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Opening of Aryl-Substituted Epoxides To Form Quaternary Stereogenic Centers: Synthesis of (−)-Mesembrine

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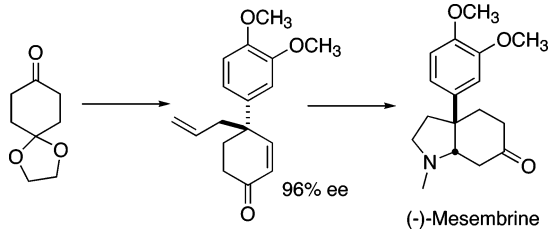
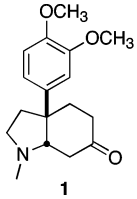


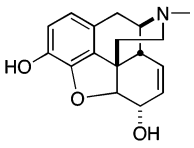
Cycloalkanones are easily converted into aryl-substituted cyclic alkenes by the addition of an aryl Grignard reagent followed by dehydration. These alkenes are good substrates for asymmetric epoxidation. We have found that the addition of allylic and benzylic Grignard reagents can occur preferentially at the benzylic position of the derived epoxides to give the quaternary stereogenic center. This approach led to a short synthesis of the nanomolar serotonin re-uptake inhibitor (−)-mesembrine.

Introduction

Alicyclic rings containing quaternary stereogenic centers[1] with attached aromatic rings are a common motif both among physiologically active alkaloids, including mesembrine **1** and morphine **2**, and in medicinal chemistry. We report what promises to be a general enantioselective method for the construction of such stereogenic centers. We have illustrated the power of this approach with a short synthesis of (−)-mesembrine **1**.[2−4]



1



2

(−)-Mesembrine **1** was isolated as the major alkaloid component of *Sceletium tortuosum*, chewed for its stimulant properties by the indigenous population of the Kalahari. In a limited trial,[5] the dried and powdered plant preparation, a mild stimulant, was shown to have marked anxiolytic properties. This crude preparation was also shown to be a powerful anti-addictive. The pure alkaloid **1** was recently shown[6] to be a nanomolar inhibitor of serotonin re-uptake, with efficacy being observed at a once-a-day oral dose of 100 μg.

(1) For reviews on the enantioselective construction of quaternary stereogenic centers, see: (a) Martin, S. F. *Tetrahedron* **1980**, *36*, 419. (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. (c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (d) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (e) Dennisova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (f) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363.

(2) For the isolation and structural determination of (−)-mesembrine, see: (a) Popelak, A.; Haack, E.; Lettenbauer, G.; Spingler, H. *Naturwissenschaften* **1960**, *47*, 156. (b) Smith, E.; Hosansky, N.; Shamma, M.; Moss, J. B. *Chem. Ind.* **1961**, 402.

(3) For leading references to previous enantioselective syntheses of (−)-mesembrine, see: (a) Takano, S.; Imamura, Y.; Ogasawara, K. *Tetrahedron Lett.* **1981**, *22*, 4479. (b) Takano, S.; Samizu, K.; Ogasawara, K. *Chem. Lett.* **1990**, 1239. (c) Fukumoto, K.; Tanabe, T.; Nemoto, H. *J. Org. Chem.* **1995**, *60*, 6785. (d) Mori, M.; Kuroda, S.; Zhang, C.; Sato, Y. *J. Org. Chem.* **1997**, *62*, 3263. (e) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1997**, *62*, 1675. (f) Langlois, Y.; Dalko, P. I.; Brun, V. *Tetrahedron Lett.* **1998**, *39*, 8979. (g) Ogasawara, K.; Yamada, O. *Tetrahedron Lett.* **1998**, *39*, 7747. (h) Taber, D. F.; Neubert, T. D. *J. Org. Chem.* **2001**, *66*, 143. For leading references to previous enantioselective syntheses of (+)-mesembrine, see: (i) Meyers, A. I.; Hanreich, R.; Wanner, K. T. *J. Am. Chem. Soc.* **1985**, *107*, 7776. (j) Kosugi, H.; Miura, Y.; Kanna, H.; Uda, H. *Tetrahedron: Asymmetry* **1993**, *4*, 1409.

