carbon–deuterium absorption at 2200 and 2100 $cm^{-1}$ and carbonyl absorption at 1730 and 1680 $cm^{-1}$ corresponding to the ester and thioester groups. The mass spectrum (70 eV) showed peaks at $m/e$ (relative intensity) 243 (16.6, $M^+$ – SEt), 225 (10, $M^+$ – SEt – $H_2O$), 197 (8, $M^+$ – COSEt – $H_2O$), 87 (100, methyltetrahydrofuryl-$d_2$). The spectrum showed a peak at $m/e$ 86 with intensity 9.3% of that at $m/e$ 87. The second band at $R_f$ 0.49 was removed from the plate and eluted from the silica gel with ether yielding 0.008 g of an oil. The spectral properties of the latter were identical with those of the starting bromide X-$d_2$.

**Reaction of the Bromide X-$d_2$ with Vitamin $B_{12s}$ in $H_2O$ with Potassium Carbonate.** Hydroxocobalamin (0.090 g, 0.000067 mol) was added to a solution of 0.362 g (0.0026 mol) of anhydrous $K_2CO_3$ in 2 mL of $H_2O$. The resulting suspension was placed under nitrogen and a solution of 0.060 g (0.0016 mol) of $NaBH_4$ in 1 mL of $H_2O$ was added. The reaction mixture was stirred at room temperature for 30 min. The reduced vitamin $B_{12s}$ was not dissolved but remained as a dark grey precipitate in a brown colored solution. The reaction mixture was taken into the darkroom and a solution of the 0.080 g (0.00021 mol) of the bromide X-$d_2$ in 0.25 mL of absolute methanol was added. The reaction mixture, pH 12.5, was stirred at room temperature for 24 h. The reaction was extracted with four 25-mL portions of ether, dried over $MgSO_4$, filtered, and evaporated. The residue weighing 0.049 g was spotted on a 2-mm silica gel prep plate and developed four times in 24:76 ether–hexane.

Band 1 at $R_f$ 0.39 was the rearranged product XVIII-$d_2$ weighing 0.029 g (45%). The spectral data (infrared, 250-MHz NMR and deuterium NMR) were identical with those of the rearranged product XVIII-$d_2$ obtained in the reaction in water described above. The mass spectrum showed fragmentation ($m/e$ 243, 197, 87) similar to that shown by the rearranged product XVIII-$d_2$. The spectrum showed a peak at $m/e$ 86 with intensity 13.7% of that at $m/e$ 87. The $m/e$ 86 peak in the starting bromide VIII-$d_2$ was 8.4% of the $m/e$ 87 peak. Band 2 at $R_f$ 0.47 was the unrearranged product XVI-$d_2$ weighing 0.014 g (22%). The spectral data (infrared and nmr) were similar to those of the unrearranged product XVI-$d_2$. The deuterium NMR spectrum showed a single resonance at $\delta$ 3.76 corresponding to deuterium at the carbon adjacent to oxygen on the tetrahydrofuran ring. The mass spectrum showed fragmentation ($m/e$ 243, 225, 197, 87) similar to that shown by the unreacted product (64). The spectrum showed the peak at $m/e$ 86 with inensity 17.25% of that at $m/e$ 87. It appears then that both rearranged and unrearranged products, XVIII-$d_2$ and XIX-$d_2$, are undergoing exchange, to a limited degree, at the position $\alpha$ to oxygen on the tetrahydrofuran ring.

**Control Reaction without Hydroxocobalamin.** A solution of 30 mg (0.8 mmol) of sodium borohydride in 0.5 mL of $D_2O$ was added to a solution of 181 mg (1.3 mmol) of anhydrous potassium carbonate in 1 mL of $D_2O$. This solution was then treated with 40 mg (0.1 mmol) of bromide X in 0.1 mL of MeOD. The reaction was stirred at room temperature for 24 h and then extracted with three 20-mL portions of ether. After drying over anhydrous $MgSO_4$, evaporation yielded 39 mg of product identical in every respect with the starting bromide X. No rearrangement product was detected by TLC or NMR. The mass spectrum showed that no deuterium had been incorporated during the reaction.

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# Studies Directed at a Synthesis of the Morphine Alkaloids. A Photochemical Approach

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Studies directed at a synthesis of the morphine alkaloids by photocyclization of aryl vinyl ethers (e.g., A → B) has resulted in preparation of representatives of the *trans*-morphine ring system; e.g., **49**, **51**, and **52**. Photocyclization substrates **1a–c**, **25a–e**, and **33a–d** are prepared by reaction of the appropriate substituted phenol with epoxy ketones of type **8** or by annelation of 4-oxopiperidines with (aryloxy)methyl vinyl ketones of type **30**. Photocyclization conditions have been developed to provide a generally high level of chemical efficiency; photocyclization of **33d** provides tetracyclic benzodihydrofuran **35b** in 95% yield on a 30-g reaction scale. The remaining ring in morphine is constructed by addition of cyanide ion to an immonium ion derived from enamine **40b** to give **47b**. Amino nitrile **47b** is converted to *trans*-morphine derivative **49c** by nitrile addition with methyllithium, imine hydrolysis, and cyclodehydration of the resulting methyl ketone.

The first total synthesis of morphine (R = H) and codeine (R = Me) was reported by Gates and Tschudi over 30 years ago.[1] This landmark in organic chemistry provided chemical confirmation of the structure of morphine proposed by Robinson in 1925.[2] The well-exploited analgesic properties of natural morphine and codeine have stimulated intense interest in the development of practical total syntheses of these opium-derived alkaloids. Several approaches have been developed,[3] but a common inter-

(1) Gates, M.; Tschudi, G. *J. Am. Chem. Soc.* **1952**, *74*, 1109; **1956**, *78*, 1380.

(2) Gulland, J. M.; Robinson, R. *Mem. Proc. Manchester Lit. Phil. Soc.* **1925**, *69*, 79.

(3) For some of the most recent work, see: (a) Moos, W. H.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 227. (b) Evans, D. A.; Mitch, C. H. *Tetrahedron Lett.* **1982**, *23*, 285. (c) Rice, K. C. *J. Org. Chem.* **1980**, *45*, 3135. (d) Weller, D. D.; Weller, D. L. *Tetrahedron Lett.* **1982**, *23*, 5239. (e) Ciganek, E. *J. Am. Chem. Soc.* **1981**, *103*, 6261. (f) Szántay, C.; Blaskó, G.; Bárczai-Beke, M.; Péchy, P.; Dörnyei, G. *Tetrahedron Lett.* **1980**, *21*, 3509. (g) Schwartz, M. A.; Zoda, M. F. *J. Org. Chem.* **1981**, *46*, 4623. These papers provide references to most of the work directed at synthesis of the morphine alkaloids.

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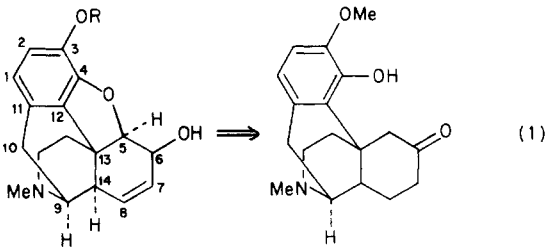
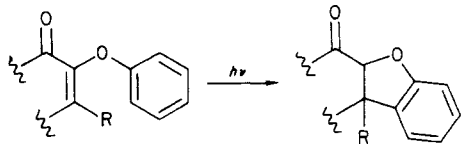
mediate in all of these has been dihydrothebainone (eq 1), which was utilized in the original Gates synthesis.[4]




(1)

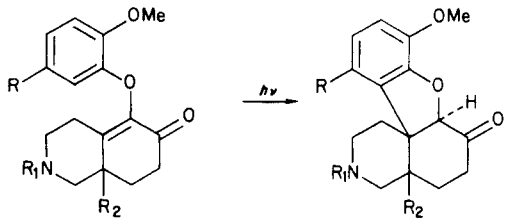
Our approach is fundamentally different and is based on an early benzodihydrofuran ring construction by photocyclization of an aryl vinyl ether; e.g., A → B.[5] We have




A B

applied this methodology to a total synthesis of the Amaryllidaceae alkaloid *dl*-lycoramine.[6] In this paper, we report the details of our photochemical approach to the morphine alkaloids. Several strategies have been investigated, but all are related by the common photocyclization process A → B. Several new morphine structural analogues have evolved from this study and we have succeeded in the preparation of representatives of the *trans*-morphine ring system; e.g., **49**, **51**, and **52**.

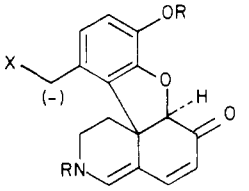
**The Octahydroisoquinoline Photoannelation Route to Morphine.** Several years ago, we reported preliminary studies involving the photocyclization of **1a** to **2a** (88% isolated yield).[7] This reaction served as a model for further study of the octahydroisoquinoline photoannelation route to the morphine ring system.



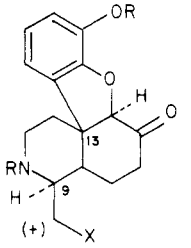

**1a**, R = CN; $R_1$ = Me; $R_2$ = $CO_2Et$
**b**, R = CN; $R_1$ = $R_2$ = $CO_2Me$
**c**, R = $R_1$ = $R_2$ = $CO_2Me$

**2**

At the outset of these studies, we envisioned two conceptually different strategies for construction of the remaining ring of the morphine skeleton. Conversion of **2**, or a related substance, to a stabilized anion of type **3** might result in intramolecular 1,6-Michael addition. Alternatively, a stabilized carbocation of type **4** might undergo intramolecular aromatic ring alkylation or acylation. Both of these approaches have been pursued and that based on **4** has been reduced to practice. We now present a detailed account of these studies.




**3**



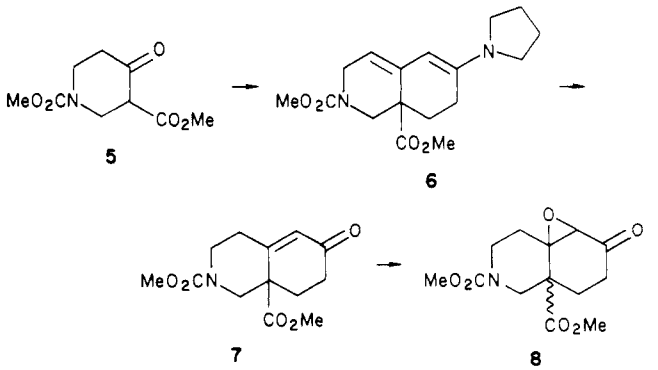

**4**

With regard to development of substrates of type **3**, we found (vide infra) that the basic nitrogen atom in **2a** was incompatible with reactions desired of other functional groups. Aryloxy enones **1b** and **1c** were prepared by methods developed for the synthesis of **1a**.[7]

Addition of 1,3-dicarbomethoxy-4-oxopiperidine (**5**)[8] to methyl vinyl ketone in benzene solution containing a catalytic amount of sodium hydride (Scheme I), followed by cyclization–dehydration of the intermediate diketone with pyrrolidine in refluxing benzene gives dienamine **6**; hydrolysis of **6** gives enone **7** (mp 121–122 °C) in 75% overall yield from **5**. Epoxidation of **7** with basic hydrogen peroxide in methanol affords crystalline (97–98 °C) epoxy ketone **8** in 70% yield. Aryloxy enone **1b** (mp 131–132 °C) is obtained by reaction of epoxy ketone **8** and 2-methoxy-5-cyanophenol in refluxing THF solution containing potassium hydride (~0.15 equiv) and 18-crown-6 (~0.15 equiv) in 90% yield (47% overall yield from oxopiperidine **5**). Similarly, **1c** is prepared from epoxy ketone **8** and 2-methoxy-5-carbomethoxyphenol in 75% yield. These experiments demonstrate the high efficiency and substituent compatibility of the epoxy ketone route[9] to aryloxy enones of type **1**. Using this procedure, large quantities of **1a–c** were available for photochemical study.

Irradiations of **1a–c** in the aprotic solvent benzene results in isolation of the highly strained trans-fused dihydrofurans **10a–c** in >90% yield. We have proposed[10] that, in effect, only one of two possible conrotatory photocyclizations of **1a–c** occurs. This electrocyclic process generates intermediate ylides **9a–c**, which undergo a ste-

**Scheme I**




**5** **6** **7** **8**

(4) Recent developments make dihydrothebainone an attractive intermediate in morphine and codeine synthesis plans: (a) Weller, D. D.; Rapoport, H. *J. Med. Chem.* **1976**, *19*, 1171. (b) Rice, K. C. *J. Med. Chem.* **1977**, *20*, 164. (c) Lawson, J. A.; Degraw, J. I. *J. Med. Chem.* **1977**, *20*, 165. (d) Iijma, I.; Rice, K. C.; Silverton, J. V. *Heterocycles* **1977**, *6*, 1157.

(5) For reviews of this type of photocyclization, see: (a) Schultz, A. G. *Acc. Chem. Res.* **1983**, *16*, 210. (b) Schultz, A. G.; Motyka, L. A. In "Organic Photochemistry", Padwa, A., Ed.; Marcel Dekker: New York, 1983; Vol. 6, p 1.

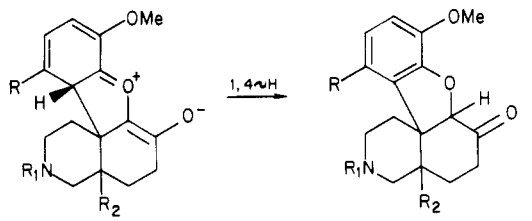
(6) (a) Schultz, A. G.; Yee, Y. K.; Berger, M. H. *J. Am. Chem. Soc.* **1977**, *99*, 8065. (b) For details of the synthesis of *dl*-lycoramine, see: Yee, Y. K. Ph.D. Thesis, Cornell University, 1978.

(7) (a) Schultz, A. G.; Lucci, R. D. *J. Chem. Soc., Chem. Commun.* **1976**, 925. (b) Schultz, A. G.; Lucci, R. D.; Fu, W. Y.; Berger, M. H.; Erhardt, J.; Hagmann, W. K. *J. Am. Chem. Soc.* **1978**, *100*, 2150. (c) For additional detail, see: Lucci, R. D. Ph.D. Thesis, Cornell University, 1977.

(8) Prepared by modification of the procedure described by Clark-Lewis, J. W.; Mortimer, P. I. *J. Chem. Soc.* **1961**, 189; see ref 7c for the modified experimental procedure.

(9) Structural requirements for the epoxy ketone are discussed in ref 7b. For an interesting base-catalyzed rearrangement of a 2-(aryloxy)-2-cyclohexen-1-one, see: Schultz, A. G.; Napier, J. J. *J. Chem. Soc., Chem. Commun.* **1981**, 224.

(10) For a discussion of the stereoselectivity of aryloxy enone photocyclization, see ref 5 or 7b.

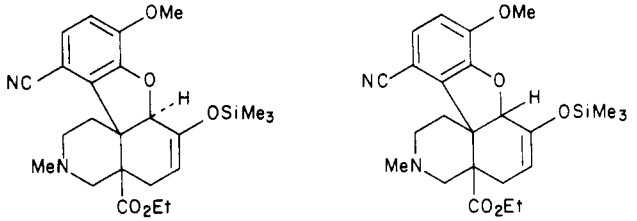


9 10

reospecific suprafacial [1,4] hydrogen rearrangement to give **10a–c**. The trans-fused dihydrofurans **10a,b** are quantitatively epimerized to the more stable cis-fused isomers **2a,b**. Alternatively, mixtures of **2a,b** and **10a,b** (~1:1) are obtained on irradiation of **1a,b** in methanol–benzene solution. Mechanistic studies[7] indicate that **9** undergoes (1) ylide protonation in methanol to give the more stable *cis*-dihydrofuran **2a**, and (2) the competing intramolecular [1,4] hydrogen rearrangement to give **10a**.

Thus, both isomer series **2** and **10** are available in pure, crystalline form by a photochemical technique that is adaptable to relatively large-scale laboratory synthesis. On several occasions we have performed aryloxy enone photocyclizations on an ~100-g scale using a 2000-mL Pyrex photoreaction flask. When photosubstrates are reasonably pure, irradiation with a 450-W mercury arc lamp requires ~24 h for complete conversion of starting material. In general, it is important to monitor photoreactions carefully because photoproducts may possess significant photoreactivity.[11]

With conditions for efficient photocyclization defined, attention was directed to the introduction of unsaturation necessary for construction of the remaining ring in the morphine ring skeleton. Treatment of ketone **2a** with lithium diisopropylamide (LDA) in THF at −78 °C followed by addition of chlorotrimethylsilane gives enol silyl ether **11** in 64% yield. Similarly, the strained *trans*-di-

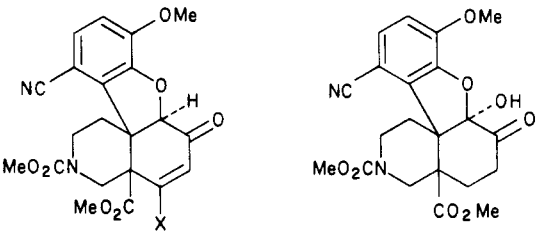


11 12

hydrofuran **10a** gives enol silyl ether **12** in 93% yield. While the lithium enolate generated from **2a** reacts with phenylselenenyl chloride[12] at −78 °C to give a C(7) phenylseleno ketone (not shown), reaction with bromine[13] did not produce the desired C(7) bromo ketone. Furthermore, the phenylseleno ketone failed to give the desired enone on oxidation with *m*-chloroperbenzoic acid. Reaction of **2a** and **10a** with phenylselenenyl chloride and concentrated hydrochloric acid in ethyl acetate[14] or bromine in acetic acid resulted in apparent introduction of the heteroatom at C(5); ketone **2a** did not react with DDQ in refluxing dioxane.[15]

Treatment of either **2b** or **10b** with DDQ in refluxing dioxane affords enone **13a** in ~60% yield. This uncatalyzed dehydrogenation is difficult to consistently reproduce. In an attempt to improve the efficiency of dehydrogenation, HCl-catalyzed DDQ reactions were studied.[16] When dioxane saturated with dry HCl is used as solvent, three products are obtained from **10b** in quantitative yield; e.g., enone **13a** (50%), chloroenone **13b** (27%), and a compound tentatively identified as diketone hemiketal **14** (23%).

