current dropped from 100 mA (initial value) to a negligible value after consumption of 193 C (2 mmol of electrons). The electrolysis was interrupted, and **2a** (2 mmol) was added; then a working potential of −1.6 ± 0.1 V was applied. The electrolysis was stopped after partial (electrolysis 1) or total depletion (electrolyses 2 and 3) of the faradaic current. Fluorene (2 mmol) was present during the second stage of electrolysis 3. The cathodic solution was diluted with water, and the electrolysis products were extracted with diethyl ether. After the solution was dried, the ether was removed. The crude product was separated by column chromatography with 2/8 diethyl ether/hexane or 1/9 acetone/hexane as eluant and 70–230-mesh silica gel.

The electrolyses of Table III were performed as follows. Diphenyl dichalcogenide (2 mmol) was reduced to PhE^- as above, and then a mixture of azobenzene (0.4 mmol), **2** (4 mmol), and fluorene or malononitrile (2 mmol) was introduced. A working potential of −1.25 ± 0.05 V was applied, and the second stage of the electrolysis was carried out until total depletion of the faradaic current. Treatment of the cathodic solution was performed as above.

The physical and spectroscopic data of the isolated chalcogeno derivatives are summarized in Table IV. Satisfactory analytical data (0.4% for C and H) were reported for all compounds listed in this table, except for **3b** which contained an impurity as mentioned in the text.

Acknowledgment. Work was supported by CNRS (Pirsem grant) and by EDF (Club Electrochimie Organique). We are grateful to Mrs. Raveau-Fouquet for technical assistance and Mr. Nour for identifying compound **1d**.

Registry No. **1a**, 110589-51-0; **1b**, 110589-52-1; **1c**, 106467-87-2; **1d**, 110589-53-2; **1e**, 110589-54-3; **2a**, 90-90-4; **2b**, 1016-77-9; **2c**, 13047-06-8; **2d**, 134-85-0; **2e**, 1016-78-0; **2f**, 5162-03-8; **3a**, 110589-57-6; **3b**, 110589-58-7; **4c**, 110589-56-5; *cis*-**5c**, 110589-55-4; *trans*-**5c**, 110589-59-8; PhTeTePh, 32294-60-3; PhSeSePh, 1666-13-3; $PhSe^-$, 14971-39-2; $PhTe^-$, 65081-67-6; azobenzene, 103-33-3; fluorene, 86-73-7; malononitrile, 109-77-3; benzophenone, 119-61-9.

Studies on the Synthesis of Morphinan and Its Related Compounds: Construction of Morphinan Skeleton

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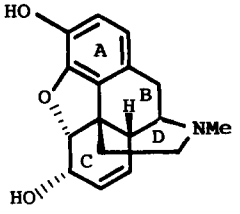
Diels–Alder reaction of the cyclohexadiene derivatives **1** and **2** with α-chloroacrylonitrile afforded the adducts **7** and **8**, whose hydrolysis, followed by the fragmentation reaction, gave rise to the cyanides **13** and **14**. Since these compounds were transformed into mesembrine (**15**) and *O*-methyljoubertiamine (**16**), this synthesis constitutes their formal synthesis. Furthermore, the cyanide **13** was converted to the alcohol **24**, whose Claisen rearrangement furnished the aldehyde **29**. After formation of the B ring of the morphinan skeleton by dehydration of **29**, the olefin **30** was transformed into the amine **32**, whose cyclization through the aminylium ion intermediate, followed by demethoxylation under the Birch reduction condition, provided the morphinan **34**.

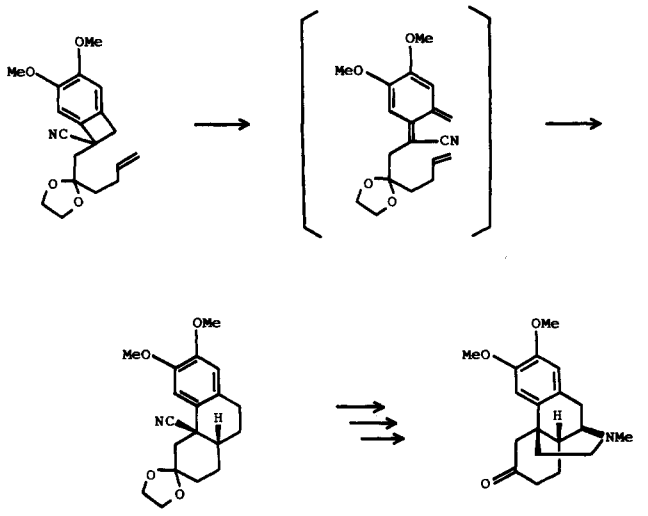
Morphine is the major constituent of opium, and its structure has been established[1] from spectroscopic characteristics including X-ray technique[2] and by syntheses.[1] Since this class of alkaloids exhibits important physiological activities, a number of synthetic routes have been elaborated in a variety of ways.[1]



morphine

During the last several years, we have been involved in the development of a general route to morphinans and have reported the stereoselective synthesis of the morphinan ring skeleton employing an intramolecular [4 + 2]-cycloaddition reaction of *o*-quinodimethane generated in situ by thermolysis of a corresponding benzocyclobutene as a key step to control the stereochemistry of its B/C ring juncture[3] (Scheme I). Here we report an alternative synthetic approach to morphinans.

Scheme I



(1) (a) Holmes, H.; Stork, G. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic: New York, 1952; Vol. II, p 1. (b) Stork, G. *Ibid.* 1960; Vol. VI, p 219. (c) Bentley, K. W. *Ibid.* 1971; Vol. XIII, p 1 and references cited therein. (d) Skenvi, A. B.; Ciganek, E. *J. Org. Chem.* **1984**, *49*, 2942. (e) Evans, D. A.; Mitch, C. H. *Tetrahedron Lett.* **1982**, *23*, 285. (f) Evans, D. A.; Mitch, C. H.; Thomas, R. C.; Zimmerman, D. M.; Robey, R. W. *J. Am. Chem. Soc.* **1980**, *102*, 5955. (g) Moos, W. H.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 227.

(2) Kupchan, S. M.; Suffness, M. I.; McClure, R. J.; Sim, G. A. *J. Am. Chem. Soc.* **1970**, *92*, 5756.

(3) (a) Kametani, T.; Suzuki, Y.; Honda, T. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1373. (b) Kametani, T.; Suzuki, Y.; Honda, T. *Chem. Pharm. Bull.* **1986**, *34*, 4971.

