Synthesis of 8-*epi*-Dendrobine

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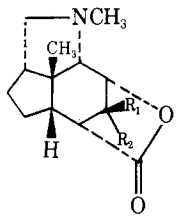
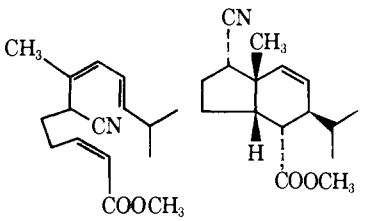
Abstract: The synthesis of 8-*epi*-dendrobine (**1b**) is described in which stereochemistry is established via intramolecular Diels-Alder cyclization of triene ester **2** to give the unsaturated nitrile ester **3**. Intermediate **3** is elaborated to **1b** via two independent synthetic routes, one proceeding via keto lactone **12d** and the other via amino ester **14.** Inversion of stereochemistry at C-8 is believed to occur as a consequence of diene isomerization under Diels-Alder conditions.

Dendrobine (**1a**) is representative of a group of sesquiterpene lactone alkaloids produced by the orchid species *Dendrobium nobile* whose skeletal structure and pharmacological properties are similar to those of the potent convulsant picrotoxin.[1] Extensive synthetic efforts have been carried out on this complex tetracyclic structure, culminating in three independent total syntheses of **1a.**[2] Our plan for the stereospecific synthesis of dendrobine was based on the convergent synthesis of the triene ester **2** and subsequent intramolecular Diels-Alder reaction of **2** to give the cyano ester **3** with five of the seven asymmetric centers established. Further transformations of this molecule would utilize existing functional groups to establish the remaining two asymmetric centers. We describe herein the execution of this plan which resulted in the synthesis of 8-*epi*-dendrobine (**1b**) via a totally unexpected diene isomerization during the course of the intramolecular Diels-Alder cyclization.[3]



1a, $R_1 = CH(CH_3)_2$, $R_2 = H$
b, $R_1 = H$, $R_2 = CH(CH_3)_2$



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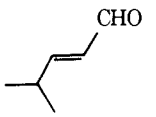

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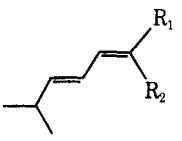
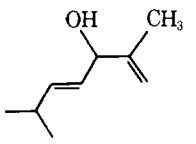


5a, $R_1 = CH_3$, $R_2 = CH_2OH$
b, $R_1 = CH_3$, $R_2 = CHO$
c, $R_1 = CH_3$, $R_2 = CH_2CN$
d, $R_1 = CH_2OH$, $R_2 = CH_3$
e, $R_1 = CHO$, $R_2 = CH_3$
f, $R_1 = CH_2CN$, $R_2 = CH_3$
g, $R_1 = CH_3$, $R_2 = CH(CN)CH_2CH_3$



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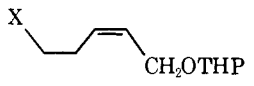
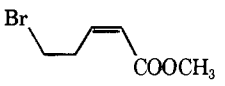


7a, X = OH
b, X = Br
c, X = I



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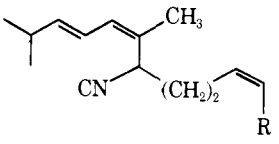
Our approach to the synthesis of triene ester **2** is based on a convergent synthesis involving union of unsaturated nitrile **5c** and homoallylic halide **7b** via alkylation. The directed aldol condensation[4] of isobutyraldehyde and ethylidine-*tert*-butylamine produced trans aldehyde **4** in 50% yield; the trans configuration was confirmed by the olefinic proton coupling constant of 15 Hz. Corey has described a method for stereospecific homologation of an aldehyde to the corresponding cis methallyl alcohol by reaction with ethylidene-triphenylphosphine at −78 °C, followed by subsequent reaction with *n*-butyllithium and paraformaldehyde.[5] Application of this procedure to aldehyde **4** resulted in equal amounts of alcohols **5a** and **5d** contaminated with the secondary alcohol **6.** When the formaldehyde was introduced in the gaseous state via a stream of nitrogen, however, a 40% yield of allylic alcohols was obtained with **5a:5d:6** in the ratios 80:5:15. The coupling constant $J = 14$ Hz for the C(4) and C(5) protons confirmed the trans configuration about the C(4)-C(5) double bond. Alcohols **5a** and **5d** were oxidized to the corresponding aldehydes **5b** and **5e** using activated manganese dioxide. Comparison of the ^{1}H NMR spectra revealed that the chemical shift of the aldehyde proton was farther downfield (at 10.27 ppm) for the aldehyde derived from the major isomer than the corresponding proton (at 9.51 ppm) from the minor isomer. This significant downfield shift of the aldehyde proton is characteristic of cis α,β-unsaturated aldehydes.[6] Thus, the major isomer was assigned the structure **5a.**

Synthesis of the requisite nitrile without alteration of the stereochemistry thus far established was accomplished by modification of a procedure reported by Stork[7] for the conversion of an allylic alcohol to its corresponding chloride without rearrangement or isomerization. Alcohol **5a** was reacted sequentially with exactly 1 equiv each of methyllithium, *p*-toluenesulfonyl chloride, and lithium chloride. The resulting crude allylic chloride was reacted with lithium iodide and cuprous cyanide to afford the desired nitrile **5c** in 50% yield. The -C≡N absorption at 2240 cm^{-1} and the UV_{max} at 234 nm confirmed that conversion to the nitrile had occurred without double bond migration. Similar reaction of a 1:1 mixture of **5a** and **5d** led to a 1:1 mixture of the corresponding nitriles **5c** and **5f** which was indistinguishable spectroscopically from pure **5c.** Although not conclusive, these results suggest that conversion to the nitrile proceeds without isomerization about the double bond.

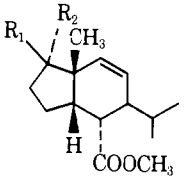
Alcohol **7a** was prepared in 54% yield by reaction of the sodium salt of propargyl THP ether with ethylene oxide, followed by Lindlar[8] reduction of the triple bond. Reaction of **7a** with triphenylphosphine dibromide in pyridine proceeded in 83% yield to give bromide **7b;** treatment of **7b** with sodium iodide in acetone gave the iodo compound **7c** in 88% yield. It should be noted that halo ester **8** is, in principle, a more attractive intermediate than **7b** or **7c** in this convergent synthesis because it avoids having to carry out several complex procedures *after* union of the two synthons. Bromo ester **8** was prepared from **7a,** but, as expected for a vinylogous β-halo ester, it proved far too unstable to be synthetically useful.

Alkylation of **5c** with ethyl iodide was studied initially as a model for the coupling of **5c** and **7c.** The anion of **5c** was prepared by reaction with lithium isopropylcyclohexyl amide (LiICA) in THF at −70 °C. Addition of the anion to ethyl

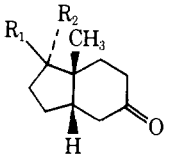
iodide in Me_2SO at room temperature resulted in the formation of **5g** in 61% yield; IR, UV, and ^1H NMR spectra confirmed that alkylation had occurred without concomitant double bond migration. When this procedure was repeated with iodide **7c,** however, the desired alkylation product **9a** was not obtained. The only compounds isolable were **5c** and the diene arising from elimination of HI from **7c.** After extensive experimentation, the triene **9a** was ultimately obtained in 85% yield by rapid addition of the iodide **7c** in HMPA-THF at −25 °C to a solution of the anion of **5c** in THF at −25 °C (vide infra). Once again, IR, ^1H NMR, and UV spectra confirmed that alkylation proceeded without double bond migration; HPLC analysis confirmed that **9a** was homogeneous.



