Synthesis of *cis*- and *trans*-4a-Phenyldecahydroisoquinolines

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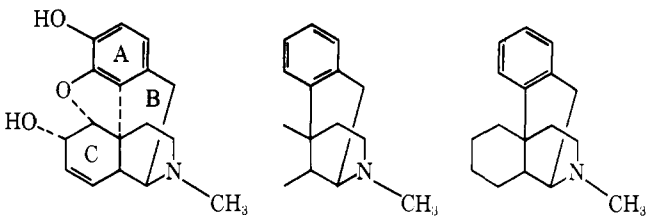
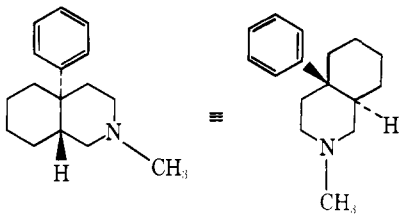
Abstract: *cis*- and *trans*-4a-phenyldecahydroisoquinolines have been synthesized by a process involving the methylenelactam rearrangement of substituted nipecotic acids and culminating in a stereospecific internal Michael cyclization. Limitations in the preparation of the requisite 1-methyl-4-phenyl-2-substituted nipecotic acids **14** via dihydropyridine ring synthesis are discussed. Treatment of these nipecotic acids with acetic anhydride produces the versatile α-methylenelactam intermediates **15**, into which the quaternary carbon, C-4 of the piperidone, is introduced by selenium dioxide oxidation and allylic and Claisen rearrangement. Elaboration to β-keto ester **48** and ketone **45e** proceeds in good yield by standard procedures. Cyclization of β-keto ester **48** under nonequilibrating conditions leads to *trans*-1,6-dioxo-2-methyl-4a-phenyldecahydroisoquinoline (**51**). In contrast, ketone **45e** under equilibrating conditions gives mostly the cis-fused ketoamide **49**. Structural and steric assignments are based upon reduction of **49** and **51** to known *cis*- and *trans*-4a-phenyldecahydroisoquinolines **52d** and **53d**.

There is a continual search for new morphine analogues in the hope of finding analgesics possessing less of the undesirable side effects of morphine. For this purpose, the morphine molecule may be depicted in a number of ways in order to reflect various structural elements. As drawn in structure **1**, its dissection into simpler fragments such as the benzomorphans (**2**) and the morphinans (**3**) is clear. Another fragment which has until recently[1] received little attention is the 4a-aryldecahydroisoquinoline portion (**4**). While the primary synthetic challenge of this system is the angular aryl group, which cannot be incorporated in an intramolecular fashion as is the case for **2** and **3**,[2] there are other important considerations in the con-



1 2 3



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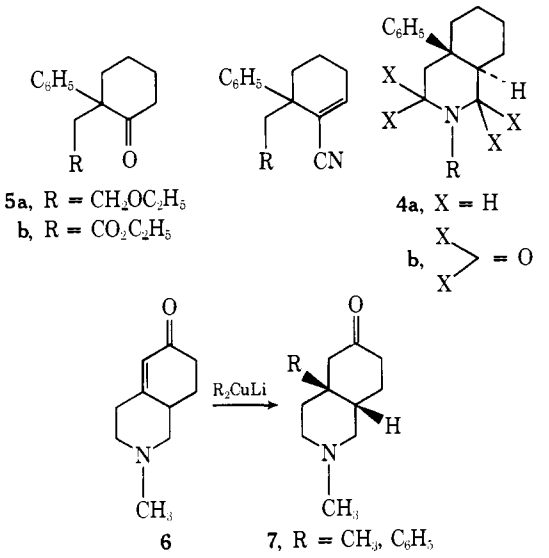
struction of this moiety. Thus no synthesis is available which can assure steric control at the ring juncture (trans in morphine) and functionalization in the C ring (in analogy to the C ring of morphine) necessary for the preparation of compounds akin to the natural materials.

In one reported synthesis[1a] a suitably substituted 2-arylcyclohexanone (**5a**) is converted to the unsaturated nitrile and then annelated to **4a** by reduction, ether cleavage, and closure of the piperidine ring. In another,[1e] proceeding from **5b**, the nitrile is hydrolytically converted to the glutarimide, then catalytically reduced to **4b** followed by lithium aluminum hydride reduction to **4a**. While both methods give mostly *trans*-decahydroisoquinoline and also allow for the introduction of an 8a-hydroxyl function, they have not been extended to C-ring functionalization.

The only other reported route for the preparation of 4a-substituted decahydroisoquinolines involves the conjugate



5a, R = $CH_2OC_2H_5$
b, R = $CO_2C_2H_5$

4a, X = H
b, X, X = O

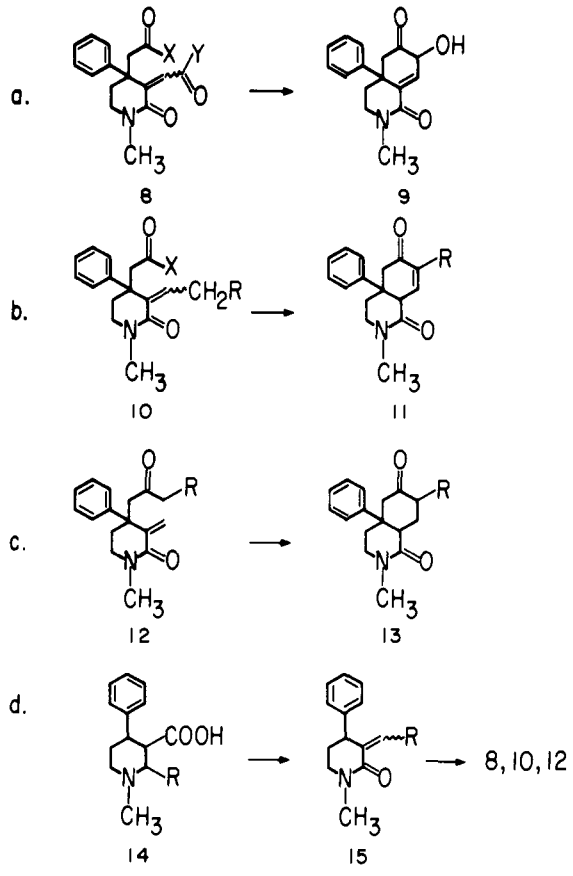
6 7, R = CH_3, C_6H_5

addition of organocuprates to the readily available α,β-unsaturated ketone **6**, giving exclusively the cis-fused compounds **7**.[1c,d] Addition is successful with methyl and phenyl cuprates, but significantly not for *m*-methoxyphenyl, and the adduct **7** is obtained in good yields. The stereochemistry of the addition product (**7**, R = C_6H_5) has been determined by x-ray crystallography and served as the basis for the assignment of the trans series.

Our approach has been to invert the synthetic sequence and to explore the possibility that transformations of substituted piperidines would satisfy both the steric and functionality requirements of this system. We planned to start with the N ring, to incorporate the quaternary center early, and to proceed to develop the C ring in a manner such that functional groups could be present. Three approaches were considered. In the first (Scheme I, path a) we envisioned the reductive acyloin-type ring closure of a diacyl compound, as represented by the conversion of **8** to **9**. The product resembles the morphinandienone system similar to compounds such as salutaridine. In the second case, path b, we projected a Dieckmann or Claisen cyclization of **10** which would yield **11**, a cousin of codeinone. In the third method, path c, compound **12** appears ideally arranged for an internal Michael reaction to give **13**. All paths would be concluded by reduction of the piperidones to piperidines.

A key reaction for the synthesis of all the potential precursors **8**, **10**, and **12** was to be the acetic anhydride promoted

Scheme I. Approaches to the Synthesis of 4a-Aryldecahydroisoquinolines

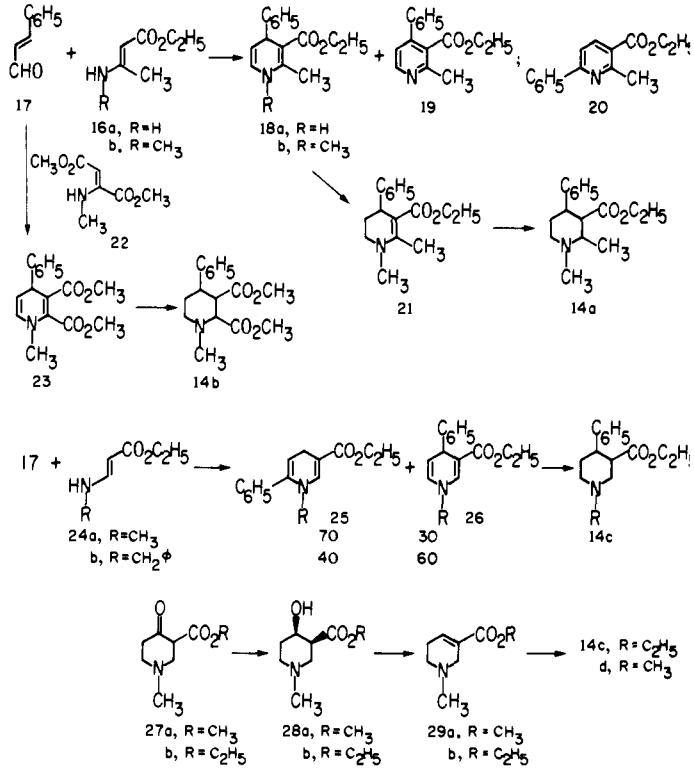


rearrangement of cyclic β-amino acids.[3] This high-yield reaction (path d) to form the versatile α-methylenelactam intermediate has been found applicable with a large variety of 2-substituents. Although 4-substituted nipecotic acids have not been used, predictably they should react just as well. Thus the synthesis was planned in three stages: (1) the preparation and rearrangement of the requisite 4-phenylnipecotic acids **14;** (2) the conversion of these substituted α-methylenelactams **15** into the decahydroisoquinoline precursors **8, 10,** and **12;** and (3) the formation of the carbocyclic ring, as in **9, 11,** and **13,** and its stereochemical consequences, followed by reduction.