The formation of these products is explained by hydride abstraction from the C(7) enol form of **2b**[17] at both C(5) and C(8). Capture of the C(8) carbocation by chloride ion would give a β-chloro ketone, from which elimination of HCl would generate **13a**. DDQ oxidation of the β-chloro

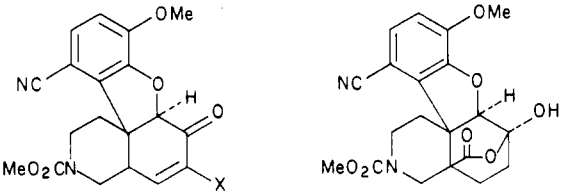


**13a**, X = H
**b**, X = Cl

**14**

ketone would give the chloro enone **13b**. On the other hand, capture of the C(5) carbocation with chloride ion would give an α-chloro ether which apparently undergoes hydrolysis to hemiketal **14** on workup with aqueous base. Enone **13a** also might be generated by abstraction of a C(8) proton from the C(5) carbocation. The optimum yield of enone **13a** (70–75%) is obtained by using a one-half-saturated solution of dry HCl in dioxane as reaction solvent.

We next sought a method for decarbalkoxylation of the vinylogous β-keto ester **13a** to give enone **15a**. The pro-



**15a**, X = H
**b**, X = Br

**16**

cedures employing bases such as 1,5-diazabicyclo[4.3.0]non-4-ene (DBN), 1.6-diazabicyclo[5.4.0]undec-6-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (Dabco), and quinuclidine[18] resulted in extensive decomposition of **13a** with no enone **15a** detectable by $^1$H NMR and TLC analyses. Methods involving NaCl in wet $Me_2SO$[19] and lithium iodide in refluxing collidine[20] also resulted in decomposition of **13a**. However, enone **15a** is obtained by treatment of **13a** with basic alumina in refluxing aqueous dioxane[21] in 26% yield. The low yield coupled with the variable reproducibility encountered with this decarbomethoxylation method necessitated the development of an alternative preparation of **15a**.

(11) (a) Schultz, A. G.; Napier, J. J.; Lee, R. *J. Org. Chem.* **1979**, *44*, 663. (b) Schultz, A. G.; Ranganathan, R.; Kulkarni, Y. *Tetrahedron Lett.* **1982**, *23*, 4527.

(12) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

(13) Stotter, P. L.; Hill, K. A. *J. Org. Chem.* **1973**, *38*, 2576.

(14) Sharpless, K. B.; Laure, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137.

(15) The unreactivity of **2a** toward DDQ is believed to be a result of the formation of a complex between DDQ and the basic nitrogen atom of **2a**. See ref 4a and 4d for problems encountered on attempted oxidative-elimination of a phenylselenide in the presence of a basic nitrogen atom.

(16) Walker, D.; Hiebert, J. D. *Chem. Rev.* **1967**, *67*, 153.

(17) Ringold, H. J.; Turner, A. *Chem. Ind. (London)* **1962**, 211.

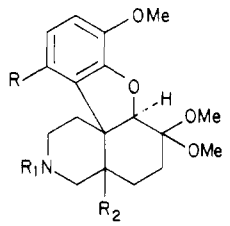
(18) Parish, E. J.; Haung, B.-S.; Miles, D. H. *Synth. Commun.* **1975**, *5*, 341 and references cited therein.

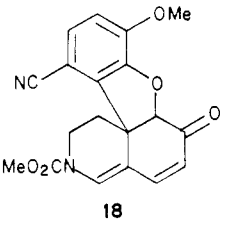
(19) (a) Krapcho, A. P.; Lovey, A. J. *Tetrahedron Lett.* **1973**, 957. (b) Krapcho, A. P.; Jahngen, E. G. E.; Lovey, A. J. *Tetrahedron Lett.* **1974**, 1091.

(20) (a) Elsinger, F. *Org. Synth.* **1965**, *45*, 7. (b) Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. 1, p 617.

(21) Greene, A. E.; Cruz, A.; Crabbe, P. *Tetrahedron Lett.* **1976**, 2707.

Saponification of the hindered angular ester group in **2b** is accomplished with remarkable facility. Treatment of **2b** with 1 M methanolic sodium or potassium hydroxide at room temperature results in quantitative conversion to the pseudo acid **16** in less than 30 min. The hydrolysis is believed to occur by participation of the neighboring C(6) carbonyl group.[22] This supposition is supported by the observation that ketal **17b** is recovered unchanged after treatment for 48 h with excess KOH in refluxing methanol solution.





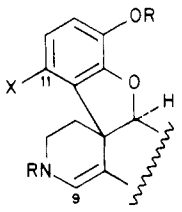
18

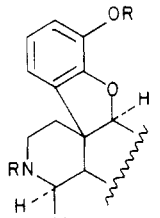
**17a**, R = CN; $R_1$ = Me; $R_2$ = $CO_2Et$
**b**, R = CN; $R_1$ = $R_2$ = $CO_2Me$
**c**, R = $R_1$ = $R_2$ = $CO_2Me$

Oxidative decarboxylation of pseudo acid **16** with $Pb(OAc)_4$ or $Pb(OAc)_4$–$Cu(OAc)_2$ in benzene–pyridine solution gives uncharacterized decomposition. However, treatment of **16** with DDQ in dry HCl-saturated dioxane solution provides enone **15a** in 60% overall yield from photoproduct **2b**.

Bromination of **15a** was expected to give a 7-bromo-$\beta,\gamma$-unsaturated ketone, from which dienone **18** might be obtained by 1,4-elimination of HBr. Instead, 7-bromo enone **15b** was obtained in 94% isolated yield. Unfortunately, **15b** could not be converted to dienone **18** either directly or as the C(6) ethylene glycol derived ketal.[23]

**A Photochemical Synthesis of the B/C Trans-Fused Morphine System.** We envisioned that the remaining ring in morphine might be built from **19a** by (1) addition of cyanide ion to an immonium ion derived from **19a** to give **20** and (2) intramolecular aromatic ring acylation in **20** or a derivative. Alternatively, morphine might be synthesized from **19b** by conversion of the nitrile group into a suitable one-carbon nucleophilic attachment at C(11) and (2) cyclization of *pro*-morphine C(10) with a C(9) immonium ion. The approach based on utilization of **19a** follows.





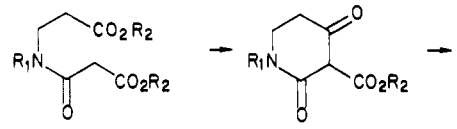
**19a**, X = H
**b**, X = CN

20

The enamine function in **19** was to be established by reduction of a lactam precursor. Epoxy ketones **24a–c** serve as key intermediates in the preparation of the required lactams (Scheme II). Thus *N*-methyl-$\beta$-alanine ethyl ester[24] is reacted with ethyl malonyl chloride[25] to give diester **21**. Dieckman cyclization with sodium hydride in benzene–ethanol gives **22a** in 80% yield. Purification of **22a** could not be accomplished without significant decarbethoxylation; however, annelation of crude **22a** with methyl vinyl ketone gives enone **23a** in 48% yield. Epoxidation of **23a** with basic hydrogen peroxide affords epoxy ketone **24a** as a mixture of diastereoisomers in 68–78% yield. Using analogous methods, epoxy ketones **24b** and **24c** were also prepared.

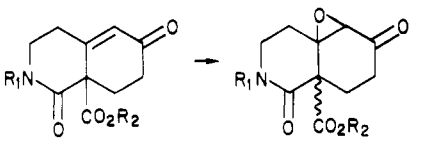
A series of aryloxy enones **25a–e** was prepared by reaction of the appropriate phenol with epoxy ketones **24a–c** and, in the case of **25b** and **25d**, by annelation of **22a** or **22b** with (aryloxy)methyl vinyl ketones **30a**[7] or **30b**, respectively.

**Scheme II**

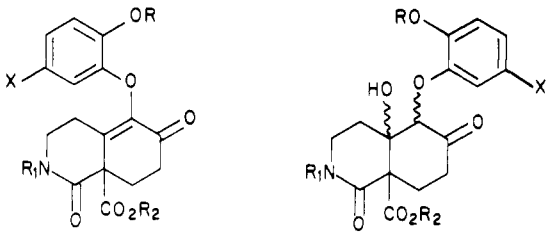


**21a**, $R_1$ = Me; $R_2$ = Et
**b**, $R_1$ = $R_2$ = Me
**c**, $R_1$ = $CH_2Ph$; $R_2$ = Me

22



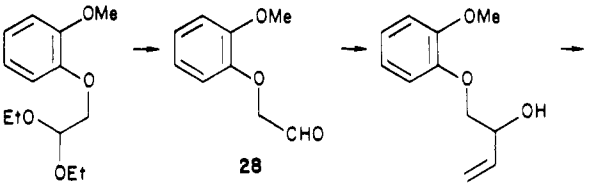
23 24



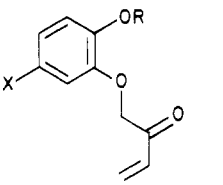
**25a**, X = CN; R = $R_1$ = Me; $R_2$ = Et
**b**, X = CN; R = $R_1$ = $R_2$ = Me
**c**, X = H; R = $R_2$ = Me; $R_1$ = $CH_2Ph$
**d**, X = H; R = $CH_2Ph$; $R_1$ = $R_2$ = Me
**e**, X = H; R = $CH_2OMe$; $R_1$ = $CH_2Ph$; $R_2$ = Me

26

**Scheme III**



27 28 29



**30a**, R = Me; X = H
**b**, R = Me; X = CN
**c**, R = $CH_2Ph$; X = H

(22) Similar reactivity has been observed for 2-oxo-10-carbethoxydecahydronaphthalene; (a) Hussey, A. S.; Laio, H. P.; Baker, R. H. *J. Am. Chem. Soc.* **1953**, *75*, 4727. (b) Dauben, W. G.; Tweit, R. C.; McLean, R. L. *J. Am. Chem. Soc.* **1955**, *77*, 48.

(23) Ketalization of $\gamma$-substituted $\alpha,\beta$-unsaturated cyclohexanones often results in deconjugation to the $\beta,\gamma$-unsaturated ketal; cf.: Johnson, W. S.; Rogier, E. R.; Szmuskovicz, J.; Hadler, H. I.; Ackerman, J.; Battacharyya, B. K.; Bloom, B. M.; Stalmann, L.; Clement, R. A.; Bannister, B.; Wynberg, H. *J. Am. Chem. Soc.* **1956**, *78*, 6289. However, ketalization of **15b** gives the $\alpha,\beta$-unsaturated ketal in 72% yield. See ref 7c for the preparation and unsuccessful dehydrobromination experiments with this ketal.

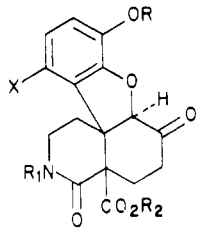
(24) Schloegl, K.; Schloegl, R. *Monatsh.* **1964**, 922; *Chem. Abstr.* **1964**, *61*, 11995f.

(25) (a) Stoube, R. *Org. Synth.* **1957**, *37*, 34. (b) Goldfarb, Y. L.; Taitz, S. Z.; Bulgarkova, V. N. *Izv. Akad. Nauk SSSR, Energ. Transp.* **1963**, 1299.

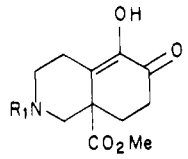
The preparation of **30** is outlined in Scheme III. Alkylation of the potassium salt of *o*-methoxyphenol with bromoacetaldehyde diethyl acetal gives acetal **27**, which is converted to the crystalline aldehyde **28** by hydrolysis with 1 equiv of perchloric acid in refluxing aqueous THF. Aldehyde **28** reacts with vinylmagnesium bromide to give the relatively stable allylic alcohol **29**. Jones oxidation of **29** gives the sensitive enone **30** in 50–70% yield. Generally, enones **30a–c** were prepared, distilled, and used immediately.

In the annelation approach, the intermediate aldol **26b** is dehydrated by treatment with pyrrolidine in refluxing benzene solution, followed by enamine hydrolysis with aqueous sodium acetate–acetic acid. On the other hand, **26d** undergoes dehydration with potassium hydride (catalytic) in refluxing dioxane solution.

Photocyclization of **25a** in $CH_2Cl_2$–$Me_2SO$ solution gives a mixture of epimeric benzodihydrofurans, from which epimerization affords crystalline **31a** (mp 193–194 °C) in 80% isolated yield. The efficiency of this route is illustrated with **31a**, which is obtained in 11% overall yield from the starting *N*-methyl-β-alanine methyl ester.



**31**

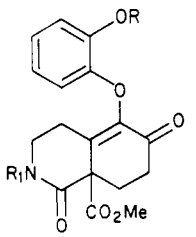


**32a**, $R_1$ = Me
**b**, $R_2$ = $CH_2Ph$

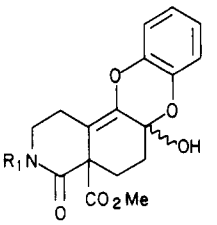
In contrast to the high-yield photocyclizations observed with **25a** and **25b**, irradiations of **25c** in protic solvents result in a complex mixture of photolysis products; irradiation in $Me_2SO$ gives three major products. Partition of the $Me_2SO$ reaction mixture between aqueous base and ether gives photohydrolysis products 2-methoxyphenol (55% yield) and α-diketone **32b** (59%) from the basic layer. The base-insoluble material is treated with $Na_2CO_3$ in benzene–methanol solution to effect epimerization; purification by chromatography gives benzodihydrofuran **31c** in 8% yield.

A similar type of photohydrolysis has been observed during photolysis of a related naphthyl vinyl sulfide.[27] While the source of water in these reactions is unknown, photohydrolysis seems to correlate with the presence of strongly electron-donating ortho substituents on the aromatic ring.[7] The electron-withdrawing cyano group offsets the deleterious effect of the methoxy group (e.g., **25** → **31a**), and the benzyloxy derivative **25d** gives the desired benzodihydrofuran **31d** in ~50% yield, along with some α-diketone **32a**. The *o*-acetoxy derivatives **33c** and **33d** undergo photocyclization in excellent yield. Thus, **35a** is obtained in 79% yield and **35b** has been prepared on a 30-g reaction scale in ~95% yield.

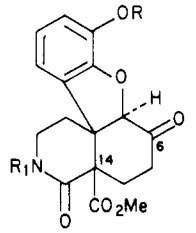
The *o*-acetoxy derivative **33c** is obtained by hydrogenolysis of the benzyl ether **25d** to give a mixture of **33a** and hemiketal **34a**, followed by phenolic acylation of the mixture with acetic anhydride and pyridine. Different methodology is required for the preparation of *N*-benzyl



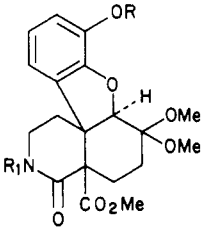
**33a**, R = H; $R_1$ = Me
**b**, R = H; $R_1$ = $CH_2Ph$
**c**, R = Ac; $R_1$ = Me
**d**, R = Ac; $R_1$ = $CH_2Ph$



**34a**, $R_1$ = Me
**b**, $R_1$ = $CH_2Ph$



**35a**, R = Ac; $R_1$ = Me
**b**, R = Ac; $R_1$ = $CH_2Ph$

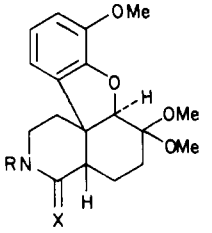


**36a**, R = H; $R_1$ = Me
**b**, R = H; $R_1$ = $CH_2Ph$
**c**, R = $R_1$ = Me
**d**, R = Me; $R_1$ = $CH_2Ph$
**e**, R = H; $R_1$ = $CH_2Ph$; $CO_2Me$ = H

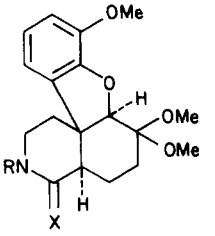
derivative **33d**; aqueous acetic acid hydrolysis of the methoxymethyl ether **25e** gives **33b** and **34b**, from which **33d** is cleanly obtained by acetylation with acetic anhydride–pyridine.

Conversion of photoproducts **31a,b** and **35a,b** to enamines of type **19** requires decarbomethoxylation at C(14). Saponification of **31b** gives a pseudo acid analogous in structure to **16**; however, we were not able to decarboxylate this pseudo acid under a variety of acidic or basic reaction conditions. The complicating pseudo acid formation could be prevented by protection of the C(6) carbonyl group. At this point, we decided to concentrate our efforts on the conversion of **35a,b** to enamine type **19a**.

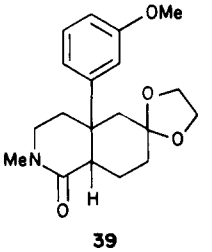
Ketalization of **35a** and **35b** occurs with cleavage of the phenolic acetate to give **36a** and **36b**, respectively. Alkylation with methyl iodide and $K_2CO_3$ in DMF or acetone gives **36c** and **36d** in ~75% overall yield. Decarbomethoxylation of **36c** with EtSK in DMF at 80 °C gives a mixture of epimeric lactams **37a** (62% yield) and **38a**



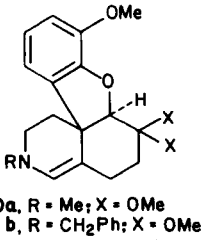
**37a**, R = Me; X = O
**b**, R = $CH_2Ph$; X = O
**c**, R = Me; X = $H_2$



**38**



**39**



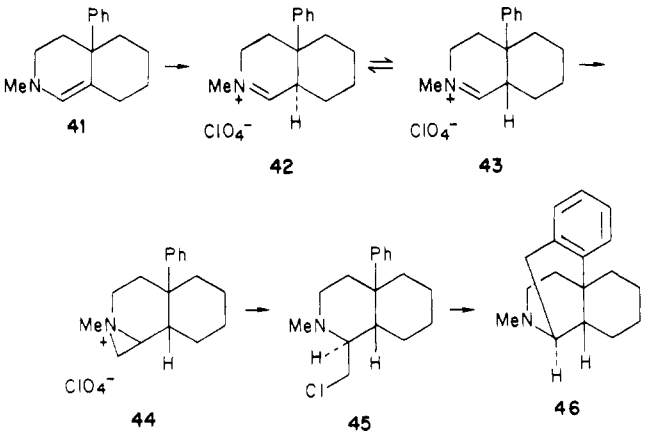
**40a**, R = Me; X = OMe
**b**, R = $CH_2Ph$; X = OMe
**c**, R = Me; X, X = O

(18%), which is separated by silica gel chromatography for purposes of characterization. Treatment of the minor lactam **38b** with KOH in refluxing ethanol results in clean

(26) The preparation of **21c** is superior to that for **21a** and **21b**, because the required β-alanine is prepared in 99% yield by the addition of benzylamine to methyl acrylate. The addition of methylamine to methyl and ethyl acrylate results in low yields of product because of competing addition of methylamine to 2 equiv of methyl or ethyl acrylate.

(27) Schultz, A. G.; Fu, W. Y.; Lucci, R. D.; Kurr, B. G.; Lo, K. M.; Boxer, M. *J. Am. Chem. Soc.* **1978**, *100*, 2140.

