of pure N-nucleoside 9 was isolated after flash chromatography. The reaction likewise proceeded similarly with 0.25 mmol of red HgO as the catalyst.

Acknowledgment. We thank Drs. John S. Driscoll and James A. Kelley of this laboratory for their many helpful discussions during the course of this work.

Registry No. 1, 18023-41-1; **2a**, 16205-60-0; **2b**, 80963-16-2; **4**, 80963-17-3; **5**, 80963-18-4; **9**, 77249-70-8; $HgBr_2$, 7789-47-1; HgO, 21908-53-2; tetramethylene urea, 19055-93-7; 2,3,5-tri-*O*-benzoyl-1-*O*-acetyl-β-D-ribofuranose, 6974-32-9.

Total Synthesis of (±)-3-Deoxy-7,8-dihydromorphinone

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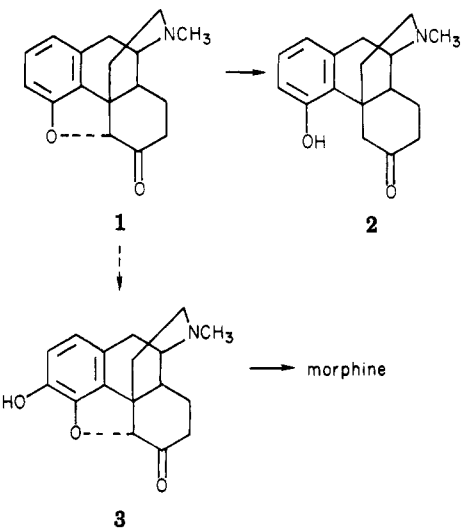
The total synthesis of (±)-3-deoxy-7,8-dihydromorphinone (1), starting from readily available [3,5-bis(benzyloxy)phenyl]acetic acid (4) is described. The amide 6, obtained from acid 4 and *m*-methoxyphenethylamine, was converted by Bischler–Napieralski cyclization to the dihydroisoquinoline hydrochloride 7. Birch reduction of 7 gave the dihydroxydihydroanisole 8, which was acid cyclized in situ and then converted to (±)-2,4-bis-[(methoxycarbonyl)oxy)]-17-(methoxycarbonyl)morphinan-6-one (10). The conversion of 7 to 10 was carried out without isolation of intermediates. Hydrolysis with THF/Et_2NH gave the 4-hydroxy compound 14. Reaction of 14 with cupric bromide followed by treatment with NaOH/$CHCl_3$ and hydrolysis gave 4,5-epoxy-2-hydroxymorphinan-6-one (16). The 2-oxygen function was removed by Li/NH_3 reduction of the phosphate ester 18 obtained by acylation of the ketal 17 with diethyl chlorophosphate. LAH reduction of the ketal 19 followed by acid hydrolysis gave the title compound (±)-3-deoxy-7,8-dihydromorphinone (1) in an overall yield (from 4) of 27%.

Our continuing interest in opioid chemistry and analgesics suggested to us that a total synthesis of (±)-3-deoxy-7,8-dihydromorphinone (1) will be of value, since it can be regarded as a key intermediate for carrying out further studies in this area. Thus, it can serve as a convenient source for the preparation of 4-hydroxymorphinanones, such as 2, which represent a relatively unexplored class of potent antinociceptive agents.[1,2] It can also potentially allow the synthesis of uniquely substituted morphine and morphinan structures and a study of their structure–activity relationships (SAR). In addition, it could lead to a novel synthesis of morphine (via 3) if a phenolic group could be successfully introduced at C-3. With these objectives in mind, we embarked on a total synthesis of 1. However, a recent communication by Hsu et al.,[3] who utilized the same materials and essentially the same strategy as ours (Grewe-type cyclization) for the synthesis of (±)-1, has prompted us to describe our own findings. Our synthesis differs clearly from theirs in the sequence and the method used for the removal of the 2-phenolic group and the formation of the 4,5-epoxy ring, for which we have devised a more efficient procedure. We describe in this paper the total synthesis of (±)-3-deoxy-7,8-dihydromorphinone (1) in an overall yield of 27% from readily available starting materials.

The basis of our synthesis strategy was the Grewe-type electrophilic cyclization of a (±)-1-benzylhexahydroisoquinoline[4] such as 8, which could be prepared from readily



available starting materials and which, upon acid cyclization, would furnish a single product 9, because of its symmetrical substitution in the benzyl radical. This dioxygenated morphinan 9, upon closure of the 4,5-epoxy bridge and removal of the 2-oxygen function, would then furnish the desired deoxydihydromorphinone (1). Hsu et al.[3] reached the same conclusion and used the same starting materials, but their intermediates and processes used were quite different from ours.

