**Molecular Mechanics and Computer Graphics.** The coordinates for the atoms in **6a** were calculated with the program MMII,[17] These data were used with the Lederle molecular modeling system VAX 11/780 with an Evans and Sutherland Multi Picture System to graphically superimpose **6a** with the morphine crystal structure[18] so that the root mean square deviations in the nonbonded distances between the N, 1'-phenyl C, 1-C, and 7-β-methoxyl oxygen atoms of **6a** and the N, C-12, C-13, and the ether oxygen of morphine were minimized.[19,20] The phenyl ring of **6a** was then rotated around the C-1–C-1' bond to align the ring and its oxygen atom with the corresponding features of morphine. The degree of superimposition of the molecules was then studied by rotating the structures around the various axes.

**Acknowledgment.** Maleimide **4d** was originally synthesized by Dr. Patrick T. Izzo. We acknowledge G. Jordan, G. O. Morton, and group for spectral analyses and L. Gehrlein and group for the microanalyses.

**Registry No.** **3**, 922-69-0; **4a**, 66504-57-2; **4b**, 64643-37-4; **4c**, 54433-49-7; **4d**, 716-00-7; **5a**, 88905-19-5; **5b**, 88905-20-8; **5c**, 88905-21-9; **5d**, 88905-22-0; **6a**, 88905-31-1; **6a** (base), 88905-23-1; **6b**, 88905-32-2; **6b** (base), 88905-24-2; **6c**, 88905-33-3; **6c** (base), 88905-25-3; **6d**, 88905-34-4; **6d** (base), 88905-26-4; **7**, 88905-27-5; **8**, 88905-28-6; **9**, 88905-35-5; **9** (base), 88905-29-7; **10**, 88905-36-6; **10** (base), 88905-30-0; 3-$CH_3OC_6H_4NH_2$, 536-90-3; 3-$CH_3OC_6H_4N_2^+Cl^-$, 19183-05-2; $C_6H_5NH_2$, 62-53-3; $C_6H_5N_2^+Cl^-$, 100-34-5; 4-$CH_3NH_2$, 106-49-0; 4-$CH_3C_6H_4N_2^+Cl^-$, 2028-84-4; $HOCH_2C(CH_3)_2CH_2OH$, 126-30-7; maleimide, 541-59-3; *N*-methylmaleimide, 930-88-1.

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(17) Burkert, U.; Allinger, N. L. "Molecular Mechanics" (*ACS Monogr. no. 177*); American Chemical Society: Washington, DC; 1982.
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# Novel Opiates and Antagonists. 6.[1] 7-Alkyl-6,7-didehydromorphinans

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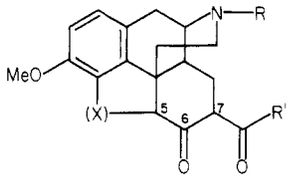
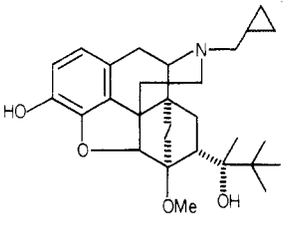
A method for preparing a variety of 7-alkyl-6,7-didehydromorphinans from the corresponding 6-morphinanones is described. The key intermediates in this sequence are the 7-formyl derivatives. The two epimeric *B/C-trans*-7-(1-hydroxypentyl)morphinans (**16a,b**) are stereochemically similar to the *endo*-ethanotetrahydrooripavines and are extremely potent in the mouse writhing test. The corresponding *B/C-cis*-7-(1-hydroxypentyl)morphinans are inactive in this test.

Recently, it was demonstrated that acyl group substitution at position 7 of hydromorphone afforded a series of compounds (**1a**) whose narcotic analgesic agonist and




1a, X = -O-
b, X = -H, H-

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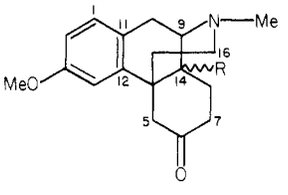
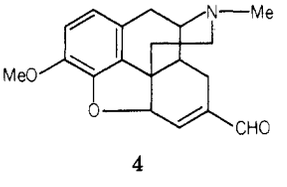
antagonist activities paralleled those of the *endo*-ethanotetrahydrooripavines, e.g., buprenorphine (**2**).[3] In order to further enhance the structural similarity of these 7-acyl derivatives to **2**, we desired to make two further modifications on **1a**. Removal of the furano ring would allow the preparation of *B/C-trans*-morphinans and, thus, yield compounds with the same stereochemistry as **2** at C-14. Secondly, removal of the carbonyl at position 6 would stabilize the desired α-hydroxyl group on the alkyl side chain.

Accomplishment of the first goal was initially attempted by preparation of diketone **1b** from the morphinan enamine or enol. There have been no reports of enamine formation from the morphinanones **3**; likewise, all our attempts failed.[4] Our efforts were then turned to the development of a new methodology that might accomplish both goals simultaneously. We report here the details of




3a, R = H
b, R = IIIH

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that method, which requires the 7-formyl derivatives **4** or **14** as key intermediates. The effects of such modifications on the analgesic activity are also reported.

**Chemistry.** The reduction of, or alkyllithium addition to, (alkylthio)methylene ketones, followed by acid hydrolysis, affords α,β-unsaturated aldehydes.[5] The (alkylthio)methylene ketones may be prepared by treatment of either the α-formyl ketones[5] or the (dimethylamino)-methylene ketones[6] with an alkanethiol. The latter route was attractive for the preparation of the key intermediates,

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(1) For Part 5, see: Herlihy, P.; Dalzell, H. C.; Howes, J. F.; Razdan, R. K.; *J. Med. Chem.* **1982**, *25*, 986.
(2) (a) Address for reprints: SISA Pharmaceutical Laboratories, Inc., Cambridge, MA 02138. (b) Current address: Key Pharmaceuticals, Inc., Miami, FL 33169-1307.
(3) Quick, J.; Herlihy, P.; Razdan, R. K.; Howes, J. F. *J. Med. Chem.* **1982**, *25*, 983.
(4) The normal azetropic methods as described in ref 3 were attempted, as well as the method utilizing (trimethylsilyl)-morpholine described by: Comi, R.; French, R. W.; Reitano, M.; Weinreb, S. M. *Tetrahedron Lett.* **1973**, 3107.
(5) (a) Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1962**, *27*, 1615. (b) Bernstein, P. R. *Tetrahedron Lett.* **1979**, 1015.
(6) Martin, S. F.; Moore, D. R. *Tetrahedron Lett.* **1976**, 4459.

