^{18}O-labeled sulfoxide carboxylic acid **5a**, sulfoxide ^{18}O-labeled sulfoxide ester, and sulfoxide ^{18}O-labeled endo acid **5a**, control experiments with carboxyl ^{18}O-labeled endo acid sulfoxide **5a**, sulfoxide ^{18}O-labeled endo acid sulfoxide **5a**, carboxyl ^{18}O-labeled endo acid sulfoxide **5a**, and sulfoxide ^{18}O-labeled endo acid sulfoxide **5a**, and Table II of mass spectral data for control experiments (8 pages). Ordering information is given on any current masthead page.

Chiral and Achiral Formamidines in Synthesis. The First Asymmetric Route to (-)-Yohimbone and an Efficient Total Synthesis of (±)-Yohimbone†

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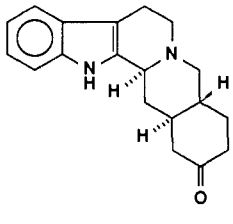
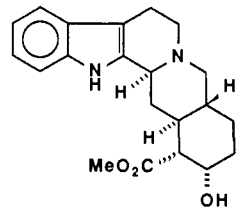
Abstract: An asymmetric synthesis of (-)-yohimbone from chiral formamidines is presented. The synthetic pathway intercepts a previously reported route to yohimbenone (**6**) reported by Winterfeldt. An investigation of the [3,3]-rearrangement involving iminium salts **8** and **9** reveals that this process loses its stereochemical integrity since when optically active **7** is used as the starting material, only racemic **6** is obtained. Removal of the keto group by reduction to **19**, however, allows the ring closure to yohimbenone to proceed with complete conservation of chirality. Thus, the [3,3]-rearrangement was circumvented in going from **19** to **21** and **22**. This latter sequence proceeded by a Pictet-Spengler-Grieco ring closure rather than the [3,3]-rearrangement. The asymmetric synthesis of (-)-yohimbone was accomplished in 11 steps in 17% overall yield. Furthermore, a racemic synthesis of yohimbone, **1**, was also performed with achiral formamidine **25** and was carried out in six steps in 38% overall yield.

Our continuing studies utilizing achiral and chiral formamidines[1] as vehicles for elaboration of secondary amines (Scheme I) has led to a number of approaches to various alkaloid systems. To date we have demonstrated the total synthesis of racemic indole[2] and isoquinoline[3] alkaloids as well as asymmetric total syntheses of indole,[4] morphine,[5] and isoquinoline[6] alkaloids. A total synthesis of (+)-anisomycin[7] has also been recently described. The underlying reasons for this powerful asymmetric process are still not completely understood, although recent reports[8,9] have examined the stereochemistry of the deprotonation and alkylation steps.

We present here the first report of an asymmetric total synthesis of yohimbone (**1**), a key member of the yohimboid class of alkaloids, and a product of the oxidative decarboxylation of yohimbine (**2**) historically the most important member of this group.[10] These complex and architecturally interesting systems



1, Yohimbone



2, Yohimbine

have been the subject of a vast number of chemical degradation and synthetic studies as well as pharmacological endeavors due to their important hypertensive activity. A recent report by Martin[11] details the historical efforts dedicated to this class of alkaloids. A general approach to the yohimboids (±)-reserpine and (±) α-yohimbine are reported in this highly informative paper. The basic strategy of Martin[11] and Wender[12] to reach the pentacyclic alkaloids, reserpine, and/or α-yohimbine (Scheme II) involved coupling of the preconstructued DE ring to tryptophyl bromide with all or some of the requisite stereocenters in place.

The approach to be described herein was based on our previous successes involving asymmetric alkylation of a carbanion adjacent to nitrogen (Scheme I), and we will demonstrate (vide infra) how both racemic and enantiomerically enriched (~99% ee) yohimbone (**1**) may be reached in a relatively few steps in good overall yields. The basic plan (Scheme III) was to employ the intact β-carboline (ABC rings) and via its carbanion **3** to alkylate with 3-methoxybenzyl bromide or give the benzylated adduct **4**. The latter was a pivotal intermediate in the syntheses of (±)-yohimbenone (**6**) described by Winterfeldt.[13] As the latter has shown, reduction of the enol ether **5** followed by cyclization with formaldehyde to give **6** posed a convenient test for our methodology. Reduction of the α,β-unsaturated ketone, yohimbenone (**6**), would

† Dedicated to Professor E. J. Corey on the occasion of his 60th birthday.

(1) For a review of earlier studies, see: Meyers, A. I. *Aldrichimica Acta* **1985**, *18*, 59. Meyers, A. I. *Lect. Heterocycl. Chem.* **1984**, *7*, 75.
(2) Meyers, A. I.; Loewe, M. F. *Tetrahedron Lett.* **1984**, *25*, 2641. Meyers, A. I.; Hellring, S. *J. Org. Chem.* **1982**, *47*, 2229.
(3) Meyers, A. I.; Hellring, S.; ten Hoeve, W. *Tetrahedron Lett.* **1981**, *22*, 5115.
(4) (a) Meyers, A. I.; Sohda, T.; Loewe, M. F. *J. Org. Chem.* **1986**, *51*, 3108. (b) Loewe, M. F.; Meyers, A. I. *Tetrahedron Lett.* **1985**, *26*, 1985.
(5) (a) Meyers, A. I.; Bailey, T. R. *J. Org. Chem.* **1986**, *51*, 872. (b) Meyers, A. I.; Dickman, D. A.; Bailey, T. R. *J. Am. Chem. Soc.* **1985**, *107*, 7974.
(6) Meyers, A. I.; Bös, M.; Dickman, D. A. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 458. Meyers, A. I.; Bös, M.; Dickman, D. A. *Tetrahedron* **1987**, *43*, 5095.
(7) Meyers, A. I.; Dupre, B. *Heterocycles* **1987**, *25*, 113.
(8) Meyers, A. I.; Rieker, W. F.; Fuentes, L. M. *J. Am. Chem. Soc.* **1983**, *105*, 2082. Al-Aseer, M.; Beak, P.; Hay, D.; Kempf, D. J.; Mills, S.; Smith, S. G. *J. Am. Chem. Soc.* **1983**, *105*, 2080.
(9) Meyers, A. I.; Dickman, D. A. *J. Am. Chem. Soc.* **1987**, *109*, 1263. Gawley, R. E. *J. Am. Chem. Soc.* **1987**, *109*, 1265.
(10) For review on the yohimboid alkaloids, see: (a) *The Alkaloids, Chemistry and Physiology*; Manske, R. H. F., Ed.; Academic: New York, 1981; Vol. XX. (b) Saxton, J. E. In *Specialist Periodical Reports, The Alkaloids*; The Royal Society of Chemistry, Burlington House: London, 1983; Vol. 13, pp 221-237. See also in Vol. 1-12 (c) Cordell, G. A *Introduction to Alkaloids, A Biogenetic Approach*; Wiley-Interscience: New York, 1981; pp 574-832.
(11) Martin, S. F.; Rüeger, H.; Williamson, S. A.; Grzejszczak, S. *J. Am. Chem. Soc.* **1987**, *109*, 6214. For a thorough accumulation of pertinent references dealing with the yohimboid class of alkaloids, consult this article.
(12) Wender, P. M.; Schaus, J. M.; White, A. W. *J. Am. Chem. Soc.* **1980**, *102*, 6157; *Heterocycles*, **1987**, *25*, 263.
(13) Benson, W.; Winterfeldt, E. *Chem. Ber.* **1979**, *112*, 1913.

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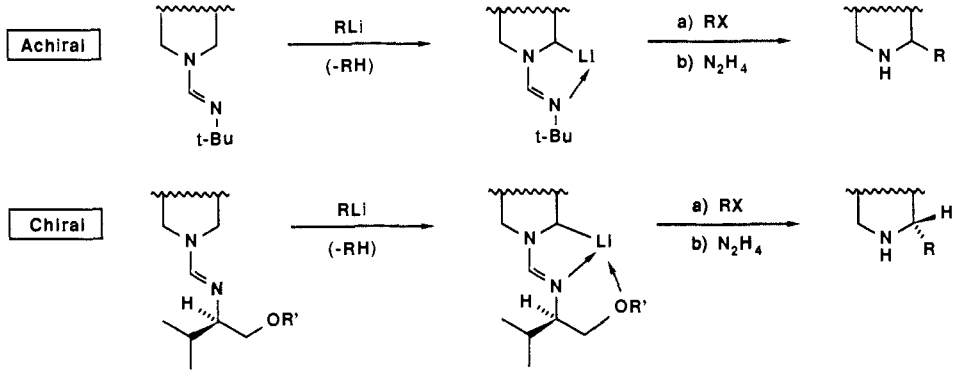
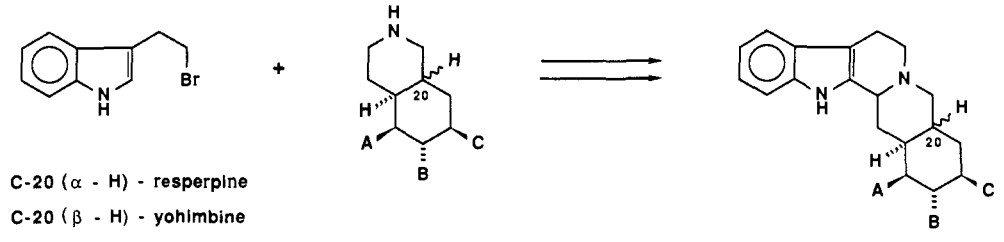
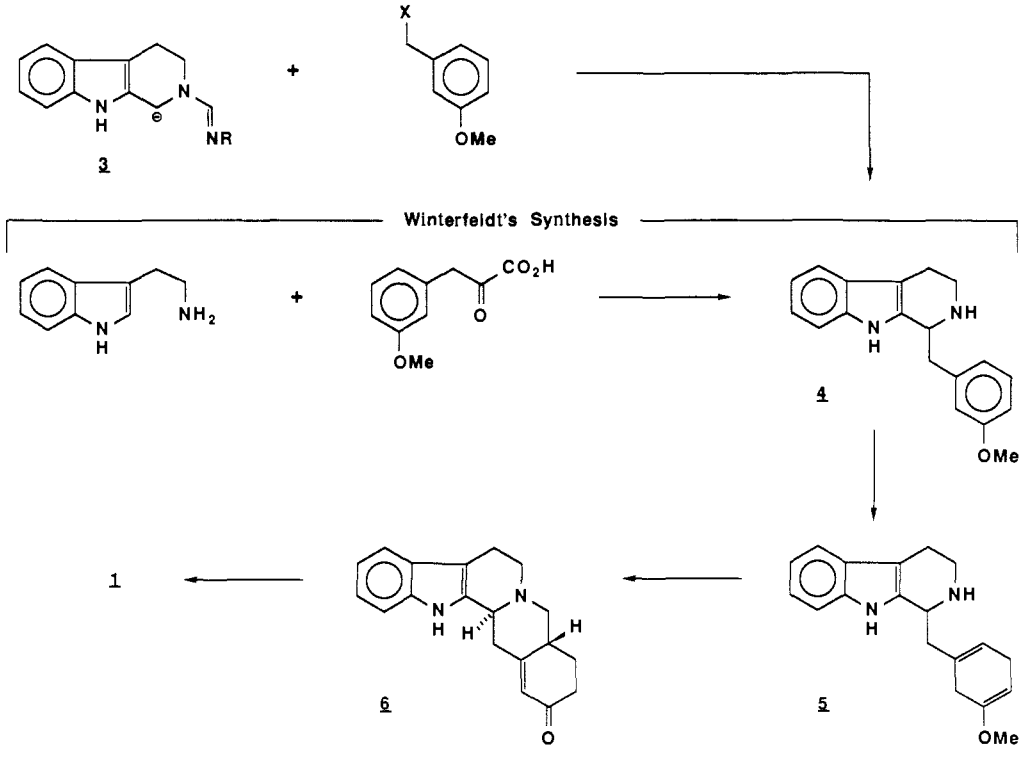
Scheme I



Scheme II



Scheme III



provide the target, **1**. Thus, after careful examination of the Winterfeldt synthesis shown in Scheme III, we felt we could intercept this route at **4**. Another fascinating aspect of the Winterfeldt synthesis was the [3,3] sigmatropic rearrangement[14] observed spectroscopically in going from **5** to **6** (Scheme **IV**) The question was therefore asked: If **7** is a single enantiomer, would the [3,3]-rearrangement (**8** → **9** → **6**) proceed with conservation of chirality at the C-1 stereocenter? If so, this would provide further information on the concertedness of this reorganization-process. However, if the product **6** is racemic, then it would indicate the total reversibility of the two iminium ions **8** and **9** and provide unequivocal proof that the reaction of **7** with formaldehyde is truly a [3,3]-rearrangement and not simply a Pictet–Spengler reaction of **7** going directly to **6** (without the intermediacy of **8** and **9**).