Preparation and Rearrangement of 4-Phenylnipecotic Acids. The amino acids necessary for conversion to isoquinoline precursors **8, 10,** and **12** are the nipecotic acids **14** (Scheme II). We sought to devise a general synthetic method which would encompass all of these compounds. Since the literature teaches[4] that the condensation of crotonaldehyde and ethyl β-aminocrotonate (**16a**) yields 75% of the ethyl 2,4-dimethyl-1,4-dihydronicotinate, we applied these conditions to cinnamaldehyde (**17**). A mixture of compounds was obtained in 55% yield, consisting mostly of dihydropyridine **18a** and pyridine **19** in a 3:1 ratio. Each was contaminated with the corresponding 6-phenyl isomer. In order to determine the isomer ratio (4- vs. 6-phenyl substituted) the mixture was oxidized with iodine to give the two pyridines, **19** and **20,** in a 9:1 ratio. That the isomer comprising 10% of the mixture was ethyl 2-methyl-6-phenylnicotinate (**20**) was shown by synthesis of an authentic sample[5] and chromatographic and spectral comparison.

Although 90% of the isolated material of the cinnamaldehyde condensation is potentially convertible into nipecotic ester **14a,** we wished to avoid the pyridine/dihydropyridine mixture and the necessity of removing the 10% of 6-isomer. With the objective of blocking aromatization to the pyridine, ethyl β-methylaminocrotonate (**16b**) was condensed with

Scheme II. Synthesis of 4-Phenylnipecotic Acids



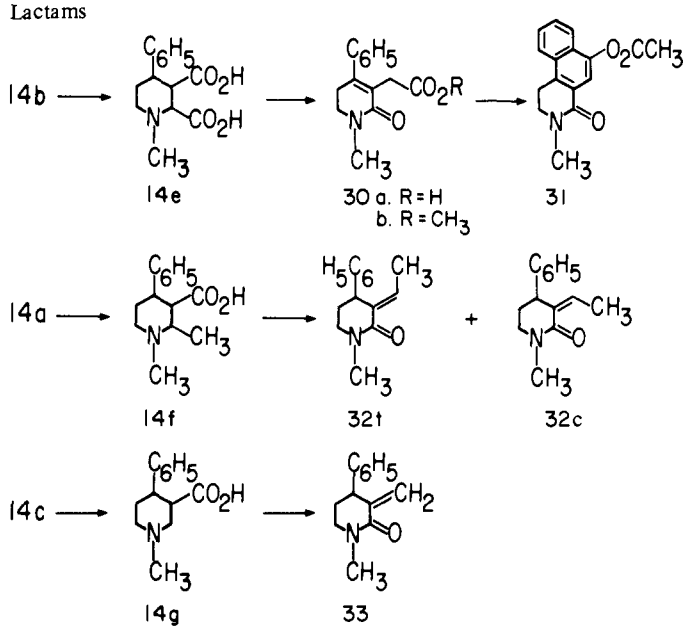
cinnamaldehyde. The reaction proceeded smoothly and yielded as a single product 77% of the expected dihydropyridine **18b.** The 6-phenyl isomer was totally absent, based on spectral and chromatographic evidence.

Hydrogenation of dihydropyridine **18b** could be separated into two stages if desired with a rapid initial uptake of 1 mol of hydrogen to give tetrahydropyridine **21,** followed by a slow absorption of the remaining mole. The rate of reduction of the tetrasubstituted double bond can be increased by the addition of hydrochloric acid to the hydrogenation medium. The product was isolated as the free amine **14a** and GC and NMR established the presence of only a single compound, presumably the all-cis isomer.

The reaction of cinnamaldehyde and dimethyl β-methylaminofumarate (**22**) produced the 1,4-dihydroquinolinic acid derivative **23** in 55% yield. In this series, reduction of the tetrasubstituted bond was very slow, even in the presence of hydrochloric acid. Although the isolated amine **14b** was a mixture of two isomers, the mixture from the hydrogenation was used directly for hydrolysis in the next step (Scheme III).

Extension of the dihydropyridine synthesis to the preparation of **14c** led to an unfavorable mixture. Ethyl β-methylaminoacrylate (**24a**) could be easily prepared by addition of methylamine to ethyl propiolate, but condensation with cinnamaldehyde gave a 30:70 mixture of the 4- and 6-phenyldihydropyridines **26a** and **25a** in a modest 43% yield. In an attempt to favor the 4-isomer by increasing the steric bulk about the nitrogen atom, ethyl β-benzylaminoacrylate (**24b**) was employed. While this indeed enhanced the amount of 4-isomer (**26b**) vs. 6-isomer (**25b**) (60:40), the combined yield was only 25%. Though some variation of this condensation may ultimately provide the most efficient synthesis for compounds like **14c,** which are unsubstituted in the 2-position, we turned to a more tedious but known method. The conjugate addition of phenylmagnesium bromide to arecoline (**29a**) has been reported[6] to give the 4-phenyl nipecotate **14d.** By substituting the ethyl ester **29b** for the methyl ester **29a,** we have found that the addition product, as the corresponding ethyl ester **14c,** is

Scheme III. Rearrangement of Nipecotic Acids to Unsaturated Lactams



formed in higher and more reproducible yields. The esters **27** were prepared as described from the substituted β-alanines; catalytic reduction gave the *cis*-β-hydroxy esters **28** and these were dehydrated with thionyl chloride in pyridine.[7]

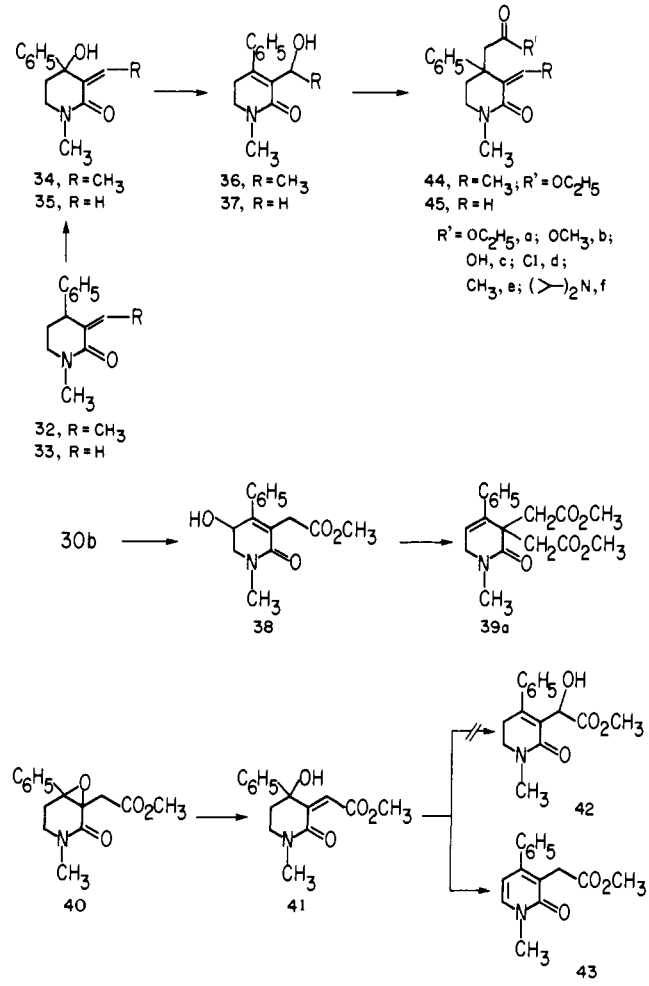
The C-2 substituent in **14** has a profound influence upon the course of the hydrolysis and rearrangement of the amino acids to the corresponding α-methylenelactams, as shown in Scheme III. In the first instance, **14b** was easily hydrolyzed via KOH in isopropyl alcohol and acidification gave the diacid hydrochloride **14e**, Treatment of this material under standard rearrangement conditions, Ac_2O and K_2CO_3 at reflux, gave none of the desired acid **30a.** Isolated instead in 35% yield was the crystalline 9-acetoxy-2-methyl-1-oxo-3,4-dihydrobenzo(*f*)-isoquinoline (**31**), implying that the intermediate **30a** had undergone a surprisingly mild internal Friedel-Crafts acylation. Since the rearrangement of diacids such as **14e** has been shown to proceed through an internal anhydride, the reaction may be effected thermally in the absence of Ac_2O.[3] Thus refluxing **14e** in xylene with removal of HCl and H_2O resulted in an homogenous solution, from which pure **30a** could be isolated in 50% yield, or alternatively, the crude acid could be esterified and the ester **30b** was isolated in 82% yield by simple distillation. That the acid **30a** may serve as a precursor to **31** was demonstrated by allowing **30a** to react under standard rearrangement conditions, whereupon the yield of **31** was 70%.

The ethyl ester **14a** proved surprisingly difficult to hydrolyze. Acid conditions were futile and vigorous alkaline conditions (KOH in either $CH_3OCH_2CH_2OH$ or $HOCH_2CH_2OH/H_2O$ at reflux) were necessary. On monitoring the hydrolysis by GC, the first observation is the rapid conversion of **14a** to a slightly more volative isomer, presumably reflecting an epimerization at C-3. When the amino acid was isolated as the HCl salt **14f** and submitted to the rearrangement reaction, this was also slow, 24 h being required for completion. The combined yield of cis and trans lactams **32c** and **32t** was consistently $\geq$70% and the isomer ratio favored the trans isomer **32t,** which was 90% of the isolated material.

In contrast to the modifications required by **14a** and **14b,** acid hydrolysis and rearrangement of **14c** proceeded normally and gave **33** in 92% yield.

