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Opening of Aryl-Substituted Epoxides to form Quaternary Stereogenic Centers: Synthesis of (–)-Mesembrine

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Abstract

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 centers¹ 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}

(–)-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 shown⁶ to be a nanomolar inhibitor of serotonin re-uptake, with efficacy being observed at a once-a-day oral dose of 100 micrograms.

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This work is dedicated to the memory of Conrad J. Kowalski, a master of the science and art of organic synthesis.

SUPPORTING INFORMATION. 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>.

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 non-activating 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 crotyl magnesium 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 epoxide. Et₃Al^{8d} gave rearrangement to the cyclohexanone followed by hydride reduction, while Et₂AlCN¹² 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 **6** (Scheme 2) to (–)-mesembrine (**1**).

The cyclohexanone **8** reacted with the aromatic Grignard reagent **9** to give the known¹⁰ alkene **10**, after dehydration using PTSA in the presence of excess ethylene glycol. Shi epoxidation¹³ 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% isopropanol / 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.

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 treatment¹⁴ of the resulting ozonide in situ with NaBH₄ in the presence of CeCl₃¹⁵ 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 MnO₂^{3h} gave (–)-mesembrine (**1**), ([α]_D²² = –55.4, lit. = –62.8,^{3a} –63.3^{3d}, –53.0,^{3e} –59.3,^{3h}), identical (¹H, ¹³C 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 allylation¹⁶ and enantioselective arylation.¹⁷

Experimental

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 dimethyldioxirane⁴ (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 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 two minutes at 0 °C. The reaction mixture was warmed slowly to room temperature, then stirred overnight. The reaction mixture was partitioned between saturated aqueous NH₄Cl and ether. The combined organic extract was dried (Na₂SO₄) 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); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (CDCl₃, 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 C₁₆H₂₁ (M+H-H₂O) 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 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 anhydrous THF over 5 min under nitrogen. After stirring at 0 °C for 30 min, then ambient temperature for 2 h, the reaction mixture was partitioned between ether and saturated aqueous NH₄Cl. The combined organic extract was dried (Na₂SO₄) 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 NaHCO₃. The organic extract was dried (Na₂SO₄) 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). ¹H NMR (400 MHz, CDCl₃) 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 Na₂EDTA 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 (Na₂SO₄) 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 N₂. 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 NH₄Cl and ether. The combined organic extract was dried over Na₂SO₄ 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); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (CDCl₃, 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 C₁₉H₂₆O₅ (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 Na₂CO₃ and CH₂Cl₂. The combined CH₂Cl₂ extract was dried (Na₂SO₄) 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); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (CDCl₃, 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 C₁₇H₂₁O₃ (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 purging with O₂ at -78 °C for 2 min, O₃ was bubbled through the solution until the red color of Sudan III disappeared. The reaction was purged with N₂ for 5 min, then CeCl₃·7H₂O⁸ (1.00 g, 2.68 mmol) was added. The reaction mixture was cooled with an ice-water bath, then NaBH₄ (554 mg, 14.6 mmol) was added in three portions over 5 min. After an additional 30 min, NaBH₄ (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 CH₂Cl₂. The combined organic extract was dried (Na₂SO₄) and concentrated, and the residue was chromatographed to give 0.474 g of diol **11** (4:1 mixture of two diastereomers, 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); ¹H NMR (400 MHz, major isomer, CDCl₃) 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); ¹³C NMR (CDCl₃, 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; ¹H NMR (400 MHz, minor isomer, CDCl₃) 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); ¹³C NMR (CDCl₃, 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 C₁₆H₂₂O₄Na (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 CH₂Cl₂ was added triethylamine (145 mg, 1.44 mmol) and tosyl chloride (91.2 mg, 0.478 mmol). After stirring under N₂ 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), $[\alpha]_D^{22}$ = -11.4 (c = 0.35, THF); IR (neat, cm^{-1}): 3390 (b), 2938 (s), 1598 (s), 1464 (m), 1359 (s), 1252 (s), 1176 (s); ^1H 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 $\text{C}_{23}\text{H}_{28}\text{O}_6\text{S}$ (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, 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 rt 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), $[\alpha]_D^{22}$ = -55.4 (c = 0.54, MeOH); IR (neat, cm^{-1}): 2944 (m), 1716 (s), 1520 (s), 1454 (m), 1253 (s), 1148 (m), 1027 (m); ^1H 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 $\text{C}_{17}\text{H}_{23}\text{NO}_3$ (M^+) 289.1678, found 289.1671.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.

Scheme 2^a

^a (a) THF, 0 °C to 20 °C, overnight; (b) benzene, PTSA (cat.), ethylene glycol (excess), reflux; (c) Shi's catalyst, DME-acetonitrile-H₂O, 0 °C, 4 h; (d) allylmagnesium chloride, THF, 0 °C to 20 °C, overnight; (e) 10% aqueous HCl, THF, reflux, 1 h; (f) O₃, MeOH, -78 °C; CeCl₃·7H₂O (1.0 equiv), NaBH₄ (8.0 equiv), 0 °C; (g) TsCl (1 equiv), Et₃N, CH₂Cl₂, 20 °C, overnight; (h) 40% aqueous CH₃NH₂, THF, 65 °C, 1 h; (i) MnO₂, CH₂Cl₂, 20 °C, 3 h.

Table 1

Opening of Arene-Substituted Cyclic Epoxides

Entry	Starting epoxide	Isolated yield (%)	Product(s)
1		77 ^b	+ 1 : 1
2		82 ^b (65 ^c)	+ 4 : 1
3		86
4		86
5		88
6		88
7		52 ^b	1:1
8		85

^a Ratio of two isomers was determined by ¹H NMR.

^b Combined yields of two isomers.

^c Isolated yield of **6b**