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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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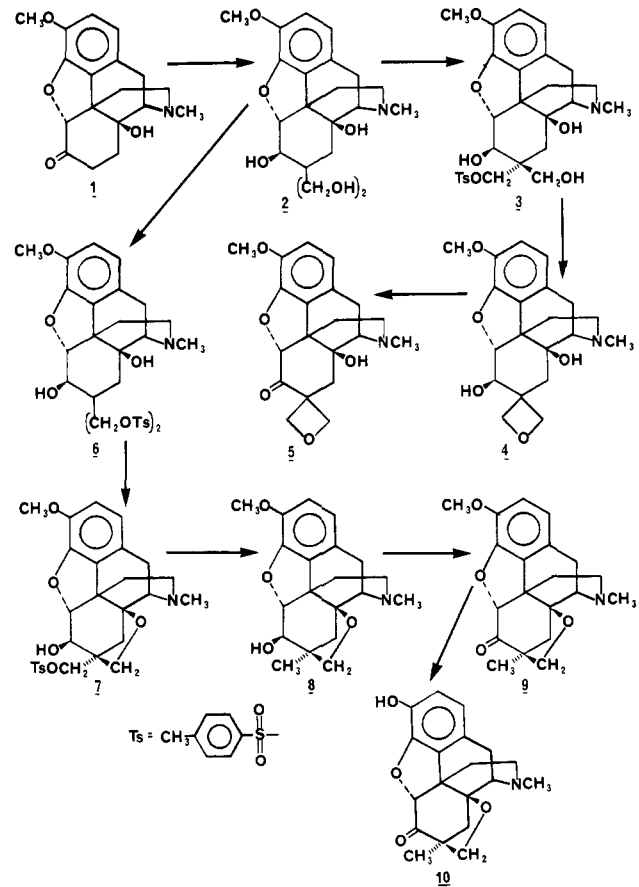
6,7α:14,7β-Bis(oxymethylene)morphinans, which contain seven ring structures within the molecule, were synthesized from 14-hydroxydihydrocodeinone (1). Conversion of 1 to 7,7-bis(hydroxymethyl)-4,5α-epoxy-3-methoxy-17-methylmorphinan-6β,14-diol (2) and then reaction with 1.2 equiv of *p*-TsCl gave 7α-tosyloxymethylene 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.

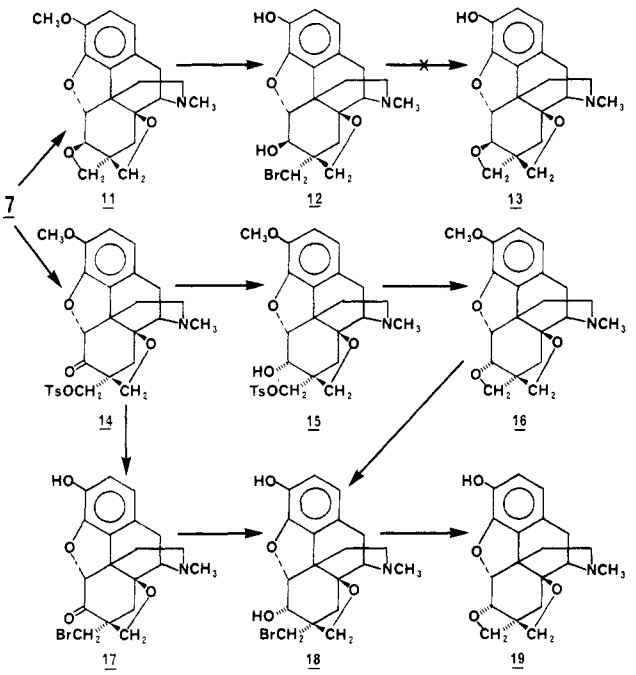
Scheme I



(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

Scheme II



The NMR and mass spectra of **7** indicated the presence of a single tosyloxy group and the loss of H_2O when compared with monotosylate **3**. Ring closure through neighboring group displacement of the 7β-tosyloxy by the 14-hydroxy function was confirmed by oxidation of the remaining secondary hydroxy group at C6 in **7** to give ketone **14**. Bond formation between the 7β-methylene and the 14β-hydroxyl, vs. the 6β-hydroxyl, reflects strain factors which favor the formation of five-membered over four-membered rings.[3] This closure also confirms the structure of monotosylate **3**. Formation of a five-membered ring to give a structure analogous to **7**, but with a hydroxyl instead of the tosyl group, would have been preferred if monotosylation had occured to give the 7β-substituted product.

