3500, 1756, 1740, 1640 $cm^{-1}$; Raman (neat) 3565, 1775–1755, 1735, 1665 $cm^{-1}$; $^1H$ NMR $\delta$ 0.86 (12 H, d), 2.08 (6 H, s), 3.29 (1 H, s, exchangeable with $D_2O$), 3.44 (1 H, s), 4.76 (1 H, d, $J$ = 9 Hz), 5.05 (1 H, br q, $J$ = 1 Hz), 5.78 (1 H, br s); MS $m/e$ 378 ($M^+$, 0.001).

Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.79, H, 9.07.

**Evillosin Acetate (2).** A solution of 37.8 mg (0.1 mmol) of **1** in 0.5 mL of pyridine was treated with 0.2 mL of acetic anhydride. The mixture was stirred at 50 °C for 3 h and then at room temperature overnight. It was diluted with 25 mL of ice-cold water and extracted with ethyl acetate (2 × 25 mL). The extract was washed with 30 mL of ice-cold 0.1 N HCl followed by saturated brine (2 × 30 mL), dried ($MgSO_4$), and evaporated to give 39 mg of a gum, which was chromatographed on 50 g of neutral alumina (Woelm, Grade II, dry pack) with 50% ethyl acetate in hexane as eluent. Collection of the main band (ascertained by TLC using 50% ethyl acetate in hexane) and evaporation of the solvents gave a gum, which crystallized after 1 week. Trituration with hexane afforded 30 mg of **2** as colorless prisms: mp 133–135 °C; $[\alpha]^{25}_D$ +178.3 ($CHCl_3$, $c$ 1.04); UV (EtOH) 209 nm ($\epsilon$ 15 000); IR 1755, 1740, 1725, 1640 $cm^{-1}$; $^1H$ NMR $\delta$ 0.78 (3 H, s), 0.90 (9 H, s), 2.0 (3 H, s), 2.09 (6 H, s), 4.65 (1 H, t, $J$ = 2 Hz), 4.75 (1 H, d, $J$ = 7 Hz), 5.05 (1 H, q, $J$ = 1 Hz), 5.77 (1 H, s); MS $m/e$ 360 ($M - CH_3CO_2H$, 0.5), the molecular ion was not observed.

Anal. Calcd for $C_{24}H_{36}O_6$: C, 68.55; H, 8.63. Found: C, 68.53; H, 8.60.

**3-Ketoevillosin (3).** A stirred solution of 94.5 mg (0.25 mmol) of **1** in 3.0 mL of acetone was oxidized with 0.1 mL of Jones reagent[5] during 5 min at room temperature. Isolation with ether in the usual manner gave 90 mg of a gum, which was subjected to preparative-scale TLC (silica gel, 70% ethyl acetate in hexane) to remove a slightly less polar substance, and afforded 75 mg of **3**. This solidified under high vacuum overnight: mp 65–70 °C; $[\alpha]^{25}_D$ +165.4 ($CHCl_3$, $c$ 1.0); UV 209 nm ($\epsilon$ 14 800); ORD (EtOH) $[\Phi]_{315}$ +4295; CD (EtOH) $[\theta]_{295}$ +3285, $[\theta]_{215}$ −3782; IR 1755, 1730, 1710, 1640 $cm^{-1}$; $^1H$ NMR $\delta$ 0.93 (3 H, d, $J$ = 5 Hz), 1.04 (6, H, s), 1.10 (3 H, s), 2.08 (3 H, s), 2.12 (3 H, d, $J$ = 1 Hz), 4.71 (1 H, d, $J$ = 5 Hz), 5.08 (1 H, s), 5.80 (1 H, s); $^1H$ NMR ($C_6D_6$) $\delta$ 0.66 (3 H, s), 0.80 (3 H, s), 0.82 (3 H, s), 1.02 (3 H, d, $J$ = 6 Hz), 1.35 (3 H, d, $J$ = 1 Hz), 1.73 (3 H, s), 4.13 (1 H, d, $J$ = 7 Hz), 5.00 (1 H, q, $J$ = 2 Hz), 5.22 (1 H, br s); MS $m/e$ 376 ($M^+$, 2).

Anal. Calcd for $C_{22}H_{32}O_5$: C, 70.21; H, 8.25. Found: C, 70.31; H, 8.14.

**X-ray Crystallographic Analysis of Evillosin (1).** Evillosin belongs to space group $P2_12_12_1$, with $a$ = 1.019 (1) Å, $b$ = 10.738 (1) Å, $c$ = 19.517 (2) Å, $Z$ = 4, $d_{calcd}$ = 1.197g $cm^{-3}$, $\mu$(Cu K$\alpha$) = 6.8 $cm^{-1}$. The intensity data, uncorrected for absorption, were measured on a fully automated Hilger-Watts diffractometer (Ni filtered Cu K$\alpha$ radiation, $\theta$–2$\theta$ scans, pulse height discrimination) using a crystal of approximately 0.10 × 0.12 × 0.55 mm that was grown from ethyl acetate. Of 1637 independent reflections for $\theta < 57°$, 1496 were considered to be observed [$I > 2.5\sigma(I)$]. The structure and relative stereochemistry of **1** was solved by a multiple solution procedure[9] and was refined by full matrix least squares. In the final refinement, anisotropic thermal parameters and isotropic temperature factors were used for non-hydrogen and hydrogen atoms, respectively. The hydrogens were included in the structure factor calculations but their parameters were not refined. The final discrepancy indices were $R$ = 0.042 and $R_w$ = 0.048 for the 1496 observed reflections. The final difference map had no peaks greater than ±0.2 e $A^{-3}$. Listings of final atomic parameters, final anisotropic thermal parameters, bond lengths, bond angles, and torsion angles are given in Tables II–VI as Supplementary Material.

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**Supplementary Material Available:** Listings of final atomic parameters, final anisotropic thermal parameters, bond lengths, bond angles, and torsion angles for **1** are given in Tables II–VI (7 pages). Ordering information is given on any current masthead page.

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# 6,7-Benzomorphans. Stereospecific Synthesis of 2,9α- and 2,9β-Dimethyl-2'-methoxy-6,7-benzomorphans

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2,9α- and 2,9β-dimethyl-2'-methoxy-6,7-benzomorphans have been synthesized from *m*-methoxybenzaldehyde by a process involving the methylene lactam rearrangement of substituted nipecotic acids. Stereospecific hydrogenation of the intermediate 1-methyl-3-methylene-4-(3-methoxyphenyl)-2-piperidone gave the *cis*-3-methyl derivative. This was followed by replacement of the amide oxygen by a cyano group, a transformation effected by partial reduction to an iminium salt and nucleophilic attack by cyanide ion. Either 3-methyl isomer could be obtained stereospecifically by control of the latter process. The synthesis was completed by conversion of the cyano group to methyl ketone, acid-catalyzed ring closure into the aryl nucleus, oxidation of the resulting exo methylene to carbonyl, and reduction/hydrogenolysis to the final methoxy-6,7-benzomorphans, which were also cleaved to the corresponding phenols.

The 6,7-benzomorphans are of interest since as a class they show separation of the analgesic properties and adverse side effects characteristic of opiates.[1] In addition to the usual structure–activity relationships, the analgesic activity of the 6,7-benzomorphans depends on the stereochemistry at C-9 and to a lesser degree on the nature of the substituents at C-5

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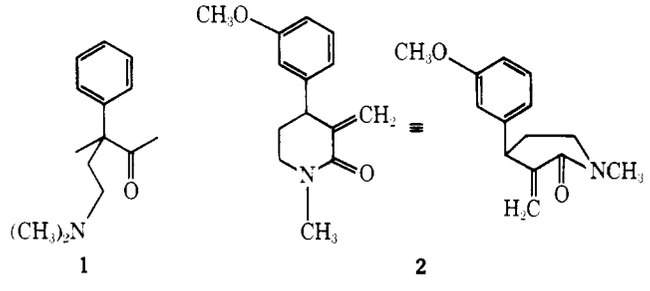
and C-9.[1] Thus, to be useful, syntheses of these materials should allow for control of both parameters.

Existing 6,7-benzomorphan syntheses[2] primarily utilize 2-benzyltetrahydropyridine intermediates which are cyclized under strong acid conditions, or similar piperidinol cyclization, or proceed via a tetralone intermediate. In principle, acid-catalyzed cyclization allows the preparation of virtually any 5,9-dialkyl- or 5-aryl-9-alkyl-6,7-benzomorphan, the limiting factor being the required 3,4-disubstituted pyridine. Benzomorphans bearing hydrogen at C-5 and a substituent at C-9 are not accessible via this acid cyclization. The more active $\beta$-isomers are produced in only minor amounts, although certain 5,9$\beta$-dialkyl-6,7-benzomorphans have been prepared in somewhat better yields, and recently contamination by the positional $\gamma$-isomer has been detected.[3] 6,7-Benzomorphans substituted at C-5 or C-9 may be prepared via the tetralone route, but this route is not amenable to compounds substituted at both C-5 and C-9 since the intermediate amino ketone 1 is unreactive with malonate derivatives. However, an alternative tetralone route to a 9-oxo-6,7-benzomorphan allows access to a mixture of 9$\alpha$ and 9$\beta$ isomers. All of these processes suffer some flaw such as low yields, isomeric mixtures, limited scope, or lack of potential for chirally specific synthesis.

Recently, interest has greatly increased in the parent 6,7-benzomorphan ring system lacking the quaternary center at C-5, long thought necessary for activity, as well as in benzomorphans bearing only methyl at C-9 because of their strong analgesic properties and absence of physical dependence capacity in monkeys.[4-6] Both isomeric 9-methyl-6,7-benzomorphans have been synthesized, but in poor yield, via a tetralone route[5,6] after an alternative approach from 1,3-dimethyl-2-carboxy-4-phenylpyridine failed.[7]

Our interest in 6,7-benzomorphan synthesis arose from the possibility of converting the readily available methylene lactam 2, an intermediate in the synthesis of 4a-aryldecahydroisoquinolines,[8] into 6,7-benzomorphans 3 and 4 and from



1 2

3, R = $CH_3$; R′ = H
4, R = H; R′ = $CH_3$

the potential for developing this approach into a general preparation from a common intermediate of 6,7-benzomorphans bearing heretofore unavailable and highly functionalized substituents at C-5 and C-9. Our initial efforts deal with both the method of introduction of the necessary C-8 bridging carbon and control of stereochemistry at C-9.

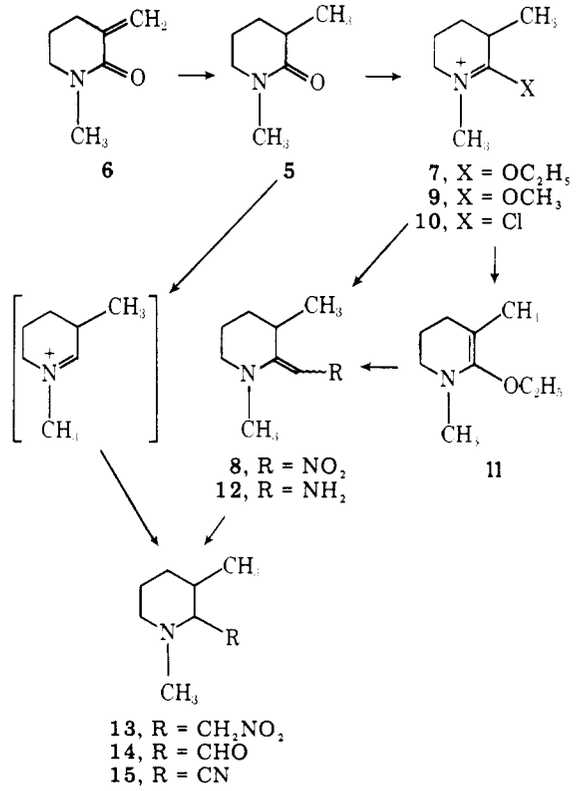
The C-8 carbon might be introduced in either of two ways: substitution of the aromatic ring or replacement of the amide oxygen. The desire for a common intermediate to both the 6,7-benzomorphans and the 4a-aryldecahydroisoquinolines and the problems associated with selective aromatic ortho functionalization or maintainence thereof throughout the synthesis of 2 dictated that functionalization of the amide followed by ring closure was the preferred route. Also, the stereochemistry at C-9 should be controllable via the amide carbonyl. Thus, hydrogenation of methylene lactam 2 was expected to give predominantly the cis isomer which would be epimerized to the more stable trans product, affording both $\alpha$ and $\beta$ isomers of the 9-methyl-6,7-benzomorphan after amide functionalization and ring closure.

**Introduction of C-8.** We envisaged replacement of the amide carbonyl by a functionalized single carbon moiety as proceeding via one of four pathways: (a) direct addition to the amide, (b) nucleophilic attack on some activated form of the amide, (c) partial reduction to iminium salt followed by addition of a suitable nucleophile, or (d) ring opening to amine and $\alpha,\beta$-unsaturated carboxylic acid followed, after appropriate functional group transformation, by reclosure of the piperidine ring. Approaches b and c held the most promise. The most direct, method a, involved addition of organometallics to N-substituted lactams and has afforded only low yields of 2,2-disubstituted or 2-substituted-$\Delta^2$-cyclic amines,[9] while approach d would require hydrolysis, protection–deprotection, and ring closure steps in addition to appropriate elaboration of the carboxylic acid.

Amides may be activated by conversion to the corresponding imidates,[10] imido halides,[11] or tautomeric $\alpha$-haloenamines,[12] amide acetals,[13] and *N*-acylamides,[14] which react with a variety of nucleophiles, in many cases affording good yields under mild conditions. Partial reduction of amides to aminols appears especially facile for N-substituted lactams,[14] and nucleophilic attack on the resulting iminium salts proceeds well. The easily accessible 1,3-dimethyl-2-piperidone (5) was selected as a model compound for initial evaluation of these possibilities.

Our first objectives were to prepare the versatile intermediates nitro olefin 8 and nitrile 15 (Scheme I). Hydrogenation of methylene lactam 6[16] afforded a 96% yield of piperidone 5, which was converted in quantitative yield to imidates 7 and 9 with the corresponding trialkyloxonium tetrafluoroborate.

**Scheme I. Replacement of Amide Carbonyl with Functionalized Single Carbon Fragment**



6 5 7, X = $OC_2H_5$
9, X = $OCH_3$
10, X = Cl

8, R = $NO_2$
12, R = $NH_2$

11

13, R = $CH_2NO_2$
14, R = CHO
15, R = CN

Ethyl imidate **7** in nitromethane containing triethylamine gave slow formation of the expected nitro olefin **8**, whereas $BF_3$·$Et_2O$ catalysis gave no reaction. Methyl imidate **9** displayed the same reactivity, but at reflux with $NaCH_2NO_2$ in methanol it gave a 1:1 mixture of amide **5** and nitro olefin **8**. Increasing the amount of $NaCH_2NO_2$ resulted in a quantitative reconversion to amide **5**. Treatment of the imido chloride **10**, formed quantitatively from **5** with $POCl_3$ in benzene, with $CH_3NO_2$ gave only tars. The tautomeric α-chloroenamine was examined briefly in a similar system but gave no useful products. Attempted addition of cyanide to imidate **9** in methanol or in $Me_2SO$ required prolonged reaction times and afforded a mixture of products.

Attempts to convert imidate **7** to amide acetal with $EtO^-$/EtOH[17] gave instead a mixture of *O,N*-ketene acetal **11** and amide **5** in a 4:1 ratio; use of methyl imidate **9** with $CH_3O^-$/$CH_3OH$ was less successful. The *O,N*-ketene acetals should react similarly to amide acetals, and this was the case; *O,N*-ketene acetal **11** reacted quantitatively with nitromethane to give nitro olefin **8**. On a preparative scale, **8** was conveniently prepared from imidate **7** without isolation of intermediate ketene acetal **11** and a 78% overall yield of crystalline **8** was obtained from **5**.

