2,4-Dinitrophenylhydrazone, mp 200–201 °C. Anal. Calcd for $C_{20}H_{24}O_4N_4$: C, 62.49; H, 6.29; N, 14.58. Found: C, 62.57; H, 6.34; N, 14.70.

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Registry No. **1a**, 106-99-0; **1b**, 78-79-5; **1c**, 2004-70-8; **2a**, 1073-14-9; **2b**, 38441-63-3; **3a**, 65595-97-3; **3a**·DNP, 85407-52-9; **3d**, 85407-53-0; **3d**·DNP, 85407-54-1; **3f**, 85407-55-2; **3g**, 85407-56-3; **3g**·DNP, 85407-57-4; **3h**, 85407-58-5; **3i**, 85407-59-6; **3i**·DNP, 85407-60-9; **4c**, 78006-86-7; **4c**·DNP, 85407-61-0; **4h**, 85407-62-1; **4h**·DNP, 85407-63-2.

7α- or 7β-(4-Phenylbutyl)dihydrocodeine Derivatives[1]

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A lipophilic 4-phenylbutyl group was selectively incorporated into the 7α- or 7β-position of the morphine nucleus by use of 6,7-oxymethylene (oxetane) intermediates. 7,7-Bis[(tosyloxy)methyl]dihydroisocodeine (**2**) with dilute NaOH gave 6β,7β-(oxymethylene)-7α-[(tosyloxy)methyl] compound **3**. Displacement of the tosyloxy group with NaOAc followed by hydrolysis and oxidation gave 6β,7β-(oxymethylene)-7α-formyl derivative **6**. Wittig condensation with cinnamyltriphenylphosphorane and hydrogenation of the resulting diene **7** gave 6β,7β-(oxymethylene)-7α-(4-phenylbutyl)dihydroisocodeine (**8**). Oxidation of **2** to 6-oxo ditosylate **10** and then $NaBH_4$ reduction, yielding 6α-ol **11**, allowed ring closure to 6α,7α-(oxymethylene)-7β-[(tosyloxy)methyl] compound **12**. Reaction of **12** with NaOAc to give **13** followed by continuation of the reaction sequence as described above yielded the α-oxetane–7β-(4-phenylbutyl) derivative **17**. Reaction of 7,7-bis(hydroxymethyl)dihydroisocodeine (**1**) with acetone–*p*-TsOH gave predominantly isopropylidene derivative **23** with the 6β- and 7α-hydroxyl functions blocked. Oxidation of **23** to 7β-formyl derivative **33**, followed by condensation with cinnamyltriphenylphosphorane, hydrolysis of the isopropylidene group, and catalytic reduction gave 7α-(hydroxymethyl)-7β-(4-phenylbutyl)dihydroisocodeine (**36**). The 7β-arylalkyl derivatives were potent narcotic agonists in contrast to the 7α-substituted compound which was inactive.

We have been engaged during the past several years in a program to explore the chemistry of the morphine C ring.[2] The objective of these studies was to delineate what factors are responsible for the potent narcotic agonist activity found in a series of 6,14-*endo*-ethenotetrahydrooripavine derivatives.[3]

Our work led to the preparation of 7,7-dimethyldihydrocodeinones[4] from 7,7-bis(hydroxymethyl)dihydroisocodeine. This latter material was prepared via the aldol–crossed Cannizzaro reaction of dihydrocodeinone with formaldehyde as reported some time ago by Mannich and Schulte.[5] The transformation of the corresponding 8β-alkyl-7,7-bis(hydroxymethyl) compounds, by way of tosylated intermediates, to 8β-alkyl-7,7-dimethyl derivatives involved oxetane ring formation.[4] These oxymethylene compounds have now been used as synthetic tools for further study of morphine C-ring chemistry. This report details the use of these novel oxetane ring containing compounds for the selective preparation of some 7α- and 7β-(arylalkyl)dihydrocodeines.

The preparation of 7α-monoalkyl-substituted derivatives of dihydrocodeinone, by use of different methodology, was recently reported by us.[6] These compounds did not have potent narcotic agonist activity. The 7α-arylalkyl derivative **8**, prepared in the course of this present work, was likewise inactive. To further explore structure–activity relations, the corresponding 7β-arylalkyl derivative **17**, which has a 6α,7α-oxymethylene ring, was prepared. Unexpectedly, this compound was found to be a very potent narcotic agonist. In light of this result, other 7β-(4-phenylbutyl) derivatives were prepared with either a hydroxymethyl or methyl group in the 7α-position.

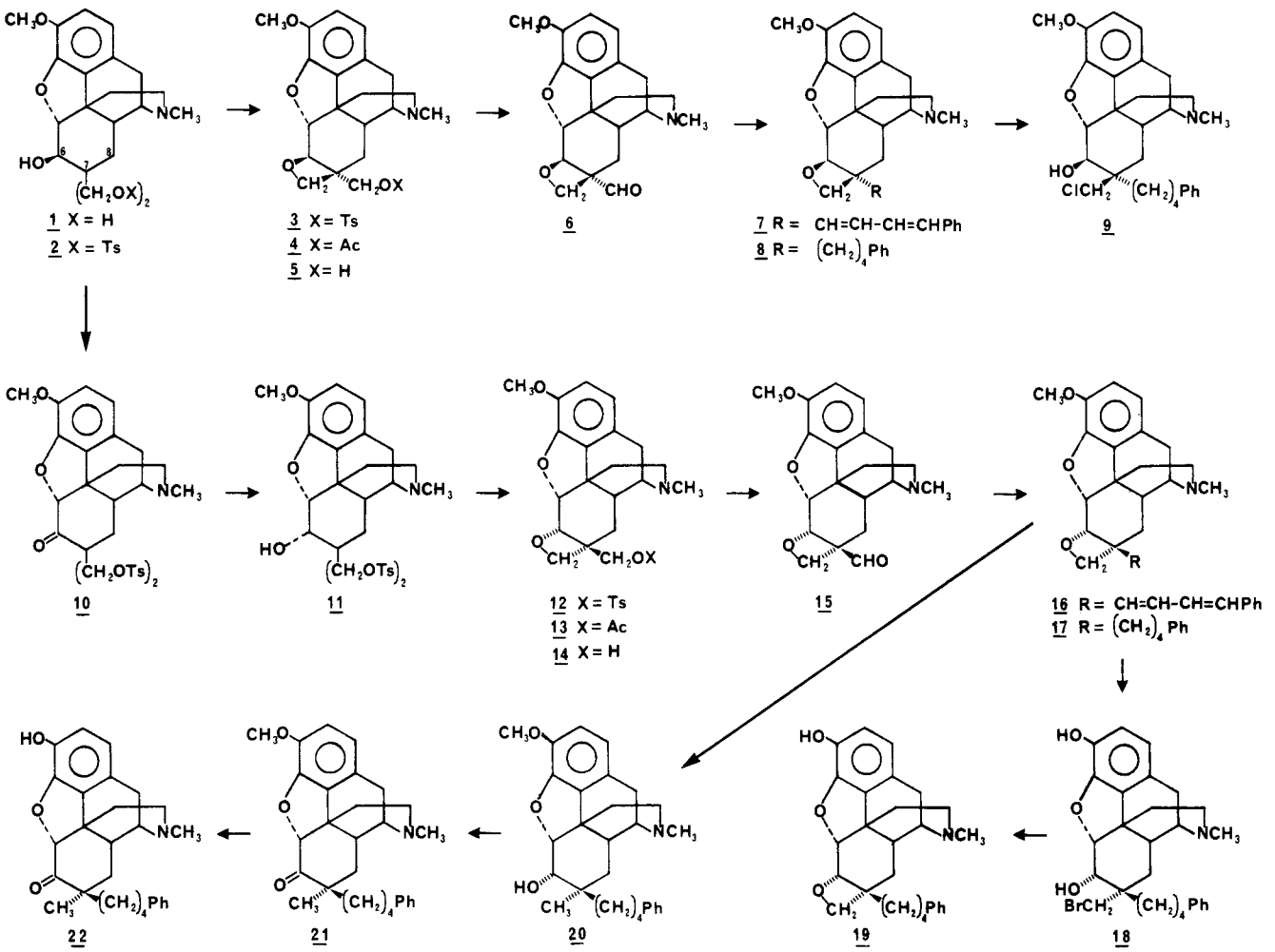
We previously reported that treatment of ditosylate **2** with $LiEt_3BH$ at reflux yielded 6β,7β-(oxymethylene)-7α-methyldihydroisocodeine.[4] More recently, we found that treatment of **2** with dilute NaOH in refluxing 2-butanone results in closure to a 6β,7β-oxetane ring with retention of the 7α-tosyloxy function to give **3** (Scheme I). Displacement of the tosyl group in **3** with NaOAc gave **4** which was hydrolyzed to 7α-hydroxymethyl compound **5**. Oxidation to formyl derivative **6** followed by Wittig condensation with cinnamyltriphenylphosphorane gave a moderate yield of diene **7**. Hydrogenation of **7**, in the presence of a trace of HCl, gave a mixture of the desired product **8** together with oxymethylene-cleaved material **9**.[7] Compound **8** did not show narcotic agonist activity at 10 mg/kg in the mouse writhing assay.

