of the initially added $SnCl_4$, acetyl chloride, and mesitylene. Results, listed in Table X, for five samples whose concentration of $SnCl_4$ varies by a factor of 2, acetyl chloride by a factor of 3, and mesitylene by a factor of 3, only show an average deviation of 10% in the ratio. Therefore it can be concluded that the extent of reaction is proportional to the concentration of each of the reactants to the first power. This does not necessarily imply a ternary collision since an intermediate, e.g., $SnCl_4$–mesitylene, might be formed in very low concentration. As an example of the data used the proton resonance spectrum of sample J just after thawing is on file as supplementary data. From a comparison of the chemical shift of the product with the species listed in Table IV one may conclude that the product is $(MMK)_2 \cdot SnCl_4 \cdot HCl$. Since the reaction rate depends upon the concentration of mesitylene to the first power, a very rapid disproportionation of the initially formed product must occur.

A quantitative comparison of the reactivity with $SnCl_4$ as metal chloride, vis-à-vis $AlCl_3$, is not possible since the overall lower reactivity of $SnCl_4$ did not allow a study with the same substrate at the same temperature. Although $SnCl_4$ is less reactive, a significant fact is the different order of reactivity of the various aromatic hydrocarbons. Thus with $AlCl_3$ toluene is slightly more reactive than mesitylene,[11] while with $SnCl_4$ mesitylene is much more reactive than toluene. Therefore it is not possible to make general statements about relative reactivities. Presumably both the extent of intermediate complex formation and its rate of rearrangement to product affect the overall reactivity.

Registry No. $(CH_3)_2O$, 115-10-6; $(CH_3)_2O \cdot HCl$, 24521-77-5; $(CH_3)_2O \cdot AlCl_3$, 14740-73-9; $2[(CH_3)_2O] \cdot AlCl_3$, 34537-62-7; $2[(CH_3)_2O] \cdot trans\text{-}SnCl_4$, 63038-95-9; $2[(CH_3)_2O] \cdot cis\text{-}SnCl_4$, 55905-92-5; $(CH_3)_2O \cdot AlCl_3 \cdot HCl$, 86822-16-4; $2[(CH_3)_2O] \cdot SnCl_4 \cdot HCl$, 86822-17-5; $C_6H_5COCH_3$, 98-86-2; $C_6H_5COCH_3 \cdot HCl$, 86822-18-6; $C_6H_5COCH_3 \cdot AlCl_3$, 23444-00-0; $2(C_6H_5COCH_3) \cdot AlCl_3$, 86851-94-7; $2(C_6H_5COCH_3) \cdot trans\text{-}SnCl_4$, 75963-09-6; $2(C_6H_5COCH_3) \cdot cis\text{-}SnCl_4$, 86851-95-8; $C_6H_5COCH_3 \cdot AlCl_3 \cdot HCl$, 86822-19-7; $2(C_6H_5COCH_3) \cdot SnCl_4 \cdot HCl$, 86822-20-0; MMK, 1667-01-2; MMK·HCl, 86822-21-1; MMK·$AlCl_3$, 86822-22-2; 2(MMK)·$AlCl_3$, 86822-23-3; 2(MMK)·$SnCl_4$, 86822-24-4; MMK·$AlCl_3$·HCl, 86822-25-5; 2(MMK)·$SnCl_4$·HCl, 86822-26-6; CH_3COCl, 75-36-5; $CH_3COCl \cdot AlCl_3$, 26273-09-6; $2(CH_3COCl) \cdot AlCl_3$, 86822-27-7; $2,5\text{-}(CH_3)_2C_6H_3COCH_3 \cdot AlCl_3 \cdot HCl$, 86822-28-8; $SiCl_4$, 10026-04-7; $GeCl_4$, 10038-98-9; $SnCl_4$, 16804-87-8; $AlCl_3$, 7446-70-0; *p*-xylene, 106-42-3; benzene, 71-43-2; toluene, 108-88-3; mesitylene, 108-67-8.

Supplementary Material Available: Computer program and NMR data (4 pages). Ordering information is given on any current masthead page.

Synthesis Applications of Cationic Aza-Cope Rearrangements.[1] Stereoselective Synthesis of *cis*- and *trans*-3a-Aryl-4-oxodecahydrocyclohepta[*b*]pyrroles

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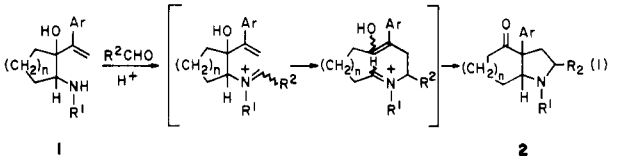
A general synthesis of 3a-aryl-4-oxodecahydrocyclohepta[*b*]pyrroles is detailed (eq 1, $n = 2$). The key step is a "ring-enlarging pyrrolidine annulation" reaction which occurs when 2-amino-1-(1-arylvinyl)cyclohexanols are treated at 25–80 °C with an aldehyde and acid. Three different methods (Schemes I and II) for assembling the 2-amino-1-(1-arylvinyl)cyclohexanol intermediates are reported. *cis*-3a-Aryl-4-oxodecahydrocyclohepta-[*b*]pyrroles can be formed with complete stereocontrol from either *cis*- or *trans*-2-amino-1-(1-arylvinyl)cyclohexanols. The corresponding trans bicyclics can be prepared with modest (~3:1) selectivity from *cis*-2-((diphenylmethyl)amino)-1-(1-arylvinyl)cyclohexanols. The stereochemical outcome of these tandem cationic aza-Cope–Mannich cyclization reactions is consistent with chair topographies for the rearrangement steps (Scheme III).

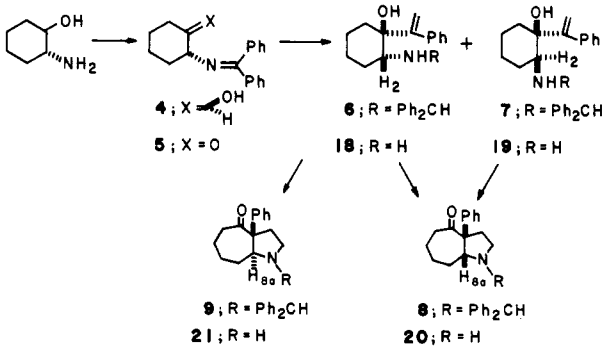
A useful ring-enlarging pyrrolidine annulation sequence has been recently reported[1,2] from these laboratories (eq 1). In this reaction, cationic aza-Cope rearrangement



1 2

(2-azonia[3,3]sigmatropic rearrangement)[3] of iminium ions derived from cyclopentanols 1 ($n = 1$), followed by capture of the azacycloalkadiene isomers in an intramolecular Mannich fashion gave 3a-aryl-4-oxooctahydroindoles ($n = 1$) in good yields.[1,4] We now wish to describe the details

Scheme I



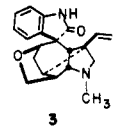
(1) Part 13 in the series. For part 12 see: Overman, L. E.; Mendelson, L. T.; Jacobsen, E. J. *J. Am. Chem. Soc.*, in press.

(2) (a) Overman, L. E.; Mendelson, L. T. *J. Am. Chem. Soc.* **1981**, *103*, 5579. (b) Overman, L. E.; Mendelson, L. T.; Flippin, L. A. *Tetrahedron Lett.* **1982**, *23*, 2733. (c) Overman, L. E.; Jacobsen, E. J. *Ibid.* **1982**, *23*, 2741.

(3) For a recent review see: Heimgartner, H.; Hansen, H.-J.; Schmid, H. In "Iminium Salts in Organic Chemistry", Part 2; Böhme, H.; Viehe, J. G., Eds.; Wiley: New York, 1979; pp 655–732.

0022-3263/83/1948-3393$01.50/0

of this reaction with cyclohexanol precursors (eq 1, n = 2), which results in a convenient stereoselective synthesis of both *cis*- and *trans*-3a-aryl-4-oxodecahydrocyclohepta[*b*]pyrroles[5] (*cis*- or *trans*-**2**, n = 2). The decahydrocyclohepta[*b*]pyrrole ring system,[6] although not common, is found in several natural products, for example, the antihypertensive alkaloid gelsemine **3**.[7,8]



3

Results

The ring-enlarging pyrrolidine annulation reaction of 2-amino-1-(1-phenylvinyl)cyclohexanols **1** (eq 1, n = 2) was explored with the nitrogen substituent R^1 = Me, Ph_2CH, and H and with formaldehyde and acetaldehyde (R^2 = H and Me) as carbonyl components.