Nitro olefin **8** provided several options for conversion to derivatives suitable for ring closure. Although selective reduction of **8** to vinylamine **12** was attractive (since simple hydrolysis would give aldehyde **14**), no precedent for such a reduction was found. Nitro olefins are reduced catalytically to nitro alkanes[18] and oximes[19] and further to saturated amines,[20] but when **8** was hydrogenated over either Pd/C or $PtO_2$, no selectivity was observed and no nitro alkane **13** resulted. Most effectively, nitro olefin **8** was reduced to **13** in 85% yield using $NaBH_4$ in ethanol.[21] Attempts to convert nitro alkane **13** to aldehyde **14** failed under classical[22] and recently modified[23] Nef conditions, as did reduction of both nitro alkane **13** and its nitronate salt with $TiCl_3$; however, reduction of **13**·HCl at pH 1 did give aldehyde **14**, but only in 35% yield.[24] Functionalization of the amide carbonyl of **5** via the iminium salt was next examined. Controlled reduction with $LiAlH_4$[15a] followed by aqueous KCN gave nitrile **15** and unreacted **5** in a 5:2 ratio, but the more selective reducing agent $LiAl(OEt)_3H$[15c] followed by cyanation afforded nitrile **15** in 80% yield.

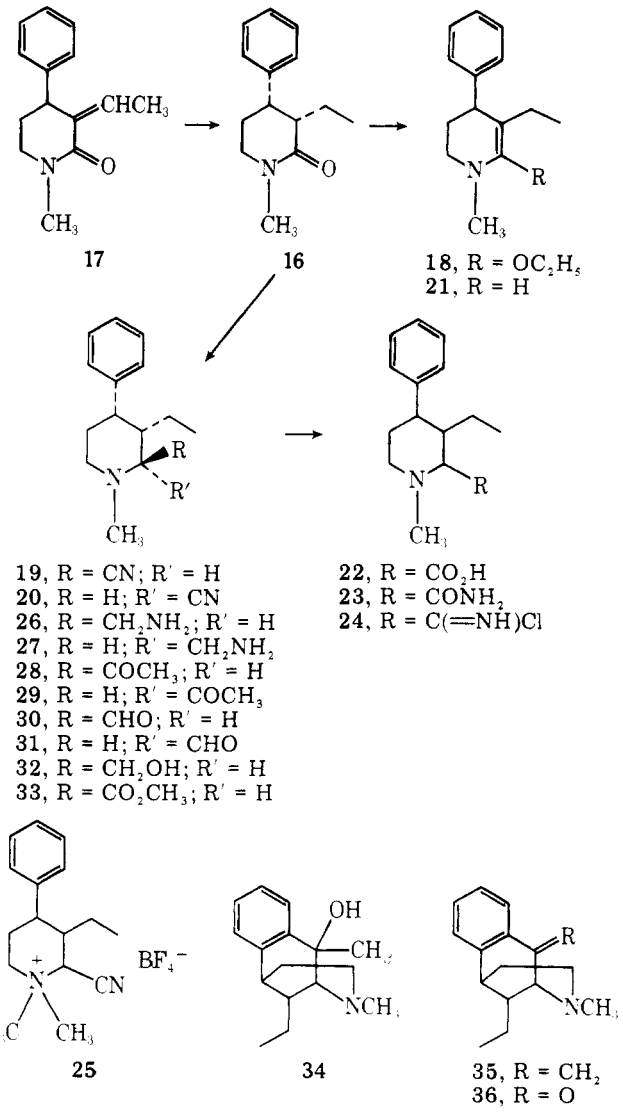
With two potentially useful methods of replacing the amide oxygen in hand, that is, replacement by a nitromethane residue or a cyano group, we extended our model studies to the more interesting, readily available lactam **16**, which would test the effect of the aromatic nucleus and steric factors.

Hydrogenation of ethylidene lactam **17**[25] (Scheme II) afforded a 95% yield of ethylpiperidone **16**, which NMR, TLC, and GC showed to be only the cis isomer. Treatment of **16** with triethyloxonium tetrafluoroborate gave a quantitative yield of imidate, but subsequent treatment with ethoxide regenerated mainly **16** with a maximum of 25% of the desired *O,N*-ketene acetal **18**. Addition of $CH_3NO_2$ to **18** resulted mainly in regenerated amide **16**, the desired nitro olefin being obtained in only 10% yield. Application of the iminium salt approach to lactam **16** was more successful. Reduction with $LiAl(OEt)_3H$[15c] followed by cyanation afforded an 89% yield of a single isomer, nitrile **19**. The C-2 proton of **19** was easily distinguishable in the NMR and showed a coupling constant of 1 Hz. Epimerization of nitrile **19** takes place quantitatively over IRA-400 ($OH^-$) in methanol to afford the isomeric nitrile **20**, which exhibits a C-2 proton coupling constant of 3 Hz. This would be consistent with the expected cis relationship between the C-3 ethyl and C-4 phenyl groups and epimerization of an axial to an equatorial cyano function.

In addition to the potential for ring closure via the nitrile group, **20** was expected to allow access to a variety of functionalities which also might be useful for ring closure, such as $CO_2H$, $CONR_2$, CHO, $COCH_3$, $CH_2OH$, and $CH_2X$. Unfortunately, simple hydrolytic conditions failed to afford the desired amino acid, proving to be either too mild, returning starting material, or causing elimination to enamine **21**. This failure prompted an extensive investigation of the conversion of nitriles **19** and **20** into the corresponding amino acids. Although many hydrolytic methods are reported for α-aminonitriles or hindered nitriles, we found no useful conditions. Treatment of nitrile **19** with peroxide and alkali[26] gave rapid epimerization to **20**, followed by slow conversion to a mixture of nitrile **20** and amide **23** in 30% yield, identical with the product obtained in low yield on LiOH hydrolysis of **19**. Transition metal complexes have been used extensively to catalyze hydrolysis of amino esters,[27] aminoamides,[28] aminonitriles,[29] and nitriles,[30,31] although none have been reported specifically for an α-tertiary aminonitrile. We found that both $CuCl_2$ and $NiCl_2$ formed complexes[32] with nitrile **19**, and a product was isolated from the reaction with $CuCl_2$/$CH_3OH$ in 70% yield for which qualitative data support structure **24**. However, further investigation of this reaction was abandoned when yields plummeted on a larger scale. Attempted nitrilium salt[33] formation from nitrile **20** with trimethyloxonium tetrafluoroborate gave only the quaternary salt **25** in methylene chloride and no reaction in trifluoroacetic acid. Conversion to the corresponding thioamide, which might be hydrolyzed to the carboxylic acid, also failed.

Unable to find a high-yield process for the conversion of

Scheme II



nitriles **19** and **20** to a carboxylic acid derivative, we next investigated the transformation of these nitriles to other possible candidates for ring closure. Although α-aminonitriles are reported to be hydrogenated in moderate yields,[34] no reaction was observed with nitrile **19**. Metal hydride reduction gives some displacement of cyanide in α-tertiary aminonitriles[35] and in some secondary α-aminonitriles,[36a] but the normal reaction is reduction to the aminomethyl compound.[35,36b] When applied to nitriles **19** and **20**, lithium aluminum hydride gave the corresponding diamines **26** and **27** in 75 and 97% yields, respectively. Similarly, organometallic reagents with α-aminonitriles give various products,[37] but alkyllithium reagents are reported to add only to the C–N triple bond[36b] to give the amino ketones. Thus, by reaction with methyllithium, the two isomeric ketones **28** and **29** were prepared in 63 and 88% yields, respectively.

Reduction of nitrile **19** with $LiAl(OEt)_3H$[15c] gave 30% conversion to aldehyde **30** along with 60% of recovered nitrile **19**. Since this reagent is reported[38] to consist of approximately a 60:40 mixture of $LiAl(OEt)_3H$ and $LiAl(OEt)_2H_2$, it appeared that only $LiAl(OEt)_2H_2$ was reacting. Accordingly, **19** was treated with $LiAl(OEt)_2H_2$,[15c] and the yield of aldehyde **30** increased to 76%. Interestingly, $LiAl(OEt)_2H_2$ was unreactive toward epimeric nitrile **20**, as were both $LiAl(n\text{-}BuO)_3H$[15c] and diisobutylaluminum hydride toward nitrile **19**. Attempted epimerization of aldehyde **30** with alkali gave polymers, with aldehyde **31** being consumed faster than **30**. Alcohol **32** was obtained in good yield from aldehyde **30** by reduction with sodium borohydride.

The alternative pathway to amino acid derivative **22** involving oxidation of aminoaldehyde **30** was also examined. Treatment of **30** with $Ag_2O$ in aqueous ethanolic KOH at room temperature followed by esterification with $CH_3OH/H_2SO_4$ gave not ester, but enamine **21** in 65% yield. Oxidation employing Jones reagent afforded the desired methyl ester **33** in 20% yield after Fischer esterification.

**Ring Closure.** From the exhaustive model studies with 1,3-dimethyl-2-piperidone (**5**) and 3-ethyl-1-methyl-4-phenyl-2-piperidone (**16**), we had developed a number of high-yield processes for replacing the amide oxygen with a single carbon functionality potentially capable of ring closure into an aromatic nucleus. In particular, nitriles **19** and **20**, as well as their amine and carbonyl derivatives, were attractive candidates. Related ring closures to form the benzomorphan nucleus have been reported with 2-carboxy-1-methyl-4-phenylpiperidine[4] and 2-(chloromethyl)-1-methyl-4-phenylpiperidine.[39]

Direct ring closure of the nitriles was explored first since the Houben–Hoesch reaction of α-aminonitriles has been reported to proceed under mild conditions,[40] including an intramolecular example with an α-aminonitrile.[41] Treatment of aminonitrile **19** in nitrobenzene with $AlCl_3$ followed by saturation with HCl gave only enamine **21** at room temperature. Similar behavior was noted for the isomeric aminonitrile **20**, although elimination was much slower. The same results were obtained with $AlBr_3/HBr$. Elimination of the α-cyano group to form iminium salt might be circumvented either by converting it to an amine or carbonyl derivative or by substituting an acyl group for the alkyl group on nitrogen. The former approach was investigated with ketone **29**; alternatively, amine **27** might undergo ring closure on diazotization or afford the corresponding alcohol which would undergo ring closure on tosylation and solvolysis.

All attempts at diazotization followed by solvolysis gave only starting material and several minor components. Nitrosation of the corresponding acetamide with $NaNO_2/HOAc/Ac_2O$[42] gave an unstable compound which contained no $N\text{–}CH_3$ group, N-demethylation apparently having resulted.[43] We next turned to intramolecular alkylation with amino ketone **29** using various Friedel–Crafts conditions. At 100 °C, $HCl/AlCl_3$ gave very slow reaction to a new product, tentatively identified as benzomorphan alcohol **34**. Changing to the more reactive system of $HBr/AlBr_3$ in *o*-dichlorobenzene gave clean conversion to methylenebenzomorphan **35** in 60% yield. Ozonolysis of the double bond in **35** to give oxobenzomorphan **36** was attempted at −78 °C in methanol. With 125 mol % of $O_3$ only 30% conversion was obtained, while increasing the $O_3$ stoichiometry led to a substantial amount of oxobenzomorphan **36** *N*-oxide.[44] Finally, ozonolysis of **35** as the hydrochloride afforded a 70% yield of ketone **36**.

At this point we had developed an effective method for forming the benzomorphan nucleus. Since compounds bearing a methoxy group at C-2′ would be of greater pharmacological interest, all further development was carried out not only on compounds satisfying this criterion but directed at stereospecifically synthesizing 2,9α- and 2,9β-dimethyl-2′-methoxy-6,7-benzomorphan. Accordingly, subsequent work utilized the readily available methylene lactam **2** as starting material.

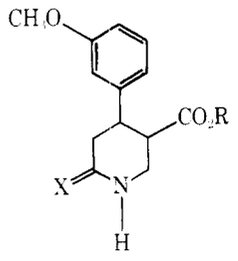
**Preparation of 6,7-Benzomorphans 3 and 4.** Methylene lactam **2** was prepared as previously described,[8] except that the intermediate ethyl *m*-methoxycinnamate was formed directly by condensation of *m*-methoxybenzaldehyde with ethyl hydrogen malonate. Improvement also was attempted in the 61% yield conversion of amide ester **37** to amino ester **38** (Chart I), the poorest step in the sequence.

Reduction of an amide in the presence of an ester is a recurring synthetic problem. Selective reductions have been reported with $Et_3OBF_4/NaBH_4$,[45] $POCl_3/NaBH_4$,[46] $PCl_5/NaBH_4$,[47] diborane,[48] $P_2S_5/RaNi$,[49] $Na/BuOH$,[50] and diborane reduction of the pentachlorophenylate.[51] The first three methods gave yields much inferior to that previously obtained. Amido ester **37** was quantitatively converted to thioamide **39** with $P_2S_5$, but RaNi desulfurization afforded maximally 40% of amino ester **38**. Reduction of amido ester **37** with 200 mol % $BH_3$/THF afforded a 73% yield of a 3:1 mixture of **38** and the over-reduced product amino alcohol **40** and 11% unreacted **37**. Decreasing the molar ratio to 150 mol % $BH_3$ improved the ratio of **38**/**40** to 83:17 (71% yield), but afforded 14% recovered **37**.

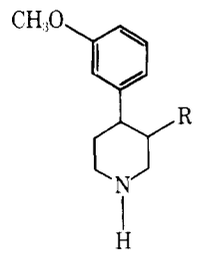
Since the rate of reduction of the ester and amide functionalities did not differ sufficiently to be useful, selective reduction of the amide moiety in the amide carboxylic acid salt was investigated. The report[52] that, relative to amides, carboxylate salts are reduced slowly led to the attractive proposal that **37** might be hydrolyzed, the carboxylate salt treated with diborane, and the resulting borane–amino acid complex decomposed in ethanolic HCl with concomitant esterification to give amino ester **38**. Accordingly, ester **37** was hydrolyzed to amide acid **41**, but since both the $Na^+$ and $Li^+$ salts were insoluble in the normal solvents utilized in diborane reductions the tetra-*n*-butylammonium salt in THF was subjected to the reduction. Again complete consumption of starting material could not be effected without generation of unacceptable amounts of the over-reduction product **40**.