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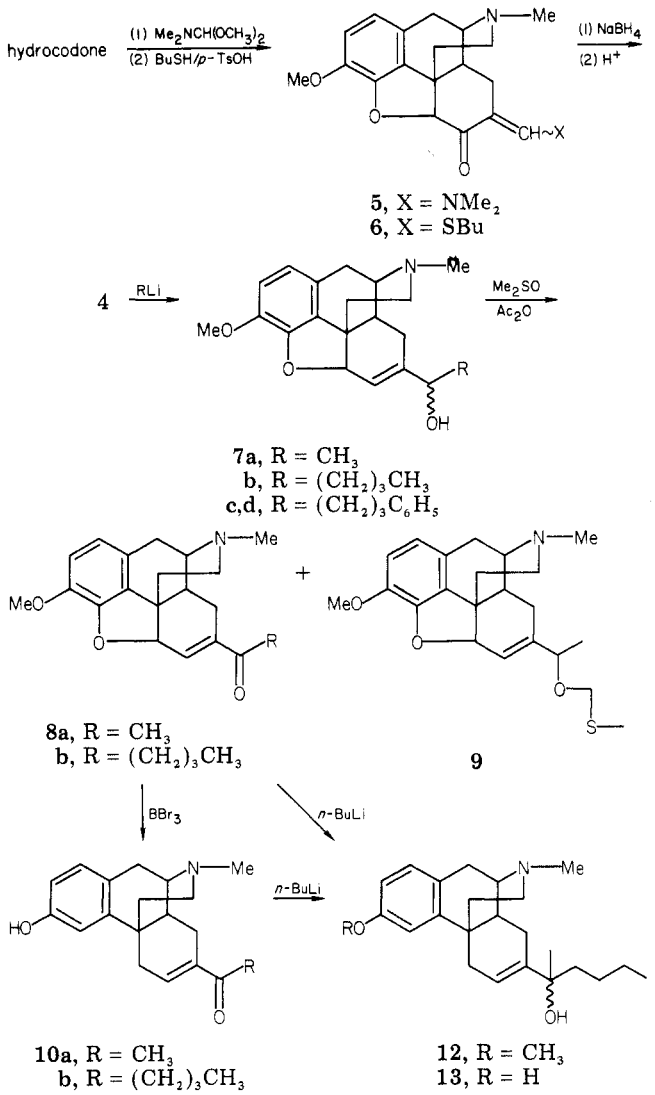
Scheme I



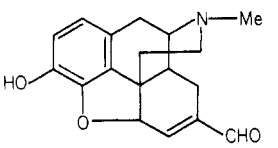

since the 7-(dimethylamino)methylene derivatives of opiates are readily prepared by treatment of the 6-keto precursors with an acetal of dimethylformamide.[7]

Thus, heating a toluene solution of hydrocodone and dimethylformamide dimethyl acetal afforded **5** in 84% yield (Scheme I). Subsequent treatment of a benzene solution of **5** with butanethiol and *p*-toluenesulfonic acid gave a 74% yield of **6**. This thioenol ketone was reduced by treatment with $NaBH_4$, and the reaction mixture was hydrolyzed by acidification with 6 N hydrochloric acid. These latter steps afforded a 91% yield of the aldehyde **4**. The structure of **4** was confirmed by examination of the NMR and IR spectra. In particular, the NMR spectrum showed a singlet at $\delta$ 8.78 and multiplets at $\delta$ 6.67 and 5.22. These are the resonances of the aldehyde, vinyl, and C-5 protons, respectively.

Addition of alkyllithium reagents to aldehyde **4**, followed by oxidation of the resultant secondary alcohols, then afforded other 7-acyl derivatives. Treatment of a tetrahydrofuran (THF) solution of **4** with methyllithium afforded **7a** in 76% yield as a mixture of epimers. The NMR spectrum showed two doublets of unequal intensity at $\delta$ 1.15 and 1.18 and a broad quartet at $\delta$ 4.07. These are due to the methyl group and the carbinol proton, respectively, of the epimeric hydroxyethyl groups. The vinyl proton resonance has moved upfield to $\delta$ 5.67 as expected. Similar treatment of **4** with *n*-butyllithium or 3-phenyl-1-lithiopropane afforded **7b** (40% yield) and **7c** and **7d**, respectively. In the latter case, the epimers were separated; however, no assignment of the configuration was made.

The best method for the oxidation of the alcohols **7** to the ketone **8** was found to be treatment with acetic anhydride and dimethyl sulfoxide.[8] In this manner, **7a** was oxidized to the 7-acetyl derivative **8a** in 61% yield. An 18% yield of the thiol ether **9** was also isolated. Attempts to reduce the yield of this common side product or to hydrolyze it to **7a** ($HgCl_2$–wet acetonitrile) were unsuccessful. A 68% yield of **8b** was obtained from **7b** by this procedure. The structures of all of these products were established by their NMR and mass spectra.

Although at each stage in this sequence (**4**, **7**, and **8**) demethylation was attempted, only with **8a** was moderate success achieved. Treatment of a chloroform solution of **8a** with $BBr_3$[9] afforded a 34% yield of **10a**. With the failure of the demethylation procedure to provide **10b**, several attempts were made at the preparation of aldehyde **11** from hydromorphone. Treatment of hydromorphone




**11**

with dimethylformamide dimethyl acetal resulted in remethylation of the phenol[10] to afford **5**. Blocking the phenol was not successful, since acetyl groups were not stable to the remethylation conditions, and methoxymethyl ethers could be prepared only in low yields. The preparation of **10b** was not further investigated.

Treatment of **8a** and **10a** with butyllithium as above afforded the tertiary alcohols **12** and **13**, respectively. These tertiary alcohols showed none of the stability problems previously found with the $\beta$-hydroxy ketones.[3] However, they were noncrystalline and strongly occluded solvent, making them difficult to purify.

This same sequence of reactions could be applied to the morphinan **3a** to produce the desired *B/C-trans*-7-substituted derivatives. Thus, **14a** was prepared from *B/C-trans*-morphinanone (**3a**) in 56% yield. Since the 7-(dimethylamino)methylene derivative was partially hydrolyzed during attempts at its purification, the entire sequence was carried out without purification of the intermediates. Similar treatment of the *B/C-cis*-morphinanone (**3b**) afforded **14b** in only 12% yield. In this case, the low yield presumably resulted from an attempted acetic acid hydrolysis of the product of the $NaBH_4$ reduction.

The structure of **14a** was determined from its NMR and mass spectra. Comparison of its $^1H$ NMR spectra with those of **3a** and the derived products **16** and **17** allowed distinction between the structures **14a** and **15**. Although the shape of the aryl proton multiplet changes from the 6-ketone **3a** to the aldehyde **14a**, there are no further changes as the aldehyde is converted to an alcohol (**16**) and back to a carbonyl compound (**17**). If structure **15** were correct, significant changes in the chemical shift of the H-4 resonance would be expected due to the proximity of the carbonyl group. The structure of **14b** follows from that of **14a**. The chemical shifts of the aldehyde and aryl

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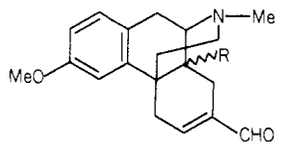
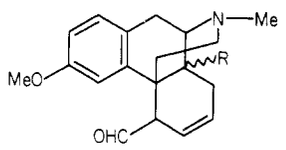
(9) Rice, K. C. *J. Med. Chem.* **1977**, *20*, 164.

(10) Abdulla, R. F.; Brinkmeyer, R. S. *Tetrahedron* **1979**, *35*, 1675.



