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Enzymatic Desymmetrization

Enantioselective Syntheses of (–)-Alloyohimbane and (–)-Yohimbane by an Efficient Enzymatic Desymmetrization Process

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Abstract: Enantioselective syntheses of (–)-alloyohimbane and (–)-yohimbane were accomplished in a convergent manner. The key step involves a modified mild protocol for the enantioselective enzymatic desymmetrization of a *meso*-diacetate. This provides convenient access to an optically active monoacetate in multi-gram quantities and in high enantiomeric purity. This monoacetate was converted to (–)-alloyohimbane. Reductive amination of the derived aldehyde caused isomerization to the *trans*-product and, ultimately, the formation of (–)-yohimbane.

Introduction

The yohimbine alkaloids, featuring a characteristic pentacyclic indole ring framework, display a wide range of pharmacological properties.[1,2] These alkaloids belong to the *Rubiaceae* family and they are isolated from the bark of the *Pausinystalia Yohimbe* tree in central Africa. Over the years, this family of alkaloids has received much attention due to its antihypertensive and antipsychotic activity.[3–6] Yohimbine (Figure 1) and related derivatives have been used as traditional medicines, specifically as adrenergic blocking agents for Angina pectoris and arteriosclerosis. They are also used as herbal medicines for the treatment of impotency. Furthermore, yohimbines have been shown to lower body fat and relieve symptoms of dry mouth.[7,8] The biological mechanism of action of the yohimbine family may be due to its potent, competitive, and selective alpha-2-adrenergic receptor antagonist properties.[9,10] They have been shown to block dopamine pathways in schizophrenic patients. Also, they weakly interact with alpha-1-adrenoreceptors. Not surprisingly, the chemistry and biology of yohimbines have attracted immense interest leading to many synthetic and biological studies. To date, several racemic syntheses,[11–13] as well as enantioselective syntheses[14–16] of yohimbine and related alkaloids have been reported. Racemic[17–20] and enantioselective[16,21–26] syntheses of alloyohimbane and yohimbane, the pentacyclic skeleton of yohimbine alkaloids have also been reported in the literature. Stemming from our interest in the use of polycyclic indoles in medicinal chemistry, we have devised practical and enantioselective syntheses of (–)-yohimbane and (–)-alloyohimbane. Herein we report convergent syntheses of these molecules using enzymatic desymmetrization as the key step. Of particular interest, we have developed a modified protocol, which provides convenient access to (1*R*, 6*S*)-6(hydroxymethylcyclohexenyl) methyl acetate in high optical purity in multigram scales.

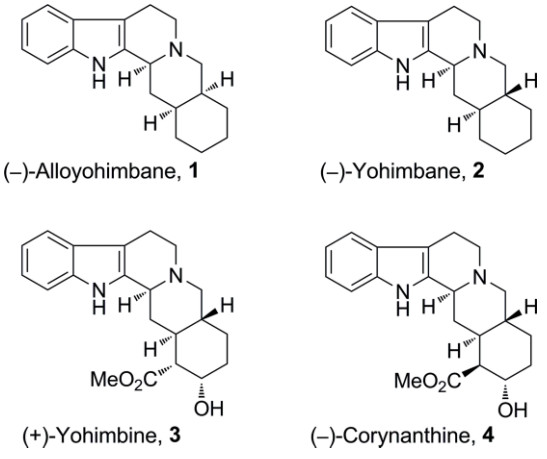

Figure 1. Structures of yohimbine and related compounds.

Results and Discussion

Our retrosynthetic analysis of (–)-alloyohimbane and (–)-yohimbane is shown in Figure 2. For the synthesis of (–)-alloyohimbane, we planned a Bischler–Napieralski reaction to construct the pentacyclic indole framework from corresponding lactams **5** and **6**. A similar saturated lactam intermediate has previously been converted to the corresponding yohimbane derivative.[19,22] Lactam **5** would be obtained from nitrile derivative **7** through its conversion to the corresponding acid followed by removal of the *tert*-butyloxycarbonyl group (Boc) and amidation of the resulting amino acid. Nitrile derivative **7** can be obtained by reductive amination of 3-indolyl acetaldehyde **8** and (1*R*, 6*S*)-6-(aminomethylcyclohexenyl)methyl acetate **9** and

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subsequent nitrile installation via standard synthetic steps. The requisite optically active amine would be derived from the corresponding (1*R*, 6*S*)-6-(hydroxymethylcyclohexenyl)methyl acetate **10**. Optically active alcohol **10** can be obtained by enzymatic desymmetrization of the corresponding *meso*-diacetate. For the synthesis of (–)-yohimbane, we planned to carry out reductive amination of (1*R*, 6*R*)-6-(formylcyclohexenyl)methyl acetate **11**, which could be obtained by oxidation of alcohol **10** and in situ epimerization of the resulting aldehyde via an enamine intermediate. Therefore, optically active alcohol **10** was envisioned to be useful for the syntheses of both alloyohimbane and yohimbane as well as their derivatives.

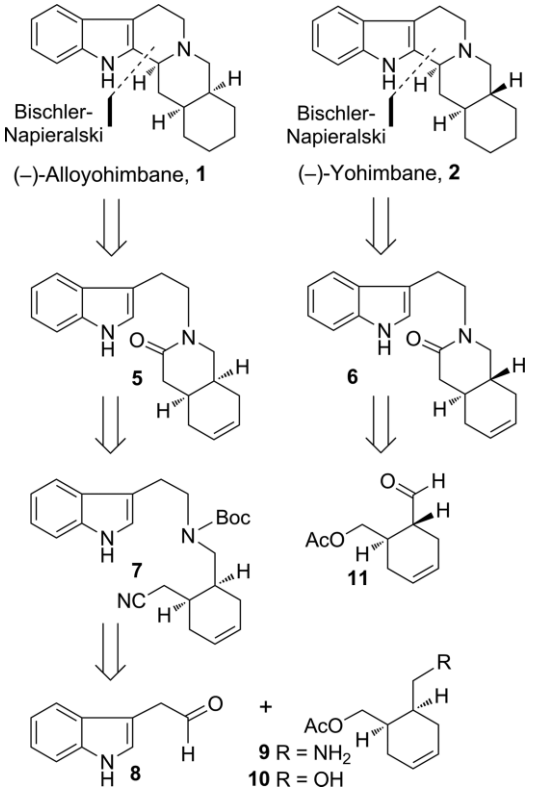
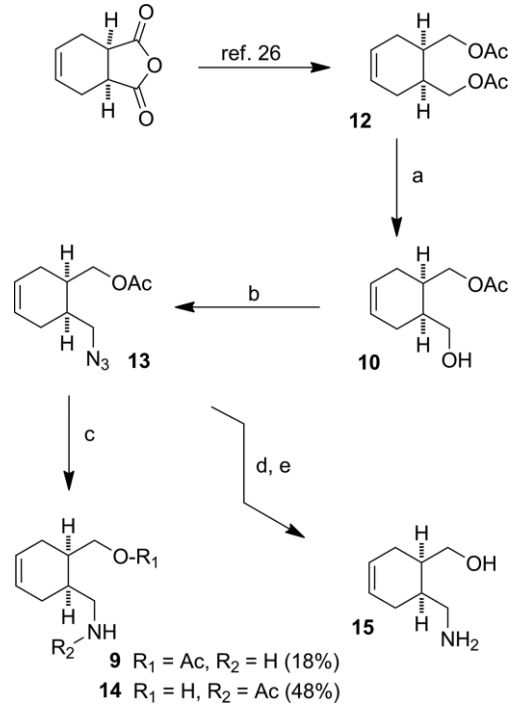


Figure 2. Retrosynthetic analysis for yohimbanes.

Our synthesis of optically active alcohol **10** via desymmetrization is shown in Scheme 1. Commercially available *meso*-1,2,3,6-tetrahydrophthalic anhydride was converted to *meso*-diacetate **12** by $LiAlH_4$ reduction followed by acetylation of the resulting diol as reported in the literature.[27] For optical resolution, we planned to utilize commercially available and inexpensive porcine pancreatic lipase (PPL), an enzyme that hydrolyzes dietary triglycerides to monoglycerides and free fatty acids.[28] This enzyme has been extensively utilized in the selective hydrolysis of esters in aqueous solution. As reported, exposure of *meso*-diacetate **12** with PPL in 0.1 M phosphate buffer (pH 7) provided monoacetate **10** with high optical purity.[27,29] The reaction protocol required continuous addition of 1 N NaOH solution to neutralize the acetic acid released in the reaction.

