Enantioselective Construction of Cyclic Quaternary Centers: (−)-Mesembrine

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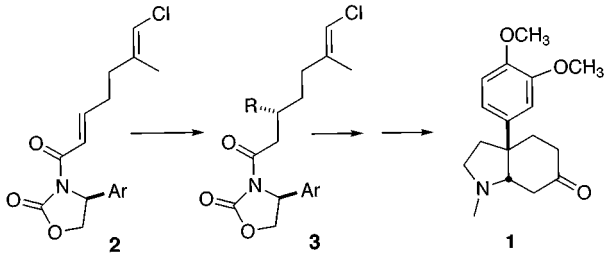
The preparation of the crystalline amide **2** is reported. Conjugate addition to **2** proceeded with the expected high diastereocontrol to give **3**. This set the stage for subsequent intramolecular alkylidene C−H insertion to give, after ozonolysis and aldol condensation, (−)-mesembrine **1**. Amide **2** should be a useful chiron for the enantioselective construction of cyclic quaternary centers.

Introduction

The *Sceletium* alkaloid (−)-mesembrine (**1**), a naturally



occurring serotonin uptake inhibitor[1] isolated from the Mesembryanthemaceae family (*Sceletium tortuosum*), has become an interesting lead compound for the preparation of antidepressants. The central challenge in the synthesis of mesembrine[2,3] and its analogues is the enantioselective construction of the chiral quaternary center.[4] We hypothesized that it might be possible to accomplish such a construction by carrying an alkenyl chloride such as **2** through several preparative steps. These steps would include the enantioselective establishment of a chiral ternary center based on stereoselective conjugate addition[5] followed by intramolecular cyclization of **3** via intramolecular alkylidene C−H insertion.[6] This C−H insertion would proceed with retention of absolute configuration[7,8] to convert the ternary center of **3** to the quaternary center of **1**.

Incorporation of the Alkenyl Chloride. The first challenge in this strategy was the incorporation of the alkenyl chloride. In previous approaches[7c] we had prepared chloroalkenes by homologation by Wittig reaction of a ketone with (chloromethylene)triphenylphosphorane. We hypothesized that the direct introduction of an alkylating agent incorporating the alkenyl chloride would offer a more efficient solution to this problem. In fact, it was known that 3-bromo-1-chloro-2-methylpropene **4** (Scheme 1) could easily be prepared by NBS bromination of the inexpensive 1-chloro-2-methylpropene.[9] With the alkylating agent **4** in hand, we effected alkylation of the acetoacetate dianion[10] to give the ketoester **5** in good yield. Reduction then gave the secondary alcohol **6**.

We next needed a dehydration method that would give predominantly the (*E*)-α,*β*-unsaturated ester from the secondary alcohol **6**.[11] In fact, mesylation followed by in situ elimination gave exclusively (^{13}C NMR) the

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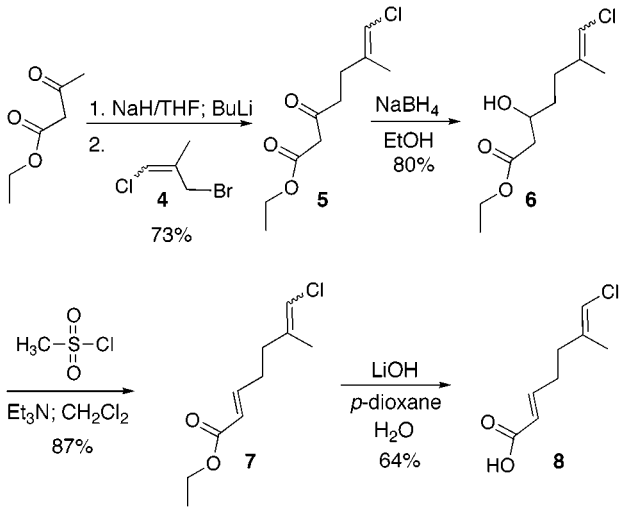
Scheme 1



(*E*)-α,*β*-unsaturated ester **7**. Hydrolysis converted **7** to the (*E*)-α,*β*-unsaturated acid **8**, the (*E*,*E*)-isomer of which was nicely crystalline. It could be isolated in 64% yield from **7** by trituration of the crude acid with Et_2O.