Preparation of 4-Phenyl-4-substituted Piperidones 8, 10, and 12. With the α,β-unsaturated lactams **30, 32,** and **33** at hand we next considered the alternatives for incorporation of the correct functionality at the benzylic C-4. An efficient route appeared to be a Claisen rearrangement of an appropriate allylic alcohol[8] such as **36** or **37** (Scheme IV), which in turn

Scheme IV. Synthesis of 4,4-Disubstituted Piperidones



should be preparable by allylic rearrangement of the tertiary allylic alcohols **34** and **35.** Thus the first step was the production of these allylic alcohols.

The preparation of tertiary allylic alcohol **35** was accomplished by a facile benzylic oxidation of **33** with selenium dioxide. Although reaction with SeO_2 in acetic acid gave mixtures of the tertiary allylic alcohol and rearranged allylic acetates, changing solvents to chlorobenzene resulted in good yields of the tertiary alcohol **35.** The solvolysis of **35** was slow in acetic acid, but extremely rapid in 97% formic acid, giving the primary allylic alcohol **36** as its formate. Both formate and acetate were easily hydrolyzed with K_2CO_3 in methanol to alcohol **37.** While intermediate compounds could be isolated, the entire sequence **33** $\rightarrow$ **35** $\rightarrow$ **37** was best performed without intervening purification and overall yields were consistently 80-85%.

The allylic alcohol **37** is stable to acid, but has proved extremely unstable to alkali. Care must be taken during any treatment with base to avoid heat or prolonged reaction times due to facile formation of 4-phenyl-1,3-dimethyl-2-pyridone (**37a**), which was produced quantitatively from **37** by treatment with hot methanolic KOH.

In the ethylidene series **32,** the oxidation was more difficult. When **32** was treated with SeO_2 in chlorobenzene, a complex mixture resulted from which the desired tertiary alcohol **34** could not be isolated. In acetic acid a mixture was obtained containing the rearranged secondary allylic alcohol **36** as its acetate. Hydrolysis led to alcohol **36** and 1-methyl-3-(α-hy-

droxyethyl)-4-phenyl-2-pyridone (**36a**), as well as a small amount of starting material. These could be separated by careful chromatography, but more conveniently could be used as the mixture for the Claisen rearrangement described below.

In the case of the endocyclic lactam **30b,** allylic oxidation took a different course. Two allylic methylenes are now available, C-5 of the pyridone ring and the *exo*-methylene α to the ester. Selenium dioxide did effect allylic oxidation, but exclusively at C-5. The resulting alcohol **38** cannot be used to introduce a quaternary substituent at C-4, but on Claisen rearrangement with trimethyl orthoacetate gave the interesting diester **39a.** This diester is very sensitive to oxidation and on attempted purification was converted to the 2,6-dioxopiperidine **39b.**

Attempts to oxidize **30b** directly to the α-hydroxyallylic alcohol **42** failed with a variety of reagents. Mercuric acetate, lead tetraacetate, bromination, and tertiary amine catalyzed oxidation with O_2/DMF/cuprous chloride all gave mostly unchanged starting material. When oxygen in the presence of *tert*-butoxide was used, the major product was 1-methyl-4-phenyl-3-methoxycarbonylmethyl-2-pyridone (**43**). When ester **30b** was treated with lithium diisopropylamide in THF, the enolate was formed and could be 90% monodeuterated by quenching with deuteriomethanol; however, the enolate was unreactive towards iodine or benzoyl peroxide.

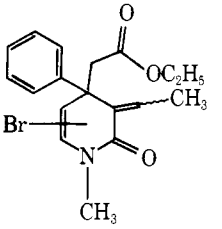
Epoxidation of **30b** was slow in refluxing methylene chloride, but was conveniently fast in refluxing 1,2-dichloroethane using *m*-chloroperbenzoic acid. The presence or absence of an inhibitor had little effect on the course of the oxidation.[9] Epoxide **40** was isolated and could be converted into allylic alcohol **41** with lithium diisopropylamide, but tertiary allylic alcohol **41** could not be rearranged solvolytically. It could not be acetylated at room temperature under a variety of conditions and more vigorous conditions, such as Ac_2O in pyridine at reflux or Ac_2O with H_2SO_4 at 25 °C, caused rapid dehydration to the pyridone **43.**

Inability to prepare allylic alcohol **42** eliminated one approach and the synthesis continued with allylic alcohols **36** and **37.** Both, upon heating with triethyl orthoacetate, gave good yields of the rearranged acetic acid ethyl esters **44** and **45a.** Preparation of methyl ester required some modification. Refluxing with trimethyl orthoacetate returned only starting material due to insufficient heat. This could be overcome in a sealed tube at 180 °C, but methyl ether was a serious side product since the liberated methanol could not be removed, even using ketene dimethylacetal as a methanol scavenger. Both the higher temperatures needed and the removal of methanol were attained using diglyme as a diluent and methyl ester **45b** was obtained in 90% yield.

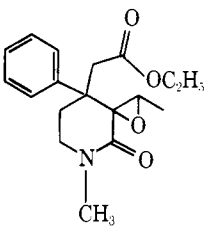
Preparation of the methyl ketone **45e** by Claisen rearrangement involved sealed reaction vessels because of the inefficient vinyl ether exchange between allylic alcohol **37** and methyl isopropenyl ether using either *p*-toluenesulfonic acid or mercuric acetate in the presence of molecular sieves or with distillative removal of methanol. Up to 70% yields of methyl ketone **45e** could be obtained at 210 °C in a sealed tube, but a more convenient synthesis was developed from the esters (**45a,b**), described below.

Formation of the Carbocyclic Ring. The C-4 quaternary-substituted derivatives **44** and **45** now provided the precursors for carbocyclic ring formation. Our first emphasis was placed on ester **44,** since it contained all the requisite carbons and required only anion formation at the vinyl methyl followed by attack at the ester carbonyl. However, neither ethoxide nor lithium diisopropylamide gave the desired ring closure; the only product was recovered ester **44** with an altered cis/trans ratio (1:3).

Oxidative attempts to functionalize the vinylic methyl also failed. Starting ester **44** was recovered from treatment with *tert*-butyl benzoate, Cu_2Br_2, or SeO_2. With *N*-bromosuccinimide/benzoyl peroxide, 2 mol of NBS were rapidly consumed with the formation of two new compounds. Chromatographic separation yielded the cis and trans isomers **46a** and **46b** in approximately equal amounts. The structures were determined by NMR, ir, and MS, the position of the bromine being uncertain. Epoxidation was more successful giving a single product, the epoxide **47** of unknown stereochemistry,



46a, cis
b, trans



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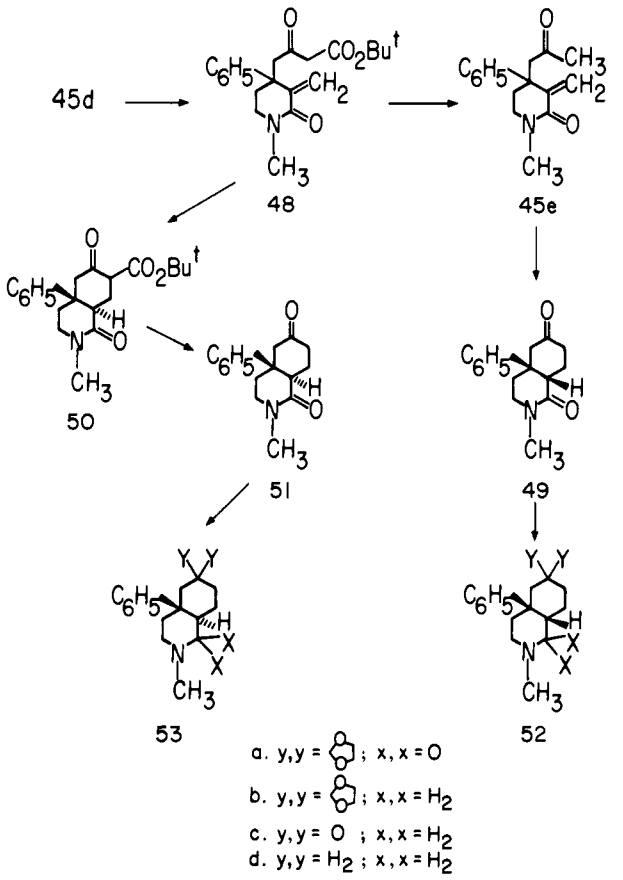
in 87% yield. Although this epoxide showed promise for ultimate ring closure, the approach through the vinyl methyl compound **44** was set aside and we examined the methylene series **45.**

Encouraging results in an internal Michael reaction with methyl ketone **45e** focused attention on a more efficacious synthesis for this ketone. This was achieved by hydrolysis of ester **45a** or **b** to the acid **45c,** conversion to acid chloride **45d,** and treatment with the anion of *tert*-butyl acetate, the latter generated from lithium diisopropylamide at −78 °C. The overall yield of β-keto ester **48** (Scheme V) was 60%, accompanied by ~15% of the tertiary amide **45f,** and hydrolysis with trifluoroacetic acid followed by decarboxylation gave a 73% yield of methyl ketone **45e.**

Scheme V. Carbocyclic Ring Formation



Internal Michael addition with **45e,** catalyzed by KOH in refluxing methanol, proceeded in 95% yield to give the cyclic ketone **49.** Similarly, β-keto ester **48** underwent an intramolecular Michael reaction to form cyclic β-keto ester **50** in quantitative yield upon treatment with triethylamine in methanol at room temperature. Hydrolysis and decarboxylation of **50** gave the cyclic ketone **51,** isomeric with **49.**

At this point, stereochemistry at the ring junction was unknown. However, ketones **50** and **51** were tentatively assigned as trans, formed by kinetic protonation of the amide enolate ion from the less-hindered side with little (~10% cis) equilibration by triethylamine or trifluoroacetic acid. Refluxing trans ketone **51** with ethanolic KOH for 2 h resulted in a 70:30 equilibrium mixture of cis ketone **49**/trans ketone **51,** indicating that cis ring fusion is the more stable configuration.