Although this protocol provided optically active alcohol **10**, the observed enantiomeric excess (*ee*) and reaction yields proved variable, particularly during large scale preparations. We presume that the erosion of *ee* could be due to competing non-

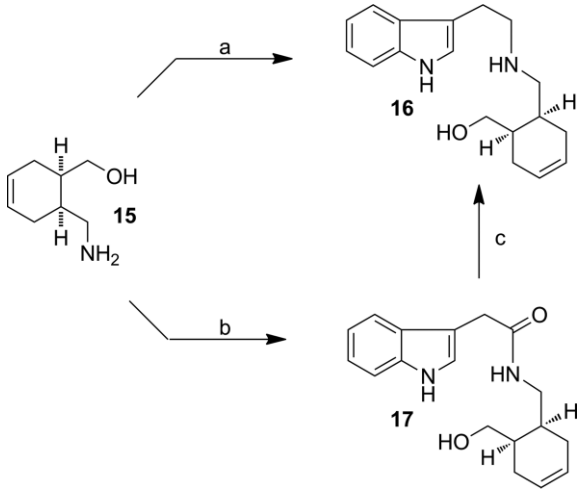


Scheme 1. Reagents and conditions: (a) PPL (5 % w/w), pH 7 buffer, 23 °C, 1 N $NaHCO_3$ (84 %); (b) PPh_3, diethyl azodicarboxylate, $(PhO)_2P(O)N_3$, 0 °C, THF (92 %); (c) PPh_3, H_2O, THF, 60 °C; (d) K_2CO_3, MeOH, 0 °C; (e) PPh_3, THF, 60 °C, then, H_2O, 60 °C (78 % over two steps).

enzymatic hydrolysis of the *meso*-diacetate **12**. Also, variability in yields may have been due to non-enzymatic hydrolysis of monoacetate **10**. In an effort to minimize this competing non-enzymatic reaction, we investigated a number of other organic and inorganic bases that can effectively neutralize liberated acetic acid without non-enzymatic side reactions. We found that enzymatic desymmetrization of the *meso*-diacetate[27] in the presence of 1 N $NaHCO_3$ aqueous solution provided monoacetate **10** in high optical purity (> 95 % *ee*) with reproducible yields (> 80 %). In a typical experiment, we carried out enzymatic desymmetrization of *meso*-diacetate **12** with 5 % (w/w) PPL (Sigma, type II, crude) in pH 7 phosphate buffer at 23 °C in the presence of 1 N aqueous $NaHCO_3$ solution over the course of 24 h. We have carried out this enzymatic desymmetrization on 51 gram scale and obtained monoacetate **10** in 84 % yield with > 95 % *ee* as determined by HPLC analysis (see Supporting Information for further details). Accordingly, we utilized this optically active alcohol in a unified synthesis of (–)-alloyohimbane and (–)-yohimbane.

For the synthesis of (–)-alloyohimbane, alcohol **10** was subjected to Mitsunobu azidation,[30,31] by using diphenylphosphoryl azide (DPPA) and triphenylphosphine in THF at 0 °C for 40 min to provide azide **13** in 92 % yield. Staudinger reduction,[32] of **13** with triphenylphosphine in aqueous THF at 60 °C, provided desired amine **9** in only 18 % yield. Acetamide **14**, resulting from intramolecular acetate transfer, was obtained as a major product in 48 % yield. Acetate **13** was therefore converted to amino alcohol **15** by exposure to K_2CO_3 in MeOH at 0 °C for 1 h followed by Staudinger reduction to provide **15** in 78 % yield over two steps.

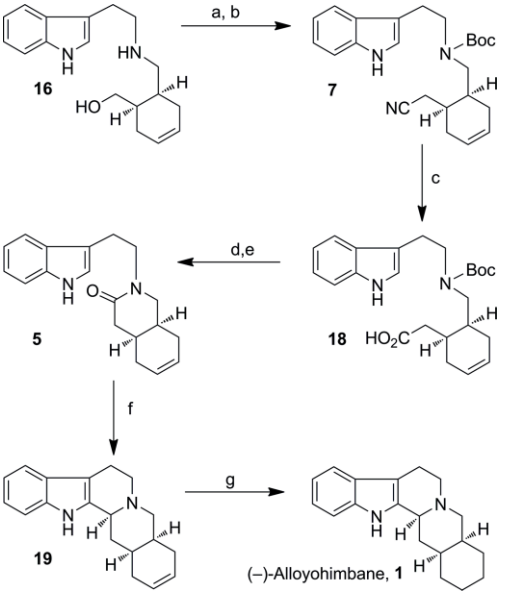
Our initial coupling of amine **15** with 3-indolyl acetaldehyde[33] did not provide satisfactory results. As shown in Scheme 2, reductive amination of **15** with 3-indolyl acetaldehyde was carried out with sodium cyanoborohydride in MeOH in the presence of acetic acid. However, this reductive amination provided amine **16** in poor yields under a variety of reaction conditions, presumably due to the instability of 3-indolyl acetaldehyde. In an alternative route, amine **15** was coupled with 3-indolylacetic acid by using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and 1-hydroxybenzotriazole (HOBt) in THF at 23 °C for 12 h to provide amide **17** in 75 % yield. Reduction of this amide with $LiAlH_4$ in THF at 80 °C for 12 h afforded amine **16** in 74 % yield.



Scheme 2. Reagents and conditions: (a) 3-indolyl acetaldehyde **8**, AcOH, MeOH, $Na(CN)BH_3$, 23 °C (24 %); (b) 3-indolylacetic acid, EDC, HOBt, NEt*i*Pr_2, THF, 23 °C (75 %); (c) $LiAlH_4$, THF, 80 °C (74 %).

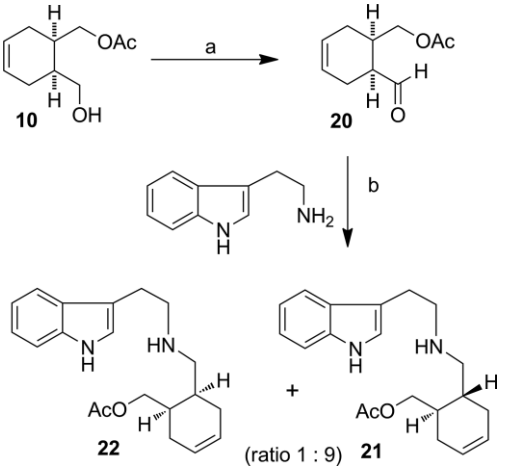
The synthesis of (–)-alloyohimbane from amine **16** is shown in Scheme 3. Amine **16** was protected as the Boc derivative by treatment with 0.95 equiv. of Boc_2O in CH_2Cl_2 at 23 °C for 5 h. These conditions provided predominantly the corresponding *N*-Boc derivative and only trace amounts of the corresponding *tert*-butylcarbonate. The free alcohol was converted to cyanide **7** by using a Mitsunobu reaction with acetone cyanohydrin[34] in the presence of diisopropyl azodicarboxylate (DIAD) and triphenylphosphine in THF at 23 °C for 6 h. Cyanide derivative **7** was obtained in 83 % yield over two steps. Compound **7** was treated with 20 % aqueous NaOH in ethanol at reflux for 18 h to provide acid **18** in 76 % yield. The Boc group was cleaved by exposure to trifluoroacetic acid in CH_2Cl_2 at 23 °C for 1 h and reaction of the resulting amino acid with EDC and HOBt in the presence of diisopropylethylamine at 23 °C for 18 h afforded lactam **5** in 45 % yield over the two steps. The lactam was converted to (–)-dehydroalloyohimbane **19** by a Bischler–Napieralski reaction[22] with phosphorus oxychloride in CH_2Cl_2 (1:1) at 50 °C for 4 h followed by sodium borohydride reduction of the resulting iminium ion to provide **19** as a single isomer in 74 % yield. The stereochemical outcome was dictated by the existing ring stereochemistry and preferred hydride attack from the sterically less hindered α-face. Catalytic hydrogenation of olefin **19** over 10 % Pd/C in ethyl acetate under a H_2-filled balloon at 23 °C for 1 h furnished (–)-alloyohimbane (–)-**1** in 91 % yield.

The spectroscopic data of our synthetic (–)-alloyohimbane and observed specific rotation {$[\alpha]_D^{20}$ = –78.8 (*c* = 0.3 EtOH)} are in complete agreement with the synthetic (–)-alloyohimbane reported in the literature.[22]



Scheme 3. Reagents and conditions: (a) Boc_2O, CH_2Cl_2, 23 °C; (b) PPh_3, DIAD, THF, $Me_2C(OH)CN$, 23 °C (83 % over two steps); (c) 20 % aq. NaOH, EtOH (1:1), reflux (76 %); (d) CF_3CO_2H, CH_2Cl_2, 23 °C; (e) EDCI, HOBt, NEt*i*Pr_2, CH_2Cl_2, 23 °C (45 % over two steps); (f) $POCl_3$, CH_2Cl_2, 50 °C, then, $NaBH_4$, MeOH/H_2O, 0 °C (74 %); (g) H_2, 10 % Pd-C, EtOAc, 23 °C (91 %).

The synthesis of (–)-yohimbane, **2** from (1*R*, 6*S*)-6-(hydroxymethylcyclohexenyl)methyl acetate **10** is shown in Scheme 4. Swern oxidation of alcohol **10** provided aldehyde **20**, which was immediately subjected to reductive amination with tryptamine in the presence of acetic acid and sodium cyanoborohydride at 23 °C for 10 h. To our delight, the reductive amination conditions led to the formation of epimerized product **21** along with unepimerized product **22** in a 9:1 diastereomeric ratio as determined by ^1H NMR spectroscopy. Swern oxidation conditions provided predominantly *cis*-aldehyde **20** and only trace amounts of epimerized *trans*-aldehyde **11** as determined by ^1H-



Scheme 4. Reagents and conditions: (a) $(COCl)_2$, DMSO, NEt_3, –78 °C, CH_2Cl_2 (93 %); (b) AcOH, MeOH, $Na(CN)BH_3$, 23 °C (73 %).

