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

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Synthesis of optically pure \( \alpha \)-tert-butyl \( \beta \)-methyl (2S,3R)-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 \( \beta \)-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 indoloquinoline. 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 \( \alpha \)-tert-butyl ester. The \( C_3 \)-diastereomers are easily separated and equilibrated, resulting in the required \( C_3 \)-\( \alpha \) epimer. Transformation of the tetracyclic indoloquinoline 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),\(^5\) a convenient precursor of (+)-vincamine,\(^6\) 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 \( \beta \)-cyano group.

Subsequently, we showed that the presumed advantages of the \( \beta \)-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 \( \alpha \)-tert-butyl \( \beta \)-methyl (2S,3R)-3-ethyl-\( \Lambda_4 \)-tetrahydroquinolinate, which was elaborated to the Aspidosperma alkaloid (-)-vindoline.\(^6\) These results, together with the availability of the recently reported method for constructing the \( E \) ring of (+)-vincamine from the indoloquinoline 10,\(^7\) 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

\( \text{Scheme I. Previous Synthesis of (+)-Apovincamine (4) from L-Asparagine} \)

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

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References


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L-Aspartate Diesters subsequently differentiated at the \( \alpha \)- and \( \beta \)-carboxyl groups and converted to hexahydroquinolinate 9. Previously, the tetrahydroquinolinate used for the synthesis of (-)-vin-
l-aspartic acid, prepared in nearly quantitative yield by intramolecular C-3 alkylation. The nitrogen monoa-
lklyl group 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. Following ring closure, a second C-3 alkylation to incorporate the ethyl group should give the target protected hexahydroquinoline 9 with the correct absolute stereochemistry at C-3.

Elaboration of the hexahydroquinoline 9 to indoloquinoline 10 follows our previous studies in both the synthesis of (+)-apovincamine and (-)-vinoldine. Recently, it has been demonstrated that conversion of (+)-10 to (-)-vincamine can be accomplished in 54% overall yield. 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. This reaction has also been shown to occur with 12, via 13, under acidic conditions. 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. 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 sensitive to the presence of moisture. The dimethyl ester of L-aspartic acid was synthesized from L-aspartic acid in 29% overall yield. Upon treatment of 16 with LDA and quenching with ethyl iodide, a 98:2 mixture of 17α/17β was isolated, and separation by silica gel chromatography yielded 17α in 82% yield. Removal of the 9-PhF protecting group was accomplished in high yield, either by acidolysis or by hydrolysis. 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 hexahydroquinolinate 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 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'-diisopropylisourea gave 18 in 89% yield. With use of this latter procedure 18 was synthesized from L-aspartic acid in 29% overall yield.
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, we considered the possible advantages of inverting the sequence by C-alkylating first and then closing the piperidine ring by N-alkylation.

Thus, the tetrahydroquinolinate 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 hexahydroquinolinate 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 eutect. 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 hexahydroquinolinate 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'-disopropylisourea, to the target hexahydroquinolinate 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. The stereochemistry of 23α was rigorously established by COSY and NOESY experiments. In particular, the NOE effects between H-5α/H-7 and H-2α/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 TMSCI followed by in situ amine protection with 9-PhFBr yielded 27 in 92% yield following a mechanistic 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'-disopropylisourea yielded diester 28, 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, o-tert-butyl and α-methyl ester impart the same effect in the alkylation of these hexahydroquinolinites. The entire sequence as outlined in Scheme IV from L-aspartic acid (6) to o-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 o-tert-butyl ester is introduced.

**Synthesis of (+)-Vincamine from 18.** N-Alkylation of either 24 or 18 with tryptophyl bromide 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 indolquinolizines 10 and 35 by heating dimethyl ester 32 in phenylphosphonic dichloride. The idea was to effect nuclophilic 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 o-tert-butyl ester of tryptamine derivative 33 was hydrolyzed by using HOAc/iPrOH/H2O4 to yield the acid 34. Heating the crude acid in PhPOCl2 yielded a 57/1 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, (10)−10 was transformed into optically pure (+)-vincamine (5) as shown in Scheme V. Our apprehension about the configurational stability of aldehydes 12was 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.

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

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

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Total Synthesis of (+)-Vincamine from L-Aspartic Acid

Therefore, the crude aldehyde was directly converted to (+)-vincamine as described for racemic material. This mixture of isomers was separated by converting the synthetic (+)-vincamine to (+)-methyl mandelate esters of apovincamine and (+)-methyl mandelate esters of epivincamine as decribed in Scheme V. Examination of the 'H 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 (+)-vincamine (5) was 44%.

