

An Efficient and Practical Total Synthesis of (+)-Vincamine from L-Aspartic Acid

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Received September 13, 1989

Synthesis of optically pure α -*tert*-butyl β -methyl (2*S*,3*R*)-3-ethylhexahydroquinolinate (**18**) in 54–59% yield from L-aspartic acid was the foundation for a practical synthesis of (+)-vincamine. Conversion of L-aspartic acid to **18** was accomplished via two routes. In the first route, esterification was followed by mono-N-alkylation to attach the three-carbon residue. Nitrogen protection and intramolecular C-alkylation gave the piperidine, which was subsequently elaborated to hexahydroquinolinate **18**. In the second route, the sequence was inverted. After appropriate N-protection, the aspartate was C-alkylated at the β -carbon and then intramolecularly N-alkylated. Both routes gave enantiomerically pure **18**; however, the latter sequence was simpler in execution and gave much higher yields. Alkylation of **18** with tryptophyl bromide gave the substrate for formation of the tetracyclic indoloquinolizine. This was accomplished either by directly heating the methyl ester in phenylphosphonic dichloride or by cyclization of the iminium ion generated after hydrolysis of the α -*tert*-butyl ester. The C3 diastereomers are easily separated and equilibrated, resulting in the required C3- α H epimer. Transformation of the tetracyclic indoloquinolizine **10** followed literature precedent and led to the pentacyclic (+)-vincamine after it was established that the intermediate aldehyde did not lose configurational integrity via a retro-Mannich reaction. This synthesis provides (+)-vincamine, demonstrated to be >99% enantiomerically pure, in 24–26% overall yield from L-aspartic acid.

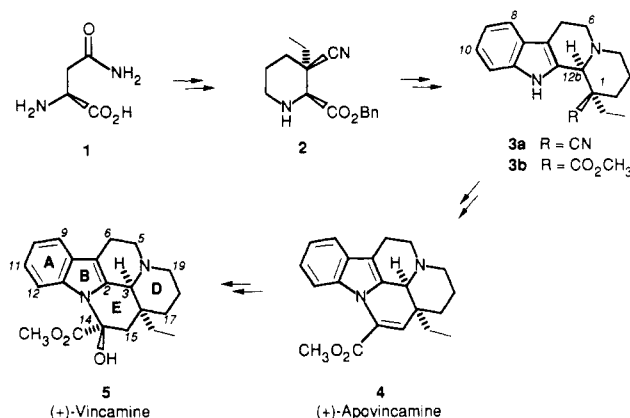
Introduction

Because of its cerebral vasodilatory effects,¹ (+)-vincamine (**5**), the major alkaloid of *Vinca minor* L.,² is a therapeutically widely used compound. Since the determination of its structure,³ several syntheses of racemic and optically active vincamine have been reported.⁴ We recently disclosed a convergent synthesis of (+)-apovincamine (**4**),^{4d} a convenient precursor of (+)-vincamine,⁵ using L-asparagine (**1**) as the chiral educt from which the optically pure alkaloid was constructed. The overall yield, however, of (+)-apovincamine from L-asparagine was only 1.5%. The major problems encountered in this sequence, summarized in Scheme I, were the result of our initial assumption of the advantages of having a β -cyano group.

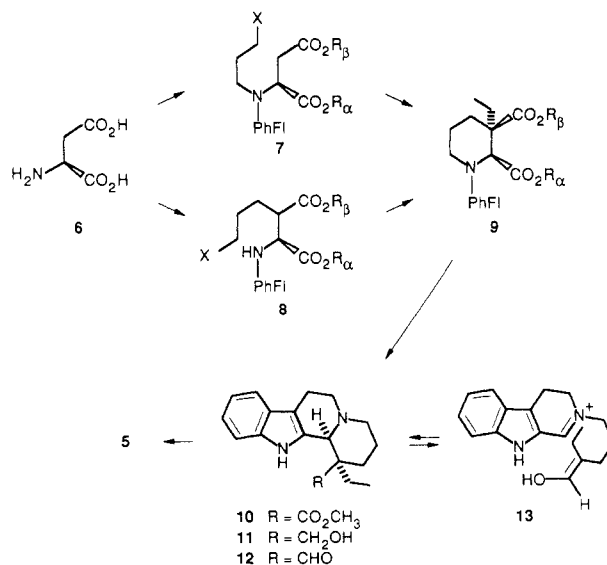
Subsequently, we showed that the presumed advantages of the β -cyano group were nonexistent.⁶ The sequence for synthesizing enantiomerically pure pipercolates was modified by substituting L-aspartic acid for L-asparagine as the chiral educt. This methodology was used to synthesize α -*tert*-butyl β -methyl (2*S*,3*R*)-3-ethyl- Δ^4 -tetrahydroquinolinate, which was elaborated to the *Aspidosperma* alkaloid (-)-vindoline.^{6a} These results, together with the availability of the recently reported method for constructing the E ring of (\pm)-vincamine from the indoloquinolizine **10**,^{4b} led us to reinvestigate this general route for a potential efficient and practical synthesis of (+)-vincamine.

Our plan of synthesis is outlined in Scheme II. An effective synthesis of (+)-vincamine using L-aspartic acid as the educt requires an aspartate derivative that can be

Scheme I. Previous Synthesis of (+)-Apovincamine (4) from L-Asparagine



Scheme II. Projected Routes to (+)-Vincamine (5) Based on L-Aspartate Diesters



(1) Hava, M. "The Pharmacology of *Vinca* species and their Alkaloids", *The Vinca Alkaloids*; Taylor, W. L., Farnsworth, N. R., Eds.; Marcel Dekker: New York, 1973; Chapter 6, p 305.

(2) Schlitter, E.; Furlenmeier, A. *Helv. Chim. Acta* 1953, 36, 2017.

(3) Trojánek, J.; Koblíková, Z.; Bláha, K. *Chem. Ind.* 1965, 1261 and references cited therein.

(4) (a) Hakam, K.; Thielmann, M.; Thielmann, T.; Winterfeldt, E. *Tetrahedron* 1987, 43, 2035. (b) Génin, D.; Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y. *J. Org. Chem.* 1987, 52, 353. (c) Takano, S.; Sato, S.; Goto, E.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* 1986, 156. (d) Christie, B. D.; Rapoport, H. *J. Org. Chem.* 1985, 50, 1239. (e) A review of the synthesis of vincamine and related alkaloids has been presented by Atta-ur-Rahman; Sultana, M. *Heterocycles* 1984, 22, 841.

(5) Pfäffli, P.; Oppolzer, W.; Wenger, R.; Hauth, H. *Helv. Chim. Acta* 1975, 58, 1131.

(6) (a) Feldman, P. L.; Rapoport, H. *J. Am. Chem. Soc.* 1987, 109, 1603. (b) Feldman, P. L.; Rapoport, H. *J. Org. Chem.* 1986, 51, 3882.

subsequently differentiated at the α - and β -carboxyl groups and converted to hexahydroquinolinate **9**. Previously, the tetrahydroquinolinate used for the synthesis of (-)-vin-

doline was prepared by mono-N-alkylating the primary amine with 1-bromo-3-chloropropane followed by an intramolecular C-3 alkylation.^{6b} The nitrogen monoalkylation proceeded in fair yield (60%) and required silica gel purification.

