105, 91, 75; CIHRMS M + NH_4^+ (calculated for $C_{17}H_{28}NO_4$) 310.2018, (found) 310.2010; $[\alpha]^{23}_D$ = +34.4° (c 0.75, CH_2Cl_2).

(*E*)-(2*S*,5*S*,6*S*)-Methyl 6-(benzyloxy)-2-methoxy-4-methyldec-3-enoate (3b): ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.25 (m, 5 H), 5.93 (dd, 1 H, *J* = 7.2, 15.6 Hz), 5.47 (dd, 1 H, *J* = 7.2, 15.6 Hz), 4.53 and 4.49 (AB q, 2 H, J_{AB} = 11.5 Hz), 4.21 (d, 1 H, *J* = 7.6 Hz), 3.74 (s, 3 H), 3.36 (s, 3 H), 3.28–3.25 (m, 1 H), 2.54–2.52 (m, 1 H), 1.60–1.25 (m, 6 H), 1.05 (d, 3 H, *J* = 3.2 Hz), 0.87 (t, 3 H, *J* = 6.8 Hz); IR (neat) ν_{max} 3000–2800, 1750, 1500, 1480, 1370, 1350, 1100 cm^{-1}; CIMS (NH_3 gas) 352, 335, 303, 247, 227, 195, 157, 127, 91, 75; CIHRMS M + NH_4^+ (calculated for $C_{20}H_{34}NO_4$) 352.2488, (found) 352.2491; $[\alpha]^{23}_D$ = +21.6° (c 0.5, CH_2Cl_2).

(*E*)-(2*S*,5*S*,6*S*)-Methyl 6-(benzyloxy)-6-isopropyl-2-methoxy-4-methylhex-3-enoate (3c): ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.23 (m, 5 H), 5.83 (dd, 1 H, *J* = 8, 15.6 Hz), 5.41 (dd, 1 H, *J* = 7.2, 15.6 Hz), 4.46 and 4.43 (AB q, 2 H, J_{AB} = 11.2 Hz), 4.12 (d, 1 H, *J* = 7.2 Hz), 3.63 (s, 3 H), 3.27 (s, 3 H), 2.91 (t, 1 H, *J* = 5.6 Hz), 2.42–2.39 (m, 1 H), 1.76–1.71 (m, 1 H), 0.99 (d, 3 H, *J* = 6.4 Hz), 0.85 (d, 6 H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 140.4, 138.9, 128.27, 127.4, 123.7, 88.5, 81.4, 75.1, 57.1, 52.1, 39.7, 37.3, 31.1, 20.3, 17.7, 15.2; IR (neat) ν_{max} 2900, 1750, 1500, 1450, 1370, 1350, 1200, 1100 cm^{-1}; CIMS (NH_3 gas) 338, 321, 289, 247, 217, 213, 181, 163, 127, 91, 75; CIHRMS M + NH_4^+ (calculated for $C_{19}H_{32}NO_4$) 338.2337, (found) 338.2331; $[\alpha]^{23}_D$ = +76° (c 0.25, CH_2Cl_2).

(*E*)-(2*S*,5*R*,6*S*)-Methyl 6-(benzyloxy)-2,5,7,7-tetramethyloct-3-enoate (3d): ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.15 (m, 5 H), 5.52 (dd, 1 H, *J* = 7.6, 15.6 Hz), 5.36 (dd, 1 H, *J* = 7.6, 15.6 Hz), 4.51 and 4.49 (AB q, 2 H, J_{AB} = 11.6 Hz), 3.55 (s, 3 H), 3.03–2.99 (m, 1 H), 2.88 (d, 1 H, *J* = 3.6 Hz), 2.45–2.43 (m, 1 H), 1.15 (d, 3 H, *J* = 7.2 Hz), 0.99 (d, 3 H, *J* = 6.8 Hz), 0.86 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 139.3, 138.9, 128.2, 127.4, 127.2, 126.6, 90.4, 74.9, 51.7, 42.8, 38.1, 37.0, 27.2, 17.3, 15.9; IR (neat) ν_{max} 3100–2800, 1740, 1450, 1380, 1200, 1100, 950, 750, 700 cm^{-1}; CIMS (NH_3 gas) 336, 276, 261, 211, 199, 155, 141, 91, 85, 73, 57; CIHRMS M + NH_4^+ (calculated for $C_{20}H_{34}NO_3$) 336.2537, (found) 336.2538; $[\alpha]^{23}_D$ = +28.1° (c 1.1, CH_2Cl_2).

(*E*)-(2*S*,5*R*,6*S*)-Methyl 6-(benzyloxy)-6-cyclohexyl-2,5-dimethylhex-3-enoate (3e): ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.25 (m, 5 H), 5.58–5.51 (m, 2 H), 4.55 and 4.49 (AB q, 2 H, J_{AB} = 11.2 Hz), 3.64 (s, 3 H), 3.14–3.10 (m, 1 H), 2.99 (t, 1 H, *J* = 5.6 Hz), 2.48–2.45 (m, 1 H), 1.92–1.61 (m, 7 H), 1.24 (d, 3 H, *J* = 6.8 Hz), 1.22–1.09 (m, 4 H), 1.05 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 139.1, 136.08, 128.3, 127.9, 127.5, 127.3, 88.2, 75.1, 57.1, 51.7, 42.8, 41.1, 39.1, 30.6, 28.3, 26.6, 26.6, 17.4, 15.1; IR (neat) ν_{max} 3100–2750, 1780, 1450, 1280, 1200, 1100, 950, 750, 700 cm^{-1}; CIMS (NH_3 gas) 237, 205, 149, 141, 91, 85; CIHRMS M + NH_4^+ (calculated for $C_{22}H_{36}NO_3$) 362.2695, (found) 362.2697; $[\alpha]^{23}_D$ = +32.9° (c 0.75, CH_2Cl_2).

