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Total Synthesis of (+)-Yohimbine via an Enantioselective Organocatalytic Pictet−Spengler Reaction

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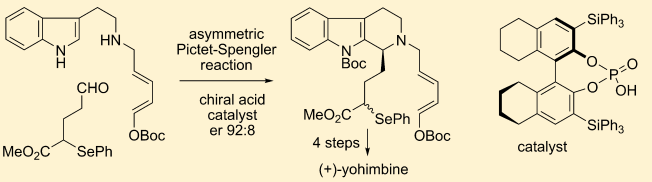
Supporting Information

ABSTRACT: The binolphosphoric acid-catalyzed Pictet−Spengler reaction of an *N*-(5-oxy-2,4-pentadienyl)tryptamine derivative with methyl 5-oxo-2-(phenylseleno)pentanoate leads to the tetrahydro-*β*-carboline in a 92:8 enantiomeric ratio. This product is easily converted into the substrate for a stereoselective intramolecular Diels−Alder reaction of the type earlier reported by Jacobsen. These two key steps constitute the basis for a nine-step total synthesis of (+)-yohimbine from tryptamine. A similar asymmetric Pictet−Spengler reaction was applied to the synthesis of an intermediate in the recent total synthesis of corynantheidine by Sato.



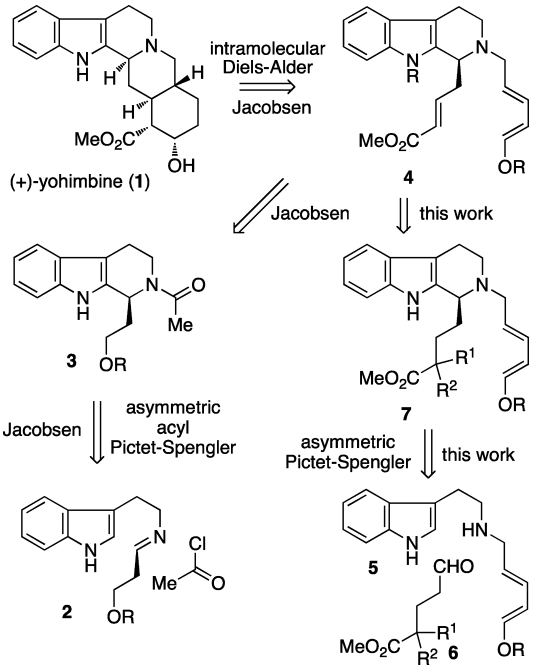
INTRODUCTION

Yohimbine (**1**) is one of the most well-known indole alkaloids with a rich chemical and medicinal history.[1] The first total synthesis of the racemic compound was achieved more than 50 years ago by Van Tamelen and co-workers.[2] Several other racemic syntheses have been reported since, until the group of Szantay published in 1986 the first preparation of the alkaloid in enantiopure form by a second-order asymmetric transformation step in the resolution of an intermediate.[3] The first asymmetric synthesis was reported by Momose and co-workers in 1990,[4] based on an asymmetric Michael-type cyclization. In 1994, Aubé et al. published a synthesis of (+)-yohimbine from the chiral pool compounds (+)-menthol and L-tryptophan.[5]

Our attention was drawn by the first catalytic enantioselective total synthesis of yohimbine, recently reported by Jacobsen and co-workers.[6] In this work the alkaloid was prepared in a fully stereocontrolled sequence of an acyl Pictet−Spengler cyclization and an intramolecular Diels−Alder reaction as the key steps, respectively (see Scheme 1). The cyclization of tryptamine imine **2** was effected by acetyl chloride and a chiral thiourea catalyst and proceeded via an *N*-acyliminium intermediate to tetrahydro-*β*-carboline **3** in an er of 97:3. The single stereocenter generated in this step determined the outcome of the next key step, that is, the intramolecular Diels−Alder reaction of **4**, in which the remaining four stereocenters of **1** were established. The Jacobsen group has carefully studied this IMDA process which appeared eminently suited to ensure high diastereoselectivity.

Recently, we discovered that the Pictet−Spengler cyclization of *N*-monosubstituted tryptamines with various aldehydes in the presence of catalytic amounts of enantiopure binolphosphoric acids may lead to tetrahydro-*β*-carbolines in good enantiomeric excesses.[7] This methodology was applied in the enantioselective total synthesis of the indole alkaloid arboricine (Scheme 2).[8] It occurred to us that this strategy should also be

Scheme 1. Synthetic Strategies toward (+)-Yohimbine



useful for the synthesis of (+)-yohimbine, if an enantioselective reaction of tryptamine **5** with aldehyde **6** would provide Pictet−Spengler product **7** in good er (see Scheme 1). The R^1 and R^2 substituents should be such that an *E*-alkene can be readily formed from **7** so as to join the Jacobsen route in **4**. The greater efficiency of our method compared to Jacobsen's approach would then lie in the early attachment of the correct substituent on nitrogen. Jacobsen required in the enantiose-

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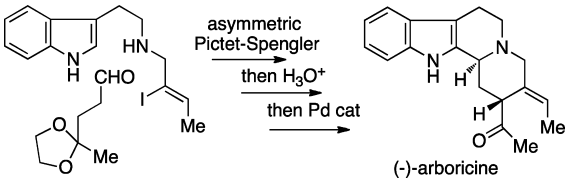
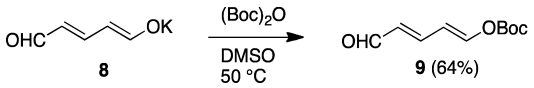
Scheme 2. Total Synthesis of (−)-Arboricine



lective Pictet−Spengler step an acetyl group, which is rather difficult to be replaced by the desired diene substituent.[6] This article reports in detail a short total synthesis of (+)-yohimbine along the above lines and serves to illustrate the general synthetic utility of the asymmetric phosphoric acid-catalyzed Pictet−Spengler cyclization.

