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Synthesis of 4a-Aryldecahydroisoquinolines. Functionality in the Carbocyclic Ring

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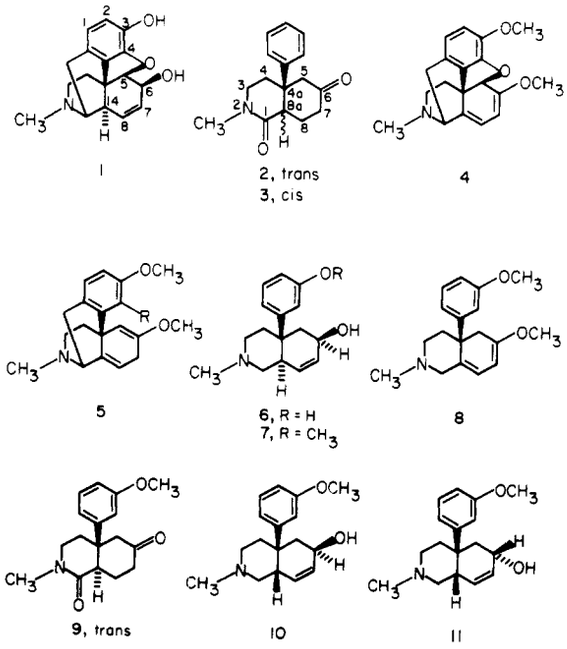
Syntheses are presented of 4a-(3′-methoxyphenyl)decahydroisoquinolines with the carbocyclic ring functionalized so as to resemble the substitution pattern in ring C of the morphine alkaloids. A versatile synthesis was developed for the starting 4-arylnipecotic acid which was then, via the methylene lactam rearrangement and intramolecular Michael reaction, stereospecifically converted to the 1,6-dioxodecahydroisoquinoline, keto amide *trans*-**9**. Reduction gave ketone *trans*-**36**, and selective functionalization at C-7 led to the key unsaturated ketal **39**. Hydrolysis yielded codeinone analogue, α,β-unsaturated ketone **40**, reduction gave codeine analogue Δ^7-allylic alcohol **7**, and ether cleavage produced the morphine analogue **6**. Cis-fused analogues were obtained through **9** and ketal amide **34** or **40** via isomerization at C-8a and were the predominant isomers at equilibrium. Alkali- or acid-catalyzed elimination of methanol from Δ^7-dimethyl ketal **39** produced mainly the thebaine analogue, $\Delta^{6(8a)}$-dienol ether **8**, which could be hydroxylated at C-8a with peracid to 14-hydroxycodeinone analogues **57** and **58**, but would not participate in Diels–Alder cycloaddition with a variety of dienophiles.

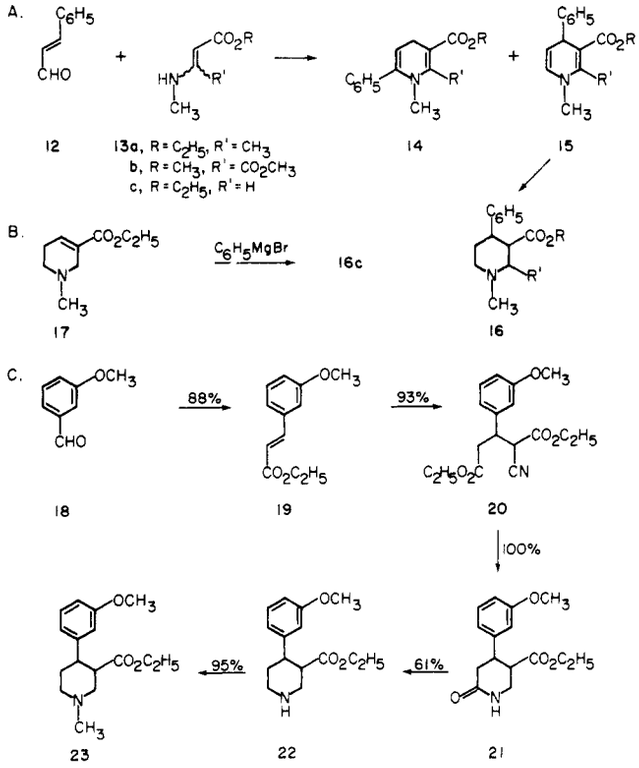
The 4a-aryldecahydroisoquinolines represent a new portion of the morphine molecule **1** which has appeared with increasing frequency in the recent literature.[1] A useful synthesis of these compounds requires both steric control of the ring juncture and functionality in the carbocyclic (C) ring. In our initial publication on this subject we demonstrated the availability of the *trans*- and *cis*-4a-phenyldecahydroisoquinolines, **2** and **3**.[1h] The C-1 and C-6 oxo functions provided control of the C-8a geometry as well as the potential for further C-ring elaboration. The logical utilization of **2** and **3** required the preparation of decahydroisoquinolines whose C rings were, with the exception of the C-5 oxygen bridge linkage, mimics of the C rings of the hydrophenanthrene opium alkaloids. An entirely analogous set of compounds with highly functionalized C rings has been prepared in the morphinan series from natural compounds, that is, directly from thebaine (**4**) or sinomenine or via prior conversion of **4** to **5**.[2,3] Parallel with these series, and to prepare the pharmacologically most interesting candidate compounds, the 4a-aryl moiety was chosen to be 3-methoxyphenyl.



We now report the synthesis of the decahydroisoquinolines **6**, **7**, and **8** (analogues of morphine, codeine, and thebaine) from the keto amide *trans*-**9**. In addition, although **9** possesses the trans ring fusion, the synthetic plan allowed for the production of both trans and cis materials, including the epimeric *cis*-codeine analogues **10** and **11**.

Formation of Decahydroisoquinolines. The synthesis of keto amide **9** required the nipecotic ester **23**. Previously we reported a general synthesis of 4-aryl 2-substituted nipecotates, but this was unsuccessful for the very important 2-substituted derivatives.[1h,4] In this process (Scheme IA) cinnamaldehyde (**12**) and readily available β-aminoacrylates **13a–c** were condensed to form the stable 1,4-dihydropyridines **15** which were easily reduced to the nipecotates **16**. The reactions with ethyl crotonate (**13a**) and the fumarate **13b** gave **15a** and **15b** in 77 and 55% yields, uncontaminated with the 6-phenyl isomers **14**. Unfortunately, the acrylate **13c** gave poor yields of mixtures of dihydropyridines **14** and **15**, forcing us to turn to a more tedious method (Scheme IB) for the preparation of 2-unsubstituted nipecotate **16c**, namely the conjugate addition of phenylmagnesium bromide to ethyl arecaidinate (**17**).[5]

Scheme I. Synthesis of 4-Arylnipecotic Acids: A, via β-Aminoacrylates; B, via Conjugate Addition of Grignard Reagents; C, via Michael Addition to Cinnamates



For the preparation of **23** a versatile synthesis of 4-aryl 2-unsubstituted nipecotic acids was developed (Scheme IC) by modification of a known procedure.[6] 3-Methoxybenzaldehyde (**18**) was converted to the amide ester **21** via standard procedures.[7,8] Selective reduction of the amide function of **21** was achieved by reaction with trimethyloxonium fluoroborate (forming the intermediate imidate) followed immediately by treatment with $NaBH_4$ in ethanol[9] to yield amino ester **22.** Reductive methylation gave the required nipecotate **23** in 48% overall yield from 3-methoxybenzaldehyde (**18**).

The conversion of nipecotate **23** into keto amide **9** followed closely the published process,[1h] relying on the methylene lactam rearrangement, selenium dioxide oxidation and allylic rearrangement, and Claisen rearrangement (Scheme II). This

Scheme II. Conversion of Nipecotate to Substituted Methylenepiperidone and Carbocyclic Ring Formation

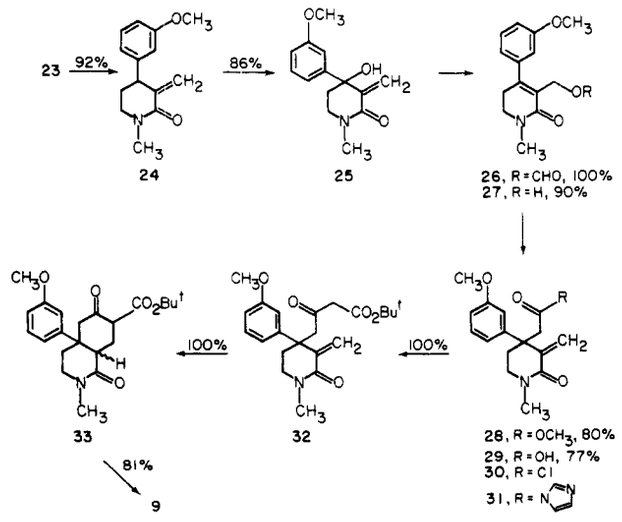


Table I. Cyclization of β-Keto Ester 32 to *cis*- and *trans*-4a-(3-Methoxyphenyl)decahydroisoquinoline (33)

Alkaline catalyst				Yield,[c] %	
Compd	Mol %	Solvent[a]	Time, h[b]	Cis	Trans
$(C_2H_5)_3N$	200	CH_3OH	48–120	12	88
CH_3ONa	10	CH_3OH	2.75	13	87
CH_3ONa	25	CH_3OH/H_2O, 2/1	2	13	87
$(CH_3)_3COK$	10	$(CH_3)_3COH$	1	45	55
$(CH_3)_3COK$	10	$(CH_3)_3COH$	12[d]	50	50
$(CH_3)_3COK$	10	$C_6H_5CH_3$	6	25	75

[a] All reactions carried out at 25 °C. [b] Reactions conducted until completion as indicated by TLC. [c] Total crude yield was a quantitative mixture of isomers. [d] Completed after 1 h; additional time for equilibration.

led to the 4-carboxymethyl-3-methylenepiperidone **29.** It was now necessary to introduce another carbon atom and close the carbocyclic ring C. To achieve this chain extension and produce a carbanionic center for conjugate addition to the methylene lactam, the carboxymethyl residue was converted to a β-keto ester.

Formation of the unstable acid chloride **30** and condensation with either *tert*-butyl lithioacetate or the magnesium enolate of *tert*-butyl hydrogen malonate accomplished this purpose and led to β-keto ester **32** but only in ~50% yield. A superior method was found in conversion of acid **29** to imidazolide **31** by the action of carbonyldiimidazole in $CHCl_3$/THF and reaction with the malonate reagent, resulting in a quantitative yield of very pure β-keto ester **32** suitable for direct use in the ring closure step.

The previous cyclization conditions (Et_3N, CH_3OH, 25 °C),[1h] when applied to the ring closure of **32** to **33,** required long times (2–5 days) and gave substantial amounts (13%) of the cis isomer. Several other alkaline catalyzed procedures were tested (Table I) and CH_3ONa/CH_3OH proved conveniently rapid although in no case could the trans/cis ratio be improved beyond 87/13. Isomeric purification may be done at this stage via recrystallization, leaving the oily *cis*-**33** in the mother liquors and returning pure *trans*-**33** in 70% (from **29**).

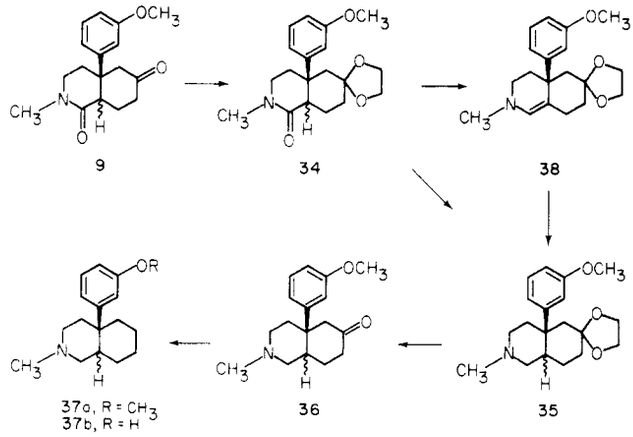
The assignment of stereochemistry and the determination of isomeric purity were performed by hydrolyzing and decarboxylating crude β-keto ester **33** to ketones **9,** followed by ketalization of the crude material to give a mixture of ethylene ketals **34.** When the crude **33** was obtained via cyclization using CH_3ONa/CH_3OH, these ketals were present in a trans/cis ratio of 87/13 by GC. This ratio was taken to be the kinetic product distribution. Compounds *trans*-**9** and *trans*-**34** are solids and were easily obtained pure by recrystallization; *cis*-**9** and *cis*-**34** are oils. That the cis isomers are the thermodynamically more stable products was shown by isomerization of *trans*-**9** and *trans*-**34** in KOH/ethanol. While the ketone was destroyed, as seen by NMR, at a rate comparable to isomerization, pure ketal *trans*-**34** was quantitatively converted to a 4/96 mix of *trans*/*cis*-**34** after 8 h at reflux.

These observations were in complete accord with the phenyl series, where the kinetic trans/cis ratio was 88/12 and the major isomer on equilibration was cis. In both series the kinetic products, which predominated in the ring closure of the β-keto esters, were solids and were assigned trans stereochemistry. The thermodynamic products, obtained under more vigorous, equilibrating conditions, were oils and were assigned as cis.[1h] The ultimate assignment in the phenyl series was based upon x-ray crystallography.[1d] The parallel results in both series (phenyl and 3-methoxyphenyl) pointed to the generality of obtaining either cis- or trans-fused materials by

these processes, independent of the angular aromatic functionality present at C-4a.

To compare our assignments with those previously reported, the amide and ketone functions at C-1 and C-6 of *trans*-**9** and *cis*-**9** were reduced (Scheme III). Not surprisingly, ether cleavage occurred under the vigorous Wolff–Kishner conditions. The methoxy amines *trans*-**37a**[1e,f] and *cis*-**37a**[1f,g] were obtained in low yields and the phenols *trans*-**37b**[1c] and *cis*-**37b**[1g] were the major products. Although the cis materials were oils and formed oily picrates, the NMR of *cis*-**37a** was in accord with the reported spectrum.[1g] Amine *trans*-**37a** formed a picrate, mp 165–166 °C (lit.[1f] mp 161–162 °C), while the phenol *trans*-**37b** was a solid, mp 210–211.5 °C (lit.[1g] mp 195–205 °C).

