injected once daily for 5 successive days. Bu-SMA described in Table I was used in the present experiments after reacting with glycine; thus little anhydride residue would remain intact. All other tested materials were used without any special modifications. The survival rate, expressed as the increase in life span over nontreated controls, was calculated 50 days after drug treatment. Male Donryu rats weighing about 250–300 g were also used for the toxicity (LD_{50}) assay.

Acknowledgment. We gratefully acknowledge the excellent cooperation of our colleagues Ryuzo Asano, Osamu Nakaji, Koichiro Kawai, Toshihiko Yoshitake, and Isao Akuta of Kuraray Co., Ltd.. Thanks are also due to Dr. Yoshiharu Amiya for NMR and to Yasuyo Omori for infrared spectroscopy and to Professor K. Kawahara of Nagasaki University for the gift of purified pullulan. This work was supported in part by an Award from the Japanese Foundation for Multidisciplinary Treatment of Cancer (1982) and a Cancer Research Grant from the Ministry of Education, Science and Culture of Japan (to H.M. for 1983 and 1984).

Supplementary Material Available: Figures 4, 5, and 7 and an appendix for theoretical justification for the molecular weight estimation (5 pages). Ordering information is given on any current masthead page.

Analgesics of the 6,14-Ethenomorphinan Type. 6-Deoxy-7α-orvinols and 6-Deoxy-8α-orvinols

Laura L. Knipmeyer and Henry Rapoport*

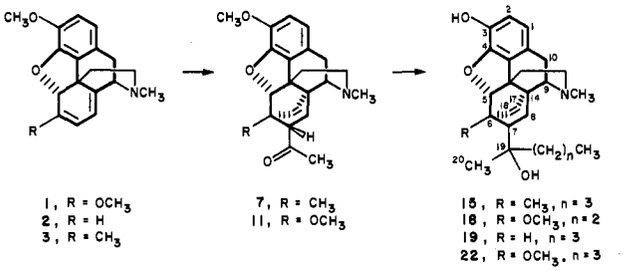
Department of Chemistry, University of California, Berkeley, California 94720. *Received June 11, 1984*

6-Deoxythebaine (3) has been prepared as a precursor to C-6 alkyl substituted orvinols 15 and 17. The C-6 methyl group was introduced by addition of methyllithium to codeinone. Transformation of 6-methylcodeine to its 6-methyl ether and 1,4-elimination of methanol with potassium *tert*-butoxide in Me_2SO then gave 6-deoxythebaine (3) in 49% overall yield. Diels–Alder addition of methyl vinyl ketone to this diene yielded four ketones: three regio- and stereoisomeric 6,14-*endo*-ethenomorphinans and one exo adduct. The major ketone isomer provided the set of C-19 diastereomeric orvinols 15 in which the pendant carbon has the 7α configuration. Regioisomeric ketone 8, in which the acetyl group is at C-8, was formed in 3% yield and was similarly converted to the corresponding orvinols 17. Orvinol (*R*)-15 (*R* at C-19) is an analgesic of very high potency, 2200 times that of morphine; regioisomeric orvinols 17, in which the pendant tertiary alcohols are on C-8, are much less potent. The higher activity of the C-6 methyl and methoxyl analogues (*R*)-15 and (*R*)-22 relative to hydrogen-substituted (*R*)-19 indicates that C-6 alkyl substitution enhances analgesic potency.

Alkylorvinols (18, 22) are extremely potent bicyclic analogues of morphine. For example, etorphine[1] (19-(*R*)-propylorvinol, 18), used for immobilization of large animals for game conservation and veterinary purposes, has an analgesic potency 1000 times that of morphine.[2] The bicyclic structure of the orvinols is formed by Diels–Alder addition of dienophiles to thebaine (1).[3] Thus methyl vinyl ketone addition gives thevinone (11), and addition of organometallic reagents to the ketone[4] at C-19 affords diastereomers that vary greatly in activity depending on the absolute stereochemistry at C-19. *R* diastereomers are highly potent, while *S* isomers have activity in the range of morphine. Hydrogen bonding between the C-6 oxygen and the C-19 hydroxyl resulting in conformational stabilization was proposed[5] as an explanation for the large difference in activity dependent on C-19 stereochemistry. The subsequent synthesis and pharmacological evaluation of 6-demethoxyorvinols (19)[6] revealed that the relationship between high activity and C-19 stereochemistry is independent of intramolecular hydrogen bonding (Scheme I).

We therefore considered synthesis of 6-alkyl analogues of the orvinols 22 for investigation of structure–activity relationships based on the C-6 substituent. For this purpose, the synthesis of 6-deoxythebaine (3) is required as substrate for the analogous Diels–Alder addition of methyl vinyl ketone to give bicyclic 6-deoxythevinone (7). Also, in the absence of the polarizing methoxy functionality at C-6, Diels–Alder addition to diene 3 can give a regioisomeric adduct in which the acetyl group is attached at C-8. Ketone 8 therefore was sought as the precursor to orvinol analogues having the stereochemically important pendant C-19 center on the adjacent C-8 carbon atom.

Scheme I. Synthesis of 19-Alkylorvinols by Diels–Alder Addition to 6,7,8,14-Tetradehydromorphinans



Chemistry. Synthesis of 6-deoxythebaine (3) was accomplished by first introducing the C-6 methyl group by methyllithium addition to codeinone, followed by 1,4-elimination from the resulting 6-methylcodeine (4). Although methyllithium addition to codeinone in ether at 0 °C has been reported[7] to give a high yield, we found that reaction in THF at −78 °C was more reproducible and

(1) Bentley, K. W.; Hardy, D. G. *J. Am. Chem. Soc.* **1967**, *89*, 3281.
(2) Lewis, J. W.; Bentley, K. W.; Cowan, A. *Ann. Rev. Pharmacol.* **1971**, *11*, 241.
(3) Bentley, K. W.; Hardy, D. G. *J. Am. Chem. Soc.* **1967**, *89*, 3267.
(4) Bentley, K. W.; Hardy, D. G.; Meek, B. *J. Am. Chem. Soc.* **1967**, *89*, 3273.
(5) Loew, G. H.; Berkowitz, D. S. *J. Med. Chem.* **1979**, *22*, 603.
(6) Hutchins, C. W.; Cooper, G. K.; Purro, S.; Rapoport, H. *J. Med. Chem.* **1981**, *24*, 773.
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Scheme II. Synthesis of 6-Deoxythebaine (3) from Codeinone