Preparation of *cis*- and *trans*-1-Alkyl-3a-aryl-4-oxodecahydrocyclohepta[*b*]pyrroles. The general sequence is summarized in Scheme I. Crystalline imine **4** was prepared from readily available *trans*-2-aminocyclohexanol[9] and benzophenone in 83% yield. Swern[10] oxidation of **4** gave ketone **5** as a slightly impure labile yellow solid, which was isolated in 76% yield after crystallization. Addition of excess (1-phenylvinyl)lithium[11-13] to **5** at −78 °C in tetrahydrofuran (THF) gave a crude mixture of imino alcohols, which, without purification, was treated with sodium cyanoborohydride[14] to afford a 8:1 mixture of amino alcohols **6** and **7** in 70% overall yield. Chromatography on silica gel gave pure samples of the crystalline major isomer **6** (50% yield, mp 78 °C) and the oily minor isomer **7** (2–10% yield). Stereochemical assignments for **6** and **7** followed most directly from chemical ionization mass spectra, which showed an intense peak at m/e 366 ($MH^+ - H_2O$, 49% relative to MH^+) for isomer **6**, and the complete absence of this fragment in the spectrum of isomer **7**. Studies by Longevialle and co-workers[15] have shown that amino alcohols in which intramolecular hydrogen bonding is possible do not have peaks for loss of water in their chemical ionization mass spectrum, while isomers without intramolecular hydrogen bonds show intense peaks for this fragmentation. Isomer **7** should exist in a chair conformation with the styrene and amine groups equatorial, thus permitting good intramolecular hydrogen bonding between the amine and OH groups. The 250-MHz ^{1}H NMR spectrum is consistent with this conformational assignment for **7**, since it shows a clean doublet of doublets (J = 4.4 and 10.7 Hz) at δ 2.69 for an axial methine hydrogen (H_2). In contrast, the 250-MHz ^{1}H NMR spectrum of isomer **6** shows H_2 as a broad singlet (half-height width = 10 Hz) at δ 2.69. This absorption would appear most consistent with **6** existing as a mixture of conformational isomers, in which the (possibly predominant) conformer with the bulky styrene group equatorial would be devoid of intramolecular hydrogen bonding. It is interesting to note that the preferential addition of lithium reagents from the side of the imine substituent was also observed[1,2a] with the related 2-iminocyclopentanones.

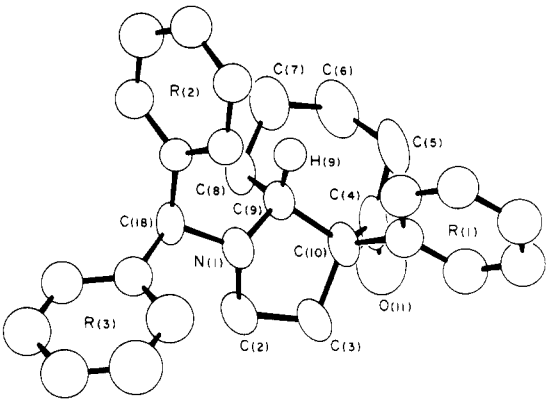


Figure 1. View of the molecular structure of **8**. Thermal ellipsoids are drawn at the 50% probability level. Hydrogens are omitted for clarity, except for H(9), which is included to clearly show the cis ring fusion. Phenyl ring R(1) contains atoms C(12)–C(17), phenyl ring R(2) contains atoms C(19)–C(24), and phenyl ring R(3) contains atoms C(25)–C(30).

Table I. Preparation of Cycloheptapyrrolidines 8 and 9 from Cyclohexanol 6

solvent[a]	8:9[b]	yield, %	time, h
PhH	1:3.5	>90[c]	22
THF	1:1	>90[c]	40
$MeNO_2$	13.5:1	>90[c]	18
$HCONMe_2$	24:1	72[d]	18
Me_2SO	>30:1	75[d]	23

[a] Heated at 80 °C. [b] Isomer ratios determined by ^{1}H NMR integration of diphenylmethine resonances at δ 4.78 and 5.28 for **8** and **9**, respectively. [c] Crude yield. [d] Yield after column chromatography.

Exposure of **7** to paraformaldehyde (1.1 equiv) and camphorsulfonic acid (0.9 equiv) in refluxing benzene for 22 h gave ketone **8** as a crystalline solid in 96% yield. Cycloheptapyrrolidine **8** showed a characteristic doublet (J = 10.3 Hz) for the angular hydrogen H_{8a} at δ 3.56 in the ^{1}H NMR spectrum. The stereochemistry of **8** was determined by single-crystal X-ray diffraction, and an ORTEP drawing of the molecular model is shown in Figure 1. The cycloheptane conformation observed in the crystal nicely rationalizes the observation of H_{8a} as a doublet in the ^{1}H NMR spectrum, since the estimated dihedral angle between H_{8a} and the cis H_8 hydrogen is 90°.[16,17]

(4) We wish to stress that although we have chosen[1,2] to discuss this sequence as a [3,3]-sigmatropic rearrangement followed by a Mannich cyclization, alternate mechanisms with *similar topographical constraints* are possible with some substrates. For example, with electron-rich styrenyl substrates, cyclization to a benzylic cation followed by pinacol rearrangement is a conceivable alternative. Experiments that address these mechanistic issues are in progress and will be reported in due course.

(5) For a preliminary report of a portion of the research described here see: Overman, L. E.; Jacobsen, E. J. *Tetrahedron Lett.* **1982**, *23*, 2737.

(6) For syntheses of the parent ring system see: (a) Prelog, V.; Geyer, U. *Helv. Chim. Acta* **1945**, *28*, 576. (b) Ayerest, G. G.; Schonfield, K. *J. Chem. Soc.* **1960**, 3445. For a recent entry see: Keck, G. E.; Webb, R. R.; Yates, J. B. *Tetrahedron* **1981**, *37*, 4007.

(7) Cf. Saxton, J. E. In "The Alkaloids", Manske, R. H. F., Ed.; Academic Press: New York, 1965; Vol. 8, Chapter 6. Bindra, J. S. "The Alkaloids", Manske, R. H. F., Ed.; Academic: New York, 1976; Vol. 14, Chapter 2.

(8) Although gelsemine has not been synthesized, it is the object of current attention in several laboratories including our own. Cf.: Fleming, I.; Loreto, M. A.; Michael, J. P.; Wallace, I. H. M. *Tetrahedron Lett.* **1982**, *23*, 2053.

(9) Prepared in 81% yield from cyclohexene oxide and ammonia water. Muller, F. In "Methoden der Organische Chemie (Houben-Weyl)", 4th ed.; Müller, E., Ed.; Thieme-Verlag: Stuttgart, 1957; Vol. 3, pp 311–326.

(10) Mancuso, A. J.; Huang, S.; Swern, P. *J. Org. Chem.* **1978**, *43*, 2480.

(11) Prepared from the corresponding bromide[12] and 1.0 equiv of *tert*-butyllithium at −78 °C in THF. The use of 2 equiv of *tert*-butyllithium[13] gave lower yields.

(12) Newman, M. S.; Dhawan, B.; Hashem, M. M.; Khanna, V. K.; Springer, J. M. *J. Org. Chem.* **1976**, *41*, 3925.

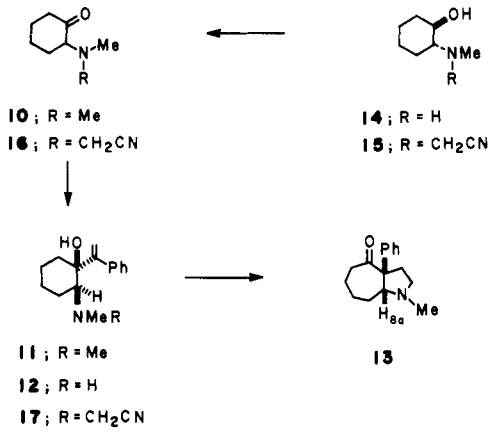
(13) Cf.: Seebach, D.; Neumann, H. *Chem. Ber.* **1974**, *107*, 847.

(14) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

(15) (a) Longevialle, P.; Milne, G. W. A.; Fales, H. M. *J. Am. Chem. Soc.* **1973**, *95*, 6666. (b) Longevialle, P.; Girard, J.-P.; Rossi, J.-C.; Tichy, M. *Org. Mass Spectrom.* **1980**, *15*, 268.

(16) The dihedral angle, based upon the crystal structure results with hydrogen atoms in calculated tetrahedral positions, is 90.0°.

Scheme II



When amino alcohol **6**, which has cis-oriented amine and vinyl groups, was treated identically in benzene with paraformaldehyde and acid, a 1:3.5 ratio of **8** and the trans isomer **9** was obtained. Two recrystallizations of this mixture allowed for isolation of **9** as a crystalline solid (88% purity) in 42% yield. The structure of **9** was consistent with extensive homonuclear ^1H NMR decoupling experiments conducted at 500 MHz. As expected from examination of a molecular model of **9**, H_{8a} (δ 2.80) appears as a doublet of doublets (J = 3.8 and 12.4 Hz) in the ^1H NMR spectrum.

The rearrangement of **6** was explored in several solvents, and the results obtained are summarized in Table I. The ratio of products **8** and **9** was extremely solvent dependent, and nearly exclusive formation of the cis isomer **8** was obtained in dimethyl sulfoxide (Me_2SO). That the product ratios shown in Table I are predominantly kinetically controlled was established in two cases. Thus, **8** was recovered unchanged when exposed to 1 equiv of camphorsulfonic acid in benzene at 80 °C for 24 h, while similar treatment of **9** in Me_2SO resulted in only a small conversion to **8** (5% after 6 h, 10–20% after 24–48 h).

An alternate, completely stereoselective, preparation of *cis*-3a-aryl-4-oxodecahydrocyclohepta[*b*]pyrroles is outlined in Scheme II. Addition of (1-phenylvinyl)lithium to 2-(dimethylamino)cyclohexanone (**10**)[18] at −78 °C in THF gave, in this case, a *single* diastereomer, **11**, which was isolated in 55% yield after distillation. The stereochemical assignment for **11** was initially made on the expectation that addition of the lithium reagent would occur preferentially from the side opposite the dimethylamino group, in analogy with related additions of Grignard reagents to 2-(alkylamino)cyclohexanones.[19] A standard chloroformate dealkylation–hydrolysis sequence[20,21] converted **10** to the secondary amine **12** in 52% yield. The stereostructure assigned to **12** was consistent with the chemical ionization mass spectrum, which showed a weak peak at m/e 214 ($MH^+ - H_2O$, 13% relative to MH^+), and the 250-MHz ^1H NMR spectrum, which showed a clean doublet of doublets (J = 10.6 Hz and 4.4 Hz) at δ 2.58 for an axial methine hydrogen H_2.

