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Total Synthesis of (+)-Mesembrine Applying Asymmetric Gold Catalysis

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Total Synthesis of (+)-Mesembrine Applying Asymmetric Gold Catalysis

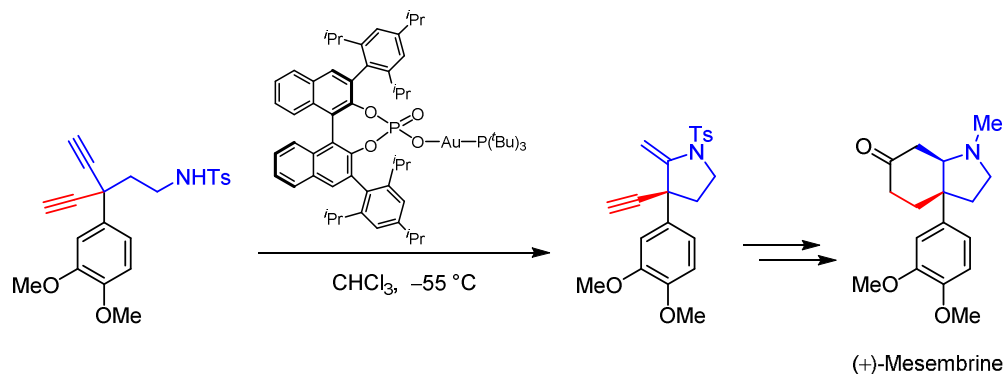
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ABSTRACT: The total synthesis of enantiomerically pure (+)-mesembrine is described. The central pyrrolidine moiety incorporating a quaternary, all-carbon-substituted stereocenter was constructed employing an asymmetric gold-catalyzed cycloisomerization of a 1,4-diyne.

(-)-Mesembrine is a naturally occurring alkaloid including a pyrrolidine substructure which was originally isolated from the succulent plant *Sceletium tortuosum*. This plant is also known as *kanna* and has been used as a stimulant by South African natives.¹ In 1957, Bodendorf and Krieger^{1a} published the first accurate structural elucidation of mesembrine and three years later Popelak et al.² determined its absolute configuration (Figure 1).

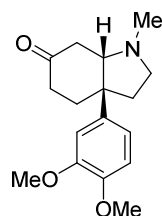
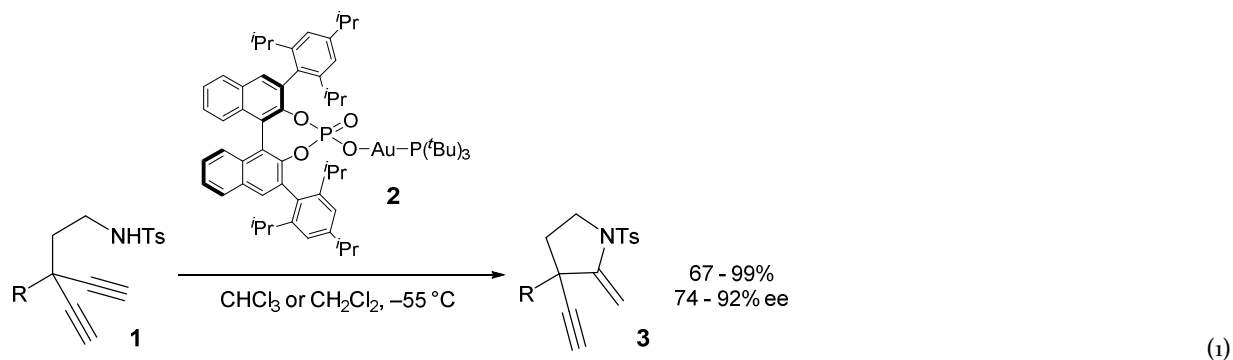


Figure 1 (–)-Mesembrine, a Naturally Occurring Alkaloid.

Shamma and Rodriguez were the first to report a total synthesis of racemic mesembrine in 1965.³ In 1971, Yamada and coworkers chose a chiral auxiliary-controlled approach to perform the first synthesis of enantiomerically enriched, non-natural (+)-mesembrine.⁴ Ten years later, the group of Takano published the ex-chiral-pool total synthesis of the naturally occurring (–)-mesembrine starting from (D)-mannitol.⁵ The first total synthesis of enantiopure (+)-mesembrine was performed by the Meyers group, following a reagent-controlled strategy.⁶ Since then, over 40 syntheses have been published, rendering mesembrine one of the calibration standards for the application of new stereoselective methodology in the context of total synthesis.⁷ In particular, the quaternary, all-carbon substituted stereocenter poses a challenge since methods for its preparation are limited in number.⁸

Within the last two decades, gold-catalyzed reactions have evolved as a remarkable field of research and today various transformations of alkenes, alkynes and allenes via carbophilic Lewis activation are well-established.⁹ Employing chiral catalysts enantioselective protocols have been developed which also found application in total synthesis.¹⁰ Recently, we have reported the desymmetrization of 1,4-diynols and 1,4-diynamides by gold-catalyzed cycloisomerization leading to heterocyclic products such as dihydro-dioxepines, tetrahydro-oxazepines, methylene tetrahydrofuranes and methylene pyrrolidines.¹¹ While catalysts with chiral phosphine or carbene ligands gave no satisfying enantioselectivities, optically active phosphate counter-anions derived from 3,3'-disubstituted BINOL¹² were successfully employed. The cycloisomerization of diynamides **1** led to methylene pyrrolidines **3** in enantioselectivities up to 92% *ee* (Equation 1).

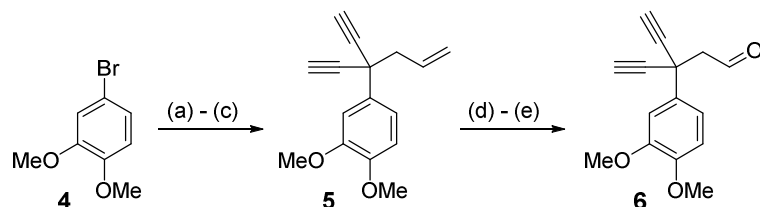


Given the new access to pyrrolidines with a quaternary stereocenter in 3-position we became interested in exemplifying our gold-catalyzed asymmetric desymmetrization for heterocyclic natural product synthesis and chose

mesembrine as a target molecule. We reasoned that not only mesembrine but also other alkaloids such as spirooxindoles or aspidospermines are accessible via the new route. Herein, we report the implementation of the enantioselective, gold-catalyzed diyne cycloisomerization as a key step for the total synthesis of (+)-mesembrine or related alkaloids including a pyrrolidine substructure.