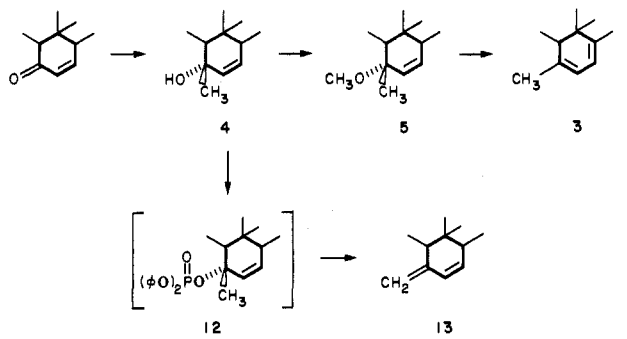


Table I. Ratios of Products from Addition of Methyl Vinyl Ketone to 6,7,8,14-Tetradehydro-4,5α-epoxy-17-methyl-3-methoxymorphinans

		ketone position			
diene	R	7α	8α	7β	exo-8β[a]
1	OCH_3	98	0	2	
2	H	88	12		
3	CH_3	96	3	1	0.1

[a] Reference 21.

consistently gave 80% yields of **4**. To effect the necessary 1,4-elimination, direct dehydration of 6-methylcodeine (**4**) with thionyl chloride was first attempted but gave only mixtures of 6- and 8-chlorocodides under a variety of conditions. Conversion of tertiary alcohol **4** to its diphenyl phosphate ester (**12**) in the presence of excess base did give elimination, but the product was exclusively exo diene **13**.

Codeinone dimethyl ketal is known to form thebaine through 1,4-elimination of methanol either with phosphorus oxychloride in pyridine or with alkoxides.[8] However, the analogous elimination applied to codeine methyl ether in an attempt to prepare 6-demethoxythebaine (**2**) did not give the desired diene.[6] This failure is presumably due to the acidity of the C-6 proton, resulting in dominant anion formation at C-6. In 6-methylcodeine methyl ether (**5**), however, this competitive anion formation does not exist, and the allylic proton at C-14 participates in a 1,4-elimination of methanol under the influence of potassium *tert*-butoxide in dimethyl sulfoxide to form endo diene **3** in 71% yield (Scheme II).

Diels–Alder addition of methyl vinyl ketone to 6-deoxythebaine (**3**) proceeded in 98% yield. The major C-7α isomer **7** was isolated in 71% yield by crystallization from the adduct mixture; chromatography of the mother liquor then lead to isolation of the minor components. Thus the four isomeric ketones **7–10** were isolated in the ratio 96/3/1/0.1 (Table I) and their structures were assigned by ^1H NMR analysis (Tables II and III).[9]

In the addition of methyl vinyl ketone to thebaine (**1**), C-6 methoxy polarization of the diene system results in formation of only the C-7 regioisomer in the adduct as a 98/2 ratio of α/β stereoisomers.[3] Formation of the C-8α isomer in the case of trisubstituted diene **2** should be slightly favored by electronic effects, but apparently the steric constraints of the morphine skeleton control the addition to favor the C-7α product.[6] Addition to tetraalkyl-substituted diene **3** is solely under steric control, and

Table II. Distinguishing ^1H Chemical Shifts of Diels–Alder Adducts

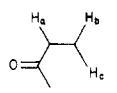
	ketone			
proton	7	8	9	10
5	4.09	4.12	5.1	4.05
7α		1.40	2.4[a]	1.35
7β	2.56	1.66		0.90
8α	1.19		1.2	1.82
8β	2.95	3.95	3.2	
9	3.19	3.49	3.16	3.45
17	5.54	5.48	5.45	6.75
18	5.60	5.60	5.5	5.62
20	2.09	2.16	2.2	1.8

[a] Overlapping H-16 resonances.

Table III. ^1H Coupling Constants[a] of Diels–Alder Adducts

	ketone			
protons	7	8	9	10
H_a, H_b (cisoid)[b]	9.5	10.0	*c*	8
H_a, H_c (transoid)[b]	6.8	4.4	*c*	2.2
H_b, H_c (geminal)[b]	12.6	13.3	13	11
9, 10α	5.8	6.2	6	6
10α, 10β	17.6	18.6	18	18

[a] Values are $|J|$ in hertz. [b] For the α and β protons of the methyl ketone,



[c] Not observed due to overlapping resonances.

again the nitrogen bridge is effective in preventing appreciable formation of the C-8α isomer **8**. These steric factors were independent of the dienophile. While addition of methyl vinyl ketone to diene **3** was complete after 20 h, butyl vinyl ketone addition was only 80% complete after 120 h. However, the butyl vinyl ketone adduct also was shown to be the C-7α isomer by its conversion with methyllithium to diastereomeric teritary alcohols **14** which were prepared independently by butyllithium addition to ketone **7**.

Adducts **7–9** are products of the usual dienophile addition to the exposed face of the diene. This arrangement of the 6,14-etheno bridge "inside" the newly defined morphinan system is termed 6,14-*endo*-ethenomorphinan. A small amount (0.1%) of exo adduct **10**, resulting from addition of methyl vinyl ketone to the underside of diene **3**, was also isolated. This mode of addition has not previously been observed in the thebaine series, but 4,5-oxide ring opened exo adducts have recently been obtained in the Diels–Alder reaction of the considerably less strained β-dihydrothebaines.[10]

NMR studies of the isomeric ketones **7–10** (Scheme III) provided many distinguishing features. The variety of functionalities influencing the protons of the rigid bicyclic system presents a set of anisotropic effects that permits structural assignments to all four adducts. Two effects observed in detailed ^1H NMR studies of the thevinone (**11**) C-7α and C-7β stereoisomers were (a) the sensitivity of H-5 to the α/β stereochemistry of the acetyl group and (b) deshielding of H-8β by the tertiary nitrogen.[9] As in the bicyclo[2.2.2]octene system, ring protons facing the etheno bridge are shielded relative to their geminal partners.[11] The ^1H NMR spectra of **7–9** appeared very similar, while the spectrum of **10** was unique. We began our assignments

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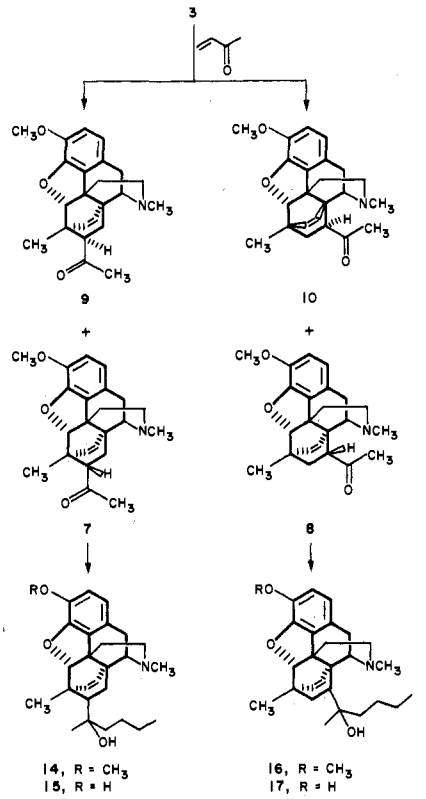
(9) NMR studies in the 6,14-ethenotetrahydrothebaine series are detailed in Fulmor, W.; Lancaster, J. E.; Morton, G. O.; Brown, J. J.; Howell, C. F.; Nora, C. T.; Hardy, R. A. *J. Am. Chem. Soc.* **1967**, *89*, 3322.
(10) Ghosh, A. C.; Portlock, D. E.; Dalzell, H. C.; Malmberg, C.; Herlihy, P.; Razdan, R. K. *J. Org. Chem.* **1983**, *48*, 4137.
(11) Tori, K.; Takano, Y.; Kitahonoki, K. *Chem. Ber.* **1964**, *97*, 2798.

