solid which crystallized from dry Me_2SO/acetone (avoiding heat) as needles: mp 196–197 °C; NMR (Me_2SO-d_6/acetone-d_6) 270 MHz δ 7.47–8.19 (m, 7, aromatic), 8.82 (d, 1, H_8), 8.94 (s, 1, H_{14}), 9.27 (s, 1, H_7) (cf. Table I for other NMR data).

***trans*-1,2-Bis(benzoyloxy)-1,2-dihydrodibenz[*a*,*h*]anthracene (3b).** Dehydrogenation of **10** (323 mg, 0.62 mmol), through bromination with NBS, and dehydrobromination with DBN were carried out by the procedures employed for the analogous reactions of **11a**; the only modifications were omission of the heat lamp and an increase in the reaction time of the second stage to 16 h. Similar workup furnished **3b** (300 mg, 94%): mp 143–145 °C; NMR data in Table I.

***trans*-1,2-Dihydroxy-1,2-dihydrodibenz[*a*,*h*]anthracene (3a).** Methanolysis of **3b** (274 mg, 0.53 mmol) by the procedure employed for preparation of **1a** gave crude **3a**. Chromatography on Florisil and elution with benzene–ethyl acetate (4:1) gave pure **3a** (123 mg, 72%): mp 257–259 °C; NMR (acetone-d_6/D_2O) δ 7.28–8.18 (m, 7, aromatic), 8.91 (m, 2, $H_{8,14}$), 9.31 (s, 1, H_7) (cf. Table I for other NMR data).

***trans*-1,2-Dihydroxy-*anti*-(and *syn*)-3,4-epoxy-1,2,3,4-tetrahydrodibenz[*a*,*h*]anthracenes (4).** Epoxidation of **3a** by the procedure employed (trituration omitted) for **2** gave a product (72%) shown by NMR and high-pressure LC analysis to be a 3:1 mixture of the syn and anti isomers (cf. Table I for NMR data). Separation was accomplished on a Du Pont Zorbax SIL column (0.6 × 25 cm) eluted with 40% THF in heptane.

***trans*-3,4-Diacetoxy-1,2,3,4-tetrahydrodibenz[*a*,*h*]anthracene (11b).** A solution of **11a** (990 mg, 1.93 mmol) in 1 N NaOH (30 mL), THF (45 mL), and methanol (85 mL) was stirred at ambient temperature for 3 h. Solvent was stripped off, cold water was added, and the precipitate of crude tetrahydro diol (590 mg) was removed by filtration and dried. Acetylation with acetic anhydride (50 mL) and pyridine (12 mL) at room temperature overnight gave **11b** (763 mg, 98%) as a pale yellow solid: mp 216–217 °C (lit.[8] mp 195–196 °C); NMR δ 2.03 (s, 3, CH_3), 2.15 (s, 3, CH_3), 2.33 (m, 2, H_2), 3.36 (t, 2, H_1), 5.12 (q, 1, H_3), 6.17 (d, 1, H_4, $J_{3,4}$ = 6 Hz), 7.4–8.04 (m, 7, aromatic), 8.36 (s, 1, H_{14}), 8.75 (m, 1, H_8), 9.05 (s, 1, H_7).

3-Acetoxy-1,2-dihydrodibenz[*a*,*h*]anthracene (13b). A solution of **11b** (1.15 g, 2.9 mmol) and *p*-tosic acid (220 mg) in benzene (200 mL) was refluxed for 1.5 h. The solvent was then evaporated, isopropenyl acetate (200 mL) and acetic anhydride (15 mL) were added, and the solution was refluxed overnight. Conventional workup, followed by chromatography on Florisil and elution with benzene, gave **13b** as a white solid (745 mg, 79%): mp 232–233 °C (benzene); NMR δ 2.2 (s, 3, CH_3), 2.68 (t, 2, H_2), 2.55 (t, 2, H_1), 6.34 (s, 1, H_4), 7.08–8.0 (m, 7, aromatic), 8.37 (s, 1, H_{14}), 8.7 (m, 1, H_8), 9.0 (s, 1, H_7).

3-Acetoxydibenz[*a*,*h*]anthracene (14b). A solution of **13b** (745 mg, 2.2 mmol) and DDQ (522 mg, 2.3 mmol) in benzene (100 mL) was refluxed for 1.5 h. The hot solution was filtered, and the filtrate was concentrated and crystallized, affording **14b** (581 mg, 74%) as a white solid: mp 247–248 °C; NMR δ 2.36 (s, 3, CH_3), 7.16–8.08 (m, 9, aromatic), 8.68–8.91 (m, 2, $H_{1,8}$), 9.01 and 9.08 (2 s, 1, $H_{7,14}$).

3-Hydroxydibenz[*a*,*h*]anthracene (14a). A suspension of **14b** (467 mg, 1.57 mmol) in a solution of *n*-butyllithium (2.3 mmol) in ether (50 mL) was heated at reflux for 1 h. The usual workup followed by chromatography on Florisil (elution with benzene) afforded crude **14a**. Crystallization from THF–benzene gave pure **14a** (450 mg, 98%): mp 288–290 °C; NMR (acetone-d_6/D_2O) δ 7.16–8.15 (m, 9, aromatic), 8.7–9.05 (m, 2, $H_{1,8}$), 9.16 and 9.22 (2 s, 2, $H_{7,14}$).

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Registry No. 1a, 66267-19-4; **1b**, 72378-81-5; **2**, 70951-81-4; **3a**, 66267-18-3; **3b**, 66302-72-5; **4**, isomer 1, 72378-82-6; **4**, isomer 2, 72402-37-0; **9**, 72378-83-7; **10**, 66267-13-8; **11a**, 72378-84-8; **11a**, 1-bromo derivative, 72378-85-9; **11b**, 66267-14-9; **13b**, 72378-86-0; **14a**, 1421-80-3; **14b**, 72378-87-1; hexahydrodibenz[*a*,*h*]anthracene isomers, 72390-47-7; octahydrodibenz[*a*,*h*]anthracene mixed trans diol benzoates, 72390-49-9.

Expedient Synthesis of Racemic and Optically Active *N*-Norreticuline and N-Substituted and 6′-Bromo-*N*-norreticulines[1]

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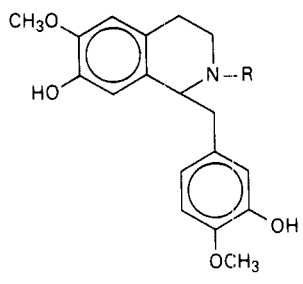
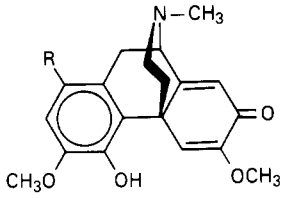
Practical methodology, utilizing unprotected diphenolic intermediates, is described for the synthesis of crystalline (±)-*N*-norreticuline, and a number of *N*-substituted and 6′-bromo congeners, which are versatile starting materials for alkaloidal syntheses. This sequence includes a simple high-yielding optical resolution of the key intermediate, (±)-*N*-norreticuline, and is readily amenable to synthesis of large quantities of these 1-benzyl-1,2,3,4-tetrahydroisoquinolines in racemic and chiral form. Thermal condensation of the readily available (from vanillin) 2-(4-hydroxy-3-methoxyphenyl)ethylamine with (3-hydroxy-4-methoxyphenyl)acetic acid afforded the amide (90%) which was transformed to (±)-*N*-norreticuline–*p*-toluenesulfonic acid–1-water (80%) via 1,2-dehydro-*N*-norreticuline generated in situ. Direct conversion of (±)-*N*-norreticuline to the *N*-carbethoxy and *N*-formyl derivatives in >90% yield is reported as is direct regioselective bromination of these compounds to the corresponding 6′-bromo compounds. Rotomers of these *N*-acyl derivatives were detected by NMR, and in the case of the *N*-formyl compounds the rotomers were separable by TLC. Direct bromination of (±)-*N*-norreticuline afforded the 6′-bromo base in 93% yield. The racemate and optical isomers of reticuline and the racemate of the 6′-bromo compound were readily obtained in >90% yield by borane reduction of the corresponding diphenolic *N*-formyl-*N*-nor derivatives. The racemate of tetrahydropapaveroline–hydrogen bromide and the 6′-bromo compound was obtained (>90%), in addition to the optical isomers of the former, by O-demethylation of the corresponding *N*-norreticuline derivatives.

The 1-benzyl-1,2,3,4-tetrahydroisoquinolines (BTIQ) *N*-norreticuline (**1**), reticuline (**2**), and their congeners are valuable intermediates for biomimetic and other syntheses of a large number of isoquinoline alkaloids and related

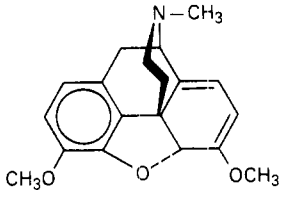
compounds;[2-4] however, progress in this area has been impeded by the relatively unavailable nature of these BTIQ. We would now like to present methodology which alleviates this problem by providing ready access to 1, 2,



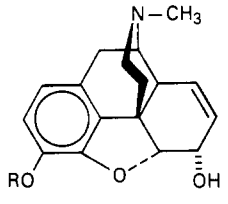
1: R = H
2: R = CH_3



3: R = H
15: R = Br



4



5: R = CH_3
6: R = H

and a number of derivatives. Since the racemates and optical isomers of these compounds can now be conveniently prepared in quantity as described below, alkaloidal syntheses and other studies utilizing these materials should be greatly facilitated.

The morphinans,[5] aporphines,[6] berbines,[7] pavinans,[8] and isopavinans[8] are representative of the diverse types of carbon–nitrogen skeletons which have been prepared from these BTIQ, and frequently, different oxygenation patterns within each class can be obtained by use of the proper experimental conditions or blocking groups. The (+) enantiomer of reticuline [(+)-2] has been employed as a substrate in an enzymatic model system for phenolic oxidation,[9] and previous work has shown that reticuline plays a central role in plant biosynthesis of berbines,[10] aporphines,[11] and, among others, the important opium alkaloids[12] (–)-thebaine (4), (–)-codeine (5), and (–)-morphine (6). In the opium poppy, *Papaver somniferum*, the latter three compounds are sequentially synthesized from (+)-salutaridine (3) which is formed by intramolecular oxidative coupling of (–)-reticuline [(–)-2].[12] The in vitro oxidation of 2 to 3 has only been accomplished in very low yield,[13] and in view of the efficient methods available for the chemical conversion of 3 → 4[14] → 5[15] → 6,[16] the direct, high-yielding oxidation of 2 to 3 remains an important unsolved problem in the chemistry of the opium alkaloids. Given the solution to this problem and the readily available source of (–)-reticuline [(–)-2] described below, production of medically useful opioids by total synthesis could become a distinct possibility.