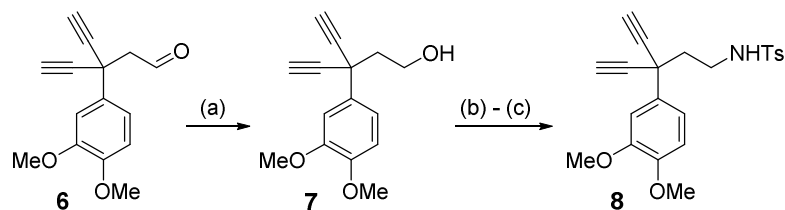
Starting from commercially available 4-bromoveratrole (**4**) an Ullmann-type cross-coupling reaction with acetylacetone was performed (Scheme 1).^{11b, 13} Copper(I) iodide was used as the catalyst and the coupling product was obtained in 43% yield. The resulting diketone was C-selectively allylated and then transformed into ene-1,4-diyne **5** via the corresponding enol phosphate ester using a modified protocol by Negishi.¹⁴ The alkene moiety was chemoselectively dihydroxylated in an Upjohn reaction and the resulting glycol was cleaved using sodium periodate on silica gel to give aldehyde **6**.¹⁵

Scheme 1 Preparation of Diynal **6**: (a) MeCOCH₂COMe, CuI, L-proline, K₂CO₃, DMSO, 90 °C, 43%; (b) allyl iodide, NaH, DMF, 74%; (c) LDA, ClPO(OEt)₂, -78 °C, 77%; (d) K₂OsO₄, NMO, ^tBuOH/H₂O, 83%; (e) NaIO₄, silica gel, 97%.

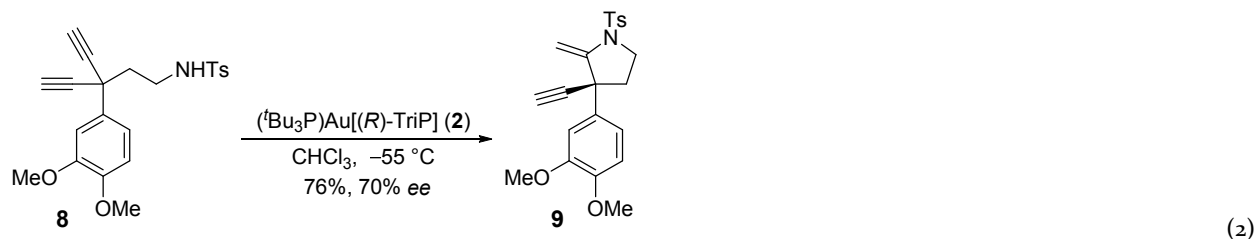


The transformation of aldehyde **6** to diynamide **8** was surprisingly challenging (Scheme 2). Following the protocol developed earlier we first investigated the formation of a *N*-tosylimine followed by a reduction.^{11c, 16} However, condensation with *p*-tosylamide and precipitation of the *p*-toluenesulfonate adduct, which was found successful for related compounds, gave no satisfying results. The reductive amination of aldehyde **6** with different ammonium salts in the presence of NaBH₃CN or via a reduction of the corresponding oxime gave the desired diynamide **8** in a maximum yield of only 30%. Therefore, we considered the nucleophilic substitution of alcohol **7** as an alternative approach. For this purpose, aldehyde **6** was reduced with sodium borohydride (Scheme 2). The nucleophilic displacement of the tosylate derived from alcohol **7** with *p*-tosylamide was not productive, however. Furthermore, the employment of other *N*-nucleophiles such as ammonia or sodium azide at elevated temperatures resulted in a non-selective ring-closure. We were pleased to find that the desired product **8** could be efficiently prepared by a Mitsunobu-type reaction with Boc-*p*-tosylamide¹⁷ followed by acid-mediated deprotection of the Boc group. This two-step procedure provided diynamide **8** in 87% yield.

Scheme 2 Preparation of 1,4-Diynamide **8**: (a) NaBH₄, MeOH, 73%; (b) *p*-TsNHBoc, PPh₃, DEAD, THF, 94%; (c) TFA, CH₂Cl₂, 93%.

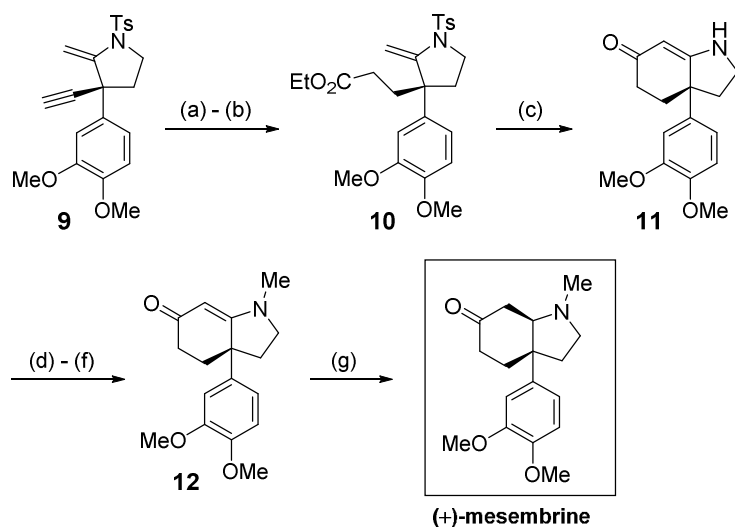


At this point the stage was set for the gold-catalyzed, enantioselective desymmetrization which was carried out under the previously optimized conditions.¹¹ In former studies it was observed that both the solvent and the reaction temperature are critical parameters for the selectivity of the reaction. The enantioselectivity was found to be highest in non-coordinating chlorinated solvents such as chloroform or dichloromethane and severely decreased in a coordinating solvent like THF. Furthermore, running the reaction at low temperatures significantly improved the enantiomeric excess. Presumably, one carbon-carbon triple bond is activated by coordination of the cationic gold complex, which forms a contact ion pair with the chiral phosphate.¹⁹ Upon this activation the amide nucleophile can attack the alkyne moiety to form methylene pyrrolidine **9**. The enantioselective cycloisomerization gave methylene pyrrolidine **9** in 76% yield and 70% *ee* after stirring for 19 h at -55°C (Equation 2).