The introduction of the same arylalkyl group into the 7β-position was accomplished in the following manner. Ditosylate **2** was smoothly oxidized to crystalline 6-oxo compound **10** in good yield by using Me_2SO–trifluoroacetic anhydride (TFAA).[8] Sodium borohydride reduction of **10** gave predominantly the 6α-ol **11**, with only traces of the 6β isomer **2** being observed. Ring closure to the α-oxetane **12**, followed by tosylate displacement with acetate and hydrolysis, yielded **14**. Oxidation of **14** to **15** and, then, Wittig condensation gave diene **16**. Catalytic reduction of **16**, in the absence of HCl, proceeded very slowly to eventually give a moderate yield of saturated compound

(1) Analgesic Narcotic Antagonists. 13. For part 12 see: Polazzi, J. O. *J. Org. Chem.* **1981**, *46*, 4262.
(2) Kotick, M. P., Leland, D. L.; Polazzi, J. O.; Schut, R. N. *J. Med. Chem.* **1980**, *23*, 166.
(3) Bentley, K. W. *Aklaoids (N.Y.)* **1971**, *13*, 1. Lewis, J. W.; Bentley, K. W.; Cowan, A. *Annu. Rev. Pharmacol.* **1971**, *11*, 241.
(4) Leland, D. L.; Kotick, M. P. *J. Med. Chem.* **1981**, *24*, 717.
(5) Mannich, C.; Schulte, K. *Arch. Pharm.* **1938**, *276*, 593.
(6) Kotick, M. P.; Leland, D. L.; Polazzi, J. O.; Howes, J. F.; Bosquet, A. R. *J. Med. Chem.* **1981**, *24*, 1445.
(7) Oxetane rings are very susceptible to acid catalyzed ring opening. See: Searles, S. In "Heterocyclic Chemistry; Heterocyclic Compounds with Three- and Four-membered Rings"; Weissberger, A., Ed; Wiley: New York, 1964; Part II, Chapter 9.
(8) Omura, K.; Sharma, A. K.; Swern, D. J. *J. Org. Chem.* **1976**, *41*, 957. Huang, S. L.; Omura, K.; Swern, D. J. *Ibid.* **1976**, *41*, 3329.

0022-3263/83/1948-1813$01.50/0

Scheme I

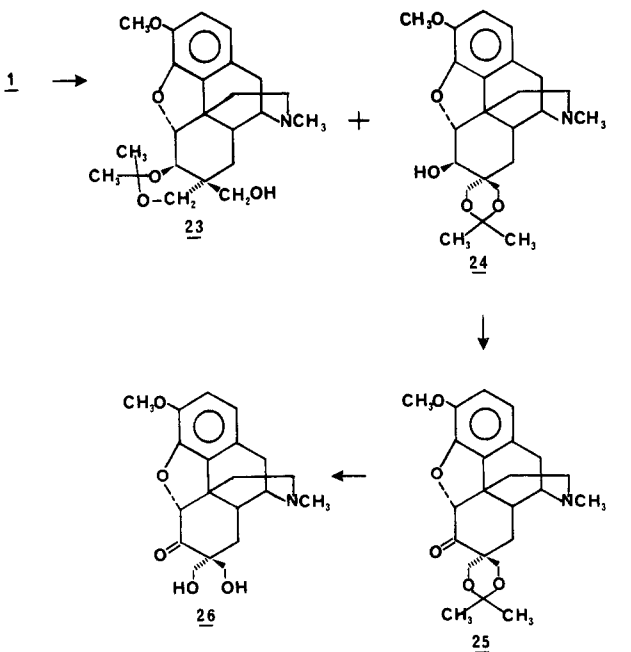


17. Compound **17** was found to be a potent narcotic agonist with an ED_{50} in the mouse writhing assay of about 0.003 mg/kg.

Treatment of **17** with HBr at reflux resulted in cleavage of the oxymethylene ring concurrent with removal of the 3-*O*-methyl group to give 6α-hydroxy-7α-(bromomethyl) compound **18**. Reclosure of the 6α,7α-oxetane ring by using dilute NaOH in hot dioxane yielded **19**. Alternatively, cleavage of the 6α,7α-oxetane ring to give 7α-methyl compound **10** was accomplished by the use of a 3:1 mixture of $LiAlH_4$–$AlCl_3$. Subsequent oxidation of the 6-hydroxy function to **21** was followed by O-demethylation go give **22**.

Having established that the presence of an arylalkyl moiety in the 7β-position confers potent narcotic agonist activity, we explored methods for the preparation of related compounds. Reaction of **1** with acetone in the presence of *p*-TsOH yielded a major (**23**) and a minor (**24**) product which could be resolved by chromatography (Scheme II). Examination of this reaction mixture by TLC several minutes after initiation showed that the minor product **24** was formed first but gradually gave rise to an equilibrium mixture with major product **23**.[9] The structure of the minor isomer was established by Me_2SO–TFAA oxidation to ketone **25**. Oxidation of the secondary alcohol at C6 was confirmed by the change in the NMR signal observed for H5 from a doublet (**24**) to a singlet (**25**).

Scheme II

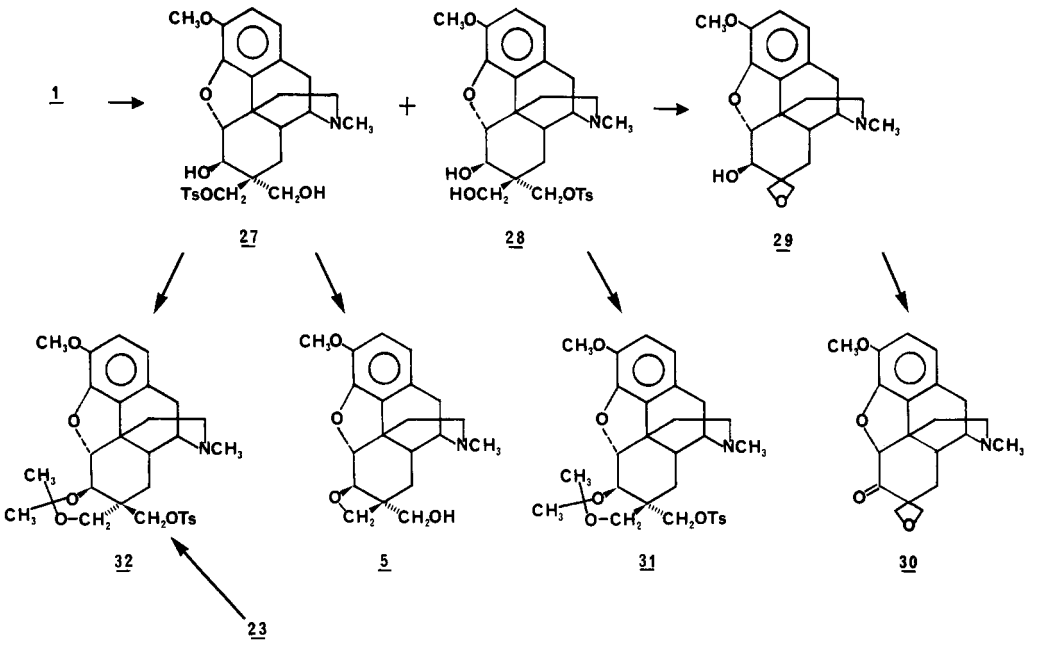


Similar oxidation of major product **23** gave aldehyde **33**, whose NMR spectra showed no change in the multiplicity for H5 and an aldehyde proton signal at low field.

