Symmetry-Driven Synthesis of Indole Alkaloids: Asymmetric Total Syntheses of (+)-Yohimbine, (−)-Yohimbone, (−)-Yohimbane, and (+)-Alloyohimbane

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Abstract: Total asymmetric syntheses of the target alkaloids are reported. The syntheses involve the preparation of enantiomerically pure (*S,S*)-1,3,3a,4,7,7a-hexahydro-2(H)-inden-2-one **7** and its meso isomer **5**. Each ketone is then converted into a ring-expanded lactam using an oxaziridine synthesis/rearrangement protocol. The applications of Bischler–Napieralski ring constructions along with appropriate functional group transformations afford enantiomerically enriched alloyohimbane or yohimbane from the *meso*- or C_2-symmetric ketones, respectively. A *cis*-5,6-diacetoxy compound (**18**) derived from the (*S,S*)-ketone served as the starting material for the total syntheses of the more highly functionalized alkaloids. Accordingly, a site-specific insertion of the indole-containing side chain was accomplished via stereoselective formation of an oxaziridine followed by its stereospecific rearrangement. The selectivity of this sequence allowed for the differentiation of alcohols at C-17 and C-18 (yohimbine numbering) and the synthesis of $\Delta^{18,19}$-yohimbone. This α,β-unsaturated ketone was converted into either (−)-yohimbone or (+)-yohimbine using standard chemistry.

The historic total synthesis of reserpine by Woodward et al.[1] is frequently cited as a model of strategy in preparative organic chemistry; the first total synthesis of yohimbine by van Tamelen[2] and co-workers displayed a similar level of accomplishment. However, not until recently have modern methods of asymmetric synthesis been brought to bear on the preparation of the yohimbine alkaloids[3] in enantiomerically pure form.[4] In fact, the asymmetric synthesis of fully functionalized yohimbine (**1**, below) has been addressed on only two occasions. In 1986, Szántay and co-workers obtained a key intermediate in enantiopure form using a second-order asymmetric transformation; this material eventually yielded

$\Delta^{15,16}$-yohimbinone, which was treated with $NaBH_4$ to give (+)-yohimbine as the minor component of a 2:1 mixture with its C-17 epimer β-yohimbine.[5] Also, Momose published a formal synthesis of yohimbine in which the key stereogenic centers were set using an asymmetric intramolecular Michael reaction.[6] This synthesis provided a 2,3-*seco*-yohimbine derivative that had previously[7] given the target alkaloid in 32% yield.
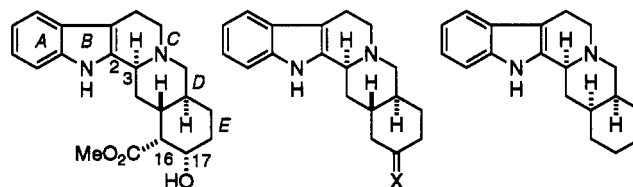
1, (+)-yohimbine　**2,** X = O, (−)-yohimbone　**4,** (−)-alloyohimbane
　　　　　　　　3, X = H₂, (−)-yohimbane　ent-**4,** (+)-allo-
　　　　　　　　　　　　　　　　　　　　　　　yohimbane

For some time, we have been interested in the preparation of nitrogen-containing molecules using ring-expansion methods, emphasizing the use of symmetry to simplify problems in asymmetric induction. Our 1988 synthesis of (−)-alloyohimbane (**4**), which has a cis ring fusion between rings D and E, featured a group-selective ring expansion reaction of a *cis*-hydrindanone (Scheme 1);[4g,i] a conceptually related approach involving the group-selective stereodifferentiation of a σ-symmetrical diester using an esterase-catalyzed hydrolysis reaction had been previously communicated.[4e] The synthesis shown in Scheme 1 utilized α-methylbenzylamine as a chiral auxiliary in the ring expansion step and therefore necessitated an awkward and low-yielding sequence to attach the indole. We wished to design a more convergent route that would additionally allow for the installation of yohimbine-appropriate functionality in the E-ring and could be extended to other stereoisomeric alkaloids in this series.

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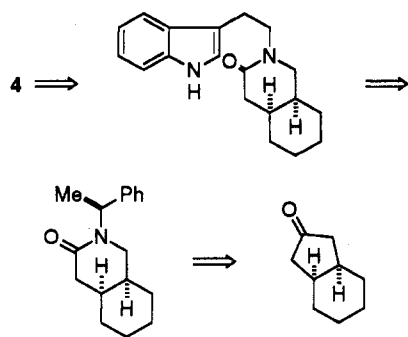⊕ Abstract published in *Advance ACS Abstracts,* August 15, 1994.
(1) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *Tetrahedron* **1958,** *2,* 1–57.
(2) (a) van Tamelen, E. E.; Shamma, M.; Burgstahler, A. W.; Wolinsky, J.; Tamm, R.; Aldrich, P. E. *J. Am. Chem. Soc.* **1958,** *80,* 5006. (b) van Tamelen, E. E.; Shamma, M.; Burgstahler, A. W.; Wolinsky, J.; Tamm, R.; Aldrich, P. E. *J. Am. Chem. Soc.* **1969,** *91,* 7315–7333.
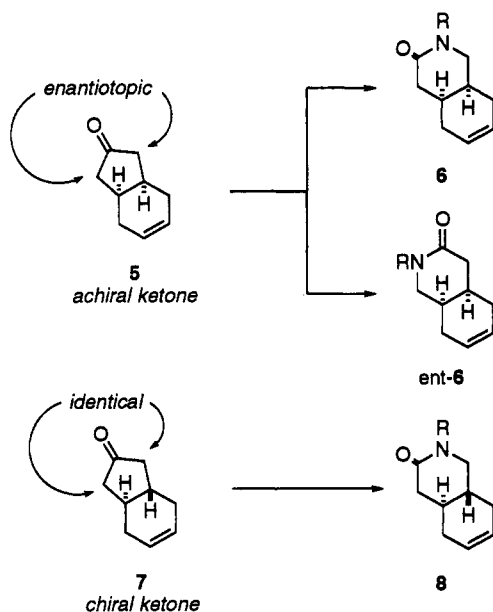(3) Reviews of yohimbine alkaloids: (a) Brown, R. T. In *The Chemistry of Heterocyclic Compounds*; Saxton, J. E., Ed.; John Wiley and Sons: New York, 1983; Vol. 25, Pt. 4, pp 147–199. (b) Santanay, C.; Blasko, G.; Honty, K.; Dörnyei, G. In *The Alkaloids*; Academic: Orlando, 1986; Vol. 27, pp 131–268. (c) Chatterjee, A. *Pure Appl. Chem.* **1986,** *58,* 685–692. (d) Szantay, C. *Pure Appl. Chem.* **1990,** *62,* 1299–1302. (e) Baxter, E. W.; Mariano, P. S. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Springer-Verlag: New York, 1992; Vol. 8, pp 197–319. A good analysis of various synthetic approaches appears in (f) Kuehne, M. E.; Muth, R. S. *J. Org. Chem.* **1991,** *56,* 2701–2712.
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Scheme 1

Scheme 2

Thus, a comprehensive and convergent approach to the yohimbine alkaloids via ring-expansion methodology has been developed and is the subject of this paper. The consequences of using stereoisomeric perhydrindanones as starting materials for nitrogen insertion chemistry will be discussed in the context of total, asymmetric syntheses of (+)-alloyohimbane (the enantiomer of **4** as drawn, ent-**4**) and (−)-yohimbane. Regiochemical issues arise with respect to E-ring functionality and have been solved en route to (−)-yohimbone. Finally, we report the total synthesis of (−)-yohimbine, using a relay at a critical point in the synthesis; this constitutes the first nonformal, asymmetric synthesis to afford this historically important alkaloid as the major product.

Results and Discussion

Symmetry Issues in Ring-Expansion Chemistry: Synthetic Strategy. As shown in Scheme 1 above, our overall strategy for yohimbinoid synthesis involved the ring expansion of a bicyclic ketone to afford a lactam that could be subjected to Bischler–Napieralski ring closure, giving the pentacyclic yohimbine skeleton. As applied to the alloyohimbine series, this retrosynthetic analysis leads to a cis-fused hydrindanone, such as **5** (Scheme 2). This molecule is achiral by virtue of a σ-plane containing the carbonyl group (i.e., it is a meso compound) and therefore the two methylene groups able to migrate in a ring-expansion sequence are enantiotopic. The formal insertion of an N-alkyl substituent could therefore give rise to enantiomeric lactams **6** and ent-**6**. An asymmetric synthesis of this ring system was thus accomplished using an oxaziridine-mediated insertion of an α-methylbenzyl moiety as previously described (Scheme

1).[4g,i,8] One goal of the present work was to effect a similar process using a chiral group *already containing the indole moiety present in the natural product*. This would avoid the aforementioned difficulties in efficiently removing the α-methylbenzyl group and only then attaching the AB ring system.

The normal yohimbine ring system has a trans DE ring fusion, suggesting bicyclic ketone **7** as a reasonable starting material. In this case, however, the planar symmetry of **5** has been replaced by a C_2 axis of symmetry that interchanges the α-keto methylene groups in **7**, rendering them identical. In this case, ring expansion of **7** can yield only one product (**8**) and the stereoselectivity/regioselectivity issue vanishes. The convenience of using a symmetrical ring-expansion step is offset, however, by the need to prepare ketone **7** in enantiomerically pure form should one wish an asymmetric synthesis of the target alkaloids, a problem not encountered with the meso compound **5**.

Finally, note that the saturated ketone used in our original synthesis (Scheme 1) has been replaced with olefin-containing versions for the purpose of this discussion. This unsaturation would presumably allow for the installation of functionality needed for the synthesis of biologically active yohimbine analogs. However, a potential drawback of this approach is that the high local symmetry of olefins like **6** or **8** could make the regioselective installation of the E-ring carbomethoxy and hydroxy groups in yohimbine difficult. This is perhaps the most vexing problem of this overall synthetic plan and, indeed, one facing many syntheses featuring group-selective reactions in their overall design. Another approach would be to carry out a group-selective insertion reaction on a ketone in which the two ends of the olefin are already differentiated. A version of this latter approach was used in the syntheses of yohimbine and yohimbone reported in this paper.

Synthesis of *cis*- and *trans*-Hydrindanones. Cheap and readily available cis-tetrahydrophthalic anhydride was used as a template for the preparation of the ketone **5**, with the requisite D,E-ring cis stereochemistry originating from the Diels–Alder cycloaddition of maleic anhydride and butadiene. The anhydride was converted to the corresponding, bis-homologated diacid **9** by the literature conditions shown in Scheme 3.[9] Although Ruzicka cyclization/decarboxylation (BaO, 260–270 °C) afforded the ketone in one step,[9] better results were obtained using a three-stage sequence featuring a Dieckmann cyclization reaction. This method reliably delivered ketone **5** in about 5 g quantities from tetrahydrophthalic anhydride in seven steps and 29% overall yield.

Access to the enantiomerically pure antipode of **7** needed for the preparation of naturally occurring (+)-yohimbine was easily attained using an asymmetric Diels–Alder reaction.[10] Thus, cycloadduct **10** was reduced to the corresponding diol,[11] which was transformed into **7** by a sequence analogous to that used for the preparation of **5** and known in the racemic series.[12,13] Ketone **7** obtained in this way was hydrogenated to afford the saturated analog. Comparison of the rotation of (1R,6R)-bicyclo[4.3.0]-nonan-8-one thus obtained ([α]D = +290 (c = 1.67, benzene) with the literature value[14] ([α]D = −303 (c = 0.47, benzene)

(8) For the use of oxaziridines in racemic alkaloid synthesis, see: (a) Langlois, Y.; Pouilhès, A.; Génin, D.; Andriamialisoa, R. Z.; Langlois, N. *Tetrahedron* **1983**, *39*, 3755–3761. (b) Kuehne, M. E.; Parsons, W. H. *Tetrahedron* **1983**, *39*, 3763–3765. The first use of oxaziridines in a group-selective ring expansion reaction was reported by Lattes and co-workers: (c) Lattes, A.; Oliveros, E.; Rivière, M.; Belzecki, C.; Mostowicz, D.; Abramskj, W.; Piccinni-Leopardi, C.; Germain, G.; Van Meerssche, M. *J. Am. Chem. Soc.* **1982**, *104*, 3929–3934.

(9) Mundy, B. P.; Theodore, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 2005–2010.

