rotameric pair:[2] NMR ($CDCl_3$) δ 2.07 and 2.17 (s, 1 H), 2.72 (m, 2 H), 3.87 (t, J = 9 Hz, 2 H), 5.26 (m, 1 H), 6.93 and 6.50 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.1, 21.5, 27.8, 29.6, 44.2, 45.7, 110.1, 111.1, 128.4, 128.9, 165.6; IR (film) 1640, 1610 cm^{-1}. The high-resolution mass spectrum requires m/e 111.06842, found 111.06798.

***N*-[(Benzyloxy)carbonyl]-2-pyrroline**: NMR ($CDCl_3$) δ 2.67 (br t, J = 9 Hz, 2 H), 3.80 (t, J = 9 Hz, 2 H), 5.10 (m, 1 H), 5.19 (s, 2 H), 6.60 (m, 1 H), 7.36 (s, 5 H); ^{13}C NMR ($CDCl_3$) δ 28.6, 45.1, 66.9, 108.6, 128.0, 128.4, 129.1, 136.6; IR (film) 1705, 1620 cm^{-1}.

***N*-(Chloroacetyl)-2-pyrroline.** The spectrum is complicated since **5** exists as a rotameric pair: NMR ($CDCl_3$) δ 2.72 (m, 2 H), 4.04 and 4.10 (s, 2 H), 4.88 (m, 2 H), 5.33 (m, 1 H), 6.65 and 6.85 (m, 1 H); IR (film) 1655, 1615 cm^{-1}.

***N*-[(2,2,2-Trichloroethoxy)carbonyl]-2-pyrroline**: NMR ($CDCl_3$) δ 2.56 (br t, J = 8.5 Hz, 2 H), 3.70 (br t, J = 8.5 Hz, 2 H), 4.60 (s, 2 H), 5.02 (m, 1 H), 6.44 (m, 1 H); IR (film) 1715, 1620 cm^{-1}.

Acknowledgment. We thank Professor T. J. Barton for valuable suggestions. We thank the Alfred P. Sloan Foundation for support of this work.

Registry No. 1 (R = OCH_3), 76460-88-3; 1 (R = OEt), 68471-56-7; 1 (R = CH_3), 23105-58-0; 1 (R = $PhCH_2O$), 68471-57-8; 1 (R = $ClCH_2$), 78964-97-3; 1 (R = Cl_3CH_2O), 78964-98-4; **2**, 5981-17-9.

Synthesis and Atropisomer Separation of Porphyrins Containing Functionalization at the 5,15-Meso Positions: Application to the Synthesis of Binuclear Ligand Systems

Maxwell J. Gunter* and Lewis N. Mander

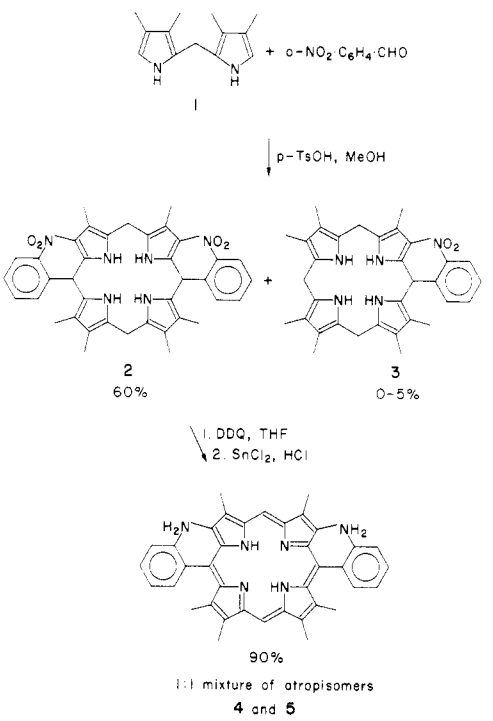
Research School of Chemistry, Australian National University, Canberra, A.C.T. 2600, Australia