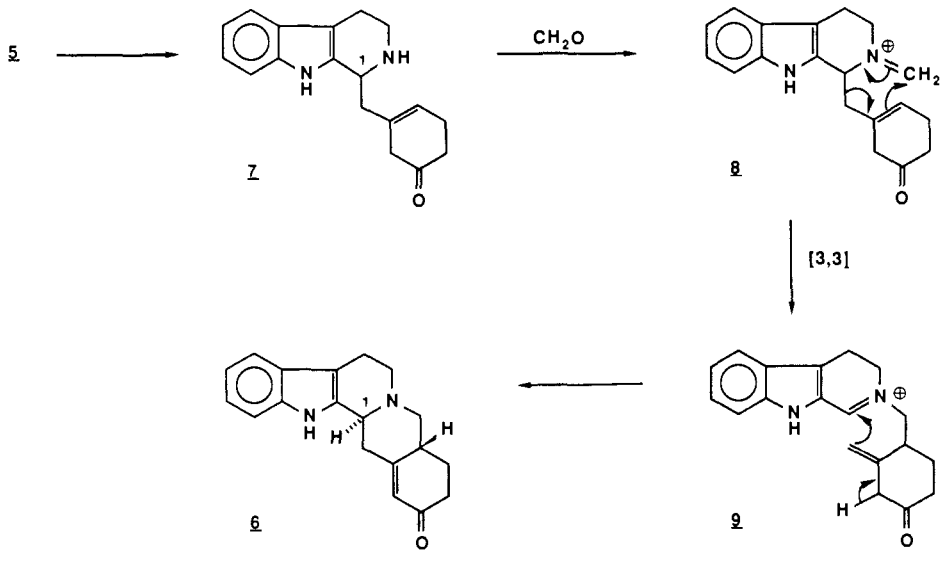
Another synthetic study on the yohimboid systems is worthy of mention. The "asymmetric synthesis" of yohimbone reported approximately 10 years ago by Yamada[15] produced the product in poor stereoselectivity starting from L-tryptophan and is actually not an enantiomeric asymmetric synthesis but rather a diastereoselective process, wherein the starting materials were optically active.

Our asymmetric route to yohimbone was initiated by transforming β-carboline **10** into its chiral formamidine **12** by exchange

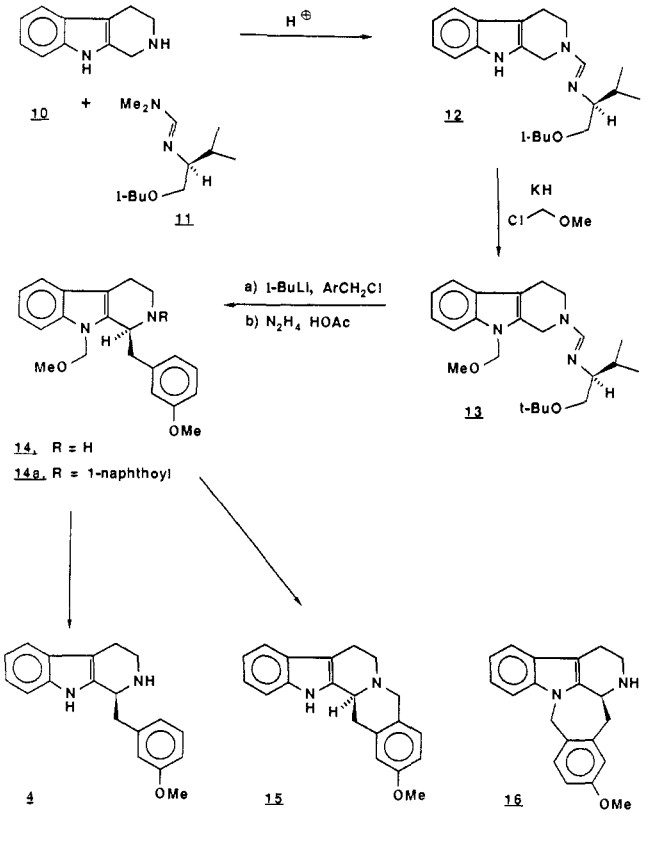
(14) (a) Rischke, H.; Wilcock, J.; Winterfeldt, E. *Chem. Ber.* **1973**, *106*, 3106. (b) Ahmad, V. U.; Feuerhard, K. H.; Winterfeldt, E. *Chem. Ber.* **1977**, *110*, 3624.

(15) Okamura, K.; Yamada S.-I. *Chem. Pharm. Bull.* **1978**, *26*, 2305.

Scheme IV



with the dimethylformamidine **11**.[4] This process occurs by simple heating in toluene for 48 h and produced the chiral starting material in 75% yield. It was necessary to protect the indole NH group since interference with the diastereoselective alkylation to follow has been observed.[4b] However, as will be seen later, this is not a necessary precaution if racemic yohimboids are desired. Addition of chloromethyl methyl ether to the potassium salt of the indole nitrogen gave the *N*-methoxymethyl derivative **13**[4] in 99% yield. The asymmetric alkylation step was now invoked, and this was performed by generating the α-lithio compound with *tert*-butyllithium at −80 °C in THF followed after 30 min by addition of 3-methoxybenzyl chloride to give the alkylated material in over 95% yield. The crude isolated material was subjected to formamidine removal by using a mixture of hydrazine–ethanol–acetic acid at 0 °C overnight and furnished **14** in 97% yield. Thus, the two-step procedure from **13** to **14** was accomplished in over 95% yield. *The percent enantiomeric excess as assessed by chiral HPLC analysis*[16] *on the 1-naphthoyl derivative* ***14a*** *was 98%.*



The next step, removal of the MOM protecting group, proved to be troublesome. Treatment of **14** with aqueous hydrochloric acid at room temperature gave incomplete removal of the MOM group, and a number of variations were attempted. The best conditions were achieved with dilute hydrochloric acid (10 °C, 3 days) followed by KOH to give a mixture of **4** and **15**. The latter arises from condensation with the released formaldehyde during the alkaline hydrolysis of the initially formed carbinol amine. These, therefore, were optimum conditions affording **4** in 65% isolated yield and **15** in 20% isolated yield. The latter has been reported[15] by Okamura and Yamada in their synthesis of (−)-yohimbone. However, significant differences in physical properties were noted ($[\alpha]_D$ −217° vs −235° in ref 15; mp 146–147 °C vs 103 °C in ref 15). Danishefsky[17] has recently reported also experiencing some difficulties with the work by Okamura and Yamada.[15]

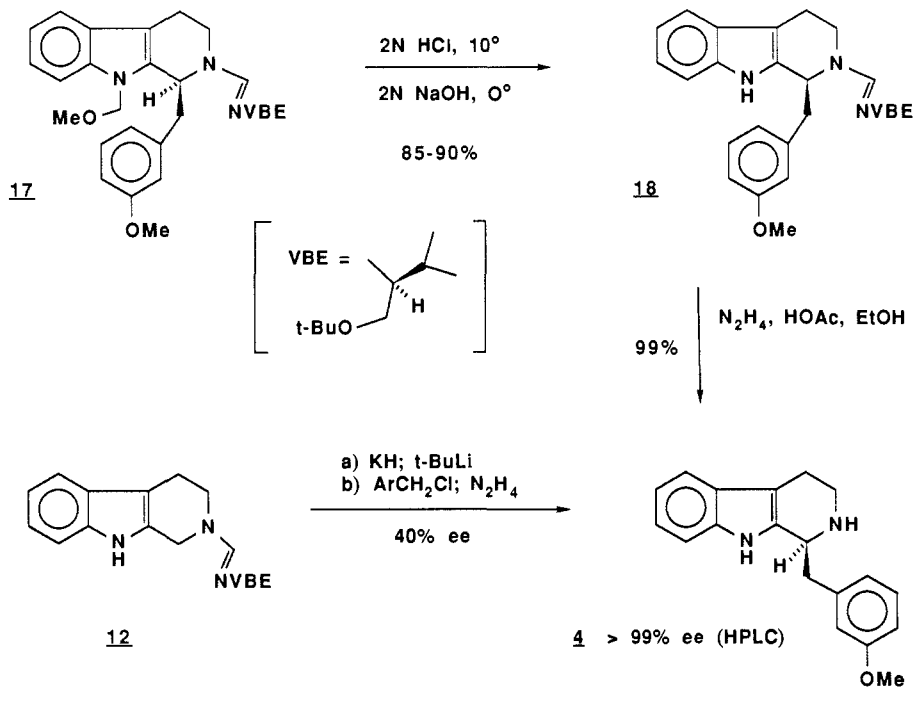
The mixture of **4** and **15**, obtained by cleavage of the MOM group, was somewhat disappointing, and alternate conditions to reach **4** in higher yield were sought. The use of diphenylboron bromide[18] or trimethylsilyl bromide[19] was unsuccessful. The former resulted in extensive decomposition while the latter reagent produced **16** in 65% yield. Intramolecular electrophilic aromatic attack by the iminium ion resulting from elimination of the methoxide group in **14** is probably the major pathway leading to **16**.

Frustrated by the efforts to cleanly remove the MOM group in **14** due to the facile Pictet–Spengler reactions that ensued in the presence of the methoxyaryl group,[20] we sought a more efficient route. The answer, fortunately, was trivial in that we simply reversed the order of the removal of the MOM and formamidine moieties. In this way, no piperidine NH was available during the release of the formaldehyde. Thus, treatment of **17** with acid followed by base gave a good yield of **18**, which was smoothly transformed into the desired adduct **4** in quantitative yield (Scheme V). Once again, the enantiomeric ratio of **4** was shown to be in excess of 99:1.