At this point neither the conversion of **37** to **38** by thioamide formation/desulfurization nor diborane reduction of either amide ester **37** or a carboxylate salt can compete with the convenience, the improved 75% yields, or the product purity (98%) now realized by the $Me_3OBF_4/NaBH_4$ reduction.[8,53] Thus, methylene lactam **2** was available in 55% overall yield from *m*-methoxybenzaldehyde. It was hydrogenated over 10% Pd/C in ethanol to a 90:10 mixture of isomeric amides **42** and **43** as determined by NMR and GC of the derived amines **44** and **45** obtained on reduction with $LiAlH_4$. That the cis isomer was formed preferentially on hydrogenation was confirmed when equilibration in ethanolic KOH at reflux gave an 18:82 mixture of **42** and the thermodynamically more favored trans

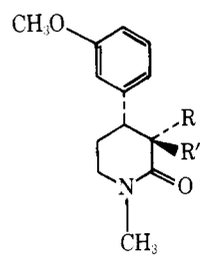
Chart I



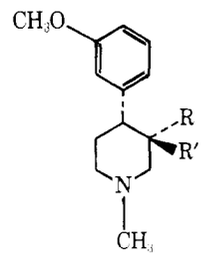
37, X = O; R = $C_2H_5$
39, X = S; R = $C_2H_5$
41, X = O; R = H



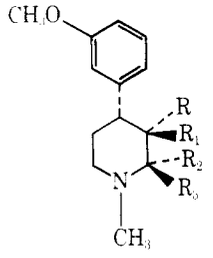
38, R = $CO_2C_2H_5$
40, R = $CH_2OH$



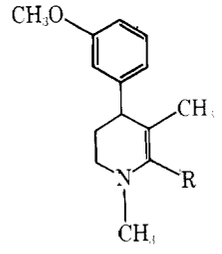
42, R = $CH_3$; R′ = H
43, R = H; R′ = $CH_3$



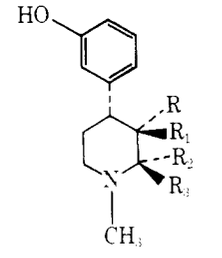
44, R = $CH_3$; R′ = H
45, R = H; R′ = $CH_3$



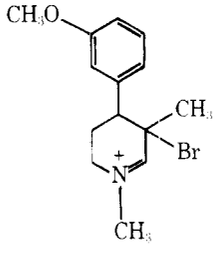
47, R = H; $R_1$ = $CH_3$; $R_2$ = CN; $R_3$ = H
48, R = H; $R_1$ = $CH_3$; $R_2$ = $COCH_3$; $R_3$ = H
51, R = H; $R_1$ = $CH_3$; $R_2$ = H; $R_3$ = $COCH_3$
52, R = H; $R_1$ = $CH_3$; $R_2$ = H; $R_3$ = C(=NH)$CH_3$
66, R = $CH_3$; $R_1$ = H; $R_2$ = CN; $R_3$ = H
67, R = $CH_3$; $R_1$ = H; $R_2$ = H; $R_3$ = CN
68, R = H; $R_1$ = $CH_3$; $R_2$ = H; $R_3$ = CN
69, R = $CH_3$; $R_1$ = H; $R_2$ = H; $R_3$ = $COCH_3$
71, R = $CH_3$; $R_1$ = H; $R_2$ = $COCH_3$; $R_3$ = H
77, R = H; $R_1$ = $CH_3$; $R_2$ = $CH_2NH_2$; $R_3$ = H



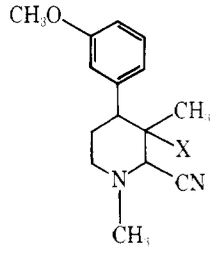
46, R = H
54, R = CN
58, R = CHO
59, R = $COCH_3$
60, R = $CH_3$



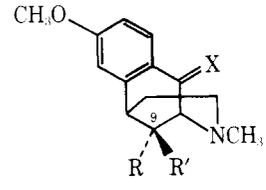
49, R, $R_3$ = H; $R_1$ = $CH_3$; $R_2$ = $COCH_3$
76, R, $R_2$ = H; $R_1$ = $CH_3$; $R_3$ = $COCH_3$



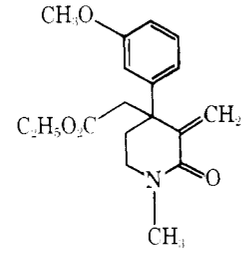
55



56, X = Br
57, X = I



50, R = H; R′ = $CH_3$; X = $CH_2$
53, R = H; R′ = $CH_3$; X = O
70, R = $CH_3$; R′ = H; X = $CH_2$
72, R = $CH_3$; R′ = H; X = O
73, R = $CH_3$; R′ = H; X = CHBr
74, R = $CH_3$; R′ = H; X = H, OH



75

isomer **43**.

The partial reduction and cyanation of amide **42** were most conveniently carried out by isolating the intermediate enamine **46**. Reduction of **42** with DIBAL/$Et_2O$ afforded a 57:43 mixture of the desired enamine **46** and the over-reduction product amine **44**, while $LiAl(OEt)_2H_2$ gave a 99% yield of only enamine **46**. Cyanation then of **46** in aqueous methanolic KCN afforded a mixture of aminonitrile isomers. Treatment of this isomer mix with aqueous methanolic NaOH gave total conversion to the more stable aminonitrile isomer, which on the basis of the NMR of the derived benzomorphan was assigned structure **47**.

Nitrile **47** was then elaborated into benzomorphan via the pathway developed in the model system. Inverse addition of **47** to $CH_3Li/Et_2O$ afforded excellent yields of ketone **48**. Cyclization of ketone **48** was first attempted with $AlBr_3$/*o*-dichlorobenzene, but only traces of cyclized product were obtained, the major product being phenol **49**. To avoid demethylation, cyclization was attempted employing acids with relatively nonnucleophilic anions. Treatment with $BF_3$·$Et_2O$ gave a 58% yield of methylenebenzomorphan **50** and 24% of epimeric ketone **51**. As expected, no significant amount of the endo isomer,[54] products isomeric at C-9, or the product arising from ring closure ortho to the methoxy group was detected. Extended reaction times, higher temperatures, and varying amounts of $BF_3$·$Et_2O$ catalyst had no significant effect on the product/starting material epimer distribution. Ketone epimer **51** also underwent ring closure, but again the reaction could not be driven beyond 70% completion; this problem was effectively remedied by simply resubmitting the crude reaction mixture to the reaction conditions.

Until the preparation of methylenebenzomorphan **50**, no definitive statement could be made concerning the stereochemistry of the protonation of enamine **46**. The $\alpha$ and $\beta$ C-9 methyl groups in benzomorphans are reported to show doublets at about $\delta$ 0.8 and 1.3, respectively, in the NMR.[55] Benzomorphan **50** exhibited a C-9 methyl group doublet at $\delta$ 1.37, confirming a $\beta$ isomer and indicating that, contrary to expectation, protonation of enamine **46** was taking place entirely on the side bearing the phenyl ring.

Although some oxidative N-demethylation had been encountered previously, ozonolysis of **50** in aqueous methanolic $H_2SO_4$ at −78 °C gave quantitative conversion to the known oxobenzomorphan **53**. Hydrogenation then afforded 9$\beta$-methylbenzomorphan **4**.[6] The physical properties of **53**·HCl and **4**·oxalate are in agreement with published values for these compounds.[6]

Since protonation of enamine **46** had apparently taken place entirely from the side bearing the phenyl ring, a different approach to the benzomorphan $\alpha$-isomer was necessary. Introduction of C-2,3 unsaturation in nitrile **47** followed by hydrogenation was expected to provide the required all-cis

precursor to **3**. The plausibility of this approach was demonstrated when hydrogenation of enamine **46**, as a model, over 5% $Pd/BaCO_3$ afforded an 89:11 ratio of *cis*- and *trans*-amines **44** and **45**.

Cyanoenamine **54** was prepared by titration of enamine **46** with $Br_2$,[56] cyanation of the intermediate bromoiminium salt **55** with aqueous methanolic KCN, and dehydrobromination of the resulting $\beta$-halonitrile **56**. Cyanoenamine **54** was thus obtained in 82% overall yield from **46**. Alternatively, **54** could be prepared by treatment of **46** with $ICN/CHCl_3$[57] to form iodonitrile **57** followed by $\beta$-elimination with aqueous methanolic NaOH.

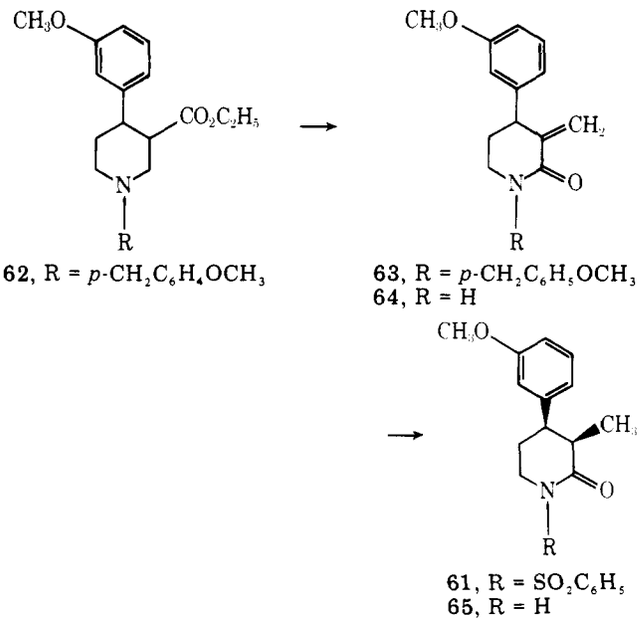
Cyanoenamine **54** proved very resistant to catalytic hydrogenation, showing no reactivity over either palladium or platinum under a variety of conditions. Hydrogenation in the presence of strong acid gave hydrolysis instead to a mixture of amides **42** and **43**. Attempted reduction of **54** to aldehyde **58** with DIBAL gave complete decomposition, while $LiAlH_2(OEt)_2$ afforded only a 23% yield of aldehyde. Conversion to the $\alpha,\beta$-unsaturated ketone with $CH_3Li$ is reported for cyanoenamines;[12] however, when applied to **54**, two products were obtained in an 8:2 ratio. The minor product appeared to be the desired unsaturated ketone **59**, but could not be separated from the major component, which NMR indicated had no unsaturation and exhibited a high field doublet at $\delta$ 0.42. Hydrolysis of **54** as well as reduction with $LiAlH_4$ to the $\alpha$-(aminomethyl) enamine[12] also failed.

This lack of success in the conversion of **54** to some useful derivative led us to investigate the preparation of $\alpha$-functionally substituted enamines by addition of an organometallic reagent to amide **42**, in spite of literature indicating that yields in such conversions were poor.[9] Probing experiments with $CH_3MgI$ and $CH_3Li$ as model nucleophiles were promising. With *cis*-amide **42**, $CH_3Li$ or $CH_3MgI$ gave quantitative conversion to methylenamine **60**, while the *trans*-amide **43** was unreactive. Of the functionalized one-carbon organometallic reagents available, the acyl anion equivalents or potential acyl anion equivalents such as the anions of ethyl vinyl ether,[58] 1,3-dithiane,[59] chloroform,[60] methylene chloride,[60] *N,N*-dimethylthioformamide,[61] $CH_3OCH_2Cl$,[62] $CH_3SCH_3$,[63] and $CH_3SOCH_3$ were the most appropriate for the conversion of **42** into the desirable 2-substituted enamine where the substituent is some carbonyl moiety. However, with the exception of $LiCCl_3$ and $LiCH_2SCH_3$, which gave low yields of the anticipated addition products, these reagents returned starting material, partially epimerized at C-3, and/or multiple unidentified products. Addition to the alternative substrate, bromoiminium salt **55**, was also investigated with the same organometallic reagents, as well as with $NaCH_2NO_2$, but no useful product was obtained. Attempted conversion of $\alpha$-halonitriles **56** and **57** to the corresponding unsaturated ketones with $CH_3Li$ also failed.

There remained yet another method of converting an amide oxygen into a single carbon functionality suitable for ring closure. If an amide is converted to a sulfonylimide, the electron pair on nitrogen is delocalized into the sulfonyl group, rendering the amide carbonyl more ketonic in nature. Thus, many of the standard ketone homologation reactions should be applicable to a sulfonylimide. The only reactions of sulfonyl lactams reported are Wittig reactions;[64] however, several ketonic reactions are known for the analogous carbonylimides.

Sulfonylimide **61** was prepared as shown in Scheme III.[65] *p*-Methoxybenzylation of amino ester **38** gave an 83% yield of amine **62**, which was hydrolyzed and rearranged in acetic anhydride to afford methylene lactam **63** in 52% yield. Deprotection of **63** in refluxing $CF_3CO_2H$ afforded methyleneamide **64**, and subsequent hydrogenation gave amide **65** in quantitative yield. N-benzenesulfonation was effected by

Scheme III. Preparation of Sulfonylimide




**62**, R = *p*-$CH_2C_6H_4OCH_3$

**63**, R = *p*-$CH_2C_6H_5OCH_3$
**64**, R = H

**61**, R = $SO_2C_6H_5$
**65**, R = H

preformation of the anion in THF with *t*-BuLi at −78 °C followed by quenching with benzenesulfonyl chloride. Anion formation in benzene solvent as reported for the preparation of *N*-triflylamides[66] gave much inferior yields.

Reaction of sulfonylimide **61** with triphenylmethylenephosphorane under a variety of conditions afforded only low mass recoveries and multiple products. With $CH_3MgI$ or $CH_3Li$, **61** gave mixtures containing epimeric alcohols, $\Delta^2$-1-(benzenesulfonyl)-2,3-dimethylpiperidine, and ring-opened products. Clearly, none of the many alternatives offered as much promise as the nitriles, to which we returned.

Since a 90:10 ratio of *cis*-/*trans*-amides **42** and **43** could be generated conveniently by hydrogenation of methylene lactam **2** and since protonation of enamine **46** on cyanation appeared to take place on the same side as the phenyl ring, the most efficient way of producing the desired "*cis*"-aminonitrile **66** would be reduction of amide **42** to aminol and cyanation without going through the intermediate enamine. Accordingly, to circumvent the formation of enamine **46**, the ethereal $LiAlH_2(OEt)_2$ reduction solution was added to 3 N $H_2SO_4$ containing 1000 mol % KCN, affording aminonitrile **67**. DIBAL hydrogenolysis of **67** to the *cis*-amine **44** confirmed the cis relationship between the C-3 methyl and C-4 aryl groups in aminonitrile **67**. Attempted epimerization of **67** to **66** gave not **66** but quantitative conversion to aminonitrile **47**. Thus, the epimerization of the aminonitrile mixture obtained on cyanation of enamine **46** had not been an epimerization of **68** to **47**, as originally thought, but an equilibrium process in which **67** was being converted via enamine **46** to the thermodynamically most stable aminonitrile **47**, with all ring substituents equatorial. Duplication of the reduction and cyanation conditions utilized in the case of **16** also afforded **67**, but in less pure form. A method was now available to prepare the aminonitrile precursor to the 9$\alpha$-methylbenzomorphan **3** since after conversion of **67** to ketone **69** epimerization at C-2 would take place under the acid ring closure conditions without concomitant epimerization at C-3. The key step of the whole sequence is the generation of "*cis*"-aminonitrile **67** by reduction of amide **42** followed by cyanation in acid and then its quantitative conversion to "*trans*"-aminonitrile **47** with alkali.

Nitrile **67** was converted to ketone **69** in the normal manner and cyclized with $BF_3{\cdot}Et_2O$ to give methylenebenzomorphan **70** and epimerized ketone **71**. Resubmission of isolated material to the ring closure conditions gave complete consump-

tion of **71** and afforded methylenebenzomorphan **70** in 60% yield.

Since the isomeric purity of the 9α-methylbenzomorphan was now dependent on the cis/trans ratio obtained in the hydrogenation of methylene lactam **2**, optimization of the 90:10 ratio of *cis-/trans*-amides **42** and **43** became desirable. The isomer distribution was examined as a function of both catalyst (Pd/C, $Pd/BaCO_3$, $Rh/Al_2O_3$, Rh/C, $PtO_2$) and solvent. With Pd catalysts, the ratio did not vary significantly either as a function of solvent or support. The normally more selective Rh catalysts gave slightly better cis/trans ratios, but also gave large amounts of material in which the double bond had been isomerized to the endocyclic position, affording a conjugated product resistant to hydrogenation. This double-bond isomerization does not occur in the absence of hydrogen even at 50 °C. Pt catalysts gave much better cis/trans ratios, but still generated 10–20% of the endocyclic isomer. Addition of base has been reported to decrease the extent of double-bond isomerization during hydrogenation over Pd catalysts.[67] Utilizing this observation in conjunction with the most selective catalyst, $PtO_2$, the presence of aqueous NaOH was found to completely suppress double-bond isomerization while still affording a 97:3 ratio of *cis/trans*-amides **42** and **43**.

Ozonolysis of methylenebenzomorphan **50** had proceeded in 95% yield to ketone **53**, but the same reaction conditions with the 9α isomer **70** gave only a 27% yield of ketone **72**. Apparently, either the 8-methylene group is now sufficiently hindered so that ozonolysis is slow compared to ozone attack at other positions or the intermediate ozone adduct or molozonide can decompose (the C-9 hydrogen and C-1,8 bond are trans diaxial in the α series) to an enamine which undergoes further reaction.

