Regioselective and Stereoselective Syntheses of 1,2,3-Triaminocyclohexane Derivatives

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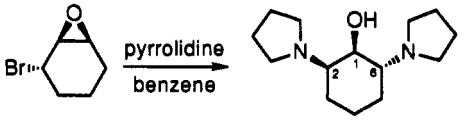
The reactions of *trans*- and *cis*-3-bromo-1,2-epoxycyclohexanes with pyrrolidine are described. While in the case of the *trans*-epoxide **2** the diamino alcohol **3** was obtained in benzene, the *cis*-epoxide **5** unexpectedly led to bromo amino alcohol **7** in benzene. Compound **7** could be converted to **3** using pyrrolidine in DMF. The *trans*-3-chloro-1,2-epoxycyclohexane **11** was the source of the isomeric diamino alcohol **4**. The diamino alcohols **3** and **4** were used to produce triamines containing two pyrrolidine and one methylamine residues (**14**, **15**, **22**). The bromo amino alcohol **7** was used to prepare a triamine containing two methylamine and one pyrrolidine residues (**25**). The triamines were converted to amide derivatives. The structure of one of these amides (**23**) was confirmed by single crystal X-ray analysis.

We became interested in a synthesis of 3-pyrrolidinyl-1,2-epoxycyclohexane (**1**) which was not known in the literature. It had been reported that the *cis*-3-piperidino analog could be prepared by the action of piperidine with *trans*-3-bromo-1,2-epoxycyclohexane,[1] but it was suggested that this was a unique transformation which was not seen with other amines.[2] The stereochemistry of this amino epoxide must be due to S_N2 displacement of the bromine since a pathway involving anti-opening of the epoxide followed by backside displacement of bromine to reform the epoxide would have produced the trans isomer.

Treatment of *trans*-3-bromo-1,2-epoxycyclohexane (**2**) with an excess of pyrrolidine in benzene produced *cis,trans*-2,6-dipyrrolidinylcyclohexanol (**3**).



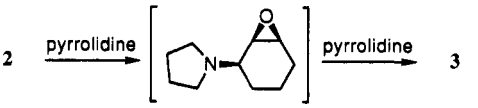
2 **3**

The structure and the stereochemistry of **3** was suggested by consideration of the reaction mechanism (S_N2 displacement of bromine followed by anti-ring opening of the epoxide) and was confirmed by analysis of its NMR spectrum.

In the ^1H NMR spectrum of **3**, two CHN hydrogens were found at 2.3 ppm, an OH singlet was found at 2.18 ppm (exchanges with D_2O), and the CHO hydrogen was at 4.05 ppm (triplet, J = 3.4 Hz). Irradiation at 2.45 ppm collapsed the CHO hydrogen to a singlet proving that this hydrogen is between the two CHN hydrogens. The size of the coupling constant (J = 3.4 Hz) suggests no diaxial coupling was present between the CHO and CHN groups. The molecule lacks a symmetry plane as seen from the presence of separate signals for the CHN carbons (64.04 and 61.67 ppm), the 3 and 5 carbons (26.07 and 23.71 ppm), and the CH_2N carbons of the pyrrolidine rings (51.80 and 51.08 ppm). The only way to account for no symmetry plane and no diaxial coupling between the CHO and CHN hydrogens is to have the OH in an axial position.

The NMR analysis is consistent with the computational molecular modeling.[2a] The most-favored conformation was obtained by the energy minimization of the molecule. The molecule adopts a boat-like conformation in which the hydroxy group is in the axial position and the two pyrrolidine rings are in the equatorial positions.

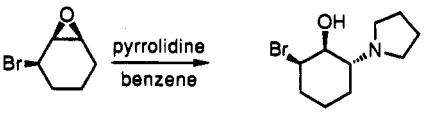
Apparently the first-formed *cis*-1,2-epoxy-3-pyrrolidinocyclohexane (**1**) is more reactive than its piperidine analog and is further attacked in an anti-fashion exclusively at the less-hindered carbon of the epoxide to produce **3**. [Even in the presence of limited amounts of pyrrolidine only compound **3** could be isolated; product **1** was never seen in this reaction (vide infra).]



1

A diastereoisomer of **3**, the *trans,trans*-dipyrrolidinyl alcohol **4**, should have a chair-like conformation. A retrosynthetic route to this alcohol is outlined in Scheme I.

cis-Bromo-1,2-epoxycyclohexane[1] (**5**) was allowed to react with pyrrolidine in benzene. In this case an epoxide-opening product **7** was obtained unexpectedly instead of the bromine-substitution product **6**.



5 **7**

The chemoselectivity of the two bromo epoxide isomers (**2** and **5**) can be understood in terms of their conformations. The conformations were determined by analysis of the proton NMR data. In the spectrum of compound **2**, the

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(1) Barili, P. L.; Bellucci, G.; Marioni, F.; Scartoni, V. *J. Org. Chem.* **1975**, *40*, 3331.

(2) Lier, E.; Berthold, R.; Troxler, F. *Helv. Chim. Acta.* **1979**, *62*, 932.

(2a) The computational molecular modeling was carried out using *Chem3D Plus* with a Macintosh IIsi computer. MM2 force field was used to minimize the energy of the molecule. *Chem3D Plus*, The Molecular Modeling System, Version 3.0, is available from Cambridge Scientific Computing, Inc., 875 Massachusetts Ave., Suite 61, Cambridge, MA 02139. We thank Professor Bradley D. Smith for the use of the software and the computer.

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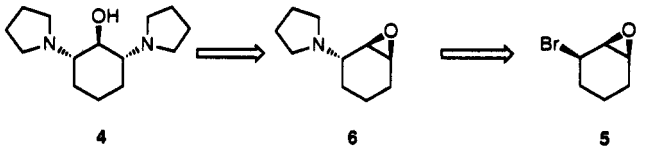
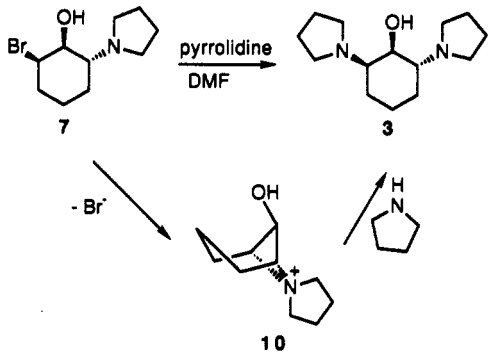
Scheme I



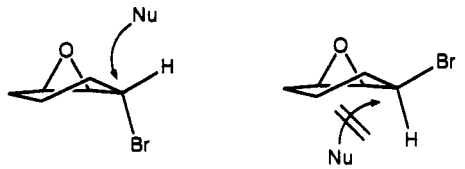
4 6 5

Scheme II



7 3 10

CHBr signal is a triplet (J = 4.7 Hz), which suggests that the bromine is in an axial position. In the spectrum of **5**, the CHBr signal is a triplet of doublets (J = 8.2, 8.2, 2.1 Hz), which suggests that the bromine is in an equatorial position. The nucleophile (pyrrolidine) would prefer an anti-periplanar attack from the side of the ring opposite to the bromine. This is favorable for trans-compound **2**, but not *cis*-**5** as shown in **8** and **9**.



