One-Step Conversion of Galanthamine to Lycoraminone: A Novel Hydride-Transfer Reaction

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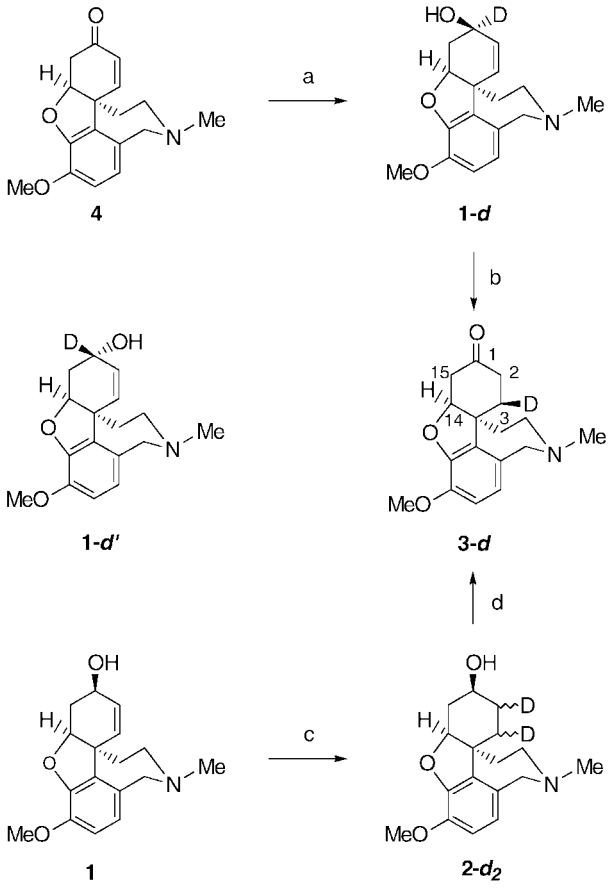
Galanthamine (**1**) and its structurally related compounds such as lycoramine (**2**) are members of the Amaryllidaceae family of alkaloids that have been known for more than 4 decades.[1] There were relatively few publications in the early years, and they were mainly focused on the structure identification[2] and the total synthesis of these alkaloids.[3] Since 1986, galanthamine research was stimulated by the discovery of its acetylcholine esterase inhibition activity and its potential clinical application for the treatment of Alzheimer's disease. Recent work has been focused on its practical synthesis, mechanism of action, pharmacological profile, and structure−activity relationships.[4] In the past few years, a variety of galanthamine derivatives have been synthesized in order to improve potency and to reduce side effects.[4a]

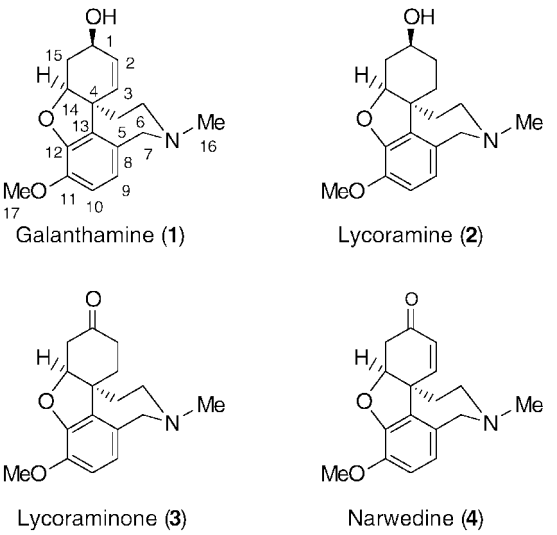
During our development of novel pharmaceuticals for the treatment of Alzheimer's disease, we observed that galanthamine (**1**) was converted to lycoraminone (**3**) in a single step. This transformation normally requires a two-step process involving the oxidation of the allylic alcohol and the reduction of the olefin double bond.[4a] Thus, when **1** was treated with potassium hydride (KH) in toluene in the presence of hexamethylphosphoramide (HMPA) at 60 °C for 4 h, **3** was obtained in 85% yield.[5] The structure of **3** was confirmed by Swern oxidation of **1** to narwedine (**4**) followed by catalytic hydrogenation of **4** to **3**. This reaction represents a novel redox process such that within the same molecule one functional group (−OH) is being oxidized and another functional group (−C=C−) is being reduced. Because of the great mechanistic interest and synthetic potential of such reactions, we decided to further elucidate the stereochemical course and the reaction mechanism of this transformation.