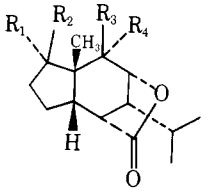
9a, R = CH_2OTHP
b, R = CH_2OH
c, R = CHO



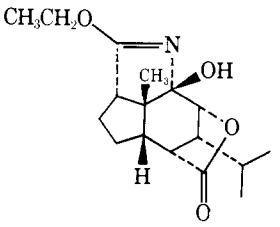
10a, R_1 = H, R_2 = CN
b, R_1 = CN, R_2 = H
c, R_1 = H, R_2 = $CONHCH_3$
d, R_1 = $CONHCH_3$, R_2 = H
e, R_1 = H, R_2 = CH_2NHCH_3
f, R_1 = H, R_2 = $CH_2N(Cl)CH_3$



11a, R_1 = H, R_2 = $CONH_2$
b, R_1 = $CONH_2$, R_2 = H



12a, R_1 = CN, R_2 = H, R_3 = Br, R_4 = H
b, R_1 = CH_2NHCH_3, R_2 = H, R_3 = Br, R_4 = H
c, R_1 = CN, R_2 = H, R_3 = OH, R_4 = H
d, R_1 = CN, R_2 = H, R_3 = R_4 = O
e, R_1 = H, R_2 = CN, R_3 = Br, R_4 = H
f, R_1 = H, R_2 = CH_2NHCH_3, R_3 = Br, R_4 = H
g, R_1 = H, R_2 = CN, R_3 = OH, R_4 = H
h, R_1 = H, R_2 = CN, R_3 = R_4 = O



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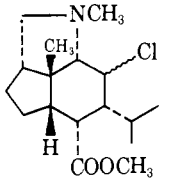
Hydrolysis of **9a** with aqueous sulfuric acid in THF afforded the alcohol **9b** in 56% yield. Attempted oxidation of alcohol **9b** directly to its corresponding carboxylic acid using a number of oxidizing agents failed, resulting in products of decomposition. Thus, **9b** was converted to the aldehyde **9c** in 84% yield by reaction with chromium trioxide–pyridine complex in methylene chloride.[9] HPLC revealed that both **9b** and **9c** were contaminated with ~15% of the corresponding isomers trans at the C(2)–C(3) double bond. Assignment of the major isomer as cis is based on the chemical shift of the aldehyde protons at 10.01 ppm for the major isomer and 9.5 ppm for the minor isomer (vide supra).[6] In view of the homogeneity of **9a** by HPLC, the trans isomer presumably arises during hydrolysis of the THP ether. Direct conversion of aldehyde **9c** to the methyl ester **2** was achieved by reaction with sodium cyanide, glacial acetic acid, and activated manganese dioxide in methanol.[10] Preparative HPLC afforded **2** as a stereochemically pure material in 40% yield.

Having the requisite triene ester **2** at hand, the stage was set for the intramolecular Diels-Alder cyclization. When this compound was refluxed in a variety of solvents (benzene, chloroform, 1,2-dichloroethane, decalin, chlorobenzene), only unreacted starting material was obtained. When **2** was refluxed for 3 days in *o*-dichlorobenzene, however, two compounds which proved to be **10a** and **10b** were isolated in 25 and 24% yields after preparative HPLC. Spectral analysis indicated that **10a** and **10b** had saturated nitrile and ester groups, a single cis-disubstituted double bond, a methyl group attached to a quaternary carbon, and an isopropyl group. Mass spectral analysis revealed that **10a** and **10b** had identical molecular weights. The stereochemical assignment of the cyano groups in **10a** and **10b** was based on the chemical shift of the 7a-methyl group in the corresponding *N*-methylamides **10c** and **10d.** The amides **10c** and **10d** were readily prepared by reaction of the corresponding nitriles with dimethylbromonium hexafluoroantimonate and quenching of the resulting nitrilium salt with water.[11] Inubushi had observed[2b] that the chemical shift of the 7a-methyl group in a variety of 1-substituted *cis*-perhydroindenes was dependent on the stereochemistry at C(1). In particular, he found that the chemical shift of the 7a-methyl group was farther upfield if the methyl and C(1) substituent was cis (1.16 ppm in **11b**) than if the methyl and C(1) substituents were trans (1.42 ppm in **11a**).[2b] Comparison of the 7a-methyl chemical shifts in **10c** (1.23 ppm) and **10d** (0.97 ppm) confirms that the relative configuration of 7a-methyl and 1-cyano is trans in **10a** and cis in **10b.**

Further transformations of **10a** ultimately produced a compound which proved to be an epimer of dendrobine at the isopropyl group (C(8)). Because the Diels-Alder reaction appeared to be a likely step for isomerization, this reaction was monitored by HPLC analysis. In addition to UV-transparent peaks at 27.5 and 32.5 min for **10a** and **10b** (1:1 CH_3CN–H_2O, 90 cm μ-Bondapak column, 2.0 ml/min) and a UV-absorbing peak at 45.0 min for **2,** a new UV-absorbing peak at 43.0 min appeared during the course of the reaction which was consistently <10% of the reaction mixture. Isolation of a small sample by preparative HPLC showed that it had a FT 100 mHz ^1H NMR spectrum which was indistinguishable from that of **2.** HPLC analysis of this isolated sample confirmed that it was different from **2.** Assignment of structure **15** to the isomerized triene ester accounts for these observations and provides a rationale for the stereochemical outcome of the reaction. Examination of the requisite cis coplanar arrangement for the Diels-Alder reaction of **2** reveals a severely hindered configuration which involves no secondary orbital overlap between diene and ester. Similar cis coplanar arrangement of **15,** however, leads to a less hindered configuration which provides for secondary orbital overlap in the transition state.[24] Presumably triene ester **2** is unable to cyclize and after prolonged heating at 170 °C, rearrangement to **15** occurs with



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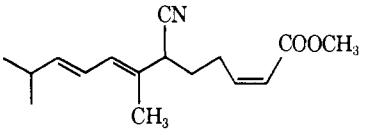

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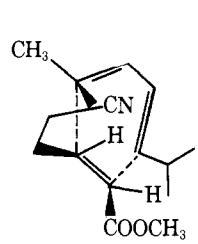
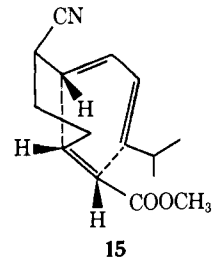
subsequent cyclization. Careful examination of structure **15** below reveals that it will cyclize to give a product in which carbomethoxy, hydrogen, and methyl substituents are inverted and the isopropyl substituent remains unchanged as compared with **2.** *This is equivalent to an inversion only at the carbon bearing the isopropyl group.*



2



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Thus, the Diels-Alder products were assigned structures **10a** and **10b.** Utilization of the cyano and ester groups to functionalize the double bond would provide stereospecificity at C(6) and C(7). Conversion of ester **10a** to its corresponding carboxylic acid proved difficult using standard hydrolytic methods but was ultimately achieved by reaction with lithium iodide in refluxing lutidine.[12] The crude acid was easily converted to **12a** by reaction with bromine–potassium bromide in aqueous bicarbonate solution[13] in 90% yield. Attempted N-methylation of **12a** with trimethyloxonium fluoroborate, dimethoxycarbonium fluoroborate,[14] and methyl fluorosulfonate[15] were unsuccessful. However, reaction of **12a** with dimethylbromonium hexafluoroantimonate[16] in refluxing liquid sulfur dioxide followed by addition of anhydrous methanol and reduction with sodium cyanoborohydride[17] gave the desired amine **12b** as an impure material; all attempts to obtain this compound in a pure state failed. Attempts to cyclize **12b** to the dendrobine skeleton by refluxing in ethyl acetate, toluene, mesitylene, or 1,2-dimethoxyethane, or by reaction with silver nitrate in ethanol or with sodium hydride were uniformly unsuccessful, leading only to recovery of starting material. It was conceivable that assignment of **10a** and **10b** was reversed, so the reaction sequence described above was carried out on the other cyano isomer **10b,** giving as expected the corresponding bromo lactone **12e** and amino lactone **12f.** Unfortunately, cyclization of **12f** to the dendrobine skeleton also proved unsuccessful.

Thus, we turned our attention to the synthesis of keto lactone **12d** in the hope that intramolecular reductive amination[17] of the corresponding methylamino compound would give dendrobine. Conversion of **10a** to its acid followed by reaction with *m*-chloroperbenzoic acid[18] afforded the hydroxy lactone **12c** in 90% yield; Jones oxidation[19] of **12c** gave a 77% yield of the desired keto lactone **12d.** Similarly, **12h** was prepared from **10b** for use as a model compound. All attempts to convert **12d** and **12h** to their corresponding methylaminomethyl compounds via the *N*-methylnitrilium salt were unsuccessful. Under mild conditions, starting material was recovered. When dimethylbromonium hexafluoroantimonate was used in large excess, products were obtained in which the lactone ring had been destroyed. Attempts to carry out this conversion on the hydroxy lactones **12c** and **12g** were similarly unsuccessful. It is not clear why **12c** and **12d** were refractory to reaction conditions which were successful in the conversion of **12a** to **12b.**