It was shown earlier that the enantiomeric excess of related pyrrolidine compounds could be improved by recrystallization (e.g. from *n*-hexane). However, in the case of product **9** recrystallization attempts from various solvents did not significantly increase the enantiomeric excess. Therefore, we decided to proceed with the synthetic sequence since recrystallization of a later intermediate was known to result in enantiomerically pure material.^{7a} Methylene pyrrolidine **9** was transformed into the corresponding unsaturated ester by treatment of the acetylide with methyl chloroformate (Scheme 3). The subsequent conjugate reduction was performed by catalytic hydrogenation using palladium on carbon at 85 bar. Ester **10** was formed in 98% yield without concomitant reduction of the enamide moiety or the aromatic substituent. In contrast, reduction using Stryker's reagent gave mixtures of the desired ester **10** and the partially reduced alkenoic ester.

Scheme 3 Total Synthesis of (+)-Mesembrine: (a) ClCO_2Et , $n\text{BuLi}$, 98%; (b) 85 bar H_2 , Pd/C, 98%; (c) $\text{NaC}_{10}\text{H}_8$, THF, -78°C , 87%; (d) Boc_2O , DMAP, Et_3N , 91%; (e) recrystallization from *n*-hexane/ Et_2O ; (f) 1. $(\text{CF}_3)_2\text{CHOH}$, MW, 120°C , 40 min; 2. NaH , MeI, THF, 97%; (g) Li/NH_3 (liq.), $t\text{BuOH}$, -78°C , 77%.



Gratifyingly, deprotection of the *p*-tosyl protecting group with sodium naphthalenide directly resulted in the formation of the bicyclic hexahydro-6*H*-indol-6-one **11** in a yield of 87%.²⁰ Vinylogous amide **11** was converted into the *N*-Boc-protected derivative, recrystallized from *n*-hexane/Et₂O to increase the enantiomeric excess to >99% and then transformed into the *N*-methylation product **12**.^{7a} For the conjugate reduction of **12**, lithium in liquid ammonia was used and (+)-mesembrine was obtained in 77% yield.^{7a, 21} ¹H-NMR, ¹³C-NMR data^{7a} and the optical rotation [α]_D²³ = +56 (*c* = 0.37, MeOH) are in line with literature values.^{6, 7t}

CONCLUSION

In summary, we have demonstrated the applicability of asymmetric gold catalysis for the total synthesis of (+)-mesembrine. We have shown that pyrrolidine natural products incorporating a quaternary stereocenter, a challenging but also common structural motif, are accessible by an asymmetric 1,4-dynamide cycloisomerization. Using this general method not only mesembrine, but also various related natural products like spirooxindole or aspidospermine alkaloids could be synthesized.

EXPERIMENTAL SECTION

General

All reagents used were purchased or purified to reagent grade. Solvents were dried by common laboratory techniques. Reactions were monitored with thin-layer chromatography. For reactions requiring an inert atmosphere the glassware was dried at 120 °C and standard Schlenk techniques were employed. For column chromatography silica gel 60 or aluminum oxide were used. Silica gel was deactivated by conditioning with the respective eluent and 1% (v/v) triethylamine. For reactions under microwave irradiation the CEM Discover SP-D microwave was used with 100 W. The

enantiomeric excess was determined using a HPLCsystem equipped with a DAICEL CHIRALPAK[®] IA[™] or DAICEL CHIRALPAK[®] IC[™] column. ¹H- and ¹³C-NMR-spectra were recorded at 600 and 300 or 151 and 75 MHz, respectively. IR-spectra were measured as thin films on a NaCl single crystal. High resolution mass spectra (HRMS) were measured with a Q-TOF spectrometer.

3-Ethynyl-3-(3,4-dimethoxyphenyl)hex-1-ene-5-yne (5): Under N₂ atmosphere, dry diisopropylamine (5.5 g, 54 mmol, 2.4 eq.) was dissolved in dry THF (135 mL, 0.4 M). At -78 °C *n*-butyllithium (1.6 M in hexane, 31 mL, 49 mmol, 2.2 eq.) was added dropwise. The solution was stirred at -78 °C for 30 min, warmed up to rt and stirred for 30 min. A solution of allylated product **14** (6.2 g, 23 mmol, 1 eq.) in THF (45 mL, 0.5 M), which was cooled in an ice bath, was transferred into the LDA-solution *via* cannula. After stirring for 1 h at -78 °C, diethyl chlorophosphate (7.3 g, 42 mmol, 2.1 eq.) was added *via* a nitrogen-flushed syringe. The solution was stirred at -78 °C for 2.5 h and then allowed to warm to rt. It was cooled to -78 °C again and in another flask dry diisopropylamine (9.7 g, 96 mmol, 4.8 eq.) was dissolved in dry THF (430 mL, 0.25 M). At -78 °C *n*-butyllithium (1.6 M in hexane, 55 mL, 88 mmol, 4.4 eq.) was added dropwise. The solution was stirred at -78 °C for 30 min, warmed up to rt and stirred for 30 min. It was cooled again to -78 °C and to this solution the enol phosphate ester solution was added *via* cannula. The solution was stirred in the acetone/ dry ice bath and allowed to warm to rt overnight. The reaction was quenched with a mixture of dist. water and brine (2:1) after 20 h reaction time. The aqueous phase was extracted with diethyl ether and the organic phase was washed with brine. The organic phase was dried over Na₂SO₄ and concentrated under reduced pressure. Purification by flash chromatography (eluent = *n*-hexane:EtOAc = 5:1) gave a viscous oil (4.2 g, 17 mmol, 77%). *R*_f = 0.44 (*n*-hexane:EtOAc = 3:1). ¹H-NMR (300 MHz, CDCl₃): δ [ppm] = 7.24 - 7.17 (m, 2H), 6.84 (d, *J* = 8.3 Hz, 1H), 5.86 (ddt, *J* = 17.4, 10.3, 7.1 Hz, 1H), 5.19 - 4.95 (m, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 2.69 (dt, *J* = 7.1, 1.1 Hz, 2H), 2.53 (s, 2H). ¹³C-NMR (75 MHz, CDCl₃): δ [ppm] = 148.8, 148.5, 133.1, 132.9, 119.1, 118.7, 110.9, 110.0, 84.3, 72.2, 56.0, 50.2, 39.8. IR (film), $\tilde{\nu}$ [cm⁻¹]: 3289, 3078, 3003, 2955, 2936, 2912, 2836, 1516, 1264, 1236, 1144, 1028, 649. HRMS (ESI): *m/z* calculated for C₁₆H₁₇O₂ [M+H]⁺: 241.1223; found: 241.1223.