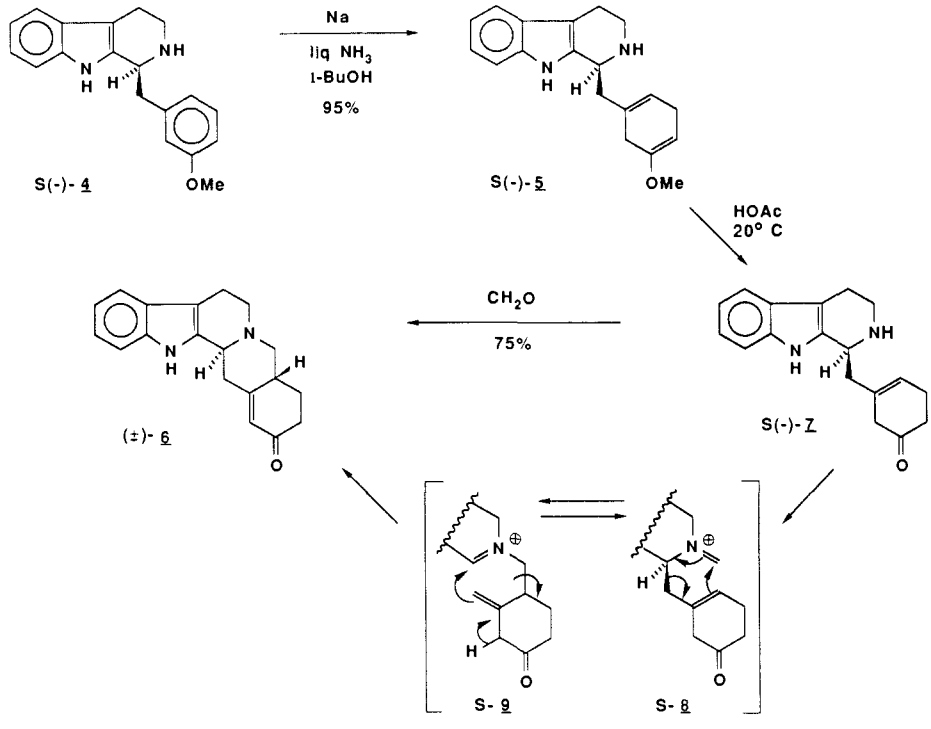
In an effort to alkylate the unprotected β-carboline to reach **4** we attempted alkylation on **12** by initially forming the potassium

(16) Pirkle, W. H.; Welch, C. J.; Mahler, G. S.; Meyers, A. I.; Fuentes, L. M.; Bös, M. *J. Org. Chem.* **1984**, *49*, 2504.
(17) Danishefsky, S.; Langer, M. E.; Vogel, C. *Tetrahedron Lett.* **1985**, *26*, 5983.
(18) Guindon, Y.; Yoakim, C.; Morton, H. E. *J. Org. Chem.* **1984**, *49*, 3912.
(19) Hanessian, S.; Delorme, D.; Dufresne, Y. *Tetrahedron Lett.* **1984**, *25*, 2515.
(20) MOM group removal in the indole series has been accomplished without difficulty by using acid or acid followed by base in systems not containing a "formaldehyde trap" such as an electron-rich aromatic ring. See, for example, the work described in ref 4 above.

Scheme V



Scheme VI

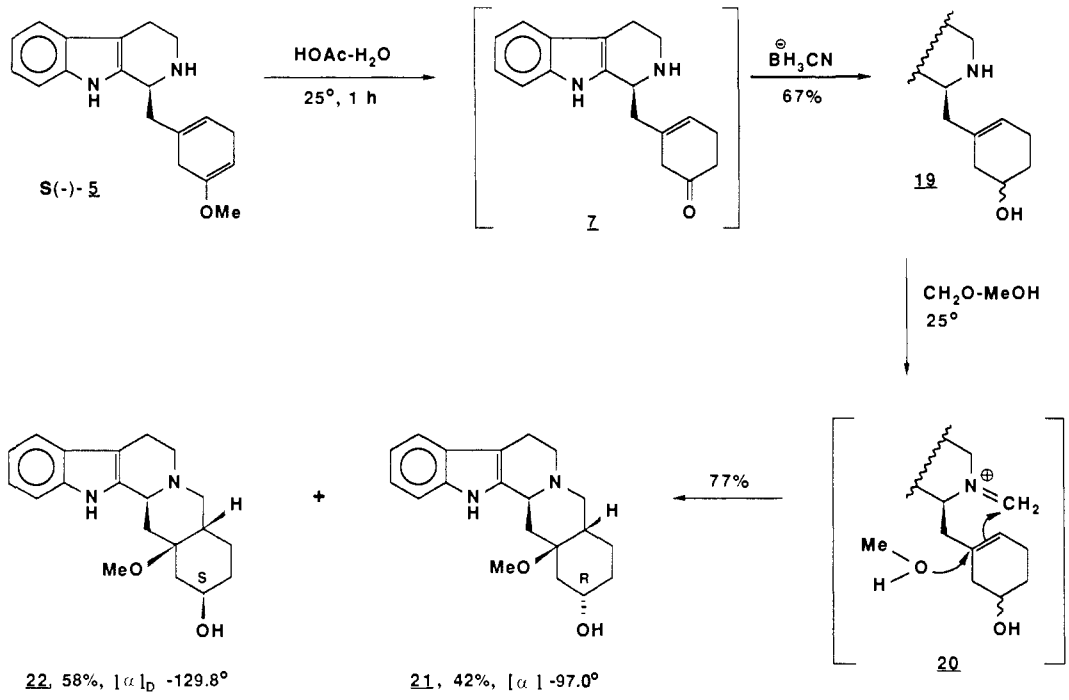


salt followed by lithiation. This was shown earlier in our studies[2] to provide good yields of alkylated products in achiral formamidines, whereas the *N*-lithio salt of **12** would not metalate adjacent to the formamidine.

The potassium salt of **12** was indeed smoothly transformed into the Li–K dianion and alkylated with 3-methoxybenzyl chloride. Treatment with hydrazine–acetic acid–ethanol at 25 °C then furnished **4**. HPLC analyses with use of a chiral Pirkle column[16] indicated that the enantiomeric ratio was no better than 70:30 (40% ee). A similar result was mentioned earlier from this laboratory[4b] with regard to another system. Thus, it is imperative that the indole nitrogen be covalently bound prior to metalation in order to achieve high degrees of stereoselectivity.

With an efficient route to (−)-**4** in hand, we proceeded now to enter the Winterfeldt synthesis of yohimbenone **6** and hopefully reach this material in high enantiomeric excess. On the other hand, if the [3,3]-rearrangement is indeed reversible, then **6** could well be racemic. The experiments to answer these questions were carried out and are depicted in Scheme VI with enantiomeric materials. Birch reduction of (*S*)-**4** proceeded cleanly to give, after methanol quench, the enol ether (*S*)-**5** in excellent yield. Without further purification, the latter was treated with aqueous acetic acid to produce the β,γ-enone (*S*)-**7**, which was not isolated but treated directly with methanolic formaldehyde. After 2.5 h at 20 °C, the mixture was worked up to give a 75%yield of **6**, *which was completely racemic.* Thus, the [3,3]-rearrangement, passing through (*S*)-**8** and (*S*)-**9**, was verified and shows that the *proces possesses no stereochemical integrity.* Presumably, there is a self-immolative transfer of stereocenters in going from (*S*)-**8** to (*S*)-**9** preserving the chirality. However, bond rotation in (*S*)-**9**

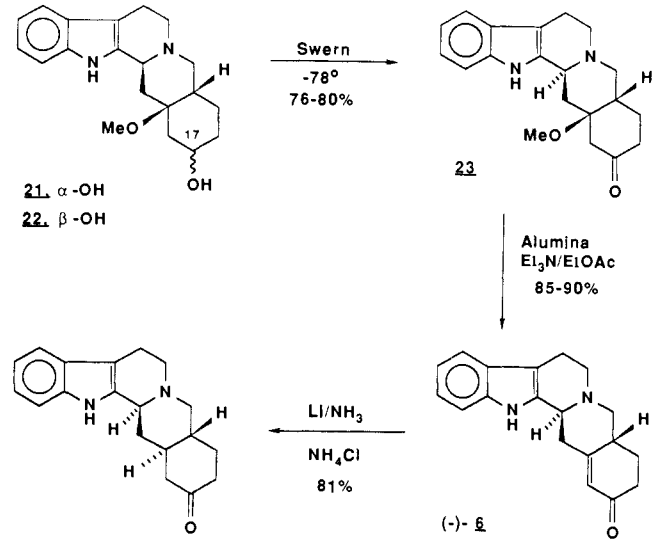
Scheme VII



must be very rapid, causing the "ene" reaction to take place from both faces of the iminium bond. When this occurs, both give **8** stereospecifically and respectively resulting in diastereomer **6** in racemic form. Proof that we were dealing with a single racemic diastereomer in **6** was obtained from its ^{13}C NMR spectrum, which exhibited 19 signals, 11 within the range 100–200 ppm (sp^2 carbons) and 8 within the 20–60 ppm range (sp^3 carbons). It is also noteworthy that Winterfeldt[13] obtained only the "trans" product **6** from racemic **4**.

This interesting but disappointing result now caused further consideration on how to transform optically pure (>99%) (*S*)-**4** into optically pure yohimbenone (**6**). Fortunately, once again, a trivial modification in procedure solved this problem. Rather than try to alter the rate of the [3,3]-rearrangement by studying conditional parameters, we proceeded to remove the carbonyl group in (*S*)-**7**, which should interfere with the rearrangement and allow a "normal" iminium ion to cyclize, thus eliminating the [3,3]-process.[14b] In this regard, we hydrolyzed the vinyl ether **5** to the β,γ-enone **7** and immediately added sodium cyanoborohydride to the acetic acid solution containing **7** (Scheme VII). The resulting hydroxy compound **19**,[14b] obtained as an inseparable 1.4:1 mixture of diastereomers, was treated with methanolic formaldehyde containing acetic acid (20 °C, 16 h). Workup furnished a 77% yield of two diastereomeric alcohols **21** and **22** in a 58:42 ratio. The methoxy group present in both diastereomers is undoubtedly the result of the solvolytic trapping of the carbonium ion formed in **20**, in a Pictet–Spengler–Grieco[21] type process, and has previously been observed by Winterfeldt.[14b] Both methoxy alcohols, **21** and **22**, were readily separated by flash chromatography. Since only two diastereomers were found, it was assumed that they differ only in the orientation of the C-17 hydroxyl, which also means that the cyclization of **19** to **21** and **22** was completely stereoselective. The substantial optical rotation exhibited by **21** and **22**, although of no structural significance, implied that the cyclization may have proceeded as predicted and that the [3,3]-rearrangement observed earlier was indeed circumvented.

Each pure diastereomer, **21** and **22**, was individually subjected to the Swern oxidation[22] and gave ketone **23** as a sensitive material on silica gel. However, chromatography of crude **23** on neutral alumina with triethylamine in ethyl acetate gave (−)-**6** in high yield. Each diastereomer (**21** and **22**) gave (−)-**6**, confirming that they differed only at C-17.



