3 H), 1.1 (s, 6 H), 1.05 (s, 3 H), 0.8 (s, 3 H, 30-Me)], and mass [m/e 514 (M^+), 499, 481, 455, 454, 439, 421, 396, 381 (base), 367, 363, 311, 299, and 297] spectra were in accord with structure **3**. Anal. Calcd for $C_{32}H_{50}O_5$: C, 74.7; H, 9.8. Found: C, 74.8; H, 10.0.

Bourjotinolone A Diene (10). This was prepared according to the procedure followed for hispidone diene (**9**). The diene, crystallized from aqueous methanol, had mp 153–155 °C. The UV [(MeOH) λ_{max} 231, 237, and 246 nm (ϵ 14 700, 15 900, and 10 200)] and mass [m/e 470 (M^+), 452 (base), 437, 434, 423, 410, 409, 394, 381, 365, 337, 309, 295, and 269] spectra were in accord with structure **10**.

Acknowledgment. This investigation was supported by Grant No. 5-R01-CA-22336-02, awarded by the National Cancer Institute, Department of Health, Education and Welfare, Bethesda, MD 20014.

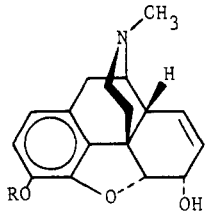
Registry No. **1**, 73891-71-1; **2**, 6985-35-9; **3**, 6985-36-0; **4**, 26790-94-3; **5**, 73891-72-2; **6**, 73891-73-3; **7**, 26808-11-7; **8**, 33573-55-6; **9**, 73891-74-4; **10**, 73891-75-5.

Communications

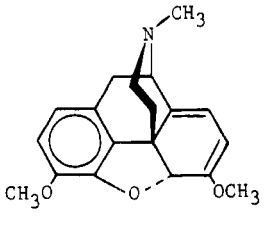
Synthetic Opium Alkaloids and Derivatives. A Short Total Synthesis of (±)-Dihydrothebainone, (±)-Dihydrocodeinone, and (±)-Nordihydrocodeinone as an Approach to a Practical Synthesis of Morphine, Codeine, and Congeners

Summary: Racemic dihydrothebainone (**19**), nordihydrocodeinone (**21**), and dihydrocodeinone (**22**) were synthesized in high overall yield from 3-methoxyphenethylamine (**4**), via the key intermediate (±)-1-bromonordihydrothebainone (**18**); the route utilized unprotected phenolic intermediates, involved directed Grewe-type cyclization, and, for **21** and **22**, exploited novel oxide bridge closure in the N-nor series.

Sir: Natural (−)-codeine (**1**) continues to occupy a position of central importance among the medically valuable derivatives of the opium poppy as the most frequently prescribed analgesic–antitussive agent worldwide. Since the first total synthesis[1] of (−)-codeine (**1**) and (−)-morphine (**2**), other successful routes,[2-8] including Grewe-type[4-6] and biomimetic approaches,[7,8] have appeared. However, a practical total synthesis of these drugs has remained elusive. These and continuing efforts,[9] together with possible shortages,[10,11] underscore the desirability of securing a route which could render licit production of medical



1: R = CH_3
2: R = H



3

opiates independent of the natural and sole commercial source of these drugs. Since the reports[4,5] that Grewe-type electrophilic cyclization of (±)-1-benzylhexahydroisoquinoline **9** afforded a 3% yield of the codeine precursor dihydrothebainone (**19**) (with isomeric **20** as the vastly predominant cyclization product), several groups have attempted to utilize this approach to codeine by introduction of a blocking substituent at the 6-position of the benzyl moiety in order to direct cyclization to the desired dihydrothebainone oxygenation pattern. Studies utilizing a methyl substituent were successful in this regard; however, such an approach must also employ a readily removable group to be of value in synthesis of codeine and congeners, of course not the case in the methyl series.[12] Substitution of bromine for methyl, unsuccessful heretofore,[12b,13,14] would be ideal since transformation of 4-hydroxymorphinans such as **19** to **22** (with the oxide bridge closed as in codeine) first involves bromination at C-1 of the morphinan system and later removal of the C-1 bromine atom by hydrogenolysis.[15] Recent work[16] describing conversion of (−)-dihydrothebainone [(−)-**19**] to (−)-codeine (**1**) (68% overall) via (−)-dihydrocodeinone [(−)-**22**] and to (−)-thebaine (**3**) (an important minor opium alkaloid) in somewhat higher yield renders any totally synthetic ap-

