lution was diluted with 50 ml of ether and washed successively with 50 ml of water and 50 ml of saturated NaCl solution. After drying over potassium carbonate, the solvent was removed, yielding 400 mg of product. Analysis of this crude material by GLC (10 ft × 0.25 in. 15% NPGS, 175°, 120 ml/min) indicated that it consisted of three components: 36.2% **10** (retention time 4.0 min), 34.8% **11** (retention time 4.4 min), and 30.0% C-methylated ketone (retention time 8.2 min). This was rather surprising, since enolate equilibration is not usually encountered under the reaction conditions employed. To check if the observed equilibration was taking place in the chromatograph, the remaining product was purified by column chromatography (15 g of Silicar CC-7, 200–325 mesh, 10% ether–hexane elutant). This was indeed the case as the 200 mg of enol ether obtained from the chromatography column was identified as pure **10**. See Figure 9 (supplementary material) for the mass spectrum of **10**: ir (neat) 1665 (enol ether), 889 cm^{-1} (methallyl double bond); ^1H NMR (CCl_4) τ 5.33 (m, 1, vinyl H), 6.55 (s, 3, enol Me), 8.27 (s, 3, vinyl Me), 9.03 (d, 3, ring Me).

A sample of **11** was obtained by preparative GLC of the initial crude product. See Figure 10 (supplementary material) for the mass spectrum of **11**: ir (neat) 1665 (enol ether), 890 cm^{-1} (methallyl double bond).

Acknowledgment. The authors express their gratitude to the National Science Foundation for support of this research under Grant GP 31321X.

Registry No.—**1**, 55373-31-4; **2**, 55373-32-5; **3**, 55373-33-6; **4**, 55373-34-7; **5**, 55373-35-8; **6**, 55449-02-0; **7**, 55449-03-1; **8**, 55373-36-9; **9** epimer 1, 55373-37-0; **9** epimer 2, 55373-38-1; **10**, 55373-39-2; **11**, 55373-40-5; **14**, 55373-41-6; 1-trimethylsiloxy-*trans*-3-allyl-5-methylcyclohex-1-ene, 55373-42-7; potassium amide, 17242-52-3; butyl iodide, 542-69-8; 1-trimethylsiloxy-*cis*-3-methallyl-5-methylcyclohex-1-ene, 55400-55-0; isobutyl chloride, 513-36-0; 5-methylcyclohex-2-en-1-one, 7214-50-8; trimethylchlorosilane, 75-77-4; 1-trimethylsiloxy-*trans*-3-isobutyl-5-methylcyclohex-1-ene, 55373-43-8; 1-trimethylsiloxy-*trans*-3-methylallyl-5-methylcyclohex-1-ene, 55373-44-9.

Supplementary Material Available. Mass spectra of compounds **4–11** will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2160.

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A Synthetic Approach to the Dendrobine Skeleton

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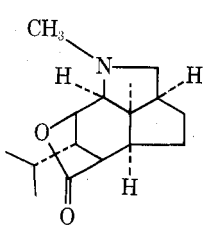
A possible synthetic route to the alkaloid dendrobine has been explored. Intramolecular Michael cyclization of unsaturated keto nitrile **17** yields only stereoisomer **18**. The stereochemistry of **18** has been established by the synthesis of a compound with the opposite stereochemistry of the cyanomethyl side chain (**28**). A rationale for the stereospecificity of the cyclization reaction is proposed.

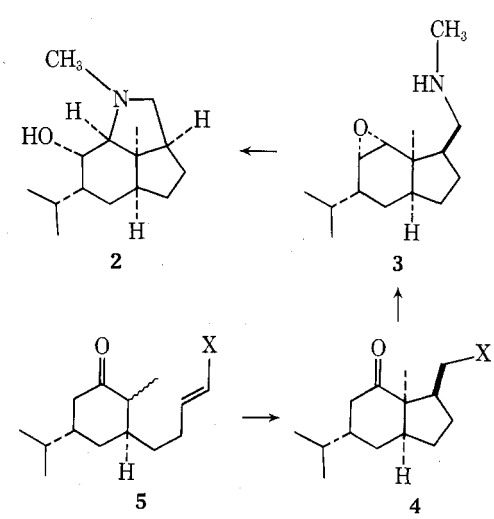
The sesquiterpene alkaloid dendrobine (**1**) occurs as a component of the Chinese drug Chin-Shih-Hu, which is prepared from the ornamental orchid *Dendrobium nobile* (Orchidaceae). It was first isolated from the stem of the



1

plant by Suzuki and coworkers.[1] Recently, the alkaloid, as well as a number of its congeners, has been extensively investigated by Hirata,[2] Inubushi,[3] and Okamoto,[4] who have determined the stereostructure shown in **1**. Dendrobine's interesting structure has elicited considerable attention from synthetic chemists, resulting in three total syntheses of the alkaloid itself[5–7] as well as a synthesis of the basic tricyclic skeleton.[8] In this communication we outline our own approach to the synthesis of the alkaloid.

In our projected synthesis of the basic skeleton, presented below in gross outline, the key step would be the Michael reaction **5** → **4**. The group X must be the synthetic

