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Total Synthesis of (±)-Dendrobine[1†]

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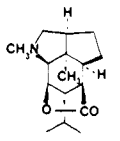
Contribution from the Department of Chemistry, Harvard University, Cambridge, Massachusetts 02139. *Received June 15, 1979*

Abstract: A total synthesis of (±)-dendrobine is described. (*E,E,E*)-Triene **9a**, available stereoselectively in six steps from methyl 4-(diethylphosphono)crotonate, cyclizes by an intramolecular Diels–Alder reaction to afford 75–83% of a mixture of four perhydroindanols containing 83% of endo isomers **8a** and **8b**. Epimers **8a** and **8b** were transformed into nitrile **25** by two separate routes, each of which involves epimerization of C4, oxidation, angular methylation, and reductive cyanation. Nitrile **25** served as a precursor of amino ester **3** by two separate routes, the most efficient of which proceeded via bromolactone **40**. Epoxidation of the trichloroethylurethane **58** prepared from **3** afforded a mixture of two epoxides, both of which were utilized in the synthesis. The minor epoxide, **59** (38–40% yields), was transformed into dendrobine via methyl ketodendrobinate **57**, while the major epoxide **60** (45–48% yields) was recycled to **58**. Additional strategies for the synthesis of dendrobine from **3** are discussed.

Dendrobine (**1**) was the first alkaloid to be isolated from *Dendrobium nobile* Lindl, the ornamental orchid thought to be the original plant used to make the Chinese drug "Chin-Shih-Hu".[3,4a] To date, a total of 14 structurally related alkaloids have been isolated from *D. nobile* and other *Dendrobium* species.[4] Structures have been assigned to these alkaloids on the basis of extensive degradation studies, by chemical interconversions, and/or by spectroscopic methods.[4] The structural and pharmacological similarities[4a] between dendrobine and picrotoxinin (**2**) have stimulated interest in the total synthesis



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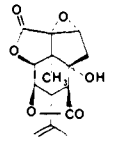


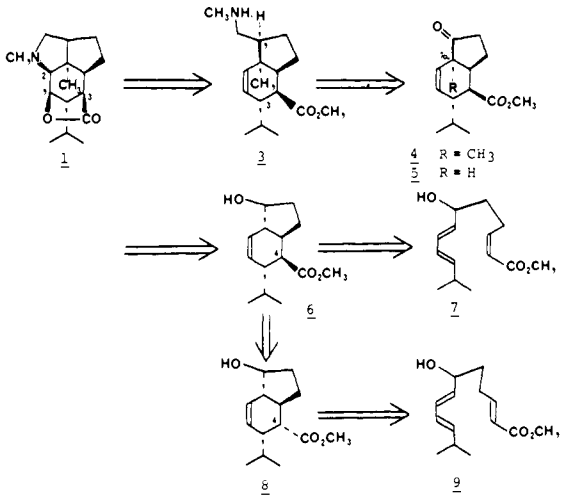
2

of **1**.[5,6] Herein we describe the details of our total synthesis of this alkaloid, a preliminary account of which has been previously reported.[7]

Synthetic Strategy

Dendrobine is a challenging synthetic target owing to the presence of seven asymmetric centers on a compact carbon skeleton. Scheme I contains an outline of our analysis of the synthetic problem. It was anticipated that the two heterocyclic rings of the alkaloid could be formed by an oxidative cyclization sequence involving amino ester **3**. The stereocenter at C1 of **3** would be generated by attaching a functionalized one-carbon unit to C1 of ketone **4** with stereochemical induction from the cis ring fusion. Ketone **4** would be prepared by angular methylation of **5**, the generation of a cis fusion being anticipated on the basis of the well-known preference for alkylations of perhydroindanones to afford the cis-fused isomer.[8] As a consequence, the stereochemistry at C7a of **5** and its precursors was of relatively minor strategic importance. Thus, trans-fused hydroxy ester **6** was regarded as a potential precursor of **5**. A trans fusion in **6** was considered to be advantageous since all four stereocenters could be *formally* introduced by the intramolecular Diels–Alder reaction of **7**.[9] However, in that preparation of **6** from **7** would require that **7** cyclize by way of an exo transition state in preference to the endo pathway, which we assumed would be a much more facile process, an alternative route to **6** was sought. The solution arrived at called for the synthesis of **8**, the C4 carbomethoxyl epimer of **6**, by the endo Diels–Alder reaction of **9** in anticipation that **8**, or subsequent intermediates derived therefrom, could be equilibrated with the natural C4 ester epimers.

Scheme I



1 **3** **4** R = CH_3; **5** R = H **6** **7** **8** **9**

Synthesis of Triene 9

Having chosen triene **9** to serve as the Diels–Alder substrate, a stereoselective synthesis of this intermediate was sought. Few problems of stereochemical control were anticipated since each olefinic unit in **9** is in its most stable geometrical form. It was anticipated that the dienophilic unit would be introduced using a Wadsworth–Emmons modified Wittig reaction,[10] and that the (*E,E*)-butadiene would be elaborated from methyl (*E,E*)-6-methylhepta-2,4-dienoate (**11a**) (Scheme II).

Sato et al. have reported that treatment of 4-(triethylphosphono)crotonate with NaH and isobutyraldehyde affords the ethyl ester corresponding to **11a** in 52% yield.[11] Attempts

† This paper is dedicated to the memory of the late Professor Robert Burns Woodward in grateful recognition and deepest admiration for his pervasive contribution of example, inspiration, and support.

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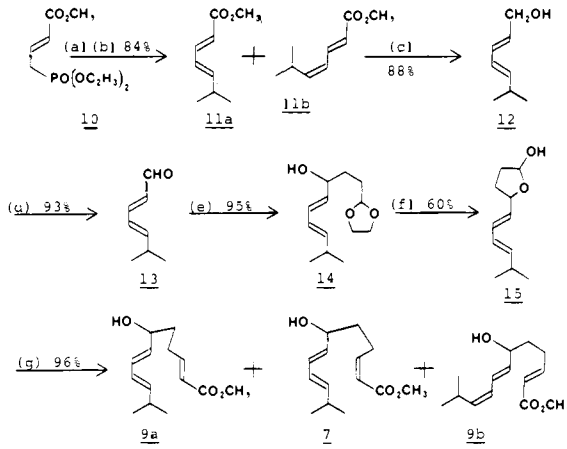
Scheme II



Key

(a) TMS_2NLi, THF, −78 °C; (b) isobutyraldehyde, −40 °C; (c) DIBAH, Et_2O; (d) Me_2SO, oxalyl chloride, CH_2Cl_2, −78 °C followed by Et_3N; (e) $BrMgCH_2CH_2CHOCH_2CH_2$, THF; (f) THF, aqueous HCl; (g) carbomethoxymethylenetriphenylphosphorane, CH_2Cl_2.

to apply this method to methyl 4-(diethylphosphono)crotonate[12] **10** afforded low yields (30–40%) of distilled diene esters. The expected ester **11a** was identified by its characteristic NMR (δ 7.26 (m, 1 H), 6.10 (m, 2 H, H_4H_5), 5.79 (d, J = 15 Hz, H_2)) and UV (λ_{max} 259 nm, log ϵ 4.36 (EtOH)) spectra, each of which bear a striking resemblance to those of sorbic acid.[13] However, the distilled product usually contained no more than 60–70% of **11a** under these conditions. The major isomeric impurity in these samples was **11b**, the presence of which was determined by VPC and by the presence of a one-proton signal for C3-H in the NMR spectrum (δ 7.62 (dd, J = 12, 15 Hz)).

When the lithium anion of **10**, prepared by treatment of **10** with lithium hexamethyldisilazide at −78 °C in THF, was treated with isobutyraldehyde at −40 °C, a mixture of diene esters containing 93% of **11a** (GC analysis) was obtained in 84–86% yield after distillation.[14] Isomerically pure **11a** could be obtained from these mixtures in 75% yield from **10** by spinning-band distillation. However, the 93% pure material was routinely used in subsequent steps since **9b**, which derives from **11b**, fails to cyclize under the conditions employed for the Diels–Alder reactions of **9a**.

Reduction of **11** with DIBAL-H in Et_2O at 0 °C afforded diene alcohol **12** in 88% yield.[15] Oxidation of **12** with 9 equiv of CrO_3–pyridine in CH_2Cl_2[16] afforded 60–67% of diene aldehyde **13**, semicarbazone mp 193.5–195 °C, whose NMR and UV spectra were reminiscent of those of sorbaldehyde.[13] Alternatively, aldehyde **13** is more conveniently prepared by oxidation of **12** with the reagent prepared from Me_2SO and oxalyl chloride (93% yield).[17,18a,19]

Treatment of **13** with the Grignard reagent prepared from 1.8–2.0 equiv of 2-(2-bromoethyl)-1,3-dioxolane in THF[20] smoothly afforded **14** in isolated yields greater than 95%. Hydrolysis of **14** was achieved by treating the acetal with aqueous HCl in DME or THF at 23 °C for 40–48 h. Under these conditions there were obtained 60–70% yields of hemiacetal **15** and 15–20% yields of mixed acetal **16**, which were easily separated by chromatography on Florisil. Although **16** is undoubtedly an intermediate in the hydrolysis of **14** → **15**,

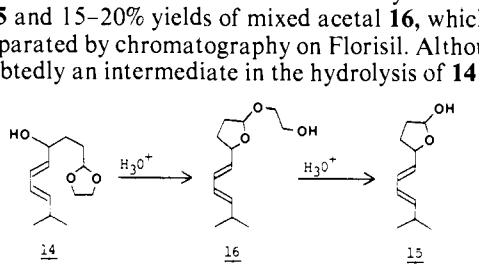
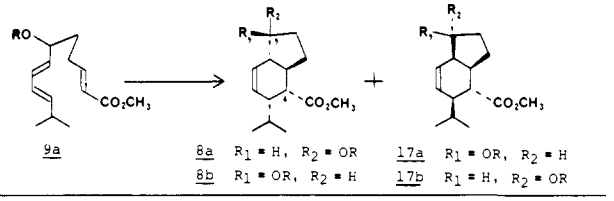


Table I. Intramolecular Diels–Alder Reactions of **9a**



substrate	temp, °C	yield,[b] %	product ratios[a] 8a	8b	17a	17b	endo:exo[a]
R = H[c]	150	71	37[g]	37	(4)	26	70:30[g]
R = $CH_2C_6H_5$[d]	270	[f]	26	49	5[h]	20	75:25
	150	78	31	51	4[h]	14	82:18
	115	64	30	53	4[h]	13	83:17
R = $SiMe_3$[c,e]	150	83	52[g]	31	(4)	17	79:21[g]
	115	82	53[g]	32	(2)	15	83:17[g]

[a] Determined by analytical GC and are the normalized average of two to four integrations. The values in parentheses were determined by product isolation. [b] The total yield of chromatographed products. [c] The GC analysis was performed on the corresponding Me_3Si ethers using a 7-ft, 4% Zonyl E-7 on Chromosorb G column at 145 °C. [d] The GC analysis was performed at 195 °C on the column described in *c*. [e] Products were isolated at R = H after deprotection. [f] This reaction occurred upon injection of **9** (R = $CH_2C_6H_5$) into the GC port at 270 °C. [g] The Me_3Si ethers of **8a** and **17a** do not resolve by analytical GC. The ratio indicated for **8a** represents the sum of **8a** and **17a**. The endo:exo ratio in these cases are corrected for the normalized amount of **17a** isolated by silica gel chromatography. [h] Tentative assignment based upon the detection of four products by GC; this isomer could not be separated from benzyl ether **8a** by silica gel chromatography.

attempts to increase the yield of **15** by increasing the reaction time or by increasing the acid strength were unsuccessful owing to the sensitivity and ready decomposition of **15**. However, the separated **16** could be hydrolyzed to afford additional quantities of **15**.

The final step of the synthesis of **9** was accomplished by treating hemiacetal **15** with 1.05 equiv of carbomethoxymethylenetriphenylphosphorane in CH_2Cl_2.[21] Filtration of the reaction mixture through silica gel to remove triphenylphosphine oxide afforded the crude product (90–96% yield) which was carefully separated by column chromatography. In this manner there were obtained **9a** (82%), **7** (5%), and **9b** (0.6%), the latter of which was not observed when the sequence was begun starting with isomerically pure **11a**. The ^1H NMR spectra of **9a** (δ 6.98 (dt, J = 16, 7 Hz, H_3), 2.28 (m, H_4)) and **7** (δ 2.6 (m, H_4)) clearly indicated that the dienophilic double bonds were trans and cis, respectively.[22] The stereochemistry depicted for **9b** was unambiguously assigned on the basis of double-irradiation experiments which indicated that $J_{2,3}$ = 16, $J_{7,8}$ = 15, and $J_{9,10}$ = 11 Hz.

Stereochemistry of the Intramolecular Diels–Alder Reaction

The Diels–Alder reactions of **9a** and various protected derivatives were performed by heating a 0.1–0.2 M toluene solution of the substrate in a resealable Carius tube until the reactions were judged complete by NMR analysis. Product distributions were then determined by GC analysis. These analyses, in conjunction with product isolation, indicated that four diastereomeric adducts were formed (Table I) and that the most favorable endo:exo ratio was obtained when the reactions were performed at as low a temperature as possible. In addition, it was evident that protection of the hydroxyl group increased the yield and the endo:exo ratio. Owing to the ease with which the trimethylsilyl protecting group can be introduced and removed,[23] this mode of protection proved to be the method of choice.[24,25]

Preparative cyclizations were performed by treating a tol-

Table II. ^{13}C NMR Spectra of **6**, **8**, and **17**[a,b]

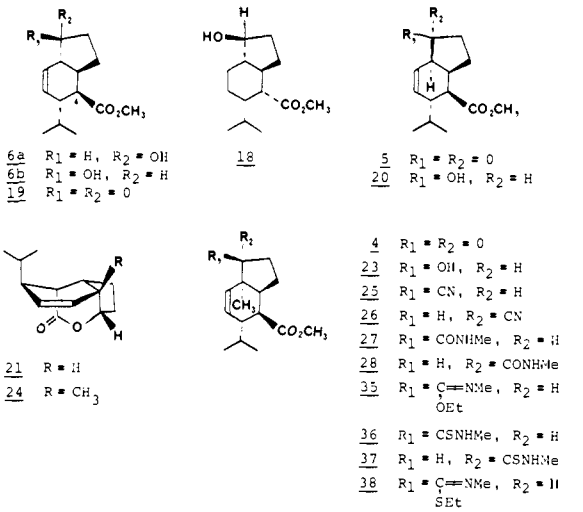
carbon[c]	6a	6b	8a	8b	17a	17b	multiplicity[d]
C=O	175.9	175.6	175.0	174.7	177.6	177.1	s
[C6]	132.3	129.7	129.6	128.9	132.9	128.5	d
[C7]	127.0	128.8	127.7	127.4	125.0	127.6	d
C1	72.5	75.9	72.4	75.7	74.9	78.8	d
CH_3O	51.6	51.7	51.5	51.6	51.8	51.8	q
[C4]	45.6	47.0	51.2	52.4	49.5	48.6	d
[C5]	44.3	44.8	50.9	50.9	46.9	48.6	d
[C7a]	43.2	43.7	44.0	43.8	44.5	44.3	d
[C2]	34.5	33.5	34.8	33.5	33.8	34.2	t
[C3]	26.1	25.7	28.1	27.5	28.5	27.3	t
[C3a]	38.0	39.6	37.0	38.4	39.3	39.3	d
[C8]	33.5	33.5	30.6	30.6	29.6	29.6	d
[C9]	20.7	20.6	23.5	23.5	21.2	21.1	q
[C10]	20.7	20.6	19.4	19.3	16.8	16.7	q

[a] Spectra were measured in $CDCl_3$ at 25.1 MHz. [b] Chemical shifts are expressed in δ_C units. [c] The resonances corresponding to the bracketed carbon atoms have not been unambiguously assigned. [d] Multiplicity of the signals observed in the off-resonance decoupled spectra.

uene solution of **9** with 1.2 equiv of bis(trimethylsilyl)acetamide (BSA)[23] at 23 °C for up to 7 h followed by heating the solution either at 150 °C for 15 h in a sealed tube or at reflux (115 °C) for 85–100 h. The trimethylsilyl protecting groups were then removed by mild hydrolysis (MeOH, 1 N HCl, 23 °C, 15 min) to afford a mixture of **8a**, **8b**, **17a**, and **17b** (75–83% combined yield after chromatography) together with small amounts (~5%) of uncyclized trienes **9a** and **9b**. The latter isomer was observed only when the sequence was begun starting with 93% pure **11a**. The uncyclized trienes were easily separated at this stage by selective saponification (MeOH, aqueous NaOH, 23 °C, 2 h), conditions under which the cyclized isomers are completely inert. Careful chromatography of one such mixture obtained from a 115 °C cyclization afforded 1% of **17a**, 38% of **8a**, 13% of **8b**, and 27% of a 63:37 mixture of **8b:17b**. Although the latter mixture could be further separated with only a minimal loss of material, the discovery that these mixtures could be used directly in the next stage of the synthesis made such efforts unnecessary.

