excess of the **1a** thus obtained was >98% as determined by HPLC of the (+)-(1-phenylethyl)amide **1d**.[4]

Determination of Optical Purities of Pyrrolidines. To the trans pyrrolidines **27b** or **33b**, dissolved in THF and triethylamine (120 mol %), was added MTPA acid chloride (200 mol %). The reaction mixture was refluxed (1 h) then diluted with CH_2Cl_2 which was washed successively with 1 M H_3PO_4, saturated $NaHCO_3$ solution, and brine. Drying and evaporating left a residue which was directly separated by HPLC (4% EtOAc/isooctane).

Synthesis of Optically Pure Pipecolates from L-Asparagine. Application to the Total Synthesis of (+)-Apovincamine through Amino Acid Decarbonylation and Iminium Ion Cyclization

Bradley D. Christie and Henry Rapoport*

Department of Chemistry, University of California, Berkeley, California 94720

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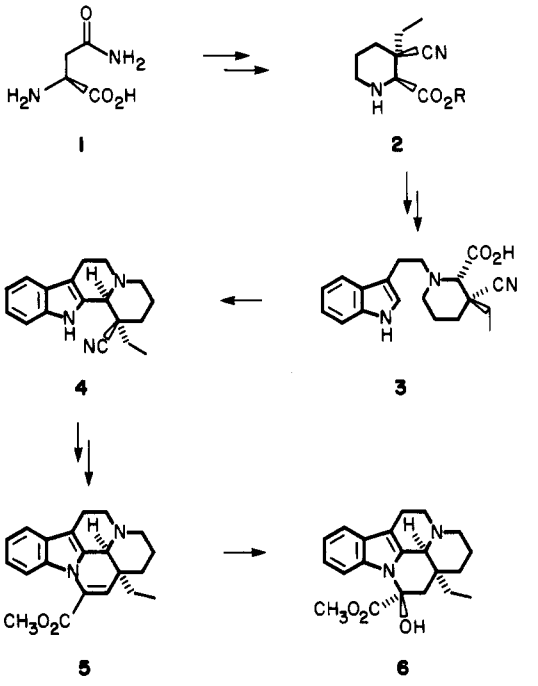
Pipecolic acid derivatives have been examined as intermediates in a synthesis of apovincamine (**5**). First, the racemic pipecolate **10** was elaborated to the pentacyclic β-keto ester **14**. Ethylation of **14** gave eburnane **15**, with the incorrect relative stereochemistry, and test experiments established that this route would be unsuitable for a chirospecific synthesis since it would lead to a racemic product. Therefore, in a second approach, the optically pure 3-cyano-3-ethylpipecolate (**2**) was synthesized from L-asparagine. The new phenylfluorenyl N-protecting group served to direct both enolate formation and alkylation stereochemistry. Pipecolate **2**, by a sequence including iminium ion formation via amino acid decarbonylation, was used to make the octahydroindolo[2,3-*a*]quinolizine **4** which was elaborated to (+)-apovincamine.

Recent work has demonstrated the usefulness of α-amino acids as educts for chirospecific alkaloid synthesis. Thus, the neurotransmitter anatoxin a[1] and ant trail pheromones[2] have been synthesized from glutamic acid. Also, we have investigated the use of pipecolic acid derivatives as precursors in indole alkaloid syntheses.[3]

In this report we combine these two concepts for the synthesis of an optically pure indole alkaloid (Scheme I). Specifically, L-asparagine (**1**) has been used to synthesize the optically pure pipecolate **2**. Further synthetic development proceeded through the decarbonylation of the tertiary amino acid **3** and cyclization to give the octahydroindolo[2,3-*a*]quinolizine **4**, which was elaborated to apovincamine (**5**), a known synthetic precursor to the antihypertensive agent vincamine (**6**).[4]

Scheme I. General Course for the Synthesis of Apovincamine (5) from Asparagine (1)



1 2 3 4 5 6

Results and Discussion

Attempted Synthesis Using Piperidine Diester 10. Initially we investigated an apovincamine synthesis as an extension of the earlier work on octahydroindolo[2,3-*a*]-quinolizines. The easily available racemic piperidine diester **10**[3] was used as a model pending developments toward optically active pipecolates. We also desired the modified tryptophyl bromide **9**, in which the *N*-[(methoxycarbonyl)methyl] substituent would be incorporated into the last ring. Compound **9** was made from tryptophyl bromide (**7**) by base-induced (K_2CO_3) formation of the spiroindolenine **8**,[3] followed by in situ alkylation with methyl bromoacetate. The proof of **8** as an intermediate in this reaction is based on experiments showing that **8** is formed by treating tryptophyl bromide (**7**) with K_2CO_3, that **8** is converted to **9** upon treatment with methyl bromoacetate, and that indole is not converted to *N*-[(methoxycarbonyl)methyl]indole under these conditions.

Alkylation of piperidine diester **10** with bromide **9** produced the tertiary indole amine **11**, which was hydrolyzed to amino acid **12** and then cyclized through the iminium ion produced by $POCl_3$ decarbonylation to give only the [1(*S*,*R*),12b(*S*,*R*)] diastereomer **13**. A small amount (10%) of enamine **16** was produced as a side product and was the sole product when acid **12** was treated with

(1) Petersen, J. S.; Fels, G.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 4539.
(2) Shiosaki, K.; Rapoport, H. *J. Org. Chem.*, preceding paper in this issue.
(3) Johansen, J. E.; Christie, B. D.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 4914.
(4) Pfäfli, P.; Oppolzer, W.; Wenger, R.; Hauth, H. *Helv. Chim. Acta.* **1975**, *58*, 1131.

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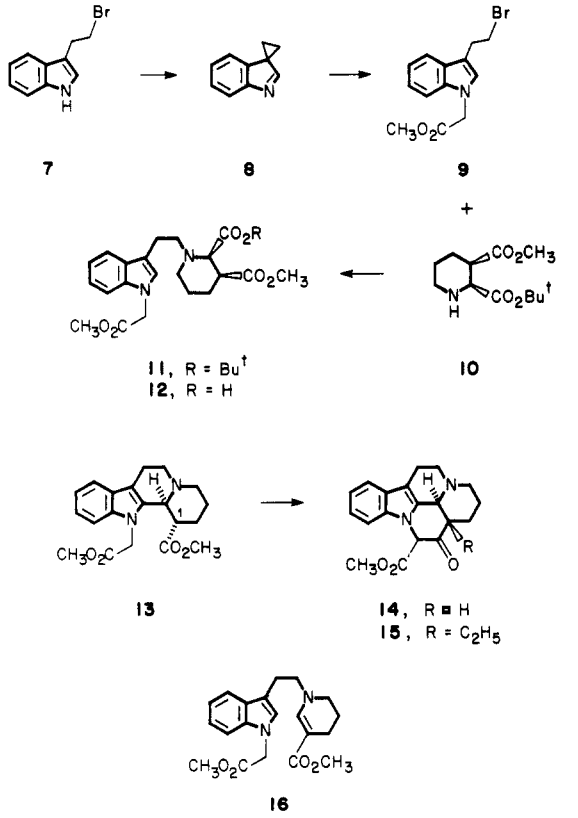
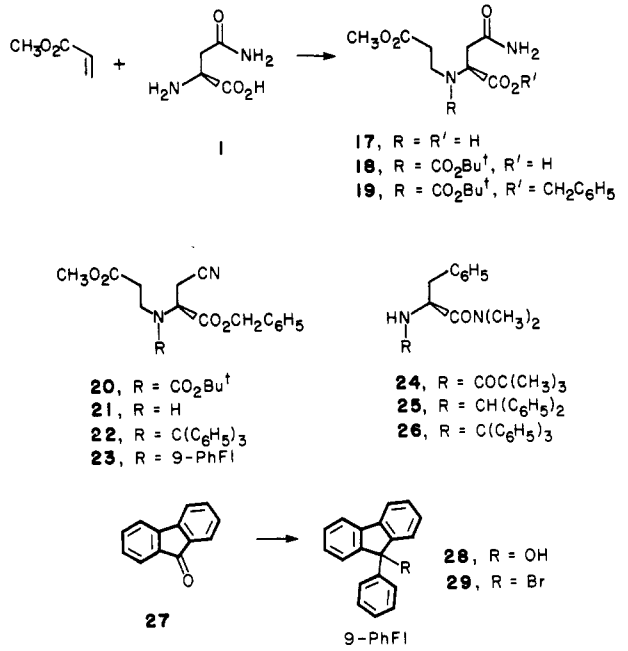
Scheme II. Attempted Synthesis of Apovincamine Using Piperidine 2,3-Diester 10



Scheme III. Attempted Synthesis of Pipecolates from L-Asparagine and Methyl Acrylate



TsCl/pyridine. Dieckmann cyclization of **13** proceeded readily to give β-keto ester **14**. Formation of the dianion of **14** with LDA, followed by alkylation with ethyl iodide, gave only the trans product **15**, with relative stereochemistry opposite to that present in apovincamine (Scheme II).

To test the applicability of this approach for an optically active synthesis, the amino acid **12** was treated with CH_3OD to exchange the carboxylic acid proton, decarbonylated with $POCl_3$, and cyclized then quenched with D_2O to give the product **13**. Analysis by ^1H NMR showed 40% deuterium incorporation at C-1. This can only be explained by the intermediacy of the achiral enamine **16**. Therefore, if this cyclization were performed with optically pure amino acid **12**, one would expect to obtain product **13** extensively racemized.

