Syntheses of *exo*-3,8-Dioxatricylo[3.2.1.0^{2,4}]octane and 4,7-Dioxatricyclo[3.2.1.0^{3,6}]octane and the Relative Basicities of Their Ethereal Moieties

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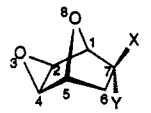
In the gas phase, proton affinities (PA) of cyclic ethers increase with their ring size (PA of oxirane, 189.6[1]; oxetane, 197[2]; tetrahydrofuran (THF), 196.4[3]; tetrahydropyran (THP), 197.1 kcal/mol[3]). From the heat of mixing of cyclic ethers with $CHCl_3$, as well as from the shift in vibrational frequency of OD bond of MeOD with the same ethers, Searles and Tamres[4] showed for the solution that the electron-donor ability of the cyclic ethers follows the order oxetane > THF > THP > oxirane. Similarly, from the equilibrium constants for equilibrium (1) measured in

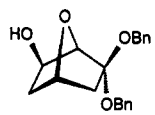
cyclohexane at 20 °C, Taft and co-workers[5] suggested the following order for cyclic of ethers: oxetane > THF > THP.[6] "True" conjugate acids of ethers (dialkyloxonium ions) are formed with strong acids such as H_2SO_4/H_2O[7,8] and SbF_5/HSO_3F[9,10] and can be characterized by NMR.[11] For nonstrained cyclic ethers, their basicity was found to decrease with their ring size, with the order THF > 7-oxabicyclo[2.2.1]heptane ≈ THP > dioxane.[7] Acidic media with Hammett acidity constant[12] H_o <−4 are usually required if one wishes to see about 10% of the oxonium ion at equilibrium with the corresponding ether.[8] Under these conditions strained ethers such as oxirane and oxetane are rapidly decomposed, explaining why the basicity of these cyclic ethers has never been evaluated directly by NMR in strongly acidic solutions.[6b] During our work on the chemistry of the "naked sugars",[13] we observed that the epoxide and oxirane moieties in the tricyclic systems **1** and **2** were relatively little reactive toward strong acids.[14,15] This suggested to us that tricyclic diethers **3** and **4** could be suitable derivatives for evaluating the relative basicity of oxirane, oxetane, and 7-oxabicyclo-[2.2.1]heptane in strongly acidic media. We report here the syntheses of **3** and **4** and shall show that for CF_3SO_3H/CD_2Cl_2 and HSO_3F/CD_2Cl_2 solutions the following order of basicity can be proposed: oxetane > 7-oxabicyclo[2.2.1]-heptane > oxirane.



1 X, Y: CN; OAc
3 X=Y=H
5 X=OH, Y=H
6 X=OC(S)OPh, Y=H
8 X, Y=OBn

2 X=OH
4 X=H
7 X=OC(S)OPh
13 X=OSO_2CF_3

Alcohol **5** obtained in four steps from furan[15] was esterified into **6** (75%) on treatment with PhOC(S)Cl and pyridine in CH_2Cl_2.[16] Radical reduction with Bu_3SnH (benzene, AIBN, 80 °C) afforded the diether **3** (17.5%).[17] Dianhydroviburnitol (**2**)[15] was converted into the corresponding thiocarbonate **7** (98%). Treatment with Bu_3SnH and AIBN in boiling benzene gave only 12% of the volatile diether **4** together with products of decomposition.



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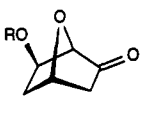
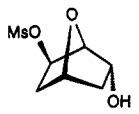


10 R=H
11 R=CH_3SO_2



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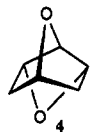

4

A second approach to the synthesis of **4** started with the $LiAlH_4$ reduction (THF, reflux 96 h) of the epoxy acetal **8**[14,18] which led to alcohol **9** (68%). Hydrogenolysis (Pd/C, AcOEt) gave **10** (86%), the mesylation (MsCl, pyridine, CH_2Cl_2, 0 °C) of which afforded **11** (88%). Reduction of the keto moiety of **10** with $NaBH_4$ in MeOH (−78 °C) was stereoselective providing the major endo alcohol **12** (83%)