(*E*)-(2*R*,5*S*,6*R*)-Methyl 6,7-bis(benzyloxy)-2-methoxy-5-methylhept-3-enoate (3f): ^1H NMR (400 MHz, $CDCl_3$) δ 7.28–7.16 (m, 10 H), 5.84–5.76 (dd, 1 H, *J* = 7.6, 15.6 Hz), 5.44–5.38 (dd, 1 H, *J* = 7.2, 15.6 Hz), 4.61 and 4.46 (AB q, 2 H, J_{AB} = 11.6 Hz), 4.43 and 4.40 (Ab q, 2 H, J_{AB} = 12.0 Hz), 4.09 (d, 1 H, *J* = 7.2 Hz), 3.62 (s, 3 H), 3.58–3.39 (m, 3 H), 3.23 (s, 3 H), 2.49–2.48 (m, 1 H), 0.97 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 139.1, 138.8, 138.3, 128.4, 128.4, 128.3, 128.2, 127.9, 127.9, 127.8, 127.6, 127.5, 124.5, 81.5, 81.4, 77.2, 73.4, 72.7, 71.2, 57.0, 52.2, 38.6, 15.2; IR (neat) ν_{max} 3100, 2200, 1725, 1635, 1450, 1200, 1100 cm^{-1}; CIMS (NH_3 gas) 416, 226, 189, 181, 145, 104, 91, 75; CIHRMS M + NH_4^+ (calculated for $C_{24}H_{34}NO_5$) 416.5377, (found) 416.53774; $[\alpha]^{23}_D$ = +32.97° (c 0.56, CH_2Cl_2).

(*E*)-(2*R*,5*S*,6*R*)-Methyl 6-(2,5-dimethoxyphenyl)-2,6-dimethoxy-5-methylhex-3-enoate (3g): ^1H NMR (400 MHz, $CDCl_3$) δ 6.88–6.87 (m, 1 H), 6.75–6.74 (m, 2 H), 5.89–5.83 (dd, 1 H, *J* = 7.6, 15.2 Hz), 5.38–5.33 (dd, 1 H, *J* = 7.6, 15.6 Hz), 4.49 (d, 1 H, *J* = 6.0 Hz), 4.13 (d, 1 H, *J* = 7.6 Hz), 3.77 (s, 3 H), 3.76 (s, 3 H), 3.72 (s, 3 H), 3.22 (s, 3 H), 3.20 (s, 3 H), 2.55 (m, 1 H), 1.02 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 153.6, 151.5, 139.6, 129.8, 123.9, 113.0, 112.6, 111.2, 81.3, 80.4, 57.1, 56.5, 55.7, 55.6, 51.9, 42.2, 14.9; IR (neat) ν_{max} 2995, 1750, 1490, 1475, 1275, 1210, 1100, 1050; CIMS (NH_3 gas) 338, 275, 243, 215, 181, 151, 95, 75, 45; CIHRMS M + NH_4^+ (calculated for $C_{18}H_{30}NO_6$) 356.2073, (found) 356.2071; $[\alpha]^{23}_D$ = +17.24° (c 1.0, CH_2Cl_2).

(*E*)-(2*S*,5*S*,6*R*)-Methyl 6-(benzyloxy)-6-(2,3-dimethoxyphenyl)-2-acetoxy-5-methylhex-3-enoate (3h): ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.26 (m, 5 H), 7.06 (t, 1 H, *J* = 8.0 Hz), 6.98 (d, 1 H, *J* = 6.4 Hz), 6.83 (d, 1 H, *J* = 6.8 Hz), 5.87 (dd, 1 H, *J* = 7.6, 15.6 Hz), 5.43 (dd, 1 H, *J* = 7.2, 15.6 Hz), 5.29 (d, 1 H, *J* = 7.6 Hz), 4.66 (d, 1 H, *J* = 6.8 Hz), 4.42 and 4.24 (AB q, 2 H, J_{AB} = 12 Hz), 3.87 (s, 3 H), 3.77 (s, 3 H), 3.65 (s, 3 H), 2.65–2.63 (m, 1 H), 2.04 (s, 3 H), 1.09 (d, 3 H, *J* = 6.4 Hz); ^{13}C NMR (67 MHz, $CDCl_3$) δ 170.1, 169.3, 152.3, 147.3, 139.9, 138.6, 133.9, 128.2, 127.6, 127.4, 123.8, 121.7, 119.6, 111.2, 78.2, 73.2, 70.7, 60.5, 55.6, 52.3, 42.6, 20.6, 15.1; IR (neat) ν_{max} 3050, 2950, 1730, 1600, 1490, 1430, 1280, 1230 cm^{-1}; CIHRMS M + NH_4^+ (calculated for $C_{25}H_{34}NO_7$) 460.2335, (found) 460.2348; $[\alpha]^{23}_D$ = +58.2° (c 1.5, CH_2Cl_2).

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Supplementary Material Available: NMR spectra for all reaction products (16 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Studies on the Synthesis of Pentacyclic *Strychnos* Indole Alkaloids. Closure of E Ring by Pummerer Cyclization

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The development of new, general synthetic routes to pentacyclic *Strychnos* indole alkaloids[1] based on the closure of the five-membered E ring, by formation of the crucial quaternary C-7[2] center in the last synthetic steps from appropriate hexahydro-1,5-methanoazocino[4,3-*b*]-indole systems, has received attention during the last years.[3,4] Cyclization of a thionium ion, such as **1a**, generated by treatment of *amino* dithioacetal **2a** with dimethyl(methylthio)sulfonium fluoroborate (DMTSF) was successful when R = H.[3] Following this procedure we have reported the total synthesis of the *Strychnos* alkaloids (±)-tubifoline, (±)-tubifolidine, (±)-19,20-dihydroakuammicine,[3] and (±)-tubotaiwine.[5] Similar cyclizations from thionium salts **1b**, generated either from *amido* dithioacetal **2b** (R = H) or by Pummerer rearrangement from *amido* sulfoxides **3b** (R = H, CO_2Me, *p*-$MeC_6H_4SO_2$, or *p*-$MeOC_6H_4SO_2$) resulted in failure.[3,4] Both our studies and those reported by Magnus have demonstrated that a limiting structural factor in the above cyclizations is the presence of an amide carbonyl group, either exocyclic or endocyclic with respect to the piperidine ring, since all

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0022-3263/92/1957-5792$03.00/0

