Oxidative Coupling of *cis*-3,*N*-Bis(methoxycarbonyl)-*N*-norreticuline. An Approach to the Asymmetric Synthesis of Morphine Alkaloids

Martin A. Schwartz* and Phuong T. K. Pham

Department of Chemistry, The Florida State University, Tallahassee, Florida 32306

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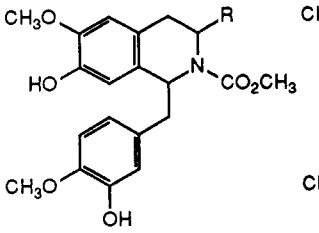
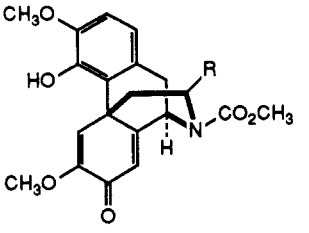
Racemic 3,*N*-bis(methoxycarbonyl)-*N*-norreticuline (1), synthesized from (±)-3-methoxytyrosine by the Bischler–Napieralski route, was shown to have cis stereochemistry by X-ray crystallography. Oxidative coupling of the title compound with iodosobenzene diacetate in the presence of trifluoroacetic acid gave results virtually identical with those obtained from the corresponding norreticuline derivative lacking the C-3 methoxycarbonyl substituent; the substituted norsalutaridine and norisoboldine derivatives **2** and **3** were isolated in yields of 25% and 21%, respectively, along with 9% of noncoupled quinone **10** and 36% of recovered starting material. Similar comparative oxidative coupling studies were carried out with the C-3 substituted and unsubstituted norreticulines using vanadium oxytrichloride and thallium(III) trifluoroacetate as oxidizing agents. Racemic 16,*N*-bis(methoxycarbonyl)norsalutaridine (**2**) was converted to the corresponding 16-(methoxycarbonyl)northebaine derivative **12** by standard methods (76% yield). The latter was decarboxylated, hydrolyzed, and reduced to afford (±)-codeine (**14**) (34% overall yield). Application of the Bischler–Napieralski synthetic approach to (*R*)-(+)-3-methoxytyrosine afforded (1*R*,3*R*)-(−)-3,*N*-bis(methoxycarbonyl)-*N*-norreticuline in 54% ee. Oxidative coupling of the latter with iodosobenzene diacetate and trifluoroacetic acid gave the (9*R*)-(+)-norsalutaridine derivative with no detectable loss in optical purity.

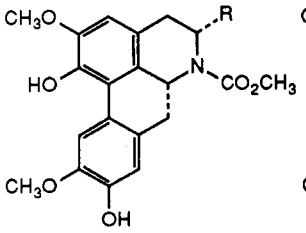
In a continuation of our studies aimed at developing efficient biomimetic approaches to morphine alkaloids and analogues,[1] we wished to prepare and examine the oxidative coupling behavior of the C-3 substituted reticuline derivative **1**. We anticipated that *cis*-**1** might give lower yields of dienone products such as the salutaridine analogue **2** and higher yields of aporphine products such as



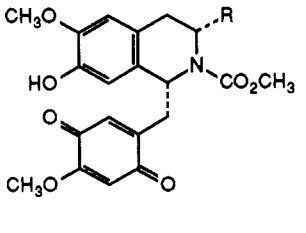
1, R = CO_2CH_3
4, R = H



2, R = CO_2CH_3
8, R = H



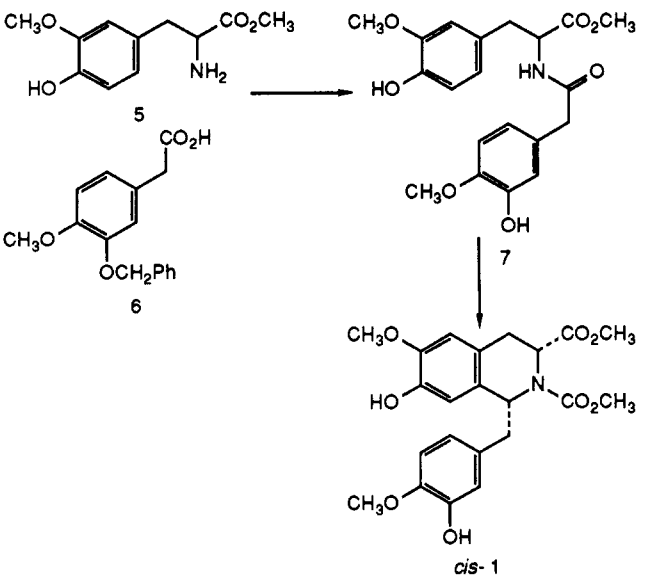
3, R = CO_2CH_3
9, R = H



10, R = CO_2CH_3
11, R = H

the isoboldine analogue **3**, in comparison to the product distribution from oxidative coupling of the corresponding C-3 unsubstituted reticuline derivative **4**. This would be the expected result if a 1,3-diaxial interaction between the C-1 and C-3 substituents arises in the transition state leading from *cis*-**1** to dienone products (C-1 substituent required to be axial) but is avoided in the transition state leading to aporphine products (C-1 substituent may be equatorial). On the other hand, oxidative coupling of *trans*-**1** might give useful yields of **2**; in that event we

Scheme I



anticipated than an asymmetric synthesis of **1** would be easily accomplished and thus could serve as the basis for an approach to the asymmetric synthesis of morphine alkaloids.[2]