Rearrangement of **12** was accomplished by treatment with paraformaldehyde (1.1 equiv) and camphorsulfonic acid (0.95 equiv) in refluxing benzene for 4.5 h to give a single product **13** in 82% yield. Cycloheptapyrrolidine **13** showed a carbonyl absorption in the infrared spectrum at 1710 cm^{-1} and a doublet of doublets (J = 9.3 and 2.0 Hz) at δ 3.21 for the angular hydrogen H_{8a}. The cis stereochemistry of **13** was confirmed by its preparation from **8**.

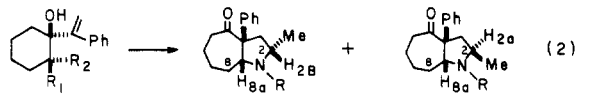
The use of a cyanomethyl group to protect the basic nitrogen of the 2-(alkylamino)cyclohexanone precursor results in a more concise preparation of *cis*-3a-aryl-4-oxocycloheptapyrrolidines, since the cyanomethyl group also functions as a source for a formaldehyde iminium ion (see Scheme II). Reaction of *trans*-2-(methylamino)-cyclohexanol (**14**)[22] with KCN and paraformaldehyde[23] gave **15**, which upon oxidation with the Swern reagent,[10] provided α-amino ketone **16** in 66% yield from **14**. Reaction of **16** with 2 equiv of (1-phenylvinyl)lithium[11–13] at −78 °C in THF gave the cis amino alcohol **17** as the nearly exclusive product, which was isolated in 50% yield after chromatographic purification. The stereostructure of **17** follows from analogy with **11**. The organolithium addition was much less clean if the reaction was conducted at higher temperature or if the reaction mixture was allowed to warm to room temperature before quenching. We assume that the cyanomethylamine functionality is reactive under these conditions.[24–26] Although **17** was stable in refluxing ethanol, it was cleanly converted to cycloheptapyrrolidine **13** in the presence of a variety of reagents capable of "trapping" cyanide anion[27,28] (see Table II). Of particular note are silver trifluoroacetate and copper trifluoroacetate, which promote the **17** → **13** conversion in good yield *within hours at room temperature*. Also significant is the somewhat slower conversion brought about by silver–pyridine, which demonstrates that the ring-enlarging annulation reaction can also be accomplished under *mildly basic reaction conditions*.

Preparation of *cis*-3a-Aryl-4-oxodecahydrocyclohepta[*b*]pyrroles. Amino alcohols **18** and **19** were prepared in 65% yield and in an ca. 5.5:1 ratio by acid hydrolysis[29] of the crude mixture of imino alcohols resulting from addition of (1-phenylvinyl)lithium to ketone **5** (Scheme I). Separation by chromatography on silica gel gave **18** (36% from **5**, mp 102–103 °C) and **19** (5% from **5**) as crystalline solids. Amino alcohols **18** and **19** showed diagnostic differences in their ^1H NMR and chemical ionization mass spectra, which were similar to those observed for the corresponding secondary amines **6** and **7**. When **19** was heated at reflux in benzene with paraformaldehyde (1.1 equiv) and camphorsulfonic acid (0.9 equiv), a single product, **20**, was obtained in >90% yield. *cis*-Cycloheptapyrrolidine **20** showed a doublet (J = 9.9 Hz) in the ^1H NMR spectrum at δ 3.89 for the angular hy-

(17) Silverstein, R. M.; Bassler, G. C.; Morrie, T. C. "Spectrometric Identification of Organic Compounds", 3rd ed.; Wiley: New York, 1974; p 190.
(18) Purchased from Aldrich Chemical Co. This ketone is no longer available from Aldrich but may be purchased from ICN K&K Laboratories.
(19) (a) Curtin, D. Y.; Schmukler, S. *J. Am. Chem. Soc.* **1955**, *77*, 1105. (b) Bernardi, L.; Fugante, C.; Ghiringhelli, O. *Gazz. Chim. Ital.* **1968**, 836.
(20) Cf.: Rice, K. C. *J. Org. Chem.* **1975**, *40*, 1850 and references cited therein.
(21) Cf.: Gassman, P. G.; Hodgeson, P. K. G.; Balchunis, R. J. *J. Am. Chem. Soc.* **1976**, *98*, 1275.
(22) Prepared in 75% yield from cyclohexene oxide and methylamine. Kován, J.; Blâha, K. *Chem. Listy.* **1958**, *52*, 283.
(23) Cf.: Kuffner, F.; Koechlin, W. *Montasch. Chem.* **1962**, *93*, 476.
(24) The addition of lithium reagents to the cyano group of cyanomethylamines is well precedented,[25] as is deprotonation α to the cyano group.[26]
(25) Cf.: (a) Hellmann, H.; Opitz, G. "α-Aminoalkylierung"; Verlag Chemie: Weinheim, 1960; pp 235–243. (b) For a recent example see: Wasserman, H. H.; Doin, R. P. *Tetrahedron Lett.* **1982**, *23*, 1413.
(26) Cf.: Stork, G.; Ozorio, A. A.; Leong, A. Y. W. *Tetrahedron Lett.* **1978**, 5175.
(27) There are numerous reports of the use of cyanomethylamines as iminium ion precursors, and a variety of reagents have been employed to promote this conversion.[2c,25a,28]
(28) Cf.: Reiber, H. G.; Stewart, T. D. *J. Am. Chem. Soc.* **1940**, *62*, 3026. Guibe, F.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1982**, *23*, 5055 and references cited therein.
(29) Cf.: Babler, J. H.; Invergo, B. J. *J. Org. Chem.* **1981**, *46*, 1937.

drogen H_{8a} and could be prepared from **8** under transfer hydrogenation conditions.[30] In contrast to the secondary amine series (vide supra), amino alcohol **18**, which has cis oriented NH_2 and vinyl groups, also gave *exclusively* the *cis*-cycloheptapyrrolidine **20** (isolated in 93% yield) when subjected to identical rearrangement conditions. The stereoselectivity of the rearrangement of **18** was >30:1, since no trace of the corresponding trans isomer **19** could be seen in the 250-MHz ^1H NMR spectrum of the crude rearrangement product. The *trans*-cycloheptapyrrolidine **19** was prepared from **9**[30] and showed characteristic multiplets at δ 3.3–3.7 for the H_{8a} and H_2 hydrogens.

Preparation of 1,2-Dialkl-3a-aryl-4-oxodecahydrocyclohepta[*b*]pyrroles. The preparation of *cis*-cycloheptapyrrolidines with an alkyl substituent at C-2 was also briefly investigated (eq 2). Reaction of **19** with acet-



(2)

19; R_1 = NH_2, R_2 = H **22**; R = H **23**; R = H

18; R_1 = H, R_2 = NH_2 **24**; R = Me **25**; R = Me

aldehyde (2 equiv) and camphorsulfonic acid (0.9 equiv) in refluxing benzene for 4 h gave a 33:1 mixture of the *cis*-cycloheptapyrrolidines **22** and **23** (56% crude yield). Although we were unsuccessful in cleanly separating these diastereomers, their structures could be assigned from spectroscopic properties of the isomer mixture. The observation of the angular hydrogen H_{8a} as a clean doublet in each isomer (**22**: δ 3.87, J = 10.0 Hz; **23**: δ 4.06, J = 9.7 Hz) is taken as evidence that both isomers have cis ring fusions. The major product **22** showed a characteristic doublet (J = 6.1 Hz) at δ 1.12 for the C-2 methyl and a multiplet centered at δ 3.00 for the methine hydrogen $H_{2\beta}$, while the doublet for the C-2 methyl of **23** was observed at δ 1.03 (J = 7.3 Hz).

The stereochemistry at C-2 was determined by N-methylation[14] of an 8:1 mixture of **22** and **23** to give the corresponding mixture of tertiary amines **24**, and **25**. The ^1H NMR spectrum of the major product **24** showed a doublet of doublets (J = 9.7 Hz and 2.1 Hz) at δ 3.26 for methine hydrogen H_{8a} and a multiplet centered at δ 2.35 for methine hydrogen $H_{2\beta}$. That N-methylation of **22** resulted in nearly *identical upfield* shifts of H_{8a} (0.61 ppm) and $H_{2\beta}$ (0.65 ppm) is consistent only with a cis relationship for these hydrogens. *cis*-Cycloheptapyrrolidine **24** should exist preferentially in a conformation with the N–Me group on the β face (trans to C_8 and the C_2–Me) and, thus, the C_{8a} and $C_{2\beta}$ hydrogens should be identically[31] shielded[32] by the syn N–Me group and the anti electron pair. Large stereochemistry-dependent ^1H NMR shielding effects for hydrogens α to nitrogen have been observed for many *N*-alkylpyrrolidines.[32,33] The ^1H NMR spectrum of the minor isomer **25** showed a doublet (J = 9.5 Hz) for the angular H_{8a} at δ 3.73 which is 0.33 ppm upfield of the comparable hydrogen in **23**.

Cyclohexanol **18**, with cis-oriented amine and vinyl groups, also reacted with acetaldehyde to give predominantly **22**; however the stereoselectivity (**22**:**23** = 8:1) was less than that observed in the similar reaction of **19**.

