62-53-3; 3-nitroaniline, 99-09-2; 4-nitroaniline, 100-01-6; formaldehyde, 50-00-0; benzaldehyde, 100-52-7; heptanal, 111-71-7; hexanal, 66-25-1; (*E*)-3,7-dimethyl-2,6-octadienal, 141-27-5; (*Z*)-3,7-dimethyl-2,6-octadienal, 106-26-3; cyclohexanecarboxaldehyde, 2043-61-0; 2-furancarboxaldehyde, 98-01-1; 3-pyridinecarboxaldehyde, 500-22-1; cyclohexanone, 108-94-1; 4-*tert*-butylcyclohexanone, 98-53-3; 2-methylcyclohexanone, 583-60-8; cyclododecanone, 830-13-7; 3-pentanone, 96-22-0; (*E*)-2-[(trimethylsilyl)oxy]-3-pentenenitrile, 87089-12-1.

Supplementary Material Available: Table IV, selected ^{13}C NMR data for 15 substituted 3-acetylpyrrolidines (3 pages). Ordering information is given on any current masthead page.

Applications of Cationic Aza-Cope Rearrangements for Alkaloid Synthesis. Stereoselective Preparation of *cis*-3a-Aryloctahydroindoles and a New Short Route to Amaryllidaceae Alkaloids[1]

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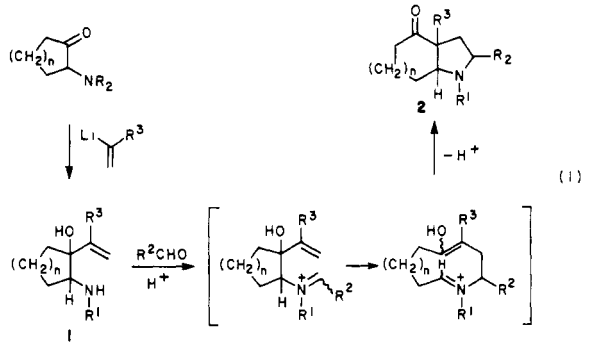
Abstract: A new synthesis of *cis*-3a-aryloctahydroindoles is detailed (eq 1). The key step is a "ring-enlarging pyrrolidine annulation" reaction which occurs when 2-amino-1-(1-arylethenyl)cyclopentanols are treated under mild conditions with an aldehyde and acid. Three different methods (Schemes I–III) for assembling the 2-amino(1-arylethenyl)cyclopentanol intermediates are reported. An efficient formal total synthesis of the Amaryllidaceae alkaloid (±)-crinine (Scheme III) is reported, in which key intermediate **26** was assembled with virtually complete stereocontrol in four steps and 44% overall yield from readily available 1,2-bis(trimethylsilyloxy)cyclopentene.

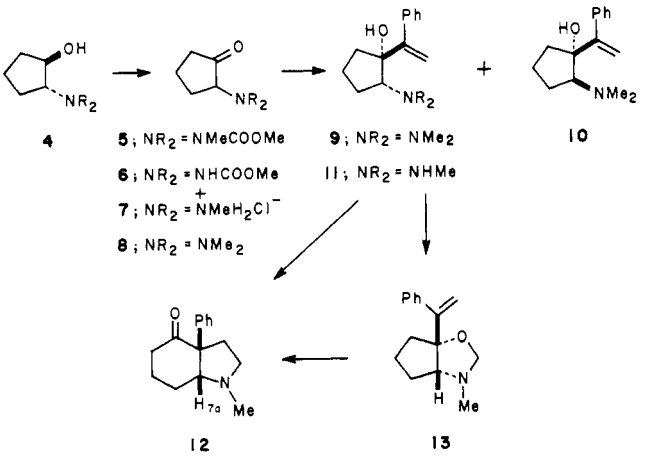
The preceding paper[1] described the development of tandem cationic aza-Cope–Mannich reactions as a new strategem for preparing substituted pyrrolidines under extremely mild conditions. A potentially useful annulation sequence that exploits this chemistry is illustrated in eq 1.[2] This unusual transformation



(1)

would convert an α-amino ketone[3] into a pyrrolidine-annulated product, in which the starting ring is expanded by one member. We chose to initially examine this sequence with cyclopentanol precursors to see if the widely occurring[4] *cis*-3a-aryloctahydroindole ring system (*cis*-**2**, $n = 1$, R^3 = Ar) could be assembled in this fashion.[5,6] If the amine and vinyl groups are oriented trans in cyclopentanol **1** ($n = 1$), this sequence should stereospecifically lead to the formation of only the *cis*-octahydroindole ring system, since rearrangement via only a single "chair-type" transition state is possible for systems of this type (eq 2).[2,7] A *cis*-octahydro-

Scheme I



(1) Part 12 in the series: Synthesis Applications of Aza-Cope Rearrangements. For part 11, see: Overman, L. E.; Kakino, M.; Okazaki, M. E.; Meier, G. P. *J. Am. Chem. Soc.*, preceding paper in this issue.

(2) We wish to stress that although we have chosen 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 and are not excluded by data currently available. 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.

(3) The preparation of α-amino ketones has been reviewed, see: Mayer, D. In "Methoden der Organische Chemie (Houben-Weyl)", 4th ed.; Müller, E., Ed.; Thieme-Verlag: Stuttgart, 1977; Vol. VII/2C, pp 2253–2307.

(4) This ring system is found, inter alia, in alkaloids of the Sceletium, Amaryllidaceae, Aspidosperma, and Strychnos families. Cf.: Dalton, D. R. "The Alkaloids. The Fundamental Chemistry"; Marcel Dekker: New York, 1979.

(5) For recent reviews that cover the preparation of this ring system, see: (a) Jeffs, P. W. In "The Alkaloids"; Manske, R. H. F., Rodrigo, R. G. A., Ed.; Academic Press: New York, 1980; Chapter 1. (b) Tsuda, Y. *Heterocycles* **1978**, *10*, 555–595. (c) Stevens, R. V. In "The Total Synthesis of Natural Products"; ApSimon, J., Ed.; Wiley: New York, 1977; Vol. 3, pp 443–453.

(6) For recent contributions, see inter alia: Danishefsky, S.; Morris, J.; Mullen, G.; Gammill, R. *J. Am. Chem. Soc.* **1982**, *104*, 7591–7599. Sanchez, I. H.; Soria, J. J.; Larraza, M. I.; Flores, H. J. *Tetrahedron Lett.* **1983**, *24*, 551–554. Keck, G. E.; Webb, R. R., II. *J. Org. Chem.* **1982**, *47*, 1302–1309. Jeffs, P. W.; Cortese, N. A.; Wolfram, J. *J. Org. Chem.* **1982**, *47*, 3881–3886. Takano, S.; Imamura, Y.; Ogasawara, K. *Tetrahedron Lett.* **1981**, *22*, 4479–4482. Keck, G. E.; Webb, R. E., II. *J. Am. Chem. Soc.* **1981**, *103*, 3173–3177.

(7) This prediction assumes that intramolecular Mannich ring closure of the presumed azacyclononadiene would be more rapid than any loss of stereochemical integrity of this intermediate.

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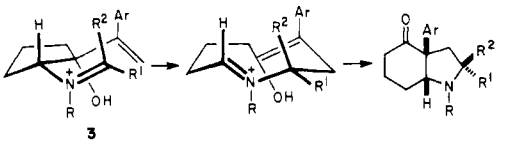


(2)

3

indolone could also result from the rearrangement of the precursor **1** (n = 1) with cis-oriented amine and vinyl groups, although a stereochemical prediction in this case is not secure, since rearrangement in four topographical senses (two "chair" and two "boat") is possible (vide infra).

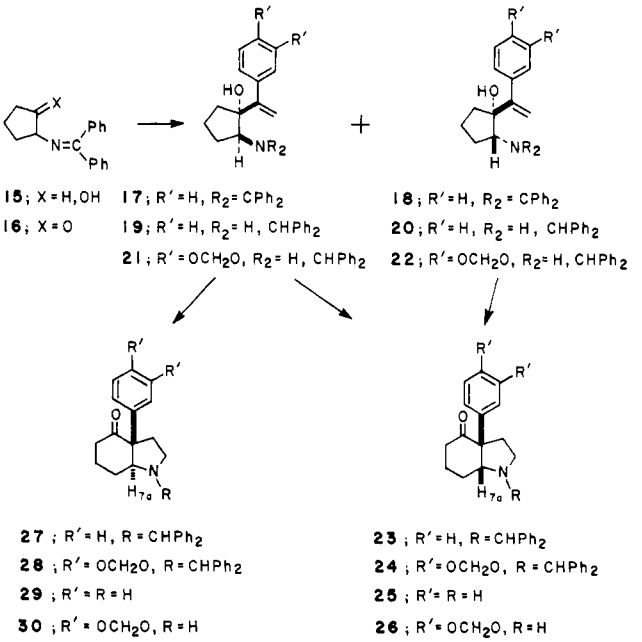
Related Cope rearrangements are known in hydrocarbon systems. Thus, *cis*-1,2-divinylcyclopentane and *cis,cis*-1,5-cyclononadiene interconvert at 220 °C.[8] *trans*-1,2-Divinylcyclopentane-1,2-diol is also transformed at 160 °C to $\Delta^{1,6}$-bicyclo-[4.3.0]nonen-2-one, presumably via a 1,6-dihydroxy-1,5-cyclononadiene intermediate.[9] It was our expectation that the acceleration provided by the positively charged nitrogen atom[1] would result in significantly lower reaction temperatures for the annulation sequence of eq 1.

In this paper, we present the details of our investigations of the preparation of hydroindoles via the "ring-enlarging pyrrolidine annulation" reaction (eq 1).[10] This sequence achieves the most convenient entry yet recorded to *cis*-3a-arylhydroindoles.

Results

Preparation of *cis*- and *trans*-3a-Aryl-4-oxooctahydroindoles. Developing efficient methods for handling the nitrogen functionality of the 2-amino ketone intermediate was the most difficult problem to be solved in implementing the sequence of eq 1. The reaction of cyclopentene oxide with amines provides access[11] to a variety of *trans*-2-aminocyclopentanols **4**, from which the corresponding amino ketones may be readily derived.[12] We initially examined the reaction of ketocarbamates **5** and **6** with (1-phenylethenyl)lithium. However, competing enolization,[13] as well as carbamate cleavage,[14] undermined the desired conversion of **5**. With carbamate **6**, the use of 2 equiv of (1-phenylethenyl)lithium gave fair yields (30–45%) of the desired tertiary alcohols.[14] The reaction of ketoamine salt **7** with 3 equiv of lithium reagent gave a mixture of amine **11** and the corresponding trans stereoisomer, albeit in modest yields.[15] Addition of (1-phenylethenyl)lithium to 2-(dimethylamino)cyclopentanone[16] (**8**) occurred primarily from the side opposite the dimethylamino group

Scheme II



15; X = H,OH **17**; R′ = H, R_2 = CPh_2 **18**; R′ = H, R_2 = CPh_2

16; X = O **19**; R′ = H, R_2 = H, $CHPh_2$ **20**; R′ = H, R_2 = H, $CHPh_2$

21; R′ = OCH_2O, R_2 = H, $CHPh_2$ **22**; R′ = OCH_2O, R_2 = H, $CHPh_2$

27; R′ = H, R = $CHPh_2$ **23**; R′ = H, R = $CHPh_2$

28; R′ = OCH_2O, R = $CHPh_2$ **24**; R′ = OCH_2O, R = $CHPh_2$

29; R′ = R = H **25**; R′ = R = H

30; R′ = OCH_2O, R = H **26**; R′ = OCH_2O, R = H

to give alcohol **9** in 54% yield after chromatographic purification (see Scheme I).[17] Less than 10% of the diastereomeric alcohol **10** was formed. Dilution infrared studies allowed the stereochemistry of these alcohols to be assigned with certainty.[18] Thus, the major alcohol **9** showed a weak absorption at 3604 cm^{-1} (CCl_4, free OH) and a strong intramolecular hydrogen-bonded OH absorption at 3340 cm^{-1} (relative intensity did not change with concentration, 0.1–0.006 M), while **10** showed absorptions at 3600 and 3430 cm^{-1} whose relative intensities depended upon concentration. Conversion of **9** to the secondary amine **11** was accomplished in 86% yield by sequential treatment with phenyl chloroformate[19] and 20% ethanolic KOH.