Attempted Synthesis of Pipecolates from L-Asparagine and Methyl Acrylate. At this point a different strategy was adopted, in which L-asparagine would be used to build the chiral pipecolate **2**, avoiding the above stereochemical problems and racemization. Thus, a controlled Michael reaction with asparagine and methyl acrylate gave N adduct **17**, containing the necessary carbon atoms to form the piperidine ring. Protection as the *N*-[(*tert*-butyloxy)carbonyl] derivative **18** followed by esterification with benzyl bromide, dehydration of the amide with toluenesulfonyl chloride, and deprotection gave the diester nitrile amine **21**.

At this point we envisioned protecting the nitrogen in such a way as to direct subsequent enolate formation away from the nitrogen and α-ester to form the nitrile enolate. Investigation on formation of enolates from N-protected phenylalanine derivatives has shown that the benzhydryl compound **25** greatly slowed and the *N*-trityl compound **26** virtually halted base-catalyzed proton–deuterium exchange at the α-carbon relative to the *N*-pivalyl compound **24**.[5] Thus we attempted to make the *N*-trityl derivative **22**; however, this compound proved extremely labile toward protic solvents and chromatography. For a more stable group of similar size, we turned to the 9-(phenylfluorenyl) (PhFl) group and introduced it into **21**, as solvolysis studies show 9-PhFlCl to be 6000 times less reactive than trityl chloride.[6] The PhFl derivative **23** was made by treating amine **21** with 9-PhFlBr (obtained by treating fluorenone (**27**) with phenyllithium followed by HBr) in CH_3CN with K_3PO_4 as a base and $Pb(NO_3)_2$ as a bromide ion scavenger. The reaction proceeded much slower and could not be driven to completion in the absence of $Pb(NO_3)_2$ (Scheme III).

Initial investigations on the selective reduction of the methyl ester of **23** were unsuccessful, and this direction was not pursued further due to the results discussed below.

Synthesis of Pipecolates from L-Asparagine and 3-Chloropropanol. The benzyl ester of β-cyanoalanine (**33**) was synthesized by protecting asparagine as the *N*-[(*tert*-butyloxy)carbonyl] derivative **30**, esterification with benzyl bromide to give **31**, followed by dehydration to nitrile **32**, and deprotection. Cyano amine **33** failed to react with 1-bromo-3-chloropropane or 3-chloropropyl mesylate, returning only educt. This is due to the inductive effects of the ester and nitrile groups of **33**, greatly decreasing the nucleophilicity of the amine. For an electrophile with greater reactivity, the β,β,β-trifluoroethanesulfonate (tresylate) **38** was made, as tresylates are known to be substantially more reactive than the corresponding mesylates.[7] We report here an improved modification of the synthesis of tresyl chloride (**37**).[8] We found that acid-catalyzed cleavage of sulfide **35** to the mercaptan **36** prior to oxidation with chlorine proceeded much better than direct oxidation of **35**. Tresyl chloride (**37**) was isolated in 76% overall yield from sulfide **35**, from which tresylate **38** was prepared in 91% yield.

Alkylation of amine **33** with the tresylate **38** gave the secondary amine **34** in good yield, with no detectable

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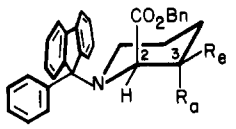
(6) Bolton, R.; Chapman, N. B.; Shorter, J. *J. Chem. Soc.* **1964**, 1895.
(7) Crossland, R. K.; Wells, W. E.; Shiner, V. J., Jr. *J. Am. Chem. Soc.* **1971**, *93*, 4217.
(8) Bunyagidj, C.; Piotrowska, H.; Aldridge, M. H. *J. Org. Chem.* **1981**, *46*, 3335.



41, R_e = CN, R_a = H
42, R_e = H, R_a = CN
43a, R_e = CN, R_a = C_2H_5

Figure 1. Conformational structures of the *N*-(9-phenylfluorenyl)-3-cyanopipecolates, resulting from the steric demand of the phenylflourenyl group.

dialkylation, which had been observed with the corresponding triflate. Azetidine formation resulted upon extended reaction times, so an excess of the tresylate was used and the reaction was stopped when the maximum amount of product was produced. The PhFl derivative **39** was made as before, and since subsequent experiments showed the chloride not to be reactive enough for an intramolecular alkylation, it was exchanged to the iodide **40**.

Upon treatment with excess LDA, iodide **40** cyclized to give a 1/1 mixture of pipecolates **41** and **42**. Examination of the ^{1}H NMR spectra of these compounds revealed their conformation as that illustrated in Figure 1, with the α-ester forced into an axial position by the PhFl group. This is clear from the coupling constants of cis isomer **41**, in which $J_{3,4\alpha}$ = 4.6 Hz and $J_{3,4\beta}$ = 13.0 Hz identify C–3–H as axial. Also, since $J_{2,3}$ = 4.6 Hz, too small for axial–axial coupling, C–2–H must be equatorial and the benzyl ester axial. The trans compound **42** shows $J_{3,4\alpha}$ and $J_{3,4\beta}$ < 4 Hz and $J_{2,3}$ < 2 Hz, consistent only with the conformation shown with both substituents positioned axially. The benzyl esters are strongly shielded by the fluorenyl ring, resonating at 4.1 to 4.6 ppm, compared to a typical benzyl ester (deprotected pipecolate **2a**) at 5.2 ppm. The axial ester deshields the axial C–6–Hβ due to the carbonyl anisotropy. The values found are 3.7 and 3.6 ppm in **41** and **42**, respectively, vs. 3.2 ppm for the equatorial C-6–Hβ and 2.6 ppm for the axial C–6–Hα in pipecolate **2a**.

Knowledge of this unusual and essentially fixed conformation allows one to predict the stereochemistry of the subsequent nitrile alkylation; specifically, since the axial benzyl ester covers the top of the piperidine ring, an electrophile will be forced to approach from the bottom, such as to give the ethylated compound **43a** with the correct absolute stereochemistry at C-3.

When iodide **40** was treated with a large excess of LDA at −78 °C, followed by excess ethyl iodide, the product, surprisingly, was pipecolate **43b** as a mix of diastereomers at the chiral phenylpropyl ester carbon, in which ethylation of the benzyl ester had occurred in addition to the desired nitrile alkylation. In a model experiment, benzyl *N*-(9-phenylfluorenyl)pipecolate (**44**), under these conditions, was alkylated on the benzylic carbon and produced product **45**. This, of course, is opposite to the normal mode of alkylation at the α-carbon of esters, and demonstrates the powerful steric directing effect of the PhFl group.

The PhFl group could be removed with TFA in CH_3CN/H_2O, giving the pipecolates **2b**. Upon chromatography a small amount of material identified as the trans isomer **46** was isolated. We found that the amount of this side product could be minimized by controlling the amount of LDA in the cyclization/alkylation reaction such that a mixture of **43a** and **43b** was produced, which by ^{1}H NMR gave a 98/2 ratio of **2** to **46**. The two esters **2a** and **2b** were separated and the subsequent reactions carried out on each; however, since they behave identically, this is not necessary and **2a** and **2b** can be used as the mixture.

To determine the optical purity of the pipecolates, **2** was converted to the mixture of tosylates **47** and hydrogenolyzed to the acid **48**. After several unsuccessful attempts to couple **48** with α-phenylethylamine, we prepared the mandelate esters **49**. The ratio of diastereomers could easily be determined by ^{1}H NMR examination of the singlet mandelate proton, by which the diastereomeric purity of **49b** (and thus the optical purity of **2**) was found to be >99% (Scheme IV).

Synthesis of Apovincamine from Pipecolates 2. With the completion of the pipecolate synthesis, the next goal was its use in a synthesis of apovincamine. Alkylation of **2** with the bromide **9**, followed by hydrogenolysis, produced the tertiary amino acid **51** (Scheme V). Upon decarbonylation with phenylphosphonic dichloride or tosyl chloride/pyridine, however, none of the desired product **54**, nor any other indolo[2,3-a]quinolizine, was obtained.

In the belief that this result was due to an unfavorable steric interaction between the indole *N*-[(methoxycarbonyl)methyl] group and the piperidine cyano and ethyl groups, pipecolate **2** was alkylated with tryptophyl bromide (**7**) and hydrogenolyzed to the amino acid **3**. Decarbonylation with phenylphosphonic dichloride gave a 60/40 mixture of diastereomers **4** and **53** in moderate yield, and tosyl chloride/pyridine gave a product mixture favoring the undesired diastereomer **53**. These ratios are much less favorable than anticipated, since we expected the indole moiety to attack the iminium ion from the direction of the small (relative to ethyl) nitrile group. However, the undesired diastereomer **53** could be recycled through equilibration with acid to a mixture of **4** and **53**. Originally done with concentrated HCl,[9] we obtained better results using TFA at reflux for 24 h, giving a 1/1 mix of **4** and **53** in 90% yield.