Synthesis of 3-(Methoxycarbonyl)reticuline Derivative 1 (Scheme I). 1-Benzyl-3-(methoxycarbonyl)-tetrahydroisoquinolines related to **1** have been synthesized from phenylalanine derivatives via the Pictet–Spengler reaction, but only in low yield.[3] We therefore investigated application of the Bischler–Napieralski cyclization route to this system. Racemic 3-methoxytyrosine methyl ester (**5**)[4] and 3-(benzyloxy)-4-methoxyphenylacetic acid (**6**)[5] were coupled via the acylimidazole method[6] to give, after

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(2) For other recent syntheses of morphine alkaloids and analogues, see: (a) Toth, J. E.; Fuchs, P. L. *J. Org. Chem.* **1987**, *52*, 473. (b) Ludwig, W.; Schaefer, H. J. *Angew. Chem.* **1986**, *98*, 1032. (c) Rice, K. C. In *The Chemistry and Biology of Isoquinoline Alkaloids*; Phillipson, J. D., Roberts, M. F., Zenk, M. H., Eds.; Springer-Verlag: Berlin, 1985; pp 191–203, and references cited therein.

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(6) Paul, R.; Anderson, G. W. *J. Am. Chem. Soc.* **1960**, *82*, 4596.

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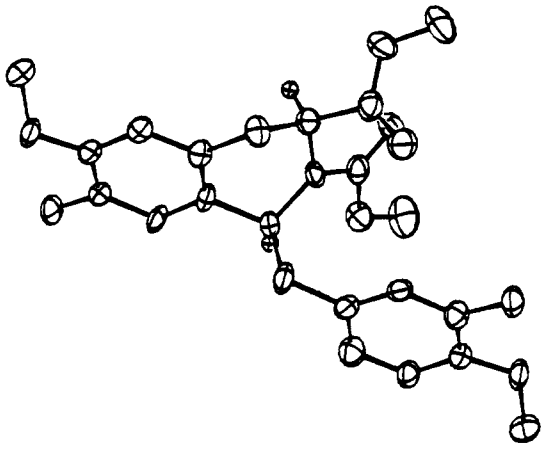


Figure 1. ORTEP plot of *cis*-1.

debenzylation, amide 7 in 79% yield. The latter was subjected to a four-step reaction sequence consisting of esterification to the bis(methoxycarbonyl)derivative, cyclization with $POCl_3$, imine reduction with $NaBH_4$, and finally N-acylation with methyl chloroformate and O-acyl hydrolysis to give (±)-*cis*-1 in 90% overall yield. The reaction sequence was carried out without purification of intermediates; the choice of blocking groups was based on our observation[7] that the carbonate functionality was particularly effective in masking phenolic functionality and giving rise to very high yields in Bischler–Napieralski reactions.

The assignment of cis stereochemistry to 1 prepared in this way was based initially on the report by Castagnoli and co-workers[8] that a *cis*-1-benzyl-3-methyltetrahydroisoquinoline resulted as the major product (25:1) from reduction of the precursor imine with $NaBH_4$ or $LiAlH_4$ and as the sole product from catalytic hydrogenation. Since *cis*-1 was nicely crystalline, it was possible to confirm the stereochemical assignment by single-crystal X-ray analysis[9] (Figure 1). An interesting feature of the ORTEP plot of *cis*-1 shown in Figure 1 is that the piperidine ring is in a pseudo-boat conformation with the C-1 benzyl substituent axially oriented and the C-3 methoxycarbonyl substituent equatorially oriented; as will be seen later, the solution chemistry of *cis*-1 is explainable on the basis of the accessibility of such a conformation as well.

All efforts to generate *trans*-1 by equilibration of *cis*-1 and derivatives failed; not even small quantities of the trans isomer were detectable. The methods attempted included treatment of the diphenol with hydrogen and platinum oxide for C-1 epimerization[10] and treatment of the bis(benzyl ether) or bis[(methoxyethoxymethyl) ether] with methanolic sodium methoxide for C-3 epimerization;[10,11] in each case 95–100% recoveries of starting material were realized. We were therefore restricted to carrying out the oxidative coupling studies on *cis*-1 only.

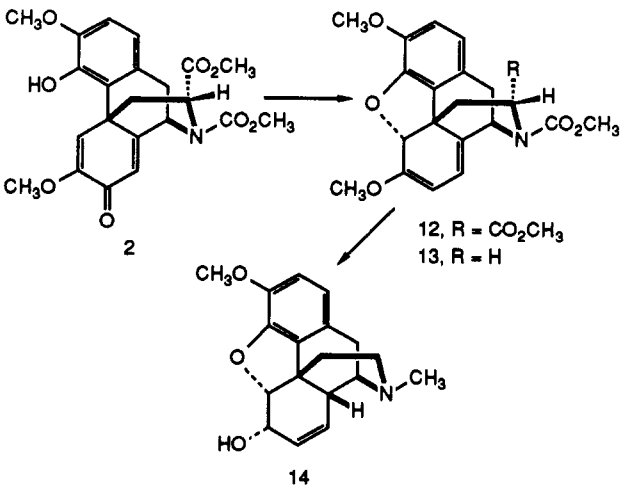
Oxidative Coupling. Oxidative coupling studies on *cis*-1 were conducted by using vanadium oxytrichloride,[12] thallium(III) trifluoroacetate,[1e,12] and iodosobenzene diacetate/trifluoroacetic acid.[1a,13] Parallel studies with the same oxidants were carried out on *N*-(methoxycarbonyl)-*N*-norreticuline (4) in order to provide comparison data needed to assess the effect of the C-3 substituent. The structures of the products were assigned on the basis of their IR, NMR, and mass spectral properties. The stereochemical assignments at C-16 of salutaridine analogue 2 and at C-5 of isoboldine analogue 3 could not be confirmed spectrally and were made solely on the basis that the compounds gave every indication of being stereochemically homogeneous (melting points and TLC behavior) with no other diastereomers being detectable in the reaction mixture. The results, summarized in Table I, were surprisingly similar between the C-3 substituted and unsubstituted compounds. The only significant difference in the course of the reaction with the two substrates was seen with thallium(III) trifluoroacetate, which gave none of the salutaridine analogue 2 in the C-3 substituted case.