Reductive displacement of the tosyloxy group in **7** with $LiEt_3BH$[4] gave the 7α-methyl derivative **8** which was oxidized by use of Me_2SO–TFAA[5] to 6-oxo compound **9**. Codeine analogue **9** was cleanly O-demethylated to give 3-hydroxy compound **10** by use of BBr_3 in $CHCl_3$.[6]

Formation of a trans-fused oxetane ring between the 6β-OH and 7α-methylene group was explored next (Scheme II). Treatment of **7** with 3.5 equiv of dilute NaOH in refluxing dioxane for 5 h gave bis(oxymethylene) derivative **11** in 76% yield. Refluxing HBr treatment of **11** cleaved both the oxetane ring and 3-methoxy function, as expected, to give 7α-bromomethylene compound **12**. Attempts to reclose the oxymethylene bridge under basic conditions, similar to those used in the formation of **11**, resulted in a complex mixture from which the desired **13** could not be isolated.

The corresponding *cis*-6α,7α-oxymethylene compound **16** was prepared by oxidation of **7** to ketone **14** followed by reduction with $NaBH_4$ to 6α-ol **15**. In agreement with previous results,[2] the NMR signal for H5 in **15** was observed (δ 4.70) at a position downfield from that found (δ 4.48 in $CDCl_3$) for the 6β-ol **7**. This observation confirms the assignment of β stereochemistry to the 6-hydroxyl in **2**. Base treatment of **15** gave the desired bis(oxymethylene) compound **16** in excellent yield.

Treatment of **16** with refluxing HBr or BBr_3 at room temperature gave complex mixtures from which the desired bromomethylene diol **18** could only be isolated in low yield. In contrast, refluxing **14** with HBr for a short time gave bromomethyl ketone **17** in high yield as a crystalline solid. Carbonyl reduction to **18** followed by oxetane ring closure in NaOH–dioxane gave 6α,7α:14,7β-bis(oxymethylene)-4,5α-epoxy-17-methylmorphinan-3-ol (**19**).[7]

The facile ring closure between the 7β-tosyloxymethylene and 14β-hydroxy functions detailed in this report complicates the preparation of 7β-(arylalkyl)-14-hydroxymorphinan derivatives by the methodology outlined in our previous work.[1] It does, however, allow us to state that a rigid structure[8] is not responsible for the extremely potent agonist activity observed with tertiary alcohols derived from Diels–Alder adducts of thebaine.[9] None of the rigid morphine derivatives prepared in the course of this work, in which the conformation of the C ring is highly constrained, exhibited antinociceptive potencies greater than that observed for morphine in the mouse writhing assay.

Experimental Section[10]

7,7-Bis(hydroxymethyl)-4,5α-epoxy-3-methoxy-17-methylmorphinan-6β,14-diol (2). A mixture of **1** (31.5 g, 0.1 mol), $Ca(OH)_2$ (14.0 g) and formaldehyde solution (140 mL) in dioxane (500 mL) and H_2O (500 mL) was stirred overnight. The suspension was filtered to remove insoluble material and the filtrate evaporated to a small volume. This solution was diluted with H_2O and extracted with EtOAc. Processing of the organic phase in the usual manner gave **2** as a foam. Crystallization from EtOAc yielded 23.1 g (61%) of **2** as light tan crystals, mp 169.5–172 °C. Recrystallization from EtOAc gave analytically pure material, mp 172–174 °C. Anal. Calcd for $C_{20}H_{27}NO_6$: C, 63.65; H, 7.21; N, 3.71. Found: C, 63.94; H, 7.34; N, 3.65.