Alternatives to ozone included direct oxidative cleavage with chromic acid or formation of glycol followed by oxidative cleavage. Oxidation of methylenebenzomorphan **70** with $CrO_3$ in dilute $H_2SO_4$[68] afforded only a 30% yield of ketone **72** in a multicomponent mixture. Oxidation with $NaIO_4$ in the presence of 10 mol % $OsO_4$ in aqueous HOAc,[69] stoichiometric osmolation either in HOAc or in ether/pyridine,[70] and $Pb(OAc)_4$/HOAc also afforded mixtures of products. Attempted epoxidation of methylenebenzomorphan **70** with MCPBA in $CH_2Cl_2$ at room temperature gave rapid conversion to *N*-oxide but no conversion to epoxide even at extended reaction times. The alternative route to epoxide via bromohydrin also failed when treatment of **70** with NBA in aqueous dioxane both in the presence and absence of $HClO_4$[71] and with NBS in aqueous $Me_2SO$[72] gave not the desired bromohydrin but the 8-(bromomethylene)benzomorphan **73**. Compound **73** was best prepared by titration of **70** with $Br_2/CHCl_3$. Attempting to prepare the epoxide by going to the stronger peracid $CF_3CO_3H$[73] gave not the epoxide but ketone **72** directly in 59% yield. The mechanistic pathway of this reaction is not known, but it requires about 300 mol % of peracid to go to completion.

Ketone **72** was found to be extremely resistant to hydrogenation, so it was first reduced in 95% yield with $LiAlH_4$ to the 8-hydroxybenzomorphan **74**, of which one isomer is known. Subsequent hydrogenolysis as described[5] afforded 9α-methylbenzomorphan **3** with properties identical with published values.[5]

Thus, a high-yield synthesis of the isomerically pure 2,9-dimethyl-2′-methoxy-6,7-benzomorphans **3** and **4** has been developed. The synthesis proceeds from the readily accessible common intermediate methylene lactam **2** with complete control of stereochemistry at C-9. Intrinsic to the process is an effective method for converting an amide oxygen into a functionalized single carbon moiety suitable for substitution into an aromatic nucleus. In this case, it was accomplished via the nitrile and methyl ketone. The aryl group may be variously substituted by starting with the appropriate benzaldehyde. The acrylamide system in methylene lactam **2** and the acrylamide system and acetate residue in the readily accessible 4a-aryldecahydroisoquinoline intermediate **75**[8] should allow the preparation of a variety of heretofore unavailable benzomorphans with complex functionality at C-5 and C-9.

## Experimental Section

All reactions were performed under a nitrogen atmosphere with magnetic stirring unless otherwise indicated, and all solvents were dried over $MgSO_4$ prior to evaporation in vacuo using a Berkeley rotary evaporator. Melting points are uncorrected, and distillation was bulb-to-bulb, Kugelrohr-type unless stated otherwise. NMR spectra were determined in $CDCl_3$ solution (except where noted) with a Varian T-60 instrument using internal $Me_4Si$ (δ 0). IR spectra were recorded neat (except where noted) on a Perkin-Elmer 137 spectrophotometer. CEC-103 and -110B mass spectrometers were used for determining mass spectra. Gas chromatographies were carried out with 80–100 mesh Chromosorb W as support on 5-ft columns with 5% SE-30 (A, metal column) or 3% OV-1 (B, glass column) as the lqiuid phase. TLC and column chromatography were done on $SiO_2$ (silica gel 60, E. M. Reagents, 63–200 μm) and TLC grade $SiO_2$ (D-5, Camag, 7–25 μm) without binder. Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley.

**1,3-Dimethyl-2-piperidone (5).** Methylene lactam **6** (25.07 g, 0.2 mol) was hydrogenated over 10% Pd/C (2.0 g) in 150 mL of absolute ethanol on a Parr apparatus for 35 min (31–47 psi). The residue after filtration and evaporation was distilled to give 23.13 g (92%) of piperidone **5**, bp 69 °C/2.5 mm (lit.[74] bp 113–114 °C/18 mm).

**General Procedure for Formation of Imidates 7 and 9.** A 10% solution of piperidone **5** in anhydrous $CH_2Cl_2$ was added to an equimolar amount of the appropriate trialkyloxonium tetrafluoroborate. The resulting solution (with $Et_3OBF_4$) or suspension (with $Me_3OBF_4$) was stirred overnight at 25 °C and was used as is, or redissolved, or resuspended in another solvent: NMR ($CH_2Cl_2$) **7**, δ 4.52 (q, *J* = 7 Hz, 2 H), 3.55 (m, 2 H), 3.13 (s, 3 H), 1.87 (m, 4 H), 1.40 (t, *J* = 7 Hz, 3 H), 1.31 (d, *J* = 7 Hz, 3 H); **9**, δ 4.18 (s, 3 H), 3.57 (m, 3 H), 3.17 (s, 3 H), 1.87 (m, 4 H), 1.29 (d, *J* = 7 Hz, 3 H).

**1,3-Dimethyl-2-ethoxy-1,4,5,6-tetrahydropyridine (11).** Ethyl imidate **7** was prepared as described from 11.3 g (88.7 mmol) of piperidone **5**. The crude residue after evaporation was redissolved in 35 mL of absolute ethanol and added to a solution of 2.14 g (93.1 mmol) of sodium in 50 mL of absolute ethanol over 5 min at 25 °C. After 3 h, the crude reaction mixture was filtered, the solvent evaporated, and the residue fractionally distilled to yield 5.43 g (43%) of *O,N*-ketene acetal **11**: bp 40–41 °C/3 mm; NMR δ 3.77 (q, *J* = 7 Hz, 2 H), 2.91 (t, *J* = 5 Hz, 2 H), 2.46 (s, 3 H), 2.82 (m, 4 H), 1.62 (s, 3 H), 1.22 (t, *J* = 7 Hz, 3 H); MS *m/e* 155 ($M^+$). Anal. Calcd for $C_9H_{17}NO$: C, 69.6; H, 11.0; N, 9.0. Found: C, 69.4; H, 11.0; N, 9.0.

**1,3-Dimethyl-2-(nitromethylene)piperidine (8). Method A.** Nitromethane (2.88 g, 47.2 mmol) was added to the ethanolic reaction solution of *O,N*-ketene acetal **11** prepared from 3.0 g (23.6 mmol) of piperidone **5** as described above. After being stirred overnight at 25 °C, the solvent was evaporated and the residue distributed between $CHCl_3$ (50 mL) and $H_2O$ (40 mL). The aqueous layer was further extracted with $CHCl_3$ (2 × 25 mL), and the combined organic extracts were dried and evaporated to afford 3.6 g of a light yellow solid. Recrystallization from $CHCl_3$/hexane gave 3.06 g (76%) of **8**.

**Method B.** A solution of methyl imidate **9** prepared from 3.1 g (24.4 mmol) of piperidone **5** in anhydrous methanol (15 mL) was added in one portion to a suspension of 26.8 mmol of $NaCH_2NO_2$ in anhydrous methanol (15 mL), and the resulting solution was refluxed for 7.5 h. Evaporation of solvent and isolation as described in method A afforded 3.6 g of crude product which NMR showed to be a 1:1 mixture of piperidone **5** and the desired product **8**. Recrystallization from $CHCl_3$/hexane gave 1.92 g (46%) of **8**: mp 111–114 °C; NMR δ 6.67 (s, 1 H), 4.19 (m, 1 H), 3.42 (t, *J* = 7 Hz, 2 H), 2.92 (s, 3 H), 1.76 (m, 4 H), 1.34 (d, *J* = 7 Hz, 3 H); IR (KBr) 1550, 1335 $cm^{-1}$; MS *m/e* 170 ($M^+$). Anal. Calcd for $C_8H_{14}N_2O_2$: C, 56.4; H, 8.3; N, 16.5. Found: C, 56.4; H, 8.1; N, 16.7.

**1,3-Dimethyl-2-(nitromethyl)piperidine (13).** A solution of nitro olefin **8** (1.00 g, 5.88 mmol) in absolute ethanol (60 mL) was treated with 444 mg (11.6 mmol) of $NaBH_4$. After being stirred overnight at 25 °C, the solvent was evaporated and the residue was partitioned between saturated aqueous NaCl (20 mL) and $CHCl_3$ (50 mL); the aqueous layer was acidified (HOAc) to pH 6 and extracted with $CHCl_3$

(3 × 40 mL), and the combined organic extracts were dried and evaporated to give 849 mg (85%) of **13** as a colorless oil: NMR δ 4.66 (d, $J$ = 4 Hz, 2 H), 2.40 (s, 3 H), 1.70 (m), 1.10 (m, 3 H); IR 1540 (s), 1370 (m) $cm^{-1}$; MS $m/e$ 172 ($M^+$). Anal. Calcd for $C_8H_{16}N_2O_2$: C, 55.8; H, 9.4; N, 16.3. Found: C, 55.9; H, 9.3; N, 16.1.

**1,3-Dimethyl-2-piperidinecarboxaldehyde (14).** Nitro alkane **13** (188 mg, 1.09 mmol) was dissolved in water (5 mL) by addition of concentrated HCl (0.8 mL, 10 mmol), and then with careful exclusion of air 2.85 mL of aqueous $TiCl_3$ (1.54 M, 4.36 mmol) was added. The resulting deep purple solution was stirred for 16 h, and after adjusting the pH to 8 with $Na_2CO_3$ it was extracted with $CHCl_3$ (3 × 40 mL). The combined organic extracts were dried and evaporated to give 54 mg (35%) of aldehyde **14** as a volatile oil: NMR major isomer, δ 9.39 (d, $J$ = 4 Hz, 1 H), 2.17 (s, 3 H), 1.7 (m), 0.86 (d, $J$ = 6 Hz, 3 H); minor isomer, δ 9.75 (d, $J$ = 5 Hz, 1 H), 2.26 (s, 3 H), 1.7 (m), 1.02 (d, $J$ = 7 Hz, 3 H). Anal. Calcd for $C_8H_{15}NO$: C, 68.0; H, 10.7; N, 9.9. Found: C, 67.9; H, 10.8; N, 9.9.

**1,3-Dimethyl-2-cyanopiperidine (15). Method A ($LiAlH_4$).** Piperidone **5** (7.5 g, 59 mmol) was reduced with $LiAlH_4$ as described for $N$-methyl-2-piperidone.[15a] The reaction solution was evaporated, the residue was overlaid with water (50 mL), KCN (11.5 g, 177 mmol) was added, and the resulting aqueous suspension was extracted with $CHCl_3$ (3 × 50 mL). The combined organic extracts were dried and evaporated to afford a crude reaction product which GC (column A, 80 °C) and NMR showed to be a 5:2 mixture of nitrile **15** and piperidone **5**, with a trace of 1,3-dimethylpiperidine. The nitrile **15** was isolated in 21% yield by fractional distillation, bp 87–91 °C/13 mmHg.

**Method B ($LiAl(OEt)_3H$).** Piperidone **5** (1.0 g, 7.86 mmol) in $Et_2O$ (5 mL) was added over 5 min to an ice-cold suspension of 9.43 mmol of $LiAl(OEt)_3H$[15c] in $Et_2O$ (10 mL). After coming to room temperature over 2 h, the excess hydride was decomposed by adding methanol, the solution was evaporated, the residue was suspended in $H_2O$ (25 mL), KCN (1.55 g, 23.6 mmol) was added, and the white suspension was stirred for 1 h and then extracted with $CHCl_3$ (3 × 40 mL). The combined organic extracts were dried and evaporated to give 630 mg (58%) of pure nitrile **15**. Considering the aliquots removed to follow the reaction, this represents a yield of 80%: NMR δ 3.68 (d, $J$ = 4 Hz, 2 H), 2.40 (s, 3 H), 1.67 (m), 1.17 (d, $J$ = 7 Hz, 3 H); IR 2225 (vw) $cm^{-1}$; MS $m/e$ 138 ($M^+$). Anal. Calcd for $C_8H_{14}N_2$: C, 69.5; H, 10.2; N, 20.3. Found: C, 69.5; H, 10.2; N, 20.1.

**1-Methyl-3-ethyl-4-phenyl-2-piperidone (16).** Ethylidene lactam **17**[25] (10 g, 46.5 mmol) was hydrogenated in absolute ethanol (100 mL) over 10% Pd/C (1 g) on a Parr apparatus overnight (39–43 psi). Filtration and evaporation afforded 10.09 g (100%) of lactam **16** as a colorless oil which was homogeneous on TLC ($SiO_2$, ethyl acetate) and GC (column A, 133 °C): NMR δ 7.18 (m, 5 H), 3.33 (t, $J$ = 6 Hz, 2 H), 3.3 (m, 1 H), 2.98 (s, 3 H), 1.0–2.8 (m, 7 H), 0.89 (t, $J$ = 7 Hz, 3 H); IR 1630 (sb) $cm^{-1}$; MS $m/e$ 217 ($M^+$). Anal. Calcd for $C_{14}H_{19}NO$: C, 77.4; H, 8.8; N, 6.4. Found: C, 77.2; H, 8.8; N, 6.4.

**1-Methyl-2-cyano-3-ethyl-4-phenylpiperidine (19).** Piperidone **16** (2 g, 9.24 mmol) in ether (10 mL) was added to an ice-cold suspension of 11.1 mmol of $LiAl(OEt)_3H$[15c] in anhydrous ether (30 mL). After 5 min, 6 mmol of additional $LiAl(OEt)_3H$ was added. Excess hydride was decomposed with $CH_3OH$, and the solvent was removed at 25 °C. The residue was suspended in $H_2O$ (50 mL) and treated with 1.80 g (27.8 mmol) of KCN followed by methanol (20 mL). After being stirred for 1.25 h at 25 °C, the crude reaction suspension was extracted with $CHCl_3$ (75 mL, 2 × 50 mL) and the combined organic extracts were dried and evaporated at 25 °C to give 1.86 g (88.5%) of **19** as a colorless oil: NMR δ 7.14 (s, 5 H), 3.83 (br s, 1 H), 2.34 (s, 3 H), 0.95–3.42 (m), 0.78 (m, 3 H); MS $m/e$ 201 ($M^+$ − HCN).

**Epimerization of Nitrile 19 to Nitrile 20.** A solution of nitrile **19** (1 g, 3.74 mmol) in $CH_3OH$ (20 mL)/$H_2O$ (1.2 mL) was treated with 500 mg of IRA-400 ($OH^-$), and the resulting mixture was stirred vigorously for 18 h. The residue after filtration and evaporation was dissolved in $CHCl_3$ (10 mL) and washed with aqueous NaCl (10 mL). The aqueous layer was extracted with $CHCl_3$ (10 mL), and the combined organic extracts were dried and evaporated to give 886 mg (89%) of **20**: mp 92–94 °C (hexane); NMR δ 7.09 (s, 5 H), 3.93 (d, 1 H, $J$ = 3 Hz), 2.43 (s, 3 H), 1.0–2.90 (m), 0.72 (t, 3 H, $J$ = 6 Hz); IR ($CHCl_3$) 2220 (w) $cm^{-1}$; MS $m/e$ 201 ($M^+$ − HCN). Anal. Calcd for $C_{15}H_{20}N_2$: C, 78.9; H, 8.8; N, 12.3. Found: C, 78.9; H, 8.7; N, 12.2.

**1-Methyl-3-ethyl-4-phenyl-1,4,5,6-tetrahydropiperidine (21)** was obtained as a side product in several reactions. An analytical sample was obtained by GC (column A, 130 °C): NMR δ 7.17 (s, 5 H), 5.74 (br s, 1 H), 3.23 (t, 1 H, $J$ = 5 Hz), 2.67 (t, 2 H, $J$ = 5 Hz), 2.59 (s, 3 H), 1.45–2.32 (m, 4 H), 0.87 (t, 3 H, $J$ = 6 Hz); IR 1660 (s) $cm^{-1}$; MS $m/e$ 201 ($M^+$). Anal. Calcd for $C_{14}H_{19}N$: C, 83.5; H, 9.5; N, 7.0. Found: C, 83.7; H, 9.3; N, 7.0.

