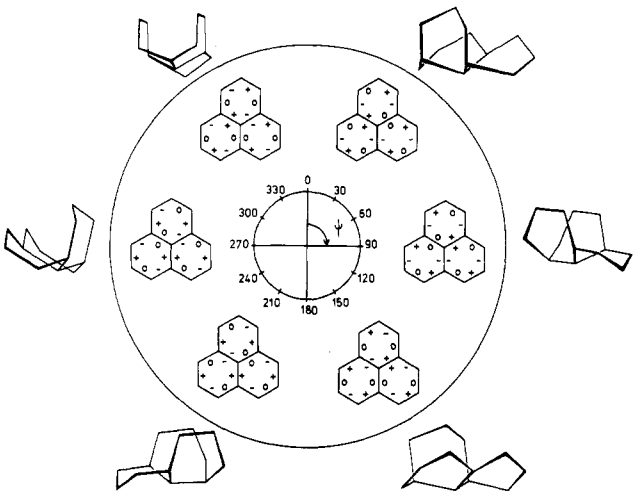


Figure 5. The pseudorototational path of the all boat conformation in the ccc form with a perspective view on the symmetrical molecules.

The two trans ring junctions restrict the maximum flexibility to some wagging around a higher symmetrical form.

The A ring of the BCC form is frozen in a twist conformation. It is the most stable conformation in this group, although 10.1 kcal/mol higher in energy than the all chair ttt configuration.

The BCB, BBB, and BBC forms are situated respectively 0.4, 5.4, and 6.1 kcal/mol higher in energy. The boat rings are all deformed twist conformations.

***cis,cis,cis*-Perhydrophenalene.** As above, no all chair conformation is possible. The CCB form is built up from two flattened chair conformations and a distorted twist. It is 14.6 kcal/mol higher in energy than the ttt-CCC form.

Two symmetrical forms of the CBB type may be distinguished, resulting from a flipping of ring A in the all boat form to a chair conformation at $\psi = 150°$ and $\psi = 330°$ (see Figure 5). They are denoted CBB1 and CBB2, respectively. Equivalent forms of CBB1 are generated at $\psi = (4n + 1)\pi/6$ and at $\psi = (4n - 1)\pi/6$, ($n = 0, 1, 2...$) for CBB2. Symmetry is lost during energy minimization however, in order to relieve the strain resulting from very short H···H distances. Stable conformations are found with energies of 31.2 (CBB1) and 34.0 (CBB2) kcal/mol.

As explained earlier, the all boat form has only one degree of freedom, and a complete potential function can be calculated by driving only one torsion angle. In practice however, it is necessary to switch to other angles during this process, owing to the ambiguous relationship between torsion angles and pseudorotation.

Owing to extremely short H···H distances, some rings in perhydrophenalene will flip from a boat to a chair conformation, rather than surmount the high potential barrier. A potential function may be calculated by imposing more constraints on the molecule, but this would lead to unrealistic results.[20] Therefore, only optimized BBB1 and BBB2 conformations are given here. The energies are 39.5 and 36.9 kcal/mol, respectively, and the boat conformations are in fact distorted twist forms.

It is seen from table I, that for both conformations, the pseudorotational phases agree very well with the values predicted from the geometrical model since $\phi_B \simeq \phi_C + 2\pi/3 \simeq \phi_A + 4\pi/3$, which is equivalent to eq 1 derived earlier.

An interesting conformation is a combination of three symmetrical twist boat rings, resulting in a *rigid* molecule with C_3 symmetry, and denoted BBBr. This form is 3.3 kcal/mol higher in energy than the CBB conformation and lies on a transition path between the CBB and all boat forms.

Conclusions

In this paper, the stable conformations of the four possible configurations of perhydrophenalene are studied.

With idealized models, the reasonable conformations are deducted, and a simple model for the "in between" conformations is derived.

As one could intuitively expect, the all chair form has the lowest energy in the ttt and cct configurations. In both the ctt and ccc forms, at least one ring must be in a boatlike conformation. In these two configurations, the difference in sterical energy between the two most stable conformations is relatively small, and it is thus uncertain that the same conformational preference will be found in the related steroids.

A molecular mechanics study of the conformations of the perhydrobenzo[4.5.6]androstanes and crystal structure elucidations of related compounds is in progress and will be reported elsewhere.

Registry No. (*ttt*)-Perhydrophenalene, 40250-64-4; (*cct*)-perhydrophenalene, 86118-18-5; (*ctt*)-perhydrophenalene, 91465-59-7; (*ccc*)-perhydrophenalene, 91465-60-0.

(20) See White and Bovill (White, D. N. J.; Bovill, M. J. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1610) for an example of completely different results using other contraints.

A New Approach to Morphinans: Total Synthesis of *O*-Methylpallidinine[1]

John E. McMurry,* Vittorio Farina, William J. Scott, Alan H. Davidson, David R. Summers, and Ashok Shenvi

Department of Chemistry, Cornell University, Ithaca, New York 14853

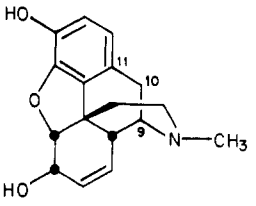
Received March 6, 1984

We have devised a general method for the synthesis of 4a-aryloctahydroisoquinolines related to morphine and have shown how these compounds may be used in a route to morphinan alkaloids. The key step in this route involves the addition of diazomethane to a 4a-aryloctahydroisoquinolinium salt, followed by spontaneous cyclization to the morphinan. Studies of this step indicate that it is not compatible with the presence of an alkoxyl group at C4 of the aryl ring. The value of this method has been demonstrated in the context of stereospecific total synthesis of *O*-methylpallidinine.

The morphine alkaloids[2] are a large class of natural products that have, over the year, provoked an extraordinary amount of activity by synthetic organic chemists. Total syntheses of morphine have been achieved by several

0022-3263/84/1949-3803$01.50/0

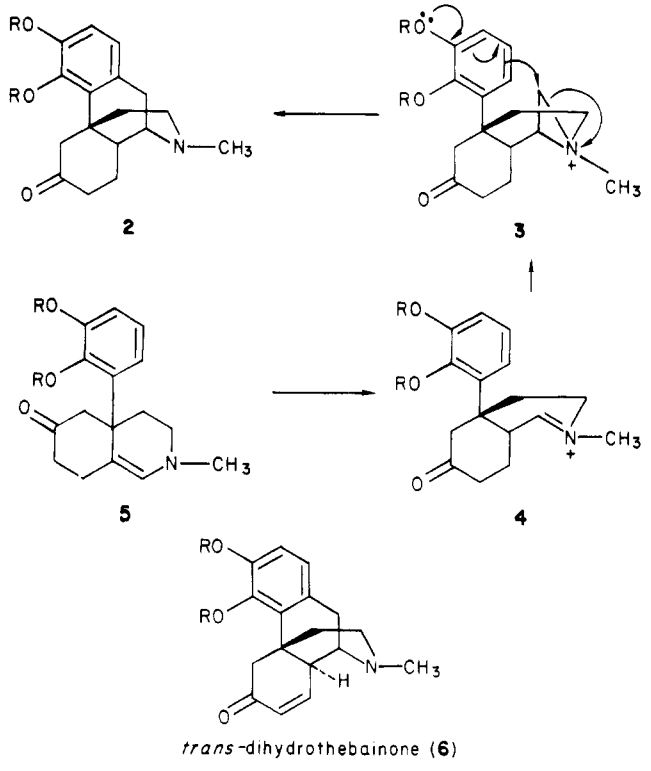
workers,[3-10] and a great many synthetic analogues of morphine have been prepared. Although different routes



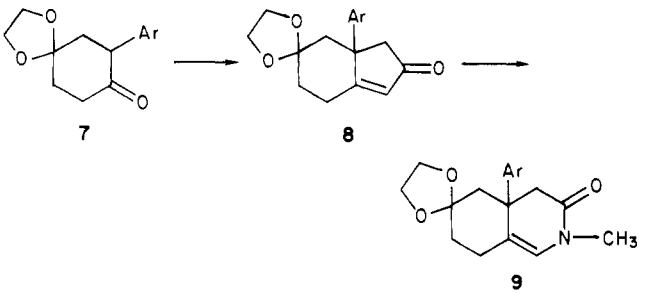
morphine (1)

to the morphinan skeleton have been used, formation of the C12–C13 bond serves as the key step in many of these syntheses. Our own interest in morphinan chemistry grew out of a desire to find an entirely new, perhaps practical, route for the total synthesis of morphine. In searching the morphine structure for potential retrosynthetic disconnections, we focused our attention on the C11–C10–C9–N segment of the molecule.

We were struck by the possibility that the C10–C11 bond might result by an intramolecular nucleophilic attack of the aromatic ring on an aziridinium ion (**3** → **2**). The



trans-dihydrothebainone (**6**)



aziridinium ion, in turn, could come from reaction[11] of diazomethane with an iminium ion (**4** → **3**). Once cyclization has been achieved, the remainder of the morphine synthesis would follow standard chemistry since **6** (*trans*-dihydrothebainone) has already been converted into morphine.[3,12-14] (While this work was in progress, a similar approach to morphinans was reported by Evans.[15]) With the rough outlines of the projected synthesis thus defined, our initial goal became the synthesis of octahydroisoquinoline **5**, which might be protonated to generate the necessary iminium ion **4**.

Synthesis of 4a-Aryloctahydroisoquinolines. Upon finding that no general routes existed for the preparation of 4a-aryloctahydroisoquinolines such as **5**, we decided to develop a new approach that would allow the introduction of a variety of substituted aryl groups and that would be amenable to relatively large scale work. Our idea was based on the possibility of carrying out a Beckmann-type ring expansion of a hydrindenone that itself should be accessible by annulation of an appropriate 2-arylcyclohexanone (**7** → **8** → **9**).

Our successful route for the synthesis of 4a-aryloctahydroisoquinolines, illustrated by the synthesis of **19a** (**19a**, R = $-CH_3$; **19b**, R, R = cyclohexylidene), began with the readily available 1,3-cyclohexanedione and followed the sequence of steps outlined in Scheme I. 1,3-Cyclohexanedione was first converted into its isopropyl enol ether by azeotropic removal of water from a benzene/hexane/isopropyl alcohol solution, and (2,3-dimethoxyphenyl)lithium, prepared[16] by treatment of veratrole with *n*-butyllithium in tetramethylethylenediamine, (TMEDA) was then added. The resultant carbinol **10a** proved extraordinarily stable to aqueous acid but could be dehydrated and hydrolyzed on treatment with 0.5 N sulfuric acid for 20 h at room temperature to give enone **11a**. Acetalization with ethylene glycol proceeded smoothly and gave the double bond migrated product **12a** as a clear oil. Hydroboration of **12a**, followed by basic hydrogen peroxide oxidation, gave the crystalline alcohol **13a**, mp 118–119 °C, and further oxidation with pyridinium chlorochromate gave ketone **14a**. Alternatively, it also proved possible to isolate **14a** directly from olefin **12a** by pyridinium chlorochromate oxidation of the intermediate organoborane.

Alkylation of **14a** proved to be the most troublesome step in the sequence and was the only step requiring chromatographic purification of the product. Under our best conditions, formation of the sodium enolate was effected by treatment with sodium hydride in dimethoxyethane (DME), and alkylation was carried out with

(1) The initial phases of this work were carried out at the University of California, Santa Cruz, CA.

(2) For reviews of morphinan–alkaloid chemistry, see: (a) Holmes, H. L.; Stork G. "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1952; Vol. II, pp 1–218. (b) Stork, G. "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1960; Vol. VI, pp 219–246. (c) Bentley, K. W. "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1971; Vol. XIII, pp 1–164.