NMR spectroscopy. The reductive amination provided epimerized product **21** as the major product presumably due to epimerization via an imine-enamine pathway. As shown in Figure 3, initial imine **23** isomerized to the more stable *trans*-imine **25** via enamine **24** under the reaction conditions. Interestingly, hydrogenation of the *cis*-aldehyde with tryptamine and 10 % Pd-C in methanol at 23 °C for 24 h resulted in significantly less epimerization and the corresponding saturated *cis*-isomer of **22** was formed as the major product (7:3 diastereomeric ratio). Additionally, the acetate group was hydrolyzed under these reaction conditions.

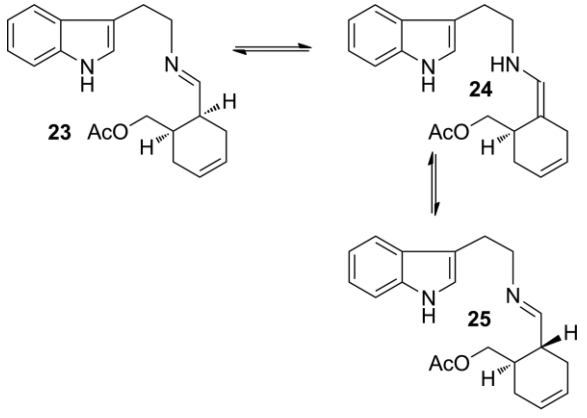
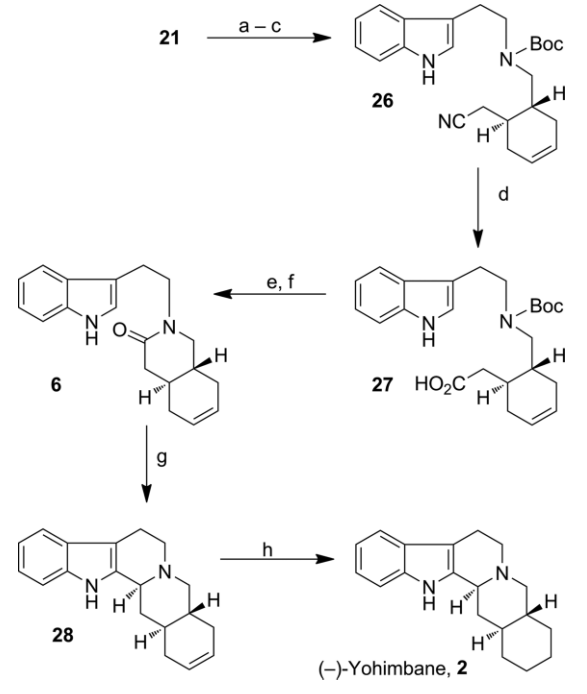


Figure 3. Plausible epimerization pathway.

Amine **21** was converted to (–)-yohimbane as shown in Scheme 5. Treatment of amine **21** with Boc_2O provided the corresponding Boc-protected amine in 92 % yield. Saponification of the acetate afforded the corresponding alcohol in 96 % yield and this alcohol was then converted to cyanide **26** in 94 % yield. The cyanide was then hydrolyzed to carboxylic acid **27** as described above. Carboxylic acid **27** was subjected to trifluoroacetic acid and the resulting amino acid was converted to lactam **6** in 42 % yield over two steps. Lactam **6** was then treated with phosphorus oxychloride in CH_2Cl_2 at 50 °C for 4 h followed by treatment with $NaBH_4$ to afford pentacyclic indole derivative **28** in 72 % yield. Catalytic hydrogenation of **28** with 10 % Pd-C under a H_2-filled balloon furnished (–)-yohimbane **2** in 92 % yield. The spectroscopic data of our synthetic (–)-yohimbane {$[\alpha]_D^{20}$ = –77.6 (*c* = 0.22, EtOH)} is in complete agreement with the synthetic (–)-yohimbane {$[\alpha]_D^{22}$ = –81 (*c* = 0.5, EtOH)} reported in the literature.[23]



Scheme 5. Reagents and conditions: (a) Boc_2O, NEt_3, CH_2Cl_2, 23 °C; (b) K_2CO_3, MeOH, 0 °C; (c) PPh_3, DIAD, $Me_2C(OH)CN$, THF, 23 °C (83 % over three steps); (d) 20 % aq. NaOH, EtOH (1:1), reflux (81 %); (e) CF_3CO_2H, CH_2Cl_2, 23 °C; (f) EDCI, HOBt, $NEtiPr_2$, CH_2Cl_2, 23 °C (42 % over two steps); (g) $POCl_3$, CH_2Cl_2, 50 °C, then, $NaBH_4$, $MeOH/H_2O$, 0 °C (72 %); (h) H_2, 10 % Pd-C, EtOAc, 23 °C (92 %).

Conclusions

In summary, we have developed stereoselective syntheses of (–)-yohimbane and (–)-alloyohimbane which feature enantioselective enzymatic desymmetrization with sodium hydrogen carbonate to neutralize the acetic acid formed. To the best of our knowledge, this procedure has not been reported in the literature and should serve as an excellent technique for large-scale synthesis of optically active starting materials due to the mild basicity of sodium hydrogen carbonate. Epimerization during reductive amination was used to our advantage and utilized for the synthesis of (–)-yohimbane. Different stereochemical consequences attained by reductive amination and amide coupling reactions enabled efficient paths to the pentacyclic cores of yohimbine alkaloids. The strategically positioned unsaturated site in pentacyclic indole derivatives **19** and **28** can be used conveniently to synthesize yohimbol, yohimbine, alloyohimbine, corynanthine and related alkaloids. The efficacy and brevity of this synthesis underscores the value of enantioenriched products that are easily accessible by enzymatic desymmetrization.

Experimental Section

All reactions were carried out under an atmosphere of Ar in oven-dried (120 °C) glassware with magnetic stirring unless otherwise noted. Solvents, reagents and chemicals were purchased from commercial suppliers. Solvents were distilled as follows: dichloromethane from calcium hydride, tetrahydrofuran from sodium/benzophenone, and methanol from activated magnesium. Purification of reaction products was carried out by flash chromatography by using Silicycle silica gel 230–400 mesh, 60 Å pore diameter. Analytical thin layer chromatography was performed on glass-backed thin-layer silica gel chromatography plates (0.25 mm thickness, 60 Å, F-254 indicator). Visualization was realized with UV light and ethanolic phosphomolybdic acid solution or ethanolic acidic *p*-anisaldehyde solution followed by heating. Optical rotations were measured by using a Perkin–Elmer 341 polarimeter with a sodium lamp and are reported as follows: $[\alpha]_D^{T(°C)}$ (*c* =g/100 mL, solvent). Infrared spectra were recorded with a Varian 2000 Infrared spectrophotometer and are reported as cm^{-1}. ^1H NMR spectra were recorded at room temperature with a Bruker ARX-400 spectrometer and are reported in ppm relative to solvent signals ($CDCl_3$ at δ =

7.26 ppm, CD_3OD at δ = 3.31 ppm) as an internal standard. Data are reported as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, qd = quartet of doublets, dt = doublet of triplets, dq = doublet of quartets, brs = broad singlet; coupling constant(s) in Hz; integration). Proton-decoupled ^{13}C NMR spectra were recorded with a Bruker ARX-400 spectrometer and are reported in ppm by using the solvent as the internal standard ($CDCl_3$ at δ = 77.16 ppm, CD_3OD at δ = 49.00 ppm). Low and High resolution mass spectra were obtained at the Purdue University Department of Chemistry Mass Spectrometry Center.

[(1*R*,6*S*)-6-(Hydroxymethyl)cyclohex-3-en-1-yl]methyl Acetate (10): To a suspension of diacetate **12** (51 g, 0.23 mol) in 0.1 M Phosphate buffer (650 mL, pH 7) was added PPL (2.55 g, Sigma type II, crude). 1 N Sodium hydrogen carbonate solution (690 mL) was added and the heterogeneous mixture was stirred for 24 h. The mixture was then filtered through Celite®. The filtrate was extracted with dichloromethane (× 3). The organic layer was washed with brine, dried with sodium sulfate, filtered and the solvent evaporated. The residue was purified by chromatography on silica gel (25 % to 30 % ethyl acetate/hexanes) to obtain **10** (34.7 g, 0.19 mol, 84 % yield) as a colorless oil. R_f 0.6 (50 % ethyl acetate/hexanes). $[\alpha]_D^{20}$ = –20.1 (*c* = 2.0, $CHCl_3$); lit.[1] $[\alpha]_D^{23}$ = –17.0 (*c* = 0.42, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.75–5.54 (m, 2 H), 4.19 (dd, *J* = 11.0, 6.0 Hz, 1 H), 3.95 (dd, *J* = 11.0, 8.0 Hz, 1 H), 3.68 (dd, *J* = 10.8, 7.1 Hz, 1 H), 3.59 (dd, *J* = 10.7, 6.9 Hz, 1 H), 2.29–2.08 (m, 3 H), 2.06 (s, 3 H), 2.01–1.68 (m, 3 H), 1.80 (br. s, 1 H, OH) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.5, 125.8, 125.3, 65.1, 63.9, 37.4, 33.4, 27.2, 26.1, 21.2 ppm. LRMS-ESI: *m/z* = 207.2 $[M + Na]^+$.

