Analgesics of the Orvinol Type. 19-Deoxy and 6,20-Epoxy Derivatives

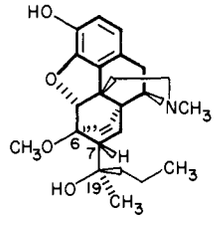
Charles W. Hutchins and Henry Rapoport*

Department of Chemistry, University of California, Berkeley, California 94720. *Received August 4, 1983*

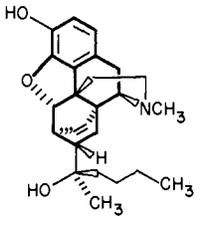
A series of new ethenotetrahydrooripavine derivatives has been prepared in which the C-19 hydroxyl group has been replaced by hydrogen. The syntheses proceed via the thioanisole adducts of the thevinones. These adducts are converted to 1,2-epoxides, which are rearranged to aldehydes and then reduced to primary alcohols. Further conversion of these alcohols result in the deoxy derivatives and the 6,20-epoxy analogues, which contain a fused tetrahydrofuran ring. The compounds in this series, some of which offer the possibility of strong hydrogen-bonding interactions and others of which contain sterically fixed lipophilic side chains, have been evaluated as analgesics by the rat tail-flick method. Based on these and previous results, a proposal is made for the interaction of the orvinols with the opiate receptor involving both lipophilic (L) and hydrophilic (H) subsites. This proposal can be extended to suggest an optimum conformation for the enkephalins.

Renewed interest in the opiate receptor has been generated by the extremely high analgesic activities of etorphine (1) and related compounds of the 6,14-ethenotetrahydrooripavine type (the orvinols). The high analgesic activity and the large difference in activity between the alcohol diastereomers (R = 1000 times the activity of morphine; S = 20 times the activity of morphine) have been considered to result from an intramolecular hydrogen bond between the alcohol and the C-6 methoxy oxygen, which would direct the propyl group of 1 into one of two regions, depending on the absolute stereochemistry at C-19.[1-3] The increased binding at a lipophilic region of the receptor would account for the increased activity of the R diastereomers.

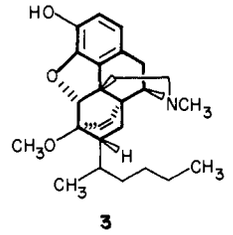
We prepared the 6-demethoxy analogue 2 and found a similar difference in analgesic activity between the diastereomers, with the R diastereomer remaining the more active.[4] Thus, an intramolecular hydrogen bond has no role in establishing the conformational preference for any R diastereomer–lipophilic site interaction. An alternative suggestion was that a second binding site exists that interacts with the hydroxyl group. To test this possibility, we have considered the diastereomeric 19-deoxy derivatives, the 19-butyl-7α-orvinans (3), and the furans, the



R-1



R-2



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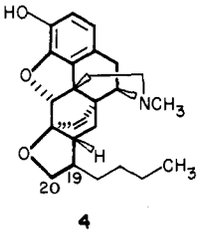

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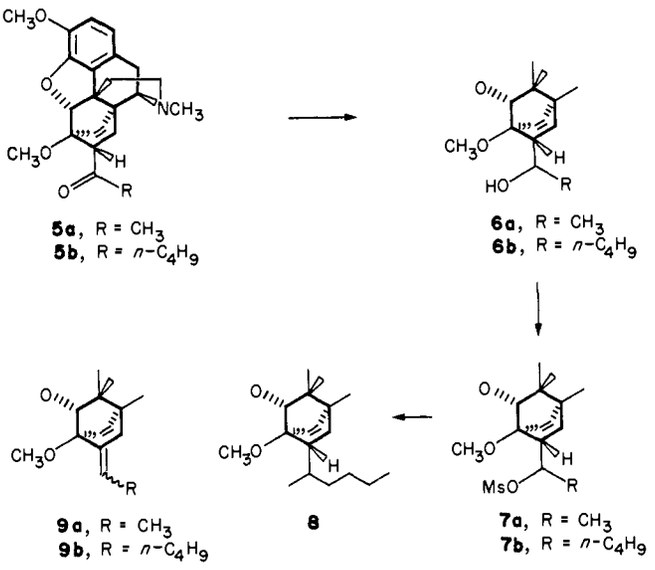
6-demethoxy-19-butyl-6,20-epoxy-7α-orvinans (4).[5] Both series still have the steric and lipophilic components of etorphine (1) and the 6-demethoxy analogues 2 but would be unable to form a hydrogen bond to a second binding site in that region. We now report the synthesis of these dehydroxy compounds and their evaluation as analgesics.

Scheme I



5a, R = CH_3
5b, R = n-C_4H_9

6a, R = CH_3
6b, R = n-C_4H_9

9a, R = CH_3
9b, R = n-C_4H_9

8

7a, R = CH_3
7b, R = n-C_4H_9

Chemistry. Our initial attempts to prepare the dehydroxy series 3 involved the stereospecific displacement of a mesylate with dibutyl cuprate (Scheme I). The diastereomeric alcohols **6a** were obtained by stereoselective reduction of the thevinone **5a** with isobutylmagnesium chloride[6] or with sodium borohydride and chromatographic separation of the diastereomers. Mesylate **7a** was prepared and on treatment with dibutyl cuprate gave as the only isolable product the olefin **9a**. Its spectral data were identical with olefin prepared by a previous procedure.[7] Similar results were obtained with the secondary alcohol **6b**, prepared from thebuvinone (**5b**), upon treatment of

(1) Lewis, J. W.; Bentley, K. W.; Cowan, A. *Annu. Rev. Pharmacol.* **1971**, *11*, 241.
(2) Loew, G. H.; Berkowitz, D. S. *J. Med. Chem.* **1979**, *22*, 603.
(3) Feinberg, A. P.; Cresse, I.; Snyder, S. H. *Proc. Natl. Acad. Sci. U.S.A.* **1976**, *73*, 4215.
(4) Hutchins, C. W.; Cooper, G. K.; Purro, S.; Rapoport, H. *J. Med. Chem.* **1981**, *24*, 773.
(5) The formal nomenclature, using Chemical Abstracts numbering, for these compounds is quite cumbersome and structurally nonsuggestive (see Experimental Section, compound 10, for an example). Therefore, we have adopted the system used commonly for these Diels–Alder adducts of thebaine. The parent compound, the methyl vinyl ketone adduct, is a thevinone, and its reduction product is a thevinol. Thus, our compounds in which the HO at C-19 has been replaced by H become thevinans. In the same sequence, the phenolic oripavine analogues (orvinones, orvinols) become orvinans.
(6) Bentley, K. W.; Hardy, D. G.; Meek, B. *J. Am. Chem. Soc.* **1967**, *89*, 3273.
(7) Bentley, K. W.; Hardy, D. G.; Lewis, J. W.; Readhead, M. J.; Rushworth, W. I. *J. Chem. Soc. C* **1969**, 826.

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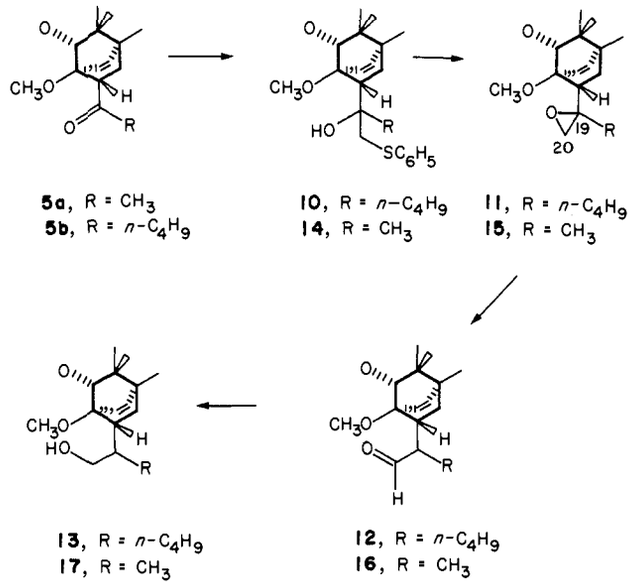
Scheme II. Synthesis of Hydroxymethyl Derivatives



5a, R = CH_3
5b, R = n-C_4H_9

10, R = n-C_4H_9
14, R = CH_3

11, R = n-C_4H_9
15, R = CH_3

13, R = n-C_4H_9
17, R = CH_3

12, R = n-C_4H_9
16, R = CH_3

its mesylate **7b** with dimethylcuprate.