RESULTS AND DISCUSSION

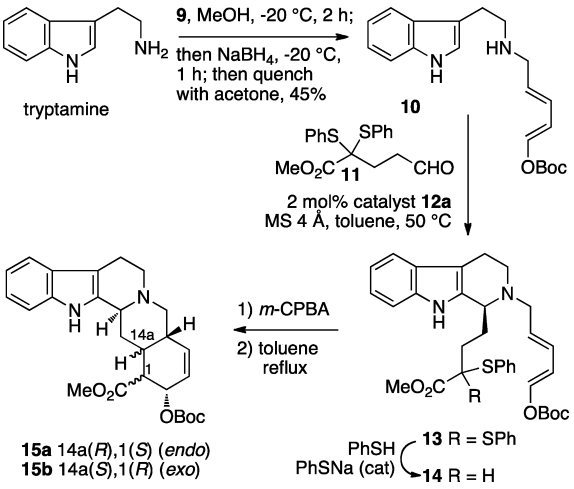
The first objective of our synthetic strategy was the preparation of tryptamine **5** with the required diene substituent on the amine nitrogen. We first investigated the use of the benzoate of glutaconaldehyde,[9] but its reductive amination with tryptamine was unsuccessful due to predominant formation of the *N*-benzoyl derivative of tryptamine. Apparently, we needed a more robust protective group on the glutaconaldehyde and chose the Boc group (eq 1).



(1)

Thus, the potassium salt of glutaconaldehyde (**8**) was converted into its Boc derivative **9**, which was readily purified by recrystallization (mp 70 °C). Reductive amination of **9** with tryptamine required extensive optimization (Scheme 3). Best

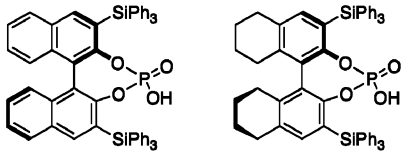
Scheme 3. Approach to Yohimbine Using Dithioacetal 11



conditions were to stir the amine and the aldehyde for 2 h in methanol as the solvent at −20 °C before adding $NaBH_4$ as reducing agent. After another hour at −20 °C the reaction was quenched with acetone. Quick column chromatography gave about 45% of product **10** as a rather unstable yellow oil which should be kept cold, but was preferably used immediately in the next reaction, that is, the asymmetric Pictet−Spengler cyclization.

We then directed our attention to the aldehyde partner **6** (see Scheme 1) for the Pictet−Spengler reaction. Earlier experience had taught us that β,γ-unsaturated aldehydes cannot be used for this process, probably because the intermediate iminium ion isomerizes to a conjugated and unreactive enamine. This meant that a chemical equivalent of the required dienophile double bond in **4** should be present in the aldehyde **6**. We first chose to investigate dithioacetal aldehyde **11** which has been used by Massiot et al. and later by Cook and co-workers in Pictet−Spengler cyclizations with tryptamine and tryptophan esters (see Scheme 3).[10]

The Pictet−Spengler reaction between freshly purified amine **10** and a slight excess of aldehyde **11** was carried out overnight in toluene at 50 °C in the presence of powdered 4 Å molecular sieves and 2 mol % of (*R*)-binolphosphoric acid **12a**.[11] These optimized conditions are the result of an elaborate screening. An excess of the aldehyde is crucial for a successful reaction (if the amine is in excess, the reaction simply does not proceed), but too much aldehyde lowers the er. Furthermore, the (*R*)-axial chirality in **12** is known to lead to the required (*S*)-stereochemistry in the tetrahydro-β-carboline.[7] The desired product **13** was isolated in ca. 45% yield after chromatographic purification, and the maximum er from a few runs was 76:24.



While clearly unsatisfactory, we continued with product **13** in order to probe whether the following chemistry would work. According to the Massiot protocol,[10] one phenylthio group was removed using thiophenol and a catalytic amount of base. The resulting thioether **14** was converted into the corresponding sulfoxide using *m*-chloroperbenzoic acid (1 equiv). Generation of the dienophile required reflux of this sulfoxide in toluene. Under these conditions the Diels−Alder reaction also took place to furnish the diastereomeric cycloadducts **15a** (*endo*) and **15b** (*exo*) in a 3:1 ratio. While this result is in good agreement with Jacobsen's work,[6] the selectivities and overall yield leave much to be desired.

We thus decided to modify our approach in order to attain a better yield and diastereoselectivity. To this end we desired to generate the dienophile at a much lower temperature and introduce a protective group on the indole nitrogen before the IMDA reaction.[6] The phenylseleno aldehyde **16** was chosen (Scheme 4) because the elimination of the selenoxide is known to occur at rt so that the dienophile does not directly engage in the Diels−Alder reaction.