Table I. Oxidative Coupling Yields from *cis*-1 and 4

product	% yield[a] from *cis*-1 (from 4) with different oxidants		
	$VOCl_3$	$Tl(TFA)_3$	$PhI(OAc)_2$/TFA
1 (4)	20 (21)	33 (28)	36 (27)
2 (8)	0 (0)	0 (23)	25 (26)
3 (9)	80 (70)	2 (16)	21 (25)
10 (11)	0 (0)	26 (8)	9 (8)

[a] Isolated yields; all reactions were carried out in anhydrous dichloromethane.

Scheme II



The fact that the iodosobenzene diacetate and vanadium oxytrichloride oxidation results were insensitive to C-3 substitution implies that there is little or no interaction between cis C-1 and C-3 substituents in the transition state leading to the dienone or aporphine products. Transition states with a boat-like piperidine ring conformation as seen in the crystal structure of *cis*-1 meet this requirement while still having the axially oriented C-1 benzyl side chain that is definitely required for formation of dienone products and that is probably also required for formation of aporphine products.[14]

Synthesis of (±)-Codeine (Scheme II). Since the C-3 methoxycarbonyl substituent did not adversely affect the conversion of reticuline derivative 1 to salutaridine derivative 2, decarboxylation of the latter would provide a

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(9) Single-crystal X-ray analysis was performed by Professor V. Goedken, Florida State University, Department of Chemistry, Tallahassee, FL 32306.
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(13) Szantay, C.; Blasko, G.; Barczai-Beke, M.; Pechy, P.; Dornyei, G. *Tetrahedron Lett.* **1980**, *21*, 3509.
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reasonable synthetic route to the morphine alkaloids. The reductive radical decarboxylation procedure of Barton and co-workers,[15] involving photolysis of an *N*-hydroxypyridine-2-thione ester in the presence of *tert*-butyl mercaptan, seemed well suited for this transformation.

Direct conversion of **2** to *N*-(methoxycarbonyl)-*N*-norsalutaridine (**8**) was prevented by the fact that basic hydrolysis of the C-16 ester moiety of **2** was slow and was accompanied by decomposition, presumably due to the presence of the acidic phenolic hydroxyl group. The ester hydrolysis step was therefore postponed. Reduction of **2** and dehydration[16] of the resulting dienol afforded the 16-(methoxycarbonyl)thebaine derivative **12** in 76% yield. Saponification and decarboxylation[15] of the latter gave a 70% yield of (±)-*N*-(methoxycarbonyl)-*N*-northebaine (**13**). Hydrolysis of **13** to the corresponding codeinone derivative was effected by the two-step procedure of Gavard and co-workers[17] and was followed by reduction with $LiAlH_4$ to furnish (±)-codeine (**14**) in 48% yield.

Asymmetric Synthesis. On the basis of the foregoing results, a versatile approach to asymmetric synthesis of the morphine alkaloids was feasible. The natural (9*R*) and unnatural[2c] (9*S*) series of alkaloids would be accessible from (*R*)- or (*S*)-3-methoxytyrosine, respectively, and either enantiomer of 3-methoxytyrosine can be readily prepared by asymmetric hydrogenation of an acetamidocinnamic acid with chiral catalysts.[18] The major uncertainty in this approach was the extent to which racemization might occur in the Bischler–Napieralski cyclization step.

(*R*)-3-Methoxytyrosine methyl ester ((*R*)-**5**) was subjected to the sequence of reactions that had been used in the racemic series (Scheme I), affording the (1*R*,3*R*)-3-(methoxycarbonyl)norreticuline (-)-*cis*-**1** in 86% overall yield; HPLC analysis of the bis Mosher ester[19] derivative of the latter showed it to be only 54% ee, however. Oxidation of (-)-*cis*-**1** with iodosobenzene diacetate gave a 25% yield of the (9*R*)-salutaridine derivative (+)-**2** in 58% ee (determined by direct HPLC analysis on the Pirkle chiral covalent column[20]), thus confirming that the oxidative coupling step proceeded without racemization.

While it might be possible to alter the Bischler–Napieralski reaction conditions somewhat to enhance the optical yield, perhaps at the expense of the chemical yield, that approach was not pursued. The recently published[21] asymmetric synthesis of (*R*)-norreticuline in high optical yield makes the necessary link to our earlier work[1d,e] to provide a biomimetric asymmetric synthetic route to the morphine alkaloids.

Experimental Section

Melting points were measured on a Kofler hot stage apparatus and are uncorrected. NMR spectra were recorded at 200 or 270 MHz in $CDCl_3$; chemical shifts are reported in parts per million downfield from tetramethylsilane, and coupling constants are reported in hertz. IR spectra were measured as $CHCl_3$ solutions unless otherwise specified. Low resolution mass spectra were obtained at 70 eV, and the data are reported as *m/e* (relative intensity). Preparative TLC plates were prepared at a thickness of 1 mm from Merck PF 254 silica gel. Flash chromatography was performed according to the Taber procedure[22] using Merck EM 7747 silica gel (10–15 μm).

