220 (M^+), 202, 121, 95, 87, 71, 69 (100); HRMS calcd for $C_5H_7F_3O_4S$ 219.9897, found 220.0023. Anal. Calcd for $C_5H_7F_3O_4S$: C,27.28; H,3.15. Found: C,26.95; H,3.34.

Ethyl (*Z*)-2-Benzyl-3-[[(trifluoromethyl)sulfonyl]oxy]-2-butenoate (13).[17] This compound was prepared in an analogous manner to that described for 11. Flash chromatography (hexanes/ethyl acetate, 19:1) gave the titled product as a pale yellow oil (12%) in addition to the *E* isomer: IR (neat) 2985, 1725, 1665, 1605, 1500, 1420, 1215, 1060, 955 cm^{-1}; ^1H NMR 1.21 (t, 3 H, J = 7.2 Hz, CH_2CH_3), 2.20 (s, 3 H, CH_3), 3.74 (s, 2 H, CH_2Ph), 4.20 (q, 2 H, J = 7.2 Hz, OCH_2), 7.27 (m, 5 H, Ph); ^{13}C NMR 13.7, 17.8, 34.9, 61.7, 118.3 (q, J = 324.5 Hz), 126.8, 128.0, 128.4, 128.6, 136.7, 149.1, 164.8; MS m/z 307 $(M - OEt)^+$, 219, 178, 173, 147, 131, 104 (100); HRMS calcd for $C_{12}H_{10}F_3O_4S$ (M – OEt) 307.0252, found 307.0241.

(*Z*)-2-Benzyl-3-[[(trifluoromethyl)sulfonyl]oxy]-2-buten-1-ol (14). This compound was prepared in an analogous manner to that described for 3. Flash chromatography (hexanes/ethyl acetate, 19:1) gave the title product as a colorless oil (81%). A small sample was distilled by Kugelrohr (105–110 °C/0.04 mm): IR (neat) 3385, 1690, 1605, 1500, 1410, 1210, 1015 cm^{-1}; ^1H NMR 2.21 (s, 3 H, CH_3), 3.62 (s, 2 H, CH_2Ph), 4.18 (m, 2 H, OCH_2), 7.26 (m, 5 H, Ph); ^{13}C NMR 16.8, 34.1, 58.4, 118.3 (q, J = 317 Hz), 126.7, 128.7, 131.1, 137.3, 142.9; MS m/z 310 (M^+), 219, 205, 177, 159, 142, 117, 91 (100); HRMS calcd for $C_{12}H_{13}F_3O_4S$ 310.0487, found 310.0502. Anal. Calcd for $C_{12}H_{13}F_3O_4S$: C,46.45; H,4.22. Found: C,46.31; H, 4.57.

Ethyl (*E*)-2-Benzyl-3-[[(trifluoromethyl)sulfonyl]oxy]-2-butenoate (15).[17] This compound was prepared in an analogous manner to that described for ethyl 2-[[(trifluoromethyl)-sulfonyl]oxy]-1-cycoheptane-1-carboxylate. Flash chromatography (hexanes/ethyl acetate, 19:1) gave the title product as a pale yellow oil (64%): ^1H NMR 1.15 (t, 3 H, J = 7.2 Hz, CH_2CH_3), 2.47 (s, 3 H, CH_3), 3.81 (s, 2 H, CH_2Ph), 4.13 (q, 2 H, J = 7.2 Hz, OCH_2), 7.24 (m, 5 H, Ph); ^{13}C NMR 13.8, 18.9, 33.7, 61.5, 118.2 (q, J = 317 Hz), 126.3, 126.7, 128.0, 128.5, 137.2, 153.7, 165.8. All other spectral and analytical data were identical to 13.

(*E*)-2-Benzyl-3-[[(trifluoromethyl)sulfonyl]oxy]-2-buten-1-ol (16). This compound was prepared in an analogous manner to that described for 3. Flash chromatography (hexanes/ethyl acetate, 19:1) gave the title product as a colorless oil (50%): ^1H NMR 2.21 (s, 3 H, CH_3), 3.68 (s, 2 H, CH_2Ph), 4.08 (m, 2 H, OCH_2), 7.31 (m, 5 H, Ph); ^{13}C NMR 16.6, 34.0, 60.0, 118.3 (q, J = 324.5 Hz), 126.8, 128.7, 128.9, 130.5, 137.3, 144.2. All other spectral and analytical data were identical to 14.

3-Methyl-2(5*H*)-furanone (17).[18] This compound was prepared in an analogous manner to that described for 5 using the hydroxy vinyl triflate 12. Upon workup this compound was not subjected to flash chromatography but distilled (55–60 °C/2 mm) [lit.[18] 82 °C/7 mm] to give the title product as a colorless oil (75%): IR (neat) 2960, 1750, 1655, 1260, 1090, 800 cm^{-1}; ^1H NMR 1.89 (m, 3 H, CH_3), 4.74 (m, 2 H, OCH_2), 7.09 (m, 1 H, CH=C); ^{13}C NMR 10.7, 70.0, 129.9, 144.9, 174.8; MS m/z 99 $(M + 1)^+$, 98, 69, 57 (100); HRMS calcd for $C_5H_6O_2$ 98.0368, found 98.0370.

3-Methyl-4-benzyl-2(5*H*)-furanone (18). This compound was prepared in an analogous manner to that described for 5 using the hydroxy vinyl triflate 14. Upon workup this compound was not subjected to flash chromatography but distilled by Kugelrohr (150–160 °C/0.04 mm) to give the title product as a pale yellow oil (71%): IR (neat) 2925, 1745, 1680, 1600, 1500, 1455, 1335, 1080, 1030, 755, 705 cm^{-1}; ^1H NMR 1.93 (s, 3 H, CH_3), 3.74 (s, 2 H, CH_2Ph), 4.56 (s, 2 H, OCH_2), 7.13–7.37 (m, 5 H, Ph); ^{13}C NMR 8.5, 33.3, 71.2, 127.1, 128.3, 128.9, 131.8, 136.1, 158.4, 175.2; MS m/z 188 (M^+), 142, 110, 91 (100); HRMS calcd for $C_{12}H_{12}O_2$ 188.0837, found 188.0847. Anal. Calcd for $C_{12}H_{12}O_2$: C,76.57; H,6.43. Found: C,76.92; H, 6.45.