Alkylation of the anion of **4** with methyl bromoacetate gave ester nitrile **54**, which was ring closed to give, after acid hydrolysis, the β-keto ester **55**. This compound is clearly distinguished from its diastereomer **15** and comparable to the corresponding ethyl ester.[9] Controlled reduction of **55** gave the hydroxy ester **56**, identical by ^{1}H NMR with that reported previously.[10] The 14*S*,15*S* stereochemistry is that proposed by Danieli;[10] however, the 14*R*,15*R* stereochemistry proposed by Katsube[9] for the ethyl ester appears equally plausible.

Dehydration of alcohol **56** by the two-step method of mesylation and base-catalyzed elimination[10] gave apovincamine (**5**). This material is identical (IR, ^{1}H NMR) with a sample prepared by acid-catalyzed dehydration of vincamine.[11] To determine optical purity, our synthetic material was hydrolyzed and coupled with methyl mandelate. As before, examination by ^{1}H NMR of the mandelate proton of samples prepared from (±)- and (+)-methyl mandelate showed our synthetic apovincamine to be >99% optically pure.

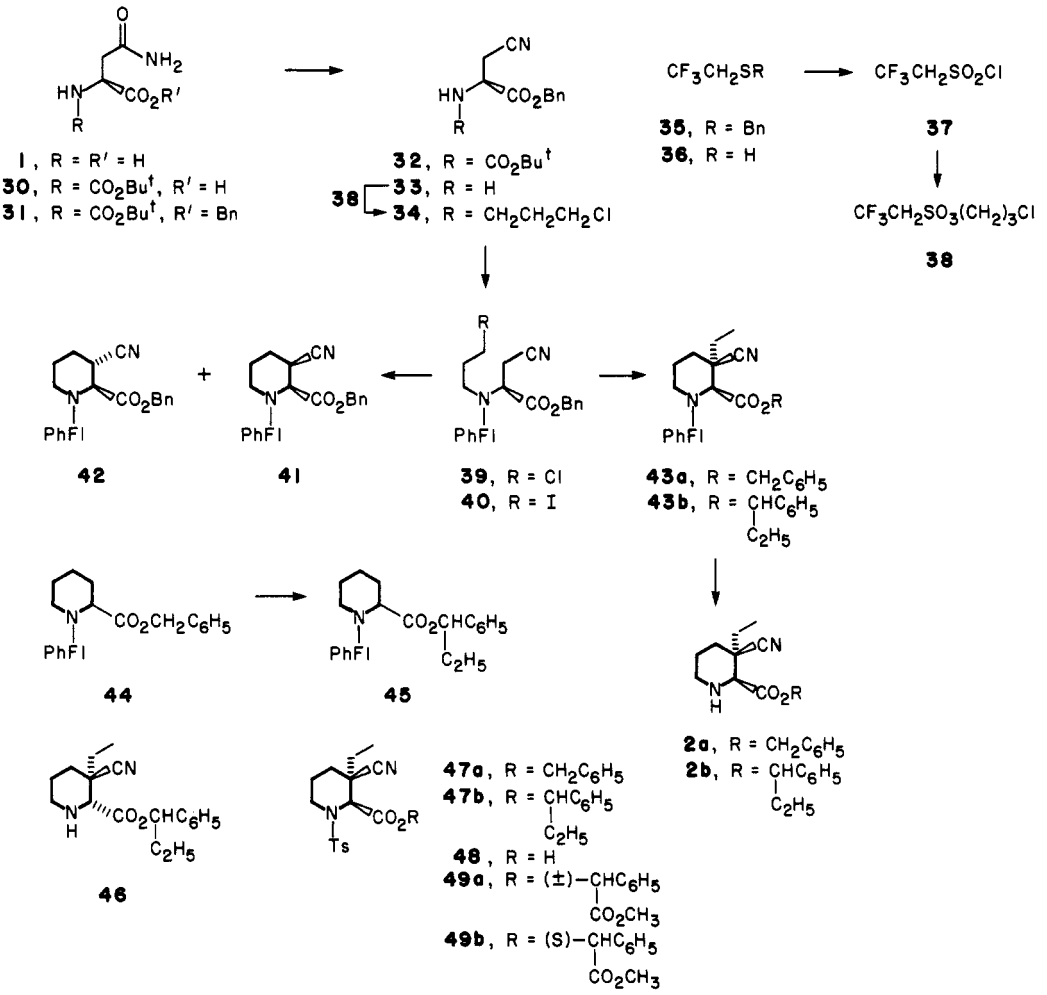
In summary, we have developed new methodology for the chirospecific synthesis of alkaloids from amino acids and have applied this to the synthesis of apovincamine. We are currently applying this methodology to the synthesis of other alkaloids.

Experimental Section

General Methods. Evaporations of organic solutions dried over $MgSO_4$ were done under aspirator vacuum with a rotary evaporator. Melting points are uncorrected. IR spectra were

(9) Ono, K.; Kawakami, K.; Katsube, J. *Heterocycles* **1980**, *14*, 411.
(10) Danieli, B.; Lesma, G.; Palmisano, G. *Gazz. Chim. Ital.* **1981**, *111*, 257.
(11) Pfäfli, P.; Hauth, H. *Helv. Chim. Acta.* **1978**, *61*, 1682.

Scheme IV. Synthesis of Pipecolates from L-Asparagine and 3-Chloropropanol



recorded for liquid films, unless otherwise indicated, and ^1H NMR spectra were recorded in $CDCl_3$ solution, in parts per million downfield from Me_4Si. Both K_2CO_3 and K_3PO_4 were dried at 400 °C for 24 h. Pyridine, CH_3CN, diisopropylamine, and DMF (at reduced pressure) were distilled from CaH_2, THF from sodium benzophenone, methyl bromoacetate from K_2CO_3, and DBU from 2-naphthalenesulfonyl chloride. Simple distillations were performed in a rotating bulb-to-bulb apparatus. Spinning disk chromatography was done on a Chromatotron. Reactions with H_2 were done on a Parr apparatus.

***N*-[(Methoxycarbonyl)methyl]tryptophyl Bromide (9).** A mixture of tryptophyl bromide[12] (7, 12.26 g), K_2CO_3 (49 g), methyl bromoacetate (9.2 mL), and CH_3CN (240 mL) was refluxed for 12 h, filtered, and evaporated. The residue was dissolved in EtOAc (20 mL) and hexane (50 mL), washed with H_2O (4 × 100 mL) and then saturated NaCl (100 mL), dried, and evaporated to give 13.06 g (81%) of 9: mp 52–53 °C; IR 1750, 743 cm^{-1}; ^1H NMR δ 7.58 (d, J = 7.7 Hz, 1 H), 7.3–7.1 (m, 3 H), 6.96 (s, 1 H), 4.79 (s, 2 H), 3.72 (s, 3 H), 3.62 (t, J = 7.7 Hz, 2 H), 3.31 (t, J = 7.7 Hz, 2 H). Anal. Calcd for $C_{13}H_{14}NO_2Br$: C, 52.7; H, 4.8; N, 4.7. Found: C, 52.9; H, 4.8; N, 4.6.

***tert*-Butyl *cis*-3-(Methoxycarbonyl)-1-[2-(3-[(methoxycarbonyl)methyl]indolyl)ethyl]pipecolate (11).** A mixture of bromide 9 (5.01 g), piperidine diester 10[3] (4.11 g), $NaHCO_3$ (6.7 g), and CH_3CN (14 mL) was refluxed with vigorous stirring for 30 h. The mixture was diluted with water (120 mL) and extracted with Et_2O (80, 40 mL). The Et_2O extracts were washed with saturated NaCl (40 mL), dried, filtered through silica (10 g), and evaporated to give 7.58 g (98%) of 11 which was used without further purification. An analytical sample was obtained by chromatography (silica, 40% EtOAc in hexane): IR 1725, 740 cm^{-1}; ^1H NMR δ 7.62 (d, J = 8 Hz, 1 H), 7.3–7.1 (m, 3 H), 6.92 (s, 1 H), 4.81 (s, 2 H), 3.97 (d, J = 4.8 Hz, 1 H), 3.73 (s, 3 H), 3.69 (s, 3 H), 3.0–2.7 (m, 7 H), 2.0–1.5 (m, 4 H), 1.44 (s, 9 H). Anal. Calcd for $C_{25}H_{34}N_2O_6$: C, 65.5; H, 7.5; N, 6.1. Found: C, 65.5; H, 7.5; N, 6.0.