(-)-**1**, Yohimbone (97-99% ee)

The final step in the scheme required reduction of (−)-**6** to (−)-yohimbone (**1**). The initial experiment attempted was to employ the previously reported [15] reduction using hydrogen–palladium, which was claimed to produce, stereospecifically, (−)-yohimbone. However, a mixture of diastereomers of **1** were obtained as was clearly evident from the ^{14}C NMR spectrum and the HPLC analysis, which indicated approximately a 1:1 mixture of (−)-**1** and another diastereomer that was not characterized. Due to this, an alternate method of reduction of (−)-**6** to yohimbone was required.

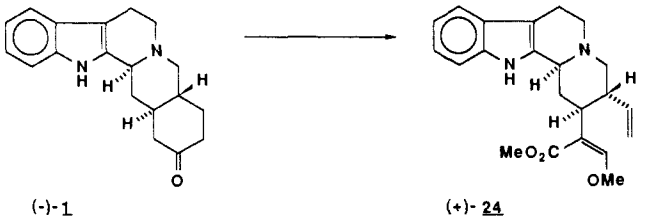
In a study reported by the Warner-Lambert group[23] on reduction of enones in isomeric yohimbenone systems, they found that catalytic reduction gave the kinetically favored DE-cis ring fused product, whereas lithium and ammonia reduction gave the thermodynamically favored DE-trans product. With this precedent

(21) Larsen, S. D.; Grieco, P. A.; Fobare, W. F. *J. Am. Chem. Soc.* **1986**, *108*, 3512.

(22) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(23) Morrison, G. C.; Waite, R. O.; Shavel, J. J. *J. Heterocyl. Chem.* **1971**, *8*, 1025.

in hand, we reduced *racemic* **6** (vide infra) with lithium–ammonia and quenching with ammonium chloride. A 70% yield of pure yohimbone, (±)-**1**, was obtained after chromatography. The melting point was 266–268 °C, which was in good agreement with the literature value (266–268 °C[24]). Thus, the dissolved metal reduction was attempted on *enantiomerically pure* (−)-**6** obtained from the asymmetric route. The lithium–ammonia reduction gave (−)-**1** in 79% yield with $[\alpha]_D$ −106.5°, which compared quite well with the specific rotations reported earlier.[24,25] However, the melting point of (−)-**1** was considerably lower than that reported by Okamura and Yamada[15] (303 °C) and Swan[24] (305–306 °C). Our observed melting point for (−)-**1** was 266–267 °C with discoloration at 230 °C and darkening at 263 °C. This is much closer to the range (279–280 °C) reported by Klyne, Schmid, and Snatzke.[25] The ^{1}H NMR and ^{13}C NMR spectra were identical with those of racemic yohimbone, and the melting point of racemic yohimbone agreed completely with the previous values (see above). In view of the melting point discrepancies, we though it advisable to confirm the stereochemistry of yohimbone, in a relative sense, so that there is no question that another diastereomer was not inadvertantly reached during this synthesis. In this regard, a single-crystal X-ray structure was taken on (−)-**1** and clearly showed that the relative stereochemistry of yohimbone was indeed correct,[26] and the (−)-enantiomer reached in >98% ee confirms the 3*S*,15*S*,20*R* absolute configuration. This asymmetric synthesis of (−)-yohimbone (**1**) may now provide a route to corynantheine **24**, which has already been reported[27] to arise from **1**. The entire scheme leading to (−)-**1** required 11 steps from commercially available material (**10** and **11**) and was accomplished in 17% overall yield.



(-)-1 (+)-24

Finally, a recent paper by Grieco[28] on the total synthesis of (±)-yohimbone, using his powerful iminium ion–allyl silane methodology, prompts us to disclose, as part of this asymmetric route to yohimbone, a racemic synthesis of this substances. The sequence (Scheme VIII) follows closely that described above except there was no concern over absolute stereochemistry, particular in the [3,3]-rearrangement from (±)-**5** to **6**, which led to racemic material (**7** → **6**). The sequence was initiated by using β-carboline **10** and exchanging it with the *tert*-butyl dimethylformamidine, furnishing the formamidine **25**. The latter was transformed into its potassium salt and then metalated with *tert*-butyllithium at −78 °C to provide the dianion of **25**, which was alkylated with 3-methoxybenzyl chloride in the presence of HMPA. The product **26**, obtained in 78–80% yield, was then treated with ethanol–water–acetic acid–hydrazine (8:1:1:12) at 0 °C for 12 h. This gave (±)-**4** in 95% yield, which was spectroscopically (IR, ^{1}H NMR, ^{13}C NMR) identical with the enantiomeric material **4** discussed earlier. Birch reduction gave (±)-**5** (92%), which was identical with that reported by Winterfeldt.[14] The next step of the synthesis followed Winterfeldt's sequence, giving (±)-**6** after hydrolysis of the enol ether in (±)-**5** and treatment with methanolic formaldehyde. Yohimbenone, (±)-**6**, was obtained in 79% yield. Reduction of (±)-**6** to yohimbone with lithium in liquid ammonia and quenching with ammonium chloride gave (±)-**1** in 68% yield. The physical data were in complete accord with the previous reports on (±)-yohimbone,[13,24,25,28]

Comparing this synthetic route to that recently described by Grieco[28] (10% overall yield), we obtained (±)-yohimbone in 38% overall yield in six steps. Thus, where there is no conern for absolute stereochemical integrity, the fromamidine route to indole, isoquinoline, and other alkaloids is seemingly superior to other methods thus far reported. When absolute stereochemistry is required (e.g. asymmetric synthesis) the only meaningful alternative to chiral formamidines may be Noyori's recent asymmetric hydrogenation of prochiral *N*-acyl enamides.[29]

Experimental Section

General Procedures. Optical rotations were measured at the sodium D line (589 nm) with a Rudolph Research (Autopol III) polarimeter, solutions were measured in a microcell (1 dm, 1 mL) in the indicated solvent, and concentration (*c*) is reported in grams of solute per 100 mL. Melting points are uncorrected. Analytical thin-layer chromatography (TLC) was performed on precoated aluminum-backed silica gel plates (E. Merck, 608 PF254). R_f values are quoted for plates of thickness 0.2 mm. preparative TLC was performed on silica gel (E. Merck, 60, PF254) coated glass backed plates of absorbant thickness 1.75 or 0.25 mm. Column chromatography was performed with silica gel (Woelm, 32–63 μm) or aluminum oxide (Baker, neutral, 50–200 m). High-pressure liquid chromatography (HPLC) was performed with a Beckman 110B solvent delivery system, a Beckman UV detector, and a Reodyne 7125 injector. Chiral HPLC determinations of enantiomeric ratios were performed on a Bakerbond DNBPG chiral phase column (Pirkle covalent *N*-[(3,5-dinitrobenzoyl)phenyl]glycine, 5 μm, 4.5 mm i.d., 25 cm).

Materials. All reactions were performed in an inert moisture-free atmosphere under a positive pressure of argon except when working in aqueous media. Purification and handling of all solvents and reagents used in synthetic procedures were conducted under an argon atmosphere except for aqueous solutions. All solvents were of reagent grade or purer. Tetrahydrofuran (THF) and diethyl ether were boiled under reflux over sodium benzophenone ketal and distilled. Methanol, toluene, and tert-butyl alcohol were boiled under reflux over sodium for several hours and distilled. Triethylamine was boiled under reflux over calcium hydride for several hours and distilled. Hexane, ethyl acetate, and methylene chloride used for extractions or chromatography were distilled prior to use in order to remove nonvolitile impurities. 3-Methoxybenzyl chloride was purchased from Aldrich Chemical Co. and was used without further purification. 1,2,3,4-Tetrahydro-β-carboline was prepared from L-tryptophan (Aldrich) by the procedure of Walker and Ho.[30] *N*′,*N*′-Dimethyl-*N*-(3-methyl-1-*tert*-butoxy-2-butyl)formamidine was prepared from L-valine (Aldrich) by the precedure developed in these laboratories.[31]

2-[[(1,2,3,4-Tetrahydro-β-carbolin-2-yl)methyl]imino]valinol *tert*-Butyl Ether (12). To a 1-L round-bottomed flask equipped with a magnetic stirring bar, a condenser, and a drying tube ($CaSO_4$) was added 1,2,3,4-tetrahydro-β-carboline (**10**) (17.6 g, 102 mmol) and dry toluene (400 mL). The mixture was stirred until the solid was dispersed, and then *N*′,*N*′-dimethyl-*N*-(3-methyl-1-*tert*-butoxybut-2-yl)formamidine (**11**)[31] (23.0 g, 107.3 mmol) and camphorsulfonic acid (1.0 g, 3.9 mmols) were added. The heterogenous mixture was heated at reflux for 48 h. The volatiles were removed under reduced pressure, and the residue was chromatographed on an 8-cm column packed with an 8-in. bed of silica gel and eluted with Et_3N–EtOAC–hexanes (1:3:6, v/v/v). Fourteeen fractions of approximately 100 mL each were collected. The product eluted in fractions 3 through 12, and the product fractions were combined and concentrated under reduced pressure. The resulting pale yellow solid was recrystallized from THF–hexane to afford 26.3 g (75% yield) of a white solid: mp 139–140 °C (lit.[4a] mp 140–141 °C). The ^{1}H NMR spectrum was identical with that described previously.[4a]

2-[[[9-(Methoxymethyl)-1,2,3,4-tetrahydro-β-carbolin-2-yl]methyl]imino]valinol *tert*-Butyl Ether (13). A suspension of potassium hydride (903 mg, 22.0 mmol) in THF (10 mL) was stirred magnetically and cooled in an ice bath. To this was added a solution of formamidine **12** (6.27 g, 18.4 mmol) in THF (40 mL). The mixture was stirred at 0 °C for 1 h, tetramethylethylenediamine (3.32 mL, 22.0 mmol) was added, and stirring was continued for 30 min. Chloromethyl methyl ether (2.09 mL, 27.5 mmol) was added dropwise, and stirring was continued for an additional hour. The reaction was shaken with water (50 mL), and the organic layer was separated. The aqueous layer was extracted with