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

(4) Ginsberg, D.; Pappo, R. *J. Chem. Soc.* **1951**, 938. Ginsberg, D.; Pappo, R. *J. Chem. Soc.* **1953**, 1524. Elad, D.; Ginsberg, G. *J. Chem. Soc.* **1953**, 2664. Elad, D.; Ginsberg, D. *J. Am. Chem. Soc.* **1954**, *76*, 312. Elad, D.; Ginsberg, D. *J. Chem. Soc.* **1956**, 3052.

(5) Barton, D. H. R.; Kirby, G. W.; Steglich, W.; Thomas, G. M. *Proc. Chem. Soc.* **1963**, 203. Barton, D. H. R.; Bhakuni, D. S.; James, R.; Kirby, G. W. *J. Chem. Soc. C* **1967**, 128.

(6) Kametani, T.; Ihara, M.; Fukumoto, K.; Yagi, H. *J. Chem. Soc. C* **1969**, 2030.

(7) Schwartz, M. A.; Mami, I. S. *J. Am. Chem. Soc.* **1975**, *97*, 1239.

(8) Grewe, R.; Friedrichsen, W. *Chem. Ber.* **1967**, *100*, 1550.

(9) Lie, T. S.; Maat, L.; Beyerman, H. C. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 419 and references therein.

(10) Rice, K. C. *J. Org. Chem.* **1980**, *45*, 3135.

(11) (a) Leonard, N. J.; Jann, K. *J. Am. Chem. Soc.* **1960**, *82*, 6418. (b) Leonard, N. J.; Jann, K. *J. Am. Chem. Soc.* **1962**, *84*, 4806.

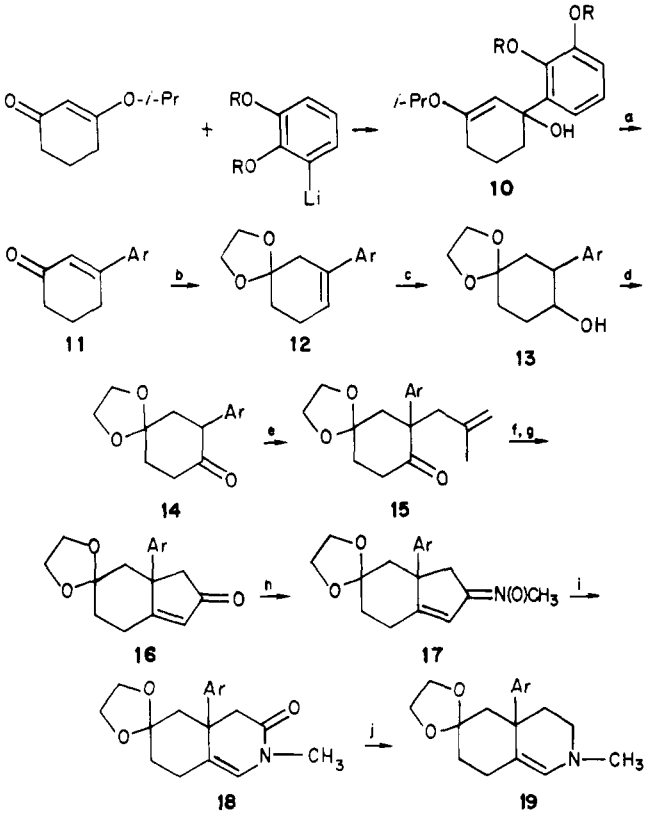
(12) Gates, M.; Shepard, M. S. *J. Am. Chem. Soc.* **1962**, *84*, 4125.

(13) Weller, D. D.; Rapoport, H. *J. Med. Chem.* **1976**, *19*, 1171.

(14) Dauben, W. G.; Baskin, C. P.; van Riel, H. C. H. A. *J. Org. Chem.* **1979**, *44*, 1567.

(15) Evans, D. A.; Mitch, C. H.; Thomas, R. C.; Zimmerman, D. M.; Robey, R. L. *J. Am. Chem. Soc.* **1980**, *102*, 5955. For a follow-up report, see: Evans, D. A.; Mitch, C. H. *Tetrahedron Lett.* **1982**, *23*, 285.

Scheme I[a,b]

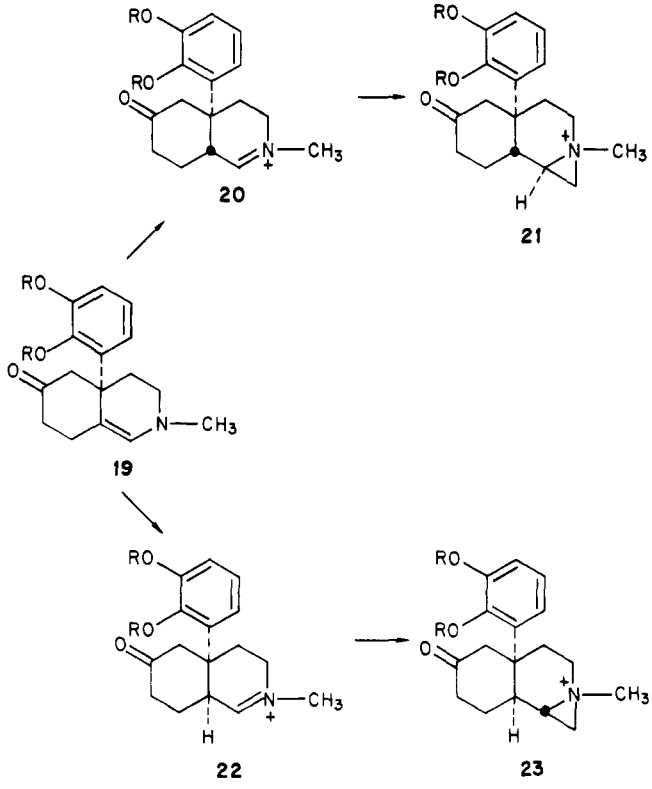


[a] a, R = CH_3; b, R,R = cyclohexylidene. [b] (a) 0.5 N H_2SO_4; (b) $HOCH_2CH_2OH$, *p*-TsOH; (c) BH_3, THF; then H_2O_2, NaOH; (d) pyridinium chlorochromate, CH_2Cl_2; (e) NaH, DME; then $CH_2=C(CH_3)CH_2Cl$; (f) OsO_4, $NaIO_4$, dioxane; (g) NaH, benzene; (h) $CH_3NHOH \cdot HCl$, NaOAc; (i) *p*-TsCl, pyridine, H_2O; (j) $LiAlH_4$, THF.

methallyl chloride. A mixture of C- and O-alkylated products was obtained, but Claisen rearrangement of the crude mixture for 36 h in refluxing toluene provided pure C-alkylated product **15a** in 60% yield. Cleavage of the double bond in **15a** was carried out using the catalytic osmium tetraoxide/sodium periodate procedure to provide a diketone that could be cyclized on treatment with sodium hydride in benzene.

Beckmann rearrangement of hydrindenone **16a** to enamide **18a** would appear to be a potential source of trouble, since rearrangements of unsaturated oximes usually occur with migration of the *alkyl*, rather than the vinylic, bond to give α,β-unsaturated lactam products. Barton has shown,[17] however, that Beckmann-type rearrangement of unsaturated *N*-methylnitrones leads to migration of the vinylic bond and gives enamide products. Thus, we treated crystalline enone **16a** with *N*-methylhydroxylamine in ethanolic sodium acetate and isolated nitrone **17a** as an oil. Rearrangement occurred on reaction of **17a** with *p*-toluenesulfonyl chloride in pyridine containing 16 equiv of water to give enamide **18a** as the sole product in 60% yield. The synthesis was then completed by reduction of **18a** with $LiAlH_4$ in refluxing tetrahydrofuran, and crystalline 4a-aryloctahydroisoquinoline **19a** was isolated in 85% yield. The entire route from 1,3-cyclohexanedione to 4a-(2,3-dimethoxyphenyl)-6,6-(ethylenedioxy)-2-methyl-2,3,4,4a,5,6,7,8-octahydroisoquinoline **19a** takes eleven steps, requires only one chromatographic purification, is amenable to large-scale preparations, and is compatible with the introduction of a variety of functionalized aryl groups. The analogous (cyclohexylidenedioxy)phenyl compound **19b** was prepared similarly (see Experimental Section).

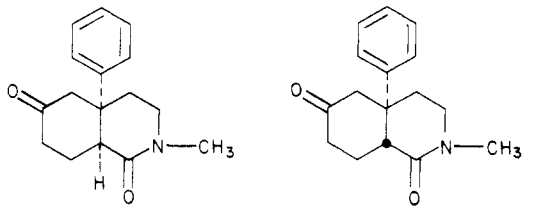
Attempted Syntheses of Morphine. With octahydroisoquinolines **19a** and **19b** available, we set out to study the proposed cyclization reaction for generating the morphine skeleton. If the cyclization is to take place as desired, it is necessary for the angular aryl group and the aziridinium ion to have a cis relationship on the perhydroisoquinoline ring (**23** rather than **21**). This, in turn,



requires that attack of diazomethane on the intermediate iminium ion occur cis to the angular aryl group. Such an attack *would* be expected for an octahydroisoquinoline iminium ion with a cis ring fusion, such as **22**, since the convex side of the molecule is more sterically accessible,[18] but would *not* be expected for an ion with a trans ring fusion, such as **20**, where the axial aryl group would shield the necessary face from attack. Since we planned to establish the cis/trans-ring-fusion stereochemistry of the iminium ion by protonation of enamine **19**, it is obviously critical that this protonation yield cis-fused product **22**. Although this cis-ring-junction stereochemistry is *opposite* to that in morphine, the matter can easily be corrected later in the synthesis since epimerization of the center can be accomplished via an α,β-unsaturated Δ^7-6-ketomorphinan.[12]

Fortunately, cis-ring-junction stereochemistry is just what one would expect for protonation of enamine **19**, based on analogy to literature precedents. For example, Rapoport has demonstrated[19] that cis-fused amide **24** is favored over trans-fused amide **25** at equilibrium. We therefore treated enamine **19a** with ethanolic perchloric acid and obtained in 91% yield a crystalline keto iminium

(16) Gilman, H.; Swiss, J.; Cheney, L. C. *J. Am. Chem. Soc.* **1940**, *62*, 1963.
(17) Barton, D. H. R.; Day, M. J.; Hesse, R. H.; Pechet, M. M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1964.
(18) See, for example: McMurry, J. *J. Am. Chem. Soc.* **1968**, *90*, 6821.
(19) Weller, D. D.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1977**, *42*, 1485.

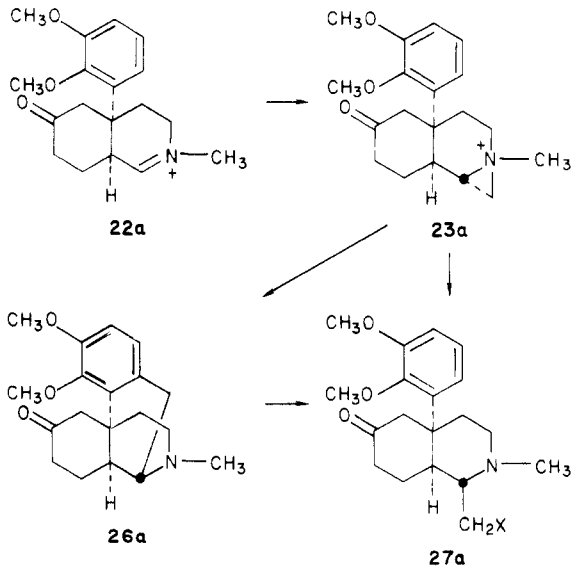


24 25

perchlorate, which was shown by X-ray crystallography[20] to be the desired cis-fused product **22a**.