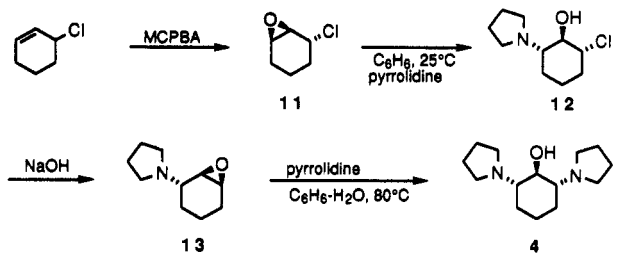
8 9

Compound **7** and pyrrolidine did not react when heated in benzene. When the more polar solvent DMF was used, the bromine was substituted by pyrrolidine. However, the product obtained was not **4**, expected from S_N2 displacement of bromine, but was identical to the one obtained previously, namely, the trans–cis isomer **3**. The formation of this product is believed to involve the azetidinium intermediate **10**, which was formed by intramolecular substitution of bromine by the pyrrolidine group from the backside. Another molecule of pyrrolidine would attack the azetidinium ring from the top to give **3**, (Scheme II). Such an azetidinium ion intermediate has been proposed previously.[3]

We then examined the reaction of *trans*-3-chloro-1,2-epoxycyclohexane (**11**) in the hope that the lower leaving group activity of the chlorine would lead to reaction at the epoxide group. Epoxide **11** was prepared by epoxidation of 3-chlorocyclohexane (in analogy to the preparation of **2**) and treated with pyrrolidine in benzene at room temperature (Scheme III). The expected epoxide ring-opened product **12** was obtained. Treatment of **12** with sodium hydroxide yielded *trans*-3-pyrrolidinyl-1,2-epoxycyclohexane **13**. When **13** was heated with pyrrolidine in benzene at 70 °C, no reaction was observed. However, when it was heated in benzene and water, the epoxide and pyrrolidine reacted to give the desired product **4**. The

(3) Kane, M. P.; Szmuszkovicz, J. *J. Org. Chem.* **1981**, *46*, 3728.

Scheme III

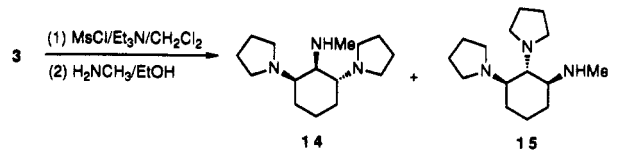


11 12 13 4

symmetrical geometry of **4** was confirmed by NMR analysis (six resonances in ^{13}C NMR and a triplet for C*H*OH with a coupling constant of 10 Hz in its ^1H NMR spectrum).

The availability of the diamino alcohols **3** and **4** suggested that they be used as precursors of 1,2,3-triamines. Our previous interest in the physiological activity of cyclohexanediamines in the form of monoamides[4-9] led us to examine the formation of some triamines and their monoamides.

The diamino alcohol **3** was allowed to react with methanesulfonyl chloride followed by methylamine. The ^1H NMR spectrum of the product showed two methyl groups in a ratio of about 1:1, together with the ^{13}C NMR spectrum which showed 22 absorptions. These data suggested that the product was a mixture of two isomers in both of which the two pyrrolidinyl groups are not identical, that is, both isomers are not symmetrical. No attempt was made to separate these two isomers. The two isomers are assigned structures **14** and **15**.

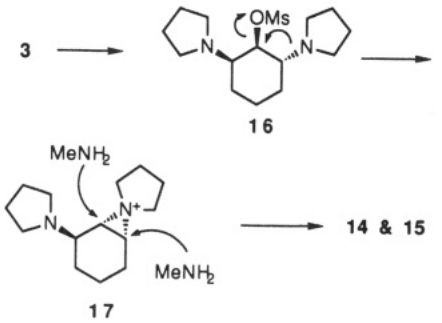


14 15

The stereochemistry was suggested by consideration of possible mechanisms of formation (Scheme IV). After formation of mesylate **16**, an aziridinium intermediate **17** may be formed by intramolecular attack of the pyrrolidinyl group which is trans to the leaving group. Indiscriminate attack of methylamine on both carbons of the aziridinium ring in a trans fashion should give triamines **14** and **15**. Possibly the small size of methylamine caused the reaction between **17** and methylamine not to be regioselective as was the opening of epoxide **1** and that of other aziridinium intermediates to be described later.

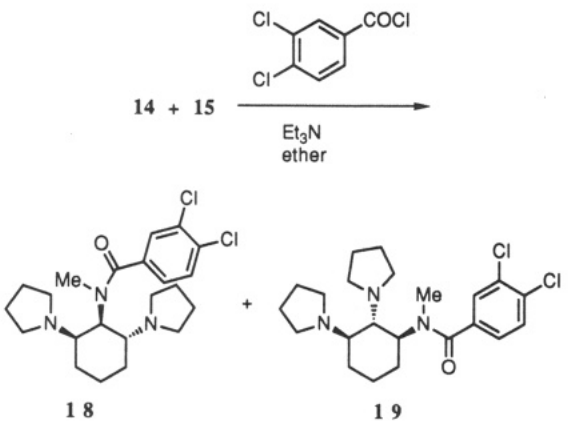
(4) Michalson, E. T.; Szmuszkovicz, J. *Prog. Drug Res.* **1989**, *33*, 135.
(5) Szmuszkovicz, J.; VonVoigtlander, P. F. *J. Med. Chem.* **1982**, *25*, 1125 (U.S. Pat. 4,098,904, U.S. Appl. No. 741,467, filed Nov. 12, 1976; *Chem. Abstr.* **1978**, *89*, 146632s. U.S. Pat. 4,145,435; *Chem. Abstr.* **1979**, *91*, 39003g). VonVoigtlander, P. F.; Lahti, R. A.; Ludens, J. H. *J. Pharmacol. Exp. Ther.* **1983**, *224*, 7.
(6) Reviews on Kappa agonists: (a) Szmuszkovicz, J. Lecture presented at the Asilomar Meeting on the Kappa Receptor, September 1990; *Pharmacol. Rev.*, submitted for publication. (b) Giardina, G.; Colle, R.; Vecchietti, V. *Curr. Opin. Ther. Pat.* **1991**, *1*, 345. (c) Rees, D. C.; Roberts, E. *Cur. Opin. Ther. Pat.* **1991**, *1*, 1139. (d) McKnight, A. T.; Rees, D. C. *Neurotransmissions* **1991**, *7*, 1. (e) Rees, D. C.; Hunter, J. C. *Opioid receptors. Comprehensive Medicinal Chemistry*, Pergamon: New York 1990, Vol. 3, pp 805–846. (f) Zimmerman, D. M.; Leander, J. D. *J. Med. Chem.* **1990**, *33*, 895. (g) Casy, A. F. Opioid receptors and their ligands: recent developments. *Adv. Drug Res.* **1989**, *18*, 177–289.
(7) Szmuszkovicz, J.; VonVoigtlander, P. F. U.S. Patent 4,801,604, issued Jan. 31, 1989.
(8) Rogawski, M. A.; Porter, R. J. *J. Pharm. Rev.* **1990**, *42*, 223.
(9) de Costa, B. R.; Rice, K. C.; Bowen, W. D.; Thurkauf, A.; Rothman, R. B.; Band, L.; Jacobson, A. E.; Radesca, L.; Contreras, P. C.; Gray, N. M.; Daly, I.; Iyengar, S.; Finn, D. T.; Vazirani, S.; Walker, J. M. *J. Med. Chem.* **1990**, *33*, 3100.

