55.5, 41.2, 30.4. Anal. Calcd for $C_{29}H_{32}D_2O_5$: C, 74.97; H 7.81. Found: C, 74.82; H, 7.88. HRMS (ESI) calcd for (M + Na^+) $C_{29}H_{32}D_2O_5$: 487.2427, found 487.2400.

(4-^{2}H,4a-^{2}H)-2,3,5-Tri-*O*-benzyl-4a-carba-*β*-D-arabinofuranose (27). The conversion of **26** (40 mg, 0.086 mmol) into **27** was carried out as described above for the preparation of **16** from **15**. The compound was purified by chromatography (hexanes/EtOAc, 8:1) to give **27** (33 mg, 92%) as a colorless oil: R_f 0.21 (hexanes/EtOAc, 8:1); $[\alpha]_D$ +22.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ) 7.35−7.25 (m, 15 H), 4.62−4.58 (m, 4 H), 4.51 (d, 1 H, J = 12.1 Hz), 4.50 (d, 1 H, J = 12 Hz), 4.15 (dd, 1 H, J = 8.6, 4.3), 3.92 (dd, 1 H, J = 5.5, 5.4), 3.83 (dd, 1 H, J = 10.0, 4.7 Hz), 3.51 (m, 2 H), 2.67 (d, 1 H, 5.5 Hz),

1.58 (d, 1 H, J = 5.9 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$, δ) 138.7, 138.2, 137.9, 128.4, 128.3, 128.2 (2), 127.8, 127.7 (2), 127.6 (2), 127.5, 86.6, 84.6, 73.1, 73.0, 72.0, 71.9, 70.5, 41.6, 32.9. Anal. Calcd for $C_{27}H_{28}D_2O_4$: C, 73.12; H 7.27. Found: C, 73.01; H, 7.22. HRMS (ESI) calcd for (M + Na^+) $C_{27}H_{28}D_2O_4$: 443.2165, found 443.2160.

(4-^{2}H,4a-^{2}H)-Methyl-4a-carba-α-D-arabinofuranoside (28). The conversion of **27** (100 mg, 0.238 mmol) into **28** was carried out as described for the preparation of **3** from **16**. The compound was purified by chromatography ($CHCl_3$/CH_3OH, 20:1) to yield **28** (29 mg, 77%) as a colorless oil: R_f 0.21 ($CHCl_3$/CH_3OH, 10:1); $[\alpha]_D$ +8.1 (*c* 1.0, H_2O); ^{1}H NMR (500 MHz, D_2O, δ) 3.78 (dd, 1 H, J = 6.2, 5.3 Hz), 3.65 (d, 1 H, J = 11.5), 3.61 (dd, 1 H, J = 6.2, 7.4 Hz), 3.60 (d, 1 H, J = 7.4), 3.51 (d, 1 H, J = 11.8 Hz), 3.34 (s, 3 H), 1.77 (d, 1 H, J = 5.3 Hz); ^{13}C NMR (125.7 MHz, D_2O, δ) 83.1, 82.3, 77.0, 63.2, 56.8, 42.9, 28.9. HRMS (ESI) calcd for (M + Na^+) $C_7H_{12}D_2O_4$: 187.0913, found 187.0898.

(4-^{2}H,4a-^{2}H)-Methyl-4a-carba-β-D-arabinofuranoside (29). The conversion of **27** (100 mg, 0.238 mmol) into **29** was carried out as described above for the preparation of **3**. The compound was purified by chromatography ($CHCl_3$/CH_3OH, 20:1) to yield **29** (36 mg, 94%) as a colorless oil: R_f 0.16 ($CHCl_3$/CH_3OH, 8:1); $[\alpha]_D$ +20.9 (*c* 1.0, H_2O); ^{1}H NMR (500 MHz, D_2O, δ) 3.89 (dd, 1 H, J = 5.0, 6.2 Hz), 3.75 (dd, 1 H, J = 5.1, 6.4 Hz), 3.71 (d, 1 H, J = 6.4 Hz), 3.66 (d, 1 H, J = 12.1 Hz), 3.51 (d, 1 H, J = 12.0 Hz), 3.32 (s, 3 H), 1.48 (d, 1 H, J = 6.0 Hz); ^{13}C NMR (125.7 MHz, D_2O, δ) 80.2, 78.0, 77.6, 64.5, 57.0, 43.5, 29.3. HRMS (ESI) calcd for (M + Na^+) $C_7H_{12}D_2O_4$: 187.0913, found 187.0902.

