NMR (unlabeled compound) (CD_3OD, 250 MHz) δ 8.01 (s, 1 H, C-2'), 4.10 (q, 2 H, $-OCH_2$), 2.80 (m, 2 H, CH_2), 2.53 (m, 2 H, CH_2), 2.34 (s, 3 H, CH_3), 1.21 (t, 3 H, $-OCH_2CH_3$); ^{13}C NMR (unlabeled compound) (CD_3CN, 75.45 MHz) 173.7, 162.3, 161.1, 146.6, 124.4, 61.1, 32.7, 22.3, 21.6, 14.5 ppm; MS m/z 42, 123, 136, 164, 210 (M^+); HRMS m/z (M^+, $C_{10}H_{14}N_2O_3$) calcd 210.100 42, obsd 210.100 15; ^{13}C NMR (labeled) (CD_3CN, 75.45 MHz) 146.6 (enriched) ppm; MS m/z 124, 137, 165, 211 (M^+).

C. Ethyl (2'-^{13}C)-(*E*)-3-(4'-Hydroxy-6'-methyl-5'-pyrimidinyl)acrylate (30). Isopropylamine (1.66 mL, 11.9 mmol) was dissolved in 15 mL of freshly distilled THF and the solution was cooled to -78 °C under N_2. A solution of *n*-butyllithium in hexane (1.86 M, 6.4 mL, 11.9 mmol) was added to the cooled solution and the mixture was stirred at -78 °C for 15 min to generate LDA solution. Ethyl (2'-^{13}C)-3-(4'-hydroxy-6'-methyl-5'-pyrimidinyl)propionate (1.14 g, 5.40 mmol) dissolved in 80 mL of THF was added dropwise to the LDA solution at -78 °C. After the addition, the mixture was stirred at -78 °C for 1 h. A solution of phenylselenyl chloride (2.11 g, 10.8 mmol) in 20 mL of THF was then added dropwise to the cooled enolate solution; stirring was continued for another 30 min at low temperature. The mixture was then gradually warmed to room temperature. Water was added to quench the reaction and the two layers were separated. The aqueous layer was neutralized with 1 N HCl to pH 6 and extracted several times with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, and evaporated in vacuo to yield a dark gum. The dark gum was purified by silica gel flash chromatography, with elution using EtOAc/MeOH (9:1). The fractions containing the product were combined and evaporated to yield a yellow gum (1.07 g). The yellow gum was dissolved in 8 mL of ethyl acetate, and hydrogen peroxide (1.66 mL, 30%, 14.6 mmol) as well as water (8 mL) were added. The mixture was stirred at room temperature for 1 h. Sodium sulfite solution was added to decompose the excess hydrogen peroxide (monitored by potassium iodide-starch paper). The aqueous solution was extracted with ethyl acetate several times. The EtOAc extracts were combined and dried over anhydrous sodium sulfate and evaporated to afford 0.56 g (2.7 mmol, 50%) of crude product. The product could be further purified by silica gel flash chromatography eluted with a solution of EtOAc/MeOH (9:1). The product exhibited an R_f of 0.61 on a silica gel plate developed with EtOAc/MeOH (9:1), mp 194-196 °C: ^1H NMR (unlabeled compound) (CD_3CN, 250 MHz) δ 1.28 (t, 3 H, $-OCH_2CH_3$), 2.45 (s, 3 H, CH_3), 4.21 (m, 2 H, $-OCH_2$), 7.26-7.20 (d, 1 H, J = 15.7 Hz), 7.64-7.58 (d, 1 H, J = 15.7 Hz), 8.03 (s, 1 H, C-2'); ^{13}C NMR (CD_3CN, 75.45 MHz) 170.0, 165.5, 162.3, 149.3, 136.8, 123.3, 61.7, 21.8, 14.6 ppm; MS m/z 135, 163, 179, 208 (M^+); HRMS m/z (M^+, $C_{10}H_{12}N_2O_3$) calcd 208.084 77, obsd 208.084 38; ^1H NMR (labeled compound) (CD_3CN, 250 MHz) δ 1.26 (t, 3 H, $-OCH_2CH_3$), 2.44 (s, 3 H, CH_3), 4.19 (m, 2 H, $-OCH_2$), 7.24-7.19 (d, 1 H, J = 15.7 Hz), 7.63-7.57 (d, 1 H, J = 15.7 Hz), 8.00 (d, 1 H, $^1J_{CH}$ = 205.8 Hz, C-2'); ^{13}C NMR (labeled compound) (CD_3CN, 75.45 MHz) 148.60 (enriched) ppm.

D. (2'-^{13}C)-(*E*)-3-(4'-Hydroxy-6'-methyl-5'-pyrimidinyl)acrylic Acid (27). Ethyl (2'-^{13}C)-(*E*)-3-(4'-hydroxy-6'-methyl-5'-pyrimidinyl)acrylate (335 mg, 1.60 mmol) was dissolved in 15 mL of MeOH, and 1.65 mL of 4 N NaOH as well as 10 mL of water were added. The solution was stirred at 40 °C for 8 h. The mixture was evaporated and the aqueous solution was washed twice with chloroform. The aqueous solution was then acidified to pH 5 with 1 N HCl and evaporated in vacuo. The residue was extracted with MeOH several times. The MeOH extracts were combined and evaporated to yield a light brown solid, mp 275 °C (dec). The product displayed an R_f of 0.35 on silica gel plate developed with a solution of EtOAc/MeOH (9:1) containing 3% acetic acid: ^1H NMR (unlabeled compound) (D_2O, 300 MHz) δ 2.61 (s, 3 H, CH_3), 7.09-7.15 (d, 1 H, J = 15.7 Hz), 7.57-7.62 (d, 1 H, J = 15.7 Hz), 9.01 (s, 1 H, C-2'); ^{13}C NMR (unlabeled compound) (D_2O, 75.45 MHz) 149.3, 134.3, 125.1, 17.3 ppm; UV λ^{H_2O} 302 (ϵ = 4181); MS m/z 135, 180 (M^+); HRMS m/z (M^+, $C_8H_8N_2O_2$) calcd 180.053 47, obsd 180.053 34; ^1H NMR (labeled compound) (D_2O, 300 MHz) δ 2.52 (s, 3 H, CH_3), 6.99-7.05 (d, 1 H, J = 15.7 Hz), 7.61-7.66 (d, 1 H, J = 15.7 Hz), 8.26 (d, J_{CH} = 206.6 Hz, 1 H, C-2'); ^{13}C NMR (labeled compound) (D_2O, 75.45 MHz) 148.6 (enriched) ppm.

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A Novel Approach to the Synthesis of Morphine Alkaloids: The Synthesis of (*d,l*)-Thebainone-A

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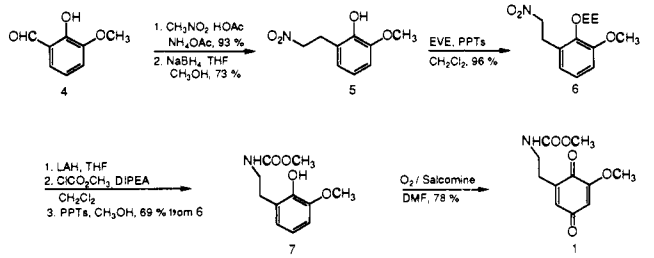
Abstract: A nonconventional approach to the preparation of morphinans has been applied to the total synthesis of thebainone-A and β-thebainone-A. Noteworthy features of this synthesis are the regiospecificity of the Diels-Alder reaction to form **9** and of the enolization-hydroxylation of **11**, the unusual aromatization of **14** as well as the selectivity of the intramolecular Michael addition of the amine to form **41**. This route offers access to several alkaloid skeleta which are related to morphine as well as demonstrating a new approach to the synthesis of aromatic molecules.

A long-standing interest in the synthesis of aromatic rings from nonaromatic precursors led to a consideration of the total synthesis of morphine alkaloids.[2] Conventional wisdom holds that the retrosynthetic disconnection of aryl or arylalkyl C-C bonds is not strategic.[3] We felt that this was no longer invariably true and that the development in recent years of efficient methods for the assembly of regiospecifically substituted benzene rings[4] might open new pathways for total synthesis. One could consider a synthesis

Scheme I



(1) Fellow of the Alfred P. Sloan Foundation, 1988-1991.

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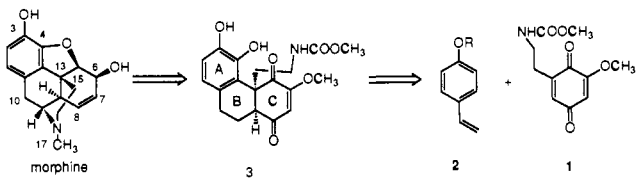
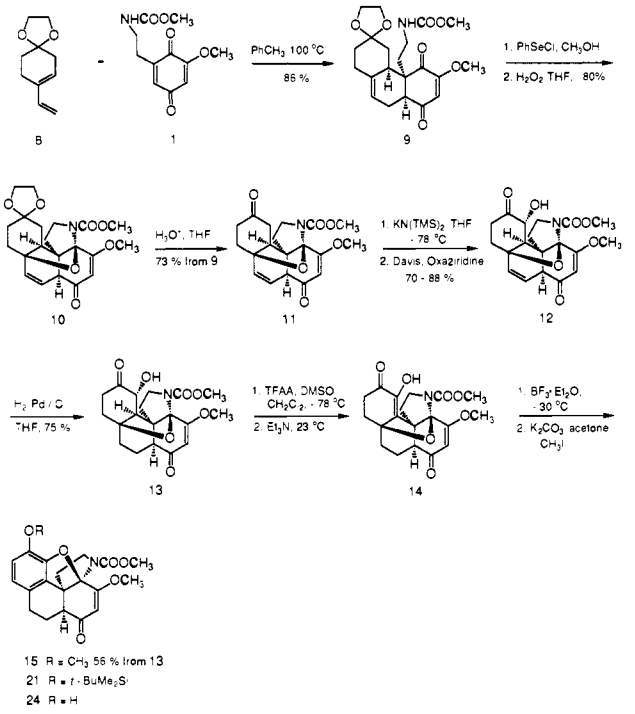
of morphine[5] to proceed from the combination of substituted benzoquinone **1** with the equivalent of styrene **2** to produce intermediate **3**. The subsequent conversion of **3** to morphine would require formation of the piperidine and dihydrofuran rings and adjustment of the oxidation state of the carbocyclic C ring. This simple analysis provided the foundation for our work.



