Total Synthesis of (−)-Tetrahydropalmatine via Chiral Formamidine Carbanions: Unexpected Behavior with Certain Ortho-Substituted Electrophiles

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Received September 5, 1995[⊗]

A method has been developed by alkylation of chiral lithioformamidines to construct protoberberine alkaloids with a C(9) and C(10) D-ring substitution pattern. This ring pattern was established using an ortho-substituted hydroxymethylbenzene electrophile protected as a silyl ether to ultimately provide (−)-tetrahydropalmatine in 88% ee. Additionally, we have discovered limitations with ortho-substituted electrophiles in the asymmetric formamidine alkylation. These electrophiles have the potential to disrupt the lithium formamidine chelate and cause the selectivity in the alkylation to be uncharacteristically low. The total synthesis of (±)-canadine and (−)-tetrahydropalmatine along with the limitations to the formamidine alkylation technology are delineated herein.

Introduction

Protoberberines are a large class of natural products typically characterized by a tetracyclic ring skeleton with an isoquinoline core.[1] These molecules display a wide range of substitution patterns surrounding the ring skeleton particularly in the A- and D-rings. Additionally, a stereogenic carbon atom is sometimes present at C(14). Considerable efforts have been expended in the study of these molecules for both their synthetic[2] and their biological[3] significance. The biological activity that these molecules display varies widely and includes anti-inflammatory, antimicrobial, and antileukemic, as well as antitumor, properties. We have been interested in the construction of stereogenic carbon centers similar to that found in the protoberberines and have been able to accomplish this by utilizing α-stabilized carbanions activated by chiral formamidines.[4] Efforts directed toward the asymmetric synthesis of isoquinoline alkaloids have resulted in numerous natural products[4,5] as well as serving in the exploration of the mechanistic aspects[6] of such alkylations. The present work was initiated in an attempt to uncover a rapid entry into the protoberberine ring system in chiral, nonracemic form.

The goals for this project were 3-fold. First, the synthesis of (−)-canadine[1] (**1**) was desired to confirm the reported absolute configuration at C(14).[7] Second, a solution to the C(9) and C(10) D-ring substitution pattern[8] in canadine and (−)-tetrahydropalmatine (**2**), with the formamidine methodology, had to be devised. Lastly, because of the D-ring substitution, ortho-substituted electrophiles were needed in the formamidine alkylation. As a result of the latter requirement, we encountered some interesting and unexpected results.

The required bond disconnection (Figure 1) for these protoberberine alkaloids (e.g. canadine) was made between N(7) and C(8) to provide the ring-opened 1-benzylisoquinoline **3**. Further cleavage of the C(13) and C(14) bond gives two fragments: an ortho-substituted electrophile **7** and the chiral formamidine (**5** or **6**) needed in the asymmetric alkylation. The utilization of the chiral formamidine technology, however, forces the synthetic sequence to proceed through **8** (Figure 2). Formation of the berberine bridge by the Pictet-Spengler[9] process or related processes (Y = H) will not give the desired methoxy pattern in the D-ring (**11**) but, instead, would produce the undesired C(10) and C(11) ring substitution (**9**).[10] Thus, the success of this project hinged on the placement of an ortho substituent on the benzyl moiety (Y = CH_2OTBS or CO_2Et) in **8** such that the ring closure would favor the D-ring substitution present in canadine and tetrahydropalmatine. During the course

[⊗] Abstract published in *Advance ACS Abstracts,* January 1, 1996.

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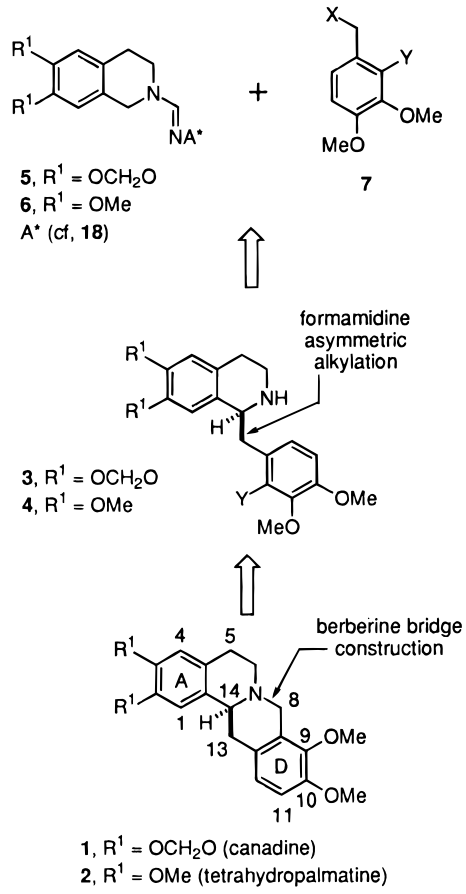


Figure 1.

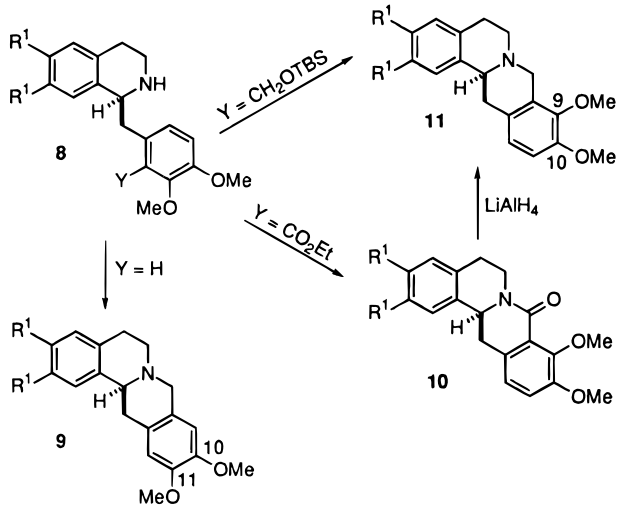


Figure 2.

of these studies, certain unexpected problems surfaced utilizing ortho-substituted benzyl halides in the asymmetric alkylation leading to **8**.

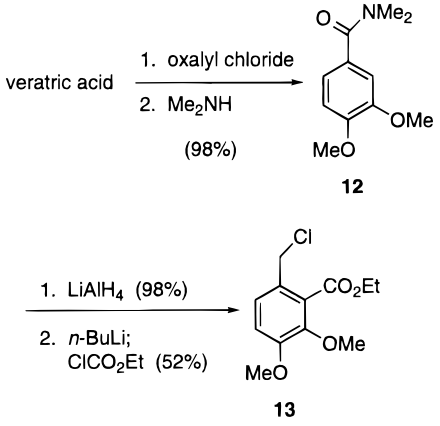
Results and Discussion

The placement of a carboethoxy substituent in the ortho position of the requisite benzyl derivative **13** was envisioned to provide the D-ring substitution pattern.[11] This sequence was expected to furnish lactam **10** followed by reduction to give the desired natural products (e.g. **11**). Numerous biological studies of lactams such as **10** have revealed considerable antitumor and anticancer activity,[12] and therefore we perceived this route to be a viable solution to the canadine or tetrahydropalmatine synthesis.

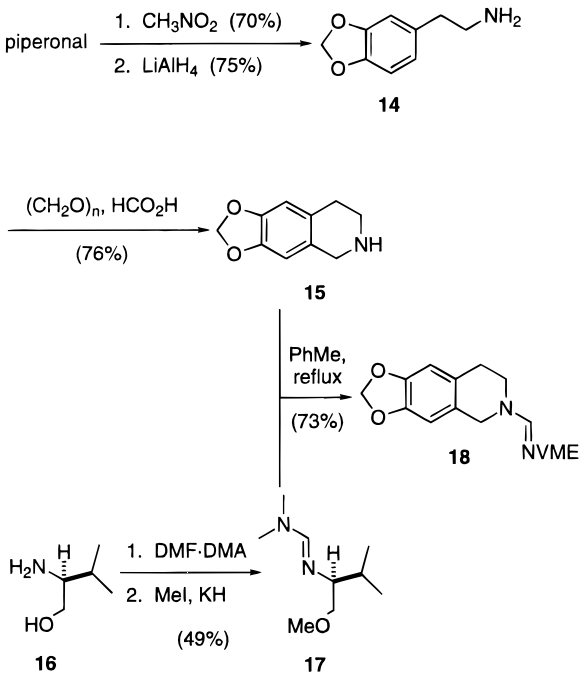
Acquisition of the required carboethoxy electrophile **13**[13] is outlined in Scheme 1 and proceeded without event. The metalation step[14] followed by addition of ethyl chloroformate gave **13** in moderate yield.