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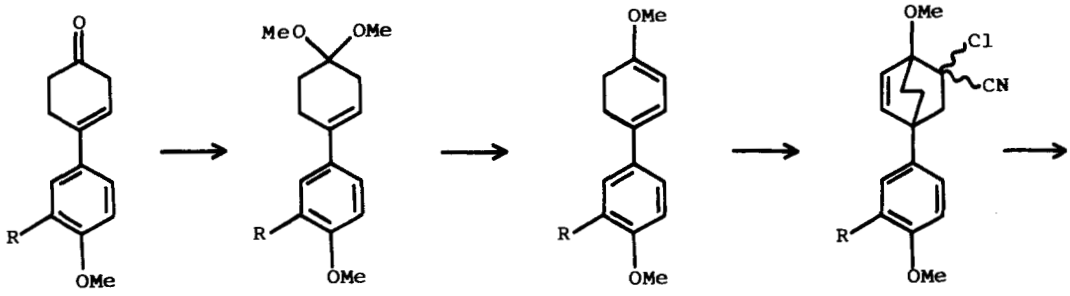
Scheme II

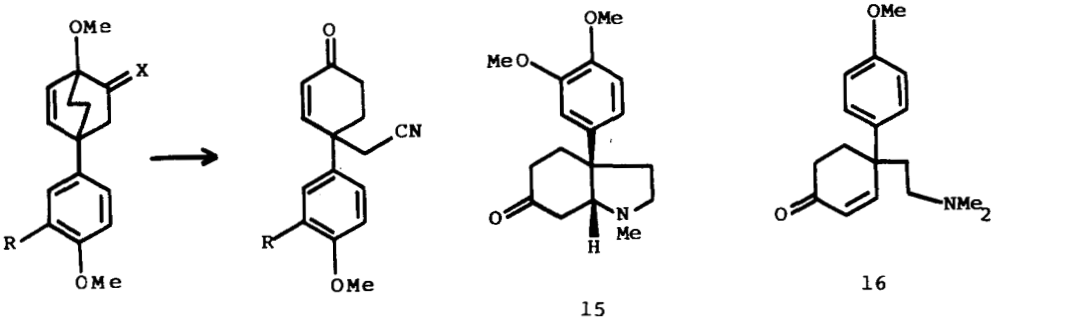


1 R=OMe
2 R=H

3 R=OMe
4 R=H

5 R=OMe
6 R=H

7 R=OMe
8 R=H



9 R=OMe, X=O
10 R=H, X=O
11 R=OMe, X=NOH
12 R=H, X=NOH

13 R=OMe
14 R=H

15

16

Results and Discussion

The key feature of our approach involved an intermolecular Diels–Alder reaction of a 1,3-cyclohexadiene derivative with α-chloroacrylonitrile and subsequently a Beckmann-type fragmentation reaction to construct a benzylic quaternary carbon center. Our synthesis thus began with the preparation of the 1,3-cyclohexadiene derivatives. The ketone **1**[4] was treated with trimethyl orthoformate to give the ketal **3**, which was then converted to the diene derivative **5** by adopting Miller's procedure[5] using trimethylsilyl iodide and hexamethyldisilazane in 50% yield from **1**. Intermolecular Diels–Alder reaction[6] of the diene **5** with α-chloroacrylonitrile in toluene was carried out in a sealed tube at 180 °C for 5 h to afford the desired adduct **7** as a mixture of diastereomers in 25.8% yield. Although various reaction conditions were employed in order to increase the reaction yield, no satisfactory results were obtained. The poor yield of cycloaddition product in this reaction was rationalized by the unstable diene structure **5** arising from the easy oxidative aromatization of diene to the diphenyl compound, even in the presence of phenothiazine. Hydrolysis of the adduct **7** with sodium sulfide[6] in ethanol furnished the ketone **9**, which was then condensed with hydroxylamine to give the oxime **11**. Mesylation of the oxime **11** by treatment with mesyl chloride and triethylamine in methylene chloride at 0 °C for 3 h brought about the desired fragmentation reaction to provide the enone **13**, in 91% yield, whose spectral data were identical with those reported.[7]

Since the enone **13** was already transformed[7] into mesembrine (**15**) by Sanchez, this synthesis constitutes its formal synthesis.

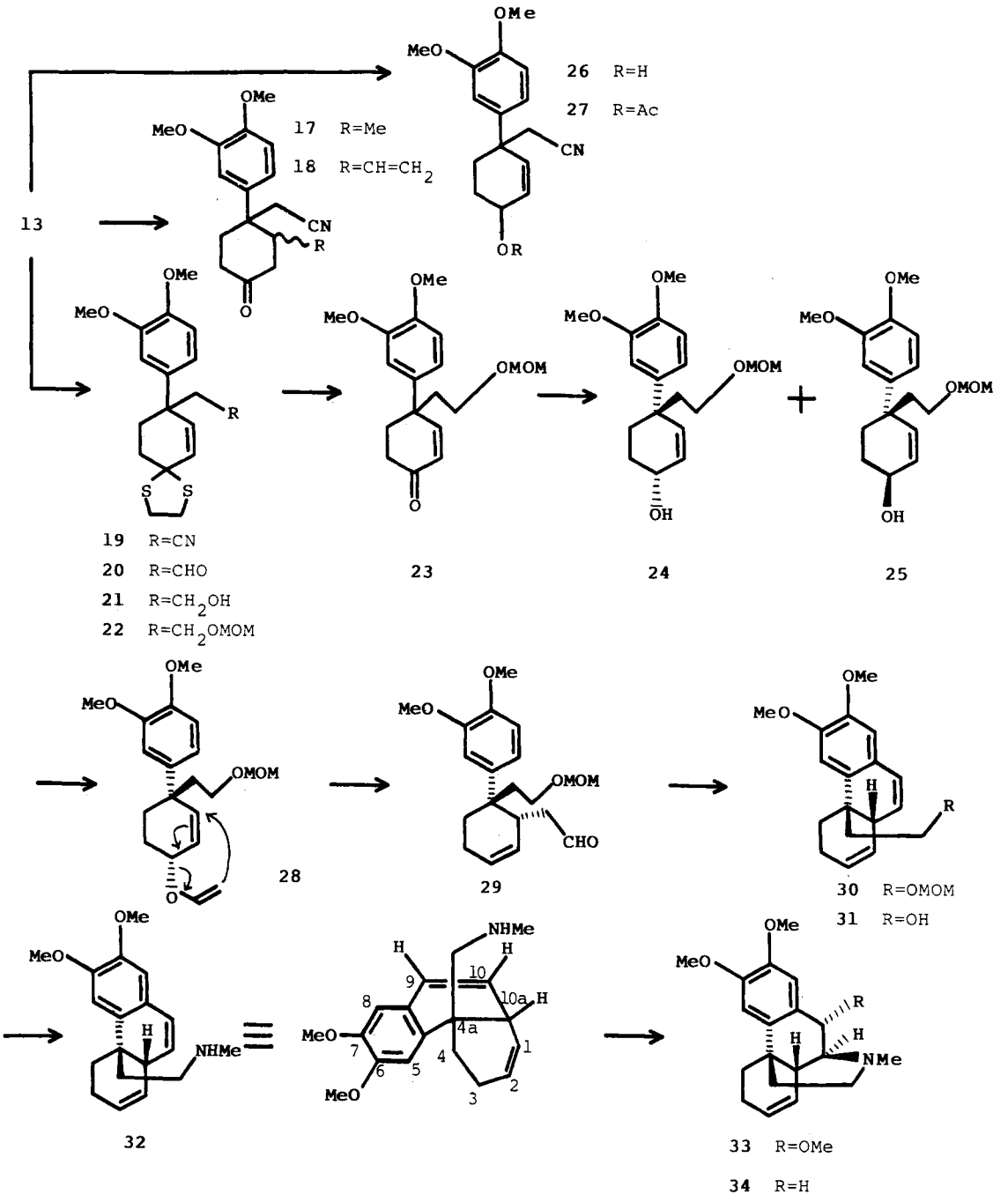
Similarly, the diene **6** derived from **2**[8] via **4** was converted into the enone **14**,[7] the key intermediate for the synthesis of *O*-methyljoubertiamine (**16**), by adopting the above synthetic strategy via **8**, **10**, and **12** as shown in Scheme II.

Thus, we succeeded in the construction of the A/C ring part of morphinan, involving the formation of a benzylic quaternary carbon center, and could develop a new synthetic route to *Amaryllidaceae* alkaloids.