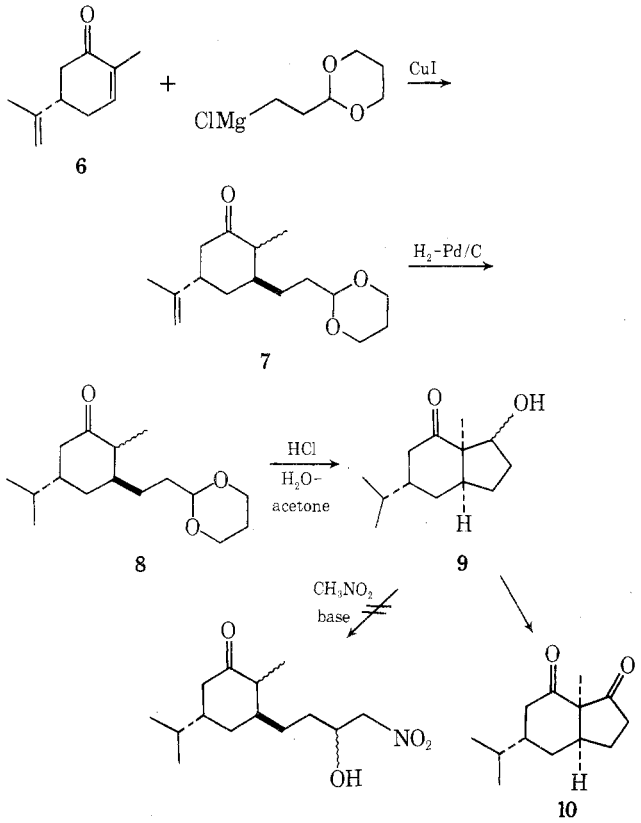


2 **3** **5** **4**

equivalent of $NHCH_3$, i.e., NO_2, CO_2R, CN, etc. Although the cis fusion of the product hydrindanone **4** could reasonably be expected,[9] the steric disposition of CH_2X in such a reaction is difficult to predict. As will be seen in the sequel, the desired intramolecular Michael reaction does indeed occur readily when X = CN, albeit in precisely the opposite steric sense. Although we were able to invert the stereo-

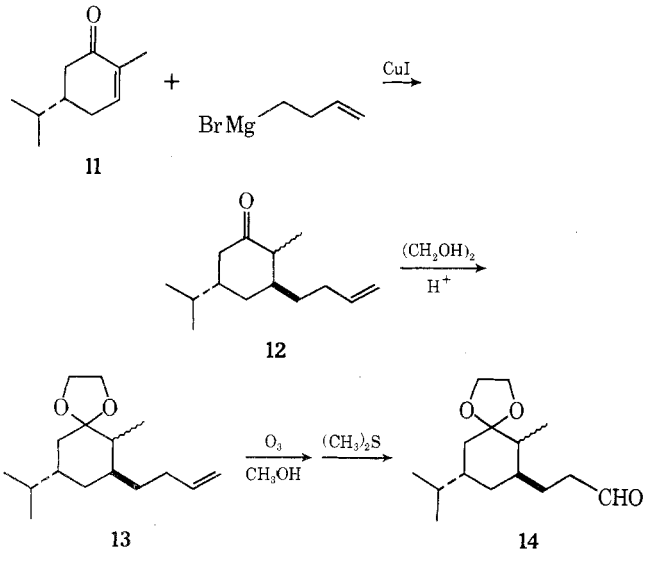
chemistry of the cyanomethyl side chain, the resulting synthesis of **4**, R = CN, is too awkward for use in a synthesis of the alkaloid.

For the preparation of compounds of type **5**, we began with (+)-carvone (**6**). Copper-catalyzed addition of the Grignard reagent derived from β-chloropropionaldehyde trimethylene acetal yields the keto acetal **7**, which is smoothly hydrogenated to **8**. The trans disposition of the groups at C-3 and C-5 is assumed by analogy with the conjugate addition of methylmagnesium bromide to 5-methylcyclohexenone.[10] Hydrolysis of **8**, even under very mild conditions, yields only the cyclic aldol **9**, which may be oxidized to dione **10** (ν_{max} 1755, 1710 cm^{-1}). Various attempts to utilize aldol **9** directly, e.g., in a Knoevenagel condensation with nitromethane, were unsuccessful.[11]

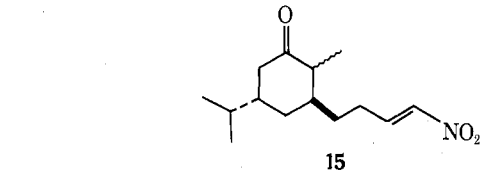


6 7 8 9 10

In order to circumvent this problem, we carried out the conjugate addition of 4-butenylmagnesium bromide onto (+)-carvotanacetone (**11**). The adduct **12** is smoothly ketalized and the resulting unsaturated ketal **13** reacts with ozone in methanol to give ketal aldehyde **14**. After numerous unsuccessful attempts to convert **13** or **14** into nitroalkene **15**,[11] we decided to explore the use of an α,β-unsaturated nitrile as the Michael acceptor group in formation of the cyclopentane ring. To this end, aldehyde **14** was condensed with diethyl cyanomethylphosphonate after the method of Wadsworth and Emmons.[12] Unsaturated nitrile **16** is produced in this research in good yield, as a mixture of geometric isomers. Hydrolysis of **16** yields the corresponding cyano ketone **17**, which reacts with potassium *tert*-butoxide in *tert*-butyl alcohol to yield hydrindanone **18**. The ^1H NMR spectrum of **18**, at 60 and at 220 MHz, shows the angular methyl group as a sharp singlet at δ 1.10 ppm, with an intensity 50% that of the isopropyl doublet at δ 0.92 ppm, suggesting that a single stereoisomer is produced in the cyclization.



11 12 13 14



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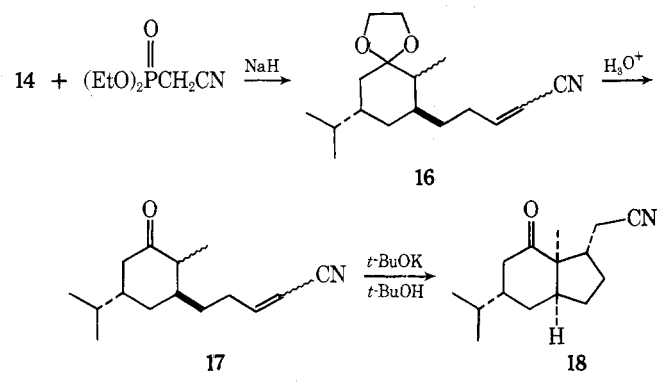
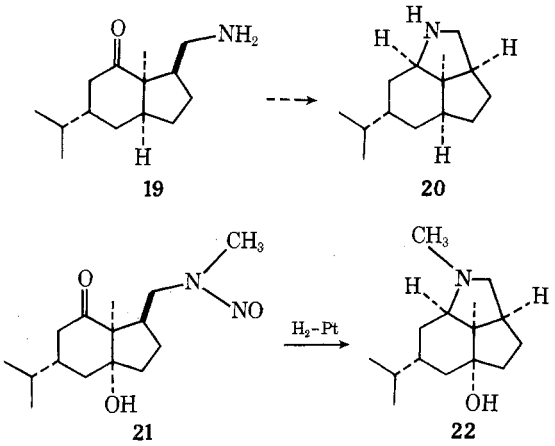