[^{13}C]-Methyl-4a-carba-α-D-arabinofuranoside (31). The procedure used for the synthesis of **31** from **18** (100 mg, 0.238 mmol) was identical to that for the synthesis of **4** from **16** except for the use of $^{13}CH_3I$. The compound was purified by chromatography ($CHCl_3$/CH_3OH, 20:1) to yield **30** (31 mg, 90%) as a colorless oil: R_f 0.21 ($CHCl_3$/CH_3OH, 10:1); $[\alpha]_D$ +16.9 (*c* 1.0, H_2O); ^{1}H NMR (500 MHz, D_2O, δ) 3.78 (dd, 1 H, J = 6.2, 5.4 Hz), 3.65 (dd, 1 H, J = 11.1, 4.6 Hz), 3.61 (dd, 1 H, J = 6.2, 7.5 Hz), 3.60 (dd, 1 H, J = 7.5, 8.4 Hz), 3.51 (dd, 1 H, J = 6.8, 11.1 Hz), 3.34 (d, 3 H, 143.1 Hz), 2.03 (m, 1 H), 1.83 (ddd, 1 H, J = 8.4, 8.4, 11.1 Hz), 1.77 (ddd, 1 H, J = 5.4, 9.8, 14.1 Hz); ^{13}C NMR (125.7 MHz, D_2O, δ) 83.1 (d, J = 1.8 Hz), 82.3, 77.0 (d, J = 1.8 Hz), 63.2, 56.8, 42.9, 28.9 (d, J = 1.8 Hz). HRMS (ESI) calcd for (M + Na^+) $C_613CH_{14}O_4$: 186.0823, found 186.0811.

[^{13}C]-Methyl-4a-carba-β-D-arabinofuranoside (**32**). The procedure used for the synthesis of **32** from **16** (100 mg, 0.238 mmol) was identical to that for the synthesis of **4** from **16** except for the use of $^{13}CH_3I$. The compound was purified by chromatography ($CHCl_3$/CH_3OH, 20:1) to yield **31** (34 mg, 94%) as a colorless oil: R_f 0.16 ($CHCl_3$/CH_3OH, 8:1); $[\alpha]_D$ +10.3 (*c* 1.0, H_2O); ^{1}H NMR (500 MHz, D_2O, δ) 3.89 (dd, 1 H, J = 5.1, 6.2 Hz), 3.75 (dd, 1 H, J = 5.1, 6.5 Hz), 3.71 (dd, 1 H, J = 6.5, 6.8 Hz), 3.66 (dd, 1 H, J = 5.7, 10.9 Hz), 3.51 (dd, 1 H, J = 7.6, 11.0 Hz), 3.32 (d, 3 H, J = 142.8 Hz), 2.13 (ddd, 1 H, J = 4.9, 7.5, 13.9 Hz), 1.89 (m, 1 H), 1.48 (ddd, 1 H, 6.2, 9.3, 12.4 Hz); ^{13}C NMR (125.7 MHz, D_2O, δ) 80.2 (d, J = 1.9 Hz), 78.0, 77.6 (d, J = 1.9 Hz), 64.5, 57.0, 43.5, 29.3 (d, J = 1.9 Hz). HRMS (ESI) calcd for (M + Na^+) $C_613CH_{14}O_4$: 186.0823, found 186.0833.