Discussion

The chemistry described herein provides a quick, efficient, and stereocontrolled entry into the decahydrocyclohepta[*b*]pyrrole ring system. The preparation of *cis*-3a-aryl-4-oxodecahydrocyclohepta[*b*]pyrroles with complete stereocontrol can be accomplished by cationic aza-Cope rearrangement of either *cis*- or *trans*-2-amino-1-(1-phenylvinyl)cyclohexanols. The corresponding trans bicyclics can also be prepared with modest stereoselectivity (~3:1) by rearrangement of *cis*-2-((diphenylmethyl)-amino)-1-(1-phenylvinyl)cyclohexanols. The ring-enlarging pyrrolidine annulation reaction also allows a trans methyl group to be incorporated with nearly complete stereocontrol at the 2-position of the pyrrolidine ring, and one would anticipate that similar rearrangements with other aldehydes would allow a variety of 2-substituted *cis*-3a-aryl-4-oxodecahydrocyclohepta[*b*]pyrroles to be prepared as well. We note that other routes to the hydrocyclohepta[*b*]pyrrole ring system proceed with little or no stereocontrol.[5a,5b]

Cope rearrangements of *both cis*- and *trans*-1,2-divinylcyclohexanes are known to occur preferentially via chair transition states.[34] The stereoselectivities of the cycloheptapyrrolidine syntheses reported here are nicely rationalized by similar chair topographies for the corresponding cationic aza-Cope rearrangements.[4] Thus, the rearrangement of iminium ions derived from cyclohexanols **7**, **12**, or **19** (where the amine and vinyl groups are trans) to give exclusively cis-fused cycloheptapyrrolidines (see Scheme III) is expected as long as intramolecular Mannich ring closure of the *trans,trans*-1,5-azacyclodecadiene **27** is more rapid than any loss of stereochemistry of this intermediate.

The rearrangements of iminium ions derived from cyclohexanols with cis-oriented amine and vinyl groups is more complex, since two chair transition states are possible (see Scheme III). The stereospecific formation of *cis*-hydrocyclohepta[*b*]pyrrole **20** from primary amine **18**, is consistent with the intermediacy of the *cis,trans*-1,5-azacyclodecadiene **29** (R^1 = H). This event is reasonable, since rearrangement in the alternate chair sense thrusts the bulky phenyl group under the cyclohexane ring. When the nitrogen substituent is the large diphenylmethyl group (R^1 = $CHPh_2$), the two chair processes are more nearly balanced in energy, since destablilizing steric interactions with the Ph or $CHPh_2$ group are expected in either transition state. The formation of mixtures of **8** and **9** from the rearrangement of the formaldehyde iminium ion derived from secondary amine **7** thus is not surprising. The preferential formation of only the cis product when this rearrangement was conducted in Me_2SO may be rationalized by an effective increase in size of the OH group in Me_2SO[35] and a resulting increase in the quasi 1,3-diaxial interaction of this group with the bulky R substituent in the transition state leading to intermediate **30**.

The stereoselective formation of the *trans*-2-methyl-*cis*-3a-phenyl-4-oxohydrocycloheptapyrrole **22** from the reaction of cyclohexanols **18** and **19** with acetaldehyde can also be understood in terms of the chair conversions summarized in Scheme III. Thus, it is reasonable that the

(30) Cf.: Jackson, A. E.; Johnstone, R. A. W. *Synthesis* **1976**, 685.
(31) If the protons were anti, then methylation would cause a large upfield shift for the hydrogen syn to the methyl group or a very small upfield shift for both hydrogens, resulting from a mixture of *N*-methyl conformers.
(32) Cf.: Lambert, J. B.; Oliver, W. L. *J. Am. Chem. Soc.* **1969**, *91*, 7774. Breur, E.; Melumad, D. *J. Org. Chem.* **1973**, *38*, 1601. Pitner, T. P.; Edwards, W. B.; Bassfield, R. L.; Whidby, J. F. *J. Am. Chem. Soc.* **1978**, *100*, 246.
(33) For analogous effects in the piperdine series see: Vierhapper, F. W.; Eliel, E. L.; Zuniga, G. *J. Org. Chem.* **1980**, *45*, 4844.
(34) Cf.: (a) Grob, C. A.; Link, H.; Scheiss, P. W. *Helv. Chim. Acta* **1963**, *51*, 483. Many related examples in the sesqueterpine area are summarized in: (b) Rhoads, S. J.; Paulins, N. R. *Org. React.* (*N.Y.*) **1975**, *22*, 1.
(35) Cf.: Gordon, J.; Ford, R. A. "The Chemist Companion"; Wiley: New York, 1972; p 157.

Table II. Preparation of Cycloheptapyrrolidine 13 from Cyanomethyl Precursor 17

entry	reaction conditions: additive (equiv)	solvent	temp, °C	time, h	yield, %
1	RSO_3H (1.2)	PhH	80	11	70
2	none[a]	EtOH	80	11	no reaction
3	$AgOCOCF_3$ (1.1)	$CHCl_3$	25	1.5	77
4	$AgNO_3$ (1.1)	EtOH	25	1.0	63
5	$AgNO_3$ (1.1)/pyridine (13.5)	$CHCl_3$	40	16	82
6	AgOAc (2.5)	EtOH	25	23	76
7	$CuOCOCF_3$ (2.8)	$CHCl_3$	25	1	91
8	$CuOCOCF_3$ (1.2)/Et_3N (1.5)	$CHCl_3$	25	3.5	no reaction

[a] This reaction was conducted with base-washed glassware.

reaction of acetaldehyde and **19**, would proceed preferentially via the (*E*)-iminium ion intermediate **26** (R^1 = H, R^2 = CH_3), since this stereoisomer is both more stable and would rearrange in a chair sense with the methyl group in a favored[34b] quasi-equatorial orientation. A similar preference for the reaction of acetaldehyde and **18** to proceed via (*E*)-iminium ion **28** (R^1 = H, R^2 = CH_3) would also account for the preferential formation of **22** from this cyclohexanol as well.

Conclusion

The efficient, stereocontrolled assembly of the hydrocyclohepta[*b*]pyrrole ring system detailed herein provides another illustration of the utility of tandem cationic aza-Cope–Mannich rearrangements in organic synthesis. Since this annulation reaction occurs readily at near neutral pH (amine–amine salt buffer) and 25–80 °C, we would anticipate success for the reaction with more highly functionalized systems. The ability to predict the stereochemical outcome from the often, known topographical preferences of related rearrangements in all carbon systems should allow stereorational applications of this annulation method to a variety of synthesis objectives.

Expermental Section[36]

***trans*-2-((Diphenylmethylidene)amino)cyclohexanol (4).** A solution of *trans*-2-aminocyclohexanol[9] (9.80 g, 85.2 mmol), benzophenone (15.3 g, 84.0 mmol), *p*-toluenesulfonic acid monohydrate (1.62 g, 8.52 mmol), and toluene (250 mL) was heated at reflux in a Dean–Stark apparatus for 42 h. After cooling to room temperature, basic workup (toluene, $MgSO_4$) gave a crude white solid which was recrystallized from hot hexane to afford 19.7 g (83%) of pure **4**. An analytical sample was prepared by three recrystallizations from hot hexane to give fine translucent needles: mp 104–104.5 °C; IR (CCl_4) 3605, 1624, 1449, 1031, 692 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.1–7.7 (m, 10 H), 3.83 (ddd, *J* = 11.0 Hz, *J* = 8.5 Hz, *J* = 4.4 Hz, CHN), 3.05–3.30 (m, C*H*OH), 0.8–2.2 (m, 9 H); ^{13}C NMR (63 MHz, $CDCl_3$) 169.6, 140.2, 137.2, 130.2, 128.7, 128.6, 128.4, 128.2, 75.0, 68.3, 32.3, 32.0, 24.8, 24.3; mass spectrum, *m/e* (EI, relative percent) 279 (53), 278 (45), 262 (49), 220 (27), 208 (69), 206 (44), 182 (54), 166 (37), 165 (100), 104 (80), 91 (31), 77 (41). Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.83; H, 7.63; N, 4.92.

2-((Diphenylmethylidene)amino)cyclohexanone (5). Following the procedure of Swern,[10] **4** (10.0 g, 35.8 mmol) was oxidized with the reagent prepared from Me_2SO (80 mmol) and oxalyl chloride (40 mmol). Aqueous workup (CH_2Cl_2, $MgSO_4$) provided 10.2 g of an oily solid, which upon trituration with hexane gave 7.6 g (76%) of a yellow solid, mp 76–77 °C. This compound could not be recrystallized, and was also not stable for prolonged periods. An analysis was therefore not obtained: IR (CCl_4) 1717, 1623, 1447, 1283, 691 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.1–7.7 (m, Ph H), 3.94 (br dd, *J* = 9.6 Hz, *J* = 5.5 Hz, CHN), 2.62 (dt, *J* = 15.1 Hz, *J* = 5.9 Hz, C*H*HC=O), 1.5–2.3 (m, 7 H); ^{13}C NMR (63 MHz, $CDCl_3$) 208.5, 169.5, 139.8, 136.7, 130.3, 128.9, 128.6, 128.1, 127.7, 70.9, 40.9, 36.0, 27.4, 23.1; mass spectrum, *m/e* (EI, relative percent) 277 (32), 249 (22), 248 (68), 166 (60), 165 (100), 103 (33), 77 (22).