Formation of the requisite chiral formamidine **18** began by treatment of piperonal (Scheme 2) with nitromethane to afford[15] the intermediate β-nitrostyrene, which was reduced with lithium aluminum hydride[16] to the phenethylamine **14**. A modified Pictet-Spengler step[17] using formic acid and paraformaldehyde yielded

Scheme 1



Scheme 2



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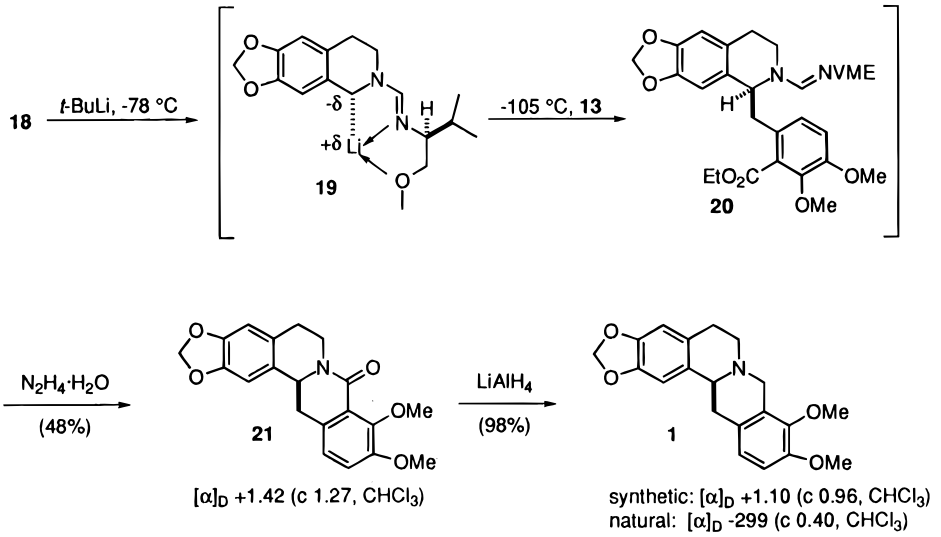
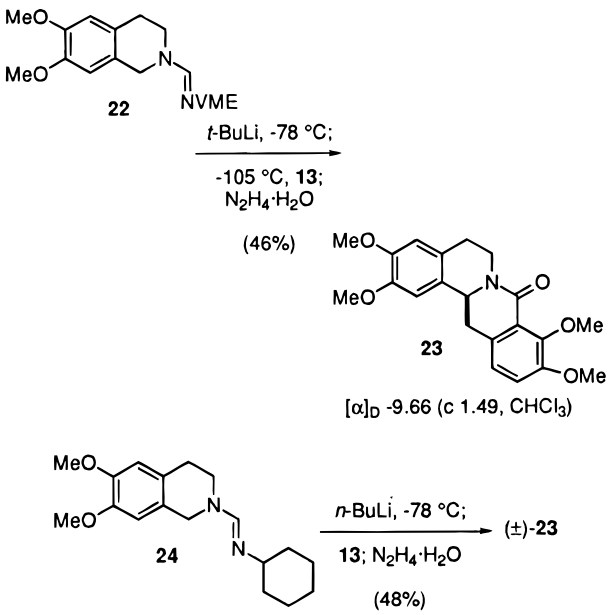
Scheme 3



the desired tetrahydroisoquinoline **15**. The chiral formamidine **18** was constructed utilizing the previously reported[18] exchange formamidine protocol with **17**. Lithiation (Scheme 3) of **18** was effected with *t*-BuLi at −78 °C, producing the characteristic deep red anion. The solution was then cooled to −105 °C and treated with electrophile **13**, furnishing **20**. The formamidine in **20** was directly removed with hydrazine hydrate[6] which, under the reaction conditions, resulted in spontaneous ring closure to 8-oxocanadine (**21**) in 48% overall yield from **18**. Spectroscopic comparison of this material with published data[19] was satisfactory, but the specific rotation was found to be quite low. To confirm the low optical purity, the lactam was reduced using known procedures,[20] affording canadine (**1**) in 98% yield. Again, the spectroscopic comparison with published data was satisfactory, but both the specific rotation and the melting point suggested that the compound was nearly racemic. These results were surprising since such low enantioselectivity had never been observed in alkylations of chiral formamidines.[21] An inquiry into the source of this low selectivity seemed to be in order; however, we felt that a variation in synthetic targets was also necessary. This was due to the fact that the methylenedioxyisoquinoline **15** required several steps to reach, while the 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline was commercially available. The final result of using the latter isoquinoline would be the synthesis of the natural product (−)-tetrahydropalmatine (**2**).[22] To confirm the previously observed poor enantioselectivity with lactam **21**, the alkylation of **22** was carried out under the previously described conditions. 8-Oxotetrahydropalmatine (**23**)[19] was isolated in 46% yield, but once again the product was virtually racemic. In addition to assessing the enantiomeric purity by specific rotation, lactam **23** was also examined by chiral HPLC and compared to the racemic material (±)-**23** obtained from the achiral *N*-cyclohexylformamidine (**24**). These results clearly showed that the material (**23**) obtained from **22** was nearly racemic and raised questions as to possible basis for the racemization. The lithium anion **19**, with its chelation character, could be disrupted by competitive chelation by the ortho carboethoxy group, thus affecting both the topology and steric bulk of the anion. On the other hand, racemization could have occurred on the lactam **21** under the reaction conditions leading to its formation.



In order to determine the source of the observed poor selectivity, the alkylation of **22** had to be performed without interference from the lactam **23**. In this way, the stereochemical efficiency of the alkylation alone could be examined. Thus, alkylation (Scheme 4) of **22** was carried out as before; however, the formamidine was removed, instead, with $LiAlH_4$ to provide the amino alcohol **25**. These conditions precluded the lactam ring closure to **23**. Ring closure was then effected with *N*-bromosuccinimide (NBS) and methyl sulfide (DMS) to give the desired natural product, tetrahydropalmatine (**2**), in 85% yield, thus avoiding the possibility of racemization of **23**. The specific rotation of **2** and comparison to material obtained from natural sources revealed the

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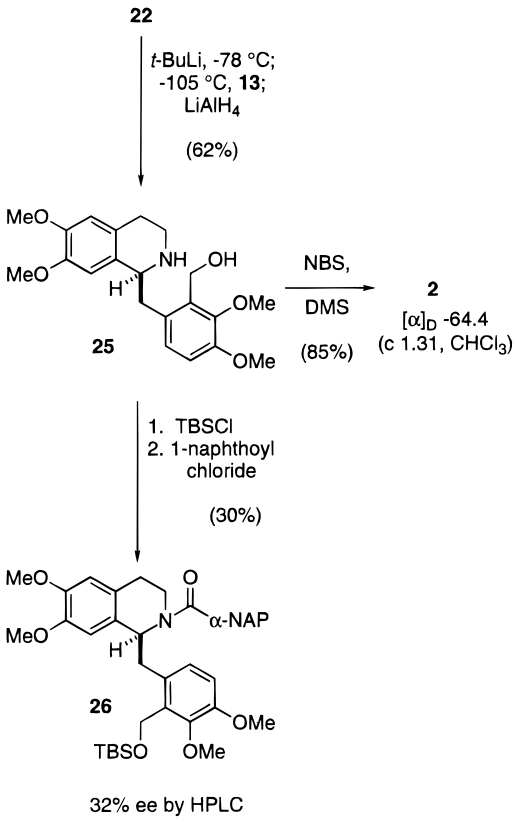
(21) The enantioselectivity in over 30 alkylations[4] has, without exception, exceeded 95% ee. However, in an early experiment (M. Bös in this laboratory), it was noted that a benzyl chloride containing an *o*-carboethoxy substituent gave nearly racemic material when alkylating a chiral formamidine such as **18** (unpublished result, 1984).
(22) Bartley, J. P.; Baker, L. T.; Carvalho, C. F. *Phytochemistry* **1994**, *36*, 1327.