Methyl (*E*)-2-Methyl-3-benzyl-2-buten-1-ol (19). Carbon monoxide was bubbled through a solution of 16 (0.15 g, 0.48 mmol), $Pd(PPh_3)_4$ (0.056 g, 0.048 mmol), tri-*n*-butylamine (0.23 mL, 0.96 mmol), lithium chloride (0.021 g, 0.48 mmol), and methanol (0.1 mL, 2.42 mmol) in acetonitrile (20 mL) for 20 min. The mixture was heated to 65 °C under 1 atmosphere of carbon monoxide. Workup as described for 5 gave the titled compound as a yellow oil (0.025 g, 23%): IR (neat) 3410, 2950, 1715, 1655, 1600, 1495, 1435, 1235, 1165, 1010, 740, 700 cm^{-1}; ^1H NMR 1.99 (s, 3 H, CH_3), 3.77 (s, 3 H, OCH_3), 3.80 (s, 2 H, CH_2Ph), 4.14 (s, 2 H, OCH_2), 7.17–7.31 (m, 5 H, Ph); ^{13}C NMR 15.4, 37.4, 51.8, 61.3, 126.3, 127.1, 128.6, 128.9, 139.0, 143.9, 170.2; MS m/z 202 $(M - H_2O)^+$, 186, 159, 143 (100); HRMS calcd for $C_{13}H_{14}O_2$ (M – H_2O) 202.0994, found 202.0977. Anal. Calcd for $C_{13}H_{16}O_3$: C,70.89; H,7.32. Found: C,70.62; H, 7.52.

Registry No. 1, 122948-55-4; 2, 144242-01-3; 3, 144242-02-4; 4, 144242-03-5; 5, 14668-64-5; 6, 66309-76-0; 7, 935-90-0; 8, 99172-53-9; 9, 112533-09-2; 10, 87-41-2; 11, 122135-84-6; 12, 144242-04-6; 13, 143564-88-9; 14, 144242-05-7; 15, 134405-93-9; 16, 144242-06-8; 17, 22122-36-7; 18, 144242-07-9; 19, 144242-08-0; ethyl 2-[[(trifluoromethyl)sulfonyl]oxy]-1-cyclopentene-1-carboxylate, 122539-74-6; ethyl 2-[[(trifluoromethyl)sulfonyl]-oxy]-1-cyclohexene-1-carboxylate, 122135-83-5; ethyl 2-[[(trifluoromethyl)sulfonyl]oxy]-1-cycloheptene-1-carboxylate, 144242-09-1; ethyl 2-[[(trifluoromethyl)sulfonyl]oxy]-1-cyclooctene-1-carboxylate, 144242-10-4; ethyl 1-oxo-2-cyclopentanecarboxylate, 611-10-9; ethyl 1-oxo-2-cyclohexanecarboxylate, 1655-07-8; ethyl 1-oxo-2-cycloheptanecarboxylate, 774-05-0; ethyl 1-oxo-2-cyclooctanecarboxylate, 4017-56-5; ethyl acetoacetate, 141-97-9; ethyl α-benzylacetoacetate, 620-79-1.

(17) Finkelstein, J. A.; Weinstock, J.; Keenan, R. M. Eur. Pat. App. EP 90-306203, 1990.
(18) Houff, W. H.; Sell, H. M. *J. Am. Chem. Soc.* **1952**, *74*, 3183.

Novel Synthetic Route to Benzopolyazamacrocycles. Synthesis of 16-Membered Tetrabenzotetraazamacrocyles via Bisquinazolinone Annelation and Reductive Ring Enlargement[1]

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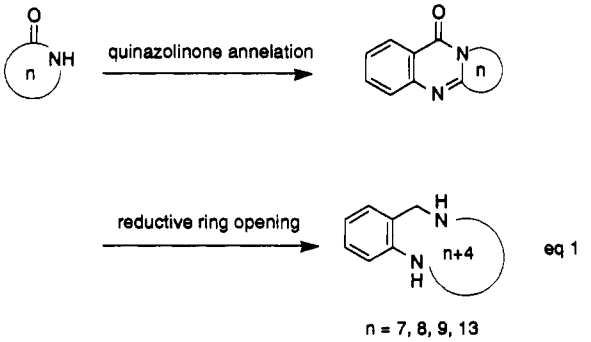
Received July 9, 1992

Recently we reported a new synthesis of benzoannelated macrocyclic 1,4-diamines via quinazolinone annelation of lactams, followed by reductive ring enlargement (eq 1).[2,3]