With these considerations and our general interest in phenolic oxidation in mind, we addressed ourselves to the problem of finding a practical route, amenable to large-scale work, for synthesis of the racemic and chiral forms of 1, 2, and their congeners. One of our major considerations early in this work was the development of a highly efficient method for the synthesis of large quantities of (±)-1. It was also hoped that this method would prove to be of general utility for the synthesis of phenolic BTIQ related to (±)-1. We envisioned (±)-1 as a key compound in this work since optical resolution would provide the two enantiomers, either of which could, in principle, be racemized and recycled if desired. Variation of the nitrogen substituent in secondary amine (±)-1 seemed readily attainable and was anticipated to provide additional flexibility for this route. Classical routes to (±)-1[17,18a,b] and (±)-2[18a,b] are lengthy sequences, involving *O*-benzyl-protected intermediates and finally cleavage of the two *O*-benzyl functions in the last step. The *O*-benzyl ether scheme has been utilized by many and extended to the preparation of ^{14}C- and tritium-labeled isomers.[12,17,19] The enantiomers of (±)-1[20] and (±)-2[21a,b] have been obtained by resolution of the appropriate *O*-benzyl derivatives followed by cleavage of the protecting groups. In a more direct synthesis of (±)-reticuline [(±)-2] which avoids the cumbersome protection and deprotection of the two phenolic functions, Teitel and Brossi reported condensation of amine 7 and acid 8 (see Scheme I) to amide 9, which

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(15) The transformation of 4 to 5 involves intermediate formation of codeinone and hydride reduction to codeine (5). For formation of codeinone from 4, see: (a) F. Krauz, U.S. Patent 3 223 323 (1963); (b) J. P. Garard, F. Krauz, and T. Rull, *Bull. Soc. Chim. Fr.*, 486 (1965). For later studies describing conversion of 4 to 5, see: (c) R. Barber and H. Rapoport, *J. Med. Chem.*, **19**, 1175 (1976); (d) W. G. Dauben, C. P. Baskin, H. C. H. A. van Riel, *J. Org. Chem.*, **44**, 1567 (1979).

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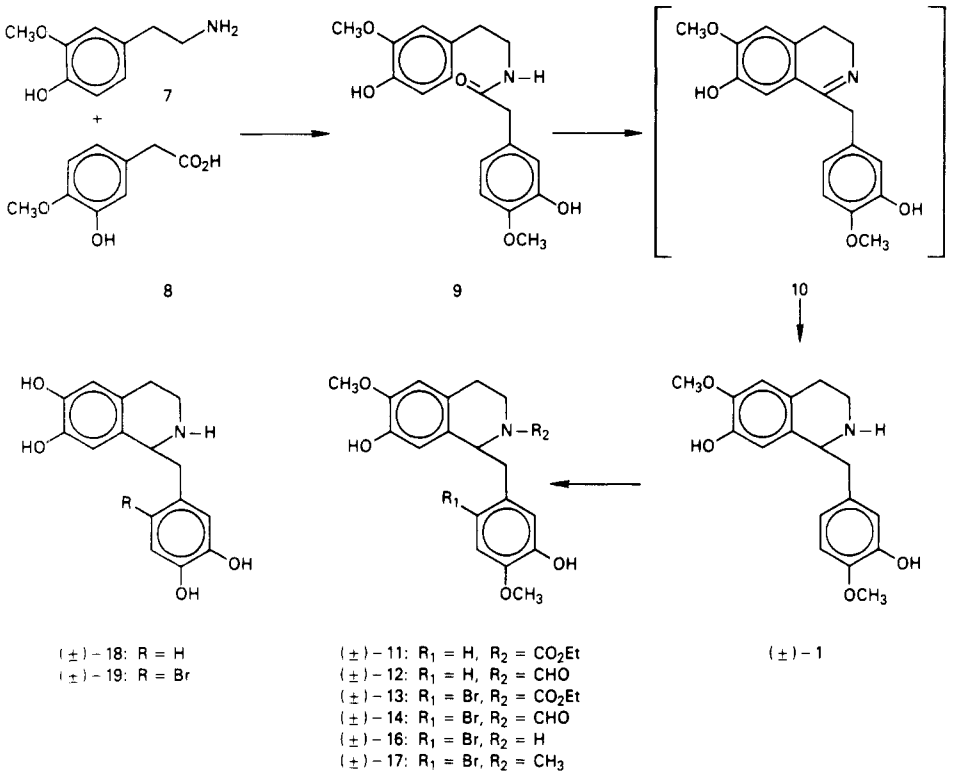
Scheme I



afforded (±)-2 in 33% overall yield after cyclization, quaternization of the intermediate 1,2-dehydro-*N*-norreticuline (10) with iodomethane, and reduction.[22] Isolation of amide 9 and the labile 1,2-dehydro compound 10 as described did, however, prove troublesome in our hands during large-scale work. Nevertheless, the results reported[22] and the availability of amine salt 7·HCl[23,24] from vanillin and acid 8[25] from isovanillin appeared to be a good foundation for further work toward our objectives. Since isovanillin can be prepared[26] from vanillin via veratraldehyde and selective O-demethylation, both 7 and 8 are available from the common intermediate vanillin.

We have now investigated in detail the vanillin route to *N*-norreticuline (1) and reticuline (2) as well as to useful congeners and now report the practical and experimentally simple methods we have worked out for synthesis of these compounds. Isolation of base 7[27] from 7·HCl[23,24] was accomplished nearly quantitatively. Acid 8 was prepared from isovanillin by a modification of the method of Grewe[25] that provided extremely pure material. Direct condensation of amine 7 and acid 8 at 200 °C as described,[22] followed by a superior workup that consisted of dissolving the cooled melt in acetic acid and diluting it with water, readily afforded a 90% yield of dimorphic amide 9 of sufficient purity for direct conversion to (±)-1. For this transformation, we intended to avoid isolation of the 1,2-dehydro compound 10, which initial work has shown to be labile and not easily handled. Cyclization of amide 9 in the acetonitrile–phosphoryl chloride system previously utilized[22] generated 10; however, initial experiments dealing with sodium borohydride reduction of unisolated 10 did not give reproducible yields of (±)-1. This difficulty was overcome by simple evaporation of the solvent from the cyclization and heating of the strongly acidic residue with water, an operation that presumably resulted in acid-catalyzed hydrolysis of phosphate ester functions formed by reaction of phosphoryl chloride with phenolic hydroxyl groups during cyclization of amide 9. Neutralization of the hydrolysate under argon with concentrated aqueous ammonia, followed by reduction of intermediate 10 with sodium borohydride, then afforded (±)-1 which was consistently isolated as analytically pure (±)-1·TsOH·H_2O in 78–81% yield. Crystalline (±)-1, which showed the expected spectral properties, was readily obtained nearly quantitatively from the tosylate salt. Racemic base 1 has not previously been described in crystalline condition;[28] however, (±)-1·HCl·H_2O[17,29] obtained from the base showed physical data in agreement with that reported. In the subsequent reactions discussed below involving functionalization of the basic nitrogen in (±)-1, it was found quite convenient to utilize (±)-1·TsOH·H_2O directly.

Since it is frequently desirable to protect the basic nitrogen of BTIQ in phenolic oxidation and other synthetic operations involving these compounds, we examined methods for direct formation of the *N*-carbethoxy and *N*-formyl derivatives of (±)-1. In previous synthetic work[5,30] involving BTIQ, both types of nitrogen substitution have served the dual role of the protecting group for nitrogen and of the direct precursor for the *N*-methyl

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group, a function which is quite abundant within the alkaloid series. The N-formyl group offers certain advantages in these respects, especially in phenolic systems where the N-methyl functionality is ultimately desired, since the frequently applicable borane reduction usually affords the easily isolated N-methyl compound in high yield[8] (also see below). In contrast, the carbamate usually requires lithium aluminum hydride (LAH)[5,31] or a similar reagent for reduction, and in many cases isolation of phenolic amines from reductions of this type is difficult. Also, in contrast to the carbamate function, the N-formyl substituent is easily removed,[8] affording the corresponding N-nor compounds, which in the morphinan series are of paramount importance for synthesis of narcotic antagonists such as nalorphine and its surrogates.

Selective acylation at nitrogen in (±)-1 was readily accomplished by treatment of 1·TsOH·H_2O with sodium bicarbonate–ethyl chloroformate in a two-phase system and readily afforded a 94% yield of crystalline carbamate (±)-11, previously obtained as an oil from the corresponding O,O′-dibenzyl ether[32] and from the N,O,O′-tricarbethoxy derivative[6] by selective hydrolyses of the carbonate ester functions. The N-formyl derivative, (±)-12, of (±)-1, previously prepared[30] by the dibenzyl ether scheme, was also prepared (93%) directly from (±)-1·TsOH·H_2O by treatment with sodium methoxide and ethyl formate in DMF.

The N-acyl diphenolic 6′-bromo derivatives (±)-13 and (±)-14 are of potential value as intermediates in various synthetic schemes leading to more complex ring systems since reaction at the 6′-position is effectively blocked for many synthetic operations. This blocking effect can lead to the frequently desirable "abnormal" oxygenation patterns in the products, and the halogen atom can generally be removed (LAH or catalytic reduction) or utilized for further reaction. This concept was employed in an early attempt[18a] at synthesis of 1-bromosalutaridine (15) and has been utilized a number of times in subsequent work.[6,33] Carbamate (±)-13 had previously been prepared[6] by bromination of O,O′-dibenzyl-N-norreticuline to the 6′-bromo derivative, debenzylation to (±)-16,[34] conversion to the N,O,O′-tricarbethoxy derivative, and selective hydrolysis of the carbonate ester functions. We hoped to prepare (±)-13 and (±)-14 by direct bromination, which had proved satisfactory in the nonphenolic system,[34] but undertook bromination of diphenolic (±)-11 and (±)-12 with some apprehension since, in principle, bromination could occur at each of the three positions ortho or para to the two phenolic functions in 11 and 12. We were gratified to find that regioselective bromination was readily accomplished by slow addition (~0.5 h) of an equimolar amount of bromine in acetic acid to a solution of N-acyl compounds (±)-11 and (±)-12 in the same solvent and afforded the corresponding crystalline (±)-13 and (±)-14 in 91 and 90% yields, respectively. The structure of (±)-14 followed from analytical and spectral data and was secured by acid hydrolysis to the known (±)-16.[6] Rapid addition of bromine gave lower isolated yields of these compounds, presumably because of high local concentrations of bromine which gave polybrominated material and left unchanged starting material. Direct bromination of diphenolic N-norreticuline–hydrogen bromide [(±)-1·HBr] in acetic acid also afforded a 93% yield of 6′-bromo compound (±)-16.[34] The mass spectra of (±)-13, (±)-14, and (±)-16 showed the loss of the 1-benzyl substituent as the major fragmentation pathway as expected and confirmed introduction of bromine in this group.

