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(28) Dr. K. Smith, University of Liverpool, kindly communicated to us that he found a similar product in the Tl(III) oxidation of etioiporphyrin I. The ^{1}H NMR spectrum was very similar to the spectrum reported here (two methine proton signals), and elemental analysis also yielded additional hydrogen and oxygen.
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(30) W. Nolte, Dissertation, Braunschweig, 1967.
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(32) The X-ray analysis of crystalline green material **8b,B** revealed that this material contains a molecule of methanol as fifth ligand on each zinc ion. This did not show up in the elemental analysis; it may have evaporated on drying in high vacuum. The methanolic proton is hydrogen bonded to a ketone oxygen of a neighboring dioxoporphomethene molecule. Therefore two methanol molecules connect two chromophore molecules. The facile reducibility of this system, if it also occurred in solution, could be explained by the possibility of a proton shift toward the primarily formed anion radical to form a semiquinone-type of radical. The crystals for the X-ray analysis were obtained by crystallization from chloroform–methanol and recrystallization from ethanol. The crystal solvent molecule was exclusively methanol. Therefore the assumption of stability of this dimer in solution seems justified. The X-ray analysis of the red compound **8b,A** is in progress. We predict it to be the nonhydrogen bonded monomer of α,γ-dioxoporphodimethene (**8b**). We thank Dr. W. S. Sheldrick for allowing us to publish this note before publication of his structural work.
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Methods in Alkaloid Synthesis. Imino Ethers as Donors in the Michael Reaction

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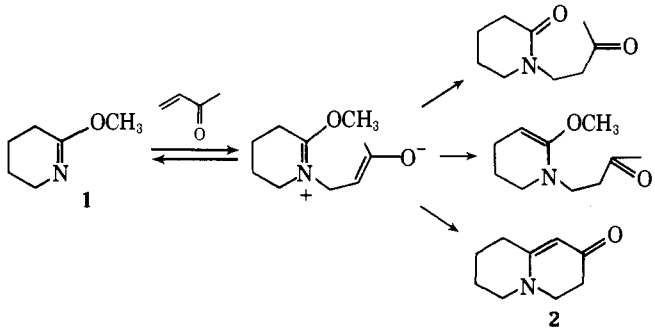
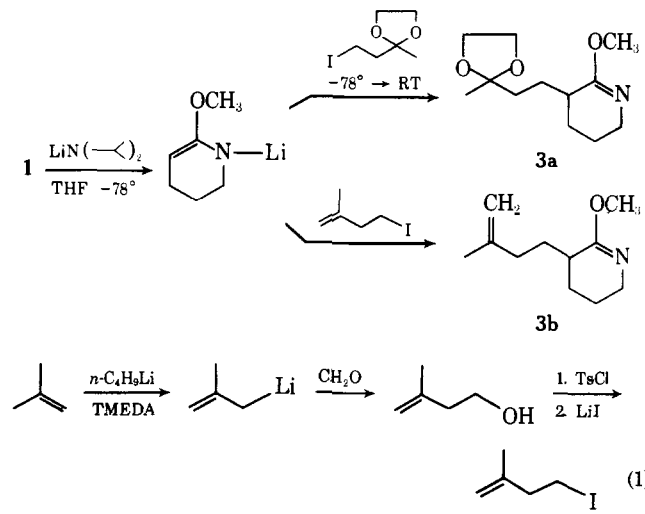
Abstract: Iminoethers serve as Michael donors toward α,β-unsaturated ketones provided the initial adduct is rapidly trapped. Ketal formation via amide acetals as the ketalizing agent constitutes a novel trapping method. Alternatively, rapid prototropic shift followed by cyclization onto the imino carbon when utilizing methyl 3-oxo-4-pentenoate also succeeds. The latter offers a convenient approach to 3,4,6,7,8,9-hexahydro-2-quinolizones, a good building block in alkaloid synthesis. The direct C-alkylation of lactims even with moderately unreactive alkyl halides and the synthesis of 2-cyanomethyldithiane and 5,5-trimethylenedithio-3-oxo-1-pentene, potentially useful reagents, are described.

The Michael reaction is an important synthetic method for creation of a wide range of structural types. For example, it serves as the key step in the Robinson annelation sequence. While many nucleophiles, including enolates of carbonyl systems, amines, thiols, etc., have served as Michael donors, secondary amides do not generally serve in this capacity, presumably because of an unfavorable equilibrium. In conjunction with an interest in the total synthesis of alkaloids, we became intrigued with the use of lactims, e.g., **1**, as Michael donors. Such a reaction could provide a facile entry into quinolizidines which form an important part of many alkaloids, e.g., lycopodine, yohimbine, lupinine, sparteine, eburnamine, etc. In particular, the 3,4,6,7,8,9-hexahydro-2-quinolizone (**2**) is an attractive building block,



however, not readily accessible.[2,3] Its formation via a Michael reaction is complicated by the anticipated enhanced reversibility of formation of the initial adduct because of the excellent leaving-group abilities of the imino ether. Indeed, attempts to condense 2-methoxy-3,4,5,6-tetrahydropyridine (**1**) with methyl vinyl ketone lead to no reaction. In this paper, we report the realization of this approach by trapping the initial Michael adduct in an irreversible fashion and its application for the synthesis of the hexahydro-2-quinolizones.

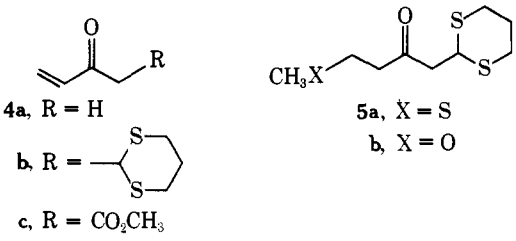
Preparation of Starting Materials. The systems chosen for study were the parent lactim **1** and the 3-alkylated lactims **3**. The lactims **3** were prepared by the alkylation of the lithium derivative of **1** with 1-iodo-3,3-ethylenedioxybutane and 1-iodo-3-methyl-3-butene, respectively.[4,5] The latter was available from isobutylene by the method outlined in eq 1.[6] Generation of the anions required the use of nonnucleo-



(1)

philic bases like lithium diisopropylamide. Carbon–carbon bond formation proceeded smoothly with no complications of N-alkylation. Since the imino ethers can be hydrolyzed to the lactams, this represents a useful approach for C-alkylation of secondary amides (lactams).

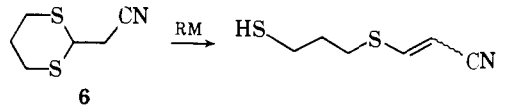
The initial Michael acceptor examined was dithiane **4b**.



