Studies Relating to the Alleged Structure of Cannivonine and Synthetically Derived (±)-Dihydrocannivonine

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Abstract: The proposed structure, **1**, for the alkaloid cannivonine has been shown to be incorrect. An unambiguous total synthesis of **1** confirmed the structural misassignment. In addition, a recently reported total synthesis of (±)-dihydrocannivonine (**5**) has been shown to be in error. An unambiguous synthesis of **5** and a comparison of the spectral data reveal the nonidentity of the two compounds. The structure proof for both **1** and **5** prepared in this study rested upon X-ray diffraction analysis of intermediate **20**.

Introduction

The New Brunswick cranberry (*Vaccinium oxycoccus*) has been employed in folklore medicine and in tumor chemotherapy.[2a] Recently, in an investigation of the active principles of this plant, a number of alkaloids had been isolated by Jankowski.[2-5] Based upon spectroscopic studies as well as chemical degradation, the structures of cannivonine (**1**)[2b] and related alkaloids **2, 3**, and **4** have been proposed for four of the alkaloid constituents. Biogenetically, the structures of these nitrogen bases are significant in that they possess the heretofore unknown 2-azatricyclo[5.3.1.0^{3,8}]undecane skeleton.[6] Pursuant to his structural elucidation studies, Jankowski reported a synthesis of (±)-dihydrocannivonine (**5**); however, in this
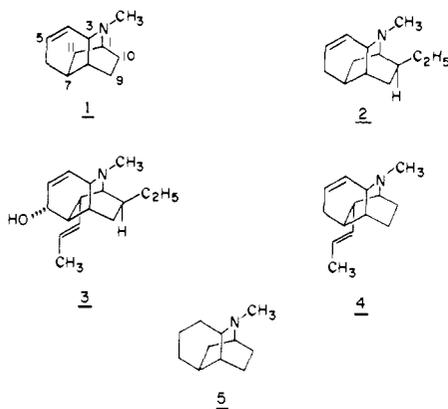
investigation no reported correlation was made between synthetic **5** and **5** produced by the hydrogenation of cannivonine (**1**).[7]

An examination of the evidence accumulated by Jankowski in his degradation studies[2b] convinced us that the proposed structure of cannivonine (**1**) was by no means secure. Accordingly, we have undertaken an unambiguous total synthesis of **1**.

Results and Discussion

The general approach to the synthesis of **1** is illustrated in a retrosynthetic format in Scheme I. Through our own studies[8] and those of Berson,[9] bicyclic ketones III (Y = H, OMe) are readily available from IV via Cope rearrangement. It was felt that a variety of ring closure reactions could be employed to transform amine II to the desired tricyclic ring system I. For example, the stereoelectronically controlled ring closure of II to I with electrophilic reagents, X$^+$, is readily predictable based upon the diaxial opening of onium and epoxide intermediates.

In conjunction with these and related studies we have found

Scheme I
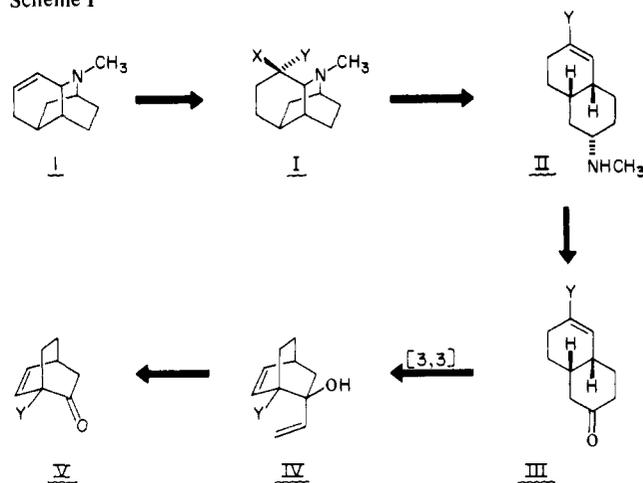
that the most expedient ketene equivalent[10] to utilize in the synthesis of bicyclooctenone **8** was di-*n*-butyl vinylboronate (**6**).[11] The Diels–Alder reaction between 1,3-cyclohexadiene and **6** (200 °C, 36 h) afforded the adduct **7** (endo:exo = 4:1) in good yield.[11] Without purification, the boronate ester was
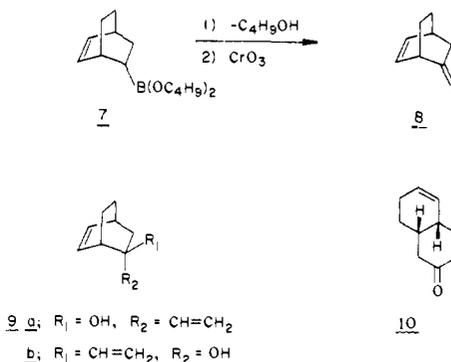
successively hydrolyzed and oxidized with Jones reagent[12] to ketone **8** in an overall yield of 51%. Following literature precedent,[9,10] the addition of vinylmagnesium bromide to **8** afforded a 98% yield of a 2:1 mixture of exo and endo alcohols **9a** and **9b** which were either separated by column chromatography or utilized directly in the subsequent step. Base-catalyzed Cope rearrangement of the exo alcohol **9a** with excess potassium hydride (THF, 66 °C, 18 h) afforded the bicyclic ketone **10** in a 98% isolated yield. From a practical standpoint it was found that the rearrangement of the endo-exo alcohol mixture was preferred. From this latter experiment, the chromatographic separation of unrearranged endo alcohol