The solution NMR of the N-acyl derivatives (±)-11–(±)-14 showed the presence of two rotomers, probably resulting from hindered rotation about the amide bond. The existence of rotomers has been observed previously in similar compounds[8] and other amides,[35] and in a few cases the individual rotomers have been isolated.[8,35a,b] In contrast to carbamates (±)-11 and (±)-13, the rotomers of N-formyl compounds (±)-12 and (±)-14 could be separated on thin-layer chromatography (TLC). The energy barrier for interconversion of rotomers of the two carbamates appeared to be lower than that for the N-formyl compounds (±)-12 and (±)-14 since heating dimethyl-d_6 sulfoxide solutions of the carbamates to ~80 °C resulted in apparent coalescence of the C-methyl triplets, whereas little change was observed in the spectrum of the N-formyl compounds at approximately the same temperature. The rotomers in this and a related series[8] are being studied in more detail, and the results of this investigation will be reported in due course.

Racemic reticuline [(±)-2][12] and 6′-bromoreticuline [(±)-17][18] were readily obtained as crystalline bases in 97 and 94% yield, respectively, by reduction of the corresponding N-formyl precursors (±)-12 and (±)-14 with borane in THF. The simple and efficient nature of borane reduction of N-formyl precursors to yield phenolic amines in this series is thus clearly demonstrated as is the compatibility of this reducing agent with 6′-bromine substitution.

With highly efficient routes to the racemic compounds secured, we next investigated optical resolution of (±)-N-norreticuline [(±)-1] as a potential route to the corresponding optical isomers of these and related compounds such as the tetrahydropapverolines 18 and 19 (see below). The optical isomers of (±)-1 have previously been obtained by resolution of the O,O′-dibenzyl ether of (±)-1, followed by cleavage of the ether functions.[20] We desired a more efficient direct resolution of diphenolic (±)-1, since our sequence had not required benzyloxy intermediates to this point. A large number of the commercially available resolving agents were investigated during the initial unsuccessful attempts at resolution of (±)-1. The tartranilic acids employed by Montzka[36] for resolution of two nonphenolic tetrahydroisoquinolines were then examined since both enantiomers are easily prepared from commercially available (+)- and (−)-tartaric acids. Indeed, the first members of this series examined, the 2′-bromotartranilic acids (BTA), proved to be extremely suitable for resolution of (±)-1. When an ethanol solution of (±)-1 was treated with (+)-BTA, crystalline material separated rapidly and afforded 88% of pure (+)-1·(+)-BTA after recrystallization. Heating this salt to solution in aqueous 2-propanol containing a slight excess of 37% aqueous HCl gave (+)-1·HCl·H_2O nearly quantitatively from which crystalline (+)-1 base was obtained in similar yield. Isolation of the basic

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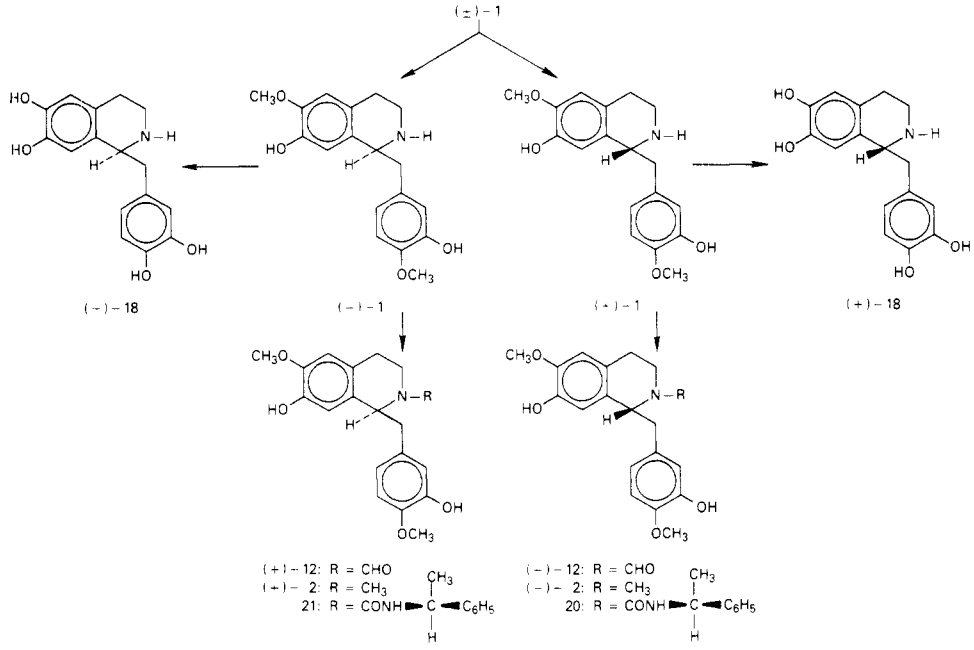
(35) (a) R. R. Frasher and K. Taymaz, *Tetrahedron Lett.*, 4573 (1976); (b) H. Volter and G. Helmcher, *ibid.*, 1251 (1978); (c) H. C. Beyerman, E. Buurman, T. S. Lie, and L. Maat, *Recl. Trav. Chim. Pays-Bas*, **95**, 43 (1976); (d) H. C. Beyerman, L. van Bommet, L. Maat, and C. Olieman, *ibid.*, **95**, 312 (1976); (e) C. Olieman, L. Maat, K. Waliszewski, and H. C. Beyerman, *J. Chromatogr.*, **133**, 382 (1977).
(36) T. A. Montzka, T. L. Pindell, and J. D. Motiskella, *J. Org. Chem.*, **33**, 3993 (1968).

Scheme II



fraction from the resolution filtrates and similar treatment with (-)-BTA directly afforded 94% of (-)-1·(-)-BTA from which the corresponding HCl salt and base were obtained. Optical rotations for our samples of (+)- and (-)-1·HCl agreed well with the reported values;[20] nevertheless, we desired to confirm the optical purity of these enantiomers. This was readily accomplished by reaction of the bases (+)- and (-)-1 with (*S*)-(-)-α-methylbenzyl isocyanate in deuteriochloroform followed by 220-MHz NMR analysis of the resulting diasterisomeric urea derivatives **20** and **21** (see Scheme II). The reaction between a slight excess of the isocyanate and these bases proceeded rapidly and quantitatively by TLC. The doublets observed for the methyl resonances of the urea derivatives **20** and **21** from reaction of the isocyanate with (+)- and (-)-1 were well separated ($\Delta\delta$ = 0.25 ppm) and provided a basis for analysis of optical purity of the corresponding enantiomers. When (+)-1 was treated with the isocyanate and the NMR spectrum recorded at high signal amplitude, essentially no resonance was observed that could have corresponded to diasterisomeric **21**, indicating little if any enantiomeric contamination in the original sample of (+)-1. A parallel experiment with (-)-1 under the same conditions revealed a very low intensity resonance that may have corresponded to **20**. In a repetition of this experiment with (-)-1 to which had been added 1% of (+)-1, the methyl resonance for **20** was clearly visible and was of substantially more than twice the intensity of that observed in the case of (-)-1. Thus, the limit of detection of enantiomeric impurity in this system is somewhat less than 1%, and it appears that our sample of (-)-1 was of at least 99%, and probably of greater, optical purity. We conclude that the enantiomers of 1 obtained as described are optically pure, or very nearly so, and are thus suitable as chiral intermediates for further synthetic work. This opinion is supported by the recent transformation of (-)-1 to the natural forms of a series of pavinan and isopavinan alkaloids.[8]

The enantiomers of reticuline, (+)- and (-)-**2**, were readily prepared from (+)- and (-)-1 by using the formylation–borane reduction sequence discussed above for the racemate (±)-**2**. Treatment of (-)-1 with ethyl chloroformate, followed by reduction of the resulting carbamate with LAH as described by Kondo,[31] also afforded (+)-**2**. The physical data collected for the salts of (+)- and (-)-**2** were in agreement with that previously reported.[21b,37a] Another important subclass of BTIQ closely related to 1 is comprised of tetrahydropapaveroline (THP) and its congeners. Racemic THP [(±)-**18**] shows several important effects in both the peripheral and the central nervous system by virtue of alteration of the catecholamine function,[38] and recent findings suggest that (±)-**18** may be involved in certain aspects of alcoholism.[39] The racemate (±)-**18**[40] and its enantiomers,[41] (+)- and (-)-**18**, were previously obtained by O-demethylation of the corresponding forms of tetrahydropapaverine. These compounds are now available in quantity, nearly quantitatively, by O-demethylation of the corresponding forms of 1 with 48% HBr, followed by crystallization of the anhydrous HBr salts from DMF–acetic acid. These amino dicatechols are labile to air oxidation in aqueous solution, and even the hydrated crystalline salts darken in air. The anhydrous salts, however, undergo no apparent change when stored under argon. The 6′-bromo derivative (±)-**19** could also be obtained by treatment of (±)-**16** with 48% HBr but was best prepared from (±)-**16** by O-demethylation with boron tribromide in chloroform.

In summary, the practical methodology described above (which will probably be applicable in a number of similar systems) now permits convenient synthesis via unprotected phenolic intermediates of *N*-norreticuline and a number

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(41) S. Teitel, J. O'Brien, and A. Brossi, *J. Med. Chem.*, **15**, 845 (1972).

of other important related BTIQ in racemic and chiral forms. Syntheses of various types of isoquinoline alkaloids should now be facilitated, and it is hoped that the results of this study will provide new impetus for the study of phenolic oxidative coupling, particularly as it pertains to the total synthesis of medically valuable opium alkaloids and their relatives.