Scheme III. Adducts Formed in the Reaction of Methyl Vinyl Ketone and 6-Deoxythebaine (3)



based only on the assumption that ketones **7–9** were 6,14-*endo*-ethenomorphinans.

Deshielding of H-5 by the carbonyl group in **9** (δ 5.1) relative to the H-5 resonances of the other isomers (δ 4.1) led to assignment of **9** as the C-7β isomer. Ketones **7** and **8** therefore appeared to be regioisomeric adducts having α stereochemistry. Decoupling studies have shown each isomer to have an isolated three-spin system at C-7 and C-8. In each isomer the large coupling constant (J_{HH}) was taken to indicate a geminal relationship and the small J to indicate a transoid relationship[12] (Table III). By this analysis the chemical shifts of the protons α to each ketone were assigned (Table II). In **7**, one of the protons with geminal coupling (δ 2.95) appears downfield of the proton α to the ketone (δ 2.56). In ketone **8** this proton is α to the ketone, but now it appears even further downfield at δ 3.95. This large deshielding effect is due to the proximity of the tertiary amine, and these resonances were assigned to H-8β. Thus ketone **7** is the C-7α isomer and **8** is the C-8α regioisomer. Further support for this assignment is the resonance of H-9 in **8** at δ 3.49. Deshielding by the C-8α carbonyl group results in resonance of H-9 downfield by 0.28 ppm from its position in either ketone **7** or **9**.

NOE experiments were investigated as further demonstrations of regiochemical relationships. In **7**, the C-6 methyl (δ 1.33) could not be irradiated to enhance the acetyl resonance (δ 2.09) because the H-8α resonance (δ 1.19) was too close. A large difference in chemical shifts of the investigated protons was required to avoid cosaturation of nearby resonances whose protons also may be close in physical distance. We reduced the carbonyl of **7** with sodium borohydride to the secondary alcohols **6** so that the new H-19 could be a downfield handle for the NOE of the C-6 methyl resonance. In each diastereomer of **6** the H-19 resonance was too close to the H-5 resonance to avoid coirradiation. The reverse experiment of irradiating the C-6 methyl gave enhancement of the H-19 resonance, but the origin of the enhancement was ambiguous; the resonance of H-7β, no longer α to the ketone, had shifted upfield under the 6-methyl singlet.

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Table IV. Distinguishing ^{1}H NMR Resonances of 19(*R*) and 19(*S*) Tertiary Alcohols **14**

proton	19(*R*)	19(*S*)	proton	19(*R*)	19(*S*)
20	0.99	1.09	18	5.48	5.43
8α	0.78	0.9	6-CH_3	1.55	1.51
7β	1.63	1.68			

In the spectrum of **10** the morphinan skeleton appeared to be intact, but the nitrogen bridge resonances had shifted upfield and one of the vinyl protons was far downfield at δ 6.75. The nitrogen bridge protons would be shielded by the double bond in a 6,14-*exo*-etheno system. In this system H-17 occupies the same region of space as H-8β in the other adducts where deshielding by the nitrogen is observed. The downfield shift of H-9 to δ 3.5 leads to the regioassignment of the acetyl group in **10** as C-8. Since the Diels–Alder addition would be expected to occur in an endo fashion,[13] selectivity of β stereochemistry of the acetyl would be predicted when the dienophile adds to the opposite face of diene **3**. The 7β configuration was ruled out by the observance of W coupling[14] (J = 1.5 Hz) to H-5, indicating a proton must reside there. The other small differences in ^{1}H NMR chemical shifts between the isomeric adducts as well as their ^{13}C data[15] are all also consistent with our assignments of structures **7–10**.

19-Butyl-6-deoxy-7α- and -8α-thevinols (**14** and **16**) were prepared by the addition of butyllithium to regioisomeric ketones **7** and **8**, respectively. In THF at −78 °C enolization of the methyl ketones competed with addition to give 1/1 mixtures of tertiary alcohols and recovered ketone. When the reaction was repeated four times on the product mixture without intermediate purification, conversion to tertiary alcohol was greater than 90%. The C-19 *R* and *S* diastereomers of **14** were easily separated by MPLC and isolated in 35% and 50% yield, respectively.

We considered the conformers of the C-19 *R* and *S* stereoisomers **14** using models and observed significant steric hindrance to rotation about the C-7/C-19 bond due to interaction of the C-19 alkyl groups with the C-6 methyl group. Each isomer would therefore be expected to favor conformations in which the hydroxyl group resides on the side toward C-6 and the alkyl groups reside on the side toward C-8. It is interesting that this conformation is preferred on steric grounds in the C-6 methyl tertiary alcohols **14**, since this is also the conformation observed in the thevinols **21** where hydrogen bonding between the C-19 hydroxyl and the oxygen on C-6 retards rotation. In the absence of hydrogen bonding, rotation about the C-7/C-19 bond appears less hindered in the thevinols, since the oxygen at C-6 holds its methyl group at a distance from the rigid bicyclic system.

With this conformational analysis we assigned the configuration of the 19(*R*) and 19(*S*) diastereomers on the basis of the ^{1}H NMR data given in Table IV. The *R* isomer, with hydroxyl set toward C-6, has its C-20 methyl group below the plane of the ring, near the etheno bridge where shielding results in a resonance 0.1 ppm upfield from

(13) Gleiter, R.; Bohm, M. C. *Pure Appl. Chem.* **1983**, *55*, 237.
(14) Sternhell, S. *Rev. Pure Appl. Chem.* **1964**, *14*, 15.
(15) ^{13}C chemical shifts in related series are reported in Carroll, F. I.; Moreland, C. G.; Brine, G. A.; Kepler, J. A. *J. Org. Chem.* **1976**, *41*, 996.

the corresponding resonance of the *S* isomer. The lipophilic butyl chain between C-7 and C-8 may also account for the upfield positions of H-8α at δ 0.78 and H-7β at δ 1.63. The hydroxyl group is in position to give the observed deshielding of both the C-6 methyl and the vinyl H-18. The corresponding arguments taken with the ^{1}H NMR data from the other isomer lead to assignment of *S* stereochemistry. Although the chemical shift differences are small, assignment of *R* and *S* on this basis is consistent with assignments made in analogous series based on the upfield shift of the C-20 methyl group, indicating the C-19 *R* configuration.

