threshold is sometimes increased.

The procedure for determining the maximum driving frequency was as follows. The spontaneous rate was determined and a recording was made with the tissue stimulated at a frequency of 20% greater than the spontaneous frequency. This frequency was used to determine the contractile strength of the tissue by measurement of the peak height for the remainder of the study on the tissue. The driving frequency was then increased slowly until the tissue failed to follow the stimulator as indicated by skipped beats followed by supramaximal contractions. The determination was repeated twice and an average of the three values was used as the MDF. After the control readings were taken, the lowest concentration of the drug (as the hydrochloride or hydrobromide salt) to be tested was added to the bath in a small volume of buffer solution (0.1–0.4 mL). Readings were taken at 15 min after addition of the compound and the second dose was added to the bath without washing. The second reading was taken 15 min later and the procedure was repeated until the MDF was decreased by about 60% of control. Usually four to six data points could be obtained in a cumulative manner. Three tissues were used for each compound tested.

The percent decrease in response (MDF or peak height) was plotted vs. the logarithm of the molar concentration of drug, and a straight line was fitted to the data by linear regression. The log dose required to decrease the response by 40% was determined graphically (log ED_{40}). The values from the three tissues were averaged and standard deviations were then calculated for the replicates.

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Antimalarials. 4. Trichloronaphthalene Amino Alcohols[1]

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An improved procedure for the synthesis of naphthalene amino alcohols is described. Four new compounds were prepared and tested by Rane Laboratories for activity vs. *Plasmodium berghei* in mice. All compounds were active, the most active being 1-[3-(4-chlorophenyl)-5,7-dichloro-1-naphthyl]-3-(di-*n*-butylamino)propanol hydrochloride (**16b**). Structure–activity relationships between the naphthalene and quinoline isosteres are discussed.

3-Substituted 1-naphthalenemethanols have been shown to be active against *Plasmodium berghei* in mice.[1a] The activity is approximately the same as that of the better known 4-quinolinemethanols, although the structure–activity relationships operative for the quinoline compounds do not in all cases apply to the naphthalene isosteres.

Earlier synthetic procedures[2,3] were incapable of producing the 3-phenyl-5,7-dichloronaphthalenemethanols, isosteric with highly active 4-quinolinemethanols, because of the difficulty of ring closure meta to two chlorines. We have now devised a scheme which has provided a facile route to the compounds and is, with appropriate modifications, applicable to the general synthesis of 1-methyl-3-arylnaphthalenes, starting materials for the antimalarial naphthalenemethanols.

Chemistry. The synthetic sequence to the 1-methylnaphthalene **9** is illustrated in Scheme I. Previously described procedures[1a] were followed to obtain the naphthalene amino alcohols from **9**. 3,5-Dichloro-α-methylstyrene (**4**) was obtained in excellent overall yield (90%) from the acid **1**. Brown and Lane's[4] method of specific hydrobromination yielded only the desired 2-(3,5-dichlorophenyl)-1-bromopropane (**5**) in 70% yield. In the alkylation step the use of 1.5 equiv of (4-chlorophenyl)acetic acid increased the yield of pure 2-(4-chlorophenyl)-4-(3,5-dichlorophenyl)pentanoic acid (**6**) to 90% from the 50–60% range obtained with equimolar quantities.

Investigation to determine the optimum conditions for the cyclization of **6** revealed that no reaction occurred unless the polyphosphoric acid (PPA) reaction mixture was heated above 140 °C. At 185 and 190 °C a 1:3 mixture of the expected tetralin **7** and 3-(4-chlorophenyl)-5,7-dichloro-1-methylnaphthalene (**9**) was obtained. Further experimental evidence is required to explain this unexpected result.

Conversion of **7** to **9** through the dihydronaphthalene **8** proceeded routinely, except that the aromatization of **8** required reaction with dichlorodicyanoquinone (DDQ) when chloroanil failed to accomplish the dehydrogenation.