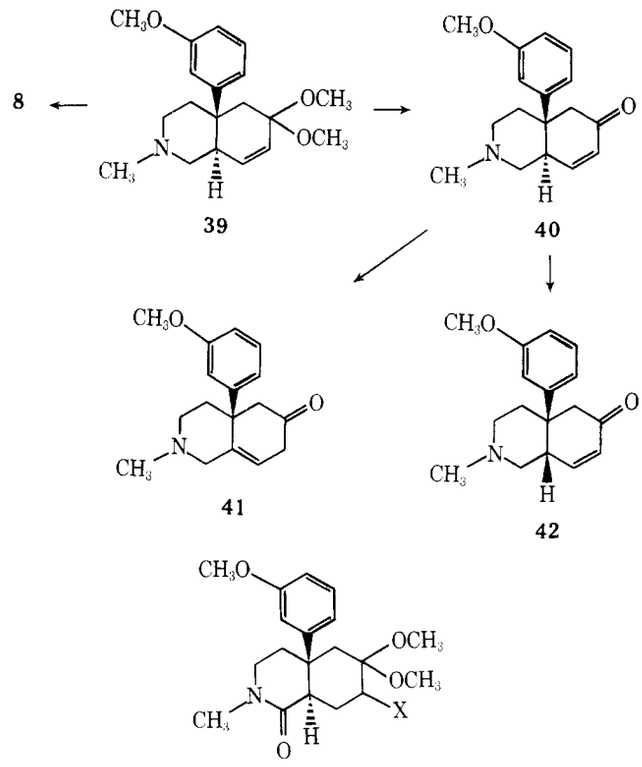
Scheme III. Reduction of Keto Amide 9



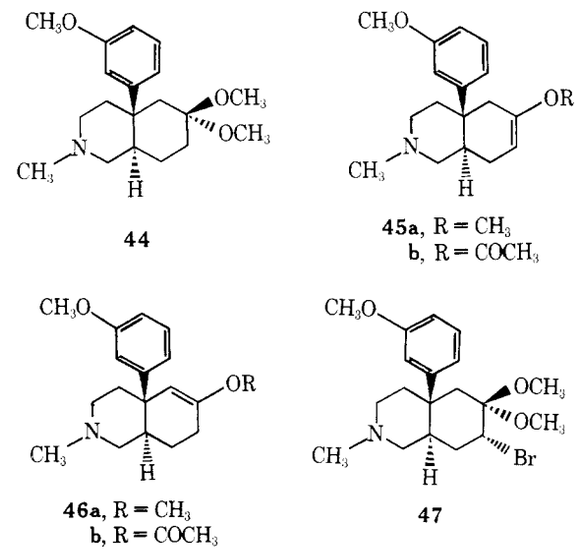
As in the phenyl series, reduction of the amide ketal *trans*-**34** with AlH_3/THF gave considerable amounts of enamine **38** which was converted to *trans*-**35** using H_2 and Rh/Al_2O_3. We investigated this sequence in the hope of finding a clean reaction which might give *trans*-**35** in a single step. Lithium aluminum hydride was without effect, as was diborane, at 25 °C; at reflux diborane gave reaction but several products resulted. Diisobutylaluminum hydride in toluene or THF gave **38** as the major product. The ratio of *trans*-**35** to **38** in the AlH_3 reduction of *trans*-**34** (57/43) could be improved by the addition of lithium aluminum hydride to a cold (−78 °C) solution of AlH_3 and *trans*-**34** in THF and warming. The ratio was now 83/17 in favor of the amine. Reverse order of hydride addition gave the same ratio of *trans*-**35** to **38** and considerable amide **34** remained.

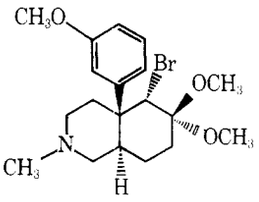
Functionalization of the Carbocyclic Ring. The prime consideration in the construction of the decahydroisoquinoline C-ring analogues of the morphine alkaloids was the incorporation of functionality sufficient to allow for formation of both the C-6 oxygen function and the Δ^7-ene and $\Delta^{6,8(8a)}$-diene. Our route to these derivatives inherently produced the C-6 ketone; thus the problem of introducing the remaining unsaturation was formally reduced to converting an one to an enone and thence to a dienol ether. Since direct action upon the ketone carried the potential of sacrificing the stereochemical integrity at C-8a, we envisioned our key intermediate to be the unsaturated ketal **39** which should yield exclusively the α,β-unsaturated ketone **40** (analogue of codeinone) via mild acid hydrolysis. The preference for the cis ring fusion in the decahydroisoquinoline series should allow production of conjugate ketone **42** and β,γ-unsaturated ketone **41** under equilibrating conditions. Additionally, **39** appeared an ideal candidate for the preparation of dienol ether **8** (thebaine analogue) via loss of methanol.

We considered two approaches to the synthesis of unsaturated ketal **39.** In the first, the doubly activated C-7 position of β-keto ester **33** should allow easy differentiation of C-5 and C-7 and introduction of a suitable substituent would be followed by hydrolysis, decarboxylation, and ketalization to give the generalized 7-substituted ketal **43.** This route would face the difficult problem of amide reduction while retaining additional functionality at C-7. In the alternative approach, amide reduction would precede ketone functionalization and the intermediate would be ketone *trans*-**36,** obtainable from **33** in 80% yield. This plan required selective reactivity at an undifferentiated C-7 position. Our recent report[10] of a high-yield conversion of dihydrocodeinone to codeinone dimethyl ketal via dihydrocodeinone enol ether had obvious applicability if selectivity at C-7 could be achieved; thus we explored the latter approach.



Ketone *trans*-**36** was easily ketalized in methanol containing trimethyl orthoformate and treatment of crude ketal **44** with phosphorus oxychloride and pyridine in toluene afforded a 91% yield of enol ethers **45a** and **46a** in an 83/17 ratio. The assignment of structure and the determination of the isomeric purity were done via NMR. The larger $W_{1/2}$ for the





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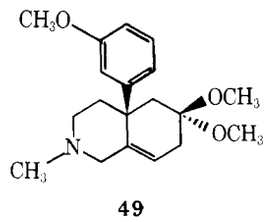

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vinyl proton of **45a** (7 Hz) compared to that of **46a** (2 Hz) was taken to reflect the larger coupling expected for the C-7 proton. A similar situation holds for enol acetates **45b** and **46b** obtained in 79/21 ratio after refluxing with tosic acid and acetic anhydride ($W_{1/2}$ for **45b**, 7 Hz; for **46b**, 4 Hz). Thus the C-7 enol predominated over the C-5 enol by a synthetically useful margin. Treatment of the enol ether mixture with *N*-bromoacetamide in methanol (methyl hypobromite) resulted in a clean conversion to the two bromo ketals **47** and **48.** Once again the predominant material (87/13 by NMR) had the larger $W_{1/2}$ ($W_{1/2}$ for **47**, 6 Hz; for **48**, 4 Hz). Neither the enol ethers nor the bromo ketals showed evidence of chromatographic separation (GC, TLC).

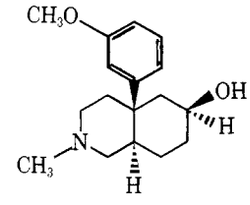
Treatment of the crude mixture of bromo ketals **47/48** with potassium *tert*-butoxide in Me_2SO at 60 °C resulted in two easily separable materials. Eluted first from silica was 7% of unreacted **48** followed by the unexpected neopinone dimethyl ketal analogue **49** in 74% yield. With the same reagents at 25 °C, a 60/40 mixture of Δ^7-ketal **39** and Δ^8-ketal **49** was obtained. Incorporation of *tert*-butyl alcohol as a cosolvent lead to prolonged reaction times but did not improve the **39/49** ratio while *tert*-butoxide in refluxing *tert*-butyl alcohol or *tert*-amyl alcohol had no effect upon the bromides. Lithium fluoride, chloride, or carbonate in Me_2SO at high temperatures lead to extensive decomposition. Fortunately, DBN in Me_2SO at 120 °C produced dehydrobromination without rearrangement and returned a 68% yield of Δ^7-ketal **39** after chromatography. The overall yields for introduction of the additional unsaturation into the C ring to produce the versatile intermediates **39** and **49** were 62 and 67%, respectively, from ketone *trans*-**36** (49 and 54% from keto amide *trans*-**9**).

When pure Δ^7-ketal **39** was treated briefly with *tert*-butoxide/Me_2SO at 60 °C a clean isomerization to Δ^8-ketal **49** was observed. At 120 °C, **49** underwent rapid loss of methanol and low yields of dienol ether **8** were isolated. The lack of some accompanying elimination to **8** during dehydrobromination of **47** at 60 °C was surprising, considering that treatment of codeinone dimethyl ketal at slightly higher temperatures gave clean elimination to thebaine with no detectable isomerization in reactions stopped prior to completion.[11] It was apparent that the replacement of a trans sp^3 center at C-8a with an sp^2 carbon was an extremely facile process in these decahydroisoquinolines and was entirely consistent with the high ratios of enamine **38** formed via AlH_3 reduction of **34.** An additional example of this process was later obtained from the acid hydrolysis of ketal **39.**

Preparation of Ring C Analogues. We planned the preparation of close relatives to the morphine alkaloids via the synthesis of unsaturated ketones **40, 41,** and **42.** With Δ^7-ketal **39** and Δ^8-ketal **49** at hand the route to **40** and **41** appeared straightforward and the only unanswered question was the formation of the cis enone **42.** Hydrolysis of **49** returned neopinone analogue **41** but **39** afforded a mixture of Δ^7- and Δ^8-enones **40** and **41** (3/1) under the standard hydrolysis conditions (3 N acetic acid, 25 °C). Both **40** and **41** proved stable to the hydrolysis conditions. As the hydrolysis of codeinone dimethyl ketal under the same nonequilibrating conditions produced no neopinone,[12] this behavior provided an additional example of the difference between the decahydroisoquinolines and the natural materials caused by the lability in the former of the trans proton at C-8a. After several trials 0.2 N $HClO_4$ was found to produce the least amount of Δ^8-enone **41** in the hydrolysis (~20%).

The synthesis of the cis Δ^7-enone **42** was performed under equilibrating conditions (CH_3ONa, CH_3OH). Beginning with either ketone **40** or **41,** a mixture of **41** and **42** was produced with no detectable trans enone **40.** The separation of conjugated and nonconjugated enones was readily accomplished via the bisulfite extraction procedure developed for ketones in the morphine series.[13] The unconjugated ketone **41** could be recovered pure after adjusting the pH of the bisulfite extract to 8.5 since only 1,2-addition to the carbonyl had occurred. The conjugated isomers **40** and **42** remained in the aqueous phase since 1,4-addition of bisulfite had occurred producing a sulfonic acid which was not regenerated via β-elimination until pH 12. Significantly no isomerization occurred in this strongly alkaline medium and both trans and cis enones, **40** and **42,** were recovered pure. From the hydrolysis of Δ^7-trans ketal **39** were obtained **41** (16%) and **40** (62%) after separation while the equilibrating conditions produced **41** (32%) and **42** (57%).

To provide a basis for the stereochemical assignment of the unsaturated alcohols to be obtained via reduction of enones **40, 41,** and **42** we first investigated the reduction products of saturated ketones *trans*- and *cis*-**36.** Treatment of ketone *trans*-**36** with H_2/Pt in acetic acid gave a single substance identified as the axial isomer **50** ($W_{1/2}$ for C-6 H, 6 Hz[14]). Reduction with either $NaBH_4$/ethanol or Na/2-propanol in toluene afforded mixtures of **50** and the equatorial isomer **51**



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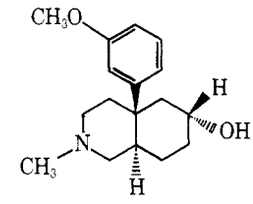

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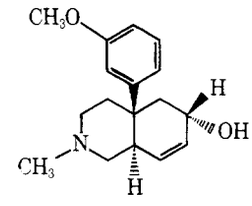

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($W_{1/2}$ for C-6 H, ~20 Hz), readily distinguished spectrally and chromatographically. Catalytic reduction of ketone *cis*-**36** under the same conditions produced two materials, A and B (1/2), while the borohydride procedure returned the same materials with an A/B ratio of 3/2. That A and B were the cis axial and equatorial alcohol isomers was shown by chromatographic separation and characterization. Although a tentative assignment for these alcohols was made in the 4a-phenyldecahydroisoquinoline series,[1d] our results were not comparable. In the previous case a single material was reported from the catalytic reduction (H_2, Pd/C, acetic acid, 1000 psi) and the *same* isomer predominated in the borohydride reduction. The assignment of stereochemistry to A and B was not possible solely from the data for the saturated alcohols but was made later using the assignments of the corresponding unsaturated alcohols.

The reduction of β,γ-enone **41** with $NaBH_4$ in ethanol produced a complex mixture from which was isolated 47% of a chromatographically homogeneous β,γ-unsaturated alcohol. Certain NMR resonances (C-6 H, NCH_3) were broadened and when the unsaturation was reduced with H_2/Pt in methanol a mixture of products was obtained. The two major products

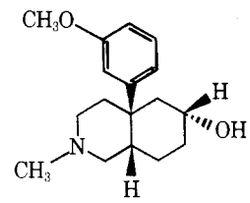
were trans axial alcohol **50** (major) and trans equatorial alcohol **51**, which presumably reflected the isomeric constitution at C-6 of the original unsaturated alcohols.

The reduction of trans α,β-enone **40** proceeded without incident using AlH_3/THF and two allylic alcohols were readily obtainable accompanied by a small amount (5%) of saturated ketone *trans*-**36**. The major material (56%) was found to be codeine analogue **7** by reduction to axial alcohol **50**, while the minor isomer (31%) was converted to equatorial alcohol **51** and thus represented the isocodeine analogue **52**. Treatment of codeine analogue **7** with potassium thioethoxide in DMF[15] yielded the morphine analogue **6** in 60% yield.

