of 2 M were concentrated to a slurry by rotary evaporation, and the product was precipitated with cold ethanol (20 mL) and washed on a sintered glass funnel with cold absolute ethanol (3 × 10 mL) to remove residual LiCl. Drying in vacuo over P_2O_5 yielded compound **5** (1.0 mmol, 0.63 g, 65% yield based on compound 4), which was 98% homogeneous as determined by HPLC (t_R = 8.8 min): ^{1}H NMR δ 8.63 (s, 1), 7.76 (s, 2), 6.25 (s, 1), 4.3–5.0 (m, 5), 3.64 (m, 2), 3.28 (m, 2), 2.31 (m, 2); ^{13}C NMR (aromatic region) δ 151, 144.5, 143.9, 140, 128, 119, 115 (sugar region), 91, 86(d), 77, 73, 68 (alkyl region), 41, 31, 29; UV λ_{max} nm (ε × 10^{-3}) pH 1, 293 (16.7), 234 (22.5); pH 11, 304 (9.9), 282 (10.1), sh 273 (8.32). Anal.[22] ($C_{15}H_{22}N_6P_2O_{10}S$) C, P; H: calcd, 3.86; found, 4.63; N: calcd, 14.74; found, 14.19. This compound appears to be susceptible to atmospheric oxidation, possibly to a sulfoxide. Thin-layer chromatography on silica in isobutyric acid (70%)/water (25%)/ammonium hydroxide (5%) gave two spots when run in one dimension and each spot could be resolved further into two spots when run with the same buffer in the second dimension, indicating that the second spot was formed during the chromatography: this oxidation was avoided by carrying out TLC in a N_2 atmosphere.

2-[(3-Aminopropyl)thio]-ADP (6). The etheno group was removed from compound **5** (0.95 g, 1.5 mmol) with *N*-bromosuccinimide (350 mg, 2 mmol) in a manner similar to that reported by Yamaji.[15] The solution was stirred at 25 °C while the pH was maintained at 3.0 by periodic addition of 1 M NaOH. After 2 h the pH was raised to 12 with NaOH and the solution stirred for an additional hour. The pH of the solution was then lowered to 3 with 6 M HCl and added to a column (1.5 × 30 cm) of cation-exchange resin (AG-50 × 8, H^+) that had been equilibrated with 10 mM acetic acid. After the column was washed with 1 column volume of 10 mM acetic acid, the product was eluted with a 600-mL linear gradient of 0–2.5 M LiCl containing 10 mM acetic acid. The UV-absorbing fractions eluting at 1 M LiCl were concentrated to a slurry by rotary evaporation and cold ethanol (20 mL) was added to yield the nucleotide product (ca. 200 mg) that was homogeneous as judged by HPLC (>95%) but was slightly yellow.

A further purification was effected by dissolving this solid (100 mg) in water (5 mL) and applying it to a column (1.5 cm × 18 cm) of anion-exchange resin (DEAE-cellulose) equilibrated with distilled water. The column was washed with 1 column volume of water and eluted with a 600-mL linear gradient of 0–0.1 M LiCl. UV-absorbing fractions eluting at 0.04 M LiCl were combined and concentrated to a slurry. The product was precipitated with cold ethanol (20 mL), collected on a sintered glass funnel, washed with cold absolute ethanol (3 × 10 mL) to remove residual LiCl, and dried in vacuo over P_2O_5. This procedure yielded compound **6** (0.4 mmol, 24% yield based on compound **5** by UV analysis), which was 98% homogeneous by HPLC (t_R = 6.5 min): ^{1}H NMR δ 8.48 (s, 1), 6.24 (d, 1, J = 6 Hz), 4.3–5.0 (m, 5), 3.42 (m, 2), 3.19 (m, 2), 2.21 (m, 2); ^{13}C NMR (aromatic region) δ 167, 158, 153, 142, 119 (sugar region) 91, 86 (d), 76, 73, 67 (d) (alkyl region) 41, 30 (2× intensity); UV λ_{max} nm (ε × 10^{-3}) pH 1, 268 (14.7); pH 11, 274 (15). Anal.[22] ($C_{13}H_{22}N_6P_2O_{10}S$) C, N, P; H: calcd, 4.02; found, 4.85.

Biochemistry. Whole blood, collected into $^1/_{10}$ volume of acid/citrate/dextrose buffer (5.5 mM dextrose, 128 mM NaCl, 4.26 mM NaH_2PO_4, 7.46 mM Na_2HPO_4, 4.77 mM Na_3·citrate, 2.35 mM citric acid), was used to prepare platelet-rich plasma (PRP) by centrifugation (3 min × 3000*g*). Aggregations were performed in a Payton Dual Channel aggregometer, using PRP (490 μL, containing (3–5) × 10^8 platelets/mL), which was stirred at 37 °C in a glass cuvette. After sufficient time for temperature equilibration, the sample of PRP was challenged with varying amounts of nucleotide dissolved in 10 μL of water. Platelet-poor plasma (PPP) was used as the optical standard for complete aggregation and was prepared by centrifugation of PRP (3 min × 10000*g*). The change in light transmission upon platelet activation was recorded and the extent of maximum change in light transmittance for each addition of nucleotide was compared.

Registry No. 1, 58-64-0; 2, 38806-39-2; 3, 50663-84-8; 4, 110224-43-6; 5, 110224-44-7; 6, 110224-45-8; $ClCH_2CHO$, 107-20-0; $Br(CH_2)_3NH_2$·HBr, 5003-71-4.

(22) The percent compositions are calculated as the dilithium monohydrates. The amount of water of hydration was substantiated by ^{1}H NMR and was consistent with the difference found between the amount of weight loss upon drying and the total water content determined by the Karl Fisher method.

Nitrogen-Bridged Conformationally Constrained Etorphine Analogues. Synthesis and Biological Evaluation

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Three N–C8-bridged analogues 4–6 of the opiate etorphine (3) were synthesized and evaluated for opiate agonism and antagonism. In each case ring closure was effected by intramolecular N-alkylation with a suitably developed C8 side chain. Another key synthetic step was the selective monoprotection of diol 11, which allowed independent elaborations of the C7 and C8 side chains. All three analogues showed distinctly diminished agonist activities when compared to the corresponding *N*-methyl compound, 19(*R*)-*n*-butylorvinol (3). Furthermore, no antagonist activity was detectable. The results demonstrate that the conformation at the amino nitrogen in rigid morphinans is critical for potent opiate activity.

The necessity of a basic amino group in a molecule for the expression of opiate activity may be regarded as established fact and is undoubtedly the most clear-cut aspect of structure–activity relationships associated with the opiates. Yet, despite a vast amount of research and more than a few theories on the subject, the precise role of the amino group remains elusive. This is not surprising, considering the inherent difficulties associated with a direct study of the opiate–receptor complex. Recently, we focused our attention on two aspects of this problem, namely, the geometric orientation of the nitrogen lone pair of electrons in the active conformation of rigid morphinan opiates and the possibility of a conformational inversion being a determinant in agonist/antagonist differentiation.

An evaluation of the literature indicates that these topics have been previously addressed. For example, it has been shown that *D*-norlevorphanol (1), an inactive analogue of the opiate levorphanol (2), has its *N*-methyl group inverted with respect to that of levorphanol in the solid, as shown by the X-ray crystal structures of the hydrobromide salts.[1,2]

(1) Belleau, B.; Conway, T.; Ahmed, F. R.; Hardy, A. D. *J. Med. Chem.* **1974**, *17*, 907.
(2) Belleau, B.; Morgan, P. *J. Med. Chem.* **1974**, *17*, 908.

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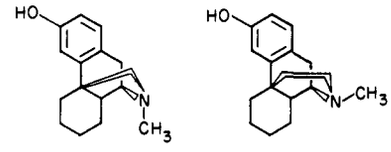
The conclusion was reached that this structural feature was related to the failure of 1 to show opiate activity and that lone-pair orientation was critical for productive opiate binding. It was proposed that "clastic binding", binding with regiospecific electron transfer to the receptor, was a factor in eliciting the opiate response. Additional reports[3-7] have presented other interesting experiments and theories designed to elucidate any relationship between the conformation about the nitrogen atom and opiate activity, as well as agonist/antagonist differentiation. In particular, the models of Snyder[6] and of Kolb,[7] although quite dissimilar, each provide exceptional rationalizations for much of the available SAR data. Indeed, we were influenced by these models as guides in the interpretation of our own data at the outset of our experiments.



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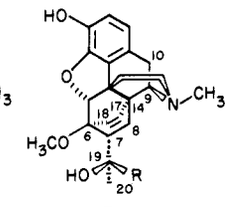
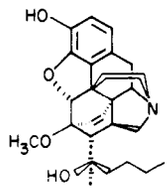
2

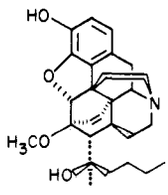


3

R = *n*-Pr, Etorphine
R = *n*-Bu, "Homoetorphine"



4



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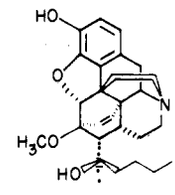

6

Our experimental plan was conceptually simple and involved the design, synthesis, and biological evaluation of novel analogues of the constrained and highly potent opiate etorphine (3).[8] These analogues were to have fixed N lone pair orientations by virtue of their conformationally restricting, "tied back" N-substituents. This would be accomplished by building a covalent bridge between the nitrogen and C8. Ring strain is minimal if the bridge is β at C8 and should allow formation of a five- or six-membered ring. However, if the bridge is α at C8, ring strain increases greatly and permits only a six-membered ring or larger. The target molecules **4** (β-5 membered), **5** (β-6), and **6** (α-6) were synthesized and tested for opiate analgesia in rats by using the tail-flick method.

Results and Discussion

Synthesis. Initially, we chose an intramolecular Diels–Alder reaction as the simplest way to prepare the target ring structures. Several N-substituted northebaines of general structure **7** were prepared and tested for their ability to undergo cyclization. Regardless of various permutations of X, E, and double-bond geometry, these reactions were all unsuccessful. To realistically expect such a cyclization to proceed and be useful, certain criteria would have to be met. First, X would have to contain a second activating group since monoactivated 1,2-disubstituted olefins do not form Diels–Alder adducts with thebaine. Second, the double bond should be cis since diactivated trans olefins give adducts with 7β geometry, the preference for α geometry being greater at the C8 than at C7.[9] However, even within these guidelines our substrates could not be made to cyclize. It is likely that proper orbital overlap requires a very high energy conformation since a two- or three-atom bridge between N and C8α involves a high degree of ring strain.

Obviously then, an intermolecular Diels–Alder reaction would be required followed by bridge formation between N and C8. In order to simplify the ring-forming reaction, we decided to build an appendage out from C8 and close the ring with formation of a C–N bond. If the appendage were built out from nitrogen, then ring closure would require C–C bond formation, and we wished to avoid this prospect. Also, since thebaine was to be our starting material, the *N*-methyl group would have to be removed at some stage of the synthesis. Conversion of thebaine to northebaine is a well-established, high-yield reaction[10] that would eliminate the *N*-methyl from the very outset. The benzoyl group served as a temporary N-substituent, which was soon converted cleanly to an *N*-benzyl group during the course of a lithium aluminum hydride reduction in a subsequent step.

The syntheses thus began with northebaine (**8**), which was benzoylated with benzoic anhydride to give *N*-benzoylnorthebaine (**9**) in high yield. Diels–Alder reaction of **9** with maleic anhydride gave the expected adduct **10**, and subsequent LAH reduction gave the dihydroxy *N*-benzyl derivative **11** in about 80% yield overall. No chromatography was required up to this step, allowing easy and large-scale (100 g) preparations of **11**.

Selective protection of either hydroxyl group of **11** was surprisingly simple. Mono-*tert*-butyldimethylsilylation could be made to predominate at either site by varying conditions as shown in Scheme I. With *tert*-butyldimethylsilyl chloride, triethylamine, and catalytic 4-(dimethylamino)pyridine in CH_2Cl_2, isomer **12** was obtained in 70% yield and was readily separated from regioisomer **13** (27%) by column chromatography. This degree of selectivity is undoubtedly due, in part, to steric hindrance provided by the *N*-benzyl group. This minor isomer **13** could be made the predominant isomer by silylation of the dianion of **11**, prepared with a 1:1 ratio of Li^+ and K^+ counterions. The lithium ion apparently becomes bonded between the 7-hydroxymethyl group and the 6-methoxy group in a more stable complex, leaving the remaining anionic site countered by potassium ion and, therefore, considerably more reactive. Thus, under the latter conditions the yields of **13** and **12** were 82% and 12%, respectively. Each of these regioisomers was essential to this work since they allowed manipulations to be performed selectively at either the C7 or C8 appendages.