The major products **8a**, mp 53–54 °C, and **8b**, mp 75–76 °C, were initially assumed to be endo adducts on the basis of literature analogy.[26] The assignment of relative stereochemistry to C1 rests upon NMR data which is consistent only with C1-H being cis to C7a-H in **8a** (H_1: δ 4.28, dt, J = 2, 5 Hz) and trans in **8b** (H_1: δ 3.88, q, J = 8 Hz). The signal for C4-H of each isomer appears as a doublet of doublets, $J_{3a,4}$ = 10.5 and $J_{4,5}$ = 7 Hz, which indicates that the carbomethoxyl group is in an equatorial position and that the isopropyl is pseudoaxial. These assignments were confirmed by hydrogenation of **8b** to **18**, mp 77–78 °C, for which $J_{3a,4}$ = 10.5 and $J_{4,5}$ = 4 Hz.

Epimerization of either **8a** or **8b** with 3–5 equiv of NaOMe in MeOH at 110 °C for 20–24 h resulted in partial epimerization of the C4 carbomethoxyl groups. In this manner there were obtained **6a** (68%) from **8a** (77% based upon unrecovered **8a**) and **6b** (67–75%) from **8b** (80–89% based upon unrecovered **8b**). Noteworthy of these epimerizations is that the carbomethoxyl group moves from an equatorial position in **8a** and **8b** to an axial position in **6a** and **6b** (for each, the ^1H NMR signal for C4-H appears as a broad doublet, J = 2 Hz) as a consequence of a destabilizing gauche interaction in the equatorial isomers **8a** and **8b**.[27] Also, unseparated mixtures of **8b** and **17b** may be subjected to the epimerization reaction as **17b** is stable toward the reaction conditions. For example, the 63:37 mixture of **8b** and **17b** described above was epimerized to afford 45% of **6b**, 70% based upon the amount of **8b** present in the mixture.

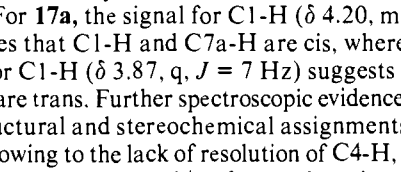


Oxidation of either **6a** or **6b** with Swern's TFAA–Me_2SO reagent[28] afforded in high yield a crude, unstable ketone **19** (NMR δ 6.12 (dt, J = 10, 3 Hz, 1 H), 5.61 (dt, J = 10, 3.5 Hz, 1 H), 3.68 (s, 3 H), 0.96 and 0.92 (two d, J = 6 Hz, 6 H)) which smoothly isomerized to **5**, mp 69–71 °C (NMR δ 5.76 (dt, J = 10, 3 Hz, 1 H), 5.49 (dt, J = 10, 2 Hz, 1 H), 3.74 (s, 3 H), 1.03 and 0.78 (two d, 6 H, J = 6 Hz)) upon silica gel chromatography. The yields of **5** were 91% from **6a** and 84% from **6b**. The isomerization of **19** → **5** is consistent with the assignment of a trans ring fusion to the former and a cis fusion to the latter.[29] That **5** possesses a cis ring junction was proven by reduction with $NaBH_4$ in EtOH to afford a single alcohol **20**, mp 76–77 °C (73%), which upon treatment with trifluoroacetic acid in CH_2Cl_2 (23 °C, 2 days) afforded lactone **21** (73%). Therefore, the stereochemical assignments made for **8a** and **8b** were proven.

The stereochemical assignments made for **17a** and **17b** rest largely upon theoretical considerations.[30] That these isomers possess identical ring systems is suggested by the striking similarities of their ^{13}C NMR spectra (Table II). Inspection of the data in Table II reveals that the ^{13}C spectra of **6a** and **6b** as well as those of **8a** and **8b** are also similar within each epimeric series. Moreover, there is almost no overlap of signals between isomers from different stereochemical series. Hence, it is unlikely that the similarities in the spectra of **17a** and **17b** are merely coincidental.

The stereochemistry at C1 of **17a** and **17b** was assigned by ^1H NMR. For **17a**, the signal for C1-H (δ 4.20, m, $W_{1/2}$ = 8 Hz) indicates that C1-H and C7a-H are cis, whereas for **17b** the signal for C1-H (δ 3.87, q, J = 7 Hz) suggests that C1-H and C7a-H are trans. Further spectroscopic evidence in support of these structural and stereochemical assignments could not be obtained owing to the lack of resolution of C4-H, C5-H, and C7a-H from each other and/or from other signals in their 270-MHz spectra.

However, **17b** has been correlated with **22**, a minor product obtained from the Diels–Alder reactions of **7** (Table III). Thus,



22 17b

treatment of **22** with excess KOMe in MeOH (110 °C, 6 h) afforded **17b** in 85% yield. This data is consistent with the carbomethoxyl moving from an axial position in **22** (C4-H: dd, J = 4,5 Hz) to an equatorial position in **17b**.

It is interesting to note that our initial assumption that cis ester **7** would cyclize primarily by endo transition states is in-

correct, as trans-fused adducts **6a** and **6b** are formed with selectivity approaching that observed for the cyclizations of **9** (see Tables I and III). These results have been discussed in more detail elsewhere.[31] It is now apparent that utilization of **7** as a synthetic intermediate would provide stereoselective entry into the natural series of C4 carbomethoxyl epimers, thereby obviating the need to generate this stereocenter by an epimerization reaction as required by the routes described herein. A stereoselective synthesis of the *tert*-butyldimethylsilyl ether of **7** has been achieved.[18b] This chemistry will be the subject of a subsequent publication from our laboratory.

Synthesis of Nitrile 25

The next stage of the synthesis involved angular methylation of **5**. This crucial transformation was accomplished by treating a DME solution of **5** and excess CH_3I with exactly 1.0 equiv of 1 M KO-*t*-Bu in *t*-BuOH. There was thus obtained crude, crystalline **4** in greater than 95% yield. Pure **4** was obtained in 88% yield by direct crystallization (76%) and chromatography of the mother liquors (12%). However, crude **4** was sufficiently pure for use directly in subsequent stages of the synthesis.

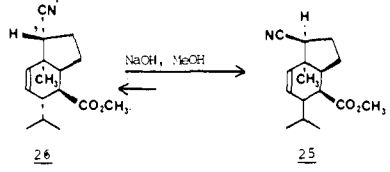
The stereochemistry of the ring fusion in **4** was shown to be cis by $NaBH_4$ reduction (giving a single alcohol **23**, mp 83–87 °C) and trifluoroacetic acid catalyzed lactonization to give lactone **24**, mp 55–56 °C, in 73% overall yield.

Our attention next turned to introducing the functionalized carbon atom required for eventual elaboration of the pyrrolidine ring. It was apparent that a nitrile would serve our purposes, since reductive amination[32] might transform **25** into amino ester **3**. Of a variety of methods considered, only the reductive cyanation procedures of Schöllkopf and van Leusen could be successfully applied to **4**.[33]

Thus, treatment of crude **4** with 3–4 equiv of tosylmethyl isocyanide and 5 equiv of KO-*t*-Bu in DME–*t*-BuOH solution afforded an easily separated mixture of two epimeric nitriles in 52–58% combined yield after chromatography.[34] Under these conditions, the ratio of separated products was 78:22. It was anticipated that the stereochemistry at C1 could be assigned by comparison of the chemical shifts of the angular methyl groups, as the isomer with the more deshielded methyl would have a cis relationship between it and the nitrile.[35] The angular methyl of the major isomer **25**, mp 47–51 °C, appears at 1.26 ppm, whereas the methyl of **26**, mp 90–91 °C, appears at 1.35 ppm. Consequently, **25** was assigned a trans relationship between the methyl and the nitrile.

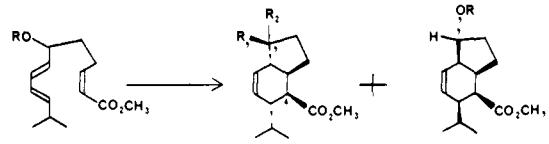
These assignments were confirmed by comparison of the chemical shifts of the angular methyl groups of the derived *N*-methyl amides **27** and **28**, which were prepared from **25** and **26** in 44–52 and 80% yields, respectively, by sequential reaction with methyl fluorosulfonate[36] and water.[37] In contrast to the deshielding influence of the nitrile on a cis methyl group, a methyl group cis to an amide is shielded by the amide carbonyl.[5a] In agreement with this prediction, the angular methyl group of **27** (prepared from **25**), mp 124–126 °C, appears at 1.25 ppm, whereas that of **28**, mp 155–157 °C, appears at 1.07 ppm.

Attempts were made to transform the minor nitrile **26** into the desired **25** by equilibration at C1. Although it was possible that four nitriles would be obtained by epimerization at C4 as well as at C1, treatment of **26** with excess NaOH in MeOH (80 °C, 20 h) followed by diazomethane esterification afforded a binary mixture of **25** and **26**, from which **25** was isolated in



26 25

Table III. Intramolecular Diels–Alder Reactions of **7**



7 → **6a** R_1 = H, R_2 = OR; **6b** R_1 = OR, R_2 = H; **22**

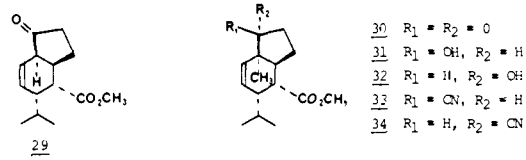
substrate	temp, °C	yield,[b] %	product ratios[a] 6a	6b	22	endo:exo[a]
R = H[c]	150	60	45	32	23	23:77
R = $SiMe_3$[c,d]	180	77	49	28	23	23:77
	150	73	49	27	24	24:76
	130	50	(52)	(23)	(25)	(25:75)
	115	71	50	25	25	25:75

[a] Determined by analytical GC and are the normalized average of two to four integrations. The values in parentheses were determined by product isolation. [b] The total yield of chromatographed products. [c] The GC analysis was performed on the corresponding Me_3Si ethers using a 7-ft, 4% Zonyl E-7 on Chromosorb G column at 165 °C. [d] Products were isolated as R = H after deprotection.

68% yield (92% based upon unrecovered **26**) by silica gel chromatography. The overall yield of **25** from **4** was therefore raised to 49–55% by efficient recyclizing of **26**.

The complete carbon skeleton and five of the seven stereocenters of dendrobine were now assembled in the form of **25**. Each stereocenter of this intermediate had been introduced stereoselectively in five steps starting from triene **9**, a sequence which was accomplished in ~21% overall yield (including recycles). However, successful execution of this sequence required that the Diels–Alder reaction mixture and the two subsequent epimerization mixtures be carefully separated by chromatography. Since each of these separations required a considerable investment of time and effort, an alternative route to **25** was sought. The development of the new route was stimulated in part by the observation that the stereocenter at C4 of **25** and **26** was undisturbed, and hence was already in the most stable configuration, during the epimerizations of C1 of **26**.

Oxidation of pure **8a** with the reagent prepared from trifluoroacetic anhydride and Me_2SO[28] afforded **29**, mp 76–77 °C, in 95% yield following silica gel chromatography. Angular methylation of **29** (1.0 equiv of KO-*t*-Bu, DME, excess CH_3I)



29 → **30** R_1 = R_2 = O; **31** R_1 = OH, R_2 = H; **32** R_1 = H, R_2 = OH; **33** R_1 = CN, R_2 = H; **34** R_1 = H, R_2 = CN

afforded **30**, mp 75–76 °C (>95% crude yield), in 90% yield by direct crystallization and chromatography of the mother liquors.

The same sequence was performed starting with an *unseparated* mixture of Diels–Alder adducts **8a**, **8b**, **17a**, and **17b** which contained 83% of **8a** and **8b**. Oxidation of this mixture as described above afforded a mixture consisting mostly of **29** in 82% yield. Angular methylation of this impure material followed by fractional crystallization afforded pure **30** in 51% yield. Thus, **30** was readily available in large quantity from triene **9** without the need to carefully chromatograph any intermediates.

The stereochemistry of **30** was confirmed by correlation with alcohol **23**. Thus, reduction of **30** with $NaBH_4$ in EtOH afforded a mixture of two readily separable alcohols: **31** (63% isolated) and **32**, mp 50–55 °C (30% isolated). Treatment of **31** with 6 equiv of KOMe in MeOH (110 °C, 18 h) afforded **23** (87%) uncontaminated by detectable (TLC, NMR)

quantities of **31**. This experiment provided unequivocal verification that the natural C4 carbomethoxyl epimers are much more stable than their unnatural isomers.

Reductive cyanation (TOSMIC, KO-*t*-Bu, DME–*t*-BuOH) of **30** afforded a 1:1 mixture of nitriles **33**, mp 45–50 °C (NMR: δ 1.16, 3 H, s), and **34**, mp 58–60 °C (NMR: δ 1.22, 3 H, s) in 48–55% yield. These isomer mixtures were not routinely separated. Rather, they were indirectly epimerized (5 equiv of NaOMe, MeOH, 90 °C, 17 h) to afford an easily separated mixture of **25** (59% isolated) and **26** (23%). Recycling **26** under the same conditions afforded an additional 17% of **25** (two recycles), which increased the yield of **25** from 33–34 to 77%.

The alternative synthesis of **25** was thus complete. Although the overall yield of **25** from **9** by this method was only 14%, somewhat lower than the 21% yield realized by the original method, it proved to be much easier to perform than the original. Consequently, this route was the method generally used to prepare large quantities of **25**.

Synthesis of Amine 3

It was initially anticipated that amine **3** could be synthesized directly from nitrile **25** by reductive amination. Unfortunately, **3** was not obtained when **25** was sequentially treated with methyl fluorosulfonate and $NaBH_4$ or $NaCNBH_3$[38] in dry EtOH or MeOH. Instead, amide **27** was obtained in low yield. Attempts to reduce the nitrilium ion prepared by the reaction of **25** with trimethyloxonium tetrafluoroborate or dimethylbromonium hexafluoroantimonate[6c] were equally unsuccessful.

The failure of this reduction step prompted us to explore the reduction of amide **27** to amine **3**.[39] However, sequential treatment of **27** with either triethyloxonium tetrafluoroborate or methyl fluorosulfonate and either $NaBH_4$ or $NaCNBH_3$ resulted in no net reaction. Attempts to isolate ethyl imino ether **35** from the reaction of **27** with triethyloxonium tetrafluoroborate were also unsuccessful.

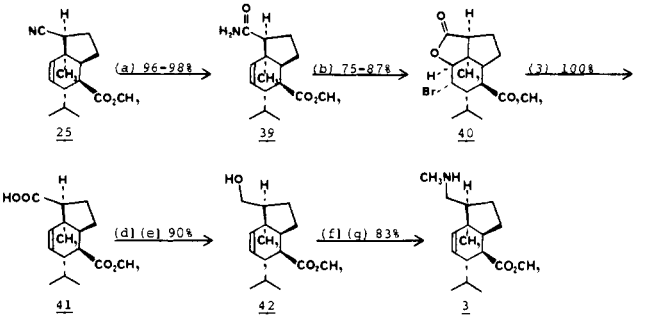
The transformation of **27** into **3** was eventually accomplished in the following manner. Treatment of **27** with P_2S_5[40] in refluxing benzene or toluene afforded a mixture of two thioamides which were separated by silica gel chromatography. The stereochemistry at C1 of the two isomers **36** (57% yield; NMR δ 1.25, 3 H, s) and **37** (20% yield; NMR δ 1.03, 3 H, s) was assigned on the basis of the chemical shifts of their respective angular methyl groups.[5a] Attempts to minimize the formation of **37**, which was presumably formed by an acid-catalyzed isomerization of **36**, by conducting the reaction in the presence of pyridine were unsuccessful. Under such conditions, no reaction was observed.

Thioamide **36** was reduced to amine **3** by a two-step reaction sequence patterned after Borch's method for reduction of amides.[39] Thus, treatment of **36** with triethyloxonium tetrafluoroborate in CH_2Cl_2 followed by in situ reduction of the presumed thioimino ether intermediate **38** with a solution of $NaBH_4$ in EtOH afforded amine **3** in 70% yield.

Although these preliminary studies established that **3** could be prepared from **25**, the low overall yield (~20%) and the loss of stereochemistry at C1 during the P_2S_5 reaction were unacceptable. An alternate route to **3** was therefore sought. A very successful solution to this problem is outlined in Scheme III.

Hydrolysis of **25** by treatment with alkaline hydrogen peroxide afforded amide **39**, mp 185–186 °C, in yields of 95–98%.[41] Oxidation of **39** with NBS in wet THF containing acetic acid afford bromolactone **40**, mp 107–108 °C, in 75–87% yield.[42] The obtainment of **40** from **25** unequivocally confirms the stereochemical assignment for C1 of these intermediates. Reduction of **40** with Zn in refluxing acetic acid afforded carboxylic acid **41**, mp 112–113 °C, quantitatively.[43]

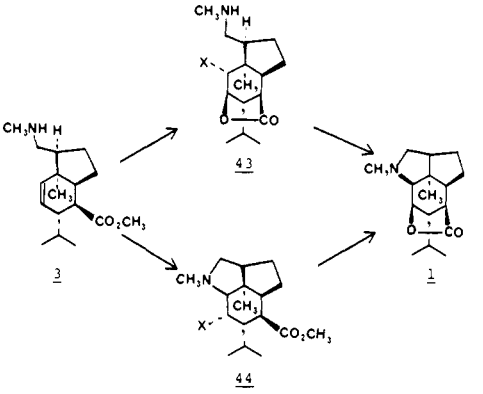
Scheme III



Key

(a) H_2O_2, NaOH, EtOH; (b) NBS, THF, H_2O, HOAc; (c) Zn, HOAc, reflux; (d) oxalyl chloride; (e) $LiAlH(O\text{-}t\text{-}Bu)_3$; (f) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C; (g) Me_2SO, xs CH_3NH_2, 85 °C, 18 h.