**1-Methyl-2-(aminomethyl)-3-ethyl-4-phenylpiperidines 26 and 27.** Nitrile **19** (214 mg, 0.94 mmol) in ether (2 mL) was added quickly to 71 mg (1.87 mmol) of $LiAlH_4$ in 5 mL of ether, and the resulting suspension was refluxed for 1 h. The cooled reaction solution was treated sequentially with 0.07 mL of water, 0.07 mL of 15% aqueous NaOH, and 0.21 mL of water. Filtration and evaporation afforded 182 mg (75%) of diamine **26**: NMR δ 7.15 (s, 5 H), 1.0–3.55 (m, 11 H), 2.46 (s, 3 H), 1.12 (br s, 2 H, exchanges in $D_2O$), 0.78 (m, 3 H); IR 3300 (w), 3400 (w) $cm^{-1}$. Anal. Calcd for $C_{15}H_{24}N_2$: C, 77.5; H, 10.4; N, 12.1. Found: C, 77.5; H, 10.3; N, 11.9.

Isomer **27** was prepared in a similar fashion from nitrile **20**, giving a 97% yield: NMR δ 7.12 (s, 5 H), 2.61 (s, 3 H), 1.46 (br s, 2 H, exchanges in $D_2O$), 1.2–3.2 (m), 0.77 (m, 3 H).

**1-Methyl-2-acetyl-3-ethyl-4-phenylpiperidines 28 and 29.** Nitrile **19** (215 mg, 0.94 mmol) in anhydrous ether (5 mL) was treated with 1.0 mL of 1.59 M (1.59 mmol) $CH_3Li$ in ether over 6 min. The resulting solution was then refluxed for 15 min and cooled, and methanol was added to decompose excess methyllithium. The reaction solution was diluted with $H_2O$ (10 mL) and extracted with $CHCl_3$ (3 × 15 mL). The combined organic extracts were dried and evaporated to give 215 mg (93%) of the imine: NMR δ 7.07 (s, 5 H), 2.55 (m, 4 H), 2.22 (s, 3 H), 1.92 (s, 3 H), 1.04–1.92 (m, 5 H), 0.78 (m, 3 H); IR 3200 (w), 1640 (s) $cm^{-1}$; MS $m/e$ 244 ($M^+$).

A solution of the crude imine in a mixture of ethanol (3 mL), water (1 mL), and concentrated HCl (0.2 mL, 2.4 mmol) was refluxed for 3.5 h. The reaction mixture was cooled and added to $H_2O$ (10 mL), the pH was adjusted to 9 with $Na_2CO_3$, and the mixture was extracted with $CHCl_3$ (3 × 15 mL). The combined organic extracts were dried and evaporated to give 185 mg of ketone **28**. NMR and GC (column A, 152 °C) showed 22% enamine **21**, which did not appear in the intermediate imine; yield 63% from nitrile to **28**: NMR δ 7.08 (s, 5 H), 3.35 (d, 1 H, $J$ = 2 Hz), 1.0–3.40 (m), 2.45 (s, 3 H), 2.12 (s, 3 H), 0.87 (m, 3 H); IR 1710 (s) $cm^{-1}$. Anal. Calcd for $C_{16}H_{23}NO$: C, 78.3; H, 9.4; N, 5.7. Found: C, 78.2; H, 9.4; N, 5.7.

The isomeric ketone **29** was obtained in 88% yield by similar treatment of nitrile **20**. The intermediate imine was hydrolyzed directly by quenching and stirring the ethereal reaction solution at 25 °C with 5 N sulfuric acid for 30 min: NMR δ 7.25 (s, 5 H), 3.91 (d, 1 H, $J$ = 5 Hz), 2.50 (s, 3 H), 2.20 (s, 3 H); IR 1710 (s) $cm^{-1}$.

**1-Methyl-3-ethyl-4-phenyl-2-piperidinecarboxaldehyde (30).** A solution of 1.19 g (4.43 mmol) of nitrile **19** in anhydrous ether (5 mL) was added to an ice-cold suspension of 5.75 mmol of $LiAl(OEt)_2H_2$[15c] in 5 mL of ether over 45 s. After 10 min, 5 N aqueous sulfuric acid (15 mL) was added and the resulting biphasic mixture was stirred vigorously for 15 min. The reaction mixture was then diluted with $H_2O$ (10 mL), the pH adjusted to 8–9 using $Na_2CO_3$, and the mixture extracted with ether (4 × 25 mL). The combined ethereal extracts were washed once with aqueous NaCl (50 mL), and the NaCl solution was back-extracted once with $CHCl_3$ (10 mL). The combined organic extracts were dried and evaporated to give 1.01 g (76%) of **30** as a colorless oil: NMR δ 9.82 (s, 1 H), 7.05 (s, 5 H), 1.10–3.40 (m), 2.60 (s, 3 H), 0.73 (m, 3 H); IR 1723 (s) $cm^{-1}$; MS $m/e$ 231 ($M^+$). Anal. Calcd for $C_{15}H_{21}NO$: C, 77.9; H, 9.2; N, 6.1. Found: C, 77.8; H, 9.1; N, 6.1.

Attempted epimerization gave small amounts of crude aldehyde **31** with an aldehyde absorption as a doublet at δ 9.55 in the NMR as well as extensive decomposition.

**1-Methyl-2-(hydroxymethyl)-3-ethyl-4-phenylpiperidine (32).** Aldehyde **30** (160 mg, 0.42 mmol) was dissolved in ethanol (3 mL) and treated with 52 mg (1.39 mmol) of $NaBH_4$. After being stirred at 25 °C for 14 h, the solvent was evaporated and the residue partitioned between $H_2O$ (10 mL) and $CHCl_3$ (10 mL). The aqueous layer was extracted with $CHCl_3$ (2 × 10 mL). The combined organic extracts were dried and evaporated to give 157 mg of alcohol **32**: mp 118–119 °C (hexane); NMR δ 7.20 (s, 5 H), 3.81 (d of d, 1 H, $J$ = 11 and 26 Hz), 3.81 (d of d, 1 H, $J$ = 11 and 14 Hz), 2.61 (s, 3 H), 0.90–3.30 (m), 0.73 (m, 3 H); IR (KBr) 3150 (sb) $cm^{-1}$; MS $m/e$ 233 ($M^+$). Anal. Calcd for $C_{15}H_{23}NO$: C, 77.2; H, 9.9; N, 6.0. Found: C, 77.3; H, 9.7; N, 6.0.

**Reaction of Nitrile 19 with $CuCl_2 \cdot 2H_2O$.** Nitrile **19** (50 mg, 0.17 mmol) was dissolved in methanol (1.5 mL), and 36 mg (0.20 mmol) of $CuCl_2 \cdot 2H_2O$ in methanol (0.5 mL) was added. The resulting green solution was stirred for 1.5 h and then poured into $H_2O$ (10 mL) and extracted with $CHCl_3$ (3 × 15 mL). The combined extracts were dried and evaporated to give 25 mg of **24** as an oily mixture of isomers. An analytical sample was prepared by preparative TLC (chloroform/ethyl acetate, 1:1) followed by recrystallization in hexane: mp 94–96 °C; NMR δ 7.35 (s, 5 H), 4.0 and 4.12 (two s, 1 H), 2.45 and 2.51 (two s, 3 H), 1.1–3.6 (m), 0.93 (t, 3 H, $J$ = 7 Hz). Anal. Calcd for $C_{15}H_{21}N_2Cl$: C, 68.0; H, 8.0; N, 10.6; Cl, 13.4. Found: C, 67.5; H, 7.2; N, 10.3; Cl, 12.3.

**1-Methyl-2-(carbomethoxy)-3-ethyl-4-phenylpiperidine (33).**

Amino aldehyde **30** (179 mg, 0.62 mmol) was suspended in 5 N $H_2SO_4$ (5 mL), and acetone (1 mL) was added to give a clear solution which was cooled to 0 °C. Jones reagent (0.81 mmol) was added dropwise to the stirred solution, followed by additional acetone (7 mL). After 24 h at room temperature, aqueous sodium bisulfite was added followed by addition of 4 M aqueous NaOH to pH 8. After the solvent was removed, the residue was suspended in $CH_3OH$ (50 mL) and saturated with HCl at 0 °C. After 48 h, the reaction suspension was concentrated to one-fourth the original volume, neutralized with saturated $NaHCO_3$/ice to pH 8–9, and extracted with $CHCl_3$ (3 × 35 mL). The combined organic extracts were dried and evaporated to give 54 mg of an oil which was chromatographed ($SiO_2$, $CHCl_3$) to give 33 mg (20%) of amino ester **33**: NMR δ 7.32 (m, 5 H), 3.8 (s, 3 H), 2.53 (s, 3 H), 1.0–3.8 (m), 0.85 (m, 3 H); IR 1730 (s) $cm^{-1}$. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.5; H, 8.9; N, 5.4. Found: C, 73.6; H, 8.7; N, 5.5.

**1-Methyl-3-ethyl-4-phenyl-2-piperidinecarboxamide (23).** Nitrile **19** (206 mg, 0.82 mmol) was dissolved in $CH_3OH$ (10 mL) and treated with 9.4 M aqueous $H_2O_2$ (0.21 mL, 1.9 mmol) followed by 3.75 M aqueous NaOH (0.54 mL, 2.02 mmol). The resulting clear colorless solution was heated at 45 °C for 24 h and then evaporated, and the residue was distributed between saturated aqueous NaCl (15 mL) and $CHCl_3$ (15 mL). The salt solution was extracted with $CHCl_3$ (2 × 15 mL), and the combined organic extracts were dried and evaporated to give 166 mg of residue. Crystallization from $CHCl_3$/hexane gave 60 mg (30%) of **23**: mp 192–194 °C; NMR δ 7.32 (s, 5 H), 6.5 (brs, 1 H), 5.85 (br s, 1 H), 2.97 (m, 1 H), 2.30 (s, 3 H), 1.0–2.6 (m, 8 H), 0.72 (t, 3 H, $J$ = 6 Hz); IR (KBr) 3300, 1635, 1660, 1685 $cm^{-1}$.

**2-Methyl-8-methylene-9-ethyl-6,7-benzomorphan (35).** A solution of 202 mg (0.82 mmol) of ketone **29** in *o*-dichlorobenzene (7 mL) was saturated with HBr, and 1.57 M $AlBr_3$ (1.31 mL, 2.06 mmol) in *o*-dichlorobenzene was added. The resulting solution was heated at 120 °C for 24 h; completion of the reaction was ascertained by TLC of an isolated aliquot (1:1 benzene/EtOAc; **29**, $R_f$ 2.1; **35**, $R_f$ 3.6). When ketone **29** was consumed, $H_2O$ (20 mL) was added and the resulting mixture was added to $CHCl_3$ (15 mL). The pH of the aqueous layer was adjusted to 8 with 1.25 M aqueous NaOH, and the solution was extracted with $CHCl_3$ (2 × 15 mL). The combined organic extracts were washed once with saturated aqueous NaCl (30 mL), filtered through $Na_2SO_4$, and evaporated, and the residue was chromatographed ($SiO_2$, 1:1 benzene/EtOAc) to give 112 mg (60%) of **35**: bp 100–110 °C/0.5 mm; NMR δ 7.70 (m, 1 H), 7.15 (m, 3 H), 5.84 (s, 1 H), 4.83 (s, 1 H), 3.20 (br s, 1 H), 2.83 (br s, 1 H), 2.18 (s, 3 H), 1.05–2.45 (m), 0.94 (t, 3 H, $J$ = 6 Hz); IR 1625 $cm^{-1}$; MS $m/e$ 227 ($M^+$). Anal. Calcd for $C_{16}H_{21}N$: C, 84.5; H, 9.3; N, 6.2. Found: C, 84.3; H, 9.1; N, 6.1.

**2-Methyl-8-oxo-9-ethyl-6,7-benzomorphan (36) *N*-Oxide.** Methylenebenzomorphan **35** (32 mg, 0.11 mmol) in $CH_3OH$ (5 mL) was treated with 0.35 mmol of $O_3$ at −78 °C. Dimethyl sulfide (0.25 mL) was added, and the reaction solution was allowed to warm slowly overnight. The residue after evaporation was dissolved in $CHCl_3$ (10 mL) and washed with $H_2O$ (2 × 20 mL) and saturated aqueous NaCl (15 mL). The $CHCl_3$ layer was then dried and evaporated to a residue which on PTLC (1:1 benzene/EtOAc) gave as the main product ($R_f$ 9.5) 14 mg (56%) of **36** *N*-oxide: NMR δ 8.15 (m, 1 H), 7.31 (m, 3 H), 3.48 (m, 1 H), 2.84 (s, 3 H), 0.8–2.1 (m); IR 1675 $cm^{-1}$.

**2-Methyl-8-oxo-9-ethyl-6,7-benzomorphan (36).** Methylenebenzomorphan **35** (37 mg, 0.16 mmol) was dissolved in anhydrous $Et_2O$ (5 mL), and 2 drops of saturated ethanolic HCl was added. The resulting suspension was evaporated, and the residue was dissolved in $CH_3OH$ (5 mL), cooled to −78 °C, and treated with 0.625 mmol of $O_3$. Dimethyl sulfide (0.25 mL) was added and the reaction solution allowed to slowly warm to 25 °C overnight. The residue after evaporation was dissolved in $CHCl_3$ (10 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL), $H_2O$ (10 mL), and saturated aqueous NaCl (10 mL). The organic layer was dried and evaporated to give 36 mg of a pale yellow oil. GC (column A, 145 °C) showed 10% **35**, 74% **36**, and 16% of a higher boiling material. This corresponds to a 70% yield of **36**, separated by PTLC: NMR δ 8.05 (d, 1 H, $J$ = 7 Hz), 7.34 (m, 3 H), 3.21 (br s, 1 H), 3.0 (br s, 1 H), 2.31 (s, 3 H), 1.0–2.8 (m), 0.96 (t, 3 H, $J$ = 7 Hz); IR 1680 $cm^{-1}$; MS $m/e$ 229 ($M^+$). Anal. Calcd for $C_{15}H_{19}NO$: C, 78.6; H, 8.4; N, 6.1. Found: C, 78.5; H, 8.5; N, 6.2.

**Ethyl *m*-Methoxycinnamate.** A solution of 48.0 g (0.35 mol) of *m*-anisaldehyde, 56.1 g (0.42 mol) of ethyl hydrogen malonate, and 7 mL (0.07 mol) of piperidine in pyridine (170 mL) was heated at reflux for 1.25 h. After being cooled, the reaction solution was evaporated and the residue dissolved in $Et_2O$ (500 mL), which was washed with 1:1 $H_2O$/saturated aqueous $NaHCO_3$ (500 mL), 2 N $H_2SO_4$ (500 mL), and saturated aqueous NaCl (500 mL). The ethereal extract was filtered through $Na_2SO_4$, dried, and evaporated. Distillation afforded 66.43 g (91%) of a clear colorless oil, bp 107–111 °C/0.1–0.2 mm, identical with the material obtained by esterification of *m*-methoxycinnamic acid.[8]

**4-(3-Methoxyphenyl)-5-(ethoxycarbonyl)-2-piperidinethione (39).** Amide ester **37** (2.02 g, 7.27 mmol), anhydrous THF (50 mL), and 805 mg (0.36 mmol) of $P_2S_5$ were heated at reflux for 3 h. After being cooled, the reaction mixture was poured into aqueous $NaHCO_3$ (70 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried and evaporated to give 1.90 g (89%) of thioamide **39**: mp 107–109 °C ($CHCl_3$/hexane); NMR δ 7.20 (m, 1 H), 6.77 (m, 3 H), 4.14 and 4.02 (isomeric q, total 2 H, $J$ = 7 Hz), 3.84 (s, 3 H), 2.8–3.8 (m), 1.22 and 1.07 (isomeric t, 3 H, $J$ = 7 Hz); IR ($CHCl_3$) 1720 $cm^{-1}$; MS $m/e$ 293 ($M^+$). Anal. Calcd for $C_{15}H_{19}NO_3S$: C, 61.4; H, 6.5; N, 4.8. Found: C, 61.2; H, 6.5; N, 4.7.

**Desulfurization of Thioamide 39.** A mixture of thioamide **39** (910 mg, 3.11 mmol), 80% aqueous dioxane (30 mL), and freshly prepared W-4 RaNi (3.3 g)[75] was degassed with $N_2$ and then refluxed for 2 h, at which time TLC (1:1 $CHCl_3$/EtOAc) showed complete disappearance of **39**. The reaction mixture was cooled, filtered, evaporated, and Kugelrohr distilled to afford 361 mg (39% overall from amido ester **37**) of amino ester **38**, bp 110–130 °C/0.1 mm.