4a, R = H
b, R =
c, R = CO_2CH_3

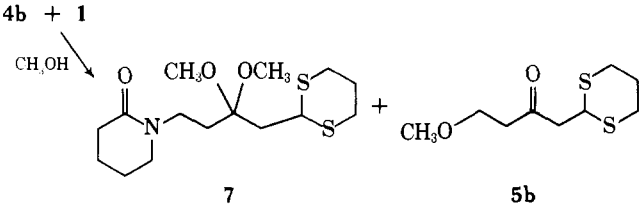
5a, X = S
b, X = O

Scheme I outlines the synthesis of this compound. The major stumbling block proved to be the oxidation of the allylic alcohol.[7] While on small scale, up to 90% yields were obtained utilizing manganese dioxide, larger scale reactions led to 79% yields. Moffatt oxidations were complicated by the production of **5a** which presumably arises by the conjugate addition of methyl mercaptan to the desired product. Attempts to circumvent this step by the use of cyanothioketal **6**[8] failed (see Experimental Section).



6

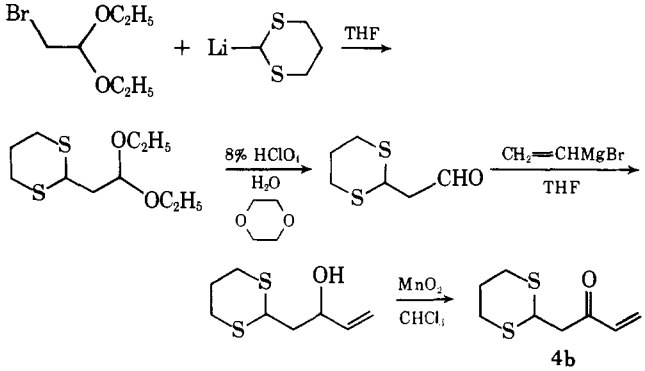
Conjugate Additions. Reaction of lactim **1** with enone **4b** in methanol (but not benzene, chloroform, ethanol, or *tert*-butyl alcohol) led successfully to the desired adduct **7** with varying amounts of a by-product **5b**. The structure of **7** was



	7	5b
RT	46%	34%
−15°	65%	
reflux		only

established by its spectral properties. High resolution mass spectrometry established the formula as $C_{15}H_{27}NO_3S_2$. The infrared spectrum showed only the presence of a lactam carbonyl group (1639 cm^{-1}). The NMR spectrum showed, in addition to the triplet (J = 7 Hz) for the methine proton of the dithiane ring at δ 4.18, the presence of 2 × CH_2N at δ 3.22 and 2 × CH_3O at δ 3.17. The spectral properties (see Experimental Section) also allow assignment of structure **5b** to the minor product. The adduct formed by conjugate addition of methanol to the Michael acceptor was the exclusive product in refluxing methanol but was totally eliminated at −15°. Decreasing the temperature of the reaction further was precluded by the sluggishness of the reaction at low temperature. The requirement of

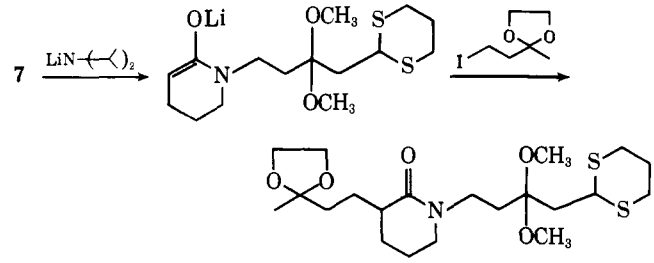
Scheme I. Synthesis of Annelating Agent 4b



4b

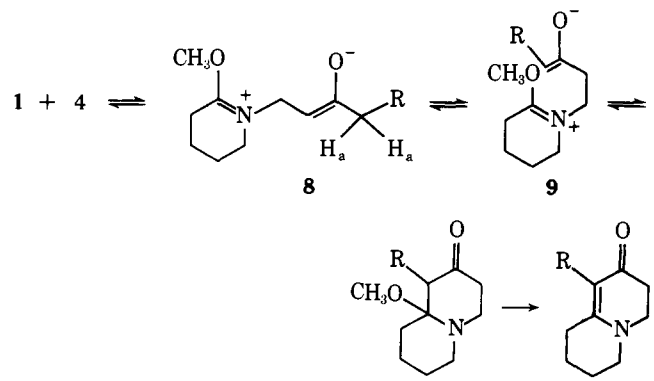
methanol as solvent suggests that the unfavorable equilibrium between starting material and product requires "locking" the product by ketal formation.[9] The failure of ethanol or 2-propanol to lock the product indicates that ketal formation may involve a displacement mechanism similar to esterification by amide acetals which shows a parallel effect.[10]

Support for the above interpretation derived from the sensitivity of the reaction to steric hindrance around the methoxy group of the lactim. Reaction of **3a** with the Michael acceptor **4b** led to no adduct under a wide variety of conditions. An authentic sample of the anticipated product was prepared by the direct alkylation of **7**. Seebach has



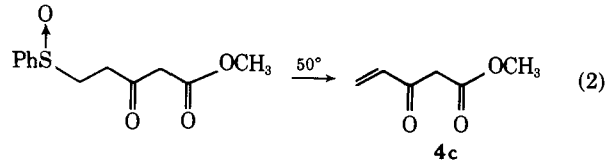
shown that an amide is more acidic than *s*-trithiane.[11] Similar results were obtained with **3b**.

The failure for the additions of **4a,b** as Michael acceptors in a solvent other than methanol suggests that proton transfer in the intermediate adduct (i.e., **8** ⇄ **9**) required to lock



the adduct by cyclization cannot compete with the reversal of **8**. To preclude the need for such proton transfer for cyclization, ethyl 3-chloro-2,4-pentadienoate was employed as a Michael acceptor. Nevertheless, no addition of the latter to **1** occurred. An alternative approach involves enhancing the acidity of H_a (**8**) to facilitate the equilibration and thereby cyclization of **7** and **9**.