(±)-*N*-[(3-Hydroxy-4-methoxyphenyl)acetyl]-3-methoxytyrosine Methyl Ester (7). A solution of 8.71 g (32.0 mmol) of 3-(benzyloxy)-4-methoxyphenylacetic acid[5] (**6**, mp 128–129 °C) and 5.19 g (32.0 mmol) of 1,1'-carbonyldiimidazole in 200 mL of anhydrous THF was stirred at 0 °C for 1.5 h and at room temperature for 1 h.[6] The mixture was cooled again in an ice bath and stirred for 1 h; then 7.20 g (32.0 mmol) of (±)-3-methoxytyrosine methyl ester[4] (**5**, mp 88–89 °C) was added and the solution was stirred at 0 °C for 4 h and at room temperaure overnight. The THF was evaporated under reduced pressure and the residue was dissolved in ethyl acetate and was extracted with 1 N HCl, water, aqueous sodium bicarbonate, and water. The organic layer was evaporated and the crude product was crystallized from ethyl acetate–ether to give 12.3 g (80%) of the amide monobenzyl ether: mp 92–93 °C; IR 3540, 3415, 1740, 1665, 1610 cm^{-1}; ^1H NMR 7.37 (5, br m), 6.83 (1, d, *J* = 8), 6.77 (1, d, *J* = 1.5), 6.73 (1, d, *J* = 5), 6.71 (1, dd, *J* = 1.5, 5), 6.46 (1, d, *J* = 2), 6.33 (1, dd, *J* = 2, 8), 5.8 (1, br d, *J* = 9, NH), 5.49 (1, s, OH), 5.09 (2, s), 4.78 (1, m), 3.89 (3, s), 3.76 (3, s), 3.70 (3, s), 3.43 (2, s), 2.92 (2, m); mass spectrum, *m/e* 479 (5), 420 (0.5), 298 (10), 227 (11), 208 (19), 137 (56), 91 (100).

A solution of 2.00 g (4.18 mmol) of the amide from above in 400 mL of ethyl acetate was degassed with nitrogen for 1 h; then 0.500 g of 10% Pd/C was added and hydrogen was introduced via a gas dispersion tube with stirring for 20 h. The catalyst was removed by filtration through Celite and the solvent was evaporated. Recrystallization of the resulting white solid from methanol gave 1.62 g (99%) of amide **7**: mp 156–157 °C; IR 3540, 3410, 1738, 1658, cm^{-1}; ^1H NMR 6.76 (1, d, *J* = 9), 6.74 (1, d, *J* = 3), 6.72 (1, d, *J* = 8), 6.62 (1, dd, *J* = 3, 9), 6.47 (1, d, *J* = 2), 6.36 (1, dd, *J* = 2, 8), 5.8 (1, br d, *J* = 8, NH), 5.61 (1, s, OH), 5.47 (1, s, OH), 4.77 (1, m), 3.89 (3, s), 3.77 (3, s), 3.68 (3, s), 3.43 (2, s), 2.94 (2, m); mass spectrum, *m/e* 389 (1), 330 (1), 208 (59), 181 (38), 137 (100).

(±)-*cis*-1-[(3-Hydroxy-4-methoxyphenyl)methyl]-3,4-dihydro-7-hydroxy-6-methoxy-2,3(1*H*)-isoquinolinedicarboxylic Acid Dimethyl Ester (*cis*-1). A solution of 9.00 g (23.1 mmol) of amide **7** in 2.5 L of dichloromethane was cooled to 0 °C under nitrogen, 25.0 mL (179 mmol) of triethylamine was added, and then 20.0 mL (259 mmol) of methyl chloroformate was added dropwise over a period of 30 min. The solution was allowed to warm slowly to room temperature and then was stirred under nitrogen for 48 h. The reaction mixture was washed three times with water, the organic layer was evaporated, and the residue was dried under high vacuum.

To a boiling solution of the product from above in 600 mL of anhydrous acetonitrile under nitrogen was added 50.0 mL (536 mmol) of freshly distilled phosphorus oxytrichloride in one portion, and the solution was stirred at reflux for 9 h. The solvent was evaporated and the residue was dried under high vacuum.

To a solution of the product from above in 1.0 L of absolute methanol was added excess sodium borohydride in small portions with stirring at 0 °C, and the solution was stirred at 0 °C under nitrogen for 3 h and at room temperature for 45 min. The mixture was diluted with 1.0 L of water and was extracted three times with dichloromethane. The organic extract was washed with water, dried, and evaporated, and the residue was dried under high vacuum.

To a solution of the product from above in 1.0 L of methanol was added 5.00 g (47.2 mmol) of sodium carbonate and 5.00 mL (64.7 mmol) of methyl chloroformate, and the solution was stirred for 2 h at room temperature. Water (100 mL) was added and the mixture was stirred overnight at room temperature under nitrogen. The solid was removed by filtration, the filtrate was evaporated, water and dichloromethane were added to the residue, and the aqueous layer was extracted three times with dichloromethane.

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(21) Noyori, R.; Ohta, M.; Hsiao, Y.; Kitamura, M.; Ohta, T.; Takaya, H. *J. Am. Chem. Soc.* **1986**, *108*, 7117.

