Aziridine−Allylsilane-Mediated Total Synthesis of (−)-Yohimbane

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Received December 28, 1998

A total asymmetric synthesis of (−)-yohimbane and *ent*-alloyohimbane is reported. The synthesis utilizes a novel aziridine−allylsilane cyclization reaction as a key step in the synthesis. Treatment of optically pure aziridine−allylsilane **16** with $BF_3{\cdot}OEt_2$ provided a mixture of aminomethyl substituted carbocycles *trans*-**20a** and *cis*-**20b** in excellent yield and modest diastereoselectivity (trans/cis 3:1). Alkylation of the tosylamide followed by oxidation of the olefin in **20** provided the lactam **38**, which was converted to (−)-yohimbane and *ent*-alloyohimbane by a Bischler−Napieralski reaction. The synthesis provided (−)-yohimbane in eight steps and 24% overall yield (from **16**).

Introduction

(−)-Yohimbane **1** and (−)-alloyohimbane **2** (Figure 1) are members of the rauwolfia alkaloid family.[1] Representative members of this family include reserpine, ajmalicine, and yohimbine (Figure 1). These alkaloids have a characteristic pentacyclic ring framework with the indole ring comprising rings A and B. Much of the stereochemical and functional group complexity resides on the E ring. These alkaloids possess a wide range of interesting biological activities, including antihypertensive and antipsychotic.[2] Yohimbine and related compounds have served as important pharmacological tools for the differentiation of α-adrenergic receptors.[3] Due to the structural complexity and interesting biological activity of this class of alkaloids, they have piqued the interest of synthetic organic chemists for decades.

Since the first synthesis of reserpine[4] and yohimbine,[5] a number of other synthetic approaches to this alkaloid family have been reported.[6] While the synthesis of racemic **1** and **2** has been addressed on numerous occasions,[7] only two asymmetric syntheses of (−)-yohimbane have been reported. The first asymmetric synthesis of (−)-yohimbane was reported in 1991.[8] These authors synthesized (−)-yohimbane utilizing an in situ 1,4-addition/ring-closure reaction of a chiral α-sulfinyl

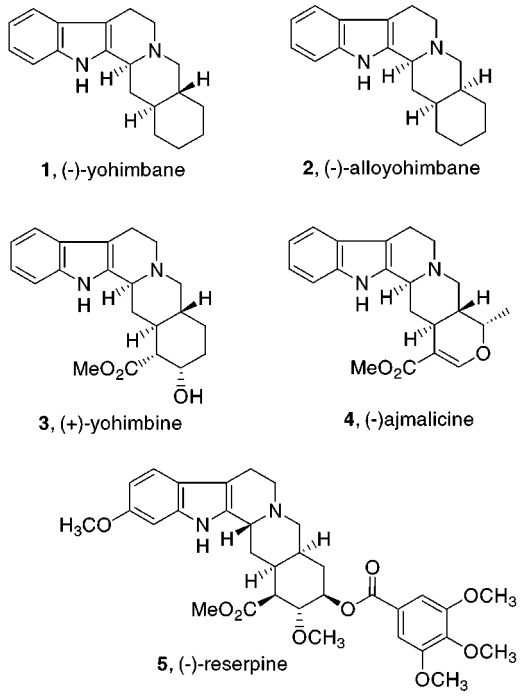

Figure 1.

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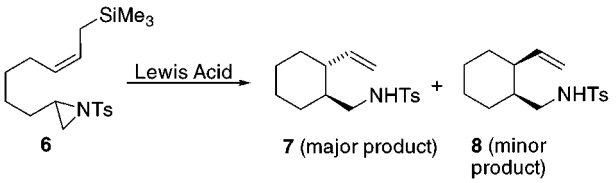
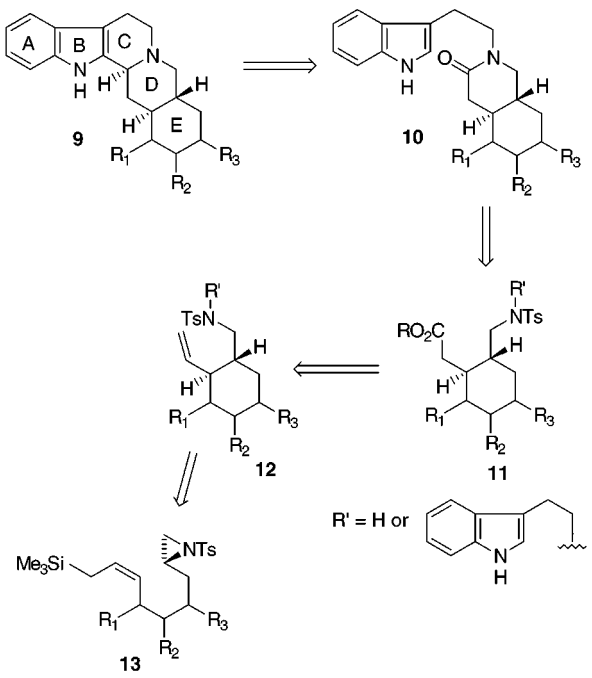
10.1021/jo9825097 CCC: $18.00
Published on Web 04/13/1999

Scheme 1



Scheme 2



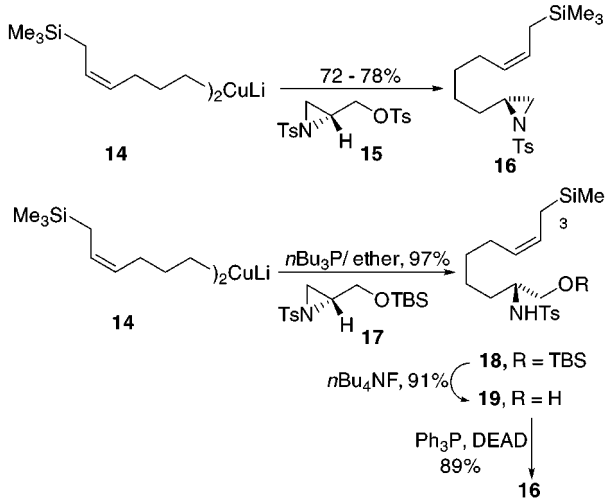
ketimine anion with an ene ester. Recently, Aube published an elegant oxaziridine rearrangement approach to this alkaloid family.[9]

We recently communicated a novel intramolecular cyclization reaction between aziridines and allylsilanes[10] (Scheme 1). The product of this reaction is an aminomethyl-substituted carbocycle **7**. We envisioned that amino olefins such as **7** could be extremely useful for the asymmetric synthesis of alkaloids, especially the rauwolfia family. To demonstrate the synthetic utility of these amino olefins, we report here the use of this cyclization reaction as a key step in the synthesis of (−)-yohimbane as a means to developing a general synthetic route to this alkaloid family.