Treatment[1] of **11** with paraformaldehyde (1.0 equiv) in refluxing ethanol[20] for 20 h gave *cis*-octahydroindolone **12** (mp 84–85 °C) in 78% yield. No trace of the corresponding trans isomer could be detected by GLC,[21] TLC, or ^{13}C NMR analysis of the crude reaction product. A diagnostic[22,23] narrow multiplet (half-height width = 7 Hz) was observed at δ 3.15 in the ^1H NMR spectrum for the angular hydrogen H_{7a} of *cis*-octahydroindolone **12**.[24,25] Oxazolidine **13** was an intermediate in this conversion and could be prepared from **11** in nearly quantitative yield by reaction with paraformaldehyde at room temperature in the presence of anhydrous sodium sulfate. To pursue further the reaction conditions necessary for the "ring-enlarging pyrrolidine annulation" reaction, identical samples of **13** were dissolved in several solvents and heated at 80 °C in sealed ampules for 4 h. The observed extent of conversion to **12** was <2% in benzene, <2%

(8) Vogel, E.; Grimme, W.; Dinne, E. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 739–740.

(9) Conia, J. M.; Leriverend, P. *Bull. Soc. Chim. Fr.* **1970**, 1040–1050. Brown, E.; Leriverend, P.; Conia, J. M. *Tetrahedron Lett.* **1966**, 6115–6119; Brown, E.; Conia, J. M. *Bull. Soc. Chim. Fr.* **1970**, 1050–1060.

(10) Preliminary accounts of portions of this work have been published: (a) Overman, L. E.; Mendelson, L. T. *J. Am. Chem. Soc.* **1981**, *103*, 5579–5581. (b) Overman, L. E.; Mendelson, L. T.; Flippin, L. A. *Tetrahedron Lett.* **1982**, 2733–2736. (c) Overman, L. E.; Jacobsen, E. J. *Ibid.* **1982**, 2741–2744.

(11) For references to classical procedures, as well as an efficient alternative, see: Overman, L. E.; Flippin, L. A. *Tetrahedron Lett.* **1981**, *22*, 195–198. See also ref 1.

(12) Although several oxidizing agents may be employed,[3] we have found the Swern reagent to be generally the oxidant of choice, see: Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.

(13) That enolization is a troublesome complication in the addition of basic nucleophiles to cyclopentanones is well known. For a recent example and leading references, see: Dauben, W. G.; Walker, D. M. *J. Org. Chem.* **1981**, *46*, 1103–1108.

(14) (a) Very similar results have been reported recently for related reactions of acyclic α-amino ketones, see: Buckley, T. F., III; Rapoport, H. *J. Am. Chem. Soc.* **1981**, *103*, 6157–6163. (b) For a recent review of 1,2-relative asymmetric induction in the addition of nucleophiles to 2-amino ketones, see: Tramontini, M. *Synthesis* **1982**, 605–643.

(15) The hydrochloride salt is insoluble in THF and ether, and the heterogeneity of these reactions may have been responsible for the low yields that were observed. The use of salts with more soluble counterions is a possible solution, which was not explored. The addition of Grignard reagents to related salts of 2-aminocyclohexanones has been described, see: Bernardi, L.; Fuganti, C.; Ghiringhell, D. *Gazz. Chim. Ital.* **1968**, 836–842.

(16) (a) Fries, S. L.; Baldridge, H. D. *J. Am. Chem. Soc.* **1956**, *78*, 2482–2485. A more convenient synthesis from *trans*-2-(dimethylamino)-cyclopentanol[16b] is detailed in the experimental section. (b) Mousseron, M.; Granger, R.; Combes, G.; Pertzoff, V. A. *Bull. Soc. Chim. Fr.* **1947**, 850–853.

(17) The addition of (1-phenylethenyl)lithium to 2-[(dibenzyl)amino]-cyclopentanone also occurred in good yield; however, we were unsuccessful in subsequently removing one of the benzyl groups. Both transfer hydrogenation (competing reduction of the alkene) and chloroformate dealkylation (no reaction under standard conditions)[19] failed.

(18) Cf.: Golfer, M. In "Stereochemistry: Fundamentals and Methods"; Kagan, H. B., Ed.; Georg Thieme: Stuttgart, 1977; Vol. I, pp 29–34.

(19) Cf.: Rice, K. C. *J. Org. Chem.* **1975**, *40*, 1850–1851 and references cited therein.

(20) This conversion may be catalyzed by traces of formic acid in the paraformaldehyde.

(21) A 5-m 3% SP 2100 column was used for this analysis.

(22) *cis*-3a-Arylhydroindoles preferentially adopt conformations with the aryl group and the angular H_{7a} hydrogen axial and equatorial, respectively, with respect to the cyclohexane ring.[23]

(23) Cf.: Stevens, R. V.; Dupree, L. E.; Lowenstein, R. L. *J. Org. Chem.* **1972**, *37*, 977–982. Reference 5a.

(24) Correlation of **12** with known 1-methyl-3a-phenyl-*cis*-octahydroindole has been accomplished.[10a,25]

(25) Mendelson, L. T. Ph.D. Thesis, University of California, Irvine, CA, 1981.

in ethanol containing 1% Et_3N, 5% in acetone, 27% in EtOH, and 92% in 2-nitropropane. Clearly, the conversion of **13** to **12** is accelerated as the solvent acidity increases.

An alternate mode of nitrogen protection, which provides ready access to cyclopentanols **19** and **21** with cis-oriented amine and vinyl groups, is summarized in Scheme II. Crystalline imino ketone **16** was prepared in 53% yield from *trans*-2-aminocyclopentanol[26] by reaction with benzophenone followed by Swern oxidation.[12] To our initial surprise, the reaction of (1-phenylethenyl)lithium with **16** occurred preferentially (~2:1) from the side of the imine group. Chromatographic purification provided the crystalline imino alcohol **17** in 55% yield, together with 4% of recovered **16** and ~30% of a mixture of imino alcohol **18** and the corresponding oxazolidine. These products could be processed separately, although it was more convenient to directly reduce the crude addition product with $NaBH_3CN$[27] to give amino alcohols **19** and **20** in 39% and 24% overall yields from cyclopentanone **16**, respectively. These isomers could be distinguished by the characteristic intramolecular hydrogen-bonded OH absorption[18] at 3460 cm^{-1} in the infrared spectrum, which was observed for the *cis*-amino alcohol **20**. Stereochemical assignments were confirmed by X-ray analysis of the crystalline trans isomer **19**.[25] In a similar fashion, **16** reacted with [1-(3,4-(methylenedioxy)phenyl)ethenyl]lithium to give, after $NaCNBH_3$ reduction, amino alcohols **21** (mp 98.5–99 °C) and **22** in 55% and 15% overall yields from cyclopentanone **16**, respectively. The excellent yields of tertiary alcohols formed from the reaction of cyclopentanone imine **16** with lithium reagents is noteworthy, as is the preference (2–3:1) for addition from the face of the imine substituent. Both characteristics suggest the more general use of this mode of α-amino ketone protection. Preferential syn addition of lithium reagents to α-imino ketones has now been observed by us in several cases[28] and we presume reflects stabilization of the transition state for addition via coordination of the lithium reagent with the imine substituent. Similar stabilization is apparently not important in the reaction of organolithium reagents with α-amino ketones (see Schemes I and III).[28]

As was observed with **11**, the reaction of amino alcohols **20** and **22** with 1.0 equiv of paraformaldehyde and 0.9 equiv of camphorsulfonic acid occurred cleanly at 50–80 °C to afford the crystalline *cis*-octahydroindolones **23** (78%) and **24** (91%). Both products showed diagnostic narrow multiplets (half-height width ~ 7 Hz) for the cis H_{7a} hydrogen,[22,23] and careful integration of the 250-MHz ^1H NMR spectrum of crude reaction mixtures failed to detect any trace (cis/trans > 30:1) of the corresponding trans isomers **27** and **28**. There was no apparent effect of solvent on the stereoselectivity of this rearrangement, since **22** was cleanly converted to **24** at 80 °C in benzene, THF, or Me_2SO. The structures of **23** and **24** were further confirmed by removing the diphenylmethyl group under transfer-hydrogenation conditions[29] to give the known[30] *cis*-3a-aryloctahydroindolones **25** and **26** in excellent yields.[31,32]

Table I. Preparation of *cis*- and *trans*-3a-Aryl-4-oxooctahydroindoles from Cyclopentanols **19** and **21**

cyclopentanol	reaction conditions: solvent, concn, M	reaction conditions: temp, °C	octahydroindolone product cis:trans[a]
19	PhH, 0.15	80	3:1
21	PhH, 0.08	80	2:1
19	THF, 0.08–0.01	65	1.5:1
19	2% aq THF, 0.08	65	3.8:1
19	EtOH, 0.15	78	11:1
21	2% aq THF, 0.07	65	2.7:1
19	Me_2SO, 0.15	83	>30:1
21	Me_2SO, 0.15	73	>30:1

[a] **23**(**24**):**27**(**28**). Isomer ratios determined by integration of the Ph_2CH singlets (δ 5.2 cis; δ 4.8 trans) in the 250-MHz ^1H NMR spectra of crude reaction mixtures.

Amino alcohols **19** and **21**, which have cis-related amine and vinyl groups, reacted with the paraformaldehyde and acid considerably less cleanly than stereoisomers **20** and **22**. Thus, the reaction of **19** with paraformaldehyde and camphorsulfonic acid in refluxing benzene for 24 h gave (82% yield) a 3:1 mixture of *cis*- and *trans*-octahydroindolones **23** and **27**, respectively. The structure of isomer **27** was confirmed by N-deprotection[29] to give the known[30] *trans*-octahydroindolone **29**, which showed a diagnostic doublet of doublets (J = 3.7 and 13 Hz) at δ 3.25 in the ^1H NMR spectrum for the angular hydrogen H_{7a}. Rearrangement of **21** proceeded similarly in refluxing benzene to give a 2:1 mixture (86% yield) of **24** and **28**, which upon N-deprotection, gave the known *cis*- and *trans*-octahydroindolones **26** and **30** in good yields.

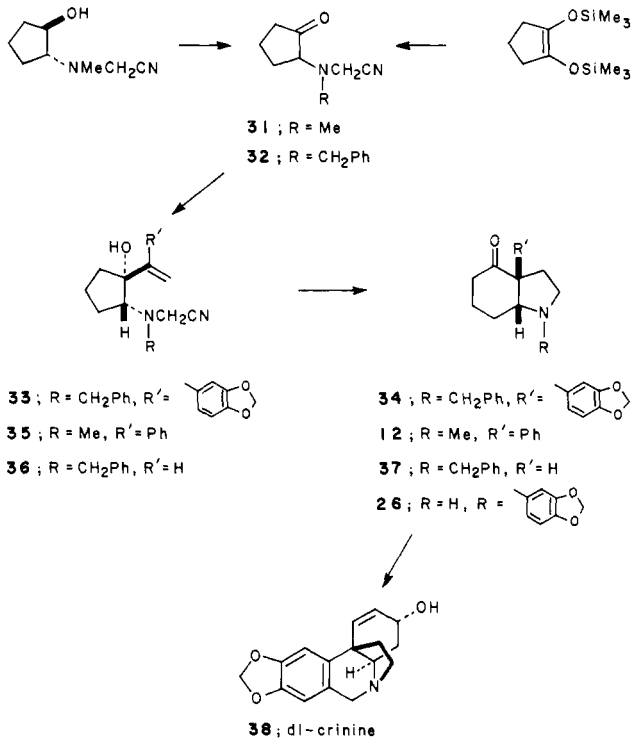
The mixture of octahydroindolones produced from the reaction of amino alcohols **19** and **21** with formaldehyde and acid proved to be markedly solvent dependent (see Table I). When Me_2SO was employed, the cis isomer was formed with high stereoselectivity (>30:1) and pure *cis*-octahydroindolones **23** and **24** could be isolated in 68% and 65% yields, respectively, after chromatographic purification. That the product ratios shown in Table I reflect predominantly kinetic control[33] was established in three cases. Thus, a 72:28 mixture of **23** and **27** was unchanged when heated in Me_2SO at 80 °C with 0.9 equiv of camphorsulfonic acid for 19 h. Similar treatment of **30** in Me_2SO for 48 h gave no trace of **26**, nor was **27** detected when **23** was heated in THF (80 °C, 19 h) in the presence of 0.9 equiv of camphorsulfonic acid.

cis-Octahydroindolone **26** was a key intermediate in the Whitlock and Smith synthesis of *dl*-crinine.[30] The sequence outlined in Scheme II afforded **26** in 47% yield from imino ketone **16** and 24% overall yield from *trans*-2-aminocyclopentanol. A more efficient construction of this bicyclic is outlined in the next section.

