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Absence of Reverse Anomeric Effect in Furanosides

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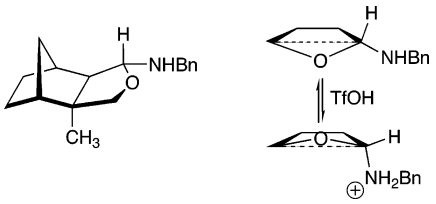

A series of conformationally restricted *N*-"furanosides" has been synthesized, where the carbons of the tetrahydrofuran ring are kept in one plane by a rigid norbornane skeleton, permitting only the ring oxygen to move above or below the tetrahydrofuran ring plane. This causes the substituents of the anomeric carbon to occupy a pseudoaxial or a pseudoequatorial position. On protonation of these "norbornane-furanosides" with trifluoromethanesulfonic acid, all three compounds exhibited decreasing coupling constants for the anomeric proton, indicating a shift toward the pseudoaxial conformation. The coupling constant measurements were supported by volume integration of NOESY cross-peaks, which also showed a change toward the pseudoaxial conformation upon protonation of the nitrogen. These results provide no evidence for the so-called reverse anomeric effect; on the contrary they are in full agreement with a small normal anomeric effect.

Introduction

The anomeric effect, the preference for an electronegative substituent at C_1 of pyranose derivatives to adopt an axial position instead of the sterically more favored equatorial orientation, is a well-established stereoelectronic effect.[1−3] The generalized anomeric effect is an extension to include acyclic systems and rings other than six-membered ones. The anomeric effect has been observed in a number of structural types and is of highest importance for the conformational analysis of biologically important molecules such as carbohydrates and nucleosides.

Two conceptually different theories have been proposed to account for the anomeric effect. Its origin may be found in the destabilization of equatorial substituents due to unfavorable dipole−dipole interactions (Figure 1a). An alternative view is stabilization due to a favorable overlap between one of the ring-oxygen lone pair orbitals and the antibonding σ^* orbital of the axial substituent (Figure 1b).

It was early recognized that some positively charged substituents at C_1 adopted an equatorial orientation, even if other substituents had to adopt axial orientations.[4−7] This phenomenon was first observed in glycosyl pyridinium ions and was attributed to a so-called reverse anomeric effect, indicating a stereoelectronic origin. Fragments of the type $R-O-C-N^{\oplus}$ are found in a number of biologically important systems and would also be important in glycosidic compounds complexed to Lewis acids, thus making the existence of a reverse anomeric effect highly

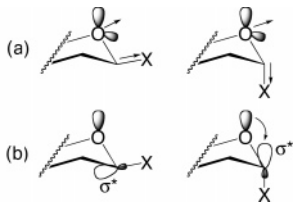

FIGURE 1. Anomeric effect, described by (a) unfavorable dipole−dipole interaction with equatorial substituents; (b) favorable overlap between a filled ring oxygen lone-pair orbital and an empty σ^* orbital.

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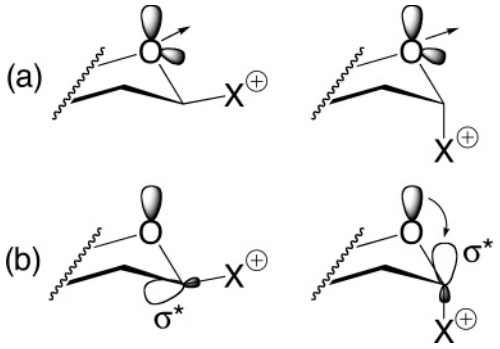

FIGURE 2. Different interpretations of the anomeric effect in a system with a cationic substituent: (a) favorable monopole−dipole interaction with equatorial substituents; (b) favorable overlap between a filled ring oxygen lone-pair orbital and an empty σ^* orbital of the axial cationic substituent.

important.[8] The term reverse anomeric effect has been used in many contexts, for example, to explain the participation of solvents in glycosylation reactions[9,10] and the configuration of anomeric amides.[11] Theoretical interpretations for a reverse anomeric effect are, however, contradictory. The destabilization of equatorial electronegative substituents due to unfavorable dipole−dipole interactions (as seen for a normal anomeric effect) would be diminished with the introduction of a positive charge. The equatorial conformation might in fact be slightly stabilized by attractive electrostatic interactions with the positive charge closer to the negative end of the dipole (Figure 2a). Although electrostatics give some support for a reverse anomeric effect, molecular orbital interactions do not. The introduction of a positive charge makes the substituent even more electronegative, which would actually enhance a normal anomeric effect by lowering the energy of the antibonding σ^* orbital of the axial substituent (Figure 2b).