3-(3,4-Dimethoxyphenyl)-3-ethynyl-pent-4-ynal (6): To a vigorously stirred solution of diol **15** (2.79 g, 10.2 mmol, 1 eq.) in dry dichloromethane (100 mL, 0.1 M) NaIO₄ adsorbed on silica gel (21.6 g; 0.613 mmol·g⁻¹, 13.2 mmol, 1.30 eq.) was added. After complete conversion the silica gel was filtered off and the residue was washed with dichloromethane. The filtrate was evaporated and the residue dried *in vacuo*. A yellowish, viscous product was obtained (2.39 g, 9.85 mmol, 97 %). No further purification was necessary. *R*_f = 0.87 (*n*-hexane:EtOAc = 1:1). mp = 61-64 °C. ¹H-NMR (300 MHz, CDCl₃): δ [ppm] = 9.85 (t, *J* = 2.6 Hz, 1H), 7.22 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.18 (d, *J* = 2.3 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 2.89 (d, *J* = 2.7 Hz, 2H), 2.65 (s, 2H). ¹³C-NMR (75 MHz, CDCl₃): δ [ppm] = 199.6, 149.2, 148.9, 131.7, 118.4, 111.2, 109.5,

82.8, 73.7, 56.7, 56.1, 35.7. IR (film), $\tilde{\nu}$ [cm^{-1}]: 3284, 3004, 2961, 2937, 2912, 2838, 2744, 1726, 1517, 1262, 1146, 1026, 666.

HRMS (ESI): m/z calculated for $\text{C}_{15}\text{H}_{15}\text{O}_3$ $[\text{M}+\text{H}]^+$: 243.1016; found: 243.1011.

3-(3,4-Dimethoxyphenyl)-3-ethynyl-pent-4-yn-1-ol (**7**): Under nitrogen atmosphere aldehyde **6** (0.205 g, 0.845 mmol, 1 eq.) was dissolved in dry methanol (8.5 mL, 0.1 M) and cooled to 0 °C. NaBH_4 (64.0 mg, 1.69 mmol, 2.00 eq.) was added. After complete conversion within 15 min the reaction was quenched with dist. water and hydrochloric acid (1 M) was added until pH = 2 was reached. The solution was stirred for 30 min and then neutralised with sodium hydroxide solution. Brine was added and the aqueous phase was extracted with EtOAc. The organic phase was washed with brine and dried over Na_2SO_4 . The product was purified by column chromatography over silica gel (eluent = *n*-hexane:EtOAc: CH_2Cl_2 = 62:28:10). The alcohol **7** was obtained as a white solid (0.150 g, 0.614 mmol, 73%). R_f = 0.45 (*n*-hexane:EtOAc = 1:1). mp = 78–79 °C. ^1H -NMR (300 MHz, CDCl_3): δ [ppm] = 7.29 – 7.16 (m, 2H), 6.86 (d, J = 8.4 Hz, 1H), 3.97 – 3.85 (m, 8H), 2.57 (s, 2H), 2.26 (t, J = 6.4 Hz, 2H), 1.77 (s, 1H). ^{13}C -NMR (75 MHz, CDCl_3): δ [ppm] = 149.0, 148.6, 133.2, 118.4, 111.0, 109.6, 84.3, 77.2, 72.5, 60.4, 56.0, 48.0, 37.8. IR (film), $\tilde{\nu}$ [cm^{-1}]: 3499, 3393, 3287, 3005, 2960, 2935, 2837, 1516, 1261, 1145, 1027, 651. HRMS (ESI): m/z calculated for $\text{C}_{15}\text{H}_{17}\text{O}_3$ $[\text{M}+\text{H}]^+$: 245.1172; found: 245.1171.

N-(4-Toluenesulfonyl)-(3-(3,4-dimethoxyphenyl)-3-ethynyl-pent-4-yn-1-amine) (**8**): To a solution of protected sulfonamide **17** (0.134 g, 0.270 mmol, 1 eq.) in dichloromethane (3 mL, 0.1 M) was added trifluoroacetic acid (0.56 mL, 7.3 mmol, 27 eq.). After stirring for 7 h at rt, a saturated NaHCO_3 solution was added dropwise until the gas evolution ceased and pH = 8 was reached. The aqueous phase was extracted with dichloromethane and the organic phase was dried over Na_2SO_4 . The drying agent was filtered off, the solution was concentrated and the residue dried *in vacuo* giving a brownish solid (0.998 g, 0.251 mmol, 93%). No further purification was necessary. R_f = 0.54 (*n*-hexane:EtOAc = 1:1). mp = 117–120 °C. ^1H -NMR (300 MHz, CDCl_3): δ [ppm] = 7.73 – 7.66 (m, 2H), 7.33 – 7.27 (m, 2H), 7.13 (dd, J = 8.3, 2.3 Hz, 1H), 7.09 (d, J = 2.2 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 4.69 (s, 1H), 3.87 (s, 6H), 3.23 (ddd, J = 8.1, 7.1, 6.2 Hz, 2H), 2.53 (s, 2H), 2.43 (s, 3H), 2.18 – 2.09 (m, 2H). ^{13}C -NMR (75 MHz, CDCl_3): δ [ppm] = 149.0, 148.7, 143.5, 137.0, 132.5, 129.8, 127.2, 118.4, 111.0, 109.5, 83.6, 72.9, 56.1, 56.0, 44.9, 40.4, 38.1, 21.6. IR (film), $\tilde{\nu}$ [cm^{-1}]: 3285, 3003, 2960, 2937, 2838, 1597, 1515, 1260, 1160, 661. HRMS (ESI): m/z calculated for $\text{C}_{22}\text{H}_{24}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 398.1421; found: 398.1419.

(S)-3-(3,4-Dimethoxyphenyl)-3-ethynyl-2-methylene-1-(4-toluene-sulfonyl)-pyrrolidine (**9**): Under N_2 atmosphere, diynamide **8** (0.435 g, 1.10 mmol, 1 eq.) was dissolved in dry CHCl_3 (5.5 mL, 0.2 M). At –55 °C, freshly prepared (*R*)-TriPAu(P^tBu_3) (**2**) (56 mg, 0.049 mmol, 4.4 mol%) in dry CHCl_3 (5.5 mL, 0.01 M) was added and the solution stirred for 19 h at –55 °C. The reaction was quenched by adding triethylamine (50 μL , 0.36 mmol) and the solvent was evaporated. Purification by flash chromatography on deactivated silica gel (*n*-hexane:EtOAc: CH_2Cl_2 = 65:11:24) gave a

colorless solid (0.334 g, 0.840 mmol, 76%, 70% *ee*). The product was combined with material from earlier experiments and recrystallized from *n*-hexane/ CH_2Cl_2 (3:1) giving pyrrolidine **9** with an enantiomeric excess of 68% *ee*.