The major isopropylidination product **23** has the 2,2-dimethyl-1,3-dioxolane ring transfused to the morphinan nucleus through the secondary 6β-hydroxy and primary

(9) For a discussion on the formation of fused cyclic acetals with 1,3-dioxolane ring systems see: Stoddart, J. F. "Stereochemistry of Carbohydrates"; Wiley-Interscience: New York, 1971; Chapter 5.

Scheme III



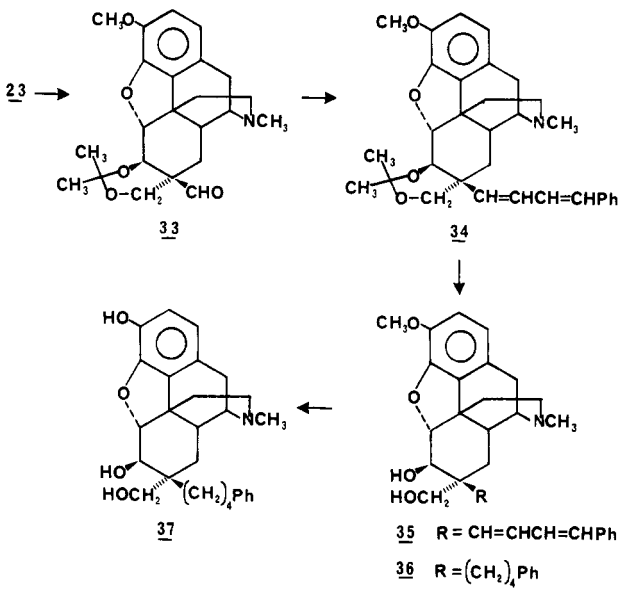
7α-hydroxymethyl functions. This assignment is based on several observations (see Scheme III). Treatment of 1 with 1.1 molar equiv of *p*-TsCl in pyridine gave, in addition to ditosylate 2 and unreacted starting material, a major and minor monotosylate. Treatment of the major tosylate 27 with dilute base yielded an oxetane which was identical with 5 obtained above. Similar reaction of the minor tosylate with base gave a new product, 29. Compound 29 was shown to be a spirooxetane derivative by oxidation to ketone 30. The NMR signal for H5 in 30 was observed as a singlet in contrast to the doublet for H5 in 29. The closure of the major monotosylate 27 to oxetane–alcohol 5, in contrast to the closure of 28 to spiro oxetane 29, demonstrates that in the major monotosylate the tosyloxy group is attached to the 7β-hydroxymethyl function.

Isopropylidination of major β-tosylate 27 gave 32 which was identical with material prepared from the reaction of the major isopropylidene compound 23 with *p*-TsCl. This derivative 32 was different from that prepared by reaction of minor tosylate 28 with acetone under acidic conditions. Thus, it is conclusively demonstrated that 2,2-dimethyl-1,3-dioxolane ring formation from 1 yields, as the thermodynamic product, the isomer in which the acetal ring is trans fused between the primary 7α-hydroxymethyl group and the secondary 6β-ol.

Oxidation of the 7β-hydroxymethyl group of 23 gave aldehyde 33 which was condensed with the Wittig reagent as previously described to give 34 (Scheme IV). The isopropylidene group was cleaved from the crude reaction product by acid treatment and the resultant dihydroxy derivative 35 catalytically hydrogenated to give 36. Treatment of 36 with HBr at reflux gave a good yield of 3-hydroxy compound 37. Both compounds 36 and 37 were potent narcotic agonists.

The facile formation of oxetane derivatives from 7,7-bis(hydroxymethyl)dihydroisocodeine (1), via the ditosylate 2, has enabled the stereospecific introduction of lipophilic groups into the 7α- or 7β-position of the morphine nucleus. The presence of the 4-phenylbutyl group in the 7β-position resulted in potent narcotic agonist activity. In contrast, similar substitution in the 7α-position did not give active compounds. The results of pharmacological assays with the compounds reported in this work and those containing other 7β-arylalkyl and 7β-alkyl groups, as well as 17-(cycloalkylmethyl) moieties, will be reported.

Scheme IV



Experimental Section[10]

Methods have previously been described.[2,4] Processing in the usual manner implies that the combined organic phases were washed with dilute NH_4OH, dried ($MgSO_4$), filtered, and evaporated at a 40–45 °C bath temperature. The residue was further dried under high vaccum at a 50–60 °C bath temperature. Column chromatography was carried out over silica gel 60 G (E. Merck) by using $CHCl_3$–MeOH mixtures containing 0.25–1% v/v concentrated NH_4OH. NMR spectra were determined in $CDCl_3$ unless otherwise noted.

4,5α-Epoxy-3-methoxy-17-methyl-7α-[(tosyloxy)methyl]-6β,7β-(oxymethylene)morphinan (3). A solution of 2 (16.3 g, 24 mmol) in 2-butanone (200 mL) containing 1 N NaOH (25 mL)

(10) The systematic nomenclature of the compounds included in this report is quite complex, and trivial alternatives have been utilized throughout. For example, the current *Chemical Abstracts* index name for 8 is based on the isoquinoline ring system and is [8*R*-(4b*S**,8α,8aβ,9aα,11aα,11bβ)]-5,6,7,8,8a,9,9a,10,11a,11b-decahydro-1-methoxy-7-methyl-9a-(4-phenylbutyl)-4,8-methanobenzofuro[3,2-*e*]oxeto[2,3-*g*]isoquinoline. We are indebted to Dr. K. L. Loening, Nomenclature Director, CAS, for his advice in this matter.

was refluxed for 2 h. After concentration, the residue was partitioned between dilute NH_4OH and $CHCl_3$. Processing of the $CHCl_3$ extracts in the usual fashion gave 11.0 g (95%) of a glass which contained ca. 90% of **3** as indicated by TLC. This glass was used without further purification in the succeeding reaction. Material prepared in another reaction was purified by chromatography to give a 73% yield of homogeneous **3**: NMR δ 7.87–7.27 (m, 4 H, tosyl aromatic), 6.73 (m, 2 H, H1 and H2), 4.47 (d, 2 H, J = 5 Hz), 4.30 (q, 2 H), 3.90 (s, 3 H, CH_3O), 2.48 (s, 6 H, CH_3N, tosyl CH_3).

7α-(Acetoxymethyl)-4,5α-epoxy-3-methoxy-17-methyl-6β,7β-(oxymethylene)morphinan (4). A mixture of **3** (2.5 g, 5 mmol) and NaOAc (0.6 g, 7.5 mmol) in DMF (75 mL) was heated in an oil bath at 100 °C while under argon for 18 h. The mixture was evaporated under high vacuum and the residue partitioned between dilute NH_4OH and PhMe. Evaporation of the organic phase gave 1.87 g (97%) of **4** as a glass which contained traces of **5** as indicated by TLC; NMR δ 1.83 (s, 3 H, CH_3COO).

4,5α-Epoxy-7α-(hydroxymethyl)-3-methoxy-17-methyl-6β,7β-(oxymethylene)morphinan (5). A solution of **4** (3.25 g, 8.4 mmol) in MeOH (50 mL) was stirred with NaOMe (0.68 g, 12.6 mmol) for 30 min. The solution was evaporated to dryness and the residue partitioned between H_2O and $CHCl_3$. Processing in the usual fashion gave 2.65 g of foam which was chromatographed to yield 1.90 g (66%) of **5** as a foam. This foam was converted to the *d*-tartrate salt which gave crystals of the tartrate of **5**: mp, sinters at 170 °C, melts at 198–218 °C with foaming (from aqueous EtOH). Anal. Calcd for $C_{20}H_{25}NO_4 \cdot C_4H_6O_6$: C, 58.41; H, 6.33; N, 2.64. Found: C, 58.80; H, 6.22; N, 2.82.

