[1S*,2S*,(S)R*]- and [1R*,2S*,(S)R*]-4,4-Dimethyl-2-(phenylsulfinyl)cyclohexanol (23[a] and 23[e]). Reduction of compound **17** following methods B, D, E, and G afforded a mixture of diastereomers **23[a]** and **23[e]** (Table I). Method A yielded pure **23[a]**, mp 154-155 °C (from hexane-ethyl acetate): MS, *m/z* (rel intensity) 252 (1) M^+, 127 (10), 126 (100), 109 (20), 78 (18); ^1H NMR δ 7.65-7.42 (m, 5 H), 4.60-4.35 (m, 1 H), 3.87 (dt, 1 H, *J* = 10.7 and 5.1 Hz), 2.78 (ddd, 1 H, *J* = 13.0, 10.7, and 3.8 Hz), 1.95 (ddd, 1 H, *J* = 13.2, 5.1, and 3.8 Hz), 1.66 (ddd, 1 H, *J* = 13.2, 10.7, and 4.1 Hz), 1.40-1.10 (m, 3 H), 0.94 (ddd, 1 H, *J* = 13.2, 3.8, and 2.7 Hz), 0.86 (s, 3 H), 0.80 (s, 3 H); IR (Nujol) 3220, 1012 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_2S$: C, 66.66; H, 7.94, S, 12.70. Found: C, 66.79; H, 8.24; S, 13.10. Fractional crystallization (hexane-acetone) of the mixture obtained by method E afforded pure **23[e]**, mp 150-151 °C: MS, *m/z* (rel intensity) 252 (1) M^+, 126 (100), 109 (4), 78 (3); ^1H NMR δ 7.70-7.45 (m, 5 H), 4.32 (c, 1 H, *J* = 2.2 Hz), 3.20 (m, 1 H), 2.63 (ddd, 1 H, *J* = 13.3, 3.8, and 2.2 Hz), 1.93 (t, 1 H, *J* = 13.3 Hz), 1.84-1.50 (m, 3 H), 1.30-1.00 (m, 2 H), 0.96 (s, 3 H), 0.78 (s, 3 H); IR (Nujol) 3339, 1012 cm^{-1}.

[1S*,2S*,(S)S*]- and [1R*,2S*,(S)S*]-4,4-Dimethyl-2-(phenylsulfinyl)cyclohexanol (24[a] and 24[e]). Reduction of compound **18** following methods B, D, E, and G yielded a mixture of diastereomers **24[a]** and **24[e]** (Table III). Crystallization of the 95:5 mixture obtained with $LiAlH_4$ (method E) from hexane-acetone afforded pure diastereomer **24[a]** mp 172-173 °C: MS, *m/z* (rel intensity) 252 (1) M^+, 126 (100), 109 (22), 78 (32), 67 (22); ^1H NMR δ 7.80-7.50 (m, 5 H), 4.40 (br s, 1 H), 4.09 (dt, 1 H, *J* = 10.0 and 5.2 Hz), 2.93 (ddd, 1 H, *J* = 12.9, 10.0, and 4.6 Hz), 1.98 (m, 1 H), 1.80-0.92 (m, 5 H), 0.91 (s, 3 H), 0.78 (s, 3 H); IR (Nujol) 3388, 1015 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_2S$: C, 66.66; H, 7.94; S, 12.70. Found: C, 66.57; H, 8.03; S, 12.86. Pure diastereomer **24[e]** was obtained by following method B, mp 167-168 °C (from hexane-ethyl acetate); MS, *m/z* (rel intensity) 252 (1) M^+, 126 (100), 109 (23), 78 (31), 67 (23); ^1H NMR δ 7.80-7.35 (m, 5 H), 4.26 (m, 1 H), 4.12 (br s, 1 H), 2.44 (ddd, 1 H, *J* = 13.9, 3.7, and 2.2 Hz), 2.07 (t, 1 H, *J* = 13.9 Hz), 1.76-1.58 (m, 2 H), 1.36 (ddd, 1 H, *J* = 13.9, 3.7, and 2.7 Hz), 1.27-1.16 (m, 1 H), 1.08-0.97 (m, 1 H), 0.93 (s, 3 H), 0.75 (s, 3 H); IR (Nujol) 3304, 1019 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_2S$: C, 66.66; H, 7.94, S, 12.70. Found: C, 66.60; H, 7.84; S, 12.97.

[1S*,2R*,4S*,(S)R*]- and [1R*,2R*,4S*,(S)R*]-4-(1,1-Dimethylethyl)-2-(methylsulfinyl)cyclohexanol (25[a] and 25[e]). Reduction of compound **19** following method A yielded mixtures of diastereomers **25[a]** and **25[b]** (Table III). Method B afforded pure **25[a]**, mp 182-183 °C (from hexane-acetone): MS, *m/z* (rel intensity) 218 (4) M^+, 109 (4), 81 (31), 57 (100); ^1H NMR δ 4.02 (td, 1 H, *J* = 10.7 and 4.8 Hz), 3.70 (br s, 1 H), 3.22 (c, 1 H, *J* = 4.8 Hz), 2.79 (s, 3 H), 2.45 (m, 1 H), 2.00-1.70 (m, 3 H), 1.52-1.05 (m, 3 H), 0.88 (s, 9 H); IR (KBr) 3340, 1100, 1060, 1015 cm^{-1}. Column chromatography of the mixture obtained by method A (eluent acetone) afforded pure **25[e]** as a white solid, mp 109-110 °C (from hexane-acetone): MS, *m/z* (rel intensity) 218 (1) M^+, 137 (24), 109 (3), 95 (15), 81 (54), 57 (100); ^1H NMR δ 3.88 (c, 1 H, *J* = 3.3 Hz), 3.15 (br s, 1 H), 2.95 (m, 1 H), 2.63 (s, 3 H), 2.23 (m, 1 H), 1.93-1.30 (m, 6 H), 0.90 (s, 9 H); IR (KBr) 3400, 1035, 1025, 1005 cm^{-1}.