16 17 18

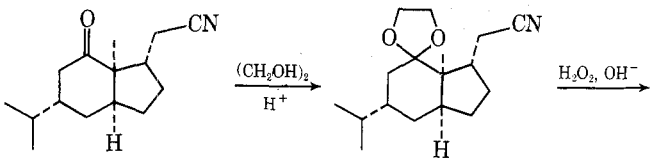
In order to determine the stereochemistry of the cyanomethyl side chain in **18**, we decided to convert it into an amino ketone, which should undergo reductive amination to yield the tricyclic amine **20** if the cyanomethyl group is trans to the angular methyl (e.g., **19**). The related bicyclic amine *N*-nitroso-6-hydroxynornobilonine (**21**) has previously been cyclized to yield dendramine (**22**) by treatment with hydrogen at atmospheric pressure over Adams catalyst.[13] Examination of Dreiding stereomodels suggests that the ring closure is not possible when the aminomethyl group is cis to the angular methyl.



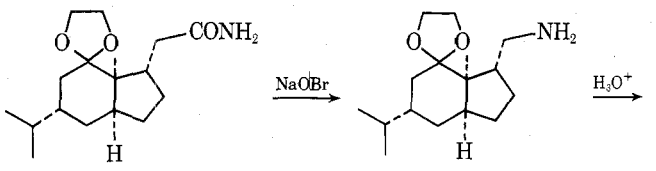
19 20 21 22

Toward this end, **18** was ketalized and ketal **23** was hydrolyzed to amide **24**. Hofmann degradation of **24** yields amine **25**, which may be hydrolyzed to amino ketone **26**. All attempts at the reductive cyclization of **26** failed,[11] suggest-

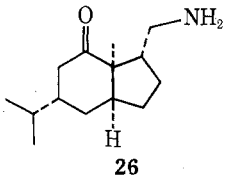
ing that the aminomethyl group indeed has the α configuration.[14]



18 23

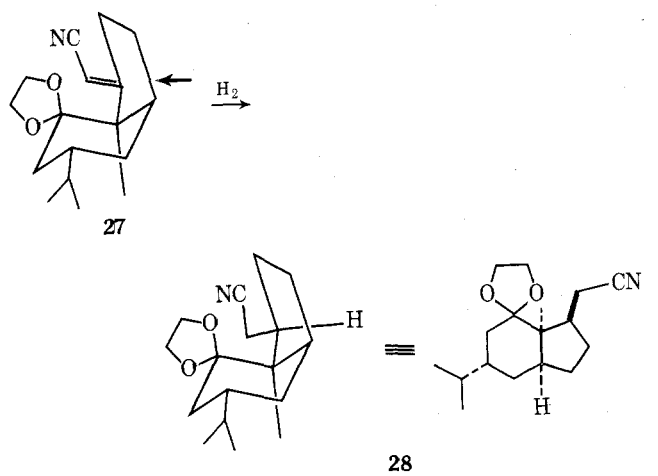


24 25



26

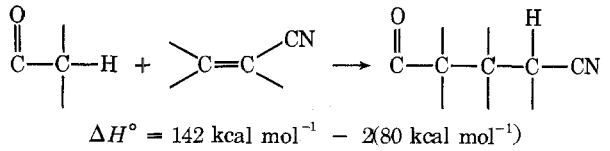
In order to provide more definitive evidence for the suspected stereochemistry of **18**, we decided to invert the stereochemistry of the cyanomethyl group and examine the resulting epimer. Examination of Dreiding models reveals that the ketal oxygen so encumbers the β face of unsaturated nitrile **27** that catalytic hydrogenation of the double



27 28

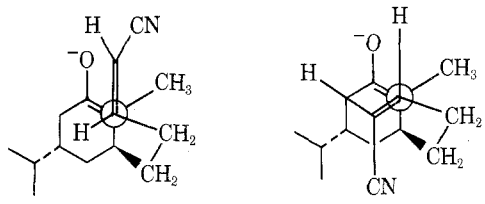
bond is highly likely to produce the desired β configuration[14] at the new chiral center. As suspected, compound **27**, prepared from **23** by selenylation, followed by elimination of the derived selenoxide,[16] gives a ketal nitrile isomeric with **23** upon catalytic hydrogenation.

On the basis of the failure of **26** to cyclize and the β-face hindrance in **27**, it seems clear that the cyanomethyl group is α in **23** and β in **28**. In searching for an explanation for the observed stereospecificity, we must first ask whether the stereochemistry is established thermodynamically or kinetically. An estimate of the overall reaction energetics involved in the conversion of one carbon–carbon double bond into two carbon–carbon single bonds predicts $\Delta H^\circ \approx -18$ kcal mol^{-1}.[17] Thus, the reverse Michael reaction (**18** → **17**) must have $E_{act} \approx 18$ kcal mol^{-1} greater than for the forward reaction (**17** → **18**). From this estimate of ΔE_{act}, the ratio $k_{reverse}/k_{forward} \approx 3 \times 10^{-12}$. Furthermore, a simple experiment showed that the α hydrogens in octanonitrile are not exchanged for deuterium under conditions more drastic than the conditions required to convert **17** into **18**.[18] Thus, it is reasonable to assume that the cyclization is effectively irreversible under the conditions employed and that **18** is, in fact, a kinetic product.



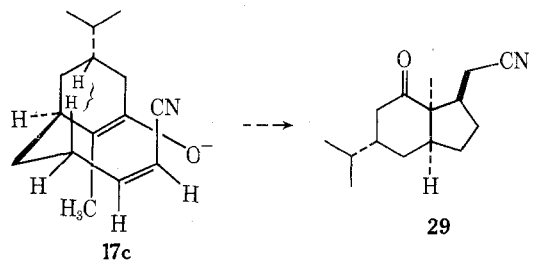
ΔH° = 142 kcal mol^{-1} − 2(80 kcal mol^{-1})

The observed stereochemical result probably has its origin in steric effects in the two alternate transition states. An examination of Dreiding stereomodels reveals that there are three reasonable conformations whereby the enolate ion derived from **17** may cyclize.[19] In two of the conformations, the two reacting double bonds are staggered relative to one another at a dihedral angle of approximately 60° (see structures **17a** and **17b**, below). Conformation **17b**,



17a 17b

in which the side-chain double bond lies directly over the cyclohexane ring, appears to be far less stable than **17a**, which gives rise to the observed product, **18**. Like **17b**, a third conceivable cyclizing conformation of **17**, depicted below in a different perspective, would also yield the β-cyanomethyl stereochemistry (**29**). However, this conformation suffers from a severe H–H interaction, as indicated. The internuclear distance between the two interacting hydrogens is only 1.6 Å.[20]



17c 29

In principle, compound **28** may serve as a synthetic intermediate for further elaboration into dendrobine. However, in light of the success of other workers in synthesizing the alkaloid,[5-7] we have abandoned further work on the project.