(4) For leading references to the synthesis of racemic mesembrine, see: (a) Chavan, S. P.; Khobragade, D. A.; Pathak, A. B.; Kalkote, U. R. *Tetrahedron Lett.* **2004**, *45*, 5263. (b) Kulkarni, M. G.; Rasne, R. M.; Davawala, S. I.; Doke, A. K. *Tetrahedron Lett.* **2002**, *43*, 2297. (c) Rigby, J. H.; Dong, W. *Org. Lett.* **2000**, *2*, 1673.

(5) For cultural background and some limited activity trials of *Sceletium tortuosum*, see: Smith, M. T.; Crouch, N.; Gericke, N.; Hirst, M. *J. Ethnopharmacol.* **1996**, *50*, 119.

(6) For the in vitro and in vivo activity of (−)-mesembrine, see: Gericke, N. P.; VanWyk, B.-E. PCT Int. Appl., WO 9746234 CAN 128: 80030, 1997.

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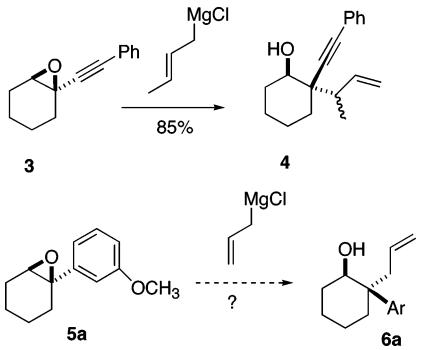
SCHEME 1



Results and Discussion

We recently observed (Scheme 1)[7] that allylic and benzylic Grignard reagents would open epoxides such as **3** to give selectively the product **4**. We envisioned that an epoxide such as **5**, with an attached *arene*,[8] might be similarly activated.

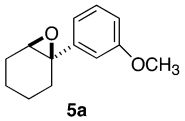
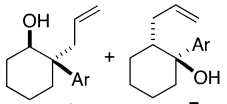
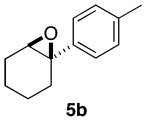
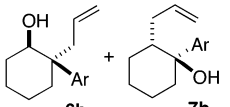
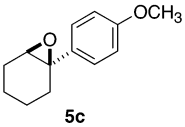
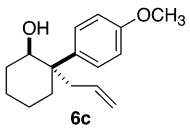
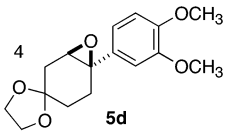
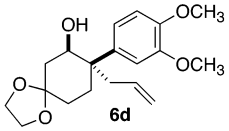
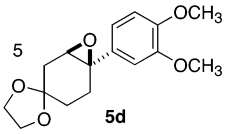
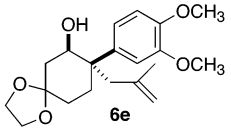
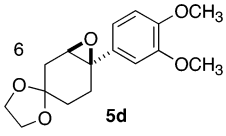
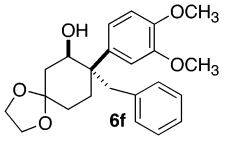
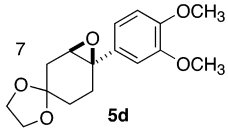
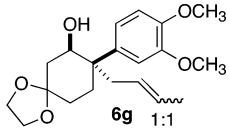
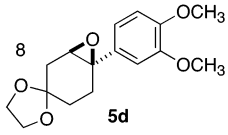
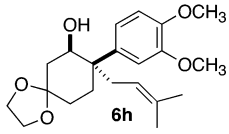
In the event (Table 1), we were not disappointed. Even a simple nonactivating arene[9–11] (entry 1) gave a substantial portion of the desired product. An activating *p*-methyl (entry 2) increased the fraction of the desired secondary alcohol. With the still more activating *p*-methoxy (entry 3), the cyclic quaternary stereogenic center was formed smoothly.