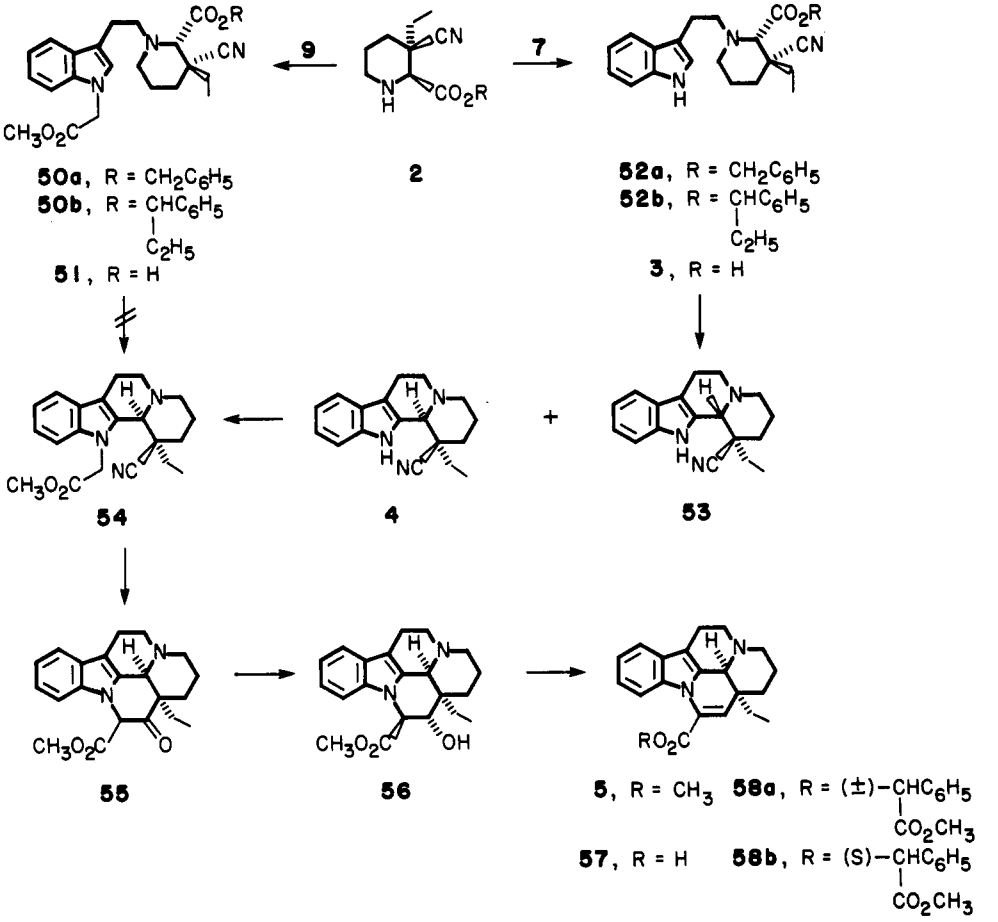
3-(Methoxycarbonyl)-1-[2-(3-[(methoxycarbonyl)methyl]indolyl)ethyl]pipecolic Acid (12). A solution of 11 (7.58 g) in 1-propanol (90 mL), water (90 mL), and acetic acid (20 mL) was refluxed for 4 h. The solution was evaporated, dissolved in hot EtOH (90 mL), and poured into hexane (900 mL). The cooled (0 °C) solution was filtered and the solid heated (60 °C) in vacuum to give 6.17 g (93%) of 12: IR (Nujol) 1720, 1610, 750 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.5–6.8 (m, 4 H), 4.92 (s, 2 H), 3.82 (d, J = 4.8 Hz, 1 H), 3.56 (s, 3 H), 3.48 (s, 3 H), 2.9–2.5 (m, 7 H), 1.9–1.5 (m, 4 H). Anal. Calcd for $C_{21}H_{26}N_2O_6$: C, 62.7; H, 6.5; N, 7.0. Found: C, 62.4; H, 6.5; N, 6.8.

1-(Methoxycarbonyl)-12-[(methoxycarbonyl)methyl]-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (13). The pipecolic acid 12 (195 mg) was heated in $POCl_3$ (2.0 mL) at 50 °C for 1 h. This solution was added to a mixture of EtOAc (50 mL) and saturated $NaHCO_3$ (100 mL) and stirred for 1 h. The separated organic phase was extracted with 1 M H_3PO_4 (2 × 50 mL), and the combined acid extracts were basified to pH 8 with K_2CO_3 and extracted with EtOAc (3 × 50 mL). The combined EtOAc extracts were dried, evaporated, and heated (70 °C) in vacuum to give 110 mg (64%) of 13: mp 149–151 °C; IR (Nujol) 1740, 750 cm^{-1}; ^1H NMR δ 7.48 (d, J = 7.5 Hz, 1 H), 7.2–7.0 (m, 3 H), 4.82 (d, J = 17.9, 1 H), 4.63 (d, J = 17.9, 1 H), 4.19 (d, J = 9.8, 1 H), 3.70 (s, 3 H), 3.57 (s, 3 H), 3.6–2.8 (m, 7 H), 2.1–1.4 (m, 4 H). Anal. Calcd for $C_{20}H_{24}N_2O_4$: C. 67.4; H, 6.8; N, 7.9. Found: C, 67.6; H, 6.9; N, 7.6.

Cyclization of Pipecolic Acid 12 with Deuterium Incorporation. Amino acid 12 was dissolved in CH_3OD (5 mL),

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

Scheme V. Synthesis of Apovincamine from 3-Cyano-3-ethylpipecolates (2)



evaporated, and heated (70 °C) in vacuum. To the residue was added $POCl_3$ (1 mL), and the solution was stirred at 60 °C for 1 h. The solution was then added to D_2O (10 mL) and stirred for 30 min, EtOAc (10 mL) was added, and the mixture was basified to pH 8 with K_2CO_3. The separated aqueous phase was extracted with an additional 10 mL of EtOAc, and the combined EtOAc extracts were dried, evaporated, and heated (70 °C) in vacuum to give 85 mg (88%) of **13** contaminated with the enamine **16**. ^1H NMR showed C-12b–H as an overlapping doublet and singlet, in a ratio of 6:4.

Methyl 1-[2-(3-[(Methoxycarbonyl)methyl]indolyl)-ethyl]-1,4,5,6-tetrahydronicotinate (16). To a suspension of amino acid **12** (117 mg) in CH_3CN (3 mL) and pyridine (0.20 mL) at 0 °C was added TsCl (150 mg). After it was stirred for 1 h, the resulting solution was diluted with saturated $NaHCO_3$ (10 mL) and Et_2O (5 mL), stirred at 20 °C for 4 h, and further diluted with water (10 mL) and Et_2O (10 mL). The organic phase was washed with 1 M H_3PO_4 (2 × 10 mL), evaporated, and heated (70 °C) in vacuum to give 103 mg (99%) of **16**: ^1H NMR δ 7.4 (m, 1 H), 7.23 (s, 1 H), 7.2–6.9 (m, 3 H), 6.70 (s, 1 H), 4.64 (s, 2 H), 3.58 (s, 3 H), 3.52 (s, 3 H), 3.25 (m, 2 H), 3.0–2.7 (m, 4 H), 2.19 (t, J = 6 Hz, 2 H), 1.72 (quintet, J = 6 Hz, 2 H). Anal. Calcd for $C_{20}H_{24}N_2O_4$: C, 67.4; H, 6.8; N, 7.9. Found: C, 67.5; H, 6.6; N, 8.0.

(3*S,16*S**)-16-Deethyl-15-oxo-14-(methoxycarbonyl)-eburnane (14).** To a solution of MeOH (0.50 mL) in THF (50 mL) was added *n*-BuLi (2.8 mL, 2.3 M in hexane). This solution of MeOLi was added by syringe to quinolizine **13** (1.20 g) and the resulting solution was refluxed for 1 h. After cooling, AcOH (3 mL) was added, the mixture was evaporated, and the residue was dissolved in saturated $NaHCO_3$ (100 mL) and extracted with EtOAc (3×50 L). The combined EtOAc extracts were washed with saturated NaCl (50 mL), dried, and evaporated to give 1.10 g (100%) of **14**, which was used as is. The analytical sample was crystallized from cold EtOH: mp 131–134 °C; IR (Nujol) 1765, 1725, 751 cm^{-1}; ^1H NMR δ 7.56 (m, 1 H), 7.26–7.14 (m, 3 H), 5.43 (s, 1 H), 3.76 (s, 3 H), 3.5–1.5 (m, 12 H). Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.3; H, 6.2; N, 8.6. Found: C, 70.0; H, 6.2; N, 8.6.

(3*S,16*S**)-15-Oxo-14-(methoxycarbonyl)eburnane (15).** To a solution of diisopropylamine (0.36 mL) in THF (2.5 mL) at 0 °C was added *n*-BuLi (0.93 mL, 2.3 M in hexane). After 15 min, a solution of **14** (302 mg) in THF (3.5 mL) was added, the mixture was stirred for 30 min, and EtI (0.14 mL) was added. After an additional 30 min at 0 °C, the reaction was quenched with AcOH (1 mL), diluted with water, basified to pH 8 with K_2CO_3, and extracted with EtOAc (2 × 10 mL). The EtOAc extracts were washed with saturated NaCl (10 mL), dried, and evaporated to give 307 mg (94%) of crude **15** containing a trace of educt **14** as the only impurity. The analytical sample was isolated as a hydrate upon trituration with MeOH: IR (Nujol) 1750, 1725, 746 cm^{-1}; ^1H NMR δ 7.5 (m, 1 H), 7.3–7.1 (m, 3 H), 5.41 (s, 1 H), 3.77 (s, 3 H), 3.40 (s, 1 H), 3.2–0.9 (m, 12 H), 0.66 (t, J = 7.6 Hz, 3 H). Anal. Calcd for $C_{21}H_{24}N_2O_3 \cdot H_2O$: C, 68.1; H, 7.1; N, 7.6. Found: C, 68.1; H, 6.8; N, 7.8.