Scheme I

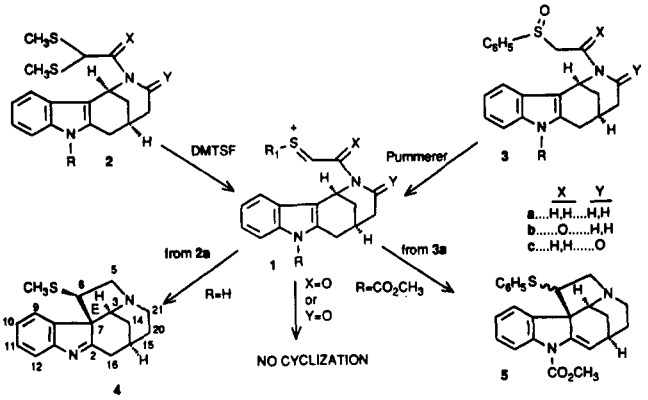
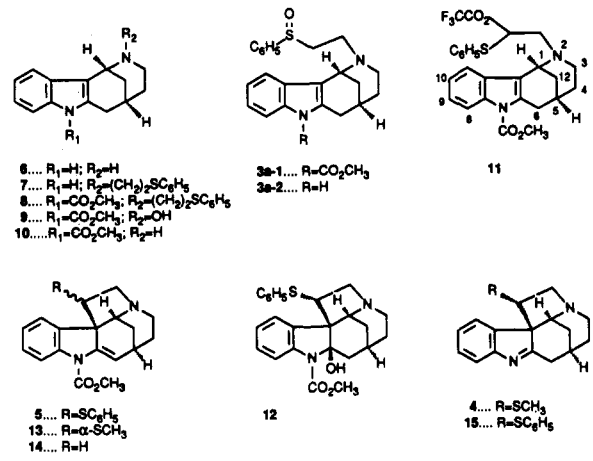


Chart I



attempts to bring about the cyclization from lactam dithioacetals **2c** (R = H, CO_2Me, or *p*-$MeOC_6H_4SO_2$) or from lactam sulfoxide **3c** (R = *p*-$MeOC_6H_4SO_2$) were also unsuccessful.[4,6] Related cyclizations of thionium ions generated by Pummerer reaction from sulfoxides have been extensively used by Magnus in the context of the synthesis of *Aspidosperma* aklaloids,[7] although in all reported cases the piperidine nitrogen in part of an *amide* (exocyclic or endocyclic) group.[8] The differences observed in the Pummerer reaction applied to the closure of the E ring of *Aspidosperma* and *Strychnos* alkaloids probably reflect the higher conformational flexibility of the fused tetracyclic precursors of *Aspidosperma* systems as compared with the conformationally rigid bridged *Strychnos* analogs.

We report now the use of the Pummerer reaction from *amino* sulfoxides **3a** as an alternative way of generating the required thionium ion intermediate **1a** and its cyclization to pentacyclic *Strychnos* systems, which constitutes the first synthetic entry to the *Strychnos* skeleton via a Pummerer cyclization. Worthy of mention is also the fact that there are few examples of Pummerer reactions[9] from *β-amino* sulfoxides.

The required sulfoxide **3a**–**1** was prepared in three steps as an equimolecular mixture of diastereomers from the tetracyclic secondary amine **6**,[10] by N_b-alkylation with 2-(phenylthio)ethyl bromide followed by methoxycarbonylation of the indole nitrogen in the resulting sulfide **7** and further oxidation of **8**·hydrochloride with $NaIO_4$. Attempts to effect the oxidation either with *m*-CPBA or from the sulfide **8** as the base produced sulfoxide **3a**-**1** in lower yields. In the latter case hydroxylamine **9** and phenyl vinyl sulfoxide, probably formed by β-elimination via an *N*-oxide intermediate, were also isolated from the reaction mixture.

As expected, conversion of sulfoxides **3a**-**1** to the presumed acyloxy sulfide intermediate **11** by the Pummerer reaction took place more slowly than from the analogous β-keto sulfoxides **3b**,[3] as it could be followed by ^1H NMR. Thus, when a sample of **3a**-**1** was treated with TFAA in $CDCl_3$, the signals at δ 3.99 and 4.19 (H-1 for both diastereomers) shifted to δ 4.94 and 5.04. After 5 min only small signals at δ 5.12 and 5.20 along with two doublets of doublets at δ 6.40 (J = 10.0 and 2.6 Hz) and 6.56 (J = 9.4 and 1.8 Hz), corresponding to the methine H-1 and SC*H*O protons, respectively, of both diastereomers of **11**, could be observed. Conversion of sulfoxides **3a**-**1** to acyloxy sulfides **11** was complete after 2 h. Consequently, sulfoxides **3a**-**1** were allowed to react with TFAA in CH_2Cl_2 at room temperature for 2 h, the solvent was eliminated under vacuum, and the mixture was refluxed in toluene for 3 h. Under these conditions the major product was the secondary amine **10** resulting from hydrolysis of the exocyclic iminium ion formed through the equilibrium thionium ion ⇄ vinyl sulfide (enamine) ⇄ iminium ion.[11] Only traces of the desired pentacyclic compound **5** (H-6β epimer) could be detected by ^1H NMR. However, when BF_3·Et_2O was added to the initially formed acyloxy sulfide intermediate **11**, and the resulting solution was refluxed in CH_2Cl_2 for 4 h, a mixture of pentacyclic compounds **5** (epimeric mixture at C-6) and **12** was obtained in approximately 50% overall yield. The assignment of the two epimers **5** was effected by comparison of the ^1H NMR signals with those of the methylthio analog **13**, prepared by N-methoxycarbonylation of **4**, and by the upfield shift observed for H-6 in the H-6α epimer (δ 3.70), as compared with the H-6β epimer (δ 4.40), due to the anisotropic effect of the aromatic ring. The major compound **12**, which was converted to the H-6β epimer of **5** by treatment with *p*-TsOH in benzene at room temperature, probably arises from the *N*-acyliminium salt initially formed after the cyclization step, either by direct addition of water or by addition of trifluoroacetate ion followed by hydrolysis. The ^1H NMR resonance of H-6 in **12** is dramatically shifted to δ 5.21 (compare with the values in **5**), due to the deshielding effect exerted by the C-2 hydroxy group.

The success in the BF_3·Et_2O-induced Pummerer cyclization of **3a**-**1** may be attributed to the ability of this reagent to generate a thionium ion under milder conditions by enhancing the leaving group character of the acyloxy substituent in the intermediate **11**. On the other hand, under these conditions a piperidine–BF_3 adduct probably prevents the formation of the exocyclic iminium ion, thus avoiding the competing undesirable N-dealkylation.