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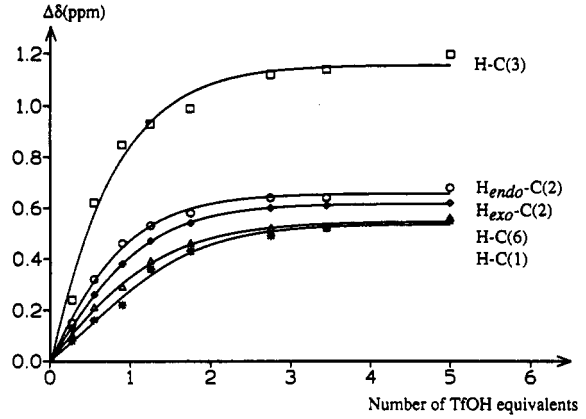

Figure 1. ^{1}H-NMR titration curves for 4 + CF_3SO_3H in CD_2Cl_2 showing acid-induced ^{1}H-chemical shifts.

and its exo stereomer 12′ (17%). The cyclization[19] of 12 into 4 (50%, 20% recovered 12) was accomplished by treatment with KH in THF/Et_2O. Attempts to reduce the triflate 13 with lithium triethylborhydride (superhydride)[20] failed to give 4.

When THF in CD_2Cl_2 (−63 °C) was mixed with increasing amounts of CF_3SO_3H (TfOH), both the H_α and H_β protons were deshielded linearly with the concentration of the acid until 1 equiv of TfOH was added ($\Delta\delta H_\alpha - \Delta\delta H_\beta$ = 0.21 ppm). A plateau was reached when more than 3 equiv of TfOH were added ($\Delta\delta H_\alpha - \Delta\delta H_\beta$ = 0.40 ppm). The same ^{1}H-NMR titration curve (with almost identical figures) was observed for THF mixed with HSO_3F in CD_2Cl_2 at −63 °C ($\Delta\delta H_\alpha - \Delta\delta H_\beta$ = 0.38 ppm in H_2SO_4/H_2O[11]).

Although oxetane was quickly decomposed in the presence of 0.3 equiv of TfOH at −70 °C, the tricyclic diether 3 was moderately stable at −63 °C in CD_2Cl_2 when mixed with less than 0.5 equiv of TfOH or HSO_3F (inductive effect of the oxa bridge on the adjacent oxonium ion). In the presence of 0.5 equiv of TfOH, the acid-induced shifts of H–C(1), H–C(2), H_{endo}–C(6), and H_{exo}–C(6) of 3 were 0.37, 0.29, 0.19, and 0.18 ppm, respectively, leading to the differences $\Delta\delta H_1 - \Delta\delta H_{6exo}$ = 0.19 ppm and $\Delta\delta H_2 - \Delta\delta H_{6exo}$ = 0.11 ppm. With 0.5 equiv of HSO_3F these differences were 0.27 and 0.10 ppm at −63 °C. These data are best interpreted in terms of favored protonation of the 8-oxa bridge rather than the oxirane moiety (3-oxa bridge).

The ^{1}H-NMR titration curves for the mixing of diether 4 with TfOH are reproduced in Figure 1. The acid-induced chemical shifts are definitively larger for the oxetane protons at C(3) and C(5) ($\Delta\delta H_3$) than for the protons at C(2) and C(8) ($\Delta\delta H_2$) and the bridgehead protons at C(1) ($\Delta\delta H_1$) and C(6) ($\Delta\delta H_6$). In the presence of 3 equiv of TfOH, the differential effect $\Delta\delta H_3 - \Delta\delta H_1$ = 0.62 ppm was measured implying preferential protonation of the oxetane moiety (4-oxa bridge) than the 7-oxa bridge. It should be noted also that the induced shifts are nearly the same for H_1 and H_6 and are even smaller than $\Delta\delta H_2$. On mixing 4 with HSO_3F in CD_2Cl_2 (−63 °C) very similar ^{1}H NMR titration curves were recorded.

Our data on the relative basicity of the ethereal moieties in the tricyclic diethers 3 and 4 suggest the order of intrinsic basicities in strongly acidic solutions as oxtane > 7-oxabicyclo[2.2.1]heptane > oxirane, an order parallel to that derived from the relative stabilities of hydrogen-bonded complexes of the parent cyclic ethers with MeOD,[4] $CHCl_3$,[4] and phenols.[5]

Experimental Section

For general remarks, see ref 21.

