Stereospecific Cyclizations of Iminium Salts from α-Amino Acid Decarbonylation. Synthesis of 8- and 13-Methylberbines

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Berbines containing methyl substituents at C-8 and C-13 have been synthesized by stereospecific cyclizations of iminium salts generated by α-amino acid decarbonylation. (8*S*,13a*R*)-(+)-8-Methyl-2,3,10,11-tetramethoxyberbine [(+)-*O*-methylcorytenchirine (**5**)] was synthesized starting from dihydroxyphenyl-L-alanine (**7**) via a previously described stereoselective introduction of the 1-methyl substituent to give (1*S*,3*S*)-(−)-1,2,3,4-tetrahydro-6,7-dihydroxy-1-methyl-3-isoquinolinecarboxylic acid (**8**). This was efficiently converted to ethyl (1*S*,3*S*)-(−)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyl-3-isoquinolinecarboxylate (**10**) by esterification, N-formylation, methylation of the phenolic hydroxyls, and selective deformylation. Alkylation, hydrolysis, iminium salt formation, and cyclization then proceeded in high yield stereospecifically to give (+)-*O*-methylcorytenchirine (**5**). β-Methyl(3,4-dimethoxyphenyl)alanine was synthesized with the methyl substituent enantiomerically pure by resolving 3-(3,4-dimethoxyphenyl)butyric acid and then aminating via the malonate derivative **31** using chloramine. Hydrolysis and decarboxylation of the optically active aminomalonate proceeded with little stereoselectivity. The resulting β-methyl(3,4-dimethoxyphenyl)alanine (**19**) was then converted to 2-[2-(3,4-dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-4-methyl-3-isoquinolinecarboxylic acid (**23**), decarbonylated to the iminium salt **1**, and cyclized stereospecifically to give racemic *trans*-13-methyl-2,3,10-11-tetramethoxyberbine (**2**). Disproportionation was observed as a side reaction, and modified conditions are considered which decrease this disproportionation of the intermediate dihydroisoquinoline.

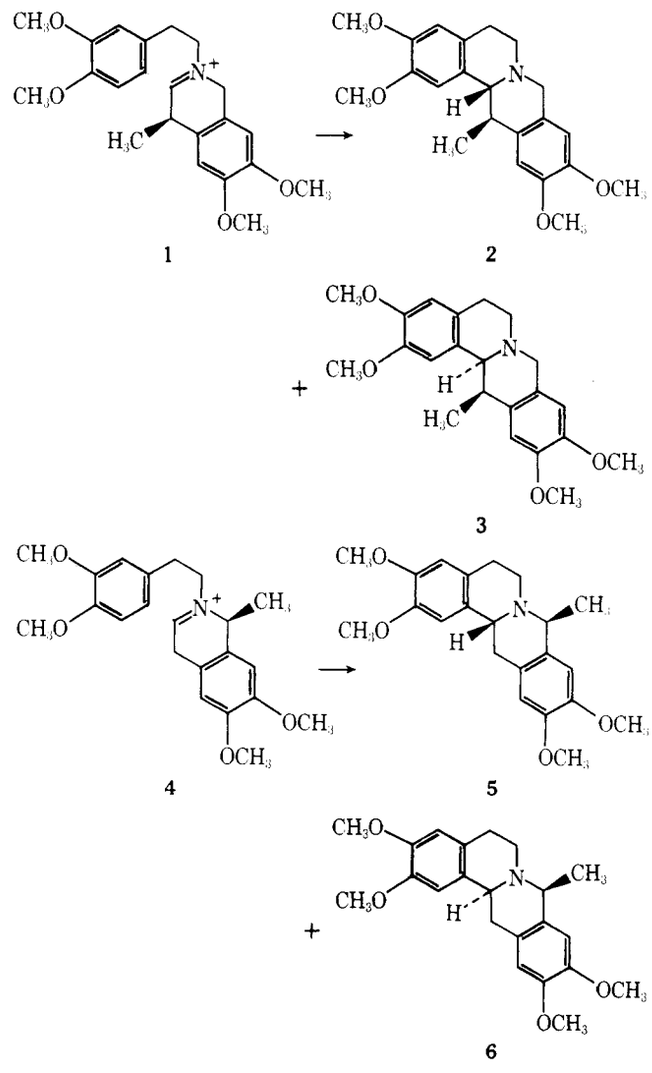
The decarbonylation of α-tertiary amino acids has been demonstrated to be an efficient method for regiospecifically generating iminium salts.[1] That the starting material, an α-amino acid, also may be asymmetric suggests two additional potential advantages. Although the α-carbon asymmetry is lost on iminium salt generation, the chirality of the amino acid may be used to induce asymmetry in earlier reactions introducing additional substituents. Secondly, enantiomerically pure products may be possible by prior resolution of the amino acid or amino acid precursors. To address these questions, we chose to investigate the synthesis of 8- and 13-methylberbines, applying the general method for synthesis of berbines described in our earlier work.[2] The synthesis of both classes of compounds presents a stereochemical question in the outcome of the cyclization step since diastereomers are possible (Scheme I).

8-Methylberbines. Obligatory to the synthesis of berbines by the general method we have developed is an intermediate 1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid. A substituent at C-8 of the subsequently formed berbine requires a corresponding C-1 substituent in the tetrahydroisoquinoline. Such a compound has been described[3] in the asymmetric synthesis of (1*S*,3*S*)-(−)-1,2,3,4-tetrahydro-6,7-dihydroxy-1-methyl-3-isoquinolinecarboxylic acid (**8**) from dihydroxyphenyl-L-alanine (**7**) (Scheme II). This reaction allows for the preparation of an 8-methylberbine enantiomerically pure at the 8 position. However, the phenolic secondary amine **8** must be N-alkylated and the phenolic hydroxyls converted to methyl ethers to realize the α-tertiary amino acid necessary for iminium salt generation.

The simplest route to the required dimethoxy tertiary amine would be to selectively methylate the phenols and then N-alkylate. However, treatment of ethyl ester **9** with diazomethane gave mostly the permethylated compound **11** with a small amount of the selectively alkylated compound **10**.[4] Applying a method which had previously[5] been selective for the methylation of phenols, the phenolic amine **8** was treated with *N,N'*-diisopropyl-*O*-methylisourea, but gave exclusively the permethylated compound **11** with partial racemization. This unexpected racemization foreshadowed difficulties in this seemingly simple conversion.

Another scheme was to protect the catechol portion of the molecule, alkylate the nitrogen, and then deprotect and methylate the phenols. Thus, **9** was treated with phenylboronic anhydride to form the cyclic borate ester **12**, which was N-alkylated to give **13**. The catechol was deprotected during

Scheme I. Iminium Salt Cyclization to Diastereomeric 8- and 13-Methyl-2,3,10,11-tetramethoxyberbines