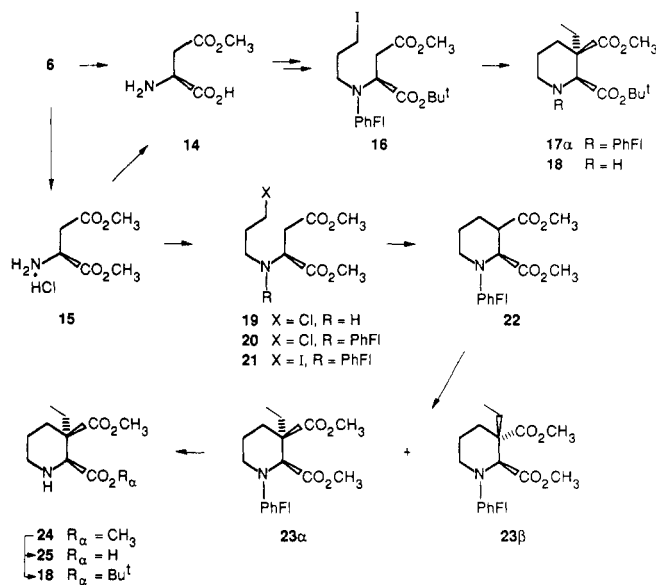
An alternative strategy is to change the sequence and C-alkylate the C-3 position of a suitably protected aspartate derivative first and then close the ring by an intramolecular N-alkylation. Crucial to the success of this route is that no C-2 or NH deprotonation takes place during the first carbon alkylation. As we have shown, using a 9-phenylfluoren-9-yl (9-PhF) protecting group on the nitrogen prevents any such undesired deprotonation.^{4d,6b,7} Following ring closure, a second C-3 alkylation to incorporate the ethyl group should give the target protected hexahydroquinolinolate **9** with the correct absolute stereochemistry at C-3.^{4d,6b}

Elaboration of the hexahydroquinolinolate **9** to indoloquinolizine **10** follows our previous studies in both the synthesis of (+)-apovincamine and (-)-vindoline.^{4d,6a} Recently, it has been demonstrated that conversion of (\pm)-**10** to (\pm)-vincamine can be accomplished in 54% overall yield.^{4b} This route from **10** to vincamine is short, high-yielding, and easily accessed from one of our projected intermediates. We have previously shown, however, that electrophilic groups at C-1 of indoloquinolizines related to aldehyde **12** readily lead to a racemizing, reversible Mannich reaction under a variety of conditions.^{6b} This reaction has also been shown to occur with **12**, via **13**, under acidic conditions.⁸ Therefore, care in handling **12** would have to be exercised to avoid vincamine of compromised optical integrity.

Results

Aspartate Esters. Our strategy depended upon a specific and high-yield differentiation of the aspartic acid α - and β -carboxyl groups. The initial route employed to prepare α -*tert*-butyl β -methyl aspartate involved a nitrogen protection/deprotection sequence, which we wanted to avoid.^{6b} Therefore, we turned to the dimethyl ester of L-aspartic acid, prepared in nearly quantitative yield by using thionyl chloride in methanol. This reaction is very convenient for synthesizing dimethyl ester **15**, compared to the literature protocol.⁹ We studied the formation of α -methyl,¹⁰ β -methyl,¹¹ and dimethyl aspartate hydrochlorides in detail as a function of time. All three of these compounds were synthesized independently and their formation could be monitored by the appearance and/or disappearance of their respective methyl and methine resonances in the ¹H NMR spectra. The selective formation of the β -methyl ester can be controlled by carefully monitoring both the temperature and the time of the reaction. None of the α -methyl ester was seen within the limits of detection of the ¹H NMR (1%). Thus, after 15 min at room temperature the ratio of β -methyl aspartate to dimethyl aspartate was maximal (5/1), and after 16 h, the reaction mixture consisted solely of dimethyl ester. Subsequently, we found that the most convenient method to prepare the pure β -methyl aspartate (**14**) was to use copper(II)-assisted specific hydrolysis of the α -ester of dimethyl aspartate (**15**). Though this hydrolysis required

Scheme III. Synthesis of Hexahydroquinolinates from L-Aspartate via Initial N-Alkylation Followed by Intramolecular C-Alkylation



heating at 70 °C, there was no racemization, as determined by diastereomer formation with 1-phenylethyl isocyanate, and no contamination with α -methyl aspartate. The yield from aspartic acid (**6**) was practically quantitative.

β -Methyl (2*S*,3*R*)-3-Ethylhexahydroquinolinates. The key compounds in our synthetic route are the β -methyl hexahydroquinolinates **18**, **24**, and **25**, differing only in the state of the α -carboxyl group among *tert*-butyl ester, methyl ester, and free acid. Four different routes were investigated in order to find the most efficient means of synthesizing these hexahydroquinolinates beginning with L-aspartic acid; the first two are shown in Scheme III. Following the identical protocol that was used in the (-)-vindoline synthesis, *N*-iodopropyl aspartate **16** was synthesized from L-aspartic acid in 26% yield.^{6b} Upon treatment of **16** with LDA and quenching with ethyl iodide, a 98/2 mixture of **17** α /**17** β was isolated, and separation by silica gel chromatography yielded **17** α in 82% yield. Removal of the 9-PhF protecting group was accomplished in high yield, either by acidolysis or by hydrogenolysis. The latter procedure is preferred since one of the byproducts that is troublesome to remove in the acidolysis reaction is *N*-(9-PhF)acetamide formed via the Ritter reaction. With this sequence, L-aspartic acid (**6**) can be converted to optically pure **18** in 17% yield.

The second route involving initial N-propylation proceeds from dimethyl aspartate (**15**), which could be converted to the dimethyl hexahydroquinolinolate **24** by the same methods as used for the corresponding α -*tert*-butyl β -methyl ester; the overall yield from L-aspartic acid to **24** was 35%. Many attempts at selective hydrolysis of the α -methyl ester, however, either the *N*-9-PhF compound **23** α or the NH compound **24**, failed using either acid or base. Finally, total selectivity was achieved by copper(II)-assisted hydrolysis of **24** to yield **25**. This hydrolysis was accompanied by partial (15%) epimerization at the α -center; however, this is not a loss since the asymmetry at this center is destroyed in later generation of iminium ion. Reesterification of the α -carboxyl group in **25** with *O*-*tert*-butyl-*N,N'*-diisopropylisourea¹² gave **18** in 89% yield. With use of this latter procedure **18** was synthesized from L-aspartic acid in 29% overall yield.

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(7) Wolf, J.-P.; Rapoport, H. J. *Org. Chem.* 1989, 54, 3164.

(8) Oppolzer, W.; Hauth, H.; Pfäffli, P.; Wenger, R. *Helv. Chim. Acta* 1977, 60, 1801.

(9) Grassman, W.; Wünsch, E. *Chem. Ber.* 1958, 91, 499.

(10) Kovacs, J.; Kovacs, H. N.; Ballina, R. *J. Am. Chem. Soc.* 1963, 85, 1839.

(11) Schwarz, H.; Bumpus, F. M.; Page, I. H. *J. Am. Chem. Soc.* 1957, 79, 5697. Coleman, D. J. *Chem. Soc. C* 1951, 2294.

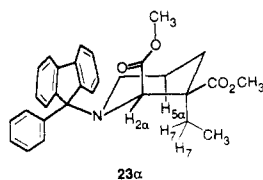


Figure 1. Conformational representation of dimethyl (2*S*,3*R*)-3-ethyl-1-(9-phenylfluoren-9-yl)hexahydroquinolininate (**23α**).

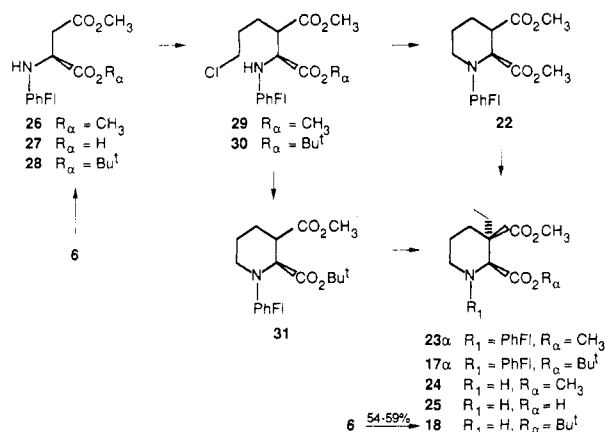
Although both routes shown in Scheme III are distinct improvements over the original process from asparagine (1), they clearly leave room for further improvement. The most effective place for such improvement would be in the mono-*N*-alkylation of aspartate, which proceeds in both routes in yields of 60–73% and involves a demanding purification. Since deprotonation of a suitably substituted aspartate can proceed at C-3 without any loss of configurational integrity at C-2,^{4d,6b,7} we considered the possible advantages of inverting the sequence by C-alkylating first and then closing the piperidine ring by *N*-alkylation.