The reduction of the cis α,β-unsaturated ketone **42** was complicated by facile saturation of the C-7,8 double bond. Using AlH_3/THF as in the reduction of **40**, the major product was the saturated ketone *cis*-**36** accompanied by small amounts of unsaturated materials, and borohydride in ethanol produced a complex mixture of saturated and unsaturated alcohols. Fortunately, diisobutylaluminum hydride in toluene displayed a minimal amount of conjugate reduction, yielding only 9% of **36** along with 68% of cis Δ^7-allylic alcohols **10** and **11**.

The stereochemical assignment of the cis allylic alcohols was made possible by the striking difference in the vinyl proton absorptions of the two isomers. The major isomer possessed a doublet of doublets (J = 10 Hz) almost coalesced to a sharp singlet ($W_{1/2}$ for the central peak was 2.5 Hz), which could only be explained by very low values for $J_{8,8a}$ and $J_{6,7}$. The NMR of the minor isomer showed one vinyl proton as a doublet (J = 9 Hz) and the other downfield vinyl proton as a doublet of doublets (J = 4, 9 Hz) indicating that only one of these J values was very small. In order to apply these data we needed to identify the stable conformations of **10** and **11** and proceeded to do so by making two assumptions. Firstly, we assumed that the cyclohexene ring was represented by the half-chair conformation.[16,17] Thus **10** and **11** were restricted to the conformers **10a**, **10b**, and **11a**, **11b**. Secondly, we assumed that the conformer which possessed a pseudoequatorial hydroxyl function would be the *more* stable. In simple cyclohexenes (i.e., 3-chloro, 3-bromo) the pseudoequatorial stereoisomers are *less* stable owing to eclipsing of the C-3 substituent with the vinyl proton on C-1,[18] but in 4,4-dimethyl 6-substituted 1-phenylcyclohexenes the group at C-6 was largely pseudoequatorial.[19] Since the system at hand was a 4,4-disubstituted 6-hydroxycyclohexene we therefore assigned the stable conformers of **10** and **11** to be **10a** and **11b**. The stereochemical assignments were based on the expected weaker coupling of pseudoaxial allylic protons H-6 and H-8a with the neighboring vinyl protons H-7 and H-8.[19] Thus the NMR of **10a** would show $J_{7,8}$ as the only strong coupling while the spectrum of **11b** would reflect the strong couplings of $J_{7,8}$ and $J_{8,8a}$. These predictions were in complete accord with the actual data for **10** and **11**; thus the major isomer was assigned structure **10** and the minor isomer was assigned structure **11**.

When these arguments were applied to the trans unsaturated alcohols **7** and **52**, predictions were in accord with the assignments already made. In the case of **7**, our two basic assumptions were in conflict since the strain energy produced by the interaction of the 4a-α-aromatic ring and the 6-α-hydroxyl was surely comparable to $\Delta H°$ (2.7 kcal/mol)[20] for the half-chair and half-boat forms. The observed NMR was most consistent with the half-chair form, showing a sharp doublet (H-8) and a severely broadened doublet (H-7). The NMR of epimer **51** showed only a doublet of doublets. Reduction of **10** and **11** to the saturated alcohols produced B from **10** and A from **11**. Thus A was assigned to be **53** and B was the all-cis isomer **54**.



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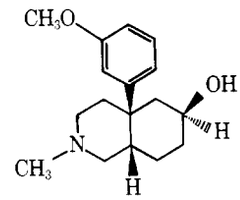
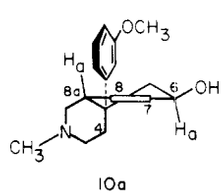


54

Although thebaine analogue **8** was available by the base-catalyzed elimination of CH_3OH from **49**, the low yield and the difficulty in obtaining pure material hindered its preparation in quantity. A more efficient procedure was the treatment of **39** with $POCl_3$/pyridine in hot toluene, which cleanly gave CH_3OH elimination with a 75% recovery but produced an 85/15 mixture of dienes **8** and **55**. The structure of **55** was readily assigned on the basis of the NMR of the H-5 and H-8 vinyl protons (singlet and triplet). These isomers could not be completely separated by chromatography and some of isomer **55** was present in all subsequent reactions of **8**.

The homoannular conjugate diene common to both thebaine (**4**) and **8** is, in the case of thebaine, a highly reactive



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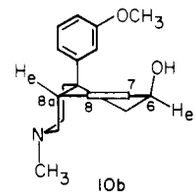

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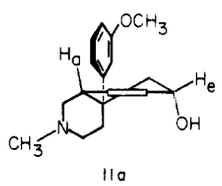

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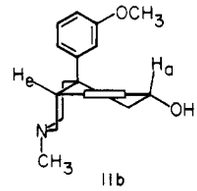

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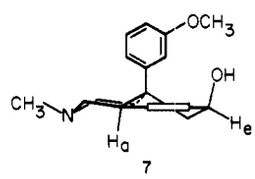

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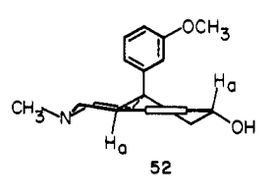

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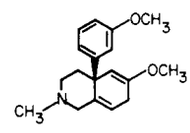

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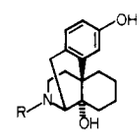

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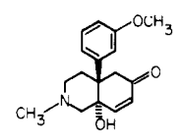

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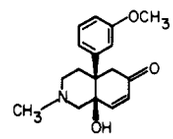

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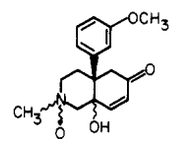

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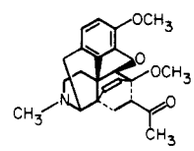

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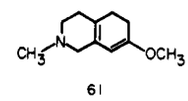

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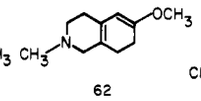

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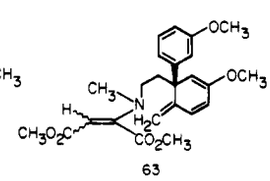
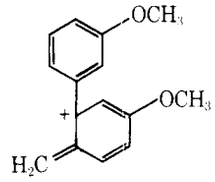


63

system capable of many transformations. Thus oxidation of **4** with peracid yields 14-hydroxycodeinone,[21] which is transformed to the important narcotic antagonist naloxone.[22] Simple 14-hydroxymorphinans such as **56** have been prepared and are both potent agonists and antagonists.[23] It was therefore of interest to prepare 14-hydroxylated derivatives in the decahydroisoquinoline series. Treatment of **8** with *m*-chloroperbenzoic acid in a mixture of acetic acid and trifluoroacetic acid at 95 °C returned two materials which were identified as **57** and **58** in 50% yield. In addition, a significant amount (14%) of the *N*-oxide **59** was isolated. Stereochemical assignments to **57** and **58** were not made, but presumably the major material (43%) was trans fused and the minor isomer (7%) was the cis material, since reactions performed under kinetically controlled conditions tend to preferentially attack the β face of the molecule at C-8a (e.g., the ring closure of **32** to **33** and the hydrogenation of **38** to *trans*-**35**). Thus the potential availability of the 14-hydroxylated compounds was clearly demonstrated.

A second important reaction of the thebaine C ring is the facile addition of dienophiles s to give 6,14-etheno bridged species such as **60** (from methyl vinyl ketone) which have been converted into highly potent analgesics.[24] When the mixture of dienes **8** and **55** was subjected to identical Diels–Alder conditions with either ethyl acrylate or methyl vinyl ketone no new products were formed and the starting dienes were recovered after chromatographic separation from polymer. These results were in direct contrast to the thebaine example and also to work done with the simpler decahydroisoquinolines **61** and **62** where fair yields of adducts were obtained under the same conditions.[25] The more reactive dimethyl acetylenedicarboxylate (DMAD) returned no cycloadduct (thebaine reacts easily)[26] but instead the unstable triene **63** was obtained in 45% yield accompanied by many other products. The structure of **63** was evident from its NMR (six distinct vinyl protons) and its mass spectral fragmentation, giving ion **64** as the base peak. This type of C–N bond cleavage with DMAD has been observed previously; e.g., the cleavage of



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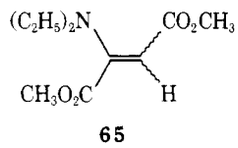

65

triethylamine hydrobromide with DMAD in refluxing CH_2Cl_2 yielded enamine **65** in 85% yield[27] and similar reactions with other tertiary amines have been reported.[28] The facility with which **8** was cleaved was undoubtedly due to the allylic nature of the bond being broken.

Our last attempt to form a Diels–Alder adduct was with the extremely powerful dienophile *N*-phenylmaleimide. After 12 h in toluene at 110 °C only a negligible amount of reaction had occurred and only after 170 h were both reactants consumed. An NMR analysis of both the crude reaction mixture and of chromatographic fractions revealed no materials which possessed a 6,8a-etheno bridge. No attempt to achieve cycloaddition other than by the usual thermal conditions was made.

In summary, beginning with the easily obtainable keto amide *trans*-**9** close relatives of the morphine alkaloids possessing both cis and trans ring fusions have been prepared by a facile process and in good overall yield. The chemistry of these materials qualitatively resembled that of the natural series but quantitative differences arose owing to the additional features in the morphine skeleton. Thus enol ether **46** and diene **55** have no counterpart in the alkaloids since enolization toward C-5 is hindered by the 4,5-oxide bridge. Similarly the reduction of codeinone and neopinone and the oxidation of thebaine proceed with exclusive β-attack due to the extraordinary hindrance of the α face,[12,21] while their analogues **40, 41,** and **8** give mixtures of epimers in these reactions. Two distinct differences did emerge, namely, the facile isomerization of the double bond from Δ^7 to $\Delta^{8(8a)}$ and the surprising nonreactivity of thebaine analogue **8** toward Diels–Alder cycloaddition, giving rise, in the case of DMAD, to the interesting triene **63.**

Experimental Section[29]

Ethyl 3-Methoxycinnamate (19). 3-Methoxycinnamic acid was prepared as described[30] except that β-picoline was used as solvent. The yield of acid was 100%, mp 118–120 °C (lit.[30] mp 117 °C). This material, diethyl sulfate (102 g, 0.66 mol), tris(2-hydroxypropyl)amine (151 g, 0.79 mol), and acetone (100 mL) were concentrated on a steam bath for 1.5 h, cooled (25 °C), poured into H_2O (1600 mL), and extracted with ether (3 × 800 mL). The combined organic phases were washed with saturated $NaHCO_3$ (800 mL) and saturated NaCl (800 mL), dried, evaporated, and distilled, affording 120 g (88%) of the cinnamate: bp 96–101 °C (0.1 mm) [lit.[31] 185–186 °C (15 mm)0; NMR δ 7.72 (d, J , 16 Hz, 1 H), 7.17 (m, 4 H), 6.46 (d, J = 16 Hz, 1 H), 4.30 (q, J = 7 Hz, 2 H), 3.83 (s, 3 H), 1.38 (t, J = 7 Hz, 3 H).

Diethyl 2-Cyano-3-(3′-methoxyphenyl)pentanedioate (20). Michael addition with ethyl cyanoacetate was carried out as directed[8] for the phenyl case, giving a 93% yield of **20:** bp 150–160 °C (0.3 mm); NMR δ 7.42–6.66 (m, 4 H), 4.25–3.79 (m, 6 H), 3.79 (s, 3 H), 2.90 (m, 2 H), 1.21 (t, J = 7 Hz, 3 H), 1.15 (t, J = 7 Hz, 3 H); IR (neat) 2235, 1725 cm^{-1}; mass spectrum m/e (rel intensity) 319 (30), 245 (73), 161 (100). Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.9; H, 6.6; N, 4.4. Found: C, 64.1; H, 6.6; N, 4.5.

Ethyl 4-(3′-Methoxyphenyl)-2-piperidone-5-carboxylate (21). The adduct **20** (30.2 g, 92.7 mmol), PtO_2 (1.5 g), ethanolic HCl (12 N, 31.5 mL, 0.38 mol), and ethanol were shaken under H_2 (33–49 psi) for 7 h. The residue after filtration and evaporation was dissolved in $CHCl_3$ (100 mL), washed with saturated $NaHCO_3$ (200 mL), dried, and evaporated. After addition of toluene (200 mL) the solution was refluxed for 1 h and the solvent removed to give 26.7 g (100%) of crude amide **21** as a mixture of isomers. On crystallization from CH_2Cl_2/hexane a single isomer was obtained: mp 144–145.5 °C; NMR δ 7.20 (m, 2 H), 6.8 (m, 3 H), 4.14 (q, J = 7 Hz, 2 H), 3.83 (s, 3 H), 3.8–3.3 (m, 3 H), 3.17 (m, 1 H), 2.87 (d, J = 5 Hz, 2 H), 1.23 (t, J = 7 Hz, 3 H); IR (KBr) 1735, 1665 cm^{-1}; mass spectrum m/e (rel intensity) 277 (41), 134 (100). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 65.0; H, 6.9; N, 5.0. Found: C, 65.1; H, 6.8; N, 5.02.

