Total Syntheses of *Yohimbe* Alkaloids, with Stereoselection for the Normal, Allo, and 3-Epiallo Series, Based on Annelations of 4-Methoxy-1,2-dihydropyridones

Martin E. Kuehne* and Randy S. Muth

Department of Chemistry, University of Vermont, Burlington, Vermont 05405

Received August 14, 1990

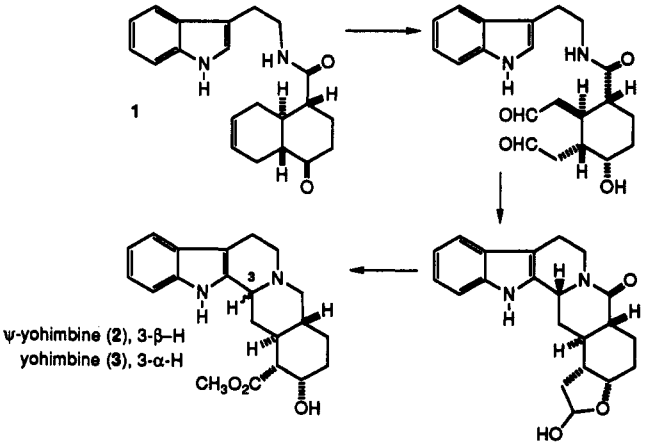
N-[2-(1*H*-3-indolyl)ethyl]-2,3-dihydro-4-pyridone (**31**) was generated in two steps (77% yield) from tryptamine and *N*-methyl-4-piperidone methiodide. Its cyclization (90% yield) and oxidation (91% yield) provided the tetracyclic analogue **32**. *O*-Methylation and Robinson-type annelation of these vinylogous lactams (the latter in form of its N^a-carbamate) furnished the dienones **38** (64%) and **43** (90%). Further elaboration by cyclization and/or reduction reactions selectively provided the 15,16-didehydroyohimbinones **7** or **44**. Their reductions then led to yohimbinone (**52**, 20% overall yield from tryptamine), alloyohimbinone (**11**, 19% overall yield), and 3-*epi*-alloyohimbinone (**10**, 23% overall yield), which led to yohimbine (**3**), β-yohimbine (**9**), 3-*epi*-alloyohimbine (**53**), and 3-*epi*-17-*epi*-alloyohimbine (**54**).

Background

Starting with the synthesis of yohimbone by Swan in 1950,[1] synthetic studies directed at the *Yohimbe* alkaloids have provided a variety of approaches that, apart from their specific goals, advanced organic chemistry through the development of important synthetic methodologies. While a complete review of those syntheses is beyond the scope of this paper (and already available),[2] we summarize here, for comparison, only the most limiting considerations of each approach, with the hope that this negative perspective will not detract from recognition of the significant enrichment of organic synthesis, which these studies have provided.

On the basis of elaboration of a *trans*-decalone-derived carboxamide **1**, the pioneering work of van Tamelen led to a synthesis of racemic ψ-yohimbine (**2**) in 0.02–0.03% yield.[3] This then gave access to yohimbine (**3**) through an oxidation and reduction sequence (Scheme I).[4] More recently, Szántay's annelation of a dihydro-β-carboline **4** (Scheme II) with a substituted vinyl methyl ketone **5** and a following Wittig reaction provided an olefinic diester **6**. Its Dieckmann cyclization to 15,16-didehydroyohimbinone (**7**),[5] formed in 13% overall yield, surmounted the earlier lack of regioselectivity experienced on cyclization of the corresponding saturated diester.[6] This general reaction scheme resulted not only in the generation of yohimbinone (**8**) and its reduction products yohimbine (**3**) and β-yohimbine (**9**), but also of some 3-*epi*-alloyohimbinone (**10**) and of alloyohimbinone (**11**), α-yohimbine (**12**), alloyohimbine (**13**), 17-*epi*-alloyohimbine (**14a**), and 17-*epi*-α-yohimbine (**14b**).[7] Notably, this strategy also allowed an asymmetric generation of the initial tetracyclic intermediate **15** through a deracemization reaction![8]

Scheme I



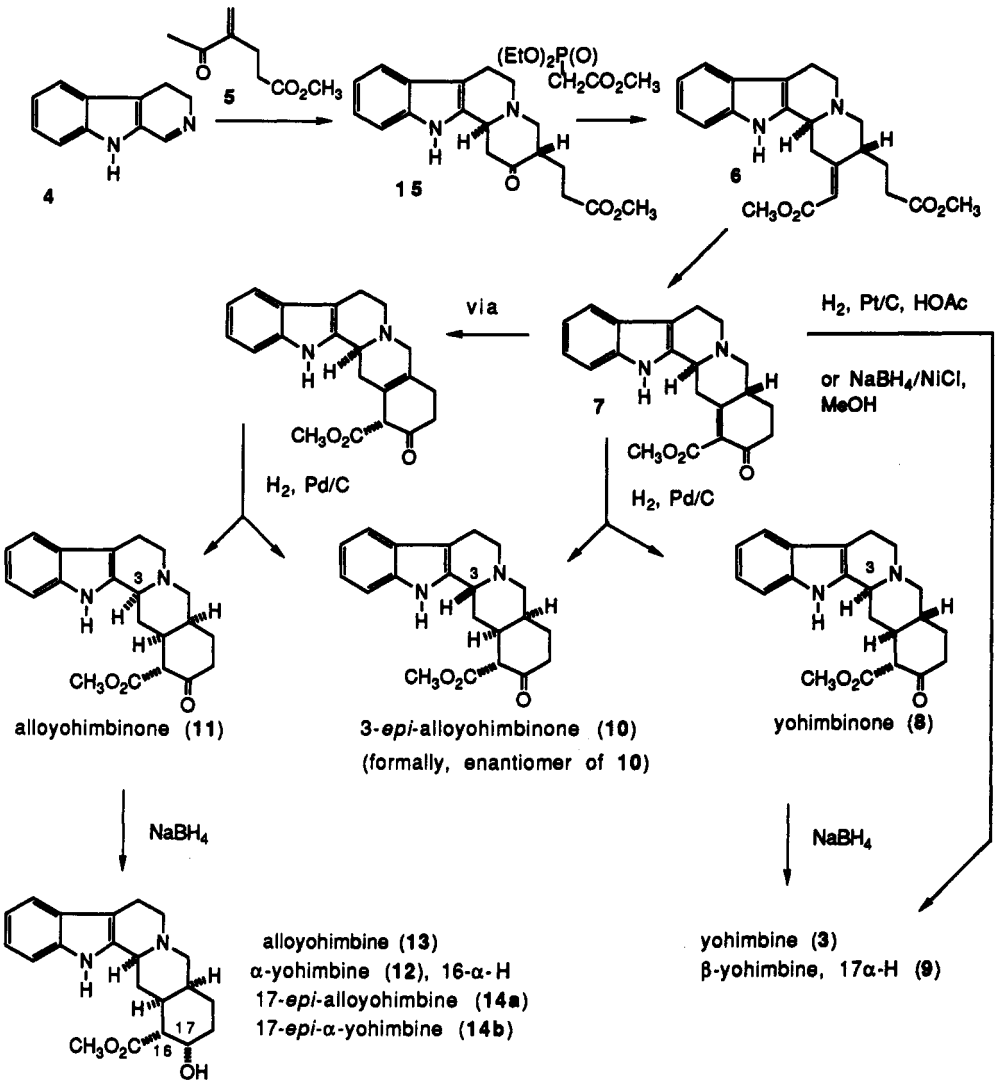
A Robinson-type annelation of ring E with carbomethoxymethyl vinyl ketone on a ring-D ketone **16** derived enamine (Scheme III) gave Kametani only a 17% yield of the desired didehydroyohimbinone **7** (6% overall),[9] while the same type of reaction on the *N*-methyl-4-piperidone derivative **17** provided Stork with an 80% yield of an analogous product **18**.[10] Its reduction and replacement of the *N*-methyl substituent by a β-indolylethyl group and reduction to a saturated alcohol then provided a substrate **19** for oxidative cyclization with mercuric acetate. In the presence of EDTA, yohimbine (**3**) was formed in 32% yield, while without EDTA, ψ-yohimbine (**2**) was obtained in 27% yield. An analogous cyclization in the D/E cis series (Scheme IV), where the D/E ring system was elegantly formed by an intramolecular Diels–Alder reaction of a 2-pyranone **20**, resulted in formation of regioisomers in the oxidative cyclization reaction, with the desired isomer obtained in 31% yield, and α-yohimbine (**12**) was then formed in only 3% overall yield.[11]

In the Wenkert approach (Scheme V), addition of dimethyl sodiomalonate to an (indolylethyl)pyridinium salt **21** furnished a dienamine. On protonation, it cyclized to

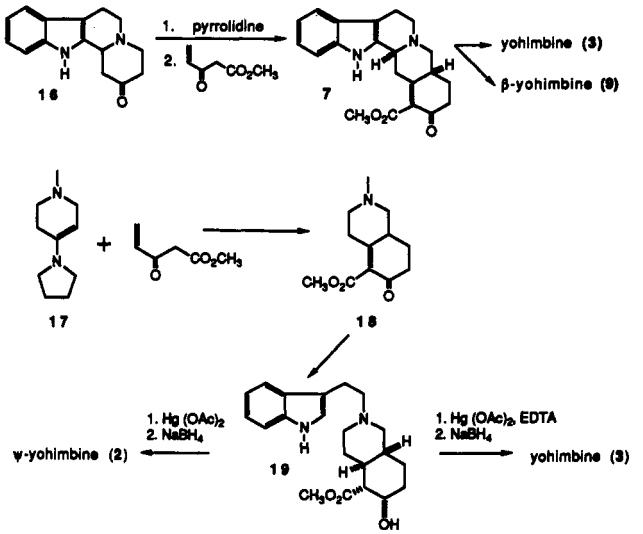
(1) Swan, G. A. *J. Chem. Soc.* **1950**, 1534.
(2) (a) Cordell, G. A. In *Heterocyclic Compounds: The Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; Wiley: New York, 1983; Vol. 25, Part 4, p 539. (b) Szántay, Cs.; Blaskó, G.; Honty, K.; Dörnyei, G. *Alkaloids* **1986**, *27*, 131.
(3) van Tamelen, E. E.; Shamma, M.; Burgstahler, A. W.; Wolinsky, J.; Tamm, R.; Aldrich, P. E. *J. Am. Chem. Soc.* **1958**, *80*, 5006. *J. Am. Chem. Soc.* **1969**, *91*, 7315.
(4) Godtfredsen, W. O.; Vangedal, S. *Acta Chem. Scand.* **1956**, *10*, 1414.
(5) (a) Szántay, Cs.; Töke, L.; Honty, K.; Kalaus, G. *J. Org. Chem.* **1967**, *32*, 423. (b) Szántay, Cs.; Honty, K.; Töke, L.; Buzas, A.; Jacquet, J. P. *Tetrahedron Lett.* **1971**, 4871.
(6) Töke, L.; Honty, K.; Szántay, Cs. *Chem. Ber.* **1969**, *102*, 3248.
(7) Szántay, Cs.; Honty, K.; Töke, L.; Szabó, L. *Chem. Ber.* **1976**, *109*, 1737.
(8) Knight, H.; Honty, K.; Szántay, Cs.; Blaskó, G. *Liebigs Ann. Chem.* **1986**, 655.
(9) Kametani, T.; Hirai, Y.; Kajiwara, M.; Takahashi, T.; Fukumoto, K. *Chem. Pharm. Bull.* **1975**, *23*, 2634.
(10) Stork, G.; Guthikonda, R. N. *J. Am. Chem. Soc.* **1972**, *94*, 5109.
(11) Martin, S. F.; Rueger, H. *Tetrahedron Lett.* **1985**, *26*, 5227. Martin, S. F.; Grzejszczak, S.; Rueger, H.; Williamson, S. A. *J. Am. Chem. Soc.* **1985**, *107*, 4072.

0022-3263/91/1956-2701$02.50/0

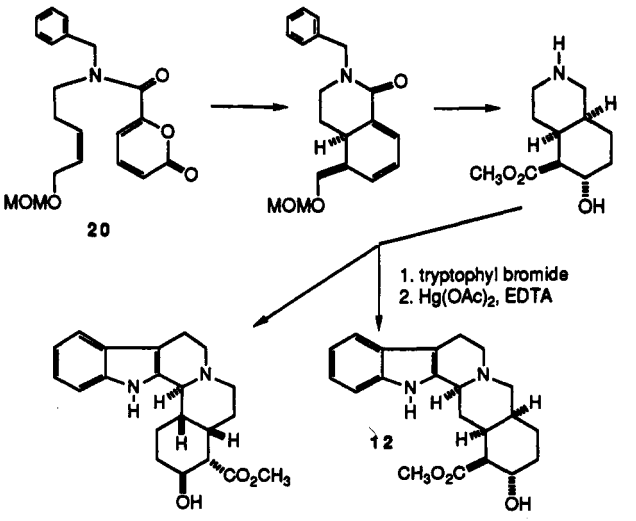
Scheme II



Scheme III



Scheme IV

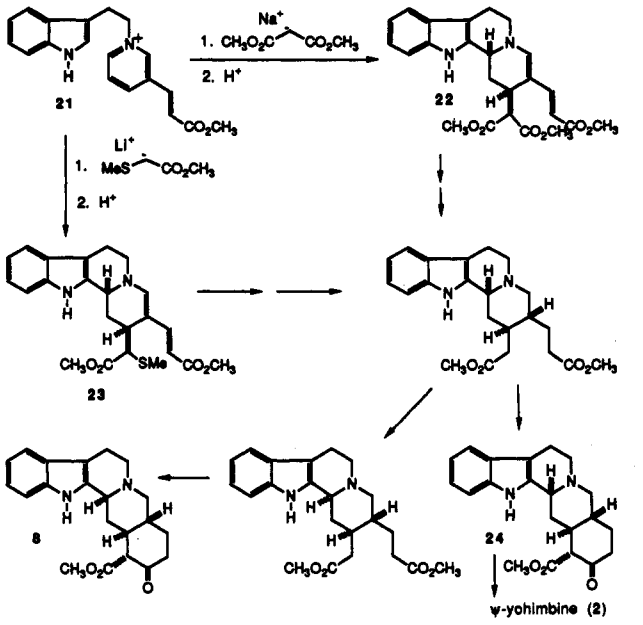


a tetracyclic triester **22** in 18% yield. When the softer methyl lithiothioacetate was used as reactant, the nucleophilic addition reaction was improved and a cyclization product **23** was obtained in 28% overall yield. Reduction and nonregioselective Dieckmann cyclization, in 47% yield, then led to ψ-yohimbinone (**24**), which provided ψ-yohimbine (**2**) in 5% overall yield upon hydrogenation.[12] C-3 epimerization prior to the Dieckmann cyclization gave access to yohimbinone (**8**).