14a, R = ||||H
b, R = ||||H



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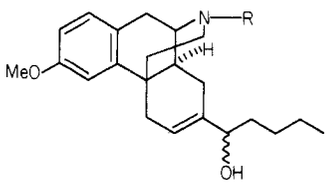
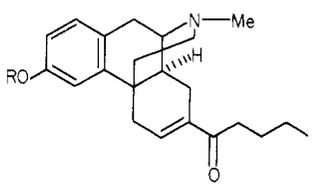
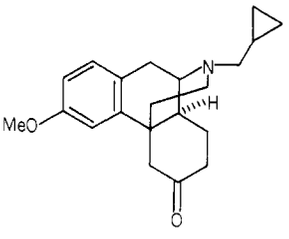


16a,b, R = $CH_3$
c, R = $CH_2$-c-$C_3H_5$



17, R = Me
20, R = H



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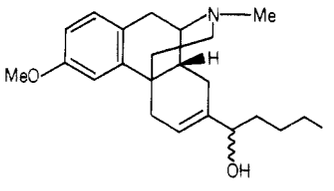

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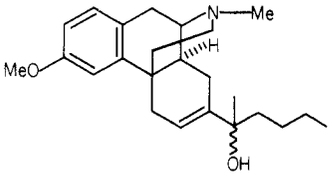

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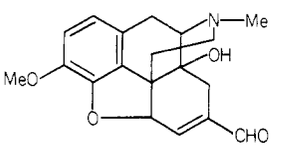
carbons in the $^{13}C$ NMR spectra are remarkably similar, indicating that the gross structural features are the same.

Treatment of a THF solution of **14a** with *n*-butyllithium afforded the epimeric alcohols **16a,b**, which were readily separated by column chromatography. The epimeric nature of these alcohols was established by their separate oxidation ($Me_2SO$–acetic anhydride) to the identical ketone **17**. Reduction of **17** ($NaBH_4$–methanol) afforded a mixture of **16a,b**. The configuration of these epimers was not determined. The *N*-(cyclopropylmethyl) analogue **16c** was prepared as a mixture of isomers from morphinanone (**18**), without characterization of the intermediates. The epimeric alcohols **19** were prepared from the *B/C-cis*-aldehyde **14b** by the addition of *n*-butyllithium.

Ketone **17**, which was most efficiently prepared by oxidation of the mixture **16a,b**, could be demethylated ($BBr_3$–$CHCl_3$) to afford the 3-hydroxy derivative **20**. The desired tertiary alcohol **21**, which is analogous to the oripavine opiates, was prepared by treatment of **17** with methyllithium. This reaction sequence could also be used to prepare 14-hydroxy-substituted opiates. Thus, **22** was prepared from oxycodone in 65% yield. The tertiary alcohol is not alkylated by treatment with the DMF–acetal. The secondary alcohol **23** was prepared in the usual way.

Condensation reactions of these aldehydes were also attempted. The phenyl- and dinitrophenylhydrazones of **22** could not be prepared. However, the unique amino-substituted codeine analogue (**24**) was prepared from **4**. Thus, reductive alkylation of **4** with *n*-butylamine afforded **24** in 17% yield.

**Pharmacology.** The preparation of these compounds was guided by assessment of their analgesic activity in the acetic acid mouse writhing test and the rat tail-flick test. These procedures have been described previously.[11] The



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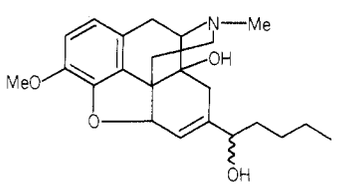
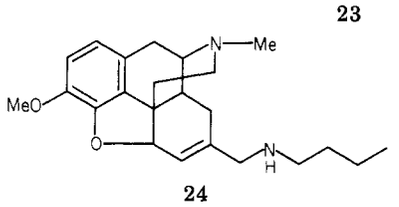


23



24

results are listed in Table I.

The aldehydes that were tested (**4**, **14a,b**, and **22**) had approximately the same analgesic activity as the precursor ketones. However, the other derivatives of **4** with short side chains were much less active. The five-carbon secondary alcohols **7b** had moderate activity in the writhing test. Hydromorphone derivatives bearing a phenylbutyl group at position 7 have been found to be very potent in the writhing test.[12] The analogous compounds in this series (**7c,d**) were equipotent to morphine. However, they were deemed not so potent as to warrant further development.

The 14-hydroxy derivatives of diketones **1a** are extremely potent in the writhing test.[13] However, the 14-hydroxy-7-hydroxypentyl derivative **23** was only a weak analgesic.

Among those compounds without the furano ring, the *B/C-trans*-7-(hydroxypentyl) derivatives **16a,b** are notable. These are among the most potent compounds that have been evaluated in the mouse writhing test in these laboratories. Although these two epimers were equipotent in this test, the faster eluting epimer **16a** was clearly more potent in the rat tail-flick test. By contrast, the B/C-cis analogue **19** was inactive at 10 mg/kg in the writhing test.

The potency of the alcohols **16a,b** led us to introduce nitrogen substituents that might lead to derivatives that possess morphine antagonist activity. However, the *N*-cyclopropylmethyl derivative **16c** had no antagonist activity in the rat tail-flick antagonist test[12] at a dose of 10 mg/kg. In comparison, the 6-keto precursor **18** had an $AD_{50}$ of 1.3 mg/kg in this test.[1]

The 7-acyl compounds were found to be less active than the corresponding secondary alcohols. For example, **16a,b** are 100 times as potent as **17** in the writhing test. The O-demethylation of **17** to afford **20** increased its potency by a factor of 20. The latter compound is unusual in being more active in the tail-flick test than in the writhing test. Conversion of the ketones to tertiary alcohols (**12**, **13**, and **20**) did not significantly recover the activity found in the secondary alcohols.

## Discussion

This simple procedure allows the preparation of a variety of opiate derivatives containing a 7-formyl group and lacking an oxygen function at position 6. Each of these aldehydes may be further derivatized by addition reactions, but condensation reactions are very difficult. Thus, the structural goals of the project were achieved. As with the

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(12) Leland, D. L.; Kotick, M. P. *J. Org. Chem.* **1983**, *48*, 1813.
(13) Quick, J., unpublished results.

