Improved Synthesis of Pseudo-β-D-fructopyranose, a Carbocyclic Monosaccharide, from (-)-Quinic Acid

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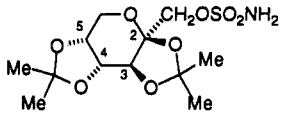
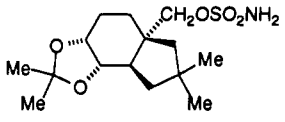
Replacement of the ring oxygen atom of cyclic monosaccharides by a methylene group can provide interesting carbohydrate analogues for biological and structural studies.[1] Our involvement with such carbocyclic isosteres of sugars, which have been referred to as "pseudo-sugars",[2] stemmed from a medicinal chemistry investigation surrounding the clinically useful antiepileptic drug, topiramate (1).[3] We have described the synthesis of topiramate analogue 2 (racemic form), in which three oxygens of topiramate are replaced by methylene groups.[4] Surprisingly, this change resulted in a complete loss of anticonvulsant activity. As a follow-up, we sought to alter just one oxygen atom of topiramate, the one contained within the pyranose ring, to obtain branched-chain cyclitol derivative 3, a carba isostere of topiramate (1), for biological evaluation. This objective necessitated the synthesis of pseudo-β-D-fructopyranose (4).



1 (topiramate)



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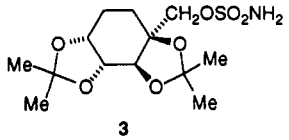

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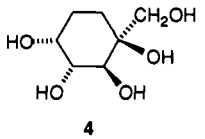

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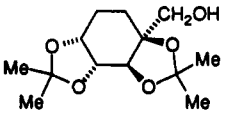
Pseudo-β-D-fructopyranose (4) has been prepared in enantiomerically pure form by two different methods.[1c,5] One route involves a 15-step synthesis beginning with the Diels-Alder reaction of furan and acrylic acid, followed by resolution of the racemic endo cycloadduct.[1c] Unfortunately, the cycloaddition proved inconvenient because it requires a reaction time of 45-75 days; also, we experienced problems with this route due to the instability of certain intermediates. As an alternative, we turned to the 13-step synthesis of 4 that begins with (-)-quinic acid (Scheme 1).[5-7] An advantage of this route is the occurrence of the requisite bis-acetonide structure as a penultimate intermediate (viz. 5, in Scheme 1). This avoids having to perform an independent conversion of 4 to bis-acetonide 6, which would risk the possibility of forming undesired bis-acetonide 7, as well.[8]



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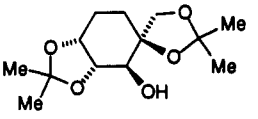

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Our initial assessment of the quinic acid route (Scheme 1) was that it could be streamlined. For example, the acetylation and silylation steps might be viewed as extraneous, and an advantage would be garnered by conducting the deoxygenation at an earlier stage, particularly on hydroxy ester 8. Indeed, Shing and Tang had considered the deoxygenation of 8, but were unable to effect it ("In our hands, attempts to deoxygenate the free alcohol in [this compound] were unsuccessful").[5b] They also proposed that the enoate double bond was the source of the problem and then proceeded to remove it prior to effecting the deoxygenation. Although experimental details for the attempted deoxygenation of 8 are lacking,[5b] we presume that Shing and Tang employed the radical-based method (Bu_3SnH on the phenyl thiocarbonate), which was successfully applied to the preparation of 4 (Scheme 1).

We prepared epishikimate 8 by the reported chemistry and derivatized it with phenyl chlorothioformate/pyridine to thiocarbonate 9 in 67% yield (not optimized). On treatment of 9 with Bu_3SnH (*tert*-butyl peroxide as a radical initiator) for 2 h at 110 °C, we observed little change in the reaction based on TLC (R_f), yet UV visualization of the TLC plate hinted at a difference in the material. Upon workup of the reaction,[9] MS and NMR analysis of the isolated material indicated that 9 had been completely transformed to desired ester 10. Indeed, this deoxygenation reaction is reproducible and isolated yields of 10 have been as high as 76%.