At this time there were no reports of any 8β-substituted *endo*-ethylenetetrahydrothebaines. Disubstituted olefins give only 8α adducts with thebaine, and hydrogenation of the C7–C8 double bond of acetylenic adducts also gives only 8α stereochemistry. Therefore, our entry into the 8β series was made in the following way. The free hdyroxyl group of monosilyl isomer **12** was oxidized to the aldehyde,[11] the yield being quantitative. The aldehyde **15** so

(3) Loew, G. H.; Berkowitz, D. S. *J. Med. Chem.* **1978**, *21*, 101.
(4) Kobylecki, R. J.; Carling, R. W.; Lord, J. A. H.; Smith, C. F. C.; Lane, A. C. *J. Med. Chem.* **1982**, *25*, 116.
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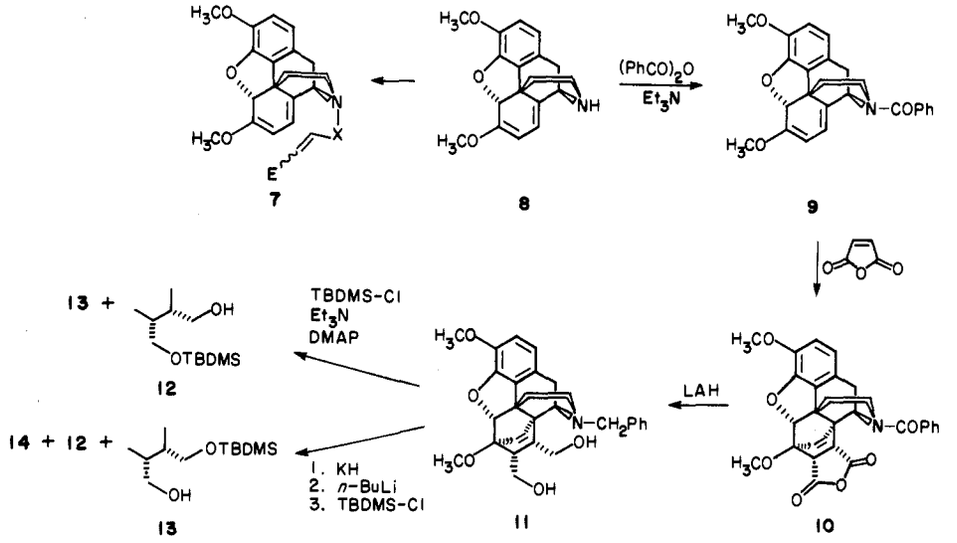
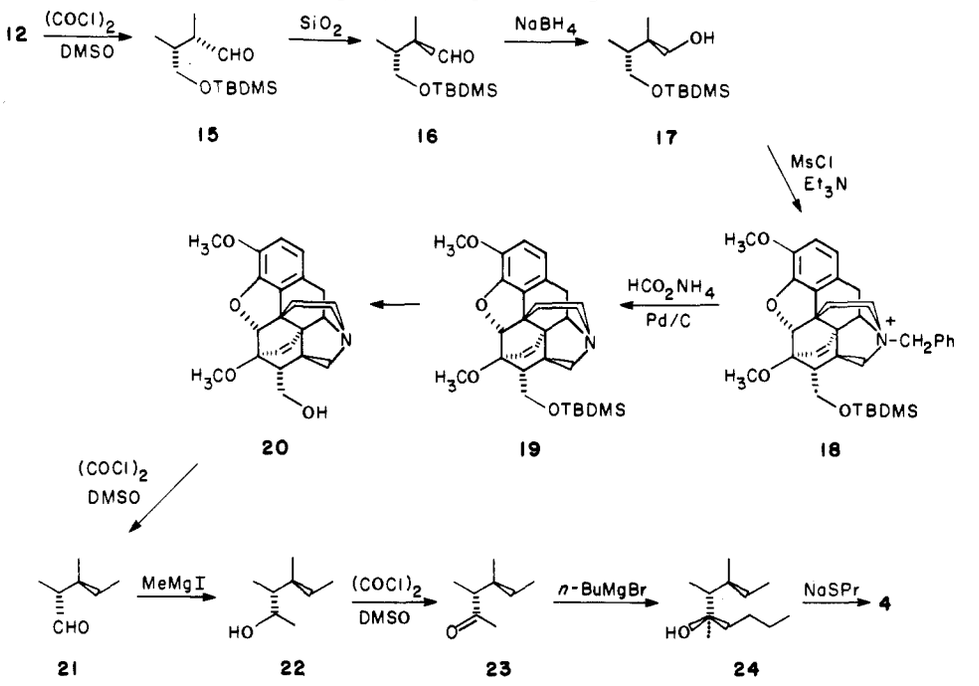
(7) Kolb, V. M. *J. Pharm. Sci.* **1978**, *67*, 999.
(8) Bentley, K. W.; Hardy, D. G. *J. Am. Chem. Soc.* **1967**, *89*, 3267.
(9) Rubinstein, R.; Haviv, F.; Ginsburg, D. *Tetrahedron* **1974**, *30*, 1201.
(10) Schwab, L. S. *J. Med. Chem.* **1980**, *23*, 698.
(11) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

Scheme I. Selective Regioisomer Formation at C7 and C8 of Thebaine–Maleic Anhydride Adduct



Scheme II. Synthesis of Nitrogen–C8β Methano Bridged (β-5) Etorphine Analogue

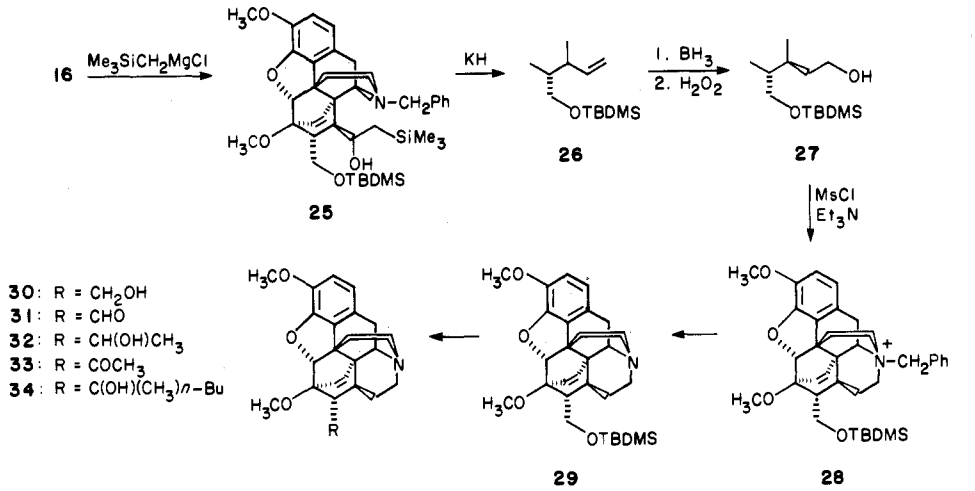


obtained was subjected to silica gel catalyzed epimerization, which gave a 2:1 ratio of 8β- to 8α-aldehydes. Pure 8β-aldehyde **16** was obtained by simple crystallization from isooctane leaving a mother liquor which could then be reequilibrated by further silica gel treatment, and so on. The 8α-aldehyde resisted crystallization completely but could be purified without epimerization by rapid radial chromatography using relatively inactive (methanol pretreated) silica gel. Thus, excellent yields of both aldehydes could be obtained in very high purity.

It was now clear that the β-5 ring structure was close at hand, and its synthesis is shown in Scheme II. The 8β-aldehyde **16** was reduced to alcohol **17** ($NaBH_4$, quantitative) and, upon treatment with methanesulfonyl chloride and Et_3N, yielded the quaternary salt **18** directly and quantitatively. The *N*-benzyl group was then removed catalytically, giving tertiary amine heptacycle **19** (β-5). The C17–C18 double bond is considerably more active toward reduction in this heptacyclic system than in most *endo*-ethylenetetrahydrothebaines and can be saturated quite readily. Our procedure for debenzylation of the quaternary salt (Pd/C, NH_4HCO_2, MeOH; reflux 45 s) rapidly removes the benzyl group with less than 2% double-bond reduction.

All that remained was elaboration of the C7 side chain and 3-*O*-methyl ether cleavage. To this end the *tert*-butyldimethylsilyl (TBDMS) group was protolytically cleaved to give primary alcohol **20**. The alcohol was then oxidized,[11] affording aldehyde **21**, and treatment with CH_3MgI gave 11/1 mixture of secondary alcohol epimers **22** quantitatively. Oxidation of the secondary alcohol then provided methyl ketone **23**, which upon treatment with *n*-C_4H_9MgBr gave exclusively the (*R*)-methylbutylcarbinol **24**. The yield was essentially quantitative and no rearrangement products were observed, in contrast with Grignard reactions with thevinone. The *S* isomer could also be obtained, although less selectively, by reversing the order of Grignard additions and proceeding via the butyl ketone. This ketone reacted with CH_3MgI to give a 4/1 ratio of *S* and *R* isomers, thus aiding in assignment of stereochemistry. These assignments were made on the basis of chemical shifts of the hydrogen-bonded 19-OH protons,[12] which are substantially similar to the *R* and *S*

Scheme III. Synthesis of Nitrogen–C8β Ethano Bridged (β-6) Etorphine Analogue

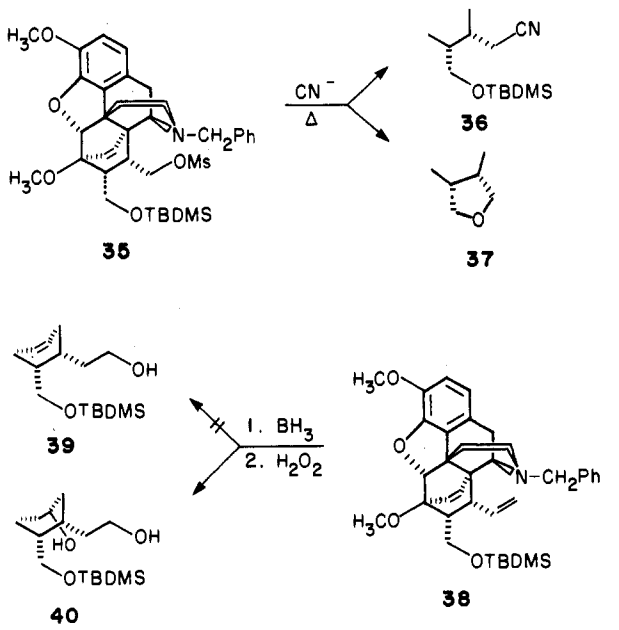


forms of butylthevinol. Furthermore, synthetic precedent (with thevinone) is quite clear and carries over into this heptacyclic analogue. Finally, the 3-*O*-methyl ether was cleaved with sodium propanethiolate in DMF, giving our first target phenol **4**. *N*,8β-Methano-19(*R*)-*n*-butylnororvinol is a simple but complete description of this new analogue.

Methods next were examined for homologating the C8 side chain of aldehyde **16** in order to prepare the six-membered ring (β-6) analogue. Many reactions that give good yields with a variety of aldehydes utterly failed when applied to this substrate. For example, (methoxymethylene)triphenylphosphorane failed to react. [Methoxy(trimethylsilyl)methyl]lithium[13] gave products that could not be characterized. Reductive cyanation[14] of the triisopropylbenzenesulfonohydrazide gave no nitrile. Nitromethane failed to aldol-condense under a variety of conditions. After examining these and several other possible one-carbon extensions, we found that [(trimethylsilyl)methyl]magnesium chloride[15,16] added cleanly, although slowly, to the aldehyde. The adduct **25** was smoothly converted to the 8β-vinyl compound **26** upon treatment with KH. Hydroboration/oxidation provided the 2-hydroxyethyl derivative **27** well enough (77% yield), although some desilylation also occurred.

The remaining steps are shown in Scheme III and proceeded from primary alcohol **27** via mesylation and ring closure to **28**, which was hydrogenolytically dequarternized to ethano-bridged tertiary amine **29**. Hydrolysis to primary carbinol **30** was then followed by various oxidations and organometallic reactions, finally yielding *N*,8β-ethano-19-(*R*)-*n*-butylnororvinol (**5**). Each reaction in this β-6 series gave essentially identical results as in the previous β-5 series except for the addition of *n*-butylmagnesium bromide to the methyl ketone. In the β-6 case about 25% of the starting ketone was always recovered. Fortunately, no epimerization occurred so the crude mixture of tertiary alcohol and ketone could be re-treated with the Grignard reagent, after which the pure *R* tertiary alcohol **34** could be crystallized from the reaction mixture after a simple extractive isolation.

