Isomerization of Exocyclic Double Bonds. A Comparison of Homoadamantyl *vs* Protoadamantyl Derivatives

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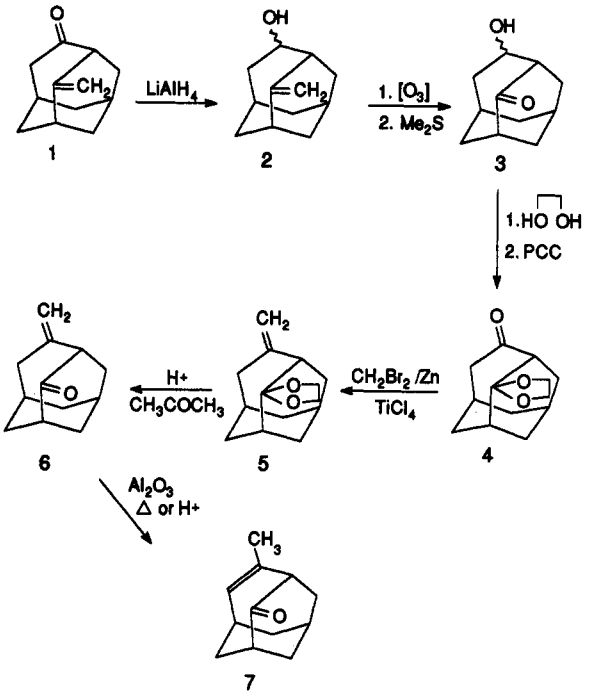
Received July 28, 1993

Isomerizations of olefinic compounds have received much attention in the literature.[2] A study of the isomerization of a series of methylenecycloalkanes in the presence of *p*-toluenesulfonic acid revealed that the *endo*-isomers are always more stable than the *exo*-isomers.[3] It was observed that the *exo*-isomer:*endo*-isomer ratio depends on the ring size. It was found that, in the case of medium-sized rings, the amount of exocyclic isomer present at equilibrium is very small. This was explained by the release of ring strain which accompanies the migration of the double bond from the exocyclic to the endocyclic position. This work has also been extended to the study of double-bond migration in the rigid polycyclic molecules, such as protoadamantane and homoadamantane derivatives. In the protoadamantane derivatives such as **8** and **13** the olefinic moiety is incorporated into six- and/or seven-membered rings, while the exocyclic double bond in **6** and **11** is a part of two seven-membered rings.

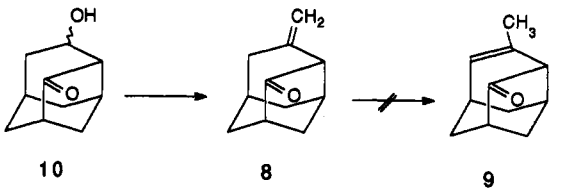
Results and Discussion

The synthesis of 4-methylene-4-homoadamantan-2-one (**6**) is shown in Scheme 1. Lithium aluminum hydride reduction of 2-methylene-4-homoadamantanone (**1**)[4] gave a mixture of alcohols **2** from which the hydroxy ketones **3** and ethylenedioxy ketone **4** were prepared in the usual manner. 4-Methylene-4-homoadamantan-2-one (**6**) was readily prepared from **4** by a Wittig-type carbonyl methylenation using the electrophilic reagent $Zn/CH_2Br_2/TiCl_4$, followed by hydrolysis. 4-Methylene-2-protoadamantanone (**8**)[5] was prepared by the same method, starting from the 4-hydroxy-2-protoadamantanone (**10**), Scheme 2. During chromatography **6** rearranged to **7**, while 4-methylene-2-protoadamantanone (**8**) was completely stable.[6] Methylene ketone **6** was also thermally labile and readily isomerized to the *endo*-isomer **7** above 60 °C. In the presence of a catalytic amount of *p*-toluenesulfonic acid at ambient temperature **6** was rapidly converted into **7** in a quantitative yield. By contrast, 4-methylene-2-protoadamantanone (**8**) was completely inert under these