Retrosynthetic Analysis

The lactam **10** is a well-known intermediate for the final cyclization to form the C ring of the pentacyclic compound **9** (Scheme 2). This cyclization is readily done by a Bischler−Napieralski reaction.[11] The lactam **10** should be accessible from the ester **11** (where R′ is either H or 3-ethylindole) by removal of the tosyl group. The ester **11** can, in turn, be prepared from the olefin **12** via

Scheme 3



a hydroboration/oxidation sequence. The 3-ethylindole group will have to be added by an alkylation to either the olefin **12** (R′ = H) or ester **11** (R′ = H). The olefin **12** is readily accessible in enantiomerically pure form via our aziridine−allylsilane cyclization.

Results and Discussion

Our initial synthetic efforts were directed toward developing a convenient synthesis of enantiopure aziridine−allylsilane **16** (Scheme 3). Our first-generation synthesis of this type of molecule was racemic and involved two low-yielding steps to introduce both the aziridine and the allylsilane moeities.[10] After exploring a few other routes, we realized that **16** could be synthesized by the reaction of an aziridine **15** with an appropriate organometallic reagent **14**.[12] While this was a useful method to provide a quick access to chiral **16** (>97% ee), we could not obtain reproducible yields when the reaction was carried out on a scale >2 mmol. Hence, we decided to synthesize **16** via a stepwise process starting from the aziridine **17**.[12] Reaction with the cuprate **14** provided the ring-opened intermediate **18** in almost quantitative yield. Deprotection of the silyl ether using $^{n}Bu_4NF$ provided the alcohol **19**, which was then converted to the aziridine **16** via a Mitsunobu reaction.[13] This sequence provided us with an equivalent yield of **16** (83% from **17**) as compared to the single-step procedure. More importantly, this sequence could be conveniently carried out on a 5 mmol or greater scale.

The aziridine **16** was then cyclized by treatment with $BF_3{\cdot}OEt_2$ (300−400 mol %) to provide the amino olefins *trans*-**20a** and *cis*-**20b** (Scheme 4) as an inseparable mixture (diastereoselectivity 2.8:1−2:1).[14] A number of different Lewis acids were used in an attempt to improve the stereoselectivity of the reaction. Unfortunately, use

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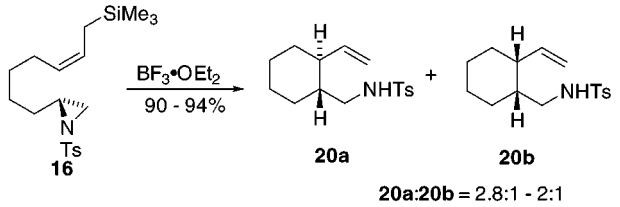
(14) The stereoselectivity of the reaction was dependent on the temperature at which the Lewis acid was added to the reaction. Typically, when $BF_3{\cdot}OEt_2$ was added to the reaction at −78 °C and the reaction was allowed to warm to room temperature gradually and then stirred for 24 h, the ratio of **20a**:**20b** was observed to be 2.8:1. However when the $BF_3{\cdot}OEt_2$ was added to the reaction at 0 °C and the reaction then allowed to warm to room temperature and stirred for 24 h, the ratio of **20b**:**20b** was observed to be ca. 2:1.

Scheme 4



of stronger Lewis acids such as $TiCl_4$ and $SnCl_4$ or Lewis acids with strongly nucleophilic counterions such as $MgBr_2$ resulted in opening of the aziridine ring with the Lewis acid counterion even at −78 °C. Use of TMSOTf did provide us with some of the desired product, but this was usually accompanied by protodesilyation as well as formation of some other unidentified products. Use of weaker Lewis acids such as $Ti(OiPr)_4$, $Yb(OTf)_3$, and $Zn(OTf)_2$ did not result in any reaction even at elevated temperatures. Use of protic acids such as CF_3CO_2H resulted in decomposition. Use of solvents other than CH_2Cl_2 was also unsuccessful.

The formation of the major trans isomer could be explained as occurring via a chairlike conformation (Scheme 5). Here, the aziridine and the allylsilane arrange themselves in an equatorial orientation (conformation A). This arrangement reduces the unfavorable steric interactions that are seen in conformation B. An alternate arrangement, in which the allylsilane is in an axial arrangement, would seem to be precluded due to $A^{(1,3)}$ strain.[15] Coordination of the Lewis acid with the aziridine causes polarization of the more substituted C−N bond of the aziridine ring. This induces nucleophilic attack by the allylsilane to form the positively charged intermediate **21**, which can then undergo an elimination reaction to provide **20a**.[16] The aziridine ring opening takes place in an S_N2 fashion, with approach of the nucleophile being anti to the aziridine ring. The formation of the minor cis isomer **20b** could be explained as occurring via conformation B. In this conformation, the aziridine adopts an axial conformation. This results in unfavorable steric interactions, culminating in the formation of the cis-fused carbocycle **20b** (minor product).

The stereochemistry of the trans- and the cis-fused carbocycles was previously assigned by us using NOE and NOESY spectroscopy.[10] To unambiguously assign the stereochemistry of **20a** and **20b**, we first attempted to separate the diastereomeric sulfonamides by HPLC. While we could separate **20a**,**b** on an analytical scale, the HPLC procedure was not suitable for separation of **20a**,**b** on a preparative scale.[17] We therefore decided to convert them to the lactams **24** and **25**, respectively (Scheme 6). To this end, the olefin of **20** was hydroborated using 9-BBN to provide the primary alcohol **23** as the exclusive product. The alcohol **23** was then oxidized[18] to the *N*-tosyl lactams **24** (47%) and **25** (22%), which were separable by flash chromatography. The stereochemistry of these lactams was then confirmed by examination of coupling constants and by NOE spectroscopy.

In lactam **24**, hydrogens H_a−H_f showed up as distinct signals in the ^1H NMR spectrum. Due to the trans ring fusion, the coupling constants J_{HaHd} (11.5 Hz) and J_{HbHe} (11.8 Hz) were large (diaxial coupling constants). In comparison, the coupling constants between J_{HaHc} (4.5 Hz) and J_{HbHf} (4.9 Hz) were small (axial−equatorial coupling constants). H_d also showed an NOE to H_b (4.2%) but not to H_a, while H_c showed an NOE to H_a (6.1%) but not to H_b, further confirming the trans ring fusion.

In lactam **25**, hydrogens H_a−H_d showed up as distinct signals in the ^1H NMR spectrum. Due to the cis ring fusion, the dihedral angle between both H_a−H_c and H_a−H_d should be small. As a result, the coupling constants between J_{HaHc} (6.3 Hz) and J_{HaHd} (5 Hz) were smaller and of similar magnitude. Irradiation of H_c in the NOE experiment showed enhancements in the signals for both H_a (6.6%) and H_b (2.1%), indicating a cis relationship between these protons and consequently confirming the cis ring fusion in **25**.