Scheme 4



product to have an optical purity of 24%. Because this material was not completely racemic, further proof of enantiomeric purity was needed. Formation of the amino alcohol **25**, as before, followed by conversion to α-naphthoylamide **26** and examination by chiral HPLC, showed the ratio of enantiomers to be 66:34 (32% ee), in rough agreement with the 24% *via* optical rotation. While this seems to imply that the selectivity in the alkylation step of **22** has been lowered significantly, it has not been completely reduced to that of the racemic amide **23**. Other factors must, therefore, also be at work to reduce the enantiomeric purity, either prior to or subsequent to the lactam formation (**22** to **23**).

Three plausible mechanisms (Figure 3) may be considered for the observed racemization at the benzylic carbon C(14) in **23**. In mechanism A,[23] the proton at C(13) could be removed, causing the C(14) and N(7) bond to be cleaved, thereby destroying the stereogenic center and yielding racemic material upon nonstereoselective reclosure of the C-ring. In B, there could be a cascade of electrons previously seen,[24] initiated from the methoxy substituent to the protonated carbonyl. This would, once again, cause the bond rupture between C(14) and N(7) and lead to nonstereoselective ring closure. Lastly, in C the formation of an iminium ion under the acidic conditions could trigger an electrocylic ring opening[25] to form the open C-ring compound, thus providing racemic material upon reclosure.

Mechanism A could be discarded or verified by resubjecting lactam **23** to the previously employed conditions to remove the formamidine but replacing the protonated materials by their deuterated isotopes. Deuterium should

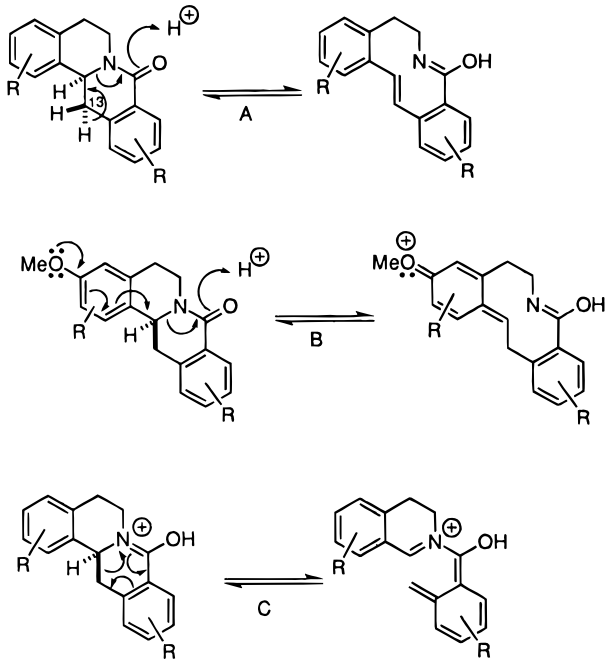
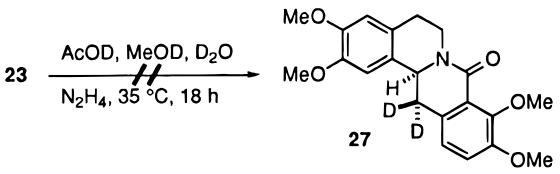


Figure 3. Possible routes to racemization of **23**.

then be observed at C(13) in lactam **23**. In fact, when **23** was treated with acetic acid-d_1, methanol-d_1, D_2O, and hydrazine (35 °C, 18 h), quantitative recovery of the lactam was obtained with no detectable deuterium incorporation. Thus, path A can be ruled out as a mode of racemization, leaving the remaining two mechanisms (B and C), which will be more difficult to prove, or disprove.



It was still important, however, to establish that partial racemization occurred during or after the lactam formation to **23**. This dictated the need for pure chiral, nonracemic lactam **23**. The racemic lactam was cleanly separated on a chiral semipreparative column[26] to give quantitative recovery of materials each possessing an enantiomeric ratio >98:2. Studies were initiated in an attempt to epimerize the C(14) stereogenic center of the (−)-lactam enantiomer (Table 1). Surprisingly, no significant levels of racemization were observed. Even under conditions that are known[27] to form iminium ions (entries 6, 7, and 8), we were unable to effect the desired epimerization. *These results strongly suggest that once the lactam is formed, the C(14) center is completely stable to racemization under acidic conditions.* This forces the conclusion that the destruction of the C(14) center is taking place prior to lactam formation. Investigations are continuing to provide further insight into the major cause of the racemization of **22** → **23**.

While the answer to the racemization step remains incomplete, the focus was to obtain (−)-tetrahydropal-

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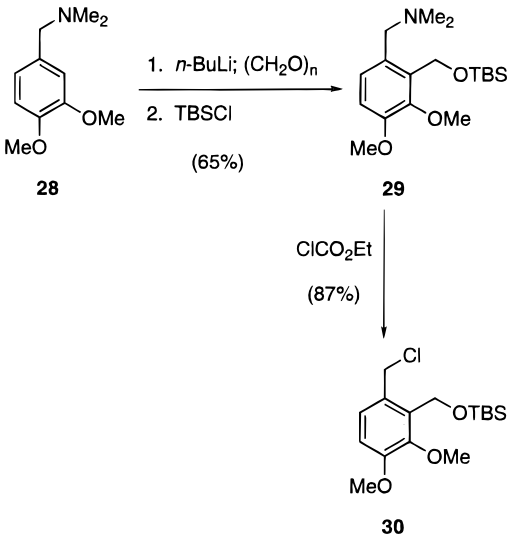
Table 1. Attempts to Racemize (−)-23

entry	acid conditions	solvent	T (°C)	t (h)	enantiomeric ratio
1	AcOH	95% EtOH	23	12	>98:2
2	AcOH	95% EtOH	23	290	>98:2
3	AcOH, N_2H_4	95% EtOH	23	12	>98:2
4	SiO_2	EtOAc	23	12	>98:2
5	10% HCl	THF	23	12	>98:2
6	TMSOTf	CH_2Cl_2	−10−23	14	>98:2
7	Et_3OBF_4[a]	CH_2Cl_2	23	5	>98:2
8	Et_3OBF_4[a]	CH_2Cl_2	40	5	>90:10[b]

[a] 2M in CH_2Cl_2. [b] Accompanied by decomposition products which obscured measurement.