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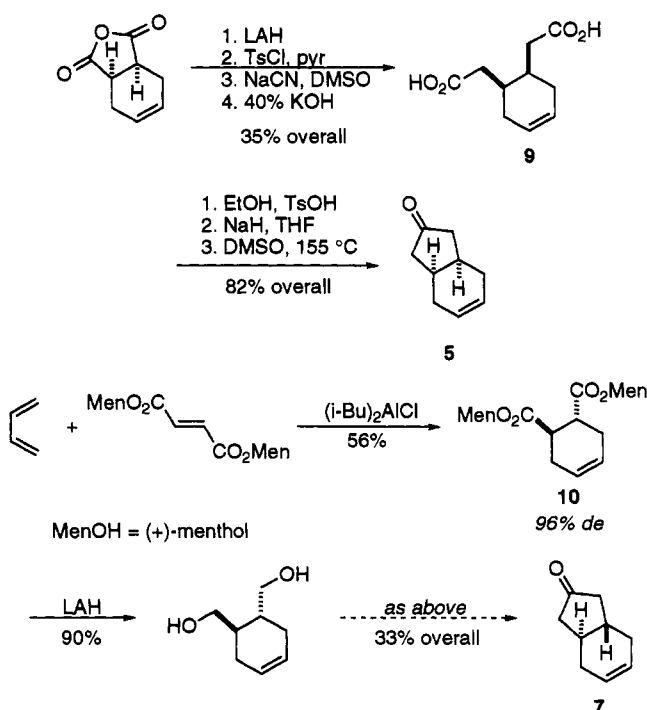
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Asymmetric Total Synthesis of (+)-Yohimbine

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Scheme 3

1. LAH
2. TsCl, pyr
3. NaCN, DMSO
4. 40% KOH

35% overall

9

1. EtOH, TsOH
2. NaH, THF
3. DMSO, 155 °C

82% overall

5

$MenO_2C$ + CO_2Men → (i-Bu)$_2$AlCl, 56% → $MenO_2C$, CO_2Men

10

96% de

MenOH = (+)-menthol

LAH, 90% → HO, OH → as above, 33% overall → **7**

results in an enantiomeric excess (ee) of ca. 96%, which corresponds to the diastereomeric purity of **10** as determined by 500 MHz NMR. Based on menthol (needed to prepare the chiral dienophile), the overall yield of this 11-step sequence—routinely resulting in 2–3 g of **7**—was approximately 16%.

Convergent Preparation of the Pentacyclic Ring System: Syntheses of (+)-Alloyohimbane and (–)-Yohimbane. We sought first to establish the viability of the overall synthetic plan in the preparation of ring systems lacking additional functionalization. In particular, we wished to establish that an indole could be used directly in the oxaziridine formation/rearrangement sequence, thus allowing for a convergent path to the target alkaloids. The realization of this strategy in the allo series, which additionally requires stereochemical induction in the ring-expansion step, is shown in Scheme 4.

L-Tryptophan methyl ester was used as the source of chirality. Accordingly, the free base of the amino acid ester could be directly condensed with ketone **5** in refluxing toluene and the mixture cooled to –78 °C and treated with *m*-CPBA to afford a mixture of four oxaziridine stereoisomers in a ratio of 64:25:8:3 (40% yield). Subsequent experimentation showed, however, that the starting amino acid had racemized under these reaction conditions, probably at the stage of imine formation. Still, a crystal suitable for X-ray analysis could be isolated from this experiment and was shown to have the stereostructure depicted for compound **11a** in Scheme 4.[15] Oxidation occurred exo to the bicyclic ring system as expected, and the tryptophan stereogenic center induced *like* stereochemistry at the newly-formed nitrogen stereocenter, as observed with oxaziridines derived from other amino acids.[16] Recourse to a tin-catalyzed imine-forming reaction[17] prior to oxidation solved the racemization problem, giving a similar ratio of oxaziridines in 68% yield (the ee was verified by a ¹H NMR chiral solvating agent experiment carried out on compound **13a**; see below). Photolysis (Rayonet merry-go-round, 254 nm, CH₃-

(15) All X-ray analyses were carried out by Fusao Takusagawa of the University of Kansas. The authors have deposited atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
(16) Aubé, J.; Wolfe, M. S. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 925–928.
(17) Stetin, C.; de Jeso, B.; Pommier, J. C. *Synth. Commun.* **1982**, *12*, 495–499.

CN) then gave an inseparable mixture of two lactams **12a** and **12b** in a 2.2:1 ratio (HPLC); as usual,[4g,i,8] the major isomer in this reaction corresponds to that formed by migration of the methylene group anti to the lone pair on the oxaziridine nitrogen.

The mixture of lactams was subjected to Bischler–Napieralski conditions known[2] to induce the desired relative C-3, C-15 syn stereochemistry (yohimbine numbering is used throughout); pentacyclic amines **13a** and **13b** were separately isolated in 60 and 23% yields, respectively. Removal of the now-superfluous carbomethoxy group was accomplished by a route analogous to Okamura's;[4b] this gave **14**, the enantiomer of which had previously been converted to (–)-alloyohimbane by Isobe and co-workers using hydrogenation in 92% yield.[4d]

This synthesis validated the use of an unprotected indole in the oxaziridine-forming reaction, no doubt thanks to the brevity of the low-temperature oxidation reaction. Also note the chemoselectivity of this step vis à vis the double bond in the E ring, which was untouched. Even so, the overall stereoselectivity was still disappointing, and use of the less expensive tryptophan antipode resulted in formation of the unnatural enantiomer of alloyohimbane—we have yet to come up with an acceptable route to the cis-DE series of yohimbinoid alkaloids (e.g., alloyohimbine, reserpine). However, contrast this situation to the analogous sequence as applied to the synthesis of (–)-yohimbane (Scheme 5).

With the directionality of the ring-expansion reaction no longer an issue, achiral tryptamine was condensed with ketone **7** and oxidized, yielding N-epimeric oxaziridines **15a** and **15b** in 75% overall yield. The assignment of the major isomer as **15a**, in which the (3′-indolyl)ethyl substituent is anti to the ring-fusion hydrogen atom occupying the same face of the *trans*-hydrindane as the oxaziridine nitrogen (H$_\beta$ in Scheme 5), is made on the basis of an analogous reaction in the synthesis of E-ring functionalized yohimbine (see compound **19a** in Scheme 7, below). This sensitivity of the nitrogen stereocenter to ring junction stereochemistry turned out to be significant in the synthesis of fully functionalized alkaloid described in the next section. For the time being, however, it suffices to point out that the nitrogen stereocenter disappears in the conversion of oxaziridine to lactam, carried out photochemically as before to provide a single lactam **16** in 77% yield. This material was easily and stereoselectively converted to (–)-yohimbane **3** via Bischler–Napieralski cyclization and hydrogenation. The ee of **3** thus obtained was estimated to be ca. 95% by comparison of specific rotations, which corresponds closely to the ee of starting ketone **7**. Overall, yohimbane was synthesized in six steps and 31% overall yield from ketone **7**.

The Problem of Regioselective E-Ring Functionalization: A Serendipitous Solution. As discussed in the introduction, the local symmetry of the olefins in molecules like **14**, **16**, or **17** make it difficult to imagine methods that could differentiate between the two ends of this functional group (path A, Scheme 6). Alternatively, a group-selective differentiation of an already unsymmetrical *trans*-hydrindane—path B—requires a stereoselective synthesis of the ketone and its regiocontrolled ring expansion; although both are conceivable, the substantial benefit of symmetry in the starting material is lost. We opted instead to try an intermediate route, path C, in which ketone **7** is converted into an analog in which the two ends of the former double bond are now differentiated by their relative stereochemistry in a (presumably) chair-like six-membered ring.
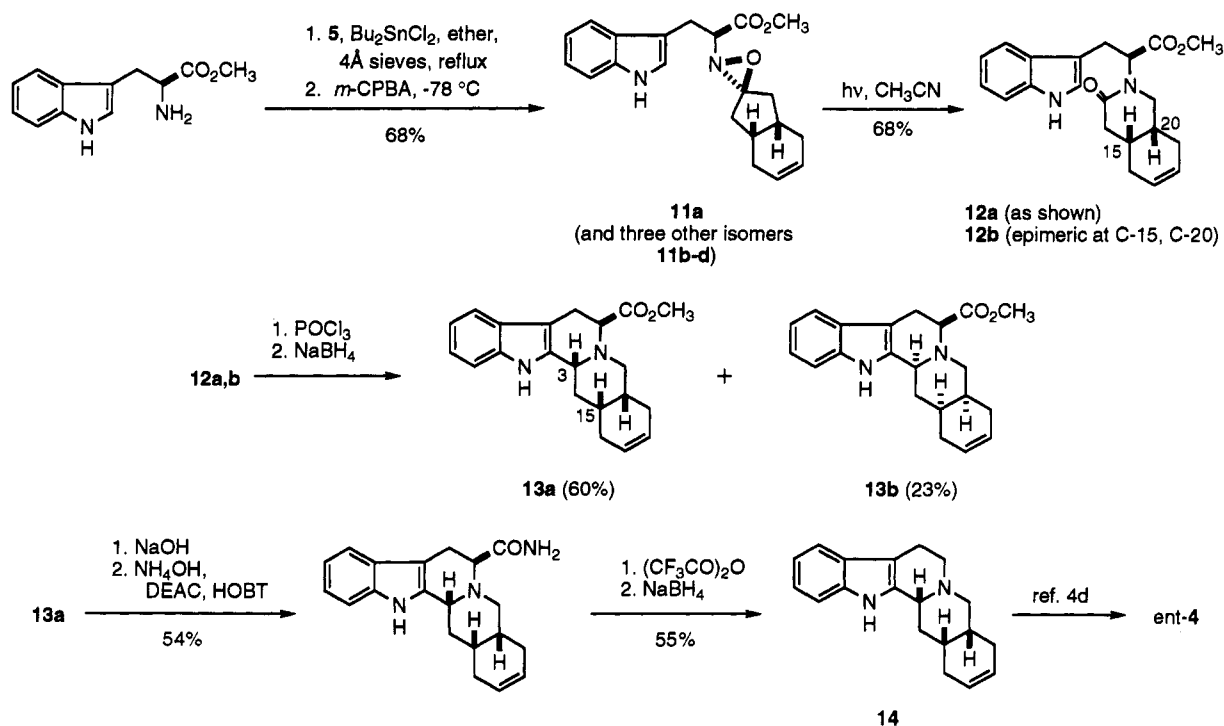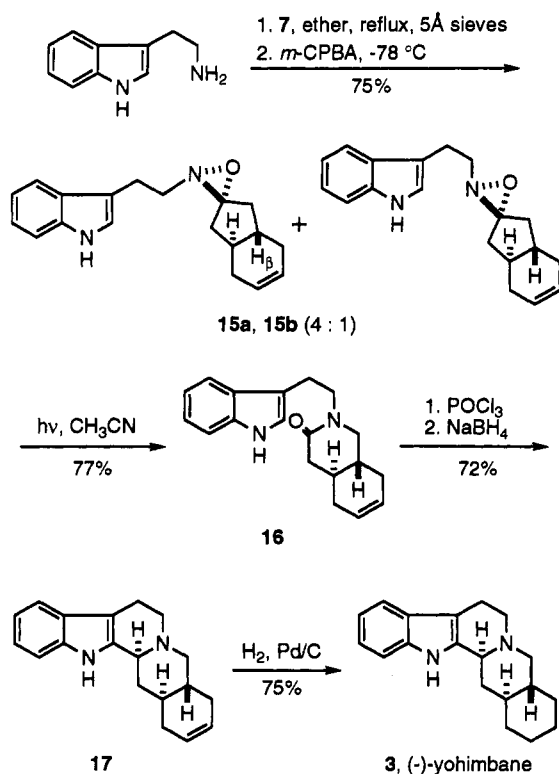
In this way, it was possible to take advantage of the C_2 symmetry of ketone **7** inasmuch as both faces of the double bond are identical. Accordingly, treatment of **7** with osmium tetraoxide followed by acetylation afforded a single diacetoxy ketone (**18**) which was subjected to oxaziridination. Condensation of **18** with tryptamine and oxidation of the resultant imine (*m*-CPBA, –78 °C, 30 min) afforded a mixture of oxaziridines **19a–d** in a combined yield of 90–95%. The four isomers, formed in a ratio of 71:4:13:13

Scheme 4

11a
(and three other isomers
11b–d)

12a (as shown)
12b (epimeric at C-15, C-20)

13a (60%)   +   **13b** (23%)

14

ent-4

Scheme 5

15a, 15b (4 : 1)

16

17   **3**, (-)-yohimbane

(HPLC), respectively, arose via approach of the oxidant from both faces of the bicyclic ketone—relative to the distal acetoxy groups—and again reflects a bias for the substituent on nitrogen to emerge trans to its nearest ring-fusion hydrogen atom (H_α in **19a**). The selectivity obtained in this reaction was remarkable given the distance between the reacting imine and the acetates; we currently do not have a satisfactory explanation for this effect. Molecular models indicate that delivery of the oxidizing agent by the pseudoaxial acetate group would be thwarted by the intervention of one of the ring-fusion hydrogen atoms. In addition,