[1S*,2R*,4S*,(S)S*]- and [1R*,2R*,4S*,(S)S*]-4-(1,1-Dimethylethyl)-2-(methylsulfinyl)cyclohexanol (26[a] and 26[e]). Reduction of a 33:7:60 mixture of compounds **19**, **20**, and *m*-chlorobenzoic acid following method A afforded a 66:8:20:6 mixture of **25[a]**/**26[a]**/**25[e]**/**26[e]** and the acid (**26[a]**/**26[e]** ratio: 57:43, see Table III), which was chromatographed (eluent acetone) to give pure **25[a]** and **25[e]**. The minor diastereomers could not be isolated pure and **26[a]** was characterized in a 84:16 mixture of **25[a]** and **26[a]**: MS, *m/z* (rel intensity) 218 (2) M^+, 95 (10), 81 (52), 57 (100); ^1H NMR δ 4.02 (td, 1 H, *J* = 10.7 and 4.8 Hz), 3.32 (dc, 1 H, *J* = 3.6 and 1.8 Hz), 2.72 (s, 3 H), 2.20-1.05 (m, 8 H), 0.85 (m, 9 H); IR (KBr) 3340, 1100, 1080, 1060, 1010 cm^{-1}. Diastereomer **26[e]** was identified in a 79:21 mixture of **26[e]** and **25[e]**: MS, *m/z* (rel intensity) 218 (3), 137 (14), 95 (7), 81 (53), 57 (100); ^1H NMR δ 4.48 (c, 1 H, *J* = 3.4 Hz), 2.95 (m, 1 H), 2.64 (s, 3 H), 2.00-1.00 (m, 8 H), 0.86 (s, 9 H); IR (KBr) 3300, 1370, 1110, 1100, 1020 cm^{-1}.

Acknowledgment. We thank Dirección General de Investigación Científica y Técnica (Grant PB86-0120) and Asociación Hispano-Francesa (Grant 45/235 and Action Integrée no. 226) for financial support.

Registry No. **1**, 52154-24-2; **2**, 124992-49-0; **3**, 124992-50-3; **4**, 124992-51-4; **5**, 124992-52-5; **6α**, 39201-99-5; **6β**, 39201-98-4; **7α**, 94661-72-0; **7β**, 94661-73-1; **8α**, 124733-62-6; **8β**, 124733-63-7; **9α**, 125074-79-5; **9β**, 125074-87-5; **10α**, 125074-80-8; **10β**, 125074-88-6; **11**, 110452-14-7; **12**, 124992-53-6; **14**, 124992-54-7; **15**, 124992-55-8; **16**, 124992-56-9; **17**, 124992-57-0; **18**, 124992-58-1; **19**, 125074-81-9; **20**, 125074-82-0; **21[a]**, 125074-83-1; **21[e]**, 125074-89-7; **22[a]**, 125074-84-2; **22[e]**, 125074-90-0; **23[a]**, 124992-59-2; **23[e]**, 125074-91-1; **24[a]**, 125074-85-3; **24[e]**, 125074-92-2; **25[a]**, 124992-60-5; **25[e]**, 125074-93-3; **26[a]**, 125074-86-4; **26[e]**, 125074-94-4; (*R*)-(+)-4-$MeC_6H_4S(O)Me$, 1519-39-7; PhSSPh, 882-33-7; ethyl 2-pyridinecarboxylate, 2524-52-9; ethyl 4-pyridinecarboxylate, 1570-45-2; 4,4-dimethylcyclohexanone, 4255-62-3.

Supplementary Material Available: Listing of ^{13}C NMR spectral data of all studied compounds (4 pages). Ordering information is given on any current masthead page.

Asymmetric Total Syntheses of Elaeokanines A and B via α-Sulfinyl Ketimine[1]

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Received September 29, 1989

α-Lithiated (+)-(*R*)-4,5-dihydro-2-[[(4-methylphenyl)sulfinyl]methyl]-3*H*-pyrrole (**4**) underwent annulation with 1,3-diiodopropane to give (-)-(SS)-1,2,3,5,6,7-hexahydro-8-[(4-methylphenyl)sulfinyl]indolizine (**6**), which was converted into (-)-elaeokanine B (three steps) and (+)-elaeokanine A (four steps).

Introduction

The in-situ 1,4-addition/ring closure reactions of chiral α-sulfinyl ketimine anions[3] occur in useful yield and offer a unique, convenient route for the construction of chiral indolizidine alkaloids. Beside 1,4-addition, α-sulfinyl ketimine anions also undergo annulation with 1,3-diiodopropane;[4] the resulting cyclic chiral β-sulfinyl enamines can be transformed into various indolizidine alkaloids such

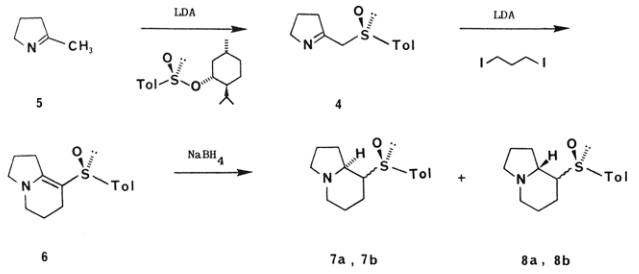
† Fellow of the Alfred P. Sloan Foundation, 1989-1991.

(1) Presented at the 198th National Meeting of the American Chemical Society, Miami Beach, FL, September 10-15, 1989. Poster ORGN 9.

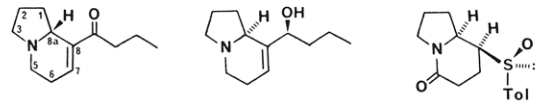
(2) Author to whom correspondence concerning the X-ray crystal structure determination should be addressed: Department of Geology, Southern Illinois University at Carbondale, Carbondale, IL 62901.

0022-3263/90/1955-2128$02.50/0

Scheme I



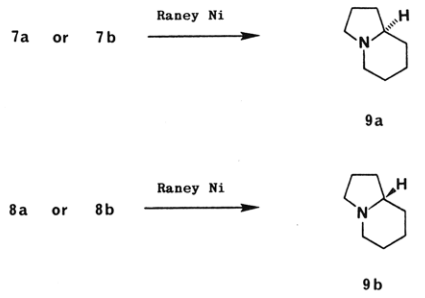
as elaeokanine alkaloids.[5] Along with other elaeocarpus alkaloids, (+)-elaeokanine A [(+)-**1**] and (−)-elaeokanine B [(−)-**2**][5a,b] were isolated from the extraction of the dried leaves of *Elaeocarpus kaniensis* Schltr., a large rain-forest tree occurring in New Guinea. Although total syntheses of (±)-elaeokanines have been reported,[5c-l] the absolute configurations remained unknown. The present asymmetric syntheses and the X-ray diffraction analysis of the synthetic intermediate establish the absolute configurations of (+)-elaeokanine A [(+)-**1**] and (−)-elaeokanine B [(−)-**2**].