Experimental Section

All melting and boiling points are uncorrected. The nuclear magnetic resonance (NMR) spectra were determined on a Varian T-60 or HR-220 spectrometer in CCl_4 solution containing tetramethylsilane as internal standard. Chemical shifts are given on the δ scale; the multiplicity, peak areas, and proton assignments are given in parentheses. The infrared (ir) spectra were measured as thin films between NaCl plates on a Perkin-Elmer 137 or 237 infrared spectrophotomer unless otherwise indicated. Consolidated 21-110B and AEI MS-12 mass spectrometers provided the mass spectra. Microanalyses were performed by the University of California Microanalytical Laboratory, Berkeley, Calif.

2-Methyl-3β-(3-trimethylenedioxypropyl)-5α-isopropenylcyclohexanone (7). To a 300-ml round-bottom flask equipped with a dropping funnel (pressure equalized), magnetic stirrer, reflux condenser, and a N_2 inlet tube was added 1.22 g (0.05 mol) of magnesium turnings. The N_2 purge was started and maintained throughout the reaction; the flask and dropping funnel were carefully flamed using a soft flame in order to remove traces of moisture. A 20-ml portion of dry tetrahydrofuran (THF) was added to

the flask along with a small crystal of iodine. A few drops of β-chloropropionaldehyde trimethylene acetal[21] were added and the stirred reaction mixture was refluxed for 15 min; however, the reaction failed to commence. A few drops of ethyl iodide were added and the mixture was refluxed briefly; the iodine coloration disappeared and was replaced by a faint cloudiness. Dropwise addition of a solution of the chloroacetal (7.53 g, 0.05 mol, 6.54 ml) in 10 ml of dry THF was started, and the reaction mixture now developed a dark color, indicating that the reaction was underway. The reaction mixture was occasionally heated to reflux during addition of the chloroacetal solution over a 45-min period.

After refluxing for 75 min, during which time almost all of the magnesium was consumed, the reaction mixture was diluted with 30 ml of dry THF and cooled to 0° by stirring in an ice bath for 20 min. Cuprous iodide (0.476 g, 0.0025 mol, 5 mol % based on Mg) was added to the stirred solution at 0°, and stirring was continued for an additional 20 min. A solution of (+)-carvone (7.51 g, 0.05 mol) in 10 ml of dry THF was added dropwise to the reaction mixture (0°) over a 10-min period and the solution was then stirred at 0° for 1 hr.

The mixture was poured into a cold (0°) aqueous solution (200 ml) of ammonia and ammonium chloride (pH ~8); the organic layer was separated and the aqueous layer was extracted with ether. The combined organic solutions were dried and the ether was evaporated. The residual liquid was fractionally distilled at reduced pressure to yield a forerun [bp 49–74° (2 mm), 1.69 g, mainly (+)-carvone and β-chloropropionaldehyde trimethylene acetal]. The main fraction was 5.43 g of **7** (41%) as a clear, viscous liquid, bp 157–167° (1 mm).

GLC analysis (20% Carbowax 20M, 60/80 Chromosorb W, 5 ft × 0.25 in., 206°, flow rate 80 ml/min) of the main fraction showed only one broad peak at 35.5-min retention time. There was no trace of either (+)-carvone or the chloroacetal in the product.

Ir 2980, 2870, (C–H), 1715 (C=O), 1650 (alkene), 1150, 1075, 1010 cm^{-1} (C–O–C); NMR δ 1.00 (m, 3, Me), 1.75 (s, 3, vinyl Me), 3.85 (m, 5, CH next to O), 4.72 (broad s, 2, CH_2=); low-resolution mass spectrum M^+ *m/e* 266.

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.32; H, 9.68.

The above preparation was repeated using carefully redistilled (+)-carvone and chloroacetal, and the Grignard reagent was prepared at 48–50° for 20 hr to ensure complete reaction. Also, the conjugate addition reaction mixture was stirred at 0° for 8 hr instead of only 1 hr. These modifications gave, upon work-up in the above manner, 6.97 g (52.5%) of adduct **7**.

2-Methyl-3β-(3-trimethylenedioxypropyl)-5α-isopropylcyclohexanone (8). To a 125-ml round-bottom hydrogenation flask fitted with a ground glass joint and a Teflon-coated magnetic stirring bar were added the following: conjugate addition product **7** (3.81 g, 14.3 mmol), 10% Pd/C (191 mg, 5 wt % based on **7**), and ethyl acetate (50 ml). The stirred reaction mixture was hydrogenated at 23–24° over a 25.5-hr period during which 360.8 ml (92% of theory) of H_2 was taken up at atmospheric pressure. The catalyst was removed by filtration and the solvent was evaporated to give a residual yellow oil which was purified by distillation at reduced pressure to yield 2.89 g (75.4% of theory) of clear, colorless liquid product, bp 149–152° (0.5 mm).

GLC analysis (4% FFAP, 198°, flow rate ~120 ml/min) of the clear liquid product shows two major peaks: hydrogenated conjugate adduct (91%, 18.8 min) and starting conjugate adduct (9%, 21.2 min).

Ir 2980, 2880 (C–H), 1720 (C=O), 1150, 1080, 1010 cm^{-1} (C–O–C); NMR δ 0.93 (d, 9, CH_3 and isopropyl), 1.43 (m, CH_2), 3.90 (m, 5, CH next to O); high-resolution mass spectrum M^+ *m/e* 268.2043 (calcd for $C_{16}H_{28}O_3$, 268.2041, Δm = +0.2 mmu).

Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.35; H, 10.46.