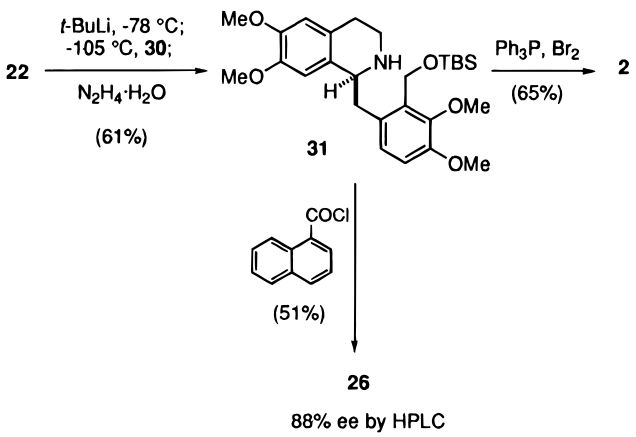
Scheme 5



matine (**2**) in suitable optically pure form and to establish methodology for the C(9) and C(10) D-ring substitution. Electrophile **30** was chosen (Scheme 5) as a possible solution to the present substitution problem. A few comments concerning the choice of this particular benzyl chloride are in order. First, the ortho substituent is flexible enough (methylene linkage) to swing out of the way during the alkylation, thus leaving the important formamidine chelate intact.[6b] Second, the hydroxyl group is masked as a bulky silyl ether to minimize the potential of the oxygen lone pairs for chelation.[28] Finally, the silyl group can be removed and the berberine bridge formed in a single operation.[29]

Benzylamine **28** was subjected to directed lithiation conditions, and the resulting anion was treated with paraformaldehyde.[30] The resulting primary alcohol was then protected[31] to give silyl ether **29** in 65% overall yield from **28**. Deamination with ethyl chloroformate furnished the benzyl chloride **30** in 87% yield. Alkylation of the lithium anion (Scheme 6) derived from **22** and subsequent removal of the formamidine resulted in the isolation of the protected amino alcohol **31** in 61% yield. The enantiomeric ratio was found to be 94:6 (88% ee) by chiral HPLC using the α-naphthoylamide **26**. Final closure of the berberine bridge was accomplished with triphenylphosphine and bromine to give (−)-tetrahydropalmatine **2** in 65% yield. Comparison of the specific rotation showed the sign and magnitude to be the same

Scheme 6



as in the natural material.[22] The dramatic increase in enantiomer ratios (94:6 *vs* 62:38) using the *tert*-butyl dimethylsilyl ether in place of the carboethoxy group augurs well for the importance of nonchelating groups adjacent to the electrophilic site. Nevertheless, the less than perfect enantioselective product indicates that even a bulky group cannot completely retard the effect of the oxygen lone pairs in chelation to the lithium ion in **19**.

In summary, the total asymmetric synthesis of (−)-tetrahydropalmatine has been accomplished utilizing ortho-substituted electrophiles with a 94:6 (88% ee) mixture of enantiomers. The ability of certain ortho-substituted electrophiles to disrupt the lithium chelate during the alkylation has been uncovered. Additionally, it has been proposed that the 8-oxoprotoberberines (e.g. **21** and **23**) racemize during the course of their formation after removal of the formamidine. Investigations into a possible mechanism of racemization and further studies with ortho-substituted electrophiles are currently underway.

Experimental Section

General Information. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA. All moisture-sensitive reactions were performed in flame-dried or oven-dried glassware under a positive pressure of argon. Argon for inert atmosphere reactions was passed through a heated (200−220 °C), activated oxygen trap (BASF copper-based catalyst, Chemical Dynamics Corporation, Plainfield, NJ) and a tube of Drierite (W. A. Hammond Drierite Co., Xenia, OH). Alkyllithiums were purchased from Aldrich Chemical Company (Milwaukee, WI) and titrated in Et_2O with 2,5-dimethoxybenzyl alcohol.[32] Flash chromatography was performed as described by Still *et al.*[33] on Davison Chemical (Grace Division, Baltimore, MD) Al_2O_3/SiO_2 mixture grade 135X. Chiral HPLC analyses were carried out using a chiracel OD column (J. T. Baker, Inc.) at flow rates and solvent mixtures as indicated.

3,4-Dimethoxy-*N*,*N*-dimethylbenzamide (12). To a slurry of veratric acid (5.06 g, 27.8 mmol) in CH_2Cl_2 (70.0 mL) at rt was added DMF (10 drops) followed by oxalyl chloride (7.30 mL, 10.6 g, 83.7 mmol). After 3 h, the solvent and excess oxalyl chloride were removed *in vacuo*, and the residue was taken up in CH_2Cl_2 (90.0 mL). To this solution was then added a mixture of dimethylamine hydrochloride (13.43 g, 164.7 mmol) and 2 M NaOH (250 mL) dropwise over 15 min; stirring was continued for 12 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 70 mL). The organic layers were combined, dried (Na_2SO_4), and concen-

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trated *in vacuo* to provide 5.71 g (98%) of amide **12**: white solid; mp 99−101 °C; R_f 0.30 (EtOAc). ^{1}H NMR (300 MHz, C_6D_6): δ 7.08 (d, 1 H, J = 1.8 Hz), 6.99 (dd, 1 H, J = 8.2, 1.8 Hz), 6.49 (m, 1 H), 3.35 (s, 3 H), 3.37 (s, 3 H), 2.70 (br s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.25 (s), 149.93 (s), 148.63 (s), 128.46 (s), 120.03 (d), 110.71 (d), 110.21 (d), 55.79 (q), 39.57 (q), 35.36 (q). IR (thin film): 3000, 2936, 1629 cm^{-1}. Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.13; H, 7.24. Found: C, 63.08; H, 7.33.

3,4-Dimethoxy-*N*,*N*-dimethylbenzenemethanamine (28). To a slurry of $LiAlH_4$ (95%, 1.46 g, 36.6 mmol) in THF (25.0 mL) at rt was added amide **12** (3.04 g, 14.5 mmol) as a solution in THF (50.0 mL), and the reaction mixture was heated to reflux for 4 h. The gray slurry was cooled to rt, 100 mL of Et_2O added, and the mixture slowly quenched with Na_2SO_4·$10H_2O$ (15 g). After 0.5 h, the white slurry was filtered through a 2 in. plug of Celite and the cake washed with several portions of EtOAc. The solvent was removed *in vacuo* and the residue purified by bulb to bulb distillation to give 2.78 g (98%) of amine **28**: colorless oil; bp 113 °C (3 mmHg);[13] R_f 0.13 (EtOAc). ^{1}H NMR (300 MHz, C_6D_6): δ 7.00 (d, 1 H, J = 1.8 Hz), 6.89 (dd, 1 H, J = 8.1, 1.8 Hz), 6.64 (d, 1 H, J = 8.1 Hz), 3.46 (s, 3 H), 3.44 (s, 3 H), 3.31 (s, 2 H), 2.16 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.80 (s), 147.98 (s), 131.52 (s), 121.09 (d), 111.92 (d), 110.61 (d), 64.14 (t), 55.76 (q), 45.23 (q).

Ethyl 6-(chloromethyl)-2,3-dimethoxybenzoate (13). To a solution of amine **28** (2.78 g, 14.2 mmol) in THF (35.0 mL) at 0 °C was added *n*-BuLi (2.18 M in hexanes, 7.40 mL, 16.1 mmol), and stirring was continued for 1 h. The mixture was then cooled to −78 °C, ethyl chloroformate (3.00 mL, 3.41 g, 31.4 mmol) was added dropwise, and stirring was continued for 10 min. The brown solution was warmed to rt and stirred for an additional 12 h. The solvent was removed *in vacuo* and the residue transferred to a separatory funnel with water (50 mL) and CH_2Cl_2 (150 mL). The layers were partitioned, and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by bulb to bulb distillation to afford 1.91 g (52%) of desired benzyl chloride **13**: light yellow oil; R_f 0.46 (1:1 EtOAc:hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.09 (d, 1 H, J = 8.5 Hz), 6.89 (d, 1 H, J = 8.6 Hz), 4.59 (s, 2 H), 4.42 (q, 2 H, J = 7.2 Hz), 3.86 (s, 3 H), 3.85 (s, 3 H), 1.39 (t, 3 H, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.63 (s), 153.05 (s), 146.67 (s), 129.03 (s), 127.29 (s), 125.78 (d), 113.26 (d), 61.55 (t), 61.49 (q), 55.88 (q), 43.56 (t), 14.17 (q). IR (thin film): 2980, 2941, 2906, 2840, 1732 cm^{-1}.