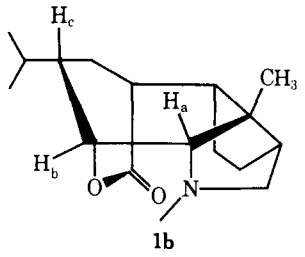
Efforts were next directed to the reduction of the cyano group in **12d** to the corresponding primary amine. Reaction of **12d** with borane–THF reduced the ketone carbonyl group preferentially; catalytic reduction of **12d** with hydrogen over rhodium/alumina gave unreacted starting material, whereas similar reaction of **12h** caused preferential reduction of the ketone carbonyl group. Attempted Stephen reduction[21] of the model compound **12h** to the corresponding imine using stannous chloride–HCl in ether gave only unreacted starting material. Addition of absolute ethanol (in the hope of converting the nitrile to its corresponding imino ester) had no effect upon **12h.** However, when **12d** was subjected to these reaction conditions ($SnCl_2$–HCl, ether, ethanol), a new compound identified as **13** was obtained in 68% yield. The structure of **13** was assigned on the basis of a molecular ion in the mass spectrum at 307, the presence of hydroxyl, lactone, and imine absorption in the infrared spectrum at 3170, 1770, and 1630 cm^{-1}, respectively, and the presence of an ethoxy group in the NMR spectrum. The mechanism for the formation of this most unusual species is not clear. The fact that **12h** was totally inert to the identical reaction conditions suggests that interaction of the ketone carbonyl group is critical to the success of the reaction. Although one might anticipate that ethanol would serve to trap any nitrilium salt present, the fact the unreacted **12d** is obtained in its absence suggests that it plays a more central role in the reaction. On this basis we postulate the following mechanism: stannous ion acts as a Lewis acid to form a cyclic complex involving the unshared pairs on the cyano and ketone moieties which activates the cyano group toward attack by nucleophile; addition of ethanol at the activated nitrile leads to the corresponding cyclic imino ester which subsequently undergoes cyclization to carbinolamine **13.**

This serendipitous result provided a compound (**13**) in which the requisite skeleton and functional groups were all present, albeit in modified form. Methylation of **13** with methyl florosulfonate in chloroform was rapid and quantitative; reduction of the resulting iminium salt with sodium cyanoborohydride in acidic methanol gave a new crystalline product (**1b**) in 77% yield. The mass spectrum of this product was virtually identical with that for authentic dendrobine, and high-resolution mass spectrometry confirmed a molecular formula of $C_{16}H_{25}O_2N$. The ^1H NMR spectrum confirmed the presence of an isopropyl group, a ring junction methyl group, an *N*-methyl group, and a methine hydrogen geminal to oxygen. The IR spectrum suggested the presence of an *N*-methyl group and a lactone ring. However, the infrared solution spectrum of this new compound was *not* identical with that of authentic dendrobine. Chromatographic analysis via TLC and HPLC confirmed that, although **1b** was very similar to dendrobine, the two compounds were not identical.

While this scheme was under investigation, an independent route from **10a** to dendrobine which involved cyclization of the pyrrolidine ring prior to lactonization was being explored. The synthesis of pyrrolidines via titanium trichloride-promoted cyclization of olefinic *N*-chloramines has been reported,[22] and the methylaminomethyl compound derived from nitrile **10a** appeared to be an ideal candidate for this reaction. Reaction of **10a** with dimethylbromonium hexafluoroantimonate in liquid SO_2 followed by addition of methanol and reduction with sodium cyanoborohydride afforded the desired amine **10e** in 54% yield. The *N*-chloramine **10f** was prepared in 91% yield by reaction of **10e** in methylene chloride with aqueous sodium hypochlorite.[23] When a solution of **10e** in aqueous acetic acid was reacted with excess aqueous titanium trichloride at −8 °C, a crude product was obtained which showed no olefinic or *N*-chloro-*N*-methyl peaks but did have an *N*-methylamine peak in the ^1H NMR spectrum. Without further characterization this compound, presumed to be chloroamine **14,** was reacted with lithium iodide in refluxing lutidine to give a 45% yield of product **1b,** identical in all respects with that obtained by the previous route but different from authentic dendrobine.

Having confirmed that our product prepared by two independent routes was different from authentic dendrobine, we attempted to establish its stereochemistry. Configuration of the cyano group (and hence the pyrrolidine ring) relative to the ring-junction methyl group is established on the basis of

NMR analysis of amides **11a** and **11b** (vide supra) and on the fact that **12d** undergoes cyclization to **13** whereas **12h** does not. Thus, ring-junction methyl and H_a are cis in **1b.** Careful



1b

analysis of the coupling constants in **1b** showed that J_{AB} = 4 Hz, which compares favorably with that of dendrobine (J_{AB} = 5 Hz) and is consistent with assignment of H_b as cis to H_a. This in turn establishes the stereochemistry of the lactone ring as "cis" to the pyrrolidine ring. At this point the relative stereochemistries of **1b** and dendrobine are established as identical for all asymmetric centers except the other ring-junction carbon and the carbon bearing the isopropyl group. The structure which has the 6-5 carbocyclic rings trans-fused appears unlikely based upon measurement of the dihedral angle θ_{AB} 15-30° from Dreiding models for this structure; this dihedral angle should give coupling constant J_{AB} = 6.0-7.5 Hz, whereas the observed J_{AB} = 4.0 Hz. Finally, configuration at C(8) can be assigned as *opposite* to that of dendrobine on the basis of coupling constant J_{BC} = ≤2 Hz for **1b,** which is consistent with H_b cis to H_c; in dendrobine, however, where H_b and H_c are known to be trans, J_{BC} = 5 Hz. Thus, our compound can be assigned structure **1b,** differing from dendrobine only in the configuration of the isopropyl group at C(8).

Experimental Section

Anhydrous tetrahydrofuran (THF) was prepared by distillation from lithium aluminum hydride. Anhydrous methanol was prepared by distillation from dimethoxymagnesium. 2,6-Lutidine was dried over Linde 4A molecular sieves. Hexamethylphosphoramide (HMPA) was distilled from Linde 13X molecular sieves and stored over Linde 13X molecular sieves. Methyllithium and *n*-butyllithium were standarized by integration of the proton magnetic resonance (^{1}H NMR) spectrum peaks for CH_3li or -CH_2Li relative to benzene in solutions of 50 μl of benzene in 1 ml of the alkyllithium solution.

Preparative thin-layer chromatography was performed on a 1.5 mm thickness of silica gel on 20 × 20 cm plates. Dry column chromatography was carried out using nylon tubing containing silica gel Woelm or alumina Woelm, dry-column grade, as adsorbants. Elution was continued until the solvent front reached the bottom of the column, bands were visualized under ultraviolet light, and the column was sliced into sections which were extracted with 15% methanol in chloroform. High-pressure liquid chromatography (HPLC) was performed on a Waters ALC-100 instrument.

Melting points were determined on a Kofler hot stage and are corrected. Ultraviolet (UV) spectra were determined on a Perkin-Elmer Coleman 124 double-beam spectrophotometer. Infrared (IR) spectra were measured on a Beckman Model 33 grating spectrophotometer. ^{1}H NMR spectra were measured on a Varian Associates T-60 or on an XL-100-15 instrument equipped with Fourier transform and are given in parts per million δ downfield from tetramethylsilane as an internal standard. Mass spectra were obtained at 70 eV on an AEI-MS-30 double-beam mass spectrometer by the Mass Spectrometry Laboratory, University of Minnesota. Elemental analyses were determined by M-H-W Laboratories, Garden City, Mich.

***trans*-4-Methyl-2-pentenal (4).** To a solution of methyllithium (100 ml of 1.8 M in ether, 0.18 mol) in 80 ml of dry ether, cooled to −10 °C under a nitrogen atmosphere, was added dropwise a solution of 29.0 ml (0.21 mol) of diisopropylamine in 30 ml of ether; stirring was continued for 20 min at −10 °C. Ethylidene-*tert*-butylamine (18.0 g, 0.182 mol) was added dropwise, and stirring was continued for 30 min at 0 °C. The mixture was cooled to −70 °C, and 14.0 g (0.194 mol) of freshly distilled isobutyraldehyde, in 20 ml of ether, was added dropwise at −70 °C. This mixture was stirred 2 h at −70 °C and 1 h at 0 °C, then poured into a 3-l. flask containing a solution of 90 g of oxalic acid monohydrate in 800 ml of water. Hydroquinone (~30 mg) was added, and the mixture was steam distilled. Six 500-ml fractions of distillate were collected; each fraction was saturated with sodium chloride and extracted with three 100-ml portions of ether. The combined ether extracts were dried ($MgSO_4$) and evaporated in vacuo. The combined residues were distilled through a 15-cm Vigreux column at reduced pressure to yield 7.62 g (43%) of **4** as a clear, colorless liquid: bp 58-61 °C (45 mm); ^{1}H NMR (CCl_4) δ 9.50 (d, 1, J = 7 Hz, -CHO), 6.78 (d of d, 1, J_{ab} = 15 Hz, J_{am} = 6 Hz, -CH=C*H*CH(CH_3)$_2$), 5.96 (d of d of d, 1, J_{ab} = 16 Hz, J_{bm} = 7 Hz, J_{bx} = 2 Hz, OHCC*H*=CHCH), 1.13 (d, 6, J = 7 Hz, -CH(CH_3)$_2$); IR (neat) 1695, 1635, 1140, 970 cm^{-1}.