**Scheme IV**




conversion to a mixture of **37b** and **38b** in a ratio of 10:1. This result is consistent with that of Rapoport and co-workers; they showed that *cis*-phenylisoquinoline **39** is more stable than the trans isomer.[28] The mixture of lactams **37a** and **38a** is converted into enamine **40a** on reduction with diisobutylaluminum hydride (Dibal)[29] in THF. Similarly, **36d** is transformed into enamine **40b** in ~90% overall yield.

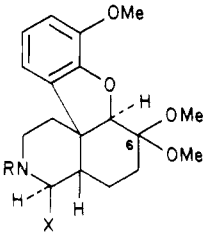
Several research groups have pursued benzomorphan and morphine syntheses by strategies which involve late formation of the C(10)–C(11) bond. Stella and co-workers[30] have described the $AlCl_3$-promoted cyclization of a 2-(chloromethyl)-4-phenylpiperdine to a benzomorphan in 60% yield. Rapoport and Gless[28c] made use of a Friedel–Crafts cyclization in the synthesis of 9-methyl-6,7-benzomorphan from 4-aryl-2-piperidones. However, this methodology could not be extended to cyclizations leading to dihydrothebainone derivatives.[3a]

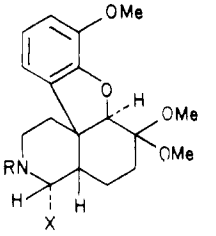
Evans and co-workers[31] have developed a synthesis of the morphinan skeleton from bicyclic enamine **41** (Scheme IV). Kinetic protonation of **41** gives trans-fused immonium perchlorate **42** with >95% stereoselectivity. In solution, **42** equilibrates to a mixture of cis-fused **43** and **42** (>95:1) and treatment of **43** with diazomethane gives the aziridinium perchlorate **44**, which is converted to morphinan **46** via cyclization[30] of the chloride **45**.[32] An analogous transformation of the trans-fused immonium perchlorate was not reported; however, a total synthesis of morphine based on the chemistry presented in Scheme IV has been accomplished.[3b] Rapoport and co-workers have modified their earlier approach[28c] by incorporating an aziridinium perchlorate of type **44**[3b] in their total synthesis of codeine.[3a]

We have discovered several interesting differences in reactivity between enamine **40a** and the Evans enamine **41**. Whereas hydrogenation of **41** in absolute ethanol has been reported to give exclusively the trans-fused perhydroisoquinoline,[31] we find that hydrogenation of **40a** in the presence of platinum catalyst in ethanol (60 psi, 3.5 h, 25 °C) gives cis-fused **37c** in 75% yield. Likewise, the "kinetically generated" perchlorate salt **42** is reported to undergo reduction with $NaBH_4$[31] to give the same trans-fused perhydroisoquinoline obtained from hydrogenation of **41**. We find that the apparent "kinetic" immonium perchlorate generated from enamine **40a** using the procedures of Evans[31] and Rapoport[3a] undergoes reduction by $NaBH_4$ to give the cis-fused **37c** in >90% yield. It should be noted that stereochemistry of amine **37c**, obtained from reduction of **40a**, has been rigorously established by comparison to **37c** and **38c** generated by stereospecific $LiAlH_4$ reduction of lactams **37a** and **38a**.

It appears that the important structural feature affecting the stereoselectivity of protonation at C(14) in **40** is the presence of the fully developed benzodihydrofuran ring fusion in these derivatives.[33] Whatever the reason, the "kinetic" protonation of **40a** apparently gives the more stable immonium ion, because no change in product composition is observed after subjecting **40a** to immonium ion equilibrating conditions.[31]

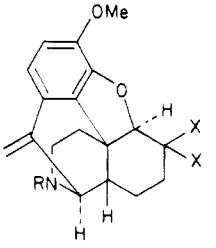
With the stereochemistry of enamine protonation secure, we proceeded with the construction of the B/C trans-fused morphine ring system **49** by methodology developed by

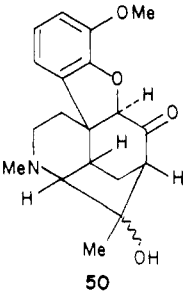



**48**

**47a**, R = Me; X = CN
**b**, R = $CH_2Ph$; X = CN
**c**, R = Me; X = COMe
**d**, R = $CH_2Ph$; X = COMe
**e**, R = $CH_2Ph$; X = $CHCH_2$
**f**, R = Me; X = COMe; C(6)C=O
**g**, R = $CH_2Ph$; X = COMe; C(6)C=O




**49a**, R = Me; X, X = O
**b**, R = Me; X = OMe
**c**, R = $CH_2Ph$; X, X = O

**50**

Rapoport and Gless.[28c] Reaction of enamine **40a** with perchloric acid in methanol followed by addition of KCN at 0 °C results in formation of a mixture of aminonitriles. Chromatography of the reaction mixture on silica gel affords pure **47a** (46%) and **48a** (8%). When the addition of KCN is performed at room temperature and the reaction mixture is allowed to equilibrate over several hours, **47a** and **48a** are obtained in yields of 19% and 34%, respectively. Furthermore, treatment of purified **47a** and **48a** with the amino nitrile equilibration reagent Amberlite IRA-400[28c] produces mixtures of both **47a** and **48a**.

The interconversion of **47a** with **48a** might be difficult to control in large-scale manipulations, and we, therefore, were pleased to find that the *N*-benzylamine **40b** adds the elements of HCN to give **47b**, uncontaminated with ep-

(28) (a) Weller, D. D.; Rapoport, H. *J. Am. Chem. Soc.* **1976**, *98*, 6650. (b) Weller, D. D.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1977**, *42*, 1485. (c) Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 1324.

(29) Winterfeldt, E. *Synthesis* **1975**, 617.

(30) Stella, L.; Raynier, B.; Sufzur, J. *Tetrahedron Lett.* **1977**, 2721.

(31) Evans, D. A.; Mitch, C. H.; Thomas, R. C.; Zimmerman, D. M.; Robey, R. L. *J. Am. Chem. Soc.* **1980**, *102*, 5955.

(32) For an altogether different approach to morphinans and 14-hydroxymorphinans, see: Monkovic, I.; Wong, H. *Can. J. Chem.* **1976**, *54*, 883. Monkovic, I.; Conway, T. T.; Wong, H.; Perron, Y. G.; Pachter, I. J.; Belleau, B. *J. Am. Chem. Soc.* **1975**, *95*, 7910.

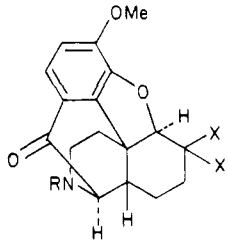
(33) The ketal function at C(6) in **40a** would not be expected to have a significant effect on the stereoselectivity of enamine hydrogenation; for hydrogenation of ketal and thioketal enamines related to **41**, see Scheme IV, ref 3a.

(34) For leading references to *trans*-morphine, see: (a) Gates, M.; Webb, W. G. *J. Am. Chem. Soc.* **1958**, *80*, 1186. (b) Gates, M.; Shepard, M. S. *J. Am. Chem. Soc.* **1962**, *84*, 4125. (c) Kugita, H.; Takeda, M.; Inoue, H. *J. Med. Chem.* **1970**, *13*, 973 and references cited therein.

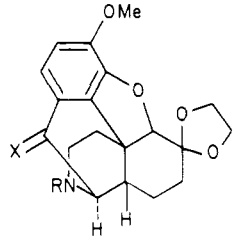
imers, in ~80% yield. Of potentially greater interest is the conversion of enamine **40b** to the C(9) vinyl derivative **47e** by treatment of the intermediate immonium perchlorate with vinylmagnesium bromide.

Amino nitrile **47a** undergoes addition with methyllithium to give an amine, which is converted to methyl ketone **47c** by mild aqueous acid hydrolysis or diketone **47f** by C(6) ketal hydrolysis using more vigorous conditions. Treatment of **47f** with trifluoromethanesulfonic acid results in cyclodehydration to give the trans-fused morphine derivative **49a** in ~75% yield. The successful construction of **49** by this Friedel–Crafts methodology is striking, particularly in light of the reported failure[3a] of this approach with synthetic intermediates lacking the benzodihydrofuran ring system. Similar methodology is used to convert **47b** to *trans*-morphine derivative **49c** in ~32% overall yield.

The Friedel–Crafts annelation sequence was carried out with epimeric amino nitrile **48a**, with the hope that diketone **48c** might undergo equilibration to **47f** with trifluoromethanesulfonic acid; instead, pentacyclic aldol **50** is obtained. The formation of **50** provides confirmation of the stereochemical assignment at C(14) in **48**.




**51a**, R = Me; X = OMe
**b**, R = $CH_2Ph$; X,X = O




**52a**, R = $CH_2Ph$; X = $CH_2$
**b**, R = CN; X = $CH_2$
**c**, R = CN; X = O

Ozonolysis of **49b** in methanol, followed by reduction with dimethyl sulfide gives the C(10) ketone derivative **51a** in ~60% yield. Ozonolysis studies with **49c** were considerably less successful; however, diketone **51b** could be obtained in 20–30% yield by oxidation of **49c** with $OsO_4$–$NaIO_4$ using an acidic solvent system (THF–$H_2O$–HOAc).

The marginal efficiency for the oxidative cleavage of the olefinic bond in **49a–c** was thought to be a result of the basic nitrogen atom in these derivatives. We, therefore, converted **49c** to **52b** by ketalization, followed by N-debenzylation with CNBr. Oxidative cleavage of the olefinic cyanamide **52b** with $OsO_4$–$NaIO_4$ occurs in near quantitative yield to give the C(10) ketone **52c** in ~74% yield from **49c**.

**Conclusion.** A photochemical approach to the synthesis of the morphine alkaloids has resulted in the preparation of B/C trans-fused morphine derivatives **49**, **51**, and **52**. As a logical consequence of these studies, several new morphine structural analogues have been prepared. In all of the syntheses, photocyclization conditions have been developed to provide a generally high level of chemical efficiency.

Future efforts will be directed at the conversion of *trans*-morphine derivatives[34] to the natural morphine alkaloids by known methods. The successful cyclization studies with **47f** and **47g** demonstrate, for the first time, that it is possible to construct the morphine skeleton with the benzodihydrofuran ring already intact.

## Experimental Section

**Nomenclature.** Throughout this section, the names of the fusion compounds are given nonsystematically. The numbering associated with the individual ring systems is retained. Thus, there will be duplication of numbers. As a result, consider the brackets as separators: the numbering preceding the brackets refers to the ring system cited before the brackets; the numbering after the brackets refers to the ring system cited after the brackets. For a comparison between the numbering employed in this paper and the IUPAC/CA name, see compound **10b**.

**Instrumentation.** ($^1H$ NMR spectra were obtained on Varian T-60 (60 MHz) or Varian XL-200 (200 MHz) and Hitachi-Perkin-Elmer R-600 (60 MHz) $^1H$ NMR spectrometers using tetramethylsilane as an internal standard. Infrared spectra were recorded on either a Perkin-Elmer 137B or Perkin-Elmer 680 spectrometer. Ultraviolet spectra were obtained on a Perkin-Elmer 552 spectrophotometer. Melting points were determined on a Thomas-Hoover apparatus in open capillary tubes and are corrected. Mass spectra were obtained on either a Hitachi-Perkin-Elmer RMU-6E mass spectrometer at RPI or a Finnigan 3300 gas chromatograph–mass spectrometer at Cornell University.

The light source for photochemistry was a Hanovia 450-W medium pressure mercury arc lamp. The lamp was placed in a water-cooled Pyrex immersion well. Reaction vessels containing solutions to be irradiated were attached to the immersion well and were saturated with argon prior to irradiation.

Analytical thin-layer chromatography (TLC) was conducted on precoated TLC sheets (silica gel 60 F-254, layer thickness 0.25 mm) manufactured by E. Merck and Co. Preparative silica gel thick-layer chromatography was performed on 20 × 20 cm glass plates coated with E. Merck AG Darmstadt silica gel PF-254 or GF-254. Preparative alumina thick-layer chromatography was performed on glass plates coated with aluminum oxide 60 PF-254.

Silica gel columns for chromatography utilized dry column chromatography Woelm silica gel (Activity III) from Woelm Pharma, West Germany, and flash chromatography was carried out with silica gel 60 from EM Reagents. Analytical and preparative liquid chromatography separations were performed with an analytical Waters HPLC (using a 3.9 mm i.d. × 30 cm μ-Porasil column) and a Waters Prep LC/system 500 (using Prep PAK-500 silica cartridges), respectively.

Analytical vapor-phase chromatography was performed on a Hewlett-Packard HP 5710A gas chromatograph equipped with a flame ionization detector (300 °C) and nitrogen carrier gas. The column used for all analyses consisted of a 10 ft × $^1/_8$ in. stainless steel tube filled with 10% UC W-98 on Chromosorb W, 80–100-mesh size. Peak areas were measured with a HP 3380A integrator. Microanalyses were carried out by Spang Microanalytical Laboratory, Eagle Harbor, MI, and Galbraith Laboratories, Knoxville, TN.

**Solvents.** Tetrahydrofuran (THF) was dried by distillation in the presence of potassium metal under a nitrogen atmosphere with benzophenone ketyl as indicator.

Hexamethylphosphoramide (HMPA) and dimethylformamide (DMF) were distilled at reduced pressure from calcium hydride and stored over 4-Å molecular sieves. Methylene chloride was distilled from phosphorus pentoxide and stored over 4-Å molecular sieves. Mallinckrodt anhydrous ethyl ether was used without further purification and dry methanol was obtained via distillation over magnesium turnings. Aldrich spectrophotometric grade methanol and benzene were used as solvents for photoreactions.

Aqueous extracts usually were dried with anhydrous $MgSO_4$ and solvents were removed under reduced pressure with a Buchi Rotovapor-R rotary evaporator. The last traces of solvent were removed by using a Welch Duo-Seal floor pump (~0.05 mm).

**1,2,3,4,6,7,8,9-Octahydro-2,9-dicarbomethoxy-6-oxoisoquinoline (7).** A vigorously stirred solution of piperidone **5**[8] (21.5 g, 100 mmol) in benzene (60 mL) was treated with sodium hydride (120 mg, 5 mmol) under $N_2$. After 10–15 min, when most of the sodium hydride had reacted, a solution of methyl vinyl ketone (12.2 mL, 10.5 g, 150 mmol) in benzene (20 mL) was added. After 12–18 h, the benzene solution was washed with brine (2 × 10 mL), dried, and evaporated. The residue was dissolved in benzene (80 mL), pyrrolidine (21 mL, 250 mmol) was added, and the solution was heated at reflux under $N_2$ using a Dean–Stark apparatus for 24 h. After the reaction mixture, which contained dienamine **6**, was cooled to room temperature, 50 mL of acetic acid–sodium acetate solution was added and reflux was continued for 2 h. Benzene (20 mL) was added and the organic solution was washed with water (50 mL), saturated sodium bicarbonate solution (50

mL), and brine (50 mL) and dried. Removal of solvent and trituration of the solid residue from ether gave **7** (20.02 g, 75%, mp 121–122 °C): IR (neat) 3.40, 5.75, 5.88, 5.97, 6.12 μm; $^1$H NMR ($CDCl_3$) δ 5.98 (1 H, br s), 4.88–3.94 (2 H, m), 3.74 (3 H, s), 3.34–1.60 (8 H, m).

Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41. Found: C, 58.46; H, 6.32.

**Decahydro-2,9-dicarbomethoxy-5,10-epoxy-6-oxoisoquinoline (8).** Aqueous sodium hydroxide (1 N, 36 mL) was added to a stirred solution of enone **7** (19.0 g, 71.2 mmol) and 30% hydrogen peroxide (20.5 mL, 214 mmol) in methanol (70 mL) at 15–20 °C over 30 min. Stirring was continued for 30 min at 15–20 °C and 6 h at room temperature. Saturated sodium chloride (50 mL) was added and continuous extraction with ether was conducted for 16 h. The ether extract (~300 mL) was washed with brine (25 mL) and dried. Removal of solvent, filtration through $SiO_2$ (activity III, 20 g) using methylene chloride, and crystallization from ether–petroleum ether gave **8** (14.15 g, 70%, mp 97–99 °C): IR ($CHCl_3$) 3.54, 5.77–5.90, 8.03, 11.64 μm; $^1$H NMR ($CDCl_3$) δ 4.95–4.15 (2 H, m), 3.82 (6 H, s), 3.35 (1 H, s), 3.25–1.60 (8 H, m).

Anal. Calcd for $C_{13}H_{17}NO_6$: C, 55.12; H, 6.05. Found: C, 55.11; H, 5.86.

**1,2,3,4,6,7,8,9-Octahydro-2,9-dicarbomethoxy-5-(2-methoxy-5-cyanophenoxy)-6-oxoisoquinoline (1b).** To a stirred mixture of potassium hydride (300 mg, 7.5 mmol, 1.3 g of an oil suspension) in THF (20 mL) under $N_2$ was added 3-hydroxy-4-methoxybenzonitrile (7.50 g, 50 mmol), 18-crown-6 (1.98 g, 7.5 mmol), and epoxide **8** (11.30 g, 40 mmol). The addition funnel was rinsed with THF (15 mL) and the mixture was heated at reflux temperature for 40 h. Benzene (20 mL), brine (25 mL), and water (25 mL) were added, and after separation of the layers, the aqueous layer was extracted with benzene–methylene chloride (1:1, 3 × 20 mL). The organic solution was washed with 10% potassium hydroxide (2 × 20 mL), water (4 × 20 mL), and brine (1 × 20 mL) and dried. Removal of solvent and crystallization from methylene chloride–ether–petroleum ether gave **1b** (14.88 g, 90%, mp 131–132 °C): IR ($CHCl_3$) 3.40, 4.49, 5.75–5.95, 6.10, 6.22, 6.31 μm; $^1$H NMR ($CDCl_3$) δ 6.83–7.43 (3 H, m), 4.00–4.95 (2 H, m), 3.97 (3 H, s), 3.84 (3 H, s), 3.72 (3 H, s), 1.94–3.17 (8 H, m); chemical ionization mass spectrum, *m/e* (relative intensity) 415 (100).

Anal. Calcd for $C_{21}H_{22}N_2O_7$: C, 60.86; H, 5.35. Found: C, 60.97; H, 5.46.