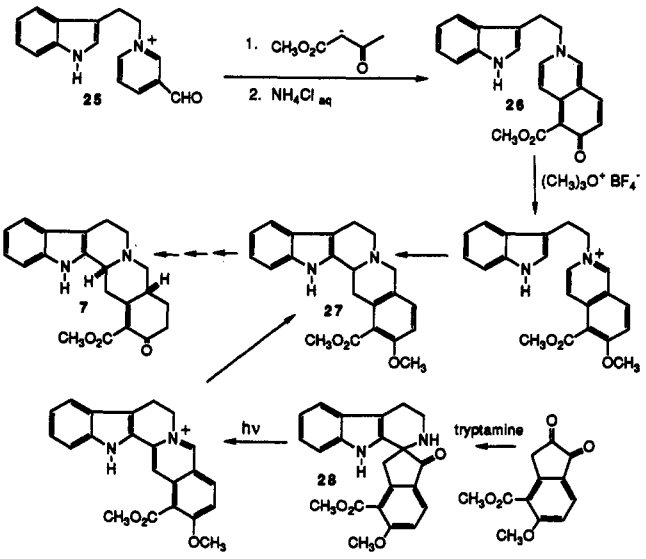
A reaction of the indolylethyl pyridinium aldehyde **25** (Scheme VI) with methyl acetoacetate and cyclization with

(12) Wenkert, E.; Kunesch, G.; Orito, K.; Temple, W. A.; Yadav, J. S. *J. Am. Chem. Soc.* **1978**, *100*, 4894. Wenkert, E.; Angell, C.; Drexler, J.; Moeller, P. D. R.; Pyrek, J. St.; Shi, Y.; Sultana, M.; Vankar, Y. D. *J. Org. Chem.* **1986**, *51*, 2995.

Scheme V



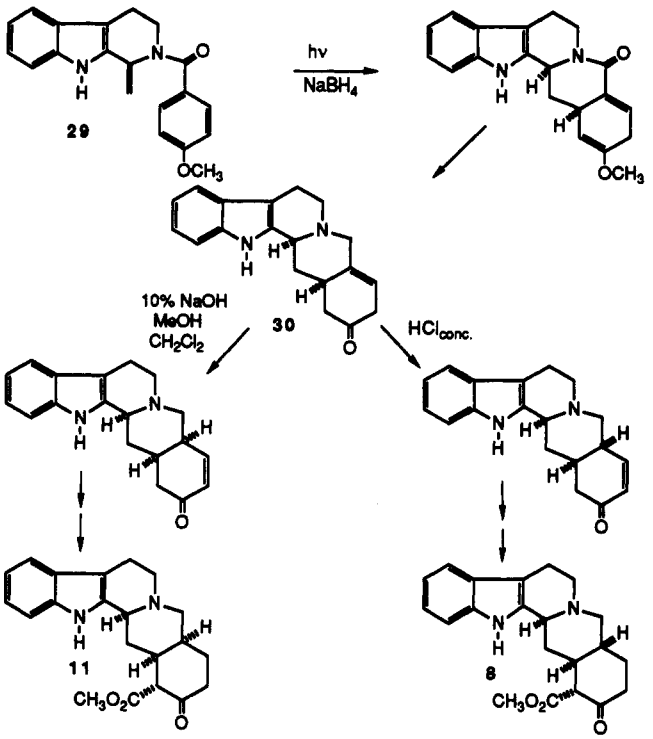
Scheme VI



ammonium chloride provided a highly conjugated tetraene **26**, which could be converted to the ring-E aromatic ester **27**.[13] The latter had been taken to 15,16-didehydroyohimbinone (**7**).[14] Since this product was obtained in only 0.3% yield, this route to yohimbine (**3**) proved less fruitful than the preceding one to ψ-yohimbine (**2**).

15,16-Didehydroyohimbinone (**7**) was furthermore obtained in 0.2% overall yield through a photochemical rearrangement of the spiroindanone β-carboline **28** (Scheme VI) followed by reduction reactions.[14] Photochemistry was also used for closure of ring D (90%) in the amide **29** derived from harmaline and 4-methoxybenzoyl chloride (Scheme VII).[15] Subsequent elaboration to yohimbinone (**8**) through the enone **30** in 42% overall yield and to alloyohimbinone (**11**) in 64% overall yield established this

Scheme VII

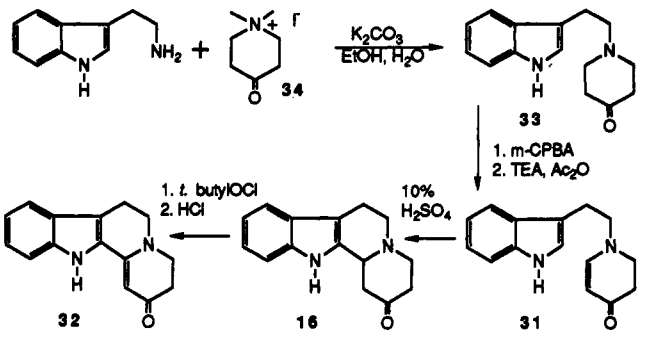


strategy as the most effective route to yohimbinone-type structures.

Synthetic Strategy. Our present entry into yohimbinoid alkaloid syntheses was prompted by the desire to explore oxygen-4-substituted 1,2-dihydropyridines as key synthons for assembly of these alkaloids. We had found that such intermediates are accessible from 2,3-dihydro-4-pyridones on O-silylation, and we had utilized their dienamine reactivity for high-yielding intramolecular Michael reactions and for (formal) Diels–Alder additions in syntheses of carbomethoxycleavamines and catharanthine.[16] While the alkylation of vinylogous amides, including 2,3-dihydro-4-pyridones, had been well explored for reactions on O, N, and at the α-carbon (relative to the carbonyl group),[17,18] there seemed to be only one report of an alkylation of a vinylogous amide at the α′-position.[19] The basic conditions of that reaction, methylation of an LDA-derived enolate of 3-(*N*-pyrrolidino)-2-methyl-2-cyclohexen-1-one, were, however, incompatible with our need for a reaction with an acidic Michael acceptor such as 1-carbomethoxy-3-buten-2-one. Consequently, our approach was directed to the dienamine reactions of corresponding enolate derivatives. While mono- and dialkylation of linear dienamines with Michael acceptors such as acrylates are selective for the internal, rather than the desired terminal olefin position,[20] simple 1,2-dihydropyridines are known to furnish, in low yield, Diels–Alder products.[21-23] The quantitative yields that were obtained

(13) Wenkert, E.; Pyrek, J. St.; Uesato, S.; Vankar, Y. D. *J. Am. Chem. Soc.* **1982**, *104*, 2244.
(14) Kametani, T.; Hirai, Y.; Fukumoto, K. *Chem. Pharm. Bull.* **1976**, *24*, 2500.
(15) Miyata, O.; Hirata, Y.; Naito, T.; Ninomiya, I. *J. Chem. Soc., Chem. Commun.*, **1983**, 1231. Naito, T.; Hirata, Y.; Miyata, O.; Ninomiya, I. *J. Chem. Soc., Perkin Trans. 1*, **1988**, 2219.
(16) Kuehne, M. E.; Bornmann, W. G.; Earley, W. G.; Markó, I. *J. Org. Chem.* **1986**, *51*, 2913.
(17) Meyers, A. I.; Reine, A. H.; Gault, R. *J. Org. Chem.* **1969**, *34*, 698. Onda, M.; Sugama, Y.; Yabuki, R. *Heterocycles* **1985**, *23*, 111.
(18) Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277.
(19) Reusch, W.; Telschow, J. E. *J. Org. Chem.* **1975**, *40*, 862.
(20) Unpublished results from our laboratory.
(21) Mumm, O.; Diederichsen, J. *Liebigs Ann. Chem.* **1939**, *538*, 195. Agawa, T.; Miller, S. I. *J. Am. Chem. Soc.* **1961**, *83*, 449. Schenker, K.; Druey, J. *Helv. Chim. Acta* **1959**, *42*, 1971; **1962**, *45*, 1344.
(22) Buchi, G.; Coffen, D.; Kocsis, K.; Sonnet, P.; Ziegler, F. *J. Am. Chem. Soc.* **1966**, *88*, 3099.
(23) Ban, Y.; Wakamatsu, T.; Fujimoto, Y.; Oishi, T. *Tetrahedron Lett.* **1968**, 3383.

Scheme VIII

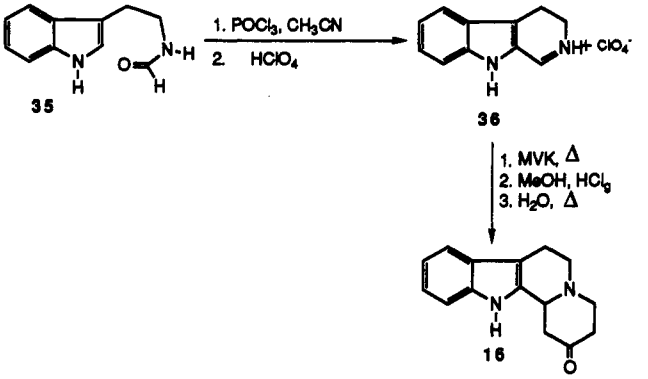


in reactions of 4-silyloxy-substituted 1,2-dihydropyridines, which were used for our cleavamine and catharanthine syntheses,[16] might be ascribed not only to the increased activation of the diene by a silyloxy substituent, but also to the intramolecularity of those reactions. Consequently, the projected intermolecular annelations were not necessarily secure. Indeed, direct extrapolation of our previous procedures for *O*-silylation of 2,3-dihydro-4-pyridones, followed by addition of Michael acceptors, failed to give the desired products, perhaps mostly due to disproportionation of the initial dihydropyridines.

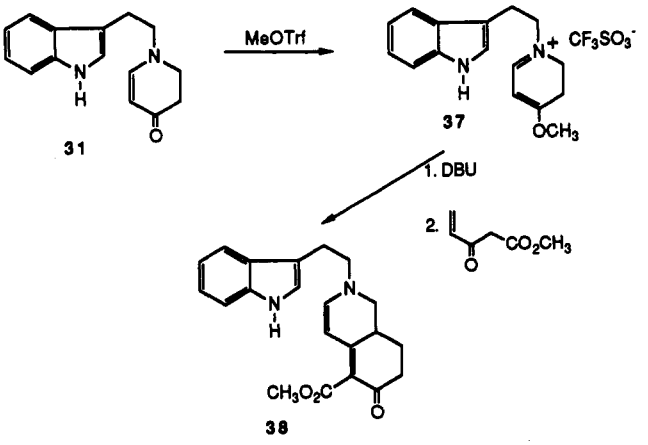
Generation of the *Yohimbe* Alkaloid Skeleton. Two 1,2-dihydro-4-pyridones, **31** and **32**, were studied in our annelation reactions. Both were known compounds, but more efficacious syntheses of these intermediates had to be developed. While the Winterfeldt synthesis of the tricyclic compound **31** (by alkylation of 4-methoxypyridine with tryptophyl bromide, demethylation by hydroxide, and partial reduction with lithium aluminum hydride)[24] could be repeated, it could not be improved. More satisfactory was a synthesis (Scheme VIII) through *N*-[2-(1*H*-3-indolyl)ethyl]-4-piperidone (**33**), which was obtained by a reaction of *N*-methyl-4-piperidone methiodide (**34**) with tryptamine (90% yield) by modification of a preparation of *N*-benzylpiperidone.[25] A Polonovsky oxidation of this amino ketone **33** (85% yield)[26,27] allowed good preparative accumulation (10–20 g batches) of the required vinylogous amide **31**.

The tetracyclic 1,2-dihydro-4-pyridone **32** had previously been obtained by condensation of demethoxyharmaline with methyl acrylate (17% yield).[28] We initially prepared this compound, also in modest yields, by a one-pot sequence of oxidation–cyclization–oxidation of the piperidone **33** with mercuric acetate in acetic acid. For a more productive and less biohazardous synthesis, cyclization of the 2,3-dihydro-4-pyridone **31** with 10% sulfuric acid (90% yield)[24] was followed by oxidation of the resulting tetracyclic amino ketone **16**. To assure complete regioselectivity for this final introduction of a double bond, oxidation of the amine or ketone functions was rejected in favor of attack at the indole moiety. Chlorination with *tert*-butyl hypochlorite[4] followed by addition of gaseous HCl to the generated chloroindolenine resulted in rearrangement to a chloroindoline alkene and loss of HCl, which produced the 2,3-dihydro-4-pyridone **32** in 91% yield (63% from tryptamine).

Scheme IX



Scheme X



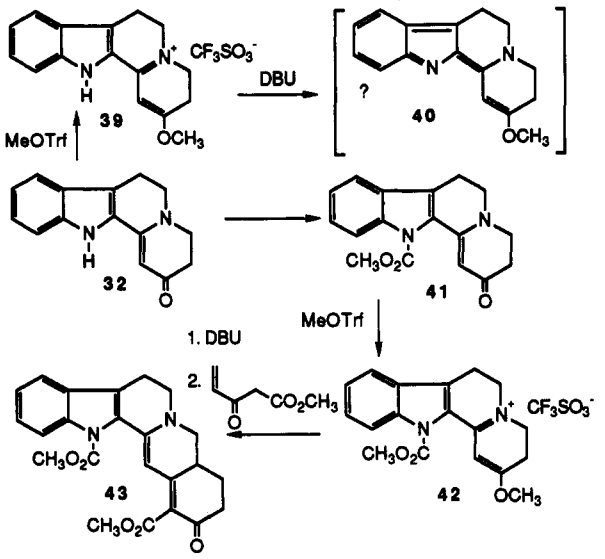
The amino ketone intermediate **16** could also be obtained from *N*-formyltryptamine **35** by modifications of a reported reaction sequence used for preparation of analogous compounds.[29,30] Cyclization with $POCl_3$ in acetonitrile at 0 °C (rather than in benzene at reflux) and reaction of the dihydro-β-carboline product, as its perchlorate **36**, with methyl vinyl ketone and cyclization with methanolic HCl (rather than triethylamine (46%),[28] where the cyclization was reported to have failed, but was achieved with the N^a-benzyl derivative)[30] followed by hydrolysis of an initial dimethyl ketal gave the amino ketone **16** in 64% overall yield from tryptamine formate through *N*-formyltryptamine (**35**) (Scheme IX).