**Table I.** Reduction of Imines **11, 13,** and **15**

reducing agent	$12\alpha{:}12\beta^a$	$14\alpha{:}14\beta^b$	$16\alpha{:}16\beta^b$
$\mathrm{Li; CH_3NH_2}^c$	>95:5	90:10	>99:1
$\mathrm{LiBH}(sec\text{-Bu})_3{}^d$	>99:1		
$\mathrm{LiAlH_4}^e$		50:50	75:25
$\mathrm{NaBH_3CN}^f$		50:50	60:40

^{a} Ratios determined by ^{13}C NMR. ^{b} Ratio determined by GLC; ref 14. ^{c} THF cosolvent; ref 15. ^{d} THF (25 °C); ref 16. ^{e} THF (25 °C). ^{f} CH$_3$OH (25 °C), pH ≤ 4; ref 17.
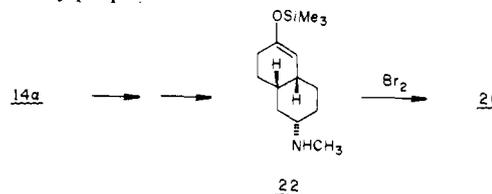
9b from the desired ketone **10** was exceptionally straightforward.

Stereoselective Reduction of *N*-Methylimines. The required stereoselective reductive amination illustrated in Scheme I (III → II) prompted a short study on the reduction of the three imines illustrated in Scheme II under various conditions (Table I). Imines **11, 13,** and **15** were each prepared in high yield from the respective ketones and excess methylamine employing magnesium sulfate as a dehydrating agent.[13] The stereochemical assignments for the secondary amines **12α** and **14α** were unambiguously determined from subsequent transformations (vide infra) while amines **16α** and **16β** have been previously prepared and characterized.[14] Since both bicyclic imines are conformationally labile systems, the stereochemical course of reduction in these instances is ambiguous. However, in the reduction of bicyclic imine **11** we were pleasantly surprised to find that *both* lithium metal (CH$_3$NH$_2$) and lithium tri-*sec*-butylborohydride (L-Selectride) reductions produced a single amine reduction product, **12α.** The origin of the high stereoselectivity in the L-Selectride reduction of **11** can be rationalized via this reagent's significant propensity for equatorial attack[16] upon that conformation of **11** which *also* provides access to the convex face of the molecule. On the other hand, the high stereoselectivity observed in the Birch reduction of both **11** and **13** was not anticipated.
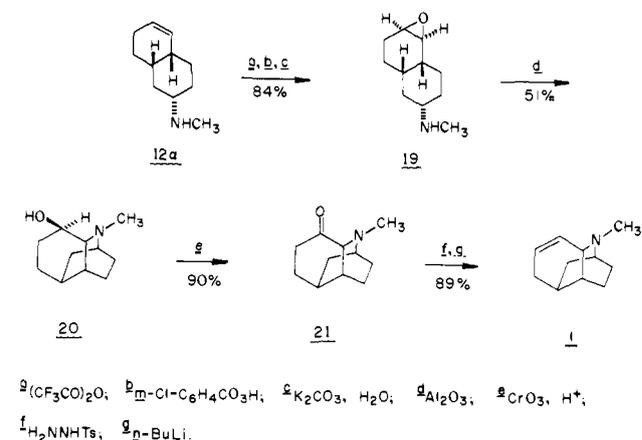
One plan for the construction of the desired "cannivonine" tricyclic ring system from amine **12α** is shown below. Diaxial opening of the boat–chair conformer **17,** derived from amine **12α,** should proceed in the illustrated manner to give **18.** Unfortunately, efforts to effect direct ring closure of **12α** to **18** were unsuccessful. Both aminoselenation (PhSeBr, CH$_2$Cl$_2$) and aminomercuration proved unsuccessful in the present instance. However, a successful solution was achieved via the amino epoxide (cf. **17,** X = 0). Epoxidation of the trifluo-
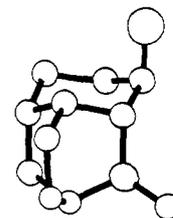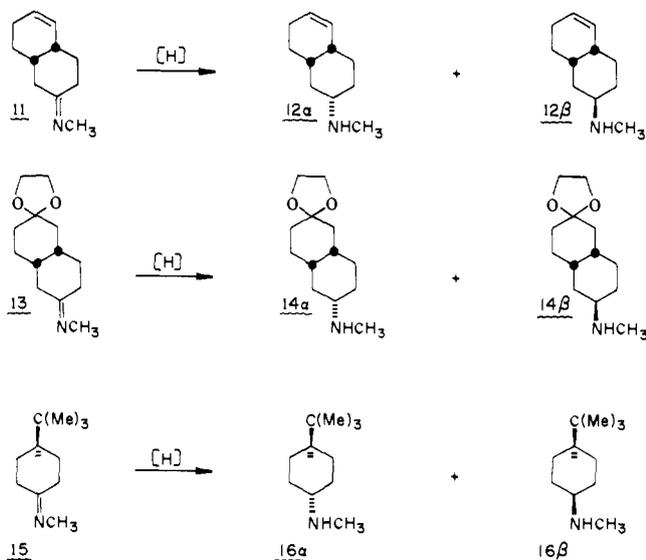
Figure 1. X-ray structure of the picrate salt of amino alcohol **20.**