Tertiary alcohols **16** were obtained by addition of butyllithium to ketone **8**. Separation of the alcohols from remaining ketone gave an 88% yield of **16** as a 1/1 mixture of diastereomers. The C-19 *R* and *S* isomers could not be separated so the mixture was used for subsequent chemistry and pharmacological testing.

The C-3 methyl ethers of each 7α-thevinol diastereomer **14** and diastereomeric mixture **16** were cleaved to the phenols by sodium propanethiolate in dimethylformamide[16] in yields varying from 11% to 82%. Good yields of the orvinols, however, were consistently obtained when propanethiol was distilled immediately before use.

A sample of 19(*R*)-butylorvinol (**22**) was needed for comparison of the pharmacological data among the C-6 substituted analogues. Addition of *n*-butylmagnesium bromide to thevinone (**11**) is reported to be highly selective for the formation of the *R* diastereomer while addition of methyl organometallic reagents to butyl ketone **20** is required for formation of the *S* diastereomer.[4] We found, on the contrary, that treatment of 7α-thebuvinone (**20**) with methyllithium in THF at −78 °C formed predominantly the *R* diastereomer. Separation by column chromatography gave a 48% yield of (*R*)-**21** and only a 2% yield of (*S*)-**21**.

Stereochemistry at C-19 in these diastereomers was assigned on the basis of the C-19 hydroxyl ^{1}H NMR resonances. X-ray crystallographic analysis[17] of 19(*R*)-propylthevinol (**18**) hydrobromide established these resonances as diagnostic in the homologous set of diastereoners. The intramolecularly hydrogen bonded hydroxyl resonances appear at δ 4.8 in (*R*)-**18** and δ 4.45 in the *S* somer.[9] The corresponding resonances at δ 4.8 and 4.5 for the diastereomers **21** therefore lead to assignment of the δ 4.8 hydroxyl resonances as indicative of C-19 *R* stereochemistry. Hydroxyl resonances are not observed when hydrogen bonding is not possible, as in **15** and **19**. In comparing (*R*)-**21** and (*S*)-**21**, the C-20-methyl resonance of the *R* isomer is at higher field but by ~0.05 ppm. The 3-methyl ether of (*R*)-**21** was selectively cleaved in the presence of the 6-methyl ether with use of potassium hydroxide in refluxing diethylene glycol,[3] giving 19(*R*)-butylorvinol (**22**) in 31% yield.

Pharmacology. The analgesic activities of 7α-orvinols (*R*)- and (*S*)-**15** and 8α-orvinols **17** were determined in the tail-flick test[18] with Sprague–Dawley rats, using the up–down method[19] of evaluation of ED_{50}. 19(*R*)-Butylorvinol (**22**)[1] and its demethoxy analogue (*R*)-**19**[6] were also tested at the same time by use of this method so that the relative analgesic activities in Table V could be directly compared. Naloxone antagonized the analgesia of compounds (*R*)- and (*S*)-**15** and (*R*)-**22**, an indication that their effects are produced through the opiate receptors.

Table V. Relative Analgesic Potency of C-6 Substituted 19-Butylorvinols

compound	C-6 substit	ED_{50},[a] μmol/kg	rel analgesic potency
morphine		2.2	1
(*R*)-**15**	CH_3	0.0010	2200
(*S*)-**15**	CH_3	0.034	65
(*R*)- and (*S*)-**17**	CH_3	0.44	5
(*R*)-**22**	OCH_3	0.0013	1700
(*R*)-**19**	H	0.0052	420

[a] These values are ±20%.

19(*R*)-Butyl-6-deoxy-7α-orvinol ((*R*)-**15**) is the most potent of the C-6 substituted 19-butylorvinols with analgesic potency 2200 times that of morphine. Similar relationships between the highly potent *R* diastereomer and the much less active *S* isomer have been demonstrated in several 19-alkylorvinol diastereomeric pairs.[1,6,20]

A liphophilic (L) subsite below the major plane of the orvinols and a hydrophilic (H) subsite above this plane have been proposed[20] to explain the sensitivity of the opiate receptor to C-19 stereochemistry in the orvinols. Although the hydroxyl and butyl groups in (*S*)-**17** appear by inspection of models to be capable of occupying the same regions of space as those in (*R*)-**15**, the very low potency of 8α-orvinols **17** indicates that the pendant carbon in the C-8α configuration is not well accommodated.

Conclusions. 19(*R*)-Butyl-6-deoxy-7α-orvinol ((*R*)-**15**) is an extremely potent analgesic (2200× morphine) while its C-19 *S* diastereomer *S*-15 and C-8α regioisomers **17** have lower (5–65× morphine) analgesic activity, as determined by the tail-flick method. The sensitivity of the receptor to structural features in the C-19 region requires that the pendant tertiary alcohol possesses the C-7α configuration for high activity.

Within the C-6 substituted series of the 19(*R*)-butyl-7α-orvinols, the higher activity of the C-6 methyl and methoxyl analogues (*R*)-**15** and (*R*)-**22** relative to the hydrogen-substituted compound (*R*)-**19** indicates that C-6 alkyl substitution enhances analgesic potency. Higher alkyl C-6 analogues may be of interest.

Experimental Section

All reactions were conducted under a positive pressure of argon. Starting materials for anhydrous reactions were dried by azeotropic distillation with benzene. Benzene and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl immediately before use; dimethyl sulfoxide (Me_2SO) was distilled from calcium hydride; dimethylformamide (DMF) was stirred over calcium hydride and then barium oxide and distilled from neutral alumina. Melting points are uncorrected. Analytical TLC was conducted on aluminum-backed, precoated silica gel 60 F-254, eluting with either 10% or 20% methanol in chloroform. Silica 60 or Waters neutral activity III alumina was used for column chromatography. HPLC was done on a Lichrosorb SI-60 column, 4.6 × 250 mm. ^{1}H NMR absorptions were recorded in $CDCl_3$ on a 250-MHz spectrometer; chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Microanalyses and mass spectra were obtained by the Analytical Laboratory, Chemistry Department, University of California, Berkeley.