Unable to expand our previous alkylation chemistry of silyloxy-substituted dihydropyridines to intermolecular Michael reactions,[16] we turned to the more robust alkoxy analogues and were rewarded with a useful method of annelation of dihydro-4-pyridones. Thus, methylation of the tricyclic 2,3-dihydropyridone **31** (Scheme X) with methyl triflate gave, quantitatively, the *O*-methyl imonium salt **37**. Its deprotonation with DBU in DMF was followed by immediate addition of carbomethoxymethyl vinyl ketone, resulting in formation of the annelation product **38** in 64% yield.

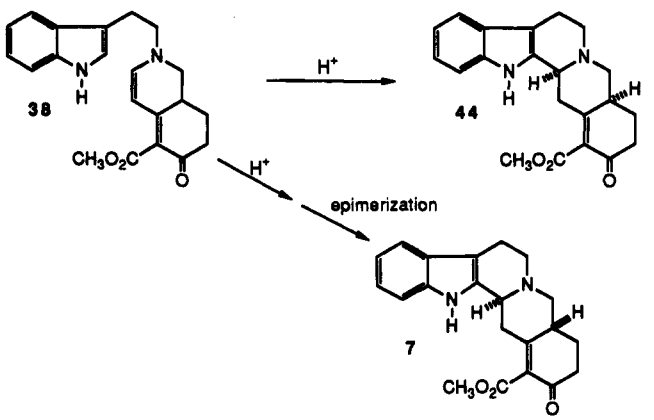
A direct extension of this methodology to the tetracyclic 2,3-dihydropyridone **32** was not possible because, in this case, the methoxy imonium salt **39** (Scheme XI) suffered deprotonation of the indolic NH function, rather than loss of the α′-proton of the enol ether, on treatment with DBU. The generated bright green, presumed imine **40** did not react with carbomethoxymethyl vinyl ketone. Masking of

(24) Winterfeldt, E. *Chem. Ber.* **1964**, *97*, 2463.
(25) Mistryukov, E. A.; Aronova, N. I.; Kucherov, V. F. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1961**, 932.
(26) Polonovski, M.; Polonovski, M. *Bull. Soc. Chim. Fr.* **1927**, *41*, 1190.
(27) Stadler, P. A.; Stutz, P. *Tetrahedron Lett.* **1973**, 5095.
(28) Szántay, Cs.; Blaskó, G.; Honty, K.; Novak, L. *Acta Chim. Acad. Sci. Hung.* **1979**, *99*, 35.
(29) Szántay, Cs.; Töke, L.; Barczai, B.; Kalaus, Gy. *Periodica Polytech.* **1965**, *9*, 231; *Chem. Abstr.* **1966**, *65*, 3848e.
(30) Novak, L.; Szántay, Cs. *Chem. Ber.* **1969**, *102*, 3959.

Scheme XI



Scheme XII



the indolic moiety was achieved by its reaction with dimethylcarbonic anhydride and (*N*,*N*-dimethylamino)-pyridine (82% yield).[31] The resulting urethane **41**, on *O*-methylation **42** and condensation with carbomethoxymethyl vinyl ketone, then provided the tetradehydroyohimbinone derivative **43** in 90% yield.

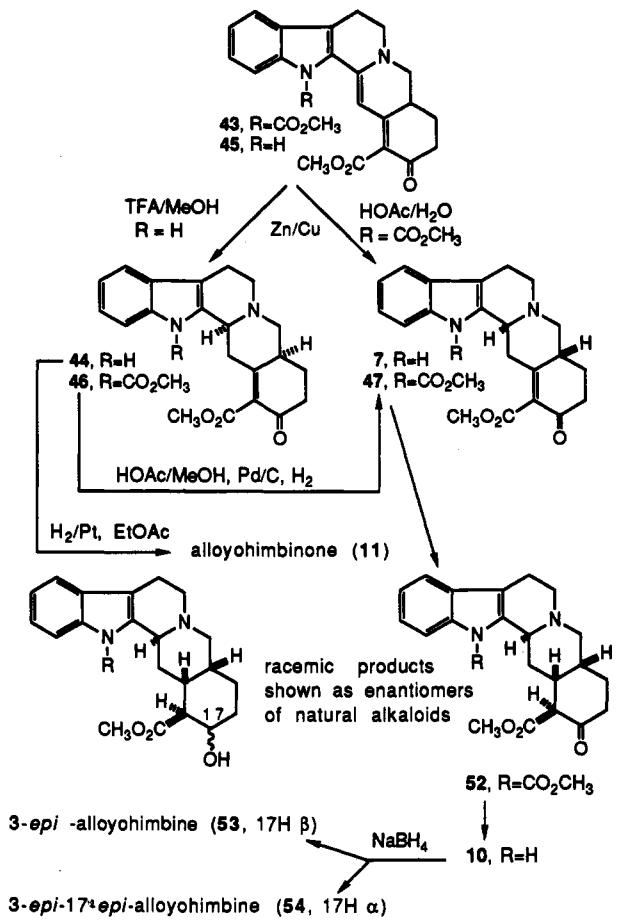
Acid-catalyzed cyclization of the tetracyclic dienone **38** (Scheme XII) was attempted under a variety of conditions including the following: aqueous HCl or H_2SO_4; trifluoroacetic acid under a variety of conditions including aqueous HCl or H_2SO_4; trifluoroacetic acid in benzene, methanol, or neat; *p*-toluenesulfonic acid in dichloromethane, benzene, or methanol; and BF_3 in methanol or tetrahydrofuran. While under most of these conditions only unreacted starting material was seen, best results were obtained with 50% aqueous H_2SO_4. Since a large shift toward lower wavelength could be observed in the UV–vis spectra on addition of trifluoroacetic acid to a methanolic solution of the dienone **38**, the lack of its cyclization under such conditions is apparently not due to lack of protonation of the amino dienone **38** but due to the relative stability of the resulting conjugated imonium product.

It was found that the reaction temperature plays a critical role in this cyclization and that it can be used to control the stereochemical outcome. When the reaction was carried out at 0 °C for 7.5 h, the new, 3,20-*cis*-15,16-didehydroyohimbinone **44** was formed in 68% yield, along with 23% of the known 3,20-trans isomer **7**. At 20 °C for 24 h, the latter isomer was obtained in 50% yield. No cyclization occurred at −20 °C over 36 h. Epimerization of the 3,20-cis to the 3,20-trans isomer under the reaction conditions could be monitored by TLC. By controlling the temperature of this cyclization step, it was thus possible to obtain the 3,20-cis isomer **44** in 32% overall yield or the 3,20-trans isomer **7** in 23% overall yield for their total syntheses.

Methanolysis of the urethane **43** quantitatively furnished the pentacyclic dienone **45**. Its reduction with the hydride reagents $NaBH_4$, $NaCNBH_3$, $NaB(OAc)_3H$, and $NaCNB(OAc)_2H$ led to complex mixtures. However, reductions

(31) Ragnarsson, U.; Grehn, L. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 296.

Scheme XIII



Scheme XIV

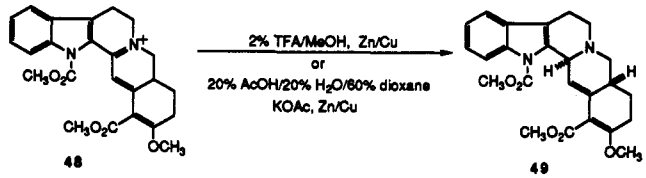
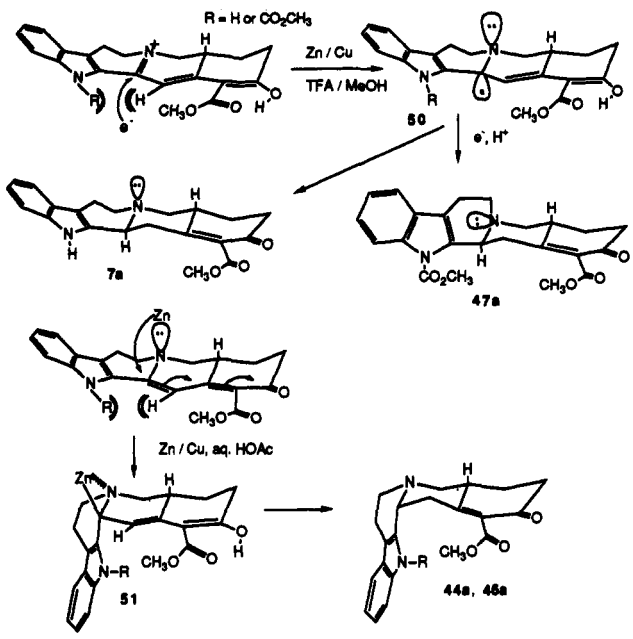


Table I. Zn/Cu Reductions of Tetradehydroyohimbinones 43 and 45

N[a] subst R	1.5–2.0% TFA/MeOH	20% AcOH/20% H_2O/60% dioxane
H (**45**)	H-3/H-20 ≈ 100% trans (**7**) 75% yield	H-3/H-20 ≈ 7:1 cis/trans (**44**:**7**) 72% combined yield
CO_2CH_3 (**43**)	H-3/H-20 ≈ 1:1 cis/trans (**46**:**47**) 66% yield[a]	H-3/H-20 100% cis (**46**) 72% yield

[a] Product ratio by TLC after 10 min. After 35 min, more **47** by epimerization.

Scheme XV



of the dienone **45** (Scheme XIII) or of the urethane **43** with Zn/Cu, under various acidic conditions, produced the 15,16-didehydro products as 3,20-trans **7** (**47**) and/or cis isomers **44** (**46**), depending on the solvent (see Table I). A reduction of the *O*-methyl triflate **48** (Scheme XIV), on the other hand, resulted in formation of only the 3,20-trans isomer **49**. Reduction of an imonium salt, which is formed under stronger acidic conditions or on *O*-alkylation, was thus found to favor the 3,20-trans products, while an N^a-carbomethoxy substituent promoted generation of 3,20-cis products. The kinetically favored formation of these products can be understood in terms of electron addition to the imonium salts to give rise to a thermodynamically favored C/D-trans radical **50** (Scheme XV) with optimal orbital overlap with the indole and dienone functionalities, which on second electron addition and protonation would lead to the 3,20-trans product.[32] On the other hand, reduction of the dienone by electron transfer from zinc coordinated to N^b on the β-face of the molecule[33] and preservation of that geometry (**51**) on protonation would explain formation of 3,20-cis products under less acidic conditions. Inversion of an initial C/D-cis radical or anion would be hindered in reductions of substrates with the N^a-carbomethoxy urethane substituent because of its steric compression with the C-14 hydrogen in such a conformational inversion.

Structural Elucidations of the 15,16-Didehydroyohimbinones 7, 47, 44, and 46. The unacylated indole **7**, with C-3,20 hydrogen trans orientation, showed IR Wenkert–Bohlmann bands[34] at 2802 and 2766 cm^{-1} and an upfield NMR signal at δ 3.42 as a doublet with J = 11 Hz, in accord with reported values[7] and with a conformation that has an axial hydrogen at C-3 and a trans coplanar axial electron pair on N^b. In contrast, its N^a-acyl derivative **47** lacked the IR and NMR characteristics of this C-3 hydrogen and N^b interaction, while still retaining the 11-Hz coupling constant of an axial C-3 hydrogen. Consequently, a conformation **47a** (Scheme XV) in which the N^b electron pair is equatorial to ring D, with relief of steric compression of the N^a-carbomethoxy substituent, was assigned to this compound. An X-ray structure analysis of its hydrogenation product **52** (see the following text and Figure 1) confirmed the relative C-3–C-20 stereochemistry.

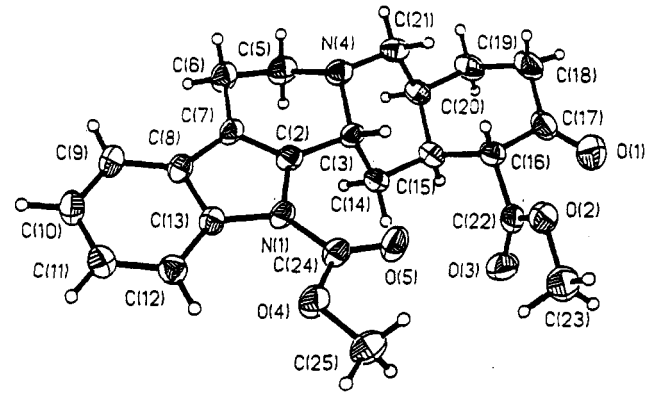
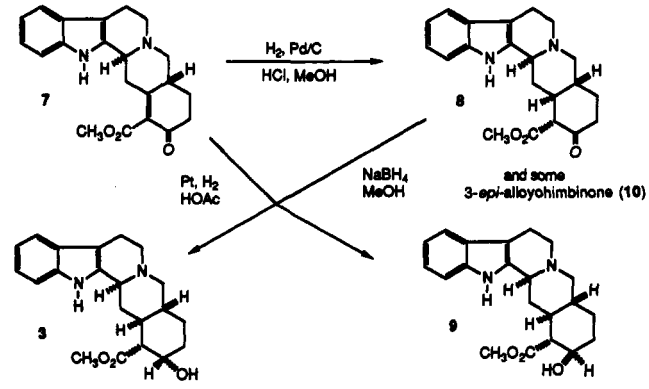


Figure 1. X-ray structure of *N*-carbomethoxy-3-*epi*-alloyohimbinone (**52**).

Scheme XVI



Generation of Stereoisomeric Yohimbinones and Their Reductions. Hydrogenation of the 3,20-*trans*-15,16-didehydroyohimbinone **7** with 10% Pd/C in methanol/HCl gave yohimbinone (**8**) in 65% yield (Scheme XVI), together with a minor amount of 3-*epi*-alloyohimbinone (**10**) in accord with previous results.[7] Thus, this key intermediate was obtained in 15% overall yield by the sequence of annelation of the C-*seco*-dihydropyridone **31** and in 20% overall yield through annelation of the tetracyclic dihydropyridone **32**. A reduction with sodium borohydride in methanol then provided racemic yohimbine (**3**; 22%) and β-yohimbine (**9**; 53%), for which spectroscopic data (IR, UV, ^1H NMR, ^{13}C NMR, MS) were in accord with literature values.[6,35] It should be noted that direct hydrogenation of the didehydroyohimbinone **7** with Pt in acetic acid has led directly to yohimbine (**3**) and β-yohimbine (**9**) in good combined yield.[7,8] With this shortcut, our synthesis of these alkaloids is contracted to

(32) Pradhan, S. K. *Tetrahedron* **1986**, *421*, 6351.
(33) Moeller, T. *Inorganic Chemistry, An Advanced Textbook*; John Wiley and Sons: New York, 1952; Chapter 19.
(34) Wenkert, E.; Roychaudhuri, D. *J. Am. Chem. Soc.* **1956**, *78*, 6417. Bohlmann, F. *Chem. Ber.* **1958**, *91*, 2147.
(35) Wenkert, E.; Chang, C. J.; Chawla, H. P. S.; Cochran, D. W.; Hagaman, E. W.; King, J. C.; Orito, K. *J. Am. Chem. Soc.* **1976**, *98*, 3645.

six steps through intermediate **31**, with improved overall yields of 6% for yohimbine (**3**) and 10% for β-yohimbine (**9**).