The structure and stereochemistry of these 4a-phenyldecahydroisoquinoline ketones **49** and **51** were further proved by conversion to the oxygen-free compounds, **52d** and **53d,** respectively. Reactions proceeded normally to form the amide ketals **52a** and **53a** and these were reduced to amino ketals **52b** and **53b** with aluminum hydride. In the case of the trans isomer **53a,** the major product was the enamine, but this was reduced stereospecifically to **53b.** Hydrolysis to the amino ketones **52c** and **53c** and Wolff-Kishner reduction gave the *cis*- and *trans*-4a-phenyldecahydroisoquinolines [**52d,** equivalent to **7** (R = C_6H_5), and **53d,** equivalent to **4**]. Comparison with the properties reported for the known compounds, where stereochemistry has been established by x-ray crystallography,[1d] confirmed our assignments.

We now possess a method for forming functionalized 4a-aryldecahydroisoquinolines with either cis or trans ring fusion. The aryl group may be variously substituted, since our synthesis proceeds from 4-arylnipecotic acids available by a number of synthetic approaches. Also, the oxo function at C-6 corresponds to the oxygen function at C-6 in morphine and should allow the preparation of close relatives.

Experimental Section[10]

Ethyl 2-Methyl-4-phenyl-1,4-dihydronicotinate (18a). Cinnamaldehyde (**17,** 3.63 g, 27.5 mmol) and ethyl β-aminocrotonate (3.23 g, 25 mmol) were introduced into 30 ml of absolute ethanol containing piperidine (120 μl, 103 mg, 1.20 mmol). The mixture was refluxed for 1 h followed by removal of solvent and distillation of the residue to give 3.3 g (55%), bp 155–165 °C (0.3 mm), of a mixture of dihydropyridine **18a** and pyridine **19.** The dihydro compound was extremely air sensitive and difficult to obtain pure. It was characterized by the following spectral data: NMR δ 7.13 (s, 5 H), 5.82 (m, 2 H), 4.8 (t, 1 H), 4.45 (d, J = 5 Hz, 1 H), 3.98 (q, J = 7 Hz, 2 H), 2.7 (s, 3 H), 1.06 (t, J = 7 Hz, 3 H); ir (film) 3340, 3060, 1730, 1672, 1595, 1570 cm^{-1}.

It was also characterized by hydrogenation of the crude reaction mixture with H_2/Pd/C in methanol to give **ethyl 2-methyl-4-phenyl-1,4,5,6-tetrahydronicotinate,** which was crystallized from $CHCl_3$/hexane: mp 126–128 °C; NMR δ 7.17 (s, 5 H), 4.1 (br, 1 H), 3.95 (q, J = 7 Hz, 2 H), 3.05 (m, 2 H), 2.40 (s, 3 H), 1.55 (m, 2 H), 1.01 (t, J = 7 Hz, 3 H); ir (CCl_4) 3440, 2930, 1680 cm^{-1}; MS 245 (45), 216 (49), 200 (29), 172 (100). Anal. ($C_{15}H_{19}NO_2$): C, H, N.

Ethyl 2-Methyl-4-phenylnicotinate (19). The crude dihydropyridine mixture above (1.0 g, 4.12 mmol) was placed in 70 ml of ethanol along with $NaHCO_3$ (342 mg, 4.2 mmol), and to the heterogeneous mixture was added dropwise a 10% solution of I_2 in ethanol until the color persisted for 2 min, then back-titrated to a colorless solution with 0.1 N $Na_2S_2O_3$. Solvents were removed until salt precipitation and 20 ml of ether was added, washed with 10 ml of H_2O and saturated NaCl solution, dried ($MgSO_4$), and evaporated. The residue was chromatographed on system A and the products in order of elution were **ethyl 2-methyl-6-phenylnicotinate (20,** 80 mg, 8%, mp 45–46 °C (lit.[5] mp 46–46.5 °C)), identical with authentic material, and **ethyl 2-methyl-4-phenylnicotinate (19,** 800 mg, 80%): NMR δ 8.35 (d, J = 5 Hz, 1 H), 7.29 (s, 5 H), 6.95 (d, J = 5 Hz, 1 H), 3.79 (q, J = 7 Hz, 2 H); ir (CCl_4) 1723 cm^{-1}; MS *m/e* 241 (60), 196 (100), 168 (57). An analytical sample was prepared by preparative GC, system A. Anal. ($C_{15}H_{15}NO_2$): C, H, N.

Ethyl 1,2-Dimethyl-4-phenyl-1,4-dihydronicotinate (18b). Cinnamaldehyde (3.63 g, 27.5 mmol), ethyl β-methylaminocrotonate (3.58 g, 25 mmol), and piperidine (120 μl, 103 mg, 1.2 mmol) were refluxed in 12 ml of absolute ethanol for 1 h. The solvent was removed and the residue distilled, bp 132–133 °C (0.2 mm), to give 4.9 g (77%) of the dihydropyridine **18b,** which on standing at 0 °C slowly crystallized: mp 59–60 °C (from 3:2 CH_3OH/H_2O); NMR δ 7.05 (s, 5 H), 5.70 (d, 1 H, J = 7 Hz), 4.91 (d of d, 1 H, J = 5, 8 Hz), 4.10 (d, 1 H, J = 5 Hz), 3.84 (q, 2 H, J = 7 Hz), 3.02 (s, 3 H), 2.37 (s, 3 H), 1.07 (t, 3 H, J = 7 Hz); ir 1681 cm^{-1}; MS *m/e* 257 (21.4), 242 (44.9), 214 (37.9), 1.80 (100). Anal. ($C_{16}H_{19}NO_2$): C, H, N.

Ethyl 1,2-Dimethyl-4-phenylnipecotate (14a). The dihydropyridine **18b** (4.2 g, 16.3 mmol) and Pd/C (10%, 400 mg) were placed in CH_3OH (100 ml, anhydrous) and hydrogenated at 55 psi of H_2. After 12 h, HCl (100 mol %) in ethanol was added and the solution hydrogenated for an additional 12 h at 55 psi of H_2. After solvent removal, distribution between aqueous alkali and ether, and evaporation of the ether, 4.2 g (95%) of the nipecotate **14a** was isolated as an oil, which by GC (A) and NMR was a single isomer: NMR δ 7.18 (s, 5 H), 3.84 (q, J = 7 Hz, 2 H), 2.32 (s, 3 H), 1.18 (d, J = 6 Hz, 2 H), 0.92 (t, 3 H), J = 7 Hz); ir (film) 1740 cm^{-1}; MS *m/e* 261 (70), 246 (77), 216 (16), 42 (100). Anal. ($C_{16}H_{23}NO_2$): C, H, N.

Interruption of the hydrogenation after uptake of 1 mol gave exclusively the tetrahydropyridine **21:** NMR δ 7.15 (s, 5 H), 3.84 (q, J = 7 Hz, 2 H), 3.1 (m, 2 H), 2.95 (s, 3 H), 2.37 (s, 3 H), 1.95 (m, 2 H), 1.04 (t, J = 7 Hz, 3 H).

Dimethyl 1-Methyl-4-phenyl-1,4-dihydroquinolinic Acid (23). Cinnamaldehyde (4.22 g, 32 mmol), methyl β-methylaminofumarate (**22,** 5.22 g, 30 mmol),[11] and piperidine (120 μl, 103 mg, 1.2 mmol) were placed in methoxyethanol (25 ml, anhydrous), the mixture was heated at reflux for 3 h, solvent was evaporated, and the residue was distilled (Kugelrohr) to yield 4.8 g (56%) of the dihydropyridine **23,** bp 180 °C (0.05 mm). A portion was crystallized from methanol: mp 125–126 °C; NMR δ 7.21 (br s, 5 H), 5.80 (d, J = 7 Hz), 4.90 (d of d, J = 4.5, 7 Hz, 1 H), 4.46 (d, J = 4.5 Hz, 1 H), 3.90 (s, 3 H), 3.53 (s, 3 H), 3.00 (s, 3 H); ir ($CHCl_3$) 1742, 1690, 1580 cm^{-1}; MS *m/e* 287 (8.42), 228 (81.9), 210 (100). Anal. ($C_{16}H_{17}NO_4$): C, H, N.

Dimethyl 1-Methyl-4-phenylhexahydroquinolinate (14b). Dihydropyridine **23** (1.6 g, 5.59 mmol), Pd/C (10%, 250 mg), CH_3OH (20 ml, anhydrous), and 11 ml of 1.1 N HCl/CH_3OH were shaken with hydrogen at 40 psi for 12 h. Filtration, evaporation, distribution between aqueous alkali and ether, and evaporation of the ether gave 1.6 g (95%) of the piperidines **14b** as an oil: NMR δ 3.73 (s, 3 H), 3.41 (s, 3 H), 2.32 (s, 3 H); ir 1750 cm^{-1}; MS *m/e* 291 (76), 232 (65), 128 (94), 42 (100). An analytical sample was prepared by preparative GC (A). Anal. ($C_{16}H_{21}NO_4$): C, H, N.

Without added HCl, only the tetrahydropyridine results: NMR δ 3.97 (s, 3 H), 3.52 (s, 3 H), 2.93 (s, 3 H), 3.05 (m, 2 H), 1.95 (m, 2 H).

Ethyl 1-Methyl-4-phenylnipecotate (14c). To the Grignard reagent prepared from bromobenzene (152 g, 0.97 mol) and magnesium filings (23.8 g, 1 mol) in 300 ml of ether, cooled to −10 °C and well stirred, was added dropwise arecaidine ethyl ester[7] (75 g, 0.3 mol) in 180 ml of ether. The reaction mass was stirred for 30 min in the cold after completion of addition, then poured into 100 g of crushed ice and 500 ml of 6 N HCl. The separated aqueous layer was washed with ether (200 ml) and then brought to pH 8 with saturated K_2CO_3; the precipitated $Mg(OH)_2$ was filtered and washed well with ether (2 × 200 ml). The aqueous phase was washed with ether (3 × 300 ml) and the combined ethereal layers were washed (saturated NaCl, 200 ml) dried (K_2CO_3), and evaporated to yield a residue which was distilled, giving 82.1 g (75%) of the nipecotate **14** as a mixture of isomers: NMR δ 7.28 (s, 5 H), 3.95 (q, J = 7 Hz, 2 H), 2.30 (s, 3 H), 1.00 (t, J = 7 Hz, 3 H); ir 1739 cm^{-1}; MS *m/e* 257 (58.4), 218 (23.3), 174 (56.2), 44 (100). Anal. ($C_{15}H_{21}NO_2$): C, H, N.