The next step in the synthesis involved alkylation of the tosylamide **20** with indole **26**.[19] Although this transformation appeared fairly straightforward, it proved to be rather difficult (Scheme 7). Reaction of the indole **26** with **20** did not provide any of the desired alkylated product. Instead only the vinyl indole **27** was obtained along with unreacted **20**. Similar results were obtained even when a large excess of the bromide **26** was used. A number of different bases and solvents were also tried without any success.

We next attempted the coupling by means of a Mitsunobu reaction[20] between the alcohol **28** and the tosylamide **20**. Once again, the only product obtained was the unreacted tosylamide. Use of a large excess of reagents and different reaction conditions also failed completely. The coupling was also attempted by utilizing the chlorides **29**[21] and **30**[22] again with no success. We therefore turned our attention toward deprotection of the tosylamide **20** with the intention of alkylating the amine **31**, which we thought would be relatively facile. A number of standard protocols for the deprotection of the tosyl group including Na/NH_3,[23] SmI_2,[24] and HBr/phenol[25] were attempted. All of these resulted in decomposition of the starting tosylamide. The desired amine was only obtained in trace amounts from the above reactions. We then decided to examine leaving groups other than bromide in the alkylation reaction. To this end, the mesylate **32**

(15) Synclinal transition states (allylsilane equatorial) are preferred over antiperiplanar transition states (allylsilane axial) in intramolecular reactions of allylsilanes. A possible explanation for this preference could be the unfavorable $A^{(1,3)}$ interaction between the allylic protons of the allylsilane and axial hydrogen of the forming ring when the allylsilane is in an axial orientation. (a) Lolkema, L. D. M.; Semeyn, C.; Ashek, L.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1994**, *50*, 7129. (b) Mann, A.; Nativi, C. Taddei, M. *Tetrahedron Lett.* **1988**, *29*, 3247. For some more examples of intramolecular reactions of allylsilanes, see: (c) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063.

(16) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673. (b) Schinzer, D. *Synthesis* **1988**, 263.

(17) In our previous work,[10] we assigned the stereochemistry of a mixture of **20a** and **20b** using NOE and NOESY spectroscopy. Since then, we have developed an HPLC method for the baseline separation of these diastereomers on an analytical scale. Unfortunately, all of our attempts to separate these diastereomers on a preparative scale were not successful, as we could load only less than 1 mg of sample and still not obtain separation that was seen on an analytical scale.

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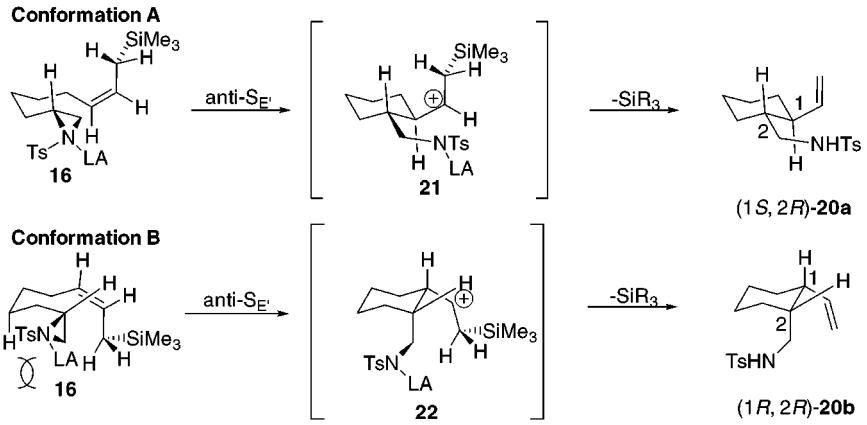
(23) Yamazaki, N.; Kibayashi, C. *J. Am. Chem. Soc.* **1989**, *111*, 1396.

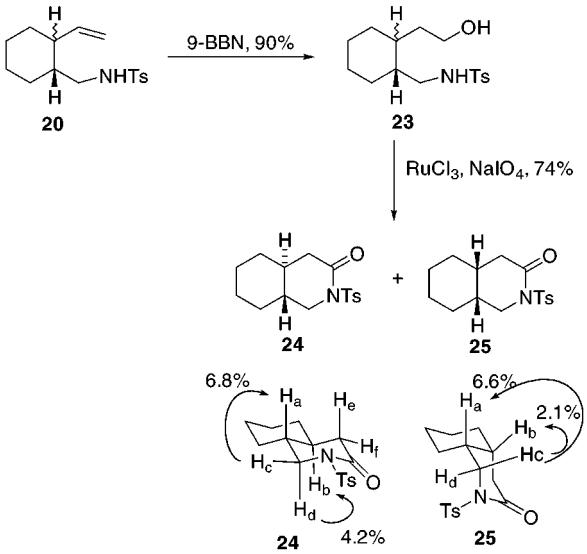
(24) Vedejs, E.; Lin, S. *J. Org. Chem.* **1994**, *59*, 1602.

(25) Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1988**, *53*, 2367.

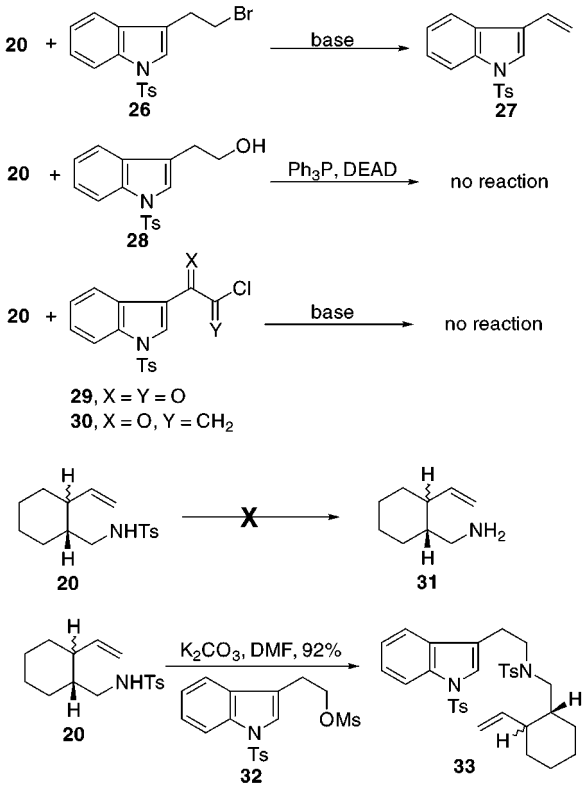
Scheme 5



Scheme 6



Scheme 7



was prepared from the alcohol **28**. To our delight, this reaction worked extremely well to provide us with the alkylated product **33** in excellent yield.[26] Although we did obtain some amount of the vinyl indole **27** from the reaction, this could be rectified by using a slight excess of the mesylate **32**.

