and methyl iodide (1 mL, 16.0 mmol) in CH_3OH (2 mL) was refluxed for 30 min. The reaction mixture was evaporated in vacuo to give crude **6** (52 mg). Recrystallization from 2-propanol afforded the methiodide (**6**) as colorless needles (30 mg, 77.8%): mp 235 °C; $[\alpha]^{23}_D$ +22.8° (*c* 1.67, CH_3OH); ^1H NMR (Pyridine-d_5, 400 MHz) 7.26–7.82 (9 H, m, aromatic H), 5.44 and 5.82 (each 1 H, d, J = 15 Hz, ArCH_2N), 4.30 and 4.56 (each 1 H, d, J = 14 Hz, CCH_2N), 3.76 and 3.89 (each 3 H, s, $N(CH_3)_2$); IR (KBr) 3338, 3010, 2970, 1476, 1449, 1346. Anal. ($C_{17}H_{20}INO$) C, H, N.

Single-Crystal X-ray Analysis of (+)-PI-OH·CH_3I (6). (+)-PI-OH·CH_3I was recrystallized by the evaporation of the 2-propanol solution at room temperature. Crystal size was 0.3 × 0.3 × 0.3 mm. Cell parameters were determined by least-squares methods for 25 reflections ranged in 15° < 2θ < 25°, on a Rigaku four-circle diffractometer equipped monochromatized Mo Kα radiation. The conditions of intensity measurements: $2\theta_{max}$ = 50°, o scan technique, scan speed 2° min^{-1}, and small drifts of three reference reflections. Reflections (1783) were collected, and 1639 were cited as observed reflections ($F > 3\sigma_F$) and corrected for Lorentz polarization, but not for absorption.

Crystal data: molecular formula $C_{16}H_{17}NO·CH_3I$, M_r 381.26; orthorhombic; space group $P2_12_12_1$; unit cell a = 12.667 (3), b = 16.119 (3), c = 8.159 (1) Å; V = 1665.9 (6) Å^3; Z = 4, D_{calcd} = 1.520 Mg m^{-3}; (Mo Kα) = 0.71069 Å; μ (Mo Kα) = 1.943 mm^{-1}; F(000) = 760; room temperature.

The structure was solved by the Patterson heavy atom method, which revealed the position of the iodine atom. The remaining atoms were located in succeeding difference Fourier syntheses. Their atomic parameters were refined by block-diagonal least-squares methods, minimizing w $(|F_o| - |F_c|)^2$, $w^{-1} = \sigma_F + 0.0001 \times F_o^2$, anisotropically. All H atoms were located on difference Fourier syntheses and refined isotropically. The final R value was 0.029 (R_w = 0.034, S = 4.306). In order to determine the absolute configuration of PI-OH·CH_3I, an anomalous dispersion factor for iodine atom was introduced. Then, the 101 Bijvoet pairs which have greatest values for the function: $[F_o(hkl) - F_o(\overline{hkl})]/[F_o(hkl) + F_o(\overline{hkl})]$ had as the same sign as those of the corresponding $F_c(hkl)$ calculated by the structure of **6**. Atomic scattering factors taken from *International Tables for X-Ray Crystallography*.[25] All calculations were performed by applications of the program packages; RASA,[26] X-SRANP,[27] and PLUTO[28] on PANAFACOM U1400 and micro VAX II computers of Tokushima Bunri University.

Pharmacology. Detailed methods used in evaluating these compounds were reported in the previous paper[3] from our laboratory. The isolated rat anococcygeus muscles were used for the assay of potentiating activity of PI-OH on the response to NE, which was evaluated from a shift in the concentration–response curves at low concentration of NE. The ability of a drug in potentiating the action of NE is expressed as the activity ratio, which was determined from the antilogarithm of the difference between the pD_2 values for NE (negative logarithm of the molar concentration of the agonist producing 50% of the maximum response) in the presence and absence of the test compounds.

Supplementary Material Available: Fractional coordinates, bond lengths, bond angles, anisotropic parameters, torsion angles, Bijvoet pairs, and fractional coordinates of hydrogen atoms (8 pages); a listing of structure factors (9 pages). Ordering information is given on any masthead page.

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Electrophilic α-Methylene-γ-lactone and Isothiocyanate Opioid Ligands Related to Etorphine

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Isothiocyanate and α-methylene-γ-lactone analogues of 6,14-*endo*-ethenotetrahydrothebaine and -oripavine were prepared with the electrophilic groups being located at C-19 in the C-7α-side chain. Isothiocyanates were prepared in the *N*-Me and *N*-CPM (*N*-cyclopropylmethyl) series, both as the phenols and 3-*O*-methyl ethers from the diastereomeric amines formed from reductive amination of thevinone (**2**) and *N*-(cyclopropylmethyl)northevinone (**13**). Although addition of the organozinc reagent from methyl α-bromomethacrylate to **25** failed, addition to 3-O-protected aldehydes **27** and **35** produced, after subsequent deprotection, α-methylene-γ-lactones **29** and **37**, respectively. In the opioid receptor displacement assays against [^{3}H]bremazocine as the radiolabeled ligand, the phenolic compounds were most potent with *N*-CPM isothiocyanates **20** and **21** showing IC_{50}s of 0.32 and 0.76 nM, respectively, and *N*-CPM α-methylene-γ-lactone **37** having an IC_{50} = 1.0 nM. Compound **37** showed irreversible effects in the binding assay which were μ-selective, as demonstrated by analogous experiments using [^{3}H]DAGO, and naloxone was found to protect against the irreversible effects. This observation suggests that a receptor-bound nucleophile is located at a position where it can readily reach the α-methylene group of lactone **37**.

Electrophilic ligands derived from opioid agonist and antagonist molecules have provided an important approach to aid in characterization of opioid drug–receptor interactions.[1] Ligands with an isothiocyanate group have been made in several series including 6α- and 6β-isothiocyanato-4,5-epoxymorphinans,[2] fentanyl- and etonitazene-derived isothiocyanates FIT, SUPERFIT, and BIT,[3] *N*-alkyl-6,14-*endo*-ethenotetrahydrooripavine-derived isothiocyanates,[4] and a derivative of U-50,488H.[5] Some of these are bound irreversibly in opioid-receptor prepa-

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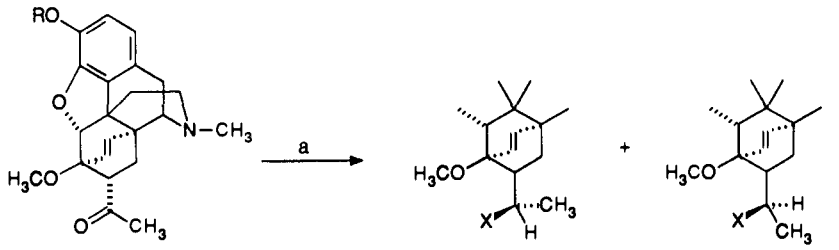
0022-2623/90/1833-2286$02.50/0

Scheme I[a]



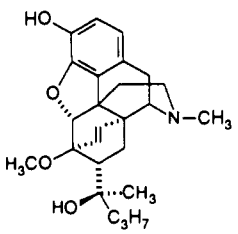
2 R = Me

3 or 4 $\xrightarrow{b}$ 5 or 6
3 or 4 $\xrightarrow{c}$ 8 or 9
8 or 9 $\xrightarrow{b}$ 10 or 11

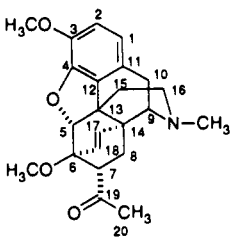
3 X = NH_2	R = Me	4 X = NH_2	R = Me	$\xrightarrow{H_2}$ 7
5 X = N=C=S	R = Me	6 X = N=C=S	R = Me	
8 X = NH_2	R = H	9 X = NH_2	R = H	
10 X = N=C=S	R = H	11 X = N=C=S	R = H	

[a] Reagents: (a) NH_4OAc, $NaCNBH_3$; (b) $Cl_2C{=}S$; (c) KOH, 210 °C.

rations. In addition, the α-methylene-γ-lactone electrophile and the analogous open-chain α,β-unsaturated esters, when incorporated into 6-substituted 4,5-epoxymorphinans, have provided some μ-receptor selective agents which are irreversibly bound in opioid-receptor preparations.[6] On the basis of the high potency of 6,14-*endo*-ethenotetrahydrooripavine analogues as analgesics, e.g. etorphine (1),[7] and antagonists[8] and the ease with



1



2 thevinone

which thevinone (2),[9] the Diels–Alder adduct of thebaine and methyl vinyl ketone, is obtained, analogues have been prepared in which the 19-carbonyl group attached at the 7α-position of the nucleus provides a logical functional group for addition of electrophilic substituents. In this paper, we report the preparation of isothiocyanates and α-methylene-γ-lactones based on 6,14-*endo*-ethenotetrahydrothebaine and -oripavine. Results of testing in the opioid receptor displacement and irreversible binding assays are reported.

Chemistry. The carbonyl group at C-19 of thevinone (2) provided a means for preparing the isomeric isothiocyanates with the 3-*O*-methyl ether, as well as with the 3-hydroxyl group, in both the *N*-Me and *N*-cyclopropylmethyl (*N*-CPM) series after subsequent transformations. For the *N*-Me series, thevinone (2) was transformed to an approximately 1:1 mixture of diastereomeric primary amines **3** and **4** by reductive amination using $NaBH_3CN$ and excess NH_4OAc (Scheme I).[10] These diastereomers were readily separated by flash column chromatography.[11] The corresponding isothiocyanates **5** and **6** were prepared from amines **3** and **4**, respectively, by reaction with thiophosgene in CH_2Cl_2 in the presence of $NaHCO_3$.

The stereochemistry at the newly created C-19 asymmetric center of diastereomeric amines **3** and **4** was assigned indirectly. Hydrogenation at 30 psi of initial pressure was successful for the conversion of **4** to its 17,18-dihydro derivative **7**,[12] but **3** was not reduced under these reaction conditions. Amine **4** is tentatively assigned the *R* configuration at C-19 based on the assumption that intramolecular hydrogen bonding occurs between the

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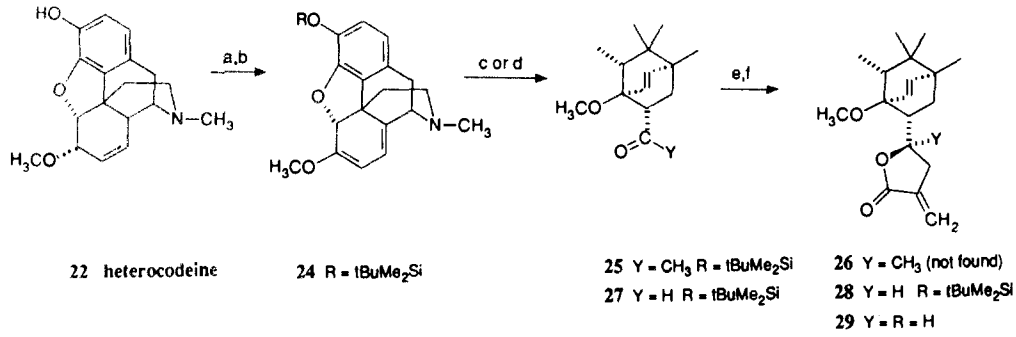
Scheme II[a]



22 heterocodeine 24 R = $tBuMe_2Si$

25 Y = CH_3 R = $tBuMe_2Si$ 26 Y = CH_3 (not found)
27 Y = H R = $tBuMe_2Si$ 28 Y = H R = $tBuMe_2Si$
29 Y = R = H

[a] Reagents: (a) t-$BuMe_2SiCl$; (b) γ-MnO_2; (c) methyl vinyl ketone; (d) acrolein; (e) $BrZnCH_2C(CH_2)COOCH_3$; (f) n-$Bu_4N^+F^-$.

amine attached at the C-19 position and the ether oxygen at C-6. In this conformation, the C-20 methyl group is directed away from the 17,18-double bond thereby allowing facile catalytic reduction of this diastereomer. Amine **3** is assigned the *S* configuration at C-19 because approach of hydrogen for reduction of the 17,18-double bond would be blocked by the presence of the C-20 methyl group in such a conformation. Analogous intramolecular hydrogen bonding between a C-19 OH and the C-6 OMe group of 7α-alkyl-substituted etorphine analogues has been used to explain conformational preferences consistent with the observed ^{1}H NMR and IR spectra of these compounds.[13] The spectral data were consistent with their absolute configurations as determined by X-ray crystallography.[14]

The analogous compounds with a phenolic OH group at the 3-position were also prepared. A number of reagents were examined for possible selectivity in the demethylation of the aromatic methyl ether without affecting the tertiary alkyl methyl ether at C-6 in diastereomers **3** and **4**. Of these, TMSI,[15] BBr_3,[16] BBr_3SMe_2,[17] and $PrSNa$[18,19] showed little selectivity, and AlI_3[20] showed selectivity for demethylation of the C-6 methyl ether only. The desired phenols **8** and **9** were obtained cleanly from **3** and **4**, respectively, by demethylation with excess KOH in diethylene glycol at 210 °C.[21] These phenolic amines **8** and **9** exist as hydrates, and their characterization proved to be difficult due to their insolubility in most solvents. Isothiocyanates **10** and **11** were prepared by carefully controlling the reaction conditions (see the Experimental Section) using thiophosgene.

The *N*-CPM series was obtained in a similar manner to that described above for the preparation of the *N*-Me series after northevinone (**12**)[21] was treated with cyclopropylmethyl bromide in DMF in the presence of $NaHCO_3$ at 85 °C for 4 h to give *N*-(cyclopropylmethyl)northevinone (**13**). Reductive amination with $NaBH_3CN$ and excess NH_4OAc provided an approximately 1:1 mixture of diastereomers **14** and **15**, which were readily separated by flash chromatography.[11] The stereochemistry at C-19 of these diastereomers was assigned by comparison of the ^{1}H NMR spectrum of **14** with that of **3**, and of **15** with that of **4**. In particular, the chemical shifts of the C-19 protons were diagnostic in both cases. In the spectra of **14** and **3**, these signals appear at δ 3.35 and 3.37, respectively, and in **15** and **4**, these signals appear at δ 3.10 and 3.06, respectively. Other parts of the spectra also showed significant similarities. Similar hydrogen-bonded structures have been suggested to account for ^{1}H NMR spectral characteristics of C-19 alcohols of known absolute configuration.[13,14,19] The corresponding isothiocyanates **16** and **17** were obtained by reaction of **14** and **15**, respectively, with thiophosgene and $NaHCO_3$ in CH_2Cl_2. The diastereomeric amines **14** and **15** were converted to the corresponding phenols **18** and **19** by treatment with excess KOH in diethylene glycol at 210 °C. The resulting insoluble phenolic amines, when treated with thiophosgene, gave isothiocyanates **20** and **21**, respectively.