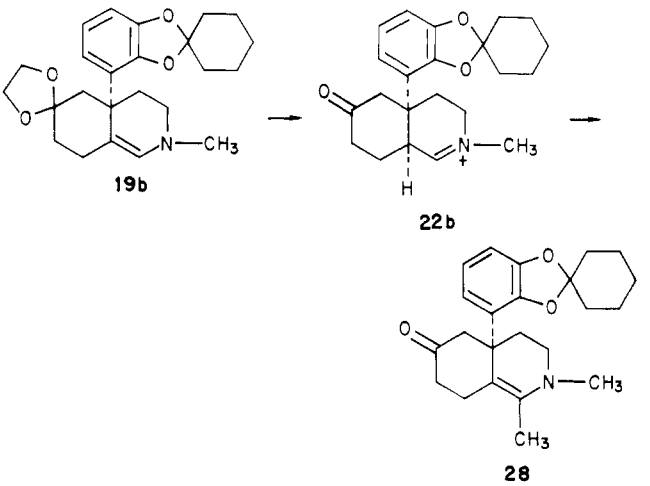
It was now time to prepare the aziridinium ion necessary for attempts at cyclization. Treatment of iminium perchlorate **22a** in acetonitrile with a methylene chloride solution of diazomethane led to the evolution of nitrogen and production of a light yellow solid. IR spectroscopy showed the absence of an iminium ion C=N stretch, and 300-MHz ^{1}H NMR spectroscopy showed a pattern consistent with that expected for aziridinium ion **23a**. Unfortunately, however, none of the desired product (**26a**) was detected, either by TLC or by 300-MHz NMR. (We estimate that <1% of **26a** could have been detected, since an authentic sample prepared from thebaine by Small's procedure[21] was available for comparison.)

In light of the failure of **23a** to undergo spontaneous closure, a great many experiments were conducted in attempts to force cyclization. All were unsuccessful. For example, heating **23a** at temperatures from 50 to 300 °C yielded no morphinan. Reaction of **23a** with lithium halides led cleanly to β-halo amines **27a** (X = Cl, I), but all attempts at Friedel–Crafts-like cyclizations[22] with a variety of Lewis acid catalysts led either to no reaction, to destruction of the molecule, or in one experiment to halogenation of the aromatic ring. No morphinan corresponding to structure **26a** was obtained, however,



22a 23a 26a 27a

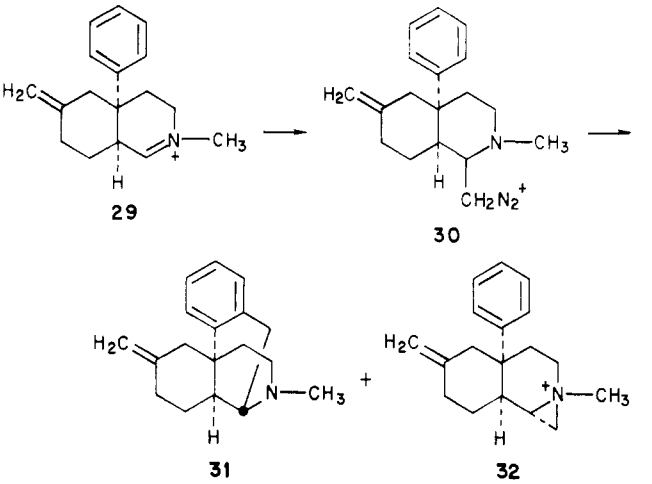
Cyclization experiments with **19b**, which contains a (cyclohexylidenedioxy)phenyl ring in place of a dimethoxyphenyl ring, were more revealing. Protonation and deacetalization of **19b** occurred normally to yield iminium perchlorate **22b**, which was treated with diazomethane. In marked contrast to the previous results, however, the major



19b 22b 28

product was methylated enamine **28**. Once, again, no morphinan was produced.

At this point in our research, the publication appeared by Evans[15] describing the results of his own independent work that had been proceeding along similar lines.[23] Working with an unsubstituted aromatic ring, Evans reported that reaction of iminium ion **29** with diazomethane



29 30 31 32

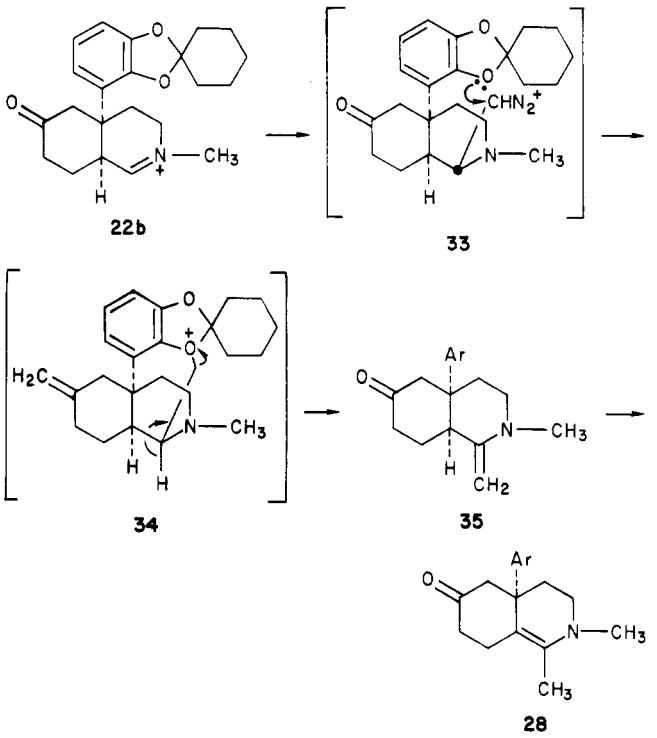
led to a mixture of morphinan **31** and aziridinium ion **32**. He also reported that aziridinium ion **32** could be converted into morphinan **31** under Friedel–Crafts conditions but not under purely thermal conditions. He therefore concluded that the morphinan he obtained arose from direct attack of the aromatic ring on intermediate diazonium ion **30**.

Why does **29**, which contains an unsubstituted aromatic ring, yield morphinan more readily than **22b**, which contains a more nucleophilic dialkoxy-substituted ring? We suggest that these results can be interpreted by assuming that the alkoxy group at C4 of the aromatic ring in **22b** is interfering with the desired reaction course by displacing nitrogen from the intermediate diazonium ion **33** in competition with aziridinium ion formation. Opening of oxonium ion **34** by elimination of the neighboring bridgehead proton (antiperiplanar relationship) would yield exocyclic enamine **35**, which could isomerize to the more stable endocyclic enamine isomer **28** under the acidic reaction conditions.

If this analysis is correct, it implies that the presence of the C4 oxygen substituent is preventing the desired cyclization from occurring and that morphinan formation

(20) We thank Professor Jon Clardy and Dr. Edward Arnold, Cornell University, for help in carrying out this X-ray structural study.
(21) Small, L.; Browning, G. L. *J. Org. Chem.* **1939**, *3*, 618.
(22) A related cyclization has been reported: Stella, L.; Raynier, B.; Surzur, J. *Tetrahedron Lett.* **1977**, 2721.
(23) After our work was concluded, work along similar lines was also reported by Rapoport: Moos, W. H.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 227.

might ensue, as Evans found, if that substituent were absent. Although such a limitation would preclude use of the reaction for the synthesis either of morphine itself or of analogues having the morphine oxygenation pattern, morphinans *without* an oxygen substituent at C4 should be amenable to synthesis.

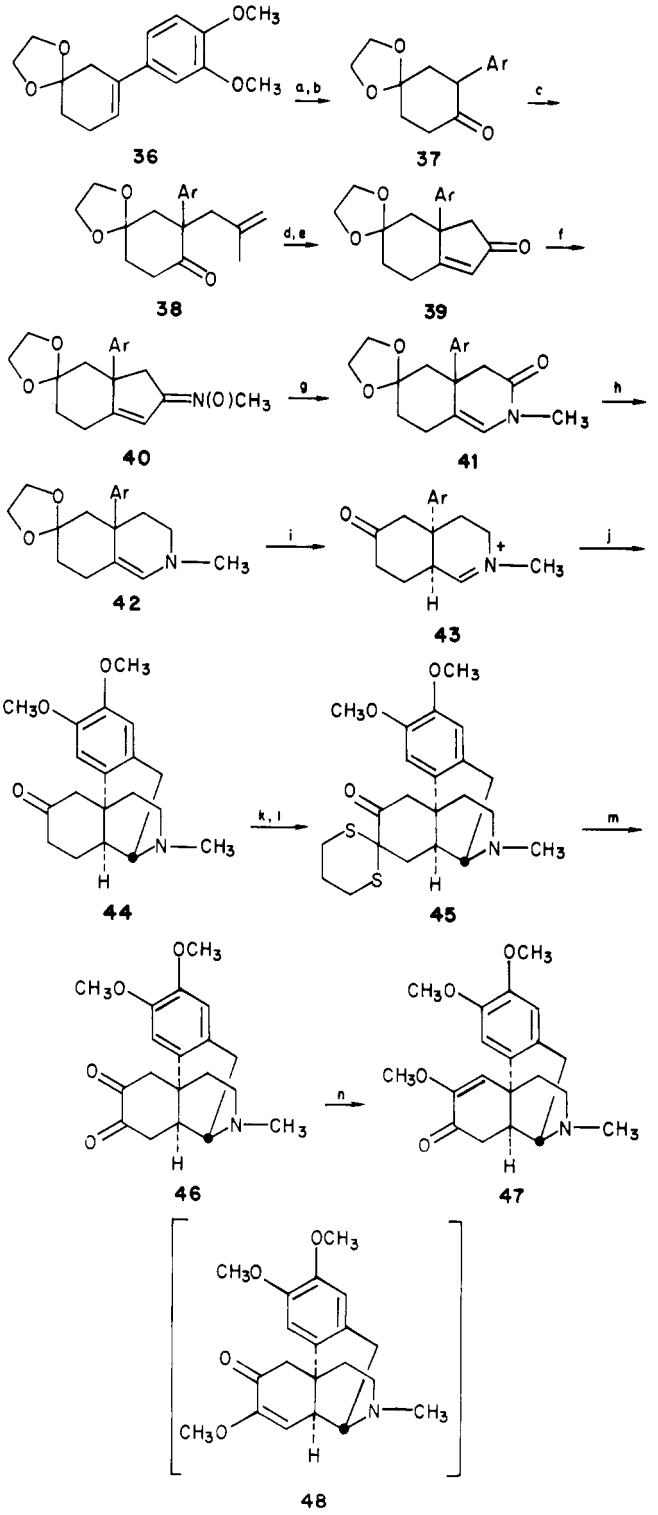


Synthesis of *O*-Methylpallidinine.[24] We decided to test this hypothesis in the context of a total synthesis of *O*-methylpallidinine (**47**), a B/C *trans*-morphinan recently isolated[25] from leaves of the South American plant *Ocotea acutangula* (Mez). Since *O*-methylpallidinine is unsubstituted at C4, it should result from reaction of diazomethane with iminium ion **43** if our hypothesis is correct. (One further advantage to the choice of *O*-methylpallidinine as target is that the molecule has a cis relationship between the aryl ring and the ring-junction hydrogen at C14. This stereochemistry results directly in our route.)

