A Short, General Access to Folded, *all-cis*-Azatetraquinane Ring Systems

Goverdhan Mehta* and Chebiyyam Prabhakar

Molecular Design and Synthesis Unit of JNCASR, School of Chemistry, University of Hyderabad, Hyderabad 500 046, India

Received February 3, 1995

As a part of our program[1] to craft macrocyclic cyclophane systems based on the rigid, folded, and readily available *cis,syn,cis*-triquinane dione **1**,[2] we contemplated a protocol based on the Borch reductive amination procedure[3] to generate a cavity **2** fenced by aromatic spacers (Scheme 1). As a prelude to this objective, we have investigated the Borch reduction[3] of **1** in the presence of several aromatic amines and encountered facile and efficient formation of the novel, convoluted, *all-cis*-azatetraquinane ring system.[4] This observation and some related excursions form the subject matter of this note.

Reaction of **1** with aniline (**3a**), *p*-toluidine (**3b**), and p-anisidine (**3c**) in methanolic hydrochloride, in the presence of sodium cyanoborohydride, furnished the *N*-arylazatetraquinanes **4a–c** in good yield as the only major characterizable products, as shown in Scheme 2. The structures **4a–c** could be readily recognized on the basis of symmetry (six lines in the ^{13}C NMR due to the triquinane core) and characteristic resonance at $\delta \approx 69$ due to the carbon attached to the nitrogen atom. The ^1H NMR spectra of **4a–c** had complementary resonances, particularly the signal at $\delta \approx 4$ diagnostic of the **H**–C–N–Ar moiety.

To explore Scheme 1, we next studied the reductive amination of **1** in the presence of 4,4′-methylenedianiline (**5a**), 4,4′-ethylenedianiline (**5b**), and 4,4′-oxydianiline (**5c**) and once again conveniently realized the azatetraquinane derivatives **6a–c** in good yield (Scheme 2). The ^1H and ^{13}C NMR spectra in **6a–c** (*vide* the Experimental Section) exhibited all the expected features and additionally the aromatic proton region exhibited two AB quartets, which completely ruled out of contention formulation **2**. Clearly, under the reductive protocols deployed in this study, the transannular interaction between the proximal C_3 and C_{11} substituents[2] overwhelms the possibility of intermolecular cyclization envisaged in Scheme 1 and eventuates in the formation of the azatetraquinane ring system.

With the ready availability of an azatetraquinane with an aromatic spacer, e.g., **6a**, we further elaborated it to a flexible, noncyclic host system with a capacity to preorganize in the presence of an appropriate guest. Reaction of **6a** with 0.5 equiv of terephthalaldehyde **7** furnished the bis-Schiff base **8**, which was reduced with sodium borohydride to tetraamine **9**, bearing two terminal azatetraquinane moieties (Scheme 3). Concurrently, we also elaborated the azatetraquinane **6a** to **12** *via* **10** and **11** in order to modulate the flexibility and binding sites, shown in Scheme 4. Thus, **12** had an azatetraquinane and an oxatetraquinane moiety at the two termini. Both **9** and **12** were fully characterized on the basis of incisive analyses of their ^1H and ^{13}C NMR data. Initial guest-binding studies with **9** and **12** are not very promising, but further efforts are underway.

Experimental Section

Reductive Amination of *cis,syn,cis*-Triquinanedione 1 with Aniline (3a). Formation of Azatetraquinane 4a (General Procedure). To a solution of 314 mg (3.37 mmol) of aniline **3a** in 25 mL of methanol was added 4 mL of 5 N HCl in methanol, followed by 100 mg (0.56 mmol) of the dione **1** and 44 mg (0.68 mmol) of $NaCNBH_3$. The solution was stirred at rt for 72 h under N_2. Methanol was then removed *in vacuo*, and the residue was diluted with 10 mL of water and extracted with ether (3 × 10 mL) to remove neutral material. The aqueous solution was brought to pH > 10 with KOH, saturated with NaCl, and extracted with ether (5 × 10 mL). Removal of solvent followed by chromatography on a silica gel column and elution with 20% ethyl acetate–hexane furnished 100 mg (75%) of the azatetraquinane **4a** as a syrupy oil: IR (neat) 2900, 1600, 1350, 730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.10 (m, 3H), 6.54 (m, 2H), 4.06 (m, 2H), 3.06 (m, 2H), 2.54 (m, 2H), 0.76–2.10 (m, 10H); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ 147.3, 129.1, 115.4, 112.3, 69.1, 55.1, 47.3, 37.5, 34.4, 32.4; LRMS *m/z* 239 (M^+). Anal. Calcd for $C_{17}H_{21}N$: C, 85.31; H, 8.84; N, 5.85. Found: C, 85.40; H, 8.81; N, 5.83.