Deuterium-labeled galanthamine (**1-*d***) was thus prepared to probe the reaction process (Scheme 1). Reduc-

Scheme 1[a]



[a] Conditions: (a) $NaBD_4$, CH_3OD; (b) KH, HMPA, toluene, 80 °C, 5 h; (c) D_2, Pd−C, toluene; (d) DMSO, $(COCl)_2$, CH_2Cl_2, then KOH, CH_3OH.



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(3) See ref 2a and (a) Kametani, T.; Shishido, K.; Hayashi, E.; Seino, C.; Kohno, T.; Shibuya, S.; Fukumoto, K. *J. Org. Chem.* **1971**, *36*, 1295. (b) Fuganti, C.; Ghiringhelli, D.; Grasselli, P.; Mazza, M. *Tetrahedron Lett.* **1974**, 2261. (c) Schultz, A. G.; Yee, Y. K.; Berger, M. H. *J. Am. Chem. Soc.* **1977**, *99*, 8066. (d) Sanchez, I. H.; Siria, J. J.; Lopez, F. J.; Larraza, M. I.; Flores, H. J. *J. Org. Chem.* **1984**, *49*, 157. (e) Ackland, D. J.; Pinhey, J. T. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2695. (f) Szewezyk, J.; Lewin, A. H.; Carroll, F. I. *J. Heterocycl. Chem.* **1988**, *25*, 1809. (g) Shieh, W.-C.; Carlson, J. A. *J. Org. Chem.* **1994**, *59*, 5463. (h) Chaplin, D. A.; Fraser, N.; Tiffin, P. D. *Tetrahedron Lett.* **1997**, *38*, 7931.

(4) For reviews, see: (a) Bores, G. M.; Kosley, R. W. *Drugs Future* **1996**, *21*, 621. (b) Mucke, H. A. M. *Drugs Today* **1997**, *33*, 251.

(5) The counterion has a large effect on the reaction. When LiH was used, no reaction occurred. NaH provided reaction product but required a higher temperature. For a similar counterion effect, see: Wilson, S. R.; Mao, D. T.; Jernberg, K. M.; Ezmirly, S. T. *Tetrahedron Lett.* **1977**, 2559.

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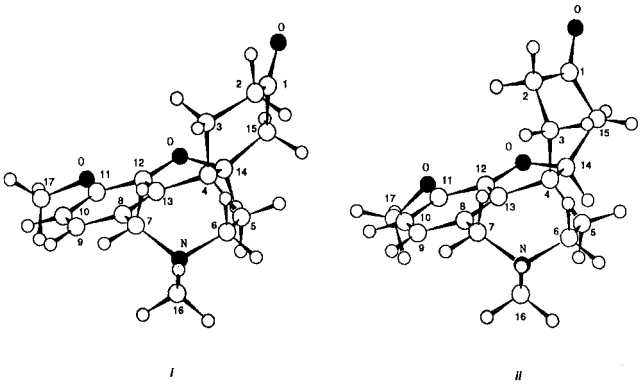
Table 1. ^{1}H and ^{13}C Chemical Shifts of Compound 3 and 3-*d*[a]