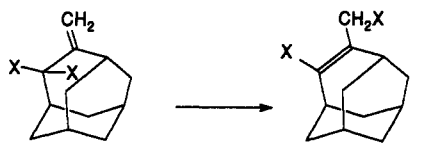
Scheme 1



Scheme 2

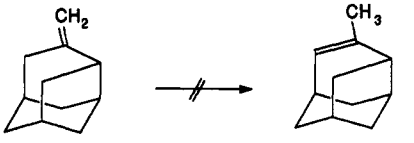


reaction conditions. To compare the protoadamantyl *vs* homoadamantyl system we also prepared 4-methylene-homoadamantane (**11**) and 4-methyleneprotoadamantane (**13**). The *exo*-olefins **11** and **13** were obtained by the Wittig



11a X = H
11b X = D

12a X = H
12b X = D



13 **14**

reaction[7] of the corresponding ketones with methylenetriphenylphosphorane in dry ether. Olefin **13** also could be obtained in the mixture with its *endo*-isomer **14** by dehydration of 4-methyl-4-protoadamantanol with HMPTA at 200 °C in a 1.5:1 ratio, respectively. Acid-catalyzed dehydration of the 4-methyl-4-protoadamantanol gave rise to **13** and **14** in a 3:1 ratio, respectively. It has also been shown that **13** and **14** are the products in the solvolysis of 4-*endo*- and 4-*exo*-4-methylprotoadamantyl and 1-methyl-

(1) (a)Ruder Bošković Institute. (b) The University of Toledo.
(2) For reviews see: Hubert, A. J.; Reimlinger, H. *Synthesis* **1969**, 97; **1969**, 405.
(3) Cope, A. C.; Ambros, D.; Ciganek, E.; Howell, C. F.; Jacura, Z. *J. Am. Chem. Soc.* **1960**, *82*, 1750.
(4) Majerski, Z.; Kostov, V.; Hibšer, M.; Mlinarić-Majerski, K. *Tetrahedron Lett.* **1990**, *31*, 915.
(5) Mlinarić-Majerski, K.; Pavlović, D.; Šindler-Kulyk, M. *J. Org. Chem.* **1993**, *58*, 252.
(6) The migration of the double bond on alumina or silica gel, a general phenomenon for stationary phases containing acid sites, is sometimes troublesome during chromatography of olefins. In the case of the widely used alumina–silica catalyst, it has been suggested that the isomerization takes place via π-complexes at the acidic centers of the catalyst. For references see: (a) Landa, S.; Markovec, L. *Collect. Czech. Chem. Commun.* **1964**, *29*, 2309. (b) Lucchesi, P. J.; Baeder, D. L.; Longwell, J. P. *J. Am. Chem. Soc.* **1967**, *89*, 778.
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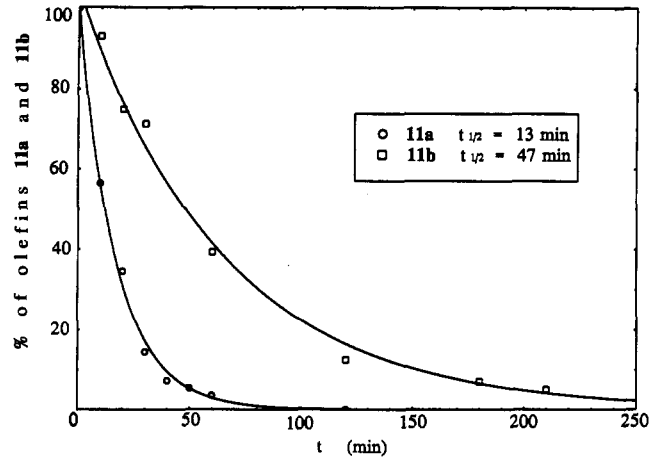
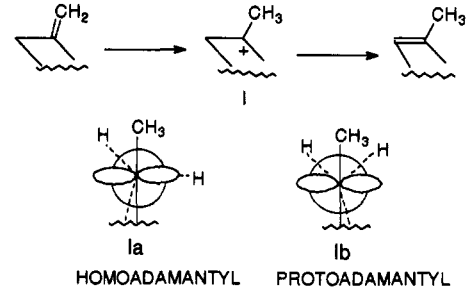


Figure 1. Isomerization rate of **11a** and **11b** to the endocyclic isomers **12a** and **12b** in $CDCl_3$ at 25 °C in the presence of *p*-toluenesulfonic acid. Experimental data points based on ^1H NMR spectra.