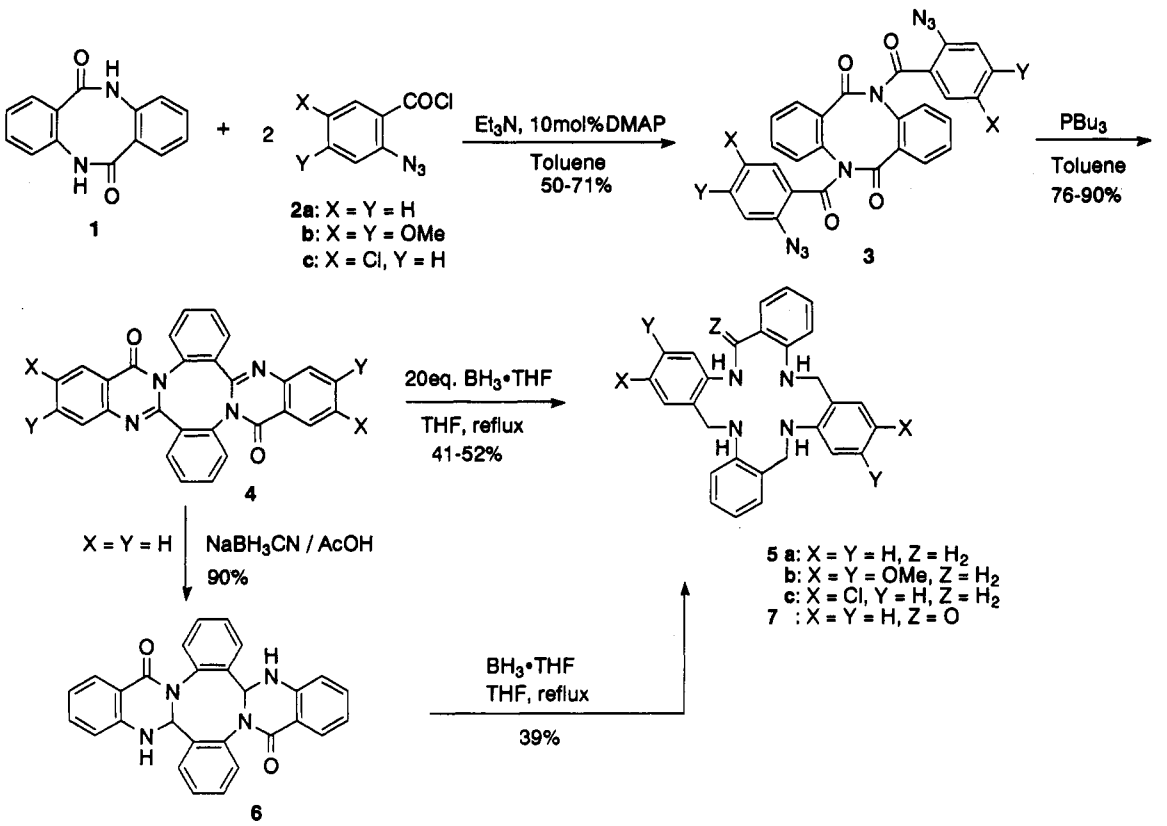


Polyazamacrocycles have drawn continued interest because of their utility as ligands as well as their ability to mimic enzyme functions.[4,5] As an application of our metho-

(1) Synthesis of Novel Carbo- and Heteropolycycles. 22. For part 21, see: Eguchi, S.; Yamashita, K.; Matsushita, Y. *Synlett.* **1992**, 295.
(2) Takeuchi, H.; Matsushita, Y.; Eguchi, S. *J. Org. Chem.* **1991**, *56*, 1535.
(3) For a recent review on ring enlargement, see: Hesse, M. *Ring Enlargement in Organic Chemistry*; VCH: Weinheim, 1991.

0022-3263/92/1957-6975$03.00/0

Scheme I



dology, we describe here novel syntheses of tetrabenzotetraaza-16-membered macrocycles known as unique ligand for Zn(II).[4b] As the starting lactam, we first employed readily available dianthranilide **1**,[6] which was treated in toluene with 2-azidobenzoyl chloride (**2a**)[7] in the presence of triethylamine and DMAP at room temperature to afford the bis-2-azidobenzoyl derivative **3a** in 71% yield (Scheme I). The structure of **3a** was supported by spectral data and CHN analysis. The Staudinger reaction–aza-Wittig reaction sequence on **3a** was attempted to provide bisquinazolinone **4a**.[2] Indeed, the cyclization proceeded smoothly on treatment of azide **3a** with tributylphosphine in toluene at room temperature, affording **4a** as colorless crystals in 82% yield after chromatography. Appearance of 14 lines in the ^{13}C NMR spectrum as well as other spectral data supported the assigned bisquinazolinone structure **4a**.

The reductive ring enlargement of **4a** was carried out by heating for 27 h in THF with 20 molar equiv of BH_3·THF complex as reported previously[2] to give the desired 5,6,11,12,17,18,23,24-octahydrotetrabenzo[*b,f,j,n*]-[1,5,9,13]tetraazacyclohexadecine (**5a**) in 52% yield. The C_4 symmetric macrocyclic structure was supported by appearance of six aromatic and one methylene (δ 47.6 ppm) peaks in ^{13}C NMR spectrum as well as other spectral and analytical data.[8] The above synthetic method can be also applied to the synthesis of substituted benzoazamacrocycles. Thus, by using 4,5-dimethoxy- (**2b**) and 5-chloro-2-azidobenzoyl chlorides (**2c**), the corresponding tetramethoxy- and dichloro-substituted benzoazamacrocycles **5b** and **5c** were prepared as shown in Scheme I.

We also examined the reduction of bisquinazolinone **4a** with sodium cyanoborohydride in acetic acid because the structurally related 2,3-trimethylene-4-hydroxy-5,6-dihydropyrimidine system is known to afford the reductively ring enlarged product under these conditions.[9] However, only tetrahydro derivative **6** was obtained in 90% yield, revealing this aminal moiety is stable, in contrast with the known facile ring cleavage of trimethylene-bridged or dihydroisoindolyl-fused tetrahydropyrimidine systems.[10] However, the aminal **6** could be reductively cleaved to afford **5a** on further treatment with BH_3·THF under reflux as shown in Scheme I. In the direct reductive ring enlargement of **4a** with excess BH_3·THF, the use of a shorter heating time (13 h compared to 27 h) gave a new ring-cleaved product **7** (17%) having an amide moiety as well

(4) For recent reviews, see for example: (a) Izatt, R. M.; Pawlak, K.; Bradshaw, J. S. *Chem. Rev.* **1991**, *91*, 1721. (b) Bianchi, A.; Micheloni, M.; Paoletti, P. *Coord. Chem. Rev.* **1991**, *110*, 17. (c) Parker, D. *Chem. Soc. Rev.* **1990**, *19*, 271.

(5) For recent leading references, see for example: (a) Alder, R. W.; Mowlam, R. W., Vachon, D. J.; Weisman, G. R. *J. Chem. Soc., Chem. Commun.* **1992**. 507. (b) Kobayashi, K.; Ikeuchi, F.; Inaba, S.; Aoyama, Y. *J. Am. Chem. Soc.* **1992**, *114*, 1106. (c) Qian, L.; Sun, Z.; Mertes, M. P.; Mertes, K. B. *J. Org. Chem.* **1991**, *56*, 4904. (d) Koike, T.; Kimura, E. *J. Am. Chem. Soc.* **1991**, *113*, 8935. (e) Cole, E.; Parker, D.; Ferguson, G.; Gallagher, J.; Kaitner, B. *J. Chem. Soc., Chem. Commun.* **1991**, 1473. (f) Lazar, I.; Sherry, A. D. *J. Chem. Soc., Chem. Commun.* **1991**, 1252. (g) Nam, W.; Ho, R.; Valentine, J. S. *J. Am. Chem. Soc.* **1991**, *113*, 7052 and references cited therein.

(6) Hoorfar, A.; Ollis, W. D.; Price, J. A.; Stephanatou, J. S.; Stoddart, J. F. *J. Chem. Soc., Pekrin Trans. I* **1982**, 1649.

(7) Ardakani, M. A.; Smalley, R. K.; Smith, R. H. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2501.