Reductive Amination of 1 with *p*-Toluidine (3b). Formation of 4b: yield 69% from **3b**, syrupy oil; IR (neat) 2950, 2900, 1600, 720 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.88 ($^1/_2$ AB q, J = 8 Hz, 2H), 6.41 ($^1/_2$ AB q, J = 8 Hz, 2H), 4.24 (m, 2H), 3.95 (m, 2H), 2.36–3.20 (m, 4H), 2.15 (s, 3H), 1.2–2.0 (m, 8H); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ 145.3, 125.5, 118.3, 87.4, 69.4, 57.2, 55.1, 47.1, 37.5, 34.7, 32.2; LRMS *m/z* 253 (M^+); Anal. Calcd for $C_{18}H_{23}N$: C, 85.32; H, 9.15; N, 5.53. Found: C, 85.41; H, 9.14; N, 5.53.

Reductive Amination of 1 with *p*-Anisidine (3c). Formation of 4c: yield 72% from **3c**, syrupy oil: IR (neat) 2950, 1600, 720 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.78 ($^1/_2$ AB q, J = 8 Hz, 2H), 6.54 ($^1/_2$ AB q, J = 8 Hz, 2H), 3.98 (m, 2H), 3.72 (s, 3H), 3.08 (m, 2H), 2.58 (m, 2H), 0.86–2.06 (m, 10H); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ 151.0, 142.4, 114.8, 113.3, 70.0, 55.8, 55.1, 47.3, 37.4, 34.7, 32.4; LRMS *m/z* 269 (M^+); Anal. Calcd for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.20. Found: C, 80.29; H, 8.52; N, 5.19.

Reductive Amination of 1 with 4,4′-Methylenedianiline (5a). Formation of 6a: yield 70% from **5a**, syrupy oil: IR (neat) 2900, 1600, 730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.02 ($^1/_2$ AB q, J = 8 Hz, 2H), 6.96 ($^1/_2$ AB q, J = 8 Hz, 2H), 6.62 ($^1/_2$ AB q, J = 8.4 Hz, 2H), 6.56 ($^1/_2$ AB q, J = 8.4 Hz, 2H), 4.09 (m, 2H), 3.79 (s, 2H), 3.60 (br s, 2H), 3.10 (m, 2H), 2.61 (m, 2H), 1.70–2.08 (m, 8H), 1.35 (m, 2H); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ 145.2, 143.8, 132.0, 129.2, 129.0, 128.3, 115.0, 111.9, 68.9, 54.6, 46.8, 39.6, 37.0, 34.1, 32.0; FABMS *m/z* 344 (M^+). Anal. Calcd for $C_{24}H_{28}N_2$: C, 83.68; H, 8.19; N, 8.13. Found: C, 83.25; H, 8.02; N, 7.98.

Reductive Amination of 1 with 4,4′-Ethylenedianiline (5b). Formation of 6b: yield 75% from **5b**, syrupy oil: IR (neat) 3300, 2950, 1600, 730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.92 (m, 4H), 6.42 (m, 4H), 4.00 (m, 2H), 3.36 (br s, 2H), 3.00 (m, 2H), 2.68 (s, 4H), 0.80–2.60 (m, 12H); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ 145.5, 144.2, 132.3, 129.0, 128.8, 115.1, 112.1, 69.2, 54.9, 47.1, 37.4, 37.3, 37.1, 34.4, 32.2; LRMS *m/z* 358 (M^+). Anal. Calcd for $C_{25}H_{30}N_2$: C, 83.75; H, 8.43; N, 7.81. Found: C, 83.68; H, 8.34; N, 7.79.