Thus, the tetrahydroquinolininate **18** could be made by C-alkylating the enolate of the β -ester with a three-carbon bis-electrophile followed by an intramolecular *N*-alkylation. Regeneration of the enolate and quenching with ethyl iodide would then produce the desired protected hexahydroquinolininate in a stereospecific fashion. In practice two different routes to **18** were developed. Protection of the primary amine of **15** with 9-PhFBr gave **26** in 93% yield. Attempted alkylation of 9-PhF aspartate **26** using LDA (100 mol %)/THF/−78 °C followed by quenching with 1-bromo-3-chloropropane gave only educt. Use of the more potent electrophile, 3-chloropropyl triflate, yielded the desired monoalkylated product **29** as a 6/1 mixture of diastereomers. It was not necessary to separate the diastereomers since the C-3 stereogenic center would be set in the proper orientation in a subsequent step. Ring closure of **29** to the hexahydroquinolininate **22** proceeded in quantitative yield by refluxing **29** with NaI in acetonitrile. This mixture of diastereomers (8/1), **22**, was then deprotonated with LDA and quenched with ethyl iodide to give primarily **23α** (ratio α/β , 93/1), which was easily obtained by silica gel chromatography. With use of the identical procedure outlined previously, **23α** was converted to **24** (shown to be enantiomerically pure by diastereomer formation with 1-phenylethyl isocyanate) and then, via selective copper(II)-assisted hydrolysis to **25** and reesterification with *O*-*tert*-butyl-*N,N'*-diisopropylisourea, to the target hexahydroquinolininate **18**.

The high diastereoselectivity obtained in the alkylation of **22** to yield primarily **23α** is undoubtedly due to the electrophile, ethyl iodide, approaching the less-hindered face opposite the axial C-2 methoxycarbonyl group.^{4d,6b} The stereochemistry of **23α** was rigorously established by COSY and NOESY experiments. In particular, the NOE effects between H-5 α /H-7 and H-2 α /H-7 proved the indicated configuration and conformation, as shown in Figure 1.

It also proved possible to differentiate the two carboxyl groups of L-aspartic acid early in the synthesis without a nitrogen protection/deprotection step and then to convert this derivative to **18** using the aforementioned methodology. Protection of the α -carboxyl group of β -methyl ester **14** with TMSBr or TMSCl followed by in situ amino protection with 9-PhFBr yielded **27** in 92% yield following a methanolic workup to cleave the TMS ester. Although several steps are required, all transformations are carried out in the same vessel. α -Esterification of **27** with *O*-*tert*-butyl-*N,N'*-diisopropylisourea yielded diester **28**,

Scheme IV. Synthesis of Hexahydroquinolinates from L-Aspartate via Initial C-Alkylation Followed by Intramolecular N-Alkylation



which was then converted to **18** by the same methodology used in the conversion of **26** to **24**. No significant difference in the diastereoselectivity of the alkylation reaction of **31** to **17** vs **22** to **23** was noted. Therefore, α -*tert*-butyl and α -methyl ester impart the same effect in the alkylation of these hexahydroquinolinates. The entire sequence as outlined in Scheme IV from L-aspartic acid (**6**) to α -*tert*-butyl β -methyl diester **18** proceeds in 54% yield via **22** and 59% yield via **31**. Both routes are similar, differing only in the stage at which the α -*tert*-butyl ester is introduced.

Synthesis of (+)-Vincamine from 18. *N*-Alkylation of either **24** or **18** with tryptophyl bromide¹³ yielded **32** and **33**, respectively, in high yields. However, alkylation of the α -amino acid **25** with tryptophyl bromide gave at best 28% of the desired tertiary amino acid **34**. Efforts to selectively hydrolyze the α -methyl ester of **32** to give acid **34** failed, and copper-assisted hydrolysis of this α -tertiary amine methyl ester caused extensive decomposition.

These failures to hydrolyze the α -methyl ester of **32** selectively led us to attempt direct formation of the indoloquinolizines **10** and **35** by heating dimethyl ester **32** in phenylphosphonic dichloride. The idea was to effect nucleophilic cleavage of the α -ester to acid **34**, which would then undergo decarbonylation to iminium ion and cyclization to **10** and **35**. In practice, a 49% yield of **10** and **35** (1/2 ratio) resulted along with 34% of recovered dimethyl ester **32**. Addition of salts such as lithium chloride, sodium iodide, or pyridine hydrochloride gave no improvement.

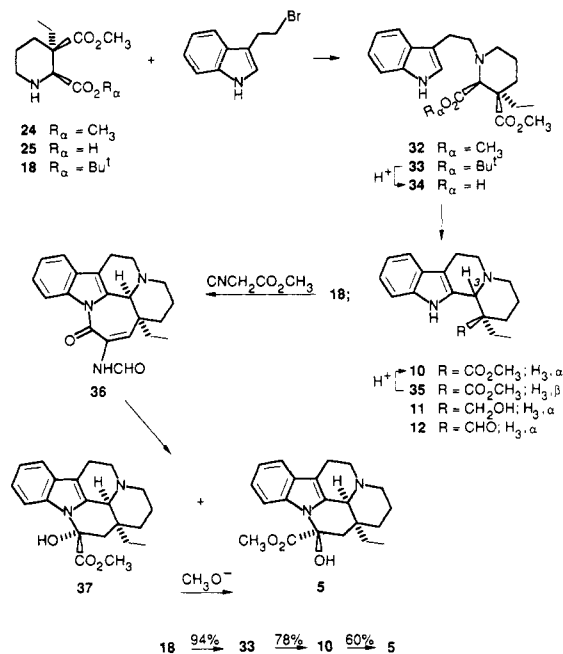
The α -*tert*-butyl ester of tryptamine derivative **33** was hydrolyzed by using HOAc/*i*PrOH/H₂O¹⁴ to yield the acid **34**. Heating the crude acid in PhPOCl₂ yielded a 5.7/1 mixture of **35** and **10**. Since the α -isomer was needed for the synthesis, **35**·HCl was equilibrated to a 3.2/1 mixture of **10**/**35** in 93% yield by being refluxed in trifluoroacetic acid for 18 h. This efficient recycling of the undesired β -epimer **35** allows ready access to optically pure (−)-**10**.

With use of the same procedure as that reported to convert (±)-**10** to (±)-vincamine,^{4b} (−)-**10** was transformed into optically pure (+)-vincamine (**5**) as shown in Scheme V. Our apprehension about the configurational stability of aldehyde **12**^{6b,8} was indeed confirmed when we sought to purify it by silica gel chromatography. Under alkaline conditions, however, **12** is stable. Thus heating a solution of **12** in DMSO containing 100 mol % of triethylamine at 60 °C for 3 h caused no change in optical rotation.

(13) Neumeyer, J. L.; Moyer, U. V.; Leonard, J. E. *J. Med. Chem.* **1969**, *12*, 450.

(14) Johansen, J. E.; Christie, B. D.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 4914.

Scheme V. Conversion of Hexahydroquinolinates via Indoloquinolizine 10 to (+)-Vincamine (5)



Therefore, the crude aldehyde was directly converted to a 7/1 mixture of (+)-vincamine and epivincamine as described for racemic material.^{4b} This mixture of isomers can be quantitatively converted to pure (+)-vincamine by treatment with NaOMe/MeOH ¹⁵ or $\text{Na}_2\text{CO}_3/\text{MeOH}$.^{4b} The overall yield from hexahydroquinolinate 18 to (+)-vincamine (5) was 44%.

The configurational integrity of the intermediates was established by converting the synthetic (+)-vincamine to the (\pm)- and (+)-methyl mandelate esters of apovincamine.^{4d} Examination of the ^1H NMR spectra, calibrated by doping experiments, revealed the synthetic material to be >99% optically pure.

In summary, a synthesis of (+)-vincamine has been accomplished in 24–26% overall yield. The process proceeds from L-aspartic acid (6) to 18 via hexahydroquinolinates 22 or 31 as depicted in Scheme IV. Application of the C-alkylation of aspartate 26 or 28 followed by an intramolecular N-alkylation to give 22 or 31 dramatically simplifies and improves the synthesis of optically pure hexahydroquinolinates compared to the route in which the amine is propylated first (Scheme III). Subsequent conversion of 18 to (+)-vincamine utilizes a high-yielding intramolecular iminium ion cyclization to convert 34 to 10, which is then taken on to (+)-vincamine by using established methodology.

Experimental Section

General. Tetrahydrofuran (THF) was distilled from sodium/benzophenone; diisopropylamine, acetonitrile, dichloromethane, pyridine, and *tert*-butyl alcohol were distilled from CaH_2 ; chloroform was distilled from P_2O_5 ; and methanol and ethanol were distilled from Mg. Potassium hexamethyldisilazide (KHMDS) in toluene was obtained from Callery Chemical. All reactions were carried out under N_2 , and final organic solutions in the isolations were dried over Na_2SO_4 and rotary-evaporated in vacuum. Melting points are uncorrected. ^1H NMR and IR spectra were determined in CDCl_3 , unless otherwise stated; NMR shifts are expressed in ppm downfield from internal tetra-

methylsilane and coupling constants (J) are in hertz. Column chromatography was performed with 230–400-mesh silica gel. Elemental analyses were performed by the Analytical Laboratory, College of Chemistry, University of California, Berkeley, CA.