***trans*- and *cis*-2-((Diphenylmethyl)amino)-1-(1-phenylethenyl)cyclohexanols (6 and 7).** To a solution of freshly prepared[12] α-bromostyrene (1.64 g, 8.97 mmol) and THF (40 mL) at −78 °C was added *tert*-butylithium (5.0 mL of a 1.80 M solution in pentane) dropwise over 20 min. After the deep red solution was stirred for an additional 20 min at −78 °C, a solution of **5** (1.00 g, 3.61 mmol) and THF (13 mL) was added dropwise over 10 min. After stirring for 1 h at −78 °C, the yellow solution was allowed to warm to room temperature for 1 hour. Aqueous workup (Et_2O, $MgSO_4$) gave a yellow oil, which was used directly in the next step. This oil was dissolved in MeOH (37 mL), $NaBH_4$ (0.550 g, 8.75 mmol) and 1 N HCl (4.2 mL) were added, and the resulting solution was heated at reflux for 21 h. After cooling to 25 °C, concentration and acidic workup (Et_2O–$CHCl_3$, $MgSO_4$) gave 0.979 g (70%) of an 8:1 mixture (as determined by ^1H NMR integration of the diphenylmethine hydrogens at δ 4.75 and 4.85) of **6**:**7**. Column chromatography (hexane/ethyl acetate/triethylamine 18:1:0.2) resulted in elution of the minor isomer **7** (2–10%) first as a thick oil, which resisted recrystallization: ^1H NMR (250 MHz, $CDCl_3$) 6.9–7.3 (m, 15 H, Ph H), 5.54 (d, *J* = 1.8 Hz, *H*HC=), 5.07 (d, *J* = 1.8 Hz, H*H*C=), 4.85 (s, Ph_2CH), 2.69 (dd, *J* = 10.7 Hz, *J* = 4.4 Hz, CHN), 0.9–1.8 (m, 10 H); ^{13}C NMR (63 MHz, $CDCl_3$) 156.0, 144.6, 143.6, 141.7, 129.2, 128.8, 128.5, 128.4, 127.8, 127.4, 127.3, 127.1, 116.4, 75.8, 62.5, 56.4, 36.7, 27.0, 24.1, 21.3; mass spectrum, *m/e* (isobutane CI, relative percent) 385 (30), 384 (MH^+, 100), 269 (20), 185 (22) 167 (54).

The slower eluting major isomer was triturated with hexane to give 0.695 g (50%) of **6** as a crystalline solid. An analytical sample was prepared by recrystallization from hot hexane to yield clear needles: mp 78–78.5 °C; IR (CCl_4) 3605, 1602, 1494, 1030,

(36) In cases where synthetic intermediates or products were isolated by "aqueous workup (organic solvent, drying agent)", the procedure was to quench the reaction mixture with H_2O, dilute with the indicated organic solvent, separate the organic layer, extract the aqueous layer several times with the organic solvent, dry the combined organic layers with the indicated drying agent, and remove the solvent with a rotary evaporator at reduced pressure. When "basic workup (organic solvent, drying agent)" is indicated, the procedure was similar to aqueous workup except 1 N NaOH was used instead of H_2O. When "acidic workup (organic solvent, organic solvent, drying agent)" is indicated, the procedure was to dilute the reaction mixture with the first indicated organic solvent, extract the organic solution several times with 1 N HCl, basify the combined acidic layers with solid KOH, extract the basic solution with the second indicated organic solvent several times, dry the organic layers with the indicated drying agent, and remove the solvent with a rotary evaporator under reduced pressure. Tetrahydrofuran (THF) and ether were distilled from sodium and benzophenone. Dimethylformamide (DMF) was distilled from CaH_2 at 20 mm. Benzene and toluene were distilled from calcium hydride. The molarities indicated for *tert*-butyllithium were established by titration with 2,5-dimethoxybenzyl alcohol. ^1H NMR and ^{13}C NMR spectra were determined at 250 MHz and 63 MHz, respectively, with a Bruker WM 250 spectrometer. ^1H NMR and ^{13}C NMR shifts were reported as δ values in parts per million relative to internal tetramethylsilane. ^1H NMR coupling constants (*J*) are reported in hertz, and they refer to apparent multiplicities and not true coupling constants; abbreviations used are s, singlet, d, doublet, t, triplet, and m, complex multiplet. Infrared spectra were determined with a Perkin-Elmer Model 283 spectrometer. Electron impact and high-resolution mass spectra were determined with a Kratos MS-50 at the Midwest Center for Mass Spectroscopy, University of Nebraska. Chemical ionization mass spectra were determined on a Finnigan 4000 GC/MS/DS. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. TLC and column chromatography utilized E. Merck silica gel. All reactions were run under a nitrogen or argon atmosphere.

918, 699 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) 7.0–7.4 (m, 15 H, Ph H), 5.41 (d, J = 1.1 Hz, *H*HC=), 5.22 (d, J = 1.1 Hz, H*H*C=), 4.75 (s, Ph_2CHN), 2.67 (br s, $W_{h/2}$ = 10 Hz, CHN), 2.21 (m, 1 H), 2.01 (br s, 1 H), 1.2–1.8 (m, 8 H); ^{13}C NMR (63 MHz, $CDCl_3$) 153.9, 145.3, 143.7, 141.5, 129.2, 128.6, 128.4, 128.1, 127.8, 127.4, 127.3, 127.0, 126.9, 117.0, 75.9, 63.9, 57.8, 35.1, 24.6, 22.2, 20.7; mass spectrum, m/e (isobutane CI, relative percent) 385 (28), 384 (MH^+, 100), 366 ($MH^+ - H_2O$, 49), 209 (32), 185 (36), 182 (65), 167 (82), 91 (46). Anal. Calcd for $C_{27}H_{29}NO$: C, 84.78; H, 7.38; N, 3.66. Found: C, 84.91; H, 7.70; N, 3.62.

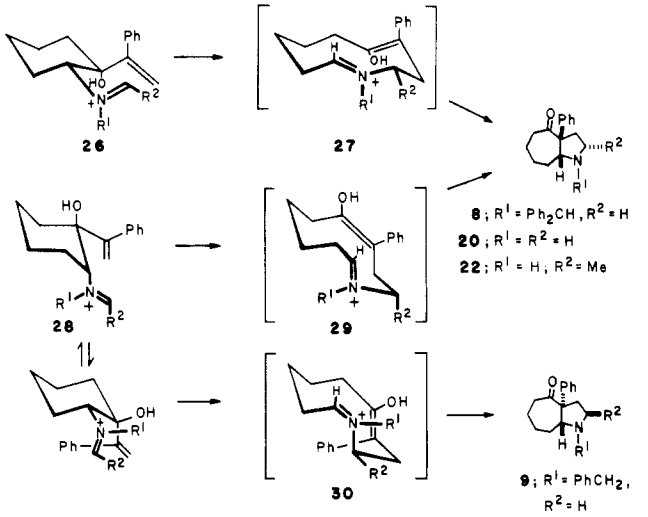
1-(Diphenylmethyl)-*cis*-3a-phenyl-4-oxodecahydrocyclohepta[*b*]pyrrole (8). A mixture of **7** (53 mg, 0.14 mmol), paraformaldehyde (4.3 mg, 0.14 mmol), camphorsulfonic acid (29 mg, 0.12 mmol), and benzene (4 mL) was heated at reflux for 22 h. After cooling to room temperature, basic workup (CH_2Cl_2, $MgSO_4$) gave 53 mg (96%) of **8** (a single isomer by 250-MHz ^{1}H NMR analysis) as a thick oil, which crystallized upon trituration with hexane. Dissolution of these crystals in hot hexane and slow cooling to room temperature gave crystals of sufficient quality for X-ray analysis: mp 122 °C; IR (CCl_4) 1706, 1600, 1447, 691 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) 7.0–7.5 (m, 15 H, Ph H), 4.78 (s, Ph_2CH), 3.56 (d, J = 10.3 Hz, CHN), 2.4–2.8 (m, CH_2N, C*H*H), 1.95–2.25 (m, 3 H), 1.85–1.95 (m, 1 H), 1.0–1.8 (m, 4 H), 0.75–1.00 (m, 1 H); ^{13}C NMR (63 MHz, $CDCl_3$) 212.0, 143.3, 143.0, 142.2, 128.9, 128.7, 128.6, 128.6, 128.5, 128.1, 127.3, 127.1, 127.0, 70.5, 68.3, 63.7, 48.0, 41.6, 34.1, 29.8, 27.9, 27.5; mass spectrum, m/e (EI, relative percent) 395 (4), 311 (29), 167 (100). Anal. Calcd for $C_{28}H_{29}NO$: C, 85.02; H, 7.39; N, 3.54. Found: C, 85.37; H, 7.52; N, 3.47.

1-(Diphenylmethyl)-*trans*-3a-phenyl-4-oxodecahydrocyclohepta[*b*]pyrrole (9). Crystalline trans amino alcohol **6** (0.200 g, 0.522 mmol), paraformaldehyde (16.4 mg, 0.547 mmol), camphorsulfonic acid (109 mg, 0.470 mmol), and benzene (15 mL) were heated at reflux for 22 h. After cooling, basic workup (CH_2Cl_2, $MgSO_4$) afforded, in quantitative yield, a 3.5:1 mixture (as determined by 250-MHz ^{1}H NMR integration of the diphenylmethine singlets at δ 5.28 and 4.78) of ketones **9**:**8**. Three recrystallizations from hexane gave 86 mg (42%) of the *trans*-ketone **9**, as white needles, which were contaminated with 12% of **8**: mp 135 °C; IR (CCl_4) 1696, 1491, 1448, 694 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$)[37] 7.1–7.6 (m, 15 H), 5.28 (s, Ph_2CHN), 2.95–3.05 (m, C*H*HN), 2.80 (dd, J = 10.4 Hz, J = 3.8 Hz, CHN), 2.70–2.80 (m, *H*HCC=O), 2.61 (ddd, J = 10.1 Hz, J = 9.2 Hz, J = 4.2 Hz, CH*H*N), 2.35–2.55 (m, 2 H), 1.95–2.15 (m, 2 H), 1.6–1.8 (m, 1 H), 1.4–1.5 (m, 2 H), 1.1–1.3 (m, 2 H); ^{13}C NMR (63 MHz, $CDCl_3$) 212.1, 143.2, 142.8, 139.5, 129.9, 128.8, 128.7, 128.5, 128.2, 127.5, 126.9, 126.5, 67.5, 67.3, 66.8, 46.4, 44.4, 36.3, 28.3, 27.3, 22.4; mass spectrum, m/e (EI, relative percent) 395 (3), 311 (32), 167 (100), 165 (23). Anal. Calcd for $C_{28}H_{29}NO$: C, 85.02; H, 7.39; N, 3.54. Found: C, 84.94; H, 7.74; N, 3.32.