Reductive Amination of 1 with 4,4′-Oxydianiline (5c). Formation of 6c: yield 61% from **5c**, syrupy oil: IR (neat) 3350,

(1) Mehta, G.; Prabhakar, C.; Nethaji, M.; Venkatesan, K. *J. Chem. Soc., Chem. Commun.* **1993**, 483. For recent reviews on macrocyclic cyclophane-based host systems, see: Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 362. Schneider, H.-J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1417. Seel, C.; Vogtle, F. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 528.

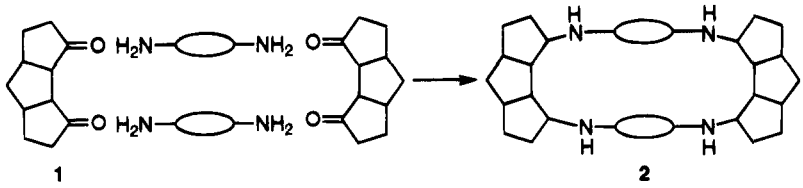
(2) Mehta, G.; Srikrishna, A.; Reddy, A. V.; Nair, M. S. *Tetrahedron* **1981**, *37*, 4543.

(3) (a) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897. (b) Hassner, A.; Stumer, C. *Organic Syntheses Based on Name Reactions and Unnamed Reactions*; Pergamon, Elsevier Science Ltd.: U.K., 1994; p 42.

(4) To our knowledge, the interesting *all-cis*-5-azatetracyclo-[7.2.1.$0^{4,11}$.$0^{6,10}$]dodecane (azatetraquinane) ring system has not been reported previously. See: Mehta, G.; Prabhakar, C.; Murthy, N. K.; Nair, M. S. *Synth. Commun.* **1990**, *20*, 3467.