**3-(Hydroxymethyl)-4-(3-methoxyphenyl)piperidine (40).** A solution of 163 mg (0.59 mmol) of amide ester **37** in THF (5 mL) was treated with 110 mg (2.94 mmol) of $LiAlH_4$ in one portion at 25 °C. After 26 h, the reaction mixture was treated sequentially with 0.1 mL of $H_2O$, 0.1 mL of 15% aqueous NaOH, and 0.3 mL of $H_2O$. Filtration and evaporation afforded 121 mg (93%) of **40** as a colorless oil. GC (column B, 195 °C) shows two isomeric amino alcohol products: NMR δ 7.22 (m, 1 H), 6.81 (m, 3 H), 3.78 (s, 3 H), 1.4–3.8 (m); IR 3340 $cm^{-1}$; MS $m/e$ 221 ($M^+$). Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.6; H, 8.7; N, 6.3. Found: C, 70.6; H, 8.7; N, 6.1.

**3-Carboxy-4-(3-methoxyphenyl)-2-piperidone (41).** A solution of 1.026 g (3.71 mmol) of amide ester **37** and 163 mg (4.08 mmol) of NaOH in 75% aqueous $CH_3OH$ (20 mL) was stirred at 25 °C for 19 h. The reaction solution was poured into 1.1 N $H_2SO_4$ (30 mL) and extracted with $CHCl_3$ (3 × 15 mL). The combined organic extracts were dried and evaporated to give 702 mg (75%) of amide acid **41**: mp 222–223 °C ($CH_3OH$/$CHCl_3$); NMR δ 7.20 (m, 1 H), 6.77 (m, 3 H), 3.77 (s, 3 H), 2.8–3.7 (m, 4 H), 2.6 (m, 2 H); IR (KBr) 1710, 1630 $cm^{-1}$; MS $m/e$ 249 ($M^+$). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.7; H, 6.1; N, 5.6. Found: C, 62.6; H, 6.1; N, 5.6.

**Diborane Reduction of the Tetra-*n*-butylammonium Salt of 41.** The tetra-*n*-butylammonium salt, prepared from 500 mg (1.99 mmol) of amide acid **41**, in anhydrous THF (7 mL) was cooled in an ice bath while 0.97 M diborane/THF (4.5 mL, 4.4 mmol) was added over 1 min. The solution was stirred for 13 h at 1 °C and then evaporated. The residue was overlaid with absolute EtOH (10 mL), $HC(OEt)_3$ (1 mL) was added, and the resulting solution was saturated with HCl with ice-bath cooling. After 68 h at 25 °C, the reaction mixture was evaporated and the residue partitioned between $H_2O$ (20 mL) and $Et_2O$ (15 mL). The aqueous layer was further washed with $Et_2O$ (2 × 15 mL). The pH of the aqueous phase was then adjusted to 9 with $Na_2CO_3$, and the solution was extracted with $Et_2O$ (3 × 15 mL). The combined ethereal extracts were dried, evaporated, and Kugelrohr distilled to give 204 mg (39%) of a colorless oil which NMR, GC (column B, 190 °C), and TLC (MeOH/EtOAc, 1:1) indicated was 95% the desired amino ester **38** contaminated by 5% of amino alcohol **40**.

**Stereoselective Hydrogenations of Methylene Lactam 2. General Procedure.** Methylene lactam **2** (85 mg, 0.368 mmol) was hydrogenated in the appropriate solvent (5 mL) over 2–6 mg of the appropriate catalyst (40–50 psi) for 12–20 h. After filtration and evaporation, the product distribution was determined by NMR and GC of the $LiAlH_4$ reduction products (see below).

***cis*-1,3-Dimethyl-4-(3-methoxyphenyl)-2-piperidone (42).** Methylene lactam **2** (1.019 g, 4.37 mmol) in absolute EtOH (40 mL) and 3.75 M aqueous NaOH (0.7 mL) was hydrogenated over 83% $PtO_2$ (33 mg). After distillation, acetic acid (0.25 mL) was added and the solution evaporated. The residue was dissolved in $CHCl_3$ (25 mL) and washed with saturated aqueous $NaHCO_3$ (25 mL). The alkali wash was extracted with $CHCl_3$ (25 mL), and the combined organic extracts were dried and evaporated to yield material which NMR showed contained no endo isomer and only traces of the trans product **43**. Kugelrohr distillation afforded 960 mg (94%) of piperidone **42**: bp 130–140 °C/0.1 mm; NMR δ 7.26 (m, 1 H), 6.74 (m, 3 H), 3.76 (s, 3 H), 1.8–3.5 (m), 2.97 (s, 3 H), 0.98 (d, 3 H, $J$ = 7 Hz); IR 1640 $cm^{-1}$; MS $m/e$ 233 ($M^+$). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.1; H, 8.2; N, 6.0. Found: C, 72.2; H, 8.3; N, 6.1.

The cis/trans isomer ratio was determined by reducing 51 mg (0.218 mmol) of **42** in $Et_2O$ (7 mL) with 50 mg (1.32 mmol) of $LiAlH_4$ at 25 °C for 21 h. Isolation in the normal manner (sequential addition of

0.05 mL of $H_2O$, 0.05 mL of 15% aqueous NaOH, and 0.15 mL of $H_2O$ and filtration) afforded material which GC (column B, 145 °C) showed to be a 98:2 mixture of the corresponding *cis*- and *trans*-amines **44** and **45**.

***trans*-1,3-Dimethyl-4-(3-methoxyphenyl)-2-piperidone (43).** A solution of 277 mg (1.19 mmol) of *cis*-piperidone **42** and 470 mg (7.14 mmol) of KOH in EtOH (7 mL) was refluxed for 22.5 h. After being cooled, the reaction solution was poured into 1:3 saturated aqueous NaCl/$H_2O$ (40 mL) and extracted with $CHCl_3$ (1 × 30 mL, 2 × 10 mL). The combined organic extracts were dried and evaporated to yield 149 mg (54%) of a waxy solid. NMR and reduction with $LiAlH_4$ to a mixture of amines indicated an 82:18 ratio of *trans*-/*cis*-amides **43** and **42**: NMR δ 7.30 (m, 1 H), 6.82 (m, 3 H), 3.76 (s, 3 H), 3.40 (m, 2 H), 2.97 (s, 3 H), 2.62 (m, 2 H), 2.08 (m, 2 H), 1.17 (d, 3 H, $J$ = 7 Hz); IR 1620 $cm^{-1}$; MS $m/e$ 233 ($M^+$). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.1; H, 8.2; N, 6.0. Found: C, 72.2, H, 8.3; N, 5.9.

***cis*-1,3-Dimethyl-4-(3-methoxyphenyl)piperidine (44).** A solution of 69 mg (0.296 mmol) of piperidone **42** in $Et_2O$ (4 mL) was treated with 58 mg (1.48 mmol) of $LiAlH_4$ in one portion at 25 °C. After 20 h, the solution was treated sequentially with 0.06 mL of $H_2O$, 0.06 mL of 15% aqueous NaOH, and 0.18 mL of $H_2O$. Filtration and evaporation afforded 57 mg (89%) of amine **44** as a colorless oil which GC (column B, 140 °C) showed contained 2.5% of the trans isomer **45** (**44**, $R_t$ 4.2 min; **45**, $R_t$ 5.4 min): NMR δ 7.20 (m, 1 H), 6.74 (m, 3 H), 3.77 (s, 3 H), 2.29 (s, 3 H), 2.6–3.3 (m, 3 H), 1.4–2.4 (m, 5 H), 0.81 (d, 3 H, $J$ = 7 Hz); MS $m/e$ 219 ($M^+$). Anal. Calcd for $C_{14}H_{21}NO$: C, 76.7; H, 9.7; N, 6.4. Found: C, 77.0; H, 9.7; N, 6.3.

***trans*-1,3-Dimethyl-4-(3-methoxyphenyl)piperidine (45).** *trans*-Amine **45** was prepared by $LiAlH_4$ reduction of *trans*-piperidone **43** in a manner analogous to that for **42** followed by separation by GC (column B, 140 °C) or more conveniently by DIBAL reduction of nitrile **47**. A solution of 51 mg (0.21 mmol) of nitrile **47** in $Et_2O$ (4 mL) was cooled in an ice bath and treated dropwise with 0.5 mL of 20% DIBAL/hexane over 1 min. After 1 h, 5 mL of 1.1 N $H_2SO_4$ was added and stirring continued for an additional hour. The colorless, biophasic reaction mixture was poured into saturated aqueous $NaHCO_3$ (20 mL), the pH adjusted to 8 with $K_2CO_3$, and the mixture extracted with $Et_2O$ (3 × 15 mL). The combined ethereal extracts were dried and evaporated to yield 38 mg (83%) of *trans*-amine **45** as a colorless oil: NMR δ 7.23 (m, 1 H), 6.80 (m, 3 H), 3.81 (s, 3 H), 3.03 (m, 2 H), 2.39 (s, 3 H), 1.90 (m), 0.72 (m, 3 H); MS $m/e$ 219 ($M^+$). Anal. Calcd for $C_{14}H_{21}NO$: C, 76.7; H, 9.7; N, 6.4. Found: C, 76.9; H, 9.6; N, 6.1.

**1,3-Dimethyl-4-(3-methoxyphenyl)-1,4,5,6-tetrahydropyridine (46).** An ice-cold solution of 2.03 g (8.68 mmol) of piperidone **42** in $Et_2O$ (15 mL) was treated with 1.45 M $LiAl(OEt)_2H_2$ (7.0 mL, 10.02 mmol) over 3 min. Excess reagent was decomposed with $CH_3OH$, and the resulting solution was poured into 2.5 M NaOH (150 mL) and extracted with $Et_2O$ (3 × 75 mL). The combined ethereal extracts were dried and evaporated to give 1.88 g (99%) of enamine **46** which GC (column B, 140 °C) and NMR showed to contain no amine or amide: NMR δ 7.08 (m, 1 H), 6.67 (m, 3 H), 5.73 (m, 1 H), 3.72 (s, 3 H), 3.18 (t, 1 H, $J$ = 4 Hz), 2.52 (s, 3 H), 1.68–2.35 (m, 2 H), 1.45 (d, 3 H, $J$ = 2 Hz); IR 1660 $cm^{-1}$; MS $m/e$ 217 ($M^+$). Anal. Calcd for $C_{14}H_{19}NO$: C, 77.4; H, 8.8; N, 6.5. Found: C, 77.2; H, 8.7; N, 6.4.

**1,3β-Dimethyl-2α-cyano-4α-(3-methoxyphenyl)piperidine (47).** A solution of 5.65 g (86.8 mmol) of KCN in 80% aqueous $CH_3OH$ (57 mL) was added to 1.88 g (8.65 mmol) of enamine **46**. After being stirred at 25 °C for 1 h, the reaction solution was poured into saturated aqueous NaCl (150 mL) and extracted with $CHCl_3$ (3 × 50 mL). The combined organic extracts were dried and evaporated to yield an oil which NMR showed was a 5:4 mixture of **67** and **47**. This mixture was dissolved in $CH_3OH$ (35 mL)/3.75 M aqueous NaOH (9 mL). After 22.5 h at 25 °C, the solution was poured into $H_2O$ (150 mL) and extracted with $CHCl_3$ (4 × 50 mL). The combined organic extracts were dried and evaporated to give 2.10 g (99%) of pure nitrile **47**: bp 110–120 °C/0.1 mm; NMR δ 7.27 (m, 1 H), 6.83 (m, 3 H), 3.89 (s, 3 H), 3.89 (m, 1 H), 2.45 (s, 3 H), 1.5–3.5 (m), 0.86 (d, 3 H, $J$ = 7 Hz); MS $m/e$ 244 ($M^+$). Anal. Calcd for $C_{15}H_{20}N_2O$: C, 73.7; H, 8.3; N, 11.5. Found: C, 73.7; H, 8.3; N, 11.0.

**1,3β-Dimethyl-2α-acetimino-4α-(3-methoxyphenyl)piperidine and 1,3β-Dimethyl-2β-acetimino-4α-(3-methoxyphenyl)piperidine (52).** A solution of 60 mg (0.23 mmol) of nitrile **47** in $Et_2O$ (5 mL) was treated with 1.73 M $CH_3Li/Et_2O$ (0.4 mL, 0.69 mmol) over 1 min at 25 °C. After 15 min, the solution was poured into saturated aqueous $NaHCO_3$ (20 mL) and extracted with $CHCl_3$ (3 × 30 mL). The combined organic extracts were dried and evaporated to afford 52 mg (87%) of imine; Kugelrohr distillation (130–150 °C/0.1 mm) afforded imine epimer **52**. Imine: NMR δ 7.23 (m, 1 H), 6.77 (m, 3 H), 3.84 (s, 3 H), 3.37 (d, 1 H, $J$ = 5 Hz), 2.39 (s, 3 H), 2.07 (s, 3 H), 1.5–3.5 (m), 0.86 (d, 3 H, $J$ = 7 Hz). Imine epimer **52**: NMR δ 7.22 (m, 1 ), 6.78 (m, 3 H), 2.18 (s, 3 H), 2.07 (s, 3 H), 1.5–3.5 (m), 0.63 (d, 3 H, $J$ = 6 Hz).

**1,3β-Dimethyl-2α-acetyl-4α-(3-methoxyphenyl)piperidine (48).** A solution of 1.72 g (7.05 mmol) of nitrile **47** in $Et_2O$ (20 mL) was added dropwise to 1.73 M $CH_3Li/Et_2O$ (7.65 mL, 13.2 mmol) at 25 °C over 11 min. After an additional 15 min, 1.1 N aqueous $H_2SO_4$ (25 mL) was added and the resulting two-phase mixture was stirred vigorously for 7 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (40 mL), the pH was adjusted to 9 with $K_2CO_3$, and the mixture was extracted with $CHCl_3$ (3 × 30 mL). The combined organic extracts were dried and evaporated to yield 1.73 g (94%) of **48**: NMR δ 7.27 (m, 1 H), 6.86 (m, 3 H), 3.85 (s, 4 H), 2.57 (s, 3 H), 2.27 (s, 3 H), 1.6–2.45 (m), 0.73 (d, 3 H, $J$ = 7 Hz); IR 1700 (s) $cm^{-1}$; MS $m/e$ 218 ($M^+ - COCH_3$). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.5; H, 8.9; N, 5.4. Found: C, 73.8; H, 8.9; N, 5.1.

**1,3β-Dimethyl-2α-(aminomethyl)-4α-(3-methoxyphenyl)piperidine (77).** A solution of 80 mg (0.33 mmol) of nitrile **47** in $Et_2O$ (40 mL) was treated with 62 mg (1.64 mmol) of $LiAlH_4$ in one portion at 25 °C. After 21 h, 0.06 mL of $H_2O$, 0.06 mL of 15% aqueous NaOH, and 0.18 mL of $H_2O$ were added to the vigorously stirred reaction mixture. Filtration and evaporation afforded 81 mg (100%) of **77** as a colorless oil: NMR δ 7.29 (m, 1 H), 6.81 (m, 3 H), 3.82 (s, 3 H), 1.15–3.30 (m), 0.70 (br d, 3 H, $J$ = 6 Hz); IR 3350 (w) $cm^{-1}$; MS $m/e$ 245 ($M^+ - 2$), 218 ($M^+ - CH_2NH_2$). Anal. Calcd for $C_{15}H_{24}N_2O$: C, 72.5; H, 9.7; N, 11.3. Found: C, 72.7; H, 9.7; N, 11.0.