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The combined organic extract was washed with water and was evaporated. The resulting crude product was purified by flash chromatography on 300 g of silica gel, eluting with chloroform, followed by crystallization from ethyl acetate, to yield 9.00 g (90%) of *cis*-1: mp 136–138 °C; IR 3540, 1750, 1690 cm^{-1}; ^1H NMR 6.72 and 6.69 (1, d, J = 3), 6.66 (1, s), 6.60 (1, dd, J = 2, 3), 6.53 and 6.51 (1, d, J = 2), 6.21 and 6.16 (1, s), 5.17 and 5.03 (1, m, H-1), 4.32 (1, m, H-3), 3.87 (3, s), 3.86 (3, s), 3.81 and 3.80 (3, s), 3.70 (3, s), 3.23 (1, m), 3.04 (2, m), 2.71 (1, m); mass spectrum, m/e 431 (0.1), 400 (0.4), 372 (0.8), 294 (100), 234 (9.2), 190 (8.1), 137 (5.7). Anal. Calcd for $C_{22}H_{25}NO_8$: C, 61.25; H, 5.84; N, 3.25. Found: C, 60.97; H, 5.95; N, 3.09.

Vanadium Oxytrichloride Oxidation of *cis*-1 and 4. A solution of 118 mg (0.274 mmol) of *cis*-1 in 160 mL of anhydrous dichloromethane was cooled to −78 °C and was scrubbed with nitrogen for 1 h; then 85.0 μL (0.902 mmol) of $VOCl_3$ was added via syringe. The solution was stirred under nitrogen at −78 °C for 3 h, at room temperature for 1.5 h, and at reflux for 1 h. The resulting dark green solution was washed with 5% aqueous sodium bicarbonate, water, and saturated aqueous NaCl, and the solvent was evaporated. The crude product was subjected to preparative TLC (5% methanol in $CHCl_3$) to give, in order of decreasing R_f, 24 mg (20%) of starting *cis*-1 and 95 mg (80%) of **3**: mp 250–251 °C (from ethyl acetate); IR 3520, 1740, 1690, 1610 cm^{-1}; ^1H NMR 8.03 (1, s), 6.83 (1, s), 6.58 (1, s), 6.15 (1, s, OH), 5.68 (1, s, OH), 5.45 (1, br m), 4.71 (1, br m), 3.92 (6, s), 3.82 (3, s), 3.61 (3, s), 3.25 (2, m), 3.05 (2, m); mass spectrum, m/e 429 (23), 370 (8), 310 (3), 283 (100). Anal. Calcd for $C_{22}H_{23}NO_8$: C, 61.53; H, 5.40; N, 3.26. Found: C, 61.45; H, 5.39, N, 3.20.

The same procedure was applied using 108 mg (0.289 mmol) of **4** and 90 μL of $VOCl_3$ in 160 mL of dichloromethane to afford 23 mg (21%) of recovered **4** and 75 mg (70%) of *N*-(methoxycarbonyl)-*N*-norisoboldine (**9**) as a colorless glass: IR 3530, 1685, 1610 cm^{-1}; ^1H NMR 8.08 (1, s), 6.84 (1, s), 6.58 (1, s), 6.20 (2, s, OH), 4.75 (1, m), 4.45 (1, m), 3.94 (3, s), 3.92 (3, s), 3.78 (3, s), 2.8 (5, m); mass spectrum, m/e 371 (40), 283 (100), 240 (5), 225 (3), 185 (7).

Thallium(III) Trifluoroacetate Oxidation of *cis*-1 and 4. A solution of 150 mg (0.348 mmol) of *cis*-1 in 150 mL of anhydrous degassed dichloromethane was added dropwise to a stirred slurry of 189 mg (0.348 mmol) of thallium(III) trifluoroacetate in 250 mL of dichloromethane at −78 °C under nitrogen. The mixture was stirred at −78 °C for 3 h, at −20 °C for 10 h, and at room temperature for 30 min. The resulting deep green solution was evaporated under reduced pressure and the residue was subjected to flash chromatography on a column of 50 g of silica gel, eluting with 10% methanol in $CHCl_3$, to remove the thallium salts. The crude product was separated by preparative TLC (100% ether) to give, in order of decreasing R_f, 3 mg (2%) of **3**, 49 mg (33%) of starting material, and 48 mg of a mixture. The latter was subjected to further preparative TLC (1% methanol in $CHCl_3$, continuous elution) to give 40 mg (26%) of quinone **10**: mp 205–208 °C (from ethyl acetate); IR 3540, 1740, 1690, 1650, 1605, cm^{-1}; ^1H NMR 6.86 and 6.83 (1, s), 6.80 (1, s), 6.67 (1, s), 5.98 and 5.95 (1, s), 5.52 (1, br s, OH), 5.18 and 5.06 (1, m), 4.38 (1, m), 3.88 (3, s), 3.83 and 3.80 (3, s), 3.69 (3, s), 3.55 (3, s), 3.11 (3, m), 2.65 (1, m); mass spectrum, m/e 445 (5), 294 (100), 234 (17), 176 (16), 161 (6). Anal. Calcd for $C_{22}H_{23}NO_9$: C, 59.32; H, 5.20; N, 3.14. Found: C, 59.22; H, 5.28; N, 3.02.