Received May 21, 1981

The synthetic model approach has been particularly successful in probing the relationship between structure and function of the active sites of heme-containing proteins.[1] An array of "capped", "strapped", "picket-fence", and other variously described sterically constrained porphyrins has been synthesized, together with porphyrins containing a variety of potentially ligating "tails". Most of the syntheses described are lengthy, low yielding, or allow little convenient variation. More importantly, there are no syntheses described which unambiguously allow facial discrimination, either with regard to attaching a (functionalized) "strap", or to constraining two attached ligand "tails" (either identical or dissimilar) to opposite faces of the porphyrin. We now describe an efficient synthesis of such a system. The utility of this approach is demonstrated by the synthesis of a porphyrin-containing ligand system appropriate for cytochrome *c* oxidase models: an [NS_2] ligand "strap" as a potential binding site for Cu(II) ions is linked across one face of a porphyrin capable of binding Fe. Full experimental details of the ligand synthesis are now presented, and the properties of the Fe/Cu complexes are described elsewhere.[2]

meso-(Ortho-substituted)aryl porphyrins offer an advantage in the synthesis of suitable model systems in that restricted rotation around the meso C–aryl C bond allows the possibility of separation of atropisomers.[3] Additional alkyl substituents on the pyrroles should further enhance stability toward isomerization.[4] Thus, a synthesis of an appropriately disubstituted porphyrin incorporating these concepts was planned and executed as outlined in Scheme I.

Scheme I



The (tetramethyldipyrryl)methane **1** was obtained by standard procedures: ethyl 3,4,5-trimethylpyrrole-2-carboxylate (conveniently prepared in large quantities by either of two[5,6] modifications to the original[7] procedure) was converted via the 2-acetoxymethyl derivative to diethyl 3,3′,4,4′-tetramethyl-2,2′-dipyrrylmethane-5,5′-dicarboxylate;[8] hydrolysis and decarboxylation[9] gave **1**. Condensation of **1** with *o*-nitrobenzaldehyde produced a good yield of the porphyrinogen **2**, together with a variable (0–5%) yield of the monoaryl porphyrinogen **3**, which presumably arises through the well-documented[10] acid-catalyzed rearrangement of the di- or tetrapyrrole intermediates. Variations in reaction time, temperature, catalyst, or solvent generally resulted in either increased yields of **3** at the expense of **2** or, alternatively, mixtures of the corresponding porphyrins were isolated in considerably

(1) For a review, see: J. P. Collman, *Acc. Chem. Res.* **10**, 265 (1977); J. W. Buchler, *Angew. Chem., Int. Ed. Engl.*, **17**, 407 (1978).
(2) M. J. Gunter, L. N. Mander, K. S. Murray, and P. E. Clark, manuscript submitted to *J. Am. Chem. Soc.*
(3) This is the basis of Collman's "picket-fence" [J. P. Collman, R. R. Gagne, C. A. Reed, T. R. Halbert, G. Lang, and W. T. Robinson, *J. Am. Chem. Soc.*, **97**, 427 (1975)], and subsequent "tailed picket-fence" porphyrin synthesis [J. P. Collman, J. I. Brauman, K. M. Doxsee, T. R. Halbert, E. Bunnenberg, R. E. Linder, G. N. LaMar, J. Del Gaudio, G. Lang, and K. Spartalian, *ibid.*, **102**, 4182 (1980)].
(4) The synthesis of other sterically crowded *meso*-aryloctaalkyl porphyrins has been described. B. Evans and K. M. Smith, *Tetrahedron Lett.*, 443 (1977); H. Ogoshi, H,. Sugimoto, T. Nishiguchi, T. Watanabe, Y. Matsuda, and Z. Yoshida, *Chem. Lett.* 29 (1978).
(5) J. B. Paine III in "The Porphyrins", D. Dolphin, Ed., Academic Press, New York, 1979, Vol. 1, Chapter 4, p 107.
(6) C.-B. Wang and C. K. Chang, *Synthesis*, 548 (1979).
(7) E. Bullock, A. W. Johnson, E. Markham, and K. B. Shaw, *J. Chem. Soc.*, 1430 (1958).
(8) A. W. Johnson, I. T. Kay, E. Markham, R. Price, and K. B. Shaw, *J. Chem. Soc.*, 3416 (1959).
(9) P. S. Clezy and A. W. Nichol, *Aust. J. Chem.*, **11**, 1835 (1965). A series of Carius tubes was found more convenient than a stainless steel pressure vessel for the decarboxylation reaction.
(10) J. B. Paine III in "The Porphyrins", D. Dolphin, Ed., Academic Press, New York, 1979, Vol. 1, p 163 et seq.