Since the displacement of the secondary alcohol with dialkylcuprates was not successful, we considered the possibility of applying this method to a primary alcohol. This would reduce any steric problems, and the necessary primary alcohols might be prepared from thebuvinone (**5b**) by a reductive homologation procedure. Our first choice was the Wittig reaction as an effective process for conversion of a ketone to the homologous aldehyde. Unfortunately, ketone **5b** gave only rearrangement products derived from the ketone anion upon treatment with (methoxymethylene)triphenylphosphorane.[8]

The next approach investigated was based on the conversion of a ketone into an epoxide. Rearrangement of this epoxide should produce an aldehyde, which could be easily reduced to the desired primary alcohol. Following a method for the preparation of epoxides from sterically hindered ketones via thioanisole,[9] the anion of thioanisole was formed by using n-butyllithium and DABCO and was treated with thebuvinone (**5b**). The mixture of diastereomeric adducts, purified by chromatography to thoroughly remove unreacted ketone, was treated with trimethyloxonium tetrafluoroborate and then aqueous sodium hydroxide. Isolation afforded a 1.5:1 mixture of diastereomeric epoxides **11** in 30–45% yield (Scheme II). Rearrangement of the epoxides **11** with boron trifluoride etherate[10] produced the aldehydes **12**, which were reduced with sodium borohydride to the alcohols **13**. The mixture of alcohols was separated into the pure diastereomers by column chromatography, affording (*R*)-**13** in 42% yield and (*S*)-**13** in 36% yield.

In a similar manner, reaction of thevinone (**5a**) with thioanisole anion gave the adducts **14** in 84% yield after careful chromatography. The mixture of diastereomeric adducts **14** was treated with trimethyloxonium tetrafluoroborate to give the epoxides **15** in 65% yield. Treatment of epoxides **15** with boron trifluoride etherate in benzene afforded the crude aldehydes **16**, which were reduced with sodium borohydride. The alcohols **17** were

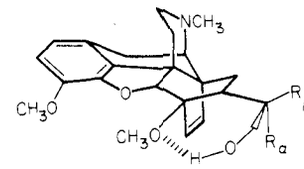
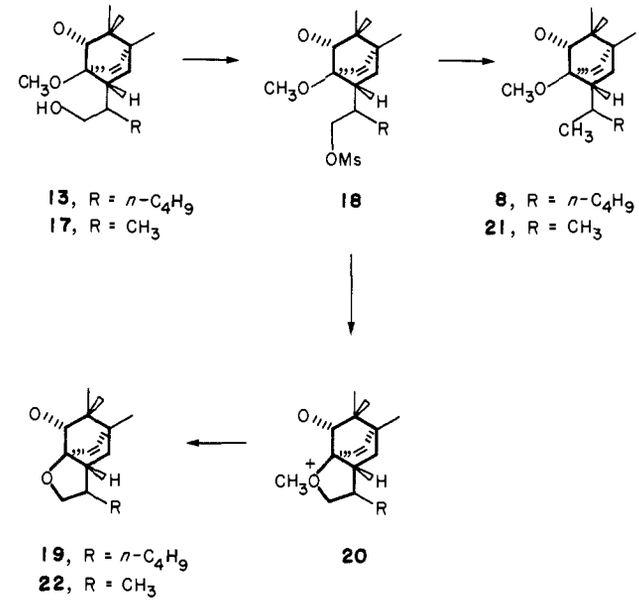


Figure 1. Intramolecular hydrogen-bonded conformation of the (hydroxymethyl)thevinans **13** and **17**. The proximity of the R_α group and the etheno bridge results in shielding and an upfield NMR shift.

Scheme III. Synthesis of 6,20-Epoxy Derivatives



13, R = n-C_4H_9
17, R = CH_3

18

8, R = n-C_4H_9
21, R = CH_3

19, R = n-C_4H_9
22, R = CH_3

20

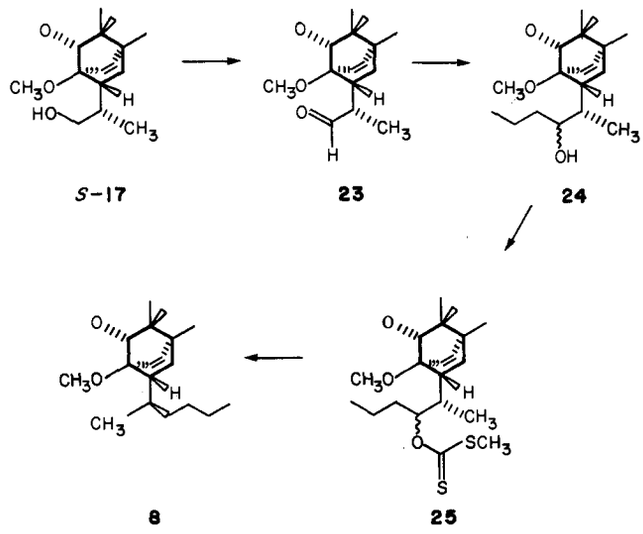
isolated and separated by silica gel chromatography to provide (*R*)-**17** in 26–33% yield and (*S*)-**17** in 25–30% yield.

The stereochemistry of the alcohols **13** and **17** was determined by NMR spectroscopy. Since the most stable conformation of the side chain involves a hydrogen bond between the alcohol hydrogen and the methoxy oxygen (Figure 1), the alkyl side chain will occupy one of two areas, either down (R_α) near the etheno bridge or above (R_β) and away from the ring system. The NMR signals of the side chain nearer the etheno bridge will be shielded relative to the signals of the diastereomer. The NMR signals of the etheno bridge will also be shielded and appear more upfield. The high R_f diastereomer of **17** has a methyl resonance at δ 0.89, a C-18 vinyl proton at δ 5.78, and a C-17 vinyl proton at δ 5.39. The low R_f diastereomer has corresponding NMR signals at δ 0.65, 5.72, and 5.30. The chemical shifts of the corresponding signals of the low R_f diastereomer are all upfield relative to the high R_f diastereomer. Therefore, the methyl group and the etheno bridge are in closer proximity in the low R_f diastereomer, indicating *S* stereochemistry. Similar arguments can be made for the butyl alcohols **13**, where the high R_f diastereomer was shown to have the *R* configuration. These NMR assignments are consistent with those made in the etorphine and 6-demethoxy series[4,11] and with the X-ray crystallographic determination.[12]

The next target was to reduce the hydroxymethyl to a methyl group. For this purpose the mesylate was prepared

(8) Greenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128.
(9) Shanklin, J. R.; Johnson, C. R.; Ollinger, J.; Coates, R. M. *J. Am. Chem. Soc.* **1973**, *95*, 3429.
(10) Blackett, B. N.; Coxon, J. M.; Hartshorn, M. P.; Richards, K. E. *Tetrahedron* **1969**, *25*, 4999.
(11) Fulmor, W.; Lancaster, J. E.; Morton, G. O.; Brown, J. J.; Howell, C. F.; Nora, C. T.; Hardy, R. A. Jr. *J. Am. Chem. Soc.* **1967**, *89*, 3322.
(12) van den Hende, J. H.; Nelson, N. R. *J. Am. Chem. Soc.* **1967**, *89*, 2901.