Structure–Activity Relationships. The activity[5] (as determined by Rane Laboratories) of the trichloronaphthalene amino alcohols vs. *P. berghei* is presented in

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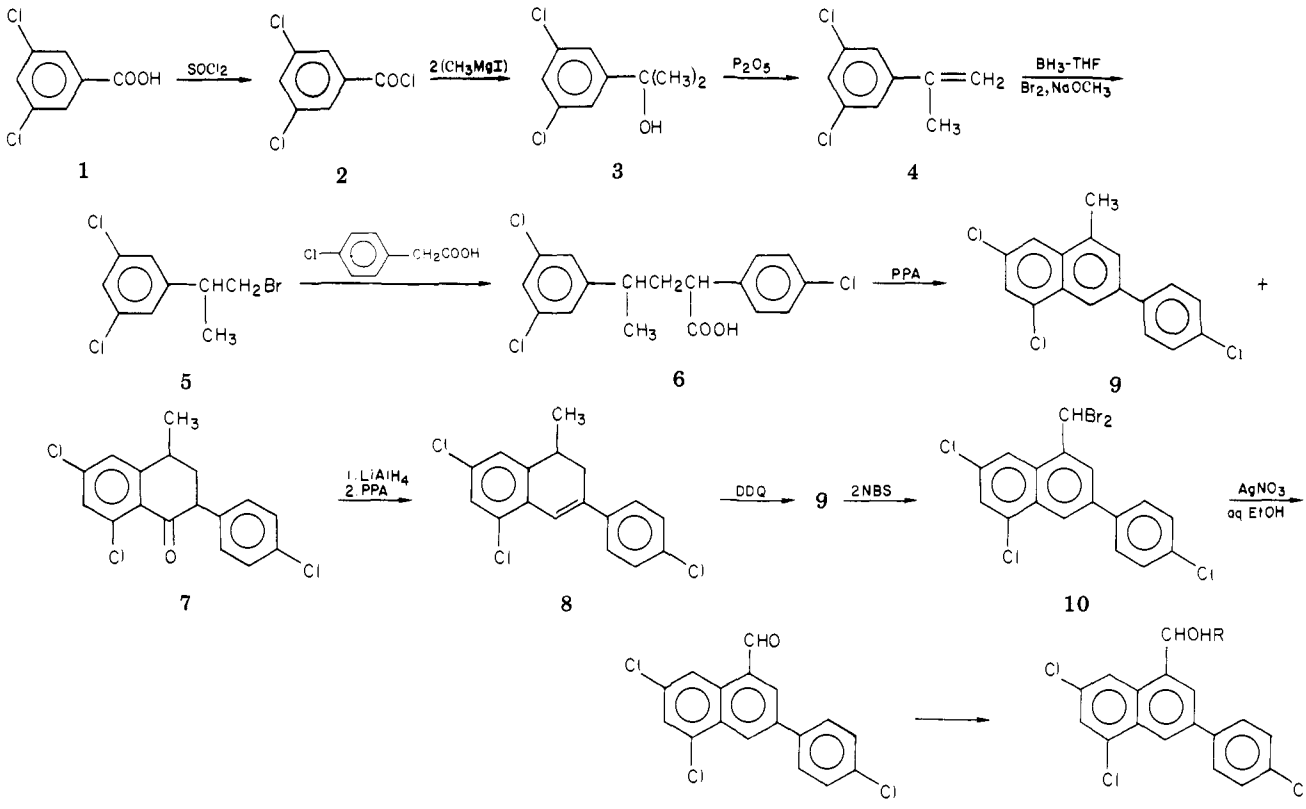
Scheme I



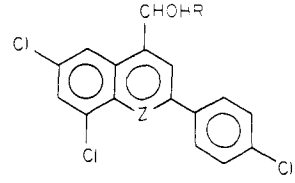
16a, R = $CH_2N(C_4H_9)_2 \cdot HCl$
b, R = $CH_2CH_2N(C_4H_9)_2 \cdot HCl$
c, R = 2-c-$C_5H_{10}N \cdot CH_3COOH$
d, R = 2-CH_2-c-$C_5H_{10}N \cdot HCl$