Scheme IV

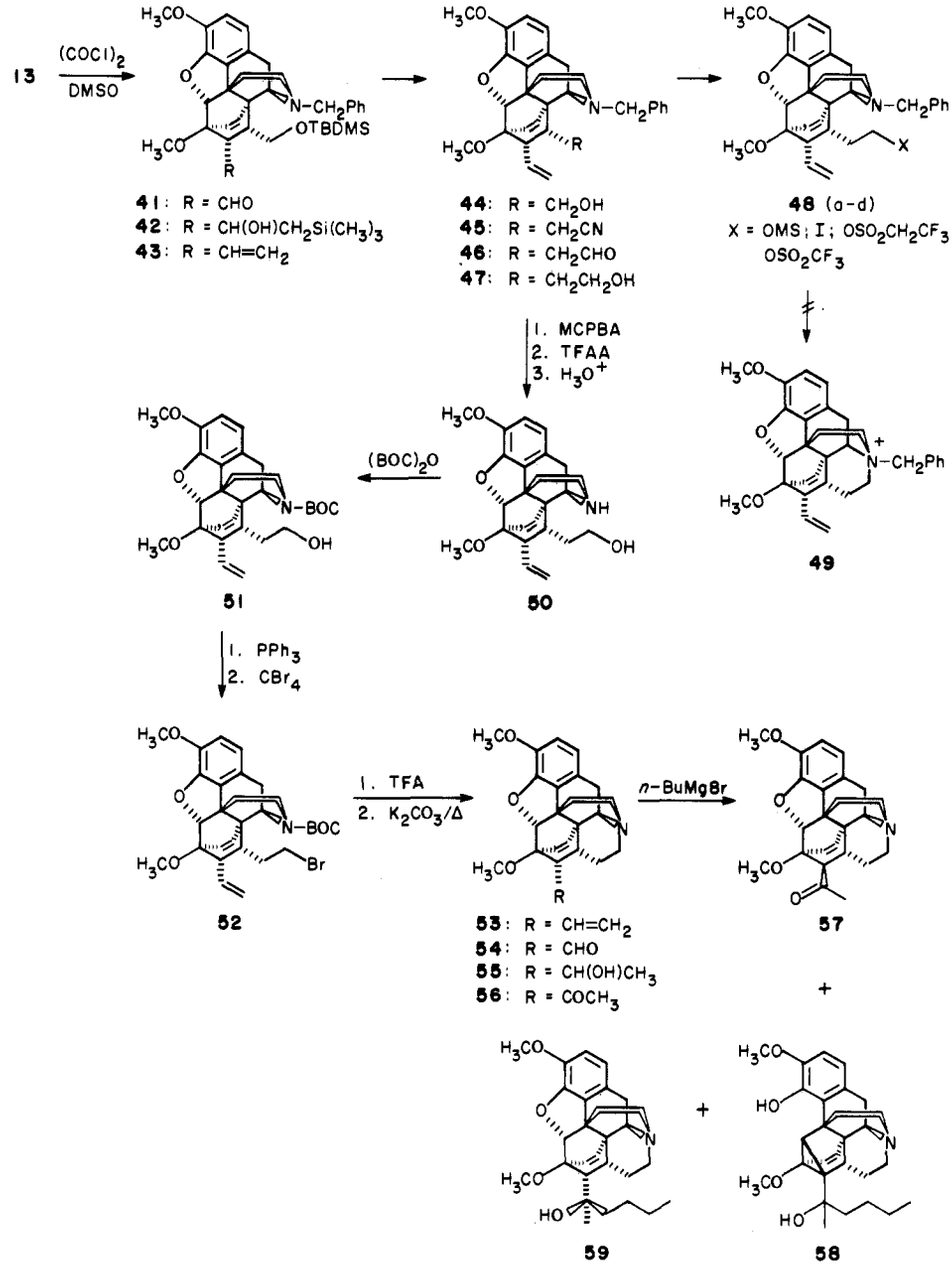


The α-6 analogue was by far the most difficult of the three to synthesize. Alcohol **12** could be easily converted to mesylate **35**, but intermolecular S_N2 displacement could not compete with intramolecular attack by the neighboring oxygen, producing tetrahydrofuran **37**. Chain extension analogous to the β-6 synthesis was also attempted. While the 8α-vinyl derivative **38** was easily produced, hydroboration/oxidation failed to give **39**. Rather, **40** was produced, apparently by intramolecular delivery of borane to the 17,18 double bond via a six-membered ring. Several dialkylboranes failed completely to react with **38** so this methodology was abandoned. These reactions are summarized in Scheme IV.

After several other failures at 8α chain extension, the S_N2 route was revived. It was, however, necessary to proceed with a substrate bearing no nucleophilic heteroatoms on the 7α appendage, as delineated in Scheme V. Thus, the 7α-vinyl compound **44** was prepared in four steps from monosilyl regioisomer **13** via aldehyde **41**, Peterson olefination to **43**, and desilylation to **44**, which was then easily converted into nitrile **45** by formation of the mesylate and cyanide displacement. Aldehyde **46** was produced from the nitrile by Dibal reduction, and further reduction

(12) Fulmor, W.; Lancaster, J. E.; Morton, G. O.; Brown, J. J.; Howell, C. F.; Nora, C. T.; Hardy, R. A. *J. Am. Chem. Soc.* **1967**, *89*, 3322.
(13) Magnus, P.; Roy, G. *Organometallics* **1982**, *1*, 553.
(14) Orere, D. M.; Reese, C. B. *J. Chem. Soc., Chem. Commun.* **1977**, 280.
(15) Whitmore, F. C.; Sommer, L. H. *J. Am. Chem. Soc.* **1946**, *68*, 481.
(16) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780.

Scheme V. Synthesis of Nitrogen–C8α Ethano Bridged (α-6) Etorphine Analogue



gave the hydroxyethyl derivative **47**. The hydroxyl group of **47** was converted to several different leaving groups (mesylate, iodide, tresylate, triflate), but all of these failed to alkylate the amino group to give the anticipated quarternary salt **49**.

In order to form the α-6 ring it was necessary to remove the *N*-benzyl group to facilitate N-alkylation by the 8α side chain. Hydrogenolysis was impractical with the 7α-vinyl group present; therefore, **47** was debenzylated by the Polonovski reaction, and the resulting secondary amine **50** was reprotected as the *N*-BOC derivative **51** and then converted into bromide **52**. After removal of the BOC group, cyclization was successful, giving **53** in high yield.

Elaboration of the 7α-vinyl group of **53** also proved to be problematic. Fortunately, however, cleavage with $OsO_4/NaIO_4$ was found to afford aldehyde **54** under carefully controlled conditions. In particular, both the stoichiometry and concentration of osmium were critical for success. If the concentration of osmium was increased above 5 mM, either by increasing stoichiometry or by reducing the amount of solvent, the reaction produced only intractable tar. Even under optimum conditions a 62/38 mixture of aldehyde **54** and recovered olefin **53** was obtained. Attempts to consume **53** completely only reduced the yield of **54**. Attempts to separate **53** and **54** failed, so the mixture was treated directly with CH_3MgI to obtain the carbinol epimers of **55**. These epimers were readily separated from olefin **53** and from each other. Oxidation of each epimer independently gave the same ketone **56**, thus proving the stereorelationship between the two. This was important since aldehyde **54** was labile toward epimerization, with equilibrium favoring the 7β form. Thus, the possibility that the two isomers of **55** may have been 7α and 7β derivatives was ruled out.

Further complications were encountered with the reaction of ketone **56** with *n*-BuMgBr. In contrast with the β-5 and β-6 analogues **23** and **33**, **56** gave a very poor yield of desired tertiary alcohol **59**. The main products **57** (50%), recovered **56** (25%), and **58** (15%) can all be formed by enolization of **56**, which is apparently strongly favored over normal Grignard addition because of steric hindrance by the 8α bridge.

Fortunately, 3-O-demethylation of **59** proceeded smoothly and provided enough of the α-6 etorphine ana-

Table I. Relative Analgesic Potency of Nitrogen-Bridged Etorphine Analogues

compound	ED_{50},[a] μmol/kg	rel analgesic potency
morphine	1.8	1
3 (homoetorphine)	0.0019	1000
4 (β-5)	>14	<0.13
5 (β-6)	>14	<0.13
6 (α-6)	2.8	0.64

[a] Using the rat tail withdrawal method and subcutaneous administration. Values are ±20%.

logue *N*,8α-ethano-19(*R*)-*n*-butylnororvinol (**6**) for biological testing.

Biological Evaluations and Discussion

The three etorphine analogues **4** (β-5), **5** (β-6), and **6** (α-6) were tested in rats for analgesia and morphine antagonism by using the rat tail withdrawal method. The compounds were injected subcutaneously as the acetate salts. Morphine and 19(*R*)-*n*-butylorvinol (**3**, homoetorphine) were used as analgesic standards, and naloxone was used as an antagonist standard. Compounds **4** and **5** showed no analgesia at doses up to 6 mg/kg whereas morphine was active at 0.25–0.5 mg/kg and homoetorphine was active at 0.8 μg/kg. Compound **6** showed analgesia at a dose of about 1.2 mg/kg and is thus about $^2/_3$ as potent as morphine and about 1500 times less potent than homoetorphine. These results are summarized in Table I. When challenged with 1 mg/kg of morphine, none of the new analogues showed antagonism. Compounds **4** and **5** were tested up to 6 mg/kg, and **6** was tested up to 0.4 mg/kg, or one-third of its analgesic dose. On the other hand, naloxone showed complete antagonism at a dose of 0.04 mg/kg.

Thus all three phenols **4–6** show severely diminished activities when compared to homoetorphine. The most active compound, **6**, is about 1500 times less potent than this standard. This indicates that by locking the N lone pair of electrons so as to point toward the aromatic ring side of the molecule (equatorial assuming a piperidine chair conformation), analgesic activity is essentially abolished. Furthermore, this lone-pair orientation does not permit significant antagonist activity.

These results do not conform to either the model of Snyder[6] nor that of Kolb.[7] They do, however, conform completely with the original postulate of Belleau[1,2] concerning the effect of nitrogen lone pair orientation on opiate agonist activity.

The corollary that opiate activity requires an axial nitrogen lone pair arrangement appears to be supported by recent results with constrained benzomorphans.[17] Synthesis and evaluation of similarly constrained etorphine analogues that are bridged from nitrogen to C10 are underway. These synthese are also directed at derivatives in which the new carbon α to N will bear benzyl, vinyl, cyclopropyl, and cyclobutyl groups.

Experimental Section

Pharmacological Methods. Analgesia was determined by using the tail-flick test with male Sprague–Dawley rats (260–300 g) as described.[18] Values for ED_{50} were calculated by using the up–down method.[19] New compounds were converted to their acetates, and all compounds were injected subcutaneously. Antagonism was defined as a lack of analgesia when a compound was co-injected with 1 mg/kg of morphine sulfate.

General Chemistry. All NMR spectra were recorded at 250 MHz in $CDCl_3$. Chemical shifts were assigned relative to residual $CHCl_3$ defined as 7.23 ppm. Melting points are uncorrected. Microanalyses and mass spectra were performed by the Analytical Laboratories, Chemistry Department, University of California, Berkeley. When required, solvents were dried by distillation from appropriate drying agents and reactions were conducted under nitrogen.

***N*-Benzoylnorthebaine (9).** To northebaine hydrochloride[10] (46.4 g, 0.139 mol), ground to a fine powder and suspended in CH_2Cl_2 (350 mL), was added Et_3N (40 g, 0.4 mol) followed by benzoic anhydride (37.3 g, 0.165 mol). The exothermic reaction mixture was cooled on ice for 30 min, then stirred at room temperature overnight, washed twice with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated. Trituration of the residue with $EtOH/Et_2O$ gave **9** as a white powder: 47 g, 84% yield; mp 137–140 °C; ^1H NMR δ 1.8–2.3 (m, 2 H), 2.9–3.2 (m, 1 H), 3.08 (d, 1 H, J = 17.3 Hz), 3.1–3.4 (m, 1 H), 3.4–3.6 (m, 1 H), 3.59 (s, 3 H), 3.82 (s, 3 H), 4.66 (m, 1 H), 5.01 (2 d, 1 H, J = 6.4 Hz, rotomers), 5.30 (2 s, 1 H, H-5 rotomers), 5.75 (2 d, 1 H, J = 7.4 Hz, rotomers), 6.5–6.7 (m, 2 H), 7.39 (2 s, 5 H, rotomers).

Anal. ($C_{25}H_{23}NO_4$) C, H, N.

***N*-Benzoylnorthebaine Maleic Anhydride Adduct (10).** *N*-Benzoylnorthebaine (**9**, 44.4 g, 0.11 mol) was dissolved in benzene (1 L), and 200 mL of the benzene was distilled to ensure dryness. Maleic anhydride (11.9 g, 0.12 mol) was added to the hot solution, which was then refluxed for 7 h. More benzene was distilled at atmospheric pressure until the remaining volume was 350 mL. Cooling gave the adduct **10** as gleaming crystals: 55 g, 99% yield; mp 270–272 °C dec; ^1H NMR δ 1.8–2.0 (m, 1 H), 1.95–2.2 (m, 1 H), 3.17 (br s, 3 H), 3.33 (d, 1 H, J = 8.6 Hz), 3.65 (s, 3 H), 3.80 (s, 3 H), 3.87 (d, 1 H, J = 9.4 Hz), 4.64 (d, 1 H, J = 1.3 Hz), 4.75 (br s, 1 H), 5.08 (br s, 1 H), 5.33 (br s, 1 H), 5.90 (br s, 1 H), 6.61 (d, 1 H, J = 8.3 Hz), 6.69 (d, 1 H, J = 8.2 Hz), 7.42 (s, 5 H).

Anal. ($C_{29}H_{25}NO_7$) C, H, N.

***N*-Benzyl-7α,8α-bis(hydroxymethyl)-*endo*-ethylene-tetrahydronorthebaine (11).** The maleic anhydride adduct **10** (54 g, 0.108 mol) in THF (700 mL) was added to lithium aluminum hydride (17.7 g, 0.466 mol) in THF (50 mL) over 15 min. The mixture was refluxed for 3 h, then cooled, and quenched with water (12 mL), 15% NaOH (18 mL), and water (50 mL), while cooling on ice. Filtration of the granular precipitate and evaporation of the filtrate left a residue, which was crystallized (benzene/moist ether) to give **11** as the monohydrate: 33 g, 64% yield; mp 155–156 °C; ^1H NMR δ 3.57 (s, 3 H), 3.79 (s, 3 H), 4.58 (d, 1 H, J = 1.2 Hz), 5.28 (d, 1 H, J = 8.8 Hz), 5.76 (d, 1 H, J = 8.7 Hz), 6.52 (d, 1 H, J = 8.1 Hz), 6.61 (d, 1 H, J = 8.1 Hz), 7.3 (m, 5 H).

Anal. ($C_{29}H_{33}NO_5 \cdot H_2O$) C, H, N.

7α-*tert*-Butyldimethylsilyl Ether 12. The hydrated diol **11** (28 g, 58.9 mmol) was dissolved in benzene (300 mL), and the benzene was distilled out at atmospheric pressure, leaving anhydrous **11** as a syrup. This was redissolved in CH_2Cl_2 (250 mL) and treated with Et_3N (9.03 mL, 65 mmol), DMAP (720 mg, 5.9 mmol), and TBDMS-Cl (9.32 g, 61.8 mmol). After being stirred overnight at room temperature, the solution was washed with water and then saturated aqueous $NaHCO_3$ and dried (K_2CO_3). Evaporation of the CH_2Cl_2 and chromatography of the residue (silica gel; $CHCl_3$/isooctane, 80/20) gave regioisomer **12** (23.2 g, 69.3% yield) as an oil, as well as isomer **13** (9.4 g, 28% yield) also as an oil.

