A New Facile Anionic Domino Ring Expansion of Cyclopentanones by Two and Three Carbons for the Flexible Preparation of Functionalized Seven- and Eight-Membered Rings

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The construction of seven- and eight-membered rings remains a significant synthetic challenge since they constitute common structural cores of a large number of biologically important natural and nonnatural products.[1] Among the numerous methods available, ring expansion of relatively strained bicyclic intermediates occupies an important position.[2] Since the pioneer work of De Mayo,[3] one of the most successful approaches for two-carbon ring expansions of cyclopentane derivatives to cycloheptanes is based on ionic, radical, or photochemical fragmentations of cyclobutane-[4] or cyclobutene-containing[5] intermediates. On the other hand, the related three-atom carbocycle enlargement to eight-membered rings generally involves the sequential or in situ ring formation−fragmentation of fused bicyclo[3.3.0]octane intermediates.[6]

We wish to report here a facile one-pot base-induced anionic sequence involving three successive reactions allowing for the efficient synthesis of various seven- and eight-membered rings **4** and **11**−**15** starting from easily accessible cyclopentanone **1**[7] and 1,3- or 1,4-dihalides **2** and **5**−**9** (Scheme 1). The overall transformation, using diazabicycloundecene (DBU) as base, starts with a selective C−C cycloalkylation of **1** leading to the corresponding bridgehead methoxycarbonyl bicyclo[3.2.1]octan-8-ones **3** or bicyclo[4.2.1]nonan-9-ones **10**, which are cleaved in situ by a retro-Dieckmann reaction with MeOH.[8]

The method has been applied to several benzylic or allylic dihalides, and the results are summarized in Table 1. All reactions are unoptimized but give reproducible results under the standard conditions. Interestingly, cyclopentanone **1** reacts with total chemoselectivity with both 1,3- and 1,4-dichlorides **2a** and **5** (entries 1, 4), dibromides **2b**,**c** and **6**−**8** (entries 2, 3, 5−7), or diodide **9** (entry 8) with relative rates in agreement with the scale of electrophilicity of the halogen atom (compare, for example, entries 4, 7, and 8).

Alkylidenecycloheptanes **4** can be obtained in satisfactory yields by using simple 1,3-dihalides **2** (entries 1−3) with a modest regioselectivity depending upon the bulkiness of the substituent R on the double bond (entries 2 and 3). Similarly, new fused monocyclic and polycyclic structures incorporating an eight-membered ring are also easily accessible in good yields (entries 4−8). For example, the bicyclo[6.4.0]dodecane nucleus **12**, present in many important naturally occurring cyclooctanoids,[1b] such as taxane, neolemnanes, and parvifoline, can be obtained either directly from commercially available α,α′-*O*-dibromoxylene **6** (entry 5) or by using the previously reported[8b] reactivity of the synthetically valuable 1,3-exocyclic diene **15** arising from the condensation of **1** with diodide **9** (entry 8).

Interestingly, in the case of indole **7** (entry 6) the fragmentation proceeds with good regioselectivity to give the corresponding fused heterocycles **13a** and its regioisomer **13b** in a 6:1 ratio determined by ^{1}H NMR. It is worth noting that this fused indole substructure is found in caulerpin, a naturally occurring plant growth regulator pigment,[9] and also constitutes the basic skeleton of the

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(1) (a) Devon, T. K.; Scott, A. J. In *Handbook of Naturally Occurring Compounds*; Academic Press: New York and London, 1972; Vol. II. For representative examples of seven-membered rings, see: Ayer, W. A.; Browne, L. M. *Tetrahedron* **1981**, *37*, 2199. Wender, P. A.; McDonald, F. E. *J. Am. Chem. Soc.* **1990**, *112*, 4956. Tori, M.; Nakashima, K.; Takeda, T.; Kan, Y.; Takaoka, S.; Asakawa, Y. *Tetrahedron* **1996**, *52*, 6339. (b) For a review on eight-membered rings, see: Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757.