L-Aspartic Acid β -Methyl Ester (14). A. By Selective Esterification of L-Aspartic Acid (6). To a stirred suspension of L-aspartic acid (6; 40 g, 0.3 mol) in dry MeOH (100 mL) was added acetyl chloride (33.4 g, 0.42 mol) in MeOH (100 mL), both components were premixed at 5 °C and stirred in an ice bath for 30 min) at 8–10 °C. After 3 h the ice bath was removed and stirring continued for 15 h; then the solution was poured into Et_2O (600 mL) and cooled for 2 h. The precipitate was collected and the mother liquor evaporated to yield more product after addition of MeOH (50 mL) and Et_2O (70 mL); combined yield of 14-HCl, 53 g, 77%, mp 191–193 °C (lit.¹¹ mp 190 °C). 14-HCl and propylene oxide (75 mL) were refluxed in dry EtOH (225 mL) for 6 h to liberate the free amino acid. After the mixture was cooled, the precipitate was separated and the mother liquors were concentrated to give amino acid 14 in a total yield of 91%: mp 194–195 °C; ^1H NMR ($\text{MeOH}-d_4$) δ 2.8 (dd, 1 H, $J = 17.5, 10.0$, HC-3), 3.02 (dd, 1 H, $J = 17.5, 5.0$, HC-3), 3.7 (s, 3 H, CH_3O), 3.85 (dd, 1 H, $J = 10.0, 5.0$, HC-2). Anal. Calcd for $\text{C}_8\text{H}_9\text{NO}_4$: C, 40.8; H, 6.2; N, 9.5. Found: C, 40.7; H, 6.0; N, 9.5.

B. By Selective Hydrolysis of Dimethyl L-Aspartate Hydrochloride (15). Dimethyl ester hydrochloride 15 (3.95 g, 20 mmol) and $\text{CuCO}_3\cdot\text{Cu}(\text{OH})_2$ (22.1 g, 100 mmol) were stirred in a mixture of EtOH (150 mL) and H_2O (525 mL) at 70 °C for 2 h. After the mixture was cooled to room temperature, excess H_2S was passed through the reaction mixture and it was filtered through Celite. After addition of H_2S and filtering the solution for a second time, the filtrate was evaporated to leave 3.60 g (98%) of 14-HCl, mp 190–191 °C, identical with material prepared by process A.

Dimethyl L-Aspartate Hydrochloride (15). Thionyl chloride (16.7 g, 0.14 mol) was added dropwise to a suspension of L-aspartic acid (6; 13.3 g, 0.10 mol) in methanol (75 mL) at 0 °C. The bath was removed and the solution was allowed to stir at room temperature for 45 h and then concentrated. The residual oil was triturated with ether and the resulting white crystalline solid was filtered, washed with cold ether, and dried to give 19.4 g (98%) of 15: mp 114–115 °C (lit.⁹ mp 116–117 °C); ^1H NMR (D_2O) δ 3.18 (t, 2 H, CH_2 , $J = 5$), 3.67 (s, 3 H, $\beta\text{-OCH}_3$), 3.85 (s, 3 H, $\alpha\text{-OCH}_3$), 4.51 (dd, 1 H, CH, $J = 5.7, 4.9$).

α -*tert*-Butyl β -Methyl (2*S*,3*R*)-3-Ethyl-1-(9-phenylfluoren-9-yl)hexahydroquinolinate (17 α) and α -*tert*-Butyl β -Methyl (2*S*,3*S*)-3-Ethyl-1-(9-phenylfluoren-9-yl)hexahydroquinolinate (17 β). To a solution of diisopropylamine (5.25 mL, 37.5 mmol) in THF (200 mL) was added *n*-BuLi (22.6 mL, 1.54 M in hexanes) at –78 °C. After being stirred at 0 °C for 30 min, the mixture was recooled to –78 °C and a solution of 31 (12.0 g, 24.8 mmol, as a mixture of diastereomers) was added dropwise. After 30 min, ethyl iodide (15.6 g, 100 mmol) was added and stirring continued for 150 min. The cold reaction mixture was added to Et_2O (2 L) and 0.5 M H_3PO_4 (500 mL) and the aqueous phase was extracted with Et_2O (2 \times 1 L). The combined organic extracts were dried and evaporated, and the residue was purified by radial chromatography (hexane/ EtOAc , 12/1) to leave 17 α (12.0 g, 95%) and 17 β (140 mg, 1%).

17 α : mp 172–173 °C; $[\alpha]_D^{23} -386^\circ$ (c 1.0, CHCl_3); IR 2980, 1730 cm^{-1} ; ^1H NMR δ 7.72–7.16 (m, 13 H), 3.56 (td, 1 H, $J = 11.7, 4.0$), 3.52 (s, 1 H), 3.49 (s, 3 H), 3.13 (br d, 1 H, $J = 11.7$), 2.56 (m, 1 H), 2.38 (m, 2 H), 2.04 (m, 1 H), 1.84 (m, 1 H), 1.55 (m, 1 H), 0.9 (s, 9 H), 0.87 (t, 3 H, $J = 7.5$). Anal. Calcd for $\text{C}_{33}\text{H}_{37}\text{NO}_4$: C, 77.5; H, 7.3; N, 2.7. Found: C, 77.6; H, 7.4; N, 2.7.

17 β : mp 151–152 °C; ^1H NMR δ 7.78–7.10 (m, 13 H), 3.90 (s, 3 H), 3.86 (s, 1 H), 3.85–3.72 (m, 1 H), 3.03 (m, 1 H), 2.2–1.0 (m, 6 H), 0.95 (s, 9 H), 0.67 (t, 3 H, $J = 7.5$).

α -*tert*-Butyl β -Methyl (2*S*,3*R*)-3-Ethylhexahydroquinolinate (18). To a solution of α -hydrogen β -methyl (2*S*,3*R*)-3-ethylhexahydroquinolinate (25; 120 mg, 0.56 mmol, obtained by $\text{CuCO}_3\cdot\text{Cu}(\text{OH})_2$ hydrolysis of dimethyl ester 24 and containing 15% of the 2*R* diastereomer) in *t*-BuOH (3 mL) was added *O*-*tert*-butyl-*N,N'*-diisopropylisourea (440 mg, 2.2 mmol) at room temperature. After 90 min, H_2O (0.8 mL) was added and stirring continued for 20 min; then the reaction mixture was evaporated and the residue was purified by radial chromatography

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(CH₂Cl₂/MeOH, 97/3) to give 135 mg (89%) of (2*S*,3*R*)-18, which contained 15% of the diastereomeric (2*R*,3*R*)-18. The corresponding ¹H NMR signals for the 2*R*,3*R* isomer are identical with those of (2*S*,3*S*)-18.

Dimethyl (2*S*,3*R*)-1-(9-Phenylfluoren-9-yl)hexahydroquinolinolate (cis-22) and Dimethyl (2*S*,3*S*)-1-(9-Phenylfluoren-9-yl)hexahydroquinolinolate (trans-22). To crude 3-(chloropropyl)aspartate **29** (160 mg) in refluxing acetonitrile (25 mL) was added NaHCO₃ (500 mg). After 10 min, NaI (300 mg, 2.0 mmol) was added and refluxing was continued for 36 h. The cooled reaction mixture was evaporated, CHCl₃ (20 mL) was added, and the mixture was filtered. The filtrate was evaporated and the residue was added to CH₃OH/H₂O (2 mL, 1/1). Filtration and washing of the resulting solid with CH₃OH (1 mL) gave 90 mg of pure *trans*-22. The combined filtrate and washings were evaporated and the residue chromatographed (hexane/EtOAc, 9/1); total yield (from **26**) of 95 mg of *trans*-22 (70%), 12 mg of *cis*-22 (9%), and 13 mg of recovered **26** present in the crude **29**.

trans-22: ¹H NMR δ 7.75–7.6 (m, 2 H), 7.4–7.0 (m, 1 H), 3.98 (s, 1 H), 3.84 (s, 3 H), 3.57 (td, 1 H, *J* = 12.5, 2.5), 3.08 (br d, 1 H, *J* = 9), 2.9 (s, 3 H), 2.54 (m, 1 H), 2.09 (br d, 1 H, *J* = 13), 2.01 (m, 1 H), 1.83 (m, 1 H), 1.60 (m, 1 H). Anal. Calcd for C₂₈H₂₇NO₄: C, 76.2; H, 6.2; N, 3.2. Found: C, 75.9; H, 6.1; N, 3.1.

cis-22: ¹H NMR δ 7.73–7.61 (m, 2 H), 7.42–7.16 (m, 11 H), 3.75 (d, 1 H, *J* = 4.7), 3.51 (s, 3 H), 3.49 (td, 1 H, *J* = 11.9, 2.9), 3.11 (br d, 1 H, *J* = 11.8), 2.89 (td, 1 H, *J* = 13, 4.5), 2.85 (s, 3 H), 2.18 (ddd, 1 H, *J* = 26, 13, 4.7), 1.92 (br d, 1 H, *J* = 13), 1.78 (m, 2 H); HRMS calcd for C₂₈H₂₇NO₄ (M⁺), *m/z* 441.1831, found 441.1810.