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The Pummerer reaction from the N_a-unsubstituted sulfoxide **3a-2** should induce the formation of a thionium ion **1a** (R = H, R_1 = SC_6H_5), similar to the one (**1a**: R = H, R_1 = SCH_3) generated by DMTSF treatment of dithioacetal **2a** (R = H) which satisfactorily cyclizes[3] to pentacycle **4**. However, rather surprisingly, when sulfoxide **3a-2**, prepared as a diastereomeric mixture by $NaIO_4$ oxidation of sulfide **7**·hydrochloride, was subjected to standard Pummerer conditions (TFAA followed by heating at 130 °C in chlorobenzene), the known tetracyclic secondary amine **6** was obtained as the only identifiable product. This result makes evident that the protonation–deprotonation equilibria leading to the exocyclic iminium salt again occur faster than cyclization, even in the absence of the deactivating effect of the N_a-methoxycarbonyl substituent. The success of the DMTSF-induced cyclization of **2a** (R = H),[3] in contrast with the failure of the Pummerer cyclization of **3a-2**, can be accounted for by considering that, in the presence of DMTSF, methylsulfenylation occurs on the piperidine nitrogen to give a (methylthio)ammonium ion,[12] which is hydrolyzed once the cyclization has taken place, a role similar to that played by BF_3·Et_2O in the above successful cyclization of **3a-1**. When the Pummerer reaction from sulfoxide **3a-2** was carried out under the conditions satisfactorily used for the cyclization of **3a-1** (in the presence of BF_3·Et_2O in refluxing CH_2Cl_2) untractable mixtures were formed, from which neither the desired pentacyclic compound **15** nor the secondary amine **6** could be isolated. The instability of tetracyclic hexahydro-1,5-methanoazocino[4,3-*b*]indoles[13] or the resulting pentacyclic indolenines under the acylating conditions of the Pummerer reaction could explain this result.

Finally, Raney nickel hydrogenolysis of the C-S bond of **5** (separate epimers) and **13** afforded the same pentacyclic compound **14**, the C-20 deethyl analog of the last synthetic intermediate in our synthesis of tubifoline, 19,20-dihydroakuammicine and tubotaiwine.[3,5]

The results here described establish that the closure of the five-membered E ring of pentacyclic *Strychnos* indole alkaloids can be efficiently achieved by intramolecular electrophilic attack on the indole 3-position of a thionium ion generated by the Pummerer reaction from an appropriate sulfoxide provided that the piperidine nitrogen is an amine rather than an amide. On the other hand, the use for the first time of a *β-amino* sulfoxide in the intramolecular Pummerer reaction applied to the synthesis of pentacyclic indole alkaloids deserves interest and further application.

Experimental Section

Melting points were determined in open capillary tubes and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 200 and 50.3 MHz, respectively. Chemical shifts are expressed in parts per million downfield (δ) from TMS as internal standard. Only noteworthy IR absorptions (reciprocal centimeters) are listed. Flash chromatography was carried out on SiO_2 (silica gel 60, 0.040–0.063 mm). Thin-layer chromatography was carried out on SiO_2 (silica gel 60 F_{254}, 0.063–0.200 mm), and the spots were located with iodoplatinate reagent or UV light. Purification of reagents and solvents was effected according to standard methods. All reactions were carried out under nitrogen or argon atmosphere. Prior to concentration, under reduced pressure, all organic extracts were dried over anhydrous $MgSO_4$ or Na_2SO_4 powder. All compounds were synthesized in the racemic series. Microanalyses were performed by Centro de Investigación y Desarrollo (CSIC), Barcelona.

2-[2-(Phenylthio)ethyl]-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (7). A mixture of **6**[10] (600 mg, 2.8 mmol), 2-(phenylthio)ethyl bromide[14] (920 mg, 4.2 mmol), and anhydrous Na_2CO_3 (450 mg, 4.2 mmol) in dioxane (45 mL) was refluxed for 24 h. Removal of the solvent afforded a residue which was taken up with CH_2Cl_2. The solution was washed with brine, dried, and evaporated. Purification of the residue by flash chromatography (95:5 Et_2O–DEA) afforded **7** (837 mg, 85%): IR (KBr) 1620, 1580, 1450, 740 cm^{-1}; ^1H NMR δ 1.59 (dm, *J* = 13.0 Hz, 1 H, H-4eq), 1.81 (dq, *J* = 12.5, 5.5, 3.0 Hz, 1 H, H-12*R*), 1.50–2.65 (m, 2 H, H-3ax and H-4ax), 2.20 (dt, *J* = 12.5, 3.5 Hz, 1 H, H-12*S*), 2.36 (m, 1 H, H-5), 2.37 (m, 1 H, NCH), 2.58 (masked, 1 H, H-3eq), 2.59 (d, *J* = 17.0 Hz, 1 H, H-6ax), 2.95 (m, 1 H, NCH), 3.01 (dd, *J* = 17.0, 9.6 Hz, 1 H, H-6eq), 3.15 (m, 2 H, SCH_2), 4.18 (apparent t, 1 H, H-1), 7.00–7.45 (m, 9 H, Ar), 8.00 (br s, 1 H, NH); ^{13}C NMR δ 25.1 (C-5), 29.0 (C-6), 31.8 (CH_2S), 32.7 (C-4), 33.0 (C-12), 44.4 (C-3), 50.6 (CH_2N), 56.0 (C-1), 106.7 (C-11b), 110.4 (C-8), 118.2 (C-11), 119.6 (C-9), 120.8 (C-10), 125.9 (C-4′), 128.2 (C-11a), 128.9 (C-2′ and C-6′), 129.4 (C-3′ and C-5′), 135.7 (C-6a), 136.7 (C-1′), 136.8 (C-7a); mp 145–147 °C (Et_2O). Anal. Calcd for $C_{22}H_{24}N_2S$: C, 75.82; H, 6.94; N, 8.04; S, 9.20. Found: C, 75.85; H, 6.94; N, 8.16; S, 9.15.