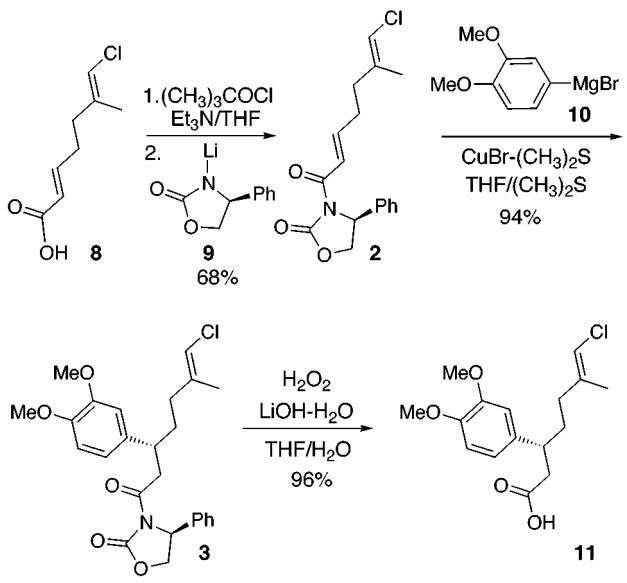
The (*E*,*E*)-material was employed in the subsequent synthetic steps to minimize the complexity of the ^1H and ^{13}C NMR spectra. However, it should be noted that the initial *E*/*Z*-alkenyl chloride isomeric mixture produced the same yield for each of those steps, including the intramolecular alkylidene carbene C−H insertion.

Conjugate Addition: Establishment of the Ternary Center. The second challenge in this approach was the establishment of the ternary center with high enantiomeric purity. We envisioned that this could be accomplished by conjugate addition to an (*E*)-4-phenyl-2-oxazolidinone α,*β*-unsaturated amide, following the precedent of Hruby.[5b,c] Introduction of the chiral auxiliary was accomplished by the reaction of lithiated (*S*)-(+)-4-phenyl-2-oxazolidinone **9** with the mixed pivalic acid anhydride derivative of **8** (Scheme 2). Conjugate addition to the derived acyl oxazolidinone **2** proceeded with high stereoselectivity[5b,c] to give **3**. We were unable to detect the alternative diastereomer by ^{13}C NMR of the crude reaction mixture, and X-ray crystallography showed that the desired diastereomer of **3** had indeed been obtained. Hydrolysis of the oxazolidinone amide **3** then gave the acid **11**. An attractive feature of this approach is that the chiral auxiliary **9** can easily be recovered in almost quantitative yield following the hydrolysis.

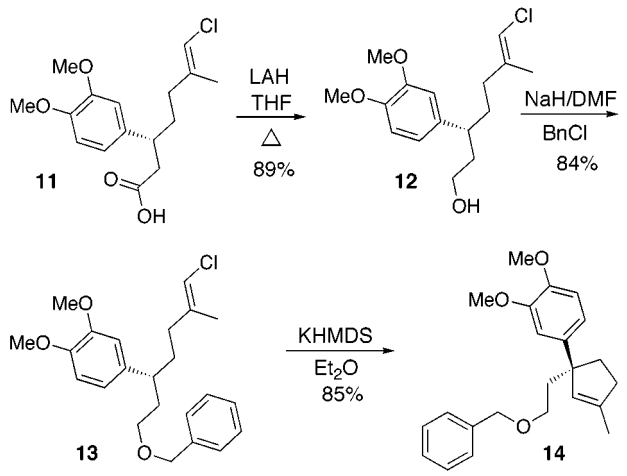
Intramolecular Alkylidene Insertion: Incorporation of the Quaternary Center. With **11** in hand, we proceeded to investigate intramolecular alkylidene C−H insertion (Scheme 3).[6,7] As we had expected, the strongly basic conditions of the cyclization were not compatible with the acyl oxazolidinone **3**, nor with the unprotected primary alcohol **12**. The derived benzyl ether **13**, however, cyclized smoothly to give the desired cyclopentene **14**. As expected, the C−H insertion proceeded with retention of absolute configuration.

Ozonolysis/Aldol Condensation: Synthesis of (−)-Mesembrine. Ozonolysis of **14** gave the intermediate keto aldehyde (Scheme 4). Although in the past we have

Scheme 2



Scheme 3



induced cyclization of these with KOH/methanol,[7c] we found in this case that the intramolecular aldol reaction and subsequent dehydration to give the cyclohexenone **15** proceeded more efficiently under acid catalysis. The cyclohexenone **15** was reduced to the secondary alcohol **16** to avoid Michael-type addition with the formed primary alcohol upon removal of the benzyl protecting group. Debenzylation of **16** gave the primary alcohol **17,** which was then converted selectively to the mesylate **18.** Amination, oxidation, and cyclization then gave (−)-mesembrine **1**. The synthetic material so prepared gave ^1H and ^{13}C NMR, IR, MS, and optical rotation results identical with the literature values.[2a,d,e]

Conclusion

The strategy outlined here for the enantioselective construction of quaternary centers will have many applications in target-directed organic synthesis. The acyl oxazolidinone **2** in particular should be a useful chiron for the enantioselective construction of physiologically active natural products, due to its ease of use and exceptional ability to impart stereocontrol.