Scheme IV

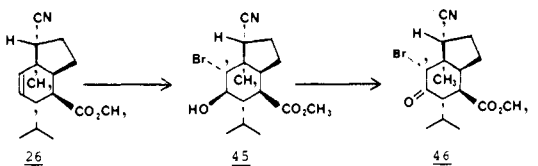


Note that this oxidation–reduction sequence effects the selective hydrolysis of the C1 carboxamide, a process which could not be accomplished using more classical methods. Reduction of the acid chloride of **41** with lithium tri-*tert*-butoxyaluminum hydride in THF at 0 °C afforded primary alcohol **42** in 90% overall yield from **40** (99% based upon unrecovered **41**).[44] Substitution of the alcohol in **42** was smoothly accomplished by displacing the corresponding mesylate[45] with methylamine in Me_2SO at 85 °C. In this manner, an 83% yield of amine **3** was obtained which was identical in all respects with the material prepared by reduction of thiamide **36**.

Total Synthesis of (±)-Dendrobine

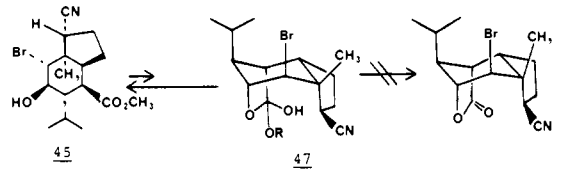
Two strategies were initially considered for the elaboration of **3** into dendrobine (Scheme IV). In one approach, a halolactonization would be effected (**3** → **43**) prior to an intramolecular amine alkylation (**43** → **1**). In the second, an oxidative cyclization (**3** → **44**) would precede the lactonization step (**44** → **1**).

The halolactonization approach was studied briefly using nitriles **25**, and **26** and their corresponding carboxylic acids as model systems. Although these acids would not halolactonize under a variety of conditions, the acids and their esters were oxidized stereoselectively by HOBr. As an illustration, treatment of **26** with NBS in wet DME containing HOAc afforded bromohydrin **45** as the major product in 65% yield.[46] The ^1H NMR signal for C7-H in **45** (d, J = 10 Hz) requires that the bromine and the alcohol occupy equatorial positions. The regiochemistry of the oxidation was ascertained by Jones oxidation of **45**, affording **46** (85% yield) in which the signal for



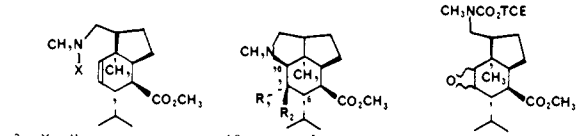
C7-H (eq, -CHBr-) appears as a sharp singlet. Similar results were obtained in the HOBr oxidations of **25**.

Thus, a method was available for introducing the stereochemical elements at C6 and C7 necessary for a lactonization–pyrrolidination sequence. However, attempts to directly lactonize **45** by reaction with trifluoroacetic acid at room temperature or with *p*-toluenesulfonic acid in refluxing benzene were unsuccessful, possibly as a result of a severe 1,3-diaxial interaction which develops in the tetrahedral intermediate **47**. Although it remained a possibility that lactonizations of intermediates analogous to **45** could be driven by dehydrating the corresponding carboxylic acids under irreversible conditions (DCC, mixed anhydride, etc.), our attention turned to an examination of the second oxidative cyclization strategy.



45 **47**

In recent years a number of groups have examined the addition of chloro amines to olefins.[47-49] Pyrrolidines are generally formed to the exclusion of piperidines except in cases where steric factors intervene.[47,50] The $TiCl_3$-catalyzed cyclization was chosen for study since this catalyst has been shown to be the best available for such reactions.[47d] In the event, treatment of amine **3** with 2 equiv of commercial NaOCl[51] followed by reaction of the crude chloro amine **48** with 0.1–0.2 equiv of $TiCl_3$ in 50% aqueous acetic acid at −10 °C provided product mixtures containing at best only 20–30% of a chloropyrrolidine tentatively assigned structure **49**; the remainder of the mixtures consisted largely of **3**, a product of simple reduction of **48**. That a compound with the molecular formula of **49** had been produced was suggested by the mass spectra of the mixtures which exhibited molecular ions at *m/e* 315 and 313. In addition, the NMR spectra of the crude product contained a new one-proton triplet, J = 2 Hz, at 4.45 ppm (-CHCl-), the multiplicity of which suggested that the chloride was bonded axially to C7. (By comparison, the signal for C7-H of alcohol **50** is a doublet of doublets, $J_{7,10}$ = 3.0, $J_{6,7}$ = 2.5 Hz, vide infra).



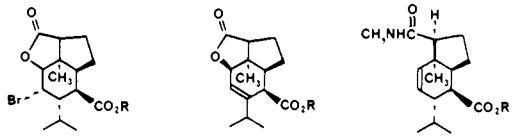
3 X = H
48 X = Cl
55 X = NO
58 X = $CO_2CH_2CCl_3$

49 R_1 = Cl, R_2 = H
50 R_1 = OH, R_2 = H
56 R_1 = R_2 = NOH
57 R_1 = R_2 = O
62 R_1 = H, R_2 = OH

59 α-epoxide
60 β-epoxide

While attempts to optimize the yield of **49** were in progress, the next stage of the planned synthesis—the intramolecular displacement of halide by carboxyl or carboxylate—was explored using bromolactone **40** as a model substrate. Attempts to induce lactonization of **40** by direct solvolysis were unsuccessful, as were attempts to induce ring closure by treatment of **40** with AgOAc in wet HOAc at 100 °C[52] or with AgOAc in wet Me_2SO. A reaction was observed when **40** was treated with $AgBF_4$ in Me_2SO,[53] but the single product proved to be olefinic lactone **51**.

Our attention next turned toward the preparation of carboxylic acid **52**, as we anticipated that a salt of **52** might be induced to undergo an S_N2 displacement of bromide. Attempts to induce ester cleavage by treatment of **40** with LiI in lutidine[54] or DMF[55] were unsuccessful. These reactions directly afforded **51** as the major product, together with smaller quantities of the corresponding carboxylic acid **53**. As other methods (NaOH in EtOH; LiSPr-HMPA[56]) also failed to provide **52**,[57] the following synthesis was devised.



40 R = CH_3
52 R = H

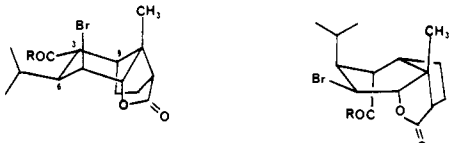
51 R = CH_3
53 R = H

27 R = CH_3
54 R = H

Saponification of **27** followed by treatment of the crude carboxylic acid **54** with NBS in aqueous THF containing HOAc afforded **52** (63%), mp 184–190 °C. The structure of **52** was confirmed by diazomethane esterification of a small sample, which quantitatively afforded **40**.

With acid **52** now available its lactonizations were studied. Unfortunately, treatment of **52** with $NaHCO_3$ and AgOAc in Me_2SO at 60 °C[58] did not afford any dilactone. Instead, the acid **53** was cleanly produced. Elimination of HBr from **52** proved to be a very facile process, and was observed even when a solution of **52** in pyridine was stirred at 60 °C for 20 h.

The failure to observe lactonizations of **40** or **52** may be a consequence of an unfavorable conformational equilibrium in these systems. Examination of the ^1H NMR spectra of **40** and **52** reveals that the isopropyl and carboxyl groups occupy equatorial positions ($J_{5,6}$ = 11, $J_{5,9}$ = 6 Hz). Moreover, the marked deshielding of C5-H (δ 3.26) and the angular methyl group (δ 1.54) relative to other compounds in the series requires that the bromine is axially oriented. A conformational change which places the isopropyl and the carbomethoxyl groups in axial positions (**40** → **40′** or **52** → **52′**) must precede bromine displacement. Evidently, the energy requirement for these conformational changes (and/or the activation energy for halide displacement from **40′** or **52′**) is greater than the activation energy for HBr elimination from **40** or **52**. Similar conformational problems may be responsible for the unsuccessful halolactonizations of **25**, **26**, and their corresponding acids, as mentioned previously.



40 R = OCH_3
52 R = OH

40′ R = OCH_3
52′ R = OH

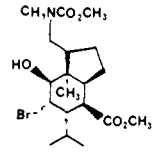
These discouraging results suggested that a synthesis of dendrobine proceeding via chloropyrrolidine **49**, which should have a conformation similar to that of **40**, might prove to be very difficult. Indeed, treatment of crude **49** with LiI in lutidine[6c,54] did not afford any detectable quantities of synthetic dendrobine as determined by TLC and NMR analysis. The NMR spectrum of the reaction mixture contained a new olefinic signal which suggested that HCl had been eliminated from **49**.

At this stage our strategy was modified in order to introduce an oxygen functionality, or its equivalent, at C7 in a step coupled with the pyrrolidine-forming reaction. A very promising sequence involved the nitrosamine photolysis previously developed by Chow et al.,[59] which in the case of **55** afforded oxime **56** in 51% overall yield from **3**.

The total synthesis of dendrobine would be assured if conversion of oxime **56** into ketone **57** could be effected, since **57** had already been transformed into dendrobine by Kende et al.[5c] However, this result eluded our repeated attempts as **56** proved to be inert to, or to decompose under, a variety of standard oxime cleavage or hydrolysis conditions.[61] Once again, an alternative approach was sought.

The solution devised involved epoxidation of a protected derivative of **3** followed by intramolecular S_N2 epoxide ring opening by the amino group. Protection of the amine was achieved by treating **3** with trichloroethyl chloroformate and pyridine in CH_2Cl_2,[62] thereby affording the crystalline urethane **58**, mp 90–91 °C, in 96–98% yield. Epoxidation of **58** under a variety of conditions afforded a mixture of two isomeric epoxides. Under optimum conditions epoxidation of **58** with 10 equiv of MCPBA at 120 °C in toluene containing 4,4′-thiobis(6-*tert*-butyl-3-methylphenol)[63] afforded 38–40% of α-epoxide **59**, mp 107.5–109 °C, together with 45–48% of β-epoxide **60**. The structural assignments for these compounds was based in part upon the smooth conversion of **59** into alcohol **50** (97% yield) on treatment of **59** with activated Zn dust in 1:1 DME–HOAc.[62] Under the same conditions **60** yielded an epoxy amine which could be reprotected with trichloroethyl chloroformate to afford unchanged **60**.

The poor stereoselectivity of the epoxidation reaction prompted a search for methods which would enable the β-epoxide **60** to be utilized in the synthesis. It was discovered that the oxirane of **60** underwent smooth ring opening with HBr in HOAc to afford an unstable bromohydrin **61**. Reduction of **61**

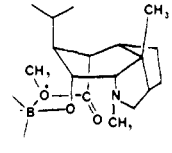


61

with Zn in HOAc afforded crude **3** which was treated with trichloroethyl chloroformate and pyridine to afford **58** in 63% overall yield from **60** (77% based upon consumed **60**). After recycling **60** in this manner, it was possible to raise the yield of β-epoxide **59** from **58** to 60% (two recycles).

The synthesis of dendrobine was smoothly accomplished in two steps starting from alcohol **50**. Treatment of an ice-cold solution of **50** in 1:1 acetone–2 N HCl with a large excess of Jones reagent for 1.5 h resulted in an uneventful oxidation reaction. There was thus obtained crystalline **57**, mp 67–75 °C, in 90–92% yield. The spectroscopic properties of this unstable substance were in excellent agreement with those reported by Kende et al.[5c]

Finally, reduction of **57** with $NaBH_4$ in 2-propanol at 23 °C for 24 h led directly to (±)-dendrobine. TLC analysis of the reaction mixtures *prior* to workup clearly indicated that dendrobine was present, and that hydroxy ester **62** was not.[64] Since *natural* **62**[64] does not lactonize on silica gel chromatography, the lactonization most likely proceeds in situ by way of a borate ester intermediate such as **63**. Chromatography of the crude



63

dendrobine obtained on acidic workup afforded 59–62% yields of the crystalline alkaloid. In this manner, a total of 45 mg of chromatographically homogeneous **1** was prepared, from which 22 mg of analytically pure material, mp 130–132 °C (lit. mp (a) 131–132,[5a] (b) 128–130 °C[5b]), was obtained after three recrystallizations from an ether–hexane mixture. The 100-MHz NMR spectra, the CH_2Cl_2 solution IR spectra, and the 70-eV mass spectra of the synthetic and natural alkaloids were superimposable, and the chromatographic properties of the two substances were identical.[65]

This successful approach constitutes formal syntheses of nobiline,[68] dendrine,[69] 2-hydroxydendrobine,[68b] *N*-methyldendrobium iodide, *N*-isopentenyldendrobium bromide, and dendrobine *N*-oxide,[70] as these natural products have all been synthesized from (+)-dendrobine.

Experimental Section

^1H nuclear magnetic resonance spectra were measured at 100 MHz on Varian HA-100 or XL-100 instruments, and at 80 MHz on a Varian HFT-80 instrument. Spectra at 270 MHz were obtained on a Bruker 270 instrument at the NMR Facility, Francis Bitter National Magnet Laboratory. Chemical shifts are reported in δ units relative to internal Me_4Si. ^{13}C NMR spectra were measured at 25.1 MHz on the XL-100. Carbon resonances are reported in δ_C units calibrated against the 77.5-ppm line of $CDCl_3$. Infrared spectra were measured on a Perkin-Elmer Model 137 instrument and were calibrated with the 1601-cm^{-1} absorption of polystyrene. UV spectra were measured on a Carey Model 14 spectrophotometer. Mass spectra were measured on an AEI-MS-9 double-focusing instrument at 70 eV. High-resolution mass spectra were provided by the Facility supported by NIH Grant RR0317 (principal investigator, Professor K. Biemann) from the Biotechnology Resources Branch, Division of Research Resources, and were obtained on a CEC 21-110B high-resolution mass spectrometer equipped with an IBM 1800 computer system to process data recorded on photographic plates. Elemental analyses were performed by Scandinavian Microanalytical Laboratories, Herlev, Denmark. Melting points were taken on a Kofler hot stage instrument and are uncorrected. Boiling points are uncorrected.

All reactions were conducted in oven-dried (120 °C) glassware under atmospheres of dry argon or nitrogen. All solvents were purified before use: ether, THF, and DME were distilled from sodium–benzophenone ketyl; methylene chloride, Me_2SO, DMF, pyridine, and *tert*-butyl alcohol were distilled from CaH_2; toluene was distilled from sodium metal. Preparative thin layer chromatography (TLC) was performed using 20 × 20 cm plates coated with 0.25-, 0.50-, and 2-mm thicknesses of silica gel containing PF 254 indicator (Analtech). Unless indicated otherwise, compounds were eluted from the adsorbents with ether. Column chromatography was performed using activity 1 Woelm silica gel. All chromatography solvents were distilled prior to use.

Systematic names for all bicyclic intermediates are based upon the perhydroindan nucleus. All tricyclic intermediates are named as derivatives of decahydroindeno[7,1-*bc*]furan and decahydrocyclopenteno[*cd*]indole.[4a] All intermediates are racemic.

Methyl(*E,E*)-6-Methylhepta-2,4-dienoate (11a) and Methyl(*E,Z*)-6-Methylhepta-2,4-dienoate (11b).[14] To a solution of lithium hexamethyldisilazide prepared from 36 g (0.225 mol) of hexamethyldisilazane and 0.180 mol of butyllithium (2.4 M in hexane) in THF (300 mL) at −78°C was added 40.0 g of phosphonate **10**[12] (0.169 mol) in 50 mL of THF. The solution was warmed to −40 °C, and 16.0 mL of isobutyraldehyde (12.6 g, 0.175 mol) in 25 mL of THF was added dropwise. The reaction mixture was then warmed to room temperature, and the THF was removed in vacuo. The residue was partitioned between 500 mL of H_2O and 100 mL of ether; after separation of the phases, the aqueous phase was extracted with two additional 100-mL portions of ether. The combined extracts were washed with 200 mL of 1 N HCl and dried over Na_2SO_4. The filtered solution was distilled, giving 21.3 g (84.5%) of a mixture of isomers, bp 90–100 °C (10 mm). Analytical VPC (5 ft × 1/4 in. 20% SE-30 on 68/80 Chromosorb W, 140 °C) indicated that the mixture consisted of 93% of **11a**. The mixture was further separated by a spinning-band distillation, providing three fractions: 0.810 g, bp 67–68 °C (6 mm), one peak by VPC, but was determined by NMR to be ~80% pure **11b** (NMR ($CDCl_3$) δ 7.62 (dd, J = 12, 15 Hz, 1 H, H_3), 3.73 (s, 3 H, CH_3O–), 2.95 (m, 1 H, H_6), 1.00 (d, J = 6 Hz, 6 H), CH_3–); IR (neat) cm^{-1} 1725, 1640, 1600; mass spectrum *m/e* 154 (parent ion)); 1.70 g, bp 69–74 °C (6 mm), a mixture of **11a** and **11b**; 18.76 g (75%), bp 77–78 °C (6 mm), of isomerically pure **11a** (NMR ($CDCl_3$) δ 7.26 (m, 1 H, H_3), 6.10 (m, 2 H, H_4 and H_5), 5.79 (d, J = 15 Hz, 1 H, H_2), 3.70 (s, 3 H, CH_3O–), 2.40 (m, 1 H, H_6), 1.02 (d, J = 6 Hz, 6 H, CH_3–); IR (neat) cm^{-1} 1720, 1640, 1610; mass spectrum *m/e* 154 (parent ion); UV (95% EtOH) λ_{max} (log ϵ_{max}) 259 (4.36). Anal. Calcd for $C_9H_{14}O$: C, 70.10; H, 9.15. Found: C, 69.65; H, 9.22).