Efficient Preparation of *cis*-4-Oxooctahydroindoles from 2-[(Cyanomethyl)amino]cyclopentanones. A Short Formal Total Synthesis of *dl*-Crinine. The use of a cyanomethyl group to *both* protect the basic nitrogen of a 2-aminocyclopentanone starting material and serve subsequently as a source for a formaldehyde iminium ion[34] significantly simplifies the preparation of *cis*-4-oxooctahydroindoles (see Scheme III). The required 2-[alkyl(cyanomethyl)amino]cyclopentanones were prepared in several ways. Reaction of *trans*-2-(methylamino)cyclopentanol with KCN and paraformaldehyde[35] followed by oxidation[12] gave amino ketone **31** in 59% yield. Amino ketone **32** was prepared in one step and ~70% yield from the reaction[36] of readily available 1,2-bis((trimethylsilyl)oxy)cyclopentene[37] with benzyl(cyanomethyl)-

(26) Bannard, R. A. B.; Gibson, N. C. C.; Parkkari, J. H. *Can. J. Chem.* **1971**, *49*, 2064–2072.
(27) Cf.: Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897–2904.
(28) Cf.: Overman, L. E.; Jacobsen, E. J. *J. Org. Chem.*, in press. Overman, L. E.; Jacobsen, E. J. *Tetrahedron Lett.* **1982**, *23*, 2737–2740.
(29) Cf.: Jackson, A. E.; Johnstone, R. A. W. *Synthesis* **1976**, 685–687.
(30) Whitlock, H. W.; Smith, G. L. *J. Am. Chem. Soc.* **1967**, *89*, 3600–3606.
(31) The narrow ^1H NMR resonances for the H_{7a} hydrogens of **25** (δ 4.08) and **26** (δ 3.96) were erroneously assigned by Whitlock and Smith[30] to NH hydrogens. However, these signals do *not* exchange with D_2O, while signals at higher field, whose positions vary with sample concentrations (δ 1.5–2.5), do exchange with D_2O. The surprising feature of the ^1H NMR spectrum of **25**, **26**, and related 4-oxooctahydroindoles is that four hydrogens (H_{7a}, $H_{2\alpha}$, $H_{2\beta}$, and one other) absorb at low field (e.g., δ 3–4.1 for **25**). Careful decoupling experiments at 250–500 MHz have, in several cases, identified[25] the "extra" hydrogen as bonded to C-3. We believe this is the $H_{3\alpha}$ hydrogen that is shifted downfield due to its near coplanarity and proximity (~2.3 Å from measurements on Dreiding models) to the carbonyl group. Deshielding effects of this type are well-known.[32] Further discussion of the ^1H NMR spectra of many of the hydroindoles reported in this paper, together with details of decoupling studies, can be found in the Ph.D. Thesis of L. T. Mendelson.[25]
(32) Jackson, L.; Sternhell, S. "Applications of NMR Spectroscopy in Organic Chemistry"; Pergamon Press: Oxford, 1969; p 89.
(33) Equilibration of *cis*- and *trans*-4-oxooctahydroindoles via a retro-Mannich–Mannich sequence is possible.
(34) Cyanoamines have been often employed as iminium ion precursors. For a recent example and leading references, see: Grierson, D. S.; Harris, M.; Husson, H.-P. *J. Am. Chem. Soc.* **1980**, *102*, 1064–1082.
(35) Cf.: Kuffner, F.; Koechlin, W. *Monatsh. Chem.* **1962**, *93*, 476–482.
(36) Cf.: Heine, H.-G.; Fischer, H.-M. *Chem. Ber.* **1972**, *105*, 975–981.

Scheme III



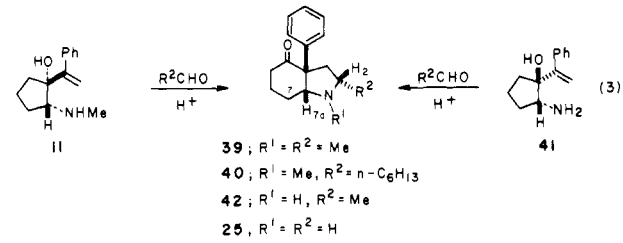
amine. Alternatively, **32** was prepared in slightly higher purity but somewhat lower yield (56–61%), from the reaction of 2-hydroxycyclopentanone[36] and benzyl(cyanomethyl)amine.

Exposure of aminocyclopentanone **32** to 2 equiv of [1-(3,4-(methylenedioxy)phenyl)ethenyl]lithium at −78 °C in THF gave a 14:1 mixture of alcohol **33** and the corresponding trans isomer. Cyclopentanol **33** was obtained in 67% yield after chromatography, and showed a diagnostic[18] intramolecular hydrogen-bonded OH absorption at 3420 cm^{-1} in the infrared spectrum. This addition was much less clean if the reaction was conducted at higher temperature of if the reaction mixture was allowed to warm to room temperature before quenching. We assume that the cyanomethylamine functionality is reactive under those conditions.[38,39] Treatment of **33** with 1.1 equiv of $AgNO_3$ in ethanol for 2 h at 50 °C gave **34** in 94% yield after purification on silica gel. *cis*-Octahydroindolone **34** (mp 102–103 °C after crystallization from hexane) showed a diagnostic narrow multiplet (half-height width = 5.2 Hz) for H_{7a} at δ 3.39 in the ^1H NMR spectrum.[22,23] Debenzylation[29] of **34** provided **26** in essentially quantitative yield. *In this way, cis-3a-aryloctahydroindolone **26** was assembled with virtually complete stereocontrol in four steps and 44% overall yield from 1,2-bis((trimethylsilyl)oxy)cyclopentene.* Since **26** has been previously[30] converted in six steps to *dl*-crinine (**38**), the sequence presented in Scheme III constitutes a concise formal total synthesis of this alkaloid.

In closely related studies, aminocyclopentanone **31** was treated with (1-phenylethenyl)lithium to give, in 76% yield, a 10:1 mixture of cyclopentanol **35** and the corresponding trans isomer. The stereostructure of **35** was confirmed by correlation with aminocyclopentanol **9** (see Scheme I) upon reduction with $NaCNBH_3$.[27] The facility of the tandem aza-Cope–Mannich sequence is nicely illustrated with **35**, which was transformed to crystalline *cis*-octahydroindolone **12** in 74% yield upon treatment at *room temperature for 1.5 h* with 1.1 equiv of $AgNO_3$.

As a single demonstration that octahydroindolones with substituents other than aryl at the angular 3a-position can be prepared in this way, cyclopentanone **32** was treated at −90 °C with 1.2 equiv of vinyllithium to give cyclopentanol **36** in 22% yield. This reaction was much less clean than reactions of **32** with (1-arylethenyl)lithium reagents and presumably reflects the greater basicity and reactivity of vinyllithium. The conversion of **36** to *cis*-octahydroindolone **37** was cleanly accomplished by exposure of **36** to 1.1 equiv of $AgNO_3$ (50 °C, ethanol). The ^1H NMR spectrum of the crude rearrangement product showed that a single product, **37**, had been formed, which was subsequently isolated in 40% yield after chromatography on silica gel.[40] The 250-MHz ^1H NMR spectrum provides no definitive evidence for the stereochemistry of **37**, and our assignment of cis stereochemistry follows only from analogy with **12** and **34**.

Preparation of 1,2-Dialkyl-3a-aryl-4-oxo-*cis*-octahydroindoles. The preparation of *cis*-3a-aryloctahydroindolones with alkyl substituents at C-2 was also briefly investigated. Reaction of cyclopentanol **11** with acetaldehyde (2 equiv) and camphorsulfonic acid (0.95 equiv) in refluxing ethanol gave *cis*-octahydroindolone **39** in 81% yield after purification on silica gel. GC analysis[21] of the crude rearrangement mixture indicated that other products were formed to the extent of <2%. The ring fusion stereochemistry for **39** followed from the diagnostic[22,23] narrow multiplet (half-height width = 5 Hz) observed for equatorial H_{7a} at δ 3.19 in the ^1H NMR spectrum. A complex absorption at δ 2.36 was assigned to H_2 (collapses to a dd, J = 5.5 and 10 Hz when the C-2 Me is irradiated). The reaction of **11** with heptanal proceeded similarly and gave *cis*-octahydroindolone **40** in 77% yield. In this case, GC analysis[21] of the crude reaction mixture showed the presence of a minor product of similar retention time (~5%, assumed to be an isomer). The reaction of amino alcohol **41**,[10b] which has cis-oriented amine and vinyl groups, with acetaldehyde proceeded with similar selectivity to give a single product, **42**, in 66% yield. Octahydroindolone **42** showed a narrow multiplet in the ^1H NMR spectrum at δ 4.10 for H_{7a} (half-height width = 6 Hz) and complex absorption at δ 3.30 for H_2 (dd, J = 5.9 and 9.6 Hz when the C-2 Me is irradiated). Methylation of **42** gave **40** in high yield. Amino alcohol **41** was also transformed to a single product, *cis*-octa hydroindolone **25**, when heated in EtOH or benzene with paraformaldehyde and acid. This clean transformation to the *cis*-octahydroindolone ring system contrasts sharply with the reaction of the *N*-diphenylmethyl analogue **19** under analogous conditions (see Table I).



The stereochemistry at C-2 for **39** and **42** follows from the identical[41] upfield shifts for H_{7a} (0.91 ppm) and H_2 (0.94 ppm), which are observed upon N-methylation of **42**. *cis*-Octahydroindolone **39** should exist preferentially in a conformation with the NMe group *trans* to C-7 and the C-2 Me, and thus, the C-7a and C-2 hydrogens should be *identically* shielded[42] by the syn NMe group and the anti nonbonded electron pair. Large stereochemistry-dependent ^1H NMR shielding effects for hydrogens α to nitrogen have been observed for many *N*-alkylpyrrolidines.[42,43]

(37) Bloomfield, J. J.; Nelke, J. M. *Org. Syn.* **1977**, *57*, 1–7.

(38) The addition of lithium reagents to the cyano group of cyanomethyl amines is well-known.[39]

(39) Cf.: Wasserman, H. H.; Doin, R. P. *Tetrahedron Lett.* **1982**, *23*, 1413–1416.

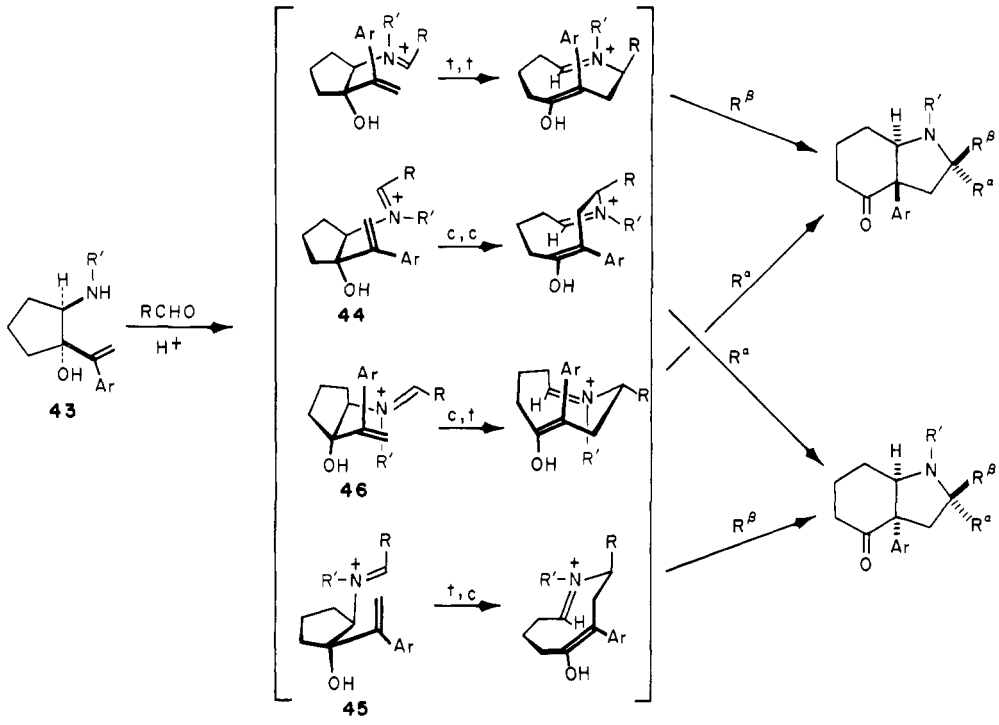
(40) This yield is believed to be unrepresentatively low. This experiment was conducted only one time.