[(1*R*,6*S*)-6-(Azidomethyl)cyclohex-3-en-1-yl]methyl Acetate (13): To a solution of alcohol **10** (1.25 g, 6.8 mmol) and PPh_3 (3.6 g, 13.6 mmol) in tetrahydrofuran (65 mL) at 0 °C was added diethyl azodicarboxylate (5.3 mL, 13.6 mmol) and the solution was stirred for 5 min. Diphenyl phosphoryl azide (2.9 mL, 13.6 mmol) was then added at room temperature and the solution was stirred for 20 min. The solvent was evaporated and the crude mixture was purified over silica gel by using 5 % ethyl acetate/hexanes to yield **13** (1.3 g, 6.2 mmol, 92 % yield) as a yellow liquid. R_f 0.25 (5 % ethyl acetate/hexanes). $[\alpha]_D^{25}$ = –1.7 (*c* = 0.35, $CHCl_3$). IR: $\tilde{\nu}$ = 3028, 2900, 2845, 2094, 1976, 1737, 1653, 1439, 1396, 1387, 1336, 1035, 922, 909 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.57 (s, 2 H), 4.02 (dd, *J* = 11.0, 7.0 Hz, 1 H), 3.93 (dd, *J* = 11.1, 7.3 Hz, 1 H), 3.31 (dd, *J* = 12.1, 6.3 Hz, 1 H), 3.18 (dd, *J* = 12.0, 8.3 Hz, 1 H), 2.22–2.02 (m, 4 H), 1.99 (s, 3 H), 1.94–1.79 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.9, 125.0, 124.9, 64.6, 52.4, 34.4, 33.8, 27.0, 26.5, 20.8 ppm. HRMS (ESI) *m/z* calcd. for $C_{10}H_{15}N_3O_2Na$ $[M + Na]^+$: 232.1062, found 232.1058.

***N*-{[(1*S*,6*R*)-6-(Hydroxymethyl)cyclohex-3-en-1-yl]methyl}-acetamide (14):** To a solution of azide **13** (60 mg, 0.29 mmol) in tetrahydrofuran (4 mL) was added triphenylphosphine (151 mg, 0.58 mmol), followed by few drops of water. The solution was heated at 60 °C for 2 h. The solvent was evaporated, and the residue was purified over silica gel with 5–10 % (5 % ammonia/methanol)/dichloromethane to afford acetamide **14** as a brown oil (25 mg, 0.14 mmol, 48 % yield) along with amino-acetate **9** (vide article) (10 mg, 0.05 mmol, 18 % yield). Analytical data for **9** could not be collected because it gradually converted to **14** under purification conditions and upon standing. Analytical data for **14**: R_f 0.1 [5 % (5 % ammonia/methanol)/dichloromethane]. $[\alpha]_D^{25}$ = +27.1 (*c* = 1.9, $CHCl_3$). ^1H NMR (400 MHz, CD_3OD): δ = 5.73–5.53 (m, 2 H), 3.62 (dd, *J* = 10.8, 6.1 Hz, 1 H), 3.48 (dd, *J* = 10.8, 7.5 Hz, 1 H), 3.24 (dd, *J* = 13.3, 5.5 Hz, 1 H), 3.14–3.03 (m, 1 H), 2.20–1.96 (m, 5 H), 1.94 (s, 3 H), 1.89–1.78 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.9, 125.7, 125.3, 63.0, 40.1, 36.9, 34.1, 27.8, 26.6, 23.0 ppm. LRMS-ESI: *m/z* = 183.2. HRMS (ESI) *m/z* calcd. for $C_{10}H_{17}NO_2Na$ $[M + Na]^+$: 206.1157, found 206.1155.

[(1*R*,6*S*)-6-(Aminomethyl)cyclohex-3-en-1-yl]methanol (15): To a solution of azido-acetate **13** (1.02 g, 4.9 mmol) in methanol (30 mL) was added potassium carbonate (672 mg, 4.9 mmol), and stirred for 2 h. Methanol was removed under reduced pressure, dichloromethane was added and the mixture was washed with water. The organic layer was washed with brine, dried with sodium sulfate and the solvent was evaporated to produce 774 mg (4.7 mmol, 96 % yield) of the corresponding alcohol as a pale yellow viscous liquid. R_f 0.75 (40 % ethyl acetate/hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.72–5.52 (m, 2 H), 3.63 (dd, *J* = 10.8, 6.9 Hz, 1 H), 3.55 (dd, *J* = 10.8, 6.7 Hz, 1 H), 3.40 (dd, *J* = 12.2, 6.3 Hz, 1 H), 3.23 (dd, *J* = 12.1, 8.1 Hz, 1 H), 2.22–2.01 (m, 4 H), 2.00–1.81 (m, 2 H) ppm.

The azido-alcohol (750 mg, 4.5 mmol) obtained above was dissolved in tetrahydrofuran (25 mL) and triphenylphosphine (2.35 g, 9 mmol) was added. The mixture was heated at 60 °C for 1 h. A few drops of water were added, and further heated at 60 °C for 1 h. The solvent and water were removed under vacuum, and the residue was purified by column chromatography by using 5–20 % (5 % ammonia/methanol)/dichloromethane to obtain amino-alcohol **15** (513 mg, 3.63 mmol, 81 % yield) as a yellow oil in 78 % yield over two steps. R_f 0.3 [20 % (5 % ammonia/methanol)/dichloromethane]. $[\alpha]_D^{20}$ = –7.95 (*c* = 2, Methanol). ^1H NMR (400 MHz, CD_3OD): δ = 5.62 (s, 2 H), 3.57 (dt, *J* = 10.0, 5.0 Hz, 1 H), 3.45 (dd, *J* = 10.9, 6.2 Hz, 1 H), 2.70 (dd, *J* = 12.5, 6.0 Hz, 1 H), 2.57 (dd, *J* = 12.6, 7.1 Hz, 1 H), 2.17–1.89 (m, 6 H) ppm. ^{13}C NMR (101 MHz, CD_3OD): δ = 126.9, 126.6, 63.3, 43.1, 39.0, 28.8, 27.8 ppm. LRMS (TWA-CI): *m/z* = 142.25 $[M + H]^+$. HRMS (ESI) *m/z* calcd. for $C_8H_{16}NO$ $[M + H]^+$: 142.1232, found 142.1226.

***N*-{[(1*S*,6*R*)-6-(Hydroxymethyl)cyclohex-3-en-1-yl]methyl}-2-(1*H*-indol-3-yl)acetamide (17):** A solution of indole-3-acetic acid (666 mg, 3.82 mmol) and HOBt hydrate (703 mg, 5.2 mmol) in dry tetrahydrofuran (15 mL) was cooled to 0 °C. EDCI·HCl (732 mg, 3.82 mmol) was added and the mixture was stirred for 1 h at 0 °C. A solution of amino-alcohol **15** (490 mg, 3.47 mmol) and DIPEA (1.81 mL, 10.4 mmol) in tetrahydrofuran (10 mL) was then added at room temp., and the reaction mixture was stirred for 12 h. The solvent was evaporated and the residue was dissolved in ethyl acetate. The solution was washed with saturated aqueous sodium hydrogen carbonate, brine and dried with Na_2SO_4. Ethyl acetate was evaporated and the residue was purified over silica gel by using 75 % ethyl acetate/hexanes to ethyl acetate to furnish light yellow solid **17** (850 mg, 2.85 mmol, 75 % yield). R_f 0.19 (ethyl acetate). $[\alpha]_D^{20}$ = +32.7 (*c* = 2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.26 (s, 1 H), 7.51 (d, *J* = 7.8 Hz, 1 H), 7.36 (d, *J* = 8.1 Hz, 1 H), 7.19 (t, *J* = 7.3 Hz, 1 H), 7.10 (t, *J* = 7.4 Hz, 1 H), 7.05 (s, 1 H), 6.39 (s, 1 H), 5.50 (q, *J* = 9.9 Hz, 2 H), 3.70 (s, 2 H), 3.58–3.48 (m, 1 H), 3.39 (ddd, *J* = 25.9, 11.7, 5.7 Hz, 3 H), 2.87 (dt, *J* = 13.1, 6.3 Hz, 1 H), 2.00–1.80 (m, 4 H), 1.79–1.60 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.8, 127.0, 125.7, 125.2, 124.3, 122.4, 119.8, 118.5, 111.7, 108.3, 63.4, 40.1, 36.9, 34.0, 33.4, 27.8, 26.3 ppm. LRMS (ESI): *m/z* = 321.3 $[M + Na]^+$. HRMS (ESI) *m/z* calcd. for $C_{18}H_{22}N_2O_2Na$ $[M + Na]^+$: 321.1279, found 321.1569.