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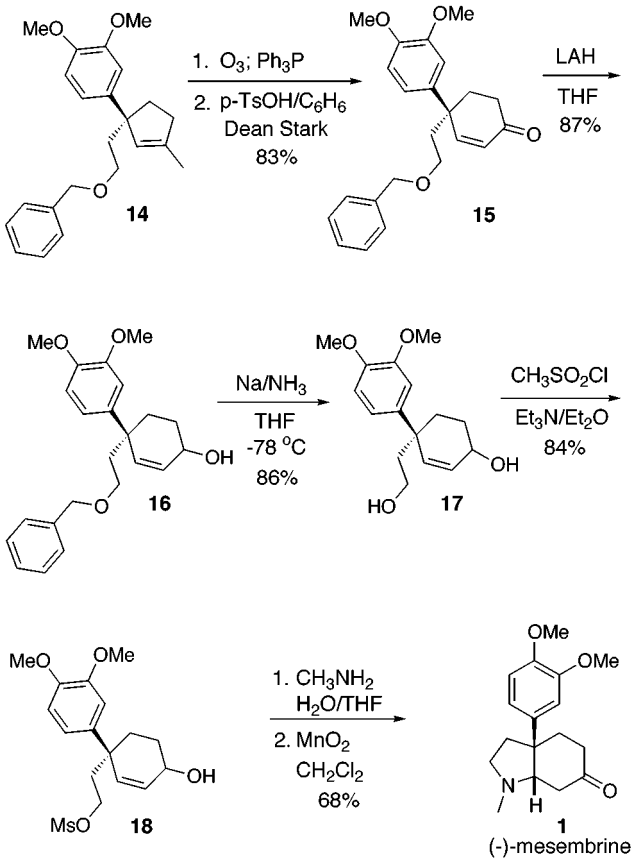
Scheme 4



Experimental Section

General. The general experimental method was identical to that previously published[12] except for combustion analysis, which was carried out by Quantitative Technologies Inc., P.O. Box 389, Chimney Rock Road, Bldg. 29E, Bound Brook, NJ 08805.

7-Chloro-6-methyl-3-oxohept-6-enoic Acid Ethyl Ester (5). To a stirring suspension of sodium hydride (3.9 g, 97 mmol, 60% in mineral oil) and anhydrous THF (350 mL) at 0 °C, under N_2, was added dropwise a solution of ethyl acetoacetate (11.5 g, 97 mmol) and anhydrous THF (10 mL). The clear solution was stirred at 0 °C for 10 min. A solution of 2.5 M *n*-butyllithium in hexanes (37 mL, 93 mmol) was added dropwise at 0 °C followed by stirring for 10 min. Next, 3-bromo-1-chloro-2-methyl-1-propene (15.0 g, 88.4 mmol) was added dropwise at 0 °C, and the solution was then allowed to warm to room temperature over 1 h. Water (20 mL) was added and the solution was neutralized with 1 N HCl. The reaction mixture was partitioned between Et_2O and H_2O. The combined organic extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed to give **5** (14.1 g, 64.5 mmol, 73% yield) as a clear oil: TLC $R_f = 0.35$, 10% EtOAc/hexane; ^{1}H NMR δ (major isomer) 1.28 (t, $J = 7.2$ Hz, 3H), 1.75 (s, 3H), 2.38 (t, $J = 6.7$ Hz, 2H), 2.68 (t, $J = 7.8$ Hz, 2H), 3.43 (s, 2H), 4.19 (q, $J = 7.2$ Hz, 2H), 5.82 (s, 1H); ^{1}H NMR δ (minor isomer) 1.28 (t, $J = 7.2$ Hz, 3H), 1.78 (s, 3H), 2.44 (t, $J = 6.7$ Hz, 2H), 2.68 (t, $J = 7.8$ Hz, 2H), 3.44 (s, 2H), 4.19 (q, $J = 7.2$ Hz, 2H), 5.80 (s, 1H); ^{13}C NMR δ (major isomer) C 199.9, 165.4, 135.3, CH 111.7, CH_2 59.9, 47.5, 39.3, 30.0, CH_3 19.3, 14.7; ^{13}C NMR δ (minor isomer) C 200.3, 165.5, 135.5, CH 111.2, CH_2 59.8, 47.7, 38.4, 24.3, CH_3 19.3, 12.7; IR cm^{-1} 2983 (m), 1743 (s), 1718 (s), 1641 (m), 1318 (m).