***N*-(2-(Methoxycarbonyl)ethyl)asparagine (17).** To a solution of asparagine–H_2O (3.00 g), Et_3N (6 mL), water (30 mL), and MeOH (15 mL) at 0 °C was added methyl acrylate (4.0 mL), and the solution was stirred at 0 °C for 6 h. After addition of 5 mL of AcOH, the solution was diluted with 300 mL of acetone and kept at 0 °C for 15 min. The precipitated product was removed by filtration, washed with acetone and dried to give 3.72 g (85%) of **17**: mp 195 °C dec; $[\alpha]^{20}_D$ +17° (*c* 1, 10% HCl); IR (Nujol) 1705, 1655, 1600 cm^{-1}; ^1H NMR δ 4.38 (t, J = 5.3 Hz, 1 H), 3.76 (s, 3 H), 3.50 (t, J = 6.4, 2 H), 3.15 (d, J = 5.3 Hz, 2 H), 2.94 (t, J = 6.4 Hz, 2 H). Anal. Calcd for $C_8H_{14}N_2O_5$: C, 44.0; H, 6.5; N, 12.8. Found: C, 44.1; H, 6.5; N, 12.8.

***N*-[(*tert*-Butyloxy)carbonyl]-*N*-[2-(methoxycarbonyl)-ethyl]asparagine (18).** To a solution of **17** (1.5 g) in water (7.5 mL) and Et_3N (1.5 mL) was added *n*-PrOH (7.5 mL) followed by di-*tert*-butyl dicarbonate (1.8 g). After stirring for 24 h, the solution was evaporated to 5 mL, diluted with water (50 mL),

washed with Et_2O (20 mL), acidified to pH 1 with 10% HCl, and extracted with 25% *i*-PrOH in $CHCl_3$ (3 × 30 mL). The combined extracts were dried and evaporated to give 1.10 g (50%) of **18**: mp 117–119 °C. Anal. Calcd for $C_{13}H_{22}N_2O_7$: C, 49.0; H, 7.0; N, 8.8. Found: C, 49.3; H, 7.0; N, 8.8.

***N*-[2-(Methoxycarbonyl)ethyl]-3-cyanoalanine Benzyl Ester (21).** A mixture of the acid **18** (870 mg), THF (4 mL), Et_3N (0.45 mL), and benzyl bromide (0.5 mL) was refluxed for 2 h, diluted with EtOAc (20 mL), washed with H_2O (20 mL) and 1 M H_3PO_4 (20 mL), and saturated $NaHCO_3$ (20 mL), dried, and evaporated to give crude benzyl ester **19**. This was dissolved in CH_2Cl_2 (4 mL), and pyridine (1 mL) and TsCl (1.0 g) were added. After the solution stood for 24 h, it was poured into saturated $NaHCO_3$ (20 mL), stirred 1 h, and diluted with EtOAc (20 mL). The organic phase was washed with 1 M H_3PO_4 (20 mL), dried, and evaporated to give the crude ester nitrile **20**.

This material was dissolved in CH_3CN (6 mL), water (0.6 mL), and TFA (6 mL). After it was stirred 1 h, the solution was added to NH_4OH (10 mL) in water (20 mL) and extracted with CH_2Cl_2 (3 × 10 mL), and the extracts were dried, evaporated, and chromatographed (20 g of silica, 60/40, EtOAc/isooctane) to give 547 mg, 57% yield from **18**, of **21**: $[\alpha]^{20}_D$ −17° (*c* 2, $CHCl_3$); IR 3340, 2260, 1730, 750, 700 cm^{-1}; ^1H NMR δ 7.37 (s, 5 H), 5.21 (s, 2 H), 3.68 (s, 3 H), 3.60 (dd, *J* = 6.8, 6.0 Hz, 1 H), 3.00 (dt, *J* = 11.8, 6.5 Hz, 1 H), 2.80 (m, 1 H), 2.74 (dd, *J* = 16.8, 6.1 Hz, 1 H), 2.67 (dd, *J* = 16.8, 7.0 Hz, 1 H), 2.50 (t, *J* = 6.4 Hz, 2 H). Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.1; H, 6.2; N, 9.6. Found: C, 62.1; H, 6.2; N, 9.5.

9-Bromo-9-phenylfluorene (29). To a solution of bromobenzene (15.8 mL) in Et_2O (100 mL, distilled from sodium benzophenone) at 0 °C was added *n*-BuLi (76 mL, 1.5 M in hexane). After the mixture was stirred for 30 min, a solution of fluorenone (18 g) in THF (50 mL) was added over 45 min. The mixture was warmed to 20 °C, stirred for 2 h, and diluted with water (500 mL) and Et_2O (200 mL). The separated organic phase was washed with saturated NaCl (100 mL), dried, evaporated, and heated (70 °C) in vacuum. The residue of crude alcohol **28** was dissolved in toluene (100 mL), 48% HBr (50 mL) was added and the mixture was stirred for 24 h. The aqueous phase was extracted with toluene (50 mL), and the combined organic phases were dried and evaporated, and the residue was recrystallized from isooctane (150 mL) to give 25.5 g (80%) of **29**: mp 98–99 °C (lit.[6] mp 99 °C).

***N*-[2-(Methoxycarbonyl)ethyl]-*N*-(9-phenylfluorenyl)-3-cyanoalanine Benzyl Ester (23).** A mixture of secondary amine **21** (495 mg), 9-PhFlBr (660 mg), K_3PO_4 (500 mg), $Pb(NO_3)_2$ (500 mg), and CH_3CN (5 mL) was stirred for 4 h, filtered, evaporated, and chromatographed (disk, 2 mm, 15/85, EtOAc/isooctane) to give 781 mg (88%) of **23**: $[\alpha]^{20}_D$ +20° (*c* 2, $CHCl_3$); IR (Nujol) 2250, 1730 cm^{-1}; ^1H NMR δ 7.8–7.1 (m, 18 H), 5.04 (d, *J* = 12.1 Hz, 1 H), 4.84 (d, *J* = 12.1 Hz, 1 H), 3.71 (dd, *J* = 8.6, 5.8 Hz, 1 H), 3.61 (s, 3 H), 3.46–3.17 (m, 2 H), 2.56 (dd, *J* = 16.5, 8.6 Hz, 1 H), 2.53–2.45 (m, 2 H), 2.14 (dd, *J* = 16.5, 5.8 Hz, 1 H). Anal. Calcd for $C_{34}H_{30}N_2O_4$: C, 77.0; H, 5.7; N, 5.3. Found: C, 76.9; H, 5.8; N, 5.3.

***N*-(*tert*-Butoxycarbonyl)-3-cyanoalanine Benzyl Ester (32).** To a solution of L-asparagine–H_2O (10 g) in water (50 mL) and Et_3N (10 mL) was added *n*-PrOH (50 mL), followed by di-*tert*-butyl dicarbonate (17.4 g). The mixture was stirred for 24 h, then evaporated to a residue. This was dissolved in THF (40 mL), benzyl bromide (9.1 mL) was added, and the mixture was refluxed for 2 h, filtered, and evaporated. The solid residue was dissolved in EtOAc (100 mL), washed with saturated $NaHCO_3$ (2 × 50 mL), dried, and evaporated, and the residue was recrystallized from toluene (200 mL) to give 16.0 g (75%) of ester **31**.

This material was dissolved in CH_2Cl_2 (80 mL), and pyridine (20 mL) and TsCl (20 g) were added. After standing for 48 h, the solution was poured into saturated $NaHCO_3$ (200 mL), stirred for 1 h, and diluted with CH_2Cl_2 (100 mL). The organic phase was washed with 1 M H_3PO_4 (300 mL), dried, and evaporated, and the residue was recrystallized from EtOH/water (150 mL/100 mL) to give 12.0 g (79%; 59% from Asn) of nitrile **32**: $[\alpha]^{20}_D$ +26.1° (*c* 1, $CHCl_3$); IR (Nujol) 3360, 2260, 1730, 1675, 750, 700 cm^{-1}; ^1H NMR δ 7.38 (s, 5 H), 5.52 (d, *J* = 6.7 Hz, 1 H), 5.26 (s, 2 H), 4.54 (m, 1 H), 3.01 (dd, *J* = 17.0, 5.3 Hz, 1 H), 2.93 (dd, *J* = 17.0, 5.1, 1 H), 1.46 (s, 9 H). Anal. Calcd for $C_{16}H_{20}N_2O_4$: C, 63.1; H, 6.6; N, 9.2. Found: C, 63.2; H, 6.7; N, 9.2.

3-Cyanoalanine Benzyl Ester (33). The protected amine **32** (12.0 g) was added to a solution of TFA (60 mL), CH_3CN (60 mL), and water (6 mL). After it was stirred for 1 h, the solution was added to a 0 °C solution of NH_4OH (100 mL) in water (200 mL) and extracted with CH_2Cl_2 (100, 2 × 50 mL). The organic extracts were dried and evaporated to a residue, which was dissolved in CH_2Cl_2 (50 mL), and excess HCl gas was introduced. The solid was removed by filtration and dried in vacuum to give 6.83 g (72%) of **33**·HCl: mp 158–160 °C; $[\alpha]^{20}_D$ −22.2° (*c* 1, H_2O); IR (Nujol) 2260, 1750, 755, 705 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.19 (br s, 3 H), 7.5–7.3 (m, 5 H), 5.27 (s, 2 H), 4.58 (dd, *J* = 6.6, 5.3 Hz, 1 H), 3.33 (dd, *J* = 17.1, 5.3 Hz, 1 H), 3.25 (dd, *J* = 17.1, 6.6 Hz, 1 H). Anal. Calcd for $C_{11}H_{13}ClN_2O_2$: C, 54.9; H, 5.4; N, 11.6. Found: C, 54.8; H, 5.4; N, 11.6.