[(1*R*,6*S*)-6-({[2-(1*H*-Indol-3-yl)ethyl]amino}methyl)cyclohex-3-en-1-yl]methanol (16): To a solution of amide **17** (800 mg, 2.68 mmol) in tetrahydrofuran (40 mL) was added $LiAlH_4$ (407 mg, 10.7 mmol). The suspension was stirred at 80 °C for 12 h. The mixture was cooled to 0 °C and ethyl acetate was added until bubbling ceased. 5 N NaOH solution (9 mL) was added, followed by solid

sodium sulfate. The mixture was filtered through Celite® and the filtrate was evaporated. The residue was taken in ethyl acetate, washed with water and brine. The solvent was evaporated, and the residue was purified over silica gel with 5 % (5 % ammonia/methanol)/dichloromethane to afford amino-alcohol **16** (561 mg, 1.97 mmol, 74 % yield) as a yellow oil. R_f 0.5 [10 % (5 % ammonia/methanol)/dichloromethane]. $[\alpha]_D^{20}$ = –20.7 (*c* = 1.46, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.92 (s, 1 H), 7.61 (d, *J* = 7.6 Hz, 1 H), 7.36 (d, *J* = 7.9 Hz, 1 H), 7.19 (t, *J* = 7.2 Hz, 1 H), 7.12 (d, *J* = 7.2 Hz, 1 H), 6.98 (s, 1 H), 5.75–5.51 (m, 2 H), 4.40 (s, 1 H), 3.75–3.53 (m, 2 H), 3.07–2.80 (m, 4 H), 2.74 (t, *J* = 10.7 Hz, 1 H), 2.42 (d, *J* = 12.2 Hz, 1 H), 2.29–2.15 (m, 2 H), 2.08–1.78 (m, 5 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.4, 127.2, 126.6, 124.6, 122.2, 122.0, 119.2, 118.7, 113.1, 111.2, 64.6, 50.3, 49.3, 39.1, 37.1, 30.8, 25.3, 25.1 ppm. LRMS (ESI): *m/z* = 285.3 $[M + H]^+$. HRMS (ESI) *m/z* calcd. for $C_{18}H_{25}N_2O$ $[M + H]^+$: 285.1967, found 285.1961.

***tert*-Butyl [2-(1*H*-Indol-3-yl)ethyl]{[(1*S*,6*S*)-6-(cyanomethyl)-cyclohex-3-en-1-yl]methyl}carbamate (7):** To a solution of amino-alcohol **16** (450 mg, 1.58 mmol) in dichloromethane (10 mL) was added di-*tert*-butyl dicarbonate (Boc anhydride, 328 mg, 1.5 mmol). The solution was stirred for 5 h at room temperature. The solvent was evaporated under reduced pressure and the residue was purified over silica gel by using 15 % ethyl acetate/hexanes to yield the *N*-boc derivative (535 mg, 1.39 mmol, 88 % yield) along with traces of the corresponding *tert*-butylcarbonate (*O*-Boc derivative). R_f 0.25 (40 % ethyl acetate/hexanes). $[\alpha]_D^{20}$ = +7.8 (*c* = 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.04 (s, 1 H), 7.62 (d, *J* = 7.5 Hz, 1 H), 7.36 (d, *J* = 8.1 Hz, 1 H), 7.19 (d, *J* = 7.4 Hz, 1 H), 7.12 (t, *J* = 7.4 Hz, 1 H), 6.99 (s, 1 H), 5.81–5.46 (m, 2 H), 3.86–3.40 (m, 5 H), 3.36–3.20 (m, 1 H), 3.07–2.89 (m, 2 H), 2.18 (s, 1 H), 2.00 (d, *J* = 15.3 Hz, 3 H), 1.77 (d, *J* = 14.2 Hz, 1 H), 1.61 (d, *J* = 19.2 Hz, 2 H), 1.44 (s, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.4, 136.3, 127.3, 126.0, 125.6, 121.9, 119.2, 118.6, 113.1, 111.2, 79.8, 63.4, 49.3, 47.2, 37.1, 33.1, 28.3, 27.9, 26.6, 24.5 ppm.

To a solution of the above Boc-protected amino-alcohol (500 mg, 1.3 mmol) in dry tetrahydrofuran (8 mL) was added triphenylphosphine (1.02 g, 3.9 mmol), followed by dropwise addition of diisopropyl azodicarboxylate (0.77 mL, 3.9 mmol) at 0 °C. The solution turned cloudy after 5 min. After 5 more minutes, acetone cyanohydrin (0.6 mL, 6.5 mmol) was added and the reaction mixture turned clear yellow. The solution was warmed to room temperature and stirred for 6 h. The mixture was then poured into water and extracted with ethyl acetate (× 3). The organic layer was washed with brine, dried with Na_2SO_4, filtered and the solvents evaporated to dryness. The residue was purified by silica gel chromatography (5 % to 30 % ethyl acetate/hexanes) to yield pale yellow amorphous solid **7** (480 mg, 1.22 mmol, 94 % yield). R_f 0.6 (40 % ethyl acetate/hexanes). $[\alpha]_D^{20}$ = –4.0 (*c* = 0.42, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.29 (s, 1 H), 7.62 (d, *J* = 6.5 Hz, 1 H), 7.36 (d, *J* = 7.5 Hz, 1 H), 7.24–7.16 (m, 1 H), 7.16–7.05 (m, 1 H), 6.97 (s, 1 H), 5.62 (s, 2 H), 3.58 (dt, *J* = 14.0, 7.2 Hz, 1 H), 3.50–3.19 (m, 2 H), 3.14–2.91 (m, 3 H), 2.14 (dd, *J* = 36.6, 21.1 Hz, 6 H), 1.99 (d, *J* = 19.5 Hz, 1 H), 1.86–1.63 (m, 1 H), 1.52 (s, 3 H), 1.46 (s, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.2, 136.4, 125.6, 124.6, 122.3, 122.0, 119.6, 118.8, 111.4, 79.7, 48.0, 35.0, 31.4, 29.5, 28.6, 26.6, 26.3, 22.1 ppm. LRMS-ESI: *m/z* = 416.3 $[M + Na]^+$. HRMS (ESI) *m/z* calcd. for $C_{24}H_{31}N_3O_2Na$ $[M + Na]^+$: 416.2314, found 416.2308.

2-[(1*S*,6*S*)-6-({[2-(1*H*-Indol-3-yl)ethyl](*tert*-butoxycarbonyl)-amino}methyl)cyclohex-3-en-1-yl]acetic Acid (18): To **7** (430 mg, 1.09 mmol) was added 1:1 20 % aqueous sodium hydroxide/ethanol (6 mL). The mixture was stirred at room temperature for 1 h, followed by addition of water (1 mL). The reaction was then refluxed for 18 h. The mixture was cooled to 0 °C, acidified to pH 3 by careful addition of saturated aqueous citric acid, and then extracted with ethyl acetate (× 3). The organic layer was washed with brine, dried with Na_2SO_4, filtered and the solvent was evaporated. The residue was purified by silica gel chromatography with 60 % ethyl acetate/hexanes to obtain carboxylic acid **18** (341 mg, 0.83 mmol, 76 % yield) as a yellow amorphous solid. R_f 0.2 (60 % ethyl acetate/hexanes). $[\alpha]_D^{20}$ = +28.9 (*c* = 1.9, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.22 (s, 1 H), 7.60 (d, *J* = 8.3 Hz, 1 H), 7.36 (d, *J* = 8.0 Hz, 1 H), 7.23–7.16 (m, 1 H), 7.12 (t, *J* = 7.1 Hz, 1 H), 6.98 (s, 1 H), 5.61 (s, 2 H), 3.60 (dq, *J* = 15.4, 8.1, 7.5 Hz, 1 H), 3.46 (dd, *J* = 14.2, 8.9 Hz, 1 H), 3.35 (dt, *J* = 13.5, 6.8 Hz, 1 H), 3.12–2.95 (m, 2 H), 2.90 (dd, *J* = 14.8, 5.6 Hz, 1 H), 2.55 (d, *J* = 10.3 Hz, 1 H), 2.37–2.06 (m, 4 H), 2.04–1.76 (m, 3 H), 1.44 (m, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.2, 157.1, 136.4, 127.5, 125.6, 125.4, 122.2, 122.1, 119.5, 118.7, 113.1, 111.4, 80.6, 48.4, 35.8, 33.7, 30.9, 29.8, 28.6, 26.3, 24.5 ppm. LRMS (ESI): *m/z* = 435.3 $[M + Na]^+$. HRMS (ESI) *m/z* calcd. for $C_{24}H_{32}N_2O_4$ $[M + Na]^+$: 435.2260, found 435.2256.

(4a*S*,8a*S*)-2-[2-(1*H*-Indol-3-yl)ethyl]-1,4,4a,5,8,8a-hexahydroisoquinolin-3(2*H*)-one (5): To a solution of carboxylic acid **18** (165 mg, 0.4 mmol) in dichloromethane (2 mL) at 0 °C was added trifluoroacetic acid (0.67 mL). The solution turned from yellow to orange as it was gradually warmed to room temperature. After 1 h, the reaction mixture was concentrated in vacuo. The residue was taken in dichloromethane (4 mL), and diisopropylethylamine (0.35 mL, 2 mmol) was added at 0 °C. HOBt hydrate (73 mg, 0.48 mmol) was then added, followed by EDCI·HCl (84 mg, 0.44 mmol). Diisopropylethylamine (0.35 mL, 2 mmol) was added again and the solution was warmed to room temperature. After 18 h, water was added to the reaction mixture, and it was extracted with ethyl acetate (× 3). The combined organic layers washed with brine, dried with Na_2SO_4, filtered and the solvent was evaporated. The residue was subjected to silica gel chromatography with ethyl acetate to afford lactam **5** (74 mg, 0.25 mmol, 45 % yield) as a white solid. R_f 0.1 (ethyl acetate). $[\alpha]_D^{20}$ = –18.1 (*c* = 0.16, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.31 (s, 1 H), 7.67 (d, *J* = 7.9 Hz, 1 H), 7.36 (d, *J* = 8.1 Hz, 1 H), 7.23–7.09 (m, 2 H), 7.03 (s, 1 H), 5.58 (s, 2 H), 3.72 (dt, *J* = 14.7, 7.7 Hz, 1 H), 3.61 (dt, *J* = 13.6, 7.6 Hz, 1 H), 3.17 (qd, *J* = 12.0, 5.5 Hz, 2 H), 3.04 (t, *J* = 6.2 Hz, 2 H), 2.38 (qd, *J* = 17.8, 5.8 Hz, 2 H), 2.21–2.06 (m, 4 H), 1.90–1.80 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.1, 136.2, 127.4, 124.7, 124.4, 122.0, 121.8, 119.2, 118.7, 113.0. 111.1, 50.9, 48.0, 35.7, 30.0, 29.3, 28.0, 26.1, 22.8 ppm. LRMS-ESI: *m/z* = 317.3 $[M + Na]^+$. HRMS (ESI) *m/z* calcd. for $C_{19}H_{22}N_2ONa$ $[M + Na]^+$: 317.1630, found 317.1628.