X$^+$ = HgX, SePh, O
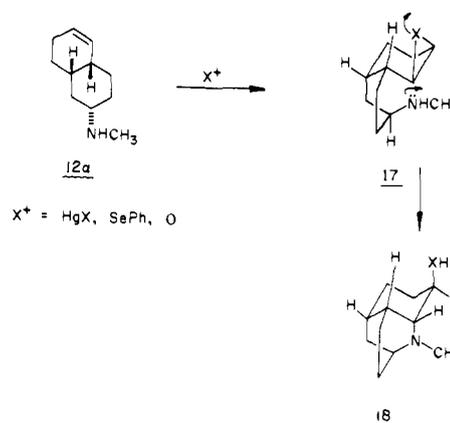
roacetamide derived from **12α** with *m*-chloroperbenzoic acid and subsequent hydrolysis afforded epoxide **19** in 84% yield (Scheme III). Alumina-catalyzed[18] ring closure of **19** gave the anticipated amino alcohol **20** (51%) whose structure was unambiguously determined by single-crystal X-ray diffraction on the picrate salt (Figure 1). The transformation of amino alcohol **20** to the proposed cannivonine structure **1** was carried out under conditions chosen to eliminate the possibility of skeletal rearrangement. Oxidation of **20** to amino ketone **21** was accomplished with Jones reagent (90%). The structural integrity of this step was known to be secure since we have independently prepared **21** from **14α** via enol ether **22.**[19] Com-

pletion of the synthesis was accomplished by conversion of **21,** via the tosylhydrazone, to **1** with 4 equiv of *n*-butyllithium (89%). Subsequent catalytic hydrogenation of a sample of **1** afforded the saturated tricyclic skeleton **5** whose alleged synthesis via an independent route has been recently reported by
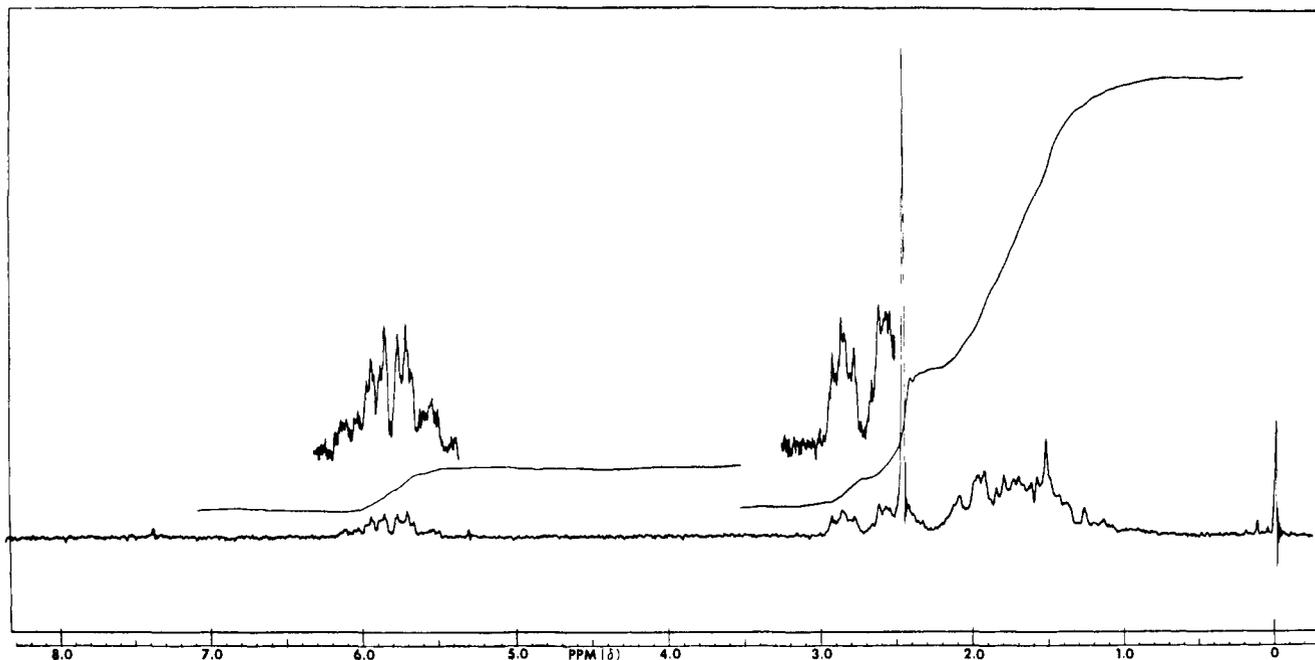
Scheme II

Scheme III

^{a}(CF$_3$CO)$_2$O; ^{b}*m*-Cl-C$_6$H$_4$CO$_3$H; ^{c}K$_2$CO$_3$, H$_2$O; ^{d}Al$_2$O$_3$; ^{e}CrO$_3$, H$^+$; ^{f}H$_2$NNHTs; ^{g}*n*-BuLi.