**Isovanillic Acid, Methyl Ester.** A solution of 3-hydroxy-4-methoxybenzonitrile (60.0 g, 0.40 mol) and potassium hydroxide (200.0 g, 3.6 mol) in water (500 mL) was heated at reflux temperature under $N_2$ for 6 h. After being cooled to 0 °C, the solution was acidified with concentrated HCl to pH 1. The precipitated product was removed by filtration, washed with cold water and ether, and dried in a vacuum oven at ~50 °C for 24 h. The dry solid (67.5 g, 100%) was dissolved in methanol (500 mL), concentrated $H_2SO_4$ (5 mL) was added, and the solution was heated to reflux temperature under $N_2$ for 16 h. The methanol was evaporated and the residue was dissolved in ether (200 mL). The ether solution was washed with water, saturated sodium bicarbonate solution, and brine and dried. Removal of solvent and crystallization from ether–petroleum ether gave the methyl ester (72.3 g, 99%, mp 65.5–66 °C): IR ($CHCl_3$) 3.00, 3.40, 5.88, 6.20, 6.28 μm; $^1$H NMR ($CDCl_3$) δ 7.76–7.50 (2 H, m), 6.86 (1 H, d, *J* = 9 Hz), 5.79 (1 H, s), 3.94 (3 H, s), 3.89 (3 H, s).

Anal. Calcd for $C_9H_{10}O_4$: C, 59.34, H, 5.53. Found: C, 59.31; H, 5.47.

**1,2,3,4,6,7,8,9-Octahydro-2,9-dicarbomethoxy-5-(2-methoxy-5-carbomethoxyphenoxy)-6-oxoisoquinoline (1c)** was prepared from isovanillic acid, methyl ester by the method described for **1b** (75%, mp 152–154 °C): IR ($CHCl_3$) 3.40, 5.74–5.90, 6.02, 6.20, and 6.28 μm; $^1$H NMR ($CDCl_3$) δ 7.68 (1 H, dd, *J* = 8.5, 2.0 Hz), 7.32 (1 H, d, *J* = 2.0 Hz), 6.92 (1 H, d, *J* = 8.5 Hz), 5.0–3.8 (2 H, m), 3.97 (3 H, s), 3.87 (3 H, s), 3.72 (3 H, s), 3.20–1.80 (8 H, m); chemical ionization mass spectrum, *m/e* (relative intensity) 448 (21), 416 (100).

Anal. Calcd for $C_{22}H_{25}NO_9$: C, 59.06; H, 5.63. Found: C, 59.19; H, 5.56.

**Irradiation of 1a in Benzene–Methanol.** A solution of enone **1a** (1.00 g, 2.60 mmol, 0.037 M) in benzene–methanol (1:1, 70 mL) was irradiated (Pyrex glassware) for 3.5 h. Removal of solvent and $^1$H NMR analysis indicated that **10a** and **2a** were present in a ratio of 6:4. Chromatography on $SiO_2$ (50 g, gradient eluant methylene chloride to 20% ether–methylene chloride) gave *trans*-dihydrofuran **10a** [310 mg, 31%, mp 145–147 °C; IR (KBr) 3.44–3.62, 4.50, 5.75, 5.82, 6.20, 6.38 μm; $^1$H NMR ($CDCl_3$) δ 7.28, 6.84 (2 H, AB quartet, *J* = 9 Hz), 5.22 (1 H, s), 4.18 (2 H, q, *J* = 7 Hz), 3.94 (3 H, s), 4.02–3.82 (1 H, m), 3.30–1.50 (9 H, m), 2.44 (3 H, s), 1.18 (3 H, t, *J* = 7 Hz); chemical ionization mass spectrum, *m/e* (relative intensity) 385 (100)] and *cis*-dihydrofuran **2a** [280 mg, 28%, mp 163–165 °C; IR (KBr) 3.45–3.60, 4.50, 5.80, 5.88, 6.21, 6.37 μm; $^1$H NMR ($CDCl_3$) δ 7.20, 6.82 (2 H, AB quartet, *J* = 9 Hz), 4.55 (1 H, s), 4.12 (2 H, q, *J* = 7 Hz), 3.95 (3 H, s), 3.70–1.60 (10 H, m), 2.13 (3 H, s), 1.11 (3 H, t, *J* = 7 Hz); chemical ionization mass spectrum, *m/e* (relative intensity) 385 (100)].

Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 65.61; H, 6.29. Found for **41a**: C, 65.57; H, 6.17. Found for **33a**: C, 65.66; H, 6.22.

**Irradiation of 1a in Benzene.** A solution of enone **1a** (14.0 g, 36.5 mmol, 0.12 M) in benzene (300 mL) was irradiated for 3 h. Removal of solvent gave **10a** (14.0 g, 100%) as a crystalline solid, of sufficient purity for use in subsequent reactions.

**Epimerization of 10a.** A solution of *trans*-dihydrofuran **10a** (1.00 g, 2.60 mmol) in benzene–methanol (1:1, 20 mL) with suspended sodium carbonate was stirred under $N_2$ for 24 h. Removal of solvent, filtration through Celite, using benzene as wash solvent, and crystallization from methylene chloride–ether–petroleum ether gave *cis*-dihydrofuran **2a** (874 mg, 87%).

**Irradiation of 1b in Benzene–Methanol.** Sealed-tube photolysis of **1b** (50 mg, 0.121 mmol) in benzene–methanol was performed for 4 h. TLC and $^1$H NMR analyses indicated that no starting material was present and **2b** and **10b** had formed in a ratio of ~1:1.

**Irradiation of 1b in Benzene–Methanol Saturated with Sodium Carbonate.** A solution of **1b** (400 mg, 0.99 mmol, 0.050 M) in benzene–methanol (1:1, 20 mL) with suspended sodium carbonate was irradiated for 3 h. Removal of solvent and filtration through silica gel (2 g, methylene chloride) gave **2b** (275 mg, 69%), which was crystallized from methylene chloride–ether (244 mg, 61%, mp 170–172 °C).

**Decahydro-2,9β-dicarbomethoxy-6-oxoisoquinolino-[5α,10β-*c*]-4-cyano-7-methoxy-2,3-dihydrobenzofuran (1,2,3,4,4a,5,6,7a-Octahydro-12-cyano-3,4a-dicarbomethoxy-9-methoxybenzofuro[3,2-*e*]isoquinolin-7-one, 10b).** A solution of **1b** (8.40 g, 20.3 mmol, 0.63 M) in benzene (320 mL) was irradiated for 4 h. The product, which crystallized directly from the reaction solvent, was isolated by filtration; more product was obtained upon complete evaporation and crystallization of the residue from methylene chloride–ether (total 7.50 g, 89%, mp 214–215 °C dec): IR (KBr) 3.40, 4.50, 5.76, 5.88, 6.19, 6.37 μm; $^1$H NMR ($CDCl_3$) δ 7.35, 6.88 (2 H, AB, q, *J* = 8.5 Hz), 5.25 (1 H, br s), 4.87–3.94 (2 H, m), 3.92 (3 H, s), 3.77 (3 H, s), 3.72 (3 H, s), 3.90–1.50 (8 H, m); chemical ionization mass spectrum, *m/e* (relative intensity) 415 (100).

Anal. Calcd for $C_{21}H_{22}N_2O_7$: C, 60.86; H, 5.35. Found: C, 60.98; H, 5.25.

**Decahydro-2,9β-dicarbomethoxy-6-oxoisoquinolino-[5β,10β-*c*]-4-cyano-7-methoxy-2,3-dihydrobenzofuran (2b).** **10b** (500 mg, 1.21 mmol) was dissolved in methylene chloride (10 mL), and while cooling in ice, the solution was saturated with dry hydrogen bromide. The reaction mixture was stirred at room temperature for 30 min, diluted with ether (10 mL), washed with 1 N sodium carbonate solution (2 × 5 mL) and brine (2 × 5 mL), and dried. Removal of solvent and crystallization from methylene chloride–ether gave **2b** (485 mg, 97%, mp 170–172 °C): IR ($CHCl_3$) 3.40, 4.49, 5.72, 5.78, 5.89, 6.19, 6.35 μm; $^1$H NMR ($CDCl_3$) δ 7.35, 6.86 (2 H, AB quartet, *J* = 8.5 Hz), 4.65 (1 H, br s), 4.20–3.60 (2 H, m), 3.95 (3 H, s), 3.75 (3 H, s), 3.67 (3 H, s), 3.60–1.70 (8 H, m); chemical ionization mass spectrum, *m/e* (relative intensity) 415 (100).

Anal. Calcd for $C_{21}H_{22}N_2O_7$: C, 60.86; H, 5.35. Found: C, 60.82; H, 5.23.

**Decahydro-2,9-dicarbomethoxy-6-oxoisoquinolino-[5α,10β-*c*]-4-carbomethoxy-7-methoxy-2,3-dihydrobenzofuran (10c).** A solution of **1c** (1.00 g, 2.24 mmol, 0.03 M) in benzene (75 mL) was irradiated for 1 h. Removal of solvent and crystallization from methylene chloride–ether gave **10c** (0.80 g,

80%, mp 184–185 °C): IR ($CHCl_3$) 3.42, 5.75–5.95, 6.20, 6.36 μm; $^1H$ NMR ($CDCl_3$) δ 7.35, 6.86 (2 H, m), 5.95 (1 H, br s), 4.25–3.60 (2 H, m), 3.95 (3 H, s), 3.90 (3 H, s), 3.77 (6 H, s), 3.1–1.6 (8 H, m); chemical ionization mass spectrum, *m/e* (relative intensity) 448 (29), 416 (100).

Anal. Calcd for $C_{22}H_{25}NO_9$: C, 59.06; H, 5.63. Found: C, 58.94; H, 5.58.

**Formation and Trapping of the Enolate of 10a.** A solution of diisopropylamine (20 μL, 0.143 mmol) in dry THF (0.2 mL) was treated with *n*-butyllithium (56 μL of 2.55 M solution in hexane, 0.143 mmol) at 0 °C under $N_2$. The solution was cooled to −78 °C and a solution of **10a** (40 mg, 0.104 mmol) in dry THF (0.5 mL) was added (30 s). The solution was stirred for 20 min at −78 °C and chlorotrimethylsilane (20 μL, 0.157 mmol) was added. After 20 min of stirring at −78 °C, the cold solution was poured into hexane (50 mL) and filtered through Celite. Removal of solvent gave **12** as a colorless oil (43 mg, 93%): IR ($CHCl_3$) 3.40, 4.50, 5.80, 6.00, 6.22, 6.38 μm; $^1H$ NMR ($CDCl_3$) δ 7.24, 6.79 (2 H, AB quartet, $J$ = 9 Hz), 4.96–4.68 (2 H, m), 4.07 (2 H, q, $J$ = 7 Hz), 3.90 (3 H, s), 3.86–1.98 (8 H, m), 2.45 (3 H, s), 1.10 (3 H, t, $J$ = 7 Hz), 0.28 (9 H, s).

**Formation and Trapping of the Enolate of 2a.** With use of the method described above, **11** was prepared from **2a** (64%): IR ($CHCl_3$) 3.40, 4.50, 5.82, 6.02, 6.20, 6.36 μm; $^1H$ NMR ($CDCl_3$) δ 7.24, 6.76 (2 H, AB quartet, $J$ = 9 Hz), 5.30–4.98 (1 H, m), 4.35 (1 H, br s), 3.88 (3 H, s), 3.96–1.65 (10 H, m), 2.47 (3 H, s), 0.95 (3 H, t, $J$ = 7 Hz), 3.30 (9 H, s).

**1,2,3,4,5,6,9,10-Octahydro-2,9-dicarbomethoxy-6-oxoisoquinolino[5β,10β-*c*]-4-cyano-7-methoxy-2,3-dihydrobenzofuran (13a).** A mixture of **10b** (200 mg, 0.483 mmol), DDQ (150 mg, 0.66 mmol) and dioxane (~0.5 mL) was heated at 130 °C under $N_2$ for 18 h. The tarry residue was dissolved in methylene chloride (50 mL), washed with 1 N sodium carbonate (5 × 10 mL), and dried. Removal of solvent gave crystalline **13a** (139 mg, 70%). Preparation of the analytical sample was accomplished by filtration through a small amount of silica gel (methylene chloride) and crystallization from methylene chloride–ether (101 mg, 51%, mp 170–172 °C): IR (KBr) 3.40, 4.50, 5.78, 5.90, 6.05, 6.20, 6.36 μm; $^1H$ NMR ($CDCl_3$) δ 7.31, 6.90 (2 H, AB quartet, $J$ = 9 Hz), 6.79, 6.42 (2 H, AB quartet, $J$ = 9 Hz), 4.58 (1 H, s), 4.50–3.60 (2 H, m), 3.92 (3 H, s), 3.73 (3 H, s), 3.28 (3 H, s), 2.93–2.55 (2 H, m), 2.28–1.80 (2 H, m); chemical ionization mass spectrum, *m/e* (relative intensity) 413 (100).

Anal. Calcd for $C_{21}H_{20}N_2O_7$: C, 61.16; H, 4.89. Found: C, 61.10; H, 4.80.

**Acid-Catalyzed Dehydrogenation of 10b.** A solution of **10b** (500 mg, 1.21 mmol) and DDQ (400 mg, 1.76 mmol) in 1.5 mL of dioxane saturated with dry hydrogen chloride was heated to reflux temperature under $N_2$ for 24 h. The workup procedure used in the previous DDQ reaction gave a colorless glass, which was shown by $^1H$ NMR analysis to be a mixture of enone **13a** (50%) and **13b** (27%) and a third compound believed to be **14** (23%). Chromatography of the reaction mixture gave pure **13b** (mp 187–188 °C): IR ($CDCl_3$) 3.40, 4.50, 5.75, 5.88, 6.20, 6.36 μm; $^1H$ NMR ($CDCl_3$) δ 7.35, 6.90 (2 H, AB quartet, $J$ = 9 Hz), 6.90 (1 H, br s), 4.70 (1 H, s), 4.55–3.60 (2 H, m), 3.94 (3 H, s), 3.78 (3 H, s), 3.33 (3 H, s), 2.90–2.44 (2 H, m), 2.32–1.80 (2 h, m); chemical ionization mass spectrum, *m/e* (relative intensity) 447 (98). **14** was obtained as a mixture with **13a**, for which a $^1H$ NMR spectrum indicated that **14** displayed methoxy singlets at δ 3.90, 3.68 and 3.65, an aromatic AB pattern overlapping that of **13a**, and a singlet at δ 5.56.

**1,2,3,4,5,6,9,10-Octahydro-2-carbomethoxy-6-oxoisoquinolino[5β,10β-*c*]-4-cyano-7-methoxy-2,3-dihydrobenzofuran (15a).** A mixture of **13a** (400 mg, 0.97 mmol), basic alumina (Merck Type T, 8 g), dioxane (20 mL), and water (0.3 mL) was heated at reflux temperature under $N_2$ for 40 h. The alumina was filtered and washed with ether and chloroform. Removal of solvent gave 240 mg of crude product containing enone **15a** and starting material (3:1). Preparative TLC ($SiO_2$, 10% ether–methylene chloride) and crystallization from methylene chloride–ether gave **15a** (90 mg, 26%, mp 214.5–215.5 °C): IR ($CHCl_3$) 3.40, 4.50, 5.90, 6.02, 6.16, 6.32 μm; $^1H$ NMR ($CDCl_3$) δ 7.22, 6.80 (2 H, AB quartet, $J$ = 9 Hz), 7.00 (1 H, dd, $J$ = 9.7 Hz), 6.25 (1 H, d, $J$ = 9 Hz), 5.01 (1 H, s), 4.65–4.08 (2 H, m), 3.88 (3 H, s), 3.74 (3 H, s), 3.70 (1 H, m), 3.40–1.50 (4 H, m); chemical ionization mass spectrum, *m/e* (relative intensity) 355 (100).

Anal. Calcd for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.12. Found: C, 64.28; H, 5.06.

**Base Hydrolysis of Keto Ester 2b.** Keto ester **2b** (2.00 g, 4.83 mmol) was treated with 1.0 M methanolic potassium hydroxide (40 mL). The solution was stirred under $N_2$ at room temperature for 20 min and then poured into a mixture of brine (50 mL) and water (50 mL). The resulting solution was cooled to 0 °C, acidified to pH 1 (6 N HCl; a thick precipitate formed), and extracted with methylene chloride (3 × 40 mL). The organic solution was washed with brine (2 × 20 mL) and dried. Removal of solvent and crystallization from methylene chloride–ether gave **16** as the pseudo acid (1.89, 98%, mp 231–232 °C): IR (Nujol) 3.05, 4.50, 5.68, 5.90, 6.21, 6.38 μm; $^1H$ NMR ($CDCl_3$) δ 7.35, 6.88 (2 H, AB quartet, $J$ = 9 Hz), 4.70–3.56 (2 H, m), 4.38 (1 H, s), 3.90 (3 H, s), 3.72 (3 H, s), 2.76–1.40 (8 H, m); chemical ionization mass spectrum, *m/e* (relative intensity) 401 (100).

**Reaction of 16 with DDQ. Alternative Method for Preparation of 15a.** A mixture of pseudo acid **16** (500 mg, 1.25 mmol), DDQ (430 mg, 1.90 mmol), and dioxane saturated with dry hydrogen chloride (0.3 mL) was heated at ~130 °C under $N_2$ for 36 h. Upon cooling, methylene chloride was added to the black tarry mixture and workup was conducted as described for other DDQ reactions. Removal of solvent gave the previously characterized **15a** (272 mg, 62%).

**1,2,3,4,5,6,9,10-Octahydro-2-carbomethoxy-6-oxo-7-bromoisoquinolino[5β,10β-*c*]-4-cyano-7-methoxy-2,3-dihydrobenzofuran (15b).** A solution of **15a** (52 mg, 0.1476 mmol) in methylene chloride (1.0 mL) was treated with bromine (0.15 mL of 1.0 M solution in methylene chloride, 1 equiv) under $N_2$. After being stirred for 5 h at room temperature, the reaction mixture was diluted with methylene chloride–ether (1:1, 20 mL), washed with saturated sodium bicarbonate (5 mL), water (5 mL), and brine (5 mL) and dried. Removal of solvent and crystallization from methylene chloride–ether gave **15b** (60 mg, 94%, mp 235 °C dec): IR (KBr) 3.40, 4.50, 5.90, 6.02, 6.18, 6.34 μm; $^1H$ NMR ($CDCl_3$) δ 7.45 (1 H, d, $J$ = 7 Hz), 7.26, 6.84 (2 H, AB quartet, $J$ = 9 Hz), 5.21 (1 H, s), 4.75–4.03 (2 H, m), 3.92 (3 H, s), 3.76 (3 H, s), 3.86–1.80 (5 H, m); chemical ionization mass spectrum, *m/e* (relative intensity) 433, 435 (100, 98).