0022-3263/81/1946-4792$01.25/0

Table I. Analytical Data [a]

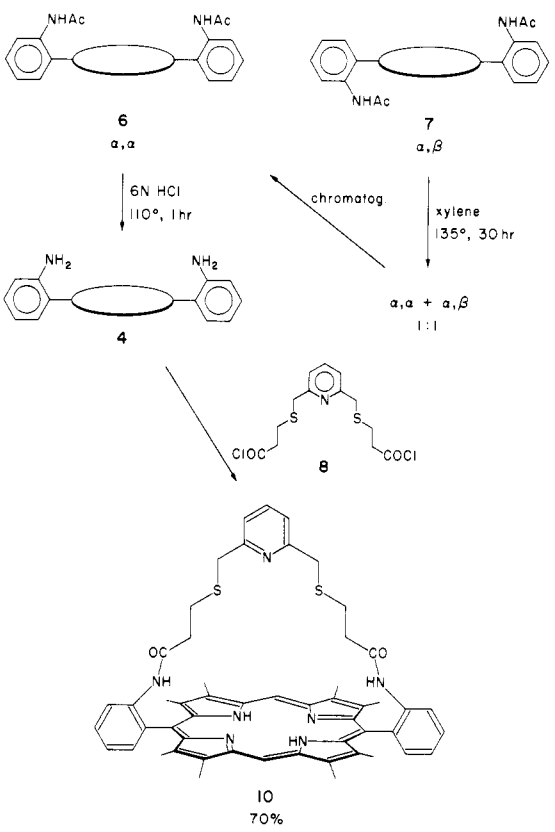
compd	formula	calcd C	calcd H	calcd N	found C	found H	found N
o-NO_2DPOMP [b]	$C_{40}H_{36}N_6O_4$	72.27	5.46	12.64	72.6	5.6	(11.9)
4 and 5	$C_{40}H_{40}N_6 \cdot 0.7CHCl_3$	71.01	5.97	12.20	71.3	6.1	12.1
4	$C_{40}H_{40}N_6 \cdot 0.6CHCl_3$	72.08	6.05	12.42	72.4	6.1	12.5
6	$C_{44}H_{44}N_6O_2 \cdot H_2O$	74.76	6.56	11.89	74.8	6.5	11.8
7	$C_{44}H_{44}N_6O_2 \cdot H_2O$	74.76	6.56	11.89	75.2	6.4	11.6
9	$C_{13}H_{17}NO_4S_2$	49.50	5.43	4.43	49.7	5.5	4.4
10	$C_{53}H_{53}N_7O_2S_2 \cdot H_2O$	70.56	6.14	10.87	70.9	6.1	11.0

[a] Satisfactory analyses (±0.4% for C, H, N) were obtained for all new compounds except where indicated in the text, or above by parentheses. [b] Abbreviation for 5,15-bis(o-nitrophenyl)-2,3,7,8,12,13,17,18-octamethylporphyrin.

reduced yields.[11] Because of the moderate instability of **2** and **3** it was found that separation was better not attempted at this stage but was more conveniently carried during the final chromatographic separation of the porphyrin atropisomers (vide infra). Oxidation of **2** (or a mixture of **2** and **3**) to the corresponding porphyrins with DDQ proceeded quantitatively.[12] Stannous chloride/HCl reduction to the atropisomeric amino porphyrins **4** and **5** and to the corresponding monoaminophenylporphyrin in those instances where **3** was present in admixture with **2** resulted in some overreduction of the porphyrin nucleus, so this was corrected by aerobic irradiation of an acidified solution of the product mixture. Because of limited solubility of the amino porphyrins **4** and **5** chromatographic separation of the expected atropisomers was achieved via the derived acetates **6** and **7**, respectively (Scheme II). Although the NMR spectra of the two isomers **6** and **7** are identical, the more polar compound is assigned the α,α-configuration **6**. This was confirmed by a successful "strapping" reaction (vide infra). **6** and **7** are indefinitely stable toward isomerization in the solid state at ambient temperature; either isomer can be reequilibrated in refluxing xylene to a 1:1 mixture of **6** and **7**, however. Thus, by a series of separation and reequilibration steps, a good yield of either desired isomer can be obtained. Hydrolysis of the respective diacetates proceeded without isomerization to give the α,α- and α,β-diamino porphyrins **4** and **5** quantitatively.

As an indication of the utility of these compounds, and for confirmation of the structural assignment of the atropisomers **6** and **7**, and thereby **4** and **5**, a functionalized "strap" capable of acting as a tridentate ligand for transition-metal ions was easily attached across one face of the porphyrin **4** (Scheme II). Thus, the dicarboxylic acid chloride **8** (obtained by condensation of 2,6-bis(bromomethyl)pyridine with the bis(sodium salt) of 3-mercaptopropionic acid to give the diacid **9** and subsequent reaction with thionyl chloride), was treated with **4** to give the potential binuclear ligand system **10** [abbreviated (P)–(NS_2)]. The relatively high yield (70%) obtained in this high-dilution condensation is a reflection of the restricted conformational freedom in the porphyrin coreactant. The mass spectrum, the symmetrical nature of the ^1H NMR spectrum, and the upfield shifts of the protons on the pyridine ring are consistent with the monomeric structure **10**. The large upfield shifts of the protons at the C-3,5 and C-4 positions of the pyridine ring (2.8 and 2.6 ppm, respectively, compared to the di-p-toluidide derivative of **8**) imply sufficient flexibility of **10** in solution for the pyridine and porphyrin rings to approach a parallel orientation

Scheme II



where π–π interactions are possible.