Experimental Section

Melting points (corrected) were determined in open capillary tubes by using a Thomas-Hoover apparatus. Elemental analyses were performed by the Section on Microanalytical Services and Instrumentation of this laboratory. IR spectra were recorded on a Perkin-Elmer 257 or Beckman IR 4230 instrument. Optical rotations were measured by using a Perkin-Elmer Model 141 polarimeter with the solvents and concentrations specified. NMR spectra were determined by using a Varian HR-220 spectrometer with $(CH_3)_4Si$ as the internal reference. Chemical-ionization (CI) mass spectra were obtained by using a Finnigan 1015D spectrometer with a Model 6000 data collection system, and electron-ionization (EI) mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6E spectrometer (70 eV). Short-range Hydrion paper was used for pH determinations. Silica gel GF analytical and preparative thin-layer chromatography (TLC) plates used throughout this work were purchased from Analtech, Inc. Silica gel 60 (70–230 mesh) was purchased from EM Laboratories. Solvent systems used for TLC were as follows: (A) 4.9 mL of $CHCl_3$, 0.1 mL of AcOH; (B) 80 mL of $CHCl_3$, 18 mL of MeOH, 2.0 mL of concentrated aqueous NH_3; (C) 90 mL of $CHCl_3$, 9 mL of MeOH, 1 mL of concentrated aqueous NH_3; (D) CH_2Cl_2. Rotomer ratios reported below were determined by integration of the appropriate NMR spectrum.

β-(4-Hydroxy-3-methoxyphenyl)ethylamine (7).[27] A mixture of 274.3 g (1.34 mol) of 7·HCl[23,24] and 550 mL of H_2O was heated to solution and treated with 100 mL of concentrated aqueous NH_3 while being stirred. Base 7 crystallized rapidly, and after the slurry was cooled to 10 °C, the solid was filtered and washed with distilled H_2O at 5 °C until the filtrate did not give a white precipitate of AgCl when treated with 10% aqueous $AgNO_3$. The 7 obtained was dried in vacuo to afford 214.9 g (95%) of pure (TLC system B) 7, mp 158.5–160.5 °C (lit.[27] mp 156–157 °C).

(3-Hydroxy-4-methoxyphenyl)acetic Acid (8). Crude 8 was prepared from isovanillin, via the unpurified cyanohydrin, essentially as reported by Grewe[25] and purified as described below. From 310.5 g (2.0 mol) of 98% isovanillin, 343.7 g (95%) of crude cyanohydrin, mp 98–100 °C (one spot in system D), was obtained. This material afforded 341.2 g (93.6%) of crude 8, mp 115–124 °C (lit.[25] mp 119 °C), that showed two significant impurities on TLC in system A which were difficult to remove by recrystallization. The crude 8 from above was heated to solution in 1 L of 2-propanol and treated with 160 mL of concentrated aqueous NH_3 to afford crystalline material almost immediately. The slurry was cooled to 25 °C, and the solid was filtered, washed with 600 mL of 2-propanol, and dried to afford 313.8 g (72%) of off-white 8·NH_3·H_2O which was essentially homogenous on TLC in system A. In a similar run an analytical sample was prepared by heating the salt to solution in 1.25 volumes of 50% aqueous 2-propanol and diluting with 4 volumes of 2-propanol; mp 166.5–168.5 °C (loses H_2O and softens at ~150 °C).

Anal. Calcd for $C_9H_{10}O_4$·NH_3·H_2O: C, 49.76; H, 6.96; N, 6.45. Found: C, 49.37; H, 6.86; N, 6.63.

A mixture of 313.2 g (1.44 mol) of 8·NH_3·H_2O from above was heated to solution in 546 mL of H_2O and diluted with 546 mL of 37% HCl. After the mixture was cooled to 15 °C, the acid 8 was filtered, pressed well, and washed with 1 L of 6 N HCl (0 °C) in five portions. Drying in vacuo afforded 243.9 g (67% yield from isovanillin, 92% recovery) of 8, mp 128.5–130.5 °C (lit.[42] mp 127–128 °C).

N-(β-4-Hydroxy-3-methoxyphenethyl)-(3-hydroxy-4-methoxyphenyl)acetamide (9). The following modification of the procedure of Teitel and Brossi[22] was more convenient and gave a somewhat higher yield than that previously reported. An intimate mixture of 91.0 g (0.5 mol) of dry acid 8, purified via the ammonium salt as described above, and 83.5 g (0.5 mol) of dry amine 7 contained in a 1-L flask was evacuated and refilled with argon (4×). The flask was placed in an oil bath at 195–200 °C while passing a slow continuous stream of argon over the solid. When the solid had completely melted, the mixture was heated for 2.0 h (bath temperature 195–200 °C) while passing argon over the melt to sweep out the H_2O formed. The melt was cooled to ~110 °C, heated to solution in 220 mL of AcOH, and diluted with 220 mL of H_2O. The solution was slowly cooled to 20 °C, and when crystallization was complete, the solid was filtered, pressed well, and washed with 300 mL of ice-cold 1:1 AcOH–H_2O in small portions. Drying in vacuo gave 144.9 g (87.5%) of 9: mp 151.5–154 °C (lit.[22] mp 124–126 °C); EI MS m/e 331 (M^+). This material showed two minor impurities on TLC (system A) but was sufficiently pure for direct conversion to (±)-1. Occasionally the lower melting modification of 9 was obtained, which upon recrystallization from ethyl acetate (seeding with the higher melting form) gave the higher melting form of 9. The filtrate and washings from the first crop of 9 were evaporated to a syrup, dissolved in 60 mL of 1:1 AcOH–H_2O, and seeded to afford an additional 4.8 g (2.9%) of 9: mp 148.5–151.5 °C; total yield 149.7 g (90.4%).

(±)-N-Norreticuline Tosylate Salt Monohydrate [(±)-1·TsOH·H_2O]. A stirred, refluxing solution of 82.9 g (0.25 mol) of amide 9 in 1250 mL of acetonitrile was treated with 150 mL (1.60 mol) of $POCl_3$ during 10 min (exothermic reaction). The mixture was refluxed 1.0 h, cooled, and evaporated thoroughly to a red-yellow foam which was heated to solution in 250 mL of H_2O (**Caution**: exothermic reaction). When the exothermic reaction had subsided, the solution was heated on a steam bath 1.0 h and transferred to a 2-L three-necked flask by using 150 mL of H_2O. The mechanically stirred mixture was cooled until a yellow oil separated, 250 mL of THF was added, and passage of argon *through* the solution was begun and continued for the duration of the reaction (see below). The solution was cooled to 0–5 °C during 0.5 h, and sufficient concentrated aqueous NH_3 (140 mL in this case[43]) was added (T < 15 °C) to give a final pH of 8.5–9.5 when checked after dilution of 1 drop of the reaction mixture with 3 drops of H_2O. The reaction mixture, which contained a yellow solid, was cooled to 0 °C, and 5.0 g (0.13 mol) of solid $NaBH_4$ was rapidly added in portions while the temperature of the mixture was maintained at <5 °C. Reduction of intermediate 10 was apparent by the color change of the mixture from yellow to light tan. When the addition of $NaBH_4$ was complete, the mixture was stirred at 0 °C for 0.5 h and then at 25 °C for 0.5 h. The flow of argon was discontinued, 500 mL of $CHCl_3$ and 500 mL of H_2O were added, and stirring was continued for 5–10 min until the solids had dissolved. (The pH of the aqueous phase should be checked at this point and adjusted to 9.0–9.5 if necessary.) The $CHCl_3$ was removed and the aqueous phase reextracted with $CHCl_3$ (4 × 200 mL). The combined wet $CHCl_3$ extracts were evaporated to a foam and heated to solution in 500 mL of H_2O containing 43.7 g of TsOH·H_2O (0.23 mol).[44] After being cooled to 5 °C for 1 h, the solid was filtered, washed with H_2O (3 × 100 mL, 0 °C) and then 200 mL of H_2O (0 °C), and dried at 50 °C in vacuo to afford 99.1 g (78.4%) of analytically pure, off-white (±)-1·TsOH·H_2O, mp 138–140 °C (shrinks before melting point). Evaporation of the filtrate and washings gave a solid that was recrystallized from 10 mL of 1:9 MeOH–H_2O to give 2.90 g of (±)-1·TsOH·H_2O: mp 136–138 °C, total yield 102.0 g (80.7%).

Anal. Calcd for $C_{25}H_{29}NSO_7$·H_2O: C, 59.38; H, 6.18; N, 2.77. Found: C, 59.66; H, 6.45; N, 2.80.

(±)-N-Norreticuline [(±)-1]. A mixture of 75.8 g (0.15 mol) of (±)-1·TsOH·H_2O and 75 mL of methanol was heated to solution,

(42) H. W. Bersch, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, **89**, 271 (1939).

(43) The amount of concentrated aqueous NH_3 required to neutralize the mixture to the specified pH range varies as the amount of $POCl_3$ remaining after the stripping operation.

(44) The solid 1·TsOH·H_2O usually begins to separate before the mixture is heated completely to solution. If a significant amount of $CHCl_3$ remains unevaporated from the crude (±)-1, foaming frequently occurs as the mixture is heated to solution. This problem could probably be avoided if the stirred (±)-1 base–H_2O mixture was heated to ~70–80 °C in order to distill residual $CHCl_3$ before addition of TsOH·H_2O.

and to the stirred mixture was added *in order* 375 mL of $CHCl_3$, 50 mL of concentrated aqueous NH_3, and 250 mL of H_2O. The $CHCl_3$ was removed, and the aqueous phase was reextracted with $CHCl_3$ (3 × 100 mL). The combined $CHCl_3$ extracts were evaporated and dried under high vacuum to a foam which was heated to solution in 150 mL of butyronitrile and crystallized (cooling to 0 °C for 1 h). The tiny crystals were filtered, washed with 100 mL of ice-cold butyronitrile, and dried overnight in vacuo to directly afford 45.1 g (95.3%) of pure (±)-1: mp 155–157 °C;[28] EI MS *m/e* 315 (M^+); NMR (1:4 Me_2SO-d_6:$CDCl_3$) δ 2.60–3.33 (m, 6 H), 3.79 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.99 (br d, 1 H, *J* = 10 Hz, C-1 H), 5.53 (br s, 3 H, OH, NH, exchanges with D_2O), 6.46–6.87 (m, 4 H, ArH).

Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.26; H, 6.85; N, 4.42.

Treatment of (±)-1 with a slight excess of 37% aqueous HCl in 95% ethanol afforded (±)-1·HCl·H_2O, mp 165–167 °C (lit.[29] mp 165–166 °C).

