Total Synthesis of (-)-Alloaristoteline, (-)-Serratoline, and (+)-Aristotelone

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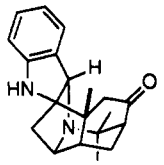
Received October 8, 1992

The *Aristotelia* alkaloids (-)-alloaristoteline (4), (-)-serratoline (12), and (+)-aristotelone (13) have been prepared as summarized in Scheme IV. Thus, via the method of Stevens, (1*S*)-(-)-β-pinene (9) and 3-indolylacetonitrile (10) were coupled by a $Hg(NO_3)_2$-mediated Ritter reaction followed by reduction of the resulting imine to give (+)-makomakine (11). An intramolecular Friedel-Crafts reaction delivered (+)-aristoteline (3), which was oxidized by reaction with oxygen and platinum. Reduction of the intermediate hydroperoxide delivered alkaloid 12. Base-catalyzed skeletal rearrangement of 12 provided alkaloid 13, which was reduced with $LiAlH_4$ to obtain a mixture of secondary alcohols, **14a,b**. Treatment of each of these alcohols with HCl in methanol afforded (-)-alloaristoteline (4).

In work directed toward a biomimetic synthesis of the hexacyclic *Aristotelia* alkaloid[1] aristone[2] (1), we are currently attempting the synthesis of the 19-desoxy analog (2) from (+)-aristoteline[3] (3). The two biomimetic routes that we have pursued also lend themselves to the synthesis of (-)-alloaristoteline[4] (4), one of two isolated indole alkaloids in which the indole unit is inverted.[4c] Herein we report the results of our investigations, which have provided a biomimetic synthesis of 4 from 3, a transformation that has also been recently reported by Borschberg and co-workers.[5]



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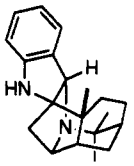

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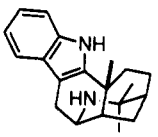

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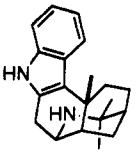

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We initially envisaged that both 2 and 4 might arise from 3 through the hypothetical acid-catalyzed skeletal rearrangement shown in Scheme I. Protonation at the indole C(3) position[6] followed by a 1,2-alkyl migration could form the spiro intermediate 5, which might undergo alkyl shifts to return to 3 (path a) or rearrange to 4 (path b) or suffer attack by the secondary amine (path c) to generate hexacyclic structure 2. Precedent for such a skeletal rearrangement is found in the work of Nakazaki,[7] who has shown that 2,3-disubstituted indoles undergo a double Wagner-Meerwein type rearrangement when heated at 220-240 °C for 15-20 min in an $AlCl_3$-NaCl melt. The mechanism invoked by Nakazaki to explain the observed scrambling of C-2 and C-3 substituents is that shown for the conversion of 3 into 4, with $AlCl_3$ acting as the electrophile instead of a proton.

Our research towards the synthesis of 2 and 4 began with a search for a protic acid catalyst to affect the proposed skeletal rearrangement. We anticipated that conditions that would cause the interconversion of tetrahydrocarbazole isomers 6 and 7 (Scheme II) might be successfully applied to the synthesis of 2 and 4. Compounds 6 and 7 were synthesized by application of the Fischer indole synthesis to 4-methylcyclohexanone and 3-methylcyclohexanone, respectively (Scheme II).[8] As expected, the reaction with 4-methylcyclohexanone gives a single isomer, whereas the reaction with 3-methylcyclohexanone gives isomers 7 and 8 in a ratio of approximately 10:1.

The desired skeletal rearrangement was observed[9] when either 6 or 7 was heated at reflux in formic acid or a solution of 0.05 M H_2SO_4 in acetic acid. However, the reaction was disappointingly slow under these conditions. An equilibrium mixture (approximately 1:1) of the two isomers was obtained when a solution of either 6 or 7 in formic acid was maintained at reflux for 1 month (Scheme III).[10] Harsher conditions, such as 1.8 M H_2SO_4 in acetic acid at reflux and 2.0 M HCl in acetic acid at reflux, resulted only in substrate decomposition. Indole alkaloid 3, whose

(1) For reviews of the *Aristotelia* alkaloids, see: (a) Borschberg, H.-J. *Chimia* **1991**, *45*, 329-341. (b) Bick, I. R. C.; Hai, M. A. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. XXIV, Chapter 3.

(2) (a) Bittner, M.; Silva, M.; Gopalakrishna, E. M.; Watson, W. H.; Zabel, V.; Matlin, S. A.; Sammes, P. G. *J. Chem. Soc., Chem. Commun.* **1978**, 79. (b) Zabel, V.; Watson, W. H.; Bittner, M.; Silva, M. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2842.

(3) (a) Anderson, B. F.; Robertson, G. B.; Avey, H. P.; Donovan, W. F.; Bick, I. R. C.; Bremner, J. B.; Finney, A. J. T.; Preston, N. W.; Gallagher, R. T.; Russell, G. B. *J. Chem. Soc., Chem. Commun.* **1975**, 511. (b) Bhakuni, D. S.; Silva, M.; Matlin, S. A.; Sammes, P. G. *Phytochemistry* **1976**, *15*, 574. (c) Kyburz, R.; Schöpp, E.; Bick, I. R. C.; Hesse, M. *Helv. Chim. Acta* **1981**, *64*, 2555.

