aqueous layer was extracted with chloroform, and the combined organic layers were dried and concentrated to give 0.53 g (97%) of an oil: NMR as reported.[5]

1- and 3-Tropyl-2-butanone (2 and 3). A solution of tropylium fluoroborate (1.0 g, 5.6 mmol) and 2-butanone (0.35 g, 4.9 mmol) in 4 mL of methanol containing 15 drops of acetic acid was stirred for 4.5 h at room temperature. Water (15 mL) was added, and the aqueous layer was extracted with three 15-mL portions of ether. The combined organic layers were washed with three 15-mL portions of water, dried, concentrated, and passed through a short silica gel column with methylene chloride as the eluant. Evaporation of the solvent left 0.59 g (75%) of a mixture of the two products as a brownish orange oil: IR ($CHCl_3$) 1675, 1350, 685 cm^{-1}; mass spectrum, m/e 91 (no parent peak was observed). A portion of the mixture was distilled twice [bp 60–65 °C (0.8 torr)] to provide a pale yellow oil. Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 80.95; H, 8.75.

A sample was separated on a Chromatotron to provide samples of the separated isomers, which were characterized by the following NMR spectra. **2**: δ 6.60 (2 H, t, J = 3 Hz), 6.15 (2 H, dt, J = 9, 3 Hz), 5.12 (2 H, dd, J = 9, 6 Hz), 2.73 (2 H, d, J = 7 Hz), 2.5–2.1 (3 H, m), 1.04 (3 H, t, J = 7 Hz). **3**: δ 6.58 (2 H, m), 6.15 (2 H, m), 5.13 (2 H, m), 2.83 (1 H, dq, J = 7, 10 Hz), 2.07 (3 H, s), 2.2–1.8 (1 H, m), 1.24 (3 H, d, J = 7 Hz).

Tropylacetophenone. A solution of tropylium fluoroborate (0.62 g, 3.5 mmol) and acetophenone (0.35 g, 2.9 mmol) in 5 mL of methanol containing 5 drops of acetic acid was stirred for 3 h at room temperature. Water (10 mL) was added, and the mixture was extracted with three 25-mL portions of ether. The combined organic layers were washed with two 25-mL portions of water, dried, and concentrated. The resulting oil was passed through a short silica gel column by using methylene chloride as the eluant. Evaporation of the solvent left 0.57 g of an oil, which by NMR analysis contained 70% tropylacetophenone[5] and 30% unchanged acetophenone.

2-Tropylcyclohexanone. A solution of tropylium fluoroborate (0.50 g, 2.8 mmol) and cyclohexanone (0.30 g, 3.1 mmol) in 5 mL of methanol containing 5 drops of acetic acid was stirred for 2 h at room temperature. Chloroform and water were added, and each layer was washed five times with 20 mL of the other solvent. The combined organic layers were dried, concentrated, and passed through a short silica gel column with methylene chloride as the eluant. Evaporation of the solvent left 0.40 g (77%) of an oil. The proton NMR spectrum is identical with that previously reported for 2-tropylcyclohexanone,[5] but all attempts to crystallize the material failed until a sample was distilled. The distillate formed yellow plates, mp 59–60 °C (lit.[5] mp 60 °C).

2- and 6-Tropyl-2-methylcyclohexanone. A solution of tropylium fluoroborate (1.02 g, 5.73 mmol) and 2-methylcyclohexanone (0.58 g, 5.2 mmol) in 7 mL of methanol containing 10 drops of acetic acid was stirred for 1.5 h at room temperature. Water (20 mL) was added, and the mixture was extracted with three 10-mL portions of ether. The combined organic layers were washed with three 20-mL portions of water, dried, and concentrated. The residue was passed through a short silica gel column using methylene chloride as the eluant. Evaporation of the solvent left 0.90 g (91%) of a mixture of the two products as an amber oil. Analysis of the mixture by proton NMR spectroscopy revealed the two products[5] to be present, in this case, in a 1:1 ratio.