Our successful two-step conversion of 8 to 10 permits one to obtain 6, and thus 4, more expeditiously (Scheme 2). Thus, 10 was oxidized with osmium tetraoxide to diol 11, which was converted with 2-methoxypropene to bis-acetonide 12. Careful reduction of 12 with diisobutylaluminum hydride (DIBAL-H) afforded 6 in good yield. We also synthesized our ultimate target compound, 3, by reacting 6 with sulfamoyl chloride and triethylamine.[10]

(1) (a) Miwa, I; Hara, H.; Okuda, T.; Suami, T.; Agawa, S. *Biochem. Int.* **1985**, *11*, 809-816. (b) Wilcox, C. S.; Gaudino, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 3102-3104. (c) Ogawa, S.; Uematsu, Y; Yoshida, S.; Sasaki, N.; Suami, T. *J. Carbohydr. Chem.* **1987**, *6*, 471-478 and references cited therein.

(2) McCasland, G. E.; Furuta, S.; Durham, L. J. *J. Org. Chem.* **1966**, *31*, 1516-1521.

(3) (a) Maryanoff, B. E.; Nortey, S. O.; Gardocki, J. F.; Shank, R. P.; Dodgson, S. P. *J. Med. Chem.* **1987**, *30*, 880-887. (b) Maryanoff, B. E.; Margul, B. L. *Drugs Future* **1989**, *14*, 342-344. For a clinical update, see: *Drugs Future* **1993**, *18*, 397-398. (c) Shank, R. P.; Gardocki, J. F.; Vaught, J. L.; Davis, C. B.; Schupsky, J. J.; Raffa, R. B.; Dodgson, S. J.; Nortey, S. O.; Maryanoff, B. E. *Epilepsia* **1994**, in press.

(4) Greco, M. N.; Maryanoff, B. E. *Tetrahedron Lett.* **1992**, *33*, 5009-5012.

(5) (a) Shing, T. K. M.; Tang, Y. *J. Chem. Soc., Chem. Commun.* **1990**, 748-749. (b) Shing, T. K. M.; Tang, Y. *Tetrahedron* **1991**, *47*, 4571-4578.

(6) Shing, T. K. M.; Tang, Y. *Tetrahedron* **1990**, *46*, 6575-6584.

(7) For syntheses of other carbocyclic carbohydrate derivatives from (-)-quinic acid, see: (a) Shing, T. K. M.; Cui, Y.; Tang, Y. *Tetrahedron* **1992**, *48*, 2349-2358. (b) Shing, T. K. M.; Cui, Y.; Tang, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 756-757. (c) Shing, T. K. M.; Tai, V. W.-F. *Ibid.* **1993**, 995-997. (d) Maycock, C. D.; Barros, M. T.; Santos, A. G.; Godinho, L. S. *Tetrahedron Lett.* **1993**, *34*, 7985-7988.