(*Z,E*)-2,6-Dimethyl-2,4-heptadien-1-ol (5a). A dry, nitrogen-filled, 1000-ml, three-necked flask was fitted with a rubber septum, mechanical stirrer, and U-tube to a 250-ml, three-necked flask half-filled with paraformaldehyde and fitted with a glass stopper and nitrogen inlet. Ethyltriphenylphosphonium bromide (56.4 g, 0.152 mol) was suspended in 500 ml of anhydrous THF, and *n*-butyllithium (67 ml, 2.29 M in hexane, 0.153 mol) was added dropwise over 15 min. After stirring at room temperature for 15 min, the red-orange solution was chilled to −78 °C and 15.2 g (0.155 mol) of the aldehyde **4** was added dropwise over 30 min. The pale suspension was stirred for 15 min at −78 °C, and *n*-butyllithium (67 ml, 2.29 M in hexane, 0.153 mol) was added dropwise over 40 min. After stirring the deep-red solution for 25 min at −78 °C, the rubber septum was replaced with a dry ice condenser. The 250-ml flask containing the paraformaldehyde was flame heated, and the gaseous formaldehyde was blown into the reaction flask with a slow stream of nitrogen. Addition of formaldehyde was continued until the reaction mixture was a pale suspension (2 h), refilling the 250-ml flask with paraformaldehyde when necessary.[25] Stirring was continued for 20 min at −78 °C, 30 min at 0 °C, and for 2½ h at room temperature. Distilled water (500 ml) was added, the organic layer was separated, and the aqueous layer was extracted with three 400-ml portions of ether. Combined organic layers were washed with 400 ml of water and two 400-ml portions of brine, dried ($MgSO_4$), and evaporated in vacuo to give an orange oil. Hexane (500 ml) was added, and the white crystals of triphenylphosphine oxide were filtered off and washed with two 70-ml portions of ether. The hexane filtrate and ether washings were combined, evaporated in vacuo, and chromatographed on an alumina dry column (2 × 32 in., elution with ether, R_f 0.49-0.74) to give 8.50 g (40%) of isomeric dienols which contained 80% of the desired dienol **5a:** ^{1}H NMR (CCl_4) 6.17 (d of d, 1 H), 5.74 (d, 1 H), 5.47 (d of d, 1 H), 4.08 (s, 2 H), 2.45 (s, 1 H), 2.32 (m, 1 H), 1.80 (s, 3 H), 1.02 (d, 6 H); IR (neat) 3350, 990, 955 cm^{-1}; UV max (95% EtOH) 236 nm (ε 24 000).

Anal. Calcd for $C_9H_{16}O$, C, 77.09; H, 11.50. Found: C, 77.30; H, 11.47.

(*Z,E*)-3,7-Dimethyl-3,5-octadienonitrile (5c). To a solution of 9.55 g (68.2 mmol) of the alcohol **5a** in 50 ml of anhydrous ether and 25 ml of HMPA in a dry, nitrogen-filled, 500-ml, round-bottomed flask fitted with a magnetic stirrer and rubber septum was added 42.5 ml (1.61 M, 68.4 mmol) of ethereal methyllithium dropwise over 35 min. The resulting solution was stirred for 35 min at 0 °C, and a solution of 13.0 g (68.4 mmol) of *p*-toluenesulfonyl chloride in 50 ml of ether and 25 ml of HMPA was added dropwise over 55 min at room temperature. after stirring for 10 min, 2.89 g (68.2 mmol) of anhydrous lithium chloride was added, and the solution was stirred for 45 min. The ether was evaporated from the solution in a stream of nitrogen, and 9.25 g (69.1 mmol) of anhydrous lithium iodide, 24.4 g (272 mmol) of cuprous cyanide, and 4.0 ml of water were added. The resulting thick brown suspension was heated in a 60 °C oil bath under nitrogen for 16 h, allowed to cool, and triturated with three 75-ml portions of ether. Distilled water (200 ml) was added, and the suspension was extracted with three 200-ml portions of ether, dissolving enough sodium chloride in the aqueous layer to prevent formation of an emulsion. The combined ether solutions were washed with three 75-ml portions of water and two 200-ml portions of brine, dried ($MgSO_4$), and evaporated in vacuo to give 10 g of brown oil. Silica gel dry column chromatography (42 × 1½ in., elution with 1-chlorobutane, R_f 0.45-0.76) gave 5.00 g (50%) of the nitrile **5c** as a pale-yellow oil: ^{1}H NMR (CCl_4) δ 6.4-5.5 (m, 3 H, olefinic), 3.01 (s, 2 H, CH_2CN), 1.83 (s, 3 H, CH_3C=), 1.01 (d, 6 H, $(CH_3)_2C$); IR (neat) 2240, 960 cm^{-1}; UV max (95% EtOH) 234 nm (ε 22 900); high-res-

olution mass spectrum: calcd for $C_{10}H_{15}N$, 149.1204; found, 149.1204.

***cis*-1-(2-Tetrahydropyranyloxy)-5-hydroxy-2-pentene (7a).** To suspension of sodium amide prepared from 11.5 g (0.500 g-atom) of sodium in 500 ml of liquid ammonia was added dropwise over 20 min 68.2 g (0.487 mol) of propargyl tetrahydropyranyl ether. After stirring for 1½ h, 31 ml (27.5 g, 0.626 mol) of ethylene oxide was added all at once. After stirring for 19 h, the reaction was quenched by the addition of 27 g of ammonium chloride; 100 ml of ether was added, and the ammonia was allowed to evaporate. The residual salts were dissolved in 250 ml of water, the ether phase was separated, and the aqueous phase was extracted with three 100-ml portions of ether. The combined ether extracts were washed with 100 ml of water, then with 100-ml portions of brine until the washings were neutral to litmus (six washings). The ether fraction was dried ($MgSO_4$) and evaporated in vacuo. The residue was distilled at reduced pressure through a 15-cm Vigreux column to obtain first 14.3 g of the starting material, propargyl tetrahydropyranyl ether, bp 55–60 °C (4.5 mm). *cis*-1-(2-Tetrahydropyranyloxy)-5-hydroxy-2-pentyne was then obtained as a clear, colorless liquid amounting to 48.6 g (54%; 69% based on recovered starting material): bp 116–120 °C (0.7 mm); ^{1}H NMR (CCl_4) δ 4.77 (s, 1 H), 4.15 (τ, 2 H), 3.62 (m, 4 H), 2.40 (m, 2 H), 1.9–1.2 (m, 6 H); IR (neat) 3450, 2210 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.06; H, 8.99.

To a solution of 28.8 g (0.157 mol) of the acetylenic alcohol obtained above in 150 ml of benzene was added 1.0 g of Lindlar catalyst. This mixture was hydrogenated on a Parr apparatus, initially at 28 psi; hydrogen uptake was complete after 1 h. Filtration through hyflo, evaporation of the filtrate in vacuo, and distillation of the concentrate at reduced pressure yielded 28.0 g (96%) of **7a** as a clear, colorless liquid: bp 94–96 °C (0.35 mm); ^{1}H NMR (CCl_4) δ 5.8–5.4 (m, 2 H), 4.62 (s, 1 H), 4.10 (d of d, 2 H), 3.52 (τ, 2 H), 2.28 (q, 2 H); IR (neat) 3420, 3030, 1020 cm^{-1}.

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.26; H, 10.01.

***cis*-1-(2-Tetrahydropyranyloxy)-5-bromo-2-pentene (7b).** To a solution of 4.60 g (17.5 mmol) of triphenylphosphine in 25 ml of ether, cooled to 0 °C, was added dropwise over 15 min 2.65 g (16.5 mmol) of bromine. The solvent was evaporated in vacuo, and the residue was dried at 50–60 °C and 5 mm for 1 h. The yellow solid was cooled at 0 °C while a solution of 1.91 g (10.3 mmol) of the alcohol **7a** in 25 ml of dry pyridine was added dropwise over 15 min. The mixture was stirred for 1 h at room temperature, then carefully poured into 40 ml of cold, saturated aqueous $NaHCO_3$. The mixture was extracted with four 40-ml portions of hexane; the combined extracts were washed with 50 ml of water and two 50-ml portions of brine, dried ($MgSO_4$), and evaporated in vacuo to give **7b** as a cloudy, yellow liquid. This material was chromatographed by the dry column technique (neutral alumina, 15 × 1½ in., eluting with carbon tetrachloride), taking all of the material between (but not including) the UV-absorbant regions (these were due to triphenylphosphine and triphenylphosphine oxide), to yield 2.5 g of yellow liquid. Elution of this material through 30 g of alumina, using 100 ml of benzene followed by 100 ml of 1% ethyl acetate in benzene, yielded 2.13 g (83%) of the bromide **7b**: ^{1}H NMR (CCl_4) δ 5.9–5.4 (m, 2 H), 4.58 (s, 1 H), 3.38 (τ, 2 H), 2.68 (g, 2 H); IR (neat) 3030, 1260, 1010 cm^{-1}.

