^{1}H NMR (300 MHz, $CDCl_3$) δ 5.44 (dd, J = 11.8, 4.2 Hz, 1 H), 3.80 (m, 2 H), 2.57 (s, 3 H), 2.02-1.83 (series of m, 7 H), 1.51 (m, 2 H), 1.40-1.33 (m, 2 H), 1.31 (s, 3 H), 1.29-1.18 (m, 2 H), 1.15 (s, 3 H), 1.12 (s, 3 H), 1.09 (m, 1 H), 0.90 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.4, 90.8, 74.4, 59.7, 51.9, 47.2, 40.1, 34.7, 34.2, 33.7, 31.0, 30.6, 28.2, 24.1, 21.8, 21.0, 19.4, 18.9, 18.2; MS m/z (M^+) calcd 356.1844, obsd 356.1797; $[\alpha]_D^{25}$ -15.5° (c 0.3, $CHCl_3$).

A 17.9 mg (0.050 mmol) mixture of this xanthate was reduced in the manner described previously to give 8 (11.3 mg, 90%) as a colorless oil; IR ($CHCl_3$, cm^{-1}) 1441, 1379, 1348, 1102, 905; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84 (m, 1 H), 3.69 (dd, J = 11.7, 6.5 Hz, 1 H), 2.17-1.70 (series of m, 5 H), 1.66-1.42 (m, 5 H), 1.39-1.26 (m, 4 H), 1.24 (s, 3 H), 1.13 (s, 3 H), 1.10 (s, 3 H), 0.97 (d, J = 5.6 Hz, 1 H), 0.90 (s, 3 H), 0.89 (m, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 72.3, 60.2, 54.2, 47.1, 41.8, 39.9, 34.7, 34.4, 33.8, 31.0, 30.8, 28.7, 25.7, 22.3, 19.7, 19.6, 18.7; MS m/z (M^+) calcd 250.2297, obsd 250.2250; $[\alpha]_D^{25}$ -5.6° (c 0.8, $CHCl_3$). Anal. Calcd for $C_{17}H_{30}O$: C, 81.54; H, 12.07. Found: C, 81.21; H, 12.00.

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Studies Directed at the Synthesis of Optically Active Pretazettine via Intramolecular Nitrone/Alkene Cycloaddition Reactions[1]

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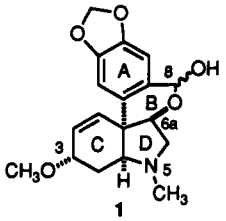
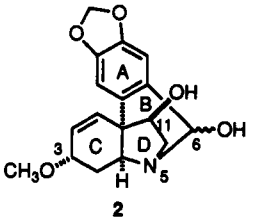
A protocol for the synthesis of optically active pretazettine which focuses on both the control of relative stereochemistry between the angular aryl and C6a hydroxyl groups and absolute stereochemistry has been developed and executed. The synthesis of the 1,3-dithiane ketal of (*Z*)-ethyl 3-(1,3-benzodioxol-5-yl)-5,7-dioxo-2-heptanoate is described. Treatment of this alkene aldehyde with *N*-(α-methylbenzyl)hydroxylamine afforded a nitrone, which underwent intramolecular 1,3-dipolar cycloaddition to afford the two diastereomeric isoxazolidine cycloadducts in a 16:1 ratio. The sense of chirality transfer was determined by a single-crystal X-ray analysis of the major isomer.

Introduction

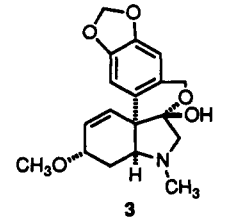
Pretazettine (1), a member of the crinine class of Amaryllidaceae alkaloids, was first characterized in the early 1960s.[2,3] Interest in pretazettine stems from its promising antitumor[4] and antiviral[5] activity. Any synthetic work directed at pretazettine must take into account the complex relationships which exist among pretazettine (1), haemanthidine (2), and tazettine (3), which have been elegantly detailed by Wildman,[3] as well as 6a-epipretazettine (4).[6] In particular, Wildman showed that haemanthidine methiodide is converted to pretazettine under mildly acidic conditions (pH 4) and that pretazettine is further converted to tazettine under basic conditions. This tendency to rearrange to tazettine constitutes one of the more interesting yet frustrating features of pretazettine architecture.



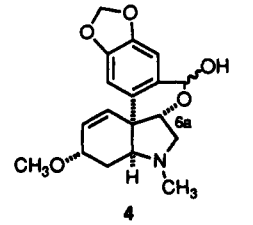
1



2



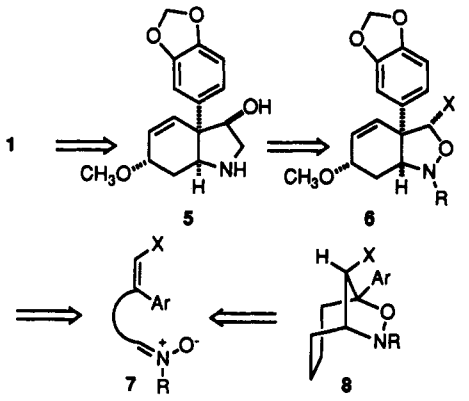
3



4

The first successful synthesis in the pretazettine area was that of Hendrickson in 1970,[7] who prepared racemic haemanthidine and, therefore, pretazettine. All other syntheses of pretazettine have also involved the intermediacy of haemanthidine.[8-10] Without exception, attempts

Scheme I



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(1) (a) Taken in part from the Ph.D. dissertation of J.A., Duke University, 1984. (b) A portion of this work was presented at the 188th National Meeting of the American Chemical Society, Philadelphia, PA, August 27-31, 1984; paper ORGN 171. (c) Partial support from the National Institutes of Health is gratefully acknowledged (GM 31634).