12: ^1H NMR δ 0.053 (s, 3 H), 0.074 (s, 3 H), 0.85 (s, 9 H), 3.54 (s, 3 H), 3.79 (s, 3 H), 4.54 (d, 1 H, J = 1.2 Hz), 5.29 (d, 1 H, J = 8.8 Hz), 5.68 (d, 1 H, J = 8.7 Hz), 6.52 (d, 1 H, J = 8.1 Hz), 6.60 (d, 1 H, J = 8.1 Hz), 7.2–7.4 (m, 5 H).

Anal. ($C_{35}H_{47}NO_5Si$) C, H, N.

13: ^1H NMR: δ −0.076 (s, 3 H), −0.022 (s, 3 H), 0.84 (s, 9 H), 3.60 (s, 3 H), 3.79 (s, 3 H), 4.12 (t, 1 H, J = 5.9 Hz, hydrogen-bonded OH), 4.58 (d, 1 H, J = 1.2 Hz), 5.29 (d, 1 H, J = 8.8 Hz),

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5.81 (d, 1 H, J = 8.8 Hz), 6.52 (d, 1 H, J = 8.1 Hz), 6.61 (d, 1 H, J = 8.2 Hz), 7.2–7.4 (m, 5 H).

Anal. ($C_{35}H_{47}NO_5Si$) C, H, N.

8α-*tert*-Butyldimethylsilyl Ether 13. Diol 11·H_2O (4.31 g, 8.73 mmol) was dissolved in benzene, and the benzene was distilled out to give anhydrous 11. The anhydrous 11 was dissolved in THF (40 mL) under N_2 and added to degreased KH (0.37 g, 9.17 mmol), and the mixture was stirred for 1 **h** at room temperature, then cooled to −78 °C, and treated with *n*-BuLi (1.55 M in hexane; 5.63 mL; 8.73 mmol). The red solution was warmed briefly to 0 °C when the color faded to pale yellow and then cooled again to −78 °C, and TBDMS-Cl (1.45 g, 9.6 mmol) in THF (8 mL) was added, followed by stirring and slow warming to room temperature (over about 8 h). Quenching with saturated aqueous $NaHCO_3$ (10 mL) and evaporating left a residue, which was dissolved in $CHCl_3$, washed with saturated aqueous $NaHCO_3$, dried, evaporated, and chromatographed (silica gel; $CHCl_3$/isooctane, 80/20) to give 4.2 g, 82% yield, of 8α isomer **13**. Also obtained were 7α isomer **12** (12%) and bis(silyl ether) **14** (6%).

***N*-Benzyl-8α-formyl-7α-[[(*tert*-butyldimethylsilyl)oxy]methyl]-*endo*-ethylenetetrahydronorthebaine (15).** This procedure is illustrative of all the oxidations[11] performed in this work. To a solution of oxalyl chloride (7.10 mL, 81.4 mmol, 300 mol %) in CH_2Cl_2 (300 mL) at −78 °C was added dropwise DMSO (9.62 mL, 136 mmol, 500 mol %) in CH_2Cl_2 (170 mL). After the reaction mixture was stirred for 5 min at −78 °C, a solution of **12** (16 g, 27.1 mmol) in CH_2Cl_2 (100 mL) was also added dropwise and stirring was continued at −78 °C for $^1/_2$ h and then as the temperature was raised to −40 °C for another $^1/_2$ h. At this point, Et_3N (30.2 mL, 217 mmol, 800 mol %) was added and the stirred solution was allowed to rise to 0 °C, then poured into saturated aqueous $NaHCO_3$, and shaken. The organic phase was washed twice with water and again with saturated aqueous $NaHCO_3$ and then dried (K_2CO_3) and the solvent evaporated to give nearly pure aldehyde **15** suitable for use in the next step: 15.5 g (97% yield) as an oil. An analytical sample was obtained by rapid radial chromatography (silica gel deactivated with MeOH and dried at room temperature; $CHCl_3$/isooctane, 80/20): ^{1}H NMR: δ −0.032 (s, 3 H), −0.023 (s, 3 H), 0.81 (s, 9 H), 1.7–2.0 (m, 2 H), 2.4–2.6 (m, 4 H), 3.23 (d, 1 H, J = 18.6 Hz), 3.43 (d, 1 H, J = 6.4 Hz), 3.45–3.8 (m, 4 H), 3.56 (s, 3 H), 3.79 (s, 3 H), 3.97 (dd, 1 H, J_1 = 3.9 Hz, J_2 = 10.2 Hz), 4.54 (d, 1 H, J = 0.9 Hz), 5.46 (d, J = 8.8 Hz), 5.91 (d, 1 H, J = 8.8 Hz), 6.53 (d, 1 H, J = 8.2 Hz), 6.62 (d, 1 H, J = 8.2 Hz), 7.2–7.5 (m, 5 H), 9.51 (d, 1 H, J = 3.9 Hz).

Anal. ($C_{35}H_{45}NO_5Si$) C, H, N.

***N*-Benzyl-8β-formyl-7α-[[(*tert*-butyldimethylsilyl)oxy]methyl]-*endo*-ethylenetetrahydronorthebaine (16).** The 8α-aldehyde **15** (10.0 g; 17.0 mmol), dissolved in $CHCl_3$ (ethanol free, 200 mL), was added to silica gel (200–400 mesh, activated at 160 °C, 25 g) and stirred for 2 days. The mixture was filtered, the filtrate was evaporated, and the residue was dissolved in isooctane and left overnight. The crystals of **16** were collected, and the mother liquors were reequilibrated to give another crop: combined yield, 5.2 g, 52%; mp 125–126 °C; ^{1}H NMR δ −0.047 (s, 3 H), −0.040 (s, 3 H), 0.80 (s, 9 H), 1.6–1.75 (m, 1 H), 2.1–2.3 (m, 1 H), 2.3–2.65 (m, 4 H), 2.7–2.9 (m, 1 H), 3.17 (dd, 1 H, J_1 = 8.8 Hz, J_2 = 10.0 Hz), 3.26 (d, 1 H, J = 18.5 Hz), 3.5–3.6 (m, 1 H), 3.53 (s, 3 H), 3.6–3.75 (m, 3 H), 3.78 (s, 3 H), 4.71 (d, 1 H, J = 1.2 Hz), 5.45 (d, 1 H, J = 8.4 Hz), 5.65 (d, 1 H, J = 8.5 Hz), 6.51 (d, 1 H, J = 7.9 Hz), 6.60 (d, 1 H, J = 7.9 Hz), 7.25–7.35 (m, 5 H), 9.96 (d, 1 H, J = 2.8 Hz).

Anal. ($C_{35}H_{45}NO_5Si$) C, H, N.

***N*-Benzyl-8β-(hydroxymethyl)-7α-[[(*tert*-butyldimethylsilyl)oxy]methyl]-*endo*-ethylenetetrahydronorthebaine (17).** The 8β-aldehyde **16** (2.43 g, 4.13 mmol) was dissolved in MeOH (17 mL) plus benzene (7 mL) and added to a freshly prepared solution of $NaBH_4$ (1.0 g in 30 mL of MeOH), which was stirred at room temperature for 30 min, quenched with 10% HOAc, and poured into saturated aqueous $NaHCO_3$. The mixture was extracted with $CHCl_3$, the extracts were dried (K_2CO_3), and the solvent was evaporated to leave alcohol **17** as an analytically pure oil: 2.44 g, 100% yield; ^{1}H NMR δ −0.005 (s, 6 H), 0.84 (s, 9 H), 1.45–1.6 (m, 1 H), 1.75–1.9 (m, 2 H), 2.2–2.35 (m, 1 H), 2.35–2.5 (m, 1 H), 2.52 (dd, 1 H, J_1 = 6.3 Hz, J_2 = 19 Hz), 2.6–2.75 (m, 1 H), 3.24 (dd, 1 H, J_1 = 7.6 Hz, J_2 = 10.1 Hz), 3.42 (d, 1 H, J = 20 Hz), 3.46 (s, 3 H), 3.5–3.8 (2 m, 4 H), 3.79 (s, 3 H), 3.8–4.05 (m, 2 H), 4.64 (d, 1 H, J = 1.3 Hz), 5.44 (d, 1 H, J = 8.7 Hz), 5.58 (d, 1 H, J = 8.7 Hz), 6.53 (d, 1 H, J = 8.2 Hz), 6.60 (d, 1 H, J = 8.2 Hz), 7.2–7.4 (m, 5 H), 7.6–7.8 (br d, 1 H, J = 5–6 Hz).

Anal. ($C_{35}H_{47}NO_5Si$) C, H, N.

***N*-Benzyl-*N*,8β-methano-7α-[[(*tert*-butyldimethylsilyl)oxy]methyl]-*endo*-ethylenetetrahydronorthebaine Quaternary Salt (18).** To the 8β-hydroxymethyl derivative **17** (1.43 g, 2.42 mmol) dissolved in CH_2Cl_2 (25 mL) and cooled to 0 °C were added Et_3N (0.85 mL, 6 mmol) and then methanesulfonyl chloride (0.23 mL, 2.90 mmol), and the solution was stirred at 0 °C for 5 min. It was then washed with saturated aqueous $NaHCO_3$ twice and with saturated aqueous $NaHCO_3$/saturated aqueous NaCl, 1/9, once. The organic phase was dried (Na_2SO_4) and evaporated to leave the quaternary chloride **18** as a brittle glass: 1.46 g, 99% yield; ^{1}H NMR δ −0.040 (s, 3 H), −0.028 (s, 3 H), 0.79 (s, 9 H), 1.9–2.1 (m, 1 H), 2.1–2.4 (m, 3 H), 3.0–3.2 (m, 2 H), 3.4–3.6 (m, 1 H), 3.51 (s, 3 H), 3.6–3.8 (m, 2 H), 3.74 (s, 3 H), 3.8–4.0 (m, 1 H), 4.02 (d, 1 H, J = 20.0 Hz), 4.42 (t, 1 H, J = 12.0 Hz), 4.65 (s, 1 H), 4.92 (d, 1 H, J = 8.1 Hz), 5.29 (d, 1 H, J = 12.8 Hz), 5.45 (d, 1 H, J = 8.7 Hz), 5.46 (d, 1 H, J = 12.8 Hz), 5.81 (d, 1 H, J = 8.7 Hz), 6.42 (d, 1 H, J = 8.2 Hz), 6.56 (d, 1 H, J = 8.2 Hz), 7.3–7.5 (m, 3 H), 7.72 (d, 2 H, J = 6.0 Hz).

***N*,8β-Methano-7α-[[(*tert*-butyldimethylsilyl)oxy]methyl]-*endo*-ethylenetetrahydronorthebaine (19).** To the quaternary salt **18** (0.70 g, 1.15 mmol) dissolved in MeOH (12 mL) were added ammonium formate (0.70 g) and 5% Pd/C (230 mg). After the reaction mixture was stirred at room temperature for $^1/_2$ h, another equal portion of catalyst was added, and the mixture was rapidly heated to reflux (preheated sandbath) and held there for 45 s. The mixture was then allowed to cool over 3–5 min while stirring was continued. Filtering (Celite) and evaporating the filtrate left a residue, which was distributed between $CHCl_3$ and saturated aqueous $NaHCO_3$. The $CHCl_3$ layer was dried (K_2CO_3) and evaporated, and the residue was crystallized ($CHCl_3$/hexanes) to give **19**: 440 mg, 79% yield; mp 199–199.5 °C; ^{1}H NMR δ −0.017 (s, 3 H), 0.00 (s, 3 H), 0.84 (s, 9 H), 1.7–2.0 (m, 3 H), 2.2–2.4 (m, 1 H), 2.6–2.7 (m, 1 H), 2.75–3.0 (m, 2 H), 3.11 (t, 1 H, J = 9.9 Hz), 3.1–3.3 (m, 1 H), 3.24 (d, 1 H, J = 18.8 Hz), 3.4–3.5 (m, 2 H), 3.56 (s, 3 H), 3.78 (s, 3 H), 3.89 (dd, 1 H, J_1 = 4.8 Hz, J_2 = 9.6 Hz), 4.64 (s, 1 H), 5.41 (d, 1 H, J = 8.6 Hz), 5.78 (d, 1 H, J = 8.7 Hz), 6.56 (unsym d, 1 H, J = 8.2 Hz), 6.58 (unsym d, 1 H, J = 8.2 Hz).

Anal. ($C_{28}H_{39}NO_4Si$) C, H, N.

***N*,8β-Methano-7α-(hydroxymethyl)-*endo*-ethylenetetrahydronorthebaine (20).** Compound **19** (300 mg, 0.62 mmol) was dissolved in MeOH (8 mL) and stirred at room temperature for 40 min with 1 N HCl (2 mL). After 3 N NaOH (0.7 mL) was added, the mixture was distributed between $CHCl_3$ and saturated aqueous $NaHCO_3$, the $CHCl_3$ layer was dried (K_2CO_3) and evaporated, and the residue was crystallized ($CHCl_3$/hexanes) to give alcohol **20**: 210 mg, 92% yield; mp 244–248 °C dec; ^{1}H NMR δ 1.3–1.5 (m, 1 H), 1.8–2.0 (m, 2 H), 2.2–2.3 (m, 1 H), 2.6–2.75 (m, 1 H), 2.85–3.0 (m, 2 H), 3.1–3.6 (m, 6 H), 3.68 (s, 3 H) 3.78 (s, 3 H), 4.61 (d, 1 H, J = 1.0 Hz), 5.44 (d, 1 H, J = 8.7 Hz), 5.96 (d, 1 H, J = 8.7 Hz), 6.56 (unsym d, 1 H, J = 8.2 Hz), 6.59 (unsym d, 1 H, J = 8.2 Hz).

Anal. ($C_{22}H_{25}NO_4$) C, H, N.