(±)-*N*-Carbethoxy-*N*-norreticuline [(±)-11]. A stirred mixture of 15.17 g (30.0 mmol) of (±)-1·TsOH·H_2O in 25 mL of methanol was heated to solution and treated with 3.36 g (40.0 mmol) of $NaHCO_3$ and 30 mL of H_2O. The mixture was refluxed 10 min and cooled to 20–25 °C, and 4.41 g (52.5 mmol) of $NaHCO_3$, 150 mL of $CHCl_3$, and 50 mL of H_2O were added in order. To the vigorously stirred mixture was then added 4.88 g (45.0 mmol) of redistilled ethyl chloroformate during 10 min. Stirring was continued 1.0 h, the $CHCl_3$ phase, which showed no (±)-1 on TLC in system C, was removed, and the aqueous phase was reextracted with $CHCl_3$ (2 × 50 mL). The combined $CHCl_3$ extract was evaporated to a foam which was crystallized from 30 mL of propionitrile (cooling to 0 °C) to give 10.88 g (94%) of (±)-11, mp 146–148 °C. Recrystallization from propionitrile afforded an analytical sample: mp 147–148.5 °C; EI MS *m/e* 387 (M^+); IR (film) 1673 cm^{-1} (lit.[6] 1675 cm^{-1}); NMR (1:4 Me_2SO-d_6:$CDCl_3$; for the mixture of rotomers) δ 1.06 and 1.20 (2 t, 3 H, *J* = 7 Hz, CH_2CH_3), 3.81 (s, 6 H, 2 OCH_3), 5.00–5.20 (m, 1 H), 6.42–6.77 (m, 5 H, ArH), 8.19–8.73 (4 s, 2 H, exchanges with D_2O, OH). The ratio of rotomers in this sample was ~1.0:1.4.

Anal. Calcd for $C_{21}H_{25}NO_6$: C, 65.10; H, 6.50; N, 3.61. Found: C, 65.25; H, 6.63; N, 3.41.

(±)-*N*-Formyl-*N*-norreticuline [(±)-12]. A stirred mixture of 30.33 g (60.0 mmol) of (±)-1·TsOH·H_2O, 245 mL of DMF, and 3.56 g (66.0 mmol) of sodium methoxide was heated at 90–95 °C until the solids had dissolved (~15 min). To the mixture was then added 72.0 mL of redistilled ethyl formate (redistilled and stored over anhydrous K_2CO_3), and the mixture was stirred and refluxed 24–48 h until TLC in system C indicated essentially no (±)-1 remained. The mixture was evaporated to a reddish paste which was partitioned between 200 mL of $CHCl_3$ and 100 mL of H_2O. The $CHCl_3$ was carefully separated, washed with 80 mL of 5% aqueous HCl, and thoroughly evaporated to a solid which was digested with 55 mL of boiling ethanol for 15 min and allowed to stand overnight at 5 °C. The solid was filtered, washed with cold methanol (2 × 25 mL), and dried to afford 18.9 g (92%) of analytically pure (±)-12, mp 184.5–186 °C (lit.[30] mp 183 °C). TLC of this material in system C showed two closely running spots corresponding to the two rotomers of (±)-12 which were clearly apparent from the NMR spectrum: EI MS (for the mixture of rotomers) *m/e* 343 (M^+); NMR (1:4 Me_2SO-d_6:$CDCl_3$) δ 2.57–3.78 (m, 6 H), 3.88 and 3.91 (2 s, 6 H, 2 OCH_3), 4.39–4.62 (m, 1 H, C-1 H), 6.51–6.93 (m, 5 H, ArH), 7.59 and 8.04 (2 s, 1 H, CHO), 8.12–8.35 (4 s, 2 H, exchanges with D_2O, OH). The ratio of rotomers in this sample was ~1:2.

(±)-6′-Bromo-*N*-carbethoxy-*N*-norreticuline [(±)-13]. A mixture of 7.75 g (20.0 mmol) of (±)-11 and 150 mL of glacial acetic acid was heated to solution and rapidly cooled to 20–25 °C. A solution of 3.20 g (20.0 mmol) of Br_2 in 100 mL of acetic acid was then added dropwise during 0.5 h to the vigorously stirred solution (*T* < 25 °C). The mixture was then stirred 20 min, evaporated to a crystalline residue which was heated to solution in 75 mL of butyronitrile, and cooled to 0 °C to directly afford 8.49 g (91%) of analytically pure (±)-13: mp 215.5–217.5 °C (lit.[6] mp 215–217 °C); EI MS *m/e* 465 and 467 (M^+); NMR (1:4 Me_2SO-d_6:$CDCl_3$; for the mixture of rotomers) δ 0.95 and 1.16 (2 t, 3 H, CH_2CH_3, *J* = 7 Hz), 3.82 (2 s, 6 H, OCH_3), 5.23–5.34 (m, 1 H), 6.59, 6.60, 6.63, 6.68, 6.82, 6.95, and 7.00 (7 s, 4 H, ArH), 8.39, 8.43, 8.64, and 8.80 (4 s, 2 H, exchange with D_2O, OH). The ratio of rotomers in this sample was ~1.0:2.5.

Anal. Calcd for $C_{21}H_{24}BrNO_6$: C, 54.08; H, 5.19; N, 3.00. Found: C, 54.18; H, 5.31; N, 3.08.

(±)-6′-Bromo-*N*-formyl-*N*-norreticuline [(±)-14]. A mixture of 10.30 g (30.0 mmol) of (±)-12 and 200 mL of acetic acid was heated to solution and cooled rapidly to 20–25 °C. To the rapidly stirred solution was added dropwise 4.80 g (30.0 mmol) of Br_2 in 100 mL of acetic acid during 0.5 h. The mixture was stirred an additional 0.5 h and evaporated to a foam which was crystallized from 35 mL of absolute ethanol (cooling to 0–5 °C) to afford 6.46 g of analytically pure (±)-14, mp 221–222 °C. Evaporation of the filtrate and washings to a foam and crystallization from 15 mL of absolute ethanol at 0 °C gave an additional 3.98 g of (±)-14, mp 220–221 °C. Finally, evaporation of the filtrate and washings from this crop to a foam and crystallization from 5 mL of 2-propanol gave 920 mg of (±)-14, mp 217.5–219 °C. The total yield was 11.36 g (90%). TLC of (±)-14 in system C indicated the two rotomers as closely running spots which were separated slightly better than those of (±)-12. For (±)-14: EI MS (for the mixture of rotomers of (±)-14) *m/e* 421 and 423 (M^+); IR (KBr) 3320 and 3370 (OH), 1670 (C=O) cm^{-1}; NMR (1:4 Me_2SO-d_6:$CDCl_3$) δ 2.64–3.30 (m, ~4 H), 3.43–3.91 (m, ~2 H), 3.82 (s, 6 H, OCH_3), 4.61–4.75 and 5.39–5.55 (2 m, ~1 H), 6.64, 6.59, 6.66, 6.74, 6.85, 6.98, and 7.05 (7 s, 4 H, ArH), 7.46 and 7.99 (2 s, 1 H, CHO), 8.73, 8.77, 8.91, and 9.10 (4 br s, 2 H, exchange with D_2O, OH). The ratio of rotomers in this sample was ~1.0:2.5.

Anal. Calcd for $C_{19}H_{20}BrNO_5$: C, 54.04; H, 4.74; N, 3.32. Found: C, 54.28; H, 4.80; N, 3.21.

(±)-6′-Bromo-*N*-norreticuline [(±)-16]. A. From Hydrolysis of (±)-14. A stirred mixture of 2.11 g (5.0 mmol) of (±)-14, 55 mL of methanol, and 20 mL of 37% aqueous HCl was refluxed ~4 h to afford a homogeneous solution, refluxed for an additional 20 h, and evaporated. Addition of 30 mL of H_2O afforded a slurry which was boiled 5 min and cooled to 0 °C. The solid was filtered, washed with 10 mL of H_2O (0 °C), and dried to afford 2.02 g (90%) of (±)-16·HCl·H_2O, mp 192–194 °C dec.

Anal. Calcd for $C_{18}H_{20}BrNO_4$·HCl·H_2O: C, 48.17; H, 5.16; N, 3.25. Found: C, 48.03; H, 5.39; N, 3.01.

A mixture of 1.50 g (3.3 mmol) of (±)-16·HCl·H_2O was heated to solution in 10 mL of methanol and treated with 0.5 mL of concentrated aqueous NH_3. The solid material that separated was collected, washed with methanol (3 × 7 mL, 0 °C), and dried to afford 1.24 g (94% recovery) of (±)-16: mp 215.5–217.5 °C (lit.[34] mp 225 °C); NMR (1:3 Me_2SO-d_6:$CDCl_3$) δ 2.59–3.00 (m, 4 H), 3.02–3.30 (m, 2 H), 3.80 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 4.70 (br d, 1 H, C-1 H), 6.57 (s, 1 H, ArH), 6.82 (2 s, 2 H, ArH), 7.02 (s, 1 H, ArH).

B. By Bromination of (±)-1. A stirred solution of 3.15 g (10.0 mmol) of (±)-1 and 1.4 mL of 48% HBr (12.3 mmol) in 100 mL of acetic acid was treated dropwise with a solution of 1.60 g (10.0 mmol) of Br_2 in 50 mL of acetic acid during 1.5 h. After being stirred an additional 1.5 h, the slurry was evaporated to a solid (which still contained acetic acid) that was heated to solution in 25 mL of 1:4 H_2O–methanol and rendered alkaline to pH 9.0–9.5 with 10 mL of concentrated aqueous NH_3. The base was collected, washed with 1:1 H_2O–methanol (2 × 10 mL) at 0 °C and 10 mL of H_2O, and dried to afford 3.65 g (93%) of purified (±)-16, mp 211.5–213.5 °C. A mixture of 20 mL of methanol, 10 mL of H_2O, and the purified base from above was acidified with 37% aqueous HCl and evaporated to a crystalline solid that was heated to solution in the minimum amount (~35 mL) of boiling H_2O to which was added 5 mL of 37% aqueous HCl. The crystalline solid was collected (cooling to 0 °C), washed with 30 mL of 1:5 37% aqueous HCl–H_2O and dried to afford 4.04 g (90%) of (±)-16·HCl·H_2O, mp 193–195 °C. This salt was heated to solution in 30 mL of 2:1 methanol–H_2O and rendered alkaline to pH 9–9.5 with ~3 mL of concentrated aqueous NH_3, and the crystalline base that rapidly separated was filtered, washed with 1:1 methanol–H_2O (2 × 10 mL, 0 °C) and 10 mL of H_2O, and dried to afford 3.37 g (86%) of (±)-16, mp 212–214 °C. This material was identical with that prepared in part A (IR, TLC system C).