(2) For a recent review, see Amaryllidaceae alkaloids: Martin, S. F. The Amaryllidaceae Alkaloids. In The Alkaloids; Brossi, A., Ed.; Academic Press: San Diego, 1987; Vol. 30, pp 251-376.

(3) (a) Wildman, W. C.; Bailey, D. T. *J. Org. Chem.* **1968**, *33*, 3749. (b) Wildman, W. C.; Bailey, D. T. *J. Am. Chem. Soc.* **1969**, *91*, 150 and references therein.

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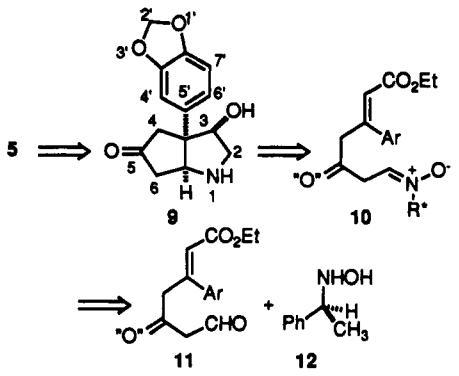
0022-3263/91/1956-6546$02.50/0

Scheme II



to prepare pretazettine directly, that is, without involving an haemanthidine-to-pretazettine conversion, have been unsuccessful.[11,12] Several studies which could, in principal, have afforded either pretazettine or 6a-epipretazettine (cis B/D ring fusion) have all resulted in the more stable 6a-epi isomer.[13] For these reasons the control of the relative stereochemistry (trans) between the secondary C6a hydroxyl group and the angular aryl group remains the most challenging issue associated with this synthetic target. In addition, the question of absolute stereochemical control in a pretazettine synthesis has not yet been addressed.

While considering a variety of solutions to these stereochemical problems, the possibility of securing the desired result through an intramolecular nitrone/alkene cycloaddition reaction was pursued (Scheme I).[14] By this scheme, cycloaddition of nitrone/alkene **7** would provide isoxazolidine **6** (X = CH_2Y), which after reduction of the labile N–O bond and intramolecular alkylation on nitrogen would yield an intermediate such as **5**. Previous studies which have led to haemanthidine (**2**) have involved intermediates similar to **5**, and therefore this route represents the "safest" approach at this time. The desired stereochemical outcome would thus be a consequence of the alkene stereochemistry in the cycloaddition precursor **7**, with several potential solutions to alkene stereochemistry problems being available. During a series of model studies to test this hypothesis it was discovered that the cycloaddition of compounds such as **7** (X = CO_2Et), in which the connecting tether contained *four* atoms, led exclusively to [4.2.1]-bridged products such as **8** (X = CO_2Et) rather than to the desired [4.3.0]-fused products related to **6**. This result is what would be expected on the basis of FMO considerations for similarly substituted bimolecular processes.[14] Interestingly, when the tether length was reduced to *three* atoms, the regiochemical sense of the cycloaddition was totally reversed to yield only the [3.3.0]-fused products related to **6**. These results have been reported previously.[15]

Armed with this information, a strategy for a pretazettine synthesis was devised which addressed the stereochemical issues discussed above by incorporating a five-membered C ring (pretazettine numbering) with the expectation that the desired target would be available through a one-carbon ring-expansion process (Scheme II). It was expected that incorporating a ketone into ring A of **9** would provide the requisite handle for the ring-expansion process as well as serve as the source for the functional groups in the C ring of pretazettine. A protected version of keto aldehyde **11** was chosen as the target substrate for this synthesis. Of further interest was the possibility that the cycloaddition reaction with an achiral substrate such as **11** might provide optically active products if an optically active hydroxylamine such as *N*-(α-methylbenzyl)-hydroxylamine (**12**) were used to make nitrone **10**. Reported here are the results of these studies.

Cycloaddition Studies

The synthesis of aldehyde **19** was relatively straightforward (Scheme III). Alkylation of the 2-lithiodithiane derivative **13**[16] with epoxide **14**[17] proceeded as expected to afford alcohol **15** (53%), which was then oxidized with activated MnO_2 to give ketone **16** (59%). Other oxidants (PCC; $DMSO/COCl_2$) led to numerous other products in addition to **16**. Olefination of **16** proved to be rather difficult. Standard Wittig and Horner–Emmons–Wadsworth reactions were completely ineffective. In similar systems we have found that aryl ketones unsubstituted in the aryl ring react well with a variety of phosphonate derivatives. In aryl ketones such as **16**, however, the presence of the electron-donating methylenedioxy group apparently is sufficient to reduce the electrophilicity of the carbonyl group and render it unreactive toward phosphorus-based reagents.[18] Addition of the anion of ethyl acetate to **16** afforded the expected tertiary alcohol, but dehydration proved to be difficult. On the other hand, a Peterson olefination using the lithium anion of ethyl (trimethylsilyl)acetate occurred smoothly at −78 °C to afford a mixture of alkenes **17** and **18** in good yield.[19] Purification by flash chromatography[20] yielded **17** and **18**