(8) Compound **5a** was previously prepared by stepwise $NaBH_4$ and $LiAlH_4$ reductions of tetrabenzo[*b,f,g,n*][1,5,9,13]tetraazacyclohexadecine (TAAB) obtainable by self- or template-condensation of 2-aminobenzaldehyde. In the initial $NaBH_4$ reduction, however, undesirable byproduct formation was reported: (a) For **5a**, see: Skuratowicz, J. S.; Madden, I. L.; Busch, D. H. *Inorg. Chem.* **1977**, *16*, 1721. (b) For metal cation complexes of **5a**, see: Katovic, V.; Taylor, L. T.; Urbach, F. L.; White, W. H.; Busch, D. H. *Inorg. Chem.* **1972**, *11*, 479. (c) For the template condensation of 2-aminobenzaldehyde, see for example: Bhula, R.; Osvath, P.; Weatherburn, D. C. *Coord. Chem. Rev.* **1988**, *91*, 129–130.

(9) Wasserman, H. H.; Robinson, R. P.; Matsuyama, H. *Tetrahedron Lett.* **1980**, *21*, 3493.

(10) These cyclic animals are known to be readily cleaved to ring enlarged and/or other products by silica gel: Aeberli, P.; Houlihan, W. *J. Heterocycl. Chem.* **1978**, *15*, 1141.

Scheme II

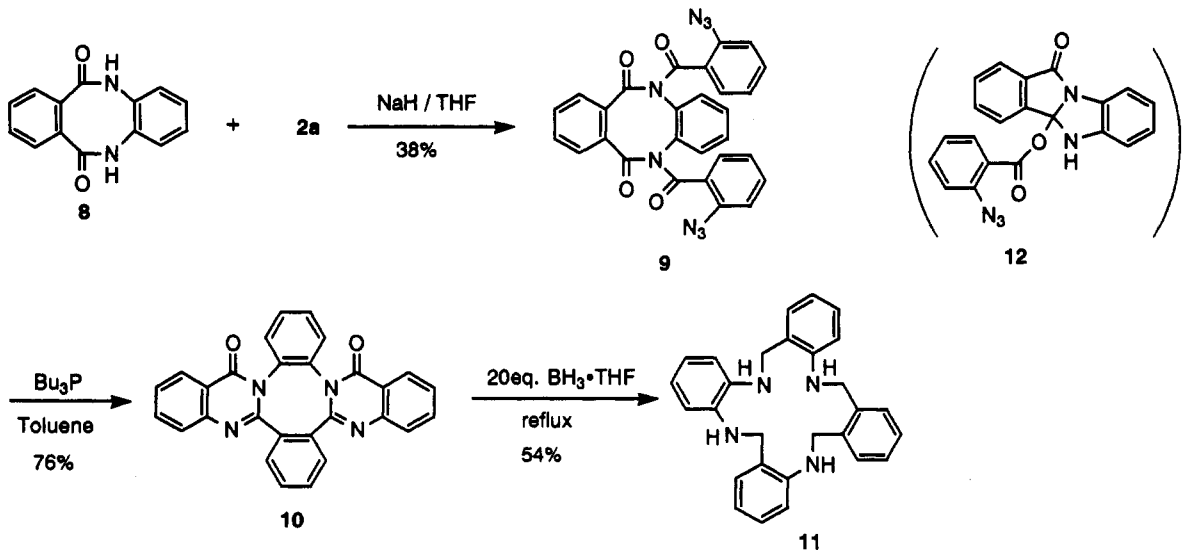
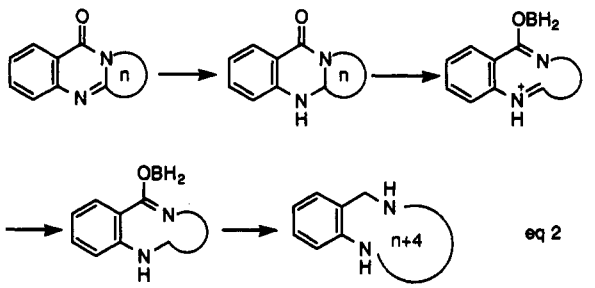


Table I[a]

entry	base	solvent	reaction conditions	yield, % 9	11
1	NaH	THF	20–25 °C, 48 h	37.8	c
2	NaH	DMF	20–25 °C, 3 h	trace	30.3
3	Et_3N–DMAP[b]	THF	20–25 °C, 48 h	21.6	c
4	Et_3N–DMAP	toluene	reflux, 1 h	30.3	33.9
5	Et_3N–DMAP	toluene	reflux, 3 h	trace	35.0

[a] To a stirred equimolar mixture of 8 and base was added a toluene solution of 2, and then stirring was continued under the given conditions. [b] 10 mol % was used for each case. [c] Not isolated.

as fully reduced **4a** (26%). These results clearly indicate the reductive ring enlargement of **4** with BH_3·THF takes a stepwise course as shown in eq 2.



eq 2

Finally, we have applied this reductive ring enlargement reaction to synthesis of octahydrotetrabenzo[*b,f,j,n*]-[1,4,8,13]tetraazacyclohexadecine **11**, a positional isomer of **5a** (Scheme II). Dibenzo[*b,f*][1,4]diazocine-6,11-(5*H*,12*H*)-dione (**8**), readily obtainable by the Paudler–Zeiler method,[11] was bis-2-azidobenzoylated to **9** (38%) with **2a** and sodium hydride in THF (20–25 °C, 48 h). Due to facile formation of transannular cyclization product **12**, the yield of **9** could not be improved under several other conditions as summarized in Table I. The same reaction in DMF instead of THF as the solvent afforded only 2-azidobenzoylated transannular cyclization product **12** (30%). The use of Et_3N (1 equiv)–DMAP (10 mol %) as the base in THF gave **9** in lower yield (22%). The same reaction in toluene under reflux for 1 h gave **9** (30%) and **12** (34%). But the same reaction for 3 h gave only **12** (35%). The tendency of such facile ring contraction of **8** was previously recognized by formation of a ring-contracted dehydrated product.[11] The Staudinger reaction followed by intramolecular aza-Wittig cyclization of **9** proceeded cleanly on treatment with Bu_3P in toluene at 20–25 °C affording the fused-bisquinazolinone **10** (76%). The reaction of **10** with excess BH_3·THF complex in refluxing THF for 15 h afforded tetraaza-16-membered macrocycle **11** in 54% yield (Scheme II).