With olefin **33** in hand, all that remained to complete the synthesis was oxidation of the olefin followed by a Bischler−Napieralski reaction. The olefin of **33** was hydroborated using 9-BBN to provide the alcohol **34** (Scheme 8). Use of BH_3·THF provided mixtures of the primary and secondary alcohols. The next step in the synthesis involved oxidation of the alcohol **34** to the carboxylic acid **36**. A number of different oxidants were available for this purpose.[27] We initially decided to use RuO_2 as our oxidizing agent.[18,28] In our hands, this oxidizing system gave very poor results. The major products of this reaction appeared to be the corresponding aldehyde, which showed considerable decomposition in the aromatic region of the ^{1}H NMR spectra of the crude product. A number of other reaction conditions including Jones,[29] TEMPO,[30] CrO_3−acetic anhydride[31] were also attempted but without success. The primary product seen with these oxidants was the aldehyde.

Due to the poor results obtained, we decided to attempt this transformation in a stepwise fashion. The alcohol **34** was oxidized to the aldehyde **35** using the Swern conditions[32] in excellent yield. The oxidation was also successful when DMP[33] or PCC[34] was used as the oxidant. However, the Swern conditions were found to give the best results. We then attempted to oxidize the aldehyde

(26) The best results for the alkylation reaction were obtained when DMF was used straight from the bottle. Use of DMF that had been distilled over BaO resulted in lower yields and longer reaction times. Also, under anhydrous conditions, use of KH instead of K_2CO_3 resulted in lower yields of the alkylated product.

(27) (a) Larock, R. C. In *Comprehensive Organic Transformations. A guide to functional group preparations*; VCH Publishers: New York, 1989; pp 834−841.

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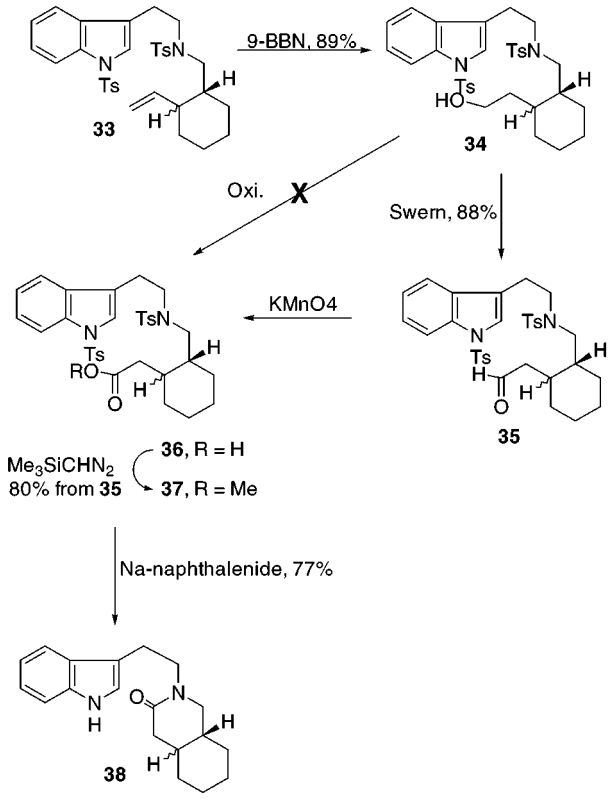
(29) Millar, J. G.; Oehlschlager, A. C.; Wong, J. W. *J. Org. Chem.* **1983**, *48*, 4404.

(30) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559.

(31) Corey, E. J.; Samuelsson, B. *J. Org. Chem.* **1984**, *49*, 4735.

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

Scheme 8

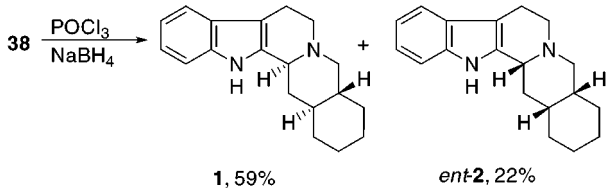


to the acid using $RuCl_3$−$NaIO_4$[27] and NaOCl[35] but again without any success. The aldehyde was finally oxidized to the acid using $KMnO_4$ in buffered phosphate solution[36] in good yield. The crude acid **36** was then readily converted to the methyl ester **37** using methyl chloroformate and triethylamine[37] (65% from **35**) or Me_3SiCHN_2[38] (80% from **35**).

The next crucial step in the synthesis was deprotection of the two tosylamide protecting groups in **37**. We first attempted the deprotection using SmI_2.[24] This reaction did not provide us with the desired product. We then attempted the reaction using sodium naphthalenide.[39] This procedure did not provide us with the corresponding deprotected ester but instead provided us with the lactam **38**, which was now set for a ring closure to provide us with our final product. The lactam **38** was then subjected to the Bischler−Napieralski conditions to provide (−)-yohimbane and *ent*-alloyohimbane (Scheme 9) as a mixture that could be easily separated by chromatography on silica gel, thus completing our total synthesis. The analytical data of our synthesized product were in complete agreement with those reported in the literature.[7g,9c]

In conclusion, we have synthesized (−)-yohimbane in eight steps and 24% overall yield (from **16**), utilizing a

Scheme 9



novel aziridine−allysilane cyclization reaction as the key step in the synthesis to form the E ring. By incorporating appropriate functionality along the tether between the aziridine and the allylsilane, this cyclization should also serve as an effective route for the synthesis of more complex members of the rauwolfia alkaloid family.

Experimental Section[40]

(8*R*)-1-(Trimethylsilyl)-8-[(4-methylphenyl)sulfonyl]-amino-9-[(*tert*-butyldimethyl)silyl]oxonon-2-ene (18). *t*-BuLi (19.5 mL of a 1.58 M solution in pentane, 30.8 mmol) was added dropwise to a solution of 1-(trimethylsilyl)-6-iodohex-2-ene[12] (3.95 g, 14 mmol) in Et_2O (28 mL) at −78 °C. The reaction mixture was then allowed to stir at −78 °C for 10 min, after which it was allowed to warm to room temperature and stirred for an additional 60 min. The reaction mixture was then recooled to −78 °C. In a separate flask, CuI (0.95 g, 5 mmol) was dissolved in *n*-Bu_3P (5.8 mL, 23.5 mmol) and Et_2O (2 mL). The slightly turbid solution of CuI/*n*-Bu_3P in Et_2O was then transferred to the organolithium prepared above using additional Et_2O (26 mL). The yellowish cuprate solution thus formed was warmed to −40 °C and stirred for 10 min, after which it was recooled to −78 °C. The aziridine **17**[12](1.71 g, 5 mmol) was dissolved in Et_2O (2 mL) and added to the reaction mixture via cannula. The reaction was stirred at −78 °C for 30 min, after which it was warmed to room temperature and stirred for another 30 min. The reaction was quenched by adding saturated NH_4Cl solution and the organic layer washed with saturated NH_4Cl and brine, dried ($MgSO_4$), and concentrated. Chromatography (4% EtOAc in hexanes−15% EtOAc in hexanes) provided **18** (2.42 g, 97%) as a colorless oil: R_f 0.3 (15% EtOAc in hexanes); $[\alpha]_D$ +20.9° (*c* 2.1, EtOAc); ^{1}H NMR δ 7.69 (d, 2H, J = 8.26), 7.22 (d, 2H, J = 8.05), 5.33−5.13 (m, 2H), 4.76 (d, 1H, J = 8.32), 3.37 (dd, 1H, J = 3.25, 9.97), 3.26 (dd, 1H, J = 4.39, 9.97), 3.15 (m, 1H), 2.36 (s, 3H), 1.85 (m, 2H), 1.37 (d, overlapped, 2H, J = 7.76), 1.46−1.1 (m, 6H), 0.78 (s, 9H), −0.06 (s, 9H), −0.09 (s, 3H), −0.1 (s, 3H); ^{13}C NMR δ 143.1, 138.4, 129.5, 127.2, 127, 125.4, 64.1, 54.9, 32, 29.4, 26.8, 25.8, 25.3, 21.4, 18.4, 18.2, −1.8, −5.7. Anal. Calcd for $C_{25}H_{47}NO_3Si_2S$ 0.25 H_2O: C, 59.78; H, 9.53; N, 2.78. Found: C, 59.69; H, 9.52; N, 2.67.