(41) If the stereochemistry at C-2 were reversed, either (a) small upfield shifts would have been observed for these hydrogens from a mixture of *N*-methyl conformers, or (b) only one of these hydrogens (the one syn to the NMe group) would be shifted upfield.

(42) Cf.: Lambert, J. B.; Oliver, W. L. *J. Am. Chem. Soc.* **1969**, *91*, 7774–7775. Breuer, E.; Melumad, D. *J. Org. Chem.* **1973**, *38*, 1601–1602. Pitner, T. P.; Edwards, W. B.; Bassfield, R. L.; Whidby, J. F. *J. Am. Chem. Soc.* **1978**, *100*, 246–251.

(43) For leading references to similar effects in the piperidine series, see: Vierhapper, F. W.; Eliel, E. L.; Zuniga, G. *J. Org. Chem.* **1980**, *45*, 4844–4850.

Scheme IV



Discussion

Synthesis Applications. The annulation sequence of eq 1 allows a variety of 3a-aryl-4-oxooctahydroindoles to be efficiently constructed from cyclopentane precursors. Rearrangement of iminium ions derived from *cis*-2-(alkylamino)-1-(1-arylethenyl)cyclopentanols occurred, in all cases, with complete stereoselectivity to provide cis-fused hydroindoles in excellent yields. The corresponding reaction of *trans*-2-(alkylamino)-1-(1-arylethenyl)-cyclopentanols was less stereoselective and gave mixtures (which were markedly solvent dependent) of *cis*- and *trans*-3a-aryl-4-oxooctahydroindoles. If Me_2SO was used as the rearrangement solvent or the primary amino alcohol precursor **41** was employed, *cis*-octahydroindolones were also formed in high selectivity from *trans*-aminocyclopentanol precursors. The "ring-enlarging pyrrolidine annulation" reaction also allows a 2-alkyl group to be introduced, with virtually complete stereocontrol, on the more-hindered concave face of the *cis*-octahydroindole ring system.

Of the three methods developed for handling the amine group of the 2-aminocyclopentanone intermediates (Schemes I–III), cyanomethylamine protection is clearly best. With this protecting group, the addition of (1-arylethenyl)lithium reagents occurred with high selectivity (>10:1) and good efficiency, from the side opposite the amine group, to give the more desirable *cis*-2-(alkylamino)-1-(1-arylethenyl)cyclopentanol intermediates. Moreover, nitrogen deprotection is not required, since the cyanomethyl group serves as a convenient trigger for the rearrangement. The sequence presented in Scheme III is the most convenient and efficient method yet developed for assembling the important[4] *cis*-3a-aryloctahydroindole ring system.

Mechanistic Implications. Our original expectation (eq 2) that cationic aza-Cope rearrangement of iminium ions derived from *cis*-2-amino-1-(1-arylethenyl)cyclopentanols would selectively yield *cis*-octahydroindole products has proven correct. The sequence of eq 2[2,7] also nicely rationalizes the selective formation of 2-alkyloctahydroindolones **39** and **40** from the reaction of aldehydes with aminocyclopentanol **11**, since the *E* iminium ion isomer **3** (R^1 = alkyl, R^2 = H) should more rapidly undergo pericyclic rearrangement (R^1 is quasi-equatorial).[44,45]

An analysis of the rearrangement of iminium ions derived from *trans*-2-amino-1-(1-arylethenyl)cyclopentanols (**43**) is considerably more complex (see Scheme IV),[2] since there are four distinct ways to bring the cis-oriented vinyl and azavinyl groups within bonding distance. A *cis*-octahydroindolone could be formed via two topographically different pathways (represented by "boat-like" and "chair-like" conformers **44** and **45**).[7] Which of these two pathways is preferred can be surmised from the reaction of **41** with acetaldehyde and acid to give exclusively the 2-methyl-substituted *cis*-octahydroindolone **42** (see eq 3). Preferential rearrangement of the *E* iminium ion isomer[46] in this case would lead[7] to the observed product **42** (Me trans to the bridgehead substituents), only if rearrangement occurred in the "chair" topographical sense illustrated at the bottom of Scheme IV.[2,47] That *cis*-3a-aryl-4-oxooctahydroindolones are preferentially formed by this pathway also provides a nice rationalization for the clean formation of *cis*-octahydroindolone **25** from primary amine **41**, while rearrangement of the corresponding secondary amine **19** gave mixtures of cis and trans products in most solvents. Clearly, rearrangement in the sense illustrated by conformer **45** would be more favorable when the R^1 substituent is H, rather than the bulky diphenylmethyl group. We also speculate that the preferential formation of only the cis product when the rearrangement of **19** was conducted in Me_2SO may reflect the increase in size of the OH group in Me_2SO[48] and the resulting increase in the quasi-1,3-diaxial interaction of this group with the bulky nitrogen substituent (R^1 = $CHPh_2$) in the chair topographical pathway (cf. conformer **46**) which leads to trans-fused products.

Conclusion

The efficient stereocontrolled assembly of the octahydroindole ring system detailed herein provides a good illustration of the utility of tandem aza-Cope–Mannich reactions in organic synthesis. Since the annulation reactions occur at near-neutral pH (amine–amine salt buffer) and 25–80 °C, we anticipate success for this reaction with more highly functionalized systems. The extension of this strategy to the construction of the pentacyclic

(44) Cf.: Perrin, C. L.; Faulkner, D. J. *Tetrahedron Lett.* **1969**, 2783–2786.

(45) This explanation would require that the pericyclic rearrangement be rate determining, i.e., that iminium ion formation is rapid and reversible.

(46) The (*Z*)-iminium ion related to "boat" conformer **44** would experience serious repulsive interactions between R and the cyclopentane ring.

(47) In contrast, [3,3]-sigmatropic rearrangement of *cis*-1,2-divinylcyclopentane appears to occur preferentially in a boat sense.[8]

(48) Cf.: Gordon, J.; Ford, R. A. "The Chemists Companions"; Wiley: New York, 1972; p 157.

ring system common to Aspidosperma alkaloids has already been accomplished.[49]

Experimental Section[50]

2-(Dimethylamino)cyclopentanone (8). The general procedure of Swern[12] was followed. A solution of Me_2SO (7.9 mL, 110 mmol) and CH_2Cl_2 (45 mL) was added dropwise over 9 min to a solution of oxalyl chloride (8.9 mL, 100 mmol) and CH_2Cl_2 (220 mL) at −50 to −60 °C. The resulting solution was stirred for 2 min and a solution of *trans*-2-(dimethylamino)cyclopentanol[16b] (12 g, 93 mmol) and CH_2Cl_2 (93 mL) was added dropwise over 10 min. After 15 min, Et_3N (65 mL, 465 mmol) was added, and after 5 min the reaction mixture was allowed to warm to ambient temperature. Aqueous workup (CH_2Cl_2, Na_2SO_4) gave 11 g (95%) of an orange liquid. Distillation (bulb to bulb, oven temperature 70 °C, 1 mm; lit.[16] bp 84–86 °C (24 mm)) gave 9.7 g (82%) of **8** as pure light yellow liquid: IR (CCl_4) 1745 cm^{-1}.

***cis*-2-(Dimethylamino)-1-(1-phenylethenyl)cyclopentanol (9).** A pentane solution of *t*-BuLi (44 mL, 62 mmol) was added dropwise over 15 min to a solution of α-bromostyrene[51] (8.1 mL, 62 mmol) and ether (250 mL) at −78 °C.[52,53] After 1 h at −78 °C, a solution of **8** (8.0 g, 62 mmol) and ether (8 mL) was added dropwise. The reaction was maintained at −78 °C for 2 h and then quenched with saturated aqueous NH_4Cl (50 mL). Isolation with ether (Na_2SO_4) gave 11 g (76%) of an orange liquid. A 1-g sample of this material was purified by flash chromatography (90:10:1 hexane/ethyl acetate/Et_3N) to give 0.70 g (54%) of **9** as a yellow liquid, which was contaminated with only a trace of isomer **10**: bp 150 °C (2 mm); IR (CCl_4) 3340, 3604 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) 7.35 (apparent s, Ph), 5.64 (d, J = 2 Hz, C=C*H*H), 5.09 (d, J = 2 Hz, C=CH*H*), 3.05–2.6 (m, CHN), 2.28 (s, NMe_2); ^{13}C NMR (23 MHz, $CDCl_3$) 157.0, 141.6, 128.7, 127.8, 126.8, 113.3, 79.9, 72.0, 44.6, 42.1, 30.0, 22.0; MS (isobutane CI), m/z 232 (MH^+), 231, 84; MS (EI), m/z 231.162 (231.162 calcd for $C_{15}H_{21}NO$).

Analysis of the crude reaction mixture by ^1H NMR indicated that ~5% of *trans*-2-(dimethylamino)-1-(1-phenylethenyl)cyclopentanol (**10**) was formed. A sample, separated by flash chromatography (90:10:1 hexane/ethyl acetate/Et_3N), showed the following properties: IR (CCl_4) 3600, 3430 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) 7.8–7.2 (m, Ph), 5.52 (d, J = 1 Hz, C=C*H*H), 5.19 (d, J = 1 Hz, C=C*H*H), 3.1–2.7 (m, CHN), 2.19 (NMe_2); ^{13}C NMR (23 MHz, $CDCl_3$) 153.0, 142.1, 129.3, 127.7, 126.9, 115.0, 85.8, 75.8, 43.4, 39.3, 25.4, 20.8; MS (isobutane, CI), m/z 232 (MH^+), 214 ($MH^+ - H_2O$), 171, 84.

***cis*-2-(Methylamino)-1-(1-phenylethenyl)cyclopentanol (11).** A mixture of **10** (0.76 g, 3.3 mmol), phenyl chloroformate (2.6 g, 16 mmol), sodium bicarbonate (2.8 g, 33 mmol), and $CHCl_3$ (50 mL) was heated at reflux for 4.5 h. The solid was removed by filtration, the solution was concentrated, and then the excess phenyl chloroformate was removed by bulb-to-bulb distillation (oven temperature 70 °C, 1 mm) to give 1.9 g of a slightly red residue [IR (CCl_4) 1768 (OCO_2Ph) 1715 cm^{-1} (NCO_2Ph)]. A solution of this material, KOH (20 g), water (10 mL), and ethanol (100 mL) was heated at reflux for 23 h. Basic workup (50 mL of 1 N NaOH, CH_2Cl_2, Na_2CO_3) gave 0.63 g (88%) of **11** as a yellow liquid, which was a single spot by TLC analysis (60:40:1 hexane/ethyl acetate/Et_3N): IR (CCl_4) 3200–3500 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) 7.34 (apparent s, Ph), 5.60 (d, J = 2 Hz, C=C*H*H), 5.06 (d, J = 2 Hz, C=CH*H*), 3.3–2.9 (m, CHN), 2.46 (s, NMe); ^{13}C NMR (23 MHz, $CDCl_3$) 154.8, 141.8, 128.8, 127.7, 126.9, 114.4, 81.0, 65.3, 37.9, 35.2, 30.2, 20.9; MS (isobutane CI), m/z 218 (MH^+), 200 ($MH^+ - H_2O$), 70. Anal. Calcd for $C_{14}H_{19}NO$: C, 77.42; H, 8.76; N, 6.45. Found: C, 77.59; H, 8.61; N, 6.57.

