Syntheses of Calix[4]naphthalenes Derived from 1-Naphthol

Paris E. Georghiou,* Muhammad Ashram, Zhaopeng Li, and Steven G. Chaulk

Department of Chemistry, Memorial University of Newfoundland, St. John's, Newfoundland, Canada A1B 3X7

Received March 22, 1995 (Revised Manuscript Received July 20, 1995®)

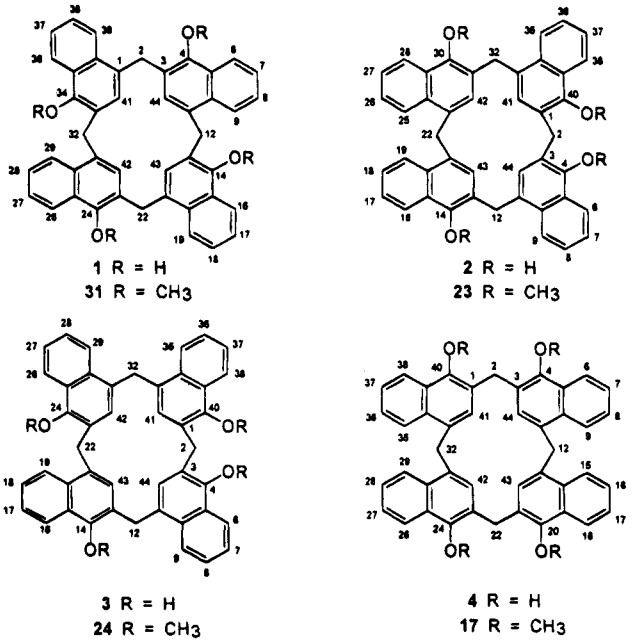
Using a convergent synthetic strategy, the synthesis of the previously elusive C_{4v}-symmetrical calix[4]naphthalene from 1-naphthol is described. Using other independent convergent routes, syntheses of the other three isomeric calix[4]naphthalenes originally formed from the direct base-catalyzed condensation of formaldehyde with 1-naphthol are also described. All of these methods involved either a $TiCl_4$- or TFA-assisted coupling reaction to achieve the cyclization steps. A mechanism is proposed to account for the formation of the original three isomeric calix[4]naphthalenes from the base-catalyzed condensation of formaldehyde with 1-naphthol.

Introduction

In 1944 Zincke and Ziegler[1] assigned cyclic tetrameric structures to substances produced from the base-induced reaction of *para*-substituted phenols with formaldehyde. Due to the pioneering efforts of Gutsche[2] and others[3] in recent years, these types of compounds have become more familiar as being members of the class of compounds known as calix[*n*]arenes. However, it was only in 1993, almost 50 years after Zincke and Ziegler's original postulate, that the first report appeared of examples of analogous cyclic tetrameric compounds that are formed between formaldehyde and 1-naphthol.[4]

The naphthols are naphthalene analogues of phenol but they are generally more reactive and resemble resorcinol rather than phenol in many of their reactions.[5] In particular, the complexity of the reaction of 1-naphthol with formaldehyde is well-known[6] and it had long been assumed that only cross-linked polymers are formed since reaction can occur at the C-2 and C-4 positions which are, respectively, *ortho* and *para* to the hydroxyl group. In 1993 we reported[4] the synthesis of three isomeric "calix[4]naphthalenes", **1**–**3**, from the direct condensation of 1-naphthol with formaldehyde in dimethylformamide (DMF) using potassium carbonate as the base. In principle there is a fourth possible tetrameric isomer having C_{4v} symmetry, **4**, which could be formed, but we were unable to either isolate or detect its presence in the crude reaction mixture. We now report that we have succeeded in synthesizing all four cyclic tetramers by independent convergent routes that can afford synthetically useful quantities of these compounds which, besides being inherently interesting, are also potentially useful novel supramolecular building blocks.

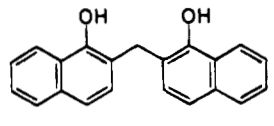
If the reactions at C-2 and C-4 only are considered, condensation of 1-naphthol and formaldehyde can result in the formation of three isomeric bis(1-hydroxynaphthyl)methanes. These are the *ortho,ortho*, the *ortho,para*, and the *para,para* condensation products **5**–**7**, respectively. We did not isolate any of these intermediates from the highly colored crude reaction mixtures which in addition to containing compounds **1**–**3** also appeared to contain quinone-type products. We had hypothesized[7] earlier that tetramer formation could occur via condensation–dimerization of these initially formed intermediates, but this hypothesis is unable to account for the fact that **4** was not obtained. In order for **4** to be produced, the initial formation of either the *ortho,ortho* or *para-para* methylene-linked dinaphthols **5** or **7**, respectively, would be required. However, neither **5** nor **7** could result in the formation of **1**. Only the *ortho,para* dinaphthyl com-



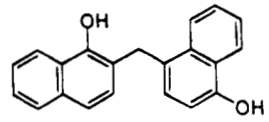
® Abstract published in *Advance ACS Abstracts,* September 15, 1995.

(1) Zincke, A.; Ziegler, E. *Ber.* **1944**, *77*, 264.
(2) Gutsche, C. D. *Calixarenes*; Royal Society of Chemistry: Cambridge, U.K., 1989.
(3) Vicens, J.; Böhmer, V. *Calixarenes: A Versatile Class of Macrocyclic Class of Macrocyclic Compounds*; Kluwer Academic Publishers: Dordrecht, Netherlands, 1991.
(4) Georghiou, P. E.; Li, Z. *Tetrahedron Lett.* **1993**, *34*, 2887.
(5) Donaldson, N. In *The Chemistry and Technology of Naphthalene Compounds*, Edward Arnold Publishers Ltd.: London, 1958.
(6) Walker, J. F. In *Formaldehyde*; American Chemical Society Monograph Series; Reinhold Publishing Corp.: New York, No. 159, 1964.
(7) Georghiou, P. E.; Li, Z. *J. Incl. Phenom. Mol. Recogn. Chem.* **1995**, *19*, 55.
(8) We have recently obtained a crystalline [4 + 2] dimer from the base-catalyzed reaction of **19** with paraformaldehyde which further supports our hypothesis that **8** is indeed formed as an intermediate. Georghiou, P. E.; Chaulk, S. G. Unpublished results.
(9) Georghiou, P. E.; Ashram, M. *J. Org. Chem.* **1995**, *60*, 2909.
(10) Bycroft, B. W.; Cashyap, M. M.; Leung, T. K. *J. Chem. Soc., Chem. Commun.* **1974**, 443.
(11) Schriber, K. C.; Kennedy, M. C. *J. Org. Chem.* **1956**, *21*, 1310.