7-Chloro-3-hydroxy-6-methylhept-6-enoic Acid Ethyl Ester (6). To a stirring solution of **5** (10.0 g, 45.7 mmol) and ethanol (100 mL) at 0 °C, under N_2, was added portionwise sodium borohydride (2.1 g, 54.8 mmol) over a 10 min period. Saturated NH_4Cl aqueous solution (100 mL) was added, and the solution was then neutralized with 1 N HCl. The reaction mixture was concentrated in vacuo and then partitioned between Et_2O and H_2O. The combined organic extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed to give **6** (8.1 g, 36.6 mmol, 80% yield) as a clear oil: TLC $R_f = 0.47$, 30% EtOAc/hexane; ^{1}H NMR δ 1.28 (t, $J = 7.1$ Hz, 3H), 1.59−1.76 (m, 2H), 1.77−1.79 (m, 3H), 2.09−2.59 (m, 4H), 3.05−3.07 (m, 1H), 3.91−4.04 (m, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 5.85 (d, $J = 14.2$ Hz, 1H); ^{13}C NMR δ (major isomer) C 177.2, 136.6, CH 110.4, 65.6, CH_2 58.8, 39.8, 32.7,31.5, CH_3 19.3, 12.6; ^{13}C NMR δ (minor isomer) C 177.2, 136.5, CH 110.9, 66.1, CH_2 59.2, 39.7, 31.9, 26.4, CH_3 19.3, 14.8; IR cm^{-1} 3464 (b), 2982 (m), 1738 (s), 1640 (w), 1244 (m).

(2*E*,6*E*)-7-Chloro-6-methylhepta-2,6-dienoic Acid (8). To a stirring mixture of **7** (2.0 g, 9.9 mmol), lithium hydroxide monohydrate (457 mg, 10.9 mmol), and *p*-dioxane (40 mL) at room temperature was added H_2O until a clear solution formed. The solution was stirred at ambient temperature for 17 h. The solution was acidified to pH = 1 by addition of aqueous sodium hydrogen sulfate solution (10%). The reaction mixture was partitioned between EtOAc and H_2O. The combined organic extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed to give **8** (1.7 g, 9.7 mmol, 98% yield) as a clear oil. The major isomer was isolated as a white solid (1.1 g, 6.3 mmol, 64% yield) by recrystallization from 20:1 Et_2O/hexane (0.1 g/mL): mp = 45−46 °C; TLC $R_f =$ 0.19, 30% EtOAc/hexane; ^{1}H NMR δ 1.79 (s, 3H), 2.43 (t, $J =$ 7.5 Hz, 2H), 2.38 (q, $J = 7.1$ Hz, 2H), 5.82−5.87 (m, 2H), 6.98−7.27(m, 1H); ^{13}C NMR δ C 170.5, 1355, CH 148.9, 119.9, 111.7, CH_2 33.7, 28.7, CH_3 14.8; IR cm^{-1} 2919 (s), 2200−3000 (b), 1691 (s), 1642 (m), 1314 (m). Anal. Calcd for $C_8H_{11}NO_2Cl$: C, 55.02; H, 6.35. Found: C, 55.06; H, 6.22.

(2*E*,6*E*)-(4*S*)-3-(7-Chloro-6-methylhepta-2,6-dienoyl)-4-phenyloxazolidin-2-one (2). To a stirring solution of **8** (1.3 g, 7.4 mmol) and anhydrous THF (150 mL) at −78 °C under N_2, was added triethylamine (890 mg, 8.9 mmol) followed by the dropwise addition of pivaloyl chloride (990 mg, 8.2 mmol) over a 5 min period. The formed suspension was stirred at −78 °C for 15 min and then at 0 °C for 45 min followed by cooling to −78 °C. This suspension was transferred dropwise via cannula at −78 °C to a preformed suspension of (4*S*)-(+)-4-phenyl-2-oxazolidinone (1.2 g, 7.4 mmol), *n*-butyllithium (3.0 mL, 7.4 mmol, 2.5 M in hexanes), and anhydrous THF (30 mL) (*n*-butyllithium added to (*S*)-(+)-4-phenyl-2-oxazolidinone and THF at −78 °C, stirred 20 min). The resulting suspension was stirred at −78 °C for 20 min and then at room temperature for 2 h. The reaction mixture was partitioned between EtOAc and H_2O. The combined organic extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed to give **2** (1.6 g, 5.0 mmol, 68% yield) as a white solid: mp = 55−56 °C; TLC $R_f = 0.22$, 20% EtOAc/hexane; ^{1}H NMR δ 1.73 (s, 3H), 2.21−2.27 (m, 2H), 2.31−2.42 (m, 2H), 4.17 (dd, $J =$ 8.8 Hz, $J = 3.8$ Hz, 1H), 4.76 (t, $J = 8.7$ Hz, 1H), 5.50 (dd, J = 8.4 Hz, $J = 3.8$ Hz, 1H), 6.07 (s, 1H), 6.81−6.97 (m, 1H), 7.16−7.41 (m, 6H); ^{13}C NMR δ C 162.8, 152.2, 137.6, 135.5, CH 148.4, 127.6, 127.3, 124.4, 119.4, 111.6, 56.2, CH_2 68.5, 33.9, 29.1, CH_3 14.9; IR cm^{-1} 2917 (w), 1779 (s), 1688 (s), 1635 (m), 1199 (m). Anal. Calcd for $C_{17}H_{18}NO_3Cl$: C, 63.85; H, 5.67; N, 4.38. Found: C, 63.90; H, 5.54; N, 4.19.