	3		**3-*d***	
position	δ C-13	δ H-1	δ C-13	δ H-1
1	208.8		208.8	
2	35.6	a: 2.09 (ddd, J = 18.0, 15.0, 4.0 Hz) e: 2.34 (ddd, J = 18.0, 4.0, 3.6 Hz)	35.6	a: 2.08 (dd, J = 18.0, 15.0 Hz) e: 2.33 (dd, J = 18.0, 3.6 Hz)
3	29.5	a: 1.79 (ddd, J = 15.0, 15.0, 3.6 Hz) e: 2.40 (ddd, J = 15.0, 4.0, 4.0 Hz)	29.3 (t)[b]	a: 1.78 (br dd, J = 15.0, 3.6 Hz)
4	47.5		47.4	
5	36.2	a: 2.26 (ddd, J = 13.5, 13.5, 3.0 Hz) e: 1.66 (br d, J = 13.5 Hz)	36.2	a: 2.25 (ddd, 13.5, J = 13.5, 3.0 Hz) e: 1.62 (br dd, J = 13.5, 3.0 Hz)
6	54.0	a: 3.28 (br dd, J = 13.5, 13.5 Hz) e: 3.15 (br d, J = 13.5 Hz)	54.0	a: 3.24 (br dd, J = 13.5, 13.5 Hz) e: 3.12 (br d, J = 13.5 Hz)
7	59.8	a: 4.16 (d, J = 17.5 Hz) e: 3.70 (d, J = 17.5 Hz)	59.8	a: 4.12 (d, J = 17.5 Hz) e: 3.67 (d, J = 17.5 Hz)
8	131.7		131.7	
9	111.0	6.66 (AB q) with 10	111.0	6.65 (AB q) with 10
10	122.3	6.69 (AB q) with 9	122.3	6.69 (AB q) with 9
11	143.7		143.7	
12	129.0		129.0	
13	146.7		146.7	
14	88.3	4.78 (dd, J = 3.3, 2.7 Hz)	88.3	4.78 (dd, J = 3.4, 2.7 Hz)
15	40.1	a: 2.65 (dd, J = 20.0, 2.7 Hz) e: 3.03 (dd, J = 20.0, 3.3 Hz)	40.1	a: 2.65 (dd, J = 20.0, 2.7 Hz) e: 3.03 (dd, J = 20.0, 3.3 Hz)
16	41.9	2.37 (s)	41.9	2.40 (s)
17	55.9	3.85 (s)	55.9	3.85 (s)

[a] a, axial proton; e, equatorial proton. [b] Triplet and reduced intensity.

tion of **4** with sodium borodeuteride provided deuterium-labeled galanthamine (**1-*d***) and *epi*-galanthamine (**1-*d′***) in an 87:13 ratio. Compound **1-*d*** was isolated and then subjected to rearrangement conditions (KH/HMPA/toluene, 80 °C, 5 h)[6] to provide deuterium-labeled lycoraminone (**3-*d***).[7] All protons and carbons in compound **3** were assigned by COSY and HETCOR experiments through H−H correlation, H−C correlation, and coupling constants (Table 1). The ^{1}H NMR spectrum of **3-*d*** indicated that the peak at 2.40 ppm corresponding to the equatorial proton at the 3-position was completely absent. Meanwhile the peak at 1.79 ppm corresponding to the axial proton at the 3-position remained undiminished. The ^{13}C NMR spectrum of **3-*d*** showed that the peak at 29.5 ppm, corresponding to the 3-carbon, was significantly reduced and was split into a triplet. These data indicated that the deuterium has moved completely to the 3-position. This conclusion was further confirmed by synthesis (Scheme 1). Catalytic deuteration of **1** provided deuterium-labeled lycoramine (**2-*d*$_2$**). Swern oxidation followed by deuterium exchange provided a mixture of **3-*d*** and its C-3 diastereomer.

The ^{1}H NMR data for compound **3-*d*** revealed that the deuterium was completely transferred to the equatorial position on the 3-carbon, and this conclusion was further supported by the deuterium NMR experiments. The deuterium NMR spectrum of **3-*d*** showed only a single peak at 2.39 ppm and no detectable amount of deuterium at any other position indicating a stereospecific reaction. To determine the absolute stereochemistry of **3-*d***, a NOESY experiment was performed. There are four possible conformations for the six-membered ring in compound **3**.[8] The coupling constants between the 14-proton and the two 15-protons are 2.7 and 3.3 Hz, respectively. Only two conformations, i and ii, in which the 14-proton is gauche to both of the 15-protons, are consistent with these coupling constants. The NOEs between protons 3a−15a, 3a−5e, 3a−6a, and 5e−15a indicated that ii is the most favored conformation.[9] Of the four possible conformations, only ii is consistent with all the NOE data. On the basis of NMR experiments, the absolute structure of **3-*d*** was then determined to be as shown in Scheme 1.