The above quinazolinone annelation of lactams followed by reductive ring enlargement sequence provides a novel route to benzofused polyazamacrocycles. Further extension of this methodology to other ring systems is in progress.

Experimental Section[12]

5,11-Bis(2-azidobenzoyl)dibenzo[*b,f*][1,5]diazocine-6,12-(5*H*,11*H*)-dione (3a). A mixture of 2-azidobenzoic acid (163 mg, 1.00 mmol) and thionyl chloride (0.82 mL, 1.33 g, 11.2 mmol) was heated at 80 °C for 2 h under nitrogen.[7] The mixture was cooled to rt, and the excess $SOCl_2$ was evaporated under reduced pressure. The residue was dissolved in dry toluene (5.0 mL) and was added to a stirred mixture of dianthranilide **1**[6] (238 mg, 1.0 mmol), Et_3N (101 mg, 1.0 mmol), and DMAP (12 mg, 0.1 mmol) in toluene (5.0 mL) under nitrogen. After stirring for 5 h, the mixture was filtered, and the filtrate was evaporated under reduced pressure to give crude azide which was purified by flash chromatography on silica gel (hexane/CH_2Cl_2, 1:4) to afford pure azide **3a** as a faintly yellowish crystalline solid (373 mg, 71%): mp 106–107 °C; IR (KBr) 2130 cm^{-1}; ^{13}C NMR δ (C=O), 168.4 (C=O), 137.8, 136.3, 133.3, 133.2, 132.5, 131.0, 130.6, 130.4, 130.4, 128.2, 125.4, 118.8.[13] Anal. Calcd for $C_{28}H_{16}N_8O_4$: C, 63.62; H, 3.05; N, 21.20. Found: C, 63.51; H, 3.19; N, 21.19.

5,11-Bis(2-azido-4,5-dimethoxybenzoyl)dibenzo[*b,f*]-[1,5]diazocine-6,12(5*H*,11*H*)-dione (3b). This azide was prepared as above from 2-azido-4,5-dimethoxybenzoic acid.[14] The crude 2-azidoaroyl product was purified by flash chromatography on silica gel (hexane/AcOEt, 1:1) to afford pure azide derivative **3b** as a faintly yellowish crystalline solid (324 mg, 50%): mp 129–132 °C; IR(KBr) 2116 cm^{-1}; ^1H NMR δ 7.68–7.63 (m, 2 H), 7.55–7.33 (m, 6 H), 7.19 (s, 2 H), 6.58 (s, 2 H), 3.93 (s, 6 H), 3.81 (s, 6 H); ^{13}C NMR δ 168.9, 168.5, 152.8, 146.7, 136.7, 133.4, 132.8, 131.3, 130.9, 130.2, 119.2, 113.6, 102.0, 56.4. Anal. Calcd for $C_{32}H_{24}N_8O_8$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.40; H, 3.88; N, 16.99.

5,11-Bis(2-azido-5-chlorobenzoyl)dibenzo[*b,f*][1,5]diazocine-6,12(5*H*,11*H*)-dione (3c). This azide was prepared as above

(11) Paudler, W. W.; Zeiler, A. G. *J. Org. Chem.* **1969**, *34*, 2138.

(12) The general methods are similar to those reported in ref 2.

(13) Each peak corresponds to one carbon unless otherwise noted.

(14) This azide was obtained by diazotization of the corresponding 2-amino compound by the procedure of ref 7.

from dianthranilide 1 (1.0 mmol) and 2-azido-5-chlorobenzoyl chloride (2c).[7] The pure azide was obtained after chromatography on silica gel (hexane/CH_2Cl_2, 1:3) as a colorless crystalline solid (331 mg, 55%): mp 172.5–175.0 °C; IR (KBr) 2133 cm^{-1}; ^1H NMR δ 7.62 (d, 2 H, J = 2.2 Hz), 7.59–7.29 (m, 10 H), 7.09 (d, 2 H, J = 8.6 Hz); ^{13}C NMR δ 168.3, 168.0, 136.2, 136.1, 133.6, 132.7, 132.4, 130.9, 130.7, 130.5, 129.3, 120.1, 77.5, 53.6. Anal. Calcd for $C_{28}H_{14}N_8O_4Cl_2$: C, 56.30; H, 2.30; N, 18.76. Found: C, 56.55; H, 2.44; N, 18.43.

5,12-Bis(2-azidobenzoyl)dibenzo[*b*,*f*][1,4]diazocine-6,11-(5*H*,12*H*)-dione (9). To an ice-cooled and stirred mixture of diazocine 8 (119 mg, 0.50 mmol) in dry THF (7 mL) was added NaH (60% in mineral oil, 44 mg, 1.1 mmol) under nitrogen. After stirring for 15 min, the mixture was brought to rt. Chloride 2a (prepared from 2-azidobenzoic acid, 163 mg, 1.00 mmol) in THF (2 mL) was added under nitrogen. After stirring for 48 h, the mixture was poured into ice–water and extracted with CH_2Cl_2 (4 × 10 mL). The combined extracts were washed with 1 N HCl (10 mL × 2) and H_2O and dried (Na_2SO_4). Evaporation of the solvent followed by chromatography (AcOEt/hexane, 1:2) gave 9 as a colorless crystalline solid (100 mg, 38%): mp 179–183 °C; IR(KBr) 2135 cm^{-1}; ^1H NMR δ 7.61–7.35 (m, 12 H), 7.32–7.19 (m, 4 H); ^{13}C NMR δ 169.6, 169.0, 137.4, 132.4, 1321.0, 130.6, 130.1, 128.7, 127.8, 125.6, 118.4; MS m/z (rel intensity) 528 (M^+, 0.70), 250 (26), 221 (59), 220 (100), 146 (64), 90 (50); HRMS calcd for $C_{28}H_{16}N_8O_4$ (M^+) 528.1295, found 528.1288.