We attempted to prepare analogues with the α-methylene-γ-lactone functionality attached at C-19. The starting material for these reactions, 3-*O*-(*tert*-butyldimethylsilyl)oripavine (**24**) was prepared from heterocodeine (**22**) (Scheme II) by methodology analogous to that reported by Rapoport for syntheses of thebaine and oripavine from codeine and morphine, respectively.[22] Silylation of **22** with *tert*-butyldimethylsilyl chloride gave 3-*O*-(*tert*-butyldimethylsilyl)heterocodeine (**23**), which in turn was transformed to dienol ether **24** by oxidation with γ-MnO_2[23] in 36% yield. Initially, we attempted to convert Diels–Alder adduct **25**, formed from 3-*O*(*tert*-butyldimethylsilyl)oripavine (**24**) and methyl vinyl ketone, to α-methylene-γ-lactone **26** by reaction with the modified Reformatsky reagent prepared from methyl α-(bromomethyl)acrylate[24] and zinc.[25] α-Methylene-γ-lactone **26** was not obtained, presumably because of steric congestion at C-19 preventing approach of the alkylzinc reagent. Unreacted starting material was isolated.

We then examined a sterically less hindered molecule. When dienol ether **24** was allowed to react with acrolein in benzene at 60 °C, Diels–Alder adduct **27**, having the α-configuration at C-7, was obtained as the only isolated

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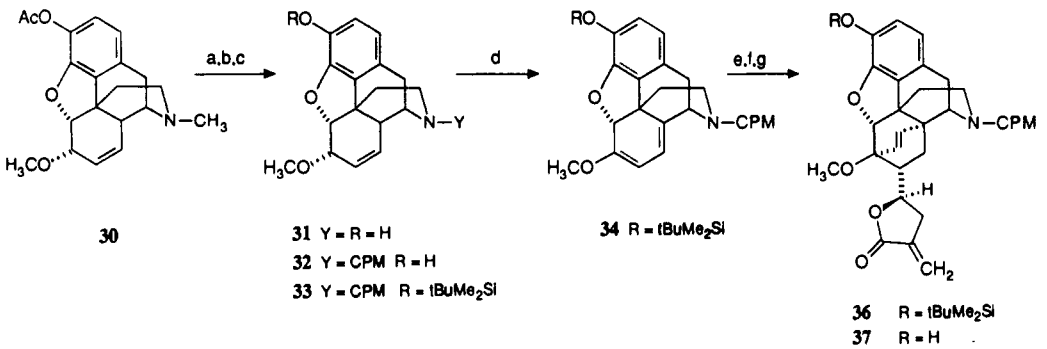
Scheme III[a]



30

31 Y = R = H
32 Y = CPM R = H
33 Y = CPM R = $tBuMe_2Si$

34 R = $tBuMe_2Si$

36 R = $tBuMe_2Si$
37 R = H

[a] Reagents: (a) $ClCOOCH(Cl)CH_3$; (b) CPM-Br; (c) t-$BuMe_2SiCl$; (d) γ-MnO_2; (e) acrolein; (f) $BrZnCH_2C(CH_2)COOCH_3$; (g) n-$Bu_4N^+F^-$.

product. Aldehyde **27** was allowed to react with the modified Reformatsky reagent prepared from methyl α-(bromomethyl)acrylate[24] and zinc[25] to give the corresponding α-methylene-γ-lactone **28**, as a single diastereomer in 84% yield. Steric congestion at C-19 in **28** is decreased by the absence of a C-20 methyl substituent as is found in ketone **26**. The phenolic α-methylene-γ-lactone **29** was obtained after removal of silyl protecting group.

Presently, the absolute configuration at C-19 in α-methylene-γ-lactone **28** is not known with certainty. Bentley et al.[12] established the stereochemistry at C-19 of the products from the reaction of Grignard reagents with thevinone (**2**) and attributed the specificity of these processes to complexation of the magnesium to both the carbonyl oxygen and the C-6 methoxy group oxygen prior to delivery of the alkyl group to the β-face of the carbonyl carbon (C-19). In the reaction of alkylzinc reagents, a similar complexation and β-face transfer of the alkyl group can be envisioned, leading to formation of the α-methylene-γ-lactone with R configuration at C-19.

The N-CPM α-methylene-γ-lactone **37** was prepared as outlined in Scheme III. N-Demethylation of heterocodeine 3-acetate (**30**)[22] with α-chloroethyl chloroformate[26] afforded norheterocodeine (**31**). After conversion to N-CPM derivative **32**, the 3-hydroxyl group was converted to the 3-*O*-*tert*-butyldimethylsilyl ether **33**. Subsequent oxidation with γ-MnO_2[23] gave dienol ether **34** suitable for Diels–Alder reaction with acrolein. The resulting aldehyde **35** was converted to α-methylene-γ-lactone **37** as a single diastereomer in two steps in 65% yield.

Opioid Receptor Binding. The isothiocyanates and α-methylene-γ-lactones prepared above were examined for their ability to displace [^{3}H]bremazocine from binding sites on cell membranes prepared from the bovine striatum (Table I). Most of the phenolic compounds exhibited activity (IC_{50}) in the dispacement assay in the nanomolar range with N-CPM compounds **20** and **21** displaying activities at less than 1 nM. As expected, the 3-phenol increases potency substantially over the 3-*O*-Me ethers, by 10–50-fold in the N-Me compounds and by about 500-fold in the N-CPM compounds. The N-CPM compounds are more potent than the corresponding N-Me compounds by 2–20-fold, with the largest differences occurring in the most potent phenolic compounds. Of the two phenolic α-methylene-γ-lactones, the N-CPM analogue was more potent than the N-Me analogue by 30-fold, and it was only slightly less potent than the most potent isothiocyanates **20** and **21**. In general, the C-19 S diastereomers of the C-19 isothiocyanates displayed a 2–3-fold increase in potency over the corresponding C-19 R diastereomers.

Table I. Comparison of Opioid Receptor Binding against 0.5 nM [^{3}H]Bremazocine of Isothiocyanates and α-Methylene-γ-lactones in the Bovine Striatum Membrane Preparation

	C-3	C-19	IC_{50},[a] nM
	Isothiocyanates		
5 (*N*-Me)	OMe	*S*	323 ± 12
6 (*N*-Me)	OMe	*R*	1160 ± 50
10 (*N*-Me)	OH	*S*	6.2 ± 0.2
11 (*N*-Me)	OH	*R*	63 ± 1
16 (*N*-CPM)	OMe	*S*	171 ± 12
17 (*N*-CPM)	OMe	*R*	434 ± 32
20 (*N*-CPM)	OH	*S*	0.32 ± 0.04
21 (*N*-CPM)	OH	*R*	0.76 ± 0.05
	Lactones		
28 (*N*-Me)	OH	*R*	34 ± 2
37 (*N*-CPM)	OH	*R*	1 ± 0.1
	Controls		
bremazocine			0.5
diprenorphine			1.4[b]
naloxone			5.0[b]

[a] Values are means ± SD of three determinations. Duplicate incubations of five to seven concentrations of displacing ligand were used for determination of each IC_{50} value. [b] Reference 27.

In the tests for irreversibility of binding, isothiocyanates **10**, **20**, and **21** and α-methylene-γ-lactone **37** were screened (Table II). All showed irreversibility, but naloxone protected only partially against the effects of **21** and quite effectively against the irreversible effects of lactone **37**. The irreversible effects of **37** appear to be μ-receptor selective, since they were similar when the experiment was repeated at a lower electrophile concentration with the highly μ-selective ligand [^{3}H]DAGO.

The irreversible effects of the isothiocyanates after washing, associated with the lack of protection by a high concentration of naloxone, is puzzling. Although etorphine-related molecules show slow rates of dissociation from μ-receptor preparations,[28] which could render interpretation of the washing experiments problematic, we would then expect the isothiocyanates and α-methylene-γ-lactone **37** to behave similarly in the naloxone protection experiment. Likewise, if the observations in the washing experiments are due to nonspecific partitioning of ligand into lipid with slow redistribution after washing, the effects would be expected to be similar in the naloxone protection experiment. The small structural difference between **37** and isothiocyanates **10**, **20**, and **21** would not appear to

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account for great differences in nonspecific lipid solubility. It is possible that non μ-specific covalent binding occurs, and there are different receptor subtype selectivities for isothiocyanates **10**, **20**, and **21** and α-methylene-γ-lactone **37**. Differential reactivities of these two electrophilic groups may be a factor. In a somewhat related study, Bidlack et al.[29] also observed only partial protection of irreversible binding of 14-(bromoacetamido)morphine by morphine and by naloxone.

Although isothiocyanates **10**, **20**, and **21** had irreversible effects, analogues with the isothiocyanate moiety directly attached to the C ring reported by Lessor et al.[4] appeared to have less irreversible effects and had δ-selectivity in vitro but produced some analgesic effects in vivo. Clearly, small structural changes alter selectivity as measured by current assay techniques.

The irreversible effects of ligand **37**, with high μ-selectivity and demonstrated naloxone protection, indicate that the alkylating functionality must align with a receptor nucleophile when it is bound at this receptor. Considerable conformational freedom of rotation in an arc about C-19–C-7α bond of the α-methylene-γ-lactone would be expected, allowing for alignment of the relatively unhindered terminal methylene unit. This possibility is consistent with a nucleophile being located at a distance of about 6 Å from the C-7 carbon atom when the ligand is bound at the receptor. Additional work related to these observations is in progress.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 283 spectrometer or a Perkin-Elmer 1610 FTIR. NMR spectra were recorded on a Varian VXR-300 spectrometer. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as an internal standard. Electron impact mass spectra were obtained on a VG-7070 mass spectrometer and FAB mass spectra were obtained on a VG-70 SEQ mass spectrometer, both by direct insertion probe. Optical rotations were measured on a JASCO-DIP-4 digital polarimeter. Analytical thin-layer chromatography (TLC) was performed on Analtech silica gel HLF glass plates. Preparative TLC was performed on (20 × 20 cm) Analtech silica gel GF glass plates (2000 μm thick). Flash chromatography was performed with Merck silica gel 60 (230–400 mesh). Dichloromethane (CH_2Cl_2), dimethylformamide (DMF), and benzene were stored over 3-Å molecular sieves prior to use. Triethylamine was stored over KOH. Tetrahydrofuran (THF) was distilled over sodium benzophenone ketyl. All reactions were run in flame-dried glassware under an argon atmosphere. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN. Where indicated by symbols of the elements, analyses were within ±0.4% of theoretical values.

6,14-*endo*-Etheno-7α-[1(*S*)-aminoethyl]tetrahydrothebaine (3) and 6,14-*endo*-Etheno-7α-[1(*R*)-aminoethyl]tetrahydrothebaine (4). A mixture of thevinone (**2**;[9] 2.3 g, 6.03 mmol), ammonium acetate (4.65 g, 60.3 mmol), and sodium cyanoborohydride (758 mg, 12.06 mmol) in methanol (30 mL) was stirred with 3-Å molecular sieves for 3 days. The mixture was treated with saturated aqueous ammonium chloride solution (10 mL), followed by a 20% aqueous K_2CO_3 solution (30 mL) and lastly with CH_2Cl_2 (60 mL). The resulting mixture was stirred vigorously for 5 min and then filtered through Celite under suction. The solids were rinsed with CH_2Cl_2 (80 mL), and the filtrates were combined. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried (Na_2SO_4), and the solvents were evaporated. The residue was purified by flash chromatography (160 g of silica gel) eluting with 2% triethylamine–30% methanol–ethyl acetate (1 L) and then with 2% triethylamine–40% methanol–ethyl acetate (500 mL) to give amine **3** (910 mg, 40%) as a white foam [mp 65–70 °C; $[\alpha]^{20}_D$ = −200.0° (c = 1.00, CH_2Cl_2)] and lastly with 2% triethylamine–50% methanol–ethyl acetate (300 mL) to give amine **4** (1.15 g, 50%) which was precipitated from ethyl acetate–ether [mp 129–135 °C; $[\alpha]^{20}_D$ = −178.5° (c = 1.00, CH_2Cl_2)].

3: ^{1}H NMR ($CDCl_3$) δ 0.98 (d, J = 6.8 Hz, 3 H, C-20 CH_3), 1.15 (dd, J = 7.4 and 12.8 Hz, 1 H, C-8α H), 1.45 (br s, movable, 2 H, NH_2), 1.8–1.9 (m, 2 H, C-7β H and C-15 H), 1.9–2.1 (m, 1 H, C-15 H), 2.39 (s, 3 H, NCH_3), 2.3–2.5 (m, 2 H, C-10α H and C-16 H), 2.5–2.6 (m, 1 H, C-16 H), 2.70 (dd, J = 9.4 and 12.5 Hz, 1 H, C-8β H), 3.15–3.3 (m, 2 H, C-9 H and C-10β H), 3.35 (dq, J = 2.5 and 6.6 Hz, 1 H, C-19 H), 3.60 (s, 3 H, C-6 OCH_3), 3.81 (s, 3 H, C-3 OCH_3), 4.58 (s, 1 H, C-5 H), 5.41 (d, J = 8.7 Hz, 1 H, C-17 H), 5.76 (d, J = 8.8 Hz, 1 H, C-18 H), 6.51 (d, J = 8.2 Hz, 1 H, C-1 H), 6.61 (d, J = 8.1 Hz, 1 H, C-2 H); ^{13}C NMR ($CDCl_3$) δ 21.30, 22.24, 25.34, 33.71, 42.08, 42.85, 43.49, 44.35, 45.55, 47.41, 52.42, 56.42, 60.02, 80.68, 94.58, 113.03, 118.93, 127.19, 128.10, 133.97, 134.76, 141.52, 148.07; IR (KBr) 3750–3000 (NH_2 and OH), 1675, 1645 cm^{-1}; HREIMS calcd for $C_{23}H_{30}N_2O_3$ 382.2256, found 382.2235.