6-Methylcodeine Methyl Ether (5). Potassium hydride (1.34 g of a 25% suspension in oil, 8.4 mmol) was degreased with THF

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(17) van den Hende, J. H.; Nelson, N. R. *J. Am. Chem. Soc.* **1967**, *89*, 2901.
(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) Hutchins, C. W.; Rapoport, H. *J. Med. Chem.* **1984**, *27*, 521.
(21) Designation of adduct **10** as the exo-8β isomer in Table I is in keeping with numbering of the newly added dienophile carbons as C-7 and C-8. The new bonds define a plane and α and β denote stereochemistry below and above this plane in the usual fashion.

(4 × 20 mL) and suspended in 40 mL of THF. With vigorous stirring, a solution of 6-methylcodeine (**4**, 1.29 g, 4.1 mmol)[7] in 40 mL of THF was added over 90 min and then stirred an additional 1 h. Methyl iodide (0.6 mL, 10 mmol) was quickly added, the reaction was quenched after 90 s by addition of 25 mL of 1 N NaOEt, water was immediately added, and the mixture was concentrated to remove organic solvents. The aqueous residue was extracted with chloroform (6 × 30 mL), and the extracts were washed with water and dried (Na_2SO_4). Evaporation gave 1.28 g of a brown oil that was purified by silica chromatography using 1% methanol in chloroform as eluent: yield, 1.18 g, 87% of **5**; ^{1}H NMR δ 6.63 (d, 1 H, J = 8 Hz, H-2), 6.46 (d, 1 H, J = 8 Hz, H-1) 5.74 (ddd, 1 H, J = 11, 1, 1 Hz, H-8), 5.28 (dd, 1 H, J = 11, 1 Hz, H-7), 4.56 (d, 1 H, J = 1 Hz, H-5), 3.82 (s, 3 H, 3-OCH_3), 3.36 (s, 3 H, 6-OCH_3), 2.38 (s, 3 H, NCH_3), 1.17 (s, 3 H, 6-CH_3). Anal. ($C_{20}H_{25}NO_3$) C, H, N.

6-Deoxythebaine (6,7,8,14-Tetradehydro-4,5α-epoxy-6,17-dimethyl-3-methoxymorphinan, 3). Methyl ether **5** (1.08 g, 3.3 mmol) was dissolved in 20 mL of Me_2SO and a solution of potassium *tert*-butoxide (freshly sublimed, 16 mL of a 0.9 M solution in Me_2SO, 14 mmol) was added over 5 min. The deep red mixture was heated at 72 °C for 41 min and then cooled immediately to 50 °C, saturated aqueous $NaHCO_3$ (30 mL) was added, and the mixture was evaporated (Kugelrohr) to a brown residue that was partitioned between water (50 mL) and chloroform (50 mL). The organic layer was washed with water, the combined aqueous phases were extracted with chloroform, and the combined extracts were washed with water and brine, dried (Na_2SO_4), and evaporated to give 0.95 g of crude diene **3**. Chromatography by MPLC on silica with 0.5% methanol, 0.5% triethylamine in chloroform as eluent gave 0.68 g (71%) of **3**: recrystallization from ethyl acetate, mp 201–202 °C; ^{1}H NMR δ 6.66 (d, 1 H, J = 8 Hz, H-2), 6.58 (d, 1 H, J = 8 Hz, H-1), 5.67 (dq, 1 H, J = 6, 1.4 Hz, H-7), 5.56 (d, 1 H, J = 6 Hz, H-8), 5.52 (s, 1 H, H-5), 3.87 (s, 3 H, 3-OCH_3), 3.61 (d, 1 H, J = 7 Hz, H-9), 3.33 (d, 1 H, J = 18 Hz, H-10), 2.47 (s, 3 H, NCH_3), 1.89 (d, 3 H, J = 1 Hz, C-6-CH_3); ^{13}C NMR δ 144.5 (C-4), 142.6 (C-3), 137.6 (C-14), 133.4 (C-12), 129.9 (C-6), 127.5 (C-11), 121.5 (C-7), 118.7 (C-1), 112.8 (C-2), 112.1 (C-8), 92.7 (C-5), 60.9 (C-9), 56.4 (OCH_3), 46.0 (C-16), 43.9 (C-13), 42.3 (NCH_3), 37.3 (C-15), 29.3 (C-10), 19.6 (C-6-CH_3). Anal. ($C_{19}H_{21}NO_2$) C, H, N.

Exocyclic Diene 13 (7,8-Didehydro-4,5α-epoxy-3-methoxy-6-methylene-17-methylmorphinan). A solution of codeinone (0.90 g, 3.0 mmol) in 50 mL of benzene was chilled in a 0 °C bath and methyllithium (6.0 mL of a 1.6 M solution in ether, 9.6 mmol) was added dropwise. After 40 min of stirring, diphenyl chlorophosphate (distilled, 1.30 mL, 2.3 g, 8.7 mmol) was added. The mixture was stirred 40 min more at room temperature, washed with water (50 mL), dried (Na_2SO_4), and evaporated to 2.57 g of brown oil. Chromatography on silica with a gradient of chloroform to 3% methanol in chloroform gave 253 mg (29%) of **13**: mp 198–202 °C after sublimation (171 °C (0.1 mmHg)); ^{1}H NMR δ 6.68 (d, 1 H, J = 8 Hz, H-2), 6.51 (d, 1 H, J = 8 Hz, H-1), 6.18 (dd, 1 H, J = 10, 4 Hz, H-8), 5.43 (m, 2 H, vinyl), 5.17 (m, 2 H, vinyl and H-5), 3.83 (s, 3 H, OCH_3), 3.31 (dd, 1 H, H-9), 3.06 (d, 1 H, J = 20 Hz, H-10), 2.44 (s, 3 H, NCH_3). Anal. ($C_{19}H_{21}NO_2$) C, H, N.