5,6,7,8-Tetrahydro-1,3-dioxolo[4,5-*g*]isoquinoline (15). To a solution of **14**[15] (2.30 g, 13.9 mmol) in formic acid (14.0 mL) at 50 °C was added paraformaldehyde (419 mg, 13.6 mmol). After 30 h, the reaction was cooled to rt, the solvent removed *in vacuo*, and the residue transferred to a separatory funnel with CH_2Cl_2 (150 mL). The organic phase was washed with 1 M NaOH (2 × 50 mL), and the resulting aqueous layers were back extracted with CH_2Cl_2 (2 × 50 mL). The layers were combined, the solvent was removed *in vacuo*, and the residue was taken up in 10% HCl and washed with EtOAc. The aqueous layer was made basic with 1 M NaOH and extracted with CH_2Cl_2 (5 × 100 mL), and the organic layers were combined, dried (Na_2SO_4), and concentrated *in vacuo* to give 1.87 g (76%) of the desired tetrahydroisoquinoline **15**: white solid; mp 78−80 °C; R_f 0.16 (4:2:2:1 CH_2Cl_2:EtOAc:hexanes:Et_3N). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.52 (s, 1 H), 6.44 (s, 1 H), 5.85 (s, 2 H), 3.87 (s, 2 H), 3.05 (app t, 2 H, J = 5.9 Hz), 2.66 (app t, 2 H, J = 5.4 Hz), 1.98 (br s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.77 (s), 145.61 (s), 128.71 (s), 127.53 (s), 108.93 (d), 106.09 (d), 100.47 (t), 48.32 (t), 43.80 (t), 29.18 (t). IR (CCl_4): 3321, 3039, 3012 cm^{-1}. LRMS (GC−MS) for $C_{10}H_{11}NO_2$ (M^+): Calcd 177.22, found 177.05.

(*S*)-N′-[1-(Methoxymethyl)-2-methylpropyl]-*N*,*N*-dimethylmethanimidamide (17). To a solution of (*S*)-valinol (5.10 g, 49.4 mmol) in benzene (5.0 mL) at rt was added *N*,*N*-dimethylformamide dimethylacetal (6.70 mL, 6.01 g, 50.4 mmol). After 12 h, the volatile materials were removed *in vacuo*, and the residue was used in the next reaction without further purification. To a slurry of KH (35%, 5.70 g, 49.7 mmol) and MeI (3.50 mL, 7.98 g, 56.2 mmol) in THF (25.0 mL) at 0 °C was added the formamidine as a solution in THF (10.0 mL with 2 × 2 mL rinses). After 0.5 h at rt, the reaction was quenched with Na_2SO_4·$10H_2O$, $MgSO_4$ was added, and the slurry was filtered through a 2 in. plug of Celite. The filtrate was concentrated and the residue purified by bulb to bulb distillation (100 °C oven temperature at 0.5 mmHg) to afford 4.15 g (48%) of exchange formamidine **17**: colorless oil; R_f 0.26 (7:2:1 EtOAc:hexanes:Et_3N); $[\alpha]_D^{23}$ −96.5 (*c* 1.03, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19 (s, 1 H), 3.47 (dd, 1 H, J = 9.4, 4.2 Hz), 3.30 (s, 3 H), 3.30 (m, 1 H), 2.79 (s, 6 H), 2.75 (m, 1 H), 1.68 (m, 1 H), 0.83 (d, 3 H, J = 3.9 Hz), 0.81 (d, 3 H, J = 3.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.24 (d), 76.35 (t), 71.00 (d), 58.82 (q), 37.04 (q), 30.75 (d), 19.99 (q), 18.50 (q). IR (thin film): 2956, 2925, 2873, 2822, 1655 cm^{-1}. LRMS (GC−MS): for $C_9H_{20}N_2O$ (M^+): calcd 172.31, found 172.10.

(*S*)-2-[[(1-(Methoxymethyl)-2-methylpropyl)imino]-methyl]-5,6,7,8-tetrahydro-1,3-dioxolo[4,5-*g*]isoquinoline (18). To a solution of exchange formamidine **17** (1.91 g, 11.1 mmol) and isoquinoline **15** (1.58 g, 8.92 mmol) in toluene (9.0 mL) at rt was added ammonium sulfate (135 mg, 1.02 mmol), and the reaction was heated to reflux for 18 h open to air. The brown mixture was cooled to rt and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (elution with 6:3:1 EtOAc:hexanes:Et_3N) to provide 1.99 g (73%) of the desired valine methyl ether formamidine **18**: light yellow oil; R_f 0.53 (6:3:1 EtOAc:hexanes:Et_3N); $[\alpha]_D^{25}$ −55.6 (*c* 1.21, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (s, 1 H), 6.57 (s, 1 H), 6.55 (s, 1 H), 5.87 (s, 2 H), 4.39 (ABq, 2 H, J_{AB} = 16.7 Hz, $\Delta\nu_{AB}$ = 23.3 Hz), 3.46 (m, 4 H), 3.31 (s, 3 H), 2.78 (m, 1 H), 2.73 (app t, 2 H, J = 5.7 Hz), 1.71 (m, 1 H), 0.85 (d, 3 H, J = 5.6 Hz), 0.82 (d, 3 H, J = 5.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.57 (d), 146.10 (s), 145.98 (s), 127.65 (s), 126.59 (s), 108.55 (d), 106.34 (d), 100.70 (t), 76.30 (t), 71.49 (d), 58.99 (q), 46.79 (t), 44.43 (t), 30.85 (d), 29.20 (t), 20.10 (q), 18.74 (q). IR (thin film): 2956, 2884, 1649 cm^{-1}. LRMS (GC−MS) for $C_{17}H_{24}N_2O_3$ (M^+): calcd 304.43, found 304.20.

(±)-5,6,13,13a-Tetrahydro-9,10-dimethoxy-2,3-methylenedioxy-8*H*-dibenzo[*a*,*g*]quinolizin-8-one (21). To a solution of **18** (211 mg, 0.69 mmol) in THF (15.0 mL) at −78 °C was added *n*-BuLi (2.18 M in hexanes, 0.50 mL, 1.1 mmol), and stirring was continued for 1 h. The dark red anion was then cooled to −105 °C, and the electrophile **13** (198 mg, 0.765 mmol) was added dropwise as a solution in THF (5.0 mL). The reaction temperature was raised to −90 °C, and the reaction mixture was stirred for 5 h. The light yellow mixture was quenched with MeOH (3 mL) and warmed to rt. The solvent was removed *in vacuo*, the residue was taken up in EtOH (8.0 mL), and cooled to 0 °C, and the solution was treated with N_2H_4·H_2O (2.0 mL) and AcOH (1.0 mL). The mixture was warmed to rt and stirred for 12 h. The volatiles were removed *in vacuo*, and the residue was purified by flash column chromatography (elution with 3:1 EtOAc:hexanes) to provide 108 mg (44%) of the desired amide **21**: white solid; mp 217−218 °C;[19] R_f 0.35 (3:1 EtOAc:hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.97 (d, 1 H, J = 8.3 Hz), 6.90 (d, 1 H, J = 8.2 Hz), 6.64 (s, 1 H), 6.63 (s, 1 H), 5.92 (s, 2 H), 4.96 (m, 1 H), 4.66 (dd, 1 H, J = 12.9, 2.8 Hz), 3.99 (s, 3 H), 3.86 (s, 3 H), 2.97 (dd, 1 H, J = 15.2, 3.1 Hz), 2.83 (m, 4 H).