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(40) Thin-layer chromatography (TLC) was performed on Whatman precoated silica gel F_{254} aluminum foil. Visualization was accomplished with UV light and/or phosphomolybdic acid solution followed by heating. Purification of the reaction products was carried out by flash column chromatography using glass column dry packed with silica gel (230−400 mesh ASTM) according to the method of Still.[43] ^{1}H NMR and ^{13}C NMR spectra referenced to TMS were recorded using a Bruker AF 250 or Bruker DRX 400 model spectrometer. NOE experiments were carried out using a Bruker DRX 400 spectrometer. Unless noted, all spectra were recorded in $CDCl_3$. Data are reported as follows: chemical shift in ppm from internal standard tetramethylsilane on the δ scale, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, coupling constant (Hz). All reactions were carried out under an atmosphere of nitrogen unless specified otherwise. Glassware was flame dried under a flow of nitrogen. Tetrahydrofuran and diethyl ether were distilled over Sodium/benzophenone ketyl immediately prior to use. Dichloromethane, DME, and benzene were distilled over CaH_2 prior to use. Exact mass measurements recorded in the electron impact (EI) or fast atom bombardment (FAB) modes were determined at The Ohio State University Campus Chemical Instrument Center with a Kratos MS-30 mass spectrometer. Combustion analyses were performed at Quantitative Technologies Inc., Whitehouse, NJ. Optical rotations were recorded using a Perkin-Elmer 241 model polarimeter.

(*R*)-2-[7-(Trimethylsilyl)hept-5-en]-*N*-[(4-methylphenyl)-sulfonyl]aziridine (16). *n*-Bu_4NF (5.5 mL of a 1 M solution in THF, 5.5 mmol) was added dropwise over 5 min to a solution of the alcohol **18** (2.42 g, 4.85 mmol) in THF (5 mL) at 0 °C. The reaction mixture was stirred for 30 min, after which it was diluted with water. The aqueous layer was then extracted with EtOAc (3 × 10 mL), and the combined organic layers washed with brine, dried ($MgSO_4$), and concentrated. The crude product thus obtained was dried under vacuum (2 mmHg) overnight and used without any further purification. The crude alcohol **19** obtained from above was transferred to a flame-dried flask containing Ph_3P (1.34 g, 5.11 mmol), using THF (19 mL). The resulting solution was cooled in an ice bath. Diethylazodicarboxylate (0.81 mL, 5.11 mmol) was added to the reaction over 5 min via a syringe, and the reaction mixture was then allowed to stir for 3 h after which the solvent was removed under vacuum. The resulting thick oil was triturated with hexanes resulting in precipitation of a white solid (Ph_3-PO), which was filtered to provide a solution that was then concentrated. Chromatography (8% EtOAc in hexanes) provided the aziridine **16** (1.51 g, 86% from **18**) as a colorless oil. The analytical data for **16** were identical to those reported earlier.[12]

(1*S*,2*R*)-1-Ethene-2-[(4-methylphenyl)sulfonyl]aminomethylcyclohexane (20a) and (1*R*,2*R*)-1-Ethene-2-[(4-methylphenyl)sulfonyl]aminomethylcyclohexane (20b). Freshly distilled $BF_3{\cdot}OEt_2$ (1.5 mL, 12.3 mmol) in CH_2Cl_2 (3 mL) was added to a solution of the aziridine **16** (1.5 g, 4.1 mmol) in CH_2Cl_2 (38 mL) at 0 °C over 5 min. The reaction mixture was stirred at 0 °C for 60 min, after which it was warmed to room temperature and stirred for 18 h. The reaction mixture was quenched by the addition of saturated K_2CO_3 solution. The organic layer was then washed with saturated K_2CO_3, brine, dried ($MgSO_4$), and concentrated. Chromatography (12% EtOAc in hexanes) provided an inseparable mixture of **20a**:**20b** (2:1, 1.13 g, 94%) as a colorless oil. Analytical data were identical to those reported earlier.[10]

(1*S*,2*R*)-1-(2-Hydroxyethyl)-2-[(4-methylphenyl)sulfonyl]aminomethylcyclohexane (23a) and (1*R*,2*R*)-1-(2-Hydroxyethyl)-2-[(4-methylphenyl)sulfonyl]aminomethylcyclohexane (23b). 9-BBN (5.5 mL of a 0.5 M solution in THF, 2.7 mmol) was added to a solution of the olefin **20** (0.2 g, 0.68 mmol) in THF (1.4 mL). The reaction was then stirred at room temperature for 3.5 h. The reaction mixture was cooled in an ice bath, and the excess 9-BBN was quenched with EtOH (1.6 mL) and stirred for 5 min followed by addition of 6 N NaOH (0.54 mL) and H_2O_2 (1 mL, 30% solution). The reaction mixture was refluxed for 60 min and cooled to room temperature. The reaction mixture was then diluted with water and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Chromatography (35% EtOAc in hexanes) provided **23** (0.19 g, 90%, 2:1 mixture of trans and cis isomers): R_f 0.24 (35% EtOAc in hexanes); ^{1}H NMR δ 7.69 (d, 2H, J = 8.26), 7.22 (d, 2H, J = 8.15), 5.88* (t, 1H, J = 6.41), 5.67 (t, 1H, J = 6.43), 3.7−3.5 (m, 2H), 2.9−2.4 (m, 3H), 2.36 (s, 3H), 1.85−1.09 (m, 10H), 1.08−0.8 (m, 1H); ^{13}C NMR (* indicates signal arising from minor cis isomer) δ 143, 142.9*, 137.1*, 137, 129.5, 126.9, 61*, 60.2, 46.1, 44.2*, 41.4, 39.4*, 35.5, 35.4, 32.2*, 31.6, 30.1, 28.8*, 26.2*, 25.6, 25.5, 24.1*, 22.1*, 21.3. Anal. Calcd for $C_{16}H_{25}NO_3S$: C, 61.7; H, 8.09; N, 4.49. Found: C, 61.9; H, 8.37; N, 4.1.