Ethyl 4-(3′-Methoxyphenyl)piperidine-3-carboxylate (22). To a solution of trimethyloxonium fluoroborate (14.78, 99 mmol) in CH_2Cl_2 (250 mL) was added a 24.9-g portion of the crude amide obtained above. After 43 h at 25 °C the solvent was evaporated, and the residue was dissolved in ethanol (250 mL), cooled (−10 °C, internal) and treated portionwise with $NaBH_4$ (10.2 g, 0.27 mol, 20 min) with vigorous mechanical stirring while maintaining the solution at 5–10 °C. The solution was stirred for 24 h (25 °C), H_2O (250 mL) was added, and the mixture was concentrated and acidified (pH 1) with 1.5 N HCl, neutralized with saturated $NaHCO_3$ (pH 8), and extracted with $CHCl_3$ (3 × 200 mL). The combined organic extracts were dried, evaporated, and distilled, yielding 14.47 g (61% from **20**) of amine **22:** bp 110–130 °C (0.3 mm); NMR δ 7.27 (m, 1 H), 6.80 (m, 3 H), 3.93 (q, J = 7 Hz, 2 H), 3.79 (s, 3 H), 1.99 (s, 1 H), 0.99 (t, J = 7 Hz, 3 H); IR (neat) 3350, 1725 cm^{-1}; mass spectrum m/e (rel intensity) 263 (35), 190 (30), 129 (37), 57 (100), 56 (72). Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.4; H, 8.0; N, 5.3. Found: C, 68.4; H, 8.0; N, 5.2.

Ethyl 4-(3′-Methoxyphenyl)-1-methylpiperidine-3-carboxylate (23). A suspension of amine **22** (12.27 g, 44.7 mmol), 37% aqueous CH_2O (15 mL, 0.2 mol), 10% Pd/C (1.75 g), and ethanol (100 mL) were shaken for 12 h under H_2 (50 psi). The reaction mixture was filtered, evaporated, and distilled, giving 12.05 g of **23** (94.5%): bp 130–140 °C (0.3 mm); NMR δ 7.14 (m, 1 H), 6.75 (m, 3 H), 3.86 and 3.93 (isomeric quartets, J = 7 and 8 Hz, 2 H), 3.69 (s, 3 H), 3.28 and 3.33 (isomeric singlets, 3 H), 1.03 and 0.95 (isomeric triplets, J = 7 and 8 Hz, 3 H); IR (neat) 1725 cm^{-1}; mass spectrum m/e (rel intensity) 277 (31), 276 (10), 71 (37), 70 (50), 44 (100). Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.3; H, 8.4; N, 5.0. Found: C, 69.2; H, 8.2; N, 5.0.

4-(3′-Methoxyphenyl)-1-methyl-3-methylene-2-piperidone (24). The ester **23** (5.0 g, 17.5 mmol), NaOH (1.49 g, 35 mmol), CH_3OH (50 mL), and H_2O (25 mL) were refluxed for 5 h. After the thorough removal of solvents, the residue was mixed with acetic anhydride (50

mL) and refluxed for 1 h, then cooled and evaporated and the crude reaction product partitioned between $CHCl_3$ (50 mL) and saturated $NaHCO_3$ (50 mL, pH 8). The aqueous layer was extracted with $CHCl_3$ (2 × 50 mL) and the combined organic phases dried and evaporated. Distillation gave 3.77 g (92%) of **24**. Recrystallization (CH_2Cl_2/hexane) gave the anlytical sample: mp 67–70 °C; NMR δ 7.29 (m, 1 H), 6.82 (m, 3 H), 6.40 (t, J = 2 Hz, 1 H), 5.07 (t, J = 2 Hz, 1 H), 3.75 (s, 3 H), 3.34 (m, 2 H), 3.04 (s, 3 H), 2.17 (m, 2 H); IR (KBr) 1645, 1600 cm^{-1}; mass spectrum m/e (rel intensity) 231 (100), 216 (13). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.7; H, 7.4; N, 6.1. Found: C, 72.6; H, 7.3; N, 6.0.

4-Hydroxy-4-(3′-methoxyphenyl)-1-methyl-3-methylene-2-piperidone (25). Methylene lactam **24** (633 mg, 2.68 mmol), SeO_2 (228 mg, 2.06 mmol), and chlorobenzene (8 mL) were heated at 100 °C for 50 min. Filtration, evaporation, and chromatography (SiO_2, $CHCl_3$/CH_3OH, 99/1) gave 575 mg (86%) of the tertiary alcohol **25**: mp 127–128 °C from benzene; NMR δ 7.5–6.7 (m, 4 H), 6.41 (d, J = 7 Hz, 1 H), 5.43 (d, J = 2 Hz, 1 H), 4.18 (bs, 1 H), 380 (s, 3 H), 3.8–3.0 (m, 2 H), 2.95 (s, 3 H), 2.10 (m, 2 H); IR (KBr) 3350, 1640, 1585 cm^{-1}; mass spectrum m/e (rel intensity) 247 (100), 230 (20), 229 (11), 228 (13), 112 (92). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.0; H, 6.9; N, 5.7. Found: C, 68.2; H, 6.9; N, 5.6.

3-Formyloxymethyl-4-(3′-methoxyphenyl)-1-methyl-5,6-dihydro-2-pyridone (26). The tertiary alcohol **25** (254 mg, 1.04 mmol) was solvolyzed in 97% HCO_2H (10 mL) for 16 h at 25 °C and the solvent evaporated. The residue was dissolved in $CHCl_3$ (15 mL) and washed with saturated $NaHCO_3$ (15 mL), the aqueous layer was extracted with $CHCl_3$ (2 × 15 mL), and the combined organic phases were dried and evaporated to yield 288 mg (100%) of the formate. Distillation [155–165 °C (0.07 mm)] and recrystallization (benzene/hexane) gave a solid: mp 87–88 °C; NMR δ 8.08 (s, 1 H), 7.26 (m, 1 H), 6.80 (m, 3 H), 4.88 (s, 2 H), 3.80 (s, 3 H), 3.53 (t, J = 7 Hz, 2 H), 3.07 (t, J = 7 Hz, 2 H); IR 1700, 1645, 1610 cm^{-1}; mass spectrum m/e (rel intensity) 275 (221), 246 (75), 230 (52), 229 (100). Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.4; H, 6.2; N, 5.1. Found: C, 65.5; H, 6.1; N, 5.0.

3-Hydroxymethyl-4-(3′-methoxyphenyl)-1-methyl-5,6-dihydro-2-pyridone (27). Methylene lactam **24** (4.78 g, 20.3 mmol), SeO_2 (1.69 g, 15.2 mmol), and chlorobenzene (50 mL) were heated at 100 °C for 1 h, cooled, filtered, and evaporated. The crude alcohol was dissolved in 97% HCO_2H (50 mL) and stirred at 25 °C for 27 h, and formate **26** was isolated as above. The crude formate was dissolved in CH_3OH (50 mL), K_2CO_3 (1.42 g, 10.3 mmol) was added, and after 1.5 h at 25 °C the mixture was evaporated and the residue partitioned between $CHCl_3$ (50 mL) and saturated NaCl (50 mL). The aqueous layer was extracted with $CHCl_3$ (2 × 50 mL), and the combined organic phases dried and evaporated to give 4.50 g (90% overall) of pure allylic alcohol **27** which crystallized upon standing. This product was used directly in the following Claisen rearrangement. Recrystallization (benzene/hexane) gave material of mp 81–83 °C: NMR δ 7.18 (m, 1 H), 6.74 (m, 3 H), 4.10 (s, 2 H), 3.66 (s, 3 H), 3.35 (t, J = 7 Hz, 2 H), 3.17 (bs, 1 H), 2.90 (s, 3 H), 2.53 (t, J = 7 Hz, 2 H); IR (KBr) 3400, 1655, 1600 cm^{-1}; mass spectrum m/e (rel intensity) 247 (3), 230 (2), 229 (7), 44 (100). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.0; H, 6.9; N, 5.7. Found: C, 68.0; H, 6.8; N, 5.6.

4-Methoxycarbonylmethyl-4-(3′-methoxyphenyl)-1-methyl-3-methylene-2-piperidone (28). The allylic alcohol **27** (1.22 g, 4.96 mmol), trimethyl orthoacetate (5.52 g, 46 mmol), and pivalic acid (25 mg, 0.50 mmol) were placed in diglyme (25 mL) and refluxed at 155–160 °C (internal) with fractionation to remove CH_3OH. After 18 h the solvents were evaporated and the residue distilled [bp 175–185 °C (0.15 mm)] to return 1.21 g (80%) of methyl ester **28**. Upon standing the ester crystallized: mp 85–86 °C; NMR δ 7.30 (m, 1 H), 6.86 (m, 4 H), 6.65 (s, 1 H), 5.57 (s, 1 H), 3.76 (s, 3 H), 3.47 (s, 3 H), 3.17 (m, 3 H), 2.87 (s, 4 H), 2.53 (m, 2 H); IR 1733, 1653, 1595 cm^{-1}; mass spectrum m/e (rel intensity) 303 (38), 230 (100). Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.3; H, 7.0; N, 4.6. Found: C, 67.2; H, 7.0; N, 4.6.

4-Carboxymethyl-4-(3′-methoxyphenyl)-1-methyl-3-methylene-2-piperidone (29). To methyl ester **28** (1.20 g, 3.97 mmol) dissolved in CH_3OH (5 mL, 0 °C) was rapidly added KOH (775 mg, 11.9 mmol) in 5 mL of 1/1 CH_3OH/H_2O. After 20 h at 25 °C, $CHCl_3$ (20 mL) and H_2O (20 mL) were added, the separated aqueous layer was extracted with $CHCl_3$ (20 mL), and the combined organic phases were dried and evaporated to give 178 mg (20%) of **1,3-dimethyl-4-(3′-methoxyphenyl)-2-pyridone** (this arises from unreacted allylic alcohol under the alkaline hydrolysis conditions[1h]): NMR δ 7.20 (m, 2 H), 6.86 (m, 3 H), 6.07 (d, J = 7 Hz, 1 H), 3.81 (s, 3 H), 3.57 (s, 3 H), 2.10 (s, 3 H); IR (neat) 1640 cm^{-1} (broad); mass spectrum m/e (rel intensity) 229 (63), 228 (100). Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.3; H, 6.6; N, 6.1. Found: C, 73.0; H, 6.6; N, 6.1.

The pH of the aqueous layer was adjusted to 1, the solution was extracted with $CHCl_3$ (3 × 15 mL), and the combined organic extracts were dried and evaporated to yield **29** (884 mg, 77%): mp 177–178 °C ($CHCl_3$/hexane); NMR δ 9.4 (bs, 1 H), 7.23 (m, 1 H), 6.86 (m, 3 H), 6.59 (s, 1 H), 5.59 (s, 1 H), 3.76 (s, 3 H), 3.18 (m, 2 H), 2.92 (s, 5 H), 2.62 (m, 2 H); IR (KBr) 1720, 1645, 1590 cm^{-1}; mass spectrum m/e (rel intensity) 289 (32), 230 (100). Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.4; H, 6.6; N, 4.8. Found: C, 66.2; H, 6.6; N, 5.2.

***tert*-Butyl 4-[4′-[4′-(3″-Methoxyphenyl)-1′-methyl-3′-methylene-2′-oxopiperidyl]]-3-oxobutyrate (32). A. Via *tert*-Butyl Lithioacetate and 4-Chlorocarbonylmethyl-4-(3′-methoxyphenyl)-1-methyl-3-methylene-2-piperidone (30).** Thionyl chloride (9.16 g, 77 mmol) in CH_2Cl_2 (100 mL) was cooled (−70 °C) and the acid **29** (5.78 g, 20 mmol) was added at a rate of 2 mL/min. After addition, the bath was removed, the solution allowed to warm to 25 °C (1 h), and the volatiles evaporated. Benzene (100 mL) was added and evaporated and the residual **30** used immediately: NMR δ 7.27 (m, 1 H), 6.80 (m, 4 H), 5.53 (s, 1 H), 3.78 (s, 3 H), 3.52 (s, 2 H), 3.21 (t, J = 6 Hz, 2 H), 2.87 (s, 3 H), 2.51 (bt, J = 6 Hz, 2 H); IR (neat) 1800, 1640, 1600 cm^{-1}.

To THF (33 mL) and 2,2,6,6-tetramethylpiperidine (5.78 g, 41 mmol) at −78 °C was added *n*-butyllithium (16.4 mL, 2.5 M in hexane, 41 mmol). After 5 min *tert*-butyl acetate (2.38 g, 20.5 mmol) was added dropwise followed 10 min later by the acid chloride **30** in THF (40 mL) at a rate of 2 mL/min. The solution was maintained at −78 °C for 15 min and then the reaction was quenched by addition of saturated NH_4Cl (55 mL) followed by slowly warming the slurry at 25 °C, separating the layers, and washing the aqueous phase with ether (2 × 40 mL). The combined ethereal layers were washed with 1 N HCl (20 mL) and saturated NaCl (20 mL), dried, and evaporated to give 6.92 g (90%) of crude β-keto ester **32**. Chromatography (SiO_2, $CHCl_3$/acetone, 3/1) returned 3.5 g (45%) of pure **32**.

B. Via the Acid Chloride 30 and the Magnesium Enolate of *tert*-Butyl Hydrogen Malonate. Acid chloride formation as above followed by treatment with the magnesium enolate and isolation as below yielded 59% of pure **32** after chromatography.

C. Via the Imidazolide 31 and the Magnesium Enolate of *tert*-Butyl Hydrogen Malonate. To carbonyldiimidazole (365 mg, 2.2 mmol) dissolved in 20 mL of THF was added acid **29** (578 mg, 2 mmol) in 20 mL of $CHCl_3$. After 60 min at 25 °C the clear solution was evaporated, and the residue dissolved in benzene (20 mL), reevaporated, and redissolved in THF (10 mL). Independently $LiO_2CCH_2CO_2C_4H_9$[32] (895 mg, 5.4 mmol) in 20 mL of THF was treated dropwise with isopropylmagnesium bromide (5.2 mmol, 6.65 mL of 0.78 N in THF) giving a pale yellow solution which was heated on a steam bath until precipitation of LiBr was complete. To the heterogeneous magnesium enolate solution was added the solution of crude imidazolide and the suspension was stirred for 16 h. The mixture was poured into Et_2O (25 mL), saturated NaCl (25 mL), and 2 N HCl (10 mL). The separated aqueous layer was washed with Et_2O (2 × 10 mL), and the combined organic phases were washed with saturated NaCl (10 mL), dried, mixed with benzene (20 mL), and evaporated. The residue was taken up in benzene (50 mL), washed with saturated $NaHCO_3$ (2 × 10 mL) and saturated NaCl (10 mL), dried, and evaporated to give β-keto ester **32** (789 mg, 100%) as a colorless oil. Chromatography (SiO_2, $CHCl_3$/acetone, 3/1) returned 697 mg (90%) of pure **32**: NMR δ 7.30 (m, 1 H), 6.88 (m, 3 H), 6.60 (s, 1 H), 3.82 (s, 3 H), 2.90 (s, 3 H), 1.47 (s, 9 H); IR 1720, 1645, 1600 cm^{-1}.