4,5α-Epoxy-7α-formyl-3-methoxy-17-methyl-6β,7β-(oxymethylene)morphinan (6). A solution of trifluoroacetic anhydride (1.97 mL, 14.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of Me_2SO (1.32 mL, 18.6 mmol) in CH_2Cl_2 (15 mL) under argon at −60 °C. After this mixture was stirred for 10 min, a solution of **5** (3.2 g, 9.3 mmol) in CH_2Cl_2 (50 mL) was added slowly dropwise at −60 °C. The mixture was stirred for 90 min at dry ice–acetone bath temperature and TEA (2 mL) added dropwise. The solution was warmed to room temperature and washed with several portions of dilute NH_4OH. Processing gave 3.0 g of a foam which was chromatographed. First eluted was 2.3 g (72%) of **6** which was obtained as a foam; NMR δ 9.55 (s, 1 H, 7α-CHO). Continued elution gave 0.9 g (28%) of recovered starting material **5**.

4,5α-Epoxy-3-methoxy-17-methyl-7α-(4-phenyl-1,3-butadienyl)-6β,7β-(oxymethylene)morphinan (7). A suspension of 50% NaH (641 mg, 13.3 mmol) in mineral oil was washed with hexane under an atmosphere of argon, and then Me_2SO (10 mL) was added. The mixture was heated at 60–70 °C until the evolution of H_2 ceased (ca. 30 min),[11] it was cooled to 25 °C, and a solution of triphenylcinnamylphosphonium chloride[12] (5.54 g, 13.3 mmol) in Me_2SO (50 mL) was added dropwise. The deep red solution was stirred 10 min and **6** (2.28 g, 6.7 mmol) in Me_2SO (50 mL) added rapidly dropwise. The mixture was stirred for 30 min at ambient temperature and then heated at 65–70 °C for 30 min. The mixture was cooled and diluted with water, and the resulting solution was adjusted to ca. pH 3 with concentrated HCl. After extraction with three portions of PhMe, the solution was made basic with NH_4OH and again extracted with PhMe. The organic extracts of the basic solution were evaporated to give 4.24 g of a red syrup which consisted of a major and minor alkaloidal product. Chromatography gave 1.02 g (35%) of the pure major product **7** as a foam. Continued elution gave an additional 0.74 g of a double bond isomeric mixture of **7** for an overall yield of 60%. Crystallization of the initially eluted pure isomer from EtOH gave an analytical sample of **7**: mp, sinters at 76 °C, melts at 84–86 °C; mass spectrum, m/e (relative intensity) 441 (M^+, 100), 412 (49). Anal. Calcd for $C_{29}H_{31}NO_3$: C, 78.88; H, 7.08; N, 3.17. Found: C, 78.55; H, 7.17; N, 2.98.

4,5α-Epoxy-3-methoxy-17-methyl-7α-(4-phenylbutyl)-6β,7β-(oxymethylene)morphinan (8) and 7β-(Chloromethyl)-4,5α-epoxy-3-methoxy-17-methyl-7α-(4-phenylbutyl)morphinan-6β-ol (9). A solution of **7** (1.0 g) in 95% EtOH was made slightly acidic with HCl and then hydrogenated over 10% Pd/C (0.4 g) at an initial pressure of 50 psi for 3 h. The catalyst was removed by filtration, the filtrate evaporated, and the residue dissolved in H_2O. After the addition of NH_4OH, the mixture was extracted with $CHCl_3$. Processing in the usual manner gave 1.1 g of a foam which was chromatographed. Eluted first from the column was 509 mg (47%) of **9** which was obtained as a foam on evaporation: NMR δ 7.23 (s, 5 H, Ph), 6.73 (s, 2 H, H1 and H2), 4.52 (d, 1 H, H5, J = 7 Hz); mass spectrum, m/e (relative intensity) 483 (38), 481 (100).

Continued elution followed by evaporation of homogeneous fractions gave 293 mg (29%) of crystalline **8** which was recrystallized from EtOAc to give shiny white crystals: mp 144–145 °C; NMR δ 7.5–7.0 (m, 5 H, Ph), 6.72 (m, 2 H, H1 and H2), broad s at 4.63 and 4.48 for 1 H each and at 4.3 for 2 H; mass spectrum, m/e (relative intensity) 445 (M^+, 100), 414 (30), 388 (26). Anal. Calcd for $C_{29}H_{35}NO_3$: C, 78.17; H, 7.92; N, 3.14. Found: C, 78.02; H, 8.00; N, 3.02.

7,7-Bis[(tosyloxy)methyl]-4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one (10). A solution of crude **2** (66.6 g, 99.4 mmol) in CH_2Cl_2 (250 mL) was added dropwise under argon to a mixture prepared from Me_2SO (14.2 mL, 200 mmol) in CH_2Cl_2 (100 mL) and TFAA (21.2 mL, 150 mmole in CH_2Cl_2 (70 mL) as reported above for **6**. The mixture was stirred in a dry ice–acetone bath for 90 min, TEA (40 mL) was added, and the mixture was allowed to warm to room temperature. The solution was evaporated, and the residue was dissolved in $CHCl_3$ and washed three times with dilute NH_4OH. Evaporation of the dried organic phase gave a foam which crystallized from 95% EtOH to give 53.8 (81%) of **10** as white crystals, mp 150–153 °C. Recrystallization from 95% EtOH gave analytically pure **10**: mp 155–156 °C; NMR δ 7.2–7.9 (m, 8 H, tosyl H's), 7.70 (s, 2 H, H1 and H2), 4.47 (s, H5). Anal. Calcd for $C_{23}H_{37}NO_9S_2$: C, 61.15; H, 5.58; N, 2.10. Found: C, 61.18; H, 5.58; N, 1.85.

7,7-Bis[(tosyloxy)methyl]-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol (11). A solution of **10** (20.0 g, 30 mmol) in a mixture of 95% EtOH (200 mL) and $CHCl_3$ (100 mL) was cooled in an ice bath and $NaBH_4$ (3.4 g, 90 mmol) added portionwise over 10 min. The mixture was stirred for 90 min in the cold, excess HOAc was added to destroy the hydride, and the solution was evaporated. The residue was partitioned between $CHCl_3$ and dilute NH_4OH and further processed in the usual fashion. Evaporation gave a quantitative yield of **11** as a foam which contained traces of 6β-ol **2** and other impurities; NMR δ 4.41 (d, 1 H, H5, J = 5.5 Hz). This material was converted to **12** without further purification.

4,5α-Epoxy-3-methoxy-17-methyl-7β-[(tosyloxy)methyl]-6β,7β-(oxymethylene)morphinan (12). Compound **11** (20.0 g, 29.9 mmol) in dioxane (600 mL) containing 1 N NaOH (90 mL) was stirred in a preheated oil bath at 65–70 °C for 1 h. The mixture was evaporated to a small volume and the residue processed with $CHCl_3$ in the usual fashion. Evaporation of the $CHCl_3$ gave 13.8 g (93%) of **12** as a foam which contained trace impurities. Material purified by chromatography had the following NMR signals: δ 7.93–7.26 (q, tosyl H's), 6.68 (m, H1 and H2), 4.60 (pair of d, 2 H, 7α-CH_2O, J = 8, 24 Hz), 4.26 (d, 1 H, H5, $J_{5,6}$ = 5.5 Hz), 4.02 (s, 2 H, CH_2OTs), 3.90 (CH_3O), 3.42 (d, 1 H, H6).