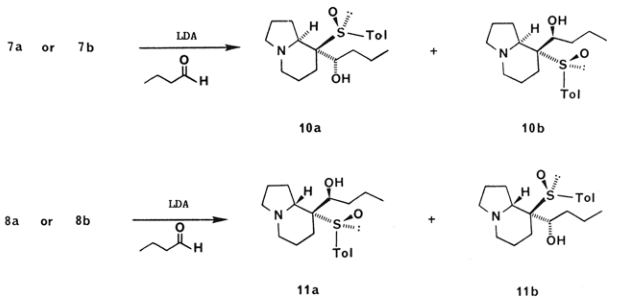
Results and Discussion

In synthesizing the elaeokanines we initially attempted to reduce the amido carbonyl of **3**[3] (derived from 1,4-addition of α-lithiated ketimine **4** to methyl acrylate followed by stereoselective reduction of the resulting enamide with $NaCNBH_3$) without affecting the sulfinyl group or its reduced form, the sulfide. All attempts, including the use of lithium aluminum hydride in THF and borane in THF, failed. An alternative route, annulation with 1,3-dihalopropanes, was investigated. (+)-(*R*)-Sulfinyl ketimine **4**[6] was prepared[3] from the reaction of α-lithiated 3,4-dihydro-5-methyl-2*H*-pyrrole (**5**)[7] with (−)-(*S*)-**l**-menthyl *p*-toluenesulfinate[8] (92% yield) (Scheme I). Treatment of (+)-**4** with 1.2 equiv of lithium diisopropylamide (LDA) in THF followed by 1.1 equiv of 1,3-diiodopropane gave

Scheme II



Scheme III



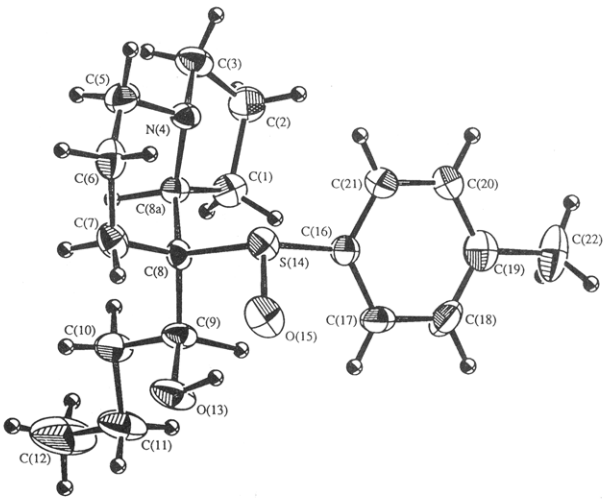


Figure 1. ORTEP drawing of X-ray crystallographically determined structure of **10a**. Carbon, nitrogen, oxygen, and sulfur atoms are drawn as 50% ellipsoids. H atoms shown with isotropic *B*'s of 1.0 Å^2.

β-enamino sulfoxide **6** in 61% yield; with 1,3-dibromopropane the yield was 32%.

Various hydridic reducing agents, such as $NaCNBH_3$ in AcOH, $ZnCl_2$–$NaCNBH_3$ (1:2) in MeOH, $Zn(BH_4)_2$ in THF, and $NaBH_4$ in MeOH, have been studied for the reduction of the cyclic alkenyl group of enamine **6**. All provided mixtures of sulfoxides **7a**, **7b**, **8a**, and **8b** in various ratios, along with recovered **6**. Of these reagents, $NaBH_4$ afforded the best yield and selectivity; e.g., treatment of **6** with 6 equiv of $NaBH_4$ in MeOH at 15–20 °C gave an 81% yield of **7a**, **7b**, **8a**, and **8b** in a ratio of 4:4:1:1 and 15% recovery of substrate. All of these products were separated by column chromatography. The stereochemistry at C-8a of each of these sulfoxides was determined by desulfurization of each isomer with W-2 Raney nickel[9] in ethanol at 25 °C for 2 h (90–92% yield), which gave either (−)-(*R*)-indolizidine (**9a**)[10] or (+)-(*S*)-

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(6) All enantiomers are depicted with the actual absolute stereochemistry.

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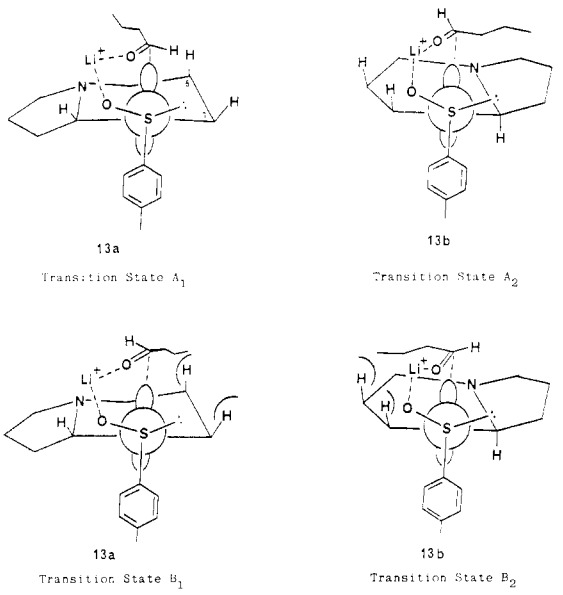
Scheme IV

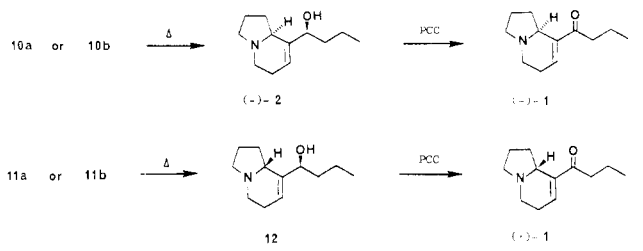


indolizidine (**9b**)[3] (Scheme II). The stereochemistry at C-8 was not determined.