The aldehyde **16** was made according to the procedure reported by Clive et al.[12] The Pictet−Spengler cyclization of freshly purified amine **10** with aldehyde **16** was carried out under identical conditions as with aldehyde **11** and produced the desired product **17** as a mixture of diastereomers. This mixture was directly treated in the same pot with di-*tert*-butyl dicarbonate and DMAP at 40 °C for 2 h to give the Boc-protected product **18** in 82% overall yield when using 2 mol % of the octahydrobinolphosphoric acid catalyst **12b**. Subsequently, **18** was subjected to oxidation with peracid at −78 °C. After 2 h the mixture was warmed up to rt in the presence of triethylamine, which led to to the elimination product **19** in

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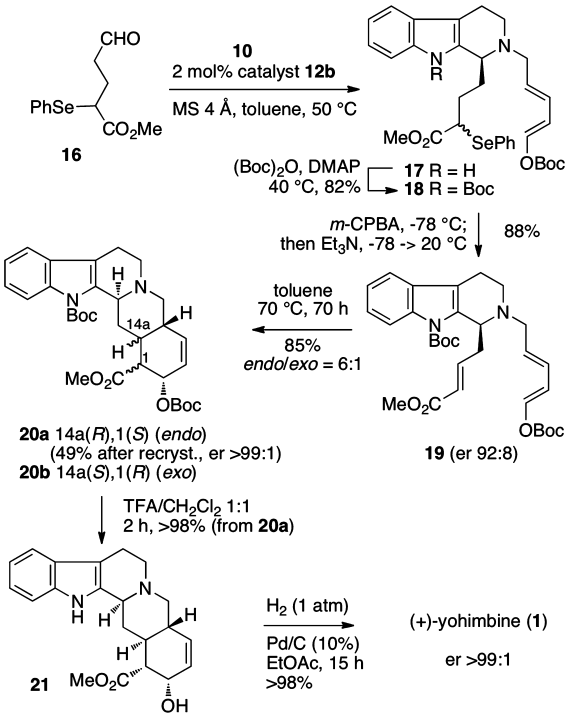
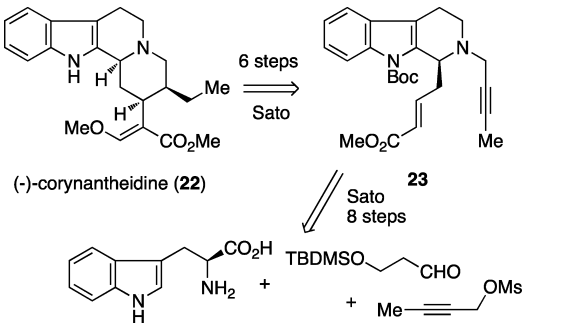
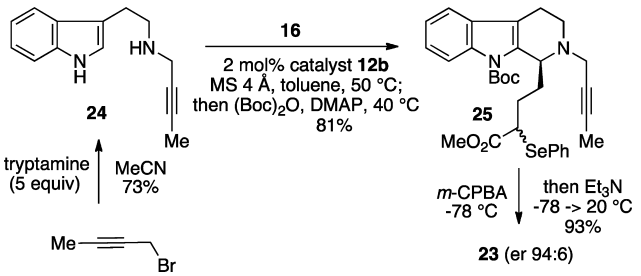
Scheme 4. Synthesis of (+)-Yohimbine Using Selenide 16



Scheme 5. Synthesis of (−)-Corynantheidine by Sato



Scheme 6. Enantioselective Synthesis of Compound 23



88% yield. The product was the pure (*E*)-isomer and showed an er of 92:8 by chiral HPLC. The same process starting from **10** and **18** was also carried out with catalyst **12a**, which led to a similar yield of **19** in an er of 84:16.

The key IMDA reaction of **19** was carried out on a 1 g scale in toluene at 70 °C for 70 h and led to a 6:1 mixture of the *endo*/*exo* isomers of the cycloadduct **20**, fully in accord with the results of Jacobsen et al., which only differ in the protective groups.[6] The isomers were easily separated on a column. The major isomer **20a** gave the pure enantiomer after one recrystallization (mp 189 °C, $[\alpha]_D$ = +49.7 (*c* 0.51, $CHCl_3$), yield 49%).

The final steps were easy. Removal of the Boc protective groups occurred in quantitative yield on stirring **20a** in a 1:1 mixture of trifluoroacetic acid and DCM for 2 h at rt. Hydrogenation of the alkene in **21** with atmospheric hydrogen in ethyl acetate in the presence of Pd/C as catalyst furnished the alkaloid yohimbine (**1**) in virtually quantitative yield as off-white crystals (mp 227−229 °C, $[\alpha]_D$ = +51.8 (*c* 0.54, EtOH)). Spectral and physical data were in full agreement with literature data. The total synthesis of enantiopure (+)-yohimbine from tryptamine involved nine steps (only six pots) and gave an overall yield of 16%.

To illustrate the more general applicability of this approach to indole alkaloids, we also investigated the synthesis of an intermediate in the recent total synthesis of (−)-corynantheidine (**22**) by Sato and co-workers.[13] Tetrahydro-*β*-carboline **23** was made from L-tryptophan in eight steps including a Pictet−Spengler reaction (Scheme 5). Six further steps (including a nickel-catalyzed carboxylative cyclization) then furnished the alkaloid **22**. We set out to prepare optically active **23** from tryptamine using an organocatalytic enantioselective Pictet−Spengler reaction.

Amine **24** was best prepared by amination of 1-bromo-2-butyne with excess tryptamine (Scheme 6). The enantioselective Pictet−Spengler cyclization using aldehyde **16** and catalyst **12b** followed by indole nitrogen protection proceeded as before and gave the tetrahydro-*β*-carboline **25** in 81% yield from **24**.

Selenoxide elimination led to **23** in excellent yield. The er of **23** was determined by HPLC to be 94:6 ($[\alpha]_D$ = −18.3 (*c* 0.76, $CHCl_3$)), and its spectral data were identical to those detemined by Sato et al.[13] Thus, we have shortened the Sato eight-step synthesis of **23** in 31% overall yield from tryptophan into a four-step synthesis in 52% overall yield from bromobutyne.