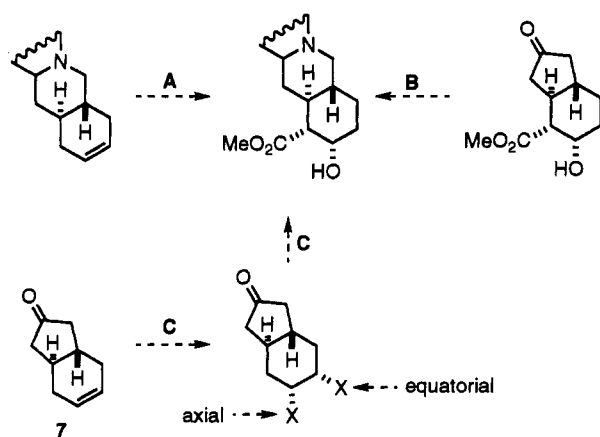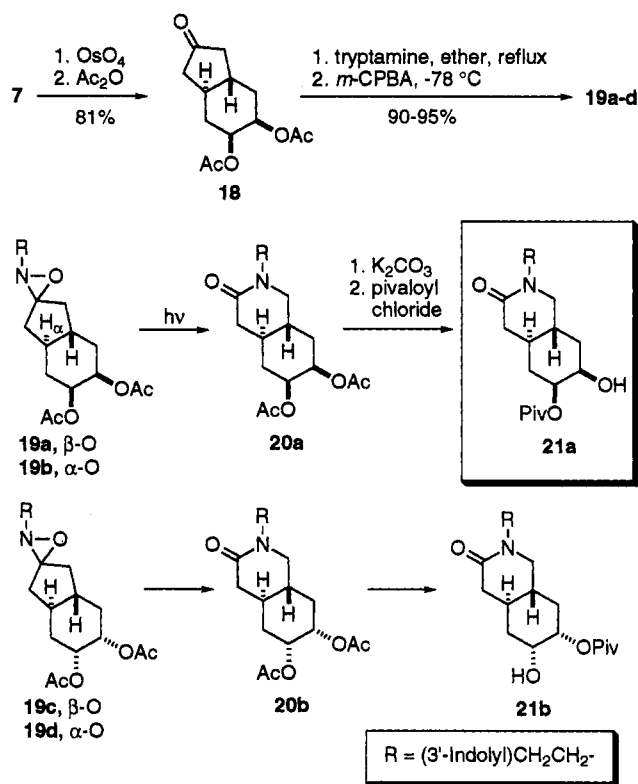**Scheme 6**

the effect seems to be limited to compound **18**; all other combinations of protecting groups tried resulted in diminished selectivity. In any event, the identity of the major isomeric oxaziridine was proven by an X-ray crystallographic study of compound **19a**,[15] which could be isolated by preparative HPLC and subsequent recrystallization.

The mixture of oxaziridines **19a–d** smoothly underwent photolysis to give an inseparable 2.5:1 mixture of lactams **20a,b** in 77% overall yield. The emergence of the trans-fused isoquinolone permitted the easy differentiation of the two hydroxyl groups in each molecule by hydrolysis followed by selective esterification of the equatorial hydroxyl group with pivaloyl chloride, giving lactams **21a** and **21b** in 55 and 25% isolated yields, respectively. In each lactam, the equatorial hydroxyl group has been protected by the bulky esterification agent and its axial partner has been left exposed. The hydroxy esters were differentiated on the basis of a combination of 2D NMR techniques. In both **21a** and **21b**, the methine bearing the alcohol was upfield to and broader than the methine substituted by the pivaloyloxy group. The entire connectivity of the isoquinolone portion of each molecule was ascertained by careful consideration of its COSY and HETCOR spectra. In the case of **21a**, the pivaloyloxy-bearing methine at δ 4.54 could be traced (via only a single
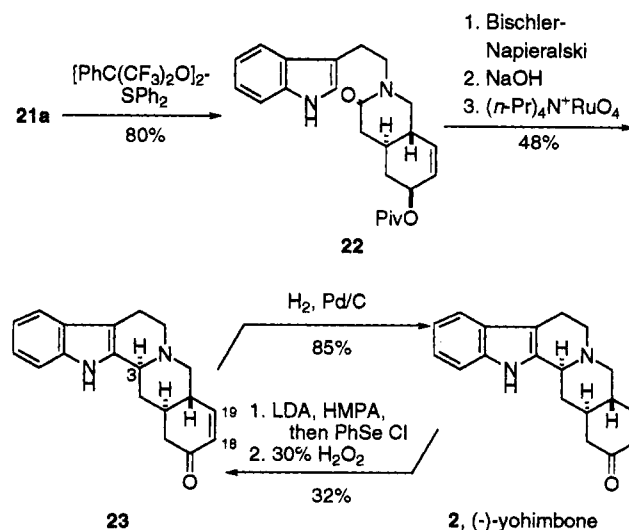
Scheme 7

Scheme 8

Scheme 9

methine, and therefore not crossing the ring fusion) to a methylene group, having protons at 1.96 and 2.28 ppm and no further coupling partners. For **21b**, the analogous methine (4.57 ppm) was similarly connected to a methylene with signals at 2.97 and 3.18 ppm. The methylene group having the downfield pair of signals should be attached to the nitrogen of the lactam instead of the carbonyl group. We therefore assign the monoesterified lactams as shown, with the assignment for **21a** being strongly bolstered by this compound's eventual conversion to yohimbine.[18]

Thus, with the overall chirality of the DE unit being assured by the trans ring fusion (set by the asymmetric Diels–Alder reaction), the oxaziridine → lactam conversion indirectly results in the desymmetrization of the E ring functionality by occurring with an overall preference for migration of the α-methylene group nearest the pseudoaxial acetoxy group three bonds away.

Preparation of a Pivotal E-Ring Enone and the Total Synthesis of (–)-Yohimbone. It is noteworthy that either lactam could in principle be converted to yohimbine, since both are in the same enantiomeric series (as defined by the absolute stereochemistry of the ring junctions) and differ solely with respect to the placement of the hydroxy and pivaloyloxy functional groups. However, only the predominant isomer **21a** was carried on (Scheme 8). Elimination of the hydroxyl group at C-19 was unexpectedly nontrivial, but was eventually effected by treatment with Martin's sulfurane reagent.[19] Practically speaking, this reaction could only be brought on to partial completion, but **22** could be obtained in 80% overall yield by a single recycling maneuver. This compound was subjected to Bischler–Napieralski cyclization, which again resulted solely in the desired C-3 stereochemistry. Hydrolysis of the pivaloyl ester and oxidation[20] led to enone **23**, which had previously been converted to yohimbine in the racemic series.[21] As a bonus, hydrogenation of **23** (H₂, Pd/C, MeOH) gave (–)-yohimbone in 85% yield (and 10% overall from **7**), having
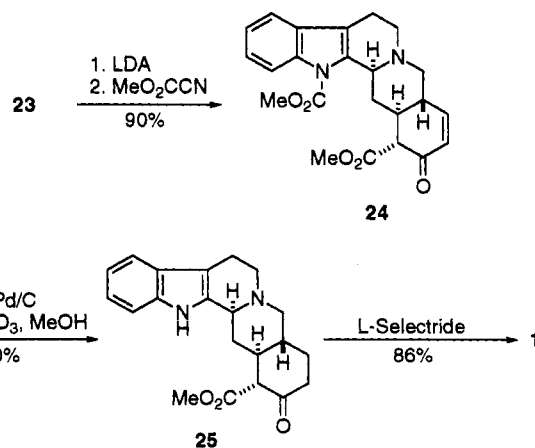
the expected spectral characteristics[4f] and rotation data ([α]D −105.3 (*c* = 0.3, pyridine); lit.[4b] [α]D −108.8 (*c* = 0.34, pyridine)) again consistent with the enantiomeric purity of the starting ketone.

As a structure proof, and to provide more material for the final few experiments of this project, (+)-yohimbine (Aldrich) was converted to (–)-yohimbone, which was converted to enone **23** by a selenation/elimination protocol (Scheme 8). This sequence, which depends on the known[22] propensity of enolates to form toward C-18 in this series, represents a convenient semisynthesis of **23**, expected to be useful for the synthesis of a variety of yohimbine analogs. Enones prepared in both ways had similar physical and spectral properties.[23]

Asymmetric Synthesis of (+)-Yohimbine. As mentioned above, the previous transformation of (±)-**23** to racemic yohimbine by Naito and colleagues[21] might be construed as the basis for a formal synthesis of the target alkaloid. However, in addition to concerns about extrapolating results from experiments carried out on racemic material to enantiomerically enriched substrates, the Naito route depended on literature methods for the reduction of yohimbinone (**25**, Scheme 9) to yohimbine **1**, which only gave the target alkaloid as the minor component of a 3:1 mixture with the C-17 epimer, β-yohimbine.[24,25] We therefore opted to explicitly complete the synthesis.

(18) Details of these assignments can be found in the Ph.D. dissertation of Shomir Ghosh, University of Kansas, 1993.

(19) Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003–5010.

(20) Griffith, W. P.; Ley, S. V. *Alrichichim. Acta* **1990**, *23*, 13–19.

(21) Naito, T.; Hirata, Y.; Miyata, O.; Ninomiya, I. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2219–2225.

(22) Albright, J. D.; Mitscher, L. A.; Goldman, L. *J. Org. Chem.* **1963**, *28*, 38–45.

(23) Enone **23** prepared via total synthesis: mp 228–231 °C, [α]D = −119.8 (*c* = 0.73, CHCl₃). Enone **23** prepared via semisynthesis from (+)-yohimbine (Aldrich): mp 226–228 °C, [α]D = −117.3 (*c* = 0.73, CHCl₃).

(24) Tőke, L.; Honty, K.; Szántay, C. *Chem. Ber.* **1969**, *102*, 3248–3259.

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Accordingly, the presence of the enone in **23** made possible the regioselective placement of the carbomethoxy group at C-16 (cf. **2 → 23** in Scheme 8), along with (in our hands) the superfluous acylation of the indole nitrogen. This was tolerated because superior overall yields were obtained by carrying out the enolate generation/trapping with an excess of LDA and then Mander's reagent,[26] followed by reduction of the $\Delta^{18,19}$ olefin and selective deacylation of the indole nitrogen with K_2CO_3. Yohimbinone **25** thus obtained was then cleanly reduced (≥95% de by NMR and TLC) using L-Selectride following the precedent of Momose, whose group carried out the analogous reduction on an earlier intermediate.[6] Reduction of **25** with $NaBH_4$ gave β-yohimbine,[27] which was shown to be absent from the reaction mixture resulting from the Selectride reduction reaction (TLC, NMR). Overall, then, (+)-yohimbine[28] was synthesized from ketone **7** in 7.8% overall yield and 13 steps despite the loss of the minor regioisomer **21b**.

Summary. We have demonstrated the utility of nitrogen ring-expansion chemistry in the asymmetric, convergent syntheses of yohimbine alkaloids. Conceptually, the stereochemical consequences of using σ- or C_2-symmetrical ketones in such a strategy were demonstrated in the syntheses of members of the both the normal and allo series of yohimbane stereoisomers. In addition, the extension of a group-selective insertion reaction to a remote regiochemical problem has been realized in synthesis of (−)-yohimbine and (+)-yohimbone. Along the way, the issues of stereoselectivity in the final stages common to many approaches to these alkaloids have been sorted out so that a relay route delivering isomerically correct yohimbine as the major product has been accomplished for the first time. Thus, aside from the ring expansion step, which had a selectivity of 2.2–2.5:1 and in which either product could have been brought onward, every step that generated one or more stereocenter was accomplished in better than 95% de. And pragmatically, a convergent method applicable to the synthesis of yohimbine congeners bearing other AB ring systems, such as berbane-derived α_2 antagonists (e.g. **26**),[29] has been realized.
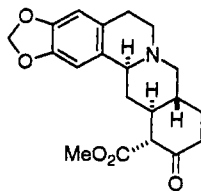
26

Experimental Section

General Methods. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-500 Aspect 3000 (500 and 125.5 MHz, respectively), QE 300, or a Varian XL 300 (300 and 75.6 MHz, respectively) instrument. All NMR samples were dissolved in deuteriochloroform except where indicated, and the chemical shifts are expressed in parts per million (δ) relative to tetramethylsilane with either TMS or residual chloroform as an internal reference. Abbreviations are: s, singlet; d, doublet; t, triplet; q, quartet; br, broad. Infrared spectra were recorded on a Perkin-Elmer 1420 spectrometer. Low-resolution mass spectra (EI, electron impact or CI, chemical ionization) were obtained using a Ribermag R10-10

quadrupole instrument and high-resolution mass spectra (HRMS) were obtained using a VG Analytical ZAB double focusing spectrometer. Optical rotations were taken on a Perkin-Elmer 241 polarimeter and the concentrations are reported in g/dL. Melting points were determined using a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were carried out in-house. HPLC was done using a Shimadzu LC-6A with two pumps and an SPD-6A UV detector set at 254 nm. A Chromegasphere SI-60 (25 cm × 4.6 mm) silica gel column was used for analytical work. An AllTech Econosil silica gel column (250 mm × 10 mm) was used for preparative work. THF was distilled from sodium benzophenone ketyl; other solvents were dried over molecular sieves before use. Except where noted, all starting materials were purchased from Aldrich and used as received.

