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BIOMIMETIC TOTAL SYNTHESIS OF (−)-CODEINE

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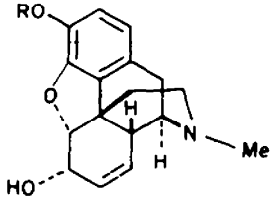
Abstract—The opium alkaloid (−)-codeine was synthesized in eight steps from (±)-N-norreticuline. *R*-(−)-norreticuline, obtained by resolution, was converted to (*R*)-N-trifluoroacetyl-6'-bromonorreticuline and the latter was subjected to phenolic oxidative coupling with a variety of aryliodoso complexes in dichloromethane. N-Trifluoroacetyl-1-bromonorsalutaridine prepared by this means was transformed to 1-bromosalutaridinol (as a mixture of epimers), and the latter were dehydrated separately to 1-bromothebaine with dimethylformamide dineopentyl acetal. Hydrolysis to 1-bromocodeinone, followed by reductive removal of Br with LAH, afforded (−)-codeine.

Elucidation of the detailed biosynthesis of morphine (**1**) stands as a singular achievement which continues to exert a major influence on biogenetic theory and practice.[1] A pivotal result from this work was Barton's demonstration that the tetracyclic skeleton of salutaridine (**3**) arises from oxidative coupling of *R*-(−)-reticuline (**2**), a finding that not only confirmed the remarkably prescient suggestion made many years earlier by Robinson,[2] but which also launched a frontal attack on the general problem of phenolic oxidative coupling.[3]

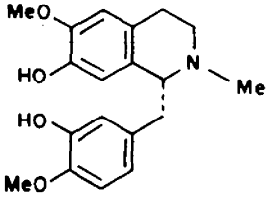
The important analgesic properties of morphine and its immediate biological precursor, (−)-codeine (**4**), lends particular significance to chemical simulation of the biosynthetic steps leading to these opium alkaloids and, to this end, a great deal of effort has been invested in devising methodology for the efficient synthesis of **3** from a 1-benzyltetrahydroisoquinoline.[4] A formal synthesis of **1** was achieved by Barton *et al.*, in which construction of the salutaridine nucleus via biomimetic oxidation of a reticuline was realized in 0.03% yield.[5] More recently, Schwartz has improved this transformation with the use of thallium tristrifluoroacetate to give N-acylnorsalutaridines in 11–23% yield.[6]

In searching for nonmetallic oxidants which might avoid the relatively harsh conditions employed in phenolic coupling, we have examined processes mediated by species based on hypervalent iodine.[7] Our rationale was drawn from the expectation that the iodine (III⇄I) redox would closely match the potential required for oxidation of reticuline to salutaridine and, furthermore, that the entire sequence, including genesis of the interannular bond, would take place via a *two*-electron transfer. Specifically, the coupling process (Scheme 1) depends upon prior formation of a phenol iodosobenzene complex A, which would be expected to react with a second equivalent of phenol to generate B. In this scenario, an aryl iodide and B are produced via heterolytic bond formation-scission processes, and the radical intermediates which prevail in one-electron phenolic oxidations are thereby circumvented.

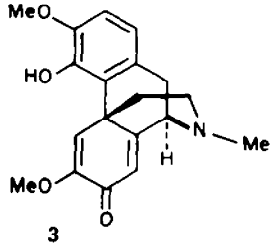
It was recognized that, in order to test this scheme in the context of a codeine synthesis, it would be necessary to prevent oxidation at the basic nitrogen of the reticuline nucleus and, for this reason, a N-acylnorreticuline was selected as the substrate. We were also cognizant of the possibility that undesired para–para coupling of a system such as **2** could intervene and, to forestall this outcome, we elected to follow the example adumbrated by Jackson[8] and developed extensively by Kametani,[9] in which a Br substituent is placed at the 6' position of the reticuline nucleus.[10] While our oxidation studies were in progress, Szántay and coworkers reported the cyclization of (±)-N-carboethoxy-6'-bromonorreticuline with phenyliodoso bistrifluoroacetate and cer-