Scheme IV. Confirmation of the Stereochemistry of 19(*R*)-Butyl-7α-thevinan (8)



and treated with lithium triethylborohydride.[13] 19-Butyl-7α-thevinan (8) could be isolated, but the yields ranged from 0 to 80%. The accompanying product was shown to have ring closed to a tetrahydrofuran and to be the 6,20-epoxy derivative **19** (Scheme III). Presumably, furan ring formation to **19** occurs by a mechanism in which the C-6 methoxy oxygen attacks the carbon bearing the mesyloxy group to form oxonium ion **20**. Nucleophilic attack then removes the methyl group and gives furan **19**. The reaction pathway and kinetics of the solvolysis and reduction of brosylates with a nearby methoxyl group have been studied, and furan formation has been found to be a minor pathway in these systems.[14]

The ratio of the 19-deoxy derivative **8** to the 6,20-epoxyfuran **19** formed in the reduction reaction could be kept near 1:1 by the use of low temperatures in the preparation and reduction of the mesylate and by minimizing the residence time of the mesylate in tetrahydrofuran prior to addition to the reducing agent. The most consistent results were obtained with lithium aluminum hydride as reductant. Thus, the mesylate of each diastereomer of **13** was prepared by using methanesulfonyl chloride, and the crude mesylate was dissolved in tetrahydrofuran and immediately added to a cold mixture of lithium aluminum hydride in tetrahydrofuran. The products were separated by preparative thin-layer chromatography. Reduction of (*R*)-**13** in this manner gave (*R*)-**8** in 19% yield and (*R*)-**19** in 18% yield. The alcohol (*S*)-**13** gave (*S*)-**8** in 38% yield and (*S*)-**19** in 41% yield. The primary alcohols **17** were treated in a similar manner, and after purification by chromatography, (*R*)-**17** gave 19-methyl-7α-thevinan (**21**) in 42% yield and 6-demethoxy-19(*R*)-methyl-6,20-epoxy-7α-thevinan [(*R*)-**22**] in 33% yield (Scheme III).

The stereochemistry of 19-butyl-7α-thevinan [(*R*)-**8**] was confirmed by its formation from primary alcohol (*S*)-**17** (Scheme IV). For this purpose, alcohol (*S*)-**17** was oxidized to aldehyde (*S*)-**23** in 82% yield with dimethyl sulfoxide and trifluoroacetic anhydride.[15] The aldehyde was treated with *n*-propyllithium to give the secondary alcohol **24** in 64% yield, and this alcohol was deoxygenated via the xanthate **25** and radical cleavage with tributyltin hydride.[16] The 19-butyl-7α-thevinan (**8**) thus obtained showed a methyl doublet at δ 0.58 in its NMR absorption, indicative of *R* stereochemistry.

Table I. Comparative Agonist Activity of the Orvinans

compound	ED_{50}, μmol/kg	rel analgesic act.
morphine	1.67	1
19-methyl-7α-orvinan (**26**)	0.18	9
19(*R*)-butyl-7α-orvinan [(*R*)-**3**]	0.0089	187
19(*S*)-butyl-7α-orvinan [(*S*)-**3**]	0.387	4
6-demethoxy-19(*R*)-butyl-6,20-epoxy-7α-orvinan [(*R*)-**4**]	0.090	19
6-demethoxy-19(*S*)-butyl-6,20-epoxy-7α-orvinan [(*S*)-**4**]	0.0081	206
19(*R*)-butyl-20-hydroxy-7α-orvinan [(*R*)-**27**]	0.0021	773
19(*S*)-butyl-20-hydroxy-7α-orvinans [(*S*)-**27**]	0.386	4

Demethylation of the aromatic methyl ethers to afford the phenols was accomplished with sodium propanethiolate in dimethylformamide.[17] The crude products were purified by alumina chromatography to produce the phenols in 50–60% yield.

Pharmacology. The analgesic activities of the 19-butylorvinans [(*R*)- and (*S*)-**3**], the 19-methylorvinan (**26**), the 6-demethoxy-19-butyl-6,20-epoxyorvinans [(*R*)- and (*S*)-**4**], and the 19-butyl-20-hydroxyorvinans [(*R*)- and (*S*)-**27**] were determined by the tail-flick method in Sprague–Dawley rats.[18] The ED_{50} values shown in Table I were acquired by the up–down method using a cutoff level of 6 s.[19] The analgesia of the phenols was antagonized by naloxone, indicating that the activity was produced through the opiate receptors.

Discussion

Most earlier proposals concerning structure–activity relationships and opiate receptor modeling using etorphine and its analogues have been based on the existence of an intramolecular hydrogen bond between the C-6 methoxy and the C-19 alcohol which would fix the position of the lipophilic side chain in one region of space.[3,20] The increased binding of the compound to the receptor, due to both the lipophilic interaction of the alkyl group in a specific area of the receptor and the hydrogen bonding ability of the hydroxyl group, is considered necessary for high analgesic activity. Our earlier results using the 6-demethoxyorvinols **2** showed that an intramolecular hydrogen bond is not necessary for potent activity. Similar conclusions have recently been reached based on derivatives lacking the 6,14-etheno bridge.[21]

There remains the possibility that an intermolecular hydrogen bond may assist in orienting the side chain to the lipophilic region of the receptor. Preparation of the 6,20-epoxy derivative, furan **4**, allows an examination of this hypothesis. The butyl group in the rigid tetrahydrofurans is locked in the α or β stereochemistry. Previous models have placed the side chain in the β pos-

(13) Holder, R. W.; Matturro, M. G. *J. Org. Chem.* **1977**, *42*, 2166; Leland, D. L.; Kotick, M. P. *J. Med. Chem.* **1981**, *24*, 717.
(14) Allred, E. L.; Winstein, S. *J. Am. Chem. Soc.* **1967**, *89*, 3991, 3998, 4008.
(15) Huang, S. L.; Omura, K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 3329.
(16) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans 1* **1975**, 1574. Hart, D. S. *J. Org. Chem.* **1981**, *46*, 367.
(17) Michne, W. F. *J. Med. Chem.* **1978**, *21*, 1322.
(18) Janssen, P. A. J.; Niemegeers, C. J. E.; Dony, J. G. H. *Arzneim.-Forsch.* **1963**, *13*, 502.
(19) Dixon, W. J. *Am. Stat. Assoc. J.* **1965**, 967.
(20) Bradybury, A. F.; Smyth, D. G.; Small, C. R. *Nature (London)* **1976**, *260*, 165.
(21) Kotick, M. P.; Leland, D. L.; Polazzi, J. O.; Howes, J. F.; Bousquet, A. *J. Med. Chem.* **1983**, *26*, 1050.

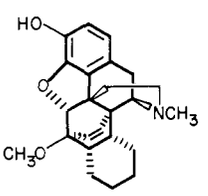
ition in order to achieve maximum activity. However, the *S* furan **4**, with the butyl group down in the α position, is the more active diastereomer.

Therefore, we propose that the lipophilic site of the opiate receptor that accommodates the side chain of **1** and **2** is located below C-8 nearer to the 6,14-etheno bridge. The tertiary hydroxyl group is directed above the bicyclic ring system toward a hydrophilic site on the receptor (Figure 2). It is the synergism and competition of binding at these two regions that determine the activity of the bridged-oripavine analgesics. If both a hydrophilic and a lipophilic interaction cannot occur, the compound will have poor activity. If both sites are occupied, the analgesic response will be significantly magnified. The lipophilic side chain is needed for high activity, but the formation of an intermolecular hydrogen bond is a necessary supplement to achieve the extremely potent activity of etorphine and similar derivatives. This model for the side-chain locale provides a rationale for understanding the activity of the compounds prepared in this report and of other opiates and should have predictive application.

The poor activity of (*S*)-**1** and (*S*)-**2** is the result of the inability of the carbinol group at C-7α to interact simultaneously at both lipophilic and hydrophilic sites. As the chiral carbon rotates about the C7–C19 bond to place the hydroxyl group in a position to form a hydrogen bond, the butyl group is withdrawn from the lipophilic area. The increased activity of the *R* isomer is due to the synergism of the interactions at both binding sites.

The difference in activity between the orvinans (*R*)- and (*S*)-**3** is a result of rotation of the asymmetric carbon to place the butyl in the binding site. In the *S* isomer the methyl group is moved into the hydrophilic area. This destabilization decreases interaction of the butyl group with the lipophilic area, and the activity remains low, only 4 times morphine. In (*R*)-**3**, bond rotation will move the methyl group away from the hydrophilic area, and the increased butyl interaction raises the activity to 190 times morphine. The high activity of 19(*R*)-butyl-20-hydroxyorvinan [(*R*)-**27**] is due both to formation of a hydrogen bond and a strong lipophilic interaction of the alkyl group. The *S* diastereomer cannot form a similar hydrogen bond without bond rotation and removal of the butyl group from the binding area.

The analgesic activities of the oripavine derivatives prepared earlier[1] can be explained by this model in which the tertiary alcohol of the orvinols is oriented above the plane of the other oxygens. The side chain projecting in the proper direction will enhance the potency. If the lipophilic site of the receptor is bound to an appropriate group of the opiate, the hydroxyl function may not be necessary. Thus, phenol **28** is 1000 times as potent as



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morphine; the activity is explained by the observation that the fixed cyclohexano portion can strongly interact with the lipophilic area of the receptor and does not require the assistance of an auxiliary hydroxyl group.