The preparation of quinone **1** which is summarized in Scheme I follows established precedent.[6] Acid-catalyzed condensation of *o*-vanillin **4** with nitromethane,[7] followed by treatment with sodium borohydride in methanolic tetrahydrofuran (THF),[8] produced nitroethyl phenol **5**. Protection of the phenolic hydroxyl as the ethoxyethyl (EE) ether took place in 96% yield. Reduction of the nitro group with lithium aluminum hydride (LAH),[9] followed by conversion of the resulting primary amine to its carbomethoxy derivative and phenolic protecting group removal produced phenol **7** in 69% yield from **6**. Oxidation of the phenol to quinone **1** with molecular oxygen and salcomine[6,10] was straightforward and proceeded in 78% yield. The overall yield of **1** from *o*-vanillin **4** was 35%. Because of the simplicity of the reaction scheme, large quantities of **1** were easily prepared.

A suitable equivalent of styrene **2** was provided by diene **8**. Commercially available 1,4-cyclohexanedione *mono*-ethylene ketal was treated with vinylmagnesium bromide to produce the tertiary allylic alcohol in 87% yield. Clean dehydration of this alcohol to the diene was unexpectedly difficult, and a variety of reaction conditions were examined. The most convenient method was treatment at 23 °C in benzene with 5 Å molecular sieves and *p*-toluenesulfonic acid for several days. The yield for the reaction was 30–40% on a preparatively useful scale (10 g). On a small scale the dehydration could be performed in better yield (ca. 60%) by exposure of the tertiary alcohol to triflic anhydride and 2,6-lutidine in acetonitrile at −30 °C followed by gradual warming to 0 °C. The low yield for the dehydration was attributed to the participation of the ketal in cationic rearrangements as evidenced by the appearance of aromatic byproducts. Similarly constituted alcohols lacking the ketal moiety undergo clean dehydration.[11] The Diels–Alder reaction between quinone **1** and diene **8** was uncomplicated. Heating at 100 °C in toluene produced a single product, **9**, in 86% yield (Scheme II). The reaction was expected to be chemoselective for the nonoxygenated carbon–carbon double bond of **1**; however, the endo selectivity and the orientational specificity with respect to the diene were surprising, though not without precedent.[6] The structural assignment of **9** was confirmed by single-crystal X-ray diffraction.[12]

Scheme II



The next task was the aromatization of the A-ring, preferably with simultaneous introduction of the dihydrofuran oxygen. Hydrolytic removal of the ketal from **9** was accomplished easily in 90% yield. Both the direct dehydrogenation of this ketone with DDQ in benzene,[13] or of the corresponding trimethylsilyl enol ether with palladium acetate and diallylcarbonate,[14] failed to produce aromatic product. Attempts to sulfenylate[15] or to selenate[16] the ketone likewise led to complicated reaction mixtures. Exposure of **9** to phenylselenium bromide or chloride in anhydrous dichloromethane[17] in an effort to functionalize the trisubstituted

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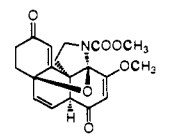
double bond led only to the recovery of unreacted starting material. This observation appeared odd, since the selenation reaction is general. Trans attack by halide from the hindered *endo* face of the selenonium ion can be expected to be very slow. When the same reaction was conducted in anhydrous methanol,[18] clean incorporation of phenylselenide into **9** took place through an unusual tandem selenocyclization. It is conceivable that the polar solvent is necessary to stabilize the selenonium ion. Oxidative elimination produced alkene **10** in 80% yield from **9**. The structure of **10** was determined unambiguously by single-crystal X-ray diffraction.[12] The participation of the carbonyl oxygen and the carbamate nitrogen in the selenation reaction had not been anticipated. Acid-catalyzed hydrolysis of the ketal unit from **10** produced ketone **11** in an overall yield of 73% from **9** with no intermediate purification steps. It had been predicted that the conformational constraints on **11** which were imposed by the ether ring would bias the regiochemistry of enolization of **11**. Although the A,B-ring junction stereochemistry was trans, it was postulated that the presence of the ether bridge might override the normal preference[19] for enolization in *trans*-decalones which have a non-hydrogen bridgehead substituent. A cursory examination of molecular models of the two possible enolates confirmed this suspicion, and it soon became apparent that kinetic enolization of **11** was indeed highly selective and took place at C4. For example, treatment of **11** with potassium bis(trimethylsilyl)amide in THF at −78 °C, followed by phenylselenium chloride,[16] after oxidative elimination of selenium gave enone **16** in 65% yield. Treatment of the potassium enolate of **11** with Davis' 2-(*p*-toluenesulfonyl)-3-phenyloxaziridine[20] produced acyloin **12** in 70–88% yield. This provided a practical, regiospecific solution to the problem of introducing the second aromatic oxygen. The alternative of incorporating the oxygen into diene **8** would have required considerably greater effort. The oxidation reaction was very sensitive to the conditions. Excellent selectivity was seen when exactly 1 equiv of base was added to a solution of the substrate at −78 °C, followed by the oxaziridine. Generation of the enolate at −20 °C resulted in the formation of a 1/1 mixture of the two possible enolates. Also, addition of **11** to a solution of the base led to diminished yields of the product.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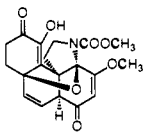
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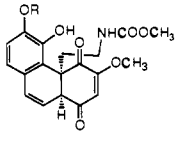
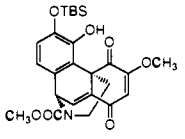

18 R = H
19 R = *t*-BuMe$_2$Si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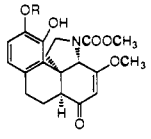
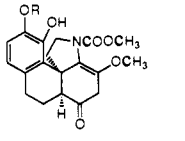
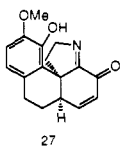

22 R = *t*-BuMe$_2$Si
25 R = H
26 R = CH$_3$


23 R = *t*-BuMe$_2$Si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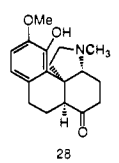
28

The synthesis now required the aromatization of the A ring. The bridging oxide was used to advantage: Swern oxidation[21] of **12** presumably led to α-diketone **17**. This compound was never isolated, but spontaneously underwent elimination of the β-oxide bridge to produce catechol **18** as an air-sensitive solid which was immediately converted to the corresponding monosilyl ether **19** in 60% overall yield from **12**. All attempts to scale this reaction up resulted in sharply diminished yields.

Closure of the piperidine ring through C–C double bond activation in **19**, followed by intramolecular attack by nitrogen, was the next goal. The hope that a kinetic preference would be observed for formation of the six-membered rather than the seven-membered ring from **19** was unfounded. Exposure of **19** to phenylselenium chloride in methanol produced the seven-membered nitrogen heterocycle **20**; elimination of the phenylseleno group took place spontaneously. Similar results were obtained in dichloromethane as the solvent and with *N*-phenylselenium phthalimide.[22] Attempts to isomerize the styrene double bond in **19** into conjugation with the carbonyl group with base led instead to decomposition of the starting material. Acid catalysis also failed to isomerize the styrene. Therefore, a different sequence of steps was used. Palladium on carbon catalyzed the saturation of the disubstituted double bond of **12** in 75% yield (Scheme II). Swern oxidation[21] produced α-diketone **14** which was far more stable than **17**. Exposure of **14** to boron trifluoride etherate at −30 °C caused aromatization to **24** to take place. Methylation of the resulting phenolic hydroxyl group with iodomethane/potassium carbonate in acetone produced **15** in 56% overall yield from **13**. Silyl ether **21** could be prepared by protecting the phenolic product with *tert*-butyldimethylsilyl chloride. It is perhaps worth noting that **14** was converted to the free catechol, dihydro-**18**, upon brief treatment with boron trifluoride etherate. Exposure of this material to Lewis acid in a subsequent step led to the formation of **24**.

The formation of the dihydrofuran ring during the aromatization reaction which led to **15** appeared to be a fortunate turn of events, for it was postulated that this intermediate could be converted to thebainone or morphine in relatively few steps. Reductive cleavage of the C–N bond in **15** or **21**, followed by reattachment of the nitrogen to form the piperidine ring of the final product and adjustment of the oxidation state of the C ring, would lead to morphine. The first attempt to cleave the C–N bond selectively through treatment of **21** with lithium dimethyl cuprate at −78 °C in ether[23] produced ketones **22** and **23** in 65 and 23% yield, respectively. The reaction was complete in 5 min. Since C–O bond cleavage in **21** was so rapid, an obvious strategy would be to slow the process so that C–N reductive cleavage could compete. To this end **24** was subjected to treatment with excess lithium dimethyl cuprate on the assumption that reductive cleavage of the C–O bond in the phenoxide would be much slower than in the corresponding phenolic ethers, since such a reaction would require formation of a dialkoxide of a catechol. This hypothesis was borne out, since after 8 h a modest (30% yield of **25**) amount of C–O bond cleavage had taken place, the balance of the material consisting of unreacted **24**. Although C–O cleavage had been made more difficult, no C–N reduction was observed. Exposure of **15** or **21** to activated zinc dust in refluxing acetic acid[24] produced **26** or **22**, respectively, in 88% yield. Treatment of **21** with samarium diiodide[25] led to a complex mixture of products which were neither separated nor characterized.