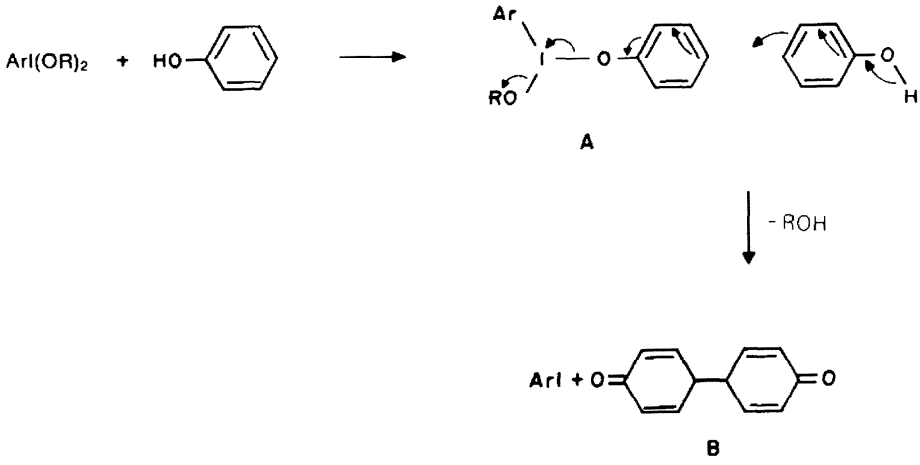
1, R = H
4, R = Me



2



3



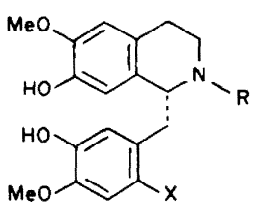
tain other iodine (III) systems in the presence of organic acids to give the corresponding salutaridine in modest yield (corrected for recovered starting materials).[11] We now present our results, which offer a more detailed view of aryliodoso complexes as oxidants for phenolic coupling and which have led to a total synthesis of natural (−)-codeine in seven steps from *R*-(−)-norreticuline, (**5**).

The starting material, **5**, was obtained by resolution of (±)-N-norreticuline, as previously described,[12] and was brominated by a procedure analogous to that employed with racemic norreticuline. The resulting *R*-(−)-6′-bromo-N-norreticuline (**6**) was converted to N-carboethoxy[9] and N-trifluoroacetyl derivatives, **7** and **8**, with ethyl chloroformate and trifluoroacetic anhydride respectively.

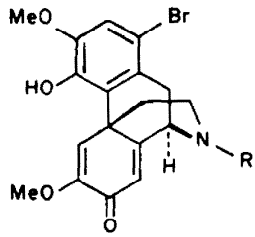
For the iodine (III) mediated oxidative coupling step, we surmised that an aryliodoso derivative was required which would be sufficiently reactive to produce the phenol complex A (Scheme 1), yet would not be so electrophilic that attack on the benzenoid ring could interfere. Since the diacetate and bistrifluoroacetate of iodosobenzene in dichloromethane have been shown to be mild and efficient oxidants for various systems, including phenols,[13] it was decided to investigate these derivatives as oxidants for **7** and **8**. Several aryl iodosodiacetates and bistrifluoroacetates were prepared from the corresponding aryliodo compounds, with the intention of determining whether substituents on the aryl ring would influence the coupling process. The preparation of these derivatives was effected by (a) oxidation of the iodo compound with peracetic acid, followed by exchange with trifluoroacetic acid (Method A),[14] or (b) by chlorination to give the aryliodo dichloride, followed by hydrolysis with sodium hydroxide to the aryliodoso compound and subsequent conversion to the diacetate with acetic acid (Method B).[15] Method A is effective for benzenoid substituents which are electron-releasing (except that *p*-methoxyiodobenzene gave a product with peracetic acid which was unstable and could not be characterized), whereas an electron-withdrawing substituent such as nitro necessitates Method B. Attempts to prepare the aryliodoso bistrifluoroacetate directly by either Method A (with trifluoroperacetic acid) or Method B (trifluoroacetic acid and an aryliodoso compound) were not successful.

Oxidative coupling was first attempted with **7**, in the hope that a direct conversion of the carboethoxy function to an N-methyl substituent could be effected in a subsequent reductive step. Exposure of **7** to phenyliodoso bistrifluoroacetate in dichloromethane afforded **9** in 28% yield after chromatographic purification, followed by crystallization. However, reduction of **9** with LAH gave no evidence for the formation of either salutaridinol (**14**) or its bromo derivative **13**, nor was it practical to cleave the urethane to produce the N-nor compound **11**. Consequently, we turned to **8**, in the expectation that unmasking of the nitrogen after coupling would be straightforward.

