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Synthesis in the Tropane Class of Alkaloids. Pseudotropine and dl-Cocaine

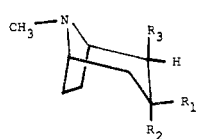
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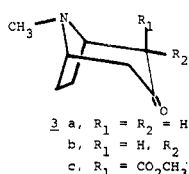
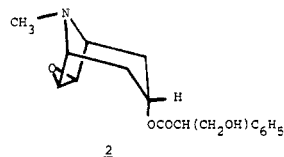
Abstract: A nitron-based entry into the tropane class of alkaloids is described. Syntheses of pseudotropine and dl-cocaine are discussed. The synthetic utility and the high degree of regiochemical and stereochemical control inherent in the nitron cycloadditions are stressed.

Introduction

The tropane alkaloids (e.g., atropine (**1a**), scopolamine (**2**), pseudotropine (**1c**), cocaine (**1d**)) incorporate an 8-azabicyclo[3.2.1]octane moiety, usually esterified at the 3 position in combination with a tropic acid.^{1,2} These alkaloids, isolated from a variety of plant sources (e.g., *Hyoscyamus niger*, *At-*



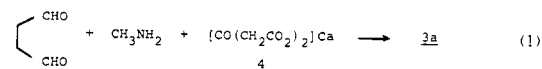
- 1a, $R_1 = H$, $R_2 = OCOCH(CH_2OH)C_6H_5$, $R_3 = H$
 b, $R_1 = R_2 = H$, $R_3 = OH$
 c, $R_2 = R_3 = H$, $R_1 = OH$
 d, $R_1 = OCOCH_2C_6H_5$, $R_2 = H$, $R_3 = CO_2CH_3$
 e, $R_1 = OH$, $R_2 = H$, $R_3 = CO_2CH_3$



ropa belladonna), have a long and important history in medicine. *Hyoscyamus* was mentioned in the Ebers papyrus (ca. 1550 B.C.) as a treatment for abdominal distress and to expel "magic of the belly".³ Belladonna extract is still widely used for its antispasmodic, antisecretory, and sedative action in the

symptomatic treatment of functional gastrointestinal disorders.⁴ Cocaine, a notorious member of this alkaloidal family, is found in *Erythroxylon coca*, indigenous to the higher elevations of Peru. The natives of this region, descendants of the Incas, still chew the coca leaf for its stimulatory properties. The drug has significant historical importance in the pioneering development of local anesthesia; however, owing to its unpredictability, toxicity, and addictive nature, its medicinal use has been limited to topical application, primarily in ophthalmology.³

Synthesis in the tropane family was initiated by Willstätter's preparation of tropinone (**3a**) in an extended series of transformations starting from cycloheptanone.^{1a} Soon thereafter, Robinson devised an efficient, superbly elegant approach involving the condensation of succindialdehyde, methylamine, and the calcium salt of 1,3-acetonedicarboxylic acid (**4**) to afford (eq 1) tropinone (**3a**) in 42% yield.⁶ This yield was in-



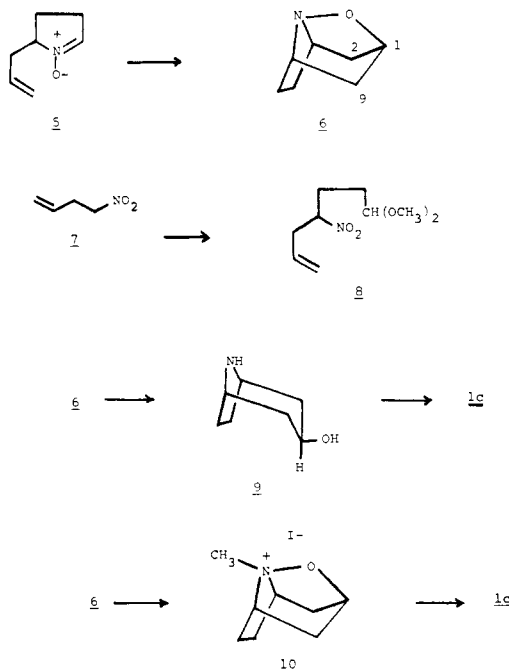
creased to 92.5% by careful control of reaction conditions (i.e., pH, temperature, etc.).⁷ Efforts to extend the Robinson synthesis to cocaine encountered stereochemical complication. Thus, condensation of the monomethyl ester of acetonedicarboxylic acid, methylamine, and succindialdehyde led to a

mixture of diastereomeric tropinone esters (**3b** and **3c**) which, upon reduction with sodium amalgam, produced a difficultly separable mixture of hydroxy esters, the methyl ester of *dl*-ecgonine (**1e**) and the epimeric *dl*-pseudococaine methyl ester, the latter predominating. The ester mixture was converted to a mixture of *dl*-cocaine (**1d**) and *dl*-pseudococaine (epimeric with cocaine at C-2).^{1a,8,9} This synthesis is complicated by the ready epimerization of the ester function at C-2 under base catalysis.¹⁰ The degree of stereoselectivity inherent in this route is clearly deficient. A more recent investigation of this approach led to similar stereochemical problems.¹¹

A number of other synthetic entries into the tropane skeleton have been reported,^{1,2} including the Michael addition of methylamine to cycloheptyl systems,¹²⁻¹⁴ the reaction of pyrroles with cyclopropanones¹⁵ and related substrates,¹⁶ the addition of oxallyl intermediates to pyrroles,^{17,18} the ring opening of aziridines,¹⁹ the alkylation of nitriles with 2,5-disubstituted pyrrolidines,^{20,21} and the reaction of activated olefins with 1-methyl-3-oxidopyridinium betaine.²²

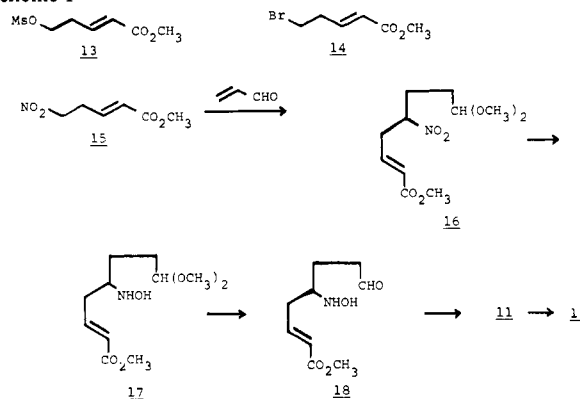
Results and Discussion

Pseudotropine. A retrosynthetic analysis of the tropane problem suggests that an intramolecular nitron-induced cycloaddition (i.e., **5** → **6**) would afford the desired skeleton and embody sufficient stereochemical control to access certain of the more complex alkaloids of this class.²³ Intramolecular cycloadditions of nitrones to carbon-carbon double bonds have been the subject of some scrutiny²⁴⁻²⁶ and can lead to the synthesis of systems which incorporate some degree of strain. The synthesis of the desired nitron (i.e., **5**) was initiated from 4-nitrobut-1-ene (**7**)²⁷ by reaction with acrolein in methanol



containing sodium methoxide, followed by acidification with dry hydrogen chloride to give the nitro acetal **8** in 62% yield. Formation of the acetal in situ avoided the isolation of a labile aldehyde. Indeed, protection of the aldehyde was considered advisable²⁸ during the nitro group reduction step. Treatment of **8** with zinc and ammonium chloride, followed by aqueous acid, gave nitron **5** (85%), which was refluxed in toluene (1% solution) to effect cyclization. The cycloadduct **6** was isolated as a readily sublimable solid whose NMR spectrum exhibited a triplet at δ 4.7 ppm ($J = 5$ Hz) assignable to the proton at the 1 position. Inspection of molecular models indicates that the endo protons at C-2 and C-9 and the C-1 proton form dihedral angles of approximately 90° . Therefore, the triplet pattern

Scheme I

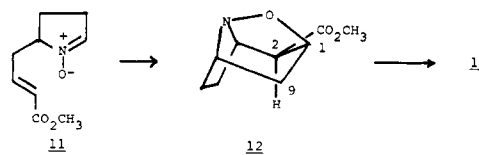


arises by coupling of the two exo protons at the 2 and 9 position with the proton at C-1. A multiplet at δ 3.5 ppm was assigned to the methine protons at C-3 and C-6. Double irradiation of this multiplet decreased the multiplicity of all the absorptions in the spectrum save for the triplet at δ 4.7 ppm. The remaining, readily characterizable absorption in the spectrum appears at δ 1.2 ppm (dd, 2, $J = 3, 11$ Hz). Double irradiation of the multiplet at δ 3.5 ppm caused the collapse of the pattern at δ 1.2 ppm to a sharp doublet ($J = 11$ Hz). The signal at δ 1.2 ppm is therefore assigned to the endo protons at C-2 and C-9 with the larger splitting (i.e., 11 Hz) attributable to geminate coupling.