Methyl 2-[2-(Phenylthio)ethyl]-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole-7-carboxylate (8). To a solution of sulfide **7** (2.0 g, 5.8 mmol) in THF (60 mL) was added *n*-BuLi (4.3 mL, 1.6 M in hexane, 6.9 mmol) at −78 °C. The temperature was raised to −50 °C, and the mixture was stirred for 45 min. Then, a solution of methyl chloroformate (0.67 mL, 8.6 mmol) in THF (10 mL) was slowly added at −78 °C, and stirring was continued for 3 h at 0 °C. The resulting mixture was poured into saturated aqueous $NaHCO_3$ solution and extracted with AcOEt. The organic extracts were dried and evaporated to give a foam which, after flash chromatography (97:3 Et_2O–DEA), afforded pure **8** (2.0 g, 87%): IR (KBr) 1720 cm^{-1}; ^1H NMR δ 1.60 (dm, *J* = 12.8 Hz, 1 H, H-4eq), 1.73 (dm, *J* = 12.0 Hz, 1 H, H-12*R*), 1.94 (tt, *J* = 12.8, 4.2 Hz, 1 H, H-4ax), 2.11 (masked, 1 H, H-3ax), 2.14 (dt, *J* = 12.0, 3.0 Hz, 1 H, H-12*S*), 2.34 (m, 1 H, NCH), 2.37 (m, 1 H, H-5), 2.62 (dm, *J* = 11.0 Hz, 1 H, H-3eq), 2.92 (m, 1 H, NCH), 2.94 (d, *J* = 18.0 Hz, 1 H, H-6ax), 3.06 (m, 2 H, SCH_2), 3.18 (dd, *J* = 18.0, 8.0 Hz, 1 H, H-6eq), 4.02 (s, 3 H, CH_3O), 4.11 (apparent t, 1 H, H-1), 7.10–7.40 (m, 8 H, Ar-H), 8.10 (m, 1 H, H-8); ^{13}C NMR δ 25.4 (C-5), 32.0 (C-6), 32.0 (CH_2S), 32.1 (C-4), 32.7 (C-12), 44.2 (C-3), 50.5 (C-1), 53.2 (CH_3O), 56.2 (CH_2N), 113.7 (C-11b), 115.4 (C-8), 118.2 (C-11), 123.1 (C-10), 123.4 (C-9), 126.0 (C-4′), 128.9 (C-2′ and C-6′), 129.6 (C-3′ and C-5′), 130.1 (C-11a), 135.7 (C-6a), 136.7 (C-7a), 138.3 (C-1′), 152.7 (C=O). For the picrate: mp 185–187 °C (EtOH). Anal. Calcd for $C_{30}H_{29}N_5O_9S$: C, 56.69; H, 4.60; N, 11.02; S, 5.04. Found: C, 56.58; H, 4.68; N, 10.89; S, 4.87.

Methyl 2-[2-(Phenylsulfinyl)ethyl]-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole-7-carboxylate (3a-1). To an ice-cold solution of **8**·hydrochloride (900 mg, 2.0 mmol) in 2:1 dioxane–EtOH (90 mL) was added dropwise a solution of $NaIO_4$ (457 mg, 2.1 mmol) in H_2O (11 mL). The mixture was stirred at rt for 48 h, filtered, concentrated under vacuum, diluted with 10% aqueous Na_2CO_3, and extracted with AcOEt. The extracts were washed with brine and dried. Removal of the solvent followed by flash chromatography (95:5 Et_2O–DEA) afforded starting material **8** (250 mg) and sulfoxide **3a-1** (582 mg, 68%, mixture of diastereomers): IR (KBr) 1720, 1020 cm^{-1}; ^1H NMR δ 1.60 (dm, *J* = 12.8 Hz, H-4eq), 2.38 (m, H-5), 2.94 (d, *J* = 18.0 Hz, H-6ax), 3.15 (dd, *J* = 18.0, 8.0 Hz, H-6eq), 3.99 and 4.19 (2 apparent t, 1 H, H-1), 4.01 (s, 3 H, CH_3O), 7.10–7.70 (m, 8 H, Ar), 8.10 (m, 1 H, Ar); ^{13}C NMR δ 24.5 (C-5), 31.1 (C-4), 31.2 (C-6), 31.7 and 31.9 (C-12), 42.9 and 43.1 (C-4), 48.6 and 48.7 (CH_2SO), 49.6 and 50.2 (C-1), 52.5 (CH_3O), 55.0 and 55.4 (CH_2N), 112.7 and 112.8 (C-11b), 114.6 (C-8), 117.2 and 117.5 (C-11), 122.3 (C-9), 122.7 (C-2′ and C-6′), 123.3 and 123.5 (C-10), 128.4 (C-3′ and C-5′), 129.1 (C-11a), 130.1 and 130.2 (C-4′), 134.8 (C-6a), 137.5 and 137.6

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(C-7a), 143.3 and 143.6 (C-1'), 151.8 (C=O). For a mixture of diastereomers: mp 165–168 °C (C_6H_6). Anal. Calcd for $C_{24}H_{26}N_2O_3S$: C, 68.22; H, 6.20; N, 6.63; S, 7.59. Found: C, 68.13; H, 6.33; N, 6.58; S, 7.74.

Operating as above, from **8** as the base (1.5 g, 3.7 mmol) and $NaIO_4$ (1.0 g, 4.8 mmol) in 2:1:1 dioxane–EtOH–H_2O (80 mL) for 18 h, a mixture of **3a-1** and **methyl 2-hydroxy-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole-7-carboxylate (9)** was obtained and then separated by flash chromatography. Elution with AcOEt afforded **9** (215 mg, 31%): IR (KBr) 3205, 1735 cm^{-1}; ^1H NMR δ 1.73 (dm, J = 13.0 Hz, 1 H, H-4eq), 1.85–2.05 (m, 2 H, H-4ax and H-12R), 2.12 (dt, J = 12.5, 3.3 Hz, 1 H, H-12S), 2.32 (br s, 1 H, H-5eq), 2.54 (td, J = 12.5, 3.7 Hz, 1 H, H-3ax), 2.95 (d, J = 19.0 Hz, 1 H, H-6ax), 3.00 (masked, 1 H, H-3eq), 3.24 (dd, J = 19.0, 7.0 Hz, 1 H, H-6eq), 4.05 (s, 3 H, CH_3O), 4.61 (br s, 1 H, H-1), 7.25 (m, 2 H, H-9 and H-10), 7.67 (m, 1 H, H-11), 8.12 (m, 1 H, H-8); ^{13}C NMR δ 24.4 (C-5), 31.1 (C-12), 32.0 (C-6), 32.4 (C-4), 49.5 (C-3), 53.2 (CH_3O), 54.9 (C-1), 113.7 (C-11b), 115.3 (C-8), 119.4 (C-11), 123.1 (C-10), 123.6 (C-9), 130.3 (C-11a), 135.8 (C-6a), 138.5 (C-7a), 152.7 (C=O); MS m/e 286 (M^+), 269, 252, 227, 226, 225, 194, 180, 168, 167 (base), 166, 59; mp 165–167 °C (EtOH). Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.16; H, 6.47; N, 9.53. On elution with 95:5 AcOEt–DEA, pure **3a-1** (470 mg, 45%) was obtained.