NMR Spectroscopy for Conformational Studies. All NMR spectra used for obtaining conformational information were recorded on samples at 15−20 mM concentration in 0.6 mL of D_2O (pH 6.0). The $^3J_{H,H}$ used in the PSEUROT calculations or in the determination of the C_4−C_5 rotamer populations were measured from the 500 MHz one-dimensional ^{1}H NMR spectrum of **3**, **4**, **28**, or **29**. In some cases, resolution enhancement of the FIDs was necessary in order to measure small coupling constants. Simulation of the ^{1}H NMR spectrum of **3** and **4** was done using the Bruker program NMRSim.[39] A comparison of the simulated and experimental spectra is provided in the Supporting Information. To assess the effect of temperature on conformer identity and population, a series of variable-temperature NMR experiments were done using **28** and **29**. In these experiments, a one-dimensional ^{1}H NMR spectrum was recorded at 10° increments between 288 and 328 K. The $^3J_{C,H}$ and $^3J_{C,C}$ were measured using **31** and **32**, via either the 125 MHz one-dimensional ^{13}C NMR spectrum ($^3J_{C,C}$) or the 500 MHz one-dimensional ^{13}H NMR spectrum ($^3J_{C,H}$). These values were confirmed by simulation of these spectra.

Table 7. Values of *A* and *B* Used in PSEUROT Calculations[a]

^3J	**3**/**28**		**4**/**29**	
$\Phi_{H,H}$	*A*	*B*[b]	*A*	*B*[b]
$\Phi_{1,2}$	1.113	−123.3	1.113	3.3
$\Phi_{2,3}$	1.129	122.0	1.129	122.0
$\Phi_{3,4}$	1.469	−123.8	1.469	−123.8
$\Phi_{4,4a}$	1.093	124.1	1.093	124.1
$\Phi_{4,4a'}$	1.098	4.4	1.098	4.4
$\Phi_{1,4a}$	1.172	3.4	1.172	−122.1
$\Phi_{1,4a'}$	1.172	122.1	1.172	3.4

[a] See Experimental Section and Supporting Information for the method used for determining these values. [b] In degrees.

PSEUROT Calculations. All calculations were done with PSEUROT 6.2 following modification of the default parameters provided for the arabinofuranosyl ring. The electonegativities (in D_2O) used were as follows: 1.25 for OH; 1.26 for OR; 0.0 for CH_2; 0.68 for CH_2OH; 0.62 for CH(OR); 0.0 for H; 0.0 for D.[49] For each endocyclic torsion angle, the parameters α and ϵ were set to 1 and 0, respectively, as was done previously for a related study on carbocyclic nucleosides.[29]

To translate the exocyclic H,H torsion angles (Φ_{HH}) into the endocyclic torsion angles (ν_i) that are used to determine the pseudorotational phase angle (*P*), the program makes use of the relationship: $\Phi_{HH} = A\nu_i + B$. The values of *A* and *B* for **3** and **4** are unknown, and the approach we used to define them for each torsion angle was similar to that described by Chattopadhyaya and co-workers for carbocyclic nucleosides.[29] For both **3** and **4**, a Monte Carlo search using MacroModel Version 6.5[50] and the AMBER* force field was carried out to generate a family of conformers[47,51] for each ring system, which were in turn optimized at the HF/6-31G* level of theory,[52] using Gaussian 98.[53] The geometrical data for these conformers were analyzed using the program ConforMole[54] and then Φ_{HH} was plotted against ν_i in order to determine *A* and *B* for a particular endocyclic torsion angle. These graphs are included in the Supporting Information, and the values of *A* and *B* used in the PSEUROT calculations are given in Table 7.

In the calculations reported in the main text of the paper, the puckering amplitude, τ_m, was kept constant at 40°. This value represents the average puckering amplitude of all conformers identified from the Monte Carlo search/HF-

(49) 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.

(50) (a) MacroModel V6.5: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caulfield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440. (b) Goodman, J.; Still, W. C. *J. Comput. Chem.* **1991**, *12*, 1110.