(4a*S*,8a*R*)-*N*-[(4-Methylphenyl)sulfonyl]decahydroisoquinolin-3-one (24) and (4a*R*,8a*R*)-*N*-[(4-Methylphenyl)-sulfonyl]decahydroisoquinolin-3-one (25). $RuCl_3{\cdot}3H_2O$ (4.4 mg, 0.02 mmol) in H_2O (2 mL) was added to a mixture of the alcohol **23** (165 mg, 0.53 mmol) in CCl_4/CH_3CN (1:1, 2.4 mL) and $NaIO_4$ (0.41 g, 1.9 mmol). The reaction mixture was then stirred for 18 h, after which it was diluted with water (5 mL), the aqueous layer was extracted with $CHCl_3$ (2 × 5 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated. Chromatography (20% EtOAc in hexanes) provided **24** (78 mg, 47%) and **25** (36 mg, 22%). Analytical data for **24**: R_f 0.6 (35% EtOAc in hexanes); $[\alpha]_D$ = +31.4° (*c* 1.52, EtOAc); ^{1}H NMR δ 7.9 (d, 2H, J = 8.36), 7.3 (d, 2H, J = 8.31), 4.16 (dd, 1H, J = 4.52, 11.73), 3.16 (t, 1H, J = 11.46), 2.45 (partially overlapped dd, 1H, J = 4.9, 17.97), 2.42 (s, 3H), 2.05 (dd, 1H, J = 11.75, 17.83), 1.9−1.65 (m, 4H), 1.6−0.8 (m, 6H); ^{13}C NMR 169.7, 144.5, 136.1, 129.1, 128.5, 52.1, 40.9, 38.5, 36.5, 32.1, 29.3, 25.1, 25, 21.5. Analytical data for **25**: R_f 0.51 (35% EtOAc in hexanes); $[\alpha]_D$ = +27.3° (*c* 1.35, EtOAc); ^{1}H NMR δ 7.86 (d, 2H, J = 8.41), 7.28 (d, 2H, J = 8.58), 3.95 (dd, 1H, J = 6.26, 12.3), 3.79 (dd, 1H, J = 5, 12.3), 2.42 (s, 3H), 2.35 (partially overlapped dd, 2H, J = 2.95, 6.93), 1.9 (m, 2H), 1.7−1.2 (m, 8H); ^{13}C NMR δ 170, 144.6, 136.2, 129.2, 128.6, 49.3, 36.7, 33.4, 32.1, 28.2, 25.9, 23.1, 21.9, 21.6. Anal. Calcd for $C_{16}H_{21}NO_3S$: C, 62.51; H, 6.89; N, 4.56. Found: C, 62.57; H, 7.05; N, 4.36.

***N*-(4-Methylphenyl)sulfonyl-3-[(2-methylsulfonyloxo)-ethyl]indole (32).** *tert*-Butyldimethylsilyl chloride (7 g, 46 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 20 min to a cold solution (0 °C) of tryptophol[41] (6.8 g, 42 mmol), triethylamine (8.8 mL, 63 mmol), and DMAP (0.5 g, 4.2 mmol) in CH_2Cl_2 (45 mL). The reaction mixture was stirred for 12 h, after which it was diluted with $CHCl_3$ (50 mL), and the organic phase was washed with 1 M HCl, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated to provide *O*-(*tert*-butyldimethylsilyl)tryptophol (18 g, crude): ^{1}H NMR δ 7.9 (br, 1H), 7.56 (d, 1H, J = 8.75), 7.25 (m, 3H), 6.95 (s, 1H), 3.85 (t, 2H, J = 7.5), 2.94 (t, 2H, J = 7.5), 0.92 (s, 9H), 0.0 (s, 6 H). The crude *O*-(*tert*-butyldimethylsilyl)tryptophol (18 g, 42 mmol), tosyl chloride (9.8 g, 51 mmol), and *n*-Bu_4NHSO_4[42] (0.3 g, 0.84 mmol) were dissolved in toluene (250 mL). The resulting solution was vigorously stirred with 10% NaOH solution (500 mL) for 18 h, after which the phases were separated and the organic phase was washed with water (200 mL), dried ($MgSO_4$) and concentrated to provide *N*-tosyl-*O*-(*tert*-butyldimethylsilyl)tryptophol (9.5 g, crude): ^{1}H NMR δ 8.0 (d, 1H, J = 8.75), 7.74 (d, 2H, J = 8.31), 7.48−7.16 (m, 6H), 3.85 (t, 2H, J = 7.5), 2.94 (t, 2H, J = 7.5), 2.28 (s, 3 H), 0.9 (s, 9H), 0.0 (s, 6H). The crude *N*-tosyl-*O*-(*tert*-butyldimethylsilyl)tryptophol (9.5 g, 22 mmol) was dissolved in THF (25 mL), and the solution was cooled in an ice bath. *n*-Bu_4NF (24 mL, 24 mmol) was added to the above solution, and the reaction mixture was stirred for 4 h. The reaction mixture was stopped by addition of water (50 mL) and extracted with EtOAc (2 × 25 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated to provide *N*-tosyltryptophol (6.2 g, crude): ^{1}H NMR δ 8.0 (d, 1H, J = 8.75), 7.74 (d, 2H, J = 8.31), 7.48−7.16 (m, 6H), 3.85 (t, 2H, J = 7.5), 2.94 (t, 2H, J = 7.5), 2.28 (s, 3 H), 2.12 (br, 1H). The crude *N*-tosyltryptophol (6.2 g, 19.7 mmol), triethylamine (4.12 mL, 29.55 mmol), and DMAP (0.25 g, 2 mmol) were dissolved in CH_2Cl_2 (20 mL), and the resulting solution was cooled in an ice bath (0 °C). Freshly distilled methanesulfonyl chloride (2.48 g, 21.7 mmol) in CH_2Cl_2 (5 mL) was slowly added to the solution above, and the reaction mixture was stirred for 3 h, after which it was diluted with $CHCl_3$ and the organic phase was extracted with 1 M HCl, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. Chromatography (35% EtOAc in hexanes) provided the mesylate **32** (7.73 g, 46% from tryptophol) as a viscous, sticky oil: R_f 0.3 (35% EtOAc in hexanes); ^{1}H NMR δ 7.98 (d, 1H, J = 8.32), 7.74 (d, 2H, J = 8.41 Hz), 7.45 (m, 2H), 7.4−7.2 (m, 4H), 4.43 (t, 2H, J = 6.84), 3.12 (t, 2H, J = 7), 2.83 (s, 3H), 2.32 (s, 3H); ^{13}C NMR δ 144.9, 135.4, 135.2, 130.3, 129.9, 126.8, 125.0, 124.2, 123.3, 119.1, 117.3, 113.8, 68.4, 37.4, 25.2, 21.4; HRMS for $C_{18}H_{19}NO_5S_2$ calcd 393.0706, found 393.0712.