Preparation of 8 from 6. The reaction was carried out as described for the preparation of **9**, except Me_2SO was used (80 °C for 22–24 h) as the solvent instead of benzene. Purification of the crude product on silica gel (hexane/ethyl acetate/triethylamine 18:1:0.2) gave chromatographically pure **8** in 75% yield as a thick oil. Crystallization from hexane gave crystalline **8** (mp 122 °C), which was identical (by 250-MHz ^{1}H NMR) with material prepared from **7**.

(37) Homonuclear decoupling of **9** Irradiation of the signal for $H_{2\alpha}$ at δ 2.95–3.00 caused partial collapse for $H_{2\beta}$ at δ 2.61 to a distorted doublet of doublets and also caused partial collapse of the signals for $H_{3\alpha}$ at δ 2.35–2.55 and for $H_{3\beta}$ at δ 1.40–1.50. Irradiation of the signal for H_{8a} at δ 2.80 caused the multiplet for $H_{8\alpha,\beta}$ at δ 1.95–2.15 to collapse to a broad singlet. At the same time unavoidable irradiation of the signal for $H_{5\alpha}$ at δ 2.70–2.80 occurred, causing an additional disturbance in the multiplet at δ 2.35–2.55 for $H_{5\beta}$. Irradiation of the signal for $H_{2\beta}$ at δ 2.61 caused distortions of the multiplets for $H_{3\alpha}$ at δ 2.35–2.55 and $H_{3\beta}$ at δ 1.40–1.50 and the partial collapse to a doublet of doublets of the signal for $H_{2\alpha}$ at δ 2.95–3.05. Irradiation of the signal for the multiplet for $H_{3\alpha}$ (and also $H_{5\beta}$) at δ 2.35–2.55 caused partial collapse of the signals for $H_{2\alpha}$ at δ 2.95–3.05, $H_{5\alpha}$ at δ 2.70–2.80, $H_{2\beta}$ at δ 2.61, and $H_{3\beta}$ at δ 1.40–1.50. Irradiation of the signal for $H_{8\alpha,\beta}$ at δ 1.95–2.15 caused the signal for H_{8a} at δ 2.80 to collapse to a broad singlet. Irradiation of the signal for $H_{3\alpha}$ at δ 1.60–1.80 caused a partial collapse for $H_{2\beta}$ at δ 2.61 and for $H_{3\beta}$ in the multiplet at δ 2.35–2.45. The labels α and β are used only to distinguish individual hydrogens of a methylene group, and imply nothing about stereochemistry.

Scheme III



This reaction was carried out in other solvents with the results shown in Table I. Workup consisted of purification by column chromatography[38] (when DMF or Me_2SO were employed as solvents) or by removal of solvent and a basic workup. In all cases the diastereomeric ratio was determined by ^{1}H NMR integration of the appropriate diphenylmethine resonances.

***cis*-2-(Dimethylamino)-1-(1-phenylethenyl)cyclohexanol (11).** A solution of 2-(dimethylamino)cyclohexanone[18] (100 mg, 0.708 mmol) was added dropwise over 20 min at −78 °C to a solution of (1-phenylvinyl)lithium (28 mL of a 0.2 M solution in 10:1 THF/pentane, prepared as detailed for the preparation of **6** and **7**). After stirring for 1 h at −78 °C, the yellow solution was allowed to warm to 0 °C for an additional hour. Acid workup (Et_2O–$CHCl_3$, $MgSO_4$) followed by bulb-to-bulb distillation (oven temperature 150 °C, 0.1 mm) gave 94.6 mg (55%) of **11** as a light yellow oil, which was homogeneous by TLC analysis and a single diastereomer by 250-MHz ^{1}H NMR analysis; IR (CCl_4) 3602, 1443, 1063, 909, 890, 699 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) 7.2–7.4 (m, 5 H, Ph H), 5.48 (d, J = 1.8 Hz, *H*HC=), 5.04 (d, J = 1.8 Hz, H*H*C=), 2.53 (dd, J = 7.9 Hz, J = 7.9 Hz, C*H*NMe_2), 2.31 (s, Me_2N), 1.4–1.9 (m, 8 H), 1.0–1.3 (m, 1 H); ^{13}C NMR (63 MHz, $CDCl_3$) 158.1, 142.3, 129.2, 127.6, 126.8, 113.1, 78.8, 66.0, 43.2 (2C), 40.1, 25.7, 21.7, 19.7; mass spectrum, m/e (isobutane CI, relative percent) 246 (MH^+, 100) 228 ($MH^+ - H_2O$, 20), 97 (18); high resolution mass spectrum (70 ev) 245.1782, 245.1780 calcd for $C_{16}H_{23}NO$.

***cis*-2-(Methylamino)-1-(1-phenylethenyl)cyclohexanol (12).** A solution of **11** (244 mg, 0.995 mmol), sodium bicarbonate (900 mg, 11 mmol), freshly distilled phenyl chloroformate (850 mg, 5.43 mmol), and $CHCl_3$ (15 mL, freshly distilled from P_2O_5) was heated at reflux for 16 h. The solution was cooled to room temperature and filtered, and excess phenyl chloroformate was removed by bulb-to-bulb distillation (oven temperature 55 °C, 0.8 mm). The crude residue was combined with KOH (6.05 g, 0.108 mol), water (3 mL), and MeOH (25 mL). The resulting solution was heated at reflux for 24 h and cooled to room temperature, and the solvent was removed under reduced pressure. Basic workup (CH_2Cl_2, $MgSO_4$) gave 121 mg (52%) of **12** as a yellow oil, which was one spot by TLC analysis: IR (CCl_4) 3479, 1442, 1304, 695 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) 7.25–7.40 (m, 3 H, Ph H), 7.10–7.22 (m, 2 H, Ph H), 5.62 (d, J = 2.2 Hz, *H*HC=), 5.09 (d, J = 2.2 Hz, H*H*C=), 2.58 (dd, J = 10.6 Hz, J = 4.4 Hz, CHN), 2.38 (s, MeN), 1.0–1.9 (m, 10 H); ^{13}C NMR (63 MHz, $CDCl_3$) 156.1, 141.9, 128.8, 127.9, 127.1, 115.5, 75.9, 59.8, 35.9, 33.3, 26.1, 24.1, 21.2; mass spectrum, m/e (isobutane CI, relative percent) 232 (MH^+, 100), 214 ($MH^+ - H_2O$, 13), 83 (14), 70 (12).

1-Methyl-*cis*-3a-phenyl-4-oxodecahydrocyclohepta[*b*]pyrrole (13). A solution of **12** (141 mg, 0.610 mmol), camphorsulfonic acid (124 mg, 0.535 mmol), paraformaldehyde (20 mg, 0.67 mmol), and benzene (31 mL) was heated at reflux for

(38) Care was taken so diastereomeric separation did not occur during the chromatography process.

4.5 h. After cooling to room temperature, basic workup ($CHCl_3$, $MgSO_4$) gave 122 mg (82%) of pure (by TLC and 250-MHz ^1H NMR analysis) *cis*-ketone **13** as a colorless liquid: IR (CCl_4) 2938, 1710, 1446, 693 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.15–7.45 (m, 5 H, PhH), 3.21 (dd, J = 9.3 Hz, J = 2.0 Hz, CHN), 2.85–3.00 (m, C*H*HN), 2.65–2.85 (m, CH*H*N), 2.53 (s, MeN), 2.20–2.40 (m, 3 H), 1.3–2.1 (m, 7 H); ^{13}C NMR (63 MHz, $CDCl_3$) 211.2, 143.3, 128.3, 127.0, 126.9, 68.2, 53.5, 52.8, 41.2, 39.8, 35.3, 31.9, 26.2, 25.6; mass spectrum, m/e (EI, relative percent) 243 (16), 159 (100), 158 (49). The oxalic acid salt was recrystallized from chloroform–ether to give a pure sample, mp 176 °C. Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.89; H, 7.13; N, 4.19.

***trans*-2-(Methyl(cyanomethyl)amino)cyclohexanol (15).** The general procedure of Kuffner[23] was employed. *trans*-2-(Methylamino)cyclohexanol[22] (1.00 g, 7.75 mmol) was treated dropwise with concentrated HCl until just acidic, KCN (0.504 g, 7.75 mmol) and H_2O (10 mL) were added, and the resulting solution was cooled to 0 °C. Paraformaldehyde (233 mg, 7.75 mmol) was added and the resulting mixture was stirred at room temperature overnight. Sufficient K_2CO_3 was then added to saturate the aqueous solution. Isolation with ether (K_2CO_3) gave 980 mg (75%) of crude **15**, which was sufficiently pure to be utilized directly in the next step: IR (CCl_4) 3523, 1450, 1076, 1037 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 3.58 (s, NCH_2CN), 2.9–3.4 (m, C*H*OH), 2.44 (s, MeN), 2.3–2.5 (m, CHN), 1.9–2.2 (m, 2 H), 1.6–1.9 (m, 2 H), 1.1–1.4 (m, 4 H); ^{13}C NMR (63 MHz, $CDCl_3$) 117.0, 69.6, 69.5, 42.8, 36.4, 33.3, 25.2, 24.0, 23.2; mass spectrum, m/e (EI, relative percent) 168.1292 (168.1264 calcd for $C_9H_{16}N_2O$, 11%), 141 (26), 140 (32), 109 (100), 98 (38), 96 (33), 84 (62), 83 (56), 71 (40), 70 (73).