This model of the oripavine–receptor interaction has some features in common with a model proposed for the biologically active conformation of an enkephalin (Figure 3a).[22,23] The computer-drawn projection[24] of 19(*R*)-butyorvinol (Figure 3b) is an adaptation of the crystal structure data for 19-propylthevinol hydrobromide.[12] The projection of the enkephalin is derived from the data of the conformation search of the Tyr[1]-Gly[2]-Gly[3]-Phe[4] tetrapeptide.[22] The fifth amino acid has been added in a conformation that reflects the similar orientation of the lipophilic groups of the orvinol and the enkephalin. The cis amide bond has been included to enhance these correlations. The energy necessary to achieve this higher energy conformer may be achieved through increased receptor interaction.

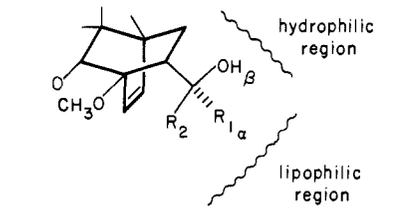

Figure 2. Proposed orvinol conformer of greatest agonist activity. The pendant alcohol is oriented for maximum interaction with the hydrophilic (H) and lipophilic (L) subsites.

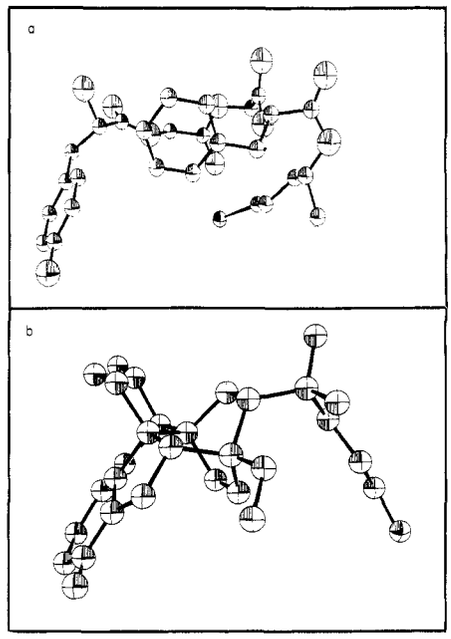

Figure 3. Computer-drawn projections of (a) an enkephalin, Tyr[1]-Gly[2]-Gly[3]-Phe-Met[5], and (b) 19(*R*)-butyorvinol. The conformation of the pentapeptide, with the Phe[4]-Met[5] amide bond cis, is drawn to reflect maximum coincidence with the active conformer of the orvinol.

The benzene ring of the Phe[4] of enkephalin corresponds to the C5–C6 area, and the Tyr[1] corresponds to the phenethylamine portion of the ethenotetrahydrooripavine. The fifth amino acid, methionine, is away from and below the Phe.[4] The side chain of Met[5] would correspond to the lipophilic alkyl group of the bridged opiates. The carbonyl groups of Gly[3] and Phe[4] are located in a hydrophilic area into which the C-19 hydroxyl of the orvinol is also directed.

These models of the active conformer of the orvinols and the proposed active conformation of the enkephalins are in agreement with the three-site receptor proposal[25] as

(22) Gorin, F. A.; Marshall, G. R. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 5179.
(23) Gorin, F. A.; Balasubramanian, T. M.; Barry, C. D.; Marshall, G. R. *J. Supramol. Struct.* **1978**, *9*, 27.
(24) We are indebted to Dr. J. Barstow of Molecular Design, Ltd., for the computer projections.
(25) Protoghese, P. S. *J. Med. Chem.* **1965**, *8*, 609.

recently modified.[26] In both cases, the anionic subsite of the receptor is paired with a quaternary nitrogen. The Tyr[1] can bind in the T subsite by hydrogen bonding of the phenol. The P subsite is occupied by the phenyl ring of Phe[4] and is located in the region of C-6 of morphine, in close proximity to the T subsite. Our data support the presence of two additional areas on opposite sides that contribute to the activity of the enkephalins and the orvinols. Thus, the large alkyl group of each is associated with a lipophilic (L) subsite situated below the major plane of the compounds. A hydrophilic (H) subsite recognizes the functional groups that are capable of forming hydrogen bonds and is an important factor for the alignment of the C-19 of the ethenotetrahydroripavines. The increased binding to the receptor due to the added hydrophilic and lipophilic interactions confers enhanced analgesic activity to the appropriate stereoisomer of the orvinols and related derivatives.

Conclusion

The preparation of the 19-deoxy derivatives (the orvinans **3**) and the 6,20-epoxy derivatives (the furans **4**) and the determination of their analgesic activities have led to a proposal for the biologically active conformation of the C-19 side chain of the ethenotetrahydrooripavines. This conformation was matched with a proposed biologically relevant conformer of enkephalin. These conformers are utilized to locate more specifically the T and P subsites of the opiate receptor and to postulate the existence and location of two additional subsites of receptor recognition, the lipophilic (L) subsite and hydrophilic (H) subsite. Examination of this receptor model may lead to the design of other ethenotetrahydrooripavines and new analogues of the enkephalins with enhanced agonist activity.[27]

Experimental Section

^{1}H NMR spectra were recorded on a Varian EM-390 spectrometer in $CDCl_3$; IR spectra were recorded on a Perkin-Elmer 137 spectrophotometer in $CHCl_3$. Analytical TLC was conducted on precoated silica gel 60 F-254 on aluminum plates, which were developed with 9:1 chloroform/methanol or with diethyl ether. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl immediately before reaction, and benzene was distilled from calcium hydride. All reactions were performed under a static positive pressure of nitrogen. Organic solvent solutions were dried over Na_2SO_4 before evaporations, which were performed at reduced pressure with a Berkeley rotary evaporator. MS spectra and microanalyses were obtained by the Analytical Laboratory, Chemistry Department, University of California, Berkeley.

19-Butyl-20-(phenylthio)-7α-thevinol (4,5α-Epoxy-3,6-dimethoxy-17-methyl-α-butyl-α-[(phenylthio)methyl]-6,14-ethenomorphinan-7α-methanol, 10). A 4.8-mL (6.48 mmol) portion of 1.35 M *n*-butyllithium in hexane was added to a solution of 0.72 g (6.42 mmol) of 1,4-diazabicyclo[2.2.2]octane and 0.76 g (6.16 mmol) of thioanisole in 7 mL of tetrahydrofuran cooled in an ice bath. The solution was stirred for 1.25 h at room temperature and then cooled again in an ice bath as a solution of 2.27 g (5.36 mmol) of thebuvinone (**5b**)[4] in 6 mL of tetrahydrofuran was added with stirring. The bath was allowed to warm to room temperature, after 24 h, water and ammonia were added, and the mixture was extracted with 4 × 25 mL of chloroform. The combined organic layers were washed with water, dried, and evaporated, and the residue was purified by column chromatography on silica gel with 0.6% methanol in chloroform. Mixed fractions were rechromatographed on silica gel with 0.7% methanol in chloroform as eluant: yield 1.30 g (44%).

High R_f diastereomer: mp 166.5–168 °C (ethanol); ^{1}H NMR δ 0.86 (m, CCH_3), 2.30 (s, 3 H, NCH_3), 3.73 (s, 3 H, OCH_3, C-6), 3.79 (3 H, OCH_3, C-3), 4.56 (s, 1 H, C-5 H), 5.39 (d, J = 9 Hz, 1 H, C-17 H), 5.93 (d, J = 9 Hz, 1 H, C-18 H), 6.44 (d, J = 8 Hz, 1 H, Ar H), 6.58 (d, J = 8 Hz, 1 H, Ar H), 7.1–7.5 (m, 5 H, S-Ar H); IR 3500, 2950, 1630, 1600, 1580 cm^{-1}. Anal. ($C_{33}H_{41}NO_4S$) C, H, N.