Dimethyl (2*S*,3*R*)-3-Ethyl-1-(9-phenylfluoren-9-yl)hexahydroquinolinolate (23α) and Dimethyl (2*S*,3*S*)-3-Ethyl-1-(9-phenylfluoren-9-yl)hexahydroquinolinolate (23β). To a solution of diisopropylamine (5.25 mL, 37.5 mmol, 150 mol %) in THF (200 mL) was added *n*-BuLi (22.7 mL, 1.54 M in hexanes, 140 mol %) at -78 °C. After being stirred at 0 °C for 30 min, the mixture was again cooled to -78 °C, and a solution of diester pipercolate **22** (11.0 g, 25 mmol, as a diastereomeric mixture) in THF (100 mL) was added dropwise. After 30 min, ethyl iodide (15.6 g, 100 mmol) was added, stirring was continued for 150 min, and the cold reaction mixture was added to Et₂O (2 L) and 0.5 M H₃PO₄ (500 mL). The aqueous phase was extracted with Et₂O (2 × 1 L) and the combined, dried organic extracts were evaporated. The residue was chromatographed (hexane/EtOAc, 9/1) to leave 10.6 g (93%) of **23α**, 120 mg (1%) of **23β**, and 100 mg (0.9%) of unethylated intermediate **22**.

23α: [α]_D²⁰ -489° (*c* 0.4, CHCl₃); mp 152–154 °C; ¹H NMR δ 7.73–7.14 (m, 13 H, Ar), 3.51 (s, 1 H, H-2), 3.48 (s, 3 H, β-CH₃O), 3.40 (td, 1 H, H-6a, *J* = 12.2, 2.5), 3.13 (br d, 1 H, H-6e, *J* = 12), 2.74 (s, 3 H, α-CH₃O), 2.42 (td, 1 H, H-4a, *J* = 12.2, 3.2), 2.25 (dq, 2 H, CH₂CH₃, *J* = 7.5, 2.7), 1.95–1.85 (m, 1 H, H-5a), 1.87–1.80 (br d, 1 H, H-4e, *J* = 12), 1.62 (br d, 1 H, H-5e, *J* = 12), 0.83 (t, 3 H, CH₃CH₂, *J* = 7.5). Anal. Calcd for C₃₀H₃₁NO₄: C, 76.7; H, 6.7; N, 3.0. Found: C, 76.6; H, 6.6; N, 3.0.

23β: ¹H NMR δ 7.72–7.53 (m, 2 H), 7.41–7.17 (m, 11 H), 3.86 (s, 3 H), 3.84 (s, 1 H), 3.65 (td, 1 H, *J* = 10.5, 3), 3.03 (m, 1 H), 2.88 (s, 3 H), 2.2 (m, 3 H), 1.65 (m, 2 H), 1.25 (m, 1 H), 0.63 (t, 3 H, *J* = 6.5).

Dimethyl (2*S*,3*R*)-3-Ethylhexahydroquinolinolate (24). A mixture of **23α** (4.69 g, 10 mmol) and 10% Pd/C (2.35 g) in acetic acid (250 mL) was stirred under a balloon of H₂ for 150 min at room temperature. The reaction mixture was filtered through Celite, the filtrate was evaporated, and the residue was distributed between H₂O (200 mL) and Et₂O (200 mL). The aqueous layer was basified with NaHCO₃ and extracted with CHCl₃ (3 × 200 mL), and the combined organic layers were dried and evaporated to leave 2.25 g (98%) of **24** as a colorless liquid: ¹H NMR δ 3.73 (s, 3 H), 3.67 (s, 3 H), 3.54 (s, 1 H), 2.76 (quin, 1 H, *J* = 6), 2.70 (quin, 1 H, *J* = 6), 2.08 (quin, 1 H, *J* = 6.5), 1.97 (br s, 1 H), 1.92 (td, 1 H, *J* = 19.5, 7.5), 1.93 (td, 1 H, *J* = 19.5, 7.5), 1.66 (m, 1 H), 1.57 (quin, 2 H, *J* = 6), 0.86 (t, 3 H, *J* = 7.5). Anal. Calcd for C₁₁H₁₉NO₄: C, 57.6; H, 8.4; N, 6.1. Found: C, 57.8; H, 8.4; N, 6.3.

α-Hydrogen β-Methyl (2*S*,3*R*)-3-Ethylhexahydroquinolinolate (25). A mixture of dimethyl ester **24** (2.29 g, 10 mmol) and CuCO₃·Cu(OH)₂ (11.0 g, 50 mmol) was stirred in EtOH

(150 mL) and H₂O (525 mL) for 3 days at 70 °C. After the mixture was cooled to room temperature, an excess of H₂S was passed into the reaction mixture. This was filtered through Celite, evaporated and, after addition of EtOH (50 mL), again filtered. The filtrate was evaporated, and the residue was heated in refluxing toluene, using a Dean-Stark trap, and again evaporated (drying was repeated 2×) to leave 2.0 g (93%) of **25** shown by NMR to contain 15% of the 2*R*,3*R* diastereomer: mp > 155 °C dec; ¹H NMR (methanol-*d*₄) δ 3.90 (s, 0.15 × 1 H), 3.74 (s, 0.15 × 3 H), 3.71 (s, 0.85 × 3 H), 3.63 (s, 0.85 × 1 H), 3.12 (m, 1 H), 2.95 (m, 1 H), 2.10–1.87 (m, 2 H), 1.85–1.60 (m, 2 H), 0.96 (t, 0.15 × 3 H, *J* = 7.5), 0.96 (t, 0.85 × 3 H, *J* = 7.5). Anal. Calcd for C₁₀H₁₇NO₄: C, 55.8; H, 7.9; N, 6.5. Found: C, 55.7; H, 7.8; N, 6.8.

Dimethyl L-N-(9-Phenylfluoren-9-yl)aspartate (26). To a stirred suspension of dimethyl ester hydrochloride **15** (10 g, 50.3 mmol) in dry CH₃CN (80 mL) were added anhydrous Pb(NO₃)₂ (13.8 g, 41.7 mmol) and anhydrous K₃PO₄ (22.2 g, 105 mmol), followed by 9-bromo-9-phenylfluorene (20.6 g, 63.5 mmol) in CH₃CN (40 mL) at room temperature. The suspension was stirred for 24 h; then the reaction mixture was filtered through Celite and the inorganic residue was washed with CHCl₃. The combined filtrate and washings were evaporated and the residue was partitioned between 5% aqueous citric acid (200 mL) and Et₂O (400 mL). The dried organic layer was evaporated and the thick yellow residue was purified by MPLC (silica gel, hexane/EtOAc, 8/1) to leave **26**, 18.9 g, 93% yield, as a colorless oil: ¹H NMR δ 7.70–7.16 (m, 13 H), 3.65 (s, 3 H), 3.34 (s, 3 H), 3.01 (m, 1 H), 2.52 (dd, 1 H, *J* = 15, 6.8), 2.35 (dd, 1 H, *J* = 15, 5.4). Anal. Calcd for C₂₅H₂₃NO₄: C, 74.8; H, 5.8; N, 3.5. Found: C, 74.7; H, 5.7; N, 3.5.