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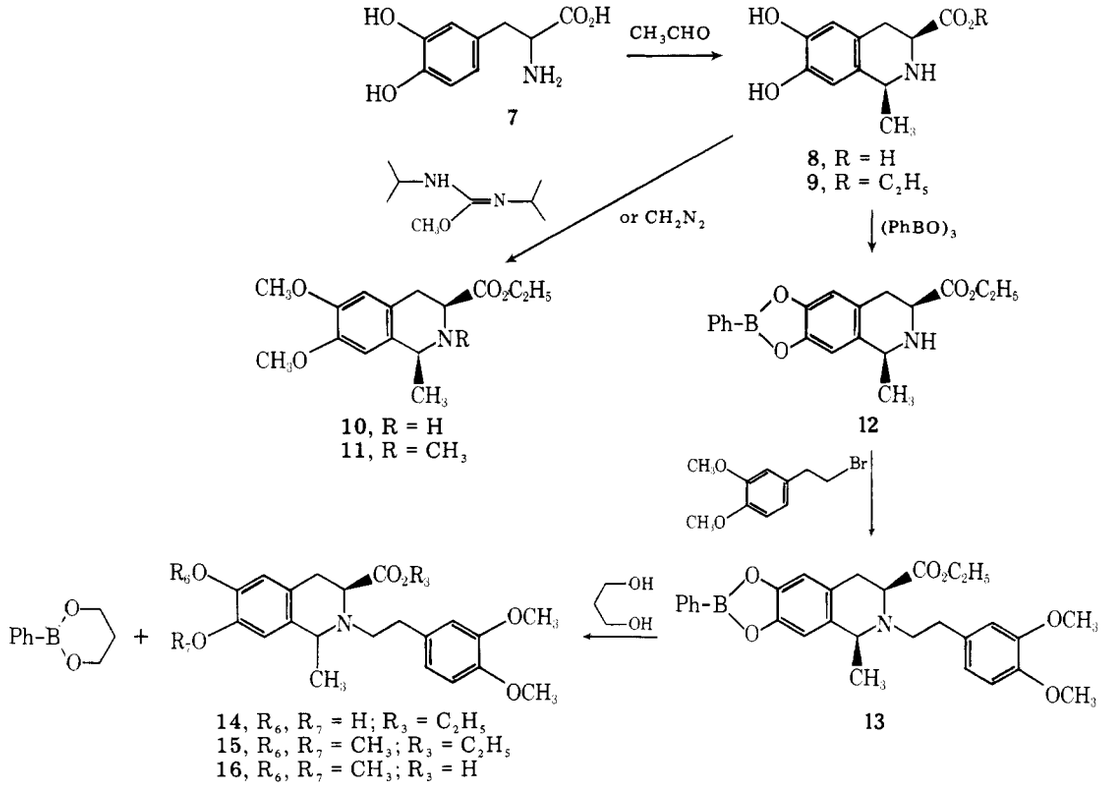
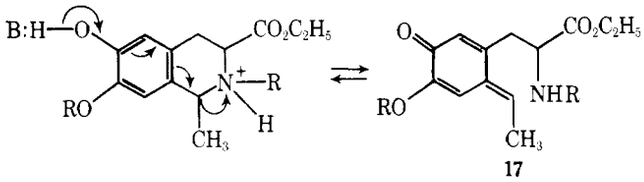
Scheme II. Synthesis of 6,7-Dimethoxy-1-methyltetrahydro-3-isoquinolinecarboxylates with Partial Racemization



isolation by exchange with 1,3-propanediol, and the phenolic tertiary amine was methylated with *N,N'*-diisopropyl-*O*-methylisourea to give **15** in 57% overall yield (Scheme II). This ester was hydrolyzed, the acid **16** was decarbonylated, and the iminium salt **4** was cyclized to give the berbine. Ring closure took place exclusively to form isomer **5** with the 8-methyl and 13a-hydrogen cis as shown in Scheme I. To our surprise, however, the optical rotation of the product indicated that only 16% of the optical activity had been retained through this series of reactions.

In considering where this substantial racemization might have occurred, we focused on the conversion of the catechol **14** to the veratrole **15.** Either the catechol or its monomethyl ether, with a free hydroxyl at C-6, could lead to racemization at C-1 of the tetrahydroisoquinoline through methide inter-

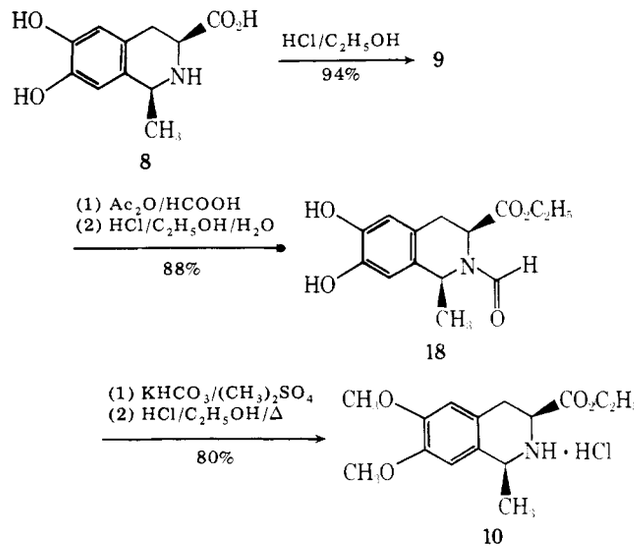


mediate **17.** Racemizations of various tetrahydroisoquinolines analogous to ours have been observed.[6]

Thus, it became mandatory, for a chirally specific synthesis, to avoid conversions of the type **14** → **15,** that is, to avoid methylation of the phenolic tertiary amine. Actually, the desired transformation of the dihydroxytetrahydroisoquinoline **8** to the dimethoxy secondary amine **10** has been accomplished[4] with complete chiral integrity. However, the overall yield was poor (~6%). The transformation was effected by selectively protecting the amine as its acetyl derivative after esterification, but difficulties in removing the *N*-acetyl were responsible in part for the poor yield.

We have modified this process and improved the overall yield to 66%. A key change was the use of the formyl group to protect the nitrogen. This allowed its facile selective removal in the presence of the ethyl ester and avoided the additional

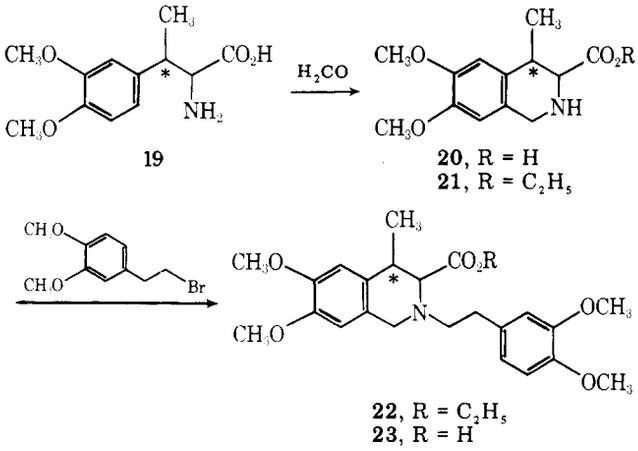
Scheme III. Synthesis of Chirally Pure 6,7-Dimethoxy-1-methyltetrahydro-3-isoquinolinecarboxylates



reesterification step. Also, a possible side reaction in the methylation step is conversion of the *N*-formyl group to methyl imidate salt. This is accommodated by using an alkaline isolation procedure at this stage of the synthesis. The product, a mixture of amine and amide, was heated with HCl/C_2H_5OH to remove all remaining formyl residues, and chirally pure ethyl (1*S*,3*S*)-(−)-1,2,3,4-tetrahydro-1-methyl-6,7-dimethoxy-3-isoquinolinecarboxylate (**10**) was isolated as its hydrochloride (Scheme III).

