Synthesis and Conformational Analysis of (6*R*)-[6-$^2H_1$]-1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose. NMR and Molecular Modeling Studies

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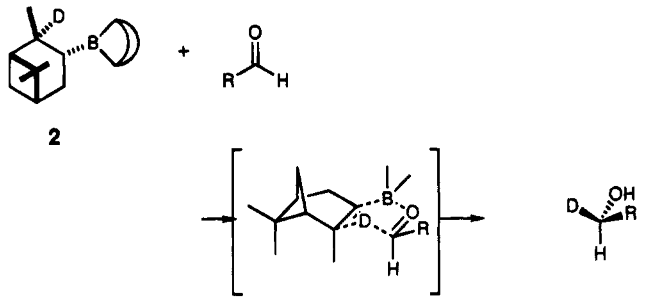
The conformation preferences of 1,2:3,4-di-*O*-isopropylidine-α-D-galactopyranose have been determined using NMR and molecular modeling (conformational searching) techniques. The pyranose ring assumes a skew-boat conformation. Coupling constants for the C_6 side chain and hydroxyl proton indicate that the predominant conformation places the oxygen anti to C_4 (gt conformation) with the hydroxyl hydrogen aligned toward the pyranose oxygen in deuteriochloroform. A similar orientation of the $C_5—C_6$ bond was observed in water and toluene. In DMSO the C_6 oxygen is anti to the pyranose oxygen (tg conformation) with the hydroxyl hydrogen anti to C_5. A similar orientation of the $C_5—C_6$ bond was observed in methanol.

Conformational analysis of the freely rotating $C_5—C_6$ bond of carbohydrates is a long-standing problem in carbohydrate chemistry.[1] The orientation of the 6-OH group is presumably important for biological transformations and properties. Assignment of the conformation of the $C_5—C_6$ bond is complicated by the fact that it is difficult to assign PMR chemical shifts and determine coupling constants for the H_{6R} and H_{6S} protons. These protons, along with H_5, often produce a complex, non-first-order ABC pattern which is difficult to interpret even at high field. The situation is further complicated by intra- and intermolecular hydrogen-bonding possibilities. To simplify the spectrum one may specifically label one of the prochiral hydrogens.[1,2] Although this simplifies the PMR spectrum, the conformational analysis is still complicated by the fact that the $C_5—C_6$ bond is freely rotating and thus the coupling constants are an average of the solution populations. In order to determine the preferred conformation one must make assumptions about the population of the various staggered conformations and their respective coupling constants. Molecular modeling[3] may be used to determine torsional angles, coupling constants, and relative energies for the staggered conformations. However, individual examination of the three possible staggered conformations may be misleading since long-range interactions may distort the local conformation about the $C_5—C_6$ bond. A single coupling constant must still be extrapolated into three conformational populations. Ideally, one would like to examine all possible combinations of conformations for the entire molecule and obtain relative energies for all accessible structures. Thus, one could obtain a Boltzmann average distribution for the staggered conformations. Herein we provide the results of such a study.

Results and Discussion

We chose to examine readily available 1,2:3,4-di-*O*-isopropylidine-α-D-galactopyranose. This compound is soluble in a number of solvents, and this would permit an examination of solvent effects on rotamer populations. Furthermore, in some solvents coupling of the hydroxyl proton to the C_6 protons could be observed ($J = 9.3$, 3.0 Hz in chloroform). This observation provides a unique opportunity to determine the orientation of the hydroxyl group, a problem not addressed in previous studies.[1,4]

Synthesis of Labeled 1. Chiral enantiomerically enriched 1-deuterio (and tritio) primary alcohols may be readily prepared by reduction of the corresponding aldehyde with *B*-3-pinanyl-9-borabicyclo[3.3.1]nonane (*B*-3-pinanyl-9-BBN, **2**, Alpine-Borane[5]).[6] This reaction proceeds through a cyclic transition state which may be used to predict the absolute configuration of the resulting alcohol. The predicted absolute configuration is obtained even in cases in which the carbonyl contains an adjacent stereocenter.[7]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The deuterated analog of Alpine-Borane may be prepared by conventional routes[8] or by treatment of *B*-methoxy-9-BBN with lithium aluminum deuteride in the presence of α-pinene using a modified version of Brown's method.[9] Compound **1** was oxidized to the aldehyde **3** and reduced with **2**. After oxidative workup and chromatography, deuterated **1** was obtained. Mass spectral