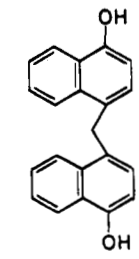
0022-3263/95/1960-7284$09.00/0



5



6



7

pound **6** could produce all three cyclic tetramers **1**–**3** via a stepwise homologation as depicted in Schemes 1 and 2.

In these schemes, it is assumed that the reaction of 1-naphthol initially occurs at the *ortho* position and leads to the *o*-naphthoqinone methide intermediate **8**.[8] This step is analogous to the initial steps that are proposed for the formation of the calixarenes under basic conditions.[2] Condensation of **8** can occur at either the *ortho* or *para* position of a second 1-naphthol to give **5** or **6**, respectively. Our experience,[9] and that of others,[10] with *ortho*-substituted 1-naphthol derivatives suggest that if **5** is indeed formed during the reaction it would be labile to oxidation under the reaction conditions which were employed. The corresponding *o*-naphthoquinone methide intermediate, **9**, obtained from **6** could in turn condense with a third naphthol to give either **10** or **11**. The trinaphthyl adduct **10** can couple with another methide, **8**, at either of the two terminal reactive sites to give **12** and **13**, respectively. Intermediate **12** is the penultimate precursor of **3** and intermediate **13** is the penultimate precursor of **2**. The trinaphthyl intermediate **11** however, could react with methide **8** to produce either **14**, the penultimate precursor of **1**, or **13**. None of the steps envisioned in this scheme would lead to formation of the C_{2v}-symmetrical tetramer **4**.

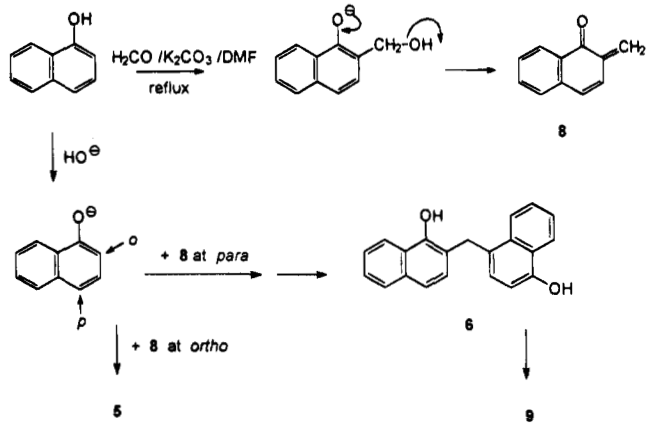
The separation of the three calix[4]naphthalenes and the relatively low yields rendered the direct synthesis as having little synthetic value for producing sufficient amounts of these compounds for further investigations. Many different reaction conditions were evaluated to no avail, including varying the nature and concentrations of base, reaction times, and temperatures. Convergent approaches were therefore investigated, for which the syntheses of **5**–**7** were necessary.

Results and Discussion

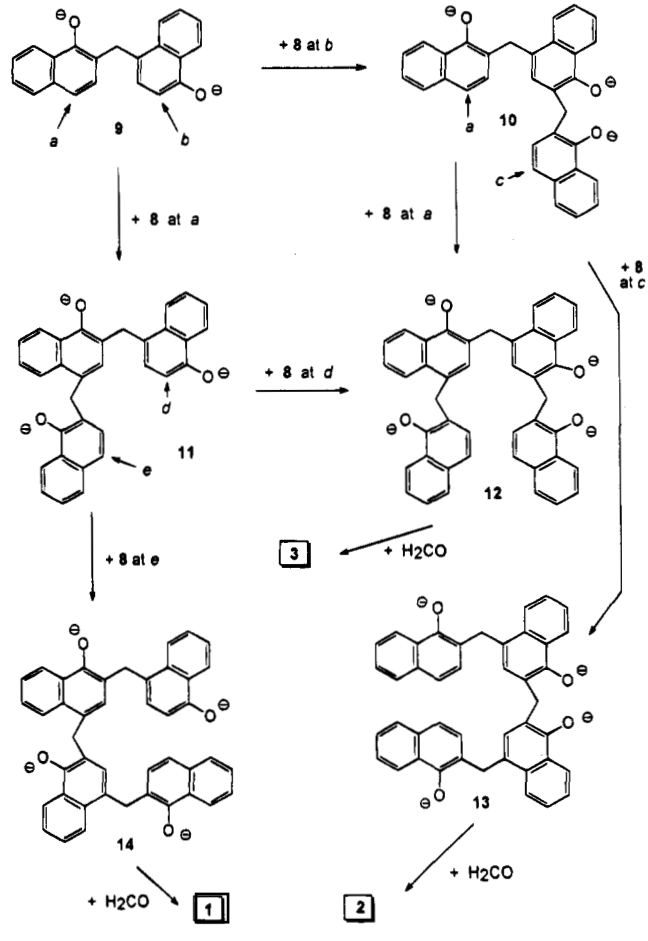
None of compounds **5**–**7** could be synthesized directly from 1-naphthol and formaldehyde using a variety of conditions employing acid- or base-catalysis. However, we found that **5** and **6** could be synthesized via their corresponding dimethoxy derivatives, as described below.

The synthesis of the previously unknown calix[4]-naphthalene, **4**, was achieved as depicted in Scheme 3. Schriber and Kennedy[11] have reported that the dimethoxy derivative of **7**, namely bis(4-methoxy-1-naphthyl)methane, **15**, could be synthesized by an acid-catalyzed reaction of paraformaldehyde with 1-methoxynaphthalene. Employing their reaction conditions with 1-naphthol itself did not produce **7** and yielded only an intractable resinous product, although with 1-methoxynaphthalene, **15** could be synthesized in good yields. Under a variety of different conditions the direct condensation of **15** with formaldehyde could not be effected. The corresponding bis-bromomethyl compound **16** could be obtained in good yield, however, by reacting **15** with paraformaldehyde in hydrobromic acid/glacial acetic acid. Using Böhmer's[12] $TiCl_4$-catalyzed coupling conditions in dioxane, **15** and **16** coupled to afford the tetra-*O*-methoxy C_{4v} calix[4]-naphthalene **17** in 23% yield from **15**. A more convenient alternative synthesis of **17** was achieved by first converting **16** to the corresponding bis-hydroxymethyl compound **18**, and then coupling **18** with **15** using 5% trifluoroacetic acid (TFA)[13] in chloroform. The product, **17**, which was