Anal. Calcd for $C_{10}H_{17}O_2Br$: C, 48.20; H, 6.88; Br, 32.07. Found: C, 48.44; H, 6.57; Br, 32.22.

***cis*-1-(2-Tetrahydropyranyloxy)-5-iodo-2-pentene (7c).** To a saturated solution of sodium iodide in 8 ml of acetone was added 252 mg (1.01 mmol) of the alkyl bromide **7b**. This mixture was stirred for 18 h at room temperature; the precipitated salts were removed by filtration through glass wool, and the filtrate was evaporated in vacuo. The residue was partitioned between water (4 ml) and ether (5 ml). The ether phase was separated and the aqueous phase was extracted with 5 ml of ether. The combined organic layers were washed with 5 ml of dilute sodium thiosulfate solution and two 5-ml portions of brine, dried ($MgSO_4$), and evaporated in vacuo to give 263 mg (88%) of **7c** as a pale-yellow oil: ^{1}H NMR (CCl_4) δ 6.0–6.7 (m, 2 H), 4.60 (s, 1 H), 3.17 (τ, 2 H), 2.70 (q, 2 H); IR (neat) 3030, 1235, 1010 cm^{-1}.

***(Z,E)*-2-Ethyl-3,7-dimethyl-3,5-octadienonitrile (5g).** To a solution of lithium isopropylcyclohexylamide (0.50 ml of 0.50 M in THF, 0.25 mmol) in 0.5 ml of THF at −70 °C under a nitrogen atmosphere was added dropwise a solution of 37 mg (0.25 mmol) of the nitrile **5c** in 0.5 ml of THF. The resulting brown solution was stirred for 1 h at −70 °C, then allowed to come to room temperature. This solution was added dropwise to a solution of 55 mg (0.35 mmol) of ethyl iodide in 1 ml of dimethyl sulfoxide under a nitrogen atmosphere. This mixture was stirred for 4 h at room temperature, then treated with 4 ml of saturated NH_4Cl solution. The mixture was extracted with two 7-ml portions of ether; the combined organic extracts were washed with two 5-ml portions of saturated NH_4Cl solution and three 5-ml portions of brine, dried ($MgSO_4$), and evaporated in vacuo to 34 mg of yellow liquid. Purification by preparative TLC (silica gel, elution with benzene, R_f 0.45) yielded 27 mg (61%) of the alkylated nitrile **5g**: ^{1}H NMR (CCl_4) δ 6.4–5.5 (m, 3 H), 3.01 (τ, 1 H), 1.8 (s, 3 H), 1.77 (m, 2 H), 1.02 (d, 6 H), 0.96 (τ, 3 H); IR (neat) 3040, 2230, 1455, 955 cm^{-1}; UV max (95% EtOH) 236 nm (ϵ 23 900); mass spectrum *m/e* 177 (mol ion), 162, 148, 109.

***(Z,Z,E)*-1-(2-Tetrahydropyranyloxy)-6-cyano-7,11-dimethyl-2,7,9-dodecatriene (9a).** A solution of 5.3 ml (29 mmol) of isopropylcyclohexylamine in 28 ml of anhydrous THF was chilled to 0 °C in a dry, nitrogen-filled, 250-ml, round-bottomed flask fitted with a magnetic stirrer and a rubber septum. *n*-Butyllithium (10.8 ml, 2.29 M in hexane, 24.8 mmol) was added dropwise over 8 min. The solution was stirred for 10 min at 0 °C, 30 min at room temperature, and then chilled to −78 °C. A solution of 3.33 g (22.3 mmol) of the nitrile **5c** in 26 ml of THF was added dropwise over 50 min. The brown solution was stirred for 1 h at −78 °C and warmed to −25 °C (carbon tetrachloride–dry ice bath). While the nitrile anion was warming to −25 °C, a solution of 9.0 g (30.4 mmol) of the iodide **7c** in 26 ml of anhydrous THF and 26 ml of HMPA was chilled in a −78 °C bath under nitrogen until HMPA crystals formed. This mixture was allowed to warm until the crystals melted and was immediately added as rapidly as possible by syringe to the nitrile anion solution at −25 °C. The resulting brown solution was stirred at −25 °C for 2 h. Ice cold saturated ammonium chloride (75 ml) was added, the organic layer was separated, and the resulting suspension was extracted with three 100-ml portions of ether. Combined ether layers were washed with two 100-ml portions of water and two 100-ml portions of brine, dried ($MgSO_4$), and evaporated in vacuo to give 9.8 g of brown oil. Dry column chromatography (1½ × 38 in. silica gel, elution with chloroform, R_f 0.39–0.72) gave 6.01 g (85%) of the alkylated nitrile **9a** as a yellow oil: ^{1}H NMR (CCl_4) δ 6.5–5.0 (m, 5 H), 4.57 (s, 1 H), 3.10 (τ, 1 H), 1.81 (s, 3 H), 1.02 (d, 6 H); IR (neat) 3030, 2240, 1015, 960 cm^{-1}; UV max (95% EtOH) 236 nm (ϵ 23 400). High-resolution mass spectrum: calcd for $C_{15}H_{22}N$ (base peak, loss of 2-tetrahydropyranyloxy), 216.1751; found, 216.1765.

***(Z,Z,E)*-6-Cyano-7,11-dimethyl-2,7,9-dodecatrien-1-ol (9b).** To a solution of 6.01 g (18.9 mmol) of the tetrahydropyranyl ether **9a** in 115 ml of THF was added 115 ml of 20% sulfuric acid. The initially inhomogeneous system was stirred vigorously at room temperature for 11½ h, and the resulting homogeneous solution was extracted with three 200-ml portions of ether. Combined ether layers were washed with two 75-ml portions of brine and evaporated in vacuo. The residue was dissolved in 150 ml of benzene, washed with four 75-ml portions of water and 75 ml of brine, dried ($MgSO_4$), and evaporated in vacuo to give 5.0 g of a yellow oil. Dry column chromatography (1½ × 30 in silica gel, elution with methylene chloride, R_f 0.08–0.40) gave 2.48 g (56%) of the trienol **9b**. HPLC analysis (30 cm μ Bondapak, 1:1 CH_3CN–H_2O) showed this product to be contaminated with ca. 15% of a compound with similar chromatographic mobility identified as the trans allylic alcohol on the basis of the following experiment: ^{1}H NMR (CCl_4) δ 6.2–5.0 (m, 5 H), 4.10 (d, 2 H), 3.17 (τ, 1 H), 1.83 (s, 3 H), 1.03 (d, 6 H); IR (neat) 3460, 2240, 2220, 1060, 1030, 960 cm^{-1}.

***(Z,Z,E)*-6-Cyano-7,11-dimethyl-2,7,9-dodecatrienal (9c).** To a solution of 10.3 g (130 mmol) of pyridine (distilled from barium oxide) in 200 ml of methylene chloride (dried over anhydrous potassium carbonate) at 0 °C was added 6.38 g (63.8 mmol) of anhydrous chromium trioxide. After stirring the deep-red solution at 0 °C for 30 min, a solution of 2.48 g (10.7 mmol) of the allylic alcohol **9b** in 7 ml of methylene chloride was added in one portion. The resulting brown suspension was stirred at 0 °C for 20 min, the solution was decanted, and the gummy inorganic solids were triturated with 240 ml of ether. Combined organic extracts were washed with three 120-ml portions of 1% sodium hydroxide, two 120-ml portions of 5% hydrochloric acid, 120 ml of saturated sodium bicarbonate, and two 120-ml portions of brine, dried ($MgSO_4$), and evaporated in vacuo to give 2.06 g (84%) of isomeric aldehydes which contained 86% of the desired *Z,Z,E* isomer **9c** by ^{1}H NMR and HPLC analysis: ^{1}H NMR (CCl_4)

δ 10.01 (d, 1 H), 6.6–5.3 (m, 5 H), 3.18 (τ, 1 H), 1.83 (s, 3 H), 1.03 (d, 6 H); IR (neat) 2240, 2220, 1680, 1060, 960 cm^{-1}. High-resolution mass spectrum: calcd for $C_{15}H_{21}ON$, 231.1623; found, 231.1641.