Table I. Narcotic Agonist Activities

| compound[a] | $ED_{50}$, mg/kg writhing[b] | tail flick[c] |
|---|---|---|
| morphine sulfate | 0.79 (0.42-1.5) | 7.32 |
| hydrocodone bitartrate | 1.06 (0.7-1.6) | |
| hydromorphone hydrochloride | 0.08 (0.04-0.14) | |
| oxycodone hydrochloride | 0.3 (0.21-0.42) | |
| **3a** | 1.58 (1.14-2.2) | >20 |
| **3b** | 0.49 (0.26-0.92) | 0.66 |
| **4** | 1.45 (0.62-3.4) | Ia[d] |
| **5** | Ia | Ia |
| **6** | >10 | >10 |
| **7a** | Ia | Ia |
| **7b** | 3.13 (0.81-12.1) | Ia |
| **7c** | 1.6 (0.67-3.8) | |
| **7d** | 0.72 (0.49-1.1) | |
| **8a**·HCl | Ia | Ia |
| **8b**·HCl | Ia | >10 |
| **10a** | >10 | >10 |
| **12** | Ia | Ia |
| **13** | Ia | |
| **14a**·HCl | 4.55 (2.2-9.5) | |
| **14b** | 0.28 (0.05-1.43) | Ia |
| **16a** | 0.0058 (0.002-0.014) | 0.3 (0.15-0.59) |
| **16b** | 0.0062 (0.002-0.022) | 1.8 (1.4-2.2) |
| **16c** | 0.21 (0.001-6.44) | |
| **17**·HCl | 0.82 (0.6-1.04) | |
| **18** | >10 | |
| **19** | Ia | |
| **20** | 0.046 (0.041-0.052) | 0.0135 (0.008-0.021) |
| **21** | 0.125 (0.04-0.042) | 3.2 (1.3-7.7) |
| **22** | 3.6 (2.2-6.05) | |
| **23**·HCl | 9.8 (5.7-17) | |
| **24**·HCl | Ia | |

[a] Compounds that were prepared as salts were administered in distilled water; free bases were dissolved by the addition of hydrochloric acid and then further diluted. All compounds were administered by the subcutaneous route. [b] Mouse acetic acid writhing test: ref 11; cf.: Whittle, B. A. *Br. J. Pharmacol.* **1964**, *22*, 246. 95% confidence limits. [c] Rat tail-flick test: Harris, L. S., Pierson, A. K. *J. Pharmacol. Exp. Ther.* **1964**, *143*, 141. 95% confidence limits. [d] Ia = inactive at the highest dose tested (10 mg/kg).

*endo*-ethanotetrahydrooripavines (**2**), the derivatives in this series with the longer side chain were found to be the more potent analgesics. Of particular interest is the finding that the *B/C-trans*-morphinan derivatives, which correspond sterically to the oripavines, are very potent, while the analogous compound with opposite stereochemistry has no analgesic activity. Similarly, an *exo*-ethanodeoxyoripavine compound was recently found to have no analgesic activity.[14] The similarity in the potencies of the epimers **16a,b** is contrary to what is found in the tertiary alcohols such as **2**. In the latter series, one diastereomer is much more active than the other.[15] The similarity does, however, correspond to what is found for the secondary alcohols in the *endo*-ethanotetrahydrooripavine series.[16] In this case, intramolecular hydrogen bonding is not an important factor.[16] Thus, the side chain can be found in several low-energy conformations, and the configurational differences in the drug–receptor interactions are less pronounced.

## Experimental Section

Melting points were determined on a Thomas-Hoover or Fisher-Johns melting point apparatus and are uncorrected. $^1H$ NMR spectra were recorded on a Varian T-60 spectrometer, with tetramethylsilane as an internal standard and in $CDCl_3$ solution unless otherwise stated. Infrared spectra were obtained on a Perkin-Elmer 700 spectrometer. Precoated TLC plates (silica gel 60F; EM Reagent) were used for TLC analysis. Column chromatographic separations used EM Reagent silica gel 60 (0.063–0.200 mm) and gradient elution with chloroform–methanol unless noted otherwise. Flash chromatography[17] was performed with EM Reagent silica gel 60 (0.040–0.063 mm). Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, GA. Where analyses are indicated only by symbols, analytical results obtained for those elements were within ±0.4% of the theoretical values. Mass spectra were obtained by the Mass Spectrometry Laboratory, Cornell University, Ithaca, NY and are reported as *m/e* (relative intensity). $^{13}C$ NMR spectra were obtained by Miles Laboratories, Inc., Elkhart, IN. All organic layers were dried after extractions with $Na_2SO_4$. Except as noted, all reagents and solvents were used as obtained from the supplier. Tetrahydrofuran was distilled from sodium ketyl.

**7-[(Dimethylamino)methylene]hydrocodone (5).** A solution of hydrocodone (10.0 g, 33 mmol) and dimethylformamide diethyl acetal (6.0 g, 40 mmol) in toluene (125 mL) was heated at reflux for 16 h. While the solution was cooling, a precipitate slowly formed, which was filtered and washed with toluene to afford 6.2 g (52% yield) of **5**: mp 212–215 °C (lit.[7] mp 212–215 °C). The mother liquors were resubmitted to the reaction conditions to afford another 1.5 g (32%) of **5**.

**7-[(*n*-Butylthio)methylene]hydrocodone (6).** A solution of the enaminone **5** (1.0 g, 2.8 mmol), *n*-butanethiol (0.4 mL, 3.7 mmol), and *p*-toluenesulfonic acid hydrate (5 mg) in benzene (25 mL) was heated at reflux for 20 h. After cooling, the solution was washed with saturated $NaHCO_3$ and water, dried, and concentrated. The resulting yellow solid was recrystallized from ethanol to afford pure **6** (0.83 mg, 74% yield): mp 136–137.5 °C; NMR

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δ 0.7–3.3 (m's), 2.50 (s, ~3 H, $NCH_3$), 3.88 (s, 3 H, $OCH_3$), 4.53 (s, 1 H, H-5), 6.75 (s, 2 H, aryl), 7.7 (2 s, 1 H, =CHS). Anal. ($C_{23}H_{29}NO_3S$) C, H, N, S. Yields of 90% have been obtained by crystallization of the mother liquors.

**4,5α-Epoxy-7-formyl-3-methoxy-17-methyl-6,7-didehydromorphinan (4).** To a methanolic (30 mL) solution of **6** (0.50 g, 1.3 mmol) was added a solution of $NaBH_4$ (0.4 g, 12 mmol) in 0.25 N NaOH (5 mL). After 2 h, the reaction mixture was diluted with 10% $H_2SO_4$ (30 mL) and heated at reflux for 2 h. After cooling and being made basic with $NH_4OH$, the mixture was extracted with chloroform. The residue from the organic layer was subjected to chromatography to afford a 91% yield of crystalline **4**: mp 146–152 °C; NMR δ 1.7–3.3 (m's), 2.43 (s, ~3, $NCH_3$), 3.87 (s, 3 H, $OCH_3$), 5.22 (m, 1 H, H-5), 6.67 (m, ~1 H, vinyl), 6.72 (s, ~2 H, aryl), 8.78 (s, 1 H, CHO); IR (film) 1685 $cm^{-1}$; MS, *m/e* 311 (100, $M^+$), 296 (17, $M^+ - CH_3$), 282 (41, $M^+ - CHO$). Anal. ($C_{19}H_{21}NO_3$) C, H, N.