**Ketalization of 2a.** Ketalization (methanol, trimethyl orthoformate, *p*-toluenesulfonic acid) and crystallization from methylene chloride–ether–petroleum ether gave **17a** (98%, mp 165–166 °C): IR (Nujol) 3.40, 4.50, 5.78, 6.20, 6.38 μm; $^1H$ NMR ($CDCl_3$) δ 7.26, 6.80 (2 H, AB quartet, $J$ = 9 Hz), 4.07 (1 H, m), 3.88 (3 H, s), 3.39 (3 H, s), 3.28 (3 H, s), 3.80–1.45 (12 H, m), 2.38 (3 H, s), 0.94 (3 H, t, $J$ = 7 Hz).

Anal. Calcd for $C_{23}H_{30}N_2O_6$: C, 64.17; H, 7.02. Found: C, 64.15; H, 6.92.

**Ketalization of 2b.** Ketalization and crystallization from methylene chloride–ether gave **17b** (92%, mp 167–169 °C): IR ($CHCl_3$) 3.40, 4.50, 5.78, 5.90, 6.18, 6.22, 8.00 μm; $^1H$ NMR ($CDCl_3$) δ 7.22, 6.83 (2 H, AB quartet, $J$ = 9 Hz), 4.28 (1 H, s), 4.25–3.50 (2 H, m), 3.90 (3 H, s), 3.72 (3 H, s), 3.39 (3 H, s), 3.29 (3 H, s), 3.12 (3 H, s), 3.20–1.55 (8 H, m).

Anal. Calcd for $C_{23}H_{28}N_2O_8$: C, 59.99; H, 6.13. Found: C, 59.93; H, 6.05.

**Ketalization of 2c.** Ketalization and crystallization from methylene chloride–ether gave **17c** (75%, mp 151–152 °C): IR ($CHCl_3$) 3.40, 5.80, 5.90, 6.18, 6.36 μm; $^1H$ NMR ($CDCl_3$) δ 7.42, 6.76 (2 H, AB quartet, $J$ = 9 Hz), 4.31 (1 H, s), 4.40–3.50 (2 H, m), 3.87 (3 H, s), 3.85 (3 H, s), 3.72 (3 H, s), 3.40 (3 H, s), 3.22 (3 H, s), 3.03 (3 H, s), 2.84–1.50 (8 H, m).

Anal. Calcd for $C_{24}H_{31}NO_{10}$: C, 58.41; H, 6.33. Found: C, 58.42; H, 6.30.

**3-Hydroxy-4-(2-methoxyphenoxy)but-1-ene (29).** To a suspension of Mg turnings (7.20 g, 0.30 mol) in THF (300 mL) was added a 15-mL portion of a solution of vinyl bromide (32.0 mL, 0.45 mol) in THF (50 mL) to initiate reaction. The rest of the vinyl bromide solution was added over 1 h at 10–15 °C with stirring. After 2 h, a solution of **28** (29.40 g, 0.18 mol) in THF (150 mL) was added and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was poured on a mixture of ice and 6 N HCl (50 mL) and then extracted with ether–hexane (1:1). The combined organic layers were washed with saturated $NaHCO_3$ and brine, then dried and evaporated

to give **29** as a yellow oil. Chromatography on a Waters Prep 500 (hexane–ethyl acetate, 2:1) afforded **29** (23.8 g, 70%). The phenyl urethane derivative displayed a melting point of 116 °C (ethyl acetate–hexane): IR ($CHCl_3$) 2.90, 6.29 μm; $^1H$ NMR ($CDCl_3$) δ 7.93 (4 H, s), 6.20–5.20 (3 H, m), 4.45 (1 H, m), 4.0 (2 H, d), 3.83 (3 H, s), 3.15 (1 H, d).

Anal. Calcd for $C_{18}H_{19}NO_4$: C, 69.00; H, 6.11. Found: C, 69.01; H, 6.32.

**(2-Methoxyphenoxy)methyl Vinyl Ketone (30a).** To a solution of **29** (5.83 g, 30 mmol) in acetone (100 mL) cooled to 0 °C was added Jones reagent (30 mL) over 2 min. The mixture was stirred at 0 °C for 5 min, after which 2-propanol (5 mL) was added. The mixture was diluted with water and extracted with ether. The combined organic extracts were washed with saturated $NaHCO_3$, water, and brine, then dried, concentrated, and distilled in a Kugelrohr apparatus to give **30a** (3.4 g, 59%, 97–105 °C, 0.1 mmHg): IR ($CHCl_3$) 5.88, 6.15, 6.27 μm; $^1H$ NMR ($CDCl_3$) δ 7.0–6.5 (m, 5 H), 5.88 (dd, 1 H), 4.82 (s, 2 H), 3.90 (s, 3 H). Enone **30a** undergoes decomposition on standing and should be used immediately after preparation.

**1,2,3,4,6,7,8,9-Octahydro-1,6-dioxo-2-methyl-9-carbethoxyisoquinoline (23a).** To a suspension of sodium hydride (0.20 g, 0.008 mol) in benzene (40 mL) was added **22a** (13.21 g, 0.066 mol). After being stirred at room temperature for 2 h, a solution of methyl vinyl ketone (5.40 mL, 4.60 g, 0.066 mol) in benzene (20 mL) was added. The reaction mixture was heated at 42–44 °C under $N_2$ for 24 h, after which more methyl vinyl ketone (5.40 mL) was added. After being heated for an additional 24 h, the solution was cooled to room temperature and washed with water (20 mL). The aqueous phase was washed with methylene chloride (50 mL) and the combined organic washes were dried and evaporated to give a yellow oil. The oil was dissolved in benzene (60 mL), pyrrolidine (11 mL, 9.4 g, 0.13 mol) was added, and the resulting solution was heated to reflux temperature for 19 h with a Dean–Stark apparatus. After being cooled to room temperature, a solution of acetic acid–water–sodium acetate (2:2:1, 50 mL) was added and the resulting two-phase system was heated at reflux temperature for 1.5 h under $N_2$. The reaction mixture was then cooled to room temperature and methylene chloride (175 mL) and 1 N HCl (20 mL) were added. After separation of the two phases, the organic layer was washed with 1 N $Na_2CO_3$ (2 × 50 mL) and brine (2 × 25 mL), dried, and evaporated to give **23a** as a tan solid (11.52 g, 70%). Column chromatography ($SiO_2$ ether) gave pure **23a** (7.92 g, 48% mp 75–77 °C): IR ($CHCl_3$) 3.40, 5.82, 5.95, 6.06, 6.14, 8.12, 8.52 μm; $^1H$ NMR ($CDCl_3$) δ 5.88 (1 H, br s), 4.18 (2 H, q, $J$ = 7 Hz), 3.60–3.10 (2 H, m), 2.99 (3 H, s), 2.90–1.80 (6 H, m), 1.32 (3 H, t, $J$ = 7 Hz).

**Decahydro-1,6-dioxo-2-methyl-5,10-epoxy-9-carbethoxyisoquinoline (24a).** A solution of **23a** (7.03 g, 0.028 mol) in methanol (35 mL) was cooled in an ice bath to 10–15 °C under $N_2$. Hydrogen peroxide (10 mL, 30%, 0.08 mol) and 1 N NaOH (40 mL) were added sequentially over 30 min at 10–15 °C. The reaction mixture was cooled for an additional 30 min and then stirred at room temperature for 2 h. Brine (50 mL) was added and the solution was extracted with methylene chloride (4 × 75 mL). The combined organic washes were dried and evaporated to give **24a** (5.80 g, 78%) as an oil. Crystallization from ether–petroleum ether gave **24a** (5.10 g, 68%, mp 134–162 °C): IR ($CHCl_3$) 3.40, 5.80, 5.92, 6.06, 7.90–8.10 μm; $^1H$ NMR ($CDCl_3$) δ 4.24 (0.7 H, q, $J$ = 7 Hz), 4.18 (1.3 H, q, $J$ = 7 Hz), 3.60–3.30 (2 H, m), 3.31 (0.7 H, s), 3.08 (1.3 H, s), 3.01 (3 H, s), 3.00–1.50 (6 H, m), 1.36 (1 H, t, $J$ = 7 Hz), 1.22 (2 H, t, $J$ = 7 Hz).

**1,2,3,4,6,7,8,9-Octahydro-1,6-dioxo-2-methyl-9-carbomethoxyisoquinoline (23b)** was prepared from **22b** and methyl vinyl ketone by the method described for preparation of **23a**. Recrystallization from ethyl acetate–hexane gave pure **23b** (55%, 117–118 °C): IR ($CHCl_3$) 3.40, 5.82, 5.95, 6.06, 6.14 μm; $^1H$ NMR ($CDCl_3$) δ 5.88 (1 H, s), 3.81 (3 H, s), 3.60–3.10 (2 H, m), 2.99 (3 H, s), 2.90–1.80 (6 H, m).

**Decahydro-1,6-dioxo-2-methyl-5,10-epoxy-9-carbomethoxyisoquinoline (24b)** was prepared from **23b** by the method described for the preparation of **24a**. Recrystallization from ether–hexane gave pure **24b** (69%, 119–150 °C): IR ($CHCl_3$) 3.40, 5.80, 5.92, 6.06 μm; $^1H$ NMR ($CDCl_3$) δ 3.82, 3.77 (3 H, 2 s, 3:2), 3.70–3.30 (2 H, m), 3.37, 3.10 (1 H, 2 s, 3:2), 3.05, 3.02 (3 H, 2 s, 3:2), 3.00–1.40 (6 H, m).

**1,2,3,4,6,7,8,9-Octahydro-1,6-dioxo-2-benzyl-9-carbomethoxyisoquinoline (23c).** To a solution of **22c** (282.0 g, 1.08 mol) in dry benzene (1050 mL) and *tert*-butyl alcohol (525 mL) was added potassium *tert*-butoxide (12.80 g, 114.1 mmol). The mixture was slowly warmed to 50–70 °C over 2 h. After the dark reaction mixture was cooled to room temperature, methyl vinyl ketone (128.0 mL, 110.6 g, 1.58 mol) was added over 10 min. The solution was slowly heated to reflux temperature (1 h). After 10 h at reflux, the reaction mixture was cooled to room temperature and then poured into ether–ethyl acetate (9:1) and saturated ammonium chloride solution. The organic phase was washed with brine, dried, and evaporated to give the intermediate Michael adduct (284.4 g, 79%) as a thick brown oil. The crude diketone was dissolved in dry benzene (1300 mL) and pyrrolidine (91.0 mL, 77.5 g, 1.09 mol). The resulting solution was heated at reflux temperature for 6 h with a Dean–Stark apparatus. After the reaction mixture was cooled to room temperature, a solution of acetic acid–water–sodium acetate (2:2:1, 477 mL) was added, and the resulting mixture was heated to reflux temperature for 3 h. The crude reaction mixture was poured into water and extracted with ethyl acetate. The combined ethyl acetate layers were washed with 1 N HCl, saturated $NaHCO_3$, and brine, dried, and evaporated to give **23c** as a thick brown oil. Crystallization from methanol afforded 168 g of **23c** (49%) as a pale yellow crystalline solid: mp 121–122 °C (MeOH); IR ($CHCl_3$) 3.33, 5.75, 6.02, 6.15, 6.71 μm; $^1H$ NMR ($CDCl_3$) δ 7.22–7.42 (5 H, m), 5.98 (1 H, s), 4.83, 4.48 (2 H, AB quartet, $J$ = 14 Hz), 3.80 (3 H, s), 2.02–3.48 (8 H, m); electron impact mass spectrum, $m/e$ 313 ($M^+$).

Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99.; H, 6.11. Found: 68.95; H, 6.11.

**Decahydro-1,6-dioxo-2-benzyl-5,10-epoxy-9-carbomethoxyisoquinoline (24c)** was prepared from **23c** by the method described for preparation of **24a** as a pale yellow foam ~1:3 mixture of epimers; the crude material (84% yield) was used in the subsequent step without further purification. An analytical sample (ethyl acetate–hexane) had mp 117–119 °C (major epimer): IR ($CHCl_3$) 3.33, 5.81, 6.06, 6.71 μm; $^1H$ NMR ($CDCl_3$) δ 7.02–7.42 (5 H, m), 4.97 and 4.34 (2 H, AB quartet, $J$ = 14 Hz), 3.74 (3 H, s), 3.34 (1 H, s), 3.18–3.52 (2 H, m), 2.16–2.64 (4 H, m), 1.40–1.60 (2 H, m); electron impact mass spectrum, $m/e$ 329 ($M^+$).

Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.63; H, 5.83. Found: C, 65.62; H, 5.91.

**1,2,3,4,6,7,8,9-Octahydro-1,6-dioxo-2-methyl-5-(2-methoxy-5-cyanophenoxy)-9-carbethoxyisoquinoline (25a).** To a stirred suspension of potassium hydride (80 mg, 2 mmol, 380-mg suspension) in THF (20 mL) under $N_2$ was added a solution of 5-cyano-2-methoxyphenol (3.30 g, 2 mmol) in THF (15 mL) and HMPA (5 mL). Epoxide **24a** (5.10 g, 19.2 mmol) was added and the resulting solution was stirred at room temperature for 3 h. The reaction mixture was heated at reflux temperature for 19 h and cooled to room temperature. Water (80 mL) and benzene (100 mL) were added, the phases were separated, and the aqueous phase was washed with benzene (2 × 75 mL). The combined benzene extracts were washed with 1 N NaOH (2 × 50 mL) and brine (3 × 75 mL), dried, and evaporated to give **25a** as a tan solid (5.60 g, 75%). Recrystallization from methylene chloride–petroleum ether gave **25a** as a white crystalline solid (5.13 g, 66%, mp 168–170 °C): IR ($CHCl_3$) 3.40, 4.48, 5.80, 5.95, 6.05, 6.21, 6.67, 7.81, 8.22 μm; $^1H$ NMR ($CDCl_3$) δ 7.45–6.90 (3 H, m), 4.34 (2 H, q, $J$ = 7 Hz), 3.93 (3 H, s), 3.60–3.20 (2 H, m), 3.06 (3 H, s), 3.00–2.10 (6 H, m), 1.32 (3 H, t, $J$ = 7 Hz).

**1,2,3,4,6,7,8,9-Octahydro-1,6-dioxo-2-methyl-5-(2-methoxy-5-cyanophenoxy)-9-carbomethoxyisoquinoline (25b)** was prepared from 5-cyano-2-methoxyphenol and **24b** by the method described for **25a**, except that the reaction mixture was poured into water and the precipitated **25b** was isolated by filtration. The crystalline material was dissolved in methylene chloride (50 mL), washed with brine (2 × 20 mL), and dried. Evaporation of solvent and recrystallization from methylene chloride–hexane gave **25b** (72%, mp 231 °C dec): IR (Nujol) 3.40, 4.52, 5.82, 5.95, 6.05, 8.10 μm; $^1H$ NMR ($CDCl_3$) δ 7.40–6.85 (3 H, m), 3.92 (3 H, s), 3.83 (3 H, s), 3.60–3.20 (2 H, m), 3.08 (3 H, s), 3.00–2.00 (6 H, m); electron impact mass spectrum, $m/e$ (relative intensity) 394 (92), 329 (100).

**Decahydro-1,6-dioxo-2-methyl-5-(2-methoxy-5-cyanophenoxy)-9-carbomethoxy-10-hydroxyisoquinoline (26b).** To a solution of **22b** (1.90 g, 10 mmol) in methanol (5 mL) was added

1 M KOH in methanol (1 mL), and the solution was stirred at room temperature for 10 min under $N_2$. A solution of **30b** (2.20 g, 10 mmol) in benzene (10 mL) was added, and the reaction mixture was stirred at room temperature for 37 h. The majority of the solvent was removed under vacuum, methylene chloride (100 mL) was added, and the organic solution was washed with brine, dried, and evaporated to give **26b** as a mixture of isomers (3.92 g, 96%). Crystallization from benzene–petroleum ether gave **26b** (2.93 g, 73%, mp 175–178 °C): IR (Nujol) 2.90, 3.40, 4.48, 5.78, 5.85, 6.05, 7.83 μm; $^1$H NMR ($CDCl_3$) δ 7.40–6.80 (3 H, m), 4.00–3.80 (2 H, m), 3.80, 3.78 (3 H, 2 s), 3.60–3.20 (2 H, m), 3.10, 3.06 (3 H, 2 s), 3.00–1.60 (6 H, m).

**Dehydration of Aldol 26b.** A solution of **26b** (510 mg, 1.24 mmol) and pyrrolidine (0.21 mL, 2.48 mmol) in benzene (10 mL) was heated at reflux temperature for 20 h with a Dean–Stark apparatus. The reaction mixture was cooled to room temperature and a solution of acetic acid–water–sodium acetate (2:2:1, 5 mL) was added. Refluxing was continued (2 h), after which the cooled reaction mixture was poured into methylene chloride (50 mL) and water (20 mL). The organic layer was washed with 1 N $NaHCO_3$ (15 mL) and brine (15 mL) and dried. Removal of solvent and crystallization from chloroform–ether gave **25b** (324 mg, 67%).

**1,2,3,4,6,7,8,9-Octahydro-1,6-dioxo-2-benzyl-5-(2-methoxyphenoxy)-9-carbomethoxyisoquinoline (25c)** was prepared from **24c** and 2-methoxyphenol by the method described for **25a**. Column chromatography ($SiO_2$, methylene chloride) gave **25c** as a colorless oil (56%): IR (neat) 3.40, 5.78, 5.95, 6.03, 6.26, 6.29 μm; $^1$H NMR ($CDCl_3$) δ 7.33 (5 H, s), 7.00–6.60 (4 H, m), 4.83, 4.50 (2 H, AB quartet, $J$ = 15 Hz), 3.90 (3 H, s), 3.83 (3 H, s), 3.40–3.00 (2 H, m), 3.00–2.00 (6 H, m).

**1,2,3,4,6,7,8,9-Octahydro-1,6-dioxo-2-methyl-5-[2-(benzyloxy)phenoxy]-9-carbomethoxyisoquinoline (25d).** To a solution of **22b** (1.52 g, 9.2 mmol) in 5 mL of dry methanol was added methanolic 1 N KOH solution (0.92 mL) under $N_2$. After stirring at room temperature for 20 min, a solution of **30c** (2.74 g, 10.2 mmol) in 10 mL of dry benzene was added. The reaction mixture was stirred at room temperature for 48 h and then was evaporated under reduced pressure. The residue was dissolved in methylene chloride, washed with brine, dried, and evaporated to give **26d** (3.43 g, 86%) as a mixture of epimeric aldols. A solution of **26d** in 16 mL of dioxane–benzene (1:1) was added to a suspension of potassium hydride (137 mg, 3.43 mmol) in 10 mL of dry dioxane. The mixture was heated at reflux temperature for 12 h under $N_2$, after which solvent was evaporated and the residue was dissolved in methylene chloride, washed with brine, dried, and evaporated to give **25d**. Chromatography on a Waters Prep 500 ($SiO_2$, ethyl acetate) afforded pure **25d** (550 mg, 21%): mp 118–120 °C (ethyl acetate–ether–hexane); IR ($CDCl_3$) 5.78, 5.95, 6.03, 6.31, 8.02, 8.37 μm; $^1$H NMR ($CDCl_3$) δ 7.15–7.66 (5 H, br s), 6.50–7.10 (4 H, m), 5.19 (2 H, s), 3.79 (3 H, s), 3.01 (3 H, s), 1.67–3.59 (8 H, m); electron impact mass spectrum, $m/e$ 435 ($M^+$).