1-Methyl-4-oxo-3a-phenyl-*cis*-octahydroindole (12). A mixture of paraformaldehyde (21 mg, 0.69 mmol), **11** (0.15 g, 0.69 mmol), and EtOH (2 mL) was heated at reflux for 20 h. The solution was concentrated and the residue was crystallized from hexane–ethyl acetate to give 98 mg of a white solid, mp 78–79 °C. The mother liquor was purified by chromatography (silica gel, 90:10:1 hexane/ethyl acetate/Et_3N) to give an additional 25 mg of white solid, mp 74–75 °C. The combined yield was 123 mg (78%). Two recrystallizations from hexane–ethyl acetate gave an analytical sample of **12**: mp 84–85 °C; IR (CCl_4) 1711 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.35–7.2 (m, Ph), 3.15 (m, half-height width = 7.1 Hz, H_{7a}), 3.18–3.0 (m, $H_{3\alpha}$, $H_{2\alpha}$), 2.29 (s, NMe), 2.36–1.45 (m); ^{13}C NMR (23 MHz, $CDCl_3$) 209.9, 141.0, 128.9, 126.8, 126.4, 69.7, 63.3, 53.1, 39.5, 39.4, 33.5, 22.9, 21.9; MS (isobutane CI), m/z 230 (MH^+), 229, 228, 159. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.60; H, 8.30; N, 6.11. Found: C, 78.72; H, 8.35; N, 6.04.

3-Methyl-5-(1-phenylethenyl)-4,5-trimethyleneoxazolidine (13). A mixture of **11** (0.15 g, 0.69 mmol), paraformaldehyde (21 mg, 0.69 mmol), anhydrous Na_2SO_4 (0.20 g, 1.4 mmol) and THF (2 mL) was stirred at ambient temperature for 23 h. The solids were removed by filtration and the solution was concentrated to give a yellow liquid. Distillation (bulb to bulb, oven temperature 130 °C, 0.5 mm) gave 0.15 g (97%) of a light yellow liquid, which contained only a trace impurity by GLC analysis:[20a] IR (CCl_4) 2940 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) 7.37 (apparent s, Ph), 5.44 (d, J = 1.5 Hz, C=C*H*H), 5.10 (d, J = 1.5 Hz, C=CH*H*), 4.56 (d, J = 4 Hz, NC*H*HO), 4.06 (d, J = 4 Hz, NCH*H*O), 3.5–3.2 (m, CHN), 2.38 (s, NCH_3); MS (isobutane CI), m/z 230 (MH^+), 228, 158.

***trans*-2-Aminocyclopentanol (14).**[26] A mixture of NH_4OH (12 M, 100 mL) and *trans*-2-bromocyclopentanol[1] (10 g, 61 mmol) was stirred at ambient temperature for 48 h. Solid KOH was added until the solution was saturated, and the amino alcohol product was isolated with CH_2Cl_2 (Na_2SO_4) to give 6.0 g of a brown liquid. Distillation (63 °C, 0.5 mm (lit.[26] 65 °C, 1.5 mm)) gave 4.1 g (66%) of **14** as a colorless liquid.

***trans*-2-((Diphenylmethylene)amino)cyclopentanol (15).** A mixture of **14** (5.2 g, 51 mmol), benzophenone (9.1 g, 50 mmol), monohydrated *p*-toluenesulfonic acid (0.95 g, 5.0 mmol), and dry toluene (100 mL) was heated at reflux in a Dean Stark apparatus for 18 h. The solution was allowed to cool to ambient temperature and 20 mL of 1 N NaOH was added. The layers were separated, the toluene layer was concentrated to ~50 mL, and the resulting precipitate was separated and dried to give 9.8 g (74%) of a white solid: mp 111–112 °C. Further concentration of the mother liquor afforded a second crop (0.9 g, 7%): mp 111–112 °C. Two recrystallizations from hexane gave an analytical sample of **15**: mp 112–112.5 °C; IR (CCl_4) 3630, 1622 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.7–7.1 (m, Ph), 4.3 (m, CHN), 3.6 (m, CHO); ^{13}C NMR (63 MHz, $CDCl_3$) 167.9, 140.1, 137.2, 129.8, 128.5, 128.4, 128.3, 128.1, 128.0, 79.8, 70.5, 32.8, 31.6, 20.9; MS (isobutane CI), m/z 266 (MH^+), 256, 248. Anal. Calcd for $C_{18}H_{19}NO$: C, 81.51; H, 7.17; N, 5.28. Found: C, 81.60; H, 7.20; N, 5.25.

2-((Diphenylmethylene)amino)cyclopentanone (16) was prepared from 10 g (38 mmol) of **15** by the Swern[12] procedure, as detailed for the preparation of **8**. The resulting oil was immediately purified by chromatography (100:1 hexane/Et_3N) to give 8.7 g (86%) of a light yellow oil. Trituration with hexane gave 6.0 g (60%) of a white solid (mp 66–67.5 °C). A second crop (0.5 g, 5%) of solid (mp 63–65 °C) was obtained from the mother liquor. This material was not stable to prolonged storage, and crystalline **16** was used directly in the next reaction. Characterization data for **16** are: IR (CCl_4) 1750, 1668 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) 8.0–7.0 (m, Ph), 4.1–3.6 (m, CHN); ^{13}C NMR (23 MHz, $CDCl_3$) 215.0, 171.1, 139.6, 137.6, 136.3, 132.4, 130.1, 130.0, 128.7, 128.4, 128.3, 128.2, 128.0, 69.7, 36.9, 32.2, 19.2; MS (isobutane CI), m/z 264 (MH^+), 213.

***trans*- and *cis*-2-((Diphenylmethyl)amino)-1-(1-phenylethenyl)cyclopentanols (19) and (20).** A solution of (1-phenylethenyl)lithium (21 mmol of 0.18 M in ether) was prepared and allowed to react with 5.0 g (19 mmol) of **16**, following the procedure described previously for the preparation of **9**, to give 7.05 g of a thick yellow oil, which was typically reduced with $NaCNBH_3$ without further purification. Chromatography (silica gel, 100:1 hexane/Et_3N) of a 6-g sample of this oil gave 1.8 g (30%) of a yellow oil which appeared to be a mixture of the imino alcohol **18** and the corresponding oxazolidine: [IR (CCl_4) 3460, 3320, 1629 cm^{-1}; ^{13}C NMR (23 MHz, $CDCl_3$) 100.4 (OCN), 168 (C=N very weak)]. Continued elution gave 3.3 g (55%) of **17** as a thick yellow oil, followed by 0.2 g (4%) of **16**. Trituration of this oily sample of **17** with hexane gave a white solid, and two subsequent recrystallizations (hexane) afforded an analytical specimen of **17**: mp 82.5–83 °C; IR (CCl_4) 3605, 3460, 1627; ^1H NMR (250 MHz, $CDCl_3$) 5.49 (d, J = 1.5 Hz, C=C*H*H), 5.25 (d, J = 1.5 Hz, C=CH*H*), 3.69 (apparent d, J = 6.6 Hz, CHN); ^{13}C NMR (δ, $CDCl_3$) 165.5, 152.3, 148.5, 142.0, 140.3, 136.6, 129.5, 128.5, 128.3, 128.1, 128.0, 127.8, 126.8, 121.8, 116.3, 87.3, 69.5, 37.1, 33.7, 21.3; MS (isobutane CI), m/z 368 (MH^+), 367, 351, 350. Anal. Calcd for $C_{26}H_{25}NO$: C, 85.01; H, 6.81; N, 3.81. Found: C, 84.88; H, 6.99; N, 3.77.

A 1.0-g sample of the crude adduct formed from **16**, $NaCNBH_3$ (0.36 g, 5.7 mmol), 1 N HCl (2.8 mL), and methanol (60 mL) was heated at reflux for 21 h.[27] Concentration, followed by basic workup (20 mL 1 N NaOH, CH_2Cl_2, K_2CO_3) gave 0.85 g of a light yellow liquid. Chromatography (silica gel, 100:1 hexane/Et_3N) afforded 0.24 g (24%) of pure **20** as a light yellow oil: IR (CCl_4) 3600 (OH), 3460 (OH, no change upon dilution), 3350 (NH) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.4–6.9 (m, Ph), 5.60 (d, J = 1.8 Hz, C=C*H*H), 5.09 (d, J = 1.8 Hz C=CH*H*), 4.86 (C*H*Ph_2), 3.05 (apparent t, J = 9 Hz, CHN); ^{13}C NMR (63 MHz,

(49) For use of the "ring-enlarging pyrrolidine annulation" reaction as the key step in the total synthesis of (±)-16-methoxytabersonine, see: Overman, L. E.; Sworin, M.; Burk, R. M. *J. Org. Chem.* **1983**, *48*, 2685–2690.

(50) General experimental details have been described recently; see: Overman, L. E.; Lesuisse, D. L.; Hashimoto, M. *J. Am. Chem. Soc.* **1983**, *105*, 5373–5380.

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

$CDCl_3$), 154.6, 143.6, 143.4, 141.6, 128.7, 128.6, 128.4, 127.8, 127.7, 127.4, 127.2, 127.1, 126.4, 115.0, 81.8, 64.3, 61.1, 37.6, 30.2, 20.8; MS (isobutane CI), m/z 370 (MH^+), 352 (very weak, $MH^+ - H_2O$), 167; MS (EI), m/z 369.208 (369.209 calcd for $C_{26}H_{27}NO$).

Continued elution gave 0.39 g (39%) of **19** as a light yellow oil, which solidified upon setting. Two recrystallizations from hexane gave an analytical sample of **19**: mp 63–64 °C; IR (CCl_4) 3608 (OH), 3460 (OH, disappears upon dilution from 0.09 to 0.006 M in CCl_4), 3315 (NH) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.4–7.1 (m, Ph), 6.9–6.8 (m, Ph), 5.40 (d, J = 1.1 Hz, C=C*H*H), 5.31 (d, J = 1.1 Hz, C=CH*H*), 4.72 (s, Ph_2CH), 2.95 (apparent d, J = 4.4 Hz, CHN); ^{13}C NMR (63 MHz, $CDCl_3$), 151.6, 144.9, 143.6, 141.2, 128.4, 128.1, 127.7, 127.5, 127.3, 126.7, 126.6, 117.0, 86.9, 63.8, 63.5, 36.5, 28.5, 20.4; MS (isobutane CI), m/z 370 (MH^+), 183. Anal. Calcd for $C_{26}H_{27}NO$: C, 84.55; H, 7.32; N, 3.79. Found: C, 84.70; H, 7.44; N, 3.74.

1-Bromo-1-(3,4-(methylenedioxy)phenyl)ethylene. 3,4-(Methylenedioxy)styrene[54] (2.0 g, 14 mmol) was brominated and dehydrobrominated, as described by Newman[51] for the preparation of α-bromostyrene, to give 2.5 g of a light yellow liquid: bp 87 °C (0.6 mm); IR (CCl_4) 1685 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) 7.3–6.6 (m, Ar H), 5.97 (m, OCH_2O and C=C*H*H), 5.60 (d, J = 2 Hz, C=CH*H*); MS (isobutane CI), m/z 229, 228, 227, 226, 148, 147.