7-(Nitromethyl)cycloheptatriene. Tropylium fluoroborate (0.45 g, 2.5 mmol) was dissolved in 10 mL of nitromethane containing 1 mL of triethylamine. The solution was heated to 60 °C for 15 min, then allowed to cool, and added to 15 mL of water. The mixture was extracted twice with 10 mL of ether, and the combined organic layers were washed with 10 mL of 10% aqueous sulfuric acid solution, dried, and concentrated. The residue was passed through a short silica gel column by using chloroform as the eluant; evaporation of the solvent left 0.31 g (82% of a yellow oil. The proton NMR of this material is identical with that previously reported.[12]

Acknowledgment. We thank the Research Corporation for financial support of this research.

(12) Hoskinson, R. M. *Aust. J. Chem.* **1970**, *23*, 399.

Registry No. 1, 16000-59-2; 2, 101198-70-3; 3, 101198-69-0; tropylium fluoroborate, 27081-10-3; acetone, 67-64-1; 3-pentanone, 96-22-0; 2-butanone, 78-93-3; acetophenone, 98-86-2; cyclohexanone, 108-94-1; 2-methyl cyclohexanone, 583-60-8; nitromethane, 75-52-5; 2-tropyl-3-pentanone, 29647-94-7; tropylacetophenone, 29647-95-8; 2-tropylcyclohexanone, 29647-89-0; 6-tropyl-2-methylcyclohexanone, 29647-91-4; 2-tropyl-2-methylcyclohexanone, 29647-92-5; 7-(nitromethyl)cycloheptatriene, 25928-20-5.

An Efficient Formal Synthesis of *d,l*-Mesembrine via a β-(Methoxy(phenylthio)methylidene) Enolate Robinson Annulation Sequence

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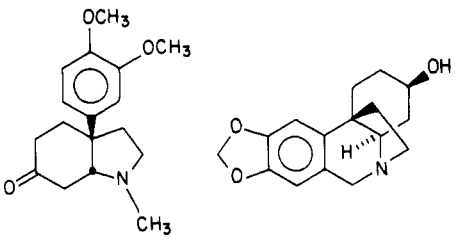
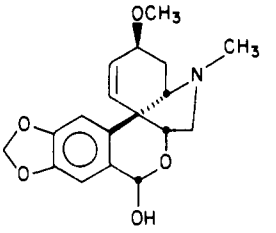
Alkaloids derived from various plants belonging to the family Aizoaceae[1] have remained attractive molecular targets for total synthesis.[2-7] The sceletium alkaloid mesembrine (**1**) can be regarded as a structural prototype for the more complex *cis*-3a-aryloctahydroindole alkaloids epielwesine (**2**)[8] and pretazettine (**3**). We envisaged the



1 **2**



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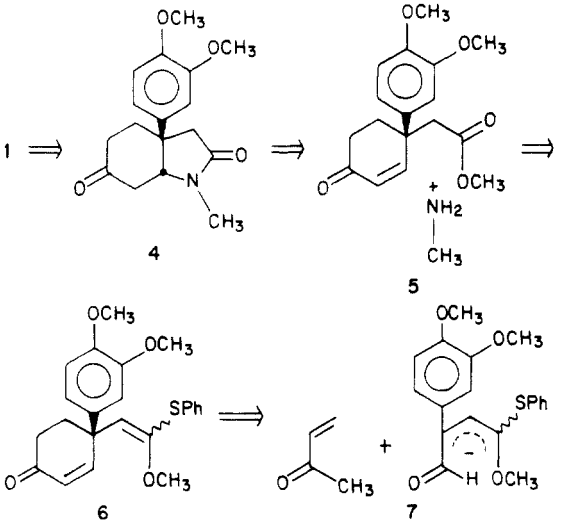
azabicyclic skeleton of mesembrine (**1**) as arising from the cyclocondensation of the keto ester **5** with methylamine. The keto ester **5**, in turn, was expected to be available from the ketene *O,S*-acetal **6** via selective hydrolysis (H^+, THF–H_2O). We have previously reported that the alkylation of β-(methoxy(phenylthio)methylidene) enolates (e.g., **7**) provide products derived from α-substitution.[9] In