The chemical proof of structure for **6** was based on its conversion to pseudotropine. Thus, hydrogenation of the nitro-oxygen bond in **6** with 10% palladium on carbon gave norpseudotropine (**9**), which was converted into pseudotropine (**1c**) by an Eschweiler-Clarke procedure.²⁹ Alternatively, **6** was methylated with methyl iodide to give the quaternary salt **10**, which gives pseudotropine (75%) upon reduction with lithium aluminum hydride. The pseudotropine so prepared is identical with an authentic sample obtained from tropinone.³⁰ An independently conceived nitron-based approach has resulted in the production of a trimethylated derivative of pseudotropine.³¹

***dl*-Cocaine. Method A.** A proposed synthesis of *dl*-cocaine must confront the problem of the relative stereochemistries at C-2 and C-3 and, most significantly, the presence of the thermodynamically less stable axial orientation of the carbomethoxyl function at C-2. This center has been reported¹⁰ to be epimerized, affording pseudococaine, under relatively mild conditions. Indeed, no stereoselective total synthesis of *dl*-cocaine has appeared to the present time.^{32,33}

With the successful scheme involving the construction of the tropane skeleton in mind, the nitron ester **11** was sought as the key intermediate in the synthesis of *dl*-cocaine (**1d**). The *E* configuration at the olefinic center in **11** and the concerted nature of the cycloaddition compel the ester function to adopt



the exo configuration depicted in **12**. The conversion of the latter into *dl*-cocaine was expected to be uncomplicated.²³

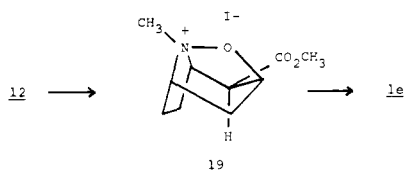
Our approach commences with mesylate olefin **13**, previously used as part of a nitron-based entry into the lupin class of alkaloids,³⁴ which was converted into nitro ester **15**, via bromo ester **14** (cf. Scheme I). Michael addition of nitro compound **15** to acrolein in the presence of methanol containing sodium methoxide, followed by in situ protection of the aldehyde functionality, provided dimethyl acetal **16** in 94% yield. The conversion of **16** into the desired nitron **11** proved

to be a vexing problem. Reduction of the nitro group with zinc and aqueous ammonium chloride solution was designed to produce the hydroxylamine acetal **17** which, upon acidification, was expected to generate the hydroxylamine aldehyde **18**, capable of spontaneous cyclization to the desired nitrone **11**, and thence to cycloadduct **12**.

Unfortunately, numerous attempts at this sequence (i.e., **16** → **12**) resulted in yields of cycloadduct ranging from 4 to 11%. Although the side products of the zinc reduction were not carefully characterized, it appears that either the hydroxylamine moiety in **17** or **18** or the intermediates involved in the electron-transfer reduction of the nitro group are capable of Michael addition to the α,β -unsaturated ester moiety.³⁵ In fact, the crude product from the zinc reduction showed, by spectral examination, a loss of olefinic absorption and a retention of carbonyl absorption without producing a major amount of the desired cycloadduct (i.e., **12**).

The adduct **12** has an NMR spectrum which exhibits a one-proton doublet at δ 4.95 ppm ($J = 5.5$ Hz) which was assigned to the C-1 proton since it is only coupled to the exo proton at C-9 (cf. NMR spectrum of **6**). A one-proton doublet of doublets (δ 1.24 ppm, $J = 3, 12.5$ Hz) was assigned to the endo proton at C-9. One-proton multiplets at δ 3.53 (m, 1) and 3.86 ppm (q, 1, $J = 3.0$ Hz) were assigned to the two methine protons at C-3 and C-6.

Methylation of cycloadduct **12** with methyl iodide in methylene chloride at room temperature afforded methiodide **19**, which was then treated with activated zinc in 50% aqueous

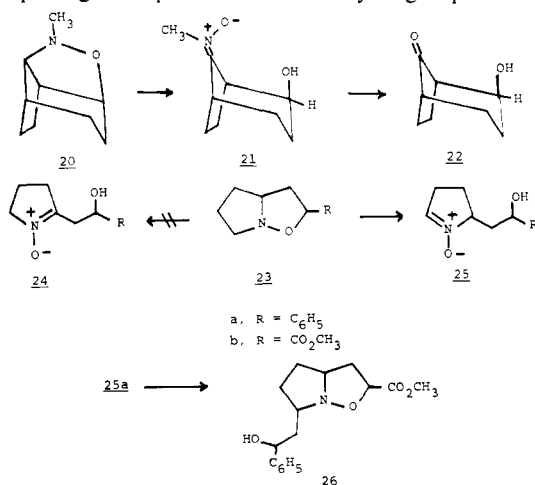


acetic acid at 70 °C in order to effect the scission of the nitrogen–oxygen bond and provide ecgonine methyl ester (**1e**) in 50% yield. The IR spectrum of **1e** displayed the expected absorption at 2.60 μ for hydroxyl stretching and a strong absorption at 5.86 μ for the ester carbonyl stretch.

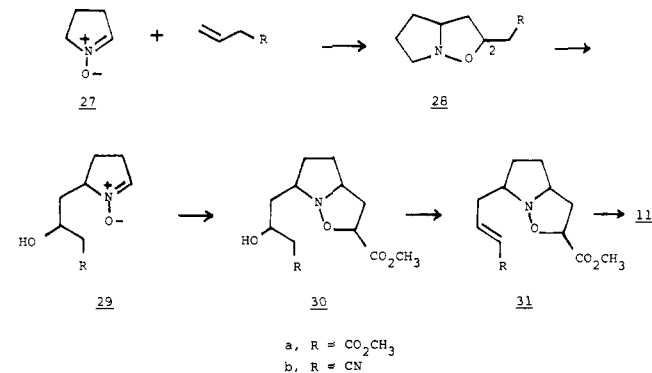
The ecgonine methyl ester was then benzoylated, as described by de Jong,⁹ to afford *dl*-cocaine possessing IR, NMR, and mass spectral characteristics virtually identical with those of an authentic sample of the natural product.

dl-Cocaine. Method B. While the approach described above was successful in accessing nitrone **11**, and ultimately producing *dl*-cocaine in a stereocontrolled manner, the yields encountered in the **16** → **12** interconversion are clearly unacceptable. A method was sought which would afford the desired nitrone with greater efficiency.

Isloxazolidines have been reported^{24,36} to undergo oxidative ring opening with peracetic acid or hydrogen peroxide. For



Scheme II



example, isloxazolidine **20**, upon treatment with peracetic acid, apparently gave nitrone **21**, the structure of which was confirmed by acid hydrolysis to hydroxy ketone **22** (40% yield from **20**). This interesting series of transformations apparently proceeds via N-oxidation and ring opening to a nitrosonium ion, followed by tautomerization to the nitrone.³⁶

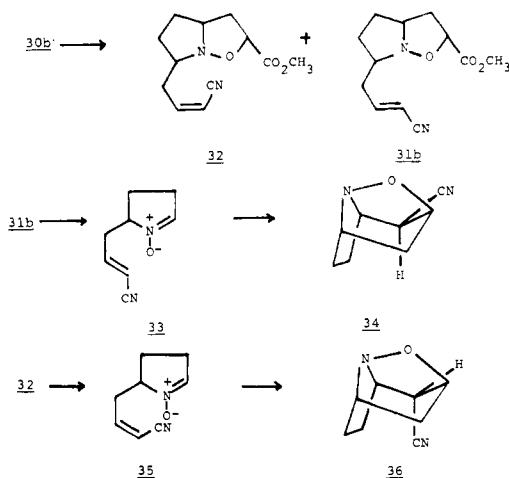
Certain of our synthetic objectives, unrelated to the present investigation, demanded the oxidative opening of isloxazolidines **23a** and **23b** to hydroxy nitrones **24a** and **24b**. Since the formation of the more substituted of the two possible regioisomeric nitrones appeared to be indicated by the published reports^{24,36} (cf. the **20** → **21** conversion), we were surprised to discover that oxidation of isloxazolidine **23a** with *m*-chloroperbenzoic acid in methylene chloride gave the isomeric, less substituted hydroxy nitrone **25a** in 98% yield. The infrared spectrum contains a broad hydroxyl absorption at 2.8–3.2 μ and bands at 6.3 (s) and 8.12 μ (s), characteristic of nitrones. The NMR spectrum contains a multiplet at δ 3.87 ppm (1 H) for the proton at the 5 position of the pyrroline ring, an exchangeable proton at δ 6.00 ppm (broad m), and the nitrone C-2 proton at δ 6.70 ppm (m, 1 H). Further evidence that **25a** is a nitrone is indicated by its cycloaddition to methyl acrylate to give **26**, whose IR spectrum shows the expected alcohol and carbonyl bands at 2.90 and 5.75 μ , respectively. Adduct **25b** obtained from the oxidation of **23b** with *m*-chloroperbenzoic acid was assigned the structure indicated on the basis of spectral data (cf. Experimental Section).