Failure to secure the selective cleavage of the C–N bond in the carbamate series suggested a simple modification of the approach. Conversion of the carbamate nitrogen to an *N*-methylamine would produce a better nitrogen Lewis base. Selective cleavage of the C–N bond might then be possible by prior complexation with an acid. Exposure of **15** to lithium aluminum hydride in refluxing THF[26] unexpectedly led to imine **27**. Treatment of **26** with LAH under identical conditions produced *N*-methylamine **28**, a sur-

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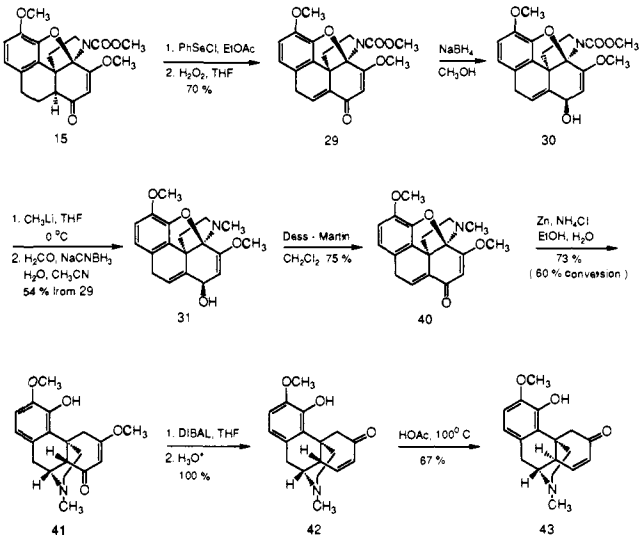
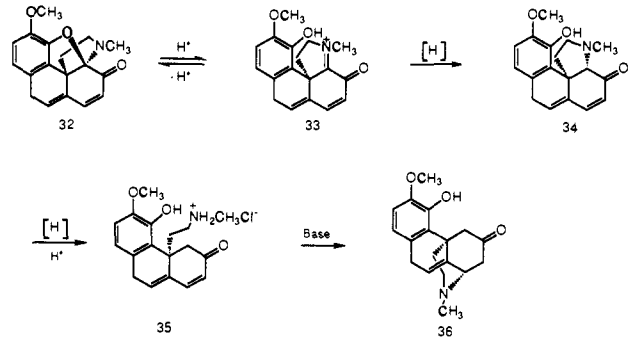
Scheme III



Scheme IV



prising product which was derived from the desired reduction of the carbamate, followed by conjugate reduction of the vinylogous methyl ester, perhaps by intramolecular delivery of hydride. The ketone function in **28** was presumably protected by conversion to an aluminum enolate. Milder reaction conditions failed to produce the *N*-methylamino function.

Scheme III summarizes the successful formation of the piperidine ring. The first task was to functionalize the B-ring so that attachment of the nitrogen could take place. Treatment of **15** with phenylselenium chloride in ethyl acetate,[27] followed by the immediate oxidation of the crude selenide, produced enone **29** in 70% yield. Carbonyl reduction with sodium borohydride in methanol gave alcohol **30** which was treated with methyllithium in THF in order to cleave the methylcarbamate. Exposure of the resulting secondary amine to aqueous formaldehyde and sodium cyanoborohydride[28] produced amino alcohol **31** in 54% overall yield from **29**. Amino alcohol **31** was converted to dienone **32** (Scheme IV) in 81% yield following exposure to trifluoroacetic anhydride and 2,6-lutidine in dichloromethane. The dienone appeared to be separated from the natural product by very few steps. In the event, treatment of **32** with zinc dust and aqueous ammonium chloride in ethanol[29] produced the product of 1,4-addition **36** in 65% yield. Under no circumstance could selective C–N bond cleavage be accomplished. The reason for the ease of reductive scission of the C–O bond in **32** as well as in **15**, **21**, and **24** may be rationalized according to Scheme IV. Acid catalyzed equilibration of **32** with imonium species **33** would be followed by rapid reduction of the imonium ion, leading to **34**. Reductive cleavage

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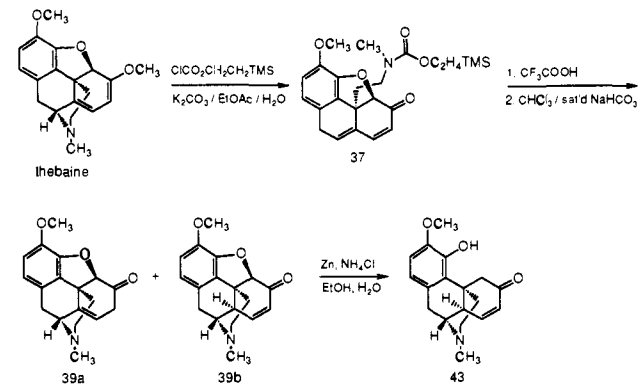
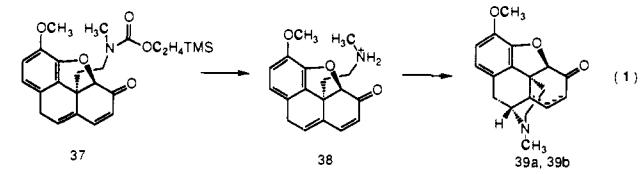
Scheme V



of the C–N bond in **34** would then lead to ammonium ion **35**, which upon exposure to base would give rise to the observed product. The fact that none of the 1,6-adduct was formed during this reaction and that **36** resisted all attempts at isomerization was puzzling, the more so since Fuchs and co-workers had reported that removal of the carbamate protecting group from **37** led selectively to 1,6-adducts **39a** and **39b** (eq 1) via ammonium salt **38**.[30] Ammonium ions **35** and **38** differ only by the presence of the 4,5-oxide bridge in the latter. This indicates that the bridge imposes a strong stereoelectronic bias for 1,6-addition.



The remaining option was to provide an overwhelming bias for attachment of the nitrogen at C9. Dess–Martin oxidation[31] of **31** produced ketone **40** in 75% yield (Scheme III). Reductive cleavage of both nitrogen and oxygen took place during 24 h by exposure to zinc dust and ammonium chloride[29] to produce *trans*-morphinan **41** in 73% yield at 60% conversion. Exposure of **40** to the same reaction conditions for 5 min resulted in selective cleavage of the C–O bond in 85% yield. Reduction with diisobutylaluminum hydride (DIBAL) followed by immediate hydrolysis of the hydroxy enol ether intermediate, produced β-thebainone-A (**42**) in quantitative yield. Heating of **42** in glacial acetic acid[32] produced thebainone-A (**43**) in 67% yield.

The structure of (racemic) **43** was proven by comparison with a sample of (optically active) thebainone-A which was derived by degradation of thebaine. Scheme V summarizes the synthesis of **43** from thebaine. Treatment of thebaine with trimethylsilylethyl chloroformate and potassium carbonate produced dienone **37**[30] which upon removal of the protecting group gave a mixture of neopinone **39a** and codeinone **39b**. Reduction of **39b** with zinc gave thebainone-A which was identical with synthetic thebainone-A by spectroscopic and chromatographic comparison.

Conclusion

An unusual synthesis of morphinan alkaloids has been described. By virtue of the fact that thebainone-A and β-thebainone-A have been converted to morphine by Gates,[5a] the present work also constitutes a formal synthesis of racemic morphine. The total synthesis of thebainone-A was accomplished in 24 steps from **4** and in an overall yield of 1.1%. Important features of the sequence include the rapid construction of the carbon skeleton of morphine, the highly regioselective oxygenation of the A-ring, the aromatization rearrangement, and the formation of the piperidine ring by cleavage of the α-amino ketone.

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Experimental Section

All moisture- and air-sensitive reactions were performed in a flame-dried glass apparatus equipped with rubber septa under a static nitrogen or argon atmosphere. THF and ether were distilled from sodium benzophenone ketyl. Dichloromethane was distilled from phosphorus pentoxide. Melting points were reported for all crystalline products and are uncorrected. All other products were isolated as clear oils. Thin-layer chromatography was performed on EM Reagents precoated silica gel 60 F-254 analytical plates (0.25 mm). Flash column chromatography was performed on 230–400 mesh silica gel. Elemental analyses were performed by MicAnal (Tucson, AZ).

Infrared spectra were recorded on a Perkin-Elmer 710B, a Perkin-Elmer 1430, or a Nicolet 740 FT-IR. Electron impact mass spectra were recorded at 70 eV on a Varian MAT-311 or on a Varian VG-70SE spectrometer. Proton nuclear magnetic resonance spectra were recorded at 300 MHz on a Nicolet NT-300 or a General Electric QE-300 (Oxford magnet) spectrometer. High field spectra were recorded at 500 MHz on a General Electric GN Omega 500 spectrometer. Proton NMR data were recorded in ppm from residual $CHCl_3$ (7.26 ppm). Carbon NMR spectra were recorded either at 75 MHz on the QE-300 instrument or at 125 MHz on the GN Omega 500 instrument.

2-Hydroxy-1-methoxy-3-(2-nitroethyl)benzene 5. To a solution of 30 g (0.390 mol) of ammonium acetate in 200 mL of glacial acetic acid was added 51 g of *o*-vanillin (0.336 mol) and 70 mL (1.29 mol) of nitromethane. The mixture was heated under gentle reflux for several hours, and the progress of the reaction was monitored by TLC. If the temperature of the reaction exceeded 110–120 °C, there was significant loss of material due to polymerization. When no starting material remained, as judged by TLC, the mixture was cooled to ambient temperature and poured onto crushed ice. The orange-brown crystals were collected by filtration. The crude product was first air-dried and then dried further under high vacuum. The purity of the nitrostyrene was sufficient (>95%) for use in the next reaction. Material of higher purity was obtained by recrystallization from ethanol. The yield of crude nitrostyrene was 60.7 g (93% yield): TLC R_f = 0.38 (30% EtOAc/hexanes); mp 115–118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.14 (d, J = 13.6 Hz, 1 H), 8.09 (d, J = 13.6 Hz, 1 H), 7.04–6.91 (m, 3 H), 6.47 (br s, 1 H), 3.95 (s, 3 H) ppm; IR (CH_2Cl_2) 3570, 2960, 2890, 1640, 1610, 1530, 1490, 1360, 1110, 1090, 990 cm^{-1}; mass spectrum m/e 196 (M^+ + 1, 10.3), 195 (M^+, 100.0), 178 (6.2), 163 (5.5), 148 (83.4), 134 (32.7), 133 (35.5), 121 (10.3), 105 (25.1); exact mass calcd for $C_9H_9NO_4$ 195.0532, found 195.0535.