Anal. Calcd for $C_{25}H_{25}NO_6$: C, 68.95; H, 5.79, N, 3.22. Found: C, 68.91;, H, 5.73, N, 3.16.

**Alternative Preparation of 25d.** To a suspension of potassium hydride (11.8 mg, 0.30 mmol) in 4 mL of THF was added a solution of 2-(benzyloxy)phenol (590 mg, 2.95 mmol) in 6 mL of THF–HMPA (2:1) under $N_2$. Epoxy ketone **24b** (679 mg, 2.68 mmol) was added, and the mixture was stirred at room temperature for 3.5 h and then was heated to reflux temperature for 25 h. Solvent was evaporated under reduced pressure and the residue was partitioned between ethyl acetate and water. The aqueous layer was extracted with ether and the combined etheral extracts were washed with water, dried, and evaporated to give **25d** (517 mg, 46%), identical in all respects with **25d** prepared by the previous route.

**2-[(Methoxymethyl)oxy]-1-(benzyloxy)benzene.** To a suspension of sodium hydride (23.3 g of 50% dispersion, 465 mmol, washed with hexane under $N_2$) in 80 mL of THF was added a solution of 2-(benzyloxy)phenol (84.0 g, 420 mmol) in DMF (40 mL) and THF (560 mL) over 30 min. The mixture was stirred at room temperature for 1.5 h and cooled to 0 °C. Chloromethyl methyl ether (36.2 mL, 478 mmol) was added and the reaction mixture was warmed to room temperature and stirred for 12 h. The mixture was then poured into ether–water and the layers were separated. The aqueous phase was extracted with ether and the combined organic layers were washed with 1 N NaOH, water, and brine, dried, and evaporated to give a light yellow oil (102 g, 100%, bp 133–136 °C, 0.03 mm): IR (neat) 4.67, 6.29, 6.67 μm; $^1$H NMR ($CDCl_3$) δ 7.30–7.54 (5 H, m), 7.14–7.20 (1 H, m), 6.80–7.02 (3 H, m) 5.24 (2 H, s), 5.16 (2 H, s), 3.51 (3 H, s); electron impact mass spectrum, $m/e$ 244 ($M^+$).

Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.67; H, 6.57.

**2-[(Methoxymethyl)oxy]phenol.** A mixture of 2-[(methoxymethyl)oxy]-1-(benzyloxy)benzene (20.0 g, 82.0 mmol) and 5% Pd/C (2.40 g) in ethyl acetate–acetic acid (200 mL, 9:1) was stirred under 1 atm of hydrogen for 4 h in a Parr apparatus. The suspended catalyst was removed by filtration and washed with ether. The filtrate was washed with saturated $NaHCO_3$ solution and brine, dried, and evaporated to give a colorless oil. The procedure was repeated several times to give a total of 65.2 g of product (94%). Distillation under reduced pressure gave analytically pure 2-[(methoxymethyl)oxy]phenol (56.0 g, 81%, bp 80 °C, 1.3 mm): IR (neat) 2.92 (br), 3.39, 6.27, 6.67 μm; $^1$H NMR ($CDCl_3$) δ 7.04–7.14 (1 H, d), 6.74–7.00 (3 H, m), 6.08 (1 H, s), 5.20 (2 H, s), 3.52 (3 H, s); electron impact mass spectrum, $m/e$ 154 ($M^+$).

Anal. Calcd for $C_8H_{10}O_3$: C, 62.32; H, 6.55. Found: C, 62.18; H, 6.77.

**1,2,3,4,6,7,8,9-Octahydro-1,6-dioxo-2-benzyl-5-[2-[(methoxymethyl)oxy]phenoxy]-9-carbomethoxyisoquinoline (25e)** was prepared in 59% yield from **24c** and 2-[(methoxymethyl)oxy]phenol by the method described for preparation of **25a**: IR ($CHCl_3$) 5.76, 5.92, 6.02, 6.67 μm; $^1$H NMR ($CDCl_3$) δ 7.16–7.44 (5 H, m), 6.84–7.02 (3 H, m), 6.70–6.78 (1 H, m), 5.28 (2 H, s), 4.82, 4.57 (2 H, AB quartet, $J$ = 14 Hz), 3.84 (3 H, s), 3.52 (3 H, s), 2.34–3.20 (8 H, m); electron impact mass spectrum, $m/e$ 466 ($M^+$). An acceptable elemental analysis for **25e** could not be obtained.

**Decahydro-1,6-dioxo-2-methyl-9β-carbethoxyisoquinolino[5β,10β-*c*]-4-cyano-7-methoxy-2,3-dihydrobenzofuran (31a).** A solution of **25a** (5.04 g, 12.6 mmol, 0.042 M) in methylene chloride–dimethyl sulfoxide (4:1, 300 mL) was purged with argon for 40 min and irradiated through Pyrex glassware for 13 h. Methylene chloride (125 mL) was added and the resulting solution was washed with 1 N NaOH (3 × 75 mL), water (3 × 125 mL), and brine (1 × 125 mL), dried, and evaporated to give **31a** as a mixture of epimers (4.57 g, 93%). To a solution of this mixture in methanol (35 mL) was added anhydrous $Na_2CO_3$ (600 mg). The solution was stirred at room temperature for 3.5 h, methylene chloride (200 mL) was added, and the resulting solution was washed with water (2 × 75 mL) and brine, dried, and evaporated to give a white crystalline solid (4.26 g, 85%). Recrystallization from methylene chloride–petroleum ether gave **31a** (4.03 g, 80% overall, mp 193–194 °C): IR (Nujol) 3.40, 4.52, 5.82, 6.00, 6.10, 7.83 μm; $^1$H NMR ($CDCl_3$) δ 7.31, 6.96 (2 H, AB q, $J$ = 10 Hz), 4.51 (1 H, s), 4.30 (2 H, q, $J$ = 7 Hz), 3.94 (3 H, s), 3.70–3.20 (2 H, m), 2.92 (3 H, s), 2.80–1.80 (6 H, m), 1.23 (3 H, t, $J$ = 7 Hz); electron impact mass spectrum, $m/e$ (relative intensity) 398 (32), 198 (100).

Anal. Calcd for $C_{21}H_{22}N_2O_6$: C, 63.30; H, 5.58. Found: C, 63.43, H, 5.56.

**Decahydro-1,6-dioxo-2-methyl-9β-carbomethoxyisoquinolino[5β,10β-*c*]-4-cyano-7-methoxy-2,3-dihydrobenzofuran (31b)** was prepared from **25b** by the method described for **31a**. Crystallization from ether–hexane gave **31b** (76%, 218–220 °C dec): IR ($CHCl_3$) 3.40, 4.48, 5.76, 6.05, 7.76, 8.00 μm; $^1$H NMR ($CDCl_3$) δ 7.31, 6.90 (2 H, AB quartet, $J$ = 9 Hz), 4.51 (1 H, s), 3.96 (3 H, s), 3.82 (3 H, s), 3.70–3.20 (2 H, m), 2.91 (3 H, s), 2.95–1.60 (6 H, m); $^1$H NMR ($CDCl_3$) for the C(5) epimer of **31b** δ 7.30, 6.85 (2 H, AB quartet, $J$ = 9 Hz), 4.78 (1 H, s), 3.89 (3 H, s), 3.70 (3 H, s), 3.60–3.10 (2 H, m), 3.01 (3 H, s), 2.90–1.80 (6 H, m).

**Irradiation of 25c.** An argon-purged solution of **25c** (102 mg, 0.23 mmol) in $Me_2SO$ (6 mL, 0.04 M) was irradiated for 4 h. The reaction mixture was poured into methylene chloride (50 mL), and the resulting solution was washed with water (4 × 50 mL), 1 N NaOH (3 × 15 mL), and brine (30 mL) and evaporated to give an oil (31 mg); epimerization was performed as described above. Preparative TLC ($SiO_2$, ether) gave **31c** as a colorless oil [8 mg, 8%, analytical TLC ($SiO_2$, ether) $R_f$ 0.47]: IR (neat) 3.40, 5.75, 5.81, 6.09, 6.35 μm; $^1$H NMR ($CDCl_3$) δ 7.33 (5 H, s), 7.05–6.75 (2 H, m), 6.75–6.40 (1 H, m), 5.02, 4.23 (2 H, AB q, $J$ = 15 Hz),

4.42 (1 H, s), 3.92 (3 H, s), 3.68 (3 H, s), 3.60–1.20 (8 H, m). The combined sodium hydroxide washes were acidified with 10% HCl and extracted with methylene chloride (3 × 40 mL). The combined methylene chloride extracts were washed with brine and dried. Removal of solvent and preparative TLC [$SiO_2$, ether–chloroform (1:1)] gave two components. The more mobile component was identical with 2-methoxyphenol (TLC, $^1H$ NMR, IR) (16 mg, 55%, $R_f$ 0.75). The less mobile component was recrystallized from ether to give **32b** (45 mg, 59%, mp 125–126 °C, $R_f$ 0.29): IR ($CHCl_3$) 2.92, 3.40, 5.78, 5.95–6.10 μm; $^1H$ NMR ($CDCl_3$) δ 7.27 (5 H, s), 6.43 (1 H, s), 4.87, 4.43 (2 H, AB quartet, $J$ = 16 Hz), 3.77 (3 H, s), 6.43 (1 H, s), 4.87, 4.43 (2 H, AB quartet, $J$ = 16 Hz), 3.77 (3 H, s), 3.60–2.00 (8 H, m); electron impact mass spectrum, $m/e$ (relative intensity) 329 (100), 270 (28), 209 (80).

**Irradiation of 25d.** A solution of **25d** (50 mg, 0.12 mmol) in 3 mL of methylene chloride–$Me_2SO$ (1:1) was degassed with argon for 40 min and irradiated for 5 h. The reaction mixture was poured into 30 mL of ether–ethyl acetate (1:1), and the resulting solution was washed with water, dried, and evaporated. Preparative TLC ($SiO_2$, chloroform–methanol, 15:1) afforded **31d** and its epimer (1:1, 25 mg, 50%). **31d**: IR ($CDCl_3$) 5.75, 6.05, 7.95, 8.35, 9.10 μm; $^1H$ NMR ($CDCl_3$) δ 7.36 (5 H, s), 6.39–7.10 (3 H, m), 5.17 (2 H, s), 4.45 (1 H, s), 3.62 (3 H, s), 2.94 (3 H, s), 1.60–3.53 (8 H, m); IR ($CDCl_3$) for the C(5) epimer of **31d** 5.80, 6.10, 9.90 and 9.25 μm; $^1H$ NMR ($CDCl_3$) δ 7.30–7.63 (5 H, m), 6.86 (3 H, s), 5.16 (2 H, s), 4.96 (1 H, s), 3.61 (3 H, s), 3.04 (3 H, s), 1.53–3.50 (8 H, m). Most of the remainder of the crude reaction mixture consisted of the α-diketone **32a**: IR ($CDCl_3$) 5.71, 5.93, 6.00 μm; $^1H$ NMR ($CDCl_3$) δ 3.76 (3 H, s), 3.03 (3 H, s), 1.53–3.66 (1 H, m).

**1,2,3,4,6,7,8,9-Octahydro-1,6-dioxo-2-methyl-5-(2-acetoxyphenoxy)-9-carbomethoxyisoquinoline (33c).** To a solution of **25d** (517 mg, 1.25 mmol) in 25 mL of ethyl acetate was added 5% Pd/C (300 mg) and the resulting suspension was hydrogenated under 1 atm of $H_2$. After 5 h, the catalyst was removed by filtration and the filtrate was evaporated under reduced pressure to give an oil (390 mg, 96%). $^1H$ NMR analysis indicated a mixture of phenol **33a** and hemiketal **34a**. To a solution of this mixture (3.20 g, 9.80 mmol) in 23 mL of methylene chloride was added pyridine (3.1 g, 39.2 mmol), followed by acetic anhydride (2.00 g, 19.6 mmol). After stirring at room temperature for 12 h, the solvent and excess acetic anhydride were removed under reduced pressure. The residue was washed with 1 M HCL, $NaHCO_3$ solution, and brine, dried, and evaporated to give crystalline **33c** (13.42 g, 95%). An analytical sample was prepared: mp 160–162 °C (ethyl acetate–hexane); IR ($CDCl_3$) 5.74, 5.94, 6.02, 6.26, 8.02, 8.37 μm; $^1H$ NMR ($CDCl_3$) δ 6.53–7.30 (4 H, m), 3.80 (3 H, s), 3.01 (3 H, s), 2.40–3.69 (8 H, m), 2.27 (3 H, s); electron impact mass spectrum, $m/e$ 387 ($M^+$).

Anal. Calcd for $C_{20}H_{21}NO_7$: C, 62.01; H, 5.46, N, 3.62. Found: C, 61.92; H, 5.50, N, 3.54.

**Decahydro-1,6-dioxo-2-methyl-9β-carbomethoxyisoquinolino[5β,10β-*c*]-7-acetoxy-2,3-dihydrobenzofuran (35a).** A solution of **33c** (300 mg, 0.78 mmol) in 10 mL of a 1:1:1 mixture of benzene–MeOH–HOAc) was purged with argon for 30 min and irradiated for 3.5 h. The solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate. The resulting solution was washed with $NaHOC_3$ solution and brine, dried, and evaporated to give an oil. Crystallization from ethyl acetate–hexane afforded **35a** (195 mg, 65%): mp 192–194 °C; IR ($CHCl_3$) 5.65, 5.80, 6.10 μm; $^1H$ NMR ($CDCl_3$) δ 6.61–7.14 (3 H, m), 4.42 (1 H, s), 3.58 (3 H, s), 3.20–3.63 (2 H, br s), 2.89 (3 H, s), 2.25 (3 H, s), 1.47–2.83 (6 H, m); electron impact mass spectrum, $m/e$ 387 ($M^+$).

Anal. Calcd for $C_{20}H_{21}NO_7$: C, 62.01; H, 5.46. Found: C, 62.12; H, 5.49.

**1,2,3,4,6,7,8,9-Octahydro-1,6-dioxo-2-benzyl-5-(2-hydroxyphenoxy)-9-carbomethoxyisoquinoline (33b).** A solution of **25e** (13.6 g, 29.25 mmol) in 126 mL of 1:1:1 THF–$H_2O$–HOAc was heated at 80 °C for 15 h. Most of the solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. The resulting solution was washed with water, $NaHCO_3$ solution, and brine, dried, and evaporated to give **33b**. Chromatography on a Waters Prep 500 ($SiO_2$, ethyl acetate–hexane, 1.6:1) afforded analytically pure **33b**: mp 145–147 °C (ethyl acetate–hexane); IR ($CHCl_3$) 2.81, 5.78, 6.02, 6.71 μm; $^1H$ NMR ($CDCl_3$) δ 7.22–7.44 (5 H, m), 6.92–7.08 (4 H, m), 4.89, 4.41 (2 H, AB quartet, $J$ = 14 Hz), 3.76 (3 H, s), 3.30 (2 H, t, $J$ = 4 Hz), 2.14–3.02 (6 H, m), 1.58 (1 H, br s); electron impact mass spectrum, $m/e$ 421 ($M^+$).

Anal. Calcd for $C_{24}H_{23}NO_6$: C, 68.39; H, 5.51. Found: C, 68.23; H, 5.47.

**1,2,3,4,6,7,8,9-Octahydro-1,6-dioxo-2-benzyl-5-(2-acetoxyphenoxy)-9-carbomethoxyisoquinoline (33d).** To a solution of **33b** (12.30 g, 29.18 mmol) in methylene chloride (83 mL) was added pyridine (9.70 mL, 9.49 g, 120.0 mmol) and acetic anhydride (5.60 mL, 6.06 g, 59.35 mmol). After stirring at room temperature for 12 h, the solvent and excess acetic anhydride was removed under reduced pressure, and the residue was dissolved in ethyl acetate. The resulting solution was washed with water, 1 N HCl, $NaHCO_3$ solution, and brine, dried, and evaporated to give crystalline **33d** (12.50 g, 92%). Chromatography on a Waters Prep 500 ($SiO_2$, hexane–ethyl acetate, 1:1) afforded **33d** (6.00 g, 44%): mp 166–167 °C (ethyl acetate–hexane); IR ($CHCl_3$) 3.33, 5.68, 5.75, 5.92, 6.02, 6.71 μm; $^1H$ NMR ($CDCl_3$) δ 7.20–7.42 (5 H, m), 6.96–7.16 (3 H, m), 6.71 (1 H, d, $J$ = 6 Hz), 4.90 and 4.42 (2 H, AB quartet, $J$ = 16 Hz), 3.82 (3 H, s), 3.16–3.30 (2 H, m), 2.40–3.00 (6 H, m), 2.28 (3 H, s); electron impact mass spectrum, $m/e$ 463 ($M^+$).

Anal. Calcd for $C_{26}H_{25}NO_7$: C, 67.37; H, 5.44. Found: C, 67.19; H, 5.43.

**Decahydro-1,6-dioxo-2-benzyl-9β-carbomethoxyisoquinolino[5β,10β-*c*]-7-acetoxy-2,3-dihydrobenzofuran (35b).** A solution of **33d** (30.40 g, 65.59 mmol) in 1500 mL of benzene–MeOH–HOAc (1:1:1) was purged with argon for 30 min and irradiated for 6 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate and washed with water, $NaHCO_3$ solution, and brine, dried, and evaporated to give crystalline **35b** (30.0 g, 99%). An analytical sample was prepared: mp 159–160 °C (ethyl acetate–hexane); IR ($CHCl_3$) 5.65, 5.71, 5.80, 6.10 μm; $^1H$ NMR ($CDCl_3$) δ 7.20–7.46 (5 H, m), 6.88–7.08 (2 H, m), 6.80 (1 H, dd, $J$ = 6, 2 Hz), 5.02 and 4.14 (2 H, AB quartet, $J$ = 16 Hz), 4.42 (1 H, s), 3.64 (3 H, s), 2.28 (3 H, s), 2.12–3.36 (8 H, m); electron impact mass spectrum, $m/e$ 464 ($M^+$).

Anal. Calcd for $C_{26}H_{25}NO_7$: C, 67.37; H, 5.44. Found: C, 67.50; H, 5.49.