(1) Capps, T. M.; Hargrave, K. D.; Jeffs, P. W.; and McPhail, A. T., *J. Chem. Soc., Perkin Trans. 2* **1977**, 1098 and references therein.
(2) An asymmetric synthesis of (+)-mesembrine has appeared recently: Meyers, A. I.; Hanreich, R.; Wanner, K. T. *J. Am. Chem. Soc.* **1985**, *107*, 7776.
(3) Keck, G. E.; Webb, R. R., II. *J. Org. Chem.* **1982**, *47*, 1302.
(4) Oh-ishi, T.; Kugita, H., *Chem. Pharm. Bull.* **1970**, *18*, 299.
(5) Jeffs, P. W.; Cortese, N. A.; Wolfram, J. *J. Org. Chem.* **1982**, *47*, 3881.
(6) Martin, S. F.; Puckett, T. A.; Colapret, J. A. *J. Org. Chem.* **1979**, *44*, 3391.
(7) Stevens, R. V.; Lesko, P. M.; LaPalme, R. *J. Org. Chem.* **1975**, *40*, 3495.
(8) Overman, L. E.; Burk, R. M. *Tetrahedron Lett.* **1984**, *25*, 5739.
(9) Hackett, S.; Livinghouse, T. *J. Chem. Soc., Chem. Commun.* **1986**, 75.

0022-3263/86/1951-1629$01.50/0

Scheme I



this note we describe an efficient formal synthesis of **1** which relies on this principle (Scheme I).

3-(Dimethylamino)-2-(3,4-dimethoxyphenyl)prop-2-en-1-al (**8**), the key starting material for this synthesis, was prepared as described previously[10] by the exhaustive formylation of 3,4-dimethoxyphenylacetic acid using $POCl_3$ in DMF. Exposure of **8** to [methoxy(phenylthio)-methyl]lithium (**9**) (−78 °C, 27 h) followed by hydrolysis of the resultant adduct (10% aqueous H_2SO_4, 0 °C) provided the enal **10** in 63% recrystallized yield. After a series of experimental trials, the following procedure was determined optimum for the Robinson annulation of **10**. Sequential treatment of a THF solution of **10** with methyl vinyl ketone (1.2 equiv) in the presence of DBN (0.2 equiv, 0 °C → room temperature, 24 h) followed by 0.3 N ethanolic NaOEt (0.5 equiv, reflux, 24 h) furnished the cyclohexenones **6** [*E*/*Z*: 10/1]. It is noteworthy that the use of KO-*t*-Bu as the base in either catalytic or stoichiometric quantities proved ineffective in the above Robinson annulation sequence. Direct subjection of the unpurified cyclohexenones **6** to acid-catalyzed hydrolysis [0.1 equiv of TsOH, THF–H_2O (10:1), reflux 24 h] provided the corresponding methyl ester **5** (91% overall from **10**). With a reliable supply of the key intermediate **5** in hand, we were suitably positioned to implement the crucial cyclocondensation reaction with methylamine. Exposure of **5** to 50 equiv of methylamine (THF, 80 °C, 10 h) followed directly by imine hydrolysis [THF–H_2O (10:1), 25 °C, 10 h] afforded 3a-(3,4-dimethoxyphenyl)octahydro-1-methyl-(3a*S*,*cis*)-6*H*-indole-2,6-dione (**4**) in 71% isolated yield. Since the bicyclic keto lactam **4** has previously been converted into *d*,*l*-mesembrine (**1**) via reduction ($LiAlH_4$) followed by oxidation ($H_2Cr_2O_7$)[5] or by protection ($HOCH_2CH_2OH$, H^+) followed by reduction ($LiAlH_4$) and deprotection,[3,4] the foregoing preparation of **4** constitutes a concise formal synthesis of this alkaloid.

The present formal synthesis of *d*,*l*-mesembrine (**1**) by way of the bicyclic keto lactam **4** is prominantly characterized by its brevity (three steps) as well as the ease of its experimental execution.

Experimental Section

General Methods. Melting points were determined on a electrothermal capillary melting point apparatus and are uncorrected. Infrared spectra were run on a Beckman Model 4250 infrared spectrometer. ^1H NMR spectra were obtained on a Varian HFT-80 and Nicolet NT-300 spectrometers. Microanalyses were performed at MHW Laboratories, Phoenix, AZ. Mass spectra were determined with a AEI MS-30 mass spectrometer at an ionizing voltage of 70 eV.