Table I. Antimalarial Activity[a] of Naphthalene Amino Alcohols

	ΔMST, days, or no. of cures (C) at dosage (mg/kg)						
compd	10	20	40	80	160	320	640
16a	7.9	9.5	10.5	1C	2C	4C	5C
16b	2.9	12.1	3C	3C	5C	5C	5C
16c	0.5	1.1	3C	4C	4C	3C	4C
16d	3.6	9.8	11.8	16.6	1C	1C	6.0

[a] Activity vs. *P. berghei* in five mice, determined by Rane Laboratories, University of Miami, as described by Osdene and co-workers.[5] The mean survival time (MST) of infected controls was 6.1 days. An increase in mean survival time (ΔMST) of mice treated with a single dose of compound administered subcutaneously 72 h after infection is considered evidence of antimalarial activity if the increase is at least 100% (6.1 days). The number of cures (C) is the number of mice surviving out of five at 60-days postinfection.

Table II. Comparative Antimalarial Activity of Quinoline and Naphthalene Amino Alcohols



compd	Z	R	MED,[a] mg/kg
16a	CH	$CH_2N(C_4H_9)_2 \cdot HCl$	~10
	N	$CH_2N(C_4H_9)_2 \cdot HCl$	~10[b]
16c	CH	2-piperidyl acetate	~20
	N	2-piperidyl hydrochloride	~5[b]

[a] Minimum effective dose, i.e., the dose which gives a ΔMST of at least 6.1 days. [b] Data furnished by Walter Reed Army Institute of Research.

Table I. In Table II a comparison is made between the isosteric quinoline and naphthalene amino alcohols. The activity, expressed as the minimum effective dose (MED), of the naphthalene compounds is approximately the same as that of the quinoline derivatives. Colwell and coworkers[6] showed that increasing the distance between the side-chain amino and hydroxy groups by one $-CH_2-$ increased the activity of antimalarial phenanthrene amino alcohols. The same effect was noted with the naphthalene derivatives (cf. **16a,b**). Extending the variation to the piperidyl compounds (cf. **16c,d**) appeared to affect the activity adversely.

None of the compounds was as active as 6-chloro-α-[(dibutylamino)methyl]-3-(3,4-dichlorophenyl)-1-naphthalenemethanol.[1a]

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded with a Beckman IR8 spectrophotometer; nuclear magnetic resonance spectra were recorded at 60 MHz with a Varian A-60 spectrometer. Molecular weights were determined from the mass spectra recorded with a Hitachi Perkin-Elmer RMU-6H spectrometer at 70 eV. All spectra were in accord with the structures assigned. Where analyses are indicated by symbols of the elements, analytical results obtained are within 0.4% of the theoretical values.

3,5-Dichlorobenzoyl Chloride (2). 3,5-Dichlorobenzoic acid (1; Aldrich Chemical Co., Milwaukee, WI; 50 g, 0.26 mol) was mixed with $SOCl_2$ (93.0 g, 0.78 mol) and the solution was heated under reflux for 3 h. Excess $SOCl_2$ was removed at aspirator vacuum, and the residue was distilled under high vacuum. **2** (48.8

g, 89%) was collected as a colorless liquid: bp 45 °C (0.01 mm); IR (neat) 3100 (CH), 1750 (C=O), 1195, 953, and 725 cm^{-1}; NMR ($CDCl_3$) δ 7.57–8.00 (m, 3 H, aromatic); mol wt 208.

2-(3,5-Dichlorophenyl)-2-propanol (3). A Grignard reagent was prepared from methyl iodide (110.0 g, 0.775 mol) and Mg (19.5 g, 0.8 mol) and treated with a solution of **2** (48.5 g, 0.23 mol) in Et_2O (100 mL). When addition was complete, the solution was heated under reflux overnight. The reaction mixture on usual workup gave 47.1 g (99%) of a yellow oil: IR (neat) 3330 (OH), 2960 (CH), 1550, 1410, 862, and 794 cm^{-1}; NMR ($CDCl_3$) δ 1.55 (s, 6 H, CH_3), 1.87 (br s, 1 H, OH), 7.33 (m, 3 H, aromatic); mol wt 204.