**Decahydro-1-oxo-2-methyl-6,6-dimethoxy-9β-carbomethoxyisoquinolino[5β,10β-*c*]-7-hydroxy-2,3-dihydrobenzofuran (36a).** To a solution of **35a** (1.60 g, 4.30 mmol) in dry methanol (60 mL) was added trimethyl orthoformate (1.73 g, 16,8 mmol) and concentrated $H_2SO_4$ (0.05 mL). After being heated at reflux temperature for 6 h, the reaction mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and water. The aqueous layer was washed with ethyl acetate and the combined organic layers were washed with $NaHCO_3$ solution and brine, dried, and evaporated to give crystalline **36a** (1.65 g, 100%): mp 225–227 °C (ethyl acetate–hexane); IR ($CHCl_3$) 2.80, 6.15, 8.15 μm; $^1H$ NMR ($CDCl_3$) δ 6.34–7.08 (3 H, m), 5.52 (1 H, s), 4.50 (1 H, s), 3.52 (3 H, s), 3.28 (3 H, s), 3.11 (3 H, s), 2.95 (3 H, s), 1.50–3.90 (8 H, m); electron impact mass spectrum, $m/e$ 391 ($M^+$).

Anal. Calcd for $C_{20}H_{25}NO_7$: C, 61.36; H, 6.44. Found: C, 61.12; H, 6.33.

**Decahydro-1-oxo-2-methyl-6,6-dimethoxy-9β-carbomethoxyisoquinolino[5β,10β-*c*]-7-methoxy-2,3-dihydrobenzofuran (36c).** To a solution of **36a** (1.56 g, 4.20 mmol) in dry DMF (25 mL) was added anhydrous $K_2CO_3$ (2.90 g, 21.0 mmol) followed by methyl iodide (1.79 g, 12.60 mmol). After the reaction mixture was stirred at room temperature for 12 h, the solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate. The resulting solution was washed with water, dried, and evaporated to give crystalline **36c** (1.58 g, 98%): mp 188–191 °C ($CCl_4$–hexane); IR ($CDCl_3$) 5.70, 6.10 μm; $^1H$ NMR ($CDCl_3$) δ 6.40–7.30 (3 H, m), 4.52 (1 H, s), 3.82 (3 H, s), 3.54 (3 H, s), 3.28 (3 H, s), 3.11 (3 H, s), 2.95 (3 H, s), 1.45–3.83 (8 H, m); electron impact mass spectrum, $m/e$ 405 ($M^+$).

Anal. Calcd for $C_{21}H_{25}NO_7$: C, 62.52; H, 6.25. Found: C, 62.51; H, 6.36.

**Decahydro-1-oxo-2-benzyl-6,6-dimethoxy-9β-carbomethoxyisoquinolino[5β,10β-*c*]-7-hydroxy-2,3-dihydrobenzofuran (36b)** was prepared from **35b** by the method described for preparation of **36a**. Chromatography on a Waters Prep 500 ($SiO_2$, hexane–ethyl acetate, 1:1) afforded 7.50 g of ketal **36b** (74%) and

500 mg of the corresponding enol ether. An analytical sample of **36b** was prepared: mp 185–187 °C (ethyl acetate–hexane); IR ($CHCl_3$) 2.83, 5.75, 5.83, 6.12, 6.71 μm; $^1H$ NMR ($CDCl_3$) δ 7.20–7.44 (5 H, m), 6.68–6.86 (2 H, m), 6.42 (1 H, dd, $J$ = 8, 2 Hz), 6.26 (1 H, br s), 5.56, 3.72 (2 H, AB quartet, $J$ = 16 Hz), 4.45 (1 H, s), 3.58 (3 H, s), 3.32 (3 H, s), 3.10 (3 H, s), 3.48 (1 H, br s), 2.88–3.08 (1 H, m), 1.60–2.48 (5 H, m); electron impact mass spectrum, $m/e$ 468 ($M^+$).

Anal. Calcd for $C_{26}H_{29}NO_7$: C, 66.79; H, 6.26. Found: C, 66.67; H, 6.43.

An analytical sample of the enol ether was prepared: mp 280 °C dec (THF–$H_2O$); IR (KBr) 3.13 (br), 5.85, 5.99, 6.21, 6.29 μm; $^1H$ NMR ($Me_2SO$-$d_6$) δ 9.40 (1 H, s), 7.16–7.46 (6 H, m), 6.79 (1 H, m), 6.38 (1 H, m), 4.95, 4.23 (2 H, AB quartet, $J$ = 14 Hz), 4.92 (1 H, s), 4.85 (1 H, s), 3.64 (3 H, s), 3.44 (3 H, s), 2.16–3.50 (6 H, m); electron impact mass spectrum, $m/e$ 436 ($M^+$).

Anal. Calcd for $C_{25}H_{25}NO_6$: C, 68.94; H, 5.80. Found: C, 68.65; H, 5.85.

**Decahydro-1-oxo-2-benzyl-6,6-dimethoxy-9β-carbomethoxyisoquinolino[5β,10β-*c*]-7-methoxy-2,3-dihydrobenzofuran (36d).** To a solution of **36b** (9.00 g, 19.23 mmol) in 125 mL of acetone was added $K_2CO_3$ (13.29 g, 96.15 mmol) followed by methyl iodide (3.59 mL, 8.19 g, 57.7 mmol). After the suspension was heated at reflux temperature for 12 h, acetone was removed under reduced pressure and the residue was dissolved in methylene chloride. The resulting solution was washed with water and brine and dried to give **36d** (8.90 g, 96%). Trituration with ether followed by crystallization (ethyl acetate–hexane) afforded 6.70 g of analytically pure **36d** (72%, mp 186–188 °C): IR ($CHCl_3$) 3.33, 5.75, 5.83, 5.10, 6.71 μm; NMR ($CDCl_3$) δ 7.04–7.10 (5 H, m), 6.50–6.66 (2 H, m), 6.22–6.30 (1 H, m), 5.36 and 3.46 (2 H, AB quartet, $J$ = 16 Hz), 3.62 (3 H, s), 3.38 (3 H, s), 3.10 (3 H, s), 2.87 (3 H, s), 1.40–3.50 (8 H, m); electron impact mass spectrum, $m/e$ 482 ($M^+$).

Anal. Calcd for $C_{27}H_{31}NO_7$: C, 67.33; H, 6.50. Found: C, 67.22; H, 6.37.

**Decahydro-1-oxo-2-methyl-6,6-dimethoxyisoquinolino-[5β,10β-*c*]-7-methoxy-2,3-dihydrobenzofuran (37a, 38a).** To a suspension of potassium hydride (770 mg, 19.3 mmol) in 32 mL of dry DMF under $N_2$ was added ethanethiol (2.14 g, 31 mmol). After evolution of gas had ceased, a solution of **36c** (1.19 g, 2.95 mmol) in 10 mL of dry DMF was added and the reaction mixture was heated at 80 °C for 3 h. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate and the combined organic extracts were washed with brine, dried, and evaporated. Preparative TLC ($SiO_2$, $CHCl_3$–MeOH, 70:1) afforded **37a** (630 mg, 62%) and **38a** (189 mg, 18%). **37a**: IR ($CDCl_3$) 6.17, 7.60, 9.03, 9.43 μm; $^1H$ NMR ($CDCl_3$) δ 6.50–7.00 (3 H, m), 4.31 (1 H, s), 3.88 (3 H, s), 3.41 (3 H, s), 3.19 (3 H, s), 3.03 (3 H, s), 1.43–3.76 (9 H, m); electron impact mass spectrum, $m/e$ 347 ($M^+$). **38a**: IR ($CDCl_3$) 6.08, 7.87, 8.33, 9.08, 9.48 μm; $^1H$ NMR ($CDCl_3$) δ 6.20–7.13 (3 H, m), 4.38 (1 H, s), 3.84 (3 H, s), 3.35 (3 H, s), 3.22 (3 H, s), 2.97 (3 H, s), 1.00–3.90 (9 H, m); electron impact mass spectrum, $m/e$ 347 ($M^+$).

**Decahydro-1-oxo-2-benzyl-6,6-dimethoxyisoquinolino-[5β,10β-*c*]-7-hydroxy-2,3-dihydrobenzofuran (36e).** To a suspension of hexane-washed potassium hydride (25% dispersion, 8.66 g, of 54 mmol) in 80 mL of DMF was added ethanethiol (5.70 mL, 4.78 g, 77 mmol). After evolution of gas had ceased, a solution of **36b** (3.60 g, 7.69 mmol) in 50 mL of DMF was added. After 6 h at 80 °C, the solvent was removed under reduced pressure, and the residue was dissolved in water and acidified with 1 N HCl to pH 1 and extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried, and evaporated to give **36e** (3.0 g, 95%). Chromatography on a Waters Prep 500 ($SiO_2$, hexane–ethyl acetate, 1:1) and crystallization from ethyl acetate–hexane gave **36e** (1.60 g, 51%, mp 200–201 °C dec): IR ($CHCl_3$) 2.83, 6.17, 6.71 μm; $^1H$ NMR ($CDCl_3$) δ 7.30–7.46 (5 H, br s), 6.77 (1 H, d, $J$ = 8 Hz), 6.64 (1 H, t, $J$ = 8 Hz), 6.37 (1 H, d, $J$ = 8 Hz), 6.2 (1 H, br s), 4.91 and 4.42 (2 H, AB quartet, $J$ = 12 Hz), 4.23 (1 H, s), 3.48–3.68 (1 H, m), 3.30–3.46 (1 H, m), 3.36 (3 H, s), 3.18 (3 H, s), 2.20–2.52 (2 H, m), 1.54–2.10 (5 H, m); electron impact mass spectrum, $m/e$ 410 ($M^+$).

Anal. Calcd for $C_{24}H_{27}NO_5$: C, 70.39; H, 6.66. Found: C, 70.37; H, 6.70.

**Decahydro-1-oxo-2-benzyl-6,6-dimethoxyisoquinolino-[5β,10β-*c*]-7-methoxy-2,3-dihydrobenzofuran (37b).** To a suspension of NaH (99%, 137.0 mg, 5.71 mmol) in 10 mL of DMF was added ethanethiol (0.80 mL, 11 mmol). After evolution of gas had ceased, a solution of **36d** (480.0 mg, 0.99 mmol) was added. After 3 h at 80 °C, the reaction mixture was worked up as described above to give crystalline **37b** (380.0 mg, 90%). An analytical sample was prepared: mp 136–137 °C (ethyl acetate–hexane); IR ($CHCl_3$) 6.17, 6.71 μm; $^1H$ NMR ($CDCl_3$) δ 7.38 (5 H, br s), 6.72–6.84 (2 H, m), 6.47 (1 H, d of d, $J$ = 6, 2 Hz), 4.93 and 4.41 (2 H, AB quartet, $J$ = 12 Hz), 4.26 (1 H, s), 3.84 (3 H, s), 3.38 (3 H, s), 3.20 (3 H, s), 3.56 (1 H, m), 2.30–2.48 (2 H, m), 1.60–2.10 (6 H, m); electron impact mass spectrum, $m/e$ 424 ($M^+$).

Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.89; H, 6.92. Found: C, 70.83; H, 6.84.

**2,3,4,5,6,7,8,10-Octahydro-2-methyl-6,6-dimethoxyisoquinolino[5β,10β-*c*]-7-methoxy-2,3-dihydrobenzofuran (40a).** To a solution of **37a** (97 mg, 0.28 mmol) in 3 mL of dry THF at 0 °C under $N_2$ was added diisobutylaluminum hydride (1.17 mL, 1 M in hexane). After stirring at 10 °C for 12 min, methanol was carefully added. Evaporation of solvent gave an oil, which was partitioned between chloroform and 3 M NaOH solution. The aqueous layer was extracted with chloroform and the combined organic extracts were washed with brine, dried, and evaporated to give **40a** (yellow oil, 79 mg, 85%): IR ($CHCl_3$) 6.00 and 6.25 μm; $^1H$ NMR ($CDCl_3$) δ 6.63–6.92 (3 H, m), 5.79 (1 H, s), 4.36 (1 H, s), 3.86 (3 H, s), 3.26 (3 H, s), 3.20 (3 H, s), 2.58 (3 H, s), 1.20–3.10 (8 H, m); electron impact mass spectrum, $m/e$ 331 ($M^+$). The crude enamine was used without further purification.

**2,3,4,5,6,7,8,10-Octahydro-2-benzyl-6,6-dimethoxyisoquinolino[5β,10β-*c*]-7-methoxy-2,3-dihydrobenzofuran (40b)** was prepared in 98% yield from **37b** by the method described for preparation of **40a**. Crude **40b** (pale yellow oil, 897 mg, 98% was used without further purification: IR ($CHCl_3$) 6.00, 6.25 μm; $^1H$ NMR ($CDCl_3$) δ 7.20–7.46 (5 H, m), 6.70–6.92 (3 H, m), 6.52 (1 H, t, $J$ = 4 Hz), 6.04 (1 H, s), 4.43 (1 H, s), 4.06 (2 H, s), 3.88 (3 H, s), 3.34 (3 H, s), 3.24 (3 H, s), 1.54–3.00 (8 H, m).

**Catalytic Hydrogenation of Enamine 40a.** To a solution of **40a** (8 mg, 0.024 mmol) in 5 mL of absolute ethanol was added 5% Pt/C (13 mg). The resulting mixture was hydrogenated under $H_2$ (60 psi) at room temperature for 3.5 h. After filtration of the catalyst, the filtrate was evaporated to give **37c** (oil, 6 mg, 75%): IR ($CDCl_3$) 6.16, 6.31, 7.82, 8.36, 9.00, 9.43 μm; $^1H$ NMR ($CDCl_3$) δ 1.10–3.17 (11 H, m), 2.29 (3 H, s), 3.19 (3 H, s), 3.35 (3 H, s), 3.82 (3 H, s), 4.03 (1 H, s), 6.60–7.40 (3 H, m).

**Reduction of Enamine 40a.** To a solution of **40a** (15 mg, 0.045 mmol) in 1 mL of methanol at 0 °C was added 70% $HClO_4$ (6 μL, 1 equiv). After stirring at 0 °C for 30 min, a large excess of $NaBH_4$ was added. After stirring at 0 °C for 1 h, hydrochloric acid (1 M) was added. The solvent was removed under reduced pressure, the aqueous residue was made alkaline with solid $K_2CO_3$, and the product was extracted with chloroform. The combined organic extracts were dried and evaporated to give **37c** (14 mg, 93%).

**Reduction of Lactam 37a.** A solution of **37a** (10.0 mg, 0.03 mmol) and lithium aluminum hydride (0.05 mmol) in THF (0.05 mL) was heated at reflux temperature for 7 h. After careful addition of methanol, the solvent was removed under reduced pressure and the residue was partitioned between chloroform and 1 M NaOH solution. The aqueous layer was extracted with chloroform and the combined organic extracts were washed with brine, dried, and evaporated to give **37c** (5.0 mg, 52%).

**Reduction of Lactam 38a.** Lithium aluminum hydride reduction of **38a** (90 mg) as described for **37a** gave **38c** (76 mg, 87%, mp 110 °C from *n*-octane); IR (KBr) 2920, 2780, 1600, 1580, 1260, 1053 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.12 (1 H, d, $J$ = 7.0 Hz), 6.73–6.83 (2 H, m), 4.34 (1 H, s), 3.86 (3 H, s), 3.38 (3 H, s), 3.04 (3 H, s), 2.63–2.80 (2 H, m), 2.44 (3 H, s), 2.42–2.58 (2 H, m), 1.73–1.99 (4 H, m), 1.45–1.56 (1 H, m), 1.25–1.39 (1 H, m), 1.07–1.17 (1 H, m); electron impact mass spectrum, $m/e$ 333 ($M^+$).

Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.22; H, 8.20; N, 4.19.

**Decahydro-1β-cyano-2-benzyl-6,6-dimethoxyisoquinolino[5β,10β-*c*]-7-methoxy-2,3-dihydrobenzofuran (47b).** To the crude enamine **40b** (897.0 mg, 2.20 mmol) in 31 mL of dry methanol at 0 °C was added 70% $HClO_4$ (0.31 mL, 3.63 mmol).

After stirring at 0 °C for 30 min, a solution of KCN (303 mg, 4.65 mmol) in 25 mL of dry methanol was added. The resulting suspension was stirred at 0 °C for 2 h, after which the solvent was removed under reduced pressure at room temperature and the residue was extracted with chloroform. The combined organic layers were washed with water and brine, dried, and evaporated to give **47b** (750 mg, 78%). Flash column chromatography ($SiO_2$, hexane–ethyl acetate, 3:1) afforded analytically pure **47b** (586 mg, 60% from **37b**): mp 161–163 °C (hexane–ethyl acetate); IR ($CHCl_3$) 4.46, 6.17, 6.29, 6.71 μm; $^1H$ NMR ($CDCl_3$) δ 7.20–7.54 (5 H, m), 6.80–7.00 (3 H, m), 4.06 (1 H, br s), 3.92 and 3.67 (2 H, AB quartet, $J$ = 12 Hz), 3.90 (3 H, s), 3.54 (1 H, br s), 3.41 (3 H, s), 3.31 (3 H, s), 1.20–2.30 (9 H, m); electron impact mass spectrum, $m/e$ 435 ($M^+$).

Anal. Calcd for $C_{26}H_{30}N_2O_4$: C, 71.86; H, 6.98. Found: C, 71.94; H, 6.87.

**Decahydro-1β-vinyl-2-benzyl-6,6-dimethoxyisoquinolino-[5β,10β-*c*]-7-methoxy-2,3-dihydrobenzofuran (47e).** To a solution of **37b** (50.0 mg, 0.12 mmol) in 2 mL of THF at 0 °C was added diisobutylaluminum hydride (1 M in hexane, 0.50 mL, 0.50 mmol). After 10 min of reaction at 0 °C, followed by the workup described for the preparation of **40a**, the crude enamine **40b** (45.0 mg) dissolved in dry THF (5 mL); 70% $HClO_4$ (0.01 mL) was added at 0 °C and after 30 min, vinyl magnesium bromide (1.2 M, 1.0 mL, 1.2 mmol) was added. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for an additional 1 h. The excess Grignard reagent was carefully hydrolyzed with water. The reaction mixture was extracted with chloroform and the combined chloroform layers were washed with brine, dried, and evaporated to give crude **47e** (55.0 mg). Preparative TLC ($SiO_2$, hexane–ethyl acetate, 4:1) afforded **47e** (foam, 35.0 mg, 68%): IR ($CHCl_3$) 3.40, 6.17, 6.71, 6.90 μm; $^1H$ NMR ($CDCl_3$) δ 7.20–7.46 (5 H, m), 6.70–6.96 (3 H, m), 5.72–5.94 (1 H, m), 5.00–5.30 (2 H, m), 4.38 (1 H, s), 4.07 and 3.16 (2 H, AB quartet, $J$ = 14 Hz), 3.84 (3 H, s), 3.30 (3 H, s), 3.25 (3 H, s), 3.00 (1 H, t, $J$ = 8 Hz), 2.74–2.90 (1 H, m), 2.20–2.30 (1 H, m), 1.40–2.10 (7 H, m).