A sample of the minor isomer was collected by HPLC (30 cm μ Bondapak, 1:1 CH_3CN–H_2O) and identified as the trans aldehyde on the basis of spectral similarity to **9c** with the exception of the aldehyde proton chemical shift at 9.50 ppm.[6]

Methyl (*Z,Z,E*)-6-Cyano-7,11-dimethyl-2,7,9-dodecatrienoate (2). To a solution of 2.06 g (8.92 mmol) of the α,β-unsaturated aldehyde **9c** in 250 ml of anhydrous methanol under nitrogen was added 1.25 ml (21.9 mmol) of glacial acetic acid and 1.98 g (4.04 mmol) of sodium cyanide. After stirring for 13 min at room temperature, the solution was chilled to 0 °C, and 26.1 g of active manganese dioxide[26] was cautiously added.[27] The resulting suspension was stirred at room temperature for 16 h, the manganese dioxide was removed by filtration through diatomaceous earth, and the filtrate was evaporated in vacuo. The residue was partitioned between 100 ml of water and 100 ml of ether. The aqueous layer was extracted with two additional 100-ml portions of ether. Combined ether layers were washed with two 100-ml portions of brine, dried ($MgSO_4$), and evaporated in vacuo to give 2.3 g of an orange oil. Dry column chromatography (1½ × 22½ in silica gel, elution with chloroform, R_f 0.55–0.93) gave 1.44 g of yellow oil, which after preparative HPLC (4 ft × ⅜ in. Porasil A column, injection in three portions, elution with 10% ether in hexane, 3.0 ml/min, eluent from 120–210 ml collected) gave 0.93 g (40%) of the pure *Z,Z,E*-trienoate **2** as a colorless oil: ^1H NMR ($CDCl_3$) δ 5.2–6.5 (m, 5 H), 3.68 (s, 3 H), 3.14 (τ, 1 H), 1.86 (s, 3 H), 1.03 (d, 6 H); IR (neat) 3040, 2230, 1720, 1640, 960, 810 cm^{-1}; UV max (95% ethanol) 237 mμ (ε 21 000), sh 232, 215 mμ; high-resolution mass spectrum: calcd for $C_{16}H_{23}O_2N$, 261.1738; found, 261.1752.

Methyl 1-Cyano-7aβ-methyl-5α(2-propyl)-2,3,3aα,4,5,7a-hexahydro-1*H*-indene-4α-carboxylate (10a and 10b). A solution of 928 mg (3.55 mmol) of the triene ester **2** in 125 ml of *o*-dichlorobenzene was refluxed under nitrogen for 76 h. The *o*-dichlorobenzene was removed by column chromatography on 30 g of silica gel (elution with 300 ml of benzene, followed by 250 ml of 10% ethyl acetate in benzene, collection of all but the initial fractions containing the *o*-dichlorobenzene). Preparative thin-layer chromatography of the resulting orange oil on four silica gel plates (elution with 5% ethyl acetate in benzene, taking all but the strongly UV absorbing edge of the band with R_f 0.32) gave 550 mg of the impure Diels-Alder product. Purification by HPLC (4 ft × ⅜ in. Porasil A column, elution with 10% ether in hexane, 3.0 ml/min, eluent from 185–285 ml collected) gave 232 mg (25%) of the methyl ester **10a.** An analytical sample which crystallized to a low melting solid after long standing in the freezer was prepared by HPLC purification with recycling (4 ft × ⅜ in. Porasil A column, elution with 10% ether in hexane, 3.0 ml/min, collection of the last half of the main peak seen with the refractive index detector after three cycles): ^1H NMR (CCl_4) δ 6.02 (d of d, 1 H), 5.63 (t, 1 H), 3.69 (s, 3 H), 1.21 (s, 3 H), 0.95 (2 d, 6 H); IR (neat) 3040, 2240, 1735, 1190, 1160, 735 cm^{-1}; high-resolution mass spectrum: calcd for $C_{16}H_{23}O_2$, 261.1728; found, 261.1723.

Collection of the HPLC fraction from 135–185 ml gave 0.223 g (24%) of the pure 1β-cyano epimer **10b** which crystallized to a low melting solid after long standing in the freezer: ^1H NMR ($CDCl_3$) δ 5.67 (s, 2 H), 3.58 (s, 3 H), 1.18 (s, 3 H), 0.95 (2 d, 6 H); IR (neat) 3040, 2240, 1735, 1285, 705 cm^{-1}; high-resolution mass spectrum: calcd for $C_{16}H_{23}O_2N$, 261-1728; found, 261.1724.

Methyl 1α-(*N*-Methylcarboxamido)-7aβ-methyl-5α(2-propyl)-2,3,3aα,4,5,7a-hexahydro-1*H*-indene-4α-carboxylate (10c). Anhydrous sulfur dioxide (6 ml) was condensed into a dry, nitrogen-filled, 15-ml, three-necked flask fitted with a glass stopper, dry ice condenser topped by a nitrogen inlet, and magnetic stirrer. After chilling to −78 °C, 24.6 mg (0.071 mmol) of dimethylbromonium hexafluoroantimonate was added and the solution was stirred at −78 °C for 30 min. The cold sulfur dioxide solution was quickly poured into a dry, nitrogen-filled, 15-ml, round-bottomed flask containing 9.8 mg (0.37 mmol) of the nitrile **10a** at −78 °C. After topping the flask with a dry ice condenser, the reaction mixture was stirred at −78 °C under nitrogen for 10 min, allowed to warm to reflux temperature, and refluxed for 25 min. The sulfur dioxide was evaporated in a stream of nitrogen, and 10 ml of ice cold saturated sodium bicarbonate was added. The mixture was extracted with three 10-ml portions of brine, dried ($MgSO_4$), and evaporated in vacuo to give 19 mg of a yellow oil. Purification by preparative thin-layer chromatography gave 7.7 mg (70%) of the *N*-methylamide **10c**: ^1H NMR ($CDCl_3$) δ 5.9 (d of d, 1 H), 5.46 (broad doublet, 1 H), 3.72 (s, 3 H), 2.94 (d, 3 H), 1.23 (s, 3 H), 0.96 (2 d, 6 H); IR (neat) 3330, 3030, 1735, 1645, 1545, 1410, 740 cm^{-1}.

The 1β-(*N*-methylcarboxamido) epimer **10d** was obtained similarly: ^1H NMR ($CDCl_3$) δ 5.79 (s, 2 H), 3.66 (s, 3 H), 2.82 (d, 3 H), 0.97 (singlet superimposed on two doublets, 9 H); IR (neat) 3330, 3030, 1730, 1645, 1535, 1400 cm^{-1}.

5β-Bromo-6α-cyano-5aβ-methyl-9α(2-propyl)-1β,4β-methano-1,4,5,5a,6,7,8,8aβ-octahydro-2*H*-cyclopent[*d*]oxepin-2-one (12a). A solution of 104 mg (0.39 mmol) of the methyl ester **10a** and 340 mg (2.54 mmol) of anhydrous lithium iodide in 6 ml of dry 2,6-lutidine was refluxed under nitrogen for 12 h. After the resulting suspension had cooled, 30 ml of 1 N hydrochloric acid was added, and the mixture was extracted with four 30-ml portions of 33% methylene chloride in ether. The combined organic extracts were washed with three 15-ml portions of 1 N hydrochloric acid and three 20-ml portions of brine, dried (Na_2SO_4), and evaporated in vacuo to give 124 mg of the crude carboxylic acid as an oily solid: ^1H NMR ($CDCl_3$) δ 10.98 (s, 1 H), 6.02 (d of d, 1 H), 5.62 (d, 1 H), 1.23 (s, 3 H), 1.01 (2 d, 6 H); IR (neat) 3600–2400, 2240, 1700, 900, 725 cm^{-1}.

To a solution of the crude acid dissolved in 8 ml of 0.5 M sodium bicarbonate was added a solution of 0.125 ml (2.28 mmol) of bromine and 500 mg of potassium bromide in 3 ml of distilled water. An immediate reaction took place, and the resulting suspension was stirred in the dark for 21 h, then extracted with four 10-ml portions of methylene chloride. The combined organic layers were washed with 10 ml of dilute sodium thiosulfate and two 10-ml portions of brine, dried ($MgSO_4$), and evaporated in vacuo to give 166 mg of a light colored solid. Preparative thin-layer chromatography (silica gel, elution with 5% ethyl acetate in benzene, R_f 0.06–0.30) gave 72 mg (55%) of the bromolactone **12a** as a cream colored solid. An analytical sample was prepared by crystallizing twice from hexane: mp 85–86.5 °C; ^1H NMR ($CDCl_3$) δ 4.91 (s, 2 H), 1.51 (s, 3 H), 1.00 (2 d, 6 H); IR (neat) 2230, 1775 cm^{-1}; high-resolution mass spectrum: calcd for $C_{15}H_{20}O_2N^{79}Br$, 325.0676; found, 325.0676.

The 1β-cyano methyl ester **10b** was similarly converted to the crude 1β-cyano carboxylic acid: ^1H NMR ($CDCl_3$) δ 10.41 (s, 1 H), 5.74 (s, 2 H), 1.22 (s, 3 H), 0.97 (d, 6 H); IR (neat) 3500–2400, 2240, 1705, 1255, 700 cm^{-1}.