(2) For reviews on ring expansions, see: Gutsche, C. D.; Redmore, D. *Carbocyclic Ring Expansion Reactions*; Academic Press: New York, 1968; Chapter 9, p 161. Haufe, G.; Mann, G. *Chemistry of Alicyclic Compounds: Structure and Chemical Transformations*; Elsevier Science Publishers: Amsterdam, 1989. Wovkulich, P. M. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I. Eds.; Pergamon: Oxford, 1991; Vol. 1, Chapter 3.3. Hesse, M. *Ring Enlargement in Organic Chemistry*; VCH: Weinheim, 1991. Tochtermann, W.; Kraft, P. *Synlett* **1996**, 1029. For selected recent one-carbon ring expansions, see inter alia: Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *J. Org. Chem.* **1994**, *59*, 4725. Takemoto, Y.; Ohra, T.; Koike, H.; Furuse, S.-I.; Iwata, C. *J. Org. Chem.* **1994**, *59*, 4727. Satoh, T.; Itoh, N.; Gengyo, K.; Takeda, S.; Asakawa, N.; Yamani, Y.; Yamakawa, K. *Tetrahedron* **1994**, *50*, 11839. U, J. S.; Lee, J.; Cha, J. K. *Tetrahedron Lett.* **1997**, *38*, 5233. See also ref 1b.

(3) De Mayo, P. *Pure Appl. Chem.* **1964**, *9*, 597. For a recent review on synthetic applications, see: Winkler, J. D.; Bowen, C. M.; Liotta, F. *Chem. Rev. (Washington, D.C.)* **1995**, *95*, 2003.

(4) For selected recent approaches, see: Hellendahl, B.; Wartenberg, F.-H.; Blechert, S. *Synlett* **1993**, 539. Ranu, B. C.; Das, A. R. *J. Chem. Soc., Perkin Trans. 1* **1994**, 921. Lange, G. L. Gottardo, C. *J. Org. Chem.* **1995**, *60*, 2183. Suginome, H.; Takeda, T.; Itoh, M.; Nakayama, Y.; Kobayashi, K. *J. Chem. Soc., Perkin Trans. 1* **1995**, 49. Zhang, W.; Dowd, P. *Tetrahedron Lett.* **1995**, *36*, 8539. Crimmins, M. T.; Huang, S.; Guise-Zawacki, L. E. *Tetrahedron Lett.* **1996**, *37*, 6519. Li, C.-J.; Chen, D.-L.; Lu, Y.-Q.; Haberman, J. X.; Mague, J. T. *J. Am. Chem. Soc.* **1996**, *118*, 4216.

(5) Chapman, O. L.; Pasto, D. J. *J. Am. Chem. Soc.* **1960**, *82*, 3642. Challand, B. D.; Hikino, H.; Kornis, G.; Lange, G.; De Mayo, P. *J. Org. Chem.* **1969**, *34*, 794. De Mayo, P. *Acc. Chem. Res.* **1971**, *4*, 41. Higo, M.; Sakashita, T.; Toyoda, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 250. Cargill, R. L.; Jackson, T. E.; Peet, N. P.; Pond, D. M. *Acc. Chem. Res.* **1974**, *7*, 106. Clark, R. D.; Untch, K. G. *J. Org. Chem.* **1979**, *44*, 248. Van Audenhove, M.; De Keukeleire, D.; Vandewalle, M. *Bull. Soc. Chim. Belg.* **1981**, *90*, 255. Audenaert, F.; De Keukeleire, D.; Vandewalle, M. *Tetrahedron* **1987**, *43*, 5593. Pak, C. S.; Kim, S. K. *J. Org. Chem.* **1990**, *55*, 1954. Kim, S. K.; Pak, C. S. *J. Org. Chem.* **1991**, *56*, 6829. Ruder, S. M.; Norwood, B. K. *Tetrahedron Lett.* **1994**, *35*, 3473. Ruder, S. M.; Kulkarni, V. R. *J. Org. Chem.* **1995**, *60*, 3084.