***N*,8β-Methano-7α-formyl-*endo*-ethylenetetrahydronorthebaine (21).** Oxidation of **20** proceeded as described for compound **15**; however, since alcohol **20** was only slightly soluble in CH_2Cl_2, it was added as a light, syringe-transferable suspension in CH_2Cl_2/DMSO, 80/20. The aldehyde **21** was crystallized (benzene/hexanes) in 77% yield: mp 180–182 °C; ^{1}H NMR δ 1.7–1.85 (m, 1 H), 1.8–2.0 (m, 1 H), 2.1–2.3 (m, 1 H), 2.67 (dd, 1 H, J_1 = 7.0 Hz, J_2 = 16 Hz), 2.8–2.95 (m, 2 H), 3.00 (d, 1 H, J = 8.3 Hz), 3.2–3.3 (m, 1 H), 3.27 (d, 1 H, J = 18.8 Hz), 3.40 (dd, 1 H, J_1 = 10.6 Hz, J_2 = 13.4 Hz), 3.52 (d, 1 H, J = 8.2 Hz), 3.61 (s, 3 H), 3.78 (s, 3 H), 4.66 (d, 1 H, J = 1.2 Hz), 5.56 (d, 1 H, J = 8.7 Hz), 6.00 (d, 1 H, J = 8.7 Hz), 6.60 (s, 2 H), 9.40 (d, 1 H, J = 4.1 Hz).

Anal. ($C_{22}H_{23}NO_4$) C, H, N.

***N*,8β-Methano-7α-(1-hydroxyethyl)-*endo*-ethylenetetrahydronorthebaine (22).** A solution of 2 M MeMgI in Et_2O (0.294 mL, 0.586 mmol) was diluted into THF (4 mL), and to this solution was added aldehyde **21** (107.2 mg, 0.294 mmol) in THF (4 mL). The mixture was stirred at room temperature for $^1/_2$ h,

then poured into saturated aqueous $NaHCO_3$, and extracted with $CHCl_3$. Evaporation of the dried (K_2CO_3) extracts left secondary alcohol **22**: 109 mg, 97% yield; 11/1 mixture of carbinol epimers; oil; ^1H NMR (major epimer only) δ 1.033 (d, 3 H, J = 6.5 Hz), 1.7–2.1 (m, 4 H), 2.25 (br s, 1 H), 2.64 (dd, 1 H, J_1 = 6.8 Hz, J_2 = 11 Hz), 2.79 (dd, 1 H, J_1 = 4.8 Hz, J_2 = 12.9 Hz), 2.92 (dd, 1 H, J_1 = 8.7 Hz, J_2 = 19.0 Hz) 3.1–3.3 (m, 1 H), 3.23 (d, 1 H, J = 18.8 Hz), 3.3–3.5 (m, 1 H), 3.45 (d, 1 H, J = 7.9 Hz), 3.64 (s, 3 H), 3.77 (s, 3 H), 4.1–4.25 (m, 1 H), 4.59 (d, 1 H, J = 1.0 Hz), 5.35 (d, 1 H, J = 8.6 Hz), 5.88 (d, 1 H, J = 0.9 Hz), 6.55 (unsym d, 1 H, J = 8 Hz), 6.57 (unsym d, 1 H, J = 8 Hz).

***N*,8β-Methano-7α-acetyl-*endo*-ethylenetetrahydronorthebaine (23).** Ketone **23** was prepared by oxidation of **22** as described for compound **15** and was crystallized from benzene/hexanes: 84% yield; mp 180–182 °C; ^1H NMR δ 1.7–2.0 (m, 2 H), 2.14 (s, 3 H), 2.1–2.3 (m, 1 H), 2.67 (dd, 1 H, J_1 = 6.6 Hz, J_2 = 14.5 Hz), 2.86 (dd, 1 H, J_1 = 5.5 Hz, J_2 = 13.4 Hz), 2.95 (dd, 1 H, J_1 = 8.3 Hz, J_2 = 19.0 Hz), 3.05 (d, 1 H, J = 8.0 Hz), 3.15–3.3 (m, 1 H), 3.27 (d, 1 H, J = 18.8 Hz), 3.36 (dd, 1 H, J_1 = 10 Hz, J_2 = 13.3 Hz), 3.48 (d, 1 H, J = 8.2 Hz), 3.58 (s, 3 H), 3.78 (s, 3 H), 4.62 (d, 1 H, J = 1.1 Hz), 5.52 (d, 1 H, J = 8.7 Hz), 6.01 (d, 1 H, J = 8.6 Hz), 6.58 (unsym d, 1 H, J = 8 Hz), 6.63 (unsym d, 1 H, J = 8 Hz).

Anal. ($C_{23}H_{25}NO_4$) C, H, N.

***N*,8β-Methano-19(*R*)-butylnorthevinol (24).** The reaction of ketone and *n*-BuMgBr was carried out as described for the reaction of MeMgI and **21**. A trace (≈2%) of ketone remained and was eliminated by subjecting the reaction mixture to $NaBH_4$ reduction, followed by radial chromatography (silica gel; $CHCl_3$/MeOH, 92/8): 84% yield; oil; ^1H NMR δ 0.86 (t, 3 H, J = 7.0 Hz), 0.99 (s, 3 H), 1.1–1.5 (m, 6 H), 1.45–1.6 (m, 1 H), 1.8–1.95 (m, 2 H), 2.19 (d, 1 H, J = 8.7 Hz), 2.6–2.75 (m, 1 H), 2.8–3.0 (m, 2 H), 3.15–3.45 (m, 2 H), 3.22 (d, 1 H, J = 19.0 Hz), 3.41 (d, 1 H, J = 7.9 Hz), 3.71 (s, 3 H), 3.77 (s, 3 H), 4.59 (d, 1 H, J = 0.7 Hz), 4.83 (s, 1 H, O*H*), 5.32 (d, 1 H, J = 8.7 Hz), 6.01 (d, 1 H, J = 8.6 Hz), 6.53 (unsym d, 1 H, J = 8.2 Hz), 6.57 (unsym d, 1 H, J = 8.1 Hz); MS, m/e calcd for $C_{27}H_{35}NO_4$ 437.2556, found 437.2573 (intensity, 64.9).

***N*,8β-Methano-19(*R*)-butylnororvinol (4).** A solution of **24** (39 mg, 89 μmol) and propanethiol (80.7 μL, 0.89 mmol) in DMF (5 mL) was added to degreased NaH (50 mg) and refluxed for 1 h. The cooled reaction mixture was diluted with 0.5 M H_3PO_4 and washed with Et_2O, and the aqueous phase was basified (to pH 9) with concentrated NH_3 (aqueous) and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O (3×) and saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated, and the residue was crystallized from benzene/hexanes to give phenol **4**: 29 mg, 77% yield; mp 231–233 °C; ^1H NMR δ 0.86 (t, 3 H, J = 6.8 Hz), 1.00 (s, 3 H), 1.0–1.5 (m, 6 H), 1.5–1.7 (m, 1 H), 1.8–2.05 (m, 2 H), 2.19 (d, 1 H, J = 8.6 Hz), 2.65–2.85 (m, 1 H), 2.8–3.0 (m, 2 H), 3.15–3.4 (m, 1 H), 3.23 (d, 1 H, J = 19.0 Hz), 3.35–3.5 (m, 1 H), 3.49 (d, 1 H, J = 8.0 Hz), 3.73 (s, 3 H), 4.61 (s, 1 H), 4.83 (s, 1 H), 5.34 (d, 1 H, J = 8.7 Hz), 6.03 (d, 1 H, J = 8.7 Hz), 6.49 (s, 2 H); MS, m/e calcd for $C_{26}H_{33}NO_4$ 423.2414, found 423.2406 (intensity, 93.5).

***N*-Benzyl-8β-[1-hydroxy-2-(trimethylsilyl)ethyl]-7α-[[(*tert*-butyldimethylsilyl)oxy]methyl]-*endo*-ethylenetetrahydronorthebaine (25).** A solution of aldehyde **16** (2.0 g, 3.4 mmol) in THF (15 mL) was treated with [(trimethylsilyl)-methyl]magnesium chloride[15,16] (1.7 M in THF, 5.00 mL, 8.51 mmol) and stirred at room temperature for 25 h. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$, and the extracts were dried (K_2CO_3) and evaporated. The residue was crystallized from isooctane to give **25** as a single epimer: 1.93 g, 84% yield; mp 142–143 °C; ^1H NMR δ −0.021 (s, 3 H), −0.010 (s, 3 H), 0.091 (s, 9 H), 0.82 (s, 9 H), 1.09 (dd, 1 H, J_1 = 11.8 Hz, J_2 = 14.4 Hz), 1.70 (d, 1 H, J = 7.7 Hz), 1.81 (dd, 1 H, J_1 = 3.8 Hz, J_2 = 8.3 Hz), 2.12 (m, 1 H), 2.4–2.6 (m, 4 H), 3.31 (d, 1 H, J = 18.5 Hz), 3.48 (s, 3 H), 3.5–3.9 (m, 6 H), 3.78 (s, 3 H), 4.58 (m, 1 H), 4.64 (d, 1 H, J = 0.9 Hz), 4.82 (d, 1 H, J = 5.2 Hz), 5.42 (unsym d, 1 H, J = 8.8 Hz), 5.48 (unsym d, 1 H, J = 8.6 Hz), 6.47 (d, 1 H, J = 8.1 Hz), 6.56 (d, 1 H, J = 8.1 Hz), 7.25–7.4 (m, 5 H).

Anal. ($C_{39}H_{57}NO_5Si_2$) C, H, N.

***N*-Benzyl-8β-vinyl-7α-[[(*tert*-butyldimethylsilyl)oxy]-methyl]-*endo*-ethylenetetrahydronorthebaine (26).** Compound **25** (1.93 g, 2.85 mmol) in THF (35 mL) was added to degreased KH (171 mg, 4.27 mmol). Stirring at room temperature for 24 h was followed by addition of saturated aqueous $NaHCO_3$ and extraction into $CHCl_3$. The $CHCl_3$ layer was dried (K_2CO_3) and evaporated, and the residue was chromatographed (silica gel; $CHCl_3$/isooctane, 80/20) to give **26**: 1.49 g, 89% yield; oil; ^1H NMR δ 0.001 (s, 6 H), 0.84 (s, 9 H), 1.6 (m, 1 H), 1.7–1.9 (m, 1 H), 2.13 (m, 1 H), 2.23 (t, J = 8.8 Hz, 1 H), 2.3–2.6 (m, 3 H), 3.29 (d, J = 18.4 Hz, 1 H), 3.40 (d, 1 H, J = 6.0 Hz), 3.47–3.69 (m, 4 H), 3.58 (s, 3 H), 3.81 (s, 3 H), 4.64 (d, 1 H, J = 1.0 Hz), 4.87 (dd, 1 H, J_1 = 1.1 Hz, J_2 = 16.7 Hz), 4.99 (dd, 1 H, J_1 = 1.9 Hz, J_2 = 9.8 Hz), 5.41 (d, 1 H, J = 8.7 Hz), 5.66 (d, 1 H, J = 8.7 Hz), 6.51 (d, 1 H, J = 9.3 Hz), 6.60 (d, 1 H, J = 8.2 Hz), 6.6 (m, 1 H), 7.2–7.38 (m, 3 H), 7.38–7.48 (m, 2 H).

Anal. ($C_{36}H_{47}NO_4Si$) C, H, N.

***N*-Benzyl-8β-(2-hydroxyethyl)-7α-[[(*tert*-butyldimethylsilyl)oxy]methyl]-*endo*-ethylenetetrahydronorthebaine (27).** Olefin **26** (0.94 g, 1.60 mmol) in THF (35 mL) was treated with BH_3·THF (0.9 M in THF, 2.67 mL, 2.40 mmol) and stirred at room temperature for 1 h. Aqueous NaOH (3 M, 2.67 mL, 8.0 mmol) was added followed by H_2O_2 (30%, 1.2 mL, 12 mmol), and stirring was continued for 3.5 h. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extracts were washed with saturated aqueous $NaHCO_3$ containing Na_2SO_3, then dried (K_2CO_3), and evaporated to a residue, which was chromatographed (silica gel, $CHCl_3$) to give alcohol **27**: 750 mg, 77% yield; oil; ^1H NMR δ 0.033 (s, 3 H), 0.041 (s, 3 H), 0.86 (s, 9 H), 1.5–2.0 (m, 5–6 H), 2.15–2.3 (m, 1 H), 2.35–2.5 (m, 2 H), 2.5–2.7 (m, 1 H), 3.3–3.5 (m, 2 H), 3.49 (s, 3 H), 3.5–3.65 (m, 3–4 H), 3.65–3.9 (m, 2 H), 3.79 (s, 3 H), 4.65 (d, 1 H, J = 1.0 Hz), 5.45 (d, 1 H, J = 8.7 Hz), 5.52 (d, 1 H, J = 8.7 Hz), 6.50 (d, 1 H, J = 8.1 Hz), 6.58 (d, 1 H, J = 8.1 Hz), 7.3 (s, 5 H).

Anal. ($C_{36}H_{49}NO_5Si$) C, H, N.

***N*-Benzyl-*N*,8β-ethano-7α-[[(*tert*-butyldimethylsilyl)-oxy]methyl]-*endo*-ethylenetetrahydronorthebaine quaternary salt (28)** was prepared by mesylation/quaternization of **27** as described for compound **18**. It was obtained as the chloride: 100% yield; brittle glass; ^1H NMR δ −0.09 (s, 3 H), −0.07 (s, 3 H), 0.75 (s, 9 H), 1.6–1.8 (m, 2 H), 2.0–2.4 (m, 3 H), 2.5–2.7 (m, 1 H), 3.0–3.2 (m, 2 H), 3.3–3.7 (m, 2 H), 3.46 (s, 3 H), 3.72 (d, 1 H, J = 4.0 Hz), 3.77 (s, 3 H), 3.91 (d, 1 H, J = 7.5 Hz), 4.27 (d, 1 H, J = 19.8 Hz), 4.4 (m, 1 H), 4.65 (m, 1 H), 4.71 (d, 1 H, J = 0.9 Hz), 5.22 (d, 1 H, J = 13.0 Hz), 5.26 (d, 1 H, J = 8.7 Hz), 5.57 (d, 1 H, J = 13.2 Hz), 5.67 (d, 1 H, J = 8.7 Hz), 6.65 (s, 2 H), 7.4 (m, 3 H), 7.7 (m, 2 H).