3aα,4,5,7a-Tetrahydro-1-hydroxy-5α-isopropyl-7aα-methyl-7(6*H*)-indanone (9). To a 50-ml round-bottom flask equipped with a ground glass joint and a Teflon-coated magnetic stirring bar were added the following: keto acetal **7** (1.72 g, 6.4 mmol), 90% aqueous acetone containing 1.34% HCl (20 ml). The solution was stirred under N_2 at room temperature for 72 hr. After a normal work-up, aldol **9** was obtained as a dark yellow oil. Distillation at reduced pressure through a short-path still gave 0.816 g (60.7%) of nearly colorless, clear liquid product: bp 125–130° (0.5 mm); ir 3450 (HO), 2980 (C–H), 1710 (C=O), 1470, 1070 cm^{-1}; NMR δ 0.92 (d, 6, isopropyl), 1.11 (s, 3, angular CH_3), 3.52 (broad s, 1, HO), 4.42 (broad s, 1, CH next to OH); high-resolution mass spectrum M^+ *m/e* 210.1621 (calcd for $C_{13}H_{22}O_2$, 210.1619, Δm = +0.2 mmu).

3aα,4,5,7a-Tetrahydro-5α-isopropyl-7aα-methyl-1,7(2*H*,6*H*)-indanedione (10). To a 50-ml round-bottom flask equipped with a Teflon-coated magnetic stirring bar and a reflux condenser fitted with a drying tube filled with Drierite were added CH_2Cl_2 (5 ml) and pyridine (0.273 g, 0.278 ml, 34.44×10^{-4} mol). The solution was stirred, and CrO_3 (0.1728 g, 17.28×10^{-4} mol) was added in one portion. The deep burgundy solution was then stirred at room temperature (29°) for 30 min. A solution of keto alcohol **9** (0.0603 g, 2.87×10^{-4} mol) in a small volume of CH_2Cl_2 was added in one portion; a black, tarry precipitate separated immediately. The solution was allowed to stir at room temperature (31°) for 30 min, after which ether (25 ml) was added, and the organic layer was washed with water (5 × 5 ml) followed by drying over anhydrous $MgSO_4$. The solvent was removed at reduced pressure (rotary evaporator, 40°, 1 hr) to give an amber oil still containing pyridine. The oil was dried in vacuo (1 mm, 55°, 3 hr) to give 0.0422 g (70.6%) of liquid product: ir 2950 (C–H), 1755 (cyclopentanone C=O), 1710 cm^{-1} (cyclohexanone C=O); NMR δ 0.93 (d, 6, isopropyl), 1.20 (s, 3, angular CH_3), 2.00 (m, 11, CH_2); low-resolution mass spectrum M^+ *m/e* 208.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.71; H, 9.42.

2-Methyl-3β-(3-butenyl)-5α-isopropylcyclohexanone (12). To a 200-ml round-bottom three-necked flask equipped with a pressure-equalized dropping funnel, mechanical stirrer (Teflon paddle), reflux condenser, and a N_2 purge bubbler was added 1.22 g (0.05 mol) of magnesium turnings. A solution of 6.75 g (0.05 mol) of 4-bromo-1-butene in 10 ml of dry THF was added to the dropping funnel; a few drops of alkenyl halide were added to the reaction flask along with a small crystal of iodine. The reaction was initiated by heating to reflux. The solution of alkenyl halide was added dropwise to the stirring, refluxing mixture of THF–Mg over a 50-min period. The solution was then refluxed for an additional 6 hr, after which almost all of the magnesium had been consumed. A 50-ml portion of dry THF was added and the solution was cooled to 0° over a 20-min period, during which a white precipitate formed in the dark solution.

To the stirring mixture at 0° was added 0.4883 g (2.56 mmol, 5.12 mol % based on Mg) of CuI in one portion. After 50 min at 0°, a solution of 7.61 g (0.05 mol) of carvotanacetone (**11**) in 10 ml of dry THF was added in a dropwise manner over a 15-min period. The reaction mixture was stirred overnight at 0° and was then poured into 400 ml of a cold solution of aqueous NH_3–NH_4Cl (pH ~8). The organic layer was separated and the aqueous phase was extracted with ether. The organic layers were combined, dried, and evaporated to give 8.95 g (86%) of amber oil which was distilled (9-in. Vigreux) to give fraction 1 [0.57 g, bp 63–103° (1.2 mmHg), carvotanacetone], fraction 2 [5.57 g, bp 107–108° (1.2 mmHg), 52.4%], and finally, by replacement of the fractionating column with a short-path still, fraction 3 [0.93 g, bp 169–172° (0.1 mmHg)].

GLC analysis of fraction 2 (4% FFAP, 10 ft × 0.25 in., 172°, 120 ml/min) shows the presence of ca. 98% pure product at retention time 2.6 min.

Ir 2950, 2930, 2870 (C–H), 1710 (C=O), 1640 (alkene), 910 (CH_2=); NMR δ 0.95 (d, 6, isopropyl), 0.95 (s, 3, CH_3 next to carbonyl), 4.99 (m, 2, CH_2=), 5.70 (m, 1, vinyl H next to CH_2=); high-resolution mass spectrum M^+ *m/e* 208.1821 (calcd for $C_{14}H_{24}O$: 208.1827, Δm = −0.6 mmu).

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.84; H, 11.82.

2-Methyl-3β-(3-oxopropyl)-5α-isopropylcyclohexanone Ethylene Ketal (14). A solution of 2.52 g of ketal **13** in 10 ml of methanol was cooled to −65° and ozonized on a commercial Welsbach ozonator (0.1 mmol O_3/min) for 100 min (10 mmol O_3). The cold solution was flushed with N_2 for 40 min and then 1.0 ml (13.5 mmol) of dimethyl sulfide was added. The solution was then stirred at −12 to −4° for 1 hr, then at ice-bath temperature (0°) for 1 hr, and finally at room temperature for 70 min. After evaporation of the solvent at reduced pressure, the residue was treated with 25 ml of water and 40 ml of light petroleum ether. The aqueous layer was separated and further extracted with petroleum ether. The combined organic layer was washed with water, dried, and evaporated to give 2.37 g (93.4% yield) of viscous, clear liquid.

GLC (4% FFAP, 10 ft × 0.25 in., 196°, 100 ml/min) shows the presence of ca. 95% pure ketal aldehyde (14.0 min) with a small amount of lower boiling material (1.75, 2.1, 3.1 min).