The results of oxidative coupling of **8** with various aryliodoso bistrifluoroacetates are given in Table 1. Generally, it was preferable to run the reaction to partial completion and then carry out a chromatographic separation of dienone **12** from unreacted **8** and brown, polymeric material which was invariably produced. The yields of **12** refer to recrystallized product and do not



5. R = X = H
6. R = H, X = Br
7. R = CO_2Et, X = Br
8. R = $COCF_3$, X = Br



9. R = CO_2Et
10. R = CH_3
11. R = H
12. R = $COCF_3$

Table 1. Oxidative coupling of **8** with aryliodoso bistrifluoroacetate compiexes

Oxidant	mp (°C)	Method of Preparation	Yield of 12 (%)
$C_6H_5I(OCOCF_3)_2$	121 - 126	A	21
$o\text{-}CH_3C_6H_4I(OCOCF_3)_2$	93 - 95	A	10
$m\text{-}CH_3C_6H_4I(OCOCF_3)_2$	87 - 90	A	12
$p\text{-}CH_3C_6H_4I(OCOCF_3)_2$	100 - 106	A	12
$m\text{-}CH_3OC_6H_4I(OCOCF_3)_2$	103 - 106	A	14
$m\text{-}O_2NC_6H_4I(OCOCF_3)_2$	150 - 154	B	8
$p\text{-}ClC_6H_4I(OCOCF_3)_2$	131 - 133	A	9
$p\text{-}C_6H_5C_6H_4I(OAc)_2$	133 - 139	B	0
$P\text{-}I(OAc)_2$[23]			8
C_6H_5IO.[15]TFA			11

take account of recovered starting material. Oxidative coupling of **8** was accompanied by the appearance of a deep green coloration and proceeded rapidly at −40°. However, the reaction was independent of the nature of the aryl substituent in the iodoso complex.

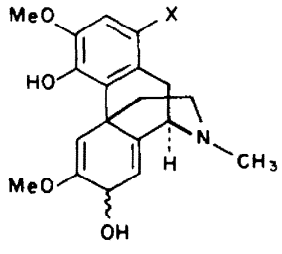
The formation of *R*-(−)-1-bromo-N-trifluoroacetylnorsalutaridine (**12**) was readily recognized from its UV spectrum with maxima at 239.5 and 280 nm corresponding to the dienone chromophore, and from its IR spectrum, which displayed a series of strong bands at 1690 (ketone), 1680 (trifluoroacetyl), 1660 (5,6-double bond), and 1615 cm^{-1} (8,9-double bond).

The trifluoroacetyl blocking group was removed cleanly from **12** with potassium carbonate in methanol to give 1-bromo-N-norsalutaridine (**11**) and the latter, without purification, was treated with 37% aqueous formaldehyde and then with sodium borohydride in water. A 1 : 1 mixture of epimeric 1-bromosalutaridinols **13** was obtained (68% from **12**), which were readily separable by chromatography into a crystalline alcohol, **13A**, and an oily isomer, **13B**. Thus, borohydride accomplishes reduction of both the carbinolamine intermediate from 11 to set the N-Me substituent in place[16] and also the dienone CO, in preparation for closure to the thebaine nucleus. The formation of a pair of epimeric alcohols in this reduction is in accord with the corresponding reduction of **3** to a mixture of salutaridinols **14** (I and II).[17] In the present case, it was not possible to assign configurations to **13A** and **13B**.

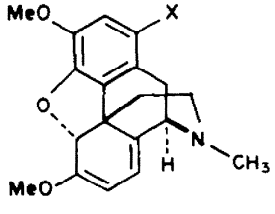
With the acquisition of the stereoisomeric bromosalutaridinols it became important to establish a pathway from *both* of these alcohols to the thebaine nucleus. Previously, the conversion of salutaridinol to thebaine (**15**) has been accomplished in low yield with aqueous acid[5] or with thionyl chloride in pyridine-sodium hydroxide.[18] Neither of these protocols was satisfactory when applied to **13**, and we therefore sought a new tactic to bring about this formal dehydration.