The configurational integrity of the intermediates was established by converting the (+)-vincamine and the (+)-methyl mandelate esters of apo- and (+)-methyl mandelate esters of epivincamine. Examination of the 1H NMR spectra, calibrated by doping experiments, revealed the synthetic material to be >99% optically pure.

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**Experimental Section**

**General.** Tetrahydrofuran (THF) was distilled from sodium/benzophenone; disopropylamine, acetonitrile, dichloromethane, pyridine, and tert-butyl alcohol were distilled from CaH₂. Chloroform was distilled from P₂O₅ and methanol and ethanol were distilled from Mg. Potassium hexamethyldisilazide (KHDMDS) in toluene was obtained from Commercial Chemical. All reactions were carried out under N₂ or argon. Final organic solutions in the isolations were dried over Na₂SO₄ and rotary-evaporated in vacuum. Melting points are uncorrected. 1H NMR and IR spectra were determined in CDCl₃, unless otherwise stated. NMR shifts are expressed in ppm downfield from internal methane.


methyloxilane 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 (300 mL) was added acetyl chloride (33.4 g, 0.42 mol) in MeOH (100 mL). Both components were premixed at 5°C and stirred for 0.5 h until a white solid precipitated. After the mixture was cooled, the precipitate was recovered by filtration, washed with ether, and dried. The crude aldehyde was directly converted to (+)-vincamine as described for racemic material. This mixture of isomers was separated by converting the synthetic (+)-vincamine to (+)-methyl mandelate esters of apo- and (+)-methyl mandelate esters of epivincamine as described in Scheme V. Examination of the 'H NMR spectra, calibrated by doping experiments, revealed the synthetic material to be >99% optically pure.

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

Dimethyl (2S,3R)-1-(9-Phenylfluoren-9-yl)hexahydroquinolinate (cis-22) and Dimethyl (2S,3S)-1-(9-Phenylfluoren-9-yl)hexahydroquinolinate (trans-22). To crude 3-(chloropropyl)aspartate (20 mg) in refluxing toluene (2 L), was added NaHCO₃ (500 mg). After 10 min, NaI (300 mg, 7.8 mmol) was added, and the mixture was filtered. The filtrate was evaporated, and the residue was added to CH₂OH/H₂O (2 mL, 1/1). Filtration and washing of the resulting solid with CH₂OH (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 (99%), and 13 mg of recovered 26 present in the crude.

**trans-22:** 1H NMR δ 7.75-7.6 (m, 2 H), 7.4-7.0 (m, 11 H), 3.98 (s, 1 H, H-3), 3.85 (s, 1 H, H-2); HRMS calcd for C₂₅H₂₃NO₄ (M⁺) = 409.1748, found = 409.1744.

**cis-22:** 1H NMR δ 7.73-7.61 (m, 2 H), 7.42-7.16 (m, 11 H), 3.75 (s, 1 H, H-3), 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 = 10.3, 4.5), 2.85 (s, 3 H), 1.58 (m, 1 H, H-5b), 1.38 (m, 1 H, H-5a), 0.85 (t, 3 H, J = 6.5). Anal. Calcd for C₂₅H₂₃NO₄: C, 75.9; H, 6.1; N, 3.1.

Dimethyl (2S,3R)-3-Ethyl-1-(9-phenylfluoren-9-yl)hexahydroquinolinate (23a) and Dimethyl (2S,3S)-3-Ethyl-1-(9-phenylfluoren-9-yl)hexahydroquinolinate (23p). To a solution of diisopropylamine (5.25 mL, 37.5 mmol, 150 mol%) in dry CH₂Cl₂ (400 mL) was added n-BuLi (22.7 mL, 1.54 M in hexanes, 34.2 mmol) at room temperature. After 2 h, Et₃N (4.46 mL, 32 mmol) was added, stirring was continued at -78 °C for 45 min. After being stirred at 0 °C for another 15 min, an excess of H₂S was passed into the reaction mixture. The suspension was stirred for 24 h; then the reaction mixture was filtered through Celite and the inorganic residue was washed with CH₂Cl₂. 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).