(–)-Dehydroalloyohimbane (19): To a solution of the lactam **5** (45 mg, 0.15 mmol) in dichloromethane (1 mL) was added phosphorus oxychloride (1 mL). The mixture was heated for 4 h at 50 °C. The reaction was then cooled to room temperature and phosphorus oxychloride was removed in vacuo. The residue was dissolved in methanol/water (9:1) (1 mL) and cooled to 0 °C. Sodium borohydride was added until the pH > 7. Then 1 mL of saturated aqueous ammonium chloride solution and ice were added to the reaction mixture. The mixture was then extracted with dichloromethane (× 3). The combined organic layers were washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography with 30 % ethyl acetate/hexanes to obtain **19** (31 mg, 0.11 mmol, 74 % yield). R_f 0.3 (30 % ethyl acetate/hexanes). $[\alpha]_D^{20}$ = –59.2 (*c* = 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.73 (s, 1 H), 7.47 (d, *J* = 7.6 Hz, 1 H), 7.27 (d, *J* = 6.8 Hz, 1 H), 7.10 (dt, *J* = 14.8, 7.0 Hz, 2 H), 5.80–5.41 (m, 2 H), 3.24 (d, *J* = 10.7 Hz, 1 H), 3.04–2.90 (m, 2 H), 2.83 (d, *J* = 11.2 Hz, 1 H), 2.73–2.51 (m, 4 H), 2.43 (d, *J* = 17.9 Hz, 1 H), 2.08–1.95 (m, 3 H), 1.90–1.69 (m, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$):

δ = 136.1, 135.6, 126.2, 123.4, 121.3, 119.5, 118.2, 110.8, 108.3, 60.7, 60.4, 53.3, 33.3, 32.2, 32.0, 31.4, 25.7, 22.0 ppm. LRMS (ESI): *m/z* = 279.4 $[M + H]^+$. HRMS (ESI) *m/z* calcd. for $C_{19}H_{23}N_2$ $[M + H]^+$: 279.1861, found 279.1857.

(–)-Alloyohimbane (1): A 2-neck round-bottomed flask was evacuated and filled with Ar. 10 % Pd/C (5 mg) was added under Ar. 0.5 mL of ethyl acetate was added down the sides of the flask to wash down any Pd/C in the walls. A solution of **19** (8 mg, 0.029 mmol) in 0.5 mL ethyl acetate was then added. The mixture was stirred. The flask was evacuated and re-filled with Ar three times. An H_2 balloon was then attached. The flask was evacuated and filled with H_2 three times. After 2 h, the balloon was removed and the flask was filled with Ar. The mixture was filtered through Celite® and the solvent was concentrated in vacuo. The residue was purified by chromatography over silica gel (30 % ethyl acetate/hexanes) to yield (–)-Alloyohimbane **1** (7.4 mg, 0.026 mmol, 91 % yield). R_f 0.3 (20 % ethyl acetate/hexanes). $[\alpha]_D^{20}$ = –78.8 (*c* = 0.3, Ethanol); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (s, 1 H), 7.47 (d, *J* = 7.6 Hz, 1 H), 7.30 (d, *J* = 7.7 Hz, 1 H), 7.10 (dt, *J* = 17.9, 7.1 Hz, 2 H), 3.24–3.18 (m, 1 H), 3.00–2.93 (m, 2 H), 2.79 (d, *J* = 11.3 Hz, 1 H), 2.68 (d, *J* = 14.9 Hz, 1 H), 2.52 (dq, *J* = 14.3, 8.7, 6.1 Hz, 2 H), 2.01–1.86 (m, 3 H), 1.75–1.57 (m, 5 H), 1.42 (ddd, *J* = 16.8, 9.8, 5.7 Hz, 2 H), 1.38–1.26 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 135.9, 135.4, 127.4, 121.1, 119.3, 118.0, 110.6, 108.1, 61.7, 60.3, 53.3, 36.5, 34.7, 31.8, 30.4, 26.4, 21.6, 20.8 ppm. LRMS (ESI): *m/z* = 281.4 [M + H]. HRMS (ESI) *m/z* calcd. for $C_{19}H_{25}N_2$ $[M + H]^+$: 281.2018, found 281.2009.

[(1*R*,6*S*)-6-Formylcyclohex-3-en-1-yl]methyl Acetate (20): To a solution of oxalyl chloride (0.76 mL, 8.69 mmol) in dichloromethane (10 mL) at –78 °C was added dropwise a solution of dry dimethyl sulfoxide (1.23 mL, 17.4 mmol) in dichloromethane (10 mL). The mixture was stirred at –78 °C for 5 min. A solution of the alcohol **10** (800 mg, 4.35 mmol) in dichloromethane (10 mL) was then added dropwise to the mixture. After 30 min, triethylamine (2.43 mL, 17.4 mmol) was added and the mixture was stirred at –78 °C for 10 min. The reaction was then warmed to room temperature. The mixture was washed successively with water, 2N HCl, water, brine and dried with Na_2SO_4. The solvent was evaporated to obtain aldehyde **20** (736 mg, 4.05 mmol, 93 % yield) as a colorless oil. R_f 0.8 (50 % ethyl acetate/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.69 (s, 1 H), 5.74–5.54 (m, 2 H), 4.23–3.85 (m, 2 H), 2.59 (q, *J* = 7.8, 7.1 Hz, 2 H), 2.31–2.17 (m, 3 H), 2.05–1.98 (m, 1 H), 1.96 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 202.9, 170.2, 125.2, 124.5, 64.1, 46.9, 32.5, 26.5, 22.4, 20.3 ppm.

[(1*R*,6*R*)-6-({[2-(1*H*-Indol-3-yl)ethyl]amino}methyl)cyclohex-3-en-1-yl]methyl Acetate (21): To a solution of aldehyde **20** (700 mg, 3.85 mmol) and tryptamine (801 mg, 5 mmol) in methanol (25 mL) was added glacial acetic acid (0.22 mL, 3.85 mmol) and 4 Å molecular sieves (1.5 g, powdered, activated). The orange solution was stirred for 1 h. Sodium cyanoborohydride was then added and the reaction was stirred for 10 h. The mixture was then filtered and the methanol was evaporated. The residue was purified by silica gel chromatography with ethyl acetate to obtain the secondary amine **21** (917 mg, 2.81 mmol, 73 % yield) as an orange semi-solid. R_f 0.2 [5 %(5 % ammonia/methanol)/dichloromethane]. $[\alpha]_D^{20}$ = –30.7 (*c* = 7.0, Methanol). ^{1}H NMR (400 MHz, CD_3OD): δ = 7.60 (d, *J* = 7.8 Hz, 1 H), 7.39 (d, *J* = 8.1 Hz, 1 H), 7.16–7.00 (m, 3 H), 5.56 (s, 2 H), 3.93 (h, *J* = 5.6 Hz, 2 H), 3.20–3.07 (m, 4 H), 2.97 (dd, *J* = 12.5, 5.0 Hz, 1 H), 2.78 (dd, *J* = 12.6, 9.0 Hz, 1 H), 2.15 (d, *J* = 18.1 Hz, 1 H), 2.05–1.98 (m, 5 H), 1.90–1.76 (m, 3 H) ppm. ^{13}C NMR (101 MHz, CD_3OD): δ = 172.7, 137.7, 127.8, 125.9, 124.6, 124.0, 122.6, 120.0, 118.9, 112.4, 110.1, 66.5, 51.7, 49.7, 34.8, 32.5, 26.6, 25.9, 22.9, 20.9 ppm. LRMS (ESI): *m/z* = 327 $[M + H]^+$. HRMS (ESI) *m/z* calcd. for $C_{20}H_{27}N_2O_2$ $[M + H]^+$: 327.2073, found 327.2062.