It has been shown that alcohols can be smoothly dehydrated with acetals of dimethylformamide (DMF)[19] and, when crystalline **13A** was exposed to the dineopentyl acetal of DMF in dichloromethane at room temperature, 1-bromothebaine (**16**) was produced in 80% yield after crystallization. Oily **13B**, under the same conditions, afforded a 63% yield of **16**. The formation of relatively volatile byproducts (neopentanol and DMF) in this reaction greatly simplifies the isolation of **16** and this methodology substantially improves a troublesome biomimetic step en route to the morphine alkaloids.

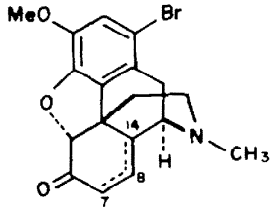
Our expectation that **16** could be converted directly to thebaine (**15**) (thereby bringing our route into convergence with preexisting morphine syntheses) was thwarted by the finding that conditions needed for reductive removal of the bromine substituent caused extensive degradation of the alkaloid nucleus. Thus, treatment of **16** with lithium aluminum hydride in refluxing tetrahydrofuran yielded no more than a trace of **15**. Since the cyclohexadienyl moiety of **16** appeared to



13, X = Br
14, X = H



15, X = H
16, X = Br



17, $\Delta^{7,8}$
18, $\Delta^{8,14}$

be the source of difficulty, this was hydrolyzed with aqueous formic acid in the presence of mercuric acetate, following a procedure of Dauben.[20] A mixture of 1-bromocodeinone (**17**) and 1-bromoneopinone (**18**) was obtained as expected, and the mixture was treated with hydrogen chloride, followed by sodium hydroxide, to isomerize the $\beta\gamma$ double bond into conjugation.[21] This procedure afforded **17** in 67% yield from **16**. Finally, reduction of **17** with lithium aluminum hydride in tetrahydrofuran[22] gave (−)-codeine (**4**), identical in all respects including optical rotation with a sample of natural material liberated from a commercial sample of codeine sulfate.

EXPERIMENTAL

M.p. were determined on a Thomas–Hoover or a Büchi apparatus and are uncorrected. IR spectra were obtained with a Perkin–Elmer 727B spectrophotometer. NMR spectra were obtained with a Varian EM-360A, HA-100, or FT-80A spectrometer: chemical shifts are reported in ppm downfield from TMS internal standard ($\delta = 0$). Coupling constants are given in hertz, with the following abbreviations for splitting patterns: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet. Optical rotations were measured with a Perkin–Elmer 243 polarimeter. MS were obtained on a Varian MAT CH-7 or a Hitachi-Perkin–Elmer RMU-6E spectrometer at 70 eV. Exact mass measurements were made by the peak match technique on a CEC-110B mass spectrometer. Combustion analyses were performed by Micanal, Tucson, AZ.

R-(−)-6′-*Bromo*-N-*norreticuline* (**6**). A soln of 3.07 g (19.2 mmol) of Br_2 in 200 mL AcOH was added dropwise during 1.5 hr to a mechanically stirred soln of 6.04 g (19.2 mmol) optically pure *R* (**5**)[12] at 25°. When the addition was complete, the soln was stirred 15 min, evaporated to a foam, dissolved in 50 ml MeOH, and filtered through Celite. The filter was washed with 75 ml MeOH and the combined filtrate and washings were heated to boiling and treated with 8 ml conc NH_4OH to give pH 9–9.5 (moist Hydrion paper). Crystalline material separated rapidly as fine needles and, after cooling the slurry to 15°, the solid was filtered, washed with 125 ml MeOH and dried to give 6.67 g (88%) of analytically and chromatographically pure **6**: m.p. 223.5–224.5° (dec); $[\alpha]_D^{23}$ −42.4° (*c* 0.8, DMSO); MS *m/e* 393/395 (M^+). (Found: C, 54.75; H, 4.95; N, 3.46. Calc. for $C_{18}H_{20}NO_4Br$: C, 54.83; H, 5.11; N, 3.55).