The experimental support for a reverse anomeric effect derives mainly from experiments using glycosyl imidazoles, where protonation of the distant nitrogen was supposed not to change the size of the substituent.[5,6,12] These experiments have lately been re-examined, indicating a steric origin of the found equatorial orientation of the imidazole moeity.[13] As a result of changes in the solvation shell, the repulsion from a protonated imidazolyl substituent in the axial position of a cyclohexane ring is greater, compared to the unprotonated form.[14]

A series of *N*-(4-*tert*-butylcyclohexyl)anilines was compared with a series of *N*-(tetra-*O*-methylglucopyranosyl)anilines using NMR titrations.[15] In both series there was a shift of the aniline group toward an equatorial orientation upon protonation. However, the shift was smaller for the glucosyl derivatives than for the cyclohexylanilines, consistent with a normal anomeric effect that counteracts the steric hindrance of the protonated

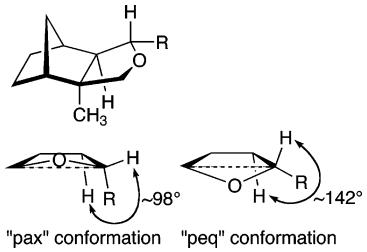

FIGURE 3. Substituent R occupies either a pseudoaxial (pax) or a pseudoequatorial (peq) orientation in a conformationally restricted furanose molecule, where the ring carbons are locked in a planar arrangement. The arrows show the dihedral angle H_5-H_6 that changes when going from the pseudoaxial to the psudoequatorial orientation.

forms. Similar experiments using imidazoles point in the same direction.[16]

NMR titrations were also used to measure differences in the pK_a of α- and β-glucosyl imidazoles. The results indicate that the protonated imidazolyl group has a greater preference for the axial orientation compared to the unprotonated form.[17]

A recent ab initio study of methylated methylendiamines in the gas phase as well as aqueous solution on the HF/6-31G**// HF/6-31G** level showed that less substituted derivatives (e.g., methylenediamine and *N*-methyl-methylenediamine) adopted conformers related to the presence of an anomeric effect.[18] However, sterically crowded analogues (e.g., *N*,*N*,*N*′,*N*′-tetramethyl-methylenediamine) adopted a reverse orientation, indicating that the origin for a reverse anomeric effect is due to steric crowding.

Finally, the reverse anomeric effect has been tested in an innovatively designed conformationally locked azaadamantane system, which showed a clear preference for a conformation favored by a normal anomeric effect.[19,20]

To conclude, there is no proof of a reverse anomeric effect. Most experimental results can be explained by a normal anomeric effect and increased steric bulk of the substituent due to solvation of the positive charge. However, the presence of a reverse anomeric effect is still debated.[21,22]

Most experimental investigations of a reverse anomeric effect have been performed with substituted pyranosides. Unfortunately the number of protected or unprotected hydroxyl groups in the investigated pyranosides makes it difficult to separate a possible reverse anomeric effect from other effects active in carbohydrates. Because of the higher conformational flexibility of five-membered rings, furanosides have received much less attention regarding anomeric effects, compared to pyranosides.

We have earlier used conformationally restricted "norbornane-furanosides" to demonstrate the existence of the anomeric effect in furanosides (Figure 3).[23] The norbornane skeleton is highly rigid and keeps the furanoside ring carbons in one plane, thus allowing only two envelope conformations, with the ring oxygen

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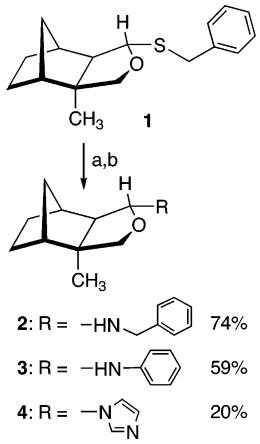
SCHEME 1 [a]



[a] Reagents and conditions: (a) Br_2/CH_2Cl_2, 0 °C, 15 min; (b) Amine, 20 °C, 3−16 h.

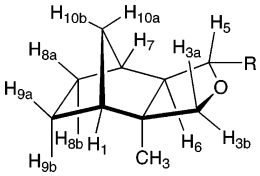


FIGURE 4. Numbering system used for compounds **2**−**4**.

either above or below the ring plane. The anomeric substituent then occupies a pseudoaxial (pax) or pseudoequatorial (peq) orientation. The sterical demand of the anomeric substituent is similar in the two conformers, thus separating stereoelectronic effects from purely steric effects.