6-Deoxythevinones[23] 7–10. 6-Deoxythebaine (3.07 g, 10.4 mmol), methyl vinyl ketone (freshly distilled, 45 mL, 39 g), and hydroquinone (25 mg) were heated at reflux for 20 h, the excess methyl vinyl ketone was removed by distillation, and the residue was partitioned between ether (100 mL) and 1 M H_3PO_4 (150 mL). The ether layer was extracted with 1 M H_3PO_4 (4 × 50 mL), and the combined aqueous extracts were washed with ether and then basified to pH 10 with solid K_2CO_3. The white precipitate was collected by filtration, washed with water, and dried to 3.71 g (98%) of solid, mp 114–116 °C, which was recrystallized from ethyl acetate. Three crystalline crops gave 2.71 g, 71% yield, of ketone **7**: mp 119–120 °C; ^{1}H NMR δ 6.63 (d, 1 H, J = 8 Hz, H-2), 6.53 (d, 1 H, J = 8 Hz, H-1), 5.60 (d, 1 H, J = 9 Hz, H-18), 5.54 (d, 1 H, J = 9 Hz, H-17), 4.09 (s, 1 H, H-5), 3.84 (s, 3 H, OCH_3), 3.23 (d, 1 H, J = 17.6 Hz, H-10β), 3.19 (d, 1 H, J = 5.8 Hz, H-9), 2.95 (dd, 1 H, J = 9.5, 12.6 Hz, H-8β), 2.56 (dd, 1 H, J = 6.8, 8.5 Hz, H-7β), 2.54 (m, 1 H, H-16), 2.42 (dd, 1 H, J = 5.8, 17.6 Hz, H-10α), 2.40 (m, 1 H, H-16), 2.38 (s, 3 H, NCH_3), 2.09 (s, 3 H, $COCH_3$), 1.94 (m, 1 H, H-15), 1.83 (m, 1 H, H-15), 1.33 (s, 3 H, 6-CH_3), 1.19 (dd, 1 H, J = 6.8, 12.6 Hz, H-8α); ^{13}C NMR δ 208.6 (C-19), 147.6 (C-4), 141.6 (C-3), 135.8 (C-18), 133.9 (C-12), 129.4 (C-17), 127.9 (C-11), 118.6 (C-1), 112.7 (C-2), 97.7 (C-5), 59.7 (C-9), 56.0 (OCH_3), 52.4 (C-7), 45.7 (C-13), 45.1 (C-16), 43.1 (NCH_3), 42.8 (C-14), 40.8 (C-6), 32.8 (C-15), 29.9 (C-8), 29.8 (C-20), 21.9 (C-10), 17.8 (6-CH_3). Anal. ($C_{23}H_{37}NO_3$) C, H, N.

Ketone 8. A fourth crystalline crop was chromatographed on silica gel with 0.5% triethylamine in 50/50 ethyl acetate/isooctane, leading to the separation of 0.34 g (9%) more **7** and 0.06 g (1.5%) of ketone **8**: ^{1}H NMR, see Tables II and III;[22] ^{13}C NMR δ 210.1 (C-19), 147.8 (C-4), 141.7 (C-3), 134.7 (C-18), 133.9 (C-12), 131.4 (C-17), 127.8 (C-11), 118.8 (C-1), 113.0 (C-2), 98.6 (C-5), 58.1 (C-9), 56.4 (OCH_3), 47.7, 46.9, 45.5 (C-13), 45.5 (C-16), 43.4 (NCH_3), 39.4, 34.8, 33.0 (C-15), 30.3 (C-20), 22.3 (C-10), 20.9 (6-CH_3); MS, m/e calcd for $C_{23}H_{27}NO_3$ 365.1992, found 365.1991.

Ketones 9 and 10. The mother liquor remaining after the fourth crop of crystals was chromatographed with use of the same conditions as above. More **8** (0.05 g, 1%) was obtained, as well as 0.32 g (8%) of a 9/1 mixture of **7** and **9** and a 4-mg fraction (0.1%) of **10**. Ketone **9**: ^{1}H NMR, see Tables II and III;[22] ^{13}C NMR δ 211.0 (C-19), 147.9 (C-4), 141.7 (C-3), 136.5 (C-18), 133.7 (C-12), 128.2 (C-17), 127.9 (C-11), 118.5 (C-1), 112.6 (C-2), 93.5 (C-5), 60.8 (C-9), 56.3 (OCH_3), 54.4 (C-7), 43.4 (C-13), 46.0 (C-16), 43.5 (NCH_3), 43.4 (C-14), 40.9 (C-6), 30.1 (C-15), 29.9 (C-8), 28.5 (C-20), 22.3 (C-10), 18.9 (6-CH_3); MS, m/e calcd for $C_{23}H_{27}NO_3$ 365.1992, found 365.1991. Ketone **10**: ^{1}H NMR, see Tables II and III;[22] MS, m/e calcd for $C_{23}H_{27}NO_3$ 365.1992, found 365.1983.

(19*R*)- and (19*S*)-6-Deoxy-7α-thevinols (6). 6-Deoxy-7-α-thevinone (**7**; 255 mg, 0.7 mmol) was dissolved in abs ethanol (12 mL) with warming, sodium borohydride (229 mg, 6 mmol) was added to the cooled solution, stirring was continued for 1 h, water (45 mL) was added, and the mixture was extracted with chloroform (3 × 20 mL). The extracts were washed with water, dried (Na_2SO_4), and evaporated to give 251 mg of **6** as a mixture of diastereomers. Chromatography on silica with 5% methanol in chloroform gave 211 mg (82%) of (19*S*)-**6** and 20 mg (7%) of (19*R*)-**6**. (19*S*)-**6**: ^{1}H NMR δ 6.63 (d, 1 H, J = 8 Hz, H-2), 6.53 (d, 1 H, J = 8 Hz, H-1), 5.56 (s, 2 H, H-17,18), 4.15 (dq, 1 H, J = 18, 6.5 Hz, H-19), 4.08 (s, 1 H, H-5), 3.83 (s, 3 H, OCH_3), 3.25 (d, 1 H, J = 19.2 Hz, H-10β), 3.21 (d, 1 H, J = 5.7 Hz, H-9), 2.71 (dd, 1 H, J = 9.1, 12.8 Hz, H-8β), 2.53–2.4 (m, 3 H, H-16, 10α), 2.42 (s, 3 H, NCH_3), 1.98 (m, 1 H, H-15), 1.83 (m, 1 H, H-15), 1.44 (ddd, 1 H, J = 1.8, 7.1, 9.1 Hz, H-7β), 1.39 (s, 3 H, 6-CH_3), 1.19 (dd, 1 H, J = 7.1, 12.8 Hz, H-8α), 1.12 (d, 3 H, J = 6.5 Hz, 19-CH_3). Anal. ($C_{23}H_{29}NO_3$) C, H, N. (19*R*)-**6**: ^{1}H NMR δ 6.62 (d, 1 H, J = 8 Hz, H-2), 6.53 (d, 1 H, J = 8 Hz, H-1), 5.47 (d, 1 H, H-18), 5.17 (d, 1 H, H-17), 4.10 (s, 1 H, H-5), 4.01 (dq, 1 H, J = 5.2, 6.4 Hz, H-19), 3.23 (d, 1 H, J = 16.6 Hz, H-10β), 3.19 (d, 1 H, J = 5.7 Hz, H-9), 2.71 (dd, 1 H, J = 9.1, 13 Hz, H-8β), 2.52–2.4 (m, 3 H, H-16, 10α), 2.40 (s, 3 H, NCH_3), 1.99 (m, 1 H, H-15), 1.83 (ddd, 1 H, J = 5.2, 7.0, 9.1 Hz, H-7β), 1.82 (m, 1 H, H-15), 1.33 (s, 3 H, 6-CH_3), 1.01 (dd, 1 H, J = 7, 12.0 Hz, H-8α), 0.95 (d, 3 H, J = 6.4 Hz); MS, m/e calcd for $C_{23}H_{29}NO_3$ 367.2149, found 367.2147.