2-adamantyl derivatives and that they remain stable under the reaction conditions.[8,9] Deuterium was introduced into molecule **11b** by the standard procedure of treating the corresponding ketone with sodium and D_2O in refluxing dioxane.[10]

We studied the rearrangement of **11** and **13** in the presence of a catalytic amount of *p*-toluenesulfonic acid, as well as thermal rearrangement at 60 °C in deuteriochloroform, and followed the reaction by ^1H NMR spectroscopy. Olefin **13** was stable, while **11** rearranged completely to its *endo*-isomer **12**. In the presence of DABCO (1,4-diazabicyclo[2.2.2]octane) at 60 °C, **11** was stable, which implies that rearrangement at 60 °C in $CDCl_3$ is acid catalyzed. The rates of isomerization of **11a** and **11b** are derived from the plots shown in Figure 1. The least-squares treatment gave an isomerization rate of 8.55×10^{-4} s^{-1} for **11a** and 2.45×10^{-4} s^{-1} for **11b** resulting in a value of $k_H/k_D \cong 3.4$. This value of k_H/k_D is suggestive that the rate-determining step for the acid-catalyzed isomerization of **11** → **12** may be the loss of a β-proton from the intermediate carbocation.

The fact that **6** and **11** isomerize to endocyclic olefins can be explained by the addition of a proton and formation of carbocation **I**. Models show that there should be a difference in the stereochemistry of carbenium ions **Ia** and **Ib** owing to the difference in flexibility of the ethano bridge of the homoadamantyl and protoadamantyl derivatives, respectively. Assuming that in the transition state which permits elimination the leaving proton should be in the plane of the empty orbital of the carbenium ion, then only carbenium ion **Ia** will give rise to endocyclic elimination products. In addition, because of ring strain, the endocyclic isomers **9** and **14** should be less stable than the exocyclic isomers **8** and **13**. It was shown that in the protoadamantene skeleton the molecule is quite strained and the double bond is unsymmetrically disposed.[11] To



prove that this rearrangement is thermodynamically controlled we calculated heats of formation of the isomers **6–9** and **11–14**, as well as expected carbocation intermediates using the AM1 semiempirical method.[12] The results are shown in Table 1. As can be seen, in the protoadamantyl systems, the exocyclic methylene isomers are the same as, or just a little more stable than, the endocyclic isomers. On the other hand, in the homoadamantyl systems, the endocyclic isomers are more stable by 4–5 kcal mol^{-1} than the exocyclic methylene isomers.

In conclusion, we have demonstrated that the migrations of exocyclic double bonds in homoadamantyl and protoadamantyl systems are controlled by thermodynamics and likely proceed through the carbenium ions **I**.

Experimental Section

General. ^1H NMR and ^{13}C NMR spectra were taken on JEOL FX 90Q and Varian Gemini 300 spectrometers. IR spectra were recorded with a Perkin-Elmer 297 spectrophotometer, and mass spectra were recorded on Extrel FTMS 2001 and Shimadzu GC-MS QP-1000 spectrometers. The purity of all compounds was controlled by GC. GC analyses were carried out on a Varian 3300 gas chromatograph with capillary column DB-210.

Methods of Calculation. Estimates of the enthalpies of formation for optimized structures of the species were performed by the AM1 semiempirical molecular orbital method.[12] The calculations were conducted using the MOPAC 5.0 semiempirical molecular orbital package[13] running on a CRAY Y-MP8/864 at the Ohio Supercomputer Center with the Broyden–Fletcher–Goldfarb–Shanno (BFGS) optimization procedure.[14] Geometries were optimized in internal coordinates and were terminated when Herberts test was satisfied in the BFGS method. All optimizations were terminated when the change in energy on successive iterations was less than 0.000 01 kcal mol^{-1} and the change in density matrix elements on two successive iterations was less than 0.001. All calculations were performed with closed-shell structures using the restricted Hartree–Fock (RHF) method[15] with full optimization of all geometrical variables (bond lengths, bond angles, and dihedral angles) without imposition of symmetry restrictions.