**1,3β-Dimethyl-2α-acetyl-4α-(3-hydroxyphenyl)piperidine (49) and 1,3β-Dimethyl-2-β-acetyl-4α-(3-hydroxyphenyl)piperidine (76).** A solution of 112 mg (0.43 mmol) of ketone **48** in benzene (5 mL) was saturated with HBr gas and then evaporated to give 153 mg of **48**·HBr, which was dissolved in *o*-dichlorobenzene (4 mL) and 1.29 M $AlBr_3$ in *o*-dichlorobenzene (0.67 mL, 0.86 mmol) added. The resulting solution was heated at 60 °C for 20 h. After cooling, $CHCl_3$ (10 mL) and $H_2O$ (20 mL) were added and the aqueous layer was acidified (0.5 M $H_2SO_5$) to pH 2 and extracted with $Et_2O$ (3 × 10 mL). The pH was then adjusted to 8.3 with 1.25 M aqueous NaOH, and it was extracted with 3:1 $CHCl_3$/IPA (3 × 15 mL). The combined organic extracts were filtered through $Na_2SO_4$, dried, and evaporated to yield 82 mg of **49**: GC (column B, 190 °C) showed one product; NMR δ 7.07 (m, 1 H), 6.62 (m, 3 H), 3.80 (d, 1 H, $J$ = 5 Hz), 2.43 (s, 3 H), 2.24 (s, 3 H), 1.3–3.4 (m), 0.67 (d, 3 H, $J$ = 7 Hz).

This material was distilled at 120–130 °C/0.1 mm to give the epimeric 2β-acetyl compound **76**: NMR δ 7.06 (m, 1 H), 6.86 (m, 3 H), 1.7–2.55 (m), 2.75–3.3 (m), 2.32 (s, 3 H), 2.27 (s, 3 H), 0.64 (d, 3 H, $J$ = 5 Hz). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.8; H, 8.6; N, 5.7. Found: C, 72.7; H, 8.5; N, 5.7.

**2,9β-Dimethyl-8-methylene-2′-methoxy-6,7-benzomorphan (50).** A solution of 1.14 g (4.37 mmol) of ketone **48** in *o*-dichlorobenzene (25 mL) was treated with 2.74 mL (3.09 g, 21.8 mmol) of $BF_3 \cdot Et_2O$ and heated at 120 °C for 23 h. The reaction mixture was cooled to 25 °C and triturated with 1.75 M aqueous NaOH (70 mL) until all of the precipitate had decomposed. This heterogeneous mixture was then extracted with $CHCl_3$ (3 × 30 mL), and the combined organic extracts were dried and evaporated to an oil which was resubmitted to the reaction conditions described above, yielding 752 mg, 59%: bp 120–130 °C/0.1 mm; GC (column B, 185 °C) showed 84% of **50**, 3.5% of α isomer **70**, 8.5% unknown, and 9% of enamine **46**. The hydrochloride had mp 265–266 °C dec (EtOH). For **50**: NMR δ 7.73 (d, 1 H, $J$ = 9 Hz), 6.81 (d of d, 1 H, $J$ = 9 and 3 Hz), 6.67 (d, 1 H, $J$ = 3 Hz), 5.72 (s, 1 H), 4.75 (s, 1 H), 3.86 (s, 3 H), 3.14 (br s, 1 H), 1.9–2.9 (m), 2.17 (s, 3 H), 1.37 (d, 3 H, $J$ = 8 Hz). Anal. Calcd for $C_{16}H_{21}NO$: C, 79.0; H, 8.7; N, 5.8. Found: C, 78.9; H, 8.7; N, 5.8.

In a similar experiment the crude reaction product was not resubmitted to the reaction conditions but chromatographed ($SiO_2$, EtOAc) to afford 24% of ketone epimer **51** followed by 58% of **50**. Ketone **51**: NMR δ 7.23 (m, 1 H), 6.79 (m, 3 H), 3.90 (s, 4 H), 2.98 (m, 1 H), 1.5–2.7 (m), 2.24 (s, 3 H), 2.14 (s, 3 H), 0.58 (d, 3 H, $J$ = 6 Hz). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.5; H, 8.9; N, 5.4. Found: C, 73.8; H, 8.9; N, 5.4.

**2,9β-Dimethyl-8-oxo-2′-methoxy-6,7-benzomorphan (53).** A solution of 384 mg (1.31 mmol) of methylenebenzomorphan **50** in $CH_3OH$ (35 mL)/4.5 M $H_2SO_4$ (7 mL) was ozonized at −78 °C for 20 min at 1.2 mmol of $O_3$/min (24 mmol). Dimethyl sulfide (2 mL) was added and the solution allowed to warm to 25 °C over 6 h. Excess dimethyl sulfide was removed by degassing with $N_2$, the solution was poured into saturated aqueous $NaHCO_3$ (100 mL), the pH was adjusted to 9 with $K_2CO_3$, and the mixture was extracted with $CHCl_3$ (3 × 50 mL). The combined organic extracts were dried and evaporated, and the residue was distilled at 100–140 °C/0.1 mm to afford 332 mg (95%) of **53**, which GC (column B, 190 °C) showed to be >95% pure: NMR δ 8.03 (d, 1 H, $J$ = 9 Hz), 6.91 (d of d, 1 H, $J$ = 9 and 3 Hz),

6.68 (d, 1 H, $J$ = 3 Hz), 3.86 (s, 3 H), 2.32 (s, 3 H), 1.9–3.1 (m), 1.34 (d, 3 H, $J$ = 7 Hz).

The hydrochloride was prepared by saturating an ethereal solution of **53** with HCl and crystallizing from absolute EtOH: mp 233–235 °C dec (lit.[6] mp 227–229 °C); NMR ($D_2O$) δ 1.39 (d, 3 H, $J$ = 7 Hz), 2.83 (s, 3 H), 3.88 (s, 3 H), 2.2–3.5 (m), 6.88 (m, 2 H), 7.88 (d, 1 H, $J$ = 9 Hz) [lit.[6] NMR ($D_2O$) δ 1.37 (d, 3 H, $J$ = 7 Hz), 2.80 (s, 3 H), 3.91 (s, 3 H)].

**2,9β-Dimethyl-2′-methoxy-6,7-benzomorphan 4·Oxalate.** 9β-Methylbenzomorphan **4** was prepared from oxobenzomorphan **53** and converted to the oxalate as described:[6] mp 201–202 °C (lit.[6] mp 204–205 °C); NMR δ 6.93 (d, 1 H, $J$ = 8 Hz), 6.67 (d, 1 H, $J$ = 2 Hz), 6.50 (s, 1 H), 3.70 (s, 3 H), 2.19 (s, 3 H), 2.8–3.3 (m), 1.30 (d, 3 H, $J$ = 7 Hz); NMR ($D_2O$) δ 7.26 (d, 1 H, $J$ = 9 Hz), 6.96 (d, 1 H, $J$ = 3 Hz), 6.78 (m, 1 H), 3.89 (s, 3 H), 3.70 (m), 3.23 (m), 2.93 (s, 3 H), 2.0–2.9 (m), 1.37 (d, 3 H, $J$ = 7 Hz) [lit.[6] NMR ($D_2O$) C-9 $CH_3$ at δ 1.42 ($J$ = 7 Hz)].

**2,9β-Dimethyl-2′-hydroxy-6,7-benzomorphan·HBr.** The phenol was prepared from 4·oxalate as described[3] and converted to the hydrobromide: mp 281–282 °C dec (lit.[3] mp 243–245 °C dec).

**Hydrogenation of Enamine 46.** The following is a typical procedure for the investigation of the stereoselective hydrogenation of enamine **46**. A solution of 60 mg (0.28 mmol) of enamine **46** in EtOAc (5 mL) was hydrogenated over 5% Pd/$BaCO_3$ (6 mg) on a micro Parr apparatus at 50 psi for 24 h. The reaction mixture was filtered and evaporated. GC analysis of the mixture (column B, 150 °C) showed an 89:11 ratio of *cis*- and *trans*-amines **44** and **45**.

**1,3-Dimethyl-2-cyano-4-(3-methoxyphenyl)-1,4,5,6-tetrahydropyridine (54).** A solution of 59 mg (0.27 mmol) of enamine **46** in $CHCl_3$ (6 mL) was cooled in an ice bath and treated dropwise over 1 min with a solution of 0.1 M $Br_2$ in $CHCl_3$ (2.8 mL, 0.28 mmol). After 2.75 h, the solution was evaporated to give bromoiminium salt **55** as a light yellow foam: NMR δ 9.3 and 9.54 (broad singlets, isomeric $>N^+{=}C(H')-$, 1 H), 7.9 (m, 1 H), 7.3 (m, 3 H), 4.0 (m), 3.80 (s, 3 H), 3.12 (m), 2.16 (br s, 3 H).

This foam was overlaid with a solution of 175 mg (2.77 mmol) of KCN in 90% aqueous MeOH (5 mL). After 1.25 h at 25 °C, the solution was poured in $H_2O$ (30 mL) and extracted with $CHCl_3$ (3 × 15 mL). The combined organic extracts were dried and evaporated to yield 68 mg of an intermediate **56**: NMR δ 7.24 (m, 1 H), 6.82 (m, 3 H), 4.08 (br s, 1 H), 3.84 (s, 3 H), 2.80 (m), 2.80 (s, 3 H), 2.59 (m), 1.80 (br s, 3 H). This oil was redissolved in MeOH (5 mL) and treated with 3.75 M aqueous NaOH (1.0 mL). After 18 h at 25 °C, the solution was poured into $H_2O$ (30 mL) and extracted with $CHCl_3$ (3 × 10 mL). The combined organic extracts were dried and evaporated to yield 54 mg (82%) of cyanoenamine **54**, mp 67–68.5 °C from $CH_2Cl_2$/hexane.

Alternatively, intermediate **56** could be prepared by the action of BrCN on enamine **46**. Treatment with alkali then afforded **54** in yields comparable to the above procedure. Use of ICN gave lower yields: NMR δ 7.19 (m, 1 H), 6.68 (m, 3 H), 3.79 (s, 3 H), 3.34 (br t, 1 H, $J$ = 5 Hz), 3.83 (t, 2 H, $J$ = 5 Hz), 2.81 (s, 3 H), 2.07 (m, 2 H), 1.85 (s, 3 H). Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.4; H, 7.5; N, 11.6. Found: C, 74.4; H, 7.5; N, 11.5.

**1,3-Dimethyl-4-(3-methoxyphenyl)-1,4,5,6-tetrahydropyridine-2-carboxaldehyde (58).** A solution of 59 mg (0.42 mmol) of cyanoenamine **54** was cooled in an ice bath and treated with 1.23 M $LiAl(OEt)_2H_2$ (1.0 mL, 1.23 mmol) over 20 s. After being allowed 1.5 h to warm to 25 °C, the mixture was diluted with 1.1 N $H_2SO_4$ (5 mL) and stirred for an additional 24 h. The resulting colorless biphasic mixture was poured into saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$ (3 × 15 mL). The combined organic extracts were dried and evaporated to yield 65 mg of a red oil which NMR and GC (column B, 195 °C) showed to contain the desired aldehyde as well as a large amount of nonvolatile, polar material. Preparative TLC ($SiO_2$, 3:1 $CHCl_3$/EtOAc) afforded 15 mg (25%) of aldehyde **58**: NMR δ 9.87 (s, 1 H), 7.13 (m, 1 H), 6.72 (m, 3 H), 3.79 (s, 3 H), 3.38 (t, 1 H, $J$ = 5 Hz), 2.91 (t, 2 H, $J$ = 5 Hz), 2.7 (s, 3 H), 1.8–2.6 (m, 2 H), 1.96 (s, 3 H); IR 1670 $cm^{-1}$.

**1,3-Dimethyl-2-acetyl-4-(3-methoxyphenyl)-1,4,5,6-tetrahydropyridine (59).** A solution of 79 mg (0.27 mmol) of cyanoenamine **54** in $Et_2O$ (7 mL) was cooled in an ice bath and treated with 2.05 M $CH_3Li/Et_2O$ (0.32 mL, 0.66 mmol) over 20 s. After 15 min, the resulting suspension was diluted with 1.1 N $H_2SO_4$ (5 mL) and stirred for 16 h. The resulting biphasic mixture was poured into saturated aqueous $NaHCO_3$ (30 mL), and the pH was adjusted to 9 with $K_2CO_3$. Extraction with $CHCl_3$ (3 × 15 mL), drying, and evaporating afforded 74 mg of an oil which GC (column B, 195 °C) showed to contain two substances in an 8:2 ratio: NMR showed a major component with δ 0.42 (d, 3 H, $J$ = 6 Hz), 2.05 (s, 3 H, $COCH_3$), 2.33 (s, 3 H, $NCH_3$), and 4.03 (s, 1 H) and a minor component **59** with δ 1.56 (s, 3 H), 2.33 (s, 3 H), 2.33 (s, 3 H, $COCH_3$), and 2.50 (s, 3 H, $NCH_3$); MS $m/e$ 259 ($M^+$).

**1,2,3-Trimethyl-4-(3-methoxyphenyl)-1,4,5,6-tetrahydropyridine (60).** A solution of 2.10 M $CH_3Li/Et_2O$ (0.45 mL, 0.95 mmol) in $Et_2O$ (3 mL) was cooled in an ice bath while a solution of 212 mg (0.91 mmol) of piperidone **42** in $Et_2O$ (2 mL) was added dropwise over 3 min. The resulting white suspension was allowed to come to 25 °C over 4 h and then was poured into 1.25 M aqueous NaOH (30 mL) and extracted with $CHCl_3$ (3 × 15 mL). The combined organic extracts were dried and evaporated to yield 206 mg (98%) of **60** as a colorless oil which decomposed on standing. NMR indicated clean conversion of the cis isomer **42** to methylenamine **60**, while the contaminating trans isomer **43** remained unreacted: NMR δ 7.10 (m, 1 H), 6.68 (m, 3 H), 3.37 (s, 3 H), 3.20 (m, 2 H), 2.63 (s, 3 H), 2.16 (m, 2 H), 1.82 (s, 3 H), 1.50 (s, 3 H).

**Ethyl 1-(4-Methoxybenzyl)-4-(3-methoxyphenyl)piperidine-3-carboxylate (62).** A mixture of 6.42 g (25.1 mmol) of amine **38**, 8.53 g (25.1 mmol) of *p*-methoxybenzyl trichoroacetate,[65] and 3.46 g (25.1 mmol) of anhydrous $K_2CO_3$ in anhydrous benzene (100 mL) was refluxed for 18 h. The cooled reaction mixture was washed with saturated aqueous $NaHCO_3$ (1 × 25 mL) and the aqueous layer extracted with 100 mL of $CHCl_3$. The combined organic extracts were dried, evaporated, and distilled to give two fractions, a forerun (1.32 g), bp 130–170 °C/0.1 mm, consisting mainly of anisyl alcohol and 8.0 g (83%) of amine **62**: bp 170–210 °C/0.1 mm; NMR δ 7.24 (m, 3 H), 7.86 (m, 5 H), 3.98 and 3.90 (isomeric quartets, 2 H, $J$ = 7 Hz), 3.90 (s, 6 H), 3.55 and 3.44 (isomeric singlets, 2 H), 1.5–3.4 (m), 1.03 and 0.95 (isomeric triplets, 3 H, $J$ = 7 Hz). Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.0; H, 7.6; N, 3.7. Found: C, 72.0; H, 7.7; N, 3.7.

**1-(4-Methoxyphenyl)-3-methylene-4-(3-methoxyphenyl)-2-piperidone (63).** A suspension of 8.0 g (20.9 mmol) of amine **62** and 1.67 g (41.8 mmol) of NaOH in 80% aqueous $CH_3OH$ (90 mL) was heated at reflux for 23 h. The cooled reaction solution was poured into $H_2O$ (120 mL) and extracted with $Et_2O$ (150 mL). The aqueous layer was evaporated to yield the Na salt, which was overlaid with $Ac_2O$ (320 mL) and heated at 170 °C, distilling off $Ac_2O$ (100 mL), over 20 min (final bp 136 °C). The reaction mixture was refluxed for an additional 2 h, and the residue was treated with $CHCl_3$ (100 mL)/saturated aqueous $NaHCO_3$ (100 mL), adjusting the pH of the aqueous layer to 8–9 with $K_2CO_3$. Further extraction with $CHCl_3$ (2 × 50 mL), combination of the organic extracts, evaporation, and distillation yielded two fractions, a forerun (1.2 g), bp 120–160 °C/0.1 mm, consisting of *p*-methoxybenzyl acetate and 2.97 g (42%) of **63**: NMR δ 7.22 (m, 3 H), 6.81 (m, 5 H), 6.49 (t, 1 H, $J$ = 2 Hz), 5.16 (t, 1 H, $J$ = 2 Hz), 4.63 (s, 2 H), 3.80 (s, 6 H), 3.30 (t, 2 H, $J$ = 6 Hz), 2.14 (m, 3 H); IR 1600 (s), 1650 (s) $cm^{-1}$. $C_{21}H_{23}NO_3$ requires 337.1678; found 337.1672.