(4) (a) Kan-Fan, C.; Quirion, J.-C.; Bick, I. R. C.; Husson, H.-P. *Tetrahedron* **1988**, *44*, 1651. (b) Güller, R.; Borschberg, H.-J. *Helv. Chim. Acta* **1991**, *74*, 1643. (c) Structure revision: Quirion, J.-C.; Husson, H.-P.; Kan, C.; Laprévote, O.; Chiaroni, A.; Riche, C.; Burkard, S.; Borschberg, H.-J.; Bick, I. R. C. *J. Org. Chem.* **1992**, *57*, 5848.

(5) Güller, R.; Borschberg, H.-J. *Tetrahedron Asymmetry* **1992**, *3*, 1197.

(6) Hinman, R. L.; Whipple, E. B. *J. Am. Chem. Soc.* **1962**, *84*, 2534.

(7) Nakazaki, M. *Bull. Chem. Soc. Jpn.* **1960**, *33*, 461. The $AlCl_3$-induced rearrangements were performed on 2-methyl-3-phenylindole and 5,6-dihydro-7-benzo[*c*]carbazole and isolated yields of the rearrangement products were 60% and 21%, respectively.

(8) Rogers, C. U.; Corson, B. B. *J. Am. Chem. Soc.* **1947**, *69*, 2910.

(9) The reaction could be monitored quantitatively by GC and qualitatively by TLC, as the two isomers stained differently on silica gel with *p*-anisaldehyde stain.

(10) During this period, substrate decomposition was observed but not measured.

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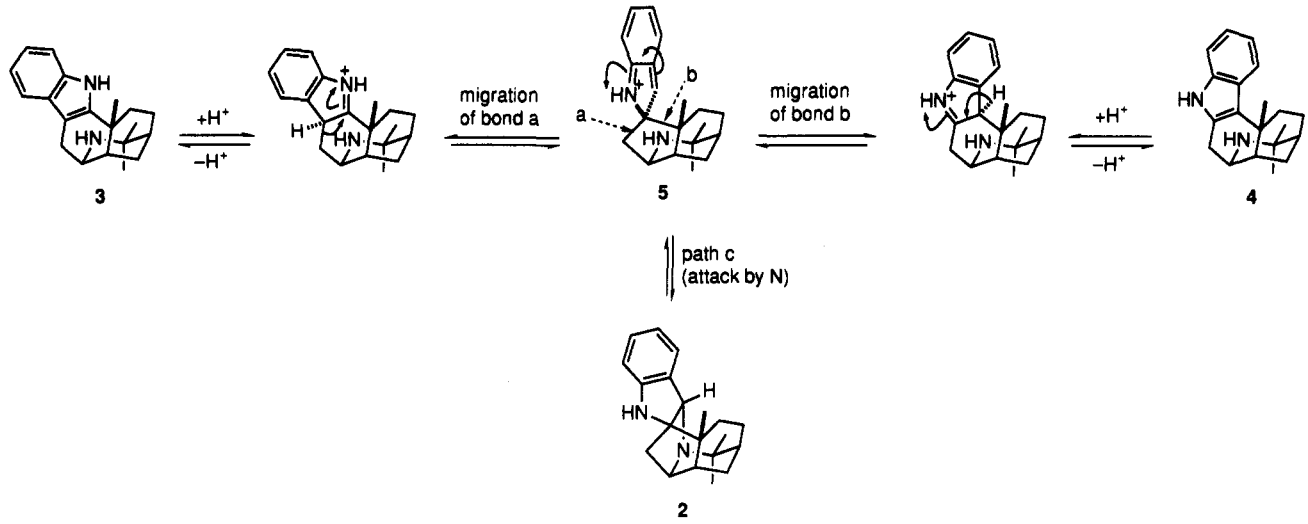
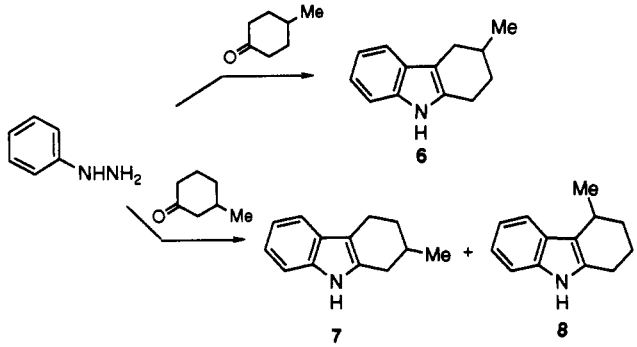
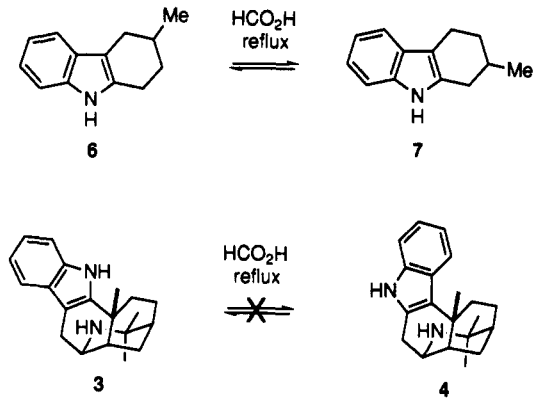
Scheme I