4-Homoadamantanone,[16] 4-protoadamantanone,[17] pyridinium chlorochromate (PCC),[18] and Lombardo reagent[19] were prepared according to published procedures.

2-Methylene-4-hydroxyhomoadamantane (2). Following the standard procedure of $LiAlH_4$ reduction of 0.87 g (5.0 mmol) of **1** in dry ether, 0.75 g (85%) of **2** was obtained as a mixture of two isomers in a 1.7:1 ratio. The mixture of isomers was submitted to the next reaction without separation. Spectral data of the mixture of **2**: IR (KBr) 3400, 3070, 2920, 2860, 1645, 1450, 885 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.90 (d, 1H, $=CH_2$ *endo*-isomer), 4.72

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(9) Kovačević, D.; Goričnik, B.; Majerski, Z. *J. Org. Chem.* **1978**, *43*, 4008.
(10) According to the mass spectral analysis 95% of **11b**-d_2 and 5% of **11b**-d_1 were obtained.
(11) For the references of the reactions of protoadamantene in different acids see: (a) Nordlander, J. E.; Haky, J. E.; Lardino, J. P. *J. Am. Chem. Soc.* **1980**, *102*, 7487. (b) Allen, A. D.; Tidwell, T. T. *J. Am. Chem. Soc.* **1982**, *104*, 3145.
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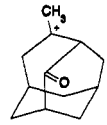
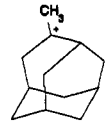
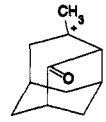
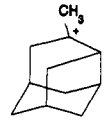
Table 1. Calculated Heats of Formation (ΔH_f)[a] of Homoadamantyl and Protoadamantyl Derivatives

compd	cation I	ΔH_f[a]
6		-44.91
↓		128.59
7		-49.28
11		-20.41
↓		147.14
12		-24.72
8		-32.60
↓		141.29
9		-31.75
13		-8.74
↓		160.64
14		-7.48

[a] Heats of formation are given in kcal mol^{-1}.

(d, 1H, =CH_2 *endo*-isomer), 4.67 (s, 2H, =CH_2 *exo*-isomer), 4.03–3.74 (m, 2H), 2.77–1.30 (m, 30 H); ^{13}C NMR ($CDCl_3$) δ major *exo*-isomer 154.8 (s), 107.7 (t), 75.2 (d), 50.4 (d) 43.6 (t), 39.9 (t), 38.2 (d), 37.4 (t), 36.4 (t), 30.6 (t), 29.5 (d) 26.8 (d); minor *endo*-isomer 151.6, 111.4, 73.5, 49.4, 44.5, 39.0, 37.6, 36.6, 36.1, 29.6, 27.1; HRMS calcd for $C_{12}H_{18}O$ 178.1357, found 178.1355.

***endo*- and *exo*-4-Hydroxy-4-homoadamantan-2-one (3).** The solution of 0.60 g (3.4 mmol) of the mixture of isomers **2** in 20 mL of absolute methanol and 10 mL of dry methylene chloride was cooled to -78 °C, and stream of ozone was bubbled through the solution for 45 min. Then, 0.26 mL (3.6 mmol) of dimethyl sulfide was added, the reaction mixture was warmed to room temperature, and stirring was continued for 1 h. The solvent was removed by evaporation, and the residue was dissolved in 150 mL of ether, washed with saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate. After filtration and evaporation of solvent 0.62 g (100%) of the mixture of **3** was obtained, more than 95% pure by GC. Spectral data of the mixture of **3**: IR (KBr) 3390, 2925, 2860, 1700, 1445 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.27–3.96 (m, 2H), 3.06–1.44 (m, 30H); ^{13}C NMR ($CDCl_3$) δ 217.0, 216.5, 71.2, 69.3, 58.6, 56.8, 45.7, 45.3, 43.1, 42.0, 39.6, 37.1, 36.1, 35.4, 32.6, 31.8, 30.4, 29.6, 28.5 (2C), 26.6, 26.1.