$[\alpha]_{\text{D}}^{20} = +87 \text{ ml}\cdot\text{g}^{-1}\cdot\text{dm}^{-1}$ ($c = 0.58$; 68% *ee*, CHCl_3). Enantiomeric excess was determined by chiral HPLC analysis (DAICEL CHIRALPAK[®] IC[™], 4.6 x 250 mm, eluent = *n*-hexane:*iso*-propanol = 55:45, 0.63 $\text{mL}\cdot\text{min}^{-1}$, $\lambda = 254 \text{ nm}$) R_{f} (major) = 25.8 min, R_{f} (minor) = 33.0 min). $R_{\text{f}} = 0.50$ (*n*-hexane:EtOAc = 6:4). mp = 143–145 °C. ¹H-NMR (300 MHz, CDCl_3): δ [ppm] = 7.80 – 7.72 (m, 2H), 7.32 – 7.26 (m, 2H), 6.89 (d, $J = 2.2 \text{ Hz}$, 1H), 6.82 (dd, $J = 8.4, 2.2 \text{ Hz}$, 1H), 6.67 (d, $J = 8.4 \text{ Hz}$, 1H), 5.34 (d, $J = 1.7 \text{ Hz}$, 1H), 4.32 (d, $J = 1.7 \text{ Hz}$, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.77 (dd, $J = 7.1, 5.8 \text{ Hz}$, 2H), 2.43 (s, 3H), 2.27 (tt, $J = 12.2, 5.8 \text{ Hz}$, 2H), 2.10 (s, 1H). ¹³C-NMR (151 MHz, CDCl_3): δ [ppm] = 148.8, 148.8, 148.5, 144.1, 134.0, 132.1, 129.4, 127.9, 119.5, 110.7, 110.6, 94.0, 84.4, 77.2, 73.4, 56.0, 50.8, 48.2, 38.9, 21.7. IR (film), $\tilde{\nu}$ [cm^{-1}]: 3283, 2956, 2935, 2837, 1646, 1518, 1259, 1167, 659. HRMS (ESI): m/z calculated for $\text{C}_{22}\text{H}_{24}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 398.1421; found: 398.1423.

(*R*)-Methyl 3-(3-(3,4-dimethoxyphenyl)-2-methylene-1-(4-toluenesulfo-nyl)-pyrrolidin-3-yl)propanoate (**10**): Ester **18** (0.121 g, 0.266 mmol) was dissolved in a mixture of THF:MeOH (1:1, 2.8 mL, 0.1 M) and Pd/C (12.1 mg, 10 w%) was added under inert conditions. The reaction was carried out in an autoclave at 85 bar hydrogen pressure for 18.5 h. Pd/C was filtered off by filtration through a celite pad and the solvent was removed to obtain a viscous white product (0.12 g, 0.26 mmol, 98%). No further purification was necessary. $R_{\text{f}} = 0.35$ (*n*-hexane:EtOAc = 6:4). $[\alpha]_{\text{D}}^{20} = +17 \text{ ml}\cdot\text{g}^{-1}\cdot\text{dm}^{-1}$ ($c = 0.42$; 67.9% *ee*, CHCl_3). ¹H-NMR (300 MHz, C_6D_6): δ = 7.52 – 7.46 (m, 2H), 6.62 – 6.55 (m, 2H), 6.37 (d, $J = 2.1 \text{ Hz}$, 1H), 6.29 – 6.16 (m, 2H), 5.71 (d, $J = 1.4 \text{ Hz}$, 1H), 4.36 (d, $J = 1.4 \text{ Hz}$, 1H), 3.61 (ddd, $J = 9.7, 7.6, 2.3 \text{ Hz}$, 1H), 3.37 (s, 3H), 3.25 (d, $J = 13.4 \text{ Hz}$, 7H), 2.10 – 1.98 (m, 1H), 1.96 (s, 3H), 1.95 – 1.82 (m, 3H), 1.76 (ddd, $J = 12.6, 5.8, 2.0 \text{ Hz}$, 1H), 1.27 (ddd, $J = 12.7, 10.1, 7.7 \text{ Hz}$, 1H). ¹³C-NMR (75 MHz, C_6D_6): δ [ppm] = 173.0, 150.3, 149.7, 148.9, 143.5, 135.0, 132.5, 127.6, 118.5, 111.2, 111.1, 92.1, 55.4, 55.1, 51.1, 48.0, 34.5, 32.0, 30.0, 21.2. IR (film), $\tilde{\nu}$ [cm^{-1}]: 2953, 2926, 2854, 1735, 1519, 1342, 1166, 661. HRMS (ESI): m/z calculated for $\text{C}_{24}\text{H}_{30}\text{NO}_6\text{S}$ $[\text{M}+\text{H}]^+$: 460.1788; found: 460.1789.

(*R*)-3a-(3,4-Dimethoxyphenyl)-1,2,3,3a,4,5-hexahydro-6H-indol-6-one (**11**):⁷⁸ Under inert conditions pyrrolidine **10** (0.167 g, 0.363 mmol, 1 eq.) was dissolved in dry THF (2 mL, 0.2 M). In another flask naphthalene (0.335 g, 2.61 mmol, 7.19 eq.) was dissolved in THF (3 mL, 0.9 M) and sodium (50 mg, 2.2 mmol, 6.1 eq.) was added. The educt solution was cooled to –78 °C and the $\text{NaC}_{10}\text{H}_8$ solution was added dropwise until a slight green colouring persisted (1.6 mL $\text{NaC}_{10}\text{H}_8$ solution, ≈ 3 eq.). The reaction was quenched with sat. NaHCO_3 solution and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine and the solvent was removed. Purification by column chromatography (eluent = CH_2Cl_2 :MeOH = 97:3) on neutral aluminum oxide (Brockmann III) yielded the product as a white solid (86.4 mg, 0.316 mmol, 87%). $R_{\text{f}} = 0.10$ (CH_2Cl_2 :MeOH = 20:1). $[\alpha]_{\text{D}}^{20} = +155 \text{ ml}\cdot\text{g}^{-1}\cdot\text{dm}^{-1}$ ($c = 0.505$; 67.9% *ee*, CHCl_3). ¹H-NMR (300 MHz, CDCl_3): δ [ppm] = 7.07 (s, 1H, -NH-), 6.90 – 6.81 (m, 2H), 6.75 (d, $J = 8.4 \text{ Hz}$, 1H),