Indole Olefin (33). K_2CO_3 (1.41 g, 10.2 mmol) was added to a solution of the tosylamide **20** (0.75 g, 2.5 mmol) and the mesylate **32** (2 g, 5.11 mmol) in DMF (7 mL), and the reaction mixture was then warmed to 70 °C and stirred for 24 h. The reaction mixture was then diluted with water and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated. Chromatography (25% hexanes in $CHCl_3$) provided **33**

(41) Tryptophol is commercially available (Aldrich) or can be easily prepared by a two-step process from indole.[21]

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(1.32 g, 92%, 3:1 mixture of trans and cis isomers) as a foamy solid: R_f 0.33 (20% hexanes in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.89 (d, 1H, J = 8.25), 7.69 (d, 2H, J = 8.21), 7.41 (m, 1H), 7.27, 7.14 (m, 7H), 5.8* (m, 1H), 5.43 (m, 1H), 4.97−4.83 (m, 2H), 3.3−2.68 (m, 6H), 2.35 (s, 3H), 2.27 (s, 3H), 1.9 (m, 1H), 1.59−0.5 (m, 11H); ^{13}C NMR (* indicates signal arising form minor cis isomer) δ 144.7, 143.1*, 143, 142.4, 138.6*, 136.6, 136.5*, 135.2, 135.1, 130.4, 129.7, 129.5, 127.1, 127*, 126.9*, 126.7, 124.6, 123.4, 123.3*, 123, 119.2, 119.1, 115.6*, 114.6, 113.6, 53.4, 51.4*, 48.5, 46.3, 41.8*, 40.1, 38.3*, 33.4, 30.4*, 29.8, 25.8*, 25.5, 25.4, 25*, 24.8, 24.1*, 22.3*, 21.4, 21.3. Anal. Calcd for $C_{33}H_{38}N_2O_4S_2\cdot 0.5H_2O$: C, 66.08; H, 6.65; N, 4.67. Found: C, 66.14; H, 6.4; N, 4.39.

Indole Alcohol (34). 9-BBN (17.6 mL of a 0.5 M solution in THF, 8.8 mmol) was added to a solution of the olefin **33** (1.3 g, 2.2 mmol) in THF (4 mL). The reaction mixture was stirred at room temperature for 3.5 h. The reaction was cooled in an ice bath, and the excess 9-BBN was quenched with EtOH (5.2 mL) and stirred for 5 min followed by addition of 6 N NaOH (1.8 mL) and H_2O_2 (3.5 mL, 30% solution). The reaction was refluxed for 60 min and cooled to room temperature. The reaction was then diluted with water and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. Chromatography (35% EtOAc in hexanes) provided **34** (1.17 g, 90%, 3:1 mixture of trans and cis isomers): R_f = 0.32 (40% EtOAc in hexanes); ^{1}H NMR δ 7.94 (d, 1H, J = 7.72), 7.73 (d, 2H, J = 8.37), 7.66 (d, 2H, J = 8.3), 7.44 (m, 1H), 7.29−7.17 (m, 8H), 3.7−3.5 (m, 2H), 3.4−3.15 (m, 2H), 3.05−2.79 (m, 3H), 2.4 (s, 3H), 2.3 (s, 3H), 1.9−0.9 (m, 14H); ^{13}C NMR (* indicates signal arising form minor cis isomer) δ 144.9, 143.3, 143.2*, 136.6, 136.4*, 135.4, 135.2, 130.5, 129.8, 129.7, 127.2, 126.8, 124.7, 123.5, 123.4*, 123.2, 119.3, 113.7, 61.2*, 60.6, 53.1, 50.2*, 48.7, 48.5*, 40.1, 38.2*, 36.7, 36.1, 33.2*, 31.3*, 31.2, 29.7, 28.5*, 26*, 25.4*, 25.1, 25, 23.8*, 22.7*, 21.5, 21.4. Anal. Calcd for $C_{33}H_{40}N_2O_5S_2$: C, 65.1; H, 6.62; N, 4.6. Found C, 64.8; H, 6.75; N, 4.2.

Indole Aldehyde (35). Dimethyl sulfoxide (0.16 mL, 2.2 mmol) in CH_2Cl_2 (1 mL) was slowly added to a cold (−78 °C) solution of freshly distilled oxalyl chloride (0.1 mL, 1.2 mmol) in CH_2Cl_2 (1 mL). The resulting solution was then stirred for 45 min at −78 °C. The alcohol **34** (0.54 g, 0.88 mmol) in CH_2Cl_2 (1 mL) was then added to the reaction mixture via a cannula and the whole stirred at −78 °C for 60 min. Et_3N (0.4 mL, 3 mmol) in CH_2Cl_2 (1 mL) was then added to the reaction mixture, which was then slowly allowed to warm to room temperature over 30 min. The reaction was quenched by the addition of a few drops of 1 M HCl and diluted with $CHCl_3$. The organic phase was then washed with 1 M HCl, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. Chromatography (30% EtOAc in hexanes) provided the aldehyde **35** (0.47 g, 88%, 3:1 mixture of trans/cis isomers): R_f 0.35 (30% EtOAc in hexanes); ^{1}H NMR δ 9.65 (m, 1H), 7.96 (d, 1H, J = 7.09). 7.75 (d, 2H, J = 8.28), 7.56 (d, 2H, J = 8.28), 7.5 (m, 1H), 7.45−7.2 (m, 8H), 3.4−3.25 (m 2H), 3.1−2.9 (m, 4H), 2.5−2.4 (m, overlapped, 1H), 2.4 (s, 3H), 2.33 (s, 3H), 2.33−2.11 (m, overlapped, 1H), 1.9−1.6 (m, 4H), 1.5−0.9 (m, 5H); ^{13}C NMR (* indicates signal arising form minor cis isomer) δ 202.3*, 202.1, 144.9, 143.5*, 143.4, 136.4, 136.2*, 135.4, 135.2, 130.5, 129.9, 129.8*, 129.7, 127.2, 126.8, 124.8, 123.6, 123.5*, 123.2, 119.3, 119.2, 113.7, 53, 48.8, 48.4*, 48.1, 42.9*, 40, 37.7*, 34.9, 32.4, 30.9*, 29.6, 29.3*, 26*, 25.2, 25, 24.8, 23.7*, 22.2*, 21.5, 21.4. Anal. Calcd for $C_{33}H_{38}N_2O_5S_2\cdot 0.5H_2O$: C, 64.36; H, 6.38; N, 4.54. Found C, 64.12; H, 6.27; N, 4.42.