2-(Methyl(cyanomethyl)amino)cyclohexanone (16). Alcohol **15** (1.00 g, 5.96 mmol) was oxidized by the Swern procedure[10] as described for the preparation of **5**. Aqueous workup (CH_2Cl_2, K_2CO_3/Na_2SO_4) followed by bulb-to-bulb distillation (oven temperature 165 °C, 0.7 mm) gave 871 mg (88%) of **16** as a light yellow liquid: IR (CCl_4) 1725, 1451, 1053 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 3.71 (s, NCH_2CN), 3.23 (dd, J = 10.4, 5.1 Hz, CHN), 2.46 (s, MeN), 2.15–2.55 (m, 3 H), 1.85–2.1 (m, 2 H), 1.6–1.85 (m, 3 H); ^{13}C NMR (63 MHz, $CDCl_3$) 209.4, 115.7, 69.7, 42.2, 40.9, 39.0, 30.9, 27.4, 23.2; mass spectrum, m/e (isobutane CI) 167 (MH^+), 142, 141, 140. This material deteriorated upon storage and was used immediately in subsequent reactions.

***cis*-2-(Methyl(cyanomethyl)amino)-1-(1-phenylethenyl)-cyclohexanol (17).** A solution of (1-phenylvinyl)lithium (17 mL of a 0.2 M solution in 15:2 THF–pentane, prepared as described for the preparation of **6** and **7**) was transferred over 20 min via cannula at −78 °C to a solution of **16** (250 mg, 1.51 mmol) and THF (8 mL). After an additional 40 min at −78 °C, the reaction was quenched at −78 °C by adding 10 mL of a 10:1 mixture of THF and H_2O and then allowed to warm to room temperature. Aqueous workup (ether, K_2CO_3/Na_2SO_4) followed by purification of the orange residue on silica gel (hexane/ethyl acetate/triethylamine: 90:10:1) gave 205 mg (50%) of pure (TLC and 250-MHz ^1H NMR analysis) **17** as a colorless oil: IR (CCl_4) 3604, 3491, 1446, 694 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.1–7.4 (m, 5 H, PhH), 5.47 (d, J = 1.5 Hz, *H*HC=), 5.01 (d, J = 1.5 Hz, H*H*C=), 3.71 (AB q, J = 17.3 Hz, $\Delta\nu$ = 80.9 Hz, NCH_2CN), 2.45–2.6 (m, CHN), 2.44 (s, MeN), 1.4–1.9 (m, 8 H), 1.0–1.3 (m, 1 H); ^{13}C NMR (63 MHz, $CDCl_3$) 157.3, 141.8, 129.1, 127.9, 127.2, 118.4, 113.5, 79.4, 65.9, 42.3, 40.7, 40.6, 25.7, 21.4, 20.9; mass spectrum, m/e (EI, relative percent) 270.1709 (270.1732 calcd for $C_{17}H_{22}N_2O$, 2%), 243 (8), 159 (100), 158 (32), 122 (25), 109 (23), 98 (11), 83 (34), 70 (30), 57 (26).

Preparation of 1-Methyl-*cis*-3a-phenyl-4-oxodecahydrocyclohepta[*b*]pyrrole (13) from Cyanomethyl Precursor 17. A. Acid-Promoted Rearrangement. A solution of **17**, (70.5 mg, 0.261 mmol), camphorsulfonic acid (71 mg, 0.31 mmol), and benzene (5 mL) was heated at reflux for 11 h. Basic workup (ether, K_2CO_3/Na_2SO_4) gave 45 mg (70%) of **13** as a pure (TLC and 250-MHz ^1H NMR analysis) colorless liquid, which was identical with a sample prepared from **12**. **B. Silver-Promoted Rearrangement. Aprotic Conditions.** A solution of **17** (30.1 mg, 0.111 mmol), silver trifluoroacetate (27 mg, 0.12 mmol), and $CHCl_3$ (5 mL) was stirred at room temperature for 1.5 h. Basic workup (ether, K_2CO_3/Na_2SO_4) gave 21 mg (77%) of **13** as a pure colorless liquid. **C. Silver-Promoted Rearrangement. Protic Conditions.** A solution of **17** (142 mg, 0.525 mmol), $AgNO_3$ (98.2 mg, 0.578 mmol), and ethanol (22 mL) was stirred for 1 h at room temperature. A precipitate (AgCN) formed immediately. Basic workup (ether, Na_2SO_4/K_2CO_3) gave 89 mg (70%) of pure (TLC and 250-MHz ^1H NMR analysis) **17**. Purification on silica gel ($CHCl_3$/MeOH: 10:1) afforded 80.1 mg (63%) of **13** as a chromatographically pure colorless liquid.

***trans*- and *cis*-2-Amino-1-(1-phenylethenyl)cyclohexanols (18 and 19).** A solution of the crude imino alcohol (prepared from 5.00 g, 18.1 mmol, of **5** as described for the preparation of **6** and **7**), oxalic acid dihydrate (16 g, 130 mmol), THF (150 mL), methanol (100 mL), and water (25 mL) was stirred at room temperature for 2 h.[29] Acidic workup ($CHCl_3$, $MgSO_4$) gave 2.57 g (65%) of a 5.5:1 mixture of **18** and **19**. Purification of a 213-mg sample of this material on silica gel ($CHCl_3$/MeOH 3.5:1) resulted in elution of the major isomer **18**, 77 mg (36%), as a thick oil, which slowly crystallized. Recrystallization from hot hexane provided an analytical sample of **18**: mp 102–103 °C; IR (CCl_4) 3609, 1441, 913, 694 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.2–7.45 (m, 5 H, Ph H), 5.35 (d, J = 1.1 Hz, *H*HC=), 5.19 (d, J = 1.1 Hz, H*H*C=), 2.89 (br s, $W_{h/2}$ = 8.5 Hz, CHN), 2.8–3.0 (m, 1 H), 1.3–2.2 (m, 10 H); ^{13}C NMR (63 MHz, $CDCl_3$) 154.2, 141.0, 129.2, 128.1, 127.5, 116.5, 75.8, 52.1, 30.8, 28.2, 21.6, 19.6; mass spectrum, m/e (isobutane CI) 218 (MH^+), 200, 130.

The slower eluting minor isomer **19**, 14 mg (7%), also solidified upon standing, mp 119–120 °C. However, this solid was not successfully recrystallized: IR (CCl_4) 3469, 977, 918, 695 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.1–7.4 (m, 5 H, Ph H), 5.58 (d, J = 1.8 Hz, *H*HC=), 5.06 (d, J = 1.8 Hz, H*H*C=), 2.94 (dd, J = 10.5 Hz, J = 4.9 Hz, C*H*NH_2), 1.0–1.9 (m, 11 H); ^{13}C NMR (63 MHz, $CDCl_3$) 156.4, 142.1, 128.8, 128.0, 127.2, 115.3, 75.4, 51.9, 35.7, 30.0, 24.7, 21.1; mass spectrum, m/e (isobutane CI) 218 (MH^+), 200, 130. A 73 mg (34%) fraction which was a mixture of **18** and **19** was also isolated from this chromatography.

Preparation of *cis*-3a-Phenyl-4-oxodecahydrocyclohepta[*b*]pyrrole (20) from Amino Alcohol 19. A solution of **19** (9.0 mg, 0.041 mmol), paraformaldehyde (1.4 mg, 0.046 mmol), camphorsulfonic acid (7.7 mg, 0.033 mmol), and benzene (1 mL) was heated at reflux for 18 h. After cooling to room temperature, basic workup (Et_2O, K_2CO_3/Na_2SO_4) gave 9 mg (95%) of **15**, which was isomerically pure by 250-MHz ^1H NMR analysis: IR (CCl_4) 1707, 1447, 1261, 906, 696 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.2–7.5 (m, 5 H, Ph H), 3.89 (d, J = 9.9 Hz, CHN), 2.95–3.10 (m, C*H*HN), 2.69 (dt, J = 5.7 Hz, J = 10.7 Hz, CH*H*N), 2.2–2.65 (m, 3 H), 1.2–2.0 (m, 8 H); ^{13}C NMR (63 MHz, $CDCl_3$) 211.7, 142.7, 129.1, 127.2, 126.7, 69.0, 62.3, 44.5, 41.9, 37.0, 36.2, 27.5 (2C); mass spectrum, m/e (EI, relative percent) 229 (44), 212 (44), 187 (20), 146 (22), 145 (100), 91 (23). This sample was identical (by 250-MHz ^1H NMR, TLC) with material prepared from **8** by catalytic hydrogenolysis (10% Pd on C, EtOH, cyclohexene, HCl).[30]

Preparation of 20 from Amino Alcohol 18. Reaction of **18** under the identical conditions described for the preparation of **20** from **19** provided **20**, which was isomerically pure by 250-MHz ^1H NMR analysis, in 93% yield.