Hydrogenation of mixtures of the N^a-carbomethoxy-3,20-*cis*- and -*trans*-didehydroyohimbinones **46** and **47**, obtained from the Zn/C reduction of the tetradehydro compound **43**, with 10% Pd/C in 5% acetic acid in methanol produced N^a-carbomethoxy-3-*epi*-alloyohimbinone (**52**) in 71% yield from the dienone **43** (Scheme XIII). In this acidic medium, the 3,20-cis isomer **46**, which appears to be more resistant to hydrogenation, epimerized to the trans isomer **47**. Removal of the *N*-carbomethoxy substituent with methanolic sodium methoxide then provided 3-*epi*-alloyohimbinone (**10**; 75%). *Thus, this first stereoselective route to 3-epi-alloyohimbinone* (**10**), *with reserpine skeletal stereochemistry, provided this compound in 23% overall yield.*

The stereochemically divergent directions and selectivities of reduction of the N^a–H and N^a-carbomethoxy-3,20-didehydroyohimbinones **7** and **47** are a consequence of their respective alternative conformations **7a** and **47a** (Scheme XV), which are retained in their reduction products **8** and **52** as seen from their corresponding IR and NMR spectra. The orthogonal direction of the N^b electron pair and the C-3 hydrogen in N^a-carbomethoxy-3-*epi*-alloyohimbinone (**52**) could also be confirmed by an X-ray crystallographic structure (Figure 1). Apparently, protonation and an associated, solvated acetate counterion at N^b on the β(axial) side for **7** and the α(equatorial) side of N^b for **47** direct hydrogenation of the C-15,16 double bond to the respective opposite face of the enone. After removal of the *N*-carbomethoxy substituent, 3-*epi*-alloyohimbinone (**10**) undergoes an N^b conformational inversion with generation of the expected Wenkert–Bohlmann IR bands and upfield shift of the C-3 hydrogen NMR signal.

Reduction of 3-*epi*-alloyohimbinone (**10**) with sodium borohydride, as described by Szántay,[7] gave 3-*epi*-alloyohimbine (**53**) and 3-*epi*-17-*epi*-alloyohimbine (**54**) in a combined 78% yield (Scheme XIII). Their separation required reversed-phase chromatography and crystallization. Spectroscopic data for the products were consistent with previously reported values.[36]

A synthesis of alloyohimbinone (**11**) was obtained by hydrogenation (60% yield) of the 3,20-*cis*-15,16-didehydro-ψ-yohimbinone (**44**) with Pt in ethyl acetate. In this reduction, which was expected to occur from the convex face of the molecule (**44a**), essentially no epimerization occurred under these nonacidic conditions but some dehydrogenation to the dienone **45** was seen. No reduction occurred with 10% Pd/C.

Spectroscopic data for the product were consistent with those previously reported for alloyohimbinone (**11**).[37] It is interesting to note that the ketone function of this compound is completely enolized in a chloroform solution, whereas no enolization is seen in the 3-*epi*-allo and in the *normal* yohimbinones, because of peri-type compression in the conjugated esters.[7,38]

This stereoselective synthesis of alloyohimbinone (**11**) was thus completed in 18% overall yield through the C-*seco*-dihydropyridone **31** and in 19% overall yield through the tetracyclic dihydropyridone **32**. It constitutes formal syntheses (Scheme II) of alloyohimbine (**13**), α-yohimbine (**12**), and 17-*epi*-alloyohimbine (**14a**).

(36) Töke, L.; Honty, K.; Szabó, L.; Blaskó, G.; Szántay, Cs. *J. Org. Chem.* **1973**, *38*, 2496. Honty, K.; Baitz-Gács, E.; Blaskó, G.; Szántay, Cs. *J. Org. Chem.* **1982**, *47*, 5111.

(37) Töke, L.; Gombos, Zs.; Blaskó, G.; Honty, K.; Szabó, L.; Tamás, J.; Szántay, Cs. *J. Org. Chem.* **1973**, *38*, 2501.

(38) Albright, J. D.; Goldman, L. *J. Am. Chem. Soc.* **1967**, *89*, 2416.

Conclusion

The new annelation of dihydro-4-pyridones with carbomethoxymethyl vinyl ketone, shown in this study, has thus provided an efficient, regioselective and stereoselective access to yohimbe alkaloids of the *normal*, allo, and 3-*epi*-allo classes.

Experimental Section

General Methods. All reactions were started under a nitrogen atmosphere unless otherwise stated. Melting points were obtained on a Kofler microhotstage with thermometers calibrated against a National Bureau of Standards certified set. NMR spectra were obtained with Bruker 250-MHz or 270-MHz instruments, and chemical shifts are expressed as parts per million (δ) downfield from tetramethylsilane unless otherwise stated. Mass spectra were obtained with a Finnigan 4610 quadrupole instrument at 70 eV, calibrated with perfluorotributylamine and hexafluorotriphenyl-*s*-triazine for higher molecular weight compounds. High-resolution mass spectra, providing accurate mass data, were obtained by electron-impact ionization and direct-probe sample insertion on a Finnigan MAT-90 instrument at resolution 10 000, using 30–40 scan averages. IR spectra were obtained with a Nicolet 6000 Ft instrument. Perkin-Elmer 402 and Lambda instruments were used for recording UV spectra. TLC data were obtained with Merck 60 PF 254 precoated silica gel on aluminum sheets. Indole derivatives were visualized with a 10% solution of ceric ammonium sulfate (CAS) in phosphoric acid as a spray reagent, and other compounds were visualized by either UV or iodine vapor. Chromatography employed Baker 3405 60–200 mesh silica gel. Microanalyses were provided by Robertson Laboratories, Florham Park, NJ.

1-[2-(1*H*-Indol-3-yl)ethyl]-4-piperidinone (33). Tryptamine (19.25 g, 0.12 mol), ethanol (500 mL), potassium carbonate (35.30 g, 0.25 mol), and water (250 mL) were stirred together in a two-neck flask equipped with a reflux condenser and a dropping funnel containing *N,N*-dimethyloxopiperidinium iodide (**34**; 30.80 g, 0.12 mol) in water (250 mL). After the solution was heated to vigorous reflux, the oxopiperidinium iodide was added over 45 min and the mixture heated at reflux for another 30 min. The reaction mixture was then cooled, the ethanol was removed under reduced pressure, and the residue was extracted with 3 × 200 mL of dichloromethane. The dichloromethane layers were combined, washed with brine (200 mL), dried over sodium sulfate, and concentrated to give the crude product. The residue was dissolved in 1:1 ethyl acetate/chloroform and passed through 200 g of silica gel to give 26.2 g of the title compound (90%): TLC (SiO_2, 4% methanol/CH_2Cl_2) R_f 0.28 (CAS, orange-brown); UV (ethanol) λ_{max} 208, 228, 280, 288, 297 nm; IR (KBr) ν_{max} 3145, 3104, 3077, 3046, 3036, 3013, 2964, 2830, 2810, 2773, 1715, 1618, 1475, 1402, 1374, 1361, 1350, 1341, 1332, 1317, 1235, 1225, 1218, 1194, 1124, 1112, 1091, 1072, 1049, 1015, 1007, 971, 814, 749, 434, 428 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 2.48–2.59 (m, 4 H), 2.76–2.89 (m, 6 H), 2.96–3.04 (m, 2 H), 7.03 (s, 1 H), 7.09–7.20 (m, 2 H), 7.35 (d, J = 8 Hz, 1 H), 7.61 (d, J = 8 Hz, 1 H), 8.10 (bs, 1 H); MS m/z (relative intensity) 243 (M^+ + 1, 2), 242 (M^+, 10), 144 (2), 143 (2), 130 (9), 126 (5), 115 (2), 113 (7), 112 (100), 77 (5), 55 (4); mp 137–138 °C, crystallized from benzene (lit.[39] mp 134–135 °C). Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.58; H, 7.60; N, 11.34.

2,3-Dihydro-1-[2-(1*H*-indol-3-yl)ethyl]-4(1*H*)-pyridinone (31). Compound **33** (10.0 g, 41.3 mmol) was dissolved in dichloromethane (250 mL) and cooled to 0 °C. To this was added dropwise a solution of purified (prewashed with phosphate buffer) *m*-(chloroperoxy)benzoic acid (9.0 g, 1.26 eq) in 3:7 diethyl ether/dichloromethane (100 mL) over 1 h. This was allowed to warm to 20 °C over 2 h and then cooled again to 0 °C. Triethylamine (30 mL, 10 eq) was then slowly added, followed by dropwise addition of a solution of acetic anhydride (5 mL, 1.1 equiv) in 25 mL of dichloromethane over 30 min. After being stirred an additional 30 min at 0 °C, the solution was washed with saturated sodium carbonate solution (3 × 150 mL) and twice with 150 mL

(39) Potts, K. T.; Nasri, I. D. *J. Org. Chem.* **1964**, *29*, 3407.

of cold water. The organic layer was dried over sodium sulfate and the dichloromethane removed under reduced pressure. The residue was triturated with benzene (20 mL) and dried to give 8.24 g of the title compound as a pale yellow solid (85%): TLC (SiO_2, 4% methanol/CH_2Cl_2) R_f 0.26 (CAS, green-brown fade to orange); UV (ethanol) λ_{max} 201, 220, 271, 282, 290, 327 nm; IR (KBr) ν_{max} 3202, 3177, 3111, 3079, 3060, 3047, 3013, 2966, 2927, 1615, 1561, 1468, 1456, 1437, 1408, 1395, 1357, 1352, 1325, 1286, 1248, 1232, 1195, 1177, 1111, 793, 737 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 2.41 (t, J = 8 Hz, 2 H), 3.03 (t, J = 7 Hz, 2 H), 3.44 (t, J = 8 Hz, 2 H), 3.52 (t, J = 7 Hz, 2 H), 4.78 (d, J = 7 Hz, 1 H), 6.73 (d, J = 7 Hz, 1 H), 6.98 (d, J = 2 Hz, 1 H), 7.09–7.25 (m, 2 H), 7.38 (d, J = 8 Hz, 1 H), 7.55 (d, J = 8 Hz, 1 H), 8.97 (bs, 1 H); MS m/z (relative intensity) 241 (M^+ + 1, 11), 240 (M^+, 43), 149 (2), 144 (3), 143 (5), 131 (10), 130 (100), 115 (5), 112 (5), 111 (73), 110 (49), 103 (7), 102 (4), 89 (2), 82 (27), 77 (12), 63 (2), 55 (7), 51 (10); mp 162–163 °C, crystallized from acetone (lit.[24] mp 164 °C). Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.94; H, 6.75; N, 11.49.

2,3-Dihydro-1-[2-(1*H*-indol-3-yl)ethyl]-4-methoxypyridinium Trifluoromethanesulfonate (37). Dihydropyridone **31** (2.00 g, 8.33 mmol) was dissolved in dichloromethane (50 mL) to which methyl trifluoromethanesulfonate (1.2 mL, 1.27 equiv) was added. After the solution was stirred at 20 °C for 30 min, the dichloromethane was removed under reduced pressure and the residue triturated with diethyl ether to give 3.2 g of the title compound as a pale beige powder (95%): TLC (SiO_2, 4% methanol/CH_2Cl_2) R_f 0.09 (CAS, brown fade to orange); UV (ethanol) λ_{max} 207, 226, 289, 296, 326 nm; IR (KBr) ν_{max} 3293, 1658, 1560, 1460, 1448, 1435, 1416, 1393, 1356, 1343, 1323, 1291, 1257, 1240, 1221, 1199, 1169, 1160, 1128, 1113, 1029, 1015, 958, 798, 749, 638, 623, 517 cm^{-1}; 270-MHz ^1H NMR (DMSO-d_6) δ 2.87 (t, J = 9 Hz, 2 H), 3.33 (t, J = 7 Hz, 2 H), 3.96 (s, 3 H), 4.10 (t, J = 9 Hz, 2 H), 4.19 (t, J = 7 Hz, 2 H), 5.67 (d, J = 6 Hz, 1 H), 7.03 (d of d, J = 8, 7 Hz, 1 H), 7.12 (d of d, J = 8, 7 Hz, 1 H), 7.32 (s, 1 H), 7.44 (d, J = 8 Hz, 1 H), 7.64 (d, J = 8 Hz, 1 H), 8.90 (d, J = 6 Hz, 1 H), 10.28 (b s, 1 H); MS m/z (relative intensity) 255 (M^+ + 1), 254 (M^+, 3), 253 (1), 240 (22), 182 (3), 172 (5), 158 (14), 145 (12), 144 (37), 143 (17), 131 (22), 130 (100), 123 (6), 117 (14), 115 (11), 111 (48), 110 (36), 109 (37), 103 (9), 102 (6), 99 (10), 95 (37), 90 (7), 89 (8), 82 (19), 79 (37), 77 (19), 69 (89), 65 (18), 58 (10), 55 (13), 53 (11), 52 (26), 51 (22); mp 102–102.5 °C, crystallized from methanol.

4,9-Dihydro-3*H*-pyrido[3,4-*b*]indole Monoperchlorate (36). The procedure given is a modification of one by Szántay et al.[29] Tryptamine formate (8.17 g, 39.6 mmol) was heated at 180 °C (oil bath) for 45 min to give N_b-formyltryptamine, which was not isolated. The product was cooled, and any remaining water was removed under reduced pressure. The oil was then dissolved in acetonitrile (40 mL) and filtered and the filtrate cooled to 0 °C. To this was added dropwise a solution of phosphorous oxychloride (6.0 mL, 64.4 mmol) in acetonitrile (10 mL) over 45 min. The reaction mixture was stirred for an additional 3 h at 0 °C and then poured into 5% aqueous hydrochloric acid (200 mL). The aqueous solution was washed with benzene (3 × 75 mL), basified with 20% aqueous potassium hydroxide solution, and extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with brine (150 mL), dried over sodium sulfate, and decanted into another flask. To this was added dropwise 1:5 70% aqueous perchloric acid/methanol to give a bright yellow precipitate. This was filtered to give 9.10 g of the title compound (85%): TLC (free base, SiO_2, 4% methanol/CH_2Cl_2) R_f 0.18; UV (ethanol) λ_{max} 204, 236, 241, 322, 350 nm; IR (KBr) ν_{max} 3232, 3128, 3066, 1633, 1569, 1556, 1432, 1338, 1193, 1169, 1142, 1107, 1091, 743, 636, 627 cm^{-1}; 270-MHz ^1H NMR (DMSO-d_6) δ 3.46 (t, J = 9 Hz, 2 H), 4.24 (t, J = 9 Hz, 2 H), 7.23 (d of d, J = 8, 7 Hz, 1 H), 7.50 (d of d, J = 8, 7 Hz, 1 H), 7.63 (d, J = 8 Hz, 1 H), 7.80 (d, J = 8 Hz, 1 H), 9.1 (s, 1 H), 11.20 (b s, 1 H); MS m/z (relative intensity) 171 (M^+, 7), 170 (32), 169 (47), 168 (44), 167 (29), 149 (66), 142 (6), 140 (6), 115 (7), 113 (8), 88 (25), 82 (12), 75 (17), 71 (31), 70 (98), 69 (100), 67 (24), 57 (70), 55 (55), 51 (21); mp 222–224 °C, crystallized from methanol (lit.[29] mp 216–217 °C). Anal. Calcd for $C_{11}H_{11}ClN_2O_4$: C, 48.81; H, 4.10; N, 10.35; Cl, 13.10. Found: C, 48.74; H, 4.06; N, 10.35; Cl, 13.17.