We also explored alternative nucleophiles with the epoxide **5d**[10] (Table 1). We found that allylic and benzylic Grignard reagents gave the desired ring-opening products. It was striking that, although the alkyne-activated epoxide (Scheme 1) gave the branched product **4** with crotylmagnesium chloride, the arene-activated epoxide gave only the complementary linear product **6g**. The less reactive and more basic alkyl, phenyl, and vinyl Grignard reagents gave primarily undesired side products. This difference is attributable at least in part to the lack of reactivity of these nucleophiles toward the trisubstituted cyclic expoxide. Et_3Al[8d] gave rearrangement to the cyclohexanone followed by hydride reduction, while Et_2AlCN[12] gave only rearrangement to the ketone.

The beauty of this approach is that it allows the construction of a quaternary stereogenic center on an *existing* ring. It is particularly exciting that, using the Shi epoxidation,[13] one can convert a prochiral cyclic alkene to the enantiomerically defined product. To establish the viability of this approach and to confirm the sense of absolute stereocontrol of the process, we converted the monoprotected cyclohexanone **6d** (Scheme 2) to (−)-mesembrine (**1**).

The cyclohexanone **8** reacted with the aromatic Grignard reagent **9** to give the known[10] alkene **10**, after dehydration using PTSA in the presence of excess ethylene glycol. Shi expoxidation[13] of **10** followed by ring-opening of the resulting crude epoxide by allylmagnesium chloride gave the enantiomerically enriched secondary alcohol **6d**.[10] The enantiomers of **6d** were well-resolved by chiral HPLC (Chiralcel OD, 15% 2-propanol/hexane, 1 mL/min, retention time: 17.6 min for the minor enantiomer and 34.2 min for the major enantiomer). The alcohol **6d** derived from Shi epoxidation had 96% ee.

TABLE 1. Opening of Arene-Substituted Cyclic Epoxides

Entry	Starting epoxide	Isolated yield (%)	Product(s)
1	 **5a**	77[b]	 **6a** 1 : 1 **7a**
2	 **5b**	82[b] (65[c])	 **6b** 4 : 1 **7b**
3	 **5c**	86	 **6c**
4	 **5d**	86	 **6d**
5	 **5d**	88	 **6e**
6	 **5d**	88	 **6f**
7	 **5d**	52[b]	 **6g** 1:1
8	 **5d**	85	 **6h**

[a] Ratio of two isomers was determined by ^1H NMR. [b] Combined yields of two isomers. [c] Isolated yield of **6b**.

(7) Taber, D. F.; He, Y.; Xu, M. *J. Am. Chem. Soc.* **2004**, *126*, 13900.

(8) For reports of the opening of arene-activated trisubstituted epoxides at the more substituted carbon to establish a quaternary center, see: (a) Gerteisen, T. J.; Kleinfelter, D. C. *J. Org. Chem.* **1971**, *36*, 3255. (b) Krause, N.; Seebach, D. *Chem. Ber.* **1988**, *121*, 1315. (c) Kauffmann, T.; Neiteler, C.; Robbe, S. *Chem. Ber.* **1992**, *125*, 2409. (d) Jansen, J.; Knopp, M.; Amberg, W.; Bernard, H.; Koser, S.; Müller, S.; Münster, I.; Pfeiffer, T.; Riechers, H. *Org. Process Res. Dev.* **2001**, *5*, 16.

(9) (a) For the preparation of the alkenes corresponding to **5a** and **5c**, see: Balsamo, A.; Crotti, P.; Macchia, B.; Macchia, F. *Tetrahedron* **1973**, *29*, 2183. (b) For the preparation of the alkenes corresponding to **5b** and **5c**, see: Doan, L.; Bradley, K.; Gerdes, S.; Whalen, D. L. *J. Org. Chem.* **1999**, *64*, 6227.

(10) For the preparation of **5d**, see: Hoshino, O.; Sawaki, S.; Shimamura, N.; Onodera, A.; Umezawa, B. *Chem. Pharm. Bull.* **1987**, *35*, 2734.

(11) We found that the sensitive epoxides could be prepared efficiently from the alkenes with dimethyl dioxirane: Murray, R. W.; Singh, M. *Org. Synth.* **1997**, *74*, 91.

(12) Newbold, R. C.; Shih, T. L.; Mrozik, H.; Fisher, M. H. *Tetrahedron Lett.* **1993**, *34*, 3825.