(5) Papas, T. S.; Sandhaus, L.; Chirigos, M. A.; Furusawa, E. *Biochem. Biophys. Res. Commun.* **1973**, *52*, 88.
(6) The numbering system employed here for compounds 1–4 is as originally suggested by Wildman (ref 3).
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(9) (a) Martin, S. F.; Davidsen, S. K. *J. Am. Chem. Soc.* **1984**, *106*, 6431. (b) Martin, S. F.; Davidsen, S. K.; Puckette, T. A. *J. Org. Chem.* **1987**, *52*, 1962.
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(11) (a) Danishefsky, S.; Morris, J.; Mullen, G.; Gammill, R. *J. Am. Chem. Soc.* **1980**, *102*, 2838. (b) Danishefsky, S.; Morris, J.; Mullen, G.; Gammill, R. *Ibid.* **1982**, *104*, 7591.
(12) Kobayashi has reported that tazettine can be converted to pretazettine in 4% yield by reduction with $LiAlH_4$ followed by MnO_2 oxidation. (a) Kobayashi, S.; Kihara, M.; Shingu, T. *Heterocycles* **1979**, *12*, 1547. (b) Kobayshi, S.; Kihara, M.; Shingu, T.; Shingu, K. *Chem. Pharm. Bull.* **1980**, *28*, 2924.
(13) (a) White, J. D.; Chong, W. K. M.; Thirring, K. *J. Org. Chem.* **1983**, *48*, 2302. (b) Overman, L. E.; Wild, H. *Tetrahedron Lett.* **1989**, *30*, 647. (c) Abelman, M. M.; Overman, L. E.; Tran, V. D. *J. Am. Chem. Soc.* **1990**, *112*, 6959.
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(15) Baldwin, S. W.; Wilson, J. D.; Aubé, J. *J. Org. Chem.* **1985**, *50*, 4432.
(16) Krug, R.; Jugelt, W. *Z. Chem.* **1981**, *21*, 406.
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in 36% and 38% yields, respectively. The structures of the two alkenes were assigned on the basis of their ^1H NMR spectra. Particularly diagnostic were the resonances for the two allylic methylene groups, which appeared at δ 3.13 in *Z* isomer **17** and at δ 3.88 (deshielded by the syn CO_2Et) in the undesired *E* isomer **18**. These assignments were subsequently confirmed by a single-crystal X-ray analysis of a later intermediate (vide infra). Interestingly, the vinyl resonances in the two isomers were too close to be of value (δ 6.09 and 6.03, respectively) in differentiating between the two double-bond isomers. Attempts to convert **18** to **17** under a variety of conditions (H_2SO_4/EtOH; NaOEt/EtOH; PhSH/Δ; PhH/$h\nu$) were unproductive.[21]

Efforts to improve the stereoselectivity of the Peterson olefination step were also unsuccessful. Although it is generally possible to achieve either of the potential stereoselective eliminations from a given α-hydroxy silane intermediate by a correct choice of reaction conditions (acid or base), the α-hydroxy silanes derived from esters are usually so reactive that they undergo elimination under the conditions of the addition reaction. Because the initial addition step is generally stereorandom, there is little hope for stereochemical control in these olefination reactions. Even so, this three-step route to **17** did provide ready access to multigram quantities of this stereochemically homogeneous key intermediate. The olefination problem has since been addressed with several related methylenedioxy-substituted aryl ketones, with promising general solutions under active investigation.[18]

Liberation of the aldehyde group to give **19** (98%) was followed by treatment with the oxalate salt of racemic *N*-(α-methylbenzyl)hydroxylamine (**12**)[22] in benzene containing suspended K_2CO_3. The resulting nitrone **20**, which existed as a ~5:1 mixture of *Z*/*E* isomers on the basis of its ^1H NMR spectrum, was then heated at reflux in benzene for 2 h to afford a mixture of the crude diastereomeric isoxazolidines **21** and **22**. Analysis of the ^1H NMR spectrum of the product mixture showed it to be a 16:1 mixture of the two product isomers, which were isolated in 70% overall yield from acetal **17**. The major isomer was then obtained in pure form by chromatographic separation of the two products. To our knowledge, this selectivity is the highest observed to date for intramolecular nitrone/alkene cycloadditions of this type,[23] and the prospect of using this reaction to obtain optically pure alkaloids from achiral substrates is very encouraging since gram quantities of diastereomerically pure products were obtained in a relatively short time.

The sense of the chirality transfer in this cycloaddition process is an important issue, and the identity of the major isomer (racemic, mp 132–4 °C) and its important stereochemical relationships were determined by a single-crystal X-ray analysis.[24] This study established that the required *S* configuration at C6a in **21** is the result of a cycloaddition reaction using the nitrone derived from (*S*)-*N*-(α-methylbenzyl)hydroxylamine, and thus optically active pretazettine (**1**) of the correct absolute configuration will require that the cycloaddition reaction be carried out with (*S*)-*N*-(α-methylbenzyl)hydroxylamine (**12**). It is important to emphasize that, from an achiral substrate such as **19**, the cycloaddition reaction employing (*S*)-hydroxylamine **12** has afforded a compound with three new chiral centers of the correct relative and absolute stereochemistry in a single step.

Similar cyclization of the (*E*)-alkene nitrone isomer **23** afforded the corresponding isoxazolidine cycloadducts **24** and **25** (78% yield) in a 4.0:1 ratio. This isomer ratio is significantly lower than the 16:1 ratio observed for the cycloaddition of nitrone **20** and is more in line with the ratios of similar cycloaddition reactions previously reported in the literature.[23] The absolute sense of chiral transfer in this latter case has not been determined.[25]

At this point we turned our attention to elaboration of **21**, with the first goal being the conversion of the isoxazolidine B ring into a pyrrolidine derivative more closely resembling that found in pretazettine (Scheme IV). Exposure of **21** to excess metallic Zn in acetic acid at reflux for 12 h yielded lactam acetate **26** in 75% yield by a process involving N–O bond reduction, lactamization, and esterification.[26] It is worth noting that this process has established the necessary B ring of pretazettine, with the nitrogen protected as its lactam, as well as the trans relationship between the C6a hydroxyl group and angular aryl group (pretazettine numbering) of the target alkaloid. Incorporation of a more robust alcohol protecting group was then accomplished in 65% yield by hydrolysis (NaOMe/MeOH) followed by benzylation to give benzyl ether **27**. Although a variety of conditions were ineffective in hydrolyzing the A-ring dithiane to a carbonyl group,[27] the two-step procedure of Carlson proved satisfactory.[28] Thus, initial treatment of **27** with NBS in methanol at −10 °C yielded ketal **28**, which was rapidly hydrolyzed to ketone **29** in 60–70% yield on exposure to aqueous acid. Ketone **29** represents the result of an efficient assembling of the critical stereochemical features of pretazettine from readily available starting materials, with the added benefit of absolute stereochemical control.