■ CONCLUSION

This article illustrates new applications in total synthesis for the venerable Pictet−Spengler reaction, which was first reported a century ago.[14,15] When an achiral *N*-monosubstituted tryptamine is reacted with an achiral aldehyde in the presence of an enantiopure binolphosphoric acid catalyst, the tetrahydro-*β*-carboline product may show good to excellent enantiomeric excess.[16,17] We first discovered this useful process for *N*-sulfenyltryptamines, which led to optically active NH tetrahydro-*β*-carbolines.[18] It also worked well for *N*-alkyltryptamines as was proven in the key chirality introducing step of the total syntheses of arboricine[8] and now yohimbine and corynantheidine. More examples can be expected in the near future, increasing the relevance of asymmetric organocatalysis in natural product synthesis.[19]

■ EXPERIMENTAL SECTION

General Remarks. All reactions were carried out in oven-dried glassware with magnetic stirring under an atmosphere of nitrogen, unless otherwise noted. Tetrahydrofuran (THF) was freshly distilled from sodium and benzophenone. Toluene (used for the Pictet−Spengler reaction) was stored over 4 Å molecular sieves. Other commercial reagents and solvents were used as received. Powdered 4 Å molecular sieves were dried at 200 °C and 0.1 mbar.

All ^{1}H NMR (at 400 MHz) and ^{13}C NMR spectra (APT, at 100 MHz) were recorded at rt in $CDCl_3$ and calibrated to the residual solvent signals. Analytical thin layer chromatography was performed

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using a Merck TLC plastic roll 500 × 20 cm silica gel 60 F_{254}. Chromatographic purification refers to flash chromatography over Biosolve 60 Å (0.032−0.063 mm) silica gel. The er determinations were carried out using HPLC with a Chiralcel OD-H columns (Chiral Technologies Europe, 0.46 cm × 25 cm). Melting points are uncorrected.

***tert*-Butyl (1*E*,3*E*-5-Oxopenta-1,3-dien-1-yl)carbonate (9).** Glutaconaldehyde potassium salt[9] (**8**) (17.0 g, 125 mmol) was dissolved as well as possible in dry DMSO (300 mL) at 50 °C under vigorous mechanical stirring. Then, under continuous stirring, di-*tert*-butyl dicarbonate (34.8 g, 159.5 mmol, 1.28 equiv) dissolved in dry DMSO (60 mL) was added as quickly as possible. A dark red gel was immediately formed, which hindered stirring. Diethyl ether (300 mL) was added after 10 min and vigorous stirring was continued for 1 h. Water was then added whereupon the gel immediately dissolved, releasing heat and gas. The reaction mixture was extracted a few times with diethyl ether and the combined extracts dried over sodium sulfate. The solvent was removed in vacuo and the residue dissolved in toluene. The solvent was again evaporated in vacuo to remove all of the *tert*-butanol. The pure compound **9** was obtained after recrystallization from hexanes in 64% yield as pale yellow needles: mp 68−72 °C. ^{1}H NMR δ: 9.57 (d, J = 7.9 Hz, 1H), 7.63 (d, J = 12.3 Hz, 1H), 7.12, (dd, J = 15.2, 11.6 Hz, 1H), 6.24 (t, J = 11.6 Hz, 1H), 6.22, (dd, J = 15.2, 7.9 Hz, 1H), 1.56 (s, 9H). ^{13}C NMR δ: 193.0 (CH), 149.6 (C), 148.0 (CH), 146.9 (CH), 131.3 (CH), 112.4 (CH), 84.8 (C), 27.3 (3C, CH_3). IR (thin film) ν: 1764, 1686, 1648, 1122 cm^{-1}. HRMS (FAB) calcd for $C_{10}H_{15}O_4$ $[M + H]^+$ 199.0970; found 199.0966 m/z. Elemental anal. calcd for $C_{10}H_{14}O_4$ C 60.59, H 7.12; found C 60.28, H 7.09.

(1*E*,3*E*)-5-((2-(1*H*-Indol-3-yl)ethyl)amino)penta-1,3-dien-1-yl *tert*-butyl Carbonate (10). A mixture of methanol (480 mL), Boc-protected glutaconaldehyde **9** (9.90 g, 50 mmol), and tryptamine (8.01 g, 50 mmol) was stirred for 2 h at −20 °C. Then sodium borohydride (2.85 g, 75 mmol, 1.5 equiv) was added, and the solution was stirred for another hour at −20 °C. Acetone (5 mL) was added, and the solution was allowed to warm to rt. Ethyl acetate was then added, and the volatiles removed in vacuo. The residue was directly brought onto a short column and the product purified (eluent 85:10:5 ethyl acetate/methanol/triethylamine). The unstable product **10** was obtained as yellow oil, which turned dark red (near black) over time. The compound decomposed at higher temperatures and should be kept as cool as possible. ^{1}H NMR δ: 8.05 (bs, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 7.16 (t, J = 8.0 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 7.07 (s, 1H), 6.06 (dd, J = 14, 11 Hz, 1H), 5.99 (t, J = 11 Hz, 1H), 5.74 (dt, J = 7.4, 6.3 Hz, 1H), 3.31 (d, J = 6.3 Hz, 2H), 3.00 (m, 4H), 1.53 (s, 9H), one NH signal is not discernible. ^{13}C NMR δ: 150.6 (C), 139.1 (CH), 136.3 (C), 131.2 (CH), 127.2 (C), 125.9 (CH), 122.1 (CH), 121.7 (CH), 119.0 (CH), 118.7 (CH), 114.4 (CH), 113.3 (C), 111.2 (CH), 83.5 (C), 51.2 (CH_2), 49.1 (CH_2), 27.5 (3C, CH_3), 25.5 (CH_2). IR (thin film) ν: 1754 cm^{-1}. HRMS (FAB) calcd for $C_{20}H_{27}N_2O_3$ $[M + H]^+$ 343.2022, found 343.2023 m/z.