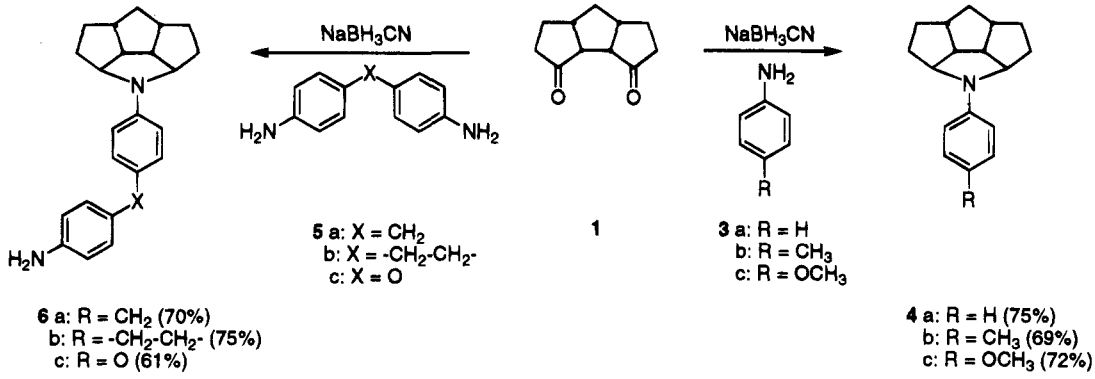
0022-3263/95/1960-4638$09.00/0

Scheme 1

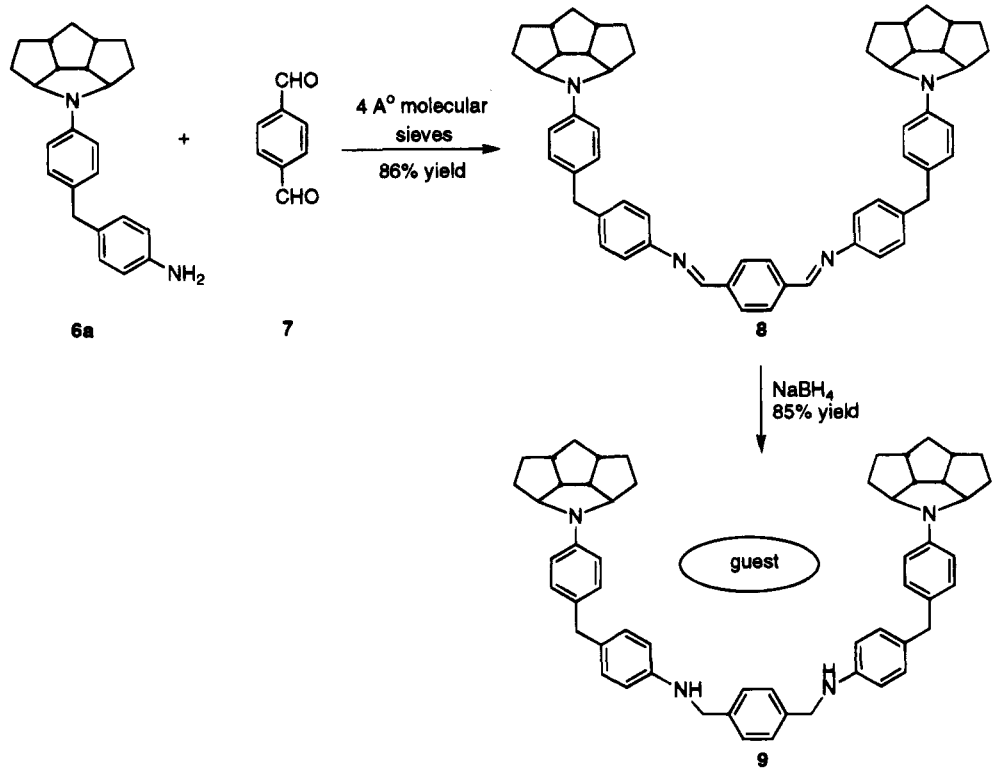


1 2

Scheme 2



Scheme 3

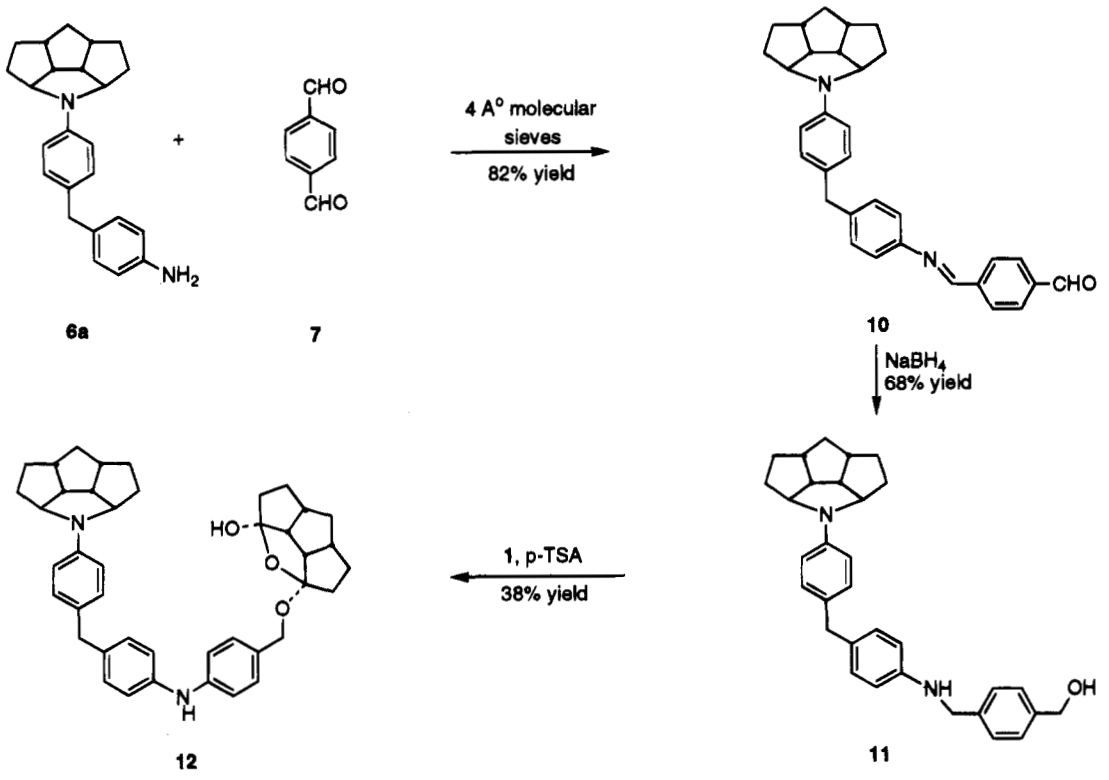


2900, 1600, 1490, 720 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.68 (m, 8H), 4.04 (m, 2H), 3.68 (br s, 2H), 3.08 (m, 2H), 2.56 (m, 2H), 1.20–2.12 (m, 10H); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ 151.5, 148.1, 143.8, 141.0, 119.7, 119.1, 116.4, 112.9, 69.7, 55.1, 47.3, 37.4, 34.6, 32.4; LRMS *m/z* 346 (M^+). Anal. Calcd for $C_{23}H_{26}N_2O$: C, 79.73; H, 7.56; N, 8.09. Found: C, 79.86; H, 7.55; N, 8.07.

Reaction of Azatetraquinane 6a with Terephthalaldehyde (7). Formation of Bis-Schiff Base 8. To a mixture of 50 mg (0.15 mmol) of **6a** and 10 mg (0.08 mmol) of terephthalaldehyde (**7**) in 10 mL of dry CH_2Cl_2 was added 4 Å molecular sieves (500 mg), and the reaction mixture was stirred at rt under N_2 for 1 h. The solvent was removed under vacuum at rt, and the residue was washed with ether to remove the unreacted amine and terephthalaldehyde. The residue was dried under vacuum to give 97 mg (85%) of the bis-Schiff base **8**: IR (KBr) 2900, 1680, 1600, 1500, 1350, 800, 780 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.49 (s, 2H), 7.96 (s, 4H), 7.04 ($^1/_2$ AB q, J = 8 Hz, 8H), 6.56 ($^1/_2$ AB q, J = 8 Hz, 8H), 4.08 (m, 4H), 3.90 (s, 4H), 3.10 (m, 4H), 2.60 (m, 4H), 1.20–2.12 (m, 22H); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ 191.6, 157.9, 144.8, 141.4, 137.9, 130.2, 130.1, 129.7, 129.5, 129.2, 121.1, 112.4, 69.3, 55.1, 47.2, 40.4, 37.5, 34.5, 32.4.

Sodium Borohydride Reduction of Bis-Schiff Base 8. Formation of 9. The above bis-Schiff base **8** (75 mg, 0.095 mmol) was taken up in 10 mL of absolute methanol, and 10 mg of $NaBH_4$ was added at 0 °C. The reaction mixture was allowed to attain rt and stirred for an additional 1 h. Methanol was removed under reduced pressure, and the residue was diluted with 10 mL of water and extracted with ethyl acetate (4 × 10 mL). Removal of the solvent and column chromatography (SiO_2, 20 g) using 10% ethyl acetate–hexane as eluent furnished 70 mg (71%) of **9** as a solid powder: mp 147–148 °C: IR (KBr) 2900, 1600, 1350, 1180, 810, 790 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.28 (s, 4H), 6.98 (AB q, J = 8 Hz, 8H), 6.52 (AB q, J

Scheme 4



= 8 Hz, 8H), 4.24 (s, 4H), 4.06 (m, 4H), 3.76 (s, 4H), 3.08 (m, 4H), 2.56 (m, 4H), 0.88–2.16 (m, 22H); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ 145.7, 138.5, 132.1, 129.8, 129.4, 128.8, 128.1, 113.5, 112.4, 69.4, 55.1, 48.7, 47.4, 40.0, 37.5, 34.6, 32.5. Anal. Calcd for $C_{56}H_{62}N_4$: C, 85.02; H, 7.90; N, 7.08. Found: C, 84.98; H, 7.81; N, 7.15.