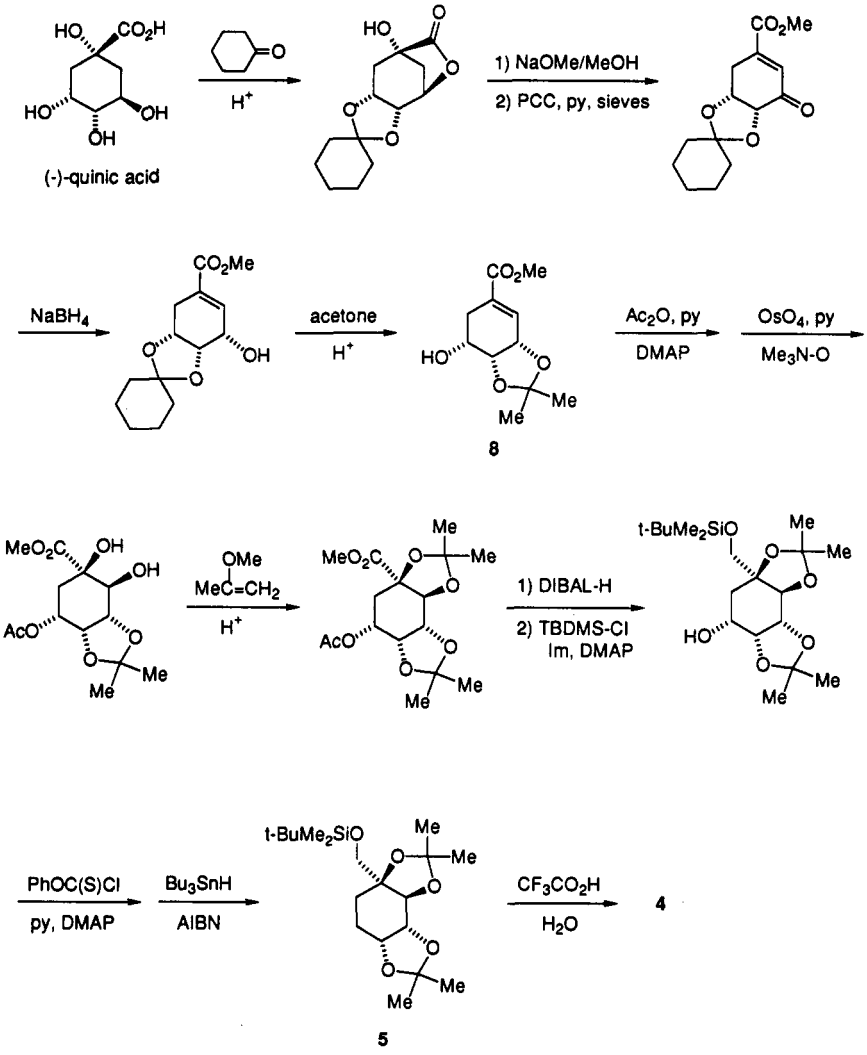
(8) Brady, R. F., Jr. *Carbohydr. Res.* **1970**, *15*, 35. It is not possible to predict whether the reaction of 4 with acetone and acid could be controlled to furnish bis-acetonide 6 selectively, as was the case with D-fructose.

(9) Because the deoxygenation reaction was fairly clean by TLC, we ruled out the idea that the olefin might be causing a problem by serving as a radical trap and thereby affording polymeric material.

(10) The anticonvulsant activity of 3 was significant. We obtained an ED_{50} of 16.6 mg/kg in the standard maximal electroshock seizure (MES) assay on oral dosing in mice at 4 h, which makes 3 approximately 3 times more potent than topiramate.[3a]

0022-3263/94/1959-2652$04.50/0

Scheme 1



In summary, hydroxy enoate 8 was readily deoxygenated by radical-based methodology to enoate 10 in good yield, contrary to what is reported in the literature.[5b] Given this finding, the synthesis of pseudo-β-D-fructopyranose (4) from (−)-quinic acid was improved, such that it can now be performed in 11 steps. A 22% overall yield (unoptimized) was realized for the final six steps of the synthesis, from 8 to 4.