(6) Trost, B. M.; Vincent, J. E. *J. Am. Chem. Soc.* **1980**, *102*, 5680. Dowd, P.; Choi, S.-C. *J. Am. Chem. Soc.* **1987**, *109*, 6548. Xie, Z.-F.; Suemune, H.; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1988**, 612. Villagómez-Ibarra, R.; Alvarez-Cisneros, C.; Joseph-Nathan, P. *Tetrahedron* **1995**, *51*, 9285. Dowd, P.; Zhang, W. *Chem. Rev. (Washington, D.C.)* **1993**, *93*, 2091.

(7) Lavoisier-Gallo, T. Ph.D. Thesis, University of Marseille, 1996.

(8) For recent examples of the utilization of related ring cleavages, see: (a) Filippini, M. H.; Faure, R.; Rodriguez, J. *J. Org. Chem.* **1995**, *60*, 6872. Filippini, M. H.; Rodriguez, J. *J. Org. Chem.* **1997**, *62*, 3034. (b) Lavoisier, T.; Rodriguez, J. *Synlett* **1995**, 1241 and references therein.

(9) Raub, M. F.; Cardilla, J. H., III; Schwede, J. G. *Phytochemistry* **1987**, *26*, 619. For other related naturally occurring indole structures, see: Wenkert, E.; Hagaman, E. W.; Kunesch, N.; Wang, N.-Y.; Zsadon, B. *Helv. Chim. Acta* **1976**, *59*, 2711.

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Scheme 1. Domino Reaction Leading to Cycloheptenes 4 and Cyclooctenes 11−15

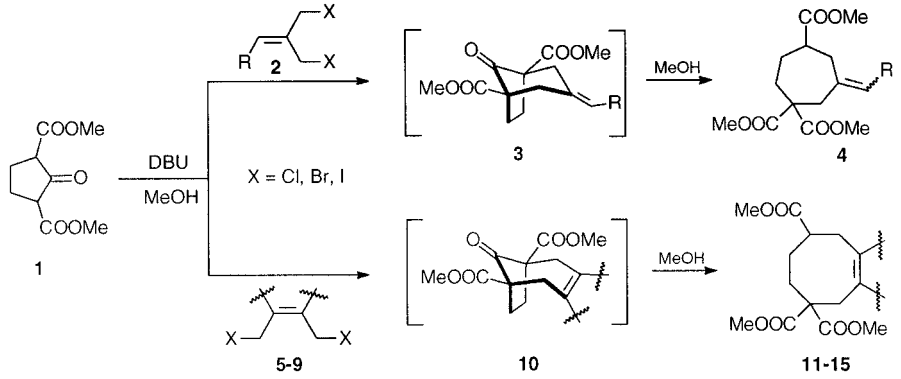

Table 1. Seven- and Eight-Membered Rings (Z = COOMe)[a]

Entry	Halide	t, h	Product (isomer ratio)[b]	Yield (%)[c]
1	**2a**: R = H; X = Cl	26	**4a**	65
2	**2b**: R = C_5H_{11}; X = Br	18	**4b**: (1:1)	78
3	**2c**: R = Ph; X = Br	16	**4c**: (1.8:1)	77
4	**5**	48	**11**	87
5	**6**	18	**12**	68
6	**7**	20	**13a**: (6); **13b**: (1)	81
7	**8**	17	**14**	87
8	**9**	7	**15**	85

[a] All reactions were performed in refluxing MeOH. [b] Determined by ^{1}H NMR of the crude. [c] Isolated.

nonnatural potent tricyclic antidepressant iprindole.[10] Another example of the synthetic potential of the method is the facile construction of eight-membered ring **14** present in the biologically important quinoxaline series.[11]

Our new one-pot two- and three-carbon cyclopentanone enlargement proved to be quite general and allows for the facile construction of relatively complex monocyclic and fused polycyclic seven- and eight-membered rings with promising synthetic and biologic values. Synthetic exploitations of this new anionic domino ring expansion reaction are now under active investigation.