**Decahydro-1β-acetyl-2-methyl-6-oxoisoquinolino[5β,10β-*c*]-7-methoxy-2,3-dihydrobenzofuran (47f).** To a solution of **47a** (135.0 mg, 0.38 mmol) in 10 mL of ether was added 0.4 mL of MeLi/$Et_2O$ (1.2 M, 0.48 mmol) at room temperature under $N_2$. The reaction mixture was stirred at room temperature for 10 min, heated at reflux temperature for 15 min, and then cooled to room temperature. With cooling, 4 N $H_2SO_4$ (2 mL) was added and after stirring at room temperature for 30 min, $K_2CO_3$ was carefully added. The resulting mixture was extracted with chloroform and the combined organic layers were washed with water and brine, dried, and evaporated to give crude **47f**. Purification by preparative TLC ($SiO_2$, hexane–ethyl acetate, 1:3) afforded pure **47f** (46 mg, 37%): IR ($CDCl_3$) 5.80 μm; $^1H$ NMR ($CDCl_3$) δ 6.54–6.98 (3 H, m), 4.60 (1 H, s), 3.87 (3 H, s), 2.25 (3 H, s), 2.17 (3 H, s), 1.29–3.58 (10 H, m); electron impact mass spectrum, $m/e$ 329 ($M^+$).

Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.27; H, 7.05. Found: C, 68.97; H, 6.97.

**(±)-(14α)-4,5-Epoxy-3-methoxy-10-methylene-17-methylmorphinan-6-one (49a).** A solution of **47f** (5.0 mg, 0.02 mL) in $CF_3SO_3H$ (0.2 mL) was stirred at room temperature for 2 h. Water was carefully added to the dark red reaction mixture, solid $K_2CO_3$ was added, and the mixture was extracted with $CHCl_3$. The organic layers were combined, washed with brine, dried, and evaporated to give **49a** (3.7 mg, 74%): IR ($CDCl_3$) 5.80, 5.10, 6.20, 9.35 μm; $^1H$ NMR ($CDCl_3$) δ 7.14 and 6.75 (2 H, AB quartet, $J$ = 8.6 Hz), 5.85 (1 H, s), 4.87 (1 H, s), 4.77 (1 H, s), 3.93 (3 H, s), 2.53 (3 H, s), 1.39–3.53 (10 H, m); electron impact mass spectrum, $m/e$ 357 ($M^+$).

**Aldol 50.** To a solution of **48a** (28.0 mg, 0.08 mmol) in 3 mL of ether at room temperature was added methyl lithium in ether (1.1 M, 0.14 mmol). The reaction mixture was heated at reflux temperature for 30 min. After cooling and careful addition of methanol, the solvent was evaporated and the residue was dissolved in chloroform. The resulting solution was washed with brine, dried, and evaporated to give the intermediate imine. To a solution of the imine in 3 mL of methanol and 1 mL of water was added concentrated HCl (0.2 mL). After being heated to reflux temperature for 3 h, the reaction mixture was evaporated. Solid $NaHCO_3$ was added and the mixture was extracted with chloroform. The combined organic extracts were washed with brine, dried, and evaporated to give **50**. Preparative TLC ($SiO_2$, $CHCl_3$–MeOH, 5:1) afforded pure **50** (17 mg, 65%): mp 167–168 °C (chloroform–hexane); IR ($CDCl_3$) 3.02, 5.80, 7.83 μm; $^1H$ NMR ($CDCl_3$) δ 6.56–7.02 (3 H, m), 4.81 (1 H, s), 3.86 (3 H, s), 2.44 (3 H, s), 1.37 (3 H, s), 1.13–3.19 (10 H, m); electron impact mass spectrum, $m/e$ 329 ($M^+$).

Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.14; H, 7.08; N, 4.32.

**Decahydro-1β-acetyl-2-benzyl-6-oxoisoquinolino[5β,10β-*c*]-7-methoxy-2,3-dihydrobenzofuran (47g).** To a solution of **47b** (586.0 mg, 1.35 mmol) in dry ether (11 mL) was added 1.60 mL of methyl lithium in ether (1.5 M, 2.40 mmol). The cloudy yellow reaction mixture was stirred at room temperature for 10 min and then was heated at reflux temperature for 30 min. With cooling, 4 N $H_2SO_4$ (6 mL) was added. After 1 h at room temperature, $K_2CO_3$ was carefully added and the reaction mixture was extracted with chloroform. The combined organic extracts were washed with water and brine, dried, and evaporated to give **47g** (oil, 545 mg, 99%). **47g** was purified by preparative TLC ($SiO_2$, hexane–ethyl acetate, 4:1): mp 159–160 °C; IR ($CHCl_3$) 5.81, 5.85, 6.16, 6.67 μm; $^1H$ NMR ($CDCl_3$) δ 7.28–7.54 (5 H, m), 6.76–7.08 (3 H, m), 4.66 (1 H, s), 3.94 (3 H, s), 3.68 and 3.18 (2 H, AB quartet, $J$ = 14 Hz), 2.40 (3 H, s), 1.80–2.02 (10 H, m); electron impact mass spectrum, $m/e$ 406 ($M^+$).

Anal. Calcd for $C_{25}H_{27}NO_4$: C, 74.04; H, 6.72. Found: C, 73.88; H, 6.60.

**(±)-(14α)-4,5-Epoxy-3-methoxy-10-methylene-17-benzylmorphinan-6-one (49c)** was prepared from **47g** by the method described for the preparation of **49a**. Flash column chromatography ($SiO_2$, hexane–ethyl acetate, 3:1) afforded pure **49c** (75.0 mg, 57%) as a colorless foam: IR ($CHCl_3$) 5.78, 6.17, 6.29, 6.67 μm; $^1H$ NMR ($CDCl_3$) δ 7.22–7.54 (5 H, m), 7.14 and 6.76 (2 H, AB quartet, $J$ = 12 Hz), 5.90 (1 H, s), 4.88 (1 H, s), 4.82 (1 H, s), 3.92 (3 H, s), 3.77 and 3.59 (2 H, AB quartet, $J$ = 12 Hz), 3.54 (1 H, br s), 1.40–3.10 (9 H, m); electron impact mass spectrum, $m/e$ 388 ($M^+$).

**(±)-(14α)-4,5-Epoxy-3-methoxy-6,6-dimethoxy-10-methylene-17-methylmorphinan (49b).** A solution of **47f** (18.0 mg, 0.05 mmol) in 0.5 mL of $CF_3SO_3H$ was stirred for 2.5 h at room temperature under $N_2$. To the reaction mixture were added dry methanol (1.5 mL) and trimethyl orthoformate (0.15 mL) at 0 °C, and the resulting solution was stirred for 12 h at room temperature and was then poured into 0.7 mL of 50% KOH solution containing ice. The combined organic extracts from chloroform extraction were washed with brine, dried, and evaporated to give **49b**. Preparative TLC ($SiO_2$, ethyl acetate) afforded pure **49b** (12.0 mg, 60%): IR ($CDCl_3$) 6.18, 6.30, 7.80, 8.85, 9.50 μm; $^1H$ NMR ($CDCl_3$) δ 7.06 and 6.73 (2 H, AB quartet, $J$ = 8.6 Hz), 5.85 (1 H, s), 4.85 (1 H, s), 4.36 (1 H, s), 3.91 (3 H, s), 3.47 (3 H, s), 3.17 (1 H, s), 2.35 (3 H, s), 1.40–3.46 (10 H, m); electron impact mass spectrum, $m/e$ 357 ($M^+$).

**(±)-(14α)-4,5-Epoxy-3-methoxy-10-oxo-6,6-dimethoxy-17-methylmorphinan (51a).** To a solution of **49b** (5.0 mg, 0.02 mmol) in methanol (2 mL) containing 70% $HClO_4$ (3 μL) was added ozone (2 equiv) in methylene chloride at −78 °C. Dimethyl sulfide (0.05 mL) was added and the reaction mixture was allowed to warm to room temperature and then was stirred for 6 h. Addition of 10% $NaHCO_3$ solution was followed by extraction with chloroform. The combined organic layers were washed with brine, dried, and evaporated to give crude **51a**. Preparative TLC ($SiO_2$, hexane–ethyl acetate, 1:3) gave pure **51a** (3.0 mg, 60%). IR ($CDCl_3$) 5.98, 6.17, 6.25, 7.73, 8.00, 8.84, and 9.48 μm; $^1H$ NMR ($CDCl_3$) δ 7.32 and 6.79 (2 H, AB quartet, $J$ = 8.2 Hz), 4.44 (1 H, s), 3.97 (3 H, s), 3.47 (3 H, s), 3.17 (3 H, s), 2.47 (3 H, s), 1.43–3.40 (10 H, m); electron impact mass spectrum, $m/e$ 359 ($M^+$).

**(±)-(14α)-4,5-Epoxy-3-methoxy-6,6-(ethylenedioxy)-10-methylene-17-benzylmorphinan (52a).** A solution of the ketone **49c** (102.0 mg, 0.26 mmol), ethylene glycol (97.9 mg, 88 μL, 1.58 mmol) and *p*-toluenesulfonic acid monohydrate (72.0 mg, 0.38 mmol) in dry benzene (5 mL) was heated at reflux temperature, with a Dean–Stark apparatus (containing 4-Å molecular sieves). After 5 h, the reaction mixture was washed with saturated $NaHCO_3$ solution and brine, dried, and evaporated to give yellow, oily **52a** (112.0 mg, 99%). This material was used without further purification: IR ($CHCl_3$) 6.17 and 6.67 μm; $^1H$ NMR ($CDCl_3$) δ 7.22–7.50 (5 H, m), 7.14 and 6.77 (2 H, AB quartet, $J$ = 8 Hz),

5.88 (1 H, s), 4.86 (1 H, s), 4.42 (1 H, s), 4.20 (1 H, m), 3.82–4.02 (6 H, m), 3.77 and 3.57 (2 H, AB quartet, $J$ = 12 Hz), 3.46 (1 H, br s) and 1.50–2.60 (9 H, m); electron impact mass spectrum, $m/e$ 432 ($M^+$).

**(±)-(14α)-4,5-Epoxy-3-methoxy-6,6-(ethylenedioxy)-10-methylene-17-cyanomorphinan (52b).** To a solution of the ketal **52a** (112.0 mg, 0.26 mmol) in chloroform (5 mL) were added cyanogen bromide (41.0 mg, 0.39 mmol) and anhydrous $K_2CO_3$ (380.0 mg, 2.75 mmol), and the resulting suspension was heated at reflux temperature for 7 h. The reaction mixture was diluted with chloroform, washed with water and brine, dried, and evaporated to give **52b** (90.0 mg, 95%). Flash column chromatography ($SiO_2$, hexane–ethyl acetate, 1.5:1) afforded **52b** (70.0 mg, 74%). An analytical sample was prepared: mp 214–215 °C dec (ethyl acetate/hexane); IR ($CHCl_3$) 4.55, 6.17, 6.67 μm; $^1H$ NMR ($CDCl_3$) δ 7.10 and 6.80 (2 H, AB quartet, $J$ = 8 Hz), 5.90 (1 H, s), 5.48 (1 H, s), 4.38 (1 H, s), 3.80–4.20 (8 H, m), 3.20 (2 H, m), 1.60–2.30 (7 H, m); electron impact mass spectrum, $m/e$ 366 ($M^+$).

Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.83; H, 6.06. Found: C, 68.10; H, 5.72.

**(±)-(14α)-4,5-Epoxy-3-methoxy-10-oxo-17-cyanomorphinan-6-one (52c).** To a solution of **52b** (23.0 mg, 0.06 mmol) THF–$H_2O$ (2 mL, 1:1) was added 23 μL of 2.5 wt % solution of osmium tetraoxide in *tert*-butyl alcohol, and to the resulting rapidly darkening solution was added sodium periodate (46.0 mg, 0.22 mmol). After being stirred at room temperature for 12 h, the pale yellow solution was diluted with methylene chloride (15 mL), washed with water and brine, dried, and evaporated to give crystalline **52c** (23.0 mg, 99%). An analytical sample was prepared: mp 208–210 °C dec (ethyl acetate/hexane). IR ($CHCl_3$) 4.52, 5.92, 6.19 μm; $^1H$ NMR ($CDCl_3$) δ 7.50 and 6.91 (2 H, AB quartet, $J$ = 8 Hz), 4.46 (1 H, s), 4.18 (1 H, m), 3.91–3.98 (6 H, m with a sharp s at 3.98), 3.71 (1 H, d, $J$ = 2.8 Hz), 3.34–3.41 (2 H, m), 2.64–2.80 (2 H, m), 2.04–2.40 (2 H, m), 1.80–2.00 (4 H, m); electron impact mass spectrum, $m/e$ 368 ($M^+$).

Anal. Calcd for $C_{20}H_{20}N_2O_5$: C, 65.20; H, 5.48. Found: C, 65.03; H, 5.30.

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**Registry No.** (±)-**1a**, 93757-87-0; (±)-**1b**, 93757-86-9; (±)-**1c**, 93757-88-1; (±)-**2a**, 93859-96-2; (±)-**2b**, 94061-98-0; (±)-**2c**, 93859-99-5; (±)-**5**, 93757-83-6; (±)-**7**, 93757-84-7; **8**, 93757-85-8; (±)-**10a**, 93859-95-1; (±)-**10b**, 93757-89-2; (±)-**10c**, 93757-90-5; (±)-**11**, 93859-97-3; (±)-**12**, 93757-91-6; (±)-**13a**, 93757-92-7; (±)-**14**, 93757-93-8; (±)-**15a**, 93757-94-9; (±)-**15b**, 93757-96-1; (±)-**16**, 93757-95-0; (±)-**17a**, 93757-97-2; (±)-**17b**, 93757-98-3; (±)-**17c**, 93757-99-4; (±)-**22a**, 93758-44-2; (±)-**22b**, 93758-45-3; (±)-**22c**, 93758-46-4; (±)-**23a**, 93758-02-2; (±)-**23b**, 93758-04-4; (±)-**23c**, 93758-06-6; **24a**, 93758-03-3; **24b**, 93758-05-5; **24c**, 93758-07-7; (±)-**25a**, 93758-08-8; (±)-**25b**, 93758-09-9; (±)-**25c**, 93758-11-3; (±)-**25d**, 93758-12-4; (±)-**25e**, 93758-14-6; **26b**, 93758-10-2; **26d**, 93758-48-6; **28**, 18167-91-4; (±)-**29**, 93758-00-0; **30a**, 93758-01-1; **30b**, 62787-67-1; **30c**, 93758-47-5; (±)-**31a**, 93758-15-7; (±)-**31b**, 93758-16-8; (±)-**31c**, 93758-17-9; (±)-**31d**, 93758-19-1; (±)-**32a**, 93758-49-7; (±)-**32b**, 93758-18-0; (±)-**33a**, 93758-50-0; (±)-**33b**, 93781-86-3; (±)-**33c**, 93758-20-4; (±)-**33d**, 93781-87-4; **34a**, 93758-51-1; (±)-**35a**, 93781-85-2; (±)-**35b**, 93758-21-5; (±)-**36a**, 93758-22-6; (±)-**36b**, 93758-24-8; (±)-**36c**, 93758-23-7; (±)-**36d**, 93758-25-9; (±)-**36e**, 93758-27-1; (±)-**37a**, 93758-26-0; (±)-**37b**, 93758-28-2; (±)-**37c**, 93758-31-7; (±)-**38a**, 93859-98-4; (±)-**40a**, 93758-29-3; (±)-**40b**, 93758-30-6; (±)-**47a**, 93758-52-2; (±)-**47b**, 93758-32-8; (±)-**47e**, 93758-33-9; (±)-**47f**, 93758-34-0; (±)-**47g**, 93758-37-3; (±)-**48a**, 93758-53-3; (±)-**49a**, 93758-35-1; (±)-**49b**, 93758-39-5; (±)-**49c**, 93758-38-4; **50**, 93758-36-2; (±)-**51a**, 93758-40-8; (±)-**52a**, 93758-41-9; (±)-**52b**, 93758-42-0; (±)-**52c**, 93758-43-1; isovanillic acid methyl ester, 6702-50-7; 2-[(methoxymethyl)oxy]-1-(benzyloxy)benzene, 93758-13-5; 2-[(methoxymethyl)oxy]phenol, 52702-30-4; 3-hydroxy-4-methoxybenzonitrile, 52805-46-6; 2-(benzyloxy)phenol, 6272-38-4; vinyl bromide, 593-60-2; methyl vinyl ketone, 78-94-4; 2-methoxyphenol, 90-05-1; chloromethyl methyl ether, 107-30-2.

# Mechanisms of Epoxidation during Ozonation of Carbon–Carbon Double Bonds

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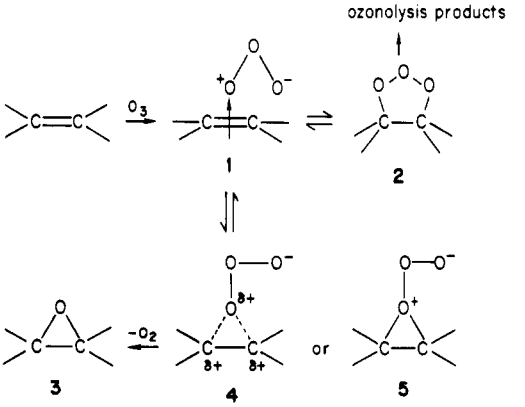
Epoxidation of several highly hindered olefins with ozone is stereospecific in all solvents, nucleophilic or nonnucleophilic. This is in agreement with expectations based on the initial formation of a π rather than an open σ complex.

Epoxidation and other "partial cleavage" reactions have long been known as reactions competitive with ozonolysis during ozonation of alkenes, olefins with various other functional groups, and related substances such as allenes and ketenes.[1,2] In many cases the epoxide itself is the product, whereas in other cases substances are obtained which could be derived from the epoxide by rearrangement, reactions with other functional groups in the molecule, or reactions with the solvent etc. Yields vary from less than 10% to nearly 100%. In many cases molecular oxygen has been observed as a product in approximately equal molar quantities with the epoxides.[1-4]

**Scheme I**




The various examples can roughly be divided into two groups: sterically hindered and unhindered olefins.[1] In the first category the degree of "partial cleavage" appears

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(4) Bailey, P. S.; Ward, J. W.; Hornish, R. E.; Potts, F. E., III *Adv. Chem. Ser.* **1972**, *No. 112*, 1.

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