Scheme IV



The stereochemistry of **14** and **15** could be individually confirmed after conversion of the triamine mixture to a mixture of amides, which were more easily separated and characterized.

The mixture of the two regioisomers, **14** and **15**, was allowed to react with 3,4-dichlorobenzoyl chloride in the presence of triethylamine. As expected, a mixture of two products, **18** and **19**, was obtained. These two compounds were separated by chromatography and crystallization. NMR analysis at 20 °C indicates that compound **18** is conformationally homogeneous while compound **19** exists as a mixture of two conformational isomers.



The structure assignments were mainly based on the analysis of ^{1}H NMR spectra. The absorption of the hydrogen adjacent to the amido group in **18** is a triplet (J = 5.9 Hz), which suggests that the hydrogen should be in the equatorial position. Molecular modeling[2a] showed that the most-favored conformation of **18** is boat-like, as in the alcohol **3**, in which the amido group is in the axial position (Figure 1). The signal of the hydrogen adjacent to the amido group in **19** is a broad singlet. The broadness implies that the hydrogen has large coupling constants derived from axial–axial couplings of a chair conformation. Molecular modeling[2a] showed that **19** has a chair-like conformation with all substituents in equatorial positions (Figure 1).

Homologous amides of **18** and **19**, namely **18a** and **19a**, were also prepared; their properties are described in the Experimental Section.

A diastereoisomer of **18**, *trans,trans*-dipyrrolidinyl amide **20**, should have a chair-like conformation. A retrosynthetic route to the triamine precursor **21** is outlined in Scheme V.

However, when diamino alcohol **4** was subjected to the methylamination sequence, the formation of triamine did not occur according to our plan. The product was identified as 1-(methylamino)-2,3-dipyrrolidinylcyclohexane (**22**). The desired compound **21** was not observed at all. Note the complete regiospecificity in this case compared to the nonselectivity in the reaction of isomer **3**.

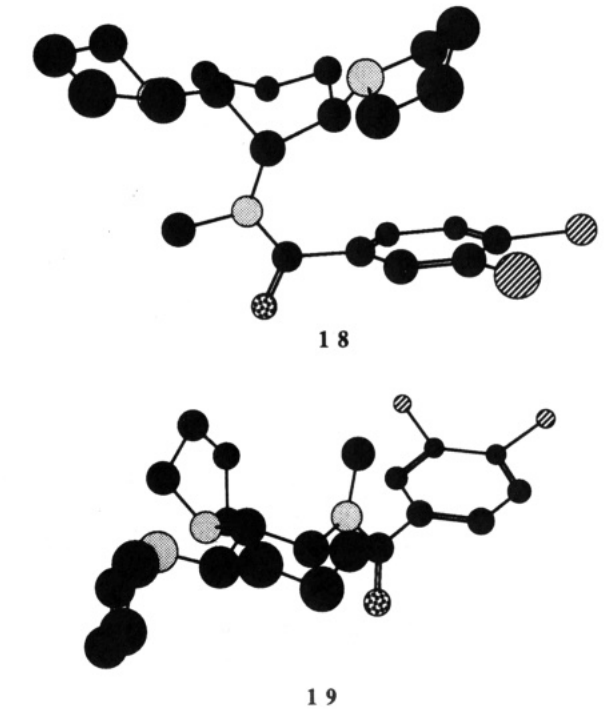
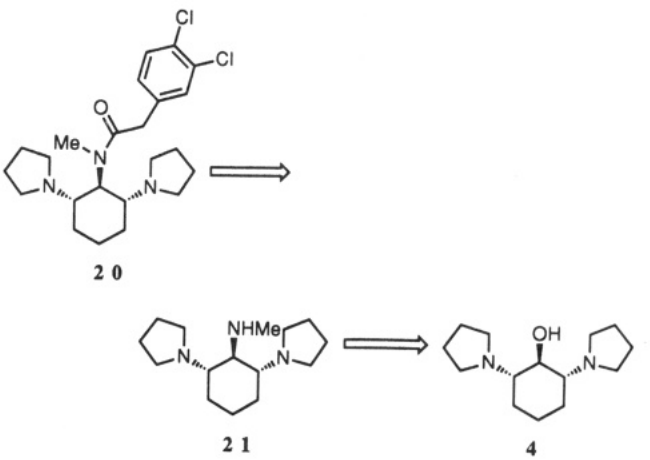
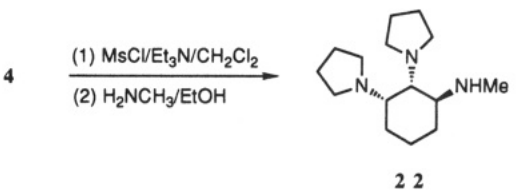


Figure 1.