R-(−)-6′-*Bromo*-N-*trifluoroacetylnorreticuline* (**8**). To a suspension of 3.39 g (8.60 mmol) of **6** in 40 ml CH_2Cl_2 containing 2.5 ml dry pyridine in a water bath at 20° was added dropwise 4 ml (35 mmol) trifluoroacetic anhydride. The mixture was stirred for 15 hr at room temp during which the solid dissolved to give a dark orange-colored soln. To this was added 15 ml water with cooling, and the organic layer was separated and washed 3 times with 30 ml 2M H_2SO_4, twice with 20 ml sat $NaHCO_3$aq and with 10 ml brine. After drying (Na_2SO_4), the solvent was removed to give N,O,O,-trifluoroacetylnorreticuline as a foam. This was taken up into 50 ml MeOH and the soln was cooled in an ice-bath as 12 ml 1M K_2CO_3 was added. After stirring for 2 min, the soln was diluted with 6 ml 2M H_2SO_4, followed by 50 ml water. The mixture was extracted twice with 150 ml CH_2Cl_2 and, after drying (Na_2SO_4) and removal of the solvent, 3.37 g (80%) of virtually pure **8** was obtained as a foam: $[\alpha]_D^{23}$ −65.7° (*c* 1.44, $CHCl_3$); IR (KBr) 3400, 1680, 1500, 1460, 1440, 1370, 1350, 1285, 1255, 1190, 1155, 1115, 1020, 860 and 800 cm^{-1}; NMR ($CDCl_3$) δ 7.01 (1*H*, *s*), 6.82 (1*H*, s), 6.69 (1H, s), 6.60 (1H, s), 5.78 (1H, dd, J = 11, 6 Hz), 5.53 (2H, m), 3.88 (6H, s), 3.45–2.70 (4H, m); MS *m/e* 489/491. (Found: C, 48.75; H, 3.97; N, 2.68. Calc. for $C_{20}H_{19}BrF_3NO_5$: C, 48.95; H, 3.91; N, 2.86).

Aryliodoso Bistrifluoroacetates

Method A. The aryliodoso diacetate was prepared from the corresponding aryl iodide following the procedure described for the parent phenyl compound.[14] The diacetate was taken up into trifluoroacetic acid and warmed at 50–60° until dissolution was complete. Upon cooling the soln. the aryliodoso bistrifluoroacetate crystallized and was collected and dried *in vacuo*.

Method B. The aryliodo dichloride was prepared from the aryl iodide and converted to the corresponding aryliodoso compound by the procedure used for the parent phenyl compound.[15] The iodoso compound was dissolved in warm glacial ACOH containing a few drops Ac_2O and the aryliodoso diacetate was collected upon cooling. This material was converted to the bistrifluoroacetate as described under Method A.

(±)-1-*Bromo*-N-*carbethoxynorsalutaridine* (**9**). To a stirred, N_2-swept soln of (±)-**7** (0.261 g, 0.60 mmol) in 10 ml CH_2Cl_2 containing nitrobenzene (6.1 μl, 0.06 mmol) at −78° was added a soln of phenyliodoso bistrifluoroacetate (0.26 g, 0.66 mmol) in 2 ml CH_2Cl_2. The mixture was stirred at −78° for 2.5 hr and quenched by addition of sat $NaHCO_3$aq (20 ml). The organic phase was separated, dried ($MgSO_4$), and concentrated *in vacuo* to a green oily residue which was applied to a column of silica gel (10 g) and eluted with $CHCl_3$. The product was further purified by medium-pressure LC on silica gel (30% hexane/EtOAc as eluant, 42 psi, 4.6 ml/min). Fractions were collected every minute and concentrated *in vacuo* to give 0.072 g (28%) of **9** as an amorphous solid: UV (EtOH) λ_{max} 238, 283 nm; IR ($CHCl_3$) 3340, 2940, 1675, 1440, 1285 cm^{-1}; NMR($CDCl_3$) δ 7.46 (1H, s), 7.04 (1H, s), 6.35 (1H, s), 5.30 (1H, broad s), 4.17 (2H, q, J = 7 Hz), 3.90 (3H, s), 3.72 (3H, s), 3.12 (2H, t, J = 7 Hz), 1.28 (3H, t, J = 7 Hz); MS *m/e* 463/465 (1:1).