Ir 2990, 2900 (C–H), 2740 (aldehyde C–H), 1725 (CHO), 1170, 1150, 1095, 1075, 1040, 950 cm^{-1} (C–O–C); NMR δ 0.90 (t, 9, CH_3, isopropyl), 1.41 (m, CH_2), 3.82 (s, 4, OCH_2), 9.44 (t, 1, aldehyde H); low-resolution mass spectrum M^+ *m/e* 255; 141.

Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.59; H, 10.27.

2-Methyl-3β-(4-cyano-3-butenyl)-5α-isopropylcyclohexanone Ethylene Ketal (16). To a 25-ml round-bottom three-necked flask equipped with a Teflon-coated magnetic stirring bar, N_2 gas bubbler, and a serum cap was added NaH (0.21 g of a 57% dispersion in mineral oil, 0.120 g NaH, 5 mmol). The NaH was freed of mineral oil by washing with dry pentane. Dry glyme (5 ml) was added and the stirred suspension was cooled to 20°. Diethyl cyanomethylphosphonate (0.89 g, 5 mmol) was added dropwise over a 15-min period and the solution was stirred at room temperature for 35 min. At this point, a solution of ketal aldehyde **14** (1.27 g, 5 mmol) in dry glyme (2.5 ml) was added in a dropwise fashion over a 15-min period; during the addition a gummy precipitate separated. The reaction mixture was stirred at room temperature for 2 hr and then diluted with 30 ml of water. The resulting mixture was extracted with ether and the organic layer was washed with water and saturated aqueous NaCl, dried, and evaporated to give 1.18 g (86%) of amber liquid.

GLC analysis (4% FFAP, 10 ft × 0.25 in., 210°, 120 ml/min) showed two major components (*E* and *Z* stereoisomers) with retention times of 33.3 and 36.5 min.

Ir 3020, 2950, (C–H), 2240 (CN), 1630 (alkene), 1170, 1150, 1100, 1080, 1045, 950 cm^{-1} (C–O–C); NMR δ 0.89 (d, 9, CH_3, isopropyl), 1.42 (m, CH_2), 3.83 (s, 4, OCH_2CH_2O), 5.26 (m, 1, vinyl H α to CN), 6.56 (m, 1, vinyl H β to CN); low-resolution mass spectrum M^+ *m/e* 277.

Anal. Calcd for $C_{17}H_{27}NO_2$: C, 73.61; H, 9.81; N, 5.05. Found: C, 73.34; H, 9.66; N, 5.05.

2-Methyl-3β-(4-cyano-3-butenyl)-5α-isopropylcyclohexanone (17). A solution of 0.450 g (1.62 mmol) of ketal **16** in a mixture of 8 ml of formic acid and 2 ml of water was stirred at room temperature for 15 min and then poured into 50 ml of distilled water. After a normal work-up procedure, 0.354 g of ketone **17** was obtained as an amber liquid (94%).

GLC analysis (4% FFAP, 10 ft × 0.25 in., 249°, 120 ml/min) shows the presence of virtually pure product as a mixture of epimers and geometric isomers (50:50) about the double bond.

Ir 3020, 2940 (C–H), 2230 (α,β-unsaturated CN), 1710 (C=O), 1630 cm^{-1} (alkene); NMR δ 0.95 (t, 9, CH_3, isopropyl), 1.68 (m, CH_2), 2.22 (m, allylic CH_2), 5.36 (m, 1, vinyl H α to CN), 6.58 (m, 1, vinyl H β to CN); low-resolution mass spectrum M^+ *m/e* 233.

Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 76.89; H, 9.79; N, 6.27.

3aα,4,5,7a-Tetrahydro-1α-cyanomethyl-5α-isopropyl-7aα-methyl-7(6*H*)-indanone (18). To a 10-ml pear-shaped flask equipped with a Teflon-coated magnetic stirring bar were added potassium *tert*-butoxide (0.0052 g, 0.0465 mmol, 13.5 mol % based on ketone) and dry *tert*-butyl alcohol (0.3 ml). To the stirred solution at room temperature was added dropwise a solution of keto nitrile **17** (0.0798 g, 0.343 mmol) in dry benzene (0.2 ml). The solution was then stirred at 65–70° for 2 hr and reaction was then quenched by the addition of acetic acid (2.79 μl, 0.0465 mmol). The reaction mixture was poured into 20 ml of distilled water and extracted with ether. The organic layer was washed with water and saturated aqueous NaCl, dried, and evaporated at reduced pressure to give 0.0718 g (90%) of amber liquid.

GLC analysis (4% FFAP, 10 ft × 0.25 in., 248°, 120 ml/min) shows the almost completely pure product (85%) as a single isomer (13.0 min).

Ir 3020, 2940 (C–H), 2270 (CN), 1710 cm^{-1} (C=O); NMR δ 0.92 (d, 6, isopropyl), 1.10 (s, 3, angular CH_3), 1.67 (m, CH_2), 2.24 (m, allylic H) (14 H); low-resolution mass spectrum M^+ *m/e* 233.

Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 76.94; H, 9.69; N, 6.13.

The 220-MHz NMR spectrum shows the clear presence of isopropyl and angular CH_3 protons in a ratio of 2:1 in accord with a single bicyclic isomer.

3aα,4,5,7a-Tetrahydro-1α-cyanomethyl-5α-isopropyl-7aα-methyl-7(6*H*)-indanone Ethylene Ketal (23). To a 50-ml round-bottom flask equipped with a Teflon-coated magnetic stirring bar, small Soxhlet extractor containing a thimble filled with CaH_2 (4.2 g, 100 mmol), reflux condenser, and a N_2 gas bubbler were added keto nitrile **18** (0.268 g, 1.15 mmol), ethylene glycol (0.750 g, 12.10 mmol, 10.5 equiv), 2-naphthalenesulfonic acid (0.0228 g, 0.11 mmol, 9.6 mol %), and dry benzene (10 ml). The stirred reaction mixture was refluxed under N_2 for 22.5 hr, during which periodic GLC analysis (4% FFAP, 10 ft × 0.25 in., 250°, 120 ml/min) showed the disappearance of starting bicyclic keto nitrile (retention time 10 min) and the appearance of the product (retention time 11.5 min). The reaction mixture was cooled and poured into 20 ml of 5% aqueous $NaHCO_3$, and the mixture was extracted with ether. The combined organic solution was washed with 5% aqueous $NaHCO_3$, water, and saturated aqueous NaCl and dried. The solvent was removed at reduced pressure to give 0.315 g (99%) of amber liquid.