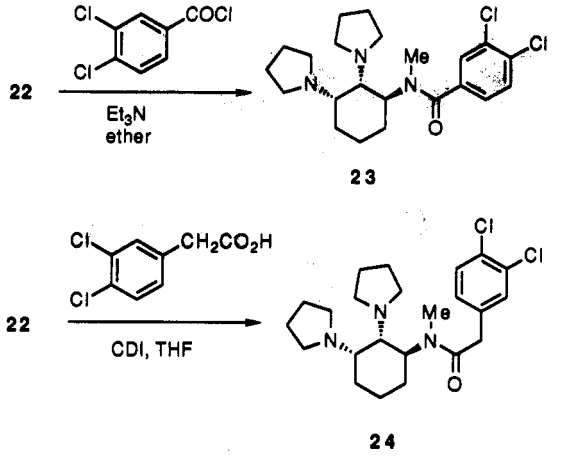
Scheme V





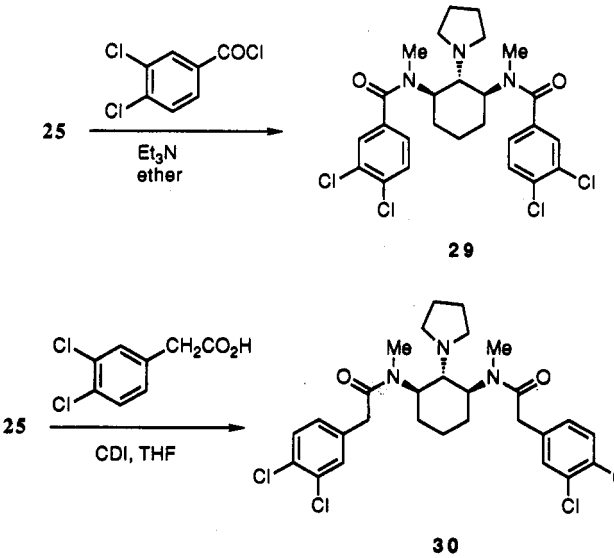
Two amides, **23** and **24** were also prepared from triamine **22**. The structural assignment of benzamide **23** was confirmed by single crystal X-ray analysis (*vide infra*).

A triamine with the stereochemistry of **21** was obtained by modification of this route. When compound **7** was subjected to our general methylamination sequence, a bis(methylamino) compound **25** was obtained. Compound **25** exhibits symmetry based on its NMR spectra (7 resonances in ^{13}C NMR and 1 resonance in ^{1}H NMR for CH_3 which integrates for 6 hydrogens). The trans–trans



stereochemistry is explained by the mechanism shown in Scheme VI, which involves two aziridinium intermediates. The first intermediate **26** is formed by elimination of mesylate ion. Addition of one molecule of methylamine to **26** shifts the pyrrolidine group to the center position (**27**). The second aziridinium intermediate **28** is formed when **27** loses bromide ion. Again, addition of the second molecule of methylamine places the pyrrolidine group back in the center. It is of interest that, in contrast to the reaction of mesylate of alcohol **3**, the mesylate of alcohol **7** reacts regioselectively with methylamine in two successive reactions, both at the less-hindered carbon of the aziridinium intermediate.

The triamine compound **25** was converted into the corresponding bis(amides) **29** and **30** by conventional procedures.

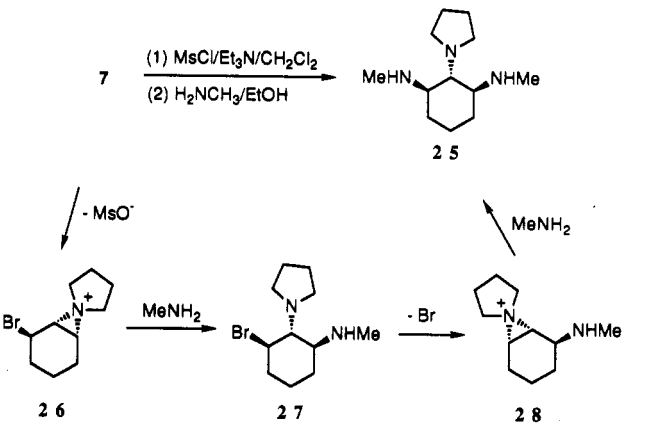


In summary, it has been established that the regiochemistry and stereochemistry of 2,6-diaminocyclohexanols are related to the stereochemistry of the starting 3-halo-1,2-epoxycyclohexanes and to the nature of the halogen. The stereochemistry of the 1,2,3-triaminocyclohexanes obtained from these diamino alcohols is determined by the intermediate aziridinium ions, and the regiochemistry of their ring opening parallels results obtained previously.

Experimental Section

^{1}H NMR spectra were obtained at 300 MHz unless otherwise stated, and ^{13}C NMR spectra were obtained at 75 MHz with $CDCl_3$ as a solvent. Methylamine (33% in absolute ethanol) was purchased from Fluka Chemical Corp. 3-Chlorocyclohexene was purchased from Pfaltz & Bauer, Inc. 3-Bromocyclohexene was purchased from Alfa Products.

Scheme VI



***trans*-3-Bromo-1,2-epoxycyclohexane (5)** was prepared according to the literature:[1] ^{1}H NMR[2] (300 MHz) δ 4.49 (t, J = 4.6 Hz, 1 H, H-3), 3.42 (dd, J = 3.7, 1.4 Hz, 1 H, H-1 or H-2), 3.28 (q, J = 2.9 Hz, 1 H, H-2 or H-1), 2.06 (dddd, J = 15.2 , 11.6, 4.3, 3.0 Hz, 1 H), 1.93–1.99 (m, 2 H), 1.57–1.77 (m, 2 H), 1.38 (m, 1 H); ^{13}C NMR (75 MHz) δ 55.32, 52.89, 47.51, 28.52, 22.80, 15.69.

Synthesis of *cis,trans*-2,6-Di-(1-pyrrolidinyl)cyclohexanol (3). Pyrrolidine (26.4 mmol, 2.2 mL) was added all at once to the solution of **2** (13.2 mmol, 2.34 g) in benzene (5 mL). The mixture was stirred at room temperature for 3 days. It was diluted with ether (150 mL) and washed with NaOH (4 N, 20 mL × 2) and then brine (20 mL × 3), dried with sodium sulfate, and concentrated to give a brown solid. It was recrystallized from ethanol to give **3** as golden crystals (498 mg): mp 117–118 °C; ^{1}H NMR (500 MHz) δ 4.05 (t, J = 3.4 Hz, 1 H, H-1), 3.13 (br s, 1 H, OH), 2.63–2.68 (m, 2 H), 2.53–2.59 (m, 2 H), 2.48–2.53 (m, 4 H), 2.44 (m, 1 H, H-2 or H-6), 2.42 (m, 1 H, H-6 or H-2), 1.40–1.81 (m, 14 H); ^{13}C NMR δ 67.90 (d), 64.04 (d), 61.67 (d), 51.80 (t), 51.07 (t), 26.07 (t), 23.71 (t), 23.25 (t), 23.16 (t), 18.86 (t); MS (FAB), m/e (rel inten) 239 (100, M + H), 168 (20), 150 (28), 110 (20), 70 (11, C_4H_8N); HRMS (FAB) m/e calcd for ($C_{14}H_{26}N_2O$ + H) 239.2123, found 239.2125. Anal. Calcd for $C_{14}H_{26}N_2O$: C, 70.54; H, 10.99; N, 11.75. Found: C, 70.26; H, 11.13; N, 11.68. The mother liquor was concentrated to a thick oil (1.1 g), the ^{1}H NMR spectrum of which showed the major component is still **3**.