***N*,8β-Ethano-7α-[[(*tert*-butyldimethylsilyl)oxy]-methyl]-*endo*-ethylenetetrahydronorthebaine (29)** was prepared from **28** by reductive debenzylation as described for **19**: 100% yield; foam; ^1H NMR δ −0.12 (s, 3 H), −0.005 (s, 3 H), 0.83 (s, 9 H), 1.65–2.1 (m, 5 H), 2.1–2.25 (m, 1 H), 2.83 (dd, 1 H, J_1 = 6.6 Hz, J_2 = 15.0 Hz), 2.94 (d, 1 H, J = 18.7 Hz), 3.05 (d, 1 H, J = 7.7 Hz), 3.1–3.4 (m, 4 H), 3.43 (d, 1 H, J = 7.5 Hz), 3.50 (s, 3 H), 3.78 (s, 3 H), 3.8–3.9 (m, 1 H), 4.65 (d, 1 H, J = 1.2 Hz), 5.26 (d, 1 H, J = 8.6 Hz), 5.66 (d, 1 H, J = 8.6 Hz), 6.51 (d, 1 H, J = 8.1 Hz), 6.59 (d, 1 H, J = 8.1 Hz).

Anal. ($C_{29}H_{41}NO_4Si$) C, H, N.

***N*,8β-Ethano-7α-(hydroxymethyl)-*endo*-ethylenetetrahydronorthebaine (30)** was prepared by acidic desilylation of **29** as described for compound **20** and purified by acid/base distribution: 100% yield; oil; ^1H NMR δ 1.1–1.3 (m, 1 H), 1.6–1.8 (m, 1 H), 1.75–2.0 (m, 3 H), 2.0–2.2 (m, 1 H), 2.75–3.0 (m, 2 H), 3.0–3.4 (m, 7 H), 3.4–3.6 (m, 1 H), 3.69 (s, 3 H), 3.80 (s, 3 H), 4.60 (d, 1 H, J = 1.2 Hz), 5.35 (d, 1 H, J = 8.7 Hz), 5.93 (d, 1 H, J = 8.7 Hz), 6.51 (d, 1 H, J = 8.1 Hz), 6.61 (d, 1 H, J = 8.1 Hz).

Anal. ($C_{23}H_{27}NO_4$) C, H, N.

***N*,8β-Ethano-7α-formyl-*endo*-ethylenetetrahydronorthebaine (31)** was prepared by oxidation of **30** as described for compound **15** and crystallized (benzene/hexanes) in 90% yield: mp 212–214 °C; ^1H NMR δ 1.7–1.95 (m, 3 H), 1.95–2.2 (m, 3 H), 2.37 (dd, 1 H, J = 4.4 Hz, J_2 = 5.7 Hz), 2.85 (dd, 1 H, J_1 = 6.7 Hz, J_2 = 15.1 Hz), 2.98 (d, 1 H, J = 18.8 Hz), 3.05–3.2 (m, 2 H), 3.2–3.45 (m, 1 H), 3.48 (d, 1 H, J = 7.6 Hz), 3.57 (s, 3 H), 3.78 (s, 3 H), 4.65 (d, 1 H, J = 1.3 Hz), 5.46 (d, 1 H, J = 8.7 Hz), 5.92 (ddd, 1 H, J_1 = 8.6 Hz, J_2 = 1.0 Hz, J_3 = 1.0 Hz), 6.53 (d, 1 H, J = 8.2 Hz), 6.61 (d, 1 H, J = 8.2 Hz), 9.36 (d, 1 H, J = 4.2 Hz).

Anal. ($C_{23}H_{25}NO_4$) C, H, N.

N,8β-Ethano-7α-(1-hydroxyethyl)-*endo*-ethylenetetrahydronorthebaine (32) was prepared by treating aldehyde **31** with MeMgI as described for compound **22**. The product was obtained as an oily, 5/1 mixture of carbinol epimers in 99% yield: ^{1}H NMR (major epimer only) δ 1.08 (d, 3 H, J = 6.6 Hz), 1.6–1.8 (m, 2 H), 1.8–2.0 (m, 3 H), 2.05–2.25 (m, 1 H), 2.8–2.9 (m, 2 H), 2.94 (d, 1 H, J = 18.7 Hz), 3.04 (d, 1 H, J = 7.5 Hz), 3.1–3.2 (m, 2 H), 3.2–3.4 (m, 1 H), 3.41 (d, 1 H, J = 7.3 Hz), 3.64 (s, 3 H), 3.78 (s, 3 H), 3.8–4.0 (m, 1 H), 4.58 (d, 1 H, J = 1.1 Hz), 5.27 (d, 1 H, J = 8.7 Hz), 5.88 (d, 1 H, J = 8.7 Hz), 6.49 (d, 1 H, J = 8.1 Hz), 6.59 (d, 1 H, J = 8.2 Hz).

N,8β-Ethano-7α-acetyl-*endo*-ethylenetetrahydronorthebaine (33) was prepared by oxidation of **32** as described for compound **15**. The ketone was crystallized from benzene/hexanes: 92% yield; mp 148–149 °C; ^{1}H NMR δ 1.7–1.95 (m, 3 H), 1.95–2.2 (m, 2 H), 2.12 (s, 3 H), 2.56 (s, 1 H, J = 7.0 Hz), 2.83 (dd, 1 H, J_1 = 6.7 Hz, J_2 = 15.1 Hz), 2.96 (d, 1 H, J = 18.7 Hz), 3.08 (d, 1 H, J = 7.7 Hz), 3.16 (d, 1 H, J = 5.5 Hz), 3.1–3.4 (m, 2 H), 3.45 (d, 1 H, J = 7.5 Hz), 3.54 (s, 3 H), 3.78 (s, 3 H), 4.61 (d, 1 H, J = 1.2 Hz), 5.43 (d, 1 H, J = 8.7 Hz), 5.91 (d, 1 H, J = 8.7 Hz), 6.51 (d, 1 H, J = 8.1 Hz), 6.61 (d, 1 H, J = 8.2 Hz).

Anal. ($C_{24}H_{27}NO_4$) C, H, N.

N,8β-Ethano-19(*R*)-*n*-butylnorthevinol (34). Reaction of **33** with *n*-BuMgBr as described for compound **22** gave a 2.5/1 mixture of tertiary alcohol **34** and starting ketone. The mixture was resubjected to the Grignard reaction, and the pure 19(*R*)-tertiary alcohol was crystallized from benzene/hexanes: 61% yield; mp 166–167 °C; ^{1}H NMR δ 0.87 (t, 3 H, J = 7.1 Hz), 0.99 (s, 3 H), 1.2–1.5 (m, 6 H), 1.7–2.1 (m, 5 H), 2.1–2.3 (m, 1 H), 2.87 (dd, 1 H, J_1 = 6.6 Hz, J_2 = 15.2 Hz), 2.94 (d, 1 H, J = 18.8 Hz), 3.04 (d, 1 H, J = 7.7 Hz), 3.1–3.4 (m, 3 H), 3.40 (d, 1 H, J = 7.7 Hz), 3.74 (s, 3 H), 3.79 (s, 3 H), 4.58 (d, 1 H, J = 1.2 Hz), 5.11 (s, 1 H), 5.26 (d, 1 H, J = 8.8 Hz), 6.00 (d, 1 H, J = 8.8 Hz), 6.50 (d, 1 H, J = 8.1 Hz), 6.60 (d, 1 H, J = 8.1 Hz).

Anal. ($C_{28}H_{37}NO_4$) C, H, N.

N,8β-Ethano-19(*R*)-*n*-butylnororvinol (5) was prepared from **34** by O-demethylation as described for compound **4** in 71% yield. Crystallization from benzene/hexanes gave the anhydrous form, mp 243–245 °C, while the monohydrate was obtained from benzene/moist ether, mp 149–155 °C (upon further heating resolidifies, then remelts at 243–245 °C): ^{1}H NMR δ 0.87 (t, 3 H, J = 7.0 Hz), 0.99 (s, 3 H), 1.1–1.6 (m, 6 H), 1.71 (d, 1 H, J = 6.9 Hz), 1.8–2.1 (m, 4 H), 2.1–2.3 (m, 1 H), 2.8–3.4 (m, 6 H), 3.42 (d, 1 H, J = 6.0 Hz), 3.73 (s, 3 H), 4.59 (s, 1 H), 5.07 (s, 1 H), 5.25 (d, 1 H, J = 8.8 Hz), 5.99 (d, 1 H, J = 8.7 Hz), 6.42 (d, 1 H, J = 8.0 Hz), 6.54 (d, 1 H, J = 8.0 Hz).

Anal. ($C_{27}H_{35}NO_4 \cdot H_2O$) C, H, N.

N-Benzyl-7α-formyl-8α-[[(*tert*-butyldimethylsilyl)oxy]methyl]-*endo*-ethylenetetrahydronorthebaine (41) was prepared by oxidation of **13** as described for the regioisomeric aldehyde **15**. The product was obtained as an oil in 99% yield. An analytical sample was prepared by radial chromatography (silica gel; $CHCl_3$/isooctane, 80/20): ^{1}H NMR δ −0.21 (s, 3 H), −0.13 (s, 3 H), 0.75 (s, 9 H), 1.7–1.9 (m, 1 H), 1.95–2.1 (m, 1 H), 2.4–2.65 (m, 3 H), 2.7–2.9 (m, 1 H), 2.31 (d, 1 H, J = 18.3 Hz), 3.4–3.55 (m, 4 H), 3.48 (s, 3 H), 3.60 (s, 2 H), 3.80 (s, 3 H), 4.56 (d, 1 H, J = 1.2 Hz), 5.46 (d, 1 H, J = 8.8 Hz), 5.92 (d, 1 H, J = 8.8 Hz), 6.55 (d, 1 H, J = 8.2 Hz), 6.63 (d, 1 H, J = 8.2 Hz), 7.2–7.4 (m, 5 H), 9.29 (d, 1 H, J = 5.6 Hz).

Anal. ($C_{35}H_{45}NO_5Si$) C, H, N.

N-Benzyl-7α-[1-hydroxy-2-(trimethylsilyl)ethyl]-8α-[[(*tert*-butyldimethylsilyl)oxy]methyl]-*endo*-ethylenetetrahydronorthebaine (42). Aldehyde **41** (4.89 g, 8.32 mmol) in THF (20 mL) under N_2 was treated with [(trimethylsilyl)methyl]magnesium chloride (1.7 M in THF, 12.2 mL, 20.8 mmol). The solution was stirred at room temperature for 48 h, then poured into a mixture of ice and saturated aqueous $NaHCO_3$, and extracted with $CHCl_3$. The extracts were dried (K_2CO_3) and evaporated to leave **42** as an oil sufficiently pure for use in the next step: 5.59 g, 99% yield; ^{1}H NMR δ −0.04 (s, 3 H), 0.001 (s, 3 H), 0.025 (s, 9 H), 0.86 (s, 9 H), 0.7–1.0 (m, 2 H), 1.7–1.85 (m, 2 H), 1.8–2.05 (m, 1 H), 2.2–2.4 (m, 2 H), 2.4–2.6 (m, 2 H), 3.29 (d, 1 H, J = 18.5 Hz), 3.4–3.6 (m, 3 H), 3.60 (s, 3 H), 3.4–3.9 (m, 3 H), 3.79 (s, 3 H), 4.23 (br s, 1 H), 4.54 (s, 1 H), 5.27 (d, 1 H, J = 8.8 Hz), 5.93 (d, 1 H, J = 8.7 Hz), 6.51 (d, 1 H, J = 8.1 Hz), 6.61 (d, 1 H, J = 8.1 Hz), 7.2–7.4 (m, 5 H).

N-Benzyl-7α-vinyl-8α-[[(*tert*-butyldimethylsilyl)oxy]methyl]-*endo*-ethylenetetrahydronorthebaine (43). Potassium hydride (35% in oil, 1.38 g, 484 mg of KH) under N_2 was washed with THF (50 mL), a solution of **42** (5.44 g, 8.05 mmol) in THF (40 mL) was added, and the mixture was stirred at room temperature for 22 h, then quenched with saturated aqueous $NaHCO_3$, and extracted with benzene. The organic phase was washed twice with saturated aqueous $NaHCO_3$, once with H_2O, and once again with $NaHCO_3$. Drying (K_2CO_3) and evaporating gave **43** as an oil: 4.00 g, 85% yield. An analytical sample was prepared by radial chromatography (silica gel; $CHCl_3$/isooctane, 80/20): ^{1}H NMR δ −0.23 (s, 3 H), −0.14 (s, 3 H), 0.75 (s, 9 H), 1.80 (dd, 1 H, J = 2.4 Hz, J_2 = 13.0 Hz), 2.0–2.2 (m, 1 H), 2.4–2.6 (m, 3 H), 2.81 (t, 1 H, J = 10.2 Hz), 3.1–3.2 (m, 1 H), 3.28 (d, 1 H, J = 18.3 Hz), 3.43 (s, 3 H), 3.4–3.7 (m, 5 H), 3.79 (s, 3 H), 4.63 (d, 1 H, J = 1.2 Hz), 5.05 (s, 1 H), 5.11 (dd, 1 H, J_1 = 2.1 Hz, J_2 = 6.7 Hz), 5.39 (d, 1 H, J = 8.8 Hz), 5.63 (d, 1 H, J = 8.7 Hz), 5.6–5.8 (m, 1 H), 6.54 (d, 1 H, J = 8.1 Hz), 6.62 (d, 1 H, J = 8.1 Hz), 7.2–7.4 (m, 5 H).