1-Methyl-4-phenylhexahydroquinolinic Acid (14e). The diester **14b** was hydrolyzed by refluxing with 500 mol % of KOH in isopropyl alcohol for 1 h. Acidification with concentrated HCl caused precipitation of nearly all the KCl and evaporation gave the crude amino acid **14e** hydrochloride, which was used without purification; NMR revealed the complete loss of the ester methyl groups.

3-Carboxymethyl-1-methyl-4-phenyl-5,6-dihydro-2-pyridone (30a). A. Attempted Preparation via Ac_2O/K_2CO_3. Amino acid hydrochloride **14e** (410 mg, 1.37 mmol), Ac_2O (25 ml), and K_2CO_3 (87 mg, 0.63

mmol) were refluxed for 6 h, then the mixture was evaporated to dryness. The residue was partitioned between CH_2Cl_2 (20 ml) and H_2O (20 ml, pH 2) and the organic phase dried over Na_2SO_4 and evaporated to yield an oil (360 mg). Chromatography (system A) and crystallization (CH_2Cl_2/hexane) gave 140 mg (35%) of **9-acetoxy-2-methyl-1-oxo-3,4-dihydrobenzo(*f*)isoquinoline (31):** mp 145–147 °C; NMR δ 8.0–7.1 (m, 5 H), 3.60 (d, J = 5 Hz, 2 H), 3.37 (d, J = 5 Hz, 2 H), 3.17 (s, 3 H), 2.45 (s, 3 H); ir 1760, 1640 cm^{-1}; MS *m/e* 269 (5.2), 22 (63.3), 184 (45.4), 156 (62.1), 43 (100). Anal. ($C_{16}H_{15}NO_3$): C, H, N.

The same product was obtained in 70% yield when the acid **30a** (below) was treated under the same conditions.

B. Via Thermal Rearrangement of 14e. Into a flask equipped with a Soxhlet extractor filled with $MgSO_4$ were placed diacid **14e** (200 mg, 0.63 mmol) and xylene (25 ml). The solution was refluxed for 24 h, cooled (25 °C), washed with 2 N HCl, evaporated, and chromatographed (SiO_2, 5% HOAc/ethyl acetate) to give 80 mg (50%) of acid **30a,** which was crystallized from C_6H_6/hexane: mp 121–122 °C; NMR δ 10.01 (br), 1 H), 7.1 (m, 5 H), 3.57 (t, J = 7 Hz, 2 H), 3.10 (s, 3 H), 3.07 (s, 2 H), 2.73 (t, J = 7 Hz, 2 H); ir ($CHCl_3$) 3420, 2900–2400 (br), 1730, 1635, 1585 cm^{-1}; MS *m/e* 227 (-H_2O, 1), 201 (14), 200 (19). Anal. ($C_{14}H_{15}NO_3$): C, H, N.

3-Methoxycarbonylmethyl-1-methyl-4-phenyl-5,6-dihydro-2-pyridone (30b). Amino acid hydrochloride **14e** (3.3 g, 11.33 mmol) and xylene (90 ml) were heated in the manner described above. The crude reaction product (2.35 g) was placed in CH_3OH (15 ml) along with tris(2-hydroxypropyl)amine (2.11 g, 12.3 mmol) and dimethyl sulfate (1.6 g, 12.3 mmol) and heated vigorously on a steam bath for 20 min to yield a brown oil. After cooling, H_2O (5 ml) was added, the slurry allowed to sit for 5 min, then partitioned between $CHCl_3$ (50 ml) and 2 N HCl (50 ml). The organic phase was washed with $NaHCO_3$, evaporated, and distilled (Kugelrohr) to yield 2.40 g (82%), bp 145 °C (0.2 mm) of the methyl ester **30b,** which solidified on standing: mp 93–104 °C; NMR δ 7.29 (s, 5 H), 3.67 (s, 3 H), 3.51 (t, J = 7.5 Hz, 2 H), 3.28 (s, 2 H), 3.03 (s, 3 H), 2.70 (t, J = 7.5 Hz, 2 H); ir 1730, 1660, 1625 cm^{-1}; MS *m/e* 259 (15), 228 (19), 227 (56), 128 (100). The analytical sample was prepared by recrystallization from ch_2Cl_2/hexane, mp 110–111 °C. Anal. ($C_{15}H_{17}NO_3$): C, H, N.

3-Ethylidene-1-methyl-4-phenyl-2-piperidone (32). Ethyl 1,2-dimethyl-4-phenylnipecotate (**14a**) (4 g, 15.3 mmol), 50 ml of methoxyethanol, and 5 g of potassium hydroxide were refluxed for 4 h. Solvent was evaporated, the residue was dissolved in 200 ml of 2 N HCl and washed with chloroform, and the aqueous portion was concentrated to dryness to yield the nipecotic acid hydrochloride **14f** as a glass which was dissolved in Ac_2O (200 ml) with K_2CO_3 (15.3 mmol) present. The solution was maintained at reflux for 24 h then evaporated to near dryness, and ice and H_2O (200 ml) were added. After being stirred for 6 h, the solution was basified with K_2CO_3 and extracted with methylene chloride (3 × 200 ml). The organic phase was washed with 1 N HCl (50 ml), dried over Na_2SO_4, and evaporated, and the residue was chromatographed (system A) to give >95% of pure lactams (2.5 g), which were distilled (Kugelrohr, 125 °C (0.3 mm) to yield **32** (2.3 g, 70%) with a cis/trans ratio of 1:10: NMR δ 7.23 (m, 5 H), 4.10 (t, J = 6.2 Hz, 1 H), 3.02 (s, 3 H), 1.63 (d, J = 7 Hz, 3 H); ir 1670, 1618 cm^{-1}; MS *m/e* 215 (73), 214 (64), 200 (61), 43 (100). Anal. ($C_{14}H_{17}NO$): C, H, N.

1-Methyl-3-methylene-4-phenyl-2-piperidone (33). The ethyl ester **14c** (82.1 g, 332 mmol) was dissolved in 450 ml of 8 N HCl and 200 ml was distilled. The remaining solution then was evaporated to give 89 g of the amino acid hydrochloride **14g;** NMR revealed complete hydrolysis. Ac_2O (1100 ml) and K_2CO_3 (65 g, 0.66 mmol) were added and the mixture refluxed for 0.5 h. The residue after evaporation of the solvent was partitioned between CH_2Cl_2 (300 ml) and 5% K_2CO_3 (200 ml), the aqueous phase was washed with CH_2Cl_2 (2 × 150 ml), and the combined CH_2Cl_2 layers were dried (Na_2SO_4) and evaporated to yield 65 g (97%) of the methylene lactam **33,** mp 73–74 °C on crystallization from C_6H_6/hexane/ethanol (90:10:0.5): NMR δ 7.70 (m, 5 H), 6.25 (t, J = 2 Hz, 1 H), 4.90 (t, J = 2 Hz, 1 H), 3.73 (t, J = 8 Hz, 1 H), 3.36 (m, 2 H), 2.95 (s, 3 H), 2.12 (m, 2 H); ir 1657, 1618 cm^{-1}; MS *m/e* 201, 200. Anal. ($C_{13}H_{15}NO$): C, H, N.

4-Hydroxy-1-methyl-3-methylene-4-phenyl-2-piperidone (35). α-Methylene lactam **33** (400 mg, 2.0 mmol), SeO_2 (167 mg, 1.5 mmol), and chlorobenzene (15 ml, anhydrous) were heated at 100 °C for 90 min. Filtration, evaporation, and chromatography (system A) gave 260 mg (60%) of the tertiary alcohol **35,** which was recrystallized from $CHCl_2$/hexane: mp 112–113 °C; NMR δ 7.30 (m, 5 H), 6.32 (d, J = 2 Hz, 1 H), 5.48 (d, J = 2 Hz, 1 H), 4.72 (s, br, 1 H), 3.7–3.1 (m, 2 H), 2.87 (s, 3 H), 2.73)m, 2 H); ir 3650, 3400, 1650, 1610 cm^{-1}; MS *m/e* 217, 216, 200, 199. Anal. ($C_{13}H_{15}NO_2$): C, H, N.

3-Hydroxymethyl-1-methyl-4-phenyl-5,6-dihydro-2-pyridone (37). α-Methylene lactam **33** (15 g, 75 mmol), SeO_2 (6.3 g, 5 mmol), and chlorobenzene (300 ml, anhydrous) were heated at 100 °C for 1 h. Cooling (25 °C), filtering (Celite), and evaporating gave an oil which was dissolved in HCO_2H (500 g, 97%) and allowed to stand overnight, after which it was filtered and evaporated. The residue was taken up in $CHCl_3$ (400 ml), washed with saturated $NaHCO_3$, dried over Na_2SO_4, and evaporated to yield a solid which was dissolved in 300 ml of CH_3OH, and K_2CO_3 (0.25 g, 1.8 mmol) was added. After 1 h the methanol was evaporated, the residue was dissolved in $CHCl_3$ (300 ml), washed with H_2O (100 ml), dried (Na_2SO_4), and evaporated to a residue which was crystallized from C_6H_6/hexane to give 13.25 g, 82%, of primary allylic alcohol **37:** mp 126–127 °C; NMR δ 7.31 (m, 5 H), 4.27 (s, 2 H), 3.8 (s, br, 1 H), 3.52 (t, J = 7 Hz, 2 H), 3.03 (s, 3 H), 2.22 (t, J = 7 Hz, 2 H); ir 1654, 1610 cm^{-1}; MS *m/e* 217, 216, 199. Anal. ($C_{13}H_{15}NO_2$): C, H, N.