Synthesis of *cis,trans*-1-(Methylamino)-2,6-di-(1-pyrrolidinyl)cyclohexane (14) and *trans,trans*-6-(methylamino)-1,2-di-(1-pyrrolidinyl)cyclohexane (15). Et_3N (2.76 mmol, 384 μL) and MsCl (2.76 mmol, 213 μL) was added to a solution of compound **3** (2.51 mmol, 631 mg) in CH_2Cl_2 (10 mL) under nitrogen at 0 °C. The mixture was stirred at 0 °C for 2.5 h and then concentrated in vacuo. The colorless solid was dissolved in a solution of methylamine in absolute ethanol (10 mL of 33% solution), transferred to a bomb, and heated for 20 h at 80 °C. Ethanol was removed in vacuo and the residue was diluted with ether (200 mL). The ether solution was washed with saturated KOH (30 mL), brine (2 × 30 mL), dried with sodium sulfate, and concentrated to give the mixture of **14** and **15** as a yellow oil (611 mg, 97%): ^{1}H NMR δ 2.35 (s, CH_3), 2.32 (s, CH_3); ^{13}C NMR δ 63.43, 62.32, 61.61, 60.79, 59.97, 59.15, 52.25, 51.50, 48.59, 47.93, 35.98, 34.30, 29.43, 26.62, 24.02, 23.93, 23.54, 23.42, 23.32, 23.24, 21.25, 19.35; MS (FAB), m/e (rel inten) 252 (100, M + H), 181 (13), 150 (26), 110 (54), 84 (25), 70 (23, C_4H_8N); HRMS (FAB) m/e calcd for ($C_{15}H_{29}N_3$ + H) 252.2440, found 252.2424.

Synthesis of *N*-Methyl-*N*-[2,6-di-(1-pyrrolidinyl)cyclohexyl]-3,4-dichlorobenzamide (18) and *N*-Methyl-*N*-[2,3-di-(1-pyrrolidinyl)cyclohexyl]-3,4-dichlorobenzamide (19). 3,4-Dichlorobenzoyl chloride (3.63 mmol, 759 mg) and triethylamine (3.63 mmol, 505 uL) were added to the solution of the mixture of **14** and **15** (3.30 mmol, 827 mg) in ether (20 mL). The white suspension was stirred at room temperature for 20 h. It was then diluted with ether (200 mL) and washed with saturated sodium carbonate (30 mL × 2) and brine (30 mL × 2). The ether solution was dried with sodium sulfate and concentrated in vacuo to give

a thick yellow oil. The oil was crystallized with $CHCl_3$/ether to give **19** as a pale yellow solid (535 mg). The mother liquor was chromatographed on silica gel ($CHCl_3/CH_3OH/NH_4OH$ = 95/4/1) to give **18** as a yellow oil (322 mg, 23%) and more **19** (36 mg, combined yield of **19**: 41%).

18: ^1H NMR δ 7.47 (d, J = 8.2 Hz, 1 H, H-6), 7.44 (d, J = 1.5 Hz, 1 H, H-2), 7.18 (dd, J = 8.2, 1.4 Hz, 1 H, H-5), 4.73 (t, J = 5.9 Hz, 1 H, H-1'), 3.20 (s, 3 H, CH_3), 2.25–3.10 (m), 1.50-2.00 (m); ^{13}C NMR δ 169.49 (CO), 137.63 (s), 133.05 (s), 132.55 (s), 130.33 (d), 128.81 (d), 125.97 (d), 59.64 (d), 59.52 (d), 55.86 (d), 52.37 (t), 48.84 (t), 36.88 (q), 27.18 (t), 23.98 (t), 23.74 (t), 23.24 (t), 20.03 (t); MS (FAB), m/e (rel inten) 424 (42, M + H), 353 (14), 173 (27), 150 (76), 110 (100), 70 (15); HRMS (FAB m/e calcd for ($C_{22}H_{31}Cl_2N_3O$ + H) 424.1922, found 424.1888.

19: recrystallized from $CHCl_3$/ether, mp = 144–146 °C; ^1H NMR δ 7.46 (m, 2 H, H-2 and H-6), 7.19 (dd, J = 8.2, 1.9 Hz, 1 H, H-5), 4.57 (br s, 1 H, H-1'), 3.37 (m, 1 H), 2.38-3.05 (m), 2.92 (s, 3 H, CH_3), 2.76 (s, 3 H, CH_3), 0.98–1.98 (m); ^{13}C NMR δ 170.38, 168.98, 137.72, 137.35, 133.19, 133.12, 132.60, 132.51, 130.45, 130.15, 129.08, 128.86, 125.96, 125.87, 60.92, 59.32, 59.09, 47.89, 47.77, 46.72, 30.15, 28.93, 27.86, 24.13, 23.77, 23.62, 23.60, 22.85, 22.64, 22.53; MS (FAB), m/e (rel inten) 424 (100, M + H) 423 (41), 221 (27), 173 (21), 150 (86), 110 (65), 84 (79). Anal. Calcd for $C_{22}H_{31}Cl_2N_3O$: C, 62.26; H, 7.36; Cl, 16.71; N, 9.90. Found: C, 61.90; H, 7.45; Cl, 16.58; N, 9.66.

Synthesis of *N*-Methyl-*N*-[2,6-di-(1-pyrrolidinyl)cyclohexyl]-3,4-dichlorophenylacetamide (18a) and *N*-Methyl-*N*-[2,3-di-(1-pyrrolidinyl)cyclohexyl]-3,4-dichlorophenylacetamide (19a). THF (10 mL) was added to a mixture of 3,4-dichlorophenylacetic acid (2.32 mmol, 476 mg) and 1.1'-carbonyldiimidazole (2.40 mmol, 389 mg). The resulting clear solution was stirred at room temperature for 2.5 h. Then a solution of the mixture of **14** and **15** (2.19 mmol, 550 mg) in THF (5 mL) was added during 5 min by cannulation. The yellow solution was stirred at room temperature for 40 h. The solvent was removed in vacuo and the residue was dissolved in ether (150 mL). The ether solution was washed with saturated sodium carbonate (20 mL × 2) and extracted with aqueous HCl (10%, 30 mL × 3). The acidic solution was neutralized by the addition of solid sodium carbonate and was extracted with ether (50 mL × 3). The extract was dried with magnesium sulfate and concentrated in vacuo. The yellow oily residue was chromatographed on a silica gel column ($CHCl_3/CH_3OH/NH_4OH$ = 95/4/1) to give **18a** as a yellow oil (158 mg, 17%) and **19a** as a yellow solid (289 mg, 30%) which resisted crystallization.