Choice of the Nazarov reagent[12] was suggested by its successful use in annelation reactions[12-16] and the anticipated enhanced kinetic acidity of a methylene unit of an acetoacetate unit. We found the reagent to be most conveniently prepared by the sulfoxide elimination (eq 2).[17-19]



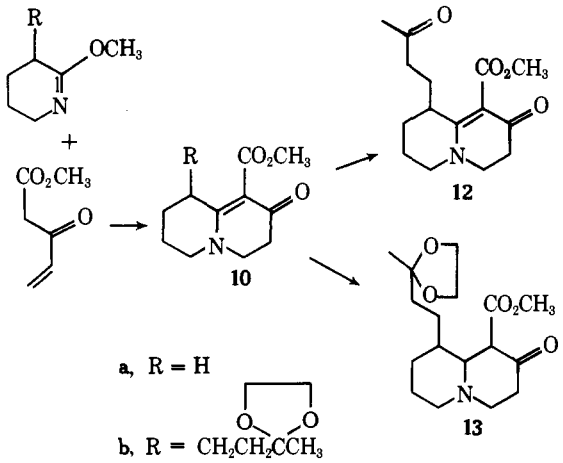
(2)

4c

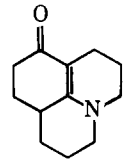
Simply allowing a methanolic solution of the lactim **1** and the vinyl ketone **4c** to stand produced a 54% yield of the adduct **10a** after purification. High resolution mass spectrometry established the formula to be $C_{11}H_{15}NO_3$. The infrared spectrum showed the presence of the vinylogous urethane as well as the vinylogous amide (1730, 1689, 1634, and 1550 cm^{-1}). The NMR was most helpful. The two

methylene groups flanking N appeared as a multiplet at δ 3.4, the allylic methylene group deshielded by the ester as a broad triplet (J = 6 Hz) at δ 2.68, the allylic methylene as the AB part of an ABCD pattern at δ 2.29, and the remaining four hydrogens as a multiplet at δ 1.8.

This reaction did not suffer from steric interference of a 3-substituent. Thus, the alkylated lactim **3a** also reacts quite cleanly to give consistently 60-70% isolated yields of the hexahydro-2-quinolizone **10b**. High resolution mass



spectroscopy established the formula as $C_{17}H_{25}NO_5$. The uv spectrum showed λ_{max} at 317 nm (ϵ 9000) and 253 (2200) compared with 315 (8200) for **11**[20] and 304 (16400) for **2**.[2] The infrared spectrum had bands at 1722, 1685,



11

1640, and 1550 cm^{-1} suggestive of the vinylogous urethane and amide units. The NMR spectrum showed singlets at δ 3.92, 3.76, and 1.30 for the ethylene ketal, the methyl ester, and the saturated methyl groups, respectively.

The ketal was easily hydrolyzed with aqueous hydrochloric acid at room temperature to give **12**. The chromophore remained intact (uv), and the ketal was removed as shown by the disappearance of the singlet for the ethylenedioxy unit and the shift of the *C*-methyl group to δ 2.15. Reduction of **10b** with DIBAL (diisobutylaluminum hydride) saturated the double bond chemospecifically to produce **13** as a mixture of isomers. High resolution mass spectroscopy established the fact that it picked up only two hydrogens. The infrared spectrum showed a saturated ester (1740 cm^{-1}) and ketone (1715 cm^{-1}), and the complexity of the NMR spectrum suggested an isomeric mixture. These reactions provide further characterization of **10b**.

Thus, the intrinsic nucleophilicity of imino ethers as Michael donors can be realized provided the initial enolate is rapidly trapped. Ketal formation via amide acetals and proton transfer from acetoacetate are efficient locking methods. Furthermore, the latter reaction provides a direct approach for the synthesis of hydrogenated 2-quinolizones.

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were determined on a Beckman IR-8 spectrophotometer and are calibrated at 1601 cm^{-1}. Nuclear magnetic resonance spectra were determined on a Varian A60A spectrometer. Chemical shifts are given in δ units relative to internal Me_4Si with the following abbreviations for multiplicity, s = singlet, d = doublet, t = triplet, q = quartet, b = broad. Mass spectra were taken on an AEI MS-902 at an ionizing current and voltage of 98 mA and 70 eV, respectively.

All reactions were carried out under an atmosphere of nitrogen. THF and DME were distilled from sodium benzophenone ketyl. Methanol was dried by distillation from magnesium methoxide. Benzene and methylene chloride were dried by distillation from calcium hydride. Glassware for experiments requiring anhydrous conditions was dried by flaming under a stream of nitrogen.

Column chromatography was performed on Grace silica gel, grade 62, mesh size 60-200. Preparative TLC was performed on 200 × 200 × 1.5 mm or 200 × 400 × 1.5 mm layers of Merck silica gel PF-254. Compounds were removed from the absorbent by repeated washings with ethyl acetate.

Preparation of 3,3-Diethoxypropionitrile. A mixture of 36.1 g (0.183 mol) of bromoacetaldehyde diethyl acetal (Aldrich) and 12.9 g (0.263 mol) of sodium cyanide in 75 ml of Me_2SO was stirred at 80° for 5 hr. After cooling 1 hr, the reaction was poured into 300 ml of water and extracted with 4 × 120 ml of ether. The combined ether layers were washed with 5 × 100 ml of saturated aqueous sodium chloride solution and dried over magnesium sulfate, and the solvent was removed by rotary evaporation in vacuo. Fractional distillation provided 21.0 g (80.0%) of a colorless liquid: bp 90-92° (8 mm); ir (CCl_4) 2262, 1123, 1064 cm^{-1}; NMR (CCl_4) δ 4.73 (2 H, t, J = 5.5 Hz, $-CH_2CN$), 3.60 (4 H, m, $-OCH_2CH_3$, nonequivalent), 2.58 (1 H, d, J = 5.5 Hz), 1.20 (6 H, t, J = 7 Hz, $-OCH_2CH_3$); mass spectrum *m/e* (% rel intensity) 103 (60), 98 (43), 75 (35), 70 (100), 47 (82), 45 (14), 43 (10), 42 (26), 31 (10); mol wt (calcd for $C_7H_{13}NO_2$, 143.0946) 143.0967.

Preparation of 3,3-Trimethylenedithiopropionitrile (6). A solution of 14.9 g (0.138 mol) of 1,3-propanedithiol and 20.0 g (0.140 mol) of 3,3-diethoxypropionitrile in 200 ml of chloroform was stirred at room temperature while a solution of 15 ml of boron trifluoride etherate (freshly distilled from CaH_2) was added dropwise over a 1-hr period. The reaction was then poured into 200 ml of 10% aqueous potassium hydroxide solution and extracted with 4 × 200 ml of ether. The combined ether layers were washed with 5 × 150 ml of saturated aqueous sodium chloride solution and dried over magnesium sulfate, and the solvent was removed by rotary evaporation in vacuo. Fractional distillation provided 21.01 g (94%) of a colorless liquid: bp 108-112° (0.03 mm); ir (CCl_4) 2281 cm^{-1}; NMR (CCl_4) δ 4.21 (t, J = 7 Hz, 1 H), 2.9 (m, 6 H), 2.0 (m, 2 H); mass spectrum *m/e* (% rel intensity) 159 (64), 121 (16), 119 (100), 91 (6), 85 (24), 84 (7), 75 (9), 74 (16), 73 (9), 59 (9), 58 (7), 47 (13), 46 (38), 45 (43); mol wt (calcd for $C_6H_9NS_2$, 159.0177) 159.0177.