4,5α-Epoxy-7β-(hydroxymethyl)-3-methoxy-17-methyl-7α-[(tosyloxy)methyl]morphinan-6β,14-diol (3). Compound **2** (6.80 g, 18.0 mmol) was azeotroped several times with dry pyridine and finally dissolved in dry pyridine (150 mL). After the mixture was cooled in ice, *p*-TsCl (4.12 g, 21.6 mmol) was added and stirring continued in the cold for 1 h followed by stirring at room temperature for 22 h. Several chips of ice were added, and the mixture was evaporated at a bath temperature of 55 °C. The residue was azeotropically distilled with 50% aqueous EtOH, EtOH, EtOH–toluene, and finally toluene. The residue was suspended in H_2O and the acidic solution extracted three times with $CHCl_3$. The combined $CHCl_3$ extracts were backwashed with H_2O, dried, and evaporated to give 6.60 g (69%) of a foam which contained predominently **3**. Chromatography of a portion of this foam gave pure **3**: NMR δ 7.7–7.1 (4 H, aromatic tosyl), 6.73 (2 H, aromatic), 4.62 (d, 1 H, H5, J = 7 Hz), 3.95 (CH_3O), 2.70 (CH_3N), 2.67 (CH_3 tosyl). Two crystallizations from dioxane gave the dioxane solvate of **3** which melts slowly above 130 °C. Anal. Calcd for $C_{27}H_{33}NO_8S \cdot C_4H_8O_2$: C, 60.09; H, 6.67; N, 2.26. Found: C,59.87; H, 6.91; N, 2.19.

7,7-(Oxydimethylene)-4,5α-epoxy-3-methoxy-17-methylmorphinan-6β,14-diol (4). A suspension of **3** (2.40 g, 4.5 mmol) in dioxane (75 mL) was warmed to give a clear solution and 1 N

(3) Eliel, E. L. "Stereochemistry of Carbon Compounds"; McGraw-Hill: New York, 1962; p 198.
(4) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1976**, *41*, 3064. Holder, R. W.; Matturro, M. G. *Ibid.* **1977**, *42*, 2166.
(5) Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957. Huang, S. L.; Omura, K.; Swern, D. *Ibid.* **1976**, *41*, 3329.
(6) Rice, K. C. *J. Med. Chem.* **1977**, *20*, 164.
(7) Trivial nomenclative has been used throughout this report. The IUPAC name for **19** is (4b*S*,8*R*,8a*S*,10a*R*,12a*S*,12b*R*)-5,6,7,8,12a,12b-hexahydro-7-methyl-11*H*-4,8:8a,10a-dimethano-8a*H*,10*H*-benzofuro-[3′,2′:3,4]oxeto[2′,3′:5,6]oxepino[2,3-*c*]pyridin-1-ol. I am indebted to Dr. K. L. Loening, Nomenclature Director, CAS, for this information.
(8) Kotick, M. P. *J. Med. Chem.* **1981**, *24*, 722. See this paper for another example of attempts to confer rigidity to the C ring of morphine compounds and references therein.
(9) Kotick, M. P., Leland, D. L.; Polazzi, J. O.; Schut, R. N. *J. Med. Chem.* **1980**, *23*, 166. See this paper for some of the leading references in this area.
(10) Methods were as previously reported (see ref 1 or 2). NMR spectra were recorded in $CDCl_3$ unless noted otherwise.

NaOH (15 mL) added. The mixture was refluxed for 30 min, cooled, and evaporated. The residue was diluted with H_2O and extracted with $CHCl_3$. Processing of the organic extracts in the usual manner gave 1.60 g of a foam which was purified by chromatography to give 1.35 g (83%) of **4** as a foam, homogeneous by TLC; mass spectrum, *m/e* (relative intensity) 359 (M+, 100), 329 (20), 230 (28), 210 (26). A portion of this foam was converted to the *d*-tartrate salt which was obtained as an amorphous solid with an indefinite melting point. Elemented analysis and NMR (Me_2SO-d_6) indicated that this material was the ethanol solvate of **4**. Anal. Calcd for $C_{20}H_{25}NO_5 \cdot C_4H_6O_6 \cdot C_2H_6O$: C, 58.02; H, 6.43; N, 2.42. Found: C, 58.08; H, 6.67; N, 2.72.