(*E,E*)-6-Methylhepta-2,4-dienol (12).[15] A solution of 44.9 g of **11** (0.291 mol) in 100 mL of dry ether was added to a stirred solution of 620 mL of 20% DIBAL in hexane (1.0 M, 0.62 mol) at 0 °C under argon. Thirty minutes after the addition was complete, 25 mL of MeOH was cautiously added to destroy the excess hydride. The re-

sulting solution was slowly poured into 500 mL of ice-cold 2 N HCl with stirring; ice and concentrated HCl were added as needed to keep the solution cold and acidic. The organic layer was separated and the aqueous phase was extracted twice with 200-mL portions of ether. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and saturated brine, and were dried over Na_2SO_4. The filtered solution was evaporated in vacuo to give the crude product. This material was dissolved in 50 mL of pentane and was extracted with three 25-mL portions of acetonitrile. The combined acetonitrile extracts were distilled to give **12:** 32.1 g (88%); bp 90–92 °C (6 mm); NMR ($CDCl_3$) δ 5.5–6.3 (m, 4 H, H_2, H_3, H_4 and H_5), 4.10 (d, J = 6 Hz, 2 H, H_1), 2.70 (broad s, 1 H, -OH), 2.33 (m, 1 H, H_6), 1.00 (d, J = 6 Hz, 6 H, CH_3-); IR (neat) cm^{-1} 3300, 1655; mass spectrum *m/e* 126 (parent ion); UV (hexane) nm (log ϵ_{max}) 227 (4.34). Anal. ($C_8H_{14}O$) C, H.

(*E,E*)-6-Methylhepta-2,4-dienal (13). Method A.[16] A 5-L three neck flask equipped with an overhead stirrer was charged with 140 mL of dry pyridine (1.72 mol) and 1.5 L of dry CH_2Cl_2. The solution was cooled to 0 °C under argon and 90 g (0.90 mol) of CrO_3 was added in 10–15-g portions. Fifteen minutes later a solution of 12.6 g of **12** (0.100 mol) in 50 mL of dry CH_2Cl_2 was rapidly added. There was an immediate separation of a thick, black sludge. After being stirred for 20 min, the reaction mixture was diluted with 3 L of dry ether and filtered through a pad of Florisil. The filtrate was concentrated to a volume of 500 mL, and then was extracted with 500 mL of 6 N HCl. The organic phase was washed with saturated $NaHCO_3$ and saturated NaCl, dried over Na_2SO_4, filtered, and distilled, giving aldehyde **13:** 8.28 g (67%); bp 75–80 °C (8 mm); NMR ($CDCl_3$) δ 9.53 (d, J = 8 Hz, 1 H, CHO), 7.09 (m, 1 H, H_3), 6.24 (m, 2 H, H_4, H_5), 6.06 (dd, J = 8, 16 Hz, 1 H, H_2), 2.49 (m, 1 H, H_6), 1.06 (d, J = 7 Hz, 6 H, CH_3-); IR (neat) cm^{-1} 2900, 1680, 1640, 1600; mass spectrum *m/e* 124 (parent ion); UV (95% EtOH) nm (log ϵ_{max}) 272 (4.42).

The semicarbazone prepared from **13** had mp 193.5–195 °C. Anal. ($C_9H_{15}NO_3$) C, H, N.

Method B.[17,18a] A solution of 35.8 g of Me_2SO (459 mmol) in 90 mL of CH_2Cl_2 was added dropwise over 5 min to a solution of 29.0 g (228 mmol) of oxalyl chloride in 350 mL of CH_2Cl_2 maintained between −60 and −70 °C. Thirty minutes later a solution of 26.1 g (207 mmol) of **12** in CH_2Cl_2 (200 mL) was added dropwise. The resulting solution was maintained at −60 °C for 1 h, and then 132 mL (950 mmol) of Et_3N was added. The reaction solution was warmed to room temperature and was partitioned between H_2O and CH_2Cl_2. The organic extracts were washed with 5% aqueous HCl and saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and evaporated to give crude **13** (27.3 g). Distillation of this material afforded pure **13:** 23.8 g (93%); bp 79–82 °C (10 mm).

2-((*E,E*)-3-Hydroxy-8-methylnona-4,6-dienyl)-1,3-dioxolane (14). To a vigorously stirred mixture of 3.9 g of Mg turnings (160 mg-atoms) in 100 mL of dry THF containing one crystal of I_2 was added 5 mL of a solution of 24.4 g of 2-(2-bromoethyl)-1,3-dioxolane[20] (0.135 mol) in 50 mL of dry THF. External heat was applied to the reaction mixture until the I_2 color disappeared, and then the mixture was cooled with an ice bath. The remainder of the bromide was then added over a 30-min interval. The reaction mixture was then stirred for 1 h at room temperature prior to the next step.

A solution of freshly distilled **13** (8.28 g, 0.668 mol) in 50 mL of dry THF was added to the cooled Grignard reagent. One hour later the excess reagent was destroyed by the cautious addition of 25 mL of MeOH. The resulting solution was poured through a glass-wool plug into a separatory funnel containing 200 mL of ether and 200 mL of pH 9 ammonium chloride buffer. The aqueous combined extracts were washed with 200-mL portions of pH 9 buffer, H_2O, and brine. After drying over Na_2SO_4, the filtered extracts were concentrated in vacuo to give a yellow, crude product. Purification was effected by chromatography of the crude product on 250 g of silica gel using 1:1 ether–hexane as eluent, affording adduct **14:** 14.6 g (96.4%); R_f 0.25; NMR ($CDCl_3$) δ 5.5–6.3 (m, 4 H), 4.92 (t, J = 4 Hz, 1 H, $-CH(OR)_2$), 3.8–4.1 (m, 4 H, $-OCH_2CH_2O-$), 2.33 (m, 1 H, $-CHMe_2$), 2.05 (broad s, 1 H, OH), 1.00 (d, J = 7 Hz, 6 H, $-CH_3$); IR (neat) cm^{-1} 3370, 1650; mass spectrum *m/e* 226 (parent ion); UV (95% EtOH) nm (log ϵ_{max}) 229 (4.45). Exact mass. Calcd for $C_{12}H_{22}O_3$: 226.1569. Found: 226.1588.

1-Hydroxy-4-((*E,E*)-6-methylhexa-1,3-dienyl)tetrahydrofuran (15). A solution of 12.5 g of acetal **14** (55.5 mmol) in a mixture of 100 mL of DME and 40 mL of H_2O was degassed with argon before 10 mL of 1 N HCl was added. The resulting solution was stirred for 48 h at 23 °C. The reaction solution was quenched with 200 mL of sautrated $NaHCO_3$ and extracted with three 50-mL portions of CH_2Cl_2. The combined extracts were passed through a cotton plug and concentrated in vacuo. The crude product was purified by chromatography on Florisil (200 g) using 1:1 ether–hexane as eluent to give hemiacetal **15:** 6.07 g (60%); R_f 0.47; NMR ($CDCl_3$) δ 5.4–6.4 (m, 4 H), 4.70, 4.42 (1 H, two quartets, -CH(OH)(OR), diastereomers), 3.46 (m, 1 H, -CHOR), 1.02 (d, J = 6 Hz, 6 H, $-CH_3$); IR (neat) cm^{-1} 3400, 1670; mass spectrum *m/e* 182 (parent ion); UV (95% EtOH) nm (log ϵ_{max}) 230 (4.43). Exact mass. Calcd for $C_{11}H_{18}O_2$: 182.1307. Found: 182.1290.

Slower moving fractions containing **16** (R_f 0.22) were discarded.

Methyl (*E,E,E*)-4-Hydroxy-11-methyldodeca-2,7,9-trienoate (9a), Methyl (*Z,E,E*)-4-Hydroxy-11-methyldodeca-2,7,9-trienoate (7), and Methyl (*E,E,Z*)-4-Hydroxy-11-methyldodeca-2,7,9-trienoate (9b). In two identical experiments, a total of 9.62 g of hemiacetal **15** (52.9 mmol) was treated with 17.15 g of carbomethoxymethylenetriphenylphosphorane[21] (54 mmol) in 100 mL of dry CH_2Cl_2 for 8 h at room temperature. The combined reaction mixtures were passed through 200 g of silica gel using 1:1 ether–hexane as eluent, giving a fraction containing all three isomers (2.44 g, 19.7%) and a fraction of **9a** (containing ≤5% of **9b**): 8.95 g (71.5%); NMR ($CDCl_3$) δ 6.98 (dt, J = 16, 7 Hz, 1 H, H_3), 6.4–5.4 (m, 5 H), 4.12 (q, J = 7 Hz, 1 H, H_6), 3.68 (s, 3 H, CH_3O-), 2.28 (m, 3 H, H_4 and H_{11}), 1.69 (m, 2 H), 0.99 (d, J = 7 Hz, 6 H, CH_3-); IR (neat) cm^{-1} 3380, 1710, 1645; mass spectrum *m/e* 238 (parent ion); UV (95% EtOH) nm (log ϵ_{max}) 231 (4.35). Anal. ($C_{14}H_{22}O_3$) C, H.

The mixture of three isomers was further separated by chromatography on silica gel (100 g) using 3:1 hexane as eluent (20-mL fractions). Fractions 31–50 yielded triene **7:** 505 mg (4%); NMR ($CDCl_3$) δ 6.4–5.4 (m, 6 H), 4.15 (q, J = 7 Hz, 1 H, H_6), 3.62 (s, 3 H, CH_3O-), 2.2–3.0 (m, 3 H, H_4 and H_{11}), 1.58 (m, 2 H, H_5), 1.00 (d, J = 7 Hz, 6 H, CH_3-); IR (neat) cm^{-1} 3380, 1715, 1640; mass spectrum *m/e* 238 (parent ion); UV (95% EtOH) nm (log ϵ_{max}) 228 (4.56). Anal. ($C_{14}H_{22}O_3$) C, H. Fractions 61–100 yielded pure **9a:** 1.07 g (8.1%). Fractions 51–60 afforded 500 mg of a mixture of all three isomers. This mixture was resolved by preparative LC (two 4-ft Porasil columns using 3:1 hexane–ether as eluent) giving **7**, 106 mg (0.9%, total yield 611 mg (4.9%), **9a**, 211 mg (1.7%, total yield 10.23 g (82%)), and **9b:** 74 mg (0.6%); NMR ($CDCl_3$) δ 7.05 (dt, J = 16, 6.5 Hz, 1 H, H_3), 6.53 (dd, J = 10, 15 Hz, 1 H, H_8), 5.88 (dt, J = 10, 1.5 Hz, 1 H, H_2), 5.86 (dd, J = 11, 10 Hz, 1 H, H_9), 5.64 (dd, J = 15, 7 Hz, 1 H, H_7), 5.32 (t, J = 11 Hz, 1 H, H_{10}), 4.19 (q, J = 7 Hz, 1 H, H_6), 3.64 (s, 3 H, CH_3O-), 2.80 (m, 1 H, H_{11}), 2.34 (m, 2 H, H_4), 1.62 (m, 2 H, H_5), 1.00 (d, J = 7 Hz, 6 H, CH_3-); IR (CH_2Cl_2) cm^{-1} 3600, 3550, 1715, 1645, 1600; mass spectrum *m/e* 238 (parent ion); UV (95% EtOH) nm (log ϵ_{max}) 228 (4.52). Exact mass. Calcd for $C_{14}H_{22}O_3$: 238.1569. Found: 238.1542.

Methyl 1α-Hydroxy-5α-(2-propyl)-2,3,3aα,4,5,7β-hexahydro-1*H*-indene-4α-carboxylate (8a), Methyl 1β-Hydroxy-5α-(2-propyl)-2,3,3aα,4,5,7aα-hexahydro-1H-indene-4α-carboxylate (8b), Methyl 1β-Hydroxy-5β-(2-propyl)-2,3,3aα,4,5,7aα-hexahydro-1H-indene-4α-carboxylate (17a), and Methyl 1α-Hydroxy-5β-(2-propyl)-2,3,3aα,4,5,7aα-hexahydro-1*H*-indene-4α-carboxylate (17b). A solution of 6.8 g of **9a** (28.6 mmol) and 7.0 g of BSA[23] (34 mmol) in 125 mL of dry toluene was thoroughly degassed with argon. The reaction mixture was stirred at 23 °C for 8 h and then heated at reflux for 83 h. The solvent was removed in vacuo, and the residue was dissolved in 50 mL of MeOH. The resulting mixture was treated with 10 mL of 1 N HCl for 15 min at 23 °C. The mixture was then diluted with 100 mL of saturated $NaHCO_3$ and extracted with four 50-mL portions of CH_2Cl_2, giving 7.10 g of crude product. An NMR spectrum of this material indicated that 5–7% of **9a** remained.

The product was chromatographed over 400 g of silica gel using 3:1 hexane–ether as eluent. The first 1700 mL was collected as a single fraction and was discarded. Thereafter, 15–20-mL fractions were taken.

Fractions 91–110 yielded a mixture of **9a** and **17a**, from which pure **17a** was obtained after treatment with methanolic NaOH and silica gel chromatography: 70 mg (1.0%); NMR ($CDCl_3$) δ 5.91 (broad d, J = 10 Hz, 1 H), 5.73 (broad d, J = 10 Hz, 1 H), 4.20 (m, $W_{1/2}$ = 8 Hz, 1 H, H_1), 3.66 (s, 3 H, CH_3O-), 0.97, 0.78 (two d, J = 6 Hz, 6 H, CH_3-); IR (CH_2Cl_2) cm^{-1} 3550, 1725; mass spectrum *m/e* 238 (parent ion). Exact mass. Calcd for $C_{14}H_{22}O_3$: 238.1569. Found: 238.1548.

Fractions 111-220 afforded 2.66 g (40%) of **8a** which was contaminated with 15% of **9a** (NMR analysis). Thus, this fraction contained 2.26 g (34%) of **8a**. A similar mixture obtained from another experiment (3.55 g) was treated with NaOH in aqueous MeOH (2.5 h, 23 °C) to afford pure **8a:** 3.01 g (85%); mp 53-54 °C (hexane); NMR ($CDCl_3$) δ 6.03 (broad d, J = 10 Hz, 1 H), 5.73 (dt, J = 10, 3 Hz, 1 H), 4.28 (dt, J = 2, 5 Hz, 1 H), 3.66 (s, 3 H, CH_3O-), 2.75 (dd, J = 10.5, 7 Hz, 1 H, H_4), 0.97, 0.89 (two d, J = 6 Hz, 6 H, CH_3-); IR (KBr) cm^{-1} 3350, 1725; mass spectrum *m/e* 238 (parent ion). Anal. ($C_{14}H_{22}O_3$) C, H.

Fractions 221-300 afforded 1.47 g (22%) of a 25:75 mixture of **8a** and **8b** (NMR analysis). Rechromatography of this mixture over silical gel afforded 0.28 g of **8a** (total yield 2.54 g (38%)) and **8b:** 0.89 g (13%); mp 75-76 °C (hexane); NMR ($CDCl_3$) δ 6.11 (broad d, J = 10 Hz, 1 H), 5.65 (ddd, J = 10, 3, 2 Hz, 1 H), 3.88 (q, J = 8 Hz, 1 H, H_1), 2.78 (dd, J = 10.5, 7 Hz, 1 H, H_4), 0.97 and 0.82 (two d, J = 6 Hz, 6 H, CH_3-); IR (KBr) cm^{-1} 3200, 1725; mass spectrum *m/e* 238 (parent ion). Anal. ($C_{14}H_{22}O_3$) C, H.

Fractions 301-500 afforded 1.86 g (27%) of a 63:37 mixture (NMR analysis) of **8b:17b.** Such mixtures could be separated by preparative LC (two 4-ft Porasil columns, 3:1 hexane-ether). For example, chromatography of a 278-mg sample afforded 150 mg of **8b** and 80 mg of pure **17b:** mp 72-76 °C (hexane); NMR ($CDCl_3$) δ 5.97 (dt, J = 10, 2 Hz, 1 H), 5.65 (dt, J = 10, 1 Hz), 3.87 (q, J = 7 Hz, 1 H, H_1), 3.61 (s, 3 H, CH_3O-), 0.97, 0.78 (two d, J = 6 Hz, 6 H, CH_3-); IR (KBr) cm^{-1} 3300, 1725; mass spectrum *m/e* 238 (parent ion). Anal. ($C_{14}H_{22}O_3$) C, H.