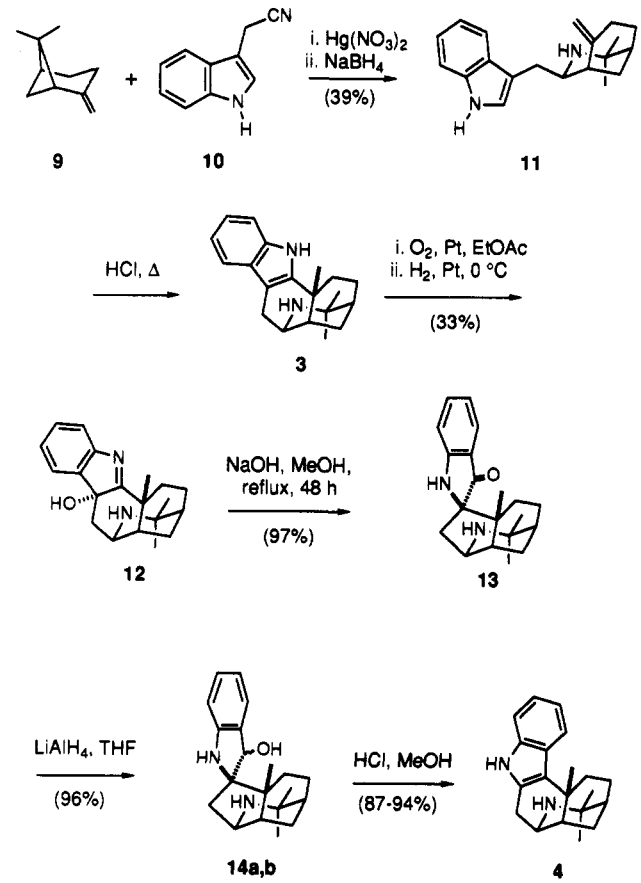
Scheme II



Scheme III



Scheme IV



synthesis will be discussed in the following paragraph, was subjected to the rearrangement conditions (formic acid at reflux for 1 month). A ^{1}H NMR spectrum of the reaction mixture after workup showed primarily **3**, with no **4** detectable, and nothing which could be positively be attributed to the structure **2**. The absence of the anticipated rearrangement product **4** may be explained by the recent observation by Borshberg et al.[4b] that **4** is significantly less stable **3**. Because all the steps in the rearrangement are reversible, an equilibrium involving structures **2**, **3**, and **4** would eventually be established and the amount of each structure present at equilibrium would be dictated by their relative stabilities. This equilibrium may also account for the absence of desoxyaristone (**2**), since the structure of aristone (**1**) is known to embody a significant amount of ring strain. The elongation of several bonds, presumably to relieve ring strain, has been observed in the X-ray crystal structure of **1**.[2b] As a consequence, **2** may also be relatively unstable when compared to **3**.

Our second approach (Scheme IV) to **2** and **4** from **3** is based on biosynthetic schemes suggested by Bittner et al.[2a] and Hesse et al.[3c] This approach was especially attractive because two of the synthetic intermediates are the *Aristotelia* alkaloids (−)-serratoline (**12**)[11] and (+)-aristotelone (**13**),[3b] which had not yet been made by total synthesis. (+)-Aristoteline (**3**) was synthesized following the procedure of Stevens and Kenney.[12] (1*S*)-(−)-β-Pinene (**9**) and 3-indolylacetonitrile (**10**) were coupled in a

(11) (a) Bick, I. R. C.; Hai, M. A.; Preston, N. W.; Gallagher, R. T. *Tetrahedron Lett.* **1980**, *21*, 545. (b) Structure revision: Bick, I. R. C.; Hai, M. A.; Preston, N. W. *Heterocycles* **1983**, *20*, 667.

mercuric nitrate-mediated Ritter reaction to afford an imine, which was stereospecifically reduced in situ with $NaBH_4$ to afford (+)-makomakine (11)[13] in 39% yield. Although the reaction conditions were not altered significantly from those of Stevens and Kenney, the yield that we obtained is more than double the reported yield. This may be attributed to the use of freshly-prepared, anhydrous mercuric nitrate.[14] The hydrochloride salt of 11 was transformed into 3 in 59% yield by treatment with concentrated HCl at reflux.[12,15] Treatment of 3 with oxygen over Adams catalyst for 24 h, followed by hydrogen for 30 min at 0 °C,[16] resulted in a 33% of yield 12, along with 10% of recovered 3. Surprisingly, none of the diastereomeric hydroxyindolenine was isolated. (+)-Aristotelone (13) was produced in 97% yield when a solution of 12 in methanolic NaOH was heated at reflux for 48 h. Although the conversion of hydroxyindolenines to ψ-indoxyl compounds with base is well documented,[1c] the two publications dealing with the isolation of 12[11a,b] report that it is unreactive under basic conditions. Reduction of ψ-indoxyl 13 with excess $LiAlH_4$ in THF afforded two diastereomeric alcohols **14a,b** in a combined yield of 96%. Treatment of both these alcohols with dilute HCl in methanol afforded in 4 in approximately 90% yield.

We are currently investigating conditions under which the synthesis of 2 may be achieved. Following the biosynthetic scheme for 1 proposed by Bittner et al. would involve transforming 13 into 2 directly through the reduction of an immonium ion formed by the attack of the secondary amine on the benzylic center. Hesse et al. have suggested that the sixth ring in 2 may be formed by an intramolecular nucleophilic substitution reaction starting with hydroxyindoline 14.