Our attention was next focused on the conversion of the enone **13** into a morphinan derivative. The introduction of a functionalized C_2 unit, such as a vinyl group, at the β-position of the enone was required for construction of the B ring of morphinan. Prior to this experiment, 1,4 conjugate addition of a methyl group to the enone **13** was investigated using lithium dimethylcuprate to examine the stereoselectivity; however, the product **17** was shown to be a mixture of diastereoisomers in the ratio of 1:1. Moreover, conjugate addition of a vinyl group to the enone **13** using various types of cuprate reagents[9] yielded only a trace amount of the desired product **18**. These results forced us to change the synthetic route originally planned, and we decided to adopt a Claisen rearrangement to in-

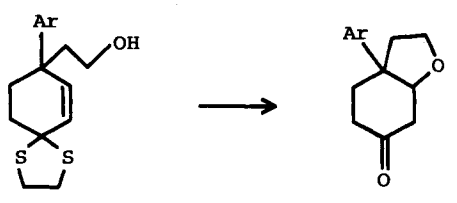
(4) Hoshino, O.; Sawaki, S.; Shimamura, N.; Onodera, A.; Umezawa, B. *Heterocycles* **1978**, *10*, 61.
(5) Miller, R. D.; McKean, D. R. *Tetrahedron Lett.* **1982**, *23*, 323.
(6) Evans, D. A.; Scott, W. L.; Truesdale, L. K. *Tetrahedron Lett.* **1972**, 121.
(7) Sanchez, I. H.; Tallabs, F. R. *Chem. Lett.* **1981**, 891.
(8) Humphreys, D. J.; Lawrence, P. M.; Newall, C. E.; Phillips, G. H.; Wall, P. A. *J. Chem. Soc., Perkin Trans. 1* **1978**, 24.
(9) (a) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. *Tetrahedron Lett.* **1982**, *23*, 3755. (b) House, H. O.; Chu, C.-Y.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460.

Scheme III



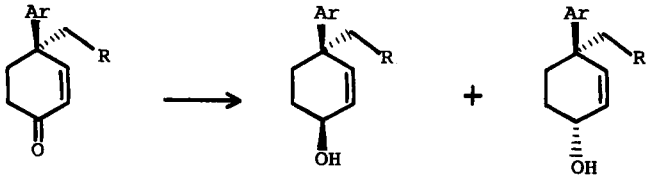
troduce a functionalized C_2 unit at the desired position (Scheme III). After thioketalization of **13**, the cyanide group of **19** was converted into the alcohol **21** by successive reduction with diisobutylaluminum hydride and sodium borohydride via **20**, and the alcohol **21** was then protected as its methoxymethyl ether.[10] Dethioketalization of **22**

(10) When dethioketalization was carried out for **18**, an intramolecular Michael addition of the alcohol function took place to give the ether.



18

Table I. Reduction of the Enone with $NaBH_4$



cis trans

R	catalyst	solvent	cis:trans ratio
CN	$CeCl_3$	MeOH	3:1
CH_2OMOM	$CeCl_3$	MeOH	10:1
CH_2OMOM	$CeCl_3$	THF	5:1
CH_2OMOM		MeOH	8:3
CH_2OMOM		THF	5:2

with *N*-chlorosuccinimide (NCS) and silver nitrate[11] in aqueous acetonitrile regenerated the enone **23** in 89%

yield. Reduction of the enone carbonyl function was attempted under several reaction conditions, and the results obtained are summarized in Table I. Stereoselectivity was observed when the reduction of the enone **23** with sodium borohydride was carried out in methanol in the presence of cerium chloride,[12] furnishing the alcohols **24** and **25** in 87% and 8.7% yields, respectively. The alcohols without separation were then subjected to a Claisen rearrangement,[13] via the vinyl ether **28**, to give the aldehyde **29** as the sole product in 79% yield. Treatment of **29** with *p*-toluenesulfonic acid in benzene at ambient temperature for 1 h brought about the dehydration reaction, resulting in formation of the B ring to give **30** in 95% yield. Deprotection of the MOM ether of **30** with hydrochloric acid gave the alcohol **31**, whose consequent treatment with mesyl chloride and triethylamine in methylene chloride at 0 °C and with methylamine in benzene in a sealed tube at 80 °C afforded the desired amine **32** in 79% yield from **30**. The stereochemistry of **31** was determined at this stage to have a cis B/C ring juncture by comparison of its NMR spectrum (showing 9-H and 10-H protons at δ 5.80 as double doublet with J = 9.5 and 6.0 Hz and at δ 6.27 as doublet with J = 9.5 Hz) with the well-established Conway's report[14] and also with our previous report.[3] Hence the stereochemistry of the enol **24** was deduced to have the cis hydroxy group to the aromatic ring.

Finally, D ring formation was achieved through an aminylium ion intermediate[15] as follows. Reaction of the amine **32** with NCS in methylene chloride gave the corresponding *N*-chloro derivative, which without purification was then treated with silver oxide in methanol at 50 °C for 5 h, yielding the methoxy derivative **33** in 47% yield. Demethoxylation of **33** under the Birch reduction condition using sodium metal in liquid ammonia afforded the desired morphinan **34**.

These results comprise a novel construction of the morphinan ring skeleton, which should be applicable to the naturally occurring morphinan alkaloids.

Experimental Section

Infrared (IR) spectra were taken on a Hitachi 260-10 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ solution, unless otherwise noted, on a JEOL JNM-FX-100 or JNM-GX-400 spectrometer with tetramethylsilane as an internal standard. Low-resolution and exact mass spectra (MS) were taken on a JEOL JMS-D-300 spectrometer. Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected.

1,1-Dimethoxy-4-(3,4-dimethoxyphenyl)cyclohex-3-ene (3). To a stirred solution of the ketone **1** (5.15 g, 22 mmol) in dry methanol (150 mL) was added trimethyl orthoformate (4.85 mL, 44 mmol) and a catalytic amount of *p*-toluenesulfonic acid at ambient temperature, and the mixture was further stirred for 3 h. After basification with saturated aqueous sodium hydrogen carbonate solution, the solvent was evaporated to give the residue, which was taken up with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent afforded the residue, which was subjected to column chromatography on neutral alumina. Elution with ethyl acetate–hexane (1:9, v/v) gave the ketal **3** (4.34 g, 70%) as colorless needles: mp 83–84 °C (MeOH); IR ($CHCl_3$) 1600 cm^{-1}; ^1H NMR (CCl_4) δ 1.66–3.10 (2 H, m, 6-CH_2), 2.20–2.69 (4 H, m, 2-CH_2, 5-CH_2), 3.13 (6 H, s, 2 OMe), 3.74 (3 H, s, OMe), 3.76 (3 H, s, OMe), 5.60–5.86 (1 H, br s, 3-CH), 6.66–7.03 (3 H, m, ArH); MS, m/z 278 (M^+). Anal. Calcd for $C_{16}H_{22}O_4 \cdot 0.1H_2O$: C, 68.60; H, 7.99. Found: C, 68.93; H, 8.03.

1,1-Dimethoxy-4-(4-methoxyphenyl)cyclohex-3-ene (4). Ketalization of **2** (2.9 g, 14 mmol) with trimethyl orthoformate (3.1 mL, 28 mmol) and a catalytic amount of *p*-toluenesulfonic acid in dry methanol (80 mL) was carried out as above to give the ketal **4** (3.2 g, 92%) as colorless needles: mp 71–72 °C (MeOH); IR ($CHCl_3$) 1600 cm^{-1}; ^1H NMR δ 1.60–2.13 (2 H, m, 6-CH_2), 2.13–2.63 (4 H, m, 2-CH_2, 5-CH_2), 3.20 (6 H, s, 2 OMe), 3.70 (3 H, s, OMe), 5.77 (1 H, br s, 3-CH), 6.75 (2 H, d, J = 9.0 Hz, ArH), 7.25 (2 H, d, J = 9.0 Hz, ArH); MS, m/z 248 (M^+). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.38; H, 8.26.