Our synthesis of the morphinan skeleton is shown in Scheme I. [3,5-Bis(benzyloxy)phenyl]acetic acid (4), prepared from 3,5-dihydroxybenzoic acid in six steps in an overall yield of 65%,[14] was condensed with *m*-meth-

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(2) (a) M. D. Rozwadowska, F. L. Hsu, A. E. Jacobson, K. C. Rice, and A. Brossi, *Can. J. Chem.* **58**, 1885 (1980); (b) F. L. Hsu, K. C. Rice, and A. Brossi, *Heterocycles*, **13**, 259 (1979); (c) J. Reden, M. F. Reich, K. C. Rice, A. E. Jacobson, A. Brossi, R. A. Streaty and W. Klee, *J. Med. Chem.* **22**, 256 (1979).

(3) F. L. Hsu, A. E. Jacobson, K. C. Rice, and A. Brossi, *Helv. Chim. Acta*, **63**, 2042 (1980).

(4) The problems associated with Grewe-type cyclization of (±)-1-benzylhexahydroisoquinolines substituted unsymmetrically, for the synthesis of various morphinans are well documented. See, for example, ref 5–13.

(5) (a) R. Grewe and A. Mondon, *Chem. Ber.*, **81**, 279 (1948); (b) R. Grewe, H. Fisher, and W. Fredrickson, *ibid.*, **100**, 1 (1967); (c) R. Grewe and W. Fredrickson, *ibid.*, **100**, 1550 (1967).

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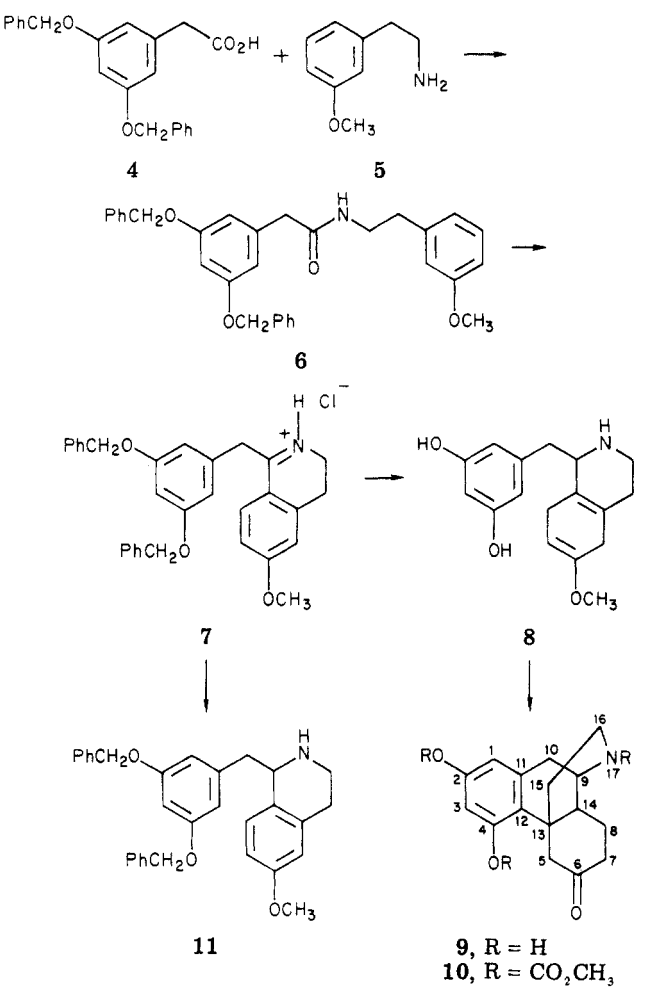
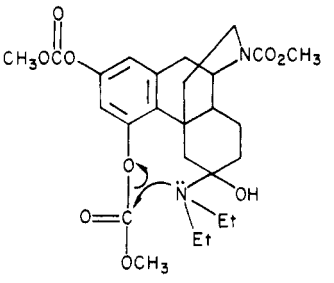
Scheme I



oxyphenethylamine (5) in refluxing xylene to give the crystalline amide 6 (97%). Bischler–Napieralski cyclization of the amide 6 with $POCl_3$ in CH_3CN gave the dihydroisoquinoline 7 as its hydrochloride in 91% yield as colorless needles, mp 175–175.5 °C ($MeOH/Et_2O$). Although we prepared 8 from 7 by way of the tetrahydroisoquinoline 11 (formed either by $NaBH_4$/MeOH or by hydrogenation in MeOH in the presence of Pt), we found it possible and more convenient to use 7 directly in the Birch reduction.