7,7-(Oxydimethylene)-4,5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one (5). A solution of trifluoroacetic anhydride (1.23 mL, 8.66 mmol) in CH_2Cl_2 (6 mL) was added slowly, dropwise, under an argon atmosphere to a −60 °C solution of Me_2SO (0.82 mL, 11.54 mmol) in CH_2Cl_2 (15 mL). After the mixture was stirred for 10 min, a solution containing the free base of **4** (2.07 g, 5.76 mmol) in CH_2Cl_2 (20 mL) was added slowly, while maintaining the −60 °C temperature. The mixture was stirred at −60 °C for 90 min, TEA (2 mL) was added dropwise, and the mixture was allowed to warm to room temperature. The solution was diluted with CH_2Cl_2 and extracted three times with H_2O. Evaporation of the dried organic phase gave 1.97 g of a crystalline residue which was chromatographed to give 1.84 g (90%) of crystalline **5**. This material was boiled with EtOH to give an analytical sample of **5**: mp 247–250 °C; NMR δ 6.67 (s, 2 H, aromatic), 5.15 (m, 2 H, 7-CH_2), 4.78 (s, 1 H, H5), 4.55 (d, 1 H, 7-CH_2, J = 7 Hz), 4.17 (d, 1 H, 7-CH_2, J = 5 Hz), 3.93 (s, CH_3O), 2.41 (s, CH_3N). Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 66.96; H, 6.68; N, 3.74.

4,5α-Epoxy-3-methoxy-17-methyl-7α-[(tosyloxy)methyl]-14,7β-(oxymethylene)morphinan-6β-ol (7). Compound **2** (10.0 g, 26.5 mmol) was azeotroped several times with dry pyridine and then dissolved in pyridine (200 mL) and cooled in ice. *p*-TsCl (15.15 g, 79.5 mmol) was added in one portion, and the mixture was stirred in the cold for 1 h and then kept at room temperature for 1 week while being protected from moisture. Several chips of ice were added, and the mixture was concentrated at a bath temperature at 55 °C. The residue was azeotroped four times with 50% aqueous EtOH and then EtOH. The residual syrup was dissolved in MeOH (150 mL) and 5 N NaOH (30 mL) added. The strongly basic solution was stirred at ambient temperature for 30 min and then was concentrated to a small volume, and the residue was partitioned between H_2O and $CHCl_3$. After further $CHCl_3$ extractions, the organic extracts were washed with H_2O and evaporated. The residue was azeotroped with aqueous EtOH to remove traces of pyridine and then azeotroped with EtOH–PhMe followed by PhMe until a crystalline residue formed. This residue was boiled with EtOH (100 mL), and the mixture then kept in the cold overnight. Crystals of **7** [7.25 g (53%); mp 234–236 °C] were collected. Recrystallization from EtOH gave analytically pure **7**: mp 234–237 °C; NMR (Me_2SO-d_6) δ 7.9–7.4 (4 H, tosyl aromatic), 6.73 (m, 2 H, aromatic), 5.76 (d, HO), 4.43 (d, H 5, J = 5 Hz); mass spectrum, *m/e* (relative intensity) 513 (M^+, 100), 456 (99), 254 (47), 198 (79). Anal. Calcd for $C_{27}H_{31}NO_7S$: C, 63.15; H, 6.08; N, 2.73. Found: C, 62.77; H, 6.04; N, 2.52.

7α,17-Dimethyl-4,5α-epoxy-3-methoxy-14,7β-(oxymethylene)morphinan-6β-ol (8). A solution of **7** (5.13 g, 10 mmol) in THF (250 mL), under an atmosphere of argon, was cooled in an ice bath and $LiEt_3BH$ (22 mL of a 1 M solution in THF) added slowly dropwise. The mixture was stirred at room temperature for 2 h, additional $LiEt_3BH$ (10 mL) added, and stirring continued for 1 h. The mixture was cooled in ice, and the following were added sequentially and dropwise: H_2O (6 mL), 3 N NaOH (12 mL), 30% H_2O_2 (12 mL). The mixture was refluxed for 2 h and cooled, and the bulk of the THF was evaporated. The residue was dissolved in H_2O which was extracted with $CHCl_3$. Processing of the organic phase in the usual fashion gave 4.63 g of a solid residue. Crystallization of this residue from EtOH gave 2.25 g (58%) of the EtOH solvate of **8**, mp 248–250 °C. Recrystallization from MeOH–EtOAc gave pure, solvent free **8**: mp 253–255 °C; NMR (Me_2SO-d_6) δ 6.68 (m, 2 H, aromatic), 5.42 (d, 1 H, HO), 4.32 (d, 1 H, H5, J = 5 Hz), 0.99 (s, 3 H, 7α-CH_3); mass spectrum, *m/e* (relative intensity) 343 (M+, 100), 312 (46), 286 (48), 255 (21), 198 (64). Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.72; H, 6.97; N, 3.93.