3,5-Dichloro-α-methylstyrene (4). A mixture of **3** (47.0 g, 0.23 mol) and P_2O_5 (4 g, 0.03 mol) was heated at 115 °C under aspirator vacuum for 7 min. The cooled mixture was partitioned between CH_2Cl_2 (200 mL) and H_2O (100 mL). The organic layer was separated, washed (H_2O), dried (Na_2SO_4), and concentrated. The residue was distilled to give **4** (42.5 g, 99%) as a colorless, thin liquid: bp 56 °C (0.6 mm); IR (neat) 2980 (CH), 1580, 1550, 850, and 797 cm^{-1}; NMR ($CDCl_3$) δ 2.05 (s, 3 H, CH_3), 5.25 (d of t, 2 H, $C=CH_2$), 7.25 (m, 3 H, aromatic); mol wt 186.

2-(3,5-Dichlorophenyl)-1-bromopropane (5). The procedure used is that of Brown and Lane.[4] A solution of **4** (54.3 g, 0.29 mol) in dry THF (100 mL) was placed in a dry, 1-L, three-neck flask equipped with magnetic stirrer, thermometer, dropping funnel, and nitrogen inlet tube. The solution was cooled to 0 °C and hydroboration was achieved by the addition of borane in THF (100 mL of 1 M solution). The solution was stirred for 30 min at 0 °C and 30 min at 20 °C; then MeOH (2 mL) was added to destroy the excess hydride. The mixture was cooled to 15 °C and maintained below 20 °C while Br_2 (16 mL, 0.30 mol) and MeONa solution (83 mL of 4 M in MeOH) were added simultaneously from two dropping funnels, so that a slight yellow color was always present. The addition required 45 min, and the mixture was stirred for an additional 30 min. The mixture was treated with K_2CO_3 solution (60 mL, saturated) and H_2O (80 mL); the organic component was extracted into petroleum ether (120 mL) and the organic layer was separated. The aqueous layer was washed with two 80-mL portions of petroleum ether, and the combined organic fractions were washed with two 50-mL portions of H_2O, dried (Na_2SO_4), and concentrated. The residue was distilled to give **5** as a colorless liquid: bp 92 °C (0.03 mm); IR (neat) 2950 (CH), 1560, 1430, 855, and 795 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (d, 3 H, CH_3), 3.08 (m, 1 H, CH), 3.47 (d, 2 H, CH_2Br), 7.18 (m, 3 H, aromatic); mol wt 266. Anal. ($C_9H_9BrCl_2$) C, H.

2-(4-Chlorophenyl)-4-(3,5-dichlorophenyl)pentanoic Acid (6). This compound was prepared by a slight modification of Creger's[5] procedure. Diisopropylamine (20.4 g, 0.20 mol), 57% NaH–mineral oil dispersion (8.5 g, 0.20 mol), and dry THF (200 mL) were placed in a 1-L, three-neck flask equipped with mechanical stirrer, thermometer, dropping funnel, condenser, and nitrogen inlet tube. (4-Chlorophenyl)acetic acid (Aldrich Chemical Co., Milwaukee, WI; 34.2 g, 0.20 mol) in dry THF (150 mL) was added dropwise. The mixture was heated under reflux for 1 h and then cooled to 0 °C. The temperature was maintained below 5 °C while butyllithium in hexane (127 mL of 1.57 M, 0.20 mol) was added dropwise. When the addition was complete, the mixture was heated at 35–40 °C to complete the metalation.

The milky yellow mixture was cooled to 25 °C and **5** (40.2 g, 0.15 mol) was added. The mixture was heated under reflux for 12 h and then cooled to 15 °C. HCl (80 mL of 6 N) and Et_2O (200 mL) were added. After separating the organic layer, the aqueous layer was extracted with Et_2O (100 mL). The combined ethereal fractions were washed with two 100-mL portions of H_2O, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel (1.1 kg), eluting with 5% Me_2CO in C_6H_6. The yield of **6**, a yellow syrup, pure by NMR and TLC, was 48.2 g (90%): IR (neat) 2960 (CH), 1695 (C=O), 1090, 1010, and 795 cm^{-1}; NMR ($CDCl_3$) δ 1.20 (d, 3 H, CH_3), 1.80–2.80 (m, 3 H, $CHCH_2$), 3.40 (m, 1 H, $CHCOOH$), 7.18 (m, 7 H, aromatic), 11.61 (s, 1 H, COOH); mol wt 356.