1,3-Dimethyl-4-phenyl-2-pyridone (37a). To primary allylic alcohol **37** (21.7 mg, 0.1 mmol) in 2 ml of CH_3OH was added KOH (19.5 mg, 3 mmol, 85%) and the solution was refluxed 1 h, then poured into H_2O (5 ml), extracted (2 × 5 ml of $CHCl_3$), and the organic phase washed with H_2O (5 ml) and saturated NaCl (5 ml), then dried with Na_2SO_4. Evaporation yielded 19 mg (95%) of pyridone **37a:** mp 75 °C (after sublimation, 50 °C (0.05 mm)), NMR δ 7.23 (s, 5 H), 7. 02 (d, J = 7 Hz, 1 H), 5.87 (d, J = 7 Hz, 1 H), 3.47 (s, 3 H), 1.97 (s, 3 H); ir 1650, 1600 cm^{-1}; MS *m/e* 199, 198. Anal. ($C_{13}H_{13}NO$): C, H, N.

3-(1-Hydroxyethyl)-1-methyl-4-phenyl-5,6-dihydro-2-pyridone (36). Ethylidene lactam **32** (5.38 g, 25 mmol), SeO_2 (14 g, 125 mmol), and 100 ml acetic acid were heated at 100 °C with vigorous stirring for 1 h. Following filtration and evaporation the residue, which is primarily the acetate of allylic alcohol **36,** was dissolved in 100 ml of 97% formic acid. After 1 h at 25 °C, the solution was filtered and evaporated to give an oil which was taken up in 100 ml of chloroform, washed with saturated $NaHCO_3$ and saturated NaCl, dried over Na_2SO_4, and evaporated. The residual oil was dissolved in 100 ml of CH_3OH, K_2CO_3 (0.345 g, 2.5 mmol) was added, and the methanolysis allowed to proceed for 1 h. The homogenous solution was then evaporated to near dryness and $CHCl_3$ (100 ml) was added, washed with H_2O, saturated NaCl, dried over Na_2SO_4, and the solvent evaporated. The residue was chromatographed (SiO_2, 350 g, 1:1 $CHCl_3$/EtOAc) to give 3.1 g of material, which by GC (A) was 80% the desired dihydropyridone alcohol **36,** 15% pyridone alcohol **36a,** and 5% **32.** Careful rechromatography yielded pure **36:** mp 122–123 °C from CH_2Cl_2/hexane; NMR δ 7.2 (m, 5 H), 4.47 (q, J = 6.5 Hz, 1 H), 3.03 (s, 3 H), 1.4 (d, J = 6.5 Hz, 3 H); ir 3450, 1652, 1615 cm^{-1}; MS *m/e* 216 (18.7), 41 (100). Anal. ($C_{14}H_{17}NO_2$): C, H, N.

The pyridone alcohol **36a** showed NMR absorption at δ 7.30 (m, 6 H), 6.06 (d, J = 7 Hz, 1 H), 5.40 (q, J = 6 Hz, 1 H), 3.60 (s, 3 H), 1.52 (d, J = 7 Hz, 3 H).

5-Hydroxy-3-methoxycarbonylmethyl-1-methyl-4-phenyl-5,6-dihydro-2-pyridone (38). A mixture of lactam ester **30b** (777 mg, 3 mmol), SeO_2 (367 mg, 3.3 mmol), and 15 ml of chlorobenzene was refluxed for 3 h, after which the mixture was filtered, the filtrate evaporated, and the residue chromatographed (system B) to obtain 335 mg (40%) of allylic alcohol **38,** mp 135–137 °C after recrystallization from benzene/hexane: NMR δ 7.30 (s, 5 H), 4.2 (br, OH), 3.6 (m, including 6 at 3.66, OCH_3), 3.27 (d, J = 5 Hz, 2 H), 3.05 (s, 3 H); ir 3450, 1732, 1650, 1620 cm^{-1}; MS *m/e* 275 (31), 257 (10), 244 (27), 172 (100). Anal. ($C_{15}H_{17}NO_4$): C, H, N.

Treatment of 335 mg of the allylic alcohol **38** under Claisen rearrangement conditions (see below) gave two materials after chromatography. Eluted first (system B) was 104 mg (26%) of **3,3-bis(methoxycarbonylmethyl)-1-methyl-4-phenyl-3,6-dihydro-2-pyridone (39a):** NMR δ 7.3 (m, 5 H), 5.73 (t, J = 3 Hz, 1 H), 4.03 (d, J = 3 Hz, 2 H), 3.57 (s, 6 H), 3.10 (s, 3 H), 3.00 (d, J = 16 Hz, 2 H), 2.43 (d, J = 16 Hz, 2 H). Attempted purification of this material by recrystallization or sublimation resulted in its conversion into **3,3-bis(methoxycarbonylmethyl)-4,5-dihydro-2,6-dioxo-1-methyl-4-phenylpiperidine (39b):** mp 131–132 °C; NMR δ 7.3 (m, 5 H), 6.25 (s, 1 H), 3.65 (s, 6 H), 3.33 (s, 3 H), 3.03 (d, J = 16 Hz, 2 H), 2.56 (d, J = 16 Hz, 2 H); ir 1742, 1715, 1678, 1637 cm^{-1}; MS *m/e* 345 (10), 228 (17), 196 (10), 55 (100). Anal. ($C_{18}H_{19}NO_6$): C, H, N.

Eluted next was 62 mg (21%) of **3-methoxycarbonylmethyl-1-methyl-4-phenyl-2-pyridone (43),** mp 152–154 °C after crystallization

from cyclohexane/benzene (10:1) and sublimation: NMR δ 7.39 (s, 5 H), 7.25 (d, J = 7Hz, 1 H), 6.15 (d, J = 7 Hz, 1 H), 3.72 (s, 3 H), 3.60 (s, 3 H), 3.50 (s, 2 H); ir 1733, 1650, 1600 cm^{-1}; MS *m/e* 257 (60), 225 (60), 198 (100). Anal. ($C_{15}H_{15}NO_3$): C, H, N.

3-Methoxycarbonylmethyl-1-methyl-4-phenyl-5,6-dihydro-2-pyridone Epoxide (40). Lactam **30b** (2.57 g, 10 mmol), *m*-chloroperbenzoic acid (5.16 g, 30 mmol, 85%), and $ClCH_2CH_2Cl$ (50 ml, anhydrous) were refluxed for 10 h, the solution was cooled and washed with 3 N NaOH, the solvent was dried (Na_2SO_4) and evaporated, and the residue was chromatographed (SiO_2, 1:1 CH_2Cl_2/EtOAc) to yield 1.17 g (45%) of pure epoxide **40:** mp 99–101 °C from CH_2Cl_2/hexane; NMR δ 7.35 (s, 5 H), 3.58 (s, 3 H), 3.06 (d, J = 16 Hz, 1 H); 3.00 (s, 3 H), 2.06 (d, J = 16 Hz, 1 H); ir 1740, 1660 cm^{-1}; MS *m/e* 275 (2), 244 (2), 146 (88), 82 (100). Anal. ($C_{15}H_{17}NO_4$): C, H, N.

4-Hydroxy-3-methoxycarbonylmethylene-1-methyl-4-phenyl-2-piperidone (41). The epoxide **40** (135 mg, 0.5 mmol) in 25 ml of THF was added to a solution of lithium diisopropylamide (0.6 mmol, prepared from diisopropylamine and butyllithium) in 2.5 ml of THF at −78 °C. The bath was removed and the solution allowed to warm to 25 °C for 30 min, whereupon 5 ml of 1 N HCl in CH_3OH was added. The solvents were evaporated and the residue partitioned between H_2O (10 ml) and $CHCl_3$ (10 ml), the aqueous layer was washed with $CHCl_3$ (5 ml), and the combined organic phase was dried (Na_2SO_4) and evaporated to yield 140 mg of a mixture of allylic alcohol **41** and epoxide **40**. Chromatography (system A) gave 81 mg (67%) of the pure allylic alcohol **41:** NMR δ 7.37 (s, 5 H), 6.19 (s, 1 (H), 3.79 (s, 3 H), 2.89 (s, 3 H); ir 1724, 16 H61, 1623 cm^{-1}; MS *m/e* 275 (17), 244 (16), 243 (16), 138 (100). Anal. ($C_{15}H_{17}NO_4$): C, H, N.

4-Ethoxycarbonylmethyl-3-ethylidene-1-methyl-4-phenyl-2-piperidone (44). The secondary allylic alcohol **36** (104 mg, 0.45 mmol), triethyl orthoacetate (520 mg, 3.16 mmol), and propionic acid (2.3 ml, 0.03 mmol) were heated at 142 °C for 23 h. Evaporation of excess orthoester and chromatography (SiO_2, 1:1 $CHCl_3$/EtOAc) of the residue gave 105 mg (78%) of cis and 8 mg (6%) of trans Claisen product **44:** NMR (trans) δ 7.26 (s, 5 H), 7.1 (q, J = 11 Hz, 1 H), 4.08 (q, J = 7 Hz, 2 H), 3.08 (s, 2 H), 2.98 (s, 3 H), 1.41 (d, J = 8 Hz, 3 H), 1.20 (t, J = 7 Hz, 3 H); NMR (cis) δ 7.21 (s, 5 H), 5.90 (q, J = 7.5 Hz, 1 H), 3.90 (q, J = 7.5 Hz, 2 H), 2.75 (s, 3 H), 2.03 (d, J = 7.5 Hz, 3 H), 1.03 (t, J = 7.5 Hz, 3 H); ir 1730, 1662, 1640 cm^{-1}; MS *m/e* 301 (31.5), 256 (9.0), 228 (11.0), 214 (100). An analytical sample of *cis*-**44** was obtained by preparative GC (C). Anal. ($C_{18}H_{23}NO_3$): C, H, N.