7α,17-Dimethyl-4,5α-epoxy-3-methoxy-14,7β-(oxymethylene)morphinan-6-one (9). An oxidation mixture was prepared under argon as described previously from Me_2SO (1.42 mL, 20 mmol) in CH_2Cl_2 (20 mL) and TFAA (2.12 mL, 15 mmol) in CH_2Cl_2 (15 mL) at −60 °C. A solution of **8** (3.29 g, 9.58 mmol) in CH_2Cl_2 (50 mL) and Me_2SO (10 mL) was added slowly. The mixture was stirred for 90 min at −60 °C, TEA (4 mL) was added dropwise, and the mixture was allowed to warm to room temperature. The solution was washed five times with H_2O, dried, and evaporated to give 3.48 g of a residue. This residue was chromatographed to give 2.99 g (91%) of **9** as a foam: NMR δ 6.70 (s, 2 H), 4.82 (s, 1 H, H5), 3.95 (q, 2 H, CH_2O, J = 7, 16 Hz), 3.92 (s, CH_3O), 2.45 (s, CH_3N), 1.16 (s, 3 H, 7α-CH_3); mass spectrum, *m/e* (relative intensity) 341 (M+, 100), 310 (26), 284 (27), 256 (64). A portion of this material was converted to the *d*-tartrate salt which was obtained as crystals, mp 210–212 °C (from aqueous EtOH). Anal. Calcd for $C_{20}H_{23}NO_4 \cdot C_4H_6O_6$: C, 58.65; H, 5.95; N, 2.85. Found: C, 58.43; H, 5.96; N, 2.57.

7α,17-Dimethyl-4,5α-epoxy-3-hydroxy-14,7β-(oxymethylene)morphinan-6-one (10). A solution of **9** (1.79 g, 5.2 mmol) in $CHCl_3$ (50 mL) was added rapidly dropwise, while the internal temperature was kept at 20 °C, to a stirred solution of BBr_3 (3.0 mL, 32 mmol) in $CHCl_3$ (50 mL) under an argon atmosphere. The mixture was stirred at room temperature for 30 min and then cooled to 0 °C. Methanol (20 mL) was added slowly and dropwise followed by concentrated NH_4OH (20 mL). The mixture was evaporated to a small volume, partitioned between dilute NH_4OH and $CHCl_3$, and further processed in the usual fashion to give 1.78 g of a white foam. Chromatography of this foam allowed isolation of unchanged **9** (0.36 g, 20%) and 1.25 g (73%) of **10**. Crystallization from EtOH and recrystallization from MeOH–EtOAc gave analytically pure **10**: mp, dec above 265 °C; NMR δ 6.70 (m, 2 H, aromatic), 4.88 (s, H5), 3.97 (q, CH_2O, J = 10, 16 Hz), 1.18 (s, 7α-CH_3); mass spectrum, *m/e* (relative intensity) 327 (M^+, 100). Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.52; H, 6.67; N, 4.11.

6β,7α:14,7β-Bis(oxymethylene)-4,5α-epoxy-3-methoxy-17-methylmorphinan (11). A solution of **7** (3.00 g, 5.65 mmol) in dioxane (70 mL) containing 1 N NaOH (20 mL) was refluxed for 5 h. The mixture was evaporated and the residue dissolved in H_2O which was extracted with $CHCl_3$. Further processing of the organic phase gave 2.20 g of a foam which was chromatographed. Pure fractions were combined and evaporated to give 1.48 g (76%) of **11** as a foam. Crystallization of this foam from EtOAc gave 0.50 g of **11**, mp 163–164 °C. Recrystallization from the same solvent gave an analytical sample of **11**: mp 164–165 °C; NMR δ 6.70 (m, 2 H, aromatic), 4.90 (d, 1 H, H5, J = 7 Hz), 4.85–4.53 (m, 3 H), 4.15 (m, 2 H, 7β-CH_2O), 3.89 (CH_3O), 2.40 (CH_3N); mass spectrum, *m/e* (relative intensity) 341 (M^+, 63), 284 (26), 254 (26), 223 (30), 115 (40), 42 (100). Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.47; H, 7.07; N, 3.91.