(51) McCarren, P. R.; Gordon, M. T.; Lowary, T. L.; Hadad, C. M. *J. Phys. Chem. A.* **2001**, *105*, 5911.

(52) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab initio Molecular Orbital Theory*; John Wiley & Sons: New York, 1986.

(53) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, Revision A.7, Gaussian, Inc.; Pittsburgh, PA, 1998.

(54) ConforMole, McCarren, P. R. The Ohio State University; this program is available upon request.

Table 8. Dihedral Angles Used for Calculating Limiting ^3J for gg, gt, and tg Rotamers[a,b]

	C_4-C_5 bond		C_1-O_1 bond	
rotamer	$H_4-C_4-C_5-H_{5R}$	$H_4-C_4-C_5-H_{5S}$	$C_{CH3}-O-C_1-C_2$	$C_{CH3}-O-C_1-C_{4a}$
gg	62	−60	44	78
gt	−177	63	72	167
tg	−66	178	172	65

[a] See Experimental Section for the protocol used for determining these values. [b] Angles in degrees.

optimization protocol described above. The range of τ_m found in this family of conformers was 36−43°, and we have therefore carried out a series of PSEUROT calculations in which the puckering amplitude was changed in 1° increments across this range (see Supporting Information). Over this range of τ_m, the identities of the N/S conformers for **3** and **4** remained unchanged; however, there were slight differences in the relative populations of each.

Determination of C_4-C_5 Rotamer Populations. The rotamer populations about the C_4-C_5 were determined by analysis of the three bond $^1H-^1H$ coupling constants between H_4 and H_{5R} ($^3J_{4,5R}$) and H_4 and H_{5S} ($^3J_{4,5S}$) using eqs 1−3. The coefficients for eqs 1 and 2 were determined by calculating the limiting $^3J_{H,H}$ for each rotamer using eq 7.

$$^3J_{H,H} = 13.22\cos^2\theta - 0.99\cos\theta + \sum_i[0.87-2.46\cos^2(\xi_i\theta + 19.9|\Delta x_i|)]\Delta x_i \quad (7)$$

For eq 7, $\Delta x_i = (x_{subst} - x_H)$ where x is the electronegativity (see above) and $\xi_i = +1$ or -1 as previously defined.[55] The angles θ used in this equation (Table 8) were determined by an analysis of the data obtained from the previously described Monte Carlo search/HF-optimization protocol. The geometrical data for all conformers was analyzed using ConforMole,[54] and each structure was assigned as gg, gt, or tg (Figure 4A) based on the $C_{4a}-C_4-C_5-O_5$ angle. For each of the three sets of conformers, an average of $H_4-C_4-C_5-H_{5R}$ and $H_4-C_4-C_5-H_{5S}$ angles was taken and those numbers are shown in Table 8.

Determination of C_1-O_1 Rotamer Populations. The rotamer populations about the C_1-O_1 bond were determined by analysis of the three bond $^{13}C-^{13}C$ coupling constants between the methyl group and C_{4a} ($^3J_{CH3,4a}$) and between the methyl group and C_2 ($^3J_{CH3,2}$) using eq 5−7. The coefficients for eq 4 and 5 were determined by calculating the $^3J_{C,C}$ for each rotamer using eq 8.

$$^3J_{C,C} = 4.96\cos^2\theta + 0.63\cos\theta - 0.01 \quad (8)$$

The angles used in this equation (Table 8) were determined as described above for the C_4-C_5 bond. See Figure 6 for definitions of gg, gt, and tg rotamers about the C_1-O_1 bond.

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Supporting Information Available: NMR spectra for all new compounds, details on the preparation of **8** via an improved route, details on the calculation of *A* and *B* for the PSEUROT calculations, details of calculations, coupling constants measured from variable temperature studies, results of PSUEROT calculations at differing puckering angles and comparison of simulated spectra for **3** and **4** with those obtained from experiment. This material is available free of charge via the Internet at http://pubs.acs.org.

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(55) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; de Leeuw, H. P. M.; Altona, C. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 576.