2-(Ethylenedioxy)-4-homoadamantanone (4). Ethylene glycol (0.22 mL, 4.0 mmol) and 20 mg of *p*-toluenesulfonic acid were added to the solution of 0.62 g (3.4 mmol) of **3** in 20 mL of benzene. The reaction mixture was stirred at reflux for 8 h. After cooling and addition of 10 mL of 10% aqueous Na_2CO_3, the mixture was extracted with methylene chloride (3 × 30 mL). The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, and evaporated. The oily residue was dissolved in 10 mL of dry CH_2Cl_2 and added to the mixture of 0.81 g (3.8 mmol) of pyridinium chlorochromate in 10 mL of CH_2Cl_2. The reaction mixture was stirred for 3 h at room temperature, and then 75 mL of dry ether was added. The formed yellowish mixture was filtered through a pad of Florisil, the residue was washed with dry ether (3 × 5 mL), and the combined filtrates were concentrated to give 0.44 g (58%) of **4**.

4: IR (KBr) 2920, 1705, 1450, 1120 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.95 (s, 4H), 2.88–2.71 (m, 1 H), 2.52 (br, s, 2 H), 2.41–1.40 (m, 11 H); ^{13}C NMR ($CDCl_3$) 212.1 (s), 108.7 (s), 64.6 (t), 64.3 (t), 59.4 (d), 49.2 (t), 37.2 (d), 36.6 (t), 33.0 (t), 32.5 (t), 31.5 (t), 26.5 (d), 25.8 (d); HRMS calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1258.

2-(Ethylenedioxy)-4-methylenehomoadamantane (5). To the stirred solution of 0.44 g (2.0 mmol) of keto ketal **4** in 10 mL of CH_2Cl_2 at 0 °C was added 35 mL (15 mmol) of a freshly prepared solution of Lombardo reagent.[19] The reaction mixture was stirred for 2.5 h and then poured into 30 mL of saturated aqueous $NaHCO_3$, extracted with ether (4 × 50 mL), and dried over anhydrous $MgSO_4$. The solvent was evaporated to afford 0.39 g (90%) of **5** as a colorless oil.

5: IR (KBr film) 3070, 2900, 1630, 1450, 1120 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.82–4.57 (m, 2H), 3.91 (s, 4H), 2.88–2.43 (m, 3H), 2.43–1.33 (m, 11H); ^{13}C NMR ($CDCl_3$) δ 150.1 (s), 112.1 (t), 111.4 (s), 64.4 (t), 63.9 (t), 52.0 (d), 41.7 (t), 37.0 (t, 2C), 36.8 (d), 33.8 (t), 32.8 (t), 29.0 (d), 26.8 (d).

4-Methylene-4-homoadamantan-2-one (6). A solution of 0.28 g (1.3 mmol) of **5** in 15 mL of dry acetone and a catalytic amount of *p*-toluenesulfonic acid was stirred at room temperature for 3.5 h, and then 0.33 g (3.9 mmol) of solid $NaHCO_3$ was added. After filtration and evaporation of solvent, 0.20 g (86%) of crude methylene ketone **6** was obtained, 95% pure (by ^{13}C NMR spectra). The spectra of crude product **6**: IR (KBr film) 3070, 2920, 2860, 1710, 1450 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.99 (d, 1H), 4.78 (d, 1H), 3.40 (d, 1H), 2.72–1.55 (m, 13H); ^{13}C NMR ($CDCl_3$) δ 214.2 (s), 145.0 (s), 114.3 (t), 59.7 (d), 45.3 (d), 41.1 (t), 38.8 (t), 37.3 (t), 36.0 (t), 31.8 (t), 28.6 (d), 26.8 (d).

An attempt to get an analytical sample by column chromatography on silica gel or Al_2O_3 (activity II/III) or by sublimation failed. Instead of **6**, **7** was isolated in quantitative yield.