To form berbine, ester hydrochloride **10** was then converted to the free amine, alkylated with the phenylethyl bromide, hydrolyzed, decarbonylated, and cyclized in the usual manner to give **5** in high yield with an optical rotation for the hydrochloride of $[\alpha]_D$ +136° (lit.[4] $[\alpha]_D$ +148°), corresponding to 94% retention of optical purity from isoquinoline **10.** Ring closure of iminium salt **4** was stereospecific with less than 1% of isomer

Scheme IV



6 as established by LC and GC. The product was identical with (+)-*O*-methylcorytenchirine (**5**) by comparison of its physical and spectral properties with those reported.[7]

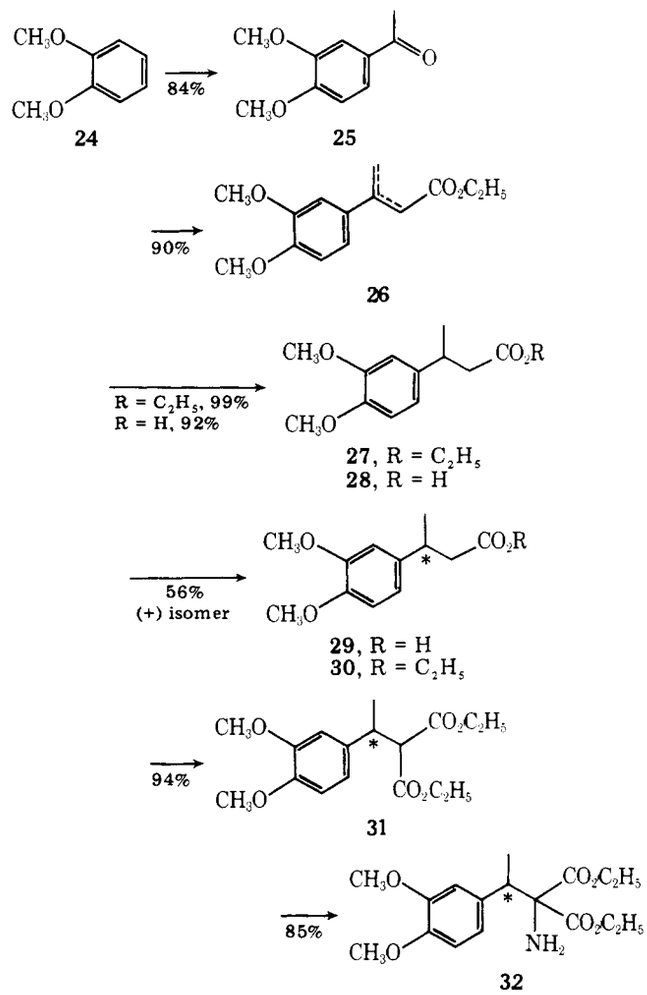
Thus, the optically active amino acid was able to effect a stereospecific introduction of what ultimately became the 8-methyl group of the berbine. Even if the α carbon of the amino acid may have racemized in subsequent steps, its function of inducing asymmetry was complete and it need only serve to create iminium salt regiospecifically by a self-destruction process. The methyl group, now of a single stereochemistry, directed a stereospecific ring closure to a single, optically pure compound. Interestingly, the methyl group did this from a position relatively remote from the bond-forming site. This can be rationalized by assuming that the methyl group influenced the conformation of the transition state and thus the mode of attack by the aromatic ring of the iminium salt.

13-Methylberbines. The complimentary substitution pattern with a 13-methyl substituent can be envisioned as being derived from a β-methylphenylalanine derivative (**19**; Scheme IV). Our plan was to resolve the asymmetry due to the methyl group at some point in the scheme prior to iminium salt cyclization. This should allow a chirally specific synthesis and the direct preparation of an optically active final product. Thus, we chose to synthesize the β-methylphenylalanine **19** with the chirality at the β carbon resolved. Since the carboxyl group would be lost in decarbonylation to form iminium salt, its stereochemistry was of no concern and we sought the diastereomeric pair with only the β carbon configurationally pure.

The synthetic options at this point were to prepare all four isomeric β-phenylalanines, separate diastereomers, and then resolve to obtain a single compound. Alternatively, we could resolve only the asymmetry resulting from the β-methyl group by resolving 3-(3,4-dimethoxyphenyl)butyric acid (**28**) and then aminate to obtain the phenylalanine derivative. The former method has been reported,[8] but is troublesome and inefficient. The target then became **28**. Our synthesis (Scheme V) began with veratrole (**24**), which was converted to acetoveratrone[9] (**25**) and thence in a carefully controlled Reformatsky reaction to give, after dehydration, a mixture of the three isomeric unsaturated esters **26** in 90% yield. Catalytic reduction gave a single product, ethyl 3-(3,4-dimethoxyphenyl)butyrate (**27**). This was hydrolyzed to the free acid **28** for resolution.

The resolution of 3-(3,4-dimethoxyphenyl)butyric acid (**28**), after a series of preliminary tests,[10] was effected with *d*-α-phenylethylamine in chloroform for the (−) isomer and quinine in acetone for the (+) isomer. In four recrystallizations, constant rotation (+) acid was obtained in 56% yield. Acid thus obtained was established as optically pure by quantitative amide formation using *d*-α-phenylethylamine-*d* and analysis for diastereomeric purity by GC. This classical resolution is quite efficient and superior to kinetic resolution available through optically active oxazolines.[11] The comparable 3-phenylbutyric acid was obtained by the latter process in 50% yield, 13% optically pure.

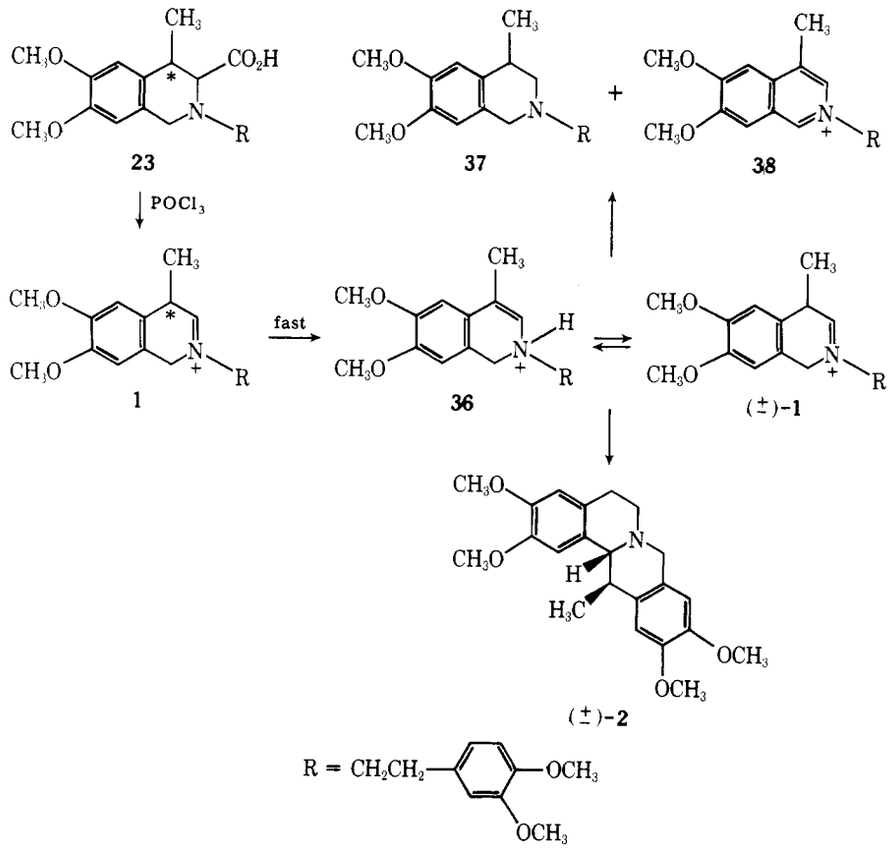
Scheme V. Intermediates in the Synthesis of β-Methyl-3,4-dimethoxyphenylalanine Enantiomerically Pure at the β Position



Conversion of (+)-3-(3,4-dimethoxyphenyl)butyric acid (**29**) to the desired β-methylphenylalanine (**19**) requires an α-amination, which was attempted first through the α-bromo acid. The acid chloride was brominated with *N*-bromosuccinimide (NBS) in carbon tetrachloride,[12] using 2 equiv of NBS since ring bromination was more facile than α-bromination. The α-bromo ester resulting from addition of methanol was treated with potassium phthalimide in DMF.[13] Removal of the aromatic bromine by hydrogenolysis and hydrazinolysis–hydrolysis of the α-phthalimido ester give the desired amino acid **19**; however, it was obtained in less than 15% overall yield for seven steps.