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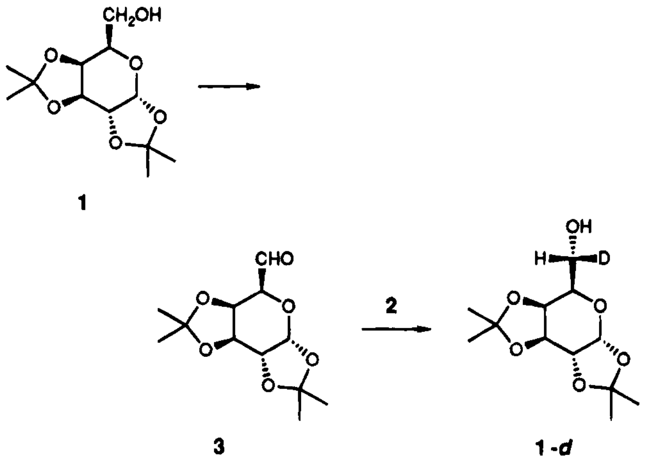


1

3

1-*d*

analysis indicated 97.2% deuterium incorporation. Analysis using NMR shift reagents indicated that the sample was greater than 20:1 diastereotopically pure.

Proton NMR Analysis. The coupling constants for the ring protons of **1** were in agreement with a skew-boat conformation as previously reported.[10] The NMR spectrum of **1**-*d* ($CDCl_3$) indicated the absence of one proton (assigned H_{6R} according to the mechanism of reduction and in agreement with a previous assignment)[2b] in the 3.8–4.0 ppm range. The doublet of doublets for the hydroxyl proton was now reduced to a doublet (J = 9.3 Hz). Proton H_{6S} was reduced to a doublet of doublets (J = 9.3, 4.3 Hz) which collapsed to a doublet (J = 4.3 Hz) upon irradiation of the hydroxyl proton.

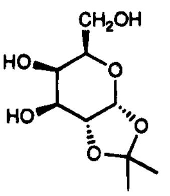
It is difficult to determine the H_5—H_{6R} coupling constant from the proton spectrum of **1** in $CDCl_3$. The H_5 and H_6 absorptions partially overlap even at 500 MHz, and the spectrum is complicated by inclusion of the geminal coupling constant ($J_{H_{6R}-H_{6S}}$ = 11 Hz). Therefore, we reduced aldehyde **3** with $LiAlD_4$ in order to obtain a sample in which the geminal coupling constant would be removed. Irradiation of the hydroxyl proton left a doublet for proton H_{6S} with a coupling constant of 8 Hz. The coupling constants for **1** were essentially identical in D_2O and deuterated toluene. However, the OH proton was not clearly resolved in toluene, and exchange prevented a determination of the OH coupling constants in D_2O.

The proton spectrum of **1** in DMSO-d_6 also indicated coupling between the hydroxyl proton and the H_{6S} and H_{6R} protons. But in this case, the coupling constants were of comparable magnitude (5.4 and 6.5 Hz). The coupling constants for H_{6S}—H_5 and H_{6R}—H_5 are also very nearly equal (6.3 and 6.4 Hz). Very similar coupling constants were observed in methanol-d_4, but coupling to the hydroxyl group could not be observed because of deuterium exchange.

Molecular Modeling. As stated in the Introduction, it is desirable to examine all possible accessible conformations in order to obtain a profile of the molecule. Until recently[11] such a search was often impractical. We have recently developed an efficient method for searching populated conformational space.[12] This method starts with an initial structure and through a series of random bond rotations and atom movements followed by geometry optimization generates the global minimum and all other conformations within a given energy window, arbitrarily chosen as 3.0 kcal since conformations higher in energy contribute negligibly to the solution structure.