These findings suggested a facile approach to nitrone ester **11**, uncomplicated by the vagaries of zinc-induced nitro group reductions (cf. Scheme II). Reaction of 1-pyrroline 1-oxide (**27**) with methyl 3-butenoate in refluxing toluene for 15 h produced adduct **28a** in 96% yield. The regiochemistry assigned to **28a** is supported by the quintet at δ 4.47 ppm (1 H, $J = 7$ Hz) in its NMR spectrum associated with the hydrogen at C-2. A pair of doublets at δ 2.55 and 2.64 ppm (2 H, $J = 7$ Hz), assigned to the methylene protons α to the ester group, suggests that both stereoisomers (i.e., epimeric at C-2) were formed in this reaction (ratio approximately 1:1).

Addition of 1 equiv of *m*-chloroperbenzoic acid to adduct **28a** in methylene chloride gave, after chromatography, 89% of nitrone **29a** as a clear oil. This nitrone displays a broad hydroxyl absorption at 2.8–3.2 μ and a strong carbonyl absorption at 5.80 μ . The NMR spectrum exhibits a multiplet at 7.07 ppm (1 H), assigned to the nitrone C-2 proton. Nitrone **29a** was remarkably resistant to dehydration in aqueous mineral acid or in refluxing benzene containing *p*-toluenesulfonic acid.

Nitrone **29b**, prepared by oxidative opening of the isloxazolidine (**28b**) derived from 1-pyrroline 1-oxide (**27**) and allyl cyanide, also resisted dehydration under the conditions stated above. Moreover, attempted dehydration with phosphorus oxychloride led to intractable material, possibly associated with the competing reactions of dehydration and Beckmann rearrangement of the nitrone.^{37,38}

Since the nitron functionality was complicating the dehydration process, a nitron blocking group was deemed advantageous. While we were unaware of the use of blocking groups in the synthetic applications of nitron chemistry, the precedented reversal of nitron cycloadditions suggested the use of dipolarophiles as agents incorporating the desired characteristics of a successful protecting group.³⁹ Thus, the reaction of nitron **29b** with methyl acrylate in refluxing benzene gave adduct **30b** in quantitative yield as a mixture of stereoisomers. The IR spectrum of **30b** exhibits nitrile absorption at 4.45μ (w) and a strong carbonyl stretch at 5.78μ . The NMR spectrum contained the expected singlet at δ 3.74 μ (3 H) associated with the carbomethoxyl group and an absence of nitron-related signals. Dehydration of **30b** with POCl_3 in pyridine produced a 4:1 ratio of cis and trans olefins (**32** and **31b**) respectively. Both isomers, as expected, show carbonyl absorption (5.77μ) and nitrile absorption (4.54μ for **32** and 4.52

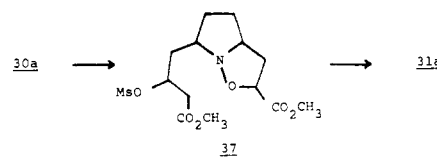


μ for **31b**). The NMR spectrum of **32** displays a doublet at δ 5.34 ppm (1 H, $J = 11$ Hz), indicative of a cis configuration at the olefinic center, while **31b** shows a doublet at δ 5.38 ppm (1 H, $J = 16$ Hz), indicative of a trans double bond. The same two alkenes, **32** and **31b**, were prepared in a 6:5 ratio, respectively, by treatment of the methanesulfonate ester of **30b** with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in benzene.

Cycloreversion of **31b** to the cyanonitrone **33** by refluxing in xylene was accompanied by concomitant intramolecular cycloaddition to give the tricycloadduct **34** in 56% yield. The IR spectrum of **34** shows the nitrile absorption at 4.46μ and the absence of an ester carbonyl. The NMR spectrum contained a one-proton doublet at δ 5.03 ppm ($J = 5$ Hz) which is assigned to the C-1 proton since it is expected to be coupled only to the exo proton at C-9 (vide supra).

When a dilute solution of cis olefin **32** is refluxed in xylene, tricycloadduct **36** is produced via cyanonitrone **35**. The C-1 proton of **36** appears as a triplet, δ 4.84 ppm ($J = 4.5$ Hz), since this proton is now permitted, by virtue of favorable dihedral angle relationships, to couple to both flanking exo protons (i.e., at C-2 and C-9).

The production of both cis and trans double bond isomers **32** and **31b** in the dehydration experiments suggested a return to investigations leading to ester nitron **11**, rather than cyanonitrone **33**. Trapping of hydroxy ester nitron **29** with methyl acrylate in refluxing benzene gave **30a** as a mixture of stereoisomers in 77% yield. This adduct displayed the expected IR absorptions (i.e., 2.89μ for OH stretching, 5.81μ for carbonyl stretching). The adduct was allowed to react with methanesulfonyl chloride to produce the corresponding methanesulfonate (**37**), which was subjected to conditions of β -elimination (DBN) to afford the α,β -unsaturated ester isoxazolidine **31a** in 86% yield. The NMR spectrum of **31a** possesses a one-proton doublet at δ 5.92 ppm ($J = 16$ Hz),



indicative of trans geometry at the olefinic center. No evidence for the presence of the isomeric cis olefin was uncovered. The difference in the configurational outcome of the dehydromethylations of **37** and the mesylate of **30b** appears related to a manifestation of steric differences between the cyano and ester groupings. Thus, the larger ester grouping, in comparison to the linear cyano group, has a greater preference for a trans relationship to the carbon chain in the transition state for the elimination.

When **31a** was refluxed in xylene, methyl acrylate was expelled and the resulting nitron (i.e., **11**) then spontaneously cyclized to tricycloadduct **12** as noted in method A. This route provides **12** in 40% yield from the readily available methyl 3-butenate. The overall approach provides a very efficient and highly stereoselective synthesis of *dl*-cocaine.

The virtues of the use of nitrones in organic synthesis are illustrated forcefully in the synthesis of *dl*-cocaine. Both the C₁-C₂ and the C₄-C₅ bonds of the natural product are formed by 1,3-dipolar cycloaddition processes. The oxygen function at C-3 is introduced stereospecifically in the second of these cycloadditions. The latter is accompanied by the crucial, highly stereoselective introduction of the carbomethoxyl group. The trans configuration of this functionality in **11** predetermines its axial orientation in the synthetic *dl*-cocaine. While the recently reported condensation of pyrroles with cyclopropanones^{15,16} and oxallyl intermediates^{17,18} provides efficient and elegant entries to the tropane skeleton, the nitron-based approach offers the advantage of the high degree of stereochemical control manifest in the introduction of carbomethoxyl moiety. The regioselectivity of the intramolecular cycloaddition of the nitron onto the activated double bond of **11** is, in this case, undoubtedly associated with the strain related to the alternative regiochemical mode of addition; however, it might be noted that this is the preferred mode of addition even in intermolecular cases.⁴⁰⁻⁴³ The regioselectivity of the oxidative ring openings of isoxazolidines suggests an attractive procedure for the symmetrical dialkylation of amines. We are currently exploring this possibility in greater detail. Finally, we note that, while nitrones are reactive functional groups that are prone to numerous side reactions, it now becomes possible by blocking to carry this useful moiety through a number of transformations before it is liberated.

Experimental Section

All melting points, determined on a Mel-Temp capillary tube apparatus, and boiling points are reported in °C (uncorrected).

Infrared spectra (IR) were recorded on a Perkin-Elmer 727 spectrophotometer and calibrated using the 6.245- μ band of polystyrene; infrared data are reported in microns, where w, m, and s indicate the intensity of absorptions as weak, medium, and strong, respectively. Nuclear magnetic resonance (NMR) spectra were recorded on either a JEOL MH-100 or a Varian T-60 spectrometer using tetramethylsilane as an internal standard. The chemical shifts determined at 100 MHz are reported to two decimal places. Chemical shift data are reported in parts per million (ppm) downfield from tetramethylsilane, where s, d, dd, t, q, quint, m, and cp designate singlet, doublet, doublet of doublets, triplet, quartet, quintet, multiplet, and complex pattern, respectively. The integration numbers are shown in parentheses. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6E spectrometer. The ionization voltage was 70 V with a current of 80 μ A.

Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, Ga.; Instranal Microanalytical Laboratory, Rensselaer, N.Y.; and Department of Chemistry, SUNY at Buffalo, Buffalo, N.Y.

1-Nitrobut-3-ene (7). Using the procedure of Kornblum,⁴⁴ nitro compound **7** was prepared. The crude product was fractionally distilled

by means of a variable takeoff stillhead and an 8-in. Vigreux column to give 3-buten-1-ol and 19.1 g (50%) of a light yellow liquid, bp 58–60 °C (22 mm) [lit.²⁷ 144 °C (670 mm)].

4-Nitro-6-heptenal Dimethyl Acetal (8). A solution of sodium methoxide in methanol was prepared by the addition of 2.90 g (127 mmol) of freshly cut sodium to 250 mL of freshly distilled methanol. When all of the sodium had reacted, the methanol solution was cooled to –20 °C and 62.9 g (615 mmol) of 1-nitrobut-3-ene (7) was added. To this mixture was added 8.40 mL (127 mmol) of acrolein, in 50 mL of methanol, over 1.5 h. After acidification with dry hydrogen chloride, the mixture was warmed to room temperature and stirred for 30 min. The resulting solution was filtered, the methanol was removed at reduced pressure, and the excess 1-nitrobut-3-ene was collected in a dry ice trap (0.8 mm). Distillation of the residue gave 15.8 g (61.5% yield) of a light yellow oil: bp 64–68 °C (0.05 mm); IR (neat) 6.1 (w), 6.45 (s), 7.25 (m), 8.85 (s), 9.3 (s), 10.05 (w), and 10.8 μ (m); NMR (CDCl₃) δ 1.7 (m, 2), 1.9 (m, 2), 2.6 (m, 2), 3.3 (s, 6), 4.3 (t, 1, J = 4 Hz), 4.5 (m, 1), 5.1 (m, 1), and 5.7 ppm (cp, 1); MS (M⁺) m/e 203.

Anal. (C₉H₁₇NO₄) C, H, N.

5-Allyl-1-pyrroline 1-Oxide (5). To a suspension of 1.20 g (5.95 mmol) of 4-nitro-6-heptenal dimethyl acetal (8) and 50 mL of water, containing 0.33 g (6.1 mmol) of ammonium chloride, was added 1.45 g (23.0 mmol) of freshly activated zinc dust in three portions over 30 min. Stirring at room temperature was continued for 1.5 h. The zinc salts were removed by filtration and washed with 25 mL of hot water (ca. 70 °C). The filtrate was acidified with 3 mL of concentrated hydrochloric acid, and the resulting solution stirred at room temperature overnight. The aqueous solution was neutralized with solid sodium bicarbonate, saturated with sodium chloride, and continuously extracted with methylene chloride for 24 h. The methylene chloride solution was dried over anhydrous magnesium sulfate, and the methylene chloride removed at reduced pressure. Distillation of the residue gave 0.75 g (85%) of a light yellow oil: bp 80 °C (9.15 mm); IR (neat) 6.1 (m), and 6.3 μ (s); NMR (CDCl₃) δ 2.3 (m, 6), 4.0 (m, 1), 5.1 (m, 2), 5.6 (m, 1) and 6.8 ppm (broad singlet, 1).

8-Aza-7-oxatricyclo[4.2.1.0^{3,7}]nonane (6). A sample of 5-allyl-1-pyrroline 1-oxide (5) was prepared without purification from 5.00 g (24.6 mmol) of 4-nitro-6-heptenal dimethyl acetal (8) in the usual fashion (vide supra). The brown oil was dissolved in 450 mL of toluene and refluxed under argon for 6 h. The volume of toluene was reduced to 200 mL by distillation at atmospheric pressure. The resulting toluene solution was extracted with 10% aqueous hydrochloric acid (3 \times 25 mL). The aqueous solution was basified with solid sodium bicarbonate, saturated with sodium chloride, and extracted with methylene chloride (7 \times 25 mL). The methylene chloride solution was dried over anhydrous magnesium sulfate, and the methylene chloride removed at reduced pressure. The residue was distilled into a dry ice trap at 80 °C (7.5 mm) to give a yellow semisolid. The semisolid was sublimed at 27 °C (15 mm) to give 0.98 g (32%) of a white solid: mp 46–48 °C; IR (melt) 8.05 (w), 10.2 (m), 10.5 (m), 11.4 (s), 11.65 (m), and 12.3 μ (s); NMR (CDCl₃) δ 1.2 (dd, 2, J = 3, 11 Hz), 1.7–2.4 (cp, 6), 3.5 (m, 2), and 4.7 ppm (t, 1, J = 5 Hz).

Anal. (C₇H₁₁NO) C, H, N.

Norpseudotropine (9). A mixture of 0.75 g (6.0 mmol) of 8-aza-7-oxatricyclo[4.2.1.0^{3,7}]nonane (6), 50 mL of methanol, and 0.2 g of 10% palladium on carbon was hydrogenated in a Parr apparatus overnight. The product was recrystallized from benzene–pentane to give 0.52 g (69% yield) of a white solid, mp 128–130 °C (lit.²⁹ mp 134.5–135.0 °C).

Pseudotropine (1c). Using the procedure of Fieser,²⁹ pseudotropine (1c) was prepared from norpseudotropine (9) in a 36% yield (mp 105–106 °C). It gave a mixture melting point of 105–106 °C when mixed with an authentic sample of 1c.

Methiodide of 8-Aza-7-oxatricyclo[4.2.1.0^{3,7}]nonane (10). To a solution of 0.20 g (1.6 mmol) of 8-aza-7-oxatricyclo[4.2.1.0^{3,7}]nonane (10), in 25 mL of ether, was added 3.0 mL (48 mmol) of methyl iodide. The solution was stirred at room temperature for 24 h. The yellow solid was filtered and recrystallized from ethanol–ether to give 338 mg (91%) of a white, hygroscopic solid: mp 190–192 °C; IR (KBr) 8.0 (s), 10.05 (m), 10.2 (m), 10.5 (m), 11.4 (s), and 1.21 μ (s); NMR (dimethyl-*d*₆ sulfoxide-*d*₂O) δ 2.0 (dd, 2, J = 2, 11 Hz), 2.35 (m, 4), 2.8 (m, 2), 3.5 (s, 3), 4.25 (m, 2), and 5.2 ppm (t, 1, J = 5 Hz).

Pseudotropine (1c). **Method A.** To a suspension of 0.414 g (1.55 mmol) of methiodide 10 and 75 mL of tetrahydrofuran was added 0.75 g (20 mmol) of lithium aluminum hydride. The resulting mixture was

refluxed for 24 h. After the addition of 0.75 mL of water, 0.75 mL of 10% aqueous sodium hydroxide, and 3.0 mL of water the resulting white solid was removed by filtration and washed with ether. The filtrate was dried over anhydrous magnesium sulfate and the ether removed at reduced pressure. The remaining white solid was sublimed at 80 °C (18 mm) to give 163 mg (74.5% yield) of a white solid, mp 104.5–105.5 °C.

Method B. To a solution of 194 mg (0.720 mmol) of the methiodide 10, in 4.0 mL of 50% aqueous acetic acid, was added 2.1 g (32 mmol) of zinc dust. The resulting mixture was heated to 70 °C for 24 h. The remaining zinc metal was removed by filtration and washed with hot water (ca. 70 °C). The filtrate was basified with sodium hydroxide pellets and continuously extracted with methylene chloride for 24 h. The methylene chloride solution was dried over anhydrous magnesium sulfate and the solvent removed at reduced pressure. The resulting solid was sublimed at 75–80 °C (18 mm) to give 52 mg (51% yield) of a white solid, mp 105–106 °C.

Reduction of Tropinone (3a) with Sodium in Ethanol. Using the procedure of Willstätter,³⁰ pseudotropine (1c) was prepared in 76% yield, mp 105–106 °C (lit.³⁰ mp 108 °C).

Methanesulfonate Ester of Methyl (E)-5-Hydroxy-2-pentenoate (13). Using the procedure of Crossland,⁴⁵ the mesylate ester 13 was prepared. To a solution of 30 g (0.23 mol) of the (E)-5-hydroxy-2-pentenoate and 58 mL (0.415 mol) of freshly distilled triethylamine, in 800 mL of methylene chloride at 0 °C, was added 20.8 mL (0.272 mol) of freshly distilled methanesulfonyl chloride in 20 mL of methylene chloride. After workup, there resulted 45.4 g (94%) of a yellow oil which was used without further purification for the subsequent step: IR (neat) 5.8 (s), 6.1 (m), 6.95 (m), 7.4 (s), 8.6 (s) and 10.5 μ (s); NMR (CDCl₃) 2.7 (q, 2), 3.0 (s, 3), 3.7 (s, 3), 4.3 (t, 2), 5.8 (d, 1, J = 16 Hz), and 6.8 ppm (m, 1).