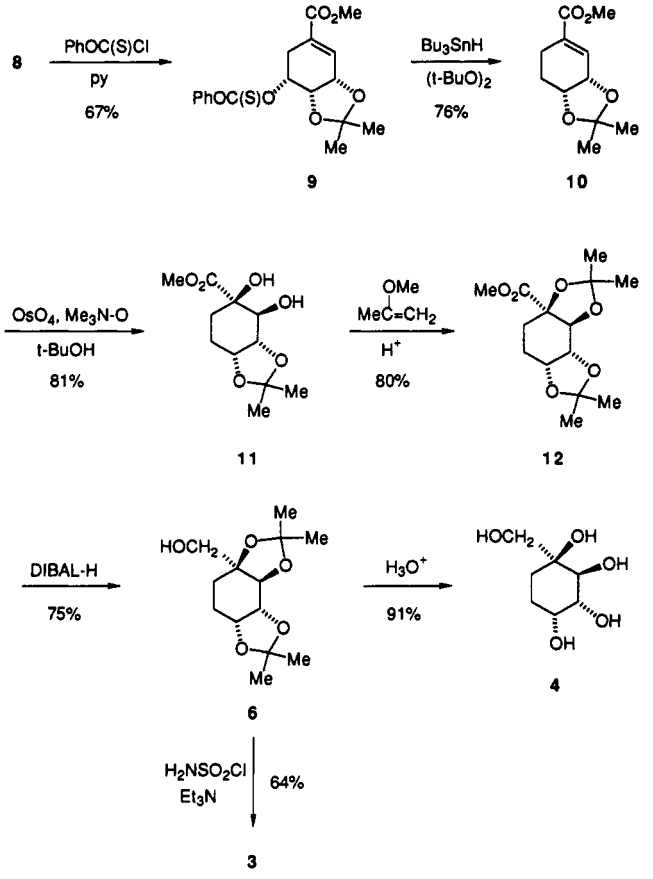
Experimental Section

General Methods. All melting points are corrected by calibration to a set of reference standards. ^{1}H NMR spectra were obtained at 300.13 MHz in $CDCl_3$ (unless otherwise indicated) with Me_4Si as an internal reference (NMR abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet, br = broadened). Chemical-ionization mass spectra (CI-MS) were recorded with CH_4 or NH_3 as the reagent gas. Preparative HPLC separations were performed on silica gel columns with a Waters Prep 500A instrument. TLC analyses were performed on Whatman 250-μm silica gel plates with visualization by UV fluorescence, iodine staining, and/or sulfuric acid charring; the products reported were generally homogeneous by TLC. Preparative TLC purifications were performed on Analtech 1000-μm silica gel GF plates.

(1*R*,2*R*,3*S*)-1-*O*-(Phenoxythionocarbonyl)-2,3-*O*-isopropylidene-5-(methoxycarbonyl)-4-cyclohexene-1,2,3-triol (9). (1*R*,2*R*,3*S*)-2,3-*O*-Isopropylidene-5-(methoxycarbonyl)-4-cyclohexene-1,2,3-triol[5,6] (8) (1.56 g, 6.8 mmol), pyridine (2.16 g, 27 mmol), and a catalytic amount of 4-(dimethylamino)pyridine were dissolved in CH_2Cl_2 (35 mL) and phenyl chlorothioformate (1.77 g, 10.2 mmol) was added slowly under argon at 23 °C. After 2 h, the reaction mixture was poured into saturated aqueous NH_4Cl (200 mL) and diluted with CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated in vacuo to a yellow oil (3.00 g), which was purified by preparative HPLC (ethyl acetate/hexane, 1:8) to afford a white solid (1.66 g, 67%). Recrystallization from CH_2Cl_2/2-propanol gave analytically pure material: mp 123–125 °C; CI-MS (CH_4) *m/z* 365 (MH^+); ^{1}H NMR δ 1.42 (s, 3 H), 1.45 (s, 3 H), 2.77 (m, 1 H), 3.00 (dd, 1 H, *J* = 16.5, 5.5 Hz), 3.80 (s, 3 H), 4.67 (br d, 1 H, *J* = 3.4 Hz), 4.85 (br m, 1 H), 5.60 (ddd, 1 H, *J* = 10.1, 5.5, 2.3 Hz), 6.81 (m, 1 H), 7.13 (dd, 2 H, *J* = 7.4, 1.2 Hz), 7.31 (dd, 1 H, *J* = 7.3, 7.4 Hz), 7.43 (dd, 2 H, *J* = 7.4, 8.0 Hz);[11] $[\alpha]^{20}_D$ −6.07° (*c* 0.692, MeOH). Anal. Calcd for $C_{18}H_{20}O_6S$: C, 59.33; H, 5.53. Found: C, 59.22; H, 5.48.

(1*R*,2*S*)-1,2-*O*-Isopropylidene-4-(methoxycarbonyl)-3-cyclohexene-1,2-diol (10). Thiocarbonate 9 (1.53 g, 4.2 mmol), tributyltin hydride (1.83 g, 6.3 mmol), and *tert*-butyl peroxide (123 mg, 0.84 mmol) were combined in toluene (80 mL) and heated at reflux for 1.5 h. Upon cooling, the reaction mixture was evaporated in vacuo to a clear oil, which was dissolved in ether (100 mL). The ether solution was washed sequentially with 1 N NaOH (100 mL), water (50 mL), and brine (50 mL), dried ($MgSO_4$), and evaporated in vacuo to give crude product (3.0 g). This was purified by preparative HPLC (ethyl acetate/hexane, 1:8) to afford ester 10 as a clear oil (0.68 g, 76%): CI-MS (CH_4) *m/z* 213 (MH^+); ^{1}H NMR δ 1.37 (s, 3 H), 1.39 (s, 3 H), 1.80 (m, 1 H), 2.05 (m, 1 H), 2.25–2.45 (m, 2 H), 3.76 (s, 3 H), 4.35 (ddd, 1 H, *J* = 3.0, 5.4, 5.4 Hz), 4.59 (m, 1 H, H_2), 6.78 (br s, 1 H, H_3).[11]