4-Ethoxycarbonylmethyl-1-methyl-3-methylene-4-phenyl-2-piperidone (45a). The primary allylic alcohol **37** (150 mg, 0.69 mmol), triethyl orthoacetate (2 ml, 10.9 mmol), and propionic acid (4 μl, 0.056 mmol) were heated at 142 °C for 10 h. Evaporation of excess orthoester and chromatography (system A) of the residue gave 178 mg (90%) of ester **45a.** Alternatively it may be distilled (Kugelrohr, bp 125–130 °C (0.1 mm): NMR δ 7.19 (s, 5 H), 6.45 (s, 1 H), 5.52 (s, 1 H), 4.0 (q, J = 8 Hz, 2 H), 3.7–2.4 (m, 9 H) with 2.85 (s, 3 H), 1.15 (t, J = 8 Hz, 3 H); ir 1720, 1650, 1600 cm^{-1}; MS *m/e* 287, 272, 258, 242, 200 (100). Anal. ($C_{17}H_{21}NO_3$): C, H, N.

4-Methoxycarbonylmethyl-1-methyl-3-methylene-4-phenyl-2-piperidone (45b). The allylic alcohol **37** (3.68 g, 17.0 mmol), trimethyl orthoacetate (10.2 g, 85 mmol), and propionic acid (170 μl, 0.17 mmol) were placed in diglyme (150 ml, anhydrous) and refluxed at 155–160 °C (internal temperature) with fractionation to remove CH_3OH. After 18 h the solvents were evaporated and the residue distilled (bp 125–130 °C (0.1 mm) to give 4.16 g (90%) of pure methyl ester **45b:** mp 67–70 °C; NMR δ 7.30 (s, 5 H), 6.63 (s, 1 H), 5.5 (s, 1 H), 3.55 (s, 3 H), 3.3–2.4 (m, 9 H, including 2.85, s); ir 1731, 1661, 1605 cm^{-1}; MS *m/e* 273 (57), 200 (100). Anal. ($C_{16}H_{19}NO_3$): C, H, N.

4-Carboxymethyl-1-methyl-3-methylene-4-phenyl-2-piperidone (45c). To ethyl ester **45a** (430 mg, 1.5 mmol) dissolved in 4.5 ml of methanol at 0 °C was added KOH (338 mg, 5.2 mmol) in 2.3 ml of methanol and 3 ml of H_2O. After 40 h at room temperature, 20 ml of H_2O and 10 ml of $CHCl_3$ were added, the aqueous phase was separated and adjusted to pH 1 with concentrated HCl and then extracted with $CHCl_3$ (3 × 10 ml). The $CHCl_3$ was dried (Na_2SO_4) and evaporated and the residue on recrystallization from $CHCl_3$/hexane gave 362 mg (93%) of pure acid **45c:** mp 185–187 °C; NMR δ 7.17 (m, 5 H), 6.51 (s, 1 H), 5.47 (s, 1 H), 2.83 (s, 3 H); ir 1745, 1712, 1656, 1601 cm^{-1}; MS *m/e* 259 (45), 200 (45), 42 (100). Anal. ($C_{15}H_{17}NO_3$): C, H, N.

4-Chlorocarbonylmethyl-1-methyl-3-methylene-4-phenyl-2-piperidone (45d). Thionyl chloride (5 g, 42 mmol, from $(PhO)_3P$) and CH_2Cl_2 (5 ml, anhydrous) were cooled to −70 °C. The acid **45c** (1.294 g, 5.00 mmol) in 30 ml of $CHCl_3$ was added at a rate of 2 ml/min. After addition, the bath was removed, the solution was allowed to warm to 25 °C, the volatiles were evaporated, and the residue was crystallized from C_6H_6/hexane to yield 1.31 g (95%) of acid chloride **45d:** mp 149–151 °C; NMR δ 7.35 (s, 5 H), 6.74 (s, 1 H), 5.51 (s, 1 H), 3.65 (s, 2 H), 3.1 (m, 2 H), 3.02 (s, 3 H), 2.7 (m, 2 H); ir 1802, 1653, 1598 cm^{-1}; MS *m/e* 272 (3), 242 (12), 241 (19), 200 (13), 199 (36), 198 (27), 184 (97), 128 (100). Anal. ($C_{15}H_{16}NO_2Cl$): C, H, N.

4-Acetonyl-1-methyl-3-methylene-4-phenyl-2-piperidone (45e). A. By Claisen Rearrangement. The primary allylic alcohol **37** (2.17 g, 10 mmol), methyl isopropenyl ether (5.04 ml, 50 mmol), CH_2Cl_2 (5 ml, anhydrous), and $Hg(OAc)_2$ (100 mg, from ethanol) were stirred for 24 h in the presence of molecular sieves (4 g, 4 Å), after which K_2CO_3 (1 g, anhydrous) was added. Filtration and evaporation gave an oil which was heated at 215 °C for 15 min and then chromatographed (system A) to yield 777 mg (31%) of methyl ketone **45e** and 590 mg (27%) of starting alcohol **37.** The ketone was crystallized from benzene/hexane: mp 85–87 °C; NMR δ 7.30 (s, 5 H), 6.53 (s, 1 H), 5.37 (s, 1 H), 2.87 (s, 3 H), 1.90 (s, 3 H); ir 1712, 1653, 1601 cm^{-1}; MS *m/e* 257 (7), 239 (15), 215 (18), 201 (16), 200 (21), 199 (34), 78 (100). Anal. ($C_{16}H_{19}NO_2$): C, H, N.

Alternatively, in a thick-walled glass tube were placed **37** (217 mg, 1 mmol), methyl isopropenyl ether (1 ml), and $TsOH \cdot H_2O$ (5 mg). The vacuum sealed tube was heated at 215 °C for 5 h, cooled, and the contents were triturated with 10 ml of ether. After concentration and hexane addition (5 ml), 208 mg (72%) of crystalline ketone was obtained, mp 84–87 °C.

B. Via β-Keto Ester 48. The β-keto ester **48** (170 mg, 0.475 mmol) in CH_2Cl_2 (5 ml, anhydrous) was added rapidly to TFA (5 ml, 0 °C) After 5 h, the solution was evaporated and the residual oil dissolved in 15 ml of toluene and refluxed for 15 min. The solution was washed (saturated $NaHCO_3$, 10 ml), dried (Na_2SO_4), and evaporated to give 98 mg (73%) of pure methyl ketone **45e.**

***tert*-Butyl 4-[4′-(1′-Methyl-3′-methylene-4′-phenyl-2′-oxopiperidyl)]-3-oxobutyrate (48).** To THF (50 ml, anhydrous) and diisopropylamine (8.39 ml, 6.06 g, 60 mmol) at −78 °C was added *n*-butyllithium (17.15 ml, 3.5 M in hexane, 60 mmol). After 5 min *tert*-butyl acetate (4.04 ml, 3.48 g, 30 mmol) was added dropwise, and 10 min later the acid chloride **45d** (8.26 g, 29.8 mmol) was added in THF (60 ml) at a rate of 2 ml/min. The solution was maintained at −78 °C for 15 min following addition, and then the reaction was quenched by addition of 70 ml of saturated aq NH_4Cl. The slurry was warmed slowly to 25 °C, the layers separated, and the aqueous phase washed with ether (2 × 50 ml). The combined ethereal layers were washed with saturated NaCl, dried over Na_2SO_4, and evaporated to yield 10.0 g (95%) of a material which contained two major materials by TLC (B). Chromatography (system B) gave 6.44 g (61%) of the β-keto ester **48,** bp 155 °C (0.07 mm) (short path): NMR δ 7.31 (s, 5 H), 6.58 (s, 1 H), 5.37 (s, 3 H), 1.43 (s, 9 H); ir 1718, 1656, 1605 cm^{-1}; MS *m/e* 357 (1), 257 (5), 198 (21), 59 (100). Anal. ($C_{21}H_{27}NO_4$): C, H, N.

Diisopropylamide 45f (1.85 g, 18%) was recrystallized from benzene/hexane: mp 148.5–150 °C; NMR δ 7.27 (s, 5 H), 6.50 (s, 1 H), 5.41 (s, 1 H), 2.78 (s, 3 H), 1.33 (d, J = 7 Hz, 6 H), 1.00 (d, J = 7 Hz, 3 H), 0.88 (d, J = 7 Hz, 3 H); ir 1653, 1613 (br) cm^{-1}; MS *m/e* 343 (2), 342 (10), 341 (14), 200 (72), 53 (100). Anal. ($C_{21}H_{30}N_2O_2$): C, H, N.

***tert*-Butyl *trans*-1,6-Dioxo-2-methyl-4a-phenyldecahydroisoquinoline-7-carboxylate (50).** A solution of β-keto ester **48** (6.44 g, 1.81 mmol) in CH_3OH (200 ml, anhydrous) was treated with triethylamine (1.82 g, 1.81 mmol) and allowed to stand at 25 °C for 7 days. Evaporation gives 6.44 g (100%) of cyclized β-keto ester **50** as a foam, which was crystallized from benzene/hexane (1:2): mp 155–158 °C; NMR δ 7.25 (s, 5 H), 2.85 (s, 3 H), 1.48 (s, 9 H); ir 1715, 1664 (br) cm^{-1}; MS *m/e* 357 (1), 301 (37), 284 (16), 283 (22), 257 (12), 256 (11), 255 (23), 59 (100). Anal: ($C_{21}H_{27}NO_4$): C, H, N.

***trans*-1,6-Dioxo-2-methyl-4a-phenyldecahydroisoquinoline (51).** The cyclic β-keto ester **50** (1.75 g, 4.9 mmol) in CH_2Cl_2 (25 ml, anhydrous) was added dropwise to 25 ml of TFA at 0 °C, and after 3 h the solvents were evaporated, leaving a solid residue which was refluxed in 25 ml of toluene for 3 min. Evaporation gave a residue (0.99 g, 79%) which slowly crystallized and was recrystallized from benzene/hexane (1:1): mp 162–163 °C; NMR δ 7.23 (s, 5 H), 2.90 (s,

3 H), ir 1715, 1664 cm^{-1}; MS *m/e* 257 (51), 188 (36), 43 (100). Anal. ($C_{16}H_{19}NO_2$): C, H, N.

Crude material, prior to crystallization, contained about 10% of the cis isomer, as indicated by NMR integration.