GLC analysis (4% FFAP, 10 ft × 0.25 in., 250°, 120 ml/min) showed the product to be virtually pure ketal.

Ir 3020, 2940 (C–H), 2260 (CN), 1120, 1050, 1035, 1000, 950 cm^{-1} (C–O–C); NMR δ 0.88 (d, 6, isopropyl), 1.00 (s, 3, angular CH_3), 1.42 (m, CH_2), 2.20 (m, allylic H), 3.82 (broad s, 4, OCH_2CH_2O); low-resolution mass spectrum *m/e* 277 (M^+), 234 (M^+ − 43, loss of isopropyl).

Anal. Calcd for $C_{17}H_{27}NO_2$: C, 73.61; H, 9.81; N, 5.05. Found: C, 73.27; H, 9.89; N, 4.97.

3aα,4,5,7a-Tetrahydro-1α-acetamido-5α-isopropyl-7aα-methyl-7(6*H*)-indanone Ethylene Ketal (24). To a 10-ml pear-shaped flask equipped with a Teflon-coated magnetic stirring bar were added bicyclic ketal nitrile **23** (0.0925 g, 0.333 mmol), 95% EtOH (0.328 ml), 30% aqueous H_2O_2 (0.133 ml, 1.15 mmol), and 5 *M* NaOH (0.016 ml, 0.08 mmol). The solution was stirred under N_2 at 69–70° for 2 hr and then poured into 20 ml of distilled water. The product amide was isolated as a viscous, clear oil (0.0742 g, 75%) by ether extraction in the normal manner.

GLC analysis (4% FFAP, 10 ft × 0.25 in., 250°, 120 ml/min) showed the product to be virtually pure (retention time 16.0 min).

Ir (10% w/v in CCl_4) 3450, 3320 (N–H), 3010, 2940 (C–H), 1670 (C=O, amide I band), 1610 (NH, amide II band), 1120, 1060, 1040, 1000, 950 cm^{-1} (C–O–C); NMR δ 0.88 (d, 9, CH_3, isopropyl), 1.43 (broad m, CH_2), 3.89 (broad s, 4, OCH_2CH_2O), 6.63 (broad, 2, amide NH_2); low-resolution mass spectrum *m/e* 295 (M^+), 252 (M^+ − 43, loss of isopropyl).

3aα,4,5,7a-Tetrahydro-1α-aminomethyl-5α-isopropyl-7aα-methyl-7(6*H*)-indanone Ethylene Ketal (25). To a cold mixture of 0.014 ml (0.276 mmol) of bromine, 0.502 ml (1.506 mmol) of 3 *M* NaOH, and 0.15 ml of water was added a solution of 0.0742 g (0.251 mmol) of amide **24** in 1.0 ml of 1,2-dimethoxyethane. The resulting mixture was stirred at room temperature for 0.5 hr and then at 70° for a further 1.5 hr. After this time, the mixture was diluted with 20 ml of water and extracted with ether. The ether extracts were washed well, dried, and evaporated to yield 0.0510 g of amine **25** (76%) as a clear oil: ir 3400, 3300 (N–H), 3000, 2930 (C–H), 1650 (N–H), 1120, 1040, 995, 950 cm^{-1} (C–O–C); NMR δ 0.89 (d, 9, CH_3, isopropyl), 1.43 (broad m, 16, CH_2 and NH_2), 3.89 (broad s, 4, OCH_2CH_2O); low-resolution mass spectrum *m/e* 267 (M^+), 252 (M^+ − 15, loss of CH_3), 224 (M^+ − 43, loss of isopropyl), 30 ($CH_2{=}NH_2^+$); high-resolution mass spectrum M^+ *m/e* 267.2205 (calcd for $C_{16}H_{29}NO_2$, 267.2198, Δm = 0.7 mmu).

Amine **25** was further characterized by conversion into its acetamide; 0.020 g of **25** was treated with 0.014 ml of acetic anhydride in 0.3 ml of pyridine at 100° for 1 hr. After a normal water–ether work-up, 0.020 g of the amide was obtained as a clear oil: ir (10% w/v in CCl_4) 3430 (N–H), 3010, 2930 (C–H), 1670 (C=O, amide I band), 1510 (NH, amide II band), 1115, 1035, 1000, 950 cm^{-1} (C–O–C); NMR δ 0.88 (t, 9, CH_3, isopropyl), 1.43 (broad m, CH_2), 1.82 (s, 3, CH_3CO), 3.00 (t, 2, CH_2N), 3.90 (broad s, 4, OCH_2CH_2O), 6.10 (broad, 1, NHCO); low-resolution mass spectrum *m/e* 309 (M^+), 266 (M^+ − 43, loss of acetyl or isopropyl), 72 ($CH_3CONHCH_2$), 43 (CH_3CO), 30 ($CH_2{=}NH^+_2$); high-resolution mass spectrum M^+ *m/e* 309.2335 (calcd for $C_{18}H_{31}NO_3$, 309.2303, Δm = 3.2 mmu).

3aα,4,5,7a-Tetrahydro-1α-aminomethyl-5α-isopropyl-7aα-methyl-7(6*H*)-indanone (26). A solution of 0.0195 g (0.073 mmol) of ketal amine **25** in 0.5 ml of 80% aqueous formic acid (80:20 HCO_2H–H_2O) was stirred at room temperature for 1 hr, then poured into 20 ml of H_2O and made basic with NaOH. The aqueous mixture was extracted with ether. After washing, the ether extract was dried and evaporated to yield 0.0150 g (92%) of amino ketone **26** as a clear oil: ir (10% w/v in CCl_4) 3420, 3300 (N–H), 3020, 2930 (C–H), 1710 (C=O), 1650 cm^{-1} (N–H); NMR δ 0.95 (d, 9, CH_3, isopropyl), 1.65 (broad m, 16, CH_2 and NH_2); low-resolution mass spectrum *m/e* 223 (M^+), 180 (M^+ − 43, loss of isopropyl), 30 ($CH_2{=}NH_2^+$); high-resolution mass spectrum M^+ − 43 *m/e* 180.1399 (calcd for $C_{11}H_{18}NO$, 180.1410, Δm = −1.1 mmu).