Low R_f diastereomer: ^{1}H NMR δ 0.90 (m, CCH_3), 2.36 (s, 3 H, NCH_3), 3.75 (s, 3 H, OCH_3, C-6), 3.80 (s, 3 H, OCH_3, C-3), 4.53 (s, 1 H, C-5 H), 4.82 (s, 1 H, OH), 5.47 (d, J = 9 Hz, 1 H, C-17 H), 5.98 (d, J = 9 Hz, 1 H, C-18 H), 6.46 (d, J = 8 Hz, 1 H, Ar H), 6.60 (d, J = 8 Hz, 1 H, Ar H), 7.1–7.5 (m, 5 H, S-Ar H); IR 3500, 2940, 1635, 1600, 1575, 1490 cm^{-1}; MS, m/e calcd for $C_{33}H_{41}NO_4S$, 547.2756; found, 547.2735.

19-Butyl-19,20-epoxy-7α-thevinan (11). To a solution of 0.91 g (1.66 mmol) of (phenylthio)thevinol **10** in 30 mL of dichloromethane cooled in an ice bath was added 1.92 g (13.8 mmol) of trimethyloxonium tetrafluoroborate, and the mixture was stirred at room temperature for 2 h. Then 1 mL of tetrahydrofuran and 60 mL of 2 M aqueous sodium hydroxide were added, and the mixture was stirred vigorously at room temperature for 24 h. The layers were separated, the aqueous layer was extracted with chloroform, the combined organic layers were washed with water, dried, and evaporated, and the residue was chromatographed on silica gel with 1% methanol in chloroform as eluant to afford 0.69 g (95%) of epoxythevinan **11** as a mixture of diastereomers.

High R_f diastereomer: ^{1}H NMR δ 0.82 (t, J = 6 Hz, 3 H, CCH_3), 2.34 (s, 3 H, NCH_3), 3.61 (s, 3 H, OCH_3, C-6), 3.79 (s, 3 H, OCH_3, C-3), 4.54 (d, J = 2 Hz, 1 H, C-5 H), 5.35 (d, J = 9 Hz, 1 H, C-17 H), 5.73 (d, J = 9 Hz, 1 H, C-18 H), 6.45 (d, J = 9 Hz, 1 H, Ar H), 6.58 (d, J = 9 Hz, 1 H, Ar H); IR 2950, 1630, 1600, 1495, 1105, 1050 cm^{-1}; MS, m/e calcd for $C_{27}H_{35}NO_4$, 437.2565; found, 437.2555.

Low R_f diastereomer: ^{1}H NMR δ 0.81 (t, J = 6 Hz, 3 H, CCH_3), 2.33 (s, 3 H, NCH_3), 3.59 (s, 3 H, OCH_3, C-6), 3.81 (s, 3 H, OCH_3, C-3), 4.46 (d, J = 2 Hz, 1 H, C-5 H), 5.42 (d, J = 9 Hz, 1 H, C-17 H), 5.80 (d, J = 9 Hz, 1 H, C-18 H), 6.45 (d, J = 9 Hz, 1 H, Ar H), 6.58 (d, J = 9 Hz, 1 H, Ar H). Anal. ($C_{27}H_{35}NO_4$) C, H, N.

19-Butyl-20-hydroxy-7α-thevinan (13). A 1.45 mL (1.67 g, 11.8 mmol) portion of boron trifluoride etherate was added over 0.5 min to a solution of 1.08 g (2.5 mmol) of epoxythevinan **11** in 55 mL of benzene at room temperature. After 10 min, 100 mL of aqueous potassium carbonate solution was added, the layers were separated, the aqueous layer was extracted with chloroform, the organic layers were washed with water, combined, dried, and evaporated, and the residue of crude aldehyde **12** was dissolved in 20 mL of absolute ethanol. Sodium borohydride (0.50 g, 13.2 mmol) was added, the mixture was stirred for 4 h at room temperature, water was added, and the mixture was extracted well with chloroform. The combined organic layers were washed with water, dried, and evaporated to give a residue, which was chromatographed on silica gel (18 × 268 mm) with 1.6% methanol in chloroform as eluent. The appropriate fractions were combined to afford 0.46 g (42%) of (*R*)-**13** and 0.39 g (36%) of (*S*)-**13**, both as foams.

(*R*)-**13**: ^{1}H NMR δ 0.90 (m, 3 H, CCH_3), 2.36 (s, 3 H, NCH_3), 3.60 (s, 3 H, OCH_3, C-6), 3.80 (s, 3 H, OCH_3, C-3), 4.58 (s, 1 H, C-5 H), 5.39 (d, J = 9 Hz, 1 H, C-17 H), 5.79 (d, J = 9 Hz, 1 H, C-18 H), 6.47 (d, J = 9 Hz, 1 H, Ar H), 6.60 (d, J = 9 Hz, 1 H, Ar H). Anal. ($C_{27}H_{37}NO_4$) C, H, N.

(*S*)-**13**: ^{1}H NMR δ 0.84 (m, CCH_3), 2.37 (s, 3 H, NCH_3), 3.58 (s, 3 H, OCH_3, C-6), 3.80 (s, 3 H, OCH_3, C-3), 4.57 (s, 1 H, C-5 H), 5.32 (d, J = 9 Hz, 1 H, C-17 H), 5.76 (d, J = 9 Hz, 1 H, C-18 H), 6.45 (d, J = 9 Hz, 1 H, Ar H), 6.58 (d, J = 9 Hz, 1 H, Ar H); IR 3700, 3510, 2960, 1635, 1600, 1495, 1440 cm^{-1}; MS, m/e calcd for $C_{27}H_{37}NO_4$, 439.2723; found, 439.2716.

19-[(Phenylthio)methyl]-7α-thevinol (14). To a solution of 2.83 g (25.2 mmol) of 1,4-diazabicyclo[2.2.2]octane and 3.07 g (24.7 mmol) of thioanisole in 30 mL of tetrahydrofuran, cooled in an ice bath, was added 17.9 mL (24.2 mmol) of *n*-butyllithium in hexane, the solution was stirred at 0 °C for 5 min, then the bath

(26) Portoghese, P. S.; Alreja, B. D.; Larson, D. L. *J. Med. Chem.* **1981**, *24*, 782.

(27) Attempts in this direction have recently been made using a different conformer of enkephalin and resulted in compounds with weak binding ability: Belanger, P. C.; Dufresne, C.; Scheigetz, J.; Young, R. N.; Springer, J. P.; Dmitrienko, G. I. *Can. J. Chem.* **1982**, *60*, 1019. For other conformational studies on enkephalins, see: Krstenansky, J. L.; Baranowski, R. L.; Currie, B. L. *Biochem. Biophys. Res. Commun.* **1982**, *109*, 1368. Di Maio, J.; Nguyen, T. M.-D.; Lemieux, C.; Schiller, P. W. *J. Med. Chem.* **1982**, *25*, 1432.

was removed, and the solution was allowed to warm to room temperature and stir for 1.5 h. Cooling in an ice bath was followed by the addition of a solution of 7.84 g (20.6 mmol) of thevinone (**5a**) in 20 mL of tetrahydrofuran over 10 min. After 5 min the cooling bath was removed, the solution was stirred at room temperature for 24 h, water and ammonia were added, the mixture was extracted with chloroform, the combined organic layers were washed with water, dried, and evaporated, and the residue was chromatographed on silica gel with 1% methanol in chloroform as eluent to afford 8.68 g (84%) of 14 as a mixture of diastereomers.

High R_f diastereomer: mp 185.5–187.5 °C (chloroform/ether); ^{1}H NMR δ 0.94 (dd, J = 8 and 13 Hz, 1 H), 1.20 (s, 3 H, CCH_3), 2.35 (s, 3 H, NCH_3), 3.74 (s, 3 H, OCH_3, C-6), 3.79 (s, 3 H, OCH_3, C-3), 4.51 (s, 1 H, C-5 H), 4.67 (s, 1 H, OH), 5.47 (d, J = 9 Hz, 1 H, C-17 H), 5.96 (d, J = 9 Hz, 1 H, C-18 H), 6.46 (d, J = 9 Hz, 1 H, Ar H), 6.60 (d, J = 9 Hz, 1 H, Ar H), 7.02–7.38 (m, Ar H); IR 3530, 3010, 2950, 1630, 1600, 1575, 1490 cm^{-1}. Anal. ($C_{30}H_{35}NO_4S$) C, H, N.