Results and Discussion

Three norbornane furanosides with different nitrogen substituents were synthesized (Scheme 1). Compound **1** was synthesized as described[23] and treated with bromine in dichloromethane at 0 °C to give the corresponding anomeric bromide, which was used immediately for the synthesis of compounds **2**−**4**, as depicted in Scheme 1. Treatment of the bromide with benzylamine at room temperature overnight gave compound **2** in 74% yield as an unseparable anomeric mixture (*R*/*S* 5.9:1). Reaction of the bromide with aniline at room temperature overnight gave compound **3** in 59% yield. Treatment of the bromide with imidazole for 3 h at room temperature and subsequent separation of the diastereomers gave **4** in 20% yield (*R*/*S* 9:1) The structures and stereochemistry of all new compounds were determined by NMR analysis, including COSY, NOESY, and HETCOR. The hydrogen atom numbering used is shown in Figure 4.

To find low energy conformers, the conformational space of compound **2** was investigated with the MMFF molecular mechanics force field and with the AM1 semiempirical method. Both methods only yielded envelope conformers with the benzylamino group in pseudoaxial position. Therefore a simplified methylamino analogue was used for the modeling. Four conformers were constructed to be in accord with the expectations of the exo-anomeric effect, and each was geometry optimized at the B3LYP/6-31+G** level of theory, both in gas phase and solvated with carbon tetrachloride.[24] The envelope with the methylamino group in equatorial position was found to be more stable by 0.66 kcal/mol, both with and without solvation.

We have earlier shown, by a combination of molecular modeling, NOE measurements, and X-ray crystallography, that the coupling constant H_5-H_6 of the *O*-furanoside (R = OBn), which occupies the pseudoaxial conformation, was 0, whereas the *C*-furanoside ($R = CH_2CH_2Ph$), which mainly occupies the pseudoequatorial orientation, showed a coupling constant of 7.9.[23] The vicinal proton−proton coupling constants depend on several parameters. The most important is the torsional angle between the protons, which is described by the Karplus equation. However, the substituent electronegativity is also an important contributor, and several generalized Karplus equations have been proposed. The Haasnoot−de Leeuw−Altona equation is the most widely used with empirical group electronegativities (described as substituent parameters λ_i).[25,26] On protonation of the NH_2 group the λ_i value is lowered by 0.28 units, thus making it almost as electronegative as an NO_2 substituent.[27] By using the Haasnoot−de Leeuw−Altona equation we estimate that the proton−proton coupling constants (H_5-H_6) of compounds **2**−**4** would increase by approximately 0.5 Hz as a result of the changed electronegativity on protonation of the nitrogen. An even further increased coupling constant upon protonation would consequently indicate a change in the populations from the pseudoaxial to the pseudoequatorial conformation, which would show the presence of a reverse anomeric effect in this system.

Several different acids (i.e., trifluoroacetic acid, trichloroacetic acid, dichloroacetic acid, and *p*-toluenesulfonic acid) in a variety of deuterated solvents (i.e., $CDCl_3$, acetone-d_6, DMSO-d_6) were used in attempts to perform the titrations of compounds **2**−**4**. In all cases the NMR signals were broadened and coupling constants could not be measured. However, addition of trifluoromethanesulfonic acid (TfOH) in carbon tetrachloride (CCl_4) gave good results with measurable coupling constants. Since the solubility of TfOH in CCl_4 is low, a sonicated emulsion was used. The TfOH/CCl_4 standard solution was sonicated before each addition to maintain the same concentration of TfOH throughout the experiment.

Compounds **2**−**4** were dissolved in $CDCl_3$, the TfOH/CCl_4 standard solution was added in 0.1 equiv increments, and the NMR spectrum was recorded. The coupling constants for H_5-H_6 were determined after each addition and plotted against the addition of TfOH (Figure 5). The NMR titrations for compounds **3** and **4** were discontinued after 0.6 equiv of TfOH because of broadening of the NMR signals that made measuring of the coupling constants impossible. Other coupling constants in compounds **2**−**4** were observed but showed no changes comparable to those of H_5-H_6. On protonation of compounds **2**−**4** with trifluoromethanesulfonic acid, all compounds exhibited decreasing coupling constants (0.6−2.4 Hz) of the anomeric proton, indicating a shift toward the pseudoaxial conformation.