4: ^{1}H NMR ($CDCl_3$) δ 0.91 (d, J = 6.5 Hz, 3 H, C-20 CH_3), 0.95 (dd, J = 6.8 and 12.7 Hz, 1 H, C-8α H), 1.8–1.9 (m, 1 H, C-15 H), 1.9–2.05 (m, 4 H, C-7β H, C-15 H and NH_2), 2.37 (s, 3 H, NCH_3), 2.3–2.45 (m, 2 H, C-10α H and C-16 H), 2.45–2.6 (m, 1 H, C-16 H), 2.77 (dd, J = 9.2 and 12.6 Hz, 1 H, C-8β H), 3.06 (quintet, J = 6.3 Hz, 1 H, C-19 H), 3.15 (d, J = 6.5 Hz, 1 H, C-9 H), 3.21 (d, J = 18.6 Hz, 1 H, C-10β H), 3.61 (s, 3 H, C-6 OCH_3), 3.82 (s, 3 H, C-3 OCH_3), 4.59 (s, 1 H, C-5 H), 5.40 (d, J = 8.8 Hz, 1 H, C-17 H), 5.75 (d, J = 8.8 Hz, 1 H, C-18 H), 6.51 (d, J = 8.1 Hz, 1 H, C-1 H), 6.61 (d, J = 8.2 Hz, 1 H, C-2 H); ^{13}C NMR ($CDCl_3$) δ 20.57, 22.21, 27.87, 33.55, 42.54, 42.98, 43.48, 45.55, 46.85, 47.42, 52.70, 56.51, 60.06, 81.77, 95.09, 113.20, 118.94, 127.19, 128.01, 134.25, 134.73, 141.56, 147.93; IR (KBr) 3800–2500 (NH_2 and OH), 1730, 1670, 1645, 1615 cm^{-1}; HREIMS calcd for $C_{23}H_{30}N_2O_3$ 382.2256, found 382.2258.

6,14-*endo*-Etheno-7α-[1(*S*)-isothiocyanatoethyl]tetrahydrothebaine (5). To a mixture of amine **3** (100 mg, 0.26 mmol) and $NaHCO_3$ (88 mg, 1.05 mmol) in CH_2Cl_2 (1.5 mL) was added thiophosgene (30 μL, 0.39 mmol) dropwise. The mixture was stirred for 1 h, treated with 15% aqueous NH_4OH solution (15 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried (Na_2SO_4) and the volatiles were evaporated. The residue was purified by flash chromatography (4 g of silica gel) eluting with ethyl acetate (50 mL) to give isothiocyanate **5** (100 mg, 99%) as white crystals: mp 215.5–217.5 °C; $[\alpha]^{20}_D$ = −175.5° (c = 1.00, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.15 (dd, J = 6.8 and 12.8 Hz, 1 H, C-8α H), 1.27 (d, J = 6.8 Hz, 3 H, C-20 CH_3), 1.75–1.9 (m, 2 H, C-7β H and C-15 H), 1.95 (dt, J = 5.8 and 12.4 Hz, 1 H, C-15 H), 2.40 (s, 3 H, NCH_3), 2.35–2.6 (m, 3 H, C-10α H and C-16 CH_2), 2.87 (dd, J = 9.3 and 12.7 Hz, 1 H, C-8β H), 3.15–3.3 (m, 2 H, C-9 H and C-10β H), 3.65 (s, 3 H, C-6 OCH_3), 3.82 (s, 3 H, C-3 OCH_3), 4.30 (dq, J = 2.4 and 6.9 Hz, 1 H, C-19 H), 4.45 (d, J = 1.4 Hz, 1 H, C-5 H), 5.54 (d, J = 8.9 Hz, 1 H, C-17 H), 5.91 (d, J = 8.9 Hz, 1 H, C-18 H), 6.53 (d, J = 8.0 Hz, 1 H, C-1 H), 6.62 (d, J = 8.1 Hz, 1 H, C-2 H); ^{13}C NMR ($CDCl_3$) δ 20.24, 22.29, 26.47, 33.44, 42.62, 42.94, 43.45, 45.51, 47.17, 51.27, 53.68, 56.59, 59.95, 79.71, 96.26, 113.47, 119.20, 125.61, 127.97, 129.22, 133.76, 134.58, 141.62, 147.95; FTIR (KBr) 2157 (NCS), 1623, 1599 cm^{-1}; FAB MS [M + H]$^+$ calcd for $C_{24}H_{29}N_2O_3S$ 425.1896, found 425.1908. Anal. ($C_{24}H_{28}N_2O_3S$·0.5H_2O) C, H, N, S.

6,14-*endo*-Etheno-7α-[1(*R*)-isothiocyanatoethyl]tetrahydrothebaine (6). To a mixture of amine **4** (100 mg, 0.26 mmol) and $NaHCO_3$ (88 mg, 1.05 mmol) in CH_2Cl_2 (1.5 mL) was added thiophosgene (30 μL, 0.39 mmol) dropwise. The mixture was stirred for 1 h, treated with 15% aqueous NH_4OH solution (15 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried (Na_2SO_4) and the volatiles were evaporated. The residue was purified by flash chromatography (4 g of silica gel) eluting with ethyl acetate (50 mL) to give isothiocyanate **6** (100 mg, 99%) as white crystals: mp 147–148.5 °C; $[\alpha]^{20}_D$ = −107.5° (c = 1.00, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.14 (d, J = 6.6 Hz, 3 H, C-20 CH_3), 1.1–1.2 (m, 1 H, C-8α H), 1.8–1.9 (m, 1 H, C-15 H), 1.99 (dt, J = 5.7 and 12.6 Hz, 1 H, C-15 H), 2.38 (s, 3 H, NCH_3), 2.25–2.45 (m, 3 H, C-7β H, C-10α H, and C-16 H),

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2.5–2.6 (m, 1 H, C-16 H), 2.91 (dd, J = 9.3 and 13.1 Hz, 1 H, C-8β H), 3.15–3.3 (m, 2 H, C-9 H and C-10β H), 3.60 (s, 3 H, C-6 OCH_3), 3.81 (s, 3 H, C-3 OCH_3), 4.12 (m, 1 H, C-19 H), 4.55 (d, J = 1.4 Hz, 1 H, C-5 H), 5.43 (d, J = 8.8 Hz, 1 H, C-17 H), 5.71 (d, J = 8.8 Hz, 1 H, C-18 H), 6.52 (d, J = 8.1 Hz, 1 H, C-1 H), 6.62 (d, J = 8.2 Hz, 1 H, C-2 H); ^{13}C NMR ($CDCl_3$) δ 18.15, 22.28, 26.97, 33.53, 40.90, 42.63, 43.46, 45.40, 47.34, 52.99, 53.66, 56.55, 59.85, 80.00, 95.06, 113.39, 119.18, 126.60, 127.96, 129.33, 133.80, 135.24, 141.58, 147.87; FTIR (KBr) 2122 (NCS), 1630, 1601 cm^{-1}; FAB MS [M + H]$^+$ calcd for $C_{24}H_{29}N_2O_3S$ 425.1896, found 425.1888. Anal. ($C_{24}H_{28}N_2O_3S\cdot0.25H_2O$) C, H, N, S.

6,14-*endo*-Ethano-7α-[1(*R*)-aminoethyl]tetrahydrothebaine (7). A mixture of olefin **4** (200 mg, 0.52 mmol) and 10% Pd on carbon (40 mg) in methanol (20 mL) was treated with hydrogen gas at 30 psi on a Parr apparatus for 26 h and then filtered through a 1-in. plug of Celite under suction. The solids were rinsed with methanol (50 mL) and the combined filtrates were evaporated to give **7** as a white foam (200 mg, 100%): $[\alpha]^{20}_D$ = −119.5° (c = 0.89, 10% MeOH–CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.65–0.8 (m, 1 H, C-17 H), 0.9–1.05 (m, 1 H, C-17 H), 1.10 (dd, J = 6.8 and 13.2 Hz, 1 H, C-8α H), 1.18 (d, J = 5.9 Hz, 3 H, C-20 CH_3), 1.5–1.6 (m, 2 H, C-18 CH_2), 1.6–1.7 (m, 1 H, C-15 H), 1.7–1.8 (m, 1 H, C-7β H), 2.04 (dt, J = 5.6 and 12.5 Hz, 1 H, C-15 H), 2.23 (dd, J = 6.0 and 18.7 Hz, 1 H, C-10α H), 2.25–2.35 (m, 1 H, C-16 H), 2.30 (s, 3 H, NCH_3), 2.4–2.5 (m, 1 H, C-16 H), 2.64 (d, J = 6.2 Hz. 1 H, C-9 H), 2.7–2.85 (m, 1 H, C-8β H), 3.10 (d, J = 18.5 Hz, 1 H, C-10β H), 3.15–3.3 (m, 1 H, C-19 H), 3.3 (br s, movable, 2 H, NH_2), 3.47 (s, 3 H, C-6 OCH_3), 3.86 (s, 3 H, C-3 OCH_3), 4.50 (s, 1 H, C-5 H), 6.57 (d, J = 8.3 Hz, 1 H, C-1 H), 6.70 (d, J = 8.3 Hz, 1 H, C-2 H); ^{13}C NMR ($CDCl_3$) δ 19.07, 21.23, 21.82, 29.26, 31.99, 35.20, 35.36, 41.75, 43.41, 44.67, 45.16, 48.97, 51.36, 56.54, 61.33, 78.28, 92.76, 113.67, 118.85, 128.30, 132.37, 141.46, 146.59; FTIR (neat) 3700–2500 (NH_2), 1627, 1598 cm^{-1}; HREIMS calcd for $C_{23}H_{32}N_2O_3$ 384.2413, found 384.2423.

6,14-*endo*-Etheno-7α-[1(*S*)-aminoethyl]tetrahydrooripavine (8). A mixture of amine **3** (191 mg, 0.5 mmol), KOH (1.5 g, 26.7 mmol), and diethylene glycol (3 mL) was heated at 210 °C on an oil bath for 140 min. The reaction mixture was cooled to room temperature, treated with 1 M aqueous H_3PO_4 solution (50 mL), mixed thoroughly, and then the solution was extracted with ether (50 mL). The aqueous phase was basified by the addition of 30% aqueous NH_4OH solution (50 mL) and extracted with 25% 2-propanol–CH_2Cl_2 (4 × 25 mL). The combined organic phases were dried (Na_2SO_4) and the solvents were evaporated. The gummy residue was triturated with ether (3 × 10 mL) to give phenol **8** (150 mg, 78%) as a pale pink powder which decomposes above 245 °C; FTIR (KBr) 3500–2300 (OH), 1627, 1601 cm^{-1}; FAB MS [M + H]$^+$ calcd for $C_{22}H_{29}N_2O_3$ 369.2175, found 369.2160.

6,14-*endo*-Etheno-7α-[1(*R*)-aminoethyl]tetrahydrooripavine (9). A mixture of amine **4** (191 mg, 0.5 mmol), KOH (1.5 g, 26.7 mmol), and diethylene glycol (3 mL) was heated at 210 °C on an oil bath for 140 min. The reaction mixture was cooled to room temperature, treated with 1 M aqueous H_3PO_4 solution (50 mL), mixed thoroughly, and then extracted with ether (50 mL). The aqueous phase was made alkaline by the addition of 30% aqueous NH_4OH solution (50 mL) and extracted with 25% 2-propanol–CH_2Cl_2 (4 × 25 mL). The combined organic phases were dried (Na_2SO_4) and the solvents were evaporated. The gummy residue was triturated with ether (3 × 10 mL) to give phenol **9** (150 mg, 78%) as a beige powder which decomposes above 235 °C; ^{1}H NMR (DMSO-d_6) δ 0.69 (d, J = 6.3 Hz, 3 H, C-20 CH_3), 0.88 (dd, J = 6.8 and 12.8 Hz, 1 H, C-8α H), 1.6–1.7 (m, 1 H, C-15 H), 1.85–2.05 (m, 2 H, C-7β H and C-15 H), 2.27 (s, 3 H, NCH_3), 2.2–2.5 (m, 3 H, C-10α H and C-16 CH_2), 2.62 (dd, J = 9.3 and 12.7 Hz, 1 H, C-8β H), 2.95–3.2 (m, 3 H, C-9 H, C-10β H and C-19 H), 3.0–3.5 (br s, movable 3 H, NH_2 and OH), 3.43 (s, 3 H, C-6 OCH_3), 4.52 (s, 1 H, C-5 H), 5.31 (d, J = 8.7 Hz, 1 H, C-17 H), 5.50 (d, J = 8.9 Hz, 1 H, C-18 H), 6.32 (d, J = 7.9 Hz, 1 H, C-1 H), 6.40 (d, J = 7.9 Hz, 1 H, C-2 H); FTIR (neat) 3600–2700 (NH_2 and OH), 1630, 1606 cm^{-1}; FAB MS [M + H]$^+$ calcd for $C_{22}H_{29}N_2O_3$ 369.2175, found 369.2145.

6,14-*endo*-Etheno-7α-[1(*S*)-isothiocyanatoethyl]tetrahydrooripavine (10). To a mixture of amine **8** (47 mg, 0.13 mmol) and $NaHCO_3$ (65 mg, 0.78 mmol) in CH_2Cl_2 (1.0 mL) was added thiophosgene (40 μL, 0.52 mmol) dropwise. The mixture was stirred for 27 h, treated with 15% aqueous NH_4OH solution (20 mL), and extracted with CH_2Cl_2 (3 × 12 mL). The combined extracts were dried (Na_2SO_4) and the volatiles were evaporated. The residue was purified by flash chromatography (5 g of silica gel) eluting with 4% triethylamine–ether (120 mL) to give isothiocyanate **10** (45 mg, 84%) as a white powder: mp 223–226 °C; $[\alpha]^{20}_D$ = −124.5° (c = 1.00, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.16 (dd, J = 6.8 and 12.8 Hz, 1 H, C-8α H), 1.24 (d, J = 6.8 Hz, 3 H, C-20 CH_3), 1.75–1.9 (m, 2 H, C-7β H and C-15 H), 1.94 (dt, J = 5.6 and 12.2 Hz, 1 H, C-15 H), 2.40 (s, 3 H, NCH_3), 2.35–2.5 (m, 2 H, C-10α H, and C-16 H), 2.56 (dd, J = 4.3 and 11.7 Hz, 1 H, C-16 H), 2.86 (dd, J = 9.3 and 12.7 Hz, 1 H, C-8β H), 3.15–3.3 (m, 2 H, C-9H and C-10β H), 3.61 (s, 3 H, C-6 OCH_3), 4.25 (dq, J = 2.3 and 6.8 Hz, 1 H, C-19 H), 4.48 (s, 1 H, C-5 H), 5.53 (d, J = 8.8 Hz, 1 H, C-17 H), 5.85 (d, J = 8.8 Hz, 1 H, C-18 H), 6.49 (d, J = 8.1 Hz, 1 H, C-1 H), 6.60 (d, J = 8.0 Hz, 1 H, C-2 H); ^{13}C NMR ($CDCl_3$) δ 20.23, 22.40, 26.41, 33.27, 42.57, 42.69, 43.37, 45.53, 47.45, 51.22, 53.28, 59.92, 79.83, 95.94, 116.25, 119.73, 125.41, 127.25, 129.39, 133.45, 134.62, 137.30, 146.49; FTIR (neat) 3600–2500 (OH), 2141 (NCS), 1606 cm^{-1}; HREIMS calcd for $C_{23}H_{26}N_2O_3S$ 410.1664, found 410.1661. Anal. ($C_{23}H_{26}N_2O_3S$) C, H, N, S.