In this reaction, on treatment with excess Li in liquid ammonia in the presence of *tert*-butyl alcohol and THF, 7 readily undergoes initial reduction of the C=N bond with concomitant loss of benzyl groups. The Birch reduction subsequently forms 8. The dihydroxydihydroanisole 8 could be isolated as crystalline prisms, but it was found more advantageous to cyclize crude 8 directly. With concentrated HCl in the presence of ether (bath temperature, 40–50 °C), it gave morphinan 9. The cyclization could also be carried out at room temperature, but prolonged treatment was needed. As the tetracyclic base 9 was not very easy to handle because of limited solubility and stability, it was immediately converted to (±)-2,4-bis[(methoxycarbonyl)oxy)]-17-(methoxycarbonyl)morphinan-6-one (10). Pure 10 was obtained (95%) as colorless crystals, mp 133–135 °C (*i*-PrOH), after flash chromatography over silica gel. The four steps from 7 were performed without isolation of any intermediates (overall yield from 4, 84%). Hsu et al.[3] in their procedure treated 7 with $NaBH_4$ to get 11, which was catalytically debenzylated and converted to 8 by Birch reduction. They prepared the formamide derivative of 8 prior to ring closure with acid.

After the technique for forming the tetracyclic framework was established, we focused our attention on deoxygenation at C-2. This required selective formation of a reducible group at C-2, such as phenyltetrazole,[3,10a,15,16] diethyl phosphate,[17-20] sulfonate ester,[21] sulfate ester,[22] isourea,[23] or phenyl ether.[24,25] Therefore, in view of this, we proceeded to investigate conditions for selective hydrolysis of the carbonate groups. Controlled solvolysis of 10 with triethylamine in refluxing methanol for 15 min gave predominately the 2-hydroxy derivative along with the 4-hydroxy compound in a 3:1 ratio. Much better selectivity was achieved with diethylamine in tetrahydrofuran at room temperature. Under these conditions, surprisingly the 4-hydroxy isomer predominated over the 2-hydroxy isomer in a ratio of 9:1. This reverse selectivity may be related to the proximity of the ketone group to the 4-methoxycarbonyl group. The hydrolysis could be assisted by attack of the nitrogen of the amino alcohol formed as a reversible intermediate during the reaction, as shown:



With the fortuitous formation of the 4-hydroxy group, it

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(14) The synthesis of [bis(benzyloxy)phenyl]acetic acid (4) was developed in these laboratories by R. A. Minns and J. L. Marshall. For experimental details, see P. Meltzer, H. C. Dalzell, and R. K. Razdan, *J. Chem. Soc., Perkin Trans 1*, 2825 (1981).

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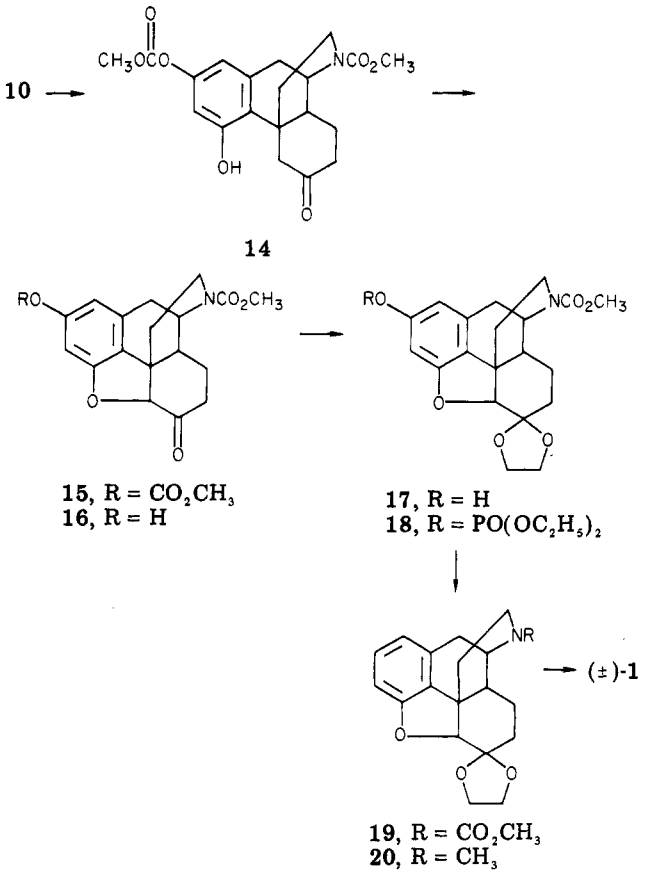
(24) W. H. Pirkle and J. L. Zabriskie, *J. Org. Chem.*, **29**, 3124 (1964).

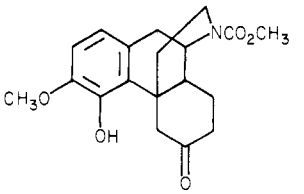
(25) Y. K. Sawa, N. Tsuji, and S. Maeda, *Tetrahedron*, **20**, 2255 (1964).