Reaction of 6a with Terephthalaldehyde (7). Formation of Mono-Schiff Base 10. To a mixture of 100 mg (0.30 mmol) of **6a** and 40 mg (0.32 mmol) of terephthalaldehyde (**7**) in 10 mL of dry CH_2Cl_2 was added 4 Å molecular sieves, and the reaction mixture was stirred at rt under N_2 for 1 h. The solvent was removed under reduced pressure, and the residue was washed with ether to remove the unreacted amine and terephthalaldehyde. The residue was dried under vacuum to give 110 mg (82%) of the mono-Schiff base **10**: IR (KBr) 2900, 2850, 2730, 1680, 1650, 1600, 1200 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.07 (s, 1H), 8.49 (s, 1H), 7.96 (s, 4H), 7.04 ($^1/_2$ AB q, J = 8 Hz, 4H), 6.56 ($^1/_2$ AB q, J = 8 Hz, 4H), 4.08 (m, 2H), 3.91 (s, 2H), 3.12 (m, 2H), 2.61 (m, 2H), 1.20–2.12 (m, 10H); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ 219.7, 191.6, 157.9, 144.8, 141.4, 137.9, 130.2, 130.1, 129.7, 129.5, 129.2, 121.1, 112.4, 69.3, 55.1, 47.2, 40.4, 37.5, 34.5, 32.4.

Sodium Borohydride Reduction of Mono-Schiff Base 10. Formation of Alcohol 11. To 100 mg (0.22 mmol) of the above mono-Schiff base **10** in 10 mL of absolute methanol was added 10 mg of $NaBH_4$ at 0 °C. The reaction mixture was allowed to attain rt and stirred for an additional 1 h. Methanol was removed under reduced pressure, and the reaction mixture was diluted with 10 mL of water and extracted with ethyl acetate (4 × 10 mL). Removal of solvent under vacuum followed by column chromatography (SiO_2, 40 g) using 20% ethyl acetate–hexane as eluent furnished 70 mg (68%) of **11** as an oil: IR (neat) 3350, 2900, 1600, 1200, 800, 780 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.29 (s, 4H), 6.98 (m, 4H), 6.52 (m, 4H), 4.59 (s, 2H), 4.24 (s, 2H), 4.05 (m, 2H), 3.75 (s, 2H), 3.06 (m, 2H), 2.90 (br s, 1H), 2.55 (m, 2H), 1.70–2.06 (m, 11H); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ 145.9, 145.4, 139.7, 138.8, 131.4, 129.5, 129.2, 128.5, 127.5, 127.1, 113.0, 112.2, 69.2, 64.8, 55.0, 48.3, 47.2, 39.9, 37.4, 34.5, 32.3; LRMS m/z 464 (M$^+$). Anal. Calcd for $C_{32}H_{36}N_2O$: C, 82.72; H, 7.81; N, 6.03. Found: C, 82.85; H, 7.77; N, 6.21.

Reaction of Dione 1 with Alcohol 11. Formation of 12. To 15 mg (0.08 mmol) of dione **1** and 70 mg (0.15 mmol) of the alcohol **11** in 15 mL of dry benzene was added 2 mg of *p*-TSA, and the mixture was refluxed using a Dean–Stark trap for 4 h. Saturated $NaHCO_3$ was added to the reaction mixture, and the organic layer was separated. Solvent was removed under reduced pressure, and the resulting crude product was purified on a silica gel column (20 g) using 30% ethyl acetate–hexane as eluent to give **12** (21 mg, 38%) as a glass: IR (neat) 3350, 2900, 1600, 800, 740 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30 (s, 4H), 6.95 (m, 4H), 6.55 (m, 4H), 4.65 (s, 2H), 4.25 (s, 2H), 4.10 (m, 2H), 3.75 (s, 2H), 3.10 (m, 4H), 2.85 (br s, 2H), 2.60 (m, 4H), 1.10–2.50 (m, 20H); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ 145.9, 145.6, 139.9, 139.0, 131.7, 129.6, 129.3, 128.7, 127.8, 127.3, 113.2, 112.3, 69.4, 65.2, 56.1, 55.1, 48.5, 47.4, 43.6, 40.0, 38.7, 37.5, 37.2, 34.6, 32.5, 26.2. Anal. Calcd for $C_{43}H_{50}N_2O_3$: C, 80.33; H, 7.84; N, 4.36. Found: C, 80.12; H, 7.71; N, 4.22.

Acknowledgment. One of us (C.P.) thanks UGC, New Delhi, for the award of a Junior Research Fellowship. This research was also supported by the Jawaharlal Nehru Center for Advanced Scientific Research, Bangalore.

JO950218H