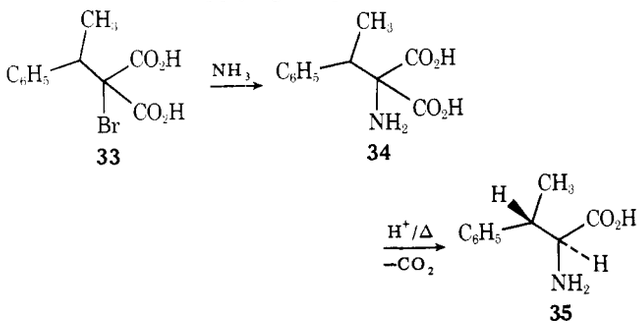
Amination of the acid was considered but dismissed since poor results have been reported.[14] Amination of the ester by first forming the enolate with lithium diisopropylamide followed by treatment with chloramine yielded product, but again in less than 15% yield. A possible reason for the poor amination yields of these strong bases with chloramine is that chloramine has a pK_a of 14 ± 2.[15] Proton transfer could be occurring faster than amination. On this basis, amination should be more successful on the anion of malonate **31**, a weaker base. Indeed, when the anion of **31** was treated with chloramine in ether, an 85% yield of amino ester **32** was ob-

Scheme VI



tained. Chloramine was conveniently prepared by adding an NaOCl solution to a cold NH_4OH solution buffered with NH_4Cl and then extracting into ether.[16] This avoids decomposition caused by excess alkali and gives >90% yields of chloramine without the troublesome distillation.[17] The malonate needed, **31**, was prepared from ethyl ester **30** in 94% yield by forming the enolate with lithium diisopropylamide and treating with 150 mol % of ethyl chloroformate at −78 °C.[18] The aminomalonate **32** was then converted to amino acid **19** by hydrolysis followed by decarboxylation.

Of interest was a report[19] that aminomalonic acid **34** could be decarboxylated to phenylalanine **35** sterospecifically. We were interested in applying this process to our aminomalonate



32 and thereby obtaining a single amino acid. No experimental details were given, and **35** was stated to be obtained in 47% yield from **33.**

We hydrolyzed **32** in refluxing 1 N HCl to produce amino acid **19** as a 4:3 mixture of diastereomers in 89% yield. When **32** was hydrolyzed with alkali, the dipotassium salt isolated, and this subjected to decarboxylation in 1 N HCl, a 3:2 mixture of diastereomers was obtained. In the last case, our aminomalonic acid intermediate prior to decarboxylation should be identical (except for the two methoxyls) with the reported[19] example **34.** One possible explanation for this apparent difference might be that the reported reaction was not stereospecific but slightly stereoselective and that only the erythro isomer was isolated (47% yield) by fractional crystallization. Indeed, in a similar report of the hydrolysis and decarboxylation of ethyl (±)-2-acetylamino-2-ethoxycarbonyl-3-phenylbutyrate to (±)-α-methylphenylalanine [(±)-**35**], the erythro isomer predominates (1.5–1.7:1), but is not exclusive, in the product.[8]

The amino acid **19,** enantiomerically pure at C-3 and mixed at C-2, was converted to the 3-isoquinolinecarboxylic acid **20,** and the ethyl ester **21** was formed in 79% overall yield. The secondary amine was then alkylated to give **22** in 76% yield. Hydrolysis proceeded in 89% yield to acid **23** (Scheme IV), now ready for iminium salt formation and ring closure.

When **23** was subjected to the standard decarbonylation and cyclization conditions, a mixture of the desired berbine **2** and one of the dihydroisoquinoline disproportionation products, 2-[2-(3,4-dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-4-methylisoquinoline (**37**), was obtained. These two compounds were isolated as the only basic products from this reaction. Berbine **2** was established to have the stereochemistry shown (Scheme VI) with the hydrogens at C-13 and C-13a trans. This assignment is based on the NMR absorption, which for trans 13- and 13a-hydrogens shows a chemical shift for the 13-methyl group of ca. δ 1.5 compared to ca. δ 1.0 for the case where the hydrogens are cis.[20–24] This is the expected mode of attack by the aromatic ring on an iminium salt with a substituted carbon adjacent to the bond-forming site and provides synthetically based evidence corroborating earlier assignments. Finally, both products are racemic, indicating a loss of optical integrity at the 4 position of the isoquinoline prior to ring closure.

Disproportionation of 4-alkyldihydroisoquinolines has been previously reported. For example, when 4-alkyl-1,2-dihydroisoquinolines were treated with acid in an attempt to obtain the iminium salt (i.e., the 1,4-dihydroisoquinolinium salt), disproportionation was reported as the exclusive result.[25,26] The mechanism and conditions promoting this dispropor-

tionation are poorly understood. In an attempt to evaluate some of the possible variables, the effect of conditions on the production of berbine **2** was briefly investigated. The factors studied were concentration, time, and temperature during both iminium salt formation and acid cyclization and acid strength in the latter. The results show that **2** is favored over the disproportionation products under (1) minimum time, lower temperatures, and lower concentrations during decarbonylation in $POCl_3$ and (2) higher acidity in the aqueous cyclization step. Concentration of reactant in the aqueous medium appears unimportant.

These data suggest that disporportionation is a bimolecular reaction and that it occurs primarily in the $POCl_3$ solution. Earlier studies showed that no cyclization occurs in the $POCl_3$ with this system, but takes place only in the subsequent aqueous acid treatment. The loss of optical activity in all products is explicable only if a rapid equilibrium between initially formed iminium salt **1** and enamine **36** is established prior to cyclization and disproportionation. Scheme VI summarizes our observations and hypothesis. Our results are suggestive of additional steps now under investigation which might avoid disproportionation in this system such as formation of an activated acyl derivative under milder conditions and decarbonylation under strongly acidic or catalytic conditions.

Experimental Section[27]

Ethyl 2-[2-(3,4-Dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyl-3-isoquinolinecarboxylate (15a).[27a] To ethyl (1*S*,3*S*)-(−)-1,2,3,4-tetrahydro-6,7-dihdroxy-1-methyl-3-isoquinolinecarboxylate (**9**)[4] (3.24 g, 12.9 mmol) was added phenylboronic anhydride (1.39 g, 4.5 mmol), benzene (60 mL), and DMF (10 mL), and this mixture was refluxed for 1 h, followed by distillation of 40 mL over 2.5 h. To the remaining mixture was added K_2CO_3 (3.82 g, 26 mmol) and 1-(2-bromoethyl)-3,4-dimethoxybenzene (3.94 g, 1.6 mmol), and the mixture was refluxed for 22 h and cooled. Ether (100 mL), H_2O (20 mL), 1,3-propanediol (0.3 mL, 40 mmol), and then 1 N HCl (52 mL) were added; after 2 h, the ether layer was separated and extracted with 1 N HCl (50, 25, and 25 mL). The acidic extracts were neutralized to pH 8 with $NaHCO_3$, and extracted with $CHCl_3$ (50, 25, 25, and 20 mL), and the dried $CHCl_3$ extracts were evaporated to give a crude residue (8.4 g). To this residue was added *N,N'*-diisopropyl-*O*-methylisourea (16.5 g, 104 mmol), and heating was maintained at 100 °C for 26 h until all of the material was converted to a single product by TLC ($CHCl_3$/MeOH, 9:1; R_f 0.73). The mixture was distilled, collecting ester **15a** between 150–210 °C (0.01 torr), to give 3.25 g (7.3 mmol, 57%): NMR δ 6.8–6.5 (5 H, m), 4.3–3.5 (2 H, m), 4.1 (2 H, q), 3.9 (12 H, s), 3.0–2.7 (6 H, m), 1.35 (3 H, d), 1.15 (3 H, t); IR 1728 cm^{-1}; MS *m/e* (relative intensity) 443 (1), 428 (4), 370 (13), 292 (100).