7β-(Acetoxymethyl)-4,5α-epoxy-3-methoxy-17-methyl-6α,7α-(oxymethylene)morphinan (13). A mixture of **12** (13.8 g, 27.7 mmol) and NaOAc (3.45 g, 41.6 mmol) in DMF (325 mL) was heated for 18 h at 80 °C under an argon atmosphere. The DMF was removed under high vaccum, and the residue was dissolved in $CHCl_3$ and washed with dilute NH_4OH. Further processing gave 12.3 g of **13** as a crystalline solid. Another similar reaction gave a 93% yield of **13** which was crystallized from EtOH to give an analytical sample of **13**, mp 149–150 °C. Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.42; H, 7.38; N, 3.50.

4,5α-Epoxy-7β-(hydroxymethyl)-3-methoxy-17-methyl-6α,7α-(oxymethylene)morphinan (14). To a solution of **13** (12.3 g, 32 mmol) in MeOH (200 mL) was added 1 N NaOH (25 mL), and the mixture was stirred for 1 h. The solution was evaporated and the residue partitioned between $CHCl_3$ and dilute NH_4OH. Further processing gave 12.6 g of a foam which was predominantly **14**. Crystallization from EtOAc–Et_2O gave 8.4 g (77%) of **14**, mp 179–181 °C. Recrystallization from EtOH gave an analytical

(11) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1345. Greenwald, R.; Chaykovsky, M; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128.
(12) McDonald, R. N.; Campbell, T. W. *J. Org. Chem.* **1959**, *24*, 1969.

sample of **14**: mp 180–181.5 °C; NMR δ 3.63 (s, 2 H, CH_2OH); mass spectrum, *m/e* (relative intensity) 343 (M^+, 100), 272 (77). Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.67; H, 7.62; N, 4.22.

4,5α-Epoxy-7β-formyl-3-methoxy-17-methyl-6α,7α-(oxymethylene)morphinan (15). A solution of **14** (17.2 g, 50 mmol) in CH_2Cl_2 (225 mL) was oxidized by using Me_2SO (100 mmol) and TFAA (75 mmol) in CH_2Cl_2 (90 mL) for 90 min as described above. After the addition of TEA (20 mL) and processing in the usual fashion, 15.2 g (89%) of **15** was obtained as a foam: NMR δ 9.10 (s, CHO), 6.67 (m, aromatic), 5.25 (d, 1 H, CHO, J = 7 Hz), 4.53 (m, 2H, CHO and H5), 3.87 (CH_3O), 3.45 (d, H6, J = 5.5 Hz).

4,5α-Epoxy-3-methoxy-17-methyl-7β-(4-phenyl-1,3-butadienyl)-6α,7α-(oxymethylene)morphinan (16). Compound **16**, as a mixture of double bond isomers, was prepared as described above for **7** from 50% NaH dispersion (2.92 g, 60.9 mmol), Me_2SO (75 mL), and the phosphonium chloride (25.3 g, 60.9 mmol) in Me_2SO (200 mL) with addition of the aldehyde **15** (18.9 g, 55.3 mmol) in Me_2SO (350 mL).

Further processing followed by extraction of the basic solution with $CHCl_3$ gave 22.7 g of a foam which contained two major alkaloidal spots in addition to traces of Ph_3PO. The mixture was chromatographed. Partial resolution of the alkaloidal material provided fractions for further characterization. The faster migrating component crystallized from EtOAc to give gray crystals: mp 188–189 °C; NMR δ 7.25 (m, 5 H, phenyl), 6.70–5.56 (m, 6 H, H1, H2 and CH=CHCH=CH), 4.86 (q, 2 H, 7α-CH_2O, J = 7, 26 Hz), 4.28 (2, 1 H, H5, J = 5 Hz), 3.87 (CH_3O), 3.52 (d, 1 H, H6); mass spectrum, *m/e* (relative intensity) 441 (M^+, 59), 412 (58), 91 (100). Anal. Calcd for $C_{29}H_{31}NO_3$: C, 78.88; H, 7.08; N, 3.17. Found: C, 78.60; H, 7.36; N, 3.46.

The slower migrating fraction had the following NMR signals: δ 7.30 (2, 5 H, phenyl), 6.68 (m, 2 H, H1 and H2), 6.53–5.36 (m, 4 H, CH=CHCH=CH), 4.85 (q, 2 H, 7α-CH_2O, J = 7, 22 Hz), 4.47 (d, 1 H, H5, J = 4.5 Hz), 3.90 (CH_3O and H6).

4,5α-Epoxy-3-methoxy-17-methyl-7β-(4-phenylbutyl)-6α,7α-(oxymethylene)morphinan (17). A solution of **16** (11.5 g, 26 mmol) in 95% EtOH (250 mL) containing 10% Pd/C (2.5 g) was hydrogenated at an initial pressure of 50 psi and 50 °C for 24 h. The catalyst was removed and the filtrate evaporated to dryness. The residue was redissolved in 95% EtOH (200 mL) and H_2O (50 mL), fresh 10% Pd/C (2.5 g) added, and the mixture hydrogenated at 50 psi and 50 °C for 3 days. The workup gave 9.5 g (82%) of **17** as a foam which contained trace impurities. Material prepared in another reaction was purified by chromatography: NMR δ 7.23 (m, 5 H, phenyl), 6.67 (m, 2 H, H1 and H2), 4.58 (q, 2 H, 7α-CH_2O, J = 7, 15 Hz), 4.15 (d, 1 H, H5, J = 5 Hz), 3.87 (CH_3O), 3.38 (d, 1 H, H6), 2.42 (CH_3N). Conversion of pure **17** to the *d*-tartrate salt gave material which was recrystallized from EtOH to give shiny white crystals of the *d*-tartrate of **7**, mp 119–121 °C. Anal. Calcd for $C_{29}H_{35}NO_3 \cdot C_4H_6O_6$: C, 66.54; H, 6.94; N, 2.35. Found: C, 66.27; H, 7.16; N, 2.57.

4,5α-Epoxy-17-methyl-7β-(4-phenylbutyl)-6α,7α-(oxymethylene)morphinan-3-ol (19). A mixture of free base **17** (1.70 g, 3.8 mmol) and 48% HBr (20 mL) was refluxed in a 140 °C preheated oil bath for 15 min. The solution was cooled, diluted with H_2O, and made basic by the addition of concentrated NH_4OH. Extraction with EtOAc gave 2.07 g of **18** as a foam. The foam was dissolved in dioxane (50 mL) and 1 N NaOH (11 mL) added. The mixture was stirred at 65–70 °C while under argon for 2 h. After evaporation and dilution with water, the mixture was adjusted to ca. pH 8 with HOAc and extracted with $CHCl_3$. Processing gave a foam (1.83 g) which was purified by chromatography. Homogeneous fractions were pooled and evaporated to give 0.87 g (53%) of **19** as foam: NMR δ 7.16 (m, 5 H, phenyl), 6.56 (m, 2 H, H1 and H2), 5.67 (br, 1 H, HO), 4.56 (q, 2 H, 7α-CH_2O, J = 8, 16 Hz), 4.17 (d, 1 H, H5, J = 5 Hz), 3.40 (d, 1 H, H6). The *d*-tartrate salt of **19**: mp, sinters at 90 °C, melts at 116–125 °C, resolidifies, remelts at 160–165 °C (twice crystallized from EtOH). Anal. Calcd for $C_{28}H_{33}NO_3 \cdot C_4H_6O_6$: C, 66.08; H, 6.76; N, 2.41. Found: C, 65.86; H, 6.83; N, 2.37.