Low R_f diastereomer: mp 186–189 °C (chloroform/ether); ^{1}H NMR δ 0.93 (dd, J = 9 and 13 Hz, 1 H), 1.19 (s, 3 H, CCH_3), 2.34 (s, 3 H, NCH_3), 3.73 (s, 3 H, OCH_3, C-6), 3.78 (s, 3 H, OCH_3, C-3), 4.50 (s, 1 H, C-5 H), 4.66 (s, 1 H, OH), 5.47 (d, J = 9 Hz, C-17 H), 5.95 (d, J = 9 Hz, 1 H, C-18 H), 6.46 (d, J = 9 Hz, 1 H, Ar H), 6.59 (d, J = 9 Hz, 1 H, Ar H), 7.05–7.4 (m, S-Ar H); IR 3500, 3000, 2950, 1635, 1600, 1575, 1495 cm^{-1}. Anal. ($C_{30}H_{35}NO_4S$) C, H, N.

19-Methyl-19,20-epoxy-7α-thevinan (15). A solution of 8.68 g (17.2 mmol) of 19-[(phenylthio)methyl]-7α-thevinol (14) in 30 mL of dichloromethane was added over 5 min to a suspension of 3.2 g (21.6 mmol) of trimethyloxonium tetrafluoroborate in 75 mL of dichloromethane at 0 °C. After the addition was complete, the bath was removed, the reaction was allowed to warm to room temperature and stir for 2 h, 2 mL of tetrahydrofuran and 100 mL of 2 M aqueous sodium hydroxide solution were added, the mixture was stirred vigorously for 18 h, water was added, the layers were separated, the aqueous layer was extracted with dichloromethane, and the combined organic layers were washed with water, dried, and evaporated. The residue was chromatographed on silica gel with 1% methanol in chloroform as eluent to afford 4.32 g (64%) of the epoxide **15** as a mixture of diastereomers.

High R_f diastereomer: ^{1}H NMR δ 1.16 (s, 3 H, CCH_3), 2.33 (s, 3 H, NCH_3), 3.63 (s, 3 H, OCH_3, C-6), 3.79 (s, 3 H, OCH_3, C-3), 4.57 (s, 1 H, C-5 H), 5.36 (d, J = 9 Hz, 1 H, C-17 H), 5.75 (d, J = 9 Hz, 1 H, C-18 H), 6.45 (d, J = 9 Hz, 1 H, Ar H), 6.58 (d, J = 9 Hz, 1 H, Ar H); MS, m/e calcd for $C_{24}H_{29}NO_4$, 395.2096; found 395.2094.

Low R_f diastereomer: ^{1}H NMR δ 1.06 (s, 3 H, CCH_3), 2.32 (s, 3 H, NCH_3), 3.60 (s, 3 H, OCH_3, C-6), 3.80 (s, 3 H, OCH_3, C-3), 4.46 (s, 1 H, C-5 H), 5.43 (d, J = 9 Hz, 1 H, C-17 H), 5.77 (d, J = 9 Hz, 1 H, C-18 H), 6.46 (d, J = 9 Hz, 1 H, Ar H), 6.60 (d, J = 9 Hz, 1 H, Ar H); IR 2940, 1625, 1600, 1490, 1100 cm^{-1}. Anal. ($C_{24}H_{29}NO_4$) C, H, N.

19-(Hydroxymethyl)-7α-thevinan (17). A 2.0 mL (2.30 g, 16.2 mmol) portion of boron trifluoride etherate was added to a solution of 1.96 g (5.0 mmol) of epoxide **15** in 80 mL of benzene at room temperature. After 10 min, aqueous sodium carbonate solution was added, the mixture was extracted with ether and then with chloroform, and the organic layers were washed with water, combined, and dried. Evaporation gave the aldehyde **16** as a foam, which was dissolved in 40 mL of anhydrous ethanol to which 1.48 g (38.9 mmol) of sodium borohydride was added; the mixture was then stirred at room temperature for 2 h. Water was added, the mixture was extracted with chloroform, and the combined organic layers were washed with water and dried. Evaporation gave a residue, which was chromatographed on silica gel with 3% methanol in chloroform as eluent to afford the pure diastereomers.

(*R*)-**17**: ^{1}H NMR δ 0.89 (d, J = 7 Hz, 3 H, CCH_3), 2.37 (s, 3 H, NCH_3), 3.63 (s, 3 H, OCH_3, C-6), 3.80 (s, 3 H, OCH_3, C-3), 4.57 (s, 1 H, C-5 H), 5.39 (d, J = 9 Hz, 1 H, C-17 H), 5.78 (d, J = 9 Hz, 1 H, C-18 H), 6.48 (d, J = 9 Hz, 1 H, Ar H), 6.62 (d, J = 9 Hz, 1 H, Ar H); IR 3410, 2940, 1635, 1600, 1500 cm^{-1}; MS, m/e calcd for $C_{24}H_{31}NO_4$, 397.2253; found, 397.2249.

(*S*)-**17**: ^{1}H NMR δ 0.65 (d, J = 6 Hz, 3 H, CCH_3), 0.97 (dd, J = 6 and 12 Hz, 1 H), 2.35 (s, 3 H, NCH_3), 3.57 (s, 3 H, OCH_3, C-6), 3.80 (s, 3 H, OCH_3, C-3), 4.58 (s, 1 H, C-5 H), 5.30 (d, J = 9 Hz, 1 H, C-17 H), 5.72 (d, J = 9 Hz, 1 H, C-18 H), 6.46 (d, J = 8 Hz, 1 H, Ar H), 6.60 (d, J = 8 Hz, 1 H, Ar H); MS, m/e (relative intensity) 397 (M$^+$, 15), 395 (20), 365 (15), 338 (36), 229 (49), 44 (100); calcd for $C_{24}H_{31}NO_4$, 397.2253; found, 397.2245.

Dehydroxylation of 19(*R*)-Butyl-20-hydroxy-7α-thevinan [(*R*)-13]. 19(*R*)-Butyl-7α-thevinan [(*R*)-8] and 6-Demethoxy-19(*R*)-butyl-6,20-epoxy-7α-thevinan [(*R*)-19]. A 0.12 g (1.0 mmol) portion of methanesulfonyl chloride was added to a solution of 0.10 g (1.0 mmol) of triethylamine and 0.27 g (0.6 mmol) of (*R*)-**13** in 7 mL of dichloromethane cooled in an ice bath. The solution was stirred, the bath was allowed to warm to room temperature, water was added after 3 h, and the mixture was extracted with chloroform. The combined organic layers were washed with water, dried, and evaporated to a residue, which was dissolved in 5 mL of tetrahydrofuran and *immediately* added to a stirred mixture of 0.2 g (5.3 mmol) of lithium aluminum hydride in 5 mL of tetrahydrofuran cooled in an ice bath. The mixture was stirred and the bath was allowed to warm to room temperature. After 24 h, sodium sulfate decahydrate was added, followed by water and aqueous sodium hydroxide, and the mixture was extracted with ether and then chloroform. The organic layers were washed with water, combined, dried, and evaporated to a residue, which was purified by preparative thin-layer chromatography with ether as eluent.

(*R*)-**8**: yield 50 mg (19%); ^{1}H NMR δ 0.58 (d, J = 7 Hz, 3 H, $CHCH_3$), 0.87 (m, CH_3), 2.37 (s, 3 H, NCH_3) 3.53 (s, 3 H, OCH_3, C-6), 3.79 (s, 3 H, OCH_3, C-3), 4.56 (d, J = 2 Hz, 1 H, C-5 H), 5.26 (d, J = 9 Hz, 1 H, C-17 H), 5.68 (dd, J = 2 and 9 Hz, 1 H, C-18 H), 6.45 (d, J = 9 Hz, 1 H, Ar H), 6.58 (d, J = 9 Hz, 1 H, Ar H); MS, m/e (relative intensity) 423 (M$^+$, 50), 408 (12), 338 (51), 248 (100); calcd for $C_{27}H_{37}NO_3$, 423.2773; found 423.2771.

(*R*)-**19**: yield 44 mg (18%); ^{1}H NMR δ 0.83 (t, J = 6 Hz, 3 H, CH_2CH_3), 2.36 (s, 3 H, NCH_3), 3.70 (dd, J = 4 and 9 Hz, 1 H, OCH), 3.78 (s, 3 H, OCH_3), 4.22 (dd, J = 7 and 9 Hz, 1 H, OCH), 4.39 (s, 1 H, C-5 H), 5.35 (d, J = 9 Hz, 1 H, C-17 H), 5.61 (d, J = 9 Hz, 1 H, C-18 H), 6.42 (d, J = 9 Hz, 1 H, Ar H), 6.57 (d, J = 9 Hz, 1 H, Ar H); MS, m/e calcd for $C_{26}H_{33}NO_3$, 407.2460; found 407.2465.

