The preparation of the crystalline amide 2 is reported. Conjugate addition to 2 proceeded with the expected high diastereocntrol to give 3. This set the stage for subsequent intramolecular alkyldiene 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.

Incorporation of the Alkenyl Chloride. The first challenge in this strategy was the incorporation of the alkenyl chloride. In previous approaches we had prepared chloroalkenes by homologation with Wittig reaction of a ketone with (chloromethyl)triphenylphosphorane. We hypothesized that the direct introduction of an alkylation 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 alkylation agent 4 in hand, we effected alkylation of the acetocetate diianion10 to give the ketoster 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 In fact, mesylation followed by in situ elimination gave exclusively (13C NMR) the expected high diastereocontrol to give amide 2 through several preparative steps. These steps would include the enantioselective establishment of a chiral ternary center based on stereoselective conjugate addition9 followed by intramolecular cyclization of 3 via intramolecular alkyldiene C–H insertion.6 This C–H insertion would proceed with retention of absolute configuration7 to convert the ternary center of 3 to the quaternary center of 1.


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

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The Sceletium alkaloid (−)-mesembrine (1), a naturally occurring serotonin uptake inhibitor1 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 mesembrine2,3 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 addition5 followed by intramolecular cyclization of 3 via intramolecular alkyldiene C–H insertion.6 This C–H insertion would proceed with retention of absolute configuration7 to convert the ternary center of 3 to the quaternary center of 1.

In the preparation of the crystalline amide 2 is reported. Conjugate addition to 2 proceeded with the expected high diastereocntrol to give 3. This set the stage for subsequent intramolecular alkyldiene 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 inhibitor1 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 mesembrine2,3 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 addition5 followed by intramolecular cyclization of 3 via intramolecular alkyldiene C–H insertion.6 This C–H insertion would proceed with retention of absolute configuration7 to convert the ternary center of 3 to the quaternary center of 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 Et₂O.

The (E,E)-material was employed in the subsequent synthetic steps to minimize the complexity of the ¹H and ¹³C 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 stereoselectivity⁵b,c to give 3. We were unable to detect the alternative diastereomer by ¹³C 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 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 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 ¹³C NMR, IR, MS, and optical rotation results identical with the literature values.⁵a,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 stereocenters.

Footnotes

Experimental Section

General. The general experimental method was identical to that previously published 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 N₂, was added dropwise a solution of ethyl acetoacetate (6.5 g, 66.5 mmol) in THF (10 mL) at 0 °C, and concentrated in vacuo. The residue was chromatographed to give 8 (1.7 g, 97% yield) as a white solid: mp 78 °C; TLC Rf 0.35, 10% EtOAc/hexane; IR (film) 3364 (b), 2982 (m), 1738 (s), 1640 (w), 1244 (m). Anal. Calcd for C₁₇H₁₈NO₃Cl: C, 63.85; H, 5.67; N, 4.38. Found: C, 63.90; H, 5.54; N, 4.19.

(6E)-(3S),(4S)-3-(7-Chloro-6-methylhept-6-enoyl)-4-phenylazolidin-2-one (3). To a stirring solution of magnesium (4.8 g, 194 mg) and anhydrous THF (150 mL) at −78 °C under N₂, 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 following cooling to −78 °C. This suspension was transferred dropwise via cannula at −78 °C to a solution of 4-phenyl-2-oxazolidinone and dimethyl sulfoxide complex (1.9 g, 9.5 mmol), anhydrous THF (30 mL) containing lithium hydroxide monohydrate (457 mg, 10.9 mmol), and concentrated in vacuo. The residue was chromatographed to give 9 (1.6 g, 5.0 mmol, 68% yield) as a white solid: mp 55–55.5 °C; TLC Rf 0.22, 20% EtOAc/hexane; IR (film) 1730 (s), 1683 (w), 1645 (w). Anal. Calcd for C₁₇H₁₈NO₃Cl: C, 63.85; H, 5.67; N, 4.38. Found: C, 63.90; H, 5.54; N, 4.19.
°C for 10 min. The reaction mixture was partitioned between EtOAc and H2O. The combined organic extract was dried (MgSO4) and concentrated in vacuo. The residue was chromatographed to give 2 (3.2 g, 5.9 mmol, 94% yield) as a white solid mp: 95–97 °C; TLC Rf 0.29; 30% EtOAc/hexanes; 1H 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), 6.27 (d, J = 8.9 Hz, 1H), 6.51 (s, 1H), 6.62 (s, 1H), 6.63–6.78 (m, 2H), 6.91–6.93 (m, 2H), 7.21–7.24 (m, 3H); 13C 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, 31.7, 30.3, 22.2, 18.3, 17.1, 14.7; IR cm⁻¹ 3293 (m), 2934 (s), 2861 (s), 1780 (s), 1736 (m), 1704 (m), 1700 (m), 1518 (m).