Reduction of the Nitrostyrene to Nitroalkane 5. To a stirring solution of the nitrostyrene (21.50 g, 110 mmol) in 350 mL of THF and 50 mL methanol was added in small portions 11.30 g (299 mmol) of $NaBH_4$ (frothing occurs). The reaction took several hours and was followed by TLC. When no styrene remained, as judged by TLC, 200 mL of water was added, and the volatile solvents were evaporated. The pH of the aqueous layer was raised to 8 by careful addition of 3% aqueous HCl. Extraction of the aqueous phase with ether, washing with brine, drying ($MgSO_4$), and solvent evaporation produced the crude nitroalkane as a dark oil. Flash column chromatography on silica gel (15% EtOAc/hexanes) produced 15.77 g (73% yield) of the pure **5** as an oil or a low melting waxy solid: TLC R_f = 0.45 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 6.79–6.71 (m, 3 H), 5.76 (s, 1 H), 4.64 (t, J = 7.3 Hz, 2 H), 3.87 (s, 3 H), 3.32 (t, J = 7.4 Hz, 2 H) ppm; IR (neat) 3500, 3050, 3010, 2960, 2940, 2920, 2840, 1620, 1595, 1550, 1485, 1440, 1380, 1355, 1270, 1220, 1085 cm^{-1}; mass spectrum m/e 198 (M^+ + 1, 10.4), 197 (M^+, 93.6), 151 ($M^+ - NO_2$, 69.3), 150 ($M^+ - HNO_2$, 100.0), 149 (87.5), 137 (25.6), 136 (76.7), 135 (51.9), 121 (47.6), 119 (44.9), 107 (81.4); exact mass calcd for $C_9H_{11}NO_4$ 197.0688, found 197.0677.

Preparation of the Ethoxyethyl Ether 6 of Phenol 5. To a solution of phenol **5** (15.0 g, 0.076 mol) in 200 mL of dry methylene chloride was added ethyl vinyl ether (14.5 mL, 0.152 mol) followed by 1 g of pyridinium *p*-toluenesulfonate. The mixture was stirred at room temperature until TLC indicated that the starting material had been consumed (several hours). The mixture was washed twice each with 10% NaOH and distilled water before drying the organic layer over anhydrous $MgSO_4$. Evaporation of the solvent gave the crude product as a yellow oil. Flash column chromatography on silica gel (10% EtOAc/hexanes) produced 19.74 g (96% yield) of pure **6**: TLC R_f = 0.40 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 6.99 (t, J = 7.9 Hz, 1 H), 6.85–6.76 (m, 2 H), 5.47 (q, J = 5.2 Hz, 1 H), 4.67 (dt, J = 7.8, 1.8 Hz, 2 H), 3.85 (s, 3 H), 3.62–3.28 (m, 4 H), 1.47 (d, J = 5.1 Hz, 3 H), 1.10 (t, J = 7.0 Hz, 3 H) ppm; IR (neat) 3010, 2980, 2930, 1585, 1495, 1400, 1285, 1100 cm^{-1}.

2-Hydroxy-1-methoxy-3-[2-((methoxycarbonyl)amino)ethyl]benzene 7. A solution of LAH was prepared by adding 200 mL of a 1 M LAH solution in THF to 50 mL of THF. To this stirring solution was added slowly at ambient temperature a solution of **6** (21.0 g, 78.1 mmol) in 50 mL of THF. (Caution: Exothermic!) The reaction mixture was stirred at ambient temperature for 1 h. Sodium fluoride (33.6 g, 0.80 mol) and water (10.8 mL, 0.60 mol) were carefully added, and the mixture was stirred for several hours until a granular precipitate was formed. The mixture was diluted with ether (200 mL) and filtered. The solid was washed with ether, and the combined filtrates were concentrated to give 14.56 g of the crude amine which was neither purified nor characterized but used directly in the next reaction.

Carbamoylation of the Primary Amine. To a solution of the crude amine from the previous reaction (14.56 g, ca. 62 mmol) in dry methylene chloride (200 mL) was added 30.0 mL (172 mmol) of diisopropylethylamine. Methyl chloroformate (9.6 mL, 124 mmol) was added slowly, and the mixture was stirred at ambient temperature for 3 h. The reaction mixture was washed with water, three times with 3% HCl, and once each with saturated aqueous $NaHCO_3$ and brine before drying over anhydrous $MgSO_4$. Evaporation of the solvent gave the crude carbamate which was used directly in the next reaction: TLC R_f = 0.57 (50% EtOAc/hexanes).

Ethoxyethyl Protecting Group Removal. The crude product from the previous reaction (assumed to be 62 mmol) was dissolved in 200 mL of methanol. Pyridinium *p*-toluenesulfonate (0.50 g) was added, and the mixture was stirred at ambient temperature for 2 h until TLC indicated that the starting material had been consumed. Most of the methanol was removed under reduced pressure, and the mixture was diluted with water and extracted with 100 mL of ether six times. The combined ether extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave the crude phenol which was purified by flash chromatography on silica gel (30% EtOAc/hexanes). The yield was 9.68 g (69% yield over three steps from nitroalkane **6**): TLC R_f = 0.42 (50% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 6.81–6.71 (m, 3 H), 5.93 (s, 1 H), 5.02 (br s, 1 H), 3.86 (s, 3 H), 3.64 (br s, 3 H), 3.44 (br m, 2 H), 2.84 (br t, J = 6.7 Hz, 2 H) ppm; IR (neat) 3400, 2990, 2880, 1780, 1720, 1540, 1500, 1460, 1360, 1280, 1220, 1100 cm^{-1}; mass spectrum m/e 226 (M^+ + 1, 1.7), 225 (M^+, 14.1), 193 (12.9), 150 (75.8), 137 ($M^+ - CH_2NHCOOCH_3$, 54.6), 122 (10.8), 107 (12.6), 88 ($CH_2NHCOOCH_3$, 100); exact mass calcd for $C_{11}H_{15}NO_4$ 225.1002, found 225.1006.

2-Methoxy-6-[2-((methoxycarbonyl)amino)ethyl]-1,4-benzoquinone 1. Phenol **7** (9.60 g, 42.7 mmol) was dissolved in 50 mL of dry *N*,*N*-dimethylformamide in a 250-mL sidearm flask. The neck of the flask was equipped with a bubbler, and the sidearm was fitted with a rubber septum. The solution was saturated with oxygen, delivered with a pipet through the septum, and then 1.39 g (4.27 mmol) of *N*,*N*-bis(salicylidene)ethylenediaminocobalt(II) (salcomine) was added portionwise. The mixture was stirred, and oxygen was continuously bubbled through the suspension until TLC indicated that no starting material remained. The time of the reaction was dependent on the amount of substrate and the oxygen flow rate (1–2 days). Upon completion of the reaction Celite was added, and the solvent was removed under high vacuum leaving a solid which was crushed and placed into a Soxhlet apparatus. The powdery solid was extracted with ether continuously until the TLC of the extraction solvent showed no quinone remaining (3–7 days). The ether was evaporated to give the crude quinone as a orange brown solid. It was possible use the quinone without further purification, but better results were obtained when it was purified by flash chromatography on silica gel (50% EtOAc/hexanes). It was important not to overload the column since the product crystallized on the column. The yield of pure **1** was 7.60 g (78% yield): TLC R_f = 0.20 (50% EtOAc/hexanes); mp 133–134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 6.54–6.53 (m, 1 H), 5.90 (d, J = 2.1 Hz, 1 H), 4.87 (br s, 1 H), 3.83 (s, 3 H), 3.64 (br s, 3 H), 3.41–3.35 (br m, 2 H), 2.66 (t, J = 6.5 Hz, 2 H) ppm; IR (CH_2Cl_2) 3500, 3110, 3080, 2990, 2900, 1740, 1710, 1670, 1630, 1530, 1460, 1340, 1250, 1065 cm^{-1}; mass spectrum m/e 239 (M^+, 6.3), 207 (3.0), 165 (10.0), 164 (28.9), 152.1 (100), 88 ($CH_2NHCOOCH_3$, 54.9); exact mass calcd for $C_{11}H_{13}NO_5$ 239.0794, found 239.0798.

Diene 8. A commercial 1 M solution of vinylmagnesium bromide in THF was diluted with an additional 50 mL of THF. To this solution at ambient temperature was added slowly through a dropping funnel 20 g (128 mmol) of 1,4-cyclohexanedione *mono*-ethylene ketal in 100 mL of THF. After the addition was complete, the mixture was stirred for several hours, and the progress of the reaction was monitored by TLC. When the starting material had been consumed, the reaction was quenched by slow addition of 3% HCl, bringing the reaction mixture to approximately pH 7. The majority of the THF was evaporated, and the residue was diluted with ether. The organic layer was separated, and the aqueous phase was extracted twice with ether. The combined ether extracts were washed once each with 3% aqueous HCl, saturated aqueous $NaHCO_3$, and brine and were dried ($MgSO_4$). Solvent evaporation gave the crude alcohol (20.55 g, 87% yield) which was of high purity and was used directly in the next reaction. Flash chromatography (50% Et-

OAc/hexanes) produced a pure sample for analysis: TLC R_f = 0.42 (50% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 5.98 (dd, J = 17.4, 10.8 Hz, 1 H), 5.28 (d, J = 17.1 Hz, 1 H), 5.06 (d, J = 10.5 Hz, 1 H), 3.99–3.91 (m, 4 H), 3.76–3.72 (m, 1 H), 2.01–1.76 (m, 4 H), 1.67–1.60 (m, 4 H) ppm; IR (neat) 3450, 3080, 2930, 2880, 1640, 1440, 1360, 1250, 1100, 1030, 990, 970, 925 cm^{-1}.