Scheme 1



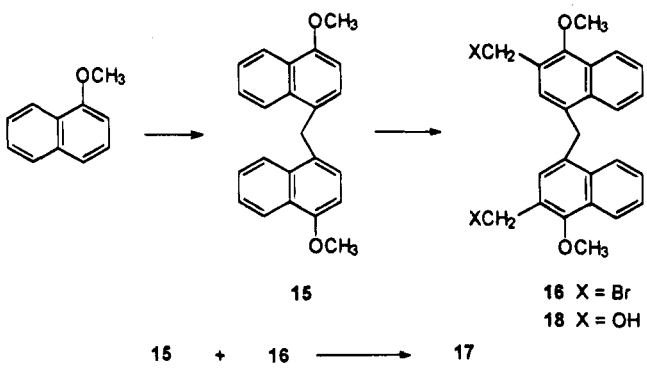
Scheme 2



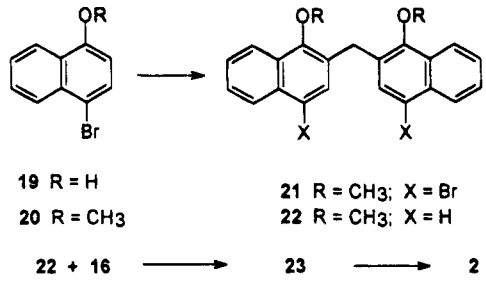
(12) Böhmer, V.; Marschollek, F.; Zetta, L. *J. Org. Chem.* **1987**, *52*, 3200.

(13) Falana, O. M.; Al-Farhan, E.; Keehn, P. M.; Stevenson, R. *Tetrahedron Lett.* **1994**, *35*, 65.

Scheme 3



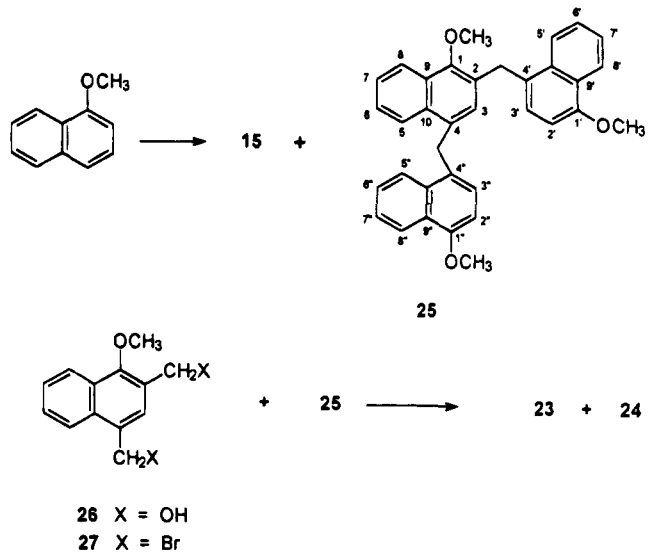
Scheme 4



obtained in 28% yield from **18** in this way, was easier to isolate from the crude reaction mixture than when $TiCl_4$ was used. Demethylation of **17** using BBr_3 produced the previously elusive fourth calix[4]naphthelene, **4**. The ^1H and and ^{13}C NMR spectra, aided by 2-D (HETCOR, APT, and COSY) and NOED experiments were consistent with the assigned structures for both **4** and **17**. The HETCOR and APT-^{13}C NMR spectrum of **17** in $CDCl_3$ clearly indicates five methine aromatic carbon signals, two aliphatic methylene carbon signals, and the methoxy carbon signal. Only four of the five quaternary aromatic carbon signals are obviously resolved, as noted previously for these types of carbon atoms in some of the other calix[4]naphthalenes.[7] The demethylated product **4** in DMSO-d_6, however, shows all twelve carbon signals clearly resolved. The ^1H NMR spectra of both **4** and **17** are unambiguous, both indicating, as in the cases of **1**–**3** previously noted,[4,7] sharp singlets for the methylene bridge and intraannular naphthalene protons. That the methylene protons appear as singlets at ambient temperature indicates that the compounds have flexible structures, with the positions of these protons rapidly interchanging. The ^1H NMR spectrum of **4** (in DMSO-d_6) revealed the presence of two D_2O-exchangeable signals, at $\delta = 6.55$ (sharp, 4H) and 9.23 (broad, 4H). By way of contrast, the corresponding ^1H NMR spectra (in DMSO-d_6) of all three compounds **1**, **2**, and **3** each show only the broad D_2O-exchangeable signals due to the hydroxyl groups at $\delta = 9.00$, 9.30, and 9.10, respectively. The presence of the extra signal at $\delta = 6.55$ in the case of **4** is similar to the observation reported by Chasar[14] for a dihydrate of a calix[4]arene type molecule whose symmetry is analogous to calix[4]naphthalene **4**.

A convergent synthesis of calix[4]naphthalene **2** was achieved by the route depicted in Scheme 4. The *para* position of 1-naphthol was blocked using bromine to give 4-bromo-1-hydroxynaphthalene (**19**). Attempts at the direct condensation of **19** with formaldehyde were unsuccessful, but when **19** was first converted to its methoxy derivative **20**, the *ortho,ortho* methylene-coupled bis-bromonaphthyl compound **21** was obtained in good yield. Removal of both bromine atoms with light-initiated reduction with tri-*n*-butyltin hydride[15] gave quantitative yields of **22**, the dimethoxy derivative of **5**. Demethylation with BBr_3 gave **5** in good yield. Coupling of **22** with **16** using $TiCl_4$ in dioxane gave compound **23**, the C_{2v}-symmetrical tetra-*O*-methylated calix[4]naphthalene derivative of **2**, in 24% yield. This compound could also be synthesized more conveniently in 30% yield by the TFA-catalyzed coupling of **22** with the bis-hydroxymethyl compound **18**. Demethylation of **23** with BBr_3 gave **2** whose spectral properties were identical to those described previously.[4]