***tert*-Butyl 1,6-Dioxo-4a-(3′-methoxyphenyl)-2-methyldecahydroisoquinoline-7-carboxylate (33).** In the same manner as above acid **29** (8.67 g, 30 mmol) was converted to crude β-keto ester **32** (11.5 g, 100%) which was treated with CH_3OH (300 mL) containing CH_3ONa (3 mmol) for 7 h, then poured into saturated NaCl (400 mL) and benzene (500 mL). The aqueous phase was washed with benzene (3 × 100 mL) and the combined organic layers were dried and evaporated. The crystalline residue was dissolved in boiling benzene (20 mL), hot hexane (200 mL) was added, then the solution was concentrated to 80 mL and cooled (25 °C) to give 8.03 g (70%) of pure β-keto ester *trans*-**33**: mp 159–161 °C; NMR δ 7.22 (m, 1 H), 6.78 (m, 3 H), 3.78 (s, 3 H), 2.93 (s, 3 H), 1.49 (s, 9 H); IR 1650, 1629 cm^{-1}; mass spectrum m/e (rel intensity) 387 (1), 331 (5), 287 (16), 59 (100). Anal. Calcd for $C_{22}H_{29}NO_5$: C, 68.1; H, 7.5; N, 3.6. Found: C, 68.0; H, 7.5; N, 3.6.

Chromatography (SiO_2, $CHCl_3$/acetone, 9/1) of the mother liquors returned 2.73 g (24%) of a 3/1 mix of β-keto esters *cis*- and *trans*-**33**. Isomeric compositions were determined by hydrolysis, decarboxylation, and ketalization as described below (see **34**). Likewise **32** was cyclized to **33** as shown in Table I. In all cases the recovery of cyclized material was quantitative and isomer ratios were determined as below (see **34**).

***trans*-1,6-Dioxo-4a-(3′-methoxyphenyl)-2-methyldecahydroisoquinoline (*trans*-9).** The cyclic β-keto ester *trans*-**33** (3.5 g,

9 mmol) in benzene (50 mL) was treated with TFA (50 mL) at 25 °C. After 3 h the solvents were removed, and the residue was taken up in 200 mL of toluene and refluxed for 60 min. Evaporation gave a residue which was recrystallized (benzene/hexane) to yield 2.1 g (81%) of pure *trans*-**9**: mp 156–158 °C; NMR δ 7.20 (m, 1 H), 6.75 (m, 3 H), 3.72 (s, 3 H), 2.90 (s, 3 H); IR (KBr) 1705, 1635 cm^{-1}; mass spectrum *m/e* (rel intensity) 287 (61), 57 (94), 55 (100). Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.0; H, 7.4; N, 4.9. Found: C, 70.8; H, 7.4; N, 4.9.

***trans*-6,6-Ethylenedioxy-4a-(3′-methoxyphenyl)-2-methyl-1-oxodecahydroisoquinoline (*trans*-34).** To a solution of ketone *trans*-**9** (86.1 mg, 0.3 mmol) in benzene (20 mL) were added TsOH·H_2O (19.2 mg) and ethylene glycol (56 μL, 1 mmol) and the solution heated with removal of 15 mL of cloudy solvent. Cooling to 25 °C, pouring into 5% Na_2CO_3 (10 mL), washing the organic phase with saturated NaCl (5 mL), drying, and evaporating gave 105 mg (100%) of crude **34**. Recrystallization (benzene/hexane, 1:6) gave 91 mg (92%) of pure *trans*-**34**: mp 180–181 °C; NMR δ 7.1 (m, 1 H), 6.7 (m, 3 H), 3.9–3.6 (m, 7 H), 3.65 (s, 3 H); 2.67 (s, 3 H); IR 1623 (s), 1600 (sh), 1575 cm^{-1}; mass spectrum *m/e* (rel intensity) 331 (79), 232 (57), 99 (100). Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.9; H, 7.6; N, 4.2. Found: C, 68.6; H, 7.5; N, 4.4.

***cis*-6,6-Ethylenedioxy-4a-(3′-methoxyphenyl)-2-methyl-1-oxodecahydroisoquinoline (*cis*-34).** Ketal *trans*-**34** (66 mg, 0.2 mmol) was dissolved in ethanol (4 mL) containing KOH (40 mg, 0.6 mmol) and refluxed (32 h). The equilibrium point (96/4, cis/trans) was reached after 8 h. The reaction was quenched by pouring into saturated NaCl (10 mL), extracted with $CHCl_3$ (2 × 5 mL), dried, and evaporated to give 65.6 mg (98%) of the mixture. Preparative GC (240 °C) gave 41 mg (63% recovery) of pure *cis*-**34** as a colorless oil: NMR δ 7.2 (m, 1 H), 6.9 (m, 3 H), 3.95 (m, 4 H), 3.50 (s, 3 H), 2.70 (s, 3 H); IR 1620, 1603, 1578 cm^{-1}; mass spectrum *m/e* (rel intensity) 331 (19), 99 (35), 55 (100). Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.9; H, 7.6; N, 4.2. Found: C, 68.9; H, 7.6; N, 4.4.

trans-**34** has a GC retention time (237 °C) of 2.6 min while that for *cis*-**34** is 3.4 min. Analysis of the isomeric ratio obtained in the cyclization of **32** to **33** was by hydrolysis of the crude cyclized material (as per **33** to **9**) and ketalization (as per *trans*-**9** to **34**) without purification of intermediates. GC of the crude ketals gave the isomeric ratios in Table I.

***cis*-1,6-Dioxo-4a-(3′-methoxyphenyl)-2-methyldecahydroisoquinoline (*cis*-9).** Ketal *cis*-**34** (20 mg, 0.06 mmol) was dissolved in 1:1 THF/1 N H_2SO_4 (2 mL) and stirred for 60 h. Ether (2 mL) and saturated NaCl (1 mL) were added, the aqueous phase washed with ether (1 mL), and the combined organic phases washed with saturated NaCl (2 mL), dried, and evaporated to yield 17 mg (99%) of pure *cis*-**9**: NMR δ 7.30 (t, J = 9 Hz, 1 H), 6.9 (m, 3 H), 3.78 (s, 3 H), 7.87 (s, 3 H), 2.63 (s, 2 H); IR 1712, 1634, 1603, 1580 cm^{-1}; mass spectrum *m/e* (rel intensity) 287 (32), 218 (26), 55 (100). Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.0; H, 7.4; N, 4.9. Found: C, 71.0, H, 7.4; N, 4.9.

Reduction of *trans*-34. The general procedure involved dissolving *trans*-**34** (0.1–0.2 mmol) in THF (2–4 mL), adding 500 mol % of either $LiAlH_4$ (1.0 M in THF), B_2H_6 (1.0 M in THF), AlH_3 (0.65 M in THF), or DIBAL (1.98 M in hexane), and stirring for 30 min at various temperatures. Reactions were monitored as described below for *trans*-**35** and by NMR.

A. AlH_3, 0 °C. Reduction and isolation gave a 57/43 ratio of amine *trans*-**35** and enamine **38**: NMR δ 5.96 (s, 1 H) and 2.60 (s, 3 H); IR 1673 cm^{-1} [compared to the known[1h] phenyl compound: NMR δ 5.97 (s, 1 H), 2.42 (s, 3 H); IR 1671 cm^{-1}]. Resubmission of the crude reduction product to the reaction conditions resulted in reisolation of the same mixture.

B. $LiAlH_4$; AlH_3, 0 °C. The THF solution of *trans*-**34** at −78 °C was treated with $LiAlH_4$, stirred for 30 s, then treated with AlH_3. After stirring for 30 min, isolation gave a mixture consisting of 61% of amine *trans*-**35**, 13% of enamine **38**, and 26% of *trans*-**34**.

C. AlH_3; $LiAlH_4$, −78 °C. The procedure was as in B, but with AlH_3 added before $LiAlH_4$. Isolation gave an 82/18 amine *trans*-**35** to enamine **38** ratio with no starting material present.

D. $LiAlH_4$. No reaction occurred at 0 °C, 25 °C, or at reflux.

E. B_2H_6. No reaction occurred at 25 °C. At reflux a complex mixture was obtained.

F. DiBAL, 0 °C. After isolation there was obtained amine *trans*-**35** and enamine **38** in a 10/90 ratio.

***trans*-6,6-Ethylenedioxy-4a-(3′-methoxyphenyl)-2-methyldecahydroisoquinoline (*trans*-35).** Ketal amide *trans*-**34** (450 mg, 1.35 mmol) in THF (25 mL, anhydrous) in a dry ice/acetone bath was treated with AlH_3 (4.05 mmol in THF, 0.65 M) and stirred for 1 min. $LiAlH_4$ (6.75 mmol in THF, 1.01 M) was added, and the solution was warmed gradually to 0 °C and maintained at that temperature for 60 min. Excess hydride was decomposed by the addition of 1:1 THF/H_2O (125 μL) followed by 3.33 N NaOH (325 μL). The reaction solution was poured into Et_2O (50 mL) and saturated NaCl (10 mL) along with two washings of the salts with Et_2O (5 mL). Drying and evaporating yielded 426 mg (100%) of crystalline material which by NMR was 25% enamine **38** and 75% *trans*-**35.** This residue was dissolved in methanol (25 mL) and hydrogenated at 50 psi H_2 in the presence of 5% Rh/Al_2O_3 (130 mg) for 10 h. Filtration and evaporation gave 441 mg of material which was recrystallized (benzene/hexane, 1:2), returning 182 mg (42%) of pure *trans*-**35,** mp 124.5–126 °C. Chromatography (SiO_2, 1–10% NH_4OH/C_2H_5OH) of the mother liquor afforded 177 mg (41%) of pure *trans*-**35** (83% overall): NMR δ 7.3–6.9 (m, 3 H), 6.68 (dt, J = 2 Hz, 7, 1 H), 3.88 (s, 3 H), 4.0–3.2 (m, 7), 2.25 (s, 3 H); IR 1605, 1580 cm^{-1}; mass spectrum *m/e* (rel intensity) 317 (80), 316 (45), 99 (21), 71 (100), 70 (62). Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.9; H, 8.6; N, 4.4. Found: C, 71.7; H, 8.5; N, 4.5.

***cis*-6,6-Ethylenedioxy-4a-(3′-methoxyphenyl)-2-methyldecahydroisoquinoline (*cis*-35).** Crude ketal amide *cis*-**34** (360 mg, 1.09 mmol, 96% cis, 4% trans) in THF (10 mL) at 0 °C was treated with AlH_3 (5.50 mmol in THF, 0.65 M) and the cloudy solution stirred for 60 min. Isolation as for the trans amine yielded 362 mg of crude *cis*-**35.** Chromatography (SiO_2, 1–10% NH_4OH/C_2H_5OH) returned 264 mg (73%) of pure amine ketal *cis*-**35**: NMR δ 7.2–6.9 (m, 3 H), 6.71 (bd, J = 8 Hz, 1 H), 4.1–3.6 (m, 7 H), 3.88 (s, 3 H), 2.12 (s, 3 H); IR 1603, 1577 cm^{-1}; mass spectrum *m/e* (rel intensity) 317 (99), 272 (82), 99 (20), 71 (100), 70 (63). Anal. Calcd for $C_{19}H_{27}N_3$: C, 71.9; H, 8.6; N, 4.4. Found: C, 71.8; H, 8.5; N, 4.3.

***cis*- and *trans*-4a-(3′-Methoxyphenyl)-2-methyl-6-oxodecahydroisoquinolines (*cis*- and *trans*-36). Trans.** The ketal amine *trans*-**35** (170 mg, 0.536 mmol) was dissolved in 1 N H_2SO_4 (15 mL) and stirred for 26 h at 25 °C. Basification (2 N NaOH) and extraction with $CHCl_3$ (3 × 10 mL), followed by washing the organic phase with saturated NaCl (10 mL), drying, and evaporating yielded 145 mg (99%) of pure amino ketone *trans*-**36** which was recrystallized from benzene/hexane, 1/1: mp 94–95 °C; NMR δ 7.4–6.9 (m, 3 H), 6.70 (dt, J = 2, 7 Hz, 1 H), 3.77 (s, 3 H), 2.32 (s, 3 H); IR 1706, 1603, 1580 cm^{-1}; mass spectrum *m/e* (rel intensity) 273 (31), 272 (21), 71 (93), 70 (100). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.7; H, 8.5; N, 5.1. Found: C, 74.6; H, 8.3; N, 5.1.

Cis. In a manner exactly as above ketal amine *cis*-**35** (263 mg, 0.83 mmol) was converted into the ketone amine *cis*-**36** (233 mg) as an oil which was homogenous by GC: NMR δ 7.4–6.6 (m, 4 H), 3.78 (s, 3 H), 2.35 (s, 3 H); IR 1701, 1598, 1577 cm^{-1}; mass spectrum *m/e* (rel intensity) 273 (68), 71 (100), 70 (87). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.7; H, 8.5; N, 5.1. Found: C, 74.8; H, 8.5; N, 5.1.