1-Methoxy-4-(3,4-dimethoxyphenyl)cyclohexa-1,3-diene (5). To a stirred solution of the acetal **3** (5.9 g, 21.2 mmol) in dry methylene chloride (200 mL) was added hexamethyldisilazane (6.83 mL, 32 mmol) and iodotrimethylsilane (3.93 mL, 27.6 mmol) at −10 °C. After being stirred for 2 h at 0 °C, the resulting mixture was warmed to room temperature over the period of 2 h and diluted with benzene. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution and water and dried over Na_2SO_4. Removal of the solvent gave the residue, which was subjected to column chromatography on neutral alumina. Elution with 5% ethyl acetate in hexane afforded the diene **5** (3.80 g, 72.0%) as a colorless powder: IR ($CHCl_3$) 1640, 1580 cm^{-1}; ^1H NMR (CCl_4) δ 2.06–3.06 (4 H, m, 5-CH_2, 6-CH_2), 3.56 (3 H, s, OMe), 3.76 (6 H, s, 2 OMe), 4.96 (1 H, d, J = 7.0 Hz, 3-CH), 6.06 (1 H, d, J = 7.0 Hz, 2-CH), 6.66–7.10 (3 H, ArH).

1-Methoxy-4-(4-methoxyphenyl)cyclohexa-1,3-diene (6). By the same procedure as described above for the preparation of **5**, the reaction of **4** (0.56 g, 2.4 mmol) with hexamethyldisilazane (0.7 mL, 3.4 mmol) and iodotrimethylsilane (0.4 mL, 2.9 mmol) in methylene chloride (20 mL) gave the diene **6** (0.44 g, 90.5%) as an unstable colorless powder: IR ($CHCl_3$) 1640, 1600, 1580 cm^{-1}; ^1H NMR δ 2.16–2.86 (4 H, m, 5-CH_2, 6-CH_2), 3.60 (3 H, s, OMe), 3.76 (3 H, s, OMe), 5.06 (1 H, d, J = 7.0 Hz, 3-CH), 6.20 (1 H, d, J = 7.0 Hz, 2-CH), 6.83 (2 H, d, J = 9.0 Hz, ArH), 7.33 (3 H, d, J = 9.0 Hz, ArH).

2-Chloro-2-cyano-1-methoxy-4-(3,4-dimethoxyphenyl)bicyclo[2.2.2]oct-5-ene (7). A solution of the diene **5** (360 mg, 1.46 mmol), α-chloroacrylonitrile (0.6 mL, 7.3 mmol), and a catalytic amount of phenothiazine in toluene (15 mL) was heated at 180 °C for 5 h in a sealed tube. After evaporation of the solvent, the residue was subjected to column chromatography on silica gel. Elution with benzene gave the adduct **7** (126 mg, 25.8%) as a gum: IR ($CHCl_3$) 2250, 1610 cm^{-1}; ^1H NMR (CCl_4) δ 3.56 (3 H, s, OMe), 3.78 (3 H, s, OMe), 3.80 (3 H, s, OMe), 6.25 (1 H, d, J = 9.0 Hz, 5-CH), 6.45 (1 H, d, J = 9.0 Hz, 6-CH), 6.73 (3 H, s, ArH); MS, m/z 333 (M^+); exact mass calcd for $C_{18}H_{20}NO_3Cl$ 333.1130 (M^+), found 333.1118.

2-Chloro-2-cyano-1-methoxy-4-(4-methoxyphenyl)bicyclo[2.2.2]oct-5-ene (8). Diels–Alder reaction of the diene **6** (400 mg, 1.84 mmol) with α-chloroacrylonitrile (1.47 mL, 18.4 mmol) in toluene (30 mL) in the presence of a catalytic amount of phenothiazine was carried out as above to give the adduct **8** (121 mg, 21.3%) as a gum: IR ($CHCl_3$) 2250, 1610 cm^{-1}; ^1H NMR δ 3.60 (3 H, s, OMe), 3.83 (3 H, s, OMe), 6.33 (1 H, d, J = 9.0 Hz, 5-CH), 6.50 (1 H, d, J = 9.0 Hz, 6-CH), 6.87 (2 H, d, J = 9.0 Hz, ArH), 7.23 (2 H, d, J = 9.0 Hz, ArH); MS, m/z 303 (M^+); exact mass calcd for $C_{17}H_{18}NO_2Cl$ 303.1024 (M^+), found 303.1018.

1-Methoxy-4-(3,4-dimethoxyphenyl)-2-oxobicyclo[2.2.2]-oct-5-ene (9). A mixture of the adduct **7** (313 mg, 0.94 mmol) and $Na_2S \cdot 9H_2O$ (1.13 g, 4.7 mmol) in ethanol (25 mL) was heated at reflux for 42 h. After treatment with aqueous ammonium chloride solution, the solvent was removed and the residue was taken up with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the residue, which was subjected to column chromatography on silica gel. Elution with ethyl acetate–benzene (1:9, v/v) afforded the ketone **9** (100 mg, 37%) as colorless needles: mp 97–98 °C (MeOH); IR ($CHCl_3$) 1740, 1600 cm^{-1}; ^1H NMR (CCl_4) δ 1.56–2.20 (4 H, m, 7-CH_2, 8-CH_2), 2.30 (2 H, s, 3-CH_2), 3.48 (3 H, s, OMe), 3.78 (6 H, s, 2 OMe), 6.20 (1 H, d, J = 9.0 Hz, 5-CH), 6.41 (1 H, d, J = 9.0 Hz, 6-CH), 6.72 (3 H, s, ArH); MS, m/z 288 (M^+). Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.54; H, 7.10.

1-Methoxy-4-(4-methoxyphenyl)-2-oxobicyclo[2.2.2]oct-5-ene (10). By the same procedure as described for the preparation

(11) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.
(12) Gema, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
(13) Dauben, W. G.; Dietsche, T. J. *J. Org. Chem.* **1972**, *37*, 1212.
(14) Conway, T. T.; Doyle, T. W.; Perron, Y. G.; Chapuis, J.; Belleau, B. *Can. J. Chem.* **1975**, *53*, 245.
(15) Stella, L. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 337.

of **9**, the reaction of the adduct **8** (240 mg, 0.79 mmol) with $Na_2S·9H_2O$ (950 mg, 4 mmol) in refluxing ethanol (15 mL) for 12 h afforded the ketone **10** (105 mg, 52%) as colorless needles: mp 89–90 °C (MeOH); IR ($CHCl_3$) 1730, 1610 cm^{-1}; ^1H NMR δ 1.70–2.20 (4 H, m, 7-CH_2, 8-CH_2), 2.42 (2 H, s, 3-CH_2), 3.60 (3 H, s, OMe), 3.82 (3 H, s, OMe), 6.33 (1 H, d, J = 9.0 Hz, 5-CH), 6.56 (1 H, d, J = 9.0 Hz, 6-CH), 6.90 (2 H, d, J = 9.0 Hz, ArH), 7.27 (2 H, d, J = 9.0 Hz, ArH); MS, m/z 258 (M^+). Anal. Calcd for $C_{16}H_{18}O_3·0.1H_2O$: C, 73.88; H, 7.05. Found: C, 73.90; H, 7.04.