Scheme 5



A different synthesis of **23** was achieved using the reaction sequence depicted in Scheme 5. In this synthesis, both **23** and **24**, the tetra-*O*-methoxy derivative of **3**, were produced. Refluxing 1-methoxynaphthalene for 6 h with paraformaldehyde in 30% sulfuric acid/dioxane afforded a mixture which contained linear oligomers including dimer **15** and trimer **25**. The structure of **25** was established on the basis of its spectroscopic properties including 2-D ^1H and ^{13}C NMR experiments and NOED correlations. Several attempts at either the acid- or base-catalyzed condensation of formaldehyde with **15** or **25** were conducted in order to ascertain whether cyclization could be effected directly from these precursors. Only intractable resinous products were obtained with no cyclic oligomeric products being formed. However, when **25** reacted with the bis(hydroxymethyl)-naphthyl derivative **26**, using TFA-catalyzed conditions a 3:1 mixture of both **24** and **23** was obtained in 8% overall yield. Compound **26** was synthesized from the corresponding bis-bromomethyl precursor **27**, which, in turn was obtained from the reaction of 1-methoxynaphthalene with paraformaldehyde in hydrobromic acid/glacial acetic acid.

An unusual feature of the ^1H NMR spectrum of **24** is that the chemical shifts of two methoxy methyl groups are situated at relatively high fields, namely, $\delta = 2.61$ and 2.85. These clearly indicate that these two methyl groups are shielded, most probably by the naphthalene rings. The two other methoxy methyl groups have more

(14) Chasar, D. W. *J. Org. Chem.* **1985**, *50*, 545.

(15) Neumann, W. P.; Hillgartner, H. *Synthesis* **1971**, 537.

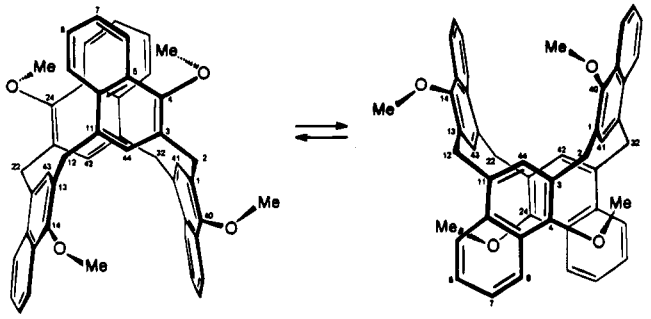
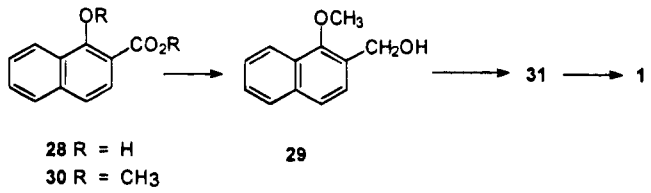


Figure 1. Dynamic equilibrium between 1,3-alternate conformations of calix[4]naphthalene **24**.

Scheme 6



typical chemical shifts at $\delta = 4.03$ and 4.04. Examination of molecular models suggests that the molecule is rapidly inverting between two 1,3-alternate type conformations[2] (Figure 1). In these conformations, the methoxy methyl groups situated on C4 and C24 are deshielded by the opposing naphthalene rings. The methoxy methyl groups on C14 and C40 are not similarly situated with respect to their opposing naphthalene rings and are therefore not deshielded. Rapid inversion must be occurring at ambient temperature since all four methylene protons appear as singlets and not as AB quartets as we have observed with the corresponding tetra-*O*-benzoates.[7] The NOED spectra of **24** are also consistent with this hypothesis.

A convergent synthesis of **1** was achieved using the reactions depicted in Scheme 6. The starting naphthol chosen for this sequence of reactions was 1-hydroxy-2-naphthoic acid, **28**, which was converted to 2-(hydroxymethyl)-1-methoxynaphthalene (**29**) via methyl 1-methoxy-2-naphthoate (**30**). When **29** was treated with sulfuric acid-TFA, tetra-*O*-methoxycalix[4]naphthalene **31** was obtained in 15% yield. Removal of the methoxy groups with BBr_3 gave **1** whose spectral properties were identical to those reported, apart from those signals previously noted as being due to acetone.[4]

In conclusion, using independent synthetically useful convergent routes we have succeeded in synthesizing all four isomeric calix[4]naphthalenes that are derived from 1-naphthol. The cyclization steps were achieved using either $TiCl_4$- or TFA-mediated coupling reactions. The methods described in this paper complement our original discovery that direct base-catalyzed condensation of formaldehyde with 1-naphthol afforded only three of these calix[4]naphthalenes. We are continuing to investigate syntheses of this class of molecules in order to exploit their potentially useful properties.

Experimental Section

General Methods. For general experimental data see ref 9. ^{1}H-NMR and ^{13}C-NMR spectra in the solvents noted were recorded at 300 and 75.47 MHz, respectively.

Bis(4-hydroxy-1-naphthyl)methane (7). To a solution of **15** (0.106 g, 0.31 mmol) in 4.0 mL of dry CH_2Cl_2 under N_2 and at −75 °C was added 0.16 mL (1.75 mmol) of BBr_3 dropwise, with stirring. After 2 h the temperature was raised to −25 °C, and the reaction maintained at this temperature for 2 h. The temperature was then raised and maintained at room temperature for another 2 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ until the solution became basic. The mixture was extracted with 25-mL portions of CH_2Cl_2, and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The crude product was chromatographed by PLC using ethyl acetate:petroleum ether 30:70 to give **7** (40 mg, 43%) which crystallized from ethanol−water as a colorless solid, mp 216−218 °C; ^{1}H NMR (acetone-d_6): $\delta = 4.68$ (s, 2H), 6.75 (d, $J = 7.7$ Hz, 2H), 6.88 (d, $J = 7.7$ Hz, 2H), 7.35−7.48 (m, 4H), 7.90−7.99 (m, 2H), 8.31−8.36 (m, 2H) 8.36 (s, 2H); ^{13}C NMR (acetone-d_6) $\delta = 35.2$, 108.5, 123.7, 124.8, 125.2, 127.1, 126.3, 128.0, 128.4, 134.2, 152.9; MS *m/z* (%) 300 (100, M^+), 157 (68), 144 (46); HRMS M^+ 300.1153 calcd for $C_{21}H_{16}O_2$ 300.1149.