Experimental Section

General. Unless otherwise indicated, all starting materials were obtained from commercial suppliers and used without further purification. CH_2Cl_2 was distilled under N_2 from CaH_2, and THF was distilled under N_2 from sodium/benzophenone prior to use. All reactions were conducted under a N_2 atmosphere. When reactions were worked up by extraction with CH_2Cl_2, $CHCl_3$, or EtOAc, organic solutions were dried with anhydrous K_2CO_3 and concentrated with a rotory evaporator. Flash chromatography was performed according to the procedure of Still[17] using Merck 60 230–400-mesh silica gel. Reactions and chromatography fractions were analyzed using Merck silica gel 60 F-254 TLC plates. ^1H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ at 500 and 100 MHz, respectively. Chemical shifts are expressed in ppm relative to internal $CHCl_3$. J values are in hertz. For ^{13}C NMR spectra, carbon type is defined as 3 (3), 2 (2), 1 (1), or 0 (C) on the basis of DEPT experiments. Melting points were determined in Pyrex capillaries. IR spectra were measured as solutions in the solvent indicated. Gas chromatography was performed using a Hewlett-Packard 5890A gas chromatograph with a Hewlett-Packard Ultra 2 column. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. The $CHCl_3$ used to measure optical rotations was filtered through alumina, basic Brockman activity I, 60–325 mesh.

3-Methyl-1,2,3,4-tetrahydrocarbazole (6) was prepared according to the procedure of Rogers and Corson.[8] To 70.0 mL of glacial acetic acid (1.12 mol) was added 25.0 mL of 4-methylcyclohexanone (0.204 mol) in a 250-mL round-bottomed flask fitted with a reflux condenser and an addition funnel charged with 20.0 mL of phenylhydrazine (0.204 mol). The solution was brought to reflux, and phenylhydrazine was added to the solution over 30 min. The resulting red-brown solution was maintained at reflux for 1 h. The hot solution was poured into a beaker and allowed to cool to room temperature. The crude pale brown solid which formed upon cooling was isolated by filtration and washed with 20 mL of cold water and 20 mL of cold 75% ethanol. The solid was crystallized from methanol, and the combined first, second, and third crops of white crystals were isolated (23.6 g, 62%), mp 107.5–109.0 °C (lit.[8] mp 108–111 °C). IR (CCl_4): 3480, 3060, 2960, 2920, 2880, 2840, 1465, 1325, 1230, 1010 cm^{-1}. ^1H NMR (500 MHz): δ 1.16 (d, 3, J = 6.5), 1.59 (dddd, 1, J = 6.2, 9.9, 11.2, 13.2), 1.94–2.01 (m, 2), 2.30 (dddd, 1, J = 1.6, 2.4, 9.4, 15.3), 2.73–2.81 (m, 2), 2.86 (mdd, 1, J = 5.0, 15.3), 7.09 (dt, 1, J = 1.3, 7.4), 7.13 (dt, 1, J = 1.4, 7.4), 7.27 (ddd, 1, J = 0.8, 1.3, 7.7), 7.47 (md, 1, J = 7.5), 7.64 (br s, 1). ^{13}C NMR (100 MHz): δ 21.8 (3), 22.9 (2), 29.4 (2), 29.7 (1), 31.4 (2), 110.2 (0), 110.4 (1), 117.7 (1), 119.1 (1), 121.0 (1), 127.8 (0), 133.9 (0), 136.0 (0). Anal. Calcd for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.23; H, 8.17; N, 7.23.

2-Methyl-1,2,3,4-tetrahydrocarbazole (7) was prepared according to the procedure of Rogers and Corson.[8] In a 50-mL flask fitted with a reflux condenser and an addition funnel charged with 4.92 mL of phenylhydrazine (50.0 mmol) was brought to reflux a solution of 6.14 mL of 3-methylcyclohexanone (50.0 mmol) in 17.1 mL of glacial acetic acid (0.30 mol). The phenylhydrazine was added to the refluxing solution over 30 min. The red-brown solution was maintained at reflux for 2 h, then poured into a beaker, and allowed to cool to room temperature. The crude brown solid product that formed upon cooling was isolated by filtration and washed with four 5-mL portions of cold water. The crude solid, a 10:1 mixture of 7 and 8, was crystallized and recrystallized from methanol to afford 4.71 g of pale green crystals (51%), mp 102.0–103.0 °C (lit.[8] mp 98–100 °C). IR ($CHCl_3$): 3480, 3010, 2960, 2940, 2920, 2880, 2860, 1470, 1305, 1230 cm^{-1}. ^1H NMR (500 MHz): δ 1.16 (d, 3, J = 6.7), 1.49–1.57 (m, 1), 1.96–2.01 (m, 1), 2.02–2.10 (m, 1), 2.37 (tdd, 1, J = 2.1, 9.6, 15.9), 2.67–2.75 (m, 1), 2.77 (dd, 1, J = 5.2, 16.1), 2.83 (md, 1, J = 15.4), 7.10 (dt, 1, J = 1.4, 7.4), 7.14 (dt, 1, J = 1.4, 7.5), 7.28 (ddd, 1, J = 0.7, 1.3, 7.9), 7.49 (md, 1, J = 7.6), 7.59 (br s, 1). ^{13}C NMR (100 MHz): δ 20.5 (2), 21.8 (3), 29.7 (1), 31.5 (2), 31.7 (2), 109.8 (0), 110.4 (1), 117.8 (1), 119.1 (1), 121.0 (1), 127.7 (0), 134.1 (0), 135.7 (0). Anal. Calcd for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.27; H, 8.27; N, 7.33.