Reductive Amination Under Hydrogenation Conditions: To a solution of aldehyde **20** (63 mg, 0.35 mmol) in dry methanol (2 mL) under Ar was added tryptamine (55 mg, 0.35 mmol). Molecular sieves (150 mg, 4 Å, powdered, oven-dried) were then added, followed by 10 % Pd-C (19 mg). The Ar balloon was replaced with an H_2 balloon, and the reaction was stirred for 24 h at room temperature. The mixture was then filtered through Celite®, the methanol was removed under reduced pressure, and the residue was purified with 5 %(5 % ammonia/methanol)/dichloromethane to afford saturated *cis*-amine (31 mg, 0.11 mmol, 31 % yield) and saturated *trans*-amine (13 mg, 0.045 mmol, 13 % yield). ^{1}H NMR for saturated *trans* amine (400 MHz, $CDCl_3$): δ = 9.00 (s, 1 H), 7.54 (d, *J* = 7.8 Hz, 1 H), 7.38 (t, *J* = 7.6 Hz, 1 H), 7.16 (d, *J* = 7.7 Hz, 1 H), 7.13 (d, *J* = 5.0 Hz, 1 H), 7.07 (d, *J* = 7.7 Hz, 1 H), 3.48 (dd, *J* = 11.1, 2.3 Hz, 1 H), 3.43–3.27 (m, 1 H), 3.24–3.18 (m, 2 H), 3.15–3.10 (m, 1 H), 3.07–3.00 (m, 1 H), 2.76–2.73 (m, 1 H), 1.70–1.53 (m, 3 H), 1.45–1.37 (m, 2 H), 1.26–1.18 (m, 2 H), 1.16–0.99 (m, 3 H), 0.78–0.68 (m, 1 H) ppm. LRMS (APCI): *m/z* = 287 $[M + H]^+$. ^{1}H NMR for saturated *cis* amine (400 MHz, $CDCl_3$): δ = 8.41 (s, 1 H), 7.61 (d, *J* = 7.8 Hz, 1 H), 7.36 (d, *J* = 8.1 Hz, 1 H), 7.20 (t, *J* = 7.3 Hz, 1 H), 7.12 (t, *J* = 7.4 Hz, 1 H), 7.01 (d, *J* = 1.9 Hz, 1 H), 3.67–3.55 (m, 1 H), 3.55–3.48 (m, 1 H), 2.99–2.93 (m, 2 H), 2.93–2.86 (m, 1 H), 2.86–2.75 (m, 1 H), 2.52–2.40 (m, 1 H), 1.79 (s, 2 H), 1.62–1.46 (m, 3 H), 1.46–0.99 (m, 6 H) ppm. LRMS (ESI): *m/z* = 287.4 $[M + H]^+$.

***tert*-Butyl [2-(1*H*-Indol-3-yl)ethyl]{[(1*S*,6*S*)-6-(cyanomethyl)-cyclohex-3-en-1-yl]methyl}carbamate (26):** To a solution of amine **21** (800 mg, 2.45 mmol) in dichloromethane (10 mL) was added triethylamine (0.38 mL, 2.7 mmol). The mixture was cooled to 0 °C. A solution of di-*tert*-butyl dicarbonate (Boc anhydride, 589 mg, 2.7 mmol) in dichloromethane (5 mL) was then added. The reaction was stirred for 90 min. The solvent was evaporated and the residue was purified by silica gel chromatography with 15 % ethyl acetate/hexanes to obtain the –Boc protected amino-acetate (961 mg, 2.25 mmol, 92 % yield). R_f 0.6 (40 % ethyl acetate/hexanes). $[\alpha]_D^{20}$ = –20.9 (*c* = 2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (s, 1 H), 7.63 (d, *J* = 7.4 Hz, 1 H), 7.36 (d, *J* = 8.1 Hz, 1 H), 7.19 (t, *J* = 7.3 Hz, 1 H), 7.12 (t, *J* = 7.5 Hz, 1 H), 6.99 (s, 1 H), 5.61 (d, *J* = 11.6 Hz, 2 H), 4.01 (dd, *J* = 13.2, 5.1 Hz, 2 H), 3.48 (d, *J* = 5.3 Hz, 2 H), 3.21 (s, 2 H), 3.00 (s, 2 H), 2.15–2.05 (m, 3 H), 2.03 (s, 3 H), 1.89 (d, *J* = 9.9 Hz, 1 H), 1.84–1.77 (m, 2 H), 1.51–1.41 (m, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.2, 155.9, 136.2, 127.4, 125.7, 124.9, 122.1, 121.8, 119.1, 118.6, 112.9, 111.1, 79.3, 66.5, 64.7, 48.4, 33.9, 32.5, 28.4, 26.0, 25.4, 22.6, 23.7, 20.9 ppm.

To a solution of the above amino-acetate (800 mg, 1.88 mmol) in methanol (10 mL) was added potassium carbonate (260 mg, 1.88 mmol). The mixture was stirred for 2 h at room temperature. The methanol was evaporated, water was added and extracted with dichloromethane (× 3). The combined organic layers were washed with water, brine, dried with sodium sulfate and the solvent was evaporated. The residue was purified by silica gel chromatography (30 % to 40 % ethyl acetate/hexanes) to obtain the amino-alcohol (694 mg, 1.8 mmol, 96 % yield). R_f 0.3 (40 % ethyl acetate/hexanes). $[\alpha]_D^{20}$ = –7.7 (*c* = 1.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (s, 1 H), 7.63 (d, *J* = 7.8 Hz, 1 H), 7.36 (d, *J* = 8.1 Hz, 1 H), 7.20 (t, *J* = 7.4 Hz, 1 H), 7.12 (t, *J* = 7.3 Hz, 1 H), 6.99 (s, 1 H), 5.66–5.57 (m, 2 H), 3.58–3.47 (m, 5 H), 3.02–2.98 (m, 3 H), 2.19–2.02 (m, 2 H), 1.98 (m, 2 H), 1.78 (d, *J* = 15.9 Hz, 1 H), 1.67–1.56 (m, 2 H), 1.44 (s, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.9, 136.2, 127.4, 125.5, 125.0, 121.9, 121.8, 119.2, 118.7, 113.4, 111.1, 79.4, 63.4, 50.3, 48.7, 47.1, 37.4, 33.1, 28.3, 26.5, 24.5 ppm. LRMS (ESI): *m/z* = 407.3 $[M + Na]^+$. HRMS (ESI) *m/z* calcd. for $C_{23}H_{32}N_2O_3Na$ $[M + Na]^+$: 407.2311, found 407.2303.

To a solution of the above alcohol (615 mg, 1.6 mmol) in dry tetrahydrofuran (10 mL) was added triphenylphosphine (1.26 g, 4.8 mmol), followed by dropwise addition of diisopropyl azodicarboxylate (0.94 mL, 4.8 mmol) at 0 °C. The solution turned cloudy after 5 min. After 5 more minutes, acetone cyanohydrin (0.73 mL, 8 mmol) was added. The solution was warmed to room temperature and stirred for 6 h. The mixture was then poured into water and extracted with ethyl acetate (× 3). The organic layer was washed with brine, dried with sodium sulfate, filtered and the solvents evaporated to dryness. The residue was purified by silica gel chromatography (5 % to 30 % ethyl acetate/hexanes) to yield yellow liquid **26** (592 mg, 1.5 mmol, 83 % yield over the three steps). R_f 0.7 (40 % ethyl acetate/hexanes). $[\alpha]_D^{25}$ = –7.1 (*c* = 3.9, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.49 (s, 1 H), 7.61 (t, *J* = 7.1 Hz, 1 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 7.17 (t, *J* = 7.3 Hz, 1 H), 7.11 (t, *J* = 7.0 Hz, 1 H), 6.97 (s, 1 H), 5.63–5.55 (m, 2 H), 3.61–3.50 (m, 1 H), 3.31 (s, 1 H), 3.16–2.89 (m, 3 H), 2.34–1.91 (m, 6 H), 1.83 (m, 1 H), 1.68 (s, 2 H), 1.48 (m, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.1, 136.4, 127.4, 125.5, 125.0, 124.4, 122.2, 121.9, 119.2, 118.6, 112.8, 111.4, 79.8, 71.4, 47.8, 34.8, 34.4, 28.4, 26.3, 26.1, 22.0, 21.2 ppm. LRMS (ESI): *m/z* = 416.3 $[M + Na]^+$. HRMS (ESI) *m/z* calcd. for $C_{24}H_{31}N_3O_2Na$ $[M + Na]^+$: 416.2314, found 413.2304.

2-[(1*S*,6*S*)-6-({[2-(1*H*-Indol-3-yl)ethyl](*tert*-butoxycarbonyl)-amino}methyl)cyclohex-3-en-1-yl]acetic Acid (27): To compound **26** (500 mg, 1.27 mmol) was added 20 % aqueous sodium hydroxide (4 mL) and ethanol (4 mL, to make the solution homogeneous). The mixture was stirred at room temperature for 1 h, followed by addition water (1 mL). The reaction was then refluxed for 12 h. The mixture was cooled to 0 °C, acidified to pH 3 by careful addition of saturated aqueous citric acid, and then extracted with ethyl acetate (× 3). The combined organic layers were dried with sodium sulfate, filtered and the solvent was evaporated. The residue was purified by silica gel chromatography with 60 % ethyl acetate/hexanes to obtain carboxylic acid **27** (424 mg, 1.03 mmol, 81 % yield) as a colorless oil. R_f 0.2 (60 % ethyl acetate/hexanes). $[\alpha]_D^{20}$ = +28.9 (*c* = 1.9, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.31 (s, 1 H), 7.62 (d, *J* = 7.2 Hz, 1 H), 7.34 (d, *J* = 7.0 Hz, 1 H), 7.22–7.15 (m, 1 H), 7.15–7.04 (m, 1 H), 6.96 (s, 1 H), 5.68–5.50 (m, 2 H), 3.66–3.38 (m, 2 H), 3.37–3.08 (m, 2 H), 2.99 (s, 2 H), 2.61–2.06 (m, 5 H), 1.86 (dd, *J* = 42.4, 9.0 Hz, 3 H), 1.54–1.37 (m, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 178.7, 156.2 136.4, 127.6, 125.0, 122.0, 119.3, 118.8, 113.3, 111.3, 79.7, 48.5, 38.2, 35.0, 31.3, 28.6, 28.0, 24.4 ppm. LRMS (ESI): *m/z* = 411.3 [M – H]. HRMS (ESI) *m/z* calcd. for $C_{23}H_{32}N_2O_3Na$ $[M + Na]^+$: 435.2260, found 435.2249.