Methyl (E)-5-Bromo-2-pentenoate (14). Mesylate ester 13 (27.0 g, 0.128 mol) was added to 29.3 g (0.347 mol) of lithium bromide in 800 mL of ether over 20 min with stirring. The resulting mixture was stirred at room temperature for 24 h under nitrogen. The ethereal solution was washed with 75 mL of water and 75 mL of saturated aqueous sodium chloride, then dried (MgSO₄), concentrated, and distilled to give 21.3 g (80%) of a colorless liquid, bp 62–65 °C (0.05 mm).

Anal. (C₆H₉O₂Br) C, H, Br

Methyl (E)-5-Nitro-2-pentenoate (15). **Method A.** Using the procedure of Kornblum,⁴⁴ the nitro compound 15 was prepared. A yellow oil (1.98 g, 40%) was obtained. The spectral data are reported below.

Method B. To a solution of 8.5 g (0.044 mol) of 14 in 600 mL of freshly distilled acetonitrile cooled to 0 °C was added 54 g (0.44 mol) of silver nitrite. The resulting mixture was stirred at 5 °C for 14 days. The solution was filtered and concentrated to 100 mL under reduced pressure. Then 1 L of chloroform was added, the solution filtered again, and the solvents removed at reduced pressure. The residue was chromatographed using a silica gel column with ether/benzene (1:1) as eluent. A yellow oil, 3.2 g (48%), was obtained: bp 85–88 °C (0.05 mm); IR (neat) 5.8 (s), 6.1 (m), 6.4 (s), 7.0 (m), 7.4 (m), and 11.5 μ (w); NMR (CDCl₃) 3.0 (q, 2), 3.8 (s, 3), 4.5 (t, 2), 5.8 (d, 1, J = 16 Hz), and 6.8 ppm (m, 1); MS m/e 131 (3), 113 (24), 85 (13), 81 (100), 59 (25), 55 (18), 54 (23), 53 (87), 46 (8), 41 (22), 39 (46), 30 (15).

Anal. (C₆H₉NO₄) C, H, N.

Methyl (E)-8,8-Dimethoxy-5-nitro-2-octenoate (16). To a solution of 160 mg (3 mmol) of sodium methoxide in 50 mL of dry methanol kept under argon and cooled at –30 °C was added slowly a solution of 2.78 g (17.5 mmol) of the nitro compound 3 and 1.73 mL of freshly distilled acrolein (26 mmol) in 250 mL of dry methanol over a period of 30 min. After addition was complete, stirring at –30 °C was continued for another 45 min. Then 3 mL of concentrated hydrochloric acid was added and the resulting solution was allowed to stir at room temperature for 4 h. The methanolic solution was basified with solid sodium bicarbonate and was concentrated to a volume of 20 mL. The resulting mixture was taken up in 50 mL of water and extracted with methylene chloride. The methylene chloride was dried (MgSO₄) and solvent removed to give 4.3 g (94%) of a yellow oil which was used without further purification for the subsequent step: IR (neat) 5.8 (s), 6.1 (m), 6.4 (s), 7.0 (s), 7.4 (m), 9.0 (s), and 9.5 μ (s); NMR (CDCl₃) 1.5–2.2 (m, 4), 2.5–3.0 (m, 2), 3.4 (s, 6), 3.7 (s, 3), 4.2–4.8 (m, 2), 5.8 (d, 1, J = 16 Hz), and 6.5–7.1 ppm (m, 1).

Methyl (1S*,2R*,3R*,6S*)-7-Aza-8-oxatricyclo[4.2.1.0^{3,7}]-

nonane-2-carboxylate (12). With stirring, 4.9 g (75 mmol) of activated zinc dust was added over a 30-min period to a solution of 5.4 g (21 mmol) of compound **16**, 220 mL of DME, 160 mL of water, and 2.26 g (42 mmol) of ammonium chloride. After an additional 4 h at room temperature, the mixture was filtered and the salts were washed with 80 mL of hot water (ca. 80 °C) and 80 mL of hot dimethoxyethane. The filtrates were combined and acidified with 6 mL of concentrated hydrochloric acid and stirred overnight. The resulting solution was concentrated to ca. 50 mL, saturated with sodium chloride, and extracted with methylene chloride. The methylene chloride extracts were dried (MgSO₄) and concentrated at reduced pressure to give a brown residue that was dissolved in 1 L of dry toluene and refluxed for 5 h under nitrogen. The toluene solution was extracted with 5% aqueous hydrochloric acid, then basicified with Na₂CO₃ and back-extracted with methylene chloride. The methylene chloride extract was dried (MgSO₄), concentrated, then bulb to bulb distilled in a Kugelrohr apparatus to give 165 mg (4.3%) of a white solid. An analytical sample was prepared by sublimation at 60 °C (0.05 mm); mp 71–73 °C; IR (melt) 3.39 (s), 3.46 (m), 5.80 (s), 6.95 (s), 7.32 (m), 7.78 (s), 8.26 (s), 8.48 (m), 9.75 (m), 10.40 (w), 10.80 (w), 11.30 (s), 12.25 (m), and 13.50 μ (w); NMR (CDCl₃) δ 1.24 (dd, 1, *J* = 3.0, 12.5 Hz), 1.68–2.38 (cm, 6), 3.53 (m, 1), 3.68 (s, 3), 3.86 (q, 1, *J* = 3.0 Hz), and 4.95 ppm (d, 1, *J* = 5.5 Hz); MS *m/e* (M⁺) 183.

Anal. (C₉H₁₃NO₃) C, H, N.

Methiodide of Methyl (1S*,2R*,3R*,6S*)-7-Aza-8-oxatricyclo[4.2.1.0^{3,7}]nonane-2-carboxylate (19). To a solution of 140 mg (0.77 mmol) of cycloadduct **12** in 10 mL of anhydrous ether and 3 mL of methylene chloride was added 2 mL of methyl iodide (32 mmol) and this mixture was stirred under nitrogen at room temperature for 12 h. The resulting mixture was refluxed for an additional 24 h. Concentration gave a yellow solid residue that was recrystallized from methanol/ether giving 145 mg (58%) of a white solid: mp 130–132 °C; IR (KBr) 3.35 (w), 3.39 (m), 3.44 (m), 5.79 (s), 6.92 (m), 7.06 (s), 7.25 (w), 7.57 (w), 7.65 (m), 7.72 (m), 8.10 (m), 8.30 (s), 8.65 (w), 9.15 (w), 9.70 (w), 10.10 (w), 10.30 (m), 10.40 (m), 11.40 (m), and 12.25 μ; NMR (CH₃OD) δ 2.10–3.25 (cm, 7), 3.70 (s, 3), 3.80 (s, 3), 4.42 (m, 1), 4.76 (m, 1), and 5.58 ppm (d, 1, *J* = 5.5 Hz).

Ecgonine Methyl Ester (1c). To a solution of 140 mg (0.77 mmol) of the methiodide (**19**) in 4 mL of 50% aqueous acetic acid was added 0.6 g of activated zinc dust under a nitrogen atmosphere. The resulting mixture was warmed to 70 °C for 3.5 h. The remaining solids were filtered and washed with 8 mL of hot water (ca. 70 °C). The filtrate was saturated with solid sodium carbonate and continuously extracted with methylene chloride for 18 h. The methylene chloride solution was dried (MgSO₄), concentrated, and bulb to bulb distilled in a Kugelrohr apparatus giving 43 mg (47%) of a colorless oil: bp 105–110 °C (0.06 mm, Kugelrohr) (lit.⁴⁶ mp 122–126 °C); IR (neat) 2.60 (s), 3.40 (s), 3.53 (w), 3.58 (w), 5.86 (s), 6.96 (s), 7.45 (m), 7.70 (m), 7.90 (m), 8.06 (m), 8.17 (m), 8.35 (s), 8.80 (m), 9.45 (s), 9.98 (m), 11.70 (w), and 12.85 μ (m); NMR (C₆D₆) δ 0.98–1.76 (cp, 6), 1.90 (s, 3), 2.11 (dt, 1, *J* = 3.6, 12.0 Hz), 2.48 (t, 1, *J* = 5.5 Hz), 2.66 (m, 1), 3.28 (m, 4), and 3.67 ppm (quintet, 1, *J* = 5.5 Hz); MS *m/e* (M⁺) 199.