2-[2-(Phenylsulfinyl)ethyl]-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (3a-2). To an ice-cold solution of **7**·hydrochloride (862 mg, 2.2 mmol) in EtOH (40 mL) was added dropwise a solution of $NaIO_4$ (503 mg, 2.4 mmol) in H_2O (11 mL). After being stirred at rt for 14 h and the usual workup, the mixture was chromatographed (flash; 9:1 Et_2O–DEA) to give **3a-2** (716 mg, 87%) as a mixture of diastereomers: IR ($CHCl_3$) 3460, 1035 cm^{-1}; ^1H NMR δ 1.59 (dm, J = 13.0 Hz, H-4eq), 1.82 (dm, J = 12.5 Hz, H-12R), 2.36 (m, H-5), 2.59 (d, J = 17.0 Hz, H-6ax), 3.03 (dd, J = 17.0, 9.6 Hz, H-6eq), 4.04 and 4.23 (2 apparent t, 1 H, H-1), 7.00–7.53 (m, 9 H, Ar), 8.23 and 8.25 (2 br s, 1 H, NH); ^{13}C NMR δ 25.1 (C-5), 28.9 (C-6), 32.6 (C-4), 32.9 (C-12), 43.9 (C-3), 49.2 and 49.4 (CH_2SO), 50.5 and 51.0 (C-1), 55.7 and 56.1 (CH_2N), 106.0 and 106.2 (C-11b), 110.6 (C-8), 117.7 and 117.9 (C-11), 119.3 (C-9), 120.5 (C-10), 124.2 and 124.4 (C-2' and C-6'), 128.0 (C-11a), 129.2 (C-3' and C-5'), 131.1 (C-4'), 135.8 (C-6a), 137.1 and 137.2 (C-7a), 143.8 and 144.1 (C-1').

Pummerer Rearrangement of 3a-1. Method A. To a solution of **3a-1** (380 mg, 0.9 mmol) in CH_2Cl_2 (15 mL) was added TFAA (0.5 mL, 3.6 mmol), and the mixture was stirred at rt for 2 h. Then, the solvent was evaporated, and toluene (20 mL) was added. After being stirred at 110 °C for 3 h, the mixture was poured into 2 N aqueous $NaHCO_3$ and extracted with AcOEt. The combined organic extracts were dried and evaporated to give a residue which, after column chromatography (9:1 Et_2O–DEA), afforded **methyl 1,2,3,4,5,6-hexahydro-1,5-methanoazocino-[4,3-*b*]indole-7-carboxylate (10**; 110 mg, 45%): IR ($CHCl_3$) 1710 cm^{-1}; ^1H NMR 1.58 (dm, J = 13.0 Hz, 1 H, H-4eq), 1.82 (dq, J = 12.5, 5.0, 3.0 Hz, 1 H, H-12R), 1.94 (m, 1 H, H-4ax), 2.12 (dt, J = 12.5, 3.3 Hz, 1 H, H-12S), 2.45 (m, 1 H, H-5), 2.54–2.74 (m, 2 H, H-3), 3.00 (d, J = 19.0 Hz, 1 H, H-6ax), 3.25 (dd, J = 19.0, 7.0 Hz, 1 H, H-6eq), 4.05 (s, 3 H, CH_3O), 4.33 (apparent t, 1 H, H-1), 7.24 (m, 2 H, H-9 and H-10), 7.44 (m, 1 H, H-11), 8.15 (m, 1 H, H-8); ^{13}C NMR δ 26.1 (C-5), 31.7 (C-6), 31.7 (C-12), 33.0 (C-4), 37.5 (C-3), 44.1 (C-1), 53.2 (CH_3O), 115.7 (C-8), 116.7 (C-11b), 117.2 (C-11), 123.0 (C-10), 123.7 (C-9), 128.2 (C-11a), 136.1 (C-6a), 137.7 (C-7a), 152.7 (C=O). For the picrate: mp 210–212 °C (EtOH). Anal. Calcd for $C_{22}H_{21}N_5O_9 \cdot {}^1/_2H_2O$: C, 51.97; H, 4.36; N, 13.77. Found: C, 51.96; H, 4.47; N, 13.42.