The LC separation of **8b** and **17b** was impractical to perform on a large scale. Instead, these mixtures were directly epimerized since **6b** is easily separated from the resulting epimerization mixture. For example, a mixture of 1.57 g (6.6 mmol) of **8b** and **17b** (from fractions 301-500, above) was dissolved in 25 mL of dry MeOH. The solution was degassed and treated with 2.6 g of KO-*t*-Bu (22.3 mmol). The mixture was heated in a sealed Carius tube for 20 h at 120 °C. The cooled solution was diluted with 1 N HCl, and then was extracted with three 20-mL portions of CH_2Cl_2. The combined extracts were passed through a plug of cotton and concentrated in vacuo, affording 1.37 g of crude carboxylic acids. This material was treated with ethereal diazomethane to give 1.60 g of crude esters, which were chromatographed over silica gel (150 g) using 2:1 hexane-ether as eluent giving fractions (15 mL).

Fractions 81-100 afforded 450 mg of recovered **8b** and **17b** (greater than 80% **17b** by NMR).

Fractions 101-112 afforded 400 mg of a mixture of **17b** and **6b**. Separation of this mixture by preparative TLC (three 2-mm silica gel plates, three developments of 2:1 hexane-ether) afforded 175 mg of **6b** and 122 mg of **17b.**

Fractions 113-160 afforded 525 mg of **6b.**

The total amount of **6b** obtained from this reaction was 700 mg (45%). The yield was 70% based upon the theoretical amount (0.99 g) of **8b** present in the starting material.

Methyl 1β-Hydroxy-5α-(2-propyl)-2,3,3aα,4,5,6,7,7aβ-octahydro-1*H*-indene-4α-carboxylate (18). A solution of **41** mg (0.17 mmol) of **8b** in 1 mL of methyl acetate was hydrogenated over 3 mg of 5% Pd/C for 12 h. The reaction mixture was filtered through Celite and evaporated to afford **18:** 40 mg (97%); mp 77-78 °C (hexane); NMR ($CDCl_3$) δ 3.66 (s, 3 H, CH_3O-), 2.36 (dd, J = 10.5, 4 Hz, 1 H, H_4), 0.93, 0.81 (two d, J = 6 Hz, 6 H, CH_3-); IR (KBr) cm^{-1} 3200, 1720; mass spectrum *m/e* 240 (parent ion). Anal. ($C_{14}H_{24}O_3$) C, H.

Methyl 1α-Hydroxy-5α(2-propyl)-2,3,3aα,4,5,7aβ-hexahydro-1*H*-indene-4β-carboxylate (6a). A solution of 1.30 g of **8a** (containing ca. 5% of uncyclized trienes) in 20 mL of dry, degassed MeOH containing 15 mmol of KOMe was heated in a sealed Carius tube for 16 h at 110 °C. The reaction mixture was poured into 50 mL of 1 N HCl and extracted with three 25-mL portions of CH_2Cl_2. The combined extracts were passed through a cotton plug and concentrated in vacuo, and the residue was treated with diazomethane. The crude product was chromatographed over silica gel (150 g) eluted with 4% MeOAc-CH_2Cl_2 (15-mL fractions). In this solvent system, **8a** (R_f 0.38) and **6a** (R_f 0.50) are easily separated.

Fractions 21-45 afforded 80 mg of a tetrahydrofuran formed by Michael reaction of the triene impurities.

Fractions 91-130 yielded pure **6a;** 720 mg (59%); NMR ($CDCl_3$) δ 6.00 (broad d, J = 10 Hz, 1 H), 5.73 (broad d, J = 10 Hz, 1 H), 4.32 (dd, J = 3, 5 Hz, 1 H, H_1), 3.66 (s, 3 H, CH_3O-), 2.87 (d, J = 2 Hz, 1 H, H_4), 0.97, 0.94 (two d, J = 6 Hz, 6 H, CH_3-); IR (CH_2Cl_2) cm^{-1} 3530, 1720; mass spectrum *m/e* 238 (parent ion). Anal. ($C_{14}H_{22}O_3$), C, H.

Fractions 131-155 yielded 201 mg of a mixture of the two isomers. This mixture was separated by LC (two 4-ft Porasil columns, 3:1 hexane-ether) giving 111 mg (9.1%) of **6a** and 24 mg (2%) of recovered **8a.**

Fractions 156-190 yielded 110 mg (9.1%) of recovered **8a.**

The total yield of **6a** was 831 mg (68%) and the yield of **8a** was 134 mg (10.8%), based upon the theoretical amount (1.22 g) of **8a** present in the starting material.

Methyl 1β-Hydroxy-5α-(2-propyl)-2,3,3aα,4,5,7aβ-hexahydro-1*H*-indene-4β-carboxylate (6b). A solution of 380 mg of **8b** (1.60 mmol) of 10 mL of dry, degassed MeOH containing 6.4 mmol of NaOMe (prepared from NaH) was heated in a sealed Carius tube at 110 °C for 24 h. The cooled tube was opened, its contents were poured into 25 mL of 1 N HCl, and the products were extracted with three 25-mL portions of CH_2Cl_2. The combined extracts were passed through a cotton plug and concentrated in vacuo. The residue was treated with diazomethane, and the crude product was chromatographed on two 2-mm silica gel preparative plates (three developments of 2:1 hexane-ether) to give two well-resolved bands.

The more mobile band afforded 64 mg (17%) of recovered **8b.**

The less mobile band afforded **6b:** 283 mg (75%); NMR ($CDCl_3$) δ 6.06 (dt, J = 10, 2 Hz, 1 H), 5.55 (dt, J = 10, 3 Hz, 1 H), 3.62 (s, 3 H, CH_3O-), 2.68 (broad d, J = 2 Hz, H_4), 0.93, 0.89 (two d, J = 16 Hz, 6 H, CH_3-); IR (CH_2Cl_2) cm^{-1} 3550, 3400, 1725; mass spectrum *m/e* 238 (parent ion). Anal. ($C_{14}H_{22}O_3$) C, H.

Methyl 5α-(2-Propyl)-2,3,3aα,4,5,7aα-hexahydroinden-1-one-4β-carboxylate (5). A solution of 725 mg of **6a** (3.05 mmol) in 6 mL of dry CH_2Cl_2 was added dropwise by syringe to a −78 °C solution of the Me_2SO-TFAA reagent prepared from 0.435 mL of Me_2SO (6.10 mmol) and 0.685 mL of TFAA (4.9 mmol) in 10 mL of dry CH_2Cl_2 at −78 °C according to the procedure previously described.[28] The resulting solution was stirred at −78 °C for 30 min, and then 1.0 mL of Et_3N was added. The solution was warmed to room temperature and poured into 50 mL of saturated $NaHCO_3$. The organic phase was separated, and the aqueous extract was extracted with two additional 20-mL portions of CH_2Cl_2. The combined extracts were passed through a cotton plug and concentrated in vacuo, giving the crude product: NMR ($CDCl_3$) δ 6.12 (dt, J = 10, 3 Hz, 1 H), 5.61 (dt, J = 10, 3.5 Hz, 1 H), 3.68 (s, 3 H, CH_3O-), 0.96, 0.92 (two d, J = 6 Hz, 6 H, CH_3-). Chromatography of this material over silica gel (50 g) eluted with 1:1 ether-hexane afforded crystalline **5:** 650 mg (90.5%); mp 69-71 °C (hexane); NMR ($CDCl_3$) δ 5.76 (dt, J = 10, 3 Hz, 1 H), 5.49 (dt, J = 10, 2 Hz, 1 H), 3.74 (s, 3 H, CH_3O-), 1.03, 0.78 (two d, J = 6 Hz, 6 H, CH_3-); IR (KBr) cm^{-1} 1735, 1725; mass spectrum *m/e* 236 (parent ion). Anal. ($C_{14}H_{20}O_3$) C, H.

By an identical procedure, 397 mg of **6b** was oxidized and chromatographed to afford 330 mg (84%) of **5.**

Methyl 1β-Hydroxy-5α-(2-propyl)-2,3,3aα,4,5,7aα-hexahydro-1*H*-indene-4β-carboxylate (20). A solution of 37.0 mg of ketone **5** (0.157 mmol) in 0.5 mL of 95% EtOH was treated with 6.0 mg of $NaBH_4$ (0.16 mmol). The resulting solution was stirred at ambient temperature for 2 h before the reaction solution was quenched with 10 mL of 1 N HCl. The crude material (37 mg) obtained by extraction with CH_2Cl_2 was a single product as determined by TLC (silica gel, 1:1 ether-hexane, R_f 0.42). Purification by preparative plate chromatography afforded crystalline **20:** 27 mg (73%); mp 76-77 °C (hexane); NMR ($CDCl_3$) δ 5.82 (s, 2 H), 4.42 (q, J = 6 Hz, 1 H, H_1), 3.70 (s, 3 H, CH_3O-), 1.03, 0.79 (two d, J = 6 Hz, 6 H, CH_3-); IR (KBr) cm^{-1} 3200, 1720; mass spectrum *m/e* 238 (parent ion). Anal. ($C_{14}H_{22}O_3$) C, H.

1β-Hydroxy-5α-(2-propyl)-2,3,3aα,4,5,7aα-hexahydro-1*H*-indene-4β-carboxylic Acid δ-Lactone (21). A solution of 25.5 mg of alcohol **20** (0.107 mmol) in 1.0 mL of CH_2Cl_2 was treated with 2 drops of TFA. The resulting solution was stirred at room temperature for 2 days, after which the volatile components were removed in vacuo. The single product was purified by preparative TLC on a 0.5-mm silica gel plate which was eluted with 1:1 ether-hexane, affording **21:** 15.5 mg (73%); NMR ($CDCl_3$) δ 6.04 (dd, J = 10, 4 Hz, 1 H), 5.84 (ddd, J = 10, 4, 1 Hz, 1 H), 4.60 (m, 1 H, H_1), 2.73 (m, 1 H, H_4), 1.01, 0.99 (two d, J = 6 Hz, 6 H, CH_3-); IR (CH_2Cl_2) cm^{-1} 1720; mass spectrum *m/e* 206 (parent ion). Exact mass. Calcd for $C_{13}H_{18}O_2$: 206.130 68. Found 206.127 71.

Intramolecular Diels-Alder Reaction of 7. A 10-mL resealable Carius tube was loaded with a solution of 100 mg of **7** (.042 mmol)

in 3 mL of dry toluene containing 100 mg of BSA[23] (0.5 mmol). The solution was degassed with argon and allowed to stand at room temperature for 7 h. The tube was then heated at 115 °C for 36 h. The cooled solution was concentrated in vacuo, and the crude product from a duplicate run was analyzed by GC (Table III). The crude product was then hydrolyzed in 5 mL of MeOH containing 1 mL of 1 N HCl for 15 min at room temperature. The reaction mixture was diluted with water (25 mL) and the products were extracted with three 10-mL portions of CH_2Cl_2. The product mixture thus obtained was separated by LC (two 4-ft Porasil columns, eluted with 3:1 hexane–ether) giving, in order of elution, 5 mg (5%) of recovered **7**, 32.5 mg (32.5%) of **6a**, 16.7 mg (16.7%) of **6b**, and 9.0 mg (9%) of **22**. The samples of **6b** and **22** thus obtained were cross-contaminated to the extent of ~10% each. A second chromatographic cycle afforded pure **22**: NMR ($CDCl_3$) δ 6.01 (dt, J = 10, 3 Hz, 1 H), 5.57 (dt, J = 10, 2 Hz, 1 H), 4.08 (q, J = 7 Hz, 1 H, H_1), 3.63 (s, 3 H, CH_3O–), 2.93 (dd, J = 4, 5 Hz, 1 H, H_4), 0.99, 0.94 (two d, J = 7 Hz, 6 H, CH_3–); IR (CH_2Cl_2) cm^{-1} 3530, 1725; mass spectrum *m/e* 238 (parent ion). Exact mass. Calcd for $C_{14}H_{22}O_3$: 238.156 89. Found: 238.157 05.

The combined yield of **6a**, **6b**, and **22** was 71–74% when isolated by preparative plate chromatography.

Epimerization of 22. A solution of 26 mg of **22** (0.11 mmol) in 2 mL of dry degassed MeOH containing 1.1 mmol of KOMe was heated at 110 °C for 6 h in a sealed Carius tube. The cooled vessel was opened and its contents were poured into 10 mL of 1 N HCl. This mixture was extracted with three 5-mL portions of CH_2Cl_2. Analytical TLC (silica gel, 1:1 ether–hexane, two developments) indicated that the crude product was a single compound, R_f 0.40. The product was purified by preparative TLC over silica gel giving 22 mg (85%) of hydroxy ester **7b**.

Methyl 7aα-Methyl-5α-(2-propyl)-2,3,3aα,4,5,7a-hexahydroinden-1-one-4β-carboxylate (4). A solution of 650 mg of **5** (2.75 mmol) in 15 mL of dry DME and 2 mL of CH_3I (4.5 g, 32 mmol) was prepared under an argon atmosphere. This mixture was titrated with 2.75 mL of a 1.00 M KO-*t*-Bu-*t*-BuOH solution (2.75 mmol). During the addition KI separated from solution. The reaction mixture was stirred for 15 min following the completed addition, and then it was poured into 70 mL of saturated $NaHCO_3$. The crude product was extracted with three 25-mL portions of CH_2Cl_2 to give 700 mg of crystalline material, mp 72–83 °C. Recrystallization from hexane yielded, in two crops, 522 mg of **4**. The concentrated mother liquors were chromatographed over silica gel using 1:1 ether–hexane as eluent, giving an additional 81 mg of **4**. The total yield was 603 mg (87.5%); mp 91–93 °C (hexane); NMR ($CDCl_3$) δ 5.66 (dd, J = 10, 2 Hz, 1 H), 5.28 (dd, J = 10, 2 Hz, 1 H), 3.75 (s, 3 H, CH_3O–), 1.16 (s, 3 H, angular CH_3), 1.01, 0.78 (two d, J = 6 Hz, 6 H, CH_3–); IR (KBr) cm^{-1} 1725; mass spectrum *m/e* 250 (parent ion). Anal. ($C_{15}H_{22}O_3$) C, H.

Methyl 1β-Hydroxy-7aα-methyl-5α-(2-propyl)-2,3,3aα,4,5,7a-hexahydro-1*H*-indene-4α-carboxylate (23) and δ-Lactone (24). A solution of 25.5 mg of **4** (0.105 mmol) in 1.0 mL of absolute EtOH was treated with 5 mg of $NaBH_4$ (0.13 mmol). The solution was stirred for 2.5 h at room temperature, and then it was diluted with 10 mL of 1 N HCl and 5 mL of CH_2Cl_2. The organic phase was separated and the aqueous phase was extracted with two additional 10-mL portions of CH_2Cl_2. The combined extracts were passed through a cotton plug and concentrated in vacuo affording **23**: 26 mg (100%); mp 83–87 °C (hexane); NMR ($CDCl_2$) δ 5.65 (s, 2 H), 3.75 (t, J = 9 Hz, 1 H, H_1), 3.70 (s, 3 H, CH_3O–), 1.13 (s, 3 H, angular CH_3), 1.01, 0.77 (two d, J = 6 Hz, 6 H, CH_3–); IR (KBr) cm^{-1} 3500, 3350, 1730, 1700 (hydrogen-bonded ester); mass spectrum *m/e* 252 (parent ion). Anal. ($C_{15}H_{24}O_3$) C, H.

Without purification, hydroxy ester **23** was dissolved in 1.0 mL of dry CH_2Cl_2 and treated with 6 drops of TFA. The reaction mixture stood at room temperature overnight, and then the volatile components of the mixture were removed in vacuo. The crude lactone was purified by preparative TLC on an 0.5-mm silica gel plate developed with 1:1 ether–pentane, affording crystalline **24**: 16 mg (73%); mp 55–56 °C (hexane); NMR ($CDCl_3$) δ 6.00 (ddd, $J_{6,7}$ = 10, $J_{6,5}$ = 5, $J_{6,4}$ = 1 Hz, 1 H, H_6), 5.62 (broad d, J = 10 Hz, H_7), 4.24 (m, 1 H, H_1), 2.76 (dt, $J_{4,6}$ = 1, $J_{4,5}$ = $J_{4,3a}$ = 2.5 Hz, 1 H, H_4), 1.06 (s, 3 H, angular CH_3), 1.02, 0.99 (two d, J = 6 Hz, 6 H, CH_3–); IR (CH_2Cl_2) cm^{-1} 1720; mass spectrum *m/e* 220 (parent ion). Anal. ($C_{14}H_{20}O_2$) C, H.

Methyl 1β-Cyano-7aα-methyl-5α-(2-propyl)-2,33aα,4,5,7a-hexahydro-1*H*-indene-4β-carboxylate (25) and Methyl 1α-Cyano-7aα-methyl-5α-(2-propyl)-2,3,3aα,4,5,7a-hexahydro-1*H*-indene-4β-carboxylate (26). A solution of 1.4 g of tosylmethyl isocyanide[33] (6.5 mmol) in 10 mL of dry DME under argon was added to 0.540 g of **4** (2.16 mmol). The resulting solution was cooled to 0 °C and 9.5 mmol of KO-*t*-Bu in *tert*-butyl alcohol (10 ml) was added by syringe. The reaction mixture was stirred at 0 °C for 30 min and at 23 °C for 8 h. The reaction mixture was then poured into 50 mL of saturated $NaHCO_3$ and extracted with three 25-mL portions of CH_2Cl_2. The combined organic extracts were passed through a cotton plug and concentrated in vacuo to give the crude product as a dark oil. Analytical TLC (silica gel, 2:1 hexane–ether, two developments) revealed that this mixture contained three UV-active compounds near the base line and the two nitriles: **25** (R_f 0.62) and **26** (R_f 0.75). The two isomers were separated by column chromatography over 50 g of silica gel (2:1 hexane–ether, 15-mL fractions).