Anal. (C₁₀H₁₇NO₃) C, H, N.

dl-Cocaine (1d). Following the method of de Jong,⁹ 23 mg (0.12 mmol) of compound **1e** in 1 mL of dry benzene was added to a mixture of 1.0 g (9.4 mmol) of anhydrous sodium carbonate, 0.5 mL (4.3 mmol) of benzoyl chloride, and 19 mL of dry benzene. The resulting mixture was worked up as reported⁹ to give 9.8 mg (37%) of a colorless oil that solidified on standing: mp 77–79 °C (lit.⁴⁹ mp 79–80 °C); IR (CDCl₃) 3.39 (m), 3.47 (w), 3.52 (w), 3.57 (w), 5.75 (s), 5.85 (s), 6.24 (w), 6.33 (w), 7.00 (m), 7.26 (w), 7.47 (w), 7.60 (m), 7.83 (s), 8.16 (m), 8.52 (m), 8.76 (w), 8.98 (s), 9.40 (w), 9.75 (m), 9.80 (w), 11.25 (m), and 14.40 μ; NMR (CDCl₃) δ 1.60–2.20 (cp, 5), 2.23 (s, 3), 2.44 (dt, 1, *J* = 3.5, 11.5 Hz), 3.03 (q, 1, *J* = 5.8 Hz), 3.29 (m, 1), 3.56 (m, 1), 3.71 (s, 3), 5.25 (quintet, 1, *J* = 5.8 Hz), 7.47 (m, 3), and 8.03 ppm (m, 2); MS *m/e* (M⁺) 303.

l-Cocaine. A sample of *l*-cocaine was prepared from authentic *l*-cocaine hydrochloride. To 1 mL of saturated aqueous sodium carbonate at 5 °C was added 0.03 mmol of *l*-cocaine hydrochloride. This was stirred for 3 min at 5 °C and immediately extracted with ether (4 × 6 mL). The resulting ethereal solution was dried (MgSO₄) and concentrated giving 7.0 mg (78%) of a colorless oil that solidified on standing, mp 96–97 °C (lit.⁴⁹ mp 98 °C).

2-Phenylhexahydropyrrolo[1,2-*b*]isoxazole (23a). A solution of 1-pyrroline 1-oxide (**27**) in 60 mL of methylene chloride was prepared

from 1.69 g (19.4 mmol) of *N*-hydroxypyrrolidine and 13.25 g of yellow mercuric oxide. Dry toluene (70 mL) was added and the methylene chloride was removed in vacuo; then 5 mL of styrene was added and the resulting solution was refluxed for 4 h under argon. The toluene solution was extracted with 1 N hydrochloric acid (3 × 50 mL), the acid extract was basicified with sodium bicarbonate, and the aqueous layer was then extracted with ether (3 × 100 mL). The ether layer was dried over magnesium sulfate and filtered, and the ether was removed in vacuo, giving 1.59 g (59%) of a light yellow oil. Bulb to bulb distillation gave the product as a colorless liquid: bp 110 °C (0.16 mm); IR (neat) 3.38 (s), 6.71 (m), 6.9 μ (m); NMR (100 MHz, CDCl₃) 1.67 (m, 2 H), 1.84 (m, 2 H), 2.29 (m, 2 H), 3.13 (t, 2 H, *J* = 6 Hz), 3.74 (m, 1 H), 4.90 (t, 1 H, *J* = 7 Hz), 7.15 ppm (m, 5 H); MS *m/e* (M⁺) 189.

5-(β-Hydroxy-β-phenylethyl)-1-pyrroline 1-Oxide (25a). *m*-Chloroperbenzoic acid (85%, 1.45 g, 1.1 equiv) was added to a solution of 1.23 g (6.49 mmol) of 2-phenylhexahydropyrrolo[1,2-*b*]isoxazole (**23a**) in 50 mL of dry methylene chloride, while stirring below 10 °C under nitrogen. The resulting solution was stirred for 90 min in an ice bath, then extracted with 5% sodium bicarbonate (3 × 50 mL). The aqueous layer was extracted with methylene chloride (3 × 50 mL) and the combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to give 1.30 g (98%) of the nitron as a light yellow oil: IR (neat) 2.8–3.2 (s, broad), 6.3 (s), 8.12 (s), 8.4 μ (s); NMR (100 MHz, CDCl₃) 1.6–2.6 (cp, 6 H), 3.87 (m, 1 H), 4.86 (m, 1 H), 6.00 (broad m, 1 H), 6.70 (m, 1 H), 7.19 ppm (m, 5 H); MS *m/e* (M⁺) 205.

7-(β-Hydroxy-β-phenylethyl)-2-carbomethoxyhexahydropyrrolo[1,2-*b*]isoxazole (26). A solution of 464 mg (2.26 mmol) of 5-(β-hydroxy-β-phenylethyl)-1-pyrroline 1-oxide (**25a**) and 2 mL of methyl acrylate in 50 mL of dry benzene was refluxed under nitrogen for 5 h. Removal of the solvent in vacuo gave a yellow oil, from which 374 mg (57%) of the adduct was obtained by trituration with hexane as a light yellow oil: IR (CHCl₃) 2.90 (m), 3.05 (m), 5.75 μ (s); NMR (100 MHz, CDCl₃) 1.30–2.80 (cp, 8 H), 3.30–4.0 (cp, 2 H), 3.70 (s, 3 H), 4.56 (m, 1 H), 4.93 (m, 2 H), 7.24 ppm (m, 5 H).

Anal. (C₁₆H₂₁NO₄) C, H, N.

2-Carbomethoxyhexahydropyrrolo[1,2-*b*]isoxazole (23b). A solution of 1-pyrroline 1-oxide was prepared from 1.06 g (12.17 mmol) of *N*-hydroxypyrrolidine and 7.6 g of yellow mercuric oxide in 50 mL of freshly distilled chloroform. While this solution was being stirred in an ice bath, 2.0 mL of methyl acrylate was added; the resulting solution was then warmed to room temperature and stirred for 42 h. The chloroform solution was then extracted with 1 N hydrochloric acid, the acid extract was basicified with sodium bicarbonate, and the aqueous layer was extracted with ether. The ether layer was dried over magnesium sulfate and filtered and the solvent was removed at reduced pressure, giving 850 mg (41%) of a light yellow oil. Bulb to bulb distillation at 100 °C (0.16 mm) gave the adduct as a colorless liquid: IR (CHCl₃) 3.39 (s), 5.78 (s), 6.95 μ (s); NMR (100 MHz, CDCl₃) 1.4–3.5 (cp, 8 H), 3.68 (s, 3 H), 3.8–4.2 (m, 1 H), 4.45 ppm (m, 1 H); MS *m/e* (M⁺) 171.

Anal. (C₈H₁₃NO₃) C, H, N.

5-(β-Carbomethoxy-β-hydroxyethyl)-1-pyrroline 1-Oxide (25b). *m*-Chloroperbenzoic acid (85%, 290 mg) was added to a solution of 250 mg (1.46 mmol) of 2-carbomethoxyhexahydropyrrolo[1,2-*b*]isoxazole (**23b**) in 5 mL of dry methylene chloride. The resulting solution was stirred for 3 h, diluted with 45 mL of methylene chloride, and extracted with water (2 × 50 mL). The solvent was removed from the aqueous layer at reduced pressure, giving a yellow oil (224 mg, 82%); IR (CHCl₃) 2.8–3.2 (m, broad), 3.34 (m), 3.50 (m), 5.78 (s), 6.27 (m), 6.95 (m), 8.3 μ (s, broad); NMR (60 MHz, CDCl₃) 1.8–3.0 (cp, 6 H), 3.8 (s, 3 H), 4.0 (m, 1 H), 4.4 (m, 1 H), 5.6 (broad s, 1 H), 7.0 ppm (m, 1 H).

2-Carbomethoxymethylhexahydropyrrolo[1,2-*b*]isoxazole (28a). A solution of 1-pyrroline 1-oxide in 20 mL of dry toluene was prepared from 251 mg (2.88 mmol) of *N*-hydroxypyrrolidine and 1.61 g (2.5 equiv) of yellow mercuric oxide in 20 mL of dry methylene chloride, followed by solvent exchange with toluene. A solution of 143 mg (1.30 mmol) of methyl 3-butenate in 5 mL of dry toluene was added and the mixture was refluxed for 15 h. Removal of the solvent in vacuo gave a dark oil which was chromatographed on silica gel using 90:10 benzene/acetone as eluant, from which 230 mg (96%) of the adduct was obtained. Bulb to bulb distillation at 100 °C (0.09 mm) gave a colorless liquid: IR (neat) 5.77 μ (s); NMR (100 MHz, CDCl₃) 1.5–2.0 (cp, 4 H), 2.18 (m, 2 H), 2.55, 2.64 (two d, 2 H, *J* = 7 Hz),

3.11 (m, 2 H), 3.68 (s, 3 H), 3.69 (m, 1 H), 4.47 ppm (quint, 1 H, $J = 7$ Hz); MS m/e (M^+) 185.