(±)-5,8,13,13a-Tetrahydro-9,10-dimethoxy-6*H*-benzo[*g*]-1,3-benzodioxolo[5,6-*a*]quinolizine (Canadine (1)). To a solution of **21** (49 mg, 0.14 mmol) in THF (2.5 mL) at rt was added $LiAlH_4$ (95%, 30 mg, 0.75 mmol). The mixture was heated to reflux, stirred for 2 h, and then cooled to rt. The gray slurry was carefully quenched with Na_2SO_4·$10H_2O$ followed by addition of $MgSO_4$. The white slurry was filtered through a 1 in. plug of Celite and the filtrate concentrated *in vacuo*. The residue was purified by flash column chromatography (elution with 3:1 EtOAc:hexanes) to give 46 mg (98%) of canadine: light yellow solid; mp 172−173 °C;[20] R_f 0.45 (3:1 EtOAc:hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.84 (d, 1 H, J = 8.4 Hz), 6.76 (d, 1 H, J = 8.4 Hz), 6.71 (s, 1 H), 6.57 (s, 1 H), 5.89 (s, 2 H), 4.21 (d, 1 H, J = 15.5 Hz), 3.83 (s, 6 H), 3.51 (d, 1 H, J = 15.2 Hz), 3.51 (m, 1 H), 3.20 (dd, 1 H, J = 15.6, 3.6 Hz), 3.10 (m, 2 H), 2.79 (dd, 1 H, J = 15.6, 11.4 Hz), 2.60 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.24 (s), 146.10 (s), 145.87 (s), 145.01 (s), 130.80 (s), 128.60 (s), 127.77 (s), 127.64

(s), 123.87 (d), 110.90 (d), 108.38 (d), 105.50 (d), 100.73 (t), 60.15 (q), 59.61 (q), 55.84 (d), 53.92 (t), 51.38 (t), 36.43 (t), 29.56 (t).

(*S*)-1,2,3,4-Tetrahydro-6,7-dimethoxy-2-[[(1-(methoxymethyl)-2-methylpropyl)imino]methyl]isoquinoline (22). To a solution of formamidine, **17** (1.70 g, 9.87 mmol), and the 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (2.04 g, 10.6 mmol) in toluene (10.0 mL) at rt was added ammonium sulfate (68 mg, 0.51 mmol), and the slurry was heated to reflux open to air. After 24 h, the reaction was cooled to rt, the solvent removed *in vacuo*, and the residue purified by flash column chromatography (elution with 7:2:1 EtOAc:hexanes:Et_3N) followed by bulb to bulb distillation to give 2.59 g (82%) of the desired formamidine **22**: light yellow oil; R_f 0.43 (7:2:1 EtOAc:hexanes:Et_3N); $[\alpha]_D^{25}$ −7.48 (*c* 2.46, THF). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 (s, 1 H), 6.61 (s, 1 H), 6.57 (s, 1 H), 4.42 (ABq, 2 H, J_{AB} = 16.7 Hz, $\Delta\nu_{AB}$ = 22.9 Hz), 3.83 (s, 3 H), 3.81 (s, 3 H), 3.48 (m, 4 H), 3.31 (s, 3 H), 2.80 (m, 1 H), 2.75 (app t, 2 H, J = 5.8 Hz), 1.74 (m, 1 H), 0.85 (d, 3 H, J = 4.3 Hz), 0.83 (d, 3 H, J = 4.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.62 (d), 147.54 (s), 147.36 (s), 126.45 (s), 125.51 (s), 111.49 (d), 109.14 (d), 76.32 (t), 71.39 (d), 58.98 (q), 55.88 (q), 55.84 (q), 46.38 (t), 44.46 (t), 30.85 (d), 28.69 (t), 20.10 (q), 18.67 (q). IR (thin film): 3056, 2955, 2929, 2872, 2834, 1647 cm^{-1}. LRMS (GC−MS) for $C_{18}H_{28}N_2O_3$ (M^+): calcd 320.48, found 320.35.

N′-Cyclohexyl-*N*,*N*-dimethylmethanimidamide. To freshly distilled cyclohexylamine (22.23 g, 224.1 mmol) at rt was added *N*,*N*-dimethylformamide dimethylacetal (32.0 mL, 28.7 g, 241 mmol), and the mixture was then heated to 50 °C for 5 h, cooled to rt, and stirred an additional 12 h. The volatiles were removed *in vacuo*, and the oil was placed over high vacuum (0.1 mmHg). Material crystallizes upon standing to provide 31.92 g (92%) of the desired exchange formamidine: white solid; mp 38−40 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (s, 1 H), 2.80 (m, 1 H), 2.78 (s, 6 H), 1.66 (m, 5 H), 1.29 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.26 (d), 64.76 (d), 37.12 (q), 36.23 (t), 25.70 (t), 25.50 (t). IR (thin film): 2925, 2852, 2801, 1652 cm^{-1}. LRMS (GC−MS) for $C_9H_{18}N_2$ (M^+): calcd 154.29, found 154.20. Anal. Calcd for $C_9H_{18}N_2$: C, 70.06; H, 11.78. Found: C, 70.33; H, 11.59.

2-[(Cyclohexylimino)methyl]-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (24). To a slurry of 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (4.56 g, 23.6 mmol) and *N*,*N*-dimethyl-*N*′-cyclohexylformamidine (3.56 g, 23.1 mmol) in toluene (25.0 mL) at rt was added ammonium sulfate (625 mg, 4.73 mmol), and the mixture was heated to reflux open to air. After 12 h, the solvent was removed *in vacuo*, and the residue was purified by flash column chromatography (elution with 7:2:1 EtOAc:hexanes:Et_3N) followed by bulb to bulb distillation to provide 4.94 g (71%) of the desired formamidine **24**: colorless oil, solidifies on standing; mp 85−87 °C; R_f 0.45 (7:2:1 EtOAc:hexanes:Et_3N). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 (s, 1 H), 6.60 (s, 1 H), 6.57 (s, 1 H), 4.40 (s, 2 H), 3.83 (s, 3 H), 3.80 (s, 3 H), 3.45 (app t, 2 H, J = 5.8 Hz), 2.85 (m, 1 H), 2.76 (app t, 2 H, J = 5.7 Hz), 1.65 (m, 5 H), 1.32 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.46 (d), 147.54 (s), 147.40 (s), 126.35 (s), 125.37 (s), 111.47 (d), 109.15 (d), 65.02 (d), 55.85 (q), 55.82 (q), 46.33 (t), 44.53 (t), 36.09 (t), 28.65 (t), 25.66 (t), 25.41 (t). IR (thin film): 2994, 2924, 2850, 1645 cm^{-1}. LRMS (GC−MS) for $C_{18}H_{26}N_2O_2$ (M^+): calcd 302.46, found 302.20. Anal. Calcd for $C_{18}H_{26}N_2O_2$: C, 71.47; H, 8.68. Found: C, 71.20; H, 8.75.

(±)-5,6,13,13a-Tetrahydro-2,3,9,10-tetramethoxy-8*H*-dibenzo[*a*,*g*]quinolizin-8-one (8-Oxotetrahydropalmatine, 23). To a solution of **24** (512 mg, 1.69 mmol) in THF (40.0 mL) at −78 °C was added *t*-BuLi (2.2 M in pentane, 1.05 mL, 2.31 mmol). After 1 h, electrophile **13** (515 mg, 1.99 mmol) was added as a solution in THF (10.0 mL with 2 × 2.0 mL rinses). The orange solution was stirred for 1 h, whereupon the mixture became light yellow and was quenched with 2 mL of NH_4Cl (saturated). The cooling bath was removed, followed by addition of water and EtOAc. The layers were partioned, and the aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). The organic layers were combined, dried ($NaSO_4$), and concentrated *in vacuo*, and the residue was passed through a 1 in. plug of SiO_2 (7:2:1 EtOAc:hexanes:Et_3N). The formamidine was taken up in 95% EtOH (15.0 mL), cooled to 0 °C, and treated with AcOH (1.0 mL) and $N_2H_4{\cdot}H_2O$ (2.0 mL). The yellow solution was warmed to rt and stirred for 16 h. The solvent was then removed *in vacuo* and the residue partitioned between CH_2Cl_2 and $NaHCO_3$ (saturated). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo*, and the residue was purified by flash column chromatography (elution with 3:1 EtOAc:hexanes) to provide 299 mg (48%) of the desired amide **23**. light yellow solid;[19] mp 169−170 °C; R_f 0.25 (3:1 EtOAc:hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.98 (d, 1 H, J = 8.3 Hz), 6.93 (d, 1 H, J = 8.3 Hz), 6.66 (s, 1 H), 6.65 (s, 1 H), 5.04 (m, 1 H), 4.70 (dd, 1 H, J = 13.0, 3.0 Hz), 4.00 (s, 3 H), 3.87 (s, 9 H), 3.01 (dd, 1 H, J = 15.3, 3.2 Hz), 2.85 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.66 (s), 153.08 (s), 150.09 (s), 147.96 (s), 147.89 (s), 130.86 (s), 127.67 (s), 127.50 (s), 123.61 (s), 121.99 (d), 115.14 (d), 111.36 (d), 109.07 (d), 61.54 (q), 56.18 (q), 56.12 (q), 55.91 (q), 54.97 (d), 39.19 (t), 38.14 (t), 29.41 (t).