Iminium ion **43** was prepared by again resorting to the general route described earlier (Scheme II). Treatment of 3-ethoxy-2-cyclohexenone with (3,4-dimethoxyphenyl)lithium, followed by acid-catalyzed dehydration and acetalization gave olefin **36**. Hydroboration/oxidation of **36** gave an alcohol that was oxidized with pyridinium chlorochromate to yield ketone **37**. The sodium enolate of ketone **37** was next alkylated with methallyl chloride to give keto olefin **38**, which was oxidized to a diketone and subsequently cyclized to hydrindenone **39**. Beckmann rearrangement[17] of nitrone **40** proceeded smoothly to give enamide **41**, which was reduced by $LiAlH_4$ to give enamine **42**.

Treatment of enamine **42** with aqueous ethanolic perchloric acid gave a crystalline iminium ion that, by analogy of our earlier work, was assumed to have the desired cis-ring-fusion stereochemistry (**43**). Treatment of this iminium ion with diazomethane in acetonitrile proceeded exactly as predicted to give morphinan **44** in 30% isolated yield after chromatographic purification of the crude product. We therefore conclude that our inferences about the incompatibility of the cyclization reaction with C4 oxygen substituents were correctly drawn.

Scheme II.[a] Synthesis of *O*-Methylpallidinine



[a] (a) BH_3, THF; then H_2O_2, NaOH; (b) pyridinium chlorochromate; (c) NaH, THF; then $CH_2=C(CH_3)-CH_2Cl$; (d) $KMnO_4$, $NaIO_4$, dioxane; (e) KOH, EtOH; (f) CH_3NHOH, NaOAc; (g) *p*-TsCl, H_2O, pyridine; (h) $LiAlH_4$, THF; (i) $HClO_4$, H_2O, EtOH; (j) CH_2N_2, CH_3CN; (k) HCOOEt, NaH; (l) $TsS(CH_2)_3STs$, JOAc; (m) MCPBA, then HCl, H_2O; *p*-TsOH, CH_3OH.

The conversion of morphinan **44** into *O*-methylpallidinine was accomplished as indicated in Scheme II. α-Formylation of ketone **44** by treatment with sodium hydride and ethyl formate took place on the less hindered

(24) A preliminary account of this work has appeared: McMurry, J. E.; Farina, V. *Tetrahedron Lett.* **1983**, *24*, 4653.
(25) Vecchietti, V.; Casagrande, C.; Ferrari, G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 578.

side of the carbonyl group to give a hydroxymethylene ketone that was converted into keto thioacetal **45** by treatment with 1,3-propanedithiol ditosylate. Oxidation with *m*-chloroperoxybenzoic acid and subsequent hydrolysis gave diketone **46**, which was identical with an authentic sample prepared by hydrolysis of natural *O*-methylpallidinine.[26] Although enol methylation of diketone **46** gave largely the undesired regioisomer **48** under thermodynamic conditions, treatment with *p*-toluenesulfonic acid in methanol led to a 4:1 predominance of (±)-*O*-methylpallidinine **47**. The synthetic alkaloid, mp 198–202 °C (hydrochloride), was identical with an authentic sample[26] of the natural product by 300-MHz ^{1}H NMR, ^{13}C NMR, IR, and high-resolution MS.

Conclusions

Although the goals we initially set were not fully met, our search for a new route for the synthesis of morphinan alkaloids has been successful. Morphine itself appears inaccessible by our route, but a number of related materials that do not have oxygen substituents at C4 on the aromatic ring ought to be readily available.

Experimental Section

NMR spectra were recorded on Varian EM360, JEOL FX90Q, JEOL FT-100, and Bruker WM 300 instruments, with chemical shifts reported in parts per million downfield from internal tetramethylsilane standard. IR spectra were recorded on a Perkin-Elmer 298 instrument, calibrated at the 1601 cm^{-1} polystyrene absorption. Both low- and high-resolution mass spectra were recorded on an AEI-MS 902 instrument. Melting points were determined on a Thomas-Hoover Uni-melt apparatus and are uncorrected. The phrase "worked up in the usual manner" refers to washing the reaction extract with saturated brine, drying the organic layer with powdered anhydrous sodium sulfate, filtering through a sintered glass funnel, and concentrating of the product by solvent removal at the rotary evaporator.

3-(2,3-Dimethoxyphenyl)-2-cyclohexenone (11a). A mixture of 1,3-cyclohexanedione (168 g, 1.5 mol), benzene (1500 mL), isopropyl alcohol (600 mL), hexane (200 mL), and *p*-toluenesulfonic acid monohydrate (7.5 g) was heated under reflux for 18 h. Water was azeotropically removed by means of a Dean–Stark apparatus filled with hexane to aid separation. At the end of this period, the reaction mixture was cooled and washed, first with 5% NaOH (4 × 100 mL), then with water until the aqueous layer was neutral to pH indicator paper, and then with brine. The organic layer was dried (Na_2SO_4) and concentrated at the rotary evaporator, yielding an oil that was distilled at reduced pressure to provide the isopropyl enol ether of 1,3-cyclohexanedione (210 g, 91% yield): bp 100 °C (1.0 mm); IR 1675 (C=O), 1610 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.28 (d, J = 6 Hz, 6 H), 4.40 (sept, J = 6 Hz, 1 H), 5.30 (s, 1 H).

(2,3-Dimethoxyphenyl)lithium was prepared by addition of *n*-butyllithium (264 mL, 2.2 M solution in hexane, 0.58 mol) over a period of 30 min to a stirred ice cold solution of veratrole (80 g, 0.58 mol) in dry ether (300 mL) containing dry tetramethylethylenediamine (TMEDA, 87 mL, 0.58 mol). The resulting white reaction mixture was stored at room temperature for 2 h, then cooled to −5 °C, and added over a period of 10 min to a stirred solution of 1,3-cyclohexanedione isopropyl enol ether (84 g, 0.54 mol) in dry ether (300 mL). The reaction mixture was stirred at room temperature for 18 h and then poured into water (500 mL). After washing with saturated ammonium chloride solution (2 × 100 mL), the organic layer was dried ($MgSO_4$) and concentrated at the rotary evaporator to afford a pale yellow oil (132 g). This oil was dissolved in tetrahydrofuran (THF) (400 mL) and treated with 0.5 N sulfuric acid (400 mL) for 20 h. Workup in the usual manner provided enone **11a** as a yellow oil, which was purified by distillation under reduced pressure. The fraction boiling at 190–195 °C (1.0 mm) was collected (76 g, 60%): IR ($CHCl_3$) 1670 (C=O) cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 3.8 (s, 3 H), 3.85 (s, 3 H), 6.2 (s, 1 H), 6.2–7.2 (m, 3 H).

3-(2,3-Dimethoxyphenyl)-3-cyclohexenone Ethylene Acetal (12a). A mixture of enone **11a** (70 g, 0.3 mol), ethylene glycol (75 mL), benzene (500 mL), and *p*-toluenesulfonic acid monohydrate (0.5 g) was heated under reflux while azeotropically removing water with a Dean–Stark apparatus. After 6 h, an additional quantity of *p*-toluenesulfonic acid monohydrate (0.5 g) was added to the reaction mixture, and the reflux was continued an additional 14 h. The dark red reaction mixture was cooled to room temperature, diluted with ether (400 mL), washed with saturated sodium bicarbonate solution (3 × 50 mL), and worked up in the usual manner to afford acetal **12a** as a yellow oil (75g) that was used in the next step without purification.

In a separate experiment, a sample was purified for characterization by column chromatography over silica gel (ethyl acetate/hexane, 1:1): IR ($CHCl_3$) 1600, 1580, 1500, 1475 cm^{-1}; NMR (C_6D_6, 100 MHz) δ 1.8 (t, J = 6 Hz, 2 H), 2.2–2.5 (m, 2 H), 2.81 (s, 2 H), 5.8 (m, 1 H), 6.54–6.92 (m, 3 H).

3-(2,3-Dimethoxyphenyl)-4-hydroxycyclohexanone Ethylene Acetal (13a). Borane (240 mL of 2.0 M solution in THF, 0.48 mol) was added over a period of 30 min to a stirred, ice cold solution of acetal **12a** (75 g) in dry THF (200 mL). After addition was complete, the reaction mixture was stirred at room temperature overnight, cooled in ice, and treated with 3 N NaOH solution (175 mL) followed by 30% hydrogen peroxide (125 mL). The resulting reaction mixture was stirred at room temperature for 1 h and at 45 °C overnight, then cooled, diluted with water and ether, and extracted with ether. Workup in the usual manner afforded an oil that crystallized to a white solid on stirring with diisopropyl ether (100 mL). Recrystallization of this solid from diisopropyl ether gave alcohol **13a** as white crystals (52 g, 58% from enone **11a**): mp 118–119 °C; IR ($CHCl_3$) 3500, 1600, 1470 cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 1.30–2.33 (br, 7 H), 3.00–4.50 (br, 12 H), 6.50–7.10 (br, 3 H). Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.3; H, 7.48. Found: C, 65.1; H, 7.22.

3-(2,3-Dimethoxyphenyl)-1,4-cyclohexanedione 1-(Ethylene Acetal) (14a). Pyridinium chlorochromate (39.6 g, 0.184 mol) was added in small portions to a vigorously stirred solution of alcohol **13a** (20 g, 68 mmol) in dichloromethane (200 mL). After addition was complete, the reaction mixture was let stand overnight, diluted with ether (200 mL), and filtered through a pad of Florisil. The filtrate was concentrated under reduced pressure to yield ketone **14a** as an oil (17.9 g, 88%): bp 160 °C (0.15 mm); IR (film) 1725, 1600, 1480 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 3.74 (s, 3 H), 3.84 (s, 3 H), 3.86–4.29 (m, 4 H), 6.12–7.10 (m, 3 H).

3-(2,3-Dimethoxyphenyl)-3-(2-methyl-2-propenyl)-1,4-cyclohexanedione 1-(Ethylene Acetal) (15a). Sodium hydride (56% oil dispersion, 1.47 g, 34 mmol) was washed with hexane (3 × 10 mL) and added in portions to a stirred solution of ketone **14a** (10 g, 34.2 mmol) in dimethoxyethane (DME, 20 mL). After stirring overnight, the reaction mixture was treated with methallyl chloride (3.5 g, 39.0 mmol) and stirred for an additional hour. The reaction mixture was then refluxed for 2 h, cooled to room temperature, poured into water, and extracted with ether (4 × 100 mL). Workup in the usual manner afforded an oil that was dissolved in toluene (70 mL) and refluxed for 36 h to effect Claisen rearrangement. Concentration of the resulting product under reduced pressure and chromatography on silica gel (ethyl acetate/hexane, 1:4) gave the desired olefin **15a** (7.1 g, 54%): IR (film) 1725, 1480 cm^{-1}; NMR (C_6D_6, 100 MHz) δ 1.32 (s, 3 H), 3.3 (s, 3 H), 3.4–3.52 (m, 4 H), 3.66 (s, 3 H), 4.6 (s, 1 H), 6.55 (dd, J = 8, 1.5 Hz, 1 H), 6.8–7.16 (m, 2 H); mass spectrum, m/z 346 (M^+).

3a-(2,3-Dimethoxyphenyl)-5,5-(Ethylenedioxy)-3,3a,4,5,6,7-hexahydro-2*H*-inden-2-one (16a). Osmium tetraoxide (2.1 mL of a 0.26 M solution in benzene, 0.54 mmol) was added dropwise to a stirred two-phase suspension of olefin **15a** (5.0 g, 14.5 mmol) in ether (50 mL) and water (60 mL). The resulting brown mixture was stirred for 20 min, and powdered sodium periodate (11.0 g, 51 mmol) was added in small portions. After this reaction mixture had stirred vigorously for an additional 48 h, it was diluted with water (50 mL) and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic layers were then washed with saturated sodium bisulfite (3 × 25 mL) and worked up in the usual manner to afford a pale brown

(26) We thank Dr. Vecchietti, Simes Research Laboratories, Milano, Italy, for providing us with an authentic sample of *O*-methylpallidinine.

oil (3.8 g, 75%), which was used without further purification: IR 1715, 1470 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 1.74 (s, 3 H), 3.30 (s, 3 H), 3.26–3.50 (m, 4 H), 6.44–6.92 (m, 3 H).