(1*S*)-*tert*-Butyl 2-((2*E*,4*E*)-5-((*tert*-Butoxycarbonyl)oxy)penta-2,4-dien-1-yl)-1-(4-methoxy-4-oxo-3-(phenylselenyl)butyl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-9(2*H*)-carboxylate (18). To a stirred solution of freshly purified **10** (1.076 g, 3.14 mmol) in dry toluene (15.5 mL) was added catalyst **12b** (59.7 mg, 0.63 mmol, 2 mol %). After a clear solution was obtained powdered molecular sieves 4 Å (5.5 g) and a solution of **16**[12] (989 mg, 3.45 mmol) in dry toluene (5 mL) were added, and the mixture was stirred overnight at 50 °C. The conversion was monitored through TLC (10:10:3 hexanes/DCM/ethyl acetate). When the reaction was complete, di-*tert*-butyl dicarbonate (1.026 g, 4.71 mmol) and DMAP (114.9 mg, 0.94 mmol, 30 mol %) were added, and the mixture was stirred for 2 h at 40 °C. After the reaction was complete the orange suspension was filtered over Celite, giving a reddish filtrate. The filtrate was concentrated in vacuo and directly purified by column chromatography (10:10:3 hexanes/DCM/ethyl acetate). The product **18** was obtained as a light yellow foam in 82% yield over two steps as a ca. 58:42 mixture of diastereomers (according to ^{1}H NMR). The er was determined after the next reaction. ^{1}H NMR δ: 8.14 (m, 1H) 7.61 (m, 2H), 7.42 (m, 1H), 7.29 (m, 4H), 7.12 (m, 1H), 6.04 (m, 2H), 5.72 (m, 1H), 4.23 (bm, 1H), 3.79 (m, 1H), 3.67 (m, 3H), 3.31 (m, 1H), 3.19 (m, 2H), 2.98 (m, 1H), 2.80 (m, 1H), 2.46 (dt, J = 16.4, 4.2 Hz, 1H), 2.33 (m, 1H), 2.20 (m, 1H), 2.05−1.92 (bm, 2H), 1.65−1.54 (2 × s, 9H). ^{13}C NMR δ: 173.4 (C), 173.3 (C), 150.6 (C), 150.0 (C), 139.08 (CH), 139.05 (CH), 136.5 (C), 136.2 (C), 135.9 (C), 135.7 (C), 135.52 (CH), 135.47 (CH), 135.42 (CH), 131.8 (CH), 129.29 (C), 129.23 (C), 128.84 (CH), 128.79 (CH), 128.25 (CH), 128.22 (CH), 128.1 (C), 127.9 (C), 126.68 (CH), 126.64 (CH), 123.80 (CH), 123.75 (CH), 122.5 (CH), 117.70 (CH), 117.67 (CH), 115.6 (CH), 114.5 (CH), 113.89 (C), 113.83 (C), 83.62 (C), 83.48 (C), 83.35 (C), 83.33 (C), 56.7 (CH), 55.26 (CH_2), 55.21 (CH_2), 51.79 (CH_3), 51.75 (CH_3), 43.7 (CH), 43.3 (CH), 41.5 (CH_2), 41.4 (CH_2), 32.4 (CH_2), 32.2 (CH_2), 31.1, 29.3 (CH_2), 29.1 (CH_2), 28.1 (3C, CH_3), 27.5 (3C, CH_3), 16.57 (CH_2), 16.52 (CH_2). IR (thin film) ν: 1755, 1728 cm^{-1}. HRMS (FAB) calcd for $C_{37}H_{47}N_2O_7Se$ $[M + H]^+$ 711.2552, found 711.2550 m/z.

(*S*)-*tert*-Butyl 2-((2*E*,4*E*)-5-((*tert*-Butoxycarbonyl)oxy)penta-2,4-dien-1-yl)-1-((*E*)-4-methoxy-4-oxobut-2-en-1-yl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-9(2*H*)-carboxylate (19). To a stirred solution of **18** (1.82 g, 2.57 mmol) in DCM (2.5 mL) at −78 °C was added *m*-chloroperbenzoic acid (≤77%, from Aldrich, 691 mg, 3.084 mmol, 1.2 equiv). After being stirred for 2 h at −78 °C triethylamine (1.08 mL, 7.71 mmol, 3 equiv) was added. The solution was then allowed to slowly warm up to rt by removal of the cooling bath, which led to a color change from yellow to red. Once at ambient temperature the mixture was concentrated and subjected to flash chromatography (10:10:3 hexanes/DCM/ethyl acetate) to yield **19** as an almost colorless oil in 88%. The er was determined to be 92:8 by chiral HPLC (OD-H, 1% isopropanol in *n*-heptane, 0.5 mL/min), retention time (minor): 24.1 min, retention time (major): 30.9 min. ^{1}H NMR δ: 8.16 (d, 8.0 Hz, 1H), 7.45 (d, J = 6.6, 1H), 7.29 (m, 2H), 7.15 (m, 2H), 6.08 (m, 2H), 5.92 (d, J = 15.7 Hz, 1H), 5.76 (m, 1H), 4.48 (dd, J = 10.5, 3.0 Hz, 1H) 3.77 (s, 3H), 3.35 (m, 1H), 3.23 (m, 2H), 3.05 (dd, J = 14.2, 5.6 Hz, 1H), 2.84 (m, 1H), 2.75 (m, 1H), 2.57 (m, 1H), 2.51 (dd, J = 16.6, 5.0 Hz, 1H), 1.66 (s, 9H), 1.54 (s, 9H). ^{13}C NMR δ: 166.8 (C),150.5 (C), 150.0 (C), 147.5 (CH), 139.1 (CH), 135.8 (C), 135.4 (C), 131.3 (CH), 129.1 (C), 126.8 (CH), 124.0 (CH), 122.5 (CH), 121.6 (CH), 117.8 (CH), 115.6 (CH), 114.4 (CH), 114.4 (C), 83.8 (C), 83.4 (C), 56.1 (CH), 55.2 (CH_2), 51.3 (CH_3), 41.4 (CH_2), 36.8 (CH_2), 28.1 (3C, CH_3), 27.5 (3C, CH_3), 16.6 (CH_2). IR (thin film) ν: 1755, 1725 cm^{-1}. HRMS (FAB) calcd for $C_{31}H_{41}N_2O_7$ $[M + H]^+$ 553.2914, found 553.2908 m/z.