cis-1,3,3a,4,7,7a-Hexahydro-2(*H*)-inden-2-one (5). Diacid 9[9] (10 g, 50 mmol) and EtOH (23.6 g, 30 mL, 514 mmol) were heated under reflux in benzene (100 mL) in the presence of *p*-TsOH (200 mg) for 2 days. The reaction mixture was cooled to rt and diluted with ether. The reaction mixture was then washed with saturated aqueous $NaHCO_3$ and brine and dried over Na_2SO_4. The solvent was evaporated and the residue was used for the next reaction. The crude diester in dry THF (50 mL) was added dropwise to a suspension of NaH (3.72 g, 157 mmol) in dry THF (50 mL). After the addition was complete, the reaction mixture was heated under reflux for 4.5 h. On cooling to rt, glacial AcOH (10 mL) was added to the reaction mixture. The resulting mixture was diluted with ether and washed with saturated aqueous $NaHCO_3$ and brine and dried over Na_2SO_4. The crude β-keto ester obtained on evaporation of the solvent was utilized for the next reaction. The crude substrate, dissolved in DMSO (80 mL) and water (4 mL), was heated at 155 °C for 4.5 h. Upon cooling, the reaction mixture was poured into water (60 mL) and the resulting solution extracted several times with hexane. The combined hexane layers were dried with Na_2SO_4 and concentrated. Column chromatography (15–20% EtOAc/hexane) of the residue provided **5**[13] as a colorless oil (5.6 g, 82% overall yield from **9**): bp 106–108 °C/10 mm Hg; ^1H NMR (300 MHz, $CDCl_3$) δ 1.91 (m, 2H), 2.06 (dd, J = 6.3, 18.6 Hz, 2H), 2.24–2.35 (m, 4H), 2.40–2.45 (m, 2H), 5.69 (t, J = 1.5 Hz, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 26.7, 32.7, 45.0, 125.0, 220.1; IR (neat) 1130, 1400, 1740, 2900 cm^{-1}; MS (CI/NH_3) *m/e* 152 (M$^+$ + 16), 135 (M$^+$ − 1), 119, 108 (100), 94, 79, 68, 54.

(1S,2S)-4-Cyclohexene-1,2-diacetic acid. A mixture of (1*R*,2*R*)-bis-[(*p*-toluenesulfonyloxy)methyl]-4-cyclohexene[30] (117 g, 0.258 mol) and NaCN (40.1 g, 0.818 mol) in 400 mL of DMSO was heated at 95–105 °C for 5 h. The hot reaction mixture was poured into ice water and a tan solid precipitated. The resulting suspension was maintained at 0 °C for 1 h. The suspension was then filtered, the precipitate was dried under vacuum and dissolved in 400 mL of 40% aqueous KOH, and the resulting solution was refluxed for 24 h. The reaction mixture was cooled and acidified with 85% H_3PO_4. The resulting suspension was extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$, and concentrated to yield 36 g (71%) of the title compound: mp 153–155 °C (EtOAc); ^1H NMR (300 MHz, DMSO-d_6) δ 1.70 (m, 2H), 1.86 (m, 2H), 2.01–2.09 (m, 4H), 2.28 (dd, J = 4.6, 15.1 Hz, 2H), 5.52 (s, 2H), 12.05 (s, 2H); ^{13}C NMR (75.6 MHz, DMSO-d_6) δ 28.9, 33.7, 38.9, 125.8, 174.7; IR (KBr pellet) 1170, 1250, 1270, 1400, 1690 (br), 2900 cm^{-1}; MS (EI) *m/e* 181, 180, 139, 138, 121, 105, 79, 77, 60 (100); [α]$_D$ = −55.1 (*c* = 1.02, MeOH). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.51; H, 7.12. Found: C, 60.90; H, 7.20.

(3a*S*,7a*S*)-1,3,3a,4,7,7a-Hexahydro-2*H*-inden-2-one (7). (1*S*,2*S*)-4-Cyclohexene-1,2-diacetic acid (5.1 g, 25 mmol) was treated as described for **9** to provide **7** as colorless needles (2.59 g, 75% overall yield from the diacid): mp 66–67 °C; R_f 0.40 (25% EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 1.86–1.97 (m, 6H), 2.37–2.50 (m, 4H), 5.75 (d, J = 3.2 Hz, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 31.4, 38.8, 45.3, 126.6, 217.5; IR (CCl_4) 660, 1050, 1125, 1180, 1400, 1430, 1740, 2820, 2880, 3020 cm^{-1}; MS (EI) *m/e* 136 (M$^+$, 100), 108, 91, 79, 67, 54; [α]$_D$ = +105.0 (*c* = 1.13, EtOH). Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.08; H, 9.18.

Oxaziridine 11a and Isomers. A mixture of ketone **5** (0.101 g, 0.74 mmol), L-tryptophan methyl ester (0.325 g, 1.48 mmol), crushed 5 Å molecular sieves (0.250 g), and dibutyltin dichloride (0.045 g, 0.15 mmol) in 10 mL of dry ether was heated at reflux under N_2 for 36 h. The reaction mixture was cooled to rt and then added dropwise under nitrogen to a solution of *m*-CPBA (0.166 g, 0.96 mmol) in 10 mL of dry ether at −78 °C. The resulting mixture was stirred for 30 min. **Standard**

(25) The catalytic hydrogenation of yohimbinone to yohimbine has been reported in 24% yield: Ziegler, F.; Sweeny, J. G. *J. Org. Chem.* **1969**, *34*, 3545–3548. We did not attempt to repeat this work as we found the Selectride reduction described in the text satisfactory.

(26) Mander, L. N.; Sethi, P. *Tetrahedron Lett.* **1983**, *24*, 5425–5428.

(27) Interestingly, we did not observe any yohimbine from this reduction, in contrast to literature precedent.[24]

(28) Synthetic material gave mp 233–235 °C, [α]$_D$ = +52.3 (*c* = 0.59, EtOH); authentic material (Aldrich) mp 231–233 °C, [α]$_D$ = +55.6 (*c* = 2, EtOH). The spectral data for both compounds (500 MHz ^1H NMR, ^{13}C NMR, IR, MS) were identical.

(29) Vizi, E. S.; Tóth, I.; Somogyi, G. T.; Szabó, L.; Harsing, L. G.; Szántay, C. *J. Med. Chem.* **1987**, *30*, 1355–1359 and references contained therein.

(30) Kokke, W. C. M. C.; Varkevisser, F. A. *J. Org. Chem.* **1974**, *39*, 1535–1539.

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Workup for Oxaziridinations. The reaction mixture was then warmed to rt, diluted with ether, and washed with 10% aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (25% EtOAc/hexane) to yield 0.180 g (68%) of a mixture of oxaziridines. The main isomer (**11a**): ^1H NMR (500 MHz, CDCl$_3$) δ 1.27 (m, 1H), 1.43 (m, 1H), 1.56 (dd, $J = 9.0$, 14.4 Hz, 1H), 1.74–1.79 (m, 2H), 1.85 (dd, $J = 6.5$, 14.6 Hz, 1H), 1.93–1.98 (m, 2H), 2.08 (m, 1H), 2.22 (m, 1H), 3.26 (dd, $J = 7.3$, 13.8 Hz, 1H), 3.31–3.41 (m, 2H), 3.73 (s, 3H), 5.45 (s, 2H), 7.06 (d, $J = 2.3$ Hz, 1H), 7.11 (m, 1H), 7.18 (m, 1H), 7.35 (d, $J = 8.1$ Hz, 1H), 7.58 (d, $J = 7.9$ Hz, 1H), 8.22 (s, 1H); ^{13}C NMR (125.5 MHz, CDCl$_3$) δ 25.9, 26.0, 26.7, 32.4, 32.9, 33.8, 40.5, 52.3, 68.8, 94.0, 110.1, 111.3, 118.6, 119.8, 122.4, 123.0, 124.0, 124.9, 127.2, 136.2, 171.2; IR (CHCl$_3$) 710, 1210, 1740, 3000 cm^{-1}; MS (EI) *m/e* 352 (M$^+$), 223, 216, 201 (100), 170, 130, 102, 91, 79, 49. **11c**: ^1H NMR (500 MHz, CDCl$_3$) δ 3.76 (s, 3H); **11d**: δ 3.86 (s, 3H); **11b**: δ 3.90 (s, 3H).

Racemic **11** was prepared in a similar manner, except that the imine was formed by condensing L-Trp-OMe with **5** in refluxing toluene prior to treatment with *m*-CPBA. The oxaziridines thus obtained had identical spectral data to that described above. The major isomer was isolated by HPLC (20% EtOAc/hexane, silica gel column, retention time 24.2 min); this material was submitted for X-ray crystallographic analysis[15] and elemental analysis. Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.51; H, 7.00; N, 7.85.

Lactams 12a and 12b. Standard Photolysis Procedure. The mixture of oxaziridines **11** (1.9 g, 5.4 mmol) was dissolved in CH$_3$CN (400 mL) in a quartz tube. The solution was degassed with N$_2$ for 20 min and then photolyzed, in a Rayonet RPR-100 chamber reactor (2537 Å), at reactor temperature for 5 h. The reaction mixture was concentrated and the residue chromatographed (50–70% EtOAc/hexane) to afford the title compound (a mixture of isomers) as a solid (1.35 g, 71%). **12a**: R_f 0.45 (EtOAc); ^1H NMR (500 MHz, CDCl$_3$) δ 1.76–1.85 (m, 3H), 1.91–2.13 (m, 4H), 2.34 (m, 1H), 3.01 (dd, $J = 5.9$, 11.7 Hz, 1H), 3.22 (dd, $J = 4.9$, 11.7 Hz, 1H), 3.36 (m, 1H), 3.46 (dd, $J = 5.3$, 15.7 Hz, 1H), 3.75 (s, 3H), 5.43 (m, 1H), 5.53 (s, 2H), 7.04 (d, $J = 1.3$ Hz, 1H), 7.12 (m, 1H), 7.19 (m, 1H), 7.36 (m, 1H), 7.60 (d, $J = 7.7$ Hz, 1H), 8.36 (s, 1H); ^{13}C NMR (125.6 MHz, CDCl$_3$) δ 23.8, 25.3, 28.2, 28.9, 29.8, 35.1, 48.1, 52.2, 56.7, 110.9, 111.3, 118.2, 119.3, 121.9, 122.2, 124.3, 124.5, 127.3, 136.2, 170.2, 171.6; IR (KBr pellet) 740, 1200, 1430, 1480, 1610, 1740, 2900, 3240 cm^{-1}; MS (EI) *m/e* 352 (M$^+$), 293, 201 (100), 170, 130, 84, 77, 49; HRMS calcd for $C_{21}H_{24}N_2O_3$ 352.1787, found 352.1789. **12b**: ^1H NMR (500 MHz, CDCl$_3$) δ 2.95 (dd, $J = 5.2$, 11.7 Hz, 1H), 3.13 (dd, $J = 7.7$, 11.7 Hz, 1H), 3.75 (s, 3H), 5.16 (m, 1H); ^{13}NMR (125.6 MHz, CDCl$_3$) δ 26.2, 28.9, 36.1, 52.2, 58.0, 111.0, 111.2, 118.3, 119.2, 121.8, 122.4, 124.1, 124.6, 127.3, 136.1, 169.9, 171.5.