Alcohol Dehydration. To a solution of the alcohol (7.68 g, 41.7 mmol) in dry benzene was added 100 g of 5 Å molecular sieves and ca. 1 g of *p*-toluenesulfonic acid. The mixture was stirred, and additional aliquots of acid were added until the starting material had disappeared (ca. 5 days) as determined by TLC. The mixture was filtered, and the sieves were washed with ether. The combined filtrates were washed with saturated aqueous $NaHCO_3$ and brine before drying over $MgSO_4$. Evaporation of the solvent gave the crude diene which was quickly purified by flash chromatography on silica gel (5–10% EtOAc/hexanes containing 1% triethylamine) to produce 2.34 g (34% yield) of diene **8**: TLC R_f = 0.36 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 6.37 (dd, J = 17.5, 10.7 Hz, 1 H), 5.66 (br s, 1 H), 5.10 (d, J = 17.5 Hz, 1 H), 4.96 (d, J = 10.7 Hz, 1 H), 4.00 (s, 4 H), 2.39 (br m, 4 H), 1.83 (t, J = 6.8 Hz, 2 H) ppm; IR (neat) 3080, 3020, 2950, 2930, 2880, 1640, 1600, 1360, 1250, 1120, 1060, 1040, 870 cm^{-1}; mass spectrum m/e 167 (M^+ + 1, 2.6), 166 (M^+, 19.5), 155 (2.2), 151 (2.1), 138 (4.0), 99 (8.9), 86 (100); exact mass calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.1040.

Preparation of Diels–Alder Adduct 9. Diene **8** (2.94 g, 17.7 mmol) and quinone **1** (2.82 g, 11.8 mmol) were dissolved in 50 mL of toluene in a 200-mL flask equipped with a reflux condenser. The suspension was heated in a sand bath to 100 °C, and the quinone was completely dissolved. The progress of the reaction was monitored by TLC. Upon complete disappearance of the quinone (3–4 days), the reaction was cooled, and the solvent was evaporated. The resulting brown solid was purified by flash chromatography on silica gel (70% EtOAc/hexanes) to produce 4.30 g (86% yield) of pure **9** as a white or off-white solid. A small sample of **9** was recrystallized from ethyl acetate and hexanes for melting point determination, crystallographic analysis, and combustion analysis: TLC R_f = 0.21 (70% EtOAc/hexanes); mp 190–191 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 6.01 (s, 1 H), 5.49 (d, J = 4.7 Hz, 1 H), 4.74 (br s, 1 H), 3.89–3.82 (m, 4 H), 3.78 (s, 3 H), 3.62 (s, 3 H), 3.30–3.14 (br m, 3 H), 2.94 (dd, J = 17.9, 5.1 Hz, 1 H), 2.43 (dt, J = 14.1, 8.1 Hz, 1 H), 2.24–2.05 (m, 4 H), 1.93–1.81 (m, 1 H), 1.72 (br d, J = 12.6 Hz, 1 H), 1.47 (dt, J = 12.9, 5.9 Hz, 1 H), 1.32 (d, J = 9.3 Hz, 2 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 197.6, 197.1, 161.3, 156.9, 136.0, 117.2, 112.7, 108.5, 64.2 (two signals), 56.3, 52.0, 51.7, 44.6, 44.3, 40.7, 37.2, 36.5, 35.6, 32.6, 19.6 ppm; IR (CH_2Cl_2) 3500, 2980, 2935, 1740, 1695, 1625, 1530, 1375, 1220, 1090 cm^{-1}; mass spectrum m/e 405 (M^+, 9.9), 377 (10.0), 373 (20.6), 345 (30.3), 303 ($M^+ - CH_2CH_2NHCOOCH_3$, 100), 241 (42.8), 166 (43.3); exact mass calcd for $C_{21}H_{27}NO_7$ 405.1788, found 405.1802. Anal. Calcd for $C_{21}H_{27}NO_7$: C, 62.21; H, 6.71; N, 3.45. Found: C, 62.17; H, 6.74; N, 3.31.

Tandem Selenocyclization–Oxidative Elimination of 9. Preparation of Ether 10. A suspension of Diels–Alder adduct **9** (1.88 g, 4.65 mmol) in 150 mL of methanol was stirred vigorously under an atmosphere of nitrogen. The suspension was cooled to 0 °C. A solution of 1.1 equiv of phenylselenium chloride in 25 mL of methanol was added to the suspension during 5 min. The progress of the reaction was monitored by TLC. After several hours, 10% Na_2CO_3 was added to the reaction. After stirring for several minutes, the reaction mixture was diluted with ethyl acetate, and the organic layer was separated. The aqueous portion was extracted several times with ethyl acetate, and the organic extracts were combined and washed twice with 10% Na_2CO_3 and once with brine. Solvent evaporation gave the crude selenide which was not purified but dissolved in 50 mL of THF and cooled to 0 °C. Hydrogen peroxide was added (20 mL of a 30% aqueous solution), and the ice bath was removed. The reaction mixture was stirred at ambient temperature for 2 h and then poured into a separatory funnel containing 300 mL ethyl acetate. The resulting solution was washed twice each with 10% Na_2CO_3 and 10% Na_2SO_3 and once with brine. The organic phase was dried over anhydrous $MgSO_4$, and the solvent was evaporated to yield the crude olefin. The product was of sufficient purity for the next reaction but could be purified for analytical purposes by flash chromatography on silica gel. An analytical sample was recrystallized from ethyl acetate and hexanes: TLC R_f = 0.21 (EtOAc); mp 237–238 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 5.74 (dd, J = 9.1, 1.4 Hz, 1 H), 5.48 (dd, J = 9.1, 2.4 Hz, 1 H), 5.14 (s, 1 H), 3.98–3.88 (m, 4 H), 3.74 (br s, 3 H), 3.70 (s, 3 H), 3.74–3.70 (1 H, obscured by other signals but observed from a COSY experiment), 3.43 (dt, J = 11.0, 3.6 Hz, 1 H), 3.30 (br t, 1 H), 2.29–2.23 (m, 2 H), 2.16–2.07 (m, 1 H), 1.89–1.57 (m, 6 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 197.7, 171.3, 155.5, 135.6, 127.3, 108.6, 98.2, 95.6, 84.4, 64.3, 64.2, 59.6, 57.3, 56.8, 52.7, 48.5, 47.5, 32.1, 30.3, 29.2, 24.6 ppm; IR (neat) 3060, 2950, 2940, 2890, 1730, 1700, 1670, 1605, 1450, 1370, 1360, 1080 cm^{-1}; mass spectrum m/e 404 (M^+ + 1), 403 (M^+), 388, 385, 373, 371, 359, 358, 356, 344, 326, 297, 282, 216, 173; exact mass calcd for $C_{21}H_{25}NO_7$ 403.1631, found 403.1636. Anal. Calcd for $C_{21}H_{25}NO_7$: C, 62.52; H, 6.25; N, 3.47. Found: C, 62.46; H, 6.32; N, 3.31.

Hydrolysis of Ketal 10 to Ketone 11. Ketal **10**, the crude product from the preceding reaction, ca. 4.65 mmol, was dissolved 50 mL of THF. Aqueous HCl (50 mL of a 3% solution) was added, and the mixture was stirred at room temperature until TLC indicated that no starting material remained (1–2 days). Most of the solvent was evaporated, and the resulting mixture was extracted with methylene chloride until TLC of the extraction solvent showed no product present (seven extractions totaling 500 mL). The combined extracts were dried over anhydrous $MgSO_4$, and the solvent was evaporated to yield ketone **11** as a foam. Purification by flash chromatography (EtOAc) on silica gel gave the pure product (1.210 g, 73% yield from Diels–Alder adduct **9**) as a white solid. An analytical sample was recrystallized from ether acetate and hexanes: TLC R_f = 0.15 (EtOAc); mp 209–210 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 5.86 (dd, J = 9.2, 2.1 Hz, 1 H), 5.57 (dd, J = 9.1, 2.8 Hz, 1 H), 5.21 (s, 1 H), 3.75 (br s, 3 H), 3.74 (s, 3 H), 3.79–3.71 (m, 1 H, partially obscured by other signals), 3.45 (dt, J = 7.8, 4.3 Hz, 1 H), 3.36 (t, J = 2.3 Hz, 1 H), 2.81–2.47 (m, 5 H), 2.26–2.21 (m, 1 H), 2.11 (ddd, J = 14.4, 10.0, 4.3 Hz, 1 H), 1.96 (ddd, J = 14.8, 13.2, 5.3 Hz, 1 H), 1.88–1.69 (m, 1 H); IR (CCl_4) 3020, 2985, 2940, 2895, 2840, 1745, 1730, 1700, 1680, 1610, 1450, 1360, 1230 cm^{-1}; mass spectrum m/e 359 (M^+, 8.9), 344 ($M^+ - CH_3$, 10.4), 312 (9.5), 282 (20.4), 258 (13.7), 257 (22.5), 216 (20.6), 173 (31.9), 172 (49.9); exact mass calcd for $C_{19}H_{21}NO_6$ 359.1369, found 359.1364. Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.38; H, 5.99; N, 3.88.

Acyloin 12. Ketone **11** (500 mg, 1.39 mmol) was dissolved in 90 mL of anhydrous THF under an atmosphere of dry nitrogen. The solution was cooled to −78 °C and potassium bis(trimethylsilyl)amide (2.78 mL of a 0.5 M solution in toluene, 1.39 mmol) was added dropwise. The solution was stirred for 1 h at −78 °C, and then 2-(*p*-toluenesulfonyl)-3-phenyloxaziridine (383 mg, 1.39 mmol) was added as a solution in 10 mL of THF. After 1 h the reaction was quenched at −78 °C with saturated aqueous NH_4Cl. The mixture was allowed to warm to room temperature and was partitioned between water and methylene chloride. The aqueous phase was saturated with NaCl and extracted three times with methylene chloride, and the combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave the crude hydroxy ketone **12** which produced 428 mg (82% yield) of pure product following flash chromatography on silica gel (70% EtOAc/hexanes): TLC R_f = 0.26 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 5.79 (dd, J = 9.2, 2.0 Hz, 1 H), 5.59 (dd, J = 9.2, 2.7 Hz, 1 H), 5.23 (s, 1 H), 4.47 (br dd, J = 8.9, 2.6 Hz, 1 H), 3.99–3.86 (m, 1 H), 3.77 (s, 6 H, two signals), 3.66 (d, J = 3.3 Hz, 1 H, exchangeable), 3.55 (dt, J = 11.2, 3.8 Hz, 1 H), 3.42 (br t, J = 2.4 Hz, 1 H), 2.92–2.77 (m, 2 H), 2.65 (ddd, J = 15.0, 5.8, 2.3 Hz, 1 H), 2.44 (ddd, J = 13.0, 4.4, 2.4 Hz, 1 H), 2.26 (d, J = 9.2 Hz, 1 H), 1.90 (dt, J = 14.7, 4.5 Hz, 1 H), 1.76 (ddd, J = 18.5, 11.1, 2.4 Hz, 1 H) ppm; IR (neat) 3450, 3060, 3025, 2950, 2850, 1730, 1715, 1695, 1680, 1670, 1660, 1605, 1450, 1370, 1360, 1230, 1080 cm^{-1}; mass spectrum m/e 375 (M^+, 0.5), 373 (0.7), 359 (1.3), 357 (0.6), 344 ($M^+ - OCH_3$, 3.2), 282 (7.6), 257 (6.6), 216 (5.9), 172 (23.5), 149 (15.3), 117 (17.6), 57 (100); exact mass calcd for $C_{19}H_{21}NO_7$ 375.1318, found 375.1304.