Fractions 8–12 yielded 80 mg of a mixture of **25** and **26** which was rechromatographed over silica gel (0.5-mm preparative plate, two developments of 3:1 hexane–ether) to afford **26** [57 mg (10.1%); mp 90–91 °C (hexane); NMR ($CDCl_3$) δ 5.60 (dd, J = 10, 1.5 Hz, 1 H), 5.32 (dt, J = 10, 2 Hz, 1 H), 3.71 (s, 3 H, CH_3O–), 1.35 (s, 3 H, angular CH_3), 0.99, 0.77 (two d, J = 7 Hz, 6 H, CH_3–); IR (KBr) cm^{-1} 2205, 1720; mass spectrum *m/e* 261 (parent ion). Anal. ($C_{16}H_{23}NO_2$) C, H, N] and **25** [18 mg (3.2%); mp 47–51 °C (hexane); NMR ($CDCl_3$) δ 5.69 (s, 2 H), 3.70 (s, 3 H, CH_3O–), 1.26 (s, 3 H, angular CH_3), 1.01, 0.78 (two d, J = 6 Hz, 6 H, CH_3–); IR (KBr) cm^{-1} 2220, 1725; mass spectrum *m/e* 261 (parent ion). Anal. ($C_{16}H_{23}NO_2$), C, H, N].

Fractions 13–22 yielded an additional 214 mg (41.2% total) of **25**.

Epimerization of 26. A 10-mL resealable Carius tube was loaded with a solution of 72 mg of **26** (0.275 mmol) in 1 mL of dry MeOH. The solution was degassed with argon before 1 mL of 1 N NaOH in MeOH (1 mmol) was added. The tube was sealed and heated at 85 °C for 20 h. The cooled reaction vessel was opened and its contents were poured into 15 mL of 1 N HCl. The crude acids obtained by extraction with CH_2Cl_2 were treated with ethereal diazomethane. The resulting crude esters were separated by preparative TLC on a 0.5-mm silica gel plate developed twice with 3:1 hexane–ether. The more mobile band yielded 19 mg (26%) of recovered **26**, and the less mobile band yielded 49 mg (68%) of **25**.

Methyl 1β-(*N*-Methylcarboxamido)-7-aα-methyl-5α-(2-propyl)-2,3,3aα,4,5,7a-hexahydro-1H-indene-4β-carboxylate (27). A 50-mL flask containing 300 mg of **25** (1.15 mmol) was flushed with argon and capped with a serum plug. The nitrile was dissolved in 0.8 mL of dry CH_2Cl_2, and then 2.0 mL of methyl fluorosulfonate[36] (25.0 mmol) was added by syringe. The flask stood at room temperature for 28 h, and then it was packed in ice. A syringe needle was stuck through the serum plug to serve as a vent, and 5 mL of 95% EtOH was added dropwise to destroy the excess methylating agent. Next, 3 mL of concentrated NH_4OH and enough 95% EtOH to bring the resulting solution to homogeneity were added. This mixture was allowed to stand undisturbed for 2 h at room temperature. It was then diluted with 50 mL of saturated $NaHCO_3$ and extracted with three 25-mL portions of CH_2Cl_2. Analytical TLC (silica gel, 1:1 ether–hexane) indicated that the product (325 mg) consisted of a mixture of **25** and **27** (R_f 0.1). The two compounds were separated by preparative TLC on a single 2-mm silica gel plate which was developed with 1:1 ether–hexane. The more mobile band yielded 62 mg (20.6%) of recovered **25**, and the less mobile band yielded **27**: 147 mg (44%); mp 124–126 °C (ether–hexane); NMR ($CDCl_3$) δ 5.54 (s, 2 H), 3.70 (s, 3 H, CH_3O–), 2.84 (d, J = 5 Hz, 3 H, CH_3N–), 1.25 (s, 3 H, angular CH_3), 0.99, 0.77 (two d, J = 6 Hz, 6 H, CH_3–); IR (KBr) cm^{-1} 3250, 1730, 1640, 1550; mass spectrum *m/e* 293 (parent ion). Anal. ($C_{17}H_{27}NO_3$) C, H, N.

Methyl 1α-(*N*-Methylcarboxamido)-7aα-methyl-5α-(2-propyl)-2,3,3aα,4,5,7a-hexahydro-1*H*-indene-4β-carboxylate (28). A solution of 4.5 mg of nitrile **26** (0.017 mmol) in 0.5 mL of dry CH_2Cl_2 was added to 100 μL of methyl fluorosulfonate[36] (1.3 mmol) in a dry flask under argon. The resulting mixture was maintained at room temperature for 20 h, and then it was diluted with 10 mL of saturated $NaHCO_3$. This solution was extracted with three 5-mL portions of CH_2Cl_2 to give a crude product (6 mg) consisting of a single spot on analytical TLC (silica gel, 5% MeOH–CH_2Cl_2, R_f 0.5). Crystallization of this material from an ether–hexane mixture afforded pure **28**: 4.0 mg (80%); mp 155–157 °C; NMR ($CDCl_3$) δ 5.47 (d, J = 10 Hz, 1 H), 5.33 (d, J = 10 Hz, 1 H), 3.67 (s, 3 H, CH_3O–), 2.82 (d J = 5 Hz, 3 H, CH_3N–), 1.07 (s, 3 H, angular CH_3), 0.98, 0.75 (two d, J = 6 Hz, 6 H, CH_3–); IR (KBr) cm^{-1} 3250, 1740, 1640, 1560;

mass spectrum *m/e* 293 (parent ion). Exact mass. Calcd for $C_{17}H_{27}NO_3$: 293.199 09. Found: 293.202 01.

Methyl 5α-(2-Propyl)2,3,3aα,4,5,7aα-hexahydro-indan-1-one-4aα-carboxylate (29). A solution of 1.77 mL of Me_2SO (24 mmol) in 50 mL of dry CH_2Cl_2 was cooled to −78 °C under an argon atmosphere and TFAA (2.9 mL, 20.5 mmol) was added dropwise by syringe. The resulting mixture was stirred at −78 °C for 30 min; during this time a white material precipitated. Next, a solution of 2.88 g of **8a** (12.1 mmol) in 20 mL of dry CH_2Cl_2 was added dropwise from an addition funnel. During this addition the precipitate redissolved. The resulting solution was stirred at −78 °C for 30 min, and then 8 mL of dry Et_3N was added. The reaction solution was warmed to room temperature and poured into 50 mL of saturated $NaHCO_3$. After the organic phase was separated, the aqueous phase was extracted with two additional 25-mL portions of CH_2Cl_2. The combined extracts were passed through a cotton plug and concentrated in vacuo to give the crude product. This material was chromatographed on silica gel (150 g) using 1:1 ether–hexane as eluent to give **29:** 2.73 g (95%); mp 76–77 °C (hexane); NMR ($CDCl_3$) δ 5.93, 5.81 (AB, J = 10 Hz, 2 H), 3.72 (s, 3 H, CH_3O–), 0.97, 0.91 (two d, J = 6 Hz, 6 H, CH_3–); IR (KBr) cm^{-1} 1730; mass spectrum *m/e* 236 (parent ion). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 69.77, 70.43; H, 8.40, 8.55. It was subsequently discovered that **29** is unstable to storage even at 4 °C in the crystalline state. Exact mass. Calcd: 236.141 24. Found: 236.140 18.

Methyl 7aα-Methyl-5α-(2-propyl)-2,3,3aα,4,5,7aα-hexahydro-inden-1-one-4α-carboxylate (30). A. Methyl iodide (1.0 mL, 2.3 g, 16 mmol) was added to a solution of 321 mg of **29** (1.36 mmol) in 10 mL of dry DME under argon. The resulting solution was stirred at 23 °C while 1.40 mL of a 1.00 M KO-*t*-Bu–*t*-BuOH solution (1.40 mmol) was added dropwise by syringe. During the addition KI separated from solution. The mixture was stirred for 15 min following the completed addition, and then it was poured into 25 mL of saturated $NaHCO_3$. The crude product obtained by extraction with CH_2Cl_2 (3 × 25 mL) was recrystallized from hexane giving **30:** 220 mg (65%). Chromatography of the mother liquors (silica gel, 1:1 ether–hexane, R_f 0.6) afforded an additional 86 mg (25%) of **30:** the total yield was 306 mg (90%); mp 75–76 °C; NMR ($CDCl_3$) δ 5.82 (dd, J = 10, 4 Hz, 1 H, H_6), 5.65 (dd J = 10, 1 Hz, 1 H, H_7), 3.74 (s, 3 H, CH_3O–), 1.16 (s, 3 H, angular CH_3), 0.93, 0.91 (two d, J = 6 Hz, 6 H, CH_3–); IR (KBr) cm^{-1} 1730; mass spectrum *m/e* 250 (parent ion). Anal. ($C_{15}H_{22}O_3$) C, H.

B. A solution of 11.0 g of **9** (46.3 mmol) in 300 mL of dry toluene was degassed and treated with 12.5 mL of BSA (10.4 g, 50 mmol) and 300 mg of hydroquinone. The mixture was stirred at 23 °C for 6 h, and then was gently refluxed for 110 h. The cooled mixture was concentrated in vacuo and the residue was dissolved in 50 mL of MeOH containing 10 mL of 1 N HCl. After the mixture had stood at 23 °C for 2 h, 20 mL of 1 N NaOH was added and the mixture was stirred overnight at 23 °C. This mixture was then diluted with 200 mL of saturated $NaHCO_3$ and extracted with three 50-mL portions of CH_2Cl_2. The crude product thus obtained (11.3 g) was roughly chromatographed over 300 g of silica gel using 4:1 hexane–EtOAc as eluent, giving 8.42 g (76.5%) of the unseparated mixture of Diels–Alder adducts.

The TFAA–Me_2SO reagent was prepared in the usual fashion from 4.68 mL of Me_2SO (63.6 mmol) and 7.69 mL of TFAA (54.3 mmol) in 130 mL of dry CH_2Cl_2 at −78 °C, to which was added dropwise a solution of 7.62 g (32.0 mmol) of the previously described mixture of Diels–Alder adducts in 50 mL of CH_2Cl_2. The reaction was maintained at −78 °C for 30 min and then 15 mL of Et_3N was added. The reaction mixture was warmed to room temperature and diluted with 200 mL of saturated $NaHCO_3$. The aqueous phase was extracted with two 50-mL portions of CH_2Cl_2. The combined extracts were dried and evaporated to give the crude product which was chromatographed (250 g of silica gel, 2:1 hexane–EtOAc) to give 6.19 g (83%) of a mixture consisting mostly of **29.**

A solution of 5.20 g (22.0 mmol) of the above mixture and 14 mL of CH_3I in 40 mL of dry DME was degassed with argon. This solution was titrated with 22.0 mL of 1.0 M KO-*t*-Bu in *t*-BuOH. The mixture was stirred for 15 min at 23 °C following the addition, and then it was poured into 200 mL of saturated $NaHCO_3$. The products were extracted with three 50-mL portions of CH_2Cl_2, which were combined and concentrated to afford crude **30.** The product was recrystallized from 25 mL of hexane to afford 2.05 g of pure **30**, mp 73–75 °C. The mother liquors were filtered through 200 g of silica gel (2:1 hexane–ether) to give 2.0 g of impure material, which was crystallized from hexane (two crops) to give an additional 0.74 g of **30.** The total yield was 2.79 g (51%).

Methyl 1β-Hydroxy-7aα-methyl-5α-(2-propyl)-2,3,3aα,4,5,7a-hexahydro-1*H*-indene-4α-carboxylate (31) and Methyl 1α-Hydroxy-7aα-methyl-5α-(2-propyl)-2,3,3aα,4,5,7a-hexahydro-1*H*-indene-4α-carboxylate (32). A solution of 250 mg of **30** (1.0 mmol) in 3.0 mL of absolute EtOH was treated with 36 mg (1.0 mmol) of $NaBH_4$. The mixture was stirred at 23 °C for 2 h, and then it was quenched by pouring it into 10 mL of 1 N HCl. The products were extracted with three 10-mL portions of CH_2Cl_2. The dried extracts were concentrated in vacuo and the two isomers were separated by preparative plate chromatography (two 0.5-mm silica gel plates, two developments of 5% EtOAc–CH_2Cl_2). The faster moving band afforded **31:** 160 mg (63%); NMR ($CDCl_3$) δ 6.04 (dd, J = 10, 5 Hz, 1 H, H_6), 5.66 (dd, J = 10, 2 Hz, 1 H, H_7), 3.69 (s, 3 H, CH_3O–), 2.91 (dd, J = 10, 6 Hz, 1 H, H_4), 1.03 (s, 3 H, angular CH_3), 0.92, 0.86 (two d, J = 6 Hz, 6 H, CH_3–); IR (CH_2Cl_2) cm^{-1} 3550, 1730; mass spectrum *m/e* 252 (parent ion). Exact mass. Calcd for $C_{15}H_{24}O_3$: 252.172 54. Found: 252.173 38. The slower moving band afforded **32:** 78 mg (30%); mp 50–51 °C (hexane); NMR ($CDCl_3$) δ 5.64 (s, 2 H), 3.80 (dd, J = 6, 7, Hz, 1 H, H_1), 3.63 (s, 3 H, CH_3O–), 2.64 (dd, J = 8, 5 Hz, 1 H, H_4), 0.99 (s, 3 H, angular CH_3), 0.88 (d, J = 6 Hz, 6 H, CH_3–); IR (KBr) cm^{-1} 3400, 1725; mass spectrum *m/e* 252 (parent ion). Exact mass. Found: 252.175 72.

Epimerization of 31. A 10-mL resealable Carius tube was loaded with a solution of 32.0 mg of **31** (0.127 mmol) in 0.5 mL of dry MeOH. The solution was degassed with argon before 0.4 mL of 2 M methanolic KOMe (0.8 mmol) was added. The tube was sealed and heated at 110 °C for 18 h. The cooled vessel was then opened and its contents were diluted with 15 mL of 1 N HCl. The products were extracted with three 10-mL portions of CH_2Cl_2. After evaporation, the crude product was treated with diazomethane to give 28 mg (87%) of crude **23.** The NMR spectrum and the analytical TLC of this material indicated that **31** was not present in the product. The product was crystallized from hexane giving pure **23:** 20 mg (63%); mp 82–86 °C.

Methyl 1β-Cyano-7aα-methyl-5α-(2-propyl)-2,3,3aα,4,5,7a-hexahydro-1H-indene-4α-carboxylate (33) and Methyl 1α-Cyano-7aα-methyl-5α-(2-propyl)-2,3,3aα,4,5,7a-hexahydro-1*H*-indene-4α-carboxylate (34). A solution of 5.0 g of KO-*t*-Bu (45 mmol) in 45 ml of dry *tert*-butyl alcohol and 10 mL of dry DME was prepared in a 500-mL flask equipped with a dropping funnel, an N_2 line, and a magnetic stirring bar. The dropping funnel was charged with a solution of 2.90 g of **30** (10.8 mmol) and 6 g of tosylmethyl isocyanide[33] (30.0 mmol) in 25 mL of dry DME. The solution of KO-*t*-Bu was cooled in an ice bath while the contents of the dropping funnel were slowly added. The resulting solution was warmed to room temperature, and 12 h later it was poured into 200 mL of saturated $NaHCO_3$. This mixture was extracted with three 50-mL portions of CH_2Cl_2, which were dried and concentrated in vacuo. The nitriles were isolated by filtering the crude product through 100 g of silica gel using 2:1 hexane–ether as eluent until **33** and **34** (R_f 0.7) were not detected in the eluate. The filtrate thus obtained was evaporated in vacuo, giving 1.35 g (48%) of an approximate 1:1 mixture of **33** and **34.**

Pure samples of the individual nitriles were obtained by careful preparative plate chromatography (silica gel, 4:1 hexane–ether, three developments). The more mobile band yielded **34:** mp 58–60 °C; NMR ($CDCl_3$) δ 5.79 (s, 2 H), 3.69 (s. 3 H, CH_3O–), 1.21 (s, 3 H, angular CH_3), 0.91, 0.85 (two d, J = 6 Hz, 6 H, CH_3–); IR (neat) cm^{-1} 2220, 1730; mass spectrum *m/e* 261 (parent ion). Precise mass. Calcd for $C_{16}H_{23}NO_2$: 261.172 87. Found: 261.174 86. The slower moving band afforded **33:** mp 45–50 °C; NMR δ 6.00 (dd, J = 10, 3.5 Hz, 1 H, H_6), 5.71 (dd, J = 10, 2 Hz, 1 H, H_7), 3.67 (s, 3 H, CH_3O–), 1.16 (s, 3 H, angular CH_3), 0.94, 0.89 (two d, J = 6 Hz, 6 H, CH_3–); IR (KBr) cm^{-1} 2210, 1730; mass spectrum *m/e* 261 (parent ion). Precise mass. Found: 261.173 75.