Anal. ($C_{36}H_{47}NO_4Si$) C, H, N.

N-Benzyl-7α-vinyl-8α-(hydroxymethyl)-*endo*-ethylenetetrahydronorthebaine (44). To crude **43** (3.90 g, 6.66 mol) dissolved in MeOH (90 mL) was added 6 N HCl (15 mL), and the solution was stirred at room temperature overnight, then cooled on ice, and neutralized with 3 N NaOH (30 mL). The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$, the extracts were dried (K_2CO_3) and evaporated, and the residue was chromatographed (silica gel, $CHCl_3$) to give **44** as an oil: 2.67 g, 85% yield; ^{1}H NMR δ 1.82 (dd, 1 H, J_1 = 2.7 Hz, J_2 = 13.3 Hz), 2.0–2.2 (m, 1 H), 2.35–2.7 (m, 4 H), 2.87 (t, 1 H, J = 9.6 Hz), 3.2–3.5 (m, 4 H), 3.41 (s, 3 H), 3.5–3.75 (m, 3 H), 3.79 (s, 3 H), 4.63 (d, 1 H, J = 1.1 Hz), 5.2–5.3 (m, 2 H), 5.38 (d, 1 H, J = 8.7 Hz), 5.4–5.6 (m, 1 H), 5.82 (d, 1 H, J = 8.7 Hz), 6.54 (d, 1 H, J = 8.1 Hz), 6.62 (d, 1 H, J = 8.1 Hz), 7.2–7.4 (m, 5 H).

Anal. ($C_{30}H_{33}NO_4$) C, H, N.

N-Benzyl-7α-vinyl-8α-(cyanomethyl)-*endo*-ethylenetetrahydronorthebaine (45). To alcohol **44** (2.67 g, 5.66 mmol) and Et_3N (1.97 mL, 14.15 mmol) in CH_2Cl_2 (80 mL), cooled to 0 °C under N_2, was added methanesulfonyl chloride (0.88 mL, 11.32 mmol), and the solution was stirred for 10 min at 0 °C, then quenched with saturated aqueous $NaHCO_3$, washed with saturated aqueous $NaHCO_3$, dried (K_2CO_3), and evaporated. The residue was dissolved in DMSO (28 mL), treated with KCN (1.4 g), and stirred at 70 °C for 46 h. It was then poured into benzene and washed twice with saturated aqueous $NaHCO_3$, three times with H_2O, and again with saturated aqueous $NaHCO_3$. The organic phase was dried (K_2CO_3) and evaporated to give nitrile **45** as an oil, 2.40 g, 88% yield, pure enough for the next step. An analytical sample was prepared by radial chromatography (silica gel; $CHCl_3$/isooctane, 80/20): ^{1}H NMR δ 1.7–2.0 (m, 3 H), 2.0–2.2 (m, 1 H), 2.4–2.7 (m, 3 H), 2.85 (t, 1 H, J = 9.7 Hz), 3.2–3.5 (m, 3 H), 3.41 (s, 3 H), 3.60 (unsym d, 1 H, J = 10 Hz), 3.63 (unsym d, 1 H, J = 10 Hz), 3.79 (s, 3 H), 4.62 (d, 1 H, J = 1.1 Hz), 5.2–5.5 (m, 4 H), 5.84 (d, 1 H, J = 8.7 Hz), 6.54 (d, 1 H, J = 8.1 Hz), 6.62 (d, 1 H, J = 8.1 Hz), 7.2–7.4 (m, 5 H).

Anal. ($C_{31}H_{32}N_2O_3$) C, H, N.

N-Benzyl-7α-vinyl-8α-(formylmethyl)-*endo*-ethylenetetrahydronorthebaine (46). Crude nitrile **45** (2.36 g, 4.91 mmol) was dissolved in benzene (50 mL), half the solvent was distilled to ensure dryness, and after flushing with N_2, Dibal (1.5 M in toluene, 5.88 mL, 8.82 mmol) was added, and the solution was stirred at room temperature for 20 h. The reaction was quenched with 40 mL of saturated aqueous boric acid, then poured into aqueous $NaHCO_3$, and extracted with $CHCl_3$. The extracts were dried (K_2CO_3) and evaporated, and the residue was chromatographed (silica gel; $CHCl_3$/isooctane, 80/20) to give aldehyde **46** as an oil: 2.10 g, 88% yield; ^{1}H NMR δ 1.69 (dd, 1 H, J_1 = 3.2 Hz, J_2 = 15 Hz), 1.86 (dd, 1 H, J_1 = 2.6 Hz, J_2 = 12 Hz), 2.1–2.3 (m, 2 H), 2.41 (dd, 1 H, J_1 = 6.7 Hz, J_2 = 18.6 Hz), 2.53 (m, 1 H), 2.6–2.75 (m, 1 H), 2.83 (t, 1 H, J = 10.0 Hz), 3.16 (d, 1 H, J = 6.5 Hz), 3.28 (d, 1 H, J = 18.5 Hz), 3.39 (s, 3 H), 3.51 (unsym d, 1 H, J = 13.4 Hz), 3.57 (unsym d, 1 H, J = 13.4 Hz), 3.79 (s, 3 H), 3.8–4.0 (m, 1 H), 4.65 (d, 1 H, J = 1.2 Hz), 4.98–5.11 (m, 2 H), 5.27 (d, 1 H, J = 8.2 Hz), 5.3–5.45 (m, 1 H), 5.79 (d, 1 H, J

= 8.7 Hz), 6.53 (d, 1 H, J = 8.1 Hz), 6.61 (d, 1 H, J = 8.1 Hz), 7.25 (s, 5 H), 9.61 (d, 1 H, J = 0.9 Hz).

Anal. ($C_{31}H_{33}NO_4$) C, H, N.

***N*-Benzyl-7α-vinyl-8α-(2-hydroxyethyl)-*endo*-ethylenetetrahydronorthebaine (47).** To aldehyde **46** (2.09 g, 4.32 mmol) dissolved in benzene (10 mL) plus MeOH (30 mL) was added $NaBH_4$ (327 mg, 8.64 mmol), and after the mixture was stirred at room temperature for 20 min, the reaction was quenched with 10% HOAc and distributed between $CHCl_3$ and saturated aqueous $NaHCO_3$. The organic phase was dried (K_2CO_3) and evaporated to give analytically pure alcohol **47**: 2.10 g, 100% yield; ^1H NMR (250 MHz; $CDCl_3$) δ 1.1–1.4 (m, 2 H), 1.62 (br s, 1 H, OH), 1.82 (dd, 1 H, J_1 = 2.6 Hz, J_2 = 13.2 Hz), 2.0–2.2 (m, 1 H), 2.4–2.55 (m, 2 H), 2.55–2.7 (m, 1 H), 2.74 (t, 1 H, J = 10.0 Hz), 2.97–3.02 (m, 1 H), 3.38 (d, 1 H, J = 16 Hz), 3.39 (s, 3 H), 3.4–3.75 (m, 5 H), 3.79 (s, 3 H), 4.61 (d, 1 H, J = 1.2 Hz), 5.07–5.17 (m, 2 H), 5.35 (d, 1 H, J = 8.7 Hz), 5.42–5.53 (m, 1 H), 5.77 (d, 1 H, J = 8.7 Hz), 6.53 (d, 1 H, J = 8.1 Hz), 6.61 (d, 1 H, J = 8.1 Hz), 7.2–7.4 (m, 5 H).

Anal. ($C_{31}H_{35}NO_4$) C, H, N.

***N*-BOC-7α-vinyl-8α-(2-hydroxyethyl)-*endo*-ethylenetetrahydronorthebaine (51).** To alcohol **47** (2.09 g, 4.30 mmol) dissolved in CH_2Cl_2 (45 mL) was added MCPBA (76%, 1.32 g, 1.00 g of MCPBA, 5.81 mmol), and the solution was stirred at room temperature for 20 min, then washed twice with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated. The residue was redissolved in CH_2Cl_2 (75 mL) cooled to 0 °C, treated with trifluoroacetic anhydride (6.08 mL, 43 mmol), and stirred at 0 °C for 3 h and then at room temperature overnight. Volatiles were removed and chased with benzene, and to the residue in benzene (20 mL) was added 1 N HCl (40 mL). The two phases were vigorously stirred for 2 days, and then the benzene was extracted with two more portions of 1 N HCl. The combined aqueous phases were basified (20% NaOH) and extracted with $CHCl_3$, the $CHCl_3$ was dried (K_2CO_3) and evaporated, and the residue was dissolved in THF (30 mL) plus water (3 mL) to which were added Et_3N (0.41 mL, 2.9 mmol) and $(BOC)_2O$ (0.52 g, 2.36 mmol) and stirred at room temperature overnight. The THF was evaporated, benzene was added, and the solution was washed once with saturated aqueous $NaHCO_3$, once with water, twice with 1 M citric acid, again with water, and twice again with $NaHCO_3$. The solvent was dried (Na_2SO_4) and evaporated to leave oily crystals, which were quickly washed with benzene/hexane (1/1) to remove the oil. Recrystallization (benzene/hexanes) gave pure **51**: 0.69 g, 32% yield; mp 229–231 °C dec; ^1H NMR δ 1.3–1.5 (m, 1 H), 1.43 (s, 9 H), 1.6–1.75 (m, 1 H), 1.75–1.9 (m, 1 H), 1.9–2.2 (m, 2 H), 2.7–2.9 (m, 2 H), 2.88 (d, 1 H, J = 20.0 Hz), 3.0–3.2 (m, 2 H), 3.3–3.5 (m, 1 H), 3.37 (s, 3 H), 3.55–3.7 (m, 1 H), 3.78 (s, 3 H), 3.9–4.05 (m, 1 H), 4.60 (d, 1 H, J = 1.1 Hz), 5.0–5.1 (m, 2 H), 5.14 (s, 1 H), 5.38 (d, 1 H, J = 8.8 Hz), 5.35–5.6 (m, 1 H), 5.81 (d, 1 H, J = 8.7 Hz), 6.49 (d, 1 H, J = 8.2 Hz), 6.61 (d, 1 H, J = 8.2 Hz).

Anal. ($C_{29}H_{37}NO_6$) C, H, N.

***N*-BOC-7α-vinyl-8α-(2-bromoethyl)-*endo*-ethylenetetrahydronorthebaine (52).** To alcohol **51** (0.478 g, 0.964 mmol) and triphenylphosphine (0.379 g, 1.45 mmol) dissolved in THF (10 mL) was added a solution of CBr_4 (0.51 g, 1.54 mmol) in THF (4 mL). The mixture was stirred at room temperature overnight, the solvent was evaporated, and the residue was chromatographed (silica gel; $CHCl_3$/isooctane, 80/20). Bromide **52** crystallized from hexane: 490 mg, 91% yield; mp 165–166 °C; ^1H NMR δ 1.45 and 1.51 (2 s, total 9 H), 1.8–2.1 (m, 3 H), 2.4–2.6 (m, 1 H), 2.65–2.8 (m, 1 H) 2.87 (d, 1 H, J = 18.7 Hz), 3.00 (d, 1 H, J = 6.5 Hz), 3.0–3.6 (m, 4 H), 3.39 (s, 3 H), 3.79 (s, 3 H), 3.9–4.2 (m, 1 H), 4.59 (d, 1 H, J = 1.2 Hz), 4.87 and 5.03 (2 d, 1 H, J = 6.3 Hz), 5.1–5.3 (m, 2 H), 5.38 (d, 1 H, J = 8.7 Hz), 5.4–5.65 (m, 1 H), 5.84 (d, 1 H, J = 8.6 Hz), 6.50 (d, 1 H, J = 8.2 Hz), 5.52 (d, 1 H, J = 8.2).

Anal. ($C_{29}H_{36}NO_5Br$) C, H, N.

***N*,8α-Ethano-7α-vinyl-*endo*-ethylenetetrahydronorthebaine (53).** Bromide **52** (0.471 g, 0.843 mmol) was stirred in trifluoroacetic acid (1.5 mL) for 2 min at room temperature, then stripped of volatiles, and the residue distributed between $CHCl_3$ and saturated aqueous $NaHCO_3$. The $CHCl_3$ layer was dried (K_2CO_3) and the solvent evaporated, to the residue dissolved in CH_3CN (25 mL) was added K_2CO_3 (0.75 g), and the mixture was refluxed for 20 h. The solvent was evaporated, the residue was again distributed between $CHCl_3$ and $NaHCO_3$, the $CHCl_3$ layer was dried and evaporated, and the residue was dissolved in benzene and extracted into 1 N HCl. The acidic extracts were basified (20% NaOH), and the product was extracted into $CHCl_3$, which was dried and evaporated to leave pure cyclized tertiary amine **53**: 307 mg, 97% yield; mp 128–130 °C; ^1H NMR δ 1.0–1.2 (m, 1 H), 1.35–1.5 (m, 1 H), 1.88 (dd, 1 H, J_1 = 8.2 Hz, J_2 = 14.4 Hz), 2.1–2.25 (m, 1 H), 2.55–2.7 (m, 1 H), 2.7–3.05 (m, 3 H), 3.05 (m, 2 H), 3.3 (m, 1 H), 3.54 (s, 3 H), 3.5–3.7 (m, 2 H), 3.79 (s, 3 H), 4.80 (d, 1 H, J = 1.2 Hz), 5.0–5.2 (m, 3 H), 5.45–5.6 (m, 1 H), 5.98 (d, 1 H, J = 8.6 Hz), 6.52 (d, 1 H, J = 8.0 Hz), 6.59 (d, 1 H, J = 8.0 Hz).