2-(Hydroxyimino)-1-methoxy-4-(3,4-dimethoxyphenyl)-bicyclo[2.2.2]oct-5-ene (11). A solution of the ketone **9** (290 mg, 1.0 mmol), hydroxylamine hydrochloride (140 mg, 2.0 mmol), and a catalytic amount of sodium acetate in methanol–water (40 mL, 10:1, v/v) was heated at reflux overnight. After removal of the solvent, the residue was taken up with ethyl acetate, and the organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the residue, which was subjected to column chromatography on silica gel. Elution with ethyl acetate–benzene (15:85, v/v) afforded the oxime **11** (310 mg, 100%) as colorless needles: mp 166–167 °C (MeOH); IR ($CHCl_3$) 3580, 3300, 1590 cm^{-1}; ^1H NMR δ 1.70–2.26 (4 H, m, 7-CH_2, 8-CH_2), 2.66 (2 H, distorted s, 3-CH_2), 3.76 (3 H, s, OMe), 3.90 (6 H, br s, 2 OMe); MS, m/z 303 (M^+). Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98. Found: C, 67.23; H, 7.07.

2-(Hydroxyimino)-1-methoxy-4-(4-methoxyphenyl)bicyclo[2.2.2]oct-5-ene (12). By the same procedure as above for the preparation of **11**, the reaction of the ketone **10** (38 mg, 0.15 mmol) with hydroxylamine hydrochloride (51 mg, 0.73 mmol) in refluxing methanol–water (20 mL, 10:1, v/v) in the presence of a catalytic amount of sodium acetate for 9 h afforded the oxime **12** (38 mg, 92%) as colorless needles: mp 162–163 °C (MeOH); IR ($CHCl_3$) 3580, 3300, 1610 cm^{-1}; ^1H NMR δ 1.56–2.36 (4 H, m, 7-CH_2, 8-CH_2), 2.64 (2 H, distorted s, 3-CH_2), 3.56 (3 H, s, OMe), 3.80 (3 H, s, OMe), 6.33 (2 H, s, olefinic protons), 6.86 (2 H, d, J = 9.0 Hz, ArH), 7.30 (2 H, d, J = 9.0 Hz, ArH); MS, m/z 273 (M^+). Anal. Calcd for $C_{16}H_{19}NO_3·0.2H_2O$: C, 69.48; H, 7.07; N, 5.06. Found: C, 69.40; H, 6.96; N, 4.90.

4-(Cyanomethyl)-4-(3,4-dimethoxyphenyl)cyclohex-2-en-1-one (13). To a stirred solution of the oxime **11** (130 mg, 0.4 mmol) in dry methylene chloride (20 mL) was added triethylamine (0.1 mL) and mesyl chloride (0.067 mL, 0.86 mmol) at 0 °C, and the resulting mixture was further stirred at ambient temperature for 3 h. The solution was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the residue, which was subjected to column chromatography on silica gel. Elution with ethyl acetate–benzene (15:85, v/v) afforded the enone **13** (116 mg, 91%), whose spectral data were identical with those reported.[7]

4-(Cyanomethyl)-4-(4-methoxyphenyl)cyclohex-2-en-1-one (14). Reaction of the oxime **12** (30 mg, 0.11 mmol) with mesyl chloride (0.1 mL) and triethylamine (0.1 mL) in dry methylene chloride (20 mL) was carried out as above to yield the enone **14** (18 mg, 68%), whose spectral data were identical with those reported.[7]

4-(Cyanomethyl)-4-(3,4-dimethoxyphenyl)-3-methylcyclohexan-1-one (17). To a stirred solution of the enone **13** (100 mg, 0.369 mmol) in dry tetrahydrofuran (20 mL) was added a solution of lithium dimethylcuprate [prepared from methyllithium (0.53 mL, 0.553 mmol) and CuI (105 mg, 0.738 mmol)] in dry ether (20 mL) at −78 °C. After being stirred for 1 h, the mixture was treated with 10% aqueous ammonium chloride solution, and the organic layer that separated was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the residue, which was subjected to column chromatography. Elution with ethyl acetate–benzene (15:85, v/v) afforded the ketone **17** (95 mg, 39.6%) as an inseparable mixture of diastereomers: IR ($CHCl_3$) 2250, 1700 cm^{-1}; ^1H NMR δ 0.75 (1.5 H, d, J = 6.0 Hz, 3-CH_3), 1.03 (1.5 H, d, J = 6.0 Hz, 3-CH_3), 3.83 (6 H, s, 2 OMe), 6.83 (3 H, s, ArH); MS, m/z 287 (M^+); exact mass calcd for $C_{17}H_{21}NO_3$ 287.1519 (M^+), found 287.1519.

4-(Cyanomethyl)-4-(3,4-dimethoxyphenyl)-3-vinylcyclohexan-1-one (18). To a stirred solution of the enone **13** (353 mg, 1.3 mmol) in dry tetrahydrofuran (10 mL) was added lithium divinylcuprate [prepared from vinyltriphenylstannane (1.4 g, 3.9 mmol), phenyllithium (2.1 mL, 1.8 M solution in ether), Me_2S-CuBr (400 mg, 1.95 mmol), and dimethyl sulfide (4 mL) in dry ether (10 mL)] at −78 °C. After being stirred for 3 h at −78 °C, the mixture was slowly warmed to ambient temperature over the period of 12 h and was treated with saturated aqueous sodium hydrogen carbonate. The organic layer was successively washed with 10% ammonium hydroxide solution, 10% aqueous ammonium chloride solution, and brine and dried over Na_2SO_4. Removal of the solvent gave the residue, which was subjected to column chromatography on silica gel. Elution with ethyl acetate–benzene (5:95, v/v) afforded the ketone **18** (20 mg, 3.4%) as a gum: IR ($CHCl_3$) 2250, 1720 cm^{-1}; ^1H NMR δ 3.93 (6 H, s, 2 OMe), 5.16–5.70 (3 H, m, vinyl protons); MS, m/z 299 (M^+); exact mass calcd for $C_{18}H_{21}NO_3$ 299.1519, found 299.1517.

4-(Cyanomethyl)-4-(3,4-dimethoxyphenyl)cyclohex-2-en-1-ol (26). To a stirred solution of the enone **13** (163 mg, 0.6 mmol) in methanol (20 mL) in the presence of cerium chloride (224 mg, 0.6 mmol) was added sodium borohydride (68 mg, 1.8 mmol) in small portions at 0 °C, and the resulting mixture was further stirred at ambient temperature for 1 h. After treatment with 10% aqueous ammonium chloride solution, the solvent was evaporated to leave the residue, which was taken up with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent afforded the residue, which was subjected to column chromatography on silica gel. Elution with ethyl acetate–benzene (18:82, v/v) gave the alcohol **26** (130 mg, 79%) as an inseparable mixture of diastereomers: IR ($CHCl_3$) 3450, 2250, 1580 cm^{-1}; ^1H NMR δ 3.85 (3 H, s, OMe), 3.87 (3 H, s, OMe), 5.63–6.20 (2 H, m, olefinic protons); MS, m/z 273 (M^+); exact mass calcd for $C_{16}H_{19}NO_3$ 273.1363, found 273.1361.