2,2,2-Trifluoromethanesulfonyl Chloride (Tresyl Chloride) (37). To methanesulfonic acid (250 mL) was added sulfide **35**[8] (66.85 g), and the mixture was stirred and heated at 180 °C for 45 min. The mercaptan **36** was collected by condensation at −78 °C. To this crude product at 0 °C was added concentrated HCl (200 mL), and Cl_2 gas was introduced. After the mixture was saturated, it was stirred 4 h, and the aqueous phase was separated and washed with CH_2Cl_2 (30 mL). The combined organic phases were dried, evaporated, and distilled (95 °C/(100 mm)) to give 48.66 g of **37**, 92% by ^1H NMR (3% CH_2Cl_2 and 5% CH_3SO_2Cl), 76% corrected yield, which was used as such.

3-Chloropropyl Tresylate (38). To a solution of tresyl chloride (**37**) (15.6 g) and 3-chloropropanol (6.80 mL) in CH_2Cl_2 (100 mL) at 0 °C was added Et_3N (12.4 mL) over 5 min. After stirring for 15 min, the mixture was washed with water (100 mL) and 10% HCl (100 mL), dried, evaporated, and distilled (90 °C (0.2 mm)) to give 17.92 g (91%) of **38**: ^1H NMR δ 4.46 (t, *J* = 7 Hz, 2 H), 3.94 (q, *J* = 8 Hz, 2 H), 3.68 (t, *J* = 7 Hz, 2 H), 2.24 (quintet, *J* = 7 Hz, 2 H). Anal. Calcd for $C_5H_8ClF_3O_3S$: C, 25.0; H, 3.4. Found: C, 25.2; H, 3.4.

***N*-(3-Chloropropyl)-3-cyanoalanine Benzyl Ester (34).** A mixture of **33**·HCl (10.87 g), tresylate **38** (21.88 g), $NaHCO_3$ (10.9 g), and CH_3CN (50 mL) was stirred and refluxed for 4 h. The mixture was diluted with water (100 mL), and extracted with CH_2Cl_2 (100, 2 × 50 mL), the organic extracts were dried and evaporated, and the residue was dissolved in CH_2Cl_2 (100 mL), into which excess HCl gas was introduced. The precipitate product was removed by filtration and dried in vacuum to give 10.15 g (71%) of **34**·HCl: mp 147–149 °C; $[\alpha]^{20}_D$ −12.1° (*c* 1, H_2O); IR (Nujol) 1750 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.50–7.36 (m, 5 H), 5.31 (s, 2 H), 4.67 (t, *J* = 6 Hz, 1 H), 3.74 (t, *J* = 6.4 Hz, 2 H), 3.5–3.3 (2 H obscured), 3.15 (t, *J* = 7.6 Hz, 2 H), 2.17 (m, 2 H). Anal. Calcd for $C_{14}H_{18}Cl_2N_2O_2$: C, 53.0; H, 5.7; N, 8.8. Found: C, 52.9; H, 5.8; N, 8.8.

***N*-(3-Chloropropyl)-*N*-(9-phenylfluorenyl)-3-cyanoalanine Benzyl Ester (39).** To saturated $NaHCO_3$ (30 mL) and CH_2Cl_2 (10 mL) was added **34**·HCl (1.00 g). After stirring for 30 min, the aqueous phase was separated and washed with CH_2Cl_2 (10 mL), and the combined CH_2Cl_2 phases were dried and evaporated. To the oily residue was added 9-PhFlBr (**29**, 1.20 g), K_3PO_4 (1.0 g), $Pb(NO_3)_2$ (1.0 g), and CH_3CN (10 mL). After stirring for 24 h, the mixture was filtered, then passed through 1 g of SiO_2, evaporated, and crystallized from absolute EtOH (15 mL) to give 1.48 g (90%) of **39**: mp 98–100 °C; $[\alpha]^{20}_D$ +27.7° (*c* 2, $CHCl_3$); IR (Nujol) 2250, 1745 cm^{-1}; ^1H NMR δ 7.8–7.1 (m, 18 H), 5.06 (d, *J* = 12 Hz, 1 H), 4.87 (d, *J* = 12 Hz, 1 H), 3.70 (dd, *J* = 5.4, 7.9 Hz, 1 H), 3.02 (m, 1 H), 2.47 (dd, *J* = 7.9, 16.3 Hz, 1 H), 2.14 (dd, *J* = 5.4, 16.3 Hz, 1 H), 1.90 (m, 2 H). Anal. Calcd for $C_{33}H_{29}ClN_2O_2$: C, 76.1; H, 5.6; N, 5.4. Found: C, 75.8; H, 5.7; N, 5.3.

Benzyl *N*-(9-Phenylfluorenyl)-3-cyanopipecolates (41 and 42). A mixture of chloride **39** (2.00 g), NaI (2.0 g), and CH_3CN (20 mL) was refluxed for 22 h and then diluted with water (50 mL) and Et_2O (50 mL), the organic phase was dried and evaporated, and the residue was dissolved in toluene (50 mL) and evaporated.

To a solution of diisopropylamine (1.7 mL) in THF (20 mL) at 0 °C was added BuLi (6.9 mL, 1.4 M in hexane). After it was stirred at 0 °C for 15 min, the solution was cooled to −78 °C, and a solution of the above crude iodide in THF (10 mL) was added. The solution was stirred at −78 °C for 30 min and then poured

into saturated $NaHCO_3$ (50 mL) and EtOAc (50 mL), and the organic phase was washed with 1 M H_3PO_4 (50 mL), dried, evaporated, and chromatographed (100 g SiO_2, 30/70, EtOAc/isooctane) to give 1.45 g (76%) of a 1/1 mix of isomers **41** and **42**. Samples of each were isolated by chromatography (disk, 2 mm, 60/40, CH_2Cl_2/isooctane) followed by recrystallization from MeOH.

Trans Compound 42 (less polar isomer): mp 159–161 °C; $[\alpha]^{20}_D$ −357° (*c* 2, $CHCl_3$); IR (Nujol) 2755, 1745 cm^{-1}; ^1H NMR δ 7.6–7.0 (m, 18H), 4.50 (d, J=12.5Hz, 1 H), 4.21 (d, *J* = 12.5 Hz, 1 H), 3.83 (s, 1 H), 3.61 (td, *J* = 11.9, 2.6 Hz, 1 H), 3.24 (br d, *J* = 12 Hz, 1 H), 2.92 (m, 1 H), 2.25–1.60 (m, 4H). Anal. Calcd for $C_{33}H_{28}N_2O_2$: C, 81.8; H, 5.8; N, 5.8. Found: C, 82.0; H, 5.8; N, 5.9.

Cis Compound 41: mp 161–162 °C; $[\alpha]^{20}_D$ −474° (*c* 2, $CHCl_3$); IR (Nujol) 2250, 1725 cm^{-1}; ^1H NMR δ 7.5–7.1 (m, 18 H), 4.62 (d, *J* = 12.7 Hz, 1 H), 4.07 (d, *J* = 12.7 Hz, 1 H), 3.72 (td, *J* = 11.8, 3.2 Hz, 1 H), 3.71 (d, *J* = 5, 1 H), 3.13 (br d, *J* = 11.7 Hz, 1 H), 3.00 (dt, *J* = 13.0, 4.6 Hz, 1 H), 2.24 (qd, *J* = 13.0, 4.7 Hz, 1 H), 2.04–1.62 (m, 3 H). Anal. Calcd for $C_{33}H_{28}N_2O_2$: C, 81.8; H, 5.8; N, 5.8. Found: C, 81.7; H, 5.7; N, 5.8.

Benzyl and 1-Phenylpropyl (2*S*,3*R*)-3-Cyano-3-ethylpipecolate (2). The (9-phenylfluorenyl)amine chloride **39** (2.00 g) was converted to the iodide and treated with LDA exactly as above. After it was stirred at −78 °C for 30 min, the solution was treated with EtI (0.96 mL), stirred at −78 °C an additional 30 min, and poured into 1 M H_3PO_4 (50 mL) and EtOAc (50 mL). The organic phase was washed with saturated $NaHCO_3$ (50 mL), dried, and evaporated to give 2 g of crude **43**.

This material was dissolved in CH_3CN (15 mL), water (1.5 mL), and TFA (15 mL). After stirring for 1 h, the solution was poured into saturated $NaHCO_3$ (300 mL) and extracted with EtOAc (200, 50 mL). The extracts were evaporated, and the residue was dissolved in EtOAc (200 mL) and extracted with 1 M H_3PO_4 (6 × 50 mL). The combined acid phases were basified with NH_4OH (30 mL) and extracted with CH_2Cl_2 (3 × 50 mL). These final CH_2Cl_2 extracts were dried, evaporated, and chromatographed (disk, 2 mm, two runs, 20–30% EtOAc in isooctane) to give 608 mg (53%) of the phenylpropyl ester **2b** followed by 108 mg (10%) of the benzyl ester **2a**.