The same procedure was applied using 680 mg (1.82 mmol) of **4** and 990 mg (1.82 mmol) of thallium(III) trifluoroacetate in 900 mL of dichloromethane. Preparative TLC (100% ether) separation of the crude product gave, in order of decreasing R_f, 106 mg (16%) of **9**, 189 mg (28%) of starting material, and 236 mg of a mixture. The latter was further separated by preparative TLC (5% methanol in $CHCl_3$) to give, in order of decreasing R_f, 156 mg (23%) of (±)-*N*-(methoxycarbonyl)-*N*-norsalutaridine (**8**) as a colorless glass [IR 3520, 1690, 1670, 1650, 1620 cm^{-1}; ^1H NMR 7.52 (1, s), 6.77 (1, d, J = 8), 6.64 (1, d, J = 8), 6.34 (1, s), 5.03 and 5.16 (1, br m), 4.1 (1, br m), 3.9 (3, s), 3.75 and 3.70 (6, s), 3.5 (1, br m), 3.2 (2, br m), 2.8 (1, br m), 2.57 (1, br m); mass spectrum, m/e 371 (100), 343 (22), 328 (18), 312 (25), 296 (32), 283 (77), 270 (56), 255 (31), 241 (19), 225 (19), 181 (23), 139 (25)] and 54 mg (8%) of quinone **11** as an orange solid [mp 190–193 °C; IR 3540, 1710, 1680, 1670, 1650, 1610 cm^{-1}; ^1H NMR 6.91 and 6.87 (1, s), 6.57 (1, s), 6.42 (1, s), 5.99 and 5.97 (1, s), 5.52 (1, br s, OH), 5.28–5.11 (1, m), 4.25 (1, m), 3.83 (3, s), 3.80 (3, s), 3.56 and 3.51 (3, s), 3.13 (2, m), 2.83 (1, m), 2.61 (2, m)].

Iodosobenzene Diacetate Oxidation of *cis*-1 and 4. A mixture of 1.01 g (2.34 mmol) of *cis*-1, 740 mg (2.29 mmol) of $PhI(OAc)_2$, and 0.360 mL (4.67 mmol) of CF_3COOH in 1.8 L of anhydrous degassed dichloromethane was stirred at room temperature under nitrogen for 2.5 h.[1a,13] The reaction mixture was extracted with water and was evaporated. The crude product was separated by flash chromatography on 50 g of silica gel (eluting with 20% hexane in ether) to give, in order of decreasing R_f, 210 mg (21%) of **3**, 367 mg (36%) of starting material, 89 mg (9%) of quinone **10**, and 252 mg (25%) of (±)-16,*N*-bis(methoxycarbonyl)-*N*-norsalutaridine (**2**): mp 204–206 °C (from ethyl acetate); IR 3520, 1745, 1700, 1675, 1645, 1620 cm^{-1}; ^1H NMR 7.48 (1, s), 6.78 (1, d, J = 8), 6.58 (1, d, J = 8), 6.36 and 6.34 (1, s), 6.28 (1, s, OH), 5.2 and 5.1 (1, m), 4.83 and 4.65 (1, m), 3.88, 3.83, 3.74 and 3.68 (9), 3.3 (3, m), 3.19 (3, s), 1.82 (1, m); mass spectrum, m/e 429 (8), 370 (2), 294 (3), 283 (6), 270 (100), 255 (27), 239 (40), 207 (24), 91 (60). Anal. Calcd for $C_{22}H_{23}NO_8$: C, 61.53; H, 5.40; N, 3.26. Found: C, 61.26; H, 5.51; N, 3.26.

The same procedure was applied using 101 mg (0.272 mmol) of **4**, 87.5 mg (0.272 mmol) of $PhI(OAc)_2$, and 40 μL of CF_3COOH in 200 mL of dichloromethane to give 25 mg (25%) of **9**, 27 mg (27%) of starting material, 26 mg (26%) of **8**, and 8 mg (8%) of **11**.

(±)-6,7,8,14-Tetradehydro-4,5α-epoxy-3,6-dimethoxymorphinan-16,17-dicarboxylic Acid Dimethyl Ester (12). To a solution of 49.3 mg (0.115 mmol) of the (±)-16-(methoxycarbonyl)salutaridine derivative **2** in 10 mL of absolute methanol was added excess sodium borohydride in portions with stirring at 0 °C, and the solution was stirred at room temperature for 1 h. Water (5 mL) and saturated aqueous NH_4Cl (10 mL) were added, and the mixture was extracted with dichloromethane. The organic extract was evaporated and the yellow glassy residue was dissolved in 14 mL of anhydrous dichloromethane and was treated with 0.300 mL (1.07 mmol) of *N*,*N*-dimethylformamide dineopentyl acetal.[16] The solution was stirred at room temperature under nitrogen for 96 h; then it was evaporated under reduced pressure and the residue was purified by preparative TLC (5% methanol in $CHCl_3$) and crystallized from ethyl acetate to yield 36 mg (76%) of (±)-16,*N*-bis(methoxycarbonyl)-*N*-northebaine (**12**): mp 191–193 °C; IR 1745, 1695 (br), 1625, 1610 cm^{-1}; ^1H NMR 6.64 (1, d, J = 8), 6.51 (1, d, J = 8), 5.64 (1, t, J = 6), 5.27 and 5.15 (1, d, J = 6), 5.05 (1, br d, J = 6), 4.81 (1, m), 3.83 (3, s), 3.74 (3, s), 3.61 (3, s), 3.44 (1, m), 3.31 and 3.22 (3, s), 2.8 (2, m), 2.25 (1, m); mass spectrum, m/e 413 (23), 354 (13), 267 (100), 252 (11), 239 (10); molecular ion at m/e 413.1477 (calcd for $C_{22}H_{23}NO_7$, 413.1473).

(±)-6,7,8,14-Tetradehydro-4,5α-epoxy-3,6-dimethoxymorphinan-17-carboxylic Acid Methyl Ester [(±)-*N*-(Methoxycarbonyl)-*N*-northebaine] (13). A solution of 32 mg (0.077 mmol) of thebaine derivative **12** in 15 mL of methanol, 7 mL of THF, and 12 mL of 5% aqueous NaOH was stirred at room temperature under nitrogen overnight. The solvent was evaporated under reduced pressure and the residue was acidified with dilute HCl and was extracted with ethyl acetate. Evaporation of the ethyl acetate and drying of the residue under high vacuum gave 31 mg (100%) of crude (±)-16-carboxy-*N*-(methoxycarbonyl)-*N*-northebaine.