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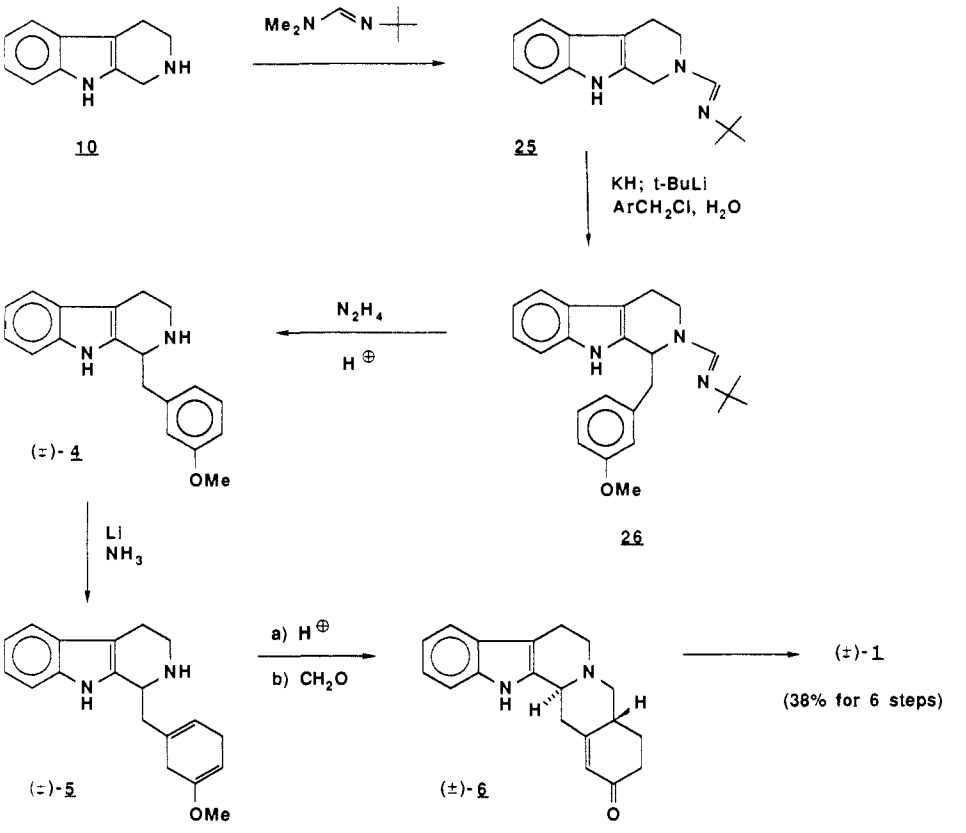
Scheme VIII



diethyl ether (2 × 75 mL). The combined organic layers were washed with water (30 mL), dried over anhydrous Na_2CO_3, filtered, and concentrated under reduced pressure. The residue was chromatographed on an 8-cm column packed with a 5-in. bed of silica gel employing a mobile phase of Et_3N–hexane (1:9, v/v). Fourteen fractions of approximately 75 mL each were collected. The product eluted in fractions 4–11, and these fractions were combined and concentrated under reduced pressure to afford 7.03 g (99% yield) of a clear pale red oil: R_f 0.40 (Et_3N–EtOAc–hexane, 1:1:8). The ^1H NMR spectrum of the product was identical with that described previously.[4a]

2-[[[9-(Methoxymethyl)-1-(3-methoxybenzyl)-1,2,3,4-tetrahydro-β-carbolin-2-yl]methyl]imino]valinol *tert*-Butyl Ether (17). A magnetically stirred solution of MOM ether **13** (7.03 g, 18.3 mmol) in THF (120 mL) was cooled to −80 °C, and *tert*-butyllithium (11.75 mL of a 1.7 M solution in hexane, 19.9 mmol, 1.1 equiv) was added slowly dropwise over 10 min. The mixture was stirred at −80 °C for 30 min, and then a solution of 3-methoxybenzyl chloride (3.28 g, 20.9 mmol) in THF (15 mL) was added dropwise over 15 min. Stirring was continued at −80 °C for 12 , and the reaction was quenched by the addition of moist THF. After the mixture was warmed to room temperature, the volatiles were removed under reduced pressure. The residue was taken into CH_2Cl_2 (75 mL) and washed with water (50 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over anhydrous Na_2CO_3, filtered, and concentrated under reduced pressure. The resulting residue was chromatographed on an 8-cm column packed with a 6-in. bed of silica gel, employing a mobile phase of Et_3N–hexane (1:9, v/v). Sixteen fractions of approximately 75 mL each were collected. The product eluted in fractions 2–14, and these fractions were combined and concentrated under reduced pressure to afford 9.17 g (95% yield) of a pale yellow oil: R_f 0.45 (Et_3N–hexane, 1:9, v/v); IR (film) 2970, 2935, 2910, 2872, 2840, 1652, 1617, 1520, 1467, 1250, 1178, 132, 825, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45 (m, 2 H), 7.17 (m, 4 H), 6.78 (m, 2 H), 6.71 (s, 1 H), 5.23 (dd, J = 11.28, 7.04 Hz, 2 H), 3.65 (s, 3 H), 3.35 (m, 3 H), 3.24 (s, 3 H), 3.15 (m, 2 H), 3.00 (apparent t, J = 8.8 Hz, 1 H), 2.81 (m, 2 H), 2.64 (m, 2 H), 1.70 (m, 1 H), 1.01 (s, 9 H), 0.82 (d, J = 6.7 Hz, 3 H), 0.76 (d, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 159.69, 153.10, 140.09, 137.66, 135.88, 129.10, 127.51, 121.96, 121.85, 119.95, 118.12, 115.18, 112.01, 109.86, 109.49, 74.33, 72.12, 70.78, 64.83, 55.63, 54.88, 46.44, 39.80, 30.19, 27.46 (three carbons, coincedent *tert*-butyl methyls), 21.11, 20.23, 17.46, 11.80.

(+)-9-(Methoxymethyl)-1(*S*)-(3-methoxybenzyl)-1,2,3,4-tetrahydro-β-carboline (14). A magnetically stirred solution of **17** (5.26 g, 10.4 mmols) in absolute ethanol (180 mL) was cooled in an ice bath, and water (20 mL), acetic acid (20 mL), and hydrazine monohydrate (37 mL) were added sequentially. Stirring was stopped, and the reaction mixture was kept at 0 °C overnight. The volatiles were removed under reduced pressure, the residue was dissolved in CH_2Cl_2 (200 mL), and this solution was washed with water (3 × 50 mL). The organic layer was dried over anhydrous Na_2CO_3, filtered, and concentrated under reduced pressure. The residue was chromatographed on a 8-cm column packed with a 5-in. bed of silica gel, employing a mobile phase of Et_3N–EtOAc–hexane (1:3:6, v/v/v). Nineteen fractions of approximately 100 mL each were collected. The product eluted in fractions 8–18, and these fractions were combined and concentrated under reduced pressure to afford 3.25 g (97% yield) of **14** as a pale yellow oil: R_f 0.31 (Et_3N–EtOAc–hexane, 1:3:6, v/v/v); IR (film) 3320 (br), 3040, 2980, 2920, 2820, 1594. 1580, 1480, 1455, 1368, 1298, 1255, 1170, 1141, 1090, 1045, 895, 753, 727, 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50 (apparent d, J = 7.8 Hz, 1 H), 7.43 (apparent d, J = 8.1 Hz, 1 H), 7.19 (m, 3 H), 6.87 (apparent d, J = 7.7 Hz, 1 H), 6.82 (s, 1 H), 6.80 (m, 1 H), 5.40 (dd, J = 11.2, 3.94 Hz, 2 H), 4.35 dd, J = 3.2, 9.9 Hz, 1 H), 3.78 (s, 3 H), 3.29 (s, 3 H), 3.24 (d, J = 4.0 Hz, 1 H), 3.19 (d, J = 3.3 Hz, 1 H), 3.10 (m, 2 H), 2.74 (m, 2 H), 1.79 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 160.05, 140.96, 137.74, 137.32, 129.59, 127.86, 121.99, 121.73, 119.99, 118.29, 115.33, 111.90, 110.52, 109.36, 74.47, 55.76, 55.18, 52.54, 40.21, 38.48, 22.62; $[\alpha]_D$ +16.5° (*c* 1.03, ethanol); HPLC chiral column analysis (2-propanol–hexane, 1:4, v/v) 98% ee, *S* configuration.

The enantiomeric excess determination was performed by treating a solution of **14** (34 mg, 0.106 mmol) in CH_2Cl_2 (1.5 mL) containing triethylamine (30 μL) with 1-naphthoyl chloride (20 μL). This solution was stirred magnetically at room temperature for 2 h, taken into a syringe, and streaked along an edge of a 0.25-mm glass-backed TLC plate. The plate was developed once with Et_3N–EtOAc–hexane (10:55:35, v/v/v). A UV-active band at R_f 0.45 was removed from the plate, and the product was removed from the silica gel by trituration under diethyl ether and filtration. The filtrate was concentrated under reduced pressure to afford 57.6 mg of a white waxy solid. This solid was dissolved in 15 mL of a mixture of 2-propanol–hexane (1:4, v/v), and 5 μL of this solution was injected onto a Bakerbond DNBPG covalent Pirkle column[16] (J. T. Baker), which was equilibrated with the above solvent mixture at a flow of 4.5 mL/min. Under these conditions only a single enantiomer, eluting 6.93 min after injection, could be detected.

For comparison purposes, the analogous racemic material was prepared from Scheme VIII. When subjected to the identical chromatographic conditions as described above, the racemate exhibited two equal area peaks at 5.48 and 6.93 min after injection onto the column.

(*S*)-(−)-(3-Methoxybenzyl)-1,2,3,4-tetrahydro-β-carboline (4) from 14. A solution of the MOM ether **14** (3.32 g, 10.4 mmol) in THF (100

mL) was cooled to 0 °C in an ice bath. To this was added 3 N HCl (35 mL) with stirring. After 30 min, the stirring was stopped, and the mixture was kept in the refrigerator (12 °C) for 4 days. The solution was then raised to pH 13 with 50% aqueous potassium hydroxide, and the mixture was stirred at room temperature for 6 h. The solution was diluted with water (50 mL), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with water (1 × 25 mL), and the aqueous wash was reextracted with CH_2Cl_2 (1 × 25 mL). The combined organics were dried over anhydrous Na_2CO_3, filtered, and concentrated under reduced pressure. The residue was chromatographed on a 8-cm column packed with a 5-in. bed of silica gel, employing a mobile phase of Et_3N–EtOAc (1:9, v/v). Twenty fractions of approximately 50 mL each were collected. Fractions 6–11 contained the product along with other less polar materials, and fractions 12–18 contained only the desired product. These latter fractions were combined and concentrated under reduced pressure to afford 1.41 g (47% yield) of **4** as a white solid (foam). Fractions 6–11 were combined and concentrated under reduced pressure to give 1.60 g of mixed products. These were rechromatographed as described above to afford an additional 511 mg (17%) of **4** for a combined yield of 64%: R_f 0.18 (Et_3N–EtOAc, 1:9, v/v); mp 129–131 °C (lit.[24] mp 124 °C); IR (film) 3478, 3420 (br), 2870, 2840, 1615, 1582, 1460, 1304, 1250, 1180, 1110, 1032, 812, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.64 (br s, 1 H), 7.47 (apparent d, J = 6.6 Hz, 1 H), 7.19 (m, 2 H), 6.81 (s, 1 H), 4.34 (apparent t, J = 7.1 Hz, 1 H), 3.76 (s, 3 H), 3.29 (m, 1 H), 3.03 (m, 3 H), 2.73 (m, 3 H), 1.82 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 160.13, 139.93, 135.71 (two coincident carbon resonances), 129.78, 127.45, 121.64, 121.54, 119.33, 118.10, 115.09, 112.50, 110.70, 109.49, 55.20, 53.96, 42.41, 41.88, 22.75; $[\alpha]_D$ −23.3° (c 0.86, pyridine).