Attention was next turned to the one-carbon ring expansion of the cyclopentanone A ring. Several different strategies were considered and attempted (pinacol related, cleavage/recyclization, etc.). Unfortunately all met with failure and **29** represents the furthest point attained by this route.[24]

Summary

The results described above detail the efficient construction of an advanced intermediate in the synthesis of pretazettine in which key stereochemical issues, relative and absolute, were addressed and solved. Difficulties encountered in converting this intermediate to pretazettine, specifically the crucial ring expansion of the A-ring cyclopentanone of **29**, have prevented successful completion of the project. Related efforts involving a similar cycloaddition approach in which a ring-expansion "handle" has been incorporated into the alkene/nitrone substrate are currently in progress.

(20) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
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(22) Polanski, T.; Chimiak, A. *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **1979**, *27*, 459. See also ref 23a for an improved preparation.
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(24) Details of the crystal structure analysis, including an ORTEP representation of **21**, are provided in the supplementary material. In addition, a summary of the attempts to perform a one-carbon ring expansion on ketone **29** is also included. See the supplementary material paragraph at the end of the paper.
(25) Two studies detailing the stereochemical aspects of related intramolecular nitrone/alkene cycloadditions have recently appeared. (a) Baldwin, S. W.; Gedon, S. C. *Syn. Commun.* **1991**, *21*(4), 587. (b) Baldwin, S. W.; McFadyen, R. B.; Aubé, J.; Wilson, J. D. *Tetrahedron Lett.* **1991**, *32*, 4431.
(26) (a) Dagne, E.; Castagnoli, N., Jr. *J. Med. Chem.* **1972**, *15*, 356. (b) Huisgen, R.; Hauck, H.; Grashey, R.; Seidl, H. *Chem. Ber.* **1968**, *101*, 2568.
(27) Normant, J. F.; Deshayes, H. *Bull. Soc. Chim. Fr.* **1972**, 2854.
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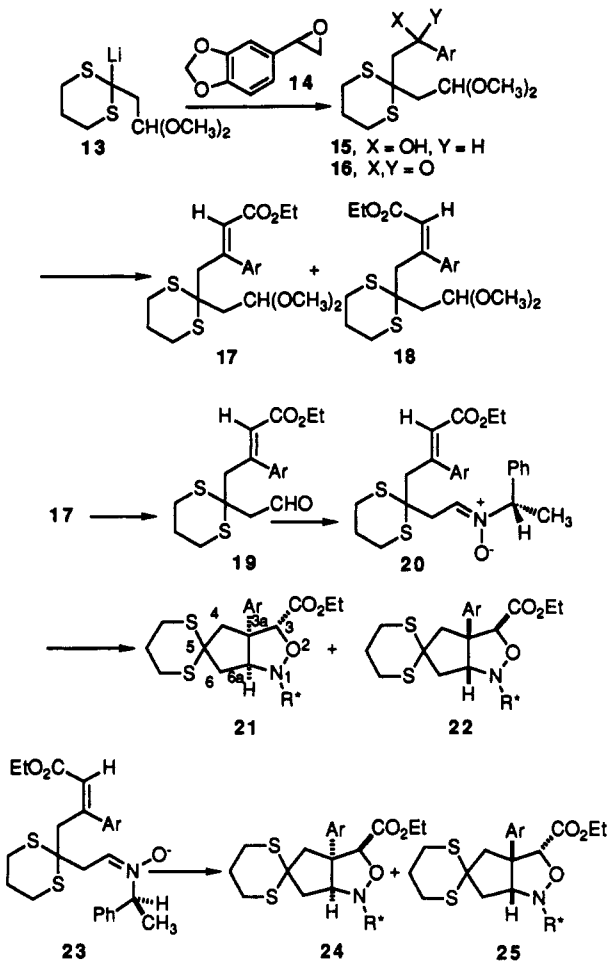
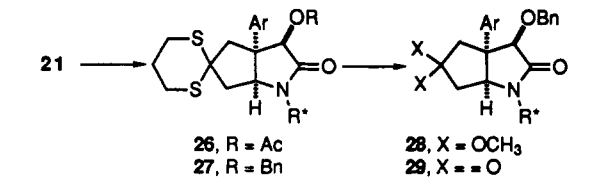
Scheme III



Scheme IV



Experimental Section

General Methods. General experimental details have been described recently.[15] All compounds reported in this work are racemic unless otherwise noted. The prefix "*d,l*" has been omitted in most cases. In cases where the name of the compound includes "*R*" or "*S*", the (*) symbol signifies that the compound with the indicated absolute stereochemistry is accompanied by its enantiomer (e.g., *R** and *S**).

2-(2,2-Dimethoxyethyl)-α-(1,3-benzodioxol-5-yl)-1,3-dithiane-2-ethanol (15). A solution of 18.9 g (0.091 mol) of 2-(2,2-dimethoxyethyl)-1,3-dithiane[16] in 200 mL of dry THF was cooled to −78 °C whereupon a 2.6 M solution of *n*-BuLi (36.7 mL, 0.095 mol) was added dropwise and the solution stirred for an additional 1 h. To the resulting anion was then added 14.9 g (0.091 mol) of 5-oxiranyl-1,3-benzodioxole (**14**)[17] in 50 mL of THF dropwise at −78 °C, and the reaction mixture was sealed and placed in the freezer (−20 °C) for 36 h. Aqueous workup (ether) gave a reddish oil, which was purified by flash chromatography[20] (3:1 petroleum ether/ether) to afford 18.0 g of **15** (53%) as a light green oil: ^{1}H NMR δ 6.79–6.81 (m, 3 H, Ar H), 5.93 (s, 2 H, OCH_2O), 5.02 (m, 1 H, C*H*(OH)CH_2), 4.76 (t, *J* = 4.8 Hz, 1 H, C*H*$(OMe)_2$), 3.92 (d, *J* = 3.3 Hz, 1 H, OH), 3.41 (s, 3 H, 1 OCH_3), 3.35 (s, 3 H, 1 OCH_3), 2.84–3.00 (m, 4 H, SCH_2's), 2.23–2.53 (m, 4 H, CH(OH)CH_2 and CH_2CH$(OMe)_2$), 1.82–2.17 (m, 2 H, SCH_2CH_2); IR (film) 3450, 3050, 1490, 1440, 1240, 1010, 920, 810 cm^{-1}.