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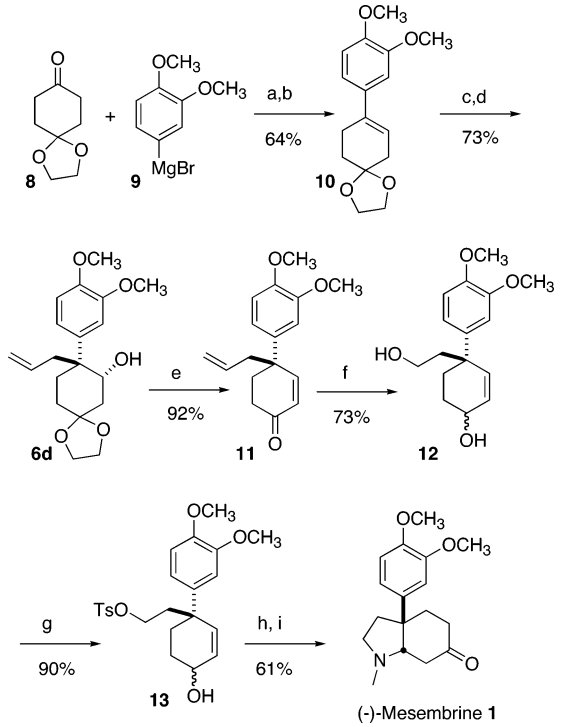
SCHEME 2[a]



[a] (a) THF, 0−20 °C, overnight; (b) benzene, PTSA (cat.), ethylene glycol (excess), reflux; (c) Shi's catalyst, DME−acetonitrile−H_2O, 0 °C, 4 h; (d) allylmagnesium chloride, THF, 0−20 °C, overnight; (e) 10% aqueous HCl, THF, reflux, 1 h; (f) O_3, MeOH, −78 °C; $CeCl_3 \cdot 7H_2O$ (1.0 equiv), $NaBH_4$ (8.0 equiv), 0 °C; (g) TsCl (1 equiv), Et_3N, CH_2Cl_2, 20 °C, overnight; (h) 40% aqueous CH_3NH_2, THF, 65 °C, 1 h; (i) MnO_2, CH_2Cl_2, 20 °C, 3 h.

Exposure of **6d** to 10% aqueous HCl in THF gave the enone **11**.[4b] Selective ozonolysis of the terminal double bond in **11** followed by treatment[14] of the resulting ozonide in situ with $NaBH_4$ in the presence of $CeCl_3$[15] furnished the diol **11**[3h] as a 4:1 mixture of diastereomers. The primary hydroxyl group in **11** was selectively converted into the corresponding tosylate **12**, which on heating with 40% aqueous methylamine followed by oxidation using activated MnO_2[3h] gave (−)-mesembrine (**1**), ($[\alpha]^{22}_D$ −55.4, lit. = −62.8,[3a] −63.3,[3d] −53.0,[3e] −59.3[3h]), identical (^{1}H, ^{13}C NMR) with authentic material.

Conclusion

We believe that the approach outlined here will be a useful strategy for the enantioselective assembly of cyclic quaternary stereogenic centers having attached aromatic rings, complementary to such recently developed methods as enantioselective allylation[16] and enantioselective arylation.[17]

(14) Sousa, J. A.; Bluhm, A. C. *J. Org. Chem.* **1960**, *25*, 108.
(15) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
(16) (a) Trost, B. M.; Pissot-Soldermann, C.; Chen, I.; Schroeder, G. M. *J. Am. Chem. Soc.* **2004**, *126*, 4480. (b) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846.
(17) (a) Aahman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918. (b) Hamada, T.; Chieffi, A.; Ahman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261.

Experimental Section

Epoxide (5c). A solution of 1-(4-methoxyphenyl)-cyclohexene (0.752 g, 3.68 mmol) in 2 mL of acetone was added to a solution of dimethyldioxirane[4] (50 mL, ∼0.07 M) in acetone at room temperature. The yellow color of dimethyldioxirane disappeared immediately. After evaporation of acetone, the residue was treated immediately with 10 mL of 2.0 M allylmagnesium chloride as described below.