(*S*)-(−)-15,16,17,18,19,20-Hexadehydro-17-methoxyyohimbone (15). Isolation was accomplished during the silica gel chromatography of **4** to produce a faster moving compound **15**: R_F 0.48 (Et_3N–EtOAc, 1:9); ^1H NMR ($CDCl_3$) δ 8.00 (br s, 1 H, NH), 7.5 1 (apparent d, J = 6.85 Hz, 1 H), 7.32 (apparent d, J = 7.17 Hz, 1 H), 7.13 (apparent dt, J = 13.13, 6.97 Hz, 2 H), 7.00 (apparent d, J = 8.42 Hz, 1 H), 6.74 (apparent dd, J = 8.34, 2.52 Hz, 1 H), 6.67 (apparent s, 1 H), 4.03 (d, J = 14.47 Hz, 1 H), 3.77 (s, 3 H), 3.68 (d, J = 14.86 Hz, 1 H), 3.62 (m, 1 H), 3.62 (dd, J = 10.70, 5.11 Hz, 1 H), 3.15 (dd, J = 16.00, 3.79 Hz, 1 H), 2.98 (m, 2 H), 2.75 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 158.18, 137.05, 136.47, 134.54, 127.37 127.00, 121.59, 119.54, 118.38, 118.23, 113.57, 112.46, 110.84, 108.82, 57.34, 56.34, 55.33, 52.47, 35.16, 21.59; IR (film) 3280 (br, 9-H), 2910, 2820, 1595, 1570, 1485, 1440; mp 146–147 °C dec (lit.[15] mp 103 °C, lit.[24] mp 168 °C); $[\alpha]^{20}_D$ −217° (c 0.60, MeOH) [lit.[15] $[\alpha]^{26}_D$ −235° (c 0.85, MeOH)]. Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 77.87; H, 6.41; N, 8.93.

Indole 16. A solution of MOM ether **14** (119 mg, 0.37 mmol) in methylene chloride (5 mL) containing 4-Å molecular sieves was cooled to −30 °C, and trimethylsilyl bromide (226 mg, 0.195 mL, 1.45 mmol) was added dropwise. The solution was stirred for 1 h at −30 °C and then for 12 h at 0 °C. The reaction mixture was poured into a solution of saturated sodium bicarbonate (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organics were dried over anhydrous Na_2CO_3, filtered, and concentrated. The residue was chromatographed on a 2-cm column packed with a 4-in. bed of silica gel, employing Et_3N–EtOAc (1:9, v/v) as the mobile phase. Twenty-five fractions of approximately 20 mL each were collected. The product **16** resulting from Mannich-type cyclization to the indole nitrogen, eluted in fractions 17–25. These fractions were combined and concentrated to afford 63 mg of solid: mp 156–160 °C; $[\alpha]_D$ −150.0° (c 0.958 MeOH); ^1H NMR ($CDCl_3$) δ 7.4 8 (apparent t, J = 7.7 Hz, 2 H), 7.28 (m, 2 H), 7.13 (apparent t, J = 7.7 Hz, 1 H), 6.89 (d, J = 2.6 Hz, 1 H), 6.75 (dd, J = 8.3, 2.6 Hz, 1 H), 5.09 (dd, J = 52.9, 14.2 Hz, 2 H), 4.06 (dd, J = 10.7, 1.8 Hz, 1 H), 3.86 (s, 3 H), 3.50 (m, 1 H), 3.2 6 (apparent t, J = 11.0 Hz, 1 H), 3.06 (m, 2 H), 2.87 (m, 1 H), 2.73 (m, 1 H), 2.21 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 159.86, 140.83, 138.23, 137.17, 130.53, 129.04, 127.30, 121.43, 119.37, 118.15, 115.65, 111.59, 109.33, 108.85, 55.30, 55.21, 48.22, 44.16, 39.82, 22.38. Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.85; H, 6.75; N, 9.15.

Improved Procedure for 4. 2-[[[1(*S*)-(3-Methoxybenzyl)-1,2,3,4-tetrahydro-β-carbolin-2-yl]methyl]imino]valinol *tert*-Butyl Ether (18). A solution of MOM ether **17** (5.43 g, 10.8 mmol) in THF (100 mL) was cooled in an ice bath, and 2 N HCl (20 mL) was added with stirring. The stirring was stopped, and the mixture was kept at 10 °C for 48 h. The reaction mixture was washed with water (50 mL) and with saturated NaCl (50 mL). The combined aqueous washes were neutralized with 2 N NaOH and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over Na_2CO_3, filtered, and concentrated. The residue was flash chromatographed on a 5-cm column packed with 5-in. bed of silica gel, employing a mobile phase of hexanes–EtOAc–Et_3N (7:2:1, v/v/v). Twelve fractions of approximately 70 mL each were collected. Fractions 2 and 3 were combined and concentrated to afford 1.53 g of recovered starting material. Fractions 4–9 combined and concentrated to afford 3.55 g of the intermediate hemiaminal. The recovered **17** was dissolved in THF (30 mL) and treated at 0 °C with 2 N HCl (6 mL). Following hydrolysis as described above and flash chromatography on a 2-cm column, there was obtained 354 mg of impure starting **17**, 220 mg of the fully deprotected indole **18**, and 891 mg of hemiaminal. The combined samples of hemiaminal (4.48 g, 9.04 mmol) were dissolved in THF (100 mL), and 2 N NaOH (12 mL) was added with vigorous stirring. The progress of the reaction was monitored by tlc employing a solvent system of hexanes–EtOAc–Et_3N (7:1:1, v/v/v). The more polar hemiaminal (R_f 0.18) disappeared with time with concomitant appearance of product **18** (R_f 0.34). After the mixture was stirred for 3 h at room temperature, no starting material could be detected. The reaction mixture was washed with water (2 × 50 mL), and the combined aqueous washes were extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over Na_2CO_3, filtered, and concentrated. The resulting residue was flash chromatographed on a 5-cm column packed with a 6-in. bed of silica gel, employing the TLC solvent system given above as the mobile phase. Ten fractions of approximately 70 mL each were collected. The product eluted in fractions 3–8 and furnished 4.09 g of **18**. To this was added the 220 mg of **18** obtained after chromatography described above, for a total of 4.31 g (87% yield): mp 112–113 °C (hexane); ^1H NMR ($CDCl_3$) δ 7.47 (apparent d, J = 6.51 Hz, 1 H), 7.44 (s, 1 H, formamidine H), 7.17 (m, 5 H), 6.87 (s, 1 H), 6.85 (m, 1 H), 5.53 (br, 1 H, 9-H), 3.77 (s, 3 H), 3.72 (m, 1 H), 3.51 (dd, J = 8.95, 5.76 Hz, 1 H), 3.32 (m, 2 H), 3.21 (apparent t, J = 7.12 Hz, 1 H), 2.97 (dd, J = 12.80, 8.75 Hz, 1 H), 2.77 (m, 4 H), 1.87 (m, 1 H), 1.14 (s, 9 H), 0.97 (d, J = 6.70 Hz, 3 H), 0.90 (d, J = 6.92 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 160.12, 152.78, 140.41, 136.00, 134.40, 129.58, 126.93, 122.12, 121.64, 119.41, 118.05, 115.10, 12.92, 110.75, 108.80, 72.54, 71.06, 65.24, 55.25, 52.88, 43.04, 39.58, 30.41, 27.77 (3 C, *tert*-butyl methyl), 22.22, 20.58, 17.67; IR (film) 3410 (N_a–H), 2962, 2918, 2832, 1638 (s), 1596, 1358, 1251, 1188, 870, 726.

(*S*)-1-(3-Methoxybenzyl)-1,2,3,4-tetrahydro-β-carboline (4) from 18. A magnetically stirred solution of valinol *tert*-butyl ether **18** (6.49 g, 14.06 mmol) in absolute ethanol (240 mL) was cooled in an ice bath, and water (27 mL), acetic acid (27 mL), and hydrazine monohydrate (57 mL) were added sequentially. Stirring was stopped, and the reaction mixture was kept at −10 °C for 16 h. The reaction mixture was concentrated, the residue was dissolved in CH_2Cl_2 (200 mL), and this solution was washed with water (3 × 50 mL). The organic layer was dried over anhydrous Na_2CO_3, filtered, and concentrated. The residue was chromatographed on a 7.5-cm column packed with a 6-in. bed of silica gel, employing a Et_3N–EtOAc (1:9, v/v) as the mobile phase. Twenty fractions of approximately 75 mL each were collected. The product eluted in fractions 10–20 and these were combined and concentrated to afford 4.08 g (99% yield) of **4** (see above for physical data).

(*S*)-1-[(5-Methoxy-1,4-cyclohexadienyl)methyl]-1,2,3,4-tetrahydro-β-carboline (5). The Birch reduction was performed by a modification of the method of Swan.[24] Thus, into a 1000-mL round-bottomed three-necked flask equipped with a magnetic stirring bar, a cold finger condenser containing dry ice–acetone, and a drying tube ($CaSO_4$) was placed **4** (3.62 g, 12.4 mmol). The flask was charged with ammonia (approximately 800 mL), and then sodium (7.0 g, 304.3 mmol, 25 equiv) and *tert*-butyl alcohol (27.6 mL, 21.7 g, 292.6 mmol, 23 equiv) were added alternately, each in 7 approximately equal portions, over 2 h with occasional stirring. Two hours after completing the additions, methanol was added until the dark blue color was dissipated, and the ammonia was allowed to evaporate. To the resulting heterogeneous mixture was added water (300 mL), and the heterogeneous mixture was extracted with methylene chloride (4 × 150 mL). The combined organics were dried over anhydrous Na_2CO_3, filtered, and concentrated under reduced pressure to afford 3.70 g of a white solid (foam) containing residual *tert*-butyl alcohol: mp 79–83 °C (lit.[14] mp 83–85 °C); IR (KBr) 3400 (br, 2895, 2810, 1670 (enol ether C=C), 1640, 1420, 1195 (enol ether C—O), 995, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.95 (br s, 1 H, indole NH), 7.49 (apparent d, J = 7.2 Hz, 1 H), 7.26 (apparent t, J = 8.0 Hz, 1 H), 7.13 (m, 2 H), 5.66 (apparent s, 2 H), 4.69 (apparent s, 1 H), 4.23 (apparent t, J = 7.0 Hz, 1 H), 3.59 (s, 3 H), 3.35 (m, 2 H), 3.02 (m, 1 H), 2.87 (m, 2 H), 2.76 (m, 4 H), 2.76 (m, 2 H), 1.67 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 152.99, 136.39, 135.91, 131.85, 127.72, 122.44, 121.59, 119.43, 118.10, 110.75, 109.43, 90.51, 53.88, 50.44, 43.10, 42.73, 32.05, 31.32, 27.02. Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.53; N, 9.52. Found: C, 77.21; H, 7.69; N, 9.25.

(±)-Yohimbenone (6) from (*S*)-(−)-5. Racemization during [3,3]-Rearrangement. The cyclization was performed essentially as described by Benson and Winterfeldt.[13] Thus, enol ether **5** (193 mg, 0.66 mmol) was dissolved in acetic acid (4 mL), and water (3 mL) was added. The solution was stirred at room temperature for 1.25 h. Freshly prepared

methanolic formaldehyde (0.5 mL) was added to the reaction mixture, and stirring was continued for an additional 2 h. The mixture was neutralized by the portionwise addition of solid Na_2CO_3, diluted with water (20 mL), and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over anhydrous Na_2CO_3, filtered, and concentrated under reduced pressure. The yellow residue was chromatographed on a 2-cm column packed with a 6-in. bed of silica gel, employing a mobile phase of Et_3N–EtOAc–hexane (1:1:8, v/v/v) to afford 150.8 mg (79% yield) of a yellow crystalline product; mp 245–247 °C (lit.[32] mp 244–245 °C). Both ^1H and ^{13}C NMR spectroscopies indicate the product was a single diastereomer; however, this material possessed little or no optical activity: IR (KBr) 3540 (br, NH), 2940, 166 (C=O), 1625 (C=C), 1450, 1255, 735 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.85 (s, 1 H, indole NH), 7.38 (apparent d, J = 7.6 Hz, 1 H), 7.30 (apparent d, J = 7.9 Hz, 1 H), 7.04 (apparent t, J = 7.2 Hz, 1 H), 6.96 (apparent t, J = 7.2 Hz, 1 H), 5.83 (s, 1 H), 3.40–3.25 (m, 1 H), 3.20–3.00 (m, 3 H), 2.85–1.95 (m, 9 H), 1.65–1.40 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 197.76 (C=O), 162.92, 135.99, 134.39, 126.33, 124.16, 120.24, 118.09, 117.22, 110.74, 106.46, 60.70, 58.61, 51.28, 37.94, 36.25, 35.90, 25.24, 21.25.