5.38 (s, 1H, =CH-CO-), 3.83 (s, 3H), 3.82 (s, 3H), 3.40 (ddd, $J = 10.4, 8.1, 2.1$ Hz, 1H, -NH-CH₂-CH₂-), 3.15 (tdd, $J = 10.8, 5.9, 3.5$ Hz, 1H, -NH-CH₂-CH₂-), 2.47 – 2.19 (m, 2H, -CO-CH₂-CH₂-), 2.19 – 1.79 (m, 4H, -NH-CH₂-CH₂- + -CO-CH₂-CH₂-). ¹³C-NMR (75 MHz, CDCl₃): δ [ppm] = 197.1, 173.5, 148.9, 148.1, 133.3, 119.6, 111.0, 110.2, 94.8, 56.1, 55.9, 51.5, 45.1, 40.2, 36.0, 33.5. IR (film), $\tilde{\nu}$ [cm⁻¹]: 3183, 2939, 2872, 1575, 1514, 1264, 1219, 1026, 753. HRMS (ESI): m/z calculated for C₁₆H₂₀NO₃ [M+H]⁺: 274.1438; found: 274.1439.

(*R*)-3-*a*-(3,4-Dimethoxyphenyl)-1-methyl-1,2,3,3a,4,5-hexahydro-6*H*-indol-6-one (**12**):^{7a} Boc-protected pyrrolidine **19** (43.4 mg, 0.116 mmol, 1 eq.) was dissolved in (CF₃)₂CHOH (1 mL) and heated to 115 °C for 40 min by microwave irradiation. The solvent was removed on a rotary evaporator and the crude product was dissolved in dry THF (1.3 mL, 0.09 M). It was added at 0 °C to a suspension of sodium hydride (60% in mineral oil, 5.6 mg, 0.14 mmol, 1.2 eq.) in THF (1 mL). After 15 min the cooling bath was removed and methyl iodide (9.0 μ L, 0.14 mmol, 1.2 eq.) was added *via* syringe. Due to an incomplete conversion methyl iodide (8.0 μ L, 0.13 mmol, 1.1 eq.) and sodium hydride (60% in mineral oil, 5.6 mg, 0.14 mmol, 1.2 eq.) were added. After quenching by addition of a mixture of dist. water and brine, the aqueous phase was extracted with EtOAc. Combined organic phases were washed with brine and dried over Na₂SO₄. Purification by column chromatography on deactivated silica gel (eluent = CH₂Cl₂:MeOH = 95:5) yielded the product as a slightly yellowish material (32.3 mg, 0.112 mmol, 97%). $R_f = 0.46$ (CH₂Cl₂:MeOH = 10:1). ¹H-NMR (300 MHz, CDCl₃): δ [ppm] = 6.81 – 6.72 (m, 3H), 5.19 (s, 1H), 3.85 (d, $J = 1.1$ Hz, 6H), 3.33 – 3.23 (m, 2H), 2.96 (s, 3H), 2.44 – 2.34 (m, 1H), 2.31 – 2.22 (m, 1H), 2.20 – 2.01 (m, 3H), 2.01 – 1.82 (m, 1H).

3-(3,4-Dimethoxyphenyl)pentane-2,4-dione (**13**):^{11b,13} Under N₂ atmosphere, copper(I) iodide (2.00 g, 10.5 mmol, 0.100 eq.), D/L-proline (2.42 g, 21.0 mmol, 0.200 eq.) and potassium carbonate (58.0 g, 420 mmol, 4.00 eq.) were suspended in dry DMSO (420 mL, 0.25 M). After addition of 4-bromo-1,2-dimethoxybenzene (22.8 g, 105 mmol, 1 eq.) and acetyl acetone (31.5 g, 200 mmol, 3.00 eq.), the mixture was stirred for 41 h at 90 °C. The dark green solution was cooled to 0 °C and slowly poured into HCl (1 M) while vigorously stirring. The layers were separated and the aqueous layer extracted with EtOAc. The combined organic phases were washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash chromatography (eluent = *n*-hexane:EtOAc = 5:1). Recrystallization from *n*-hexane yielded white crystals (10.8 g, 45.8 mmol, 43%). $R_f = 0.27$ (*n*-hexane:EtOAc = 5:1). ¹H-NMR (300 MHz, CDCl₃): δ [ppm] = 6.86 (d, $J = 8.1$ Hz, 1H), 6.70 (dd, $J = 8.1$ Hz, 2.0 Hz, 1H), 6.66 (d, $J = 2.0$ Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 1.89 (s, 6H). ¹³C-NMR (151 MHz, CDCl₃): δ [ppm] = 191.2, 149.1, 148.5, 129.5, 123.5, 115.0, 114.1, 111.4, 77.2, 77.2, 56.0, 55.9, 24.2. IR (film), $\tilde{\nu}$ [cm⁻¹]: 3006, 2952, 2929, 2831, 1587, 1521, 1454, 1252, 1137, 1021. HRMS (ESI): m/z calculated for C₁₃H₁₇O₄ [M+H]⁺: 237.1121; found: 237.1120.

3-Allyl-3-(3,4-dimethoxyphenyl)pentane-2,4-dione (**14**): Under N_2 atmosphere, dione **13** (13.0 g, 55.0 mmol, 1 eq.) was dissolved in dry DMF (220 mL, 0.25 M). The solution was cooled to 0 °C and sodium hydride (60% in mineral oil, 2.3 g, 58 mmol, 1.1 eq.) was added in portions. After stirring for 1 h at 0 °C and 1 h at rt the solution was cooled to 0 °C. Allyl iodide (5.5 mL, 61 mmol, 1.1 eq.) was added via syringe, the solution was allowed to warm to rt and it was stirred for 3 h. Cold water was added and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (eluent = *n*-hexane:EtOAc = 4:1) gave a white solid (11.3 g, 40.7 mmol, 74%). R_f = 0.24 (*n*-hexane:EtOAc = 4:1). mp = 95-96 °C. 1H -NMR (300 MHz, $CDCl_3$): δ [ppm] = 6.86 (d, J = 8.4 Hz, 1H), 6.79 (dd, J = 8.4, 2.2 Hz, 1H), 6.72 (d, J = 2.2 Hz, 1H), 5.69 (ddt, J = 17.2, 10.2, 7.0 Hz, 1H), 5.16-5.02 (m, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.02 (dt, J = 7.0, 1.4 Hz, 2H), 2.10 (s, 6H). ^{13}C -NMR (75 MHz, $CDCl_3$): δ [ppm] = 206.1, 149.2, 148.9, 133.7, 129.2, 120.7, 118.6, 111.4, 111.2, 74.2, 56.1, 56.0, 37.7, 28.0. IR (film), $\tilde{\nu}$ [cm^{-1}]: 3379, 3082, 3006, 2968, 2937, 2838, 1705, 1519, 1150, 1024, 928, 766. HRMS (ESI): m/z calculated for $C_{16}H_{21}O_4$ $[M+H]^+$: 277.1435; found: 277.1434.