Method B. A solution of **3a-1** (540 mg, 1.3 mmol) and TFAA (0.72 mL, 5.2 mmol) in CH_2Cl_2 (25 mL) was stirred at rt for 3 h. Then, BF_3·Et_2O (0.63 mL, 5.2 mmol) was added, and the mixture was refluxed for 4 h, cooled, and poured into 2 N aqueous $NaHCO_3$. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2. Evaporation of the combined organic extracts followed by flash chromatography (95:5 ether–DEA) gave a mixture of **5** and **12**, which was separated by a further flash chromatography. On elution with 95:5 $CHCl_3$–MeOH, pure **methyl 20-deethyl-2,16-didehydro-6α-(phenylthio)tubifolidine-1-carboxylate** (95 mg, 18%) followed by its C-6 epimer (45 mg, 9%) were obtained. **5** (H-6β epimer): IR (KBr) 1716 cm^{-1}; ^1H NMR δ 1.42 (dm, J = 12.7 Hz, 1 H, H-14R), 1.60–1.80 (m, 2 H, H-20), 1.96 (dm, J = 12.7 Hz, 1 H, H-14S), 2.57 (m, 1 H, H-15α), 2.66 (td, J = 12.4, 5.1 Hz, 1 H, H-21β), 2.86 (dd, J = 12.2, 10.7 Hz, 1 H, H-5α), 3.05 (dm, J = 12.4 Hz, 1 H, H-21α), 3.33 (dd, J = 12.2, 6.7 Hz, 1 H, H-5β), 3.82 (s, 3 H, CH_3O), 3.89 (br s, 1 H, H-3α), 4.40 (dd, J = 10.7, 6.7 Hz, 1 H, H-6β), 6.05 (d, J = 8.1 Hz, 1 H, H-16), 6.90–7.25 (m, 8 H, Ar-H), 7.45 (d, J = 7.8 Hz, 1 H, H-12); ^{13}C NMR Table I; MS m/e 404 (M^+), 295 (base), 268, 240, 239, 194, 180, 167, 82; HRMS calcd for $C_{24}H_{24}N_2O_2S$ 404.1558, found 404.1576. **5** (H-6α epimer): IR (KBr) 1714 cm^{-1}; ^1H NMR δ 1.42 (dm, J = 12.7 Hz, 1 H, H-14R), 1.74–1.90 (m, 2 H, H-20), 2.00 (dm, J = 12.7 Hz, 1 H, H-14S), 2.64 (m, 1 H, H-15α), 2.94–3.10 (m, 2 H, H-21), 3.00 (dd, J = 12.0, 3.3 Hz, 1 H, H-5β), 3.54 (dd, J = 12.0, 8.2 Hz, 1 H, H-5α), 3.70 (dd, J = 8.2, 3.3 Hz, 1 H, H-6α), 3.87 (s, 3 H, CH_3O), 3.99 (br s, 1 H, H-3α), 6.37 (d, J = 8.3 Hz, 1 H, H-16), 6.85–7.25 (m, 8 H, Ar-H), 7.61 (d, J = 7.8 Hz, 1 H, H-12); ^{13}C NMR Table I; MS m/e 404 (M^+), 295 (base), 268, 180, 167, 149, 83, 82, 57; HRMS calcd for $C_{24}H_{24}N_2O_2S$ 404.1558, found 404.1567. On elution with 9:1 $CHCl_3$–MeOH, pure **methyl 20-deethyl-2β-hydroxy-6α-(phenylthio)tubifolidine-1-carboxylate (12**; 127 mg, 24%) was obtained: IR (KBr) 1704 cm^{-1}; ^1H NMR δ 1.42 (dm, J = 13.5 Hz, 1 H, H-14R), 1.60–2.00 (m, 3 H, H-20 and H-14S), 1.95 (m, 1 H, H-15α), 2.41 (m, 2 H, H-16), 2.86 (ddd, J = 12.4, 5.8, 1.4 Hz, 1 H, H-21α), 3.00 (dd, J = 12.3, 9.2 Hz, 1 H, H-5α), 3.22 (td, J = 12.4, 5.4 Hz, 1 H, H-21β), 3.41 (br s, 1 H, H-3α), 3.42 (dd, J = 12.3, 7.7 Hz, 1 H, H-5β), 3.87 (s, 3 H, CH_3O), 5.21 (dd, J = 9.2, 7.7 Hz, 1 H, H-6β), 5.75 (br s, 1 H, OH), 6.85–7.30 (m, 9 H, Ar-H); ^{13}C NMR, Table I; MS m/e 422 (M^+), 313 (base), 295, 281, 237, 110, 97, 96, 82; HRMS calcd for $C_{24}H_{26}N_2O_3S$ 422.1664, found 422.1661.

Table I. ^{13}C NMR Data of Pentacyclic *Strychnos*-Type Systems[a]

C	5(H-6β)	5(H-6α)	12	13	14
C-2	148.0	144.5	93.5	147.9	148.3
C-3	61.0	61.5	65.2	60.9	61.0
C-5	62.2	61.2	63.0	62.7	53.8
C-6	56.0	62.0	47.8	55.3	41.9
C-7	55.9	57.5	60.3	56.0	52.4
C-8	135.0	134.4	135.7	131.7	136.9
C-9	122.4	120.4	122.6	122.4	119.4
C-10	123.5	123.7	125.9	123.6	123.8
C-11	126.6	126.1	126.1	127.9	127.3
C-12	114.8	115.3	114.3	114.8	115.0
C-13	142.2	143.9	139.6	142.3	141.1
C-14	29.0	28.9	29.1	29.9	29.4
C-15	26.8	26.7	23.0	27.0	27.0
C-16	114.7	119.7	42.4	114.4	114.1
C-20	26.2	25.6	26.4	26.4	26.2
C-21	46.1	46.3	44.3	46.2	45.2
C-1'	130.6	136.9	130.3		
C-2' and C-6'	128.6	128.8	128.3		
C-3' and C-5'	131.0	128.8	130.1		
C-4'	128.0	128.1	128.5		
CH_3O	52.5	52.6	52.5	52.8	52.6
C=O	152.6	154.7	154.6	152.5	153.3
CH_3S				15.8	

[a] In $CDCl_3$ solution.

Methyl 20-Deethyl-2,16-didehydro-6α-(methylthio)tubifolidine-1-carboxylate (13). To a solution of **4**[3] (100 mg, 0.35 mmol) in anhydrous DME (4 mL) was added a suspension of NaH (20 mg, 50% oil dispersion, 0.42 mmol) in DME (0.5 mL). The mixture was stirred at rt for 15 min, and then methyl chloroformate (0.06 mL, 0.77 mmol) was added. After being stirred at 60 °C for 1 h, the mixture was cooled, poured into 10% aqueous Na_2CO_3, and extracted with CH_2Cl_2. The combined organic extracts were dried and evaporated, and the residue was purified by flash chromatography (95:5 Et_2O–DEA) to give **13** (87 mg, 72%): IR ($CHCl_3$) 1700 cm^{-1}; UV (acetonitrile) λ_{max} 246, 197 nm; ^1H NMR δ 1.41 (dm, J = 13.0 Hz, 1 H, H-14R), 1.64 (s, 3 H, CH_3S), 1.70–1.86 (m, 2 H, H-20), 1.93 (dm, J = 13.0 Hz, 1 H, H-14S), 2.53 (m, 1 H, H-15α), 2.62 (td, J = 11.5, 5.4 Hz, 1 H, H-21β), 2.73 (dd, J = 12.2, 10.4 Hz, 1 H, H-5α), 3.01 (ddd, J = 11.5, 4.8, 2.4 Hz, 1 H, H-21α), 3.30 (dd, J = 12.2, 6.8 Hz, 1 H, H-5β), 3.80 (dd, J = 10.4, 6.8 Hz, 1 H, H-6β), 3.82 (br s, 1 H, H-3α), 3.90 (s, 3 H, CH_3O), 6.08 (d, J = 8.0 Hz, 1 H, H-16), 7.05 (td, J = 7.2, 1.0 Hz, 1 H, H-10), 7.12 (dm, J = 7.2 Hz, 1 H, H-9), 7.23 (ddd, J = 7.8,

7.2, 2.0 Hz, 1 H, H-11), 7.69 (d, J = 7.8 Hz, H-12); ^{13}C NMR Table I; MS m/e 342 (M^+), 295, 180, 167, 166, 82, 74, 59 (base), 41.