Anal. Calcd for $C_{17}H_{24}O_5S_2$: C, 54.81; H, 6.49. Found: C, 54.73; H, 6.43.

2-(2-(1,3-Benzodioxol-5-yl)-2-oxoethyl)-2-(2,2-dimethoxyethyl)-1,3-dithiane (16). A suspension of 18.0 g (0.048 mol) of compound **15** and 250 g of activated MnO_2 in 600 mL of CH_2Cl_2 was stirred overnight at room temperature whereupon the reaction mixture was filtered and the solids were thoroughly washed with CH_2Cl_2. The solvents were removed under reduced pressure to afford 10.6 g (59%) of **16** as an unstable yellow powder, mp 74–78 °C, which was used without further purification. A yield of 42% of **16** from **14** could be obtained for two steps on a 0.15-mol scale: ^{1}H NMR δ 7.30–7.70 (m, 2 H, 2 Ar H's), 6.83 (d, *J* = 7.7 Hz, 1 H, Ar H), 6.03 (s, 2 H, OCH_2O), 4.72 (t, *J* = 4.8 Hz, 1 H, C*H*$(OMe)_2$), 3.52 (br s, 2 H, C(OH)CH_2C$(SR)_2$), 3.25 (s, 6 H, OCH_3), 2.86–3.07 (m, 4 H, SCH_2's), 2.65 (d, *J* = 4.8 Hz, 2 H, CH_2CH$(OMe)_2$), 1.86–2.21 (m, 2 H, SCH_2CH_2); IR ($CDCl_3$) 2950, 1685, 1440, 1310, 1255, 1020 cm^{-1}; HRMS (M^+) calcd for $C_{17}H_{22}O_5S_2$ 370.0909, found 370.0919.

2-(2-(1,3-Benzodioxol-5-yl)-3-(ethoxycarbonyl)-2(*Z*)-propenyl)-2-(2,2-dimethoxyethyl)-1,3-dithiane (17) and *E*-Isomer (18). To a solution of 12.6 g (0.069 mol) of dicyclohexylamine in 350 mL of dry THF cooled to −78 °C was added dropwise 2.6 M *n*-BuLi (33 mL, 0.07 mol), and the mixture was stirred for 20 min followed by the dropwise addition of 12.2 g (0.076 mol) of ethyl (trimethylsilyl)acetate and further cooling to −95 °C (bath temperature, ether/dry ice). Ketone **16** (10.0 g, 0.027 mol) in 50 mL of THF was added dropwise and the reaction mixture stirred at −95 °C for 2 h. Aqueous workup (ether/saturated citric acid) followed by chromatography gave alkenes **17** (R_f = 0.44 (1:1 ether/petroleum ether)) (4.25 g, 36%) and **18** (R_f = 0.56 (1:1 ether/petroleum ether)) (4.55 g, 38%) as viscous oils.

17: ^{1}H NMR δ 6.76 (br s, 3 H, Ar H), 6.09 (br s, 1 H, vinyl H), 5.94 (s, 2 H, OCH_2O), 4.64 (t, *J* = 4.8 Hz, 1 H, C*H*$(OMe)_2$), 4.04 (q, *J* = 7.0 Hz, 2 H, OC*H*CH_3), 3.29 (s, 6 H, OCH_3), 3.13 (br s, 2 H, allylic CH_2), 2.49–2.94 (m, 4 H, SCH_2's), 2.15 (d, *J* = 4.8 Hz, 2 H, CH_2CH$(OMe)_2$), 1.70–2.08 (m, 2 H, SCH_2CH_2), 1.14 (t, *J* = 7.0 Hz, 3 H, OCH_2CH_3); IR ($CDCl_3$) 3000, 2940, 1710, 1610, 1440, 1220, 1040 cm^{-1}.

Anal. Calcd for $C_{21}H_{28}O_6S_2$: C, 57.25; H, 6.40; S, 14.56. Found: C, 57.19; H, 6.22; S, 14.33.

18: ^{1}H NMR δ 6.70–6.96 (m, 3 H, Ar H), 6.03 (s, 1 H, vinyl H), 5.96 (s, 2 H, OCH_2O), 4.70 (t, *J* = 4.4 Hz, C*H*$(OMe)_2$), 4.21 (q, *J* = 7.0 Hz, 2 H, OCH_2CH_3), 3.88 (br s, 2 H, allylic CH_2), 3.30 (s, 6 H, OCH_3), 2.53–2.91 (m, 4 H, SCH_2's), 2.14 (d, *J* = 4.4 Hz, 2 H, CH_2CH$(OMe)_2$), 1.60–2.01 (m, 2 H, SCH_2CH_2), 1.30 (t, *J* = 7.0 Hz, 3 H, OCH_2CH_3); IR ($CDCl_3$) 3000, 2930, 1710, 1600, 1210, 1180 cm^{-1}; HRMS (M^+) calcd for $C_{21}H_{28}O_6S_2$ 440.1327, found 440.1321.