Scheme II

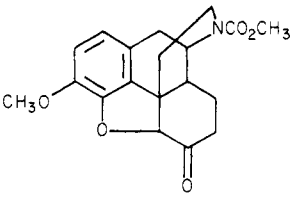


was logical to close the dihydrofuran ring as the next step. Application of Weller and Rapoport's excellent procedure[26] (i.e., bromination with Br_2/acetic acid and then treatment with dilute NaOH/$CHCl_3$) to the hydroxy compound 14 (Scheme II) did not give satisfactory results. Both Weller and Rapoport[26] and Olieman et al.[27] have demonstrated that with dihydrothebainone the first mole brominates the aromatic ring at C-1 and the second brominates α to the ketone mostly at the 7α-position. If the ring closure is attempted immediately after bromination, less than 50% of the bridge formation occurs. However, if the bromination mixture is allowed to equilibrate for 12–18 h and then treated with base, ring closure is almost quantitative. This is due to the slow conversion of the 7α-bromo to the 5β-bromo compound. The equilibration process does not appear to be very effective when N has an amide group instead of a methyl as evident from the work of Hsu et al.[3] With the *N*-formyl group, the ring closure step was accomplished in only 39% yield. In the present work with NCO_2CH_3, the bridge formation occurred in less than 40% yield.

It has been observed in morphinanones that enolization generally occurs at C-5 in the absence of a 4,5 oxygen bridge and at C-7 with the oxide bridge present.[26,28] Hence, it seemed advantageous to brominate specifically at C-5 rather than at C-7. Cupric bromide is one of the reagents useful in introducing into acetophenones a bromine atom α to the carbonyl group without aromatic bromination.[29] In these reactions, polarity of the solvent plays a vital role in the position of bromination. With more polar solvents, the primary reaction is nuclear bromination, whereas with less polar solvents, side-chain bromination is observed. Therefore, with NCO_2CH_3 nordihydrothebainone 12 as a model compound, bromination was studied with cupric bromide. The reaction was followed by NMR, where a change in position of the aromatic signals from δ 6.67 to 6.83 indicated the formation of the 1-Br compound. Chloroform was found to be the solvent of choice to give only side-chain bromination. After the starting material had disappeared, the reaction was worked up according to Weller and Rapoport's[26] procedure (a biphasal system, $CHCl_3$/2 N NaOH) to give 13 in a yield of 70%.



12



13

When the above conditions were applied to the 4-hydroxy compound 14 (Scheme II), compound 15 was isolated (71%) along with its hydrolysis product 16 (11%), for a combined yield of 82% of ring-closed products. The cyclization process was followed (NMR) by the appearance of a singlet at δ 4.63 for the C-5 proton. The mixture was hydrolyzed to give 16 cleanly, which was immediately converted to the ethylene ketal 17 by treatment with ethylene glycol and concentrated H_2SO_4 in $CHCl_3$. The formation of the ketal was confirmed by the disappearance of the carbonyl absorption in IR and the upfield shift of the H-5 singlet from δ 4.63 to 4.37.

Although reduction of a phenyltetrazolium derivative is a common technique for removing the oxygen function at C-2,[9b,9c,11a,16] it did not proceed satisfactorily with our compound. The reaction is capricious[11a] and is generally considered costly for scale-up. The alternative use of a phosphate derivative for the deoxygenation was more successful. The 2-diethyl phosphate ester 18 was then made from 17 by acylation with diethyl chlorophosphate in acetonitrile in the presence of finely powdered anhydrous K_2CO_3. Confirmation of the ester formation was indicated by the downfield shift of the aromatic signal in NMR from δ 6.2 to 6.57. The phosphate ester 18 was reduced to 19 with Li/NH_3/THF without purification. The ketal 19 was obtained as a foam, which on reduction with lithium aluminum hydride, gave the *N*-methyl ketal 20. Hydrolysis with dilute hydrochloric acid formed the target compound (±)-3-deoxy-7,8-dihydromorphinone (1) in 81% yield from 19 or 38% from 14.

All the four steps from 15 to 19 were carried out without purification of the intermediates to give chromatographically pure 19 in 47–56% yield. Thus, overall yield of 1 from [bis(benzyloxy)phenyl]acetic acid (4) is approximately 27%.

Attempted deoxygenation of 2-(diethylphosphoryl)-4-[(methoxycarbonyl)oxy]-17-(methoxycarbonyl)morphinan-6-one with Li/NH_3 resulted in hydrolysis to the 4-hydroxy compound. The facile synthesis of (±)-3-deoxy-7,8-dihydromorphinone (1) from readily available and

(26) D. D. Weller and H. Rapoport, *J. Med. Chem.*, 19, 1171 (1976).
(27) C. Olieman, L. Maat, and H. C. Beyermann, *Recl. Trav. Chim. Pays-Bas*, 97, 31 (1978).
(28) Unpublished results from our laboratory.
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inexpensive starting materials, as described above, makes this route worthy of further study. If a practical method could be developed for the introduction of a hydroxyl group at C-3, this route could potentially provide an alternative approach to a practical synthesis of morphine and related compounds.