This algorithm was applied to compound **1**. For the molecular mechanics calculations a default dielectric constant of 1.5 was used, a hydrogen bond term[13] was included, and the MM2 force field of BAKMDL(MODEL) was used. Starting with a chair form of **1** the program proceeded to produce eight conformations within the 3.0 kcal window. The global minimum (Figure 1) was 57% of the Boltzmann population. All eight structures were of a skew-boat conformation. The chair conformations were all more than 3.8 kcal above the minimum and thus would contribute less than 1% to the average structure. The importance of the skew-boat form was confirmed by the proton NMR results (*vide infra*). A ninth side chain rotomer was found just outside of the 3.0 kcal window and contributed less than 0.5% to the overall population.

The cause for the remarkably high energy of the chair form was briefly explored using mono acetonides **4** and **5**. A conformational search indicated that each had a greater conformational diversity than **1**; **4** produced 43 conformations, and **5** produced 39 conformations. Part of the reason for more conformations is the added degrees of freedom obtained from the freely rotating hydroxyl groups. However, an additional reason is that both structures were a mixture of chair and skew-boat conformations, 57% chair, 43% skew-boat for **4**, and 45% chair, 55% skew-boat for **5**. Fusing 5- and 6-membered rings in a cis manner tends to cause the cyclohexyl bonds to assume an eclipsed conformation rather than the desired 60° torsional angle. With two fused rings, as in **1**, the 6-membered ring cannot assume a chair without introducing considerable strain in the 5-membered rings and decreasing the torsional angles within the 6-membered ring. In the chair conformations of **1** torsional angles for atoms O_5—C_1—C_2—C_3, C_1—C_2—C_3—C_4, and C_2—C_3—C_4—C_5 are reduced to 42°, −35°, and 40°, respectively. These are considerably smaller than in a strain-free ring.



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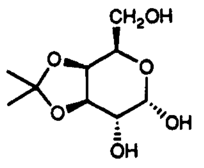

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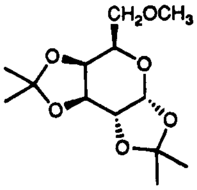

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The major differences between the eight conformations of **1** were the orientation of the C_5—C_6 bond and OH bond. Table 1 summarizes the distribution of these structures. From the relative energies, a Boltzmann distribution of

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(12) We used the MM2 force field of MODEL as incorporated in BAKMDL. Full details of this method will appear elsewhere. Steliou, K.; Midland, M. M. Manuscript in preparation.

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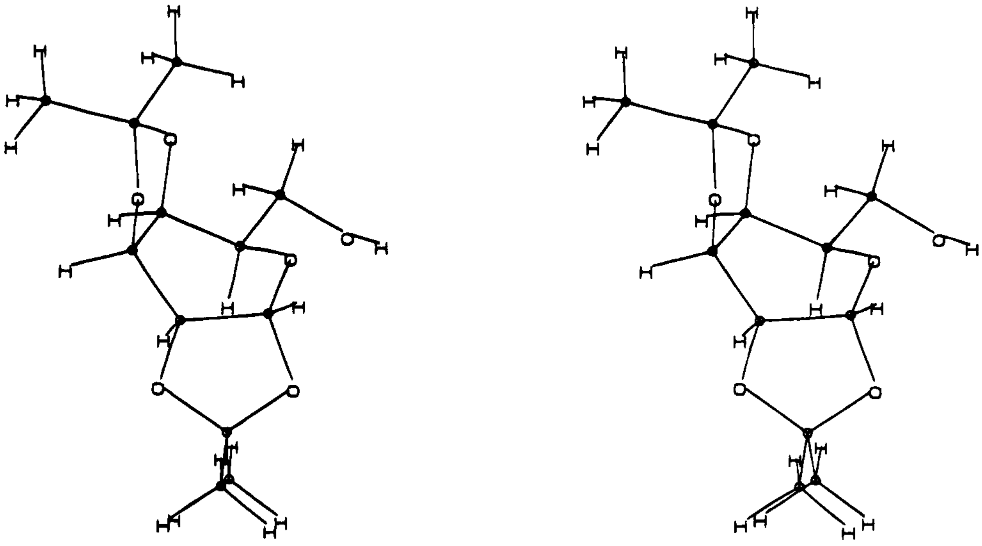
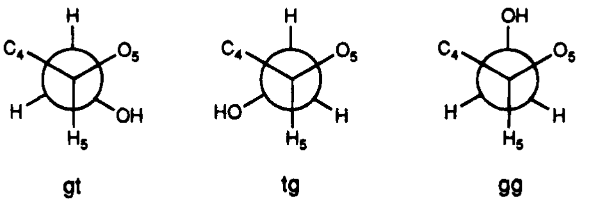


Figure 1. Stereo view of the global minimum derived from a conformational search of compound **1**.