In addition to the study of spin−spin couplings we also studied the change in 1H dipole−dipole interactions in **2** throughout a titration with TFA using the NOESY technique. Five interproton distances in the norbornane skeleton were identified as suitable for the evaluation of NOE interactions and

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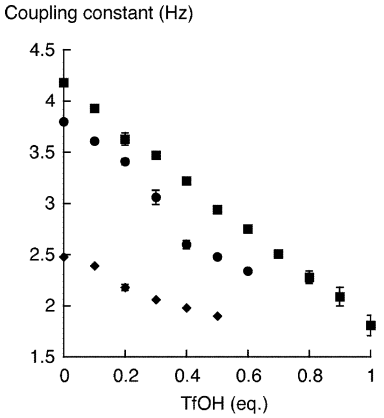

FIGURE 5. Coupling constant (H_5-H_6, Hz) versus addition of TfOH (equiv) for compound **2** (■), compound **3** (●), and compound **4** (♦). The titrations were performed at least three times for each compound. The error bars show standard deviations.

TABLE 1. Calculated Interproton Distances (Å) in Pseudoaxial (pax) and Pseudoequatorial (pex) Orientation

	conformation	
proton distance	pax	peq
$H_{3a}-H_1$	2.46	2.63
H_5-H_6	2.83	3.01
H_5-H_7	2.49	2.65
H_5-H_{10a}	2.83	2.35
$H_{3a}-H_{10a}$	2.67	2.19
$H_{10a}-H_{10b}$	1.78	1.77

the distance $H_{10a}-H_{10b}$, which was expected not to vary with conformational changes, was used as reference for normalization of the NOESY correlations (Table 1). Decreasing NOEs from $H_{3a}-H_1$, H_5-H_6, and H_5-H_7 and increasing NOEs from H_5-H_{10a} and from $H_{3a}-H_{10a}$upon protonation of the nitrogen would indicate a change in the populations from the pseudoaxial to the pseudoequatorial conformation, which would show the presence of a reverse anomeric effect.

Compound **2** was dissolved in $CDCl_3$, TfOH was added in 0.5 equiv increments, and qualitative NOEs were determined from volume integrals of NOESY cross-peaks normalized toward the cross-peak of $H_{10a}-H_{10b}$. The integral values were then plotted against the addition of TfOH (Figure 6). The cross-peaks from $H_{3a}-H_1$, H_5-H_6, and H_5-H_7 increased upon protonation of the nitrogen, whereas the cross-peaks from H_5-H_{10a} and $H_{3a}-H_{10a}$ decreased, which indicates a change in the populations from the pseudoequatorial to the pseudoaxial conformation.

Conclusions

On protonation of compounds **2**−**4** with trifluoromethanesulfonic acid, all compounds exhibited decreasing coupling constants of the anomeric proton, indicating a shift toward the pseudoaxial conformation of the substituent. The coupling constant data were confirmed by a study of NOE interactions. Altogether, these results show no evidence for a reverse anomeric effect. Instead, they are in full agreement with a small normal anomeric effect.

Experimental Section

(−)-(1*S*,2*R*,5*R*,6*R*,7*S*)-5-(*N*-Benzylamino)-2-methyl-4-oxatricyclo [5,2,1,0^{2,6}]-decane (2). Compound **1**[23] (220 mg, 0.8 mmol) was dissolved in CH_2Cl_2 (12 mL) and cooled to 0 °C. A solution of Br_2 in CH_2Cl_2 (1.50 mL, 0.5 M) was added, and the solution was allowed to reach room temperature in 15 min. Benzylamine (0.44 mL, 4.0 mmol) was added, and the mixture was left overnight protected from light. The mixture was chromatographed (SiO_2, 10:1 toluene/acetone) to give **2** (154 mg 74%) as an unseparable diastereomeric mixture (R:S 5.9:1). An analytical sample was recrystallized from heptane at −25 °C. $[\alpha]^{20}_D$ −58.5° (*c* 1.0, $CHCl_3$); mp 72−73.5 °C. ^{1}H NMR ($CDCl_3$): δ 7.23−7.41 (m, 5H, ArH), 4.41 (d, 1H, J = 4.2 Hz, H-5), 4.03, 3.82 (ABq, 1H each, J = 13.2 Hz, H-11), 3.70, 3.56 (ABq, 1H each, J = 9.0 Hz, H-3), 2.21 (bd, 1H, J = 4.0 Hz, H-7), 1.92 (bd, 1H, J = 3.5 Hz, H-1), 1.81 (dp, 1H, J = 10.4 Hz, 1.9 Hz, H-10a), 1.52−1.63 (m, 2H, H-8, H-9), 1.29−1.39 (m, 1H, H-9), 1.25 (dd, 1H, J = 4.0 Hz, 1.4 Hz, H-6), 1.18 (s, 3H, CH_3), 1.06−1.15 (m, 2H, H-8, H-10b). ^{13}C NMR ($CDCl_3$): δ 128.8, 128.64, 128.62, 127.3, 97.6, 78.7, 62.7, 50.2, 49.6, 45.8, 41.4, 36.0, 28.3, 24.5, 24.1. HRMS calcd for $C_{17}H_{23}NO$ (M + H) 258.1858, found 258.1866.