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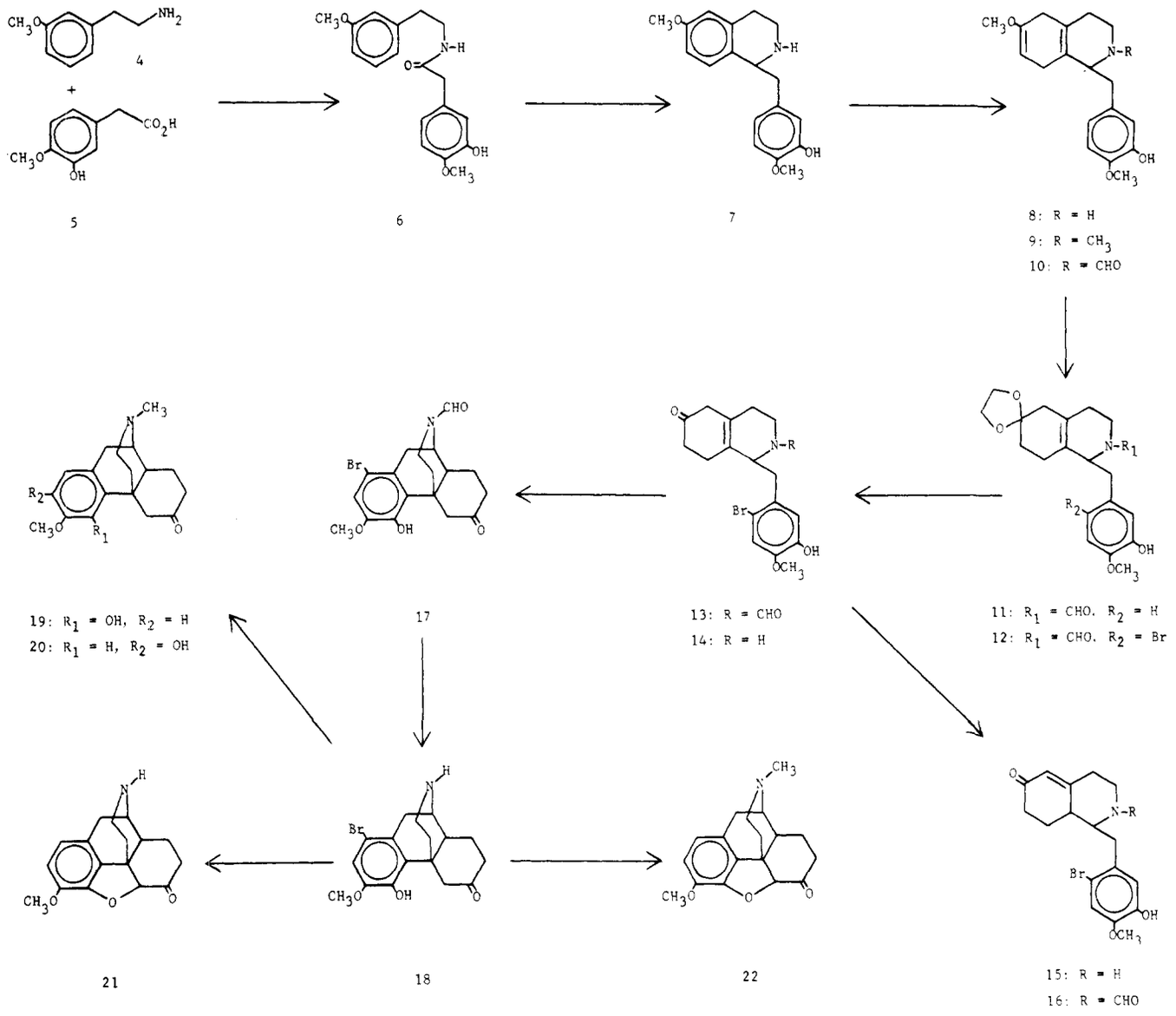
Scheme I