3,4,6,7,12,12b-Hexahydroindolo[2,3-*a*]quinolizin-2(1*H*)-one (16). Method A. The procedure given is one adapted from Winterfelt.[24] Dihydropyridinone **31** (3.00 g, 12.5 mmol), ethanol (15 mL), and 10% aqueous sulfuric acid (75 mL) were stirred together at 20 °C for 4 h. The solution was filtered and the filtrate made basic with concentrated ammonium hydroxide and extracted with chloroform (3 × 50 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate, and concentrated under reduced pressure to give 2.7 g of the title compound (90%): TLC (SiO_2, 4% methanol/CH_2Cl_2) R_f 0.35 (CAS, green-gray); UV (ethanol) λ_{max} 202, 223, 282, 289 nm; IR (KBr) ν_{max} 3375, 3051, 2951, 2906, 2839, 2815, 2767, 1708, 1492, 1475, 1465, 1453, 1435, 1391, 1381, 1370, 1349, 1327, 1312, 1294, 1283, 1249, 1227, 1216, 1203, 1175, 1127, 1105, 1043, 1008, 743, 727, 691, 537, 431 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 2.46–2.85 (m, 7 H), 2.97–3.10 (m, 1 H), 3.24 (d of d, J = 11, 6 Hz, 1 H), 3.30–3.36 (m, 1 H), 3.62 (d, J = 11 Hz, 1 H), 7.08–7.20 (m, 2 H), 7.31–7.36 (m, 1 H), 7.50 (d, J = 8 Hz, 1 H), 8.05 (b s, 1 H); MS m/z (relative intensity) 241 (M^+ + 1, 11), 240 (M^+, 66), 239 (100), 197 (18), 182 (8), 170 (14), 169 (28), 156 (23), 154 (8), 149 (8), 129 (10), 115 (6), 112 (9), 99 (5), 88 (14), 77 (4), 71 (5), 70 (4), 57 (6), 51 (51), 50 (12); mp 186–187 °C, crystallized from benzene (lit.[24] mp 180–180.5 °C). Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.94; H, 6.66; N, 11.59.

Method B. The procedure given is a modification of one by Szántay et al.[28,30] Dihydro-β-carboline perchlorate (**36**) (9.00 g, 33.3 mmol) was suspended in methyl vinyl ketone (35 mL) and heated at gentle reflux for 3 h. The excess methyl vinyl ketone was removed under reduced pressure and the residue dissolved in methanol (50 mL). Anhydrous hydrochloric acid gas was bubbled through the stirred solution until the solution was homogeneous and strongly acidic. The solution was then stirred for 30 min at 20 °C, poured into water (300 mL), and heated at reflux for 25 min with removal of the methanol. The hot solution was vacuum filtered, cooled to 20 °C, and basified with 10 M aqueous potassium hydroxide solution. The aqueous solution was then extracted with diethyl ether (3 × 150 mL), and the combined organic layers were washed with brine (100 mL). The organic layer was dried over sodium sulfate, treated with activated charcoal, filtered through Celite, and concentrated to give 6.0 g of the title compound (75%) as confirmed by NMR, MS, and TLC.

3,4,7,12-Tetrahydroindolo[2,3-*a*]quinolizin-2(6*H*)-one (32). Compound **16** (2.05 g, 8.54 mmol) was dissolved in dichloromethane (50 mL) and cooled to −10 °C. A solution of *tert*-butyl hypochlorite (1.1 mL, 1.1 equiv) in dichloromethane (10 mL) was then added dropwise over 15 min. After the solution was stirred for an additional 30 min at −10 °C, anhydrous hydrochloric acid gas was bubbled through the solution until a precipitate formed and the solution was strongly acidic. This was warmed to 20 °C and stirred for 1 h. The reaction mixture was then poured into 150 mL of dichloromethane and methanol added until the solution was homogeneous. This was washed with saturated sodium carbonate solution (2 × 150 mL) and then once with brine (150 mL). The organic layer was dried over sodium sulfate, treated with activated charcoal, filtered through Celite, and concentrated under reduced pressure to give 1.80 g of the title compound (91%): TLC (SiO_2, 4% methanol/CH_2Cl_2) R_f 0.22 (CAS, green-brown); UV (ethanol) λ_{max} 214, 232, 243, 325, 346, 364, 380 nm; IR (KBr) ν_{max} 3212, 3055, 3030, 2947, 1632, 1623, 1583, 1520, 1494, 1462, 1436, 1364, 1344, 1328, 1319, 1271, 1258, 1234, 1215, 1174, 1151, 1128, 1020, 815, 739 cm^{-1}; 270-MHz ^1H NMR (DMSO-d_6) δ 2.40 (t, J = 7 Hz, 2 H), 3.01 (7, J = 7 Hz, 2 H), 3.39 (t, J = 7 Hz, 2 H), 3.49 (t, J = 7 Hz, 2 H), 5.59 (s, 1 H), 7.04 (d of d, J = 7, 7 Hz, 1 H), 7.22 (d of d, J = 8, 7 Hz, 1 H), 7.37 (d, J = 8 Hz, 1 H), 7.56 (d, J = 8 Hz, 1 H), 11.47 (s, 1 H); MS m/z (relative intensity) 239 (M^+ + 1, 17), 238 (M^+, 100), 237 (15), 223 (8), 210 (34), 209 (82), 195 (7), 182 (7), 181 (8), 170 (26), 169 (37), 168 (16), 167 (19), 154 (35), 149 (25), 142 (7), 140 (6), 128 (8), 127 (8), 115 (10), 105 (9), 104 (7), 97 (3), 88 (6), 77 (15), 71 (10), 70 (21), 69 (19), 63 (5), 57 (19), 55 (12), 51 (12); mp 262–263 °C, crystallized from benzene/methanol (lit.[28] mp 268–270 °C). Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.66; H, 5.96; N, 11.69.

Methyl 2-Oxo-2,3,4,6,7,12-hexahydroindolo[2,3-*a*]quinolizine-12-carboxylate (41). Compound **32** (2.00 g, 8.40 mmol), dimethyl dicarbonate (4.0 mL, 4.5 equiv), and acetonitrile (250 mL) were stirred together and heated to vigorous reflux.

(*N,N*-Dimethylamino)pyridine (50 mg, 0.1 equiv) was dissolved in acetonitrile (2 mL) and added to the reaction mixture via syringe. Violent loss of carbon dioxide ensued, and the reaction mixture was kept at reflux for another 10 min. The reaction mixture was cooled, made slightly acidic with acetic acid, and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (100 mL) and washed with brine (2 × 75 mL). The organic layer was dried over sodium sulfate, treated with activated charcoal, filtered through Celite, and concentrated under reduced pressure to give an orange oil. This was triturated with 1:1 diethyl ether/hexane to give 2.05 g of the title compound as a pale yellow powder (82.4%): TLC (SiO_2, 4% methanol/CH_2Cl_2) R_f 0.40; UV (ethanol) λ_{max} 204, 225, 248, 317, 378 nm; IR (KBr) ν_{max} 3470, 2955, 2896, 2852, 1735, 1626, 1587, 1572, 1526, 1497, 1441, 1412, 1355, 1311, 1277, 1265, 1248, 1228, 1209, 1168, 1153, 1131, 1050, 1030, 1016, 789, 770, 752, 703 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 2.60 (t, J = 8 Hz, 2 H), 3.01 (t, J = 6 Hz, 2 H), 3.55 (t, J = 6 Hz, 2 H), 3.71 (t, J = 8 Hz, 2 H), 4.00 (s, 3 H), 5.29 (s, 1 H), 7.31 (d of d, J = 8, 7 Hz, 1 H), 7.45 (d of d, J = 8, 7 Hz, 1 H), 7.53 (d, J = 8 Hz, 1 H), 8.05 (d, J = 8 Hz, 1 H); MS, m/z (relative intensity) 297 (M^+ + 1, 23), 296 (M^+, 100), 295 (13), 281 (8), 268 (30), 267 (55), 253 (10), 238 (16), 224 (5), 210 (14), 207 (36), 195 (5), 181 (12), 180 (12), 168 (15), 167 (19), 154 (33), 140 (7), 127 (35), 115 (9), 102 (7), 101 (6), 91 (6), 77 (10), 63 (9), 59 (15), 56 (14), 51 (7); mp 146–148 °C, crystallized from ethyl acetate; HRMS M^+ calcd for $C_{17}H_{16}N_2O_3$ 296.1161, found 296.1157.

2-Methoxy-12-(methoxycarbonyl)-3,4,7,12-tetrahydroindolo[2,3-*a*]quinolizin-5-ium Trifluoromethanesulfonate (42). Compound **41** (2.00 g, 6.94 mmol) was dissolved in dichloromethane (50 mL) to which methyl trifluoromethanesulfonate (1.0 mL, 1.27 equiv) was added. After the solution was stirred at 20 °C for 30 min, the dichloromethane was removed under reduced pressure and the residue triturated with diethyl ether to give 2.95 g of the title compound as a pale beige powder (95%): TLC (SiO_2, 4% methanol/CH_2Cl_2) R_f 0.20 (CAS, yellow); UV (ethanol) λ_{max} 209, 225, 256, 363 nm; IR (KBr) λ_{max} 3477, 3031, 3026, 3014, 2958, 1755, 1623, 1579, 1557, 1443, 1407, 1390, 1357, 1324, 1310, 1269, 1232, 1210, 1180, 1157, 1046, 1031, 983, 958, 770, 758, 637, 573, 518 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 2.92 (t, J = 9 Hz, 2 H), 3.26 (t, J = 7 Hz, 2 H), 3.95 (s, 3 H), 4.08 (s, 3 H), 4.10 (t, J = 7 Hz, 2 H), 4.25 (t, J = 9 Hz, 2 H), 5.78 (s, 1 H), 7.39 (d of d, J = 8, 7 Hz, 1 H), 7.60 (d of d, J = 8, 8 Hz, 1 H), 7.66 (d, J = 8 Hz, 1 H), 8.10 (d, J = 9 Hz, 1 H); MS m/z (relative intensity) 311 (M^+, 8), 310 (5), 309 (11), 296 (14), 26 (7), 237 (4), 209 (3), 207 (4), 167 (5), 154 (4), 149 (5), 144 (3), 133 (5), 99 (14), 95 (47), 86 (10), 79 (25), 69 (100), 64 (7), 59 (4), 55 (16), 50 (74); mp 162–163 °C, crystallized from methanol. Anal. Calcd for $C_{19}H_{19}F_3N_2O_6S$: C, 49.57; H, 4.16; N, 6.08; S, 6.90. Found: C, 49.54; H, 4.03; N, 6.04; S, 7.07.

Methyl 3-Oxo-4-pentenoate. The procedure given is one described by Stork.[40] Methyl β-oxobicyclo[2.2.1]hept-5-ene-2-propanoate (37.5 g, 0.19 m) was placed in an addition funnel at the top of a vertical quartz column (2 × 30 cm), which was packed with quartz beads and equipped with a vacuum adapter and a receiving flask at the bottom. A vacuum (1 mmHg) was then applied to the apparatus after the column was heated to 540 °C and the receiving flask was cooled to −30 °C. The substrate was then added dropwise over 2 h while the pressure was maintained between 1 and 2 mmHg, and the crude product was collected in the receiving flask. The receiving flask was then immediately immersed in a preheated oil bath (100 °C) and the product distilled through a short column under reduced pressure (13 mmHg) to give 18.9 g (76.4%) of the title compound: bp 67–70 °C (13 mmHg), (lit.[40] bp 78–81 °C (18 mmHg); TLC (SiO_2, 25% diethyl ether/hexane) R_f 0.61; UV (ethanol) λ_{max} 210, 271 nm; IR (neat) ν_{max} 3021, 3005, 2956, 1748, 1687, 1662, 1647, 1620, 1590, 1448, 1401, 1352, 1329, 1242, 1151, 1083, 1044, 1027, 985, 946, 885, 813, 729, 633 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 3.65 (s, 1 H), 3.75 (s, 1.5 H), 3.76 (s, 1.5 H), 5.09 (s, 0.5 H), 5.56 (d of d, J = 7, 5 Hz, 0.5 H), 5.98 (d, J = 10 Hz, 0.5 H), 6.11 (d, J = 7 Hz, 0.5 H), 6.12 (d, J = 5 Hz, 0.5 H), 6.27 (d, J = 17 Hz, 0.5 H), 6.43 (d of d, J = 17, 10 Hz, 0.5 H), 11.73 (s, 0.5 H); MS m/z (relative intensity) 129 (M^+ + 1, 10), 128 (M^+, 15), 121 (1), 101 (5), 100 (9), 97 (16), 69 (4), 66 (4), 59 (11), 57 (3), 56 (5), 55 (100).