Ethyl (3*R,3a*S**,6a*R**)-Hexahydro-3a-(1,3-benzodioxol-5-yl)-1-(1′(*S**)-phenylethyl)-5-oxocyclopent[*c*]isoxazole-3-carboxylate, 1,3-Propanediyl Dithioketal (21) and Isomer 22.** To a solution of 3.64 g (8.27 mmol) of acetal **17** in 25 mL of THF was added with stirring 25 mL of 10% HCl, and the mixture was stirred for 1 h at room temperature. Aqueous workup (ether/saturated $NaHCO_3$) gave 3.20 g (98%) of an aldehyde, which was used without further purification: ^{1}H NMR δ 9.62 (t, *J* = 2.2, Hz, 1 H, C(O)*H*), 6.74 (s, 3 H, Ar H), 6.04 (s, 1 H, vinyl H), 5.96 (s, 2 H, OCH_2O), 4.07 (q, *J* = 7.6 Hz, 2 H, OCH_2CH_3), 3.23 (s, 2 H, allylic CH_2), 2.69–2.94 (m, 4 H, SCH_2's), 2.63 (d, *J* = 2.2 Hz, 2 H, CH_2CHO), 1.71–2.00 (m, 2 H, SCH_2CH_2), 1.14 (t, *J* = 7.0 Hz, 3 H, OCH_2CH_3); IR (film) 3000, 1720, 1710, 1505, 1440, 1240, 1214, 1020, 910 cm^{-1}.

The aldehyde obtained above was dissolved in 100 mL of benzene, and 1.84 g (8.11 mmol) of *N*-(α-methylbenzyl)-hydroxylamine oxalate salt[22] and 2.2 g (16.2 mmol) of K_2CO_3 were added. The suspension was stirred overnight at room temperature and then filtered through a pad of Celite. The salts were washed thoroughly with benzene, and the solvent was removed under reduced pressure to afford nitrone **20** as an approximately 5:1 mixture of isomers as a greenish oil.

Major isomer: ^{1}H NMR δ 7.30 (br s, 5 H, PhH), 6.65–6.85 (m, 4 H, Ar H and nitrone H), 5.95 (s, 1 H, vinyl H), 5.92 (s, 2 H, OCH_2O), 4.98 (q, *J* = 6.7 Hz, 1 H, C*H*(CH_3)Ph), 4.04 (q, *J* = 7.2 Hz, 2 H, OCH_2CH_3), 2.60–3.10 (m, 8 H, allylic CH_2, C$(SR)_2CH_2$, and SCH_2's), 1.72–2.00 (m, 2 H, SCH_2CH_2), 1.77 (d, *J* = 6.7 Hz, 3 H, CH(C*H*$_3$)Ph), 1.23 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3); IR (film)

2900–3100, 1720, 1640, 1510, 1490, 1260, 1180, 1040, 900 cm^{-1}.

Minor isomer: ^1H NMR (diagnostic peaks only) δ 1.65 (d, J = 6.7 Hz, 3 H, CH(CH_3)Ph), 1.01 (t, J = 7.2 Hz, 3 H, OCH_2CH_3).

The above nitrones were dissolved in 200 mL of benzene, and the resulting solution was heated at reflux for 2 h. The solution was cooled and the solvent removed under reduced pressure to afford isoxazolidinones **21** and **22** as a greenish oil, which was chromatographed (4:1 ethyl acetate/petroleum ether) to give 2.50 g of the major isomer as white crystals, mp 132–134 °C, and 0.468 g of a 1.72:1 mixture of major/minor isomers (70% total yield, 16:1 ratio of isomers).

Major isomer **21**: ^1H NMR (250 MHz) δ 7.25–7.50 (m, 5 H, PhH), 6.93 (br s, 1 H, 1 Ar H), 6.86 (br d, J = 7.4 Hz, 1 H, 1 Ar H), 6.72 (d, J = 7.4 Hz, 1 H, 1 Ar H), 5.93 (s, 2 H, OCH_2O), 4.93 (br s, 1 H, C-3 methine), 4.19 (q, J = 6.3 Hz, 1 H, CH(CH_3)Ph), 3.96 (m, 1 H, C-6a methine), 3.83–3.92 (overlapping q's, 2 H, OCH_2CH_3), 2.72–3.00 (m, 4 H, SCH_2's), 2.52–2.66 (m, 2 H, C-4 CH_2), 1.70–2.00 (m, 4 H, SCH_2CH_2 and C-6 CH_2), 1.63 (d, J = 6.3 Hz, 3 H, CH(CH_3)Ph), 1.00 (t, J = 7.2 Hz, 3 H, OCH_2CH_3); IR ($CDCl_3$) 2800, 1730 (d), 1600, 1490, 1430, 1240, 1040, 810 cm^{-1}.

Anal. Calcd for $C_{27}H_{31}NO_5S_2$: C, 63.13; H, 6.08; N, 2.73; S, 12.48. Found: C, 63.38; H, 6.16; N, 2.67; S, 12.41.

Rechromatography of several fractions enriched in the minor isomer afforded 9 mg of pure minor isomer **22**.

Minor isomer **22**: ^1H NMR (250 MHz, diagnostic peaks only) δ 5.97 (s, 2 H, OCH_2O), 1.59 (d, J = 6.3 Hz, 3 H, CH(CH_3)Ph), 1.18, (t, J = 7.1 Hz, 3 H, OCH_2CH_3); HRMS (M^+) calcd for $C_{27}H_{31}NO_5S_2$ 513.1643, found 513.1646.