proach yielding 1-bromodihydrothebainone derivatives still more attractive. Such an approach, which utilizes unprotected phenolic intermediates, is short and experimentally simple, and affords (±)-dihydrothebainone (**19**), (±)-nordihydrocodeinone (**21**), and (±)-dihydrocodeinone (**22**) in high overall yield via the key intermediate (±)-1-bromonordihydrothebainone (**18**), is reported herein (Scheme I). The sequence rests essentially on a high-yield preparation of β,γ-unsaturated bromo ketone **13**, that is converted by directed Grewe-type cyclization into (±)-1-bromo-*N*-formylnordihydrothebainone (**17**), and on the novel oxide bridge closure in the N-nor series, which optionally provides ready access to either *N*-methyl or N-nor derivatives.

Heating a mixture of amine **4** and pure acid **5**[17] at 200 °C for 2 h under argon afforded amide **6**[18] (95%, EtOAc). Cyclization of **6** (0.35-mol scale), essentially as described for preparation of the 7-OH derivative[17] of **7**, generated an aqueous solution of the 1,2-dehydro derivative of **7**. Neutralization to pH 4–5 with concentrated aqueous NH_3 and reduction with an equimolar quantity of $NaCNBH_3$ in refluxing 65% MeOH (final concentration) for 1.5 h afforded pure (TLC) **7** (86%), mp 199.5–201.5 °C (lit.[18] mp 200 °C). Birch reduction[19,20] of 85 mmol of unpurified **7** with 1.92 mol of Li in 450 mL of liquid NH_3 and 225 mL each of dry THF and *t*-BuOH at −55 to −65 °C for 4 h and then at −75 °C until no **7** remained by TLC (~1.5 h) afforded (90%) essentially pure (TLC) **8**, mp 179.5–181.5 °C (lit.[20] mp 182 °C). Refluxing unpurified **8** with 1.5 equiv of pure[21a] $PhOCHO$[21b] in 10 volumes of EtOAc until homogeneous and then for ~0.75 h until TLC showed the absence of **8** gave (94%) pure **10**,[22] mp 141–143 °C (Et_2O–PhOH), which, like the *N*-formyl derivatives described below and others,[17] existed as two distinct rotamers, as shown by NMR. Stirring a solution of **10** (25 °C, 1 h) in 20 volumes of dry THF containing 1% (v/v) CH_3SO_3H and 3 equiv of ethylene glycol generated a solution of ketal **11**

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(22) Satisfactory C, H, N analyses (±0.4%) were obtained for all new compounds (labile base **14** was analyzed as **14**·TsOH) and for **10** which was reported as amorphous in ref 4. Spectral data (IR, NMR, mass) obtained for **10** and all new compounds were consistent with the assigned structures. Furthermore, synthetic (±)-**19**, **21**, and **22** were spectroscopically (IR, NMR, mass) and chromatographically (TLC, high-performance LC) identical with authentic samples of the corresponding (−)-isomers derived from opium.