Amino ketone **26** resisted several attempts to convert it into a tricyclic amine. The following reaction conditions yielded only recovered starting material: (a) H_2 (15 psi) and Pt (200 wt %) in acetic acid at 25°; (b) H_2 (53 psi) and Pt (500 wt %) in acetic acid at 25°; (c) H_2 (1000 psi) and Pt (500 wt %) in acetic acid at 200°; and (d) $NaCNBH_3$ in a solution of 1 *M* HCl in methanol at 25° for 3 days.

3aα,4,5,7a-Tetrahydro-1-cyanomethylene-5α-isopropyl-7aα-methyl-7(6*H*)-indanone Ethylene Ketal (27). To a cold (0°) solution of 0.1458 g (1.03 mmol) of *N*-isopropylcyclohexylamine in 1.0 ml of THF was added 0.466 ml (1.00 mmol) of 2.145 *M* *n*-BuLi in hexane. The solution was allowed to warm to room temperature over a 30-min period, then was cooled to −76° and a solution of nitrile **23** (0.1387 g, 0.5 mmol) in 0.5 ml of dry THF was added over a 10-min period. After 35 min at −78°, the solution was warmed to room temperature and a solution of 0.1561 g (0.5 mmol) of diphenyl diselenide in 0.5 ml of dry THF was added dropwise over a 5-min period. The reaction mixture was stirred at room temperature for 2 hr and then diluted with 30 ml of water. The aqueous mixture was extracted with ether and the ether extract was washed well with cold 5% aqueous NaOH and water, and then dried. Evaporation of solvent gave a residual oil which was taken up in a mixture of 4 ml of ethyl acetate and 2 ml of THF. To this solution was added 0.13 ml (1.5 mmol) of 30% aqueous hydrogen peroxide and the resulting mixture was stirred at room temperature for 2 hr. It was then washed with water and 5% aqueous sodium carbonate and dried. Evaporation of solvent gave 0.1151 g of amber liquid.

GLC analysis (10% SF-96, 10 ft × 0.25 in., 240°, 120 ml/min) showed the presence of desired unsaturated nitrile **27** (8.1 min, ca. 50%) and starting nitrile **23** (8.8 min, 50%). The yield of product is, therefore, 42%. A pure sample of ketal nitrile **27** (19.4 mg) was collected by preparative GLC (4% FFAP, 10 ft × 0.25 in., 220°, 120 ml/min) along with starting ketal nitrile **23** (19.1 mg). The two compounds are separated under the column conditions used: **23** (13.5 min), **27** (10.0 min).

Ir (GLC fraction) 3020, 2930 (C–H), 2240 cm^{-1} (unsaturated CN); NMR (GLC fraction δ 0.86 (d, 6, isopropyl), 1.18 (s, 3, angular CH_3), 3.80 (broad s, 4, OCH_2CH_2O), 5.14 (t, 1, vinyl H next to CN); high-resolution mass spectrum M^+ *m/e* 275.1901 (calcd for $C_{17}H_{25}NO_2$, 275.1885, Δm = 1.6 mmu), $M^+ - 43$, 232.1366 (calcd for $C_{14}H_{18}NO_2$, 232.1338, Δm = 2.8 mmu).

3aα,4,5,6a-Tetrahydro-1β-cyanomethyl-5α-isopropyl-7aα-methyl-7(6*H*)-indanone Ethylene Ketal (28). To a 10-ml round-bottom flask equipped with a Teflon-coated magnetic stirring bar and a side arm bearing a serum cap were added 5% Pd/C (0.0198 g, 196 wt %) and a solution of unsaturated nitrile **27** (preparative GLC fraction) (0.0101 g, 0.0367 mmol) in absolute ethanol (0.72 ml). The stirred reaction mixture was hydrogenated at atmospheric pressure for 45 min, at which time GLC analysis (4% FFAP, 10 ft × 0.25 in., 220°, 120 ml/min) showed the absence of starting nitrile (13.8 min) and the presence of a new product (17.0 min). The reaction mixture was treated with K_2CO_3 to deactivate the catalyst, filtered, and evaporated under reduced pressure to give 0.0087 g (87%) of clear, colorless oil: ir (10% w/v in CCl_4) 3020, 2920 (C–H), 2270 (CN), 1185, 1130, 1115, 1100, 1035, 948 cm^{-1} (C–O–C); NMR δ 0.85 (d, 6, isopropyl), 1.18 (s, 3, angular CH_3), 1.44 (broad, CH_2), 3.86 (broad, 4, OCH_2CH_2O); low-resolution mass spectrum *m/e* 277 (M^+), 234 ($M^+ - 43$, loss of isopropyl); high-resolution mass spectrum M^+ *m/e* 277.2036 (calcd for $C_{17}H_{27}NO_2$, 277.2041, Δm = −0.5 mmu), $M^+ - 43$ 234.1493 (calcd for $C_{14}H_{20}NO_2$, 234.1493, Δm = 0.0 mmu).

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Registry No.—**6,** 2244-16-8; **7,** 55267-99-7; **8,** 55268-00-3; **9,** 55268-01-4; **10,** 55268-02-5; **11,** 499-71-8; **12,** 55268-03-6; **13,** 55268-04-7; **14,** 55268-05-8; **16,** 55268-06-9; (*E*)-**17,** 55268-07-0; (*Z*)-**17,** 55331-46-9; **18,** 55268-08-1; **23,** 55268-09-2; **24,** 55268-10-5; **25,** 55268-11-6; **25** acetamide derivative, 55268-12-7; **26,** 55268-13-8; **27,** 55268-14-9; **28,** 55331-47-0; 4-bromo-1-butene, 5162-44-7; diethyl cyanomethylphosphonate, 2537-48-6; *n*-isopropylcyclohexylamine, 1195-42-2; β-chloropropionaldehyde trimethylene acetal, 13297-07-9.

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(19) Note that **17** is approximately a 50:50 mixture of stereoisomers about the double bond. Since both stereoisomers yield the same product, double bond geometry is unimportant. We have illustrated the cyclizing conformation of **17** using the *Z* stereoisomer. The argument in favor of product **18** would appear to be even stronger for the *E* stereoisomer.
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