Reaction of 3,3-Trimethylenedithiopropionitrile with Vinyllithium. A solution of 240 mg (1.5 mmol) of 3,3-trimethylenedithiopropionitrile in 15 ml of anhydrous ether was stirred at −78°, while 2 ml (2.2 mmol) of vinyllithium[21] (1.1 *M* in THF) was injected dropwise over a 1-min period. The reaction was stirred 0.5 hr at −78° and then poured into 50 ml of a 0.5 *N* hydrochloric acid-ice mixture. The mixture was extracted with 5 × 25 ml of ether, and the combined ether layers were washed with 3 × 25 ml of saturated aqueous sodium chloride solution. The ether solution was dried over magnesium sulfate and the solvent removed by rotary evaporation in vacuo. Purification by TLC using 1:1 pentane-ether solvent gave two major products. The band of R_f 0.22 provided 85 mg (35%) of (*Z*)-3-(3′-mercaptopropylthio)acrylonitrile as a colorless oil: ir (CCl_4) 2218 cm^{-1}; NMR (CCl_4) δ 7.02 (1 H, d, J = 10.5 Hz, C=CHCN), 5.22 (1 H, d, J = 10.5 Hz, C=CHS), 2.8 (4 H, m), 1.9 (2 H, m), 1.2 (1 H, t, J = 8 Hz, -SH); mass spectrum *m/e* (% rel intensity) 119 (100), 112 (38), 99 (12), 85 (17), 74 (29), 73 (12), 59 (14), 58 (14), 47 (27), 46 (39), 45 (55), 42 (10), 41 (71), 39 (22); mol wt (calcd for $C_6H_9NS_2$, 159.0176) 159.0176. The band of R_f 0.26 provided 127 mg (53%) of (*E*)-3-(3′-mercaptopropylthio)acrylonitrile as a yellow liquid: ir (CCl_4) 2222 cm^{-1}; NMR (CCl_4) δ 7.25 (1 H, d, J = 16 Hz, *trans*-C=CHCN), 5.19 (1 H, d, J = 16 Hz, *trans*-C=CHS), 2.7 (4 H, m), 1.95 (2 H, m), 1.25 (1 H, t, J = 8 Hz, -SH); mass spectrum *m/e* (% rel intensity) 159 (81), 119 (100), 118 (17), 112 (32), 100 (6), 99 (8), 85 (12), 84 (7), 83 (5), 75 (12), 74 (20), 72 (10), 47 (22), 46 (30), 45 (64), 39 (17); mol wt (calcd for $C_6H_9NS_2$, 159.0176) 159.0176.

Preparation of 1,1-Trimethylenedithio-4-penten-3-ol. A solution

of 50.1 g (0.212 mol) of 1,1-diethoxy-3,3-trimethylenedithiopropane,[22] 60 ml of perchloric acid, and 100 ml of water in 400 ml of dioxane was stirred for 0.5 hr at room temperature. The reaction was extracted with 4 × 250 ml of ether, and the combined ether layers were washed with 6 × 200 ml of saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was removed by rotary evaporation in vacuo to give 31.8 g (93% crude yield) of brown oil of sufficient purity to be used in the next step without further purification. A 5.2-g sample was further purified by distillation to give 3.8 g (68%) of 3,3-trimethylenedithiopropanal as a colorless oil: bp 62–68° (0.2 mm); ir (CCl_4) 2720, 1722 cm^{-1}; NMR (CCl_4) δ 9.65 (1 H, m, -CHO), 4.49 (1 H, t, J = 7 Hz, dithiane ring CH), 3.1 (6 H, m), 2.0 (2 H, m).

A solution of vinyl magnesium bromide[23] (0.24 mol) in 300 ml of dry THF was stirred at −5° while a solution of 34.3 g (0.212 mol) of 3,3-trimethylenedithiopropanal in 100 ml of dry THF was added dropwise over a 20-min period. The reaction was stirred 0.5 hr at −5° and then poured into 300 ml of saturated aqueous ammonium chloride solution–ice mixture. The mixture was extracted with 3 × 200 ml of ether, and the combined ether layers were washed with 4 × 100 ml of saturated sodium chloride solution and dried over magnesium sulfate, and the solvent was removed by rotary evaporation in vacuo to give 40.5 g (95% crude yield) of brown oil. Fractional distillation gave 19.2 g (47%) of pale yellow oil: bp 103–112° (0.08 mm); ir (CCl_4) 3650 and 3510 cm^{-1}; NMR (CCl_4) δ 5.82 (1 H, ddd, J = 17, 10, 5.5 Hz), 5.2 (2 H, m), 4.25 (3 H, m), 2.83 (4 H, m), 1.92 (4 H, m); mass spectrum *m/e* (% rel intensity) 190 (3), 176 (22), 131 (19), 119 (100), 69 (58); mol wt (calcd for $C_8H_{14}OS_2$, 190.0486) 190.0483.

Preparation of 1,1-Trimethylenedithio-4-penten-3-one (4b) Using Active Manganese Dioxide. A solution of 10.0 g (0.053 mol) of 1,1-trimethylenedithio-4-penten-3-ol in 350 ml of chloroform was stirred with 100 g of active manganese dioxide (prepared according to the method of Henbest et al.[24–27]) for 96 hr at room temperature. The reaction was filtered through a Büchner funnel packed with Celite, and the residue was washed with 4 × 100 ml of chloroform. The solvent was removed by rotary evaporation in vacuo to give 9.88 g of yellow oil. Column chromatography on 360 g of silica gel with 2% ether in benzene (v/v) provided 3.76 g of alcohol and 4.92 g (62% conversion, 79% yield) of yellow oil that crystallized on standing: mp 39–41°; ir (CCl_4) 1689 and 1615 cm^{-1}; NMR (CCl_4) δ 6.45–5.95 (3 H, m, -CH=CH_2), 4.53 (1 H, t, J = 7 Hz, -SCHS-), 2.95 (6 H, m), 2.00 (2 H, m); mass spectrum *m/e* (% rel intensity) 188 (54), 128 (50), 72 (20), 55 (100), 45 (35), 41 (19), 27 (42); mol wt (calcd for $C_8H_{12}OS_2$, 188.0330) 188.0345.