Typical Procedure for the Ring Opening of Epoxides with Grignard Reagents. To a solution of epoxide (2 mmol) in anhydrous THF (15 mL) was added dropwise a solution of Grignard reagent (10 mmol, 5 equiv) over 2 min at 0 °C. The reaction mixture was warmed slowly to room temperature and then stirred overnight. The reaction mixture was partitioned between saturated aqueous NH_4Cl and ether. The combined organic extract was dried (Na_2SO_4) and concentrated, and the residue was chromatographed.

Alcohol (6b): Clear oil (58% yield), TLC R_f = 0.46 (PE/acetone, 3:1), R_f = 0.43 for the minor isomer **5f**. IR (neat, cm^{-1}): 3456 (s), 2935 (s), 2863 (s), 1638 (w), 1514 (m), 1454 (m), 1239 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.15−7.30 (m, 4H), 5.23 (m, 1H), 4.92 (d, J = 30.4 Hz, 1H), 4.89 (d, J = 23.2 Hz, 1H), 4.02 (t, J = 3.2 Hz, 1H), 2.34−2.64 (m, 2H), 2.34 (s, 3H), 1.45−2.10 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ u: 141.9, 135.9, 117.1, 45.2, 41.3, 28.3, 27.0, 21.2, 20.1; d: 134.7, 129.5, 127.0, 74.1, 21.1; HRMS calcd for $C_{16}H_{21}$ (M + H − H_2O) 213.1643, found 213.1644.

Alkene (10). To a Grignard reagent prepared from Mg (1.82 g, 75.0 mmol) and 4-bromoveratrole (13.0 g, 60.0 mmol) in 40 mL of anhydrous THF at 0 °C was added 1,4-dioxaspiro[4,5]-decan-8-one **8** (7.80 g, 50.0 mmol) in 20 mL of anhydrous THF over 5 min under nitrogen. After being stirred at 0 °C for 30 min, then ambient temperature for 2 h, the reaction mixture was partitioned between ether and saturated aqueous NH_4-Cl. The combined organic extract was dried (Na_2SO_4) and concentrated. To the residue was added benzene (200 mL), ethylene glycol (30 mL), and *p*-toluenesulfonic acid (10 mg). A Dean−Stark water separation apparatus was set up, and the solution was heated to reflux until about 0.9 mL of water had been collected. The reaction mixture was partitioned between ether and saturated aqueous $NaHCO_3$. The organic extract was dried (Na_2SO_4) and evaporated, and the residue was chromatographed to give 8.86 g of alkene **10** (64% yield from **8**) as white solid: mp 76−78 °C (lit.[10] = 77.5−78 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.80−6.95 (m, 3H), 5.91 (m, 1H), 4.01 (s, 4H), 3.88 (s, 3H), 3.87 (s, 3H), 2.64 (m, 2H), 2.46 (br, 2H), 1.90 (t, J = 6.4 Hz, 2H).

Alcohol (6d). To a 500-mL three-necked flask was added alkene **10** (2.31 g, 8.37 mmol), 85 mL of a 2:1 mixture of dimethoxymethane and acetonitrile, 50 mL of potassium carbonate-acetic acid buffer solution, tetrabutylammonium hydrogen sulfate (63 mg), and Shi's chiral ketone (0.756 g, 2.93 mmol). The flask was connected to two dropping funnels, one charged with a solution of oxone (7.72 g, 12.6 mmol) in 30 mL of aqueous 4×10^{-4} Na_2EDTA and the other charged with 30 mL of 1.47 M aqueous KOH. The two solutions were added dropwise at the same rate over 65 min to the cold reaction mixture which was stirred vigorously at 0 °C. After 3 h, ether (100 mL) was added. The biphasic mixture was partitioned between ether and, sequentially, water and brine. The organic extract was dried (Na_2SO_4) and concentrated. The residue was dissolved in 50 mL of anhydrous THF. To this solution allylmagnesium chloride (21 mL, 2.0 M) was added dropwise over 5 min at 0 °C under N_2. The reaction solution was warmed slowly from 0 °C to room temperature, then maintained at ambient temperature overnight. The reaction mixture was partitioned between saturated aqueous NH_4Cl and ether. The combined organic extract was dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed to give 2.04 g of alcohol **6d** (73% yield from **10**) as a colorless oil. TLC R_f = 0.56 (ether), $[\alpha]^{22}_D$ +37.3 (*c* 1.6, THF); IR (neat, cm^{-1}): 3514 (s), 2954 (s), 1637 (w), 1587 (w), 1518 (s), 1464 (m), 1256 (s),