***trans*-4a-(3′-Methoxyphenyl)-2-methyldecahydroisoquinoline (*trans*-37a).** A solution containing $H_2NNH_2·H_2O$ (900 mg, 18 mmol), KOH (105 mg, 1.6 mmol), and the ketone *trans*-**36** (136 mg, 0.5 mmol) in diethylene glycol (1.5 mL) was refluxed for 1 h and then distilled until the distillate reached 175 °C. The solution was then refluxed for an additional 1 h, cooled to 25 °C, diluted with H_2O (20 mL, pH 12), and extracted with benzene (3 × 10 mL). The organic layer was washed with 1 N NaOH (5 mL), H_2O (5 mL), and saturated NaCl (5 mL), dried, and evaporated to yield 16.9 mg (13%) of *trans*-**37a**: NMR δ 7.4–7.0 (m, 3 H), 6.72 (m, 1 H), 3.82 (s, 3 H), 2.24 (s, 3 H); IR 1600, 1580 cm^{-1}; mass spectrum *m/e* (rel intensity) 259 (58), 258 (51), 151 (40), 150 (27), 71 (100), 70 (58). Anal. Calcd for $C_{17}H_{25}NO$: C, 78.7; H, 9.7; N, 5.4. Found: C, 78.7; H, 9.7; N, 5.4. A picrate was prepared, mp 165–166 °C (lit.[1f] mp 161–162 °C).

***trans*-4a-(3′-Hydroxyphenyl)-2-methyldecahydroisoquinoline (*trans*-37b).** The combined alkaline aqueous layers above were adjusted to pH 8 and extracted with benzene (3 × 15 mL). The combined organic phase was washed with NaCl (10 mL), dried, and evaporated to give 82 mg (67%) of phenol *trans*-**37b** which was recrystallized from $CHCl_3$/hexane, 8/1: mp 210–211.5 °C (lit.[1g] mp 195–205 °C); NMR δ 7.03 (m, 4 H), 6.47 (d, J = 7 Hz, 1 H), 2.27 (s, 3 H); IR 3670, 3590, 1592 (sh), 1582 cm^{-1}; mass spectrum *m/e* (rel intensity) 245 (68), 244 (69), 151 (39), 150 (21), 71 (100), 70 (77). Anal. Calcd for $C_{13}H_{23}NO$: C, 78.2; H, 9.4; N, 5.7. Found: C, 78.1; H, 9.4; N, 5.7.

***cis*-4a-(3′-Methoxyphenyl)-2-methyldecahydroisoquinoline (*cis*-37a).** In exactly the same manner as for the trans ketone, 199 mg (0.73 mmol) of ketone *cis*-**36** was converted to amine *cis*-**37a** (41 mg, 22%): NMR δ 7.29 (t, J = 8 Hz, 1 H), 7.04 (m, 2 H), 6.74 (dt, J = 2, 8 Hz, 1 H), 3.82 (s, 3 H), 2.24 (s, 3 H); IR 1600, 1580 cm^{-1}; mass spectrum *m/e* (rel intensity) 259 (50), 258 (37), 151 (29), 150 (14), 71 (100), 70 (58). Anal. Calcd for $C_{17}H_{25}NO$: C, 78.7; H, 9.7; N, 5.4. Found: C, 78.6; H, 9.7; N, 5.4. A picrate was prepared and was an oil as reported.[1f]

***cis*-4a-(3′-Hydroxyphenyl)-2-methyldecahydroisoquinoline (*cis*-37b).** The combined alkaline aqueous layers above were adjusted to pH 8 and extracted with benzene (3 × 20 mL). The combined organic phase was washed with saturated NaCl (10 mL), dried, and

evaporated to give 87 mg (50%) of phenol *cis*-**37b**, which was distilled [bp 160 °C (0.1 mm)] [lit.[1g] bp 145–155 °C (0.5 mm)]: NMR δ 7.5–6.5 (m, 5 H), 2.28 (s, 3 H); IR 3663, 1595 cm^{-1} (b); mass spectrum *m/e* (rel intensity) 245 (67), 244 (60), 151 (34), 150 (17), 71 (100), 70 (79). Anal. Calcd for $C_{16}H_{23}NO$: C, 78.2; H, 9.4; N, 5.7. Found: C, 78.0; H, 9.4; N, 5.7.

***trans*-6,6-Dimethoxy-4a-(3′-methoxyphenyl)-2-methyldecahydroisoquinoline (44).** Ketone *trans*-**36** (3.215 g, 117 mmol), trimethyl orthoformate (5.3 g, 50 mmol), sulfuric acid (1.88 mL, 36 N, 34 mmol), and CH_3OH (350 mL) were refluxed for 20 min, an equal portion of the orthoformate was added, and reflux was continued for 20 min. The cooled solution was evaporated to 100 mL, cooled, and poured into H_2O (300 mL) containing NaOH (4 g, 100 mmol) and $CHCl_3$ (200 mL). The separated aqueous layer was washed with $CHCl_3$ (3 × 50 mL), and the combined organic phases were washed with saturated NaCl (50 mL), dried, and evaporated to give 3.80 g (100%) of ketal **44**. A small portion was distilled [135–140 °C (0.1 mm)] although the crude material was used in all subsequent reactions: NMR δ 7.16 (m, 3 H), 6.68 (dt, *J* = 2, 7 Hz, 1 H), 3.84 (s, 3 H), 3.14 (s, 3 H), 2.42 (s, 3 H), 2.27 (s, 3 H); IR 1601, 1580 cm^{-1}; mass spectrum *m/e* (rel intensity) 319 (10), 287 (68), 272 (100), 71 (25), 70 (41). Anal. Calcd for $C_{19}H_{29}NO_3$: C, 71.4; H, 9.1; N, 4.4. Found: C, 71.6; H, 9.1; N, 4.4.

***trans*-Δ⁵- and -Δ⁶-6-Methoxy-4a-(3′-methoxyphenyl)-2-methyloctahydroisoquinolines (46a and 45a).** The crude ketal **44** (3.8 g, 11.7 mmol) was dissolved in toluene (450 mL), treated with pyridine (11.1 g, 140 mmol) and $POCl_3$ (5.73 g, 37.4 mmol), and refluxed for 2 h at which time a clear brown oil had separated. The cooled (10 °C), vigorously stirred emulsion was rapidly treated with cold (0 °C) 1 N NaOH (224 mL), then shaken until no oil remained. The separated aqueous layer was washed with benzene (2 × 50 mL), the combined organic phases were washed with saturated NaCl (50 mL), dried and evaporated, and the residue was distilled [140–150 °C (0.1 mm)] giving 3.07 g (91%) of pure enol ethers (NMR revealed a C-5/C-7 vinyl proton ratio of 13/87; the $W_{1/2}$ for C-5 H was 2 Hz and for C-7 H was 7 Hz): NMR δ 7.27 (m, 3 H), 6.68 (dt, *J* = 2, 7 Hz, 1 H), 3.80 (s, 3 H), 2.30 (s, 3 H); Δ⁵, 4.85 (s, 1 H), 3.47 (s, 3 H); Δ⁶, 4.70 (s, 1 H), 3.40 (s, 3 H); IR 1664, 1601, 1580 cm^{-1}; mass spectrum *m/e* (rel intensity) 287 (63), 286 (23), 273 (22), 272 (100), 71 (30), 70 (45). Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.2; H, 8.8; N, 4.9. Found: C, 75.0; H, 8.7; N, 4.9.

Enol Acetates 45b and 46b. Ketone *trans*-**36** (45 mg, 0.15 mmol) and acetic anhydride (2 mL) containing $TsOH \cdot H_2O$ (34 mg, 0.20 mmol) were heated at reflux for 8 h and evaporated. The residue was dissolved in $CHCl_3$ (15 mL), washed with saturated $NaHCO_3$, dried, and evaporated to give 37 mg (78%) of **45b/46b** in a 79/21 ratio: NMR δ 7.4–6.8 (m, 3 H), 6.73 (bd, *J* = 7 Hz, 1 H), 3.82 (s, 3 H), 2.30 (s); the Δ⁵ enol acetate **46b** had δ 5.62 (s, $W_{1/2}$ = 4 Hz, 1 H), 2.08 (s, 3 H); the Δ⁷ isomer **45b** had δ 5.37 (s, $W_{1/2}$ = 7 Hz, 1 H), 2.02 (s, 3 H).

***trans*-5- and -7-Bromo-6,6-dimethoxy-4a-(3′-methoxyphenyl)-2-methyldecahydroisoquinoline (48 and 47).** The enol ether mixture (3.02 g, 10.5 mmol) at 0 °C in CH_3OH (65 mL) was treated with *N*-bromoacetamide (1.52 g, 11.02 mmol) in CH_3OH (65 mL) and allowed to stand for 12 h. The CH_3OH was evaporated and benzene (100 mL) and 2 N NaOH (50 mL) were added, then shaken until no oil remained. The separated organic layer was washed with benzene (2 × 50 mL), and the combined organic phases were washed with 2 N NaOH (15 mL), H_2O (15 mL), and saturated NaCl (25 mL), then dried and evaporated to yield 4.32 g (~100%) of a mixture of **47** and **48**. NMR revealed the C-5 H/C-7 H ratio to be 13/87 with $W_{1/2}$ of 4 Hz for C-5 H and 6 Hz for C-7 H. Pure 5-bromo compound **48** may be obtained via chromatograpy after HBr elimination from **48** to either **39** or **49**: NMR δ 7.0 (m, 4 H), 4.72 (s, 1 H), 3.84 (s, 3 H), 3.14 (s, 3 H), 2.55 (s, 3 H), 2.25 (s, 3 H); IR 1601, 1580 cm^{-1}; mass spectrum *m/e* (rel intensity) 399 (4), 397 (4), 319 (29), 318 (100), 71 (30), 70 (55); bp 150–155 °C (0.1 mm). Anal. Calcd for $C_{19}H_{28}NO_3Br$: C, 57.3; H, 7.1; N, 3.5. Found: C, 57.5; H, 7.1; N, 3.6.

The 7-bromo isomer **47** exhibits the following NMR: δ 7.05 (m, 3 H), 6.66 (dt, *J* = 2, 7 Hz, 1 H), 3.84 (s, 3 H), 3.14 (s, 3 H), 2.30 (s, 3 H), 2.25 (s, 3 H).

***trans*-Δ⁷-6,6-Dimethoxy-4a-(3′-methoxyphenyl)-2-methyloctahydroisoquinoline (39).** The crude mixture of bromo ketals **47** and **48** (4.32 g, 10.5 mmol), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN, 6.52 g, 52.5 mmol), and Me_2SO (36.9 g, 472 mmol) were heated at 120 °C for 15 h, cooled, and shaken thoroughly with benzene (200 mL), H_2O (500 mL), and saturated NaCl (50 mL). The separated aqueous layer was washed with benzene (2 × 100 mL), and the combined organic phases were washed with H_2O (90 mL), saturated NaCl (10 mL), H_2O (2 × 50 mL), and saturated NaCl (100 mL), dried, and evaporated to yield 3.46 g (~100%) of a mixture of bromo ketal **48** and ketal **39**. Chromatography (SiO_2, $CHCl_3/CH_3OH$, 9/1, 0.25% NH_4OH) returned 2.26 g (68%) of pure **39** and 318 mg (7.5%) of pure **48**. An intermediate fraction (454 mg, 12%) was also collected. The trans Δ⁷-ketal **39** was crystallized from benzene/hexane: mp 122–123 °C; NMR δ 7.4–6.8 (m, 4 H), 5.98 (d, *J* = 10 Hz, 1 H), 5.77 (bd, *J* = 10 Hz, 1 H), 3.84 (s, 3 H), 3.18 (s, 3 H), 2.73 (s, 3 H), 2.25 (s, 3 H); IR 1605, 1582 cm^{-1}; mass spectrum *m/e* (rel intensity) 317 (2), 286 (14), 285 (57), 270 (38), 257 (46), 254 (25), 150 (100), 71 (52), 70 (26). Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.9; H, 8.6; N, 4.4. Found: C, 72.0; H, 8.6; N, 4.4.

Δ⁸⁽⁸ᵃ⁾-6,6-Dimethoxy-4a-(3′-methoxyphenyl)-2-methyloctahydroisoquinoline (49). A. The crude mixture of ketals **47** and **48** (943 mg, 2.37 mmol), potassium *tert*-butoxide (610 mg, 5.0 mmol), and Me_2SO (16 mL) was heated at 60 °C for 4 h. Isolation and chromatography as for the Δ⁷ isomer yielded 66 mg (7%) recovered **48** and 557 mg (74%) of pure **49**: NMR δ 7.27 (t, *J* = 7 Hz, 1 H), 7.0–6.6 (m, 3 H), 5.84 (t, *J* = 4 Hz, 1 H), 3.84 (s, 3 H), 3.25 (s, 3 H), 2.40 (s, 3 H), 2.22 (s, 3 H); IR 1600, 1577 cm^{-1}; mass spectrum *m/e* (rel intensity) 317 (6), 287 (7), 286 (13), 285 (38), 178 (59), 146 (100).

A methiodide was prepared in CH_3OH with excess CH_3I and recrystallized from ethyl acetate/ethanol, mp 191 °C dec. Anal. Calcd for $C_{20}H_{30}NO_3I$: C, 52.3; H, 6.6; N, 3.0. Found: C, 52.1; H, 6.7; N, 3.0.

B. The Δ⁷ ketal **39** (31.7 mg, 0.1 mmol) was converted by the procedure in part A above to **49** (25 mg, 79%).

Δ⁶,Δ⁸⁽⁸ᵃ⁾-6-Methoxy-4a-(3′-methoxyphenyl)-2-methylhexahydroisoquinoline (8). A. The Δ⁸⁽⁸ᵃ⁾ ketal **49** (556 mg, 1.75 mmol), potassium *tert*-butoxide (830 mg, 7 mmol), and Me_2SO (17.5 mL) were heated at 105 °C for 90 min, followed by isolation as for the formation of **49**. The crude 363 mg after chromatography (SiO_2, $CHCl_3/CH_3OH$, 9/1, 0.25% NH_4OH) returned 102 mg (20%) of **8** as a dark oil: bp 165–170 °C (0.1 mm); NMR δ 7.4–6.6 (m, 4 H), 6.07 (dd, *J* = 2, 6 Hz, 1 H), 4.87 (dd, *J* = 2, 6 Hz, 1 H), 3.82 (s, 3 H), 3.45 (s, 3 H), 2.30 (s, 3 H); IR 1653, 1602, 1580 cm^{-1}; mass spectrum *m/e* (rel intensity) 285 (100), 284 (46), 270 (27), 254 (25), 178 (60), 71 (26), 70 (11). Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.7; H, 8.1; N, 4.9. Found: C, 75.4; H, 8.2; N, 4.7.