Indole Ester (37). A 1 M $KMnO_4$ solution (3 mL) was added to a solution of the aldehyde **35** (0.3 g, 0.45 mmol) in *t*-BuOH (3 mL) containing $CHCl_3$ (5−10 drops until **35** completely dissolves) and 5% NaH_2PO_4 solution (2 mL) at 0 °C. The reaction mixture was then stirred for 10 min and quenched by the addition of solid Na_2SO_3 until the solution turned a dark brown from the initial dark purple color. HCl (1 M) was added to the reaction mixture until the pH of the solution was <1. The reaction was then extracted with EtOAc (2 × 10 mL), and the combined layers were washed with brine, dried ($MgSO_4$), and concentrated. The crude material was then dissolved in MeOH (1 mL) and benzene (3.5 mL). Me_3SiCHN_2 (0.32 mL of a 1 M solution in hexanes, 0.64 mmol) was then added to the reaction mixture via a syringe, and the whole was stirred for 30 min, after which the reaction mixture was diluted with water and extracted with EtOAc (2 × 5 mL). The combined organic layers were then washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography (25% EtOAc in hexanes) provided the ester **37** (0.25 g, 80% from **35**) as a white foam: R_f 0.32 (25% EtOAc in hexanes); ^{1}H NMR δ 7.94 (d, 1H, J = 7.15), 7.72 (d, 2H, J = 8.38), 7.65 (d, 2H, J = 8.25), 7.48 (d, 1H, J = 6.91), 7.3−7.15 (m, 8H), 3.61* (s, 3H), 3.6 (s, 3H), 3.4−2.8 (m, 5H), 2.38 (s, 3H), 2.34−2.1 (m, overlapped, 2H), 2.29 (s, 3H), 1.9−0.9 (m, 9H). ^{13}C NMR (* indicates signal arising form minor cis isomer) δ 173.3*, 173.1, 144.7, 143.3, 143.2, 136.3, 136.2*, 135.2*, 135.1, 130.4, 129.7, 129.6*, 129.5, 127.1*, 127.1, 126.7, 124.7, 123.5*, 123.4, 123.1, 119.2, 119.1, 113.6, 52.6, 51.4*, 51.3, 48.6, 48.3*, 39.7, 38.4, 37.1, 37*, 34.3*, 31.9, 29.4, 29.1*, 25.8*, 25.2, 25.1*, 24.9, 24.8, 23*, 22.9*, 21.4, 21.3. Anal. Calcd for $C_{34}H_{40}N_2O_6S_2\cdot 0.5H_2O$: C, 63.23; H, 6.4; N, 4.33. Found: C, 63.47; H, 6.45; N, 4.17.

Indole Lactam (38). Finely chopped sodium metal (66 mg, 2.9 mmol) and naphthalene (0.37 g, 2.9 mmol) were stirred in DME (3.8 mL) for 90 min during which a greenish black solution formed. The reaction mixture was then cooled in an ice bath. The ester **37** (0.19 g, 0.29 mmol) in DME (2.3 mL) was then added to the reaction mixture via cannula and the solution stirred for 60 min. The reaction was then quenched with water, and the aqueous layer was extracted with EtOAc. The organic layer was then washed with brine, dried ($MgSO_4$), and concentrated. Chromatography (2% MeOH in $CHCl_3$) provided the lactam **38** (66 mg, 77%) as a light brown solid: R_f 0.25 (2% MeOH in $CHCl_3$); ^{1}H NMR δ 8.27 (br, 1H), 7.67 (d, 1H, J = 7.45), 7.35 (d, 1H, J = 7.64), 7.21−7 (m, 4H), 3.75−3.6 (m, 2H), 3.2−2.8 (m, 4H), 2.6−2.4 (m, 1H), 2.1−1.9 (m, 1H), 1.85−1.6 (m, 5H), 1.6−1.1 (m, 6H), 1−0.8 (m, 1H); ^{13}C NMR (* indicates signal arising form minor cis isomer) δ 169.6, 169.3*, 138.3, 128.3*, 127.6, 122*, 121.9, 121.9, 119.3, 118.8, 113.3, 111.1, 54.4, 51.1*, 48.1*, 48, 39.5, 38.4, 37.1, 35.2*, 33*, 32.6, 32.5*, 29.7, 28.3*, 26.5*, 25.4, 23.1*, 23, 22.6*. Anal. Calcd for $C_{19}H_{24}N_2O\cdot 0.75H_2O$: C, 73.82; H, 8.07; N, 9.06. Found: C, 74.04; H, 8.03; N, 8.66.

(−)-Yohimbane (1) and *ent*-Alloyohimbane (*ent*-2). The lactam **38** (39 mg, 0.13 mmol) was refluxed in freshly distilled $POCl_3$ (0.2 mL, 0.2 mmol) for 60 min. Benzene (1.3 mL) was then added to the reaction mixture, which was then refluxed for another 2.5 h. The reaction mixture was concentrated until dryness. The residue thus obtained was taken up in MeOH (2.4 mL), and the reaction mixture was cooled in an ice bath followed by addition of $NaBH_4$ (20 mg, 0.53 mmol), after which the reaction mixture was stirred for 60 min. The reaction was then quenched by the addition of a few drops of AcOH. The solvent was removed in vacuo, and the residue was partitioned between EtOAc and saturated $NaHCO_3$ solution. The organic phase was dried ($MgSO_4$) and concentrated. Chromatography (17% EtOAc, 1% Et_3N, 82% toluene) provided (−)-yohimbane (22 mg, 59%) and *ent*-alloyohimbane (8 mg, 22%). Analytical data for **1**: R_f 0.19 (17% EtOAc, 1% Et_3N, 82% toluene); $[\alpha]_D$ −82.9° (*c* 0.38, EtOH) [lit.[7g] $[\alpha]_D$ −81° (*c* 0.5, EtOH)]. Analytical data for *ent*-**2**: R_f 0.24 (17% EtOAc, 1% Et_3N, 82% toluene); $[\alpha]_D$ +146° (*c* 0.1, pyridine) [lit.[9b] $[\alpha]_D$ of (−)-alloyohimbane −164° (*c* 0.5, pyridine)]. ^{1}H and ^{13}C NMR for (−)-yohimbane and *ent*-alloyohimbane matched those previously reported.[9]

Acknowledgment. The authors would like to gratefully acknowledge Jim Mobley for his help with the HPLC separation and Dr. J. Aube (University of Kansas) for providing us with ^{1}H NMR and ^{13}C NMR spectra of yohimbane and alloyohimbane.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **1**, **ent-2**, and **32** as well as ^{1}H NMR spectra of **24** and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9825097