***N*-Methyl-*N*-[2,6-di-(1-pyrrolidinyl)cyclohexyl]-3,4-dichlorophenylacetamide (18a)**: ^1H NMR δ 7.37 (m, 2 H, H-2 and H-6), 7.10 (dd, J = 8.2, 2.1 Hz, 1 H, H-5), 4.63 (t, J = 6.0 Hz, 1 H, H-1'), 3.18 (s, 3 H, CH_3); ^{13}C NMR δ 170.23 (s, CO), 135.69 (s), 132.24 (s), 130.75 (d), 130.49 (s), 130.15 (d), 128.37 (d), 59.75 (d), 59.15 (d), 56.05 (d), 52.35 (t), 48.63 (t), 40.51 (t, $PhCH_2$), 34.68 (q, NCH_3), 27.25 (t), 23.68 (t), 23.16 (t), 19.89 (t); MS (FAB), m/e (rel inten) 438 (28, M + H), 367 (17), 159 (9), 150 (68), 110 (100), 97 (16), 70 (19); HRMS (FAB m/e calcd for ($C_{23}H_{33}Cl_2N_3O$ + H) 438.2079, found 438.2057.

***N*-Methyl-*N*-[2,3-di-(1-pyrrolidinyl)cyclohexyl]-3,4-dichlorophenylacetamide (19a)**: ^1H NMR (200 MHz) δ 7.20–7.50 (m, 3 H), 4.75 (br s, 1 H), 2.80–3.80 (m, 15 H), 1.30–2.25 (m, 14 H); ^{13}C NMR δ 170.80, 134.69, 132.53, 131.15, 131.09, 130.40, 128.82, 63.31, 59.34, 51.17, 48.34, 40.76, 28.91, 26.43, 24.17, 23.52, 22.01; MS (FAB), m/e (rel inten) 438 (100, M + H), 367 (3), 221 (4), 159 (7), 150 (60), 110 (23), 70 (15); HRMS (FAB) m/e calcd for ($C_{23}H_{33}Cl_2N_3O$ + H) 438.2079, found 438.2069.

***cis*-3-Bromo-1,2-epoxycyclohexane[1] (5)**: ^1H NMR (300 MHz) δ 4.35 (m, 1 H, H-3), 3.38 (m, 2 H, H-1 and H-2), 1.90 (m, 4 H), 1.58 (m, 1 H), 1.27 (m, 1 H); ^{13}C NMR (75 MHz) δ 57.86, 55.70, 49.05, 30.45, 22.47, 21.39.

***cis,trans*-6-Bromo-1-hydroxy-2-pyrrolidinylcyclohexane (7).** Pyrrolidine (13.0 mmol, 1.08 mL) was added to the solution of **5** (6.1 mmol, 1.08 g) in benzene (3 mL) in 1 min at 0 °C. The solution was stirred at rt for 4 days and then diluted with ether (100 mL). The ether solution was washed with saturated Na_2CO_3 (20 mL) and then extracted with aqueous HCl (10%, 3 × 30 mL). The acidic solution was basified with solid Na_2CO_3 and extracted with ether (3 × 50 mL). The ether extracts were dried over Na_2CO_3 and concentrated in vacuo to give **7** as a yellow oil (978 mg, 67%): ^1H NMR (300 MHz) δ 4.70 (dt, J = 4.5, 2.6 Hz, 1 H, H-6), 3.83 (br s, 1 H, OH), 3.38 (dd, J = 8.9, 2.6 Hz, 1 H, H-1), 2.90 (td, J = 9.6, 9.6, 3.1 Hz, 1 H, H-2), 2.59 (m, 4 H), 2.10 (m, 1 H), 1.70 (m, 6 H), 1.32 (m, 1 H); ^{13}C NMR (75 (MHz) δ 71.60 (d), 60.16 (d), 58.09 (d), 47.91 (t), 32.18 (t), 23.42 (t), 21.49 (t), 20.36 (t); MS (FAB), m/e (rel inten) 248 (76, M + H), 246 (25, M - H), 168 (100), 70 (30); HRMS (FAB) m/e calcd for ($C_{10}H_{18}BrNO$ + H) 248.0650, found 248.0658.

***trans,trans*-2,6-Bis(methylamino)-1-pyrrolidinylcyclohexane (25)**: obtained as a red oil (87% yield) from **7**; ^1H NMR δ 2.84 (m, 4 H), 2.45 (m, 2 H), 2.39 (s, 6 H, NCH_3), 2.05 (m, 4 H), 1.76 (m, 4 H), 1.70 (m, 1 H), 1.00–1.70 (m, 4 H); ^{13}C NMR (75 MHz) δ 65.55, 60.18, 48.34, 33.67, 30.51, 24.33, 21.72. A hydrochloride salt was obtained from an ether solution of **25** and HCl–ether solution and recrystallized from methanol/ether to give an off-white solid: MS (EI), m/e (rel inten) 211 (3, M^+), 180 (17), 123 (100), 110 (43), 70 (79); HRMS (EI) m/e calcd for $C_{12}H_{25}N_3$ 211.2048, found 211.2051. Anal. Calcd for $C_{12}H_{25}N_3 \cdot 3HCl \cdot H_2O$: C, 42.55; H, 8.93; Cl, 31.40; N, 12.40. Found: C, 42.53; H, 8.95; Cl, 30.92; N, 12.26.

***trans,trans*-2,6-Bis(*N*-methyl-3,4-dichlorobenzamido)-1-pyrrolidinylcyclohexane (29)**: obtained as a off-white solid in 23% yield from **25**; mp 184–186 °C ($CHCl_3$/pentane); ^1H NMR δ 7.10–7.60 (m, 6 H), 4.85 and 4.45 (two broad singlet, 1 H), 1.30–3.65 (m, 22 H); MS (FAB), m/e (rel inten) 556 (46, M + H), 382 (7), 352 (18), 282 (39), 173 (100), 150 (38), 149 (40), 70 (27). Anal. Calcd for $C_{26}H_{29}Cl_4N_3O_2$: C, 56.03; H, 5.24; Cl, 25.44; N, 7.54. Found: C, 55.79; H, 5.30; Cl, 25.82; N, 7.38.