Methyl 20-Deethyl-2,16-didehydrotubifolidine-1-carboxylate (14). To a solution of **5** (H-6β apimer) (75 mg, 0.2 mmol) in absolute EtOH (5 mL) was added freshly prepared Raney Ni (W-2, 2 spatulas), and the mixture was refluxed for 4 h. The solids were removed by filtration and washed with EtOH. Removal of the solvent and purification of the residue by flash chromatography (95:5 Et_2O–DEA) gave **14** (23 mg, 41%): IR (KBr) 1718 cm^{-1}; ^{1}H NMR δ 1.42 (dm, J = 12.6 Hz, 1 H, H-14R), 1.65 (dd, J = 11.3, 7.2 Hz, 1 H, H-6α), 1.65–1.90 (m, 2 H, H-20), 1.96 (dt, J = 12.6, 2.6 Hz, 1 H, H-14S), 2.55 (m, 1 H, H-15α), 2.57 (td, J = 12.4, 5.1 Hz, 1 H, H-21β), 2.75–3.10 (m, 3 H, H-5 and H-6β), 2.92 (dm, J = 12.4 Hz, 1 H, H-21α), 3.80 (br s, 1 H, H-3α), 3.92 (s, 3 H, CH_3O), 6.07 (d, J = 8.1 Hz, 1 H, H-16), 7.04 (td, J = 7.4, 1.2 Hz, 1 H, H-10), 7.10–7.22 (m, 2 H, H-9 and H-11), 7.60 (d, J = 8.0 Hz, 1 H, H-12); ^{13}C NMR Table I; MS m/e 296 (M^+), 255, 240, 225, 194, 180, 167, 166, 95, 71 (base), 58; HRMS calcd for $C_{18}H_{20}N_2O_2$ 296.1525, found 296.1518.

Operating as above, from **5** (H-6α epimer) (20 mg, 0.05 mmol) in EtOH (2 mL) and Raney Ni (W-2, 1 spatula), pentacycle **14** (5 mg, 34%) was obtained.

Operating as for **5**, from **13** (17 mg, 0.05 mmol) in EtOH (2 mL) and Raney Ni (W-2, 1 spatula), the pentacyclic compound **14** (4 mg, 27%) was obtained.

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Registry No. (±)-**3a-1** (isomer 1), 143370-85-8; (±)-**3a-1** (isomer 2), 143370-97-2; (±)-**3a-2** (isomer 1), 143370-95-0; (±)-**3a-2** (isomer 2), 143370-98-3; (±)-**4**, 101481-16-7; (±)-6α-**5**, 143370-86-9; (±)-6β-**5**, 143370-94-9; (±)-**5**, 99552-97-3; (±)-**7**, 143370-87-0; (±)-**7**·HCl, 143370-99-4; (±)-**8**, 143370-88-1; (±)-**8**·HCl, 143370-96-1; (±)-**9**, 143370-89-2; (±)-**10**, 143370-90-5; (±)-**12**, 143370-91-6; (±)-**13**, 143370-92-7; (±)-**14**, 143370-93-8; $C_6H_5S(CH_2)_2Br$, 4837-01-8.

Supplementary Material Available: ^{1}H NMR spectra for compounds **3a-2** and **13** and ^{13}C NMR spectra for compounds **5** (both epimers), **12**, and **14** (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Variable-Temperature Dynamic ^{1}H NMR N–H Line-Shape Analysis for Meso-Monosubstituted Octaethylporphyrins: An Indication of Remarkably Slow N–H Tautomerism

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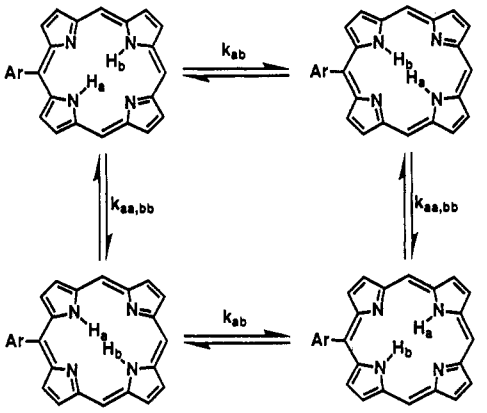
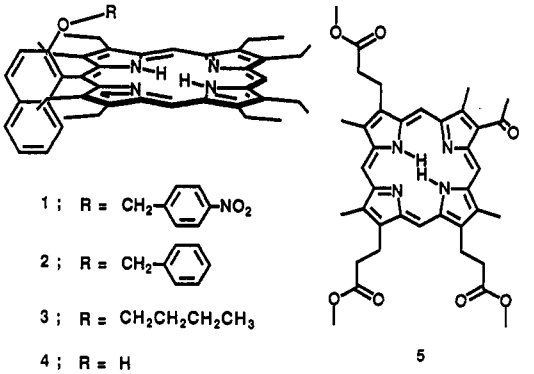
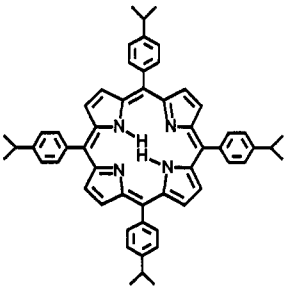
Tautomerism is an intramolecular proton transfer process coupled with migration of double bonds. The N–H tautomerism in porphyrins (Scheme I) involves a shift of highly conjugated double bond systems.[2-8] The exchange between two tautomers is usually so fast that they can be distinguished spectroscopically only at very low temperatures. The present work is concerned with meso-monosubstituted octaethylporphyrins (OEP's). We report here that the tautomerism rate constants evaluated by variable-temperature dynamic ^{1}H NMR N–H line-shape analysis for these compounds are surprisingly small.

Scheme I







Three OEP derivatives **1**–**3** having a 2-alkoxy-1-naphthyl group on a meso position were prepared by alkylating the parent 2-hydroxy-1-naphthyl compound **4** with an appropriate alkyl bromide. The ^{1}H NMR spectrum for the 4-nitrobenzyl (**1**), benzyl (**2**), or n-butyl derivative (**3**) in

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