Hydrogenation of 12 to 13. A sidearm flask equipped with a septum inlet, and a three-way stopcock was charged with 311 mg (0.24 mmol) of 10% palladium on carbon. The flask was evacuated and purged several times first with nitrogen and then with hydrogen via a balloon attached to the three-way stopcock. THF (60 mL) was added via syringe followed by 439 mg (1.17 mmol) of **12**. The transfer was accomplished with a small amount of THF. The mixture was stirred vigorously until TLC indicated that the starting material had been consumed (ca. 2 days) and was filtered through a pad of Celite. The solid residue was washed with ethyl acetate. Solvent evaporation gave the crude product which was purified by flash chromatography on silica gel (50% EtOAc/hexanes) to produce 332 mg (75% yield) of **13**: TLC R_f = 0.20 (EtOAc); IR (neat) 3440, 3050, 2940, 2920, 2840, 1725, 1710, 1690, 1665, 1600, 1445, 1365, 1220, 1085 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 5.31 (s, 1 H), 4.41 (br d, J = 7.8 Hz, 1 H), 3.79 (s, 2 signals, 6 H), 3.68 (d, J = 2.8 Hz, 1 H), 3.42 (dt, J = 11.3, 4.2 Hz, 1 H), 2.92–2.81 (m, 1 H), 2.80 (dd, J = 8.6, 6.1 Hz, 1 H), 2.69 (ddd, J = 14.2, 10.0, 4.2 Hz, 1 H), 2.59 (dt, J = 9.6, 3.6 Hz, 1 H), 2.37 (dt, J = 13.1, 3.7 Hz, 1 H), 2.08 (d, J = 8.5 Hz, 1 H), 2.12–1.95 (m, 2 H), 1.92–1.81 (m, 2 H), 1.78–1.61 (m, 3 H) ppm; mass spectrum m/e 377 (M^+), 359 ($M^+ - H_2O$), 345, 302, 275, 236, 209, 166; exact mass calcd for $C_{19}H_{23}NO_7$ 377.1474, found 377.1486; exact mass calcd for $C_{19}H_{21}NO_6$ 359.1369, found 359.1379.

Swern Oxidation of Acyloin 13 to Diketone 14. Dimethyl sulfoxide (0.43 mL, 6.05 mmol) was dissolved in 15 mL of dry methylene chloride under an atmosphere of dry nitrogen and was cooled to −78 °C. A solution of 0.43 mL (3.02 mmol) of trifluoroacetic anhydride in 15 mL

of methylene chloride was added dropwise. After 15 min 380 mg (1.01 mmol) of **13** in 15 mL of methylene chloride was added. After 1 h, triethylamine (ca. 1 mL) was added, and the mixture was warmed to ambient temperature. TLC indicated the presence of two products. After 8 h the more polar product was converted to the less polar one. The mixture was poured into 3% aqueous HCl, and the organic phase was separated. The aqueous phase was extracted several times with methylene chloride, and the combined extracts were washed successively with 3% aqueous HCl, saturated aqueous $NaHCO_3$, and brine before drying over anhydrous $MgSO_4$. Solvent evaporation gave the crude product which was used directly for the next reaction. A sample of the mildly unstable diketone **14** was purified by flash chromatography (EtOAc): TLC R_f = 0.28 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 6.31 (s, exchangeable, 1 H), 5.21 (s, 1 H), 3.77 (s, 3 H), 3.76 (s, 3 H), 3.77–3.61 (m, partially obscured by 3.77 and 3.76 s, 1 H), 3.54–3.44 (m, 1 H), 2.92–2.86 (m, 2 H), 2.72 (ddd, J = 17.7, 5.1, 2.1 Hz, 1 H), 2.49–2.04 (m, 7 H), 1.81–1.71 (m, 1 H) ppm; mass spectrum m/e 376 (M^+ + 1), 375 (M^+), 357, 347, 288, 236; exact mass calcd for $C_{19}H_{21}NO_7$ 375.1318, found 375.1315.

Aromatization of 14. Crude diketone **14** from the preceding reaction (assumed to be about 1.01 mmol) was dissolved in 25 mL of dry methylene chloride under an atmosphere of nitrogen. The mixture was cooled to −30 °C, and boron trifluoride etherate (0.62 mL, 5.00 mmol) was added dropwise. The reaction mixture was warmed to ambient temperature and stirred until TLC indicated the complete disappearance of starting material (several hours). Saturated aqueous $NaHCO_3$ (10 mL) was added, and the mixture was stirred for ca. 0.5 h. The organic layer was separated, and the aqueous layer was extracted several times with methylene chloride. The combined organic extracts were washed once each with saturated aqueous $NaHCO_3$ and brine before drying over anhydrous $MgSO_4$. Solvent evaporation gave the crude **24** which was not purified but used directly in the next reaction. This material was characterized by TLC and ^{1}H NMR only: TLC R_f = 0.60 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 6.72 (d, J = 8.2 Hz, 1 H), 6.56 (d, J = 8.3 Hz, 1 H), 6.09 (br s, 1 H), 5.36 (s, 1 H), 4.13–4.06 (m, 1 H), 3.88–3.80 (m, 1 H), 3.78 (s, 3 H), 3.69 (s, 3 H), 2.72–2.47 (m, 4 H), 2.39–2.24 (m, 1 H), 2.16–2.09 (m, 1 H), 2.01–1.91 (m, 1 H) ppm.

Preparation of Methyl Ether 15 from Phenol 24. The crude material from the previous reaction (ca. 1.01 mmol) was dissolved in 5 mL of acetone. Anhydrous K_2CO_3 (1.4 g, 10.1 mmol) was added followed by methyl iodide (0.31 mL, 5.0 mmol). The reaction flask was stoppered, and the mixture was stirred vigorously for several hours. The reaction mixture was decanted into a separatory funnel. The solid residue was washed several times with methylene chloride, and the washings were poured into the separatory funnel. The organic layer was washed once each with 3% aqueous HCl, saturated aqueous $NaHCO_3$, and brine and dried over anhydrous $MgSO_4$. Solvent evaporation gave the crude product which was purified by flash chromatography on silica gel (50% EtOAc/hexanes) to produce 209 mg (56% yield from hydroxy ketone **13**) of **15**: TLC R_f = 0.52 (70% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 6.72 (d, J = 8.3 Hz, 1 H), 6.60 (d, J = 8.3 Hz, 1 H), 5.39 (s, 1 H), 4.06 (ddd, J = 11.3, 9.2, 2.8 Hz, 1 H), 3.88 (dt, J = 10.8, 7.2 Hz, 1 H), 3.84 (s, 3 H), 3.77 (s, 3 H), 3.71 (s, 3 H), 2.70–2.54 (m, 4 H), 2.36–2.26 (m, 1 H), 2.12 (ddd, J = 12.9, 7.2, 2.5 Hz, 1 H), 2.04–1.92 (m, 1 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 195.7, 167.6, 154.2, 142.9, 142.5, 129.9, 126.2, 121.1, 115.0, 105.1, 104.9, 56.6, 56.4, 55.9, 53.0, 49.5, 43.7, 36.2, 21.6, 21.4 ppm; mass spectrum m/e 372 (M^+ + 1), 371 (M^+), 356 ($M^+ - CH_3$), 312 ($M^+ - COOCH_3$), 296; exact mass calcd for $C_{20}H_{21}NO_6$ 371.1368, found 371.1360; calcd for $C_{19}H_{18}NO_6$ 356.1135, found 356.1122.

Preparation of Enone 29 from Ketone 15. The ketone **15** (280 mg, 0.75 mmol) was dissolved in 10 mL of ethyl acetate. A small excess (1.1 equiv) of phenylselenium chloride was added, the mixture was stirred at ambient temperature, and the reaction was monitored by TLC. When the starting material had been consumed (several hours), the mixture was diluted with ethyl acetate and washed twice with 10% Na_2CO_3 and once with brine. The solvent was evaporated to give the crude selenide which was characterized only by TLC (R_f = 0.50 50% EtOAc/hexanes). The selenide was dissolved in 20 mL of THF, 30% H_2O_2 (ca. 5 mL) was added, and the mixture was stirred 1 h at ambient temperature. The reaction mixture was poured into ethyl acetate and washed twice each with 10% Na_2CO_3 and 10% Na_2SO_3 and once with brine. The organic phase was dried over anhydrous $MgSO_4$, and the solvent was evaporated. Purification by flash chromatography on silica gel gave 194 mg (70% yield) of enone **29** as a white foam: TLC R_f = 0.24 (50% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 6.90 (dd, J = 5.4, 3.3 Hz, 1 H), 6.79 (d, J = 8.0 Hz, 1 H), 6.71 (d, J = 8.1 Hz, 1 H), 5.50 (s, 1 H), 3.86 (s, 3 H), 3.80 (s, 3 H), 3.77 (s, 3 H), 3.88–3.61 (2 m, partially obscured, 2 H), 3.45–3.43 (br m, 2 H), 2.25–2.17 (m, 1 H), 2.08–1.98 (m, 1 H) ppm; IR (neat) 2950, 2840, 1740, 1730, 1710, 1650, 1640, 1630, 1590, 1500, 1440, 1370, 1225 cm^{-1}; mass spectrum m/e 370 (M^+ + 1), 369 (M^+), 354 ($M^+ - CH_3$), 326, 310 ($M^+ - COOCH_3$), 294, 266, 200; exact mass calcd for $C_{20}H_{19}NO_6$ 369.1213, found 369.1220; calcd for $C_{18}H_{16}NO_4$ 310.1079, found 310.1065.