Table 1. Calculated Conformational Distribution and Side-Group Torsional Angles for 1

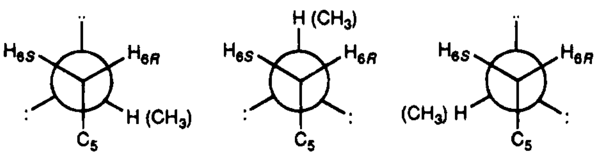
energy (rel)	% (Boltzmann)	torsional angle $O_5-C_5-C_6-O_6$	torsional angle $C_5-C_6-O_6-H$
0.00	57.3	64.4	−60.3
0.72	17.1	179.1	178.2
1.15	8.4	70.5	−177.1
1.29	6.6	−172.1	83.9
1.60	3.9	−56.2	31.4
1.63	3.7	−52.3	−60.2
2.06	1.8	177.3	−79.6
2.36	1.1	66.7	63.9

Scheme 1



gt	tg	gg	
67%	25%	8%	1
41%	57%	2%	6

Scheme 2



63%	25%	12%	1
7%	92%	1%	6

67% gt, 25% tg, and 8% gg was obtained for the C_5-C_6 bond (Scheme 1).

The orientation of the hydroxyl hydrogen was anti to H_{6S} in the global minimum. The populations of the three $C_5-C_6-O_6-H$ conformations were calculated from the relative energies (Scheme 2). The Boltzmann-averaged $H_{6S}-C_6-O_6-H$ torsional angle was 139°, and the $H_{6R}-C_6-O_6-H$ angle was 71°.

In DMSO, the hydroxyl proton is strongly hydrogen bonded to the solvent. Changing the dielectric constant for the calculations from the default of 1.5 to as high as 80 did not significantly alter the calculated coupling constants. Changing the dielectric constant does not account for the increased bulk of the hydrogen bonded ensemble. We have therefore assumed that this ensemble behaves as a methyl group. Applying the conformational search algorithm to the methyl ether **6** again resulted in the expression of the skew-boat form. However, the conformations about the C_5-C_6 bond and the C_6-O_6 bonds were considerably different from those found in **1** (Table 2). The major isomer placed the ether group anti to the ring oxygen (tg isomer) but there was also a major contribution to the gt isomer. In all the ratio of gt:tg:gg was 41:57:2 (Scheme 1). The methyl ether was almost exclusively (92%) in the anti conformation (Scheme 2).

Table 2. Calculated Conformational Distribution and Side-Group Torsional Angles for 6

energy (rel)	% (Boltzmann)	torsional angle $O_5-C_5-C_6-O_6$	torsional angle $C_5-C_6-O_6-CH_3$
0.00	55.4	−179.7	178.7
0.28	34.5	69.7	−179.6
1.47	4.7	86.6	−67.3
1.95	2.1	−55.3	176.7
2.05	1.8	−171.9	−75.3
2.22	1.4	56.1	63.6

Correlation of NMR and Molecular Modeling Data. Previous NMR data suggested that a skew-boat was an important conformation for **1**.[10] The present molecular modeling data suggest that the skew-boat is the only important conformation. To correlate the NMR and molecular modeling data, coupling constants were calculated[14] for each of the eight conformations, and a Boltzmann-averaged coupling constant was determined for both **1** and **6**. These compared very favorably to the experimental values (Table 3) and reinforce the idea that the skew-boat is the major contributor to the solution conformation. The calculated average coupling constant for H_5-H_{6S} and H_{6R} also agree fairly well with the experimental results and tends to support the reported distribution of staggered conformations. It is not possible

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[14] Haasnoot, C. A. G.; DeLeeuw, F. A. A.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.