**Acid & Methyl Ester**

A solution of 3-chloropropanol (4.73 g, 4.2 mL, 5 mmol) in CH₂Cl₂ (400 mL) was added 0-tert-butyl-N,N'-diisopropylamine (5.25 mL, 37.5 mmol, 150 mol%) to a stirred suspension of dimethyl ester hydrochloride (28 g, 50.3 mmol) in dry CH₂Cl₂ (100 mL) at room temperature. After 2 h, Et₂N (4.46 mL, 32 mmol) and 0-tert-butyl-N,N'-diisopropylamine (5.25 mL, 37.5 mmol) at room temperature. After 2 h, Et₂N (4.46 mL, 32 mmol) and 0-tert-butyl-N,N'-diisopropylamine (5.25 mL, 37.5 mmol) at room temperature. After 2 h, Et₂N (4.46 mL, 32 mmol) and 0-tert-butyl-N,N'-diisopropylamine (5.25 mL, 37.5 mmol) at room temperature. After 2 h, Et₂N (4.46 mL, 32 mmol) and 0-tert-butyl-N,N'-diisopropylamine (5.25 mL, 37.5 mmol) at room temperature. After 2 h, Et₂N (4.46 mL, 32 mmol) and 0-tert-butyl-N,N' diisopropylamine (5.25 mL, 37.5 mmol) at room temperature. After 2 h, Et₂N (4.46 mL, 32 mmol) and 0-tert-butyl-N,N'-diisopropylamine (5.25 mL, 37.5 mmol) at room temperature. After 2 h, Et₂N (4.46 mL, 32 mmol) and 0-tert-butyl-N,N'-diisopropylamine (5.25 mL, 37.5 mmol) at room temperature. After 2 h, Et₂N (4.46 mL, 32 mmol) and 0-tert-butyl-N,N'-diisopropylamine (5.25 mL, 37.5 mmol) at room temperature. After 2 h, Et₂N (4.46 mL, 32 mmol) and 0-tert-butyl-N,N'-diisopropylamine (5.25 mL, 37.5 mmol) at room temperature. After 2 h, Et₂N (4.46 mL, 32 mmol) and 0-tert-butyl-N,N'-diisopropylamine (5.25 mL, 37.5 mmol) at room temperature. After 2 h, Et₂N (4.46 mL, 32 mmol) and 0-tert-butyl-N,N'-diisopropylamine (5.25 mL, 37.5 mmol) at room temperature. After 2 h, Et₂N (4.46 mL, 32 mmol) and 0-tert-butyl-N,N'-diisopropylamine (5.25 mL, 37.5 mmol) at room temperature. After 2 h, Et₂N (4.46 mL, 32 mmol) and 0-tert-butyl-N,N'-diisopropylamine (5.25 mL, 37.5 mmol) at room temperature. After 2 h, Et₂N (4.46 mL, 32 mmol) and 0-tert-butyl-N,N'-diisopropylamine (5.25 mL, 37.5 mmol) at room temperature. After 2 h, Et₂N (4.46 mL, 32 mmol) and 0-tert-butyl-N,N'-diisopropylamine (5.25 mL, 37.5 mmol) at room temperature. After 2 h, Et₂N (4.46 mL, 32 mmol) and 0-tert-butyl-N,N'-diisopropylamine (5.25 mL, 37.5 mmol) at room temperature. After 2 h, Et₂N (4.46 mL, 32 mmol) and 0-tert-butyl-N,N'-diisopropylamine (5.25 mL, 37.5 mmol) at room temperature. After 2 h, Et₂N (4.46 mL, 32 mmol) and 0-tert-butyl-N,N'-diisopropylamine (5.25 mL, 37.5 mmol) at room temperature. After 2 h, Et₂N (4.46 mL, 32 mmol) and 0-tert-butyl-N,N'-diisopropylamine (5.25 mL, 37.5 mmol) at room temperature.
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 55 °C, 0.2 mbar, Kugelrohr) to give 3-chloropropyl triflate (7.0 g, 62%).