3-(4-Chlorophenyl)-5,7-dichloro-1-methylnaphthalene (9). A mixture of **6** (48.2 g, 0.135 mol) and PPA (300 mL) was heated at 190 °C for 4 h under aspirator vacuum. The mixture was cooled, poured into ice–H_2O (2 L), and extracted with CH_2Cl_2 (500 mL). The aqueous layer was separated and extracted with two 200-mL portions of CH_2Cl_2. The combined organic fractions were dried (Na_2SO_4) and concentrated to give 43.6 g of red crystalline residue. The crystals were triturated with petroleum ether (bp 30–60 °C), and the mixture was filtered to give 26.4 g of pale yellow crystals. Concentration of the filtrate gave 17.2 g of a red oil which was not identified. An NMR spectrum of the solid indicated that it was a 3:1 mixture of **9** and 2-(4-chlorophenyl)-6,8-dichloro-4-methyltetralone (**7**). Recrystallization from isooctane gave 19.2 g (44%) of **9** as pale yellow needles: mp 159–161 °C; IR (KBr) 1475, 1090, 1010, 880, and 820 cm^{-1}; NMR ($CDCl_3$) δ 2.69 (s, 3 H, CH_3), 7.20–8.20 (m, 8, aromatic); mol wt 320. Anal. ($C_{17}H_{11}Cl_3$) C, H.

Concentration of the mother liquor from the above recrystallization and recrystallization of the residue from cyclohexane gave 6.3 g (14%) of **7** as off-white needles (mp 105–110 °C) which were contaminated with a small amount of **9**. No solvent system could be found by which **7** could be separated completely from the contaminating **9**.

Because of the contamination by **9** compound **7** was characterized only by its NMR spectrum: NMR ($CDCl_3$) δ 1.42 (d, 3 H, CH_3), 2.00–2.60 (m, 2 H, CH_2), 2.80–3.40 (m, 1 H, $CHCH_3$), 3.60–4.15 (m, CHC=O), 7.00–7.90 (m, 6 H, aromatic).

7 was converted to **9** through the series of reactions described below. A solution of **7** (contaminated with a small amount of **9**) (5.1 g, 15 mmol) in THF (50 mL) was stirred while $LiAlH_4$ (0.6 g, 16 mmol) was added in one portion. The mixture was stirred for 2 h and then saturated NH_4Cl solution (10 mL) was added. The organic layer was separated, dried (Na_2SO_4), and concentrated to give 5.1 g of a colorless oil, identified as 3-(4-chlorophenyl)-5,7-dichloro-4-hydroxy-1-methyl-1,2,3,4-tetrahydronaphthalene (contaminated with a small amount of **9**) by its NMR spectrum: NMR ($CDCl_3$) δ 1.35 (m, 3 H, CH_3), 1.60–2.20 (m, 2 H, CH_2), 2.50–3.50 (m, 3 H, $CHCH_2CHCH$), 4.90 (br s, 1 H, OH), 7.00–7.90 (m, 6 H, aromatic).

The oil was mixed with PPA (25 mL) and heated at 130 °C for 1 h; then the mixture was cooled and poured into H_2O (200 mL). The aqueous mixture was extracted twice with Et_2O (70-mL portions), and the combined extracts were dried (Na_2SO_4) and concentrated. The residue was recrystallized from cyclohexane to give 4.6 g (96%) of solid, identified as 3-(4-chlorophenyl)-5,7-dichloro-1,2-dihydro-1-methylnaphthalene (**8**) (contaminated with a small amount of **9**) by its NMR spectrum: NMR ($CDCl_3$) δ 1.24 (d, 3 H, CH_3), 2.45–3.20 (m, 3 H, CH_2CHCH_3), 7.00–7.60 (m, 7 H, aromatic).