L-N-(9-Phenylfluoren-9-yl)aspartic Acid β-Methyl Ester (27). To a suspension of **14** (2.2 g, 15 mmol) in dry CHCl₃ (30 mL) in a 100-mL Morton flask, equipped with a mechanical stirrer, was added TMSCl (2.03 mL, 16 mmol) or TMSBr (2.24 mL, 17 mmol) at room temperature. After 2 h, Et₃N (4.46 mL, 32 mmol) and, after another 15 min, Pb(NO₃)₂ (3.3 g, 10 mmol) and 9-bromo-9-phenylfluorene (6.42 g, 20 mmol) in dry CHCl₃ (30 mL) were added. The mixture was stirred vigorously for 3 days; then MeOH (7 mL) was added and after 15 min the reaction mixture was filtered and evaporated. To the residue were added 5% aqueous citric acid (80 mL) and Et₂O (80 mL), the aqueous layer was extracted with Et₂O (3 × 50 mL), and the combined organic extract was washed with brine (20 mL), dried, and concentrated to 10 mL. After cooling, the precipitate was collected and washed with isopropyl ether (10 mL) and the mother liquor was concentrated to yield a second crop. The mother liquor was then diluted with Et₂O (10 mL) and extracted with saturated NaHCO₃ solution (5 × 20 mL); the bicarbonate extracts were acidified with concentrated H₃PO₄ to pH 5 and extracted with Et₂O (2 × 20 mL), and the dried organic layer was evaporated to give a third crop: total yield, 5.3 g, 92%; mp 160–161 °C; ¹H NMR δ 7.76–7.22 (m, 13 H), 3.65 (s, 3 H), 2.87 (t, 1 H, *J* = 3.9), 2.77 (dd, 1 H, *J* = 17.3, 3.8), 1.95 (dd, 1 H, *J* = 17.3, 3.8). Anal. Calcd for C₂₄H₂₁NO₄: C, 74.4; H, 5.5; N, 3.6. Found: C, 74.4; H, 5.5; N, 3.6.

α-tert-Butyl β-Methyl L-N-(9-Phenylfluoren-9-yl)aspartate (28). To a stirred solution of β-methyl ester **27** (11.6 g, 30 mmol) in CH₂Cl₂ (400 mL) was added *O*-tert-butyl-*N,N'*-diisopropylisourea (22 mL, 90 mmol)¹² in CH₂Cl₂ (100 mL) at room temperature. The reaction mixture was stirred at room temperature for 44 h; then H₂O (50 mL) was added and stirring was continued for 1 h. After filtration, the filtrate was washed with saturated NaHCO₃ (100 mL) and water (100 mL), dried, and evaporated. Chromatography (silica gel, hexane/EtOAc, 10/1) gave 11.2 g (84%) of **28** as a colorless solid: mp 75–76 °C; ¹H NMR δ 7.71–7.17 (m, 13 H), 3.65 (s, 3 H), 2.87 (t, 1 H, *J* = 5.6), 2.87 (t, 1 H, *J* = 5.6), 2.46 (dd, 1 H, *J* = 14.8, 5.8), 2.30 (dd, 1 H, *J* = 14.8, 5.6), 1.23 (s, 9 H). Anal. Calcd for C₂₈H₂₉NO₄: C, 75.8; H, 6.6; N, 3.2. Found: C, 76.0; H, 6.6; N, 3.1.

3-Chloropropyl Trifluoromethanesulfonate. To a stirred solution of 3-chloropropanol (4.73 g, 4.2 mL, 5 mmol) in CH₂Cl₂ (50 mL) was added *n*-BuLi (36.7 mL, 110 m%, 1.5 M in hexanes) dropwise at -78 °C. After 30 min, triflic anhydride (14.8 g, 52.5 mol, 105 mol %) was added, stirring was continued at -78 °C for 40 min, then hexane (100 mL) was added, the dry ice bath was removed, the precipitate was filtered off, and the filtrate was evaporated to leave 10.2 g of crude product. A cooled mixture

of hexane (20 mL) and saturated aqueous NaHCO₃ solution (3 mL) was added, the separated, dried organic layer was evaporated, and the residue was distilled (bp 50 °C, 0.2 mbar, Kugelrohr) to give 3-chloropropyl triflate (7.0 g, 62%): ¹H NMR δ 4.72 (t, 2 H, *J* = 6), 3.68 (t, 2 H, *J* = 6), 2.29 (quin, 2 H, *J* = 6). Anal. Calcd for C₄H₆ClF₃O₃S: C, 21.2; H, 2.7; Cl, 15.7. Found: C, 21.1; H, 2.8; Cl, 15.9.

Dimethyl L-3-(3-Chloropropyl)-N-(9-phenylfluoren-9-yl)aspartate (29). To a stirred solution of KHMDS (10.8 mL, 130 mol %, 0.6 M in toluene) in THF (60 mL) was added **26** (2.05 g, 5.1 mmol) dissolved in THF (7 mL), dropwise, at -78 °C. The pale yellow solution was stirred at -78 °C for 45 min; then 3-chloropropyl trifluoromethanesulfonate (2.26 g, 10 mmol, 200 mol %) was added. The reaction mixture was stirred for 1 h and, after addition of more 3-chloropropyl triflate (0.56 g, 2.5 mmol, 50 mol %) it was stirred for 30 min at -78 °C. The reaction mixture was added to Et₂O (300 mL) and 0.5 M H₃PO₄ (50 mL), the water layer was extracted with Et₂O (2 × 50 mL), and the combined organic layers were dried and evaporated to leave 2.0 g of crude alkylated **29** as a mixture of diastereomers (6/1). Purification of 180 mg by chromatography (CH₂Cl₂/hexane, 8/5) gave 45 mg of pure **29**: ¹H NMR δ 7.7–7.6 (m, 2 H), 7.4–7.1 (m, 11 H), 3.75 (s, 1/7 × 3 H), 3.51 (s, 6/7 × 3 H), 3.48–3.44 (m, 2 H), 3.40–3.38 (m, 1 H), 3.27 (s, 6/7 × 3 H), 3.17 s, 1/7 × 3 H), 2.86 (d, 1/7 × 1 H, *J* = 8.7), 2.8 (d, 6/7 × 1 H, *J* = 6.3), 2.58–2.51 (m, 1/7 × 1 H), 2.48–2.41 (m, 6/7 × 1 H), 1.98–1.9 (m, 1 H), 1.6–1.37 (m, 3 H).

α-tert-Butyl β-Methyl L-3-(3-Chloropropyl)-N-(9-phenylfluoren-9-yl)aspartate (30). To a solution of KHMDS (10.4 mL, 6.25 mmol, 0.6 M in toluene) in THF (60 mL) was added **28** (2.21 g, 5 mmol) dissolved in THF (7 mL), dropwise under nitrogen. After stirring at -78 °C for 45 min, 3-chloropropyl triflate (2.82 g, 12.5 mmol) was added and the reaction mixture was stirred for 3 h at -78 °C. It was then added to a mixture of Et₂O (300 mL) and 0.5 M H₃PO₄ (50 mL), the water layer was extracted with Et₂O (2 × 50 mL), the combined organic layer was dried and evaporated, and the residue was separated by radial chromatography (CH₂Cl₂/hexane, 3/2) to give 1.96 g (76%) of **30** as an oily mixture (4/1) of diastereomers and 350 mg (16%) of recovered **28**: ¹H NMR δ 7.66–7.17 (m, 13 H), 3.65 (s, 1/5 × 3 H), 3.52 (s, 4/5 × 3 H), 3.50 (m, 2 H), 3.25 (br s, 1 H), 2.81 (br d, 1/5 × 1 H, *J* = 4.5), 2.76 (br d, 4/5 × 1 H, *J* = 4.7), 2.42 (m, 1 H), 1.75 (m, 1 H), 1.61 (m, 1 H), 1.50 (m, 1 H), 1.20 (s, 4/5 × 9 H), 1.15 (s, 1/5 × 9 H).