19(*R*)- and 19(*S*)-Butyl-6-deoxy-7α-thevinols (14). To ketone **7** (2.38 g, 6.5 mmol) dissolved in 50 mL THF and chilled to −78 °C was added butyllithium (9.0 mL of a 1.49 M solution in hexane, 13 mmol) over 10 min, the mixture was stirred 40 min at −78 °C, the bath was removed, and ice water and ether were added. After the mixture was warmed to 20 °C, the aqueous layer was extracted with chloroform, and the organic extracts were combined, dried, and evaporated to yield a 40/60 mixture of diastereomeric alcohols and recovered ketone. The above procedure was repeated on the product mixture four times, until less than 10% ketone remained, and then the diastereomers were separated by silica MPLC with use of 0.5% triethylamine in ethyl acetate.

(19*R*)-**14**: 0.97 g, 35% yield; ^{1}H NMR δ 6.61 (d, 1 H, J = 8 Hz, H-2), 6.50 (d, 1 H, J = 8 Hz, H-1), 5.48 (d, 1 H, J = 9 Hz, H-18), 5.39 (d, 1 H, J = 9 Hz, H-17), 4.10 (s, 1 H, H-5), 3.83 (s, 3 H,

(22) The remaining ^{1}H shifts are identical with those reported for ketone **7** within ±0.1 ppm.

(23) An explanation and examples of the systems used for naming these 6,14-ethenomorphinans are given in ref 20, footnote 5.

OCH_3), 3.23 (d, 1 H, J = 18 Hz, H-10β), 3.13 (d, 1 H, J = 6.2 Hz, H-9), 2.76 (dd, 1 H; J = 9, 13 Hz, H-8β), 2.51 (m, 1 H, H-16), 2.4 (m, 1 H, H-16), 2.39 (dd, 1 H, J = 6.2, 18 Hz, H-10α), 1.96 (m, 1 H, H-15), 1.82 (m, 1 H, H-15), 1.63 (dd, 1 H, J = 8.6, 9 Hz, H-7β), 1.55 (s, 3 H, 6-CH_3), 0.99 (s, 3 H, 19-CH_3), 0.78 (dd, 1 H, J = 8.6, 13 Hz, H-8α); ^{13}C NMR δ 148.3 (C-4), 141.5 (C-3), 135.3 (C-18), 134.8 (C-12), 131.5 (C-17), 128.5 (C-11), 118.6 (C-1), 112.9 (C-2), 99.7 (C-5), 76.2 (C-19), 77.2, 60.4 (C-9), 56.5 (OCH_3), 48.0 (C-7), 45.7 (C-16), 43.6 (NCH_3), 42.8 (C-14), 42.8, 41.9, 33.6 (C-8), 30.9, 24.8 (C-20), 23.4, 23.2, 22.3 (C-10), 20.2 (6-CH_3), 14.2 (C-24); MS, m/e calcd for $C_{27}H_{37}NO_3$ 423.2775, found 423.2754. (19S)-14: 1.38 g, 50% yield; ^{1}H NMR δ 6.58 (d, 1 H, J = 8 Hz, H-2), 6.49 (d, 1 H, J = 8 Hz, H-1), 5.43 (d, 1 H, J = 9 Hz, H-18), 5.37 (d, 1 H, J = 9 Hz, H-17), 4.10 (s, 1 H, H-5), 3.82 (s, 3 H, OCH_3), 3.22 (d, 1 H, J = 18 Hz, H-10β), 3.14 (d, 1 H, J = 6.6 Hz, H-9), 2.76 (dd, 1 H, J = 8.9 Hz, 13, H-8β), 2.50 (m, 1 H, H-16), 2.4 (m, 1 H, H-16), 2.39 (s, 3 H, NCH_3), 2.37 (dd, 1 H, J = 6.6, 18 Hz, H-10α), 1.97 (m, 1 H, H-15), 1.80 (m, 1 H, H-15), 1.68 (dd, 1 H, J = 8.5, 8.9 Hz, H-7β), 1.51 (s, 3 H, 6-CH_3), 1.09 (s, 3 H, 19-CH_3), 0.9 (dd, 1 H, J = 8.5, 13 Hz, H-8α); ^{13}C NMR δ 148.2 (C-4), 141.4 (C-3), 135.2 (C-18), 134.7 (C-12), 131.1 (C-17), 128.3 (C-11), 118.6 (C-1), 113.0 (C-2), 99.6 (C-5), 77.2, 76.3 (C-19), 60.3 (C-9), 56.5 (OCH_3), 49.7 (C-7), 45.7 (C-16), 45.6, 43.4 (NCH_3), 42.7 (C-14), 42.5, 33.5 (C-15), 30.7 (C-8), 26.6 (C-20), 25.5, 23.3, 22.2 (C-10), 20.0 (6-CH_3), 14.0 (C-24). Anal. ($C_{27}H_{37}NO_3$) C, H, N.

19(R)- and 19(S)-Butyl-6-deoxy-8α-thevinols (16). Ketone 8 (34 mg, 0.09 mmol) was treated as above. The mixture of C-19 diastereomers was separated from remaining ketone by silica chromatography using 1% methanol in chloroform, but the diastereomeric alcohols could not be separated: 35 mg, 88% yield of a 1/1 mixture of (19R)- and (19S)-16: ^{1}H NMR δ 6.63 (d, 1 H, J = 8 Hz, H-2), 6.53 (d, 1 H, J = 8 Hz, H-1), 5.58 (d, 1 H, J = 9 Hz, H-17), 5.39 (d, 1 H, J = 9 Hz, H-18), 4.18 (s, 1 H, H-5), 3.84 (s, 3 H, OCH_3), 3.73 (d, 1 H, J = 7 Hz, H-9), 3.19 (d, 1 H, J = 18 Hz, H-10β), 3.03 (dd, 1 H, J = 7, 10 Hz, H-8β), 2.33 (s, 3 H, NCH_3), 1.26 (s, 3 H, 6-CH_3), 1.07 (s); ^{13}C NMR δ 147.4 (C-4), 141.8 (C-3), 134.3 (C-12), 132.2 (C-11), 126.8 (vinyl), 118.8 (vinyl), 118.7 (C-1), 112.9 (C-2), 98.4 (C-5), 75.3 (C-19), 58.9 (C-9), 56.5 (OCH_3), 47.9, 46.5, 45.6 (C-16), 45.3, 42.5, 39.9, 37.5, 37.2, 31.7, 26.9, 25.8, 23.7, 22.0, 21.1 (6-CH_3), 14.2 (C-24); MS, m/e calcd for $C_{27}H_{37}NO_3$ 423.2775, found 423.2766.