Anal. ($C_{24}H_{27}NO_3$) C, H, N.

***N*,8α-Ethano-7α-formyl-*endo*-ethylenetetrahydronorthebaine (54).** To **53** (252 mg, 0.67 mmol) dissolved in THF (45 mL) was added $NaIO_4$ (429 mg, 2.0 mmol) in H_2O (30 mL) followed by OsO_4 (76 mg, 0.301 mmol) and stirring at room temperature for 23 h. The mixture was distributed between saturated aqueous $NaHCO_3$ and benzene, and the benzene layer was washed twice with saturated aqueous $NaHCO_3$ containing sodium dithionite and once with $NaHCO_3$, then dried (K_2CO_3), and evaporated to leave 200 mg of a 62/38 mixture of aldehyde **54** and olefin **53**, which was used directly in the next reaction. The ^1H NMR spectrum clearly showed the CHO proton as a doublet at 9.58 ppm.

***N*,8α-Ethano-7α-(1-hydroxyethyl)-*endo*-ethylenetetrahydronorthebaine (55).** The mixture from the previous reaction was dissolved in THF (6 mL) and added to a mixture of THF (15 mL) and MeMgI (2 M in ether, 1.63 mL, 3.27 mmol). After being stirred for 30 min, the mixture was poured into saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$, the extracts were dried (K_2CO_3), and the $CHCl_3$ was evaporated. The residue was separated by radial chromatography (silica gel; $CHCl_3$/MeOH, 92/8 → 70/30) to give recovered olefin **53**, 75 mg; the minor carbinol epimer **55a**, 50 mg; and the major carbinol epimer **55**, 74 mg. The combined yhield of **55** from the vinyl compound (two steps) was 47% or 67% based on recovered **53**. ^1H NMR (minor epimer): δ 1.13 (d, 3 H, J = 6.0 Hz), 1.1–1.4 (m, 1 H), 1.6–1.8 (m, 1 H), 1.83 (dd, 1 H, J_1 = 7.8 Hz, J_2 = 14.4 Hz), 2.05–2.2 (m, 1 H), 2.23 (t, 1 H, J = 9.0 Hz), 2.5–2.9 (m, 4 H), 2.9–3.2 (m, 2 H), 3.3–3.4 (m, 1 H), 3.4–3.7 (m, 3 H), 3.62 (s, 3 H), 3.77 (s, 3 H), 4.74 (s, 1 H), 5.03 (d, 1 H, J = 8.6 Hz), 6.09 (d, 1 H, J = 8.6 Hz), 6.50 (d, 1 H, J = 7.8 Hz), 6.57 (d, 1 H, J = 8.0 Hz). ^1H NMR (major epimer): δ 1.14 (d, 3 H, J = 6.8 Hz), 1.5–1.7 (m, 1 H), 1.75–1.95 (m, 2 H), 2.0–2.3 (m, 2 H), 2.29 (dd, 1 H, J_1 = 2.5 Hz, J_2 = 9.8 Hz), 2.6–2.9 (m, 3 H), 3.02 (d, 2 H, J = 4.3 Hz), 3.35–3.4 (m, 1 H), 3.5–3.7 (m, 2 H), 3.53 (s, 3 H), 3.76 (s, 3 H), 3.9–4.1 (m, 1 H), 4.69 (d, 1 H, J = 1.1 Hz), 5.07 (d, 1 H, J = 8.5 Hz), 6.07 (d, 1 H, J = 8.5 Hz), 6.48 (d, 1 H, J = 8.0 Hz), 6.56 (d, 1 H, J = 8.0 Hz).

***N*,8α-Ethano-7α-acetyl-*endo*-ethylenetetrahydronorthebaine (56).** Each epimer of **55** was independently oxidized as described for **15**. The major epimer gave a 94% yield, and the minor epimer gave an 87% yield; 109 mg total. The resulting ketone **56** was an oil: ^1H NMR δ 1.35–1.5 (m, 1 H), 1.6–1.8 (m, 1 H) 1.8–1.95 (m, 1 H), 2.0–2.2 (m, 1 H), 2.10 (s, 3 H), 2.5–2.65 (m, 1 H), 2.65–2.9 (m, 2 H), 3.03 (d, 2 H, J = 7.3 Hz), 3.3–3.45 (m, 2 H), 3.5–3.65 (m, 2 H), 3.62 (s, 3 H), 3.76 (s, 3 H), 4.74 (d, 1 H, J = 1.1 Hz), 5.08 (d, 1 H, J = 8.6 Hz), 5.86 (dd, 1 H, J_1 = 0.4 Hz, J_2 = 8.6 Hz), 6.50 (d, 1 H, J = 8.2 Hz), 6.56 (d, 1 H, J = 8.1 Hz); MS, m/e calcd for $C_{24}H_{27}NO_4$ 393.1953, found 393.1932 (intensity, 100).

***N*,8α-Ethano-19(*R*)-*n*-butynorthevinol (59).** Ketone **56** was subjected to reaction with *n*-BuMgBr as described for **22**, except with 600 mol % of the Grignard reagent and a 1-h reaction period. Radial chromatography (silica gel; $CHCl_3$/MeOH, 88/12) gave two fractions: fraction 1 contained **57–59**; fraction 2 contained **56** and **58**. Fraction 1 was reduced with $NaBH_4$ in methanol (1200 mol % in four portions at 20-min intervals) and then separated by preparative TLC (silica gel; $CHCl_3$/MeOH, 85/15) to give the β-hydroxyethyl compound *reduced* **57** (50% yield), **58** (10% yield), and the desired **59** (2.1% yield; 2.5 mg). Fraction 2 was separated similarly to give **56** (25% yield) and more **58** (total, 15% yield). **59**: ^1H NMR δ 0.90 (t, 3 H, J = 6.8 Hz), 0.10 (s, 3 H), 1.2–1.7 (m, 6 H), 1.7–2.0 (m, 3 H), 2.05–2.35 (m, 1 H), 2.56 (d, 1 H, J = 10.2 Hz), 2.65–2.95 (m, 3 H), 2.95–3.1 (m, 2 H), 3.3–3.7 (m, 3 H), 3.67 (s, 3 H), 3.79 (s, 3 H), 4.70 (d, 1 H, J = 1.0 Hz), 5.00 (d, 1 H, J

= 8.6 Hz), 5.10 (s, 1 H), 6.15 (d, 1 H, J = 8.9 Hz), 6.51 (d, 1 H, J = 8.1 Hz), 6.59 (d, 1 H, J = 8.1 Hz). **58**: ^{1}H NMR δ 0.86 (t, 3 H, J = 7.1 Hz), 1.1–1.4 (m, 6 H), 1.38 (s, 3 H), 1.35–1.8 (m, 4 H), 2.1–2.3 (m, 1 H), 2.38 (d, 1 H, J = 13.0 Hz), 2.91 (s, 1 H), 2.9–3.1 (m, 2 H), 3.18 (d, 1 H, J = 15.8 Hz), 3.1–3.4 (m, 1 H), 3.43 (s, 3 H), 3.6–3.9 (m, 2 H), 3.80 (s, 3 H), 4.25 (s, 1 H), 4.94 (d, 1 H, J = 8.8 Hz), 5.62 (br s, 1 H), 6.35 (d, 1 H, J = 8.8 Hz), 6.43 (d, 1 H, J = 8.3 Hz), 6.61 (d, 1 H, J = 8.3 Hz); MS, m/e calcd for $C_{28}H_{37}NO_4$ 451.2715, found 451.2729 (intensity, 8.0).

***N*,8α-Ethano-19(*R*)-*n*-butylnororvinol (6)** was prepared from **59** by O-demethylation as described for **4** and obtained as a white powder in 70% yield: ^{1}H NMR δ 0.91 (t, 3 H, J = 6.8 Hz), 0.10 (s, 3 H), 1.2–1.6 (m, 6 H), 1.7–2.1 (m, 3 H), 2.0–2.3 (m, 1 H), 2.60 (d, 1 H, J = 10 Hz), 2.6–3.2 (m, 3 H), 3.0–3.2 (m, 2 H), 3.3–3.7 (m, 3 H), 3.64 (s, 3 H), 4.74 (d, 1 H, J = 1.0 Hz), 4.88 (s, 1 H), 4.99 (d, 1 H, J = 8.6 Hz), 6.10 (dd, 1 H, J_1 = 0.9 Hz, J_2 = 8.7 Hz), 6.47 (d, 1 H, J = 7.4 Hz), 6.57 (d, 1 H, J = 7.2 Hz).

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Registry No. **3** (R = *n*-Pr), 14521-96-1; **4**, 110143-22-1; **5**, 110143-23-2; **6**, 110221-12-0; **9**, 110173-63-2; **10**, 110173-64-3; **11**, 110173-65-4; **12**, 110173-66-5; **13**, 110173-67-6; **15**, 110143-24-3; **16**, 110143-26-5; **17**, 110143-27-6; **18**, 110143-28-7; **19**, 110143-29-8; **20**, 110143-30-1; **21**, 110143-31-2; **22** (epimer 1), 110143-32-3; **22** (epimer 2), 110221-13-1; **23**, 110143-33-4; **24**, 110143-34-5; **25**, 110143-25-4; **26**, 110143-35-6; **27**, 110173-26-7; **28**, 110143-36-7; **29**, 110143-37-8; **30**, 110143-38-9; **31**, 110143-39-0; **32** (epimer 1), 110143-40-3; **32** (epimer 2), 110221-14-2; **33**, 110143-41-4; **34**, 110143-42-5; **41**, 110173-27-8; **42**, 110143-43-6; **43**, 110143-44-7; **44**, 110143-45-8; **45**, 110143-46-9; **46**, 110143-47-0; **47**, 110143-48-1; **57**, 110143-49-2; **52**, 110143-50-5; **53**, 110143-51-6; **54**, 110221-15-3; **55** (epimer 1), 110221-16-4; **55** (epimer 2), 110221-17-5; **56**, 110221-18-6; **59**, 110222-26-9; $(BOC)_2O$, 24424-99-5; $TMSCH_2Cl$, 2344-80-1; TBDMS-Cl, 18162-48-6; $(PhCO)_2O$, 93-97-0; $MeSO_2Cl$, 124-63-0; MeI, 74-88-4; BuBr, 109-65-9; northebaine hydrochloride, 7679-18-7; maleic anhydride, 108-31-6.

Synthesis and Antiviral Activity of Carbocyclic Analogues of Xylofuranosides of 2-Amino-6-substituted-purines and 2-Amino-6-substituted-8-azapurines

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(±)-(1α,2β,3α,5α)-3-[(2,5-Diamino-6-chloro-4-pyrimidinyl)amino]-5-(hydroxymethyl)-1,2-cyclopentanediol (**7**) was synthesized from 2-amino-4,6-dichloropyrimidine and the carbocyclic xylofuranosylamine (±)-(1α,2β,3α,5α)-3-amino-5-(hydroxymethyl)-1,2-cyclopentanediol (**2**) by subsequent preparation of the 5-[(4-chlorophenyl)azo] derivative of the resulting pyrimidine and reduction of the azo moiety with zinc and acetic acid. The carbocyclic analogue of 2-amino-4-chloropurine xylofuranoside (**8**) and the corresponding 8-azapurine **11** were prepared from **7**. The carbocyclic analogues xylofuranosylguanine (**9**), xylofuranosyl-2,6-diaminopurine (**10**), xylofuranosyl-8-azaguanine (**13**), and xylofuranosyl-8-aza-2,6-diaminopurine (**14**) were prepared from **8** and **11**. Compounds **9** and **13** were active against herpes simplex virus (types 1 and 2), with **9** being the more potent against both viruses. Analogue **9** also exhibited potent activity against human cytomegalovirus and varicella-zoster virus.

The availability of carbocyclic nucleosides was limited to analogues of ribofuranosides until a synthetic route was developed[1,2] that provided several versatile intermediates leading to a wide variety of both purine and pyrimidine carbocyclic nucleosides. The key intermediate, 2-azabicyclo[2.2.1]hept-5-en-3-one (**1**), provided the routes to several types of previously unknown carbocyclic nucleosides. These included carbocyclic analogues of arabinofuranosylpurine nucleosides,[3-5] aminonucleosides,[1,2] lyxofuranosyladenine,[6] and xylofuranosyladenine.[7] Several of these analogues exhibit significant in vitro and in vivo antiviral and/or antitumor activities.

It has been our experience with carbocyclic nucleosides that purine derivatives other than adenine should be explored in cases where an adenine nucleoside exhibits antitumor or antiviral properties.[4] Similar observations have been reported for other types of nucleoside analogues. For example, the guanine analogue in a series of 9-[(2-hydroxyethoxy)methyl]purines exhibited antiviral effects 2 orders of magnitude greater than the corresponding adenine derivatives.[8,9] Thus, the significant antitumor activities of carbocyclic xylofuranosyladenine and its 8-aza analogue[7] prompted the synthesis of the guanosine and 2,6-diaminopurine analogues.

Chemistry

The synthesis of the carbocyclic xylofuranosylamine (±)-(1α,2β,3α,5α)-3-amino-5-(hydroxymethyl)-1,2-cyclopentanediol (**2**) from the versatile precursor 2-azabicyclo-[2.2.1]hept-5-en-3-one (**1**) was described earlier[7] (Scheme I). Condensation of **2** with 2-amino-4,6-dichloropyrimidine (**3**) gave the corresponding pyrimindinylamino derivative **4** along with disubstituted product **5**. The assignment of structure **5** is consistent with its IR, NMR, and spectral analyses. Also, the presence of two NH signals at δ 9.82 and 7.80–7.72 and one NH_2 signal at δ 6.67 rules out the possibility that both pyrimidine moieties were attacked

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