2-[2-(3,4-Dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyl-3-isoquinolinecarboxylic Acid (16a). To ester **15a** (3.22 g, 7.3 mmol) was added ethanolic KOH (800 mg in 50 mL), and the mixture was heated at reflux for 3 h. The solvent was evaporated, water and decolorizing carbon were added, the mixture was filtered, and the pH was adjusted to 6 with 6 N HCl. The filtered solution was extracted with $CHCl_3$ (3 × 20 mL) and the $CHCl_3$ evaporated to a residue, which was recrystallized from 15 mL of CH_3OH/ether (1:2) to give 1.27 g (3.1 mmol, 42%) of acid **16a**, mp 157–158 °C with softening at 152 °C. A second crop of 328 mg was obtained, and chromatography of the mother liquor gave 606 mg (80% total yield): NMR δ 6.64–6.30 (5 H, m), 4.47 (1 H, t), 3.84, 3.81, and 3.75 (12 H, s, s, s), 4.10–3.54 (1 H, m), 3.54–2.84 (6 H, m), 1.64 (3 H, d); IR 1644 cm^{-1}. Anal. Calcd for $C_{23}H_{29}NO_6$: C, 66.5; H, 7.0; N, 3.4. Found: C, 66.2; H, 7.0; N, 3.3.

8-Methyl-2,3,10,11-tetramethoxyberbine (5a). Acid **16a** (211 mg, 0.51 mmol) and $POCl_3$ (1.0 mL, 11 mmol) were heated at 70 °C for 10 min. The mixture was cooled (ice bath) and H_2O (11 mL) added, and then it was heated at 100 °C for 1.25 h, cooled, extracted with $CHCl_3$ (3 × 10 mL), saturated with NaCl, and extracted again with $CHCl_3$ (5 mL). The dried extracts were evaporated to give 210 mg which was chromatographed (after treatment with ethanolic HCl) on silica (1.1 × 11.5 cm) eluting with $CHCl_3$ (20 mL) and then acetone (260 mL) to give 66 mg of an oily hydrochloride, $[\alpha]_D$ +24° (*c* 1, $CHCl_3$) [lit.[7] $[\alpha]_D$ +148° *c* 1, $CHCl_3$)]. This was converted to the free base by addition to a saturated Na_2CO_3 solution, extraction with CH_2Cl_2, drying, and evaporating to a residue which was a single spot by TLC (EtOAc; R_f 0.16 compared to coralydine, R_f 0.27, and *O*-methylcorytenchirine, R_f 0.16, both prepared according to the literature[7]): NMR δ 6.63, 6.53 (4 H, m), 4.37–3.97 (1 H, m), 3.87 (12 H, s), 3.16 (1 H, m), 2.90 (5 H, m), 1.40 (3 H, d, J = 7 Hz); MS *m/e* (relative intensity) 369 (15), 354 (100).

Ethyl (1*S*,3*S*)-(−)-1,2,3,4-Tetrahydro-6,7-dihydroxy-1-methyl-3-isoquinolinecarboxylate Hydrochloride (9). Acid **8** (12.44 g, 56 mmol) in ethanol (100 mL) and saturated HCl/ethanol (50 mL) was refluxed for 6 h, the solvent evaporated, and the residue recrystallized from acetic acid to give ester **9** hydrochloride: 15.16 g (52.6 mmol, 94%); mp 220–221 °C dec (lit.[3] mp 229–230 °C); $[\alpha]_D$ −110.5° (*c* 1.2, CH_3OH)].

Ethyl (1*S*,3*S*)-(+)-2-Formyl-1,2,3,4-tetrahydro-6,7-dihydroxy-1-methyl-3-isoquinolinecarboxylate (18). To **9** (12.32 g, 42.8 mmol) was added 97% HCO_2H (107 mL), HCO_2K (3.96 g, 47 mmol), and then Ac_2O (43 mL) dropwise over 5 min while maintaining the internal temperature at 5 °C. The mixture was stirred at room temperature for 3 h, and then ethanol (140 mL) was added, the solvent was evaporated, ethanol (200 mL) and 1 N HCl (4 mL) were added, and this mixture was stirred at room temperature for 14 h. The solvent was evaporated, and to the residue was added 1 N HCl (20 mL) and EtOAc (200 mL). The crystalline precipitate was washed with H_2O (2 × 20 mL) and dried to give 5.42 g (19.5 mmol), mp 174.5–175 °C. The EtOAc layer was washed with saturated $NaHCO_3$ (2 × 20 mL) and saturated NaCl (50 mL), dried, and evaporated to give an additional 5 g (18 mmol; total 37.5 mmol, 88%) of formyl derivative **18**: mp 170–172 °C; single spot by TLC ($CHCl_3$/EtOH, 9:1), R_f 0.28; $[\alpha]_D$ +6.0° (*c* 1, EtOH); NMR (Me_2SO-d_6) δ 8.80 (2 H, s), 8.33 and 8.20 (2 H, s, s, 1:1), 6.66–6.56 (2 H, m), 5.17–3.90 (4 H, m), 3.11–2.87 (2 H, m), 1.55–0.94 (6 H, m); IR 3320, 2990, 1738, 1656 cm^{-1}.

Ethyl (1*S*,3*S*)-(−)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-methyl-3-isoquinolinecarboxylate Hydrochloride (10). Formyl derivative **18** (3.90 g, 14 mmol), acetone (100 mL), $KHCO_3$ (12, g, 120 mmol), and $(CH_3)_2SO_4$ (5.3 mL, 56 mmol) were refluxed for 18.5 h, the solvent was evaporated, and EtOAc (200 mL), saturated Na_2CO_3 (50 mL), and H_2O (10 ml) added. After separation, the ethyl acetate was washed with saturated NaCl (100 mL), dried and evaporated, and excess $(CH_3)_2SO_4$ was removed by distillation at 50 °C (0.03 torr). The residue, EtOH (50 mL), and saturated HCl/EtOH (25 mL) were refluxed for 3 h. Evaporating to 20 mL and cooling gave crystals which were washed with cold Et_2O/EtOH (4:3) and then Et_2O to yield 3.54 g (11.2 mmol, 80%) of ester hydrochloride **10**: mp 213 °C (lit.[4] mp 219–220°C); $[\alpha]_D$ −92.9° (*c* 1, EtOH) [lit.[4] $[\alpha]_D$ −95.8° (*c* 1, EtOH)]; single spot by TLC ($CHCl_3$/EtOH, 9:1), R_f 0.59; NMR δ 6.65 and 6.58 (2 H, s, s), 4.70 (1 H, m), 4.22 (2 H, q), 4.20 (1 H, m), 3.85 (6 H, s), 3.30 (2 H, m), 1.95 (2 H, d), 1.30 (3 H, t); IR 1750 cm^{-1}.

(1*S*,3*S*)-2-[2-(3,4-Dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyl-3-isoquinolinecarboxylic Acid (16b).[27b] To ester hydrochloride **10** (2.53 g, 8.0 mmol) was added saturated Na_2CO_3 (50 mL), and this was extracted with $CHCl_3$ (3 × 20 mL). The extracts were dried and evaporated. To the residue was added 1-(2-bromoethyl)-3,4-dimethoxybenzene (2.45 g, 10 mmol), benzene (10 mL), DMF (10 mL), and K_2CO_3 (2.21 g, 16 mmol), and this mixture was heated at 110 °C under reflux for 23 h. More 1-(2-bromoethyl)-3,4-dimethoxybenzene (1 g, 4.1 mmol) was added, and reflux was continued for 8 h; this addition was repeated and reflux continued for 13 h more. The mixture was cooled and added to H_2O (50 mL) and Et_2O (100 mL), the aqueous layer was separated, saturated NaCl (25 mL) was added, and the mixture was extracted with Et_2O (3 × 17 mL). The combined Et_2O extracts were extracted with 0.5 N HCl (50, 25, and 25 mL), and the acid extracts were basified with saturated Na_2CO_3 (60 mL), extracted with CH_2Cl_2 (3 × 20 mL), dried, and evaporated. To the residue was added EtOH (40 mL), H_2O (10 mL), and KOH (1 g). The mixture was refluxed for 5.5 h. The solvent was evaporated, H_2O (40 mL) added followed by washing with Et_2O (20 mL), and then the aqueous phase adjusted to pH 6 with 6 N HCl and stored in the cold overnight. The resulting mixture was filtered, the filtrate was extracted with $CHCl_3$ (3 × 17 mL), and the extracts were dried and evaporated to give 1.58 g (3.8 mmol, 48%). This tertiary amino acid **16b** was recrystallized from EtOH/Et_2O (1:2): mp 157–158 °C dec; NMR and IR were identical with **16a**.