(6*E*)-(3(3*S*),4*S*)-3-[7-Chloro-3-(3,4-dimethoxyphenyl)-6-methylhept-6-enoyl]-4-phenyloxazolidin-2-one (3). To a stirring suspension of magnesium (472 mg, 19.4 mmol) and anhydrous THF (10 mL) heated at reflux, under N_2, was added dropwise a solution of 4-bromoveratrole (4.1 g, 18.9 mmol) in anhydrous THF (3 mL), over a 1 h period. The formed solution was cooled to room temperature and added dropwise via cannula to a stirring solution of copper(I) bromide−dimethyl sulfide complex (1.9 g, 9.5 mmol), anhydrous THF (20 mL), and dimethyl sulfide (20 mL) at −40 °C. The resulting suspension was stirred at −40 °C for 10 min followed by the dropwise addition of **2** (2.0 g, 6.3 mmol) in THF (10 mL) at −15 °C over a 20 min period. The mixture was stirred at −15

(12) Taber, D. F.; Christos, T. E.; Neubert, T. D.; Batra, D. *J. Org. Chem.* **1999**, *64*, 9673.

°C for 10 min. The reaction mixture was partitioned between EtOAc and H_2O. The combined organic extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed to give **3** (2.7 g, 5.9 mmol, 94% yield) as a white solid: mp = 95−97 °C; TLC R_f = 0.29, 30% EtOAc/hexane; ^{1}H NMR δ 1.61−1.67 (m, 1H), 1.68 (s, 3H), 1.69−1.81 (m, 3H), 2.93 (dd, J = 14.8, 6.2 Hz, 1H), 2.99−3.08 (m, 1H), 3.63 (dd, J = 14.8, 7.7 Hz, 1H), 3.77 (s, 3H), 3.88 (s, 3H), 4.15 (dd,J = 8.6, 3.8 Hz, 1H), 4.62 (t, J = 8.9 Hz, 1H), 5.36 (dd, J = 8.6, 3.8 Hz, 1H), 5.61 (s, 1H), 6.62 (s, 1H), 6.63−6.78 (m, 2H), 6.91−6.93 (m, 2H), 7.21−7.24 (m, 3H); ^{13}C NMR δ C 169.9, 152.1, 147.2, 146.1, 137.1, 136.5, CH 127.5, 126.9, 123.9, 117.9, 110.7, 109.6, 109.5, 56.0, 39.7, CH_2 68.2, 40.1, 33.2, 32.3, CH_3 54.3, 54.2, 14.8; IR cm^{-1} 2934 (m), 1780 (s), 1736 (m), 1704 (m), 1518 (m).

(6*E*)-(3*S*)-7-Chloro-3-(3,4-dimethoxyphenyl)-6-methylhept-6-enoic Acid (11). To a stirring solution of **3** (1.2 g, 2.6 mmol), H_2O (3 mL), and THF (12 mL), at −5 °C, was added hydrogen peroxide (1.14 mL, 10.4 mmol, 30%) dropwise over a 10 min period. A solution of lithium hydroxide monohydrate (174 mg, 4.2 mmol) and H_2O (5 mL) was added dropwise, at −5 °C, over a 15 min period. The resulting mixture was stirred at 0 °C for 2 h followed by the addition of sodium sulfite solution (10.4 mmol) in H_2O (10 mL). The reaction mixture was partitioned between EtOAc and H_2O. The combined organic extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was triturated with Et_2O to give recovered (4*S*)-(+)-4-phenyl-2-oxazolidinone (390 mg, 2.4 mmol, 92% yield). The aqueous portion was acidified to pH = 2 using 1 N HCl. The reaction mixture was partitioned between CH_2Cl_2 and H_2O. The combined organics were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed to give **11** (780 mg, 2.5 mmol, 96% yield) as a clear oil: TLC R_f = 0.52, 10% MeOH/CH_2Cl_2; ^{1}H NMR δ 1.62−1.67 (m, 1H), 1.68 (s, 3H), 1.69−1.91 (m, 3H), 2.61 (d, J = 7.4 Hz, 2H), 2.91−3.02 (m, 1H), 3.86 (s, 3H), 3.87 (s, 3H), 5.68 (s, 1H), 6.63−6.82 (m, 3H); ^{13}C NMR δ C 176.9, 147.3, 146.2, 136.4, 133.9, CH 117.7, 110.8, 109.8, 109.2, 39.2, CH_2 40.3, 33.1, 32.0, CH_3 54.3, 54.2, 14.7; IR cm^{-1} 2800−3400 (b), 1708 (s), 1592 (w), 1518 (s), 1260 (m).