***trans,trans*-2,6-Bis[*N*-methyl-3,4-dichlorophenylacetamido]-1-pyrrolidinylcyclohexane (30)**: obtained as a yellow solid in 21% yield from **25**; mp 142–145 °C ($CHCl_3$/hexanes); ^1H NMR δ 7.35 (m, 2 H), 7.08 (d, J = 7.7 Hz), 4.72 (m, 2 H, CHNMe), 3.62 (m, 4 H, CH_2CO), 2.55–2.86 (m, 11 H), 1.20-1.78 (m, 10 H); MS (FAB), m/e (rel inten) 584 (19, M + H), 550 (2), 396 (3), 366 (9), 296 (20), 159 (18), 149 (36), 110 (100), 84 (35), 70 (31); HRMS (FAB) m/e calcd for ($C_{22}H_{33}Cl_4N_3O_2$ + H) 584.1405, found 584.1382. Anal. Calcd for $C_{22}H_{33}Cl_4N_3O_2 \cdot 0.05CHCl_3$: C, 56.97; H, 5.63; Cl, 24.88; N, 7.11. Found: C, 56.63; H, 5.70; Cl, 24.80; N, 7.18.

***trans*-3-Chloro-1,2-epoxycyclohexane (11)**:[10] ^1H NMR (300 MHz) δ 4.38 (t, J = 5.1 Hz, H-1), 3.28 (m, 2 H, H-2 and H-3), 1.95 (m, 3 H), 1.62 (m, 2 H), 1.34 (m, 1 H); ^{13}C NMR (75 MHz) δ 55.08, 54.51, 52.71, 28.69, 22.97, 14.85; MS (FAB), m/e (rel inten) 133 (2, M + H), 115 (6), 97 (26), 41 (100); HRMS (FAB) m/e calcd for (C_6H_9ClO) 133.0420, found 133.0418.

***trans,trans*-6-Chloro-1-hydroxy-2-pyrrolidinylcyclohexane (12).** Pyrrolidine (36.9 mmol, 3.1 mL) was added to the solution of **11** (33.6 mmol, 4.45 g) in benzene (20 mL) at 0 °C in 2 min. After the mixture was stirred at rt for 5 days, it was diluted with ether (100 mL) and extracted with aqueous HCl (10%, 3 × 50 mL). The acidic solution was basified by the addition of solid NaOH and extracted with ether (4 × 80 mL). Ether solution was dried over magnesium sulfate and concentrated in vacuo to give a pale yellow liquid (4.96 g). Part of the liquid (2.00 g) was distilled using a kugelrohr to give **12** as a colorless liquid (1.63 g, 60%, 65–70 °C/0.1 torr): ^1H NMR (300 MHz) δ 5.20 (br s, 1 H), 3.75 (ddd, J = 12.0, 9.4, 4.6 Hz, 1 H), 3.38 (t, J = 9.7 Hz, 1 H), 2.60 (m, 4 H), 2.18 (m, 1 H), 1.75 (m, 8 H), 1.27 (m, 2 H); ^{13}C NMR (75 (MHz) δ 75.77, 63.81, 63.52, 47.25, 35.15, 23.50, 23.45, 20.47; MS (EI), m/e (rel inten) 203 (5, M+), 168 (99), 110 (91), 70 (100); HRMS (EI) m/e calcd for ($C_{10}H_{18}ClNO$) 203.1077, found 203.1076.

***trans*-1-Pyrrolidinyl-2,3-epoxycyclohexane (13).** Aqueous NaOH (1 N, 7.57 mL) was added to the solution of **12** (7.57 mmol, 1.54 g) in 2-propanol (15 mL) all at once and the solution was stirred at rt for 12 h. H_2O (10 mL) and solid NaOH (1 g) was added to the solution. The solution was extracted with ether (3 × 60 mL). The combined ether extracts were washed with brine (2 × 20 mL), dried over magnesium sulfate, and concentrated in vacuo to give **13** as a colorless oil (1.14 g, 90%): ^1H NMR (300 MHz δ 3.18 (m, 2 H, H-2 and H-3), 2.60–2.80 (m, 4 H, $N(CH_2)_2$), 2.48 (dd, J = 10.5, 5.7 Hz, H-1), 2.09 (m, 1 H), 1.65–1.86 (m, 6 H), 1.10–1.51 (m, 3 H); ^{13}C NMR (75 MHz) δ 60.08 (C-1), 54.40

(10) The procedure for the epoxidation of 3-bromocyclohexane was used; see ref 2.

(C-2 or C-3), 53.03 (C-3 or C-2), 51.54, 27.13, 24.54, 23.11, 15.97; MS (EI), *m/e* (rel inten) 167 (21, M^+), 110 (100), 96 (48), 70 (19); HRMS (EI) *m/e* calcd for ($C_{10}H_{17}NO$) 167.1310, found 167.1317.

***trans,trans*-1-Hydroxy-2,6-dipyrrolidinylcyclohexane (4).** Compound **13** (6.38 mmol, 1.14 g), benzene (5 mL), H_2O (1 mL), and pyrrolidine (7.02 mmol, 0.585 mL) were placed in a bomb. The bomb was heated at 80 °C for 48 h. After it was cooled to rt the crude mixture was diluted with ether (200 mL) and extracted with aqueous HCl (10%, 2 × 50 mL). The aqueous layer was basified by the addition of solid NaOH and extracted with ether (3 × 150 mL). The combined ether extracts were dried over magnesium sulfate and concentrated in vacuo to give **4** as a red oil (1.46 g, 96%): ^1H NMR (300 MHz) δ 4.48 (br s, 1 H, OH), 3.35 (t, *J* = 9.5 Hz, 1 H, H-1), 2.70 (m, 8 H), 2.48 (td, *J* = 9.8, 9.8, 3.3 Hz, 2 H, H-2 and H-6), 1.77 (m, 12 H), 1.23 (m, 2 H); ^{13}C NMR (75 MHz) δ 73.30, 64.53, 48.66, 23.67, 23.28, 22.83; MS (FAB), *m/e* (rel inten) 239 (100, M + H), 168 (66), 150 (26), 110 (62), 84 (37), 70 (47); HRMS (FAB) *m/e* calcd for ($C_{14}H_{26}N_2O$ + H) 239.2123, found 239.2123.