Thus, we have demonstrated by the efficient synthesis of **4** and **5** the utility of bifunctionalized porphyrins which can be regarded as key synthons for a variety of porphyrin model systems. We are currently applying these systems to the synthesis of porphyrins containing dissimilar potentially ligating "tails", and to other binuclear ligand systems.

Experimental Section

NMR spectra were obtained with a JEOL JNM-MH-100 spectrometer with Me_4Si as internal standard. Mass spectra were recorded with an AEI MS-902 spectrometer at 70 eV and 320 °C inlet temperature. Column chromatography was performed on slurry-packed silica gel (Merck Kieselgel 60, 70–230 mesh), and the columns were protected from light.

Satisfactory analyses (±0.4% for C, H, N) were obtained for all new compounds except where indicated in the text (Table I). The analytical data reflect the tendency of these porphyrins to form solvates or to occlude molecules of solvent which are very difficult to remove completely by pumping.

5,15-Bis(o-nitrophenyl)-2,3,7,8,12,13,17,18-octamethylporphyrinogen (2). A solution of (3,4,3′,4′-tetramethyl-2,2′-dipyrryl)methane[9] (5.72 g, 28.3 mmmol), o-nitrobenzaldehyde (4.28 g, 28.3 mmol), and p-toluenesulfonic acid (1.42 g, 7.5 mmol) in

(11) For example, reaction in C_6H_6 with trifluoroacetic acid produced exclusively the monoaryl porphyrin in 9% yield; this represents a convenient synthesis of a monofunctionalized porphyrin.

(12) Attempted oxidation with O_2 or air in the dark or with visible light irradiation led to extensive tar formation.

methanol (350 mL) was allowed to stand at 20 °C for 6 h and at 4 °C for 16 h. The light-brown crystalline solid (5.20 g) was filtered and washed with cold methanol. Concentration of the filtrate to ~250 mL and chilling (4 °C) for 16 h produced a further 0.56 g. Total yield was 5.76 g (60%). This somewhat unstable product may be stored in the dark under N_2 at −20 °C for up to several weeks. A sample recrystallized from ethyl acetate gave light yellow needles (**2**): no definite melting point, decomposes above ~60 °C; NMR ($CDCl_3$) δ 7.86 (m, 2 H, ArH), 7.40 (m, 6 H, ArH), 6.96 (br s, 4 H, NH), 6.12 (s, 2 H, CH), 3.69 (s, 4 H, CH_2), 1.87 (s, 12 H, CH_3), 1.65 (s, 12 H, CH_3). Because of enhanced instability of **2** on removal of solvent by pumping, a satisfactory analysis was not obtained.

5,15-Bis(*o*-nitrophenyl)-2,3,7,8,12,13,17,18-octamethylporphyrin. The porphyrinogen **2** (5.15 g, 7.68 mmol) in tetrahydrofuran (THF, 500 mL) was treated with a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 6.30 g, 27.75 mmol) in THF (100 mL). The resulting dark solution was stirred 30 min at ambient temperature and left for a further 1 h. The purple solid (4.35 g) was filtered off, the filtrate evaporated to dryness, and the residual solid treated with NaOH solution (10% aqueous, 150 mL) to dissolve the hydroquinone. Filtration, washing (H_2O), and drying produced a further 0.80 g of porphyrin. Total yield was 5.15 g (100%). Anal. ($C_{40}H_{36}N_6O_4$), C, H. NMR ($CDCl_3$/5% trifluoroacetic acid) δ 10.20 (s, 2 H, H-10,20), 8.1–8.5 (m, 8 H, ArH), 3.18 (s, 12 H, CH_3), 2.25 (s, 12 H, CH_3), −2.50 (br s, 4 H, NH_2^+); mass spectrum (70 eV), *m/z* 664 (M^+), calcd 664.