(−)-1-*Bromo*-N-*trifluoroacetylnorsalutaridine* (**12**). To a soln of 0.475 g (0.969 mmol) of (−)-**8** in 50 ml CH_2Cl_2 under N_2 at −40° was added dropwise a soln of 0.415 g (0.97 mmol) iodosobenzene bistrifluoroacetate in 10 ml CH_2Cl_2. The mixture was stirred at −40° for 45 min, during which a green coloration appeared. The reaction was quenched by addition of 15 ml sat $NaHCO_3$aq and allowed to warm to room temp while stirring. The mixture was stirred for 30 min. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated to give a brown residue. This was purified by flash chromatography using 1% MeOH in ether as eluant. The mixed fractions were further purified by preparative TLC (silica gel, 1% MeOH in ether) to give 101 mg (21%) of pure **12**. A sample was recrystallized from EtOAc: m.p. 220–222°; $[\alpha]_D^{22}$ −73.3 (*c* 0.35, $CHCl_3$); UV (EtOH) λ_{max} 239.5 (ϵ 21,800), 280 nm (ϵ 7,200); IR (KBr) 3380, 2940, 1690, 1680, 1660, 1615, 1475, 1440, 1280, 1210, 1175, 1135, 1100 cm^{-1}; NMR ($CDCl_3$) δ 7.48 (1H, d, J = 3 Hz), 7.08 (1H, s), 6.38 (1H, d, J = 3 Hz), 5.59 (1H, t, J = 4 Hz), 3.92 (3H, s), 3.84 (2H, m), 3.74 (3H, s), 3.23 (2H, d, J = 4 Hz), 3.1–2.5 (2H); MS *m/e* 488/490 (1:1) *m/e* 489.023 (Calc for $C_{20}H_{17}BrF_3NO_5$, 489.022).

(−)-1-*Bromosalutaridinol* (**13**). To a soln of 0.330 g (0.676 mmol) of **12** in 40 ml MeOH was added 5 ml 1M K_2CO_3aq, and the mixture was stirred at room temp for 2.5 hr. Then 0.8 ml of a 37% aqueous soln of formaldehyde was added and the mixture was stirred at room temp for a further 3 hr. The mixture was cooled in ice as 0.5 g $NaBH_4$ was added portionwise. The slurry was stirred at 0° for 1 hr and at room temp for a further 1 hr after which the solvent was removed and the residue was partitioned between water and CH_2Cl_2. The organic phase was separated, the aqueous phase was extracted 3 times with CH_2Cl_2, and the combined organic extract was dried (Na_2SO_4). After removal of the solvent, the residue was taken up into 50 ml hot EtOAc which, upon cooling, deposited 101 mg (37%) of **13A**: m.p. 191–194°; $[\alpha]_D^{23}$ −51° (*c* 0.27, DMSO); IR (KBr) 3400, 1655, 1595, 1468, 1429, 1410, 1318, 1283, 1240, 1215, 1195, 1189, 1155, 1096, 1045, 1015, 966, 930, 885, 836, 795; NMR (DMSO-d_6) δ 7.02 (1H, s), 6.20 (1H, s), 5.71 (1H, s), 5.56 (1H, broad d, J = 4 Hz), 4.45–4.15 (1H, m), 3.76 (3H, s), 3.48 (3H, s), 2.22 (3H, s), 1.8–2.7 (6H); MS *m/e* 407/409 (1:1), *m/e* 407.073 (Calcd for $C_{19}H_{22}BrNO_4$, 407.073).

The filtrate after removal of **13A** was concentrated and the oily residue was purified by preparative layer chromatography on alumina. Elution with $CHCl_3$ gave 86 mg (31%) of **13B** as an oil: $[\alpha]_D^{23}$ −43.0° (*c* 1.85, DMSO); IR (neat) 3400, 1655, 1600, 1467,

1431, 1395, 1278, 1211, 1150, 1094, 1015, 835 cm^{-1}; NMR ($CDCl_3$) δ 7.28 (1H, s), 6.97 (1H, s), 6.31 (1H, s), 5.80 (1H, d, J = 3.5 Hz), 3.86 (3H, s), 3.67 (3H, s), 2.41 (3H, s), 3.74–1.90 (8H); MS *m/e* 407/409 (1 : 1), *m/e* 407.073 (Calc for $C_{19}H_{22}BrNO_4$, 407.073).