3-Ethynyl-3-(3,4-dimethoxyphenyl)-hex-5-yn-1,2-diol (**15**): Diyne **5** (2.95 g, 12.3 mmol, 1 eq.) was dissolved in a mixture of *tert*-butanol and water (24.5 mL, 1:1, 0.5 M). *N*-Methylmorpholine *N*-oxide (3.02 g, 25.8 mmol, 2.10 eq.) as well as potassium osmate dihydrate (67.8 mg, 0.184 mmol, 1.49 mol%) were added in portions, resulting in a brown solution. After 66 h *tert*-butanol was evaporated under reduced pressure and hydrochloric acid (1 M) was added until pH = 1 was reached. The aqueous phase was extracted with EtOAc. The organic phase was washed with brine and dried over Na_2SO_4 . The crude product was purified *via* column chromatography over silica (eluent = *n*-hexane:EtOAc = 1:3), yielding a yellowish substance (2.79 g, 10.2 mmol, 83%). R_f = 0.12 (*n*-hexane:EtOAc = 1:1). 1H -NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.42 (dd, J = 8.7, 2.6 Hz, 1H), 7.19 (d, J = 2.3 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 4.17 (s, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.66 – 3.41 (m, 2H), 2.75 (d, J = 2.9 Hz, 1H), 2.63 (s, 1H), (s, 1H), 2.21 (dd, J = 14.2, 7.9 Hz, 1H), 2.04 (dd, J = 14.2, 2.8 Hz, 1H). ^{13}C -NMR (75 MHz, $CDCl_3$): δ [ppm] = 149.1, 148.8, 133.1, 118.4, 111.1, 109.6, 84.7, 84.0, 73.1, 73.0, 70.2, 66.7, 56.1, 49.4, 38.1. IR (film), $\tilde{\nu}$ [cm^{-1}]: 3398, 3286, 3003, 2935, 2838, 1593, 1516, 1261, 1145, 1026, 648. HRMS (ESI): m/z calculated for $C_{16}H_{19}O_4$ $[M+H]^+$: 275.1278; found: 275.1278.

tert-Butyl-4-toluenesulfonyl-carbamate (**16**):²² Under nitrogen atmosphere 4-methylbenzenesulfonamide (15.8 g, 92.2 mmol, 1 eq.) and *N,N*-dimethyl-4-aminopyridine (0.563 g, 4.61 mmol, 5.00 mol%) were dissolved in dry dichloromethane (190 mL, 0.5 M). Dry triethylamine (14.1 mL, 101 mmol, 1.10 eq.) as well as di-*tert*-butyl dicarbonate (21.7 mL, 101 mmol, 1.10 eq.) were added. After 30 min the solution was concentrated and the crude product was dissolved in EtOAc. It was washed with hydrochloric acid (1 M), dist. water as well as brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give a white powder. The product was recrystallized from a

mixture of diethyl ether and *n*-hexane (1:1). The crystals were washed with ice cold *n*-hexane and vacuum dried to obtain white crystals (21.6 g, 79.6 mmol, 86%). mp = 119 °C (lit.²² mp = 117–119 °C). ¹H-NMR (300 MHz, CDCl₃): δ [ppm] = 7.93 – 7.86 (m, 2H), 7.45 (s, 1H), 7.38 – 7.31 (m, 2H), 2.44 (s, 3H), 1.38 (s, 9H).

tert-Butyl 3-(3,4-dimethoxyphenyl)-3-ethynyl-pent-4-yn-1-yl (4-toluene-sulfonyl)carbamate (**17**): Under N₂ atmosphere, alcohol **7** (1.51 g, 6.17 mmol, 1 eq.), triphenylphosphine (2.43 g, 9.26 mmol, 1.50 eq.) and *tert*-butyl tosylcarbamate (**16**) (1.84 g, 6.79 mmol, 1.10 eq.) were dissolved in dry THF (62 mL, 0.1 M). To this solution, di-ethyl azodicarboxylate (4.2 mL, 9.3 mmol, 1.5 eq., 40 w% in toluene) was added dropwise. The solution was cooled with a water bath (15 °C). After stirring for 3 h, the solution was concentrated *in vacuo*. Purification by flash column chromatography over silica gel (*n*-hexane:EtOAc = 7:2) gave a white solid (2.87 g, 5.77 mmol, 94%). *R*_f = 0.77 (*n*-hexane:EtOAc = 1:1). mp = 129–132 °C. ¹H-NMR (300 MHz, CDCl₃): δ [ppm] = 7.78 – 7.72 (m, 2H), 7.33 – 7.23 (m, 3H), 7.24 (d, *J* = 2.2 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 4.12 – 4.02 (m, 2H), 3.93 (s, 3H), 3.88 (s, 3H), 2.59 (s, 2H), 2.47 – 2.38 (m, 5H), 1.33 (s, 9H). ¹³C-NMR (75 MHz, CDCl₃): δ [ppm] = 150.8, 149.0, 148.7, 144.3, 137.3, 132.7, 129.4, 127.9, 118.6, 111.0, 109.7, 84.4, 83.4, 72.6, 56.1, 44.5, 44.4, 37.8, 28.0, 21.7. IR (film), $\tilde{\nu}$ [cm⁻¹]: 3286, 2979, 2936, 2837, 2256, 1731, 1516, 1354, 1153, 734. HRMS (ESI): *m/z* calculated for C₂₇H₃₅N₂O₆S [M+NH₄]⁺: 515.2210; found: 515.2211, C₂₇H₃₁NNaO₆S [M+Na]⁺: 520.1764; found: 520.1763.