(8*S*,13a*R*)-(+)-5,8,13,13a-Tetrahydro-2,3,10,11-tetramethoxy-8-methyl-6*H*-dibenzo[*a,g*]quinolizine [(8*S*,13a*R*)-(+)-8-Methyl-2,3,10,11-tetramethoxyberbine, (+)-*O*-Methylcorytenchirine] (5b). Tertiary amino acid **16b** (207 mg, 0.50 mmol) and $POCl_3$ (1 mL, 11 mmol) were heated at 70 °C for 10 min and then cooled (ice bath), and H_2O (11 mL) was added. The mixture was heated at 100 °C for 1.5 h, cooled, added to 2 N NaOH (30 mL), and

extracted with CH_2Cl_2 (3 × 10 mL), and the extracts were dried and evaporated to give 169 mg (0.46 mmol, 92%) of crude oily base which was chromatographed (3 g of silica, eluting with EtOAc) and converted to hydrochloride by dissolving in hot Et_2O and adding saturated HCl/EtOH (2 drops). The hydrochloride of **5b** was recrystallized from isopropyl alcohol: 162 mg, 80% yield; mp 193–194 °C (lit.[7] mp 205–206 °C); $[\alpha]_D$ +136° (*c* 0.35, $CHCl_3$) [lit.[7] $[\alpha]_D$ +148° (*c* 1, $CHCl_3$)]. The diastereomeric integrity was established by GC (5% Dexsil 300 GC on Anachrom Q, He flow rate of 30 cm^3/min, oven 262 °C, injection port 260–270 °C, detector 295 °C) using coralydine and *O*-methylcorytenchirine prepared according to the literature[7] for comparison (R_t 47.2 and 51.6 min, respectively), by TLC (Brinkman HR, EtOAc; R_f 0.16) (coralydine, R_f 0.26), (coralydine, R_f 0.26), and by LC (<1% of coralydine; silica, EtOAc); NMR and mass spectra were identical with **5a**.

Reformatsky Reaction on 3,4-Dimethoxyacetophenone (25). Formation of 26. To zinc (88 g, 1.35 mol, 30 mesh granulated; treated with 1 N HCl, washed with water, ethanol, and acetone, and dried at 160 °C) in a three-neck 5-L round-bottom flask fitted with a paddle stirrer, a 500 mL pressure equalized addition funnel, and a series of two Liebig condensors connected with adapters to the mouth of a 6-L Erlenmeyer flask was added a portion of a solution of acetoveratrone (**25**) (198 g, 1.10 mol) and ethyl bromoacetate (200 g, 1.32 mol) in benzene (1.23 L) to just cover the zinc, and the mixture was heated to reflux. Induction was observed as a rapid generation of solvent vapor condensing in the apparatus. The remaining solution was then added dropwise while applying enough heat to maintain a vigorous reflux (over 30 min). The mixture was gently refluxed for an additional 45 min and then quenched with an equal volume of 10% H_2SO_4. The organic layer was washed with 1 N NaOH (1 vol), H_2O (1 vol), and saturated NaCl (0.5 vol) and then dried. The solvent was evaporated and the residue distilled at 195–207 °C (7–11 torr) (in a 15-cm vacuum-jacketed column with platinum gauze) to give 244 g (0.98 mol, 90%) as a mixture of the three isomeric unsaturated esters **26**: GC (200 °C, 4 ft, 3% OV-17 Aeropak 30, 100–120 mesh), R_t 1.5, 2.4 min; IR 1732, 1712 cm^{-1}.

Ethyl 3-(3,4-Dimethoxyphenyl)butyrate (27). Unsaturated esters **26** (400 g, 1.6 mol) in EtOH (450 mL) were hydrogenated using 10% Pd/C (50 g) as catalyst. After uptake of hydrogen was complete (7.5 h), the mixture was filtered through Celite, the catalyst was washed with ethanol, the filtrate was evaporated, and the residue was distilled at 155 °C (0.1 torr) [lit.[28] 107 °C (0.008 torr)] to give 397 g (1.58 mol, 99%) of the saturated ester **27**: IR (neat) 1732 cm^{-1}; NMR (CCl_4) δ 6.7 (3 H, s), 4.2–3.8 (2 H, q), 3.8 (6 H, d), 3.4–3.0 (1 H, m), 2.6–2.4 (2 H, d), 1.4–1.2 (3 H, d), 1.3–1.0 (3 H, t).

3-(3,4-Dimethoxyphenyl)butyric Acid (28). Ester **27** (397 g, 1.58 mol), EtOH (1 L), KOH (119 g, 1.8 mol), and H_2O) (60 mL) were refluxed for 2 h. The solvent was evaporated, H_2O (1 L) and 6 N H_2SO_4 (350 mL) were added to the residue, the aqueous mixture was extracted with CH_2Cl_2 (3 × 200 mL), and then the organic phase was washed successively with H_2O (1 vol) and saturated NaCl (1 vol). The filtered CH_2Cl_2 solution was evaporated, benzene was added to a volume of 600 mL, and solvent was slowly evaporated in a stream of N_2 passed over the cooled solution; total yield of crystalline acid **28** (in three crops) was 334 g (92%): mp 83–84 °C (lit.[8] mp 84–85 °C); IR 1701 cm^{-1}; NMR δ 6.8 (3 H, s), 3.9 (6 H, d), 3.5–3.0 (1 H, m), 2.7–2.5 (2 H, m), 1.4–1.2 (3 H, d).

(+)-3-(3,4-Dimethoxyphenyl)butyric Acid (29). To acetone (1.3 L) was added racemic 3-(3,4-dimethoxyphenyl)butyric acid (**28**; 224 g, 1.0 mol) and quinine (324 g, 1.0 mol). Dissolution was complete at the boiling point. The mixture was allowed to cool slowly to room temperature for 24 h. The salt was recrystallized three more times from acetone to a constant rotation to give 160 g, mp 125–127 °C. Before liberating the acid, this corresponded to a 60% overall yield of the (+) isomer. The acid was recovered by adding the salt to 1 N NaOH (1.5 L) and extracting the quinine with CH_2Cl_2 (3 × 100 mL). The aqueous layer was then acidified with 6 N HCl to pH 1 and extracted with CH_2Cl_2 (3 × 167 mL), and the combined organic layers were dried and evaporated to give 57.4 g of carboxylic acid **29** (93% from salt, 56% overall for resolution): mp 78.5–79.5 °C; $[\alpha]^{20}D$ +30.2° (*c* 5.6, CH_3OH); TLC ($CHCl_3$/MeOH, 9:1), R_f 0.56 (single spot); IR 1728 cm^{-1}; NMR δ 6.8 (3 H, s), 3.8 (6 H, s), 3.4–3.0 (1 H, m), 2.7–2.5 (2 H, m), 1.4–1.2 (3 H, d). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.3; H, 7.2. Found: C, 64.4; H, 7.1.

The optical purity of this acid was established by making the amide with *d*-α-phenylethylamine and determining the diastereomeric purity by GC. Thus, both racemic and resolved *d*-3-(3,4-dimethoxyphenyl)butyric acid were treated with *d*-α-phenylethylamine as follows.