Experimental Section

Melting points were determined in a Thomas-Hoover melting-point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer Model 700 instrument, and the NMR spectra were measured in $CDCl_3$ on a Varian T-60 spectrometer. The high-pressure liquid chromatographic separations were made with a Waters Associates ALC-202 chromatograph equipped with a Model 6000 solvent delivery system and either μ-Porasil or C^{18} μ-Porasil columns. Preparative separations were achieved on Waters Prep 500 System using silica columns. Precoated silica gel plates from E. Merck were used in thin-layer chromatograpic analysis. Mass spectral determinations were carried out at Burroughs Wellcome Co. and Mass Spectral Facility at Cornell University. Microanalyses were performed by Atlantic Microlabs Inc., Atlanta, GA.

[3,5-Bis(benzyloxy)phenyl]acetic acid (4) was synthesized in six steps from 3,5-dihydroxybenzoic acid as in ref 14; mp 113–114 °C (65%).

3-Methoxyphenethylamine (5) was prepared by hydrogenation of (3-methoxyphenyl)acetonitrile in ethanol in a Parr apparatus using Raney nickel[30] as a catalyst. Pure **5** was obtained by distillation as a colorless liquid (80%), bp 70 °C (0.02 mm) [lit.[31] bp 63–65 °C (0.01 mm)].

***N*-(3-Methoxyphenethyl)-2-[3,5-bis(benzyloxy)phenyl]acetamide (6).** A mixture of acid (**4**) (21.1 g) and amine (**5**; 9.16 g) in xylene (300 mL) was refluxed for 60 h with water separation via a Dean–Stark trap. Half of the xylene was distilled and hexane was added to the solution which, upon cooling, deposited colorless crystals. Filtration gave 28.3 g (97%) of **6** as solid, mp 98–99 °C (lit.[3] mp 101–102 °C). Anal. Calcd for $C_{31}H_{31}NO_4$: C, 77.31; H, 6.41; N, 2.91. Found: C, 77.27; H, 6.44; N, 2.89.

1-[3,5-Bis(benzyloxy)benzyl]-6-methoxy-3,4-dihydroisoquinoline Hydrochloride (7). A mixture of *N*-(3-methoxyphenethyl)-2-[3,5-bis(benzyloxy)phenyl]acetamide (**6**; 50 g, 0.104 mol), $POCl_3$ (20.0 mL), and CH_3CN (500 mL) was heated at reflux for 2 h. The reaction mixture was concentrated under reduced pressure, and the gummy residue crystallized from $MeOH/Et_2O$ to give 47 g of **7** as colorless needles (91%): mp 175–175.5 °C; NMR δ 2.87 (t, 2 H, J = 7 Hz), 3.87 (s, 3 H), 3.85 (m, 2 H), 4.72 (br s, 4 H), 5.03 (s, 4 H), 6.5 (m, 1 H), 6.75 (m, 4 H), 7.37 (s, 10 H), 7.83 (d, 1 H, J = 8 Hz). Anal. Calcd for $C_{31}H_{29}NO_3 \cdot HCl$: C, 74.46; H, 6.05; N, 2.80. Found: C, 74.48; H, 6.05; N, 2.78.