(*R*)-Methyl 3-(3-(3,4-dimethoxyphenyl)-2-methylene-1-(4-toluene-sulfonyl)-pyrrolidin-3-yl)propiolate (**18**): Under N₂ atmosphere, alkyne **9** (0.228 g, 0.574 mmol, 1 eq.) was dissolved in dry THF (5.7 mL). At –80 °C, *n*-butyllithium solution (1.6 M in hexane, 0.39 mL, 0.63 mmol, 1.1 eq.) was added dropwise and stirred for 20 min. Next, methyl chloroformate (88 μL, 1.2 mmol, 2.1 eq.) was added and the solution was allowed to warm to rt. After 30 min, a mixture of water, sat. NaHCO₃ and brine (4:1:2, 28 mL) was added, EtOAc was added and the layers were separated. The aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine (15 mL) and dried over Na₂SO₄. Purification by flash chromatography on deactivated silica gel (*n*-hexane:EtOAc:CH₂Cl₂ = 65:10:25) gave a white solid (0.255 g, 0.560 mmol, 98%). *R*_f = 0.29 (*n*-hexane:EtOAc:CH₂Cl₂ = 6:1:3). mp = 115–120 °C. [α]_D²⁰ = +54 ml·g⁻¹·dm⁻¹ (c = 0.49; 67.9% ee, CHCl₃). ¹H-NMR (300 MHz, C₆D₆): δ [ppm] = 7.81 – 7.73 (m, 2H), 6.83 – 6.75 (m, 4H), 6.34 (d, *J* = 9.0 Hz, 1H), 5.75 (d, *J* = 1.6 Hz, 1H), 4.52 (d, *J* = 1.6 Hz, 1H), 3.53 (ddd, *J* = 6.8, 5.9, 2.1 Hz, 2H), 3.34 (s, 3H), 3.34 (s, 3H), 3.21 (s, 3H), 1.95 (s, 3H), 1.92 – 1.74 (m, 2H). ¹³C-NMR (75 MHz, C₆D₆): δ [ppm] = 153.5, 150.1, 149.9, 148.0, 144.0, 134.6, 131.0, 129.6, 127.9, 119.8, 111.7, 111.4, 94.7, 88.0, 77.3, 55.6, 55.5, 52.1, 51.1, 48.3, 37.9, 21.3. IR (film), $\tilde{\nu}$ [cm⁻¹]: 3004, 2955, 2838, 2235, 1715, 1518, 1266, 1167, 751, 658. HRMS (ESI): *m/z* calculated for C₂₄H₂₆NO₆S [M+H]⁺: 456.1475; found: 456.1479.

(*R*)-*tert*-Butyl 3a-(3,4-dimethoxyphenyl)-6-oxo-2,3,3a,4,5,6-hexahydro-1*H*-indole-1-carboxylate (**19**):^{7a} Pyrrolidine **11** (0.135 g, 0.494 mmol, 1 eq., 68% ee) was dissolved in dry CH₂Cl₂ (6 mL, 0.1 M). *N,N*-Dimethylaminopyridine (8.4 mg, 0.069 mmol, 14 mol%), triethylamine (95 μL, 0.68 mmol, 1.4 eq.) and di-*tert*-butyl dicarbonate (0.149 g, 146 μL,

0.684 mmol, 1.38 eq.) were added. After 20 min a mixture of dist. water and brine was added and the aqueous phase was extracted with CH_2Cl_2 . The organic phase was washed with a mixture of dist. water and brine (1:3) and the solvent was removed. Purification by flash column chromatography (eluent = *n*-hexane:EtOAc: CH_2Cl_2 = 43:42:15) on deactivated silica gel yielded the product as a white substance (0.168 g, 0.449 mmol, 91%). The product was recrystallized from *n*-hexane and a mixture of *n*-hexane:Et₂O (2:1) in two batches, giving crystals (78.9 mg) with an *ee* >99%. ¹H-NMR (300 MHz, CDCl_3): δ [ppm] = 6.84 – 6.76 (m, 3H), 6.55 (s, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.78 (dd, *J* = 11.0, 8.1 Hz, 1H), 3.24 (td, *J* = 11.4, 5.5 Hz, 1H), 2.46 – 2.35 (m, 1H), 2.31 (dd, *J* = 12.0, 5.4 Hz, 1H), 2.26 – 2.14 (m, 2H), 2.13 – 1.92 (m, 2H), 1.54 (s, 9H). The enantiomeric excess was determined by chiral HPLC analysis (DAICEL CHIRALPAK® IA™, 4.6 x 250 mm, eluent = *n*-hexane:*iso*-propanol = 82:18, 0.82 mL·min⁻¹, λ = 254 nm) *R*_t (major) = 13.8 min, *R*_t (minor) = 10.8 min. (+)-*Mesembrine*:^{7a, 21} Enone **12** (38.6 mg, 0.134 mmol, 1 eq.) and dry *tert*-butanol (24 mg, 0.32 mmol, 2.8 eq.) were dissolved in dry THF (2 mL, 0.06 M). The solution was cooled to –78 °C and liquid ammonia (≈40 mL) was condensed into the flask. A piece of lithium (1.9 mg, 0.27 mmol, 2.0 eq.) was added and the solution was stirred for 45 min. Ammonia was evaporated and the solution was diluted with a mixture of dist. water and brine. The aqueous phase was extracted with EtOAc and the combined organic phases were washed with brine and dried over Na₂SO₄. Purification by column chromatography (eluent = CH_2Cl_2 :acetone = 8:2) on neutral aluminum oxide (Brockmann III) yielded the product as a slightly yellowish substance (30.0 mg, 0.104 mmol, 77%). *R*_f = 0.25 (CH_2Cl_2 :acetone = 6:2.5). $[\alpha]_{\text{D}}^{23}$ = +56 (*c* = 0.37, MeOH); (lit.^{7t} $[\alpha]_{\text{D}}^{23}$ = +50.0, *c* = 0.53, MeOH; lit.⁶ $[\alpha]$ = +58.5, *c* = 0.04, MeOH). ¹H-NMR (300 MHz, CDCl_3): δ [ppm] = 6.93 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.89 (d, *J* = 2.2 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.14 (ddd, *J* = 9.3, 7.5, 3.1 Hz, 1H), 2.94 (t, *J* = 3.6 Hz, 1H), 2.60 (d, *J* = 3.7 Hz, 2H), 2.47 – 2.03 (m, 10H). ¹³C-NMR (75 MHz, CDCl_3): δ [ppm] = 211.5, 149.1, 147.6, 140.3, 118.0, 111.1, 110.1, 77.2, 70.5, 56.1, 56.0, 55.0, 47.6, 40.7, 40.2, 39.0, 36.4, 35.4.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Experimental details, spectral data for all new compounds and HPLC traces for compounds **9** and **19** (PDF).

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Notes

The authors declare no competing financial interest.

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