To a stirred solution of KHMDS (10.8 mL, 5.4 mmol) in THF (50 mL), tryptophyl bromide (872 mg, 3.91 mmol), and NaH (60 mg, 1.5 mmol) in THF (20 mL) at -70 °C, the reaction mixture was stirred for 1.5 h. The solvent was evaporated, and the residue was flash chromatographed (EtOAc/hexane, 1/1) to give, after treatment with MPLC (hexane/EtOAc, 1/1) to give 931 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; [α]D' = -34.0 (c 1.0, CHCl₃); IR 3460, 3170, 1820, 1800, 1725 cm⁻¹; 'H NMR δ 7.70-7.17 (m, 13 H), 3.65 (s, 3 J, 1 H, J = 4.5), 2.76 (brd, δ /J, 1 H, J = 4.7), 2.42 (br, 1 H, J = 1.7), 1.75 (m, 1 H), 1.50 (m, 1 H), 1.20 (m, δ, 1 H, J = 1.5), 1.15 (s, 1 H, J = 9/5), 0.92 (s, 1 H).

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**Dimethyl 1-3-(3-Chloropropyl)-N-(9-phenylfluoren-9-yl)aspartate (29).** To a stirred solution of KHMS (10.8 mL, 5.4 mmol) in THF (50 mL), tryptophyl bromide (872 mg, 3.91 mmol), and NaH (60 mg, 1.5 mmol) in THF (20 mL) at -70 °C, the reaction mixture was stirred for 1.5 h. The solvent was evaporated, and the residue was flash chromatographed (EtOAc/hexane, 1/1) to give, after treatment with MPLC (hexane/ EtOAc, 1/1) to give 931 mg (81%) of trans-31 and 83 mg (17%) of cis-31 (containing 20% trans-31), for a combined yield of 98%.

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**trans-31:** mp 184 °C; [α]D' = -34.0 (c 1.0, CHCl₃); IR 3460, 3170, 1820, 1800, 1725 cm⁻¹; 'H NMR δ 7.70-7.17 (m, 13 H), 3.65 (s, 3 J, 1 H, J = 4.5), 2.76 (brd, δ /J, 1 H, J = 4.7), 2.42 (br, 1 H, J = 1.7), 1.75 (m, 1 H), 1.50 (m, 1 H), 1.20 (m, δ, 1 H, J = 1.5), 1.15 (s, 1 H, J = 9/5), 0.92 (s, 1 H).

**cis-31:** [α]D' = -34.0 (c 1.0, CHCl₃); IR 3460, 3170, 1820, 1800, 1725 cm⁻¹; 'H NMR δ 7.70-7.17 (m, 13 H), 3.65 (s, 3 J, 1 H, J = 4.5), 2.76 (brd, δ /J, 1 H, J = 4.7), 2.42 (br, 1 H, J = 1.7), 1.75 (m, 1 H), 1.50 (m, 1 H), 1.20 (m, δ, 1 H, J = 1.5), 1.15 (s, 1 H, J = 9/5), 0.92 (s, 1 H).
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] Unchanged after stirring 3 h at room temperature and 2 h at 60 °C in DMSO.

(+)-15,15a-Didehydro-15-formamido-1H-pyromeburnin-14-one (36). To a solution of potassium tert-butoxide (1.48 g, 15.2 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 being evaporated to leave 1.3 g of crude 36; [α]D +159°.

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 extracted with Et₂O (3 × 25 mL). The dried organic phase was evaporated to leave 1.3 g of crude 36; [α]D +158° (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 exchanged with CH₂Cl₂ (0 × 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] mp 232-233 °C; [α]D +43° (c 0.8, pyridine) [lit.15 mp 234-235 °C; [α]D +44° (c 1, pyridine)]. The yield of 5 from pure N-(1S)-phenylethylcarbamoyl derivative, 126218-16-4; 15 (N-(1R)-phenylethylcarbamoyl derivative), 126218-17-5; 16, 104072-52-8; 17a, 126217-97-8; 17b, 126217-99-9; 18, 126218-01-7; (2R,3S)-18, 126218-20-0; (2R,3R)-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; 23a, 126218-04-0; 23b, 126218-05-1; 24, 126217-99-0; 24 (N-(1S)-phenylethylcarbamoyl derivative), 126218-18-6; 24 (N-(1R)-phenylethylcarbamoyl derivative), 126218-19-7; 25, 126218-00-6; (R,S)-25, 126218-25-5; 26, 126218-02-2; 27, 126218-21-1; 28, 126218-20-8; 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, 126372-26-0; 35-Cl, 126371-54-8; 36, 112965-87-4; 37, 6835-99-0; Cl(C₆H₄)OH, 627-30-5; Cl(C₆H₅)₂, 122876-21-5; tryptophyl bromide, 55982-76-8.

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


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