(−)-(1*S*,2*R*,5*R*,6*R*,7*S*)-2-Methyl-5-(*N*-phenylamino)-4-oxatricyclo [5,2,1,0^{2,6}]-decane (3). Compound **1**[23] (64 mg, 0.23 mmol) was dissolved in CH_2Cl_2 (3 mL) and cooled to 0 °C. A solution of Br_2 in CH_2Cl_2 (0.470 mL, 0.5 M) was added, and the solution was allowed to reach room temperature in 15 min. Aniline (0.110 mL, 1.2 mmol) was added, and the mixture was left overnight. The mixture was concentrated, and the residue chromatographed (SiO_2, 10:1 heptane/EtOAc and Al_2O_3, 20:1 heptane/EtOAc) to give **3** (33 mg 59%). An analytical sample was recrystallized from heptane at −25 °C. $[\alpha]^{20}_D$ −159.2° (*c* 0.9, $CHCl_3$); mp 92−94 °C.^{1}H NMR ($CDCl_3$): δ 7.18−7.24 (m, 2H, Ar), 6.76−6.84 (m, 3H, ArH), 5.00 (d, 1H, J = 3.8 Hz, H-5), 4.29 (bs, 1H, NH), 3.75, 3.63 (ABq, 1H each, J = 9.1 Hz, H-3), 2.27 (bd, 1H, J = 4.4 Hz, H-7), 1.98 (bd, 1H, J = 3.9 Hz, H-1), 1.95 (dp, 1H, J = 10.3 Hz, 1.9 Hz, H-10a), 1.57−1.68 (m, 2H, H-8, H-9), 1.35−1.44 (m, 1H, H-9), 1.33 (dd, 1H, J = 3.6 Hz, 1.4 Hz, H-6), 1.25 (s, 3H, CH_3), 1.12−1.22 (m, 2H, H-8, H-10b). ^{13}C NMR ($CDCl_3$): δ 129.7, 119.2, 114.6, 92.2, 79.1, 63.6, 49.8, 45.9, 41.4, 36.1, 28.4, 24.5, 23.9. HRMS calcd for $C_{16}H_{21}NO$ (M) 243.1623, found 243.1629.

(−)-(1*S*,2*R*,5*R*,6*R*,7*S*)-2-Methyl-5-(*N*-imidazolyl)-4-oxatricyclo [5,2,1,0^{2,6}]-decane (4) and (−)-(1*S*,2*R*,5*S*,6*R*,7*S*)-2-Methyl-5-(*N*-imidazolyl)-4-oxatricyclo[5,2,1,0^{2,6}]-decane (4S). Compound **1**[23] (64.5 mg, 0.235 mmol) was dissolved in CH_2Cl_2 (3 mL) and cooled to 0 °C. A solution of Br_2 in CH_2Cl_2 (0.470 mL, 0.5 M) was added, and the solution was allowed to reach room temperature in 15 min. Imidazole (80 mg, 1.17 mmol) was added, and the mixture was stirred for 3 h. The product was concentrated, and the residue was chromatographed (SiO_2, 30:5:1 toluene/MTBE/Et_3N) to give an anomeric mixture (28.5 mg 56%). The mixture was then separated by preparative, centrifugally accelerated, radial thin-layer