Figure 2. ^{1}H NMR spectrum of amine 1 in CDCl$_3$ at 60 MHz.

Table II. ^{13}C NMR Chemical Shifts for 2-Azatricyclo[5.3.1.0^{3,8}]-undecane Intermediates[a]

[a] Spectra were run in CDCl$_3$ solvent. Chemical shifts reported in ppm from Me$_4$Si. [b] Ref. 21. [c] Ref. 7.

Jankowski.[7] The ^{1}H NMR spectrum of **1** is illustrated in Figure 2. The ^{13}C chemical shifts for all compounds possessing the 2-azatricyclo[5.3.1.0^{3,8}]undecane skeleton prepared during the course of this study are shown in Table II. The ^{13}C chemical shift assignments for **20, 21, 1,** and **5** were made by the observed spin multiplicities and by comparison of the observed and calculated chemical shifts.[20] The calculated ^{13}C shifts, which were derived from the application of the appropriate substituent chemical shift additivity parameters to the hydrocarbon skeleton 4-homoisotwistane **(22),**[21] all showed ex-

cellent agreement with the observed resonances (average deviation = ±1.6 ppm).

A preliminary comparison of the ^{1}H NMR spectrum of the synthetically derived tricyclic amine **1** (Figure 2) with the fragmentary ^{1}H NMR data reported for cannivonine by Jankowski[2] revealed that the structure of this natural product was *not* **1**. Several attempts to acquire either a sample of cannivonine or copies of NMR spectra were unsuccessful. Nonetheless, it is safe to say that the structure of cannivonine is yet to be revealed. Secondly, a comparison of both the ^{1}H and ^{13}C NMR spectra of our synthetic "dihydrocannivonine" **(5)** do *not* agree with the corresponding data reported by Jankowski for his synthetic "dihydrocannivonine".[7] In addition, the ^{13}C chemical shifts reported by Jankowski (cf. Table II) match rather poorly with the calculated chemical shifts for structure **5** (average deviation = ±4.7 ppm). It thus appears that in the Jankowski "dihydrocannivonine" synthesis an unforeseen skeletal rearrangement may have occurred leading ultimately to a final product whose structure is *not* that reported as amine **5.** In at least two steps in his synthetic sequence possibilities for skeletal reorganization are feasible.

Conclusions

It is thus concluded that **1** is not the structure of cannivonine.[22] Furthermore, without additional information no alternative structures for this molecule are obvious at this time. In addition, in the Jankowski dihydrocannivonine synthesis, the anticipated target **5** was not obtained. One might speculate as to the intervention of several plausible but unanticipated skeletal rearrangements during the course of his synthetic sequence. Finally, it should be pointed out that Jankowski has apparently not correlated (in print) his synthetic dihydrocannivonine with that derived from the natural product.

Experimental Section

Proton nuclear magnetic resonance (NMR) spectra were recorded on a Varian Associates A-60 EM-390, or XL-100 spectrometer. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian Associates XL-100 at 25.2 MHz. Both NMR and ^{13}C NMR spectra are reported in parts per million (ppm) from tetramethylsilane on the δ scale; the spectra were taken on chloroform-*d* solutions, unless otherwise noted. Infrared spectra were recorded on a Beckman 4210 spectrometer. Mass spectral analysis were

performed by the California Institute of Technology Microanalytical Laboratory on a Du Pont 21-492B spectrometer at 70 eV. Gas chromatographic analyses (GLC) were performed on a Varian Aerograph 1400 gas chromatograph, using a 2 m × 0.125 in. column of 10% FFAP on 60-80 mesh Chromosorb W, AW, DMCS. Melting points were taken with a Buchi SMP-20 melting point apparatus and are uncorrected.

Reactions requiring an inert atmosphere were run under dry argon unless otherwise stated. Dry THF is reagent tetrahydrofuran distilled from sodium-benzophenone ketyl prior to use. Dry benzene is the reagent dried with magnesium sulfate. "Ether" is reagent diethyl ether. Standard workup conditions are defined as follows: most solvent is removed under reduced pressure, the residue diluted by the addition of water and extracted with three portions of solvent; organic layers are combined, extracted once with brine, and dried, and all solvent is removed under reduced pressure. Sodium sulfate is used to dry the organic layers if ether is the extraction solvent; potassium carbonate is used if dichloromethane is the extraction solvent.