6,14-*endo*-Etheno-7α-[1(*R*)-isothiocyanatoethyl]tetrahydrooripavine (11). To a mixture of amine **9** (93 mg, 0.25 mmol) and $NaHCO_3$ (85 mg, 1.0 mmol) in CH_2Cl_2 (1.0 mL) was added thiophosgene (29 μL, 0.38 mmol) dropwise. The mixture was stirred for 80 min, treated with 15% aqueous NH_4OH solution (15 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried (Na_2SO_4) and the volatiles were evaporated. The residue was purified by flash chromatography (4 g of silica gel) eluting with ethyl acetate (50 mL) to give isothiocyanate **11** (90 mg, 87%) which crystallized (ether–hexanes): mp 189.5–190.5 °C; $[\alpha]^{20}_D$ = −97.5° (c = 1.00, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.14 (d, J = 6.6 Hz, 3 H, C-20 CH_3), 1.1–1.2 (m, 1 H, C-8α H), 1.8–1.9 (m, 1 H, C-15 H), 1.99 (dt, J = 5.6 and 12.2 Hz, 1 H, C-15 H), 2.38 (s, 3 H, NCH_3), 2.25–2.45 (m, 3 H, C-7β H, C-10α H, and C-16 H), 2.54 (dd, J = 4.8 and 12.2 Hz, 1 H, C-16 H), 2.90 (dd, J = 9.3 and 13.2 Hz, 1 H, C-8β H), 3.18 (m, 2 H, C-9 H and C-10β H), 3.57 (s, 3 H, C-6 OCH_3), 4.05–4.15 (m, 1 H, C-19 H), 4.58 (s, 1 H, C-5 H), 5.42 (d, J = 8.8 Hz, 1 H, C-17 H), 5.66 (d, J = 8.7 Hz, 1 H, C-18 H), 6.48 (d, J = 8.2 Hz, 1 H, C-1 H), 6.60 (d, J = 8.0 Hz, 1 H, C-2 H); ^{13}C NMR ($CDCl_3$) δ 18.25, 22.35, 27.03, 33.41, 40.62, 42.70, 43.44, 45.41, 47.62, 52.66, 53.61, 59.84, 80.12, 94.87, 116.20, 119.74, 126.39, 127.49, 129.52, 133.58, 135.39, 137.22, 146.39; FTIR (KBr) 3600–2300 (OH), 2108 (NCS), 1609 cm^{-1}; HREIMS calcd for $C_{23}H_{26}N_2O_3S$ 410.1664, found 410.1684. Anal. ($C_{23}H_{26}N_2O_3S$) C, H, N, S.

***N*-(Cyclopropylmethyl)northevinone (13).** A mixture of northevinone (**12**;[21] 880 mg, 2.4 mmol), $NaHCO_3$ (605 mg, 7.2 mmol), and cyclopropylmethyl bromide (0.29 mL, 2.5 mmol) in DMF (5 mL) was heated at 85 °C for 4 h and then cooled to room temperature. The mixture was treated with a 15% aqueous NH_4OH solution (30 mL) and extracted with CH_2Cl_2 (2 × 30 mL). The combined extracts were dried (Na_2SO_4) and the solvents were evaporated. The residue was purified by flash chromatography (140 g of silica gel) eluting with ethyl acetate (700 mL) to give tertiary amine **13** (870 mg, 86%) as a colorless, viscous oil: $[\alpha]^{20}_D$ = −145° (c = 0.67, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.1–0.2 (m, 2 H, cyclopropyl CH_2), 0.45–0.6 (m, 2 H, cyclopropyl CH_2), 0.8–0.9 (m, 1 H, cyclopropyl CH), 1.36 (dd, J = 5.8 and 11.9 Hz, 1 H, C-8α H), 1.8–1.9 (m, 1 H, C-15 H), 1.97 (dt, J = 11.7 and 5.3 Hz, 1 H, C-15 H), 2.14 (s, 3 H, C-20 CH_3), 2.3–2.5 (m, 4 H, NCH_2-cyclopropyl, C-10α H, and C-16 H), 2.65–2.75 (m, 1 H, C-16 H), 2.9–3.15 (m, 2 H, C-7β H and C-8β H), 3.11 (d, J = 18.4 Hz, 1 H, C-10β H), 3.55 (d, J = 6.4 Hz, 1 H, C-9 H), 3.60 (s, 3 H, C-6 OCH_3), 3.81 (s, 3 H, C-3 OCH_3), 4.58 (d, J = 1.4 Hz, 1 H, C-5 H), 5.58 (d, J = 8.8 Hz, 1 H, C-17 H), 5.89 (d, J = 8.8 Hz, 1 H, C-18 H), 6.51 (d, J = 8.2 Hz, 1 H, C-1 H), 6.62 (d, J = 8.2 Hz, 1 H, C-2 H); ^{13}C NMR ($CDCl_3$) δ 3.39, 4.12, 9.45, 23.16, 29.91, 30.45, 33.57, 43.06, 43.89, 48.07, 50.64, 53.40, 56.54, 56.93, 59.65, 81.17, 95.21, 113.34, 119.15, 125.63, 128.05, 134.03, 136.00, 141.55, 147.77, 208.91; FTIR (neat) 1699, 1629, 1598 cm^{-1}; HREIMS calcd for $C_{26}H_{31}NO_4$ 421.2253, found 421.2250.

6,14-*endo*-Etheno-7α-[1(*S*)-aminoethyl]-*N*-(cyclopropylmethyl)tetrahydronorthebaine (14) and 6,14-*endo*-Etheno-7α-[1(*R*)-aminoethyl]-*N*-(cyclopropylmethyl)tetrahydrothebaine (15). To a solution of ketone **13** (870 mg, 2.07 mmol)

in methanol (12 mL) was added 3-Å molecular sieves, NH_4OAc (1.6 g, 20.7 mmol), and $NaBH_3CN$ (260 mg, 4.14 mmol). The mixture was stirred for 4 days and then treated with a saturated aqueous NH_4Cl solution (10 mL), 15% aqueous NH_4OH solution (20 mL), and then with CH_2Cl_2 solution (30 mL). The mixture was stirred vigorously for 5 min and filtered through Celite under suction, and the solids were rinsed with CH_2Cl_2 (60 mL). The filtrates were combined and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried (Na_2SO_4) and the solvents were evaporated. The residue was purified by flash chromatography (150 g of silica gel) eluting with 2% triethylamine–30% methanol–ethyl acetate (1 L) and then with 2% triethylamine–40% methanol–ethyl acetate (500 mL) to give amine 14 (320 mg, 37%) as a viscous oil, $[\alpha]^{20}_D = -179.0°$ (c = 1.02, CH_2Cl_2), followed by amine 15 (360 mg, 41%) as a viscous oil, $[\alpha]^{20}_D = -160.5°$ (c = 1.00, CH_2Cl_2).

14: ^1H NMR ($CDCl_3$) δ 0.1–0.2 (m, 2 H, cyclopropyl CH_2), 0.45–0.6 (m, 2 H, cyclopropyl CH_2), 0.8–0.9 (m, 1 H, cyclopropyl CH), 1.00 (d, J = 6.7 Hz, 3 H, C-20 CH_3), 1.14 (dd, J = 7.4 and 12.8 Hz, 1 H, C-8α H), 1.5 (br s, movable, 2 H, NH_2), 1.75–1.95 (m, 2 H, C-7β H and C-15 H), 2.00 (dt, J = 5.4 and 12.5 Hz, 1 H, C-15 H), 2.25–2.45 (m, 4 H, NCH_2-cyclopropyl, C-10α H, and C-16 H), 2.69 (dd, J = 4.8 and 11.8 Hz, 1 H, C-16 H), 2.79 (dd, J = 9.3 and 12.7 Hz, 1 H, C-8β H), 3.10 (d, J = 18.6 Hz, 1 H, C-10β H), 3.37 (dq, J = 2.1 and 6.7 Hz, 1 H, C-19 H), 3.58 (d, J = 6.4 Hz, 1 H, C-9 H), 3.61 (s, 3 H, C-6 OCH_3), 3.81 (s, 3 H, C-3 OCH_3), 4.58 (s, 1 H, C-5 H), 5.43 (d, J = 8.7 Hz, 1 H, C-17 H), 5.77 (d, J = 8.8 Hz, 1 H, C-18 H), 6.50 (d, J = 8.0 Hz, 1 H, C-1 H), 6.61 (d, J = 8.1 Hz, 1 H, C-2 H); ^{13}C NMR ($CDCl_3$) δ 3.22, 4.35, 9.43, 21.10, 22.86, 25.38, 33.82, 41.93, 42.74, 44.13, 44.53, 48.11, 52.52, 56.40, 56.71, 59.73, 80.81, 94.78, 112.94, 118.92, 126.90, 128.18, 134.19, 135.23, 141.45, 148.02; FTIR (neat) 3700–3200 (NH_2), 1629, 1599 cm^{-1}; HREIMS calcd for $C_{26}H_{34}N_2O_3$ 422.2569, found 422.2568.

15: ^1H NMR ($CDCl_3$) δ 0.1–0.2 (m, 2 H, cyclopropyl CH_2), 0.45–0.6 (m, 2 H, cyclopropyl CH_2), 0.8–0.9 (m, 1 H, cyclopropyl CH), 0.93 (dd, J = 6.8 and 12.7 Hz, 1 H, C-8α H), 1.06 (d, J = 6.7 Hz, 3 H, C-20 CH_3), 1.8–1.9 (m, 1 H, C-15 H), 1.95–2.1 (m, 2 H, C-7β H and C-15 H), 2.3–2.45 (m, 4 H, NCH_2-cyclopropyl, C-10α H, and C-16 H), 2.71 (dd, J = 4.6 and 12.0 Hz, 1 H, C-16 H), 2.89 (dd, J = 9.2 and 12.7 Hz, 1 H, C-8β H), 3.09 (d, J = 19.0 Hz, 1 H, C-10β H), 3.10 (quintet, J = 6.6 Hz, 1 H, C-19 H), 3.49 (d, J = 6.3 Hz, 1 H, C-9 H), 3.66 (s, 3 H, C-6 OCH_3), 3.71 (br s, movable, 2 H, NH_2), 3.81 (s, 3 H, C-3 OCH_3), 4.60 (s, 1 H, C-5 H), 5.45 (d, J = 8.8 Hz, 1 H, C-17 H), 5.78 (d, J = 8.8 Hz, 1 H, C-18 H), 6.49 (d, J = 8.1 Hz, 1 H, C-1 H), 6.61 (d, J = 8.1 Hz, 1 H, C-2 H); ^{13}C NMR ($CDCl_3$) δ 3.50, 4.11, 9.44, 19.61, 22.92, 28.32, 33.57, 42.38, 43.92, 46.09, 47.56, 48.07, 53.32, 56.53, 57.08, 59.85, 82.25, 95.59, 113.23, 119.00, 126.23, 128.07, 134.34, 135.88, 141.52, 147.80; FTIR (neat) 3700–3200 (NH_2), 1629, 1599 cm^{-1}; HREIMS calcd for $C_{26}H_{34}N_2O_3$ 422.2569, found 422.2568.

6,14-*endo*-Etheno-7α-[1(*S*)-isothiocyanatoethyl]-*N*-(cyclopropylmethyl)tetrahydronorthebaine (16). To a mixture of amine 14 (98 mg, 0.23 mmol) and $NaHCO_3$ (77 mg, 0.92 mmol) in CH_2Cl_2 (1.0 mL) was added thiophosgene (26 μL, 0.34 mmol) dropwise. After the mixture was stirred for 1 h, it was treated with a 15% aqueous NH_4OH solution (15 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried (Na_2SO_4) and the volatiles were evaporated. The residue was purified by flash chromatography (5 g of silica gel) eluting with ethyl acetate (50 mL) to give isothiocyanate 16 (100 mg, 94%) as a viscous oil: $[\alpha]^{20}_D = -190.0°$ (c = 1.00, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.1–0.2 n, 2 H, cyclopropyl CH_2), 0.5–0.65 (m, 2 H, cyclopropyl CH_2), 0.8–0.95 (m, 1 H, cyclopropyl CH), 1.14 (dd, J = 6.9 and 13.1 Hz, 1 H, C-8α H), 1.29 (d, J = 6.8 Hz, 3 H, C-20 CH_3), 1.75–1.9 (m, 2 H, C-7β H and C-15 H), 1.94 (dt, J = 4.9 and 12.3 Hz, 1 H, C-15 H), 2.3–2.5 (m, 4 H, NCH_2-cyclopropyl, C-10α H, and C-16 H), 2.65–2.75 (m, 1 H, C-16 H), 2.92 (dd, J = 9.3 and 12.7 Hz, 1 H, C-8β H), 3.10 (d, J = 18.6 Hz, 1 H, C-10β H), 3.59 (d, J = 6.4 Hz, 1 H, C-9 H), 3.66 (s, 3 H, C-6 OCH_3), 3.82 (s, 3 H, C-3 OCH_3), 4.32 (dq, J = 2.3 and 6.8 Hz, 1 H, C-19 H), 4.45 (s, 1 H, C-5 H), 5.55 (d, J = 8.8 Hz, 1 H, C-17 H), 5.91 (d, J = 8.8 Hz, 1 H, C-18 H), 6.51 (d, J = 8.1 Hz, 1 H, C-1 H), 6.62 (d, J = 8.1 Hz, 1 H, C-2 H); ^{13}C NMR ($CDCl_3$) δ 3.39, 4.33, 9.42, 20.23, 22.90, 26.43, 33.58, 42.53, 42.83, 44.06, 47.87, 51.29, 53.71, 56.54, 56.83, 59.82, 79.76, 96.41, 113.27, 119.15, 125.46, 128.14, 129.00, 133.97, 134.92, 141.56, 147.91; FTIR (neat) 2141 (NCS), 1629 cm^{-1}; FAB MS [M + H]$^+$ calcd for $C_{27}H_{33}N_2O_3S$ 465.2209, found 465.2196. Anal. ($C_{27}H_{32}N_2O_3S$) C, H, N, S.