7α,17-Dimethyl-4,5α-epoxy-3-methoxy-7β-(4-phenylbutyl)morphinan-6α-ol (20). To a suspension of $AlCl_3$ (1.29 g, 9.6 mmol) in Et_2O (100 mL) under argon, cooled in an ice bath, was added $LiAlH_4$ (1.10 g, 28.9 mmol). The mixture was stirred for 30 min in the cold after which a solution of **17** (4.20 g, 9.4 mmol) in Et_2O (200 mL) was added. The mixture was then refluxed for 2 days. The reaction mixture was quenched by the addition of H_2O and 3 N NaOH. After filtration from insoluble material, the filtrate was evaporated, and the residue was diluted with H_2O and extracted with EtOAc. Processing in the usual fashion followed by chromatography gave 2.41 g (57%) of **20** as a glass. Crystallization of a portion of this material from EtOAc–hexane gave crystals, mp 90–93 °C. Drying at 35 °C under high vacuum gave crystals with a melting point of 89–92 °C which were shown by NMR to be the 0.25 solvate of **20** with hexane: NMR δ 7.22 (s, 5 H, phenyl), 6.63 (s, 2 H, H1 and H2), 4.72 (d, 1 H, H5, J = 5 Hz), 3.85 (CH_3O), 3.62 (d, 1 H, H6), 0.87 (s, 7α-CH_3). Anal. Calcd for $C_{29}H_{37}NO_3 \cdot 0.25C_6H_{14}$: C, 78.08; H, 8.70; N, 2.99. Found: C, 77.75; H, 9.04; N, 2.99.

7α,17-Dimethyl-4,5α-epoxy-3-methoxy-7β-(4-phenylbutyl)morphinan-6-one (21). A mixture of Me_2SO (9.6 mmol) and TFAA (7.2 mmol) in CH_2Cl_2 (15 mL) was prepared as above at −60 °C. To this was added **20** (2.14 g, 4.78 mmol) in CH_2Cl_2 (70 mL), and the reaction was conducted in the usual fashion for 90 min. After the addition of TEA (2 mL) and processing in the usual manner, chromatography gave 1.79 g (84%) of **21** as a glass: NMR δ 7.8 (br s, 5 H), 6.61 (s, 2 H), 4.76 (s, 1 H, H5), 3.92 (CH_3O), 2.43 (CH_3N), 0.88 (s, 3 H, 7α-CH_3). A portion of this material was converted to the HCl salt which gave crystals (mp 224–226 °C) from EtOAc. Anal. Calcd for $C_{29}H_{35}NO_3 \cdot HCl$: C, 72.26; H, 7.53; N, 2.90. Found: C, 71.86; H, 7.51; N, 2.74.

7α,17-Dimethyl-4,5α-epoxy-3-hydroxy-7β-(4-phenylbutyl)morphinan-6-one (22). A solution of **21**·HCl (1.43 g, 2.97 mmol) in $CHCl_3$ (60 mL) was added to a solution of BBr_3 (1.82 mL, 19.2 mmol) in $CHCl_3$ (40 mL) cooled in an ice bath under argon. The mixture was stirred for 30 min at ambient temperature and then recooled to 0 °C, and MeOH (5 mL) was added dropwise. The resulting mixture was evaporated, the residue dissolved in H_2O and excess concentrated NH_4OH added. Processing with $CHCl_3$ gave 1.30 g of a foam which was chromatographed to give 0.87 g of recovered **21** followed by 0.50 g (39%) of **22** as a glass: NMR δ 4.70 (s, H5), 2.46 (CH_3N), 0.88 (s, 7α-CH_3). This was converted to the HCl salt which crystallized from MeOH–EtOAc to give **22**·HCl, mp >265 °C. Anal. Calcd for $C_{28}H_{33}NO_3 \cdot HCl$: C, 71.86; H, 7.32; N, 2.99. Found: C, 71.46; H, 7.16; N, 2.80.

4,5α-Epoxy-7,7-bis(hydroxymethyl)-6β,7α-*O*-isopropylidene-3-methoxy-17-methylmorphinan-6β-ol (23) and 4,5α-Epoxy-7,7-bis(hydroxymethyl)-7α,7β-*O*-isopropylidene-3-methoxy-17-methylmorphinan-6β-ol (24). A mixture of the free base of **1** (10.45 g, 28.9 mmol) and *p*-TsOH·H_2O (6.05 g, 28.9 mmol) in acetone (200 mL) was stirred for 16 h at room temperature. Molecular sieves (4-Å, 25 g) were then added and stirring continued for an additional 24 h. The suspension was made basic by the addition of concentrated NH_4OH and filtered, and the filtrate was evaporated. The residue was partitioned between H_2O and $CHCl_3$ and further processed to a foam which was chromatographed. First eluted was 2.20 g (19%) of minor product **24**; NMR δ 1.38 (d, 6 H, gem CH_3's, J = 7 Hz). Continued elution followed by pooling of appropriate fractions and evaporation gave 8.40 g (72%) of **23** as a foam; NMR δ 1.33 (d, 6 H, gem CH_3's, J = 8 Hz).

4,5α-Epoxy-7,7-bis(hydroxymethyl)-7α,7β-*O*-isopropylidene-3-methoxy-17-methylmorphinan-6-one (25). An oxidation mixture was prepared from Me_2SO (33 mmol) and TFAA (24 mmol) in CH_2Cl_2 (35 mL) as previously described. To this was added **24** (6.50 g, 16 mmol) in CH_2Cl_2 (100 mL), and the mixture was stirred 1 h in the cold. After the addition of TEA and processing in the usual manner, the residue was crystallized from EtOAc–hexane to give 3.47 g (53%) of **25**. Recrystallization from EtOH gave pure **25**: mp 158–159 °C; NMR δ 6.67 (m, 2 H, H1 and H2), 4.83 (s, 1 H, H5), 4.10 (m, 4 H, 7-CH_2O's), 3.97 (CH_3O), 2.47 (CH_3N), 1.43 (s, 6 H, *gem*-CH_3's). Anal. Calcd for $C_{23}H_{29}NO_5$: C, 69.15; H, 7.32; N, 3.51. Found: C, 69.38; H, 7.22; N, 3.33.

7,7-Bis(hydroxymethyl)-4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one (26). A mixture of **25** (2.17 g, 5.4 mmol) and 1 N HCl (25 mL) in EtOH (25 mL) was gently boiled on the steam bath for 30 min and then evaporated. The residue was diluted with H_2O, concentrated NH_4OH added, and the mixture extracted with $CHCl_3$. Evaporation of the extracts gave a solid residue which was crystallized from EtOH to give 1.14 g (58%)

of **26**. Two recrystallizations from EtOH–H_2O gave an analytical sample of **26**: mp 202–205 °C; NMR (Me_2SO-d_6) δ 6.70 (m, 2 H, H1 and H2), 4.93 (s, 1 H, H5), 3.83 (CH_3O), 2.33 (CH_3N). Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.84; H, 7.01; N, 3.90. Found: C, 66.73; H, 7.13; N, 3.77.

Monotosylation of 1. The HCl salt of **1** (1.99 g, 5 mmol) was azeotroped several times with pyridine and finally dissolved in pyridine (50 mL). The mixture was cooled and *p*-TsCl (1.95 g, 5.5 mmol) added. After the mixture was stirred overnight at room temperature, several chips of ice were added, and the mixture was evaporated. The residue was azeotroped with H_2O–EtOH, dissolved in H_2O, and extracted with $CHCl_3$. Processing gave a pink foam which was chromatographed. Elution of **2** (0.43 g, 13%) was followed by the elution of **27** (0.69 g, 27%) and then **28** (0.30 g, 12%).

Crystallization of **27** from EtOH gave pure material: mp 125–130 °C; NMR δ 7.53 (q, 4 H, tosyl), 6.76 (s, H1 and H2), 4.67–4.39 (complex m), 3.76 (s, CH_3O), 2.45 (s, CH_3N), 2.36 (s, tosyl CH_3). Anal. Calcd for $C_{27}H_{33}NO_7S$: C, 62.89; H, 6.45; N, 2.72. Found: C, 63.18; H, 6.43; N, 3.07.

Compound **28** crystallized from EtOH to give white needles: mp 122–126 °C; NMR δ 7.47 (q, 4 H, tosyl), 6.76 (s, H1 and H2), 4.62 (d, J = 7 Hz), 3.80 (s, CH_3O), 2.40 (s, CH_3N), 2.36 (s, tosyl CH_3). Anal. Found: C, 62.63; H, 6.25; N, 3.07.