Ethyl (3β,3aα,6aα)-Hexahydro-3a-(1,3-benzodioxol-5-yl)-1-(1-phenylethyl)-5-oxocyclopent[*c*]isoxazole-3-carboxylate, 1,3-Propanediyl Dithioketal (24) and Isomer 25. The procedure as described for the formation of **21** and **22** was followed. Thus, hydrolysis of 0.41 g (0.93 mmol) of acetal **18** gave 0.35 g (97%) of the corresponding aldehyde: ^1H NMR δ 9.74 (t, J = 2.2 Hz, 1 H, CHO), 6.70–7.00 (m, 3 H, Ar H), 6.06 (s, 1 H, C=C$H$$CO_2Et$), 5.99 (s, 2 H, OCH_2O), 4.22 (q, J = 6.7 Hz, 2 H, CH_2CH_3), 3.99 (br s, 2 H, allylic CH_2), 2.70–3.00 (m, 4 H, SCH_2), 2.64 (d, J = 2.2 Hz, 2 H, CH_2CHO), 1.88 (m, 2 H, SCH_2CH_2), 1.29 (t, J = 6.7 Hz, 3 H, OCH_2CH_3); IR ($CDCl_3$) 3000, 1720 (b), 1500, 1240, 1020 cm^{-1}.

Treatment of the above aldehyde with 210 mg (0.93 mmol) of *N*-(α-methylbenzyl)hydroxylamine oxalate salt as before gave nitrone **23** as an oil: ^1H NMR δ 7.33 (m, 5 H, PhH), 6.80 (m, 4 H, Ar H and nitrone H), 6.01 (s, 1 H, C=C$H$$CO_2Et$), 5.94 (s, 2 H, OCH_2O), 5.03 (q, J = 7.0 Hz, 1 H, NCH(CH_3)Ph), 4.18 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 3.82 (br s, 2 H, C-4 CH_2), 3.11 (d, J = 5.6 Hz, C-6 CH_2), 2.70 (m, 4 H, SCH_2), 1.80 (m, including d, J = 7.0 Hz, NCH(CH_3)Ph and SCH_2CH_2), 1.27 (t, J = 7.2 Hz, 3 H, OCH_2CH_3); IR ($CDCl_3$) 3000, 1720, 1640, 1500, 1260, 1020 cm^{-1}.

The above nitrone in 50 mL of benzene was cyclized as above to yield 363 mg (76%) of isoxazolidinones **24** and **25**. The major isomer could be removed as white crystals, mp 79–81 °C, by trituration with petroleum ether. The isomer ratio was 4:1 (^1H NMR).

Major isomer **24**: ^1H NMR (250 MHz) δ 7.35 (m, 5 H, PhH), 7.10 (d, J = 1.8, Hz, 1 H, 1 Ar H), 6.96 (dd, J = 8.2 Hz, 1.8, 1 H, 1 Ar H), 6.77 (d, J = 8.2 Hz, 1 H, 1 Ar H), 5.98 (m, 2 H, OCH_2O), 4.68 (s, 1 H, C-3 methine), 4.32 (m, 2 H, OCH_2CH_3), 3.95 (q, J = 6.8 Hz, 1 H, NCH(CH_3)Ph), 2.30–3.00 (m, 8 H, SCH_2 and C-4 and C-6 CH_2's), 1.90 (m, 2 H, SCH_2CH_2), 1.42 (d, J = 6.8 Hz, 3 H, NCH(CH_3)Ph), 1.36 (t, J = 7.2 Hz, 3 H, OCH_2CH_3); IR ($CDCl_3$) 2800, 1730, 1590, 1410, 1220, 1040; ^{13}C NMR δ 168.7, 147.8, 146.3, 143.2, 139.1, 128.7, 127.5, 127.2, 119.6, 107.6, 101.1, 86.9, 72.0, 66.2, 62.0, 54.1, 50.4, 45.8, 28.7, 27.6, 25.2, 22.5, 24.3.

Anal. Calcd for $C_{27}H_{31}NO_5S_2$: C, 63.13; H, 6.08; N, 2.73; S, 12.48. Found: C, 63.35; H, 5.99; N, 2.78; S, 12.20.

Chromatography of the mother liquors from the above crystallization (4:1 ethyl acetate/petroleum ether) afforded 7 mg of pure minor isoxazolidine.

Minor isomer **25**: ^1H NMR (250 MHz, diagnostic peaks only): δ 7.06 (d, J = 1.8 Hz, 1 H, 1 Ar H), 6.76 (d, J = 8.2 Hz, 1 H, 1 Ar H), 1.52 (d, J = 6.4 Hz, 3 H, NCH(CH_3)Ph); HRMS (M^+) calcd for $C_{27}H_{31}NO_5S_2$ 513.1643, found 513.1651.

Hexahydro-(3*R,3a*S**,6a*R**)-3-acetoxy-3a-(1,3-benzodioxol-5-yl)-1-(1′(*S**)-phenylethyl)cyclopenta[*b*]pyrrole-2,5(1*H*)-dione, 5-(1,3-Propanediyl dithioketal) (26).** A mixture of 1.25 g (2.5 mmol) of isoxazolidine **21** and 3.28 g (50 mmol) of zinc dust in 100 mL of glacial acetic acid was heated at reflux with stirring for 36 h, at which time the reaction mixture was cooled and filtered. Most of the solvent was then removed under reduced pressure, and the resultant oil was submitted to an aqueous workup (CH_2Cl_2/saturated $NaHCO_3$) followed by chromatography (4:1 hexane/ethyl acetate) to afford 0.964 g (75%) of lactam **26** as colorless crystals: mp 131–135 °C; ^1H NMR δ 7.30 (s, 5 H, Ph), 6.1–6.55 (m, 3 H, ArH), 5.87 (s, 2 H, OCH_2O), 5.60 (q, J = 6.7 Hz, 1 H, NC$H$$CH_3$Ph), 5.18 (s, 1 H, C-3 methine), 4.13 (dd, J = 5.8, 8.9 Hz, 1 H, C-6a methine), 2.65–3.0 (m, 6 H, SCH_2 and C-6 CH_2), 2.49 (br s, 2 H, C-4 CH_2), 2.25 (s, 3 H, $OCOCH_3$), 1.90–2.10 (m, 2 H, SCH_2CH_2), 1.68 (d, J = 6.7 Hz, 3 H, NCH(CH_3)Ph); IR ($CDCl_3$) 2800, 1735, 1685, 1500, 1420, 1230, 1040, 800 cm^{-1}.