(±)-Reticuline [(±)-2]. To a stirred solution of 125 mL of 1 M BH_3 in THF under argon was cautiously added 3.43 g (10.0 mmol) of solid (±)-12 in small portions. When H_2 evolution was nearly complete, the mixture was refluxed overnight to give a clear

solution. The mixture was cooled and cautiously treated dropwise with 15 mL of methanol, and when no more H_2 was evolved, the mixture was evaporated to a foam. This foam was dissolved in 100 mL of methanol, rendered strongly acidic with HCl gas, and refluxed ~3 h until TLC (system C) indicated complete conversion of an intermediate higher R_f material to (±)-2. The mixture was cooled and evaporated to a foam to which methanol (2 × 100 mL) was added, and the mixture was evaporated. The resulting residue was dissolved in 40 mL of H_2O to give a turbid solution which was extracted with 40 mL of Et_2O. The Et_2O extract was back-washed with H_2O (3 × 2 mL) and discarded. The combined aqueous layers were rendered alkaline to pH 9–9.5 with concentrated aqueous NH_3 and extracted with 60 mL of $CHCl_3$. The aqueous phase was reextracted with $CHCl_3$ (3 × 30 mL), and the combined $CHCl_3$ extract was washed with 20 mL of H_2O and evaporated to a foam. This foam was heated to solution in 14 mL of butyronitrile, concentrated to 9 mL, and crystallized (cooling to 0 °C, washing with cold butyronitrile) to afford 3.21 g (97%) of analytically pure and homogeneous (TLC system C) (±)-2, mp 146–147 °C (lit.[12] mp 144–145 °C).

Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.53; H, 7.00; N, 4.11.

(±)-6′-Bromoreticuline [(±)-17]. To a stirred solution of 150 mL of 1 M BH_3 in THF under argon was cautiously added 7.60 g (18.0 mmol) of solid (±)-14. When H_2 evolution was nearly complete, the mixture was refluxed overnight, cooled, and treated dropwise with 25 mL of methanol. The mixture was evaporated, dissolved in 150 mL of methanol, rendered strongly acidic with HCl gas, refluxed 1 h, and evaporated. The residue was redissolved in 150 mL of methanol, again rendered strongly acidic with HCl gas, and refluxed 3.5 h. TLC (system C) indicated complete conversion of the intermediate to (±)-17. The solution was evaporated to a residue to which methanol was added and evaporated (2 × 100 mL). The resulting material was dissolved in 70 mL of H_2O, 100 mL of $CHCl_3$ was added, and the aqueous phase was rendered alkaline to pH 9.0–9.5 with concentrated aqueous NH_3. The gummy (±)-17 that separated was extracted into the $CHCl_3$ phase, and the aqueous (pH 9.5) phase was reextracted with 100 mL of $CHCl_3$. The combined $CHCl_3$ extracts were washed with H_2O (2 × 20 mL) and evaporated to afford a residue that was crystallized from 25 mL of 2-propanol (cooling to 5 °C) to give 6.90 g (94%) of analytically pure (±)-17: mp 165.5–166.5 °C; EI MS m/e 407 and 409 (M^+), 192 (M^+ – 2-bromo-5-hydroxy-4-methoxybenzyl); IR ($CHCl_3$) 3550 (OH), 1496 cm^{-1}; NMR (1:4 Me_2SO-d_6:$CDCl_3$) δ 2.39 (s, 3 H, NCH_3), 2.48–2.64 (m, 1 H), 2.73–3.07 (m, 4 H), 3.18–3.41 (m, 1 H), 3.70–3.84 (m, 1 H), 3.82 (2 s, 6 H, OCH_3), 6.43 (s, 1 H, ArH), 6.57 (s, 1 H, ArH), 6.71 (s, 1 H, ArH), 6.95 (s, 1 H, ArH), 8.30 (br s, 2 H, exchanges with D_2O, OH).

Anal. Calcd for $C_{19}H_{22}BrNO_4$: C, 55.89; H, 5.43; N, 3.43. Found: C, 55.70; H, 5.50; N, 3.38.

The picrate salt of (±)-17 was prepared in ethanol; mp 207.5–209 °C (lit.[18a] mp 204 °C). In a similar run, reduction of 4.24 g (10.0 mmol) of (±)-14 afforded, after evaporation of the $CHCl_3$ extracts, crude (±)-17 that was suspended in 20 mL of H_2O, rendered acidic to pH 1.0 with 48% HBr, and warmed to solution. Cooling to 0 °C afforded 4.61 g (88%) of (±)-17·HBr·2H_2O in the first crop; mp 151–153 °C dec (sinters at 145 °C).

Anal. Calcd for $C_{19}H_{22}BrNO_4$·HBr·2H_2O: C, 43.44; H, 5.18; N, 2.67. Found: C, 43.60; H, 4.92; N, 2.67.

Optical Resolution of (±)-*N*-Norreticuline [(±)-1]. A mechanically stirred mixture of 31.5 g (0.1 mol) of (±)-1 was heated to solution in 700 mL of absolute ethanol at 70–75 °C and treated with 32.2 g (0.1 mol) of (+)-2′-bromotartranilic acid hydrate [(+)-2′-BTA·H_2O[36]] in 200 mL of the same solvent. Crystallization began rapidly and seemed complete in 2–3 min. The slurry was stirred at 73–78 °C for 10 min and then suction filtered hot by using an 18.5-cm Büchner funnel. A 200-mL portion of hot (70 °C) ethanol was used to complete the transfer and wash the solid on the filter. The solid was then washed with 100 mL of ethanol at 25 °C and Et_2O (2 × 100 mL) and dried in vacuo to give 29.8 g of nearly pure (+)-1·(+)-2′-BTA, mp 220.5–223.5 °C dec. This material was heated to solution on a steam bath in 70 mL of DMF and diluted with 500 mL of ethanol to give crystalline material almost immediately. The slurry was cooled to 25 °C and the solid was filtered, washed thoroughly with ethanol (2 × 100 mL) and 100 mL of Et_2O, and dried to give 27.2 g (88%) of analytically and optically pure (+)-1·(+)-2′-BTA: mp 223–225 °C dec; $[\alpha]^{23}_D$ +51.6° (c 0.8, MeOH).

Anal. Calcd for $C_{28}H_{31}BrN_2O_9$: C, 54.28; H, 5.04; N, 4.52. Found: C, 54.06; H, 4.89; N, 4.57.

The combined filtrates and washings from both recrystallizations above were evaporated to a syrup to which was added 200 mL of $CHCl_3$, 15 mL of concentrated aqueous NH_3, and 200 mL of H_2O. Thorough equilibration gave two liquid phases; the $CHCl_3$ was removed, and the aqueous phase was reextracted with $CHCl_3$ (3 × 75 mL). The combined $CHCl_3$ extracts were back-washed with 50 mL of H_2O and evaporated to a semisolid which was heated to solution (75 °C) in 400 mL of ethanol. To this mechanically stirred solution at 73–78 °C was added 18.04 g (56.0 mmol) of (–)-2′-BTA·H_2O[36] in 100 mL of warm ethanol. Crystalline material separated almost immediately, and after being stirred for 10 min, the warm slurry was suction filtered on an 18.5-cm Büchner funnel. The solid was washed successively with hot (70 °C) ethanol (2 × 100 mL), ethanol at 25 °C (2 × 100 mL), and Et_2O (2 × 100 mL). After the solid was dried in vacuo, 29.2 g (94%) of pure (–)-1·(–)-2′-BTA was obtained directly: mp 223–225 °C dec; $[\alpha]^{23}_D$ –52.0° (c 0.8, MeOH).

Anal. Calcd for $C_{28}H_{31}BrN_2O_9$: C, 54.28; H, 5.04; N, 4.52. Found: C, 54.22; H, 5.01; N, 4.52.

A suspension of 26.64 g (43.0 mmol) of (+)-1·(+)-2′-BTA in 230 mL of 95% (v/v) aqueous 2-propanol was treated with 7.0 mL of 37% aqueous HCl and heated to solution. After being cooled at 5 °C for 10 min, the slurry of crystalline material was diluted with 230 mL of Et_2O, stirred 10 min at 5–10 °C, and filtered. The resulting white solid was washed with 2-propanol (3 × 70 mL) and Et_2O (2 × 70 mL) and air-dried to directly afford 15.30 g (96%) of (+)-1·HCl·H_2O: mp 167.5–169 °C (froth); $[\alpha]^{23}_D$ +12.5° (c 1.06, MeOH); pure by TLC in system C.

Anal. Calcd for $C_{18}H_{21}NO_4$·HCl·H_2O: C, 58.45; H, 6.54; N, 3.79. Found: C, 58.20; H, 6.70; N, 3.99.

In a similar manner, 29.11 g (47.0 mmol) of (–)-1·(–)-2′-BTA was converted to 17.04 g (98%) of pure (TLC system C) (–)-1·HCl·H_2O. In this case crystallization of (–)-1·HCl·H_2O began before solution of (–)-1·(–)-2′-BTA was complete. The slurry was heated to boiling during 5 min and then treated as described for the (+) isomer. An analytical sample of (–)-1·HCl·H_2O was prepared by recrystallization from 1-propanol–H_2O (85:15): mp 166–167.5 °C (froth); $[\alpha]^{23}_D$ –12.7° (c 1.0, MeOH).

Anal. Calcd for $C_{18}H_{21}NO_4$·HCl·H_2O: C, 58.45; H, 6.54; N, 3.79. Found: C, 58.30; H, 6.68; N, 3.80.