To a solution of 10 mg (0.025 mmol) of the crude acid from above in 5 mL of freshly distilled anhydrous THF were added 14 μL (0.13 mmol) of *N*-methylmorpholine and 16 μL (0.13 mmol) of pivaloyl chloride.[15] The mixture was stirred at room temperature for 30 min, 3 mg (0.025 mmol) of 4-(dimethylamino)-pyridine was added, and then after another 5 min, 14 μL (0.10 mmol) of triethylamine and a solution of 32 mg (0.25 mmol) of *N*-hydroxypyridine-2-thione in 3 mL of THF was added. The reaction mixture was stirred at room temperature under nitrogen for 1.5 h. The solution was filtered into a new flask and 60 μL (0.53 mmol) of *tert*-butyl mercaptan and a catalytic amount of AIBN were added, and the reaction mixture was irradiated by using two 520-W tungsten slide projector lamps for 2 h. The solvent was evaporated, ethyl acetate was added, and the organic solution was washed successively with 1 N HCl, water, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. The ethyl acetate was evaporated and the residue was purified by preparative TLC

(2% methanol in $CHCl_3$) to give 6.2 mg (70%) of (±)-*N*-(methoxycarbonyl)-*N*-northebaine (**13**): IR 1690 cm^{-1}; ^1H NMR 6.68 (1, d, J = 8), 6.58 (1, d, J = 8), 5.62 (1, m), 5.22 (1, m), 5.02 (1, m), 4.1 (1, m), 3.84 (3, s), 3.72 (3, s), 3.60 (3, s), 3.20 (3, m), 2.1 (1, m), 1.83 (1, m); mass spectrum, m/e 355 (89), 340 (16), 280 (22), 267 (100), 253 (26); molecular ion at m/e 355.1422 (calcd for $C_{20}H_{21}NO_5$, 355.1418).

(±)-(5α,6α)-7,8-Didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol [(±)-Codeine] (14). A solution of 85 mg (1.05 mmol) of anhydrous HBr in 5 mL of anhydrous *n*-butyl ether was cooled to −20 °C under nitrogen and a solution of 15 mg (0.042 mmol) of **13** in 5 mL of anhydrous dichloromethane was added.[17] The yellow solution was stirred for 15 min at −10 °C, then was allowed to warm to 0 °C, and was stirred for an additional 5 min. The reaction mixture was poured into a slurry of saturated aqueous $NaHCO_3$ and ice. The aqueous mixture was extracted with dichloromethane and the organic extract was washed with water and was evaporated. Purification of the residue by preparative TLC (5% methanol in $CHCl_3$) gave 11 mg (77%) of (±)-*N*-(methoxycarbonyl)-*N*-norcodeinone as a glass: IR 1690, 1680 cm^{-1}; ^1H NMR 6.71 (1, d, J = 8), 6.64 (1, d, J = 8), 6.62 (1, d, J = 10), 6.12 (1, dd, J = 3, 10), 5.04 and 4.88 (1, br s), 4.7 (1, s), 4.2 (1, m), 3.87 (3, s), 3.78 and 3.74 (3, s), 3.05 (1, m), 2.82 (3, m), 1.95 (1, m).

To a solution of 7.0 mg (0.021 mmol) of the product from above in 5 mL of anhydrous THF was added excess lithium aluminum hydride, and the mixture was refluxed with stirring under nitrogen overnight. The excess hydride was destroyed and the pH was adjusted to 7–8 by dropwise addition of saturated aqueous NH_4Cl. The solvent was evaporated and ethyl acetate and water were added. The mixture was extracted with ethyl acetate and the organic layer was washed with saturated aqueous NaCl. Evaporation of the ethyl acetate yielded 3.8 mg (62%) of (±)-codeine (**14**) which crystallized upon standing: mp 139–141 °C (lit.[23] mp 143 °C); IR 3560, 1640, 1608, cm^{-1}; ^1H NMR 6.65 (1, d, J = 7), 6.57 (1, d, J = 7), 5.70 (1, br m), 5.30 (1, br m), 4.90 (1, dd, J = 5.5, 1), 4.18 (1, br m), 3.81 (3, s), 3.35 (1, m), 3.10 (1, br s), 3.05 (1, br s), 2.6 (2, m), 2.45 (3, s), 2.4–1.8 (4, m). The TLC and IR and NMR spectra were identical with those of an authentic sample of (−)-codeine (Mallinckrodt).

3-Methoxy-D-tyrosine Methyl Ester ((*R*)-5). A mixture of 26.4 mg (0.068 mmol) of (μ-dichloro)tetraethylenedirhodium(I) (Aldrich) and 68.0 mg (0.136 mmol) of (−)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (Aldrich) in 50 mL of anhydrous benzene was stirred at room temperature under nitrogen for 30 min. The resulting catalyst[24] solution was added via syringe to a solution of 2.00 g (6.80 mmol) of α-acetamido-3-methoxy-4-acetoxycinnamic acid[25] in 100 mL of absolute ethanol. Hydrogen was introduced via a gas dispersion tube for 12 h. The solvent was evaporated and the residue was dissolved in hot water and was filtered. The filtrate was evaporated under reduced pressure and the resulting yellow oil was crystallized from water to afford 1.58 g (78%) of (*R*)-*N*-acetyl-(4-acetoxy-3-methoxyphenyl)alanine: mp 174–174.5 °C (lit.[26] mp 173–174 °C); $[\alpha]^{25}_D$ −40.8° (1.0, MeOH) [lit.[18c] for the *S* enantiomer $[\alpha]^{20}_D$ +40.8° (1.0, MeOH)]; identical with an authentic sample.[25]

A solution of 2.69 g (9.10 mmol) of the acid prepared as described above in 10 mL of 20% aqueous sulfuric acid was refluxed for 4 h. The mixture was cooled and was basicified to pH 8 by slow addition of barium hydroxide; then it was re-acidified to pH 6 by addition of dry ice and it was filtered through Celite. The filtrate was evaporated and the resulting white solid was triturated with ethyl acetate to yield 1.90 g (100%) of (+)-(*R*)-3-methoxytyrosine: mp 230 °C dec; $[\alpha]^{25}_D$ +15.3° (0.36, 0.1 N HCl) [lit.[27] for the *S* enantiomer $[\alpha]^{20}_D$ −15.4° (0.36, 0.1 N HCl)].