1150 (m), 1028 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.83−6.95 (m, 3H), 5.28 (m, 1H), 4.96 (d, J = 23.6 Hz, 1H), 4.93 (d, J = 17.2 Hz, 1H), 4.16 (t, J = 3.6 Hz, 1H), 3.97 (m, 4H), 3.88 (s, 3H), 3.86 (s, 3H), 3.08 (d, J = 8.0 Hz, 1H), 1.65−2.50 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ u: 148.6, 147.1, 137.2, 117.3, 108.7, 64.6, 64.1, 44.6, 41.6, 36.7, 30.5, 25.2; d: 134.3, 119.1, 110.8, 110.3, 74.3, 55.8, 55.7; HRMS calcd for $C_{19}H_{26}O_5$ (M^+) 334.1780, found 334.1774.

Enone (11). To a solution of alcohol **6d** (0.90 g, 2.7 mmol) in 10 mL of THF was added 10% aqueous HCl (4 mL). After heating to reflux for 1 h, the reaction mixture was partitioned between saturated aqueous Na_2CO_3 and CH_2Cl_2. The combined CH_2Cl_2 extract was dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to give 0.67 g of enone **11** (92% yield) as a colorless oil, TLC R_f = 0.69 (PE/EtOAc, 1:1), $[\alpha]^{22}_D$ −107.6 (*c* 0.8, THF); IR (neat, cm^{-1}): 2935 (m), 1682 (s), 1639 (w), 1603 (w), 1518 (s), 1464 (m), 1255 (s), 1148 (m), 1027 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.07 (d, J = 10.0 Hz, 1H), 6.86 (s, 3H), 6.17 (d, J = 10.0 Hz, 1H), 5.56 (m, 1H), 5.11 (d, J = 15.2 Hz, 1H), 5.08 (d, J = 8.4 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 2.15−2.73 (m, 6H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ u: 199.6, 149.1, 148.0, 135.4, 119.0, 46.3, 43.6, 36.1, 34.5; d: 155.3, 133.6, 129.5, 119.4, 111.1, 110.2, 56.1, 55.9; HRMS calcd for $C_{17}H_{21}O_3$ (M + H) 273.1491, found 273.1490.

Diol (12). To a solution of enone **11** (0.663 g, 2.43 mmol) in HPLC-grade methanol (20 mL) was added an indicator amount of Sudan III. After being purged with O_2 at −78 °C for 2 min, O_3 was bubbled through the solution until the red color of Sudan III disappeared. The reaction was purged with N_2 for 5 min, and then $CeCl_3 \cdot 7H_2O$[8] (1.00 g, 2.68 mmol) was added. The reaction mixture was cooled with an ice−water bath, and then $NaBH_4$ (554 mg, 14.6 mmol) was added in three portions over 5 min. After an additional 30 min, $NaBH_4$ (92 mg, 2.43 mmol) was added followed by stirring for another 30 min. The latter procedure was repeated once more. The reaction mixture was partitioned between water and CH_2Cl_2. The combined organic extract was dried (Na_2SO_4) and concentrated, and the residue was chromatographed to give 0.474 g of diol **11** (4:1 mixture of two diasteromers, 73% yield) as a colorless oil. TLC R_f = 0.18 (wet ether), $[\alpha]^{22}_D$ −23.5 (*c* 0.55, THF); IR (neat, cm^{-1}): 3390 (b), 2941 (s), 1715 (m), 1520 (s), 1260 (s), 1026 (s); ^{1}H NMR (400 MHz, major isomer, $CDCl_3$) δ: 6.78−6.82 (m, 3H), 5.86−5.95 (m, 2H), 4.21 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.47−3.58 (m, 2H), 1.62−2.07 (m, 7H); ^{13}C NMR ($CDCl_3$, major isomer, 90 MHz) δ u: 148.8, 147.4, 139.1, 59.7, 45.0, 41.8, 35.0, 28.9; d: 134.9, 131.7, 119.4, 110.9, 110.5, 67.2, 56.1, 56.0; ^{1}H NMR (400 MHz, minor isomer, $CDCl_3$) δ: 6.80−6.82 (m, 3H), 5.60−6.06 (m, 2H), 4.13 (m, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.55−3.65 (m, 2H), 1.62−2.10 (m, 7H); ^{13}C NMR ($CDCl_3$, minor isomer, 90 MHz) δ u: 148.9, 147.5, 139.0, 59.7, 44.7, 41.9, 32.6, 28.5; d: 136.5, 130.0, 119.0, 111.1, 110.3, 64.6, 56.1, 56.0; HRMS calcd for $C_{16}H_{22}O_4Na$ (M + Na) 301.1416, found 301.1412.