Bromolactonization of the crude carboxylic acid under similar conditions gave the 6β-cyanobromo lactone **12e** in 68% yield after preparative thin-layer chromatography. An analytical sample was obtained after crystallization from hexane: mp 172–176.5 °C; ^1H NMR ($CDCl_3$) δ 4.87 (d, 1 H), 4.64 (d, 1 H), 1.43 (s, 3 H), 1.00 (2 d, 6 H); IR (CS-CCl) 2240, 1790, 1135 cm^{-1}.

5β-Bromo-5aβ-methyl-6β-methylaminomethyl-9α(2-propyl)-1β,4β-methano-1,4,5,5a,6,7,8,8aβ-octahydro-2*H*-cyclopent[*d*]-oxepin-2-one (12f). Anhydrous sulfur dioxide (20 ml) was condensed into a dry, nitrogen-filled, 50-ml, three-necked flask fitted with a glass stopper, dry ice condenser topped by a nitrogen inlet, and magnetic stirrer. After chilling to −78 °C, 2.17 g (6.30 mmol) of dimethylbromonium hexafluoroantimonate was added, and the resulting solution was stirred at −78 °C for 30 min. The chilled solution was then poured into a dry, nitrogen-filled, 50-ml, round-bottomed flask containing 107 mg (0.327 mmol) of the nitrile **12e.** The flask was topped with a dry ice condenser, and the reaction mixture was refluxed under nitrogen for 30 min. Anhydrous methanol (1.0 ml) was added, and the sulfur dioxide was blown off in a stream of nitrogen. Saturated sodium bicarbonate (20 ml) was cautiously added, and the mixture was extracted with three 10-ml portions of 33% methylene chloride in ether. Combined organic layers were washed with two 20-ml portions of brine, dried ($MgSO_4$), and evaporated in vacuo to give 116 mg of the crude imino ester.

Without further purification the imino ester, 80 mg (1.27 mmol) of sodium cyanoborohydride and a small amount of bromocresol green were dissolved in 6 ml of anhydrous methanol under nitrogen. A solution of anhydrous hydrogen chloride gas in methanol was added dropwise until the color of the indicator turned green. The solution was stirred at room temperature for 19 h, adding additional methanolic hydrogen chloride when necessary to maintain the green color. After evaporating the solvent in vacuo, 15 ml of 1 N hydrochloric acid was added, and the suspension was washed with 15 ml of chloroform. The chloroform layer was extracted with three 15-ml portions of 1 N hydrochloric acid. Combined acidic aqueous layers were washed with two 15-ml portions of chloroform, then chilled in an ice bath and made basic to pH 9 with 20% aqueous ammonia. The ammonia solution was

extracted with four 15-ml portions of chloroform. These combined chloroform layers were washed with two 30-ml portions of brine, dried ($MgSO_4$), and evaporated in vacuo to give 55 mg (49%) of the methylamine **12f** as a light colored solid: ^1H NMR ($CDCl_3$) δ 4.68 (d, 1 H), 4.08 (d of d, 1 H), 2.43 (s, 3 H), 1.35 (s, 3 H), 1.01 (t, 6 H); IR (neat) 3340, 2800, 1760, 975 cm^{-1}; high-resolution mass spectrum: calcd for $C_{16}H_{26}O_2N^{79}Br$, 343.1146; found, 343.1161.

The crude 6α-imino ester was similarly prepared from the 6α-cyano bromo lactone **12a** except that the reaction mixture was refluxed for 2 h. The ^1H NMR spectrum suggested a complex mixture of products with very little of the methylimino group present. The IR spectrum indicated that, although there was some imino ester present and some of the γ-lactone was intact, large quantities of a new saturated ester or ketone had formed.

Cyanoborohydride reduction of the imino ester under similar conditions gave the crude methyl amine **12b** in 25% yield. The ^1H NMR spectrum again suggested a complex mixture of products containing *N*-methyl, axial methyl, and isopropyl groups. The IR spectrum indicated the presence of a -NH group, a *N*-methyl group, and a γ-lactone. Because of the poor yield of this reaction and the intractable nature of the product, a pure sample of the methylamine **12b** was never obtained.

6α-Cyano-5β-hydroxyl-5aβ-methyl-9α(2-propyl)-1β,4β-methano-1,4,5,5a,6,7,8,8aβ-octahydro-2*H*-cyclopent[*d*]oxepin-2-one (12c). The bicyclic methyl ester **10a** (40.7 mg, 0.155 mmol) was converted to 40.3 mg of the carboxylic acid as outlined in the procedure for preparation of the bromo lactone **12a.** A solution of the crude olefinic acid and 66.3 mg (0.326 mmol) of 85% *m*-chloroperbenzoic acid in 2 ml of methylene chloride was stirred at room temperature for 40 h. A 33% solution of methylene chloride in ether (5 ml) was added, and the resulting solution was washed with 5 ml of 3% sodium hydroxide. The sodium hydroxide layer was extracted with three 5-ml portions of 33% methylene chloride in ether. Combined organic layers were washed with two 5-ml portions of 3% sodium hydroxide and three 10-ml portions of brine, dried ($MgSO_4$), and evaporated in vacuo to give 38.6 mg (90%) of the hydroxy lactone **12c** as a colorless oil: ^1H NMR ($CDCl_3$) δ 4.55 (d, 1 H), 4.18 (d of d, 1 H), 1.32 (s, 3 H), 0.98 (2 d, 6 H); IR ($CDCl_3$) 3615, 2240, 1770 cm^{-1}.

The 6β-cyano epimer **12g** was similarly prepared from the methyl ester **10b** in 70% yield: ^1H NMR ($CDCl_3$) δ 4.63 (d, 1 H), 4.06 (s, 1 H), 1.22 (s, 3 H), 0.96 (2 d, 6 H); IR (CH_2Cl_2) 3480, 2250, 1770 cm^{-1}.

6α-Cyano-5aβ-methyl-9α(2-propyl)-1β,4β-methano-1,4,5,5a,6,7,8,8aβ-octahydro-2*H*-cyclopent[*d*]oxepin-2,5-dione (12d). To a solution of 38.6 mg (0.147 mmol) of the hydroxy lactone **12c** in 2 ml of acetone at 10 °C was added 2 N Jones reagent[18] dropwise to maintain a yellow color for 30 min. The solution was decanted, and the solids were washed with 2 ml of acetone. Combined acetone solutions were evaporated in vacuo, and the residue was partitioned between 5 ml of water and 5 ml of ether. The aqueous layer was extracted with three additional 5-ml portions of ether. Combined organic layers were washed with 5 ml of water and two 10-ml portions of brine, dried ($MgSO_4$), and evaporated in vacuo to give 29.4 mg (77%) of the keto lactone **12d** as a white solid. An analytical sample was prepared by recrystallization from carbon tetrachloride: mp 129–130 °C; ^1H NMR ($CDCl_3$) δ 4.60 (s, 1 H), 1.46 (s, 3 H), 1.02 (2 d, 6 H); IR ($CDCl_3$) 2240, 1785, 1725 cm^{-1}; high-resolution mass spectrum: calcd for $C_{15}H_{19}O_3N$, 261.1364; found, 261.1353.

The 6β-cyano epimer **12h** was prepared from the hydroxy lactone **12g** using a similar procedure except that the oxidation was continued for 45 min and 33% methylene chloride in ether was used for the extraction solvent. An analytical sample was obtained after recrystallization from carbon tetrachloride: mp 187.5–188.5 °C; ^1H NMR ($CDCl_3$) 4.63 (s, 1 H), 1.43 (s, 3 H), 1.00 (2 d, 6 H); IR ($CDCl_3$) 2240, 1785, 1210 cm^{-1}; high-resolution mass spectrum: calcd for $C_{15}H_{19}O_3N$, 261.1364; found, 261.1344.

Hydroxy Lactone Imino Ester 13. The bispyridine complex of stannous chloride (200 mg) was heated in a 5-ml, round-bottomed flask in a 130 °C oil bath at 3 mm Hg for 30 min, then cooled to room temperature. The flask was fitted with a rubber septum and magnetic stirrer, and 2 ml of anhydrous ether was added. After chilling to 0 °C, dry hydrogen chloride gas was bubbled through the suspension for 20 min. A solution of 11 mg (0.042 mmol) of keto nitrile **12d** in 0.5 ml of dry chloroform was added rapidly followed by 40 μl of anhydrous ethanol, and the resulting suspension was stirred at room temperature for 2 h. Water (5 ml) was added, and the mixture was extracted with four 5-ml portions of methylene chloride. Saturated sodium bicarbonate (15 ml) was carefully added to the aqueous layer before extracting with two additional 5-ml portions of methylene chloride. Combined organic layers were washed with 5 ml of saturated sodium bicarbonate and two 5-ml portions of brine, dried ($MgSO_4$), and evaporated in vacuo to give 8.8 mg (68%) of the imino ester **13.** A pure sample was prepared by recrystallization from carbon tetrachloride: ^1H NMR ($CDCl_3$) δ 4.60 (s, 1 H), 4.23 (q, 2 H), 1.30 (singlet superimposed on a triplet, 6 H), 1.00 (2 d, 6 H); IR ($CHCl_3$) 3170, 1770, 1630 cm^{-1}; mass spectrum *m/e* 307 (mol ion).