***trans*- and *cis*-2-((Diphenylmethyl)amino)-1-[1-(3,4-(methylenedioxy)phenyl)ethenyl]cyclopentanols (21 and 22)** were prepared from **16** (380 mg, 1.5 mmol) and [1-(3,4-(methylenedioxy)phenyl)ethenyl]lithium [from 1-bromo-1-(3,4-(methylenedioxy)phenyl)ethylene (2.9 mmol) and *t*-BuLi (2.9 mmol)],[52] following the procedure described for the preparation of **19** and **20**. Alcohol **22** was isolated in 15% overall yield from **16** as a thick oil, which was homogeneous by TLC analysis: IR (CCl_4) 3602 (OH), 3460 (OH, invariant intensity upon dilution from 0.09 to 0.003 M in CCl_4) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.4–7.2 (m, Ar H), 6.7–6.5 (m, Ar H), 5.92 (s, OCH_2O), 5.52 (d, J = 1.8 Hz, C=C*H*H), 5.07 (d, J = 1.8 Hz, C=CH*H*), 4.85 (s, C*H*Ph_2), 3.04 (apparent t, J = 8.8 Hz, CHN); ^{13}C NMR (23 MHz, $CDCl_3$) 153.8, 147.0, 146.5, 143.5, 143.2, 135.3, 128.5, 128.4, 127.6, 127.3, 127.1, 121.9, 114.8, 109.4, 107.6, 100.9, 81.7, 64.2, 61.0, 37.6, 30.2, 20.7; MS (isobutane CI), m/z 414 (MH^+), 246, 209, 168, 167; MS (EI), m/z 413.198 (413.199 calcd for $C_{27}H_{27}NO_3$).

Alcohol **21** was isolated in 55% overall yield from **16** as a white solid: mp 98.5–99 °C (from hexane); IR (CCl_4) 3608 (OH), 3450 (OH, loses intensity upon dilution from 0.09 to 0.006 M in CCl_4), 3310 (NH) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.3–6.7 (m, Ar H), 5.96 (AB q, J = 1.3 Hz, $\Delta\nu$ = 3.5 Hz, OCH_2O), 5.36 (d, J = 0.9 Hz, C=C*H*H), 5.29 (d, J = 1.1 Hz, C=CH*H*), 4.73 (s, C*H*Ph_2), 2.94 (apparent d, J = 5.0 Hz, CHN); ^{13}C NMR (23 MHz, $CDCl_3$) 150.9, 147.4, 147.0, 144.8, 143.5, 135.2, 128.3, 128.2, 127.7, 127.3, 126.8, 126.7, 121.5, 116.6, 108.9, 107.9, 101.0, 87.9, 63.7, 63.2, 36.5, 28.4, 20.4; MS (isobutane CI), m/z 414 (MH^+), 246, 215, 209, 168, 167. Anal. Calcd for $C_{27}H_{27}NO_3$: C, 78.45; H, 6.54; N, 3.39. Found: C, 78.60; H, 6.69; N, 3.38. The stereochemistry of **21** was further confirmed by a single-crystal X-ray analysis.[25]

1-(Diphenylmethyl)-4-oxo-3a-phenyl-*cis*-octahydroindole (23). A solution of **20** (80 mg, 0.22 mmol), paraformaldehyde (13 mg, 0.43 mmol), camphorsulfonic acid (45 mg, 0.19 mmol), and dry benzene (15 mL) was heated at reflux for 21 h. Basic workup (10 mL of 1 N NaOH, benzene, K_2CO_3) gave 64 mg (78%) of a white solid, which was homogeneous by TLC analysis. Two recrystallizations from hexane gave an analytical sample of **23**: mp 117.5–118 °C; IR (CCl_4) 1711 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.4–7.1 (m, Ar H), 5.18 (s, C*H*Ph_2), 3.62 (br s, half-height width = 6 Hz, H_{7a}), 3.0–2.85 (m); ^{13}C NMR (63 MHz, $CDCl_3$), 210.6, 141.9, 140.8, 138.5, 132.5, 130.2, 130.1, 129.0, 128.3, 128.2, 127.8, 127.4, 127.3, 126.9, 126.8, 126.7, 126.5, 64.9, 62.7, 43.8, 39.7, 34.1, 23.5, 22.2; MS (isobutane CI), m/z 382 (MH^+), 214, 209, 168, 167. Anal. Calcd for $C_{27}H_{27}NO$: C, 85.04; H, 7.09; N, 3.67. Found: C, 84.84; H, 7.20; N, 3.59.

4-Oxo-3a-phenyl-*cis*-octahydroindole (25). A mixture of **23** (47 mg, 0.12 mmol), 10% Pd/C (47 mg), aqueous 1 N HCl (0.12 mL), cyclohexene (5 mL), and ethanol (5 mL) was heated at reflux for 17 h.[29] Triethylamine (5 mL) was added, the Pd/C was removed by filtration, and the solution was concentrated. The residue was partitioned between ether (5 mL) and aqueous 1 N HCl (5 mL). The aqueous layer was made basic with KOH and the product was isolated with ether (K_2CO_3) to give 21 mg (79%) of a colorless oil, which was homogeneous by TLC analysis. Crystallization from hexane gave an analytical sample of **25**: mp 62–64 °C (lit.[30] 64.5–66.5 °C); IR (CCl_4) 1711 cm^{-1}; ^1H NMR[31] (500 MHz, $CDCl_3$) 7.4–7.1 (m, Ph), 4.08 (apparent t, J = 3.2 Hz, H_{7a}), 3.10 (ddd, J = 5.0, 7.5, 12.5 Hz, $H_{2\alpha}$), 3.0 (m, $H_{2\beta}$, $H_{3\alpha}$), 2.4–1.6 (m, one hydrogen of this multiplet disappears upon addition of D_2O); ^{13}C NMR (63 MHz, $CDCl_3$) 211.2, 140.5, 129.0, 127.0, 126.6, 63.7, 63.2, 42.9, 39.4, 36.9, 25.7, 22.8; MS (isobutane CI), m/z 216 (MH^+). Acetylation with acetic anhydride gave the *N*-acetyl compound. Recrystallization from hexane gave a pure sample: mp 104.5–105 °C (lit.[30] 104.5–106.5 °C); ^1H NMR (500 MHz, $CDCl_3$) 7.2–7.35 (m, Ph), 4.86 (m, half-height width = 11.6 Hz, H_{7a}), 3.47 (ddd, J = 4.2, 7.8, 10.1 Hz, $H_{2\alpha}$), 3.41 (ddd, J = 6.7, 8.5, 10.2 Hz, $H_{2\beta}$), 2.89 (ddd, J = 4.3, 6.8, 12.6 Hz, $H_{3\alpha}$), 2.08 (s, CH_3); MS (isobutane CI), m/z 258 (MH^+).

1-(Diphenylmethyl)-3a-(3,4-(methylenedioxy)phenyl)-4-oxo-*cis*-octahydroindole (24). A mixture of **22** (43 mg, 0.10 mmol), paraformaldehyde (3.1 mg, 0.10 mmol), camphorsulfonic acid (23 mg, 0.10 mmol), and dry Me_2SO (2 mL) was heated at 70 °C for 5 days. Basic workup (ethyl acetate, K_2CO_3) gave 40 mg (91%) of **24** as a white solid. Two recrystallizations from hexane gave an analytical sample: mp 157.5–158.5 °C; IR (CCl_4) 1709 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.5–7.2 (m, Ar H), 6.7–6.6 (m, Ar H), 5.92 (br s, OCH_2O), 5.18 (s, Ph_2CH), 3.51 (br s, half-height width = 5 Hz, H_{7a}); ^{13}C NMR (63 MHz, $CDCl_3$) 210.5, 148.1, 146.3, 141.7, 138.3, 134.4, 130.0, 128.2, 128.1, 127.3, 126.7, 119.7, 108.5, 107.2, 101.1, 64.9, 64.7, 62.2, 43.5, 39.3, 34.0, 23.4, 22.1; MS (isobutane CI), m/z 426 (MH^+), 260, 168, 167, 91. Anal. Calcd for $C_{28}H_{27}NO_3$: C, 79.65; H, 6.35; N, 3.29. Found: C, 79.35; H, 6.46; N, 3.40.

Alternatively, **22** was treated with paraformaldehyde (1 equiv, THF, Na_2SO_4)[1] to give the corresponding oxazolidine, which was then heated at reflux in benzene in the presence of camphorsulfonic acid (0.95 equiv) to give **24** in 72% overall yield.

3a-(3,4-(Methylenedioxy)phenyl)-4-oxo-*cis*-octahydroindole (26). Deprotection of **24** (92 mg, 0.22 mmol), exactly as described for the preparation of **25**, gave 53 mg (95%) of **26** as a light yellow oil, which was homogeneous by TLC analysis: IR (CCl_4) 3390, 1710 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$)[31] 6.8–6.6 (m, s at 60 MHz,[30] Ar H), 5.94 (s, OCH_2O), 3.96 (br s, half-height width = 7.6 Hz, H_{7a}), 3.12–2.92 (m, CH_2N, $H_{3\alpha}$), 2.43–1.53 (m, one hydrogen of this multiplet disappears upon addition of D_2O); ^{13}C NMR (63 MHz, $CDCl_3$) 211.2, 148.1, 146.4, 134.1, 119.6, 108.5, 107.2, 101.1, 63.8, 62.7, 42.8, 39.1, 36.8, 25.6, 22.7; MS (isobutane CI), m/z 260 (MH^+), 259, 258. Acetylation with acetic anhydride gave the *N*-acetyl compound. Two recrystallizations from hexane gave a pure sample: mp 126–127 °C (lit.[30] 126.5–127.5 °C); IR (CCl_4) 1713, 1659 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 6.77 (m, Ar H), 5.95 (s, OCH_2O), 4.77 (apparent t, $J \sim 4.7$ Hz, H_{7a}), 3.43 (m, CH_2N), 2.86 (ddd, J = 4.4, 6.6, 12.5, $H_{3\alpha}$), 2.05 (s, CH_3); MS (isobutane CI), m/z 302 (MH^+), 301.

Rearrangement of Amino Alcohols 19 and 21. A solution of **19** (150 mg, 0.4 mmol), paraformaldehyde (12 mg, 0.40 mmol), camphorsulfonic acid (91 mg, 0.39 mmol), and benzene (3 mL) was heated at reflux for 24 h. Basic workup (benzene, K_2CO_3) followed by chromatographic purification (silica gel, 100:1 hexane/Et_3N) gave 130 mg (82%) of a 3:1 mixture of **23** (δ 5.18, C*H*Ph_2) and **27** (δ 4.79, C*H*Ph_2). Similar treatment of a 43 mg sample of **19** in Me_2SO (83 °C, 23 h) gave, after chromatography, 30 mg (68%) of chromatographically homogeneous *cis*-octahydroindolone **23**.

In an identical fashion, **21** (460 mg, 1.1 mmol) was heated for 4 h in refluxing benzene with paraformaldehyde (1.0 equiv) and camphorsulfonic acid (0.95 equiv) to give, after filtration through Florisil, 410 mg (86%) of a 2:1 mixture of **24** (δ 5.18, C*H*Ph_2) and **28** (δ 4.76, C*H*Ph_2) as a light yellow liquid. Similar treatment of an 11-mg sample of **21** in Me_2SO (84 °C, 16 h) gave after purification on silica gel (100:1 hexane/Et_3N) 7.1 mg (65%) of **24** as a chromatographically homogeneous oil.

4-Oxo-3a-phenyl-*trans*-octahydroindole (29). Alcohol **19** (120 mg, 0.30 mmol) was treated with paraformaldehyde and acid in wet THF (~2% H_2O) as described for the preparation of **23** to give a ~5:1 mixture of octahydroindolones **23** and **27**. Deprotection (Pd/C, cyclohexane), following the procedure described for the preparation of **25**, gave 56 mg (87%) of a crude mixture of **25** and **29** as a light yellow oil. Chromatography (silica gel, 60:40:1 hexane/ethyl acetate/Et_3N) gave 6.9 mg (11%) of **29** as a light yellow oil: IR (CCl_4) 1715 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.52 (m, Ph), 7.4–7.1 (m, Ph), 3.25 (dd, J = 3.7, 12.9 Hz, H_{7a}), 3.19 (ddd, J = 1.9, 9.9, 11.5 Hz, only 6 lines visible, C*H*HN), 2.95 (ddd, J = 7.0, 9.9, ~9.9 Hz, only 6 lines visible, CH*H*N), 2.77 (br s, NH); ^{13}C NMR (63 MHz, $CDCl_3$), 211.0, 141.1, 128.9, 128.4, 126.6, 67.9, 63.2, 42.3, 38.7, 34.5, 25.3, 24.8; MS (isobutane CI), m/z 216 (MH^+), 215, 214; MS (EI), m/z 215.130 (215.131 calcd for $C_{14}H_{17}NO$).

Continued elution gave 38 mg (59%) of *cis*-3a-phenyloctahydroindolone **25**.