19(R)- and 19(S)-Butyl-6-deoxy-7α-orvinols (15). Tertiary alcohol (R)-14 (498 mg, 1.2 mmol) was treated with a solution of sodium propanethiolate in DMF (11.8 mL of a 0.3 M solution, 3.6 mmol) at reflux for 2 h. The cooled mixture was partitioned between 1 M H_3PO_4 (50 mL) and ether (25 mL), the aqueous layer was washed with ether (25 mL) and then basified with ammonia and extracted with ether (2 × 25 mL), and the ether extracts of the alkaline solution were washed with water, dried (Na_2SO_4), and evaporated to 396 mg (82%) of crude (R)-15. Chromatography on silica with 1% methanol in chloroform gave 346 mg, 72% yield of (R)-15 as a foam: ^{1}H NMR δ 6.61 (d, 1 H, J = 8 Hz, H-2), 6.45 (d, 1 H, J = 8 Hz, H-1), 5.47 (d, 1 H, J = 9, H-18), 5.39 (d, 1 H, J = 9 Hz, H-17), 4.10 (s, 1 H, H-5), 3.23 (d, 1 H, J = 18, H-10β), 3.13 (d, 1 H, J = 6 Hz, H-9), 2.76 (dd, 1 H, J = 9, 13 Hz, H-8β), 2.43 (s, 3 H, NCH_3), 1.55 (s, 3 H, 6-CH_3), 0.78 (dd, 1 H, J = 8.6, 13 Hz, H-8α). Anal. ($C_{26}H_{35}NO_3$) C, H, N.

The (S)-14 diastereomer was treated as above; from 229 mg (0.5 mmol) of alcohol (S)-14 there was isolated 107 mg, 48% yield, of pure orvinol (S)-15 as a foam: ^{1}H NMR δ 3.17 (d, 1 H, J = 18 Hz, H-10), 3.14 (d, 1 H, J = 6 Hz, H-9), 2.76 (dd, 1 H, J = 9, 13 Hz, H-8β), 2.39 (s, 3 H, NCH_3), 1.48 (s, 3 H, 6-CH_3), 1.04 (s, 3 H, 19-CH_3). Anal. ($C_{26}H_{35}NO_3$) C, H, N.

19(R)- and 19(S)-Butyl-6-deoxy-8α-orvinols (17). Tertiary alcohols 16 were treated as above; from 29 mg of 16 (0.07 mmol) there was isolated 3 mg, 11% yield, of pure phenols 17: ^{1}H NMR δ 6.63 (d, 1 H, J = 8 Hz, H-2), 6.53 (d, 1 H, J = 8 Hz, H-1), 5.58 (d, 1 H, J = 9 Hz, H-17), 5.39 (d, 1 H, J = 9 Hz, H-18), 4.18 (s, 1 H, H-5), 3.73 (d, 1 H, J = 7 Hz, H-9), 3.19 (d, 1 H, J = 18 Hz, H-10), 3.03 (dd, 1 H, J = 1, 10 Hz, H-8β), 2.33 (s, 3 H, NCH_3), 1.26 (s, 3 H, 6-CH_3), 1.07 (s); MS, m/e calcd for $C_{26}H_{35}NO_3$ 409.2619, found 409.2626.

19-Butyl-7α-thevinols (21). Thebuvinone (**20**; 1.06 g, 2.5 mmol), prepared from thebaine and butyl vinyl ketone,[3] was dissolved in THF (20 mL) and cooled to −78 °C (b). Methyllithium (2.9 mL of a 1.6 M solution in ether, 4.6 mmol) was added, the mixture was stirred 40 min, the bath was removed, and water and ether were added. The layers were separated, and the ether portion was dried (Na_2SO_4) and evaporated to give 950 mg of an oil containing about 20% of starting ketone **20**. The above procedure was repeated three times on the crude product mixture, which was then chromatographed on 20 g of silica with chloroform as eluent to give 0.54 g, 48% yield, of (R)-21 and 20 mg, 2% yield, of (S)-21.[4]

19(R)-Butyl-7α-orvinol ((R)-22). 19(R)-Butyl-7α-thevinol ((R)-21; 500 mg, 1.14 mmol), 3.63 g of KOH, and 9.5 mL of diethylene glycol were heated at reflux for 1.5 h. The mixture was then allowed to cool to room temperature, water (45 mL) and aqueous NH_4Cl were added until pH 7–8, the mixture was extracted with ether (50 mL and 4 × 25 mL), and the ether extracts were dried (Na_2SO_4) and evaporated to a crude mixture of starting methyl ether 21 and phenol **22**. Chromatography on 10 g of silica, eluting methyl ether (R)-21 first with chloroform and then phenol (R)-22 with 2% methanol/chloroform, gave 151 mg, 31% yield, of (R)-22 as a colorless oil.[1]

Pharmacological Methods. Relative analgesic activities were determined in this series by the tail-flick[18] test, using the up–down method[19] to evaluate each ED_{50}. Five to eight male Sprague–Dawley rats weighing 286–346 g were used for each compound. Hot water (55 °C) provided the stimulus with 6 s as the cut-off time between response and no response. Tests with no response ended at 15 s. Reaction times were measured at 8, 16, and 24 min after subcutaneous injection of 1 mL/kg. Test compounds were dissolved in 0.01 M hydrochloric acid and diluted with sterile saline solution. Compounds (R)- and (S)-15 and (R)-22 were antagonized by naloxone.

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Registry No. **3**, 94800-60-9; **4**, 4682-49-9; **5**, 94800-61-0; 19(R)-**6**, 94800-74-5; 19(S)-**6**, 94800-62-1; **7**, 94800-63-2; **8**, 94800-64-3; **9**, 94800-65-4; **10**, 94842-42-9; **13**, 94800-66-5; 19(R)-**14**, 94800-67-6; 19(S)-**14**, 94800-68-7; 19(R)-**15**, 94800-69-8; 19(S)-**15**, 94800-70-1; 19(R)-**16**, 94800-71-2; 19(S)-**16**, 94800-72-3; 19(R)-**17**, 94820-21-0; 19(S)-**17**, 94800-73-4; **20**, 16193-39-8; (R)-**21**, 16180-29-3; (S)-**21**, 94842-44-1; (R)-**22**, 94842-43-0; CH_2=$CHCOCH_3$, 78-94-4; codeinone, 467-13-0.