(3R,5S,15R,20R)-5-Carbomethoxy-17,18-didehydroalloyohimbane (13a) and 5β-Carbomethoxy-17,18-didehydroalloyohimbane (13b). General Bischler–Napieralski Procedure. The lactam mixture **12a,b** (0.183 g, 0.52 mmol) was refluxed in 0.77 mL (7.7 mmol) of freshly distilled POCl$_3$ for 30 min under N$_2$. Then, 5 mL of dry benzene was added and the reaction mixture refluxed for 2.5 h. The solvent was evaporated and the residue dissolved in 10 mL of MeOH. NaBH$_4$ (0.075 g) was added and the reaction mixture was stirred at rt for 1 h, after which it was quenched with glacial AcOH. The solvent was evaporated and the residue was dissolved in EtOAc. The resulting solution was washed with saturated aqueous NaHCO$_3$ and brine and dried over MgSO$_4$. The residue obtained on concentration was chromatographed with 15% EtOAc/hexane, and 0.104 g (60%) of the major diastereomer **13a** and 0.040 g (23%) of the minor diastereomer **13b** were isolated. **13a**: mp 168–170 °C; R_f 0.70 (25% EtOAc/hexane); ^1H NMR (500 MHz, CDCl$_3$) δ 1.61–1.71 (m, 2H), 1.79–1.94 (m, 3H), 2.07 (m, 1H), 2.40 (m, 1H), 2.55 (m, 1H), 2.68 (dd, $J = 1.8$, 11.3 Hz, 1H), 3.10–3.21 (m, 2H), 3.30 (dd, $J = 2.8$, 11.3 Hz, 1H), 3.57 (s, 3H), 3.73 (d, $J = 5.3$ Hz, 1H), 4.26 (d, $J = 10.1$ Hz, 1H), 5.50–5.60 (m, 2H), 7.04–7.11 (m, 2H), 7.25 (m, 1H), 7.44 (d, $J = 7.6$ Hz, 1H), 7.68 (s, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 24.9, 25.0, 31.3, 32.0, 33.0, 33.5, 51.1, 53.5, 57.8, 61.5, 105.3, 110.6, 117.9, 119.2, 121.2, 123.4, 125.9, 127.2, 135.3, 136.0, 173.6; IR (CHCl$_3$) 660, 710, 1195, 1725, 3000 cm^{-1}; MS (EI) *m/e* 336 (M$^+$), 321, 277 (100), 169, 154, 144, 115, 84, 77, 47; $[\alpha]_D = +100.7$ ($c = 1.13$, CHCl$_3$). Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.96; H, 7.19; N, 8.32; found: C, 74.98; H, 7.50; N, 8.30. **13b**: mp 176–178 °C; R_f 0.60 (25% EtOAc/hexane); ^1H NMR (500 MHz, CDCl$_3$) δ 1.78–1.89 (m, 3H), 1.94–2.06 (m, 3H), 2.37–2.45 (m, 2H), 2.64 (br s, 1H), 2.82 (dd, $J = 2.4$, 10.8 Hz, 1H), 2.97 (ddd, $J = 1.5$, 4.3, 15.0 Hz, 1H), 3.12 (m, 1H), 3.42–3.47 (m, 2H), 3.81 (s, 3H), 5.51 (m, 1H), 5.62 (m, 1H), 7.06–7.15 (m, 2H), 7.29 (d, $J = 8.0$ Hz, 1H), 7.42 (d, $J = 7.7$ Hz, 1H), 7.76 (s, 1H); ^{13}C NMR (75.6 MHz,

CDCl$_3$) δ 25.2, 26.0, 30.7, 31.8, 32.3, 32.9, 51.9, 56.9, 59.4, 65.0, 105.8, 110.8, 117.9, 119.5, 121.5, 123.1, 125.9, 127.0, 134.0, 135.9, 174.0; IR (CHCl$_3$) 660, 710, 1210, 1730, 3000 cm^{-1}; MS (EI) *m/e* 336 (M$^+$), 321, 277 (100), 169, 84, 77, 49; $[\alpha]_D = -81.5$ ($c = 1.1$, CHCl$_3$); HRMS calcd for $C_{21}H_{24}N_2O_2$ 336.1838, found 336.1826.

(3R,5S,15R,20R)-5-Carboxy-17,18-didehydroalloyohimbane. Compound **13a** (0.319 g, 0.95 mmol) was treated with 2 g of NaOH in MeOH (50 mL) under reflux for 48 h. The solvent was evaporated and the residue taken up in H$_2$O. The pH was adjusted to 7 with 2 M HCl and the solution extracted several times with EtOAc. The organic phases were combined and dried over Na$_2$SO$_4$. Column chromatography (3–15% MeOH/CH$_2$Cl$_2$) of the residue obtained on concentration provided **14** (0.270 g, 88%) as a white solid: mp 227–229 °C; R_f 0.40 (15% MeOH/CH$_2$Cl$_2$); ^1H NMR (500 MHz, DMSO-d_6) δ 1.34 (q, $J = 11.6$ Hz, 1H), 1.75–1.98 (m, 6H), 2.36 (d, $J = 15.8$ Hz, 1H), 2.70 (d, $J = 11.1$ Hz, 1H), 2.90–3.04 (m, 2H), 3.15–3.26 (m, 2H (partially obscured by residual DMSO)), 3.67 (br s, 1H), 4.14 (d, $J = 10.4$ Hz, 1H), 5.52–5.57 (m, 2H), 6.91 (t, $J = 7.3$ Hz, 1H), 6.98 (t, $J = 7.5$ Hz, 1H), 7.24 (d, $J = 8.0$ Hz, 1H), 7.34 (d, $J = 7.7$ Hz, 1H), 10.71 (s, 1H); ^{13}C NMR (125.6 MHz, DMSO-d_6) δ 24.7, 24.8, 31.0, 31.4, 32.5, 32.8, 53.4, 57.1, 60.7, 104.0, 110.9, 117.3, 118.2, 120.3, 123.6, 125.7, 126.6, 135.8, 136.0, 174.4; IR (KBr pellet) 740, 1160, 1450, 1610, 2900, 3400 cm^{-1}; MS (EI) *m/e* 322 (M$^+$), 277, 44 (100); $[\alpha]_D = +94.5$ ($c = 1.04$, pyridine); HRMS calcd for M$^+$ + 1: 323.1760, found 323.1777.

(3R,5S,15R,20R)-5-Carbamoyl-17,18-didehydroalloyohimbane. (3R,5S,15R,20R)-5-Carboxy-17,18-didehydroalloyohimbane (0.100 g, 0.32 mmol) was suspended in anhydrous DMF (4 mL). 1-[3-(Dimethyamino)propyl]-3-ethylcarbodiimide hydrochloride (0.060 g, 0.32 mmol) and *N*-hydroxybenzotriazole (0.042 g, 0.32 mmol) were added and the reaction mixture was stirred at rt until all of the solid ingredients were dissolved (ca. 10 min). Concentrated ammonium hydroxide (0.5 mL) was added to the mixture and stirring was continued for an additonal 5 h. DMF was removed by distillation and the residue partitioned between H$_2$O and CH$_2$Cl$_2$ mixture. The water layer was extracted several times with CH$_2$Cl$_2$ and the combined organic layers dried over Na$_2$SO$_4$. The residue was chromatographed with 50–60% EtOAc/hexane as the eluent to give 0.063 g (64%) of the title amide: mp 231–233 °C; R_f 0.60 (EtOAc); ^1H NMR (500 MHz, DMSO-d_6) δ 1.34 (q, $J = 12.0$ Hz, 1H), 1.76–1.98 (m, 5H), 2.33–2.45 (m, 2H), 2.66 (br d, $J = 11.0$ Hz, 1H), 2.82 (br d, $J = 15.0$ Hz, 1H), 2.97–3.05 (m, 2H), 3.52 (d, $J = 6.9$ Hz, 1H), 4.24 (d, $J = 10.9$ Hz, 1H), 5.57–5.74 (m, 2H), 6.71 (br s, 1H), 6.89–6.99 (m, 2H), 7.15 (br s, 1H), 7.23 (d, $J = 7.8$ Hz, 1H), 7.30 (d, $J = 7.7$ Hz, 1H), 10.61 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 24.8, 24.9, 30.9, 31.5, 32.5, 32.6, 53.6, 57.0, 60.4, 103.6, 110.7, 117.1, 118.0, 120.0, 123.7, 125.6, 126.8, 135.9, 136.2, 174.6; IR (KBr pellet) 730, 1180, 1330, 1450, 1660, 2890, 3300 cm^{-1}; MS (EI) *m/e* 321 (M$^+$ − 1), 277 (100), 168, 149, 119, 115, 97, 91, 83, 77, 71, 63, 47; $[\alpha]_D = +50.6$ ($c = 0.43$, MeOH); HRMS calcd for $C_{20}H_{23}N_3O$: 321.1841, found 321.1834.

(3R,15R,20R)-17,18-Didehydroalloyohimbane (14). (3R,5S,15R,20R)-5-Carbamoyl-17,18-didehydroalloyohimbane (0.046 g, 0.14 mmol) was dissolved in dry CH$_2$Cl$_2$, and pyridine (0.026 mL, 0.31 mmol) was added. The reaction mixture was cooled to 0 °C in an ice bath and treated with trifluoroacetic anhydride (0.029 mL, 0.21 mmol). The resulting solution turned red after a few minutes. The reaction mixture was allowed to warm to rt over 1.5 h. The mixture was then poured into water and the aqueous layer was extracted with CH$_2$Cl$_2$. The organic layers were combined and washed with saturated aqueous NaHCO$_3$ and brine and dried over Na$_2$SO$_4$. The crude nitrile thus obtained was dissolved in THF (5 mL), EtOH (1.8 mL), and pyridine (0.3 mL), and the resulting solution was heated to 60 °C. NaBH$_4$ (0.104 g 2.7 mmol) was added to the hot solution in four portions over a period of 8 h and the reaction mixture stirred at that temperature for an additional 12 h. The solvents were evaporated, and the residue was taken up in CH$_2$Cl$_2$ and washed with water. The organic phase was dried over Na$_2$SO$_4$ and concentrated. Column chromatography (10–20% EtOAc/hexane) of the residue provided the title compound[4d] (0.021 g, 55%) as a white solid: mp 108–110 °C; R_f 0.40 (30% EtOAc/hexane); ^1H NMR (500 MHz, CDCl$_3$) δ 1.64–2.01 (m, 6H (partially obscured by residual water)), 2.40 (br d, $J = 16.6$ Hz, 1H), 2.52–2.69 (m, 4H), 2.81 (d, $J = 11.2$ Hz, 1H), 2.91–3.00 (m, 2H), 3.20 (m, 1H), 5.53–5.58 (m, 2H), 7.04–7.11 (m, 2H), 7.35 (d, $J = 10.6$ Hz, 1H), 7.44 (d, $J = 7.5$ Hz, 1H), 7.74 (s, 1H); ^{13}C NMR (75.6 MHz, CDCl$_3$) δ 22.3, 25.9, 31.6, 32.3, 32.4, 33.5, 53.6, 60.6, 61.0, 108.5, 111.1, 118.5, 119.8, 121.6, 123.7, 126.5, 127.9, 135.9, 136.3; IR (CHCl$_3$) 1240, 1450, 1630, 2920 cm^{-1}; MS (EI) *m/e* 277 (M$^+$ − 1, 100), 221, 184, 169, 156, 154, 144, 128, 115, 91, 84, 77, 67, 49; $[\alpha]_D = +63.3$

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(c = 0.66, CHCl$_3$) (lit. for the (3S,15S,20S)-isomer[4d] [α]$_D$ = –57.9 (c = 1.00, CHCl$_3$)).

Oxaziridines 15a,b. A mixture of ketone 7 (0.11 g, 0.73 mmol), tryptamine (0.233 g, 1.46 mmol), and crushed 5 Å molecular sieves (0.292 g) in 10 mL of dry Et$_2$O was heated at reflux under N$_2$ for 18 h. The reaction mixture was cooled to rt and then added dropwise to a solution of *m*-CPBA (73%, 0.208 g, 0.88 mmol) in 10 mL of dry ether at –78 °C under N$_2$. The resulting mixture was stirred for 30 min. The reaction mixture was worked up and the residue purified by column chromatography (15% EtOAc/hexane) to yield 0.162 g (75%) of a mixture of oxaziridines 15a,b (R_f 0.30 (25% EtOAc/hexane)). 15a: ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.33 (m, 1H), 1.47–2.25 (m, 9H), 2.92 (m, 1H), 3.10–3.24 (m, 3H), 5.67 (br s, 2H), 7.10 (s, 1H), 7.10–7.23 (m, 2H), 7.36 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 7.4 Hz, 1H), 8.09 (s, 1H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 24.2, 31.2, 31.5, 34.9, 39.0, 39.7, 40.6, 56.7, 91.7, 111.2, 113.3, 118.7, 119.3, 121.8, 126.5, 126.6 126.8, 127.3, 136.2; IR (CCl$_4$) 660, 710, 1210, 1340, 1370, 1420, 1430, 2900, 3000, 3460 cm^{-1}; MS (EI) 294 (M$^+$), 164, 143 (100), 130, 93, 91, 77, 41. Anal. Calcd for C$_{19}$H$_{22}$N$_2$O: C, 77.51; H, 7.53; N, 9.52. Found: C, 77.54; H, 7.69; N, 9.52. 15b: ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 24.2, 31.3, 32.9, 38.7, 40.1, 41.3, 57.5.