Bicyclo[2.2.2]oct-5-en-2-one (8). 1,3-Cyclohexadiene (9.46 mL, 100 mmol), di-*n*-butyl vinylboronate[11a] (21.4 mL, 100 mmol), *n*-butyl alcohol (1.8 mL, 20 mmol), and phenothiazine (100 mg, 0.50 mmol) were combined, sealed in heavy-wall Pyrex tubes under vacuum, and heated at 200 °C for 36 h in a tube furnace.[11b] The tubes were opened and the contents was dissolved in ether, water (600 mL) was added, and all solvent was removed under reduced pressure at 40-50 °C to give the boronic acid derived from 7 as a yellow-white solid. Acetone (400 mL) was added, and the resulting solution cooled to 0 °C. Jones reagent (33 mL, 67 mmol) was added dropwise, and the mixture was allowed to warm to room temperature, then stirred for 2 h. During this period, additional Jones reagent (ca. 33 mL, 67 mmol) was added, as needed, to maintain a red-brown color in the reaction mixture. The reaction was quenched by the addition of isopropyl alcohol, then the mixture was isolated by ether extraction under standard conditions to give crude 8 (11.65 g). The major impurity (GLC) was found to be the dimer dicyclohexadiene. Chromatographic purification on neutral alumina (200 g, activity III) with 1:1 hexane-ether gave 6.27 g (51%) of pure 8: NMR (60 MHz) δ 6.53 (ddd, 1 H, *J* = 8, 6, 1.5 Hz, C*H*=CH), 6.22 (ddd, 1 H, *J* = 8, 6, 2 Hz, CH=C*H*), 3.07 (m, 2 H, bridgehead protons), 2.03 (d, 2 H, *J* = 3 Hz, O=CC*H*₂), and 1.9-1.4 (broad m, 4 H, C*H*₂C*H*₂) ppm; IR (thin film) 3050, 1720, 1605 cm⁻¹.

2-Vinyl-2-hydroxybicyclo[2.2.2]oct-5-ene (9a and 9b). To 200 mL of 0.50 M vinylmagnesium bromide in dry THF at 0 °C was added a solution of 8 (6.11 g, 50.0 mmol) in dry THF (200 mL) over a 4.5-h period. The reaction mixture was stirred for an additional 1 h at 0 °C and quenched with saturated, aqueous ammonium chloride (18 mL). Standard isolation via ether extraction and filtration through neutral alumina (50 g, activity III) with ether afforded 7.35 g (98% yield) of a 2:1 mixture of 9a:9b.[9] Chromatographic separation on neutral, activity III alumina with 1:1 benzene-hexane gave pure samples of 9a and 9b. For 9a: NMR (60 MHz) δ 6.28 (m, 2 H, C*H*=C*H*), 6.02 (dd, 1 H, *J* = 17, 10 Hz, C*H*=CH₂), 5.18 (dd, 1 H, *J* = 17, 2 Hz, CH=C*H*H), 4.95 (dd, 1 H, *J* = 10, 2 Hz, CH=CH*H*), 2.5 (broad m, 2 H, bridgehead protons), and 2.4-1.0 (broad m, 7 H) ppm; IR (neat) 3400, 3080, 3040, 1660 cm⁻¹.

Exact mass. Calcd for C₁₀H₁₄O: 150.104. Found: 150.107.

For 9b: NMR (60 MHz) δ 6.48 (m, 2 H, C*H*=C*H*), 6.12 (dd, *J* = 17, 10 Hz, C*H*=CH₂), 5.37 (dd, 1 H, *J* = 17, 2 Hz, CH=C*H*H), 5.15 (dd, 1 H, *J* = 10, 2 Hz, CH=CH*H*), 2.6 (broad m, 2 H, bridgehead protons), and 2.1-1.1 (broad m, 7 H) ppm; IR (neat) 3440, 3080, 3040, 1630 cm⁻¹.

Exact mass. Calcd for C₁₀H₁₄O: 150.104. Found: 150.108.

3,4,4aα,7,8,8aα-Hexahydronaphthylen-2(1*H*)-one (10). Potassium hydride oil dispersion (17.8 g of 22% KH, equivalent to 3.92 g of KH, 97.8 mmol) was washed with dry THF (3 × 100 mL) to remove the oil. A solution of a 2:1 mixture of 9a:9b (7.35 g, 48.9 mmol) in dry THF (200 mL) was added, and the resulting alkoxide solution heated at reflux for 18 h. The reaction mixture was cooled, quenched by the addition of ethyl alcohol (20 mL) and water (20 mL), and isolated under standard conditions via ether extraction to give 7.19 g of a mixture of 9b + 10 as a brown oil. Chromatographic separation on neutral alumina (180 g, activity III) with 30% ether-hexane afforded 4.82 g (98% yield, based on 9a) of pure 10 as a near-colorless oil:[9] NMR (60 MHz) δ 5.70 (broad s, 2 H, C*H*=CH), and 2.7-1.3 (broad m, 12 H) ppm; ¹³C NMR 211.2 (C=O), 129.0 (*C*H=CH), 127.0 (CH=*C*H), 43.9, 38.5, 35.8, 34.2, 30.4, 25.5, and 22.8 ppm; IR (neat)

3020, 1700, 1640 cm⁻¹. In addition, 2.18 g (14.5 mmol) of 9b was isolated.

Exact mass. Calcd for C₁₀H₁₄O: 150.104. Found: 150.106.