Butyrylation of **7a** and **7b** individually with 1.2 equiv of LDA in THF at −78 °C for 1 h followed by 1.2 equiv of butyraldehyde furnished 76% yield of alcohols **10a** and **10b** in a ratio of 2:1 in each case (Scheme III). Single-crystal X-ray analysis of alcohol **10a** (Figure 1) firmly established the relative stereochemistry at S, C-8a, C-8, and C-1′. The crystals are monoclinic, space group $P2_1$, with a = 9.512 (7), b = 7.266 (3), and c = 13.571 (3) Å, β = 91.60 (3)°, and Z = 2. Full-matrix least-squares refinement of 207 variables including all non-H positional and anisotropic thermal parameters gave a final R of 0.043 and R_w of 0.051. Hydrogen atoms were included in the model but were not refined. The stereochemistry of diastereomer **10b** was established through its conversion into (−)-elaeokanine B [(−)-**2**] (vide infra). Under the same conditions, sulfoxides **8a** and **8b** likewise provided a 75–78% yield of alcohols **11a** and **11b** in a ratio of 2:1 in each case. The stereochemistry at C-8 of **11a** and **11b** was assumed from the structure of **10a** and the suggested mechanism of the stereoselective addition of these α-sulfinyl carbanions to butyraldehyde (vide infra). The stereochemistry at C-1′ was established from the transformation into **12**, the diastereomer of (+)-**2**. In all four butyrylation reactions, only C-1′-(*S*) configuration products were obtained.

Sulfoxides **7a** and **7b** generate the same sp^2-p hybridized α-sulfinyl carbanion[11] that might exist as conformers **13a** and **13b**. Scheme IV illustrates the suggested transition states of the stereoselective addition of conformeric anions to butyraldehyde. Transition state A_1 appears to be the lower energy one and leads to **10a**; transition state A_2 leads to **10b**. Greater repulsion between the C-6 and C-7 hydrogens of **13** and the propyl group of butyraldehyde in transition states B than between these hydrogens and the formyl hydrogen of butyraldehyde in transition states A accounts for the absence of the C-1′-(*R*) product. Chelation of the Li^+ ion and the sulfinyl and carbonyl oxygens is in line with the results of Marquet and coworkers.[11,12]

Scheme V



Dehydrosulfinylation of **10a** and **10b** separately in refluxing toluene for 3 h furnished (−)-elaeokanine B [(−)-**2**][13] in 92% and 90% yield, respectively; $[\alpha]^{22}_D$ −76° (*c* 0.4 in $CHCl_3$) (lit.[5a] $[\alpha]_D$ −76° in $CHCl_3$) (Scheme V). Oxidation of (−)-**2** with pyridinium chlorochromate (PCC)[14] in CH_2Cl_2 gave the unnatural antipode (−)-elaeokanine A [(−)-**1**][13] in 89% yield; $[\alpha]^{22}_D$ −49° (*c* 0.5 in $CHCl_3$).

Under the same reaction conditions, dehydrosulfinylation of **11a** and **11b** gave (+)-**12** in 90% and 83% yield, respectively; $[\alpha]^{22}_D$ +22° (*c* 0.4 in $CHCl_3$). Contrary to the literature,[5d] the natural (−)-elaeokanine B [(−)-**2**] is a single enantiomer, and the NMR spectra (^1H and ^{13}C) of **2** and **12** are different. Oxidation of (+)-**12** with PCC afforded (+)-elaeokanine A [(+)-**1**] in 93% yield; $[\alpha]^{22}_D$ +49° (*c* 0.5 in $CHCl_3$) (lit.[5a] $[\alpha]_D$ +13° in $CHCl_3$).

Conclusions

The first asymmetric total syntheses of (+)-elaeokanine A and (−)-elaeokanine B have been described. The absolute configurations of these alkaloids were established. The synthetic methodology developed to prepare functionalized chiral indolizidines is facile and general and is applicable to the construction of (+)-castanospermine,[15] (+)-swainsonine,[16] (+)-pumiliotoxin 251D,[17] and (+)-gephyrotoxin,[18] which are the subjects of forthcoming papers.

Experimental Section

General Methods. ^1H and ^{13}C NMR spectra were obtained at 400 and 100 MHz, respectively. Infrared spectral data are reported in wavenumbers (cm^{-1}). Davisil silica gel, grade 643 (200–425 mesh), was used for the flash chromatographic separation. Single-crystal X-ray structure determination was performed on a Rigaku AFC5S diffractometer, graphite-monochromated Mo Kα radiation; X-ray structure determination was accomplished by using the TEXSAN crystal-structure-analysis package (Molecular Structure Corporation, 1985).

3,4-Dihydro-5-methyl-2*H*-pyrrole (5):[7] IR (neat) 2940, 2850, 1630 (s, C=N), 1420, 1360, 1305, 1030, 1005, 930; ^1H NMR ($CDCl_3$) δ 3.8 (m, 2 H, CH_2N), 2.46 (t, J = 8 Hz, 2 H, CH_2), 2.03 (s, 3 H, CH_3), 1.87 (quintet, J = 7.4 Hz, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 174.91 (s, C=N), 60.65 (t, CN), 38.49 (t), 22.63 (t), 19.33 (q); MS, EI m/z 83 (M^+).

(+)-(*R*)-4,5-Dihydro-2-[[(4-methylphenyl)sulfinyl]-methyl]-3*H*-pyrrole (4). To a cold (−25 °C) solution of 0.0475

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mol of lithium diisopropylamide (LDA) in 15 mL of THF under argon was added 3.65 g (0.044 mol) of **5** in 15 mL of THF. The solution was stirred at 0 °C for 15 min and then cooled to −50 °C. To this solution was added a solution of 6.35 g (0.0216 mol) of (−)-(*S*)-*l*-menthyl *p*-toluenesulfinate[8] in 20 mL of THF via cannula. After the yellow solution was stirred at −50 °C for 1 h, it was poured into 120 mL of H_2O and extracted three times with CH_2Cl_2 (200 mL each). The combined CH_2Cl_2 extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel, using mixtures of hexane, ethyl acetate, and methanol as eluant to give 4.39 g (92% yield) of **4**: mp 88–89 °C; $[\alpha]^{22}_D$ +146° (*c* 0.645 in CH_2Cl_2); IR (CH_2Cl_2) 3040, 2950, 2860, 1590 (s, C=N), 1480, 1390, 1070, 1040, 1010, 800; ^1H NMR ($CDCl_3$) δ 7.53 (d, *J* = 8 Hz, 2 H, ortho H), 7.32 (d, *J* = 8 Hz, 2 H, meta H), 3.85 (d, *J* = 13 Hz, 1 H, CHS), 3.84 (m, 2 H, CH_2N), 3.73 (d, *J* = 13 Hz, 1 H, CHS), 2.63–2.40 (m, 2 H, CH_2), 2.42 (s, 3 H, CH_3), 1.87 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 169.4 (s, CN), 141.86 (s, Ar), 140.3 (s, Ar), 129.92 (d, 2 C, Ar), 124.09 (d, 2 C, Ar), 61.28 (t), 60.94 (t), 38.79 (t), 22.57 (t), 21.38 (q); MS, EI *m/z* 221 (M^+), CI 222 (M + 1). Anal. Calcd for $C_{12}H_{15}NOS$: C, 65.12; H, 6.83; N, 6.33; S, 14.49. Found: C, 65.33; H, 6.69; N, 6.57; S, 14.51.