**4,5α-Epoxy-7-(1-hydroxyethyl)-3-methoxy-17-methyl-6,7-dihydromorphinan (7a).** An ether solution of methyllithium (1 mL, 1.5 mmol) was added to a THF (15 mL) solution of the aldehyde **4** (320 mg, 1.0 mmol), maintained in an ice bath. After 1 h, the mixture was quenched with aqueous $NH_4Cl$, diluted with water, and extracted with chloroform. The organic layers were dried, concentrated, and chromatographed to afford 252 mg of **7a** (76% yield): mp 189–191 °C dec; NMR ($CDCl_3$–$CD_3OD$) δ 1.18 (d, *J* = 7 Hz, $CHCH_3$), 1.15 (d, ~20% of 1.18 signal, epimeric $CHCH_3$), 1.5–3.3 (m's), 2.40 (s, ~3 H, $NCH_3$), 3.82 (s, 3 H, $OCH_3$), 4.07 (br q, ~1 H, $>CHCH_3$), 4.98 (m, 1 H, H-5), 5.67 (m, 1 H, vinyl), 6.68 (AB q, 2 H, aryl); IR ($CHCl_3$) 3750 (br) $cm^{-1}$; MS, *m/e* 327 (100, $M^+$), 312 (22, $M^+ - CH_3$), 310 (8, $M^+ - OH$), 382 [19, $M^+ - CH(OH)CH_3$]. Anal. ($C_{20}H_{25}NO_3 \cdot 0.25CHCl_3$) C, H, N.

**4,5α-Epoxy-7-(1-hydroxypentyl)-3-methoxy-17-methyl-6,7-didehydromorphinan (7b).** A solution of **4** (1.06 g, 3.4 mmol) was treated with *n*-butyllithium (2 mL, 5 mmol) as described above. After chromatography, 500 mg (40% yield) of **7b** was obtained: mp 176–178 °C; NMR δ 0.7–3.5 (m's), 2.23 (s, ~3 H, $NCH_3$), 3.83 (s and m, 4 H, $OCH_3$ and >CHO), 5.0 (br d, 1 H, H-5), 5.70 (br m, 1 H, vinyl), 6.67 (AB q, 2 H, aryl); IR ($CHCl_3$) 3200 (br), 2950 (s) $cm^{-1}$. Anal. ($C_{23}H_{31}NO_3$) C, H, N.

**4,5α-Epoxy-7-(1-hydroxy-4-phenylbutyl)-3-methoxy-17-methyl-6,7-didehydromorphinan (7c,d).** A solution of **4** (502 mg, 1.6 mmol) was treated as described above with 1-lithio-3-phenylpropane, which was prepared by the dropwise addition of a solution of 3-phenyl-1-bromopropane (639 mg, 3.2 mmol) in ether (10 mL) to a cooled (−78 °C) solution of *tert*-butyllithium (6.4 mmol) in ether (20 mL). Column chromatography afforded diasteriomers **7c** (50% yield) and **7d** (20% yield), each contaminated with a small amount of the product derived from the addition of *tert*-butyllithium with **4**. Pure samples of these diastereomers were obtained by preparative TLC. **7c**: mp 147–149 °C; NMR δ 1.3–3.2 (m's), 2.32 (s, ~3 H, $NCH_3$), 3.7–4.0 (m, ~1 H, $>CHO$), 3.76 (s, ~3 H, $OCH_3$), 4.9 (m, 1 H, H-5), 5.7 (m, 1 H, vinyl), 6.67 (s, 2 H, aryl), 6.9–7.3 (m, 5 H, $C_6H_5$); IR (KBr) 3400 (br), 3100 (br), 2950 $cm^{-1}$; MS, *m/e* 431 (100, $M^+$), 416 (20, $M^+ - CH_3$), 312 (16, $M^+ - C_3H_6C_6H_5$), 282 [27, $M^+ - CH(OH)C_3H_6C_6H_5$]. Anal. ($C_{28}H_{33}NO_3 \cdot 0.5H_2O$) C, H, N.

**7d**: mp 156–158 °C; NMR δ 1.1–3.2 (m's), 2.37 (s, ~3 H, $NCH_3$), 3.7–4.0 (m, ~1 H, >CHO), 3.75 (s, ~3 H, $OCH_3$), 4.9 (m, 1 H, H-5), 5.7 (m, 1 H, vinyl), 6.67 (s, 2 H, aryl), 6.9–7.3 (m, 5 H, $C_6H_5$); IR (film) 3700–3100 (br), 2970 (s) $cm^{-1}$; MS, *m/e* 431 (100, $M^+$), 416 (18, $M^+ - CH_3$), 312 (8, $M^+ - C_3H_6C_6H_5$), 282 [19, $M^+ - CH(OH)C_3H_6C_6H_5$]. Anal. ($C_{28}H_{33}NO_3 \cdot 0.5H_2O$) C, H, N.

**7-Acetyl-4,5α-epoxy-3-methoxy-17-methyl-6,7-didehydromorphinan (8a) and 4,5α-Epoxy-3-methoxy-17-methyl-7-[1-[(methylthio)methoxy]ethyl]-6,7-didehydromorphinan (9).** A solution of the alcohol **7a** (515 mg, 1.6 mmol) in acetic anhydride (3 mL) and dimethyl sulfoxide (5 mL) was heated at 60 °C for 3 h. After cooling, the mixture was diluted with methylene chloride (50 mL), washed five times with diluted $NH_4OH$ (10 mL), dried, and concentrated. Column chromatography afforded **8a** (61% yield), and the thioether **9** (18% yield).

**8a**: NMR δ 1.7–3.3 (m's), 2.27 [s, ~3 H, $C(O)CH_3$], 2.43 (s, ~3 H, $NCH_3$), 3.87 (s, 3 H, $OCH_3$), 5.2 (br m, 1 H, H-5), 6.7 (m, 3 H, aryl and vinyl); IR (film) 1670 $cm^{-1}$; MS, *m/e* 325 (100, $M^+$), 310 (21, $M^+ - CH_3$), 282 [28, $M^+ - C(O)CH_3$]. HCl salt (foam from chloroform). Anal. ($C_{20}H_{23}NO_3 \cdot HCl \cdot 3H_2O$) C, H, N, Cl.

**9**: NMR δ 1.05 and 1.17 (unequal d's, *J* = 7 Hz, 3 H, $>CHCH_3$), 1.7–3.2 (m's), 1.97 (s, ~3 H, 5-$CH_3$), 2.42 (s, ~3 H, $NCH_3$), 3.85 (s, 3 H, $OCH_3$), 4.00 and 4.15 (s's, 2 H, $>CHOCH_2S$), 4.4 (m, 1 H, >CHO) 5.0 (br m, 1 H, H-5), 5.7 (br m, 1 H, vinyl), 6.67 (AB q, *J* = 9 Hz, 2 H, aryl); IR (film) 2940 (s) $cm^{-1}$; MS, *m/e* 387 (100, $M^+$), 372 (13, $M^+ - CH_3$), 326 (6, $M^+ - CH_2SCH_3$), 310 (59, $M^+ - OCH_2SCH_3$). Anal. ($C_{22}H_{29}NO_3S \cdot 0.5H_2O$) C, H, N, S.

**4,5α-Epoxy-3-methoxy-17-methyl-7-pentanoyl-6,7-didehydromorphinan (8b).** The alcohol **7b** (300 mg, 0.8 mmol) was treated with $Me_2SO$ and acetic anhydride, as described above, to afford **8b** (68% yield) as an oil: NMR δ 0.8–3.3 (m's), 2.43 (s, ~3 H, $NCH_3$), 3.88 (s, 3 H, $OCH_3$), 5.2 (br m, 1 H, H-5), 6.73 (m and s, 3 H, aryl and vinyl), IR ($CHCl_3$) 1685 $cm^{-1}$. Anal. ($C_{23}H_{29}NO_3 \cdot HCl$) C, H, N, Cl.