6,14-*endo*-Etheno-7α-[1(*R*)-isothiocyanatoethyl]-*N*-(cyclopropylmethyl)tetrahydronorthebaine (17). To a mixture of amine 15 (97 mg, 0.23 mmol) and $NaHCO_3$ (77 mg, 0.92 mmol) in CH_2Cl_2 (1.0 mL) was added thiophosgene (26 μL, 0.34 mmol) dropwise. The mixture was then stirred for 1 h, treated with 15% aqueous NH_4OH solution (15 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried (Na_2SO_4) and the volatiles were evaporated. The residue was purified by flash chromatography (6 g of silica gel) eluting with ethyl acetate (50 mL) to give isothiocyanate 17 (100 mg, 94%) which crystallized (ether): mp 127–128 °C; $[\alpha]^{20}_D = -105°$ (c = 1.00, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.1–0.2 (m, 2 H, cyclopropyl CH_2), 0.5–0.65 (m, 2 H, cyclopropyl CH_2), 0.8–0.95 (m, 1 H, cyclopropyl CH), 1.1–1.2 (m, 1 H, C-8α H), 1.15 (d, J = 6.7 Hz, 3 H, C-20 CH_3), 1.8–1.9 (m, 1 H, C-15 H), 1.99 (dt, J = 5.4 and 12.3 Hz, 1 H, C-15 H), 2.3–2.5 (m, 4 H, NCH_2-cyclopropyl, C-10α H, and C-16 H), 2.74 (dd, J = 4.7 and 11.8 Hz, 1 H, C-16 H), 2.98 (dd, J = 10 and 12.8 Hz, 1 H, C-8β H), 3.11 (d, J = 18.5 Hz, 1 H, C-10β H), 3.55 (d, J = 6.7 Hz, 1 H, C-9 H), 3.60 (s, 3 H, C-6 OCH_3), 3.81 (s, 3 H, C-3 OCH_3), 4.05–4.15 (m, 1 H, C-19 H), 4.55 (s, 1 H, C-5 H), 5.44 (d, J = 8.8 Hz, 1 H, C-17 H), 5.71 (d, J = 8.8 Hz, 1 H, C-18 H), 6.50 (d, J = 8.0 Hz, 1 H, C-1 H), 6.61 (d, J = 8.1 Hz, 1 H, C-2 H); ^{13}C NMR ($CDCl_3$) δ 3.50, 4.20, 9.43, 18.12, 22.98, 26.94, 33.68, 40.95, 42.53, 43.87, 48.03, 53.00, 53.77, 56.51, 56.88, 59.80, 80.06, 95.18, 113.22, 119.14, 126.48, 128.04, 129.74, 134.00, 135.49, 141.52, 147.83. FTIR (KBr) 2105 (NCS), 1629, 1598 cm^{-1}; MS [M + H]$^+$ calcd for $C_{27}H_{33}N_2O_3S$ 465.2209, found 465.2196. Anal. ($C_{27}H_{32}N_2O_3S$) C, H, N, S.

6,14-*endo*-Etheno-7α-[1(*S*)-aminoethyl]-*N*-(cyclopropylmethyl)tetrahydronororipavine (18). A mixture of amine 14 (200 mg, 0.47 mmol), KOH (1.33 g, 23.7 mmol), and diethylene glycol (3 mL) was heated at 210 °C on an oil bath for 140 min. The mixture was cooled to room temperature, treated with a 1 M aqueous H_3PO_4 solution (30 mL), mixed thoroughly, and then extracted with ether (30 mL). The aqueous phase was made alkaline by the addition of a 30% aqueous NH_4OH solution (30 mL) and extracted with 25% ethanol–CH_2Cl_2 (4 × 25 mL). The combined organic phases were dried ($MgSO_4$) and the solvents were evaporated. The residue was triturated with ether (5 × 5 mL) to give phenol 18 (160 mg, 83%) as a beige powder: mp 230–240 °C dec; ^1H NMR ($CDCl_3$) δ 0.1–0.2 (m, 2 H, cyclopropyl CH_2), 0.45–0.6 (m, 2 H, cyclopropyl CH_2), 0.8–0.95 (m, 1 H, cyclopropyl CH), 1.03 (d, J = 6.5 Hz, 3 H, C-20 CH_3), 1.10 (dd, J = 7.4 and 12.8 Hz, m, 1 H, C-8α H), 1.8–1.95 (m, 2 H, C-7β H and C-15 H), 1.98 (dt, J = 5.5 and 12.6 Hz, 1 H C-15 H), 2.25–2.5 (m, 4 H, NCH_2-cyclopropyl, C-10α H, and C-16 H), 2.7 (br s, movable, 3 H, NH_2 and OH), 2.70 (dd, J = 5.4 and 12.4 Hz, 1 H, C-16 H), 2.81 (dd, J = 8.5 and 13.0 Hz, 1 H, C-8β H), 3.07 (d, J = 18.6 Hz, 1 H, C-10β H), 3.3–3.4 (m, 1 H, C-19 H), 3.55 (d, J = 6.9 Hz, 1 H, C-9 H), 3.58 (s, 3 H, C-6 OCH_3), 4.57 (s, 1 H, C-5 H), 5.41 (d, J = 8.8 Hz, 1 H, C-17 H), 5.71 (d, J = 8.8 Hz, 1 H, C-18 H), 6.43 (d, J = 7.8 Hz, 1 H, C-1 H), 6.58 (d, J = 7.8 Hz, 1 H, C-2 H); FTIR (KBr) 3700–2200 (NH_2 and OH), 1623, 1599 cm^{-1}; HREIMS calcd for $C_{25}H_{32}N_2O_3$ 408.2413, found 408.2410.

6,14-*endo*-Etheno-7α-[1(*R*)-aminoethyl]-*N*-(cyclopropylmethyl)tetrahydronororipavine (19). A mixture of amine 15 (200 mg, 0.47 mmol), KOH (1.33 g, 23.7 mmol), and diethylene glycol (3 mL) was heated at 210 °C on an oil bath for 140 min. The mixture was cooled to room temperature, treated with a 1 M aqueous H_3PO_4 solution (30 mL), mixed thoroughly, and then extracted with ether (30 mL). The aqueous phase was made alkaline by the addition of a 30% aqueous NH_4OH solution (30 mL) and extracted with CH_2Cl_2 (4 × 20 mL). The combined organic phases were washed with water (2 × 15 mL) and dried (Na_2SO_4), and the solvents were evapd. to give phenol 19 (190 mg, 99%) which was crystallized (CH_2Cl_2–hexanes) as a white powder: mp 120–127 °C; ^1H NMR ($CDCl_3$) δ 0.05–0.2 (m, 2 H, cyclopropyl CH_2), 0.45–0.6 (m, 2 H, cyclopropyl CH_2), 0.75–1.0 (m, 2 H, cyclopropyl CH and C-8α H), 0.96 (d, J = 6.2 Hz, 3 H, C-20 CH_3), 1.75–1.85 (m, 1 H, C-15 H), 1.9–2.05 (m, 2 H, C-7β and C-15 H), 2.25–2.45 (m, 4 H, NCH_2-cyclopropyl, C-10α H, and C-16 H), 2.65–2.75 (m, 1 H, C-16 H), 2.84 (dd, J = 9.4 and 12.2 Hz, 1 H, C-8β H), 3.0–3.1 (m, 2 H, C-10β and C-19 H), 3.48 (d,

Table II. Irreversibility of Opioid Receptor Binding and Protection by Naloxone

drug (concn)	% recovery of 0.5 nM [^{3}H]bremazocine binding[a]		
	unwashed	washed	protected
naloxone (1 μM)	0	98	
20 (4.4 nM)[b]	23	51	52
21 (6 nM)	16	28	44
10 (61 nM)	38	66	66
37 (5 nM)	13	53	90
37 (1 nM) against [^{3}H]DAGO (1 nM)	10	47	100

[a] Values are averages of duplicate determinations (±10–15%). [b] The concentrations of displacing ligands are chosen to approximate a 70–85% decrease in binding of [^{3}H]bremazocine (see Table I).

J = 6.9 Hz, 1 H, C-9 H), 3.59 (s, 3 H, C-6 OCH_3), 4.45 (br s, movable, 3 H, NH_2 and OH), 4.55 (s, 1 H, C-5 H), 5.40 (d, J = 8.8 Hz, 1 H, C-17 H), 5.69 (d, J = 8.8 Hz, 1 H, C-18 H), 6.42 (d, J = 7.9 Hz, 1 H, C-1 H), 6.57 (d, J = 8.1 Hz, 1 H), C-2 H); ^{13}C NMR ($CDCl_3$) δ 3.47, 4.16, 9.43, 20.11, 22.94, 28.13, 33.61, 42.34, 42.50, 44.08, 47.58, 47.65, 52.54, 57.16, 59.84, 82.07, 94.47, 117.06, 119.43, 126.24, 126.54, 133.95, 135.44, 138.50, 146.94; FTIR (KBr) 3700–2300 (NH_2 and OH), 1628, 1602 cm^{-1}; HREIMS calcd for $C_{25}H_{32}N_2O_3$ 408.2413, found 408.2410.

6,14-*endo*-Etheno-7α-[1(*S*)-isothiocyanatoethyl]-*N*-(cyclopropylmethyl)tetrahydronororipavine (20). To a mixture of amine **18** (81 mg, 0.20 mmol) and $NaHCO_3$ (67 mg, 0.80 mmol) in CH_2Cl_2 (1.5 mL) was aded thiophosgene (23 μL, 0.30 mmol) dropwise. The mixture was stirred for 18 h, another portion of thiophosgene (23 μL, 0.30 mmol) was added dropwise, and the mixture was stirred for 1 h. The mixture was treated with a 15% aqueous NH_4OH solution (15 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried (Na_2SO_4) and the volatiles were evaporated. The residue was purified by flash chromatography (18 g of silica gel) eluting with 4% triethylamine–25% hexanes–ether (500 mL) to give isothiocyanate **20** (60 mg, 67%) as a white form: $[\alpha]^{20}_D$ = −188° (c = 1.00, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.1–0.2 (m, 2 H, cyclopropyl CH_2), 0.5–0.6 (m, 2 H, cyclopropyl CH_2), 0.8–0.9 (m, 1 H, cyclopropyl CH), 1.14 (dd, J = 6.8 and 12.7 Hz, 1 H, C-8α H), 1.29 (d, J = 6.8 Hz, 3 H, C-20 CH_3), 1.75–1.9 (m, 2 H, C-7β H and C-15 H), 1.94 (dt, J = 5.4 and 12.5 Hz, 1 H, C-15 H), 2.3–2.5 (m, 4 H, NCH_2-cyclopropyl, C-10α H, and C-16H), 2.71 (dd, J = 4.2 and 11.9 Hz, 1 H, C-16 H), 2.92 (dd, J = 9.1 and 12.7 Hz, 1 H, C-8β H), 3.09 (d, J = 18.6 Hz, 1 H, C-10β H), 3.58 (d, J = 6.3 Hz, 1 H, C-9 H), 3.63 (s, 3 H, C-6 OCH_3), 4.29 (dq, J = 2.3 and 6.8 Hz, 1 H, C-19 H), 4.48 (s, 1 H, C-5 H), 5.5 (br s, movable, 1 H, OH), 5.54 (d, J = 8.8 Hz, 1 H, C-17 H), 5.86 (d, J = 8.5 Hz, 1 H, C-18 H), 6.47 (d, J = 8.2 Hz, 1 H, C-1 H), 6.60 (d, J = 7.9 Hz, 1 H, C-2 H); ^{13}C NMR ($CDCl_3$) δ 3.43, 4.31, 9.34, 20.24, 22.96, 26.42, 33.46, 42.43, 42.61, 44.08, 48.10, 51.28, 53.25, 56.89, 59.82, 79.91, 95.89, 116.32, 119.65, 125.26, 127.39, 129.18, 133.74, 134.98, 137.41, 146.52; FTIR (KBr) 3650–2500 (OH), 2139 (NCS), 1633, 1608 cm^{-1}; HREIMS calcd for $C_{26}H_{30}N_2O_3S$ 450.1977, found 450.1974. Anal. ($C_{26}H_{30}N_2O_3S$) C, H, N, S.

6,14-*endo*-Etheno-7α-[1(*R*)-isothiocyanatoethyl]-*N*-(cyclopropylmethyl)tetrahydronororipavine (21). To a mixture of amine **19** (100 mg, 0.24 mmol) and $NaHCO_3$ (62 mg, 0.73 mmol) in CH_2Cl_2 (1.5 mL) was added thiophosgene (21 μL, 0.27 mmol) dropwise. The mixture was stirred for 30 min, treated with 15% aqueous NH_4OH solution (15 mL), and extracted with CH_2Cl_2 (3 × 15 mL). The combined extracts were dried (Na_2SO_4) and the volatiles were evaporated. The residue was purified by flash chromatography (18 g of silica gel) eluting with 4% triethylamine–25% hexanes–ether (500 mL) followed by preparative TLC eluting with 4% triethylamine–45% hexanes–ether. After the solvents were evaporated, the residue was warmed in ether (50 mL) and decanted from the insoluble material. The ether was evaporated to give isothiocyanate **21** (30 mg, 28%) as a white powder: mp 208–214 °C dec; $[\alpha]^{20}_D$ = −81° (c = 1.00, THF); ^{1}H NMR ($CDCl_3$) δ 0.1–0.2 (m, 2 H, cyclopropyl CH_2), 0.5–0.6 (m, 2 H, cyclopropyl CH_2), 0.8–0.95 (m, 1 H, cyclopropyl CH), 1.1–1.2 (m, 1 H, C-8α H), 1.15 (d, J = 6.7 Hz, 3 H, C-20 CH_3), 1.8–1.9 (m, 1 H, C-15 H), 1.98 (dt, J = 5.6 and 12.6 Hz, 1 H, C-15 H), 2.3–2.45 (m, 5 H, NCH_2-cyclopropyl, C-7β H, C-10α H, and C-16 H), 2.73 (dd, J = 4.6 and 11.8 Hz, 1 H, C-16 H), 2.97 (dd, J = 9.4 and 13.2 Hz, 1 H, C-8β H), 3.09 (d, J = 18.2 Hz, 1 H, C-10β H), 3.53 (d, J = 6.3 Hz, 1 H, C-9 H), 3.58 (s, 3 H, C-6 OCH_3), 4.05–4.15 (m, 1 H, C-19 H), 4.3 (br s, movable, 1 H, OH), 4.58 (s, 1 H, C-5 H), 5.43 (d, J = 8.7 Hz, 1 H, C-17 H), 5.65 (d, J = 8.7 Hz, 1 H, C-18 H), 6.44 (d, J = 7.9 Hz, 1 H, C-1 H), 6.56 (d, J = 8.1 Hz, 1 H, C-2 H); ^{13}C NMR (CDCl) δ 3.51, 4.17, 9.46, 18.18, 23.07, 26.99, 33.62, 40.78, 42.64, 43.89, 48.35, 52.74, 53.75, 56.96, 59.83, 80.19, 95.13, 116.14, 119.66, 126.22, 127.52, 129.92, 133.82, 135.68, 137.30, 146.47; FTIR (KBr) 3500–2500 (OH), 2063 (NCS), 1622, 1596 cm^{-1}; HREIMS calcd for $C_{26}H_{30}N_2O_3S$ 450.1977, found 450.1980. Anal. ($C_{26}H_{30}N_2O_3S·H_2O$) C, H, N, S.