(−)-(*S*)-1,2,3,5,6,7-Hexahydro-8-[(4-methylphenyl)sulfinyl]indolizine (6). To a cold (−78 °C) solution of 4.4 g (0.02 mol) of ketimine **4** in 300 mL of THF under argon was added a cold (−25 °C) solution of 0.024 mol of LDA in 100 mL of THF via cannula. After the brown solution was stirred at −78 °C for 1 h, 2.8 mL (0.024 mol) of 1,3-diiodopropane was added. The solution was stirred at −78 °C for 2 h and −40 °C for 1 h, and 300 mL of THF was added. After being stirred at 25 °C for 18 h, the solution was poured into 300 mL of water and extracted three times with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel, using a 19:1 to 9:1 (gradient) mixture of ethyl acetate and methanol as eluant to give 0.8 g (18% recovery) of **4** and 3.184 g (61% yield) of **6**: mp 105–107 °C; $[\alpha]^{22}_D$ −82° (*c* 1.13, CH_2Cl_2); IR (CH_2Cl_2) 3020, 2920, 2840, 1600 (s), 1480, 1410, 1340, 1260, 1085, 1000; ^1H NMR δ 7.42 (d, *J* = 8 Hz, 2 H, Ar), 7.26 (d, *J* = 8 Hz, 2 H, Ar), 3.31 (m, 2 H, CH_2N), 3.2 (m, 1 H, CHN), 3.1 (m, 1 H, CHN), 2.9 (dt, *J* = 15 Hz, 8 Hz, 1 H), 2.38 (s, 3 H, *p*-Me), 2.31 (dt, *J* = 13 Hz, 6 Hz, 1 H), 2.01 (quintet, *J* = 7 Hz, 2 H), 1.82 (m, 1 H), 1.73 (m, 2 H), 1.6 (m, 1 H); ^{13}C NMR δ 155.07 (s, C=), 141.3 (s, Ar), 139.06 (s, Ar), 129.22 (d, 2 C, Ar), 124.98 (d, 2 C, Ar), 96.19 (s, C=), 52.69 (t), 44.56 (t), 29.35 (t), 21.69 (t), 21.28 (t), 21.17 (q), 16.42 (t); MS, EI *m/z* 261 (M^+), CI 262 (M + 1). Anal. Calcd for $C_{15}H_{19}NOS$: C, 68.93; H, 7.33; N, 5.36; S, 12.27. Found: C, 68.77; H, 7.51; N, 5.13; S, 12.05.

(8a*S*,S*R*)- and (8a*R*,S*R*)-1,2,3,5,6,7,8,8a-Octahydro-8-[(4-methylphenyl)sulfinyl]indolizine (7a,b and 8a,b). To a solution of 0.8 g (3.07 mmol) of **6** in 16 mL of MeOH at 15–20 °C under argon was added 0.707 g (18.6 mmol) of $NaBH_4$ in small portions over 15 min. The mixture was stirred for 1 h, diluted with 20 mL of 1 N NaOH and 100 mL of H_2O, and extracted three times with CH_2Cl_2 (100 mL each). The combined CH_2Cl_2 layers were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel, using mixtures of hexanes, ether, and methanol (containing 5% of NH_4OH) as eluant to give 0.266 g (33% yield) of **7a**, 0.258 g (32% yield) of **7b**, 0.064 g (8% yield) of **8a**, 0.063 g (8% yield) of **8b**, and 0.12 g (15% recovery) of **6**.

7a: an oil, $[\alpha]^{22}_D$ +30.6° (*c* 0.43 in CH_2Cl_2); ^1H NMR δ 7.52 (d, *J* = 8 Hz, 2 H, Ar), 7.34 (d, *J* = 8 Hz, 2 H, Ar), 3.1 (m, 2 H), 2.8 (m, 1 H), 2.46 (s, 3 H, *p*-Me), 2.12 (m, 1 H), 2.0–1.6 (m, 10 H); ^{13}C NMR δ 141.73 (s, Ar), 138.03 (s, Ar), 129.64 (d, 2 C, Ar), 125.49 (d, 2 C, Ar), 66.26 (d), 64 (t), 53.3 (t), 51.77 (d), 29.49 (t), 24.9 (t), 23.31 (t), 21.43 (t), 20.99 (q); MS, EI *m/z* 263 (M^+). Anal. Calcd for $C_{15}H_{21}NOS$: C, 68.40; H, 8.04. Found: C, 68.18; H, 8.29.

7b: an oil, $[\alpha]^{22}_D$ +115° (*c* 1.1 in CH_2Cl_2); ^1H NMR δ 7.55 (d, *J* = 8 Hz, 2 H, Ar), 7.3 (d, *J* = 8 Hz, 2 H, Ar), 3.1 (t, *J* = 9 Hz, 1 H, CHN), 3.05 (m, 2 H), 2.48 (m, 1 H), 2.41 (s, 3 H, *p*-Me), 2.3 (m, 2 H), 2.2 (m, 2 H), 1.95 (m, 2 H), 1.7 (m, 2 H), 1.57 (m, 2 H); ^{13}C NMR δ 142.52 (s, Ar), 141.05 (s, Ar), 129.78 (d, 2 C, Ar), 124.73 (d, 2 C, Ar), 63.92 (s), 63.46 (t), 54.41 (t), 52.13 (s), 25.89 (t), 22.83 (t), 21.94 (t), 21.3 (q), 20.5 (t); MS, EI *m/z* 263 (M^+). Anal. Calcd for $C_{15}H_{21}NOS$: C, 68.40; H, 8.04. Found: C, 68.23; H, 8.30.