Chiral HPLC Analysis (Analytical): column, Chiracel OD chiral column, UV detector; solvent, 80:20 *n*-hexane:*i*-PrOH; flow rate, 2.50 mL/min; retention, 8.8 min for enantiomer 1, 16.2 min for enantiomer 2.

Chiral HPLC Analysis (Semipreparative): column, β-Gem I, REGIS Technology, UV detector; solvent, 34:33:33 *n*-hexane:*i*-PrOH:MeOH; flow rate, 5.00 mL/min; retention, 9.5 min for (−)-enantiomer, 11.9 min for (+)-enantiomer.

(*S*)-1,2,3,4-Tetrahydro-1-[2-(hydroxymethyl)-3,4-dimethoxybenzyl]-6,7-dimethoxyisoquinoline (25). Formamidine **22** (308 mg, 0.96 mmol) was weighed into a flame-dried flask and placed under high vacuum. The flask was gently warmed with a heat gun and argon introduced into the flask to complete one cycle. This cycle was carried out a total of five times to remove trace oxygen. The residue was taken up in THF (30.0 mL) and cooled to −78 °C. The solution was then treated with *t*-BuLi (2.2 M in pentane, 0.10 mL until yellow color was persistent and then an additional 0.40 mL added for a total of 0.50 mL, 1.10 mmol), and the red anion was stirred for 1 h. The mixture was then cooled further to −105 °C (±3 °C, 1:1 Et_2O:MeOH and N_2(l)) and benzyl chloride **13** (284 mg, 1.10 mmol) was added slowly as a solution in THF (8.0 mL) down the inside of the reaction flask. Upon addition, the mixture was maintained at −90 °C for 6 h, warmed to rt, and treated with $LiAlH_4$ (95%, 235 mg, 5.88 mmol), and the gray slurry was heated to reflux for 11 h. The reaction was slowly quenched with $Na_2SO_4{\cdot}10H_2O$, and $MgSO_4$ was added. The white slurry was filtered through a 1 in. plug of Celite, and the filtrate was concentrated *in vacuo*. TLC showed some formamidine remaining, and therefore the residue was taken up in 95% ethanol (4.0 mL), cooled to 0 °C, and treated with AcOH (1.0 mL) and $N_2H_4{\cdot}H_2O$ (0.50 mL). After 5 h at rt, the mixture was transferred to a separatory funnel with CH_2Cl_2 and $NaHCO_3$ (saturated). The layers were partitioned, and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash column chromatography (elution with 8:1:1 EtOAc:MeOH:Et_3N) to afford 223 mg (62%) of the desired amino alcohol **25**: light yellow solid; mp 135 °C dec; R_f 0.11 (7:2:1 EtOAc:hexanes:Et_3N). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.99 (d, 1 H, J = 8.4 Hz), 6.85 (d, 1 H, J = 8.4 Hz), 6.77 (s, 1 H), 6.57 (s, 1 H), 4.65 (ABq, 2 H, J_{AB} = 11.5 Hz, $\Delta\nu_{AB}$ = 107.2 Hz), 4.09 (dd, 1 H, J = 9.9, 3.3 Hz), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.85 (s, 6 H), 3.21 (dd, 1 H, J = 13.8, 3.8 Hz), 3.07−2.73 (m, 4 H), 2.56 (ddd, 1 H, J = 15.3, 4.5, 4.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.39 (s), 147.70 (s), 147.63 (s), 147.48 (s), 135.37 (s), 131.20 (s), 129.77 (s), 125.19 (d), 112.06 (d), 111.64 (d), 109.41 (d), 61.81 (q), 56.48 (d), 56.12 (q), 55.85 (2q), 55.20 (t), 40.81 (t), 40.11 (t), 29.12 (t). IR (thin film): 3307, 3167 cm^{-1}. Anal. Calcd for $C_{21}H_{27}NO_5$: C, 67.53; H, 7.30. Found: C, 67.38; H, 7.34.

3,4-Dimethoxy-*N*,*N*-dimethyl-2-(((1,1-dimethylethyl)-dimethylsilyl)oxy)methylbenzylamine (29). To a solution of **28** (3.80 g, 19.5 mmol) in THF (20.0 mL) at −78 °C was added *n*-BuLi (2.2 M in hexanes, 13.0 mL, 28.6 mmol). The light yellow mixture was warmed to 0 °C, stirred for 4 h, and then recooled to −78 °C. The anion was added *via* cannula to a slurry of paraformaldehyde (586 mg, 19.5 mmol) in THF (5.0 mL) at −78 °C. Following addition of the anion, the yellow

mixture was warmed to rt and stirred for an additional 4 h. The reaction mixture was quenched with water, transferred to a separatory funnel, and extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by filtration through a 2 in. plug of silica gel (elution with 7:2:1 EtOAc:hexanes:Et_3N) followed by bulb to bulb distillation to provide the desired alcohol as a colorless oil.[30] ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.90 (d, 1 H, J = 8.2 Hz), 6.74 (d, 1 H, J = 8.2 Hz), 4.68 (s, 2 H), 3.84 (s, 6 H), 3.43 (s, 2 H), 2.20 (s, 6 H), hydroxyl resonance obscured. ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.70, 147.46, 135.88, 130.68, 126.24, 110.30, 63.00, 61.85, 56.60, 55.73, 44.43. IR (thin film): 3391, 3193, 2945, 2825 cm^{-1}. LRMS (GC−MS) for $C_{12}H_{19}NO_3$ (M^+): calcd 225.32, found 225.10.

To a solution of the newly formed alcohol in CH_2Cl_2 (45.0 mL) was added at rt diisopropylamine (3.65 mL, 2.64 g, 26.0 mmol) followed by TBSCl (3.15 g, 20.9 mmol). After 1 h, the mixture was transferred to a separatory funnel, and the organic phase was washed with $NaHCO_3$ (saturated), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash column chromatography (elution with 7:2:1 EtOAc:hexanes:Et_3N) to provide 4.29 g (65%) of silyl ether **29**: light yellow oil; R_f 0.59 (7:2:1 EtOAc:hexanes:Et_3N). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.00 (d, 1 H, J = 8.4 Hz), 6.79 (d, 1 H, J = 8.4 Hz), 4.83 (s, 2 H), 3.83 (s, 3 H), 3.81 (s, 3 H), 3.43 (s, 2 H), 2.20 (s, 6 H), 0.89 (s, 9 H), 0.08 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.68 (s), 147.71 (s), 133.51 (s), 131.34 (s), 125.75 (d), 111.02 (d), 61.56 (q), 60.91 (t), 56.05 (t), 55.63 (q), 45.55 (q), 25.98 (q), 18.38 (s), −5.33 (q).