2a: IR 3320, 2240, 1740, 740, 695 cm^{-1}; ^1H NMR δ 7.5–7.3 (m, 5 H), 5.21 (s, 2 H), 3.28 (s, 1 H), 3.17 (10 lines, *J* = 13.5, 4.1, 2.1, 2.1 Hz, 1 H), 2.59 (ddd, *J* = 13.5, 11.9, 3.6 Hz, 1 H), 2.24 (m, 1 H), 1.9–1.3 (m, 6 H), 1.02 (t, *J* = 7.5 Hz, 3 H). Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.6; H, 7.4; N, 10.3. Found: C, 70.5; H, 7.1; N, 10.1.

2b: IR 3330, 2240, 1740, 755, 700 cm^{-1}; ^1H NMR δ 7.5–7.3 (m, 5 H), 5.7 (m, 1 H), 3.23 (s, 1 H), 3.17 (m, 1 H), 2.60 (m, 1 H), 2.23 (m, 1 H), 2.1–2.3 (m, 8 H), 1.01 (t, *J* = 7.7 Hz, 3 H), 0.90 (t, *J* = 7.4 Hz, 3 H). Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 71.9; H, 8.1; N, 9.3. Found: C, 72.0; H, 8.2; N, 9.2.

Optical Purity Determination: Methyl 3-Cyano-3-ethyl-*N*-tosylpipecolate (49). To a solution of mixed esters **2** (45 mg) in CH_2Cl_2 (1 mL) and pyridine (1 mL) was added TsCl (100 mg). After stirring for 1 h, the solution was added to saturated $NaHCO_3$ (20 mL) and EtOAc (20 mL) and stirred 30 min and the organic phase was washed with 1 M H_3PO_4 (20 mL), then dried, and evaporated to give 81 mg of crude tosylate **47**. This material was treated with 50 psi of H_2 and 10% Pd/C (50 mg) in MeOH (2 mL) for 4 h, filtered, and evaporated to give 40 mg of crude acid **48**.

To a solution of DMF (0.1 mL) in CH_3CN (1 mL) at −10 °C was added oxalyl chloride (20 μL). After the mixture was stirred for 5 min, the above acid **48** (entrained with EtOAc) was added as a solution in CH_3CN (1 mL). After the solution was stirred at −10 °C for 15 min, (+)-methyl mandelate (30 mg, prepared by Fischer esterification of mandelic acid) was added as a solution in CH_3CN (1 mL), followed by pyridine (0.2 mL). The solution was stirred at −10 °C for 15 min and room temperature for 1 h, diluted with EtOAc (10 mL), washed with 1 M H_3PO_4 (10 mL) and saturated NaCl (10 mL), dried, and evaporated to give 83 mg of a mixture of **49b** plus methyl mandelate.

This procedure was repeated using (±)-methyl mandelate, and the crude products were appropriately mixed to prepare a sample of 99% diastereomeric purity. By examination of the ^1H NMR of this sample and **49b**, specifically the mandelate benzylic proton (**49b**, δ 5.65; other diastereomer, δ 5.76), the determination of >99% optical purity was made.

The crude product from (±)-methyl mandelate was purified by chromatography (20 g of SiO_2, 2% EtOAc in CH_2Cl_2) to give 21 mg, 26% from **2**, of **49a**: ^1H NMR (**49b**, partial) δ 5.65 (s, 1 H), 4.86 (s, 1 H), 3.69 (s, 3 H), 2.38 (s, 3 H); ^1H NMR (other diastereomer, partial) δ 5.76 (s, 1 H), 4.93 (s, 1 H), 3.71 (s, 3 H), 2.36 (s, 3 H). Anal. Calcd for $C_{25}H_{28}N_2O_6S$: C, 62.0; H, 5.8; N, 5.8. Found: C, 62.0; H, 5.9; N, 5.6.

Benzyl *N*-(9-(Phenylfluorenyl)pipecolate (44). A mixture of benzyl pipecolate[13] (1.94 g), 9-PhFlBr (**29**, 3.57 g), K_3PO_4 (2 g), $Pb(NO_3)_2$ (2 g), and CH_3CN (20 mL) was stirred for 24 h, filtered, and evaporated. The residue was dissolved in EtOAc (100 mL), washed with 1 M H_3PO_4 (50 mL), then saturated $NaHCO_3$ (50 mL), dried, and evaporated, and the residue was recrystallized from absolute EtOH to give 1.49 g (37%) of **44**: mp 119–122 °C; IR (Nujol) 1730 cm^{-1}; ^1H NMR δ 7.6–7.0 (m, 18 H), 4.42 (d, *J* = 12.7 Hz, 1 H), 4.26 (d, *J* = 12.7 Hz, 1 H), 3.7 (m, 1 H), 3.47 (d, *J* = 5.1 Hz, 1 H), 3.09 (d, *J* = 11.5 Hz, 1 H). Anal. Calcd for $C_{32}H_{29}NO_2$: C, 83.6; H, 6.4; N, 3.1. Found: C, 83.7; H, 6.3; N, 3.0.

1-Phenylpropyl *N*-(9-Phenylfluorenyl)pipecolate (45). To a solution of diisopropylamine (0.41 mL) in THF (2 mL) at 0 °C was added *n*-BuLi (1.4 mL, 1.4 M in hexane). After it was stirred for 15 min, the solution was cooled to −78 °C and ester **44** (460 mg) was added as a solution in THF (2 mL). After the solution was stirred at −78 °C for 30 min, EtI (0.16 mL) was added, and the mixture was stirred an additional 30 min and then diluted with saturated $NaHCO_3$ (20 mL) and EtOAc (20 mL). The organic phase was washed with 1 M H_3PO_4 (20 mL), dried, and evaporated, and the residue was chromatographed (disk, 2 mm, 30% CH_2Cl_2 in isooctane) to give 315 mg (65%) of **45** as a 2/1 mix of diastereomers: ^1H NMR (major, minor) δ 7.7–6.8 (m, 18 H), 4.92, 5.05 (t, *J* = 7 Hz, 1 H), 3.76 (m, 1 H), 3.48,3.43 (d, *J* = 5 Hz, 1 H), 3.04 (d, *J* = 11 Hz, 1 H), 2.0–1.2 (m, 8 H), 0.63 (t, *J* = 7 Hz, 3 H). Anal. Calcd for $C_{34}H_{33}NO_2$: C, 83.7; H, 6.8; N, 2.9. Found: C, 83.7; H, 6.8; N, 2.9.

1-Phenylpropyl (2*S*,3*R*)-3-Cyano-3-ethyl-*N*-[2-(3-indolyl)ethyl]pipecolate (52b). A mixture of tryptophyl bromide[12] (3.90 g), pipecolate **2b** (3.49 g), $NaHCO_3$ (5 g), and CH_3CN (12 mL) was refluxed with vigorous stirring for 24 h. The mixture was diluted with water (100 mL) and extracted with EtOAc (100 mL). The EtOAc extract was dried and evaporated, and the residue was chromatographed (SiO_2, 200 g, CH_2Cl_2 to 50/50 EtOAc/isooctane) to give 4.10 g (80%) of **52b** as a mix of diastereomers: Anal. Calcd for $C_{28}H_{33}N_3O_2$: C, 75.8; H, 7.5; N, 9.5. Found: C, 75.8; H, 7.6; N, 9.3.

1-Cyano-1-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizines (4 and 53). The mixture of diastereotopic esters **52b** (4.10 g) in MeOH (40 mL) and EtOAc (40 mL) with 10% Pd/C (2.0 g) was shaken with 50 psi of H_2 for 4 h. The mixture was filtered and evaporated to give 3.64 g of crude acid **3**. To a suspension of this acid in CH_2Cl_2 (36 mL) and pyridine (7.2 mL) was added TsCl (3.6 g). After stirring for 1 h, the solution was diluted with saturated $NaHCO_3$ (100 mL) and stirred 1 h, and the organic phase was separated, dried, evaporated, and chromatographed (disk, 4 mm, 30 to 50% EtOAc in isooctane) to give 732 mg (28%) of **53**, followed by 536 mg (20%) of **4**.

In another experiment, 475 mg of esters **52b** was treated with H_2 as above. The crude residue was heated with $PhPOCl_2$ (5 mL) at 95 °C for 10 min, poured into saturated $NaHCO_3$ (150 mL) and EtOAc (50 mL), and stirred at room temperature for 1 h. The organic phase was separated, dried, evaporated, and chromatographed (disk, 2 mm, 30 to 50% EtOAc in isooctane) to give 66 mg (22%) of **53**, followed by 105 mg (34%) of **4**.

4: $[\alpha]^{20}_D$ −108° (*c* 1, $CHCl_3$); IR (Nujol) 3380, 2245, 745 cm^{-1}; ^1H NMR δ 8.12 (br s, 1 H), 7.5–7.1 (m, 4 H), 3.71 (s, 1 H), 3.3–1.6 (m, 12 H), 1.19 (t, *J* = 7.5 Hz, 3 H). Anal. Calcd for $C_{18}H_{21}N_3$: C, 77.4; H, 7.6; N, 15.0. Found: C, 77.3; H, 7.6; N, 15.0.

53: $[\alpha]^{20}_D$ −32° (*c* 2, $CHCl_3$); IR (Nujol) 3400, 2240, 740 cm^{-1}; ^1H NMR δ 8.66 (br s, 1 H), 7.5–7.1 (m, 4 H), 3.80 (s, 1 H), 3.1–1.3 (m, 12 H), 0.97 (t, *J* = 7 Hz, 3 H). Anal. Calcd for $C_{18}H_{21}N_3$: C,

(13) Padgett, H. C.; Csendes, I. G.; Rapoport, J. *J. Org. Chem.* **1979**, *44*, 3492.