The transformation from **1** to **3** represents a formal antarafacial 1,3-hydrogen-transfer reaction process. Conservation of orbital symmetry suggests[10] that a thermally allowed 1,3-hydrogen-transfer reaction requires an antarafacial process, and the stereochemistry of the reaction product (**3-*d***) is in agreement with that. Theoretically, lycoraminone (**3-*d***) can be formed via an antarafacial 1,3-hydrogen transfer reaction from galanthamine alkoxide (**5-*d***) to enolate (**6-*d***) as shown in Scheme 2. However,

(6) The deuterium-labeled compound **1-*d*** reacted substantially slower than the unlabeled compound **1**.

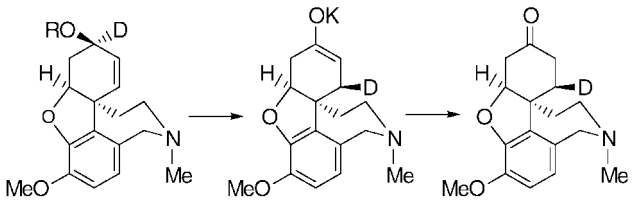
(7) Under the same conditions, **1-*d′*** and the simple 2-cyclohexen-1-ol failed to give hydride-transfer products. The coordination between potassium and the ring oxygen and the methoxy oxygen in compound **1-*d*** may play a key role in this reaction. Such coordination is not possible in **1-*d′***. For a crown ether-promoted anionic rearrangement, see: Bhupathy, M.; Cohen, T. *J. Am. Chem. Soc.* **1983**, *105*, 6978.

(8) For conformations of galanthamine, see: Vlahov, R.; Krikorian, D.; Spassov, G.; Chinova, M.; Vlahov, I.; Parushev, S.; Snatzke, G.; Ernst, L.; Kieslich, K.; Abraham, W.; Sheldrick, W. S. *Tetrahedron* **1989**, *45*, 3329.

(9) Molecular mechanics calculations indicated that ii is about 2.30 kcal/mol more stable than i.

(10) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Academic Press: New York, 1970.

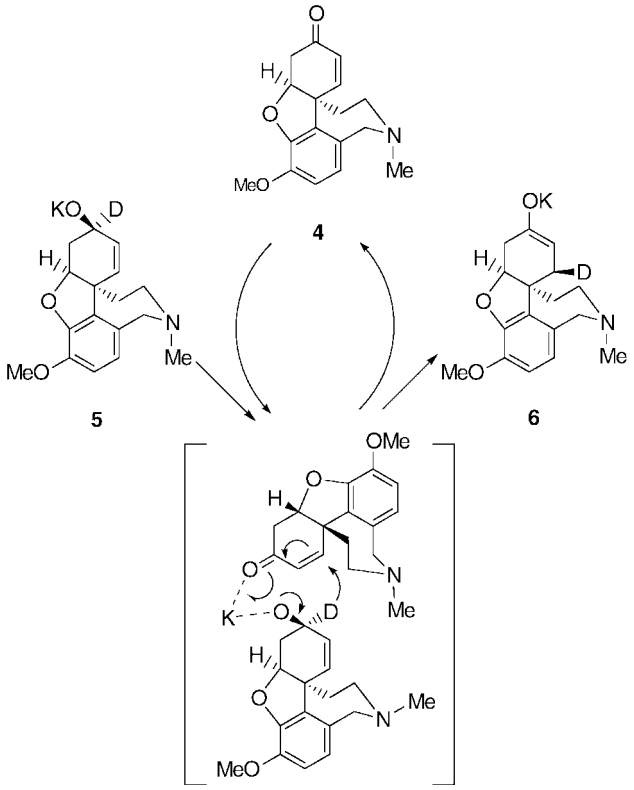
Scheme 2



1-*d*, R = H
5-*d*, R = K

6-*d* **3-*d***

Scheme 3



4 **5** **6**

4+**5** Complex

such a 1,3-antarafacial process suffers a severe steric distortion which makes the necessary transition state highly unfavorable. In fact, such a reaction has never been observed.[11] With that in mind, all the experimental evidence we observed so far supports a Meerwien−Ponndorf−Verley/Oppenauer-like intermolecular hydride-transfer reaction as shown in Scheme 3. The trace amount of narwedine (**4**) that exists in the starting material or is being generated during the reaction initiates a chain process in which alkoxide (**5**) transfers a hydride from its 1-position to the 3-position of **4** stereospecifically. During this process **4** is regenerated and **6** is produced, which is converted to **3** upon aqueous workup. Unlike the Meerwein−Ponndorf−Verley/Oppenauer reaction, the hydride from the alkoxide is transferred to the β-carbon of the α,β-unsaturated ketone instead of the carbonyl carbon.