3-*O*-(*tert*-Butyldimethylsilyl)heterocodeine (23). To a suspension of heterocodeine (**22**;[22] 2.0 g, 6.7 mmol) in CH_2Cl_2 (20 mL) was added *tert*-butyldimethylsilyl chloride (3.03 g, 20.1 mmol) and diisopropylethylamine (4.67 mL, 26.8 mmol). The solution was stirred for 48 h, washed with saturated aqueous K_2CO_3 solution (25 mL), dried (Na_2SO_4), and filtered through a 1-in. pad of silica gel under suction. The solids were rinsed with 10% methanol–CH_2Cl_2 (100 mL) and the combined filtrates were evaporated. The residue was crystallized (methanol) to give silyl ether **23** (2.45 g, 88%): mp 143–144 °C; $[\alpha]^{20}_D$ = −167.5° (c = 1.00, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.13 (s, 3 H, $SiCH_3$), 0.20 (s, 3 H, $SiCH_3$), 0.98 [s, 9 H, $SiC(CH_3)_3$], 1.85–1.95 (m, 1 H, C-15 H), 2.02 (dt, J = 5.2 and 12.3 Hz, 1 H, C-15 H), 2.29 (dd, J = 6.3 and 18.5 Hz, 1 H, C-10α H), 2.35–2.5 (m, 1 H, C-16 H), 2.43 (s, 3 H, NCH_3), 2.57 (dd, J = 5 and 12.2 Hz, 1 H, C-16 H), 2.64 (t, J = 2.7 Hz, 1 H, C-14 H), 3.02 (d, J = 18.6 Hz, 1 H, C-10β H), 3.3–3.4 (m, 1 H, C-9 H), 3.50 (s, 3 H, C-6 OCH_3), 3.75–3.85 (m, 1 H, C-6 H), 4.96 (d, J = 5.8 Hz, 1 H, C-5 H), 5.29 (dt, J = 9.8 and 2.7 Hz, 1 H, C-8 H), 5.64 (d, J = 9.9 Hz, 1 H, C-7 H), 6.42 (d, J = 8.0 Hz, 1 H, C-1 H), 6.56 (d, J = 8.1 Hz, 1 H, C-2 H); ^{13}C NMR ($CDCl_3$) δ −4.92, −4.72, 18.26, 20.54, 25.66 (3 C, *t*-Bu), 36.07, 41.18, 43.05, 43.41, 46.43, 56.18, 58.82, 75.77, 88.51, 118.52, 121.03, 127.25, 128.41, 130.59, 130.79, 136.96, 149.31; FTIR (KBr) 1635, 1603 cm^{-1}; HREIMS calcd for $C_{24}H_{35}NO_3Si$ 413.2386, found 413.2386.

3-*O*-(*tert*-Butyldimethylsilyl)oripavine (24). To a solution of allylic ether **23** (1.75 g, 4.23 mmol) in THF (150 mL) was added γ-MnO_2[23] (9.2 g, 106 mmol) in 5 portions over 4 h and then the mixture was stirred for an additional 17 h. The mixture was filtered through a pad of Celite on a fine-fritted funnel under suction, and the solids were rinsed with THF (200 mL) followed by methanol (100 mL). The combined filtrates were evaporated, and the residue was dissolved in CH_2Cl_2 (50 mL), washed with water (50 mL), and dried (Na_2SO_4), and then the solvent was evaporated. The residue was purified by flash chromatography (100 g of silica gel) eluting with 15% methanol–CH_2Cl_2 (1 L) to give dienol ether **24** (620 mg, 36%) as a viscous oil: $[\alpha]^{20}_D$ = −153.5° (c = 1.00, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.13 (s, 3 H, $SiCH_3$), 0.20 (s, 3 H, $SiCH_3$), 0.97 [s, 9 H, $SiC(CH_3)_3$], 1.7–1.8 (m, 1 H, C-15 H), 2.20 (dt, J = 5.2 and 12.6 Hz, 1 H, C-15 H), 2.49 (s, 3 H, NCH_3), 2.6–2.8 (m, 2 H, C-10α H and C-16 H), 2.87 (dt, J = 3.7 and 12.8 Hz, 1 H, C-16 H), 3.33 (d, J = 18.1 Hz, 1 H, C-10β H), 3.57 (s, 3 H, C-6 OCH_3), 3.65 (d, J = 7.1 Hz, 1 H, C-9 H), 5.00 (d, J = 6.5 Hz, 1 H, C-8 H), 5.23 (s, 1 H, C-5 H), 5.56 (d, J = 6.5 Hz, 1 H, C-7 H), 6.50 (d, J = 8.1 Hz, 1 H, C-1 H), 6.58 (d, J = 8.1 Hz, 1 H, C-2 H); ^{13}C NMR ($CDCl_3$) δ −4.88, −4.67, 18.30, 25.66 (3 C, *t*-Bu), 29.96, 36.20, 42.05, 45.90, 45.96, 54.58, 60.90, 88.36, 95.54, 112.04, 119.07, 120.95, 127.53, 131.27, 133.14, 137.61, 146.37, 152.67; FTIR (neat) 1607 cm^{-1}; HREIMS calcd for $C_{24}H_{33}NO_3Si$ 411.2229, found 411.2231.

3-*O*-(*tert*-Butyldimethylsilyl)-6,14-*endo*-etheno-7α-acetyltetrahydrooripavine (25). A solution of dienol ether **23** (205 mg, 0.5 mmol) in methyl vinyl ketone (1.5 mL, 18 mmol) was heated at 80–90 °C for 150 min. The remaining methyl vinyl ketone was removed by distillation under aspirator vacuum. The residue was purified by flash chromatography (50 g of silica gel) eluting with 4% methanol–CH_2Cl_2 (300 mL) to give ketone **25** (190 mg, 79%) as a white foam: $[\alpha]^{20}_D$ = −194.5° (c = 1.00, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.14 (s, 3 H, $SiCH_3$), 0.15 (s, 3 H, $SiCH_3$), 0.96 [s, 9 H, $SiC(CH_3)_3$], 1.36 (dd, J = 10.7 and 16.7 Hz, 1 H, C-8α H), 1.8–1.9 (m, 1 H, C-15 H), 1.95 (dt, J = 5.9 and 12.1 Hz, 1 H, C-15 H), 2.12 (s, 3 H, C-20 CH_3), 2.35 (s, 3 H, NCH_3), 2.35–2.45 (m, 2 H, C-10α H and C-16 H), 2.50 (dd, J = 4.8 and

12.1 Hz, 1 H, C-16 H), 2.85–2.95 (m, 2 H, C-7β H and C-8β H), 3.15–3.25 (m, 2 H, C-9 H and C-10β H), 3.58 (s, 3 H, C-6 OCH_3), 4.54 (d, J = 1.4 Hz, 1 H, C-5 H), 5.55 (d, J = 8.8 Hz, 1 H, C-17 H), 5.83 (d, J = 8.8 Hz, 1 H, C-18 H), 6.45 (d, J = 8.2 Hz, 1 H, C-1 H), 6.54 (d, J = 8.1 Hz, 1 H, C-2 H); ^{13}C NMR ($CDCl_3$) δ −4.65, −4.55, 18.20, 22.49, 25.57 (3 C, *t*-Bu), 29.84, 30.25, 33.41, 43.05, 43.41, 45.41, 47.44, 50.45, 53.01, 59.85, 81.05, 94.20, 119.20, 120.93, 125.99, 128.36, 133.88, 135.956, 136.56, 149.72, 208.60; FTIR (neat) 1702, 1625, 1599 cm^{-1}; HREIMS calcd for $C_{28}H_{39}NO_4Si$ 481.2648, found 481.2661.

3-*O*-(*tert*-Butyldimethylsilyl)-6,14-*endo*-etheno-7α-formyltetrahydrooripavine (27). A solution of dienol ether **24** (206 mg, 0.5 mmol) and acrolein (0.25 mL, 3.7 mmol) in benzene (1 mL) was heated at 60 °C for 6 h, and then the volatiles were evaporated. The residue was purified by flash chromatography (50 g of silica gel) eluting with 5% methanol–CH_2Cl_2 (300 mL) to give aldehyde **27** (190 mg, 81%) as white crystals: mp 189–190 °C; $[\alpha]^{20}_D$ = −193° (c = 1.00, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.15 (s, 3 H, $SiCH_3$), 0.16 (s, 3 H, $SiCH_3$), 0.97 [s, 9 H, $SiC(CH_3)_3$], 1.45 (dd, J = 5.3 and 13.1 Hz, 1 H, C-8α H), 1.8–1.9 (m, 1 H, C-15 H), 1.98 (dt, J = 5.8 and 12 Hz, 1 H, C-15 H), 2.36 (s, 3 H, NCH_3), 2.3–2.5 (m, 2 H, C-10α H and C-16 H), 2.52 (dd, J = 5.6 and 12 Hz, 1 H, C-16 H), 2.7–2.8 (m, 1 H, C-7β H), 2.89 (dd, J = 9.5 and 12.9 Hz, 1 H, C-8β H), 3.15–3.25 (m, 2 H, C-9 H and C-10β H), 3.59 (s, 3 H, C-6 OCH_3), 4.59 (s, 1 H, C-5 H), 5.55 (d, J = 8.8 Hz, 1 H, C-17 H), 5.82 (d, J = 8.8 Hz, 1 H, C-18 H), 6.45 (d, J = 8.2 Hz, 1 H, C-1 H), 6.55 (d, J = 8.1 Hz, 1 H, C-2 H), 9.40 (d, J = 3.9 Hz, 1 H, CHO); ^{13}C NMR ($CDCl_3$) δ −4.64, −4.57, 18.20, 22.50, 25.58 (3 C, *t*-Bu), 26.61, 33.20, 42.82, 43.40, 45.37, 47.31, 49.67, 52.31, 59.90, 80.68, 92.77, 119.34, 121.06, 126.47, 128.31, 133.65, 136.70, 136.83, 149.64, 201.38; IR (KBr) 1730, 1625, 1600 cm^{-1}; HREIMS calcd for $C_{27}H_{37}NO_4Si$ 467.2492, found 467.2491.

3-*O*-(*tert*-Butyldimethylsilyl)-6,14-*endo*-etheno-7α-(3-carboxy-3-*n*-butenyl)tetrahydrooripavine γ-Lactone (28). To a solution of aldehyde **27** (230 mg, 0.49 mmol) in THF (2 mL) was added activated zinc (48 mg, 0.74 mg-atom). The mixture was heated at 50 °C while a solution of methyl α-(bromomethyl)acrylate[24] (105 mg, 0.59 mmol) in THF (0.5 mL) was added over 1 min. The mixture was stirred at 50 °C for 6 h, and then the THF was evaporated. The residue was purified by flash chromatography (25 g silica gel) eluting with 4% methanol–CH_2Cl_2 (300 mL) to give α-methylene-γ-lactone **28** (220 mg, 84%) as a white powder: $[\alpha]^{20}_D$ = −89.5° (c = 1.00, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.15 [s, 6 H, $Si(CH_3)_2$], 0.97 [s, 9 H, $SiC(CH_3)_3$], 1.09 (dd, J = 6.8 and 12.7 Hz, 1 H, C-8α H), 1.8–1.9 (m, 1 H, C-15 H), 1.9–2.1 (m, 2 H, C-7β H and C-15 H), 2.36 (s, 3 H, NCH_3), 2.3–2.55 (m, 3 H, C-10α H and C-15 CH_2), 2.65–2.8 (m, 1 H, lactone β-CH), 2.84 (dd, J = 9.3 and 12.6 Hz, 1 H, C-8β H), 3.01 (ddt, J = 7.9, 17.5, and 2.3 Hz, 1 H, lactone β-CH), 3.1–3.25 (m, 2 H, C-9 H and C-10β H), 3.63 (s, 3 H, C-6 OCH_3), 4.47 (s, 1 H, C-5 H), 4.7–4.8 (m, 1 H, C-19 H), 5.44 (d, J = 8.8 Hz, 1 H, C-17 H), 5.57 (t, J = 2.3 Hz, 1 H, vinylic H), 5.84 (d, J = 8.8 Hz, 1 H, C-18 H), 6.16 (t, J = 2.7 Hz, 1 H, vinylic H), 6.44 (d, J = 7.8 Hz, 1 H, C-1 H), 6.54 (d, J = 8.0 Hz, 1 H, C-2 H); ^{13}C NMR ($CDCl_3$) δ −4.66, −4.52, 18.21, 22.32, 25.59, 26.59 (3 C, *t*-Bu), 32.60, 33.52, 42.30, 42.36, 43.44, 45.48, 47.02, 53.38, 59.89, 76.07, 80.21, 95.64, 119.19, 120.87, 121.16, 126.18, 128.44, 134.02, 134.70, 135.03, 136.56, 149.86, 170.12; FTIR (neat) 1764, 1665, 1625, 1600 cm^{-1}; HREIMS calcd for $C_{31}H_{41}NO_5Si$ 535.2754, found 535.2749.