(1*RS*,2*RS*,4*SR*,5*SR*,7*RS*)-3,8-Dioxatricyclo[3.2.1.0^{2,4}]oct-7-yl *O*-Phenylthiocarbonate (6). Pyridine (3 mL, 37 mmol) and phenoxythiocarbonyl chloride (2.24 mL, 2.8 g, 16 mmol)[16] were added successively to a solution of 5[15] (1 g, 7.8 mmol) in CH_2Cl_2 (60 mL). After being stirred for 4 h at 20 °C, the reaction mixture was evaporated and EtOAc (100 mL) was added. After being washed successively with 1 N HCl (15 mL), 20% aqueous K_2CO_3 solution (15 ml), and saturated aqueous NaCl solution (10 mL, twice) the organic phase was dried ($MgSO_4$) and evaporated. The oily residue was purified by column chromatography on silica gel (EtOAc/light petroleum (1:4)) yielding a yellow solid (1.7 g). Recrystallization from EtOAc/light petroleum gave 1.46 g of colorless crystals, mp 102.5–103.5 °C. Concentration of the mother liquor gave 80 mg: mp 101–103 °C (total yield 75%); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.43 (dd, ^3J = 8, 7.5 Hz, 2 H arom.), 7.31 (t, ^3J = 7.5 Hz, 1 H arom.), 7.10 (d, ^3J = 8 Hz, 2 H arom.), 5.24 (dd, ^3J = 7, 2.5 Hz, HC(7)), 4.80 (s, HC(1)), 4.63 (d, ^3J = 5 Hz, HC(5)), 3.38 (s, HC(2), HC(4)), 2.19 (dd, ^2J = 13.5, ^3J = 7 Hz, H_{endo}C(6)), 2.02 (ddd, ^2J = 13.5, ^3J = 5, 2.5 Hz, H_{exo}C(6)).

***exo*-3,8-Dioxatricyclo[3.2.1.0^{2,4}]octane (3).** $HSnBu_3$ (1.6 mL, 1.76 g, 6 mmol) and azoisobutyronitrile (AIBN, 100 mg, 0.6 mmol) were added to a solution of 6 (810 mg, 3.07 mmol) in PhH (70 ML) at 25 °C. The solution was freed from O_2 by bubbling N_2 for 20 min and then heated under reflux for 2 h. The bulk of benzene was removed by careful distillation at ambient pressure through a Vigreux column, and the residue was purified by column chromatography on silica gel (Lobar, size B, Et_2O/pentane (2:3)), yielding first 75 mg (9%) of starting material and then fractions containing 3. These fractions were concentrated by careful distillation at ambient pressure, and the residue was purified by preparative gas chromatography (SE 30 10% column, 100 °C, retention time ca. 9 min) to yield 60 mg (17.5%) of a white solid: mp 28–31 °C (lit.[17] oil, bp 86 °C (9 Torr)); ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.50 (part of AA′XX′, ^3J(H_{exo}C(6),H_{exo}C(7)) = 11, ^3J(HC(1),H_{exo}C(7)) = 5, ^3J(HC(1),HC(5)) = 1, ^3J(HC(1),H_{exo}C(6)) = 0.5 Hz, HC(1), HC(5)), 3.26 (s, HC(2),HC(4)), 1.70 (m, H_{endo}C(6), H_{endo}C(7)), 1.45 (m, H_{exo}C(6), H_{exo}C(7)).