Anal. ($C_9H_{15}NO_3$) C, H, N.

5-(γ -Carbomethoxy- β -hydroxypropyl)-1-pyrroline 1-Oxide (29a). *m*-Chloroperbenzoic acid (85%, 130 mg, 1 equiv) was added to a solution of 123 mg (0.66 mmol) of 2-carbomethoxymethylhexahydro-pyrrolo[1,2-*b*]isoxazole (28a) in 25 mL of dry methylene chloride. The reaction mixture was then warmed to room temperature and extracted with water (2×25 mL). The aqueous layer was vacuum distilled to give a light yellow oil, which was chromatographed on silica gel, using 95:5 methylene chloride/methanol as the eluant, to give 118 mg (89%) of the product as a clear oil: IR ($CHCl_3$) 2.8–3.2 (m, broad), 3.37 (s), 5.80 (s), 6.28 (m), 6.95 (s), 8.0–8.5 μ (s, broad); NMR (100 MHz, $CDCl_3$) δ 1.8–2.3 (m, 4 H), 2.61 (d, 2 H, $J = 6$ Hz), 2.4–2.8 (m, 2 H), 3.76 (s, 3 H), 4.32 (m, 2 H), 4.78 (m, 1 H), 7.07 ppm (m, 1 H).

Allyl Cyanide. Allyl cyanide was prepared via the method of Supniewski and Salzberg,⁴⁹ from allyl bromide and cuprous cyanide, in 47% yield.

2-Cyanomethylhexahydro-pyrrolo[1,2-*b*]isoxazole (28b). A solution of 1-pyrroline 1-oxide was prepared from 890 mg (10.2 mmol) of *N*-hydroxypyrrolidine and 5.54 g (2.5 equiv) of yellow mercuric oxide in 55 mL of dry methylene chloride. The methylene chloride was exchanged with 50 mL of dry toluene (380 mg, 95.66 mmol), allyl cyanide was added, and the reaction mixture was refluxed for 17 h under nitrogen. Upon cooling to room temperature, the solvent was removed in vacuo to give a dark oil, bulb to bulb distillation of which, at 120 °C (9.1 mm), gave a yellow liquid. The distillate was taken up in 50 mL of methylene chloride, washed successively with 50 mL of water and 50 mL of sodium chloride, then dried over sodium sulfate. Bulb to bulb distillation gave 200 mg (81%) of the product as a colorless liquid: bp 100 °C (0.09 mm); IR (neat) 4.47 μ (w); NMR (100 MHz, $CDCl_3$) 1.4–2.1 (cp, 4 H), 2.32 (m, 2 H), 2.63, 2.64 (two d, 2 H, $J = 6$ Hz), 3.14 (m, 2 H), 3.76 (m, 1 H), 4.40 ppm (quint, 1 H, $J = 7$ Hz); MS m/e (M^+) 152.

5-(γ -Cyano- β -hydroxypropyl)-1-pyrroline 1-Oxide (29b). *m*-Chloroperbenzoic acid (85%, 2.07 g, 1 equiv) was added to a solution of 1.52 g (10 mmol) of 2-cyanomethylhexahydro-pyrrolo[1,2-*b*]isoxazole in 150 mL of dry methylene chloride, in an ice bath under nitrogen. The resulting light yellow solution was stirred for 3 h, then warmed to room temperature and extracted with water (2×100 mL). The aqueous layer was distilled in vacuo, leaving a yellow oil which was chromatographed on a silica gel column, using 98:2 chloroform/methanol as the eluant. Crystallization from acetone–hexane gave 1.05 g (63%) of the nitron as white crystals: mp 100–101 °C; IR ($CHCl_3$) 2.8–3.2 (m, broad), 3.38 (s), 4.45 (w), 6.28 (s), 8.15 μ (s, broad); NMR (100 MHz, $CDCl_3$) 1.8–2.3 (m, 4 H), 2.63 (d, 2 H, $J = 6$ Hz), 2.5–2.9 (m, 2 H), 4.33 (m, 2 H), 6.02 (d, 1 H, –OH), 7.01 ppm (m, 1 H); MS m/e (M^+) 168.

Anal. ($C_8H_{12}N_2O_2$) C, H, N.

2-Carbomethoxy-7-(γ -cyano- β -hydroxypropyl)hexahydro-pyrrolo[1,2-*b*]isoxazole (30b). A solution of 228 mg (1.35 mmol) of 5-(γ -cyano- β -hydroxypropyl)-1-pyrroline 1-oxide (29b) and 5 mL of methyl acrylate in 50 mL of dry benzene was refluxed for 20 h under a nitrogen atmosphere. The solution was then cooled to room temperature and the solvent was removed in vacuo to give the product as a white solid in quantitative yield. An analytical sample was obtained by crystallization from ether: mp 84–86 °C; IR ($CHCl_3$) 2.92 (m), 4.45 (w), 5.78 μ (s); NMR (100 MHz, $CDCl_3$) δ 1.45–2.37 (cp, 8 H), 2.53 (d, 2 H, $J = 6$ Hz), 2.75 (m, 1 H), 3.42 (m, 1 H), 3.75 (s, 3 H), 4.39 (m, 1 H), 4.61 (t, 1 H, $J = 9$ Hz), 4.91 ppm (m, 1 H); MS m/e (M^+) 254.

Anal. ($C_{12}H_{18}N_2O_4$) C, H, N.

Dehydration of 2-Carbomethoxy-7-(γ -cyano- β -hydroxypropyl)hexahydro-pyrrolo[1,2-*b*]isoxazole (30b). Freshly distilled phosphorus oxychloride (0.3 mL, 1.5 equiv) was added over 5 min to a solution of 550 mg (2.16 mmol) of adduct 30b in 50 mL of dry, freshly distilled pyridine. After 2 h at 0 °C, the resulting light orange solution was warmed to room temperature and stirred for an additional 16 h. The reaction mixture was then poured into ice, 1 g of potassium carbonate was added, and the aqueous solution was extracted with chloroform. The chloroform extract was dried over sodium sulfate, filtered, and concentrated to give an orange oil. Chromatography on silica gel (90:10 benzene/acetone) gave the pure *cis* and *trans* isomers (ratio ca. 4:1) as light yellow oils in 44% combined yield.

2-Carbomethoxy-7-(3'-cyano-2'-*cis*-propenyl)hexahydro-pyr-

rolo[1,2-*b*]isoxazole (32): IR ($CHCl_3$) 3.42 (m), 4.54 (m), 5.77 (s), 6.96 μ (m); NMR (100 MHz, $CDCl_3$) δ 1.56 (m, 2 H), 2.08 (m, 2 H), 2.28 (m, 2 H), 2.60 (m, 2 H), 3.18 (m, 1 H), 3.73 (m, 1 H), 3.71 (s, 3 H), 4.57 (m, 1 H), 5.34 (d, 1 H, $J = 11$ Hz), 6.65 ppm (m, 1 H). 2-Carbomethoxy-7-(3'-cyano-2'-*trans*-propenyl)hexahydro-pyrrolo[1,2-*b*]isoxazole (31b): IR ($CHCl_3$) 3.42 (m), 4.52 (m), 5.77 (s), 6.96 μ (s); NMR (100 MHz, $CDCl_3$) δ 1.62 (m, 2 H), 2.08 (m, 4 H), 2.44 (m, 2 H), 3.00 (m, 1 H), 3.73 (s, 3 H), 4.60 (m, 1 H), 5.38 (d, 1 H, $J = 16$ Hz), 6.74 ppm (m, 1 H).

Methanesulfonate Ester of 2-Carbomethoxy-7-(γ -cyano- β -hydroxypropyl)hexahydro-pyrrolo[1,2-*b*]isoxazole (30b). Under nitrogen, 412 mg (1.62 mmol) of adduct 30b in 25 mL of dry freshly distilled pyridine was cooled in an ice bath; then 188 μ L (1.5 equiv) of freshly distilled methanesulfonyl chloride was added over 10 min via a syringe. The resulting colorless solution was stirred in an ice bath for 4 h, then for 14 h at room temperature. The reaction mixture was then poured onto ice, potassium carbonate was added, and the aqueous solution was extracted with methylene chloride. The methylene chloride extract was dried over sodium sulfate, filtered, and concentrated to give a light orange oil. Chromatography on silica gel, using 85:15 benzene/acetone as the eluant, gave 92 mg of the starting adduct and 209 mg (50%) of the methanesulfonate ester as a light yellow oil: IR ($CHCl_3$) 3.34 (m), 3.40 (m), 4.43 (w), 5.77 (s), 6.96 (m), 7.35 (s), 8.53 (s), 11.1 μ (s); NMR (100 MHz, $CDCl_3$) δ 1.32–2.40 (cp, 6 H), 2.72 (m, 2 H), 3.15 (s, 3 H), 2.90–3.20 (m, 2 H), 3.72 (s, 3 H), 3.44–4.10 (m, 2 H), 4.48 (t, 1 H, $J = 7$ Hz), 5.05 ppm (quint, 1 H, $J = 7$ Hz).