6,14-*endo*-Etheno-7α-(3-carboxy-3-*n*-butenyl)tetrahydrooripavine γ-Lactone (29). To a solution of α-methylene-γ-lactone **28** (90 mg, 0.17 mmol) in THF (1 mL) was added a 1 M solution of *n*-Bu_4NF in THF (0.20 mL). After stirring for 60 min, the solution was treated with saturated aqueous $NaHCO_3$ solution (15 mL) and extracted with CH_2Cl_2 (3 × 9 mL). The combined extracts were dried (Na_2SO_4) and the solvents were evaporated. The residue was purified by flash chromatography (6 g of silica gel) eluting with 4% triethylamine–20% hexanes–CH_2Cl_2 (125 mL) to give α-methylene-γ-lactone **29** (66 mg, 92%) as a white foam: $[\alpha]^{20}_D$ = −98° (c = 1.00, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.06 (dd, J = 6.8 and 12.8 Hz, 1 H, C-8α H), 1.8–1.9 (m, 1 H, C-15 H), 1.9–2.1 (m, 2 H, C-7β H and C-15 H), 2.37 (s, 3 H, NCH_3), 2.3–2.5 (m, 2 H, C-10α and C-16 H), 2.54 (dd, J = 4.1 and 12.1 Hz, 1 H, C-16 H), 2.6–2.75 (m, 1 H, lactone β-CH), 2.84 (dd, J = 9.3 and 12.7 Hz, 1 H, C-8β H), 2.99 (ddt, J = 7.9, 17.4, and 2.4 Hz, 1 H, lactone β-CH), 3.1–3.25 (m, 2 H, C-9 H and C-10β H), 3.62 (s, 3 H, C-6 OCH_3), 4.50 (s, 1 H, C-5 H), 4.75–4.85 (m, 1 H, C-19 H), 5.37 (d, J = 8.9 Hz, 1 H, C-17 H), 5.57 (t, J = 2.4 Hz, 1 H, vinylic H), 5.83 (d, J = 8.8 Hz, 1 H, C-18 H), 6.17 (t, J = 2.8 Hz, 1 H, vinylic H), 6.46 (d, J = 8.2 Hz, 1 H, C-1 H), 6.59 (d, J = 8.0 Hz, 1 H, C-2 H); ^{13}C NMR ($CDCl_3$) δ 22.29, 26.25, 32.27, 33.45, 42.04, 42.40, 43.40, 45.60, 47.11, 53.34, 59.92, 75.65, 80.23, 95.79, 116.72, 119.45, 121.36, 125.87, 126.69, 133.50, 134.54, 134.99, 138.08, 146.78, 170.33; FTIR (neat) 3700–2500 (OH), 1758, 1664, 1636, 1500 cm^{-1}; HREIMS calcd for $C_{25}H_{27}NO_5$ 421.1889, found 421.1877. Anal. ($C_{25}H_{27}NO_5 \cdot 0.25H_2O$) C, H, N.

Norheterocodeine (31). A solution of 3-*O*-acetylheterocodeine (**30**;[22] 1.07 g, 3.14 mmol) in 1-chloroethyl chloroformate (1.7 mL, 15.7 mmol) was heated at 80 °C for 20 h, and then the volatiles were evaporated. The residue was dissolved in methanol (10 mL) and heated at 60 °C for 1 h, and then volatiles were evaporated. The residue was treated with saturated aqueous $NaHCO_3$ solution (20 mL) and extracted with 25% isopropanol–CH_2Cl_2 (3 × 25 mL). The combined extracts were dried ($MgSO_4$) and the solvents were evaporated. The residue was triturated with ether (2 × 15 mL) to give norheterocodeine (**31**; 800 mg, 89%) as a beige powder which decomposed above 200 °C: ^1H NMR (DMSO-d_6) δ 1.6–1.7 (m, 1 H, C-15 H), 1.8–1.95 (m, 1 H, C-15 H), 2.3–2.8 (m, 5 H, C-10 CH_2, C-14 H, and C-16 CH_2), 3.37 (s, 3 H, C-6 OCH_3), 3.4–4.3 (m, 4 H, C-6 H, C-9 H, NH, and OH), 4.89 (d, J = 5.4 Hz, 1 H, C-5 H), 5.26 (d, J = 9.8 Hz, 1 H, C-8 H), 5.57 (d, J = 9.8 Hz, 1 H, C-7 H), 6.32 (d, J = 7.8 Hz, 1 H, C-1 H), 6.44 (d, J = 8.1 Hz, 1 H, C-2 H); FTIR (KBr) 3700–2500 (NH and OH), 1654, 1636 cm^{-1}; HREIMS calcd for $C_{17}H_{19}NO_3$ 285.1365, found 285.1360.

***N*-(Cyclopropylmethyl)norheterocodeine (32).** To a solution of norheterocodeine (**31**; 390 mg, 1.37 mmol) and cyclopropylmethyl bromide (0.16 mL, 1.64 mmol) in DMF (2 mL) was added $NaHCO_3$ (345 mg, 4.11 mmol). After heating at 90 °C for 7 h, the volatiles were evaporated and the residue was treated with half-saturated aqueous $NaHCO_3$ solution (25 mL). The mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined extracts were dried (Na_2SO_4) and the solvents were evaporated. The residue was purified by flash chromatography (25 g of silica gel) eluting with 4% triethylamine–CH_2Cl_2 (500 mL) to give an oil which was triturated with ether (2 × 5 mL) and then crystallized (CH_2Cl_2–ether) to give tertiary amine **32** (360 mg, 78%): mp 181–184 °C; $[\alpha]^{20}_D$ = −158.5° (c = 1.00, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.1–0.2 (m, 2 H, cyclopropyl CH_2), 0.5–0.6 (m, 2 H, cyclopropyl CH_2), 0.85–1.0 (m, 1 H, cyclopropyl CH), 1.8–1.9 (m, 1 H, C-15 H), 2.09 (dt, J = 4.7 and 12.4 Hz, 1 H, C-15 H), 2.25–2.45 (m, 2 H, C-10α H and C-16 H), 2.48 (d, J = 6.4 Hz, 2 H, NCH_2-cyclopropyl), 2.7–2.8 (m, 1 H, C-14 H), 2.85–3.0 (m, 2 H, C-10β H and C-16 H), 3.49 (s, 3 H, C-6 OCH_3), 3.7–3.8 (m, 2 H, C-6 H and C-9 H), 4.93 (d, J = 5.5 Hz, 1 H, C-5 H), 5.33 (dt, J = 9.7 and 2.6 Hz, 1 H, C-8 H), 5.69 (d, J = 9.8 Hz, 1 H, C-7 H), 6.42 (d, J = 8.1 Hz, 1 H, C-1 H), 6.60 (d, J = 8.1 Hz, 1 H, C-2 H); ^{13}C NMR ($CDCl_3$) δ 3.77, 4.10, 8.89, 21.02, 35.63, 40.83, 44.22, 44.78, 55.96, 56.90, 59.55, 76.44, 89.29, 117.17, 118.79, 125.40, 129.22, 129.52, 130.47, 138.34, 146.57; FTIR (KBr) 3300–2500 (OH), 1636, 1611 cm^{-1}; HREIMS calcd for $C_{21}H_{25}NO_3$ 339.1834, found 339.1831.

3-*O*-(*tert*-Butyldimethylsilyl)-*N*-(cyclopropylmethyl)norheterocodeine (33). A solution of tertiary amine **32** (470 mg, 1.39 mmol), *tert*-butyldimethylsilyl chloride (313 mg, 2.08 mmol), and imidazole (284 mg, 4.17 mmol) in DMF (4 mL) was stirred for 22 h, and then the volatiles were evaporated. The residue was dissolved in CH_2Cl_2 (50 mL), washed with a half-saturated aqueous $NaHCO_3$ solution (30 mL) and water (20 mL), and dried ($MgSO_4$), and then the volatiles were evaporated to give silyl ether **33** (610 mg, 97%) as an oil which crystallized on standing: mp 85–88 °C; $[\alpha]^{20}_D$ = −161.5° (c = 1.00, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.1–0.2 (m, 2 H, cyclopropyl CH_2), 0.13 (s, 3 H, $SiCH_3$), 0.20 (s, 3 H, $SiCH_3$), 0.5–0.6 (m, 2 H, cyclopropyl CH_2), 0.85–0.95 (m, 1 H, cyclopropyl CH), 0.98 [s, 9 H, $SiC(CH_3)_3$], 1.85–1.95 (m, 1 H, C-15 H), 2.04 (dt, J = 5.0 and 12.4 Hz, 1 H, C-15 H), 2.28 (dd, J = 6.6 and 18.7 Hz, 1 H, C-10α H), 2.3–2.4 (m, 1 H, C-16 H), 2.43 (d, J = 6.3 Hz, 2 H, NCH_2-cyclopropyl), 2.6–2.7 (m, 1 H, C-14 H), 2.75–2.85 (m, 1 H, C-16 H), 2.90 (d, J = 18.1 Hz, 1 H, C-10β H), 3.50 (s, 3 H, C-6 OCH_3), 3.65–3.7 (m, 1 H, C-9 H), 3.75–3.8 (m, 1 H, C-6 H), 4.96 (d, J = 5.7 Hz, 1 H, C-5 H), 5.30 (dt, J = 9.8 and 2.7 Hz, 1 H, C-8 H), 5.63 (d, J = 9.9 Hz, 1 H, C-7 H), 6.40 (d, J = 7.9 Hz, 1 H, C-1 H), 6.55 (d, J = 8.1 Hz, 1 H, C-2 H); ^{13}C

NMR ($CDCl_3$) δ -4.91, -4.72, 3.77, 3.95, 9.39, 18.25, 21.11, 25.66 (3 C, *t*-Bu), 36.07, 41.17, 44.06, 44.90, 56.16, 56.23, 59.86, 75.86, 88.62, 118.48, 120.95, 127.40, 128.78, 130.39, 131.06, 136.85, 149.28; FTIR (neat) 1679, 1632, 1603 cm^{-1}; HREIMS calcd for $C_{27}H_{39}NO_3Si$ 453.2699, found 453.2701.

3-*O*-(*tert*-Butyldimethylsilyl)-*N*-(cyclopropylmethyl)-norororipavine (34). To a solution of allylic ether **33** (810 mg, 1.79 mmol) in THF (18 mL) was added γ-MnO_2[23] (3.9 g, 44.75 mmol) in 5 portions over 4 h with vigorous stirring. After stirring for an additional 20 h, the mixture was filtered through a pad of Celite on a fine-fritted funnel under suction, and the solids were rinsed with THF (200 mL) followed by methanol (120 mL). The combined filtrates were evaporated, and then the residue was purified by flash chromatography (35 g of silica gel) eluting with 4% triethylamine–15% ether–hexanes (600 mL) to give dienol ether **34** (180 mg, 22%) as a gummy solid: $[\alpha]^{20}_D$ = -140.5° (*c* = 1.00, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.1–0.2 (m, 2 H, cyclopropyl CH_2), 0.13 (s, 3 H, $SiCH_3$), 0.20 (s, 3 H, $SiCH_3$), 0.5–0.6 (m, 2 H, cyclopropyl CH_2), 0.85–0.95 (m, 1 H, cyclopropyl CH), 0.97 [s, 9 H, $SiC(CH_3)_3$], 1.65–1.75 (m, 1 H, C-15 H), 2.17 (dt, *J* = 5.4 and 12.4 Hz, 1 H, C-15 H), 2.47 (d, *J* = 6.3 Hz, 2 H, NCH_2-cyclopropyl), 2.69 (dd, *J* = 7.3 and 17.9 Hz, 1 H, C-10α H), 2.7–2.95 (m, 2 H, C-16 CH_2), 3.21 (d, *J* = 18.1 Hz, 1 H, C-10β H), 3.56 (s, 3 H, C-6 OCH_3), 3.90 (d, *J* = 7.1 Hz, 1 H, C-9 H), 5.00 (d, *J* = 6.4 Hz, 1 H, C-8 H), 5.22 (s, 1 H, C-5 H), 5.52 (d, *J* = 6.4 Hz, 1 H, C-7 H), 6.48 (d, *J* = 7.9 Hz, 1 H, C-1 H), 6.57 (d, *J* = 8.2 Hz, 1 H, C-2 H); ^{13}C NMR ($CDCl_3$) δ -4.87, -4.67, 3.72, 3.97, 9.49, 18.31, 25.68 (3 C, *t*-Bu), 30.69, 36.49, 44.19, 46.62, 54.55, 58.54, 59.01, 88.61, 95.67, 111.49, 118.94, 120.78, 128.03, 132.50, 133.67, 137.50, 146.33, 152.46; FTIR (neat) 1627, 1607 cm^{-1}; HREIMS calcd for $C_{27}H_{37}NO_3Si$ 451.2542, found 451.2548.

3-*O*-(*tert*-Butyldimethylsilyl)-*N*-(cyclopropylmethyl)-6,14-*endo*-etheno-7α-formyltetrahydronororipavine (35). To a solution of dienol ether **34** (180 mg, 0.4 mmol) in benzene (3 mL) heated at 50 °C was added acrolein (0.8 mL, 12.8 mmol) in 4 portions over 3 h. After stirring at 50 °C for an additional 3 h, the volatiles were evaporated and the residue was purified by flash chromatography (18 g of silica gel) eluting with 4% triethylamine–hexanes (300 mL) to give aldehyde **35** (170 mg, 84%) as a viscous oil: $[\alpha]^{20}_D$ = -177.5° (*c* = 1.00, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.1–0.2 (m, 2 H, cyclopropyl CH_2), 0.15 (s, 3 H, $SiCH_3$), 0.16 (s, 3 H, $SiCH_3$), 0.45–0.55 (m, 2 H, cyclopropyl CH_2), 0.8–0.9 (m, 1 H, cyclopropyl CH), 0.97 [s, 9 H, $SiC(CH_3)_3$], 1.45 (dd, *J* = 5.5 and 13.3 Hz, 1 H, C-8α H), 1.8–1.9 (m, 1 H, C-15 H), 1.98 (dt, *J* = 5.5 and 12.6 Hz, 1 H, C-15 H), 2.3–2.45 (m, 4 H, NCH_2-cyclopropyl, C-10α H, and C-16 H), 2.65–2.8 (m, 2 H, C-7β H and C-16 H), 2.97 (dd, *J* = 9.6 and 13.2 Hz, 1 H, C-8β H), 3.09 (d, *J* = 18.2 Hz, 1 H, C-10β H), 3.55 (d, *J* = 6.5 Hz, 1 H, C-9 H), 3.60 (s, 3 H, C-6 OCH_3), 4.59 (s, 1 H, C-5 H), 5.57 (d, *J* = 8.7 Hz, 1 H, C-17 H), 5.82 (d, *J* = 8.7 Hz, 1 H, C-18 H), 6.43 (d, *J* = 8.1 Hz, 1 H, C-1 H), 6.54 (d, *J* = 8.0 Hz, 1 H, C-2 H), 9.41 (d, *J* = 3.9 Hz, 1 H, CHO); ^{13}C NMR ($CDCl_3$) δ -4.64, -4.57, 3.45, 4.08, 9.44, 18.20, 23.27, 25.58 (3 C, *t*-Bu), 26.68, 33.39, 42.77, 43.86, 48.00, 49.74, 52.38, 57.08, 59.69, 80.76, 93.00, 119.31, 121.01, 126.31, 128.40, 133.90, 136.65, 137.15, 149.65, 201.58; FTIR (neat) 1725, 1626, 1599 cm^{-1}; HREIMS calcd for $C_{30}H_{41}NO_4Si$ 507.2805, found 507.2804.