3-[Methoxy(phenylthio)methyl]-2-(3,4-dimethoxyphenyl)prop-2-en-1-al (10). A flame-dried, 100-mL, three-necked flask equipped with a magnetic stirring bar, low-temperature thermometer, nitrogen inlet adaptor, and rubber septum was charged with 1.97 g of methoxyphenylthiomethane (12.80 mmol) and 1.93 mL of TMEDA (12.80 mmol) in 25 mL of dry THF. The reaction flask was immersed in a dry ice–acetone bath and 8.29 mL of *sec*-BuLi (1.48 M in cyclohexane, 12.27 mmol) was then added so that the temperature remained below −70 °C. After being stirred at −78 °C for an additional 2.5 h, the solution was diluted with 50 mL of dry THF and then 1.93 g of the solid vinylogous amide **8** (8.2 mmol) was added in one portion without solvent. The reaction mixture was then stirred at −78 °C for an additional 27 h. After being warmed to room temperature, the solution was poured into 10% H_2SO_4 and was extracted 3 times with ether. The combined ether fractions were washed with saturated $NaHCO_3$, H_2O, and saturated brine and then dried over Na_2SO_4. Evaporation of the ether in vacuo left a solid which was recrystallized from 10% ethyl acetate–hexane to furnish 2.29 g (63%) of the enal **10** as a white solid: mp 101–103.5 °C; NMR ($CDCl_3$/Me_4Si) δ 3.51 (3 H, s, CH_3O), 3.86 (3 H, s, CH_3O), 3.91 (3 H, s, CH_3O), 5.31 (1 H, d, J = 9.2, CH), 6.37 (1 H, d, J = 9.2, vinyl CH), 6.86 (3 H, complex m, aromatic CH), 7.34 (3 H, complex m, aromatic CH), 7.48 (2 H, complex m, aromatic CH), 9.49 (1 H, s, CHO); IR (CCl_4) cm^{-1} 3100–2700 (aliphatic envelope), 1700 (C=O). Anal. Calcd for $C_{19}H_{20}O_4S$: C, 66.24; H, 5.86. Found: C, 66.14; H, 6.05.

4-(Carbomethoxymethyl)-4-(3,4-dimethoxyphenyl)cyclohex-2-en-1-one (5). A 100-mL, round-bottomed flask equipped with a serum cap, nitrogen inlet adaptor, and magnetic stirring bar was charged with 0.716 g of the enal **10** (2.08 mmol) and 25 mL of dry THF. The resultant solution was cooled to −30 °C and 0.051 mL of DBN (0.42 mmol) was added. The reaction mixture was then treated with 0.21 mL of methyl vinyl ketone (2.50 mmol) which had been distilled and stored over 4-Å molecular sieves prior to use. After the addition of the methyl vinyl ketone, the solution was allowed to slowly warm to room temperature and then stirred for an additional 10 h. To this solution was added 34.7 mL of sodium ethoxide in ethanol (0.03 N, 1.04 mmol), and the mixture was heated at reflux for 24 h. The reaction mixture was poured into saturated aqueous NH_4Cl and extracted 3 times with ether.

(10) Coppola, G. M.; Hardtmann, G. E.; Huegi, B. S. *Heterocycles* **1974**, *11*, 51.