4,5α-Epoxy-3-methoxy-17-methyl-7α-[(tosyloxy)methyl]-14,7β-(oxymethylene)morphinan-6-one (14). A solution of **7** (5.13 g, 10 mmol) in CH_2Cl_2 (50 mL) was added slowly at −60 °C under argon to a mixture of Me_2SO (20 mmol)–TFAA (15 mmol), prepared as described previously. After 90 min at −60 °C, the reaction mixture was treated with TEA (4 mL) and processed in the usual fashion to give 5.47 g of a foam. The foam was dissolved in 95% EtOH and cooled. Crystals of **14** [4.50 g (86%); mp 172–173 °C] were collected. Recrystallization from 95% EtOH gave the hemihydrate of **14**: mp 173.5–174.5 °C; NMR δ 7.8–7.2 (4 H, aromatic tosyl), 6.63 (s, 2 H, aromatic), 4.78 (s, H5), 4.17–4.00 (m, 4 H), 3.85 (CH_3O), 2.45 (CH_3N and tosyl CH_3). Anal. Calcd for $C_{27}H_{29}NO_7S \cdot 0.5H_2O$: C, 62.30; H, 5.81; N, 2.69. Found: C, 62.29; H, 5.67; N, 2.64.

4,5α-Epoxy-3-methoxy-17-methyl-7α-[(toxyloxy)methyl]-14,7β-(oxymethylene)morphinan-6α-ol (15). A solution of **14**·0.5H_2O (3.86 g, 7.4 mmol) in MeOH (100 mL) and $CHCl_3$ (25 mL) was cooled in a ice bath and $NaBH_4$ (0.29 g, 7.7 mmol) added. The mixture was stirred in the bath for 45 min, excess HOAc added to destroy the remaining hydride, and the mixture evaporated to a small volume. The residue was dissolved in H_2O, and the solution was made basic with NH_4OH and extracted with $CHCl_3$. Processing in the usual fashion gave a residue which crystallized from EtOH to give 3.05 g (74%) of **15** as the

mono-EtOH solvate, mp 114–116 °C. Recrystallization from EtOH gave pure **15**·EtOH (mp 114–116 °C) which contained a trace of the 6β-ol **7** as indicated by TLC: NMR δ 4.70 (d, H5, J = 7 Hz). Anal. Calcd for $C_{27}H_{29}NO_7S \cdot C_2H_6O$: C, 62.24; H, 6.66; N, 2.50. Found: C, 62.07; H, 6.29; N, 2.40.

6α,7α:14,7β-Bis(oxymethylene)-4,5α-epoxy-3-methoxy-17-methylmorphinan (16). A solution of **15**·EtOH (3.36 g, 6.0 mmol) in dioxane (75 mL) containing 1 N NaOH (20 mL) was refluxed for 10 h. The mixture was evaporated to a small volume and the residue partitioned between H_2O and $CHCl_3$. Processing in the usual fashion gave 2.38 g of a foam which was chromatographed to give 1.88 g (92%) of **16** as a foam. Crystallization from EtOH gave 1.21 g of **16** as white crystals, mp 213–215 °C. One additional crystallization gave analytically pure **16**: mp 214–215.5 °C; NMR δ 6.70 (m, 2 H, aromatic), 5.06 (d, 1 H, J = 7 Hz), 3.3–3.0 (m, 2 H), 2.43 (CH_3N); mass spectrum, m/e (relative intensity) 341 (M^+, 100), 284 (66), 254 (25), 230 (56). Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.08; H, 6.76; N, 4.23.

7α-(Bromomethyl)-4,5α-epoxy-3-hydroxy-14,7β-(oxymethylene)morphinan-6-one (17). A suspension of **14**·0.5H_2O (8.00 g, 15.4 mmol) in 48% HBr (80 mL) was immersed in an oil bath preheated to 140 °C and the mixture refluxed for 15 min. The clear solution was cooled, diluted with ice and H_2O, and made basic with concentrated NH_4OH. Extraction with $CHCl_3$ followed by processing in the usual fashion gave a gum which was crystallized from EtOH to give 5.80 g (93%) of **17** as white needles [mp 239–241 °C (sinters)] which contained trace impurities as indicated by TLC. Chromatography of 1.00 g of this material gave 0.98 g of pure **17** as a foam. Crystallization from EtOH gave an analytical sample of **17**: mp, sinters above 248 °C; NMR δ 6.68 (m, 2 H, aromatic), 6.2 (br, 1 H, HO), 5.00 (s, 1 H, H5), 4.17 (s, 2 H, $BrCH_2$); mass spectrum, m/e (relative intensity) 407 (71), 405 (68), 326 (23), 296 (92), 241 (100). Anal. Calcd for $C_{19}H_{20}BrNO_4$: C, 56.17; H, 4.96; N, 3.45. Found: C, 56.31; H, 5.22; N, 3.40.