Epimerization of Nitriles 33 and 34. A 40-mL resealable Carius tube was loaded with a solution of 1.35 g of the mixtue of **33** and **34** (5.18 mmol). The solution was degassed with argon and 1 g of Na_2CO_3 (9 mmol) and 20 mL of 1 N NaOH in MeOH (20 mmol) were added. The tube was sealed and heated at 90 °C for 17 h. The tube was cooled and opened, and its contents were poured into 50 mL of 1 N HCl. The products were extracted with three 25-mL portions of CH_2Cl_2, which were combined, dried, and concentrated in vacuo. The crude product (1.3 g) was chromatographed over 130 g of silica gel using 3:2 hex-

ane–ether as eluent; 15-mL fractions were collected.

Fractions 41–75 afforded 800 mg (59%) of **25.**

Fractions 25–40 afforded 310 mg (23%) of **26**, which was recycled under the same reaction conditions to give an additional 230 mg (17%) of **25** (two recycles; total yield 1.030 g (76.5%)).

Methyl 1β-Carboxamido-7aα-methyl-5α-(2-propyl)-2,3,3aα,-4,5,7a-hexahydro-1*H*-indene-4β-carboxylate (39). A solution of 480 mg of nitrile **25** (1.84 mmol) in 12 mL of absolute EtOH was treated with 4 mL of 30% H_2O_2 (32 mmol) and 2 mL of 1 N NaOH (2 mmol). The mixture was stirred at room temperature for 2.5 days. The reaction mixture was chilled to 0 °C and then saturated $NaHSO_3$ was added to destroy the excess H_2O_2 (exothermic!). The resulting solution was diluted with 50 mL of H_2O and extracted with three 25-mL portions of CH_2Cl_2. The combined extracts were passed through a cotton plug and concentrated in vacuo to afford crystalline **39:** 503 mg (98%); mp 184–186 °C (ether); NMR ($CDCl_3$) δ 5.56 (s, 2 H), 5.44 (broad, 2 H, NH_2–), 3.70 (s, 3 H, CH_3O–), 1.28 (s, 3 H, angular CH_3), 0.98, 0.75 (two d, J = 6 Hz, 6 H, CH_3–); IR (KBr) cm^{-1} 3340, 3120, 1725, 1640; mass spectrum *m/e* 279 (parent ion). Anal. ($C_{16}H_{25}NO_3$) C, H, N.

Methyl 7α-Bromo-11α-methyl-6α-(2-propyl)-3,4,5,6,7,8α,-9α,10α-octahydroindeno[7,1,-*bc*]furan-2-one-5β-carboxylate (40). A solution of 166 mg of **39** (0.594 mmol) in 5 mL of THF and 2 mL of 50% acetic acid was treated with 300 mg of NBS (1.66 mmol). The resulting solution was stirred for 2.5 h at 23 °C. It was then poured into 20 mL of saturated $NaHSO_3$ and extracted with three 20-mL portions of CH_2Cl_2. The combined extracts were passed through a cotton plug and concentrated in vacuo, giving 300 mg of crude product. This material was chromatographed on a single 2-mm silica gel plate using 1:1 ether–hexane as the eluent, affording crystalline **40:** 186 mg (87.5%); mp 107–108 °C (hexane); NMR ($CDCl_3$) δ 4.64 (s, 2 H, H_7 and H_{10}), 3.72 (s, 3 H, CH_3O–), 3.26 (dd, J = 11, 6 Hz, 1 H, H_5), 2.75 (broad d, J = 6 Hz, 1 H, H_8), 1.54 (s, 3 H, angular CH_3), 1.02 (d, J = 6 Hz, 6 H, CH_3–); IR (KBr) cm^{-1} 1760, 1725; mass spectrum *m/e* 279 (P-Br; no parent ion observed). Anal. ($C_{16}H_{23}BrO_4$) C, H, Br.

Methyl 1β-Carboxy-7aα-methyl-5α-(2-propyl)-2,3,3aα,4,5,7a-hexahydro-1*H*-indene-4β-carboxylate (41). A solution of 100 mg of **40** (0.279 mmol) in 4 mL of glacial HOAc was added to 200 mg of Zn (3.0 mmol). The solution was heated at reflux for 5 h with stirring. The reaction vessel was then cooled and its contents were poured through a glass-wool plug into a separatory funnel containing 20 mL of H_2O. The resulting mixture was extracted with three 20-mL portions of ether, and the combined extracts were dried over Na_2SO_4. The filtered solution was concentrated in vacuo to give crystalline **41:** 78 mg (100%); mp 112–113 °C (hexane); NMR ($CDCl_3$) δ 5.56 (s, 2 H), 3.71 (s, 3 H, CH_3O–), 1.30 (s, 3 H, angular CH_3), 1.01, 0.78 (two d, J = 6 Hz, 6 H, CH_3–); IR (KBr) cm^{-1} 3200–2500 (broad), 1735, 1695; mass spectrum *m/e* 280 (parent ion). Anal. ($C_{16}H_{24}O_4$) C, H.

Methyl 1β-Hydroxymethyl-7aα-methyl-5α-(2-propyl)-2,3,-3aα,4,5,7a-hexahydro-1*H*-indene-4β-carboxylate (42). A solution of 415 mg of acid **41** (1.45 mmol) in 4 mL of oxalyl chloride was stirred at room temperature for 3 h. Evaporation of the mixture in vacuo afforded 435 mg (100%) of crude acid chloride (IR: 1730, 1795 cm^{-1}) which, without purification, was dissolved in 5 mL of dry THF and added dropwise by syringe to a 0 °C solution of 2.23 g of lithium tri-*tert*-butoxyaluminum hydride (10.0 mmol) in 25 mL of dry THF under argon. The mixture was stirred for 3 h at 0 °C, and then it was quenched with 25 mL of 1 N HCl. This mixture was then extracted with three 25-mL portions of CH_2Cl_2, which were combined and concentrated in vacuo. The residue was dissolved in 25 mL of ether and extracted with three 5-mL portions of 1 N NaOH. The ether layer was dried over Na_2SO_4, filtered, and evaporated to give crystalline **42:** 353 mg (90%); mp 70.5–71 °C (hexane); NMR ($CDCl_3$) δ 5.48 (s, 2 H), 3.85, 3.57 (AM of AMX, J_{AM} = 10, J_{AX} = 7, J_{MX} = 5 Hz, 2 H, $-CH_2OH$), 3.68 (s, 3 H, CH_3O–), 1.15 (s, 3 H, angular CH_3) 0.98, 0.76 (two d, J = 6 Hz, 6 H, CH_3–); IR (KBr) cm^{-1} 3300, 1725; mass spectrum *m/e* 266 (parent ion). Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 71.65; H, 9.93. Exact mass. Calcd: 266.188 19. Found: 266.188 80.

The alkaline extracts were made acidic by the addition of concentrated HCl. This solution was extracted with three 5-mL portions of CH_2Cl_2, affording 40 mg of recovered **41** (9.6%).

Methyl 1β-Methylaminomethyl-7aα-methyl-5α-(2-propyl)-2,3,3aα,4,5,7a-hexahydro-1*H*-indene-4β-carboxylate (3). A solution of 395 mg of **42** (1.48 mmol) in 10 mL of dry CH_2Cl_2 under argon was treated with 300 mg of Et_3N (0.42 mL, 3.0 mmol) and 220 mg of methanesulfonyl chloride (0.156 mL, 2.0 mmol).[45] The resulting solution was stirred at 0 °C for 2 h, and then it was diluted with 25 mL of saturated $NaHCO_3$. This mixture was extracted with three 10-mL portions of CH_2Cl_2, which were combined, dried, and concentrated in vacuo, giving 530 mg of crude mesylate (NMR ($CDCl_3$) δ 5.60 (d, J = 10 Hz, 1 H), 5.38 (d, J = 10 Hz, 1 H), 4.41, 4.15 (AM of AMX, J_{AM} = 10, J_{AX} = 7, J_{MX} = 6 Hz, 2 H, $-CH_2OMs$), 3.70 (s, 3 H, CH_3O–), 3.00 (s, 3 H, CH_3SO_2–), 1.19 (s, 3 H, angular CH_3), 1.00, 0.77 (two d, J = 6 Hz, 6 H, CH_3–); IR (CH_2Cl_2) cm^{-1} 1720, 1350).

The crude mesylate, without purification, was dissolved in 2 mL of dry Me_2SO and was transferred to a resealable Carius tube containing a saturated solution of CH_3NH_2 in Me_2SO (20 mL). The sealed tube was heated at 85 °C for 18 h. The tube was then cooled and its contents were poured into 50 mL of 1 N HCl. This solution was extracted with three 20-mL portions of ether which were combined and were washed with four 10-mL portions of 1 N HCl. The combined aqueous phases were then made basic by the addition of excess 30% KOH and were extracted with five 20-mL portions of CH_2Cl_2. The combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo to give **3:** 345 mg (83.5%); NMR ($CDCl_3$) δ 5.54 (d, J = 10 Hz, 1 H), 5.38 (d, J = 10 Hz, 1 H), 3.68 (s, 3 H, CH_3O–), 2.42 (broad s, 3 H, CH_3N–), 1.11 (s, 3 H, angular CH_3), 0.98, 0.75 (two d, J = 6 Hz, 6 H, CH_3–); IR (CH_2Cl_2) cm^{-1} 1720; mass spectrum *m/e* 279 (parent ion). Exact mass. Calcd for $C_{17}H_{29}NO_2$: 279.219 82. Found: 279.221 19.

Methyl 7α-Bromo-1α-cyano-6β-hydroxy-7aα-methyl-5α-(2-propyl)-2,3,3aα,4,5,6,7,7a-octahydro-1*H*-indene-4β-carboxylate (45). A solution of 23 mg of **26** (0.088 mmol) in 0.5 mL of DME was treated with 5 drops of H_2O, 5 drops of HOAc, and 22 mg of NBS (0.124 mmol). The resulting solution was stirred at room temperature for 2 h; then the reaction mixture was quenched with Na_2SO_3 and diluted with 20 mL of saturated $NaHCO_3$. This mixture was extracted with three 10-mL portions of CH_2Cl_2, and the combined extracts were passed through a cotton plug and evaporated in vacuo. The crude product was chromatographed on a 0.5-mm silica gel plate using 1:1 ether–hexane as the eluent. The band (R_f 0.50) yielded **45:** 20 mg (65%); NMR ($CDCl_3$) δ 3.93 (d, $J_{6,7}$ = 10 Hz, 1 H, H_7), 3.68 (s, 3 H, CH_3O–), 3.13 (dd, J = 7, 4 Hz, 1 H, H_1), 2.68 (dd, $J_{4,5}$ = 12, $J_{4,3a}$ = 4 Hz, 1 H, H_4), 1.43 (s, 3 H, angular CH_3), 1.08, 0.93 (two d, J = 6 Hz, 6 H, CH_3–); IR (CH_2Cl_2) cm^{-1} 3500, 2215, 1725; mass spectrum *m/e* (rel %) 359 (<1), 357 (<1), 261 (10), 260 (54), 200 (100).

Methyl 11α-Methyl-6α-(2-propyl)-3,4,5,8α,9α,10α-hexahydroindeno[7,1-*bc*]furan-2-one-5δ-carboxylate (51). A solution of 8.0 mg of **40** (0.0022 mmol) in 0.6 mL of dry DMF was added to 80 mg of anhydrous LiI (0.61 mmol) and the resulting solution was heated at 120 °C for 15 h under argon.[55] The cooled solution was diluted with 5 mL of 1 N HCl and extracted with three 5-mL portions of CH_2Cl_2. The combined extracts were passed through a cotton plug and evaporated in vacuo. The crude product was then esterified with diazomethane. Analytical TLC (silica gel, 1:1 ether–hexane) revealed that the material obtained was a single compound, R_f 0.17. The product was purified by preparative TLC on $^1/_2$ of a 0.25-mm silica gel plate using 1:1 ether–hexane as eluent, giving **51:** 3.0 mg (48%); NMR ($CDCl_3$) δ 5.66 (m, 1 H, H_7), 4.42 (m, 1 H, H_{10}), 3.70 (s, 3 H, CH_3O–), 3.39 (m, 1 H, H_5), 2.79 (d, J = 8 Hz, 1 H, H_8), 1.32 (s, 3 H, angular CH_3), 1.01, 0.91 (two d, J = 6 Hz, 6 H, CH_3–); IR (CH_2Cl_2) cm^{-1} 1755, 1735; mass spectrum *m/e* 278 (parent ion). Exact mass. Calcd for $C_{16}H_{22}O_4$: 278.151 81. Found: 278.153 30.

7α-Bromo-11α-methyl-6α-(2-propyl)-3,4,5,6,7,8α,9α,10α-octahydroindeno[7,1-*bc*]-furan-2-one-5β-carboxylic Acid (52). A degassed solution of 24.0 mg of **27** (0.082 mmol) in 1.0 mL of MeOH was added to 1.0 mL of 1 N NaOH (1.0 mmol). The resulting solution was heated at 80 °C for 18 h under argon. The cooled solution was then diluted with 10 mL of 1 N HCl, and the resulting mixture was extracted with three 10-mL portions of CH_2Cl_2. The combined extracts were passed through a cotton plug and concentrated in vacuo, giving crude acid **54:** 22 mg (96%); NMR ($CDCl_3$) δ 5.48 (s, 2 H), 2.81 (d, J = 5 Hz, 3 H, CH_3N–), 1.23 (s, 3 H, angular CH_3), 1.00, 0.79 (two d, J = 6 Hz, 6 H, CH_3–); IR (CH_2Cl_2) cm^{-1} 3380, 3100–2600 (broad), 1690, 1650.

Without purification, the crude acid **54** (22 mg) was dissolved in 0.5 mL of THF to which were added 0.2 mL of 50% aqueous acetic

acid and 43 mg of NBS (0.24 mmol). The resulting yellow solution was stirred at room temperature for 2.5 h, and then the excess oxidant was destroyed with $NaHSO_3$. The mixture was diluted with 10 mL of H_2O and extracted with three 10-mL portions of CH_2Cl_2. The combined extracts were passed through a cotton plug and concentrated in vacuo, giving 35 mg of crude product. The acid **52** was purified by preparative TLC on a 0.5-mm silica gel plate using 5% MeOH-CH_2Cl_2 as the eluent, giving 17.0 mg (63%); mp 184–190 °C; NMR ($CDCl_3$) δ 4.59 (s, 2 H, H_7 and H_{10}), 3.32 (dd, $J_{5,6}$ = 10, $J_{5,9}$ = 5 Hz, 1 H, H_5), 2.71 (d, J = 6 Hz, 1 H, H_8), 1.53 (s, 3 H, angular CH_3), 1.03 (d, J = 6 Hz, 6 H, CH_3–); IR (CH_2Cl_2) cm^{-1} 3500–2600 (broad), 1775, 1700.

A small sample was esterified with diazomethane, affording **40** quantitatively.

Reaction of 52 with $NaHCO_3$ and AgOAc in Me_2SO. A solution of 10.5 mg of **52** (0.003 mmol) in 0.2 mL of dry Me_2SO was added to 5 mg of $NaHCO_3$ (0.06 mmol) and 17 mg of AgOAc (0.10 mmol).[58] The resulting solution was stirred under Ar at 60 °C for 20 h, and then it was diluted with 10 mL of 1 N HCl. This mixture was extracted with three 10-mL portions of CH_2Cl_2, and the combined extracts were passed through a cotton plug and evaporated in vacuo. The crude product was esterified with ethereal diazomethane, and then it was chromatographed on $^1/_2$ of a 0.25-mm silica gel plate using 1:1 ether–hexane as the eluent. The single band (R_f 0.2) yielded 4.0 mg (47%) of **51** which was identical with the sample previously described.

Methyl *N*-Methyl-11α-methyl-6α-(2-propyl)-7-oximino-2,3,4,5,6,8α,9α,10α-octahydrocyclopenteno[*cd*]indole-5β-carboxylate (56). A solution of 15.5 mg of **3** (0.005 55 mmol) in 1.0 mL of acetone and 1.0 mL of 1 N HCl was treated with 45 mg of $NaNO_2$ (0.66 mmol). The resulting solution was stirred for 1 h at 0 °C. It was then diluted with 10 mL of H_2O and extracted with two 10-mL portions of CH_2Cl_2. The combined extracts were passed through a cotton plug and concentrated in vacuo, giving the crude nitrosamine **55:** 18 mg; NMR ($CDCl_3$) δ 5.55 (m, 2 H), 4.33, 4.00 (AM of AMX, J_{AM} = 13, J_{AX} = 9, J_{MX} = 6 Hz, 2 H, $-CH_2N(NO)$), 3.68 (s, 3 H, CH_3O), 3.04 (s, 3 H, CH_3N), 1.12 (s, 3 H, angular CH_3), 0.99, 0.75 (two d, J = 7 Hz, 6 H, CH_3–).

Without purification, the crude nitrosamine **55** was dissolved in 50 mL of methanol and transferred to a water-jacketed Hanovia immersion well equipped with an argon sparger, a Pyrex filter, a 450-W Hg lamp, and a reflux condenser. The photolysis apparatus was wrapped in aluminum foil, the bottom half of the system was packed in ice, and cold water was circulated through the cooling jacket. Concentrated HCl (1 mL, 12 mmol) was added, and the solution was degassed with a stream of argon for 30 min.[59] The solution was then irradiated for 45 min with a continuous argon purge, the resulting solution was transferred to a round-bottom flask, and the solvent was removed in vacuo. The residue which remained was neutralized with $NaHCO_3$, diluted with 20 mL of H_2O, and extracted with three 10-mL portions of CH_2Cl_2. The combined extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo, giving 19 mg of crude **56.** NMR analysis of this product indicated that **56** was the major component (greater than 75%); TLC analysis (silica gel, 4% MeOH-CH_2Cl_2) indicated that the mixture contained two components, R_f 0.35 and 0.06.