The combined ether extracts were subsequently washed with H_2O and saturated brine and finally dried over Na_2SO_4. The solvents were evaporated in vacuo to provide the crude ketene *O,S*-acetals **6** as a mixture of *E* and *Z* isomers. The crude ketene *O,S*-acetals obtained in this manner were dissolved in 40 mL of (9:1) THF–H_2O and 42.1 mg of *p*-TsOH (0.221 mmol) was then added. The reaction mixture was heated at reflux for 6 h, diluted with ether, and successively washed with 10% aqueous $NaHCO_3$, H_2O, and saturated brine. The organic layer was then dried over Na_2SO_4 and the solvents were evaporated in vacuo. The crude product was subsequently purified by chromatography on silica gel (40% ethyl acetate–hexane for elution) to afford 0.576 g, 91% of the keto ester **5**: ^{13}C NMR δ 198.89, 170.79, 154.47, 148.95, 148.08, 134.41, 129.52, 118.98, 110.95, 109.68, 56.00, 55.89, 51.75, 45.80, 42.59, 36.46, 34.45; ^1H NMR ($CDCl_3/Me_4Si$) δ 2.29 (4 H, complex m, CH_2), 2.83 (1 H, d, J = 15, CH_2), 2.93 (1 H, d, J = 15, CH_2), 3.57 (3 H, s, CH_3O), 3.87 (6 H, s, CH_3O), 6.21 (1 H, d, J = 10, vinyl CH), 6.82 (3 H, m, aromatic CH), 7.43 (1 H, d, J = 10, vinyl CH); IR (film) cm^{-1} 3100–2720 (CH envelope), 1740 (C=O), 1680 (C=O); high resolution mass spectrum, calcd for $C_{17}H_{20}O_5$ M^+ = 304.1309, found M^+ = 304.1309. Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 67.06; H, 6.70.

3a-(3,4-Dimethoxyphenyl)octahydro-1-methyl-(3a*S*,*cis*)-6*H*-indole-2,6-dione (4). A 10-mL, resealable pressure tube equipped with a magnetic stirring bar was charged with 41 mg of the keto ester **5** (0.2 mmol). A solution of 310 mg of methylamine (10 mmol) in 5 mL of THF was added and the pressure tube was sealed. The reaction mixture was stirred at 80 °C for 10 h and the solvents were then removed in vacuo. The residue was subsequently dissolved in 10 mL of THF–H_2O (9:1) and the resultant solution was stirred at 25 °C for 10 h. After evaporation of the solvents in vacuo, the crude product was purified by chromatography on silica gel (15% isopropyl alcohol–chloroform for elution) to provide 29 mg (71%) of the bicyclic keto lactam **4**: ^1H NMR ($CDCl_3/Me_4Si$) δ 2.17–2.41 (4 H, complex m, CH_2), 2.73 (1 H, d, J = 16, CH_2), 2.80 (2 H, m, CH_2), 2.86 (3 H, s, CH_3N), 2.89 (1 H, d, J = 16, CH_2), 3.89 (3 H, s, CH_3O), 3.90 (3 H, s, CH_3O), 4.33 (1 H, dd, J = 4.3, CHN), 6.86 (1 H, apparent s, aromatic CH), 7.27 (2 H, apparent s, aromatic CH); IR (film) cm^{-1} 3100–2780 (CH envelope), 1720 (C=O), 1680 (C=O); high resolution mass spectrum, calcd for $C_{17}H_{21}NO_4$ M^+ = 303.1477, found M^+ = 303.1467. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.13; H, 7.17; N, 4.40.

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Synthesis of 10-(Hydroxymethyl)-7,12-dimethylbenz[*a*]anthracene[1]