A suspension of 7.40 g (20.0 mmol) of (+)-1·HCl·H_2O in 50 mL of H_2O and 100 mL of $CHCl_3$ was treated with 4.0 mL of concentrated aqueous NH_3 and shaken several minutes until two homogeneous liquid phases were obtained. The $CHCl_3$ was removed, and the aqueous phase was reextracted with $CHCl_3$ (3 × 25 mL). The combined $CHCl_3$ extract was back-washed with 10 mL of H_2O and evaporated to a crystalline mass which was heated to solution in 60 mL of butyronitrile and filtered through ~2 g of Celite (washing with 20 mL of hot butyronitrile). The filtrate was cooled to 5 °C, and the solid that separated was collected, washed with cold butyronitrile, and dried to afford 5.88 g (93%) of chromatographically pure (TLC system C) (+)-1 as long silky needles, mp 171.5–172.5 °C. Recrystallization from propionitrile gave an analytical sample: mp 171.5–172.5 °C; $[\alpha]^{23}_D$ +31.7° (c 0.65, $CHCl_3$); $[\alpha]^{23}_D$ +28.7° (c 0.5, MeOH) [lit.[45] $[\alpha]^{21}_D$ +34.5° (c 0.5, MeOH), amorphous].

Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.48; H, 6.55; N, 4.32.

A suspension of (+)-1 in methanol was rendered acidic with HCl gas, and Et_2O was added to afford (+)-1·HCl. Recrystallization from methanol–Et_2O afforded an analytical sample: mp 257.5–259 °C dec; $[\alpha]^{23}_D$ +13.7° (c 0.76, MeOH) [lit.[20] mp 228–230 °C; $[\alpha]^{25}_D$ +13.3° (c 1.11, MeOH)].

Anal. Calcd for $C_{18}H_{21}NO_4$·HCl: C, 61.43; H, 6.30; N, 3.98. Found: C, 61.19; H, 6.04; N, 4.25.

In a similar manner, 7.40 g (20.0 mmol) of (–)-1·HCl·H_2O directly afforded 5.83 g (93%) of analytically and chromatographically (TLC system C) pure (–)-1: mp 171.5–172.5 °C; $[\alpha]^{23}_D$

(45) H. Uprety, D. S. Bhakuni, and R. S. Kapel, *Phytochemistry*, 14, 1535 (1979).

-31.3° (c 0.68, $CHCl_3$); $[\alpha]^{23}_D$ -29.3° (c 0.5, MeOH) [lit.[45] $[\alpha]^{21}_D$ -36.6° (c 0.5, MeOH), amorphous].

Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.60; H, 6.81; N, 4.17.

Treatment of (-)-1 with methanol–HCl gas as described above for the (+) isomer gave (-)-1·HCl: mp 258–259.5 °C dec; $[\alpha]^{23}_D$ -13.6° (c 0.85, MeOH) [lit.[20] mp 228–230 °C, $[\alpha]^{25}_D$ -12.9° (c 0.52, MeOH); lit.[31] mp 237–240 °C, $[\alpha]^{20}_D$ -13.0° (c 0.66, MeOH)].

Anal. Calcd for $C_{18}H_{21}NO_4$·HCl: C, 61.43; H, 6.30; N, 3.98. Found: C, 61.59; H, 6.17; N, 3.86.

(-)-*N*-Formyl-*N*-norreticuline [(-)-12]. A mixture of 2.22 g (6.0 mmol) of (+)-1·HCl·H_2O, 25 mL of DMF, and 356 mg of sodium methoxide (6.59 mmol) was heated to solution at 80–90 °C (~10 min) and then treated with 7.2 mL of redistilled ethyl formate. The mixture was refluxed 28 h until only a trace of (+)-1 was detected on TLC in system C. The mixture was diluted with 50 mL of $CHCl_3$, treated with 5 drops of acetic acid, and filtered through a Celite pad which was washed thoroughly with $CHCl_3$. The filtrate and washings were thoroughly evaporated to a reddish syrup which was crystallized from 15 mL of 2-propanol to afford 1.86 g (90%) of (-)-12, mp 204–205.5 °C. Recrystallization of a portion of this material from butyronitrile afforded an analytical sample of (-)-12: mp 204–205.5 °C; EI MS *m/e* 343 (M^+); $[\alpha]^{23}_D$ -68.0° (c 0.63, DMF).

Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.17; N, 4.08. Found: C, 66.49; H, 5.89; N, 4.32.

(+)-*N*-Formyl-*N*-norreticuline [(+)-12]. Preparation of this compound from (-)-1·HCl·H_2O on the same scale and essentially as described above for the enantiomer afforded 1.91 g (93%) of (+)-12, mp 204.5–206 °C. Recrystallization from butyronitrile afforded the analytical sample: mp 204.5–206 °C; EI MS *m/e* 343 (M^+); $[\alpha]^{23}_D$ +68.7° (c 0.69, DMF).

Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.17; N, 4.08. Found: C, 66.53; H, 5.88; N, 4.07.

(+)-Reticuline–Perchloric Acid–0.5-Water [(+)-2·$HClO_4$·0.5H_2O]. A. By Borane Reduction of *N*-Formyl-*N*-norreticuline [(+)-12]. Reduction of 1.78 g (5.0 mmol) of (+)-12 exactly as described above for (±)-12 (but on half the scale) afforded crude (+)-2 as a syrup after evaporation of the $CHCl_3$ extracts. The syrupy (+)-2 was heated to solution in 10 mL of 2-propanol, rendered acidic with 60% aqueous $HClO_4$, and cooled to 0 °C to afford 1.99 g (93%) of (+)-2·$HClO_4$·0.5H_2O that was homogeneous on TLC in system C: mp 206–207.5 °C; $[\alpha]^{23}_D$ +77.1° (c 0.79, 99% EtOH) [lit.[37a] mp 205–206 °C, $[\alpha]^{23}_D$ +73° (c 0.93, 99% EtOH); lit.[31] mp 203–204 °C, $[\alpha]^{31}_D$ +88.3° (c 0.21, EtOH)].[37b]

Anal. Calcd for $C_{19}H_{23}NO_4$·$HClO_4$·0.5H_2O: C, 51.99; H, 5.74; N, 3.19. Found: C, 52.28; H, 5.75; N, 3.39.

A suspension of 254 mg (0.58 mmol) of (+)-2·$HClO_4$·0.5H_2O from above in a mixture of 10 mL of H_2O and 10 mL of $CHCl_3$ was shaken with excess concentrated aqueous NH_3 to afford two homogeneous phases. The $CHCl_3$ was separated, and the aqueous phase was reextracted with $CHCl_3$ (2 × 10 mL). The combined $CHCl_3$ extracts were dried (Na_2SO_4) and evaporated to a foam which was heated to solution in 3.0 mL of 95% (v/v) aqueous 2-propanol, rendered slightly acidic with HCl gas, and treated with 1.0 mL of Et_2O. The mixture was heated to solution, cooled to 20–25 °C, and seeded with crystalline material obtained as described below. Crystallization proceeded slowly and was complete after ~6 h. The cottonlike microneedles were filtered, washed with 2-propanol and then Et_2O, and air-dried to afford 117 mg (52%) of (+)-2·HCl·1.5H_2O: mp 160–162 °C (heating rate from 25 °C at 4–6 °C/min; a sample placed in an oil bath preheated to 140 °C melted immediately with frothing); $[\alpha]_D$ +76.5° (c 1.0 H_2O) [lit.[21b] $[\alpha]_D$ +73.1° (c 1.0, H_2O)]. The initial sample of crystalline (+)-2·HCl·1.5H_2O was obtained with difficulty as follows. A small portion of foamy (+)-2 from above was dissolved in 1 drop of 37% aqueous HCl, and the resulting solution was triturated thoroughly with several portions of Et_2O to afford a syrupy residue from which (+)-2·HCl·1.5H_2O slowly crystallized.

Anal. Calcd for $C_{19}H_{23}NO_4$·HCl·1.5H_2O: C, 58.08; H, 6.93; N, 3.57. Found: C, 57.87; H, 6.60; N, 3.49.

B. By LAH Reduction of the *N,O,O'*-Tricarbethoxy Derivative of (-)-1. Treatment of 360 mg (1.02 mmol) of (-)-1·HCl as described by Kondo[31] afforded crude (+)-2, which after preparative TLC (system C) afforded chromatographically homogeneous (system C) material that was converted to 172 mg (38%) of (+)-2·$HClO_4$·0.5H_2O as described above: mp 205–206.5 °C; $[\alpha]^{21}_D$ +76.3° (c 0.23, EtOH) [lit.[31] mp 203–204 °C; $[\alpha]^{18}_D$ +88.3° (c 0.21, EtOH)].[37b] Recrystallization of this material from 95% ethanol did not significantly change the melting point or $[\alpha]_D$.

Anal. Calcd for $C_{19}H_{23}NO_4$·$HClO_4$·0.5H_2O: C, 51.99; H, 5.74; N, 3.19. Found: C, 51.92; H, 5.43; N, 3.29.

(-)-Reticuline–Perchloric Acid–0.5-Water [(-)-2·$HClO_4$·0.5H_2O]. Borane reduction of 1.78 g (5.0 mmol) of (-)-12 exactly as described above for the enantiomer afforded 2.06 g (96%) of (-)-2·$HClO_4$·0.5H_2O: mp 206.5–208 °C; $[\alpha]^{23}_D$ -76.7° (c 0.70, EtOH).

Anal. Calcd for $C_{19}H_{23}NO_4$·$HClO_4$·0.5H_2O: C, 51.99; H, 5.74; N, 3.19. Found: C, 52.17; H, 5.43; N, 2.87.

Regeneration of (-)-2 from the perchlorate salt and treatment with HCl exactly as described above for the enantiomer afforded (-)-2·HCl·1.5H_2O: mp 159–161 °C (determined as described above for the enantiomeric salt); $[\alpha]^{23}_D$ -76.8° (c 1.0, H_2O) [lit.[21b] $[\alpha]_D$ -75° (c 1.0, H_2O)].

Anal. Calcd for $C_{19}H_{23}NO_4$·HCl·1.5H_2O: C, 58.08; H, 6.93; N, 3.57. Found: C, 58.09; H, 6.57; N, 3.79.

(±)-Tetrahydropapaveroline–Hydrogen Bromide [(±)-18·HBr]. A mixture of 630 mg (2.0 mmol) of (±)-1 and 15 mL of reagent grade 48% aqueous HBr was heated to solution under argon and refluxed 2.0 h. The mixture which contained crystalline material was evaporated to dryness, and the solid residue was cautiously heated to solution in 2.0 mL of DMF, diluted with 5.0 mL of acetic acid, and warmed to ~80 °C to initiate crystallization. When crystallization was complete at 25 °C, the solid was collected, washed with acetic acid and Et_2O, and dried under high vacuum to afford 597 mg of (±)-18·HBr as analytically pure white crystals: mp 277.5–278.5 °C dec; CI MS *m/e* 288 ($M^+ + 1$). Concentration of the filtrate and washings to a syrup and dilution with 2.0 mL of acetic acid afforded 102 mg of a second crop, mp 278.5–280 °C. The total yield was 699 mg (95%). The crystalline (±)-18·HBr slowly developed a bluish purple color over a period of days when stored in a closed container under the atmosphere. This apparent oxidative decomposition could be avoided if the container of freshly prepared (±)-18·HBr was placed under high vacuum and refilled with argon (3×). This deoxygenation should be repeated each time the container is opened to the atmosphere.