5,15-Bis(*o*-aminophenyl)-2,3,7,8,12,13,17,18-octamethylporphyrin 4 and 5. A mixture of the preceding dinitro porphyrin (5.10 g, 7.67 mmol), concentrated HCl (250 mL), and stannous chloride dihydrate (13.0 g, 57.6 mmol) was stirred for 18 h at 25 °C. The deep green solution was diluted with H_2O (150 mL), cooled in ice, and partially neutralized with concentrated NH_3 solution (aqueous, ~150 mL). (The solution should remain green, i.e., the porphyrin protonated. Overbasification leads to brown suspensions which cause emulsification during the subsequent extractions.) The solution was extracted with $CHCl_3$ (8 × 300 mL) until the aqueous layer was a very pale green (a strong background light is helpful to discern the interface during these extractions). The combined extracts were washed with H_2O (500 mL) and evaporated to ca. 300 mL. After a further washing with H_2O (100 mL), trifluoroacetic acid (1 mL) was added, and the solution was stirred with irradiation from a 250 watt tungsten lamp over 1.5 h. The solution was further evaporated to ca. 200 mL, and dilute NH_3 (1:2 concentrated NH_3–H_2O, 75 mL) was added with vigorous swirling. The remaining $CHCl_3$ was evaporated from the two-phase mixture, and the resultant purple solid was filtered, washed well with H_2O, and then dried, to yield the diamino porphyrins **4** and **5** (4.17 g, 90%). The solid thus obtained contained occluded $CHCl_3$ (evident from the NMR and mass spectrum) which could not be completely removed by pumping. Anal. ($C_{40}H_{40}N_6$·0.7$CHCl_3$) C, H, N. NMR ($CDCl_3$/5% trifluoroacetic acid) δ 10.38 (s, 2 H, H-10,20 CH), 8.0–8.25 (m, 8 H, ArH), 3.25 (s, 12 H, CH_3), 2.30 (s, 12 H, CH_3), −2.70 (br s, 4 H, NH_2^+); mass spectrum (70 eV), *m/z* 604 (M^+), calcd 604.

5,15-Bis[*o*-(acetylamino)phenyl]-2,3,7,8,12,13,17,18-octamethylporphyrin 6 and 7. To a stirred suspension of the mixed porphyrins **4** and **5** (4.5 g, 7.44 mmol) in CH_2Cl_2 (700 mL) at 25 °C was added acetyl chloride (4.5 mL, 63.3 mmol) followed by pyridine (5.25 mL, 64.8 mmol). After 0.5 h, H_2O (100 mL) was added. The CH_2Cl_2 layer was separated, washed ($NaHCO_3$ × 2, H_2O), and evaporated. Residual pyridine was removed by pumping. TLC (C_6H_6–Et_2O, 1:1) showed R_f 0.25 (**6**) 0.65 (**7**), and 0.82 (monoacetylamino porphyrin). The purple residue was chromatographed on silica (Merck, 70–230 mesh, 80 × 3 cm, CH_2Cl_2). Et_2O (6%) in CH_2Cl_2 eluted the (monoacetylamino)-phenyl porphyrin first (when present) followed by the α,β-isomer **7**. The α,α-isomer **6** was eluted with 5% MeOH in CH_2Cl_2. From 4.5 g of a mixture of **6** and **7** containing no monoacetylamino porphyrin was isolated 2.1 g (47% of **6** and 2.1 g (47%) of **7**. Anal. ($C_{44}H_{44}N_6O_2$·H_2O) C, H, N (**6** and **7**). NMR ($CDCl_3$; **6** and **7** identical) δ 10.28 (s, 2 H, H-10,20); 8.77 (m, 2 H, ArH), 7.86 (m, 4 H, ArH), 7.48 (m, 2 H, ArH), 6.83 (s, 2 H, NH), 3.58 (s, 12 H, CH_3), 2.52 s (s, 12 H, CH_3), 1.23 (s, 6 H, $COCH_3$), −1.6 (br, s, 2 H, pyrrole NH); mass spectrum (**6** and **7**; 70 eV), *m/z* 688 (M^+), calcd 688.

5-[*o*-(Acetylamino)phenyl]-2,3,7,8,12,13,17,18-octamethylporphyrin: NMR ($CDCl_3$ + 5% TFA) δ 9.48 (m, 3 H, H-10,15,20), 8.67 (m, 2 H, ArH), 7.93 (m, 3 H, ArH, NH), 3.57 (s, 12 H, CH_3), 3.27 (s, 6 H, CH_3), 2.35 (s, 6 H, CH_3), 1.20 (s, 3 H, $COCH_3$).