Bis(4-methoxy-1-naphthyl)methane (15). To a solution of 1-methoxynaphthalene (12.0 g, 75.9 mmol) and paraformaldehyde (2.76 g, 92.0 mmol HCHO equivalents) in 80 mL of dioxane was added 15 mL of 30% H_2SO_4 dropwise at room temperature. The mixture was stirred at room temperature for 48 h. The resulting white precipitate was filtered, washed with several portions of petroleum ether, and dried under vacuum to give 10.85 g (87%) of colorless crystalline **15**, mp 149−150 °C (150.5−152 °C[11]); ^{1}H NMR ($CDCl_3$) $\delta = 3.97$ (s, 6H), 4.71 (s, 2H), 6.67 (d, $J = 7.8$ Hz, 2H), 6.97 (d, $J = 7.8$ Hz, 2H), 7.52−7.46 (m, 4H), 7.99−7.95 (m, 2H), 8.37−8.31 (m, 2H); ^{13}C NMR ($CDCl_3$) $\delta = 34.8$, 55.4, 103.4, 122.5, 123.8, 124.9, 126.5, 125.8, 126.8, 128.2, 132.9, 154.3.

Bis[3-(bromomethyl)-4-methoxy-1-naphthyl]methane (16). To a solution of **15** (500 mg, 1.52 mmol) and paraformaldehyde (220 mg, 7.33 mmol HCHO) in 10 mL of glacial acetic acid was added 10 mL of a 15% solution of HBr in glacial acetic acid. The mixture was stirred under N_2 at room temperature for 24 h. A white precipitate formed which was filtered, washed several times with petroleum ether, and dried under vaccum. The yield of crystalline bromomethyl compound **16** obtained was 300 mg (38%), mp 138−140 °C; ^{1}H NMR ($CDCl_3$) $\delta = 4.09$ (s, 6H), 4.65 (s, 4H), 4.75 (s, 2H), 7.06 (s, 2H), 7.49−7.60 (m, 4H), 7.98 (dd, $J = 7.5$, 1.4 Hz, 2H), 8.20 (dd, $J = 7.5$, 1.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) $\delta = 28.4$, 35.1, 62.6, 123.2, 124.4, 125.9, 126.2, 126.9, 128.1, 128.9, 132.5, 133.5, 153.4; MS *m/z* (%) 514 (19, M^+), 433 (42, $M^+ - 81$), 183 (100); HRMS M^+ 511.9967 calcd for $C_{25}H_{22}Br_2O_2$ 511.9986.

Calix[4]naphthalene (17). (a) $TiCl_4$-Catalyzed Conditions. To a solution of **15** (64 mg, 0.19 mmol) and **16** (100 mg, 0.195 mmol) in 5.0 mL freshly distilled dry dioxane under nitrogen was added $TiCl_4$ (93 mg, 0.054 mL, 0.49 mmol). The temperature was raised to 70−80 °C and the reaction mixture maintained at this temperature with stirring for 72 h. The solvent was removed under vacuum. The residue was dissolved in 5 mL of CH_2Cl_2, and 2 g of silica gel was added to the solution. After evaporation of the CH_2Cl_2 on a rotary evaporator, the crude product−silica gel mixture was extracted overnight with CH_2Cl_2 using a Soxhlet apparatus. The extract was concentrated to approximately 3 mL and was chromatographed by PLC using CH_2Cl_2:petroleum ether 80:20 to give 30 mg (23%) of the tetra-*O*-methoxy compound **17**: mp > 300 °C dec; ^{1}H NMR ($CDCl_3$) $\delta = 3.39$ (s, 12H), 4.24 (s, 4H), 4.59 (s, 4H), 6.43 (s, 4H), 7.37 (dt, $J = 8.1$, 0.6 Hz), 7.46 (dt, $J = 8.1$, 0.6 Hz, 4H), 7.85 (dd, $J = 8.1$, 0.6 Hz, 4H), 8.06 (dd, $J = 8.1$, 0.6 Hz, 4H); ^{13}C NMR ($CDCl_3$) $\delta = 27.9$, 35.1, 61.4, 122.5, 124.3, 125.6, 125.7, 127.8, 128.9, 131.9, 132.1, 152.9; MS *m/z* (%) 680 (100, M^+), 665 (5.4), 650 (2.7), 619 (2.7), 649 (1.9), 340 (35), 326 (7) 171 (91), 141 (41); HRMS $M^+/2$ 340.1483 calcd for $(C_{48}H_{40}O_4)/2$ 340.1464.

Calix[4]naphthalene (17). (b) Trifluoroacetic Acid (TFA)-Catalyzed Conditions. To a solution of **15** (85 mg, 0.26 mmol) and **18** (100 mg, 0.26 mmol) in 5.0 mL of $CHCl_3$ under N_2 was added 5.0 mL of a solution of 10% TFA in $CHCl_3$. The mixture was stirred at room temperature for 48 h. Workup was effected by evaporation of both the $CHCl_3$ and TFA under vacuum. The residue was dissolved in 2 mL of $CHCl_3$ and chromatographed by PLC using CH_2Cl_2−petroleum ether 60:40 to afford 50 mg (28%) of **17** as a crystalline product

mp > 300 °C dec whose spectroscopic properties are identical with those described above.

Demethylation of 17 To Give 4. To a solution of **17** (102 mg, 0.15 mmol) in 5.0 mL of anhydrous CH_2Cl_2 maintained at −78 °C and under N_2 was added BBr_3 (0.16 mL, 1.7 mmol) dropwise, with stirring. The reaction was stirred at −78 °C for 4 h, at −20 °C for 1 h, 0 °C for 1 h, and finally at room temperature for another 1 h. Aqueous saturated $NaHCO_3$ was added dropwise until the mixture became basic. An additional 5 mL of CH_2Cl_2 was added to the mixture which was filtered. The residue was washed with aqueous saturated $NaHCO_3$, followed by several portions of acetone to give 42 mg (45%) of a light tan solid (single spot by TLC), mp > 300 °C dec; ^{1}H NMR (DMSO-d_6) δ = 4.01 (s, 4H), 4.51 (s, 4H), 6.55 (s, 3H, 1.5 H_2O, exchangeable with D_2O), 6.64 (s, 4H), 7.41−7.46 (m, 8H), 7.91 (dd, J = 7.8, 1.5 Hz), 8.17 (dd, J = 7.8, 1.5 Hz, 4H), 9.23 (b, 4H, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6) δ = 29.8, 33.3, 120.9, 122.5, 123.6, 124.6, 125.4, 125.5, 127.7, 128.8, 131.2, 147.6; MS m/z (%) 624 (100, M^+), 620 (10), 466 (1), 451 (3), 450 (1), 437 (2), 312 (23), 311 (24), 310 (36), 309 (18), 300 (15), 298 (22), 296 (30), 295 (48), 282 (27), 281 (54), 265 (19), 252 (20), 239 (12), 172 (30), 171 (16), 158 (95), 156 (76), 144 (93); HRMS M^+ 624.2303 calcd for $C_{44}H_{32}O_4$ 624.2301.