Lactam 16. Oxaziridines 15a,b (0.204 g, 0.69 mmol) were dissolved in 15 mL of acetonitrile and photolyzed for 5 h. The reaction mixture was concentrated and the residue chromatographed (2% MeOH/CH$_2$-Cl$_2$) to afford the title compound as a solid (0.159 g, 77%): mp 238–240 °C; R_f 0.30 (50% EtOAc/hexane); ^{1}H NMR (300 MHz, CD$_2$Cl$_2$) δ 1.52–1.67 (m, 4H), 1.88–2.14 (m, 3H), 2.48 (m, 1H), 2.83–2.94 (m, 3H), 3.16 (m, 1H), 3.50–3.58 (m, 2H), 5.58 (br s, 2H), 6.98–7.08 (m, 5H), 7.29 (d, J = 7.9 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H), 8.17 (br s, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 22.9, 28.6, 31.9, 32.6, 33.6, 39.4, 48.1, 54.4, 111.1, 113.2, 118.8, 119.3, 121.9, 122.0, 124.9, 125.7, 127.5, 136.2, 169.4; IR (CHCl$_3$) 740, 1230, 1340, 1440, 1500, 1610, 3300 cm^{-1}; MS (EI) *m/e* 294 (M$^+$), 164, 143 (100), 130, 79, 77, 44; [α]$_D$ = +10.09 (c = 1.02, pyridine). Anal. Calcd for C$_{19}$H$_{22}$N$_2$O: C, 77.51; H, 7.53; N, 9.51. Found: C, 77.70; H, 7.90; N, 9.40.

17,18-Didehydroyohimbane (17). Lactam 16 (0.142 g, 0.48 mmol) was submitted to the standard Bischler–Napieralski procedure. The residue obtained on concentration was chromatographed with 2% MeOH/ CH$_2$Cl$_2$, and 0.097 g (72%) of 17 was isolated: mp 209–210 °C (EtOH); R_f 0.50 (EtOAc); ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.35–1.57 (m, 2H), 1.70–1.87 (m, 3H), 2.04–2.19 (m, 4H), 2.59–2.71 (m, 2H), 2.97–3.14 (m, 3H), 3.34 (m, 1H), 5.69 (d, J = 3.0 Hz, 2H), 7.05–7.16 (m, 2H), 7.30 (m, 1H), 7.47 (m, 1H), 7.79 (br s, 1H); ^{13}C NMR (75.6 MHz, CDCl$_3$) δ 21.0, 29.3, 31.7, 35.9 (2 signals), 36.4, 52.4, 59.7, 60.9, 107.7, 110.9, 118.1, 119.4, 121.5, 125.8, 126.2, 127.2, 133.7, 136.1; IR (CDCl$_3$) 652, 965, 1380, 1460, 1560, 2260, 2360, 2900 cm^{-1}; MS (EI) *m/e* 277 (M$^+$ – 1, 100), 184, 169, 156, 143, 115, 91, 79, 77, 42; [α]$_D$ = –178.3 (c = 0.52, CHCl$_3$).

(–)-Yohimbane (3). A solution of 17 (0.107 g, 0.38 mmol) in 20 mL of dry THF was hydrogenated (55–65 psi) for 4 h, with 10% Pd/C as catalyst. The reaction mixture was filtered through a bed of Celite. The filtrate was concentrated and the residue obtained was recrystallized to give 3 as fine white needles (0.081 g, 75%): mp 204–205 °C (EtOH); R_f 0.50 (5% MeOH/CH$_2$Cl$_2$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.02–1.47 (m, 7H), 1.61–1.77 (m, 4H), 1.97 (d, J = 12.1 Hz, 1H), 2.12 (t, J = 10.9 Hz, 1H), 2.64 (m, 1H), 2.71 (d, J = 15.0 Hz, 1H), 2.90 (m, 1H), 2.98–3.10 (m, 2H), 3.27 (d, J = 10.9 Hz, 1H), 7.06–7.13 (m, 2H), 7.28 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 7.4 Hz, 1H), 7.74 (s, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 21.7, 25.9, 26.4, 30.3, 32.8, 36.9, 41.9, 53.1, 60.2, 62.0, 108.0, 110.7, 118.1, 119.3, 121.2, 127.5, 135.1, 135.9; IR (KBr pellet) 740, 1100, 1140, 1260, 1280, 1300, 1320, 1440, 2740, 2780, 2840, 2900, 3400 cm^{-1}; MS (EI) *m/e* 279 (M$^+$ – 1, 100), 184, 169, 156, 143, 67; [α]$_D$ = –77.1 (c = 0.5, EtOH) (lit.[31] [α]$_D$ = –81.0 (c = 0.5, EtOH)).

(3aS,5R,6S,7aS)-5,6-Diacetoxy-1,3,3a,4,7,7a-hexahydro-2(*H*)-inden-2-one (18). A solution of ketone 7 (2.01 g, 14.6 mmol) and *N*-methylmorpholine (2.41 g, 20.2 mmol) in 10 mL of 90% acetone/water was treated with a 0.02 M solution of OsO$_4$ in toluene (2.2 mL) and the reaction mixture stirred at rt for 15 h. The reaction mixture was quenched with Na$_2$S$_2$O$_5$ (1.93 g), stirred for 1 h, diluted with CH$_2$Cl$_2$, and finally dried with Na$_2$SO$_4$. The mixture was filtered, concentrated, and the residue purified by column chromatography (80% EtOAc/hexane) to yield 1.9 g (80%) of diol: mp 116–118 °C; R_f 0.30 (EtOAc); ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.39–2.40 (m, 10H), 3.37 (m, 2H), 3.77 (br s, 1H),

4.11 (br s, 1H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 33.6, 35.2, 35.9, 41.3, 44.4, 44.9, 69.4, 71.6, 217.7; IR (CHCl$_3$) 710, 1010, 1030, 1210, 1740, 3000, 3600 cm^{-1}; MS (EI) *m/e* 170 (M$^+$), 152, 126, 95, 70 (100), 41; [α]$_D$ = +231 (c = 1.16, CHCl$_3$). Anal. Calcd for C$_9$H$_{14}$O$_3$: C, 63.50; H, 8.29; found: C, 63.58; H, 8.60.

The above diol (2.51 g, 14.6 mmol) was treated with 4-(dimethylamino)-pyridine (0.050 g, 0.41 mmol) and Ac$_2$O (4.03 mL, 43.8 mmol) in 30 mL of pyridine at rt for 3 h. The reaction mixture was diluted with CH$_2$Cl$_2$ and washed with 2 M HCl, saturated aqueous NaHCO$_3$, and brine. The organic phases were combined, dried over Na$_2$SO$_4$, and concentrated. The residue was purified by column chromatography (45% EtOAc/ hexane) to yield 3.66 g (98%) of 18: mp 85–87 °C (hexane); R_f 0.60 (50% EtOAc/hexane); ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.54 (m, 1H), 1.71–2.22 (m, 13H), 2.33–2.45 (m, 2H), 4.93 (m, 1H), 5.42 (d, J = 2.8 Hz, 1H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 20.6, 20.7, 30.7, 33.2, 36.6, 40.9, 43.8, 44.3, 68.7, 71.6, 169.8, 169.8, 215.4; IR (CCl$_4$) 720, 1230, 1240, 1740 cm^{-1}; MS (EI) *m/e* 255 (M$^+$ + 1), 194, 169, 152, 134, 125, 108, 95, 43 (100); [α]$_D$ = +121 (c = 1.10, CHCl$_3$). Anal. Calcd for C$_{13}$H$_{18}$O$_5$: C, 61.40; H, 7.13. Found: C, 61.42; H, 7.48.

Oxaziridine 19a and Isomers. A mixture of ketone 18 (1.44 g, 5.38 mmol), tryptamine (1.72 g, 10.8 mmol), and crushed 5 Å molecular sieves (2.24 g) in 50 mL of Et$_2$O was heated at reflux under N$_2$ for 36 h. The reaction mixture was cooled to rt and then added dropwise to a solution of *m*-CPBA (1.3 g, 7.53 mmol) in 30 mL of dry ether kept at –78 °C. After 30 min, the reaction was worked up and the residue purified by column chromatography (40% EtOAc/hexane) to yield a mixture of oxaziridines 19 (2.16 g, 94%). The major isomer 19a was isolated by HPLC (25% EtOAc/hexane, silica column, retention time 21.9 min). 19a: mp 155–157 °C (50% EtOAc/hexane); R_f 0.60 (50% EtOAc/ hexane); ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.73 (m, 1H), 0.94 (m, 1H), 1.21 (m, 1H), 1.48–1.99 (m, 7H), 2.00 (s, 3H), 2.08 (s, 3H), 2.89–3.29 (m, 4H), 4.67 (m, 1H), 5.25 (m, 1H), 7.04 (d, J = 2.1 Hz, 1H), 7.12 (m, 1H), 7.21 (m, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 7.8 Hz, 1H), 8.18 (s, 1H); ^{13}C NMR (75.6 MHz, CDCl$_3$) δ 21.5, 21.6, 24.4, 31.1, 33.8, 33.9, 37.8, 40.1, 41.5, 56.9, 69.4, 72.5, 92.3, 111.6, 113.9, 119.4, 119.9, 122.5, 122.7, 127.8, 136.6, 170.7, 170.8; IR (CHCl$_3$) 710, 1220, 1730, 3000 cm^{-1}; MS (EI) *m/e* 412 (M$^+$), 194, 174, 169, 152, 141, 130, 125, 108, 77, 43 (100); [α]$_D$ = –51.0 (c = 1.05, CHCl$_3$). Anal. Calcd for C$_{23}$H$_{28}$N$_2$O$_5$: C, 66.97; H, 6.84; N, 6.79. Found: C, 67.09; H, 7.15; N, 6.82. Two other isomers were evident in the ^{1}H NMR spectrum but were not assigned to particular stereoisomers. Isomer 2: ^{1}H NMR (CDCl$_3$) δ 4.83–4.85 (m, 1H), 5.34 (s, 1H). Isomer 3: ^{1}H NMR (CDCl$_3$) δ 5.41 (s, 1H).

Lactams 20a,b. Oxaziridines 19 (2.16 g, 5.23 mmol) were dissolved in 500 mL of acetonitrile and photolyzed for 1.5 h. The reaction mixture was concentrated and the residue chromatographed (2% MeOH/CH$_2$-Cl$_2$) to afford 20 (mixture of isomers, 1.68 g, 78%). HPLC retention times (3% *i*-PrOH/CH$_2$Cl$_2$): 20a 9.2 min, 20b 13.9 min. 20a: ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.22 (m, 1H), 1.46–1.55 (m, 2H), 1.66–2.17 (m, 4H), 2.00 (s, 3H), 2.11 (s, 3H), 2.50 (m, 1H), 2.82 (t, J = 11.6 Hz, 1H), 2.97–3.12 (m, 3H), 3.59–3.70 (m, 2H), 4.78 (m, 1H), 5.29 (s, 1H), 7.02 (d, J = 2.1 Hz, 1H), 7.10 (m, 1H), 7.17 (m, 1H), 7.34 (m, 1H), 7.62 (m, 1H), 8.41 (s, 1H); ^{13}C NMR (125.6 MHz, CDCl$_3$) δ 20.9, 21.1, 22.8, 31.4, 31.9, 32.2, 35.0, 38.5, 48.3, 53.4, 68.2, 70.9, 111.2, 112.9, 118.7, 119.2, 121.9 (2 signals), 127.5, 136.2, 168.5, 170.2, 170.3; IR (CHCl$_3$) 710, 1040, 1220, 1625, 1730, 3000 cm^{-1}; MS (EI) *m/e* 412 (M$^+$), 198, 168, 152, 143 (100), 130, 43. Anal. Calcd for C$_{23}$H$_{28}$N$_2$O$_5$: C, 66.97; H, 6.84; N, 6.79. Found C, 66.59; H, 7.08; N, 6.98. 20b: ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.99 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (125.6 MHz, CDCl$_3$) δ 21.1, 28.8, 34.8, 36.1, 38.1, 48.1, 71.1, 168.7, 170.1, 170.2.