Oxidation of 1,1-Trimethylenedithio-4-penten-3-ol with Sulfur Trioxide–Pyridine Complex in Me_2SO.[28] Sulfur trioxide–pyridine complex[29] was prepared by slowly adding 33.6 g (19.0 ml, 0.288 mol) of chlorosulfonic acid to 48.0 g (51 ml, 0.608 mol) of cold (0°) pyridine, and the reaction was stirred 10 min at 0°. The resulting white solid was filtered, washed with 3 × 20 ml of carbon tetrachloride, and dissolved in 321 ml of Me_2SO to give a solution containing sulfur trioxide–pyridine and pyridine hydrochloride. This solution was added to a solution of 19.0 g (0.10 mol) of alcohol and 264 ml of triethylamine (purified by distillation from potassium hydroxide pellets) in 160 ml of Me_2SO at room temperature. After stirring 1 hr at room temperature, the reaction was poured into 200 ml of saturated aqueous sodium chloride solution–ice mixture and extracted with 3 × 400 ml of ether. The combined ether layers were washed with 6 × 200 ml of saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate, and the solvent was removed by rotary evaporation in vacuo. Purification by column chromatography on 1850 g silica gel with 20:1 benzene–ether gave 12.2 g (51.2%) of yellow oil identified as 1,1-trimethylenedithio-5-methylthiopentan-3-one: ir (CCl_4) 1725 (C=O) cm^{-1}; NMR (CCl_4) δ 4.38 (1 H, t, J = 7 Hz, -SCHS-), 2.70 (10 H, m), 2.03 (3 H, s, -SCH_3) superimposed on 2.0 (2 H, m); NMR (CCl_4 with 20% $Eu(fod)_3$) δ 5.76 (1 H, t, J = 7 Hz, C1), 4.06 (1 H, d, J = 7 Hz, C2), 3.73 (4 H, AA′BB′, -SCH_2CH_2CO-), 2.6 (4 H, m), 2.0 (3 H, s, -SCH_3), 1.75 (2 H, m); mass spectrum *m/e* (% rel intensity) 236 (100), 221 (5), 189 (15), 161 (46), 119 (98); mol wt (calcd for $C_9H_{16}OS_2$, 236.0363) 236.0358.

Reaction of 1,1-Trimethylenedithio-3-oxo-4-pentene (4b) with 2-Methoxy-3,4,5,6-tetrahydropyridine (1). A. A solution of 112 mg (0.595 mmol) of ketone **4b** and 78 mg (0.69 mmol) of imino ether **1** in 10 ml of methanol was stirred for 24 hr at room temperature. The solvent was removed by rotary evaporation in vacuo, and the residue was applied to a preparative TLC plate. One elution with 1:1 pentane–ether gave two major bands. The major band (R_f 0.21) provided 90.2 mg (46%) of **7** as a pale yellow gum: ir (CCl_4) 1639, 1050, and 909 cm^{-1}; NMR (CCl_4) δ 4.18 (1 H, t, J = 7 Hz), 3.22 (4 H, m) 3.17 (6 H, s) superimposed on 2.6–3.4 (6 H, m), 1.8–2.2 (8 H, m); mass spectrum *m/e* (% rel intensity) 301 (64), 194 (42), 189 (28), 154 (28), 119 (100), 112 (40), 101 (70), 84 (30), 55 (34), 41 (25); mol wt (calcd for $C_{15}H_{27}NO_3S_2$, 333.1432) 333.1443.

The second band provided 45 mg (34%) of 1,1-trimethylenedithio-5-methoxypentan-3-one as a colorless oil, R_f 0.58: ir (CCl_4) 1721, 1110, 909 cm^{-1}; NMR (CCl_4) δ 4.42 (1 H, t, J = 7 Hz, -SCHS-), 3.57 (2 H, t, J = 6.5 Hz, -CH_2C=O), 3.29 (3 H, s, -OCH_3), 2.75 (8 H, m), 2.0 (2 H, m); mass spectrum *m/e* (% rel intensity) 220 (20), 133 (40), 119 (86), 106 (15), 69 (100), 57 (30), 55 (30); mol wt (calcd for $C_9H_{16}O_2S_2$, 220.0592) 220.0550.

B. A solution of 102 mg (0.542 mmol) of vinyl ketone **4b** and 220 mg (1.95 mmol) of imino ether in 0.5 ml of methanol was stirred for 62 hr at −15°. The solvent was removed by rotary evaporation in vacuo, and the residue was applied to a preparative TLC plate. Elution with 1:1 benzene–ethyl acetate provided 118.2 mg (65%) of lactam **7**. No methoxy adduct or starting material was obtained.

Preparation of 1-Iodo-3,3-ethylenedioxybutane. To 200 ml of methylene chloride at 0° was added 72.30 g (0.546 mol) of anhydrous aluminum chloride through a powder funnel in ca. 5-g portions over a 15-min period. The powder funnel was then replaced with an addition funnel and 42.6 g (38.5 ml, 0.546 mmol) of acetyl chloride was added over a 10-min period. Ethylene gas bubbled into the reaction through a disposable pipet at a slow rate for 2 hr at 0° (Note: The pipet clogged easily and required periodic replacement). The reaction was then poured into a 1-l. separatory funnel and added dropwise to a stirred mixture of 125 ml of concentrated hydrochloric acid in 500 ml of ice–water. The mixture was extracted with 3 × 100 ml of methylene chloride. The combined organic layers were washed with 1 × 100 ml of water and 2 × 100 ml of saturated aqueous sodium bicarbonate solution and dried over magnesium sulfate, and the solvent was removed by rotary evaporation in vacuo. Fractional distillation gave 51.9 g (90%) of 1-chloro-3-butanone as a pale yellow liquid, bp 39–44° at 12 mm (lit[30] 48° at 15 mm). Infrared (CCl_4) 1722 cm^{-1}; NMR (CCl_4) δ 3.65 (2 H, t), 2.90 (2 H, t), 2.15 (3 H, s, -CH_3).

A solution of 95.9 g (0.638 mol) of sodium iodide in 1 l. of reagent grade acetone was added to 55.1 g (0.520 mol) of 1-chloro-3-butanone, and the reaction was refluxed for 5 hr and stirred 12 hr at room temperature. About 600 ml of solvent was removed by rotary evaporation in vacuo, and the residue was added to 500 ml of water. The mixture was extracted with 3 × 300 ml of CH_2Cl_2, and the combined organic layers were washed with 2 × 100 ml of 5% aqueous sodium thiosulfate solution and 3 × 200 ml of saturated aqueous sodium chloride solution and dried over magnesium sulfate. Removal of solvent by rotary evaporation in vacuo gave 98.1 g (95%) of 1-iodo-3-butanone as a yellow oil that darkened rapidly. The material was of sufficient purity to be used directly in the next step without further purification: ir (CCl_4) 1724 cm^{-1}; NMR (CCl_4) δ 3.25 (4 H, m), 2.16 (3 H, s).