Bis[3-(hydroxymethyl)-4-methoxy-1-naphthyl]methane (18). A solution of **16** (450 mg, 1.16 mmol) and $CaCO_3$ (878 mg, 8.77 mmol) in 14 mL of aqueous dioxane (50:50) was refluxed for 6 h. The solution was cooled to room temperature and aqueous 5% HCl was added until the mixture became acidic. The ensuing white precipitate was filtered and washed with water. The product crystallized from ethanol/water to give 250 mg (56%) of **18**, mp 180−182 °C; ^{1}H NMR (acetone-d_6) δ = 3.95 (s, 6H), 4.10 (t, J = 5.7 Hz, 2H), 4.75 (d, J = 5.7 Hz, 4H), 4.84 (s, 2H), 7.33 (s, 2H), 7.59−7.47 (m, 4H), 8.10 (dd, J = 8.7, 1.2 Hz, 2H), 8.18 (dd, J = 8.7, 1.2 Hz, 2H); ^{13}C NMR (acetone-d_6) δ = 35.7, 59.3, 59.4, 62.9, 123.5, 125.3, 126.5, 126.9, 128.9, CH), 129.1, 130.7, 133.2, 133.8, 152.9; MS m/z (%) 338 (100, M^+), 201 (30), 157 (12), 115 (9); HRMS M^+ 388.1649 calcd for $C_{25}H_{24}O_4$ 388.1675.

4-Bromo-1-hydroxynaphthalene (19). To a solution of 1-naphthol (13.2 g 0.92 mol) in dioxane (40 mL) was added dropwise, with stirring and under N_2, a solution of dioxane dibromide (22.7 g, 0.091 mol) in dioxane (160 mL). After the addition was completed, the reaction mixture was poured into ice−water (200 mL). The reaction mixture was then extracted (3×) with CH_2Cl_2, and the combined organic layers were washed with saturated aqueous NaCl. After drying over $MgSO_4$ and filtering, the CH_2Cl_2 was removed on a rotary evaporator. The product **19** was recrystallized from $CHCl_3$ to give light grey needles, mp 129 °C (lit.[5] 129 °C).

4-Bromo-1-methoxynaphthalene (20). To an ice-cooled solution of **19** (12.0 g, 0.054 mol) in 7% aqueous NaOH was added dimethyl sulfate (0.70 mL, 8.0 mmol) dropwise with sirring, under N_2. The mixture was heated to 80 °C and maintained at this temperature for 2 h. After cooling, the reaction mixture was diluted with chloroform and the organic solution washed with aqueous 10% NaOH follwed by water until washings were neutral. After drying and workup in the usual manner, **20** was vacuum distilled to give a golden-yellow oil (10.22 g, 80%), whose spectral characteristics were consistent for **20**.[16] An alternative, more convenient synthesis of **20** was effected by direct bromination of 1-methoxynaphthalene using dioxane dibromide in the same way as described for **19**, above.

Bis(4-bromo-1-methoxy-2-naphthyl)methane (21). To a solution of **20** (0.245 g, 1.03 mmol) and paraformaldehyde (0.130 g, 4.33 mmol) in dioxane (1.6 mL) under N_2 was added $BF_3{\cdot}Et_2O$ (240 μL) dropwise. The reaction mixture was heated at 80−90 °C for 7−8 h and after cooling to room temperature was extracted with three portions of CH_2Cl_2. The combined organic layers were washed with aqueous 5% $NaHCO_3$ and water and then dried over $MgSO_4$. Workup in the usual way afforded a residue which by PLC using ethyl acetate:hexane 10:90 gave **21** as crystals (0.231 g, 93%) with mp 145−146 °C; ^{1}H NMR ($CDCl_3$) δ = 3.94 (s, 6H), 4.35 (s, 2H), 7.53 (s, 2H), 7.54−7.61 (m, 4H), 8.12−8.16 (m, 2H), 8.16−8.20 (m, 2H); ^{13}C NMR ($CDCl_3$) δ = 28.8, 62.2, 117.9, 122.5, 126.9, 127.1, 127.5, 129.2, 129.4, 131.7, 132.2, 153.5; MS m/z (%) 488 (50, M^+ ^{81}Br,^{81}Br), 486 (100, M^+ ^{81}Br,^{79}Br), 484 (49, M^+ ^{79}Br,^{79}Br), 439 (11), 361 (19), 359 (19), 296 (13), 280 (13), 268 (10), 252 (10), 250 (12), 239 (26), 237 (21), 235 (20), 221 (14), 219 (15), 187 (16), 171 (50); HRMS M^+ 483.9668 calcd for $C_{23}H_{18}Br_2O_2$ 483.9674.

Bis(1-methoxy-2-naphthyl)methane (22). A solution of **21** (300 mg, 0.62 mmol) and (n-C_4H_9)$_3$SnH (0.36 mL) in cyclohexane (6.2 mL) was placed in a quartz tube. The tube was fitted to a condenser, and the solution was stirred and maintained under an Ar atmosphere while being irradiated with 254 nm lamps in a Rayonet photochemical reactor. After 4 h the reaction was terminated by the addition of excess aqueous KF. The resulting white precipitate was filtered off, and the mixture was extracted with diethyl ether and worked up in the usual manner. The crude product was chromatographed by flash chromatography using ethyl acetate:petroleum ether 10:90 as solvent. The product obtained (200 mg, 98%) was a colorless solid, mp 109−112 °C; ^{1}H NMR ($CDCl_3$) δ = 3.967 (s, 6H), 4.43 (s, 2H), 7.21 (d, J = 8.7 Hz, 2H), 7.42−7.54 (m, 4H), 7.52 (d, J = 8.7 Hz, 2H), 7.80 (d, J = 8.1 Hz, 2H), 8.14 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ = 29.1, 61.9, 118.2, 122.0, 124.1, 125.6, 125.9, 128.0, 128.5, 129.0, 133.9; MS m/z (%) 328 (100, M^+), 297 (26), 282 (11), 281 (35), 265 (10), 252 (12), 157 (32), 149 (12); HRMS M^+ 328.1464 calcd for $C_{23}H_{20}O_2$ 328.1462.