The diketone prepared above was cyclized by treatment with sodium hydride (1.2 g of a 56% oil dispersion, 28 mmol) in benzene (80 mL) containing *tert*-amyl alcohol (0.4 mL). The reaction mixture was heated under reflux for 0.5 h, cooled to room temperature, and poured onto ice. Extraction with ether (4 × 30 mL) and workup in the usual way gave a white solid. Recrystallization from ethanol produced crystalline hydrindenone **16a** (3.0 g, 90%): mp 121–122 °C; IR ($CHCl_3$) 1725, 1630, 1465 cm^{-1}; NMR (C_6D_6, 100 MHz) δ 2.53 (s, 2 H), 3.34 (s, 3 H), 3.58 (s, 3 H), 5.98 (s, 1 H), 6.50–6.88 (m, 3 H); mass spectrum, m/z 380 (M^+). Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.1; H, 6.67. Found: C, 69.01; H, 6.51.

3a-(2,3-Dimethoxyphenyl)-5,5-(ethylenedioxy)-3,3a,4,5,6,7-hexahydro-2*H*-inden-2-one *N*-Methylnitrone (17a). A mixture of hydrindenone **16a** (2.0 g, 6.0 mmol), *N*-methylhydroxylamine hydrochloride (2.60 g, 31.1 mmol), sodium acetate (6.0 g, 71.4 mmol), and ethanol (80 mL) was heated overnight under gentle reflux. Upon cooling to room temperature, the mixture was filtered and concentrated at the rotary evaporator to yield an orange oil. Column chromatography over silica gel (ethyl acetate) afforded the desired nitrone **17a** as a crystalline solid (2.12 g, 99%): mp 138–139 °C; IR (film) 1625, 1580, 1470 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 3.62 (s, 3 H), 3.78 (s, 3 H), 3.82 (s, 3 H), 6.18 (s, 1 H), 6.38–6.92 (m, 3 H).

4a-(2,3-Dimethoxyphenyl)-6,6-(ethylenedioxy)-2-methyl-3-oxo-2,3,4,4a,5,6,7,8-octahydroisoquinoline (18a). *p*-Toluenesulfonyl chloride (1.0 g, 5.3 mmol) was added to an ice cold, stirred solution of nitrone **17a** (1.55 g, 4.3 mmol) in pyridine (50 mL) containing water (1.24 mL, 70.0 mmol). The resulting red solution was stirred for 45 min at room temperature, diluted with water, and extracted with ethyl acetate (4 × 20 mL). Workup in the usual manner gave an oil that was chromatographed on silica gel (ethyl acetate/hexane; 1:1) to yield lactam **18a** as a pale yellow solid (0.93 g, 60%): IR (film) 1665, 1470 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 2.88 (s, 3 H), 3.76 (s, 3 H), 3.86 (s, 3 H), 6.02 (s, 1 H), 6.56–6.90 (m, 3 H); mass spectrum, m/z 359 (M^+).

4a-(2,3-Dimethoxyphenyl)-6,6-(ethylenedioxy)-2-methyl-2,3,4,4a,5,6,7,8-octahydroisoquinoline (19a). A solution of lactam **18a** (0.93 g, 2.6 mmol) in dry THF (20 mL) was added to a stirred suspension of lithium aluminum hydride (0.6 g, 157 mmol) in dry THF, and the reaction mixture was refluxed for 2 h. After cooling to room temperature, the reaction was quenched with 5% NaOH, and the resulting slurry was filtered. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to afford enamine **19a** as a white solid. Recrystallization from diisopropyl ether gave the pure material (0.76 g, 85%): mp 124–126 °C; IR ($CHCl_3$) 1660, 1475 cm^{-1}; NMR (C_6D_6, 100 MHz) δ 2.29 (s, 3 H), 3.36 (s, 3 H), 3.88 (s, 3 H), 5.78 (s, 1 H), 6.54 (dd, J = 8, 1.5 Hz, 1 H), 6.82–7.22 (m, 2 H); mass spectrum, m/z 345 (M^+). Anal. Calcd for $C_{20}H_{27}O_4N$: C, 69.57; H, 7.83; N, 4.1. Found: C, 69.50; H, 7.71; N, 4.1.

***cis*-4a-(2,3-Dimethoxyphenyl)-2-methyl-6-oxo-3,4,4a,5,6,7,8,8a-octahydroisoquinolinium Perchlorate (22a).** Enamine **19a** (0.049 g, 0.14 mmol) in ether (2 mL) was added to a solution of perchloric acid/hydrochloric acid/ether/water (3:1:17:1; 1.0 mL) to form a white precipitate. Ethanol (0.5 mL) was added dropwise to dissolve the precipitate, and the resulting solution was stirred overnight to give a fine white crystalline solid. Filtration and ether wash afforded iminium perchlorate **22a** (0.052 g, 91%): IR (nujol) 1713, 1697, 1090, 625 cm^{-1}; NMR (CD_3CN, 300 MHz) δ 3.34 (s, 3 H), 3.55 (s, 3 H), 3.59 (s, 3 H), 6.50 (m, 1 H), 6.75 (m, 2 H), 8.63 (s, 1 H); ^{13}C NMR (CD_3CN, 22.4 MHz) δ 25.3, 29.7, 38.6, 41.2, 45.0, 48.2, 49.7, 51.5 56.5, 61.2, 114.1, 120.2, 124.7, 135.1, 148.4, 154.6, 181.7 208.6.

A sample of this salt was recrystallized from acetonitrile/ether to give large needles; mp 163–165 °C dec. X-ray diffraction analysis of these needles verified the assigned structure.

Aziridinium Perchlorate 23a. Diazomethane (1.0 mL of a 0.18 M solution in dichloromethane, 1.83 mmol, 13 equiv) was added to a solution of iminium perchlorate **22a** (0.0055 g, 0.014 mmol) in dry acetonitrile (1 mL), and the resulting solution was stirred at room temperature for 1 h. Concentration under reduced pressure gave aziridinium perchlorate **23a** as a light yellow solid (0.0050 g, 85%): mp 185–187 °C dec; IR ($CDCl_3$) 1705, 1580, 1465, 1425 cm^{-1}; NMR (CD_3CN, 300 MHz) δ 3.26 (s, 3 H), 3.92 (s, 3 H), 3.94 (s, 3 H), 6.53 (dd, 1 H, J = 3.3, 6.3 Hz), 7.09 (m, 1 H).

3-[2,3-(Cyclohexylidenedioxy)phenyl]-3-cyclohexenone Ethylene Acetal (12b). Catechol cyclohexylidene acetal ((41.8 g, 0.22 mol), ether (300 mL, 0.73 mol), and TMEDA (20 mL, 0.22 mol, 1.02 equiv) were cooled to 0 °C, and a solution of *n*-butyllithium (100 mL of a 2.2 M solution in hexane, 0.22 mol, 1.0 equiv) was slowly added over a period of 15 min. The resulting yellow slurry was stirred at temperature for 2 h, cooled to 0 °C, and rapidly added to a solution of 1,3-cyclohexanedione isopropyl enol ether (33.7 g, 0.22 mol, 1.0 equiv) in ether (100 mL). After stirring for 16 h at room temperature, the reaction mixture was partitioned between saturated ammonium chloride (500 mL) and 1:1 *tert*-butyl methyl ether/hexane (200 mL). The organic phase was worked up in the usual manner to afford an orange oil. This oil was dissolved in *tert*-butyl methyl ether (750 mL) and stirred with 5% hydrochloric acid (100 mL) for 2 h to effect dehydration. The organic layer was then separated, washed with 3 N NaOH (3 × 500 mL), and worked up in the usual manner. Trituration of the product with hexane afforded 3-[2,3-(cyclohexylidenedioxy)-phenyl]-2-cyclohexenone as a yellow powder (39.6 g, 64%). Recrystallization from hexane gave the pure material: mp 109–110 °C; IR ($CDCl_3$) 3080, 1665, 1605, 1508 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.49 (m, 2 H), 1.72 (m, 4 H), 1.90 (m, 4 H), 2.11 (m, 2 H), 2.46 (t, 2 H, J = 6.3 Hz), 2.76 (dt, 2 H, J = 1.5, 16.0 Hz), 6.65 (t, 1 H, J = 1.5 Hz), 6.75 (m, 2 H), 6.88 (dd, 1 H, J = 1.8, 7.4 Hz); mass spectrum, calcd for $C_{18}H_{20}O_3$ 284.1412, found 284,1412.

A mixture of the above enone (39.6 g, 0.14 mol), ethylene glycol (20 mL, 0.33 mol, 2.4 equiv), benzene (900 mL), and *p*-toluenesulfonic acid monohydrate (0.85 g, 4.5 mmol) was heated under reflux for 19 h while azeotropically removing water with a Dean–Stark apparatus. The reaction mixture was then cooled to room temperature, diluted with hexane (500 mL), and washed with 3 N NaOH (5 × 200 mL). Workup in the usual manner afforded cyclohexenone acetal **12b** as a tan oil that crystallized on standing (46.8 g, 100%). Recrystallization from ethanol/water gave fine needles: mp 65–66.5 °C; IR (film) 3070, 3040, 1680, 1570 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.46–1.94 (m, 12 H), 2.42–2.48 (m, 2 H), 2.68 (br s, 2 H), 4.00 (s, 4 H), 6.35–6.38 (m 1 H), 6.61 (dd, 1 H, J = 1.8 6.6 Hz), 6.67–6.75 (m, 2 H).

3-[2,3-(Cyclohexylidenedioxy)phenyl]-1,4-cyclohexanedione 1-(Ethylene Acetal) (14b). A solution of olefin **12b** (23.9 g, 72.5 mmol), borane (200 mL of 1.0 M solution in THF, 200 mmol, 2.8 equiv), and dry THF (125 mL) was stirred at room temperature overnight. The resulting mixture was treated with a 3 N NaOH solution (100 mL), followed by addition of 30% H_2O_2 (35 mL). After heating to 40 °C for 19 h, the mixture was cooled and diluted with 1:1 ether/hexane (200 mL). Workup in the usual way gave the product as a viscous oil. Purification was effected by column chromatography on silica gel. Elution with ethyl acetate/hexane (1:9) first gave a tertiary alcohol resulting from hydroboration of **12b** with incorrect regiochemistry. Further elution with 1:3 ethyl acetate/hexane afforded the desired alcohol as a white crystalline solid (15.7 g, 63%): mp 93–95 °C.

The above alcohol (15.7 g, 45.4 mmol) was dissolved in dry dichloromethane (350 mL) to which sodium carbonate (15.0 g, 142 mmol), Florisil (8.0 g), and pyridinium chlorochromate (8.05 g, 37.3 mmol) were added. After the reaction was stirred for 8 h at room temperature, additional amounts of pyridinium chlorochromate (12.5 g, 58.1 mmol) and Florisil (12.0 g) were added in equal portions at 8-h intervals. The resultant slurry was stirred an additional 15 h at room temperature, diluted with ether (950 mL), and filtered through Florisil. Concentration at the rotary evaporator gave ketone **14b** as a yellow solid, which could be recrystallized from hexane to give crystalline material (14.3 g, 91%): mp 122–124 °C; IR ($CDCl_3$) 3080, 3050, 1725, 1645, 1605 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.43–1.48 (m, 2 H), 1.58–1.68 (m, 4 H), 1.82–1.89 (m, 4 H), 2.08–2.21 (m, 3 H), 2.40–2.52 (m, 2 H), 2.72–2.76 (m, 1 H), 3.91–4.10 (m, 5 H), 6.50 (dd, 1 H, J = 0.9, 7.7 Hz), 6.63–6.74 (m, 2 H); mass spectrum, calcd for $C_{20}H_{24}O_5$ 344.1624, found 344.1631.