1-Acetoxy-4-(cyanomethyl)-4-(3,4-dimethoxyphenyl)-cyclohex-2-ene (27). A solution of the alcohol **26** (100 mg, 0.37 mmol), a catalytic amount of (*N*,*N*-dimethylamino)pyridine, and acetic anhydride (5 mL) in pyridine (7 mL) was allowed to stand at room temperature overnight. After dilution with ethyl acetate, the organic layer was washed with 10% aqueous $KHSO_4$ solution and brine and dried over Na_2SO_4. Evaporation of the solvent gave the residue, which was subjected to column chromatography on silica gel. Elution with ethyl acetate–benzene (1:9, v/v) afforded the acetate **27** (110 mg, 100%) as a gum, and the cis and trans ratio to the aromatic ring was determined based on its NMR integration to be 3:1: IR ($CHCl_3$) 2250, 1720, 1590 cm^{-1}; ^1H NMR δ 2.05 ($^9/_4$ H, s, OAc), 2.07 ($^3/_4$ H, s, OAc), 3.86 ($^3/_4$ H, s, OMe), 3.87 ($^9/_4$ H, s, OMe), 3.88 ($^3/_4$ H, s, OMe), 3.89 ($^9/_4$ H, s, OMe), 5.19–5.23 ($^1/_4$ H, m, 1-H), 5.32–5.39 ($^3/_4$ H, m, 1-H); MS, m/z 315 (M^+); exact mass calcd for $C_{18}H_{21}NO_4$ 315.1469, found 315.1469.

4-(Cyanomethyl)-1,1-(ethylenedithio)-4-(3,4-dimethoxyphenyl)cyclohex-2-ene (19). A solution of the enone **13** (5.55 g, 0.02 mol), ethanedithiol (2.315 g, 0.024 mol), and a catalytic amount of boron trifluoride etherate in dry methylene chloride (200 mL) was stirred at 0 °C for 2 h. The solution was washed with water and dried over Na_2SO_4. Removal of the solvent gave the residue, which was subjected to column chromatography on silica gel. Elution with ethyl acetate–benzene (5:95, v/v) afforded **19** (6.0 g, 92%) as a gum: IR ($CHCl_3$) 2250, 1580 cm^{-1}; ^1H NMR δ 2.10 (4 H, s, 5-CH_2, 6-CH_2), 2.70 (2 H, s, CH_2CN), 3.35 (4 H, s, SCH_2CH_2S), 3.90 (6 H, s, 2 OMe), 5.78 (1 H, d, J = 10.0 Hz, 3-CH), 6.18 (1 H, d, J = 10.0 Hz, 2-CH), 6.87 (3 H, s, ArH); MS, m/z 347 (M^+); exact mass calcd for $C_{18}H_{21}NO_2S_2$ 347.1013, found 347.1008.

1,1-(Ethylenedithio)-4-(formylmethyl)-4-(3,4-dimethoxyphenyl)cyclohex-2-ene (20). To a stirred solution of the cyanide **19** (42 mg, 0.13 mmol) in toluene (5 mL) was added diisobutylaluminum hydride (0.15 mL, 1 M solution in hexane) at −78 °C, and the resulting mixture was further stirred for 1 h at −78 °C. After treatment with aqueous ammonium chloride solution, the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the residue, which was subjected to column chromatography on silica gel. Elution with ethyl acetate–benzene (5:95, v/v) afforded the aldehyde **20** (43 mg, 94.5%) as a gum: IR ($CHCl_3$) 1710 cm^{-1}; ^1H NMR δ 2.07 (4 H, s, 5-CH_2, 6-CH_2), 2.70–2.90 (2 H, m, CH_2CHO), 3.35 (4 H, s, SCH_2CH_2S), 3.87 (6 H, s, 2 OMe), 5.83 (1 H, d, J = 10.0 Hz, 3-CH), 6.13 (1 H, d, J = 10.0 Hz, 2-CH), 6.82 (3 H, s, ArH), 9.50–9.70 (CHO); MS, m/z 350 (M^+); exact mass calcd for $C_{18}H_{22}O_3S_2$ 350.1011, found 350.1012.

1,1-(Ethylenedithio)-4-(3,4-dimethoxyphenyl)-4-(2-hydroxyethyl)cyclohex-2-ene (21). To a stirred solution of the

aldehyde **20** (9.31 g, 26 mmol) in methanol (200 mL) was added sodium borohydride (3.0 g, 80 mmol) in small portions at 0 °C, and the resulting mixture was further stirred at ambient temperature for 2 h. After removal of the solvent, the residue was extracted with ethyl acetate, and the extract was washed with water and dried over Na_2SO_4. Removal of the solvent gave the residue, which was purified by column chromatography on silica gel with ethyl acetate–benzene (1:4, v/v) as eluant to afford the alcohol **21** (9.2 g, 98%) as a gum: IR ($CHCl_3$) 3450, 1580 cm^{-1}; ^1H NMR δ 1.70–2.56 (6 H, m, 3 CH_2), 3.35 (4 H, s, SCH_2CH_2S), 3.56 (2 H, t, J = 7.0 Hz, CH_2OH), 3.88 (6 H, s, 2 OMe), 5.78 (1 H, d, J = 10.0 Hz, 3-CH), 6.05 (1 H, d, J = 10.0 Hz, 2-CH), 6.83 (3 H, s, ArH); MS, m/z 352 (M^+); exact mass calcd for $C_{18}H_{24}O_3S_2$ 352.1165, found 352.1148.

1,1-(Ethylenedithio)-4-[2-(methoxymethoxy)ethyl]-4-(3,4-dimethoxyphenyl)cyclohex-2-ene (22). A solution of the alcohol **21** (1.38 g, 3.8 mmol), diisopropylethylamine (1.9 mL, 11.3 mmol), and methoxymethyl chloride (0.85 mL, 11.3 mmol) in dry tetrahydrofuran (70 mL) was stirred overnight at ambient temperature. After dilution with ether, the organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the residue, which was subjected to column chromatography on silica gel. Elution with ethyl acetate–benzene (1:9, v/v) yielded the MOM ether **22** (1.53 g, 98.7%) as colorless prisms: mp 87–88 °C (MeOH); IR ($CHCl_3$) 1580 cm^{-1}; ^1H NMR δ 1.70–2.60 (6 H, m, 3 CH_2), 3.96 (3 H, s, OMe), 4.00 (3 H, s, OMe), 4.66 (2 H, s, OCH_2O), 6.00 (1 H, d, J = 10.0 Hz, 3-CH), 6.27 (1 H, d, J = 10.0 Hz, 2-CH), 7.63 (3 H, s, ArH); MS, m/z, 396 (M^+). Anal. Calcd for $C_{18}H_{28}O_4S_2$: C, 60.57; H, 7.12. Found: C, 60.40; H, 7.11.

4-[2-(Methoxymethoxy)ethyl]-4-(3,4-dimethoxyphenyl)cyclohex-2-en-1-one (23). To a stirred solution of silver nitrate (2.47 g, 14.5 mmol) and NCS (1.73 g, 12.9 mmol) in acetonitrile–water (25 mL, 7:3, v/v) was added a solution of the thioketal **22** (1.28 g, 3.2 mmol) in acetonitrile (30 mL) in one portion at 0 °C, and the resulting mixture was further stirred for 10 min at 0 °C. The mixture was successively treated at 1-min intervals with saturated aqueous sodium sulfite, saturated aqueous sodium carbonate, and brine, and methylene chloride was added. An insoluble material was filtered off through Celite pad, and the filtrate was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to column chromatography on silica gel. Elution with ethyl acetate–benzene (15:85, v/v) gave the enone **23** (910 mg, 89%) as a gum: IR ($CHCl_3$) 1680, 1590 cm^{-1}; ^1H NMR δ 1.76–2.73 (6 H, m, 3 CH_2), 3.27 (3 H, s, OMe), 3.48 (2 H, t, J = 7.0 Hz, CH_2OMOM), 3.86 (6 H, s, 2 OMe), 4.50 (2 H, s, OCH_2O), 6.13 (1 H, d, J = 10.0 Hz, 2-CH), 7.23 (1 H, d, J = 10.0 Hz, 3-CH), 6.86 (3 H, s, ArH); MS, m/z 320 (M^+); exact mass calcd for $C_{18}H_{24}O_5$ 320.1622, found 320.1620.