Reaction of the Methanesulfonate Ester of 30b with 1,5-Diazabicyclo[4.3.0]non-5-ene.⁴⁸ Freshly distilled 1,5-diazabicyclo[4.3.0]non-5-ene (105 mg, 2 equiv) was added to a solution of 136 mg (0.41 mmol) of the methanesulfonate ester (30b) in 9 mL of dry benzene, while stirring under nitrogen. The resulting clear solution was stirred at room temperature for 18 h, washed with water, then extracted with 1 N HCl. The acidic extract was basified with sodium bicarbonate and extracted with methylene chloride (3×40 mL). The methylene chloride layer was dried over sodium sulfate, filtered, and concentrated in vacuo to give 55 mg (57%) of a 6:5 mixture of *cis* and *trans* compounds (32 and 31b) as a light yellow oil. The NMR spectrum was identical with that of the compounds obtained above using phosphorus oxychloride.

(1S*,2S*,3R*,6S*)-2-Cyano-7-aza-8-oxotricyclo[4.2.1.0^{3,7}]nonane (34). A solution of 42 mg (0.178 mmol) of *trans* olefin 31b in 70 mL of dry xylene was refluxed under a nitrogen atmosphere for 18 h. Upon cooling to room temperature, the solution was extracted with 1 N hydrochloric acid. The acid extract was basified with sodium bicarbonate, then extracted with chloroform. The chloroform layer was dried over sodium sulfate, filtered, and concentrated to give 23 mg of a light yellow oil. Crystallization from ether gave 15 mg (56%) of the adduct as fine, white needles: mp 134–134.5 °C; IR ($CDCl_3$) 4.46 μ (m); NMR (100 MHz, $CDCl_3$) δ 1.28 (dd, 1 H, $J = 3, 12$ Hz), 1.72–2.40 (cp, 5 H), 2.44 (d, 1 H, $J = 3$ Hz), 3.69 (m, 1 H), 3.86 (m, 1 H), 5.03 ppm (d, 1 H, $J = 5$ Hz); MS m/e (M^+) 150.

Anal. ($C_8H_{10}N_2O$) C, H, N.

(1S*,2R*,3R*,6S*)-2-Cyano-7-aza-8-oxotricyclo[4.2.1.0^{3,7}]nonane (36). A solution of 45 mg (0.19 mmol) of *cis* olefin 32 in 50 mL of dry xylene was refluxed for 8 h under a nitrogen atmosphere. Upon cooling to room temperature, the solution was extracted with 1 N hydrochloric acid. The acid extract was basified with sodium bicarbonate, then extracted with methylene chloride. The methylene chloride layer was dried over sodium sulfate, filtered, and concentrated to give 27 mg of a light yellow oil. Preparative thin layer chromatography on silica gel using 80:20 benzene/acetone gave 13 mg (46%) of 36. Recrystallization from ether–pentane gave an analytical sample: mp 80–81.5 °C; IR ($CHCl_3$) 4.46 μ (w); NMR (100 MHz, $CDCl_3$) δ 1.72 (dd, 1 H, $J = 3, 12$ Hz), 1.90–2.40 (cp, 5 H), 3.18 (m, 1 H), 3.67 (m, 2 H), 4.84 ppm (t, 1 H, $J = 4.5$ Hz).

Anal. ($C_8H_{10}N_2O$) C, H, N.

2-Carbomethoxy-7-(γ -carbomethoxy- β -hydroxypropyl)hexahydro-pyrrolo[1,2-*b*]isoxazole (30a). To 235 mg (1.27 mmol) of adduct 29a in 70 mL of dry methylene chloride, while stirring in an ice bath under nitrogen, was added 284 mg (1.1 equiv) of 85% *m*-chlorobenzoic acid. After 2 h, the solution was warmed to room temperature and extracted with water. The aqueous layer was concentrated in vacuo to give a clear oil which was taken up in methylene chloride, dried over sodium sulfate, and filtered. The solvent was removed and the residue was dissolved in 70 mL of dry benzene, to which was added 5 mL of methyl

acrylate. The resulting light yellow solution was refluxed for 20 h, cooled to room temperature, and extracted with 1 N hydrochloric acid. The acid extract was basified with sodium bicarbonate, then extracted with methylene chloride to give, after drying over sodium sulfate, 282 mg (77%) of a mixture of adducts **30a** as a light yellow oil: IR (CHCl₃) 2.89 (m, broad), 5.81 μ (s, broad); NMR (100 MHz, CDCl₃) δ 1.67 (m, 4 H), 2.09 (m, 4 H), 2.52 (m, 2 H), 3.30–3.85 (broad m, 2 H), 3.66 (s, 3 H), 3.71 and 3.74 (s and s, 3 H), 4.04–4.56 (broad m, 2 H), 4.60 ppm (m, 1 H).

2-Carbomethoxy-7-(γ -carbomethoxy- β -methanesulfonylpropyl)hexahydropyrrolo[1,2-*b*]isoxazole (37). Freshly distilled methanesulfonyl chloride (91 μ L, 2 equiv) was added dropwise via a syringe to a stirred solution of 170 mg (0.59 mmol) of hydroxy ester **30a** in 25 mL of freshly distilled, dry pyridine under a nitrogen atmosphere in an ice bath. After 1 h, the solution was warmed to room temperature, stirred for an additional 3 h, then poured onto ice. Potassium carbonate was added and the aqueous solution was extracted with methylene chloride. The organic extract was dried over sodium sulfate, filtered, and concentrated to give 204 g (95%) of **37** as a light yellow oil: IR (CHCl₃) 5.78 (s), 6.96 (m), 7.39 (s), 8.50 (s), 11.0 μ (s); NMR (100 MHz, CDCl₃) δ 1.30–2.40 (cp, 8 H), 2.84 (m, 2 H), 3.08 and 3.12 (s and s, 3 H), 3.65 (s, 3 H), 3.68 and 3.71 (s and s, 3 H), 3.20–4.20 (cp, 2 H), 4.52 (q, 1 H, $J = 7$ Hz), 5.14 ppm (broad quint, 1 H, $J = 6$ Hz).

2-Carbomethoxy-7-(3'-carbomethoxy-2'-trans-propenyl)hexahydropyrrolo[1,2-*b*]isoxazole (31a). Under nitrogen, 204 mg (0.56 mmol) of methanesulfonate ester (**37**) was dissolved in 25 mL of dry benzene, to which was then added 138 mg (2 equiv) of freshly distilled 1,5-diazabicyclo[4.3.0]non-5-ene⁴⁸ via a syringe. The resulting suspension was stirred for 4 h, washed with 25 mL of saturated sodium bicarbonate solution and twice with 25 mL of water, then dried over sodium sulfate. The solvent was removed in vacuo to give 130 mg (86%) of trans olefin **31a** as a light yellow oil: IR (CHCl₃) 5.83 μ (s); NMR (100 MHz, CDCl₃) δ 1.40–2.85 (cp, 8 H), 3.20–4.00 (broad m, 2 H), 3.75 (s, 3 H), 3.79 (s, 3 H), 4.66 (m, 1 H), 5.92 (d, 1 H, $J = 16$ Hz), 7.06 ppm (m, 1 H).

2-Carbomethoxy-(1S*,2R*,3R*,6S*)-7-aza-8-oxotricyclo[4.2.1.0^{3,7}]nonane (12). A solution of 78 mg (0.29 mmol) of the crude trans olefin **31a** in 50 mL of dry, distilled xylene was refluxed for 3 h. The solution was extracted with 1 N hydrochloric acid. The acid extract was basified with sodium bicarbonate, then back-extracted with methylene chloride. The methylene chloride extract was dried over sodium sulfate, filtered, and concentrated to give a light yellow oil. Sublimation at 70 °C (0.08 mm) gave a mixture of 9 mg of **31a** and 31 mg (66%) of **12**. Crystallization from pentane gave an analytical sample of **12** as white plates: mp 76–78 °C; IR (CHCl₃) 5.79 μ (s); NMR (100 MHz, CDCl₃) δ 1.24 (dd, 1 H, $J = 3, 12.5$ Hz), 1.76–2.36 (cp, 6 H), 3.52 (m, 1 H), 3.67 (s, 3 H), 3.86 (m, 1 H), 4.94 ppm (d, 1 H, $J = 5$ Hz).

Anal. (C₉H₁₃NO₃) C, H, N.

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