**3-Methylene-4-(3-methoxyphenyl)-2-piperidone (64).** A solution of 560 mg (1.66 mmol) of anisylamide **63** in 1.0 mL (990 mg, 9.16 mmol) of anisole was diluted with 9.0 mL of trifluoroacetic acid and refluxed for 49 h. The cooled solution was evaporated, and the residue was dissolved in $CHCl_3$ (20 mL) and washed with saturated aqueous $NaHCO_3$ (25 mL). The organic layer was dried and evaporated to a residue which on chromatography ($SiO_2$, $CHCl_3$) gave 308 mg (85%) of **64**: bp 150 °C/0.1 mm; mp 107–109 °C; NMR δ 7.78 (br s, 1 H), 7.28 (m, 1 H), 6.84 (m, 3 H), 6.42 (t, 1 H, $J$ = 2 Hz), 5.17 (m, 1 H), 3.84 (s, 3 H), 3.84 (t, 1 H, $J$ = 7 Hz), 3.44 (m, 2 H), 2.19 (m, 2 H). Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.9; H, 7.0; N, 6.5. Found: C, 71.8; H, 7.1; N, 6.4.

***cis*-3-Methyl-4-(3-methoxyphenyl)-2-piperidone (65).** A solution of 48 mg (0.221 mmol) of amide **64** in absolute EtOH (6 mL) was hydrogenated over $PtO_2$ (5 mg) for 24 h at 45 psi. Filtration and evaporation afforded a quantitative yield of amide **65**: bp 150 °C/0.1 mm; mp 83–88 °C; NMR δ 7.28 (m, 1 H), 7.07 (br s, 1 H), 6.79 (m, 3 H), 3.81 (s, 3 H), 3.34 (m, 3 H), 2.72 (m, 1 H), 2.07 (m, 2 H), 0.98 (d, 1 H, $J$ = 7 Hz). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.2; H, 7.8; N, 6.4. Found: C, 70.9; H, 7.9; N, 6.2.

**1-(Benzenesulfonyl)-3-methyl-4-(3-methoxyphenyl)-2-piperidone (61).** A solution of 313 mg (1.43 mmol) of amide **65** in anhydrous THF (5 mL) at −78 °C was treated with 1.95 M *t*-BuLi/pentane (0.77 mL, 1.50 mmol) over 1 min. After 0.5 h at −78 °C, 0.20 mL (278 mg, 1.58 mmol) of benzenesulfonyl chloride was added over 30 s and the reaction was allowed to come to room temperature for 7 h. The solution was poured into saturated aqueous NaCl (20 mL)/saturated aqueous $NaHCO_3$ (20 mL) and extracted with $CHCl_3$ (3 × 15 mL), and the combined organic extracts were dried and evaporated. PTLC ($CHCl_3$) of the residue afforded 314 mg (61%) of pure **61**: bp 230 °C/0.1 mm; NMR δ 7.98 (m, 2 H), 7.5 (m, 3 H), 6.2–7.1 (m, 4 H), 3.97 (m, 2 H), 3.67 (s, 3 H), 3.22 (m, 1 H), 2.78 (m, 1 H), 2.18 (m, 2 H), 0.91 (d, 3 H, $J$ = 7 Hz). Anal. Calcd for $C_{19}H_{21}NO_4$: C, 63.5; H, 5.9; N, 3.9. Found: C, 63.5; H, 5.9; N, 3.8.

**1,3α-Dimethyl-2β-cyano-4α-(3-methoxyphenyl)piperidine (67).** A solution of 3.0 g (12.8 mmol) of piperidone **42** in $Et_2O$ (34 mL) was cooled in an ice bath and treated with 1.33 M $LiAlH_2(OEt)_2$ (10.0 mL, 13.3 mmol) over 3 min. The resulting suspension was pipetted into a solution of 8.30 g (128 mmol) of KCN in 1.5 M $H_2SO_4$ (112 mL) with vigorous stirring and ice-bath cooling over 10 min. The mixture was allowed to come to room temperature over 14 h, degassed for 30 min with $N_2$, and then poured in 3.75 M aqueous NaOH (100 mL) and extracted with $CHCl_3$ (3 × 75 mL). The combined organic extracts were dried and evaporated to afford 3.12 g (100%) of **67**: mp 77–78 °C ($CH_2Cl_2$/hexane); NMR δ 7.16 (m, 1 H), 6.71 (m, 3 H), 3.80 (s, 3 H), 3.72 (m, 1 H), 1.4–3.3 (m), 2.40 (s, 3 H), 0.93 (d, 1 H, $J$ = 7 Hz). Anal. Calcd for $C_{15}H_{20}N_2O$: C, 73.7; H, 8.3; N, 11.5. Found: C, 73.8; H, 8.4; N, 11.5.

**1,3α-Dimethyl-2β-acetyl-4α-(3-methoxyphenyl)piperidine (69).** Ketone **69** was prepared from nitrile **67** as described for the preparation of ketone **48** to afford a 94% yield of **69**: NMR δ 7.16 (m, 1 H), 6.70 (m, 3 H), 3.77 (s, 3 H), 3.23 (d, 1 H, $J$ = 4 Hz), 2.25 (s, 3 H), 2.19 (s, 3 H), 1.5–3.4 (m), 0.92 (d, 3 H, $J$ = 7 Hz); IR 1710 (s) $cm^{-1}$; MS $m/e$ 218 ($M^+ - COCH_3$). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.5; H, 8.9; N, 5.4. Found: C, 73.8; H, 8.8; N, 5.6.

**2,9α-Dimethyl-8-methylene-2′-methoxy-6,7-benzomorphan (70).** Methylenebenzomorphan **70** was prepared as described for the β isomer with reaction times of 20 and 24 h. Distillation gave methylenebenzomorphan **70**, bp 120–150 °C/0.1 mm, in 59% yield. The hydrochloride has mp 232–235 °C dec (acetone). NMR δ 7.54 (d, 1 H, $J$ = 9 Hz), 6.66 (d of d, 1 H, $J$ = 3 and 9 Hz), 6.50 (d, 1 H, $J$ = 3 Hz), 5.72 (s, 1 H), 4.72 (s, 1 H), 3.77 (s, 3 H), 3.07 (d, 1 H, $J$ = 3 Hz), 2.74 (br s, 1 H), 1.3–2.6 (m), 2.25 (s, 3 H), 0.82 (d, 3 H, $J$ = 7 Hz). Anal. Calcd for $C_{16}H_{21}NO$: C, 79.0; H, 8.7; N, 5.8. Found: C, 78.8; H, 8.7; N, 5.7.

**2,9α-Dimethyl-8-(bromomethylene)-2′-methoxy-6,7-benzomorphan (73).** A solution of 44 mg (0.18 mmol) of methylenebenzomorphan **70** in $CHCl_3$ (3 mL) was treated dropwise with 0.97 M $Br_2/CHCl_3$ (0.2 mL, 0.194 mmol). After 15 min at 25 °C, the solution was poured into saturated aqueous $NaHCO_3$ (20 mL) and extracted with $CHCl_3$ (3 × 10 mL). The combined organic extracts were dried and evaporated to afford 57 mg (98%) of **73**. TLC (EtOH), GC (column B, 180 °C), and NMR indicated two isomers in a 4:1 ratio. This material was unstable to Kugelrohr distillation and preparative GC: NMR δ 7.41 (d, 1 H, $J$ = 9 Hz), 6.5–6.83 (m, 3 H), 7.10 and 5.90 (isomeric bromomethylene singlets, **1 H**), 4.34 (br d, 1 H, $J$ = 4 Hz), 3.78 (s, 3 H), 2.61 and 2.81 (isomeric singlets, 3 H), 2.0–3.2 (m), 0.91 and 0.93 (isomeric doublets, 3 H, $J$ = 5 and 7 Hz); IR 1605 (s) $cm^{-1}$. $C_{16}H_{20}NO^{79}Br$ requiries 321.0728, found 321.0730; $C_{16}H_{21}NO^{81}Br$ requiries 323.0709, found 323.0714.

**2,9α-Dimethyl-8-oxo-2′-methoxy-6,7-benzomorphan (72).** A solution of 1.00 g (3.90 mmol) of methylenebenzomorphan **70** in $CH_2Cl_2$ (15 mL) was treated with 0.72 mL (936 mg, 8.24 mmol) of $CF_3CO_2H$, cooled on an ice bath, and treated dropwise with 1.28 M $CF_3CO_3H/CH_2Cl_2$[73] (9.65 mL, 12.36 mmol) over 25 min. After an additional 15 min, the solution was evaporated, the residue was taken up in $CHCl_3$ (20 mL) and washed with aqueous 0.5 M NaOH (20 mL), and the aqueous phase was extracted with $CHCl_3$ (2 × 20 mL). The combined organic extracts were dried and evaporated, and the residue was distilled at 140–170 °C/0.1 mm, giving 633 mg of an oil in 60% yield. The product was freed of 2% contaminating β isomer **53** by chromatography ($SiO_2$, EtOAc). Ketone **72** had $R_f$ 0.42 while **53** had $R_f$ 0.87. Crystallization of the hydrochloride from acetone afforded material of mp 216–219 °C dec: NMR δ 7.93 (d, 1 H, $J$ = 9 Hz), 6.81 (d of d, 1 H, $J$ = 9 and 3 Hz), 6.66 (d, 1 H, $J$ = 3 Hz), 3.83 (s, 3 H), 3.03 (br d, 1 H, $J$ = 3 Hz), 2.94 (br s, 1 H), 2.37 (s, 3 H), 1.5–2.7 (m), 0.94 (d, 3 H, $J$ = 7 Hz); IR 1665 (s) $cm^{-1}$; MS $m/e$ 245 ($M^+$). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.4; H, 7.8; N, 5.7. Found: C, 73.3; H, 7.8; N, 5.6.

**2,9α-Dimethyl-8-hydroxy-2′-methoxy-6,7-benzomorphan (74).** A solution of 2.11 g (8.61 mmol) of ketone **72** in $Et_2O$ (40 mL) was treated with 1.63 g (43 mmol) of $LiAlH_4$ in one portion at 25 °C. After 18 h, sequential addition of 1.63 mL of $H_2O$, 1.63 mL of 15% aqueous NaOH, and 4.89 mL of $H_2O$ followed by filtration and evaporation afforded 2.00 g (93.8%) of **74** which NMR indicated was a 76:24 mixture of isomers. The α-hydroxy isomer is known, but characterized only as the HCl salt,[5] so **74** was characterized as the free base as a mixture of isomers: NMR δ 7.27 and 7.21 (isomeric doublets, 1 H, $J$ = 2 Hz), 4.64 and 4.40 (isomeric benzylic protons, d, br s, 1 H, $J$ = 6 Hz); 4.55 varies (brs, 1 H), 3.78 (s, 3 H), 2.66 and 2.52 (isomeric singlets, 3 H), 1.8–3.0 (m), 0.99 and 0.83 (isomeric doublets, 3 H, $J$ = 7 Hz). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.8; H, 8.6; N, 5.7. Found: C, 72.8; H, 8.6; N, 5.7.

**2,9α-Dimethyl-2′-methoxy-6,7-benzomorphan (3).** This material was prepared as described[5] from 2.00 g (8.07 mmol) of **74** in HOAc (25 mL)/70% aqueous $HClO_4$ (2.5 mL) over 10% Pd/C (300 mg) for 3 days at 43 °C (40–50 psi). The residue from filtration and evaporation of the hydrogenation solution was added to saturated aqueous $NaHCO_3$ (30 mL) and extracted with $CHCl_3$ (3 × 20 mL), filtering each extract through anhydrous $Na_2SO_4$. Further drying followed by evaporation afforded 1.72 g (92%) of **3** whose HCl salt was prepared and crystallized from acetone/EtOH: mp 256–258 °C dec (lit.[5] mp 254–256 °C dec; NMR of **3**, δ 6.96 (d, 1 H, $J$ = 8 Hz), 6.70 (d, 1 H, $J$ = 2 Hz), 6.53 (m, 1 H), 3.75 (s, 3 H), 2.39 (s, 3 H), 1.2–3.2 (m), 0.89 (d, 3 H, $J$ = 7 Hz); NMR of **3**·HCl ($CD_3OD$), δ 7.08 (d, 1 H, $J$ = 8 Hz), 6.82 (d, 1 H, $J$ = 2 Hz), 6.68 (m, 1 H), 3.74 (s, 3 H), 2.92 (s, 3 H), 0.97 (d, 3 H, $J$ = 7 Hz) [lit.[5] NMR ($CD_3OD$) δ 0.97 (C-9 $CH_3$)].

**2,9α-Dimethyl-2′-hydroxy-6,7-benzomorphan·HBr.** The phenol was prepared from **3**·HCl as described.[5] Crystallization of the crude product from EtOH afforded the phenol·HBr, mp 243–244 °C dec (lit.[2] 243–245 °C dec).

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## References and Notes


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# Notes

## Synthesis of Lepidopterene

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The formation of 1,2-di(9-anthryl)ethane (**3a**) from 9-halogenomethylanthracenes **1a** via 9-anthrylmethyl radicals **2a** is sporadically accompanied by the isomeric hydrocarbon lepidopterene (**4a**) whose structure has been established recently by X-ray analysis.[1] Lepidopterene is believed to be formed from a sandwich complex of radicals **2a** by "a new type of formal $5\pi_s + 5\pi_s$ cycloaddition resulting in the formation of three $\sigma$ bonds".[2]

During the course of a spectroscopic investigation, we have recently found that lepidopterene in solution actually is in equilibrium with a valence isomer to which we assigned structure **5a**.[3] Conclusive chemical evidence for the cycloreversion product **5** has been obtained by potassium permanganate oxidation of lepidopterene to give the heretofore unknown 9-anthrylmethyl-substituted anthrone **6**. The spectroscopically deduced thermodynamic data[3] for the equilibrium **4a** $\rightleftarrows$ **5a** have prompted us to synthesize **5a** and, consequently, **4a** by the following unambiguous route, thus showing that the formation of lepidopterene from radicals **2** is explicable in terms of an "old type" stepwise reaction. Furthermore, we can show that the structure of the compound described to be 1,2-di(9-anthryl)ethanol (**7a**) is incorrect, and so are, consequently, the structures of its derivatives **7b** and **7c**.[4,5]

Reduction of 9-anthraldehyde (**8**) with $LiAlH_4$ in tetrahydrofuran gives 9-hydroxymethyl-10-(9-anthrylmethyl)-9,10-dihydroanthracene[6] (**9a**). Previous[4,5] claims as to the formation of 1,2-di(9-anthryl)ethanol (**7a**) by reduction of 9-anthraldehyde with lithium aluminum hydride are refutable on the basis of NMR spectroscopic data of **9a** and its derivatives **9b** and **9c**, listed in Table I. Also in agreement with structures **9**, but not **7**, are the mass spectrometrically determined molecular weights.

Treatment of acetate **9b** with potassium *tert*-butoxide leads to the nonisolable **5** which spontaneously undergoes the anticipated[3] intramolecular Diels–Alder reaction to give **4a** in 92% yield. Consequently, the frequently observed incidental formation of **4** from radicals **2** can be explained by a two-step reaction in which first the "head-to-tail dimer" **5** is formed

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