Reduction of Enone 29 to Alcohol 30. A solution of 50 mg (0.136 mmol) of **29** in 10 mL of methanol was treated with 11 mg (0.289 mmol) of $NaBH_4$ at ambient temperature. After 15 min TLC indicated that the reaction was complete, and water was added. The reaction mixture was extracted with 20 mL of ethyl acetate. The aqueous phase was extracted three more times with a total of 20 mL of ethyl acetate, and the extracts were combined and washed with brine. Drying of the solvent (K_2CO_3) followed by solvent evaporation gave the crude product which was pure enough for the next reaction. A sample of **30** for analysis was purified by flash chromatography on silica gel (50% EtOAc/hexanes): TLC R_f = 0.39 (70% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 6.70 (AB, 2 H), 5.97 (m, 1 H), 5.06 (br d, J = 6.6 Hz, 1 H), 4.82 (d, J = 1.3 Hz, 1 H), 3.96–3.88 (m, 1 H), 3.84 (s, 3 H), 3.74 (s, 3 H), 3.64–3.54 (m, 1 H), 3.57 (s, 3 H), 3.29–3.25 (m, 2 H), 2.06–2.01 (m, 2 H), (OH signal not located) ppm; IR (neat) 3500, 3040, 2990, 2970, 1750, 1730, 1725, 1715, 1650, 1525, 1465, 1390, 1380 cm^{-1}; mass spectrum m/e 371 (M^+), 353 ($M^+ - H_2O$), 339 ($M^+ - CH_3OH$), 311, 119, 84 (100); exact mass calcd for $C_{20}H_{21}NO_6$ 371.1369, found 371.1381; calcd for $C_{19}H_{17}NO_5$ 339.1107, found 339.1104.

Conversion of Carbamate 30 to *N*-Methylamine 31. A solution of crude carbamate **30** from the preceding reaction (ca. 0.136 mmol) in 10 mL of dry THF was cooled to 0 °C. To this stirred solution was added methyllithium (1 mL of a 1.4 M solution in ether, 1.4 mmol). After 0.5–1 h water was carefully added, and the mixture was extracted 4 times with a total of 40 mL of methylene chloride. The organic extracts were washed once each with saturated aqueous $NaHCO_3$ and brine and dried over anhydrous K_2CO_3. Solvent evaporation produced the secondary amine which was used for the next reaction. A sample for analysis was purified by flash chromatography on silica gel (70% EtOAc/hexanes): TLC R_f = 0.41 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 6.67 (AB, 2 H), 6.18–6.15 (m, 1 H), 5.11 (br s, 1 H), 4.75 (d, J = 0.7 Hz, 1 H), 3.83 (s, 3 H), 3.60 (s, 3 H), 3.32–3.25 (m, 2 H), 3.23–3.15 (m, 2 H), 2.09–1.87 (m, 2 H), (OH signal not observed) ppm; IR (neat) 3380, 3000, 2920, 2830, 1645, 1630, 1505, 1450, 1440 cm^{-1}; mass spectrum m/e 313 (M^+), 295 ($M^+ - H_2O$), 281 ($M^+ - CH_3OH$), 149, 119, 84, 69 (100); exact mass calcd for $C_{19}H_{21}NO_4$ 313.1314, found 313.1299; calcd for $C_{18}H_{15}NO_3$ 281.1052, found 281.1062.

N-Methylation of the Secondary Amine. The material from the preceding reaction (assumed to be 0.136 mmol) was dissolved in 4 mL of acetonitrile. Aqueous formaldehyde solution was added (2 mL) followed by sodium cyanoborohydride (100 mg, 1.59 mmol), and the mixture was stirred at room temperature for 15 min. The reaction mixture was acidified to pH 6 with 10% aqueous acetic acid, and stirring was continued for 5 min. The mixture was poured into $NaHCO_3$, and the resulting solution was extracted 4 times with methylene chloride (total volume of 40 mL). The combined extracts were washed once each with saturated aqueous $NaHCO_3$ and brine, and the solvent was evaporated. The product was purified by flash chromatography on silica gel (50% EtOAc/hexanes) to give 25 mg (54% yield overall for three steps) of pure *N*-methylamine **31**: TLC R_f = 0.53 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 6.67 (AB, 2 H), 6.06–6.05 (m, 1 H), 5.11 (br s, 1 H), 4.75 (s, 1 H), 3.84 (s, 3 H), 3.58 (s, 3 H), 3.35–3.26 (m, 2 H), 3.00–2.94 (m, 1 H), 2.90–2.82 (m, 1 H), 2.78 (s, 3 H), 1.98–1.93 (m, 2 H), (OH signal not observed) ppm; IR (neat) 3280, 3050, 3020, 2950, 2930, 2825, 1640, 1630, 1595, 1500, 1460, 1450, 1440, 1355 cm^{-1}; mass spectrum m/e 328 (M^+ + 1, 27.0), 327 (M^+, 100), 312 ($M^+ - CH_3$, 28.5), 311 (12.0), 310 (20.0), 309 ($M^+ - H_2O$, 52.7), 307 (52.3), 295 ($M^+ - CH_3OH$, 82.0), 266 (27.2), 252 (32.3), 240 (40.9); exact mass calcd for $C_{19}H_{21}NO_4$ 327.1471, found 327.1452; calcd for $C_{18}H_{17}NO_3$ 295.1208, found 295.1185.

Conversion of Alcohol 31 to Dienone 32. A solution of 63 mg (0.193 mmol) of **31** in methylene chloride was cooled to −30 °C and was treated with 0.44 mL of 2,6-lutidine (3.8 mmol) followed by trifluoroacetic anhydride (0.27 mL, 1.9 mmol). The mixture was allowed to warm to ambient temperature, and the progress of the reaction was followed by TLC. The reaction time was 12–24 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$, and the organic layer was separated. The aqueous phase was extracted twice with methylene chloride, and the extracts were combined, washed once each with saturated aqueous $NaHCO_3$ and brine, and were dried (K_2CO_3). Solvent evaporation gave the dienone which was purified by flash chromatography on silica gel (50% EtOAc/hexanes). The yield of **32** was 46 mg (81% yield): TLC R_f = 0.58 (70% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 7.06 (d, J = 10.0 Hz, 1 H), 6.67 (AB, 2 H), 6.31 (dd, J = 6.4, 2.1 Hz, 1 H), 5.95 (d, J = 10.2 Hz, 1 H), 3.86 (s, 3 H), 3.53 (br d, J = 19.1 Hz, 1 H), 3.36 (dd, J = 19.4, 6.5 Hz, 1 H), 3.05 (dd, J = 8.6, 7.3 Hz, 1 H), 2.91–2.82

(ddd, J = 12.2, 8.9, 5.3 Hz, 1 H), 2.71 (s, 3 H), 2.23 (dd, J = 12.0, 5.2 Hz, 1 H), 2.07–1.96 (m, 1 H) ppm.

Reduction and Conjugate Addition of 32 to Produce Ketone 36. To a solution of dienone **32** (12 mg, 0.041 mmol) in 2 mL of ethanol was added 0.81 mL of a 1 M aqueous solution of NH_4Cl (0.81 mmol) and 27 mg of zinc dust (0.41 mmol). The solution was stirred for ca. 4 h and was filtered into a separatory funnel containing saturated aqueous $NaHCO_3$. The solid residue was washed with methylene chloride. The organic phase was separated, and the aqueous phase was extracted three times with methylene chloride. The combined organic extracts were washed once each with saturated aqueous $NaHCO_3$ and brine before drying over anhydrous Na_2SO_4. Solvent evaporation gave the amine which was purified by flash chromatography on silica gel (deactivated by passing acetone through the packed column prior to the elution solvent). The product was eluted with 5% MeOH/$CHCl_3$. The yield of **36** was 8 mg (ca. 65%): TLC R_f = 0.28 (5% MeOH/$CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 6.77 (d, J = 8.3 Hz, 1 H), 6.64 (d, J = 8.3 Hz, 1 H), 6.05 (br s, 1 H), 5.90 (t, J = 3.4 Hz, 1 H), 3.87 (s, 3 H), 3.79 (dd, J = 17.0, 1.8 Hz, 1 H), 3.65 (br d, J = 5.0 Hz, 1 H), 3.49–3.47 (m, 2 H), 3.03 (d, J = 7.1 Hz, 1 H), 2.89 (dt, J = 13.3, 2.3 Hz, 1 H), 2.73–2.68 (m, 2 H), 2.41 (s, 3 H), 2.43–2.33 (m, obscured by N-Me, 2 H), 1.88 (dt, J = 12.0, 7.1 Hz, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 210.9, 145.0, 143.7, 136.8, 126.1, 125.3, 119.4, 117.7, 109.4, 64.0, 56.2, 50.8, 47.8, 42.1, 41.5, 39.2, 35.5, 29.2 ppm; IR (neat) 3500, 3360, 2920, 1680, 1610, 1485, 1445, 1280 cm^{-1}; mass spectrum m/e 299 (M^+, 0.5), 256 (0.4), 242 (6.7), 226 (2.0), 88 (14.4), 86 (82.8), 84 (100); exact mass calcd for $C_{18}H_{21}NO_3$ 299.1521, found 299.1527.

Preparation of Dienone 37 from Thebaine. The procedure reported by Fuchs in ref 30 was followed. Proceeding from 500 mg (1.61 mmol) of thebaine, 632 mg (89% yield) of **37** was obtained: TLC R_f = 0.18 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 7.22 (d, J = 9.9 Hz, 1 H), 6.69 (AB, 2 H), 6.35 (d, J = 5.1 Hz, 1 H), 5.95 (d, J = 9.9 Hz, 1 H), 5.11 (br s, 1 H), 4.12 (dd, J = 9.3, 8.1 Hz, 2 H), 3.88 (s, 3 H), 3.60 (d, J = 18.9 Hz, 1 H), 3.38 (dd, J = 19.5, 6.3 Hz, 1 H), 1 H signal partially obscured by 3.38 dd, 3.20–3.15 (m, 1 H), 2.82 (s, 3 H), 2.07–1.96 (m, 2 H), 0.97 (t, J = 9.3 Hz, 2 H), 0.26 (s, 9 H) ppm.