(3*S*)-7-Chloro-3-(3,4-dimethoxyphenyl)-6-methylhept-6-en-1-ol (12). To a stirring solution of **11** (2.0 g, 6.4 mmol) and anhydrous THF (50 mL), at 0 °C, was added lithium aluminum hydride (270 mg, 7.1 mmol) portionwise over a 5 min period. The resulting solution was heated at reflux for 1 h. H_2O (0.27 mL) was added at 0 °C, followed by 15% NaOH (0.27 mL) and H_2O (0.81 mL). The mixture was filtered through a bed of Celite with EtOAc, and the filtrate was partitioned between EtOAc and H_2O. The combined organic extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed to give **12** (1.7 g, 5.7 mmol, 89% yield) as a clear oil: TLC R_f = 0.56, 10% MeOH/CH_2Cl_2; ^{1}H NMR δ 1.09−1.17 (m, 1H), 1.61−1.71 (m, 2H), 1.73 (s, 3H), 1.74−1.97 (m, 4H), 2.52−2.66 (m, 1H), 3.41−3.58 (m, 2H), 3.87 (s, 3H), 3.88 (s, 3H), 5.68 (s, 1H), 6.63−6.82 (m, 3H); ^{13}C NMR δ C 147.4, 145.9, 136.9, 135.2, CH 118.1, 110.5, 109.7, 109.1, 40.0, CH_2 59.5, 38.1, 33.4, 33.0, CH_3 54.3, 54.2, 14.8; IR cm^{-1} 3398 (m), 2934 (s), 1591 (w), 1517 (s), 1259 (s).

(5*S*)-1-Chloro-5-(3,4-dimethoxyphenyl)-2-methyl-7-(phenylmethoxy)hept-1-ene (13). To a stirring solution of **12** (1.0 g, 3.4 mmol) and anhydrous DMF (0.2 mL), at −0 °C, was added sodium hydride (82 mg, 3.4 mmol, 60%) portionwise over a 10 min period. The resulting solution was stirred at ambient temp for 30 min. Benzyl bromide (580 mg, 3.4 mmol) was added at 0 °C, dropwise over a 2 min period. The mixture was stirred at ambient temp for 17 h. The reaction mixture was partitioned between CH_2Cl_2 and H_2O. The combined organic extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed to give **13** (1.1 g, 2.9 mmol, 84% yield) as a clear oil: TLC R_f = 0.72, 30% EtOAc/hexane; ^{1}H NMR δ 1.50−1.70 (m, 2H), 1.71 (s, 3H), 1.72−1.99 (m, 4H), 2.49−2.66 (m, 1H), 3.20−3.39 (m, 2H), 3.84 (s, 3H), 3.87 (s, 3H), 4.41 (s, 2H), 5.65 (s, 1H), 6.61−6.82 (m, 3H), 7.23−7.38 (m, 5H); ^{13}C NMR δ C 147.3, 145.8, 137.0, 136.9, 135.4, CH 126.8, 126.0, 118.2, 110.5, 109.9, 109.6, 109.2, 40.0, CH_2 71.4, 66.8, 35.5, 33.4, 32.9, CH_3 54.3, 54.2, 14.9; IR cm^{-1} 3398(m), 2934 (s), 1591 (w), 1517 (s), 1259 (s), 1029 (s).

(3*S*)-3-(3,4-Dimethoxyphenyl)-1-methyl-3-[(2-phenylmethoxy)ethyl]cyclopentene (14). To a stirring solution of **13** (9.0 g, 23.2 mmol) and anhydrous Et_2O (180 mL), under N_2, was added KHMDS (116 mL, 57.9 mmol, 0.5 M in toluene) dropwise over a 10 min period. The resulting solution was stirred at ambient temp for 17 h. The reaction mixture was partitioned between Et_2O and H_2O. The combined organic extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed to give **14** (6.9 g, 19.7 mmol, 85% yield) as a clear oil: TLC R_f = 0.72, 30% EtOAc/hexane; ^{1}H NMR δ 1.79 (s, 3H), 2.01−2.19 (m, 4H), 2.20−2.33 (m, 2H), 3.23−3.42 (m, 2H), 3.83 (s, 3H), 3.84 (s, 3H), 4.39 (s, 2H), 5.54 (s, 1H), 6.73−6.82 (m, 3H), 7.21−7.36 (m, 5H); ^{13}C NMR δ C 147.1, 145.4, 140.1, 139.2, 137.1, 53.2, CH 128.9, 126.8, 126.0, 125.9, 116.4, 109.3, 108.3, CH_2 71.4, 66.7, 40.0, 38.9, 34.3, CH_3 54.4, 54.3, 15.4; IR cm^{-1} 2931 (m), 1516 (m), 1452 (w), 1256 (m), 1029 (m).