**7-Acetyl-4,5α-epoxy-3-hydroxy-17-methyl-6,7-didehydromorphinan (10a).** A solution of **8a** (1.3 g, 4 mmol) in chloroform (20 mL) was slowly added to a stirred solution of $BBr_3$ (4.5 mL, 48 mmol) in chloroform (150 mL). After 1 h, the reaction mixture was poured into ice/$NH_4OH$, and the resulting mixture was stirred for 2 h. After separation of the layers and extraction of the aqueous layer with chloroform, the organic fractions were combined, dried, and concentrated in vacuo to afford 721 mg of a brown oil. Column chromatography afforded **10a** (34% yield) as a solid: mp 250 °C dec; NMR δ 1.7–4.0 (m's), 2.27 [s, ~3 H, $C(O)CH_3$], 2.47 (s, ~3 H, $NCH_3$), 5.13 (br m, 1 H, H-5), 6.6 (m, 3 H, aryl and vinyl); IR ($CHCl_3$) 3500 (br), 1670 $cm^{-1}$; MS, *m/e* 311 (66, $M^+$), 296 (12, $M^+ - CH_3$), 268 [39, $M^+ - C(O)CH_3$], 253 (10, 268 − $CH_3$), 43 (100). Anal. ($C_{19}H_{21}NO_3 \cdot 0.2CHCl_3$) C, H, N.

**4,5α-Epoxy-7-(1-hydroxy-1-methylpentyl)-3-methoxy-17-methyl-6,7-didehydromorphinan (12).** To a cooled solution of enone **8a** (140 mg, 0.4 mmol) in THF was added *n*-butyllithium (~2 mmol). After 2 h, the mixture was worked up as above (**7a**). Preparative TLC afforded **12** (50 mg, 33% yield) as an oil: NMR δ 0.7–3.2 (m), 1.22 (s, ~3 H, $CCH_3$), 2.38 (s, ~3 H, $NCH_3$), 3.83 (s, 3 H, $OCH_3$), 5.0 (m, 1 H, H-5), 5.77 (m, 1-H, vinyl), 6.67 (AB q, 2 H, aryl); MS, *m/e* 383 (100, $M^+$), 368 (33, $M^+ - CH_3$), 366 (10, $M^+ - OH$), 365 (14, $M^+ - H_2O$), 326 (26, $M^+ - C_4H_9$), 282 [43, $M^+ - C(CH_3)(OH)C_4H_9$]. Anal. ($C_{24}H_{33}NO_3 \cdot 0.75H_2O \cdot 0.1CHCl_3$) C, H, N, Cl.

**4,5α-Epoxy-3-hydroxy-7-(1-hydroxy-1-methylpentyl)-17-methyl-6,7-didehydromorphinan (13).** Treatment of the hydroxy enone **10** (120 mg, 0.4 mmol) with *n*-butyllithium as described above afforded 41 mg of **13** (28% yield): NMR δ 0.6–3.2 (m's), 1.20 (s, ~3 H, $CCH_3$), 2.42 (s, ~3 H, $NCH_3$), 5.0 (m, 1 H, H-5), 5.7 (m, 1 H, vinyl), 6.60 (AB q, 2 H, aryl). Anal. ($C_{23}H_{31}NO_3 \cdot 0.5H_2O \cdot 0.1CHCl_3$) C, H, N, Cl.

***B/C-trans*- and *B/C-cis*-3-Methoxy-17-methyl-6-morphinanone (3a,b).** The morphinanones **3a,b** were prepared as reported previously.[1] The resonance assignments below are based on those of Carroll et al.[18]

**3a**: $^{13}C$ NMR δ 210.6 (s, C-6), 158.3 (s, C-3), 144.6 (s, C-12), 130.3 (s, C-11), 128.8 (d, C-1), 112.1 and 109.4 (d's, C-2 and C-4), 57.6 (d, C-9), 55.3 (q, $OCH_3$), 51.8 (t, C-16), 47.3 (br s, C-13), 42.9 (q, $NCH_3$), 40.8 (t, C-7), 40.3 (d, C-14), 33.5 (t, C-5), 28.3, 27.1, and 26.5 (t's), C-8, C-10, and C-15).

**3b**: $^{13}C$ NMR δ 208.7 (s, C-6), 158.4 (s, C-3), 138.9 (s, C-12), 128.7 (d, C-1), 128.5 (s, C-11), 112.6 and 111.5 (d's, C-2 and C-4), 57.3 (d, C-9), 55.3 (q, $OCH_3$), 51.6 (t, C-16), 46.1 (br s, C-13), 44.2 (d, C-14), 42.9 (q, $NCH_3$), 42.1 and 41.1 (t's, C-5 and C-7), 26.9 and 23.3 (t, C-8 and C-10).

***B/C-trans*-7-Formyl-3-methoxy-17-methyl-6,7-didehydromorphinan (14a).** A solution of **3a** (5.8 g, 0.02 mmol) in DMF dimethyl acetal (31 g, 0.26 mmol) was heated at 130 °C for 20 h, then cooled, and concentrated in vacuo. This crude product was heated sequentially with butanethiol, $NaBH_4$, and acid as above (see **6** and **4**) to afford, after chromatography, pure **14a** (3.4 g, 56% yield): $^1H$ NMR δ 0.9–1.3 (m, 1 H), 1.7–3.4 (m's), 2.33 (s, ~3 H, $NCH_3$), 3.80 (s, 3 H, $OCH_3$), 6.7–7.2 (m, 4 H, aryl and vinyl), 9.57 (s, 1 H, CHO); $^{13}C$ NMR δ 193.5 (d, CHO), 158.5 (s, C-3), 148.0 (d, C-6), 140.7 and 139.9 (s's, C-7 and C-12), 129.1 (d, C-1), 128.4 (s, C-11), 111.5 and 110.9 (d's, C-2 and C-4), 57.2 (d, C-9), 55.3 (q, $OCH_3$), 46.8 (br s, C-13), 42.5 (q, $NCH_3$), 40.6

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(t, C-16), 38.9 (d, C-14), 36.9 and 35.4 (t's, C-5 and C-15), 23.2 and 22.7 (t's, C-8 and C-10); IR (film 1675 $cm^{-1}$; MS, *m/e* 297 (32, $M^+$), 268 (7, $M^+ - CHO$), 59 (49), 43 (100). Hydrochloride (ethanol): mp 210 °C dec. Anal. ($C_{19}H_{23}NO_2 \cdot HCl \cdot 0.5H_2O \cdot 0.5C_2H_5OH$) C, H, N, Cl.