Equilibration of 6 or 7. A solution of **6** or **7** in $CHCl_3$ (400 mL) and xylene (800 mL) was distilled under a stream of N_2 until the liquid temperature reached 137 °C. The still head was changed to a reflux condenser, and the solution was heated with stirring under N_2 and protected from light for 30 h. TLC indicated a 1:1 mixture of **6** and **7**. Evaporation of the solvent and chromatography as above yielded **6** (0.95 g, 45%) and **7** (0.95 g, 45%). The balance of the material (10%) remains as a dark band on top of the column.

Hydrolysis of 6 and 7. A mixture of **6** and **7** (1.0 g) and 6 M HCl (150 mL) was heated under reflux for 1 h. The solution was cooled, diluted with H_2O (150 mL) and partly neutralized with NaOH (10% aqueous, ca. 300 mL). The green solution was extracted with $CHCl_3$ (8 × 100 mL) until the aqueous layer was only lightly colored. The $CHCl_3$ layers were washed with H_2O and evaporated to ca. 50 mL. Dilute NH_3 solution (concentrated NH_3/H_2O, 1:2, 50 mL) was added with vigorous swirling. The $CHCl_3$ was evaporated, and the purple solid was filtered from the aqueous solution. After washing (H_2O) and drying, **4** or **5** was obtained, respectively (0.87 g, 100%). The isomeric purity of the product was checked by reacetylation and TLC analysis, which indicated that no isomerization had occurred during hydrolysis under these conditions. Analysis, NMR, and mass spectral data were identical with that reported above.

(2,6-Pyridyl)bis(4′-thia-5′-pentanoic acid) (9). To a stirred solution of Na (0.37 g, 16 mmol) in ethanol (25 mL) under N_2 was added 3-mercaptopropionic acid (0.85 g, 8 mmol). After 5 min, a solution of 2,6-bis(bromomethyl)pyridine (1.06 g, 4 mmol) in ethanol (25 mL) was added and the mixture was heated under reflux for 1 h. After evaporation of the solvent, the residue was dissolved in H_2O (7 mL) and the pH adjusted to 3.6 with 6 M HCl. The aqueous solution was saturated with NaCl and extracted with ethyl acetate (3 × 50 mL). Afer washing (brine), drying, evaporation of solvent, and recrystallization ($CHCl_3$/petrol) the acid **9** was obtained: white needles (0.85 g, 67%), mp 104–5 °C; NMR ($CDCl_3$) δ 9.65 (br s, 2 H, CO_2H), 7.65 (m, 1 H, H-4), 7.26 (d, *J* = 8 Hz, 2 H, H-3,5), 3.85 (s, 4 H, H-5′), 2.68 (m, 8 H, H-2′,3′). Anal. ($C_{13}H_{17}NO_4S_2$) C, H, N.

Synthesis of Porphyrin 10 [(P)–(NS_2)]. A mixture of the foregoing acid **9** (0.37 g, 1.17 mmol) and thionyl chloride (2.0 mL) was heated at 50 °C for 10 min and at 25 °C for 15 min. The excess of $SOCl_2$ was pumped off; benzene (2 mL) was added, and the solution was evaporated to dryness. CH_2Cl_2 (2 mL) was added and the solution pumped to dryness. The resultant crude acid chloride **8** in CH_2Cl_2 (110 mL) was added dropwise and under N_2 to an efficiently stirred solution of pyridine (5 mL) in CH_2Cl_2 (100 mL) at 25 °C, while concurrently, and at the same drop rate, was added a solution of the porphyrin **4** (0.54 g, 0.89 mmol) in CH_2Cl_2 (110 mL) containing trifluoroacetic acid (0.15 mL, 2.0 mmol). After the addition was complete (ca. 30 min), the mixture was stirred for a further 1 h at 25 °C. Water (100 mL) was added. The organic layer was washed with $NaCHO_3$ (saturated aqueous 200 mL) and H_2O (200 mL), evaporated, and pumped to remove the excess of pyridine. After filtration of a small amount of $CHCl_3$-insoluble material, the reaction mixture was chromatographed (silica, 2.5 × 25 cm, $CHCl_3$). Elution with 5% MeOH in $CHCl_3$ first removed the major porphyrinic band, closely followed by a minor band. Recrystallization of the major fraction with $CHCl_3$–MeOH produced purple crystals of **10** as the monohydrate (0.54 g, 70%): NMR ($CDCl_3$) δ 10.27 (s, 2 H, H-10,20), 8.68 (m, 2 H, ArH), 8.08 (m, 2 H, ArH), 7.83 (m, 2 H, ArH), 7.55 (m, 2 H, ArH), 6.66 (s, 2 H, NH), 5.34 (t, *J* = 8 Hz, 1 H, pyH-4), 4.75 (d, *J* = 8 Hz, 2 H, pyH-3.5), 3.53 (s, 12 H, CH_3), 2.66 (s, 2 H, H_2O), 2.48 (s, 12 H, CH_3), 1.58 (t, *J* = 7 Hz, 4 H, CH_2), 1.13 (t, *J* = 7 Hz, 4 H, CH_2), 1.13 (s, 4 H, CH_2), −1.9 (br s, 2 H, pyrrole NH); mass spectrum (70 eV), *m/z* 882 (M^+), calcd 883; λ_{max} ($CHCl_3$) 385 (sh), 409, 498, 542, 574, 626 nm. Anal. ($C_{53}H_{53}N_7O_2S_2$·H_2O) C, H, N.