3-*O*-(*tert*-Butyldimethylsilyl)-*N*-(cyclopropylmethyl)-6,14-*endo*-etheno-7α-(3-carboxy-3-*n*-butenyl)tetrahydronororipavine γ-Lactone (36). To a solution of aldehyde **35** (150 mg, 0.30 mmol) in THF (3 mL) was added activated zinc (32 mg, 0.49 mg-atom). While heating at 50 °C, a solution of methyl α-(bromomethyl)acrylate[24] (48 μL, 0.4 mmol) in THF (0.4 mL) was added over 1 min. The mixture was stirred at 50 °C for 6 h and cooled, and the volatiles were evaporated. The residue was purified by flash chromatography (21 g of silica gel) eluting with 4% triethylamine–25% ether–hexanes (500 mL) to give α-methylene-γ-lactone **36** (110 mg, 65%) as a viscous oil: $[\alpha]^{20}_D$ = -102.5° (*c* = 1.00, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.1–0.2 (m, 2 H, cyclopropyl CH_2), 0.15 [s, 6 H, $Si(CH_3)_2$], 0.45–0.6 (m, 2 H, cyclopropyl CH_2), 0.8–0.9 (m, 1 H, cyclopropyl CH), 0.97 [s, 9 H, $SiC(CH_3)_3$], 1.11 (dd, *J* = 6.6 and 12.9 Hz, 1 H, C-8α H), 1.8–1.9 (m, 1 H, C-15 H), 1.95 (dt, *J* = 5.2 and 12.4 Hz, 1 H, C-15 H), 2.0–2.1 (m, 1 H, C-7β H), 2.25–2.45 (m, 4 H, NCH_2-cyclopropyl, C-10α H, and C-16 H), 2.65–2.8 (m, 2 H, C-16 H and lactone β-CH), 2.92 (dd, *J* = 9.3 and 13.0 Hz, 1 H, C-8β H), 2.95–3.1 (m, 1 H, lactone β-CH), 3.06 (d, *J* = 18.6 Hz, 1 H, C-10β H), 3.49 (d, *J* = 6.3 Hz, 1 H, C-9 H), 3.63 (s, 3 H, C-6 OCH_3), 4.48 (s, 1 H, C-5 H), 4.65–4.75 (m, 1 H, C-19 H), 5.44 (d, *J* = 8.8 Hz, 1 H, C-17 H), 5.5–5.6 (m, 1 H, vinylic H), 5.84 (d, *J* = 8.8 Hz, 1 H, C-18 H), 6.1–6.2 (m, 1 H, vinylic H), 6.44 (d, *J* = 7.8 Hz, 1 H, C-1 H), 6.54 (d, *J* = 8.0 Hz, 1 H, C-2 H); ^{13}C NMR ($CDCl_3$) δ -4.67, -4.53, 3.43, 4.18, 9.42, 18.20, 23.01, 25.59 (3 C, *t*-Bu), 26.89, 32.99, 33.62, 42.22, 42.43, 43.98, 47.70, 53.36, 56.93, 59.85, 76.74, 80.36, 95.75, 119.15, 120.80, 121.06, 125.96, 128.53, 134.26, 134.89, 135.60, 136.49, 149.83, 170.19; FTIR (neat) 1764, 1666, 1626, 1599 cm^{-1}; HREIMS calcd for $C_{34}H_{45}NO_5Si$ 575.3067, found 575.3064.

***N*-(Cyclopropylmethyl)-6,14-*endo*-etheno-7α-(3-carboxy-3-*n*-butenyl)tetrahydronororipavine γ-Lactone (37).** To a solution of α-methylene-γ-lactone **36** (110 mg, 0.19 mmol) in THF (1.5 mL) was added a 1 M solution of *n*-Bu_4NF in THF (0.23 mL) dropwise. After stirring for 70 min, the solution was treated with saturated aqueous $NaHCO_3$ solution (15 mL) and extracted with CH_2Cl_2 (3 × 13 mL). The combined extracts were dried (Na_2SO_4) and the solvents were evaporated. The residue was purified by flash chromatography (17 g of silica gel) eluting with 4% triethylamine–ether (600 mL) to give α-methylene-γ-lactone **37** (70 mg, 80%) as a white foam: $[\alpha]^{20}_D$ = -108° (*c* = 1.00, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.1–0.2 (m, 2 H, cyclopropyl CH_2), 0.45–0.6 (m, 2 H, cyclopropyl CH_2), 0.8–0.9 (m, 1 H, cyclopropyl CH), 1.09 (dd, *J* = 6.7 and 12.8 Hz, 1 H, C-8α H), 1.8–1.9 (m, 1 H, C-15 H), 1.9–2.1 (m, 2 H, C-7β H and C-15 H), 2.25–2.5 (m, 4 H, NCH_2-cyclopropyl, C-10α H, and C-16 H), 2.65–2.8 (m, 2 H, C-16 H and lactone β-CH), 2.91 (dd, *J* = 9.4 and 12.9 Hz, 1 H, C-8β H), 2.95–3.1 (m, 1 H, lactone β-CH), 3.06 (d, *J* = 18.6 Hz, 1 H, C-10β H), 3.50 (d, *J* = 6.3 Hz, 1 H, C-9 H), 3.63 (s, 3 H, C-6 OCH_3), 4.50 (s, 1 H, C-5 H), 4.7–4.8 (m, 1 H, C-19 H), 5.41 (d, *J* = 8.8 Hz, 1 H, C-17 H), 5.58 (t, *J* = 2.4 Hz, 1 H, vinylic H), 5.83 (d, *J* = 8.8 Hz, 1 H, C-18 H), 5.9 (br s, movable, 1 H, OH), 6.17 (t, *J* = 2.7 Hz, 1 H, vinylic H), 6.42 (d, *J* = 7.9 Hz, 1 H, C-1 H), 6.57 (d, *J* = 8.0 Hz, 1 H, C-2 H); ^{13}C NMR ($CDCl_3$) δ 3.42, 4.21, 9.36, 22.93, 26.48, 32.61, 33.47, 42.29 (2 C), 44.01, 47.80, 53.55, 56.93, 59.82, 76.30, 80.32, 96.38, 116.39, 119.44, 121.37, 125.47, 127.04, 133.82, 134.68, 135.57, 137.73, 146.60, 170.50; FTIR (KBr) 3700–2500 (OH), 1762, 1664, 1636, 1610 cm^{-1}; HREIMS calcd for $C_{28}H_{31}NO_5$ 461.2202, found 461.2200. Anal. ($C_{28}H_{31}NO_5 \cdot 0.25H_2O$) C, N; H: calcd, 6.81; found, 7.32.

Opioid Receptor Binding. The binding assay was carried out essentially as described by Lin and Simon.[30] Crude membranes were prepared from bovine striatum and were stored at -70 °C until needed. The labeled ligands used were [^{3}H]bremazocine (18.5 Ci/mmol) for total opioid receptors and [^{3}H]DAGO (33.8 Ci/mmol) [D-Ala^2-*N*MePhe^4-Gly-ol^5-enkephalin] for μ-receptors. The concentrations of labeled ligands were 0.5 nM for [^{3}H]bremazocine and 1 nM for [^{3}H]DAGO. Five concentrations of each drug to be tested were used for competition against labeled ligands. Nonspecific binding was measured in the presence of 10 μM naloxone. The samples were incubated in 50 mM potassium phosphate buffer, pH 7.4, containing 1 mM EDTA for 45 min at 25 °C. Samples were rapidly filtered through Whatman GF/B filters, rinsed twice with 4 mL of cold buffer, dried, and counted in a toluene-based scintillation cocktail in a scintillation counter.

Irreversibility and Protection Studies. Membrane preparations were incubated with drug to be tested for 45 min at 25 °C. For protection studies naloxone was added at a concentration of 1 μM (recovery was checked with naloxone alone). After incubation, the samples were diluted 4-fold with buffer and centrifuged for 15 min at 20000*g*. The supernatant was removed and the pellet was resuspended in 3 times the original volume of buffer and incubated at 37 °C for 15 min, centrifuged again, and resuspended in the original volume of buffer. A binding assay using [^{3}H]bremazocine (0.5 nM) or [^{3}H]DAGO (1.0 nM) was carried out as described above.

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5, 127130-99-8; 6, 127131-00-4; 7, 127131-01-5; 8, 127131-02-6; 9, 127131-03-7; 10, 127131-04-8; 11, 127154-02-3; 12, 16553-22-3; 13, 127131-05-9; 14, 127131-06-0; 15, 127131-07-1; 16, 127131-08-2; 17, 127131-09-3; 18, 127131-10-6; 19, 127131-11-7; 20, 127131-12-8; 21, 127131-13-9; 22, 639-47-4; 23, 127131-14-0; 24, 127131-15-1; 25, 127131-16-2; 27, 127131-17-3; 28, 127131-18-4; 29, 127131-19-5; 30, 57093-46-6; 31, 127131-20-8; 32, 127131-21-9; 33, 127131-22-0; 34, 127131-23-1; 35, 127131-24-2; 36, 127131-25-3; 37, 127154-03-4.

Antiinflammatory Agents. 4.[1] Syntheses and Biological Evaluation of Potential Prodrugs of 2-Amino-3-benzoylbenzeneacetic Acid and 2-Amino-3-(4-chlorobenzoyl)benzeneacetic Acid

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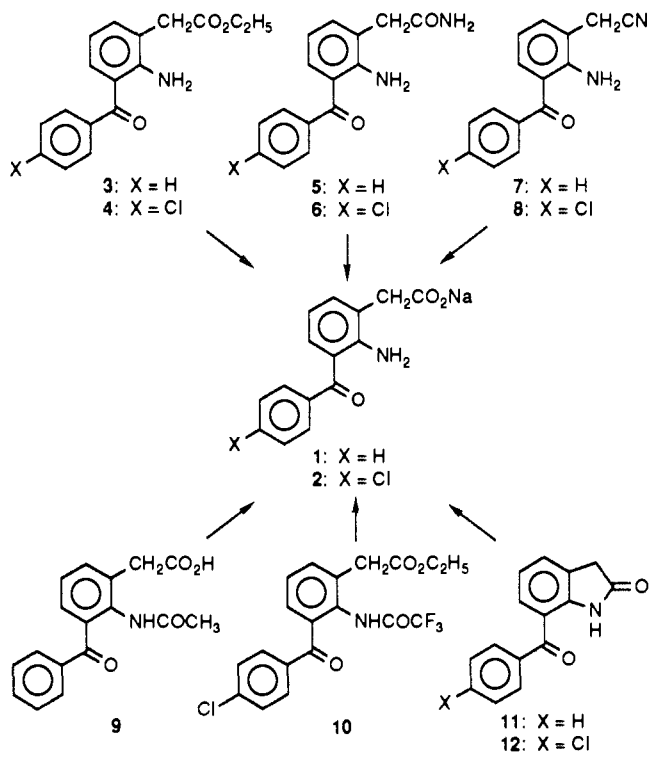
A series of potential prodrugs of 2-amino-3-benzoylbenzeneacetic acid (amfenac) and 2-amino-3-(4-chlorobenzoyl)benzeneacetic acid were synthesized and evaluated for their cyclooxygenase inhibiting properties, antiinflammatory potency, and gastrointestinal irritation liability. One compound, 2-amino-3-(4-chlorobenzoyl)benzeneacetamide, possessed a therapeutic index 1 order of magnitude greater than that of indomethacin.

In general one of the most prevalent and serious side effects of the use of nonsteroidal antiinflammatory drugs (NSAIDS) is the occurrence of gastrointestinal damage.[2] Gastric upset and irritation are a major stumbling block to patient compliance with a prescribed dosage regimen. There have been several attempts to improve the gastric tolerance of NSAIDS which have met with varying degrees of success such as formulation (e.g., buffered, sustained-release, or enteric-coated), chemical manipulation such as esterification[3,4] and coadministration of agents in an attempt to protect the stomach.[5]

As part of a continuing effort to prepare NSAIDS with minimal or no gastrointestinal side effects, several compounds (Charts I–IV) were synthesized which may be metabolically converted to 2-amino-3-benzoylbenzeneacetic acid (1, amfenac),[6] a potent cyclooxygenase inhibitor and clinically useful antiinflammatory drug,[7] or its 4-chloro derivative 2.[1] Ideally these precursors should have no inherent cyclooxygenase inhibiting activity so that when orally administered there would be no gastric side effects before absorption. They would then be metabolically converted to active species 1 or 2 and undergo enterohepatic recirculation[8] to exert the desired antiinflammatory effect. The approach used was to chemically modify 1 and 2 to provide compounds which could be broken down in vivo enzymatically or by non-enzymatic processes to release the active moiety. The term "drug latentiation" was used by Harper[9] to describe this approach.

The synthesized compounds are arbitrarily classified into four categories: compounds which may be converted to 1 or 2 by (a) hydrolysis (Chart I), (b) an oxidative process (Chart II), (c) a reductive process (Chart III), and (d) a multistep process (Chart IV). Since 1 and 2 are potent cyclooxygenase inhibitors,[1] it was assumed that a prodrug that did not possess cyclooxygenase inhibiting properties was inherently devoid of antiinflammatory activity, and any in vivo activity could be ascribed to a metabolic conversion to a cyclooxygenase inhibitor. The compounds initially were tested in vivo in the Evans blue–carrageenan-induced pleural effusion assay,[10] a model of acute inflammation (Table I), and then tested in vitro for cyclooxygenase inhibiting properties (Table II).

Chart I. Compounds That May Be Converted to 1 or 2 by Hydrolysis



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(1) For part 3 in this series, see: Walsh, D. A.; Moran, H. W.; Shamblee, D. A.; Uwaydah, I. M.; Welstead, W. J., Jr.; Sancilio, L. F.; Dannenburg, W. N. *J. Med. Chem.* **1984**, *27*, 1379–1388.
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