8a: an oil, $[\alpha]^{22}_D$ +213° (*c* 1.05 in CH_2Cl_2); ^1H NMR δ 7.4 (d, *J* = 8 Hz, Ar), 7.31 (d, *J* = 8 Hz, 2 H, Ar), 3.16 (m, 1 H), 3.06 (br d, *J* = 11 Hz, 1 H), 2.41 (s 3 H, *p*-Me), 2.37 (m, 1 H), 2.25 (m, 2 H), 2.04 (m, 1 H), 1.92–1.5 (m, 6 H), 1.28 (m, 2 H); ^{13}C NMR δ 140.89 (s, Ar), 138 (s, Ar), 129.72 (d, 2 C, Ar), 124.19 (d, 2 C, Ar), 65.6 (d, CHN), 63.53 (t), 53.94 (t), 51.72 (d), 29.13 (t), 24.25 (t), 21.32 (t), 20.62 (q), 18.18 (t); MS, EI *m/z* 263 (M^+). Anal. Calcd for $C_{15}H_{21}NOS$: C, 68.40; H, 8.04. Found: C, 68.51; H, 8.25.

8b: an oil, $[\alpha]^{22}_D$ +108° (*c* 1.305 in CH_2Cl_2); ^1H NMR δ 7.62 (d, *J* = 8 Hz, 2 H, Ar), 7.32 (d, *J* = 8 Hz, 2 H, Ar), 3.18 (td, *J* = 10 Hz, 2 Hz, 1 H, CHN), 3.11 (dt, *J* = 10 Hz, 4 Hz, 1 H), 3.03 (br s, 1 H), 2.6 (m, 2 H), 2.42 (s, 3 H, *p*-Me), 2.25 (q, *J* = 9 Hz, 1 H), 2.13 (td, *J* = 10 Hz, 3 Hz, 1 H), 2.0 (m, 2 H), 1.73 (m, 2 H), 1.62 (m, 1 H), 1.4–1.3 (m, 2 H); ^{13}C NMR δ 141.94 (s, Ar), 140 (s, Ar), 129.78 (d, 2 C, Ar), 125.68 (d, 2 C, Ar), 66.22 (d), 64.72 (t), 54.63 (t), 52.61 (d), 26.33 (t), 26.15 (t), 22.49 (t), 21.37 (q), 20.77 (t); MS, EI *m/z* 263 (M^+). Anal. Calcd for $C_{15}H_{21}NOS$: C, 68.40; H, 8.04. Found: C, 68.13; H, 8.16.

The following example serves as the general procedure for the reactions of sulfoxides **7a**, **7b**, **8a**, and **8b** with W-2 Raney nickel.

(−)-(*R*)-Indolizidine (9a). To a solution of 0.1 g (0.38 mmol) of **7a** in 4 mL of EtOH under argon was added 0.1 g of W-2 Raney nickel. The reaction was monitored by TLC. After the mixture was stirred at 25 °C for 2 h, it was diluted with MeOH and CH_2Cl_2, filtered through Celite, and concentrated to give 44 mg (92% yield) of **9a** as an oil: bp 59 °C/18 mmHg (lit.[10] bp 59–60 °C/19 mmHg); $[\alpha]^{22}_D$ −11.3° (*c* 1.76, EtOH) {lit.[10] $[\alpha]^{23}_D$ −10.2 ± 0.6° (*c* 1.76, EtOH) for *R* configuration}; ^1H NMR δ 3.1–3.0 (m, 2 H), 2.05 (q, *J* = 9 Hz, 1 H), 1.95 (td, *J* = 9, 3 Hz, 1 H), 1.87–1.5 (m, 7 H), 1.4–1.2 (m, 4 H); ^{13}C NMR δ 64.4 (d), 54.31 (t), 53.1 (t), 31.12 (t), 29.67 (t), 25.54 (t), 24.56 (t), 20.66 (t); MS, EI *m/z* 126 (M + 1), 125 (M^+). Anal. Calcd for $C_8H_{15}N$: C, 76.74; H, 12.08; N, 11.19. Found: C, 76.57; H, 12.33; N, 11.07.

(+)-(*S*)-Indolizidine (9b): 90% yield; $[\alpha]^{22}_D$ +11.1° (*c* 1.76, EtOH).

The following example serves as the general procedure for the reactions of sulfoxides **7a**, **7b**, **8a**, and **8b** with butyraldehyde.

(8*S*,8a*S*,1′*S*,S*S*)- and (8*R*,8a*S*,1′*S*,S*S*)-8-(1-Hydroxybutyl)-1,2,3,5,6,7,8,8a-octahydro-8-[(4-methylphenyl)sulfinyl]indolizine (10a and 10b). To a cold (−78 °C) solution of 1.1 g (4.18 mmol) of **7a** in 40 mL of THF under argon was added a cold (−78 °C) solution of LDA (5.016 mmol) in 20 mL of THF via cannula. After the resulting orange solution was stirred at −78 °C for 1 h, 0.4 mL (4.6 mmol) of butyraldehyde was added. The light yellow solution was slowly warmed to 25 °C, stirred at 25 °C for 1.5 h, diluted with H_2O, and extracted three times with CH_2Cl_2. The combined organic extracts were washed with H_2O and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel, using a 1:1 (gradient) mixture of hexane and acetone as eluant to give 0.714 g (51% yield) of **10a**, 0.35 g (25% yield) of **10b**, and 0.08 g (6% recovery) of a mixture of **7a** and **7b**.