In conclusion, galanthamine (**1**) was converted to lycoraminone (**3**) in a single step through a novel intermolecular hydride-transfer reaction. In the same reaction, one part of the molecule was reduced while another part of the molecule was oxidized. This transformation represents one of the most efficient and economical processes in that one functional group (−OH) was oxidized by another functional group (−C=C−) of the same molecule.

Experimental Section

Galanthamine (**1**) was prepared in 99% purity from commercial galanthamine hydrobromide.[12] All reactions were carried out in an air-tight flask with nitrogen purge except as otherwise indicated. Reactions were monitored by high-performance liquid chromatography (HPLC) on a Bondclone 10 C18 column with 20:80:0.5:0.5 acetonitrile−H_2O−triethylamine−acetic acid solution as eluting solvent (1.5 mL/min).

Preparation of Narwedine (4). To a stirred solution of oxalyl chloride (6.96 mL, 80.0 mmol) in CH_2Cl_2 (175 mL) at −60 °C was added a solution of DMSO (12 mL) in CH_2Cl_2 (36 mL) over 5 min. The reaction mixture was allowed to warm to −50 °C, and a solution of galanthamine (**1**) (10.0 g, 34.8 mmol) in CH_2Cl_2 (40 mL) was introduced over 5 min. After the reaction mixture had been stirred at −55 to −40 °C for 30 min, Et_3N (50 mL) was added over 20 min, and the mixture stirred for an additional 5 min. The reaction mixture was then allowed to warm to room temperature, and the reaction was quenched with iced water. The mixture was extracted with $CHCl_3$ (50 mL), and the organic phase was then washed with water (50 mL) and brine (50 mL) and dried over Na_2SO_4. After filtration and concentration, an off-white solid was obtained. The crude product was purified by flash column chromatography (silica gel, 1:9 MeOH−CH_2Cl_2) to give narwedine (**4**) (8.82 g, 88%) as a white solid: mp 186−188 °C (lit.[2a] mp 187−189 °C); HPLC retention time 5.12 min; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.96 (dd, 1H, J = 10.4, 2.0 Hz), 6.71 (d, 1H, J = 8.0 Hz), 6.64 (d, 1H, J = 8.0 Hz), 6.22 (d, 1H, J = 10.4 Hz), 4.73 (m, 1H), 4.09 (d, 1H, J = 15.6 Hz), 3.83 (s, 3H), 3.73 (d, 1H, J = 15.6 Hz), 3.15−3.32 (m, 3H), 2.75 (dd, 1H, J = 17.2, 4.0 Hz), 2.44 (s, 3H), 2.27 (ddd, 1H, J = 14.0, 12.4, 4.0 Hz), 1.85 (ddd, 1H, J = 14.0, 4.0, 2.4 Hz).

Preparation of Lycoraminone (3). Narwedine (**4**) (1.42 g, 5.00 mmol) was dissolved in EtOAc (100 mL), and 10% Pd−C (300 mg) was then added under nitrogen. The system was flushed with hydrogen three times and hydrogenated at atmospheric pressure for 20 h. The catalyst was removed by filtration, and the solvent was evaporated. The crude product was purified by flash column chromatography (silica gel, 1:9 MeOH−CH_2Cl_2) to provide lycoraminone (**3**) (1.31 g, 92%) as a white foam: HPLC retention time 4.84 min; for ^{1}H and ^{13}C NMR, see Table 1; IR (KBr) 3050, 1725 cm^{-1}; MS m/z (relative intensity) 288 (13), 287 (M^+, 85), 286 (100), 272 (2), 258 (3), 244 (5), 230 (8), 218 (19), 202 (34), 187 (17).