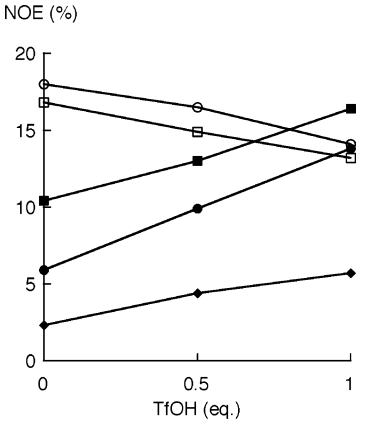

FIGURE 6. Volume integrals of NOESY cross-peaks (%) between $H_{3a}-H_1$ (■), H_5-H_7 (●), H_5-H_6 (♦), $H_{3a}-H_{10a}$ (□), and H_5-H_{10a} (○) versus addition of TfOH (equiv) for compound **2**. The integrals are normalized toward the volume integral of the correlation between $H_{10a}-H_{10b}$ which is considered constant despite conformational changes.

chromatography (20:5:1 → 25:15:2 toluene/MTBE/Et_3N) to give **4** (10.2 mg 20%, R:S 9:1) and **4S** (10.0 mg 19%). An analytical sample of **4S** was crystallized from heptane at −25 °C. Compound **4**: $[\alpha]^{20}_D$ −47.8° (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.63 (s, 1H, H-11), 7.10 (s, 1H, H-12), 7.02 (s, 1H, H-13), 5.48 (d, 1H, J = 2.5 Hz, H-5), 3.86, 3.80 (ABq, 1H each, J = 9.1 Hz, H-3), 2.31 (bd, 1H, J = 4.6 Hz, H-7), 2.05 (bd, 1H, J = 4.7 Hz, H-1), 1.85−1.91 (m, 2H,J = 4.9 Hz, 2.2 Hz, H-6, H-10a), 1.58−1.69 (m, 2H, H-8, H-9), 1.35−1.45 (m, 1H, H-9), 1.24 (s, 3H, CH_3), 1.14−1.30 (m, 2H, H-8, H-10b); ^{13}C NMR ($CDCl_3$) δ 135.9, 130.4, 117.0, 93.8, 81.9, 62.6, 50.2, 46.7, 41.9, 35.7, 28.0, 24.4, 22.9. Compound **4S**: $[\alpha]^{20}_D$ −54.9° (*c* 0.9, $CHCl_3$); mp 99−100 °C; ^{1}H NMR ($CDCl_3$) δ 7.66 (s, 1H, H-11), 7.10 (t, 1H, J = 1.0 Hz, H-12), 7.03 (t, 1H, J = 1.2 Hz, H-13), 5.84 (d, 1H, J = 6.2 Hz, H-5), 3.95, 3.72 (ABq, 1H each, J = 9.2 Hz, H-3), 2.08 (bd, 1H, J = 3.6 Hz, H-7), 1.86−1.91 (m, 1H, H-10a), 1.72 (dd, 1H, J = 6.2 Hz, 1.7 Hz, H-6) 1.65 (bd, 1H, J = 4.5 Hz, H-1), 1.55−1.62 (m, 1H, H-8), 1.44−1.52 (m, 1H, H-9), 1.31−1.40 (m, 1H, H-9), 1.23 (s, 3H, CH_3), 1.11−1.16 (m, 1H, H-10b), 1.00−1.07 (m, 1H, H-8); ^{13}C NMR ($CDCl_3$): δ 135.9, 129.5, 177.4, 90.8, 80.8, 60.1, 50.3, 47.3, 38.1, 36.9, 28.4, 24.5, 22.6. HRMS calcd for $C_{13}H_{18}N_2O$ (M + H) 219.1497, found 219.1498.

NMR Titrations of Compounds 2−4. Compounds **2**−**4** (0.023 mmol each) were dissolved in 0.7 mL of $CDCl_3$ in an NMR tube. A standard solution of TfOH in CCl_4 (0.226 mol/L) was prepared, and 0.010 mL (0.1 equiv) of the standard solution was added each time to the sample, which was thoroughly mixed to give a clear solution. The TfOH/CCl_4 standard solution was sonicated before each addition. The NMR spectrum was recorded, and the coupling constants were measured.

NOESY Experiments. The proton−proton NOE interactions of compound **2** were measured as the volume integrals from NOESY experiments. The NOESY experiments were performed at 500.20 MHz proton resonance frequency and with a sample temperature of 25 °C. Details on the NOESY experiments can be found in Supporting Information.

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Supporting Information Available: General experimental conditions, molecular modeling of a methylamino analogue of compound **2**, ^{1}H NMR spectra of compounds **2**−**4**, data for NMR titrations of compounds **2**−**4**, and NOESY data. This material is available free of charge via the Internet at http://pubs.acs.org.

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