4-[2-(Methoxymethoxy)ethyl]-4-(3,4-dimethoxyphenyl)cyclohex-2-en-1-ol (24 and 25). To a stirred solution of the enone **23** (716 mg, 2.24 mmol) in methanol (40 mL) in the presence of cerium chloride (833.65 mg, 2.24 mmol) was added sodium borohydride (253.9 mg, 6.71 mmol) at 0 °C in small portions, and the mixture was stirred at ambient temperature for 1 h. Evaporation of the solvent gave the residue, which was extracted with ethyl acetate. The extract was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to column chromatography on silica gel. Elution with ethyl acetate–benzene (18:82, v/v) afforded the alcohol **24** (627 mg, 87%) as a gum [IR ($CHCl_3$) 3450, 1590 cm^{-1}; ^1H NMR δ 3.30 (3 H, s, OMe), 4.03 (6 H, s, 2 OMe), 4.50 (2 H, s, OCH_2O), 6.80 (3 H, br s, ArH); MS, m/z 322 (M^+); exact mass calcd for $C_{18}H_{26}O_5$ 322.1779, found 322.1774.] together with the isomer **25** (63 mg, 8.7%) as an inseparable epimeric mixture, and the epimeric ratio was determined on the basis of the NMR spectrum of the corresponding acetate. The reaction conditions and the results for this reduction were summarized in the table.

Claisen Rearrangement of the Alcohol 24. To a stirred refluxing solution of the alcohols **24** and **25** (10:1; 1.2 g, 3.7 mmol) in ethyl vinyl ether (50 mL) was added mercuric acetate (0.5 g). Addition of mercuric acetate (each 0.5 g) was repeated five times in every 2 h at refluxing temperature, and the resulting mixture was further heated overnight. After cooling, a catalytic amount of acetic acid was added to the solution, and the mixture was stirred at room temperature for 3 h. The mixture was washed with 5% aqueous potassium hydroxide solution and dried over Na_2SO_4. Removal of the solvent gave the vinyl ether **28**, whose solution in toluene (50 mL) was heated at 260 °C for 4 h in a sealed tube. After evaporation of the solvent, the residue was chromatographed on silica gel with ethyl acetate–benzene (5:95, v/v) as eluant to give the aldehyde **29** (1.026 g, 79%) as a gum: IR ($CHCl_3$) 1710, 1580 cm^{-1}; ^1H NMR δ 3.25 (3 H, s, OMe), 3.88 (6 H, s, 2 OMe), 4.45 (2 H, s, OCH_2O), 5.53–5.90 (2 H, m, olefinic protons), 6.83 (3 H, s, ArH), 9.48 (1 H, distorted s, CHO); MS, m/z 348 (M^+); exact mass calcd for $C_{20}H_{28}O_5$ 348.1935, found 348.1932.

4aβ-[2-(Methoxymethoxy)ethyl]-3,4,4a,10aβ-tetrahydro-6,7-dimethoxyphenanthrene (30). A solution of the aldehyde **29** (130 mg, 0.373 mmol) and a catalytic amount of p-toluenesulfonic acid in benzene (20 mL) was stirred at ambient temperature for 1 h. After basification with saturated aqueous sodium hydrogen carbonate solution, the mixture was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the residue, which was subjected to column chromatography on silica gel. Elution with ethyl acetate–benzene (5:95, v/v) afforded **30** (118 mg, 95%) as a gum: IR ($CHCl_3$) 1610 cm^{-1}; ^1H NMR δ 3.30 (3 H, s, OMe), 3.86 (3 H, s, OMe), 3.90 (3 H, s, OMe), 4.53 (2 H, s, OCH_2O), 5.82 (1 H, dd, J = 5.5, 9.0 Hz, 5-CH), 6.32 (1 H, d, J = 9.0 Hz, 6-CH), 6.62 (1 H, s, ArH), 6.83 (1 H, s, ArH); MS, m/z 330 (M^+); exact mass calcd for $C_{20}H_{26}O_4$ 330.1831, found 330.1836.

4aβ-(2-Hydroxyethyl)-3,4,4a,10aβ-tetrahydro-6,7-dimethoxyphenanthrene (31). A solution of the MOM ether **30** (28 mg, 0.085 mmol) and a few drops of 35% hydrochloric acid in methanol (10 mL) was heated at 62 °C for 0.5 h. The solution was basified with saturated aqueous sodium hydrogen carbonate solution and extracted with ethyl acetate. The extract was washed with water and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on silica gel with ethyl acetate–benzene (1:9, v/v) as eluant to afford the alcohol **31** (22 mg, 90%) as a gum: IR ($CHCl_3$) 3500, 1600 cm^{-1}; ^1H NMR (CCl_4) δ 3.43 (2 H, t, J = 7.0 Hz, CH_2OH), 3.80 (6 H, s, 2 OMe), 5.72 (1 H, dd, J = 5.5, 9 Hz, 5-CH), 6.20 (1 H, d, J = 9.0 Hz, 6-CH), 6.48 (1 H, s, ArH), 6.73 (1 H, s, ArH); Ms, m/z 286 (M^+); exact mass calcd for $C_{18}H_{16}O_3$ 286.1567, found 286.1561.

3,4,4a,10aβ-Tetrahydro-4aβ-[2-(methylamino)ethyl]-6,7-dimethoxyphenanthrene (32). To a stirred solution of the alcohol **31** (64 mg, 0.224 mmol) in methylene chloride (15 mL) were added triethylamine (0.03 mL, 0.269 mmol) and mesyl chloride (0.02 mL, 0.269 mmol) at 0 °C. The organic layer was washed with water and dried over Na_2SO_4. After evaporation of the solvent, the residue was dissolved in benzene (20 mL) containing methylamine (1 g), and the mixture was heated at 80 °C for 3 h in a sealed tube. The solvent and an excess of methylamine were removed to leave the residue, which was chromatographed on silica gel with methanol–chloroform (5:95, v/v) as eluant to afford the amine **32** (59 mg, 88%) as a gum: IR ($CHCl_3$) 3100, 1600 cm^{-1}; ^1H NMR δ 2.33 (3 H, s, NMe), 3.86 (3 H, s, OMe), 3.87 (3 H, s, OMe), 5.80 (1 H, dd, J = 6.0, 9.0 Hz, 5-CH), 6.27 (1 H, d, J = 9.0 Hz, 6-CH), 6.58 (1 H, s, ArH), 6.76 (1 H, s, ArH); MS, m/z 299 (M^+); exact mass calcd for $C_{19}H_{25}NO_2$ 299.1885, found 299.1885.