General Experimental for the Acidic Treatment of 6 and 7. Tetrahydrocarbazole 6 or 7 was dissolved in the acidic medium (10–30 mL), and the solution was brought to reflux. Aliquots (1–2 mL) were taken from the reaction mixture periodically and prepared for injection onto the GC column in the following manner: To the aliquot was added 3.0 M NaOH until a basic pH had been reached. The aliquot was extracted with three 15-mL portions of ether or EtOAc. The organic phases were combined, washed with 10 mL of water, dried, and concentrated. The resulting residue was dissolved in ether (2–4 mL). Additional solvent was added to the solution if the volume of the reaction had significantly decreased due to the removal of aliquots. The ^1H NMR spectrum of the product after workup showed extensive decomposition.

(+)-Makomakine (11) was prepared by modifying the procedure of Stevens and Kenny.[12] In a dry 50-mL flask under N_2 was dissolved 2.75 g of 3-indolylacetonitrile (17.6 mmol) in 8 mL of CH_2Cl_2. Anhydrous mercuric nitrate[14] (0.85 g, 2.62 mmol) was quickly added to the dark red solution, and the resulting mixture was cooled in a CH_3CN/CO_2 bath for 20 min. (1S)-(−)-β-Pinene (0.40 mL, 2.52 mmol) was added over 20 min to the mixture, which was then allowed to warm slowly to rt over 2 h. The dark red solution was cooled in an ice bath for 15 min, and 10 mL of 3 M NaOH in MeOH was added, followed by 10 mL of 0.5 M $NaBH_4$ in 3 M NaOH in MeOH (5 mmol). The reaction was allowed to warm to rt and was stirred for 3 h. The reaction mixture was filtered through a Celite pad directly into a separation funnel. The Celite was rinsed throughly with EtOAc, causing an emulsion to form in the separation funnel. Water was added until the emulsion dissipated, and the organic layer was separated. The aqueous layer was extracted twice with EtOAc, and the

(12) Stevens, R. V.; Kenney, P. M. *J. Chem. Soc., Chem. Commun.* **1983**, 384.
(13) Bick, I. R. C.; Hai, M. A. *Heterocycles* **1981**, *16*, 1301.
(14) Ferraro, J. R.; Gibson, G. *J. Am. Chem. Soc.* **1953**, 5747.
(15) Mirand, C.; Massiot, G.; Lévy, J. *J. Org. Chem.* **1982**, *47*, 4170.
(16) Witkop, B.; Patrick, J. B. *J. Am. Chem. Soc.* **1951**, *73*, 2188.
(17) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

organic phases were combined, washed with water and brine, dried, and evaporated. Flash chromatography was performed on silica gel (1:10 acetone/hexane, 3% triethylamine) to separate the product from 3-indolylacetonitrile (**10**). A second flash column (eluent 1:12 acetone/hexane, 3% triethylamine) was required to purify the product. The product was isolated as a white solid (0.289 g, 39%), mp 95–97 °C (lit.[13] mp 99–100 °C) and $[\alpha]_D$ +126 ± 2 (c = 0.590, $CHCl_3$) (lit.[13] $[\alpha]_D$ +131.2 (c = 0.5, $CHCl_3$). IR (CH_2Cl_2): 3480, 3060, 2950–2880, 1640, 1460, 900 cm^{-1}. ^1H NMR (500 MHz): δ 1.11 (s, 3), 1.15 (s, 3), 1.41 (quint, 1, J = 3.2), 1.50 (ddt, 1, J = 4.1, 6.1, 13.5), 1.59 (td, 1, J = 3.2, 12.7), 2.06–2.10 (m, 1), 2.13 (qd, 1, J = 3.0, 12.9), 2.19 (mdd, 1, J = 5.7, 14.4), 2.28 (m, 1), 2.63 (ddd, 1, J = 0.9, 7.8, 14.3), 2.77 (ddd, 1 J = 0.9, 5.9, 14.3), 3.09 (dt, 1, J = 6.3, 13.9), 3.49 (ddd, 1, J = 2.7, 5.9, 7.8), 4.59 (t, 1, J = 2.6), 4.78 (t, 1 J = 2.4), 7.01 (d, 1, J = 2.3), 7.11 (ddd, 1 J = 1.1, 7.0, 8.0), 7.19 (ddd, 1, J = 1.2, 7.0, 8.2), 7.36 (td, 1, J = 0.9, 8.1), 7.64 (md, 1, J = 7.9), 7.97 (br s, 1). ^{13}C NMR (100 MHz): δ 27.1 (3), 29.3 (2), 29.8 (3), 31.4 (2), 32.0 (2), 33.2 (2), 36.7 (1), 43.2 (1), 53.2 (0), 54.1 (1), 108.8 (2), 111.0 (1), 113.7 (0), 119.1 (1), 119.3 (1), 121.8 (1), 122.4 (1), 127.8 (0), 136.4 (0), 150.5 (0). The observed NMR data were in excellent agreement with those published.[12,15]