7,7-(Oxydimethylene)-4,5α-epoxy-3-methoxy-17-methylmorphinan-6β-ol (29). A solution of **28** (4.22 g, 8.2 mmol) in dioxane (75 mL) was immersed in an oil bath preheated to 75 °C, and four portions of 1 N NaOH (8.2 mL) were added in 15-min intervals, with an additional portion being added at 2 h from the start of the reaction. The mixture was heated for a total of 4.5 h, cooled, and then evaporated to a small volume. Dilution with H_2O followed by extraction with $CHCl_3$ and processing in the usual manner gave a foam which was chromatographed. Homogeneous fractions were pooled to give 2.07 g (74%) of **29** as a foam. Crystallization from EtOAc gave pure **29**: mp 180–182 °C; NMR δ 6.67 (s, 2 H, H1 and H2), 4.76 (m, 2 H), 4.12 (m, 2 H), 4.10 (d, 2 H); mass spectrum, m/e (relative intensity) 343 (M^+, 100), 286 (28). Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 70.14; H, 7.52; N, 4.32.

7,7-(Oxydimethylene)-4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one (30). An oxidation mixture was prepared at −60 °C under argon from Me_2SO (10 mmol) in CH_2Cl_2 (15 mL) and TFAA (7.5 mmol) in CH_2Cl_2 (15 mL). Compound **29** (1.70 g, 4.95 mmol) in CH_2Cl_2 (40 mL) was added dropwise and the mixture kept at −60 °C for 90 min. After the addition of TEA (2.0 mL), processing gave 1.62 g of a foam which was chromatographed. Fractions containing **30** were pooled to give 1.34 g (79%) of a foam. Crystals of **30** (mp 228–230 °C) were obtained from EtOAc: NMR δ 6.66 (s, 2 H), 5.10 (d, 1 H, J = 6 Hz), 4.87–4.26 (m, 2 H), 4.77 (s, 1 H, H5), 4.05 (d, 1 H, J = 6 Hz), 3.92 (CH_3O); mass spectrum, m/e (relative intensity) 341 (M^+, 100). Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.07; H, 6.98; N, 3.88.

4,5α-Epoxy-7β-(hydroxymethyl)-6β,7β-*O*-isopropylidene-3-methoxy-17-methyl-7α-[(tosyloxy)methyl]morphinan-6β-ol (31). To a solution of monotosylate **28** (3.58 g, 6.97 mmol) in dry acetone (75 mL) was added a solution of *p*-TsOH (1.68 g of the monohydrate, 8.83 mmol; previously dried by three evaporations from PhMe) in acetone (30 mL). The mixture was stirred at room temperature, protected from moisture, for 18 h, and then molecular sieves (3-Å, 10 g) were added. After the mixture was stirred for 72 h, TLC indicated ca. 20–30% conversion to a new product. The mixture was filtered and the filtrate made basic with NH_4OH. After evaporation of the filtrate, the residue was partitioned between $CHCl_3$ and dilute NH_4OH. Processing in the usual fashion gave 3.72 g of a foam which was chromatographed. First eluted was 619 mg (16%) of **31** obtained as a syrup: NMR δ 4.42 (d, 1 H, H5, J = 2 Hz), 3.70 (CH_3O), 3.53 (d, H6), 1.33 (d, 6 H, *gem*-CH_3's, J = 4 Hz). Continued elution gave 3.00 g (83%) of recovered **28**.

4,5α-Epoxy-7α-(hydroxymethyl)-6β,7α-*O*-isopropylidene-3-methoxy-17-methyl-7β-[(tosyloxy)methyl]morphinan-6β-ol (32). (A) From 23. A solution of **23** (2.62 g, 6.5 mmol) and *p*-TsCl (1.49 g, 7.8 mmol) in pyridine (30 mL) was stirred overnight at room temperature while protected from moisture. The bulk of the pyridine was then evaporated, the residue diluted with NH_4OH and $CHCl_3$, and processing continued in the usual manner. Evaporation was followed by removal of the remaining pyridine by azeotropic distillation with EtOH–H_2O and then PhMe to give a residue (3.37 g). Chromatography gave 2.80 g (78%) of **32** as a foam, NMR δ 1.23 (s, 6 H, *gem*-CH_3's). This material migrated slower on TLC than did **31** prepared above.

(B) From 27. A solution of **27** (895 mg, 1.7 mmol) in acetone (30 mL) containing *p*-TsOH·H_2O (363 mg, 1.9 mmol) and molecular sieves (3-Å, 3 g) was stirred overnight at room temperature while protected from moisture. The suspension was filtered, made basic by the addition of NH_4OH, and evaporated. The residue was partitioned between dilue NH_4OH and $CHCl_3$ and further processed to give a foam which was chromatographed. First eluted was 270 mg (28%) of **32**, identical with material prepared above. Continued elution gave 517 mg of recovered **27**.

Conversion of 27 to 5. A solution of **27** (0.72 g, 1.4 mmol) in dioxane (30 mL) was stirred with 1 N NaOH (5 mL) for 90 min at 60–70 °C. Evaporation of the solvent followed by processing in the usual manner gave a foam whose NMR spectrum was identical with that obtained for **5** above.

4,5α-Epoxy-7β-formyl-7α-(hydroxymethyl)-6β,7α-*O*-isopropylidene-3-methoxy-17-methylmorphinan-6β-ol (33). To an oxidation mixture prepared from Me_2SO (7.2 mL, 101.8 mmol) in CH_2Cl_2 (80 mL) and TFAA (10.8 mL, 76.4 mmol) in CH_2Cl_2 (30 mL) was added **23** (20.0 g, 50 mmol) in CH_2Cl_2 (400 mL) slowly over a period of 1 h. After the mixture was stirred in the dry ice–acetone bath for 1 h, TEA (20 mL) was added dropwise, and the mixture allowed to warm to room temperature. The solution was evaporated, and the residue was diluted with H_2O and NH_4OH and extracted with $CHCl_3$. Processing in the usual fashion gave 18.0 g (90%) of **33** as a solid residue. Recrystallization from EtOAc–hexane gave 14.4 g of crystals, mp 157–163 °C. Recrystallization from the same solvent pair gave an analytical sample of **33**: mp 169–171 °C; NMR δ 9.86 (br s, CHO), 4.98 (d, 1 H, H5, J = 6 Hz), 3.90 (CH_3O), 2.40 (CH_3N), 1.36 (s, 6 H, *gem*-CH_3's). Anal. Calcd for $C_{23}H_{29}NO_4$: C, 69.15; H, 7.32; N, 3.51. Found: C, 69.24; H, 7.28; N, 3.33.

4,5α-Epoxy-7α-(hydroxymethyl)-3-methoxy-17-methyl-7β-(4-phenyl-1,3-butadienyl)morphinan-6β-ol (35). As previously described above for **7**, a solution of the Wittig reagent was prepared from 50% NaH (661 mg, 13.8 mmol) in Me_2SO (10 mL) with the addition of the phosphonium chloride (5.7 g, 13.8 mmol) in Me_2SO (50 mL). To this was added **33** (5.0 g, 12.5 mmol) in Me_2SO (100 mL). After being heated at 60–70 °C for 30 min, the cooled solution was diluted with water and extracted with PhMe. The organic phases were evaporated, and the residue was dissolved in EtOH (200 mL) and 1 N HCl (50 mL). The mixture was gently boiled on a steam bath for 30 min and then evaporated to a small volume. The acid concentrate was diluted with water and washed several times with PhMe. The aqueous solution was then made basic with concentrated NH_4OH and extracted with several portions of $CHCl_3$. Evaporation gave 4.2 g of a foam which was hydrogenated as described below.

4,5α-Epoxy-7α-(hydroxymethyl)-3-methoxy-17-methyl-7β-(4-phenylbutyl)morphinan-6β-ol (36). A solution of **35** (4.18 g, 9.1 mmol) in 95% EtOH (200 mL) containing concentrated HCl (2 mL) and 10% Pd/C (1.0 g) was hydrogenated at an initial pressure of 50 psi for 6 h. After removal of the catalyst by filtration, the filtrate was evaporated. The residue was dissolved in $CHCl_3$ and washed with dilute NH_4OH, and the organic extracts were further processed to give 3.76 g (89%) of **36** as a crystalline residue. Recrystallization from EtOAc–$CHCl_3$ gave analytically pure **36**: mp 196–198 °C; NMR δ 7.22 (m, 5 H, phenyl), 6.63 (m, 2 H, H1 and H2), 4.47 (d, 1 H, H5, J = 7 Hz), 3.77 (CH_3O), 2.40 (CH_3N); mass spectrum, m/e (relative intensity) 463 (M^+, 100). Anal. Calcd for $C_{29}H_{37}NO_4$: C, 75.13; H, 8.04; N, 3.02. Found: C, 74.96; H, 7.96; N, 2.92.