3-[2,3-(Cyclohexylidenedioxy)phenyl]-3-(2-methyl-2-propenyl)-1,4-cyclohexanedione 1-(Ethylene Acetal) (15b). A solution of ketone **14b** (13.8 g, 40.2 mmol) in dry THF (100 mL) was added to a slurry of sodium hydride (1.92 g of 50% oil dispersion, 40.2 mmol) in dry THF (25 mL), and the mixture was

heated to 45 °C for 6 h before cooling to room temperature. Allyl bromide (3.5 mL, 40.4 mmol) in dry THF (100 mL) was added and the reaction was heated to 60 °C for 36 h. The resulting slurry was diluted with saturated ammonioum chloride (200 mL), extracted with 1:1 ether/hexane (2 × 100 mL), and worked up in the usual manner. Column chromatography of the resultant oil on silica gel (ethyl acetate/hexane, 3:97) gave **15b** as a colorless oil (13.8 g, 90%): IR (film) 3080, 1715, 1645, 1590 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.4–2.2 (m, 13 H), 2.3–2.8 (m, 5 H), 3.8–4.0 (m, 4 H), 4.9 (m, 1 H), 5.4–5.7 (m, 2 H), 6.5–6.7 (m, 3 H); mass spectrum calcd for $C_{23}H_{28}O_5$ 384.1937, found 384.1916.

3a-[2,3-(Cyclohexylidenedioxy)phenyl]-5,5-(ethylenedioxy)-3,3a,4,5,6,7-hexahydro-2*H*-inden-2-one (16b). A mixture of olefin **15b** (13.8 g, 35.9 mmol), palladium chloride (1.0 g, 5.64 mmol), cuprous chloride (0.63 g, 6.37 mmol) dimethylformamide (DMF, 125 mL), and water (13 mL) was vigorously stirred for five days while oxygen was bubbled through. The reaction mixture was then diluted with water and extracted with ether (4 × 200 mL). Workup in the usual manner gave a brown oil (14 g). This crude product was dissolved in ethanol (500 mL) and added to a solution of sodium ethoxide (200 mL, 0.217 M in ethanol). After stirring at 50 °C for 20 h, the solution was cooled, diluted with ether, and washed with aqueous brine. Workup in the usual manner gave a yellow foam that was crystallized from hexanes to yield hydrindenone **16b** (11.55 g, 84%): mp 160–162 °C; IR ($CDCl_3$) 3035, 3020, 1695, 1625, 1610, 1585 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.47–1.97 (m, 13 H), 1.93 (d, 1 H, J = 3.6 Hz), 1.97 (d, 1 H, J = 3.7 Hz), 2.86–2.89 (m, 2 H), 3.33 (dd, 1 H, J = 2.7, 13.7 Hz), 3.70–3.90 (m, 4 H), 6.14 (s, 1 H), 6.30 (m, 1 H), 6.62 (m, 2 H); mass spectrum, calcd for $C_{23}H_{26}O_5$ 382.1780, found 382.1788.

4a-[2,3-(Cyclohexylidenedioxy)phenyl]-6,6-(ethylenedioxy)-2-methyl-2,3,4,4a,5,6,7,8-octahydroisoquinoline (19b). A mixture of hydrindenone **16b** (11.55 g, 30.1 mmol), ethanol (300 mL), sodium acetate (12.6 g, 154 mmol), and *N*-methylhydroxyamine hydrochloride (12.6 g, 151 mmol) was heated under reflux for 18 h. After cooling to room temperature, the reaction mixture was filtered, and the filtrate was concentrated at the rotary evaporator to afford a red oil. Column chromatography on silica gel (1:1 ethyl acetate/hexane followed by 1:9 methanol/ethyl acetate) gave the nitrone as a red oil (11.9 g, 96%). This nitrone (6.50 g, 15.8 mmol) was dissolved in pyridine (160 mL) and water (4.3 mL, 15 equiv), and *p*-toluenesulfonyl chloride (3.61, 19.0 mmol) was added. After stirring at room temperature for 1 h, the reaction mixture was diluted with dichloromethane (200 mL) and worked up in the usual manner to give a brown foam (6.7 g). Column chromatography of this foam on silica gel (ethyl acetate/hexane, 1:9) gave the expected enamide as an oil: IR ($CDCl_3$) 3080, 1660, 1590 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.44–1.94 (m, 13 H), 2.52 (d, 1 H, J = 15.9 Hz), 2.37–2.54 (m, 2 H), 2.95 (s, 3 H), 3.03 (d, 1 H, J = 15.9 Hz), 3.08 (dd, 1 H, J = 1.9, 13.4 Hz), 3.55–3.86 (m, 4 H), 6.09 (d, 1 H, J = 2 Hz), 6.44 (dd, 1 H, J = 2.4, 6.9 Hz), 6.60–6.70 (m, 2 H); mass spectrum, calcd for $C_{24}H_{29}NO_5$ 411.2046, found 411.2035.

The enamide prepared above (0.17 g, 0.42 mmol) in dry THF (6 mL) was added to a stirred suspension of lithium aluminum hydride (0.16 g, 4.23 mmol) in dry THF (2 mL) and the reaction mixture was refluxed for 3 h. After cooling, the reaction was quenched with water (0.25 mL) and with a 3 N NaOH solution (0.20 mL). The resulting slurry was diluted with *N*-methylpyrrolidine/hexane (20 mL, 5:95), filtered through a short pad of silica gel, and concentrated under reduced pressure to afford enamine **19b** (0.164 g, 99%) as a clear oil that crystallized on standing: IR ($CDCl_3$) 3080, 3050, 1665, 1630, 1590 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.2–1.4 (m, 2 H), 1.5–1.70 (m, 4 H), 1.70–2.03 (m, 8 H), 2.09–2.16 (m, 1 H), 2.32 (s, 3 H), 2.29–2.51 (m, 3 H), 2.81 (dt, 1 H, J = 4.8, 13.4 Hz), 3.39–3.43 (m, 1 H), 3.50 (d, 1 H, J = 14.4 Hz), 3.47–3.60 (m, 2 H), 3.64–3.68 (m, 1 H), 5.81 (s, 1 H), 6.73 (m, 2 H), 6.96 (m, 1 H); mass spectrum, calcd for $C_{24}H_{31}NO_4$ 397.2253, found 397.2233.

***cis*-4a-[2,3-(Cyclohexylidenedioxy)phenyl]-2-methyl-6-oxo-3,4,4a,5,6,7,8,8a-octahydroisoquinolinium Perchlorate (22b).** A solution of enamine **19b** (0.98 g, 2.57 mmol) in ether (100 mL) was added to a solution. of perchloric acid (41 mL, 0.075 M in ether) to give a white precipitate that slowly dissolved and reprecipitated. After stirring for 13 h at room temperature, the mixture was filtered to give iminium perchlorate **22b** as a tan powder (1.10 g, 91%): NMR (CD_3CN, 300 MHz) δ 1.4–1.6 (m, 2 H), 1.6–1.8 (m, 5 H), 1.8–1.9 (m, 3 H), 2.2–2.4 (m, 5 H), 2.4–2.7 (m, 3 H), 3.1–3.3 (m, 2 H), 3.5–3.6 (m, 1 H), 3.57 (s, 3 H), 6.62–6.76 (m, 2 H), 6.8–6.9 (m, 1 H), 8.68 (s, 1 H); ^{13}C NMR (CD_3CN, 22.4 MHz) δ 206.9, 180.8, 148.7, 144.7, 123.5, 121.4, 120.3, 119.8, 108.9, 52.5, 50.8, 49.0, 45.8, 40.9, 40.7, 36.1, 35.6, 35.4, 25.3, 24.9, 24.2, 23.8.

***cis*-4a-[2,3-(Cyclohexylidenedioxy)phenyl]-1,2-dimethyl-6-oxo-3,4,4a,5,6,7,8,8a-octahydroisoquinolinium Perchlorate (28).** A solution of iminium perchlorate **22b** (0.54 g, 1.14 mmol) in dry deoxygenated acetonitrile (150 mL) was treated with ethereal diazomethane (15 mL of 0.18 M solution) for 3 min at room temperature. Concentration of the reaction mixture at the rotary evaporator gave a brown foam that was partitioned between dichloromethane and 10% NaOH. After workup of the organic layer in the usual manner, a brown oil was obtained that was chromatographed on silica gel (*N*-methylpyrrolidine/hexane, 1:99) to give enamine **28** (0.22 g, 52%) as a yellow oil: IR ($CDCl_3$) 3070, 1710, 1630, 1590 cm^{-1}; NMR (C_6D_6, 300 MHz) δ 1.15–1.35 (m, 4 H), 1.52–1.60 (m, 4 H), 1.63 (s, 3 H), 1.66–1.91 (m, 8 H), 2.10–2.21 (m, 4 H), 2.26–2.39 (m, 3 H), 2.34 (s, 3 H), 2.54 (dd, 2 H, J = 2.9, 8.3 Hz), 3.66 (d, 1 H, J = 15.6 Hz), 6.60–6.64 (m, 2 H), 6.73 (dd, 1 H, J = 3.3, 5.8 Hz); ^{13}C NMR (C_6D_6, 22.4 MHz) δ 209.5, 148.5, 144.1, 104.6, 50.8, 48.1, 42.4, 39.4, 39.0, 35.5, 35.3, 35.1, 25.2, 23.7, 23.4, 15.3; mass spectrum calcd for $C_{23}H_{29}NO_3$ 367.2147, found 367.2124.

3-(3,4-Dimethoxyphenyl)-2-cyclohexenone Ethylene Acetal (36). 4-Bromoveratrole (58.6 g, 0.270 mol) in dry ether (1 L) was cooled to −78 °C and *n*-butyllithium (2.2 M in hexane, 123 mL, 0.271 mol) was added over a period of 1 h. The reaction mixtured was stirred an additional hour at −60 °C and then recooled to −78 °C. 3-Ethoxy-2-cyclohexenone[27] (38.38 g, 0.274 mol) was added in one portion, and the reaction slurry was stirred overnight at room temperature. The mixture was then cooled in ice and glacial acetic acid (30 mL) was added, followed by 10% aqueous HCl (500 mL). Dichlormethane (200 mL) was added and the organic phase was separated and worked up in the usual manner to afford the product. Recrystallization from 1:1 hexane/ethyl acetate gave cream colored plates of 3-(3,4-dimethoxyphenyl)-2-cyclohexenone (50.8 g, 81%): mp 116–117 °C [lit.[28] mp 116–118 °C]. This enone (49.70 g, 0.214 mol) was dissolved in a mixture of benzene (400 mL), ethylene glycol (60 mL), and pyridinium *p*-toluenesulfonate (2.45 g) and refluxed for 120 h while water was azeotropically removed with a Dean–Stark apparatus. The reaction mixture was then cooled and washed with saturated sodium bicarbonate solution. Separation of the organic phase and workup in the usual manner gave **36** as an orange oil that crystallized on standing (58.0 g, 98%). Although this sample was sufficiently pure for use in the next step, purer product could be obtained by recrystallization from ethanol/water: mp 85–87 °C; IR ($CHCl_3$) 1600, 1580, 1510 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 6.92 (br s, 1 H), 6.90 (dd, 1 H, J = 8, 1.5 Hz), 6.80 (d, 1 H, J = 8 Hz), 6.05 (m, 1 H), 4.02 (br s, 4 H), 3.92 (s, 3 H), 3.89 (s, 3 H), 2.62 (br s, 2 H), 2.40 (m, 2 H), 1.81 (br t, 2 H, J = 2 Hz); mass spectrum, calcd for $C_{16}H_{20}O_4$ 273.1361, found 276.1361.