3,4-Dimethoxy-2-((((1,1-dimethylethyl)dimethylsilyl)oxy)methyl)benzyl Chloride (30). To a slurry of **29** (1.54 g, 4.53 mmol) and K_2CO_3 (940 mg, 6.80 mmol) in THF (10.0 mL) at −78 °C was added ethyl chloroformate (0.65 mL, 738 mg, 6.80 mmol). The reaction mixture was warmed to rt and stirred for an additional 13 h. The resulting white slurry was quenched with water and extracted with EtOAc (3 × 50 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash column chromatography (elution with 4:1 hexanes:EtOAc) to give 1.30 g (87%) of the desired benzyl chloride **30**: colorless oil, solidifies on standing; mp 32−38 °C; R_f 0.66 (1:1 EtOAc:hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10 (d, 1 H, J = 8.4 Hz), 6.81 (d, 1 H, J = 8.4 Hz), 4.86 (s, 2 H), 4.75 (s, 2 H), 3.84 (s, 3 H), 3.80 (s, 3 H), 0.89 (s, 9 H), 0.10 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.94 (s), 147.42 (s), 133.29 (s), 129.99 (s), 126.28 (d), 111.37 (d), 61.56 (q), 56.12 (t), 55.67 (q), 44.05 (t), 25.88 (q), 18.27 (s), −5.44 (q). Anal. Calcd for $C_{16}H_{27}ClO_3Si$: C, 58.06; H, 8.24. Found: C, 58.28; H, 8.32.

1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[2-((((1,1-dimethylethyl)dimethylsilyl)oxy)methyl)-3,4-dimethoxybenzyl]-isoquinoline (31). Formamidine **22** (254 mg, 0.793 mmol) was weighed into a flame-dried flask and placed under high vacuum. The residue was then gently warmed with a heat gun and argon introduced to complete one cycle. This cycle (vacuum/argon purge) was repeated for a total of five times to remove any oxygen. The formamidine was taken up in THF (20.0 mL) and cooled to −78 °C, and *t*-BuLi (2.2 M in pentane, 70 μL until the yellow color was persistent and then an additional 450 μL, 1.14 mmol) was added dropwise. After 0.5 h, the deep red solution was cooled to −105 °C and the electrophile **30** (277 mg, 0.837 mmol) added slowly as a solution in THF (10.0 mL) down the inside of the reaction flask. After 30 min, the light yellow mixture was quenched with 2 mL of NH_4Cl (saturated), and the cooling bath was removed, followed by addition of water and EtOAc. The layers were partitioned, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was taken up in 95% ethanol (4.0 mL), cooled to 0 °C, and treated with AcOH (0.5 mL) followed by $N_2H_4 \cdot H_2O$ (1.0 mL). The yellow solution was warmed to rt, stirred 12 h, and then transferred to a separatory funnel with water and CH_2Cl_2. The layers were partitioned, and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash column chromatography (elution with 7:2:1 EtOAc:hexanes:Et_3N) to provide 238 mg (61%) of the desired amine **31**: white solid; mp 114−115 °C; R_f 0.30 (7:2:1 EtOAc:hexanes:Et_3N); $[\alpha]_D^{25}$ +30.8 (*c* 0.60, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.91 (d, 1 H, J = 8.4 Hz), 6.81 (d, 1 H, J = 8.4 Hz), 6.57 (s, 1 H), 6.52 (s, 1 H), 4.76 (ABq, 2 H, J_{AB} = 10.6 Hz, $\Delta\nu_{AB}$ = 34.1 Hz), 4.18 (m, 1 H), 3.84 (s, 6 H), 3.83 (s, 3 H), 3.73 (s, 3 H), 3.35 (dd, 1 H, J = 13.8, 4.8 Hz), 3.22 (m, 1 H), 2.89 (m, 2 H), 2.72 (m, 2 H), 1.71 (br s, 1 H), 0.86 (s, 9 H), 0.10 (s, 3 H), 0.07 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.21 (s), 147.90 (s), 147.23 (s), 146.69 (s), 133.09 (s), 131.68 (s), 130.91 (s), 127.06 (s), 126.26 (d), 111.63 (d), 111.60 (d), 109.57 (d), 61.46 (q), 56.64 (t), 56.07 (d), 55.76 (q), 55.68 (q), 40.40 (t), 39.24 (t), 29.48 (t), 25.96 (q), 18.29 (s), −5.24 (q), 5.32 (q). Anal. Calcd for $C_{27}H_{41}NO_5Si$: C, 66.48; H, 8.49. Found: C, 66.46; H, 8.40.

α-Naphthoylamide (26). To a solution of **31** (130 mg, 0.27 mmol) in CH_2Cl_2 (5.0 mL) at rt was added the acid chloride (50 μL, 63 mg, 0.33 mmol). After 30 min, the solvent was removed *in vacuo* and the residue purified by flash column chromatography (elution with 3:1 hexanes:EtOAc) to provide 88 mg (51%) of the amide: $[\alpha]_D^{25}$ +35.9 (*c* 2.06, $CHCl_3$). ^{1}H NMR analysis was complicated by rotamers; see Supporting Information for spectra at 23 and 55 °C. Chiral HPLC analysis was carried out on this material.

Chiral HPLC Analysis: column, Chiracel OD chiral column, UV detector; solvent, 80:20 *n*-hexane:*i*-PrOH; flow rate, 0.30 mL/min; retention, 30.6 min for minor enantiomer, 42.9 min for major enantiomer.

Data for Racemic Material: white solid; mp 92 °C dec; R_f 0.50 (4:1 EtOAc:hexanes). Anal. Calcd for $C_{38}H_{47}NO_6Si$: C, 71.09; H, 7.39. Found: C, 71.00; H, 7.38.

(*S*)-(−)-5,8,13,13a-Tetrahydro-2,3,9,10-tetramethoxy-6*H*-dibenzo[*a*,*g*]quinolizine (Tetrahydropalmatine (2)). To a solution of triphenylphosphine (264 mg, 1.01 mmol) in CH_2Cl_2 (12.0 mL) at −10 °C was added dropwise bromine (60 μL, 186 mg, 1.16 mmol). After 5 min, the silyl ether **31** (234 mg, 0.480 mmol) was added *via* cannula as a solution in CH_2Cl_2 (5.0 mL with 2 × 1.0 mL rinses). The light yellow solution was warmed to rt and stirred for an additional 14 h. The solvent was removed *in vacuo* and the residue purified by flash column chromatography (basic alumina, elution with 1:1 EtOAc:hexanes) to provide 112 mg (65%) of the desired natural product, (−)-tetrahydropalmatine (**2**). Synthetic material correlates with natural tetrahydropalmatine: light yellow solid; synthetic mp 143−144 °C (MeOH); natural[22] mp 141−142 °C (MeOH); R_f 0.52 (7:2:1 EtOAc:hexanes:Et_3N); R_f 0.50 (4:1 THF:hexanes); R_f 0.64 (4:4:1 CH_2Cl_2:Et_2O:Et_3N); synthetic $[\alpha]_D^{25}$ −230 (*c* 0.87, $CHCl_3$); natural $[\alpha]_D^{25}$ −269 (*c* 0.80, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.86 (d, 1 H, J = 8.4 Hz), 6.76 (d, 1 H, J = 8.4 Hz), 6.71 (s, 1 H), 6.60 (s, 1 H), 4.22 (app d, 1 H, J = 15.8 Hz), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.83 (s, 6 H), 3.52 (app d, 2 H, J = 15.1 Hz), 3.24 (dd, 1 H, J = 16.0, 3.6 Hz), 3.16 (m, 2 H), 2.80 (dd, 1 H, J = 15.9, 11.4 Hz), 2.62 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.21 (s), 147.39 (s), 147.35 (s), 144.99 (s), 129.64 (s), 128.65 (s), 127.68 (s), 126.73 (s), 123.81 (d), 111.24 (d), 110.83 (d), 108.48 (d), 60.11 (q), 59.27 (d), 56.00 (q), 55.78 (q), 53.96 (t), 51.47 (t), 36.31 (t), 29.07 (t).

Acknowledgment. We thank Professor F. R. Stermitz and J. J. Beck for an authentic sample of natural (−)-tetrahydropalmatine. Financial support for this study was provided by the National Science Foundation. A postdoctoral fellowship from the American Cancer Society (M.A.M.) is also gratefully acknowledged.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **2**, **12**, **13**, **15**, **17**, **18**, **21, 22**, **23**, **26**, **28**, **29**, **30**, and **31** and chiral HPLC data of **23** and **26** (36 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO951611Q