The reaction of 8 and 2a in DMF and workup as above gave only transannularly cyclized product, **4b-[(2-azidobenzoyl)-oxy]-5*H*-isoindolo[2,1-*a*]benzimidazol-11(4b*H*)-one (12)** as colorless crystals (58 mg, 30%): mp 172–174 °C; IR (KBr) 3329, 2139, 1721, 1671 cm^{-1}; ^1H NMR δ 9.50 (s, 1 H, NH), 8.44 (d, 1 H, J = 8.2 Hz), 8.26 (dd, 1 H, J = 7.8, 1.6 Hz), 8.08–7.98 (m, 2 H), 7.90–7.80 (m, 2 H), 7.58–7.44 (m, 2 H), 7.33–7.21 (m, 3 H), 7.04 (dd, 1 H, J = 8.2, 1.2 Hz); ^{13}C NMR δ 167.7 (s), 162.7 (s), 137.0 (s), 136.0 (s), 135.2 (d, 2C), 133.4 (d), 133.4 (s, d, 2C), 132.1 (s, 2C), 130.6 (d), 129.3 (d), 125.8 (d), 125.6 (d), 124.9 (s), 124.5 (d), 124.4 (d, 2C), 122.9 (s), 118.6 (d); MS m/z (rel intensity) 383 (M^+, 24), 356 (28) 355 (100), 326 (20), 310 (39), 282 (23), 76 (40); HRMS calcd for $C_{21}H_{13}N_5O_3$ (M^+) 383.1018, found, 383.1013. For the results under other reaction conditions, see Table I.

General Procedure for Synthesis of Fused Quinazolinones. To a stirred solution of bis-azide 3 (1.00 mmol) in dry toluene (10 mL) was added tributylphosphine (222 mg, 1.10 mmol) in dry toluene (1.0 mL) under nitrogen. After the stirring for 5–6 h at rt, the mixture was evaporated under reduced pressure to afford crude product, which was flash chromatographed on silica gel using solvent system noted.

Dibenzo[*b*,*f*]diquinazolino[2,3-*d*:2′,3′-*h*][1,5]diazocine-6,18(5*H*,17*H*)-dione (4a). This compound was obtained after chromatography (CH_2Cl_2/AcOEt, 4:1) as a colorless crystalline solid (82%): mp >300 °C; IR (KBr) 1686, 1607, 1584 cm^{-1}; ^1H NMR δ 8.27 (ddd, 2 H, J = 7.8, 1.4, 0.8 Hz), 7.81–7.77 (m, 4 H), 7.65–7.61 (m, 2 H), 7.55–7.45 (m, 6 H), 7.26–7.20 (m, 2 H); ^{13}C NMR δ 161.7, 152.4, 147.7, 136.4, 135.3, 134.3, 131.7, 130.3, 129.6, 129.0, 128.6, 128.2, 127.7, 121.6; MS m/z (rel intensity) 440 (M^+, 4.7), 85 (15), 83 (26), 75 (18), 51 (29), 49 (100). Anal. Calcd for $C_{28}H_{16}N_4O_2$: C, 76.35; H, 3.66; N, 12.72. Found: C, 76.07; H, 3.77; N, 12.89.

8,9,20,21-Tetramethoxydibenzo[*b*,*f*]diquinazolino[2,3-*d*:2′,3′-*h*][1,5]diazocine-6,18(5*H*,17*H*)-dione (4b). This compound was obtained after chromatography (CH_2Cl_2/AcOEt, 1:1) as a colorless crystalline solid (90%): mp >300 °C; IR (KBr) 1682, 1608, 1588 cm^{-1}; ^1H NMR δ 7.62–7.58 (m, 4 H), 7.49–7.43 (m, 4 H), 7.24–7.20 (m, 4 H), 3.98 (s, 6 H), 3.95 (s, 6 H); ^{13} NMR δ 161.1, 155.7, 151.3, 150.1, 144.0, 136.7, 134.4, 131.4, 130.1, 129.4, 129.0, 114.8, 109.0, 106.4, 56.6, 56.5; MS m/z (rel intensity) 561 (38), 560 (M^+, 100), 545 (18), 280 (10); HRMS calcd for $C_{32}H_{24}N_4O_6$ (M^+) 560.1699, found 560.1658.

8,20-Dichlorodibenzo[*b*,*f*]diquinazolino[2,3-*d*:2′,3′-*h*]-[1,5]diazocine-6,18(5*H*,17*H*)-dione (4c). This compound was obtained similarly after chromatography (hexane/AcOEt, 3:2) as a colorless crystalline solid (76%): mp >300 °C; IR (KBr) 1688, 1602, 1580 cm^{-1}; ^1H NMR δ 8.21 (dd, 2 H, J = 1.9, 1.0 Hz), 7.73–7.71 (m, 4 H), 7.64–7.59 (m, 2 H), 7.51–7.46 (m, 4 H), 7.23–7.18 (m, 2 H); ^{13}C NMR δ 160.7, 152.5, 146.1, 136.0, 135.7, 134.2, 134.0, 131.9, 130.5, 130.3, 129.6, 128.9, 126.9, 122.6; MS m/z (rel intensity) 512 (14), 511 (22), 510 (67), 509 (40), 508 (M^+, 100), 507 (14), 329 (24), 254 (15). Anal. Calcd for $C_{28}H_{14}N_4O_2Cl_2$: C, 66.03; H, 2.77; N, 11.00. Found: C, 66.01; H, 2.93; N, 10.66.

Dibenzo[*b*,*f*]diquinazolino[2,3-*d*:2′,3′-*h*][1,4]diazocine-6,23(5*H*,24*H*)-dione (10). This compound was obtained as above after chromatography (CH_2Cl_2/AcOEt, 6:1) as a colorless crystalline solid (76%): mp >300 °C; IR (KBr) 1692, 1603, 1562 cm^{-1}; ^1H NMR δ 8.31 (ddd, 2 H, J = 8.0, 1.4, 0.8 Hz), 7.82–7.71 (m, 4 H), 7.57–7.35 (m, 10 H); ^{13}C NMR δ 161.3, 153.6, 147.8, 136.1, 135.3, 134.2, 131.1, 130.8, 129.8, 128.7, 128.4, 128.1, 127.9, 121.4; MS m/z (rel intensity) 442 (2.0), 441 (M^+, 6.3), 86 (58), 84 (100), 49 (43), 47 (65). Anal. Calcd for $C_{28}H_{16}N_4O_2$: C, 76.35; H, 3.66; N, 12.72. Found: C, 76.19; H, 3.77; N, 12.77.