Oxidation of Alcohol 31 to Ketone 40. A solution of 19 mg (0.058 mmol) of allylic alcohol **31** in 2 mL of methylene chloride was treated portionwise with 3 equiv of the Dess–Martin periodinane[31] at ambient temperature. The reaction was complete within minutes. A 1:1 mixture of saturated aqueous $NaHCO_3$ and 10% Na_2SO_3 was added, and stirring was continued for 5 min. The mixture was partitioned between methylene chloride and additional sulfite/bicarbonate solution. The aqueous phase was separated and reextracted several times with methylene chloride. The combined organic extracts were washed once each with saturated aqueous $NaHCO_3$, 10% Na_2SO_3, and brine before drying over anhydrous K_2CO_3. Solvent evaporation and flash chromatography on silica gel (70% EtOAc/hexanes) produced 14 mg (74% yield) of **40**: TLC R_f = 0.35 (70% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 6.99 (t, J = 4.6 Hz, 1 H), 6.74 (d, J = 8.0 Hz, 1 H), 6.66 (d, J = 8.1 Hz, 1 H), 5.41 (s, 1 H), 3.87 (s, 3 H), 3.79 (s, 3 H), 3.43 (d, J = 4.5 Hz, 2 H), 3.06–3.01 (m, 1 H), 2.86 (s, 3 H), 2.86–2.78 (m, partially obscured by 2.86 s, 1 H). 2.16–1.95 (m, 2 H) ppm; IR (neat) 3030, 3015, 3000, 2960, 2925, 2860, 2815, 2800, 1645, 1630, 1600, 1500, 1450, 1435, 1370, 1220, 850 cm^{-1}; mass spectrum m/e 326 (M^+ + 1, 1.5), 325 (M^+, 7.9), 310 ($M^+ - CH_3$, 1.9), 248 (3.4), 231 (1.8); exact mass calcd for $C_{19}H_{19}NO_4$ 325.1304, found 325.1287; calcd for $C_{18}H_{16}NO_4$ 310.1079, found 310.1034.

Preparation of Morphinan 41 from Enone 40. Enone **40** (10 mg, 0.031 mmol) was dissolved in 2 mL of ethanol in a 10-mL flask equipped with a stirring bar. To this solution was added 1 M aqueous ammonium chloride (1 mL, 1 mmol) followed by 100 mg of zinc dust (1.54 mmol). The suspension was stirred for 10 h, and 50 additional mg of zinc dust was added. The mixture was stirred overnight for a total time of 24 h. Dilute ammonium hydroxide was added to adjust the pH of the reaction mixture to 9. The resulting mixture was partitioned between methylene chloride and dilute ammonium hydroxide. The aqueous phase was extracted three times with methylene chloride (total volume 25 mL), and the organic extracts were combined. The extracts were washed with saturated aqueous $NaHCO_3$ and brine and were dried over anhydrous Na_2SO_4. Evaporation of solvent and flash chromatography on silica gel which had been deactivated with acetone (5–15% MeOH/$CHCl_3$) produced 4.5 mg (44% yield) of morphinan **41** and 4 mg of material in which only cleavage of the C–O bond had taken place. This material was a reaction intermediate and could be converted to **41** under the same reaction conditions. The yield of **41** based on this recovered material was 73%: TLC R_f = 0.23 (5% MeOH/$CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 6.74 (d, J = 8.3 Hz, 1 H), 6.67 (d, J = 8.2 Hz, 1 H), 5.97 (s, exchangeable, 1 H), 5.55 (d, J = 1.5 Hz, 1 H), 3.90 (1 H signal obscured by 3.88 s), 3.88 (s, 3 H), 3.83 (d, J = 18.1 Hz, 1 H), 3.73 (s, 3 H), 3.17 (d, J = 18.1 Hz, 1 H), 2.85 (dd, J = 18.2, 1.5 Hz, 1 H), 2.74 (dd, J = 18.2, 5.3 Hz, 1 H), 2.43 (br s, 1 H), 2.40 (m, partially obscured by 2.43 s, 1 H), 2.34 (s, 3 H), 2.18 (dt, J = 12.3, 5.3 Hz, 1 H), 2.03 (dt, J = 11.5, 2.3 Hz, 1 H), 1.63 (d, obscured by H_2O signal, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 197.1, 176.7, 144.6, 143.6, 132.0, 127.5, 118.8, 108.9, 101.4, 56.2, 55.7, 50.9, 50.8, 47.0, 42.7, 39.1, 36.9, 30.1, 27.2; IR (85:15 mixture of trans and cis isomers, neat) 3400, 3010, 2933, 2845, 2804, 1725, 1651, 1616, 1484, 1458, 1440, 1380, 1280, 1222, 1204 cm^{-1}; mass spectrum m/e 330 (M^+ + 1, 16.7), 329 (M^+, 73.7), 314 ($M^+ - CH_3$, 47.3), 271 (32.9), 245 (41.8), 192 (100), 169 (33.5); exact mass calcd for $C_{19}H_{23}NO_4$ 329.1627, found 329.1648; calcd for $C_{18}H_{20}NO_4$ 314.1392, found 314.1393.

Preparation of β-Thebainone-A (42) from *trans*-Morphinan (41). Morphinan **41** (3 mg, 0.009 mmol) was dissolved in dry THF (2 mL) under an atmosphere of nitrogen. Diisobutylaluminum hydride (0.10 mL of a 1 M solution in hexanes, 0.10 mmol) was added, and the mixture was stirred at ambient temperature for 0.5–1 h. The reaction was quenched carefully with water and 2 mL of 3% aqueous HCl was added. After stirring for several hours 5% aqueous NaOH was added so that the mixture became slightly basic. The solution was extracted 4 times with methylene chloride (total volume 20 mL), the combined extracts were washed with brine and dried (K_2CO_3), and the solvent was evaporated. Flash chromatography on silica gel which had been deactivated with acetone (15% MeOH/$CHCl_3$) produced 3 mg (ca. 100% yield) of β-thebainone-A (**42**). A trace of thebainone-A was also detected. **42**: TLC R_f = 0.39 (15% MeOH/$CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 6.96 (dd, J = 9.9, 1.8 Hz, 1 H), 6.74 (d, J = 8.4 Hz, 1 H), 6.67 (d, J = 8.4 Hz, 1 H), 6.19 (ddd, J = 9.8, 2.8, 0.6 Hz, 1 H), 5.96 (s, exchangeable, 1 H), 4.02 (d, J = 17.5 Hz, 1 H), 3.87 (s, 3 H), 3.20 (m, 1 H, partially obscured by 3.15 d), 3.15 (d, J = 18.1 Hz, 1 H), 2.86 (dd, J = 18.1, 5.9 Hz, 1 H), 2.82 (s, 1 H), 2.61 (d, J = 17.5 Hz, 1 H), 2.40 (m, 1 H), 2.37 (s, 3 H), 2.19–2.00 (m, 2 H), 1.60 (br d, 1 H, partially obscured by H_2O signal) ppm; IR (neat) 3380, 2905, 2840, 1660, 1480, 1435, 1275, 1145, 1090, 1055 cm^{-1}; mass spectrum m/e 300 (M^+ + 1, 10.8), 299 (M^+, 52.2), 284 ($M^+ - CH_3$), 256 (6.5), 242 (8.0), 204 (9.3), 190 (11.1), 162 (98.6); exact mass calcd for $C_{18}H_{21}NO_3$ 299.1521, found 299.1550.

Preparation of Thebainone-A (43) from β-Thebainone-A (42). A solution of 3 mg (0.010 mmol) of **42** in 0.5 mL of glacial acetic acid was heated to 100 °C under an atmosphere of dry nitrogen. After 1 h the mixture was basified with dilute ammonium hydroxide. The solution was extracted with methylene chloride several times (total volume of 20 mL). The combined organic extracts were washed once each with water and brine and dried (Na_2SO_4). Solvent evaporation produced 3 mg of essentially pure thebainone-A. Purification by flash chromatography gave 2 mg of pure thebainone-A (**43**): TLC R_f = 0.21 (15% MeOH/$CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 6.67 (dd, J = 9.9, 1.5 Hz, 1 H), 6.64 (d, J = 8.1 Hz, 1 H), 6.54 (d, J = 8.1 Hz, 1 H), 6.05 (br s, 1 H), 5.88 (dd, J = 9.9, 2.7 Hz, 1 H), 4.26 (d, J = 15.6 Hz, 1 H), 3.80 (s, 3 H), 3.23 (t, J = 4.3 Hz, 1 H), 3.01 (d, J = 18.4 Hz, 1 H), 2.91 (br s, 1 H), 2.65 (dd, J = 18.3, 5.3 Hz, 1 H), 2.55 (ddd, J = 11.9, 4.0, 2.0 Hz, 1 H), 2.43 (s, 3 H), 2.38 (d, J = 15.6 Hz, 1 H), 2.07 (dt, J = 11.9, 3.7 Hz, 1 H), 1.97–1.83 (m, 2 H) ppm; IR (neat) 3360, 3050, 2920, 2840, 1675, 1580, 1480, 1430, 1275, 1145, 1095, 1050 cm^{-1}; mass spectrum m/e 300 (M^+ + 1, 17.6), 299 (M^+, 60.9), 284 ($M^+ - CH_3$, 9.4), 271 (21.4), 178 (50.4), 162 (100); exact mass calcd for $C_{18}H_{21}NO_3$ 299.1522, found 299.1550.

Preparation of Thebainone-A (43) from Codeinone (39b). A 2:1 mixture of codeinone (**39b**) and neopinone (**39a**) which was prepared according to ref 30 was subjected to the same reaction conditions which were used to prepare **36** from **32**. As this reaction was done only to characterize the product, exact amounts of reagents were not determined. The desired product was the major product and was purified by flash chromatography on silica gel which had been deactivated with acetone (15% MeOH/$CHCl_3$). The ^{1}H NMR spectrum of this material was superimposable with that for synthetic **43** which had been prepared from **41**.

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Supplementary Material Available: Tables of crystallographic data and X-ray crystallographic structures of **9** and **10** (4 pages). Ordering information is given on any current masthead page.