Reaction of Galanthamine (1). To a suspension of KH (60 mg, 1.50 mmol) in toluene (5.0 mL) under nitrogen at room temperature was added a solution of galanthamine (**1**) (287 mg, 1.00 mmol) in toluene (5.0 mL) over 5 min. HMPA (1.0 mL) was then introduced, and the reaction mixture was stirred at 60 °C for 4 h. The reaction mixture was taken up in EtOAc (50 mL), washed with water (2 × 50 mL) and brine (50 mL), and dried over Na_2SO_4. After the solvent was evaporated, lycoraminone (**3**) (240 mg, 84%) was obtained as an off-white foam: HPLC retention time 4.77 min; ^{1}H NMR and MS identical to those of lycoraminone obtained above (see Table 1).

Preparation of Deuterium-Labeled Galanthamine (1-*d*). To a stirred solution of narwedine (**4**) (1.42 g, 5.00 mmol) in CH_3OD (40 mL) at 0 °C under nitrogen was added $NaBD_4$ (837 mg, 20.0 mmol) in small portions over 1 h. The ice bath was removed, and the reaction mixture was stirred for an additional 10 min at 0−10 °C. Brine (100 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (100 mL). The organic phase was dried over Na_2SO_4 and evaporated to give a white foam.

(11) A formal antarafacial [1,3]-alkyl transfer in an *anti*-7-norbornenol system was reported but was believed to proceed through a fragmentation−recombination pathway; see: Paquette, L. A.; Pierre, F.; Cottrell, C. E. *J. Am. Chem. Soc.* **1987**, *109*, 5731. Paquette, L. A.; DeRussy, D. T. *Tetrahedron* **1988**, *44*, 3139.

(12) Carroll, P.; Furst, G. T.; Han, S. Y.; Joullie, M. *Bull Soc. Chim. Fr.* **1990**, *127*, 769.

Flash column chromatography (silica gel, 1:9 MeOH−CH_2Cl_2) provided **1-*d*** (520 mg, 37%) as a white foam: HPLC retention time 3.73 min; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.64 (AB q, 2H, J = 8.2 Hz), 6.03 (AB q, 2H, J = 10.2 Hz), 4.61 (m, 1H), 4.10 (d, 1H, J = 15.4 Hz), 3.83 (s, 3H), 3.68 (d, 1H, J = 15.4 Hz), 3.27 (m, 1H), 3.05 (m, 1H), 2.65 (m, 1H), 2.40 (s, 3H), 1.95−2.17 (m, 2H), 1.58 (m, 1H); MS (EI) *m*/*z* (relative intensity) 289 (60), 288 (69), 287 (51), 245 (17), 216 (91).

^{1}H NMR (200 MHz, $CDCl_3$) for galanthamine (**1**): δ 6.64 (AB q, 2H, J = 8.2 Hz), 6.03 (m, 2H), 4.61 (m, 1H), 4.15 (m, 1H), 4.10 (d, 1H, J = 15.6 Hz), 3.83 (s, 3H), 3.68 (d, 1H, J = 15.6 Hz), 3.26 (m, 1H), 3.04 (m, 1H), 2.66 (m, 1H), 2.40 (s, 3H), 1.95−2.17 (m, 2H), 1.57 (m, 1H).

Reaction of Deuterium-Labeled Galanthamine (1-*d*). To a suspension of KH (60 mg, 1.50 mmol) in toluene (5.0 mL) under nitrogen at room temperature was added a solution of deuterium-labeled galanthamine (**1-*d***) (288 mg, 1.00 mmol) in toluene (5.0 mL) over 5 min. HMPA (1.0 mL) was then introduced, and the reaction mixture was stirred at 60 °C for 2 h and then at 80 °C for 6 h. The reaction mixture was taken up in EtOAc (50 mL), washed with water (2 × 50 mL) and brine (50 mL), and dried over Na_2SO_4. After the solvent was evaporated, the crude product obtained was purified by flash column chromatography (silica gel, 1:4 MeOH−CH_2Cl_2) to provide **3-*d*** (150 mg, 52%) as a white foam: HPLC retention time 4.77 min; for ^{1}H NMR, see Table 1; ^{2}H NMR (500 MHz, $CHCl_3$) δ 2.39 (br s); MS (EI) *m*/*z* (relative intensity) 290 (13), 289 (53), 288 (M^+, 100), 287 (66), 273 (2), 259 (3), 245 (4), 231 (7), 219 (15), 203 (37), 188 (14).

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Supporting Information Available: Various NMR spectra for compounds **3** and **3-*d*** (13 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.

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