A mixture of **8** (3.2 g, 0.01 mol) and DDQ (2.3 g, 0.01 mol) in toluene (35 mL) was heated at reflux for 3 h. The mixture was cooled and filtered, and the filtrate was concentrated. The crystalline residue was recrystallized from isooctane to give 2.5 g (78%) of **9**.

3-(4-Chlorophenyl)-1-(dibromomethyl)-5,7-dichloronaphthalene (10). A solution of **9** (23.6 g, 73.5 mmol) in CCl_4 (500 mL) and *N*-bromosuccinimide (NBS) (27.0 g, 150 mmol) was heated under reflux for 16 h. During the first hour 0.2-g portions of benzoyl peroxide were added every 15 min. After 2 h a white light illuminating the reaction mixture was used to maintain the solvent at refluxing temperature. The mixture was cooled to 40 °C and filtered. The filtrate was washed with NaOH (50 mL of 10% solution), dried (Na_2SO_4), and concentrated: yield 35.2 g (100%). The analytical sample was recrystallized from THF: yellow needles; mp 190–192 °C; IR (KBr) 1475, 1090, 1010, 880, 820, 705 cm^{-1}; NMR ($CDCl_3$) δ 7.27 (m, 1 H, $CHBr_2$), 7.50–8.50 (m, 8 H, aromatic); mol wt 476. Anal. ($C_{17}H_9Br_2Cl_3$) C, H.

3-(4-Chlorophenyl)-5,7-dichloro-1-naphthaldehyde (11). A slurry of **10** (35.2 g, 73.5 mmol) in EtOH (95%, 1 L) was mixed with a solution of $AgNO_3$ (28.0 g, 165 mmol, in 150 mL of H_2O), and the mixture was heated at reflux for 18 h. After it was cooled, the slurry was diluted with H_2O (500 mL) and filtered. The precipitate was extracted with hot THF until only the greenish gray AgBr remained. The combined extracts were concentrated, and the crystalline residue was recrystallized from THF–Me_2CO: yield 19.5 g (75%); yellow granules; mp 199–201 °C; IR (KBr) 1680 (C=O), 1090, 1010, 880, 820, and 727 cm^{-1}; NMR (THF) δ 7.10–8.80 (m, 8 H, aromatic), 10.10 (s, 1 H, CHO); mol wt 334. Anal. ($C_{17}H_9Cl_3O$) C, H.

3-(4-Chlorophenyl)-5,7-dichloro-1-(1,2-epoxyethyl)naphthalene (12). A solution of sodium methylsulfinylmethylide

was prepared from Me_2SO (10 mL) and NaH (1.25 g, 30 mmol, of 57% NaH–oil dispersion, which had been washed with two 10-mL portions of Et_2O to remove the oil) by heating the mixture at 70 °C for 1 h and diluting with THF (20 mL). The solution was cooled to −5 °C and a solution of trimethylsulfonium iodide (TMSI; 6.1 g, 30 mmol) in Me_2SO (40 mL) was added dropwise while stirring, maintaining the temperature at or below 0 °C during the addition. The milky gray mixture was poured quickly into a cold (5 °C) solution of 11 (6.7 g, 20 mmol) in dry THF (500 mL). After the mixture was stirred for 4 h at ambient temperature, the solvent volume was reduced to 150 mL under reduced pressure. The mixture was poured into H_2O (800 mL) and extracted with three 150-mL portions of $CHCl_3$. The combined extracts were dried (Na_2SO_4) and concentrated. The residue was recrystallized from $CHCl_3$: yield 5.5 g (79%); light yellow powder; mp 148–150 °C; IR (KBr) 1475, 1090, 1010, 880, 855, and 820 cm^{-1}; NMR ($CDCl_3$) δ 2.68–3.40 (m, 2 H, CH_2), 4.34 (m, 1 H, CH), 7.20–8.30 (m, 8 H, aromatic); mol wt 348. Anal. ($C_{18}H_{11}Cl_3O$) C, H.