(1*R*,2*S*,4a*R*,13b*S*,14a*S*)-13-*tert*-Butyl 1-Methyl-2-((*tert*-butoxycarbonyl)oxy)-1,4a,5,7,8,13b,14,14a-octahydroindolo-[2′,3′:3,4]pyrido[1,2-*b*]isoquinoline-1,13(2*H*)-dicarboxylate (20). Compound **19** (360 mg, 0.65 mmol) was dissolved in dry toluene (90 mL) and heated to 70 °C for 70 h. The mixture was then cooled to rt and the solvent removed in vacuo. According to ^{1}H NMR a 6:1 mixture of diastereomers **20a** and **20b** was formed. This mixture was dissolved again in a 1:1 mixture of DCM and hexanes and separated by column chromatography (eluent 10:10:3 hexanes/DCM/ethyl acetate). The pure diastereomer **20a** was obtained in 70% yield. The er of **20a** was determined to be 92:8 by chiral HPLC (OD-H, 1% isopropanol in *n*-heptane, 0.5 mL/min), retention time (minor): 24.1 min, retention time (major): 30.9 min. After recrystallization a single enantiomer was obtained in 49% yield (176 mg, 70% yield for the recrystallization): mp 189 °C; $[\alpha]_D^{20}$ +49.7 (c 0.51, $CHCl_3$). ^{1}H NMR δ 8.20 (d, J = 7.9 Hz, 1H), 7.41 (d, J = 7.3 Hz, 1H), 7.28 (dt, J = 7.2, 1.4 Hz, 1H), 7.25 (dt, J = 7.0, 1.1 Hz, 1H), 5.88−5.80 (m, 2H), 5.38 (dt, 4.0, 1.2 Hz, 1H), 4.34 (d, 9.8 Hz, 1H), 3.65 (s, 3H), 3.23−3.16 (m, 2H), 2.90−2.76 (m, 4H), 2.62 (dd, J = 11.2, 4 Hz, 1H), 2.40 (dt, J = 12.5, 2.6 Hz, 1H), 2.27 (bt, 11.2 Hz, 1H), 2.12 (dq, 11.4, 3.0 Hz, 1H), 1.75 (s, 9H), 1.50 (s, 9H), 1.29 (q, J = 11.7 Hz, 1H). ^{13}C NMR δ: 170.4 (C), 152.8 (C), 150.1 (C), 136.8 (C), 136.3 (C), 134.5 (CH), 128.9 (C), 124.3 (CH), 123.8 (CH), 122.4 (CH), 117.6 (CH), 115.5 (CH), 115.3 (C), 84.2 (C), 82.0 (C), 68.7 (CH), 59.3 (2C, CH_2), 58.5 (CH), 51.4 (CH_3), 49.2 (CH), 46.3 (CH_2), 36.9 (CH), 35.8 (CH), 30.2 (CH_2), 27.8 (3C, CH_3), 27.7 (3C, CH_3). IR (thin film) ν:

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1734 cm^{-1}. HRMS (FAB) calcd for $C_{31}H_{41}N_2O_7$ $[M + H]^+$ 553.2914, found 553.2916 *m/z*. Elemental anal. calcd for $C_{31}H_{40}N_2O_7$ C 67.37, H 7.30, N 5.07; found C 67.39, H 7.29, N 5.07.

(1*R*,2*S*,4a*R*,13b*S*,14a*S*)-Methyl 2-Hydroxy-1,2,4a,5,7,8,13,13b,14,14a-decahydroindolo[2′,3′:3,4]pyrido-[1,2-*b*]isoquinoline-1-carboxylate (21). To a solution of crystalline **20a** (140 mg, 0.25 mmol) in DCM (2.5 mL) was added dropwise trifluoroacetic acid (2.5 mL, 32.6 mmol). After being stirred for 2 h the reaction mixture was diluted with ethyl acetate (20 mL) and then poured into a saturated sodium bicarbonate solution (20 mL). The organic layer was washed four times with saturated sodium bicarbonate and dried on sodium sulfate. Removal of the solvent in vacuo gave **21** as a white solid in quantitative yield (88.1 mg, 0.25 mmol): mp 126–130 °C; $[\alpha]_D^{20}$ +75.5 (*c* 0.50, $CHCl_3$). ^1H NMR δ: 8.21 (s, 1H), 7.49 (d, *J* = 7.3 Hz, 1H), 2.27 (d, *J* = 8.6 Hz, 1H), 7.16–7.08 (m, 2H), 5.94–5.89 (m, 1H), 5.71 (d, *J* = 9.9 Hz, 1H), 4.47 (t, *J* = 4.2 Hz, 1H), 3.82 (s, 3H), 3.36 (d, *J* = 9.8 Hz, 1H), 3.11–3.07 (m, 1H), 3.07–3.03 (m, 1H), 3.02–2.96 (m, 1H), 2,74 (dd, 15.0 Hz, 4.1 Hz, 1H), 2.67–2.60 (m, 2H), 2.54 (dt, *J* = 12.3 Hz, 2.6 Hz, 1H), 2.28–2.23 (t, *J* = 10.9 Hz, 1H), 2.19 (q, *J* = 11.1 Hz, 1H), 1.90 (dq, *J* = 11.3, 3.0 Hz, 1H), 1.37 (q, *J* = 11.9 Hz, 1H). ^{13}C NMR δ: 173.2 (C), 135.8 (C), 134.3 (C), 132.3 (CH), 127.7 (CH), 127.1 (C), 121.1 (CH), 119.1 (CH), 117.9 (CH), 110.8 (CH), 107.7 (C), 65.1 (CH), 60.0 (CH), 59.6 (CH_2), 52.8 (CH_2), 51.8 (CH_3), 50.4 (CH), 40.6 (CH), 34.6 (CH), 32.7 (CH_2), 21.6 (CH_2). IR (thin film) ν: 3366, 1725 cm^{-1}. HRMS (FAB) calcd for $C_{21}H_{25}N_2O_3$ $[M + H]^+$ 353.1865, found 353.1860 *m/z*.