Dehydroxylation of 19(*S*)-Butyl-20-hydroxy-7α-thevinan [(*S*)-13]. 19(*S*)-Butyl-7α-thevinan [(*S*)-8] and 6-Demethoxy-19(*S*)-butyl-6,20-epoxy-7α-thevinan [(*S*)-19]. A 151 mg (0.3 mmol) portion of (*S*)-**13** was treated successively with methanesulfonyl chloride/triethylamine and lithium aluminum hydride following the procedure used with (*R*)-**13**. The products were (*S*)-**8** and (*S*)-**19**.

(*S*)-**8**: yield 55 mg (38%); ^{1}H NMR δ 0.83 (d, J = 6 Hz, 3 H, $CHCH_3$), 0.83 (m, CCH_3), 2.37 (s, 3 H, NCH_3), 3.54 (s, 3 H, OCH_3, C-6), 3.79 (s, 3 H, OCH_3, C-3), 4.53 (s, 1 H, C-5 H), 5.27 (d, J = 9 Hz, 1 H, C-17 H), 5.71 (d, J = 9 Hz, 1 H, C-18 H), 6.45 (d, J = 9 Hz, 1 H, Ar H), 6.58 (d, J = 9 Hz, 1 H, Ar H): MS, m/e (relative intensity) 423 (M$^+$, 7), 338 (5), 248 (7), 84 (100); calcd for $C_{27}H_{37}NO_3$, 423.2773; found, 423.2775.

(*S*)-**19**: yield 58 mg (41%); ^{1}H NMR δ 0.86 (m, CCH_3), 2.37 (s, 3 H, NCH_3), 3.61 (apparent t, 1 H, OCH), 3.77 (s, 3 H, OCH_3, C-3), 4.17 (apparent t, 1 H, OCH), 4.43 (s, 1 H, C-5 H), 5.41 (d, J = 9 Hz, 1 H, C-17 H), 5.68 (d, J = 9 Hz, 1 H, C-18 H), 6.43 (d, J = 8 Hz, 1 H, Ar H), 6.57 (d, J = 8 Hz, 1 H, Ar H), 6.57 (d, J = 8 Hz, 1 H, Ar H); MS, m/e calcd for $C_{26}H_{33}NO_3$, 407.2460; found, 407.2463.

Dehydroxylation of 19(*R*)-(Hydroxymethyl)-7α-thevinan [(*R*)-17]. 19-Methyl-7α-thevinan (21) and 6-Demethoxy-19-(*R*)-methyl-6,20-epoxy-7α-thevinan [(*R*)-22]. A 540 mg (1.4 mmol) portion of (*R*)-**17** was treated as above successively with methanesulfonyl chloride/triethylamine followed by lithium aluminum hydride. Preparative thin-layer chromatography with ether as eluent gave **21** and (*R*)-**22**.

21: yield 215 mg (42%); mp 105–107 °C (aqueous methanol); ^{1}H NMR δ 0.66 (d, J = 7 Hz, 3 H, CCH_3), 0.82 (d, J = 7 Hz, 3 H, CCH_3), 2.35 (s, 3 H, NCH_3), 3.65 (s, 3 H, OCH_3, C-6), 3.81 (s, 3 H, OCH_3, C-3), 4.53 (s, 1 H, C-5 H), 5.26 (d, J = 9 Hz, 1 H, C-17 H), 5.66 (d, J = 9 Hz, 1 H, C-18 H), 6.43 (d, J = 8 Hz, 1 H, Ar H), 6.58 (d, J = 8 Hz, 1 H, Ar H); MS, m/e (relative intensity) 381 (M$^+$, 55), 366 (9), 338 (40), 229 (44), 206 (100). Anal. ($C_{24}H_{31}NO_3$) C, H, N.

(*R*)-**22**: yield 168 mg (33%); ^{1}H NMR δ 0.98 (d, J = 6 Hz, 3 H, CCH_3), 2.36 (s, 3 H, NCH_3), 3.55 (t, J = 6 Hz, 1 H, OCH), 3.80

(s, 3 H, OCH_3, C-3), 4.16 (t, J = 6 Hz, 1 H, OCH), 4.42 (s, 1 H, C-5 H), 5.39 (d, J = 9 Hz, 1 H, C-17 H), 5.68 (d, J = 9 Hz, 1 H, C-18 H), 6.42 (d, J = 9 Hz, 1 H, Ar H), 6.58 (d, J = 9 Hz, 1 H, Ar H); MS, m/e calcd for $C_{23}H_{27}NO_3$, 365.1991; found, 365.1983.

19(*S*)-Formyl-7α-thevinan [(*S*)-23]. To a solution of 0.11 g (1.4 mmol) of dimethyl sulfoxide and 3 mL of dichloromethane, cooled in a dry ice–acetone bath, was slowly added dropwise a solution of 0.21 g (1.0 mmol) of trifluoroacetic anhydride in 1.5 mL of dichloromethane. The white suspension was stirred at −78 °C for 10 min; then a solution of 0.22 g (0.6 mmol) of alcohol (*S*)-**17** in 2.2 mL of dichloromethane was added dropwise over 15 min, and the solution was stirred at −78 °C for 1.5 h. Triethylamine (2 mL) was added, and the mixture was allowed to warm to room temperature; after 10 h, aqueous potassium carbonate solution was added, and the mixture was extracted with ether. The combined organic layers were washed with water and brine, dried, and evaporated. The residue was chromatographed on silica gel with 1% methanol in chloroform and provided the aldehyde (*S*)-**23** as a foam: yield 0.18 g (82%); ^{1}H NMR δ 0.92 (d, J = 6 Hz, 3 H, CCH_3), 2.35 (s, 3 H, NCH_3), 3.55 (s, 3 H, OCH_3, C-6), 3.82 (s, 3 H, OCH_3, C-3), 4.49 (s, 1 H, C-5 H), 5.42 (d, J = 9 Hz, 1 H, C-17 H), 5.84 (d, J = 9 Hz, 1 H, C-18 H), 6.46 (d, J = 8 Hz, 1 H, Ar H), 6.59 (d, J = 8 Hz, 1 H Ar H), 9.44 (d, J = 3 Hz, 1 H, CHO); IR 2930, 2820, 1705, 1625, 1600, 1490, 1440 cm^{-1}; MS, m/e calcd for $C_{24}H_{29}NO_4$, 395.2096; found, 395.2091.

19-(1-Hydroxybutyl)-7α-thevinan (24). A solution of 180 mg (0.5 mmol) of (*S*)-**23** in 4 mL of tetrahydrofuran was cooled in an ice bath, 2.5 mL of 1 M *n*-propyllithium in ether was added, and the solution was stirred as the bath was allowed to warm to room temperature; after 12 h, water was added, and the mixture was extracted with chloroform. The chloroform extracts were washed with water, dried, and evaporated, and the residue was chromatographed on silica gel with 2% methanol in chloroform to afford the secondary alcohol **24** as a mixture of diastereomers: yield 140 mg (64%); ^{1}H NMR δ 0.60 (d, J = 6 Hz, CCH_3 minor), 0.73 (d, J = 6 Hz, CCH_3, major), 2.34 (s, 3 H, NCH_3), 3.56 (s, 3 H, OCH_3, C-6), 3.79 (s, 3 H, OCH_3, C-3), 4.53 (s, 1 H, C-5 H, major), 4.60 (s, 1 H, C-5 H, minor), 5.27 (d, J = 8 Hz, C-17 H, minor), 5.3 (d, J = 8 Hz, C-17 H, major), 5.70 (d, J = 8 Hz, C-18 H, minor), 5.74 (d, J = 8 Hz, C-18 H, major), 6.44 (d, J = 8 Hz, 1 H, Ar H), 6.57 (d, J = 8 Hz, 1 H, Ar H); IR 3670, 3450, 2940, 1635, 1600, 1490, 1440 cm^{-1}.