Experimental Section

General Methods. 1,3- and 1,4-Dihalides **2a**, **5**, **6**, and **8** are commercially available and used without further purification. 1,3-Dibromide **2b** was obtained by reaction of the corresponding dichloride[12] with NaBr in acetone under standard conditions, and **2c** was obtained by radical allylic halogenation of 2-methyl-1-phenyl-1-propene (Fluka) under standard protocol.[13] Finally, 1,4-dibromide **7**[14] and diodide **9**[15] were prepared as previously described. Dry MeOH, distilled over magnesium, was used in all condensations. IR spectra were recorded neat or in $CHCl_3$, and NMR spectra were obtained at 200 or 400 MHz in $CDCl_3$ using residual $CHCl_3$ as internal reference.

General Procedure for the Preparation of Seven- and Eight-Membered Rings. To a solution of cyclopentanone dicarboxylate **1** (1 mmol) and DBU (2,5 mmol) in dry MeOH (20 mL) was added, via a syringe, a solution of the corresponding dihalide (1 mmol) in dry MeOH (5 mL). The resulting reaction mixture was stirred at reflux under nitrogen for the indicated time (Table 1). After completion and evaporation of the MeOH under reduced pressure, water (50 mL) was added to the oily residue. Extraction with Et_2O (3 × 40 mL) followed by successive washing with distilled water (2 × 20 mL) and brine (20 mL) gave, after drying ($MgSO_4$) and evaporation of the solvent, the crude compounds, which were purified by flash chromatography on silical gel.[16]

1,1,5-Cycloheptanetricarboxylic acid, 3-methylene trimethyl ester (4a): R_f = 0.5 (diethyl ether−pentane 7/3); IR ($CHCl_3$) ν/cm^{-1} 2953, 1775, 1435, 1196, 909; ^{1}H NMR δ 1.68−1.96 (m, 3H), 2.27−2.65 (m, 4H), 2.79 (s, 2H), 3.65 (s, 6H), 3.70 (s, 3H), 4.85 (s broad, 1H), 4.91 (s broad, 1H); ^{13}C NMR δ 26.3, 32.3, 39.2, 39.5, 44.5, 51.8, 52.5, 52.6, 57.3, 117.0, 142.1, 171.8, 172.2, 175.7. Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.18; H, 7.07.

1,1,5-Cycloheptanetricarboxylic acid, 3-hexylidene trimethyl ester (4b): 1:1 mixture of trans and cis isomers; R_f = 0.71 (diethyl ether−pentane 7/3); IR (neat) ν/cm^{-1} 2956, 1773, 1456, 1271, 922; ^{1}H NMR δ 0.85 (t, broad, J = 7.0, 3H), 1.18−1.40 (m, 6H), 1.78−2.18 (m, 4H), 2.20−2.30 (m, 2H), 2.40−2.66 (m, 2H), 2.74 (s, broad, 1H), 2.88 (m, 1H), 3.70 (4s, 9H), 5.30 (m, 1H); ^{13}C NMR δ 14.0, 22.5, 25.7, 26.7, 27.7, 27.9, 29.1, 29.3, 31.3, 31.4, 31.6, 32.1, 33.1, 41.1, 41.5, 43.4, 45.7, 51.6, 51.7, 52.2, 52.4, 52.51, 52.59, 52.63, 57.8, 131.1, 131.3, 132.0, 171.8, 172.4, 175.7, 176.0. Anal. Calcd for $C_{19}H_{29}O_6$: C, 64.57; H, 8.27. Found: C, 64.66; H, 8.33.

1,1,5-Cycloheptanetricarboxylic acid, 3-benzylidene trimethyl ester (4c): 1.8:1 mixture of trans and cis isomers; R_f

(10) Rice, L. M.; Hertz, E.; Freed, M. E. *J. Med. Chem.* **1964**, *7*, 313. Rosloff, B. N.; Davis, J. M. *Pyschopharmacol. Berlin* **1974**, *40*, 53.
(11) Chung, W.-S.; Liu, J.-H. *J. Chem. Soc., Chem. Commun.* **1997**, 205. Baudy, R. B.; Greenblatt, L. P.; Jirkovsky, I. L.; Conklin, M.; Russo, R. J.; Bramlett, D. R.; Emrey, T. A.; Simmonds, J. T.; Kowal, D. M., Stein, R. P.; Tasse, R. P. *J. Med. Chem.* **1993**, *36*, 331.
(12) Opitz, K.; Schlüter A.-D. *Angew. Chem.* **1989**, *101*, 513; *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 456.
(13) Boeckman, R. K., Jr.; Ko, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 1033.
(14) Mohanakrishnan, A. K.; Srinivasan, P. C. *Synth. Commun.* **1995**, *16*, 2415.
(15) Hamon, D. P. G.; Spurr, P. R. *Synthesis* **1981**, 873.
(16) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