7α-(Bromomethyl)-4,5α-epoxy-14,7β-(oxymethylene)morphinan-3,6α-diol (18). A solution of **17** (4.64 g, 11.4 mmol) in MeOH (150 mL) and $CHCl_3$ (100 mL) was cooled in an ice bath and $NaBH_4$ (0.40 g, 10.6 mmol) added in one portion. The mixture was stirred for 20 min in the cold and then adjusted to ca. pH 6 with HOAc. After evaporation, the residue was dissolved in H_2O, excess NH_4OH added, and the mixture processed with $CHCl_3$ in the usual manner to give a foam which was chromatographed. Homogenous fractions were pooled and evaporated to give 4.68 g of **18** as a foam which was warmed with a small amount of dioxane. Crystals (3.84 g, 68%) of the dioxane solvate of **18** (mp 225–226 °C), were collected after cooling. Recrystallization of this material from dioxane gave solvated **18**: mp, crystal change at 130–140 °C, melts at 226–227 °C. Solvent-free material was prepared by drying at 120 °C under high vacuum: NMR δ 4.70 (d, 1 H, H5, J = 6 Hz); mass spectrum, m/e (relative intensity) 409 (74), 407 (81), 298 (100), 241 (52). Anal. Calcd for $C_{19}H_{22}BrNO_4$: C, 55.89; H, 5.43; N, 3.43. Found: C, 55.90; H, 5.45; N, 3.47.

6α,7α:14,7β-Bis(oxymethylene)-4,5α-epxoy-17-methylmorphinan-3-ol (19). A suspension of the dioxane solvate of **18** (3.00 g, 6.0 mmol) in dioxane (100 mL), under argon, was warmed to give a clear solution and 1 N NaOH (24 mL) added. The mixture was refluxed for 2 h, cooled, and concentrated to a small volume. The residue was diluted with H_2O, 1 N HCl (25 mL) was added, and then the solution was immediately made basic with excess NH_4OH. Extraction with $CHCl_3$ and processing in the usual fashion gave 1.84 g of a foam which was chromatographed. Appropriate fractions were combined and evaporated to give 1.45 g (73%) of **19** which contained trace impurities as shown by TLC. This material was rechromatographed to give homogeneous **19** which was twice crystallized from EtoAc to provide a sample of pure **19**: mp >265 °C; NMR δ 6.72 (m, 3 H, H 1, H 2, HO), 5.15 (d, 1 H, H5), 4.48 (q, 2 H, 7α CH_2, J = 20, 6 Hz), 4.65 (d, 1 H, H6), 3.73 (q, 2 H, 7β-CH_2O, J = 15, 8 Hz); mass spectrum, m/e (relative intensity) 327 (M^+, 100), 216 (29). Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.50; H, 6.65; N, 4.26.

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Sequential Ene Reactions. A New Annelation Procedure

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Alkylidenecycloalkanes **1** undergo two sequential Me_2AlCl-catalyzed ene reactions with α,β-unsaturated carbonyl compounds to give bicyclic alcohols **3**. At low temperatures, the initial ene adducts **2** can be isolated when vinyl ketones are used. This reaction has been used for the synthesis of 24-oxocholesterol. Other classes of alkenes give more complex mixtures. The scope, limitations, and mechanism of this reaction are discussed.

The use of carbon–carbon double bonds as activating groups for the formation of new carbon–carbon bonds under mild conditions is a challenge to synthetic chemists. The ene reaction provides a potential solution to this problem.[2] We have found that Lewis acid catalyzed ene reactions with acrylate esters as the enophile occur at 25 °C and that the ene reactions of α-substituted acrylate esters are regioselective and stereoselective, with the carboalkoxy group adding endo.[2b,3] Lewis acid catalysis offers significant advantages over the corresponding thermal ene reactions which occur at 200–300 °C. We have also shown that alkylaluminum halides are preferred catalysts for these reactions since the alkyl group functions as a proton scavenger.[4]

α,β-Unsaturated ketones and aldehydes have seen little use as enophiles.[5] Acrolein reacts with β-pinene at 140

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