(1*RS*,2*RS*,4*SR*)-6,6-Bis(benzyloxy)-7-oxabicyclo[2.2.1]-heptan-2-*exo*-ol (9). $LiAlH_4$ (4 g, 105 mmol) was added to a solution of epoxide 8[15] (15 g, 46 mmol) in anhyd THF (80 mL) at 20 °C. The mixture was heated under reflux for 48 h, and $LiAlH_4$ (3.5 g, 92 mmol) was added in two portions. After being heated for 96 h, the mixture was cooled to 0 °C and water (10 mL) was added dropwise cautiously. The mixture was filtered on Celite, the filtration cake was extracted with hot EtOH (250 mL, four times), and the filtrate was evaporated. Column chromatography on silica gel (EtOAc/light petroleum (2:5)) afforded 2.8 g of crude 8 and then 9.5 g of 9 as colorless crystals. The first fraction was purified by column chromatography on silica gel (Lobar, EtOAc/light petroleum (1:6)) giving 0.8 g (5%) of pure 8. The second fraction was recrystallized from Et_2O/light petroleum), giving 8.95 g of white crystals, mp 84–85 °C. After evaporation, the mother liquor was purified by chromatography on silica gel (Lobar, EtOAc/light petroleum (4:1)) and recrystallization from EtOAc/light petroleum giving 0.8 g of colorless crystals, mp 83–84 °C (total yield 65%). A second recrystallization from Et_2O/light petroleum gave an analytical sample: mp 85–86.5 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.7 (t, ^3J = 5.6 Hz, HC(4)), 4.59 (AB, ^2J = 12 Hz, $\nu_0\delta$ = 13.2 Hz, $PhCH_2$), 4.57 (AB, ^2J = 12 Hz, $\nu_0\delta$ = 22.8 Hz, $PhCH_2$), 4.51 (dd, ^3J = 6.7, 2 Hz, HC(2)), 4.47 (s, HC(1)), 2.13 (dd, ^2J = 13, ^3J = 6.8 Hz, H_{endo}C(3)), 2.11 (ddd, ^2J = 12.4, ^3J = 5.6, ^4J = 2 Hz, H_{exo}C(5)), 1.90 (br s, OH), 1.66 (d, ^2J = 12.4 Hz, H_{endo}C(5)), 1.64 (m, H_{exo}C(3)).

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(1*RS*,4*SR*,6*RS*)-6-*exo*-Hydroxy-7-oxabicyclo[2.2.1]heptan-2-one (10). A mixture of **9** (7 g, 21.5 mmol) and 5% Pd/C (200 mg) in EtOAc (70 mL) was pressurized (1 atm) with H_2. After the mixture was stirred at 22 °C for 36 h, H_2 was evacuated and replaced by N_2 and the mixture filtered through Celite. After solvent evaporation, the crude **10** was purified by column chromatography on silica gel (EtOAc/light petroleum (2:1)) yielding 2.45 g of white solid. Recrystallization from EtOAc/light petroleum gave 2.14 g (78%) of colorless crystals, mp 32–33 °C. Concentration of the mother liquor gave 0.22 g (8%): mp 30–32 °C; UV (dioxane) 326 (26), 313 (41), 303 (38), 213 (193); UV (EtOH) 324 (14), 313 (23), 302 (24), 205 (220); ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.05 (br t, ^3J = 5.5 Hz, HC(4)), 4.26 (s, HC(1)), 4.24 (dd, ^3J = 7.0, 3.0 Hz, HC(6)), 2.5 (br s, OH), 2.40 (ddd, ^2J = 17, ^3J = 5.5, ^4J = 2.5 Hz, H_{exo}C(3)), 2.19 (dd, ^2J = 13.6, ^3J = 7.0 Hz, H_{endo}C(5)), 1.92 (d, ^2J = 17 Hz, H_{endo}C(3)), 1.88 (m, H_{exo}C(5)).