(+)-Yohimbine (1). To a stirred solution of crude **21** (100 mg, 0.284 mmol) in ethyl acetate (6 mL) was added 10% Pd/C (30.2 mg, 0.028 mmol Pd). The mixture was flushed with hydrogen gas and then stirred overnight under a 1 atm hydrogen pressure. The mixture was worked up by filtration over Celite and washing the filter with a mixture of ethyl acetate and methanol, yielding yohimbine (**1**) as off-white crystals (101 mg, quantitative yield): mp 227–229 °C (lit.[5] 233–235 °C); $[\alpha]_D^{20}$ +51.8 (*c* 0.54, EtOH) (lit.[5] $[\alpha]_D^{20}$ +52.3 (*c* 0.59, EtOH)). ^1H NMR δ: 7.76 (bs, 1H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.18–7.09 (m. 2H), 4.25 (bs, 1H), 3.84 (s, 3H), 3.37 (dd, *J* = 11.5, 1,9 Hz, 1H), 3.13–3.09 (m, 1H), 3.06–2.94 (m, 3H), 2.77–2.72 (m, 1H), 2.66 (dt, *J* = 11.2, 4.6 Hz, 1H), 2.38 (dd, *J* = 11.5, 2.0 Hz, 1H), 2.28 (m, 1H), 2.09–1.98 (m, 3H), 1.60 (m, 3H), 1.46–1.44 (m, 1H), 1.40 (m, 1H). ^{13}C NMR δ: 175.5 (C), 135.8 (C), 134.2 (C), 127.2 (C), 121.3 (CH), 119.3 (CH), 118.0 (CH), 110.6 (CH), 108.1 (C), 66.8 (CH), 61.2 (CH_2), 59.7 (CH), 52.7 (CH_2), 52.2 (CH), 51.8 (CH_3), 40.6 (CH), 36.6 (CH), 34.2 (CH_2), 31.3 (CH_2), 23.2 (CH_2), 21.6 (CH_2). IR (thin film) ν: 3369, 1724 cm^{-1}. HRMS (FAB) calcd for $C_{21}H_{27}N_2O_3$ $[M + H]^+$ 355.2022, found 355.2017 *m/z*.

***N*-(2-(1*H*-Indol-3-yl)ethyl)but-2-yn-1-amine (24).** 1-Bromo-2-butyne (1.33 g, 10 mmol) was added to a solution of tryptamine (8.0 g, 50 mmol) in acetonitrile (200 mL). The mixture was stirred at rt for 18 h, and after cooling in ice the solids were removed by filtration. The filtrate was then concentrated in vacuo and the residue chromatographed (eluent EtOAc, EtOAc/MeOH 95:5 and EtOAc/MeOH 90:10, respectively) to give **24** (1.55 g, 7.32 mmol, 73%) as a slightly colored solid: mp 95–99 °C. ^1H NMR δ: 8.02 (bs, 1H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 8.16 Hz, 1H), 7.22 (m, 1H), 7.14 (m, 1H), 7.08 (d, *J* = 2.2 Hz, 1H), 3.40 (bs, 2H), (3.0–3.1 (m, 4H), 1.80 (t, *J* = 2.3 Hz, 3H). ^{13}C NMR δ: 136.3 (C), 127.3 (C), 121.9 (CH), 121.8 (CH), 119.0 (CH), 118.8 (CH), 113.6 (C), 111.6 (CH), 78.9 (C), 77.1 (C), 48.7 (CH_2), 38.4 (CH_2), 25.5 (CH_2), 3.34 (CH_3). IR (neat) ν: 3412, 1455 cm^{-1}. HRMS (FAB) calcd for $C_{14}H_{17}N_2$ $[M + H]^+$ 213.1392, found 213.1394 *m/z*.