Methyl 1,2,6,7,8,8a-Hexahydro-2-[2-(1*H*-indol-3-yl)ethyl]-6-oxo-5-isoquinolinecarboxylate (38). Dihydropyridinium salt **37** (1.00 g, 2.47 mmol) was dissolved in *N,N*-dimethylacetamide (25 mL) to which 1,4-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.37 mL, 1.0 equiv) was added via syringe, followed immediately by addition of a solution of carbomethoxymethyl vinyl ketone (0.50 g, 1.58 equiv) in *N,N*-dimethylacetamide (2 mL). The solution was stirred for 1 h at 20 °C and then heated to 70 °C for an additional 1 h. The reaction mixture was poured into brine (300 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were then washed with brine (3 × 100 mL), dried over sodium sulfate, and concentrated under reduced pressure to a residue, which was chromatographed (SiO_2, 2% methanol/chloroform) to yield 0.55 g of the title compound as a bright yellow solid (64%): TLC (SiO_2, 4% methanol/CH_2Cl_2) R_f 0.30 (CAS, red); UV (ethanol) λ_{max} 203, 220, 271, 279, 289, 415 nm; IR (KBr) ν_{max} 3282, 2948, 1717, 1620, 1588, 1530, 1456, 1434, 1397, 1378, 1320, 1302, 1225, 1193, 1162, 1132, 1101, 1069, 1057, 1035, 1016, 1000, 956, 933, 765, 747, 459 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 1.50–1.66 (m, 1 H), 1.89–1.97 (m, 1 H), 2.31–2.73 (m, 3 H), 2.97–3.07 (m, 3 H), 3.23 (d of d, J = 9, 3 Hz, 1 H), 3.55 (t, J = 7 Hz, 2 H), 3.79 (s, 3 H), 5.24 (d, J = 7 Hz, 1 H), 6.47 (d, J = 7 Hz, 1 H), 6.98 (d, J = 4 Hz, 1 H), 7.10–7.26 (m, 2 H), 7.40 (d, J = 8 Hz, 1 H), 7.55 (d, J = 8 Hz, 1 H), 8.53 (s, 1 H); MS m/z (relative intensity) 351 (M^+ + 1, 4), 350 (M^+, 32), 319 (5), 221 (52), 220 (95), 190 (9), 189 (100), 176 (3), 167 (4), 162 (3), 149 (13), 144 (15), 143 (12), 130 (48), 91 (6), 77 (13), 65 (4), 57 (11), 55 (11); mp 175.5–176.5 °C, crystallized from methanol. Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99. Found: C, 72.05; H, 6.17; N, 7.93.

Dimethyl 17-Oxo-3,14,15,16-tetradehydroyohimban-1,16-dicarboxylate (43). The trifluoromethanesulfonate **42** (1.00 g, 2.17 mmol) was dissolved in *N,N*-dimethylacetamide (25 mL), and DBU (0.32 mL, 1.0 equiv) was added via syringe, followed immediately by addition of a solution of carbomethoxymethyl vinyl ketone (0.40 g, 1.44 equiv) in *N,N*-dimethylacetamide (2 mL). After the solution was stirred for 1 h at 20 °C, an additional 1 equiv of DBU was added and stirring continued for another 1 h. The reaction mixture was poured into brine (300 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were then washed with brine (3 × 100 mL), dried over sodium sulfate, and concentrated under reduced pressure to a residue, which was chromatographed (SiO_2, 2% methanol/chloroform) to yield 0.79 g of the title compound as a bright orange solid (90%): TLC (SiO_2, 4% methanol/CH_2Cl_2) R_f 0.37 (CAS, yellow); UV (ethanol) λ_{max} 203, 212, 245, 335, 469, 484 nm; IR (KBr) ν_{max} 3429, 2948, 2913, 1737, 1635, 1589, 1571, 1538, 1440, 1390, 1355, 1337, 1319, 1295, 1232, 1210, 1191, 1180, 1156, 1134, 1105, 1086, 1058, 1046, 1037, 1024, 1015, 979, 883, 854, 775, 753, 697 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 1.64–1.80 (m, 1 H), 2.01–2.10 (m, 1 H), 2.39–2.55 (m, 1 H), 2.56–2.63 (m, 1 H), 2.85–2.94 (m, 1 H), 2.99 (t, J = 6 Hz, 2 H), 3.31–3.49 (m, 2 H), 3.52–3.61 (m, 2 H), 3.85 (s, 3 H), 4.02 (s, 3 H), 5.73 (s, 1 H), 7.30 (d of d, J = 8, 7 Hz, 1 H), 7.44 (d of d, J = 8, 7 Hz, 1 H), 7.51 (d, J = 8 Hz, 1 H), 8.08 (d, J = 8 Hz, 1 H); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 21.8, 26.6, 35.1, 36.9, 48.5, 51.7, 54.2, 55.0, 96.1, 115.2, 118.0, 119.6, 123.8, 126.7 (2 C), 127.7, 129.7, 139.8, 145.5, 152.0, 154.6, 168.3, 192.7; MS m/z (relative intensity) 407 (M^+ + 1, 15), 406 (M^+, 71), 378 (22), 377 (100), 375 (12), 347 (4), 330 (4), 319 (12), 318 (8), 317 (8), 296 (14), 295 (18), 267 (6), 259 (7), 207 (5), 187 (11), 167 (11), 149 (16), 128 (4), 127 (4), 115 (4), 71 (6), 59 (8), 57 (12), 55 (10), 51 (32); mp 165–165.5 °C, crystallized from methanol. Anal. Calcd for $C_{23}H_{22}N_2O_5$: C, 67.97; H, 5.46; N, 6.89. Found: C, 67.92; H, 5.37; N. 6.81.

Methyl 17-Oxo-3,14,15,16-tetradehydroyohimban-16-carboxylate (45). Compound **43** (0.50 g, 1.23 mmol) was dissolved in freshly prepared 5.0 mM methanolic sodium methoxide solution (50 mL) and stirred for 4 h at 20 °C. The mixture was then made slightly acidic with acetic acid and the methanol removed under reduced pressure. The residue was dissolved in dichloromethane (75 mL) and washed with saturated potassium bicarbonate (50 mL) and then with brine (50 mL). The organic layer was dried over sodium sulfate and concentrated to give 0.41 g of the title compound as a reddish orange powder (96%): TLC (SiO_2, 4% methanol/CH_2Cl_2) R_f 0.35 (CAS, brown-black); UV (ethanol) λ_{max}

(40) Stork, G; Guthikonda, N. *Tetrahedron Lett.* **1972**, 2755.

207, 221, 226, 258, 330, 388, 418, 444, 471 nm; IR (KBr) ν_{max} 3437, 3212, 2946, 1718, 1619, 1582, 1567, 1536, 1515, 1493, 1446, 1433, 1394, 1370, 1341, 1317, 1302, 1262, 1230, 1194, 1183, 1153, 1112, 1100, 1084, 1022, 763, 751, 698 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 0.51–0.68 (m, 1 H), 1.52–1.57 (m, 1 H), 2.01–2.29 (m, 3 H), 2.38–2.53 (m, 1 H), 2.94–3.07 (m, 3 H), 3.21–3.38 (m, 2 H), 4.08 (s, 3 H), 5.89 (s, 1 H), 7.03–7.09 (m, 1 H), 7.17–7.27 (m, 2 H), 7.47 (d, J = 8 Hz, 1 H), 10.19 (s, 1 H); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 20.8, 25.8, 34.4, 36.8, 51.0, 52.5, 55.0, 92.6, 115.2, 117.4, 119.2, 120.3, 125.0, 125.6, 127.7, 138.3, 147.3, 155.5, 170.6, 192.9; MS m/z (relative intensity) 348 (M^+, 31), 319 (100), 289 (3), 279 (9), 272 (3), 261 (37), 247 (7), 231 (12), 219 (9), 204 (8), 191 (3), 174 (9), 167 (24), 159 (9), 149 (52), 130 (21), 122 (5), 115 (8), 113 (6), 104 (6), 77 (5), 71 (21), 70 (18), 57 (43), 55 (19), 51 (7); mp 210–211 °C, crystallized from methanol; HRMS M^+ calcd for $C_{21}H_{20}N_2O_3$ 348.1474, found 348.1460.

Methyl (20α)-15,16-Didehydro-17-oxoyohimban-16-carboxylate (44). Method A. Tetrahydroisoquinolinecarboxylate **38** (380 mg, 1.09 mmol) was suspended in methanol (10 mL) and cooled to 0 °C. Cold (0 °C) 50% aqueous sulfuric acid (30 mL) was then added and the reaction mixture stirred at 0 °C for 7.5 h. This mixture was then poured into ice–water (250 mL), made slightly basic with concentrated ammonium hydroxide, and extracted with chloroform (3 × 75 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate, and concentrated under reduced pressure to a residue, which was chromatographed (SiO_2, 2–8% methanol/(1:1 ethyl acetate/chloroform) to yield 259 mg (68%) of the title compound along with 86.7 mg (22.8%) of its C-20 epimer **7**: TLC (SiO_2, 4% methanol/CH_2Cl_2) R_f 0.30 (CAS, green-brown); UV (ethanol) λ_{max} 223, 276, 289 nm; IR (KBr) ν_{max} 2452, 3363, 2928, 2855, 1735, 1669, 1632, 1451, 1437, 1383, 1369, 1359, 1331, 1315, 1297, 1249, 1235, 1216, 1196, 1158, 1127, 1119, 1094, 1061, 743 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 1.39–1.51 (m, 1 H), 1.96–2.07 (m 1 H), 2.35–2.41 (m, 2 H), 2.54–3.02 (m, 6 H), 3.34–3.40 (m, 3 H), 3.93 (s, 3 H), 4.64–4.66 (m, 1 H), 7.08 (d of d, J = 8, 7 Hz, 1 H), 7.16 (d of d, J = 8, 7 Hz, 1 H), 7.42 (d, J = 9 Hz, 1 H), 7.46 (d, J = 9 Hz, 1 H), 9.34 (b s, 1 H); MS m/z (relative intensity) 351 (M^+ + 1, 13), 350 (M^+, 55), 349 (28), 335 (13), 319 (7), 318 (9), 317 (21), 291 (8), 262 (5), 261 (5), 209 (6), 206 (7), 183 (28), 182 (45), 170 (10), 169 (28), 168 (12), 167 (9), 156 (9), 154 (8), 149 (26), 129 (16), 88 (14), 71 (11), 57 (22), 55 (16), 51 (100); HRMS M^+ calcd for $C_{21}H_{22}N_2O_3$ 350.1630, found 350.1632.

Method B. To a solution of tetradehydroyohimbancarboxylate **45** (100 mg, 0.287 mmol) in 20% acetic acid/20% water/60% dioxane (15 mL) was added freshly prepared Zn/Cu couple (1.0 g). After being stirred vigorously for 5 min at 20 °C, the solution was decanted and the Zn/Cu couple rinsed with the same solvent (3 × 3 mL). The combined acetic acid/water/dioxane solutions were poured into brine (75 mL), basified with saturated potassium bicarbonate solution, and extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with brine (75 mL), dried over sodium sulfate, and concentrated under reduced pressure to a residue, which was chromatographed (SiO_2, 8% methanol/(1:1 ethyl acetate/chloroform)) to give 62.3 mg (62%) of the title compound along with 9.1 mg (9%) of methyl (±)-15,16-didehydro-17-oxoyohimban-16-carboxylate (**7**) as confirmed by NMR, TLC, and MS.

Methyl (20β)-15,16-Didehydro-17-oxoyohimban-16-carboxylate (7). Method A. Isoquinolinecarboxylate **38** (100 mg, 0.286 mmol) was suspended in methanol (2.5 mL) and cooled to 0 °C. Cold (0 °C) 50% aqueous sulfuric acid (7.5 mL) was then added and the reaction mixture stirred at 20 °C for 24 h. The mixture was then poured into ice–water (75 mL), made slightly basic with concentrated ammonium hydroxide, and extracted with chloroform (3 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate and concentrated under reduced pressure to a residue, which was chromatographed (SiO_2, 2% methanol/(1:1 ethyl acetate/chloroform)) to yield 50 mg (50%) of the title compound: TLC (SiO_2, 4% methanol/CH_2Cl_2) R_f 0.39 (CAS, green-black); UV (ethanol) λ_{max} 226, 278, 290 nm; IR (KBr) ν_{max} 3373, 3054, 2947, 2918, 2848, 2802, 2766, 2756, 1732, 1696, 1668, 1626, 1452, 1437, 1381, 1366, 1339, 1329, 1307, 1258, 1207, 1190, 1138, 1110, 1012, 745 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 1.56–1.71 (m, 1 H), 1.99–2.10 (m, 1 H), 2.25 (t, J = 11 Hz, 1 H), 2.41–2.53 (m, 2 H), 2.56–2.68 (m, 2 H), 2.72–2.88 (m, 2 H), 2.93–3.03 (m, 2 H), 3.09–3.21 (m, 2 H), 3.42 (d, J = 11 Hz, 1 H), 3.94 (s, 3 H), 7.09 (d of d, J = 8, 7 Hz, 1 H), 7.16 (d of d, J = 8, 7 Hz, 1 H), 7.30 (d, J = 7 Hz, 1 H), 7.39 (d, J = 7 Hz, 1 H), 8.08 (b s, 1 H); MS m/z (relative intensity) 351 (M^+ + 1, 8), 350 (M^+, 37), 349 (28), 335 (12), 317 (24), 291 (16), 276 (5), 262 (10), 261 (10), 247 (6), 234 (7), 233 (7), 209 (10), 206 (16), 183 (59), 182 (100), 169 (67), 156 (19), 149 (30), 143 (15), 129 (6), 128 (6), 115 (9), 91 (18), 77 (17), 71 (9), 66 (8), 65 (9), 59 (16), 57 (22), 55 (23), 51 (24); HRMS M^+ calcd for $C_{21}H_{22}N_2O_3$ 350.1630, found 350.1631. The hydrochloride was prepared and crystallized from methanol (mp 240–242 °C (lit.[7] mp 238–240 °C).

Method B. To a solution of tetradehydroyohimbancarboxylate **45** (120 mg, 0.345 mmol) in 1.5% TFA/methanol (12 mL) was added freshly prepared Zn/Cu couple (1.2 g). After being stirred vigorously for 20 min at 20 °C, the solution was decanted and the Zn/Cu couple rinsed with methanol (3 × 3 mL). The combined methanol solutions were poured into brine (75 mL), basified with saturated potassium bicarbonate solution, and extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with brine (75 mL), dried over sodium sulfate, and concentrated under reduced pressure to a residue, which was chromatographed (SiO_2, 1.5% methanol/(1:1 ethyl acetate/chloroform)) to give 89.9 mg of the title compound as confirmed by NMR, MS, and TLC (74.5%).