To 3-(3,4-dimethoxyphenyl)butyric acid (103 mg, 0.46 mmol) was added thionyl chloride (1 mL, 13.94 mmol) and pyridine (1 drop). The mixture was stirred at room temperature for 60 min, and excess thionyl chloride was evaporated. To the residue was added CH_2Cl_2 (2.5 mL), then *d*-α-phenylethylamine (0.10 mL, 0.78 mmol; $[\alpha]^{20}D$ +39.6°), and finally 5% Na_2CO_3. The mixture was stirred vigorously for 15 min. The CH_2Cl_2 layer was removed and dried, acetone (2 mL) was added, and the solutions were analyzed by GC.

For the amide from racemic carboxylic acid: GC (6 ft, 6% OV-25 on Chromosorb W, acid washed, treated with dichlorodimethylsilane, 100–120 mesh, ⅛ in. diam, oven 223 °C, injection port 267 °C, detector 292 °C), R_{t-1} 52.4 min (area, 179), R_{t-2} 57.6 min (area, 182). For the amide made with the resolved carboxylic acid: GC (same conditions), R_{t-1} 52.2 min (area, 0.35), R_{t-2} 57.2 min (area, 444); purity 99.92%.

The solution containing the two diasteriomeric amides was evaporated in a stream of nitrogen. Ether (1 mL) and then hexane (1 mL) were added, and the crystals that developed melted at 90–94 °C. Anal. Calcd for $C_{20}H_{25}NO_3$:C, 73.4; H, 7.7; N, 4.3. Found: C, 73.4; H, 7.7; N, 4.4.

(+)-3-(3,4-Dimethoxyphenyl)butyric Acid Ethyl Ester (30). Acid **29** (10 g, 44 mmol), EtOH (50 mL), toluene (100 mL), and concentrated H_2SO_4 (0.5 mL) were refluxed for 12.5 h, removing H_2O with a Dean-Stark trap. The solvent was evaporated to 25 mL, the mixture cooled, and Et_2O (50 mL) added. This was washed with 5% Na_2CO_3 (50 mL) and then saturated NaCl (50 mL), the Et_2O) was evaporated, and the residue was distilled (bult-to-bulb) at 115 °C (0.05 torr) to yield 10.94 g (43.5 mmol, 98%) of ester **30**: mp 34.5–35 °C; $[\alpha]^{20}D$ +34° (*c* 6.3, CH_3OH). Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.6; H, 8.0. Found: C, 66.6; H, 7.9.

Diethyl (+)-2-(3,4-Dimethoxyphenyl)propane-1,1-dicarboxylate (31). To diisopropylamine (9.1 g, 90 mmol) in tetrahydrofuran (90 mL) was added *n*-butyllithium (30.6 mL of a 2.95 M solution, 90 mmol) at −10 to −20 °C followed after 10 min by ester **30** (21.39 g, 85 mmol) at −70 °C (internal temperature rising to −45 °C). After cooling to −73 °C, ethyl chloroformate (19.5 g, 180 mmol) was added as fast as possible (temperature rising to −10 °C). After stirring for 20 min, the solvent was evaporated and to the residue was added H_2O (200 mL) and Et_2O (200 mL). The Et_2O layer was washed with saturated NaCl (20 mL), dried, and evaporated, and the residue was distilled at 135 °C (0.08 torr) to yield 26.6 g (94%) of malonate **31**: IR 1731, 1751 cm^{-1}; NMR δ 6.8 (3 H, s), 4.4–3.5 (12 H, m), 1.4–0.9 (9 H, m).

Diethyl (+)-1-Amino-2-(3,4-dimethoxyphenyl)propane-1,1-dicarboxylate (32). To malonate **31** (14.2 g, 43.7 mmol) in THF (120 mL) was added a 50% NaH dispersion in oil (2.1 g, 43.7 mmol) and EtOH (0.2 mL). The mixture was stirred at room temperature until after gas evolution ceased (9 h total), and to the stirred mixture at room temperature was added a cooled solution of dry chloramine (170 mL of a 0.49 M Et_2O solution, 83.3 mmol), continuing the stirring at room temperature for 20 h. The solvent was evaporated and the residue distributed between Et_2O (200 mL) and 5% $Na_2S_2O_3$ (100 mL). The Et_2O layer was separated and extracted with 1 N HCl (3 × 60 mL), and the aqueous phase was basified with 10% Na_2CO_3 and extracted with CH_2Cl_2 (3 × 60 mL). Evaporation of the CH_2Cl_2 followed by distillation at 143 °C (0.25 Torr) yielded 12.6 g (37 mmol, 85%) of aminomalonate **32**: $[\alpha]^{20}D$ +46.4° (*c* 4.0, CH_3OH); MS *m/e* (relative intensity) 339 (0.3), 293 (0.6), 226 (3), 243 (1), 192 (2), 176 (2), 166 (11), 165 (100); IR 3380, 3320, 1736 cm^{-1}; NMR δ 6.9–6.7 (3 H, m), 4.5–3.5 (11 H, m), 1.9 (2 H, s), 1.4–1.0 (9 H, m). Anal. Calcd for $C_{17}H_{25}NO_6$: C, 60.2; H, 7.4; N, 4.1. Found: C, 60.0; H, 7.4; N, 4.1.

(2*R*,*S*; 3*R* or *S*)-2-Amino-3-(3,4-dimethoxyphenyl)butyric Acid (19). To aminomalonate **32** (8.95 g, 26.4 mmol) was added 1 N HCl (100 mL), and the mixture was refluxed for 5 days. The solvent was evaporated, the residue dissolved in H_2O (100 mL), and the mixture adjusted with concentrated NH_4OH to pH 6. The solution was evaporated, the residue was again dissolved in H_2O (100 mL) at the boiling point, and the solution was then reduced to 25 mL and cooled. After 1 day, the crystals were collected and washed with H_2O (2 × 5 mL, ice cold) to give 5.6 g (23.5 mmol, 89%) of amino acid **19**: mp 182–192 °C; amino acid analysis under standard conditions[29] (Phe, R_t 180 min) showed 2 peaks, R_t 199 (area 6.2) and 212 min (area, 4.3); IR 3240, 3220, 2080, 1612 cm^{-1}; NMR (CF_3CO_2H) δ 7.5–6.9 (3 H, brd), 7.0 (3 H, s), 4.8–4.2 (1 H, brd), 4.0 (6 H, s), 3.9–3.3 (1 H, brd), 1.7–1.5 (3 H, d). Anal. Calcd for $C_{12}H_{17}O_4N$: C, 60.2; H, 7.2; N, 5.9. Found: C, 60.0; H, 7.1; N, 5.9.

Dipotassium 1-Amino-2-(3,4-dimethoxyphenyl)propane-1,1-dicarboxylate. To aminomalonate **32** (4.0 g, 11.9 mmol) was added 95% EtOH (50 mL) and KOH (2 g, 36 mmol). The solution was refluxed for 20 h, and the precipitate that formed on cooling was recrystallized (aqueous EtOH, toluene) to give the dipotassium salt, mp 317–319 °C dec. Anal. Calcd for $C_{13}H_{15}K_2NO_6$: C, 43.4; H, 4.2; N, 3.9. Found: C, 43.2; H, 4.4; N, 3.7.

Decarboxylation of Dipotassium 1-Amino-2-(3,4-dimethox-

yphenyl)propane-1,1-dicarboxylate. To potassium 1-amino-2-(3,4-dimethoxyphenyl)propane-1,1-dicarboxylate (324 mg, 0.90 mmol) was added 1 N HCl (50 mL), and the mixture was refluxed for 20 h. The crude hydrolysate was subjected to amino acid analysis[29] and showed the diastereomeric β-methyl-(3,4-dimethoxyphenyl)-alanines at 203 and 217.5 min in a ratio of 61:39. The volume was reduced and the pH adjusted to 6. After several days, the crystals were collected to give 2.06 g (8.63 mmol, 73%) of amino acid **19.**

1,2,3,4-Tetrahydro-6,7-dimethoxy-4-methyl-3-isoquinolinecarboxylic Acid (20). Amino acid **19** (4.55 g, 19.1 mmol), a 37% formaldehyde solution (18 mL, 213 mmol), and 6 N HCl (38 mL) were heated at 95 °C for 35 min, the solvent was evaporated at 60–70 °C, and the residue was dried to give 5.66 g of crude product. A sample for analysis was recrystallized from EtOH/EtOAc: mp 259–263 °C dec; NMR (CF_3CO_2H) δ 7.0–6.83 (2 H, m), 4.67 (3 H, m), 4.02 (6 H, s), 3.74 (1 H, m), 1.69 and 1.50 (3 H, d, d); IR 1748 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_4 \cdot 0.25H_2O$: C, 61.0; H, 6.9; N, 5.5. Found: C, 61.2; H, 6.7; N, 5.4.