***trans,cis*-1-(Methylamino)-2,3-dipyrrolidinylcyclohexane (22):** obtained as a red oil from **4** in 82% yield; ^1H NMR (300 MHz) δ 2.18–2.95 (m, 15 H), 1.20–1.90 (m, 14 H); ^{13}C NMR (75 MHz) δ 64.26, 63.71, 58.28, 52.52, 51.58, 34.54, 25.74, 24.09, 23.11, 23.08, 20.50; MS (FAB), *m/e* (rel inten) 252 (76, M + H), 221 (5), 179 (17), 150 (29), 110 (100), 84 (47), 70 (37); HRMS (FAB) *m/e* calcd ($C_{15}H_{29}N_3$ + H) 252.2440, found 252.2424.

23: obtained as a red solid from **22** in 68% yield; mp 103–105 °C (CH_2Cl_2/hexanes); ^1H NMR (300 MHz) δ 7.20–7.67 (m, 3 H), 5.03 and 4.46 (two broad singlet, 1 H, CHCNO), 1.20–3.20 (m, 27 H); MS (FAB), *m/e* (rel inten) 424 (36, M + H), 353 (8), 221 (17), 173 (18), 150 (91), 110 (68), 84 (100), 70 (28). Anal. Calcd for $C_{22}H_{31}Cl_2N_3O$: C, 62.26; H, 7.36; Cl, 16.71; N, 9.90. Found: C, 62.07; H, 7.52; Cl, 16.83; N, 9.77.

X-ray crystallographic analysis of 23: $C_{22}H_{31}Cl_2N_3O$, formula wt. = 424.4; monoclinic; space group $P2_1/c$; $Z = 8$; a = 24.076(2), b = 11.774(2), c = 16.087(1) Å, β = 108.37(5)°, V = 4327.8(6) Å^3; calculated density = 1.31 g cm^{-3}, absorption coefficient m = 2.72 mm^{-1}. Intensity data were collected on a clear prism 0.12 × 0.18 × 0.30 mm mounted on a glass fiber on a Siemens *P*1bar diffractometer controlled by a Harris computer. Graphite monochromatized Cu $K\alpha$ radiation was used, (λ(Cu $K\alpha$) = 1.5418 Å), with $2\theta_{max}$ = 132°. Intensity data were measured at low temperature, (T = −122(2) °C), using 4°/min $\theta/2\theta$ step scans with scan widths >3.4°. 13546 measurements of 6807 unique reflectiosn were done; 5056 of these had intensities >3σ. Ten reflections periodically monitored showed no trend toward deterioration, $\sigma^2(I)$ was approximated by $\sigma^2(I)$ from counting statistics + $(dI)^2$, where the coefficient d of I was calculated from the variations in intensities of the monitored reflections and was 0.02. Cell parameters were determined by least squares fit of $K\alpha_1$ 2θ values ($\lambda K\alpha_1$ = 1.5402) for 25 high 2θ reflections.[11] An Lp correction appropriate for a monochromator with 50% perfect character was applied, and the data were corrected for absorption.[12]

The structure was solved by direct methods using SHELXS-86.[13] Hydrogens were all found in a difference Fourier map. There are two molecules in the asymmetric unit which have an approximate noncrystallographic symmetry relationship: x = 0.75 − (x' + z')/2; y = y' + 0.5; z = 0.75 − 3x'/2 + z'/2. The chlorophenyl rings in both molecules are disordered; some of the rings are flipped 180°. Population factors for the *m*-chlorines were adjusted after each refinement until the thermal parameters for those atoms were refined to values that were similar to values for the other chlorines. Because there was an apparently impossible intermolecular contact for the alternate *m*-chlorine on one of the two molecules (primed numbering), a complete refinement to convergence was carried out with only the unprimed molecule having alternate chlorine positions. However, at this point a difference map showed considerable residual density at the alternate chlorine location on the primed molecule and also the anisotropic thermal parameters for the carbonyl oxygen on that molecule (which, in the symmetry relationship x, −y − 0.5, z − 0.5, was too close to the alternate chlorine) were very high in the direction normal to the C–O bond, indicating that it was also disordered. The refinement was resumed, coupling alternate positions for the *m*-chlorine and the carbonyl oxygen on the primed molecule. Least squares refinement included coordinates for all atoms (except hydrogens at alternate *m*-chlorine positions) and anisotropic thermal parameters for non-hydrogen atoms (except the less-populated oxygen). The function minimized in the refinement was $\sum\omega(F_o^2 - F_c^2)^2$, where weights ω were $1/\sigma^2(F_o^2)$. Population factors for the *m*-chlorines were finally set at 75 and 25% (unprimed molecule) and 78 and 22% (primed molecule). The population factors for the alternate carbonyl oxygens on the primed molecule were also set at 78 and 22%. The distance between the primed molecule chlorine and the symmetry-related carbonyl oxygen in their less-populated positions refined to 3.12 Å, (the distance to the oxygen in its other position was 2.67 Å). Despite several attempts to adjust the position of the less-populated primed chlorine to a more reasonable bond length, the position always refined to a shorter bond (the final value was 1.39 Å), bond parameters for all other atoms were normal. The final agreement index R was 0.069 for all 6807 reflections and 0.054 for the 5056 reflections having intensities >3σ; there were no peaks in the final difference map larger than 0.3 Å^{-3} except those within 1 Å of a chlorine atom. Atomic form factors were from Doyle and Turner,[14] and, for hydrogen, from Stewart, Davidson and Simpson.[15] The CRYM system of computer programs was used.[16,17]

24: obtained as a red oil from **22** in 30% yield; ^1H NMR (300 MHz) δ 7.10–7.50 (m, 3 H), 4.70–5.00 (m, 1 H, CHNCO), 1.20–3.95 (m, 29 H); MS (FAB), *m/e* (rel inten) 438 (42, M + H), 367 (9), 150 (100), 110 (51); HRMS (FAB) *m/e* calcd for ($C_{23}H_{33}Cl_2N_3O$ + H) 438.2079, found 438.2077.

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Supplementary Material Available: Copies of NMR spectra (10 pages). This material is contained in 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.

(11) Duchamp, D. J. *ACS Symp. Ser.* **1977**, *6*, 98–121.
(12) Busing, W. R.; Levy, H. A. *Acta Crystallogr.* **1957**, *10*, 180.
(13) Sheldrick, G. M. SHELXS-86. *Crystallographic Computing 3*; Sheldrick, G. M., Krüger, C., Goddard, R., Eds.; Oxford Univ. Press: New York, 1985, pp 175–189.
(14) Doyle, P. A.; Turner, P. S. *Acta Crystallogr. A: Cryst. Phys. Diffr. Theor. Gen. Crystallogr.* **1968**, *A24*, 390–397.
(15) Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Chem. Phys.* **1965**, *42*, 3175–3187.
(16) Duchamp, D. J. *CRYM*, a system of crystallographic programs; The Upjohn Co.; Kalamazoo, MI, 1984.
(17) The author has deposited atomic coordinates for **23** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.