Xanthate 25 was prepared by first adding 100 mg (4.2 mmol) of degreased sodium hydride to a solution of 140 mg (0.3 mmol) of **24** and 3 mg of imidazole in 5 mL of tetrahydrofuran and heating the mixture at reflux temperature for 1.5 h. Then 0.63 g (8.3 mmol) of carbon disulfide was added, the mixture was heated at reflux for 0.5 h, 2.28 g (16.1 mmol) of iodomethane was added, and reflux was continued for 0.5 h. Water was carefully added to the cooled solution, the mixture was extracted with chloroform, and the combined organic layers were washed with water and dried. Evaporation gave a residue, which was chromatographed on silica gel with 0.4% methanol in chloroform as eluent to provide xanthate **25** as a foam: yield 130 mg (79%); ^{1}H NMR δ 0.67 (d, J = 6 Hz, CCH_3), 2.35 (s, 3 H, NCH_3), 2.53 (s, 3 H, SCH_3), 3.53 (s, 3 H, OCH_3, C-6), 3.84 (s, 3 H, OCH_3, C-3), 4.53 (s, 1 H, C-5 H), 5.27 (d, J = 9 Hz, 1 H, C-17 H), 5.68 (d, J = 9 Hz, 1 H, C-18 H), 6.44 (d, J = 8 Hz, 1 H, Ar H), 6.57 (d, J = 8 Hz, 1 H, Ar H).

Preparation of 19(*R*)-Butyl-7α-thevinan [(*R*)-8] from Xanthate 25. A solution of 130 mg (0.3 mmol) of xanthate **25** in 1 mL of toluene was added dropwise to a solution of 130 mg (0.4 mmol) of tributyltin hydride in 2 mL of toluene at reflux. Reflux was continued for 3 h, the solution was cooled to room temperature and evaporated, and the residue was extracted well with hot acetonitrile. The combined acetonitrile fractions were washed with hexane and evaporated, and the residue was subjected to preparative thin-layer chromatography with ether as eluent. (*R*)-**8** was obtained in 27% yield (28 mg) and was identical in all respects with the material prepared above from (*R*)-**13**.

19(*R*)-Butyl-20-hydroxy-7α-orvinan [(*R*)-27]. A solution of 33 mg (0.08 mmol) of (*R*)-**13** in 5 mL of dimethylformamide was stirred as 0.1 g (4.2 mmol) of degreased sodium hydride was added in portions, followed by 84 mg (1.1 mmol) of propanethiol. The mixture was heated at reflux for 1 h, then cooled to room temperature, poured into 1 M aqueous phosphoric acid, and washed with ether. The aqueous layer was adjusted to pH 11 with aqueous ammonium hydroxide and extracted with chloroform. Evaporation of the combined, washed, and dried chloroform layer gave a residue, which was chromatographed on a short alumina column with 1% methanol in chloroform as eluent and afforded (*R*)-**27** as a foam: yield 18 mg (55%); ^{1}H NMR δ 0.87 (m, CCH_3), 2.35 (s, 3 H, NCH_3), 3.56 (s, 3 H, OCH_3), 4.59 (s, 1 H, C-5 H), 5.34 (d, J = 9 Hz, 1 H, C-17 H), 5.71 (d, J = 9 Hz, 1 H, C-18), 6.41 (d, J = 9 Hz, 1 H, Ar H), 6.56 (d, J = 9 Hz, 1 H, Ar H); MS, m/e calcd for $C_{26}H_{35}NO_4$, 425.2566; found, 425.2570.

The other thevinans were converted to the corresponding orvinans by the same demethylation procedure and in similar yield.

19(*S*)-Butyl-20-hydroxy-7α-orvinan [(*S*)-27] from (*S*)-13: ^{1}H NMR δ 2.36 (s, 3 H, NCH_3), 3.56 (s, 3 H, OCH_3), 4.60 (s, 1 H, C-5 H), 5.30 (d, J = 9 Hz, 1 H, C-17 H), 5.71 (d, J = 9 Hz, 1 H, C-18 H), 6.42 (d, J = 8 Hz, 1 H, Ar H), 6.57 (d, J = 8 Hz, 1 H, Ar H); MS, m/e calcd for $C_{26}H_{35}NO_4$, 425.2566; found, 425.2568.

19-Methyl-7α-orvinan (26) from 21: mp 233–238 °C (aqueous methanol); ^{1}H NMR δ 0.59 (d, J = 7 Hz, 3 H, CCH_3), 0.80 (d, J = 7 Hz, 3 H, CCH_3), 2.36 (s, 3 H, NCH_3), 3.51 (s, 3 H, OCH_3), 4.57 (s, 1 H, C-5 H), 5.26 (d, J = 9 Hz, 1 H, C-17 H), 5.62 (d, J = 9 Hz, 1 H, C-18 H), 6.40 (d, J = 9 Hz, 1 H, Ar H), 6.56 (d, J = 9 Hz, 1 H, Ar H). Anal. ($C_{23}H_{29}NO_3$) C, H, N.

19(*R*)-Butyl-7α-orvinan [(*R*)-3] from (*R*)-8: ^{1}H NMR δ 0.57 (d, J = 7 Hz, 3 H, CCH_3), 2.37 (s, 3 H, NCH_3), 3.51 (s, 3 H, OCH_3), 4.58 (s, 1 H, C-5 H), 5.23 (d, J = 9 Hz, 1 H, C-17 H), 5.61 (d, J = 9 Hz, 1 H, C-18 H), 6.41 (d, J = 8 Hz, 1 H, Ar H), 6.56 (d, J = 8 Hz, 1 H, Ar H); MS, m/e calcd for $C_{26}H_{35}NO_3$, 409.2617; found, 409.2614.

(*S*)-3 from (*S*)-8: ^{1}H NMR δ 0.83 (d, J = 7 Hz, 3 H, CCH_3), 2.36 (s, 3 H, NCH_3), 3.53 (d, 3 H, OCH_3), 4.11 (s, 1 H, OH), 4.56 (s, 1 H, C-5-H), 5.25 (d, J = 9 Hz, 1 H, C-17 H), 5.64 (d, J = 9 Hz, 1 H, C-18 H), 6.40 (d, J = 8 Hz, 1 H, Ar H), 6.56 (d, J = 8 Hz, 1 H, Ar H); MS, m/e calcd for $C_{26}H_{35}NO_3$, 409.2617; found, 409.2616.

6-Demethoxy-19(*R*)-butyl-6,20-epoxy-7α-orvinan [(*R*)-4] from (*R*)-19: mp 209–212 °C (aqueous methanol); ^{1}H NMR δ 0.83 (m, CCH_3), 2.36 (s, 3 H, NCH_3), 3.70 (dd, J = 4 and 9 Hz, 1 H, OCH), 4.23 (dd, J = 7 and 9 Hz, 1 H, OCH), 4.43 (s, 1 H, C-5 H), 5.36 (d, J = 9 Hz, 1 H, C-17 H), 5.59 (d, J = 9 Hz, 1 H, C-18 H), 6.42 (d, J = 8 Hz, 1 H, Ar H), 6.58 (d, J = 8 Hz, 1 H, Ar H). Anal. ($C_{25}H_{31}NO_3$) C, H, N.

(*S*)-4 from (*S*)-19: ^{1}H NMR δ 0.85 (m, CCH_3), 2.36 (s, 3 H, NCH_3), 3.62 (apparent t, J = 8 Hz, 1 H, OCH), 4.19 (apparent t, J = 8 Hz, 1 H, OCH), 4.47 (s, 1 H, C-5 H), 5.39 (d, J = 9 Hz, 1 H, C-17 H), 5.63 (d, J = 9 Hz, 1 H, C-18 H), 6.40 (d, J = 8 Hz, 1 H, Ar H), 6.56 (d, J = 8 Hz, 1 H, Ar H); MS, m/e calcd for $C_{25}H_{31}NO_3$, 393.2304; found, 393.2303.

Pharmacological Methods. Sprague–Dawley male rats weighing 300–335 g, restrained in cages in the dark, were used in the tail-flick test.[18] Test compounds were dissolved in 0.01 M aqueous hydrochloric acid and diluted with sterile saline solution and then administered at 1 mL/kg, subcutaneously. Hot water (55 °C) provided the stimulus, and reaction times were measured at 8, 16, and 24 min after injection for a maximum of 15 s. Five to eight rats were used for each compound using the up–down method of determining the ED_{50}, with 6 s being the cutoff between no response and response.

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