(4*S*)-4-(3,4-Dimethoxyphenyl)-4-[2-(phenylmethoxy)-ethyl]cyclohex-2-enone (15). To a stirring solution of **14** (975 mg, 2.8 mmol) and anhydrous CH_2Cl_2 (30 mL), under N_2, at −78 °C, was bubbled a gentle stream of O_3/O_2 until the observed exotherm ceased (∼10 min). Excess O_3 was subsequently purged with a dry stream of N_2, and then triphenylphosphine (800 mg, 3.1 mmol) was added. The resulting solution was allowed to warm to room temperature over a 17 h period. The solvent was removed in vacuo, and the residue was dissolved in benzene (80 mL) followed by the addition of *p*-toluenesulfonic acid monohydrate (33 mg, 0.17 mmol). The solution was heated at reflux for 4 h using a Dean−Stark trap to remove H_2O. The reaction mixture was partitioned between EtOAc and H_2O. The combined organic extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed to give **15** (840 mg, 2.3 mmol, 83% yield) as a clear oil: TLC R_f = 0.46, 30% EtOAc/hexane; ^{1}H NMR δ 2.13−2.39 (m, 6H), 3.44 (t, J = 6.2 Hz, 2H), 3.84 (s, 3H), 3.87 (s, 3H), 6.13 (d, J = 10.1 Hz, 1H), 6.76−6.81 (m, 3H), 7.20−7.38 (m, 5H); ^{13}C NMR δ C 197.8, 147.5, 146.3, 136.5, 133.9, 41.5, CH 154.2, 127.6, 126.8, 126.1, 126.0, 117.7, 109.5, 108.4, CH_2 71.6, 65.4, 39.6, 35.0, 33.0, CH_3 54.4, 54.3; IR cm^{-1} 2935 (m), 1680 (s), 1517 (s), 1453 (w), 1259 (s), 1027 (m).

(4*S*)-4-(3,4-Dimethoxyphenyl)-4-[2-(phenymethoxy)-ethyl]cyclohex-2-enol (16). To a stirring suspension of lithium aluminum hydride (21 mg, 0.55 mmol) and anhydrous THF (10 mL), under N_2, at 0 °C, was added dropwise over a 2 min period a solution of **15** (200 mg, 0.55 mmol) and THF (1 mL). The resulting solution was stirred at room temperature for 20 min. H_2O (0.02 mL) was added at 0 °C, followed by 15% NaOH (0.02 mL) and H_2O (0.06 mL). The mixture was filtered through a bed of Celite with EtOAc and then partitioned between EtOAc and H_2O. The combined organic extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed to give **16** (176 mg, 0.48 mmol, 87% yield) as a clear oil: TLC R_f = 0.32, 50% EtOAc/hexane; ^{1}H NMR δ 1.23−2.16 (m, 6H), 3.28−3.47 (m, 2H), 3.84 (s, 3H), 3.86 (s, 3H), 4.08−4.29 (m, 1H), 5.00 (s, 3H), 5.83−6.13 (m, 2H), 6.76−6.85 (m, 3H), 7.22−7.38 (m, 5H); ^{13}C NMR δ (major isomer) C 147.1, 145.7, 137.2, 136.8, 40.4, CH 133.3, 129.9, 126.5, 126.0, 117.9, 109.3, 108.8, 65.7, CH_2 71.4, 65.7, 40.2, 33.5, 27.3, CH_3 54.4, 54.3; ^{13}C NMR δ (minor isomer) C 147.2, 145.7, 137.5, 136.8, 40.4, CH 134.9, 128.2, 126.8, 125.9, 117.5, 109.2, 108.6, 62.8, CH_2 71.4, 65.6, 39.8, 31.2, 26.8, CH_3 54.4, 54.3; IR cm^{-1} 3410 (b), 2935 (s), 2861 (m), 1580 (w), 1517 (s), 1260 (s). HRMS calcd for $C_{23}H_{27}O_3$ (M + H − H_2O), 351.19602; found, 351.1954.

(4*S*)-4-(3,4-Dimethoxyphenyl)-4-(2-hydroxyethyl)cyclohex-2-enol (17). To a solution of liquid ammonia (20 mL) and anhydrous THF (10 mL) at −78 °C was added sodium metal (24 mg, 1.1 mmol) in small portions. Alcohol **16** (100 mg, 0.27 mmol) in THF (1 mL) was added to the above dark blue solution. The mixture was stirred at −78 °C for 30 min, and then solid NH_4Cl (500 mg) was added to quench the reaction. The mixture was warmed to room temperature over 1 h, then partitioned between EtOAc and H_2O. The combined organic was dried ($MgSO_4$) and concentrated in vacuo. The