4,5α-Epoxy-7α-(hydroxymethyl)-17-methyl-7β-(4-phenylbutyl)morphinan-3,6β-diol (37). A suspension of **36** (1.0 g, 2.2 mmol) in 48% HBr (15 mL) was heated at 140 °C for 15 min. The mixture was cooled, made basic with NH_4OH, and extracted with $CHCl_3$. Processing in the usual fashion gave a residue which was chromatographed to give 0.8 g (82%) of **37** as a foam. Crystallization from EtOAc gave pure **37**, mp 192–193 °C. Anal. Calcd for $C_{28}H_{35}NO_4$: C, 74.80; H, 7.85; N, 3.12. Found: C, 74.56; H, 7.82; N, 2.95.

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Registry No. 1, 77793-96-5; 2, 77794-00-4; 3, 85454-93-9; 4, 85454-94-0; 5, 85454-95-1; 5 *d*-tartrate, 85455-27-2; 6, 85454-96-2; 7, 85454-97-3; 8, 85454-99-5; 9, 85454-98-4; 10, 85455-00-1; 11, 85455-01-2; 12, 85455-02-3; 13, 85455-03-4; 14, 85455-04-5; 15, 85455-05-6; 16, 85455-06-7; 17, 85455-07-8; 17 *d*-tartrate, 85455-28-3; 18, 85455-25-0; 19, 85455-08-9; 19 *d*-tartrate, 85455-29-4; 20, 85455-09-0; 21, 85455-10-3; 21·HCl, 85455-12-5; 22, 85455-11-4; 22·HCl, 85455-13-6; 23, 85455-14-7; 24, 85455-26-1; 25, 85455-15-8; 26, 85455-16-9; 27, 85455-17-0; 28, 85455-18-1; 29, 85455-19-2; 30, 85455-20-5; 31, 85455-21-6; 32, 85548-93-2; 33, 85455-22-7; 35, 85479-36-3; 36, 85455-23-8; 37, 85455-24-9; triphenylcinnamylphosphonium chloride, 1530-35-4.

6,7α:14,7β-Bis(oxymethylene)dihydromorphines[1]

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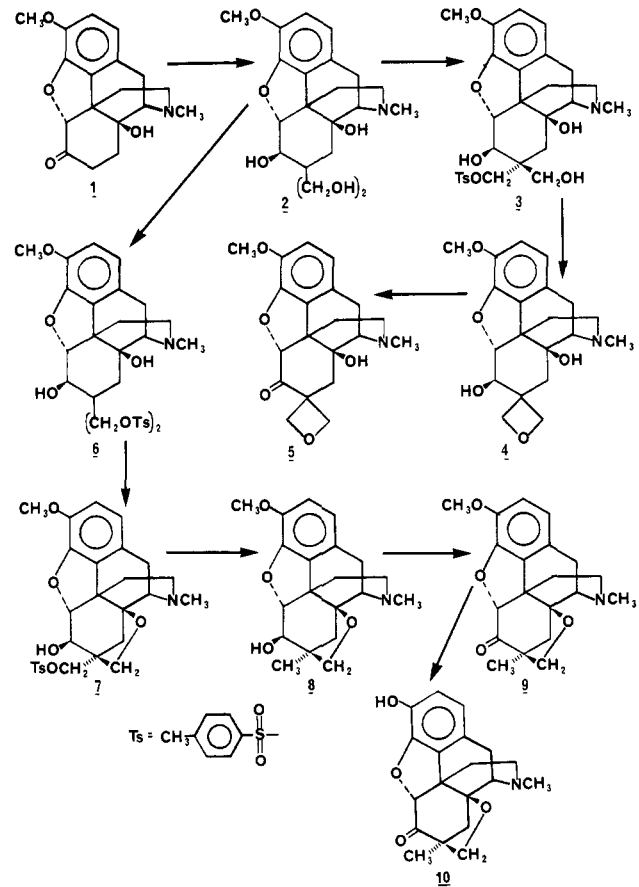
6,7α:14,7β-Bis(oxymethylene)morphinans, which contain seven ring structures within the molecule, were synthesized from 14-hydroxydihydrocodeinone (1). Conversion of 1 to 7,7-bis(hydroxymethyl)-4,5α-epoxy-3-methoxy-17-methylmorphinan-6β,14-diol (2) and then reaction with 1.2 equiv of *p*-TsCl gave 7α-tosyloxymethylene derivative 3. Base treatment of 3 gave 7,7-(oxydimethylene) compound 4 which was oxidized to the C6-oxo derivative 5. Ditosylation of 2 followed by base treatment resulted in formation of 7α-[(tosyloxy)methyl]-14,7β-(oxymethylene)morphinan-6β-ol 7 which was converted to the 3-hydroxy-7α-methyl-6-oxo derivative 10. Displacement of the tosyloxy group in 7 by the 6β-ol resulted in the formation of 6β,7α:14,7β-bis(oxymethylene)morphinan 11. Inversion of the configuration at the C6-hydroxy by oxidation to 14 followed by hydride reduction and base treatment gave 16, the 6α,7α analogue of 11. Treatment of 14 with BBr_3 gave 3-hydroxy-7α-(bromomethylene)morphinan 17 which was reduced with $NaBH_4$ and ring closed to 6α,7α:14,7β-bis(oxymethylene)-4,5-epoxy-17-methylmorphinan-3-ol (19).

The preceding paper of this series[1] described the formation of oxetane rings between the 6- and 7-positions of the morphine nucleus. These intermediates were used to selectively prepare 7α- or 7β-substituted dihydromorphine compounds, of which the 7β series were potent narcotic agonists. The present report resulted from an attempt to extend this work to the 14-hydroxydihydrocodeinone series. The presence of the additional hydroxyl group at the 14β-position in this latter series did not allow the desired transformations to be carried out. This work, however, did result in the synthesis of novel bis(oxymethylene)morphine derivatives which contain seven ring structures within the molecule.

Treatment of 14-hydroxydihydrocodeinone (1) with formaldehyde in the presence of $Ca(OH)_2$ in aqueous dioxane[2] gave a good yield of tetrahydroxy compound 2 (Scheme I). The assignment of the β configuration to the 6-hydroxyl group in 1 is based on our previous work with dihydrocodeinone.[2] Reaction of 2 with 1.2 equiv of *p*TsCl in pyridine gave a 69% yield of 7α-monotosyloxy derivative 3. The predominant formation of the 7α-tosyloxymethyl compound 3 contrasts with our results of a similar reaction in the dihydrocodeinone series.[1] The selectivity observed in this present work is the result of effects introduced by the presence of the 14β-hydroxy function. Base treatment of 3 resulted in the formation of spirooxetane 4 whose structure was chemically confirmed by oxidation to ketone 5.

Ditosylation of 2 to 6, by using 3 equiv of *p*-TsCl, proceeded slowly. The workup of these reaction mixtures with aqueous ammonia caused the fast-migrating 6 to change to a new product, 7, which had intermediate TLC mobility. On a preparative scale, ditosylation of 2 for 1 week was followed by treatment of intermediate 6 with aqueous methanolic sodium hydroxide. After a further workup, a 53% yield of 7 was obtained directly by crystallization from the crude mixture.

Scheme I



(1) Analgesic Narcotic Antagonists. 14. For part 13 see Leland, D. L.; Kotick, M. P. *J. Org Chem.*, previous paper in this issue.
(2) Leland, D. L.; Kotick, M. P. *J. Med. Chem.* **1981**, *24*, 717.

0022-3263/83/1948-1819$01.50/0