A mixture of 55.2 g (50.0 ml, 0.923 mol) of ethylene glycol, 0.5 g (0.0026 mol) of *p*-toluenesulfonic acid, and 500 ml of benzene was refluxed in a 1-l. flask equipped with a Dean-Stark trap for 2 hr to remove water. A solution of 93.5 g (0.470 mol) of 1-iodo-3-butanone was added, and the reaction was refluxed for 5 hr. The reaction was allowed to cool to room temperature, and 1.0 g of sodium bicarbonate was added to neutralize the acid. After stirring 0.5 hr at room temperature, the reaction was poured into 400 ml of saturated aqueous sodium bicarbonate solution and extracted with 3 × 200 ml of benzene. The combined organic layers were washed with 1 × 200 ml of 5% aqueous sodium thiosulfate solution and 3 × 200 ml of saturated aqueous sodium chloride solution and dried over potassium carbonate, and solvent was removed by rotary evaporation in vacuo to give 93.75 g (82% crude yield) of brown liquid. The product was purified by fractional distillation at reduced pressure to give 74.3 g (65.2%) of iodo ketal as a yellow liquid: bp 60–62° (0.05 mm); ir (CCl_4) 1050, 942, and 842 cm^{-1}; NMR (CCl_4) δ 3.89 (4 H, s, -OCH_2CH_2O-), 3.1 (2 H, m), 2.2 (2

H, m), 1.25 (3 H, s, $-CH_3$); mass spectrum *m/e* (% rel intensity) 198 (10), 99 (44), 87 (100), 55 (10), 43 (56), 41 (15); mol wt (calcd for $C_6H_{11}IO_2$, 241.9804) 241.9804.

1-(3′,3′-Dimethoxy-5′,5′-trimethylenedithiopentyl)-3-(3′,3′-ethylenedioxybutyl)-2-piperidone. A solution of 242 mg (2.39 mmol) of diisopropylamine in 5 ml of THF was stirred at −78°, while 1.6 ml (2.40 mmol) of *n*-butyllithium (1.5 *M* in hexane) was added dropwise over a 1-min period. The reaction was stirred at −78° for 1 hr, and then 200 mg (0.601 mmol) of 1-(3′,3′-dimethoxy-5′,5′-trimethylenedithiopentyl)-2-piperidone (**7**) in 2 ml of THF was added dropwise with a syringe over a 1-min period. The reaction was stirred at −78° for 1.5 hr, and then a solution of 290 mg (1.2 mmol) of 1-iodo-3,3-ethylenedioxybutane in 2 ml of THF was added dropwise over a 1-min period. The reaction was stirred for 3 hr at −78° and 12.5 hr at −16°. The reaction was cooled to −78° and quenched with 8 drops of water, and the solvent was removed by rotary evaporation in vacuo. The residue was applied directly to a preparative TLC plate and eluted with ethyl acetate to give 41.3 g (17%) of gum with an R_f 0.35: ir (CCl_4) 1635 and 1050 cm^{-1}; NMR (CCl_4) δ 4.15 (1 H, t, J = 6 Hz), 3.85 (4 H, s, $-OCH_2CH_2O-$), 3.17 (6 H, s) superimposed on multiplet (4 H), 3.0–3.5, 2.75 (4 H, m), 1.5–2.1 (15 H, m), 1.25 (3 H, s, $-CH_3$); mass spectrum *m/e* (% rel intensity) 402 (11), 387 (8), 288 (10), 190 (18), 189 (12), 188 (14), 181 (12), 176 (14), 174 (10), 115 (14), 114 (24), 106 (100), 99 (14), 93 (15), 88 (13), 86 (20), 83 (15), 74 (95), 61 (16), 42 (26); mol wt (calcd for $C_{21}H_{37}NO_5S_2$, 447.2112) 447.2113.

Preparation of 2-Methyl-4-iodo-1-butene. A solution of 32 g (0.150 mol) of tetramethylethylenediamine (freshly distilled from KOH pellets) in 100 ml of THF was stirred at 0°, while 100 ml (0.150 mol) of *n*-butyllithium (1.5 *M* in hexane) was injected dropwise over a 5-min period. The reaction was stirred 0.5 hr at 0°, and then isobutylene was bubbled through the reaction at a slow rate for 3 hr. The flow of isobutylene was shut off, and the reaction was stirred at room temperature for 11 hr. The reaction was cooled to 0°, and 5.0 g (0.167 mol) of paraformaldehyde was added to the reaction in ca. 0.5-g portions over a 10-min period, and the reaction was stirred 1 hr at 0°. The reaction was then poured into a 100 ml saturated aqueous sodium chloride solution–ice mixture and extracted with 3 × 100 ml of ether. The combined ether layers were washed with 100 ml of 5% hydrochloric acid, 100 ml of 7% aqueous sodium bicarbonate solution, and 3 × 100 ml of saturated aqueous sodium chloride solution. The ether layer was dried over magnesium sulfate, and the solvent was removed by rotary evaporation in vacuo to give 8.25 g (63.7%) of 3-methyl-3-buten-1-ol as a pale yellow oil of sufficient purity (>95%) to be used directly in the next step. A sample of the oil was purified by fractional distillation to provide a colorless oil, bp 127–131° (lit.[31] 129–133°); ir (CCl_4) 3660, 3610, 3400, and 1650 cm^{-1}; NMR (CCl_4) δ 4.70 (2 H, m), 4.30 (1 H, s), 3.6 (2 H, t, J = 6 Hz), 2.2 (2 H, t, J = 6 Hz), 1.70 (3 H, t, J = 1.3 Hz); mass spectrum *m/e* (% rel intensity) 86 (5), 69 (32), 56 (7), 55 (25), 43 (100), 42 (10), 41 (30), 40 (25), 39 (20); mol wt (calcd for $C_5H_{10}O$, 86.0732) 86.0732.