2-Methylamino-1,2α,3,4,4aα,7,8,8aα-octahydronaphthylene (12α). A stoppered flask containing anhydrous methylamine (2 mL, 40 mmol), 10 (600 mg, 4.00 mmol), dry benzene (30 mL), and anhydrous magnesium sulfate (960 mg, 8.00 mmol) was stirred for 29 h at room temperature. The reaction mixture was filtered under a blanket of dry argon, the magnesium sulfate rinsed with dry benzene, and solvent removed under reduced pressure to give 650 mg (100% yield) of the imine, 11, as a colorless oil: NMR (90 MHz) δ 5.59 (broad s, 2 H, C*H*=C*H*), 3.08 (s, 3 H, NCH₃), and 2.6-1.3 (broad m, 12 H) ppm; IR (neat) 3015, 1657, 1650 cm⁻¹.

To a solution of 11 (650 mg, 4.00 mmol) in dry THF (20 mL) was added 8 mL of a 1 M solution of lithium tri-*sec*-butylborohydride in THF.[16] After stirring at room temperature for 21 h, the reaction mixture was quenched by the addition of water (2 mL) and 6 M HCl (2 mL) and stirred for an additional 30 min. Addition of 2% aqueous NaOH (50 mL) followed by standard workup with dichloromethane gave 1.11 g of a pale-yellow oil. Chromatographic purification on neutral alumina (40 g, activity III) with 25% hexane-dichloromethane afforded 234 mg (71% yield) of pure 12α as a pale-yellow oil: NMR (90 MHz) δ 5.57 (broad s, 2 H, C*H*=C*H*), 2.65 (m, 1 H, R₂C*H*N), 2.38 (s, 3 H, NCH₃), and 2.2-0.8 (broad m, 14 H) ppm; ¹³C NMR δ 131.9 (*C*H=CH), 126.1 (CH=*C*H), 54.1 (R₂*C*HN), 38.2, 36.2, 33.5, 33.1, 32.1, 28.1, 26.1, and 24.3 ppm; IR (neat) 3280, 3020, 1660 cm⁻¹.

Exact mass. Calcd for C₁₁H₁₉N: 165.152. Found: 165.152.

2-Methylamino-1,2α,3,4,4aα,7,8,8aα-octahydronaphthylene Epoxide (19). A solution of 12α (992 mg, 6.00 mmol), pyridine (3.64 mL, 45.0 mmol), and trifluoroacetic anhydride (1.26 mL, 9.00 mmol) in dry THF (100 mL) was stirred at room temperature for 24 h. The reaction mixture was quenched by the addition of saturated, aqueous NaHCO₃ (40 mL) and isolated under standard conditions with dichloromethane to give 1.51 g of the trifluoroacetamide as a yellow oil.

To a solution of the trifluoroacetamide (1.51 g) in dichloromethane (200 mL) at 0 °C was added a solution of 85% *m*-chloroperbenzoic acid (2.45 g, 12 mmol) in dichloromethane (200 mL), and the resulting solution stirred at room temperature for 18 h. The reaction mixture was quenched by the addition of 20% aqueous Na₂SO₃ (38 mL, 60 mmol) and stirred rapidly for 1 h. Addition of 10% aqueous NaOH (50 mL) followed by standard isolation with dichloromethane gave 1.62 g of the epoxide as a colorless oil.

To a solution of the epoxide (1.62 g) in methyl alcohol (150 mL) was added a solution of potassium carbonate (14 g) in water (50 mL) and the resulting mixture stirred rapidly at room temperature for 20 h. Standard isolation with dichloromethane afforded 916 mg (84% yield, from 12α) of pure 19 as a colorless oil: NMR (90 MHz) δ 3.08 (m, 1 H, epoxide proton), 2.91 (m, 1 H, epoxide proton), 2.38 (s, 3 H, NCH₃), 2.35 (m, 1 H, R₂C*H*N), and 2.2-0.9 (broad m, 13 H) ppm; IR (neat) 3310 cm⁻¹.

Exact mass. Calcd for C₁₁H₁₉NO: 181.148. Found: 181.147.

N-Methyl-2-azatricyclo[5.3.1.0³,⁸]undecan-4-ol (20). To a solution of 19 (91 mg, 0.50 mmol) in dry THF (6 mL) was added neutral alumina (3.75 g, activity I), and the resulting mixture rapidly stirred at reflux for 21 h. The mixture was cooled, added to methyl alcohol (60 mL), and rapidly stirred at room temperature for 30 min. After filtration through Celite, the solvent was removed under reduced pressure to give 91 mg of a yellow oil. Chromatographic purification on neutral alumina (10 g, activity III) with 2% methyl alcohol-dichloromethane afforded 46 mg (51% yield) of pure 20 as a pale-yellow oil: NMR (90 MHz) δ 3.70 (m, 1 H, C*H*OH), 2.51 (m, 1 H, R₂C*H*N), 2.34 (s, 3 H, NCH₃), 2.22 (m, 1 H, HOCHC*H*N), and 2.2-1.1 (broad m, 13 H) ppm; ¹³C NMR δ 69.2 (d), 65.3 (d), 51.3 (d), 42.8 (q), 33.3 (t), 28.8 (d), 26.5 (d), 26.3 (t), 24.9 (t), 23.8 (t), and 18.6 (t) ppm; IR (neat) 3380 cm⁻¹.