Anal. Calcd for $C_{27}H_{29}NO_5S_2$: C, 63.38; H, 5.71; N, 2.74; S, 12.53. Found: C, 63.34; H, 5.86; N, 2.63; S, 12.27.

Hexahydro-(3*R,3a*S**,6a*R**)-3a-(1,3-benzodioxol-5-yl)-3-(benzyloxy)-1-(1′(*S**)-phenylethyl)cyclopenta[*b*]pyrrole-2,5(1*H*)-dione, 5-(1,3-Propanediyl dithioketal) (27).** To a solution of 166 mg (0.32 mmol) of acetate **26** in 5 mL of MeOH was added 45 mg (0.33 mmol) of K_2CO_3, and the resulting suspension was stirred at room temperature for 1.5 h. Aqueous workup (CH_2Cl_2) afforded a white solid, which was used without further purification or characterization.

The above alcohol in 10 mL of DMF was then added to a suspension of 14 mg (0.35 mmol) of NaH from a 60% mineral oil suspension (washed with pentane) in 1 mL of DMF at 0 °C. Benzyl bromide (60 mg, 0.35 mmol) was added in one portion, and the solution was gradually allowed to warm to room temperature with stirring over 2 h. After quenching with 10 mL of H_2O, aqueous workup (ether) gave the crude product as a yellow oil. Chromatography afforded 124 mg (69%) of **27** as a white solid: mp 151–152 °C; ^1H NMR δ 7.36 (br, s, 5 H, PhH), 5.95–6.60 (m, 3 H, Ar H), 5.83 (s, 2 H, OCH_2O), 5.56 (q, J = 7.0 Hz, 1 H, NCH(CH_3)Ph), 4.92 (2 H, AB q, J_{AB} = 12.5 Hz, $\Delta\nu$ = 23 Hz, 2 H, OCH_2Ph), 4.04 (dd, J = 7.3, 8.8 Hz, 1 H, C-6a methine), 3.69 (s, 1 H, C-3 methine), 2.25–3.40 (m, 8 H, C-4 and C-6 CH_2's and SCH_2), 1.80–2.20 (m, 2 H, SCH_2CH_2), 1.57 (d, J = 7.0 Hz, 3 H, NCH(CH_3)Ph); IR ($CDCl_3$) 2900, 1670, 1400–1500, 1230, 1040, 870 cm^{-1}.

Anal. Calcd for $C_{32}H_{35}NO_4S_2$: C, 68.66; H, 5.94; N, 2.50; S, 11.46. Found: C, 68.75; H, 6.09; N, 2.38; S, 11.51.

Hexahydro-(3*R,3a*S**,6a*R**)-3a-(1,3-benzodioxol-5-yl)-3-(benzyloxy)-1-(1′(*S**)-phenylethyl)cyclopenta[*b*]pyrrole-2,5(1*H*)-dione (29).** To a suspension of 864 mg (1.54 mmol) of **27** vigorously stirred in 10 mL of MeOH at −10 °C was added 1.64 g (9.24 mmol) of *N*-bromosuccinimide in 10 mL of MeOH.[27] The clear orange solution was stirred at −10 °C for 2 min, diluted with 25 mL of CH_2Cl_2, washed with saturated Na_2SO_3, saturated $NaHCO_3$, H_2O, and brine, dried (Na_2SO_4), and concentrated. The oil thus obtained was dissolved immediately in 5 mL of THF and 5 mL of 10% HCl and the solution stirred 30 min at room temperature. Aqueous workup (ether/saturated $NaHCO_3$) followed by chromatography (1:1 EtOAc/petroleum ether) afforded 473 mg (66%) of ketone **29** as white crystals, mp 164–166 °C.

Alternatively, **26** could be carried directly through the above sequence, omitting all but the final purification step. In this way 1.13 g (2.21 mmol) of **26** yielded 0.518 (50% overall for four steps) of pure **29**: ^1H NMR (250 MHz) δ 7.26–7.43 (m, 10 H, PhH), 6.43 (d, J = 8.2 Hz, 1 H, 1 Ar H), 6.17 (d, J = 1.9 Hz, 1 H, 1 Ar H), 5.98 (dd, J = 8.2, 1.9 Hz, 1 H, 1 Ar H), 5.87 (s, 2 H, OCH_2O), 5.59 (q, J = 7.3 Hz, 1 H, NCH(CH_3)Ph), 4.86 (AB q, J_{AB} = 12.2 Hz, $\Delta\nu$ = 61.6 Hz, 2 H, OCH_2Ph), 4.05 (dd, J = 8.4, 6.4 Hz, 1 H, C-6a methine), 3.92 (s, 1 H, C-3 methine), 2.73 (AB q, J_{AB} = 18.5 Hz, $\Delta\nu$ = 191 Hz, 2 H, C-4 CH_2), 2.66 (m, 2 H, C-6 CH_2), 1.61 (d, J = 7.3 Hz, 3 H, NCH(CH_3)Ph); IR ($CDCl_3$) 2950, 1740, 1680, 1460, 1370, 1240, 1090 cm^{-1}.

Anal. Calcd for $C_{26}H_{28}NO_7$: C, 74.18; H, 5.80; N, 2.98. Found: C, 74.11; H, 5.69; N, 2.77.

Supplementary Material Available: Pertinent crystallographic information for cycloadduct **21** and a summary of unsuccessful ring-expansion attempts for ketone **29** (17 pages). Ordering information is given on any current masthead page.