General Procedure of Reductive Ring Enlargement of Bisquinazolinones 4 and 10. To a stirred suspension of 4 or 10 (0.50 mmol) in dry THF (10 mL) was added dropwise a 1.0 M THF solution of BH_3·THF complex (10 mL, 10 mmol) under nitrogen. Stirring was continued for 2 h at rt, and then the mixture was heated at reflux for 15–40 h. The mixture was cooled to rt, and water (ca. 5 mL) was added dropwise cautiously to the stirred mixture. After 50% aqueous NaOH (ca. 2 mL) was added, stirring was continued for 2 h. The mixture was then extracted with CH_2Cl_2 (5 × 30 mL). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product, which was purified by chromatography on a silica gel column to afford the corresponding azamacrocyles 5 and 11.

5,6,11,12,17,18,23,24-Octahydrotetrabenzo[*b*,*f*,*j*,*n*][1,5,9,13]tetraazacyclohexadecine (5a). This compound was obtained by the reduction under reflux for 27 h, followed by workup as above and chromatography (AcOEt/hexane, 1:6) as a faintly yellowish crystalline solid (52%): mp 262–265 °C; IR (KBr) 3389, 1607, 745 cm^{-1}; ^1H NMR δ 7.35–7.25 (m, 4 H), 7.18 (dd, 4 *H*, J = 7.8, 1.8 Hz), 6.81–6.73 (m, 8 H), 4.20 (br s, 4 H, 4 × NH), 4.12 (s, 8 H); ^{13}C NMR δ 147.5 (s), 131.4 (d), 130.0 (d), 122.4 (s), 118.0 (d), 111.6 (d), 47.6 (t); MS m/z (rel intensity) 421 (8.5), 420 (M^+, 26), 314 (26), 209 (36), 208 (68), 207 (49), 206 (100), 106 (72), 91 (25); HRMS calcd for $C_{28}H_{28}N_4$ (M^+) 420.2316, found 420.2272. Anal. Calcd for $C_{28}H_{28}N_4$: C, 79.97; H, 6.71; N, 13.32. Found: C, 80.07; H, 6.86; N, 13.06.

The reaction under reflux for 13 h, followed by the above workup and chromatography, afforded 5a (26%) and a lactam C=O remaining product 7 as colorless crystals (17%): mp 283–286 °C; IR (KBr) 3318, 1665, 1607, 1588 cm^{-1}; ^1H NMR δ 8.94 (br s, 1 H, CONH), 8.03 (dd, 1 H, J = 8.0, 1.2 Hz), 7.67 (dd, 1 H, J = 7.6, 1.6 Hz), 7.45–7.24 (m, 6 H), 7.19–7.11 (m, 2 H), 6.94–6.84 (m, 4 H), 6.78–6.70 (m, 2 H), 4.50 (br s, 3 H, 3 × NH), 4.19 (s, 2 H), 4.15 (s, 2 H), 4.11 (s, 2 H); ^{13}C NMR δ 166.2, 146.3, 145.7, 145.3, 136.4, 131.9, 130.7, 130.2 (2C), 129.8, 129.1 (2C), 128.5, 127.3, 124.5, 124.0, 122.5, 121.2, 120.7, 118.7, 118.2, 116.7, 112.6, 111.9, 109.9, 47.6, 47.3, 45.6; MS m/z (rel intensity) 435 (5.0), 434 (M^+, 15), 210 (20), 209 (100), 120 (56), 103 (56); HRMS calcd for $C_{29}H_{26}N_4O$ (M^+) 434.2109, found 434.2239.

5,6,11,12,17,18,23,24-Octahydro-2,3,14,15-tetramethoxytetrabenzo[*b*,*f*,*j*,*n*][1,5,9,13]tetraazacyclohexadecine (5b). This compound was obtained by the reaction under reflux for 40 h, followed by workup as above and chromatography (AcOEt/hexane, 1:2), as a faintly yellowish crystalline solid (41%): mp 253–255 °C; IR (KBr) 3333, 1607, 752 cm^{-1}; ^1H NMR δ 7.30 (dt, 2 H, J = 7.6, 1.6 Hz), 7.17 (dd, 2 H, J = 7.6, 1.7 Hz), 6.82 (s, 2 H), 6.79–6.71 (m, 4 H), 6.44 (s, 2 H), 4.54 (br s, 2 H, 2 × NH), 4.13 (s, 4 H), 4.06 (s, 4 H), 3.92 (s, 6 H), 3.83 (s, 6 H), 3.60 (br s, 2 H, 2 × NH); ^{13}C NMR δ 150.5, 147.7, 142.2, 141.3, 131.2, 130.0, 122.4, 117.7, 116.7, 113.9, 111.2, 97.9, 57.2, 56.2, 48.0, 46.6; MS m/z (rel intesntiy) 540 (M^+, 16), 434 (22), 271 (32), 270 (61), 269 (62), 255 (31), 1781 (23), 167 (31), 166 (100), 103 (66); HRMS calcd for $C_{32}H_{36}N_4O_4$ (M^+) 540.2739, found 540.2769. Anal. Calcd for $C_{32}H_{36}N_4O_4$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.06; H, 6.99; N, 10.11.

2,14-Dichloro-5,6,11,12,17,18,23,24-octahydrotetrabenzo-[*b*,*f*,*j*,*n*][1,5,9,13]tetraazacyclohexadecine (5c). This compound was obtained by the reaction under reflux for 18 h, followed by the workup and chromatography (AcOEt/hexane, 1:10), as faintly yellowish crystals (45%): mp 263–264 °C; IR (KBr), 3399, 1605, 752 cm^{-1}; ^1H NMR δ 7.35–7.15 (m, 8 H), 6.83–6.69 (m, 6 H), 4.09 (s, 4 H), 4.07 (s, 4 H), 4.4–3.6 (br m, 4 H, 4 × NH); ^{13}C NMR δ 147.2, 145.9, 131.5, 131.1, 130.2, 129.6, 123.9, 122.6, 122.1, 118.4,

112.7, 111.7, 47.6, 47.1; MS *m/z* (rel intensity) 492 (2.2), 491 (4.4), 490 (12), 489 (6.7), 488 (M^+, 20), 384 (16), 382 (28), 348 (41), 255 (26), 245 (88), 243 (82), 209 (49), 140 (45), 118 (25), 106 (100); HRMS calcd for $C_{28}H_{26}N_4Cl_2$ (M^+) 488.1535, found 488.1533.