77.4; H, 7.6; N, 15.0. Found: C, 77.2; H, 7.9; N, 14.8.

Equilibration of Indole Nitrile 53. A solution of **53** (732 mg) in TFA (5 mL) was refluxed for 24 h, diluted with saturated $NaHCO_3$ (100 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The CH_2Cl_2 extracts were dried and evaporated, and the residue was chromatographed (disk, 2 mm, 30 to 50% EtOAc in isooctane) to give 325 mg (44%) of educt **53**, followed by 333 mg (46%) of desired indole nitrile 4.

1-Cyano-1-ethyl-12-[(methoxycarbonyl)methyl]-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (54). To a solution of 4 (482 mg) in DMF (15 mL) at 0 °C was added NaH (1.5 g, 50% in oil). After it was stirred for 1 h, the mixture was cooled to −30 °C and methyl bromoacetate (3.0 mL) was added. After the solution was stirred for 1 h, the reaction was quenched with MeOH (1 mL), diluted with saturated $NaHCO_3$ (20 mL) and water (50 mL), and extracted with EtOAc (100, 30 mL). The combined organic extracts were extracted with 1 M H_3PO_4 (3 × 50 mL), which was basified with NH_4OH (25 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined CH_2Cl_2 extracts were dried and evaporated, residual solvent was entrained with toluene (2 × 250, 50 mL), and the residue was chromatographed (disk, 2 mm, 50–100% EtOAc in isooctane) to give 413 mg (71%) of **54**: mp 203–205 °C; $[\alpha]^{20}_D$ −108° (*c* 2, $CHCl_3$); IR (Nujol) 2250, 1765, 45 cm^{-1}; ^1H NMR δ 7.54 (d, *J* = 7.5 Hz, 1 H), 7.3–7.1 (m, 3 H), 4.81 (d, *J* = 17.8 Hz, 1 H), 4.59 (d, *J* = 17.8 Hz, 1 H), 3.9 (m, 1 H), 3.68 (s, 3 H), 3.62 (s, 1 H), 3.3–1.4 (m, 11 H), 1.03 (t, *J* = 7.3 Hz, 3 H). Anal. Calcd for $C_{21}H_{25}N_3O_2$: C, 71.8; H, 7.2; N, 12.0. Found: C, 71.9; H, 7.2; N, 11.9.

(3*S*,16*R*)-14-(Methoxycarbonyl)-15-oxoeburnane (55). To a solution of diisopropylamine (0.1 mL) in THF (1 mL) at 0 °C was added *n*-BuLi (0.3 mL, 1.4 M in hexane). After it was stirred for 15 min, the solution was cooled to −78 °C and nitrile ester **54** (52 mg) was added as a solution in THF (2 mL). The reaction was stirred at −78 °C for 15 min and then at 0 °C for 9 h, diluted with saturated $NaHCO_3$ (10 mL), and extracted with EtOAc (2 × 10 mL). The combined EtOAc phases were extracted with 1 M H_3PO_4 (3 × 10 mL); the acid phases were made basic to pH 8 with $KHCO_3$ and then extracted with CH_2Cl_2 (3 × 10 mL). Evaporation of the dried CH_2Cl_2 extracts and chromatography (disk, 1 mm, 20% isooctane in EtOAc) of the residue gave 29 mg (56%) of **55**: $[\alpha]^{20}_D$ +97° (*c* 2.6, $CHCl_3$); IR ($CHCl_3$) 1755, 1720 cm^{-1}; ^1H NMR δ 7.6 (m, 1 H), 7.3–7.1 (m, 3 H), 5.54 (s, 1 H), 4.59 (s, 1 H), 3.73 (s, 3 H), 3.6–1.2 (m, 12 H), 0.95 (t, *J* = 7.4 Hz, 3 H).

(3*S*,14*S*,15*S*,16*R*)-14-(Methoxycarbonyl)-15-hydroxyeburnane (56). To a solution of **55** (29 mg) in MeOH (1 mL) at −25 °C was added $NaBH_4$ (20 mg). After the mixture was stirred for 3 min, the reaction was quenched with AcOH (0.2 mL), diluted with saturated $NaHCO_3$ (10 mL), and extracted with CH_2Cl_2 (10, 5 mL). The CH_2Cl_2 extracts were dried and evaporated, and the residue was chromatographed (disk, 1 mm, 100/40/10 isooctane/EtOAc/MeOH) to give 26 mg (90%) of **56**, identical (^1H NMR) with that reported previously.[10]

Apovincamine (5). To a solution of **56** (20 mg) in CH_2Cl_2 (1 mL) at 0 °C was added Et_3N (0.3 mL) and MsCl (0.1 mL). After stirring for 30 min, the solution was diluted with saturated $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (10, 2 × 5 mL). The CH_2Cl_2 extracts were dried and evaporated, and the residue was dissolved in DBU (0.2 mL), heated at 100 °C for 1 h, diluted with saturated $NaHCO_3$ (30 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The CH_2Cl_2 extracts were dried and evaporated, and the residue was chromatographed (disk, 1 mm, 100/40/10, isooctane/EtOAc/MeOH) to give 11 mg (55%) of **5**, identical (IR, ^1H NMR) with a sample prepared by acid-catalyzed dehydration of vincamine.[11]

Optical Purity Determination. Apovincaminic Acid Methyl Mandelate Ester (58). To a solution of apovincamine (**5**, 48 mg) in MeOH (2.5 mL) and THF (2.5 mL) was added 2 N NaOH (5 mL). After stirring for 12 h, the solution was taken to pH 6 with 1 M H_3PO_4 (5 mL), and extracted with 25% *i*-PrOH in $CHCl_3$ (3 × 20 mL). The organic extracts were dried and evaporated to give a crude residue of **57**, which was dissolved in pyridine (5 mL), (±)-methyl mandelate (50 mg) was added, the solution was cooled to 0 °C, and TsCl (200 mg) was added. After it was stirred for 1 h, the solution was diluted with saturated $NaHCO_3$ (50 mL) and CH_2Cl_2 (20 mL) and stirred at room temperature for 1 h, the phases were separated, and the aqueous phase was extracted with additional CH_2Cl_2 (2 × 20 mL). The combined CH_2Cl_2 extracts were evaporated, the residue was dissolved in EtOAc (20 mL) and extracted with 1 M H_3PO_4 (40, 2 × 20 mL), and the separate acid extracts were sequentially back extracted with EtOAc (2 × 20 mL). These acid phases were then combined, basified with NH_4OH (20 mL), and extracted with CH_2Cl_2 (20, 2 × 10 mL). The final extracts were dried and evaporated to give 57 mg (84%) of ester **58a**: ^1H NMR (**58b**, other diastereomer) δ 6.19, 6.45 (s, 1 H), 6.15, 6.16 (s, 1 H), 4.14, 4.17 (s, 1 H), 3.83, 3.77 (s, 3 H), 0.96, 1.05 (t, *J* = 7.4 Hz, 3 H). Anal. Calcd for $C_{29}H_{30}N_2O_4$: C, 74.0; H, 6.4; N, 6.0. Found: C, 74.2; H, 6.6; N, 6.0.

For the determination of optical purity, apovincamine (**5**) was coupled separately to (+)- and (±)-methyl mandelate as above, except that the acid–base extraction was omitted. The optical purity was determined exactly as described for **49**, and was found to be >99%.

Studies of Rutaecarpine and Related Quinazolinocarboline Alkaloids

Jan Bergman* and Solveig Bergman

Department of Organic Chemistry, Royal Institute of Technology, S-100 44 Stockholm, Sweden

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Quinazolinocarboline alkaloids, e.g., rutaecarpine (**1**), can readily be synthesized by treating tryptamine with 2-(trifluoromethyl)-4*H*-3,1-benzoxazin-4-one (quickly generated in situ from trifluoroacetic anhydride (TFAA) and 2*H*-3,1-benzoxazine-2,4(1*H*)-dione. The product formed, 3-[2-(3-indolyl)ethyl]-2-(trifluoromethyl)-4-(3*H*)-quinazolinone (**5**), is then cyclized (HCl/HOAc) to 13b-(trifluoromethyl)-13b,14-dihydrorutaecarpine (**6**), whereupon CF_3H is eliminated by treatment with base. The sequence can conveniently be performed as a three-reaction one-pot procedure giving rutaecarpine (**1**) in 99% yield within 3 h. The approach can readily be extended to the synthesis of evodiamine (**2**), 13,13b-dehydroevodiamine (**38a**), and 13b,14-dihydrorutaecarpine (**21**). Thus treatment of 3-[2-(3-indolyl)ethyl]-4(3*H*)-quinazolinone (**19**) with TFAA effected cyclization to 13b-(trifluoroacetyl)-13b,14-dihydrorutaecarpine (**20**), which can be readily hydrolyzed to 13b,14-dihydrorutaecarpine (**21**).

The dried fruit of *Evodia rutaecarpa* has a long traditional[1] in Chinese medicine and under the name Wu-Chu-Yu the drug has been used against, e.g., headache, dysentery, cholera and worm infestations.[2]

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