3-(3,4-Dimethoxyphenyl)-1,4-cyclohexanedione 1-(Ethylene Acetal) (37). Acetal **36** (45.12 g, 0.163 mol) was dissolved in dry THF (120 mL) at 0 °C, and diborane (1 M in THF, 290 mL, 0.29 mol) was added dropwise over 90 min. After the reaction was stirred at room temperature overnight and cooled to 0 °C, aqueous NaOH (3 N, 105 mL) was slowly added, followed by H_2O_2 (30% solution, 75 mL). The mixture was stirred at 45 °C for 5 h and at room temperature overnight, followed by diluton with ether (200 mL), extraction with dichloromethane (2 × 300 mL), and workup in the usual manner. The product alcohol (48.4 g, 100%) was sufficiently pure for use in the next step.

Alcohol prepared as above (15.10 g, 0.0513 mol) was dissolved in dry dichloromethane (150 mL), and sodium acetate (3.30 g) and pyridinium chlorochromate (31 g, 144 mmol) were added. After the reaction was stirred overnight, ether (100 mL) was added and the slurry was filtered through Florisil. Evaporation of the filtrate gave crude ketone **37** as an oil that slowly solidified (12.57

(27) Gannon, W. F.; House, H. O. "Organic Syntheses"; Wiley: New York; 1973; Collect. Vol. V, p 539.
(28) Keck, G. E.; Webb, R. R. *J. Org. Chem.* **1982**, *47*, 1302.

g, 84%): IR ($CHCl_3$) 1720, 1612, 1598, 1520 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 6.83 (d, 1 H, J = 8.1 Hz), 6.65 (dd, 1 H, J = 8.1, 1.9 Hz), 6.62 (d, 1 Hz, J = 1.9 Hz), 4.15–4.00 (m 4 H), 3.90 (dd, 1 H, J = 13, 6 Hz), 3.85 (s, 3 H), 3.85 (s, 3 H), 2.80 (dt, 1 H, J = 14.4, 9.9 Hz), 2.49 (dt, 1 H, J = 14.4, 3.7 Hz), 2.22–2.1 (m, 2 H); mass spectrum, calcd for $C_{16}H_{20}O_5$ 292.1311, found 292.1313.

3-(3,4-Dimethoxyphenyl)-3-(2-methyl-2-propenyl)-1,4-cyclohexanedione 1-(Ethylene Acetal) (38). Ketone **37** (12.27 g, 0.042 mol) was dissolved in dry dimethoxyethane (50 mL), and sodium hydride (2.05 g of 50% dispersion in mineral oil, 0.043 mol) was added in portions. After the resulting suspension was stirred for 3 h at room temperature, methallyl chloride (4.5 mL, 4.18 g, 0.046 mol) was quickly added by syringe. The mixture was stirred overnight at room temperature and then refluxed 3 h. After the mixture was cooled and washed with saturated ammonium chloride solution, extraction with dichloromethane/ether (1:3) and workup in the usual manner gave a crude product that was purified by chromatography on silica gel (ethyl acetate/hexane, 1:4). The pure alkylation product **38** was obtained as a pale yellow solid (11.52 g, 79%) that could be crystallized from ethanol/water: mp 70–72 °C; IR ($CHCl_3$) 1710, 1640, 1600, 1590, 1025 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 6.90 (br s, 1 H), 6.88 (dd, J = 8.3, 1.5 Hz, 1 H), 6.78 (d, J = 8.3 Hz, 1 H), 4.72 (br s, 1 H), 4.51 (br s, 1 H), 4.1–3.8 (m, 4 H), 3.85 (s, 6 H), 2.83 (d, J = 15 Hz), 2.62–2.45 (m, 3 H), 2.4–2.3 (m, 1 H), 2.16 (d, J = 15 Hz, 1 H), 1.95–1.8 (m, 2 H), 1.22 (s, 3 H); mass spectrum, calcd for $C_{20}H_{26}O_5$ 346.1780, found 346.1780.

3a-(3,4-Dimethoxyphenyl)-5,5-(ethylenedioxy)-3,3a,4,5,6,7-hexahydro-2*H*-inden-2-one (39). Keto olefin **38** (5.80 g, 0.0167 mol) in 1:1 water/dioxane (300 mL) was vigorously stirred for 48 h at room temperature with sodium periodate (17.1 g, 0.080 mol), potassium permanganate (1.0 g, 6.3 mmol), and potassium carbonate (19.1 g, 0.0138 mol). Dilution with water (200 mL), followed by extraction with dichloromethane, washing with saturated sodium bicarbonate solution, and workup in the usual manner gave a crude diketone (5.8 g, 99%), which was cyclized without further purification. Potassium hydroxide (20 mL of a 1 N solution) was added to a solution of the crude diketone in absolute ethanol (100 mL), and the mixture was refluxed 2 h. Addition of saturated ammonium chloride (200 mL), extraction with dichloromethane, and workup in the usual manner gave hydrindenone **39**. Crystallization from absolute ethanol provided the pure material (4.40 g, 80% from **38**): mp 153–154 °C; IR ($CHCl_3$) 1710, 1630, 1465 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 6.77 (d, J = 8.2 Hz, 1 H), 6.75–6.66 (m, 2 H), 6.19 (s, 1 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 2.98 (dd, J = 14.1, 2.5 Hz, 1 H), 2.82 (m, 1 H), 2.69 (dt, J = 12.8, 5.2 Hz, 1 H), 2.49 (d, J = 18.6 Hz, 1 H), 2.38 (d, J = 18.6 Hz, 1 H), 1.97 (m, 1 H), 1.87 (d, J = 14.1 Hz, 1 H), 1.75 (dt, J = 13.8, 5.2 Hz, 1 H); mass spectrum, calcd for $C_{19}H_{22}O_5$ 330.1467, found 330.1471.

3a-(3,4-Dimethoxyphenyl)-5,5-(ethylenedioxy)-3,3a,4,5,6,7-hexahydro-2*H*-inden-2-one *N*-Methylnitrone (40). Indenone **39** (6.423 g, 0.0194 mol) was dissolved in absolute ethanol (220 mL), and sodium acetate (11.1 g, 0.135 mol) and *N*-methylhydroxylamine hydrochloride (9.2 g, 0.110 mol) were added. The resulting suspension was stirred and refluxed for 40 h, then cooled, diluted with tetrahydrofuran (100 mL), filtered, and concentrated to yield a red oil. Chromatography on silica gel (ethyl acetate/methanol, 2:1) yielded nitrone **40** as a foam (6.96 g, 100%), which was found to be a 3:1 mixture of anti and syn nitrone isomers: IR ($CDCl_3$) 1700, 1620, 1510 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 6.88 (s, 0.25 H), 6.8–6.6 (m, 3 H), 6.30 (s, 0.75 H), 4.0–3.7 (m, 10 H), 3.70 (s, 2.25 H), 3.48 (s, 0.75 H), 3.0–2.6 (m, 5 H), 1.95–1.60 (m, 3 H); mass spectrum, calcd for $C_{20}H_{25}NO_5$ 359.1733, found 359.1725.

4a-(3,4-Dimethoxyphenyl)-6,6-(ethylenedioxy)-2-methyl-3-oxo-2,3,4,4a,5,6,7,8-octahydroisoquinoline (41). Nitrone **40** (4.80 g, 13.3 mmol) was dissolved in pyridine (150 mL). Water (3.90 mL) and *p*-toluenesulfonyl chloride (3.4 g, 0.0178 mol) were quickly added, and the resulting dark red solution was stirred for 1 h at room temperature. Dilution with ethyl acetate (200 mL) and water (200 mL), followed by extraction with ethyl acetate and workup in the usual manner gave the crude product, which was purified by chromatography on silica gel (hexane/ethyl acetate, 1:1). The pure lactam **41** was isolated as a foam (1.91 g, 40%): IR ($CDCl_3$) 1665, 1510 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 6.76 (s, 3 H), 6.14 (d, J = 2.2 Hz, 1 H), 3.86 (s, 6 H), 2.99 (s, 3 H), 2.69 (s, 2 H), 2.58 (dd, J = 14, 1.8 Hz, 1 H), 2.45 (m, 1 H), 1.77 (d, J = 14 Hz, 1 H), 1.72 (m, 1 H); mass spectrum, calcd for $C_{20}H_{25}NO_5$ 359.1733, found 359.1712.

4a-(3,4-Dimethoxyphenyl)-6,6-(ethylenedioxy)-2-methyl-2,3,4,4a,5,6,7,8-octahydroisoquinoline (42). Lactam **41** (894 mg, 2.487 mmol) in dry THF (9 mL) was quickly added to a stirred suspension of lithium aluminum hydride (793 mg, 20.9 mmol) in dry THF (25 mL), and the mixture was refluxed 2 h. After the reaction had cooled, water (0.8 mL) was slowly added, followed by 15% NaOH solution (0.8 mL), and more water (2.4 mL). The white suspension was stirred 15 min, then filtered, and washed with THF. Concentration of the filtrate left crude enamine **42** as an oil (850 mg, 100%), which could be used directly in the next step. Purification could be carried out by chromatography on silica gel (1:3 ethyl acetate/hexane containing 1% *N*-methylpyrrolidine): IR ($CDCl_3$) 1660, 1605, 1590, 1510 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 7.00 (br s, 1 H), 6.99 (d, J = 8.4 Hz, 1 H), 6.68 (d, J = 8.4 Hz, 1 H), 5.80 (s, 1 H), 3.57 (s, 3 H), 3.45 (s, 3 H), 2.32 (s, 3 H); mass spectrum, calcd for $C_{20}H_{27}NO_4$ 345.1940, found 345.1929.

***cis*-4a-(3,4-Dimethoxyphenyl)-2-methyl-6-oxo-3,4,4a,5,6,7,8,8a-octahydroisoquinolinium Perchlorate (43).** Enamine **42** (850 mg, 2.46 mmol) was suspended in ether (25 mL) and treated with a 1:1 mixture of 70% aqueous perchloric acid/ethanol (4 mL). After stirring for 48 h at room temperature, the white solid was filtered off and washed with cold methanol to yield pure iminium perchlorate **43** as a white solid (791 mg, 80%): mp 199–200 °C; NMR (CD_3CN, 300 MHz) δ 8.62 (s, 1 H), 6.91 (d, J = 8 Hz, 1 H), 6.86 (d, J = 2 Hz, 1 H), 682 (dd, J = 8, 2 Hz, 1 H), 3.81 (s, 3 H), 3.78 (s, 3 H), 3.8–3.7 (m, 2 H), 3.60 (s, 3 H), 2.76 (d, J = 15 Hz, 1 H), 2.64 (d, J = 15 Hz, 1 H), 2.52–2.30 (m, 3 H), 2.25–1.90 (m, 3 H).