2,4-Bis[(methoxycarbonyl)oxy]-17-(methoxycarbonyl)morphinan-6-one (10). Seventy-five grams (0.15 mol) of imine hydrochloride **7**, 850 mL of THF (freshly distilled over sodium benzophenone ketyl), and 850 mL of *tert*-butyl alcohol (distilled over CaH_2) were placed in a 5-L three-necked flask equipped with a dry ice condenser, a mechanical stirrer, and stopper. Ammonia (2.2 L, distilled over Na) was condensed in a flask and Li in small pieces (11.5 g, ~1.6 mol) was added slowly till a blue color was obtained and maintained for 3 h. Excess Li was decomposed by addition of 75 mL of EtOH and NH_4Cl (200 g, large excess) and the ammonia was allowed to evaporate slowly overnight under a slight pressure of N_2. The residual solvents were distilled under reduced pressure (bath temperature, ~40 °C), and to the light-buff solid were added ether (1 L) and concentrated HCl (1 L) slowly with cooling. The reaction mixture was stirred initially at 25 °C and then in a bath at 50 °C for 24 h. HPLC (C^{18} μ-Porasil CH_3OH/H_2O) indicated complete conversion. The reaction mixture was filtered (through a sintered glass funnel to remove solid NH_4Cl), concentrated under reduced pressure to a volume of 1.5 L, and made just basic with KOH (initially solid and then 4 N aqueous solution). A solution of $ClCO_2CH_3$ in CH_2Cl_2 was added slowly to the basic reaction mixture until the aqueous layer turned acidic. The mixture was extracted with CH_2Cl_2 (1 L). The aqueous layer was made alkaline with 2 N aqueous KOH, and it was again treated with $ClCO_2CH_3/CH_2Cl_2$ till it became acidic. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were stirred with anhydrous K_2CO_3 and $ClCO_2CH_3$ at room temperature overnight. The reaction mixture was filtered, and the filtrate was extracted with saturated $NaHCO_3$, dried over Na_2SO_4 (anhydrous), and concentrated to a brown oil (130 g). Purification by flash chromatography[32] over silica gel [40–63 μm, 900 g, in CH_2Cl_2/CH_3CN (4:1)] gave 64.5 g of **10** as a pale-yellow oil (96%), which solidified on standing in the refrigerator. An analytical sample was obtained by recrystallization from *i*-PrOH: mp 133–135 °C; NMR δ 1.5–3.5 (m, 13 H), 3.67 (s, 3 H, NCO_2CH_3), 3.83 (s, 3 H, C-2 $OC(O)OCH_3$), 3.92 (s, 3 H, C-4 $OC(O)OCH_3$), 4.5 (br, 1 H, CHN), 6.89 (dd, 2 H, J = 3 H, aromatic); IR (CCl_4) 2970, 1755, 1700 cm^{-1}. Anal. Calcd for $C_{22}H_{25}NO_9$: C, 59.06;, H, 5.63; N, 3.13. Found: C, 59.30; H, 5.71; N, 3.09.

The Birch reduction product, dihydroxydihydroanisole **8**, can be isolated by crystallization of the crude product from MeOH as colorless needles, mp 202–204 °C. Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.36; N, 4.87. Found: C, 70.86; H, 7.37; N, 4.85.

17-(Methoxycarbonyl)nordihydrocodeinone (13). A mixture of 17-(methoxycarbonyl)nordihydrothebainone (**12**; 240 mg, 0.7 mmol), cupric bromide (350 mg, 1.55 mmol), and $CHCl_3$ (25 mL) was heated at reflux in an oil bath until all the ketone had been brominated (3 h). After being cooled, the reaction mixture was filtered and the filtrate was concentrated to a brown gum. It was taken up in $CHCl_3$ and cooled to 5 °C. To the cold $CHCl_3$ solution was added 0.5 N NaOH, and the mixture was shaken in a separatory funnel. This process was repeated. The $CHCl_3$ layer was washed with water and saturated aqueous NH_4Cl, dried, and concentrated on the rotary evaporator to give a light-yellow foam, 205 mg (85%). Pure **13** was obtained by chromatography over silica gel and was found to be identical (NMR, IR, TLC, GLC) with that obtained by treatment of dihydrocodeinone with methyl chloroformate/K_2CO_3/CH_2Cl_2: NMR δ 1.6–3.0 (m, 11 H), 3.73 (s, 3 H, $C(O)OCH_3$), 3.9 (s, 3 H, OCH_3), 4.67 (s, 1 H, H-5), 4.7 (br, 1 H, CHN), 6.7 (dd, 2 H, J = 7 Hz, ArH).

4-Hydroxy-2-[(methoxycarbonyl)oxy]-17-(methoxycarbonyl)morphinan-6-one (14). A mixture of 2,4-bis[(methoxycarbonyl)oxy]-17-(methoxycarbonyl)morphinan-6-one (**10**; 20.5 g, 0.046 mol), THF (700 mL, freshly distilled), and diethylamine (20 mL) was stirred at room temperature under a N_2 atmosphere overnight. The hydrolysis to the 4-OH compound was followed by TLC (silica gel, 20% CH_3CN in CH_2Cl_2). After the reaction was complete, the mixture was concentrated to a brown foam under reduced pressure. Pure **14** was obtained as a colorless foam, 14.7 g (85%), by flash chromatography over silica gel (40–63 μm, 450 g), using CH_3CN/CH_2Cl_2 (1:4) as eluant. From earlier fractions, 0.9 g of unreacted starting material **10** was obtained.

An analytical sample of **14** was obtained by preparative HPLC, (silica gel, 15% CH_3CN in CH_2Cl_2) as a colorless foam: mp 132.5–134 °C; NMR δ 1.5–3.4 (m, 12 H), 3.70 (s, 3 H, $NC(O)OCH_3$), 3.83 (s, 3 H, OCO_2CH_3), 4.38 (d, J = 14 Hz, H-5), 4.6 (br, CHN), 6.55 (dd, 2 H, J = 2 Hz, aromatic); IR ($CDCl_3$) 3300, 2950, 1760, 1680, 1690 (sh) cm^{-1}; mass spectrum, m/e (relative intensity) 389 (M^+, 59), 314 (29), 287 (64), 286 (100), 243 (15), 211 (21), 187 (26). Anal. Calcd for $C_{20}H_{23}NO_7$: C, 61.69; H, 5.95; N, 3.60. Found: C, 61.60; H, 5.99; N, 3.58.