Scheme 2



(1*R*,2*R*,3*S*,4*R*)-1,2-*O*-Isopropylidene-4-(methoxycarbonyl)cyclohexane-1,2,3,4-tetrol (11). Enoate **10** (0.66 g, 3.1 mmol) was combined with trimethylamine oxide dihydrate (0.49 g, 4.40 mmol), pyridine (1.50 g, 18.8 mmol), and water (0.30 g, 16.8 mmol) in *tert*-butyl alcohol (30 mL) and then osmium tetraoxide (30 mg, 0.12 mmol) was added at 23 °C. The reaction was heated at reflux for 2 h, cooled, diluted with 20% $NaHSO_3$ (15 mL), and stirred for 30 min at 23 °C. The solution was evaporated in vacuo to a residue, which was partitioned between water and ethyl acetate. The organic extract was washed with brine, dried ($MgSO_4$), and evaporated in vacuo to give a light yellow oil, diol **11** (0.62 g, 81%): CI-MS (CH_4) *m/z* 247 (MH^+); ^1H NMR δ 1.39 (s, 3 H), 1.55 (s, 3 H), 1.65 (m, 1 H), 2.0–2.2 (m, 3 H), 2.28 (d, 1 H, J = 7.2 Hz, OH), 3.28 (s, 1 H, OH), 3.88 (dd, 1 H, J = 7.3, 7.5 Hz), 3.98 (dd, 1 H, J = 5.1, 7.7 Hz), 4.45 (m, 1 H).[11]

(1*R*,2*R*,3*S*,4*S*)-4-(Hydroxymethyl)-1,2:3,4-di-*O*-isopropylidenecyclohexane-1,2,3,4-tetrol (6). 2-Methoxypropene (0.26 g, 3.6 mmol) was added to diol **11** (0.60 g, 2.4 mmol) in CH_2Cl_2 (10 mL) under argon, followed by a catalytic amount of camphorsulfonic acid. After 1.5 h, more 2-methoxypropene (0.13 g, 1.8 mmol) was added and stirring was continued for 1 h. Saturated Na_2CO_3 (5 mL) was added and the organic phase was separated, washed with brine, dried ($MgSO_4$), and evaporated in vacuo to give crude bis-acetonide **12**, as an oil (0.55 g, 80%): CI-MS (CH_4) *m/z* 287 (MH^+); ^1H NMR δ 1.34 (s, 3 H), 1.35 (s, 3 H), 1.47 (s, 3 H), 1.48 (s, 3 H), 1.60–1.90 (m, 3 H), 2.00 (ddd, 1 H, J = 5.3, 15.0, 15.0 Hz), 3.80 (s, 3 H), 4.43 (m, 1 H), 4.50 (dd, 1 H, J = 2.2, 7.6 Hz), 4.71 (d, 1 H, J = 2.2 Hz).[11]

This ester (0.39 g, 1.36 mmol) in THF (7 mL) was cooled to −20 °C (ice/methanol bath), DIBAL-H (2.75 mL, 1 M in THF) was added over 15 min and then the reaction was allowed to warm to 23 °C. After 30 min, the reaction was recooled to −10 °C and another portion of DIBAL-H (2.75 mL) was added. When the reaction was complete (TLC), saturated NH_4Cl (10 mL) was added to the ice-cooled reaction with stirring. The mixture was evaporated in vacuo and the residue was extracted three times with $CHCl_3$ (50 mL). The organic phase was washed with brine, dried ($MgSO_4$), and evaporated in vacuo to a clear oil (0.37 g). This was purified by preparative TLC (ethyl acetate/hexane, 1:2) to afford the alcohol **6**, as a clear viscous oil (0.36 g, 75%): CI-MS (CH_4) *m/z* 259 (MH^+); ^1H NMR δ 1.34 (s, 3 H), 1.40 (s, 3 H), 1.46 (s, 3 H), 1.47 (s, 3 H), 1.60–1.95 (m, 4 H), 2.08 (dd, 1 H, J = 5.7, 7.2 Hz, OH), 3.55 (m, 2 H), 4.27 (d, 1 H, J = 2.7 Hz), 4.44 (m, 1 H), 4.54 (dd, 1 H, J = 2.7, 7.5 Hz).[11]