residue was chromatographed to give **17** (65 mg, 0.23 mmol, 86% yield) as a clear oil: TLC $R_f = 0.13$, 50% EtOAc/hexane; ^{1}H NMR δ 1.22−1.40 (m, 1H), 1.73−2.09 (m, 7H), 3.48−3.64 (m, 2H), 3.86 (s, 3H), 3.89 (s, 3H), 4.21−4.29 (m, 1H), 5.89−5.99 (m, 2H), 6.79−6.86 (m, 3H); ^{13}C NMR δ C 148.7, 147.4, 138.9, 44.8, CH 134.8, 131.5, 119.3, 110.8, 110.4, 67.0, CH_2 59.6, 41.7, 34.8, 28.8, CH_3 56.0, 55.8; IR cm^{-1} 3352 (b), 2937 (s), 1708 (w), 1517 (s), 1261 (s), 1025 (s). HRMS calcd for $C_{16}H_{21}O_3$ (M + H − H_2O), 261.14907; found, 261.1499.

(4*S*)-4-(3,4-Dimethoxyphenyl)-4-(2-methansulfonyloxyethyl)cyclohex-2-enol (18). To a stirring solution of **17** (1.3 g, 4.7 mmol) and anhydrous Et_2O (100 mL), under N_2, at 0 °C was added dropwise methanesulfonyl chloride (570 mg, 5.0 mmol) over a 3 min period. The mixture was stirred at 0 °C for 1 h. The mixture was partitioned between EtOAc and H_2O. The combined organic extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed to give **18** (1.4 g, 1.1 mmol, 84% yield) as a clear oil: TLC $R_f = 0.51$, 50% EtOAc/hexane; ^{1}H NMR δ 1.29−1.42 (m, 1H), 1.61−2.28 (m, 6H), 2.92 (s, 3H), 3.86−3.89 (m, 6H), 4.02−4.31 (m, 3H), 5.84−6.08 (m, 2H), 6.79−6.87 (m, 3H); ^{13}C NMR δ (major isomer) C 147.4, 146.0, 136.1, 40.1, CH 131.8, 131.1, 117.8, 109.5, 108.6, 65.3, CH_2 65.6, 39.4, 33.4, 27.0, CH_3 54.5, 54.3, 35.8; ^{13}C NMR δ (minor isomer) C 147.3, 146.0, 135.9, 40.0, CH 133.4, 129.3, 117.4, 109.4, 108.5, 62.4, CH_2 65.6, 39.1, 30.8, 26,7, CH_3 54.4, 54.3, 35.9; IR cm^{-1} 3384 (b), 2937 (s), 1588 (w), 1517 (s), 1351 (s), 1172 (s).

(−)-Mesembrine. A stirring solution of **18** (250 mg, 0.70 mmol), methylamine (5 mL, 40% in H_2O), and THF (10 mL), under N_2, was heated at 65 °C in a sealed tube for 1 h. The mixture was concentrated in vacuo, and the residual oil was dissolved in CH_2Cl_2 (15 mL). Activated manganese(IV) oxide (460 mg) was added, and the mixture was stirred at room temperature for 3 h. The mixture was filtered through a bed of Celite, and the filtrate was concentrated in vacuo. The residue was chromatographed to give (−)-mesembrine **1** (138 mg, 0.48 mmol, 68% yield) as a clear oil: TLC $R_f = 0.52$, 10% MeOH/CH_2Cl_2; $[\alpha]^{20}_D = -59.3$ ($c = 3.0$, MeOH) [lit.[2a] $[\alpha]_D = -62.8$ ($c = 1.4$, MeOH), lit.[2d] $[\alpha]^{30}_D = -53.0$ ($c = 0.24$, MeOH) lit.[2e] $[\alpha]^{24}_D = -63.3$ ($c = 1.13$, MeOH)]; ^{1}H NMR δ 2.04−2.26 (m, 5H), 2.32 (s, 3H), 2.34−2.46 (m, 2H), 2.59−2.61 (m, 2H), 2.95 (t, $J = 3.6$ Hz, 1H), 3.08−3.17 (m, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 6.84 (d, $J = 8.2$ Hz, 1H), 6.91 (dd, $J = 5.9$ Hz, $J = 2.2$ Hz, 1H), 6.95 (d, $J = 2.3$ Hz, 1H); ^{13}C NMR δ C 209.8, 147.5, 146.0, 138.7, 46.0, CH 116.4, 109.5, 108.5, 68.9, CH_2 53.3, 39.0, 37.3, 34.7, 33.7, CH_3 54.5, 54.3, 38.5; IR cm^{-1} 2940 (m), 1717 (s), 1519 (s), 1453 (m), 1254 (s), 1026 (m). Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.20; H, 7.80; N, 4.60.

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Supporting Information Available: ^{1}H and ^{13}C spectra for compounds **1**−**8** and **11**−**18** and X-ray data for compound **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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