7: IR (KBr) 3010, 2920, 2850, 1705, 1445 cm^{-1}; ^{1}H NMR ($CDCl_3$), δ 5.87 (d, 1H, J = 9.5 Hz), 2.87–1.53 (m, 15H, with distinguished doublet at 1.76 J = 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 211.8 (s), 138.7 (s), 133.2 (d), 56.2 (d), 47.6 (d), 38.4 (t), 36.6 (t), 34.7 (t), 33.6 (t), 30.5 (d), 28.5 (d), 25.1 (q); MS m/z 176 (M^+, 100), 162 (6), 148 (14), 133 (14), 106 (15), 96 (21), 92 (11).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.76; H, 9.16. Found: C, 81.55, H, 9.20.

Spectral Data of 11 and 12. 11a: IR (KBr) 3070, 2910, 2850, 1630, 1445, 875 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.74 (m, 1H), 4.54 (m, 1H), 2.80–2.35 (m, 3H), 2.15–1.30 (m, 13H); ^{13}C NMR ($CDCl_3$) δ 156.8 (s), 108.5 (t), 42.1 (t), 41.9 (d), 37.6 (t, 2C), 37.4 (t, 2C), 35.8 (t), 29.7 (d), 27.2 (d, 2C); MS m/z 162 (M^+, 100), 96 (33), 79 (78).

Anal. Calcd for $C_{12}H_{18}$: C, 88.82; H, 11.04. Found: C, 89.08; H, 11.08.

11b: IR (KBr) 2910, 2850, 2680, 2080, 1630, 1450, 870 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.77 (d, 1H), 4.57 (d, 1H), 2.86–2.49 (m, 1H), 2.15–1.32 (m, 13H); ^{13}C NMR ($CDCl_3$) δ 157.1 (s), 108.9 (t), 42.2 (d), 37.9 (t, 2C), 37.8 (t, 2C), 36.1 (t), 28.8 (d), 27.6 (d, 2C); MS m/z 164 (M^+, 71), 163 (5), 93 (76), 91 (44), 79 (100).

12a: IR (KBr) 3020, 2910, 2840, 1440, 820 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.67 (d, 1H, J = 8.5 Hz), 2.36–1.45 (m, 17H with distinguished doublet at 1.67, J = 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 146.43 (s), 130.75 (d), 38.27 (d), 36.66 (t), 34.39 (t, 2C), 33.11 (t, 2C), 31.39 (d), 29.32 (d, 2C), 25.02 (q); MS m/z 162 (M^+, 92), 147 (48), 133 (22), 119 (30), 105 (68), 91 (96), 79 (100).

Anal. Calcd for $C_{12}H_{18}$: C, 88.82; H, 11.18. Found: C, 88.68; H, 11.00.

12b: ^{13}C NMR ($CDCl_3$) δ 130.8, 38.5, 36.9, 34.7, 33.4, 31.7, 29.6, 24.9 (t, J_{CD} = 19 Hz).

Kinetic Measurements. The rates of isomerization for **11a** and **11b** were measured by ^{1}H NMR spectroscopy in $CDCl_3$ using a JEOL FX90Q spectrometer. The rates were determined by measuring the decrease in concentration of the starting material. The disappearance of substrate was followed by integration of olefinic proton signals relative to the methyl signal of the internal standard, *p*-nitroanisole. Approximately 0.2 mmol of olefins and 0.1 mmol of *p*-nitroanisole were dissolved in 0.5 mL of $CDCl_3$ in an NMR tube. Pseudo-first-order rate constants were obtained from a least-squares treatment of measured kinetic data.

Acknowledgment. This work was supported by the Ministry of Science and Technology of Republic of Croatia, and we are grateful to the Ohio Supercomputer Center for a grant of time on the CRAY Y-MP8/864 computer. We thank Professor James E. Gano for many valuable comments regarding computational chemistry.

Supplementary Material Available: ^{1}H and ^{13}C NMR spectra of **6** and ^{1}H NMR spectra of **11a**, **11b**, **12a**, and **12b** (6 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.