B. The Δ⁷ ketal **39** (422 mg, 1.33 mmol) was dissolved in toluene (55 mL) and treated with pyridine (1.76 g, 16 mmol) and $POCl_3$ (650 mg, 4.25 mmol), then refluxed for 30 min, after which time a clear brown oil had separated. Isolation was as for the enol ethers **45a** and **46a** and distillation returned 279 mg (74%) of an oil, bp 125–135 °C (0.05 mm), consisting of two materials, **8** (85%) and **55** (15%), indistinguishable chromatographically. NMR of **55** had δ 5.89 (t, *J* = 4 Hz, 1 H), 4.17 (s, 1 H). The mixture of dienes was used in subsequent oxidation and cycloaddition reactions.

Δ⁸⁽⁸ᵃ⁾-4a-(3′-Methoxyphenyl)-2-methyl-6-oxooctahydroisoquinoline (41). Ketal **49** (50 mg, 0.158 mmol) was dissolved in 2 mL of 3 N acetic acid and stirred for 4 h. Basification (pH 8.5), extraction with $CHCl_3$ (2 × 5 mL), drying, and evaporation gave 29 mg (68%) of **41** as an oil. Attempted distillation resulted in decomposition and **41** failed to form a crystalline methiodide: NMR δ 7.27 (t, *J* = 7 Hz, 1 H), 6.77 (m, 3 H), 5.96 (m, 1 H), 3.78 (s, 3 H), 2.27 (s, 3 H); IR 1715, 1595, 1578 cm^{-1}; mass spectrum *m/e* (rel intensity) 271 (100), 215 (43), 164 (48), 71 (55), 70 (41). $C_{17}H_{18}NO_2$ requires 271.1572; found, 271.1563.

***trans*-Δ⁷-4a-(3′-Methoxyphenyl)-2-methyl-6-oxooctahydroisoquinoline (40).** Ketal **39** (476 mg, 1.5 mmol) in benzene (30 mL) was shaken three times with 0.2 N $HClO_4$ (30, 10, 10 mL) and the aqueous solution allowed to stand for 30 min. Basification to pH 8.5, extraction with $CHCl_3$ (3 × 10 mL), drying, and evaporation gave 410 mg (100%) of a mixture of ketones. After dissolution in benzene (25 mL) the ketones were extracted into $NaHSO_3/Na_2SO_3$, pH 7.[13] The aqueous bisulfite was cooled (0 °C), basified to pH 8.5, and extracted with benzene to give after removal of solvent 67 mg (16%) of pure **41**. The remaining bisulfite solution was further basified to pH 12 and extracted with benzene using mechanical shaking, the benzene layer being separated and replaced by a fresh layer at intervals of 2, 2, 4, and 10 h. Drying and evaporation of the combined organic extracts gave ketone **40** (285 mg, 69%): mp 78–80 °C; NMR δ 7.4–7.0 (m, 1 H), 7.00 (dd, *J* = 2, 10 Hz, 1 H), 6.75 (m, 3 H), 5.95 (dd, *J* = 3.5, 10 Hz, 1 H), 3.78 (s, 3 H), 2.30 (s, 3 H); IR 1672, 1597, 1588 cm^{-1}; mass spectrum *m/e* (rel intensity) 271 (100), 228 (28), 215 (43), 214 (31), 164 (48), 122 (35), 71 (22), 70 (14). A methiodide was prepared in CH_3OH and recrystallized from acetone, mp 201 °C dec. Anal. Calcd for $C_{18}H_{24}NO_2I$: C, 52.3; H, 5.8; N, 3.4. Found: C, 52.2; H, 5.8; N, 3.4.

***cis*-Δ⁷-4a-(3′-Methoxyphenyl)-2-methyl-6-oxooctahydroisoquinoline (42).** The trans α,β-unsaturated ketone **40** (350 mg, 1.29 mmol), CH_3ONa (2.58 mL of 0.5 M in CH_3OH, 1.29 mmol), and CH_3OH (35 mL) were stirred for 13 h at 25 °C, poured into H_2O (100 mL), and extracted with CH_2Cl_2 (4 × 25 mL), and the combined or-

ganic phases were washed with saturated NaCl (20 mL), dried, and evaporated to yield 350 mg (100%) of a 65/35 mixture of **42** and **41**. Separation was exactly as for the mixtures of **40** and **41** above giving 112 mg (32%) of **41** and 199 mg (57%) of **42**: NMR δ 7.26 (t, J = 8 Hz, 1 H), 7.1–6.6 (m, 4 H), 5.98 (dd, J = 1.5, 10 Hz, 1 H), 3.80 (s, 3 H), 2.30 (s, 3 H); IR 1672, 1595, 1580 cm^{-1}; mass spectrum m/e (rel intensity) 271 (19), 243 (12), 200 (15), 71 (100), 70 (20). $C_{17}H_{21}NO_2$ requires 271.1572; found 271.1561.

***trans*-6α-Hydroxy-4aα-(3'-methoxyphenyl)-2-methyldecahydroisoquinoline (50).** To ketone *trans*-**36** (25 mg, 0.090 mmol) in acetic acid (1 mL) was added PtO_2 (10 mg) and the mixture hydrogenated at 50 psi H_2 for 60 min. Filtration and evaporation gave a residue which was dissolved in H_2O (10 mL), basified (2 N NaOH), and extracted with $CHCl_3$ (3 × 10 mL), followed by washing the organic phase with saturated NaCl, drying, and evaporation to give 25 mg (100%) of a single isomer which was crystallized from hexane: mp 117–117.5 °C; TLC ($CH_3OH/CHCl_3$, 3/20, 1% NH_4OH), R_f 0.52; NMR δ 7.4–7.0 (m, 3 H), 6.70 (dt, J = 2, 8 Hz, 1 H), 3.97 (m, $W_{1/2}$ = 6 Hz, 1 H), 3.80 (s, 3 H), 2.22 (s, 3 H); IR 3571, 3413, 1605, 1577 cm^{-1}; mass spectrum m/e (rel intensity) 275 (100), 204 (40), 71 (84), 70 (72). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.1; H, 9.1; N, 5.1. Found: C, 73.9; H, 9.0; N, 5.1.

***trans*-6β-Hydroxy-4aα-(3'-methoxyphenyl)-2-methyldecahydroisoquinoline (51). A.** Ketone *trans*-**36** (55 mg, 202 mmol) and 2-propanol (157 mg, 2.62 mmol, anhydrous) in toluene (2 mL, anhydrous) at reflux were treated with sodium (24.1 mg, 1.05 mmol) in five small portions, waiting for each portion to dissolve. After the last portion had reacted, TLC ($CH_3OH/CHCl_3$, 3/20, 1% NH_4OH) showed only two materials, R_f 0.52 and 0.35. The reaction mixture was cooled, mixed with benzene (10 mL), washed with H_2O (5 mL) and saturated NaCl (5 mL), dried, and evaporated to yield 55 mg of an oil. Preparative TLC (as above) returned 10 mg (18%) of **50** and 20 mg (36%) of **51** which was distilled: bp 125–130 °C (0.08 mm); NMR δ 7.4–6.9 (m, 3 H), 6.68 (dt, J = 2, 8 Hz, 1 H), 3.80 (s, 3 H), 3.5–3.7 (m, $W_{1/2}$ = 20 Hz, 1 H), 2.23 (s, 3 H); IR 3571, 3425, 1601, 1580 cm^{-1}; mass spectrum m/e (rel intensity) 275 (100), 274 (62), 71 (72), 70 (96). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.1; H, 9.1; N, 5.1. Found: C, 74.0; H, 9.1; N, 5.1.

B. Sodium borohydride reduction of *trans*-**36** as per reduction of *cis*-**36** below gave **50/51** in a ratio of 70/30 by GC.

***cis*-6α-Hydroxy-4aα-(3'-methoxyphenyl)-2-methyldecahydroisoquinoline (54) and *cis*-6β-Hydroxy-4aα-(3'-methoxyphenyl)-2-methyldecahydroisoquinoline (53). A.** To ketone *cis*-**36** (27.3 mg, 0.1 mmol) in acetic acid (2 mL) was added PtO_2 (10 mg) and the mixture was hydrogenated at 60 psi H_2 for 3 h. Isolation as for **50** gave 28 mg of an oil shown by TLC (as above) to be two compounds (R_f of **53**, 0.49, and R_f of **54**, 0.42). NMR revealed that the **53/54** ratio was approximately 1/2 by inspection of the NCH_3 absorptions.

B. To ketone *cis*-**36** (100 mg, 0.364 mmol) in ethanol was added $NaBH_4$ (42 mg, 1.1 mmol) in three portions over a 1-h period. After a further 1 h at 25 °C the reaction mixture was poured into H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 10 mL), and the organic phase was washed with saturated NaCl (10 mL), dried, and evaporated to an oil. NMR showed a **53/54** ratio of 3/2. Preparative TLC returned **53** (45 mg, 45%) and **54** (35 mg, 35%) and distillation furnished analytical materials.

53: bp 130–135 °C (0.08 mm); NMR δ 7.4–6.9 (m, 3 H), 6.71 (dt, J = 2, 7 Hz, 1 H), 3.80 (s, 3 H), 4.3–3.2 (m, 1 H), 2.34 (s, 3 H); IR 3571, 3436, 1608, 1850 cm^{-1}; mass spectrum m/e (rel intensity) 275 (100), 274 (47), 71 (88), 70 (68). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.1; H, 9.1; N, 5.1. Found: C, 73.9; H, 9.1; N, 5.0.

54: mp 95–97 °C from benzene; bp 130–135 °C (0.08 mm); NMR δ 7.28 (t, J = 8 Hz, 1 H), 7.02 (m, 2 H), 6.75 (bd, J = 8 Hz, 1 H), 3.84 (s, 3 H), 4.3–3.2 (m, 1 H), 2.14 (s, 3 H); IR 3571, 3413, 1595, 1572 cm^{-1}; mass spectrum m/e (rel intensity) 275 (40), 274 (26), 71 (100), 70 (66). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.1; H, 9.1; N, 5.1. Found: C, 74.3; H, 9.1; N, 5.1.

Reduction of 41. $\Delta^{8(8a)}$-6-Hydroxy-4-(3'-methoxyphenyl)-2-methyldecahydroisoquinoline. To ketone **41** (72 mg, 0.292 mmol) in ethanol (4 mL) at 0 °C was added $NaBH_4$ (63 mg, 1.6 mmol) in two portions at 15-min intervals. The solution was warmed to 25 °C and stirred for 60 min, poured into H_2O (30 mL), extracted with CH_2Cl_2 (3 × 20 mL), dried, and evaporated to yield an oil which was chromatographed (TLC grade SiO_2, $CHCl_3/CH_3OH$, 9/1, 0.5% NH_4OH) to give homogeneous material (TLC, GC) (34 mg, 47%): bp 130 °C (0.1 mm); NMR δ 7.28 (t, J = 7.5 Hz, 1 H), 6.82 (m, 3 H), 5.83 (m, 1 H), 4.2–3.4 (m, 1 H), 3.80 (s, 3 H), 2.13 (bs, 3 H); IR 3584, 2967, 2841, 2793, 1605, 1580 cm^{-1}; mass spectrum m/e (rel intensity) 273 (100), 272 (25), 271 (26), 256 (22), 255 (23), 228 (29), 167 (36), 166 (84). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.7; H, 8.5; N, 5.1. Found: C, 74.6; H, 8.5; N, 5.0.

To the alcohol (27 mg, 0.1 mmol) in CH_3OH (2 mL) was added PtO_2 (10 mg) and the mixture shaken under 55 psi H_2 for 2 h. Filtration and evaporation gave 27 mg of a material which was two major components. Chromatography (as above) returned 10 mg of trans alcohol **50** and 5 mg of trans alcohol **51**.

***trans*-Δ^7-6α- and -6β-Hydroxy-4aα-(3'-methoxyphenyl-2-methyloctahydroisoquinolines (7 and 52).** The trans ketone **40** (200 mg, 0.736 mmol) in THF (10 mL) was treated with 0.65 M AlH_3/THF (3.4 mL, 2.21 mmol) and then stirred for 30 min, all at 0 °C. THF/H_2O (1/1, 1.1 mL) was added followed by 3.3 N NaOH (3.0 mL) and ether (20 mL). The separated aqueous layer was washed with benzene (10 mL), and the combined organic phases were washed with saturated NaCl (10 mL), dried, and evaporated to give 185 mg of a colorless oil. Chromatography (TLC grade SiO_2, $CH_3OH/CHCl_3$, 9/1, 0.25–1% NH_4OH) returned first 112 mg (56%) of ***trans*-Δ^7-6α-hydroxy-4aα-(3'-methoxyphenyl)-2-methyloctahydroisoquinoline (7)**: NMR δ 7.5–6.5 (m, 3 H), 6.72 (dt, J = 2, 7 Hz, 1 H), 5.85 (distorted dd, J = 11 Hz, 2 H), 4.2–4.0 (bs, $W_{1/2}$ = 11 Hz, 1 H), 3.78 (s, 3 H), 2.22 (s, 3 H); IR 3571, 2933, 2857, 2817, 1603, 1580 cm^{-1}; mass spectrum m/e (rel intensity) 273 (95), 202 (98), 71 (100), 70 (60); bp 125 °C (0.1 mm). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.7; H, 8.5; N, 5.1. Found: C, 74.5; H, 8.4; N, 5.1.

Next eluted was 9 mg (4.5%) of ketone *trans*-**36** identified by spectral and chromatographic comparisons.