Preparation of 13 from 20. The reductive methylation procedure developed by Borch[14] was used. A solution of **20** (63.5 mg, 0.277 mmol), $NaCNBH_3$ (27.6 mg, 0.440 mmol), 37% aqueous formaldehyde (0.11 mL, 1.4 mmol), and acetonitrile (3 mL) was maintained at room temperature for 15 min. After acidification with one drop of glacial acetic acid, the mixture was stirred for an additional 40 min. Basic workup (Et_2O, K_2CO_3/Na_2SO_4) gave 56.6 mg (84%) of **13** as a light yellow oil. This sample was identical (250-MHz ^1H NMR and IR) with **13** prepared from rearrangement of **12** and **17**.

Preparation of *cis*- and *trans*-2-Methyl-*cis*-3a-phenyl-4-oxodecahydrocyclohepta[*b*]pyrroles (22 and 23) from Amino Alcohol 19. A solution of freshly distilled acetaldehyde (7.3 μl, 0.13 mmol), **19** (14 mg, 0.065 mmol), camphorsulfonic acid (14 mg, 0.060 mmol), and benzene (1.5 mL) was heated at reflux for 4 h. After cooling to room temperature, acidic workup (CH_2Cl_2, K_2CO_3/Na_2SO_4) gave 8.9 mg (56%) of a 33:1 mixture of **22** and **23** [determined by 250-MHz ^1H NMR integration of the methyl doublets at δ 1.12 (**22**) and δ 1.03 (**23**)] as a thick oil. Separation of the diastereomers was not possible by column or high-pressure LC chromatography. Major isomer (**22**): IR (CCl_4) 1708, 1446, 692; ^1H NMR (250 MHz, $CDCl_3$)[39] 7.15–7.45 (m, 5 H, Ph H), 3.87

(d, J = 10.0 Hz, CHN), 2.9–3.1 (m, MeCHN), 2.15–2.4 (m, 2 H), 2.06 (apparent t, J = 11.5 Hz, CHHCHMe), 1.3–1.9 (m, 8 H), 1.12 (d, J = 6.1 Hz, CH_3CH); ^{13}C NMR (63 MHz, $CDCl_3$) 212.0, 142.9, 129.2, 127.3, 126.9, 69.9, 62.6, 51.9, 44.6, 41.8, 37.7, 27.6, 27.4, 21.1; mass spectrum, m/e (EI, relative percent) 243 (25), 226 (33), 159 (60), 144 (73), 70 (100).

Preparation of 22 and 23 from Amino Alcohol 18. Ketones **22** and **23** were prepared from **18** following a procedure identical with that described for their preparation from **19**. The yield was similar and an 8.0:1 mixture of **22**, and **23** resulted. Characteristic NMR data for the minor isomer (**23**) are ^1H NMR (250 MHz, $CDCl_3$) 4.06 (d, J = 9.7 Hz, CHN), 1.03 (d, J = 7.3 Hz, CH_3CH).

1-Methyl-*cis*- and -*trans*-2-methyl-*cis*-3a-phenyl-4-oxodecahydrocyclohepta[*b*]pyrroles (24 and 25). Reductive methylation following the procedure of Borch[14] (as described for the preparation of **13** from **20**) of a 57.6 mg (0.237 mmol) sample of an 8.0:1 mixture of **22** and **23**, followed by basic workup (Et_2O, K_2CO_3/Na_2SO_4), gave 53 mg (87%) of an orange oil. Column chromatography (silica gel, chloroform/methanol: 4:1) afforded 43 mg (71%) of an 8.0:1 mixture of **24** and **25**. Characteristic spectral data for the major isomer **24**, are as follows: IR (CCl_4) 1709, 1445, 691; ^1H NMR (250 MHz, $CDCl_3$)[40] 7.15–7.4 (m, 5 H, Ph H), 3.26 (dd, J = 9.7 Hz, J = 2.1 Hz, CHN), 2.47 (s, MeN), 2.4–2.5 (m, MeCHN), 2.2–2.4 (m, 3 H), 1.35–2.0 (m, 7 H), 1.04 (d, J = 5.7 Hz, CH_3CH); ^{13}C NMR (63 MHz, $CDCl_3$) 211.7, 143.8, 128.9, 127.2, 127.0, 69.7, 66.4, 58.0, 44.1, 41.5, 38.2, 33.9, 26.4, 26.0, 19.0; mass spectrum, m/e (EI, relative percent) 257 (11), 173 (100), 158 (70), 149 (72), 71 (77). Minor isomer **25**: ^1H NMR (250 MHz, $CDCl_3$) 3.73 (d, J = 9.5 Hz, CHN), 0.90 (d, J = 7.1 Hz, CH_3CH).

Crystallography. Single crystals were prepared by slow crystallization from hexane. A crystal measuring approximately 0.7 × 0.5 × 0.5 mm was cut from a larger one and mounted for data collection. The crystal was found to belong to the monoclinic system with unit cell dimensions at 22 °C: a = 16.520 (6), b = 16.409 (4), c = 17.570 (5) Å; β = 108.30 (3)°. Systematic absences indicated that the space group was $P2_1/n$.[41] A density of 1.16 g cm^{-3} was calculated for Z = 8 molecules per unit cell. Thus the crystallographic asymmetric unit contains two molecules. Three dimensional intensity data were collected on a Syntex $P2_1$ automated diffractometer, using monochromatized Mo Kα radiation (λ = 0.70930 Å). The θ–2θ scan technique was used to measure the intensities of 6702 independent reflections within the range $0° < 2\theta < 45°$.[42] Of these, 2345 had $F^2 > 3\sigma(F^2)$ and were used in subsequent calculations.

The structure was solved in a straightforward fashion by direct methods, using the MULTAN 77 system of programs.[43] Refinement was by full-matrix least-squares methods[44] with phenyl rings treated as groups.[45] Phenyl carbon atoms were assigned isotropic temperature factors, and other non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the groups with fixed thermal parameters of 6.5 Å^2; nongroup hydrogens were included at their idealized positions (C–H = 1.0 Å) with fixed isotropic temperature factors. The final unweighted and weighted R values were 0.096 and 0.112, respectively. A final difference map showed no significant residual features.

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Registry No. **4**, 86632-94-2; **5**, 83196-02-5; **6**, 83196-04-7; **7**, 83196-05-8; **8**, 83196-06-9; **9**, 83196-07-0; **11**, 86632-95-3; **12**, 86632-96-4; **13**, 83196-15-0; **13**·oxalic acid, 86632-97-5; **15**, 83196-12-7; **16**, 83196-13-8; **17**, 83196-14-9; **18**, 83196-08-1; **19**, 83196-09-2; **20**, 83196-10-5; **22**, 86632-98-6; **23**, 86707-52-0; **24**, 86632-99-7; **25**, 86688-21-3; benzophenone, 119-61-9; *trans*-2-aminocyclohexanol, 6982-39-4; α-bromostyrene, 98-81-7; 2-(dimethylamino)cyclohexanone, 6970-60-1; (1-phenylvinyl)lithium, 45680-22-6; *trans*-2-(methylamino)cyclohexanol, 20431-81-6.

Supplementary Material Available: Tables of final atomic positional parameters, atomic thermal parameters, and bond distances and angles (7 pages). Ordering information is given on any current masthead page.

(39) Homonuclear decoupling of **22**. Irradiation of the signal for the methyl doublet at δ 1.12 caused the signal for $H_{2\beta}$ at δ 2.90–3.10 to collapse to a doublet of doublets (J = 5.6 Hz, J = 12.2 Hz). Irradiation of the signal for $H_{2\beta}$ at δ 2.90–3.10 caused the signal for $H_{3\alpha}$ at δ 2.00 to collapse to a doublet (J = 11.9 Hz), the signal for the methyl group at δ 1.12 to collapse to a singlet, and the multiplet for $H_{3\beta}$ at δ 1.30–1.90 to partially collapse.

(40) Homonuclear decoupling of **19**. Irradiation of the signal for the methyl group at δ 1.04 caused the signal for $H_{2\beta}$ at δ 2.43 to collapse to a doublet (J = 4.1 Hz). Irradiation of the signal for $H_{2\beta}$ at δ 2.43 caused the collapse to a singlet of the signal for the methyl group at δ 1.04, the collapse to a singlet for the signal at δ 1.83 for $H_{3\alpha}$, and the unavoidable distortion of the multiplet at δ 2.20–2.50. Irradiation of the signal for $H_{3\alpha}$ at δ 1.83 caused a collapse of the signal for $H_{2\beta}$ at δ 2.43 to a partially buried doublet of doublets (J = 5.9 Hz, J = 5.0 Hz) and an additional collapse in the multiplet at δ 2.20–2.40 for $H_{3\beta}$.

(41) Nonstandard setting of No. 14, $P2_1/c$. Equivalent general position: $\pm(x, y, z; {}^1/_2 + x, {}^1/_2 - y, {}^1/_2 + z)$.

(42) General procedures for data collection and processing have been given in: Sams, D. B.; Doedens, R. J. *Inorg. Chem.* **1979**, *18*, 153. Details specific to the current analysis include scan rate, 4–16°/min in 2θ, scan range −1.0° from Kα_1 peak to +1.25° from the Kα_2 peak, stationary background counts at each end of the scan—each for half of the scan time, p factor for calculation of standard deviations, 0.05.

(43) Main, P.; Lessinger, L.; Woolfson, M. M.; Germain, G.; Declercq, J. P.; MULTAN 77, University of York, York, England, 1977.

(44) All computations were carried out on a VAX 11/780 computer by use of a modified version of the UCLA Crystallographic Computing Package (C. E. Strouse, personal communication). Major programs in this package are derived from the MULTAN system and from the Oak Ridge ORFLS/ORFFE/ORTEP programs.

(45) Doedens, R. J. In "Crystallographic Computing"; Ahmed, F. R., Ed.; Munksgaard: Copenhagen, 1970; pp 198–200.