Exact mass. Calcd for C₁₁H₁₉NO: 181.147. Found: 181.149.

A sample of 20 was converted to its picrate salt by the addition of 0.9 equiv of picric acid, followed by recrystallization from ethyl alcohol: mp 235-238 °C dec; NMR (90 MHz) δ 8.91 (s, aromatic protons), 4.52 (m, C*H*OH), 3.60 (m, HOCHC*H*N), 2.93 (m, R₂C*H*N), 2.92 (m, 2.87 (s, NCH₃), and 2.6-1.1 (broad m) ppm.

X-ray Diffraction Analysis. The diffraction data were collected by the θ-2θ scan technique on a Syntex P2₁ automated diffractometer at room temperature with Mo Kα radiation. The scan rate varied from

$2°$/min to $10°$/min dependent on the intensity of the diffraction maxima. The base width was $2°$, and the sum of the background counting times equaled the total scan time. No decay was noted in the three check reflections monitored every 50 reflections. A total of 3487 reflections were collected out to a maximum 2 of $55°$; 2262 reflections had intensities greater than $3.0\sigma(I)$.

The structure was solved using the direct methods program MUL-TAN and three-dimensional Fourier calculations. Hydrogen atom positions were calculated using standard bond distances and angles. The structure was refined to a final $R = 0.072$ and a goodness of fit $= 2.63$ on the 2262 observed data by a Gauss-Seidel block-diagonal least-squares calculation. The calculated hydrogen positions were only included in the structure factor calculations. The scattering factors were calculated by the analytical approximation $f_s = \Sigma a_i \exp(-b_i S^2)$. Bond distances and angles are all within acceptable values.

All calculations were carried out on the Data General Eclipse S230 computer in the diffraction laboratory using local programs and programs adapted from elsewhere which together comprise the crystallographic structure package CRYSP 78.

N-Methyl-2-azatricyclo[5.3.1.0^{3,8}]undecan-4-one (21). To a solution of **20** (55 mg, 0.30 mmol) in acetone (3 mL) at 0 °C were added 10% aqueous H_2SO_4 (0.3 mL) and Jones reagent (0.15 mL, 0.30 mmol), and the resulting solution was stirred at 0 °C for 2 h. The reaction was quenched with isopropyl alcohol (0.2 mL), and 5% aqueous NaOH (5 mL) added. Standard isolation with dichloromethane and filtration through neutral alumina (5 g, activity III) afforded 49 mg (90% yield) of pure **21** as a pale-yellow oil: NMR (60 MHz) δ 3.30 (m, 1 H, O=CCHN), 2.62 (broad s, 2 H, O=CCH$_2$), 2.33 (s, 3 H, NCH$_3$), and 2.2-1.2 (broad m, 11 H) ppm; NMR (PhD$_6$, 60 MHz) δ 3.22 (m, 1 H, O=CCHN), 2.62 (broad s, 1 H, O=CCH*H*), 2.23 (m, 1 H, O=CCH*H*), 2.17 (s, 3 H, NCH$_3$), and 2.0-0.9 (broad m, 11 H) ppm; ^{13}C NMR δ 72.2 (d), 50.2 (d), 42.2 (q), 35.1 (d), 34.5 (t), 32.3 (t), 31.7 (t), 28.4 (d), 24.1 (t), and 18.6 (t) ppm; IR (neat) 1710 cm^{-1}.

Exact mass. Calcd for $C_{11}H_{17}NO$: 179.131. Found: 179.129.

N-Methyl-2-azatricyclo[5.3.1.0^{3,8}]undec-4-ene (1). A solution of **21** (268 mg, 1.49 mmol) and p-toluenesulfonhydrazide (277 mg, 1.49 mmol) in methyl alcohol (4 mL) was stirred at room temperature for 24 h. All solvent was removed under reduced pressure to give a pale-yellow gum which, after recrystallization from methyl alcohol in ether, gave 517 mg (100% yield) of pure hydrazone as an amorphous, white solid: mp 129.5-131.0 °C; NMR (60 MHz) δ 7.55 (m, 4 H, aromatic protons), 2.68 (m, 1 H, N=CCHN), 2.40 (s, 3 H, ArCH$_3$), 2.10 (s, 3 H, NCH$_3$), and 2.3-1.3 (broad m, 13 H) ppm; IR (thin film) 3220, 1640 cm^{-1}.