4-Oxo-3a-(3,4-(methylenedioxy)phenyl)-*trans*-octahydroindole 30. A 2:1 mixture of **24** and **28** (from rearrangement of 0.38 mmol of **21** in benzene) was N-deprotected, as described for the preparation of **25**, to give 82 mg (83%) of a mixture of **26** and **30**, as a light yellow oil.

(52) The use of 2.0 equiv of *tert*-butyllithium[53] was less satisfactory.
(53) Cf.: Seebach, D.; Neumann, H. *Chem. Ber.* **1974**, *107*, 847–853.
(54) Matsuo, M. *Nippon Kagaku Zasshi* **1965**, *86*, 1183–1187.

Chromatography (silica gel, 60:40:1 hexane/ethyl acetate/Et_3N) gave 25 mg (25%) of **30**, as a white solid, mp 111–114 °C. Two recrystallizations from hexane gave a pure sample of **30**: mp 117–117.5 °C (lit.[30] 119.5–120.5 °C); IR (CCl_4) 3360, 1712 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.24 (m, Ar H), 7.0 (m, Ar H), 5.93 (s, OCH_2O), 3.22 (dd, J = 3.7, 12.5 Hz, H_{7a}), 3.17 (ddd, J = 1.8, 10.3, 12.1 Hz, $H_{2\beta}$), 2.95 (ddd, J = 7.3, ~10.3, ~10.3 Hz, only six lines resolved, $H_{2\alpha}$); ^{13}C NMR (63 MHz, $CDCl_3$) 211.0, 147.9, 134.8, 121.5, 109.3, 108.6, 101.0, 67.8, 62.7, 42.2, 38.4, 34.5, 25.2, 24.7; MS (isobutane CI), m/z 260 (MH^+), 259. Acetylation with acetic anhydride gave the known[30] *N*-acetyl compound: ^1H NMR (250 MHz, $CDCl_3$) 6.78 (m, ArH), 5.97 (m, OCH_2O), 3.75–3.3 (m, CHN, CH_2N), 2.52–1.18 (m, CH_2), 2.11 (s, CH_3).

***trans*-2-[Methyl(cyanomethyl)amino]cyclopentanol.** The general procedure of Kuffner[35] was employed. *trans*-2-(Methylamino)cyclopentanol[11] (3.11 g, 27.0 mmol) was neutralized with concentrated HCl, KCN (1.76 g, 27.0 mmol) and H_2O (35 mL) were added, and the resulting solution was cooled to 0 °C. Paraformaldehyde (810 g, 27.0 mmol) was added, and the aqueous 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) and bulb-to-bulb distillation (oven temperature 130 °C, 7 mm) gave 2.49 g (60%) of *trans*-2-[methyl(cyanomethyl)amino]cyclopentanol: IR (CCl_4) 3416, 2220 (weak), 1450, 1040 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 4.02 (ddd, J = 13.8, 7.5, 6.0 Hz, C*H*OH), 3.71 (AB q, J_{AB} = 17.3 Hz, $\Delta\nu_{AB}$ = 61.6 Hz, NCH_2CN), 2.66 (ddd, J = 13.6, 7.4, 6.6 Hz, CHN), 2.43 (s, MeN); ^{13}C NMR (63 MHz, $CDCl_3$) 115.5, 76.2, 71.1, 44.2, 40.5, 34.0, 28.6, 20.4; MS (isobutane CI), m/z 155 (MH^+), 128; MS (EI), m/z 154.112 (154.111 calcd for $C_8H_{14}N_2O$).

2-[Methyl(cyanomethyl)amino]cyclopentanone (31). *trans*-2-[Methyl(cyanomethyl)amino]cyclopentanol (2.08 g, 13.5 mmol) was oxidized by the Swern procedure[12] to give, after bulb-to-bulb distillation (oven temperature 110 °C, 2.5 mm), 2.02 g (98%) of **31** as a light yellow oil: IR (CCl_4) 2220 (weak), 1741 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 3.85 (AB q, J_{AB} = 17.4 Hz, $\Delta\nu_{AB}$ = 116 Hz, CH_2CN), 3.0–3.15 (m, CHN), 2.46 (s, MeN); ^{13}C NMR (63 MHz, $CDCl_3$) 215.2, 115.5, 68.2, 43.2, 39.4, 36.4, 26.3, 17.5; MS (isobutane CI), m/z 153 (MH^+), 126. This sample deteriorated upon storage and was used immediately in the next reaction.

2-[Benzyl(cyanomethyl)amino]cyclopentanone (32). A solution of benzyl(cyanomethyl)amine (335 mg, 2.30 mmol; bp 157 °C (6 m, prepared in 67% yield from benzylamine, KCN, and paraformaldehyde by the procedure[35] described for the preparation of the alcohol precursor of **31**), 1,2-bis((trimethylsilyl)oxy)cyclopentene[37] (0.55 mL, 2.0 mmol), and MeOH (0.6 mL) was heated at reflux for 28 h. Concentration and purification of the residue by flash chromatography (50:10:0.1 hexane/ethyl acetate/Et_3N) gave 327 mg (72%) of nearly pure **32**, which was contaminated with 5% of an unknown material (NMR analysis). Alternatively, pure **32** could be prepared on larger scales by heating a solution of 2-hydroxycyclopentanone (2.05 g, 20.5 mmol; prepared from 1,2-bis((trimethylsilyl)oxy)cyclopentene[36] in ~80% yield by hydrolysis at room temperature with aqueous acetone), benzyl(cyanomethyl)amine (3.0 g, 20.5 mmol), and benzene (20 mL) at reflux (Dean-Stark H_2O separator) for 3 h. Product isolation as detailed above gave 2.6–2.8 g (56–61%) of pure **32** as a colorless liquid: IR (CCl_4) 1749, 1709 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.2–7.5 (m, Ph), 3.78 (AB q, J_{AB} = 15.2 Hz, $\Delta\nu_{AB}$ = 8.3 Hz, CH_2CN), 3.65 (AB q, J_{AB} = 15.3 Hz, $\Delta\nu_{AB}$ = 120 Hz, CH_2Ph), 3.2–3.35 (m, CHN); ^{13}C NMR (63 MHz, $CDCl_3$) 215.3, 136.8, 129.0, 128.6, 127.9, 116.1, 68.3, 55.5, 39.3, 36.6, 26.5, 17.9; MS (EI), m/z (relative %) 228 (M, 3), 200 (20), 172 (81), 145 (28), 132 (26), 91 (100), 81 (85). This material deteriorated upon storage and was used directly in subsequent reactions.

***cis*-2-[Benzyl(cyanomethyl)amino]-1-[1-(3,4-(methylenedioxy)-phenyl)ethenyl]cyclopentanol (33).** A solution of ketone **32** (440 mg, 1.93 mmol) and THF (13 mL) was added dropwise at −78 °C to a rapidly stirring solution of [1-(3,4-(methylenedioxy)phenyl)ethenyl]lithium (4.3 mmol, 0.2 M in 10:1 THF/pentane, prepared as described for the preparation of **21** and **22**). After 25 min, the resulting orange solution was quenched at −78 °C by adding wet THF. The reaction mixture was allowed to warm to room temperature and the product was isolated with ether (K_2CO_3/Na_2SO_4) to give a ~14:1 mixture (80 MHz, ^1H NMR analysis) of **33** and the corresponding trans isomer. Chromatography (silica gel, 50:10:0.1 hexane/ethyl acetate/Et_3N) gave 480 mg (67%) of a nearly pure (contaminated only with 5% of the trans isomer) sample of **33** as a colorless oil: IR (CCl_4) 3420 (OH, no change upon dilution in CCl_4 from 0.2 to 0.025 M), 1485, 1232, 1040 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.2–7.4 (m, Ph), 6.7–6.9 (m, Ar H), 5.97 (s, OCH_2O), 5.66 (d, J = 1.5 Hz, =C*H*H), 5.17 (d, J = 1.5 Hz, =CH*H*), 3.83 (AB q, J_{AB} = 13.0 Hz, $\Delta\nu_{AB}$ = 72 Hz, CH_2CN), 3.40 (very narrow AB q, CH_2Ph), 3.3–3.5 (m, CHN); ^{13}C NMR (63 MHz, $CDCl_3$) 155.3, 147.5, 147.0, 136.8, 134.5, 129.2, 128.9, 128.1, 122.0, 115.5, 114.2, 109.2, 108.1, 101.2, 80.9, 68.6, 56.5, 41.8, 39.7, 29.0, 21.4; MS (EI), m/z (relative %) 376.176 (376.179 calcd for $C_{23}H_{24}N_2O_3$) (1), 279 (11), 258 (9), 185 (8), 147 (7), 91 (100).

Further elution gave 54 mg (7%) of a 1:2 mixture of **33** and the corresponding trans isomer. The 250-MHz ^1H NMR spectrum showed characteristic signals for the latter at δ 5.88 (s, OCH_2O), 5.48 (d, J = 1.5 Hz, =C*H*H), 5.25 (d, J = 1.5 Hz, =CH*H*).

1-Benzyl-3a-(3,4-(methylenedioxy)phenyl)-4-oxo-*cis*-octahydroindole (34). A solution of **33** (43.3 mg, 0.115 mmol), $AgNO_3$ (24 mg, 0.14 mmol), and ethanol (5 mL) was heated at 50 °C for 2 h and then allowed to cool to room temperature. Filtration to remove AgCN was followed by concentration, basic workup (10 mL of 2 N NaOH, ether, K_2CO_3), and short-column chromatography (silica gel, 50:10:0.1 hexane/ethyl acetate/Et_3N) to give 38 mg (95%) of **34** as a light yellow oil, which was homogeneous by TLC analysis. Crystallization from pentane–CH_2Cl_2 gave (three crops) 25 mg (62%) of pure crystalline **34**. An analytical sample was prepared by one further recrystallization from hexane: mp 102–103 °C; IR (CCl_4) 1713, 1486, 1238, 1040 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.15–7.35 (m, Ph), 6.6–6.8 (m, Ar H), 5.94 (s, OCH_2O), 3.62 (AB q, J_{AB} = 13.3 Hz, $\Delta\nu_{AB}$ = 232 Hz, PhCH_2), 3.39 (br s, half-height width = 5.2 Hz, H_{7a}), 2.8–3.0 (m, CH_2N); ^{13}C NMR (63 MHz, $CDCl_3$) 210.0, 148.4, 146.5, 139.2, 134.7, 128.5, 128.4, 127.0, 119.7, 108.7, 107.3, 101.3, 68.1, 62.8, 57.0, 50.3, 39.6, 33.8, 23.4, 22.2; MS (EI), m/z (relative %) 349 (M, 17), 279 (55), 188 (31), 91 (100). Anal. Calcd for $C_{22}H_{23}O_3N$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.51; H, 6.67; N, 4.03.

The 250-MHz ^1H NMR spectrum of the crude rearrangement product showed no detectable trans isomer. The rearrangement of **34** could also be accomplished in good yield under basic conditions in refluxing $CHCl_3$ in the presence of $AgNO_3$ (1.1 equiv) and pyridine (~10 equiv).

Preparation of 3a-(3,4-(Methylenedioxy)phenyl)-4-oxo-*cis*-octahydroindole (26) from 34. A 20-mg (0.057 mmol) sample of crystalline **34** was deprotected, as described for the preparation of **25**, to give, after basic workup (5 mL of 1 N NaOH, ether, K_2CO_3), 14.7 mg (99%) of **26** as a light yellow oil, which was homogeneous by TLC analysis. This material was identical with a sample of **26** prepared from **24**.