***B*/*C*-*cis*-7-Formyl-3-methoxy-17-methyl-6,7-didehydromorphinan (14b).** Treatment of **3b** (8.29 g, 29 mmol) with DMF dimethyl acetal, butanethiol, and $NaBH_4$ proceeded as above. Hydrolysis was attempted with acetic acid at room temperature, followed by retreatment with $NaBH_4$ and finally with 10% $H_2SO_4$. From this mixture was isolated by chromatography 1.0 g of **14b** (12% yield), which could be recrystallized from ethanol: mp 161–163 °C; $^1H$ NMR δ 1.4–3.4 (m's), 2.40 (s, ~3 H, $NCH_3$), 3.75 (s, 3 H, $OCH_3$), 6.6–7.1 (m, 4 H, aryl and vinyl), 9.30 (s, 1 H, CHO); $^{13}C$ NMR δ 193.5 (d, CHO), 158.2 (s, C-3), 148.0 (d, C-6), 141.0 and 140.1 (s's, C-12 and C-7), 129.4 (s, C-11), 128.9 (d, C-1), 111.1 and 110.9 (d's, C-2 and C-4), 56.8 (d, C-9), 55.1 (q, $OCH_3$), 46.7 (br s, C-13), 42.9 (q, $NCH_3$), 41.4 (t, C-16), 39.7 (d, C-14), 37.3 and 35.7 (t's, C-5 and C-15), 23.0 and 22.8 (t, C-8 and C-10); IR (film) 1680 $cm^{-1}$; MS, *m/e* 297 (76, $M^+$), 268 (16, $M^+ - CHO$), 59 [100, $C_2H_5NH(CH_3)$]. Anal. ($C_{19}H_{23}NO_2$) C, H, N.

***B*/*C*-*trans*-7-(1-Hydroxypentyl)-3-methoxy-17-methyl-6,7-didehydromorphinan (16a,b).** A solution of **14a** (500 mg, 1.7 mmol) was treated with *n*-butyllithium (5 mmol) as above (**7b**). Chromatography afforded the two diasteriomers **16a** (35% yield) and **16b** (30% yield) in order of elution.

**16a**: NMR δ 0.8–3.1 (m's), 2.37 (s, ~3 H, $NCH_3$), 3.78 (s, 3 H, $OCH_3$), 4.1 (br t, 1 H, >C*H*OH), 5.7 (m, 1 H, vinyl), 6.6–7.1 (m, 3 H, aryl); IR (film) 3400 (br) $cm^{-1}$; MS, *m/e* 355 (100, $M^+$), 340 (18, $M^+ - CH_3$), 338 (25, $M^+ - OH$), 337 (15, $M^+ - H_2O$), 298 (77, $M^+ - C_4H_9$), 268 [40, $M^+ - CH(OH)C_4H_9$]. Anal. ($C_{23}H_{33}NO_2 \cdot 0.5H_2O$) C, H, N.

**16b**: NMR δ 0.8–3.4 (m's), 2.47 (s, ~3 H, $NCH_3$), 3.82 (s, 3 H, $OCH_3$), 4.1 (br t, 1 H, >C*H*OH), 5.7 (m, 1 H, vinyl), 6.7–7.2 (m, 3 H, aryl); IR (film) 3400 (br) $cm^{-1}$; MS, *m/e* 355 (100, $M^+$), 340 (18), 338 (26), 337 (12), 298 (66), 268 (36). Anal. ($C_{23}H_{33}NO_2 \cdot H_2O$) C, H, N.

***B*/*C*-*trans*-17-(Cyclopropylmethyl)-7-(1-hydroxypentyl)-3-methoxy-6,7-didehydromorphinan (16c).** From 1.8 g (5.5 mmol) of **18** treated as before (see **4**) was obtained 0.7 g (38% yield) of the 7-formyl derivative: NMR δ 0.0–0.7 (m's, 5 H, c-$C_3H_5$), 0.8–1.3 (m, 1 H), 1.7–3.3 (m's), 3.75 (s, 3 H, $OCH_3$), 6.6–7.1 (m, 4 H, aryl and vinyl), 9.53 (s, 1 H, CHO). A solution of 44 mg (1.3 mmol) of this aldehyde was treated as above (see **7b**). Flash chromatography (10% methanol in methylene chloride) afforded 50 mg (10% yield) of **16c** as a mixture of epimers: NMR δ 0.0–0.7 (m's, 5 H, c-$C_3H_5$), 0.7–3.3 (m's), 3.80 (s, 3 H, $OCH_3$), 4.07 (m, 1 H, >C*H*OH), 5.7 (m, 1 H, vinyl), 6.6–7.1 (m, 3 H, aryl); IR ($CH_2Cl_2$) 3700 (br) $cm^{-1}$; MS, *m/e* 395 (100, $M^+$), 380 (17, $M^+ - CH_3$), 378 (22, $M^+ - OH$), 338 (42, $M^+ - C_4H_9$), 308 [21, $M^+ - CH(OH)C_4H_9$]. Anal. ($C_{26}H_{37}NO_2 \cdot 0.5CH_2Cl_2$) C, H, N, Cl.

***B*/*C*-*trans*-3-Methoxy-17-methyl-7-pentanoyl-6,7-didehydromorphinan (17).** A mixture of alcohols **16a,b** (obtained from the treatment of 1.2 g of **14a** with *n*-butyllithium) was treated with $Me_2SO$-acetic anhydride as above (see **8a**) to afford, after chromatography (benzene–ethyl acetate), **17** in 51% overall yield: NMR δ 0.8–3.1 (m's), 2.33 (s, ~3 H, $NCH_3$), 3.77 (s, 3 H, $OCH_3$), 6.6–7.7 (m, 4 H, aryl and vinyl); IR (film) 1665 $cm^{-1}$; MS, *m/e* 353 (100, $M^+$), 338 (18, $M^+ - CH_3$), 311 (14, $M^+ - CH_2{=}CHCH_3$), 296 (26, 311 – $CH_3$), 268 [41, $M^+ - C(O)C_4H_9$]. Anal. ($C_{23}H_{31}NO_2 \cdot HCl \cdot 0.5H_2O$) C, H, N, Cl.

***B*/*C*-*cis*-7-(1-Hydroxypentyl)-3-methoxy-17-methyl-6,7-didehydromorphinan (19).** A solution of **14b** (345 mg, 1.2 mmol) was treated with *n*-butyllithium (3 mmol) as above. Purification by flash chromatography (15% methanol in chloroform) afforded **19** (185 mg, 45% yield) as a light yellow solid: mp 126–128 °C (washed with ether); NMR δ 0.7–3.3 (m's), 2.33 (s, ~3 H, $NCH_3$), 3.73 (s and m, 4 H, $OCH_3$ and >C*H*OH), 5.5 (br m, 1 H, vinyl), 6.5–7.0 (m, 3 H, aryl); IR ($CHCl_3$) 3200 (br), 2950 $cm^{-1}$; MS, *m/e* 355 (55, $M^+$), 338 (8, $M^+ - OH$), 298 (24, $M^+ - C_4H_9$), 268 [7, $M^+ - CH(OH)C_4H_9$], 59 (100, $C_2H_5{}^+NHCH_3$). Anal. ($C_{23}H_{33}NO_2 \cdot 0.25H_2O$) C, H, N.