α-tert-Butyl β-Methyl (2S,3R)-1-(9-Phenylfluoren-9-yl)hexahydroquinolinolate (31). The diastereomeric mixture of **30** (520 mg, 1.0 mmol) and NaHCO₃ (750 mg) was stirred in boiling acetonitrile (50 mL). After 10 min, NaI (450 mg) was added and refluxing continued for 48 h. After being cooled to room temperature, the acetonitrile was evaporated and the inorganic salts were separated by filtration after trituration with CHCl₃ (30 mL). The filtrate was evaporated and the residue purified by MPLC (hexane/EtOAc, 12/1) to give 391 mg (81%) of *trans*-**31** and 83 mg (17%) of *cis*-**31** (containing 20% *trans*-**31**), for a combined yield of 98%.

trans-31: mp 184 °C; ¹H NMR δ 7.68–7.10 (m, 13 H), 3.88 (s, 1 H), 3.85 (s, 3 H), 3.78 (td, 1 H, *J* = 12, 3), 3.04 (br d, 1 H, *J* = 11.5), 2.56 (m, 1 H), 2.10 (br d, 1 H, *J* = 13), 1.93 (m, 1 H), 1.73 (m, 1 H), 1.58 (br d, 1 H, *J* = 13), 1.02 (s, 9 H). Anal. Calcd for C₃₁H₃₃NO₄: C, 77.0; H, 6.9; N, 2.9. Found: C, 77.2; H, 6.8; N, 2.9.

cis-31: ¹H NMR δ 7.70–7.17 (m, 13 H), 3.78 (d, 1 H, *J* = 4.8), 3.66 (td, 1 H, *J* = 12, 3), 3.52 (s, 3 H), 3.07 (br d, 1 H, *J* = 11), 2.87 (td, 1 H, *J* = 13, 4.5), 2.05 (m, 1 H), 1.75 (m, 1 H), 1.70 (m, 1 H), 0.97 (s, 9 H).

Dimethyl (2S,3R)-3-Ethyl-1-[2-(3-indolyl)ethyl]hexahydroquinolinolate (32). A mixture of tryptophyl bromide (2.92 g, 13.0 mmol),¹³ dimethyl ester **24** (2.30 g, 10.0 mmol), NaHCO₃ (2.52 g), and CH₃CN (13 mL) was refluxed for 24 h, then diluted with water (25 mL), and extracted with EtOAc (3 × 25 mL). The EtOAc extracts were dried and evaporated and the residue was chromatographed (hexane/CH₂Cl₂/EtOAc, 6/3/1) to give 2.8 g (75%) of **32** as a yellow oil: ¹H NMR δ 8.10 (br s, 1 H), 7.61 (d, 1 H, *J* = 7.6), 7.33 (d, 1 H, *J* = 7.6), 7.24–7.10 (m, 2 H), 6.98 (d, 1 H, *J* = 2.0), 3.69 (s, 1 H), 3.66 (s, 3 H), 3.64 (s, 3 H), 3.02–2.69 (m, 5 H), 2.51 (m, 1 H), 2.21 (m, 1 H), 1.90–1.54 (m, 5 H), 0.72 (t, 3 H, *J* = 7.5). Anal. Calcd for C₂₁H₂₈N₂O₄: C, 67.7; H, 7.6;

N, 7.5. Found: C, 67.6; H, 7.5; N, 7.5.

α-tert-Butyl β-Methyl (2S,3R)-3-Ethyl-1-[2-(3-indolyl)ethyl]hexahydroquinolinolate (33). A mixture of **18** (848 mg, 3.13 mmol), tryptophyl bromide (872 mg, 3.91 mmol), and NaHCO₃ (787 mg, 9.38 mmol) in acetonitrile (3 mL) was vigorously stirred at 70 °C for 21 h. The solution was diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). Drying and evaporating left a residue, which was flash chromatographed (hexane/CH₂Cl₂/EtOAc, 6/3/1) on silica gel to yield a small amount of recovered bromide and 1.21 g (93%) of **33** as a heavy oil: [α]_D²⁵ -48° (c 1.0, CHCl₃); IR 3500, 2980, 1730 cm⁻¹; ¹H NMR δ 7.97 (br s, 1 H), 7.64 (dd, 1 H, *J* = 7.6, 0.4), 7.36 (d, 1 H, *J* = 7.8), 7.22–7.11 (m, 2 H), 7.02 (d, 1 H, *J* = 2.2), 3.65 (s, 3 H), 3.56 (s, 1 H), 3.07–1.5 (m, 12 H), 1.45 (s, 9 H), 0.71 (t, 3 H, *J* = 7.6). Anal. Calcd for C₂₄H₃₄N₂O₄: C, 69.5; H, 8.3; N, 6.8. Found: C, 69.5; H, 8.2; N, 6.7.

(1R,12bS)- and (1R,12bR)-1-Ethyl-1-(methoxycarbonyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizines (10 and 35). **A. From α-tert-Butyl β-Methyl Ester 33.** A solution of **33** (1.21 g, 2.92 mmol) in water (13.3 mL), 2-propanol (13.3 mL), and acetic acid (3.3 mL) was heated at 100 °C for 15 h. The solvent was evaporated, and to the residue of acid **34** was added PhPOCl₂ (10 mL). After being stirred at 100 °C for 15 min, the solution was cooled and then slowly added to saturated aqueous NaHCO₃ (25 mL). This mixture was adjusted to pH 9 by addition of solid K₂CO₃ and then extracted with ethyl acetate (3 × 35 mL). The combined organic extracts were dried and evaporated and the residue was flash chromatographed on silica gel (EtOAc/hexane, 1/1) to give, after treatment with methanolic HCl and evaporation, 752 mg (74%) of β-isomer **35-HCl** followed by 120 mg (13%) of α-isomer **10**.

35-HCl: mp 222–223 °C; IR 3460, 3170, 1820, 1800, 1725 cm⁻¹; ¹H NMR δ 8.55 (br s, 1 H), 7.46 (d, 1 H, *J* = 7.7), 7.32 (d, 1 H, *J* = 8.0), 7.26–7.09 (m, 2 H), 4.79 (br d, 1 H, *J* = 9.3), 3.95 (s, 3 H), 3.8–1.7 (m, 12 H), 0.83 (t, 3 H, *J* = 7.4). Anal. Calcd for C₁₉H₂₅N₂O₂Cl: C, 65.4; H, 7.2; N, 8.0. Found: C, 65.2; H, 7.2; N, 8.0.

10: mp 122–123 °C; [α]_D²⁵ -49.1° (c 1.0, CHCl₃); IR 3470, 2960, 2870, 2830, 2780, 1725 cm⁻¹; ¹H NMR δ 7.82 (br s, 1 H), 7.47 (d, 1 H, *J* = 7.3), 7.31 (d, 1 H, *J* = 8.3), 7.12 (m, 2 H), 4.06 (br s, 1 H), 3.71 (s, 3 H), 3.25–1.7 (m, 12 H), 0.92 (t, 3 H, *J* = 7.5). Anal. Calcd for C₁₉H₂₄N₂O₂: C, 73.1; H, 7.7; N, 9.0. Found: C, 72.9; H, 7.8; N, 8.9.

B. From Dimethyl Ester 32. A mixture of **32** (130 mg, 0.34 mmol) and PhPOCl₂ (5 mL) was submerged for 15 min in an oil bath preheated to, and maintained at, 165 °C. The reaction mixture was cooled to 0 °C, quenched with saturated aqueous NaHCO₃ (15 mL) adjusted to pH 7, and extracted with ethyl acetate (3 × 15 mL). Drying and evaporating the organic phase left a residue, which was chromatographed (EtOAc/hexane, 1/2) to give 53 mg, 49%, of the tetracycles **10** and **35** in a 1/2 ratio, and 44 mg, 34%, of recovered dimethyl ester **32**.

Equilibration of 35-HCl and 10. To **35-HCl** (350 mg, 1.0 mmol) was added trifluoroacetic acid (10 mL). The solution was refluxed for 18 h, cooled, and slowly added to saturated aqueous NaHCO₃. After neutralization, the pH was increased to 9 with solid K₂CO₃ and the solution was extracted with ethyl acetate (3 × 25 mL). The combined organic phase was dried and evaporated, and the residue was chromatographed (hexane/EtOAc, 1/1) to give, after treatment with methanolic HCl and evaporation, 80 mg (23%) of **42-HCl** and 223 mg (71%) of **10**.

(1R,12bS)-1-Ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-1-methanol (11). To a suspension of LiAlH₄ (0.2 g, 5.27 mmol) in THF (5 mL) was added a solution of **10** (1.48 g, 4.8 mmol) in THF (20 mL) at -70 °C. The reaction mixture was allowed to warm to room temperature over 90 min, then saturated aqueous Na₂SO₄ solution (20 mL) was added, and the filtrate was extracted with CH₂Cl₂ (3 × 25 mL). The combined, dried organic layers were evaporated and the residue was purified by radial chromatography (CH₂Cl₂/MeOH, 95/5) to give 1.3 g (96%) of pure alcohol **11**: [α]_D²⁰ -143° (c 1.0, CHCl₃); ¹H NMR data are in agreement with those reported.^{4b}

(1R,12bS)-1-Ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-1-carboxaldehyde (12). To a solution of alcohol **11** (1.29 g, 4.54 mmol) in DMSO (11 mL) and Et₃N (10 mL) was added at 20 °C a solution of SO₃·pyridine (2.38 g, 15 mmol) in

DMSO (11 mL). The mixture was stirred for 60 min, then ice water (70 mL) was added, and the solution was extracted with Et₂O (3 × 120 mL). The combined, dried organic layers were evaporated at room temperature to leave 1.5 g of crude **12**, contaminated with traces of DMSO and Et₃N: ¹H NMR data are in agreement with those reported.^{4b} [α]_D²⁰ -167° (c 1.0, CHCl₃), unchanged after stirring 3 h at room temperature and 2 h at 60 °C in DMSO.