5,6,11,12,17,18,23,24-Octahydrotetrabenzo[*b*,*f*,*j*,*n*][1,4,8,13]tetraazacyclohexadecine (11). This compound was obtained by the reaction under reflux for 15 h, followed by the workup and chromatography (CH_2Cl_2/hexane, 1:2), as faintly yellowish crystals (53%): mp 236–239 °C; IR (KBr) 3343, 1603, 745 cm^{-1}; ^1H NMR δ 7.41–7.18 (m, 8 H), 6.91–6.73 (m, 8 H), 4.45 (br s, 2 H, 2 × NH), 4.30 (s, 4 H), 4.14 (s, 4 H), 3.50 (br s, 2 H, 2 × NH); ^{13}C NMR δ 147.9 (s), 137.4 (s), 137.3 (s), 132.0 (d), 131.0 (d), 129.9 (d), 129.0 (d), 123.0 (s), 119.9 (d), 118.2 (d), 111.7 (d), 111.4 (d), 47.7 (t), 45.8 (t); MS *m/z* (rel intensity) 421 (4.6), 420 (M^+, 10), 316 (9.3), 208 (21), 206 (31), 106 (43), 57 (64), 55 (61), 43 (100), 41 (92). Anal. Calcd for $C_{28}H_{28}N_4$: C, 79.97; H, 6.71; N, 13.32. Found: C, 80.11; H, 6.85; N, 13.43.

Reduction of 4a with Sodium Cyanoborohydride. 11,12,23,24-Tetrahydrodibenzo[*b*,*f*]diquinazolino[2,3-*d*:2′,3′-*h*][1,5]diazocine-6,18(5*H*,17*H*)-dione (6). To a stirred mixture of **4a** (120 mg, 0.272 mmol) in glacial acetic acid (10 mL) was added $NaBH_3CN$ (170 mg, 2.71 mmol) under nitrogen. After stirring for 2 h at rt and for 8 h at 60 °C, the mixture was poured into ice–water, basified with 50% aq NaOH, and extracted with CH_2Cl_2 (5 × 10 mL). The combined extracts were washed with saturated aq NaCl solution and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave crude product, which was chromatographed on a silica gel column (CH_2Cl_2/AcOEt, 1:10) to afford the tetrahydro derivative **6** as colorless crystals (109 mg, 90%): mp >300 °C; IR (KBr) 3306, 1634, 1613, 752 cm^{-1}; ^1H NMR δ 7.91 (ddd, 2 H, *J* = 7.8, 1.4, 0.4 Hz), 7.42–7.11 (m, 10 H), 6.83 (dt, 2 H, J = 1.2, 8.0 Hz), 6.64–6.59 (m, 2 H), 6.11 (s, 2 H), 4.65 (br s, 2 H, 2 × NH); ^{13}C NMR δ 164.6, 146.8, 139.0, 135.2, 134.0, 132.1, 131.8, 130.9, 129.3, 129.2, 120.2, 117.8, 116.4, 75.4; MS *m/z* (rel intensity) 445 (33), 444 (M^+, 100), 443 (27), 442 (29), 441 (30), 325 (26), 324 (78), 297 (27), 120 (26); HRMS calcd for $C_{28}H_{20}N_4O_2$ (M^+) 444.1584, found 444.1586.

The reduction of **6** with BH_3·THF complex under the same conditions as above, followed by workup and chromatography, afforded **51** (39%).[15]

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First Asymmetric Synthesis of the Tröger's Base Unit on a Chiral Template

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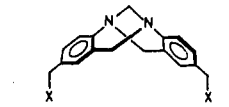
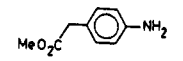
There has recently been a great deal of interest in using the V-shaped Tröger's base unit in the construction of molecular receptors.[1] Asymmetric synthesis of Tröger's base[2] **1** or its analogues has been a challenge since the enantiomers racemize under acidic reaction conditions.[3,4] We now report the *first asymmetric synthesis*[5] of the Tröger's base unit in ca. 40% ee using 7-deoxycholic acid as a chiral template.

In connection with our long-term program on the design, synthesis, and evaluation of novel molecular receptors using readily available natural products as templates it occurred to us that 7-deoxycholic acid, with two "parallel" hydroxyl groups at the 3 and 12 positions, could serve as a novel template to couple two covalently bound fragments, *provided that geometric requirements for the coupling are met*. Removal of the steroid would then constitute a template construction of a bimolecular reaction product.[6]

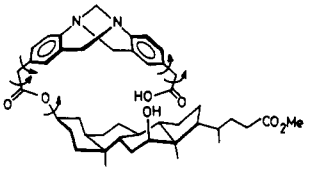
Since the steroid is chiral, one could expect some diastereoselection in the coupling process if the coupling creates a stereogenic center(s). We decided to attempt the synthesis of a Tröger's base analogue since the coupling of two aniline units creates two stereogenic nitrogen atoms and produces a rigid V-shaped unit. Computer modeling using the DTMM (Desk Top Molecular Modeller) program[7–11] suggested that compound **2** would be able to form a bis-lactone on the steroid surface using the two hydroxyl groups. This implied that **4** would be a logical precursor for the cyclization.



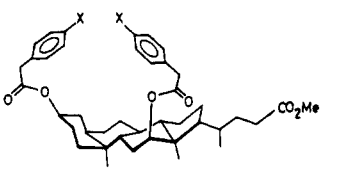
1 : X = H
2 : X = COOH
7 : X = COOMe



6



3



4 : X = NO_2
5 : X = NH_2

Compound **4** was easily synthesized in 83% yield from methyl 7-deoxycholate[12] and (*p*-nitrophenyl)acetyl chloride using a modified Oppenauer procedure.[13] Reduction with

† This paper is dedicated to the memory of my father and to Professor Ronald Breslow on the occasion of his 61st birthday.

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(7) We thank the Bioinformatic Center, Indian Institute of Science, for providing the computational facilities.

(8) The DTMM (Desk Top Molecular Modeller) program was used to generate compound **3** (both diastereomers) using the X-ray coordinates of deoxycholic acid[9] and **1**.[10] Rotations about the indicated (see arrows in **3**) single bonds (keeping both the ester and the carboxylic acid in the s-trans configuration) revealed that through *these rotations* the COOH group in compound **3** can be made to come very close (<0.5 Å) to the 12-OH group. This suggested the feasibility of the template synthesis as we felt that minor bond/dihedral angle adjustments would make a good fit of the two functionalities.

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