[15] It is not possible to calculate the absolute strength of the hydrogen bond by performing the calculation with the hydrogen-bonding term turned on and off. This is because the normal MM2 force field incorporates terms (Van der Waals attraction, dipole, etc.) which contribute to the hydrogen-bond strength.

Table 3. Experimental and Calculated Coupling Constants

protons	J_{exp} (1, $CDCl_3$) (Hz)	J_{calc}, 1 (Hz)	J_{exp} (1, DMSO) (Hz)	J_{calc}, 6 (Hz)
1–2	5.0	4.77	5.0	4.82
2–3	2.4	2.62	2.1	2.70
3–4	7.9	7.87	8.0	7.82
4–5	1.3	1.85	1.4	1.95
5–6*S*	4.3	4.65	6.3	7.00
5–6*R*	8.0	8.10	6.4	7.00

to calculate the coupling constant to the hydroxyl proton, but the observed coupling constants are consistent with the calculated torsional angles. Likewise, the calculated torsional angles for the methyl ether **6** seem to adequately represent the structure in DMSO.

Both the molecular modeling and NMR data indicated that in chloroform the hydroxyl proton is oriented toward the pyranose oxygen in the most populated conformation. This could be attributed to hydrogen bonding. However, the hydrogen bond would be within an unfavorable 5-membered ring and cannot form a 180° O—H—O bond angle. Indeed, molecular mechanics calculations with the hydrogen bonding term turned off indicated that the hydrogen bonding term lowers the energy by less than 0.2 kcal/mol.[15] A more reasonable explanation may be that the orientation places the OH and CO dipoles in opposite directions.

A second conformation (number 6, Table 1, 3.7%) is capable of forming a 6-membered ring hydrogen bond to the acetonide oxygen of carbon 4. However, increased torsional, bending, and dipole terms raise its relative energy. The NMR data in chloroform do not support this conformation as a major contributor.

Summary. Conformational preferences of compound **1** may be determined through a combination of isotope substitution, NMR data, and molecular modeling. The fact that coupling constants may be measured for the hydroxyl proton further allows a determination of its preferred orientation. In both chloroform and DMSO solution the hydroxyl proton does not appear to be evenly distributed among the staggered conformations but is oriented to a remarkably high degree.

Experimental Section

General Comments. All air- and moisture-sensitive materials were handled following standard procedures.[16] Solvents were distilled from an appropriate drying agent, stored over 3A molecular sieves, and handled under a nitrogen atmosphere. 1,2:3,4-Di-*O*-isopropylidine-α-D-galactopyranose, (+)-α-pinene (92% ee), and lithium aluminum deuteride were obtained from Aldrich Chemical Co. 9-BBN was prepared by the method of Soderquist.[17] Proton and carbon NMR spectra were recorded on a JEOL FX 200 (200 MHz), GE QE 300 (300 MHz), or GE QN 500 (500 MHz) spectrometer using Me_4Si as a reference.

Oxidation of 1,2:3,4-Di-*O*-isopropylidine-α-D-galactopyranose.[18] A solution of oxalyl chloride (0.4 mL, 4.6 mmol) in 9 mL of dry dichloromethane under nitrogen was cooled to ca. −55 °C with a $CHCl_3$/liquid N_2 bath. A solution of dimethyl sulfoxide (0.7 mL, 9.8 mmol) in 2 mL of dry CH_2Cl_2 was added dropwise via syringe. Evolution of a gas was observed. After complete addition, the reaction mixture was stirred at ca. −55 °C for 15 min. The title sugar (0.78 g, 3 mmol) was partially dissolved in 4 mL of dry CH_2Cl_2 and became completely homogeneous upon adding 2 mL of dry DMSO. The sugar/CH_2Cl_2/DMSO solution was added dropwise via syringe to the cooled oxalyl chloride/CH_2Cl_2 solution. After complete addition, the reaction mixture was stirred 30 min. at ca. −55 °C. Dry triethylamine (2.8 mL, 20 mmol) was added dropwise via syringe, and after complete addition the reaction mixture was stirred for 20 min at ca. −55 °C. The cold bath was removed, and the resulting milky mixture was allowed to warm over 20 min. Water was added and the organic layer removed, washed with saturated $NaHCO_3$ solution, and extracted with fresh CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and filtered through Celite. The solvent was removed under reduced pressure to afford 0.736 g of a yellow semisolid. Hexanes were added, and the resulting yellowish solids were removed by filtration through Celite. The filtrate was concentrated under reduced pressure. Kugelrohr distillation (108–116 °C pot, ca. 0.01 Torr) afforded 0.632 g (2.45 mmol, 81.7% yield) of the pure aldehyde as a yellow viscous oil. The NMR spectrum agreed with the literature data.[19]