(+)-Aristoteline (3) was prepared according to a modified literature procedure.[12,15] The hydrochloride salt of **11** (67.5 mg, 0.184 mmol) was dissolved in 10 mL of concentrated hydrochloric acid, and the resulting solution was heated at reflux for 3.5 h. The reaction mixture was cooled in an ice bath, and 45 mL of 3 M NaOH was slowly added with stirring. The basic mixture was extracted with $CHCl_3$ (3 × 60 mL). The combined organic phases were dried and concentrated. The product was purified by flash chromatography on silica using the lower layer of a mixture of 92:2:5 $CHCl_3$/MeOH/aqueous NH_3 as the eluent. The product was isolated as 32.0 mg of a pale yellow foam (59%) and was crystallized (hexane/acetone/triethylamine/CH_2Cl_2) to yield white crystals, mp 161.5–162.0 °C (lit.[3c] mp 160–162.5 °C); $[\alpha]_D$ +24.1 ± 0.2 (c = 1.83, $CHCl_3$) (lit.[3c] $[\alpha]_D$ +23 ± 4 (c = 1.840, $CHCl_3$)). IR (CCl_4): 3480, 2960–2880, 1460, 1290, 905 cm^{-1}. ^1H NMR (500 MHz): δ 1.09 (s, 3), 1.31 (s, 3), 1.41 (quint, 1, J = 3.3), 1.47 (s, 3), 1.61–1.72 (m, 3), 1.91–1.95 (m, 1), 1.98 (td, 1, J = 3.2, 13.4), 2.07 (qd, 1, J = 3.1, 13.5), 2.31 (m, 1), 2.63 (d, 1, J = 16.4), 3.09 (dd, 1, J = 5.8, 16.3), 3.63 (md, 1, J = 5.7), 7.08 (ddd, 1, J = 1.2, 7.1, 7.8), 7.13 (ddd, 1, J = 1.3, 7.1, 7.7), 7.30 (d, 1, J = 7.8), 7.47 (d, 1, J = 7.7), 7.79 (br s, 1). ^{13}C NMR (100 MHz): δ 25.2 (3), 25.5 (2), 27.7 (3), 27.9 (2), 28.7 (2), 29.2 (3), 33.2 (0), 35.7 (1), 36.0 (2), 39.4 (1), 50.5 (1), 53.3 (0), 104.5 (0), 110.5 (1), 118.2 (1), 119.1 (1), 121.0 (1), 128.3 (0), 136.1 (0), 142.6 (0). The observed NMR data were in excellent agreement with those published.[3c,4a]

(-)-Serratoline (12). In a 10-mL flask connected to a low-pressure hydrogenation apparatus was stirred a suspension of 122.0 mg of platinum(II) oxide (0.54 mmol) in 0.7 mL of EtOAc under H_2 for 1 h at rt. The flask was opened and 100.0 mg of **3** (0.34 mmol) was added. The flask walls were rinsed with 0.7 mL of EtOAc. The flask was evacuated, cooled in an ice bath for 10 min, and filled with O_2. The reaction was stirred under O_2 at 1 atm for 24 h at rt. The flask was again removed from the hydrogenation apparatus, and catalyst adhering to the flask walls was rinsed into the reaction mixture with 1 mL of EtOAc. The flask was evacuated, cooled in an ice bath for 10 min, and filled with H_2 (at this stage cooling is necessary to avoid an explosion). The reaction was stirred under H_2 at 1 atm for 25 min, at which time the rate of H_2 absorption had significantly declined. The reaction mixture was filtered through a pad of Celite and concentrated. The crude yellow foam was subjected to flash chromatography on silica gel (12:1 hexanes/acetone, 3% triethylamine), to obtain 35.0 mg (33%) of **12** as a white foam and 9.6 mg (10%) of recovered **3**. The product was crystallized (hexanes/THF/triethylamine) to afford white crystals, mp 167–170 °C (lit.[11a] mp 157–160 °C (MeOH)). IR (CH_2Cl_2): 3680, 3480, 3190 (br), 2980, 2950, 2920, 1620, 1605, 1575, 1465, 1390, 1245, 1100, 1050, 1020. ^1H NMR (500 MHz): δ 1.25 (s, 3), 1.30 (s, 3), 1.37 (dd, 1, J = 6.1, 14.4), 1.51 (dd, 1, J = 2.9, 14.6), 1.55 (m, 1), 1.56 (s, 3), 1.77 (ddt, 1, J = 3.9, 5.9, 14.2), 1.98–2.04 (m, 3), 2.44 (dd, 1, J = 2.8, 14.5), 3.05 (dt, 1, J = 5.9, 14.2), 3.58 (q, 1, J = 2.8), 7.19 (dt, 1, J = 0.9, 7.4), 7.32 (dt, 1, J = 1.3, 7.6), 7.36 (d, 1, J = 7.2), 7.54 (d, 1, J = 7.7). ^{13}C NMR (100 MHz): δ 23.6 (3), 24.4 (2), 26.5 (2), 28.0 (3), 28.3 (2), 29.6 (3), 35.6 (1), 41.5 (0), 43.4 (2), 44.2 (1), 52.4 (1), 53.7 (0), 83.9 (0), 120.4 (1), 122.1 (1), 125.7 (1), 129.1 (1),[18] 141.1 (0), 152.6 (0), 191.0 (0). The observed NMR data were in agreement with those reported.[5] The $[\alpha]_D$ of this compound was found to be irreproducible, and in general, greater than the published values of $[\alpha]_D$ −68.25 ($CHCl_3$)[11a] and −64 (c = 0.91, $CHCl_3$).[5] A sample recrystallized from hexanes/THF/triethylamine had $[\alpha]_D$ −87 ± 1 (c = 0.91, $CHCl_3$), but samples purified by preparative TLC (5 elutions with 10:1 hexanes/acetone/3% triethylamine) had $[\alpha]_D$ −104 ± 1 (c = 0.98, $CHCl_3$). In general, the observed rotation tended to increase as a given sample was handled. One possible explanation for this behavior is that the molecule undergoes either decomposition or reacts with a constituent of the atmosphere (e.g., O_2 or CO_2) to produce small amounts of highly levorotatory impurities. Similar behavior was observed for (+)-aristotelone (**13**).