= 0.60 (diethyl ether−pentane 7/3); IR (neat) ν/cm^{-1} 2953, 1734, 1639, 1436, 1168, 701; ^{1}H NMR δ 1.80−2.08 (m, 4H), 2.40−2.70 (m, 3H), 2.80−3.25 (m, 1H), 3.58−3.73 (superposition of 6 s, 9H), 6.40 (s, broad, 1H), 6.49 (s, broad, 1H), 7.25 (m, 5H); ^{13}C NMR δ 26.5, 26.6, 31.3, 32.3, 34.3, 34.5, 41.2, 41.6, 43.9, 45.3, 51.7, 51.8, 52.5, 52.6, 56.2, 57.7, 125.3, 126.4, 126.6, 127.2, 128.1, 128.2, 128.5, 128.6, 128.9, 130.8, 131.3, 134.8, 135.7, 137.3, 137.5, 171.7, 172.1, 172.2, 175.4, 175.6. Anal. Calcd for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71. Found: C, 66.72; H, 6.56.

6-Cyclooctene-1,1,4-tricarboxylic acid, trimethyl ester (11): R_f = 0.48 (diethyl ether−pentane 7/3); IR (neat) ν/cm^{-1} 2954, 1723, 1436, 1242, 1196, 1111, 902; ^{1}H NMR δ 1.55−1.67 (m, 1H), 1.79−1.83 (m, 2H), 1.91−2.05 (m, 1H), 2.11−2.26 (m, 1H), 2.29−2.49 (m, 2H), 2.58−2.80 (m, 2H), 3.64 (s, 3H), 3.70 (s, 6H), 5.56−5.87 (m, 2H); ^{13}C NMR δ 25.4, 28.3, 29.1, 30.1, 45.0, 51.7, 52.5, 52.6, 58.9, 127.8, 131.0, 171.8, 171.9, 175.4. Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.13; H, 7.11.

6,6,9(5*H*)-Benzocyclooctenetricarboxylic acid, 7,8,9,10-tetrahydrotrimethyl ester (12): white crystals, mp 42−44 °C; R_f = 0.21 (diethyl ether−pentane 1/1); IR ($CHCl_3$) ν/cm^{-1} 3466, 2952, 1731, 1493, 1209, 1066, 943; ^{1}H NMR δ; 1.58−1.99 (m, 3H), 2.10 (m, 1H), 2.54 (m, 1H), 2.95 (dd, J = 14.0, 3.8, 1H), 3.07 (dd, J = 14.0, 10.3, 1H), 3.29 (d, J = 14.2, 1H), 3.45 (d, J = 14.2, 1H), 3.69 (s, 3H), 3.73 (s, 3H), 3.74 (s, 3H), 6.91 (d broad, J = 6.3, 1H), 7.06−7.17 (m, 3H); ^{13}C NMR δ 24.8, 28.2, 35.4, 35.6, 47.4, 51.8, 52.5, 57.8, 59.8, 126.9, 127.6, 129.9, 130.3, 135.4, 139.1, 171.3, 171.8, 175.3. Anal. Calcd for $C_{18}H_{22}O_6$: C, 64.66; H, 6.63. Found: C, 64.66; H, 6.69.