3-(4-Chlorophenyl)-α-[(dibutylamino)methyl]-5,7-dichloro-1-naphthalenemethanol Hydrochloride (16a). A solution of **12** (5.0 g, 14.3 mmol) in di-*n*-butylamine (40 mL) was heated at 155 °C under N_2 for 12 h and then the excess amine was removed at aspirator vacuum. The residue was dissolved in a mixture of 30 mL of MeOH and 400 mL of Et_2O, and anhydrous HCl in Et_2O (5 mL of saturated solution) was added. The mixture was filtered to give **16a** (6.4 g, 86.7%) as a fluffy, white solid: mp 238–241 °C; IR (KBr) 3190 (OH), 2940 (CH), 1475, 1090, 1010, 880, and 820 cm^{-1}; NMR (Me_2SO-d_6) δ 1.00 (m, 6 H, CH_3), 1.15–2.10 (m, 8 H, CH_2), 3.00–3.55 [m, 6 H, $N^+(CH_2)_3$], 6.10 (m, 1 H, C*H*OH), 7.50–8.60 (m, 8 H, aromatic), 10.80 (m, 1 H, HCl). Anal. ($C_{26}H_{31}Cl_4NO$) C, H, N.

3-(4-Chlorophenyl)-5,7-dichloro-α-(2-pyridyl)-1-naphthalenemethanol (13). To a cold (−60 °C) solution of *n*-butyllithium (19.0 mL, 30 mmol, of 1.57 M in hexane) in Et_2O (300 mL) 2-bromopyridine (4.9 g, 31 mmol) was added dropwise. After the mixture was stirred for 30 min, a solution of 11 (3.4 g, 10 mmol) in dry THF (300 mL) was added dropwise, and the resulting black solution was stirred at −50 °C for 2 h. After the addition of aqueous 3:2 THF–H_2O (50 mL), the mixture was warmed to 20 °C, and the organic layer was separated, dried (Na_2SO_4), and concentrated. The residue was triturated with cyclohexane (50 mL), and the solid was removed by filtration and dried: yield 2.2 g (53%). A small sample dissolved in Et_2O, treated with charcoal, and recovered gave tan crystals: mp 157–159 °C; IR (KBr) 1590, 1475, 1090, 1010, 880, and 820 cm^{-1}; NMR ($CDCl_3$) δ 5.37 (m, 1 H, OH), 6.34 (s, 1 H, CH), 6.90–8.60 (m, 12 H, aromatic); mol wt 413. Anal. ($C_{22}H_{14}Cl_3NO$) C, H, N.

By a similar procedure **1-[3-(4-chlorophenyl)-5,7-dichloro-1-naphthyl]-2-(2-pyridyl)ethanol (14)** was prepared (1.7 g, 40%) from 2-picoline (1.4 g, 15 mmol) and 11 (3.4 g, 10 mmol) as tan crystals: mp 143–145 °C; IR (KBr) 3380 (OH), 1580, 1470, 1090, 1010, 880, and 820 cm^{-1}; NMR ($CDCl_3$) δ 3.23 (d, 2 H, CH_2), 5.20 (m, 1 H, OH), 5.78 (t, 1 H, C*H*OH), 6.95–8.60 (m, 12 H, aromatic); mol wt 427. Anal. ($C_{23}H_{16}Cl_3NO$) C, H, N.

3-(4-Chlorophenyl)-5,7-dichloro-α-(2-piperidyl)-1-naphthalenemethanol Acetate (16c). A solution of **13** (2.1 g, 5.1 mmol) in THF (30 mL) and glacial AcOH (30 mL) was treated with PtO_2 (200 mg) and shaken under hydrogen for 3 h in a Parr hydrogenation apparatus. The mixture was filtered (Celite), and the filtrate was concentrated under aspirator vacuum. When Et_2O (200 mL) was added, the product precipitated. Recrystallization from Me_2CO gave **16c** (1.8 g, 74%): mp 218–229 °C; IR (KBr) 1600, 1390, 1090, 1010, 880, and 820 cm^{-1}; NMR (Me_2SO-d_6) δ 1.10–1.65 [m, 6 H, $(CH_2)_3CH_2NH$], 1.85 (s, 3 H, CH_3COOH), 2.68–3.20 (m, 3 H, CH_2NHCH), 5.15–5.75 (m, 4 H, CHOH, NH, CH_3COOH), 7.20–8.25 (m, 8 H, aromatic); mol wt 419. Anal. ($C_{24}H_{24}Cl_3NO_3$) C, H, N.