21-Nor-$\Delta^{15(20)}$-yohimben-17-ol (19). The enol ether (*S*)-**5** (2.40 g, 8.2 mmol) was dissolved in acetic acid (60 mL), and water (50 mL) was added. The solution was stirred magnetically for 1 h, and then sodium cyanoborohydride (1.03 g, 16.3 mmol, 2 mole equiv) was added. The progress of the reduction was monitored by TLC, employing a solvent system of MeOH–Et_3N–EtOAc (4:10:86, v/v/v). As the reduction progressed, the spot corresponding to ketone **7** (R_f 0.43) diminished with concomitant increase of the spot corresponding to alcohol **19** (R_f 0.21). When reduction was complete, the solution was made basic by the careful portionwise addition of Na_2CO_3, and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organics were dried over Na_2CO_3, filtered, and concentrated to afford 2.28 g of a light yellow solid. This solid was chromatographed on a 5-cm column packed with a 5-in. bed of silica gel, employing the above TLC solvent system as the mobile phase. Twenty fractions of approximately 50 mL each were collected. Fractions 9–18 contained the product **19** (1.55 g, 67% yield) as an approximately 1:2 mixture of diastereomers, mp 175–179 °C. These diastereomeric alcohols were not readily separable by chromatography: ^1H NMR ($CDCl_3$–DMSO-d_6, 1:1, v/v) δ 10.45 (br, min or 9-H), 10.43 (br, major 9-H), 7.34 (apparent d, J = 7.57 Hz, 1 H), 7.26 (apparent d, J = 7.45 Hz, 1 H), 6.96 (m, 2 H), 5.53 (apparent s, min or olefinic H), 5.45 (apparent s, major olefinic H), 4.10 (m, 1 H), 3.26 (m, 1 H), 3.23 (m, 1 H), 2.91 (m, 1 H), 2.60 (m, 4 H), 2.15 (br m, 6 H), 1.76 (m, 1 H), 1.53 (m, 1 H). As expected for a mixture of diastereomers, the ^{13}C NMR ($CDCl_3$–DMSO-d_6, 1:1, v/v) δ 136.89 and 136.80, 135.90, 132.40 and 132.31, 127.23, 123.58 and 123.26, 120.31, 118.20, 117.40, 110.86, 107.56, 65.75 and 65.60, 50.48, 42.87 and 42.65, 41.87, 37.65 and 37.10, 30.60 and 30.33, 23.37 and 23.05, 22.67 and 22.58; IR (KBr) 3410 (br), 3280, 3235 (br, 2920, 2898, 2838, 2815, 1486, 1468, 1430 (s), 1312, 1230, 1158, 1088, 1067, 1044, 722 (s) cm^{-1}.

15(*S*)- and 15(*R*)-Methoxyyohimban-17-ol (22 and 21). To a magnetically stirred solution of diastereomeric homoallylic alcohols **19** (1.55 g, 5.5 mmols) in methanol (250 mL) were added acetic acid (14 mL) and 37% aqueous formaldehyde (0.56 mL). Stirring was stopped, and the mixture was allowed to stand at room temperature under argon for 16 h. The mixture was concentrated with gentle warming of the rotary flask. To the residue was added ethyl acetate (50 mL) and *n*-heptane (50 mL), and the opaque solution was again concentrated. This process of solvent addition and evaporative removal was repeated three times and afforded 1.70 g of a light yellow solid. This solid was dissolved in a minimum amount of Et_3N–EtOAc (1:9, v/v) and flash chromatographed on a 5-cm column packed with a 6-in. bed of silica gel, employing the above solvent system as the mobile phase. Twenty-two fractions of approximately 25 mL each were collected. Fractions 8–15 contained the less polar diastereomeric product (582.0 mg, 42%). Fractions 16–22 contained the more polar diastereomeric product (792.8 mg, 58%). Overall yield for this cyclization was 77%. The less polar diastereomer **22**[33] gave the following physical data: mp 193–195 °C (darkens at 180–185 °C); $[\alpha]^{20}_D$ −129.8° (*c* 1.56, pyridine); ^1H NMR ($CDCl_3$) δ 8.11 (br, 1 H, 9-H), 7.47 (apparent d, J = 7.17 Hz, 1 H), 7.31 (apparent d, J = 7.38 Hz, 1 H), 7.12 (m, 2 H), 4.48 (d, J = 9.62 Hz, 1 H, OH, exchanged with D_2O), 4.03 (m, 1 H), 3.34 (m, 1 H), 3.26 (s, 3 H), 3.19–2.53 (m, 6 H), 2.45 (m, 1 H), 2.30–1.68 (m, 5 H), 1.56 (m, 1 H), 1.35 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 136.41, 134.41, 127.43, 121.30, 119.29, 117.97, 110.78, 08.24, 77.53, 67.17, 56.98, 56.76, 52.27, 47.46, 37.67, 35.93, 34.55, 28.06, 21.82, 18.81; IR (KBr) 3380 (N_a–H), 3260 (O–H), 2920, 1460, 1446, 1112, 1050, 818, 729 cm^{-1}. Anal. Calcd for $C_{20}H_{26}NO_2$: C, 73.58; H, 8.03; N, 8.58. Found: C, 73.37; H, 7.99; N, 8.49.

The more polar diastereomer **21**[33] gave the following physical data: mp 229–230 °C (darkens at 180–185 °C) (lit.[14b] mp ~229 °C); $[\alpha]^{20}_D$ −97.0° (*c* 1.59, pyridine); ^1H NMR ($CDCl_3$–DMSO-d_6, 9:1, v/v) δ 9.38 (br, 1 H, 9-H), 7.42 (d, J = 7.95 Hz, 1 H), 7.31 (apparent d, J = 7.38 Hz, 1 H), 7.05 (m, 2 H), 3.91 (m, 1 H), 3.37 (apparent d, J = 11.78 Hz, 2 H), 3.22 (s, 3 H), 3.15–2.87 (m, 3 H), 2.82–2.48 (m, 4 H), 2.26–1.70 (m, 6 H), 1.37 (apparent t, J = 14.64 Hz, 2 H); ^{13}C NMR ($CDCl_3$–DMSO-d_6, 9:1, v/v) δ 136.63, 135.07, 127.51, 121.04, 119.09, 117.93, 111.05, 107.78, 77.81, 67.13, 57.24, 57.09, 52.50, 47.73, 38.27, 37.58, 37.35, 30.82, 23.3, 21.94; IR (KBr) 3410 (br, N_a–H), 3280 (br,O–H), 2930, 1463, 1450, 1112 (C–O–C), 1060, 730 cm^{-1}. Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.58; H, 8.03; N, 8.58. Found: C, 73.61; H, 8.40; N, 8.56.

(−)-Yohimbenone (6) from 22. A flask containing CH_2Cl_2 (2 mL) and oxalyl chloride (92.4 mg, 0.73 mmol, 64 μL) was cooled to −78 °C. A solution of DMSO (114 mg, 1.46 mmol, 2 equv, 104 μL) in CH_2Cl_2 was then added slowly dropwise. After the mixture was stirred for 3 min, a solution of the less polar diastereomeric alcohol **22** (250 mg, 0.76 mmol) in 2 mL of CH_2Cl_2–DMSO (3:1, v/v) was added dropwise over 5 min. After the mixture was stirred at −78 °C for 15 min, Et_3N (300 μL) was added. Stirring was continued at −78 °C for 10 min, and then the mixture was warmed to room temperature. Water (15 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were dried over Na_2CO_3, filtered, and concentrated to afford 238 mg of the crude ketone **6** as a yellow solid. This material was immediately chromatographed on a 5-cm column packed with a 3-in. bed of neutral alumina, employing a solvent gradient from EtOAc–Et_3N (90%10, v/v) to EtOAc–Et_3N–MeOH (88:10:2, v/v/v). Twenty-three fractions of approximately 20 mL each were collected. Clean β-elimination of methanol occurred on the column to afford (−)-yohimbenone (**6**), which eluted in fractions 9–20. These fractions were combined and concentrated to afford 172.9 mg (78% yield) of (−)-**6**: mp 238–241 °C dec (lit.[32] mp 244–245 °C; $[\alpha]_D$ −32.1° (*c* 1.18, pyridine). Spectral data matched that for (±)-**6** obtained by [3,3]-rearrangement of **5**.

For comparison purposes, the more polar diastereomeric alcohol **21** (274 mg, 0.839 mmol) was submitted to the same oxidation conditions as described above and afforded 186.4 mg (76% yield) of (−)-yohimbenone (**6**): $[\alpha]_D$ −31.5° (*c* 1.01, pyridine).

(−)-Yohimbone (1). Into a 50-mL, single-necked, round-bottomed flask equipped with a two-neck Claisen adapter having attached a dry ice–acetone-filled cold-finger condenser with drying tube ($CaSO_4$) and a gas inlet tube was placed a solution of (−)-yohimbenone (**6**) (160 mg, 0.547 mmol) in THF (7 mL). The flask was cooled to approximately −40 °C, and ammonia (ca 15 mL) was condensed into the flask. To the stirred solution was added lithium (8 mg, 1.15 mmol, 2 equiv) in two equal portions. After stirring for 1 h, NH_4Cl (15 mg) was added portionwise over 15 min, and then the ammonia was allowed to evaporate. The remaining volatiles were removed on the rotoevaporator, and the residue was taken up in water (50 mL) and extracted with CH_2Cl_2 (4 × 50 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was chromatographed on a 2-cm column packed with a 5-in. bed of neutral aluminum oxide, employing a mobile phase of EtOAc–Et_3N (9:1, v/v). Fifteen fractions of approximately 20 mL each were collected. The product eluted in fractions 6–14, and these fractions were combined and concentrated under reduced pressure to afford 127.8 mg (79% yield) of (−)-yohimbone (**1**) as a white solid. This was further purified by recrystallization from methanol, which afforded 84.6 mg of long slender colorless needles: mp 266–267 °C (lit.[25] mp 279–280 °C, lit.[24] mp 305–306 °C, lit.[15] mp 302 °C; $[\alpha]^{20}_D$ −106.5° (*c* 1.01, pyridine) [lit.[25] $[\alpha]^{20}_D$ −109.8° (*c* 0.37, pyridine), lit.[24] $[\alpha]^{20}_D$ −106° (*c* 2.6, pyridine), lit.[15] $[\alpha]^{20}_D$ −108.8° (*c* 0.34, pyridine)]. The melting point ranges are mainly a result of heating rates since considerable discoloration sets in at ~230 °C and darkening sets in at 260 °C, accompanied by considerable decomposition at the melting point: IR (KBr) 3480 (indole NH), 2940, 2845, 2805, 2760 (trans quinolizidine CD rings), 1710 (C=O), 1455 (C=C), 1370 (CH_2), 1330, 1110, 740 cm^{-1} (four adjacent ring hydrogens); ^1H NMR ($CDCl_3$–DMSO-d_6, 3:1, v/v) δ 9.49 (br s, 1 H, indole NH), 7.44 (d, J = 8.1 Hz, 1 H, aromatic), 7.32 (d, J = 7.6 Hz, 1 H, aromatic), 7.06 (m, $V_{1/2}$ = 11.5 Hz, 2 H, aromatic), 3.28 (dd, J = 12.5, 1.4 Hz, 1 H, C-3 H), 3.20–2.90 (m, 3 H), 2.90–2.55 (m, 4 H), 2.55–2.37 (m, 2 H), 2.32–2.16 (m, 4 H), 2.00–1.91 (m, 2 H), 1.68–1.50 (m, 1 H) (spectrum 18); ^{13}C NMR ($CDCl_3$–DMSO-d_6, 1:1, v/v) 208.70 (carbonyl), 135.91, 134.21, 126.56, 120.05, 118.01, 116.98, 110.33, 106.52, 60.01, 58.84, 52.29, 46.80, 40.93, 40.13, 38.91, 36.23, 29.09, 21.11.