(+)-Aristotelone (13). A solution of 264.0 mg of **12** (0.852 mmol) in 60 mL of 1.5 M NaOH in MeOH was heated at reflux under N_2 for 2 d. The resulting yellow-green solution was allowed to cool to rt and then concentrated to approximately half the volume with a rotary evaporator. Water (30 mL) was added, and the mixture was extracted with three 100-mL portions of CH_2Cl_2. The combined organic extracts were washed twice with 100-mL portions of water. The extracts were dried and concentrated to yield **13** as a yellow solid (256.0 mg, 97%), which was pure by ^1H NMR, ^{13}C NMR, TLC, with $[\alpha]_D$ +266 ± 3 (c = 1.07, $CHCl_3$) ((lit.[5] $[\alpha]_D$ +264 (c = 1.12, $CHCl_3$)) and mp 210 °C dec. This yellow solid was crystallized from MeOH to give material with mp 217–220.5 °C dec (lit.[3b] mp 218–222 °C). IR (CH_2Cl_2): 3420, 2980–2880, 1690, 1615, 1485, 1460, 1320, 1150, 1075, 900. ^1H NMR (500 MHz): δ 0.88 (d, 3, J = 0.9), 0.91 (mdd, 1, J = 6.1, 14.7), 1.14 (s, 3), 1.16 (s, 3), 1.32 (quint, 1, J = 3.3), 1.55 (ddt, 1, J = 4.0, 6.0, 14.3), 1.58 (m, 1), 1.65 (td, 1, J = 3.0, 13.5), 1.98 (md, 1, J = 14.3), 2.10 (dd, 1, J = 1.6, 15.3), 2.14 (qd, 1, J = 3.5, 13.4), 2.28 (dd, 1, J = 7.3, 15.3), 2.82 (dt, 1, J = 6.0, 14.5), 3.69 (ddd, 1, J = 1.5, 5.4, 7.1), 4.80 (br s, 1), 6.75 (ddd, 1, J = 0.9, 7.1, 7.8), 6.77 (dt, 1, J = 0.8, 8.3), 7.39 (ddd, 1, J = 1.4, 7.1, 8.3), 7.54 (md, 1, J = 7.7). ^{13}C NMR (100 MHz) δ 19.2 (3), 23.6 (2), 25.0 (2), 27.2 (3), 28.5 (2), 30.0 (3), 35.5 (1), 45.4 (1), 45.9 (2), 49.0 (0), 52.7 (1), 53.0 (0), 78.5 (0), 111.2 (1), 118.3 (1), 122 (0), 124.3 (1), 136.9 (1), 159.8 (0), 202.3 (0). The observed NMR data were in agreement with those reported.[5]

Reduction of 13. (+)-Aristotelone (**13**) (200 mg, 0.64 mmol) was dissolved in 7 mL of THF, cooled in an ice bath for 10 min, and then added by cannula to a suspension of 27 mg of $LiAlH_4$ (0.71 mmol) in 1.5 mL of THF at 0 °C. The flask that contained (+)-aristotelone was rinsed twice with 1-mL portions of THF, which were transferred by cannula to the reaction mixture. The red-brown reaction mixture was stirred at 0 °C for 1.5 h, during which time an additional 72 mg of $LiAlH_4$ (1.90 mmol) was added. The reaction was allowed to warm to rt, stirred for 1.5 h, cooled in an ice/H_2O bath for 10 min, and quenched by the addition of 0.2 mL of H_2O, 0.2 mL of 15% NaOH, and 0.6 mL of H_2O. Anhydrous K_2CO_3 was added to the flask, and the mixture was stirred for 15 min. The solids were removed by filtration through a glass frit, and the filtrate was concentrated to a yellow solid, which was subjected to flash chromatography on silica gel (1:4 acetone/hexane, 3% triethylamine). Alcohols **14a,b** were isolated in a combined yield of 96%.

Less Polar Isomer 14a. This isomer, with R_f = 0.33 (2:1 hexanes/acetone, 3% triethylamine), was isolated as an off-white solid (82.3 mg, 41%) which was crystallized ($CHCl_3$/hexanes) to long thin colorless crystals, mp 160.5–161.5 °C, $[\alpha]_D$ +140 ± 4 (c = 0.41, $CHCl_3$). IR (CH_2Cl_2): 3540, 3400, 2960, 2940, 2880, 1610, 1480, 1470, 1380, 1250, 1025. ^1H NMR (500 MHz): δ 1.11 (s, 3), 1.16 (s, 3), 1.30 (d, 3, J = 0.7), 1.33 (quint, 1, J = 3.4), 1.60 (m, 1), 1.67 (ddt, 1, J = 4.0, 6.0, 14.0), 1.73 (td, 1, J = 3.0, 13.4), 1.81 (d, 1, J = 14.9), 1.83–1.88 (m, 1), 1.87 (dd, 1, J = 6.7, 15.0), 1.93–1.97 (m, 1), 2.07 (qd, 1, J = 3.1, 13.4), 2.52 (dt, 1, J = 5.8, 13.8), 3.56 (ddd, 1, J = 1.6, 5.5, 6.9), 4.90 (s, 1), 6.67 (d, 1, J = 7.8), 6.75 (dt, 1, J = 1.0, 7.4), 7.12 (dt, 1, J = 1.3, 7.6), 7.28 (dd, 1, J = 1.3, 7.3). ^{13}C NMR (100 MHz): δ 21.7 (3), 22.8 (2), 24.7 (2), 26.9 (3), 29.9 (2), 29.9 (3), 35.9 (1), 44.7 (0), 44.9 (1), 51.5 (2), 52.0 (1), 53.4 (0), 79.7 (0), 79.9 (1), 110.9 (1), 119.0 (1), 125.3 (1),

(18) In ref 5 this ^{13}C NMR resonance is mistakenly assigned as C, rather than as CH.