***cis*-2-[Methyl(cyanomethyl)amino]-1-(1-phenylethenyl)cyclopentanol (35).** A solution of (1-phenylethenyl)lithium (0.2 M in ether, 2.1 equiv) was prepared and allowed to react at −78 °C with ketone **31** (250 mg, 1.64 mmol), following the procedure described for the preparation of **9**, to give a 8.8:1 mixture of **33** and the corresponding trans isomer, respectively. Chromatography (silica gel, 70:10:1 hexane/ethyl acetate/Et_3N) gave 320 mg (76%) of **35** as a light oil, which was contaminated with 10% of the trans isomer. This material was suitable for the rearrangement step and was not further purified. The following are spectral data for **35** obtained from this mixture: IR (CCl_4) 3435, 1448, 1323, 1021 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.2–7.5 (m, Ph), 5.64 (d, J = 1.5 Hz, =C*H*H), 5.17 (d, J = 1.5 Hz, =CH*H*), 3.57 (apparent s, CH_2CN), 3.18 (dd, J = 10.3, 6.7 Hz, CHN), 2.45 (s, Me); ^{13}C NMR (63 MHz, $CDCl_3$) 155.6, 140.6, 128.5, 128.0, 127.2, 115.2, 114.2, 80.5, 68.9, 44.5, 41.7, 41.4, 29.0, 21.3; MS (isobutane CI), m/z 257 (MH^+), 230; MS (EI), m/z 256.158 (256.158 calcd for $C_{16}H_{20}N_2O$).

Treatment of this material at room temperature with excess $NaCNBH_3$ in acidic MeOH[27] gave amine **9** (^1H NMR δ 2.28, NMe_2).

Preparation of 1-Methyl-4-oxo-3a-phenyl-*cis*-octahydroindole (12) from 35. To a solution of $AgNO_3$ (21 mg, 0.12 mmol) and ethanol (5 mL) at room temperature was added **35** (28.8 mg, 0.113 mmol, contaminated with 10% of the trans isomer). A precipitate (AgCN) formed immediately, and the resulting mixture was stirred at room temperature for an additional 1.5 h. Basic workup (5 mL of 2 N NaOH, ether, K_2CO_3/Na_2SO_4) and short-column chromatography (silica gel, 60:10:0.1 hexane/ethyl acetate/Et_3N) gave 18.8 mg (73%) of crystalline **12**, which was identical with a sample prepared from **11**.

***cis*-2-[Benzyl(cyanomethyl)amino]-1-ethenylcyclopentanol (36).** Vinyllithium (2.90 mL of a 0.57 M solution in THF, 1.65 mmol, prepared from tetravinyltin and BuLi)[55] was added dropwise over ~15 min to a solution of ketone **32** (303 mg, 1.33 mmol) and dry THF (10 mL) at −90 to −100 °C. The resulting solution was stirred at −90 °C for an additional 5 min, the reaction was quenched by adding wet THF, and the reaction mixture was allowed to warm to room temperature. Product isolation, as described for the preparation of **33**, gave a complex oil, which was chromatographed on silica gel (50:10:0.1 hexane/ethyl acetate/Et_3N) to give 75 mg (22%) of **36** as a clear oil, which was homogeneous by TLC analysis: IR (CCl_4) 3472, 1325, 919 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.2–7.4 (m, Ph), 6.04 (dd, J = 17.0, 10.6 Hz, C*H*=CH_2), 5.51 (dd, J = 17.0, 1.8 Hz, CH=C*H*H), 5.10 (dd, J = 10.6, 1.8 Hz, CH=CH*H*), 3.83 (AB q, J_{AB} = 13.2 Hz, $\Delta\nu_{AB}$ = 63.2 Hz, CH_2CN), 3.47 (AB

(55) Gassman, P. G.; Valcho, J. V.; Proehl, G. S.; Cooper, C. F. *J. Am. Chem. Soc.* **1980**, *102*, 6519–6526.

q, J_{AB} = 17.6 Hz, $\Delta\nu_{AB}$ = 64.3 Hz, CH_2Ph), 3.13 (s, OH), 3.02 (dd, J = 10.3, 6.9 Hz, CHN); ^{13}C NMR (63 MHz, $CDCl_3$) 145.2, 137.0, 129.2, 129.0, 128.2, 115.4, 112.7, 80.1, 70.4, 57.1, 40.1, 39.7, 29.6, 20.4; MS (isobutane CI), m/z 257 (MH^+), 230, 91.

1-Benzyl-4-oxo-*cis*-octahydroindole (37). A solution of **36** (47.7 mg, 0.186 mmol), $AgNO_3$ (34 mg, 0.20 mmol), and ethanol (7 mL) was stirred at 50 °C for 1.5 h. Workup, as described for the preparation of **34**, and purification on silica gel (50:10:0.1 hexane/ethyl acetate/Et_3N) gave 17.1 mg (40%) of **37** as a colorless oil, which was homogeneous by TLC analysis: IR (CCl_4) 1713, 1452, 1140 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.1–7.4 (m, Ph), 3.55 (AB q, J_{AB} = 13.3 Hz, $\Delta\nu_{AB}$ = 218 Hz, CH_2Ph), 2.8–3.0 (m, 2 H), 2.65–2.75 (m, 1 H), 2.48 (apparent ddt, J = 15.3, 1.1, 4.6 Hz, 1 H), 2.2–2.4 (m, 2 H); ^{13}C NMR (63 MHz, $CDCl_3$) 211.8, 139.5, 128.7, 128.4, 127.0, 65.2, 57.4, 52.1, 51.6, 41.2, 26.7, 22.4, 20.6; MS (isobutane, CI), m/z 230 (MH^+); MS (EI), m/z 229.141 (229.147 calcd for $C_{15}H_{19}NO$).

***trans*-1,2-Dimethyl-4-oxo-3a-phenyl-*cis*-octahydroindole (39).** A solution of **11** (0.10 g, 0.46 mmol), freshly distilled acetaldehyde (0.052 mL, 0.92 mmol), camphorsulfonic acid (0.10 g, 0.44 mmol), and ethanol (10 mL) was heated at reflux for 5.5 h and then concentrated. Basic workup (5 mL of 1 N NaOH, CH_2Cl_2, Na_2CO_3) followed by silica gel chromatography (90:10:1 hexane/ethyl acetate/Et_3N) gave 91 mg (81%) of a colorless liquid. GC analysis[21] showed that this material was greater than 98% isomerically pure: IR (CCl_4) 1714 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.4–7.2 (m, s at 60 MHz, Ph), 3.19 (br s, half-height width = 5 Hz, H_{7a}), 2.78 (dd, J = 5.6 Hz, 12.9 Hz, $H_{3\alpha}$), 2.4–1.9 (m, 3 CH_2, Me), 1.09 (d, J = 6.2 Hz, $CHMe$); ^{13}C NMR (63 MHz, $CDCl_3$) 210.3, 141.2, 128.8, 126.6, 126.4, 70.4, 61.6, 59.3, 41.6, 39.6, 37.4, 23.3, 21.4, 19.9; MS (isobutane CI), m/z 244 (MH^+), 243, 228; (EI), m/z 243.162 (243.162 calcd for $C_{16}H_{21}NO$).

***trans*-2-Hexyl-1-methyl-4-oxo-3a-phenyl-*cis*-octahydroindole (40).** A solution of **11** (0.15 g, 0.67 mmol), freshly distilled heptanal (0.10 mL, 0.76 mmol), camphorsulfonic acid (0.15 g, 0.67 mmol), and ethanol (10 mL) was treated exactly as described for the preparation of **39** to give, after chromatography (silica gel, 100:1 hexane/Et_3N), 0.17 g (77%) of a colorless oil, which was one spot by TLC analysis (90:10:1 hexane/ethyl acetate/Et_3N). GC analysis[21] showed that this sample contained 5% of an impurity of similar retention time. The following are spectral data for **40**: IR (CCl_4) 1714 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.36–7.17 (m, s at 60 MHz, Ph), 3.16 (br s, half-height width = 5.5 Hz, H_{7a}), 2.85 (dd, J = 5.1, 13.8 Hz, $H_{3\alpha}$), 2.4–1.9 (m, 3 CH_2, NMe), 0.88 (m, Me); ^{13}C NMR (63 MHz, $CDCl_3$) 210.0, 141.2, 128.8, 126.6, 126.4, 70.3, 64.6, 61.6, 39.8, 39.6, 37.8, 34.0, 31.9, 29.5, 26.5, 22.6, 23.2, 21.3, 14.0; MS (isobutane CI), m/z 314 (MH^+), 312, 228; MS (EI), m/z 313.237 (313.241 calcd for $C_{21}H_{31}NO$).

***trans*-2-Methyl-4-oxo-3a-phenyl-*cis*-octahydroindole (42).** A mixture of **41**[10b] (24 mg, 0.12 mmol), camphorsulfonic acid (24 mg, 0.10 mmol), freshly distilled acetaldehyde (32 μL, 0.59 mmol), and ethanol (2 mL) was heated at reflux for 4 h. Workup, as described for the preparation of **39**, gave 18 mg (66%) of a yellow oil, which was one spot by TLC analysis. No evidence of other products was seen in the 250-MHz ^1H NMR spectrum. The following are spectral data for **42**: IR (CCl_4) 1710 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.37–7.12 (m, Ph), 4.10 (m, half-height width = 6.7 Hz, H_{7a}), 3.30 (ddq, J = 5.8, 6.3, ~10.0 Hz, $H_{2\beta}$), 2.83 (dd, J = 5.9, 13.3 Hz, $H_{3\alpha}$), 2.36–1.78 (m, 3 CH_2, $H_{3\beta}$, NH), 1.16 (d, J = 6.3 Hz, Me); ^{13}C NMR (63 MHz, $CDCl_3$) 211.4, 141.3, 128.8, 126.7, 126.5, 64.2, 63.4, 50.7, 43.9, 39.5, 25.8, 22.5, 22.1; MS (isobutane CI), m/z 230 (MH^+). N-Methylation of **42** (MeI, NaH, THF) gave, in good yield, **39** as a light yellow oil, which was identical (TLC, ^1H NMR, ^{13}C NMR) with a sample of **39** prepared from amino alcohol **11**.

Similar treatment of **41** with 1–2 equiv of paraformaldehyde in EtOH (or benzene) gave *cis*-octahydroindolone **25** (mp 60–62 °C) in 50–70% yield. No trace of trans stereoisomer **29** could be seen in the ^1H NMR spectra of crude product mixtures.

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Registry No. (±)-**8**, 79076-02-1; (±)-**9**, 79076-04-3; (±)-**10**, 79076-05-4; (±)-**11**, 79076-06-5; (±)-**12**, 79076-12-3; (±)-**13**, 87014-52-6; (±)-**14**, 33092-86-3; (±)-**15**, 87014-53-7; (±)-**16**, 79076-03-2; (±)-**17**, 87014-54-8; (±)-**19**, 87014-55-9; (±)-**20**, 87014-56-0; (±)-**21**, 79076-10-1; (±)-**22**, 79076-07-6; (±)-**23**, 87014-57-1; (±)-**24**, 79085-72-6; (±)-**25**, 87014-58-2; (±)-**26**, 79076-11-2; (±)-**27**, 87014-59-3; (±)-**28**, 87039-35-8; (±)-**29**, 87014-60-6; (±)-**30**, 87014-61-7; (±)-**31**, 87014-62-8; (±)-**32**, 83196-16-1; (±)-**33**, 83196-17-2; (±)-*trans*-**33**, 87014-63-9; (±)-**34**, 83196-18-3; (±)-**35**, 87014-64-0; (±)-**36**, 87014-65-1; (±)-**37**, 87014-66-2; (±)-**39**, 87014-67-3; (±)-**40**, 87014-68-4; (±)-**41**, 87014-69-5; (±)-**42**, 87014-70-8; (±)-*trans*-2-(dimethylamino)cyclopentanol, 87014-71-9; α-bromostyrene, 98-81-7; phenyl chloroformate, 1885-14-9; (±)-*trans*-2-bromocyclopentanol, 87014-72-0; (1-phenylethenyl)lithium, 45680-22-6; 1-bromo-1-(3,4-(methylenedioxy)phenyl)ethylene, 87014-73-1; (±)-*trans*-2-(methylamino)cyclopentanol, 87014-74-2; (±)-*trans*-2-[methyl(cyanomethyl)amino]cyclopentanol, 87014-75-3; benzyl(cyanomethyl)amine, 3010-05-7; 1,2-bis((triethylsilyl)oxy)cyclopentene, 6838-66-0; [(1-(3,4-(methylenedioxy)phenyl)ethenyl]lithium, 79076-14-5; vinyllithium, 917-57-7; acetaldehyde, 75-07-0; 3,4-(methylenedioxy)-styrene, 7315-32-4.