***B*/*C*-*trans*-3-Hydroxy-17-methyl-7-pentanoyl-6,7-didehydromorphinan (20).** A solution of **17** (271 mg, 0.76 mmol) was treated with $BBr_3$ as above (see **10**) to afford a 63% yield of **20**: mp 164–65 °C; NMR δ 0.8–3.1 (m's), 2.35 (s, ~3 H, $NCH_3$), 5.8 (br, OH), 6.6–7.1 (m, 4 H, aryl and vinyl); IR (KBr) 3750 (br), 3250 (s), 1640 $cm^{-1}$; MS, *m/e* 339 (100, $M^+$), 324 (12, $M^+ - CH_3$), 297 (14, $M^+ - CH_2{=}CHCH_3$), 282 (24, 297 – $CH_3$), 254 [34, $M^+ - C(O)C_4H_9$]. Anal. ($C_{22}H_{29}NO_2 \cdot 0.5H_2O$) C, H, N.

***B*/*C*-*trans*-7-(1-Hydroxy-1-methylpentyl)-3-methoxy-17-methyl-6,7-didehydromorphinan (21).** A solution of **17** (150 mg, 0.4 mmol) was treated with methyllithium as above (see **7a**) to afford **21** (50% yield): NMR δ 0.8–3.1 (m's), 1.33 (s, ~3 H, $CCH_3$), 2.33 (s, ~3 H, $NCH_3$), 3.78 (s, 3 H, $OCH_3$), 5.7 (m, 1 H, vinyl), 6.6–7.1 (m, 3 H, aryl); IR (film) 3450 (br) $cm^{-1}$; MS, *m/e* 369 (100, $M^+$), 354 (18, $M^+ - CH_3$), 352 (18, $M^+ - OH$), 351 (23, $M^+ - H_2O$), 312 (68, $M^+ - C_4H_9$), 268 [53, $M^+ - C(OH)(CH_3)C_4H_9$].

**4,5α-Epoxy-7-formyl-14-hydroxy-3-methoxy-17-methyl-6,7-didehydromorphinan (22).** Treatment of 14-hydroxydihydrocodeinone (1 g, 3 mmol) with DMF dimethyl acetal in toluene (120 °C, 24 h), followed by butanethiol treatment, reduction, and hydrolysis as before, afforded **22** in 65% yield: mp 208–210 °C (ethanol); NMR δ 1.6–3.2 (m's), 2.40 (s, ~3 H, $NCH_3$), 3.85 (s, 3 H, $OCH_3$), 4.6 (br, 1 H, OH), 5.20 (m, 1 H, H-5), 6.67 (s and m, 3 H, aryl and vinyl), 9.47 (s, 1 H, CHO); IR (KBr) 3350 (br), 1690 $cm^{-1}$. Anal. ($C_{19}H_{21}NO_4$) C, H, N.

**4,5α-Epoxy-14-hydroxy-7-(1-hydroxypentyl)-3-methoxy-17-methyl-6,7-didehydromorphinan (23).** From the treatment of the aldehyde **22** (1.03 g, 31 mmol) with *n*-butyllithium as above (see **7b**) was obtained a 60% yield of **23** as an oil: NMR δ 0.7–3.4 (m's), 2.41 (s, ~3 H, $NCH_3$), 3.80 (s, 3 H, $OCH_3$), 4.1 (m, 3 H, >C*H*OH and 2 OH's), 5.0 (m, H-5), 5.7 (m, 1 H, vinyl), 6.67 (AB q, 2 H, aryl); IR (oil) 3400 (br), 2950 (s) $cm^{-1}$; MS *m/e* 385 (100, $M^+$), 370 (6, $M^+ - CH_3$), 368 (12, $M^+ - OH$), 367 (13, $M^+ - H_2O$). Hydrochloride: mp 145 °C dec. Anal. ($C_{28}H_{31}NO_4 \cdot HCl \cdot 2H_2O$) C, H, N, Cl.

**7-[(Butylamino)methyl]-4,5α-epoxy-3-methoxy-17-methyl-6,7-didehydromorphinan (24).** By a modification of the Borch procedure,[19] a mixture of **4** (315 mg, 1 mmol), *n*-butylamine (450 mg, 6 mmol), $NaCNBH_3$ (65 mg, 1 mmol), and 4 N HCl in dioxane (0.5 mL) in methanol (10 mL) was stirred under a nitrogen atmosphere for 4 days. The mixture was then made more acidic with 6 N HCl, diluted with water, made basic with $NH_4OH$, and extracted with chloroform. The chloroform layers were dried, concentrated in vacuo, and chromatographed (basic alumina; methylene chloride) to afford **24** in 17% yield: NMR δ 1.8–3.2 (m's), 2.43 (s, ~3 H, $NCH_3$), 3.87 (s, 3 H, $OCH_3$), 5.0 (m, 1 H, H-5), 5.7 (m, 1 H, vinyl), 6.70 (AB q, 2 H, aryl); IR (film) 2950 (s), 1450 (s) $cm^{-1}$. Dihydrochloride (foam): mp 200 °C dec. Anal. ($C_{23}H_{32}N_2O_2 \cdot 2HCl \cdot H_2O$) C, H, N, Cl.

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**Registry No.** **3a**, 55298-15-2; **3b**, 2246-20-0; **4**, 89178-23-4; **5**, 79413-35-7; **6**, 89178-22-3; (7*S*)-**7a**, 89178-24-5; (7*R*)-**7a**, 89178-49-4; (7*S*)-**7b**, 89178-25-6; (7*R*)-**7b**, 89178-50-7; (7*S*)-**7c**, 89196-37-2; (7*R*)-**7d**, 89178-26-7; **8a**, 89178-27-8; **8a**·HCl, 89178-47-2; **8b**, 89178-29-0; **8b**·HCl, 89178-45-0; **9**, 89178-28-9; **10a**, 89178-30-3; **12**, 89178-31-4; **13**, 89178-32-5; **14a**, 89178-33-6; **14a**·HCl, 89178-52-9; **14b**, 89253-89-4; (7*S*)-**16a**, 89178-34-7; (7*R*)-**16b**, 89178-35-8; (7*S*)-**16c**, 89178-36-9; (7*R*)-**16c**, 89178-51-8; **17**, 89178-37-0; **17**·HCl, 89178-46-1; **18**, 72747-66-1; **18** (7-formyl derivative), 89178-48-3; (7*S*)-**19**, 89253-90-7; (7*R*)-**19**, 89253-91-8; **20**, 89178-38-1; **21**, 89178-39-2; **22**, 89178-40-5; **23**, 89178-41-6; **23**·HCl, 89178-43-8; **24**, 89178-42-7; **24**·HCl, 89178-44-9; $Me_2NCH(OC_2H_5)_2$, 1188-33-6; *n*-BuSH, 109-79-5; $CH_3Li$, 917-54-4; *n*-BuLi, 109-72-8; $C_6H_5(CH_2)_3Li$, 64740-46-1; $Me_2NCH(OCH_3)_2$, 4637-24-5; *n*-$BuNH_2$, 109-73-9; hydrocodone, 125-29-1; 14-hydroxydihydrocodeinone, 76-42-6.

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