A solution of 9.0 g (0.147 mol) of *p*-toluenesulfonyl chloride in 40 ml of reagent grade pyridine was stirred at 0° while 2.05 g (0.023 mol) of alcohol was added in three portions over a 1-min period. The reaction was stirred for 24 hr at 0° and then poured into a 200 ml of a water–ice mixture. The mixture was extracted with 3 × 50 ml of ether, and the combined ether layers were washed with 5 × 30 ml of saturated aqueous sodium chloride solution. The organic layer was dried over magnesium sulfate, and the solvent was removed by rotary evaporation in vacuo to give 4.69 g (82%) of 3-methyl-3-butenyl-1-*p*-toluenesulfonate as a yellow oil of sufficient purity to be used directly in the next step: ir (CCl_4) 1175 (S=O), 1094 (C—O), 660 (Ph) cm^{-1}; NMR (CCl_4) δ 7.45 (4 H, m), 4.67 (2 H, m, $C=CH_2$), 4.00 (2 H, t, J = 6.5 Hz), 2.38 (3 H, s, $-CH_3$), 2.20 (2 H, b t, J = 6.5 Hz), 1.60 (3 H, m, $-CH_3$); mass spectrum *m/e* (% rel intensity) 240 (1), 173 (19), 155 (59), 91 (84), 68 (100), 67 (22), 65 (19), 44 (23); mol wt (calcd for $C_{12}H_{16}O_3S$, 240.0820) 240.0820.

A mixture of 3.92 g (11.6 mmol) of 3-methyl-3-butenyl-*p*-toluenesulfonate in 24 ml of saturated sodium iodide–dimethylformamide solution was stirred at 50° for 2 hr. The reaction was allowed to cool to room temperature and poured into 50 ml of water and extracted with 3 × 50 ml of ether. The combined ether layers were dried over magnesium sulfate, and solvent was removed by rotary evaporation in vacuo. Fractional distillation provided 2.68 g (88%) of iodide **9** as a pale yellow oil: bp 28–30° (0.1 mm); ir (CCl_4) 1640 cm^{-1}; NMR (CCl_4) δ 4.72 (2 H, m), 3.18 (2 H, m), 2.50 (2 H, b t, J = 7 Hz), 1.68 (3 H, b s); mass spectrum *m/e* (% rel intensity) 196 (1), 120 (5), 74 (10), 69 (55), 55 (24), 53 (15), 46 (26), 45 (45), 43 (82), 42 (15), 41 (100); mol wt (calcd for C_5H_9I, 195.9749) 195.9746.

Preparation of 2-Methoxy-3-(3′,3′-ethylenedioxybutyl)-3,4,5,6-tetrahydropyridine (3a). A solution of 25.3 g (0.25 mol) of diisopropylamine in 300 ml of THF was cooled to −78°, and 166 ml (0.249 mol) of *n*-butyllithium (1.5 *M* in hexane) was injected in a steady stream over a 3-min period. The reaction was stirred 0.5 hr at −78°, and a solution of 5 ml of HMPA and 28.0 g (0.248 mol) of imino ether **1** in 25 ml of THF was injected dropwise over a 2-min period. The reaction was stirred 1 hr at −78°, and then 53.5 g (0.221 mol) of iodo ketal was injected dropwise over a 2-min period. The reaction was stirred 1 hr at −78°, 6 hr at −15°, and 6 hr at room temperature. The reaction was quenched with 100 ml of water and the solvent removed by rotary evaporation in vacuo until the volume was reduced to ca. 200 ml. The mixture was poured into 300 ml of water and extracted with 4 × 200 ml of methylene chloride. The combined organic layers were washed with 2 × 100 ml of saturated aqueous sodium chloride solution and dried over potassium carbonate, and solvent was removed by rotary evaporation in vacuo. The oil was dissolved in 50 ml of pentane and washed with 3 × 25 ml of water to remove excess HMPA. The pentane layer was dried over potassium carbonate and solvent removed by rotary evaporation to give 36.72 g of yellow oil. Fractional distillation provided 25.86 g (51.5%) of pale yellow oil: bp 92–100° (0.05 mm); ir (CCl_4) 1676 cm^{-1}; NMR (CCl_4) δ 3.82 (4 H, s), 3.50 (3 H, s), 3.30 (2 H, m), 1.8–2.2 (1 H, m), 1.5–1.8 (8 H, m), 1.20 (3 H, s); mass spectrum *m/e* (% rel intensity) 215 (15), 200 (3), 166 (7), 165 (5), 138 (18), 114 (19), 101 (22), 100 (9), 87 (14), 75 (100), 47 (7), 48 (8), 31 (28); mol wt (calcd for $C_{12}H_{21}O_3N$, 227.1521) 227.1521.

Preparation of 2-Methoxy-3-(3′-methyl-3′-butenyl)-3,4,5,6-tetrahydropyridine (3b). A solution of 303 mg (3.00 mmol) of diisopropylamine (freshly distilled from potassium hydroxide pellets) in 3 ml of dry THF was stirred at −78°, while 2 ml (3.0 mmol) of *n*-butyllithium (1.5 *M* in hexane) was injected dropwise over a 1-min period. The reaction was stirred 0.5 hr at −78°, and 282 mg (2.5 mmol) of 3-methoxy-3,4,5,6-tetrahydropyridine (**1**) was injected dropwise over a 1-min period. After stirring 1.5 hr at −78°, a solution of 490 mg (2.5 mmol) of 2-methyl-4-iodo-1-butene was injected over a 3-min period. Stirring was continued for 3 hr at −78° and for 0.5 hr at room temperature, and the reaction was poured into 50 ml of ether. The ether solution was washed with 3 × 50 ml of saturated aqueous sodium chloride solution and dried over magnesium sulfate, and the solvent was removed by rotary evaporation in vacuo. Purification by preparative TLC provided 272 mg (60.2%) of pale yellow oil having a R_f 0.36 with two elutions of chloroform: ir (CCl_4) 1672 and 1655 cm^{-1}; NMR (CCl_4) δ 4.63 (2 H, b s), 3.50 (3 H, s), 3.35 (2 H, m), 2.0 (3 H, m), 1.70 (3 H, b s) superimposed upon multiplet centered at 1.6 (6 H); mass spectrum *m/e* (% rel intensity) 181 (2), 167 (11), 162 (20), 155 (48), 126 (85), 124 (30), 123 (15), 113 (88), 112 (100), 111 (16), 110 (34), 109 (15), 99 (14), 98 (24), 91 (53), 84 (37), 81 (30), 69 (37), 68 (55), 67 (34), 65 (18), 56 (18), 55 (70), 53 (18), 41 (76); mol wt (calcd for $C_{11}H_{19}NO$, 181.1467) 181.1466.