(1*S*)-*tert*-Butyl 2-(But-2-yn-1-yl)-1-(4-methoxy-4-oxo-3-(phenylselenyl)butyl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-9(2*H*)-carboxylate (25). Amine **24** (212 mg, 1.00 mmol) and catalyst **12b** (17.3 mg, 2 mol %) were dissolved in dry toluene (5 mL). Powdered molecular sieves 4 Å (1.5 g) and aldehyde **16**[12] (315 mg, 1.10 mmol) dissolved in dry toluene (2.5 mL) were added, and the mixture was stirred overnight at 50 °C. Then, di-*tert*-butyl dicarbonate (327.3 mg, 1.50 mmol) and DMAP (36.6 mg, 0.30 mmol) were added, and the mixture was heated to 40 °C for 2 h. Hexanes and silica gel were added, and the mixture was brought onto a column as a slurry. Column chromatography (85:15 hexanes/ethyl acetate) afforded **25** (469 mg, 0.81 mmol) as a colorless oil in 81% yield (a 1:1 mixture of diastereomers). ^1H NMR δ: 8.13 (d, *J* = 7.9 Hz, 0.5H), 8.09 (d, *J* = 7.7 Hz, 0.5H), 7.64–7.61 (m, 2H), 7.41 (td, *J* = 7.5, 0.7 Hz, 1H), 7.35–7.21 (m, 5H), 4.48 (d, *J* = 9.8 Hz, 1H), 3.89 (dd, *J* = 8.4, 6.9 Hz, 0.5H), 3.82 (dd, *J* = 8.6, 6.9 Hz, 0.5H), 3.65 (s, 1.5H), 3.62 (s, 1.5H), 3.40 (m, 2H), 3.18 (m, 2H), 2.84–2.75 (m, 1H), 2.52 (m, 0.5H), 2.48 (m, 0.5H), 2.33–2.08 (m, 2H), 2.05–1.98 (m, 1H), 1.95–1.87 (m, 0.5H), 1.84 (t, *J* = 2.3 Hz, 3H), 1.78–1.65 (m, 0.5H), 1.69 (s, 4.5H), 1.69 (s, 4.5H). ^{13}C NMR δ: 173.4 (C), 173.3 (C), 150.1 (C), 150.0 (C), 136.2 (C), 135.94 (C), 135.92 (C), 135.7 (C), 135.43 (CH), 135.37 (CH), 129.18 (C), 129.12 (C), 128.80 (CH), 128.77 (CH), 128.18 (C), 128.15 (CH), 128.0 (C), 123.84 (CH), 123.78 (CH), 122.5 (CH), 117.75 (CH), 117.73 (CH), 115.6 (CH), 113.91 (C), 113.80 (C), 83.7 (C), 83.5 (C), 79.67 (C), 79.60 (C), 76.04 (C), 76.00 (C), 56.7 (CH), 56.5 (CH), 51.77 (CH_3), 51.72 (CH_3), 43.5 (CH), 43.3 (CH), 42.83 (CH_2), 42.76 (CH_2), 41.7 (CH_2), 41.6 (CH_2), 32.2 (CH_2), 32.0 (CH_2), 28.88 (CH_2), 28.85 (CH_2), 28.16 (3C, CH_3), 28.11 (3C, CH_3), 16.65 (CH_2), 16.60 (CH_2), 3.51 (CH_3), 3.50 (CH_3). IR (thin film) ν: 1727 cm^{-1}. HRMS (FAB) calcd for $C_{31}H_{37}N_2O_4Se$ $[M + H]^+$ 581.1921, found 581.1929 *m/z*.

(*S*,*E*)-*tert*-Butyl 2-(But-2-yn-1-yl)-1-(4-methoxy-4-oxobut-2-en-1-yl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-9(2*H*)-carboxylate (23). To a stirred solution of **25** (413 mg, 0.71 mmol) in dry DCM (7 mL) at −78 °C was added *m*-chloroperbenzoic acid (≤77%, from Aldrich, 191.5 mg, 0.85 mmol). After 2 h at −78 °C triethylamine (0.298 mL, 2.14 mmol) was added, and the mixture was allowed to warm up to rt. After stirring for 30 min at rt, hexanes (7 mL) were added and the mixture was brought as such onto a silica gel column. Column chromatography (85:15, hexanes/ethyl acetate) yielded the product **23** (280 mg, 0.66 mmol) as a colorless oil in 93%. The er was determined to be 94:6 by chiral HPLC (OD-H column, 0.3% isopropanol in *n*-heptane, 0.5 mL/min), retention time (minor): 38.8 min, rentention time (major): 45.1 min. $[\alpha]_D^{20}$ −18.3 (c 0.76, $CHCl_3$) (lit.[13] $[\alpha]_D^{22}$ −15.8 (c 0.52, $CHCl_3$)). ^1H NMR δ: 8.14 (d, *J* = 8.1 Hz, 1H), 7.44 (m, 1H), 7.33–7.23 (m, 2H), 7.21–7.13 (m, 1H), 6.00 (dt, *J* = 15.8, 1.5 Hz, 1H), 4.47 (dd, *J* = 9.9, 2.2 Hz, 1H), 3.75 (s, 3H), 3.42 (dd, *J* = 2.4, 2.2 Hz, 2H), 3.21 (dd, *J* = 8.8, 3.4 Hz, 2H), 2.87–2.81 (m, 1H), 2.80–2.74 (m, 1H), 2.63–2.56 (m, 1H), 2.55 (dt, *J* = 13.1, 3.1 Hz, 1H), 1.86 (t, *J* = 2.3 Hz, 3H), 1.70 (s, 9H). ^{13}C NMR δ: 166.9 (C), 150.0 (C), 147.4 (CH), 135.9 (C), 134.9 (C), 129.0 (C), 124.0 (CH), 122.5 (CH), 121.6 (CH), 117.8 (CH), 115.6 (CH), 114.5 (C), 83.8 (C), 80.0 (C), 75.7 (C), 56.0 (CH), 51.2 (CH_3), 42.9 (CH_2), 41.8 (CH_2), 36.7 (CH_2), 28.1 (3C, CH_3), 16.7 (CH_2), 3.4 (CH_3). IR (thin film) ν: 1723 cm^{-1}. HRMS (FAB) calcd for $C_{25}H_{31}N_2O_4$ $[M + H]^+$ 423.2284, found 423.2287 *m/z*.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra of compounds **1**, **9**, **10**, **17**, **18**, **19**, **20a**, **21**, **23**, **24**, and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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DEDICATION

This paper is dedicated to the memory of Professor Hans Wynberg, a pioneer of organocatalysis, deceased May 25, 2011.

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