(1*RS*,2*RS*,4*SR*)-6-Oxo-7-oxabicyclo[2.2.1]hept-2-*exo*-yl Methanesulfonate (11). Pyridine (12 mL, 0.15 mol) and methanesulfonyl chloride (9.8 mL, 0.126 mol) were added successively to a solution of **10** (6.34 g, 49.5 mmol) in CH_2Cl_2 (100 mL) cooled to 0 °C. After being stirred at 0 °C for 3 h, the mixture was poured into EtOAc (500 mL) and washed successively with 2 M HCl (40 mL, twice) and saturated aqueous $NaHCO_3$ solution (30 mL). The aqueous phases were extracted with EtOAc (120 mL, five times). The combined extracts were dried ($MgSO_4$) and evaporated. The crude product was dissolved in boiling EtOAc (100 mL) and filtered through Celite, light petroleum was added, and the mixture was left overnight at −30 °C. The white crystals obtained were recrystallized from EtOAc/light petroleum giving 8.95 g (88%) of crystals, mp 117–118 °C. The combined mother liquors were evaported and purified by column chromatography on silica gel (Lobar, size C, EtOAc/light petroleum (6:4)) yielding after recrystallization 0.55 g (5%) of a second crop of crystals: mp 116–118 °C; UV (dioxane) 327 (31), 314 (49), 304 (47), 211 (138). UV (EtOH): 327 (22), 315 (40), 305 (42), 201 (155); ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.14 (t, ^3J = 5.5 Hz, HC(4)), 5.07 (dd, ^3J = 6.5, 3 Hz, HC(2)), 4.59 (br s, HC(1)), 3.08 (s, CH_3SO_3), 2.5 (m, ^2J = 17.5, ^3J = 5.5 Hz, H_{exo}C(5)), 2.35 (dd, ^2J = 14, ^3J = 6.5 Hz, H_{endo}C(3)), 2.29 (m, ^2J = 14, ^3J = 5.5, 3 Hz, H_{exo}C(3)), 2.01 (d, ^2J = 17.5 Hz, H_{endo}-C(5)).

(1*RS*,2*SR*,4*SR*,6*SR*)-6-*endo*-Hydroxy-7-oxabicyclo[2.2.1]-hept-2-*exo*-yl Methanesulfonate (12) and (1*RS*,2*SR*,4*SR*,6*RS*)-6-*exo*-Hydroxy-7-oxabicyclo[2.2.1]hept-2-*exo*-yl Methanesulfonate (12′). A solution of ketone **11** (2.24 g, 10.8 mmol) in dry MeOH (450 mL) was cooled to −78 °C (some crystals were formed during the cooling), and $NaBH_4$ (1.2 g, 31.5 mmol) was added. After the solution was stirred at −78 °C for 12 h, $NaBH_4$ (0.7 g, 18.5 mmol) was added and the mixture was left at −78 °C for 11 h. Acetone (10 mL, 136 mmol) was added, the mixture was warmed to −20 °C, AcOH (9 mL, 158 mmol) was added, and the mixture was allowed to reach 20 °C. The mixture was concentrated by evaporation to a volume of 40 mL and filtered through a 30-cm column of silica gel (EtOAc). After evaporation, the eluate was purified by column chromatography on silica gel (Lobar, size C, EtOAc) yielding 1.88 g (83%) of endo alcohol **12** as colorless crystals, mp 87–89 °C, and 0.39 g (17%) of exo alcohol **12′** as colorless crystals, mp 105–07 °C. The endo and exo alcohols had R_f of 0.40 and 0.25, respectively (TLC, silica gel, EtOAc).

Data of **12**. Recrystallization from EtOAc/light petroleum gave 1.82 g (80%) of colorless crystals: mp 90–91 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.58 (dd, ^3J = 7.5, 2.5 Hz, HC(2)), 4.67 (d, ^3J = 5.3 Hz, HC(1)), 4.63 (t, ^3J = 5.5 Hz, HC(4)), 4.45 (ddd, ^3J = 10, 5.3, 3 Hz, HC(6)), 3.08 (s, CH_3SO_3), 2.33 (dd, ^2J = 13.5, ^3J = 7.5 Hz, H_{endo}C(3)), 2.25 (br s, OH), 2.2 (dddd, ^2J = 12.8, ^3J = 10, 5.5, ^4J = 2 Hz, H_{exo}C(5)), 2.1 (m, ^2J = 13.5, ^3J = 5.5, 2.5, ^4J = 2 Hz, H_{exo}C(3)), 1.22 (dd, ^2J = 12.8, ^3J = 3 Hz, H_{endo}C(5)).

Data of **12′**. Recrystallization from AcOEt/light petroleum gave 0.36 g (16%) of colorless crystals: mp 108–109 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.81 (dd, ^3J = 7.2, 3 Hz, HC(2)), 4.75 (t, ^3J = 5 Hz, HC(4)), 4.57 (s, HC(1)), 4.02 (dd, ^3J = 7, 2.5 Hz, HC(6)), 3.05 (s, CH_3SO_3), 2.06 (br s, OH), 1.98 (dd, ^2J = 13.3, ^3J = 7.2 Hz, H_{endo}C(3)), 1.90 (dd, ^2J = 13.3, ^3J = 7 Hz, H_{endo}C(5)), 1.88 (dddd, ^2J = 13.5, ^3J = 5, 3, ^4J = 2.5 Hz, H_{exo}C(3)), 1.57 (ddt, ^2J = 13.3, ^3J = 5, 2.5, ^4J = 2.5 Hz, H_{exo}C(5)).