(66)-(35)-7-Chloro-3-(3,4-dimethoxyphenyl)-6-methylhex-6-enonic Acid (11). To a stirring solution of 3 (1.2 g, 2.6 mmol), H2O (3 mL), and THF (12 mL), at −5 °C, was added hydrogen peroxide (1.14 mL, 2.5 mmol, 78% yield) as a clear oil. The mixture was warmed to room temperature over a 30 min period. A solution of lithium hydroxide monohydrate (174 mg, 4.2 mmol, and H2O (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 sulfate solution (10.4 mmol in H2O (10 mL). The reaction mixture was partitioned between EtOAc and H2O. The combined organic extract was dried (MgSO4) and concentrated in vacuo. The residue was chromatographed to give 11 (780 mg, 2.5 mmol, 96% yield) as a clear oil: TLC Rf 0.52, 10% MeOH/CH2Cl2; 1H NMR δ 7.05–7.08 (m, 3H), 7.10 (s, 1H), 7.12 (s, 1H), 7.13 (d, J = 7.4 Hz, 2H), 7.21–3.02 (m, 1H), 3.86 (s, 3H), 3.87 (s, 1H), 5.66–6.62 (m, 3H); 13C 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 40.3, 33.1, 32.0, CH3 54.3, 54.2, 14.7; IR cm⁻¹ 2800–3400 (b), 1708 (m), 1706 (m), 1703 (m), 1700 (m), 1700 (m), 1518 (m), 1179 (m), 1107 (m), 1096 (m), 109.5 (m), 39.7 (s), 31.7 (s), 30.3 (s), 22.2 (s), 18.3 (s), 17.1 (s), 14.7 (s), CH2 71.4, 65.6, 39.8, 31.2, 26.8, CH3 54.4, 54.3, 15.4; IR cm⁻¹ 3293 (m), 2934 (m), 1516 (m), 1452 (w), 1256 (m), 1029 (m).

(45)-(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 CH2Cl2 (30 mL), under N2, at −78 °C, was bubbled a gentle stream of O2/O3 until the observed exotherm ceased (~10 min). Excess O3 was subsequently purged with a dry stream of N2, and then triphenylphosphine (800 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 H2O. The reaction mixture was partitioned between EtOAc and H2O. The combined organic extract was dried (MgSO4) and concentrated in vacuo. The residue was chromatographed to give 15 (1.09 g, 2.33 mmol, 98% yield) as a clear oil: TLC Rf 0.46, 30% EtOAc/hexanes; 1H NMR δ 2.13–2.39 (m, 6H), 3.44 (t, J = 6.2 Hz, 2H), 3.84 (s, 3H), 3.87 (s, 1H), 6.13 (d, J = 10.1 Hz, 1H), 6.76–6.81 (m, 1H), 7.20–7.38 (m, 5H); 13C NMR δ C 197.8, 147.5, 146.3, 136.5, 133.9, 41.5, CH 154.2, 127.7, 126.8, 126.1, 126.0, 117.7, 109.5, 108.4, CH2 71.6, 65.4, 39.6, 35.0, 33.0, CH3 54.4, 54.3, IR cm⁻¹ 2935 (m), 1680 (s), 1517 (s), 1453 (w), 1259 (m), 1027 (m).

(45)-(4)-(3,4-Dimethoxyphenyl)-4-(2-(phenylmethoxy)ethyl)cyclohex-2-enone (16). To a stirring suspension of lithium aluminum hydride (21 mg, 0.55 mmol) and anhydrous THF (50 mL) at 0 °C, was added lithium hexamethyldisilazane (70 mg, 0.55 mmol) and anhydrous DMF (0.2 mL) and heating at 0 °C. The residue was chromatographed to give 16 (1.79 g, 4.84 mmol, 87% yield) as a clear oil: TLC Rf 0.32, 50% EtOAc/hexanes; 1H 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); 13C 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, 108.5, 65.7, CH 71.4, 65.7, 40.2, 33.5, 27.3, CH3 54.4, 54.3; 13C NMR δ (minor isomer) C 147.2, 147.5, 137.5, 136.8, 14.4, 40.4, CH 134.9, 128.4, 126.8, 125.9, 117.5, 109.2, 108.6, 62.8, CH2 71.4, 65.6, 39.8, 31.2, 26.8, CH3 54.4, 54.3; IR cm⁻¹ 3410 (b), 2935 (s), 2861 (m), 1580 (w), 1517 (s), 1260 (s).

(45)-(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 NH4Cl (500 mg) was added to quench the reaction. The mixture was warmed to room temperature over 1 h, then partitioned between EtOAc and H2O. The combined organic was dried (MgSO4) and concentrated in vacuo. The...
residue was chromatographed to give 17 (65 mg, 0.23 mmol, 86% yield) as a clear oil: TLC Rf = 0.13, 50% EtOAc/hexane; 1H 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); 13C NMR δ C 148.7, 147.4, 138.9, 44.8, CH 134.8, 131.5, 119.3, 110.8, 110.4, 67.0, CH2, 59.6, 41.7, 34.8, 28.8, CH3 56.0, 55.8; IR cm⁻¹ 3352 (b), 2937 (s), 1708 (w), 1517 (s), 1261 (s), 1025 (s). HRMS calcd for C16H21O3 (M+H-H2O), 261.14907; found, 261.1499.

(4S)-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 Et2O (100 mL), under N2, a t0° 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 H2O. The combined organic extract was dried (MgSO4) and concentrated in vacuo. The residue was chromatographed to give 18 (1.4 g, 1.1 mmol, 84% yield) as a clear oil: TLC Rf = 0.51, 50% EtOAc/hexane; 1H 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); 13C 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, CH2 65.6, 39.4, 33.4, 27.0, CH3 54.5, 54.3, 35.8; 13C 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, CH2 65.6, 39.1, 30.8, 26.7, CH3 54.4, 54.3, 35.9; IR cm⁻¹ 3384 (b), 2937 (s), 1588 (m), 1536 (m), 1453 (m), 1351 (s), 1254 (s), 1026 (s). Anal. Calcd for C17H23NO3: 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: 1H and 13C 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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