Dimethyl 15,16-Didehydro-17-oxoyohimban-1,16-dicarboxylate (47). To a solution of tetradehydroyohimbandicarboxylate **43** (100 mg, 0.246 mmol) in 2% TFA/methanol (10 mL) was added freshly prepared Zn/Cu couple (1.0 g). After being stirred vigorously for 45 min at 20 °C, the solution was decanted and the Zn/Cu couple rinsed with methanol (3 × 3 mL). The combined methanol solutions were poured into brine (75 mL), basified with saturated potassium bicarbonate solution, and extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with brine (75 mL), dried over sodium sulfate, and concentrated under reduced pressure to a residue, which was chromatographed (SiO_2, 1.5% methanol/(1:1 ethyl acetate/chloroform)) to give 65.7 mg of the title compound (65.7%): TLC (SiO_2, 4% methanol/CH_2Cl_2) R_f 0.39; UV (ethanol) λ_{max} 200, 228, 262, 281, 292 nm; IR (KBr) ν_{max} 3435, 2953, 2917, 2860, 2849, 2843, 1736, 1669, 1624, 1458, 1440, 1360, 1317, 1304, 1239, 1226, 1196, 1165, 764, 748 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 1.58–1.74 (m, 1 H), 2.00–2.11 (m, 1 H), 2.36–2.62 (m, 3 H), 2.74–2.97 (m, 5 H), 3.04 (d of d, J = 15, 2 Hz, 1 H), 3.20–3.48 (m, 2 H), 3.88 (s, 3 H), 4.04 (s, 3 H), 4.38 (d, J = 11 Hz, 1 H), 7.23–7.35 (m, 2 H), 7.44 (d, J = 7 Hz, 1 H), 8.09 (d, J = 8 Hz, 1 H); MS m/z (relative intensity) 408 (M^+, 9), 407 (7), 393 (6), 377 (2), 375 (2), 349 (6), 319 (1), 304 (1), 267 (8), 241 (44), 240 (100), 227 (48), 214 (14), 204 (8), 183 (11), 182 (12), 181 (13), 169 (25), 168 (13), 154 (25), 142 (18), 128 (16), 115 (30), 93 (9), 91 (13), 79 (14), 77 (20), 65 (9), 59 (43), 57 (8), 51 (24). The hydrochloride was prepared and crystallized from methanol (mp 189–191 °C). Anal. Calcd for $C_{23}H_{25}ClN_2O_5$: C, 62.09; H, 5.66; N, 6.30; Cl, 7.97. Found: C, 61.97; H, 5.65; N, 6.26; Cl, 7.86.

Dimethyl (20α)-15,16-Didehydro-17-oxoyohimban-1,16-dicarboxylate (46). To a solution of tetradehydroyohimbandicarboxylate **43** (100 mg, 0.246 mmol) in 20% acetic acid/20% water/60% dioxane (10 mL) was added freshly prepared Zn/Cu couple (1.0 g). After being stirred vigorously for 3 min at 20 °C, the solution was decanted and the Zn/Cu couple rinsed with the same solvent (3 × 3 mL). The combined acetic acid/water/dioxane solutions were poured into brine (75 mL), basified with saturated potassium bicarbonate solution, and extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with brine (75 mL), dried over sodium sulfate, and concentrated under reduced pressure to a residue, which was chromatographed (SiO_2, 8% methanol/(1:1 ethyl acetate/chloroform)) to give 72.1 mg of the title compound (71.7%). This compound was unstable as it epimerized readily to the 3,20-trans compound as well as being oxidized back to the tetradehydro compound: TLC (SiO_2, 4% methanol/CH_2Cl_2) R_f 0.30; UV (ethanol) λ_{max}, 226, 260, 277, 284, 291 nm; IR (KBr) ν_{max} 3522, 3486, 3449, 3429, 3310, 2953, 2921, 2851, 2818, 1734, 1672, 1630, 1457, 1442, 1360, 1323, 1220, 1195, 1164, 1129, 1119 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 1.69–1.81 (m, 1 H), 2.09–2.20 (m, 1 H), 2.34–2.65 (m, 2 H), 2.66–2.74 (m, 1 H), 2.76–2.92 (m, 4 H), 2.95–3.20 (m, 3 H), 3.77 (s, 3 H), 4.03 (s, 3 H), 4.61 (d of d, J = 8, 5 Hz, 1 H), 7.23–7.35 (m, 2 H), 7.43 (d, J =

7 Hz, 1 H), 8.04 (d, J = 7 Hz, 1 H); MS m/z (relative intensity) 409 (M^+ + 1, 27), 408 (M^+, 100), 407 (37), 393 (14), 377 (11), 376 (14), 375 (12), 350 (18), 349 (49), 320 (4), 319 (4), 317 (4), 296 (3), 295 (4), 293 (3), 267 (6), 243 (13), 242 (12), 241 (19), 240 (45), 229 (36), 228 (88), 227 (68), 221 (7), 214 (4), 204 (5), 201 (5), 183 (6), 182 (4), 181 (4), 180 (6), 169 (19), 168 (11), 167 (7), 154 (6), 149 (11), 148 (9), 142 (8), 128 (4), 115 (10), 91 (7), 77 (7), 59 (20), 51 (19).

1,16-Bis(methoxycarbonyl)-3,4,14,15,16,17-hexadehydro-17-methoxyyohimbanium Trifluoromethanesulfonate (49). Tetradehydroyohimbandicarboxylate **43** (500 mg, 1.23 mmol) was dissolved in dichloromethane (25 mL) to which methyl trifluoromethanesulfonate (0.21 mL, 1.5 equiv) was added. After the solution was stirred at 20 °C for 4 h, the dichloromethane was removed under reduced pressure and the residue triturated with diethyl ether to give 600 mg of the title compound as a bright yellow powder (85%): TLC (SiO_2, 4% methanol/CH_2Cl_2) R_f 0.14 (CAS, light yellow); UV (ethanol) λ_{max} 206, 224, 262, 271, 315, 338, 385, 418, 435, 452, 487 nm; IR (KBr) ν_{max} 2958, 1747, 1731, 1610, 1577, 1545, 1524, 1452, 1404, 1383, 1352, 1273, 1224, 1156, 1031, 774, 757, 638 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 1.53–1.70 (m, 1 H), 2.44–2.49 (m, 1 H), 2.68–2.93 (m, 2 H), 3.13–3.55 (m, 4 H), 3.67–3.79 (m, 1 H), 3.84 (s, 3 H), 3.97 (s, 3 H), 4.03 (s, 3 H), 4.08–4.23 (m, 1 H), 4.34–4.46 (m, 1 H), 6.14 (s, 1 H), 7.38–7.45 (m, 1 H), 7.58–7.71 (m, 2 H), 8.18 (d, J = 8 Hz, 1 H); MS m/z (relative intensity) 420 (M^+ − 1, 0.5), 419 (0.4), 377 (3), 375 (2), 99 (8), 95 (28), 87 (13), 79 (32), 69 (100), 65 (6), 64 (4), 59 (3), 50 (11).

Dimethyl 17-Methoxy-14,15,16,17-tetradehydroyohimban-1,16-dicarboxylate (49). To a solution of dehydroyohimbanium salt **48** (150 mg, 0.263 mmol) in 1.5% TFA/methanol (12 mL) was added freshly prepared Zn/Cu couple (1.2 g). After being stirred vigorously for 10 min at 20 °C, the solution was decanted and the Zn/Cu couple rinsed with methanol (3 × 3 mL). The combined methanol solutions were poured into brine (75 mL), basified with saturated potassium bicarbonate solution, and extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with brine (75 mL), dried over sodium sulfate, and concentrated under reduced pressure to a residue, which was chromatographed (SiO_2, 1.5% methanol/(1:1 ethyl acetate/chloroform)) to give 84.6 mg of the title compound (76.2%): TLC (SiO_2, 4% methanol/CH_2Cl_2) R_f 0.32 (CAS, pale yellow); UV (ethanol) λ_{max} 195, 229, 265, 279, 290 nm; IR (KBr) ν_{max} 3451, 3420, 2945, 2921, 2850, 1729, 1635, 1458, 1442, 1361, 1316, 1292, 1235, 1217, 1204, 1161, 1049, 1034, 757 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 1.45 (d of d of d, J = 24, 13, 6 Hz, 1 H), 1.80–1.85 (m, 1 H), 2.35–2.60 (m, 3 H), 2.66–2.92 (m, 3 H), 3.01 (t, J = 11 Hz, 1 H), 3.10–3.18 (m, 1 H), 3.30 (d of d, J = 13, 4 Hz, 1 H), 3.65 (s, 3 H), 3.73 (s, 3 H), 4.02 (s, 3 H), 5.20 (b s, 1 H), 5.43 (b s, 1 H), 7.20–7.33 (m, 2 H), 7.40 (d, J = 7 Hz, 1 H), 8.15 (d, J = 7 Hz, 1 H); MS m/z (relative intensity) 423 (M^+ + 1, 7), 422 (M^+, 25), 421 (7), 391 (3), 389 (4), 376 (24), 375 (100), 364 (11), 363 (16), 349 (2), 333 (4), 317 (17), 305 (4), 259 (3), 243 (7), 221 (4), 195 (5), 185 (4), 167 (3), 149 (3), 59 (9), 58 (16); HRMS M^+ calcd for $C_{24}H_{26}N_2O_5$ 422.1842, found 422.1858.

(±)-Methyl 17-Oxoyohimban-16-carboxylate (Yohimbinone) (8). The procedure given is that of Szántay.[7] To a solution of didehydroyohimbancarboxylate **7** (100 mg, 0.286 mmol) in methanol (50 mL) was added concentrated hydrochloric acid (0.05 mL) and 10% Pd/C (50 mg). This was placed under a hydrogen atmosphere (1 atm) and stirred at 20 °C for 18 h. The solution was filtered through Celite and concentrated under reduced pressure to a residue, which was dissolved in dichloromethane (50 mL). The solution was then washed with saturated potassium bicarbonate solution (50 mL) and concentrated under reduced pressure to a residue, which was chromatographed (SiO_2, 2% methanol/(1:1 ethyl/chloroform)) to yield 66 mg of the title compound (65.6%): TLC (SiO_2, 4% methanol/CH_2Cl_2) R_f 0.34 (CAS, green-black); UV (ethanol) λ_{max} 224, 275, 280, 289 nm; IR (KBr) ν_{max} 3399, 3390, 3379, 2939, 2916, 2847, 2800, 2751, 1741, 1710, 1461, 1451, 1437, 1361, 1340, 1323, 1243, 1234, 1271, 1206, 1177, 1150, 741, cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 1.39–1.64 (m, 2 H), 1.96–2.27 (m, 5 H), 2.43 (t of d, J = 14, 6 Hz, 1 H), 2.53–2.77 (m, 3 H), 2.94–3.14 (m, 3 H), 3.23 (d, J = 11 Hz, 1 H), 3.31 (d, J = 12 Hz, 1 H), 3.84 (s, 3 H), 7.04–7.17 (m, 2 H), 7.29 (d, J = 7 Hz, 1 H), 7.46 (d, J = 7 Hz, 1 H), 7.78 (b s, 1 H); MS m/z (relative intensity) 353 (M^+ + 1, 13), 352 (M^+, 100), 351 (74), 338 (2), 337 (2), 319 (2), 223 (2), 184 (17), 170 (17), 169 (31), 156 (12), 154 (4), 144 (3), 143 (4), 129 (3), 128 (2), 115 (3), 67 (3), 55 (18), 51 (13); mp 222–224 °C, crystallized from methanol (lit.[7] mp 223–225 °C). Anal. Calcd for $C_{21}H_{24}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.11; H, 7.01; N, 7.68.

(±)-Dimethyl (3α,15β,16α,20βH)-17-Oxoyohimban-1,16-dicarboxylate (52). To a solution of tetradehydroyohimbandicarboxylate **43** (150 mg, 0.369 mmol) in 2% TFA/methanol (15 mL) was added freshly prepared Zn/Cu couple (1.5 g). After being stirred vigorously for 10 min at 20 °C, the solution was decanted and the Zn/Cu couple rinsed with methanol (3 × 3 mL). The combined methanol solutions were poured into brine (100 mL), basified with saturated potassium bicarbonate, and extracted with ethyl acetate (2 × 40 mL). The combined organic layers were washed with brine (75 mL), dried over sodium sulfate, and concentrated under reduced pressure to a residue, which was immediately dissolved in 5% methanolic acetic acid. To this was added 10% Pd/C (50 mg) and the reaction mixture stirred under a hydrogen atmosphere (1 atm) for 8 h. The reaction mixture was filtered through Celite and concentrated under reduced pressure to a residue, which was dissolved in dichloromethane (30 mL) and washed with saturated potassium bicarbonate (20 mL). The organic layer was then washed with brine (20 mL), dried over sodium sulfate, and concentrated under reduced pressure to give a residue, which was chromatographed (SiO_2, 2% methanol/(1:1 ethyl acetate/chloroform)) to yield 107 mg of the title compound (70.7%): TLC (SiO_2, 4% methanol/CH_2Cl_2) R_f 0.31; UV (ethanol) λ_{max} 200, 227, 264, 280, 293 nm; IR (KBr) ν_{max} 3447, 2956, 2918, 2861, 2843, 2818, 1742, 1713, 1681, 1479, 1458, 1440, 1413, 1364, 1313, 1270, 1192, 1165, 1120, 1039, 757, 748 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 1.74–1.85 (m, 1 H), 1.90–2.08 (m, 3 H), 2.32–2.56 (m, 3 H), 2.70–2.84 (m, 4 H), 2.92 (d of d, J = 13, 4 Hz, 1 H), 3.16–3.22 (m, 1 H), 3.31 (t, J = 14 Hz, 1 H), 3.88 (s, 3 H), 3.97 (s, 3 H), 4.05 (d, J = 13 Hz, 1 H), 4.30 (d, 11 Hz, 1 H), 7.20–7.30 (m, 2 H), 7.39–7.43 (m, 1 H), 7.93–7.97 (m, 1 H); MS m/z (relative intensity) 411 (M^+ + 1, 31), 410 (M^+, 100), 409 (43), 395 (5), 379 (13), 378 (28), 377 (24), 363 (2), 352 (18), 351 (56), 333 (4), 319 (8), 293 (5), 281 (10), 279 (8), 269 (7), 267 (7), 255 (4), 242 (18), 229 (5), 227 (15), 214 (4); mp 170–173 °C, crystallized from ethyl acetate. Anal. Calcd for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.38; N, 6.82. Found: C, 67.05; H, 6.34; N, 6.69.