4,5-Epoxy-2-[(methoxycarbonyl)oxy]-17-(methoxycarbonyl)morphinan-6-one (15). A mixture of 4-hydroxy-2-[(methoxycarbonyl)oxy]-17-(methoxycarbonyl)morphinan-6-one (**14**; 14.7 g, 0.038 mol), cupric bromide (18.2 g, 0.081 mol), and 700 mL of CH_2Cl_2 containing 5% CH_3CN was heated at reflux under N_2 in an oil bath until all the starting material had disappeared (as indicated by TLC, silica gel, 20% CH_3CN in CH_2Cl_2). The reaction mixture was cooled, filtered, and concentrated on the rotary evaporator to a brown gum. The residue was taken up in $CHCl_3$, cooled to 0–5 °C in an ice bath, and shaken in a separatory funnel with cold aqueous 1 N NaOH solution for 5 min. The $CHCl_3$ layer was shaken again with cold aqueous 1 N NaOH, washed with water, dried over anhydrous Na_2SO_4, and

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concentrated to a pale-yellow foam, 10.5 g (71%). An analytical sample of the 4,5-epoxy compound **15** was obtained by recrystallization from MeOH as colorless prisms: mp 160–161.5 °C (resolidifies and remelts at 169–170 °C); NMR δ 1.7–3.00 (m, 11 H), 3.70 (s, 3 H, $NC(O)OCH_3$), 3.87 (s, 3 H, OCO_2CH_3), 4.63 (s, 1 H, H-5), 4.73 (br, 1 H, CHN), 6.58 (dd, 2 H, J = 2 Hz, aromatic); IR 1760, 1720, 1680 cm^{-1}; mass spectrum, m/e 387 (M^+), 285. Anal. Calcd for $C_{20}H_{22}NO_7 \cdot 0.5H_2O$: C, 60.60; H, 5.59; N, 3.53. Found: C, 60.63; H, 5.60; N, 3.53.

The alkaline layer was neutralized with 2 N HCl and then extracted with $CHCl_3$ (3 × 200 mL). The $CHCl_3$ layer was washed with saturated aqueous $NaHCO_3$ and aqueous NaCl and dried over anhydrous sodium sulfate. After filtration and concentration, the $CHCl_3$ layer gave 1.41 g (11%) of a yellow foam which was assigned the structure 4,5-epoxy-2-hydroxy-17-(methoxycarbonyl)morphinan-6-one (**16**) from its spectral properties: NMR δ 1.4–3.4 (m), 3.73 (s, 3 H, $NC(O)OCH_3$), 4.63 (s, 1 H, H-5), 4.68 (br, 1 H, CHN), 6.33 (dd, 2 H, J = 2 Hz, aromatic); IR 3500, 1720, 1680 cm^{-1}.

4,5-Epoxy-17-(methoxycarbonyl)morphinan-6-one Ethylene Ketal (19). a. Hydrolysis of 2-Methoxycarbonyl Group. In a three-necked flask, equipped with a dry ice condenser, gas inlet tube, and a stopper, was placed a solution of **15** (16.59 g, 0.043 mol) in 400 mL of THF (freshly distilled) and liquid NH_3 (600 mL). The reaction was maintained at refluxing NH_3 for 3 h and then NH_3 was allowed to evaporate slowly under a N_2 stream. THF was removed on the rotary and the residue was taken up in $CHCl_3$, extracted with saturated aqueous NaCl, and dried over anhydrous Na_2SO_4. After filtration, the solution was concentrated, and the residue (**16**) was used without further purification in the ketalization step.

b. Ketalization. The ketal was produced by heating at reflux overnight a mixture of 4,5-epoxy-2-hydroxy-17-(methoxycarbonyl)morphinan-6-one (**16**; 10.2 g, 0.031 mol) in $CHCl_3$ (700 mL), ethylene glycol (12 mL), and concentrated H_2SO_4 (0.3 mL) in a Soxhlet extraction apparatus having molecular sieves (Linde 4A) in the thimble. After being cooled, the reaction mixture was concentrated, taken up in CH_2Cl_2 (500 mL), and extracted with aqueous saturated $NaHCO_3$. The organic solution was dried (Na_2SO_4) and concentrated to give 13.3 g of **17** as a yellow-brown foam: NMR δ 1.0–3.2 (m), 3.67 (s, 3 H, $NC(O)OCH_3$), 4.0 (m, 4 H, ketal H's), 4.37 (s, 1 H, H-5), 4.63 (br, 1 H, CHN), 6.20 (d, 2 H, J = 2 Hz, aromatic). This material was used in the phosphorylation step without purification.