(quantitatively by TLC), which was treated at 0–5 °C during 0.5 h with 1.05 equiv of recrystallized *N*-bromoacetamide (NBA) to afford essentially pure bromo ketal **12** after neutralization with NH_3 gas, solvent evaporation, and workup with $CHCl_3$–H_2O. Bromo ketal **12**, mp 182.5–184 °C (EtOAc), could be readily isolated in 88% yield but was most efficiently deketalized in 6 volumes of 5:1 88% HCO_2H–H_2O (25 °C, 1 h) followed by $CHCl_3$–aqueous $NaHCO_3$ workup to afford **13** (mp 203.5–206.5 °C (DMF–EtOAc); IR ($CHCl_3$) 1717 (C=O), 1665 (NCHO) cm^{-1}) in 90% yield from **10**. Bromo ketone **13** underwent Grewe-type cyclization to (±)-1-bromo-*N*-formylnordihydrothebainone (**17**), mp 229.5–231.5 °C (DMF–H_2O), in 60% isolated yield when treated in a screw-capped, high-density polyethylene bottle with 14% NH_4F·HF in dry CF_3SO_3H (0 °C, under argon for 72–96 h until **13** had essentially disappeared by TLC).[23] Also, isomerization of **13** occurred to give (TLC) the α,β-unsaturated bromo ketone **16**.[24] Pure **16** afforded (TLC) only traces of morphinan **17** and β,γ-unsaturated ketone **13** under the conditions used to cyclize **13** to **17**. Treatment of pure morphinan **17** under these conditions gave no **13** or **16** (TLC); apparently the acid-catalyzed equilibrium of **13** and **16** lies nearly exclusively toward the side of the latter, which undergoes little, if any, morphinan cyclization under these conditions.[14] Refluxing isolated **17** in 10:1 MeOH–37% aqueous HCl for 18 h afforded (±)-1-bromonordihydrothebainone (**18**), mp 220–223 °C, which was easily isolated in 92% yield by workup with NH_3–H_2O–2-propanol. (±)-Dihydrothebainone (**19**), mp 173–175 °C (lit.[4] mp 176 °C), was obtained directly and quantitatively from **17** by hydrolysis as above, evaporation to dryness, and hydrogenation[15,16] of the residue in 2 N AcOH containing 50 mg of 10% Pd/C, 0.3 mL of 37% HCHO, and 5 mmol of NaOAc per mmol of **17**, followed by workup with $CHCl_3$–aqueous NH_3. Bromination (1.1 mol of Br_2, 25 °C, 2 h) of an AcOH solution of the dry residue from hydrolysis of **17**, evaporation, treatment of the residue with $CHCl_3$–1 N NaOH[16] and hydrogenation as above without addition of HCHO afforded an 80% yield (from **17**) of (±)-nordihydrocodeinone (**21**), that was readily isolated (2-propanol, 1.1 equiv of 37% aqueous HCl) as **21**·HCl·$0.5H_2O$, mp 292–295 °C dec; anhydrous **21** base, mp 136.5–138 °C ($PhCH_3$). This appears to be the first example of closure of the oxide bridge in the basic N-nor series and is of potential interest in the synthesis of narcotic antagonists. When **17** was treated as in the preparation of **21** and 0.3 mL of 37% HCHO/mmol of **17** was added to the hydrogenation medium, (±)-dihydrocodeinone (**22**), mp 158–160 °C (lit.[25] mp 163 °C), was readily isolated as **22**·TsOH, mp 248–251 °C, in 79% yield from **17**.

This straightforward total synthesis of (±)-dihydrothebainone (**19**), (±)-nordihydrocodeinone (**21**), and (±)-dihydrocodeinone (**22**) in 37, 30, and 29% overall yields, respectively, from readily available 3-methoxyphenethylamine (**4**) requires isolation of only six intermediates; these are directly obtained sufficiently pure for further transformation. In view of these results, the high-yielding conversion[16] of (–)-**19** to (–)-thebaine (**3**) and (–)-codeine (**1**) discussed above and the facile O-demethylation[26a] of the latter to (–)-morphine (**2**), a practical total synthesis of these alkaloids (and the thebaine-based drugs) appears to be in hand.[27]

Acknowledgment. I thank Drs. Arnold Brossi and Arthur E. Jacobson for valuable advice and discussions. Thanks are also expressed to Dr. Everette L. May for his interest and encouragement. Determination of mass spectra by Mr. William Landis and Noel Whittaker and elemental analyses by Ms. Alice Wong and Paula Parisius of this Institute are gratefully acknowledged.