Pseudo-β-D-fructopyranose (4). Alcohol **6** (24 mg, 0.093 mmol) was dissolved in trifluoroacetic acid/water (1:1 v/v, 2.5 mL) under argon and stirred at 23 °C for 3.5 h.[5b] The solution was evaporated in vacuo to an oil, which was dissolved in ethanol (2 mL) and evaporated in vacuo three times. The material was redissolved in water (5 mL) and washed with CH_2Cl_2 (3 × 0.5 mL). The aqueous solution was lyophilized overnight to afford a white amorphous solid **4** (15.0 mg, 91%): CI-MS (NH_3) *m/z* 179 (MH^+), 196 (MNH_4^+); ^1H NMR (D_2O, HOD as reference) δ 1.50 (m, 1 H), 1.71 (m, 3 H), 3.44 (d, 1 H, J = 11.4 Hz), 3.53 (d, 1 H, J = 11.4 Hz), 3.62 (d, 1 H, J = 9.9 Hz), 3.68 (dd, 1 H, J = 2.6, 10 Hz), 4.03 (br m, 1 H), 4.75 (s, HDO);[11,12] $[\alpha]^{25}_D$ −53° (*c* 0.31, MeOH) [lit.[5b] $[\alpha]_D$ −53° (*c* 0.46, MeOH)].

(1*R*,2*R*,3*S*,4*S*)-[1,2:3,4-Bis(isopropylidenedioxy)cyclohex-4-yl]methyl Sulfamate (3). Alcohol **6** (0.24 g, 0.93 mmol) and triethylamine (0.20 g, 2 mmol) were combined in DMF (6 mL) and cooled to 0 °C under argon; then sulfamoyl chloride (0.215 g, 1.86 mmol) was added and the reaction was stirred for 2 h at 0 °C. Additional triethylamine (0.20 g, 2 mmol) and sulfamoyl chloride (0.215 g, 1.86 mmol) were added and stirring was continued for 1 h at 0 °C. The mixture was partitioned between CH_2Cl_2 and dilute $NaHCO_3$; the organic phase was washed three times with water and once with brine, dried ($MgSO_4$), and evaporated in vacuo to give a viscous oil (0.30 g). The product was purified by preparative TLC (ethyl acetate/hexane, 1:2) to afford **3** as a viscous oil (0.20 g, 64%): CI-MS (NH_3) *m/z* 338 (MH^+); ^1H NMR δ 1.34 (s, 3 H), 1.44 (s, 3 H), 1.45 (s, 3 H), 1.47 (s, 3 H), 1.60–1.90 (m, 4 H), 4.16 (d, 1 H, J = 11.1 Hz), 4.21 (d, 1 H, J = 2.6 Hz), 4.29 (d, 1 H, J = 11.1 Hz), 4.44 (br d, 1 H, J = 7.5 Hz), 4.53 (dd, 1 H, J = 2.6, 7.5 Hz), 4.95 (br s, 2 H, NH_2);[11] $[\alpha]^{25}_D$ +1.20° (*c* 0.5, MeOH). Anal. Calcd for $C_{13}H_{23}NO_7S$: C, 46.28; H, 6.87; N, 4.15. Found: C, 46.08; H, 6.89; N, 4.19.

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Supplementary Material Available: Copies of 300-MHz ^1H NMR spectra for compounds **3**, **4**, **10**, and **12**; ^1H NMR data with signal assignments for compounds **3**, **4**, **6**, and **9–12** (5 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.

(11) See paragraph at the end of this paper regarding supplementary material.

(12) Our ^1H NMR data for **4** are completely consistent with the data reported previously.[5b]