***cis*-1,6-Dioxo-2-methyl-4a-phenyldecahydroisoquinoline (49).** The methyl ketone **45e** (54.5 mg, 0.21 mmol) and KOH (41.5 mg, 0.64 mmol) were dissolved in 2 ml of ethanol and refluxed for 30 min. After acidification with 1.5 N HCl in ethanol, 20 ml of $CHCl_3$ and 10 ml of H_2O were added, the layers separated, and the organic phase washed with H_2O and saturated NaCl. Drying and evaporation of the $CHCl_3$ gave a residue which was chromatographed (system A) to yield 50 mg (95%) of a mixture of 90% cis ketone **49** and 10% trans ketone **51** by NMR integration. A pure sample of cis ketone **49** was prepared by GC (C): NMR δ 7.36 (s, 5H), 2.92 (s, 3 H), 2.67 (s, 2 H); ir 1717, 1630 cm^{-1}; MS *m/e* 257 (25). Anal. ($C_{16}H_{19}NO_2$): C, H, N.

Equilibration of Cis Ketone 49 and Trans Ketone 51. Trans ketone **51** (125 mg, 0.5 mmol) was dissolved in 5 ml of ethanol containing KOH (100 mg, 1.5 mmol) and the solution was refluxed for 2 h. The reaction was quenched by the addition of 1 N HCl in ethanol until pH 6 and partitioned between $CHCl_3$ (25 ml) and H_2O (10 ml). The organic phase was washed with saturated NaCl, dried over Na_2SO_4, and evaporated to give 125 mg (100%) of a clear oil. NMR analysis revealed the mixture to contain *cis*-**49** and *trans*-**51** in a 70:30 ratio; GC (D) and TLC (B) established that only these materials were present.

***trans*-6,6-Ethylenedioxy-1-oxo-2-methyl-4a-phenyldecahydroisoquinoline (53a).** To a solution of crude trans ketone **51** (980 mg, 3.84 mmol) in benzene (150 ml, anhydrous) were added $TsOH \cdot H_2O$ (10 mg) and ethylene glycol (950 mg, 15 mmol), and the solution was refluxed with separation of water for 12 h. Cooling to 25 °C, pouring into 50 ml of 5% Na_2CO_3, washing the organic phase with 2 × 25 ml of saturated NaCl, drying over Na_2SO_4, and evaporating gave 1.07 g (92%) of a solid containing 12% of the cis isomer by GC (D). Recrystallization from benzene/hexane gave pure *trans*-ethyleneketal: mp 230–235 °C; NMR δ 7.21 (s, 5 H), 3.75 (m, 4 H), 2.78 (s, 3 H); ir 1637 cm^{-1}; MS *m/e* 301 (31), 202 (48), 99 (60), 42 (100). Anal. ($C_{18}H_{23}NO_3$): C, H, N.

***cis*-6,6-Ethylenedioxy-1-oxo-2-methyl-4a-phenyldecahydroisoquinoline (52a).** Application of the above conditions to cis ketone **49** (1.00 g, 3.84 mmol) yielded 1.06 g (90%) of an oil which by GC (D) was predominantly the cis ketal **52a,** contaminated with 5% trans ketal **53a.** A pure sample was prepared via preparative GC: NMR δ 7.28 (s, 5 H), 3.94 (m, 4 H), 2.70 (s, 3 H); ir 1629 cm^{-1}; MS *m/e* 301 (42), 202 (55), 99 (73), 42 (100). Anal. ($C_{18}H_{23}NO_2$): C, H, N.

***cis*-6,6-Ethylenedioxy-2-methyl-4a-phenyldecahydroisoquinoline (52b).** To a 0.67 M solution of AlH_3 in THF[12] (7.5 ml, 5 mmol) at 0 °C was added amide **52a** (910 mg, 3.3 mmol, in 7 ml of THF) over 4 min. The reaction was kept at 0 °C for 30 min following addition, then quenched with THF/H_2O (1:1, 2.0 ml), followed by NaOH (0.3 g in 9 ml of H_2O). The aqueous phase was washed with ether; the ether was washed with saturated NaCl, dried with Na_2SO_4, and evaporated to yield 813 mg (83%) of a mixture (20:1) of cis and trans ketal amines **52b** and **53b,** which was chromatographed (SiO_2, 2.5% concentrated NH_4OH/ethanol) and 576 mg (56%) of pure **52b** was obtained: NMR δ 7.31 (s, 5 H), 3.86 (m, 4 H), 2.13 (s, 3 H); ir no C=O absorption; MS *m/e* 287 (46), 286 (32), 242 (65), 99 (24), 42 (100). Anal. ($C_{18}H_{25}NO_2$): C, H, N.

***trans*-6,6-Ethylenedioxy-2-methyl-4a-phenyldecahydroisoquinoline (53b).** The trans ketal amide **53a** (1.00 g, 3.3 mmol) was treated with AlH_3 as described above for the cis compound. Isolation and recrystallization from benzene/hexane (1:3) gave 500 mg (53%) of the enamine: mp 113–114 °C; NMR δ 7.30 (m, 5 H), 5.97 (s, 1 H), 3.68 (m, 4 H), 2.42 (s, 3 H); ir 1671 cm^{-1}; MS *m/e* 285 (61), 122 (100), 42 (100). Anal. ($C_{18}H_{23}NO_3$): C, H, N.

The mother liquors were chromatographed (SiO_2, 2.5% concentrated NH_4OH/ethanol) to yield the enamine (65 mg), the cis ketal amine **52b** (90 mg), and the trans ketal amine **53b** (77 mg). An analytical sample of **53b** was prepared via sublimation (100 °C 0.07 mm): mp 121–123 °C; NMR 7.26 (m, 5 H), 3.3–4.0 (m, 4 H), 2.25 (s, 3 H), ir no C=O or C=CN; MS *m/e* 287 (49), 286 (33), 242 (63), 99 (23), 42 (100). Anal. ($C_{18}H_{25}NO_2$): C, H, N.

Trans ketal amine **53b** is obtainable from the enamine via catalytic reduction. The enamine (470 mg, 1.65 mmol), rhodium on alumina (130 mg of 5%), and CH_3OH (16.5 ml, anhydrous) were hydrogenated at an initial pressure of 60 psi of H_2. Shaking for 2 h, filtration, and evaporation gave 496 mg of an oil which crystallized on standing. GC (D) and TLC (B) showed it to be pure trans ketal amine **53b.**

***cis*-and *trans*-6-Oxo-2-methyl-4a-phenyldecahydroisoquinoline (52c and 53c). Trans.** The trans ketal amine **53b** (496 mg, 1.73 mmol) was dissolved in 1 N H_2SO_4 (10 ml) and placed for 22 h at 25 °C. Basification (20% NaOH) and extraction with $CHCl_3$ (3 × 15 ml) was followed by washing the organic phase with saturated NaCl, drying over Na_2SO_4, and evaporating to yield a solid (425 mg, 100%) which was homogenous by GC (D) and TLC (B): mp 115–118 °C; NMR δ 7.2–7.5 (m, 5 H), 2.33 (s, 3 H); ir 1712 cm^{-1}; MS *m/e* 243 (31), 242 (21), 43 (100). Anal. ($C_{16}H_{21}NO$): C, H, N.

Cis. In a manner exactly as above, cis ketal amine **52b** (530 mg, 1.85 mmol) was converted into the cis ketone amine **52c** (468 mg) as an oil[13] which was homogenous by GC (D) (R_t at 208 °C, 2.2 min for **53c** and 2.75 min for **52c**) and TLC (B): nmr δ 7.2–7.5 (m, 5 H), 2.33 (s, 3 H) (lit.[1d] 2.34); ir 1706, 762, 701 cm^{-1} (neat) (lit.[1d] 1703, 754, 695 neat); MS *m/e* 243 (57), 242 (43), 43 (100). Anal. ($C_{16}H_{21}NO$) C, H, N.

***cis*-and *trans*-2-Methyl-4a-phenyldecahydroisoquinolines (52d and 53d). Trans.** A solution containing $H_2NNH_2 \cdot H_2O$ (1.82 g, 36 mmol), KOH (0.2 g, 85%, 3.1 mmol) and the ketone **53c** (243 mg, 1 mmol) in diethylene glycol (3 ml, distilled) was refluxed for 1 h and then distilled until the distillate reached 175 °C; the solution was then refluxed an additional 1 h, cooled to 25 °C, diluted with H_2O (22 ml), and washed with ether (10-ml portions until GC (D) showed no remaining amine). The organic phase was washed with H_2O (2 × 25 ml) and saturated NaCl (25 ml), and dried with Na_2SO_4. Evaporation gave an oil (160 mg, 66%) which showed a single peak on GC (D) (R_t 1 min at 208 °C): NMR δ 7.1–7.6 (m, 5 H), 2.25 (s, 3 H); ir, no C=O; MS *m/e* 229 (56), 228 (71), 151 (71), 44 (100). Anal. ($C_{16}H_{23}N$): C, H, N.

A picrate was prepared, mp 218.5–220 °C (lit.[1a,d] mp 213–214 °C).

Cis. In a manner exactly as above the cis ketone **52c** (170 mg, 0.70 mmol) was converted to cis amine **52d** (130 mg, 82%): GC (D), R_t at 208 °C, 1.6 min; NMR δ 7.1–7.6 (m, 5 H), 2.25 (s, 3 H); ir, no C=O; MS *m/e* 229 (63), 228 (66), 151 (71), 43 (100). Anal. ($C_{16}H_{23}N$): C, H, N.

A picrate was prepared and recrystallized from ethanol, mp 144–146 °C (lit.[1d] mp 144–146 °C).

Acknowledgment. This research was supported in part by the National Institute on Drug Abuse.

References and Notes

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