Calix[4]naphthalene (23). (a)TiCl$_4$-Catalyzed Conditions. To a solution of **22** (64 mg, 0.195 mmol) and **16** (100 mg, 0.195 mmol) in 5.0 mL of freshly distilled dry dioxane under N_2 was added $TiCl_4$ (93 mg, 0.054 mL, 0.49 mmol). The reaction was conducted and worked up exactly as described above for **17**. The tetra-*O*-methoxy compound **23**: mp > 300 °C dec was obtained in 15 mg (11%) yield; ^{1}H NMR ($CDCl_3$) δ = 3.89 (s, 6H), 3.90 (s, 6H), 4.29 (s, 2H), 4.40(s, 4H), 4.50 (s, 2H), 6.49 (s, 2H) 6.59 (s, 2H), 7.27−7.32 (m, 4H), 7.37−7.45 (m, 4H), 7.70 (dd, J = 8.1, 0.6 Hz, 2H), 7.78 (dd, J = 8.1, 0.6 Hz, 2H), 7.99 (dd, J = 8.1, 0.6 Hz, 2H), 8.04 (dd, J = 8.1, 0.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ = 29.3, 32.5, 34.7, 61.9, 122.3, 123.9, 124.1, 125.5, 125.6, 127.5, 127.8, 128.6, 129.3, 132.0, 152.2, 152.6; MS m/z (%) 680 (25, M^+), 665 (0.5), 650 (0.6), 340 (10), 171 (14), 84 (100); HRMS M^+/2 340.1443 calcd for ($C_{48}H_{40}O_4$)/2 340.1464.

Calix[4]naphthalene (23). (a)TFA-Catalyzed Conditions. To a solution of **22** (85 mg, 0.26 mmol) and **18** (100 mg, 0.26 mmol) in 5.0 mL of $CHCl_3$ under N_2 was added 5.0 mL of a solution of 10% TFA in $CHCl_3$. The mixture was refluxed for 72 h. After cooling to room temperature, workup was effected by evaporation of both the $CHCl_3$ and TFA on a vacuum pump. The residue was dissolved in 2 mL of $CHCl_3$ and chromatographed by PLC using CH_2Cl_2 to afford 30 mg of a solid product whose mp and spectroscopic properties are identical with those of **23** decribed above.

2,4-Bis[(4-methoxy-1-naphthyl)methyl]-1-methoxynaphthalene (25). To a solution of 1-methoxynaphthalene (210 mg, 1.33 mmol) and paraformaldehyde (184 mg, 6.0 mmol HCHO equiv) in 3.0 mL dioxane at room temperature was added aqueous 30% H_2SO_4. The mixture was refluxed for 6 h. After cooling to room temperature, the reaction mixture was diluted with water and extracted with two 15-mL portions of $CHCl_3$. The combined organic extract was washed with aqueous saturated $NaCO_3$ and then with aqueous saturated NaCl and worked up in the usual way. The crude residue thus obtained was chromatographed by PLC plates, using CH_2Cl_2: petroleum ether 30:70 as solvent. Two fractions were isolated to give dimer **15** (62 mg, 28%) and trimer **25** (54 mg, 24%). The trimer **25** was a colorless solid having mp 165−167 °C; ^{1}H NMR (benzene-d_6) δ = 3.37 (s, 3H), 3.45 (s, 3H), 3.68 (s, 3H), 4.28 (s, 2H), 4.46 (s, 2H), 6.18 (d, J = 7.8 Hz, 1H), 6.34 (d, J = 8.1 Hz, 1H), 6.80 (d, J = 7.8, 1H), 7.01 (s, 1H), 7.01 (d, J = 7.8 Hz, 1H), 7.20 (m, 1H), 7.25 (m, 1H), 7.26 (m, 1H), 7.27 (m, 1H), 7.36 (m, 1H), 7.40 (m, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.89 (dd, J = 8.1 and 0.9 Hz, 1H), 8.06 (dd, J = 7.5 and 0.9 Hz, 1H), 8.38 (dd, 8.4 and 0.9 Hz, 1H), 8.54 (dd, J = 7.5 and

(16) Perumal, S.; Vasuki, G.; Wilson, D. A.; Boykin, D. W. *Magn. Reson. Chem.* **1992**, *30*, 320.

0.9 Hz, 1H), 8.57 (dd, J = 8.1 and 0.9 Hz, 1H); ^{13}C NMR (benzene-d_6) δ = 32.4, 35.3, 54.8, 54.9, 61.8, 103.4, 103.6, 122.9, 123.2, 124.1, 124.4, 125.0, 125.2, 126.0, 126.2, 126.4, 126.6, 126.8, 126.9, 127.0, 129.0, 129.1, 130.3, 132.7, 133.2, 133.4, 133.5, 152.8, 154.7, 154.8; MS m/z (%) 498 (100, M$^+$), 483 (2), 467 (4), 327 (11), 249 (13), 171 (58), 158 (13), 128 (12); HRMS M$^+$ 498.2193 calcd for $C_{35}H_{30}O_3$ 498.2180.

Calix[4]naphthalenes 23 and 24. To a solution of **25** (203 mg, 0.41 mmol) and **26** (89 mg, 0.41 mmol) in 5.0 mL of $CHCl_3$ under N_2 was added 5.0 mL of a solution of 10% TFA in $CHCl_3$. The mixture was sirred at room temperature for 48 h. Workup was effected as was done for **23**. The residue was dissolved in 3 mL of $CHCl_3$ and chromatographed by PLC using CH_2Cl_2:petroleum ether 80:20 to afford in order of increasing polarity, **24** (16 mg) and **23** (5 mg). Calix[4]naphthalene **24** is a solid, mp > 300 °C; ^{1}H NMR ($CDCl_3$) δ = 2.61 (s, 3H, C24), 2.85 (s, 3H, C4), 4.03 (s, 3H), 4.04 (s, 3H), 4.27 (s, 2H), 4.40 (s, 2H), 4.44 (s, 2H), 4.67 (s, 2H), 6.07 (s, 1H), 6.15 (s, 1H), 6.91 (s, 1H), 7.01 (s, 1H), 7.04–7.09 (m, 1H), 7.04–7.09 (m, 1H), 7.18–7.24 (m, 1H), 7.27–7.32 (m, 1H), 7.48–7.52 (m, 1H), 7.55–7.63 (m, 5H), 7.83–7.86 (m, 1H), 7.86–7.89 (m, 1H), 8.12–8.15 (m, 1H), 8.18–8.20 (m, 1H), 8.22–8.25 (m, 2H); ^{13}C NMR ($CDCl_3$) δ = 27.9, 31.4, 32.9, 35.1, 61.3, 61.5, 122.3, 122.5, 122.6, 123.5, 123.6, 124.3, 125.2, 125.3, 125.4, 125.6, 125.7, 125.9, 126.0, 126.5, 126.8, 127.2, 127.7, 128.1, 128.6, 130.9, 131.1, 131.5, 131.6, 131.8, 132.5, 132.6, 132.9, 152.4, 153.5; MS m/z (%) 681 (13, M$^+$ + 1) 680 (25, M$^+$), 665 (1.5), 650 (1.6), 340 (8), 171 (10), 86 (62), 84 (100); HRMS M$^+$/2 340.1460 calcd for ($C_{48}H_{40}O_4$)/2 340.1464.