4,7-Dioxatricyclo[3.2.1.0^{3,6}]octane (4). KH (581 mg, 14.5 mmol, prepared by washing with pentane a 20% dispersion of KH in mineral oil) was added to a solution of alcohol **12** (2.52 g, 12.1 mmol) in 80 mL of THF/Et_2O (1:1). The reaction mixture was stirred at 20 °C for 20 h (50% yield of **4**, measured by analytical GC using decane as internal standard, SE 30 10% column, 110 °C). EtOH (2 mL) and saturated aqueous NH_4Cl solution (20 mL) were added successively. The layers were separated, and the aqueous layer was extracted with Et_2O (50 mL, three times). The combined organic extracts were washed with saturated aqueous NaCl solution (10 mL) and dried ($MgSO_4$), and the solvent was carefully distilled off at ambient pressure through a Vigreux column. The residue was purified by column chromatography on silica gel (Lobar, size B, Et_2O/pentane (1:2)), yielding first 476 mg (19%) of starting material **12** and then fractions containing diether **4**. These fractions were concentrated by careful distillation at ambient pressure, and the residue was purified by preparative gas chromatography (SE 30 10% column, 90 °C, retention time ca. 6 min.) to yield 550 mg (40%) of a white solid: mp 100–102 °C (sealed capillary); IR (KBr) ν 2980, 2930, 1430, 1415, 1330, 1310, 1275, 1255, 1145, 1070, 1040, 1000, 955, 855, 800, 780 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.52 (t, ^3J = 3.5 Hz, HC(6)), 5.04 (br t, ^3J = 4, ^4J(HC(1),HC(3)) ≅ 1 Hz, HC(1)), 4.85 (m, HC(3), HC(5)), 2.11 (d, ^2J = 12.5 Hz, H_{endo}C(2), H_{endo}C-(8)), 1.54 (m, H_{exo}C(2), H_{exo}C(8)); ^{13}C NMR (90.55 MHz, $CDCl_3$) δ 85.55 (dm, ^1J(C,H) = 168 Hz, C(3), C(5)), 78.5 (dm, ^1J(C,H) = 162 Hz), 77.1 (dm, ^1J(C,H) = 164 Hz, C(1), C(6)), 38.7 (br t, ^1J(C,H) = 134 Hz, C(2), C(8)); MS (70 eV) m/z 94 (1.1, $M^{\cdot+}$ − 18), 84 (2), 83 (8), 81 (3), 69 (18), 68 (100), 55 (39). Anal. Calcd for $C_6H_8O_2$ (112.1272): C, 64.27; H, 7.19. Found: C, 64.24; H, 7.12.

Relative Basicity Evaluation by ^{1}H NMR. Aliquots of 0.4 mL of a solution (solution A) of THF, **3**, or **4** (0.174 molar) in CD_2Cl_2 was placed in five 5-mm NMR tubes, which were kept at −78 °C under N_2. Various quantities (0, 40, 80, 130, and 180 μL) of a 0.48 N solution (solution B) of CF_3SO_3H in CD_2Cl_2 were added, and the tubes were sealed under vacuum and kept at −78 °C for 5–10 min before the ^{1}H NMR spectrum was recorded at −63 °C. In other tubes various mixtures of solutions A and B were prepared and the spectra recorded at −63 °C; e.g.: 300 μL of solution A + 200 μL of solution B; 200 μL of solution A + 200 μL of solution B; 200 μL of solution A + 250 μL of solution B; 200 μL of solution A + 350 μL of solution B; 150 μL of solution A + 400 μL of solution B. The acid-induced ^{1}H chemical shifts ($\Delta\delta_H$) were taken as δ_H with the acid − δ_H without acid.

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Supplementary Material Available: IR, ^{13}C, NMR, and MS spectral data and elemental analyses of **3**, **4**, **6**, **9–12**, and **12′** (4 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.