Similarly, **1-[3-(4-chlorophenyl)-5,7-dichloro-1-naphthyl]-2-(2-piperidyl)ethanol hydrochloride (16d)** was prepared from **14** (1.6 g, 3.7 mmol): yield 0.8 g (45%); off-white crystals; mp 230–238 °C; IR (KBr) 3390 (OH), 2940 (CH), 1580, 1495, 1475, 1090, 1010, 880, and 820 cm^{-1}; NMR (Me_2SO-d_6) δ 1.35–2.35 [m, 8 H, $(CH_2)_3CH_2NH$, CH_2CHOH], 2.80–3.60 (m, 3 H, $CHNHCH_2$), 5.35–5.90 (m, 1 H, CHOH), 7.30–8.50 (m, 10 H, NH, OH, aromatic), 10.60–11.10 (m, 1 H, HCl); mol wt 469. Anal. ($C_{23}H_{23}Cl_4NO$) C, H, N.

***N,N*-Di-*n*-butyl-3-[3-(4-chlorophenyl)-5,7-dichloro-1-naphthyl]-3-hydroxypropionamide (15).** The procedure is essentially that of Colwell and co-workers.[6] Lithium *N,N*-di-*n*-butylacetamide was prepared at −10 to 10 °C by adding *N,N*-di-*n*-butylacetamide (4.0 g, 23 mmol, in 10 mL of THF) to a solution of lithium di-*n*-butylamide [made from di-*n*-butylamine (3.3 g, 25 mmol) and *n*-butyllithium (15 mL, 24 mmol, of 1.57 M in hexane) in THF (30 mL)]. A cold (10 °C) solution of 11 (5.0 g, 15 mmol) in THF (350 mL) was added, and the mixture was stirred for 3 h. Saturated NH_4Cl solution (10 mL) was added, and the organic phase was separated and concentrated. The residue was dissolved in C_6H_6 (100 mL) and washed with 5 N HCl (20 mL) and H_2O (20 mL). The solution was dried (Na_2SO_4) and concentrated. The residue (9.0 g) was chromatographed on silica gel (200 g), eluting with 5% Me_2CO in C_6H_6. The product (6.5 g, 87%) was used in the next step without further purification.

1-[3-(4-Chlorophenyl)-5,7-dichloro-1-naphthyl]-3-(di-*n*-butylamino)propanol Hydrochloride (16b). **15** (6.5 g, 13 mmol) in THF (50 mL) was added dropwise to a stirred solution of borane (40 mL of 1 M) in THF; the mixture was then stirred at ambient temperature for 2 h and heated at reflux for 5 h. After cooling the mixture was treated with HCl (10 mL of 2 N). When the solvent was removed under aspirator vacuum and was replaced with MeOH (100 mL), the product–borane complex precipitated (4.2 g, mp 140–142 °C). The base was freed by heating the complex to 150 °C under aspirator vacuum. The addition of HCl in Et_2O to the residue gave **16b** (3.3 g, 49%): mp 160–163 °C; IR (KBr) 3250 (OH), 2950 (CH), 1460, 1090, 1010, 880, and 820 cm^{-1}; NMR ($CDCl_3$) δ 0.70–1.90 [m, 14 H, $(CH_2CH_2CH_3)_2$], 2.00–2.50 (m, 2 H, $CHOHCH_2$), 2.70–3.60 [m, 6 H, $^+N(CH_2)_3$], 5.15 (s, 1 H, OH), 5.35–5.75 (m, 1 H, C*H*OH), 7.20–8.20 (m, 8 H, aromatic), 10.70–11.15 (m, 1 H, HCl); mol wt 491. Anal. ($C_{27}H_{33}Cl_4NO$) C, H, N.

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References and Notes

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