10a: mp 145–147 °C; $[\alpha]^{22}_D$ +178° (*c* 0.625 in CH_2Cl_2); IR (CH_2Cl_2) 3400 (br s), 1070 (s); ^1H NMR δ 7.8 (d, *J* = 8 Hz, 2 H, Ar), 7.33 (d, *J* = 8 Hz, 2 H, Ar), 6.3 (br s, 1 H, OH), 4.49 (d, *J* = 10 Hz, 1 H, CHO), 3.35 (dd, *J* = 11 Hz, 5 Hz, 1 H, CHN), 3.05 (t, *J* = 8 Hz, 1 H), 2.93 (br d, *J* = 12 Hz, 1 H), 2.6 (m, 1 H), 2.44 (s, 3 H, *p*-Me), 2.15 (t, *J* = 9 Hz, 1 H), 2.0 (m, 1 H), 1.9–1.2 (m, 11 H), 0.88 (t, *J* = 7 Hz, 3 H, Me); ^{13}C NMR δ 142.81 (s, Ar), 136.95 (s, Ar), 129.55 (d, 2C, Ar), 127.77 (d, 2 C, Ar), 71.74 (d, CO), 68.92 (d, CN), 67.9 (s), 55.81 (t), 55.48 (t), 34.27 (t), 26.05 (t), 22.78 (t), 21.56 (2C, t, q), 20.84 (t), 18.86 (t), 13.85 (q); MS, EI *m/z* 335 (M^+). Anal. Calcd for $C_{19}H_{29}NO_2S$: C, 68.02; H, 8.71. Found: C, 67.85; H, 8.99.

10b: an oil, $[\alpha]^{22}_D$ +29.5° (*c* 0.42 in CH_2Cl_2); ^1H NMR δ 7.51 (d, *J* = 8 Hz, 2 H, Ar), 7.32 (d, *J* = 8 Hz, 2 H, Ar), 4.42 (dd, *J* = 11 Hz, 2 Hz, 1 H, CHO), 3.0 (m, 2 H), 2.43 (s, 3 H, *p*-Me), 2.22 (m, 2 H), 1.95 (m, 3 H), 1.8–1.6 (m, 9 H), 1.4 (m, 1 H), 0.95 (t, *J* = 7 Hz, 3 H, Me); ^{13}C NMR δ 141.97 (s, Ar), 136.43 (s, Ar), 129.38 (d, 2 C, Ar), 127.01 (d, 2 C, Ar), 74.4 (d, CO), 66.8 (d, CN), 65.76 (s), 53.81 (t), 52.62 (t), 36.84 (t), 25.55 (t), 25.45 (t), 22.89 (t), 21.47 (q), 21.07 (t), 20.29 (t), 14.01 (q); MS, CI *m/z* 336 (M + 1). Anal. Calcd for $C_{19}H_{29}NO_2S$: C, 68.02; H, 8.71. Found: C, 67.79; H, 8.81.

(8*R*,8a*R*,1′*S*,S*S*)- and (8*S*,8a*R*,1′*S*,S*S*)-8-(1-Hydroxybutyl)-1,2,3,5,6,7,8,8a-octahydro-8-[(4-methylphenyl)sulfinyl]indolizine (11a and 11b). **11a**: an oil, $[\alpha]^{22}_D$ +157° (*c* 1.15 in CH_2Cl_2); ^1H NMR δ 7.69 (d, *J* = 8 Hz, 2 H, Ar), 7.36

(d, J = 8 Hz, 2 H, Ar), 6.52 (br s, 1 H, OH), 4.06 (dd, J = 10 Hz, 1.4 Hz, 1 H, CHO), 3.35 (d, J = 9 Hz, 1 H), 2.5 (td, J = 8 Hz, 2 Hz, 1 H), 2.85 (m, 1 H), 2.52 (dd, J = 10 Hz, 7 Hz, 1 H), 2.44 (s, 3 H, p-Me), 2.25 (m, 1 H), 2.2–1.1 (series of m, 12 H), 0.84 (t, J = 7 Hz, 3 H, Me); ^{13}C NMR δ 142.2 (s, Ar), 136.05 (s, Ar), 129.58 (d, 2 C, Ar), 126.84 (d, 2 C, Ar), 75.06 (d, CO), 67.06 (d, CN), 63.98 (s), 54.21 (t), 53.74 (t), 34.68 (t), 29.47 (t), 27.08 (t), 21.7 (t), 21.33 (q), 20.93 (t), 19.39 (t), 13.81 (q); MS, CI m/z 336 (M + 1). Anal. Calcd for $C_{19}H_{29}NO_2S$: C, 68.02; H, 8.71. Found: C, 68.13; H, 8.60.

11b: an oil, $[\alpha]^{22}_D$ +127° (c 1 in CH_2Cl_2); ^{1}H NMR δ 7.54 (d, J = 8 Hz, 2 H, Ar), 7.29 (d, J = 2 Hz, 2 H, Ar), 5.1 (br s, 1 H, OH), 4.02 (dd, J = 11 Hz, 1.6 Hz, 1 H, CHO), 3.05 (m, 2 H), 2.42 (s, 3 H, p-Me), 2.4–2.2 (m, 2 H), 2.1–1.5 (m, 12 H), 1.27 (m, 1 H), 0.94 (t, J = 7 Hz, 3 H, Me); ^{13}C NMR δ 141.8 (s, Ar), 135.85 (s, Ar), 129.17 (d, 2 C, Ar), 126.86 (d, 2 C, Ar), 74.46 (d, CO), 66.26 (d, CN), 65.24 (2), 53.95 (t), 52.64 (t), 36.29 (t), 25.68 (t), 25.4 (t), 22.72 (t), 21.33 (q), 21.27 (t), 19.94 (t), 14.02 (q); MS, CI m/z 336 (M + 1). Anal. Calcd for $C_{19}H_{29}NO_2S$: C, 68.02; H, 8.71. Found: C, 68.21; H, 8.89.

The following example serves as the general procedure for the dehydrosulfinylation reactions of sulfoxides **10a**, **10b**, **11a**, and **11b**.

(−)-Elaeokanine B [(−)-2]. A solution of 84 mg (0.25 mmol) of alcohol **10a** and 25 mg of triethylamine in 10 mL of toluene was heated under reflux for 2 h. The solution was cooled to 25 °C, solvent was removed under vacuum, and the residue was column chromatographed on silica gel, using a mixture of acetone and methanol as eluant to give 45 mg (92% yield) of (−)-**2** as an oil: $[\alpha]^{22}_D$ −76° (c 0.4 in $CHCl_3$) (lit.[5a] $[\alpha]_D$ −76° in $CHCl_3$); IR (neat) 3300, 1640; ^{1}H NMR δ 5.67 (br s, 1 H, =CH), 4.08 (br s, 1 H, CHO), 2.96 (m, 2 H), 2.85 (m, 1 H), 2.55 (q, J = 9 Hz, 1 H), 2.46 (m, 1 H), 2.22 (m, 2 H), 1.97 (m, 1 H), 1.87 (m, 1 H), 1.73 (m, 1 H), 1.6–1.3 (m, 5 H), 0.92 (t, J = 7 Hz, 3 H, Me); ^{13}C NMR δ 142.38 (s, C=), 118.51 (d, =CH), 72.56 (d, CO), 60.85 (d, CN), 52.91 (t), 46.9 (t), 38.76 (t), 28.38 (t), 25.34 (t), 22.09 (t), 18.85 (t), 13.99 (q); MS, EI m/z 195 (M^+), 194, 178. Anal. Calcd for $C_{12}H_{21}NO$: C, 73.80; H, 10.84; N, 7.17. Found: C, 73.55, H, 11.07; N, 7.01.