Registry No. **1**, 5109-25-1; **2**, 78987-07-2; **3**, 78987-08-3; **4**, 78987-09-4; **5**, 79055-85-9; **6**, 78987-10-7; **7**, 79055-86-0; **8**, 78987-11-8;

9, 78987-12-9; 10, 78987-13-0; o-nitrobenzaldehyde, 552-89-6; 5,15-bis(o-nitrophenyl)-2,3,7,8,12,13,17,18-octamethylporphyrin, 78987-14-1; 5-[o-(acetylamino)phenyl]-2,3,7,8,12,13,17,18-octamethylporphyrin, 78987-15-2; 3-mercaptopropionic acid, 107-96-0; 2,6-bis(bromomethyl)pyridine, 7703-74-4.

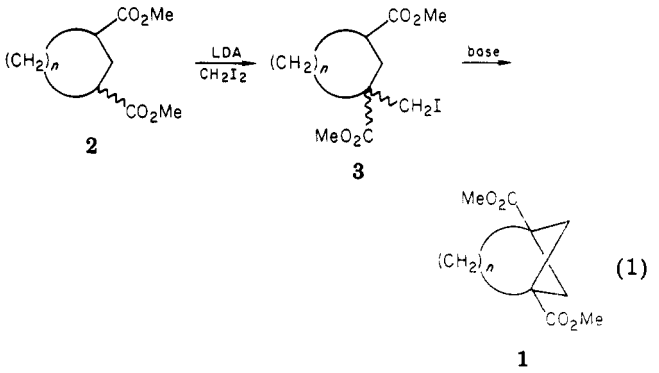
A General Approach to the Synthesis of Bridgehead-Bridgehead Disubstituted Bicyclo[n.1.1]alkanes[1]

Philip M. Warner,*[2] Bing-Lin Chen, and Eiji Wada

Department of Chemisry, Iowa State University, Ames, Iowa 50011

Received September 30, 1980

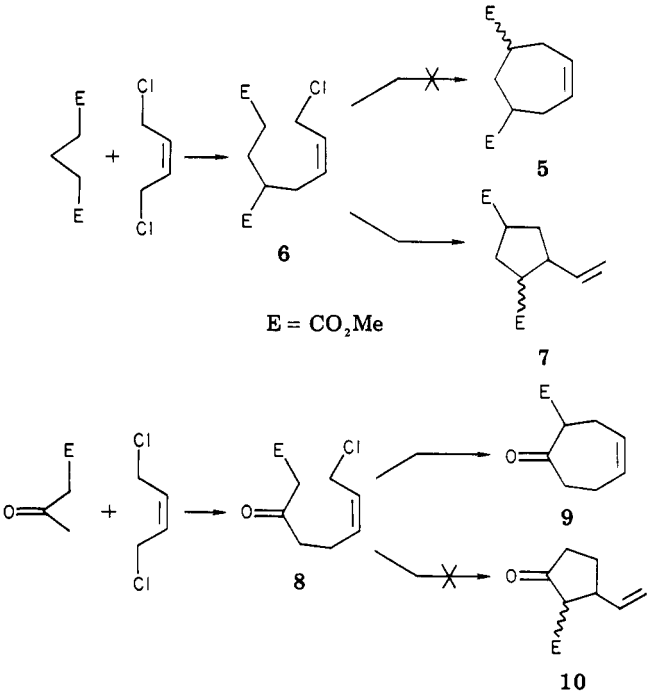
Our interest in bridgehead olefins[3] and paddlanes[4] has necessitated the synthesis of some bicyclo[n.1.1]alkanes in which both bridgeheads are substituted with functionalized groups. In particular, we have been pursuing the group of diesters 1, of which **1a**[5] and **1b**[6] are known. This report relates a simple, general approach (eq 1), so far successful for **1b–1d**.[16]