8-*epi*-Dendrobine (1b). Method A. The crude imino ester **13** from two of the above reactions (19.4 mg, 0.0633 mmol) was dissolved in 0.5 ml of dry, alcohol-free chloroform under nitrogen. Methyl fluorosulfonate (20 μl) was added, and the solution was stirred for 2 h at room temperature. After evaporating the solvent in vacuo, 1 ml of methanol, 20 mg of sodium cyanoborohydride, and a trace of bromocresol green was added. Concentrated hydrochloric acid was added in microliter quantities until the color of the solution turned pale green. The solution was stirred at room temperature for 23 h, adding more hydrochloric acid when necessary to maintain the pale-green color. After evaporation of the methanol in vacuo, 5 ml of 1% sodium hydroxide was added, and the mixture was extracted with four 5-ml portions of 33% methylene chloride in ether. Combined organic layers were washed with two 5-ml portions of 1% sodium hydroxide, then extracted with four 5-ml portions of 1 N hydrochloric acid. Combined acidic aqueous layers were washed with two 5-ml portions of 33% methylene chloride in ether, chilled in an ice bath, and made basic to pH 9 with concentrated aqueous ammonia. The ammonia solution was extracted with four 10-ml portions of 33% methylene chloride in ether. These combined organic layers were washed with two 10-ml portions of brine, dried (K_2CO_3), and evaporated in vacuo to give 12.9 mg (77%) of crude 8-*epi*-dendrobine (**1b**) as a white solid: mp 105–108 °C; ^1H NMR ($CDCl_3$) δ 4.66 (d, 1 H, *J*, 4 Hz), 2.45 (s, 3 H), 1.29 (s, 3 H), 0.98 (2 d, 6 H); IR ($CHCl_3$) 2790, 1765 cm^{-1}; high-resolution mass spectrum: calcd for $C_{16}H_{25}O_2N$, 263.1884; found, 263.1881.

Methyl 1α-Methylaminomethyl-7aβ-methyl-5α(2-propyl)-2,3,3aβ,4,5,7a-hexahydro-1*H*-indene-4α-carboxylate (10e). Anhydrous sulfur dioxide (7 ml) was condensed into a dry, nitrogen-filled, 15-ml, three-necked flask fitted with a glass stopper, dry ice condenser topped by a nitrogen inlet, and magnetic stirrer. After chilling to −78 °C, 205 mg (0.595 mmol) of dimethylbromonium hexafluoroantimonate was added, and the resulting solution was stirred at −78 °C for 30 min. The nitrile **10a** (99.8 mg, 0.382 mmol) was chilled to −78 °C in a dry, nitrogen-filled, 15-ml, round-bottomed flask, and the cold sulfur dioxide solution was added. After topping the flask with a dry ice condenser, the reaction mixture was stirred under nitrogen and refluxed for 30 min. Anhydrous methanol (50 μl) was added, and the sulfur dioxide was evaporated in a stream of nitrogen. Ice cold saturated sodium bicarbonate (10 ml) was added, and the mixture was extracted with five 5-ml portions of ether. Combined ether layers were washed with two 10-ml portions of brine, dried ($MgSO_4$), and evaporated in vacuo to give 106 mg of the crude oily imino ester.

Without further purification, the imino ester, sodium cyanoborohydride (50 mg, 0.79 mmol), and a small amount of bromocresol green were dissolved in 1 ml of anhydrous methanol under nitrogen. A solution of anhydrous hydrogen chloride gas in methanol was added dropwise until the color of the indicator turned yellow-green. The solution was stirred at room temperature for 16 h, adding additional methanolic hydrogen chloride when necessary to maintain a yellow-green color. After evaporating the solvent in vacuo, 5 ml of 3% sodium hydroxide was added, and the mixture was extracted with four 5-ml portions of ether. Combined ether layers were washed with 5 ml of water and extracted with four 5-ml portions of 1 N hydrochloric acid. Combined acidic aqueous layers were washed with two 5-ml portions of ether, chilled in an ice bath, and made basic to pH 9 with concentrated aqueous ammonia. The ammonia solution was extracted with four 10-ml portions of ether. These combined ether layers were washed with two 10-ml portions of brine, dried (K_2CO_3), and evaporated in vacuo to give 57.8 mg (54%) of the methylamine **10e:** ^1H NMR ($CDCl_3$) δ 5.85 (d of d, 1 H), 5.38 (d, 1 H), 3.67 (s, 3 H), 2.46 (s, 3 H), 1.09 (s, 3 H), 0.94 (2 d, 6 H); IR (neat) 3340, 3030, 2800, 1735 cm^{-1}; high-resolution mass spectrum: calcd for $C_{17}H_{29}O_2N$, 279.2197; found, 279.2209.

8-*epi*-Dendrobine (1b). Method B. To a solution of 16.0 mg (0.057 mmol) of the methylamine **10e** in 0.5 ml of methylene chloride was

added 0.5 ml of 0.705 M aqueous sodium hypochlorite. The heterogeneous reaction mixture was vigorously stirred for 75 min. Water (5 ml) was added, and the mixture was extracted with four 5-ml portions of ether. Combined ether layers were washed with 5 ml of water and two 5-ml portions of brine, dried (K_2CO_3), and evaporated in vacuo to give 16.3 mg (91%) of the oily *N*-chloramine **10f**: ^{1}H NMR ($CDCl_3$) δ 5.90 (d of d, 1 H), 5.43 (d, 1 H), 3.68 (s, 3 H), 2.96 (s, 3 H), 1.13 (s, 3 H), 0.93 (2 d, 6 H); IR (neat) 3030, 1735 cm^{-1}.

To a solution of 7.6 mg (0.024 mmol) of the crude *N*-chloramine **10f** in 0.5 ml of 50% aqueous acetic acid at −8 °C was added 3 drops of 20% aqueous titanium trichloride solution. After stirring for 1 h at −8 °C, ice cold water (5 ml) was added and the solution was made basic to pH 9 with concentrated aqueous ammonia. The purple suspension was extracted with four 5-ml portions of ether, and combined organic layers were washed with two 5-ml portions of brine, dried (K_2CO_3), and evaporated in vacuo to give 6.0 mg of the crude oily tertiary methylamine **14**. Although the ^{1}H NMR spectrum suggested a mixture of compounds, it was evident that peaks due to the *N*-methyl group and olefinic protons of the *N*-chloramine had disappeared, and a new peak due to an amino *N*-methyl group had appeared. The IR spectrum showed evidence of an amine *N*-methyl group and the absence of an amine -NH.

Without further purification, the crude amine **14** was dissolved in 1 ml of dry 2,6-lutidine. Anhydrous lithium iodide (50 mg) was added, and the mixture was refluxed under nitrogen for 11 h. The lutidine was evaporated in vacuo, the residue was partitioned between 5 ml of 1% sodium hydroxide and 5 ml of 33% methylene chloride in ether, and the aqueous layer was extracted with three additional 5-ml portions of 33% methylene chloride in ether. Combined organic layers were washed with two 5-ml portions of 1% sodium hydroxide, then extracted with four 5-ml portions of 1 N hydrochloric acid. Combined acidic aqueous layers were washed with two 5-ml portions of 33% methylene chloride in ether, then chilled in an ice bath and made basic to pH 9 with concentrated aqueous ammonia. The ammonia solution was extracted with four 10-ml portions of 33% methylene chloride in ether. The combined organic layers were washed with two 10-ml portions of brine, dried ($MgSO_4$), and evaporated in vacuo to give 2.9 mg (45%) of crude 8-*epi*-dendrobine (**63**) as a yellow oil. A pure sample was obtained by HPLC purification (30 cm μ Bondapak C18, elution with 3:2 acetonitrile:1% aqueous ammonium carbonate, 2.0 ml/min).

This material was identical in all respects with that prepared by the route described above.

Acknowledgment. Support of this work by a Smith Kline and French Co. Fellowship (James J. Wade), an Institute of Technology Corporate Associates Fellowship (April J. Evans), and by Grant CA-10849 from the National Cancer Institute, United States Public Health Service, is gratefully acknowledged.

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