To a solution of the hydrazone (408 mg, 1.17 mmol) in dry THF (60 mL) at −78 °C was added a 2.42 M solution of n-butyllithium in hexane (1.93 mL) over a 5-min period. The resulting orange solution was stirred at −78 °C for an additional 15 min and allowed to warm over a period of 30 min, and the resulting red solution was stirred at room temperature for 1 h. The reaction was quenched by the addition of methyl alcohol (2 mL), followed by standard isolation with dichloromethane to give 370 mg of a brown oil. Chromatographic purification on neutral alumina (20 g, activity III) with dichloromethane afforded 174 mg (89% yield) of pure **1** as a pale-yellow oil: NMR (100 MHz) δ 5.93 (dd when decoupling H-6α,β, 1 H, $J_{4,5}$ = 10.0, $J_{4,3}$ = 5.0 Hz, H-4), 5.68 (ddd when decoupling H-3, 1 H, $J_{5,4}$ = 10.0, $J_{5,6\alpha}$ = 4.0, $J_{5,6\beta}$ = 2.5 Hz, H-5), 2.87 (d when decoupling H-4, 5, 1 H, $J_{3,8}$ = 4.0 Hz, H-3), 2.50 (m, 1 H, H-1), 2.47 (s, 3 H, NCH$_3$), and 2.2-1.1 (broad m, 10 H) ppm; ^{13}C NMR 130.7 (d), 125.8 (d), 56.5 (d), 49.6 (d), 41.7 (q), 34.0 (t), 33.9 (t), 29.9 (d), 26.7 (d), 23.8 (t), and 19.7 (t) ppm; IR (neat) 3020, 1650 cm^{-1}.

Exact mass. Calcd for $C_{11}H_{17}N$: 163.135. Found: 163.135.

A sample of **1** converted to the hydrochloride salt with anhydrous hydrogen chloride gave, after recrystallization from 5% acetone in ethyl acetate, a white, amorphous solid: mp 125 °C dec; NMR (60 MHz) δ 6.28 (m, 1 H, H-4), 5.81 (m, 1 H, H-5), 4.15 (broad s, 1 H, NH), 3.2-2.8 (broad m, 2 H, H-1,3), 2.71 and 2.62 (s, 3 H, NCH$_3$), and 2.4-1.3 (broad m, 10 H) ppm; IR (thin film) 3030, 2550, 1640 cm^{-1}.

N-Methyl-2-azatricyclo[5.3.1.0^{3,8}]undecane (5). To a solution of nickel(II) acetate tetrahydrate (45 mg, 0.18 mmol) in ethyl alcohol (1 mL) was added a solution of sodium borohydride (6.8 mg, 0.18 mmol) in ethyl alcohol (1 mL).[23] To the catalyst suspension was added a solution of **1** (30 mg, 0.18 mmol) in ethyl alcohol (1 mL), the flask

purged with hydrogen gas at 1 atm pressure, and the reaction mixture stirred at room temperature for 40 h. Addition of 1% aqueous NaOH (40 mL) followed by standard isolation with dichloromethane gave 26 mg of a brown oil. Chromatographic purification on neutral alumina (3.5 g, activity III) with dichloromethane afforded 7.1 mg (24% yield) of pure **5** as a pale-yellow oil: NMR (60 MHz) δ 2.8 (m, 1 H, H-3), 2.5 (m, 1 H, H-1), 2.37 (s, 3 H, NCH$_3$), and 2.2-1.1 (broad m, 14 H) ppm; ^{13}C NMR δ 60.8, 50.8, 42.6, 34.1, 33.3, 31.8, 30.9, 29.2, 25.8, 18.1, and 15.9 ppm; IR (neat) 2930 cm^{-1}.

Exact mass. Calcd for $C_{11}H_{19}N$: 165.152. Found: 165.154.

^{13}C NMR Calculations. The calculated ^{13}C chemical shifts were determined by comparison of the ^{13}C spectrum of 4-homoisotwistane (**22**)[21] with the spectra of the following compounds: N-methyl-2-azabicyclo[2.2.2]octane,[24] bicyclo[2.2.2]octane,[25] N-methylpiperidine,[26] cyclohexanone,[26] cyclohexene,[27] and cyclohexane.[20]

For **20**:[28] δ 51.3 (52.1, 1), 65.3 (66.5, 3), 69.2 (69.5, 4), 23.8 (20.7, 5), 24.9 (25.7, 6), 26.5 (27.6, 7), 28.8 (29.1, 8), 26.3 (26.4, 9), 18.6 (19.2, 10), 33.3 (30.2, 11), and 42.8 (43.2, CH$_3$) ppm.

For **21**:[28] δ 50.2 (52.1, 1), 72.2 (73.9, 3), 31.7 (28.3, 5), 34.5 (32.4, 6), 28.4 (28.3, 7), 35.1 (36.0, 8), 24.1 (26.4, 9), 18.6 (19.2, 10), 32.3 (28.9, 11), and 42.2 (43.2, CH$_3$) ppm.

For **1**:[28] δ 49.6 (52.2, 1), 56.5 (60.8, 3), 130.7 (134.3, 4), 128.5 (127.3, 5), 33.9 (30.1, 6), 26.7 (25.7, 7), 29.9 (31.3, 8), 23.8 (26.4, 9), 19.7 (19.2, 10), 34.0 (30.2, 11), and 41.7 (43.2, CH$_3$) ppm.

For **5**:[28] δ 50.8 (52.1, 1), 60.8 (62.9, 3), 31.8 (32.0, 4), 15.9 (15.2, 5), 33.3 (32.2, 6), 29.2 (30.2, 7), 34.1 (35.8, 8), 25.8 (26.4, 9), 18.1 (19.2, 10), 30.9 (30.2, 11), and 42.6 (43.2, CH$_3$) ppm.

References and Notes

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