(4aS,8aS)-2-[2-(1*H*-Indol-3-yl)ethyl]-1,4,4a,5,8,8a-hexahydroisoquinolin-3(2*H*)-one (6): To a solution of the carboxylic acid **27** (300 mg, 0.73 mmol) in dichloromethane (3 mL) at 0 °C was added trifluoroacetic acid (1 mL). The solution turned yellow to orange to purple as it was gradually warmed to room temperature. After 1 h, the reaction mixture was concentrated in vacuo. The residue was taken in dichloromethane (4 mL), and diisopropylethylamine (0.64 mL, 3.65 mmol) was added at 0 °C. HOBt hydrate (134 mg, 0.88 mmol) was then added, followed by EDCI·HCl (154 mg, 0.8 mmol). Additional diisopropylethylamine (0.64 mL, 3.65 mmol) was added and the solution was warmed to room temperature. After 48 h, water was added to the reaction mixture, and it was extracted with ethyl acetate (× 3). The combined organic layers were washed with brine, dried with sodium sulfate, filtered and the solvent was evaporated. The residue was subjected to silica gel chromatography (50 % to 75 % ethyl acetate/hexanes) to afford lactam **6** (90 mg, 0.31 mmol, 42 % yield) as an amorphous solid. R_f 0.4 [5 %(5 % ammonia/methanol)/dichloromethane]. $[\alpha]_D^{20}$ = –13.2 (*c* = 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.06 (s, 1 H), 7.67 (dq, *J* = 7.8, 0.9 Hz, 1 H), 7.36 (d, *J* = 8.0 Hz, 1 H), 7.22–7.16 (m, 1 H), 7.13 (td, *J* = 7.5, 7.1, 1.0 Hz, 1 H), 7.06 (d, *J* = 2.2 Hz, 1 H), 5.65 (t, *J* = 4.7 Hz, 2 H), 3.77–3.57 (m, 2 H), 3.23 (dd, *J* = 12.2, 4.2 Hz, 1 H), 3.13–2.96 (m, 2 H), 2.99–2.88 (m, 1 H), 2.64 (dd, *J* = 17.6, 4.8 Hz, 1 H), 2.21 (dt, *J* = 14.6, 3.6 Hz, 1 H), 2.10–2.02 (m, 2 H), 1.81–1.71 (m, 2 H), 1.67–1.63 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.5, 132.3, 132.2, 128.7, 128.6, 125.8, 125.1, 122.1, 119.4, 118.8, 111.3, 54.5, 48.2, 39.4, 33.8, 32.8, 32.0, 28.8, 23.1 ppm. LRMS-ESI: *m/z* = 293.5 [M – H]. HRMS (ESI) *m/z*: calcd. for $C_{19}H_{22}N_2ONa$ $[M + Na]^+$: 317.1630, found 317.1626.

(4aS,13bS,14aS)-1,4,4a,5,7,8,13,13b,14,14a-Decahydroindolo-[2′,3′:3,4]pyrido[1,2-*b*]isoquinoline (28): To a solution of lactam **6** (67 mg, 0.23 mmol) in dichloromethane (1 mL) was added freshly distilled phosphorus oxychloride (1 mL). The mixture was heated for 4 h at 50 °C. The reaction was then cooled to room temperature and the phosphorus oxychloride was evaporated in vacuo. The residue was dissolved in methanol/water (9:1, 1 mL) and cooled to 0 °C. Sodium borohydride was added until the pH > 7. Then 1 mL of saturated ammonium chloride and ice were added to the reaction mixture. The mixture was then extracted with dichloromethane (× 3). The combined organic layers were washed with brine, dried with sodium sulfate, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography with 90 % ethyl acetate/toluene to obtain **28** (46 mg, 0.16 mmol, 72 % yield). R_f 0.4 (90 % ethyl acetate/toluene). $[\alpha]_D^{20}$ = –55.3 (*c* = 0.49, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.74 (br. s, 1 H), 7.47 (d, *J* = 7.6 Hz, 1 H), 7.30 (d, *J* = 7.9 Hz, 1 H), 7.13–7.08 (m, 2 H), 5.69 (d, *J* = 2.5 Hz, 2 H), 3.38–3.34 (m. 1 H), 3.13–2.96 (m, 3 H), 2.74 (dd, *J* = 3.5, 7.8 Hz, 1 H), 2.63 (td, *J* = 11.1, 4.4 Hz, 1 H), 2.53–2.27 (m, 1 H), 2.21–2.08 (m, 3 H), 1.92–1.69 (m, 3 H), 1.61–1.49 (m, 1 H), 1.47–1.35 (m, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.2, 134.9, 127.6, 126.5, 126.2, 121.5, 119.6, 118.3, 110.8, 108.4, 62.0, 60.2, 53.3, 37.0, 36.9, 32.2, 30.7, 29.6, 21.8 ppm. LRMS-ESI: *m/z* = 279.4 $[M + H]^+$. HRMS (ESI) *m/z* calcd. for $C_{19}H_{23}N_2$ $[M + H]^+$: 279.1861, found 279.1857.

(4aS,13bS,14aS)-1,2,3,4,4a,5,7,8,13,13b,14,14a-Dodecahydroindolo[2′,3′:3,4]pyrido[1,2-*b*]isoquinoline [(–)-Yohimbane (2)]: A 2-neck round-bottomed flask was evacuated and filled with Ar. 10 % Pd/C (8 mg) was added under Ar. 0.5 mL of ethyl acetate was added down the sides of the flask to wash down any Pd/C in the walls. A solution of **28** (21 mg, 0.075 mmol) in 0.5 mL ethyl acetate was then added. The mixture was stirred. The flask was evacuated and filled with Ar three times and a H_2 balloon was then attached. The flask was evacuated and re-filled with H_2 three times. After 2 h, the balloon was removed and the flask was filled with Ar. The mixture was filtered through Celite® and the solvent was removed in vacuo. The residue was purified by chromatography over silica gel (90 % Ethyl acetate/Toluene) to yield (–)-Yohimbane **2** (19 mg, 0.069 mmol, 92 % yield). R_f 0.3 (40 % ethyl acetate/hexanes). $[\alpha]_D^{20}$ = –77.6 (*c* = 0.22, ethanol); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.73 (s, 1 H), 7.47 (d, *J* = 7.3 Hz, 1 H), 7.30 (d, *J* = 7.7 Hz, 1 H), 7.10 (dt, *J* = 14.6, 6.7 Hz, 2 H), 3.29 (d, *J* = 10.7 Hz, 1 H), 3.09 (dt, *J* = 13.2, 6.3 Hz, 1 H), 3.04–2.95 (m, 1 H), 2.95–2.80 (m, 1 H), 2.72 (d, *J* = 15.3 Hz, 1 H), 2.62 (dt, *J* = 11.0, 5.8 Hz, 1 H), 2.13 (t, *J* = 10.9 Hz, 1 H), 2.00 (d, *J* = 12.1 Hz, 1 H), 1.80–1.60 (m, 4 H), 1.50–1.41 (m, 1 H), 1.31 (m, 4 H), 1.16–0.99 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 135.9, 135.0, 127.4, 121.1, 119.2, 118.0, 110.6, 108.0, 62.0, 60.2, 53.1, 41.9, 36.9, 32.8, 30.3, 26.3, 25.9, 21.7 ppm. LRMS (ESI): *m/z* = 281.3 $[M + H]^+$. HRMS (ESI) *m/z* calcd. for $C_{19}H_{25}N_2$ $[M + H]^+$: 281.2018, found 281.2005.

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Keywords: Alkaloids · Bischler–Napieralski · Enzymatic resolution · Indoles · Polycycles · Enantioselectivity · Cyclization

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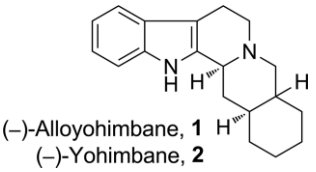
Enzymatic Desymmetrization



(–)-Alloyohimbane, **1**
(–)-Yohimbane, **2**

Enantioselective syntheses of (–)-alloyohimbane and (–)-yohimbane are described. The key step involves a mild enantioselective enzymatic desymmetrization of a *meso*-diacetate. The resulting monoacetate is an intermediate for the synthesis of (–)-alloyohimbane. Reductive amination of the derived aldehyde induces an isomerization, which leads to the *trans*-product and, ultimately, to (–)-yohimbane.

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