Cyclooct[*b*]indoletricarboxylic acid, trimethyl esters (13): 6:1 mixture of two regioisomers; white powder; mp 137−139 °C; R_f = 0.44 (diethyl ether−pentane 9/1); IR (neat) ν/cm^{-1} 2952, 1736, 1604, 1452, 1370, 1176, 750, 732. **Major isomer: 5*H*-cyclooct[*b*]indole-7,10,10(11*H*)-tricarboxylic acid, 5-(benzenesulfonyl)-6,7,8,9-tetrahydrotrimethyl ester (13a):** ^{1}H NMR δ 1.61−2.43 (m, 4H), 2.92−4.00 (m, 5H), 3.57 (s, 3H), 3.71 (s, 3H), 3.73 (s, 3H), 7.16−7.80 (m, 8H), 8.08−8.18 (m, 1H); ^{13}C NMR δ 24.9, 27.0, 27.9, 28.9, 44.5, 52.0, 52.5, 52.9, 59.0, 114.5, 118.8, 133.8, 117.4, 123.3, 124.5, 126.1, 129.4, 133.1, 135.8, 136.2, 139.1, 171.1, 171.8, 175.0. Anal. Calcd for $C_{26}H_{27}NO_8S$: C, 60.81; H, 5.30; N, 2.73. Found: C, 60.82; H, 5.35; N, 2.78. **Minor isomer: 5*H*-cyclooct[*b*]indole-7,7,10(6*H*)-tricarboxylic acid, 5-(benzenesulfonyl)-8,9,10,11-tetrahydrotrimethyl ester (13b):** ^{13}C NMR δ 26.5, 27.2, 28.1, 28.5, 44.8, 51.9, 59.7, 115.7, 118.3, 133.6, 123.4, 123.9, 125.0, 126.2, 128.9, 130.0, 137.0, 137.7, 171.7.

Cycloocta[*b*]quinoxaline-7,7,10(6*H*)-tricarboxylic acid, 8,9,10,11-tetrahydrotrimethyl ester (14): white crystals; mp 121−123 °C; R_f = 0.30 (CH_2Cl_2−MeOH 98/2); IR ($CHCl_3$) ν/cm^{-1} 2951, 1731, 1462, 1284, 1171, 1091, 908; ^{1}H NMR δ 1.22−1.39 (m, 1H), 1.59−1.78 (m, 1H), 1.81−2.36 (m, 2H), 2.73−2.81 (m, 1H), 3.41−3.49 (m, 2H), 3.66 (d, J = 13.6, 1H), 3.72 (s, 3H), 3.78 (s, 3H), 3.79 (s, 3H), 3.88 (d, J = 13.6, 1H), 7.60−7.76 (m, 2H), 7.86−8.13 (m, 2H); ^{13}C NMR δ 25.5, 28.5, 37.4, 39.0, 47.0, 52.1, 52.8, 53.1, 58.9, 127.7, 128.9, 129.6, 129.8, 141.4, 141.6, 152.2, 154.8, 170.6, 171.9, 174.8. Anal. Calcd for $C_{20}H_{22}N_2O_6$: C, 62.15; H, 5.74; N, 7.25. Found: C, 62.17; H, 5.72; N, 7.30.

1,1,4-Cyclooctanetricarboxylic acid, 6,7-bis(methylene)trimethyl ester (15): white needles, mp 84−86 °C; R_f = 0.80 ($CHCl_3$−MeOH 4/1); IR ($CHCl_3$) ν/cm^{-1} 3475, 2845, 1751, 1731, 1435, 1262, 914; ^{1}H NMR (400 MHz) δ 1.57−1.67 (m, 1H), 1.88−1.96 (m, 1H), 2.15−2.19 (m, 2H), 2.34−2.40 (m, 1H), 2.52 (tt, J = 10.9, 3.6, 1H), 2.60 (dd, J = 13.5, 3.4, 1H), 2.80 (d, J = 14.5, 1H), 3.02 (dd, J = 145, 1.0, 1H), 3.65 (s, 3H), 3.67 (s, 3H), 3.69 (s, 3H), 4.72 (m, 1H), 4.87 (m, 1H), 5.21 (d, J = 2.1, 1H), 5.27 (m, 1H); ^{13}C NMR (50 MHz) δ 24.6, 27.7, 35.1, 35.6, 48.9, 51.8, 52.4, 52.7, 58.7, 114.1, 115.4, 145.0, 148.0, 171.2, 171.9, 175.5. Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.91; H, 7.15. Found: C, 61.90; H, 7.17.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for compounds **4** and **11**−**15** (16 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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