Lastly was obtained 62 mg (31%) of ***trans*-Δ^7-6β-hydroxy-4aα-(3-methoxyphenyl)-2-methyloctahydroisoquinoline (52)**: NMR δ 7.4–6.6 (m, 4 H), 5.69 (dd, J = 10 Hz, 2 H), 3.9–3.4 (bs, 1 H), 3.78 (s, 3 H), 2.17 (s, 3 H); IR 3636, 1603, 1580 cm^{-1}; mass spectrum m/e (rel intensity) 273 (55), 256 (18), 255 (21), 71 (100), 70 (37); bp 130 °C (0.1 mm). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.7; H, 8.5; N, 5.1. Found: C, 74.5; H, 8.4; N, 5.2.

Allylic alcohol **7**, when reduced as described for the α,β-unsaturated alcohol obtained from **41**, returned only **50**. Reduction of **52** in the same manner yielded **51**.

***trans*-Δ^7-6α-Hydroxy-4aα-(3'-hydroxyphenyl)-2-methyloctahydroisoquinoline (6).** A solution of potassium thioethoxide/DMF was prepared as follows. To DMF (30 mL, degassed by freeze/thaw) was added potassium *tert*-butoxide (1.5 g, 13.4 mmol), and the suspension was degassed and flushed thoroughly with argon. Ethanethiol (1.22 mL, 1.64 mmol) was added and the butoxide dissolved leaving a clear, colorless solution. Ether **7** (40 mg, 0.15 mmol) in DMF (1 mL) was thoroughly degassed and placed under argon. The thioethoxide solution (1 mL, 0.44 mmol) was added, and the solution was heated at 150 °C for 10 h, cooled, poured into H_2O (20 mL), the pH adjusted to 14, and extracted with $CHCl_3$ (3 × 4 mL) after which the pH was lowered to 8 and the solution was extracted with 9/1 $CHCl_3$/2-propanol (4 × 4 mL). The combined organic phases were washed with saturated NaCl (10 mL), dried, and evaporated to a mixture of phenols (33 mg). Trituration of the residue with hot benzene and cooling returned 24 mg (60%) of pure **6** as an amorphous solid: NMR δ 7.3–6.5 (m, 4 H), 5.84 (distorted dd, J = 10 Hz, 2 H), 4.07 (m, 1 H), 2.29 (s, 3 H); IR 3550, 3247 (b), 1582 cm^{-1}; mass spectrum m/e (rel intensity) 259 (100), 258 (32), 188 (91), 71 (94), 70 (59). Sublimation gave mp 199–203 °C. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.1; H, 8.2; N, 5.4. Found: C, 73.8; H, 8.1; N, 5.4.

***cis*-Δ^7-6α- and *cis*-Δ^7-6β-Hydroxy-4aα-(3'-methoxyphenyl)-2-methyloctahydroisoquinolines (10 and 11).** The cis ketone **42** (171 mg, 0.63 mmol) in toluene (6.3 mL, 0 °C) was treated rapidly with diisobutylaluminum hydride (1.26 mmol, 2 M in hexane, 0 °C) and stirred for 30 min, and CH_3OH (0.25 mL) was added, followed by 2 N NaOH (10 mL) and benzene (10 mL). The separated aqueous layer was washed with benzene (10 mL), and the combined organic phases were dried and evaporated to yield 168 mg of a clear glass. Chromatography (TLC grade SiO_2, $CHCl_3/CH_3OH$, 9/1, 0.25% NH_4OH) returned in order of elution 4.2 mg (2.5%) of **42**, 17.2 mg (9%) of ketone *cis*-**36**, and 75.2 mg (44%) of ***cis*-Δ^7-6α-hydroxy-4aα-(3'-methoxyphenyl)-2-methyloctahydroisoquinoline (10)**: NMR δ 7.30 (dd, J = 7, 9 Hz, 1 H), 6.97 (m, 2 H), 6.75 (bd, J = 8 Hz, 2 H), 5.84 (dd, J = 10 Hz, 2 H), 4.27 (t, 1 H), 3.82 (s, 3 H), 2.18 (s, 3 H); IR 3571, 2924, 2857, 2817, 1601, 1580 cm^{-1}; mass spectrum m/e (rel intensity) 273 (39), 202 (53), 200 (21), 71 (100), 70 (40); mp 133–135 °C from benzene. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.7; H, 8.5; N, 5.1. Found: C, 74.6; H, 8.5; N, 5.1.

Eluted next was 21.6 mg (12.5%) of an intermediate fraction, then 19.3 mg (11%) of ***cis*-Δ^7-6β-hydroxy-4aα-(3'-methoxyphenyl)-2-methyloctahydroisoquinoline (11)**: NMR δ 7.25 (t, J = 8 Hz, 1 H), 6.81 (m, 3 H), 5.85 (dd, J = 4, 9 Hz, 1 H), 5.57 (d, J = 9 Hz, 1 H), 3.82 (s, 3 H), 3.9–4.5 (m, 1 H), 2.32 (s, 3 H); IR 3570, 2933, 2849, 2807, 1601, 1582 cm^{-1}; mass spectrum m/e (rel intensity) 273 (27), 71 (100), 70 (45); bp 125–130 °C (0.1 mm). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.7;

H, 8.5; N, 5.1. Found: C, 74.5; H, 8.5; N, 5.0.

Reduction of **10** with $PtO_2/H_2/CH_3OH$ as for **7** gave only **54.** Reduction of **11** under these conditions afforded **53.**

Δ^7-8a-Hydroxy-4a-(3'-methoxyphenyl)-2-methyl-6-oxooctahydroisoquinolines (57 and 58). To the mixture of dienes **8** and **55** (85/15) (120 mg, 0.42 mmol) in acetic acid (3 mL) was added trifluoroacetic acid (60 mg, 0.53 mmol). *m*-Chloroperbenzoic acid (62 mg, 0.37 mmol) was added and the solution heated (95 °C) for 15 min, cooled, treated with additional peracid (41.2 mg, 0.24 mmol), and heated again (95 °C) for 20 min. The dark solution was cooled (5 °C), added to H_2O (10 mL), and basified (pH 12), then extracted with $CHCl_3$ (3 × 5 mL); the combined organic phases were dried and evaporated, affording 105 mg of an oil. Chromatography (TLC grade SiO_2, $CHCl_3/CH_3OH$, 9/1, 0.1% NH_4OH) gave three compounds. Eluted first was 52 mg (43%) of a Δ^7-8a-hydroxy ketone: NMR δ 7.20 (t, J = 8 Hz, 1 H), 6.95 (d, J = 10 Hz, 1 H), 6.9–6.8 (m, 3 H), 6.03 (d, J = 10 Hz, 1 H), 3.79 (s, 3 H), 2.29 (s, 3 H); IR 3356, 1675, 1603, 1580 cm^{-1}; mass spectrum *m/e* (rel intensity) 287 (7), 259 (9), 71 (100), 70 (9). Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.0; H, 7.4; N, 4.9. Found: C, 70.9; H, 7.3; N, 4.9.

Eluted next was 9 mg (7%) of the epimeric Δ^7-8a-hydroxy ketone: NMR δ 7.22 (t, J = 8 Hz, 1 H), 6.97 (d, J = 10 Hz, 1 H), 6.8–6.6 (m, 3 H), 6.15 (d, J = 10 Hz, 1 H), 3.79 (s, 3 H), 2.28 (s, 3 H); IR 3356, 1686, 1605, 1580 cm^{-1}. $C_{17}H_{21}NO_3$ requires 287.1521; found, 287.1514.

Obtained last was 19.5 mg (16%) of the *N*-oxide **59:** NMR δ 7.26 (t, J = 8 Hz, 1 H), 6.95 (d, J = 10 Hz, 1 H), 6.9–6.7 (m, 3 H), 5.82 (d, J = 10 Hz, 1 H), 3.77 (s, 3 H), 3.14 (s, 3 H); IR 3650, 3600–2300 (bs), 1678, 1605, 1580 cm^{-1}; mass spectrum *m/e* (rel intensity) 303 (0.36), 302 (0.36), 301 (0.64), 287 (17), 43 (100).

Diels–Alder Reactions of 8 with A. Ethyl Acrylate. The mixture of dienes **8** and **55** (85/15, 28.5 mg, 0.1 mmol) was dissolved in ethyl acrylate (5 mL) and heated at reflux for 15 h, cooled, evaporated, and chromatographed (SiO_2, $CHCl_3/CH_3OH$, 9/1, 0.1% NH_4OH). The recovered dienes (25 mg, 88%) were still present in a 85/15 ratio. From the reaction in a sealed tube at 170 °C, starting material was recovered in 40% yield after chromatography.

B. Methyl vinyl ketone (MVK), as in A, with MVK at reflux for 9 h returned starting material (64%).

C. Dimethyl Acetylenedicarboxylate (DMAD). The dienes (55 mg, 0.19 mmol) and DMAD (35 mg, 0.38 mmol) were dissolved in toluene (0.5 mL) and stirred for 9.5 h at 25 °C. The solution was evaporated and chromatographed twice (SiO_2, $CHCl_3/CH_3OH$, 9/1, 0.1% NH_4OH, then with $CHCl_3$) to return 33 mg (39%) of triene **63** [NMR revealed **63** to be a mixture of the fumarate (10–20%) and the maleate (80–90%) based on the multiplicity of the enamine proton, the *N*-methyl, and the *O*-methyl region]: NMR δ 7.79 (t, J = 8 Hz, 1 H), 6.85 (m, 3 H), 6.29 (d, J = 10 Hz, 1 H), 5.87 (broadened d, J = 10 Hz, 1 H), 5.64 (bs, 0.1 H), 5.31 (s, 0.9 H), 4.89 (s, 1 H), 4.70 (d, J = 8 Hz), and 4.49 (broadened d, J = 8 Hz), total of 2 H, 3.9–3.4 (complex, four large singlets at 3.92, 3.82, 3.65, 3.62 with two small singlets at 3.55 and 3.47, total 12 H), 3.4–2.9 (m, 2 H), 2.85 and 2.73 (singlets, ~4/1, total 3 H), 2.5–1.9 (m, 2 H); IR 1739, 1653, 1577 cm^{-1}; mass spectrum *m/e* (rel intensity) 427 (26), 426 (27), 368 (40), 269 (33), 254 (47), 228 (57), 227 (100), 226 (27), 225 (72). $C_{24}H_{29}NO_6$ requires 427.1995; found, 427.1991. UV (CH_3OH) λcmax 274 nm (ϵ 20 800).

D. *N*-Phenylmaleimide. The dienes (37 mg, 0.135 mmol) and *N*-phenylmaleimide (25.6 mg, 0.148 mmol) in toluene were heated at 110 °C for 12 h and cooled and the solvent was evaporated. The NMR showed that little starting materials had been consumed and was nearly identical with an NMR of the starting mixture. The reaction mixture was again subjected to the same conditions and after 170 h neither starting material remained. Both NMR and TLC ($CHCl_3$ or $CHCl_3/CH_3OH$, 9/1, 0.1% NH_4OH) revealed several materials. Chromatography on SiO_2 gave no identifiable compounds.

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Registry No.—**6,** 61527-78-4; **7,** 61527-79-5; **8,** 61527-80-8; *trans*-**9,** 61527-81-9; *cis*-**9,** 61527-82-0; **10,** 61527-83-1; **11,** 61527-84-2; **19,** 33877-04-2; **20,** 61527-85-3; **21,** 61527-86-4; **22,** 61527-87-5; **23,** 61527-88-6; **24,** 61527-89-7; **25,** 61527-90-0; **26,** 61527-91-1; **27,** 61527-92-2; **28,** 61527-93-3; **29,** 61527-94-4; **30,** 61527-95-5; **31,** 61527-96-6; **32,** 61527-97-7; **33** isomer A, 61527-98-8; **33** isomer B, 61527-99-9; *trans*-**34,** 61528-00-5; *cis*-**34,** 61528-01-6; *trans*-**35,** 61528-02-7; *cis*-**35,** 61528-03-8; *trans*-**36,** 61528-04-9; *cis*-**36,** 61528-05-0; *trans*-**37a,** 51993-81-8; *cis*-**37a,** 59226-95-8; *trans*-**37b,** 51993-82-9; *cis*-**37b,** 59227-14-4; **38,** 61528-06-1; **39,** 61528-07-2; **40,** 61528-08-3; **40** methiodide, 61528-09-4; **41,** 61528-10-7; **42,** 61528-11-8; **44,** 61528-12-9; **45a,** 61528-13-0; **45b,** 61528-14-1; **46a,** 61528-15-2; **46b,** 61528-16-3; **47,** 61543-03-1; **48,** 61528-17-4; **49,** 61528-18-5; **49** methiodide, 61528-19-6; **50,** 61528-20-9; **51,** 61528-21-0; **52,** 61528-22-1; **53,** 61528-23-2; **54,** 61528-24-3; **55,** 61528-25-4; **57,** 61528-26-5; **58,** 61528-27-6; **59,** 61528-28-7; **63** isomer A, 61528-29-8; **63** isomer B, 61528-30-1; 3-methoxycinnamic acid, 6099-04-3; 1,3-dimethyl-4-(3'-methoxyphenyl)-2-pyridone, 61528-31-2; butyl hydrogen malonate, 5917-45-3; ethylene glycol, 107-21-1; $\Delta^{8(8a)}$-6-hydroxy-4-(3'-methoxyphenyl)-2-methyldecahydroisoquinoline, 61528-32-3.

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(29) All reactions were performed under a nitrogen atmosphere with magnetic stirring unless otherwise indicated and all solvents were dried over Na_2SO_4 prior to evaporation in vacuo using a Berkeley rotary evaporator. Melting points are corrected and distillation was bulb to bulb, Kugelrohr type. NMR spectra were determined in $CDCl_3$ solution with a Varian T-60 instrument using internal Me_4Si; IR spectra were recorded in $CHCl_3$ (except where noted) on a Perkin-Elmer 337 spectrophotometer; UV spectra were recorded on a Cary 14 instrument. CEC-103 and 110B mass spectrometers were used for determining mass spectra. GC refers to 5 ft, 3% OV-1 on 80/100 Chromosorb W (AW/DMCS). TLC and column chromatography were done on SiO_2 (silica gel 60, E. M. Reagents, 63–200 μ) and TLC grade SiO_2, D-5, Camag, 7–25 μ, without binder. Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley.

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