2,4-Bis(bromomethyl)-1-methoxynaphthalene (27). To a solution of 1-methoxynaphthalene (1.0 g, 6.3 mmol) in glacial acetic acid (10 mL) was added a 15% solution of HBr in acetic acid (10 mL), dropwise, at room temperature, under N_2. After stirring for 3 d, the reaction mixture which had formed a precipitate was filtered. The solid was washed with petroleum ether to remove any acetic acid and then dried under vacuum to give **16** (102 mg), which was identical with that synthesized above. The filtrate was diluted with water and extracted with two 25-mL portions of CH_2Cl_2. The organic layer was washed several times with water and saturated aqueous $NaHCO_3$ until the washings were neutral. After workup in the usual manner, the crude product was chromatographed on a silica gel column using CH_2Cl_2:petroleum ether 40:60 to give **27** (450 mg, 21%) as a crystalline solid, mp 112–114 °C; ^{1}H NMR ($CDCl_3$) δ = 4.07 (s, 3H), 4.73 (s, 2H), 4.90 (s, 2H), 7.53 (s, H), 7.55–7.66 (m, 2H), 8.10–8.12 (m, 1H), 8.14–8.17 (m, 1H); ^{13}C NMR ($CDCl_3$) δ = 27.7, 31.2, 62.7, 123.3, 124.3, 125.9, 126.7, 127.4, 128.5, 129.8, 130.1, 132.5, 155.4; MS m/z (%) 344 (12, M$^+$), 342 (6), 265 (100), 263 (100), 184 (27), 183 (75), 170 (12), 169 (19), 154 (29), 153 (25); HRMS M$^+$ 341.9244 calcd for ($C_{13}H_{12}Br_2O$) 341.9255.

2,4-Bis(hydroxymethyl)-1-methoxynaphthalene (26). To a solution of **27** (380 mg, 1.11 mmol) in aqueous 50% dioxane was added $CaCO_3$ (1.11 g, 11.1 mmol). With stirring, the mixture was refluxed for 3 h. After cooling to room temperature, the mixture was acidified with aqueous 5% HCl. The mixture was extracted with two 25-mL portions of CH_2Cl_2, and the combined organic extracts were worked up in the usual manner to give a colorless solid (150 mg, 0.69 mmol). Crystallization from $CHCl_3$ gave **26** as crystals having mp 121–123 °C; ^{1}H NMR ($CDCl_3$) δ = 3.96 (s, 3H), 4.88 (s, 2H), 5.08 (s, 2H), 7.51–7.56 (m, 2H), 7.53 (s, 1H), 8.08–8.13 (m, 1H), 8.13–8.16 (m, 1H); ^{13}C NMR ($CDCl_3$): δ = 60.7, 62.7, 63.4, 122.8, 124.1, 126.1, 126.4, 126.6, 128.3, 28.4, 132.5, 132.9, 154.0; MS m/z (%) 218 (100, M$^+$), 201 (14), 187 (14), 171 (26), 159 (11), 157 (21), 145 (13), 144 (13); HRMS M$^+$ 218.0953 calcd for ($C_{13}H_{14}O_3$) 218.0942.

Calix[4]naphthalene (31). To a solution of **29** (106 mg, 0.56 mmol) in 2.0 mL of TFA at room temperature, under N_2 was added 4–6 drops of concentrated H_2SO_4. The mixture was stirred for 1 h and then worked-up by the addition of 15 mL of water and solid $NaCO_3$ until the mixture became basic. The mixture was then extracted with three 30-mL portions of CH_2Cl_2. The organic layers were combined and worked up in the usual manner to give a solid product which was washed several times with diethyl ether to give calix[4]naphthalene **31** (30 mg, 32%), mp 285–290 °C dec; ^{1}H NMR ($CDCl_3$) δ = 3.37 (s, 12H), 4.21 (s, 8H), 6.70 (s, 4H), 7.32–7.38 (dt, J = 8.4, 0.6 Hz, 4H), 7.42–7.38 (dt, J = 8.4, 0.6 Hz, 4H), 7.89 (dd, J = 8.4, 0.6 Hz, 4H), 8.01 (dd, J = 8.4, 0.6 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ = 32.1, 61.8, 122.5, 124.3, 125.7, 125.8, 127.2, 128.2, 128.7, 132.0, 132.5, 152.0; MS m/z (%) 680 (100, M$^+$), 185 (23), 171 (32), 141 (16) 128 (15); HRMS M$^+$/2 340.1466 calcd for ($C_{48}H_{40}O_4$)/2 340.1464.

Acknowledgment. We are grateful to Mu'Tah University, Jordan for providing a scholarship to one of us (M.A.) and to Memorial University for providing financial assistance to Z.L. and S.G.C. We thank Dr. C. R. Jablonski, Ms. N. Brunet, and Mr. E. Vessy for the high resolution NMR spectra, and Dr. B. Gregory and Ms. M. Baggs for the mass spectra.

Supporting Information Available: High resolution ^{1}H NMR spectra and mass spectra of all new compounds reported in this paper. ^{1}H-NMR and ^{13}C-NMR signal assignments which are based on a combination of COSY, HETCOR, APT, and NOE experiments are provided (46 pages). This material is contained in libraries on microfiche, immediately follows the article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for the ordering information.

JO9505536