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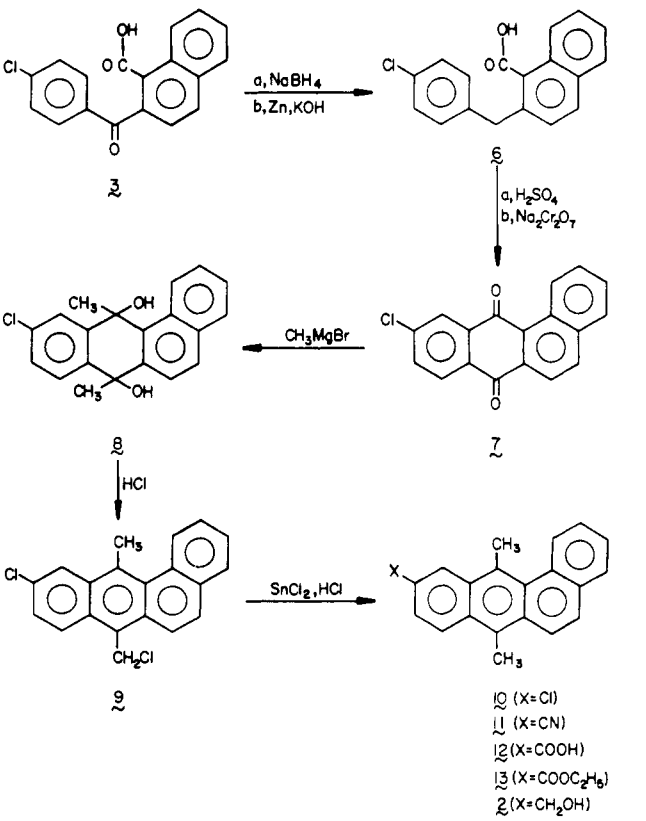
Of all the derivatives of 7,12-dimethylbenz[*a*]anthracene, **1**, prepared for study of their carcinogenic activity, no water soluble derivative is known. As a possible precursor the 10-hydroxymethyl substituent was deemed appropriate since the introduction of such a group at the 10-position would not be expected to affect the carcinogenic activity of **1** due to polar or steric effects. Although we have as yet not successfully prepared a water-soluble carcinogen, we record here the synthesis of 10-(hydroxymethyl)-7,12-dimethylbenz[*a*]anthracene, **2**.

Scheme I



The Friedel–Craft condensation of excess chlorobenzene with 1,2-naphthalic anhydride yielded 58% of a mixture of 2-(4-chlorobenzoyl)-1-naphthoic acid, **3**, and 1-(4-chlorobenzoyl)-2-naphthoic acid, **4**. Rather than separate pure **3** by recrystallization, as had been done previously with a similar mixture,[4] the mixture of **3** and **4** was isomerized mainly to **3** in 84% yield by treatment with sulfuric acid at 120–125 °C for 15 min. When such a treatment was run at 70–75 °C the ratio of **3** and **4** was unchanged.[5] The remaining steps to form **2** are shown in Scheme I.

Experimental Section[7]

2-(4-Chlorobenzoyl)-1-naphthoic Acid, 3. To a stirred mixture of 79.2 g of 1,2-naphthalic anhydride[8] in 500 mL of chlorobenzene was added 117.6 g of anhydrous $AlCl_3$ at 25–30 °C. The temperature was raised to 70–75 °C for 4 h and then kept at room temperature for 24 h. After pouring the mixture on ice and 1.6 L of 3 N HCl, steam distillation removed the chlorobenzene. The solid thus obtained was dissolved in 2.4 L of 10% K_2CO_3 and steamed. On cooling filtration removed a solid which crystallized from benzene as colorless prisms, mp 166–167 °C, and

(1) This work was supported by Grant 5 R01 CA07394 from the National Cancer Institute, DHEW.
(2) Postdoctoral Research Associate. Present address: Petrolite Corporation, St. Louis, MO 63119.
(3) Postdoctoral Research Associate.
(4) Newman, M. S.; Orchin, M. *J. Am. Chem. Soc.* **1938**, *60*, 586.
(5) For an explanation of this type of rearrangement, see: Newman, M. S.; Ihrman, K. G. *J. Am. Chem. Soc.* **1958**, *80*, 3652.
(6) Newman, M. S.; Sankaran, V. *Tetrahedron Lett.* **1977**, 2556.
(7) Compounds **2**, **5**, **6**, and **8–13** had IR and ^1H NMR spectra mass spectra consistent with the postulated structures. Satisfactory analyses were performed by the M.H.W. Laboratories. We thank Dr. Charles D. Cottrell and Richard Weisenberger of the OSU Chemical Instrument Center for NMR and mass spectra. The term "worked up as usual" means that an ether–benzene solution of the product was washed with dilute acid and/or base and saturated NaCl solution and filtered through a cone of dry $MgSO_4$. The solvent was then removed to give crude product. All melting points are uncorrected.
(8) For a convenient synthesis of 1,2-naphthalic anhydride, see: Newman, M. S.; Dhawan, B.; Hashem, M. M.; Khanna, V. K.; Springer, J. M. *J. Org. Chem.* **1976**, *41*, 3925.

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