Tosylate (13). To a solution of diol **12** (major isomer, 133 mg, 0.478 mmol) in 5 mL of anhydrous CH_2Cl_2 was added triethylamine (145 mg, 1.44 mmol) and tosyl chloride (91.2 mg, 0.478 mmol). After being stirred under N_2 at ambient temperature for 16 h, the reaction mixture was partitioned between saturated aqueous Na_2CO_3 and CH_2Cl_2. The combined organic extract was dried (Na_2SO_4) and concentrated. The crude product was chromatographed to give 0.186 g of tosylate **13** (90% yield) as a clear oil. TLC R_f = 0.34 (ether), $[\alpha]^{22}_D$ −11.4 (*c* 0.35, THF); IR (neat, cm^{-1}): 3390 (b), 2938 (s), 1598 (s), 1464 (m), 1359 (s), 1252 (s), 1176 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 6.75 (br, 3H), 5.90 (dd, J = 10.0 Hz, 1.2 Hz, 1H), 5.78 (d, J = 10.0 Hz, 1H), 4.19 (br, 1H), 3.81−3.98 (m, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 2.44 (s, 3H), 1.67−2.17 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ u: 149.0, 147.7, 144.9, 137.8, 133.2, 67.8, 41.8, 40.9, 35.0, 28.8; d: 133.7, 132.5, 129.9, 127.9, 119.4, 111.1, 110.3, 67.0, 56.1, 56.0, 21.8; HRMS calcd for $C_{23}H_{28}O_6S$ (M^+) 432.1607, found 432.1605.

(−)-Mesembrine (1). To a sealed thick-walled reaction flask was added tosylate **13** (144 mg, 0.33 mmol), methylamine (2.0 mL, 40% in water), and THF (4.0 mL). The reaction mixture was heated at 65 °C for 1 h and then concentrated in vacuo, and the residual oil was dissolved in CH_2Cl_2 (15 mL). To this solution activated MnO_2 (220 mg, 2.53 mmol) was added, and the mixture was stirred at room temperature for 3 h. After filtration through a thin layer of Celite, the filtrate was concentrated and the residue was chromatographed to give 58.8 mg of (−)-mesembrine (61% yield) as a colorless oil. TLC R_f = 0.21(wet ether), $[\alpha]^{22}_D$ −55.4 (*c* 0.54, MeOH); IR (neat, cm^{-1}): 2944 (m), 1716 (s), 1520 (s), 1454 (m), 1253 (s), 1148 (m), 1027 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.93 (dd, J = 8.4, 2.4 Hz, 1H), 6.90 (d, J = 2.0 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.13−3.17 (m, 1H), 2.96 (t, J = 3.6 Hz, 1H), 2.61 (m, 2H), 2.35−2.46 (m, 2H), 2.33 (s, 3H), 2.04−2.26 (m, 5H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ u: 211.5, 149.3, 147.8, 140.4, 55.1, 47.8, 40.8, 39.1, 36.4, 35.5; d: 118.2, 111.3, 110.3, 70.6, 56.2, 56.1, 40.3; HRMS calcd for $C_{17}H_{23}NO_3$ (M^+) 289.1678, found 289.1671.

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Supporting Information Available: General experimental details, characterization of the products from Table 1, and spectra for all new compounds and for **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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