X-ray Structural Data for (−)-1 (Mo Kα Radiation). Yohimbone, (−)-**1**, crystallizes from benzene–methanol in the monoclinic space group $P2110$, with a = 8.661 (2) Å, b = 14.907 (3) Å, c = 12.568 (3) Å, α =

(32) Czantay, C.; Honty, K.; Toke, L.; Szabo, L. *Chem. Ber.* **1976**, *109*, 1737.

(33) The assignments given to **21** and **22** are mainly arbitrary.

90.0°, β = 93.86 (2)°, γ = 90.0°, V = 1619.0 Å^3, p_{calcd} = 1.21 g/cm^3, and Z = 4. Standard direct and difference Fourier methods and least-squares refinement were carried out by using the SHELXTL program library supplied by Nicolet XRD for the DG Eclipse S/140 computer in the crystallography laboratory at Colorado State University. The structure was solved on the basis of 2500 ($I > 2.5$) reflections and led to a final R = 0.055. ORTEP drawings and all bond lengths, angles, atomic coordinates, thermal parameters, etc., have been placed in the supplementary material.

Synthesis of Racemic 1. 1-(3-Methoxybenzyl)-2-[(*tert*-butylimino)-methyl]-1,2,3,4-tetrahydro-β-carboline (26). A mixture of 2[(*tert*-butylimino)methyl]-1,2,3,4-tetrahydro-β-carboline (**25**)[2] (1.48 g, 5.8 mmol) and potassium hydride (1.16 g, 29.0 mmol, 5 equiv) was cooled in an ice water bath. To this was added ice-cold anhydrous diethyl ether (150 mL) via a cannula while stirring. After 10 min, anhydrous tetrahydrofuran (15 mL) was added, and stirring was continued at 0 °C until gas evolution had ceased (ca. 1 h). The mixture was cooled to −80 °C, and then a 1.7 M solution of *tert*-butyllithium in pentane (3.42 mL, 1.05 equiv) was added slowly dropwise. The temperature of the cooling bath was raised to −25 °C, and stirring was continued for 45 min. To the resulting dark red solution was added HMPA (5.05 mL, 5 equiv) slowly dropwise. After stirring for an additional 15 min at −25 °C, the mixture was recooled to −80 °C and 3-methoxybenzyl chloride (1.36 g, 1.5 equiv) in anhydrous diethyl ether (4 mL) was aded dropwise over 10 min. The temperature of the cooling bath was then slowly raised to −40 °C, and stirring was continued for 10 h. The reactions were quenched by the slow addition of saturated aqueous NH_4Cl (10 mL) and then allowed to warm to room temperature. The mixture was transferred to a separatory funnel and washed with water (3 × 25 mL). The combined aqueous washes were raised to pH 5 with 10% aqueous HCl and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2CO_3, filtered, and concentrated to afford 2.67 g of a viscous yellow oil. This oil was flash chromatographed on a 7.5-cm column packed with a 7-in. bed of silica gel, employing a mobile phase of Et_3N–EtOAc–hexanes (1:3:6; v/v/v). Eighteen fractions of approximately 50 mL each were collected. The title compound eluted in fractions 11–18 and these were combined and concentrated to afford 1.63 g (75% yield) of **26** as a white solid: mp 59–61 °C; IR (KBr) 3400 (br, indolic H), 2957 (s), 2910, 2895, 2858, 2830, 1635 (vs), 1450, 1255, 115, 1148, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.48 (br s, 1 H, indolic H), 7.46 (d, J = 10.8 Hz, 1 H), 7.36 (s, 1 H), 7.25–7.05 (m, 4 H), 6.88 (s, 1 H, formamidine H), 6.83 (m, 2 H), 5.37 (br m, 1 H), 3.81 (m, 1 H), 3.76 (s, 3 H), 3.34 (m, 1 H), 3.25 (m, 1 H), 2.93 (m, 1 H), 2.76 (m, 1 H), 2.72 (m, 1 H), 1.16 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 160.17, 148.64, 140.56, 136.12, 134.59, 129.58, 126.98, 122.06, 121.64, 119.42, 118.05, 115.24, 110.75, 108.80, 55.26, 53.24, 42.67, 39.71, 31.26 (3 C, *tert*-butyl), 22.17, 11.91.

(±)-1-(3-Methoxybenzyl)-1,2,3,4-tetrahydro-β-carboline (4). A magnetically stirred solution of *tert*-butylformamidine **26** (2.02 g, 5.4 mmol) in absolute ethanol (80 mL) was cooled in an ice bath, and water (10 mL), acetic acid (10 mL), and hydrazine monohydrate (20 mL) were added sequentially. Stirring was stopped, and the reaction mixture was kept at −10 °C for 16 h. The reaction mixture was concentrated, the residue was diluted with water (50 mL), and the aqueous mixture was extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were washed with water (3 × 20 mL), dried over anhydrous Na_2CO_3, filtered, and concentrated to afford a light yellow solid. This solid was flash chromatographed on a 5-cm column packed with a 6-in. bed of silica gel, employing a solvent system of Et_3N–hexanes–EtOAc (1:1:9, v/v/v) as the mobile phase. Twenty fractions of approximately 50 mL each were collected. The product eluted in fractions 10–19, and these were combined and concentrated to afford 1.5 g (95% yield) of racemic **4** as a colorless solid: mp 128–129 °C (lit.[24] 124 °C). The spectral data for this material was in complete accord with the previously characterized (*S*)-(−)-**4**.

(±)-1-[(5-Methoxy-1,4-cyclohexadienyl)methyl]-1,2,3,4-tetrahydro-β-carboline (5). Into a 500-mL round-bottomed three-necked flask equipped with a magnetic stirring bar, a cold-finger condenser containing dry ice–acetone and a drying tube ($CaSO_4$) was placed **27** (1.49 g, 5.11 mmol). The flask was charged with ammonia (approximately 300 mL), and then sodium (3.0 g, 130.5 mmol, 25 equiv) and *tert*-butyl alcohol (11.5 mL, 9.04 g, 121.9 mmol, 24 equiv) were added alternately, each in six approximately equal portions, over a 1-h period with occasional stirring. One hour after the additions were complete, an additional portion of sodium (0.7 g) was added. After 1 h, methanol was added until the dark blue color had dissipated, and the ammonia was allowed to evaporate. To the resulting heterogeneous mixture was added ice water (100 mL), and the mixture was filtered through a scintered-glass frit packed with Celite. The organic solid residue was removed from the filter with warm CH_2Cl_2 (100 mL). The organic washings were shaken with water (2 × 20 mL), and these aqueous washes were combined with the aqueous filtrate and extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were dried over anhydrous Na_2CO_3, filtered, and concentrated under reduced pressure. To the residue was added CH_2Cl_2 (20 mL) and *n*-heptane (40 mL), and these solvents were removed in vacuo with gentle warming. This procedure of solvent addition and evaporative removal was repeated three times. After the final concentration under high vacuum, 1.38 g (92% yield) of a white solid was obtained containing almost no contaminating residual *tert*-butyl alcohol, mp 85–86 °C (lit.[14] mp 83–85 °C). All spectral data were in complete accord with (*S*)-(−)-**5** prepared in the nonracemic sequence.

(±)-Yohimbenone (6). Enol ether (±)-**5** (1.375 g, 4.67 mmol) was dissolved in acetic acid (32 mL), and water (32 mL) was added. The solution was stirred at room temperature for 1 h. Then, freshly prepared methanolic formaldehyde (4.2 mL, made by thermolytic depolymerization of vacuum dried paraformaldehyde (6 g) at 150 °C and bubbling the formaldehyde gas thus formed into 25 mL of anhydrous methanol) was added to the reaction mixture, and stirring was continued for an additional 2 h. The mixture was then neutralized by the portionwise addition of solid Na_2CO_3, diluted with water (50 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with water, dried over anhydrous Na_2CO_3, filtered, and concentrated under reduced pressure. The yellow residue was chromatographed on a 7.5-cm column packed with a 4-in. bed of silica gel, employing a mobile phase of Et_3N–EtOAc (1:9, v/v) to afford 1.01 g (79% yield) of (±)-**6** as a yellow crystalline solid: mp 246–248 °C (lit.[32] mp 245–246 °C). All spectral data for this material were in complete accord with (*S*)-(−)-**6** prepared in the nonracemic series.

(±)-Yohimbone (1). Into a 100-mL, single-necked, round-bottomed flask equipped with a two-neck Claisen adapter having attached a dry ice–acetone-filled cold-finger condenser with drying tube ($CaSO_4$) and a gas inlet tube was placed a solution of (±)-**6** (607 mg, 2.07 mmol) in THF (25 mL). The flask was cooled to approximately −40 °C, and ammonia (ca. 50 mL) was condensed into the mixture. To the stirred solution was added lithium (28 mg, 4.14 mmol, 2 equiv) in two equal portions. After the mixture was stirred 1 h, NH_4Cl (40 mg) was added portionwise over a 1-h period, and then the ammonia was allowed to evaporate. The remaining volatiles were removed in vacuo, and the residue was taken up in water (50 mL) and extracted with CH_2Cl_2 (4 × 50 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was chromatographed in two equal portions on a 5-cm column packed with a 4-in. bed of neutral aluminum oxide, employing a mobile phase of ethyl acetate. For both chromatographic runs twelve fractions of approximately 50 mL each were collected. The product eluted in fractions 6–11, and these fractions from both chromatographic purifications were combined and concentrated under reduced pressure to afford 413 mg (68% yield) of (±)-yohimbone as a colorless solid. This was further purified by recrytsallization from methanol, which afforded 390 mg of (±)-**1** as long slender, colorless needles, mp 269 °C (discolors at 230 °C, darkens at 263 °C). Spectral data for this material were in complete accord with the (*S*)-(−)-enantiomer of **1** prepared by asymmetric synthesis.

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Supplementary Material Available: Atomic parameters, bond angles, and bond distances for the X-ray structure of (±)-**1** (6 pages). Ordering information is given on any current masthead page.