Pivaloyl Esters 21a and 21b. A mixture of lactams 20a,b (1.01 g, 2.41 mmol) and K$_2$CO$_3$ (0.050 g, 0.36 mmol) in 30 mL of MeOH was stirred at rt for 3 h. The solvent was evaporated and the residue dissolved in 30 mL of pyridine. The solution was cooled to 0 °C and pivaloyl chloride (0.62 mL, 4.8 mmol) was added dropwise, whereupon the reaction was allowed to warm to rt and stirred for 6.5 h. The reaction mixture was diluted with CH$_2$Cl$_2$, washed with 2 M aqueous HCl, saturated aqueous NaHCO$_3$, and brine, and dried over Na$_2$SO$_4$. The residue obtained upon evaporation was chromatographed with 1–5% MeOH/CH$_2$Cl$_2$ yielding 0.549 g (55%) of 21a and 0.250 g (25%) of 21b. 21a: mp 221–223 °C (EtOAc); R_f 0.40 (EtOAc); ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.13 (s, 9H), 1.19 (m, 1H), 1.49–1.53 (m, 3H), 1.69–1.78 (m, 2H), 1.96 (m, 1H), 2.28 (m, 1H), 2.82–2.92 (m, 3H), 3.19 (dd, J = 5.0, 11.7 Hz, 1H), 3.48 (m, 2H), 3.91 (s, 1H), 4.54 (m, 1H), 4.75 (s, 1H), 6.97 (m, 1H), 7.05 (m, 1H), 7.13 (d, J = 1.9 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 7.9 Hz, 1H), 10.80 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 22.6,

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26.9, 30.3, 30.9, 34.7, 34.7, 38.2, 38.4, 47.2, 52.6, 64.9, 73.4, 111.5, 118.2 (2 signals), 120.9, 122.6 (2 signals), 127.2, 136.2, 167.6, 177.0; IR (KBr pellet) 740, 1180, 1290, 1610, 1700, 2940, 3180 cm^{-1}; MS (EI) m/e 412 (M$^+$), 270, 168, 152, 143 (100), 130, 57; $[\alpha]_D$ = +18.2 (c = 0.38, pyridine). Anal. Calcd for C$_{24}$H$_{32}$N$_2$O$_4$: C, 69.87; H, 7.82; N, 6.79. Found: C, 69.80; H, 8.00; N, 6.50. **21b**: mp 173–175 °C (MeOH); R_f 0.20 (EtOAc); ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.13 (s, 9H), 1.19 (m, 1H), 1.51 (m, 3H), 1.75 (m, 2H), 1.87 (m, 1H), 2.18 (dd, J = 4.5, 16.9 Hz, 1H), 2.84 (m, 2H), 2.96 (m, 1H), 3.19 (m, 1H), 3.43–3.51 (m, 2H), 3.88 (s, 1H), 4.57 (m, 1H), 4.74 (br s, 1H), 6.96 (m, 1H), 7.06 (m, 1H), 7.13 (d, J = 1.2 Hz, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.57 (d, J = 7.84 Hz, 1H), 10.81 (s, 1H); ^{13}C NMR (125.6 MHz, DMSO-d_6) δ 22.6, 26.9, 27.6, 29.6, 35.8, 37.5, 38.1, 38.3, 47.2, 52.7, 64.9, 73.5, 111.4, 111.6, 118.3, 118.3, 120.9, 122.7, 127.2, 127.2, 136.3, 167.9, 177.1; IR (KBr pellet) 1150, 1610, 1730, 2920, 3400 cm^{-1}; MS (EI) m/e 412 (M$^+$), 282, 270, 254, 152, 143 (100), 130, 57; HRMS calcd for C$_{24}$H$_{32}$N$_2$O$_4$ 412.2362, found 412.2355; $[\alpha]_D$ = +19.4 (c = 1.05, pyridine).

Alkene 22. A mixture of lactam **21a** (0.2 g, 0.48 mmol) and Martin's reagent[19] (0.38 g, 0.58 mmol, 0.76 mL of a 7.4 M solution in dry THF) in 20 mL of dry THF was stirred under N$_2$ at rt for 1 h. An additional 0.38 mL (0.29 mmol) of Martin's reagent was added and the reaction mixture stirred for 2 h. The reaction mixture was diluted with ether, washed with 10% aqueous NaOH and water, and dried over Na$_2$SO$_4$. The residue obtained on concentration was chromatographed with 60–100% EtOAc/hexane to yield 0.12 g (63%) of the title compound and 0.055 g of recovered starting material. The recovered starting material was resubjected to the procedure described above. After column chromatography 0.031 g (64%) of **22** was isolated. The total yield after the recycling step was 0.151 g (80%): mp 170–172 °C; R_f 0.30 (50% EtOAc/hexane); ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.19 (s, 9H), 1.33 (m, 1H), 1.73 (m, 1H), 2.10–2.19 (m, 3H), 2.52 (dd, J = 4.8, 17.3 Hz, 1H), 2.88 (t, J = 11.9 Hz, 1H), 3.04 (m, 2H), 3.19 (dd, J = 5.1, 11.6 Hz, 1H), 3.67 (t, J = 7.4 Hz, 2H), 5.36 (m, 1H), 5.51 (d, J = 10.0 Hz, 1H), 5.64 (d, J = 10.0 Hz, 1H), 7.02 (d, J = 2.2 Hz, 1H), 7.11 (m, 1H), 7.18 (m, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 7.9 Hz, 1H), 8.34 (s, 1H); ^{13}C NMR (125.6 MHz, CDCl$_3$) δ 22.9, 27.1, 33.5, 33.9, 37.7, 38.3, 38.7, 48.4, 52.9, 69.2, 111.1, 113.0, 118.6, 119.3, 121.9, 122.0, 127.4, 128.9, 129.3, 136.3, 169.0, 178.2; IR (CHCl$_3$) 1150, 1270, 1630, 1720, 2920, 2960, 3300 cm^{-1}; MS (EI) m/e 394 (M$^+$), 175, 150, 143 (100), 130, 57; HRMS calcd for C$_{23}$H$_{30}$N$_2$O$_3$ 394.2259, found 394.2257; $[\alpha]_D$ = +19.4 (c = 0.89, CHCl$_3$).

17β-(Trimethylacetoxy)-18,19-didehydroyohimbane. Lactam **22** (0.21 g, 0.51 mmol) was submitted to the standard Bischler–Napieralski procedure. The residue obtained upon concentration was chromatographed with 10–20% EtOAc/hexane to obtain 0.140 mg (73%) of the title compound: mp 234–236 °C; R_f 0.50 (25% EtOAc/hexane); ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.22 (s, 9H), 1.43–1.58 (m, 3H), 2.01 (d, J = 11.7 Hz, 1H), 2.12–2.20 (m, 2H), 2.33 (m, 1H), 2.66–2.74 (m, 2H), 2.99–3.13 (m, 3H), 3.33 (d, J = 9.9 Hz, 1H), 5.48 (s, 1H), 5.59 (d, J = 10.0 Hz, 1H), 5.67 (d, J = 9.9 Hz, 1H), 7.07 (m, 1H), 7.12 (m, 1H), 7.31 (d, J = 7.9 Hz, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.97 (s, 1H); ^{13}C NMR (125.6 MHz, CDCl$_3$) δ 21.7, 27.1, 34.6, 35.6, 38.7 (2 signals), 40.9, 53.1, 59.9, 60.0, 70.5, 108.0, 110.8, 118.1, 119.4, 121.4, 127.3, 127.7, 132.4, 134.4, 136.0, 178.5; IR (CDCl$_3$) 700, 880, 1160, 1710, 2920 cm^{-1}; MS (EI) m/e 378 (M$^+$), 277, 184, 169, 156, 144, 91, 79, 57 (100); $[\alpha]_D$ = –85.4 (c = 0.41, CHCl$_3$). Anal. Calcd for C$_{24}$H$_{30}$N$_2$O$_2$: C, 76.15; H, 7.98; N, 7.40. Found: C, 75.78; H, 8.10; N, 7.01.

17β-Hydroxy-18,19-didehydroyohimbane. 17β-(Trimethylacetoxy)-18,19-didehydroyohimbane (0.039 g, 0.1 mmol) was stirred in 4 mL of a 1:1 solution of 3 N NaOH in EtOH for 26 h. The reaction mixture was neutralized with 2 M HCl and extracted with EtOAc. The organic layer was then washed with brine, dried over Na$_2$SO$_4$, and concentrated. Column chromatography (5–10% MeOH/CH$_2$Cl$_2$) of the residue afforded the title compound (0.024 g, 80% yield): mp 247–249 °C (MeOH); R_f 0.40 (10% MeOH/CH$_2$Cl$_2$); ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.21–1.33 (m, 2H), 1.44 (m, 1H), 1.95 (m, 1H), 2.00–2.08 (m, 2H), 2.23 (m, 1H), 2.51–2.59 (m, 2H), 2.77 (m, 1H), 2.96–3.02 (m, 2H), 3.25 (d, J = 10.3 Hz, 1H), 4.23 (m, 1H), 4.76 (d, J = 5.7 Hz, 1H), 5.46 (d, J = 9.9 Hz, 1H), 5.59 (d, J = 9.9 Hz, 1H), 6.94 (m, 1H), 6.98 (m, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 7.7 Hz, 1H), 10.7 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 21.6, 35.6, 38.7, 38.9, 41.0, 52.5, 59.7, 59.9, 66.6, 106.1, 110.9, 117.4, 118.2, 120.2, 126.6, 128.9, 133.3, 135.7, 135.9; IR (KBr pellet) 740, 1020, 1320, 1450, 2900, 3220 cm^{-1}; MS (EI) m/e 293 (M$^+$ – 1), 277, 184, 169 (100), 167, 156, 154, 143, 128, 115, 91, 79,

77, 67, 42; $[\alpha]_D$ = –148 (c = 0.33, pyridine). Anal. Calcd for C$_{19}$H$_{22}$N$_2$O: C, 77.51; H, 7.53; N, 9.52. found: C, 77.65; H, 7.40; N, 9.58.

18,19-Didehydroyohimban-17-one (23). A mixture of 17β-hydroxy-18,19-didehydroyohimbane (0.030 g, 0.078 mmol), N-methylmorpholine N-oxide (0.018 g, 0.12 mmol), and powdered 4 Å molecular sieves in dry CH$_2$Cl$_2$ (3 mL) was treated with tetra-n-propylammonium perruthenate (0.012 g). The reaction mixture was stirred at rt under N$_2$ for 30 min and then filtered through a pad of silica gel, using 90% EtOAc/Et$_3$N as the eluent, to afford the title compound (0.025 g, 85%) as a white solid: mp 228–231 °C (MeOH); R_f 0.70 (90% EtOAc/Et$_3$N); ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.60 (q, J = ca. 12 Hz, 1H), 2.00 (m, 1H), 2.12 (m, 1H), 2.28 (dd, J = 2.0, 14.2 Hz, 1H), 2.35 (t, J = 11.4 Hz, 1H), 2.57–2.61 (m, 2H), 2.71–2.77 (m, 2H), 3.03 (m, 1H), 3.16 (m, 1H), 3.23 (dd, J = 3.7, 10.9 Hz, 1H), 3.38 (br d, J = 11.2 Hz, 1H), 6.06 (dd, J = 2.8, 9.9 Hz, 1H), 6.77 (d, J = 9.9 Hz, 1H), 7.10 (m, 1H), 7.15 (m, 2H), 7.31 (d, J = 7.9 Hz, 1H), 7.48 (d, J = 7.7 Hz, 1H), 7.79 (br s, 1H); ^{13}C NMR (125.6 MHz, CDCl$_3$) δ 21.8, 35.9, 40.3, 41.1, 44.5, 53.1, 58.8, 59.3, 108.4, 110.8, 118.2, 119.6, 121.6, 127.3, 130.4, 133.9, 136.0, 151.4, 199.0; IR (CHCl$_3$) 710, 1210, 1670, 3000 cm^{-1}; MS (EI) m/e 292 (M$^+$, 100), 221, 184, 169, 167, 156, 154, 143, 128, 115, 91, 77, 65, 53; $[\alpha]_D$ = –120 (c = 0.73, CHCl$_3$). Anal. Calcd for C$_{19}$H$_{20}$N$_2$O: C, 78.05; H, 6.89; N, 9.58. Found: C, 78.23; H, 7.21; N, 9.90.

Preparation of Enone 23 from (+)-Yohimbine. n-BuLi (21.5 mL, 51.7 mmol, 2.39 M solution in hexane) was added dropwise to a solution of diisopropylamine (10 mL, 62.1 mmol) in dry THF (150 mL) at –78 °C. After 5 min, HMPA (10 mL, 58 mmol) was added and the reaction mixture allowed to warm to rt. The reaction mixture was cooled to –78 °C and stirred for 30 min. Yohimbone (prepared from (+)-yohimbine[2b,22]) (7.1 g, 24 mmol) in dry THF (200 mL) was added dropwise to the LDA solution and the reaction mixture stirred for 1 h at –78 °C. Phenylselenenyl chloride (5.5 g, 29 mmol) in dry THF (50 mL) was added dropwise and the resulting solution stirred for 2 h at –78 °C. The reaction mixture was diluted with ether, washed with saturated aqueous NaHCO$_3$ and brine, and dried over Na$_2$SO$_4$. Column chromatography (25% EtOAc/ hexane) afforded 7.76 g (70%) of a mixture of 17-oxo-18β-(phenylselenyl)-yohimbane and 17-oxo-18α-(phenylselenyl)yohimbane. **18β** isomer: ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.42–1.66 (m, 2H), 2.03–2.34 (m, 5H), 2.56–2.76 (m, 3H), 2.91–3.27 (m, 5H), 3.88 (m, 1H), 7.06–7.17 (m, 2H), 7.24–7.32 (m, 4H), 7.44–7.59 (m, 3H), 7.90 (s, 1H); ^{13}C NMR (75.6 MHz, CDCl$_3$) δ 22.2, 36.5, 37.2, 39.5, 42.0, 43.1, 50.2, 53.5, 59.7, 61.1, 108.7, 111.3, 118.6, 119.9, 121.9, 127.7, 128.8, 129.8, 134.5, 134.8, 135.9, 136.5, 206.8; IR (CDCl$_3$) 1280, 1370, 1690 cm^{-1}; MS (EI) m/e 451 (M$^+$ + 2), 450 (M$^+$ + 1), 264, 223, 211, 184, 169, 156, 144, 129, 115, 84, 77 (100), 42, HRMS calcd for C$_{25}$H$_{26}$N$_2$OSe 450.1205, found 450.1211. **18α** isomer: ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.12 (m, 1H), 7.87 (s, 1H); ^{13}C NMR (75.6 MHz, CDCl$_3$) δ 37.1, 41.8, 42.4, 47.9, 52.7, 53.3, 59.4, 119.9, 128.5.