Preparation of 1-Carbomethoxy-3,4,6,7,8,9-hexahydro-2-quinolizone (10a). A solution of 236 mg (2.11 mmol) of methyl 3-oxo-5-pentenoate[18] in 1.5 ml of methanol was stirred at room temperature, while 350 mg (2.92 mmol) of 2-methoxy-3,4,5,6-tetrahydropyridine was added dropwise over a 1-min period. After 2.5 hr, the reaction became bright yellow and TLC showed most of the starting vinyl ketone had disappeared. Solvent was removed by rotary evaporation in vacuo and the residue purified by TLC utilizing ethyl acetate to give 236 mg (54%) of product R_f 0.05: ir and NMR spectral data are detailed in the section on Results and Discussion; mass spectrum *m/e* (% rel intensity) 209 (48), 178 (100), 177 (68), 176 (26), 150 (15), 119 (43), 117 (43), 105 (28), 85 (48), 83 (74), 55 (28), 44 (38); mol wt (calcd for $C_{11}H_{15}NO_3$, 209.1052) 209.1038.

1-Carbomethoxy-9-(3′,3′-ethylenedioxybutyl)-3,4,6,7,8,9-hexahydro-2-quinolizone (10b). A solution of 1.0 g of *p*-toluenesulfonic

acid (dried by azeotropic distillation of benzene) in 30 ml of methanol (freshly distilled from magnesium methoxide) was stirred at room temperature, while 7.74 g (34.1 mmol) of 2-methoxy-3-(3′,3′-ethylenedioxybutyl)-3,4,5,6-tetrahydropyridine (**3a**) and 4.56 g (35.6 g) of methyl 3-oxo-4-pentenoate were added. After stirring for 64 hr at room temperature, the solvent was removed by rotary evaporation in vacuo, and the residue was dissolved in 100 ml of chloroform. The chloroform solution was washed with 2 × 25 ml of saturated aqueous sodium bicarbonate solution and 2 × 25 ml of saturated aqueous sodium chloride solution and dried over anhydrous potassium carbonate. Silica gel (37 g) was added to the chloroform solution, and the solvent was removed by rotary evaporation in vacuo. The impregnated silica gel was applied to a nylon chromatography column containing 200 g of silica gel containing Du Pont 609 phosphor and eluted with 1.5 l. of 20% ether in hexane. The major band visualized by uv was removed from the column and extracted with 1:1 methanol–ethyl acetate. The solvent was removed by rotary evaporation in vacuo to give 7.25 g (65.8%) of yellow oil, shown by NMR and TLC to be pure product. An analytical sample was prepared by preparative TLC of 374 mg of product to give 350 mg (94% recovery) of yellow oil: for infrared, ultraviolet, and NMR spectral data, see section on Results and Discussion; mass spectrum *m/e* (% rel intensity) 323 (15), 248 (10), 209 (82), 178 (12), 177 (14), 76 (12), 150 (25), 115 (15), 99 (80), 88 (21), 88 (100), 71 (22), 55 (40), 52 (28), 50 (85), 44 (90), 43 (92); mol wt (calcd for $C_{17}H_{25}NO_5$, 323.1733) 323.1733.

Preparation of 1-Carbomethoxy-9-(3′-oxobutyl)-3,4,6,7,8,9-hexahydro-2-quinolizone (12). A mixture of 3 ml of concentrated hydrochloric acid, 15 ml of THF, and 15 ml of water was added to 981 mg (3.04 mmol) of 1-carbomethoxy-9-(3′,3′-ethylenedioxybutyl)-3,4,6,7,8,9-hexahydro-2-quinolizone, and the reaction was stirred for 6 hr at room temperature. The reaction was poured into 40 ml of saturated aqueous sodium bicarbonate solution and extracted with 4 × 20 ml of chloroform. The combined chloroform solution was dried over magnesium sulfate, and the solvent was removed by rotary evaporation in vacuo. Purification by preparative TLC gave 848 mg (77%) of gum with an R_f 0.56 in 1:1 methanol–ethyl acetate: ir ($CHCl_3$) 1715, 1630, and 1558 cm^{-1}; uv (ethanol) 253 mμ (ε 2400), 317 (8300); NMR ($CDCl_3$) δ 3.75 (3 H, s), 3.4 (4 H, m), 2.4 (5 H, m), 2.18 (3 H, s), 1.8 (6 H, m); mass spectrum *m/e* (% rel intensity) 236 (5), 209 (8), 197 (22), 178 (15), 170 (35), 138 (20), 135 (18), 100 (29), 87 (47), 84 (100), 79 (26), 71 (20), 67 (25), 65 (24), 55 (22), 42 (45); mol wt (calcd for $C_{15}H_{21}NO_4$, 279.1496) 279.1496.

Preparation of 1-Carbomethoxy-9-(3′,3′-ethylenedioxybutyl)-1,3,4,6,7,8,9,9a-octahydro-2-quinolizone (13). A solution of 314 mg (0.97 mmol) of 1-carbomethoxy-9-(3′,3′-ethylenedioxybutyl)-3,4,6,7,8,9-hexahydro-2-quinolizone in 10 ml of toluene and stirred at 0°, while 1 ml (1.4 mmol) of diisobutylaluminum hydride (1.4 *M* in hexane) was injected dropwise over a 1-min period. After stirring for 5 hr at 0° and for 12 hr at room temperature, starting ketal was still present by TLC. An additional 0.6 ml (0.84 mmol) of diisobutylaluminum hydride (1.4 *M* in hexane) was injected dropwise over a 1-min period at room temperature, and the reaction was stirred for 2 hr at room temperature. The reaction was quenched with 2 ml of methanol, poured into 50 ml of water, and extracted with 8 × 25 ml of benzene. The combined benzene layers were washed with 3 × 25 ml of saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate solution, and the solvent was removed by rotary evaporation to give 295 mg of yellow gum. Purification by preparative TLC provided 61 mg (19%) of gum with an R_f 0.40 with 1:1 ethyl acetate–methanol: ir ($CHCl_3$) 1745 and 1720 cm^{-1}; NMR ($CDCl_3$) 3.92 (4 H, s), 3.75 (3 H, s), 3.5 (1 H, m), 3.0 (5 H, m), 2.5 (2 H, m), 1.6 (9 H, m), 1.31 and 1.33 (3 H, two s); mass spectrum *m/e* (% rel intensity) 325 (1), 211 (34), 180 (12), 153 (44), 111 (23), 110 (32), 96 (28), 85 (59), 84 (21), 83 (100), 55 (44), 47 (42), 44 (22), 43 (18), 42 (20), 41 (40); mol wt (calcd for $C_{17}H_{27}NO_5$, 325.1888) 325.1887.

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