c. Phosphorylation. A mixture of compound **17** (13.3 g, 0.0357 mol), diethyl chlorophosphate (9.5 g, 0.055 mol), finely powdered anhydrous K_2CO_3 (25 g, 0.31 mol), and acetonitrile (600 mL) was stirred at room temperature under N_2 overnight. The reaction mixture was filtered and concentrated to leave 19.5 g of **18** as a light-brown oily gum: NMR δ 1.33 (pair of t, 6 H, CH_3CH_2O), 3.70 (s, 3 H, $NC(O)OCH_3$), 3.7–4.4 (m, 9 H), 4.63 (br, 1 H, CHN), 6.57 (br, 2 H, aromatic). It was used in the next step without further purification.

d. Deoxygenation. In a 1-L three-necked flask, equipped with a polypropylene stirring bar, dry ice condenser (with KOH guard tube), stopper, and gas inlet tube, was placed a solution of compound **18** (12 g) in THF (100 mL). Liquid NH_3 (dried over Na, 600 mL) was condensed in the flask and Li in small pieces was added until the reaction mixture turned blue and maintained the color for 1 min. Excess Li was decomposed by addition of NH_4Cl solid, 5 g) and ammonia was allowed to evaporate slowly overnight under a stream of N_2. The reaction mixture was then concentrated on the rotary evaporator and the residue was taken up in CH_2Cl_2/H_2O (3:1, 400 mL). The aqueous layer was extracted with more CH_2Cl_2 (2 × 200 mL). The combined CH_2Cl_2 layer was washed with water, dried over Na_2SO_4, and concentrated on the rotary evaporator to give a yellow-brown foam, 6.9 g. An analytical sample of **19** was obtained as a colorless foam by chromatography on silica gel with CH_3CN/CH_2Cl_2 (1:5): NMR δ 1.0–3.0 (m, 11 H), 3.73 (s, 3 H, $NC(O)OCH_3$), 4.0 (m, 4 H, ketal H's), 4.38 (s, 1 H, H-5), 4.57 (br, 1 H, CHN), 6.8 (m, 3 H, aromatic); IR 1680 cm^{-1}. Anal. Calcd for $C_{20}H_{23}NO_5$; C, 67.21; H, 6.49; N, 3.92. Found: C, 67.05; H, 6.53; N, 3.88.

(±)-4,5-Epoxy-17-methylmorphinan-6-one (1). LAH (0.75 g, 20 mmol) was slowly added to 100 mL of THF in a three-necked flask equipped with a condenser, addition funnel, N_2 inlet tube, stopper, and a stirring bar. The suspension was heated at reflux for 1 h and allowed to cool to room temperature. A solution of compound **19** (3.7 g, 10.5 mmol) in THF (100 mL) was slowly added, and the reaction mixture was heated at reflux for 1 h. Excess LAH was decomposed by addition of 0.8 mL of H_2O, 0.8 mL of aqueous NaOH (10%), and 2.5 mL of H_2O. The reaction mixture was stirred at room temperature for 15 min, filtered, and concentrated to give 2.88 g of **20** as a gum which solidified on cooling (88%): NMR δ 1.4–3.3 (m), 2.40 (s, 3 H, NCH_3), 3.6–4.2 (m, 5 H, ketal), 4.40 (s, 1 H, H-5), 6.5–7.2 (m, 3 H, aromatic). It was used in the next step without further purification.

A mixture of ketal **20** (2.8 g), aqueous HCl (2 N, 15 mL), and water (10 mL) was heated in an oil bath at 90 °C for 1 h. The reaction mixture was cooled, neutralized with aqueous NH_4OH (2 N), and extracted with $CHCl_3$ (4 × 60 mL). The $CHCl_3$ layer was washed with saturated aqueous NaCl, dried, and concentrated to give 2.19 g of a light-tan solid (91%). Upon recrystallization from EtOH (±)-4,5-epoxy-17-methylmorphinan-6-one (**1**) was obtained as light-buff prisms; mp 191–192 °C dec [lit.[3] mp 213–215 °C (benzene/petroleum ether); this difference may be due to the different solvent used for recrystallization]. It was found to be identical (NMR, IR, TLC) with an authentic sample prepared from morphine.[1] **1**: NMR δ 1.6–3.4 (m, 15 H), 2.42 (s, 3 H, NCH_3), 4.40 (s, 1 H, H-5), 6.60–7.30 (m, 3 H, aromatic); IR 1725 cm^{-1}. Anal. Calcd for $C_{17}H_{19}NO_2$; C, 75.80; H, 7.11; N, 5.20. Found: C, 75.24; H, 7.28; N, 5.31.

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