To 20 mL of absolute methanol stirred at −10 °C under nitrogen was slowly added 2.0 mL (27 mmol) of thionyl chloride. The solution was stirred at −10 °C for 15 min; then 1.40 g (6.64 mmol) of (*R*)-3-methoxytyrosine from above was added in four portions over 15 min. The solution was stirred at −10 °C for 45 min and then was left at room temperature for 2 days. The solvent was evaporated and the residue was crystallized from methanol to give 1.73 g (100%) of (−)-(*R*)-3-methoxytyrosine methyl ester hydrochloride: mp 204–205 °C dec; $[\alpha]^{25}_{Hg}$ −5.25° (0.24, MeOH); mass spectrum, m/e 225 (8), 166 (7), 137 (100), 88 (12).

The hydrochloride from above was partitioned between $CHCl_3$ and saturated aqueous $NaHCO_3$, and the aqueous layer was extracted three times with $CHCl_3$. The combined organic extracts were washed with saturated aqueous NaCl and were evaporated. The residue was dried under high vacuum to afford 1.36 g (91%) of (*R*)-3-methoxytyrosine ((*R*)-**5**) which was used immediately.

***N*-[(3-Hydroxy-4-methoxyphenyl)acetyl]-3-methoxy-D-tyrosine Methyl Ester ((*R*)-7).** The procedure described for the preparation of (±)-**7** was used, starting with 1.96 g (7.21 mmol) of acid **6** and 1.62 g (7.21 mmol) of (*R*)-**5**, to yield 2.55 g (91%) of (*R*)-**7**: mp 126–129 °C; $[\alpha]^{25}_{Hg}$ −24.0° (0.1, $CHCl_3$); molecular ion at m/e 389.1469 (calcd for $C_{20}H_{23}NO_7$, 389.1474).

(−)-(1*R*,3*R*)-1-[(3-Hydroxy-4-methoxyphenyl)methyl]-3,4-dihydro-7-hydroxy-6-methoxy-2,3(1*H*)-isoquinolinedicarboxylic Acid Dimethyl Ester [(−)-*cis*-1]. The procedure described for the preparation of (±)-*cis*-**1** was used, starting with 692 mg (1.78 mmol) of (*R*)-**7**, to give 723 mg (94%) of (−)-*cis*-**1** as a colorless glass: $[\alpha]^{25}_{Hg}$ −13.5° (2.30, $CHCl_3$). Attempts to determine the enantiomeric purity of this compound by direct HPLC analysis on the Pirkle chiral covalent column[20] were not successful, so it was converted to the bis Mosher ester[19] for analysis.

To 10.0 mg (0.0232 mmol) of (−)-*cis*-**1** from above in 10 mL of anhydrous dichloromethane was added 16 μL (0.092 mmol) of diisopropylethylamine, 2.0 mg (0.016 mmol) of 4-(dimethylamino)pyridine, excess (−)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (Aldrich), and excess 1,3-dicyclohexylcarbodiimide. The mixture was stirred at room temperature under nitrogen for 3 days; then it was filtered and evaporated. The residue was dissolved in dichloromethane and was extracted with 1 N HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. The solvent was evaporated and the product was purified by preparative TLC (5% methanol in $CHCl_3$) to yield 20 mg (100%) of the bis Mosher ester. HPLC analysis of the latter on a 25-cm Supelco LC 18-S reverse phase column (isocratic 80% methanol–20% water, 1 mL/min) showed two peaks at 28 min and 30 min retention times in area ratio 23:77, respectively. HPLC analysis of the bis Mosher ester prepared in the same way from (±)-*cis*-**1** showed two peaks at 28 min and 30 min retention times in area ratio 49:51, respectively, under the same conditions.

(+)-(9*R*)-5,6,8,14-Tetradehydro-4-hydroxy-3,5-dimethoxy-7-oxomorphinan-16,17-dicarboxylic Acid Dimethyl Ester [(+)-2]. The procedure for iodosobenzene diacetate oxidation was applied, starting with 104 mg (0.242 mmol) of (−)-*cis*-**1** (54% ee), to afford 26 mg (25%) of (+)-**2** as a glass: $[\alpha]^{25}_{Hg}$ +6.89° (0.28, $CHCl_3$). HPLC analysis of the latter on a 25-cm Pirkle covalent phenylglycine column[20,28] (gradient 35% to 40% isopropyl alcohol in hexane over 10 min, 1 mL/min) gave two peaks at 35 min and 38 min retention times in area ratio 79:21, respectively. HPLC analysis of (±)-**2** under the same conditions gave peaks at 35 min and 38 min times in area ratio 49:51, respectively.

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Supplementary Material Available: Experimental details and tables of data for the single-crystal X-ray analysis of *cis*-**1** (7 pages). Ordering information is given on any current masthead page.

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