Preparation of Alpine-Borane-*d*; 2-*d*. Dry tetrahydrofuran (40 mL) was placed in a 100-mL reaction flask. Lithium aluminum deuteride (0.689 g, 16.405 mmol) and (+)-α-pinene (8.61 mL, 54.1 mmol) were added under nitrogen. Then 7.483 g (49.21 mmol) of *B*-MeO-9-BBN was added dropwise by means of a syringe. This solution was stirred for about 15 h. A small sample of the product was isolated by extracting an aliquot with water and hexane and drying with potassium carbonate. ^1H NMR (200 MHz) showed there was a small amount of unreacted pinene. Iodomethane (25 mmol) was added, gas was evolved at a moderate rate, and the flask became warm. The product was allowed to cool to room temperature and stirred for 15 h. Water (2 mL) was slowly added to the flask and gas evolved. Then 4 mL of concentrated HCl was added. Hexane was added to the flask and the solution washed two times with water, under a nitrogen atmosphere. The organic layer was dried with potassium carbonate and the hexane removed under reduced pressure to provide 1–*d* which was used directly.

Reduction of Aldehyde 3 with Alpine-Borane-*d*. Alpine-Borane-*d* (0.812 mL, 2.66 mmol) was added to aldehyde **3** (0.342 g, 1.33 mmol), and the mixture was stirred for 13 h. The reaction was quenched by addition of 0.256 mL of acetaldehyde, stirred for 30 min, and then oxidized by sequentially adding 2 mL of THF, 0.9 mL of 3 M NaOH, and 0.9 mL of 30% H_2O_2 dropwise. The product was extracted with diethyl ether and the ether dried (K_2CO_3) and concentrated. The product was isolated using a silica gel column (250–400 mesh) and ethyl acetate, with hexanes solution (1:1) as eluent. A total of 0.202 g, 58% yield, was recovered. The NMR spectrum was identical to the starting material except for the loss of the H_{6R} proton and was in agreement with the literature.[2b]

Molecular Modeling. Conformational searches were performed with the UNIX version of BAKMDL (version KS 2.96[20]) using the MM2 force field of MODEL running on an IBM RS/6000 Model 530. A full description of the conformational search procedure will be published elsewhere.[12] A chair conformation was used as a starting point. Ring conformations were generated by breaking the bond between C_1 and O_5, allowing the remaining bonds to rotate and checking whether or not C_1 and O_5 were within a bonding distance window. Bonds between C_5 and C_6 and C_6—O_6 were rotated using a 120° resolution. A randomly bond-rotated structure was then energy minimized until there was a change of less than 0.01 kcal between minimization cycles and then checked for keeping criteria. On alternate minimization cycles, randomly selected atoms were randomly moved in Cartesian coordinates and the structure energy minimized. The process was continued until 50 duplicates of structures within the lowest 3.5 kcal/mol window were found. These structures were then minimized in a second run and all those within 3.0 kcal/mol kept. In order to find the chair conformations an energy window of 15 kcal/

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[16] Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Boranes*; Wiley: New York, 1975; Chapter 9.

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[19] Horton, D.; Nakadate, M.; Tronchet, J. M. J. *Carbohydr. Res.* **1968**, 7, 56.

[20] BAKMDL and MODEL were kindly provided by Kosta Steliou, Department of Chemistry, Boston University.

mol was used for both cycles of the search. The resulting calculated proton coupling constants were virtually identical. The molecular mechanics calculations used the MM2 force field and a dielectric of 1.5 and included a hydrogen bonding term.

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Supplementary Material Available: Spectral data for compounds **1**, **1**-*d*, and **3** and a printout of calculated coupling constants and torsional angles for compounds **1** and **6** (22 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.