7,8-Dehydro-2,3,10α-trimethoxy-17-methyl-14β-morphinan (33). To a stirred solution of the amine **33** (154 mg, 0.517 mmol) in methylene chloride (20 mL) was added NCS (76 mg, 0.569 mmol) at −30 °C, and the mixture was further stirred for 0.5 h at −20 °C. After treatment with saturated aqueous sodium hydrogen carbonate, the organic layer was washed with water and dried over Na_2SO_4. Removal of the solvent gave the N-chloramine, which was dissolved into dry methanol (20 mL). To this solution was added silver oxide (132 mg, 0.569 mmol), and the resulting mixture was heated at 50 °C for 5 h. After an insoluble material was filtered through Celite pad, the filtrate was diluted with chloroform, and the organic layer was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave the residue, which was subjected to column chromatography on silica gel. Elution with methanol–chloroform (2:98, v/v) afforded the morphinan **33** (80 mg, 47%) as colorless needles: mp 143–144 °C (ether); IR ($CHCl_3$) 1600 cm^{-1}; ^1H NMR δ 2.53 (3 H, s, NMe), 3.21 (1 H, d, J = 3.0 Hz, 9-CH), 3.56 (3 H, s, OMe), 3.86 (3 H, s, OMe), 3.90 (3 H, s, OMe), 4.16 (1 H, s, 10-CH), 5.20–5.86 (2 H, m, 7-CH,

8-CH), 6.77 (1 H, s, ArH), 6.85 (1 H, s, ArH); MS, m/z 329 (M^+). Anal. Calcd for $C_{20}H_{27}NO_3 \cdot 0.1H_2O$: C, 72.52; H, 8.28; N, 4.23. Found: C, 72.43; H, 8.50; N, 3.95.

7,8-Dehydro-2,3-dimethoxy-17-methylmorphinan (34). To a stirred solution of **33** (65 mg, 0.198 mmol) in liquid NH_3 (30 mL) was added sodium metal (35 mg, 1.5 mmol), the mixture was stirred for a further 10 min at −78 °C and treated with methanol (5 mL), and then NH_3 was removed by warming. The residue was extracted with methylene chloride, and the extract was washed with water, dried over Na_2SO_4, and evaporated to give the residue, which was subjected to column chromatography on silica gel. Elution with methanol–chloroform (1:9, v/v) afforded the morphinan **34** (46 mg, 78%) as a gum: IR ($CHCl_3$) 1600 cm^{-1}; ^1H NMR δ 2.45 (3 H, s, NMe), 3.88 (6 H, s, 2 OMe), 5.52 (2 H, s, 7-H, 8-H), 6.60 (1 H, s, ArH), 6.76 (1 H, s, ArH); MS, m/z 299 (M^+); exact mass calcd for $C_{19}H_{25}NO_2$ 299.1886, found 299.1887.

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Ring Contraction Reactions of Dihydro- and Tetrahydrothiazepines to Isothiazolone Derivatives under Pummerer Conditions

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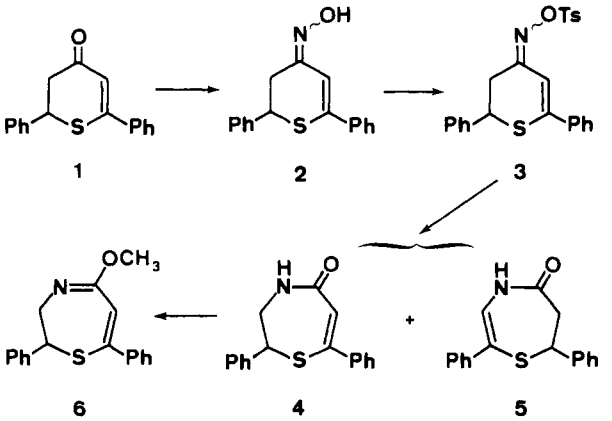
2,7-Diphenyl-5-oxo-2,3,4,5-tetrahydro-1,4-thiazepine (**4**) and 2,7-diphenyl-5-oxo-4,5,6,7-tetrahydro-1,4-thiazepine (**5**) were prepared from 2,3-dihydro-2,6-diphenyl-4*H*-thiopyran-4-one (**1**) through its *O*-tosyloxime (a mixture of syn and anti isomers) followed by Beckmann rearrangement (triethylamine in 70% aqueous dioxane). Upon Pummerer reaction (sodium acetate in acetic anhydride), 2,7-diphenyl-5-methoxy-2,3-dihydro-1,4-thiazepine 1-oxide (**7**), obtained from **4** through methylation by trimethyloxonium tetrafluoroborate followed by *m*-chloroperbenzoic acid oxidation, afforded 3-oxo-5-phenyl-(*Z*)-*N*-styrylisothiazole (**8**) quantitatively which on heating isomerized to the *E* isomer (**9**). The sulfoxide **10** derived from **4** also reacted with sodium acetate in acetic anhydride to give **9** along with 2-acetoxy-4,5-diphenylpyridine (**11**). On the other hand, when treated with trifluoroacetic anhydride in dichloromethane, the sulfoxide **10** gave *N*-[2-(trifluoroacetoxy)-2-phenylethyl]-3-oxoisothiazole (**17**) in good yield. The mechanisms of these ring contractions, **7** → **8** and **10** → **17**, which involve a common bicyclic intermediate (C), are suggested.

In general, conjugated seven-membered sulfur heterocycles such as thiepines[2] and thiazepines[3] are thermally unstable owing to their ready sulfur extrusion. It has already been demonstrated that the instability of these heterocycles can be largely overcome by introducing two bulky groups at both neighbors of the sulfur atom.[4] Recently we have reported the first synthesis of a stable monocyclic 1,4-thiazepine, 2,7-di-*tert*-butyl-5-methoxy-1,4-thiazepine,[5] utilizing the stabilizing effect of two *tert*-butyl groups. Prior to this success we had occasion to examine the 2,7-diphenyl-1,4-thiazepine system. In the course of this study we have found new ring contraction reactions of some dihydro- and tetrahydro-1,4-thiazepine derivatives.

Scheme I



Reaction of 2,3-dihydro-2,6-diphenyl-4*H*-thiopyran-4-one (**1**)[6] with hydroxylamine gave a mixture of the oximes

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(2) For reviews, see: (a) Field, L.; Tuleen, D. L.; Traynelis, V. J. In *Seven-Membered Heterocyclic Compounds Containing Oxygen and Sulfur*; Rosowsky, A., Ed.; Wiley-Interscience: New York, 1972; Chapters X and XI. (b) Murata, I.; Nakasuji, K. *Top. Curr. Chem.* **1981**, *97*, 33. (c) Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas.* **1982**, *101*, 277. (d) Eisner, U.; Krishnamurthy, U. *Int. J. Sulfur Chem.* **1971**, *6*, 267. (e) Reid, D. H. *Org. Compd. Sulphur, Selenium, Tellurium*, **1970**, *1*, 358; **1973**, *2*, 545; **1977**, *4*, 332.

(3) For a review, see: Wuensch, K. H.; Ehlers, A. *Z. Chem.* **1970**, *10*, 361.

(4) (a) Hoffman, J., Jr.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1970**, *92*, 5263. (b) Nishino, K.; Yano, S.; Kohashi, Y.; Yamamoto, K.; Murata, I. *J. Am. Chem. Soc.* **1979**, *101*, 5059. (c) Murata, I.; Nishino, K.; Yano, S.; Kohashi, Y.; Yamamoto, K. *Croat. Chem. Acta* **1980**, *53*, 615. (d) Yamamoto, K.; Yamazaki, S.; Kohashi, Y.; Murata, I.; Kai, Y.; Kanehisa, N.; Miki, M.; Kasai, N. *Tetrahedron Lett.* **1982**, *23*, 3195.

(5) Yamamoto, K.; Yamazaki, S.; Osedo, H.; Murata, I. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 635.

(6) Chen, C. H.; Reynolds, G. A.; Van Allan, J. A. *J. Org. Chem.* **1977**, *42*, 2777.

0022-3263/87/1952-5239$01.50/0