(±)-Methyl (3α,15β,16α,20βH)-17-Oxoyohimban-16-carboxylate (3-*epi*-Alloyohimbinone) (10). Compound **52** (100 mg, 0.244 mmol) was dissolved in freshly prepared 0.1 M methanolic sodium methoxide solution (25 mL) and stirred for 6 h. This was then made slightly acidic with acetic acid and the methanol removed under reduced pressure. The residue was dissolved in dichloromethane (30 mL) and washed with saturated potassium bicarbonate (20 mL) and then with brine (20 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to a residue, which was chromatographed (SiO_2, 2% methanol/(1:1 ethyl acetate/chloroform)) to yield 65.3 mg of the title compound (76%): TLC (SiO_2, 4% methanol/CH_2Cl_2) R_f 0.27 (CAS, olive-green); UV (ethanol) λ_{max} 200, 224, 282, 289 nm; IR (KBr) ν_{max} 3398, 2939, 2922, 2862, 2843, 2814, 2770, 1743, 1711, 1462, 1452, 1437, 1362, 1342, 1323, 1301, 1287, 1271, 1237, 1162, 1145, 1128, 1035, 743 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 1.86–2.04 (m, 4 H), 2.37–2.45 (m, 3 H), 2.64–2.88 (m, 5 H), 2.94–3.13 (m, 2 H), 3.50 (d, J = 11 Hz, 1 H), 3.80 (d, J = 12 Hz, 1 H), 3.87 (s, 3 H), 7.06–7.17 (m, 2 H), 7.28 (d of d, J = 7, 2 Hz, 1 H), 7.47 (d of d, J = 7, 2 Hz, 1 H), 7.89 (b s, 1 H);[36b] MS m/z (relative intensity) 353 (M^+ + 1, 20), 352 (M^+, 100), 351 (64), 337 (2), 320 (10), 319 (19), 293 (24), 235 (7), 223 (9), 221 (10), 209 (5), 197 (8), 184 (12), 170 (14), 169 (24), 156 (17), 144 (7), 143 (8), 129 (7), 128 (7), 115 (7), 77 (4), 59 (4), 55 (8); mp 219–222 °C dec, crystallized from acetone/hexane (lit.[7] mp 213–214 °C). Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.33; H, 6.97; N, 7.78.

(±)-Methyl (3α,15α,16α,20αH)-17-Oxoyohimban-16-carboxylate (Alloyohimbinone) (11). A solution of methyl (20α)-didehydroyohimbancarboxylate **44** in ethyl acetate (2 mL) was added via syringe to a suspension of 10% Pt/C (50 mg) in ethyl acetate (30 mL), which had previously been stirring under a hydrogen atmosphere (1 atm) for 15 min. The reaction mixture was stirred vigorously for 18 h at 20 °C. The reaction mixture

was then filtered through Celite and concentrated under reduced pressure to a residue that was chromatographed (SiO_2, 1:1 diethyl ether/hexane) to give 60 mg of the title compound (60%): TLC (SiO_2, 4% methanol/CH_2Cl_2) R_f 0.82 (CAS, gray); UV (ethanol) λ_{max} 221, 257, 276, 285 nm; IR (KBr) ν_{max} 3397, 2947, 2907, 2802, 2750, 1650, 1613, 1459, 1443, 1348, 1321, 1286, 1264, 1258, 1246, 1232, 1211 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 1.46 (t, J = 12 Hz, 1 H), 1.58–1.64 (m, 1 H), 1.80–1.85 (m, 1 H), 2.18–2.77 (m, 8 H), 2.87–3.02 (m, 3 H), 3.21 (d, J = 11 Hz, 1 H), 3.84 (s, 3 H), 7.06–7.28 (m, 2 H), 7.26 (d, J = 7 Hz, 1 H), 7.45 (d, J = 7 Hz, 1 H), 7.73 (b s, 1 H), 12.33 (s, 1 H);[36b] 250-MHz ^{13}C NMR ($CDCl_3$) δ 21.8, 22.5, 29.4, 30.9, 33.2, 33.4, 34.3, 51.5, 53.5, 60.1, 61.1, 101.4, 108.3, 110.7, 118.1, 119.4, 121.3, 135.0, 136.0, 172.7, 173.5; MS m/z (relative intensity) 353 (M^+ + 1, 25), 352 (M^+, 100), 351 (29), 337 (3), 355 (3), 321 (17), 320 (69), 319 (84), 293 (42), 279 (13), 235 (6), 221 (26), 209 (9), 197 (17), 184 (16), 169 (28), 167 (26), 156 (39), 149 (42), 129 (9), 115 (8), 73 (11), 71 (11), 57 (20), 55 (16), 51 (9); mp 169–171 °C, crystallized from cyclohexane (lit.[7] mp 192–193 °C, crystallized from benzene); HRMS M^+ calcd for $C_{21}H_{24}N_2O_3$ 352.1787, found 352.1796.

(±)-Yohimbine (3) and (±)-β-Yohimbine (9). The procedure described is one adapted from Szántay et al.[6] Yohimbinone 8 (65 mg, 0.185 mmol) was dissolved in methanol (25 mL) and cooled to 0 °C. To this was added sodium borohydride (40 mg, 5.7 equiv) in two portions over 10 min. After the solution was stirred at 0 °C for a total of 20 min, the excess sodium borohydride was quenched by making the solution slightly acidic with acetic acid. The methanol was removed under reduced pressure and the residue dissolved in dichloromethane (30 mL). The solution was then washed once with saturated potassium bicarbonate (20 mL) and once with brine (20 mL). After being dried over sodium sulfate, the dichloromethane layer was concentrated under reduced pressure to a residue, which was chromatographed (Al_2O_3, 1–2% methanol/dichloromethane) to yield 14.5 mg (22.2%) of (±)-yohimbine (3) and 34.5 mg (52.9%) of (±)-β-yohimbine (9).

Physical data for (±)-yohimbine (3): TLC (SiO_2, 4% methanol/CH_2Cl_2) R_f 0.15 (CAS, dark gray); UV (ethanol) λ_{max} 202, 214, 278, 288 nm; IR (KBr) ν_{max} 3372, 2925, 2854, 2808, 2761, 2753, 1725, 1623, 1453, 1438, 1364, 1339, 1324, 1297, 1270, 1211, 1155, 1112, 1096, 1069, 1050, 1019, 969, 744, 698 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 1.33–1.42 (m, 2 H), 1.48–1.58 (m, 3 H), 1.95–2.02 (m, 3 H), 2.20–2.28 (m, 1 H), 2.35 (d of d, J = 11, 2 Hz, 1 H), 2.57–2.74 (m, 2 H), 2.91–3.10 (m, 4 H), 3.32 (d of d, J = 11, 2 Hz, 1 H), 3.81 (s, 3 H), 4.23 (b s, 1 H), 7.07 (d of d, J = 7, 7 Hz, 1 H), 7.13 (d of d, J = 7, 7 Hz, 1 H), 7.29 (d, J = 7 Hz, 1 H), 7.45 (d, J = 7 Hz, 1 H), 7.79 (b s, 1 H); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 21.7, 23.3, 31.5, 34.3, 36.7, 40.7, 51.9, 52.4, 52.9, 59.9, 61.4, 67.0, 108.3, 110.7, 118.1, 119.4, 121.3, 127.4, 134.5, 136.0, 175.6; MS m/z (relative intensity); 355 (M^+ + 1, 22), 354 (M^+, 82), 353 (100), 323 (4), 295 (5), 224 (5), 184 (11), 183 (4), 171 (4), 170 (10), 169 (17), 168 (5), 167 (4), 156 (8), 144 (5), 143 (5), 129 (4), 84 (5), 73 (4), 69 (4), 60 (8), 59 (6), 57 (8), 55 (10); mp 207–210 °C, crystallized from methanol (lit.[6] mp 218–220 °C). Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 70.80; H, 7.35; N, 7.78.

Physical data for (±)-β-yohimbine (9): TLC (SiO_2, 4% methanol/CH_2Cl_2) R_f 0.17 (CAS, dark gray); UV (ethanol) λ_{max} 203, 223, 279, 288 nm; IR (KBr) ν_{max} 3404, 3395, 3373, 2927, 2854, 2810, 2761, 2751, 1719, 1452, 1438, 1375, 1349, 1324, 1295, 1269, 1233, 1197, 1157, 1096, 1061, 1032, 1010, 740 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 1.12–1.20 (m, 1 H), 1.38–1.54 (m, 3 H), 1.65–1.71 (m, 1 H), 1.89–1.94 (m, 1 H), 2.03–2.22 (m, 4 H), 2.54–2.76 (m, 2 H), 2.93–3.09 (m, 4 H), 3.19 (d, J = 11 Hz, 1 H), 3.82 (s, 3 H), 3.83–3.87 (m, 1 H), 7.07 (d of d, J = 8, 7 Hz, 1 H), 7.13 (d of d, J = 8, 7 Hz, 1 H), 7.29 (d, J = 7 Hz, 1 H), 7.45 (d, J = 7, 1 H), 7.92 (b s, 1 H); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 21.7, 27.9, 34.1, 34.2, 39.8, 42.0, 51.9, 52.9, 57.4, 59.5, 61.1, 72.2, 108.2, 110.8, 118.1, 119.4, 121.4, 127.3, 134.3, 136.2, 175.0; MS m/z (relative intensity) 355 (M^+ + 1, 22), 354 (M^+, 90), 353 (100), 351 (2), 339 (1), 325 (2), 296 (3), 295 (13), 281 (3), 267 (2), 251 (1), 235 (1), 221 (13), 207 (3), 184 (10), 170 (11), 169 (16), 156 (8), 149 (8), 147 (5), 144 (6), 143 (5), 129 (3), 115 (3), 73 (6), 59 (4), 55 (4); mp 228–232 °C, crystallized from diethyl ether/hexane (lit.[6] mp 232–236 °C); HRMS M^+ calcd for $C_{21}H_{26}N_2O_3$ 354.1943, found 354.1935.

(±)-3-*epi*-Alloyohimbine (53) and (±)-3-*epi*-17-*epi*-Alloyohimbine (54). The procedure described is one adapted from Szántay et al.[7] 3-*epi*-Alloyohimbinone (10) (65 mg, 0.185 mmol) was dissolved in methanol (25 mL) and cooled to 0 °C. To this was added sodium borohydride (40 mg, 5.7 eq) in two portions over 10 min. After the solution was stirred at 0 °C for a total of 20 min, the excess sodium borohydride was quenched by making the solution slightly acidic with acetic acid. The methanol was removed under reduced pressure and the residue dissolved in dichloromethane (30 mL). This was then washed once with saturated potassium bicarbonate (20 mL) and once with brine (20 mL). After being dried over sodium sulfate, the dichloromethane layer was concentrated under reduced pressure to a residue, which was chromatographed (SiO_2, 2% methanol/dichloromethane) to yield 51 mg (78%) of a mixture of the title compounds. Separation was accomplished via reversed-phase chromatography (SiO_2, 1:1 water/acetonitrile) to give small amounts of each compound suitable for analysis.

Physical data for (±)-3-*epi*-alloyohimbine (53): TLC (SiO_2, 1:1 water/acetonitrile) R_f 0.33 (CAS, dark gray); UV (ethanol) λ_{max} 204, 225, 279, 289 nm; IR (KBr) ν_{max} 3391, 2927, 2852, 2780, 1725, 1452, 1439, 1349, 1323, 1290, 1273, 1196, 1174, 1164, 1145, 1113, 1056, 999, 749, 620 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 1.35–1.41 (m, 1 H), 1.50–1.67 (m, 1 H), 1.73–1.85 (m, 5 H), 1.94–2.31 (m, 2 H), 2.59–2.73 (m, 4 H), 2.93–3.09 (m, 3 H), 3.44–3.49 (m, 1 H), 3.82 (s, 3 H), 4.23 (m, 1 H), 7.06 (d of d, J = 7, 7 Hz, 1 H), 7.12 (d of d, J = 7, 7 Hz, 1 H), 7.28 (d, J = 7 Hz, 1 H), 7.45 (d, J = 7 Hz, 1 H), 7.66 (b s, 1 H); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 21.6, 22.5, 27.2, 30.0, 32.8, 33.9, 45.1, 52.0, 53.3, 54.2, 54.8, 67.0, 108.7, 110.7, 118.1, 119.5, 121.4, 127.5, 134.4, 136.0, 176.0; MS m/z (relative intensity) 355 (M^+ + 1, 24), 354 (M^+, 100), 353 (87), 339 (11), 323 (4), 295 (7), 277 (2), 267 (2), 223 (5), 221 (4), 209 (4), 197 (4), 184 (8), 170 (13), 169 (22), 156 (11), 144 (10) 143 (7), 130 (5), 117 (4), 115 (5), 69 (6), 56 (21), 51 (8); HRMS M^+ calcd for $C_{21}H_{26}N_2O_3$ 354.1943, found 354.1930.

Physical data for (±)-3-*epi*-17-*epi*-alloyohimbine (54): TLC (SiO_2, 1:1 water/acetonitrile) R_f 0.44 (CAS, dark gray); UV (ethanol) λ_{max} 204, 225, 281, 290 nm; IR (KBr) ν_{max} 3404, 2934, 2855, 2814, 2773, 1720, 1451, 1348, 1321, 1287, 1273, 1237, 1197, 1176, 1160, 1125, 1105, 1080, 1057, 1034, 1007, 742, 533 cm^{-1}; 270-MHz ^1H NMR (4:1 $CDCl_3$/DMSO-d_6, shifts reported with respect to DMSO at 2.49 ppm) δ 1.31–1.40 (m, 1 H), 1.50–1.73 (m, 3 H), 1.98–2.15 (m, 3 H), 2.52–2.64 (m, 4 H), 2.71–2.99 (m, 2 H), 3.11–3.31 (m, 2 H) 3.37–3.41 (m, 1 H), 3.55–3.68 (m, 1 H), 3.73 (s, 3 H), 4.65 (d, J = 6 Hz, 1 H), 6.86 (d of d, J = 7, 6 Hz, 1 H), 6.94 (d of d, J = 7, 6 Hz, 1 H), 7.20 (d, J = 7 Hz, 1 H), 7.28 (d, J = 7 Hz, 1 H), 10.26 (b s, 1 H); 62.9-MHz ^{13}C NMR (4:1 $CDCl_3$/DMSO-d_6, shifts reported with respect to $CDCl_3$ at 77.0 ppm) δ 20.5, 26.0, 29.2, 31.4, 32.6, 35.0, 49.3, 52.2, 53.2, 53.8, 70.8, 105.7, 109.8, 116.3, 117.3, 119.3, 125.8, 134.2, 135.1, 162.3, 173.9; MS m/z (relative intensity) 355 (M + 1, 22), 354 (M^+, 95), 353 (100), 339 (14), 325 (3), 305 (3), 295 (5), 277 (3), 223 (7), 221 (5), 209 (5), 197 (5), 184 (9), 170 (16), 169 (25), 156 (13), 144 (11), 143 (8), 138 (5), 130 (5), 129 (6), 128 (5), 117 (5), 115 (6), 55 (5), 51 (10); HRMS M^+ calcd for $C_{21}H_{26}N_2O_3$ 354.1943, found 354.1936.

Acknowledgment. We thank Dr. Paul Keller of Norwich Eaton Pharmaceuticals for providing high-resolution mass spectra and Dr. John Hubbard for X-ray data. This work was supported by Grant R01-12010 from the National Cancer Institute.

Supplementary Material Available: X-ray data and NMR and IR spectra available (67 pages). Ordering information is given on any current masthead page.