(−)-1-*Bromothebaine* (**16**). A suspension of 67 mg (0.164 mmol) of **13A** in 3.2 ml CH_2Cl_2 containing 138 μl (0.495 mmol) DMF dineopentylacetal was stirred at room temp for 8 hr; during which time the solid gradually dissolved. The solvent and volatile byproducts were removed *in vacuo* and the oily residue was chromatographed on a short column of alumina (Activity I). Elution with $CHCl_3$ afforded a gummy solid which was triturated with warm ether and crystallized from MeOH to yield 51 mg (80%) of **16**: m.p. 170–175°; $[\alpha]_D^{20}$ −194.8 (*c* 0.9, $CHCl_3$); UV (MeOH) λ_{max} 287.5 nm (ε 6830); IR (KBr) 2925, 2780, 1604, 1485, 1430, 1305, 1285, 1230, 1194, 1160, 1137, 1105, 1050, 1013, 968, 915, 846, 835 cm^{-1}; NMR ($CDCl_3$) δ 6.85 (1H, s), 5.59 (1H, d, J = 6.5 Hz), 5.30 (1H, s), 5.06 (1H, d, J = 6.5 Hz), 3.84 (3H, s), 3.60 (3H, s), 2.47 (3H, s), 3.75–2.00 (7H); MS *m/e* 389/391 (1 : 1), *m/e* 389.063 (Calc for $C_{19}H_{20}BrNO_3$, 389.063).

(−)-*Codeine* (**4**). A mixture of 0.104 g (0.266 mmol) of **16**, 5.7 mg (0.018 mmol) mercuric acetate, and 7.1 ml 3N formic acid was stirred under a N_2 for 6.5 hr, and 50 m sat K_2CO_3aq was added. The mixture was extracted with three 50-ml portions $CHCl_3$, and the combined extracts were washed with water and dried (Na_2SO_4). Removal of the solvent left 111 mg of a mixture of **17** and **18** as a foam. This was dissolved in 0.4 ml CH_2Cl_2 and 0.4 ml 10% HCl in ether was added. The mixture, which contained a ppt, was stirred at room temp for 0.5 hr and 0.2 ml CH_2Cl_2 was added followed by a further 0.2 ml 10% HCl in ether. After stirring at room temp for 0.25 hr, the mixture was partitioned between 50 ml $CHCl_3$ and 50 ml 0.2M NaOH. The organic layer was separated, the aqueous phase was extracted with two 25 ml portions $CHCl_3$, and the combined organic extracts were washed with water and dried (Na_2SO_4). Removal of the solvent gave 67 mg crude **17**, which was dissolved in 1.5 ml THF. To this was added 38 mg (1 mmol) LAH and the suspension was refluxed for 12 hr. After the mixture had cooled, 0.2 ml 1 : 1 aqueous THF mixture was added, followed by 0.1 ml sat soln of potassium sodium tartrate. The mixture was extracted with CH_2Cl_2, and the extract was washed with water, dried (Na_2SO_4), and concentrated to dryness. This residue was chromatographed on silica and eluted with 5% diethylamine in $CHCl_3$ to give 20 mg (25% from **16**) of **4**, which was recrystallized from toluene: m.p. 150–152°; $[\alpha]_D^{21}$ −107.4 (*c* 0.3, $CHCl_3$); IR (KBr) 3600, 3440, 2930, 2910, 2830, 1658, 1599, 1498, 1450, 1440, 1380, 1357, 1332, 1275, 1256, 1205, 1158, 1121, 1090, 1050, 1020, 975, 941, 909, 835, 795 cm^{-1}; NMR ($CDCl_3$) δ 6.60, 6.52 (2H, AB, J = 8 Hz), 5.65 (1H, broad, d, J = 10 Hz), 5.25 (1H, d of t, J = 10, 2.5 Hz), 4.84 (d of d, 1H, J = 6.5, 1.5 Hz), 4.25–4.00 (1H, m), 3.85 (3H, s), 2.43 (3H, s), 3.35–1.75 (9H); MS *m/e* 299. This material was identical with a sample of authentic (−)-codeine by mixed m.p. and comparison of MS and NMR spectra and TLC behaviour in two solvent systems.

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