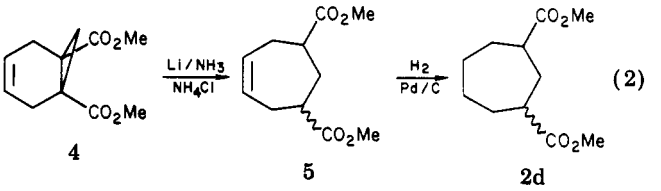
a, $n = 1$; b, $n = 2$; c, $n = 3$; d, $n = 4$

Thus the requisite starting material is the diester **2**, readily obtainable in the cases of **2b**[7] and **2c**,[8] but rather difficultly available for **2a** and **2d**. Diester **2** is alkylated with LDA/CH_2I_2, whereby **3** is produced. Further internal alkylation (i.e., cyclization) is effected with KH or LDA as the base. Our attempts to carry out the conversion of **2** to **1** in one pot (i.e., with excess LDA) have met with failure or very poor yields. (The fact that LDA can be used for the cyclization step suggests that the dianion from **2** does not react smoothly.)

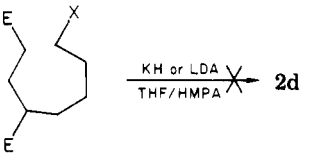
Scheme I



The synthesis of **2d** was ultimately achieved via the reduction of **4**[9] (eq 2). This method was utilized after the



approach involving dimethyl glutarate, patterned after the successful synthesis of **9**,[10] produced **7** rather than **5** (Scheme I), and all attempts to cyclize **11** failed to produce **2d** in useful amounts. The fact that **6** afforded **7**, whereas **8** did not yield the analogous five-membered ring compound, **10**, may be attributed to the prohibition of the 5-endo-trigonal transition state for cyclization,[11] which would be required for **8** to yield **10**. On the other hand, **6** gives **7** via a 5-exo-trigonal transition state.



11a, X = Cl
b, X = Br

Experimental Section

1-(Iodomethyl)-1,3-bis(carbomethoxy)cyclopentane (3b). To a solution of 4.6 g of diisopropylamine and ca. 1 mg triphenylmethane (indicator) in 200 mL of THF was added 18.2 mL of 2.5 M *n*-BuLi (45 mmol) at 0 °C under N_2. The resulting mixture was stirred for 15 min at 0 °C, whereby a red solution was obtained. To this solution at −78 °C was added dropwise a solution of 6.51 g (35 mmol) of *cis*-bis(carbomethoxy)cyclopentane[7] (**2b**) in 15 mL of THF, and the resulting mixture, was stirred for

(1) We thank the donors or the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.
(2) Alfred P. Sloan Foundation Fellow, 1976–1980.
(3) (a) Warner, P.; Chang, S.-C.; Powell, D. R.; Jacobson, R. A. *J. Am. Chem. Soc.* **1980**, *102*, 5125. (b) Warner, P.; Boulanger, W. *Tetrahedron Lett.* **1980**, 123. (c) Warner, P.; Chang, S.-C. *Ibid.* **1979**, 4141. (d) Warner, P.; Lu, S.-L.; Myers, E.; DeHaven, P. W.; Jacobson, R. A. *J. Am. Chem. Soc.* **1977**, *99*, 5102. (e) Warner, P.; Palmer, R. F.; Lu, S.-L. *Ibid.* **1977**, *99*, 3773. (f) Warner, P.; Lu, S.-L. *Ibid.* **1976**, *98*, 6752.
(4) Warner, P.; Chen, B.-L.; Bronski, C. A.; Karcher, B. A.; Jacobson, R. A. *Tetrahedron Lett.* **1981**, 375.
(5) Applequist, D. E.; Wheeler, J. W. *Ibid.* **1977**, 3411. This paper describes the synthesis of the diacid corresponding to **1a**.
(6) Bloomfield, J. J.; Owsley, D. C. *Ibid.* **1973**, 1795.
(7) Frickel, F. *Synthesis* **1974**, 507.
(8) Schneider, W.; Goetz, H., *Arch Pharm. (Weinheim, Ger.)* **1961**, *294*, 506.
(9) (a) Vogel, E.; et al. *Tetrahedron Lett.* **1970**, 1941. (b) Wilson, S. R.; Turner, R. B. *J. Org. Chem.* **1973**, *38*, 2870.
(10) Borch, R. F.; Ho, B. C. *J. Org. Chem.* **1977**, *42*, 1225.
(11) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734, 738.

0022-3263/81/1946-4795$01.25/0