Ethyl 1,2,3,4-Tetrahydro-6,7-dimethoxy-4-methyl-3-isoquinolinecarboxylate (21). To crude acid **20** (5.44 g, 18.9 mmol) was added p-TsOH·H_2O (3.8 g, 20 mmol), EtOH (100 mL), and toluene (100 mL), and the solution was refluxed through 4A molecular sieves in a Soxhlet extractor for 3.5 days, changing drying agent 3 times during this period. The solvent was evaporated, CH_2Cl_2 (20 mL), saturated Na_2CO_3 (20 mL), and H_2O (10 mL) were added, and the aqueous layer was extracted further with CH_2Cl_2 (2 × 20 mL). The dried organic extracts were evaporated, and the residue was distilled at 130 °C (0.01 torr) to give 4 g (14.4 mmol, 79% based on starting phenylalanine derivative **19**) of ester **21:** mp 67–78 °C; TLC (CH_3OH), R_f 0.60; two products by GC; IR 3350, 1736 cm^{-1}.

Ethyl 2-[2-(3,4-Dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-4-methyl-3-isoquinolinecarboxylate (22). Ester **21** (11.2 g, 40.2 mmol), benzene (50 mL), DMF (50 mL), 1-(2-bromoethyl)-3,4-dimethoxybenzene (12.3 g, 50 mmol), and K_2CO_3 (11 g, 80 mmol) were heated at 110 °C for 24 h. The mixture was added to Et_2O (200 mL) and H_2O (100 mL), and the Et_2O layer was extracted with 0.5 N HCl (100, 50, and 50 mL). Basification of the aqueous layer with excess saturated Na_2CO_3, extraction into CH_2Cl_2 (100, 50, 50, and 25 mL), drying, and evaporating the extracts left a residue which was distilled. Collecting between 120–185 °C (0.03 torr) gave 13.5 g (30.5 mmol, 76%) of tertiary amino ester **22:** NMR δ 6.80–6.48 (5 H, m), 4.27–3.97 (4 H, m), 3.87 (12 H, s), 3.80–2.86 (6 H, m), 1.36–0.86 (6 H, m); IR 1730 cm^{-1}; MS m/e (relative intensity) 443 (5), 370 (24), 292 (100), 264 (27), 239 (15), 239 (15), 204 (15), 164 (35), 151 (13).

2-[2-(3,4-Dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-4-methyl-3-isoquinolinecarboxylic Acid (23). Ester **22** (4.0 g, 9.0 mmol), 95% EtOH (50 mL), and KOH (800 mg, 14.4 mmol) were refluxed for 21 h, after which time more KOH (300 mg) was added and refluxing continued for 5 h. After stirring for an additional 16 h at room temperature, the solvent was evaporated, water added, and the solution adjusted to pH 6.5 with 6 N HCl and cooled to give in two crops 2.29 g. The mother liquors were extracted with $CHCl_3$ (3 × 17 mL), and the extracts were dried and evaporated to give 1.04 g more (total 3.33 g, 89%): mp 160–162 °C dec (from methanol); NMR δ 6.70 (5 H, m), 4.14 (3 H, m), 3.85 (12 H, s), 3.52–2.99 (6 H, m), 1.40 (3 H, d); IR 1612 cm^{-1}. Anal. Calcd for $C_{23}H_{29}NO_6$: C, 66.5; H, 7.0; N, 3.4. Found: C, 66.4; H, 7.0; N, 3.3.

***trans*-5,8,13,13a-Tetrahydro-2,3,10,11-tetramethoxy-13-methyl-6*H*-dibenzo[*a,g*]quinolizine (*trans*-13-Methyl-2,3,10,11-tetramethoxyberbine) (2) and 2-[2-(3,4-Dimethoxyphenyl)-ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-4-methylisoquinoline (37).** Acid **23** (208 mg, 0.5 mmol) and $POCl_3$ (4 mL) were heated at 50 °C for 4 min and cooled (ice bath), 3 N HCl (40 mL) was added, and the solution was heated at reflux for 1.5 h. After cooling the mixture, it was basified with Na_2CO_3 and NaOH and extracted with $CHCl_3$ (3 × 7 mL). The extract consisted of a mixture of two basic products in a ratio of 87:13, the major one being *trans*-13-methyl-2,3,10,11-tetramethoxyberbine (**2**) in 24% yield. The components were separated by chromatography (EtOAc) to give the pure components.

(a) *trans*-13-Methyl-2,3,10,11-tetramethoxyberbine (**2**): mp 148 °C; $[\alpha]_D$ 0° (*c* 1, $CHCl_3$); TLC (EtOAc), R_f 0.08, single spot; NMR δ 6.71, 6.68, 6.58, and 6.52 (4 H, s, s, s, s), 4.16 (1 H, d, J = 18 Hz), 3.86 (12 H, s), 3.69–3.34 (1 H, m), 2.90 (6 H, m), 1.47 (3 H, d, J = 7 Hz); MS m/e (relative intensity) 369 (22), 354 (9), 192 (7), 178 (100), 163 (18). Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.4; H, 7.4; N, 3.8. Found: C, 71.5 H, 7.3; N, 3.8.

(b) 2-[2-(3,4-Dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-4-methylisoquinoline (**37**): mp 84–85 °C; $[\alpha]_D$ 0° (*c* 1, $CHCl_3$); TLC (EtOAc), R_f 0.27, single spot; NMR δ 6.77, 6.67, and 6.47 (5 H, s, s, s), 3.84 (12 H, s), 3.60 (2 H, s), 2.95 (6 H, m), 1.28 (3 H, d, J = 7 Hz); MS m/e (relative intensity) 371 (1), 279 (1), 220 (100). Anal. Calcd for $C_{22}H_{29}NO_4$: C, 71.1; H, 7.9; N, 3.8. Found: C, 71.2; H, 7.8; N, 3.8.

Registry No.—2, 67408-99-5; **5a,** 58116-10-2; **5a** HCl, 58116-11-3; **5b** HCl, 58165-69-8; **8,** 35287-23-1; **9,** 55863-04-2; **9** HCl, 35287-18-4; **10** HCl, 67409-00-1; **15a,** 67409-01-2; **16a,** 67409-02-3; **16b,** 67409-03-4; **18,** 67409-04-5; **19,** 67409-05-6; **20,** 67409-06-7; **21,** 67409-07-8; **22,** 67409-08-9; **23,** 67409-09-0; **25,** 120-14-9; **26** (isomer 1), 67409-10-3; **26** (isomer 2), 67409-11-4; **26** (isomer 3), 67409-12-5; **27,** 67409-13-6; **28,** 67409-14-7; **29,** 67409-15-8; **29** quinine salt, 67409-16-9; **29** *d*-α-phenylethylamide (isomer 1), 67409-17-0; **29** *d*-α-phenylethylamide (isomer 2), 67409-22-7; **30,** 67409-18-1; **31,** 67425-68-7; **32,** 67409-19-2; **32** acid 2K salt, 67409-20-5; **37,** 67409-21-6; 1-(2-bromoethyl)-3,4-dimethoxybenzene, 40173-90-8; *d*-α-phenylethylamine, 3886-69-9.

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