2,3-Dimethoxy-14α-morphinan-6-one (44). Iminium perchlorate **43** (280.9 mg, 0.70 mmol) was dissolved in dry acetonitrile (20 mL), and a dry ethereal diazomethane solution (0.2 M, 8 mL, 1.6 mmol) was quickly added. The solution was immediately concentrated at the rotary evaporator, and the residue was taken up in dichloromethane (5 mL). After stirring overnight in the presence of silica gel (300 mg) to decompose any aziridinium ion byproduct, the product was chromatographed on silica gel (1:1 hexane/ethyl acetate containing 1% *N*-methylpyrrolidine) to give morphinan **44** as an oil (66 mg, 30%): IR ($CHCl_3$) 1705, 1610, 1505 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 6.60 (s, 1 H), 6.55 (s, 1 H), 3.84 (s, 3 H), 3.80 (s, 3 H), 3.16 (d, J = 17.8 Hz, 1 H), 2.99 (d, J = 5 Hz, 1 H), 2.87 (d, J = 13.7 Hz, 1 H), 2.71 (dd, J = 17.8, 5.4 Hz, 1 H), 2.34 (s, 3 H), 2.56 (d, J = 13.7 Hz, 1 H), 2.15 (d, J = 13 Hz, 1 H) 2.1–1.85 (m, 3 H), 1.13 (d, J = 11.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 210.8, 147.4 (two), 135.0, 129.0, 110.5, 106.9, 57.3, 55.7, 55.6, 51.8, 47.1, 42.8, 40.6, 38.6, 33.1, 27.2, 26.3; mass spectrum, calcd for $C_{19}H_{25}NO_3$ 315.1834, found 315.1828.

2,3-Dimethoxy-7,7-(trimethylenedithio)-14α-morphinan-6-one (45). Ketone **44** (75.0 mg, 0.238 mmol) was dissolved in dry benzene (7 mL), and ethyl formate (0.7 mL) and sodium hydride (50% in mineral oil, 320 mg, 6.66 mmol) were added. After stirring at room temperature overnight, the mixture was quenched by addition of methanol (1 mL), water (25 mL), and enough saturated ammonium chloride solution to bring the pH to 7.5. Extraction with dichloromethane and workup in the usual manner gave an orange oil that was purified by chromatography on silica gel (3:1 ethyl acetate/methanol containing *N*-methylpyrrolidine). The product hydroxymethylene ketone was obtained as a yellow gum (59.0 mg, 72%) and was used without further purification.

Hydroxymethylene ketone prepared as above (56 mg, 0.163 mmol), trimethylene dithiotosylate (91 mg, 0.218 mmol), and dry potassium acetate (89 mg, 0.907 mmol) in absolute ethanol (6 mL) were refluxed for 6 h. After cooling, the reaction mixture was diluted with methylene chloride, washed with aqueous sodium bicarbonate, and worked up in the usual manner. Chromatography on silica gel (1:2 ethyl acetate/hexane containing 2% *N*-methylpyrrolidine) gave pure keto thioacetal **45** as a gum (48.2 mg, 70%): IR ($CHCl_3$) 1700, 1610, 1515 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 6.60 (s, 1 H), 6.55 (s, 1 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.72 (dt, J = 14, 2 Hz, 1 H), 3.66 (d, J = 14.2 Hz, 1 H), 3.13 (d, J = 17.6 Hz, 1 H), 3.03 (t, J = 14 Hz, 1 H), 2.90 (d, J = 5 Hz, 1 H),

2.78 (d, J = 14.2 Hz, 1 H), 2.30 (s, 3 H), 1.13 (d, J = 9.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 203.6, 147.5 (two), 134.4, 128.9, 110.6, 106.9, 56.6, 56.0, 55.8, 55.3, 47.0, 46.8, 42.8, 39.6, 38.4, 35.8, 33.0, 28.5, 27.2, 26.8, 25.0; mass spectrum, calcd for $C_{22}H_{29}NO_3S_2$ 419.1589, found 419.1563.

2,3-Dimethoxy-14α-morphinan-6,7-dione (46). Dithioacetal **45** (21.0 mg, 0.050 mmol) was dissolved in dry dichloromethane (0.5 mL) at −75 °C and treated with a solution of *m*-chloroperoxybenzoic acid (0.085 M, 2.06 mL, 0.175 mmol). After the temperature had warmed to −20 °C, the mixture was kept overnight. Quenching with saturated aqueous sodium bisulfite, followed by extraction with dichloromethane and workup in the usual manner gave a crude solid that was dissolved in hydrochloric acid (2 N, 0.7 mL) and heated to 100 °C for 6 h. Upon cooling, the pH was adjusted to 8 with dilute sodium bicarbonate, and the mixture was extracted with dichloromethane. Workup in the usual manner, followed by chromatography on silica gel (ethyl acetate containing 3% *N*-methylpyrrolidine) gave diketone **46** (11.5 mg, 70%) as a colorless foam that was shown by NMR to be a 3:1 mixture of diosphenols: IR ($CDCl_3$) 3440, 1670, 1610, 1510 cm^{-1}; NMR δ 6.82 (s, 0.25 H), 6.78 (s, 0.25 H), 6.63 (s, 0.75 H), 6.61 (s, 0.25 H), 6.58 (s, 0.75 H), 6.09 (d, J = 2 Hz, 0.75 H), 3.90–3.84 (4 singlets, 6 H total); mass spectrum, calcd for $C_{19}H_{23}NO_4$ 329.1627, found 329.1603.

(±)-*O*-Methylpallidinine (47). Diketone **46** (11.5 mg, 0.035 mmol) in dry methanol (0.65 mL) was treated with *p*-toluenesulfonic acid monohydrate (21.5 mg) at room temperature for 100 h. After quenching with saturated sodium bicarbonate solution (15 mL), the reaction mixture was extracted with dichloromethane (3 × 10 mL) and worked up in the usual manner. Chromatography on silica gel (ethyl acetate containing 2% *N*-methylpyrrolidine) gave two fractions: fraction 1 consisted of pure (±)-*O*-methylpallidinine (2.5 mg, 21%, 55% after correction for recovered starting material). Fraction 2 (7 mg, 61%) was largely recovered starting material along with a trace of (±)-*O*-methylisopallidinine (**48**). (±)-*O*-methylpallidinine (**47**) had the following properties: mp 198–202 °C (hydrochloride); IR ($CHCl_3$) 1690, 1620, 1520, 1120 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 6.87 (s, 1 H), 6.64 (s, 1 H), 6.37 (s, 1 H), 3.90 (s, 3 H), 3.86 (s, 3 H), 3.70 (s, 3 H), 3.39 (dd, J = 14.1, 16.7 Hz, 1 H), 3.11 (d, J = 17.7 Hz, 1 H), 2.89 (d, J = 5.6 Hz, 1 H), 2.60 (dd, J = 17.7, 5.6 Hz, 1 H), 2.36 (s, 3 H), 2.20–2.00 (m, 2 H), 1.52 (d, J = 11 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 194.7, 151.0, 148.0, 147.6, 132.7, 130.0, 121.6, 111.5, 107.8, 56.7, 56.6, 55.9, 55.1, 45.9, 42.9, 40.2, 36.9, 36.3, 27.2; mass spectrum, calcd for $C_{20}H_{25}NO_4$ 343.1783, found 343.1781. The synthetic material was identical with an authentic sample of the natural product by the above spectral criteria.

Acknowledgment. The latter stages of this work were funded by research Grant GM-28569 from the National Institutes of Health. D.R.S. also acknowledges the Science Research Council (United Kingdom) for a postdoctoral fellowship.

Registry No. **11a**, 91712-86-6; **12a**, 91712-87-7; **12b**, 91712-88-8; **13a**, 91712-89-9; **13b**, 91712-90-2; (±)-**14a**, 91712-91-3; (±)-**14b**, 91712-92-4; (±)-**15a**, 91712-93-5; (±)-**15a** (diketone), 91712-94-6; (±)-**15b**, 91712-95-7; (±)-**15b** (diketone), 91712-96-8; (±)-**16a**, 91712-97-9; (±)-**16b**, 91712-98-0; (±)-**17a**, 91712-99-1; (±)-**17b**, 91713-00-7; (±)-**18a**, 91713-01-8; (±)-**18b**, 91713-02-9; (±)-**19a**, 91713-03-0; (±)-**19b**, 91713-04-1; (±)-**22a**, 91713-06-3; (±)-**22b**, 91713-08-5; (±)-**23a**, 91713-10-9; (±)-**28**, 91713-11-0; **36**, 88176-83-4; (±)-**37**, 91713-12-1; **37**-ol, 91713-13-2; (±)-**38**, 88176-85-6; (±)-**38** (diketone), 91713-14-3; (±)-**39**, 88176-86-7; (±)-**40**, 91713-15-4; (±)-**41**, 88176-88-9; (±)-**42**, 88176-89-0; (±)-**43**, 88176-91-4; (±)-**44**, 91796-76-8; (±)-**44** (hydroxymethylene deriv), 91713-16-5; (±)-**45**, 91713-17-6; (±)-**46**, 91796-77-9; (±)-**47**, 88199-99-9; (±)-48, 91713-18-7; 3-(3,4-dimethoxyphenyl)-2-cyclohexenone, 20036-53-7; (±)-3-(2,3-cyclohexylidenedioxy)phenyl-3-hydroxycyclohexanone ethylene acetal, 91713-19-8; 1,3-cyclohexanedione isopropyl enol ether, 58529-72-9; methallyl chloride, 563-47-3; catechol cyclohexylidene acetal, 182-55-8; 1,3-cyclohexanedione, 504-02-9; veratrole, 91-16-7; *N*-methylhydroxylamine hydrochloride, 4229-44-1; diazomethane, 334-88-3; allyl bromide, 106-95-6; 4-bromoveratrole, 2859-78-1; 3-ethoxy-2-cyclohexenone, 5323-87-5; trimethylene dithiotosylate, 3866-79-3.

Intramolecular *N*-Carbamoyliminium Ion Cyclizations of Unactivated Alkenes and Acetylenes

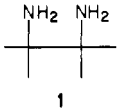
Zeng-Kun Liao and Harold Kohn*[1]

Department of Chemistry, University of Houston—University Park, Houston, Texas 77004

Received April 12, 1984

A select series of 3-alkenyl (**7a–e**) and 3-acetylenic (**7f**) 4-hydroxy-5,5-dimethylimidazolidin-2-ones were prepared. Treatment of each substrate except **7e** with acid led to the desired intramolecular amidoalkylation reaction to give the bicyclic imidazolidin-2-ones. The reactions proceeded regio- and stereoselectively in moderate to good yields. The mechanism of these and related transformations are discussed.

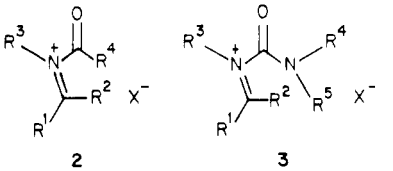
The vicinal diamine group (**1**) is incorporated in many natural products and chemotherapeutic agents. Few



1

general methods exist for the preparation of this group. Of special interest to us is the development of new procedures for the synthesis of functionalized diamines from readily accessible starting materials.[2-4]

Recently, considerable attention has been focused on intramolecular *N*-acyliminium ion (**2**) initiated cyclization



2 **3**

reactions.[4-8] These transformations have proved partic-

(1) Camille and Henry Dreyfus Teacher-Scholar Grant Recipient, 1977–1982.

(2) Kohn, H.; Jung, S. H. *J. Am. Chem. Soc.* **1983**, *105*, 4106–4108. Jung, S. H.; Kohn, H. *Tetrahedron Lett.* **1984**, *25*, 399–402.
(3) Cortes, S.; Kohn, H. *J. Org. Chem.* **1983**, *48*, 2246–2254.
(4) Kohn, H.; Liao, Z.K. *J. Org. Chem.* **1982**, *47*, 2787–2789.

0022-3263/84/1949-3812$01.50/0