(+)-(8a*R*,1′*S*)-1,2,3,5,6,8a-Hexahydro-8-(1-hydroxybutyl)indolizine [(+)-12]: an oil, $[\alpha]^{22}_D$ +22° (c 0.4 in $CHCl_3$); IR (neat) 3250, 1638; ^{1}H NMR δ 5.71 (s, 1 H, =CH), 4.03 (t, J = 7 Hz, 1 H, CHO), 3.05 (m, 1 H), 2.96 (td, J = 9 Hz, 4 Hz, 1 H), 2.86 (m, 1 H), 2.60 (q, J = 8 Hz, 1 H), 2.48 (m, 1 H), 2.4–2.1 (m, 3 H), 1.92 (m, 1 H), 1.86 (m, 1 H), 1.7–1.5 (m, 3 H), 1.45 (m, 1 H), 1.37 (m, 1 H), 0.93 (t, J = 7 Hz, 3 H, Me); ^{13}C NMR δ 141.97 (s, C=), 121.46 (d, =CH), 74.26 (d, CO), 60.88 (d, CN), 52.79 (t), 46.78 (t), 37.45 (t), 28.85 (t), 25.55 (t), 22.11 (t), 19.31 (t), 13.99 (q); MS, EI m/z 195 (M^+), 194, 178. Anal. Calcd for $C_{12}H_{21}NO$: C, 73.80; H, 10.84. Found: C, 73.61; H, 10.99.

The following example serves as the general procedure for the oxidation reactions of alcohols (−)-**2** and (+)-**12** with PCC.

(+)-Elaeokanine A [(+)-1]. To a mixture of 59 mg (0.302 mmol) of alcohol (+)-**12** and 60 mg of 3-Å molecular sieves in 5 mL of CH_2Cl_2 under argon was added 0.13 g (0.6 mmol) of PCC. The mixture was stirred at 25 °C for 2 h, diluted with H_2O, and extracted three times with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel, using hexane and acetone as eluant to give 54 m g (93% yield) of (+)-1 as an oil: $[\alpha]^{22}_D$ +49° (c 0.5 in $CHCl_3$) (lit.[5a] $[\alpha]_D$ +13° in $CHCl_3$); IR (neat) ν 2942, 1650, 1450, 1270, 1195 cm^{-1}; ^{1}H NMR δ 6.87 (s, 1 H, =CH), 3.52 (br s, 1 H, CHN), 3.0–2.8 (m, 3 H), 2.6 (td, J = 9 Hz, 3 Hz, 2 H, CH_2), 2.5–2.3 (m, 4 H), 1.9–1.7 (m, 2 H), 1.64 (q, J = 7 Hz, 2 H), 1.4 (m, 1 H), 0.93 (t, J = 7 Hz, 3 H, Me); ^{13}C NMR δ 199.35 (s, C=O), 139.03 (s, =C)8, 135.99 (d, =CH), 58.65 (d, CN), 53.14 (t), 44.85 (t), 39.1 (t), 29.48 (t), 24.14 (t), 21.76 (t), 17.83 (t), 13.76 (q). Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91. Found: C, 74.35; H, 10.17.

Acknowledgment. We gratefully acknowledge financial support from the National Institute of General Medical Sciences (Grant GM36336) and the National Science Foundation (Grant CHE-8800654). This project is in part funded by Wesley Foundation, Wichita, KS (Grant 8802041). The Wesley Foundation is an independent, nonprofit organization dedicated to improving the quality of life in Kansas through financial support for health related programs. We are indebted to Mr. Ken Walsh, Coal Research Center, Southern Illinois University of Carbondale, for obtaining mass spectra.

Registry No. (±)-1, 33023-01-7; (−)-1, 125636-82-0; (−)-**2**, 33023-02-8; **4**, 123642-79-5; **5**, 872-32-2; **6**, 125475-12-9; **7** (isomer 1), 125475-13-0; **7** (isomer 2), 125517-31-9; **8** (isomer 1), 125517-32-0; **8** (isomer 2), 125517-33-1; **9a**, 89772-92-9; **9b**, 18881-13-5; **10a**, 125475-14-1; **10b**, 125517-34-2; **11a**, 125517-35-3; **11b**, 125517-36-4; **12**, 125517-30-8; $I(CH_2)_3I$, 627-31-6.

Supplementary Material Available: Positional and equivalent isotropic thermal parameters for non-H atoms (Table 1), bond distances and bond angles (Tables 2 and 3), calculated hydrogen atom coordinates and temperature factors (Table 4), U values (Table 5), torsion angles (Table 6), and intermolecular distances involving the non-hydrogen atoms (Table 7) for sulfoxide **10a** (7 pages). Ordering information is given on any current masthead page.

Three-Different-Component [1 + 2 + n]-Annulation Reactions: Ionic and Radical Cyclizations

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Received August 15, 1989

One-carbon-atom Michael donors are used to initiate convergent and flexible [1 + 2 + 3]-hexannulations and [1 + 2 + 2]-pentannulations in which the initial nucleophilic carbon atom terminates the reaction sequence in an ionic fashion as an electrophilic center or in a carbon-centered radical fashion as a nucleophilic center. This protocol is used to prepare regiospecifically substituted bicyclic ketones and lactones and a cis-bicyclic tetrahydrofuran.

Current general practice is to construct carbocycles often by linking together *two* units, as for example in [2 + 4]-Diels–Alder cycloadditions[1] and Robinson annulations[2] and in [2 + 3]-dipolar cycloadditions.[3] Forming carbocyclic systems by sequential joining of *three* smaller carbon units, for example, a one-carbon unit, an α-enone, and an allylic

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0022-3263/90/1955-2132$02.50/0