(+)-Tetrahydropapaveroline–Hydrogen Bromide [(+)-18·HBr]. Treatment of 630 mg (2.0 mmol) of (+)-1 with 15 mL of 48% aqueous HBr as described above for the racemate gave solid materials after evaporation of the HBr and drying under high vacuum overnight. This solid was heated to solution in 1.5 mL of DMF, diluted with 5.0 mL of acetic acid, and heated to ~70 °C to initiate crystallization. After the mixture cooled, the solid was filtered, washed with acetic acid and then Et_2O, and dried at 78 °C under high vacuum to afford 535 mg of analytically pure (+)-18·HBr: mp 280–282 °C dec; CI MS *m/e* 288 ($M^+ + 1$); $[\alpha]^{23}_D$ +26.9° (c 0.41, MeOH). Concentration of the filtrate and washings to ~0.5 mL and dilution with 3.0 mL of acetic acid afforded 178 mg of (+)-18·HBr, mp 280–282 °C dec. The total yield was 713 mg (97%).[46]

Anal. Calcd for $C_{16}H_{17}NO_4$·HBr: C, 52.19; H, 4.93; N, 3.80. Found: C, 52.15; H, 4.78; N, 3.82.

(-)-Tetrahydropapaveroline–Hydrogen Bromide [(-)-18·HBr]. Treatment of (-)-1 as described above for the enantiomer gave a first crop of 648 mg of (-)-18·HBr: mp 280.5–282 °C dec; CI MS *m/e* 288 ($M^+ + 1$); $[\alpha]^{23}_D$ -26.3° (c 0.43, MeOH). A second crop of 61 mg was obtained as above; mp 279.5–280.5 °C dec. The total yield was 709 mg (97%).[46]

Anal. Calcd for $C_{16}H_{17}NO_4$·HBr: C, 52.19; H, 4.93; N, 3.80. Found: C, 51.81; H, 5.14; N, 3.77.

(±)-6'-Bromotetrahydropapaveroline–Hydrogen Bromide–1.5-Water [(±)-19·HBr·1.5H_2O]. A stirred suspension of 1.18 g (3.0 mmol) of (±)-16 in 50 mL of $CHCl_3$ was treated with 3.01 g (12.0 mmol) of BBr_3 in one portion (exothermic reaction). The mixture, which contained white solid, was heated under reflux 0.5 h, treated with 3.01 g (12.0 mmol) of BBr_3, and refluxed 1.0 h to afford a nearly homogenous solution. The mixture was cooled

(46) This enantiomer should be deoxygenated and stored as described for the racemate (±)-18.

and cautiously treated with 15 mL of methanol. When the exothermic reaction was over, the solution was evaporated to a foam which was crystallized from 8 mL of 3% aqueous HBr and dried to afford 1.29 g of (±)-19·HBr·1.5H_2O: mp 251–253 °C dec; CI MS m/e 366 and 368 ($M^+ + 1$).

Anal. Calcd for $C_{16}H_{16}BrNO_4$·HBr·1.5H_2O: C, 40.52; H, 4.03; N, 2.95. Found: C, 40.24; H, 4.11; N, 2.73.

Reaction of (±)-1, (+)-1, and (−)-1 with (*S*)-(−)-α-Methylbenzyl Isocyanate. Formation of Diastereoisomers 20 and 21. Addition of 157 mg (0.5 mmol) of the appropriate crystalline base to 74–80 mg (0.50–0.54 mmol) of freshly distilled (*S*)-(−)-α-methylbenzyl isocyanate in 2.5 mL of $DCCl_3$ afforded a homogeneous solution after shaking for ~10 min. TLC (system C) after 0.5 h indicated only one spot at higher R_f than amine 1 for the urea derivative(s) **20** and **21** which were not separated in this TLC system. These solutions were utilized directly for the NMR analyses of optical purity described above. Resonances for the methyl doublets of **20**, **21**, and the isocyanate were centered at δ 1.26, 1.01, and 1.59, respectively.

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Registry No. (±)-**1**, 13168-51-9; (±)-1·TsOH, 72258-86-7; (±)-1·HCl, 72258-87-8; (+)-1, 57231-34-2; (+)-1·(+)-2′-BTA, 72264-50-7; (+)-1·HCl, 6507-35-3; (−)-1, 4781-58-2; (−)-1·(−)-2′-BTA, 72258-88-9; (−)-1·HCl, 6451-82-7; (±)-**2**, 1699-46-3; (+)-**2**, 485-19-8; (+)-**2**·$HClO_4$, 14199-16-7; (+)-**2**·HCl, 903-91-3; (−)-**2**, 3968-19-2; (−)-**2**·$HClO_4$, 72258-89-0; (−)-**2**·HCl, 1431-01-2; **7**, 554-52-9; **7**·HCl, 1477-68-5; **8**, 1131-94-8; **8**·NH_3, 72258-90-3; **9**, 21411-19-8; **10**, 72258-91-4; (±)-**11**, 55869-76-6; (±)-**12**, 72258-92-5; (+)-**12**, 72274-69-2; (−)-**12**, 72274-70-5; (±)-**13**, 72274-71-6; (±)-**14**, 72264-51-8; (±)-**16**, 58116-06-6; (±)-**16**·HCl, 63125-28-0; (±)-**17**, 72258-93-6; (±)-**17** picrate, 72264-52-9; (±)-**17**·HBr, 72258-94-7; (±)-**18**·HBr, 67200-79-7; (+)-**18**·HBr, 72072-53-8; (−)-**18**·HBr, 72072-54-9; (±)-**19**·HBr, 72258-95-8; **20**, 72258-96-9; **21**, 72258-97-0; (*S*)-(−)-α-methylbenzyl isocyanate, 14649-03-7.

Pavinan and Isopavinan Alkaloids. Synthesis of Racemic and Natural Thalidine, Bisnorargemonine, and Congeners from *N*-Norreticuline[1a]

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The isopavinan alkaloids thalidine and *O*-methylthalisopavine and the pavinan alkaloids bisnorargemonine and argemonine were synthesized as the racemates and natural isomers from the appropriate form of *N*-norreticuline. The sequence utilizing (*S*)-(−)-*N*-norreticuline afforded the natural alkaloids and confirmed the absolute stereochemistry previously assigned to these compounds by several methods. The tetracyclic skeleton of both alkaloids was readily constructed from the same intermediate, 4-methoxy-*N*-acyl-*N*-norreticuline. In the racemic series, oxidation of (±)-*N*-formyl-*N*-norreticuline with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in methanol at low temperature afforded the crystalline 4-methoxy-*N*-formyl derivative formally through 1,6-addition of methanol to an intermediate quinone methide. Facile entry into the isopavinan series via crystalline *N*-formyl-*N*-northalidine was accomplished by treatment of the 4-methoxy compound with a catalytic amount of methanesulfonic acid in acetonitrile. Thermolytic elimination of methanol from the 4-methoxy intermediate readily provided 3,4-dehydro-*N*-norreticuline which was cleanly cyclized under the same conditions to the pavinan, *N*-formyl-*N*-norbisnorargemonine. Hydrazinolysis of these *N*-formyl derivatives provided the corresponding secondary amines in high yield, and borane reduction of the *N*-formyl functionality efficiently afforded (±)-thalidine and (±)-bisnorargemonine. In the natural series, treatment of the readily available (*S*)-(−)-*N*-norreticuline with ethyl chloroformate gave the (+)-*N*-carbethoxy derivative which was subjected to a reaction sequence analogous to that employed for the (±)-*N*-formyl compound. The corresponding (+)-*N*-carbethoxy congeners of natural (−)-thalidine and (−)-bisnorargemonine thus obtained were reduced with lithium aluminum hydride to afford the optically pure natural alkaloids. Methylation of the racemic and natural phenolic alkaloids with diazomethane gave the corresponding forms of *O*-methylthalisopavine and argemonine. Each of the *N*-formyl and *N*-carbethoxy intermediates were shown by NMR to exist as rotomers resulting from hindered rotation about the amide bond, and in several cases these rotomers were separable by TLC.

The pavinan and isopavinan alkaloids[2-5] can be formally viewed as oxidatively cyclized 1-benzyl-1,2,3,4-tetrahydroisoquinolines (BTIQ). Most frequently acid-catalyzed cyclization of appropriately oxidized congeners of BTIQ has been employed as the key step for formation of these tetracyclic systems. In recent years, a number of studies[4-6] have revealed that acid-catalyzed cyclization of 3,4-dehydro derivatives of BTIQ (1,2-dihydroisoquinolines) favors pavinan formation while isopavinans are usually obtained by similar treatment of 4-oxygenated BTIQ.

(1) (a) Presented in preliminary form by W.C.R. at the American Chemical Society/Chemical Soceity of Japan Chemical Congress, Honolulu, Hawaii, Apr 4, 1979; Abstr. No. ORGN 291. (b) Guest worker on leave from the Central Research Department, E. I. duPont de Nemours and Co., Wilmington, DE 19898. (c) Guest worker on leave from Hoechst AG, Frankfurt 80, West Germany.

(2) T. Kametani, "The Chemistry of the Isoquinoline Alkaloids", Vol. 1, Elsevier, New York, 1969, pp 41, 235. See also, *ibid.*, Vol. 2, Kimkodo Publishing Co., Sendai, Japan, 1974, p 99.

(3) It has been suggested by Soine and Stermitz [C.-C. Chen and T. O. Soine, *J. Pharm. Sci.*, 61, 55 (1972)] that the term pavinage be used for the skeleton of 6 and this was shortened to pavinan by Dyke.[9] Similarly, the skeleton of 9 will be referred to as isopavinan.

(4) M. Shamma, "The Isoquinoline Alkaloids", Academic Press, New York, 1972, p 96.

(5) M. Shamma and J. L. Moniot, "Isoquinoline Alkaloids Research: 1972–1977", Plenum Press, New York, 1978, p 61.

(6) S. F. Dyke, R. G. Kinsman, P. Warren, and A. W. C. White, *Tetrahedron*, 34, 241 (1978), and references cited therein.