The mixture of selenides (6.73 g, 14.8 mmol) and pyridine (1.8 mL, 19.2 mmol) in CH$_2$Cl$_2$ (100 mL) was treated with 30% aqueous H$_2$O$_2$ (2.23 mL, 19.2 mmol) at rt for 8 h. The two phases were separated and the aqueous layer extracted with CH$_2$Cl$_2$. The organic extractions were combined and washed with 10% aqueous NaOH and brine and dried over Na$_2$SO$_4$. The residue obtained upon concentration was chromatographed with 55% EtOAc/hexane as eluent to yield enone **23** (1.7 g, 40%) as a yellow solid: mp 226–228 °C; R_f 0.70 (90% EtOAc/triethylamine). Spectral data were identical with those obtained above; $[\alpha]_D$ = –117 (c = 0.73, CHCl$_3$).

(–)-Yohimbone (2). A solution of **23** (0.054 g, 0.18 mmol) in dry MeOH (12 mL) was hydrogenated (1 atm) with 10% Pd/C (0.013 g) as catalyst at rt for 3 h. The reaction mixture was filtered over Celite and concentrated. The residue was chromatographed with 60% EtOAc/ hexane to afford (–)-yohimbone (0.046 g, 87%) as a crystalline solid: mp 275–278 °C (lit.[4b] mp 302 °C, lit.[32] mp 305–306 °C, lit.[33] mp 279–280 °C, lit.[4f] mp 266–267 °C); ^{1}H NMR (500 MHz, CDCl$_3$:DMSO-d_6 (3: 1)) δ 1.28–1.41 (m, 2H), 1.56 (m, 1H), 1.81 (m, 1H), 1.91 (m, 1H), 2.08–2.13 (m, 2H), 2.25–2.33 (m, 4H), 2.55 (m, 1H), 2.63 (m, 1H), 2.88 (m, 1H), 2.98–3.05 (m, 3H), 3.18 (d, J = 11.3 Hz, 1H), 6.92 (m, 1H), 6.96 (m, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 7.7 Hz, 1H), 10.01 (br s, 1H); IR (KBr pellet) 740, 1320, 1450, 1700, 2800, 2900, 3325 cm^{-1}; MS (EI) m/e 293 (M$^+$ – 1, 100), 184, 169, 156, 154, 143, 129, 115, 77, 67, 55; $[\alpha]_D$ = –105 (c = 0.30, pyridine); (lit.[4b] $[\alpha]_D$ = –108.8 (c =

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0.34, pyridine), lit.[32] $[\alpha]_D$ = -106.0 (c = 2.6, pyridine), lit.[33] $[\alpha]_D$ = -109.8 (c = 0.37, pyridine), lit.[4f] $[\alpha]_D$ = -106.5 (c = 1.01, pyridine)).

Dimethyl (16α)-18,19-didehydro-17-oxoyohimban-1,16-dicarboxylate (24). n-BuLi (3.8 mL, 9.7 mmol, 2.5 M in hexane) was added dropwise to a solution of diisopropylamine in dry THF (15 mL) at -78 °C and the resulting mixture was stirred for 5 min. HMPA (1.9 mL, 11.6 mmol) was then added and the reaction mixture was warmed to rt. The reaction mixture was cooled then to -78 °C and stirred for 30 min. Enone **23** (1.1 g, 3.78 mmol) in dry THF (20 mL) was added dropwise to the solution of LDA and the resulting mixture was stirred for 1 h. Methyl cyanoformate (0.68 mL, 9.8 mmol) was added dropwise and the resulting solution stirred for 1.5 h at -78 °C. Upon warming to rt, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. Column chromatography (60% EtOAc/hexane) afforded **24** as a light yellow solid (1.3 g, 87%). R_f 0.40 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (q, J = 11.9 Hz, 1H), 2.09 (dt, J = 12.5, 2.5 Hz, 1H), 2.45 (m, 1H), 2.62 (m, 1H), 2.72–2.88 (m, 4H), 3.13–3.32 (m, 3H), 3.80 (s, 3H), 4.01 (s, 3H), 4.12 (m, 1H), 6.11 (dd, J = 10.0, 2.8 Hz, 1H), 6.75 (dd, J = 10, 1.5 Hz, 1H), 7.27 (m, 2H), 7.42 (m, 1H), 8.12 (m, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 22.7, 32.8, 37.8, 43.7, 47.9, 52.6, 54.0, 58.9, 59.1, 60.6, 115.9, 117.0, 118.5, 123.5, 124.9, 129.5, 130.1, 135.8, 137.0, 151.9, 152.3, 170.1, 194.2; IR ($CHCl_3$) 710, 985, 1165, 1200, 1365, 1440, 1460, 1680, 1740, 3020 cm^{-1}; MS (EI) m/e 408 (M[+]), 376, 349, 243, 228, 214, 183, 169, 154; HRMS calcd for $C_{23}H_{24}N_2O$ 408.1683, found 408.1677, $[\alpha]_D$ = -101.5 (c = 1.07, $CHCl_3$).

(+)-Yohimbinone (25). Compound **24** (1.1 g, 2.69 mmol) in dry MeOH (150 mL) was hydrogenated (1 atm) at rt for 15 min using 10% Pd/C (0.4 g) as catalyst. The reaction mixture was filtered over Celite and concentrated, and the residue was chromatographed (50% EtOAc/hexane) to yield dimethyl (16α)-17-oxoyohimbane-1,16-dicarboxylate as a white solid (1.08 g, 97%): R_f 0.20 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34–1.55 (m, 3H), 1.92–2.21 (m, 4H), 2.42 (td, J = 14.1, 6.1 Hz, 1H), 2.55–2.88 (m, 4H), 3.14–3.22 (m, 3H), 3.77 (s, 3H), 4.02–4.06 (m, 4H), 7.21–7.32 (m, 2H), 7.39–7.42 (m, 1H), 8.14 (d, J = 8 Hz, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 22.8, 30.1, 34.4, 36.9, 41.5, 44.9, 48.0, 52.4, 54.1, 58.9, 60.8, 63.0, 115.8, 117.0, 118.4, 123.5, 124.8, 129.6, 135.9, 137.1, 152.3, 169.9, 205.2; IR ($CHCl_3$) 710, 1215, 1440, 1715, 1740, 3020 cm^{-1}; MS (EI) m/e 410 (M[+], 100), 395, 378, 351, 293, 242, 227, 183, 169, 115; $[\alpha]_D$ = -38.1 (c = 0.63, $CHCl_3$).

The diester (0.032 g, 0.078 mmol) and K_2CO_3 (0.057 g) were stirred in MeOH (20 mL) at rt for 8 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. Column chromatography (65% EtOAc/hexane) afforded **25** as white solid (0.022 g, 82%): mp 258–260 °C (MeOH) (lit.[5] 254–256); R_f 0.30 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$–CD_3OD) δ 1.26–1.46 (m, 2H), 1.87–2.09 (m, 3H), 2.10–2.14 (m, 2H), 2.31–2.48 (m, 2H), 2.54 (m, 1H), 2.65 (m, 1H), 2.87–3.04 (m, 3H), 3.19 (d, J = 11.5 Hz, 1H), 3.73 (s, 3H), 6.94–7.05 (m, 2H), 7.22 (d, J = 7.8 Hz, 1H), 7.37 (d, J = 7.3 Hz, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$–CD_3OD) δ 21.7, 29.8, 34.5, 38.6, 40.9, 43.7, 52.3, 53.2, 59.6, 60.5, 62.6, 107.4, 111.3, 118.1, 119.2, 121.4, 127.1, 133.9, 136.7, 170.6, 205.9; IR (KBr pellet) 1150, 1700, 1740, 3380 cm^{-1}; MS (EI) m/e 351 (M[+] – 1),

320, 293, 184, 169, 156, 69, 57; $[\alpha]_D$ = +13.5 (c = 0.62, pyridine); lit.[5] $[\alpha]_D$ = +11.7 (c = 1, pyridine).

(+)-Yohimbine (1). L-Selectride (0.28 mL, 2.8 mmol, 1 M in THF) was added dropwise to a solution of **25** (0.1 g, 0.28 mmol) in THF (10 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 30 min and then quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with CH_2Cl_2. The organic layers were combined and washed with 10% NaOH solution and brine and dried over Na_2SO_4. The residue obtained on concentration was chromatographed (65% EtOAc/hexane) to afford yohimbine (0.086 g, 86%) as a light yellow solid: mp 233–235 °C (lit.[25] mp 241–242 °C; lit.[5] mp 224–225 °C; mp of commercial material (Aldrich) 231–233 °C); R_f 0.30 (EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (q, J = 11.7 Hz, 1H), 1.43 (m, 1H), 1.58 (m, 3H), 1.98–2.04 (m, 3H), 2.23–2.27 (m, 1H), 2.34 (dd, J = 11.5, 1.9 Hz, 1H), 2.62 (td, J = 11.3, 4.3 Hz, 1H), 2.72 (dd, J = 15.2, 4.2 Hz, 1H), 2.93–3.02 (m, 3H), 3.07 (m, 1H), 3.33 (br d, J = 11.3 Hz, 1H), 3.81 (s, 3H), 4.22 (br s, 1H), 7.06–7.14 (m, 2H), 7.29 (d, J = 7.9 Hz, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.77 (s, 1H); ^{13}C NMR (125.6 MHz, $CDCl_3$) δ 21.7, 23.3, 31.4, 34.3, 36.7, 40.7, 51.9, 52.3, 52.9, 59.8, 61.3, 66.9, 108.2, 110.7, 118.1, 119.4, 121.3, 127.4, 134.5, 135.9, 175.6; IR ($CHCl_3$) 1710, 2930, 3010 cm^{-1}; MS (EI) m/e 353 (M[+] – 1, 100), 184, 169, 156, 144, 129, 115, 77, 43; $[\alpha]_D$ = +52.3 (c = 0.59, EtOH); (lit.[25] $[\alpha]_D$ = +45.0 (c = 1, EtOH); lit.[5] $[\alpha]_D$ = +42.7 (c = 1, EtOH); Aldrich $[\alpha]_D$ = +55.6 (c = 2, EtOH)).

β-Yohimbine. Sodium borohydride (0.022 g, 0.59 mmol) was added in small portions to a solution of yohimbinone **25** (0.054 g, 0.15 mmol) in MeOH (6 mL) at rt. The reaction mixture was stirred at rt for 1.5 h and then quenched with a few drops of glacial AcOH. The residue obtained on evaporation of solvent was dissolved in EtOAc. The solution was washed with saturated aqueous $NaHCO_3$ and brine and dried over Na_2SO_4. Column chromatography of the residue (65% EtOAc/hexane) afforded β-yohimbine (0.040 g, 74%) as a light yellow solid: mp 223–225 °C; R_f 0.20 (EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (m, 1H), 1.36–1.51 (m, 3H), 1.68–1.69 (m, 2H, partially obscured by residual water), 1.92 (d, J = 11.9 Hz, 1H), 2.06–2.18 (m, 4H), 2.59 (td, J = 11.1, 4.1 Hz, 1H), 2.69 (d, J = 15.4 Hz, 1H), 2.95–3.00 (m, 2H), 3.06 (dd, J = 11.1, 5.8 Hz, 1H), 3.22 (d, J = 10.9 Hz, 1H), 3.81 (s, 3H), 3.84 (m, 1H), 7.04–7.12 (m, 2H), 7.29 (d, J = 8.0 Hz, 1H), 7.43 (d, J = 7.7 Hz, 1H), 7.83 (s, 1H); ^{13}C NMR (125.6 MHz, $CDCl_3$) δ 21.7, 27.8, 34.1, 34.1, 39.8, 41.9, 51.9, 52.9, 57.3, 59.5, 61.0, 72.2, 108.2, 110.8, 118.1, 119.4, 121.4, 127.3, 134.2, 136.0, 174.9; IR ($CHCl_3$) 660, 710, 1155, 1210, 1260, 1720, 2920, 3000 cm^{-1}; MS (EI) m/e 353 (M[+] – 1, 100), 184, 169, 156, 143, 129, 115, 91, 69, 43; $[\alpha]_D$ = -15.0 (c = 0.5, EtOH); lit.[5] $[\alpha]_D$ = +50.7 (c = 1, pyridine).