A 6.0-mg portion of this mixture was chromatographed on $^1/_2$ of a 0.25-mm silica gel plate using 10% MeOH-CH_2Cl_2 as the eluent. The less mobile band was removed from the plate and the absorbent was washed with four 10-mL portions of 15% MeOH-CH_2Cl_2. The combined extracts were washed with saturated $NaHCO_3$, dried, and concentrated in vacuo, giving 2.0 mg of **56.**

The yield of **56** was 51% from a similar experiment starting with 10.5 mg of **3.** In this instance, the entire reaction product was chromatographed: NMR ($CDCl_3$) δ 3.81 (t, J = 7 Hz, 1 H, A of AMX, $-CH_2N$–), 3.67 (s, 3 H, CH_3O–), 2.58 (s, 3 H, CH_3N–), 1.25 (s, 3 H, angular CH_3), 0.91, 0.88 (two d, J = 7 Hz, 6 H, CH_3–); IR (CH_2Cl_2) cm^{-1} 3500, 1730, 1610; mass spectrum *m/e* (rel %) 308 (7), 291 (100), 84 (30). Exact mass. Calcd for $C_{17}H_{28}N_2O_3$: 308.209 99. Found: 308.208 78.

Methyl 1β-(*N*-Trichloroethoxycarbonyl)-*N*-methylaminomethyl-7aα-methyl-5α-(2-propyl)-2,3,3aα,4,5,7a-hexahydro1*H*-indene-4β-carboxylate (58). A solution of 126 mg of **3** (0.452 mmol) in 2 mL of dry CH_2Cl_2 was treated with 0.130 mL of pyridine (2 mmol) and 0.120 mL of trichloroethyl chloroformate (1 mmol).[62] The resulting mixture was stirred at room temperature for 3.5 h. The purple solution was then diluted with 20 mL of saturated $NaHCO_3$ and extracted with three 10-mL portions of CH_2Cl_2. The combined extracts were passed through a cotton plug and concentrated in vacuo. The crude product was purified by preparative TLC over a single 2-mm silica gel preparative plate using 2:1 hexane–ether as the eluent. The single band (R_f 0.7–0.8) yielded crystalline **58:** 202 mg (98%); mp 90–91 °C (hexane); NMR ($CDCl_3$) δ 5.52 (m, 2 H), 4.74 (s, 2 H, $-OCH_2CCl_3$), 3.68 (s, 3 H, CH_3O–), 3.00, 2.98 (two s, rotational isomers, 3 H, CH_3N–), 1.12 (s, 3 H, angular CH_3), 0.99, 0.76 (two d, J = 7 Hz, 6 H, CH_3–); IR (KBr) cm^{-1} 1720, 1700; mass spectrum *m/e* (rel %) 459 (4), 458 (7), 457 (27), 456 (19), 455 (71), 454 (19), 453 (71), 277 (100). Anal. ($C_{12}H_{30}Cl_3NO_4$) C, H, Cl, N.

Methyl 1β-(*N*-Trichloroethoxycarbonyl)-*N*-methylaminomethyl-7aα-methyl-6α,7α-oxido-5α-(2-propyl)-2,3,3aα,4,5,6,7,7a-octahydro-1*H*-indene-4β-carboxylate (59) and Methyl 1β-(*N*-Trichloroethoxycarbonyl)-*N*-methylaminomethyl-7aα-methyl-6β,7β-oxido-5α-(2-propyl)-2,3,3aα,4,5,6,7,7a-octahydro1*H*-indene-4β-carboxylate (60). A solution of 193 mg of **58** (0.425 mmol) in 10 mL of toluene was added to a resealable Carius tube containing 900 mg of 85% MCPBA (4.3 mmol) and 36 mg of 4,4′-thiobis(6-*tert*-butyl-3-methylphenol).[63] The solution was degassed with a stream of argon, and then the tube was sealed. After being heated at 120 °C for 2 h, the tube was cooled and its contents were poured into a separatory funnel containing 10 mL of saturated $NaHCO_3$ and 10 mL of saturated Na_2SO_3. The organic layer was separated, and the aqueous phase was extracted with three 25-mL portions of CH_2Cl_2. The combined extracts were passed through a cotton plug and concentrated in vacuo. The products were separated by preparative TLC over four 0.5-mm silica gel preparative plates using 3:1 hexane–ether as the eluent (five developments).

The bands centered at R_f 0.7 afforded **60:** 94 mg (47%); NMR ($CDCl_3$) δ 4.67 (s, 2 H, $-OCH_2CCl_3$), 3.97, 3.25 (m, AM of AMX, 2 H, $-CH_2N$), 3.67 (s, 3 H, CH_3O–), 3.03 (broad s, 3 H, CH_3N–), 1.15 (s, 3 H, angular CH_3), 1.09, 0.90 (two d, J = 7 Hz, 6 H, CH_3–); IR (CH_2Cl_2) cm^{-1} 1710 (broad); mass spectrum *m/e* (rel %) 471 (1), 469 (1), 428 (16), 426 (17), 259 (97), 257 (100).

The bands centered at R_f 0.6 yielded **59:** 79 mg (40%); mp 107.5–109 °C (hexane); NMR ($CDCl_3$) δ 4.76 (s, 2 H, $-OCH_2CCl_3$), 3.65 (s, 3 H, CH_3O–), 3.02, 3.00 (two s, rotational isomers, 3 H, CH_3N–), 1.20 (s, 3 H, angular CH_3), 1.08, 0.98 (two d, J = 7 Hz, 6 H, CH_3–); IR (KBr) cm^{-1} 1725, 1710; mass spectrum *m/e* (rel %) 471 (3), 469 (3), 430 (11), 428 (35), 426 (36), 221 (100). Anal. ($C_{20}H_{30}Cl_3NO_5$) C, H, Cl, N.

Transformation of 60 into 58. A solution of 54 mg of **60** in 1.5 mL of glacial acetic acid was treated with 0.030 mL of 48% aqueous HBr. The solution was stirred for 5 h at 23 °C, and then all of the volatile components of the mixture were removed in vacuo. Analytical TLC (silica gel, 2:1 hexane–ether, two developments) indicated that the crude bromohydrin **61** (68 mg) was homogeneous (one spot, R_f 0.42). The NMR spectrum of this sample ((($CDCl_3$) δ 3.66 {2, 3 H, CH_3O–), 2.98 (broad s, 3 H, CH_3N–), 1.03, 0.96, (two d, J = 6 Hz, 6 H, CH_3–)) was complicated as a consequence of isomerism about the urethane C–N bond. Nonetheless, it was evident that this sample was not contaminated by detectable quantities of **60.** Attempts to purify **61** by preparative TLC (silica gel, 0.5-mm preparative plate, 2:1 hexane–ether) resulted in the regeneration of approximately 20% of **60** from **61** (NMR analysis). Thus, 57 mg of this mixture was obtained from the 68-mg sample of crude **61.** However, as these substances were inseparable at this stage, this mixture was used in the next step without further purification.

A solution of the previously described mixture (57 mg) in 1.5 mL of glacial acetic acid was treated with 150 mg of activated Zn. The reaction mixture was stirred at 23 °C for 5 h, and then the precipitated salts and the unreacted Zn were filtered off. The filtrate was neutralized with saturated $NaHCO_3$ and extracted with three 15-mL portions of CH_2Cl_2. The combined extracts were passed through a cotton plug and concentrated in vacuo to afford 32 mg of crude **3.**

Crude **3** (32 mg) was dissolved in 1.0 mL of dry CH_2Cl_2 and treated with 0.050 mL of pyridine and 0.025 mL of trichloroethyl chloroformate. The reaction mixture was stirred for 3 h at 23 °C before it was quenched by the addition of 5 mL of saturated $NaHCO_3$. The resulting mixture was extracted with three 10-mL portions of CH_2Cl_2, and the extracts were dried and concentrated in vacuo. The crude product (65 mg) was chromatographed over a single 0.5-mm silica gel preparative plate using 3:1 hexane–ether as eluent (two developments) to give 33 mg of **58** (63%; 77% based upon unrecovered **60**)

and 10.5 mg of recovered **60** (18.5%).

The yield of **58** was only 53% from a sequence in which crude **61** was subjected to the Zn–HOAc reduction. There was also obtained a 29% yield of an unknown, unidentified product. As a consequence, the most efficient method for recycling **60** is the one which was presented above.

Methyl *N*-Methyl-11α-methyl-6α-(2-propyl)-7α-hydroxy-2,3,4,5,6,8α,9α,10α-decahydrocyclopenteno[*cd*]indole-5β-carboxylate (50). A solution of 61 mg of **59** (0.13 mmol) in 1 mL of glacial HOAc and 1 mL of dry DME was treated with 200 mg of activated Zn dust (3.0 mg-atoms). The mixture stirred at 23 °C for 2 h, and then was filtered to remove the unreacted metal. The filtrate was neutralized with excess 30% KOH and diluted with 25 mL of H_2O. The resulting solution was extracted with four 10-mL portions of CH_2Cl_2. The combined extracts were passed through a cotton plug and concentrated in vacuo, giving **50:** 37 mg (97%); one spot by analytical TLC (silica gel, 4% MeOH–CH_2Cl_2, R_f 0.38); NMR ($CDCl_3$) δ 4.22 (dd, J = 2, 2.5 Hz, 1 H, H_7), 3.67 (s 3 H, CH_3O–), 3.04 (dd, J = 12, 4 Hz, H_5), 2.11 (s, 3 H, CH_3N–), 1.32 (s, 3 H, angular CH_3), 1.00, 0.97 (two d, J = 7 Hz, CH_3–); IR (CH_2Cl_2) cm^{-1} 3550, 2740, 1720; mass spectrum *m/e* (rel %) 295 (10), 278 (21), 218 (69), 96 (100). Exact mass. Calcd for $C_{17}H_{29}NO_2$: 295.214 74. Found: 295.213 50.

Methyl *N*-Methyl-11α-methyl-7-keto-6α-(2-propyl)-2,3,4,5,-6,8α,9α,10α-octahydrocyclopenteno[*cd*]indole-5β-carboxylate, Methyl Ketodendrobinate (57). A solution of 37 mg of **50** (0.125 mmol) in 0.5 mL of acetone was treated with 0.5 mL of 2 N HCl. The resulting solution was cooled to 0 °C and treated with 150 drops of Jones reagent.[71] The reaction solution was stirred for 1.5 h at 0 °C, and then the solution was neutralized by the dropwise addition of 30% KOH until the reaction mixture turned green. This mixture was then poured into 50 mL of saturated $NaHCO_3$ and extracted with five 15-mL portions of CH_2Cl_2. The combined extracts were passed through a cotton plug and concentrated in vacuo, giving crystalline **57:** 33.0 mg (90%); mp 67–75 °C; NMR ($CDCl_3$) δ 3.70 (s, 3 H, CH_3O–), 2.23 (s, 3 H, CH_3N–), 1.26 (s, 3 H, angular CH_3), 1.01, 0.95 (two d, J = 7 Hz, 6 H, CH_3–); IR (CH_2Cl_2) cm^{-1} 2750, 1730, 1705; mass spectrum *m/e* (rel %) 293 (6), 265 (92), 206 (56), 109 (100). Exact mass. Calcd for $C_{17}H_{27}NO_3$: 293.199 09. Found: 293.198 09.

A sample of **57** decomposed upon attempted recrystallization from an ether–hexane mixture. This intermediate was therefore used in the next step without any purification.

Synthetic Dendrobine. A solution of 21 mg of **57** (0.071 mmol) in 1 mL of 2-propanol was treated with 10 mg of $NaBH_4$ (0.3 mmol). The reaction mixture was stirred at 23 °C for 24 h, at which time analytical TLC (silica gel, 4% MeOH–CH_2Cl_2) indicated that **57** had been completely consumed. The major spot observed (R_f 0.37) had the same R_f as a cospotted sample of natural dendrobine. The reaction was quenched by the addition of 2 mL of 1 N HCl. After 30 min, the reaction mixture was diluted with 20 mL of saturated $NaHCO_3$ and extracted with three 10-mL portions of CH_2Cl_2. The extracts were dried and concentrated in vacuo to give 17.7 mg of crude synthetic dendrobine. The sample was purified by preparative TLC (silica gel, 5% MeOH–CH_2Cl_2; 10% MeOH–CH_2Cl_2 was used to elute dendrobine from the adsorbent; the extracts were washed with saturated $NaHCO_3$ prior to evaporation) to give 11.5 mg of crystalline (±)-dendrobine (62%), mp 105–126 °C.

A total of 45 mg of dendrobine was prepared by this procedure. The analytical sample was recrystallized three times from an ether–hexane mixture giving the analytically pure alkaloid: 22 mg; mp 130–132 °C (lit. mp (a) 131–132,[5a] (b) 128–130 °C[5b]); NMR ($CDCl_3$) δ 4.85 (dd, J = 5.5, 3.5 Hz, 1 H, H_7), 3.16 (t, J = 9 Hz, 1 H), 2.68 (t, J = 9 Hz, 1 H), 2.67 (d, J = 3.5 Hz, 1 H, H_{10}), 2.50 (s, 3 H, CH_3N–), 1.38 (s, 3 H, angular CH_3), 0.96 (d, J = 7 Hz, 6 H, CH_3–); IR (KBr) cm^{-1} 2740, 1760; mass spectrum *m/e* (rel %) 263 (37), 220 (100), 96 (80). Anal. Calcd for $C_{16}H_{25}NO_2$: C, 72.96; H, 9.57; N, 5.32. Found: C, 73.02; H, 9.65; N, 5.31. Exact mass. Calcd: 263.188 52. Found: 263.186 68.

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(15) Reduction of ethyl (*E,E*)-6-methylhepta-2,4-dienoate[14] with lithium aluminum hydride afforded alcohol **12** in 91% yield.
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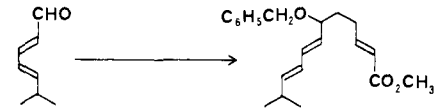

OC_2H_5, Et_2O, 54%; (ii) $C_6H_5CH_2Br$, NaH, DME, 84%; (iii) H_3O^+, 92%; (iv) CrO_3, pyridine, CH_2Cl_2, 95%; (v) carbomethoxymethylenetriphenylphosphorane, CH_2Cl_2, 74%.
(25) The benzyl ether derivatives of **8a** and **8b** were deprotected in 57–60% overall yield by a three-step sequence: (i) 5 equiv of aqueous NaOH, THF, reflux, 20 h; (ii) Li, NH_3, *t*-BuOH; (iii) CH_2N_2.
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(71) Performance of this experiment with smaller excesses of Jones reagent and/or for shorter reaction times led to incomplete oxidation.

Carbocyclic Thromboxane A_2[1]

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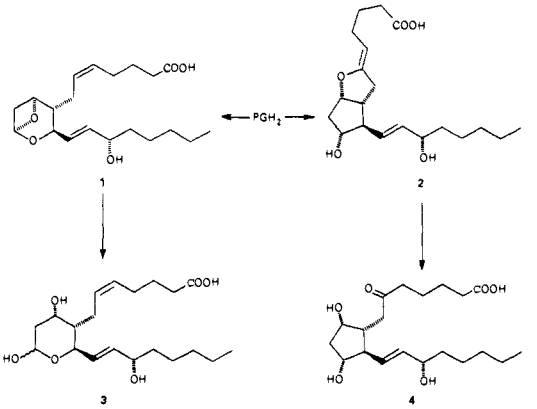
Abstract: The total synthesis of carbocyclic thromboxane A_2 (CTA_2) (**5**) and its hydroxy epimer (**5b**) has been achieved both in racemic and optically active forms. Bicyclo[3.1.1]heptan-2-one (**6**), synthesized by two alternative routes, was converted to the key intermediate **7**, which was efficiently transformed to the carbocyclic thromboxane A_2 skeleton by a cuprate 1,4 addition to introduce the lower side chain followed by homologation of the aldehyde function and Wittig reaction to complete the top chain. The resulting stable thromboxane A_2 analogues **5** and **5b** exhibited interesting and potent biological properties.

Introduction

Thromboxane A_2 (TA_2) is an unstable substance with potent thrombotic and vasoconstricting properties generated by human blood platelets[3] from the prostaglandin endoperoxide H_2 (PGH_2). Samuelsson and his associates assigned structure **1** (Scheme I) to thromboxane A_2 on the basis of its origin and chemistry and deduced a physiological half-life of a few seconds ($t_{1/2}$ = 32 s in aqueous pH 7.4 solution at 37 °C)[3] for this important biomolecule. Although this compound has not yet been isolated in pure form, a vast body of biology surrounding it has already been created.[4] Its biological profile is opposite to that of prostacyclin (PGI_2)[5] (**2**, Scheme I), a compound also generated from PGH_2 which behaves as an antithrombotic and vasodilatory agent. Although both thromboxane A_2 and prostacyclin are biologically very potent, they exhibit relatively high chemical instability, degrading rapidly to their stable metabolites, thromboxane B_2 (**3**) and 6-keto-$PGF_{1\alpha}$ (**4**)

Scheme I. Thromboxane A_2, Prostacyclin, and Their Degradation Products



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