129.9 (1), 130.6 (0), 149.9 (0). Anal. Calcd for $C_{20}H_{28}N_2O$: C, 76.88; H, 9.03; N, 8.97. Found: C, 76.66; H, 8.96; N, 8.62.

More Polar Isomer 14b. This isomer, with R_f = 0.18 (2:1 hexanes/acetone, 3% triethylamine), was isolated as a white solid (110 mg, 55%) and was crystallized ($CHCl_3$/hexanes) to yield colorless crystals, mp 160.5–162.0 °C dec, $[\alpha]_D$ = −2.9 ± 0.4 (*c* = 0.68, $CHCl_3$). IR (CH_2Cl_2): 3580, 3400, 2960, 2940, 2880, 1615, 1485, 1470, 1265. ^{1}H NMR (500 MHz): δ 0.98 (d, 3, *J* = 0.8), 1.11 (s, 3), 1.18 (s, 3), 1.26 (mdd, 1, *J* = 6.0, 13.4), 1.34 (quint, 1, *J* = 3.3), 1.58–1.68 (m, 3), 1.74 (dd, 1, *J* = 6.1, 15.1), 1.96 (m, 1), 2.07 (qd, 1, *J* = 3.1, 13.2), 2.36 (dt, 1, *J* = 5.8, 13.5), 2.58 (dd, 1, *J* = 1.1, 15.1), 3.52 (ddd, 1, *J* = 1.2, 4.6, 6.0), 3.65 (br s, 1), 5.09 (s, 1), 6.52 (d, 1, *J* = 7.8), 6.71 (dt, 1, *J* = 1.0, 7.4), 7.06 (dddd, 1, *J* = 0.7, 1.3, 7.6, 7.9), 7.24 (md, 1, *J* = 7.4). ^{13}C NMR (100 MHz): δ 21.9 (3), 23.8 (2), 25.1 (2), 27.4 (3), 29.8 (3), 30.0 (2), 35.5 (1), 43.7 (2), 44.5 (0), 44.7 (1), 51.7 (1), 53.0 (0), 74.0 (1), 81.7 (0), 108.7 (1), 118.2 (1), 124.4 (1), 128.9 (1), 130.0 (0), 148.8 (0). Anal. Calcd for $C_{20}H_{28}N_2O$: C, 76.88; H, 9.03; N, 8.97. Found: C, 76.75; H, 9.17; N, 8.59.

(+)-Alloaristoteline (4). Under a N_2 atmosphere, alcohol **14b** (46.2 mg, 0.148 mmol) was dissolved in 10 mL of MeOH in a 25-mL flask fitted with a reflux condenser. The condenser was removed, and five drops (ca. 0.1 mL) of concentrated hydrochloric acid were added to the solution with a Pasteur pipet. The condenser was replaced and the solution was quickly brought to reflux. After 10 min, the solution was cooled in an ice/H_2O bath for 10 min, and 3 M NaOH was added until a pH of 11 had been reached. The solution was diluted with 50 mL of CH_2Cl_2 and washed with two 20-mL portions of H_2O. The combined aqueous washes were extracted with 50 mL of CH_2Cl_2. The pale yellow organic extracts were combined, dried, and concentrated. The resulting off-white residue was subjected to flash chromatography of silica (1:4 acetone/hexanes, 3% triethylamine) to yield 41.0 mg of a white foam (94%) which was crystallized from CH_2Cl_2, hexanes, triethylamine, and acetone to afford colorless crystals with mp 211.5–214 °C (lit.[5] mp 219.5 °C) and $[\alpha]_D$ −30.6 (*c* = 1.01, $CHCl_3$) (lit.[4a] $[\alpha]_D$ −32 (*c* = 1.4, $CHCl_3$). IR ($CHCl_3$): 3480, 2980–2880, 1460, 1385, 1335, 1260, 1100, 1025, 920. ^{1}H NMR (500 MHz): δ 1.10 (s, 3), 1.32 (s, 3), 1.42 (quint, 1, *J* = 3.4), 1.64 (q, 1, *J* = 3.0), 1.67 (s, 3), 1.68–1.76 (m, 1), 1.87–1.93 (m, 1), 2.02–2.11 (m, 4), 2.51 (d, 1, *J* = 17.1), 3.17 (dd, 1, *J* = 5.9, 16.8), 3.57 (md, 1, *J* = 5.1), 7.06 (dt, 1, *J* = 1.3, 7.6), 7.10 (dt, 1, *J* = 1.5, 7.7), 7.23 (d, 1, *J* = 7.8), 7.69 (d, 1, *J* = 7.8), 7.96 (br s, 1). ^{13}C NMR (100 MHz): δ 25.5 (2), 26.0 (3), 27.7 (3), 28.2 (2), 29.0 (3), 30.8 (2), 33.7 (0), 35.5 (1), 36.2 (2), 40.0 (1), 50.6 (1), 53.4 (0), 110.6 (1), 118.7 (1), 119.6 (0), 120.0 (1), 120.5 (1), 126.1 (0), 129.4 (0), 136.6 (0). The observed NMR data were in excellent agreement with those reported for racemic alloaristoteline.[4b] Treatment of **14a** under similar reaction conditions also furnished **4** in 87% chromatographed yield.

Acknowledgment. This work was supported by a research grant from the National Institutes of Health (GM 46057).