Registry No. **4**, 2039-67-0; **5**, 1131-94-8; **6**, 74007-21-9; (±)-**7**, 23180-27-0; (*R*)-**7**, 74035-73-7; (*S*)-**7**, 74035-74-8; (±)-**8**, 23180-28-1; (±)-**10**, 58780-17-9; (±)-**11**, 74007-22-0; (±)-**12**, 74007-23-1; (±)-**13**, 74007-24-2; (±)-**14**, 74007-25-3; (±)-**14**·TSOH, 74007-26-4; **15**, 54186-35-5; **16**, 54186-36-6; (±)-**17**, 74007-27-5; (±)-**18**, 74007-28-6; (±)-**19**, 15172-51-7; (±)-**21**, 74007-29-7; (±)-**21**·HCl, 74007-30-0; (±)-**22**, 74035-75-9; (±)-**22**·TSOH, 74035-76-0.

(23) A lower melting form of **17**, mp ~140 °C, which gave the higher melting form when boiled briefly in EtOAc, was occasionally obtained. It has been shown in this study that the carbamate function can be used instead of the *N*-formyl substitution in this step and others; however, the *N*-formyl derivatives are preferred since the amide function is readily cleaved by mild acid hydrolysis and the formyl derivatives usually crystallize more readily than the corresponding carbamates.

(24) Similar ketalization of **8** with 2.5% (v/v) TFA in MeOH (25 °C, 2 h), bromination with 1.05 equiv of NBA (0 °C), evaporation, deketalization by warming the residue in 5 volumes of H_2O, and addition of 5 volumes of acetone and concentrated aqueous NH_3 to pH 9–9.5 afforded labile amine **14** (69%), mp 160–164 °C dec (**14**·TsOH, mp 194–195.5 °C dec), containing minor amounts of **15**. Isomerization of this crude **14** with 48% HBr (25 °C, 48 h), under conditions similar to those[20] used for preparation of the debromo derivative of **15** from **8**, gave **15** (70%), mp 224.5–226 °C dec (lit.[13] mp 204–209 °C). Formylation of crude **14** and pure **15** (PhOCHO, refluxing $CHCl_3$) afforded **13** (65%) and **16** (87%), mp 205.5–207 °C, IR ($CHCl_3$) 1668 (C=O and NCHO) cm^{-1} (lit.[13] foam), respectively. Brief treatment of **16** with base (e.g., NaOMe in MeOH) resulted predominately in isomerization to **13**.

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(27) Optical resolution of (±)-**7** and application of the reaction sequence described here to the *R* enantiomer of **7** will afford entry into the natural morphine series. This resolution has readily been accomplished to give (+)-**7**, mp 217.5–219 °C, $[\alpha]^{23}_D$ +37.8° (*c* 0.25, DMF), and (–)-**7**, mp 218–219.5 °C, $[\alpha]^{23}_D$ –38.1° (*c* 0.25, DMF). The optical purity of these was demonstrated as for the 7-hydroxy derivatives[17] (norreticulines) by NMR analysis of the urea derivatives formed with (*S*)-(–)-α-methylbenzyl isocyanate. The chemical shifts of the methyl doublets ($\Delta\delta$ = 0.25) of the ureas from (*R*)-(+)- and (*S*)-(–)-norreticuline were δ 1.26 and 1.01[17] and for those of (+)- and (–)-**7**, δ 1.28 and 1.04 ($\Delta\delta$ = 0.24), respectively. The absolute configuration of (+)- and (–)-**7** can tentatively be assigned as *R* and *S*, respectively, if one assumes the compounds with corresponding chemical shifts have the same absolute configuration. Transformation of the *R* enantiomer of **7** to (–)-dihydrothebainone [(–)-**19**] is now in progress and will be reported in due course. Similarly, the *S* enantiomer affords entry into the unnatural morphine series, some members of which are of considerable importance as neuropharmacological research tools. See, for example, ref 26b and references cited therein.

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Received March 13, 1980

Asymmetric Alkylation of Amide Anions. Product Analysis by GLC Using Cholesteryl Cinnamate, a Liquid Crystal Phase

Summary: Chiral amides derived from (*S*)-(–)-prolinol and its methyl ether were metalated and alkylated to afford α-alkyl amides in 12–82% ee. The configuration induced by (*S*)-(–)-prolinol, as the chiral auxiliary reagent, was opposite to that induced by its methyl ether. Diastereomer compositions of the alkylated products were readily, in fact, uniquely, assessed by GLC by using a capillary column coated with cholesteryl cinnamate.