(+)-**15,15a-Didehydro-15-formamido-D-homoeburnamin-14-one (36)**. To a solution of potassium *tert*-butoxide (1.48 g, 13.2 mmol) in THF (25 mL) was added freshly distilled methyl isocyanacetate (870 mg, 8.75 mmol) at 10 °C. The mixture was stirred for 10 min at 10 °C and then cooled to -78 °C before dropwise addition of 1.46 g of crude aldehyde **12** in THF (10 mL). After 1 h the temperature was raised to -50 °C and after another 30 min to -25 °C. The reaction mixture then was allowed to warm to 0 °C over 30 min, ice water (25 mL) was added, and the mixture was evaporated to leave 1.3 g of crude **36**: [α]_D²⁰ +159° (c 1.0, CHCl₃); ¹H NMR data are in agreement with those reported.^{4b}

(+)-**Vincamine (5)**. A solution of crude **36** (1.3 g, 3.72 mmol) in dry methanol/HCl, prepared by addition of 0.8 mL of acetyl chloride to 50 mL of methanol, was refluxed for 4 h. After being cooled to 15 °C, excess anhydrous Na₂CO₃ (2.35 g) was added, and the mixture was stirred for 30 min. Then the reaction medium was extracted with CH₂Cl₂ (3 × 25 mL) and the combined, dried organic layers were evaporated to leave crude vincamine (**5**) and epivincamine (**37**) as a 7/1 mixture of isomers. After separation by flash chromatography (CH₂Cl₂/MeOH, 97/3), **37** was converted to **5** with NaOCH₃/MeOH as reported:¹⁵ yield, 1.07 g, 81%; identical with an authentic sample by chromatography and ¹H NMR; mp 232–233 °C; [α]_D²⁰ +43° (c 0.8, pyridine) [lit.¹⁵ mp 234–235 °C; [α]_D²² +44° (c 1, pyridine)]. The yield of **5** from pure alcohol **11** was 72%; overall yield of **5** from **10**, 60%.

Determination of Enantiomeric Purity. Dimethyl L-Aspartate (15) and L-Aspartic Acid β -Methyl Ester (14). Conversion to *N*-(1-Phenylethyl)carbamoyl Derivatives. The β -methyl aspartates **14**, prepared either by selective esterification of aspartic acid or selective hydrolysis of the dimethyl ester, were converted to the dimethyl ester as described for the esterification of aspartic acid. The solid residue of dimethyl ester hydrochloride **15** (40 mg, 0.2 mmol) was dissolved in THF (2 mL), cooled to 0°, Et₃N (42 μ L, 0.3 mmol) and then (*S*)-1-phenylethyl isocyanate (44 mg, 0.3 mmol) were added, and the reaction mixture stirred for 30 min at 0 °C. After evaporation of the solvent, the residue was examined by NMR spectroscopy. Coupling also was carried out with (*R,S*)-1-phenylethyl isocyanate under the same conditions. For the 2*S*,2'*S* isomer: ¹H NMR δ 7.41–7.22 (m, 5 H), 5.61 (br d, 1 H, *J* = 8), 5.35 (br d, 1 H, *J* = 7), 4.81 (m, 1 H), 4.75 (m, 1 H), 3.66 (s, 3 H), 3.63 (s, 3H), 2.97 (dd, 1H, *J* = 17, 4.5), 2.79 (dd, 1H, *J* = 17, 4.5), 1.45 (d, 3H, *J* = 7). For the 2*S*,2'*R* isomer: ¹H NMR (diagnostic peaks) δ 3.69 (s, 3 H), 3.59 (s, 3 H). By doping experiments, the dimethyl L-aspartate from all sources was shown to be of >99% ee.

Dimethyl (2*S*,3*R*)-3-ethylhexahydroquinolinatate (24) was converted to the corresponding *N*-(1-phenylethyl)carbamoyl derivative by stirring a solution of **24** (23 mg, 0.1 mmol) in THF (0.5 mL) with (*S*)-1-phenylethyl isocyanate (22 mg, 0.15 mmol) at 0 °C. After complete consumption of **24** (30 min), the solvent was evaporated at room temperature and the residue examined by NMR at 500 MHz: ¹H NMR δ 7.35–7.24 (m, 5 H), 5.02 (m, 2 H), 4.91 (m, 1 H), 3.696 (s, 3 H), 3.667 (s, 3 H), 2.70 (m, 1 H), 2.0–1.6 (m, 3 H), 1.73 (q, 2 H, *J* = 7.5), 1.50 (d, 3 H, *J* = 6.8), 0.78 (t, 3 H, *J* = 7.5). (*R,S*)-1-Phenylethyl isocyanate was coupled to **24** under the same conditions: ¹H NMR of the 2*S*,2'*S*,3*R* isomer (diagnostic signals only): δ 3.690 (s, 3 H) 3.661 (s, 3 H). Doping experiments established **24** to be of >99% ee.

(+)-**Vincamine (5)** was converted to (+)-**apovincamine (4)** as described.¹⁶ The apovincamine was hydrolyzed and converted to its ester with methyl (*S*)- and (*R,S*)-mandelate.^{4d,17} By appropriate NMR doping experiments, the enantiomeric excess was found to be >99%.

Acknowledgment. P.G. thanks the Deutsche Forschungsgemeinschaft for a Fellowship. P.L.F. was the recipient of University of California Reagents and Eastman Kodak Fellowships, and M.Y.C.-M. was a President's Undergraduate Fellow.

Registry No. 4 (methyl (*S*)-mandelate ester), 95407-52-6; 4 (methyl (*R*)-mandelate ester), 95420-14-7; 5, 1617-90-9; 6, 56-84-8; 10, 126371-55-9; 11, 114420-88-1; 12, 51152-47-7; 14, 2177-62-0; 14-HCl, 16856-13-6; 15, 32213-95-9; 15 (*N*-(1*S*)-phenylethylcarbamoyl derivative), 126218-16-4; 15 (*N*-(1*R*)-phenylethylcarbamoyl derivative), 126218-17-5; 16, 104072-52-8; 17 α , 126217-97-8; 17 β , 126217-98-9; 18, 126218-01-7; (2*S*,3*S*)-18, 126218-20-0; (2*R*,3*R*)-18, 126218-24-4; 19, 126218-21-1; 20, 126218-22-2; 21, 126218-23-3; *cis*-22, 126218-02-8; *trans*-22, 126218-03-9; 23 α , 126218-04-0; 23 β , 126218-05-1; 24, 126217-99-0; 24 (*N*-(1*S*)-phenylethylcarbamoyl derivative), 126218-18-6; 24 (*N*-(1*R*)-phenylethylcarbamoyl derivative), 126218-19-7; 25, 126218-00-6; (2*R*)-25, 126218-25-5; 26, 120230-62-8; 27, 126218-06-2; 28, 120230-41-3; 29 (isomer 1), 126218-07-3; 29 (isomer 2), 126218-08-4; 30 (isomer 1), 126218-09-5; 30 (isomer 2), 126218-10-8; *cis*-31, 126218-12-0; *trans*-31, 126218-11-9; 32, 126218-13-1; 33, 126218-14-2; 34, 126218-15-3; 35, 126373-26-0; 35-HCl, 126371-54-8; 36, 112965-87-4; 37, 6835-99-0; Cl(CH₂)₃OH, 627-30-5; Cl(C-H₂)₃OSO₂CF₃, 122876-21-5; tryptophyl bromide, 55982-76-8.

Supplementary Material Available: Full experimental procedures and analytical data for compounds 17 α and 17 β from **16**, (2*S*,3*R*)- and (2*S*,3*S*)-**18**, **19**, **20**, and **21**, and 23 α and 23 β from **21** (3 pages). Ordering information is given on any current masthead page.

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(17) The optical purity of methyl (*S*)-mandelate was established by CuI-assisted coupling with (*S*)-1-phenylethyl isocyanate.